

Synthesis and Catalytic Activity of 1,2,4,3-Triazaphospholenes

by

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To My Family

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Abstract

Catalysis plays a key role in the industrial production of many refined goods. Catalysts derived from precious metals are especially prevalent in industry due to their high stereoselectivity, and low loadings. To alleviate the reliance on precious metals, catalysts derived from cheaper, more abundant main group elements have attracted much attention in recent years. 1,3,2-Diazaphospholenes developed by Gudat, Kinjo, and our group have shown great potential in the reduction of various unsaturated carbons including imines, carbonyls, olefins, etc. In an effort to uncover catalytic activity in more elaborate heterocycles, I have developed a new class of hydroboration catalysts, namely 1,2,4,3-triazaphospholenes. The synthesis towards 1,2,4,3-triazaphospholenes and their reactivity in the racemic and non-racemic hydroboration of imines and carbonyls are disclosed herein.

List of Abbreviations and Symbols Used

| | |
|------------------|--|
| α | alpha (carbon position) |
| β | beta (carbon position) |
| δ | chemical shift |
| ΔH | change in enthalpy |
| λ | wavelength |
| \AA | angstrom |
| APCI | atmospheric pressure chemical ionization |
| Ar | aryl |
| ArHet | heteroaryl |
| BAr _F | tetrakis(pentafluorophenyl)borate |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| BINOL | 1,1'-bi-2-naphthol |
| Bn | benzyl |
| Boc | <i>tert</i> -butyloxycarbonyl |
| br | broad |
| calc'd | calculated |
| cat. | catalytic <i>or</i> catalyst |
| Cy | cyclohexyl |

| | |
|-------------|------------------------------------|
| d | doublet(s) |
| <i>d</i> | deuterium |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DAP | 1,3,2-diazaphospholene |
| DBU | 1,8-diazabicyclo(5.4.0)undec-7-ene |
| DCM | dichloromethane |
| dd | doublet of doublets |
| ddd | doublet of doublet of doublets |
| Dipp | 2,6-diisopropylphenyl |
| DMAP | 4-(dimethylamino)pyridine |
| dt | doublet of triplets |
| <i>E</i> | entgegen |
| <i>e.e.</i> | enantiomeric excess |
| equiv. | equivalent |
| <i>e.r.</i> | enantiomeric ratio |
| ESI | electrospray ionization |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| EWG | electron withdrawing group |

| | |
|-----------|--|
| FLP | frustrated Lewis Pair |
| HB(cat) | catecholborane |
| HB(pin) | pinacolborane |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| <i>J</i> | coupling constant(s) |
| $K\alpha$ | K-alpha (emission line) |
| m | multiplet(s) |
| M | molar (concentration) <i>or</i> molecule |
| m/z | mass-to-charge ratio |
| MeCN | acetonitrile |
| Mes | mesityl <i>or</i> 2,4,6-trimethylphenyl |
| MeOH | methanol |
| N/A | not applicable |
| 1-Nap | 1-naphthyl |
| NHC | <i>N</i> -heterocyclic carbene |
| NMR | nuclear magnetic resonance |
| OBn | benzyloxy |
| OMe | methoxy |

| | |
|--------------------|--------------------------------|
| <i>p</i> | <i>para</i> |
| p | pentet(s) |
| Ph | phenyl |
| pin | pinacol |
| PMB | <i>para</i> -methoxybenzyl |
| PMP | <i>para</i> -methoxyphenyl |
| ppm | parts per million |
| <i>i</i> PrOH | <i>iso</i> -propanol |
| PTFE | polytetrafluoroethylene |
| 2-Py | 2-pyridyl |
| q | quartet(s) |
| R | generic group |
| <i>R</i> | <i>rectus</i> |
| rt | room temperature |
| s | singlet(s) <i>or</i> second(s) |
| <i>S</i> | <i>sinister</i> |
| sep | septet(s) |
| t | triplet(s) |
| t _{major} | elution time of major isomer |

| | |
|--------------------|--|
| t_{minor} | elution time of minor isomer |
| TAP | 1,2,4,3-triazaphospholene |
| td | triplet of doublets |
| Tf | trifluoromethanesulfonyl |
| TFT | α,α,α -trifluorotoluene |
| THF | tetrahydrofuran |
| Ts | <i>para</i> -tolylsulfonyl |
| TS | transition state |
| tt | triplet of triplets |
| X | generic anionic group |
| Z | zusammen |

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Chapter 1. Introduction

1.1 Introduction

Catalysis represents a field of chemistry that is of great importance. The use of catalysts in chemical transformations lowers the energy input required for reactions to proceed, and in some cases, facilitates reactions that otherwise would not proceed. Transition metal-catalyzed transformations are well established, with countless industrial applications.¹ In comparison, the list of industrial applications using main group catalysts is less extensive. Unfortunately, transition metal catalysts, especially Pt-group complexes, are not only costly, but are often also toxic.² Therefore, it is imperative to develop main group catalysts in order to complement, or even replace, current methods that employ transition metal catalysts.

Of current main group catalysts, carbenes have received considerable attention following the isolation of a crystalline, stable diaminocarbene (Figure 1.1).³ Much effort in this field has been made towards the synthesis of *N*-heterocyclic carbenes (NHCs) as organocatalysts in transformations such as the benzoin condensation, Stetter

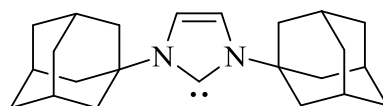
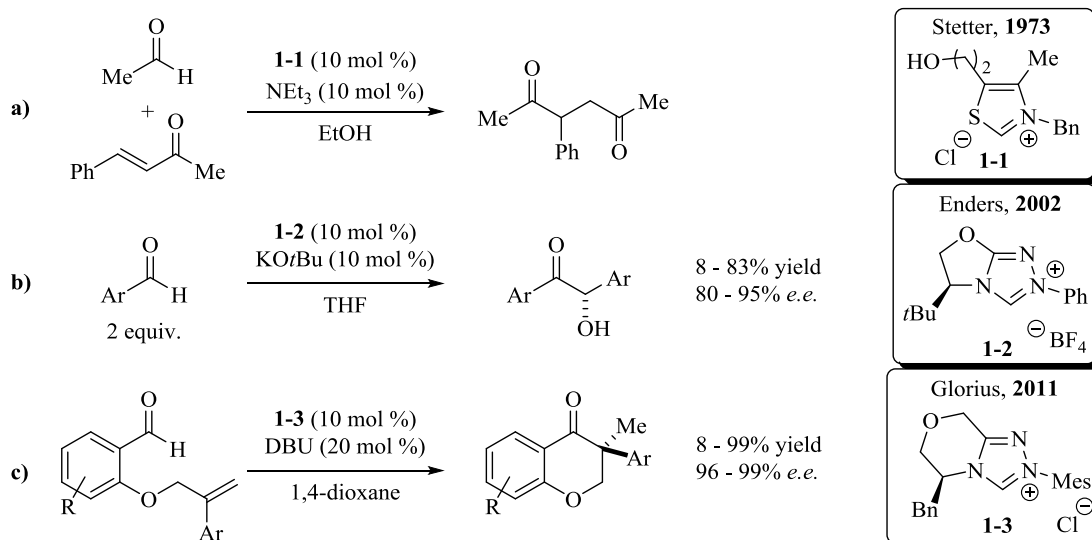


Figure 1.1 Free and stable 1,3-di-1-adamantyl-imidazol-2-ylidene carbene.



Scheme 1.1 Examples of transformations catalyzed by carbenes.

reaction, and variations thereof (Scheme 1.1).⁴ NHCs have also been widely employed as electron-rich ligands for transition metal complexes. Shown below are examples of carbene-supported transition metal complexes that are able to catalyze industrially vital transformations including olefin metathesis,⁵ hydrogenation,^{6,7} and C-C cross-coupling^{8,9} (Figure 1.2).

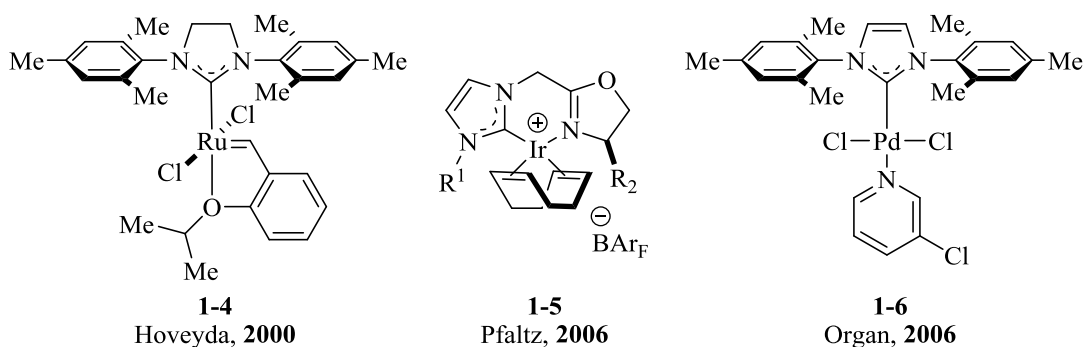
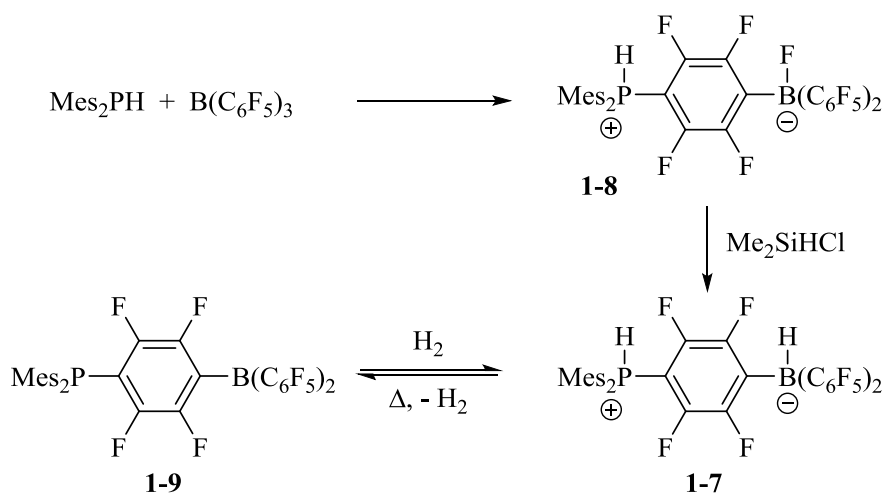


Figure 1.2 Examples of carbene-supported transition metal complexes.

Another valuable class of main group catalysts are derived from frustrated Lewis pairs (FLPs). A seminal report by Stephan showed the reversible activation of H₂



Scheme 1.2 The reversible activation of H₂ using a metal-free system.

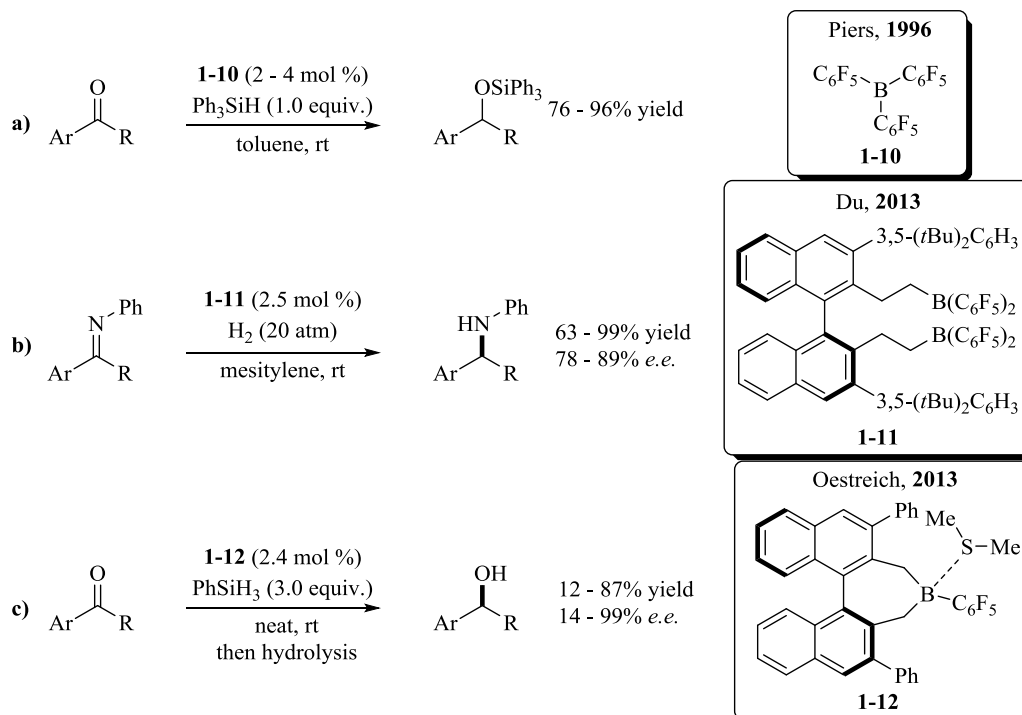
mediated by a metal-free system consisting of a bulky Lewis basic phosphine and Lewis acidic borane, **1-7** (Scheme 1.2).¹⁰ The combination of bis(2,4,6-trimethylphenyl)phosphine (dimesitylphosphine) and tris(pentafluorophenyl)borane results in **1-8**. This zwitterionic compound can be activated to form **1-7**, which can liberate H₂ to form **1-9** upon heating to 100 °C.¹⁰ Upon exposure to H₂, **1-9** can be rapidly converted to **1-7**.¹⁰ Lewis pairs that are too sterically hindered to form proper adducts are collectively coined “frustrated Lewis pairs” or FLPs.¹¹ Prior to this finding, activation of H₂ at ambient temperature was thought to be reactivity exclusive to organometallic systems employing transition metals.¹² This unprecedented reactivity prompted the pursuit of the catalytic activation of small molecules such as H₂,¹⁰ alkenes,¹³ and CO₂¹⁴ using FLPs.¹⁵ In general, the discovery of FLPs is monumental in bringing light to the field of main group catalysis, for new reactivity and selectivity previously unknown to transition metal-based catalysts can be uncovered, hence the

purpose of this project.

1.2 Main Group-Catalyzed Reductions

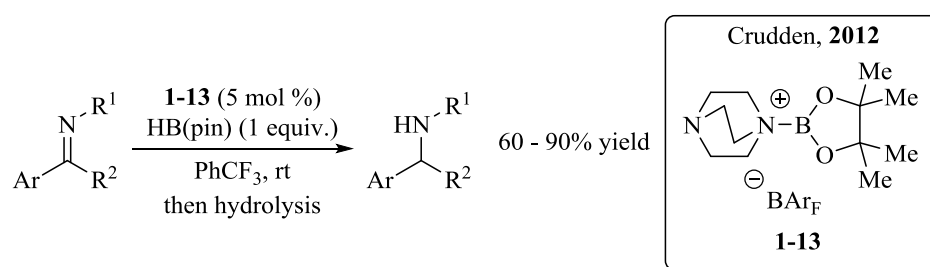
In this thesis, the term “reduction” will strictly refer to hydrogenation, hydroboration, and hydrosilylation of unsaturated functional groups. Catalytic reduction of unsaturated carbons, namely olefins, alkynes, carbonyls, and imines represent a field of high interest due to the industrial application of the corresponding products. Hydrogenations catalyzed by transition metal complexes are well known; state-of-the-art examples include chiral ruthenium-^{12e, 16} and iridium-based^{12c,d} catalysts. Despite the enhanced activity and enantioselectivity transition metal catalysts often provide, efforts to discover comparable main group catalysts have not ceased.

1.2.1 Brønsted/Lewis Acidic Catalysts



Scheme 1.3 (Pentafluorophenyl)borane-catalyzed reduction of carbonyls and imines.

Mono-, bis-, and tris-(pentafluorophenyl)boranes have emerged as the most versatile Lewis acidic main group catalysts for use in reductive catalysis since the discovery of FLPs.¹⁰ Ketones and sterically hindered imines act as Lewis bases that can form intramolecular adducts with the borane derivatives to undergo reduction in the presence of H₂, eliminating the addition of an exogenous Lewis base catalyst (Scheme 1.3).^{17,18,19} A seminal report by Piers showed tris(pentafluorophenyl)borane, **1-10**, can activate triphenylsilane to form silylium cations to promote the hydrosilylation of carbonyls (Scheme 1.3a).¹⁷ Researchers have since extended this approach to the asymmetric reduction of carbonyls and imines using chiral (pentafluorophenyl)borane derivatives such as **1-11**¹⁸ and **1-12**¹⁹ (Scheme 1.3b, c). Unfortunately, these borane catalysts are difficult to synthesize, of high molecular weight, and highly reactive. Furthermore, harsh conditions and sterically hindered substrates are often required to avoid poisoning of the catalyst by the reduced products.²⁰



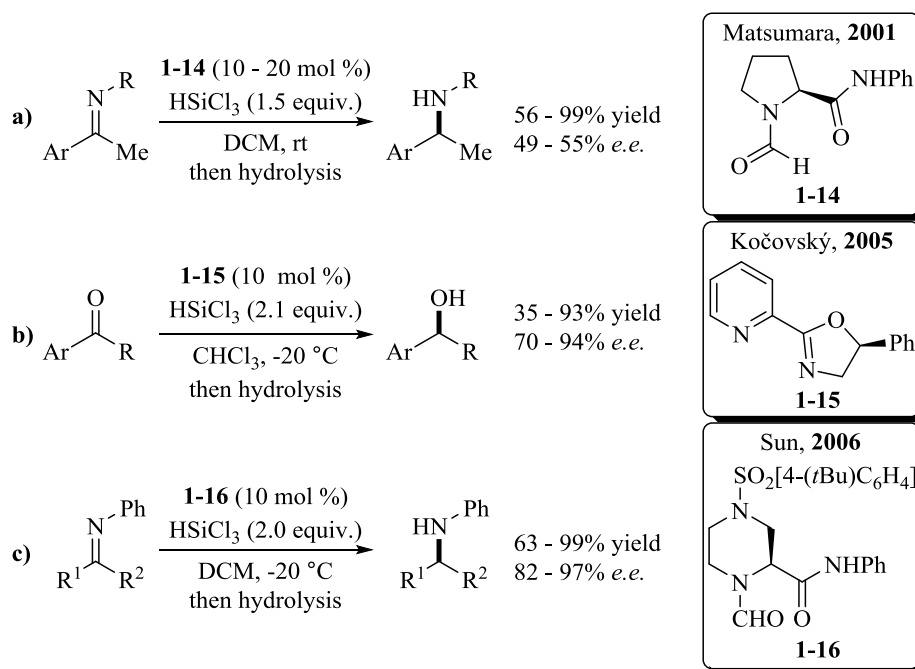
Scheme 1.4 Borenium-catalyzed hydroboration of imines.

More recently, Crudden reported the Lewis base-stabilized borenium cation, **1-13**, catalyzed hydroboration of imines (Scheme 1.4).²¹ Compared to (pentafluorophenyl)borane systems, borenium-catalyzed reductions utilize a more

easily accessible boron Lewis acid, namely pinacolborane (HB(pin)). Following this publication, many examples of carbene-stabilized boreniums have been employed in the hydrogenation of olefins,²² heterocycles,²³ and carbonyls²⁴.

1.2.2 Lewis Basic Catalysts

Lewis base-catalyzed hydrosilylation is among one of the most robust methods for the reduction of carbonyls and imines. Following Matsumara's²⁵ disclosure in 2001, Lewis basic chiral amides²⁶ and 1,3-oxazolines²⁷ have been employed extensively in

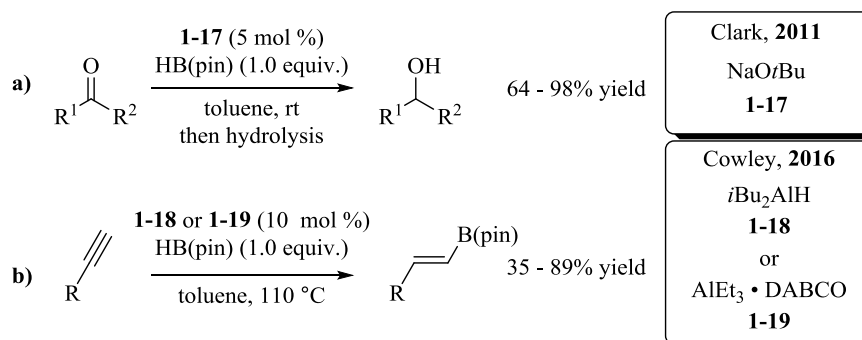


Scheme 1.5 Lewis base-catalyzed hydrosilylation of carbonyls and imines.

the asymmetric hydrosilylation of carbonyls and imines (Scheme 1.5). Most of the catalyst scaffolds are air-stable, and derived from easily accessible chiral 1,2-amino alcohols.^{26,27} Furthermore, silane sources, in particular trichlorosilane, are cheap, and easy to remove from the reaction mixture. In contrast, Lewis acid-catalyzed reductions

generally require the use of heavy, and therefore poorly atom-economical catalyst scaffolds such as 1,1'-bi-2-naphthol (BINOL), and/or air-sensitive boranes or boreniums.

More recently, nucleophiles such as *tert*-butoxide, **1-17**,²⁸ and organoaluminums, **1-18** and **1-19**,²⁹ have been shown to catalyze the hydroboration of carbonyls and alkynes, respectively (Scheme 1.6). However, activation of HB(pin) *via* these methods are more mechanistically interesting than they are operationally useful, as the functional group-tolerance is limited by the reactivity of nucleophilic catalysts employed.



Scheme 1.6 Alkoxide- and organoaluminum-catalyzed hydroboration of carbonyls and alkynes.

1.2.3 Bifunctional Catalysts

Axially chiral phosphoric acids, phosphoramides, and sulfonimides derived from BINOL and similar scaffolds are prevalent bifunctional catalysts due to their high Brønsted acidity, mild Brønsted basicity, and rigid axially chiral structures.³⁰

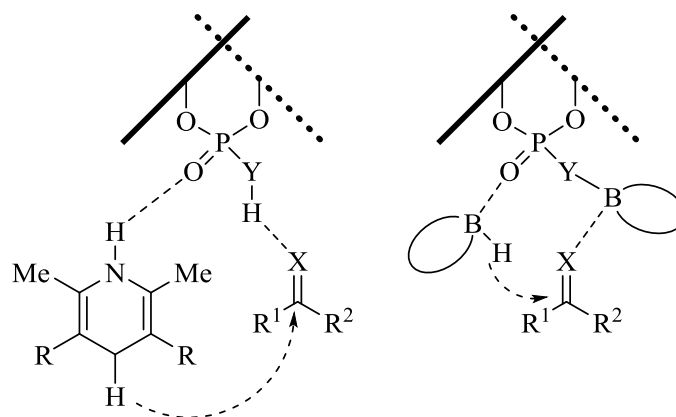
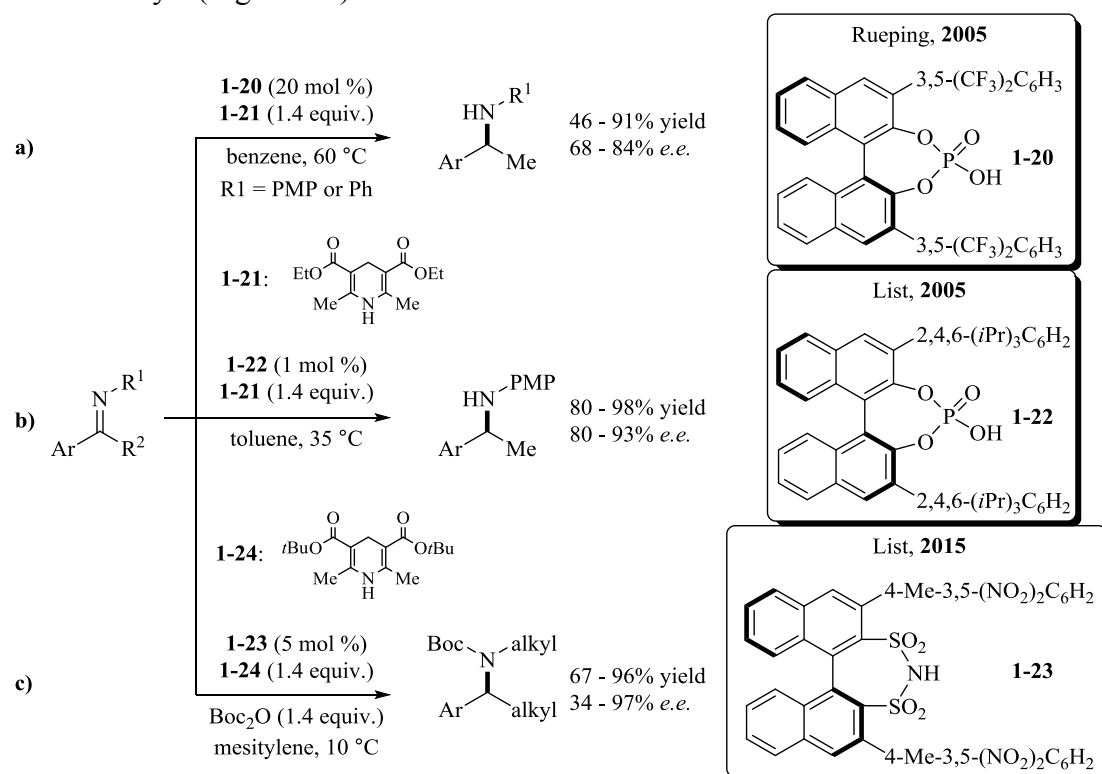


Figure 1.3 Activation of Hantzsch esters and boranes by axially chiral bifunctional phosphates. X = O, NR³; Y = O, NTf.

Imine/carbonyl hydroboration using borane reagents, and transfer hydrogenation using

Hantzsch esters require dual activation by both the Lewis basic, and Lewis acidic sites

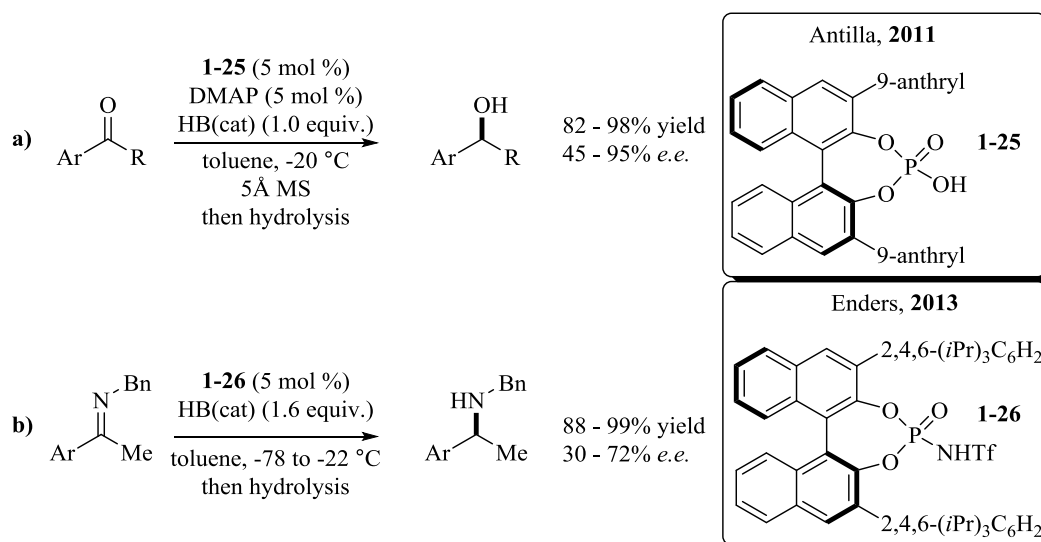
of the catalyst (Figure 1.3).³⁰



Scheme 1.7 Transfer hydrogenation of imines using Hantzsch esters catalyzed by axially chiral bifunctional phosphoric acids or disulfonimides.

In 2005, Rueping³¹ and List³² independently reported the asymmetric transfer-

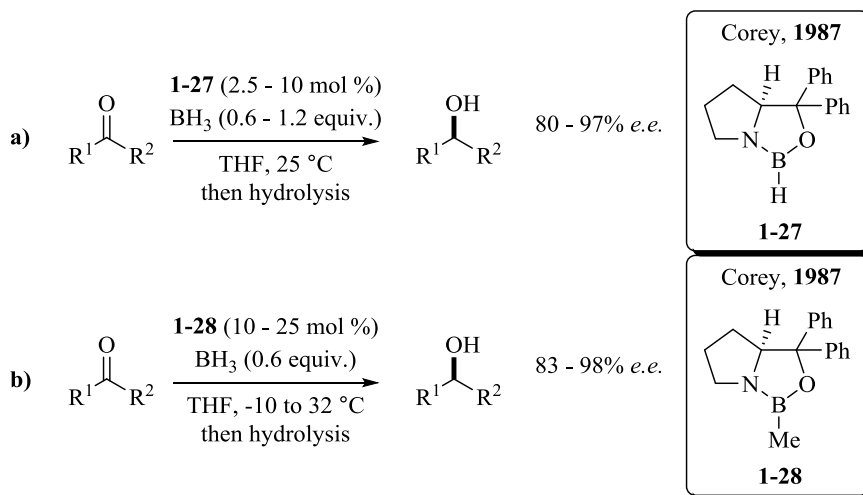
hydrogenation of aryl imines using a commercially available Hantzsch ester, **1-21**, catalyzed by axially chiral phosphoric acids, **1-20** and **1-22**, respectively (Scheme 1.7a, b). More recently, List extended this approach to *N*-alkyl imines by employing an axially chiral disulfonimide catalyst, **1-23** (Scheme 1.7c).³³ This method provides an alternative route to asymmetric reduction of sterically unhindered alkyl imines, as electron-deficient borane catalysts, namely (pentafluorophenyl)boranes, are only compatible with sterically hindered imines. However, the dehydrogenated by-products, namely substituted pyridines, are difficult to separate from the amine products, rendering this approach unattractive.



Scheme 1.8 Hydroboration of carbonyls and imines catalyzed by bifunctional phosphoric acids or phosphoramides.

Antilla reported the asymmetric hydroboration of ketones catalyzed by a sterically encumbered phosphoric acid, **1-25**, and 4-(dimethylamino)pyridine (DMAP) (Scheme 1.8a).³⁴ Subsequently, Enders reported the asymmetric hydroboration of

imines catalyzed by structurally similar **1-26**, albeit without the use of a Lewis base additive (Scheme 1.8b).³⁵ Most of these catalysts have the advantage of being bench-stable and easy to handle. However, axially chiral scaffolds generally provide poor atom economy due to the high molecular mass and relatively high catalyst loading.



Scheme 1.9 Reduction of ketones catalyzed by Itsuno/Corey oxazaborolidines.

Itsuno and co-workers reported the first asymmetric hydroboration of ketones with 1,3,2-oxazaborolidines, made from enantiopure 1,2-amino alcohols and BH_3 *in situ*.³⁶ Corey later reported the catalytic asymmetric reduction of ketones by directly employing oxazaborolidine **1-27** as the catalyst, and BH_3 as reductant to afford secondary alcohols with enantiomeric excess (*e.e.*) of up to 97% (Scheme 1.9a).³⁷ The same group later reported a more air- and moisture-stable *B*-methylated 1,3,2-oxazaborolidine **1-28** with comparable enantioselectivity for the catalytic reduction of

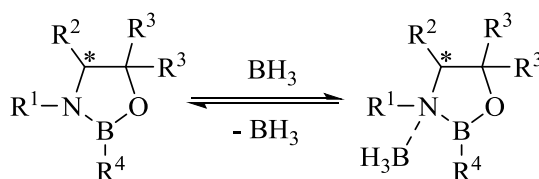
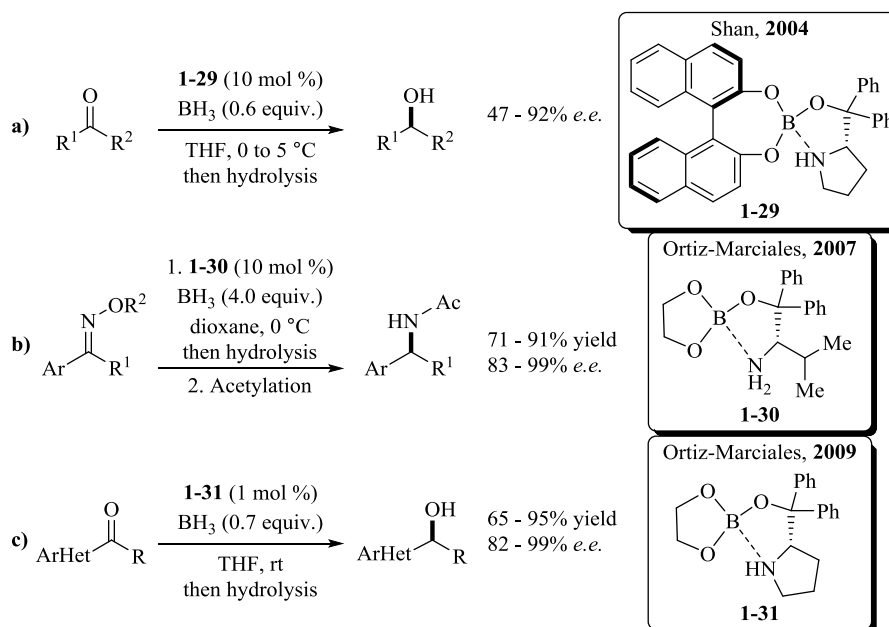


Figure 1.4 Activation of oxazaborolidines by BH_3 .

ketones (Scheme 1.9b).³⁸ Itsuno/Corey-type oxazaborolidines complex with BH₃ to form bifunctional reductants that contain both Lewis acidic, and Lewis basic boron centres (Figure 1.4).³⁶⁻³⁸



Scheme 1.10 Spiroborate ester-catalyzed reduction of ketones and oxime ethers.

Another class of bifunctional boron-based catalysts are spiroborate esters developed by Shan and co-workers.³⁹ Like the Itsuno/Corey oxazaborolidines, these spiroborate esters are derived from abundant amino acids or amino alcohols. Additionally, these borate esters can be bound to chiral alcohols, such as BINOL, **1-29** (Scheme 1.10a).³⁹ Following Shan's disclosure, Ortiz-Marciales and co-workers reported the catalytic asymmetric reduction of oxime ethers and heteroaryl-containing

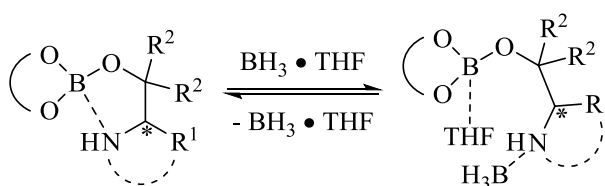
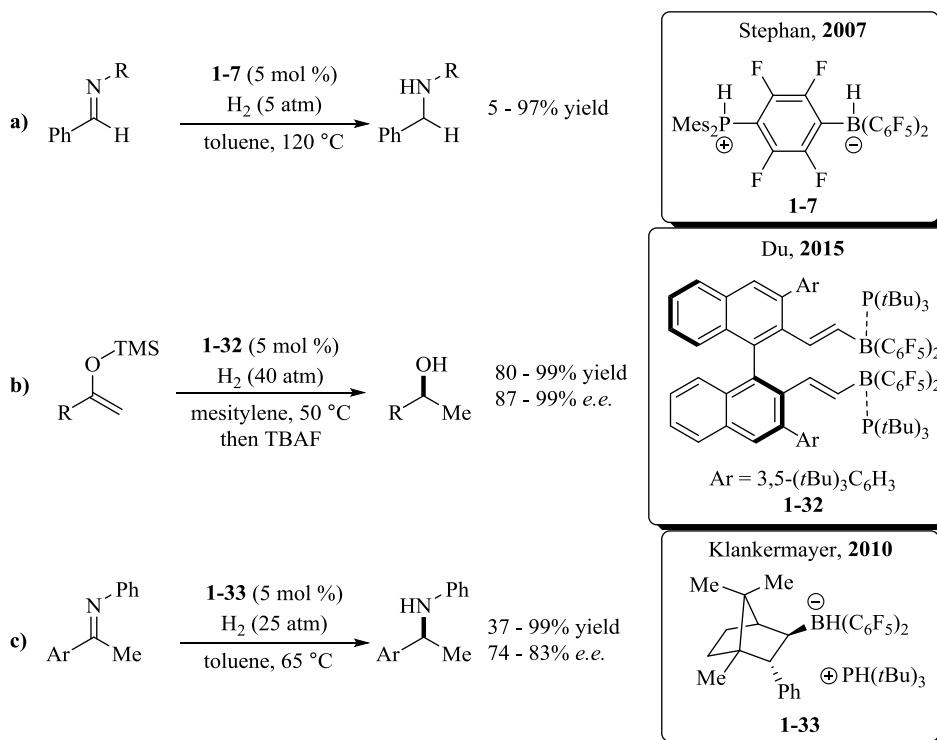


Figure 1.5 Activation of spiroborate esters by BH₃.

ketones using **1-30** and **1-31**, respectively (Scheme 1.10b, c).⁴⁰ The nitrogen moiety of the spiroborate ester acts as a pendant ligand to boron, which dissociates to coordinate with BH₃ to afford the active reductant (Figure 1.5).

1.2.4 FLP Catalysts

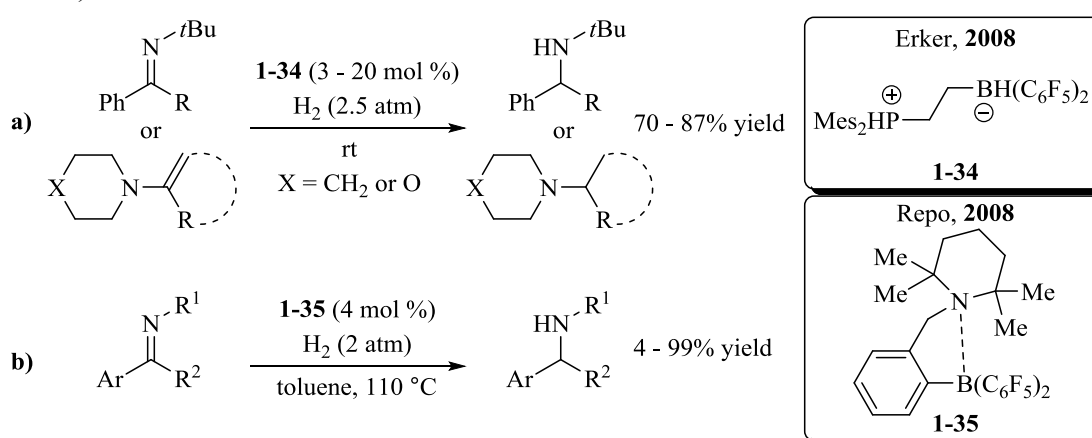


Scheme 1.11 FLP-catalyzed hydrogenation of imines and enol ethers.

The first catalytic metal-free hydrogenation of imines, using H₂ as the terminal reductant, was reported by Stephan⁴¹ following their disclosure¹⁰ on the FLP-mediated splitting of H₂ (Scheme 1.11a). Following the original publication,⁴¹ examples of more elaborate FLP scaffolds have been reported for use in asymmetric catalysis⁴² (Scheme 1.11b, c).

The group of Erker, in collaboration with Stephan, reported the splitting of H₂

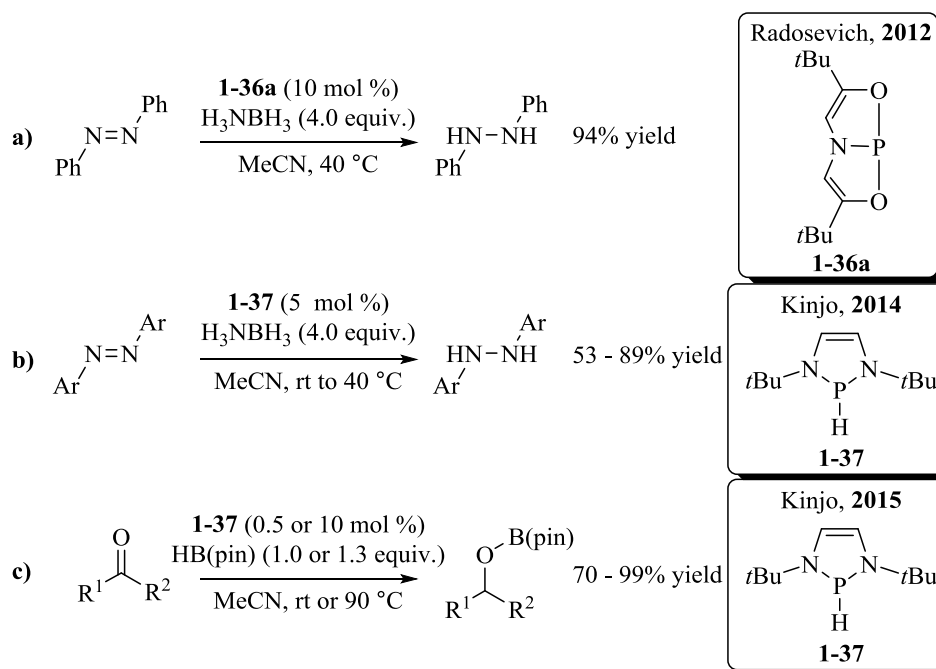
mediated by an intramolecular FLP, **1-34**, where the Lewis pair is connected *via* an ethylene bridge.⁴³ Shortly after, Erker disclosed the hydrogenation of enamines and imines using this system (Scheme 1.12a).⁴⁴ Repo and co-workers subsequently reported the hydrogenation of imines using an intramolecular amino-borane FLP, **1-35**, where the Lewis basic amine is 3 carbons away from the Lewis acidic borane (Scheme 1.12b).⁴⁵



Scheme 1.12 Hydrogenation of imines and enamines catalyzed by intramolecular FLPs.

1.2.5 Phosphorous-Based Catalysts

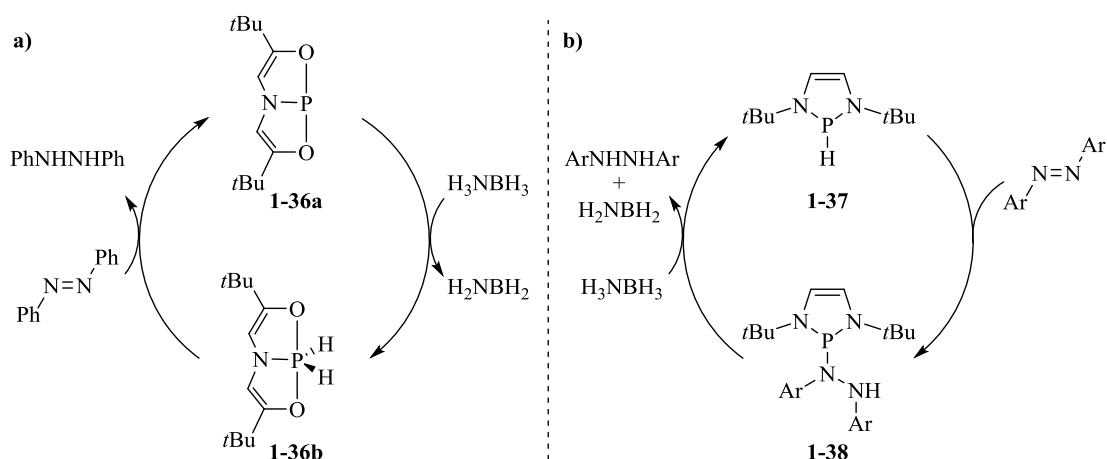
Phosphines have been extensively employed as catalysts in many transformations,⁴⁶ including annulations,⁴⁷ modified Wittig reactions,⁴⁸ and other C-C bond forming reactions⁴⁹. Many catalysts mentioned in previous subsections contain phosphorus atoms. However, examples where the phosphorus atom directly interacts with substrates, or changes oxidation states, are less common in reductive catalysis. Radosevich reported the phosphine-catalyzed transfer hydrogenation of azobenzene



Scheme 1.13 Transfer hydrogenation of diazenes, and hydroboration of carbonyls catalyzed by phosphorous-based catalysts.

using ammonia-borane as the terminal reductant (Scheme 1.13a).⁵⁰ Two hydrogen atoms from ammonia-borane are transferred to tricoordinate **1-36a** to form pentacoordinate **1-36b**; which then delivers the hydrogen atoms to azobenzene to afford the corresponding hydrogenated product, while regenerating **1-36a** (Scheme 1.14a).⁵⁰ The reversible cycling of phosphorus oxidation states in the catalytic cycle mimics that of transition metal catalysts, extending the possibility that main group elements can indeed act as surrogates for *d*-block elements in catalysis.

Two years after this discovery, Kinjo likewise reported the transfer hydrogenation of diaryldiazenes catalyzed by 1,3,2-diazaphospholene (DAP) **1-37** (Scheme 1.13b).⁵¹ Unlike the previous example, there is no change in the oxidation state of phosphorus; instead, the phosphine-hydride nucleophilically attacks the unsaturated nitrogen atom

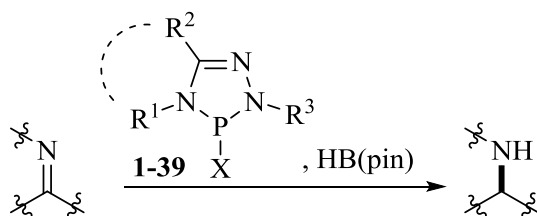


Scheme 1.14 Catalytic cycles of the transfer hydrogenation of diazenes catalyzed by **a)** **1-36**, and **b)** **1-37**.

to give a triaminophosphine intermediate, **1-38**.⁵¹ The catalyst is subsequently regenerated by ammonia-borane, to provide the 1,2-disubstituted hydrazine products.

Shortly after, the same group showed **1-37** was a competent catalyst in the hydroboration of carbonyls, using HB(pin) as the terminal reductant (Scheme 1.13c).⁵²

1.3 Overview of the Thesis



Scheme 1.15 General reaction scheme depicting the reduction of imines, mediated by a generic TAP, **1-39**.

This thesis describes the synthesis and reactivity of novel phosphorous-based heterocycles, namely 1,2,4,3-triazaphospholenes (TAPs). Chapter 2 starts with the synthesis and isolation of structurally, and electronically diverse achiral amidrazones. Various conditions were attempted to cyclize the amidrazones to the corresponding

racemic TAP-halides, which were converted to TAP-alkoxides. The reactivity of TAP-alkoxides was subsequently explored.

Chapter 3 describes the investigation into the synthesis of non-racemic TAPs, derived from chiral amidrazones. A synthetically simple, and highly modular scaffold was developed, and used in the synthesis of non-racemic TAPs. Chapter 4 outlines the catalytic capability of racemic TAPs in the hydroboration of an array of sterically, and electronically diverse imines, some of which are difficult substrates for currently known transition metal- and main group-based catalysts. In collaboration with Prof. Erin R. Johnson, a mechanism for the TAP-catalyzed reduction was proposed. The stereoselectivity of non-racemic TAPs in the hydroboration of prochiral imines was also assessed and disclosed herein. In addition, using a non-racemic DAP pre-catalyst developed by my colleague, Matt Adams, a small scope of imines was asymmetrically reduced, and the enantioselectivity assessed.

Chapter 2. Racemic 1,2,4,3-Triazaphospholenes

2.1 Contributions

Mr. Blake S. N. Huchenski (Dalhousie University) is thanked for the preparation of **2-13**. Mr. Matt R. Adams (Dalhousie University) is thanked for the preparation of **2-47**. Prof. Alexander W. H. Speed (Dalhousie University) is thanked for the preparation of mesitylhydrazine hydrochloride. Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University) is thanked for the acquisition of mass spectrometric data. Dr. Robert McDoanld (X-Ray Crystallography Laboratory, University of Alberta) and Dr. Michael J. Ferguson (X-Ray Crystallography Laboratory, University of Alberta) are thanked for the acquisition of crystallographic data and solving of crystal structures.

2.2 Introduction

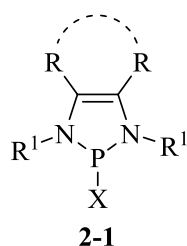
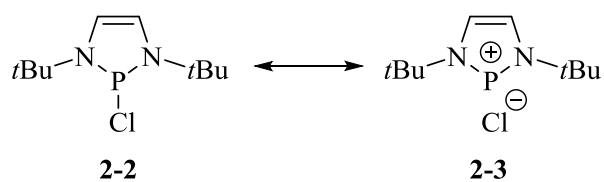


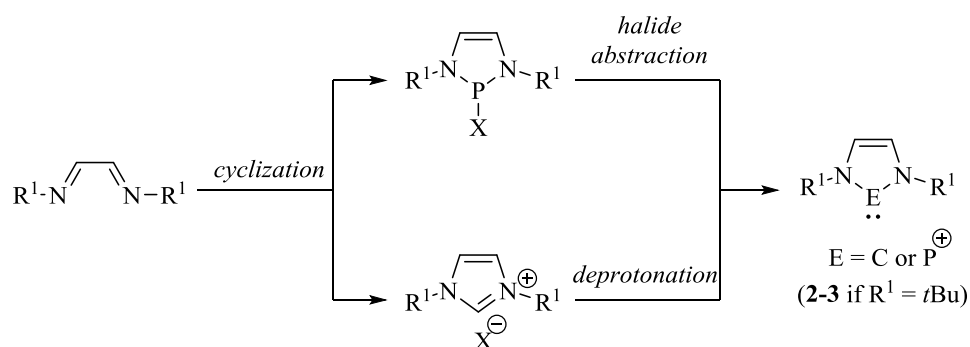
Figure 2.1 General structure of DAPs.

DAPs are a family of heterocycles with the general structure **2-1** (Figure 2.1). The first isolated DAP was reported thirty years ago,⁵³ however little attention was received.



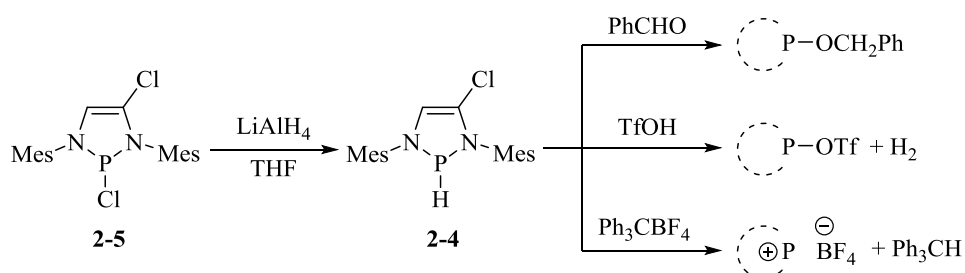
Scheme 2.1 Dissociation of P-Cl bond in **2-2**.

Chemistry of DAPs did not attract much interest until extensive studies were reported by various groups including Denk,⁵⁴ and most importantly, Gudat,⁵⁵ beginning in the late 1990's. Based on computational studies and physical properties, it was reasoned that the P-Cl bond in chloro-DAP (DAP-Cl), **2-2**, is not entirely covalent, but in fact slightly ionic in nature (Scheme 2.1).⁵⁴ The resulting phosphonium cation, **2-3**, generated from the dissociation of the halide anion, represents a valence-isoelectronic and synthetic analogue of imidazolylidene carbenes (Scheme 2.2).^{54,56} This analogy led to the investigations into TAPs, which are described in Chapters 2 and 3.



Scheme 2.2 Comparison between DAPs and imidazolylidenes.

It was discovered by Gudat and co-workers that the hydrogen of hydro-DAP (DAP-H), **2-4**, synthesized from the corresponding DAP-Cl, **2-5**, behaves as a hydride rather than a proton, as is usual for secondary phosphines (Scheme 2.3).⁵⁷ This



Scheme 2.3 Umpolung reactivity of **2-4**.

umpolung behaviour sparked a series of publications describing the use of DAP-H's in various catalytic reductive transformations.^{51,52,58,59}

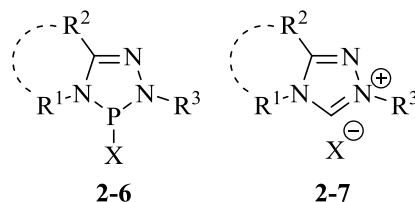
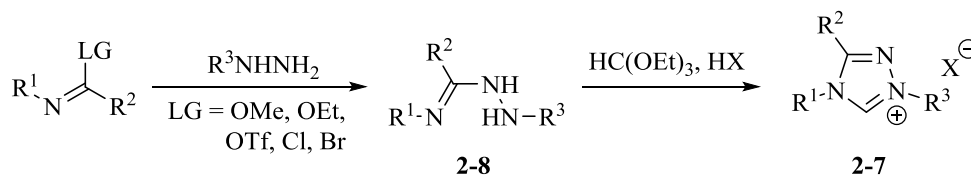


Figure 2.2 General structures of TAPs and triazoliums.

Due to the notion that DAPs are structurally and synthetically analogous to imidazolylidenes, we turned our attention to TAPs, **2-6**, which are structurally similar to triazoliums, **2-7**, precursors to triazolylidene carbenes (Figure 2.2). The first example of triazolylidene was reported by Enders in 1995.⁶⁰ Triazolium scaffolds are most commonly derived from amidrazones **2-8**, which are highly modular, due to the use of modifiable hydrazines and activated amide derivatives as starting materials (Scheme 2.4). This renders triazolylidenes as attractive catalysts for use in asymmetric transformations. Since the original disclosure, several groups including Enders, Rovis, and Glorius have expanded the scope of chiral triazolium scaffolds, which ultimately showed triazolylidenes are superior to imidazolylidenes in many areas of asymmetric catalysis.⁴

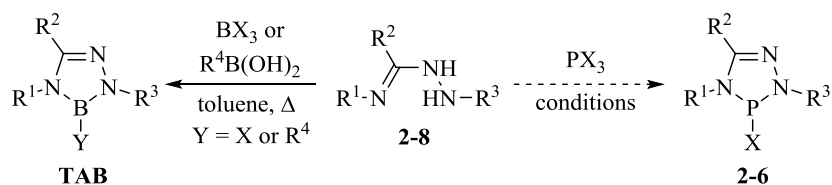


Scheme 2.4 Synthesis of triazoliums **2-7** from amidrazones **2-8**.

Despite the amount of extensive studies that have been done on DAPs, only a

handful of examples of TAPs have been reported,⁶¹ none of which were employed in catalysis. Therefore, we felt the need to explore the chemistry of TAPs, starting from racemic variants, in order to uncover reactivity that may or may not be similar to those of DAPs'. Part of this study is published in *Organic Letters*.⁶²

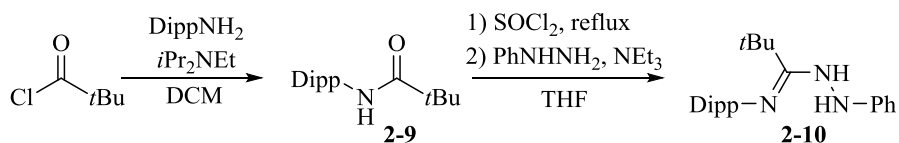
2.3 Synthesis of Achiral Amidrazones



Scheme 2.5 Synthesis of TABs and TAPs from amidrazones.

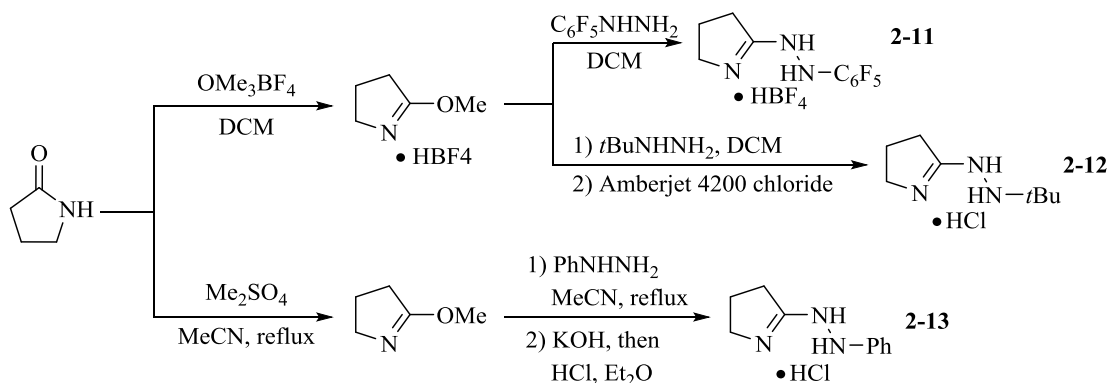
In comparison with TAPs, 1,2,4,3-triazaboroles (TABs) have recently seen an increase in popularity, with several recent papers detailing the synthesis and reactivity of said heterocycles.⁶³ TABs are synthesized from amidrazones and trivalent boron species, typically boron halides or boronic acids, through a condensation reaction (Scheme 2.5). Accordingly, we planned to synthesize TAPs through similar routes. However, since heterocyclic P^{III} species are susceptible to decomposition upon exposure to air and moisture, purification methods are limited to air-free techniques. Therefore, we proposed to isolate amidrazones before carrying out the subsequent cyclization in the hopes of minimizing the need for purification of the heterocycles. Unfortunately, amidrazones, which are strongly basic and easily hydrolyzed as the free base, are rarely isolated in literature; therefore, isolation procedures needed to be

developed.



Scheme 2.6 Synthesis of **2-10** developed by Kinjo.

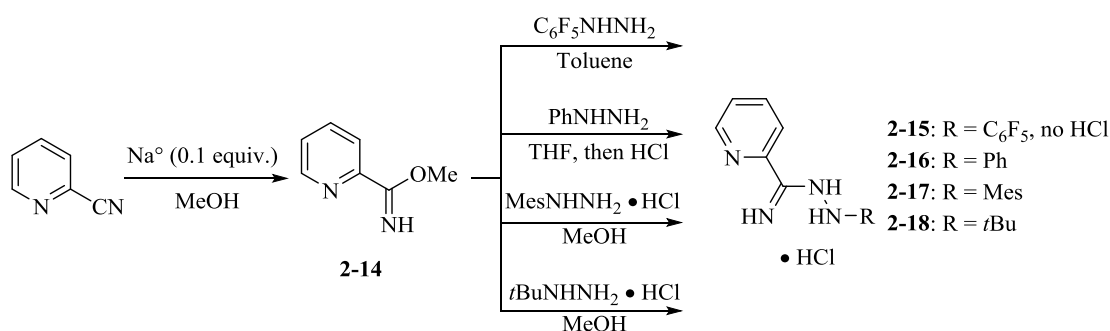
Amidrazone **2-10** developed by Kinjo^{63a,d} was deemed a suitable entry point due to the abundance of corresponding starting materials in our laboratory (Scheme 2.6). Amidrazone **2-10** was successfully isolated as a free base following a modified procedure developed in our lab. Surprisingly, the free base was stable under ambient conditions for at least 10 months, and did not decompose upon trituration with water. The unanticipated stability was speculated to be attributed to the enhanced steric profile, and reduced basicity due to the aromatic substituents.



Scheme 2.7 Synthesis of pyrrolidinone-derived amidrazones **2-11** to **2-13**.

Pyrrolidinone-derived amidrazones are common scaffolds for the synthesis of triazolylidenes,⁶⁴ therefore I aimed to develop procedures to isolate **2-11** to **2-13** (Scheme 2.7). Amidrazones **2-11** and **2-13** were successfully isolated with minor impurities following modified literature procedures.⁶⁴ Literature-unknown amidrazone

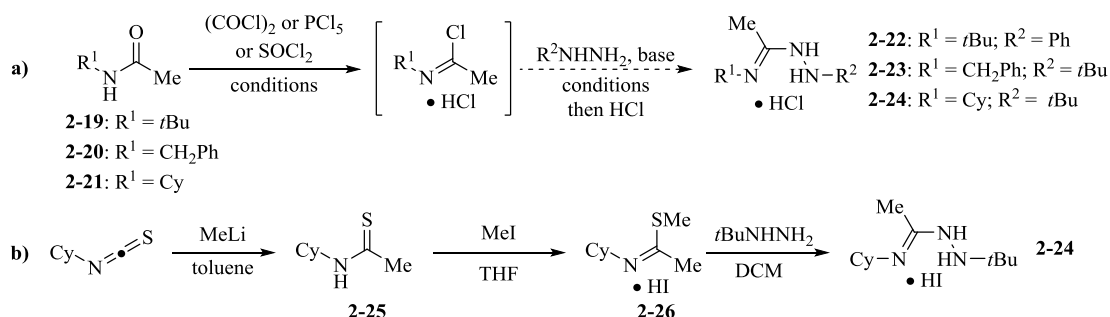
2-12 was synthesized following a modified procedure,⁶⁵ and isolated *via* crystallization in *iso*-propanol (*i*PrOH). However, this protocol is not applicable to more expensive substituted hydrazine salts, as an excess (5.5 equiv.) of *tert*-butylhydrazine hydrochloride was used to access the free hydrazine. Therefore, a more general and economical route must be developed.



Scheme 2.8 Synthesis of 2-cyanopyridine-derived amidrazones **2-15** to **2-18**.

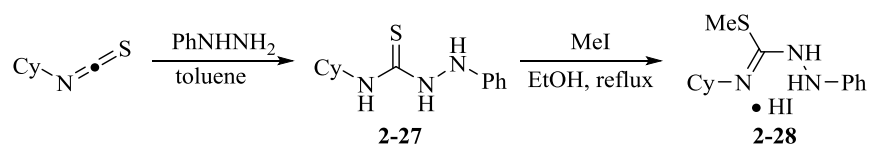
Imidate **2-14** is a common reagent for the preparation of pyridine-oxazoline ligands.⁶⁶ In order to probe the electronic effects imposed by the hydrazine substituents, I next explored amidrazones **2-15** to **2-18** (Scheme 2.8). However, since some hydrazines and their corresponding amidrazones are not stable as free bases, different synthetic and isolation procedures were employed. Amidrazone **2-15** was isolated as a free base, and was stable under ambient conditions due to the decreased reactivity imparted by the -C₆F₅ group. Amidrazone **2-16** slowly decomposed upon exposure to air, therefore it was isolated as the HCl salt. Amidrazones **2-17** and **2-18** were isolated as HCl salts without probing stability. Attempts to crystallize **2-16** and **2-18**, which were slightly contaminated with the parent hydrazine salts, were unsuccessful.

In an effort to explore more elaborate TAPs derived from non-cyclic amides, amidrazones **2-22** to **2-24** became targets of interest. Deoxychlorination and *O*-methylation of the respective acetamides, **2-19** to **2-21**, then subsequent condensation with PhNHNH₂ and *t*BuNHNH₂ yielded intractable mixtures (Scheme 2.9a). A thioamide analogue of **2-21**, namely **2-25**, was then prepared from cyclohexyl isothiocyanate in anticipation that thioimides would have comparable reactivity with imidates. *S*-Methylation of **2-25** provided an isolable thioimide **2-26**, which was successfully converted to **2-24** that was sufficiently pure to carry forward (Scheme 2.9b).



Scheme 2.9 a) Attempted synthesis of **2-22** to **2-24**; b) synthesis of **2-24** from **2-25**, which is the sulfur analogue of **2-24**.

Isothiosemicarbazides, which can also be synthesized from isothiocyanates, were recognized as thiolated pseudo-amidrazones. To the best of our knowledge, isothiosemicarbazides have not been employed in the synthesis of triazolylidenes.



Scheme 2.10 Synthesis of thiolated amidrazone **2-28**.

Therefore, I prepared only one example of such a scaffold, namely **2-28** (Scheme 2.10), to investigate its viability in the synthesis of TAPs. The reaction between cyclohexyl isothiocyanate and phenylhydrazine readily yielded **2-27**. Subsequent *S*-methylation provided **2-28** in quantitative yield.

2.4 Synthesis and Characterization of Racemic TAPs

With the amidrazones in hand, the synthesis of TAPs became the next priority. Not only was the synthesis of TAPs underdeveloped, the spectroscopic parameters were also largely uncharted. Although there has been literature precedence for the synthesis of TAPs, skepticism arose when the use of silica gel column chromatography to purify TAPs was described in said literatures.^{61a,c} Therefore, literature procedures and spectroscopic data were treated with skepticism, since it was assumed that TAPs would be too sensitive for such treatments.

2.4.1 Optimization for the Cyclization of Amidrazones

Table 2.1 Conditions attempted for the cyclization of **2-11**.

| entry | base | PX ₃ | solvent | temperature | ³¹ P NMR |
|-------|---------------------------|------------------|----------------|-------------------|----------------------------|
| 1 | 1 equiv. <i>n</i> BuLi | PCl ₃ | THF to toluene | - 84 °C to reflux | 120 ppm |
| 2 | 3 equiv. NEt ₃ | PCl ₃ | DCM | rt | 120 ppm |
| 3 | 3 equiv. DBU | PCl ₃ | DCM | rt | 122 ppm + PCl ₃ |
| 4 | 3 equiv. DBU | PBr ₃ | DCM | rt | 143 ppm + PBr ₃ |
| 5 | N/A | PBr ₃ | toluene | reflux | 143 ppm |
| 6 | N/A | PBr ₃ | MeCN | reflux | PBr ₃ |
| 7 | 3 equiv. KH | PI ₃ | toluene | rt | 102 ppm + PI ₃ |

Amidrazone **2-11** was chosen as a suitable model backbone for exploring the synthesis of TAPs due to its relative low cost and simple synthesis. Combinations of phosphines, acid scavengers, solvent, and temperature were employed. A summary of the conditions attempted, and spectroscopic results are presented in Table 2.1. PCl_3 was chosen as the initial phosphine source due to its high volatility. However, since PCl_3 is the least reactive out of the three phosphorous trihalides available in our lab, a variety of acid scavengers were used to aid in the deprotonation of the *NH* protons (entries 1 to 3, Table 2.1). A singlet at around 120 ppm in the ^{31}P NMR spectrum was observed for all three attempts (entries 1 to 3, Table 2.1). Although we were delighted to reproduce NMR results, the ^{31}P NMR chemical shifts for the mixtures obtained upon filtration are much lower than the chemical shifts reported for DAP-Cl's, which usually fall between 140 to 170 ppm.^{54,67} Therefore, it was hypothesized that only one of the nitrogen atoms of the amidrazone was coordinated to the phosphorus atom, causing a discrepancy between expected and experimental results.

A broad signal at around 143 ppm in the ^{31}P NMR spectrum was observed for two of the three reactions with PBr_3 as the phosphine source (entries 4 and 5, Table 2.1). Again, the experimental ^{31}P NMR chemical shifts are lower in comparison to chemical shifts reported for DAP-Br's, which usually fall between 170 to 200 ppm.^{59,68} Without the addition of a base, namely 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a reaction

temperature of above 100 °C was required to promote any interaction, desired or not, between the protonated amidrazone, and PBr₃ (entries 5 and 6, Table 2.1). Lastly, the reaction between **2-11** and PI₃ using KH as an acid scavenger afforded a mixture that was mostly consisted of PI₃ based on ³¹P NMR spectroscopy (entry 7, Table 2.1). A singlet at 102 ppm was also observed in the ³¹P NMR spectrum. However, since the P-I bond is more ionic than a P-Br, or P-Cl bond, the ³¹P NMR chemical shift of the reaction mixture in theory should be more downfield than for previous entries.

Table 2.2 Conditions attempted for the cyclization of **2-13**.

| entry | base | PX ₃ | solvent | temperature | ³¹ P NMR |
|-------|-----------------------------|------------------|---------|---------------|---------------------|
| 1 | 3 equiv. <i>n</i> BuLi | PCl ₃ | THF | - 84 °C to rt | 119 ppm |
| 2 | 3.5 equiv. NEt ₃ | PCl ₃ | DCM | - 15 °C to rt | 119 ppm |
| 3 | 3 equiv. NEt ₃ | PBr ₃ | DCM | 0 °C to rt | 130 ppm |

Encouraged by the recurring results (entries 1 to 7, Table 2.1), I next became interested in screening conditions with **2-13** (Table 2.2). Since **2-11** was used as a BF₄ salt, complications such as fluoride migration, or anion exchange with phosphorous could arise; therefore, **2-13** was employed as a HCl salt. Again, duplicate results were obtained using PCl₃ regardless of conditions (entries 1 and 2, Table 2.2). Compared to previous reactions of **2-11** with PBr₃ (entries 4 and 5, Table 2.1), reaction with the more electron-rich **2-13** yielded a product with a more upfield ³¹P NMR chemical shift (entry 3, Table 2.2). The cumulative results strongly suggest potential bonding interactions

between the amidrazone and the phosphorus atom.

Table 2.3 Conditions attempted for the cyclization of **2-15**.

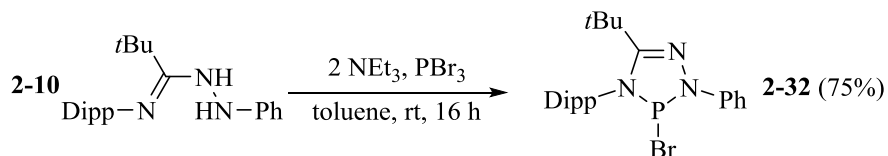
| entry | base | PX ₃ | ³¹ P NMR |
|----------------|---------------------------|------------------|----------------------------|
| 1 | 2 equiv. NEt ₃ | PCl ₃ | 123 ppm |
| 2 | N/A | PCl ₃ | 123 ppm + PCl ₃ |
| 3 | 2 equiv. NEt ₃ | PBr ₃ | 142 ppm |
| 4 | N/A | PBr ₃ | PBr ₃ |
| 5 ^b | 2 equiv. NEt ₃ | PBr ₃ | 143 ppm |

^a Unless otherwise stated. ^b Reaction performed at rt.

To explore the generality of these reactions, an amidrazone of a different scaffold, namely **2-15**, was employed (Table 2.3). Similar with previous reactions, reoccurring ³¹P NMR chemical shifts at 123 ppm and 143 ppm were observed for reactions of **2-15** with PCl₃ and PBr₃, respectively (entries 1, 2, 3 and 5, Table 2.3). The addition of a volatile acid scavenger, such as triethylamine (NEt₃), proved to be more beneficial than mild heat (50 °C), as evidenced by the complete conversion achieved at room temperature (entry 5, Table 2.3). Toluene was chosen as the optimal solvent due to its low solvation of ammonium salts. Therefore, only a simple filtration is needed to remove salt by-products to isolate the reaction product. However, without X-ray crystallographic evidence, any structure assignments of the product at this point would be mere speculation. Despite the inconclusive results obtained from the optimization stage, I decided to move on with the project and apply the optimized conditions to the

remaining amidrazones.

2.4.2 Synthesis of TAP-Halides



Scheme 2.11 Synthesis of **2-32** from **2-10** using the optimized conditions.

Due to its precedented application in TAB synthesis, **2-10** was thought to be the backbone that is most likely to cyclize with PBr_3 to form TAP **2-32** (Scheme 2.11). Amidrazone **2-10** was subjected to the optimized conditions to afford a solid, which, to our delight turned out to be the desired, cyclized TAP **2-32**, based on a single crystal X-ray diffraction analysis (Figure 2.3). A singlet at 153 ppm was observed for **2-32** with ^{31}P NMR spectroscopy, which is consistent with previously observed results based on

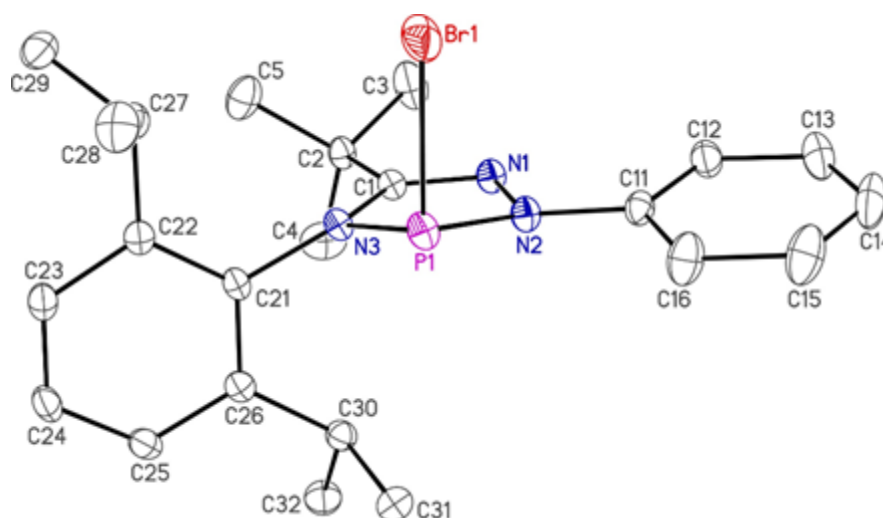
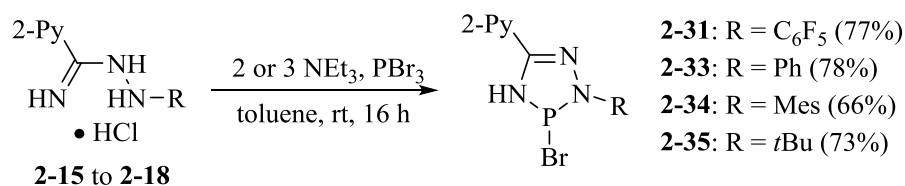


Figure 2.3 Representation of one of the two crystallographically independent molecular structure of **2-32**. Thermal ellipsoids are drawn at the 30% probability level with H atoms omitted for clarity. Selected bond lengths (\AA) and torsional angles (deg.) for this crystallographically independent structure, with estimated standard deviations in parentheses: P1-Br1 2.3893(5), P1-N2 1.6808(15), P1-N3 1.6872(15), N2-C11 1.420(2), N3-C21 1.465(2); C1-N1-N2-C11 $-177.62(15)$, C21-N3-C1-N1 $-152.97(16)$.

the electronic properties of the substituents. Unlike the phenyl substituent, the C21-N3 bond of the 2,6-diisopropylphenyl (Dipp) is distorted due to steric hindrance imposed by the Br substituent. The P-Br interatomic distance is 2.39 Å, which is longer than the P-Br bonds in PBr₃ (2.22 Å). However, it is shorter than the P-Br interatomic distance of DAPs, which usually fall between 2.6 to 2.9 Å.^{68b} This justifies the relatively more shielded ³¹P NMR chemical shift of 130 to 150 ppm for TAPs since they are comparably less ionic based on the P-Br interatomic distance. Encouraged by the positive identification of **2-32**, I proceeded to apply the optimized conditions to the remainder of the amidrazones.



Scheme 2.12 Synthesis of **2-31**, **2-33** to **2-35** from **2-15** to **2-18**, respectively.

Amidrazones **2-15** to **2-18** were converted to the corresponding TAP-Br's, **2-31**, **2-33** to **2-35**, respectively (Scheme 2.12). No elimination of HBr to form the corresponding amidine-type phosphorous was observed, based on exchangeable proton signals recorded with ¹H NMR spectroscopy. The structure of **2-33** was also confirmed by a single crystal X-ray diffraction analysis (Figure 2.4). Once again, the P-Br interatomic distance of 2.46 Å for **2-33** is shorter than that of DAP's. Interestingly, the pyridyl ring is almost in the same plane as the TAP heterocycle with the pyridyl-*N*

pointing towards the NH proton, indicating NH-N hydrogen bonding interaction. This could potentially provide TAPs derived from **2-15** to **2-18** with interesting reactivity.

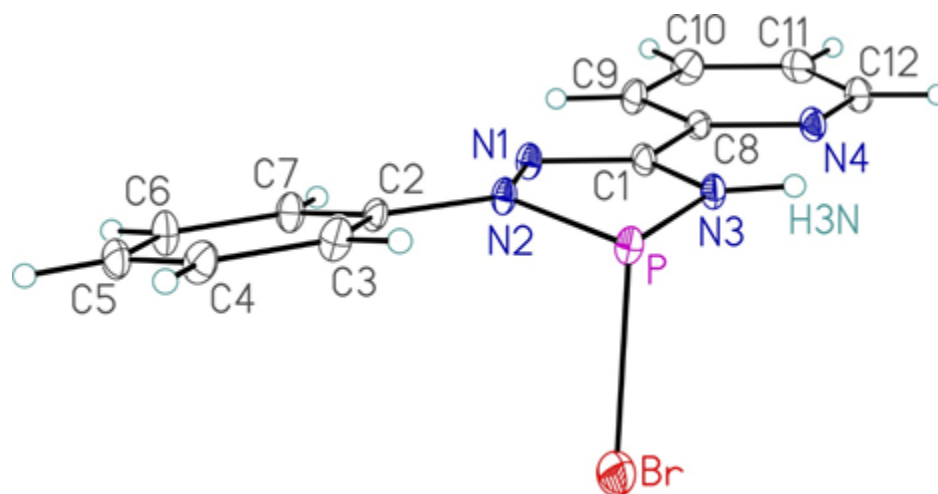
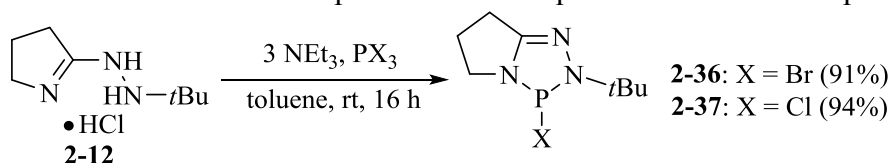


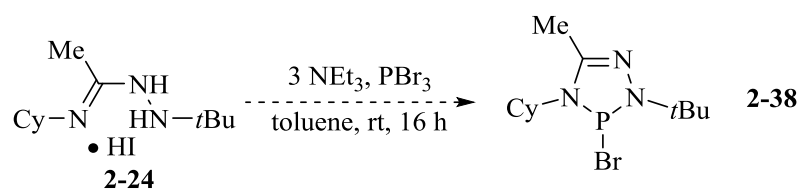
Figure 2.4 Representation of the molecular structure of **2-33**. Thermal ellipsoids are drawn at the 30% probability level for non-H atoms. Hydrogen atoms are shown with arbitrarily small thermal parameters. Selected bond lengths (Å) and torsional angles (deg.), with estimated standard deviations in parentheses: P-Br 2.4619(12), P-N2 1.682(3), P-N3 1.659(4), N2-C2 1.424(5); N3-C1-C8-N4 -0.5(6), N1-C1-C8-C9 -1.7(7).

Amidrazone **2-12** was converted to the corresponding TAP-Br **2-36** with minor impurities present in the ^{31}P NMR spectrum. After several unsuccessful purification attempts, the corresponding TAP-Cl **2-37** was synthesized and isolated as a colourless liquid with a ^{31}P NMR chemical shift of 134 ppm. To our surprise, this chemical shift is in a comparable region as the ^{31}P NMR chemical shifts for **2-29(Br)** and **2-30(Br)**, the phosphorus atoms of which are, in theory, more electron-poor. Furthermore, the CH_2 protons are not diastereotopic based on liquid-state ^1H NMR spectroscopy.



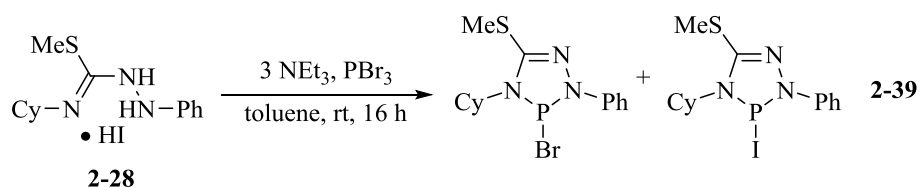
Scheme 2.13 Synthesis of **2-36** and **2-37** from **2-12**.

Therefore, it was hypothesized that, unlike the TAPs characterized by X-ray crystallography have implied, the halides could potentially dissociate from the phosphorus atoms in solution. This would give the phosphorus atoms achiral characteristics, and render them planar; which in turn make the CH_2 protons non-diastereotopic and equivalent. However, the magnitude of dissociation may depend on the electronic properties of the substituents, and the solvent.



Scheme 2.14 Attempted synthesis of **2-38**.

Amidrazone **2-24** was subjected to the optimized conditions to afford a product with a ^{31}P NMR chemical shift of 182 ppm (Scheme 2.14). Since the amidrazone is fully substituted by alkyl substituents, the corresponding TAP, namely **2-38**, should have a comparable chemical shift to **2-36** (152 ppm). It was hypothesized that the enolizable methyl proton on the backbone could have induced side reactions. Due to the unexpected downfield chemical shift, and the complex ^1H NMR spectrum, it was uncertain whether or not **2-38** was formed. However, the crude reaction mixture of **2-38** was used in subsequent experiments that are described in sections 2.3.4 and 4.2.1.



Scheme 2.15 Synthesis of **2-39** as a mixture of bromide and iodide.

Lastly, amidrazone **2-28** was converted to **2-39** using the optimized conditions (Scheme 2.15). However, unlike previous TAP-Br's, the ^{31}P NMR spectrum of **2-39** revealed a broad peak, instead of a singlet, at around 160 ppm. Single crystal X-ray diffraction analysis indicated that **2-39** is a mixture of TAP-Br and TAP-I (Figure 2.5). Anion exchange between the two halides may contribute to the dynamic behaviour exhibited by **2-39** in the ^{31}P NMR spectrum.

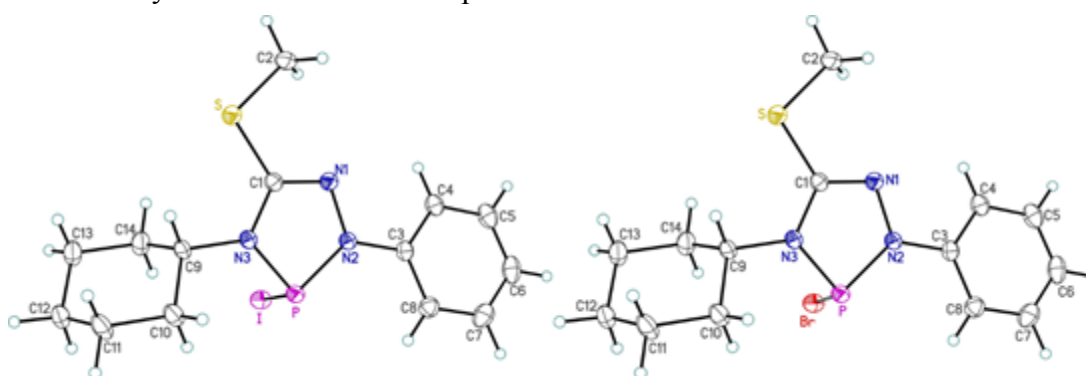
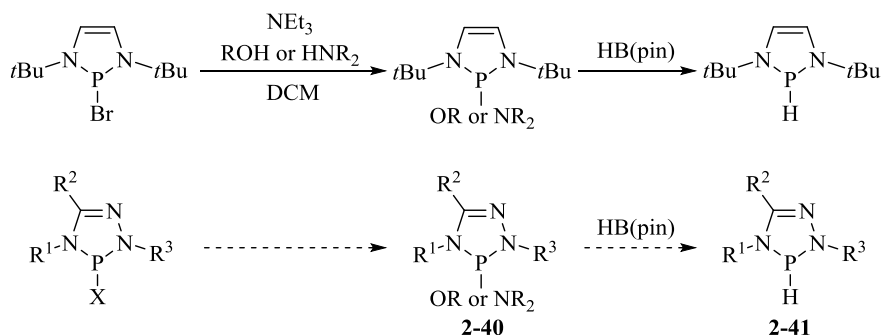


Figure 2.5 Representation of the molecular structures of **2-39**. Thermal ellipsoids are drawn at the 30% probability level for non-H atoms. Hydrogen atoms are shown with arbitrarily small thermal parameters. The halide atom was refined as 50% iodide and 50% bromide. Selected bond lengths (Å), with estimated standard deviations in parentheses: P-I 2.726(3), P-Br 2.543(5), P-N2 1.6741(18), P-N3 1.6799(18), N2-C3 1.425(3), N3-C9 1.489(3).

2.4.3 Observation and Reactivity of TAP-H



Scheme 2.16 Proposed synthesis of TAP-H's **2-41** from TAP-halides.

To probe the catalytic reductive ability of TAP-H's, and compare those with DAPs', I aimed to prepare TAP-alkoxides or -amides from the corresponding halides (Scheme 2.16). TAP **2-32** was chosen as a benchmark substrate to establish optimized conditions and spectroscopic parameters. A summary of the conditions attempted are presented in Table 2.4.

Table 2.4 Synthesis of TAP-amides /-alkoxides **2-42** to **2-45**.

| entry | nucleophile | solvent | product |
|----------------|-------------------------------|---------|-------------|
| 1 | HNEt ₂ | DCM | 2-42 |
| 2 | HNBn ₂ | DCM | 2-43 |
| 3 | HNBn ₂ | toluene | 2-43 |
| 4 | <i>t</i> BuCH ₂ OH | toluene | 2-44 |
| 5 ^b | NaOBn | toluene | 2-45 |

^a Unless otherwise stated. ^b Reaction performed without NEt₃.

Following a procedure reported previously by our group for DAPs,⁵⁹ I first attempted to synthesize TAP-amides **2-42** and **2-43** (entries 1 and 2, Table 2.4). However, despite rigorous exclusion of moisture, and desiccation of reagents and solvent, multiple doublets at around 0 to 5 ppm in the ³¹P NMR spectra are still observed. These signals are characteristic of oxidized phosphorus atoms in the P^V oxidation state,^{59a} implying the decomposition of the corresponding TAPs. The solvent was then subsequently substituted with toluene to afford **2-43** with a ³¹P NMR chemical shift at 94 ppm, with no indication of oxidation of the phosphorus atom (entry 3, Table 2.4).

This chemical shift is comparable to DAP-dibenzylamide (97 ppm).^{59a} However, due to the complexity of the ¹H NMR spectrum, the signals could not be properly assigned. Therefore, I decided to pursue TAP-alkoxides, **2-44** and **2-45**.

In an attempt to synthesize **2-44**, minor oxidation of the phosphorus atom was observed (entry 4, Table 2.4). Nevertheless, a singlet at 88 ppm was observed for the major product in the ³¹P NMR spectrum. This chemical shift is also comparable to that of *t*Bu-DAP-neopentyloxide (92 ppm).^{59a} No decomposition was observed for the synthesis of **2-45** (entry 5, Table 2.4). Analogous to **2-44**, a singlet at 88 ppm was observed for **2-45** with ³¹P NMR spectroscopy. The ¹H NMR spectrum of **2-45** shows the *i*Pr groups, along with the benzylic protons of the oxide, to be diastereotopic. This indicates that, unlike spectra previously observed for TAP-halides **2-37** and **2-38**, chirality of the phosphorus atom in TAP-oxide **2-45** is preserved, suggesting that the P-O bond has little ionic character compared to the P-halide bond.

To examine whether or not **2-45** can be converted to TAP-hydride, **2-46**, under catalytic conditions, a variety of hydride transfer agents were reacted with **2-45**. Furthermore, imine **2-47** was added to the reaction as a hydride acceptor to assess the reductive ability of **2-46**. A summary of the experimental results and the proposed catalytic cycle are presented in Table 2.5. A doublet at 68 ppm ($J = 154.0$ Hz) was observed in the ³¹P NMR spectrum upon addition of HB(cat) to a mixture of **2-45** and

2-47 in acetonitrile (MeCN) (entry 1, Table 2.5). This signal is diagnostic of a P-H bond, and is in a comparable chemical shift region of Mes-DAP-hydride (64.6 ppm).^{59a} Furthermore, imine **2-47** was fully reduced within 24 h. However, no formation of the proposed TAP-amide intermediate, **2-43**, was observed in the ³¹P NMR spectrum during the reaction.

Table 2.5 Investigation into the catalytic ability of **2-45** in the reduction of imine **2-47**.

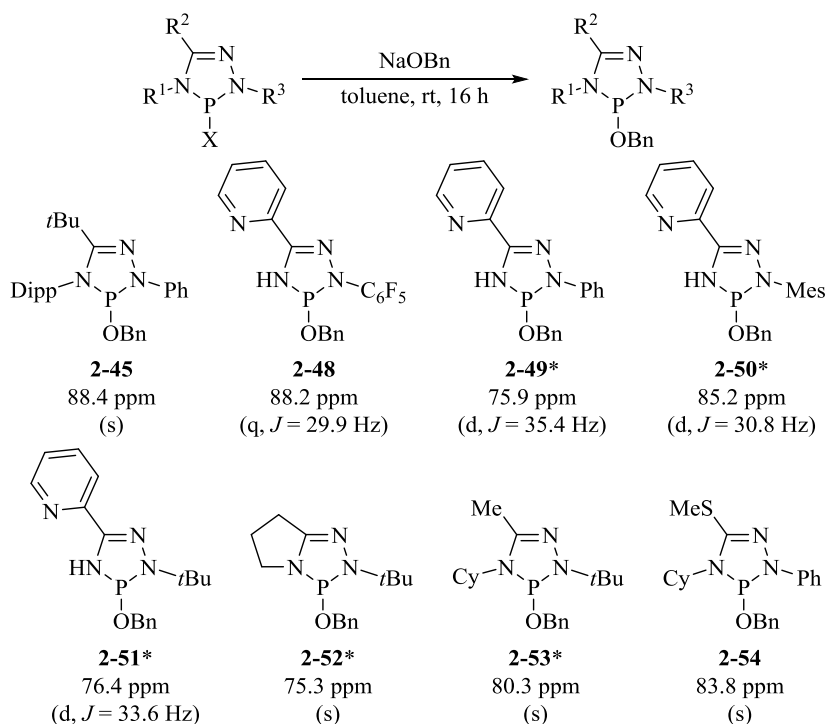
| entry | reagent | ³¹ P NMR (ppm) | conversion (%) ^a |
|-------|----------------------------------|---------------------------|-----------------------------|
| 1 | HB(cat) | 68, doublet | > 98 |
| 2 | morpholine • BH ₃ | 89, singlet | 12 |
| 3 | 9-BBN | 88, singlet | 33 |
| 4 | HB(pin) | 89, singlet | 28 |
| 5 | Ph ₂ SiH ₂ | 89, singlet | 0 |

^a Conversion by comparison of characteristic signals of starting material and product by ¹H NMR spectroscopy.

No changes in the ³¹P NMR spectra were observed for the reactions with other hydride transfer agents (entries 2 to 5, Table 2.5). However, minor reduction of the imine was observed in reactions with the boron-containing reagents (entries 2 to 4, Table 2.5). Intrigued by these results, a series of uncatalyzed control reactions containing only the borane reagents and imines was conducted. It was discovered that a certain degree of background reaction is associated with these boron-containing reagents. Furthermore, HB(cat) is capable of fully reducing imine **2-47** with no significant difference in rate observed between the catalyzed and uncatalyzed reactions.

Despite the discouraging results, we were still pleased to observe the formation of TAP-H **2-46** through ^{31}P NMR spectroscopy. It was hypothesized that, due to its steric bulk, **2-45** is not able to react with hydride transfer reagents, other than HB(cat), to form **2-46**. Less bulky TAP-oxides needed to be prepared in order to assess TAPs' use in the hydroboration of imines with less reactive hydride transfer agents, namely HB(pin).

2.4.4 Synthesis of TAP-Alkoxides

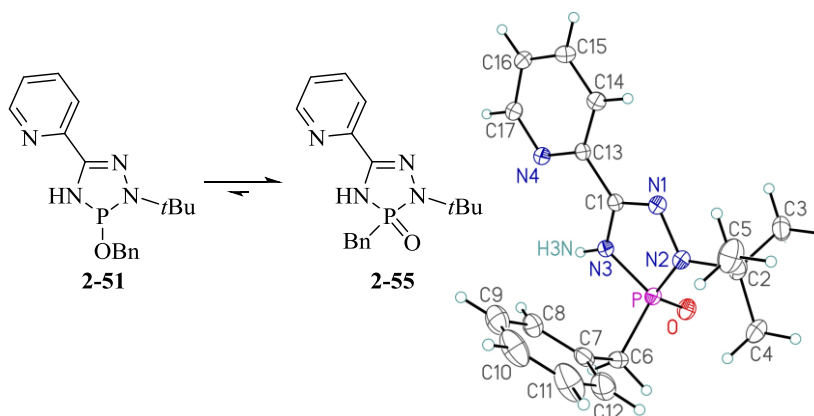


* Products are isolated with oxygenated materials and side-products.

Scheme 2.17 Synthesis of TAP-benzyloxides from TAP-halides.

Due to the lack of phosphorous oxidation observed in the synthesis of **2-45**, NaOBn was used to convert the remaining TAP-halides into alkoxides (Scheme 2.17). Unfortunately, oxidation and unidentified side-products are observed in the formation

of most TAP-alkoxides under optimized conditions. Attempts to isolate the alkoxides *via* crystallization and trituration were unsuccessful. However, a decomposition product, namely **2-55**, isomerized from **2-51** was identified through a single crystal X-ray diffraction experiment (Scheme 2.18). An analogous isomerization pathway has not been reported with DAP-oxides.⁵⁹ Despite unsuccessful attempts to isolate the TAP-benzyloxides from impurities, their reactivity in the catalyzed hydroboration was still assessed, and is discussed in Chapter 4.



Scheme 2.18 Isomerization of **2-51** to **2-55**, and representation of the molecular structure of **2-55**. Thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters. Selected interatomic bond lengths (Å) and angles (deg.), with estimated standard deviations shown in parentheses: P-O 1.4781(10), P-N2 1.6752(11), P-N3 1.6552(11), P-C6 1.8134(14); O-P-N2 119.32(6), O-P-N3 118.48(6), O-P-C6 108.52(6), N2-P-N3 89.56(5).

2.5 Conclusion

A variety of substituted amidrazones based on diverse scaffolds was synthesized, isolated, then subsequently cyclized with a phosphorus trihalide species to form literature-unknown TAP-halides. The TAP-halides were then converted to TAP-

alkoxides *via* a nucleophilic substitution reaction. Single crystal X-ray diffraction analyses confirmed the structures of 3 TAP-halides and 1 isomerized oxo-TAP. Part of this study is published in *Organic Letters*.⁶² Reactivity of less bulky TAP-alkoxides in the hydroboration of imines is discussed in Chapter 4.

2.6 Experimental Section

2.6.1 General Considerations

Synthesis of triazaphospholene derivatives was carried out using oven dried Schlenk glassware under nitrogen. Filtration of triazaphospholene derivatives was conducted in a 2001 issue IT Glovebox (O₂ levels typically 4 ppm, H₂O levels typically 5 ppm). Nucleophilic substitution reactions were carried out in 4-dram oven dried scintillation vials equipped with magnetic stir bars and green Qorpak® PTFE lined caps. Substrates, reagents and solvents were loaded into vials inside the IT Glovebox. ¹H, ¹³C{¹H}, and ³¹P NMR data were collected at 300 K on Bruker AV-500 or AV-300 NMR spectrometers. Standard NMR tubes and caps were used. Caps on sensitive samples were overwrapped with PTFE tape. Chemical shifts are reported in parts per million (ppm) from phosphoric acid for ³¹P NMR. ¹H NMR spectra are referenced to residual non-deuterated NMR solvent (CHCl₃ = 7.26 ppm, CHD₂OD = 3.31 ppm, CHD₂CN = 1.94 ppm). ¹³C{¹H} NMR spectra are referenced to the central CDCl₃ peak (77.0 ppm), CD₃OD (49.0 ppm), and CD₃CN methyl peak (1.32 ppm). Melting points were acquired

using an Electrothermal® apparatus and are uncorrected.

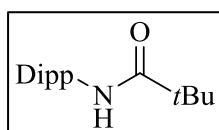
2.6.2 Crystallographic Solution and Refinement Details

Crystallographic data for **2-32** and **2-39** were obtained and solved by Dr. Michael J. Ferguson (X-Ray Crystallography Laboratory, University of Alberta). Crystallographic data for **2-33** and **2-55** were obtained and solved by Dr. Robert McDonald (X-Ray Crystallography Laboratory, University of Alberta). The crystallographic data were all obtained at -100 °C (-80 °C for **2-33**) on a Bruker D8/Apex II CCD diffractometer. Crystallographic data for **2-32**, **2-33**, and **2-39** were obtained using graphite-monochromated Mo K α ($\lambda = 0.71073 \text{ \AA}$) radiation. Crystallographic data for **2-55** was obtained using microfocus source Cu K α ($\lambda = 1.54178 \text{ \AA}$) radiation. Samples were mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs for diffractometer operation, data collection, data reduction and absorption correction were supplied by Bruker. Gaussian integration (face-indexed) was employed as the absorption correction method. The structures were solved by use of intrinsic phasing methods, and were refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$. Two crystallographically independent molecules of **2-32** were observed, structure for one independent molecule is presented. The halide atom of **2-39** was refined as 50% iodide and 50% bromide. Attempts to refine peaks of residual electron density as disordered or partial-occupancy

solvent MeCN nitrogen or carbon atoms for **2-55** were unsuccessful. The data was corrected for disordered electron density through use of the *SQUEEZE* procedure as implemented in *PLATON*.⁶⁹ A total solvent-accessible void volume of 950 Å³ with a total electron count of 205 (consistent with 9 molecules of MeCN, or 1.5 molecules per formula unit of **2-55**) was found in the unit cell.

2.6.3 Synthesis and Characterization

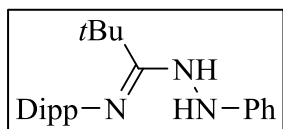
N-(2,6-Diisopropylphenyl)pivalamide (**2-9**):⁷⁰ *N*, *N*-Diisopropylethylamine



(13.9 mL, 79.5 mmol, 1.5 equiv.) was added to a solution of 2,6-diisopropylaniline (10.0 mL, 53.0 mmol, 1.0 equiv.) in DCM (60 mL). Pivaloyl chloride (8.49 mL, 68.9 mmol, 1.3 equiv.) was added dropwise, then the mixture was stirred under reflux for 5 h. The mixture was cooled to rt and water (50 mL) was added, then the layers were separated. The aqueous layer was extracted with DCM (150 mL x 3). The organic layers were combined and dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* and the remaining solid was washed with water and *n*-hexane (50 mL). The solid was dried in a desiccator over P₂O₅ under vacuum to afford the product as a colourless solid (12.4 g, 47.3 mmol, 89%). M.p. 214-217 °C. ¹H NMR (500 MHz, CDCl₃) δ: 7.28-7.15 (m, 3H), 6.83 (br s, 1H), 3.01 (sep, *J* = 7.0 Hz, 2H), 1.36 (s, 9H), 1.19 (d, *J* = 7.0 Hz, 12H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ: 177.3, 146.3, 131.6, 128.2, 123.4, 39.4, 28.8, 27.9, 23.6. HRMS (ESI) *m/z* calc'd for

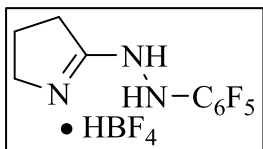
C₁₇H₂₇NONa [M+Na]⁺: 284.1985; found: 284.1985.

***N*-Phenyl-*N*'-(2,6-diisopropylphenyl)pivalamidrazone (2-10):** ^{63a} This



compound was prepared by following a modified literature procedure.^{63a} Amide **2-9** (5.00 g, 19.1 mmol, 1.0 equiv.) was dissolved in thionyl chloride (9.00 mL, 123 mmol, 6.4 equiv.) at rt and stirred under reflux for 3 h. The mixture was cooled down to rt, then volatiles were removed *in vacuo*. THF (40 mL) and NEt₃ (4.00 mL, 28.7 mmol, 1.5 equiv.) were added to the reaction flask, followed by a dropwise addition of phenylhydrazine (1.88 mL, 19.1 mmol, 1.0 equiv.). The mixture was stirred overnight at rt. The solvent was removed *in vacuo* to afford a residue which was washed with *n*-hexane (100 mL) and toluene (100 mL) over celite. The solvent from the combined organic filtrate was removed *in vacuo*. The residue was dissolved in minimal boiling *n*-hexane and cooled at -20 °C to form a suspension. The suspension was filtered, washed with cold water (5 mL) and dried in a desiccator over P₂O₅ under vacuum to afford the product as a yellow solid (4.32 g, 12.3 mmol, 64%). ¹H NMR (500 MHz, CDCl₃) δ: 7.36-6.34 (m, 8H), 5.35 (br s, 1H), 3.27-2.87 (rotamer, 2H), 1.40 (m, 9H), 1.18 (m, 12H). HRMS (ESI) m/z calc'd for C₂₃H₃₄N₃ [M+H]⁺: 352.2753; found: 352.2744.

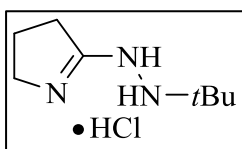
5-(Pentafluorophenylhydrazinyl)-3,4-dihydro-2*H*-pyrrolidium tetrafluoroborate (2-11): ⁶⁴ This compound was prepared by following a literature procedure.⁶⁴



Trimethyloxonium tetrafluoroborate (1.00 g, 6.76 mmol, 1.0 equiv.) was added to a solution of 2-pyrrolidinone (0.575 g, 6.76

mmol, 1.0 equiv.) in DCM (20 mL). The mixture was stirred overnight at rt. Pentafluorophenylhydrazine (2.64 g, 29.9 mmol, 1.0 equiv.) was added, then the mixture was stirred overnight at rt. The solvent was removed *in vacuo*, then the residue was triturated with diethyl ether (15 mL) and *n*-hexane (15 mL) to afford the product as an orange solid (2.241 g, 6.35 mmol, 94%). ^1H NMR (500 MHz, D_2O) δ : 3.86 (t, J = 7.5 Hz, 2H), 3.00 (t, J = 7.0 Hz, 2H), 2.39 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, D_2O) δ : 171.03, 141.3 (m), 139.4 (m), 138.8 (m), 136.7 (m), 119.8 (m), 47.4, 28.6, 20.6. ^{19}F NMR (470 MHz, D_2O) δ : -130.05 (impurity), -150.69 (impurity), -150.74, -155.29 (dd, J = 13.2, 2.8 Hz, 2F), -162.52 (t, J = 12.9 Hz, 1F), -163.53 (td, J = 12.9, 2.8 Hz, 2F), ^{11}B NMR (160 MHz, D_2O) δ : -1.41 (s).

5-(*tert*-Butylhydrazinyl)-3,4-dihydro-2*H*-pyrrolidium chloride (2-12): This

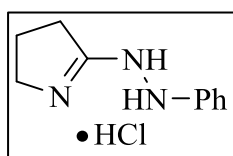


compound was prepared by following a modified literature procedure.⁶⁵ Trimethyloxonium tetrafluoroborate (4.42 g, 29.9

mmol, 1.0 equiv.) was added to a solution of 2-pyrrolidinone (2.54 g, 29.9 mmol, 1.0 equiv.) in DCM (40 mL). The mixture was stirred overnight at rt. *tert*-Butylhydrazine (2.64 g, 29.9 mmol, 1.0 equiv.) was added, then the mixture was stirred overnight at rt. The solvent was removed *in vacuo*, then the residue was triturated with diethyl ether

(30 mL) and *n*-hexane (15 mL) to afford the crude tetrafluoroborate salt (6.66 g, 27.4 mmol, 92%). Amberjet® 4200 chloride form (15.0 g, 52.5 to 67.5 mmol, 5.9 to 7.6 equiv.) was added to a crude mixture of 5-(*tert*-butylhydrazinyl)-3,4-dihydro-2*H*-pyrrolidium tetrafluoroborate (2.15 g, 8.87 mmol, 1.0 equiv.) in MeOH (75 mL), then the mixture was stirred for 72 h at rt. The mixture was filtered through celite, then washed with MeOH (50 mL). The solvent from the filtrate was removed *in vacuo*, then the residue was recrystallized in hot *i*PrOH (20 mL) to afford the product as a colourless solid (1.13 g, 5.87 mmol, 66%). M.p. 228 °C (Decomposed). ¹H NMR (500 MHz, methanol-*d*₄) δ: 3.65 (t, *J* = 7.0 Hz, 2H), 2.88 (t, *J* = 8.0 Hz, 2H), 2.25 (m, 2H), 1.13 (s, 9H). ¹³C{¹H} NMR (125 MHz, methanol-*d*₄) δ: 172.5, 55.4, 47.8, 29.4, 27.2, 22.0. HRMS (ESI) *m/z* calc'd for C₈H₁₈N₃ [M-Cl]⁺: 156.1501; found: 156.1491.

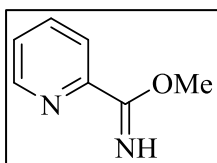
5-(Phenylhydrazinyl)-3,4-dihydro-2*H*-pyrrolidium chloride (2-13):⁶⁴ The crude



compound was prepared by my lab mate, Blake Huchenski, by following a literature procedure.⁶⁴ Minimal DCM was used to

dissolve the crude, then diethyl ether (20 mL) was added to create a suspension. The suspension was collected by filtration. This purification procedure was carried out several times to afford the product that is pure enough to carry forward with. ¹H NMR (500 MHz, D₂O) δ: 7.42 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 2H), 3.75 (t, *J* = 7.0 Hz, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 2.37 (p, *J* = 8.0 Hz, 2H).

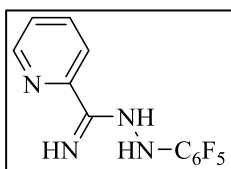
Methyl 2-pyridinecarboximidate (2-14):⁶⁶ This compound was prepared by



following a literature procedure.⁶⁶ Metallic sodium (0.221 g, 9.61 mmol, 0.09 equiv.) was added to a solution of 2-cyanopyridine (10.8

g, 103.7 mmol, 1.0 equiv.) in MeOH (100 mL), then the mixture was stirred in an ice bath for 1 h, then stirred overnight at rt. The reaction mixture was quenched by a slow addition of glacial acetic acid (0.55 mL, 9.61 mmol, 0.09 equiv.). Volatiles were removed *in vacuo*, then the residue was dissolved in EtOAc (300 mL) and washed with water (50 mL). The organic layer was dried with anhydrous Na₂SO₄, then the solvent was removed *in vacuo* to afford the product as a yellow liquid (10.4 g, 76.6 mmol, 74%), which was used without further purification. ¹H NMR (500 MHz, CDCl₃) δ: 9.21 (br s, 1H), 8.64 (d, *J* = 4.5 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.77 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.5 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H), 4.00 (s, 3H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ: 166.7, 149.1, 147.5, 137.2, 125.3, 120.9, 53.7.

***N*-(Pentafluorophenyl)picolinamidrazone (2-15):** Pentafluorophenylhydrazine

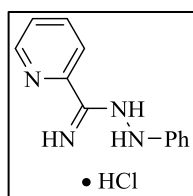


(1.46 g, 7.35 mmol, 1.0 equiv.) was added to a solution of **2-14** (1.00 g, 7.35 mmol, 1.0 equiv.) in toluene (20 mL), then the mixture

was stirred under reflux overnight. The solvent was removed *in vacuo*, then the residue was subjected to trituration with cold diethyl ether (10 mL) and *n*-hexane (10 mL) to afford the product as a yellow solid (1.72 g, 5.69 mmol, 77%). M.p. 100-103 °C. ¹H

NMR (500 MHz, CDCl₃) δ : 8.55 (d, J = 5.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.71 (dt, J = 7.5, 1.5 Hz, 1H), 7.32 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 5.93 (br s, 1H), 5.71 (br s, 2H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ : 151.9, 149.9, 148.3, 136.8, 124.8, 120.6; pentafluorophenyl carbon signals are spread across the baseline. ¹⁹F NMR (470 MHz, CDCl₃) δ : -156.0 (m, 2F), -164.0 (m, 2F), -166.5 (tt, J = 13.5, 2.3 Hz, 1F). HRMS (ESI) m/z calc'd for C₁₂H₈F₅N₄ [M+H]⁺: 303.0669; found: 303.0670.

***N*-Phenylpicolinamidrazone hydrochloride (2-16)**: Phenylhydrazine (0.43 mL,

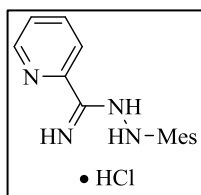


4.41 mmol, 1.0 equiv.) was added to a solution of **2-14** (0.600 g, 4.41 mmol, 1.0 equiv.) in THF (10 mL), then the mixture was stirred

overnight at rt. HCl (2.20 mL, 2 M in diethyl ether, 4.41 mmol, 1.0 equiv.) was added to the mixture, then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo*, then the residue was dissolved in a minimal amount of DCM and diethyl ether (30 mL) was added to form a suspension. The suspension was filtered and washed with diethyl ether (10 mL) to afford the product as an orange solid (1.081 g, 4.35 mmol, 98%), which was used without further purification. M.p. 185 °C (Decomposed). ¹H NMR (500 MHz, methanol-*d*₄) δ : 8.87 (d, J = 5.0 Hz, 1H), 8.20 (m, 1H), 8.15 (td, J = 8.0, 2.0 Hz, 1H), 7.80 (m, 1H), 7.31 (m, 2H), 6.96 (m, 3H), exchangeable protons not seen by ¹H NMR. ¹³C{¹H} NMR (125 MHz, methanol-*d*₄) δ : 164.0, 151.7, 147.0, 144.5, 139.5, 130.4, 129.9, 124.4, 123.1, 115.0 (impurity), 115.1. HRMS (ESI) m/z calc'd for

$C_{12}H_{13}N_4$ [M-Cl]⁺: 213.1140; found: 213.1143.

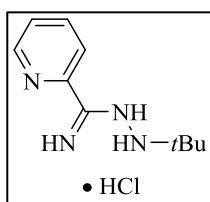
***N*-Mesitylpicolinamidrazone hydrochloride (2-17):** Mesitylhydrazine



hydrochloride (0.411 g, 2.20 mmol, 1.0 equiv.) was added to a solution of **2-14** (0.300 g, 2.20 mmol, 1.0 equiv.) in MeOH (10 mL),

then the mixture was stirred overnight at rt. The solvent was removed *in vacuo*. *n*-Hexane (20 mL) was added, then the mixture was filtered and washed with *n*-hexane (10 mL) to afford the product as a beige powder (0.497 g, 1.71 mmol, 78%), which was used without further purification. M.p. 188-189 °C. ¹H NMR (500 MHz, methanol-*d*₄) δ: 8.81 (d, *J* = 4.5 Hz, 1H), 8.09 (m, 2H), 7.74 (m, 1H), 6.91 (s, 2H), 2.29 (s, 6H), 2.25 (s, 3H), exchangeable protons not seen by ¹H NMR. ¹³C{¹H} NMR (125 MHz, methanol-*d*₄) δ: 161.7, 151.6, 144.8, 139.5, 139.4, 136.0, 132.0, 130.8, 129.6, 124.1, 20.8, 18.1. HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_4$ [M-Cl]⁺: 255.1610; found 255.1599.

***N*-(*tert*-Butyl)picolinamidrazone hydrochloride (2-18):** *tert*-Butylhydrazine

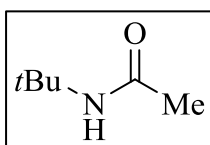


hydrochloride (0.549 g, 4.41 mmol, 1.0 equiv.) was added to a solution of **2-14** (0.600 g, 4.41 mmol, 1.0 equiv.) in MeOH (10 mL),

then the mixture was stirred overnight at rt. The solvent was removed *in vacuo*. *n*-Hexane (20 mL) was added, then the mixture was filtered and washed with *n*-hexane (10 mL) to afford the product as a beige powder (0.718 g, 2.96 mmol, 71%, contaminated with 5.8% *tert*-butylhydrazine hydrochloride), which was used without

further purification. M.p. 144-147 °C. ^1H NMR (500 MHz, methanol- d_4) δ : 8.83 (m, 1H), 8.13 (m, 2H), 7.76 (m, 1H), 1.33 (residual *tert*-butyl hydrazine hydrochloride), 1.25 (s, 9H), exchangeable protons not seen by ^1H NMR. $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, methanol- d_4) δ : 164.4, 151.5, 144.8, 139.5, 129.7, 124.5, 56.5, 27.3. HRMS (ESI) m/z calc'd for $\text{C}_{10}\text{H}_{17}\text{N}_4$ $[\text{M}-\text{Cl}]^+$: 193.1453; found: 193.1448.

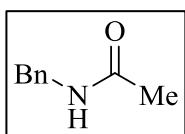
***N*-(*tert*-Butyl)acetamide (2-19):**⁷¹ *tert*-Butylamine (1.67 mL, 15.9 mmol, 1.0



equiv.) was added dropwise to a solution of acetic anhydride (1.50 mL, 15.9 mmol, 1.0 equiv.) in DCM (10 mL), then the mixture was

stirred overnight at rt. Saturated aqueous NaHCO_3 (50 mL) was added slowly to the reaction mixture, then the mixture was stirred until bubbling ceased. The biphasic mixture was extracted with DCM (50 mL) then the organic layer was dried with anhydrous Na_2SO_4 . The solvent was removed *in vacuo* to afford the product as a colourless solid (1.44 g, 12.5 mmol, 78%). ^1H NMR (500 MHz, CDCl_3) δ : 5.29 (br s, 1H), 1.91 (s, 3H), 1.34 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 169.59, 51.30, 28.93, 24.68.

***N*-Benzylacetamide (2-20):**⁷¹ Benzylamine (1.73 mL, 15.9 mmol, 1.0 equiv.) was

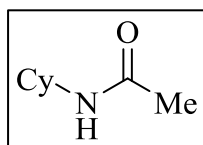


added dropwise to a solution of acetic anhydride (1.50 mL, 15.9 mmol, 1.0 equiv.) in DCM (10 mL), then the mixture was stirred overnight

at rt. Saturated aqueous NaHCO_3 (50 mL) was added slowly to the reaction mixture,

then the mixture was stirred until bubbling ceased. The biphasic mixture was extracted with DCM (50 mL), then the organic layer was washed with aqueous 2 M HCl (20 mL). The organic layer was dried with anhydrous Na₂SO₄, then the solvent was removed *in vacuo* to afford the product as a colourless solid (2.17 g, 14.5 mmol, 91%). ¹H NMR (300 MHz, CDCl₃) δ: 7.37-7.25 (m, 5H), 5.74 (br s, 1H), 4.43 (d, *J* = 5.7 Hz, 2H), 2.02 (s, 3H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ: 170.17, 138.39, 128.80, 127.94, 127.61, 43.85, 23.35.

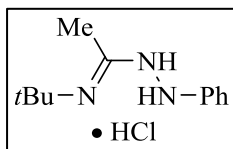
***N*-Cyclohexylacetamide (2-21):**⁷² Cyclohexylamine (1.82 mL, 15.9 mmol, 1.0



equiv.) was added dropwise to a solution of acetic anhydride (1.50 mL, 15.9 mmol, 1.0 equiv.) in DCM (10 mL), then the mixture was

stirred overnight at rt. Saturated aqueous NaHCO₃ (50 mL) was added slowly to the reaction mixture, then the mixture was stirred until bubbling ceased. The biphasic mixture was extracted with DCM (50 mL), then the organic layer was washed with aqueous 2 M HCl (20 mL). The organic layer was dried with anhydrous Na₂SO₄, then the solvent was removed *in vacuo* to afford the product as a colourless solid (1.89 g, 13.4 mmol, 84%). ¹H NMR (500 MHz, CDCl₃) δ: 5.37 (br s, 1H), 3.76 (m, 1H), 2.04 (s, 3H), 1.92 (m, 2H), 1.70 (m, 2H), 1.61 (m, 1H), 1.36 (m, 2H), 1.13 (m, 3H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ: 169.18, 48.38, 33.37, 25.68, 25.01, 23.73.

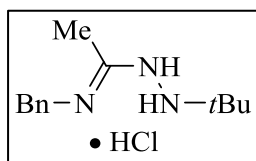
Attempted synthesis of *N*-phenyl-*N'*-(*tert*-butyl)acetamidrazone



hydrochloride (2-22): SOCl₂ (4.75 mL, 65.12 mmol, 5.0 equiv.)

was added to **2-19** (1.50 g, 13.02 mmol, 1.0 equiv.), then the mixture was stirred under reflux for 5 h. The volatiles were removed *in vacuo*, then THF (30 mL) was added, followed by NEt₃ (2.18 mL, 15.63 mmol, 1.2 equiv.) and phenylhydrazine (1.28 mL, 13.02 mmol, 1.0 equiv.). The mixture was stirred overnight at rt, then the solvent was removed *in vacuo*. Toluene (30 mL) was added, then the suspension was filtered through celite. The volatiles were removed *in vacuo* to afford an intractable mixture.

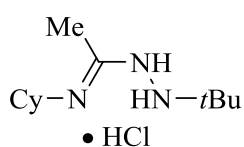
Attempted synthesis of *N*-(*tert*-butyl)-*N*''-benzylacetamidrazone



hydrochloride (2-23): Oxalyl chloride (0.681 mL, 8.04 mmol,

1.2 equiv.) was added dropwise to a solution of **2-20** (1.00 g, 6,70 mmol, 1.0 equiv.) in DCM (20 mL) at 0 °C. The mixture was warmed to rt then stirred overnight. The volatiles were removed *in vacuo*, then DCM (20 mL) was added. *tert*-Butylhydrazine (0.680 g, 7.71 mmol, 1.15 equiv.) was added, then the mixture was stirred under reflux overnight. The solvent was removed *in vacuo* to afford an intractable mixture.

Attempted synthesis of *N*-(*tert*-butyl)-*N*''-cyclohexylacetamidrazone

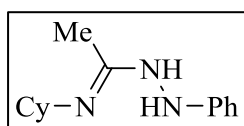


hydrochloride (2-24): PCl₅ (0.902 g, 4.33 mmol, 1.0 equiv.) was

added to a solution of **2-21** (0.612 g, 4.33 mmol, 1.0 equiv.) in

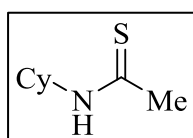
toluene, then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo*, then MeOH (15 mL) was added. *tert*-Butylhydrazine hydrochloride (0.540 g, 4.33 mmol, 1.0 equiv.) was added, then the mixture was stirred under reflux for 68 h. The solvent was removed *in vacuo*, then diethyl ether (20 mL) was added to create a suspension. The suspension was collected by filtration and washed with diethyl ether (20 mL) to afford an intractable mixture.

Attempted synthesis of *N*-phenyl-*N'*-cyclohexylacetamidrazone: Oxalyl



chloride (0.600 mL, 7.08 mmol, 1.0 equiv.) was added dropwise to a mixture of **2-21** (1.00 g, 7.08 mmol, 1.0 equiv.) and 2,6-lutidine (0.907 mL, 15.6 mmol, 1.1 equiv.) in DCM (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then the volatiles were removed *in vacuo*. Toluene (20 mL) was added, followed by 2,6-lutidine (0.907 mL, 7.08 mmol, 1.0 equiv.) and phenylhydrazine (0.697 mL, 7.08 mmol, 1.0 equiv.). The mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford an intractable mixture.

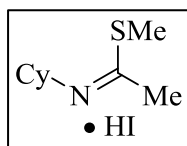
***N*-Cyclohexylthioacetamide (2-25):**⁷³ Methyllithium (1.6 M in diethyl ether,



8.82 mL, 14.1 mmol, 2.0 equiv.) was added to a solution of cyclohexyl isothiocyanate (1.00 mL, 7.05 mmol, 1.0 equiv.) in toluene (20 mL) at -84 °C. The mixture was stirred overnight at rt. Saturated aqueous NH₄Cl (10 mL) was

added dropwise to the mixture. The biphasic mixture was extracted with EtOAc (10 mL x 2), then the solvent of the combined organic layers was removed *in vacuo*. The residue was distilled under reduced pressure to afford the product as a yellow solid (0.852 g, 5.41 mmol, 77%). ¹H NMR (500 MHz, CDCl₃) δ: 6.99 (br s, 1H), 4.35 (m, 1H), 2.53 (s, 3H), 2.09 (m, 2H), 1.74 (m, 1H), 1.66 (m, 1H), 1.41 (m, 2H), 1.21 (m, 3H).

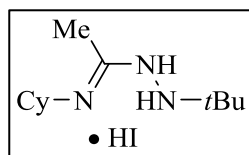
Methyl *N*-cyclohexylthioacetimidate hydroiodide (2-26): Iodomethane (1.00



mL, 16.1 mmol, 3.0 equiv.) was added dropwise to a solution of **2-25** (0.844 g, 5.37 mmol, 1.0 equiv.) in THF (10 mL). The mixture was

stirred overnight at rt. Diethyl ether (10 mL) was added, then the suspension was filtered to afford the product as a colourless solid (1.379 g, 4.61 mmol, 86%). ¹H NMR (300 MHz, methanol-*d*₄) δ: 3.82 (m, 1H), 2.82 (s, 3H), 2.72 (s, 3H), 2.07 (m, 2H), 1.87 (m, 2H), 1.72 (m, 1H), 1.50-1.25 (m, 5H). HRMS (ESI) *m/z* calc'd for C₉H₁₈N₁S₁ [M-I]⁺: 172.1154; found: 172.1151.

***N*-(*tert*-Butyl)-*N'*-cyclohexylacetamidrazone hydroiodide (2-24):** *tert*-

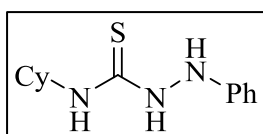


Butylhydrazine (0.324 g, 3.68 mmol, 1.0 equiv.) was added to a solution of **2-26** (1.10 g, 3.68 mmol, 1.0 equiv.) in DCM (10 mL).

The mixture was stirred under reflux overnight. The solvent was removed *in vacuo*, then a minimal amount of DCM, and diethyl ether (10 mL) was added. The mixture was heated to form a suspension that was filtered to afford the product as an off-white

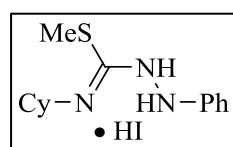
solid (1.01 g, 2.98 mmol, 81%). ^1H NMR (500 MHz, methanol- d_4) δ : 3.61 (m, 1H), 2.33 (s, 3H), 1.88 (m, 2H), 1.80 (m, 2H), 1.67 (m, 1H), 1.54-1.33 (m, 5H), 1.14 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, methanol- d_4) δ : 55.7, 54.3, 33.6, 37.2, 25.9, 25.8, 14.5. HRMS (ESI) m/z calc'd for $\text{C}_{12}\text{H}_{26}\text{N}_3$ $[\text{M-I}]^+$: 212.2121; found: 212.2127.

***N*-Cyclohexyl-2-phenylhydrazinecarbothioamide (2-27):** ⁷⁴ Cyclohexyl



isothiocyanate (1.00 mL, 7.05 mmol, 1.0 equiv.) was added to a solution of phenylhydrazine (0.693 mL, 7.05 mmol, 1.0 equiv.) in toluene (15 mL). The mixture was stirred for 40 h, during which a suspension formed. *n*-Hexane (20 mL) was added, then the suspension was filtered and washed with more *n*-hexane (10 mL) to afford the product as an off white solid (1.623 g, 6.51 mmol, 92%). ^1H NMR (500 MHz, methanol- d_4) δ : 7.21 (t, $J = 8.0$ Hz, 2H), 6.86 (t, $J = 7.5$ Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 2H), 4.23 (m, 1H), 1.95-1.17 (m, 10H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, methanol- d_4) δ : 182.3, 148.9, 121.9, 114.3, 54.1, 33.5, 26.5, 26.1. HRMS (ESI) m/z calc'd for $\text{C}_{13}\text{H}_{20}\text{N}_3\text{S}$ $[\text{M+H}]^+$: 250.1372; found: 250.1365.

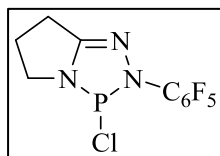
***S*-Methyl-1-cyclohexyl-4-phenylisothiosemicarbazide hydroiodide (2-28):** ⁷⁵



This compound was prepared by following a literature procedure.⁷⁵ Iodomethane (0.075 mL, 1.20 mmol, 1.0 equiv.) was added to a suspension of **2-27** (0.300 g, 1.20 mmol, 1.0 equiv.) in ethanol (EtOH) (5 mL). The mixture was heated to reflux for 2 h, then stirred at rt for 40 h. The solvent was removed

in vacuo to afford the product as a colourless solid (0.470 g, 1.20 mmol, quantitative), which was used without further purification. M.p. 173-175 °C. ¹H NMR (500 MHz, methanol-*d*₄) δ: 7.29 (m, 2H), 6.99-6.83 (m, 3H), 3.72 (m, 1H), 2.78 (s, rotamer, 2H), 2.56 (s, rotamer, 1H), 2.09-1.17 (m, 10H). ¹³C{¹H} NMR (125 MHz, methanol-*d*₄) δ: 147.1, 130.4-130.4 (rotamer), 123.1-122.9 (rotamer), 115.0-114.5 (rotamer), 56.5, 33.1, 32.7, 26.0-25.9 (rotamer), 13.9-13.5 (rotamer). HRMS (ESI) *m/z* calc'd for C₁₄H₂₂N₃S [M-I]⁺: 264.1534; found: 264.1528.

Conditions attempted for the synthesis of 3-chloro-2-pentafluorophenyl-6,7-



dihydro-5H-pyrrolo[2,1-*c*]-1,2,4,3-triazaphospholene (2-29-Cl):

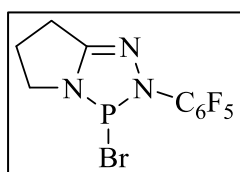
(a) *n*-BuLi (1.6 M in hexanes, 0.215 mL, 0.344 mmol, 1.0 equiv.)

was added to a suspension of **2-11** (0.121 g, 0.344 mmol, 1.0 equiv.) in THF (5 mL) at -84 °C. The mixture was stirred for 2 h while warming to rt. THF was removed *in vacuo*, then toluene (5 mL) was added. PCl₃ (0.03 mL, 0.344 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred under reflux for 6 h. The mixture was cooled to rt, then stirred overnight. The mixture was filtered through celite, then washed with toluene (5 mL). The solvent was removed *in vacuo* to afford a yellow residue (0.095 g) that is contaminated with impurities as shown in the ¹H and ¹¹B NMR spectra. **(b)** NEt₃ (0.144 mL, 1.03 mmol, 3.0 equiv.) was added to a suspension of **2-11** (0.121 g, 0.344 mmol, 1.0 equiv.) in DCM (5 mL) at rt. The mixture was stirred at rt for 2 h. PCl₃ (0.03

mL, 0.344 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The solvent was removed *in vacuo* to afford a yellow residue (0.102 g) that is contaminated with minor impurities as shown in the ^1H and ^{11}B NMR spectra.

(c) The same procedure as (b) was applied, except DBU (0.127 mL, 0.850 mmol, 3.0 equiv.) was used instead of NEt_3 , to afford a brown residue (0.088 g) that is contaminated with starting materials as evidenced by the ^{31}P NMR spectrum. ^1H NMR (500 MHz, CDCl_3) δ : 3.86 (q, $J = 7.0$ Hz, 2H), 2.88 (td, $J = 7.5, 1.5$ Hz, 2H), 2.56 (p, $J = 7.0$ Hz, 2H). ^{31}P NMR (201 MHz, CDCl_3) δ : 121 (s).

Conditions attempted for the synthesis of 3-bromo-2-pentafluorophenyl-6,7-

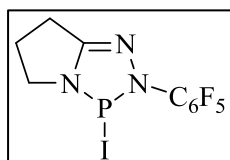


dihydro-5H-pyrrolo[2,1-c]-1,2,4,3-triazaphospholene (2-29-

Br): (a) The same procedure as 2-29-Cl-(c) was applied, except PBr_3 (0.026 mL, 0.283 mmol, 1.0 equiv.) was used instead of PCl_3 , to afford a brown residue (0.092 g) that is contaminated with starting materials as evidenced by the ^{31}P NMR spectrum. (b) PBr_3 (0.03 mL, 0.319 mmol, 1.0 equiv.) was added dropwise to a suspension of 2-11 (0.113 g, 0.319 mmol, 1.0 equiv.) in α,α,α -trifluorotoluene (TFT) (2 mL). The mixture was stirred under reflux overnight. The mixture was cooled to rt, then volatiles were removed *in vacuo* to afford a yellow residue (0.116 g, 0.310 mmol, 97%) with clean ^1H and ^{31}P NMR spectra. (c) The same procedure as (b) was applied, except MeCN (3 mL) was used instead of TFT, to afford a yellow residue (0.195 g) that

is consisted of only starting materials. ^1H NMR (500 MHz, CDCl_3) δ : 3.83 (q, $J = 7.0$ Hz, 2H), 2.91 (td, $J = 7.5, 1.5$ Hz, 2H), 2.59 (p, $J = 7.5$ Hz, 2H). ^{31}P NMR (201 MHz, CDCl_3) δ : 143 (s).

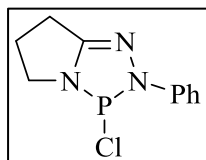
Conditions attempted for the synthesis of 3-iodo-2-pentafluorophenyl-6,7-



dihydro-5H-pyrrolo[2,1-c]-1,2,4,3-triazaphospholene (2-29-I):

KH (0.010 g, 0.249 mmol, 3.0 equiv.) was added to a suspension of **2-11** (0.029 g, 0.083 mmol, 1.0 equiv.) in toluene (3 mL). PI_3 (0.034 g, 0.083 mmol, 1.0 equiv.) was added to the mixture, then stirred overnight at rt. Volatiles were removed *in vacuo* to afford a yellow residue that is consisted of mostly PI_3 as evidenced by the ^{31}P NMR spectrum.

Conditions attempted for the synthesis of 3-chloro-2-phenyl-6,7-dihydro-5H-

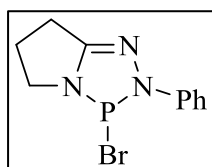


pyrrolo[2,1-c]-1,2,4,3-triazaphospholene (2-30-Cl): (a) The same

procedure as **2-29-Cl-(b)** was applied to **2-13**, except the addition of PCl_3 (0.041 mL, 0.472 mmol, 1.0 equiv.) was done at -15 $^\circ\text{C}$, to afford a yellow solid (0.092 g, contaminated with MeCN) after filtration with toluene through celite. **(b)** *n*-BuLi (0.700 mL, 1.12 mmol, 3.0 equiv.) was added dropwise to a suspension of **2-13** (0.079 g, 0.373 mmol, 1.0 equiv.) in THF (4 mL) at -84 $^\circ\text{C}$. The mixture was stirred and warmed to rt over 1 h, then cooled to -15 $^\circ\text{C}$. PCl_3 (0.033 mL, 0.373 mmol, 1.0 equiv.) was added dropwise to the mixture, then the mixture was stirred overnight at rt.

Volatiles were removed *in vacuo*, then toluene (10 mL) was added. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford a yellow solid (0.053 g, contaminated with toluene). ^1H NMR (300 MHz, CDCl_3) δ : 7.54 (m, 2H), 7.38 (m, 2H), 7.16 (m, 1H), 3.86 (q, $J = 6.6$ Hz, 2H), 2.89 (m, 2H), 2.54 (m, 2H). ^{31}P NMR (121 MHz, CDCl_3) δ : 119.1 (s).

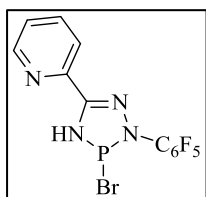
Conditions attempted for the synthesis of 3-bromo-2-phenyl-6,7-dihydro-5H-



pyrrolo[2,1-c]-1,2,4,3-triazaphospholene (2-30-Br): The same procedure as **2-29-Cl(b)** was applied, except PBr_3 (0.044 mL, 0.472

mmol, 1.0 equiv.) instead of PCl_3 was added at $0\text{ }^\circ\text{C}$, to afford a yellow residue (0.102 g). ^1H NMR (300 MHz, CDCl_3) δ : 7.54 (m, 2H), 7.39 (m, 2H), 7.18 (m, 1H), 3.86 (q, $J = 7.0$ Hz, 2H), 2.92 (td, $J = 7.5, 2.1$ Hz, 2H), 2.56 (p, $J = 7.0$ Hz, 2H). ^{31}P NMR (201 MHz, CDCl_3) δ : 128.3 (br).

3-Bromo-4H-2-pentafluorophenyl-5-(2-pyridyl)-1,2,4,3-triazaphospholene

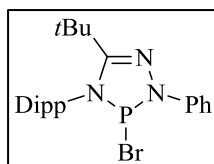


(2-31): NEt_3 (0.74 mL, 5.3 mmol, 2.0 equiv.) was added to a suspension of **2-15** (0.800 g, 2.65 mmol, 1.0 equiv.) in toluene (30

mL). PBr_3 (0.25 mL, 2.65 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (50 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as a yellow solid (0.835 g, 2.03 mmol, 77%). M.p. $91\text{ }^\circ\text{C}$ (Decomposed). ^1H NMR (500

MHz, CDCl₃) δ : 9.08 (br s, 1H), 8.66 (d, J = 5.0 Hz, 1H), 8.18 (d, J = 5.0 Hz, 1H), 7.89 (td, J = 7.5, 1.5 Hz, 1H), 7.48 (m, 1H). ¹³C{¹H} (125 MHz, CDCl₃) δ : 150.1 (d, J = 11.5 Hz), 148.5, 144.8, 138.3, 125.8, 122.5; pentafluorophenyl carbon signals are spread across the baseline. ¹⁹F (470 MHz, CDCl₃) δ : -144.7 (m, 2F), -153.9 (td, J = 13.0, 2.8 Hz, 1F), -160.9 (m, 2F). ³¹P NMR (201 MHz, CDCl₃) δ : 144.5 (t, J = 26.5 Hz). HRMS (APCI) m/z calc'd for C₁₂H₅F₅N₄P [M-Br]⁺: 331.0167; found: 331.0175.

3-Bromo-5-(*tert*-butyl)-4-(2,6-diisopropylphenyl)-2-phenyl-1,2,4,3-triaza-



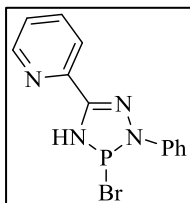
phospholene (2-32): NEt₃ (1.57 mL, 11.3 mmol, 2.0 equiv.) was

added to a solution of **2-10** (1.99 g, 5.66 mmol, 1.0 equiv.) in toluene

(30 mL). PBr₃ (0.532 mL, 5.66 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (30 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as a yellow solid (1.96 g, 4.26 mmol, 75%). Colourless crystals suitable for X-ray analysis were grown in cold MeCN. M.p. 140-142. ¹H NMR (500 MHz, acetonitrile-*d*₃) δ : 7.61-7.25 (m, 8H), 3.08 (m, 1H), 1.30 (rotamer overlap, 6H), 1.22 (s, 9H), 1.12 (rotamer overlap, 6H). ¹³C{¹H} (125 MHz, acetonitrile-*d*₃) δ : 161.0 (d, J = 6.5 Hz), 149.5 (d, J = 4.1 Hz), 142.0 (d, J = 5.1 Hz), 133.0 (d, J = 18.0 Hz), 131.4 (d, J = 1.8 Hz), 130.7, 128.9, 125.9 (d, J = 3.1 Hz), 125.8, 124.0, 119.8 (d, J = 12.1 Hz), 47.0, 36.6, 30.2, 29.6, 29.3 (rotamer), 28.3 (br, rotamer), 28.0 (rotamer), 22.5, 8.9. ³¹P NMR

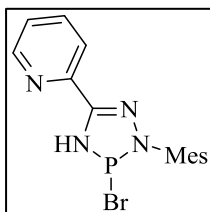
(201 MHz, acetonitrile- d_3) δ : 151.6 (s). HRMS (APCI) m/z calc'd for $C_{23}H_{31}N_3P$ [M-Br] $^+$: 380.2250; found: 380.2245.

3-Bromo-4*H*-2-phenyl-5-(2-pyridyl)-1,2,4,3-triazaphospholene (2-33): NEt₃



(0.50 mL, 3.6 mmol, 3.0 equiv.) was added to a suspension of **2-16** (0.300 g, 1.21 mmol, 1.0 equiv.) in toluene (10 mL). PBr₃ (0.113 mL, 1.21 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (5 mL) and THF (5 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as an orange solid (0.304 g, 0.95 mmol, 78%). Orange crystals suitable for X-ray analysis were grown in cold MeCN. M.p. 53 °C (Decomposed). ¹H NMR (500 MHz, CDCl₃) δ : 8.90 (br, 1H), 8.64 (d, J = 4.5 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.85 (td, J = 8.0, 1.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.47-7.40 (m, 3H), 7.23 (t, J = 8.0 Hz, 1H). ¹³C {¹H} (125 MHz, CDCl₃) δ : 140.1, 145.8, 141.4, 137.5, 129.7, 125.3-125.2 (overlapped), 121.9, 119.1 (d, J = 15.9 Hz). ³¹P NMR (201 MHz, CDCl₃) δ : 140.7 (br). HRMS (APCI) m/z calc'd for $C_{12}H_{10}N_4P$ [M-Br] $^+$: 241.0638; found: 241.0645.

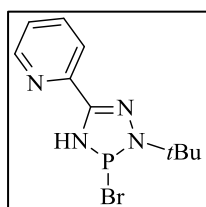
3-Bromo-4*H*-2-mesityl-5-(2-pyridyl)-1,2,4,3-triazaphospho-lene (2-34): NEt₃



(0.43 mL, 3.1 mmol, 3.0 equiv.) was added to a suspension of **2-17** (0.300 g, 1.03 mmol, 1.0 equiv.) in toluene (10 mL). PBr₃ (0.097 mL, 1.03 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at

rt. The mixture was filtered through celite and washed with toluene (5 mL) and THF (5 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as a yellow solid (0.247 g, 0.68 mmol, 66%). M.p. 95-98 °C (Decomposed). ¹H NMR (500 MHz, CDCl₃) δ: 8.67 (d, *J* = 5.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.85 (td, *J* = 8.0, 1.5 Hz, 1H), 7.44 (m, 1H), 6.99 (s, 2H), 2.38 (s, 6H), 2.33 (s, 3H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ: 148.4, 145.6, 139.1, (d, *J* = 2.5 Hz), 138.1, 136.2 (d, *J* = 5.0 Hz), 134.7 (d, *J* = 6.3 Hz), 130.0, 125.2, 122.1, 21.2, 19.1 (d, *J* = 2.9 Hz). ³¹P NMR (201 MHz, CDCl₃) δ: 151.6 (br). HRMS (APCI) *m/z* calc'd for C₁₅H₁₆N₄P [M-Br]⁺: 283.1107; found: 283.1113.

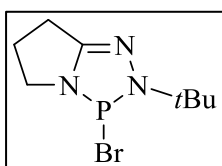
3-Bromo-2-(*tert*-butyl)-4*H*-5-(2-pyridyl)-1,2,4,3-triazaphospholene (2-35):



NEt₃ (0.300 mL, 2.15 mmol, 1.8 equiv.) was added to a suspension of **2-18** (0.291 g, 1.20 mmol, 1.0 equiv., contaminated with 5.8% of *tert*-butylhydrazine hydrochloride by ¹H NMR analysis) in toluene (10 mL). The mixture was stirred for 10 minutes, then the volatiles were removed *in vacuo*. Toluene (20 mL) was added, followed by NEt₃ (0.334 mL, 2.40 mmol, 2.0 equiv.). PBr₃ (0.113 mL, 1.20 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (2 mL) and THF (2 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as a yellow solid (0.262 g, 0.87 mmol, 73%). M.p. 138-140 °C (Decomposed). ¹H NMR

(500 MHz, CDCl₃) δ : 10.4 (br, 1H), 8.66 (d, J = 4.5 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 6.0 Hz, 1H), 1.68 (s, 9H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ : 147.9, 145.8, 138.5, 125.0, 122.1, 59.9 (d, J = 4.6 Hz), 29.8, 29.7 (d, J = 10.6 Hz). ³¹P NMR (201 MHz, CDCl₃) δ : 147.6 (br). HRMS (APCI) m/z calc'd for C₁₀H₁₄N₄P [M-Br]⁺: 221.0951; found: 221.0944.

3-Bromo-2-(*tert*-butyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*]-1,2,4,3-triazaphos-

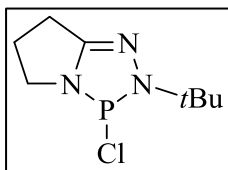


pholene (2-36): NEt₃ (0.654 mL, 4.70 mmol, 3.0 equiv.) was added to a suspension of **2-12** (0.300 g, 1.57 mmol, 1.0 equiv.) in toluene

(12 mL). PBr₃ (0.147 mL, 1.57 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (5 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as a yellow liquid (0.376 g, 1.42 mmol, 91%). ¹H NMR (500 MHz, CDCl₃) δ : 3.88 (q, J = 7.0 Hz, 2H), 2.88 (td, J = 8.0, 1.5 Hz, 2H), 2.54 (p, J = 7.5 Hz, 2H), 1.59 (d, J = 2.0 Hz, 9H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ : 162.2 (d, J = 9.1 Hz), 60.0 (d, J = 4.3 Hz), 45.4 (d, J = 2.3 Hz), 29.3 (d, J = 11.9 Hz), 26.9, 23.1. ³¹P NMR (201 MHz, CDCl₃) δ : 197.3 (s, unidentified impurity), 154.2 (s, unidentified impurity), 152.4 (br s). HRMS (APCI) m/z calc'd for C₈H₁₅N₃P [M-Br]⁺: 184.0998; found 184.0994.

3-Chloro-2-(*tert*-butyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*]-1,2,4,3-triazaphos-

pholene (2-37): NEt₃ (1.53 mL, 10.9 mmol, 3.0 equiv.) was added to a suspension of



2-12 (0.700 g, 3.65 mmol, 1.0 equiv.) in toluene (20 mL). PCl_3 (0.319 mL, 3.65 mmol, 1.0 equiv.) was added dropwise, then the

mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (5 mL). The solvent was removed from the filtrate *in vacuo* to afford the

product as a yellow liquid (0.751 g, 3.42 mmol, 94%). ^1H NMR (300 MHz, CDCl_3) δ :

3.84 (q, $J = 6.6$ Hz, 2H), 2.76 (td, $J = 7.8, 1.8$ Hz, 2H), 2.49 (p, $J = 7.4$ Hz, 2H), 1.52

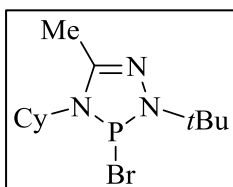
(d, $J = 1.8$ Hz, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ : 160.8 (d, $J = 9.6$ Hz), 59.0 (d,

$J = 4.5$ Hz), 44.5 (d, $J = 3.3$ Hz), 29.7 (d, $J = 11.7$ Hz), 26.9 (d, $J = 1.1$ Hz), 23.0. ^{31}P

NMR (121 MHz, CDCl_3) δ : 134.3 (s). HRMS (APCI) m/z calc'd for $\text{C}_8\text{H}_{15}\text{N}_3\text{P} [\text{M}-\text{Cl}]^+$:

184.0998; found: 184.1002.

Attempted synthesis of 3-Bromo-5-(*tert*-butyl)-4-cyclohexyl-2-methyl-1,2,4,3-



triazaphospholene (2-38): NEt_3 (0.304 mL, 3.27 mmol, 3.0 equiv.)

was added to a suspension of **2-24** (0.400 g, 1.09 mmol, 1.0 equiv.),

contaminated with 11.3% of *tert*-butylhydrazine hydroiodide by ^1H NMR analysis) in

THF (15 mL) at rt. The mixture was stirred for 10 min, then the volatiles were removed

in vacuo. THF (10 mL) was added, followed by NEt_3 (0.304 mL, 3.27 mmol, 3.0 equiv.).

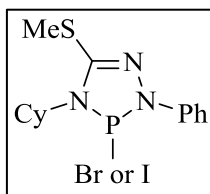
PBr_3 (0.103 mL, 1.09 mmol, 1.0 equiv.) was added dropwise, then the mixture was

stirred overnight at rt. The mixture was filtered through celite and washed with toluene

(20 mL). The solvent was removed from the filtrate *in vacuo* to afford a yellow residue

(0.315 g), which was used without further purification. The ^1H and ^{31}P NMR spectra show an intractable mixture.

3-Bromo/Iodo-4-cyclohexyl-2-phenyl-5-thiomethyl-1,2,4,3-triazaphospho-

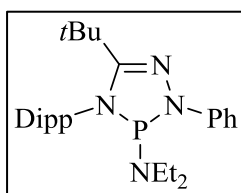


lene (2-39): NEt_3 (0.32 mL, 2.3 mmol, 3.0 equiv.) was added to a suspension of **C2** (0.300 g, 0.77 mmol, 1.0 equiv.) in toluene (7 mL).

Phosphorus tribromide (0.072 mL, 1.03 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at RT. The mixture was filtered through celite and washed with toluene (5 mL) and THF (5 mL). The solvent was removed from the filtrate *in vacuo* to afford the product as a yellow solid (0.247 g, mixture of iodide and bromide).

M.p. 157-160 °C (Decomposed). ^1H NMR (300 MHz, CDCl_3) δ : 7.58-7.54 (m, 2H), 7.40 (t, $J = 7.8$ Hz, 2H), 7.21 (td, $J = 7.2, 1.2$ Hz, 1H), 3.82 (m, 1H), 2.73 (s, 3H), 2.42-2.36 (m, 2H), 1.98-1.93 (m, 4H), 1.76-1.71 (m, 1H), 1.42-1.25 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ : 153.6 (d, $J = 13.1$ Hz), 141.1 (d, $J = 7.4$ Hz), 129.6, 125.3 (d, $J = 3.2$ Hz), 118.5 (d, $J = 13.6$ Hz), 58.0 (d, $J = 8.0$ Hz), 33.4 (d, $J = 8.9$ Hz), 25.7 (d, $J = 1.1$ Hz), 25.1, 15.5 (d, $J = 0.8$ Hz). ^{31}P NMR (121 MHz, CDCl_3) δ : 167.4 (br). HRMS (APCI) m/z calc'd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{PS}$ $[\text{M}-\text{Br}]^+$: 292.1032; found: 292.1038.

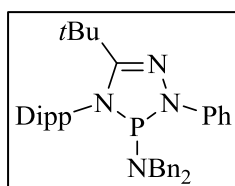
Attempted synthesis of 3-diethylamino-5-(tert-butyl)-4-(2,6-diisopropyl-



phenyl)-2-phenyl-1,2,4,3-triazaphospholene (2-42): NEt_3 (0.015 mL, 0.111 mmol, 1.0 equiv.) was added to a solution of **2-**

32 (0.051 g, 0.111 mmol, 1.0 equiv.) in DCM (5 mL). HNEt₂ (0.011 mL, 0.111 mmol, 1.0 equiv.) was added, then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo* to afford an intractable mixture (0.042 g) based on ¹H and ³¹P NMR analysis.

Attempted synthesis of 3-dibenzylamino-5-(tert-butyl)-4-(2,6-diisopropyl-

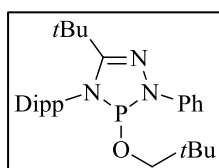


phenyl)-2-phenyl-1,2,4,3-triazaphospholene (2-43): (a) NEt₃ (0.015 mL, 0.111 mmol, 1.0 equiv.) was added to a solution of **2-**

32 (0.051 g, 0.111 mmol, 1.0 equiv.) in DCM (5 mL). HNBN₂ (0.021 mL, 0.111 mmol, 1.0 equiv.) was added, then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo* to afford an intractable mixture based on ¹H and ³¹P NMR analysis.

(b) NEt₃ (0.024 mL, 0.174 mmol, 1.0 equiv.) was added to a solution of **2-32** (0.080 g, 0.174 mmol, 1.0 equiv.) in toluene (1 mL). HNBN₂ (0.033 mL, 0.174 mmol, 1.0 equiv.) was added, then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford the crude product (0.030 g). ³¹P NMR (201 MHz, CDCl₃) δ: 94.4 (s).

Attempted synthesis of 3-neopentyloxy-5-(tert-butyl)-4-(2,6-diisopropyl-

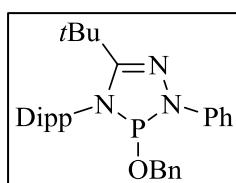


phenyl)-2-phenyl-1,2,4,3-triazaphospholene (2-44): NEt₃ (0.033 mL, 0.239 mmol, 1.0 equiv.) was added to a solution of **2-32** (0.110

g, 0.217 mmol, 1.0 equiv.) in toluene (4 mL). Neopentylalcohol (0.021 g, 0.239 mmol,

1.0 equiv.) was added, then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo* to afford a mixture of product and oxygenated materials (0.105 g) based on ^1H and ^{31}P NMR analysis. ^{31}P NMR (201 MHz, CDCl_3) δ : 88.3 (s, P-O), 5.98-2.73 (d, $J = 653.3$ Hz, O=P). HRMS (ESI) m/z calc'd for $\text{C}_{28}\text{H}_{43}\text{N}_3\text{OP}$ $[\text{M}+\text{H}]^+$: 468.3138; found: 468.3135.

3-Benzyloxy-5-(*tert*-butyl)-4-(2,6-diisopropylphenyl)-2-phenyl-1,2,4,3-triaza-



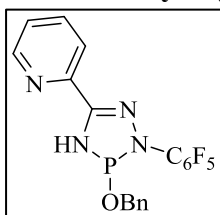
phospholene (2-45): NaOBn (0.100 g, 0.769 mmol, 1.0 equiv.)

was added to a suspension of **2-32** (354 mg, 0.769 mmol, 1.0 equiv.)

in toluene (12 mL), then the mixture was stirred for 48 h at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.286 g, 0.59 mmol, 76%), which was used without further purification. ^1H NMR (500 MHz, CDCl_3) δ : 7.56 (d, $J = 8.0$ Hz, 2H), 7.33 (m, 3H), 7.25 (m, 4H), 7.15 (m, 3H), 6.98 (t, $J = 7.5$ Hz, 1H), 4.50 (dd, $J = 11.5, 4.5$ Hz, 1H), 4.37 (dd, $J = 11.5, 4.5$ Hz, 1H), 3.56 (sep, $J = 7.0$ Hz, 1H), 2.29 (sep, $J = 6.5$ Hz, 1H), 1.32 (d, $J = 6.5$ Hz, 3H), 1.23 (s, 9H), 1.21 (d, $J = 7.0$ Hz, 3H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.02 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 156.9 (d, $J = 6.0$ Hz), 149.1 (d, $J = 3.9$ Hz), 148.1 (d, $J = 2.8$ Hz), 144.5, 144.4, 135.5, 135.3, 129.4, 128.8, 128.4, 127.9, 127.8, 124.3, 123.9, 121.5, 116.0 (d, $J = 11.1$ Hz), 67.0 (d, $J = 7.5$ Hz), 36.1, 30.6, 20.7, 28.1, 27.1, 26.4 (d, $J = 9.1$ Hz), 22.8, 22.4. HRMS (ESI) m/z calc'd for $\text{C}_{36}\text{H}_{38}\text{N}_3\text{OPNa}$ $[\text{M}+\text{Na}]^+$:

510.2650; found: 510.2655.

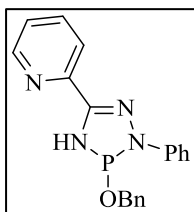
3-Benzyloxy-4H-2-pentafluorophenyl-5-(2-pyridyl)-1,2,4,3-triazaphos-



pholene (2-48): NaOBn (0.063 g, 0.487 mmol, 1.0 equiv.) was added to a suspension of **2-31** (0.200 g, 0.487 mmol, 1.0 equiv.) in

toluene (6 mL), then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.175 g, 0.399 mmol, 82%), which was used without further purification. ^1H NMR (500 MHz, CDCl_3) δ : 8.62 (d, $J = 5.0$ Hz, 1H), 8.26 (br, overlapped, 1H), 8.19 (d, $J = 8.0$ Hz, overlapped, 1H), 7.89 (t, $J = 8.0$ Hz, 1H), 7.45 (m, 1H), 7.27-7.19 (m, 5H), 4.50 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, CDCl_3) δ : 147.30, 145.59, 138.43, 137.47, 137.45, 128.50, 127.94, 127.62, 124.84, 122.31, 65.74; pentafluorophenyl signals are spread across the baseline. ^{31}P NMR (201 MHz, CDCl_3) δ : 82.1 (m).

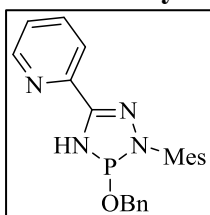
3-Benzyloxy-4H-2-phenyl-5-(2-pyridyl)-1,2,4,3-triazaphospholene (2-49):



NaOBn (0.043 g, 0.327 mmol, 1.05 equiv.) was added to a suspension of **2-33** (0.100 g, 0.487 mmol, 1.0 equiv.) in toluene (3 mL), then the

mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to provide a mixture of product and oxygenated materials (0.094 g), which was used without further purification. ^{31}P NMR (201 MHz, CDCl_3) δ : 75.9 (d, $J = 35.4$ Hz, P-O), 9.4-5.9 (m, O=P).

3-Benzoyloxy-4*H*-2-mesityl-5-(2-pyridyl)-1,2,4,3-triazaphos-pholene (2-50):



NaOBn (0.039 g, 0.303 mmol, 1.1 equiv.) was added to a suspension of **2-34** (0.100 g, 0.275 mmol, 1.0 equiv.) in toluene (3 mL), then the

mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to provide a mixture of product and oxygenated materials

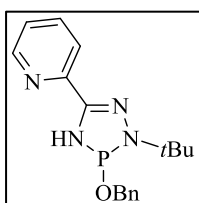
(0.080 g), which was used without further purification. ^1H NMR (300 MHz, CDCl_3) δ :

8.57 (m, 1H), 8.12 (m, 1H), 7.88 (br d, $J = 33.0$ Hz, 1H), 7.74 (m, 1H), 7.37-7.17 (m, 5H, overlapped with residual solvent signal), 6.93 (s), 5.07 (m, O=P), 4.59 (m, 2H),

3.75 (m, THF), 2.31 (s, 3H), 2.24 (s, 6H), 1.85 (m, THF). ^{31}P NMR (121 MHz, CDCl_3)

δ : 86.3 (m, P-O), 10.6-4.8 (m, O=P).

3-Benzoyloxy-2-(*tert*-butyl)-4*H*-5-(2-pyridyl)-1,2,4,3-triazaphospholene (2-51):



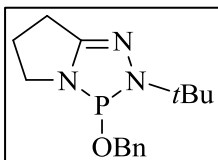
NaOBn (0.047 g, 0.364 mmol, 1.1 equiv.) was added to a suspension of **2-35** (0.100 g, 0.331 mmol, 1.0 equiv.) in toluene (3 mL), then the

mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to provide a mixture of product and oxygenated materials

(0.100 g), which was used without further purification. ^{31}P NMR (121 MHz, CDCl_3) δ :

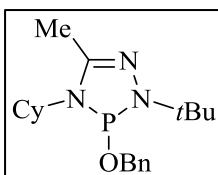
76.4 (d, $J = 34.6$ Hz, P-O), 10.6-4.8 (m, O=P), 3.0 (dd, $J = 677.2, 21.9$ Hz, O=P).

3-Benzoyloxy-2-(*tert*-butyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*]-1,2,4,3-triazaphospholene (2-52): (a) NaOBn (0.140 g, 1.08 mmol, 1.1 equiv.) was added to a solution



of **2-36** (0.259 g, 0.981 mmol, 1.0 equiv.) in toluene (5 mL), then the mixture was stirred at rt for 4 h. The mixture was filtered through celite, then the solvent was removed *in vacuo* to provide a mixture of product, oxygenated materials, and unidentified side-products (0.245 g), which was used without further purification. ^{31}P NMR (201 MHz, CDCl_3) δ : 184.3 (s, unidentified), 139.6 (m, unidentified), 75.3 (s, P-O), 9.3-5.8 (d, O=P), 2.5 to -0.8 (d, $J = 671.9$ Hz, O=P). **(b)** NaOBn (0.204 g, 1.565 mmol, 1.0 equiv.) was added to a solution of **2-37** (0.413 g, 1.565 mmol, 1.0 equiv.) in toluene, then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to provide a mixture of product and unidentified side-product (0.270 g). ^1H NMR spectrum shows CH_2 protons in **2-52** to be diastereotopic. ^{31}P NMR (201 MHz, CDCl_3) δ : 139.6 (m, unidentified), 75.3 (s, P-O).

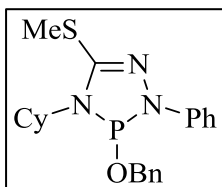
Attempted synthesis of 3-benzyloxy-5-(tert-butyl)-4-cyclohexyl-2-methyl-



1,2,4,3-triazaphospholene (2-53): NaOBn (0.139 g, 1.07 mmol, 1.1 equiv.) was added to a suspension of **2-38** (0.310 g, 0.960 mmol, 1.0 equiv.) in toluene, then stirred at rt for 40 min. The mixture was filtered through celite, then the solvent was removed *in vacuo* to provide a mixture of product, oxygenated materials, and unidentified side-products (0.267 g), which was used without further purification. ^{31}P NMR (201 MHz, CDCl_3) δ : 234.9 (d, unidentified), 165.6 (d,

unidentified), 94.4-92.7 (m, unidentified), 80.3 (s, P-O), -0.3 (m, O=P).

3-Benzyloxy-4-cyclohexyl-2-phenyl-5-thiomethyl-1,2,4,3-triazaphospholene



(2-54): NaOBn (0.019 g, 0.148 mmol, 1.1 equiv.) was added to a suspension of **2-39** (0.050 g, 0.134 mmol based on bromide mass,

1.0 equiv.) in toluene, then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.048 g, 0.120 mmol, 81%). ¹H NMR (500 MHz, CDCl₃) δ: 7.51 (m, 2H), 7.33-7.18 (m, 7H), 6.98 (m, 1H), 4.29 (m, 2H), 3.63 (m, 1H), 2.71 (s, 3H), 2.21-2.05 (m, 2H), 1.88 (m, 2H), 1.81-1.64 (m, 3H), 1.39 (m, 3H), 1.24 (m, 1H). ³¹P NMR (201 MHz, CDCl₃) δ: 83.8 (s).

Representative procedure for the reduction of imine 2-47 with a catalytic

amount 2-45: The terminal reductant (HB(cat), morpholine-borane, 9-BBN, HB(pin), or Ph₂SiH₂, 1.0 equiv.) was added to a mixture of 2-45 (0.005 g, 0.011 mmol, 0.1 equiv.) and 2-47 (0.02 mL, 0.110 mmol, 1.0 equiv.) in MeCN (0.6 mL) in an NMR tube. A capillary of C₆D₆ was inserted, then the tube was capped and overwrapped with PTFE tape. The reaction was monitored by ³¹P NMR analysis. After 4 days, the solvent was removed *in vacuo*, then CDCl₃ (0.5 mL) was added. The mixture was transferred back to an NMR tube to assess the conversion by ¹H NMR spectroscopy.

Representative procedure for the control reactions of 2-47 with various

hydride transfer reagents: The terminal reductant (HB(cat), morpholine-borane, 9-BBN, HB(pin), or Ph₂SiH₂, 1.0 equiv.) was added to a solution of **2-47** (0.02 mL, 0.110 mmol, equiv.) in MeCN (1 mL), then the mixture was stirred overnight at rt. The solvent was removed *in vacuo*, then CDCl₃ (0.5 mL) was added. The mixture was transferred to an NMR tube to assess the conversion by ¹H NMR spectroscopy.

Chapter 3. Non-Racemic 1,2,4,3-Triazaphospholenes

3.1 Contributions

Prof. Alexander W. H. Speed (Dalhousie University) is thanked for the preparation of mesitylhydrazine hydrochloride. Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University) is thanked for the acquisition of mass spectrometric data. Dr. Robert McDoanld (X-Ray Crystallography Laboratory, University of Alberta) is thanked for the acquisition of crystallographic data and solving of crystal structure.

3.2 Introduction

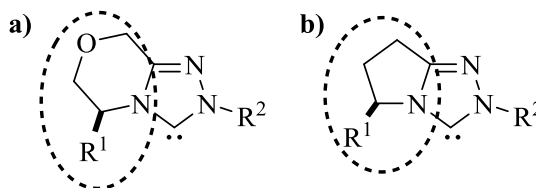
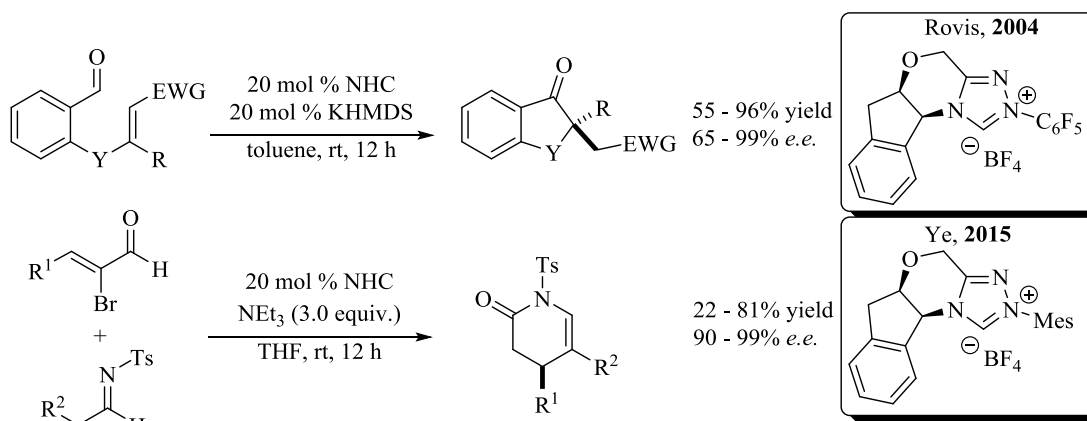


Figure 3.1 Amino acid-derived scaffolds for the synthesis of triazolylidenes.

Motivated by the success of the synthesis of racemic TAPs, we turned our attention to TAPs derived from enantioenriched amidrazones in order to assess stereoselectivity in TAP-catalyzed transformations (Chapter 4). Triazolylidenes derived from chiral amidrazones are common catalysts in asymmetric transformations.⁴ Chiral and rigid bicyclic scaffolds derived from commercially available amino acids, introduced by Knight and Leeper,⁷⁶ are among the most popular chiral inducers (Figure 3.1). Aminoindanol-derived triazolylidenes developed by Rovis and co-workers^{64,77} have received considerable attention due to their structural rigidity, and wide applicability in



Scheme 3.1 Aminoindanol-derived triazolylidene-catalyzed asymmetric transformations.

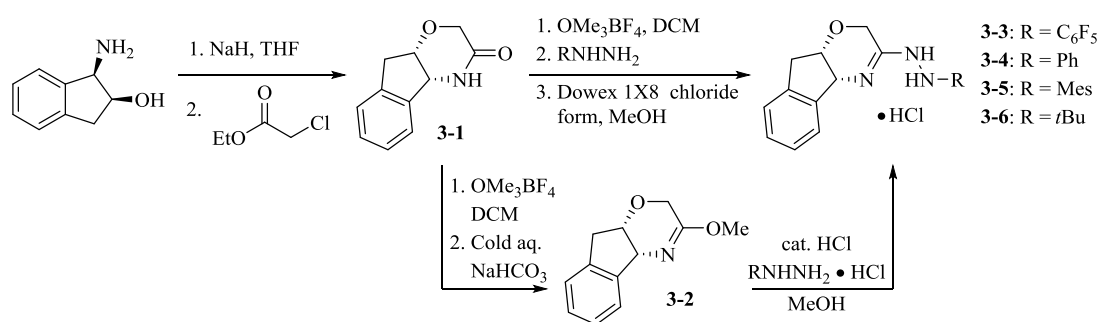
various asymmetric C-C bond forming transformations (Scheme 3.1)^{77,78} However,

much like achiral amidrazones, chiral amidrazones are also rarely isolated in literature.

Therefore, isolation of amidrazones once again became the objective.

3.3 Synthesis of Non-Racemic Amidrazones

3.3.1 Cyclic Amidrazones

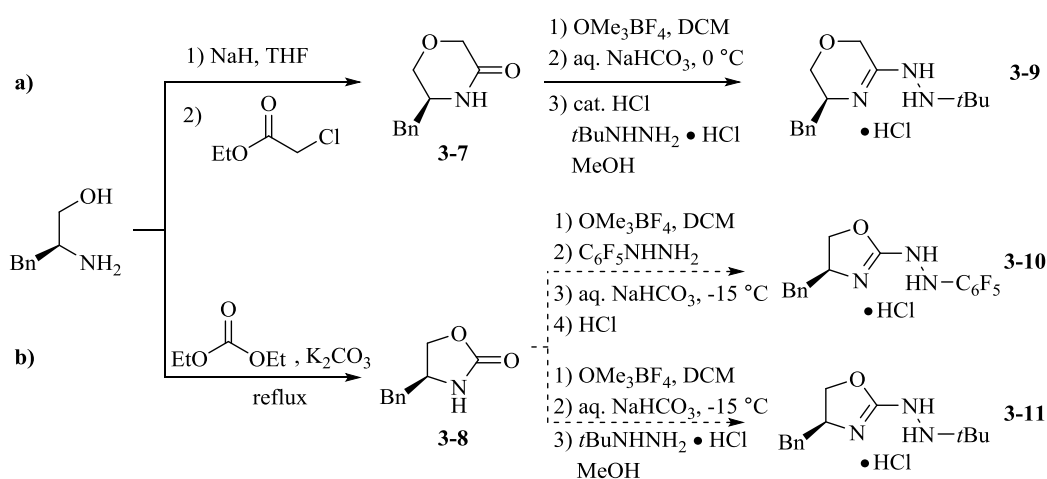


Scheme 3.2 Synthesis of amidrazones **3-3** to **3-6**.

Due to the popularity of amino alcohol-derived cyclic scaffolds in triazolylidene synthesis, we decided to investigate synthetic methods to isolate the amidrazones.

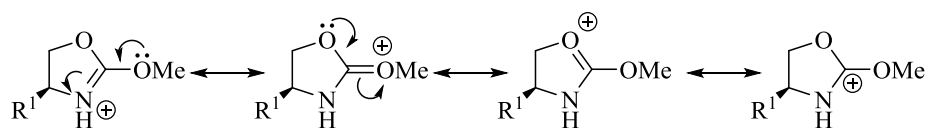
Following procedures developed by Rovis and co-workers,⁷⁷ I intended to synthesize amidrazones **3-2** and **3-3** from the corresponding amide, **3-1** (Scheme 3.2). Amidrazone

3-3 was synthesized as both the HBF₄ and HCl salts. Attempts of crystallization and precipitation did not afford the pure salt. Nevertheless, the salts were still used in the subsequent cyclizations. Amidrazone **3-4** was synthesized, however due to its high hygroscopicity, the product could not be isolated with satisfactory purity. Free-based imidate, **3-2**, was isolated before conversion to **3-5** and **3-6**, as reported by Bode and co-workers.⁷⁹ Upon condensation of **3-2** with corresponding hydrazinium salts, **3-5** and **3-6** were isolated with sufficient purity upon multiple precipitation and flash column chromatography, respectively.



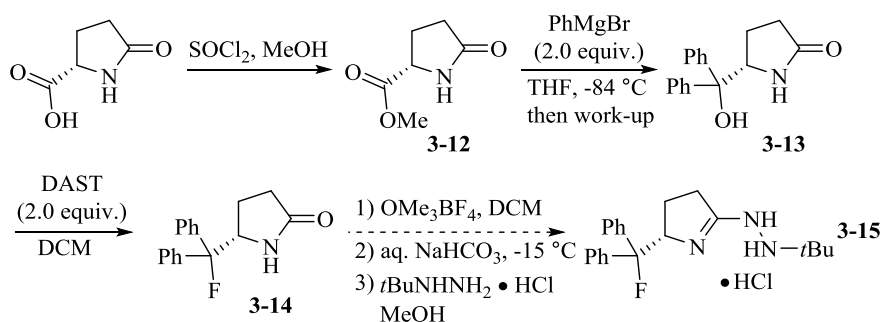
Scheme 3.3 Attempted synthesis of amidrazones **3-9** to **3-11** from (*S*)-phenylalanine.

Amidrazone **3-9**, derived from (*S*)-phenylalanine, was synthesized from **3-7** according to a procedure developed by Leeper (Scheme 3.3a).⁷⁶ However, **3-9** could only be isolated with the corresponding hydrazine salt after unsuccessful attempts of



Scheme 3.4 Reduced Lewis acidity of imidocarbonates due to contributing resonance structures.

crystallization. Amidrazones **3-10** and **3-11**, derived from oxazolidinone **3-8**, were subjected to similar procedures as for **3-3** and **3-6**, respectively (Scheme 3.3b).⁸⁰ However, **3-10** and **3-11** could not be isolated with acceptable purity. It was reasoned that the oxygen atom in the backbone lowered the electrophilicity of the imidocarbonate intermediate, causing it to react slower with hydrazinium nucleophiles (Scheme 3.4). Therefore, in an effort to explore more reactive chiral scaffolds, pyroglutamic acid-derived amidrazone, **3-15**, became a target of interest. Following a procedure developed by Gilmour and co-workers,⁸¹ **3-14** was synthesized in three steps from **3-12**. However, amidrazone **3-15** could not be isolated free of the parent hydrazine salt in a meaningful yield (Scheme 3.5).



Scheme 3.5 Attempted synthesis of pyroglutamic acid-derived amidrazone, **3-15**.

3.3.2 Acyclic Amidrazones

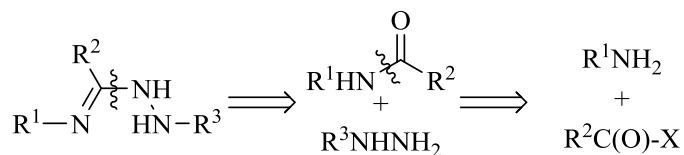
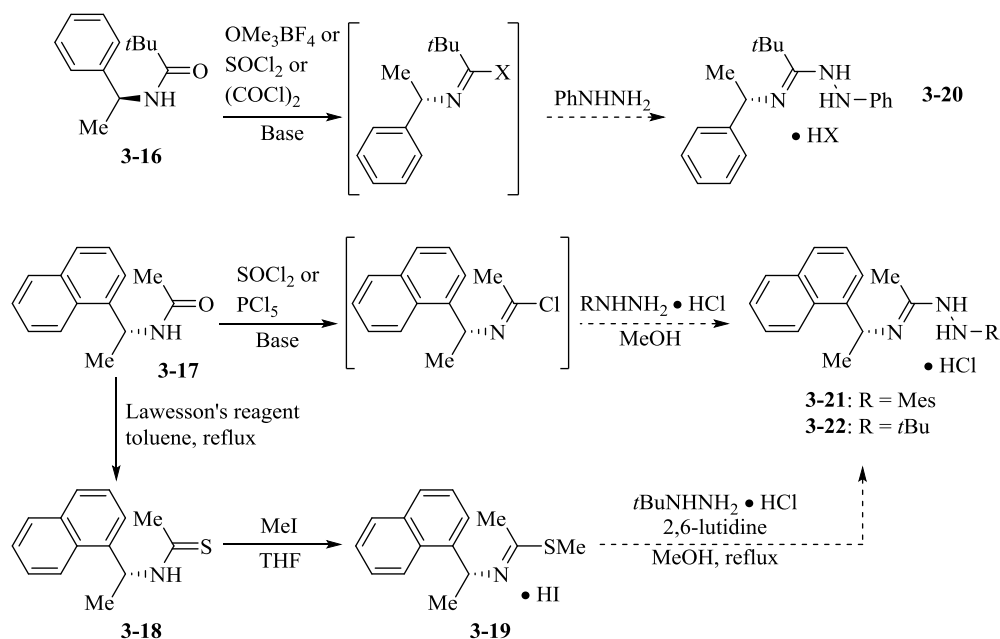


Figure 3.2 Proposed retrosynthesis of acyclic amidrazones.

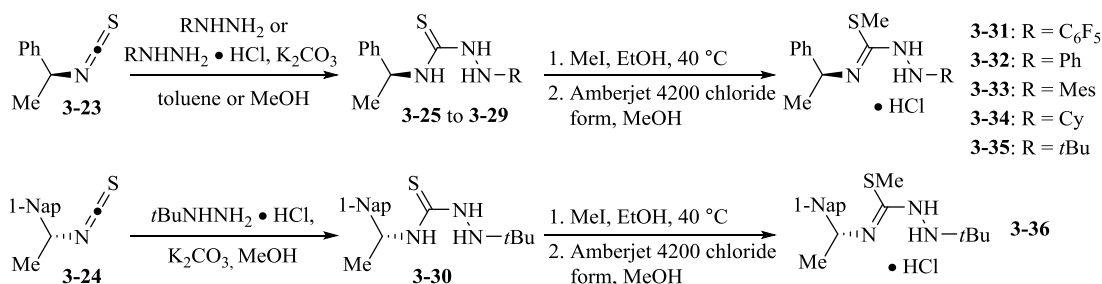
Amidrazones derived from chiral acyclic amides are more modular than those derived from cyclic amides, since the synthons are not restricted to chiral amino



Scheme 3.6 Attempted synthesis of acyclic amidrazones, **3-20** to **3-22**.

alcohols or pyrrolidinones (Figure 3.2). Therefore, the steric and electronic properties of acyclic amidrazones can be more easily tuned by varying the amine and acyl fragments. To assess the synthetic feasibility of such scaffolds, I aimed to synthesize amidrazones derived from non-racemic (*S*)-1-phenylethylamine and (*R*)-1-(1-naphthyl)ethylamine. Unfortunately, despite multiple amide-activation attempts, **3-20** to **3-22** could not be synthesized from the corresponding amides, **3-16** and **3-17**, and thioamide, **3-18** (Scheme 3.6). It was speculated that the enolizable methyl protons, and acidic benzylic proton caused side reactions which rendered the mixtures intractable.⁸²

To circumvent the unwanted reactivity, I turned my attention to non-racemic variants of thiolated amidrazones, derived from isothiocyanates **3-23** and **3-24**. Amidrazones **3-31** to **3-36** were prepared from **3-25** to **3-30** (Scheme 3.7), according to

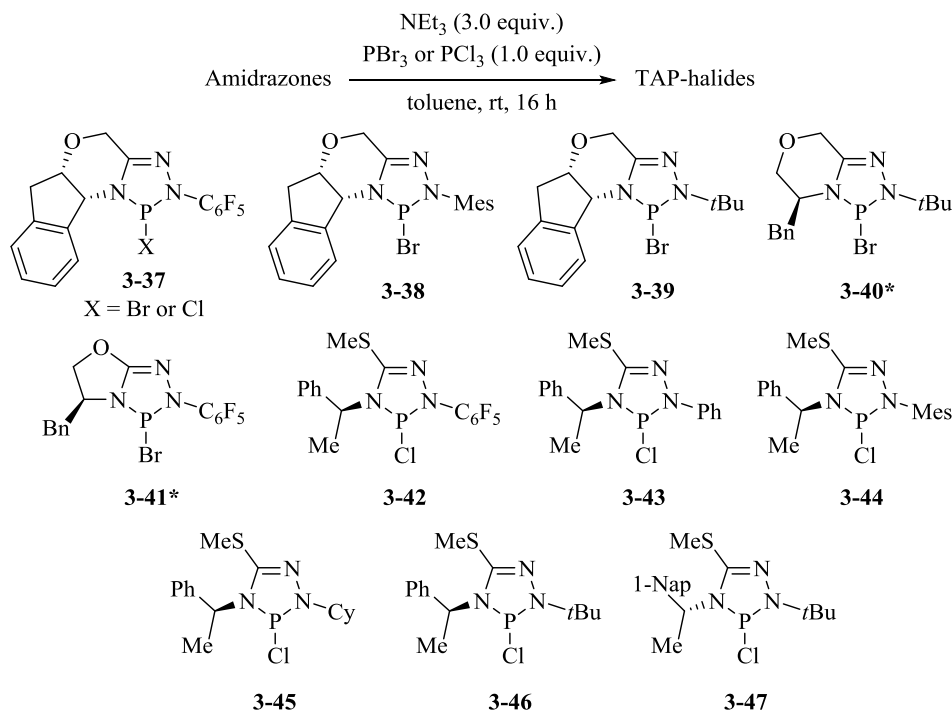


Scheme 3.7 Synthesis of thiolated amidrazones, **3-31** to **3-36**, with various electronically and sterically diverse hydrazinyl-substituents.

procedures analogous to the synthesis of **2-29**. In addition, the amidrazones were converted to the corresponding HCl salts using Amberjet[®] chloride resin to avoid anion scrambling with the TAP-halides. This proved to be a successful and efficient route for the preparation of thiolated, acyclic amidrazones.

3.4 Synthesis of Non-Racemic TAPs

3.4.1 Synthesis of TAP-Halides



* Products are isolated with oxygenated materials and side-products.

Scheme 3.8 Synthesis of non-racemic TAP-halides **3-37** to **3-47**.

A library of TAP-halides was prepared from the corresponding amidrazones using

the optimized conditions developed from the previous project (Scheme 3.8). TAP **3-37** was prepared from the corresponding amidrazone as both the chloride, and the bromide. Long-range $^4J_{P-F}$ and $^3J_{P-H}$ couplings are observed in the ^{31}P NMR spectrum for **3-37** as the TAP-Cl. However, similar coupling is not observed in the ^{31}P NMR spectrum for the corresponding TAP-Br. It was assumed no diastereomer was formed based on both the ^1H and ^{31}P NMR spectra, where only one set of NMR signals were observed.

Similarly, **3-38** and **3-39** were prepared from the corresponding amidrazones using the optimized conditions. Furthermore, the structure of **3-39** was confirmed by a single crystal X-ray diffraction experiment (Figure 3.3). The bromide is shown to be directed

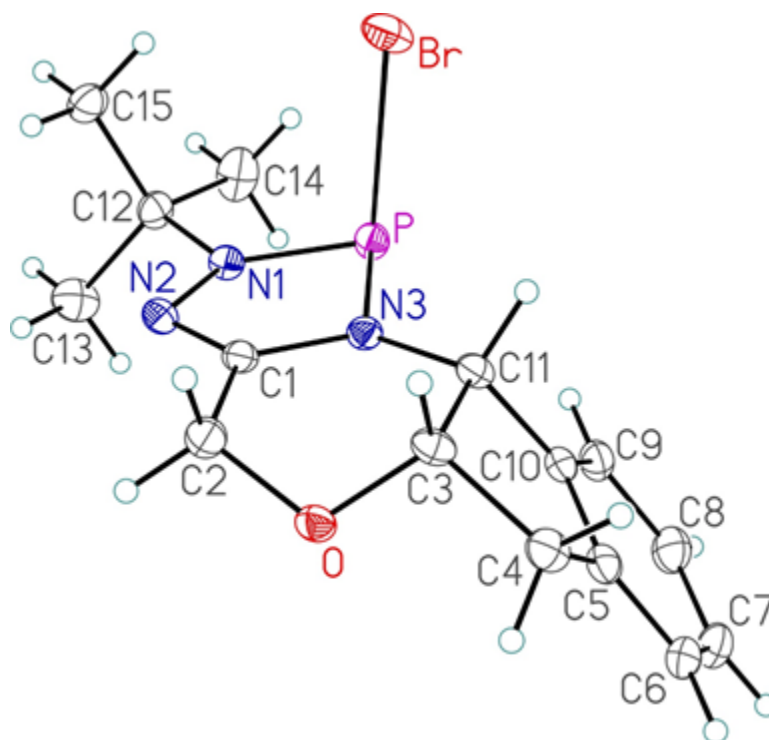
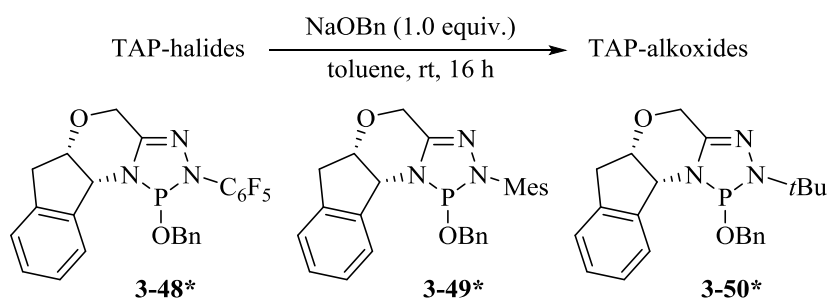


Figure 3.3 Molecular representation of **3-39**. Thermal ellipsoids are drawn at the 30% probability level for non-H atoms. Hydrogen atoms are shown with arbitrarily small thermal parameters. Selected bond lengths (Å), with estimated standard deviations in parentheses: P-Br 2.5111(7), P-N1 1.6610(19), P-N3 1.6895(19), N2-C1, 1.289(3).

away from the bulky indane group with a P-Br interatomic distance of 2.51 Å, which is comparable to previously observed P-Br interatomic distances for racemic TAPs.

Since amidrazones **3-9** and **3-10** were not pure to begin with, the attempted syntheses of **3-40** and **3-41** inevitably afforded impure mixtures as evidenced by the ^1H and ^{31}P NMR spectra. TAP-Cl's **3-42** to **3-47** were prepared from the corresponding amidrazones using the optimized conditions. The successful preparation of non-racemic thiolated TAPs represents a convenient approach towards synthesizing highly modular TAPs. Each substituent can be easily varied, or kept consistent, depending on how the electronic and steric properties affect the reactivity of TAPs, and stereoselectivity of TAP-catalyzed reactions.

3.4.2 Synthesis of TAP-Alkoxides



* Products are isolated with oxygenated materials and side-products.

Scheme 3.9 Attempted synthesis of TAP-alkoxides from the corresponding TAP-halides.

Since the synthesis of TAP-alkoxides often afforded mixtures of products and side-products, as evidenced in Chapter 2, only a handful of the non-racemic TAP-halides were converted to the corresponding TAP-alkoxides, **3-48** to **3-50** (Scheme 3.9).

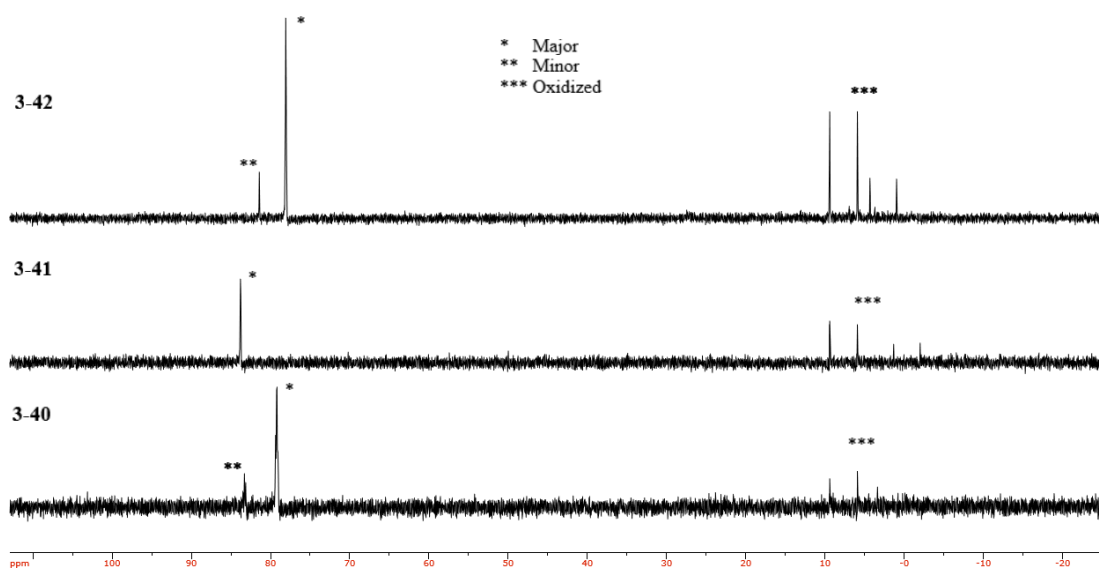


Figure 3.4 ^{31}P NMR spectra of **3-40** to **3-42** showing some minor signals neighbouring major signals, along with signals for oxidized materials.

Unfortunately, oxidized materials were also observed in the ^{31}P NMR spectra for the synthesis of non-racemic TAP-alkoxides. Furthermore, minor neighbouring ^{31}P NMR signals were often observed alongside with the major P-O signals (Figure 3.4). Therefore, it was hypothesized that diastereomers of the TAP-alkoxides were formed under the given conditions. Since P-O bonds are less ionic than P-halide bonds, it is likely that the chirality of the phosphorus atom does not scramble once the oxide is bound. Although I was not able to purify and isolate the desired TAP-alkoxides, their use in catalyzed asymmetric organic transformations was still investigated and is described in Chapter 4.

3.5 Conclusion

A number of cyclic and acyclic amidrazones were prepared following previously established procedures. Some amidrazones could not be isolated from impurities.

Nevertheless, cyclization with a phosphorus trihalide species was still carried out to form non-racemic TAP-halides. Three TAP-alkoxides were prepared; however, they could not be isolated from oxidized materials and potential diastereomers. The structure of **3-39** was confirmed by single crystal X-ray analysis. Reactivity and stereoselectivity of non-racemic TAP-catalyzed reactions is discussed in Chapter 4.

3.6 Experimental Section

3.6.1 General Considerations

Synthesis of triazaphospholene derivatives was carried out using oven dried Schlenk glassware under nitrogen. Filtration of triazaphospholene derivatives was conducted in a 2001 issue IT Glovebox (O₂ levels typically 4 ppm, H₂O levels typically 5 ppm). Nucleophilic substitution reactions were carried out in 4-dram oven dried scintillation vials equipped with magnetic stir bars and green Qorpak® PTFE lined caps. Substrates, reagents and solvents were loaded into vials inside the IT Glovebox. ¹H, ¹³C{¹H}, and ³¹P NMR data were collected at 300 K on Bruker AV-500 or AV-300 NMR spectrometers. Standard NMR tubes and caps were used. Caps on sensitive samples were overwrapped with PTFE tape. Chemical shifts are reported in ppm from phosphoric acid for ³¹P NMR. ¹H NMR spectra are referenced to residual non-deuterated NMR solvent (CHCl₃ = 7.26 ppm, CHD₂OD = 3.31 ppm, CHD₂CN = 1.94 ppm). ¹³C{¹H} NMR spectra are referenced to the central CDCl₃ peak (77.0 ppm),

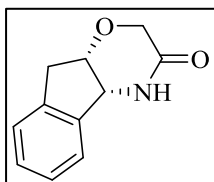
CD₃OD (49.0 ppm), and CD₃CN methyl peak (1.32 ppm). Melting points were acquired using an Electrothermal® apparatus and are uncorrected.

3.6.2 Crystallographic Solution and Refinement Details

Crystallographic data for **3-39** was obtained and solved by Dr. Robert McDonald (X-Ray Crystallography Laboratory, University of Alberta). The crystallographic data was obtained at -100 °C on a Bruker D8/Apex II CCD diffractometer using graphite-monochromated Mo K α ($\lambda = 0.71073$ Å) radiation, employing a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs for diffractometer operation, data collection, data reduction and absorption correction were supplied by Bruker. Gaussian integration (face-indexed) was employed as the absorption correction method. The structures were solved by use of intrinsic phasing methods, and were refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $Fo^2 \geq 2\sigma(Fo^2)$.

3.6.3 Synthesis and Characterization

(4a*R*,9a*S*)-4,4a,9,9a-Tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one (3-1).⁶⁴



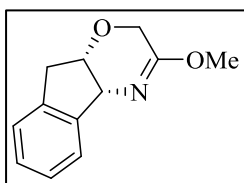
Sodium hydride (60% dispersion in mineral oil, 1.47 g, 36.9 mmol,

1.1 equiv.) was added to a 2-neck reaction flask equipped with a

water jacket condenser. The sodium hydride was washed twice with *n*-pentane (70 mL x 2), and each time the solvent was removed *via* cannula. THF (60 mL) was added, then

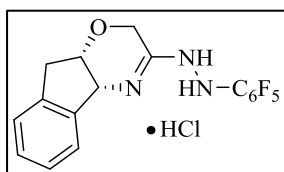
the suspension was cooled with an ice bath for 0.5 h and stirred. (1*R*,2*S*)-(-)-*Cis*-1-amino-2-indanol (5.00 g, 33.5 mmol, 1.0 equiv.) was added to the stirring suspension at once, followed by an additional aliquot of THF (40 mL) to rinse the powders off the side of the flask. The mixture was stirred for 0.5 h, then it was stirred under reflux for 2 h. After 2 h, the mixture was once again cooled with an ice bath for 10 min, and ethyl chloroacetate (3.59 mL, 33.5 mmol, 1.0 equiv.) was added dropwise. The mixture was stirred overnight at rt then stirred under reflux again for an additional 2 h. The mixture was cooled to rt, then brine (10 mL) was added to quench the reaction. THF was removed *in vacuo*, then the residue was diluted with EtOAc (100 mL) and washed with brine (30 mL). The residue was further extracted with EtOAc (100 mL x 3), and the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to afford a tan solid. To the flask containing the crude solid was added a stir bar and *n*-hexane (100 mL). The mixture was stirred under reflux for 1 h. The resultant mixture was filtered and washed with *n*-hexane to afford the product as an off-white solid (4.74 g, 75%). ¹H NMR (500 MHz, CDCl₃) δ: 7.26 (s, 4H), 4.78 (t, *J* = 4.0 Hz, 1H), 4.54 (t, *J* = 4.5 Hz, 1H), 4.16 (s, 2H), 3.22 (m, 1H), 3.10 (d, *J* = 17.0 Hz, 1H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 169.3, 140.8, 139.4, 128.5, 127.5, 125.4, 123.8, 76.3, 66.6, 58.9, 37.6.

(4aR,9aS)-3-Methoxy-2,4a,9,9a-tetrahydroindeno(2,1-b)(1,4)oxazine (3-2):⁷⁹



3-1 (1.00 g, 5.29 mmol, 1.0 equiv.) was added to a suspension of trimethyloxonium tetrafluoroborate (0.782 g, 5.29 mmol, 1.0 equiv.) in DCM (7 mL), then the mixture was stirred overnight at rt. The mixture was cooled with an ice bath for 10 min, then saturated aqueous NaHCO₃ (15 mL) was added over a period of 1 h while cooling was maintained. The biphasic mixture was extracted with DCM (20 mL x 2), then the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to afford the product as a pale brown solid (1.02 g, 5.02 mmol, 94%) which was used without further purification. ¹H NMR (500 MHz, CDCl₃) δ : 7.49 (m, 1H), 7.29-7.21 (m, 3H), 4.88 (m, 1H), 4.29 (t, *J* = 4.5 Hz, 1H), 3.99 (m, 1H), 3.93 (m, 1H), 3.79 (s, 3H), 3.19 (m, 1H), 3.01 (m, 1H).

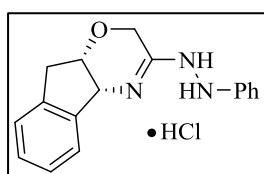
2-Pentafluorophenyl-1-[(4aR,9aS)-4,4a,9,9a-tetrahydroindeno(2,1b)(1,4)-



oxazin-3(2H)-ylidene]hydrazinium chloride (3-3):^{78a} **3-1** (0.703 g, 3.72 mmol, 1.0 equiv.) was added to a suspension of trimethyloxonium tetrafluoroborate (0.550 g, 3.72 mmol, 1.0 equiv.) in DCM (10 mL), then the mixture was stirred overnight at rt. Pentafluorophenylhydrazine (0.737 g, 3.72 mmol, 1.0 equiv.) was added, then the mixture was stirred for 48 h. Saturated aqueous NaHCO₃ (10 mL) was added, then the biphasic mixture was extracted with DCM (10 mL x 3). The combined organic layers were dried with anhydrous Na₂SO₄, then the

solvent was removed *in vacuo* to afford a residue which was dissolved in toluene (40 mL). HCl (1.0 M in diethyl ether, 6.00 mL, 1.6 equiv.) was added to create a suspension. The suspension was filtered to afford the crude product as a yellow solid (0.586 g, 1.44 mmol, 39%). The ¹H NMR chemical shifts are broad, therefore are not reported. HRMS (ESI) m/z calc'd for C₁₇H₁₃F₅N₃O [M-Cl]⁻: 370.0973; found: 370.0968.

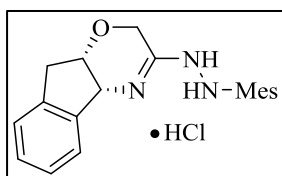
Attempted synthesis of 2-phenyl-1-[(4*aR*,9*aS*)-4,4*a*,9,9*a*-tetrahydroindeno-



(2,1b)(1,4)-oxazin-3(2*H*)-ylidene]hydrazinium chloride (3-4):⁷⁷ **3-1** (0.300 g, 1.59 mmol, 1.0 equiv.) was added to a

suspension of trimethyloxonium tetrafluoroborate (0.235 g, 1.59 mmol, 1.0 equiv.) in DCM (6 mL), then the mixture was stirred overnight at rt. Phenylhydrazine (0.156 mL, 1.59 mmol, 1.0 equiv.) was added, then the mixture was stirred for 16 h. The solvent was removed *in vacuo* to afford a red residue that was too hygroscopic to attempt purification with.

2-Mesityl-1-[(4*aR*,9*aS*)-4,4*a*,9,9*a*-tetrahydroindeno(2,1b)(1,4)-oxazin-3(2*H*)-

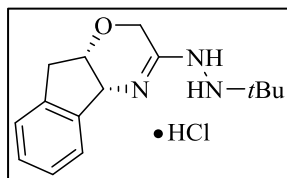


ylidene]hydrazinium chloride (3-5):⁷⁹ **3-2** (0.300 g, 1.48 mmol, 1.0 equiv.) was added to a solution of mesitylhydrazine

hydrochloride (0.276 g, 1.48 mmol, 1.0 equiv.) in MeOH (7 mL). After the mixture became homogeneous, HCl (2.0 M in diethyl ether, 0.01 mL, 0.02 mmol, 0.01 equiv.) was added, then the mixture was stirred at rt for 1 h. The mixture was then stirred under

reflux for 48 h. The mixture was cooled to rt, then the solvent was removed *in vacuo*. The residue was dissolved in minimal DCM, then diethyl ether (30 mL) was added to form a suspension. The suspension was filtered, then this process was repeated twice more to afford the product as a yellow solid (0.402 g, 1.12 mmol, 76%). ¹H NMR (500 MHz, acetonitrile-*d*₃) δ: 7.71 (m, 1H), 7.29-7.26 (m, 3H), 6.81 (s, 2H), 4.91 (m, 1H), 4.70 (leaning d, 1H), 4.54 (m, 1H), 4.34 (leaning d, 1H), 3.23 (m, 1H), 2.98 (leaning d, 1H), 2.22 (s, 6H), 2.19 (s, 3H). ¹³C{¹H} NMR (125 MHz, acetonitrile-*d*₃) δ: 161.0, 140.86, 140.85, 138.9, 136.2, 133.2, 130.4, 129.4, 128.0, 126.0, 125.9, 78.3, 61.7, 57.4, 38.3, 20.8, 18.7. HRMS (ESI) *m/z* calc'd for C₂₀H₂₄N₃O [M-Cl]⁻: 322.1914; found: 322.1904.

2-*tert*-Butyl-1-[(4*aR*,9*aS*)-4,4*a*,9,9*a*-tetrahydroindeno(2,1*b*)(1,4)-oxazin-

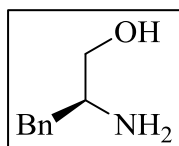


3(2*H*)-ylidene]hydrazinium chloride (3-6): 3-2 (1.02 g, 4.99 mmol, 1.1 equiv.) was added to a solution of *tert*-

butylhydrazine hydrochloride (0.541 g, 4.34 mmol, 1.0 equiv.) in MeOH (15 mL). After the mixture became homogeneous, HCl (2.0 M in diethyl ether, 0.04 mL, 0.08 mmol, 0.02 equiv.) was added, then the mixture was stirred at rt for 1 h. The mixture was then stirred under reflux for 66 h. The mixture was cooled to rt, then the solvent was removed *in vacuo*. EtOAc (15 mL) was added to the residue, and the mixture was stirred under reflux with vigorous stirring for 1 h to form a suspension. The mixture was cooled with

an ice bath, then the product was collected by suction filtration to afford the product as an off-white solid (0.538 g, 1.82 mmol, 42%). As an alternative purification procedure, the residue can be subjected to column chromatography with 230-400 mesh silica, and eluted with a mixture of DCM and MeOH to afford the product. ^1H NMR (500 MHz, methanol- d_4) δ : 7.45 (d, 7.0 Hz, 1H), 7.29-7.25 (m, 3H), 4.91 (m, 1H), 4.70 (m, 1H), 4.55 (AB q, 2H), 3.31 (dd, overlapped with solvent signal, 1H), 3.06 (m, 1H), 1.19 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, methanol- d_4) δ : 164.3, 141.1, 140.9, 129.7, 128.2, 126.2, 125.1, 78.6, 61.8, 58.0, 55.7, 38.5, 27.2. HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}$ [$\text{M}-\text{Cl}$] $^-$: 260.1757; found: 260.1764.

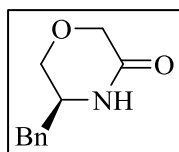
(S)-2-Amino-3-phenyl-1-propanol:⁸³ (*S*)-Phenylalanine (10.0 g, 60.5 mmol,



1.0 equiv.) was added to a suspension of sodium borohydride (10.63 g, 121.1 mmol, 2.0 equiv.) in THF (150 mL). THF (50 mL) was used to rinse the amino acid off the side of the reaction flask. The mixture was cooled with an ice bath and stirred. Iodine (15.4 g, 60.5 mmol, 1.0 equiv.) was added to the mixture in portions to prevent vigorous bubbling, then the mixture was stirred overnight at rt. After which, the mixture was stirred under reflux for 18 h. The mixture was cooled with an ice bath and stirred for 1 h. MeOH (100 mL) was added to quench the reaction. The resulting solution was stirred at rt for 2 h before the volatiles were removed *in vacuo*. Distilled water (100 mL) and KOH (24.0 g, 427.7 mmol, 7.1 equiv.) was added to the

residue, then the mixture was stirred at rt for 4 h. The mixture was extracted with DCM (330 mL x 3), then the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo*, and recrystallization in EtOAc afforded the product as colourless needles (5.03 g, 33.3 mmol, 55%). ¹H NMR (500 MHz, CDCl₃) δ: 7.32-7.29 (m, 5H), 3.62 (dd, *J* = 10.5, 4 Hz, 1H), 3.38 (dd, *J* = 10.5, 7 Hz, 1 H), 3.11 (m, 1H), 2.78 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.52 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.14 (br s, 1H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 138.8, 129.3, 128.7, 126.5, 66.3, 54.3, 40.9.

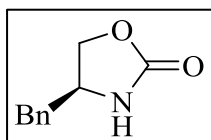
(S)-5-Benzylmorpholin-3-one (3-7):⁸⁴ (S)-2-Amino-3-phenyl-1-propanol



(7.00 g, 46.3 mmol, 1.0 equiv.) was added to a suspension of NaH (2.04 g, 50.9 mmol, 1.1 equiv.) in THF (100 mL), then the mixture was stirred at rt for 0.5 h. Ethyl chloroacetate (4.95 mL, 46.3 mmol, 1.0 equiv.) was added dropwise to the mixture over 5 min, then the mixture was stirred at rt for 2 h. The mixture was stirred under reflux for 3 h, then stirred at rt for 16 h. The solvent was removed *in vacuo*, then a mixture of *n*-hexane (30 mL) and ethyl acetate (70 mL) was added. The organic layer was washed with 2 M HCl (30 mL), then dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo*, then the residue was subjected to column chromatography with 230-400 mesh silica, eluted with a mixture of DCM and MeOH to afford the product as a colourless solid (5.84 g, 30.5 mmol, 66%). ¹H NMR (500 MHz, CDCl₃) δ: 7.36-7.33 (m, 2H), 7.28 (m, 1H), 7.20-7.18 (m, 2H), 6.07 (br s, 1H),

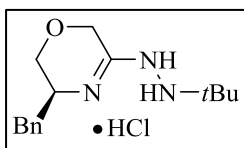
4.17 (AB q, 2H), 3.92 (dd, $J = 7.0, 4.0$ Hz, 1H), 3.77 (m, 1H), 3.56 (dd, $J = 12.0, 7.0$ Hz, 1H), 2.89 (dd, $J = 13.5, 7.0$ Hz, 1H), 2.71 (dd, $J = 13.5, 8.5$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 168.8, 136.0, 129.3, 129.2, 127.4, 68.1, 67.9, 53.0, 39.5.

(S)-4-Benzyl-1,3-oxazolidin-2-one (3-8): ⁸⁵ (S)-2-Amino-3-phenyl-1-



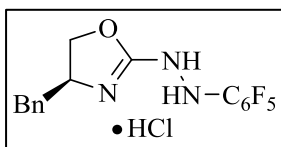
propanol (2.00 g, 13.2 mmol, 1.0 equiv.) was combined with diethyl carbonate (5.20 mL, 42.9 mmol, 3.3 equiv.) in a round bottom flask equipped with a short path distillation apparatus. The mixture was stirred under reflux for 3 h while the by-product, EtOH, was removed *via* distillation. The mixture was stirred overnight at rt, then stirred under reflux again for 5 h. After the mixture cooled to rt, saturated aqueous NaHCO_3 (50 mL) was added, then the mixture was extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL) and dried with anhydrous Na_2SO_4 . The solvent was removed *in vacuo*, then the residue was subjected to column chromatography with 230-400 mesh silica, eluted with a mixture of DCM and MeOH to afford the product as a colourless solid (1.00 g, 43%). ^1H NMR (500 MHz, CDCl_3) δ : 7.33 (m, 2H), 7.27 (m, 1H), 7.17 (m, 2H), 5.88 (br s, 1H), 4.42, (t, $J = 8$ Hz, 1H), 4.15-4.07 (m, 2H), 3.87 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 159.6, 136.1, 129.1, 127.3, 69.7, 53.9, 41.5.

(S)- 3-Benzyl- 5-(2-tert-butylhydrazinyl)-2H-1,4-oxazine hydrochloride (3-9):



3-7 (1.00 g, 5.23 mmol, 1.0 equiv.) was added to a suspension of trimethyloxonium tetrafluoroborate (0.773 g, 5.23 mmol, 1.0 equiv.) in DCM (15 mL), then the mixture was stirred overnight at rt. The mixture was cooled with an ice bath for 0.5 h, then saturated aqueous NaHCO₃ (10 mL) was added. The biphasic mixture was extracted with DCM (10 mL), then dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to afford a residue which was dissolved in MeOH (15 mL). *tert*-Butylhydrazine hydrochloride (0.651 g, 5.23 mmol, 1.0 equiv.) was added, then the mixture was stirred at rt for 1 h. HCl (2.0 M in diethyl ether, 0.26 mL, 0.52 mmol, 0.1 equiv.) was added, then the mixture was stirred at rt for 0.5 h. The mixture was stirred under reflux for 65 h, then the solvent was removed *in vacuo*. The residue was dissolved in a minimal amount of DCM (5 mL), then diethyl ether (20 mL) was added to form a suspension. The suspension was filtered to afford the product (0.615 g, contaminated with 23% of *tert*-butylhydrazine hydrochloride), which was used without further purification. ¹H NMR (500 MHz, methanol-*d*₄) δ: 7.35-7.25 (m, 5H), 4.57 (AB q, 2H), 3.85-3.76 (m, 3H), 3.05 (m, 1H), 2.93 (m, 1H), 1.33 (*tert*-butylhydrazine hydrochloride), 1.14 (s, 9H). HRMS (ESI) calc'd for C₁₅H₂₄N₃O [M-Cl]⁻: 262.1914; found: 262.1922.

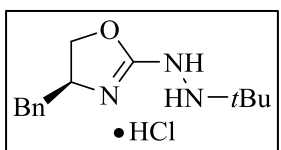
(S)-4-Benzyl-4,5-dihydro-2-(2-pentafluorophenylhydrazinyl)oxazole hydrochloride (3-10): **3-8** (0.332 g, 1.87 mmol, 1.0 equiv.) was added to a suspension of



trimethyloxonium tetrafluoroborate (0.277 g, 1.87 mmol, 1.0 equiv.) in DCM (5 mL), then the mixture was stirred overnight

at rt. Pentafluorophenylhydrazine (0.371 g, 1.87 mmol, 1.0 equiv.) was added, then the mixture was stirred overnight at rt. The mixture was cooled with an ice bath for 0.5 h, and saturated aqueous NaHCO₃ (5 mL) was added, then the mixture was stirred for 1 h. The biphasic mixture was extracted with DCM (10 mL x 2), then the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo*, then the residue was dissolved in a mixture of diethyl ether (5 mL) and toluene (5 mL). HCl (2.0 M in diethyl ether, 0.94 mL, 1.87 mL, 1.0 equiv.) was added to create a suspension, then the mixture was stirred for 6 h. The suspension was filtered to afford the crude product, which was used without further purification. HRMS (ESI) *m/z* calc'd for C₁₆H₁₃F₅N₃O [M-Cl]⁻: 358.0973; found: 358.0980.

Attempted synthesis of (*S*)-4-benzyl-2-(2-*tert*butylhydrazinyl)-4,5-dihydro-

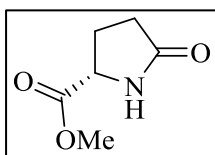


oxazole hydrochloride (**3-11**): **3-8** (1.00 g, 5.64 mmol, 1.0 equiv.) was added to a suspension of trimethyloxonium

tetrafluoroborate (0.918 g, 6.21 mmol, 1.1 equiv.) in DCM (15 mL), then the mixture was stirred overnight at rt. The mixture was cooled with an ice bath for 0.5 h, then saturated aqueous NaHCO₃ (10 mL) was added. The biphasic mixture was extracted with DCM (10 mL), then the organic layer dried with anhydrous Na₂SO₄. The solvent

was removed *in vacuo* to afford a residue which was dissolved in MeOH (15 mL). *tert*-Butylhydrazine hydrochloride (0.391 g, 3.13 mmol, 1.0 equiv.) was added, then the mixture was stirred at rt for 0.5 h. HCl (2.0 M in diethyl ether, 0.08 mL, 0.157 mmol, 0.05 equiv.) was added, then the mixture was stirred at rt for 0.5 h. The mixture was stirred under reflux for 48 h, and rt for 16 h, then the solvent was removed *in vacuo*. The residue was dissolved in a minimal amount of DCM (3 mL), then diethyl ether (20 mL) was added to form a suspension, which was filtered. No product formation was observed.

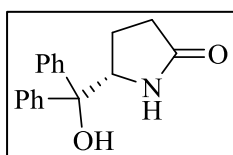
Methyl (*S*)-pyroglutamate (3-12):⁸¹ SOCl₂ (1.171 mL, 100.7 mmol, 1.3 equiv.)



was added to a solution of (*S*)-pyroglutamic acid (10.0 g, 77.5 mmol, 1.0 equiv.) in MeOH (50 mL) at 0 °C, then the mixture was stirred

overnight at rt. The solvent was removed *in vacuo* to afford the product as a clear oil (11.1 g, 77.5 mmol, quantitative). ¹H NMR (500 MHz, CDCl₃) δ: 4.33 (m, 1H), 3.82 (s, 3H), 2.56-2.27 (m, 3H).

(*S*)-5-Hydroxydiphenylmethyl-2-pyrrolidinone (3-13):⁸¹ 3-12 (1.5 mL, 12.9

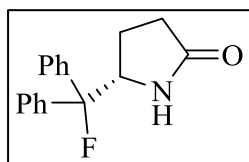


mmol, 1.0 equiv.) was dissolved in THF (25 mL) and cooled to -84 °C. PhMgBr (3.0 M in diethyl ether, 17.1 mL, 51.3 mmol, 4.0

equiv.) was added dropwise over 20 min, then the mixture was stirred for 42 h at rt. Aqueous saturated NH₄Cl (25 mL) was added to quench the reaction. A mixture of *n*-

hexane (20 mL) and ethyl acetate (30 mL) was added, then the biphasic mixture was extracted. The aqueous layer was extracted twice more with ethyl acetate (50 mL x 2), then the combined organic layers were washed with brine (20 mL), and dried with anhydrous Na₂SO₄. The volatiles were removed *in vacuo*, then the residue was recrystallized in hot ethanol (30 mL) to afford the product as a colourless solid (2.06 g, 7.69 mmol, 60%). ¹H NMR (500 MHz, CDCl₃) δ: 7.49-7.43 (m, 4H), 7.37-7.28 (m, 4H), 7.22 (m, 1H), 5.40 (br s, 1H), 4.74 (m, 1H), 2.90 (br s, 1H), 2.35-2.23 (m, 2H), 2.12 (m, 1H), 1.97 (m, 1H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 179.1, 145.2, 143.0, 129.1, 128.5, 127.8, 127.4, 125.9, 125.8, 78.9, 60.7, 30.3, 21.8.

(S)-5-Fluorodiphenylmethyl-2-pyrrolidinone (3-14):⁸¹ Diethylaminosulfur

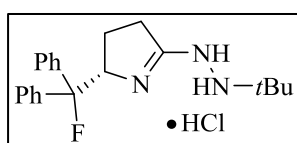


trifluoride (DAST) (0.691 mL, 5.24 mmol, 2.0 equiv.) was added dropwise to a mixture of **3-13** (0.700 g, 2.62 mmol, 1.0 equiv.) in

DCM (20 mL) at 0 °C, then the mixture was stirred overnight at rt. Aqueous saturated NaHCO₃ (10 mL) was added, then the biphasic mixture was extracted. The aqueous layer was extracted twice more with DCM (10 mL x 2), then the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo*, then the residue was subjected to column chromatography with 230-400 mesh silica, eluted with a mixture of *n*-hexane and ethyl acetate to afford the product as a yellow solid (0.452 g, 1.67 mmol, 64%). ¹H NMR (500 MHz, CDCl₃) δ: 7.40-7.29 (m, 10H), 5.51 (br s,

1H), 4.63 (m, 1H), 2.34-2.16 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 178.3, 141.0 (d, $J = 24.3$ Hz), 140.5 (d, $J = 22.4$ Hz), 129.0, 128.8, 128.3 (d, $J = 2.6$ Hz), 125.4 (d, $J = 8.4$ Hz), 125.2 (d, $J = 9.4$ Hz), 99.3 (d, $J = 183.9$ Hz), 60.0 (d, $J = 22.3$ Hz), 29.8, 22.3 (d, $J = 3.5$ Hz). ^{19}F NMR (470 MHz, CDCl_3) δ : 169.2 (s).

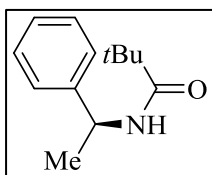
Attempted synthesis of (*S*)-5-fluorodiphenylmethyl-2-pyrrolidinone 2-*tert*-



butylhydrazone hydrochloride (3-15): 3-14 (0.300 g, 1.11 mmol, 1.0 equiv.) was added to a suspension of

trimethyloxonium tetrafluoroborate (0.165 g, 1.11 mmol, 1.0 equiv.) in DCM (10 mL), then the mixture was stirred overnight at rt. The mixture was cooled with an ice bath, and saturated aqueous NaHCO_3 (10 mL) was added, then the mixture was stirred for 0.5 h. The biphasic mixture was extracted with DCM (5 mL x 2), then the combined organic layers were dried with anhydrous Na_2SO_4 . The solvent was removed *in vacuo*, then the residue was dissolved in MeOH (10 mL). *tert*-Butylhydrazine hydrochloride (0.139 g, 1.11 mmol, 1.0 equiv.) and HCl (2.0 M in diethyl ether, 0.05 mL, 0.111 mmol, 0.1 equiv.) were added, then the mixture was stirred under reflux for 120 h. The solvent was removed *in vacuo*, then the residue was dissolved in DCM (4 mL) and diethyl ether (10 mL) were added to form a suspension, which was filtered. No product formation was observed.

(S)-N-(1-Phenylethyl)pivalamide (3-16):⁸⁶ (S)-1-Phenylethylamine (3.19 mL,

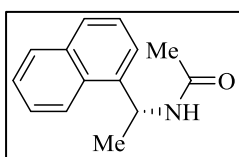


24.8 mmol, 1.0 equiv.) was added to a solution of NEt₃ (6.90 mL,

49.5 mmol, 2.0 equiv.) in DCM (50 mL) cooled with an ice bath.

Pivaloyl chloride (3.38 mL, 27.2 mmol, 1.1 equiv.) was added dropwise, then the mixture was stirred for 64 h at rt. DCM (50 mL) and water (70 mL) were added, then the biphasic mixture was separated. The organic layer was dried with anhydrous Na₂SO₄, then the solvent was removed *in vacuo*. The crude solid was washed with water (20 mL), *n*-hexane (20 mL), and dried in a desiccator over P₂O₅ at 30 torr to afford the product as a colourless solid (4.60 g, 22.4 mmol, 91%). ¹H NMR (500 MHz, CDCl₃) δ: 7.35-7.24 (m, 5H), 5.80 (br s, 1H), 5.11 (p, *J* = 7.0 Hz, 1H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.20 (s, 9H). ¹³C {¹H} NMR (125 MHz, CDCl₃) δ: 177.50, 143.65, 128.76, 127.32, 126.12, 48.56, 38.70, 27.67, 21.83.

(R)-N-(1-Naphthylethyl)acetamide (3-17):⁸⁷ (R)-1-Naphthylethylamine (3.00



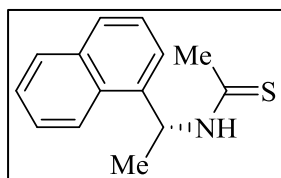
mL, 18.6 mmol, 1.0 equiv.) was added dropwise to a solution of

acetic anhydride (1.76 mL, 18.6 mmol, 1.0 equiv.) in DCM (15 mL)

at 0 °C, then the mixture was stirred overnight at rt. Aqueous saturated NaHCO₃ (10 mL) was added, then the biphasic mixture was extracted with DCM (10 mL x 2). The combined organic layers were dried washed with 2 M HCl (15 mL), then dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to afford the product as a

colourless solid (3.51 g, 16.5 mmol, 88%). ^1H NMR (500 MHz, CDCl_3) δ : 8.09 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.55-7.42 (m, 4H), 5.91 (p, J = 7.0 Hz, 1H), 5.76 (br, 1H), 1.94 (s, 3H), 1.65 (d, J = 6.5 Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, CDCl_3) δ : 169.0, 138.4, 134.1, 131.3, 128.9, 128.5, 126.7, 126.0, 125.3, 123.6, 122.7, 44.8, 33.5, 20.8.

(*R*)-*N*-(1-Naphthylethyl)thioacetamide (3-18): Lawesson's reagent (2.85 g,

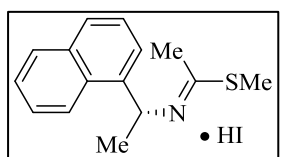


7.03 mmol, 1.0 equiv.) was added to a mixture of **3-17** (1.50 g,

7.03 mmol, 1.0 equiv.) in toluene (25 mL), then the mixture was

stirred under reflux overnight. The solvent was removed *in vacuo*, then the residue was subjected to column chromatography with 230-400 mesh silica, eluted with a mixture of *n*-hexane and ethyl acetate to afford the product as a yellow solid (1.03 g, 4.49 mmol, 64%). HRMS (ESI) calc'd for $\text{C}_{14}\text{H}_{15}\text{NNaS}$ [$\text{M}+\text{Na}$] $^+$: 252.0817; found: 252.0812.

***S*-Methyl-*N*-[(*R*)-1-naphthylethyl]thioacetimidate hydroiodide (3-19)**: MeI



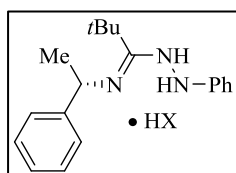
(0.839 mL, 13.5 mmol, 3.0 equiv.) was added to a mixture of **3-**

18 (1.03 g, 4.49 mmol, 1.0 equiv.) in THF (15 mL), then the

mixture was stirred overnight at rt. Diethyl ether (20 mL) was added to the mixture to form a suspension, which was filtered to afford the product as a yellow solid (0.590 g, 1.59 mmol, 35%). ^1H NMR (500 MHz, methanol- d_4) δ : 8.07 (d, J = 8.5 MHz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.92 (m, 1H), 7.64 (m, 1H), 7.59-7.51 (m, 3H), 5.87 (q, J = 6.5 Hz,

1H), 2.81 (s, 3H), 2.75 (s, 3H), d, $J = 7.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, methanol- d_4) δ : 134.2, 134.1, 130.2, 129.1, 129.0, 126.9, 126.0, 125.3, 122.9, 121.6, 55.1, 22.9, 19.8, 14.7. HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{18}\text{NS}$ $[\text{M}-\text{I}]^+$: 244.1154; found: 244.1157.

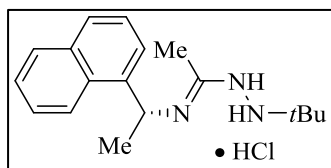
Attempted synthesis of *N*-phenyl-*N'*-[(*S*)-1-phenylethyl]pivalamidrazone



hydrochloride or hydrogen tetrafluoroborate (3-20): (a) 3-16

(0.300 g, 1.46 mmol, 1.0 equiv.) was added to a suspension of trimethyloxonium tetrafluoroborate (0.216 g, 1.46 mmol, 1.0 equiv.) in DCM (5 mL), then the mixture was stirred overnight at rt. Phenylhydrazine (0.144 mL, 1.46 mmol, 1.0 equiv.) was added, then the mixture was stirred at rt for 48 h. The solvent was removed *in vacuo*. No product formation was observed. **(b) 3-16** (1.20 g, 5.85 mmol, 1.0 equiv.) was added to SOCl_2 (2.13 mL, 29.2 mmol, 5.0 equiv.), then the mixture was stirred under reflux for 2 h. The volatiles were removed *in vacuo*, then the residue was dissolved in THF (15 mL). NEt_3 (0.978 mL, 7.01 mmol, 1.2 equiv.) and phenylhydrazine (0.576 mL, 5.85 mmol, 1.0 equiv.) were added, then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo*, then the residue was analyzed by LRMS to reveal no formation of product. **(c)** Oxalyl chloride (0.206 mL, 2.44 mmol, 1.0 equiv.) was added dropwise to a mixture of **3-20** (0.500 g, 2.44 mmol, 1.0 equiv.) and 2,6-lutidine (0.284 mL, 2.68 mmol, 1.1 equiv.) in DCM (20 mL) at 0 $^\circ\text{C}$, then the mixture was stirred for 1 h. The volatiles were removed *in vacuo*, then

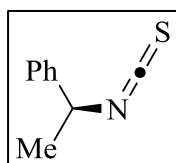
Attempted synthesis of *N*-(*tert*-butyl)-*N'*-[(*R*)-1-naphthylethyl]pival-



amidrazone hydrochloride (3-22): (a) PCl_5 (0.586 g, 2.81 mmol, 1.0 equiv.) was added to a mixture of **3-17** (0.600 g,

2.81 mmol, 1.0 equiv.) in toluene (10 mL), then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo*, then the residue was dissolved in toluene (10 mL). The mixture was cooled with an ice bath, and NEt_3 (0.392 mL, 2.81 mmol, 1.0 equiv.) was added, then the mixture was stirred for 2 h. The mixture was filtered, and *tert*-butylhydrazine hydrochloride (0.350 g, 2.81 mmol, 1.0 equiv.) was added to the filtrate. MeOH (10 mL) and HCl (2.0 M in diethyl ether, 0.02 mL, 0.4 mmol, 0.14 equiv.) were added, then the mixture was stirred under reflux for 72 h. The solvent was removed *in vacuo* to reveal no formation of product. (b) 2,6-Lutidine (0.156 mL, 1.35 mmol, 1.0 equiv.) and *tert*-butylhydrazine hydrochloride (0.168 g, 1.35 mmol, 1.0 equiv.) were added to a mixture of **3-19** (0.500 g, 1.35 mmol, 1.0 equiv.) in MeOH (5 mL), then the mixture was stirred under reflux for 16 h. The solvent was removed *in vacuo* to afford a residue that was analyzed by LRMS to reveal no formation of product.

(S)-1-Phenylethyl isothiocyanate (3-23):⁸⁸ CS_2 (3.27 mL, 54.3 mmol, 1.0

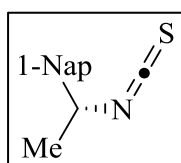


equiv.) was added to a mixture of (*S*)-1-phenylethylamine (7.00 mL, 54.3 mmol, 1.0 equiv.) and NEt_3 (25.0 mL, 179 mmol, 3.3 equiv.) in

THF (50 mL) at 0 °C, then the mixture was stirred at rt for 2.5 h. *p*-Toluenesulfonyl

chloride (11.4 g, 59.7 mmol, 1.1 equiv.) was added to form a suspension, then the mixture was stirred for 0.5 h. The suspension was filtered, then the filtrate was concentrated and washed with 1 M HCl (20 mL). The aqueous layer was extracted with diethyl ether (30 mL x 2), then the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to afford a residue which was subjected to a short silica plug, eluted with a mixture of *n*-hexane and ethyl acetate to afford the product as a yellow oil (8.32 g, 51.0 mmol, 94%). ¹H NMR (500 MHz, CDCl₃) δ: 7.40-7.37 (m, 2H), 7.34-7.31 (m, 3H), 4.91 (q, *J* = 7.0 Hz, 1H), 1.67 (d, *J* = 6.5 Hz, 3H). ¹³C{¹H} (125 MHz, CDCl₃) δ: 140.3, 129.1, 128.4, 125.6, 57.2, 25.1.

(*R*)-1-Naphthylethyl isothiocyanate (3-24): CS₂ (5.62 mL, 93.5 mmol, 1.0

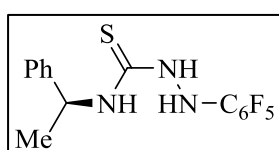


equiv.) was added to a mixture of (*R*)-1-naphthylethylamine (15.0 mL, 93.5 mmol, 1.0 equiv.) and NEt₃ (43.0 mL, 308 mmol, 3.3 equiv.) in

THF (90 mL) at 0 °C, then the mixture was stirred at rt for 2.5 h. *p*-Toluenesulfonyl chloride (19.6 g, 103 mmol, 1.1 equiv.) was added to form a suspension, then the mixture was stirred for 0.5 h. The suspension was filtered, then the solvent of the filtrate was removed *in vacuo* to afford a residue which was subjected to a short silica plug, eluted with a mixture of *n*-hexane and ethyl acetate to afford a residue that was taken up in hot *n*-hexane (60 mL), and cooled to -20 °C to afford a suspension. The suspension was filtered to afford the product as a yellow solid (12.4 g, 58.0 mmol, 62%). ¹H NMR

(500 MHz, CDCl₃) δ : 7.90-7.87 (m, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.56-7.46 (m, 3H), 5.66 (q, J = 7.0 Hz, 1H), 1.81 (d, J = 6.5 Hz, 3H). ¹³C{¹H} (125 MHz, CDCl₃) δ : 135.5, 134.0, 129.6, 129.3, 129.1, 126.8, 126.1, 125.6, 123.1, 122.3, 54.2, 24.1.

(S)-N-(1-Phenylethyl)-2-pentafluorophenylhydrazine carbothioamide (3-25):



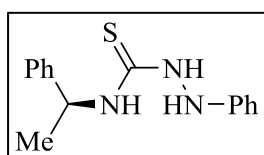
Pentafluorophenylhydrazine (1.313 g, 6.63 mmol, 1.0 equiv.)

was added to a mixture of **3-23** (1.00 mL, 6.63 mmol, 1.0 equiv.)

in toluene (15 mL), then the mixture was stirred overnight at rt, during which a suspension formed. The suspension was diluted with *n*-hexane (10 mL), then filtered and washed with *n*-hexane (10 mL) to afford the product as a colourless solid (1.94 g, 5.37 mmol, 81%). M.p. 162 °C (decomposed). ¹H NMR (500 MHz, methanol-*d*₄) δ : 7.39 (m, 2H), 7.31 (m, 2H), 7.23 (m, 1H), 5.71 (m, 1H), 1.56 (d, J = 7.0 Hz, 3H). ¹³C{¹H} (125 MHz, methanol-*d*₄) δ : 144.6, 129.4, 128.0, 127.4, 54.5, 21.7. ¹⁹F (470 MHz, methanol-*d*₄) δ : -158.1 (s, 2F), -167.0 (s, 2F), -169.0 (br, 1F). HRMS (E

SI) m/z calc'd for C₁₅H₁₂F₅N₃NaS [M+Na]⁺: 384.0564; found: 384.0553.

(S)-N-(1-Phenylethyl)-2-phenylhydrazine carbothioamide (3-26):



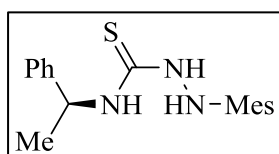
Phenylhydrazine (0.977 mL, 9.94 mmol, 1.0 equiv.) was added

to a mixture of **3-23** (1.50 mL, 9.94 mmol, 1.0 equiv.) in toluene

(20 mL), then the mixture was stirred overnight at rt, during which a suspension formed.

The suspension was diluted with *n*-hexane (10 mL), then filtered and washed with *n*-hexane (10 mL) to afford a colourless solid (2.14 g, 7.89 mmol, 79%). Either a mixture of rotamers or constitutional isomers are observed in NMR spectroscopy. M.p. 95-96 °C. ¹H NMR (500 MHz, methanol-*d*₄) δ: 7.41-7.20 (m, 8H), 6.87-6.79 (m, 2H), 5.70-5.60 (m, 1H), 1.58-1.49 (two d, *J* = 7.0 and 7.0 Hz, 3H). ¹³C {¹H} (125 MHz, methanol-*d*₄) δ: 149.0, 144.8, 130.1, 130.0, 129.5, 129.4, 128.7, 128.0, 127.3, 127.3, 122.0, 114.4, 55.0, 54.2, 22.4, 22.0. HRMS (ESI) *m/z* calc'd for C₁₅H₁₇N₃NaS [M+Na]⁺: 294.1035; found: 294.1045.

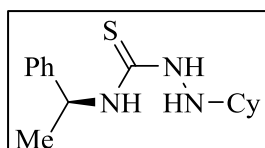
(*S*)-*N*-(1-Phenylethyl)-2-mesitylhydrazine carbothioamide (3-27): 3-23



(0.404 mL, 2.68 mmol, 1.0 equiv.) was added to a mixture of mesitylhydrazine hydrochloride (0.500 g, 2.68 mmol, 1.0 equiv.) and K₂CO₃ (0.370 g, 2.68 mmol, 1.0 equiv.) in MeOH (8 mL) and distilled water (2 mL), then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo*, then DCM (30 mL) was added. The mixture was washed with distilled water (15 mL) and brine (15 mL), then dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo*, then the residue was washed with *n*-hexane (25 mL) to afford a brown solid (0.403 g, 1.29 mmol, 48%). Either a mixture of rotamers or constitutional isomers are observed in NMR spectroscopy. M.p. 125 °C (decomposed). ¹H NMR (500 MHz, methanol-*d*₄) δ: 7.46-7.23 (m, 5H), 6.88-6.77 (m, 2H), 5.74-5.59 (m, 1H), 2.25-2.10 (m,

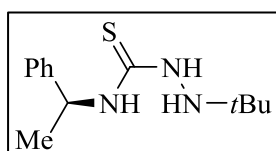
9H), 1.60-1.57 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, methanol- d_4) δ : 144.7, 141.1, 134.3, 131.0, 130.6, 130.2, 130.2, 129.5, 128.2, 128.0, 127.6, 127.2, 54.4, 22.0, 20.7, 18.2. HRMS (ESI) calc'd for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{NaS}$ $[\text{M}+\text{Na}]^+$: 336.1505; found: 336.1514.

(S)-N-(1-Phenylethyl)-2-cyclohexylhydrazine carbothioamide (3-28): 3-23



(1.50 mL, 9.94 mmol, 1.0 equiv.) was added to a mixture of cyclohexylhydrazine hydrochloride (1.50 g, 9.94 mmol, 1.0 equiv.) and K_2CO_3 (1.37 g, 9.94 mmol, 1.0 equiv.) in MeOH (25 mL) and distilled water (8 mL), then the mixture was stirred overnight at rt, during which a suspension formed. The suspension was filtered and washed with distilled water (15 mL) and *n*-hexane (30 mL) to afford the product as a colourless solid (2.07 g, 7.47 mmol, 75%). M.p. 130-132 °C. ^1H NMR (500 MHz, methanol- d_4) δ : 7.37-7.32 (m, 4H), 7.26-7.24 (m, 1H), 5.61 (q, $J = 7.0$ Hz, 1H), 5.27 (m, 1H), 1.89-1.17 (m, 13H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, methanol- d_4) δ : 181.1, 145.4, 129.5, 127.9, 127.2, 60.1, 54.7, 29.8, 29.7, 26.7, 26.6, 26.5, 22.6. HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{23}\text{N}_3\text{NaS}$ $[\text{M}+\text{Na}]^+$: 300.1505; found: 300.1512.

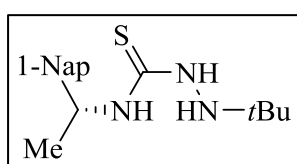
(S)-N-(1-Phenylethyl)-2-(tert-butyl)hydrazine carbothioamide (3-29): 3-23



(2.00 mL, 13.3 mmol, 1.0 equiv.) was added to a mixture of *tert*-butylhydrazine hydrochloride (1.65 g, 13.3 mmol, 1.0 equiv.) and K_2CO_3 (1.83 g, 13.3 mmol, 1.0 equiv.) in MeOH (30 mL) and distilled water (8 mL), then the mixture was stirred for 66 h at rt, during which a suspension formed. The

suspension was filtered, then the filtrate was concentrated *in vacuo*, and diluted with a mixture of *n*-hexane (15 mL) and ethyl acetate (30 mL). The mixture was washed with distilled water (10 mL x 2) and dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo* to afford the product as a yellow solid (2.84 g, 11.3 mmol, 85%). M.p. 88-90 °C. ¹H NMR (500 MHz, CDCl₃) δ: 7.68 (br d, *J* = 8.0 Hz, 1H), 7.34-7.25 (m, 5H), 7.12 (br s, 1H), 5.68 (m, 1H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.09 (s, 9H). ¹³C {¹H} (125 MHz, CDCl₃) δ: 181.9, 143.0, 128.7, 127.4, 126.3, 54.9, 52.9, 27.0, 21.7. HRMS (ESI) *m/z* calc'd for C₁₃H₂₁N₃NaS [M+Na]⁺: 274.1248; found: 274.1337.

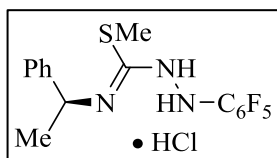
(*R*)-*N*-(1-Naphthylethyl)-2-(*tert*-butyl)hydrazine carbothioamide (3-30): 3-



24 (1.00 g, 4.69 mmol, 1.0 equiv.) was added to a mixture of *tert*-butylhydrazine hydrochloride (0.584 g, 4.69 mmol, 1.0 equiv.) and K₂CO₃ (0.648 g, 4.69 mmol, 1.0 equiv.) in MeOH (12 mL), then the mixture was stirred for 40 h at rt. The solvent was removed *in vacuo*, then DCM (25 mL) was added. The mixture was washed with distilled water (10 mL x 2) and dried with anhydrous Na₂SO₄. The solvent was removed *in vacuo*, then the residue was washed with *n*-hexane to afford the product as a colourless solid (1.177 g, 3.90 mmol, 83%). ¹H NMR (500 MHz, CDCl₃) δ: 8.22 (d, *J* = 13.5 Hz, 1H), 7.87-7.79 (m, 2H), 7.62-7.42 (m, 5H), 7.07 (br s, 1H), 6.36 (m, 1H), 3.18 (br s, 1H), 1.74 (d, *J* = 11.5 Hz, 3H), 0.98 (s, 9H). ¹³C {¹H} (125 MHz, CDCl₃) δ: 181.5, 138.1, 134.0, 131.5, 128.7, 128.6, 126.7,

126.0, 125.2, 124.2, 122.9, 54.9, 49.4, 26.9, 20.4. HRMS (ESI) m/z calc'd for $C_{17}H_{23}N_3NaS$ $[M+Na]^+$: 324.1505; found: 324.1504.

S-Methyl-(S)-1-(phenylethyl)-4-pentafluorophenyl isothiosemicarbazide

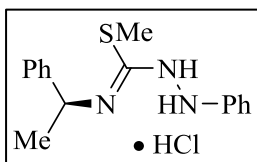


hydrochloride (3-31): MeI (0.069 mL, 1.11 mmol, 1.0 equiv.)

was added to a mixture of **3-25** (0.400 g, 1.11 mmol, 1.0 equiv.)

in EtOH (4 mL), then the mixture was stirred overnight at 40 °C. The volatiles were removed *in vacuo*, then the residue was dissolved in MeOH (10 mL). Amberjet® 4200 chloride form (2.80 g, 9.8 to 12.6 mmol, 8.8 to 11.4 equiv.) was added, then the mixture was stirred overnight at rt. The suspension was filtered through celite, then washed with MeOH (10 mL). The solvent was removed *in vacuo* to afford the product as a yellow solid (0.441 g, 1.07 mmol, 96%). ¹H NMR (300 MHz, CDCl₃) δ : 8.77 (br, 1H), 8.34 (br, 1H), 7.40-7.32 (m, 5H), 4.94 (m, 1H), 2.76 (s, 3H), 1.70 (d, $J = 11.0$ Hz, 3H). ¹⁹F (282 MHz, CDCl₃) δ : -152.7 (d, $J = 20.6$ Hz, 2F), -162.4 (m, 1F), -162.8 (m, 2F). HRMS (ESI) calc'd for $C_{16}H_{15}F_5N_3S$ $[M+H]^+$: 376.0901; found: 376.0898.

S-Methyl-(S)-1-(phenylethyl)-4-phenyl isothiosemicarbazide hydrochloride



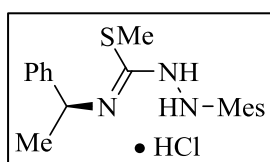
(3-32): MeI (0.115 mL, 1.84 mmol, 1.0 equiv.) was added to a

mixture of **3-26** (0.400 g, 1.84 mmol, 1.0 equiv.) in EtOH (6 mL),

then the mixture was stirred overnight at 40 °C. The volatiles were removed *in vacuo*, then the residue was dissolved in MeOH (18 mL). Amberjet® 4200 chloride form (4.61

g, 16.1 to 20.7 mmol, 8.8 to 11.3 equiv.) was added, then the mixture was stirred overnight at rt. The suspension was filtered through celite, then washed with MeOH (20 mL). The solvent was removed *in vacuo* to afford the crude product as a yellow solid (0.545 g, 1.69 mmol, 92%), which was used without further purification. HRMS (ESI) *m/z* calc'd for C₁₆H₂₀N₃S [M+H]⁺: 286.1372; found: 286.1359.

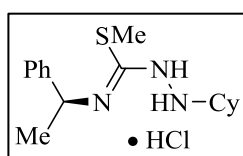
S-Methyl-(S)-1-(phenylethyl)-4-mesityl isothiosemicarbazide hydrochloride



(3-33): MeI (0.050 mL, 0.798 mmol, 1.0 equiv.) was added to a mixture of **3-27** (0.23 g, 0.798 mmol, 1.0 equiv.) in EtOH (4

mL), then the mixture was stirred overnight at 40 °C. The volatiles were removed *in vacuo*, then the residue was dissolved in MeOH (8 mL). Amberjet® 4200 chloride form (2.00 g, 7.0 to 9.0 mmol, 8.8 to 11.3 equiv.) was added, then the mixture was stirred overnight at rt. The suspension was filtered through celite, then washed with MeOH (10 mL). The solvent was removed *in vacuo* to afford the crude product as a brown solid (0.291 g, 0.798 mmol, quantitative), which was used without further purification. HRMS (ESI) *m/z* calc'd for C₁₉H₂₆N₃S [M+H]⁺: 328.1842; found: 328.1830.

S-Methyl-(S)-1-(phenylethyl)-4-cyclohexyl isothiosemicarbazide hydro-

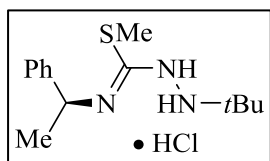


chloride (3-34): MeI (0.112 mL, 1.80 mmol, 1.0 equiv.) was added to a mixture of **3-28** (0.500 g, 1.80 mmol, 1.0 equiv.) in

EtOH (7 mL), then the mixture was stirred overnight at 40 °C. The volatiles were

removed *in vacuo*, then the residue was dissolved in MeOH (15 mL). Amberjet® 4200 chloride form (4.50 g, 15.8 to 20.3 mmol, 8.8 to 11.3 equiv.) was added, then the mixture was stirred overnight at rt. The suspension was filtered through celite, then washed with MeOH (20 mL). The solvent was removed *in vacuo* to afford the product as a colourless solid (0.589 g, 1.80 mmol, quantitative). ¹H NMR (500 MHz, CDCl₃) δ: 7.53 (m, 2H), 7.32-7.21 (m, overlapped with NH, 5H), 5.21 (m, 1H), 4.23 (m, 1H), 2.33 (s, 3H), 1.98-1.62 (m, 10H), 1.33-1.20 (m, 3H). HRMS (ESI) m/z calc'd for C₁₆H₂₆N₃S [M+H]⁺: 292.1842; found: 292.1847.

S-Methyl-(S)-1-(phenylethyl)-4-(tert-butyl) isothiosemicarbazide hydro-

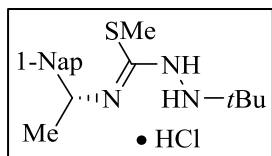


chloride (3-35): MeI (0.124 mL, 1.99 mmol, 1.0 equiv.) was added to a mixture of **3-25** (0.500 g, 1.99 mmol, 1.0 equiv.) in

EtOH (8 mL), then the mixture was stirred overnight at 40 °C. The volatiles were removed *in vacuo*, then the residue was dissolved in MeOH (20 mL). Amberjet® 4200 chloride form (5.00 g, 17.5 to 22.5 mmol, 8.8 to 11.3 equiv.) was added, then the mixture was stirred overnight at rt. The suspension was filtered through celite, then washed with MeOH (25 mL). The solvent was removed *in vacuo* to afford the product as a yellow solid (0.604 g, 1.99 mmol, quantitative). ¹H NMR (500 MHz, CDCl₃) δ: 8.25 (br, 1H), 7.39-7.25 (m, 5H), 4.78 (m, 1H), 2.67 (br, 3H), 1.59 (d, *J* = 11.0 Hz, 3H), 1.31 (br s, 9H). HRMS (ESI) m/z calc'd for C₁₄H₂₄N₃S [M+H]⁺: 266.1685; found:

266.1682.

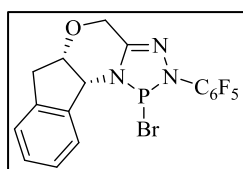
S-Methyl-(R)-1-(naphthylethyl)-4-(tert-butyl) isothiosemicarbazide hydro-



chloride (3-36): MeI (0.083 mL, 1.33 mmol, 1.0 equiv.) was added to a mixture of **3-36** (0.400 g, 1.33 mmol, 1.0 equiv.) in

MeOH (4 mL), then the mixture was stirred overnight at rt. The volatiles were removed *in vacuo*, then the residue was dissolved in MeOH (4 mL). Amberjet® 4200 chloride form (1.66 g, 5.8 to 7.5 mmol, 4.4 to 5.6 equiv.) was added, then the mixture was stirred overnight at rt. The suspension was filtered through celite, then washed with MeOH (10 mL). The solvent was removed *in vacuo* to afford the product as a yellow solid (0.435 g, 1.24 mmol, 93%). Rotamers are observed in ¹H NMR spectroscopy. ¹H NMR (500 MHz, CDCl₃) δ: 8.15-8.08 (m, 1H), 7.92-7.76 (m, overlapped with NH, 2H), 7.61-7.47 (m, 4H), 5.83-5.76 (m, 1H), 2.63 (br s, 3H), 1.77-1.67 (m, 3H), 1.19-0.93 (m, 9H). HRMS (ESI) m/z calc'd for C₁₈H₂₆N₃S [M+H]⁺: 316.1842; found: 316.1836.

1-Bromo-2-pentafluorophenyl-[2,4,6,10b]-tetrahydro-1H,5aH-indeno[2,1-b]-

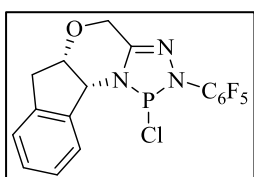


[1,2,4,3]triazaphospholo[4,5-d][1,4]oxazine (3-37-Br): NEt₃ (0.927 mL, 6.65 mmol, 3.0 equiv.) was added to a suspension of

3-3 (0.900 g, 2.22 mmol, 1.0 equiv.) in toluene (20 mL). PBr₃ (0.208 mL, 2.22 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (10 mL), then the solvent

was removed *in vacuo* to afford the product as a yellow solid (0.060 g, 0.013 mmol, 2%). ¹H NMR (500 MHz, CDCl₃) δ: 7.52 (m, 1H), 7.36 (m, 3H), 5.24 (dd, *J* = 16.0, 4.5 Hz, 1H), 4.86 (m, 1H), 4.75 (m, 2H), 3.38 (m, 1H), 3.26 (m, 1H). ³¹P NMR (202 MHz, CDCl₃) δ: 147.1 (s).

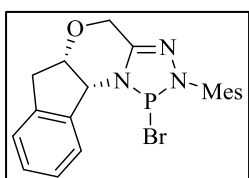
1-Chloro-2-pentafluorophenyl-[2,4,6,10b]-tetrahydro-1*H*,5*aH*-indeno[2,1-*b*]-



[1,2,4,3]triazaphospholo[4,5-*d*][1,4]oxazine (3-37-Cl): NEt₃

(0.117 mL, 0.837 mmol, 3.0 equiv.) was added to a suspension of **3-3** (0.113 g, 0.279 mmol, 1.0 equiv.) in toluene (5 mL). PCl₃ (0.024 mL, 0.837 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (5 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.046 g, 0.106 mmol, 38%). ¹H NMR (300 MHz, CDCl₃) δ: 7.54 (m, 1H), 7.35 (m, 3H), 5.28 (dd, *J* = 16.2, 4.8 MHz, 1H), 4.82 (m, 1H), 4.71 (m, 2H), 3.36 (m, 1H), 3.25 (m, 1H). ³¹P NMR {121 MHz, CDCl₃} δ: 125.3 (m).

1-Bromo-2-mesityl-[2,4,6,10b]-tetrahydro-1*H*,5*aH*-indeno[2,1-*b*][1,2,4,3]tri-

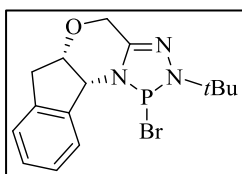


azaphospholo[4,5-*d*][1,4]oxazine (3-38): NEt₃ (0.409 mL, 2.93

mmol, 3.0 equiv.) was added to a suspension of **3-5** (0.350 g, 0.978 mmol, 1.0 equiv.) in toluene (20 mL). PBr₃ (0.092 mL, 0.978 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was

filtered through celite, and wash with toluene (10 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.270 g, 0.627 mmol, 64%). ^1H NMR (500 MHz, CDCl_3) δ : 7.51 (m, 1H), 7.35 (m, 3H), 6.96 (s, 2H), 5.44 (dd, $J = 15.5, 4.5$ Hz, 1H), 4.88 (m, 1H), 4.78 (m, 1H), 4.74 (m, 1H), 3.39 (m, 1H), 3.25 (m, 1H), 2.31 (m, 9H). ^{31}P NMR (202 MHz, CDCl_3) δ : 155.9 (s).

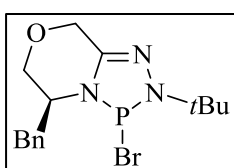
1-Bromo-2-(*tert*-butyl)-[2,4,6,10*b*]-tetrahydro-1*H*,5*aH*-indeno[2,1-*b*]-



[1,2,4,3]triazaphospholo[4,5-*d*][1,4]oxazine (3-39): NEt_3 (0.358 mL, 2.54 mmol, 3.0 equiv.) was added to a suspension of **3-6**

(0.250 g, 0.845 mmol, 1.0 equiv.) in toluene (20 mL). PBr_3 (0.08 mL, 0.845 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (10 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.160 g, 0.435 mmol, 51%). ^1H NMR (300 MHz, CDCl_3) δ : (7.49 (m, 1H), 7.33 (m, 3H), 5.36 (dd, $J = 14.7, 4.5$ Hz, 1H), 4.84 (m, 1H), 4.70 (m, 2H), 3.35 (m, 1H), 3.21 (m, 1H), 1.63 (s, 9H). ^{31}P NMR (121 MHz, CDCl_3) δ : 160.7 (br).

(*S*)-5-Benzyl-3-bromo-2-(*tert*-butyl)-5,6-dihydro-8*H*-1,2,4,3-triazaphospho-

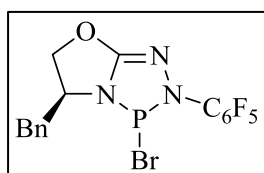


lo[1,4]oxazine (3-40): NEt_3 (0.200 mL, 1.43 mmol, 1.4 equiv.) was added to a suspension of **3-9** (0.400 g, 1.04 mmol, 1.0 equiv.,

contaminated with 23% of *tert*-butylhydrazine hydrochloride by ^1H NMR analysis) in

toluene (10 mL). The mixture was stirred for 10 minutes, then the volatiles were removed *in vacuo*. Toluene (20 mL) was added, followed by NEt₃ (0.434 mL, 3.12 mmol, 3.0 equiv.). PBr₃ (0.098 mL, 1.04 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite and washed with toluene (5 mL), then the solvent was removed *in vacuo* to afford the crude product as a yellow solid (0.127 g, 0.343 mmol, 33%). ¹H NMR (300 MHz, CDCl₃) δ: 7.35-7.21 (m, 5H), 4.77 (AB q, 2H), 4.27 (m, 1H), 3.86 (m, 1H), 3.77 (m, 1H), 3.29 (m, 1H), 3.05 (m, 1H), 1.54 (d, *J* = 1.5 Hz, 9H). ³¹P NMR (121 MHz, CDCl₃) δ: 162.0 (unidentified), 160.0 (dd, *J* = 44.4, 13.7 Hz, unidentified), 156.1 (unidentified), 155.5 (br, presumably P-Br), 152.4 (m, unidentified), 151.7 (unidentified), 131.8 (unidentified).

(S)-5-Benzyl-3-bromo-5,6-dihydro-2-pentafluorophenyl-1,2,4,3-triazaphos-

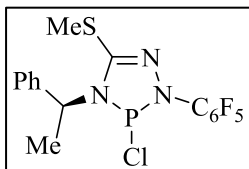


pholo[1,3]oxazole (3-41): NEt₃ (0.159 mL, 1.14 mmol, 3.0 equiv.) was added to a suspension of **3-10** (0.150 g, 0.381 mmol,

1.0 equiv.) in toluene (10 mL). PBr₃ (0.04 mL, 0.381 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (10 mL), then the solvent was removed *in vacuo* to afford the crude product as a yellow solid (0.102 g, 0.219 mmol, 57%). ³¹P NMR (202 MHz, CDCl₃) δ: 162.9 (br, unidentified), 149.3 (s, unidentified), 142.7 (dt, *J* = 97.0,

37.8 Hz, unidentified).

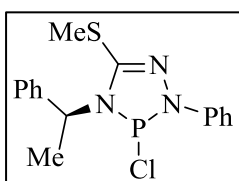
3-Chloro-2-pentafluorophenyl-4-[(S)-1-phenylethyl]-5-thiomethyl-1,2,4,3-



triazaphospholene (3-42): NEt₃ (0.102 mL, 0.728 mmol, 3.0 equiv.) was added to a suspension of **3-31** (0.100 g, 0.243 mmol,

1.0 equiv.) in toluene (3 mL). PCl₃ (0.02 mL, 0.243 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (2 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.088 g, 0.200 mmol, 82%). ¹H NMR (500 MHz, CDCl₃) δ: 7.55-7.35 (m, 5H), 5.14 (m, 1H), 2.54 (s, 3H), 2.00 (d, *J* = 5.5 Hz, 3H). ¹⁹F NMR (470 MHz, CDCl₃) δ: -144.7 (t, *J* = 21.6 Hz, 2F), -155.6 (t, *J* = 20.2 Hz, 1F), -161.7 (t, *J* = 20.7 Hz, 2F). ³¹P NMR (202 MHz, CDCl₃) δ: 134.9 (s).

3-Chloro-2-phenyl-4-[(S)-1-phenylethyl]-5-thiomethyl-1,2,4,3-triazaphos-

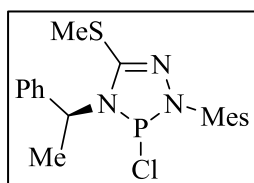


pholene (3-43): NEt₃ (0.156 mL, 1.13 mmol, 3.0 equiv.) was added to a suspension of **3-32** (0.120 g, 0.373 mmol, 1.0 equiv.) in

toluene (5 mL). PCl₃ (0.03 mL, 0.373 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (3 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.112 g, 0.320 mmol, 86%). ¹H NMR (500 MHz, CDCl₃) δ: 7.52-7.34 (m, 9H), 7.12 (m, 1H), 5.15 (m, 1H), 2.63 (s, 3H), 2.01 (d, *J* = 7.0 Hz, 3H). ³¹P NMR (202

MHz, CDCl₃) δ : 131.4 (s). HRMS (APCI) m/z calc'd for C₁₆H₁₇N₃PS [M-Cl]⁺: 314.0875; found: 314.0869.

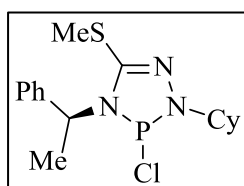
3-Chloro-2-mesityl-4-[(S)-1-phenylethyl]-5-thiomethyl-1,2,4,3-triazaphos-



pholene (3-44): NEt₃ (0.156 mL, 1.13 mmol, 3.0 equiv.) was added to a suspension of **3-33** (0.100 g, 0.275 mmol, 1.0 equiv.)

in toluene (3 mL). PCl₃ (0.02 mL, 0.275 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (4 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.074 g, 0.189 mmol, 69%). ¹H NMR (500 MHz, CDCl₃) δ : 7.41-7.34 (m, 5H), 6.93 (s, 2H), 5.18 (m, 1H), 2.50 (s, 3H), 2.36-2.29 (overlapped, 9H), 2.05 (dd, $J = 7.0, 1.5$ Hz, 3H). ³¹P NMR (202 MHz, CDCl₃) δ : 141.1 (s). HRMS (APCI) calc'd for C₁₉H₂₃N₃PS [M-Cl]⁺: 356.1345; found: 356.1346.

3-Chloro-2-cyclohexyl-4-[(S)-1-phenylethyl]-5-thiomethyl-1,2,4,3-triaza-

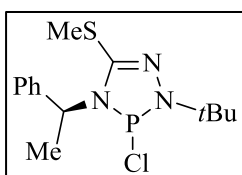


phospholene (3-45): NEt₃ (0.153 mL, 1.10 mmol, 3.0 equiv.) was added to a suspension of **3-34** (0.120 g, 0.366 mmol, 1.0 equiv.)

in toluene (5 mL). PCl₃ (0.03 mL, 0.366 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (3 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.098 g, 0.275 mmol, 75%). ¹H NMR (500 MHz, CDCl₃) δ :

7.38-7.36 (m, 3H), 7.32-7.29 (m, 2H), 5.55 (m, 1H), 4.71 (m, 1H), 2.16 (dd, $J = 7.0$, 2.0 Hz, 3H), 2.09 (s, 3H), 2.01-1.70 (m, 7H), 1.41-1.28 (m, 3H). ^{31}P NMR (202 MHz, CDCl_3) δ : 147.9 (s). HRMS (APCI) m/z calc'd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{PS}$ $[\text{M}-\text{Cl}]^+$: 320.1345; found: 320.1358.

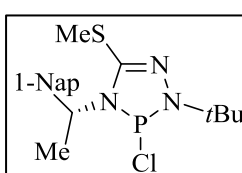
3-Chloro-2-(*tert*-butyl)-4-[(*S*)-1-phenylethyl]-5-thiomethyl-1,2,4,3-triaza-



phospholene (3-46): NEt_3 (0.208 mL, 1.49 mmol, 3.0 equiv.) was added to a suspension of **3-35** (0.150 g, 0.497 mmol, 1.0 equiv.)

in toluene (6 mL). PCl_3 (0.04 mL, 0.497 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (8 mL), then the solvent was removed *in vacuo* to afford the product as a yellow oil (0.133 g, 0.403 mmol, 81%). ^1H NMR (500 MHz, CDCl_3) δ : 7.41-7.33 (m, 5H), 5.10 (m, 1H), 2.52 (s, 3H), 2.01 (dd, $J = 7.0$, 1.5 Hz, 3H), 1.56 (d, $J = 1.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, CDCl_3) δ : 150.9, 141.5, 129.0, 128.4, 127.3 (d, $J = 1.9$ Hz), 59.2 (d, $J = 5.0$ Hz), 56.7 (d, $J = 11.0$ Hz), 29.2 (d, $J = 11.3$ Hz), 22.8 (d, $J = 14.6$ Hz), 15.9. ^{31}P NMR (202 MHz, CDCl_3) δ : 148.5 (s). HRMS (APCI) m/z calc'd for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{PS}$ $[\text{M}-\text{Cl}]^+$: 294.1188; found: 294.1174.

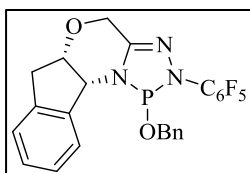
3-Chloro-2-(*tert*-butyl)-4-[(*R*)-1-naphthylethyl]-5-thiomethyl-1,2,4,3-triaza-



phospholene (3-47): NEt_3 (0.238 mL, 1.71 mmol, 3.0 equiv.) was added to a suspension of **3-36** (0.200 g, 0.568 mmol, 1.0 equiv.)

in toluene (5 mL). PCl_3 (0.05 mL, 0.568 mmol, 1.0 equiv.) was added dropwise, then the mixture was stirred overnight at rt. The mixture was filtered through celite, and washed with toluene (3 mL), then the solvent was removed *in vacuo* to afford the product as a yellow solid (0.200 g, 0.526 mmol, 93%). ^1H NMR (500 MHz, CDCl_3) δ : 7.92-7.86 (m, 3H), 7.71 (m, 1H), 7.58-7.51 (m, 3H), 5.89 (m, 1H), 2.58 (s, 3H), 2.16 (d, $J = 6.5$ Hz, 3H), 1.52 (d, $J = 1.5$ Hz, 3H). ^{31}P NMR (202 MHz, CDCl_3) δ : 149.5 (s).

1-Benzyloxy-2-pentafluorophenyl-2,4,6,10b-tetrahydro-1H,5aH-indeno[2,1-

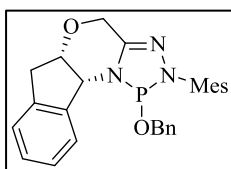


b][1,2,4,3]triazaphospholo[4,5-*d*][1,4]oxazine (3-48): NaOBn

(0.007 g, 0.056 mmol, 1.0 equiv.) was added to a suspension of

3-37-Br (0.027 g, 0.056 mmol, 1.0 equiv.) in toluene (1 mL), then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford the crude product as a yellow solid (0.016 g), which was used without further purification. ^{31}P NMR (202 MHz, CDCl_3) δ : 83.3 (m, potentially minor diastereomer), 79.2 (m, P-O major diastereomer), 7.5 (m, O=P).

1-Benzyloxy-2-mesityl-2,4,6,10b-tetrahydro-1H,5aH-indeno[2,1-*b*][1,2,4,3]-



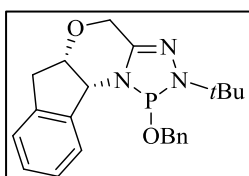
triazaphospholo[4,5-*d*][1,4]oxazine (3-49): NaOBn (0.036 g,

0.279 mmol, 1.0 equiv.) was added to a suspension of **3-38** (0.120

g, 0.279 mmol, 1.0 equiv.) in toluene (5 mL), then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to

afford the crude product as a yellow solid (0.095 g), which was used without further purification. ^{31}P NMR (202 MHz, CDCl_3) δ : 83.8 (s, P-O major diastereomer), 7.70 (m, O=P), -0.4 (m, O=P).

1-Benzyloxy-2-(*tert*-butyl)-2,4,6,10b-tetrahydro-1*H*,5*aH*-indeno[2,1-*b*]-



[1,2,4,3]triazaphospholo[4,5-*d*][1,4]oxazine (3-50): NaOBn

(0.035 g, 0.272 mmol, 1.0 equiv.) was added to a suspension of

3-39 (0.100 g, 0.272 mmol, 1.0 equiv.) in toluene (5 mL), then the mixture was stirred overnight at rt. The mixture was filtered through celite, then the solvent was removed *in vacuo* to afford the crude product as a yellow solid (0.103 g), which was used without further purification. ^{31}P NMR (202 MHz, CDCl_3) δ : 160.3 (br, P-Br), 139.5 (m, unidentified), 81.4 (s, potentially minor diastereomer), 78.1 (s, P-O major diastereomer), 7.70 (dt, $J = 704.6, 8.9$ Hz, O=P), 2.6 (m, O=P).

Chapter 4. Catalytic Activity of TAPs and DAPs

4.1 Contributions

Mr. Matt R. Adams (Dalhousie University) is thanked for the preparation of **4-2**, **4-14**, **4-19**, **4-21**, **4-22**, **4-25**, and various imines. Mr. Blake S. N. Huchenski (Dalhousie University) is thanked for the preparation of various imines. Prof. Erin R. Johnson (Dalhousie University) is thanked for the calculation of energy coordinates for the mechanistic study. Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University) is thanked for the acquisition of mass spectrometric data.

4.2 Introduction

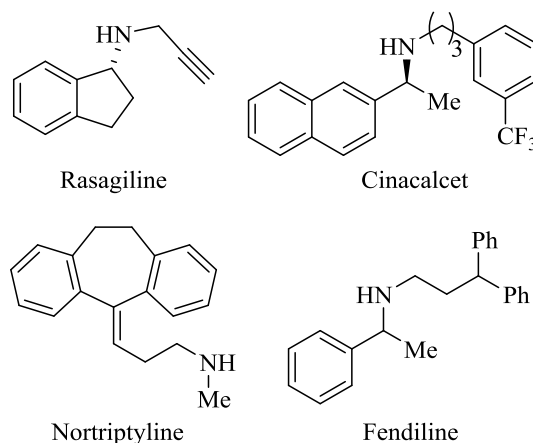


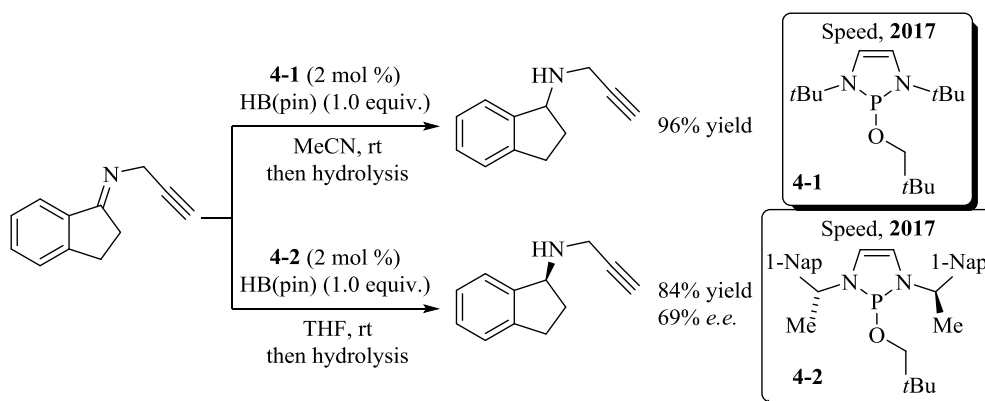
Figure 4.1 Pharmaceuticals that contain secondary amine moieties.

Catalyzed organic transformations represent a field of great importance, as described in Chapter 1. Of the transformations shown, the reduction of imines is of high interest, because the products, namely secondary amines, are prevalent scaffolds in pharmaceutical molecules (Figure 4.1).⁸⁹ Therefore, developing catalysts that are able

to facilitate such transformation is an ongoing objective for chemists worldwide. To alleviate the reliance on transition metal catalysts, development of catalysts derived from main group elements has attracted much attention. Furthermore, it is of general academic interest to develop novel systems in an effort to uncover unique properties or reactivity.

4.3 TAP-Catalyzed Racemic Hydroboration

Although cheap and commercially available reagents such as NaBH_4 and LiAlH_4 can easily facilitate the racemic reduction of unsaturated carbons such as carbonyls and imines, novel catalysts have the potential to impart better selectivity. For example, sensitive functional groups such as ketones, nitriles, and olefins are not well tolerated with the aforementioned commercialized reductants, when these are not the desired reactive sites. Furthermore, depending on the scaffolds, new catalyst systems could be rendered non-racemic, thereby potentially inducing stereoselectivity in catalyzed reactions. Such is the case with DAPs, as evidenced by the work reported by our group,



Scheme 4.1 Reduction of the precursor of Rasagiline using achiral and chiral pre-catalysts developed in the Speed group.

which is briefly discussed in this chapter (Scheme 4.1).⁵⁹

4.3.1 Screening of Conditions

Table 4.1 Screening of TAP-alkoxides as pre-catalysts in the hydroboration of **4-3**.

| entry | TAP | conversion (%) ^a |
|-------|-------------------------|-----------------------------|
| 1 | 2-45 | 0 |
| 2 | 2-48 | 22 |
| 3 | 2-49 | 17 |
| 4 | 2-50 | 20 |
| 5 | 2-51 | 28 |
| 6 | 2-52 | 7 |
| 7 | 2-53 | 9 |
| 8 | 2-54^b | 46 |
| 9 | 2-54^c | 21 |

Reaction scheme: Imine **4-3** (Ph-C(=N-Ph)-Me) reacts with HB(pin) (1.1 equiv.) in THF at room temperature for 16 hours, catalyzed by a TAP-alkoxide (10 mol %), to form the borylated amine **4-4** ((pin)B-N(Ph)-Ph-Me).

Chemical structures of TAP-alkoxides:

- 2-45**: *t*Bu-C(=N)-N(Dipp)-N(Ph)-P(OBn)
- 2-48**: 2-Py-C(=N)-N(H)-N(R)-P(OBn), R = C₆F₅
- 2-49**: 2-Py-C(=N)-N(H)-N(R)-P(OBn), R = Ph
- 2-50**: 2-Py-C(=N)-N(H)-N(R)-P(OBn), R = Mes
- 2-51**: 2-Py-C(=N)-N(H)-N(R)-P(OBn), R = *t*Bu
- 2-52**: MeS-C(=N)-N(Cy)-N(Ph)-P(OBn)
- 2-53**: Me-C(=N)-N(Cy)-N(*t*Bu)-P(OBn)
- 2-54**: Me-C(=N)-N(Cy)-N(*t*Bu)-P(OBn) (cyclic structure)

^a Conversion by comparison of characteristic signals of starting material and product by ¹H NMR spectroscopy.
^b Contaminated with **2-36**. ^c Derived from **2-37**, not contaminated with TAP-Cl.

To assess the catalytic activity of TAPs in the catalyzed hydroboration of imines, and compare the results with DAPs, I first aimed to employ crude mixtures of TAP-alkoxides as pre-catalysts in the hydroboration of imines. Imine **4-3** and HB(pin) were chosen as the model substrate and terminal reductant, respectively, since no background hydroboration reaction was observed. Furthermore, DAP **1-37** is inactive towards **4-3**, presumably due to the steric bulk imposed by the aniline moiety. Unsurprisingly, sterically hindered **2-45** was unable to catalyze the reduction of **4-3** to form the corresponding borylated amine, **4-4** (entry 1, Table 4.1).

Electron-deficient **2-48** was able to catalyze the partial reduction of **4-3** within 16

hours (entry 2, Table 4.1). It was assumed that the TAP-catalyzed hydroboration of imines operates under a similar mechanism as DAPs. Therefore, it was hypothesized that the increase in electron donating ability of the substituents would increase the hydricity of the corresponding TAP-hydride, thereby providing higher activity. Surprisingly, **2-49** to **2-51** all possessed similar activity as **2-48**, with essentially no difference in conversion of **4-3** to **4-4** as evidenced in the ¹H NMR spectra (entries 3 to 5, Table 4.1).

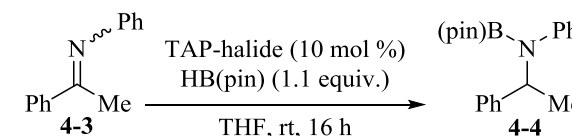
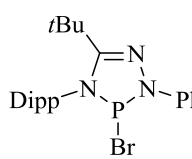
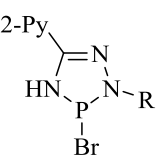
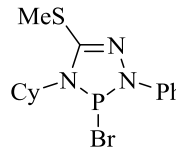
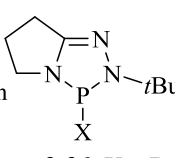
Reactions catalyzed by **2-52** and **2-53** both provided little to no borylated amine (entries 6 and 7, Table 4.1). To our delight, **2-54**, derived from the corresponding TAP-Br, **2-36**, catalyzed the hydroboration of **4-3** with greater conversion (46%, entry 8, Table 4.1). To reproduce the results, I once again prepared **2-54**, this time from the corresponding TAP-Cl, **2-37**, and subjected it to the same conditions (entry 9, Table 4.1). Surprisingly, similar results were not reproduced. Upon further investigation, it was discovered that the more active batch of **2-54**, derived from TAP-Br **2-36**, contained traces of **2-36**. Therefore, it was speculated that TAP-halides are catalytically active in the hydroboration of imines.

To verify this hypothesis, the TAP-halides were subjected to the same conditions to afford the results presented in Table 4.2. Once again, no conversion to **4-4** was observed for the reaction catalyzed by sterically hindered **2-32** (entry 1, Table 4.2).

Minor variation in conversion was observed for the hydroboration catalyzed by the electronically diverse TAPs, **2-31**, and **2-33** to **2-35** (entries 2 to 5, Table 4.2). Thiolated **2-39** possessed negligible catalytic activity in the given conditions (entry 6, Table 4.2). Bicyclic TAPs, **2-36** and **2-37**, afforded the highest conversion, with **2-37** being superior (entries 7 and 8, Table 4.2).

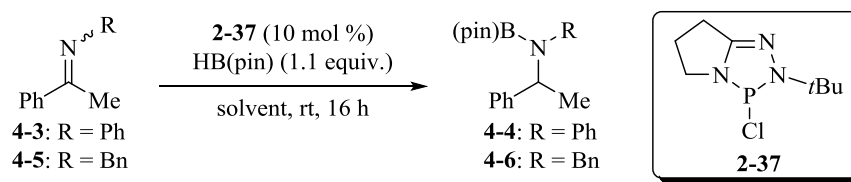
Table 4.2 Screening of TAP-halides in the hydroboration of **4-3**.

| entry | TAP | conversion (%) ^a |
|-------|-------------|-----------------------------|
| 1 | 2-32 | 0 |
| 2 | 2-31 | 10 |
| 3 | 2-33 | 19 |
| 4 | 2-34 | 19 |
| 5 | 2-35 | 20 |
| 6 | 2-39 | 12 |
| 7 | 2-36 | 44 |
| 8 | 2-37 | 34 |

| | | |
|---|---|--|
|  |  <p>2-32</p> |  <p>2-31: R = C₆F₅ 2-33: R = Ph 2-34: R = Mes 2-35: R = <i>t</i>Bu</p> |
| |  <p>2-39</p> |  <p>2-36: X = Br 2-37: X = Cl</p> |

^a Conversion by comparison of characteristic signals of starting material and product by ¹H NMR spectroscopy.

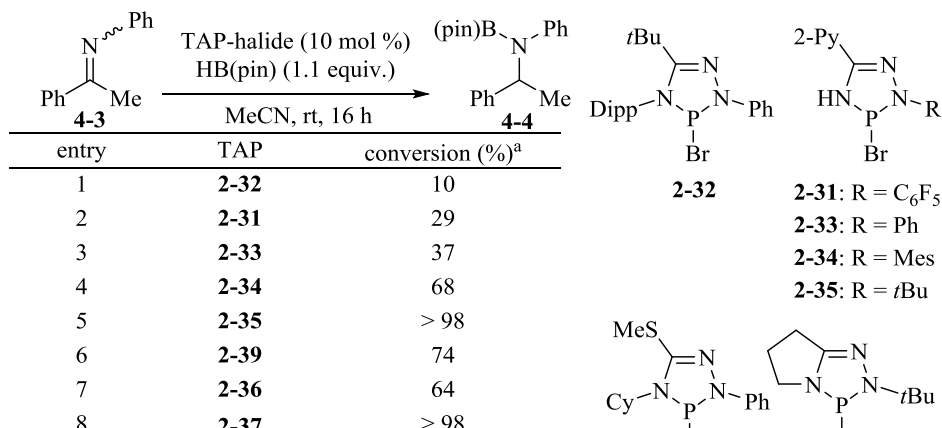
Once the catalytic activity of the TAP-halides was confirmed, I turned my attention to establishing the optimal conditions by screening various solvents. The results are presented in Table 4.3. Using **2-37** as the catalyst, and **4-5** as the model substrate, complete conversion to **4-6** was observed for the reaction in THF (entry 1, Table 4.3). To probe the effects solvent has on the activity of TAP-halides in imine hydroboration, more sterically hindered imine, **4-3**, was employed to make the reduction more challenging. Slight increases in conversions were observed for the reactions in *n*-

Table 4.3 Screening of solvents in the hydroboration of **4-3** and **4-5** catalyzed by **2-37**.


| entry ^a | solvent | conversion (%) ^b |
|--------------------|--------------------------------|-----------------------------|
| 1 ^c | THF | > 98 |
| 2 | THF | 44 |
| 3 | <i>n</i> -pentane | 52 |
| 4 | toluene | 48 |
| 5 | TFT | 78 |
| 6 | benzene- <i>d</i> ₆ | 65 |
| 7 | MeCN | > 98 |

^a Reaction performed with **4-3** unless otherwise stated. ^b Conversion by comparison of characteristic signals of starting material and product by ¹H NMR spectroscopy. ^c Reaction performed with **4-5**.

pentane and toluene (entries 3 and 4, Table 4.3). Modest conversions were observed for the reactions in TFT and benzene-*d*₆ (entries 5 and 6, Table 4.3). Delightfully, quantitative conversion was observed for the reaction performed in MeCN (entry 7, Table 4.3).

Table 4.4 Screening of TAP-halides as catalysts in the hydroboration of **4-3** in MeCN.


| entry | TAP | conversion (%) ^a |
|-------|-------------|-----------------------------|
| 1 | 2-32 | 10 |
| 2 | 2-31 | 29 |
| 3 | 2-33 | 37 |
| 4 | 2-34 | 68 |
| 5 | 2-35 | > 98 |
| 6 | 2-39 | 74 |
| 7 | 2-36 | 64 |
| 8 | 2-37 | > 98 |

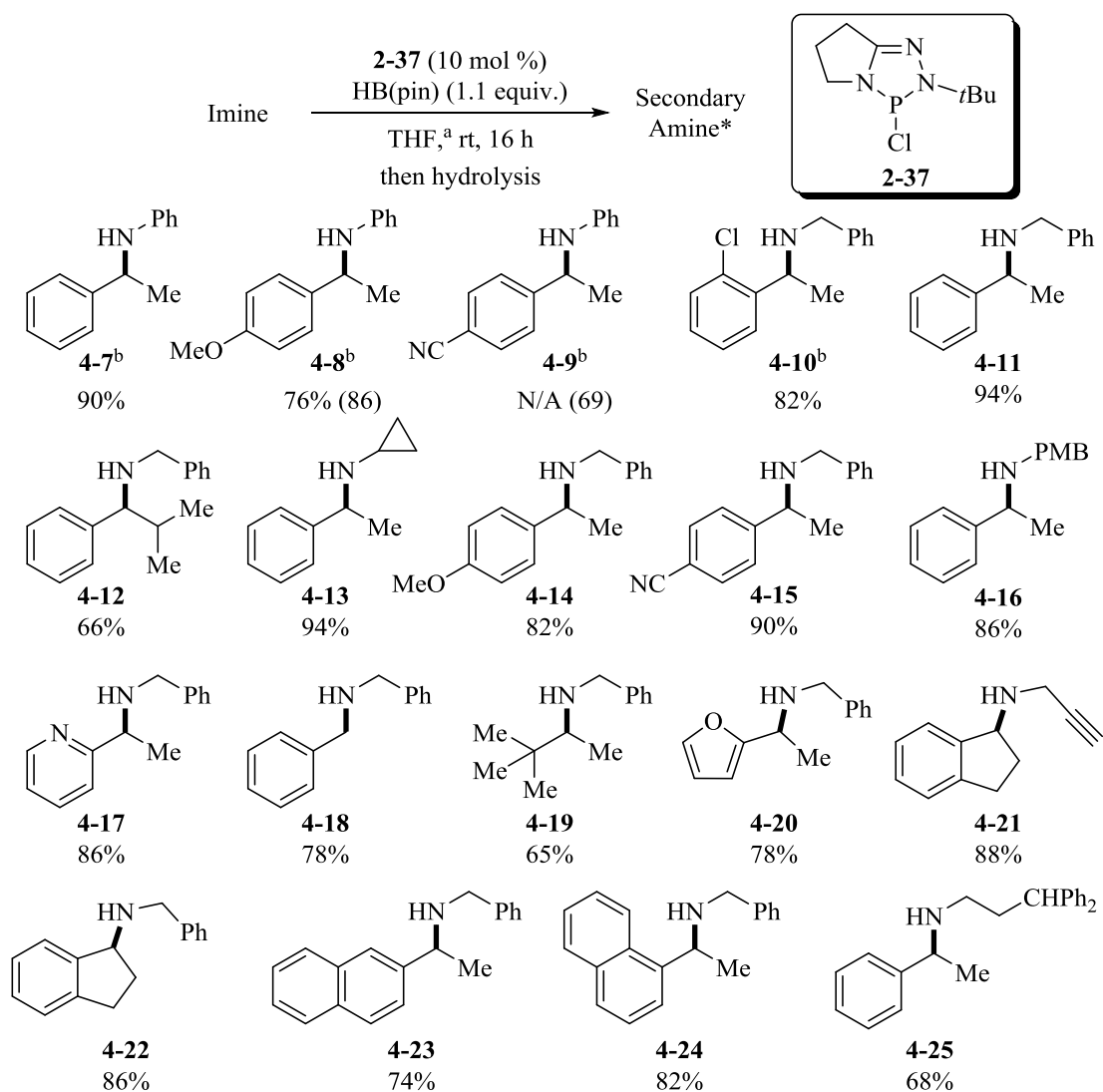
^a Conversion by comparison of characteristic signals of starting material and product by ¹H NMR spectroscopy.

To confirm that all TAP-halides have elevated catalytic activity in MeCN, I decided to perform an additional catalyst screen in MeCN. Again, using **4-3** as the

model substrate, the results are presented in Table 4.4. Sterically hindered **2-32** possessed a slightly higher catalytic activity in MeCN than in THF (entry 1, Table 4.4). A positive correlation between catalytic activity and electronic properties of substituents was observed. TAP-halides derived from more electron donating hydrazines gave higher conversions, with **2-35** being the most active out of the four pyridine-containing TAPs (entries 2 to 5, Table 4.4). TAPs **2-39** and **2-36** both facilitated modest conversion of the imine to the corresponding borylated amine (entries 6 and 7, Table 4.4).

4.3.2 Scope of Imine Hydroboration

An array of prochiral aryl, and alkyl imines were prepared and used in the hydroboration scope study (Scheme 4.2). Although **2-35** and **2-37** have comparable reactivity, **2-37** was chosen as the main catalyst due to the relative ease to prepare the corresponding amidrazone. THF is a suitable solvent for the preparation of most dialkyl amines, with the only exception being **4-10**, with an *ortho*-chloro aryl functional group (50% conversion in THF). Other amines with *ortho*-substituted aryls were afforded with high yields (**4-21**, **4-22**, **4-24**). Furthermore, the reactions furnished sterically hindered amines with modest yields (**4-12**, **4-19**, **4-23**). In cases where high conversion was not achieved, the solvent was substituted with MeCN (**4-7** to **4-10**). It is worth noting that DAPs do not catalyze the hydroboration of aryl amine-derived imines.

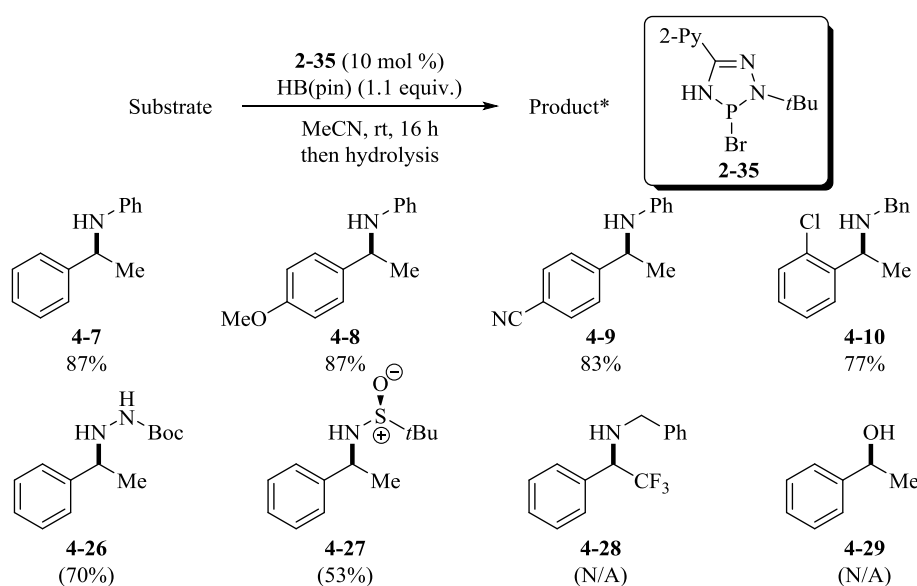


* Bolded bonds indicate former unsaturation; numbers refer to isolated yield after column chromatography; numbers in parentheses indicate conversion based on analysis by ^1H NMR spectroscopy. ^a Unless otherwise stated. ^b Reaction performed in MeCN.

Scheme 4.2 Scope study of imine hydroboration catalyzed by **2-37**.

Both electron donating, and electron withdrawing functional groups are compatible with the catalyst (**4-14** to **4-16**). Heterocycles such as pyridine and furan are well tolerated (**4-17**, **4-20**). No side reactions were observed with cyclopropyl and alkyne groups by ring-opening or reduction (**4-13** and **4-21**). Sterically unhindered imines derived from benzyl amines were all converted to the corresponding alkyl amines with high yields. No deactivation of the catalyst by complexation was observed.

This scope study covers functional groups and structurally diverse imines that may not be tolerant towards transition metal catalysts, or other main group catalysts such as (pentafluorophenyl)borane-derived systems, due to side reactions or catalyst poisoning.²⁰ Furthermore, two amine products afforded in this scope study are pharmaceuticals, namely **4-21** (*rac*-Rasagiline) and **4-25** (Fendiline), displaying applicability of this method towards the preparation of commercialized products.



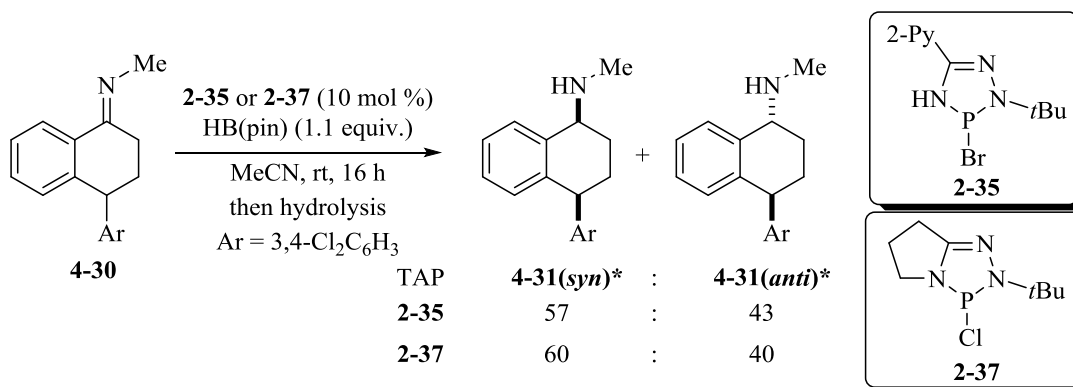
* Bolded bonds indicate former unsaturation; numbers refer to isolated yield after column chromatography; numbers in parentheses indicate conversion based on analysis by ¹H NMR spectroscopy.

Scheme 4.3 Hydroboration of sterically hindered imines, and attempted reduction of various substrates catalyzed by **2-35**.

Only a handful of sterically hindered substrates were subjected to reactions catalyzed by **2-35** (Scheme 4.3). Surprisingly, **2-35** possessed a slightly higher activity than **2-37**, with essentially quantitative conversions to the corresponding amines for all substrates. To further probe the activity of **2-35**, substrates that did not undergo reduction with **2-37** were subjected to the optimized conditions catalyzed by **2-35**

(Scheme 4.3). Disappointingly, in cases where modest conversion was observed, the corresponding hydrolyzed products could not be isolated by column chromatography.

After the catalytic activity of TAPs were established, the diastereoselectivity was explored. The racemic precursor to sertraline (Zoloft), **4-30**, became a target of interest (Scheme 4.4). Under the optimized conditions, **2-37** was able to induce a modest diastereomeric ratio (*d.r.*) of 60:40, with the major product being racemic Zoloft, **4-31(syn)**.⁹⁰ TAP **2-35** promoted a slightly lower *d.r.* of 57:43, again favouring the formation of **4-31(syn)**. To probe the effects the hydrazine substituents have on diastereoselectivity, pyridine-containing TAP-halides, **2-31** and **2-33** to **2-35**, along with **2-37** were employed in the catalyzed hydroboration of **4-32** (Table 4.5).



* Bolded bonds denote relative stereochemistry; numbers indicate enantiomeric ratio.

Scheme 4.4 Diastereoselective hydroboration of **4-30**, catalyzed by **2-35** or **2-37**.

In general, the diastereoselectivity of TAPs in reactions are modest, with mesityl-containing **2-34** providing the highest selectivity. Interestingly, selectivity between the formation of **4-33(S,S)** or **4-33(meso)** is not consistent within the same catalyst scaffold.

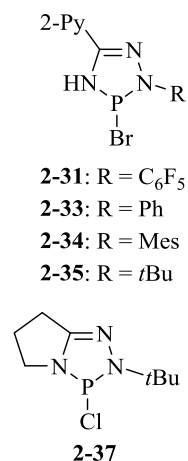
Table 4.5 Diastereoselective hydroboration of **4-32** catalyzed by TAP-halides.

| entry | TAP | yield (%) ^a | <i>d.r.</i> (<i>S,S</i> : <i>meso</i>) ^b |
|-------|-------------|------------------------|---|
| 1 | 2-37 | 80 | 44 : 56 |
| 2 | 2-31 | (74) ^c | 69 : 31 |
| 3 | 2-33 | 88 | 56 : 44 |
| 4 | 2-34 | 92 | 26 : 74 |
| 5 | 2-35 | 84 | 66 : 34 |

^a Numbers refer to isolated yield after column chromatography. ^b

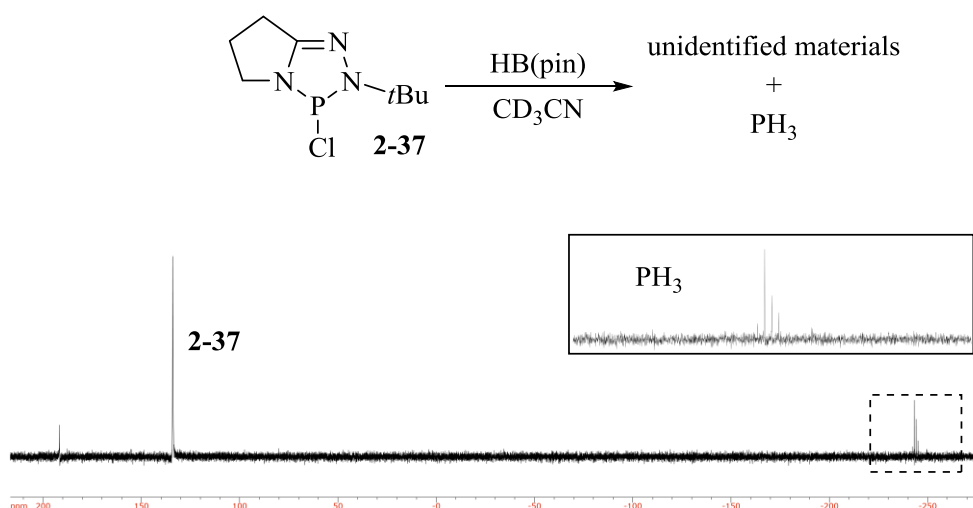
Determined by ¹H NMR spectroscopy by comparison with literature values.

^c Conversion; isolated with acetophenone as impurity.



Namely, **2-34** preferentially facilitated the formation of the *meso* compound, while the rest of the pyridine-containing TAPs catalyzed the formation of the *S,S* variant. Nevertheless, the substituent-dependent selectivity should render TAPs as attractive candidates for further investigation towards the design of highly stereoselective catalysts.

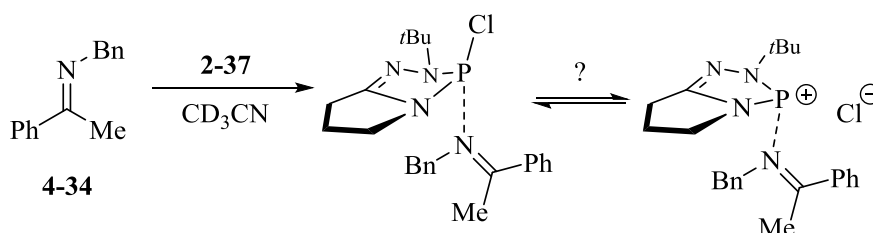
4.3.3 Imine Hydroboration Mechanistic Studies



Scheme 4.5 ³¹P NMR spectrum of reaction between **2-37** and HB(pin), forming PH₃.

Since an active TAP-hydride has not been observed thus far, a NMR mechanistic

study of the reaction was required. No TAP-H formation was observed between the reaction of **2-37** and HB(pin) in CD₃CN as evidenced by the ¹H and ³¹P NMR spectra (See Appendix B). However, insoluble materials began to crash out of solution after about one hour. ³¹P NMR spectroscopy revealed the formation of a quartet signal at -240 ppm, indicative of the decomposition of the catalyst to form PH₃ (Scheme 4.5).^{59a} The addition of 1.1 equivalent of HB(pin) to a stoichiometric mixture of **2-37** and imine **4-34** did not allow the formation of TAP-H either (See Appendix B). Upon complete conversion of **4-34** to the corresponding borylated amine, PH₃ was formed once again (See Appendix B).

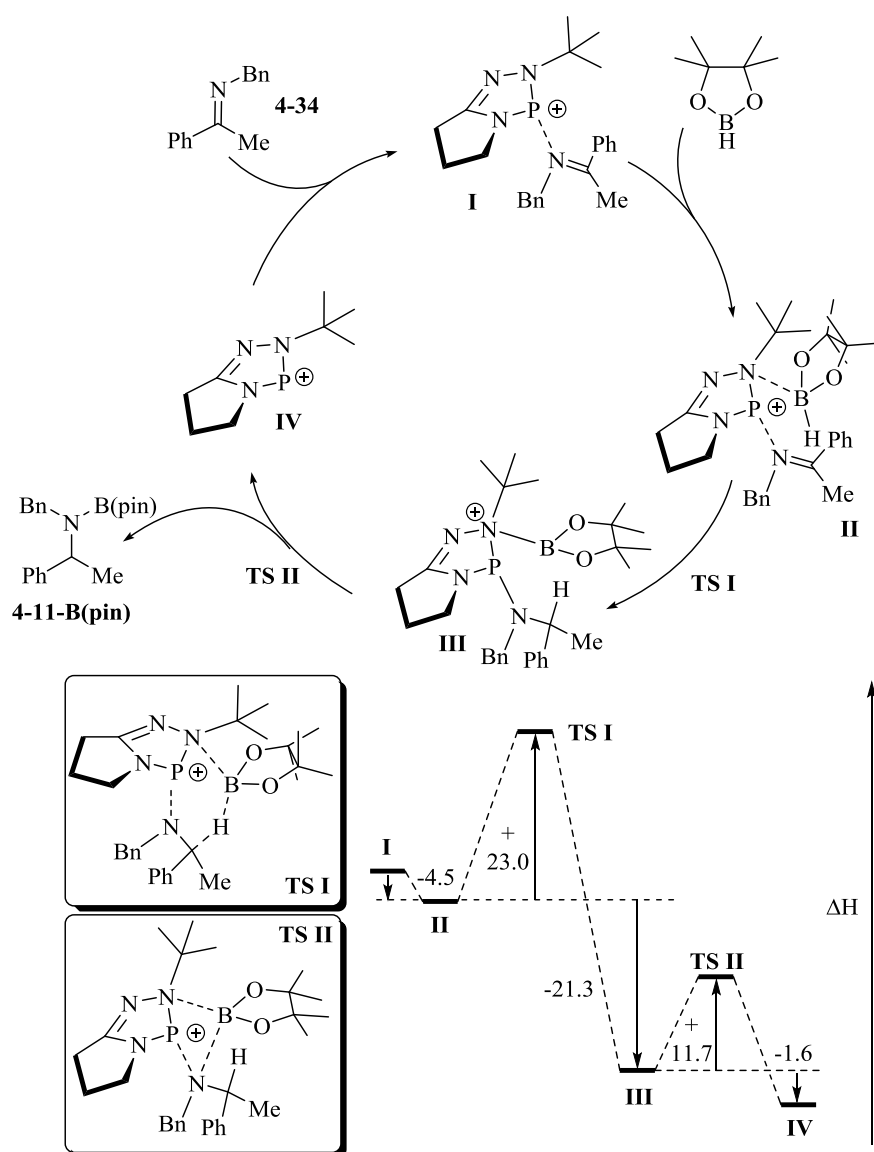


Scheme 4.6 Postulated representation of the coordination between **4-34** and **2-37**, and the dissociation of Cl and planarization of **2-37**.

A stoichiometric mixture of **2-37** and **4-34** in CD₃CN showed a downfield shift of the methyl and benzylic signals of **4-34** in the ¹H NMR spectrum; while no change was observed in the ³¹P NMR spectrum (Appendix B). This suggests a possible interaction between **4-34** and **2-37** by means of coordination (Scheme 4.6). Furthermore, it was speculated that **2-37** is ionized in CD₃CN, since the magnitude of diastereotopicity of the methylene protons of **2-37** is not as strong as the corresponding TAP-alkoxide. This

renders the phosphorous system planar, and achiral.

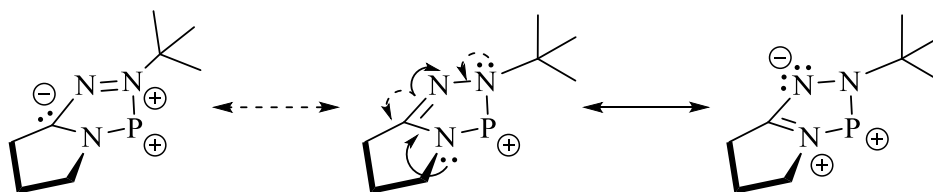
A computational study of this reaction was performed by Prof. Erin R. Johnson (Dalhousie University). Based on the results, a potential catalytic cycle was devised (Scheme 4.7). Assuming **I**, a complex consisting of triazaphosphenium **2-37**, and imine **4-34**, suggested by ^1H NMR, is formed, coordination to HB(pin) from N2 to form **II** is feasible. A subsequent hydride transfer *via* a six-membered transition state, **TS I**, is



Scheme 4.7 Proposed catalytic cycle and potential energy diagram based on ^1H NMR mechanistic studies, and computational evidence.

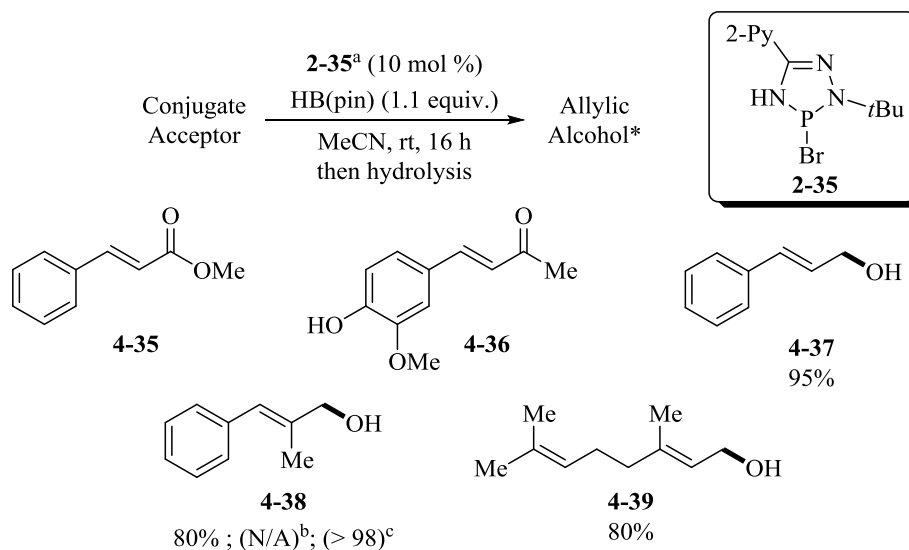
overall exothermic, with an activation barrier of 23.0 kcal/mol, leading to **III**. Complexation of HB(pin) with other Lewis basic sites of the phosphonium was found to render the subsequent elimination step, *via* **TS II**, inaccessible. Ultimately, the borylated amine is formed, exothermically regenerating the active catalyst, **IV**. If the above mechanism is correct, then this would render the TAP-catalyzed hydroboration of imines the first reported case of phosphonium-catalyzed hydroboration.

This mechanism supports not only the results obtained from the ^1H NMR mechanistic studies mentioned previously, but also the results obtained from the catalyst screening as outlined in Table 4.4. Namely, electron donating hydrazine substituents enhance the activity of the catalyst by favouring the coordination between N2 and B(pin), supporting the formation of complex **II**. Furthermore, it was proposed that the coordination preferentially occurs at N2 due to the α -effect⁹¹ imposed by the lone pairs on the neighbouring nitrogen atom in either the parent structure, or the corresponding contributing resonance structure (Scheme 4.8). The competing resonance structure where the lone pair is delocalized onto the carbon atom potentially provides less appreciable α -effect to its neighbouring nitrogen atom (Scheme 4.8).



Scheme 4.8 Resonance structures that could contribute to the α -effect.

4.3.4 1,2-Hydroboration of α,β -Unsaturated Aldehydes



* Bolded bonds indicate former unsaturation; numbers refer to isolated yield after column chromatography; numbers in parentheses indicate conversion based on analysis by ^1H NMR spectroscopy. ^a Unless otherwise stated. ^b Reaction performed with **2-37**. ^c Reaction performed with **2-51**.

Scheme 4.9 Attempted 1,4-hydroboration of **4-35** and **4-36**, and 1,2-hydroboration of conjugated aldehydes to form allylic alcohols.

Other than the hydroboration of imines, DAP-hydrides are also capable of facilitating the 1,4-hydroboration of α,β -unsaturated carbonyls.^{57,58b,59a} To further compare the reactivity between TAPs and DAPs, the reduction of conjugate acceptors was next investigated (Scheme 4.9). Despite the heightened activity **2-35** exerts towards the hydroboration of imines, conjugated carbonyls, namely **4-35** and **4-36**, did not undergo any reduction. However, conjugated aldehydes underwent exclusive 1,2-reduction to afford the corresponding allylic alcohols, **4-37** to **4-39**, respectively. This is distinct from the DAP-catalyzed 1,4-hydroboration reaction.

To add to our surprise, **2-37** was not able to catalyze the same reaction as **2-35**.

Furthermore, TAP-alkoxide **2-51** also catalyzed the 1,2-reduction of conjugated aldehydes. Therefore, it is postulated that the mechanism by which conjugated aldehydes are reduced is different than that of imines. This study, combined with part of Chapter 2, has been published in *Organic Letters*.⁶²

4.4 Catalyzed Asymmetric Hydroboration of Imines

The synthesis of enantioenriched amines represents an important step towards the preparation of pharmaceutical drugs, as previously mentioned.⁸⁹ Common methods include the asymmetric reduction of prochiral imines,^{18,25,31,32} use of chiral auxiliaries,⁹² and enzymatic resolution⁹³. Our group in particular is interested in the synthesis of chiral amines from prochiral substrates. Although many catalysts mentioned in Chapter 1 are competent in such transformation, the use of (pentafluorophenyl)borane- or binaphthyl-derived scaffolds, along with exotic reductants such as Hantzsch esters render these methods impractical. Therefore, the development of more economical, non-racemic catalysts is of interest.

4.4.1 TAP-Catalyzed Asymmetric Hydroboration of Imines

Using the indanol-derived TAP-benzyloxides and TAP-Br, **3-39**, the catalyzed reduction of two imines was attempted, and the enantioselectivity assessed (Table 4.6). Electron-deficient TAP-alkoxide **3-48** did not catalyze the reduction of **4-3** in CDCl₃ (entry 1, Table 4.6). The use of halogenated solvent and/or an electron-withdrawing

Table 4.6 Asymmetric hydroboration of imines **4-3** and **4-40**, catalyzed by indanol-derived TAPs.

| entry | TAP | conversion (%) ^d | <i>e.r.</i> ^e |
|----------------|-------------|-----------------------------|--------------------------|
| 1 ^f | 3-48 | N/A ^g | - |
| 2 | 3-49 | 20 | 76 : 24 |
| 3 | 3-50 | 50 | 81 : 19 |
| 4 | 3-39 | 67 | 62 : 38 |
| 5 | 3-49 | > 98 | 57 : 43 |
| 6 | 3-50 | 89 | 58 : 42 |

^a Used in entries 1 to 4. ^b Used in entries 5 and 6. ^c Unless otherwise stated. ^d Based on analysis by ¹H NMR spectroscopy. ^e Based on analysis by HPLC on a chiral stationary phase. ^f Reaction performed in CDCl₃.

3-39: R = *t*Bu; X = Br
3-48: R = C₆F₅; X = OBn
3-49: R = Mes; X = OBn
3-50: R = *t*Bu; X = OBn

substituent could both contribute to the observed low reactivity. Bulky **3-49** partially reduced **4-3** with a modest *e.r.* of 76:24 (entry 2, Table 4.6). The catalytically more active **3-50** on the other hand, afforded the corresponding enantioenriched amine with an *e.r.* of 81:19. (entry 3, Table 4.6). Motivated by the enhanced selectivity, I employed the even more active **3-39**, precursor to **3-50**, under the same conditions to assess the effectiveness of TAP-halides in this transformation. Disappointingly, **3-39** only catalyzed the formation of amine with a 62:38 *e.r.* (entry 4, Table 4.6). By switching from **4-3** to a sterically less hindered imine, namely **4-40**, both active TAP-alkoxides afforded the corresponding amine products with inferior *e.r.* (entries 5 and 6, Table 4.6).

Subsequently, the stereoselectivity of thiolated, non-racemic TAP-halides, **3-42** to **3-47**, in the hydroboration of imines was explored (Table 4.7). In contrast with indanol-derived TAPs, this class of TAPs has the advantage of being more easily modified,

Table 4.7 Asymmetric hydroboration of imines **4-41** and **4-3**, catalyzed by thiolated, acyclic TAPs, **3-42** to **3-47**.

| entry | TAP | yield (%) ^c | <i>e.r.</i> ^d |
|-------|-------------|------------------------|--------------------------|
| 1 | 3-42 | 47 | 47:53 |
| 2 | 3-43 | 83 | 53:47 |
| 3 | 3-44 | 77 | 42:58 |
| 4 | 3-45 | 71 | 48:52 |
| 5 | 3-46 | 85 | 46:54 |
| 6 | 3-42 | 73 | 49:51 |
| 7 | 3-43 | 79 | 49:51 |
| 8 | 3-44 | 88 | 50:50 |
| 9 | 3-45 | 81 | 49:51 |
| 10 | 3-46 | 77 | 47:53 |
| 11 | 3-47 | 62 | 51:49 |

3-42: R = C₆F₅ **3-45:** R = Cy
3-43: R = Ph **3-46:** R = *t*Bu
3-44: R = Mes

3-47

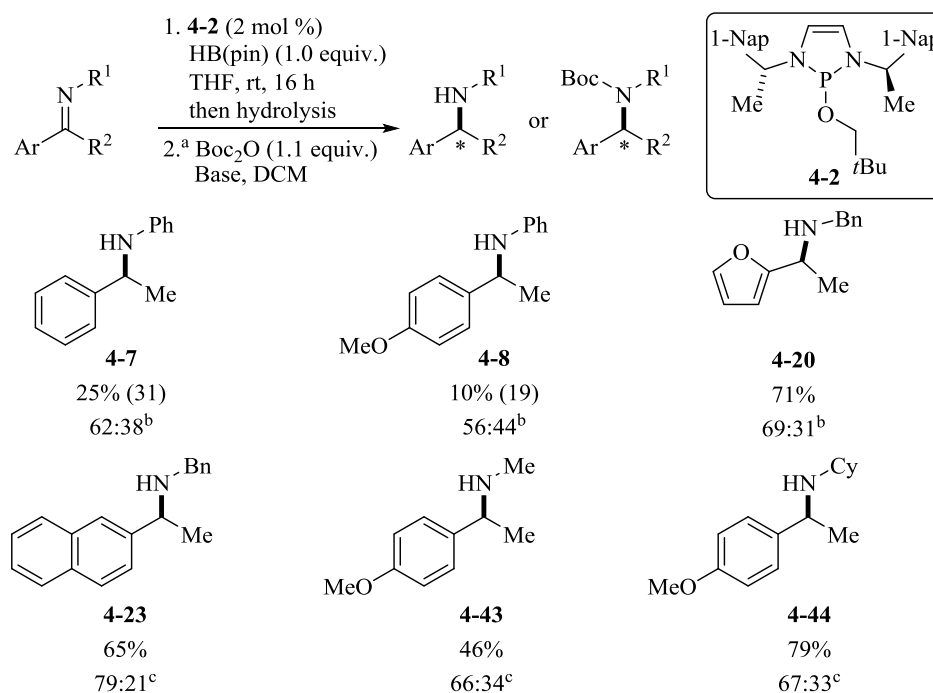
^a Used in entries 1 to 5. ^b Used in entries 6 to 11. ^c Isolated yield after column chromatography. ^d Based on analysis by HPLC on a chiral stationary phase.

starting from cheap, commercially available materials. Using the precursor to Rasagiline, **4-41**, and **4-3** as model substrates, the results are presented in Table 4.7. No correlation between the nature of the hydrazine substituent and the stereoselectivity could be deduced. Aromatic and alkyl hydrazine-derived TAPs all facilitated the formation of Rasagiline with good yields, albeit with negligible enantioselectivity under the given conditions (entries 1 to 5, Table 4.7). Racemic mixtures of **4-7** were also afforded in reactions catalyzed by TAPs derived from (*S*)-1-phenylethylamine (entries 6 to 10, Table 4.7). Switching to a more sterically hindered TAP, **3-47**, derived from (*R*)-1-naphthylethylamine, unfortunately did not enhance the stereoselectivity of

the catalyst (entry 11, Table 4.7).

In comparison with the modest selectivity afforded with cyclic TAPs, where N-C* (chiral centre) bond rotation is hindered, free rotation around the N-C* bond proved to be detrimental to stereoselectivity. As previously mentioned, no attempts were made to convert the halides to the corresponding benzyloxides to assess the stereoselectivity. Due to complications that might arise from using impure mixtures, the stereoselectivity of **3-40** and **3-41** in the catalyzed hydroboration reaction also was not assessed.

4.4.2 DAP-Catalyzed Asymmetric Hydroboration of Imines

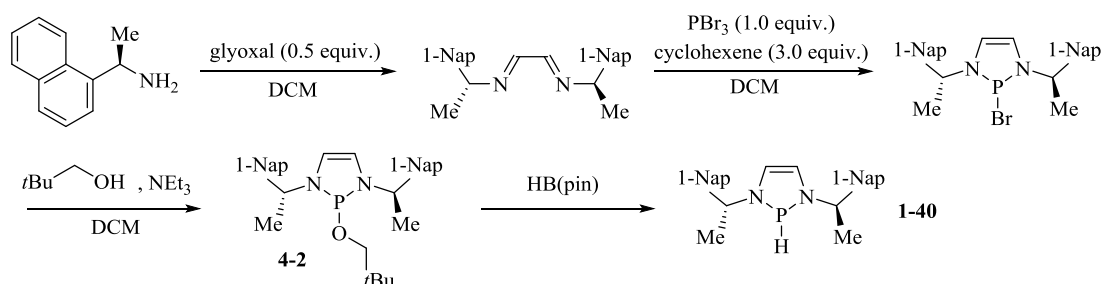


*Bolded bonds indicate relative stereochemistry; numbers refer to isolated yield after column chromatography; numbers in parentheses indicate conversion based on analysis by ¹H NMR spectroscopy. ^a Performed if the *er* of the free amine cannot be determined by HPLC. ^b *Er* determined by HPLC analysis as the amine on a chiral stationary phase. ^c *Er* determined by HPLC analysis as the carbamate on a chiral stationary phase.

Scheme 4.10 DAP-catalyzed asymmetric hydroboration of imines.

Aside from the TAP projects, I was also involved in the imine hydroboration scope

study catalyzed by DAP **1-40**. This work is published in *Angewandte Chemie International Edition*.^{59b} A small scope of prochiral imines was asymmetrically reduced by **1-40** (Scheme 4.10). The catalyst is formed *in situ* from reaction of HB(pin) with **4-2**, developed by my colleague, Mr. Matt Adams (Scheme 4.11). Unlike TAPs, where *e.r.* was highest with aniline-derived **4-7**, benzyl-derived imines were in general reduced with higher stereoselectivity. Furthermore, **4-2**, easily synthesized in three steps, can be employed at a lower loading than TAPs (2 mol % vs. 10 mol %). This renders non-racemic DAPs as more attractive catalysts than TAPs in the asymmetric reduction of the imines we have investigated.



Scheme 4.11 Synthesis of **1-40**, from **4-2**, which is made in three steps.

4.5 Conclusion

TAP-halides proved to be competent in the racemic reduction of a number of structurally, and electronically diverse imines, that would otherwise be incompatible with many transitional metal- and main group element-based catalysts. With the help of Prof. Erin R. Johnson, a catalytic cycle of the reaction was postulated. Furthermore, a difference in reactivity between TAP- and DAP-catalyzed hydroboration of

conjugated aldehydes was observed. The TAP-catalyzed asymmetric hydroboration of imines was briefly investigated, and modest results were obtained. In contrast, more promising enantioselectivity in the hydroboration of imines is displayed by DAP **4-2**.

4.6 Experimental Section

4.6.1 General Considerations

Only the best enantiomeric ratio obtained for each amine is reported. Hydroboration reactions were carried out in 1- or 4-dram oven dried scintillation vials equipped with magnetic stir bars and green Qorpak® PTFE lined caps. Substrates, reagents and solvents were loaded into vials inside the IT Glovebox. Reactions at ambient temperature were stirred within the glovebox. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR data were collected at 300 K or 338 K on Bruker AV-500 or AV-300 NMR spectrometers. Standard NMR tubes and caps were used. Caps on sensitive samples were overwrapped with PTFE tape. Chemical shifts are reported in ppm. ^1H NMR spectra are referenced to residual non-deuterated NMR solvent ($\text{CHCl}_3 = 7.26$ ppm, $\text{CHD}_2\text{CN} = 1.94$ ppm). $^{13}\text{C}\{^1\text{H}\}$ NMR spectra are referenced to the central CDCl_3 peak (77.0 ppm), and CD_3CN methyl peak (1.32 ppm).

4.6.2 Synthesis and Characterization

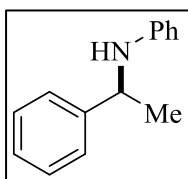
General Procedure A: Inside the glovebox, the substrate to be reduced was dissolved in THF or MeCN in a 1-dram vial (0.1 to 0.4 M). The catalyst (10 or 2 mol

%) was added, then HB(pin) (1.1 or 1.0 equiv.) was added as a neat liquid. The resulting mixture was stirred for 16 h. After completion of the reaction, the solvent was removed *in vacuo*, and a ¹H NMR spectrum was recorded to determine conversion. The solvent was removed *in vacuo*, then the residue was dissolved in diethyl ether (5 mL), and concentrated sulfuric acid (0.5 mL) was added dropwise (aqueous 2 M HCl was used for the work-up of **4-13** and **4-20**). Distilled water (10 mL) was added to dissolve the resulting product-sulfate salt, and pinacol was removed by washing this aqueous solution with diethyl ether (20 mL). The aqueous layer was made basic with 2 M KOH, then extracted with diethyl ether (30 mL x 3), which was removed *in vacuo*. The resulting residue was dissolved in minimal *n*-hexane then further purified by flash column chromatography with grade I basic alumina using a mixture of diethyl ether and *n*-hexane, then pure ethyl acetate to elute the amine (aniline derived amines were purified without the use of ethyl acetate).

General Procedure B: Inside the glovebox, the substrate to be reduced was dissolved in MeCN in a 1-dram vial (0.1 to 0.4 M). The catalyst (10 mol %) was added, then HB(pin) (1.1 equiv.) was added as a neat liquid. The resulting mixture was stirred for 16 h. After completion of the reaction, the solvent was removed *in vacuo*, and a ¹H NMR spectrum was recorded to determine conversion. Then the residue was diluted with DCM (5 mL), and 2 M KOH (5 mL) was added. The resulting biphasic mixture

was stirred for 0.5 h at rt. The organic layer was extracted then the solvent was removed *in vacuo*. The resulting residue was dissolved in minimal *n*-hexane then further purified by flash column chromatography with grade I basic alumina (amines) or 230-400 mesh silica (alcohols) using a mixture of ethyl acetate and *n*-hexane.

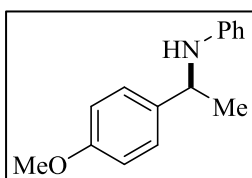
***N*-Phenyl-1-phenylethylamine (4-7):**⁹⁴ *N*-(1-Phenylethylidene)aniline (30 mg



using **2-35** and **2-37**, 0.154 mmol; 49 mg using **3-50**, 0.253 mmol; 100 mg using **4-2**, 0.512 mmol) was subjected to general procedure B in

MeCN (1 mL) using **2-35** and **2-37**, or general procedure A in THF (1 to 1.5 mL) using **3-50** and **4-2**, to afford the product as a yellow oil (26 mg, 0.132 mmol, 87% using **2-35**; 27 mg, 0.137 mmol, 90% using **2-37**; 20 mg, 0.101 mmol, 41% using **3-50**; 25 mg, 0.127 mmol, 25% using **4-2**). ¹H NMR (500 MHz, CDCl₃) δ: 7.36 (m, 2H), 7.31 (m, 2H), 7.22 (m, 1H), 7.08 (m, 2H) 6.63 (m, 1H), 6.51 (m, 2H), 4.48 (br q, *J* = 6.5 Hz, 1H), 4.00, (br s, 1H), 1.51 (d, *J* = 6.5 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 147.4, 145.4, 129.2, 128.8, 127.0, 126.0, 117.4, 113.4, 53.6, 25.1. The enantiomeric ratio of the product from the reduction using **3-50** was determined by HPLC on an Astec Cellulose DMP column eluted with 99% *n*-hexane and 1% *i*PrOH with a flow rate of 0.55 mL/min: *t*_{major} = 20.598 min; *t*_{minor} = 17.723 min; *e.r.* = 81:19.

***N*-Phenyl-1-(4-methoxyphenyl)ethylamine (4-8):**⁹⁴ *N*-[1-(4-Methoxyphenyl)-



ethylidene]aniline (30 mg using **2-35**, 0.133 mmol; 50 mg using **2-37**, 0.222 mmol; 100 mg using **4-2**, 0.444 mmol) was subjected

to general procedure B in MeCN (1 mL) using **2-35** and **2-37**, or general procedure A in THF (1.5 mL) using **4-2**, to afford the product as a colourless oil (26 mg, 0.114 mmol, 87% using **2-35**; 38 mg, 0.167 mmol, 76% using **2-37**, 10 mg, 0.044 mmol, 10% using

4-2). **Reduction of 1 mmol of substrate using 2-35 or 2-37:** *N*-[1-(4-

Methoxyphenyl)ethylidene]aniline (225 mg, 1.00 mmol) was subjected to general procedure B in MeCN (3 mL) using either **2-35** or **2-37** to afford the product as a

colourless oil (225 mg, 0.96 mmol, 96% using **2-35**; 208 mg, 0.92 mmol, 92% using **2-**

37). ¹H NMR (500 MHz, CDCl₃) δ: 7.27 (m, 2H), 7.09 (m, 2H), 6.85 (m, 2H), 6.63 (t,

J = 7.5 Hz, 1H), 6.50 (d, *J* = 7.5 Hz, 2H), 4.44 (q, *J* = 6.5 Hz, 1 H), 3.96 (br s, 1H), 3.78

(s, 3H), 1.48 (d, *J* = 6.5 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 158.6, 147.5,

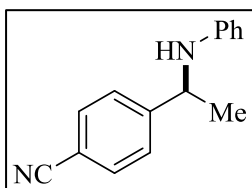
137.4, 129.2, 127.0, 117.3, 114.2, 113.5, 55.4, 53.0, 25.1. The enantiomeric ratio of the

product from the reduction using **4-2** was determined by HPLC on an Astec Cellulose

DMP column eluted with 99% *n*-hexane and 1% *i*PrOH with a flow rate of 0.55 mL/min:

*t*_{major} = 24.569 min; *t*_{minor} = 25.533 min; *e.r.* = 56:44.

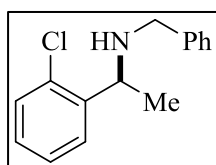
***N*-Phenyl-1-(4-cyanophenyl)ethylamine (4-9):**⁹⁴ *N*-[1-(4-Cyanophenyl)-



ethylidene]aniline (30 mg using **2-35**, 0.136 mmol; 50 mg using **2-37**, 0.227 mmol) was subjected to general procedure B in

MeCN (1 mL) to afford the product as a colourless solid (25 mg, 0.112 mmol, 83% using **2-35**). In the case where complete conversion was not achieved, the product could not be isolated from the ketone impurity. ^1H NMR (500 MHz, CDCl_3) δ : 7.60 (leaning d, $J = 8.5$ Hz, 2H), 7.48 (leaning d, $J = 8.0$ Hz, 2H), 7.09 (m, 2H), 6.68 (m, 1H), 6.43 (m, 2H), 4.51 (q, $J = 7.0$ Hz, 1H), 4.06 (br s, 1H), 1.52 (t, $J = 7.0$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 151.2, 146.7, 132.7, 129.3, 126.8, 119.1, 118.0, 113.4, 110.9, 53.6, 25.1.

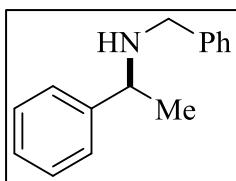
***N*-Benzyl-1-(2-chlorophenyl)ethylamine (4-10):** *N*-[1-(2-Chlorophenyl)-



ethylidene]benzylamine (30 mg using **2-35**, 0.123 mmol; 50 mg using **2-37**, 0.205 mmol) was subjected to general procedure A in

MeCN (1 mL) to afford the product as a yellow oil (23 mg, 0.094 mmol, 77% using **2-35**; 41 mg, 0.167 mmol, 82% using **2-37**). ^1H NMR (500 MHz, CDCl_3) δ : 7.61 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.35-7.22 (m, 7H), 7.17 (td, $J = 8.0, 1.5$ Hz, 1H), 4.34 (q, $J = 6.5$ Hz, 1H), 3.62 (AB q, 2H), 1.59 (br s, 1H), 1.35 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 142.6, 140.7, 133.5, 129.8, 128.5, 128.3, 127.9, 127.6, 127.3, 127.1, 54.0, 51.9, 22.9. HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{17}\text{ClN}$ $[\text{M}+\text{H}]^+$: 246.1044; found: 246.1046.

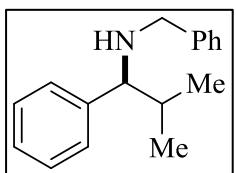
***N*-Benzyl-1-phenylethylamine (4-11):** ⁹⁵ *N*-(1-Phenylethylidene)benzylamine (50 mg using **2-37**, 0.239 mmol; 0.250 g using **4-2**, 1.20 mmol) was subjected to general



procedure A in THF (1 mL) to afford the product as a yellow oil (47 mg, 0.222 mmol, 94% using **2-37**; 0.226 g, 1.07 mmol, 90%

using **4-2**). ^1H NMR (500 MHz, CDCl_3) δ : 7.37-7.22 (m, 10H), 3.81 (q, $J = 6.5$ Hz, 1H), 3.63 (AB q, 2H), 1.54 (br s, 1H), 1.37 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 145.8, 140.9, 128.6, 128.5, 128.3, 127.1, 127.0, 126.9, 57.7, 51.8, 24.7.

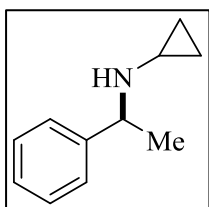
N-Benzyl-2-methyl-1-phenylpropylamine (4-12): ⁹⁶ *N*-(2-Methyl-1-phenyl-



propylidene)benzylamine (50 mg, 0.211 mmol) was subjected to general procedure A in THF (1 mL) to afford the product as a

colourless oil (33 mg, 0.138 mmol, 66%). ^1H NMR (300 MHz, CDCl_3) δ : 7.36-7.20 (m, 10H), 3.67 (leaning d, $J = 22.0$ Hz, 1H), 3.47 (leaning d, $J = 22.0$ Hz, 1H), 3.35 (d, $J = 6.9$ Hz, 1H), 2.00-1.49 (*N-H* and isopropyl *C-H* overlapped, 2H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.9$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ : 128.4, 128.4, 128.3, 128.2, 127.0, 127.0, 68.8, 51.8, 34.5, 19.8, 19.6; some signals in the aryl region are overlapped with one another.

N-Cyclopropyl-1-phenylethylamine (4-13): ⁹⁷ *N*-(1-Phenylethylidene)-



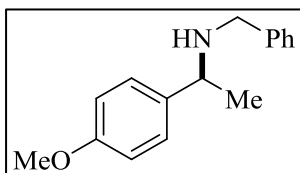
cyclopropylamine (100 mg, 0.629 mmol) was subjected to general procedure A in THF (2 mL), and work-up using aqueous 2 M HCl

instead of sulfuric acid to afford the product as a yellow oil (83 mg, 0.515 mmol, 83%).

^1H NMR (500 MHz, CDCl_3) δ : 7.34-7.21 (m, 5H), 3.85 (q, $J = 7.0$ Hz, 1H), 1.97- 1.95

(m, 1H), 1.76 (br s, 1H), 1.36 (d, $J = 7.0$ Hz, 3H), 0.40-0.27 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 146.2, 128.5, 126.9, 126.7, 58.5, 29.1, 23.8, 6.58.

***N*-Benzyl-1-(4-methoxyphenyl)ethylamine (4-14):**⁹⁸ *N*-[1-(4-Methoxyphenyl)-



ethylidene]benzylamine (50 mg using **2-37**, 0.209 mmol; 60 mg using **3-50**, 0.253 mmol) was subjected to general

procedure A in THF (1 mL) to afford the product as a yellow oil (41 mg, 0.170 mmol,

81% using **2-37**; 45 mg, 0.188 mmol, 74% using **3-50**). ^1H NMR (500 MHz, CDCl_3) δ :

7.31-7.23 (m, 7H), 6.89-6.88 (m, 2H), 3.81 (s, 3H), 3.77 (q, $J = 6.5$ Hz, 1H), 3.54 (AB

q, 2H), 1.53 (s, 1H), 1.34 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ :

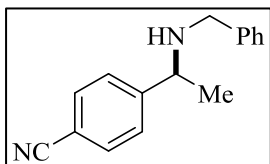
158.6, 140.8, 137.7, 128.4, 128.1, 127.7, 126.8, 113.8, 56.8, 55.3, 51.6, 24.5. The

enantiomeric ratio of the product from the reduction using **3-50** was determined by

HPLC on an Astec Cellulose DMP column eluted with 99% *n*-hexane and 1% *i*PrOH

with a flow rate of 0.55 mL/min: $t_{\text{major}} = 12.963$ min; $t_{\text{minor}} = 14.101$ min; *e.r.* = 58:42.

***N*-Benzyl-1-(4-cyanophenyl)ethylamine (4-15):** *N*-[1-(4-Cyanophenyl)-ethyl-



idene]benzylamine (50 mg, 0.213 mmol) was subjected to general procedure A in THF (1 mL) to afford the product as a

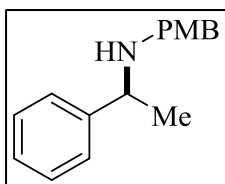
yellow oil (45 mg, 0.190 mmol, 90%). ^1H NMR (500 MHz, CDCl_3) δ : 7.62 (leaning d,

$J = 8.0$ Hz, 2H), 7.48 (leaning d, $J = 8.0$ Hz, 2H), 7.33-7.23 (m, 5H), 3.87 (q, $J = 6.5$

Hz, 1H), 3.60 (AB q, 2H), 1.62 (br s, 1H), 1.34 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125

MHz, CDCl₃) δ : 151.5, 140.2, 132.5, 128.6, 128.1, 127.7, 127.2, 119.1, 110.9, 57.5, 51.9, 24.6. HRMS (ESI) m/z calc'd for C₁₆H₁₇N₂ [M+H]⁺: 237.1386; found: 237.1387.

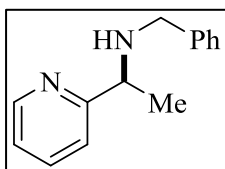
***N*-(4-Methoxybenzyl)-1-phenylethylamine (4-16)**:⁹⁵ 4-Methoxy-*N*-(1-phenyl-



ethylidene)benzylamine (50 mg, 0.209 mmol) was subjected to general procedure A in THF (1 mL) to afford the product as a yellow

oil (43 mg, 0.178 mmol, 86%). ¹H NMR (500 MHz, CDCl₃) δ : 7.36-7.32 (m, 4H), 7.26-7.24 (m, 1H), 7.19 (m, 1H), 6.84 (m, 2H), 3.82-3.78 (overlapped s and q, 4H), 3.61-3.52 (AB q, 2H), 1.50 (br s, 1H), 1.35 (d, J = 6.5 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ : 158.7, 145.8, 133.0, 129.4, 128.6, 127.0, 126.9, 113.9, 57.6, 55.4, 51.2, 24.7.

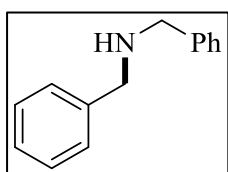
***N*-Benzyl-1-(2-pyridyl)ethylamine (4-17)**:^{59a} *N*-[1-(2-Pyridyl)ethylidene]-



benzylamine (50 mg, 0.238 mmol) was subjected to general procedure A in THF (1 mL) to afford the product as a yellow oil (43

mg, 0.203 mmol, 86%). ¹H NMR (300 MHz, CDCl₃) δ : 8.59-8.57 (m, 1H), 7.65 (td, J = 7.5, 1.8 Hz, 1H), 7.36-7.13 (m, 7H), 3.92 (q, J = 6.6 Hz, 1H), 3.65 (AB q, 2H), 1.98 (br s, 1H), 1.41 (d, J = 6.6 Hz, 3H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ : 164.8, 149.5, 140.7, 136.6, 128.5, 128.3, 127.0, 122.0, 121.4, 58.9, 51.9, 23.1.

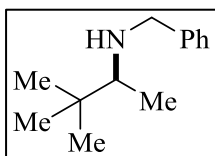
Dibenzylamine (4-18):⁹⁹ Benzyl(benzylidene)amine (50 mg, 0.256 mmol) was



subjected to general procedure A in THF (1 mL) to afford the product as a yellow oil (39 mg, 0.198 mmol, 78%). ¹H NMR (300

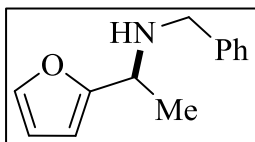
MHz, CDCl₃) δ : 7.36-7.22 (m, 10 H), 3.81 (s, 4H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ : 140.5, 128.5, 128.3, 127.1, 53.4.

***N*-Benzyl-1-(*tert*-butyl)ethylamine (4-19):**^{59a} *N*-[(*tert*-Butyl)ethylidene]-



benzylamine (50 mg, 0.264 mmol) was subjected to general procedure A in THF (1 mL) to afford the product as a yellow oil (33 mg, 0.172 mmol, 65%). ¹H NMR (500 MHz, CDCl₃) δ : 7.35-7.21 (m, 5H), 3.94-3.64 (AB q, 2H), 2.30 (q, *J* = 6.4 Hz, 1H), 1.27 (broad s, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ : 141.3, 128.2, 128.2, 126.7, 61.3, 52.7, 34.5, 26.5, 14.7.

***N*-Benzyl-1-(2-furyl)ethylamine (4-20):**⁹⁵ *N*-[1-(2-Furyl)ethylidene]benzyl-

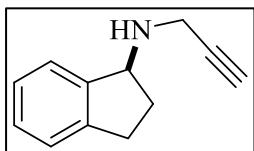


amine (50 mg using **2-37**, 0.251 mmol; 0.200 g using **4-2**, 1.00 mmol) was subjected to general procedure A in THF (1 or 3 mL), and work-up using aqueous 2 M HCl instead of sulfuric acid to afford the product as a yellow oil (39 mg, 0.194 mmol, 78% using **2-37**; 0.142 g, 0.706, 71% using **4-2**). ¹H NMR (300 MHz, CDCl₃) δ : 7.37-7.20 (m, 6H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.16 (m, 1H), 3.89 (q, *J* = 6.6 Hz, 1H), 3.70 (AB q, 2H), 1.43 (d, *J* = 6.6 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ : 158.0, 141.5, 140.5, 128.5, 128.3, 127.0, 110.0, 105.6, 51.3, 50.7, 20.6. The enantiomeric ratio of the product from the reduction using **4-2** was determined by HPLC on an Astec Cellulose DMP column eluted with 99% *n*-hexane

and 1% *i*PrOH with a flow rate of 0.55 mL/min: $t_{\text{major}} = 13.421$ min; $t_{\text{minor}} = 14.268$ min;

e.r. = 69:31.

***N*-Propargyl-1-indanamine (4-21):**^{59a} *N*-[(Indane)ethylidene]propargylamine



(50 mg using **2-37**, 0.295 mmol; 22 mg using **3-44**, 0.128 mmol)

was subjected to general procedure A using **2-37** in THF (1 mL),

and general procedure B using **3-44** to afford the product as a brown oil (44 mg, 0.257

mmol, 87% using **2-37**, 17 mg, 0.099 mmol, 78% using **3-44**). ¹H NMR (500 MHz,

CDCl₃) δ : 7.38-7.20 (m, 4H), 4.46-4.42 (m, 1H), 3.55-3.54 (m, 2H), 3.12-3.02 (m, 1H),

2.90-2.80 (m, 1H), 2.48-2.37 (m, 1H), 2.28 (t, $J = 2.4$ Hz, 1H), 1.94-1.84 (m, 1H), 1.51

(broad s, 1H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ : 144.5, 143.8, 127.6, 126.2, 124.8,

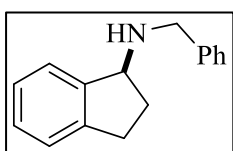
124.2, 82.5, 71.3, 61.9, 36.2, 33.3, 30.5. The enantiomeric ratio of the product from the

reduction using **3-44** was determined by HPLC on a Chiralpak ADH column eluted

with 99% *n*-hexane and 1% *i*PrOH with a flow rate of 0.75 mL/min: $t_{\text{major}} = 15.010$ min;

$t_{\text{minor}} = 14.161$ min; *e.r.* = 52:48.

***N*-Benzyl-1-indanamine (4-22):**^{59a} *N*-[(Indane)ethylidene]benzylamine (50 mg,



0.226 mmol) was subjected to general procedure A in THF (1 mL)

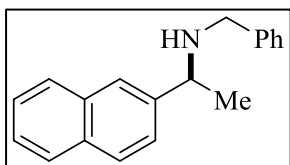
to afford the product as a brown oil (43 mg, 0.193 mmol, 85%). ¹H

NMR (500 MHz, CDCl₃) δ : 7.44-7.23 (m, 9H), 4.33 (t, $J = 6.4$ Hz, 1H), 3.98-3.88 (m,

2H), 3.11-3.01 (m, 1H), 2.89-2.81 (m, 1H), 2.48-2.42 (m, 1H), 1.97-1.90 (m, 1H), 1.69

(broad s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 145.3, 143.7, 140.7, 128.4, 128.2, 127.4, 126.9, 126.3, 124.8, 62.8, 51.4, 33.7, 30.4.

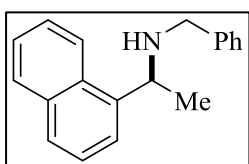
***N*-Benzyl-1-(2-naphthyl)ethylamine (4-23):**⁹⁵ *N*-[1-(2-Naphthyl)ethylidene]-



benzylamine (50 mg using **2-37**, 0.193 mmol; 0.250 g using **4-2**, 0.964 mmol) was subjected to general procedure A in THF

(1 or 2 mL) to afford the product as a colourless solid (37 mg, 0.142 mmol, 74% using **2-37**; 0.162 g, 0.620 mmol, 65% using **4-2**). ^1H NMR (300 MHz, CDCl_3) δ : 7.85-7.77 (m, 3H), 7.77 (m, 1H), 7.55-7.41 (m, 3H), 7.34-7.21 (m, 5H), 3.98 (q, $J = 6.6$ Hz, 1H), 3.65 (AB q, 2H), 1.64 (br s, 1H), 1.43 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ : 143.2, 140.8, 133.7, 133.0, 128.5, 128.4, 128.3, 127.9, 127.8, 127.0, 126.1, 125.6, 125.5, 125.1, 57.8, 51.9, 24.6. The enantiomeric ratio of the product from the reduction using **4-2** was determined by HPLC on a Chiralpak ADH column eluted with 99% *n*-hexane and 1% *i*PrOH with a flow rate of 0.75 mL/min: $t_{\text{major}} = 14.437$ min; $t_{\text{minor}} = 15.530$ min; *e.r.* = 79:21.

***N*-Benzyl-1-(1-naphthyl)ethylamine (4-24):**¹⁰⁰ *N*-[1-(1-Naphthyl)ethylidene]-

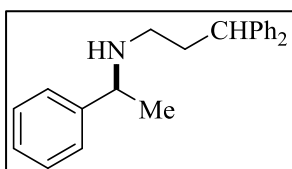


benzylamine (100 mg, 0.386 mmol) was subjected to general procedure A in THF (2 mL) to afford the product as a yellow oil

(82 mg, 0.314 mmol, 82%). ^1H NMR (300 MHz, CDCl_3) δ : 8.15 (m, 1H), 7.87 (m, 1H), 7.75 (d, $J = 7.5$ Hz, 2H), 7.52-7.46 (m, 3H), 7.31-7.24 (m, 5H), 4.69 (q, $J = 6.6$ Hz, 1H),

3.73 (AB q, 2H), 1.67 (br s, 1H), 1.51 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ : 141.2, 140.9, 134.2, 131.6, 129.1, 128.5, 128.3, 127.4, 127.0, 125.9, 125.8, 125.4, 123.2, 123.1, 53.2, 52.1, 23.8.

***N*-(3,3-Diphenylpropyl)-1-phenylethylamine (4-25):** 101 *N*-(1-Phenyl-



ethylidene)3,3-diphenylpropylamine (50 mg, 0.159 mmol)

was subjected to general procedure A in THF (1 mL) to afford

the product as a brown oil (34 mg, 0.108 mmol, 68%). ^1H NMR (500 MHz, CDCl_3) δ :

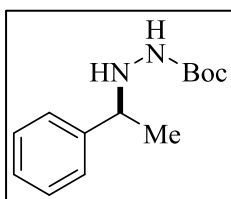
7.30-7.16 (m, 15H), 3.99 (t, $J = 7.7$ Hz, 1H), 3.69 (q, $J = 6.6$ Hz, 1H), 2.51-2.42 (m,

2H), 2.27-2.18 (m, 2H), 1.46 (s, 1H), 1.30 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125

MHz, CDCl_3) δ : 144.9, 144.7, 128.4, 128.3, 127.8, 127.7, 126.7, 126.5, 126.1, 58.1,

49.0, 45.9, 36.1, 24.3.

Attempted synthesis of *tert*-butyl 2-(1-phenylethyl)hydrazinecarboxylate (4-

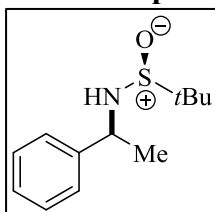


26): *N*⁷-(1-Phenylethylidene)-(*tert*-butoxy)carbohydrazide (30 mg,

0.128 mmol) was subjected to general procedure B in MeCN (1

mL) to afford a residue from which the product could not be isolated.

Attempted synthesis of *S*-(*S*)-2-methyl-*N*-(1-phenylethyl)-2-propane-



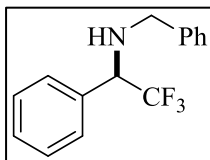
sulfonamide (4-27): [*S*-(*S*)]-2-Methyl-*N*-(1-phenylethylidene)-2-

propane-sulfonamide (30 mg, 0.134 mmol) was subjected to general

procedure B in MeCN (1 mL) to afford a residue from which the product could not be

isolated.

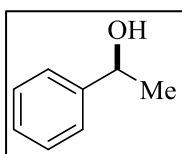
Attempted synthesis of *N*-benzyl-(2,2,2-trifluoro)-1-phenylethylamine (4-28):



N-(2,2,2-Trifluoro-1-phenylethylidene)benzylamine (30 mg, 0.114 mmol) was subjected to general procedure B in MeCN (1 mL),

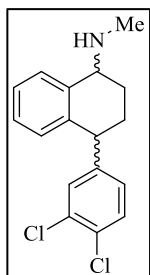
however no conversion was observed.

Attempted synthesis of 1-phenylethanol (4-29): Acetophenone (20 mg, 0.166



mmol) was subjected to general procedure B in MeCN (1 mL), however no conversion was observed.

***N*-Methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine [4-**

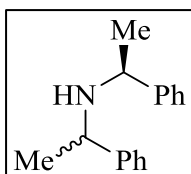


31(*syn*), 4-31(*anti*)]:⁹⁰ *N*-[4[(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenyldene]-methylamine (50 mg using **2-35, 0.164 mmol; 50 mg using **2-37**, 0.164 mmol) was subjected to general procedure B in MeCN**

(1 mL). However, no attempts at purification was performed to isolate the amine products, namely **4-31(*syn*)**, and **4-31(*anti*)**. The diastereoselectivity of the reactions was analyzed by integration of the corresponding *NMe*, and Ar-*CH-N* peaks in the ¹H NMR spectrum (57:43 major isomer *syn* using **2-35**; 60:40 major isomer *syn* using **2-37**).

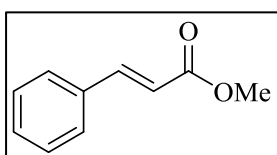
***N*-[(1*S*)-1-Phenylethyl]-1-phenylethylamine [4-33(*S,S*), 4-33(*meso*)]:¹⁰² (1*S*)-**

N-(Phenylethylidene)-1-phenylethylamine (50 mg using **2-31**, 0.224 mmol; 25 mg



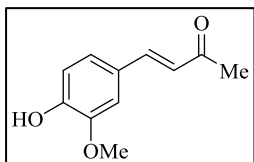
using **2-33**, 0.112 mmol; 25 mg using **2-34**, 0.112 mmol; 50 mg using **35**, 0.224 mmol; 50 mg using **2-37**, 0.224 mmol) was subjected to general procedure B in MeCN (1 mL) to afford the product as a clear oil (isolated as a mixture of product and decomposed starting material using **2-31**, 69:31 major isomer *S,S*; 22 mg, 0.098 mmol, 87% using **2-33**, 55:45 major isomer *S,S*; 23 mg, 0.102 mmol, 91% using **2-34**, 74:26 major isomer *meso*; 42 mg, 0.186 mmol, 83% using **2-35**, 66:34 major isomer *S,S*; 40 mg, 0.178 mmol, 79% using **2-37**, 56:44 major isomer *meso*). ^1H NMR (300 MHz, CDCl_3 , Integrations are not reported due to a mixture of isomers) δ : 7.35-7.19 (m, *S,S* and *meso* overlapped, *ArH*), 3.75 (q, $J = 6.6$ Hz, *meso*, *CH*), 3.49 (q, $J = 6.6$ Hz, *S,S*, *CH*), 1.35 (d, $J = 6.6$ Hz, *meso*, CH_3), 1.26 (d, $J = 6.6$ Hz, *S,S*, CH_3). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , Assignments for stereochemistry are based on signal intensity and HSQC) δ : 146.0 (*meso*), 145.9 (*S,S*), 128.55 (*meso*), 128.51 (*S,S*), 126.96 (*meso*), 126.90 (*S,S*), 126.8 (*S,S*), 126.7 (*S,S*), 55.2 (*S,S*), 54.9 (*meso*), 25.1 (*S,S*), 23.3 (*meso*).

Attempted reduction of methyl 3-phenyl-2-propenoate (4-35): Methyl



cinnamate (25 mg, 0.154 mmol) was subjected to general procedure B in MeCN (1 mL), however no conversion was observed.

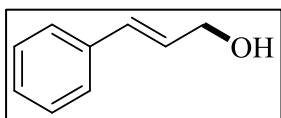
Attempted reduction of 4-(4-hydroxy-3-methoxyphenyl)-3-buten-2-one (4-36):



4-(4-Hydroxy-3-methoxyphenyl)-3-buten-2-one (30 mg, 0.156 mmol) was subjected to general procedure B in MeCN (1 mL),

however no conversion was observed.

(E)-3-Phenyl-2-propen-1-ol (4-37):¹⁰³ *Trans*-cinnamaldehyde (22 mg, 0.166



mmol) was subjected to general procedure B in MeCN (1 mL)

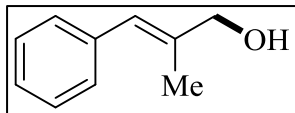
to afford the product as a colourless oil (21 mg, 0.157 mmol, 94%). ¹H NMR (300 MHz,

CDCl₃) δ: 7.40-7.22 (m, 5H), 6.62 (leaning d, *J* = 15.9 Hz, 1H), 6.37 (dt, *J* = 15.9, 5.7

Hz, 1H), 4.32 (dd, *J* = 5.7, 1.5 Hz, 2H). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ: 136.8,

131.3, 128.7, 128.6, 127.8, 126.6, 63.9.

(E)-2-Methyl-3-phenyl-2-propen-1-ol (4-38):¹⁰³ α-Methyl-*trans*-



cinnamaldehyde (20 mg, 0.151 mmol) was subjected to

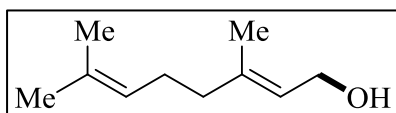
general procedure B in MeCN (1 mL) to afford the product as a colourless oil (16 mg,

0.108 mmol, 80%). ¹H NMR (500 MHz, CDCl₃) δ: 7.35-7.21 (m, 5H), 6.53, (s, 1H),

4.20 (s, 2H), 1.91 (d, *J* = 0.5 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 137.8, 137.7,

129.0, 128.3, 126.6, 125.2, 69.2, 15.4.

(E/Z)-3,7-Dimethyl-2,6-octadien-1-ol (4-39):¹⁰⁴ (*E/Z*)-Citral (50 mg, 0.328



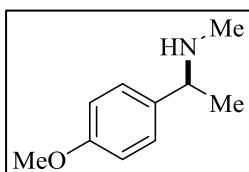
mmol, mixture of isomers) was subjected to general

procedure B in MeCN (2 mL) to afford the product as a colourless oil (40 mg, 0.259

mmol, 79%). ¹H NMR (300 MHz, CDCl₃) δ: 5.40 (m, 1H), 5.10 (m, 1H), 4.15 and 4.09

(d and d, $J = 12, 11.5$ Hz, respectively, E/Z , 2H), 2.10-2.03 (m, 4H), 1.76-1.68 (m, 6H), 1.60 (s, 3H), 1.19 (br s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3) δ : 140.2, 140.0, 132.6, 131.9, 124.5, 124.0, 123.9, 123.4, 59.6, 59.1, 39.7, 32.1, 26.7, 26.5, 25.83, 25.82, 23.6, 17.84, 17.81, 16.4.

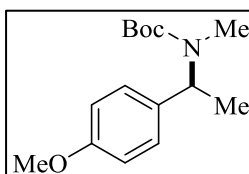
(S)-N-Methyl-1-(4-methoxyphenyl)ethylamine (4-43): N -[1-(4-Methoxy-



phenyl)-ethylidene]methylamine (0.400 g, 2.45 mmol) was subjected to general procedure A in THF (4 mL) to afford the

product as a yellow oil (0.183 g, 1.11 mmol, 46%). ^1H NMR (500 MHz, CDCl_3) δ : 7.32 (m, 2H), 6.86 (m, 2H), 3.80 (s, 3H), 3.59 (q, 1H, $J = 6.5$ Hz), 2.29 (s, 3H), 1.33 (d, 3H, $J = 6.5$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 158.7, 137.6, 127.7, 113.9, 59.7, 55.4, 34.6, 23.9.

***tert*-Butyl (S)-N-methyl-N-1-(4-methoxyphenyl)ethylcarbamate (4-43-Boc):**³³

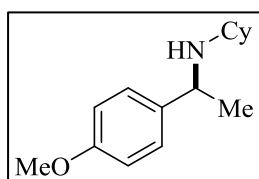


NEt_3 (0.103 mL, 0.738 mmol, 1.0 equiv.) was added to a mixture of **4-43** (0.122 g, 0.738 mmol, 1.0 equiv.) and di-*tert*-butyl

dicarbonate (0.169 mL, 0.738 mmol, 1.0 equiv.) in DCM (5 mL). The mixture was stirred for 40 h at rt. The solvent was removed *in vacuo*, then the residue was subjected to column chromatography to afford the product (0.090 g, 0.339 mmol, 46%). ^1H NMR (500 MHz, 338 K, acetonitrile- d_3): δ 7.26-7.24 (m, 2H), 6.94-6.93 (m, 2H), 5.41-5.37 (m, 1H), 3.82 (s, 3H), 2.60 (s, 3H), 1.50 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, 338 K,

acetonitrile- d_3): δ 158.9, 155.6, 134.1, 128.0, 113.8, 78.9, 55.0, 52.5, 27.7, 16.1. The enantiomeric ratio of the product from the reduction using **4-2** was determined by HPLC on a Chiralpak ADH column eluted with 99% *n*-hexane and 1% *i*PrOH with a flow rate of 0.75 mL/min: $t_{\text{major}} = 17.684$ min; $t_{\text{minor}} = 13.112$ min; *e.r.* = 66:34.

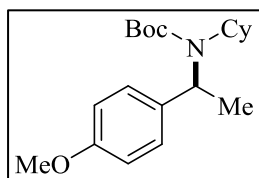
(S)-N-Cyclohexyl-1-(4-methoxyphenyl)ethylamine (4-44): *N*-[1-(4-Methoxy-



phenyl)ethylidene]cyclohexylamine (0.500 g, 2.16 mmol) was subjected to general procedure A in THF (4 mL) to afford the

product as a colourless oil (0.398 g, 1.71 mmol, 79%). ^1H NMR (500 MHz, CDCl_3): δ 7.25-7.24 (m, 2H), 6.90-6.89 (m, 2H), 3.95 (q, 1H, $J = 6.6$ Hz), 3.84 (s, 3H), 2.32-2.25 (m, 1H), 2.01-1.99 (m, 1H), 1.74-1.67 (m, 3H), 1.59 (s, 1H), 1.32 (d, 3H, $J = 6.6$ Hz), 1.22-1.01 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3): δ 158.4, 138.5, 127.4, 113.7, 55.2, 53.8, 53.5, 34.6, 33.3, 26.2, 25.3, 25.1, 25.0. HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{22}\text{NO}$ $[\text{M}+\text{H}]^+$: 232.1696; found: 232.1687.

tert-Butyl (S)-N-cyclohexyl-N-1-(4-methoxyphenyl)ethylcarbamate (4-44-



Boc): NEt_3 (0.173 mL, 1.24 mmol, 1.0 equiv.) was added to a mixture of **4-44** (0.290 g, 1.24 mmol, 1.0 equiv.) and di-*tert*-butyl

dicarbonate (0.285 mL, 1.24 mmol, 1.0 equiv.) in DCM (5 mL). The mixture was stirred for 20 h at rt. The solvent was removed *in vacuo*, then the residue was subjected to column chromatography to afford the product (0.200 g, 0.600 mmol, 48%). ^1H NMR

(500 MHz, 338 K, acetonitrile- d_3): δ 7.32-7.30 (m, 2H), 6.91-6.90 (m, 2H), 5.15-5.14 (m, 1H), 3.82 (s, 3H), 3.21-3.20 (m, 1H), 1.81-1.67 (m, 5H), 1.56 (d, 3H, $J = 7.0$ Hz), 1.43 (s, 9H), 1.12-1.07 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, 338 K, acetonitrile- d_3): δ 158.6, 135.1, 128.2, 113.3, 79.7, 55.0, 54.9, 52.2, 31.7, 30.9, 27.8, 26.2, 25.4, 17.4. HRMS (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{31}\text{NNaO}_3$ $[\text{M}+\text{Na}]^+$: 356.2196; found: 356.2199. The enantiomeric ratio of the product from the reduction using **4-2** was determined by HPLC on a Chiralpak ADH column eluted with 99% *n*-hexane and 1% *i*PrOH with a flow rate of 0.75 mL/min: $t_{\text{major}} = 11.029$ min; $t_{\text{minor}} = 9.396$ min; *e.r.* = 67:33.

Chapter 5. Conclusions and Future Work

5.1 Conclusions

Various notable main group catalysts used in the reduction of unsaturated functional groups are outlined in Chapter 1. (Pentafluorophenyl)borane-derived catalysts are common in the literature. However, their high cost and challenging synthesis render these catalysts relatively inaccessible. Phosphorous-based catalysts represent an underexplored field in reductive catalysis, despite their ability to shuttle between oxidation states.

Chapter 2 describes the investigation towards the synthesis of a novel class of heterocycles, namely 1,2,4,3-triazaphospholenes. Achiral amidrazones with different steric and electronic properties were prepared, and derivatized into the corresponding racemic TAP-halides and TAP-alkoxides. X-ray crystal structures of three TAP-halides were obtained. The ability of one TAP-alkoxide to catalyze the hydroboration of an imine was investigated. However, no catalytic activity was displayed by the TAP employed.

Chapter 3 describes the preparation of several enantioenriched amidrazones. The amidrazones were subsequently converted into the corresponding non-racemic TAP-halides and in some cases, TAP-alkoxides. The X-ray crystal structure of one non-

racemic TAP-halide was obtained.

Catalytic activity of TAPs in the hydroboration of imines are discussed in Chapter 4. Compared to previously reported 1,3,2-diazaphospholene catalysts, TAP-halides possess greater reactivity in the reduction of imines. In collaboration with Prof. Erin R. Johnson, the mechanism of the catalyzed imine hydroboration reaction was investigated. Based on the results, the reaction is proposed to proceed through a similar mechanism as for the Itsuno/CBS-type oxazaborolidine-mediated hydroboration reactions.

The asymmetric hydroboration of imines catalyzed by non-racemic TAPs were also investigated and are disclosed in Chapter 4. Bicyclic TAPs are found to induce greater enantioselectivity in comparison with TAPs derived from acyclic backbones. However, due to the difficulties associated with the synthesis of non-racemic cyclic amidrazones, no further explorations were pursued. A small scope of imines was asymmetrically reduced using a chiral DAP pre-catalyst developed by my colleague, Matt Adams. Compared to the more elaborate TAPs, greater stereoselectivity was obtained using the more easily-accessible DAP.

5.2 Future Work

Based on computation and NMR studies, it was postulated that the TAP-catalyzed hydroboration reaction proceeds *via* a Lewis acid-type mechanism. If such is the case, then synthesis of electron-poor TAPs could potentially prove fruitful in the

investigation into various Lewis acid-catalyzed transformations. Mukaiyama-aldol additions, Diels-Alder cyclizations, and alkylboration reactions represent some of the more synthetically appealing transformations. Existing non-racemic TAPs could also be employed to evaluate the potential for higher stereoselectivity than was observed for the reduction of imines.

Appendix A: NMR Spectra

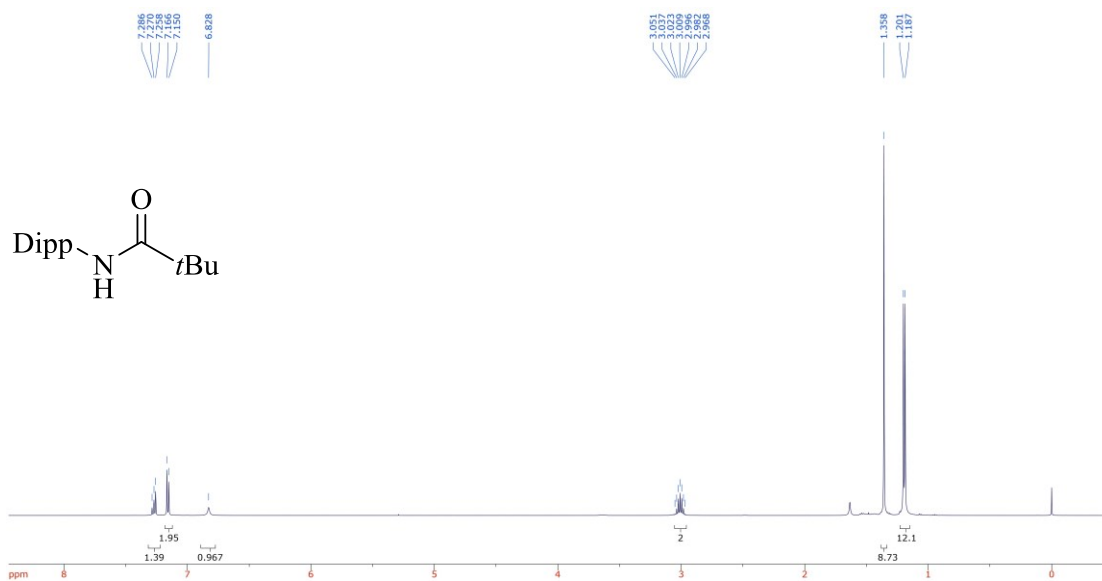


Figure S1. ¹H NMR spectrum of 2-9 (500 MHz, CDCl₃).

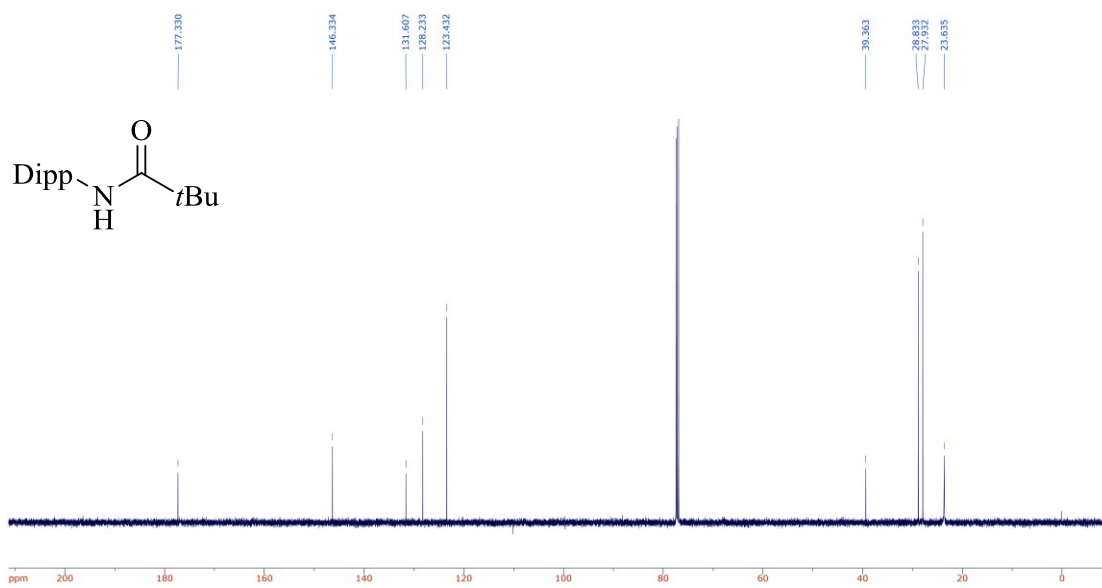


Figure S2. ¹³C{¹H} NMR spectrum of 2-9 (125 MHz, CDCl₃).

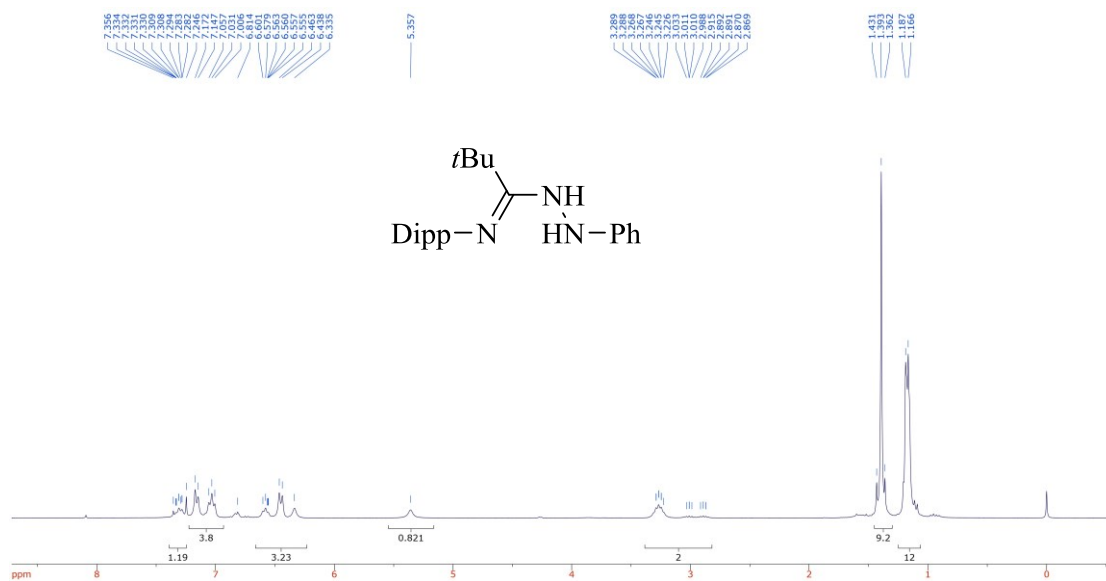
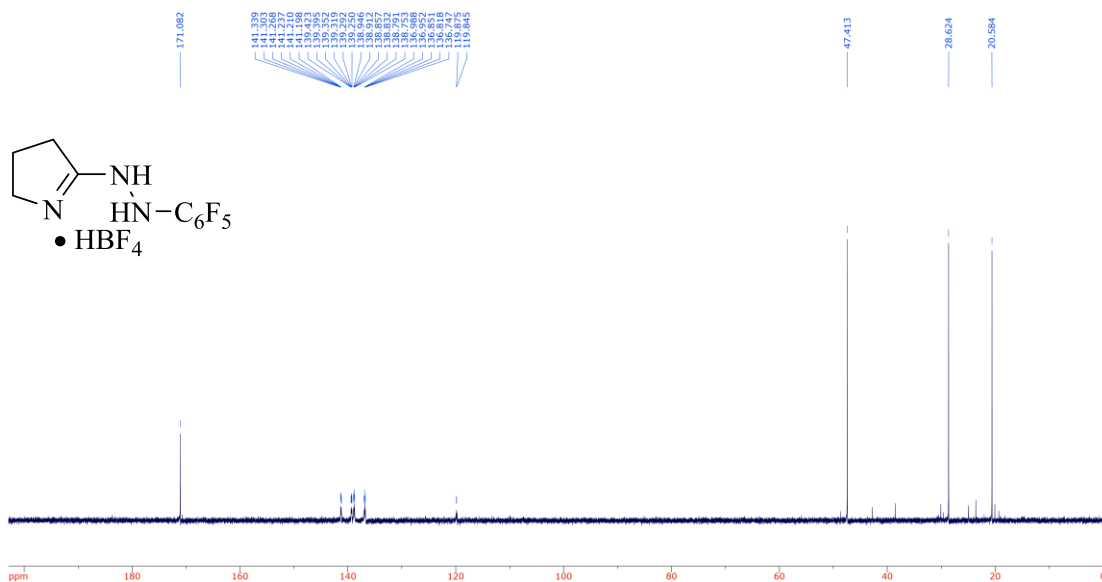
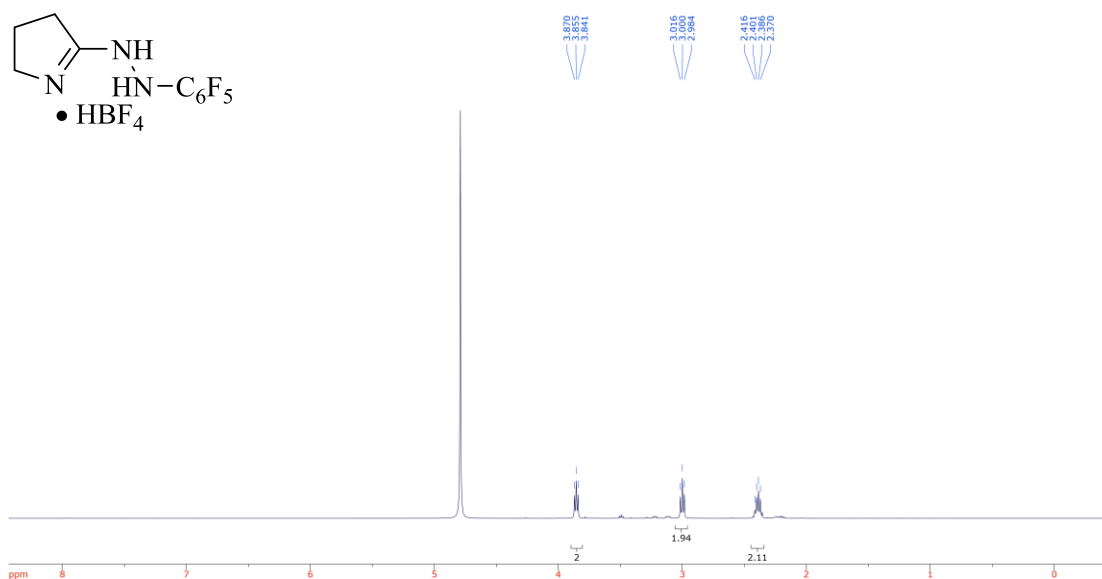


Figure S3. ¹H NMR spectrum of **2-10** (500 MHz, CDCl₃).



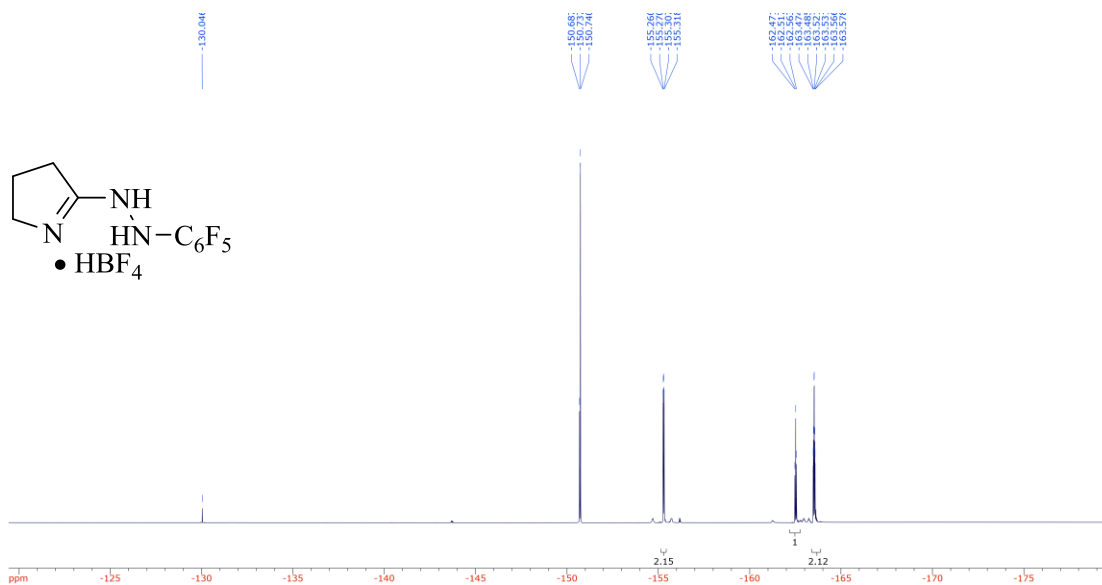


Figure S6. ¹⁹F NMR spectrum of **2-11** (470 MHz, D₂O).

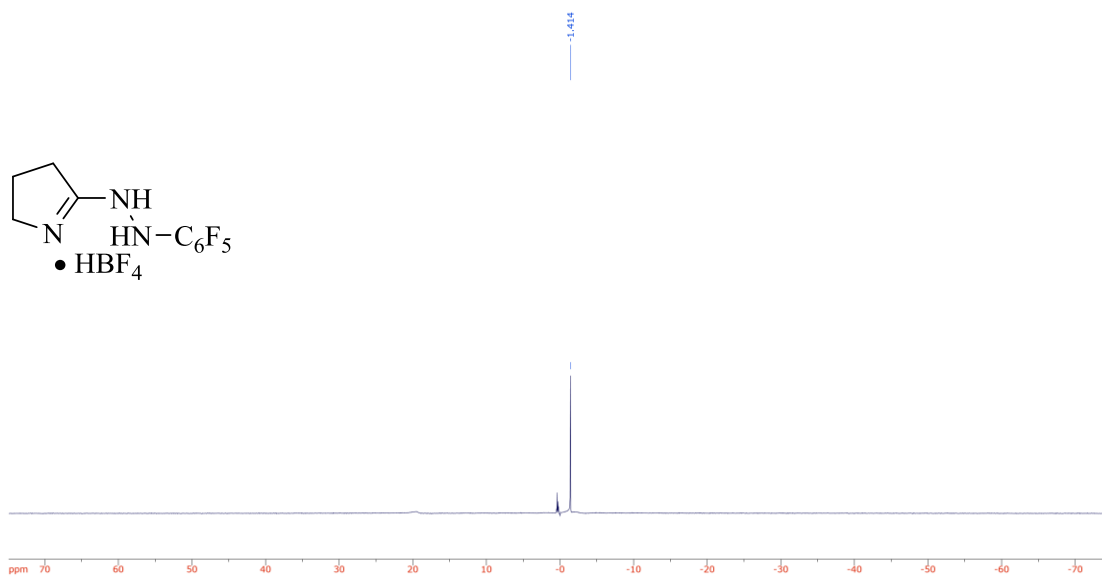
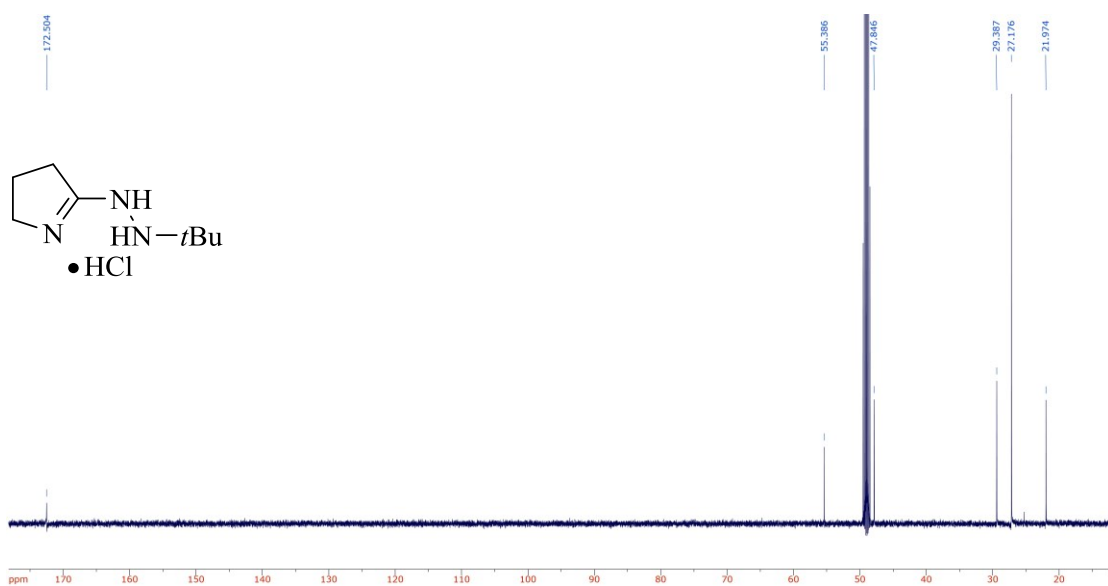
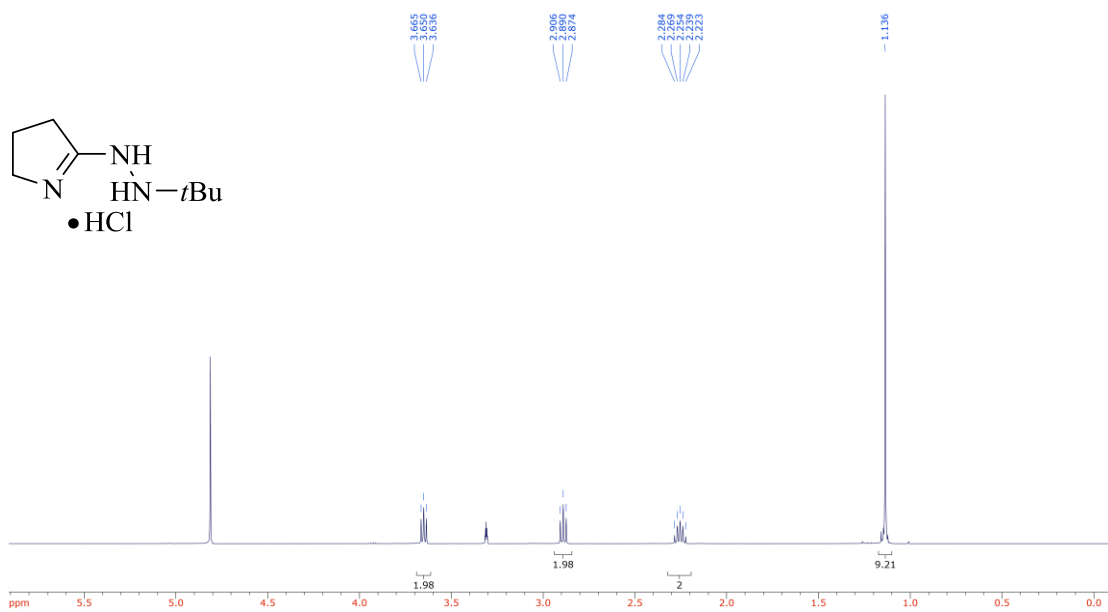


Figure S7. ¹¹B NMR spectrum of **2-11** (160 MHz, D₂O).



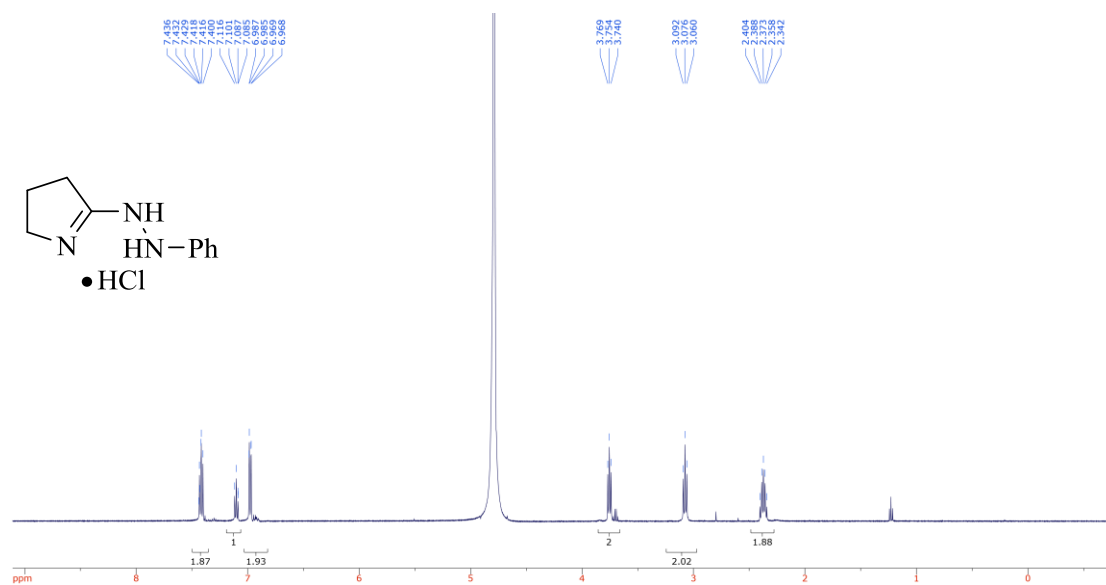


Figure S10. ¹H NMR spectrum of 2-13 (500 MHz, D₂O).

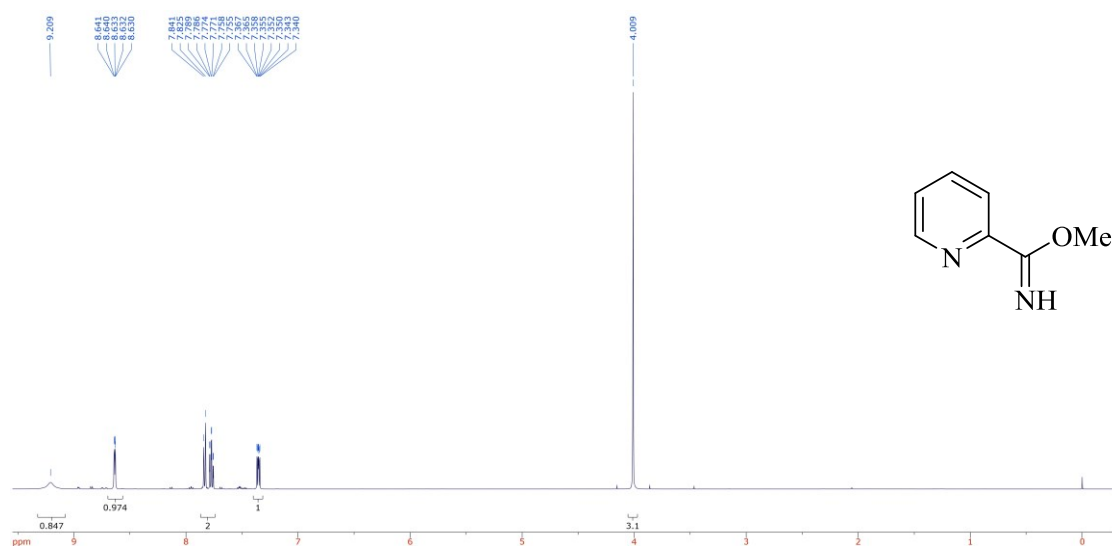


Figure S11. ^1H NMR spectrum of **2-14** (500 MHz, CDCl_3).

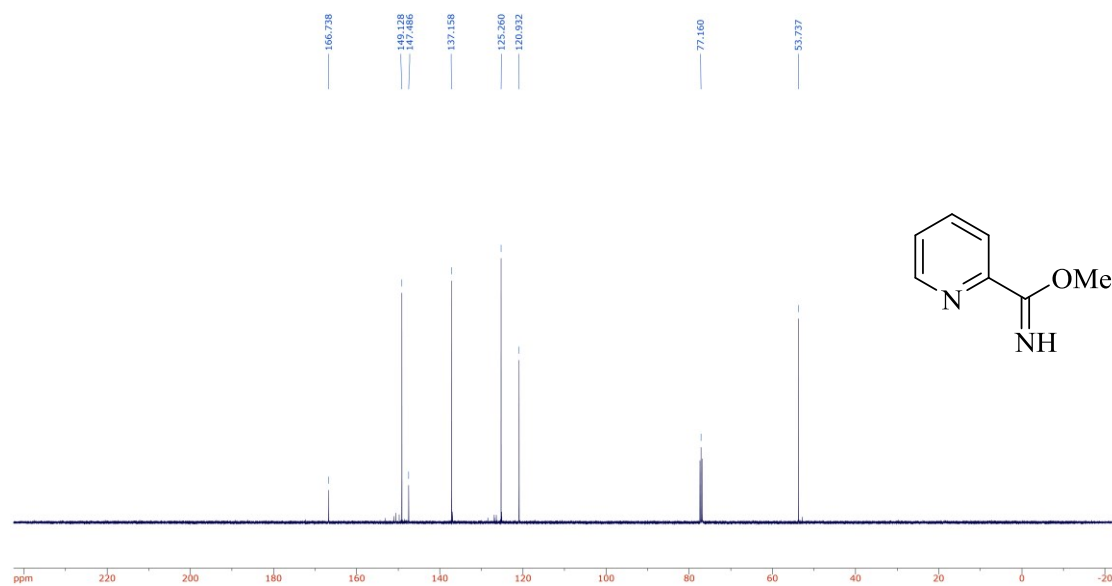


Figure S12. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-14** (125 MHz, CDCl_3).

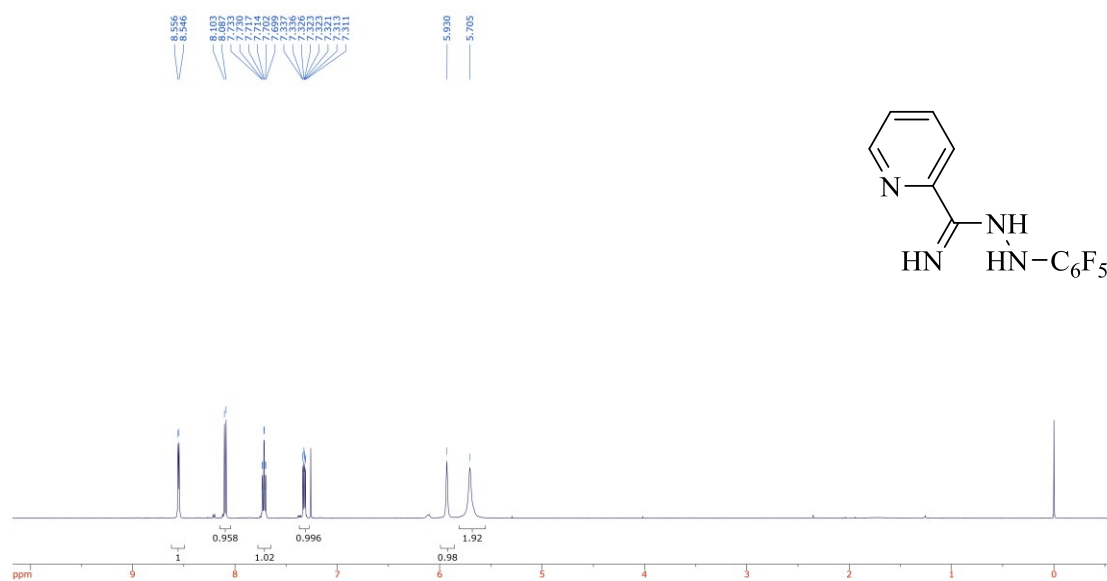


Figure S13. ¹H NMR spectrum of **2-15** (500 MHz, CDCl₃).

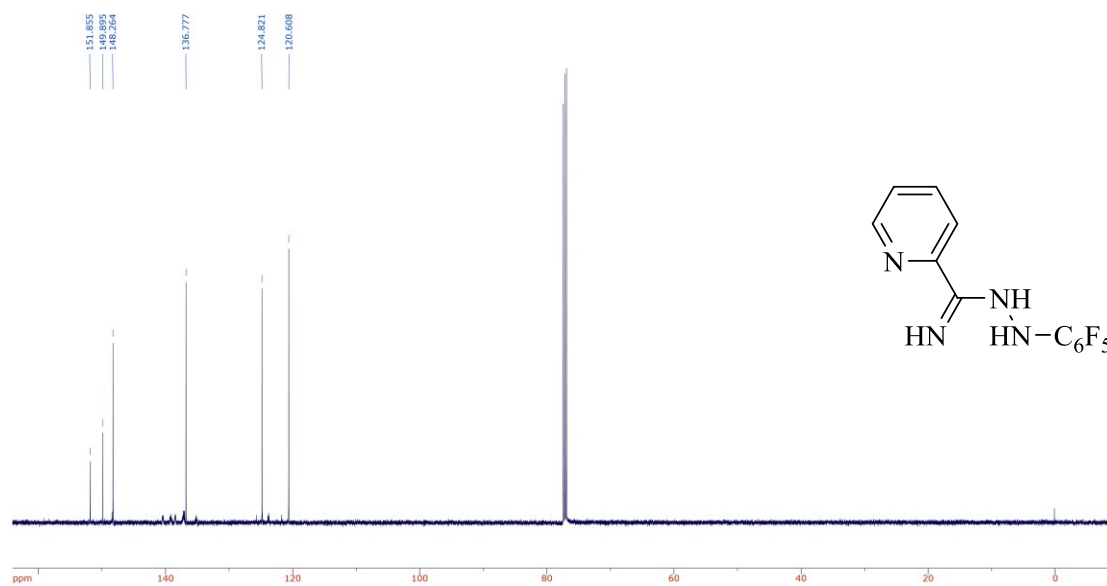


Figure S14. ¹³C {¹H} NMR spectrum of **2-15** (125 MHz, CDCl₃).

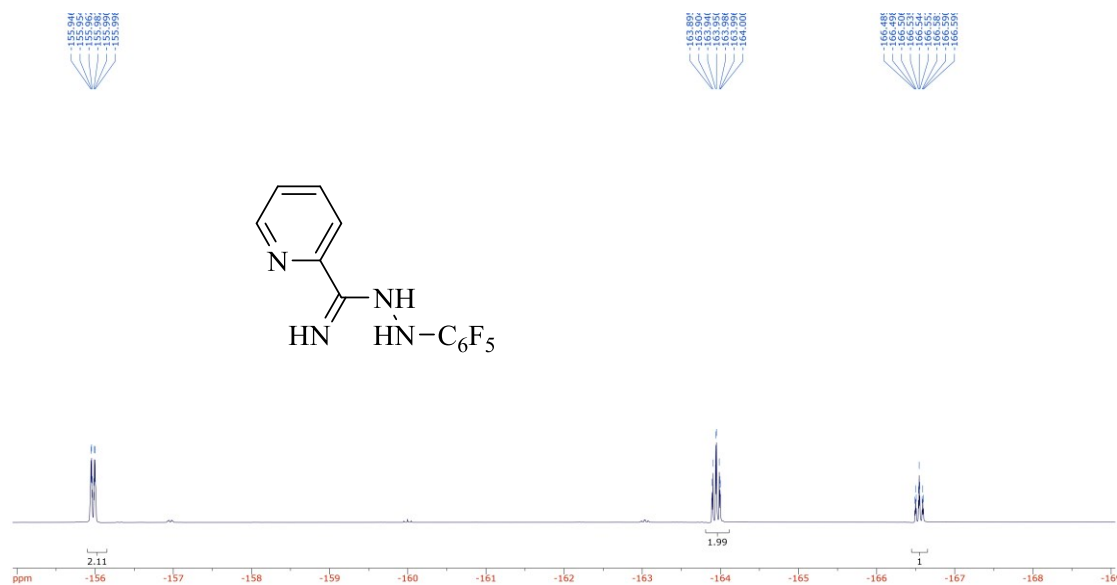


Figure S15. ¹⁹F NMR spectrum of **2-15** (470 MHz, CDCl₃).

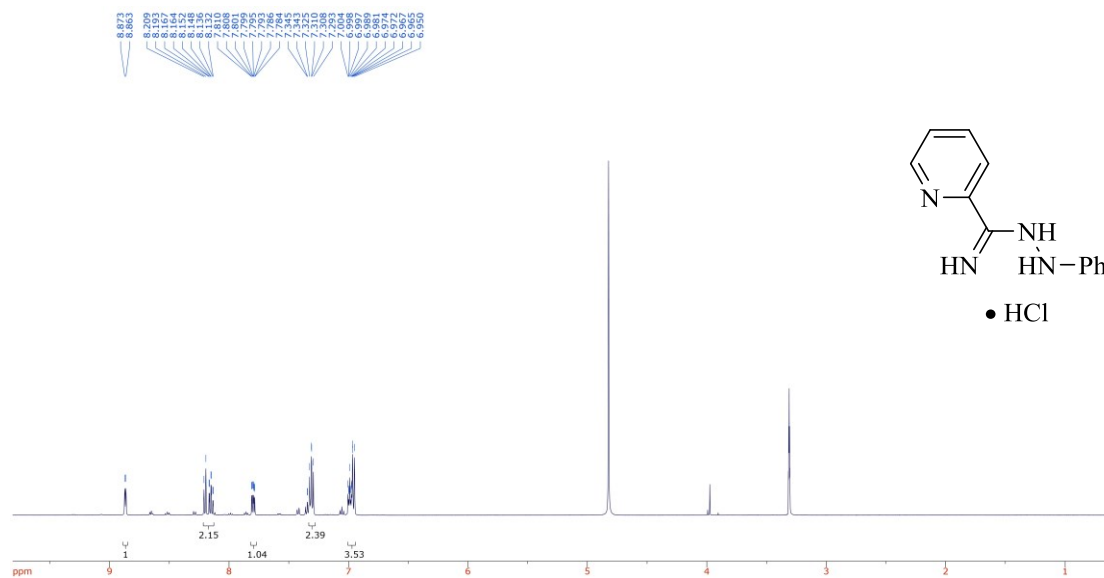


Figure S16. ^1H NMR spectrum of **2-16** (500 MHz, methanol- d_4).

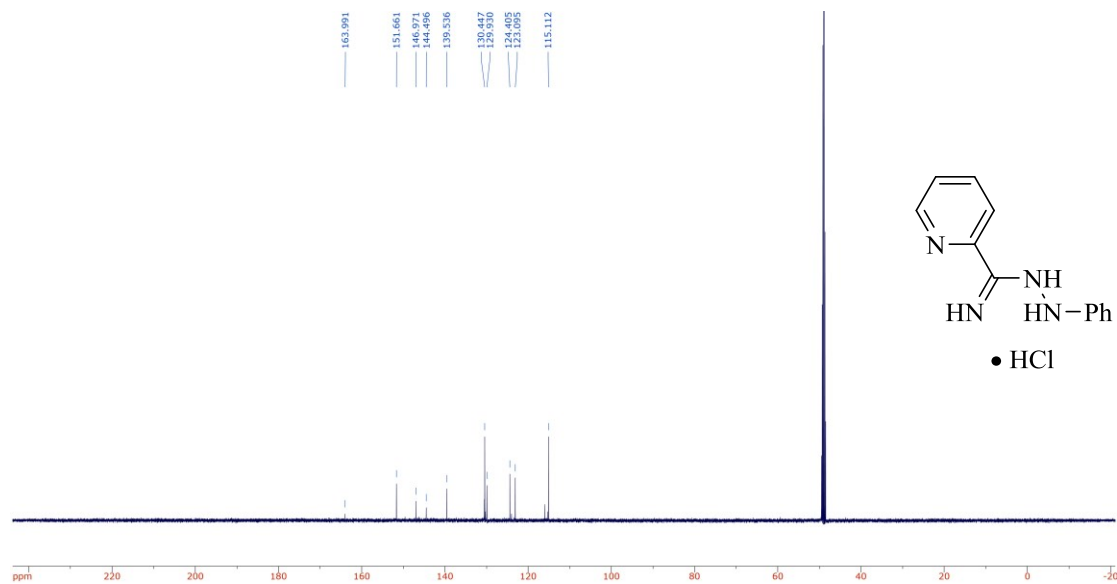


Figure S17. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-16** (125 MHz, methanol- d_4).

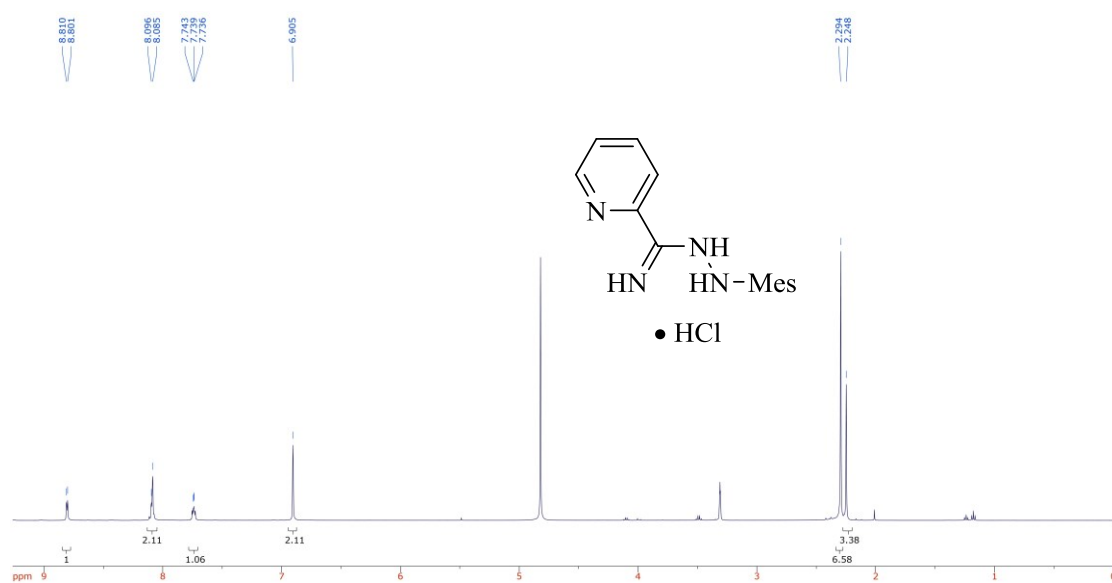


Figure S18. ^1H NMR spectrum of 2-17 (500 MHz, methanol- d_4).

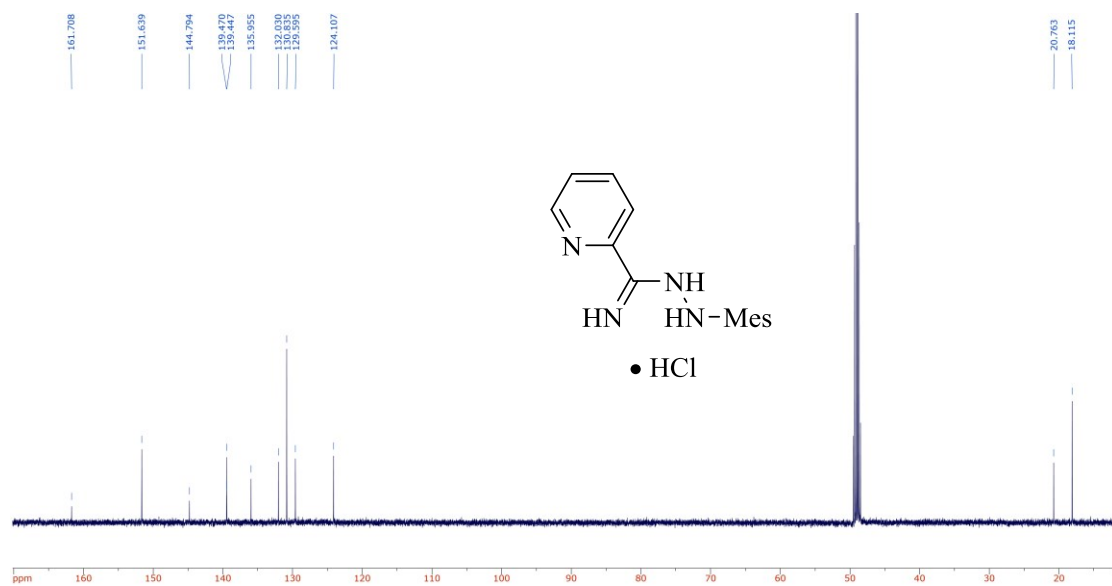
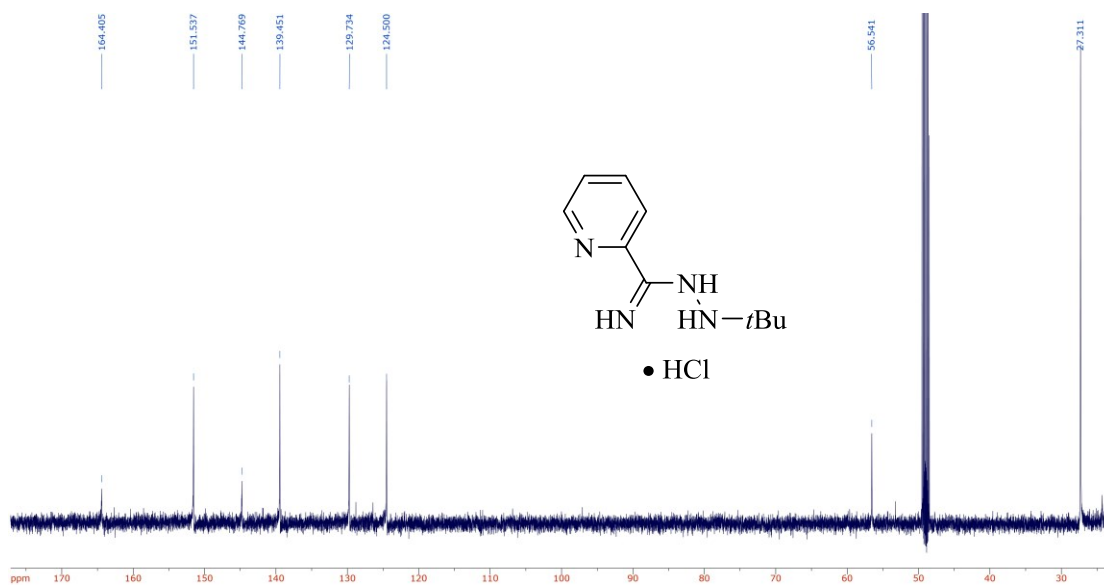
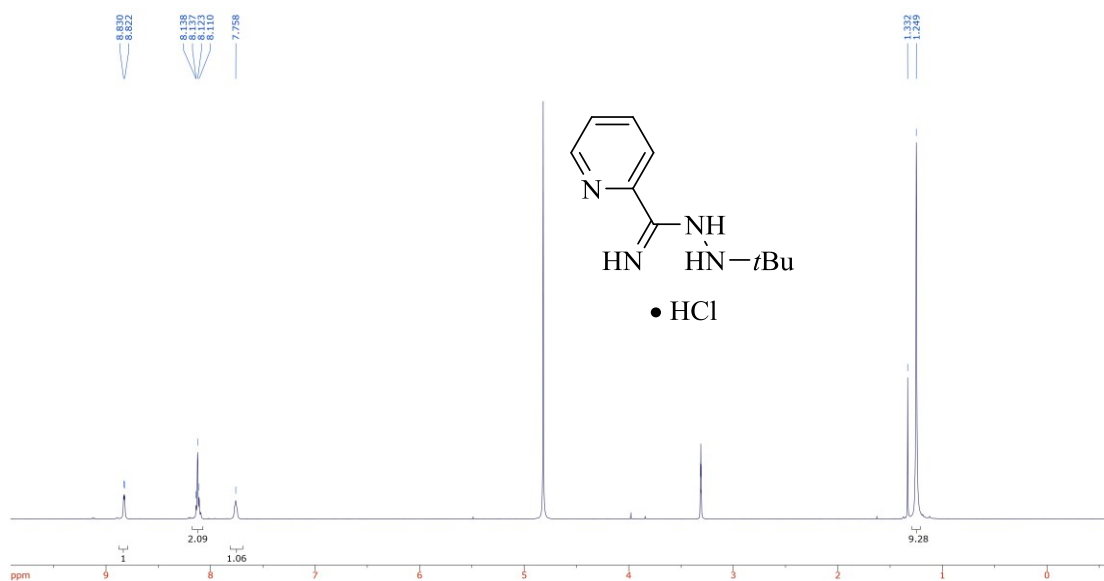


Figure S19. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 2-17 (125 MHz, methanol- d_4).



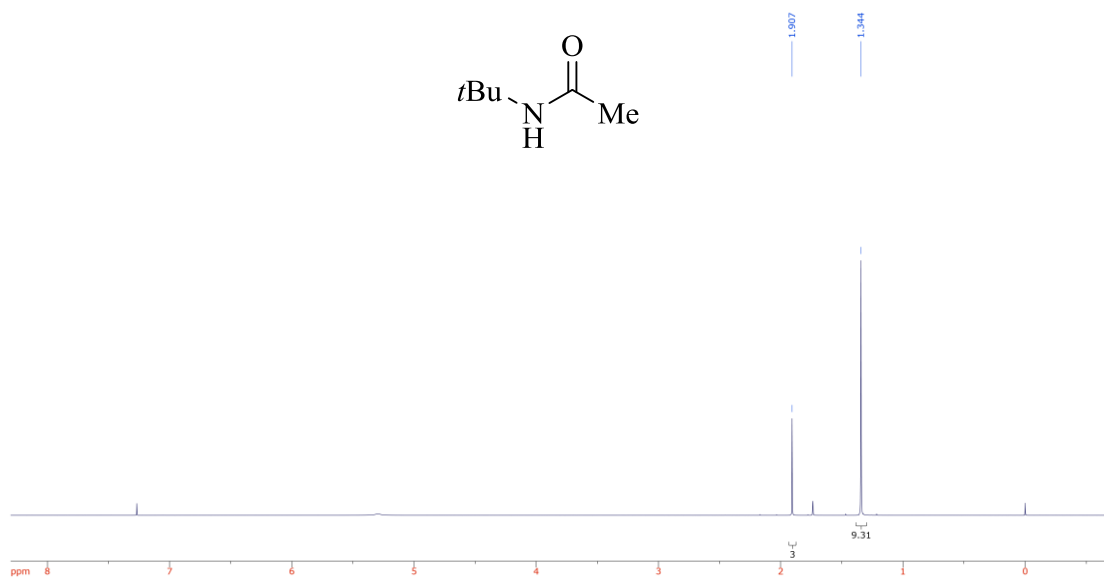


Figure S22. ^1H NMR spectrum of 2-19 (500 MHz, CDCl_3).

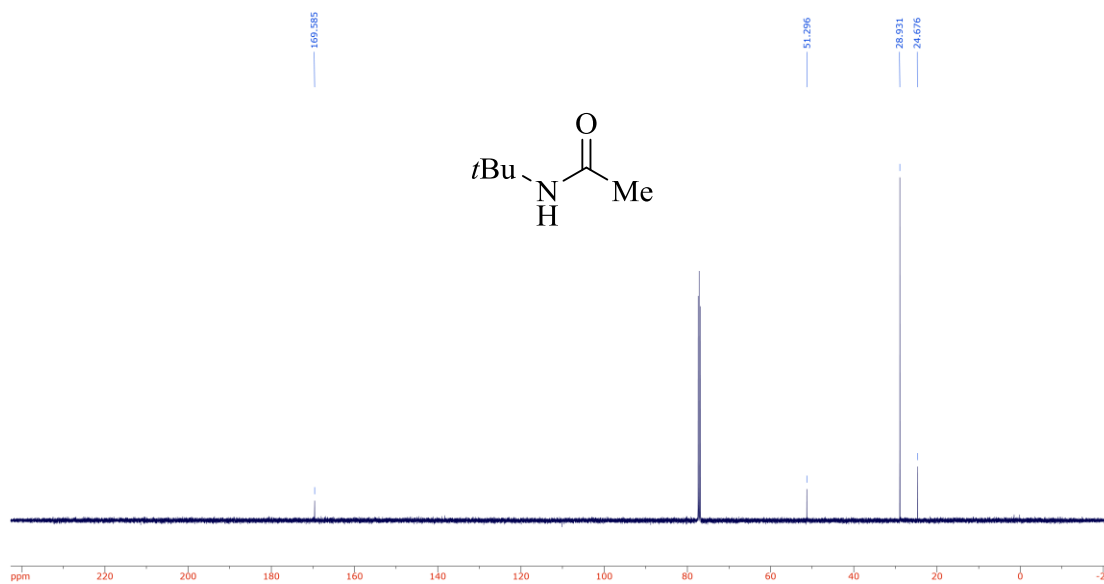


Figure S23. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 2-19 (125 MHz, CDCl_3).

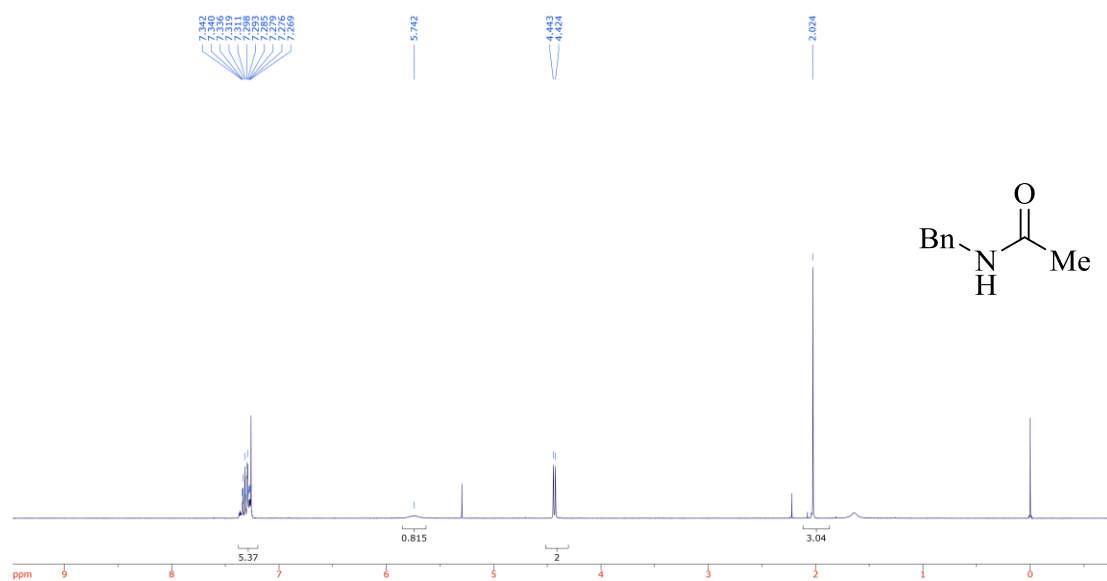


Figure S24. ^1H NMR spectrum of **2-20** (500 MHz, CDCl_3).

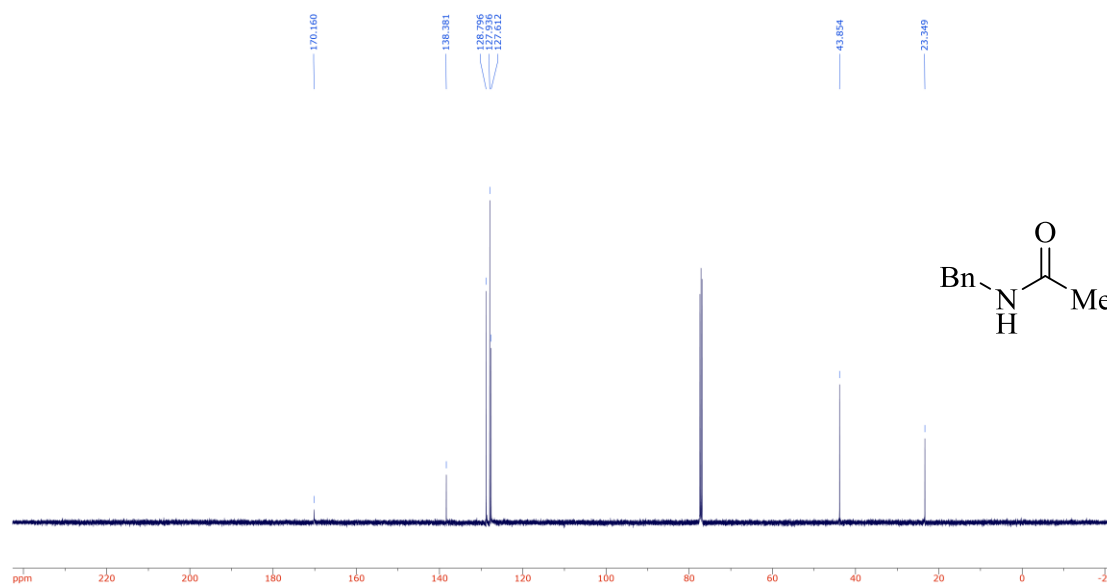


Figure S25. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-20** (125 MHz, CDCl_3).

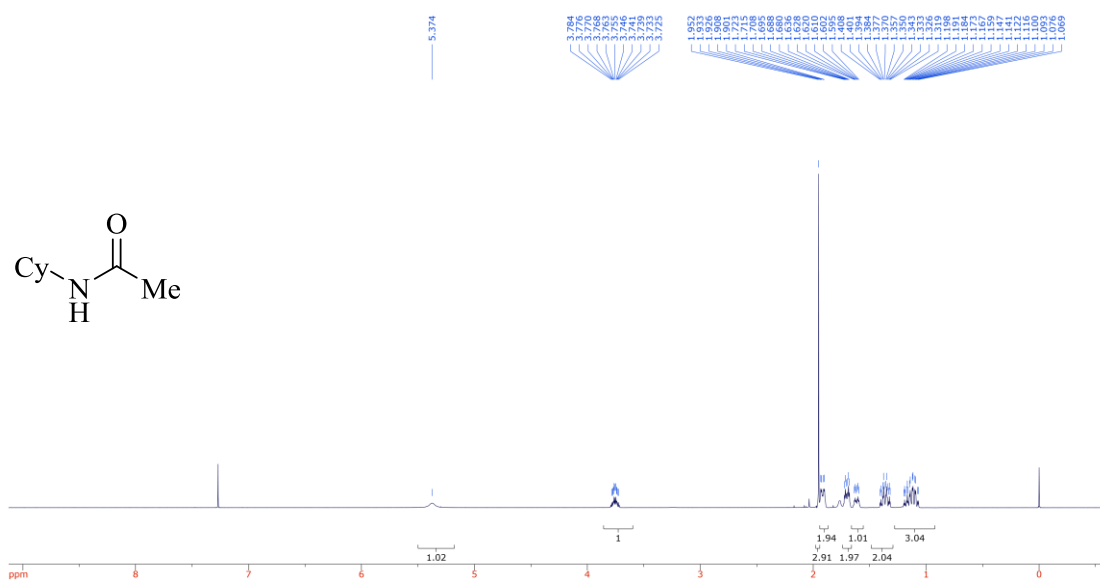


Figure S26. ^1H NMR spectrum of **2-21** (500 MHz, CDCl_3).

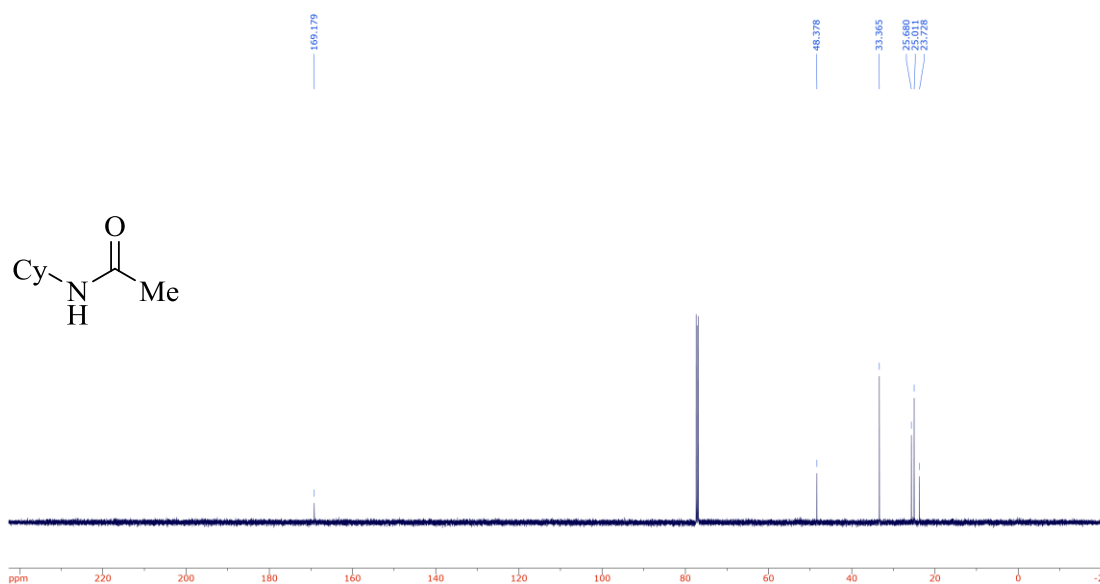


Figure S27. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-21** (125 MHz, CDCl_3).

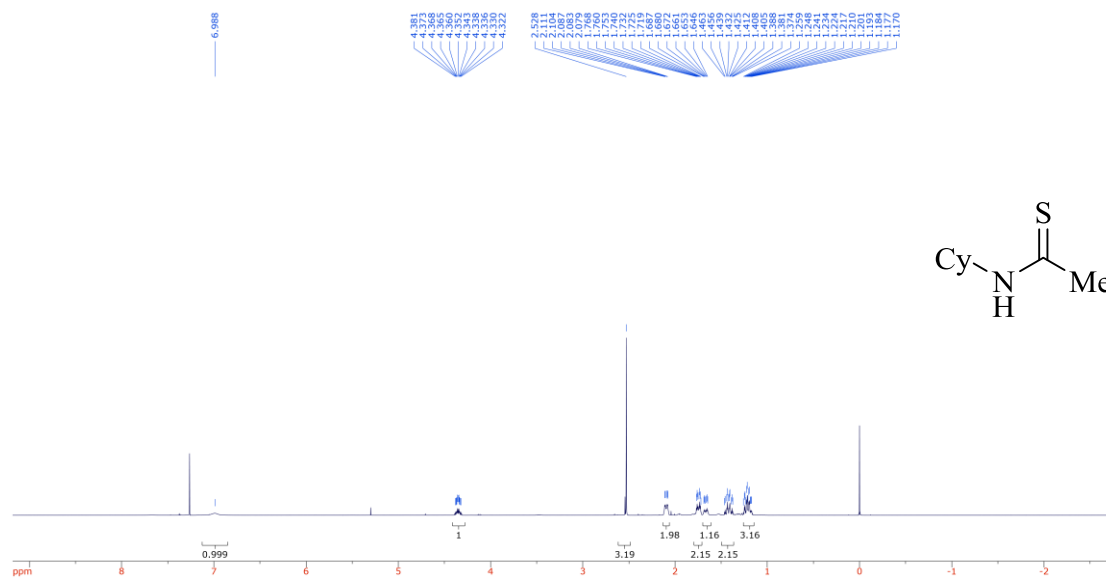


Figure S28. ¹H NMR spectrum of **2-25** (500 MHz, CDCl₃).

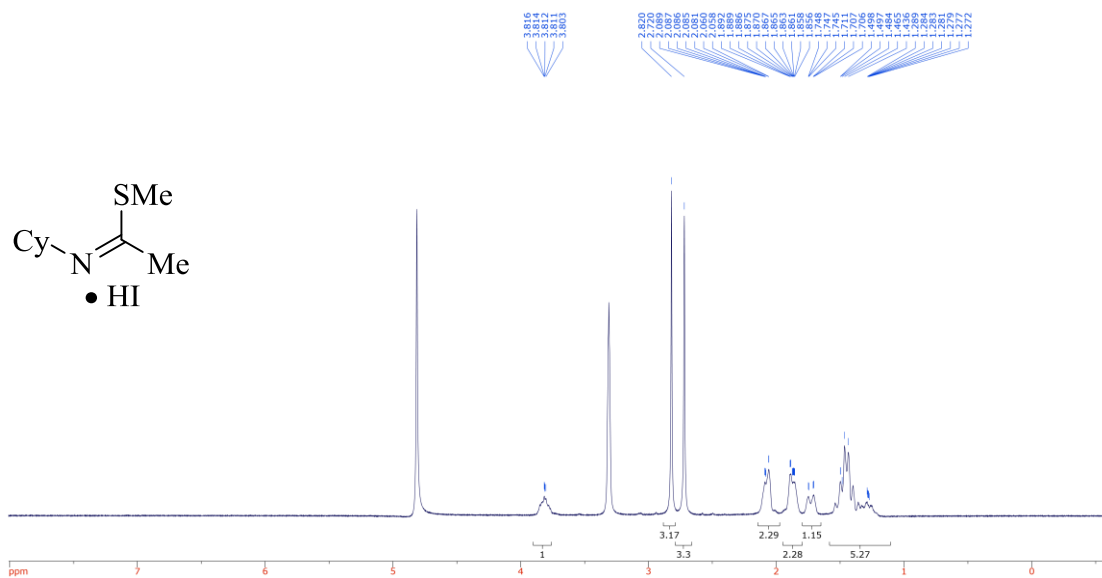


Figure S29. ^1H NMR spectrum of **2-26** (500 MHz, methanol- d_4).

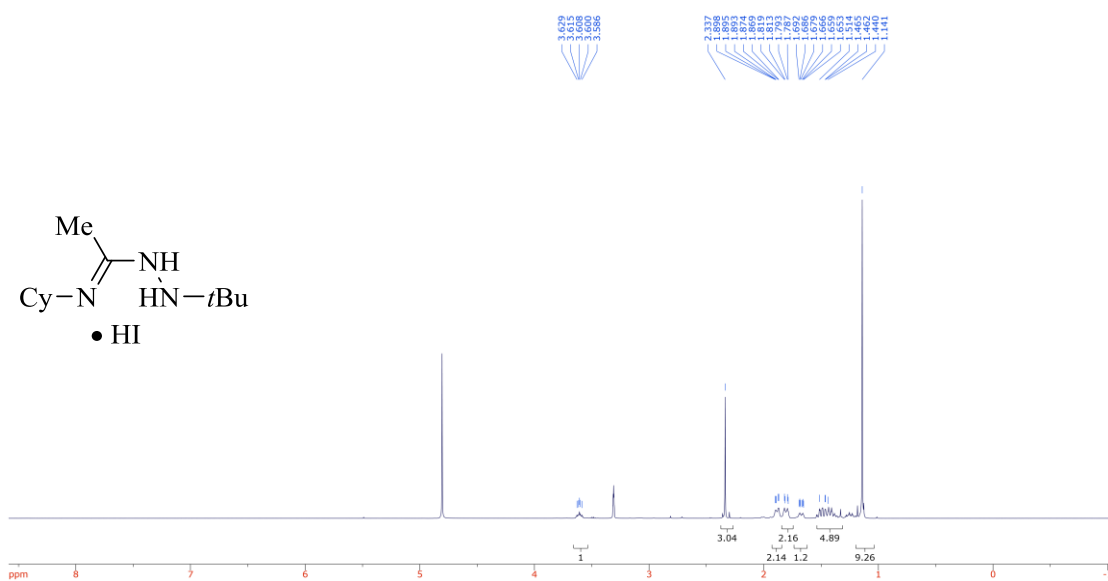


Figure S30. ^1H NMR spectrum of **2-24** (500 MHz, methanol- d_4).

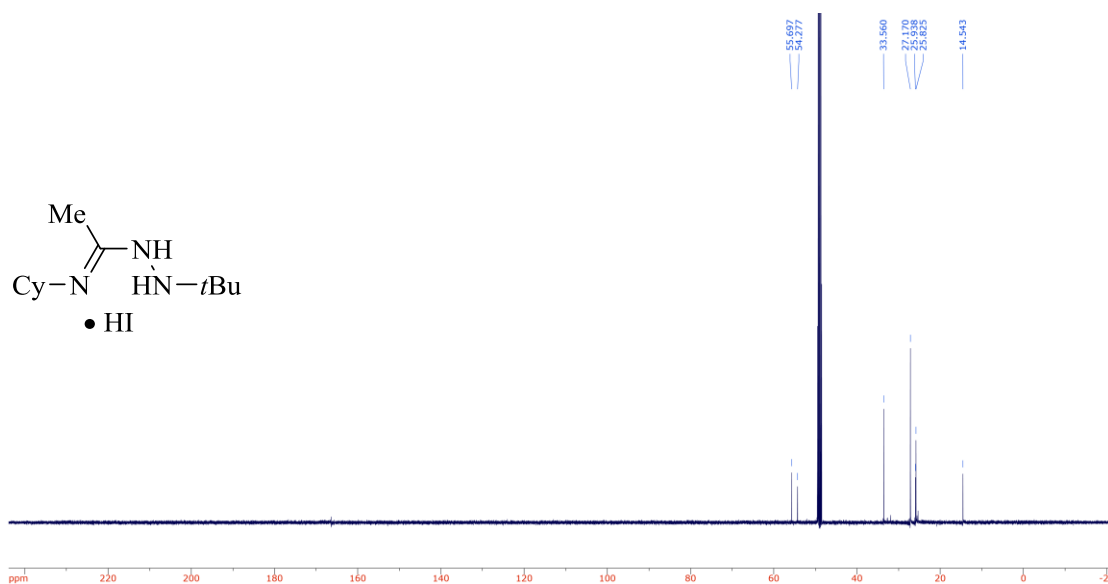


Figure S31. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-24** (125 MHz, methanol- d_4).

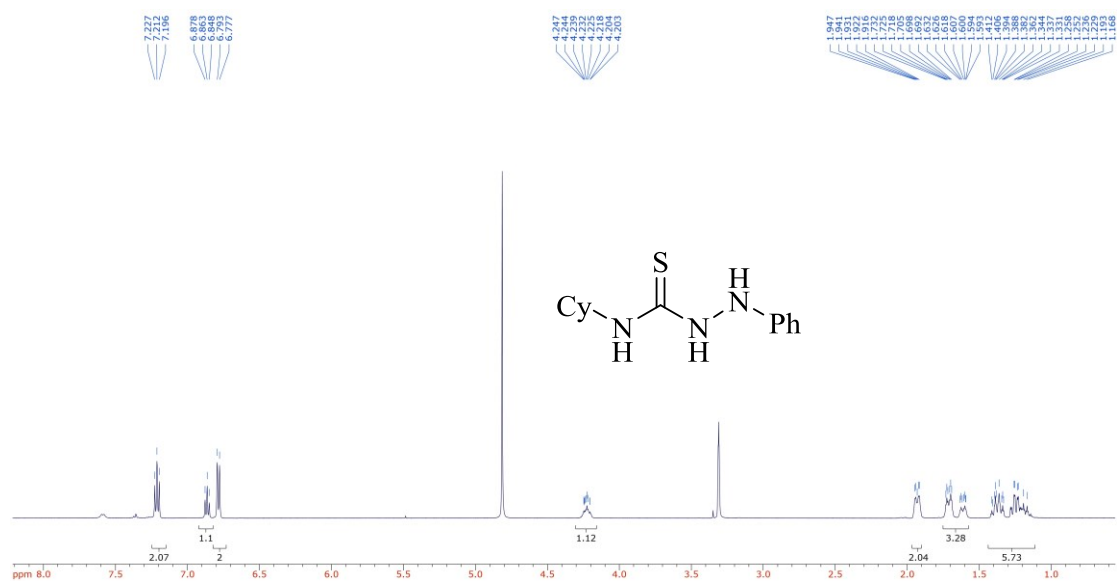


Figure S32. ¹H NMR spectrum of **2-27** (500 MHz, methanol-*d*₄).

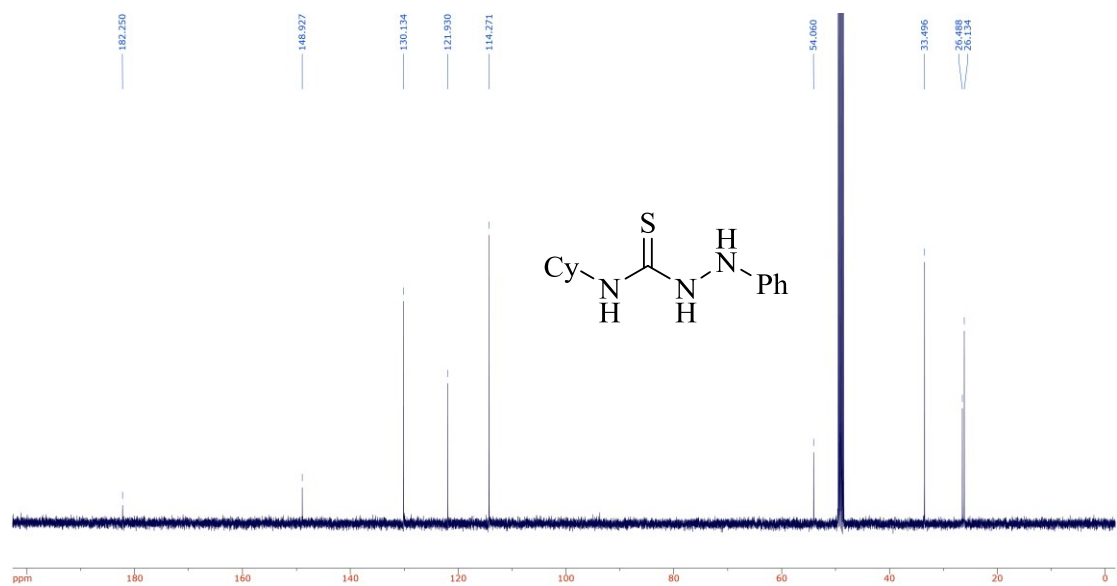


Figure S33. ¹³C{¹H} NMR spectrum of **2-27** (125 MHz, methanol-*d*₄).

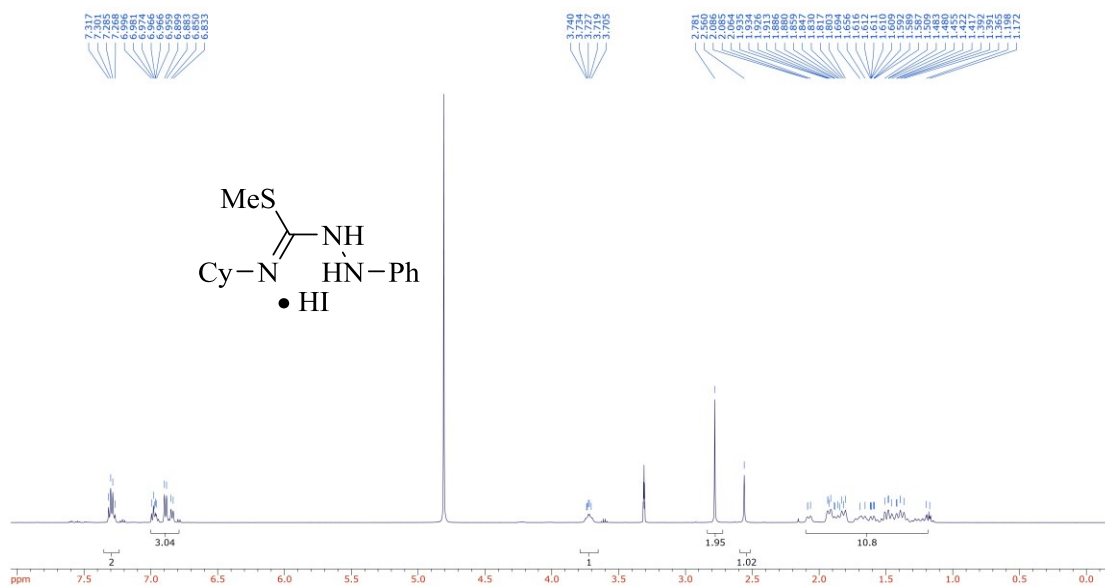


Figure S34. ^1H NMR spectrum of **2-28** (500 MHz, methanol- d_4).

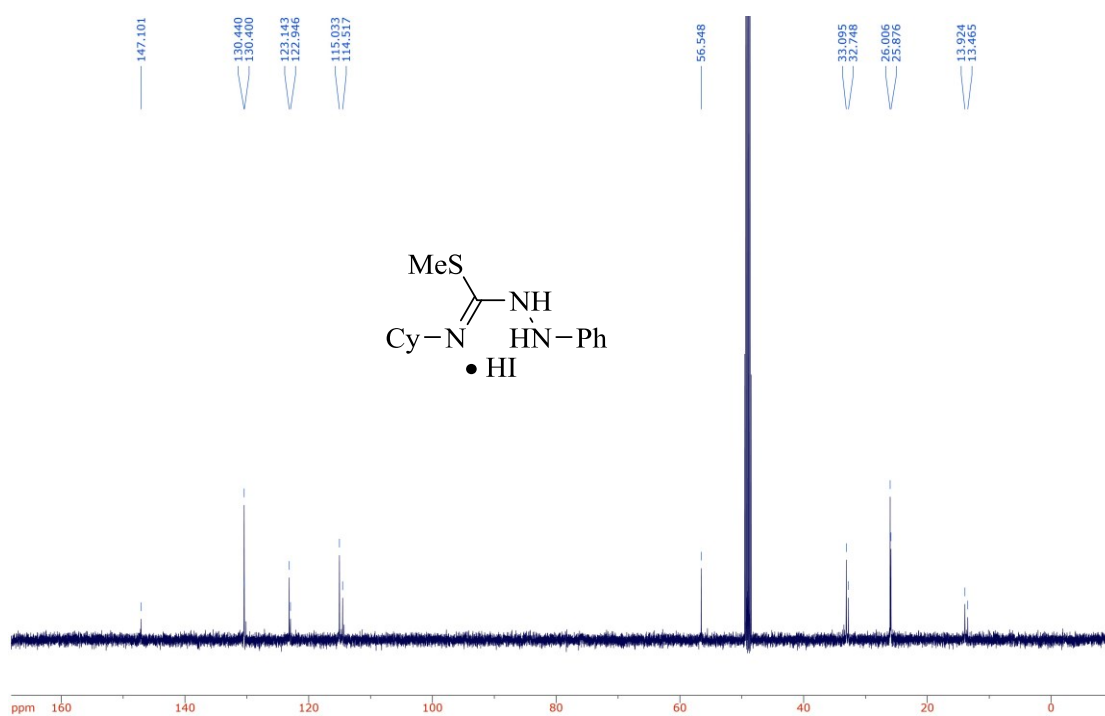


Figure S35. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-28** (125 MHz, methanol- d_4).

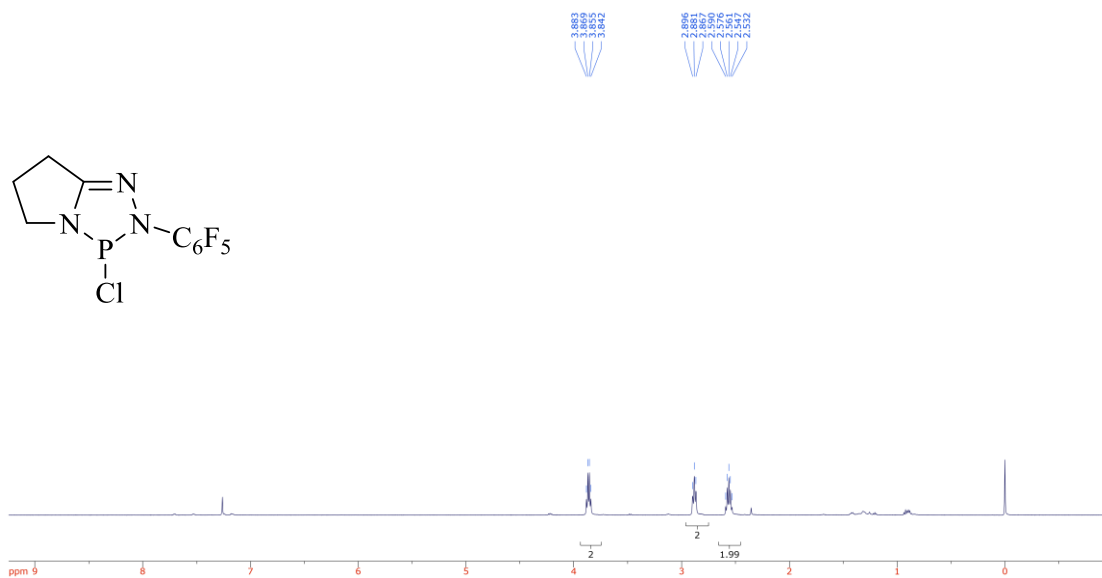


Figure S36. ¹H NMR spectrum of **2-29-Cl** (500 MHz, CDCl₃).

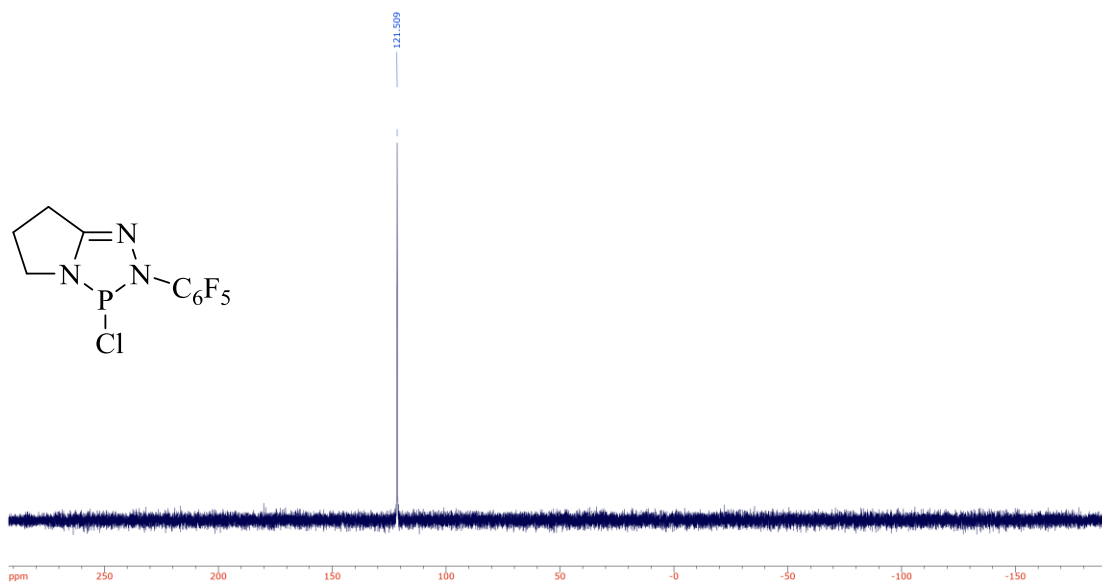


Figure S37. ³¹P NMR spectrum of **2-29-Cl** (201 MHz, CDCl₃).

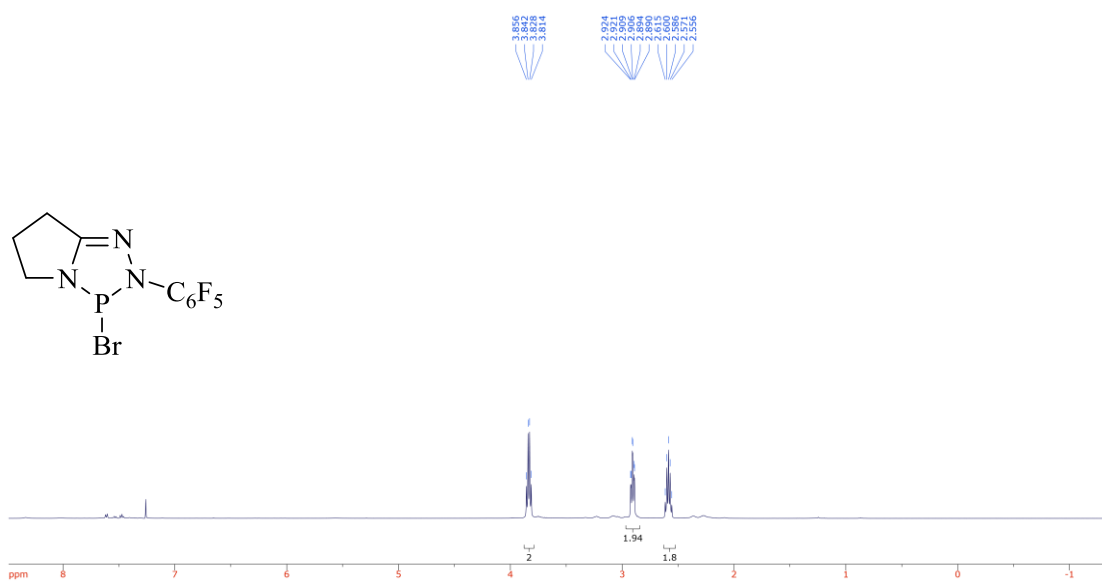


Figure S38. ¹H NMR spectrum of 2-29-Br (500 MHz, CDCl₃).

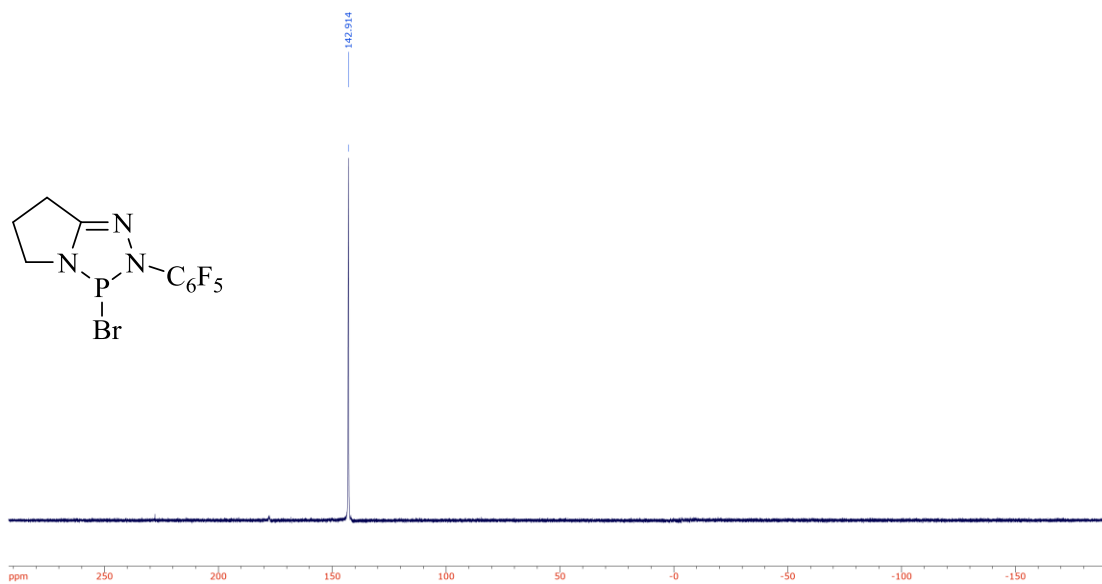


Figure S39. ³¹P NMR spectrum of 2-29-Br (201 MHz, CDCl₃).

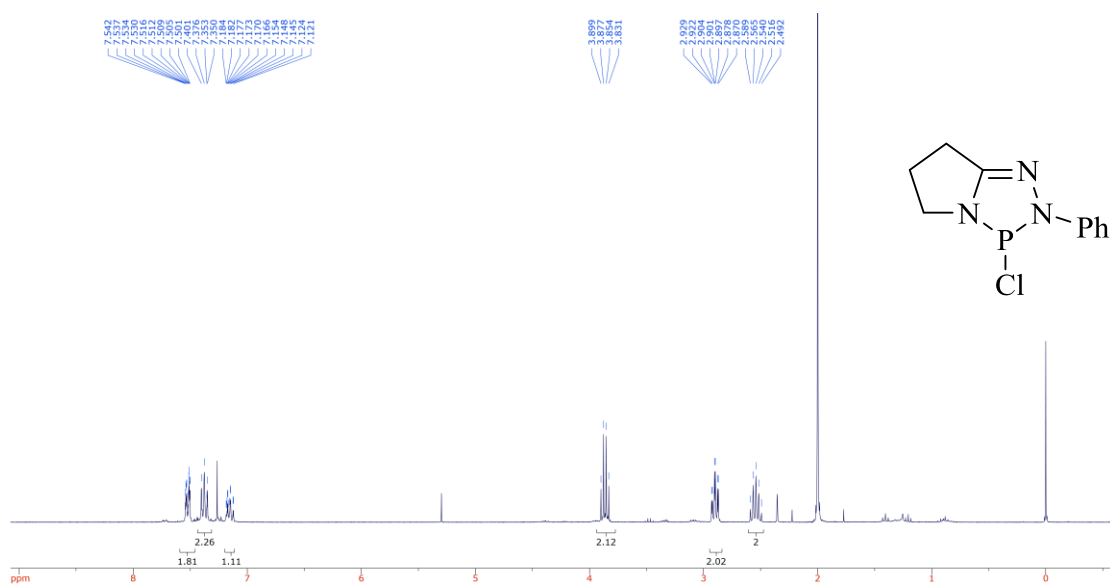


Figure S40. ^1H NMR spectrum of **2-30-Cl** (300 MHz, CDCl_3).

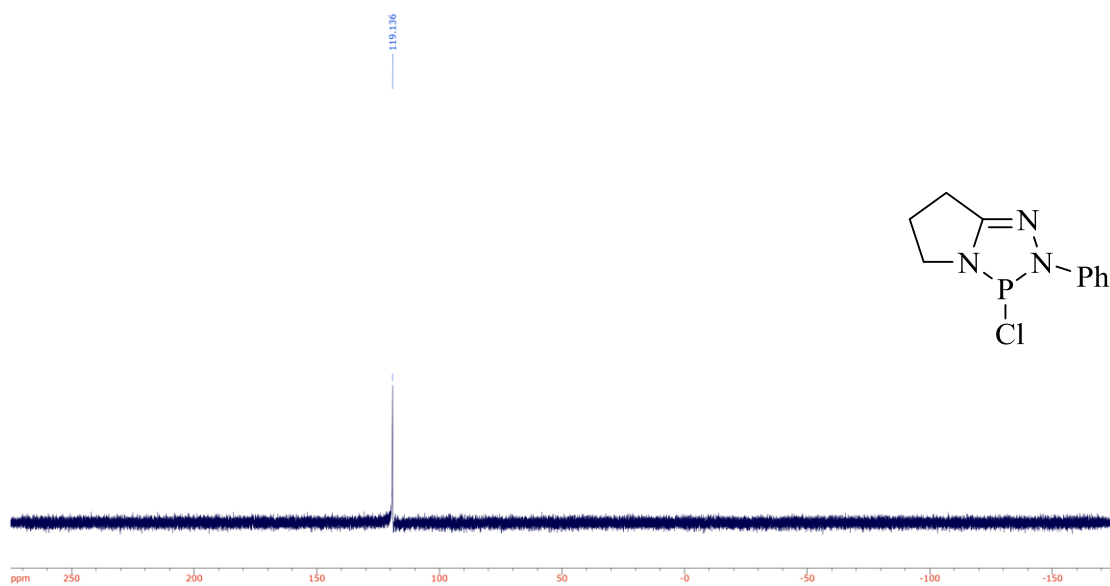


Figure S41. ^{31}P NMR spectrum of **2-30-Cl** (121 MHz, CDCl_3).

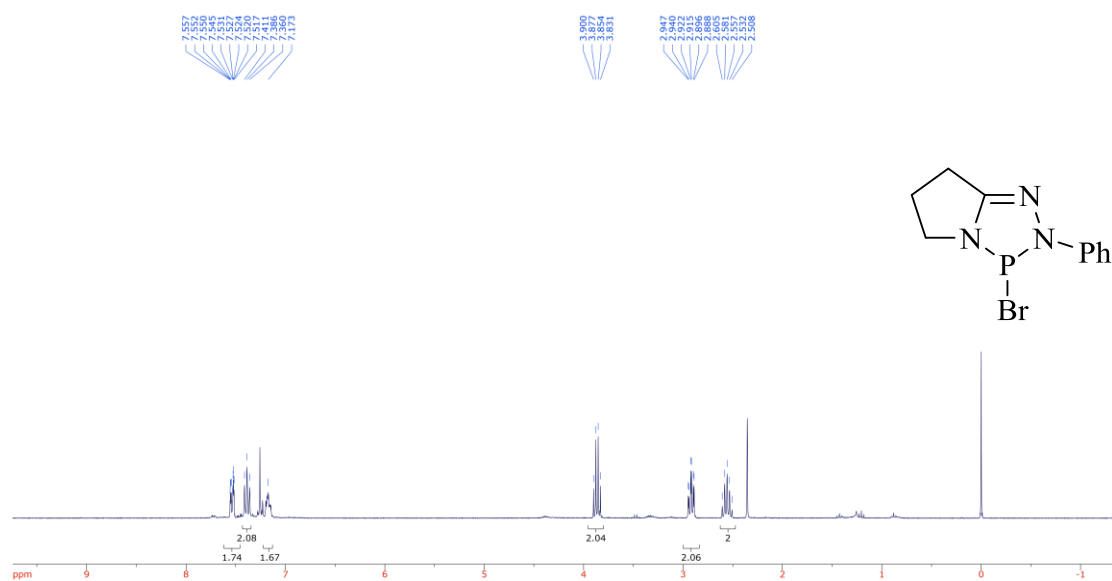


Figure S42. ¹H NMR spectrum of **2-30-Br** (300 MHz, CDCl₃).

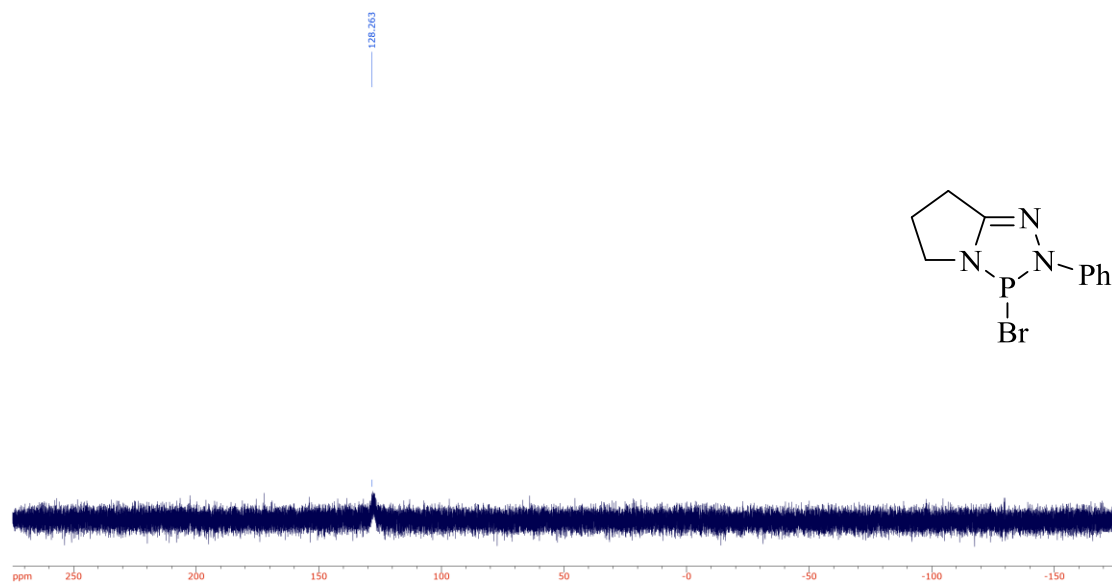


Figure S43. ³¹P NMR spectrum of **2-30-Br** (201 MHz, CDCl₃).

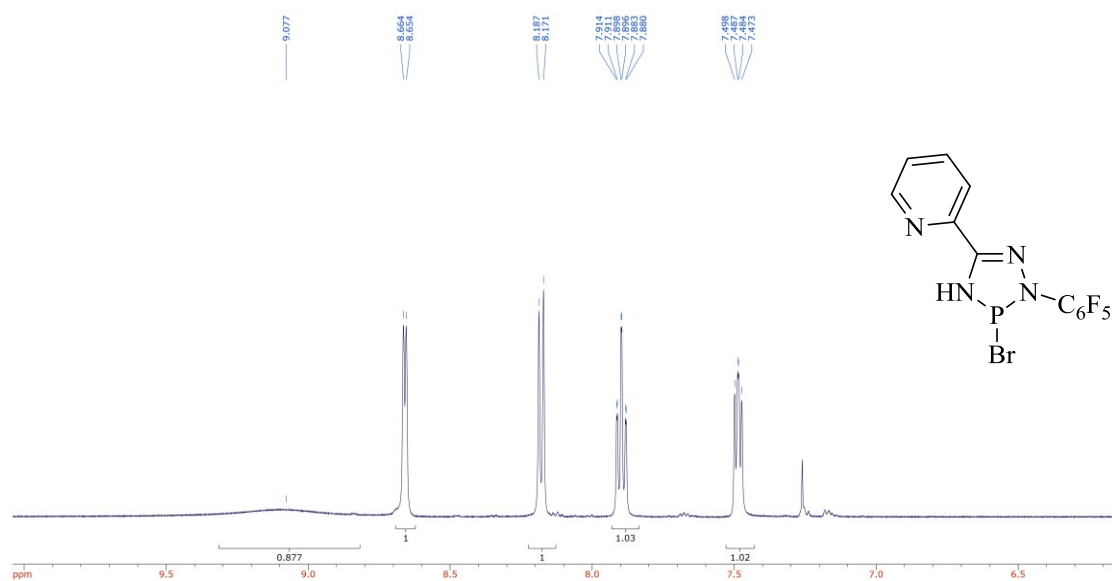


Figure S44. ^1H NMR spectrum of **2-31** (500 MHz, CDCl_3).

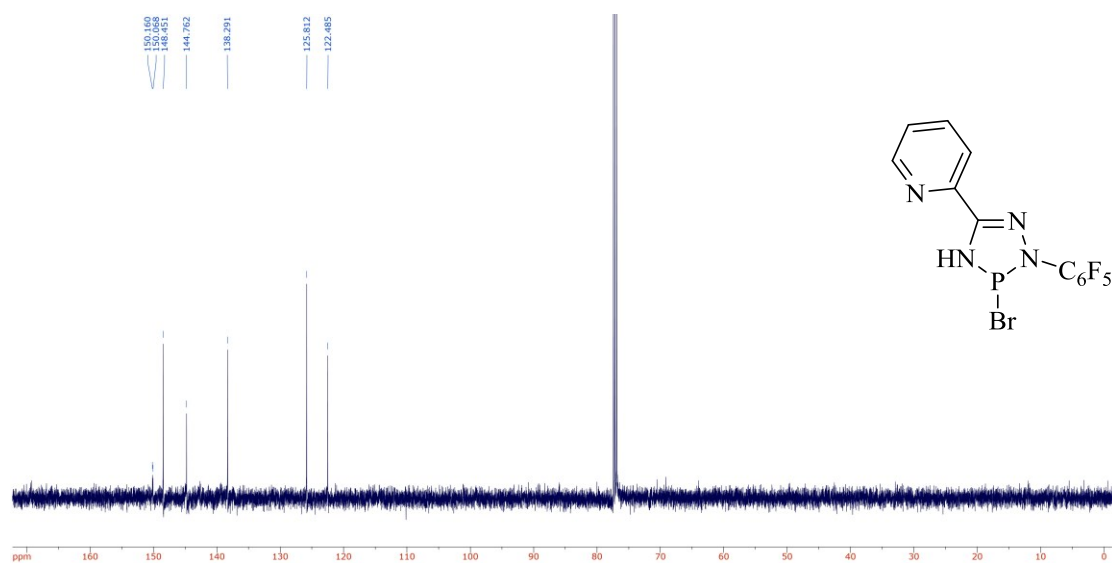
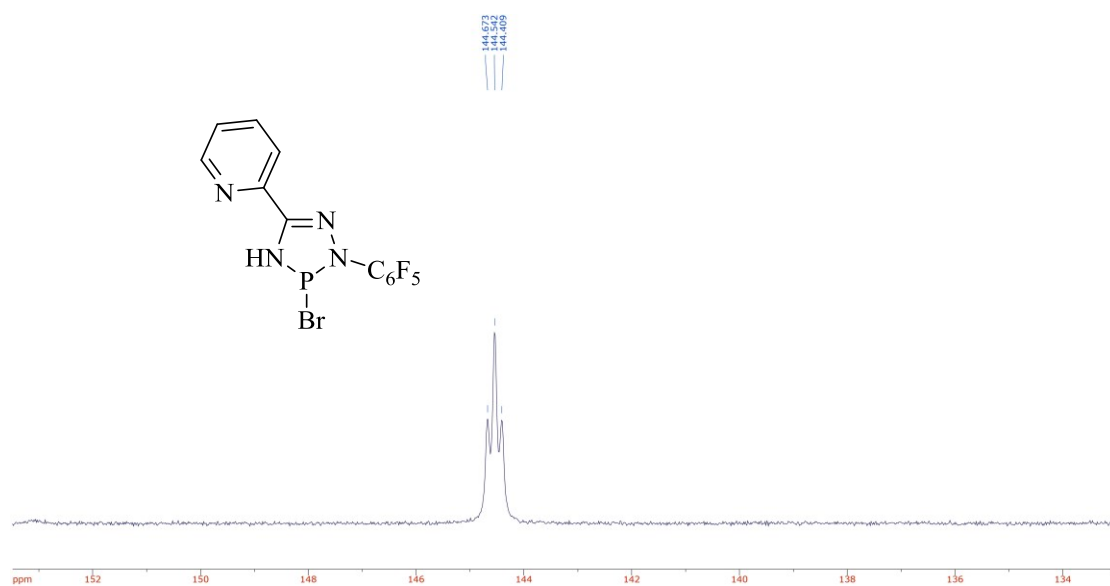
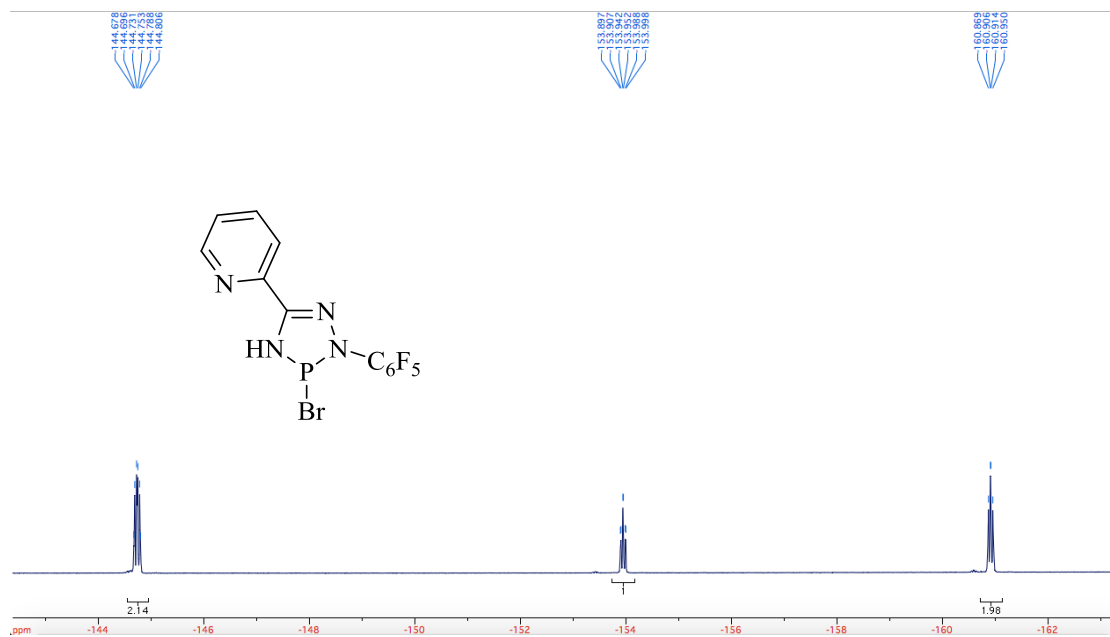
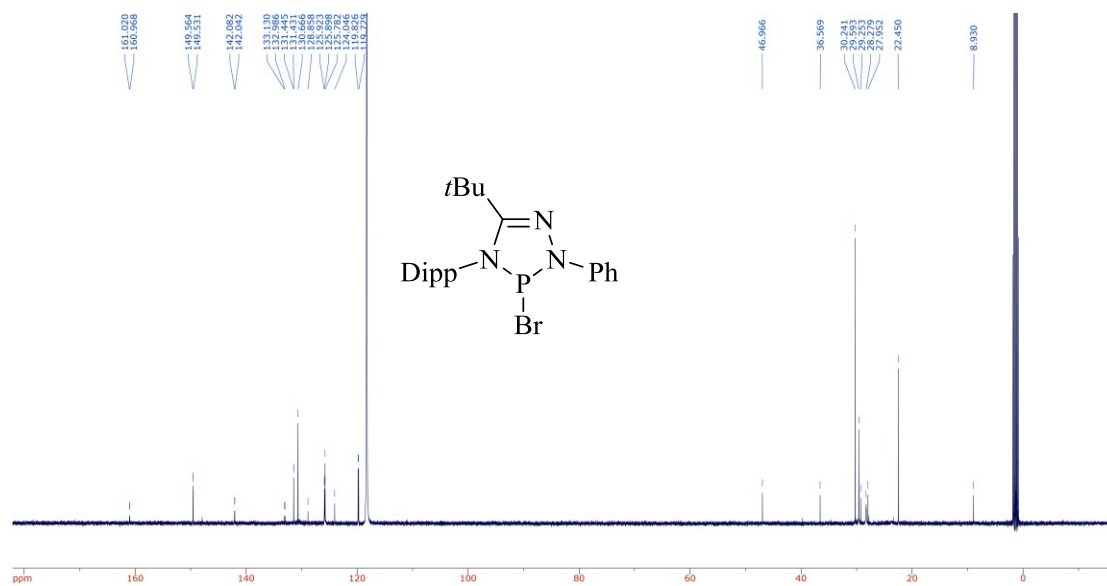
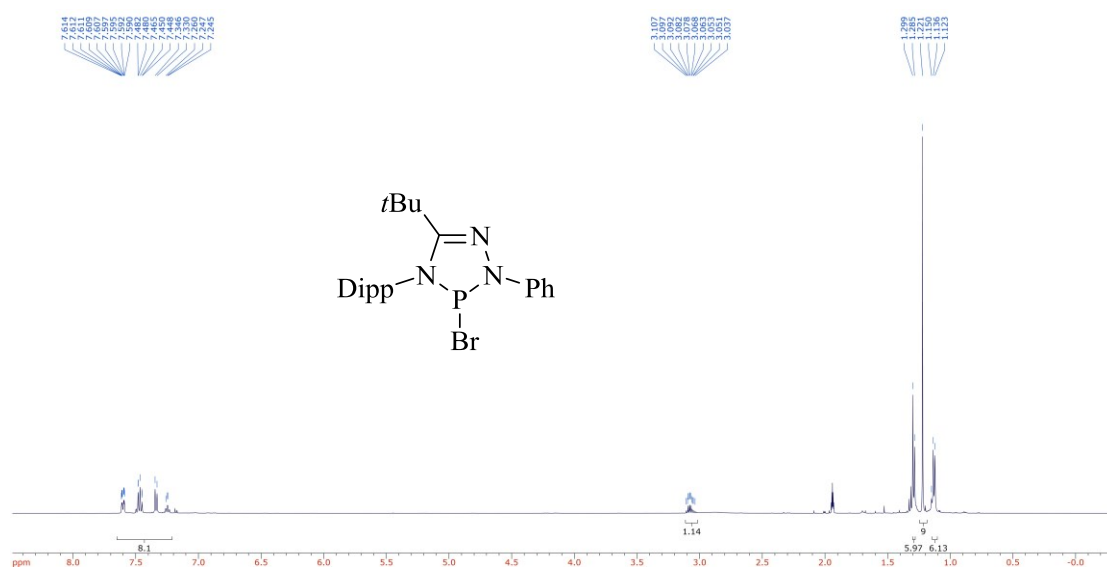


Figure S45. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-31** (125 MHz, CDCl_3).





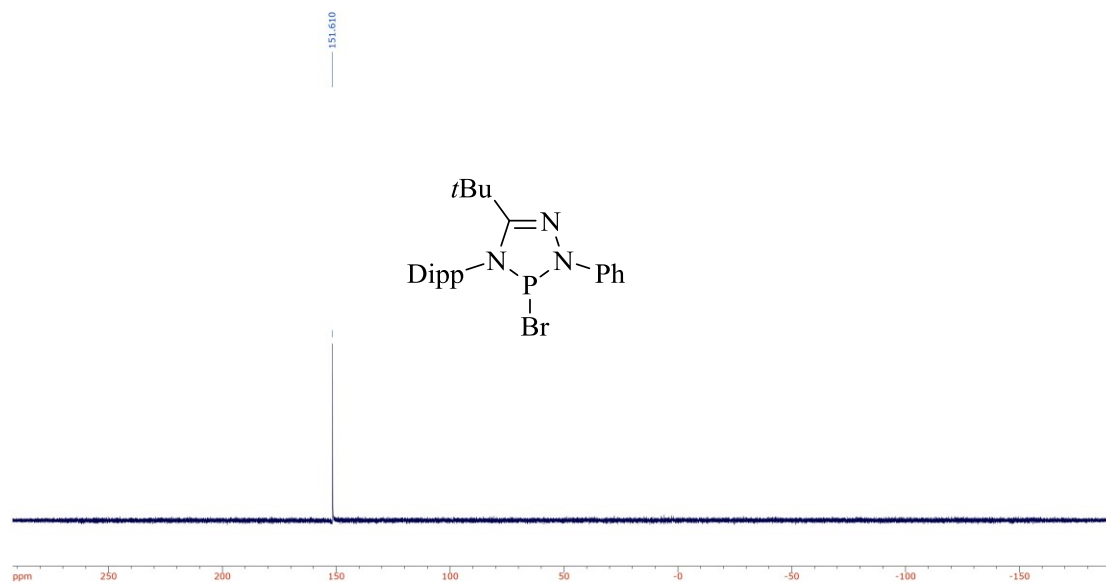


Figure S50. ^{31}P NMR spectrum of **2-32** (201 MHz, acetonitrile- d_3).

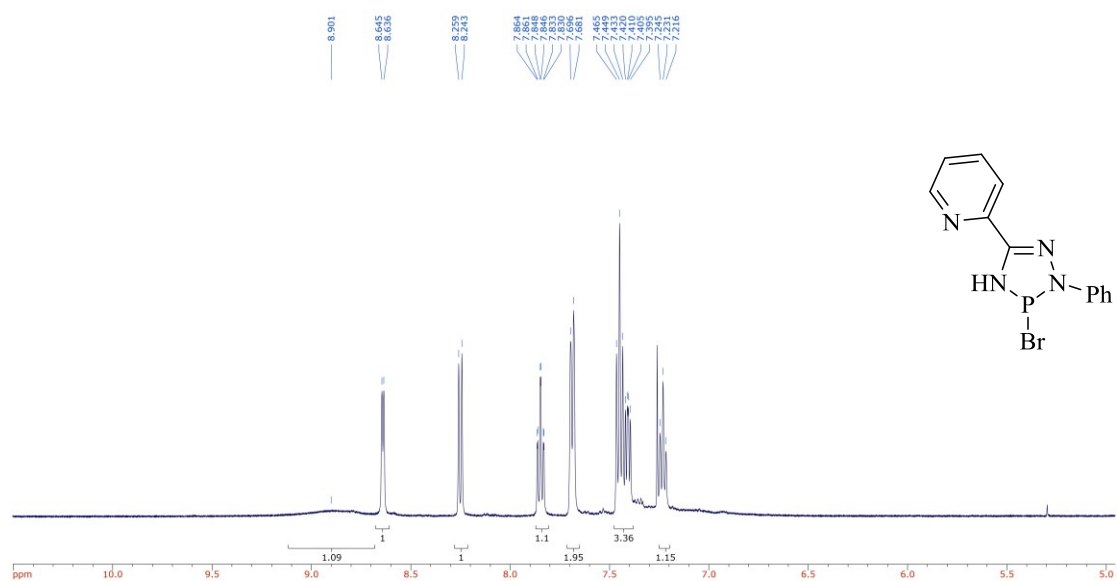


Figure S51. ^1H NMR spectrum of 2-33 (500 MHz, CDCl_3).

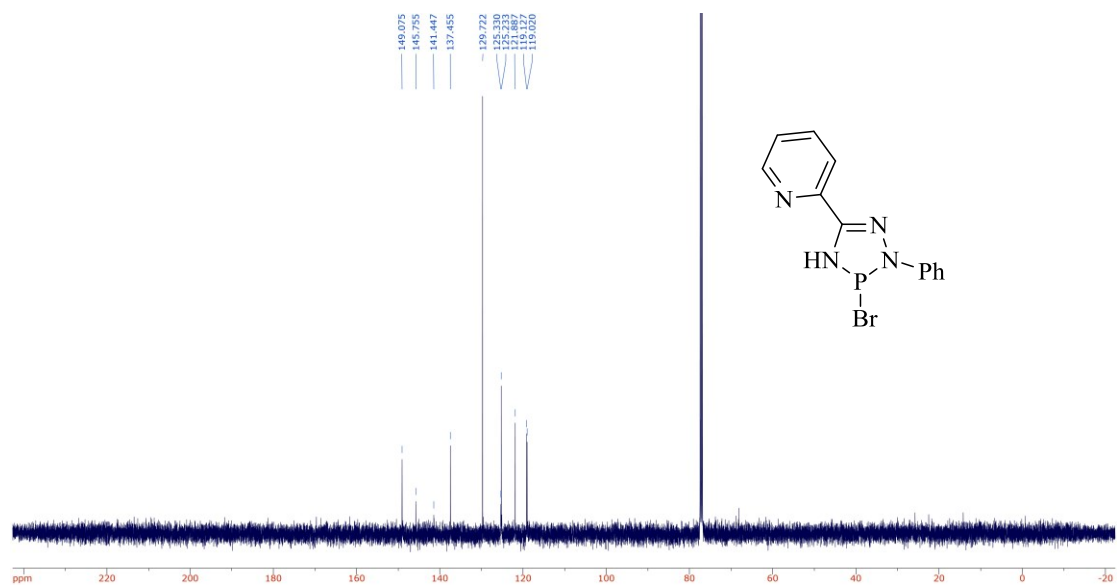


Figure S52. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 2-33 (125 MHz, CDCl_3).

140.742

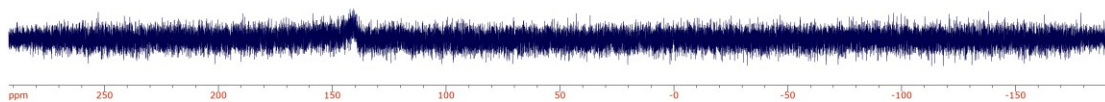
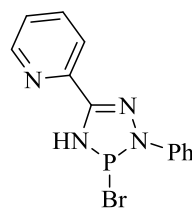


Figure S53. ^{31}P NMR spectrum of **2-33** (201 MHz, CDCl_3).

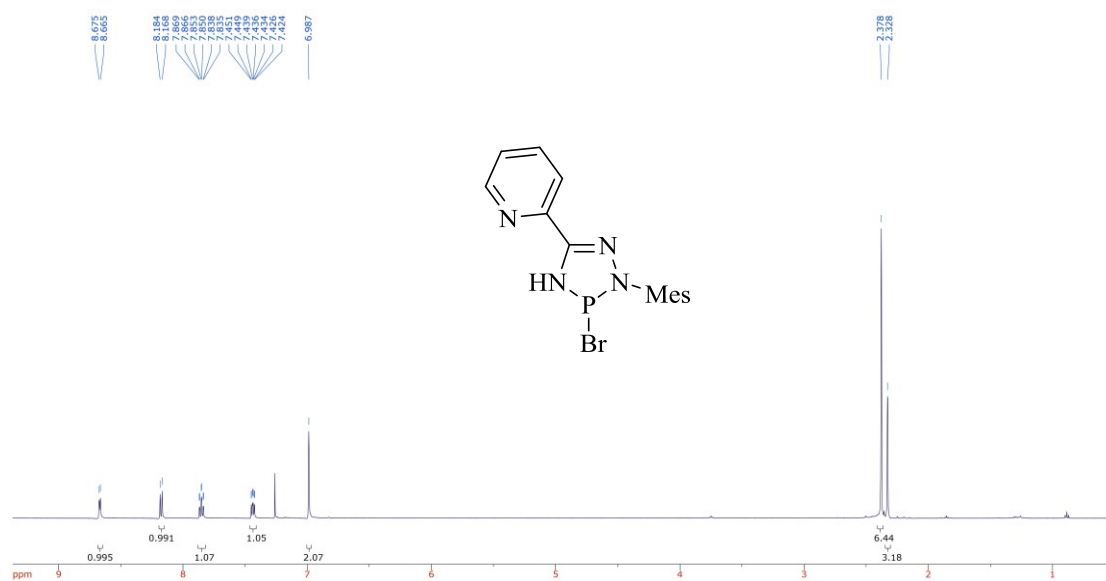


Figure S54. ^1H NMR spectrum of **2-34** (500 MHz, CDCl_3).

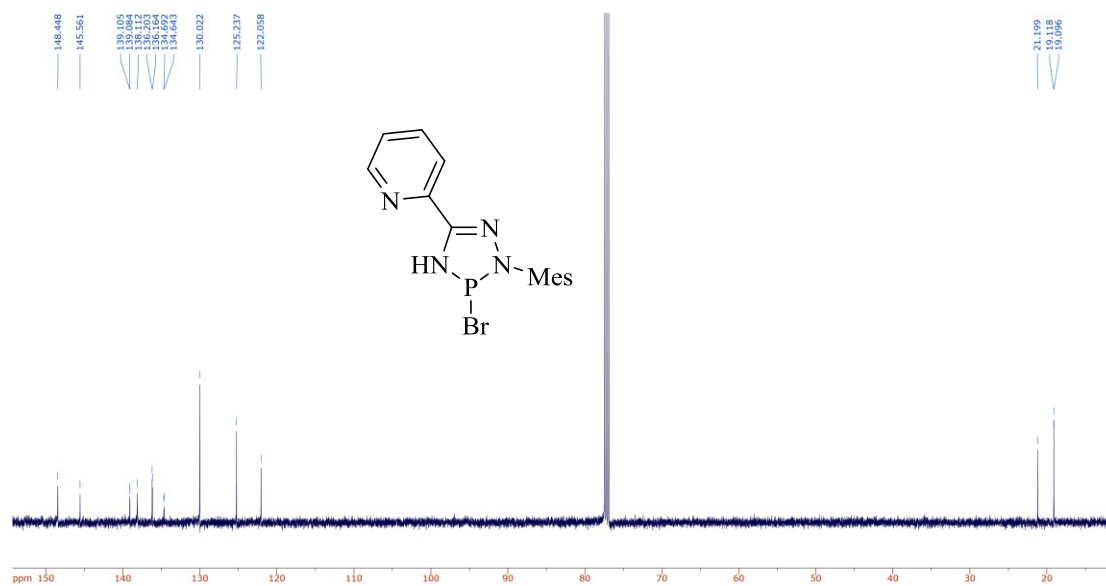


Figure S55. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **2-34** (125 MHz, CDCl_3).

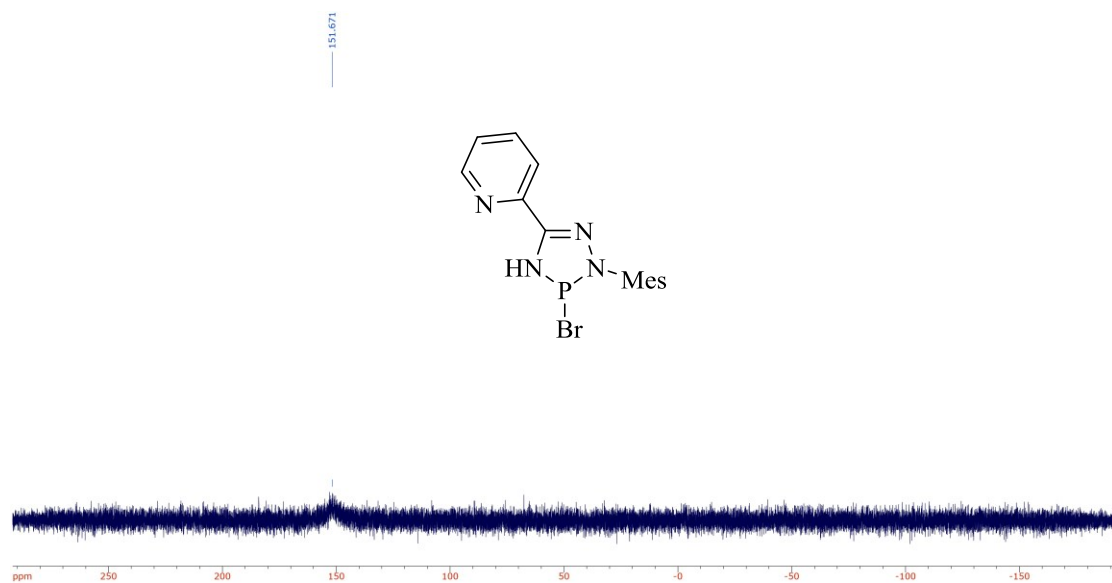


Figure S56. ^{31}P NMR spectrum of **2-34** (201 MHz, CDCl_3).

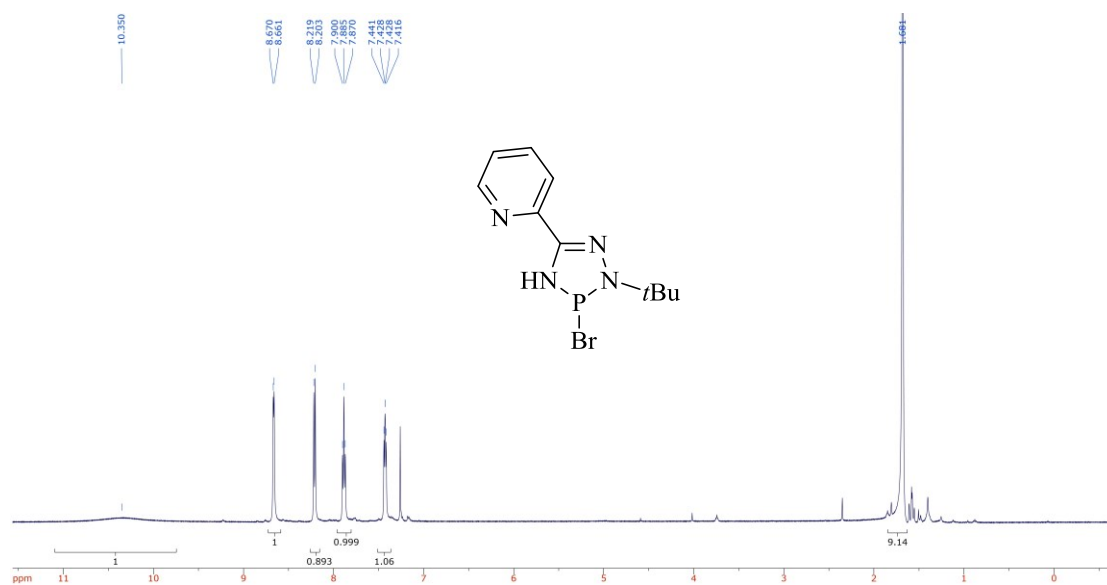


Figure S57. ^1H NMR spectrum of 2-35 (500 MHz, CDCl_3).

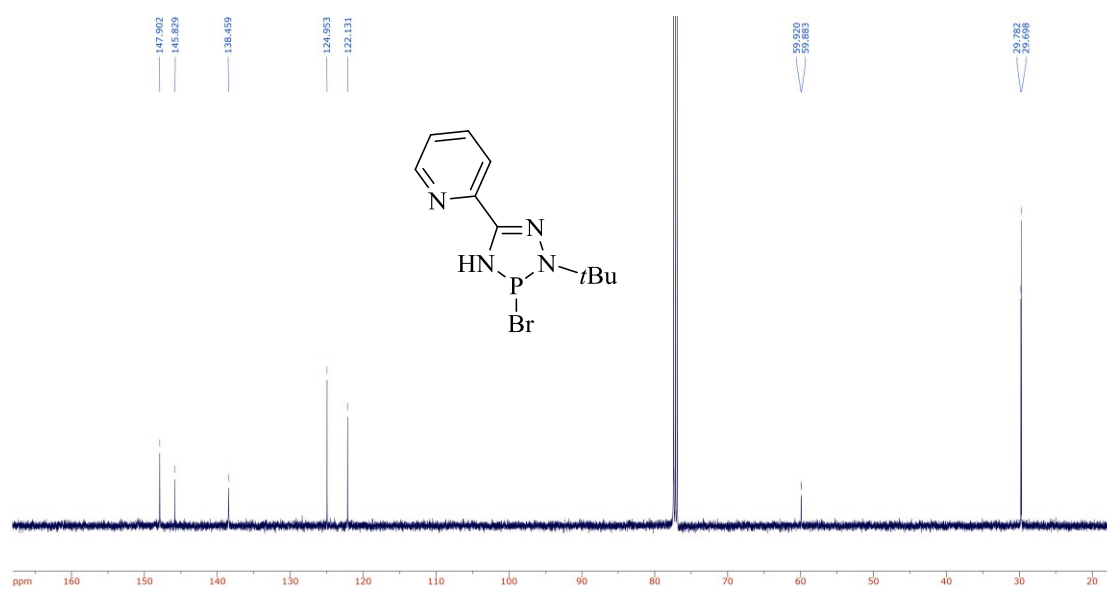


Figure S58. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 2-35 (125 MHz, CDCl_3).

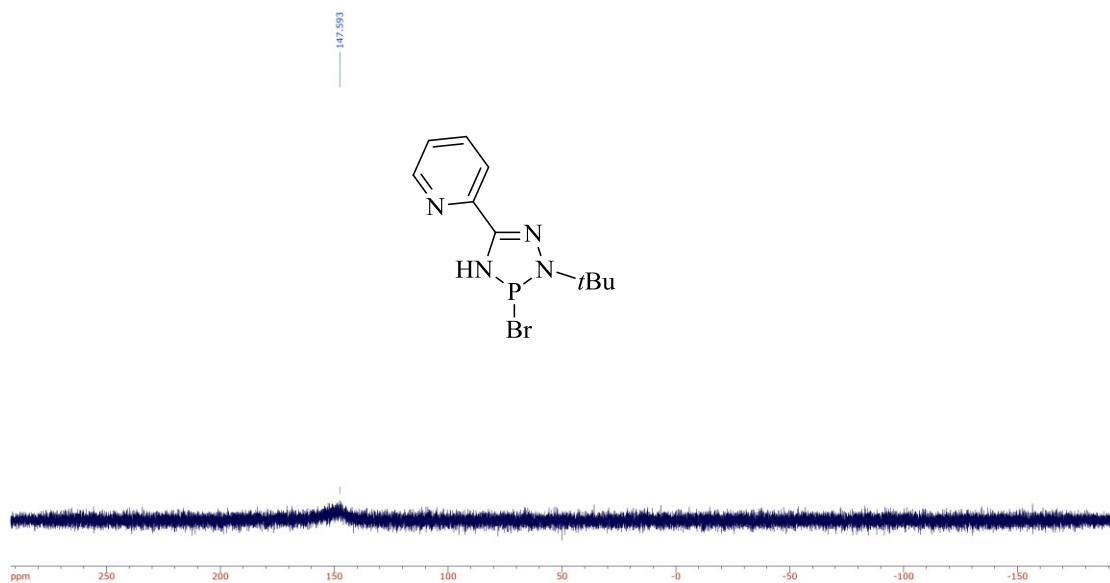


Figure S59. ^{31}P NMR spectrum of **2-35** (201 MHz, CDCl_3).

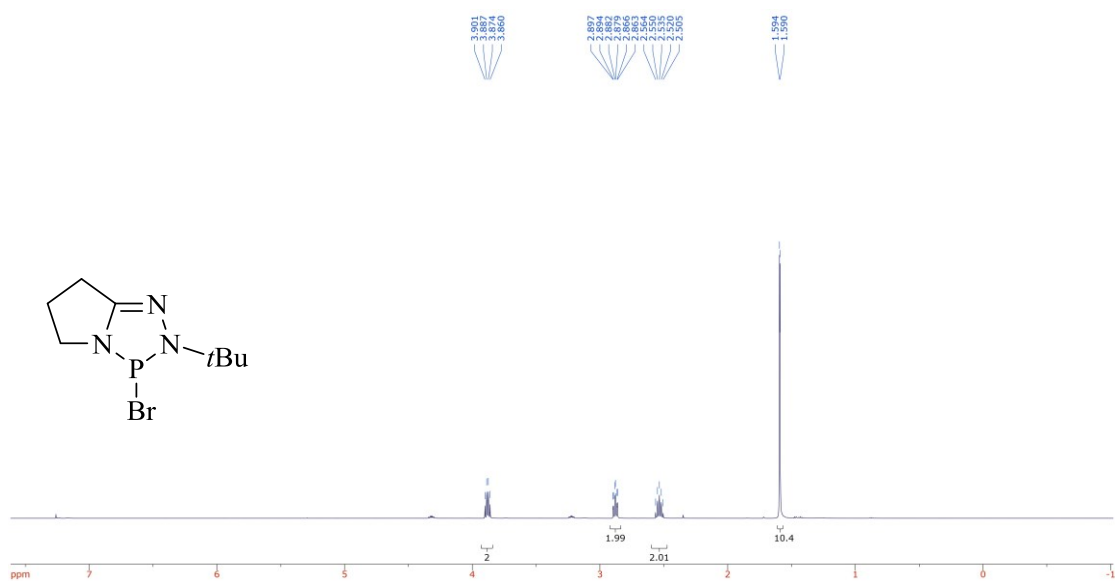


Figure S60. ^1H NMR spectrum of 2-36 (500 MHz, CDCl_3).

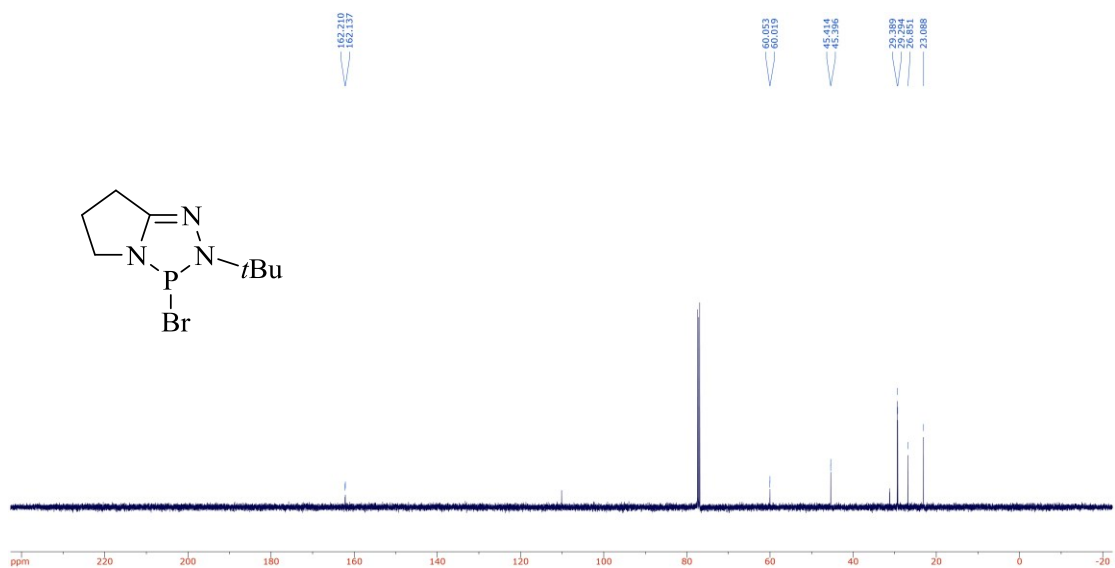


Figure S61. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 2-36 (125 MHz, CDCl_3).

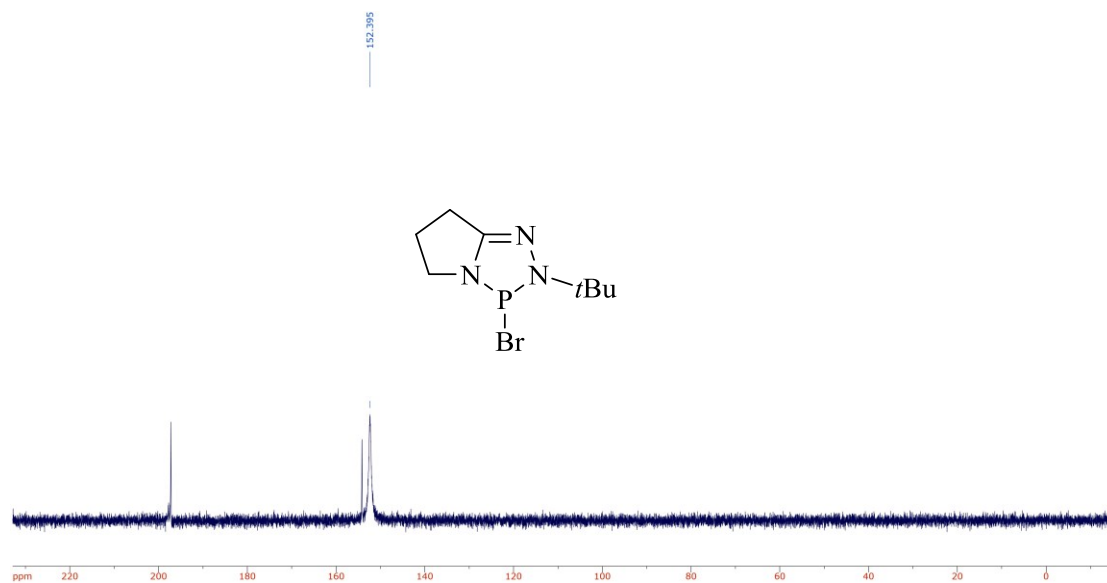


Figure S62. ^{31}P NMR spectrum of **2-36** (201 MHz, CDCl_3).

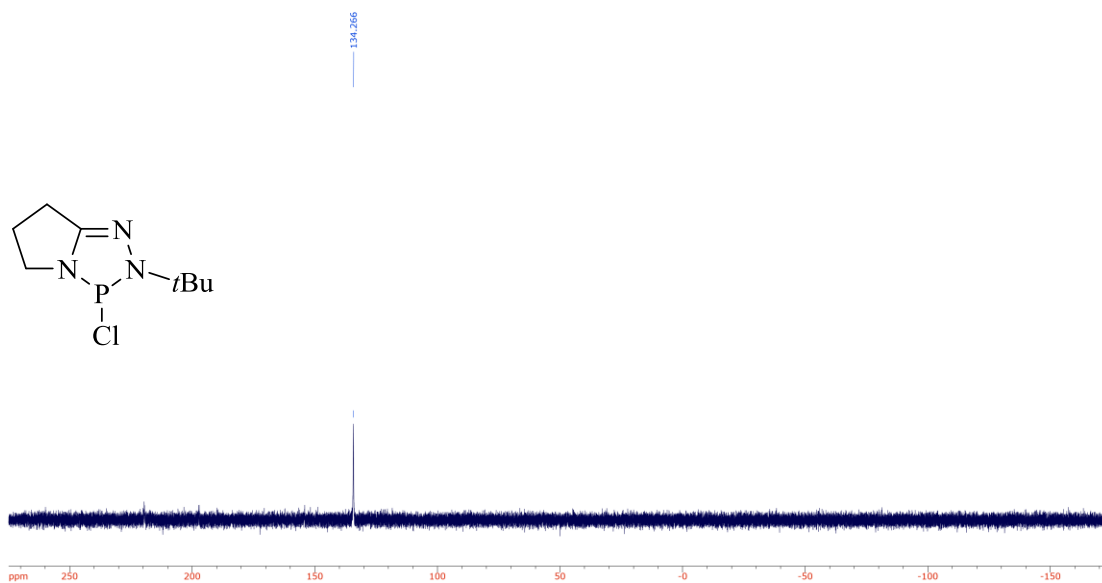


Figure S65. ^{31}P NMR spectrum of 2-37 (121 MHz, CDCl_3).

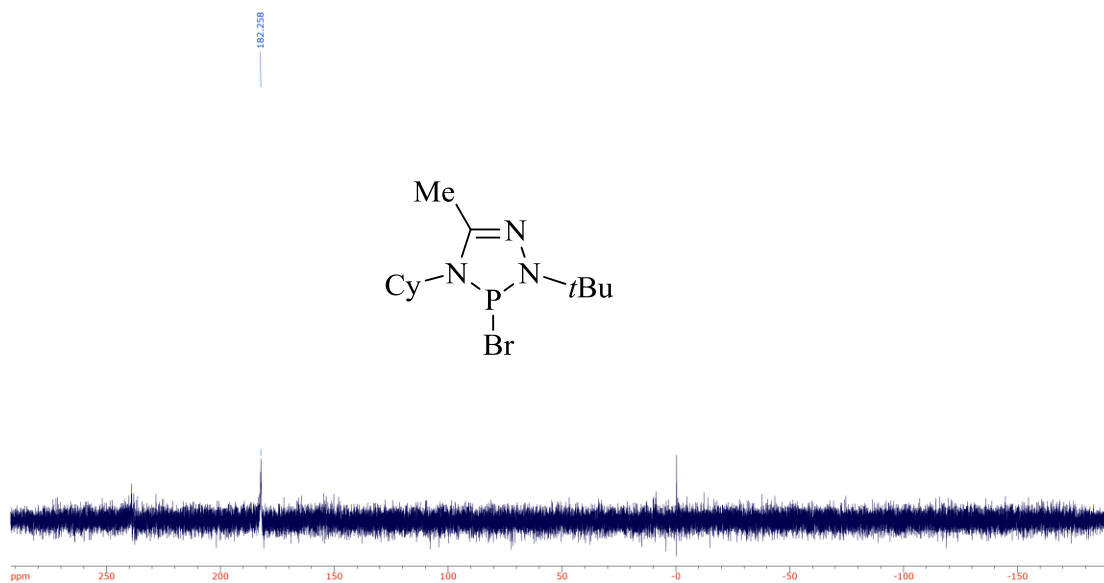
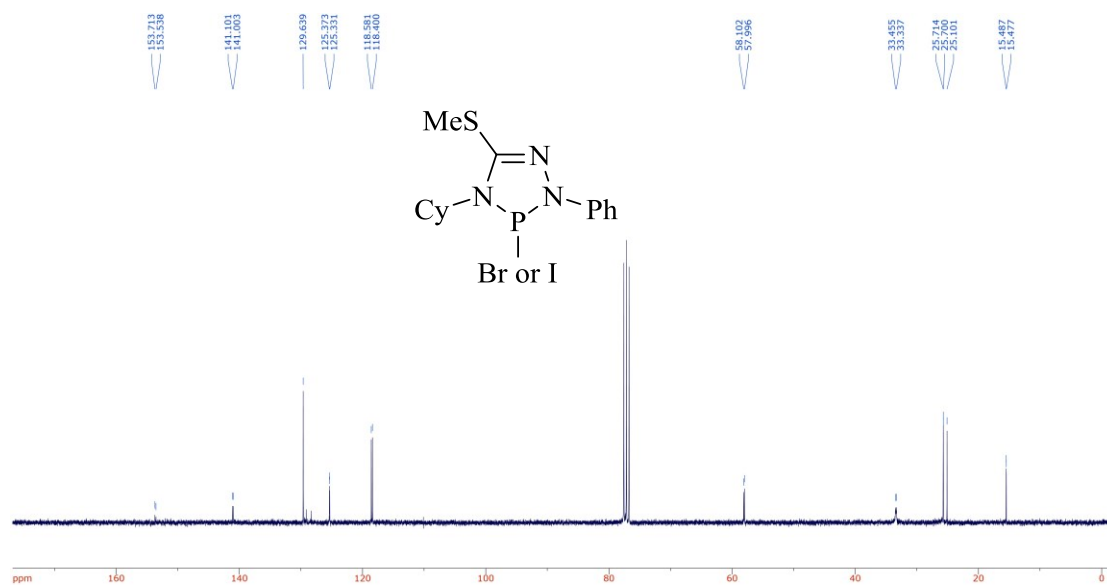
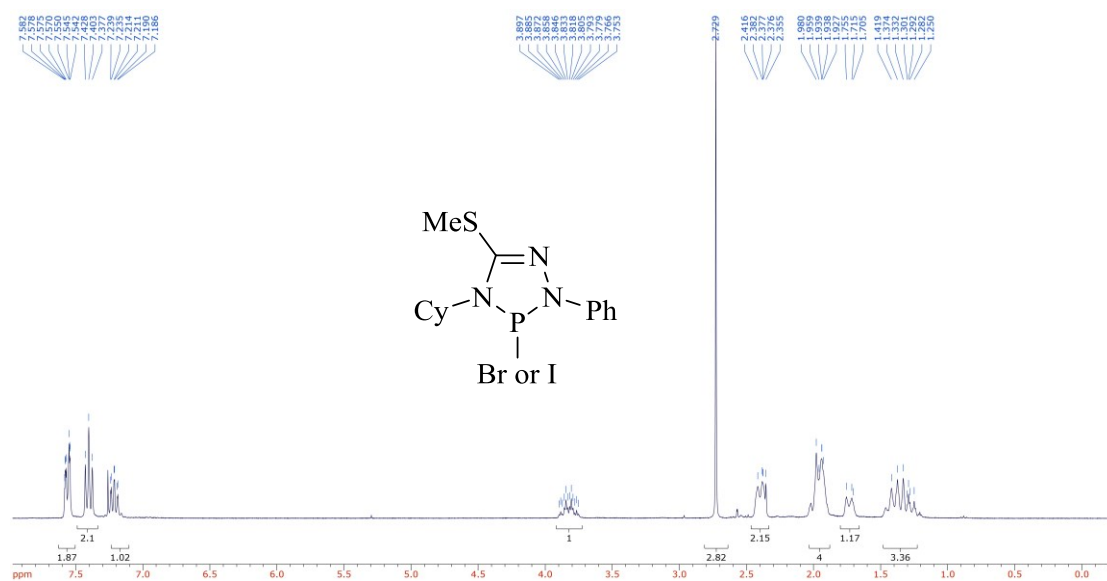


Figure S66. ^{31}P NMR spectrum of **2-38** (201 MHz, CDCl_3).



162.378

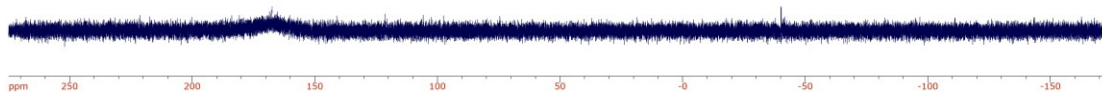
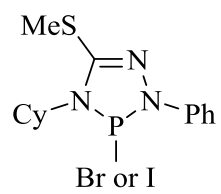


Figure S69. ^{31}P NMR spectrum of **2-39** (121 MHz, CDCl_3).

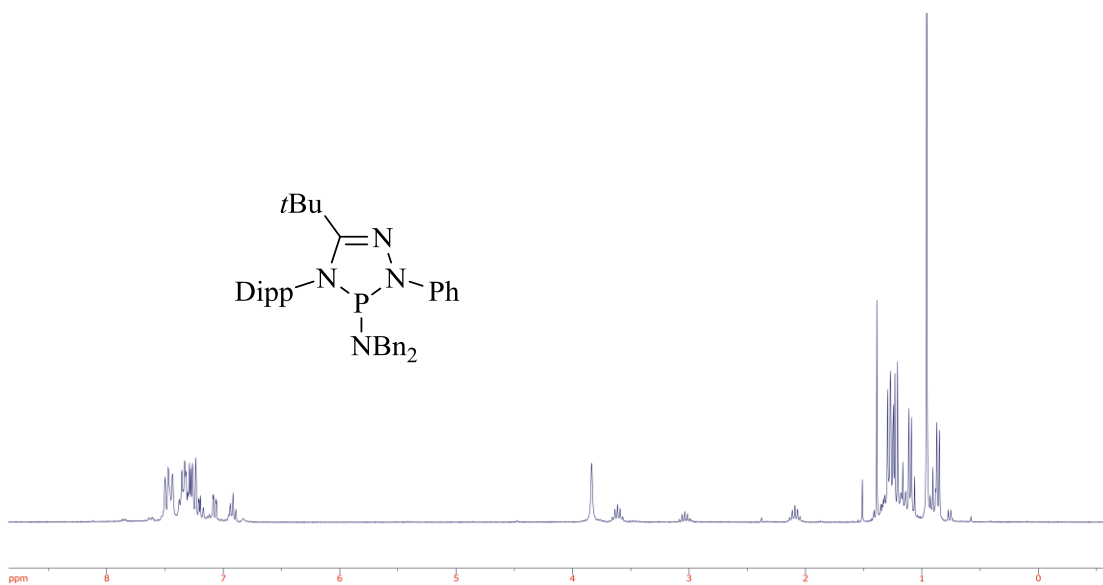


Figure S70. ^1H NMR spectrum of **2-43** (300 MHz, CDCl_3).

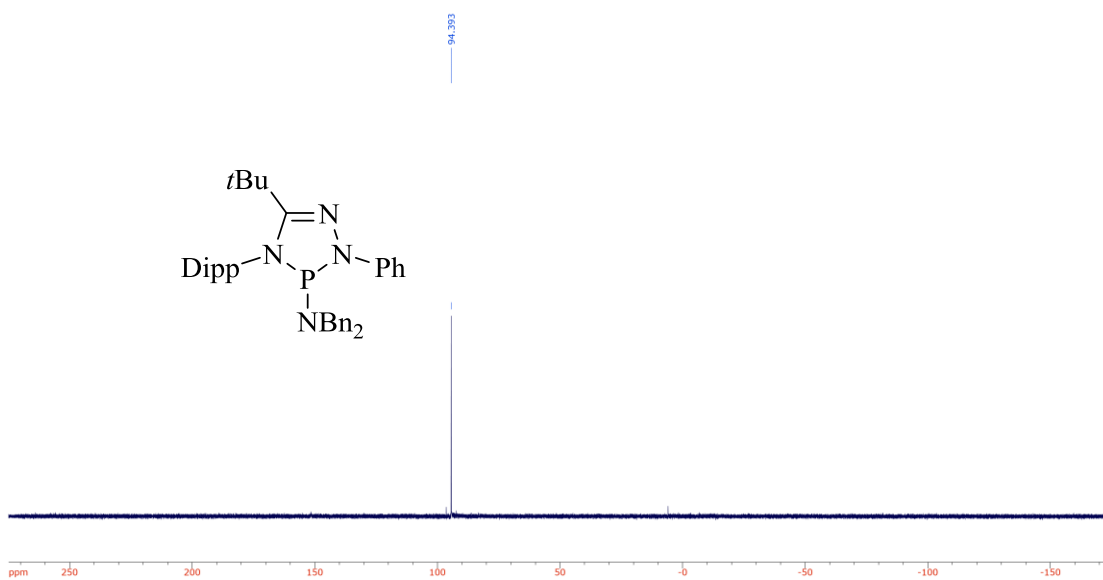


Figure S71. ^{31}P NMR spectrum of **2-43** (121 MHz, CDCl_3).

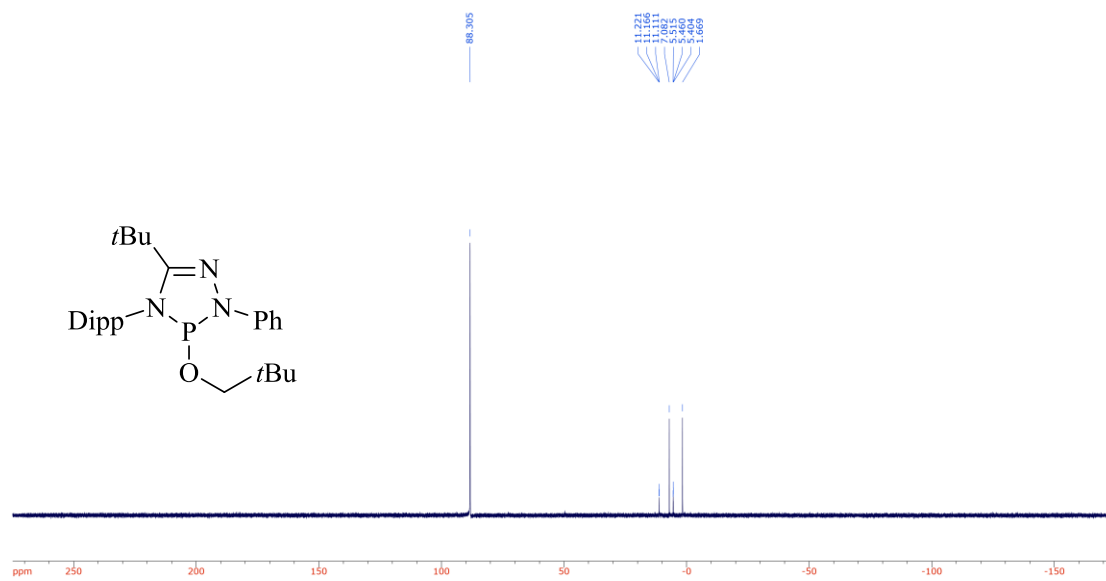
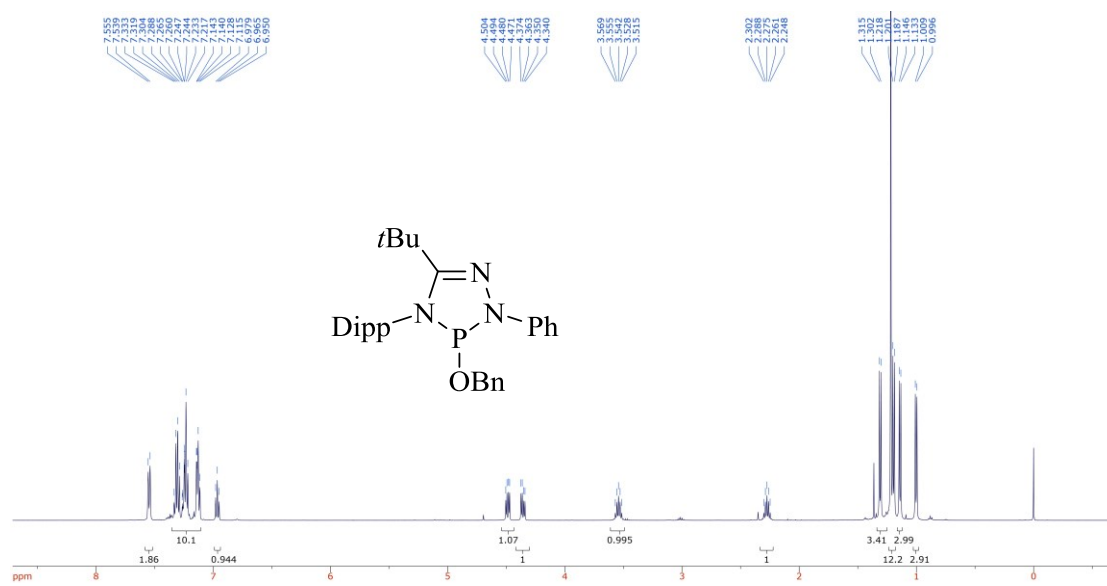


Figure S72. ^{31}P NMR spectrum of 2-44 (201 MHz, CDCl_3).



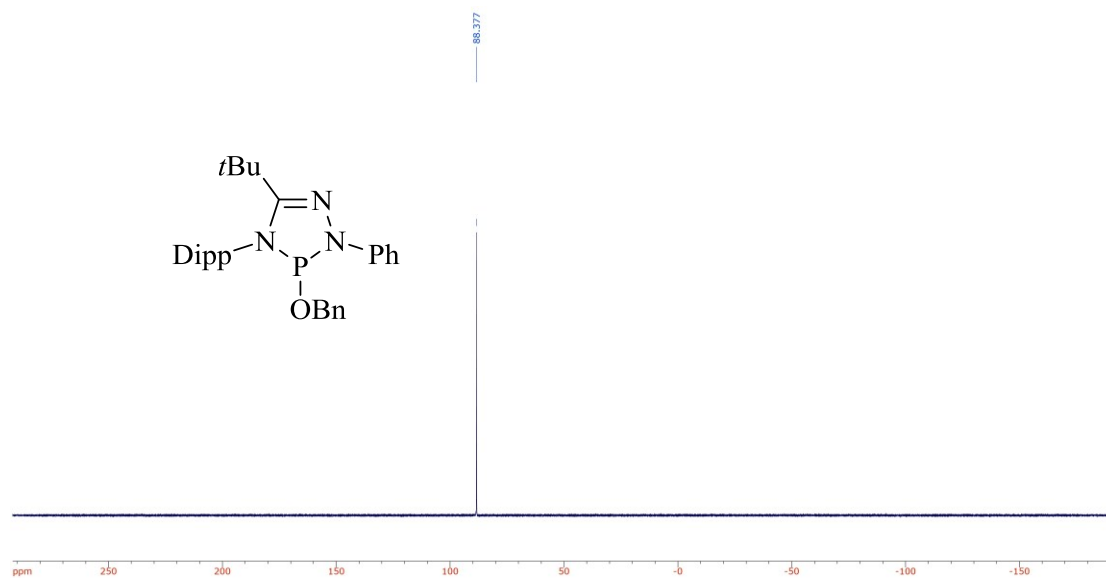


Figure S75. ^{31}P NMR spectrum of **2-45** (201 MHz, CDCl_3).

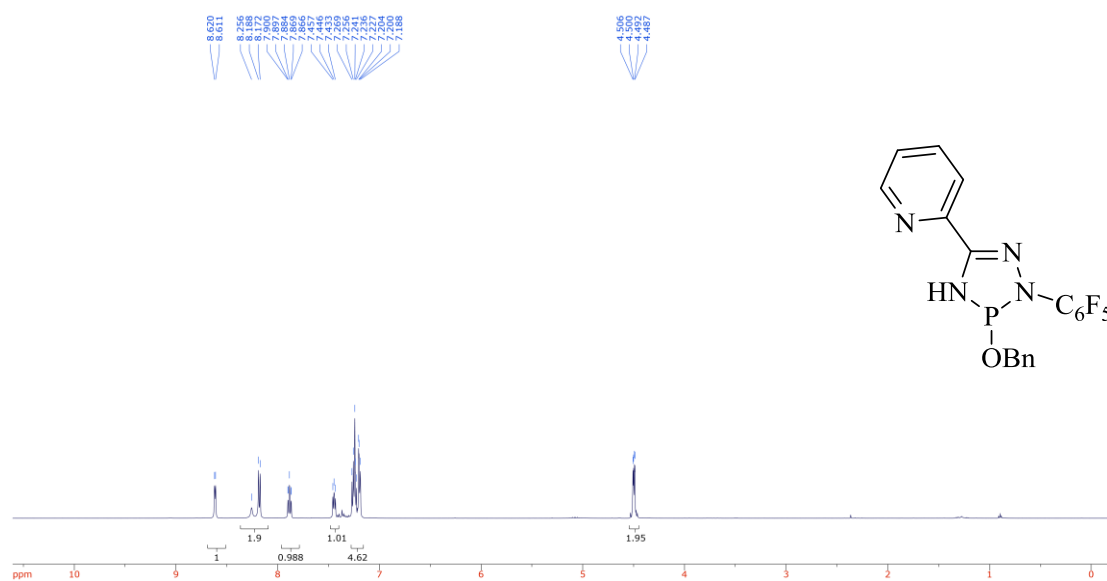


Figure S76. ¹H NMR spectrum of **2-48** (500 MHz, CDCl₃).

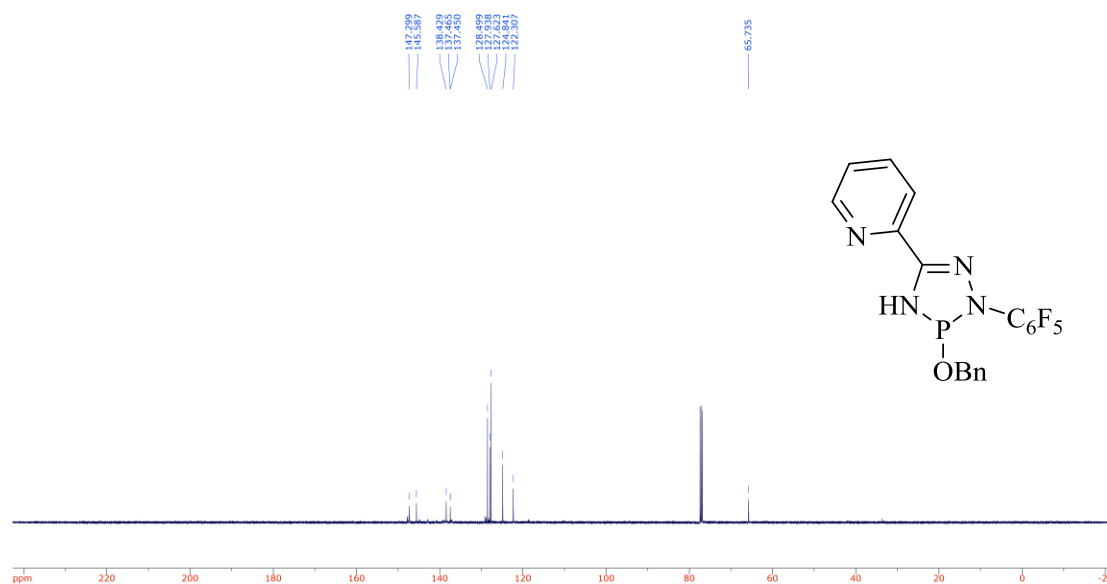


Figure S77. ¹³C{¹H} NMR spectrum of **2-48** (125 MHz, CDCl₃).

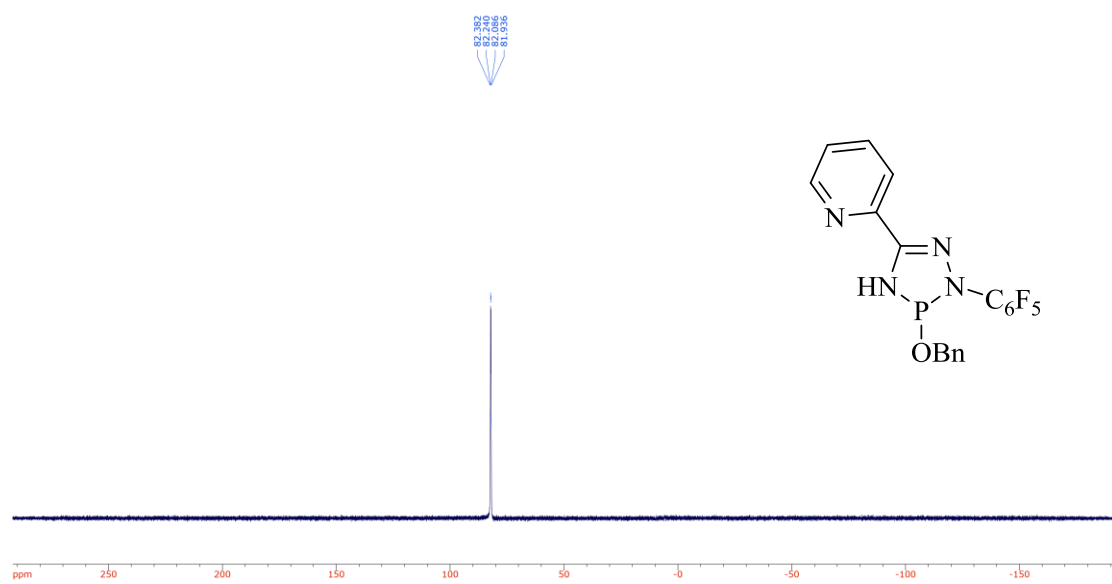


Figure S78. ^{31}P NMR spectrum of **2-48** (201 MHz, CDCl_3).

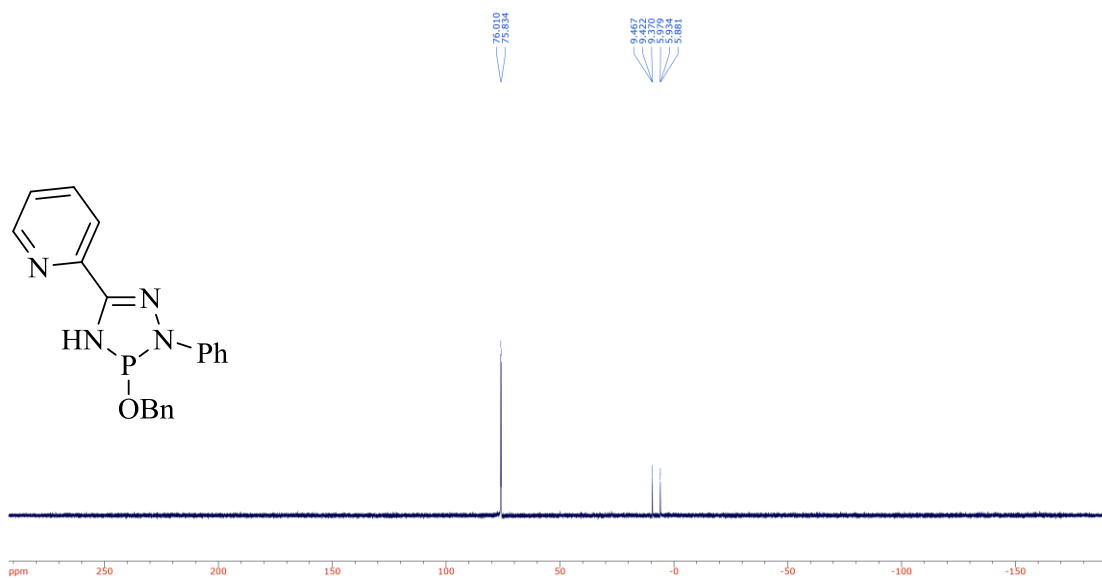


Figure S79. ^{31}P NMR spectrum of **2-49** (201 MHz, CDCl_3).

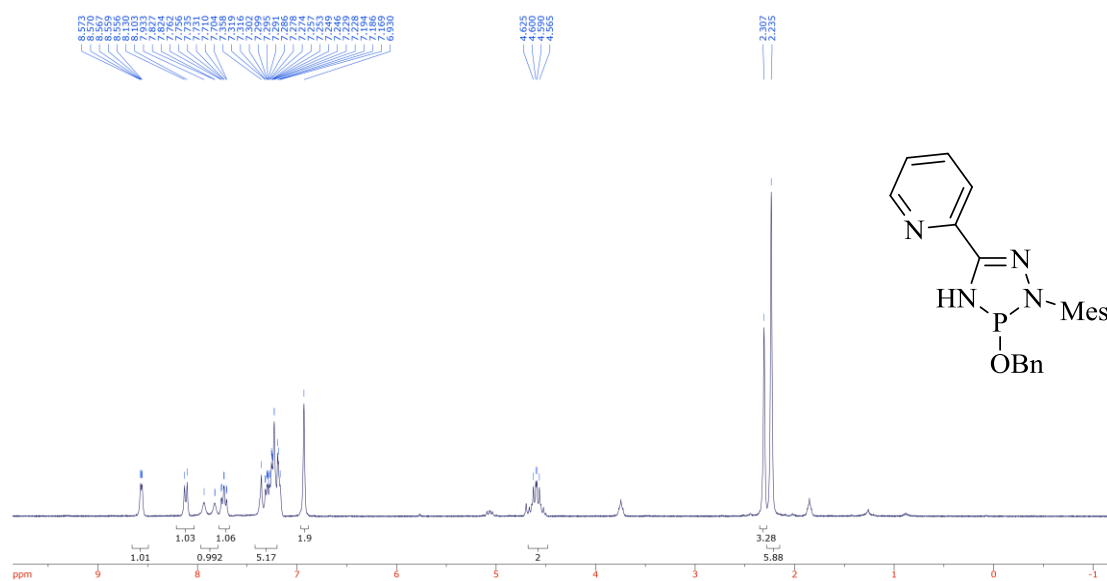


Figure S80. ^1H NMR spectrum of **2-50** (300 MHz, CDCl_3).

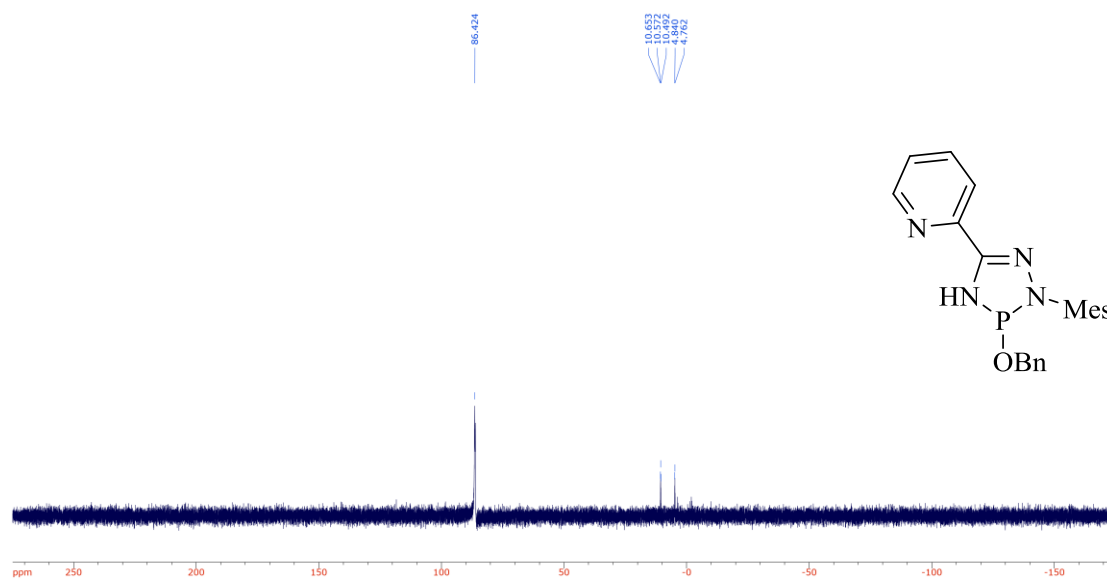


Figure S81. ^{31}P NMR spectrum of **2-50** (121 MHz, CDCl_3).

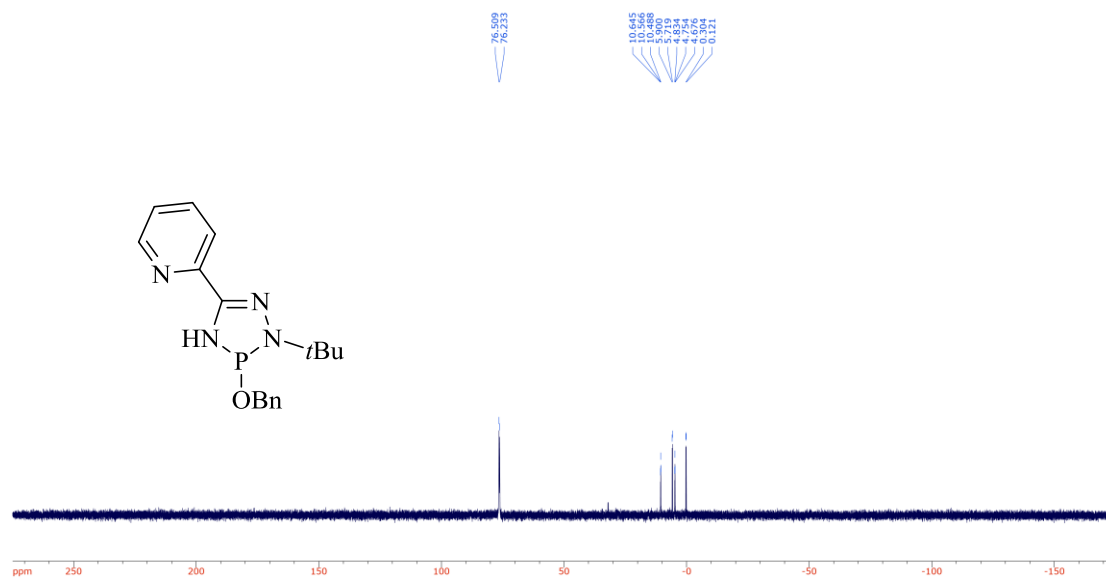


Figure S82. ^{31}P NMR spectrum of **2-51** (121 MHz, CDCl_3).

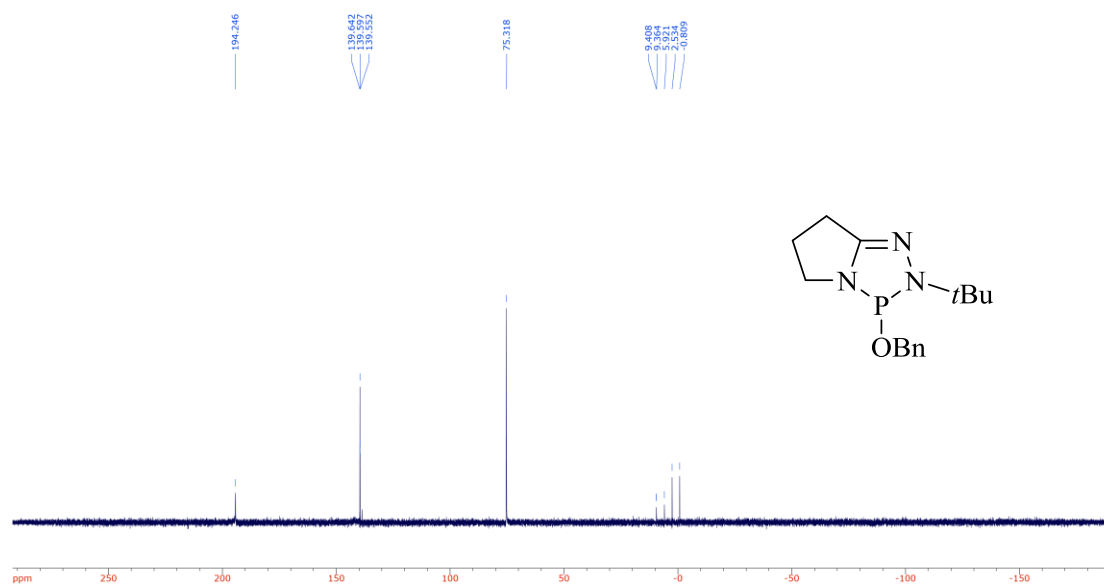


Figure S83. ^{31}P NMR spectrum of contaminated **2-52** (201 MHz, CDCl_3).

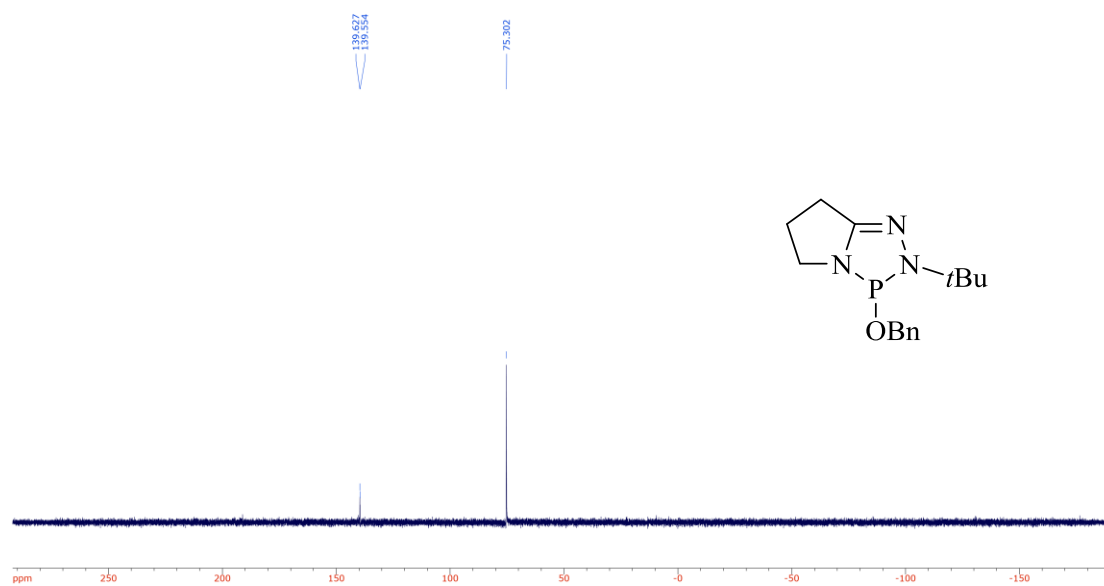


Figure S84. ^{31}P NMR spectrum of **2-52** (201 MHz, CDCl_3).

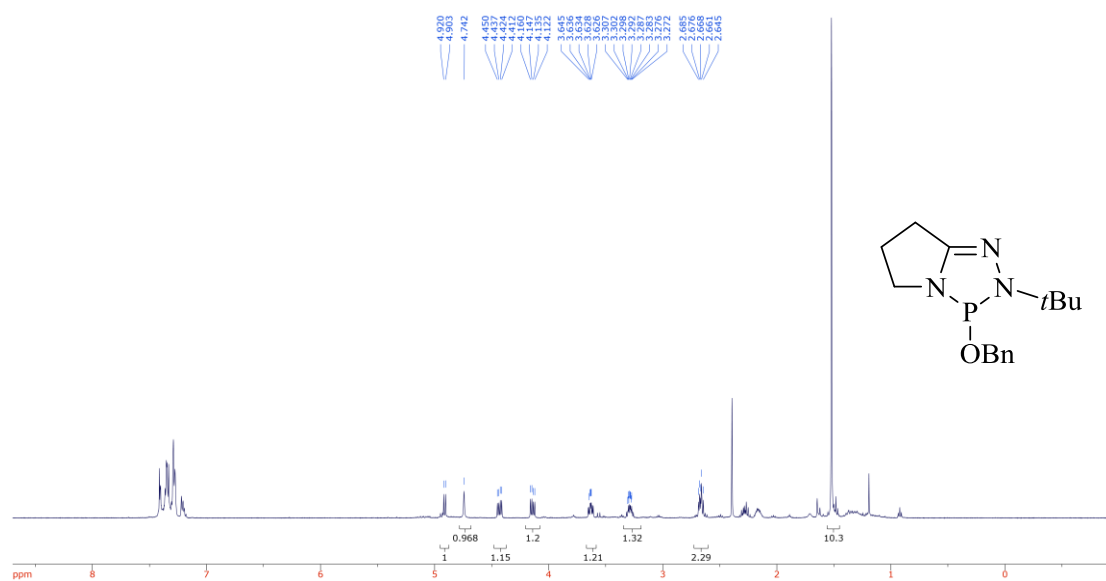


Figure S85. ^1H NMR spectrum of **2-52** (500 MHz, CDCl_3).

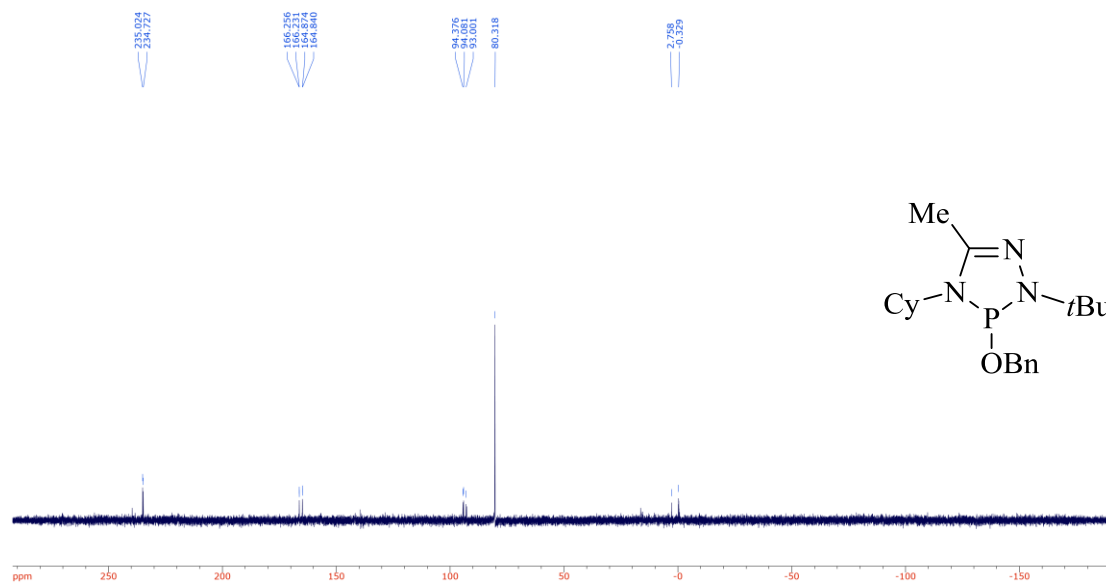


Figure S86. ^{31}P NMR spectrum of **2-53** (201 MHz, CDCl_3).

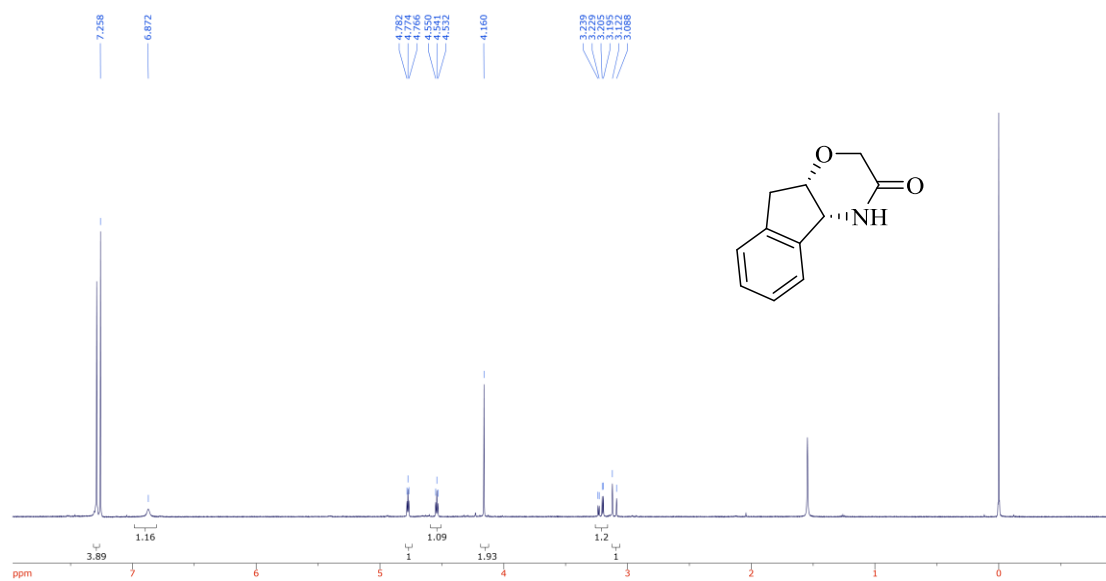


Figure S89. ^1H NMR spectrum of **3-1** (500 MHz, CDCl_3).

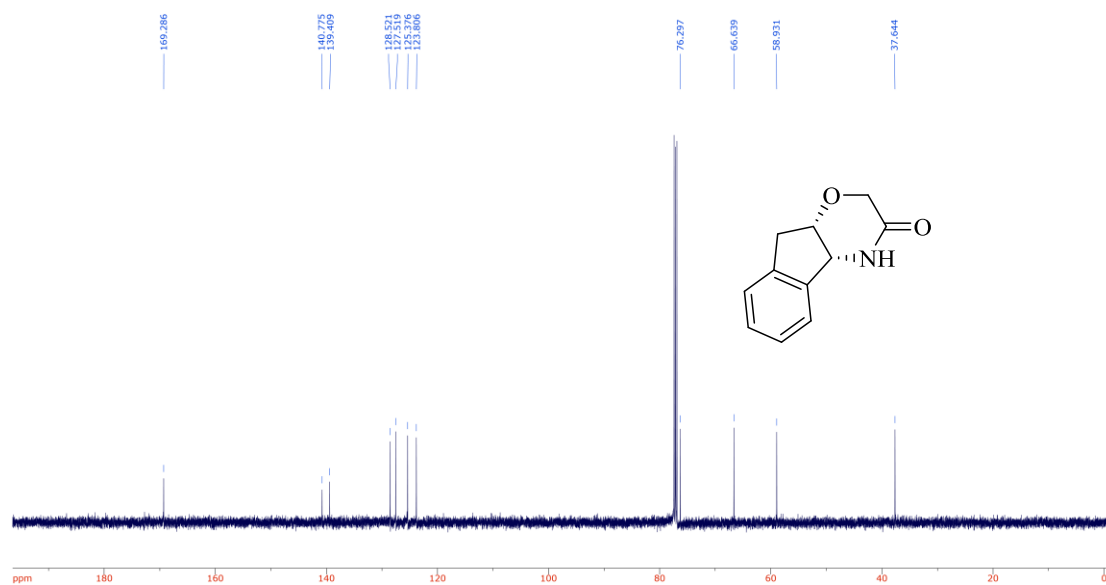


Figure S90. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **3-1** (125 MHz, CDCl_3).

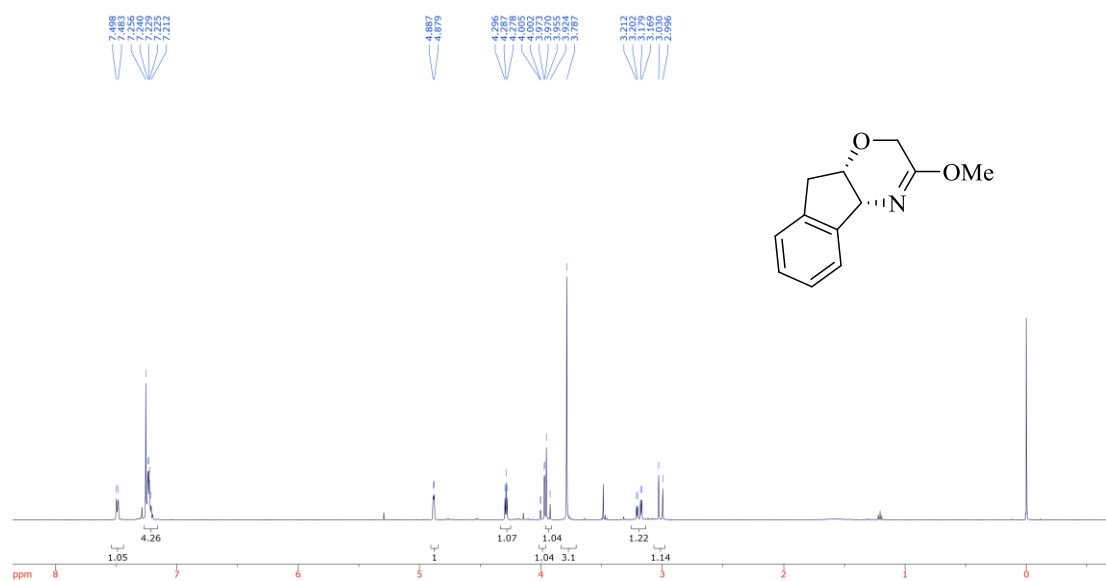


Figure S91. ^1H NMR spectrum of **3-2** (500 MHz, CDCl_3).

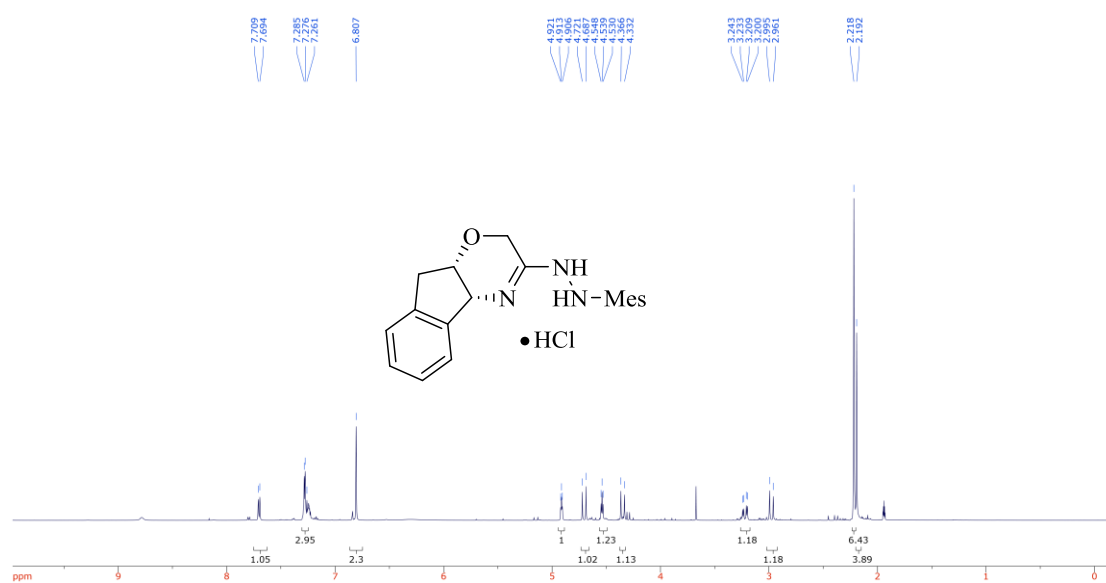


Figure S92. ^1H NMR spectrum of **3-5** (500 MHz, acetonitrile- d_3).

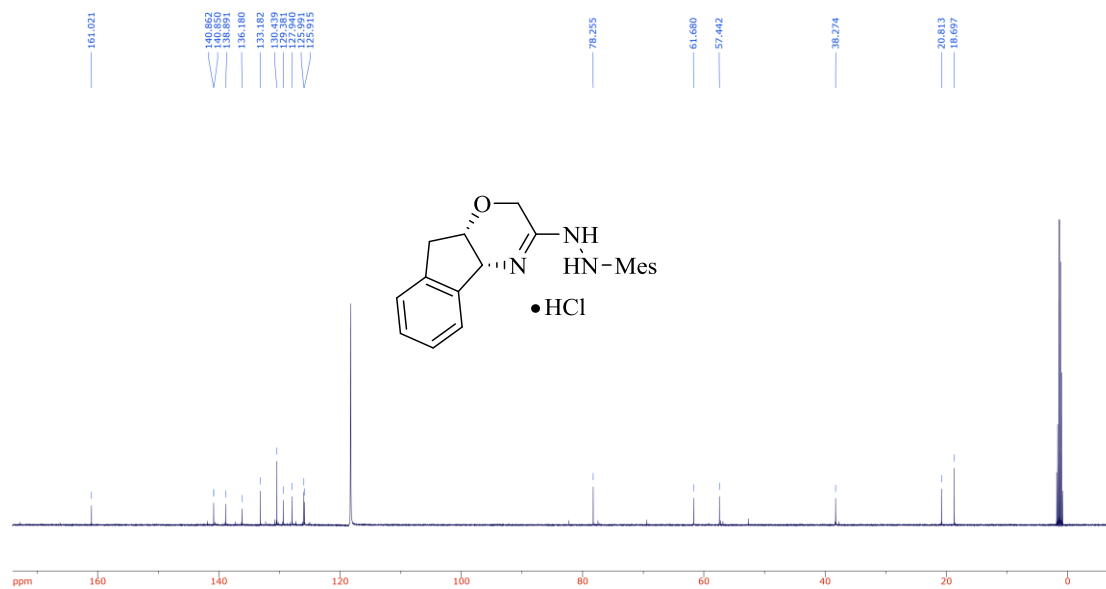


Figure S93. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **3-5** (125 MHz, acetonitrile- d_3).

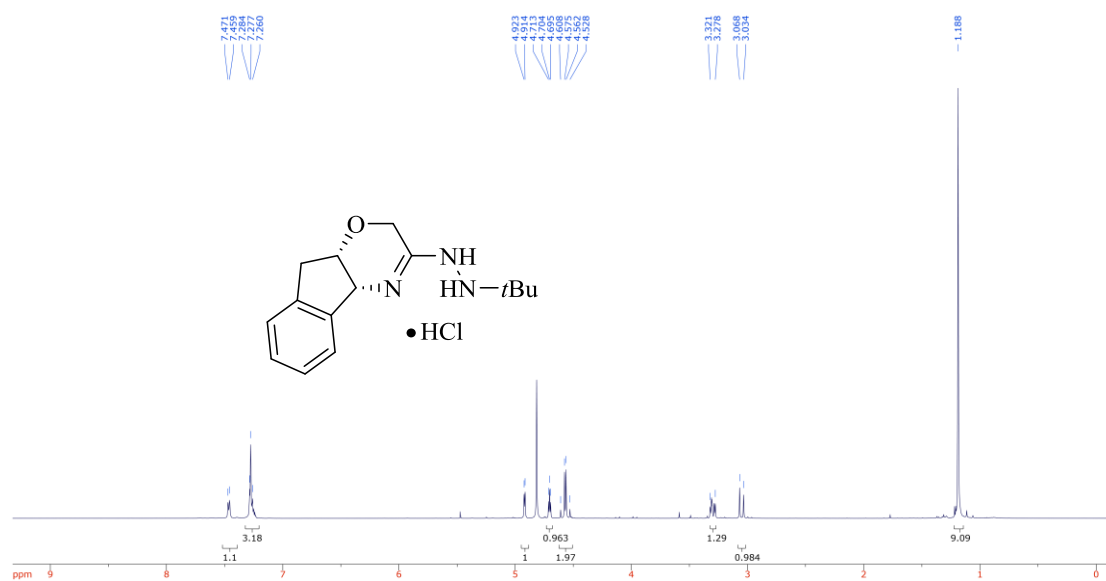


Figure S94. ^1H NMR spectrum of 3-6 (500 MHz, methanol- d_4).

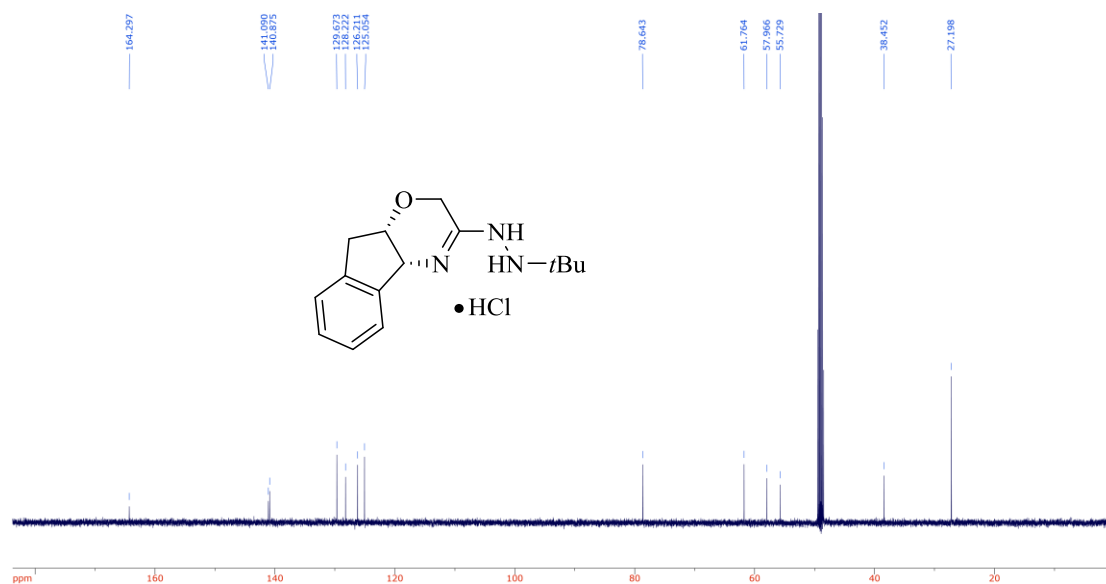


Figure S95. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 3-6 (125 MHz, methanol- d_4).

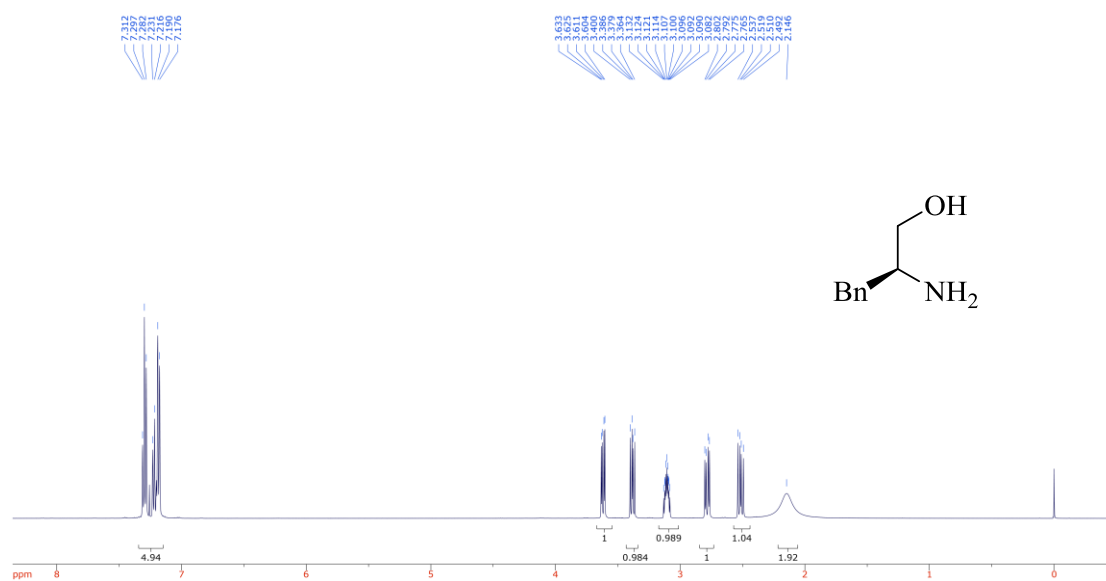


Figure S96. ¹H NMR spectrum of (*S*)-2-amino-3-phenyl-1-propanol (500 MHz, CDCl₃).

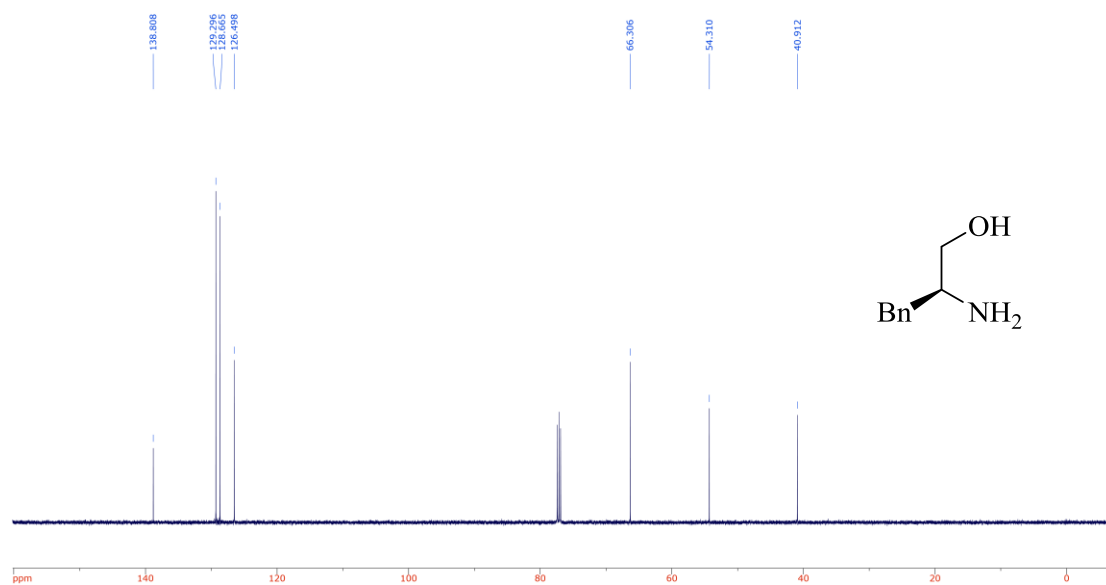


Figure S97. ¹³C{¹H} NMR spectrum of (*S*)-2-amino-3-phenyl-1-propanol (125 MHz, CDCl₃).

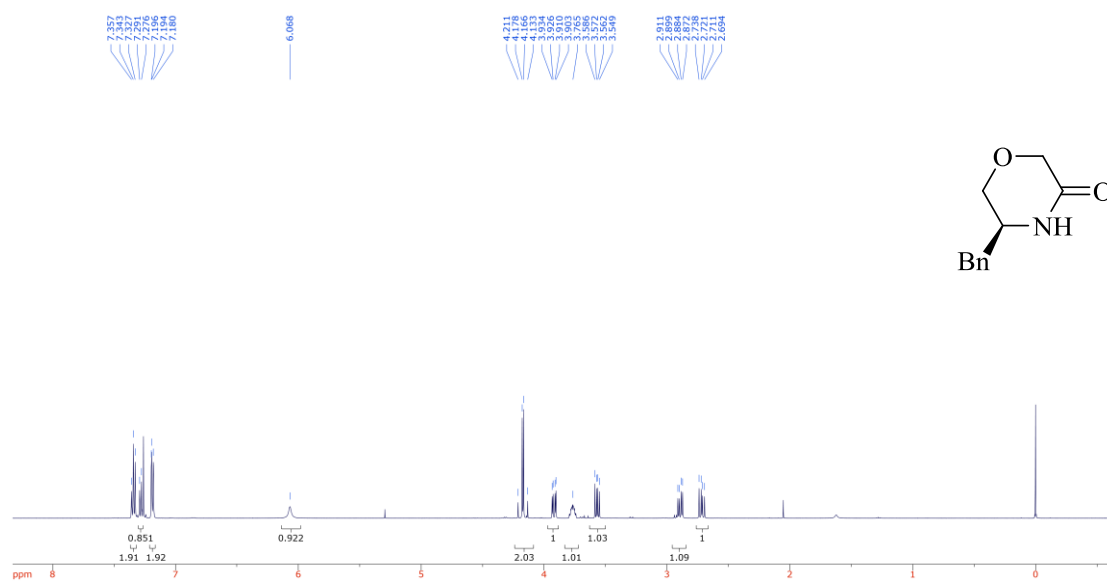


Figure S98. ¹H NMR spectrum of **3-7** (500 MHz, CDCl₃).

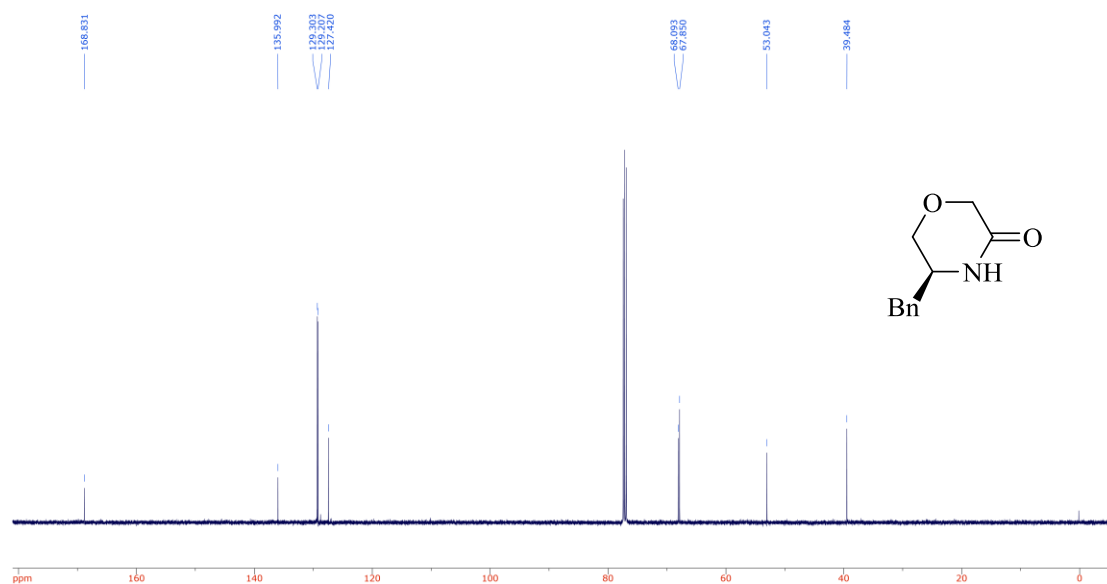


Figure S99. ¹³C {¹H} NMR spectrum of **3-7** (125 MHz, CDCl₃).

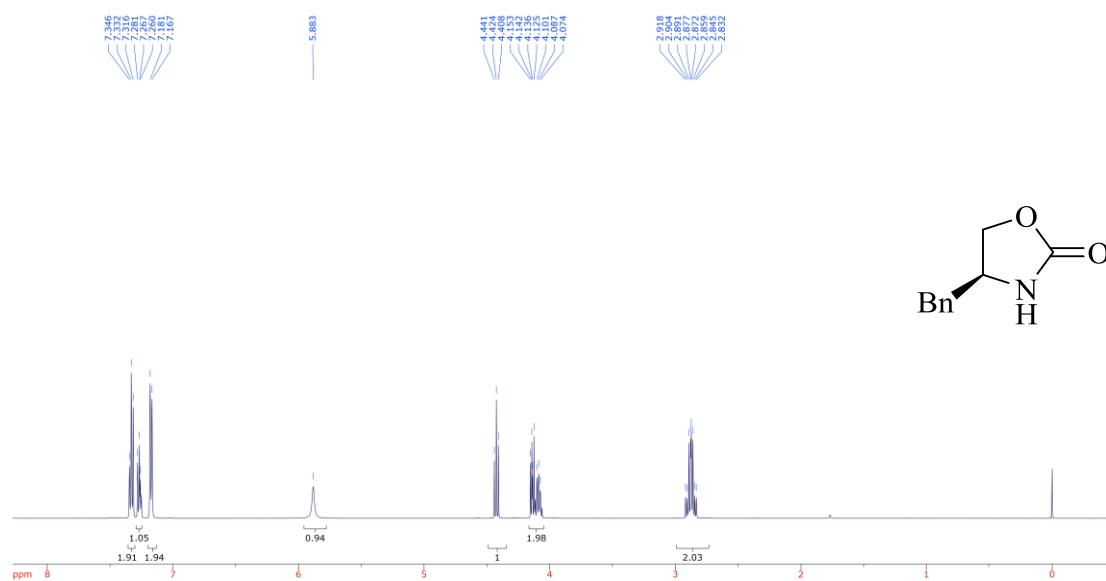


Figure S100. ^1H NMR spectrum of **3-8** (500 MHz, CDCl_3).

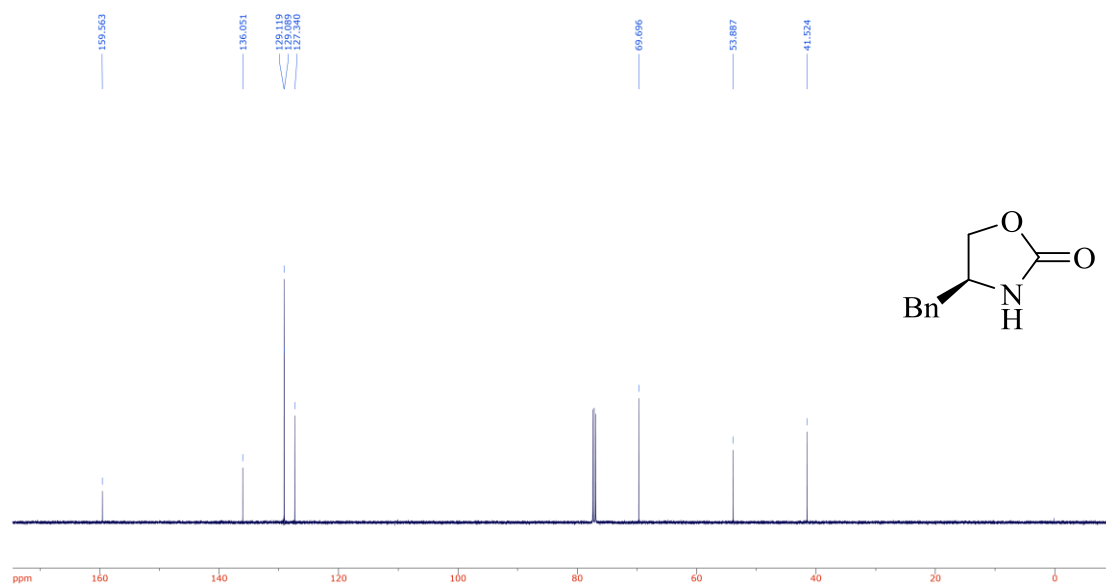


Figure S101. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **3-8** (125 MHz, CDCl_3).

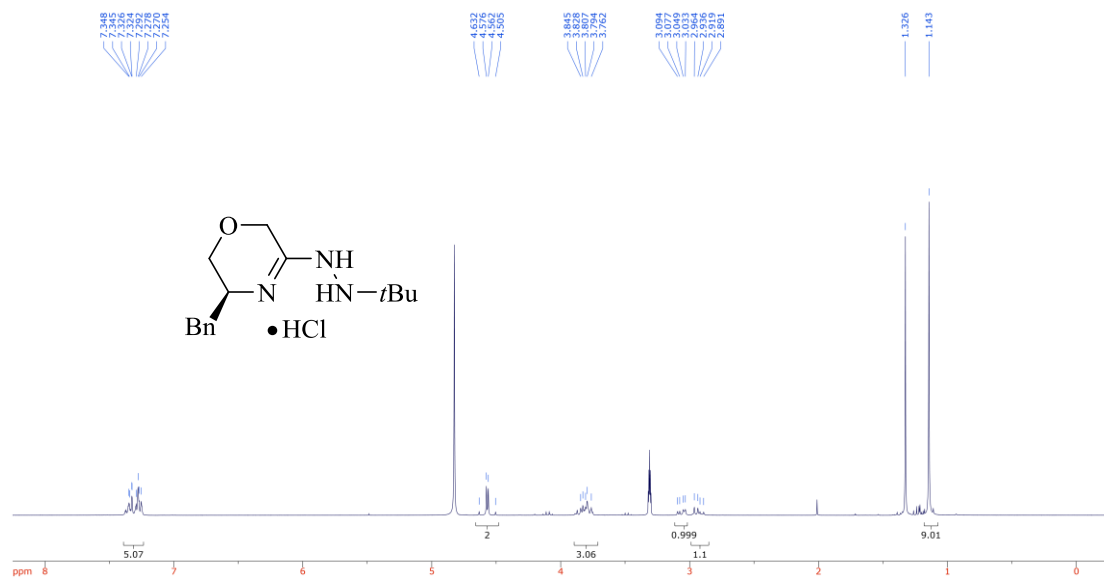


Figure S102. ^1H NMR spectrum of **3-9** (500 MHz, methanol- d_4).

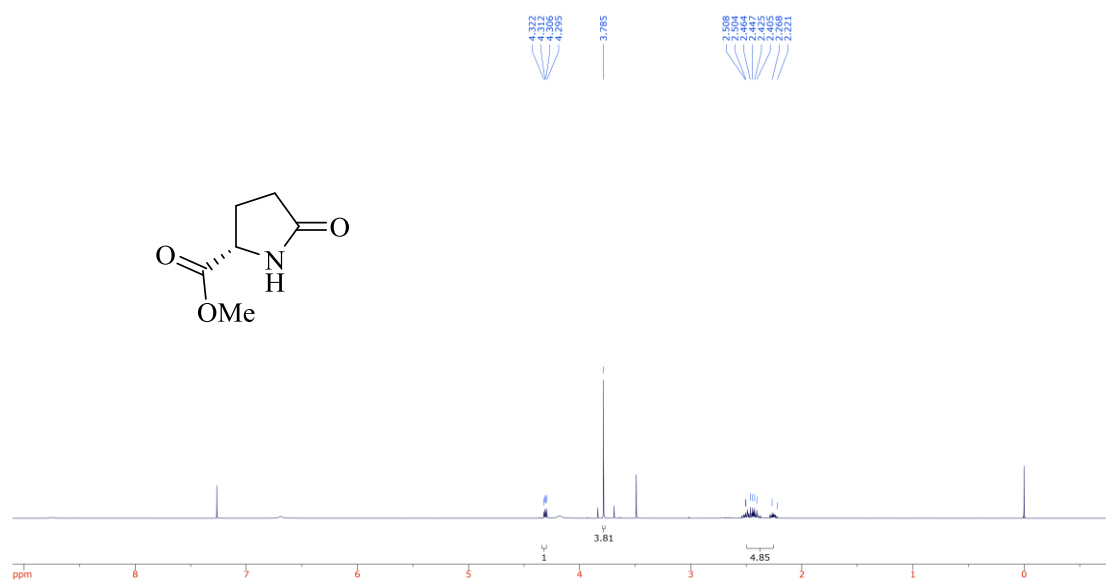


Figure S103. ^1H NMR spectrum of **3-12** (500 MHz, CDCl_3).

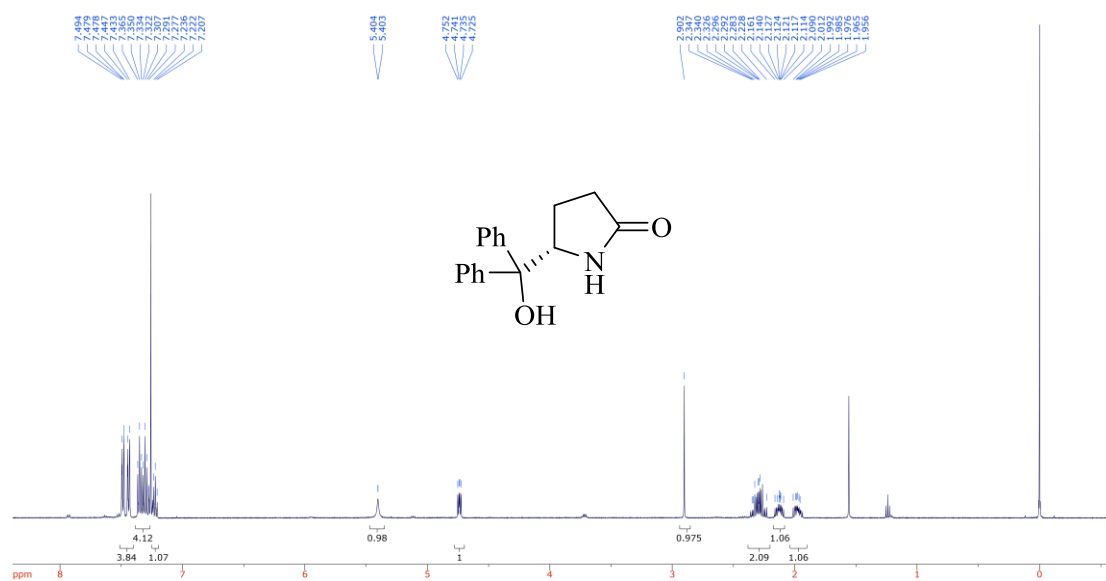


Figure S104. ^1H NMR spectrum of 3-13 (500 MHz, CDCl_3).

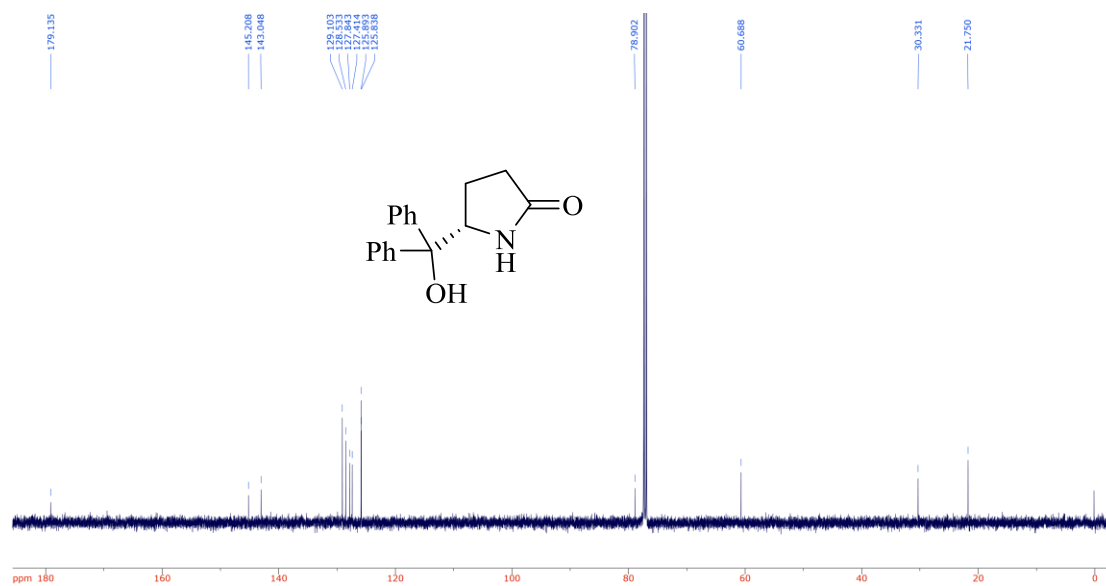


Figure S105. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 3-13 (125 MHz, CDCl_3).

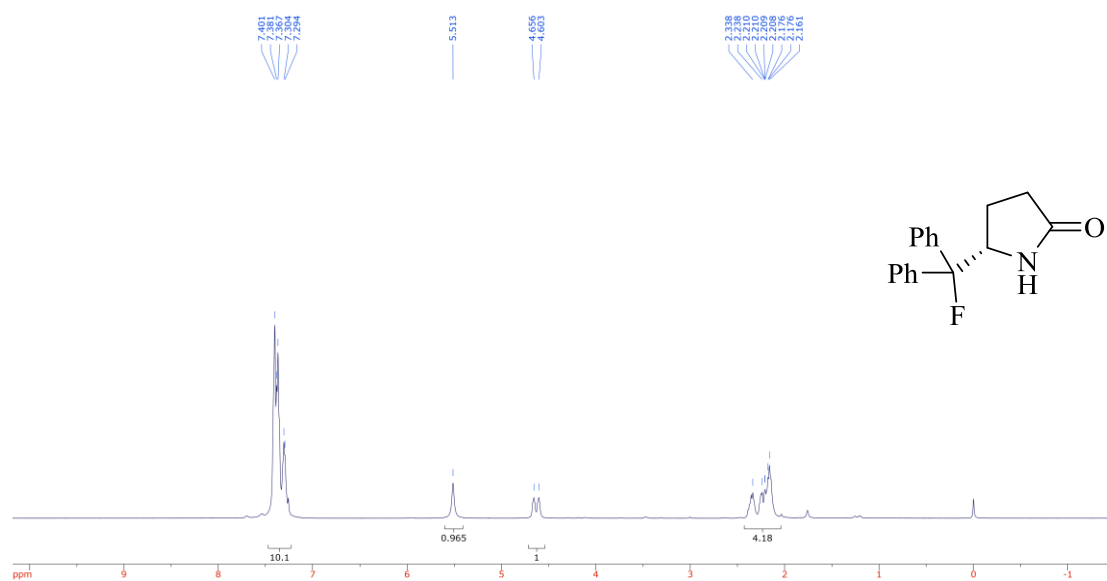


Figure S106. ^1H NMR spectrum of 3-14 (500 MHz, CDCl_3).

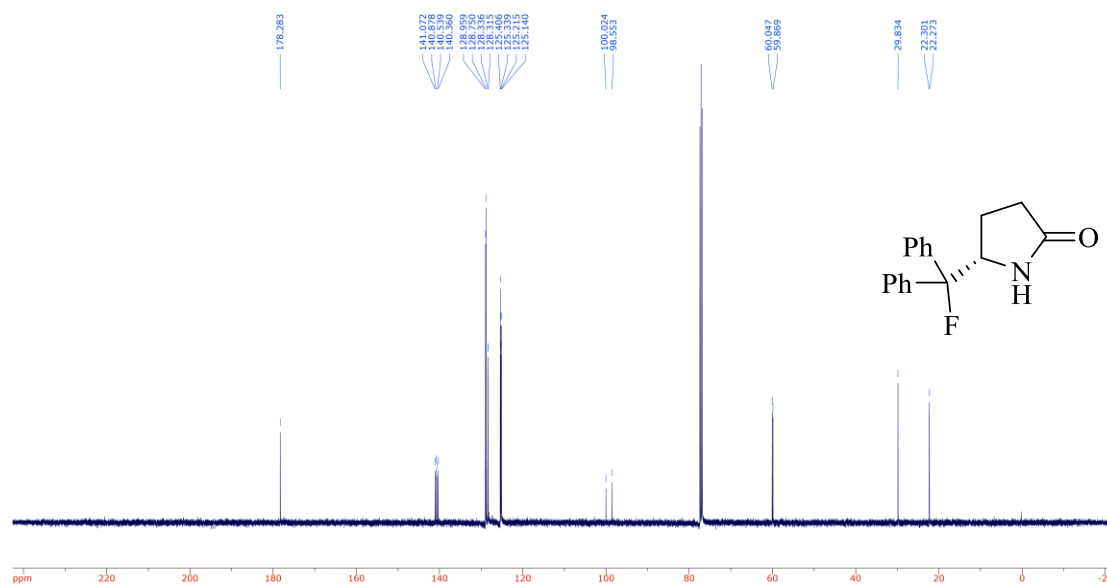


Figure S107. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 3-14 (125 MHz, CDCl_3).

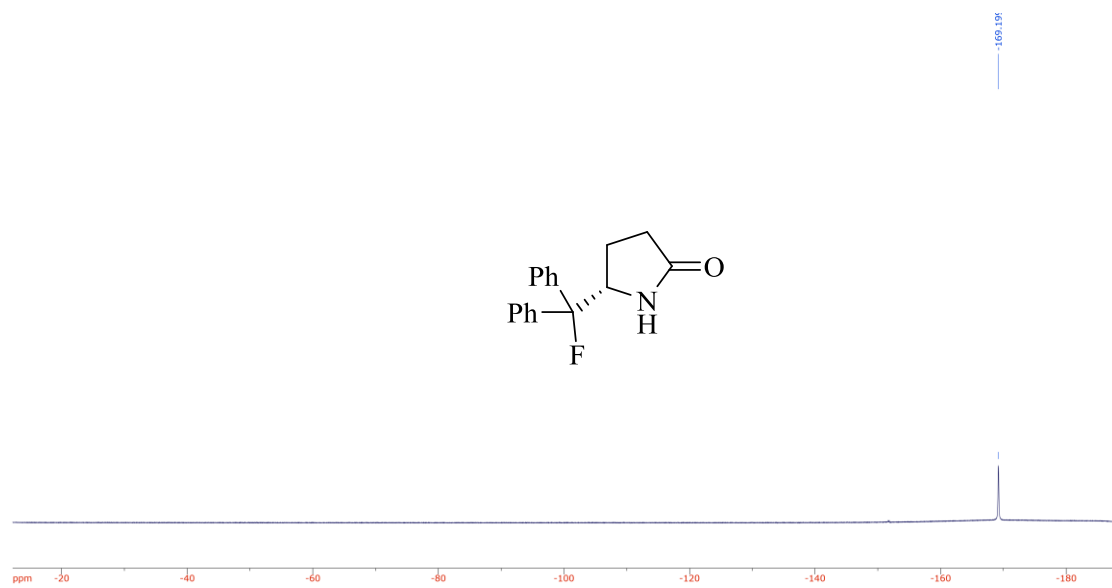


Figure S108. ^{19}F NMR spectrum of 3-14 (470 MHz, CDCl_3).

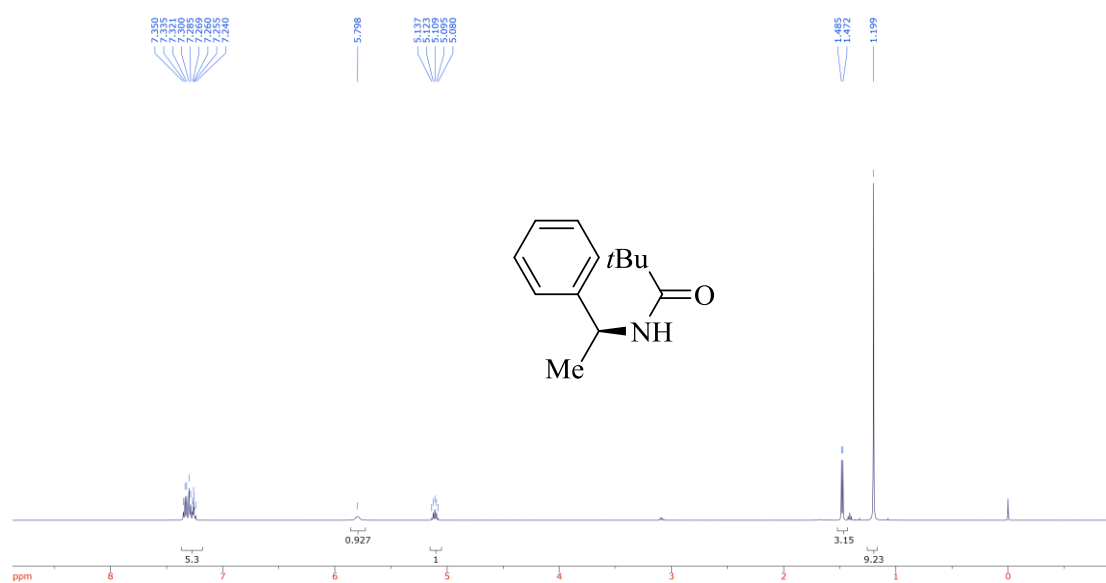


Figure S109. ^1H NMR spectrum of **3-16** (500 MHz, CDCl_3).

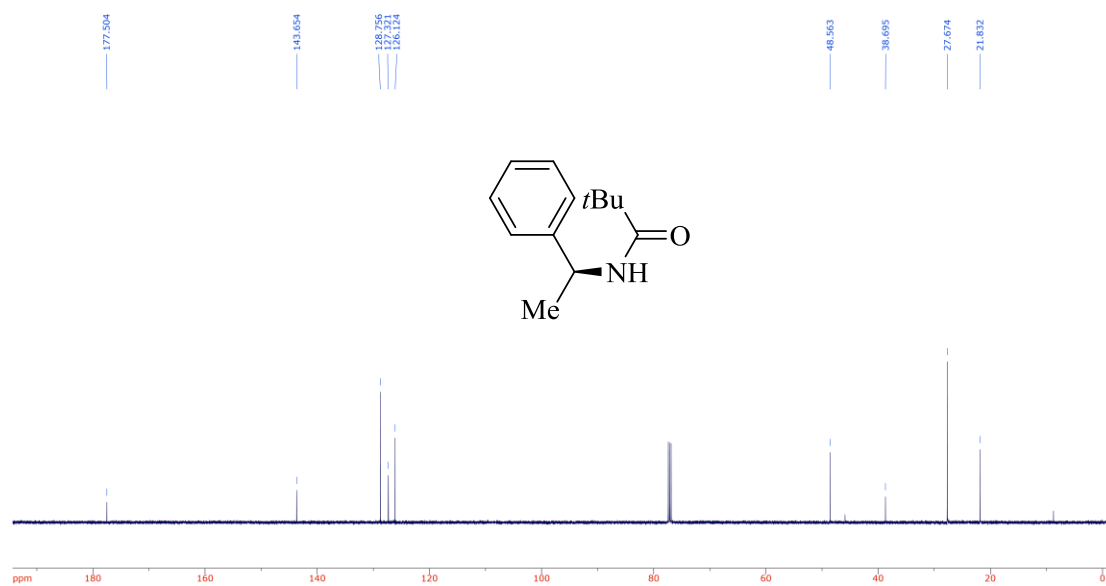


Figure S110. ^{13}C NMR spectrum of **3-16** (125 MHz, CDCl_3).

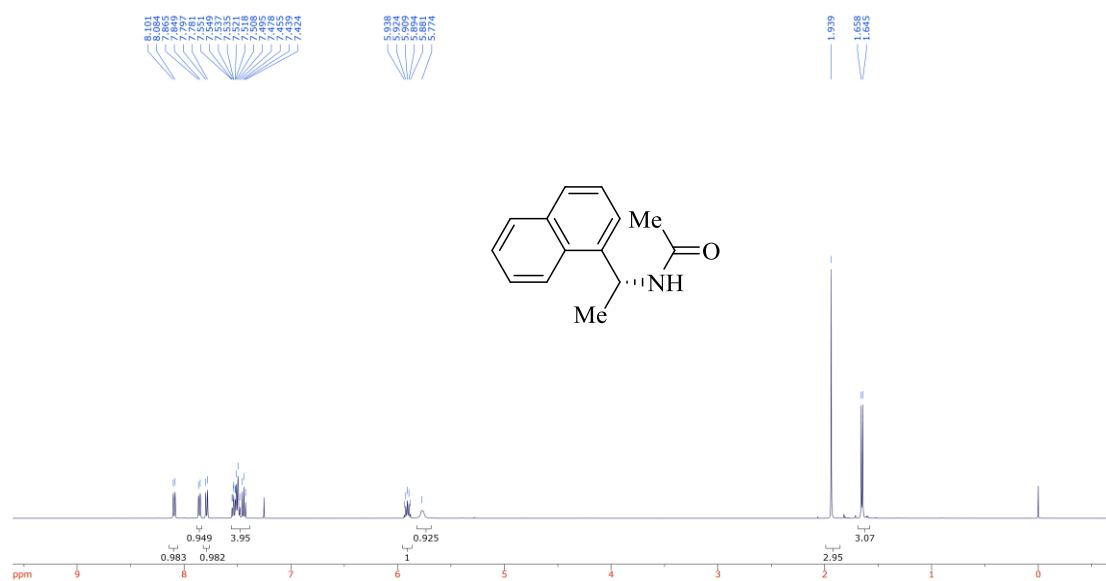


Figure S11. ^1H NMR spectrum of **3-17** (500 MHz, CDCl_3).

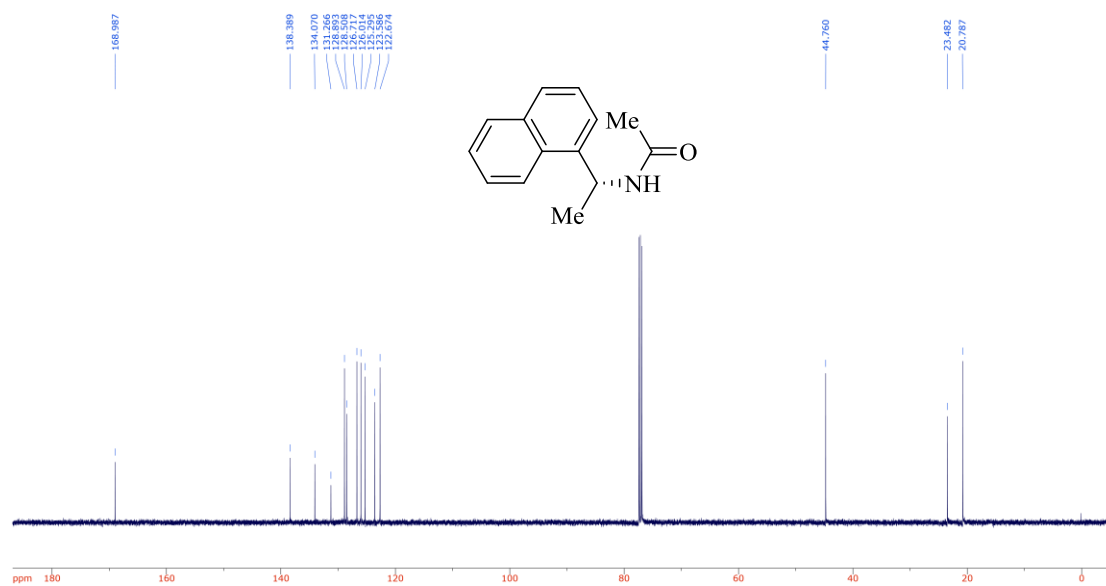
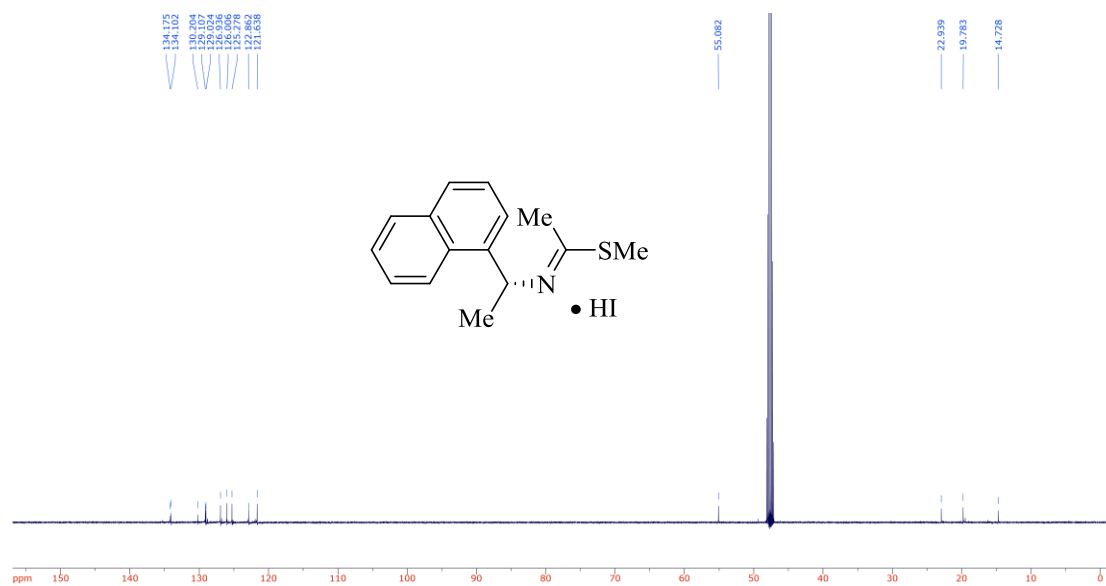
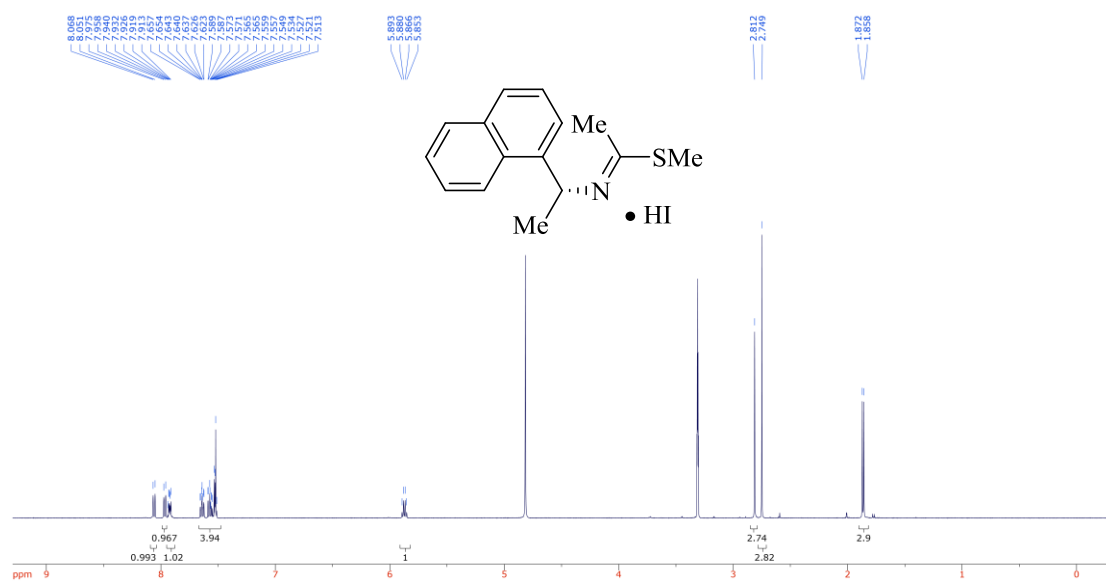


Figure S12. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **3-17** (125 MHz, CDCl_3).



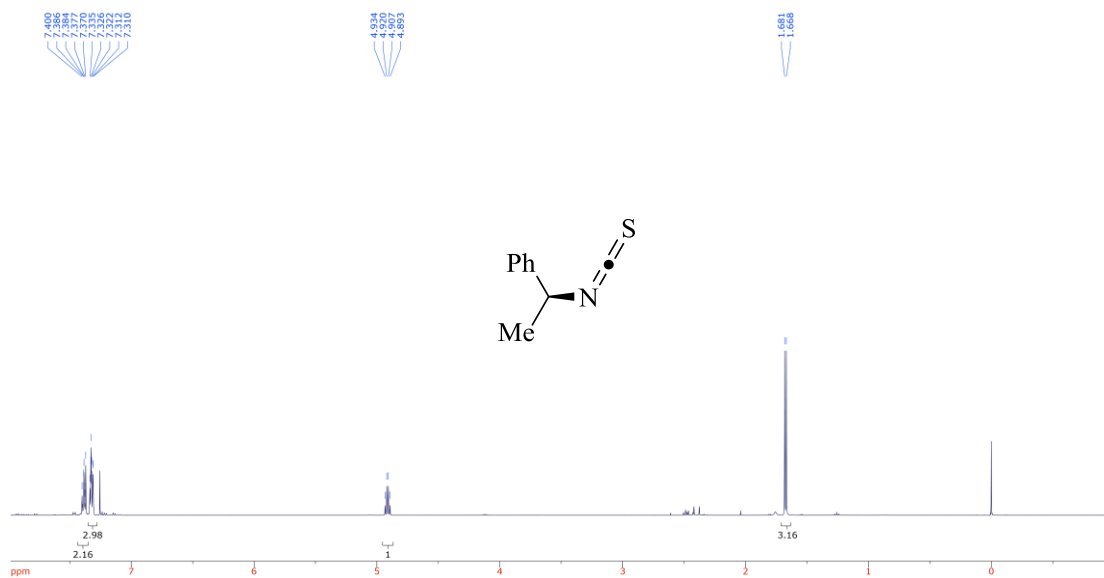


Figure S115. ¹H NMR spectrum of **3-23** (500 MHz, CDCl₃).

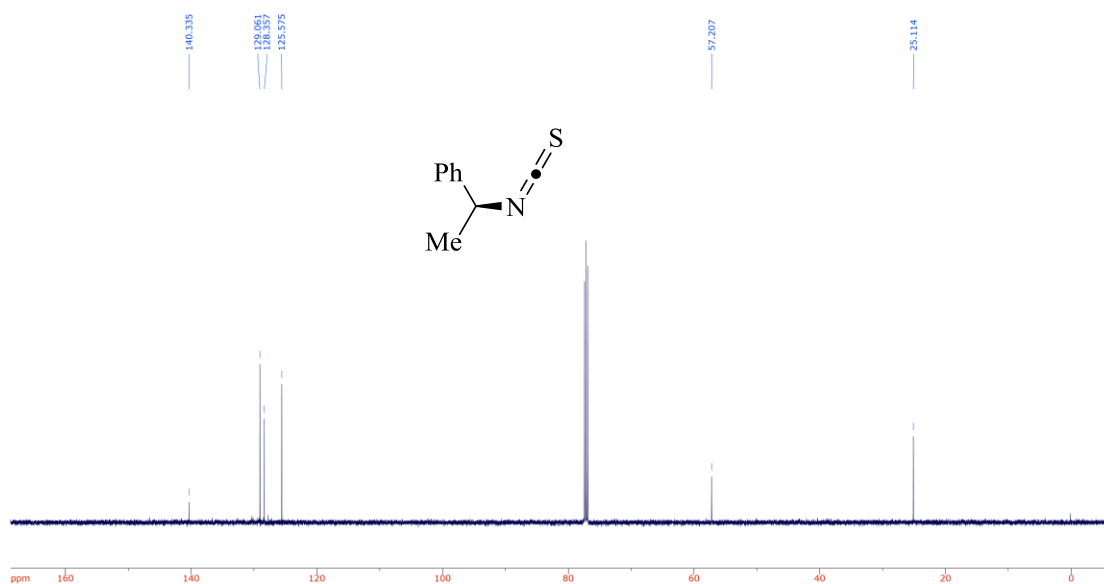


Figure S116. ¹³C{¹H} NMR spectrum of **3-23** (125 MHz, CDCl₃).

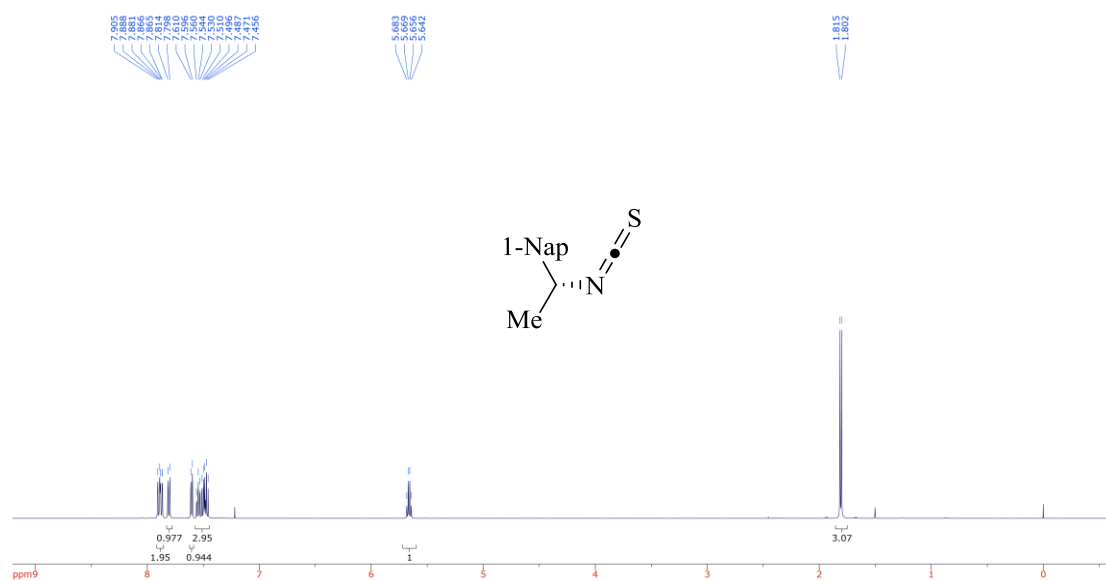


Figure S117. ^1H NMR spectrum of **3-24** (500 MHz, CDCl_3).

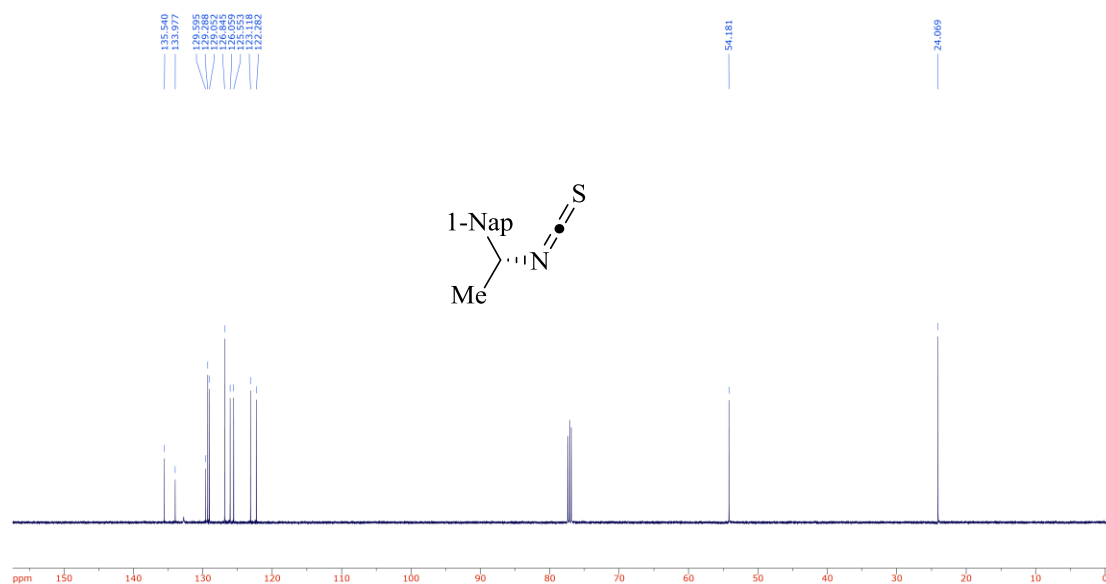


Figure S118. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **3-24** (125 MHz, CDCl_3).

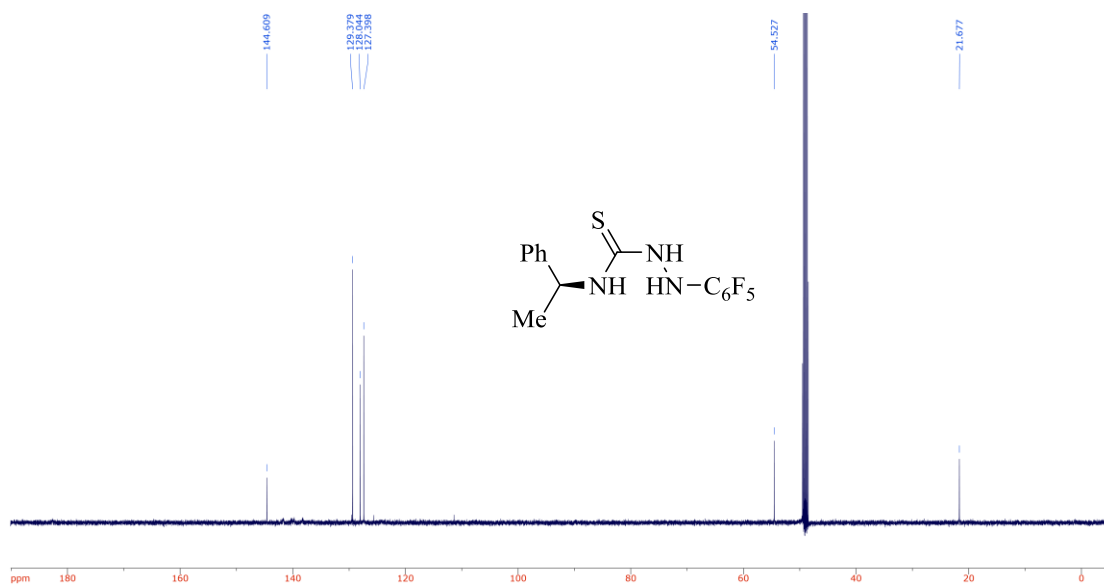
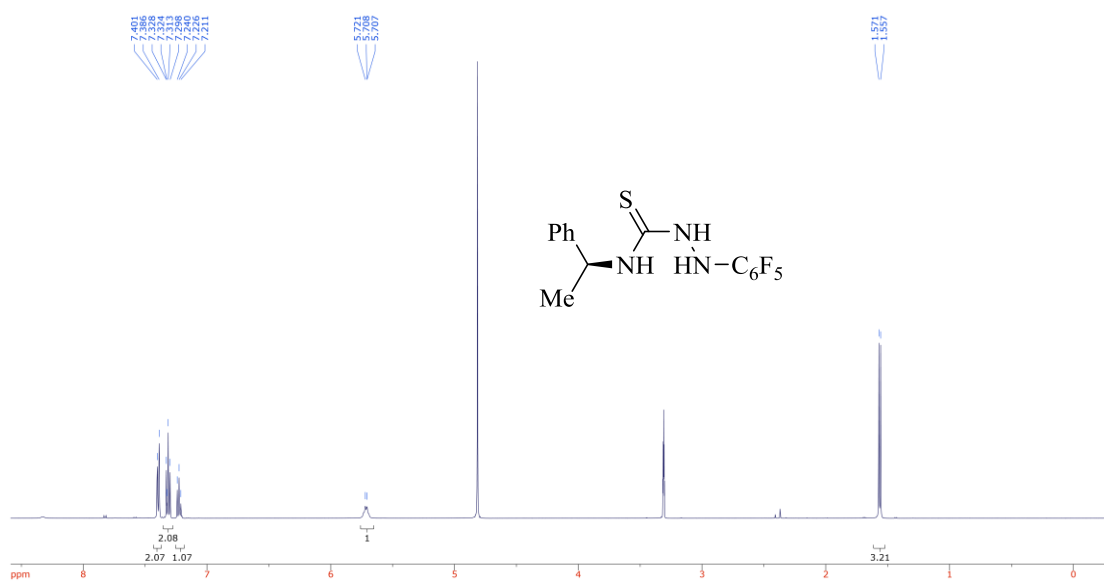
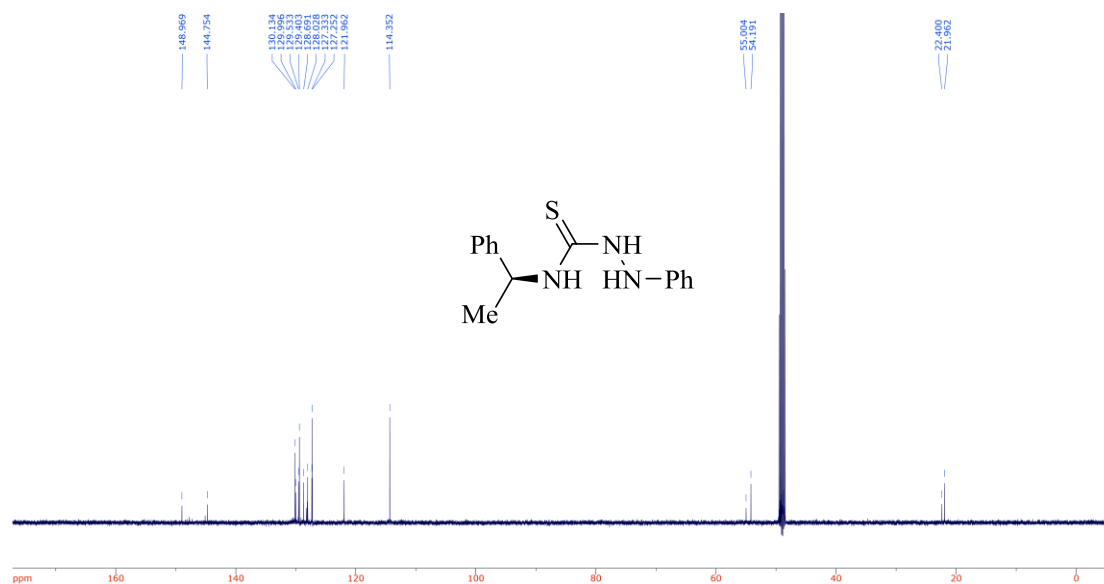
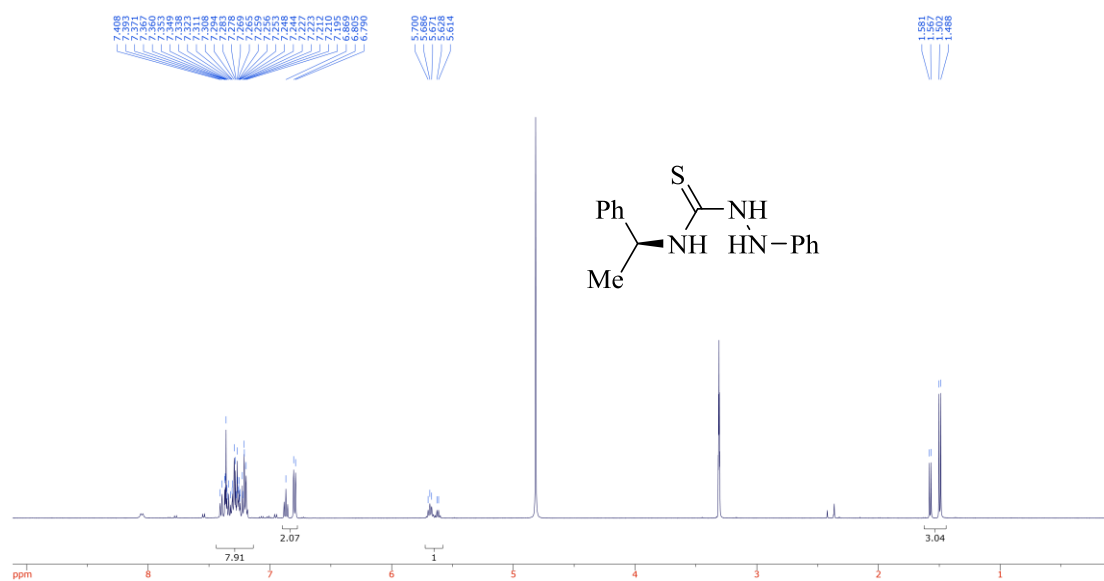




Figure S121. ^{19}F NMR spectrum of **3-25** (470 MHz, methanol- d_4).



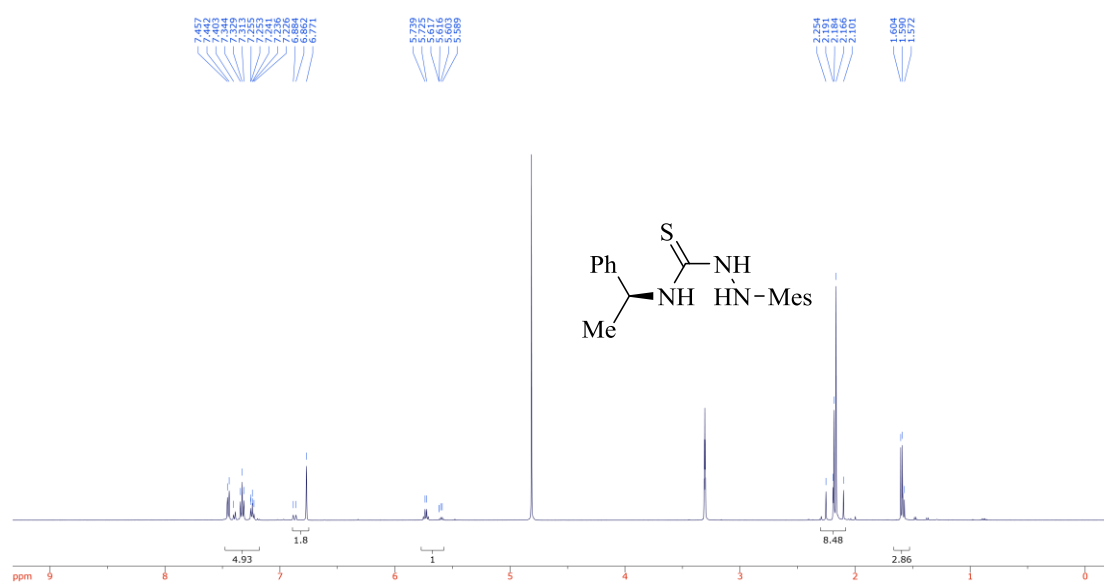


Figure S124. ^1H NMR spectrum of 3-27 (500 MHz, methanol- d_4).

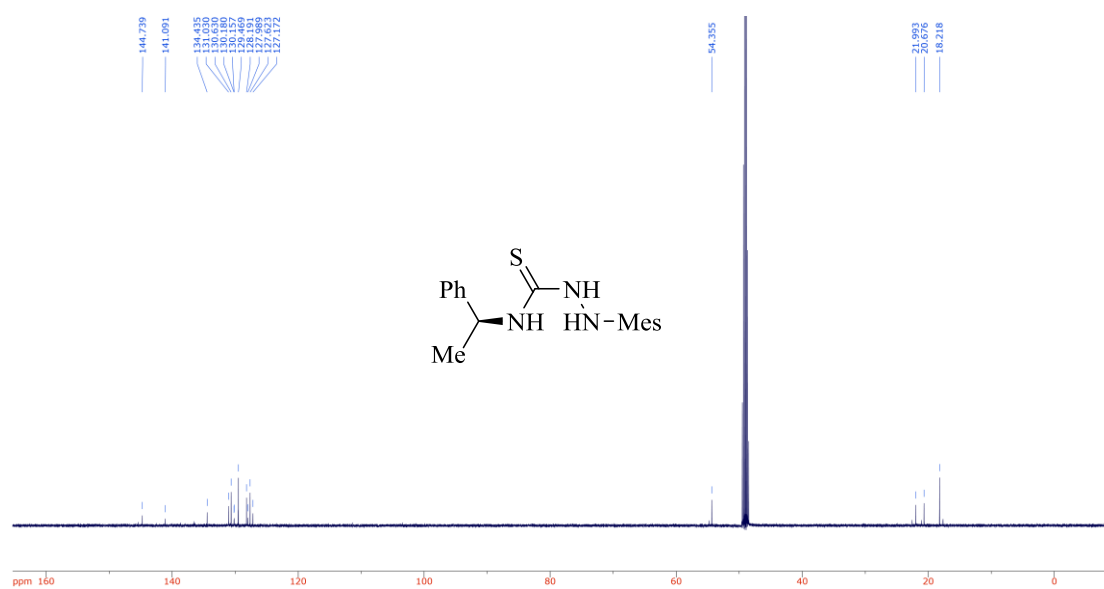


Figure S125. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 3-27 (125 MHz, methanol- d_4).

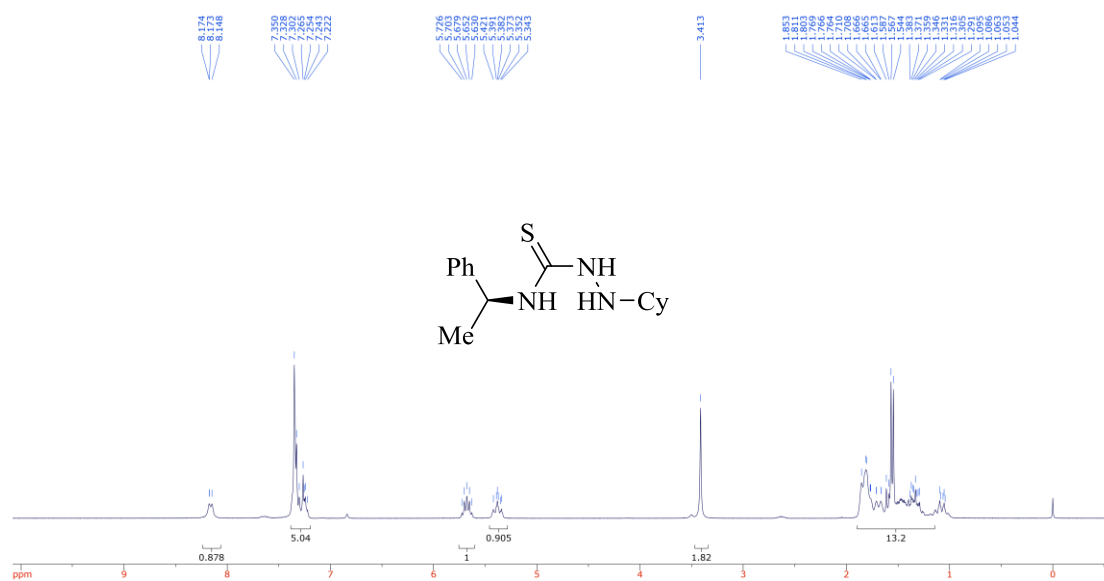


Figure S126. ¹H NMR spectrum of 3-28 (500 MHz, methanol-*d*₄).

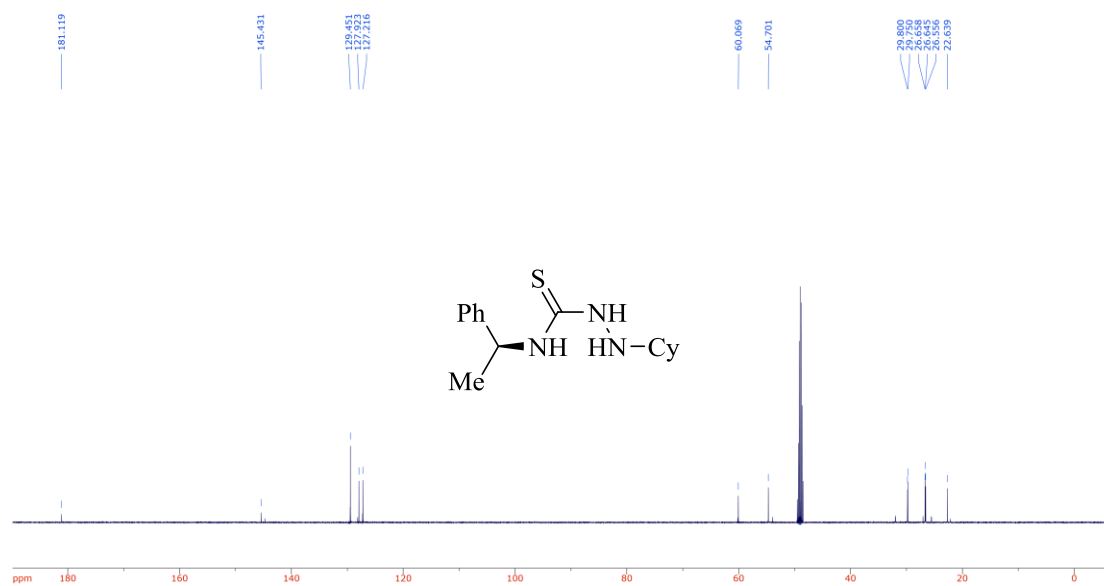
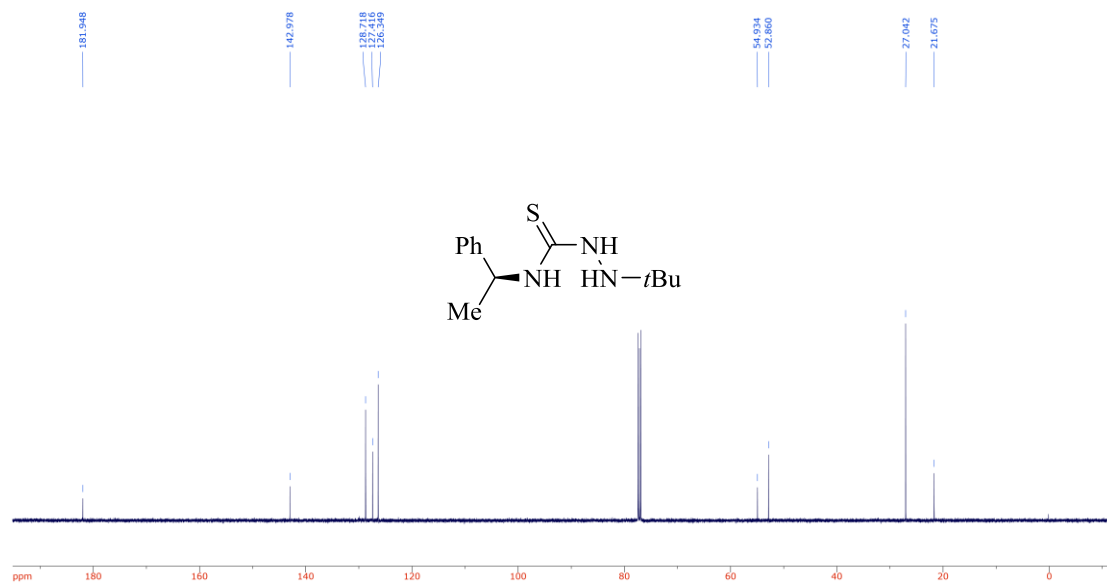
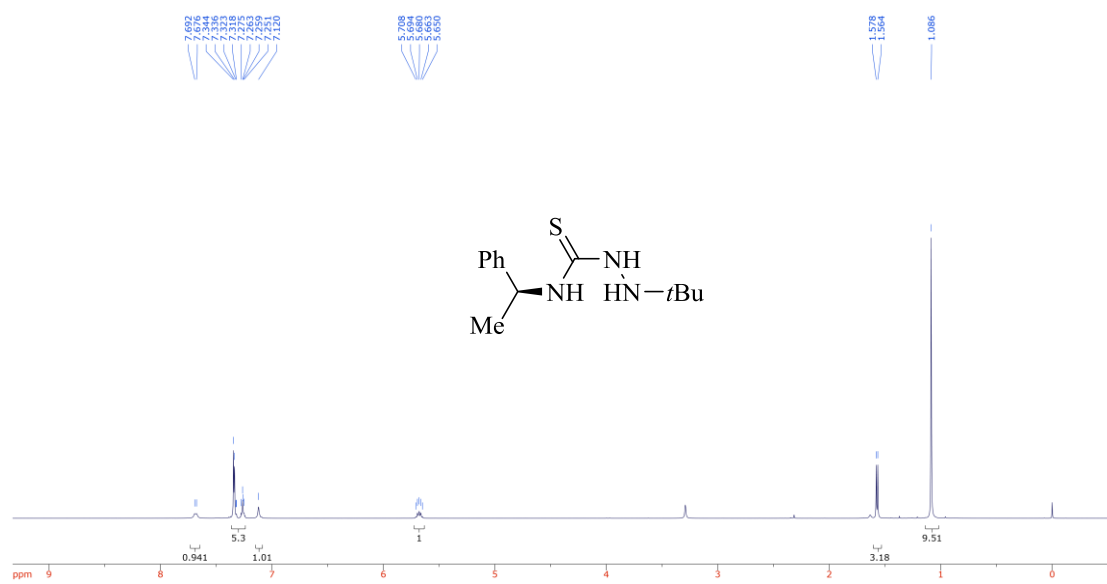
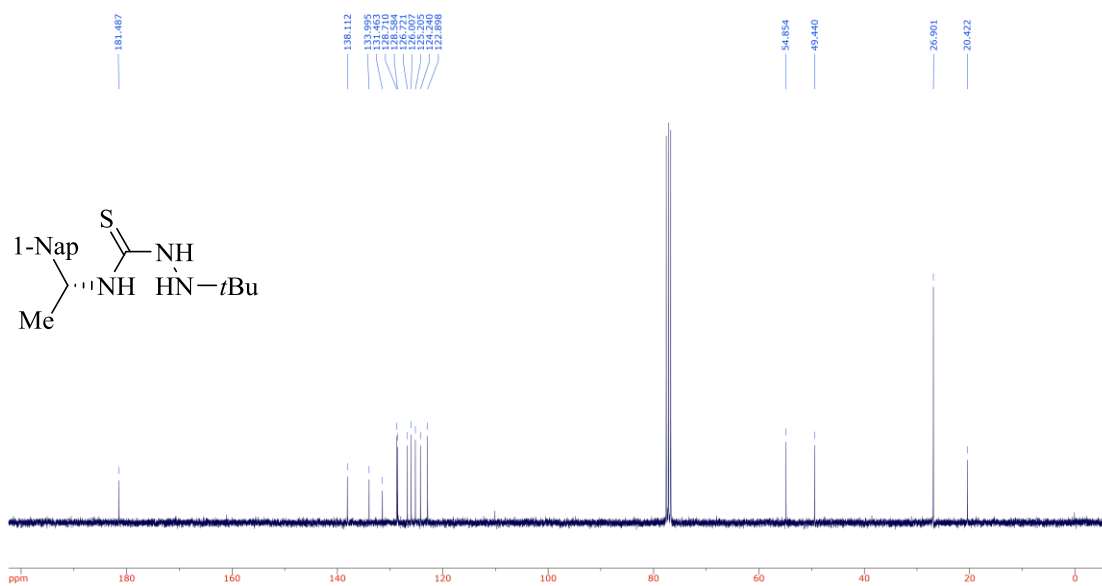
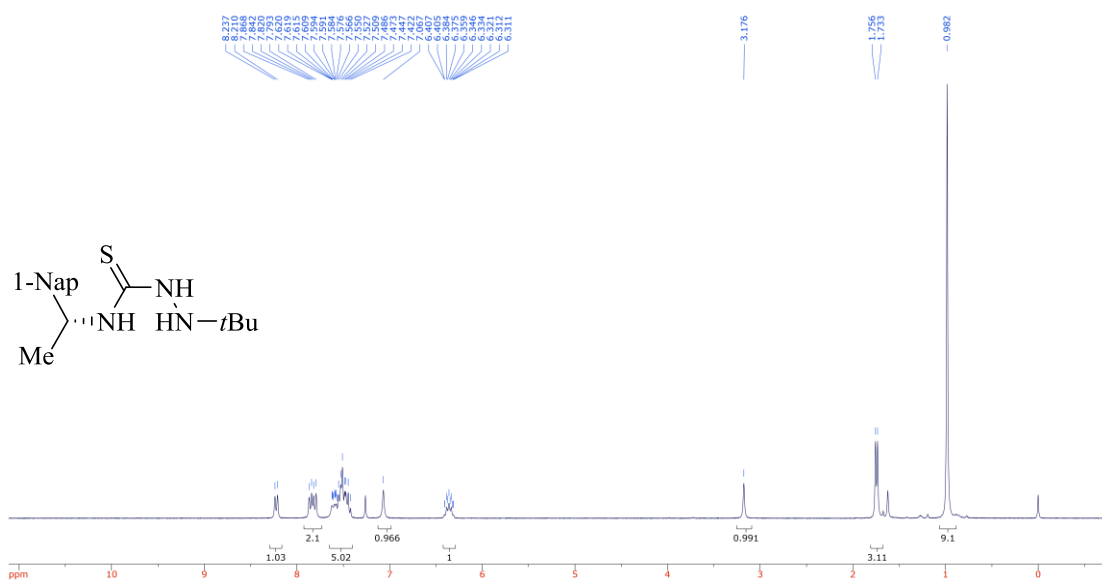


Figure S127. ¹³C{¹H} NMR spectrum of 3-28 (125 MHz, methanol-*d*₄).





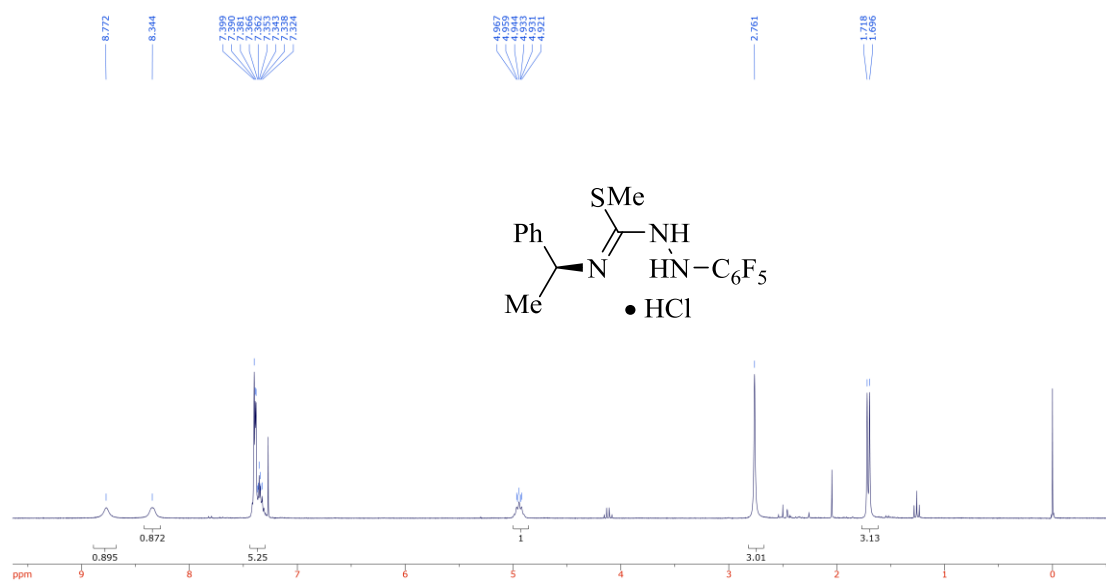


Figure S132. ^1H NMR spectrum of **3-31** (300 MHz, CDCl_3).

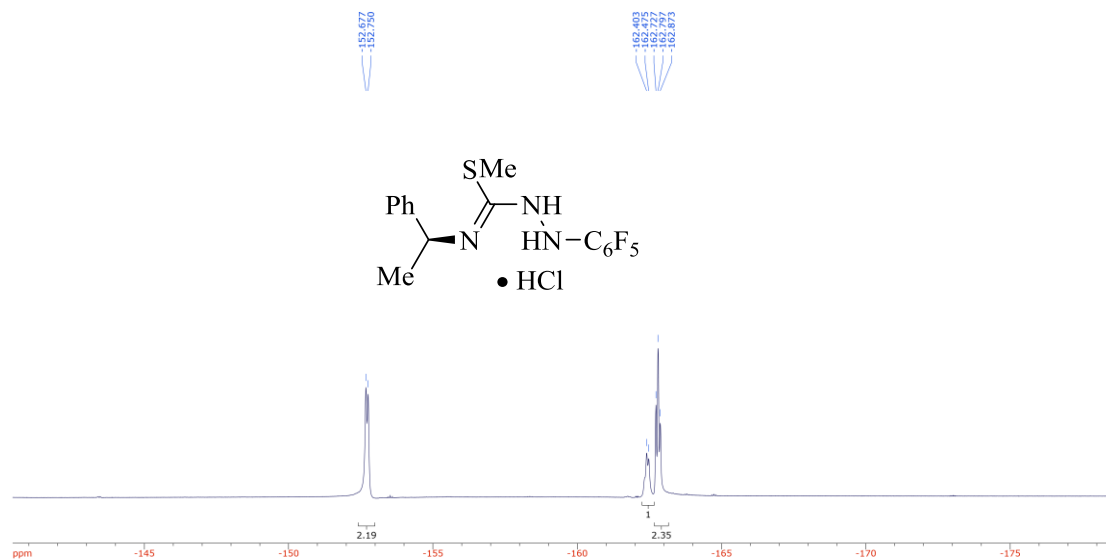
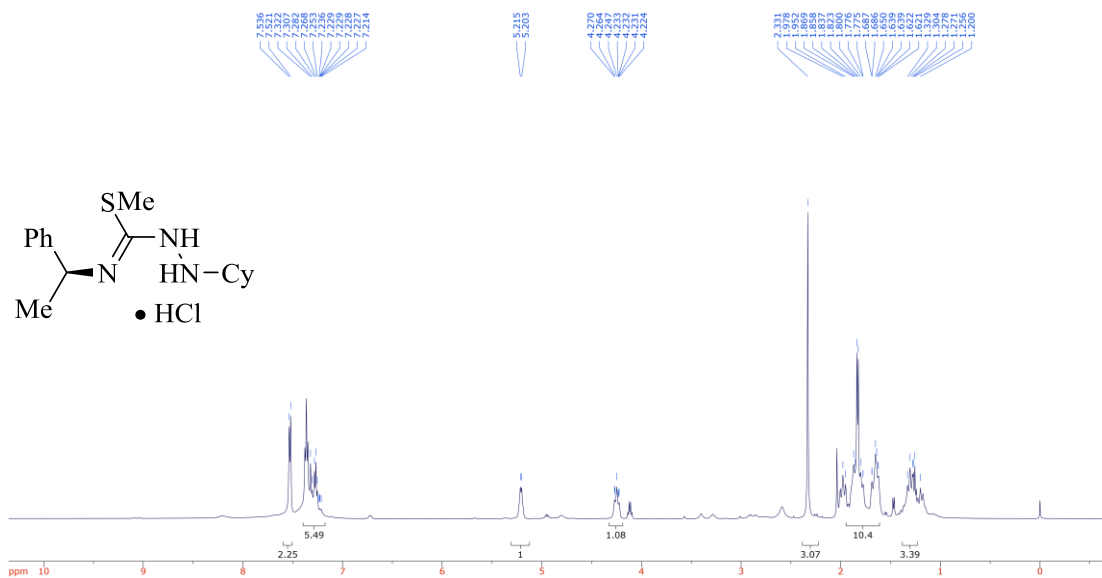


Figure S133. ^{19}F NMR spectrum of **3-31** (282 MHz, CDCl_3).



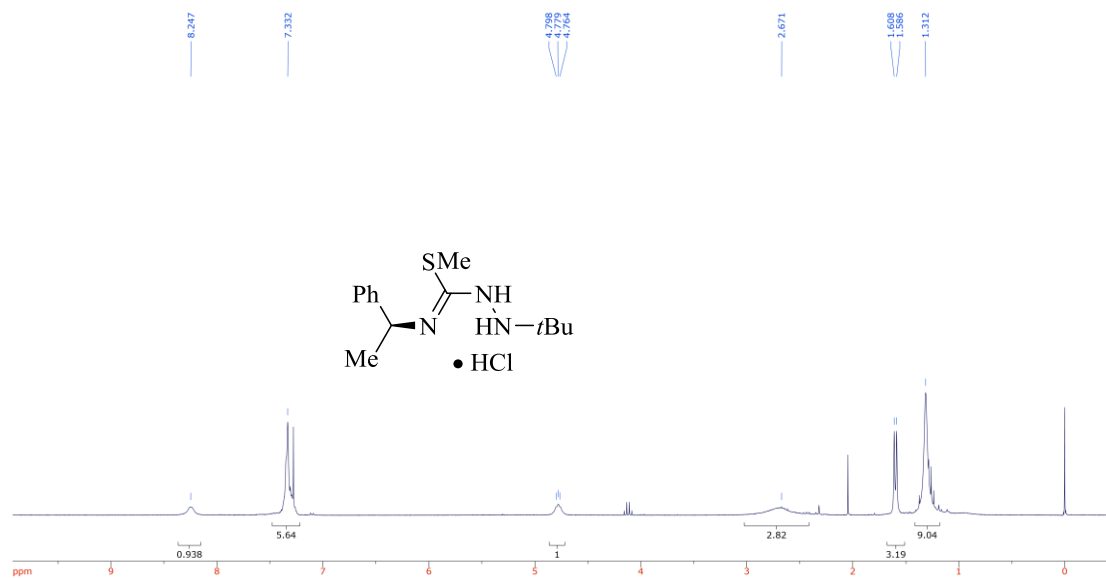
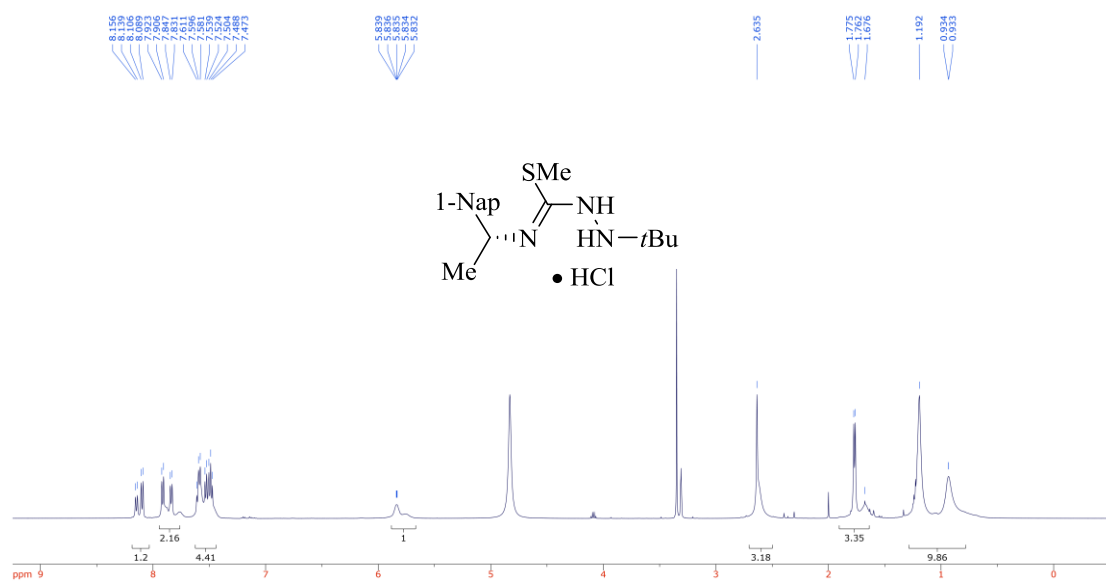


Figure S135. ^1H NMR spectrum of **3-35** (500 MHz, CDCl_3).



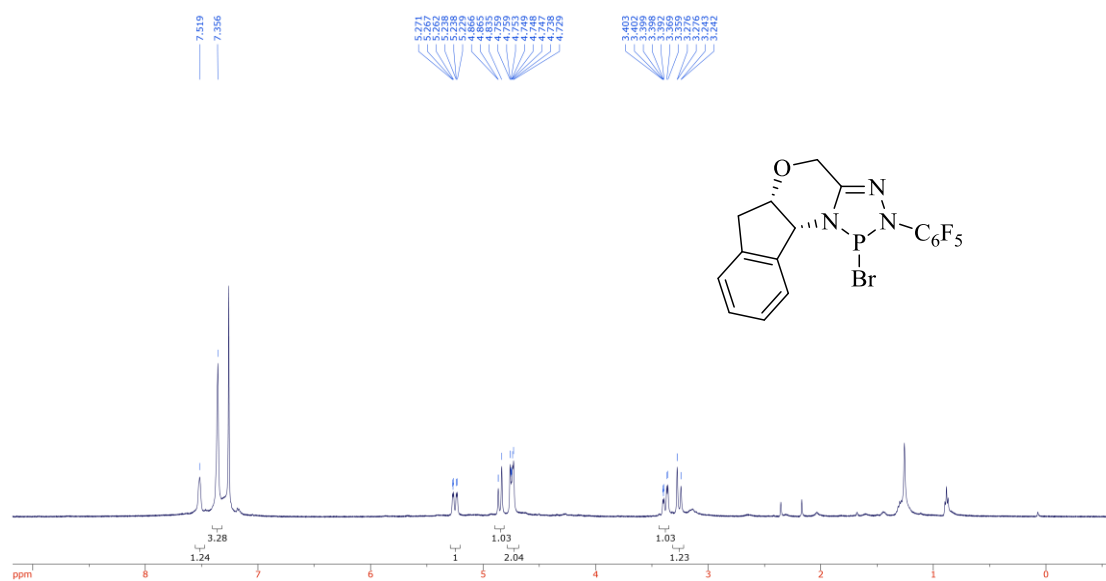


Figure S137. ^1H NMR spectrum of **3-37-Br** (500 MHz, CDCl_3).

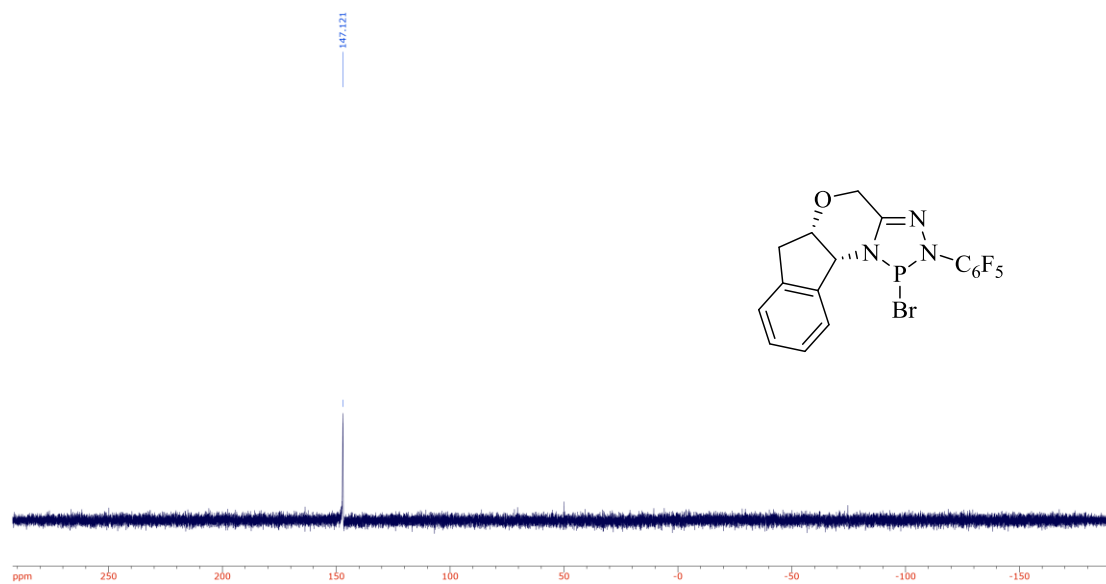


Figure S138. ^{31}P NMR spectrum of **3-37-Br** (202 MHz, CDCl_3).

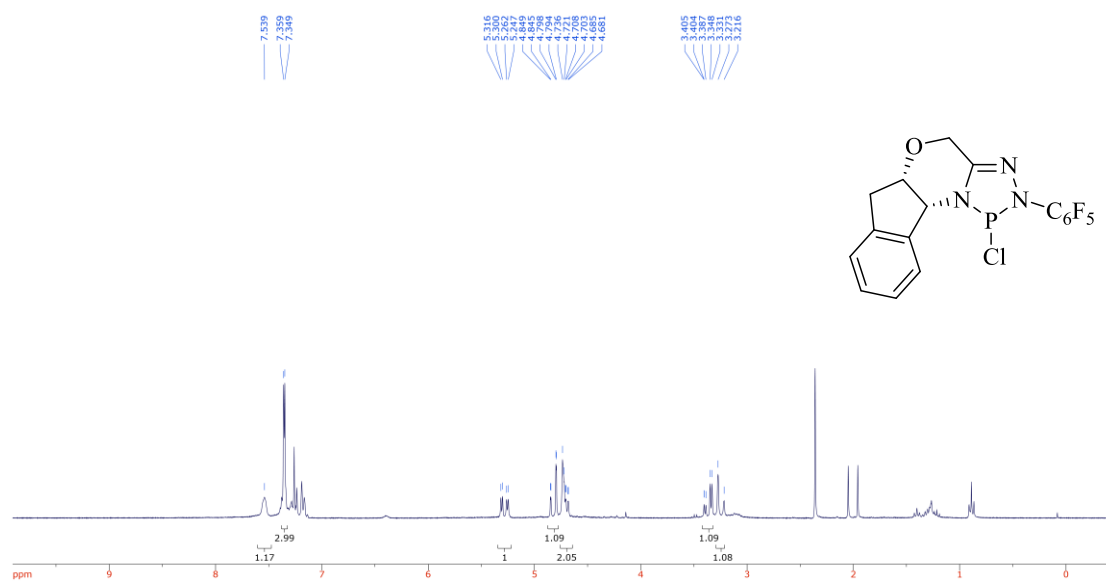


Figure S139. ¹H NMR spectrum of 3-37-Cl (300 MHz, CDCl₃).

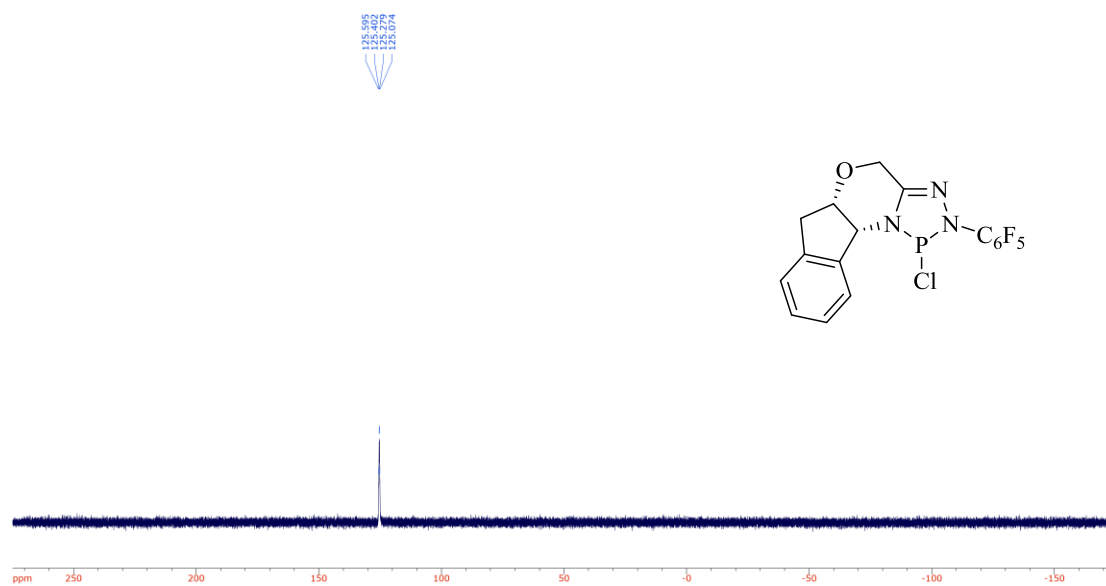


Figure S140. ³¹P NMR spectrum of 3-37-Cl (121 MHz, CDCl₃).

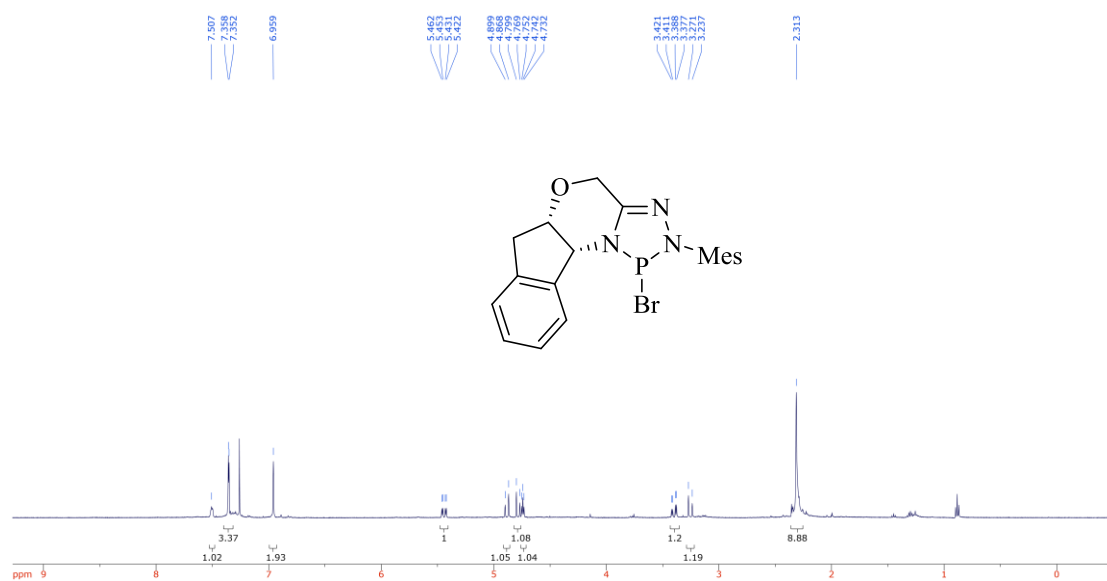


Figure S141. ^1H NMR spectrum of **3-38** (500 MHz, CDCl_3).

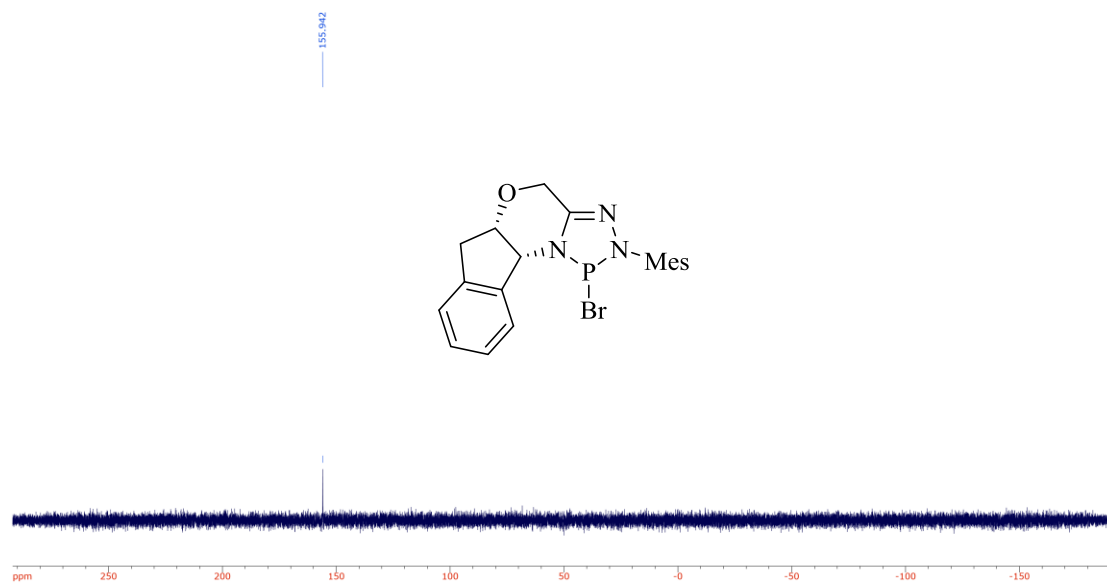


Figure S142. ^{31}P NMR spectrum of **3-38** (202 MHz, CDCl_3).

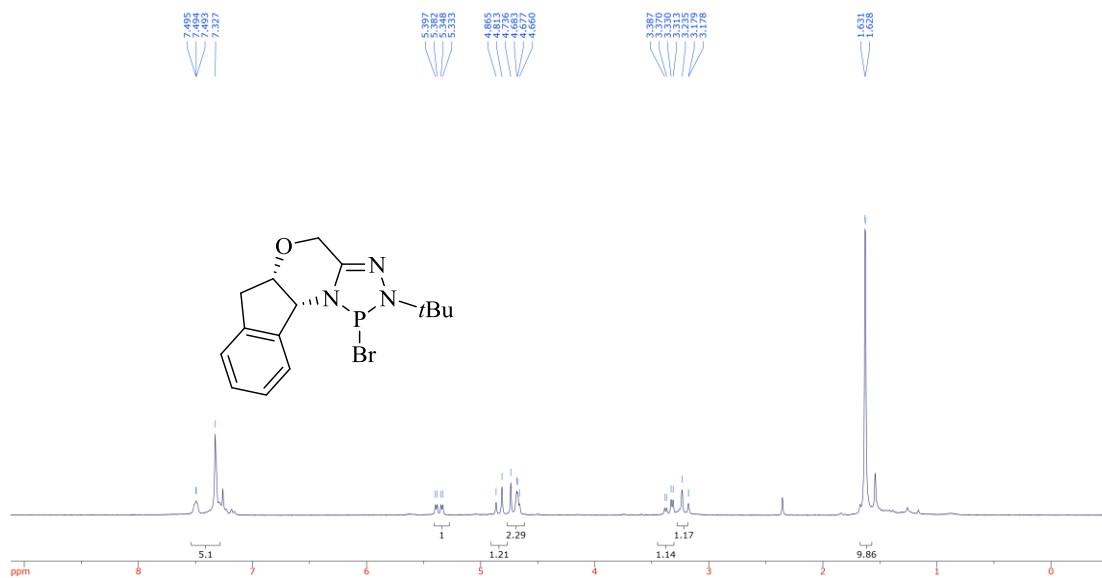


Figure S143. ¹H NMR spectrum of **3-39** (300 MHz, CDCl₃).

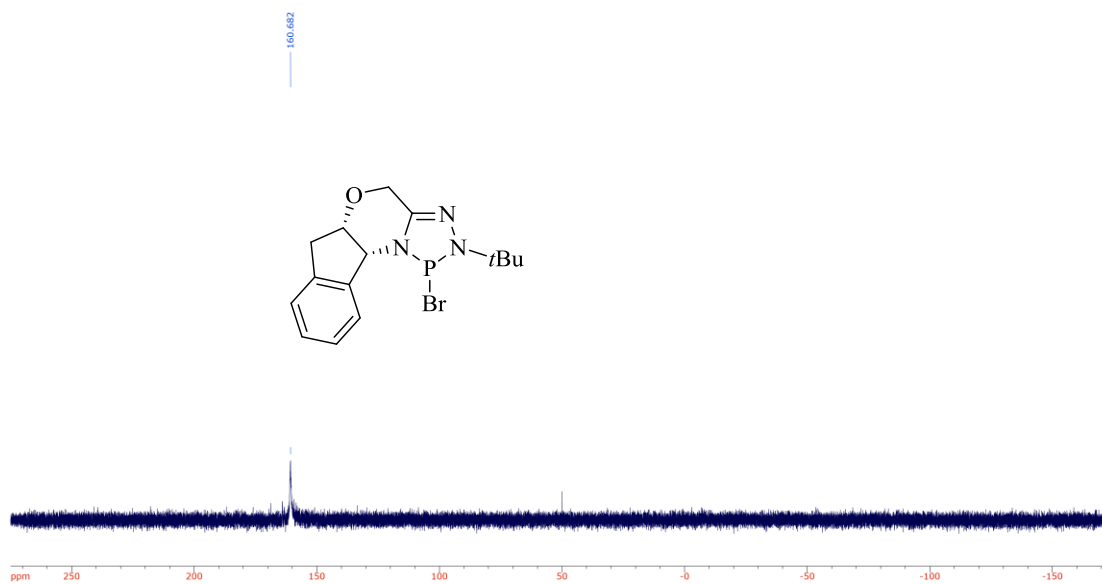


Figure S144. ³¹P NMR spectrum of **3-39** (121 MHz, CDCl₃).

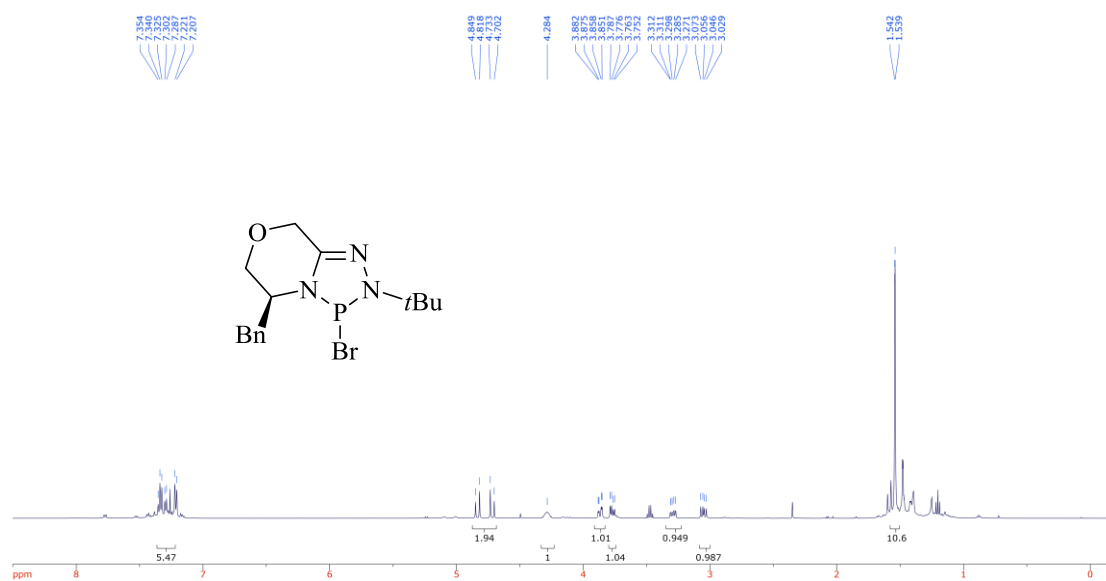


Figure S145. ¹H NMR spectrum of **3-40** (300 MHz, CDCl₃).

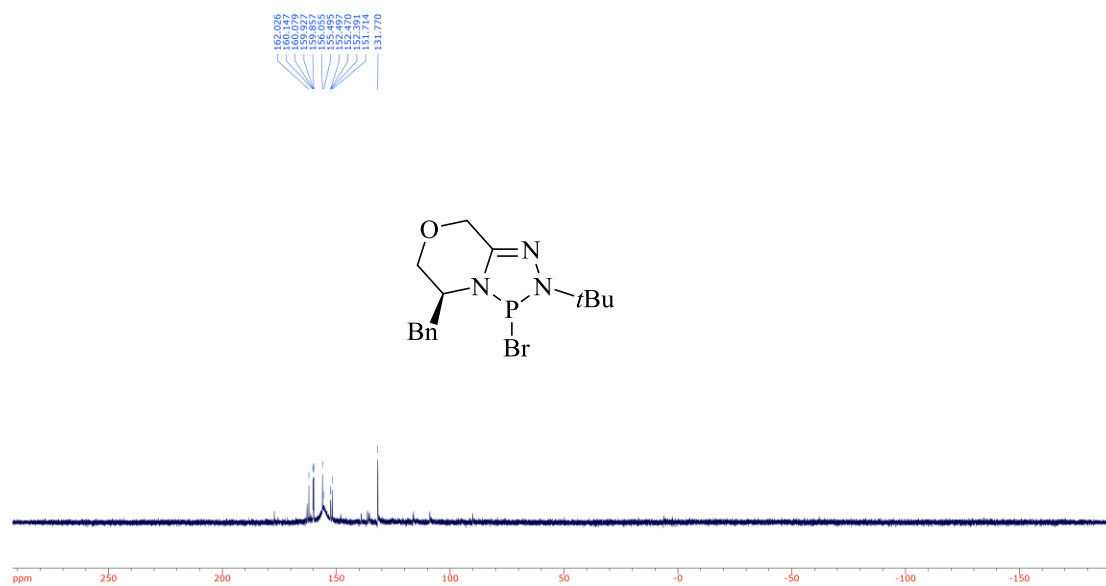


Figure S146. ³¹P NMR spectrum of **3-40** (121 MHz, CDCl₃).

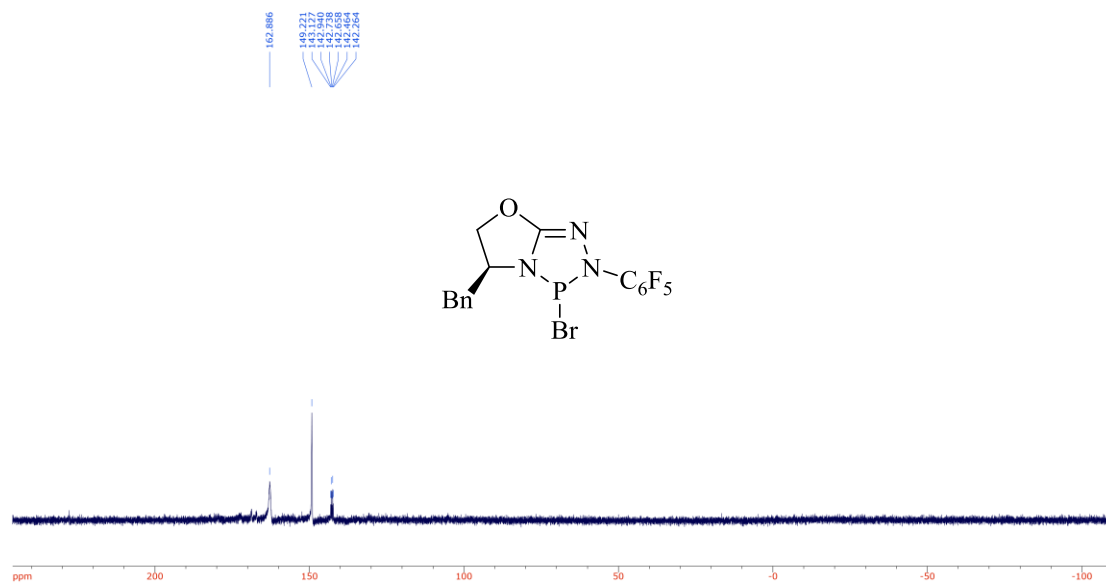


Figure S147. ^{31}P NMR spectrum of **3-41** (202 MHz, CDCl_3).

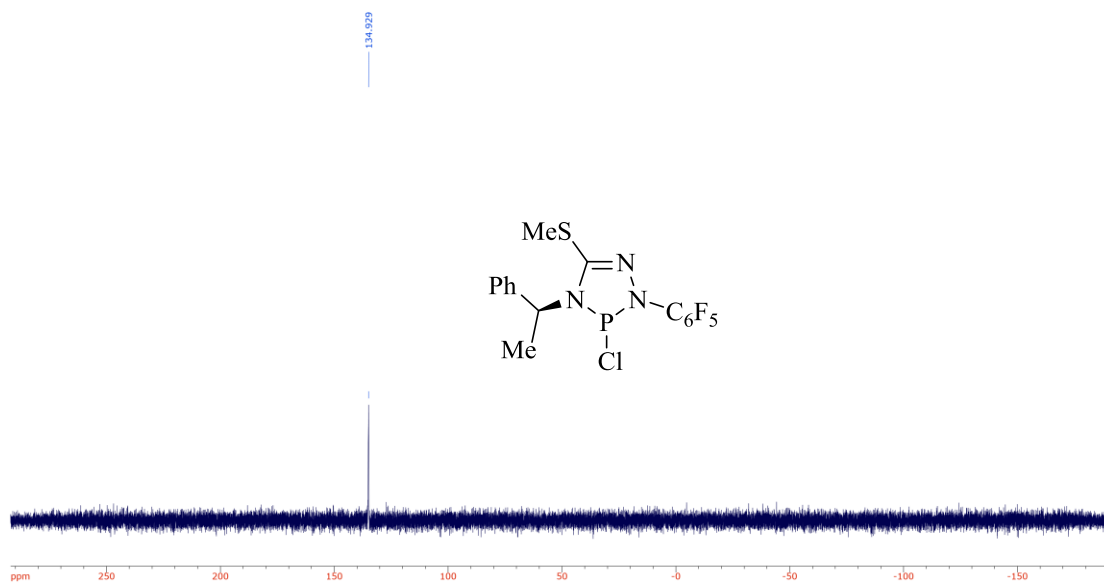
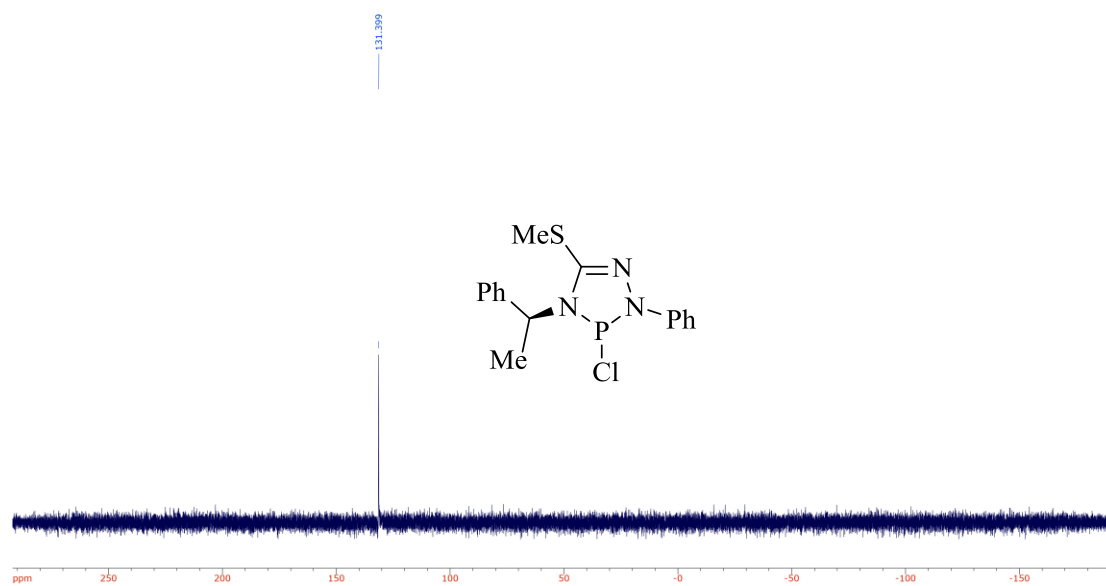
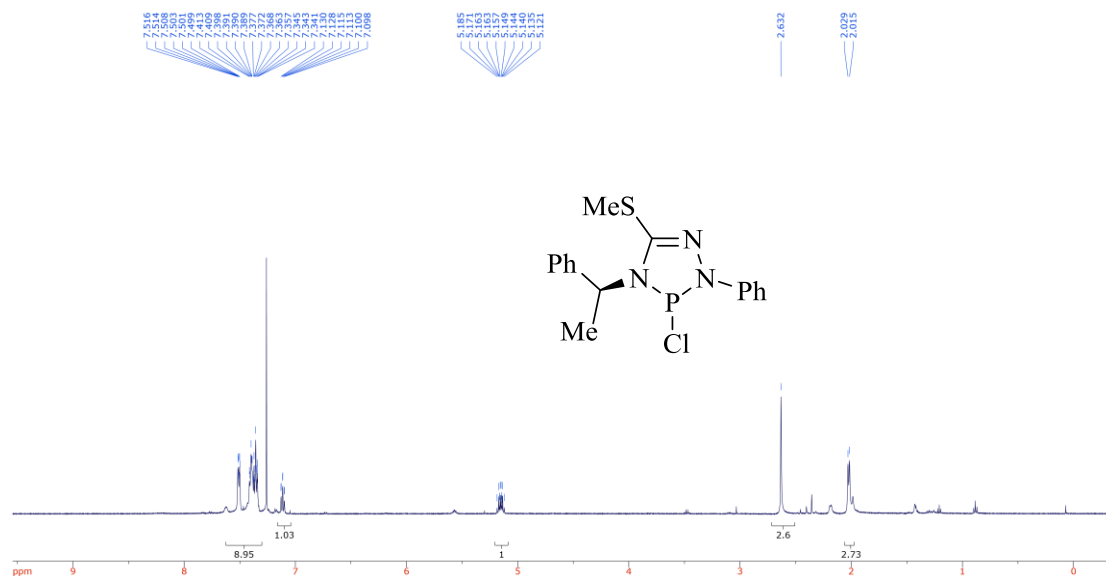


Figure S150. ^{31}P NMR spectrum of **3-42** (202 MHz, CDCl_3).



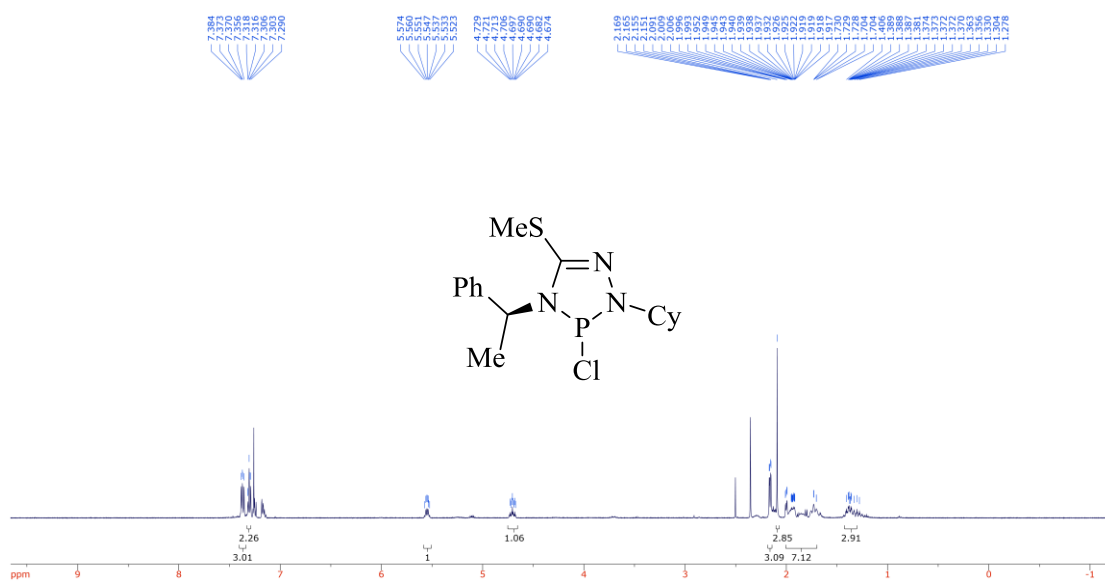


Figure S155. ¹H NMR spectrum of **3-45** (500 MHz, CDCl₃).

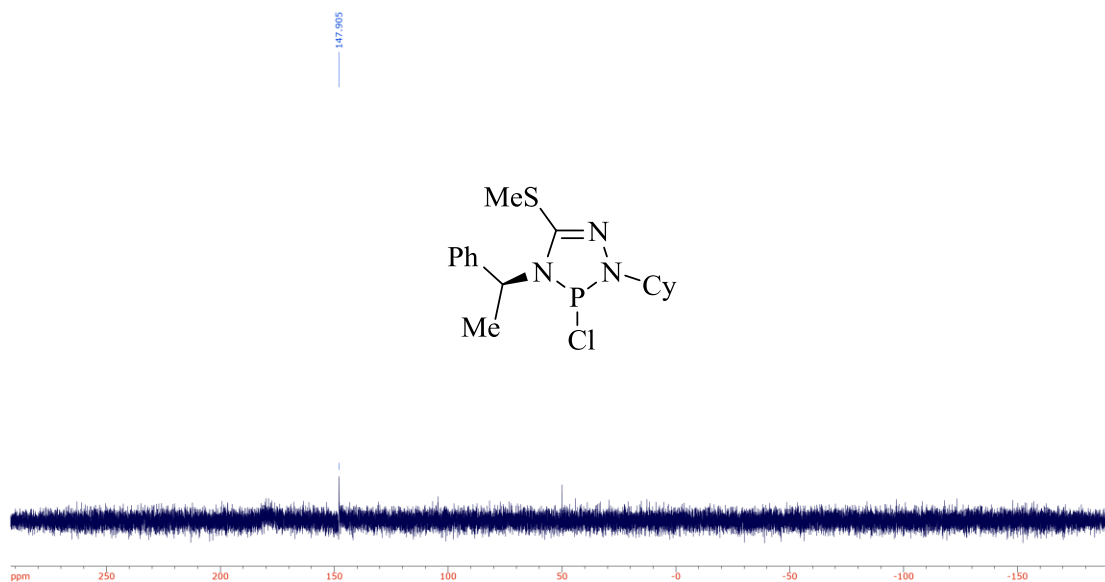
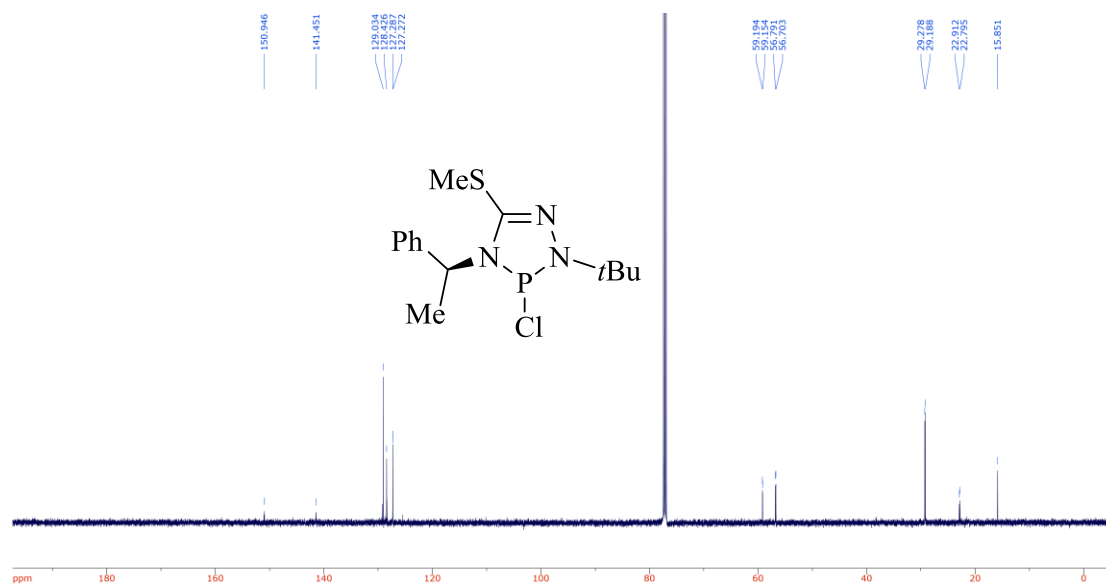
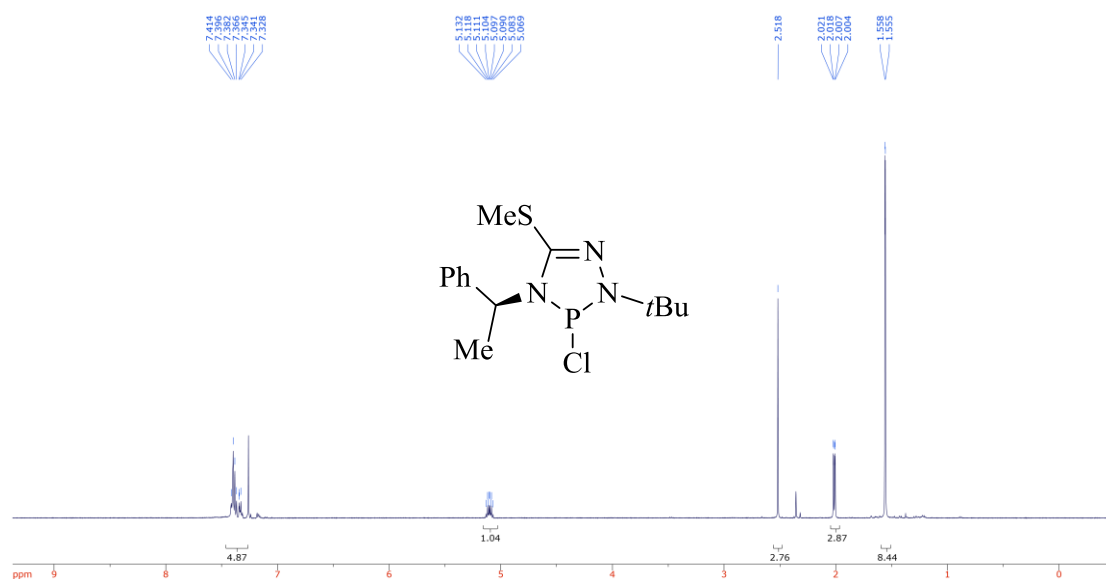


Figure S156. ³¹P NMR spectrum of **3-45** (202 MHz, CDCl₃).



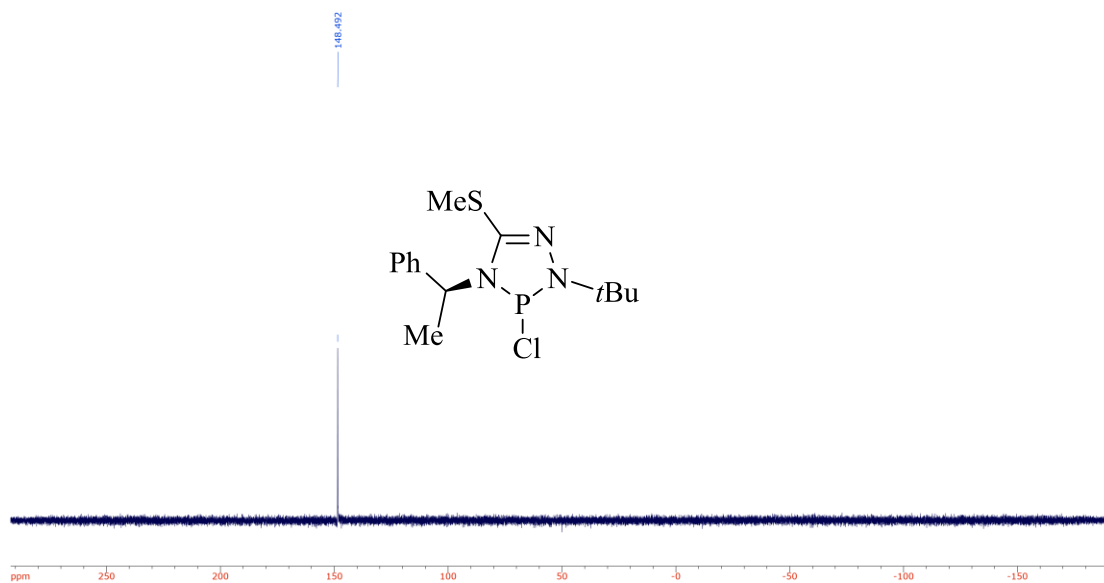


Figure S159. ^{31}P NMR spectrum of **3-46** (202 MHz, CDCl_3).

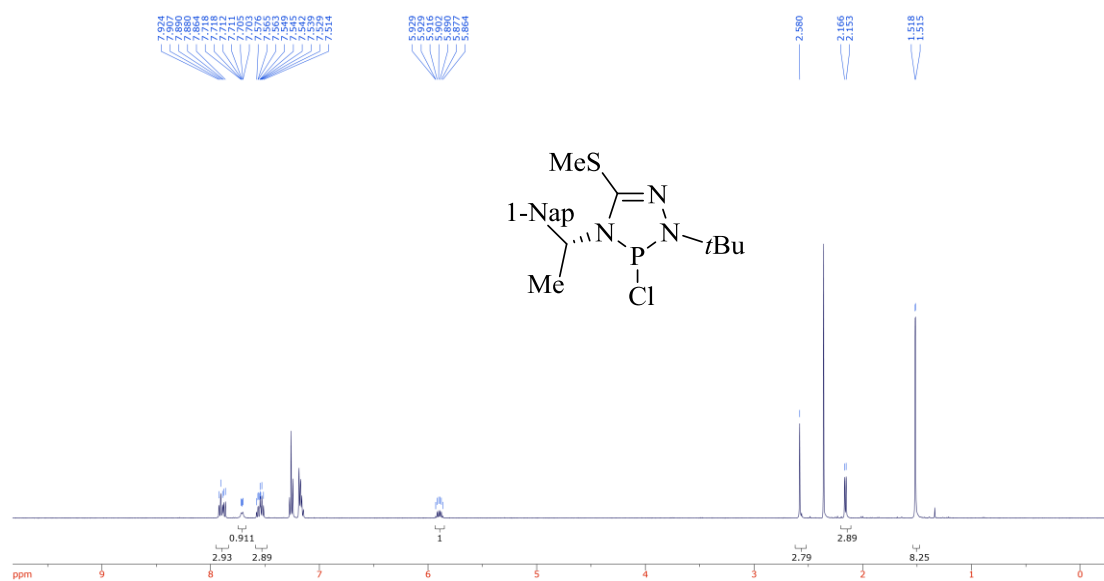


Figure S160. ^1H NMR spectrum of **3-47** (500 MHz, CDCl_3).

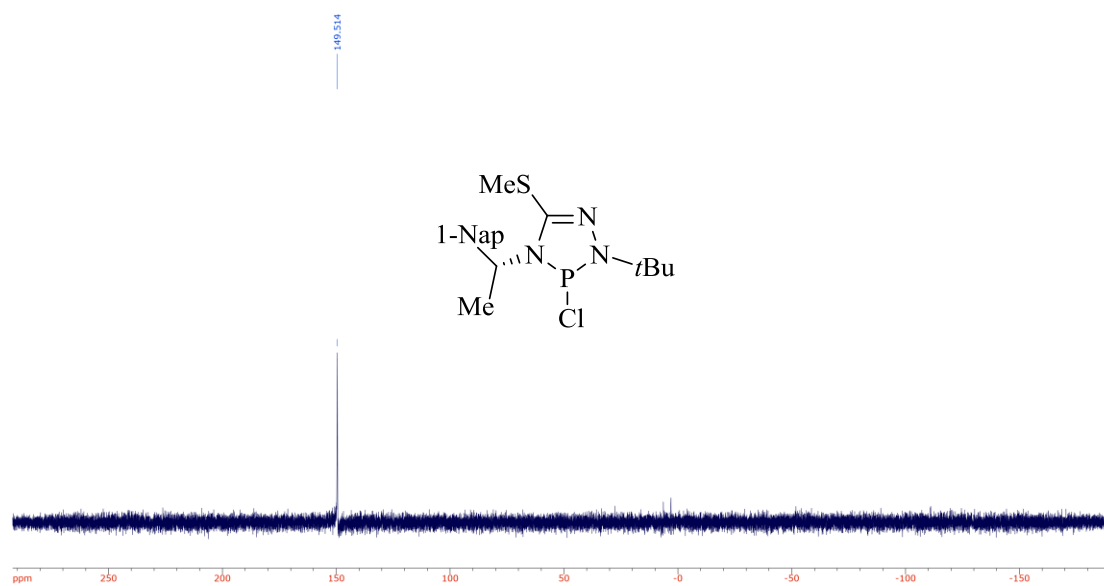


Figure S161. ^{31}P NMR spectrum of **3-47** (202 MHz, CDCl_3).

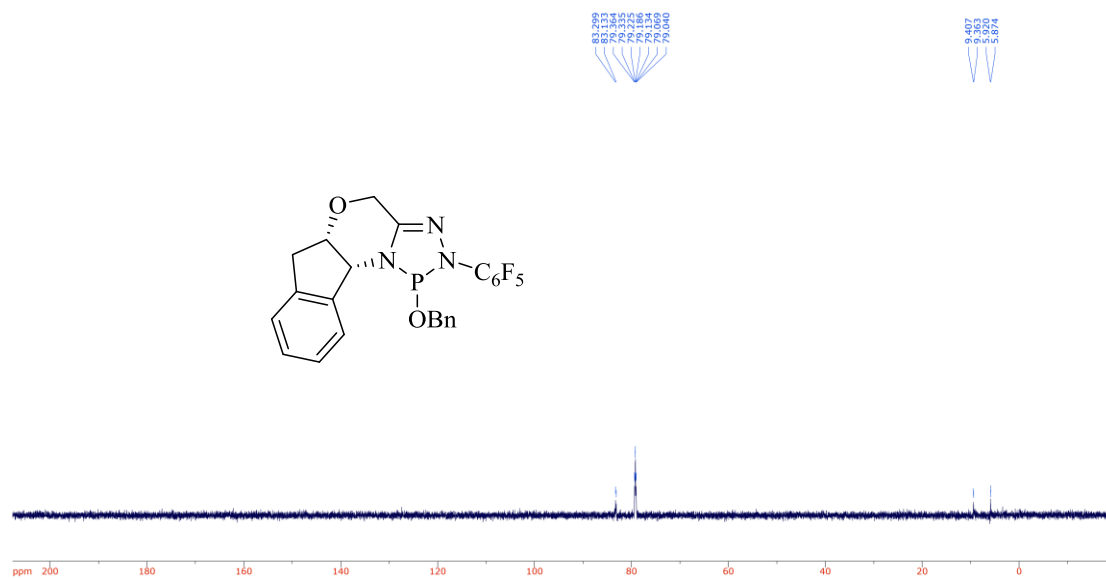


Figure S162. ^{31}P NMR spectrum of **3-48** (202 MHz, CDCl_3).

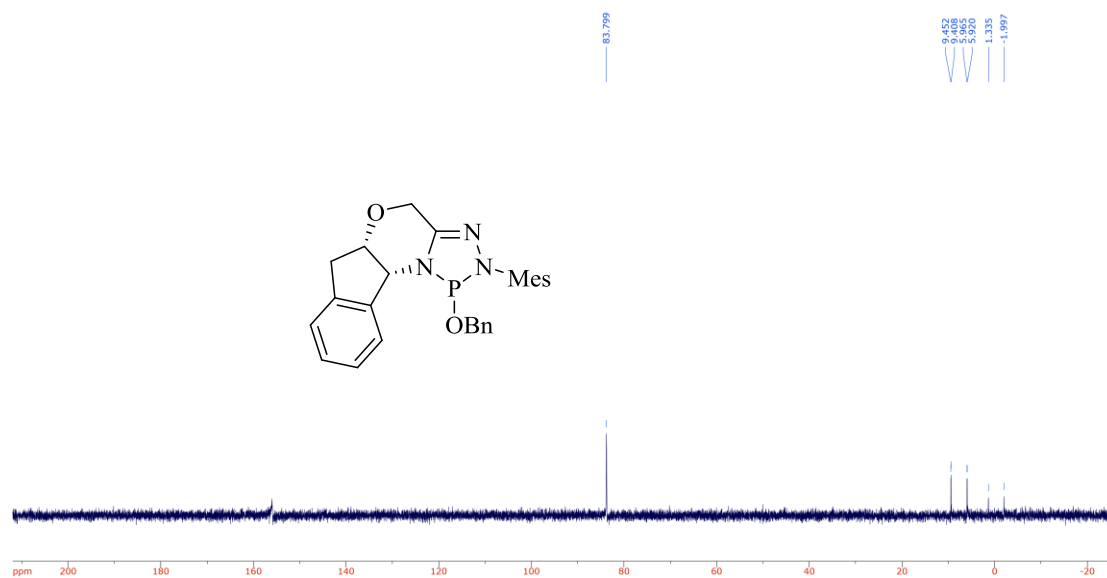


Figure S163. ^{31}P NMR spectrum of 3-49 (202 MHz, CDCl_3).

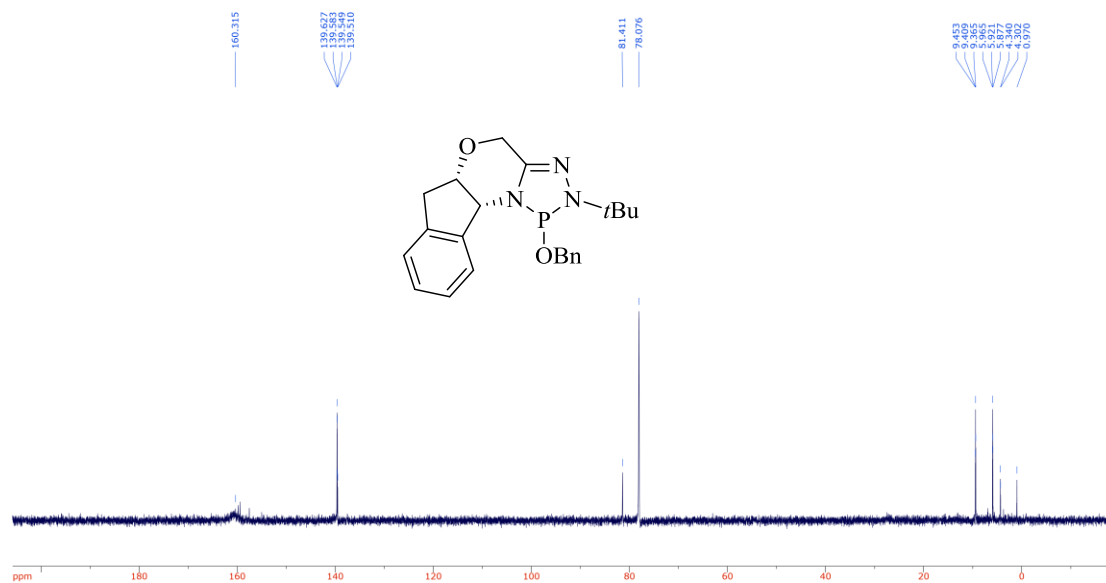


Figure S164. ^{31}P NMR spectrum of 3-50 (202 MHz, CDCl_3).

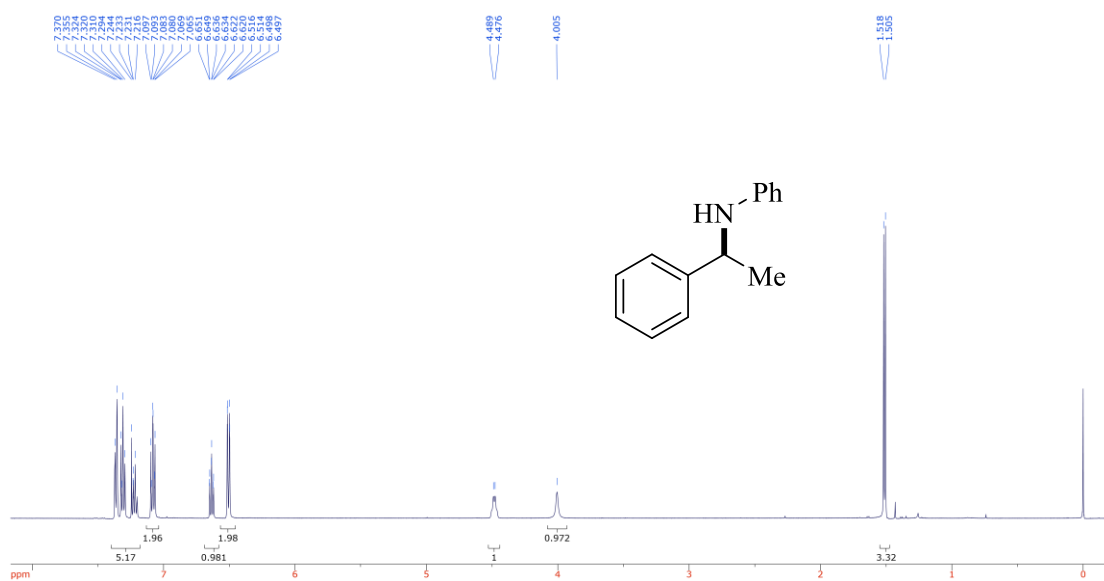


Figure S165. ^1H NMR spectrum of **4-7** (500 MHz, CDCl_3).

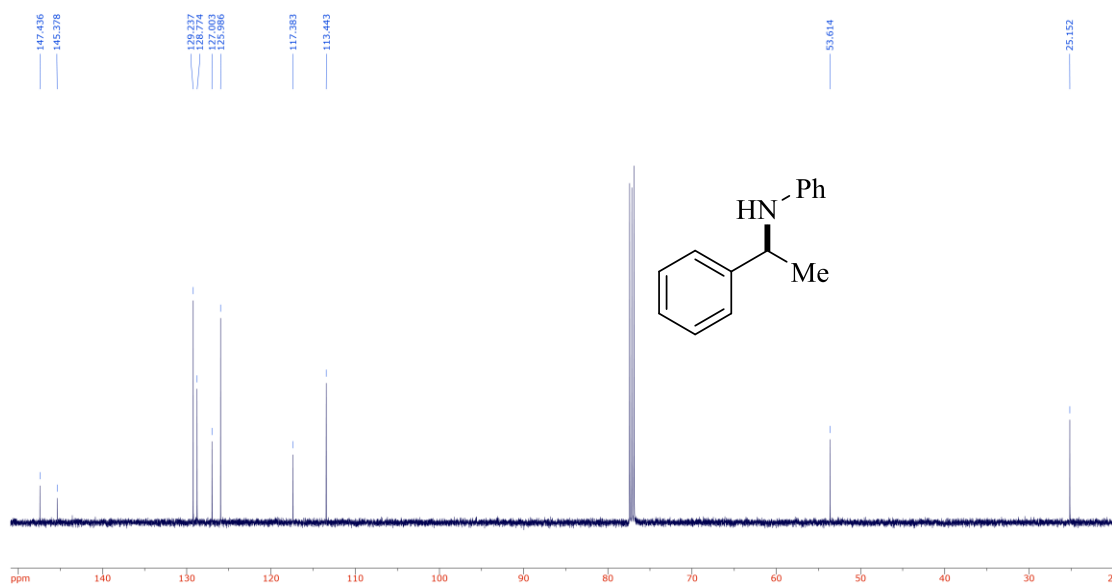


Figure S166. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-7** (125 MHz, CDCl_3).

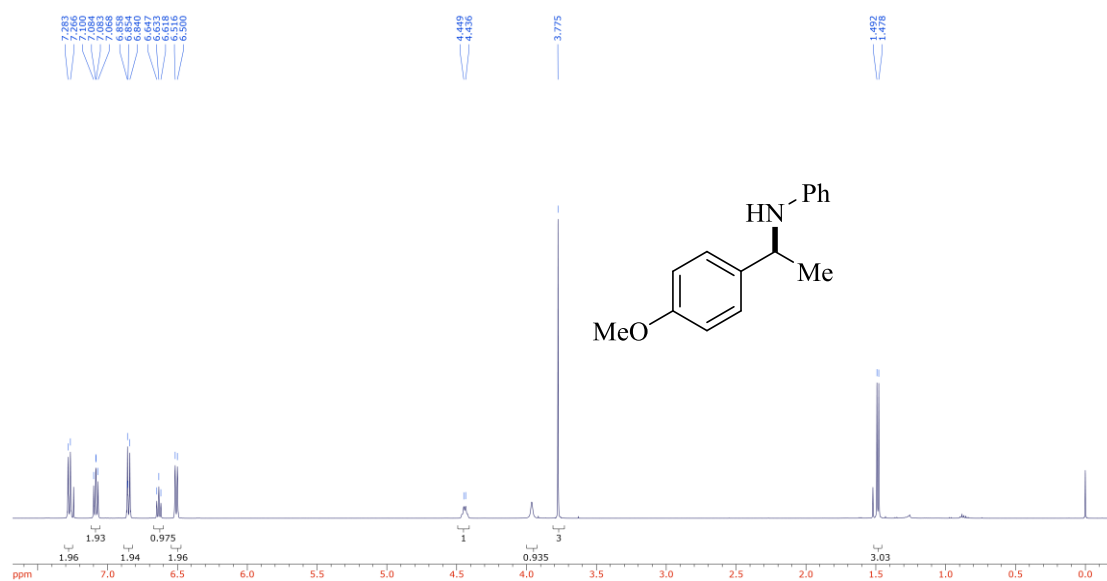


Figure S167. ^1H NMR spectrum of **4-8** (500 MHz, CDCl_3).

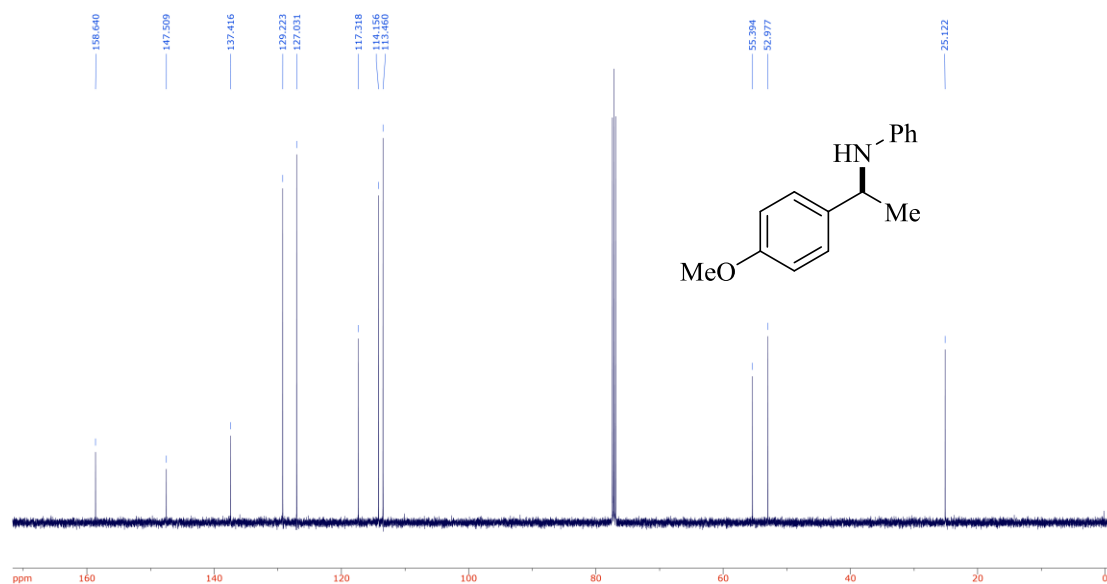


Figure S168. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-8** (125 MHz, CDCl_3).

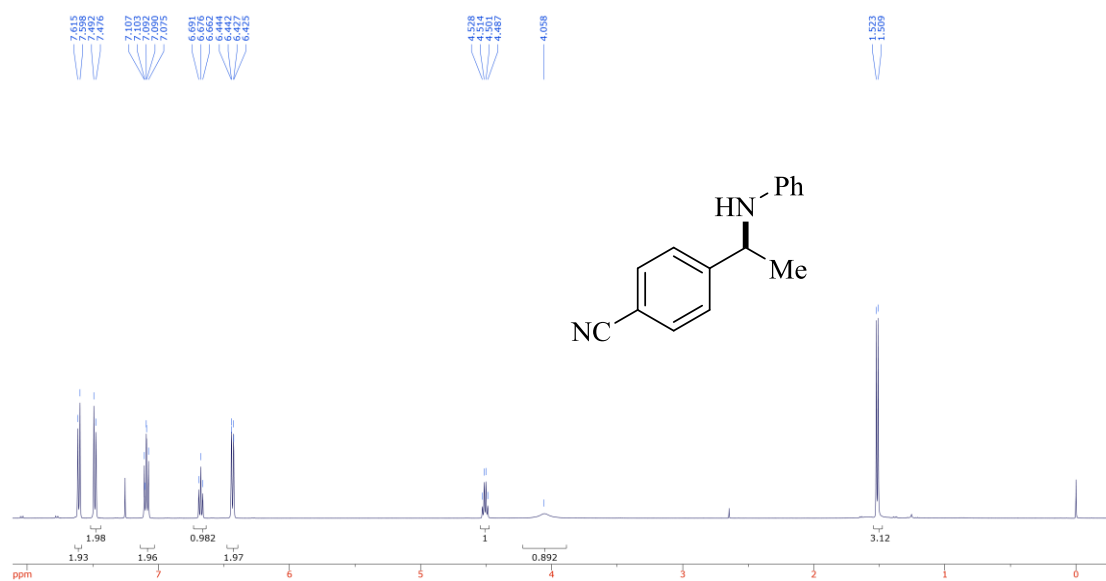


Figure S169. ¹H NMR spectrum of **4-9** (500 MHz, CDCl₃).

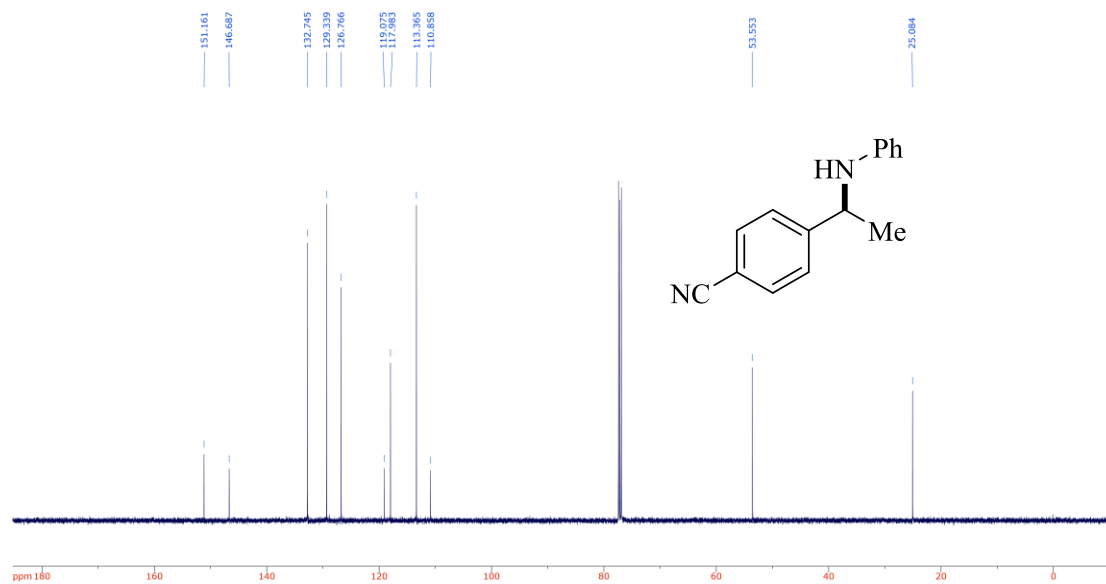


Figure S170. ¹³C{¹H} NMR spectrum of **4-9** (125 MHz, CDCl₃).

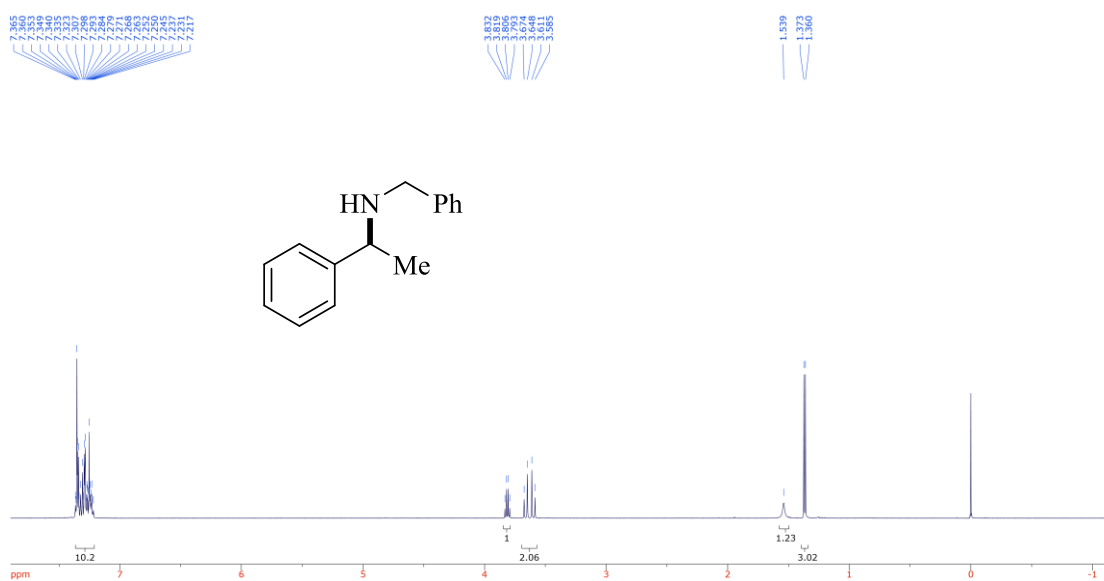


Figure S173. ^1H NMR spectrum of 4-11 (500 MHz, CDCl_3).

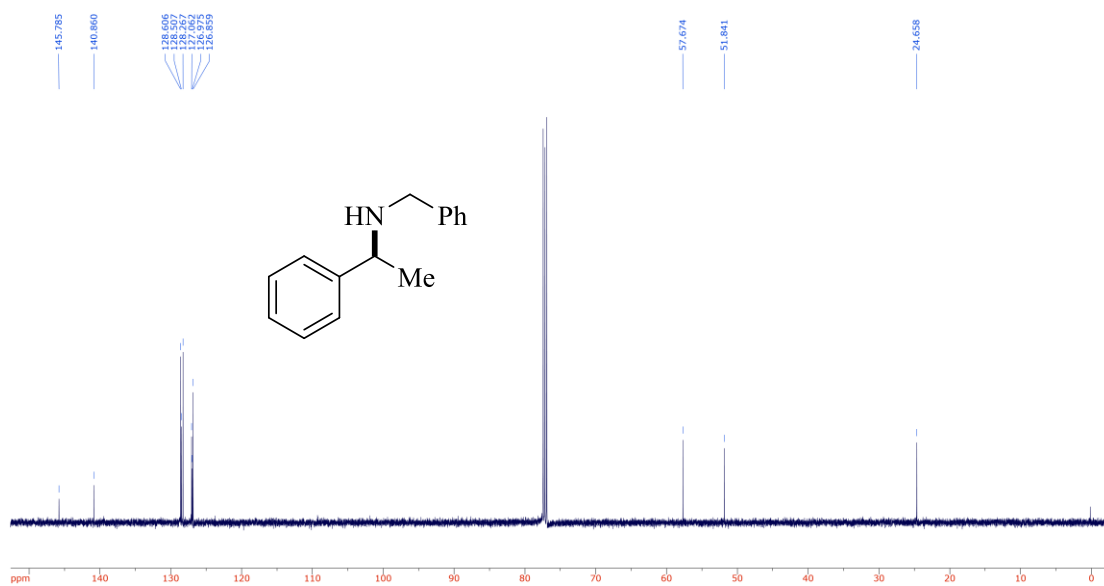


Figure S174. ^{13}C NMR spectrum of 4-11 (125 MHz, CDCl_3).

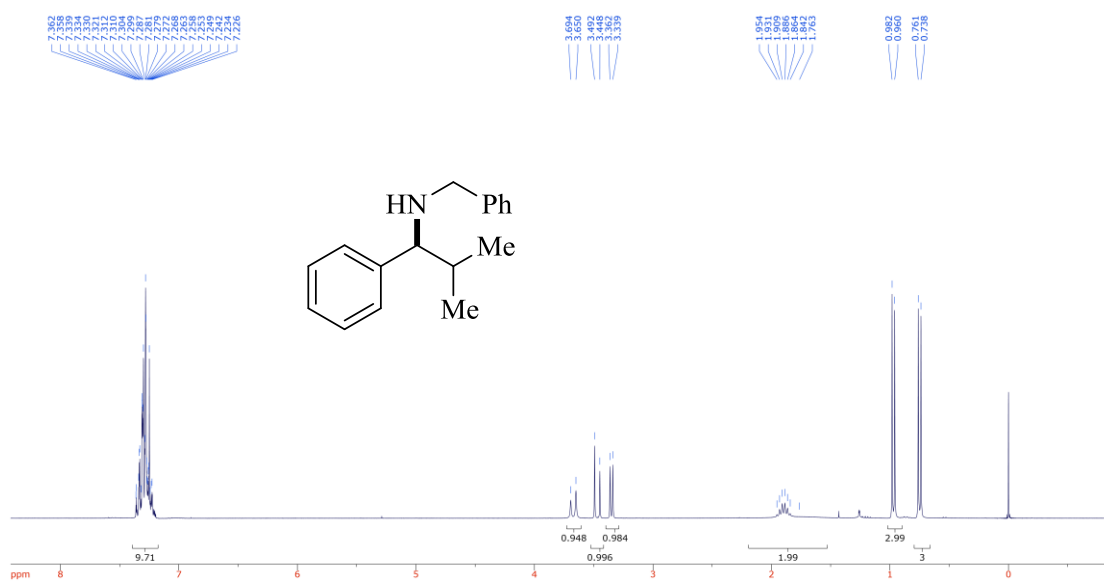


Figure S175. ^1H NMR spectrum of 4-12 (300 MHz, CDCl_3).

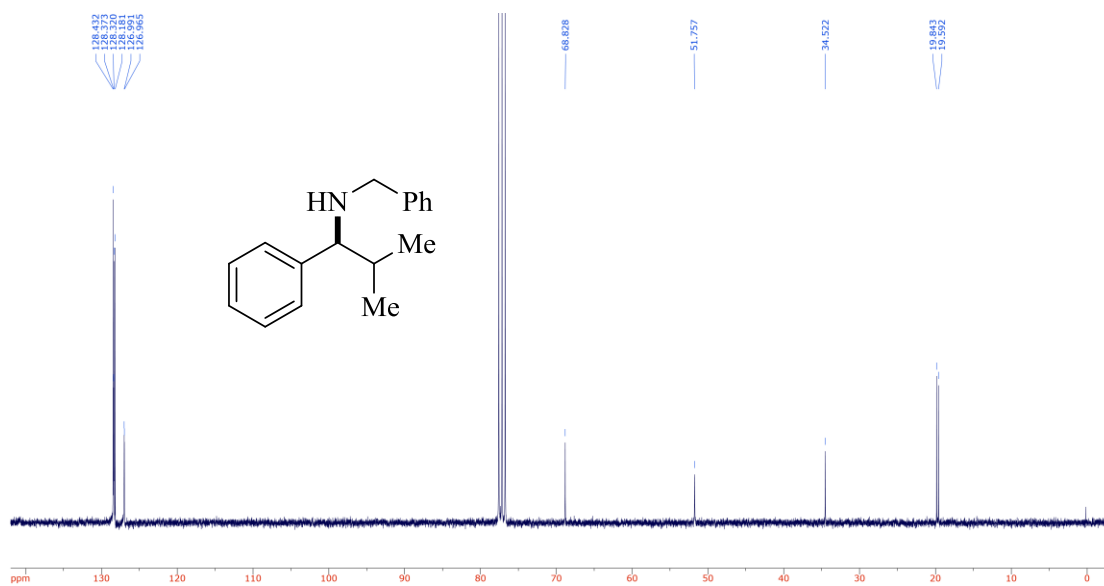


Figure S176. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 4-12 (75 MHz, CDCl_3).

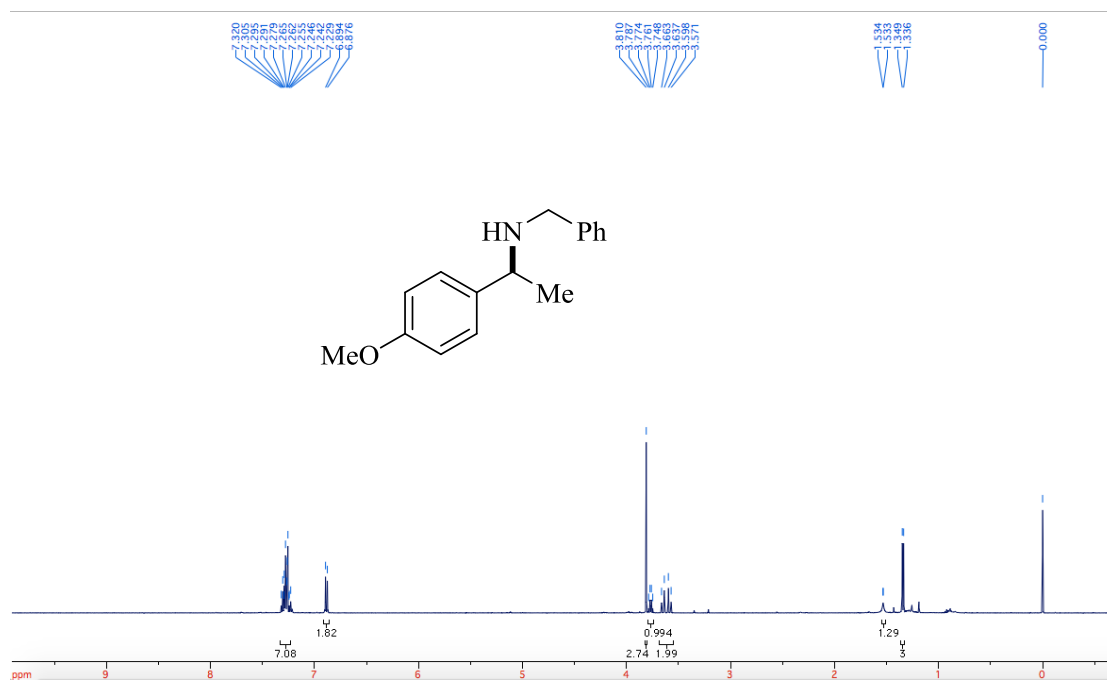


Figure S179. ¹H NMR spectrum of 4-14 (500 MHz, CDCl₃).

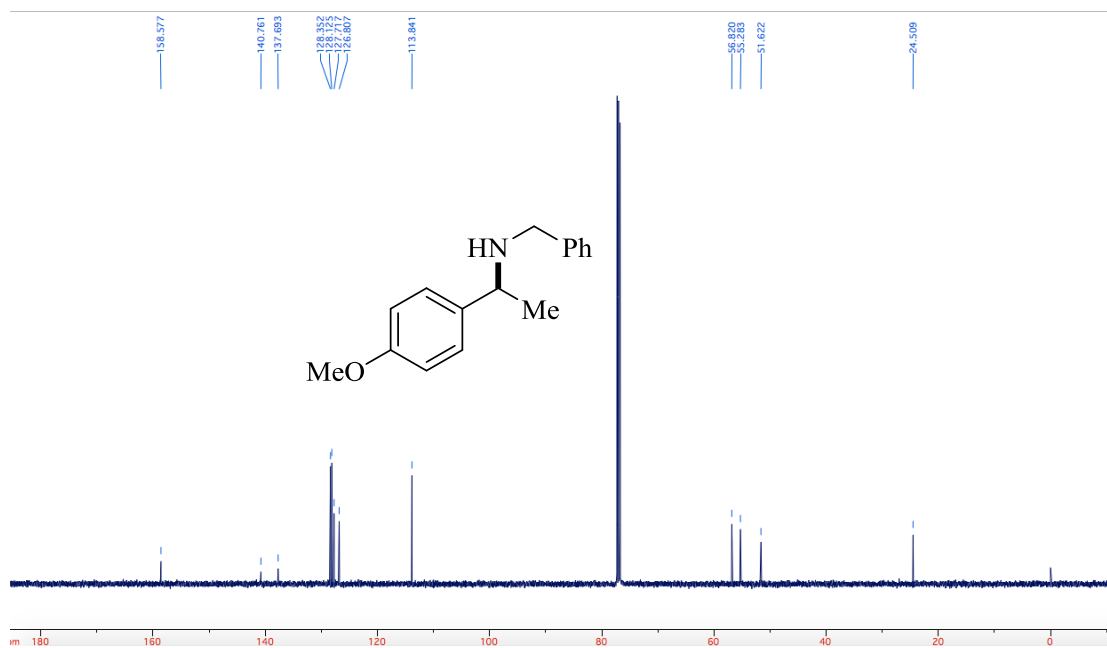


Figure S180. ¹³C {¹H} NMR spectrum of 4-14 (125 MHz, CDCl₃).

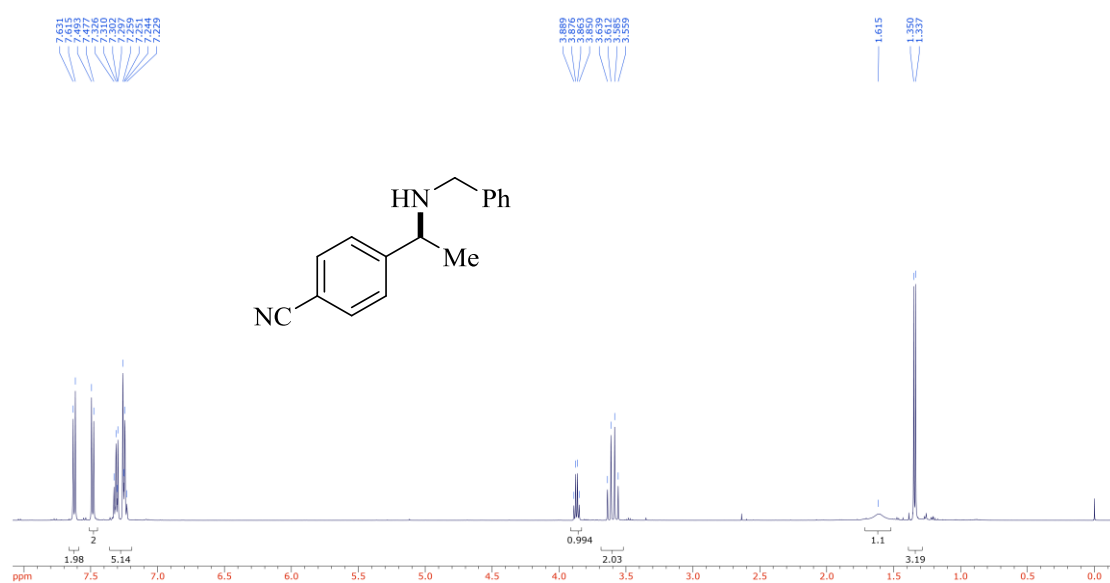


Figure S181. ^1H NMR spectrum of 4-15 (500 MHz, CDCl_3).

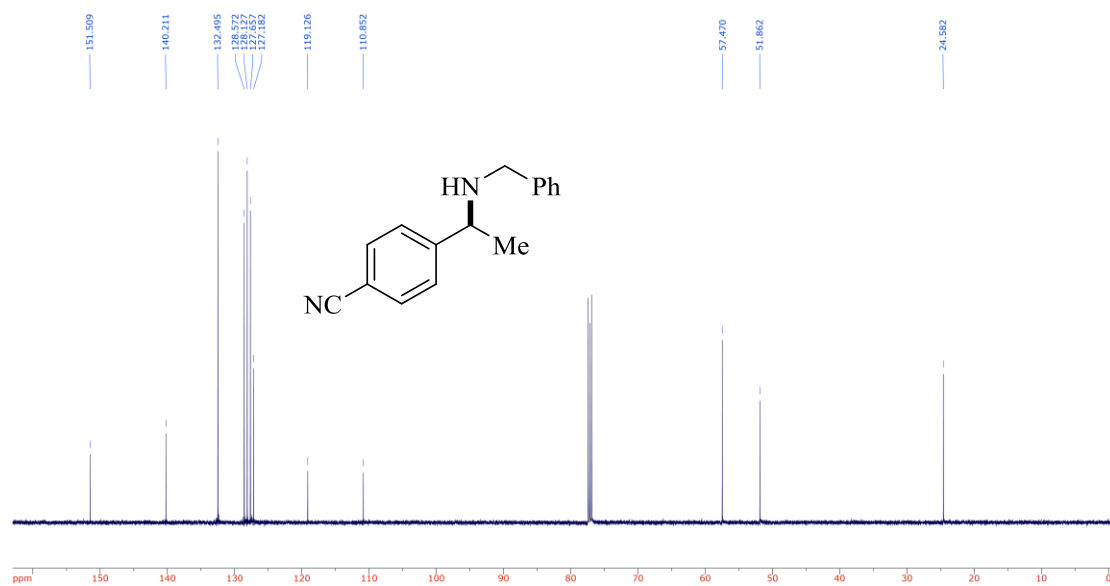


Figure S182. ^{13}C $\{^1\text{H}\}$ NMR spectrum of 4-15 (125 MHz, CDCl_3).

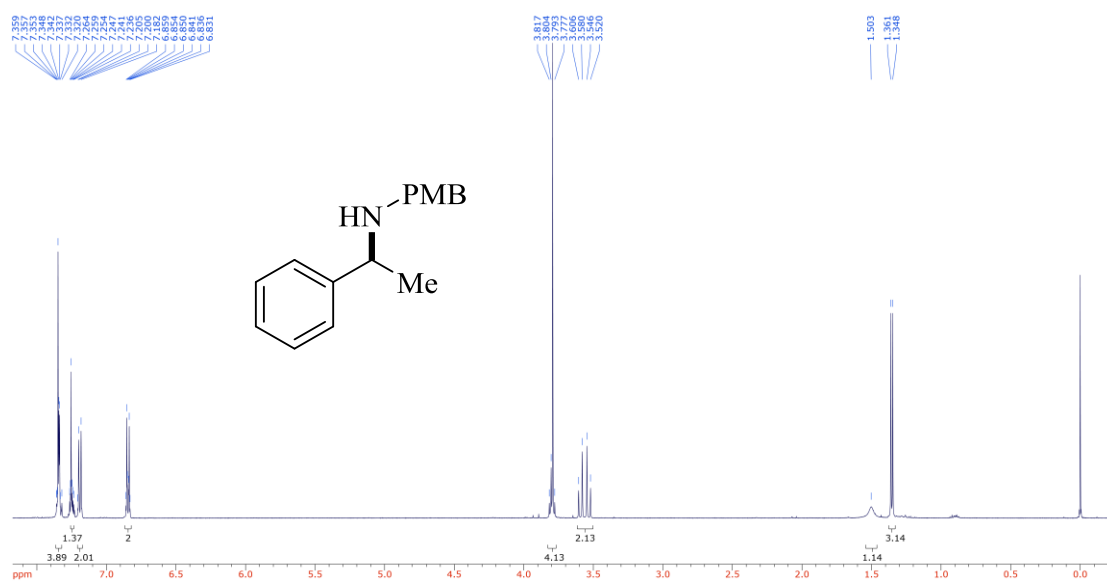


Figure S183. ¹H NMR spectrum of 4-16 (500 MHz, CDCl₃).

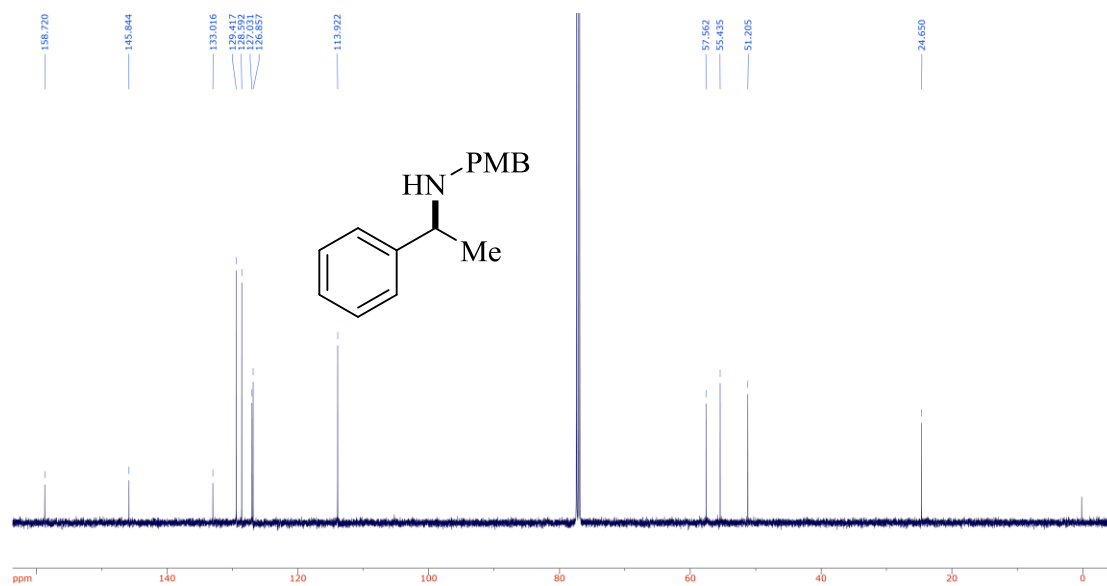


Figure S184. ¹³C {¹H} NMR spectrum of 4-16 (125 MHz, CDCl₃).

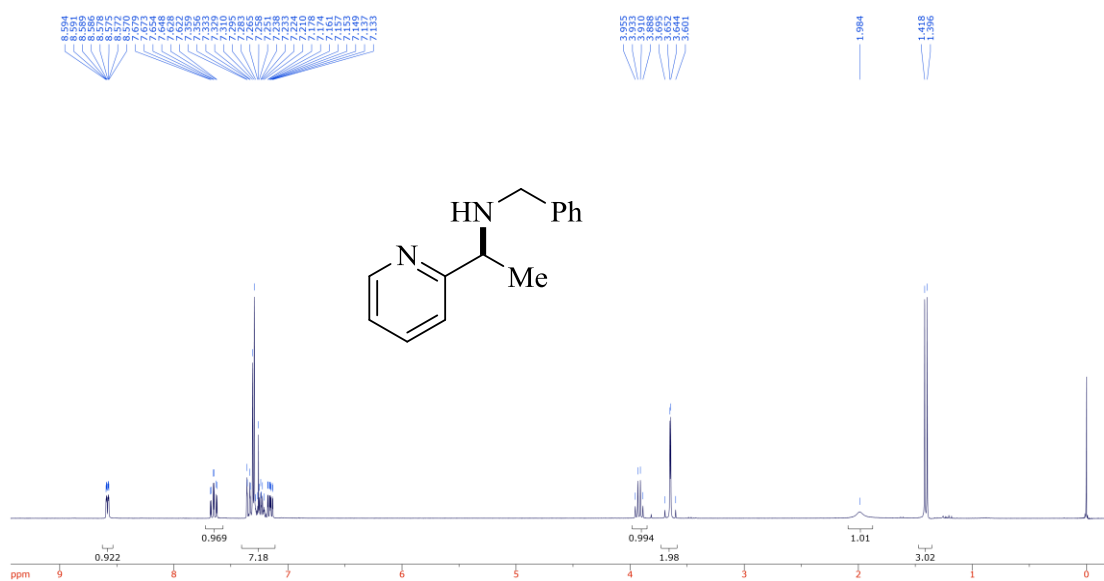


Figure S185. ^1H NMR spectrum of 4-17 (300 MHz, CDCl_3).

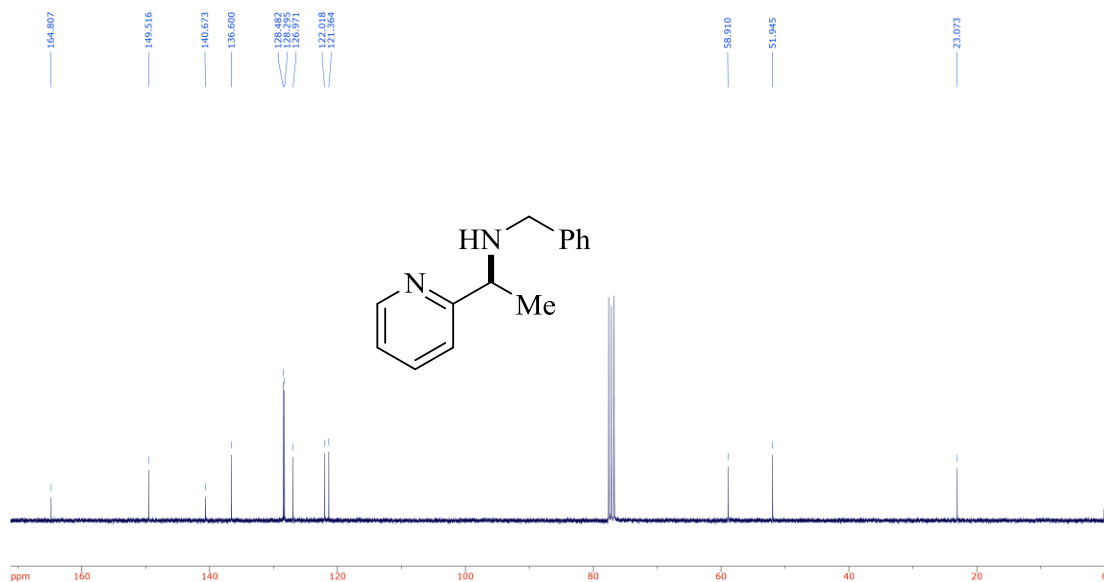


Figure S186. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 4-17 (75 MHz, CDCl_3).

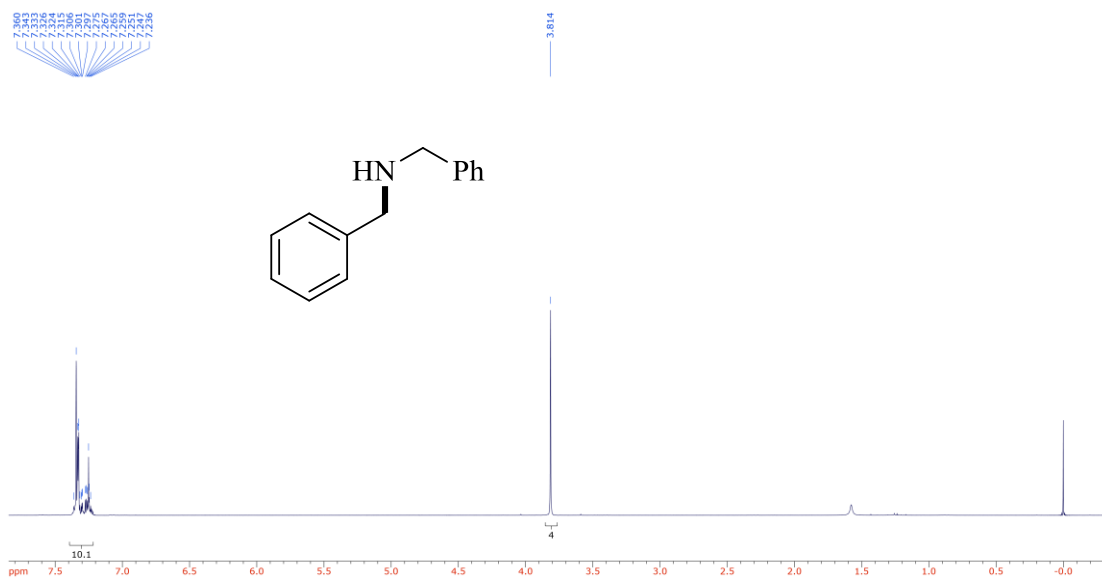


Figure S187. ^1H NMR spectrum of **4-18** (300 MHz, CDCl_3).

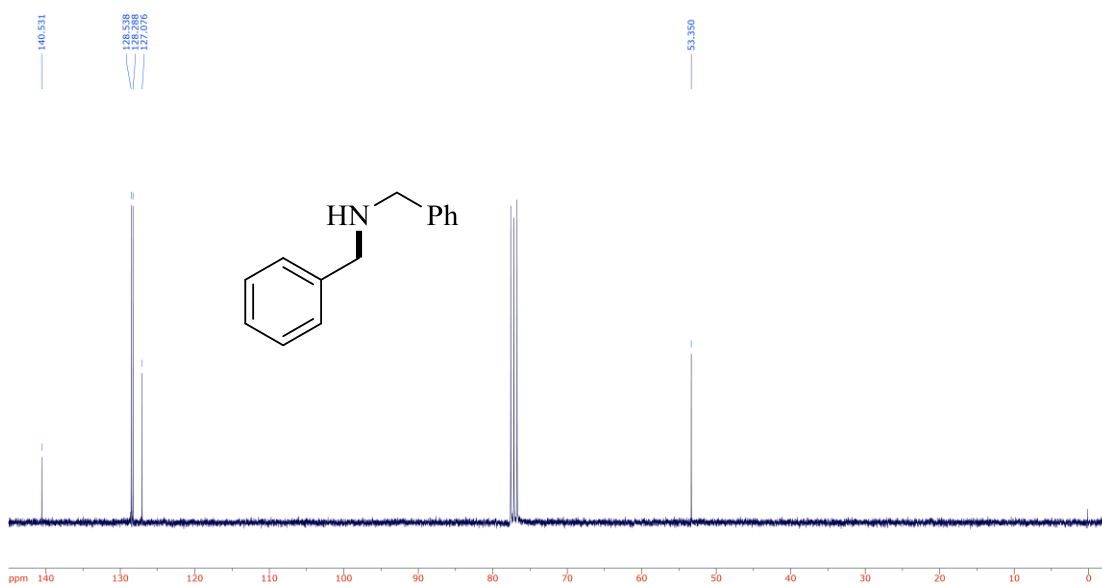


Figure S188. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-18** (75 MHz, CDCl_3).

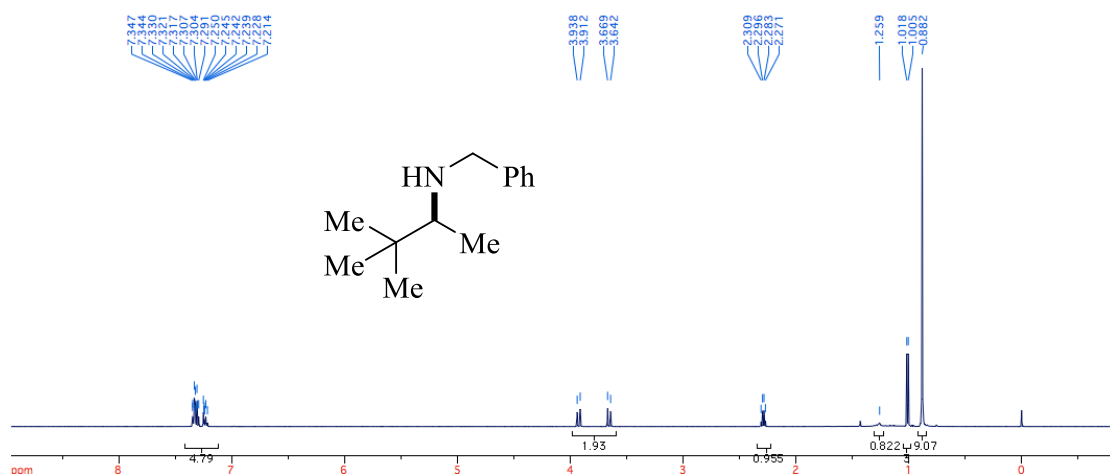


Figure S189. ^1H NMR spectrum of 4-19 (500 MHz, CDCl_3).

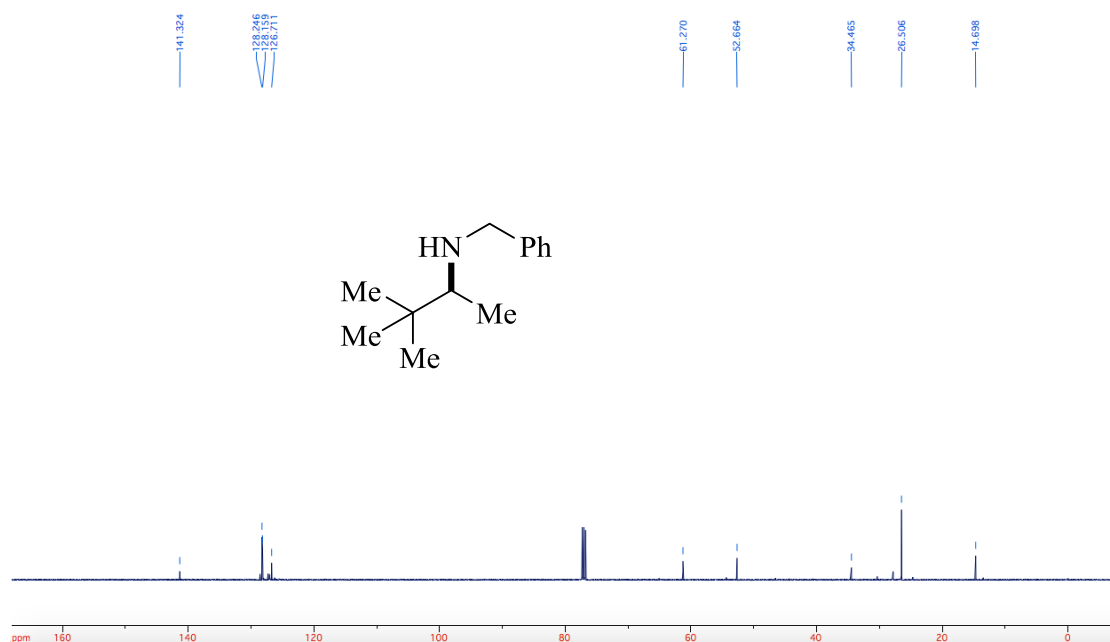


Figure S190. ^{13}C $\{^1\text{H}\}$ NMR spectrum of 4-19 (125 MHz, CDCl_3).

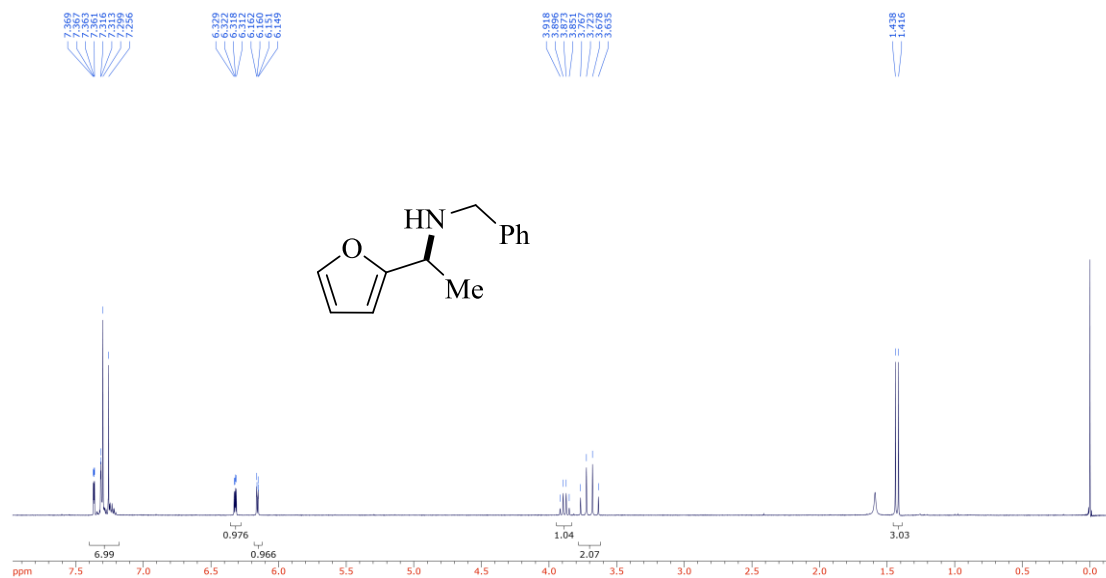


Figure S191. ^1H NMR spectrum of **4-20** (300 MHz, CDCl_3).

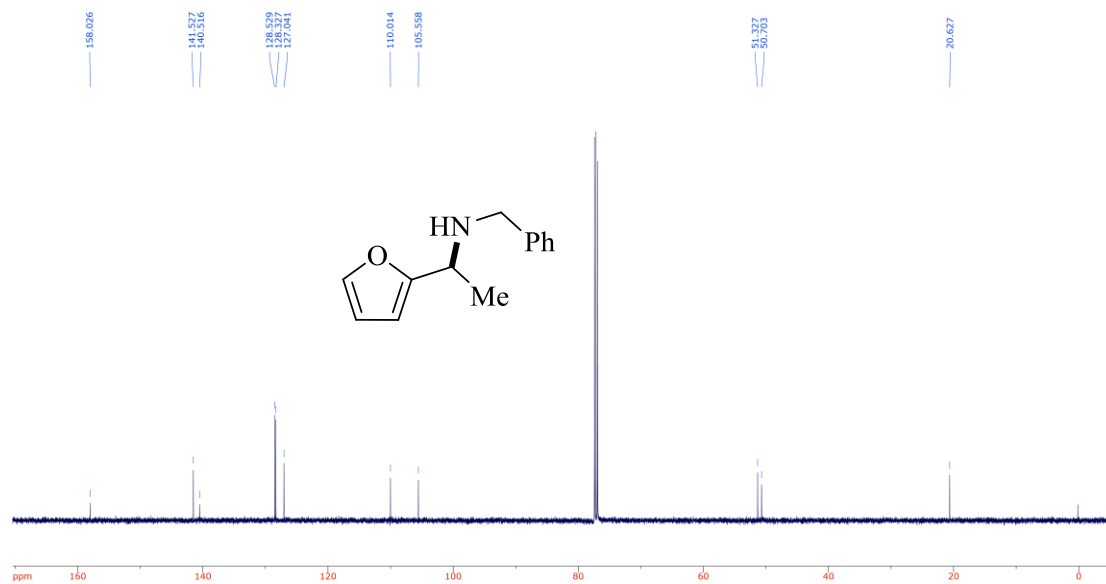


Figure S192. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-20** (75 MHz, CDCl_3).

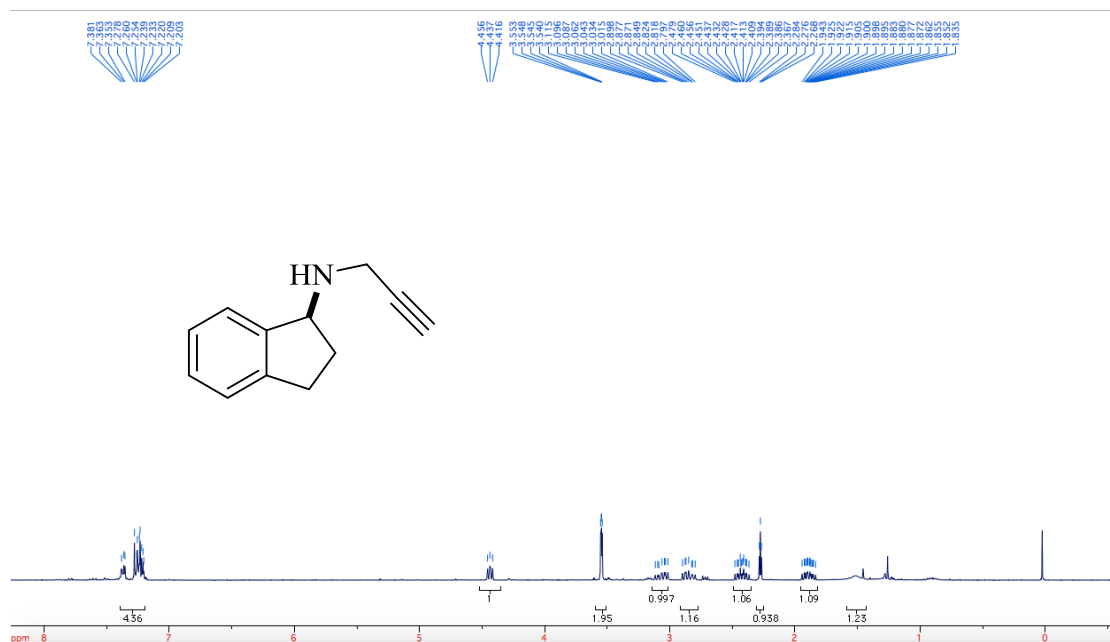


Figure S193. ^1H NMR spectrum of **4-21** (500 MHz, CDCl_3).

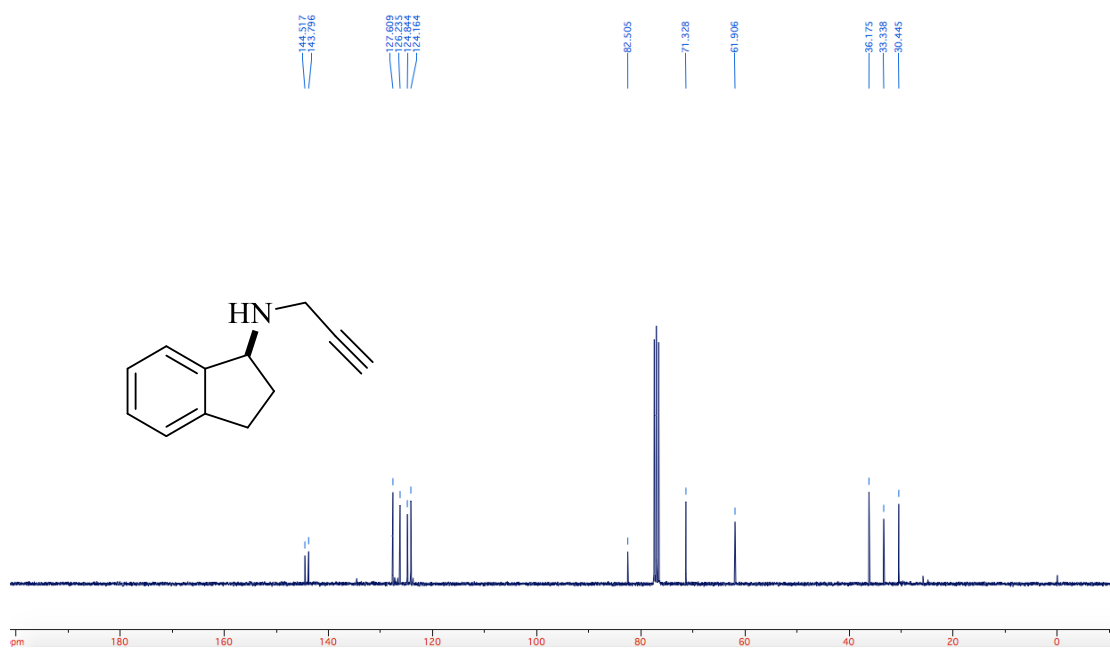


Figure S194. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-21** (125 MHz, CDCl_3).

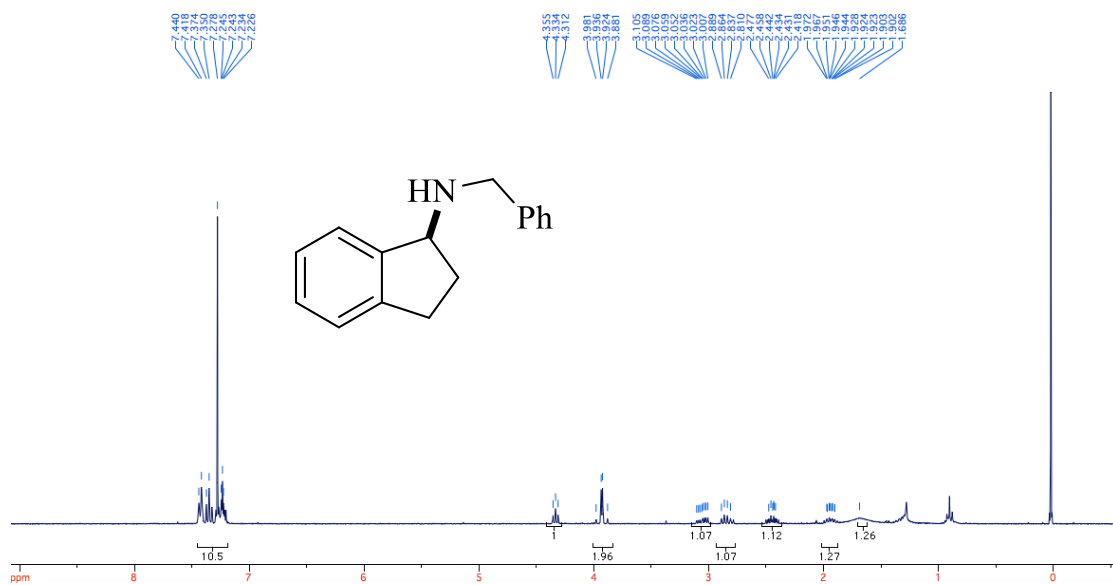


Figure S195. ¹H NMR spectrum of 4-22 (500 MHz, CDCl₃).

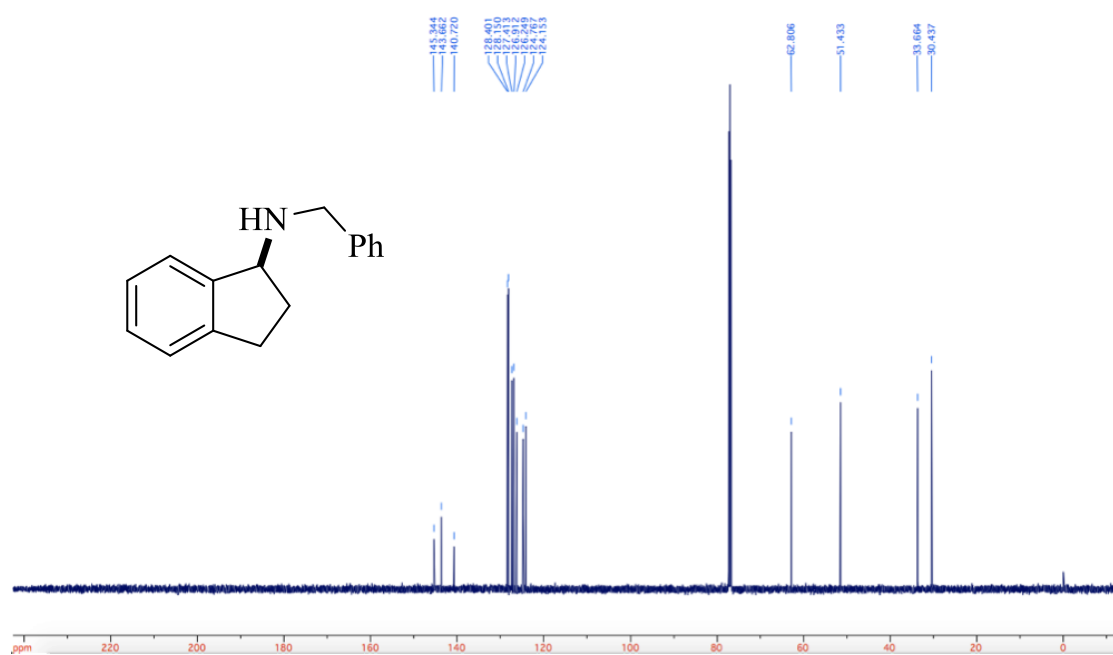


Figure S196. ¹³C {¹H} NMR spectrum of 4-22 (125 MHz, CDCl₃).

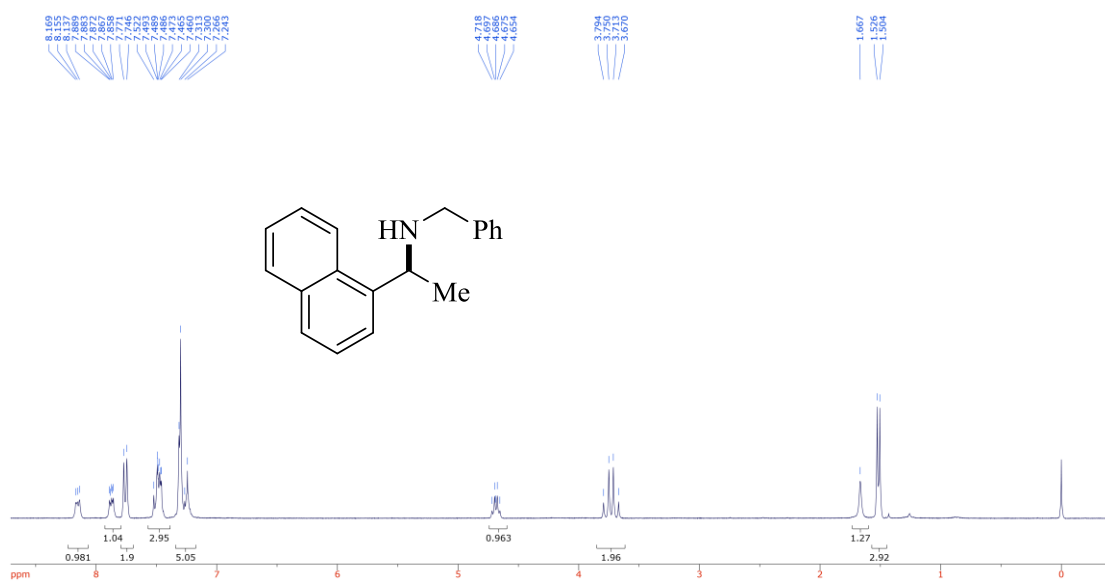


Figure S199. ^1H NMR spectrum of **4-24** (300 MHz, CDCl_3).

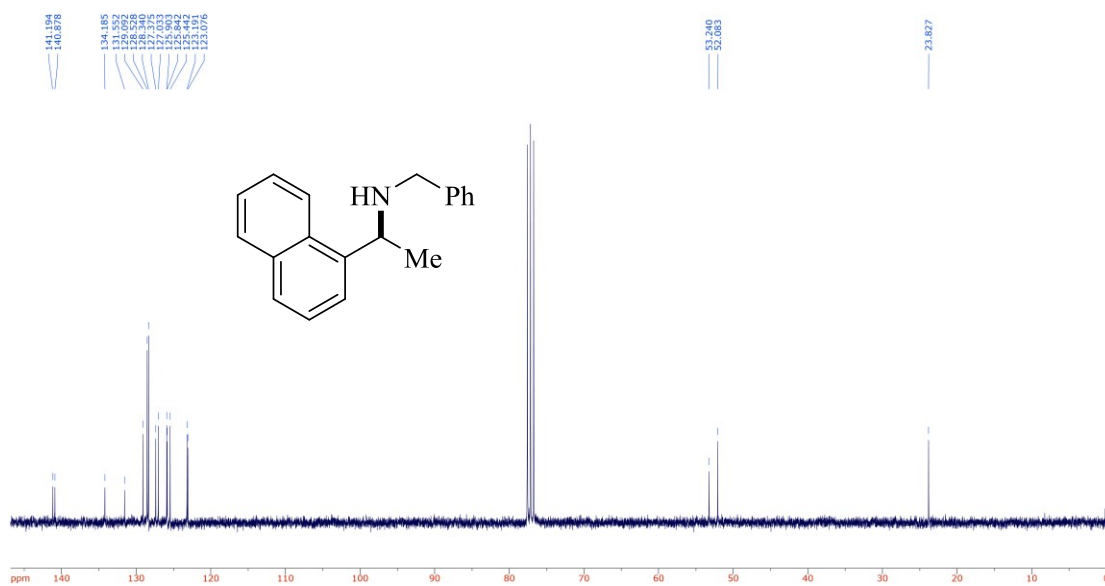


Figure S200. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-24** (75 MHz, CDCl_3).

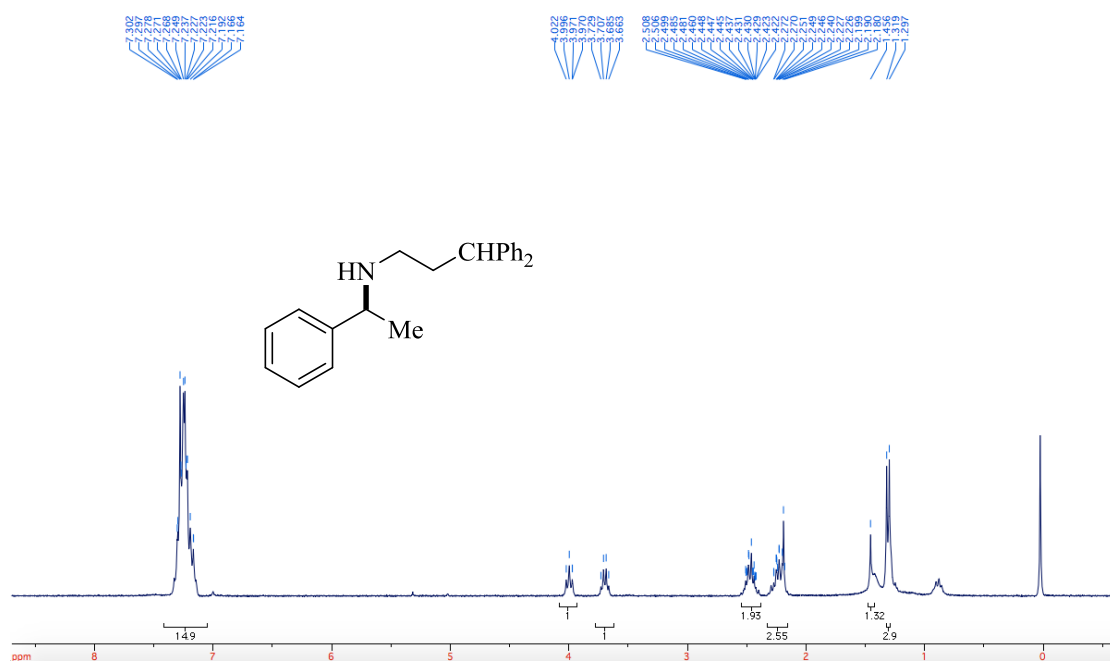


Figure S201. ^1H NMR spectrum of 4-25 (500 MHz, CDCl_3).

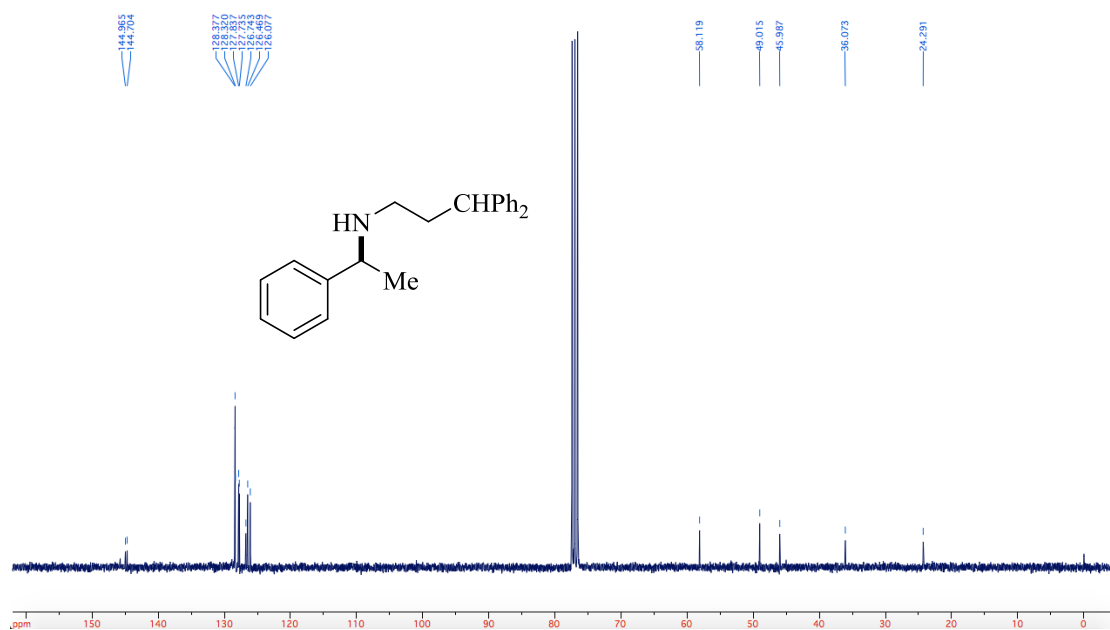


Figure S202. ^{13}C $\{^1\text{H}\}$ NMR spectrum of 4-25 (125 MHz, CDCl_3).

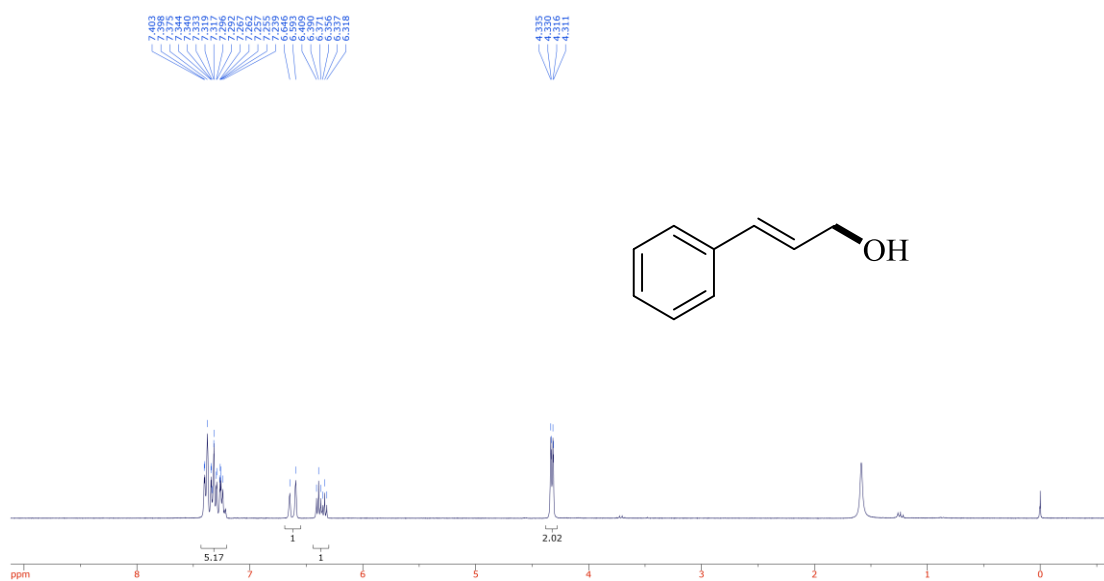


Figure S205. ^1H NMR spectrum of 4-37 (300 MHz, CDCl_3).

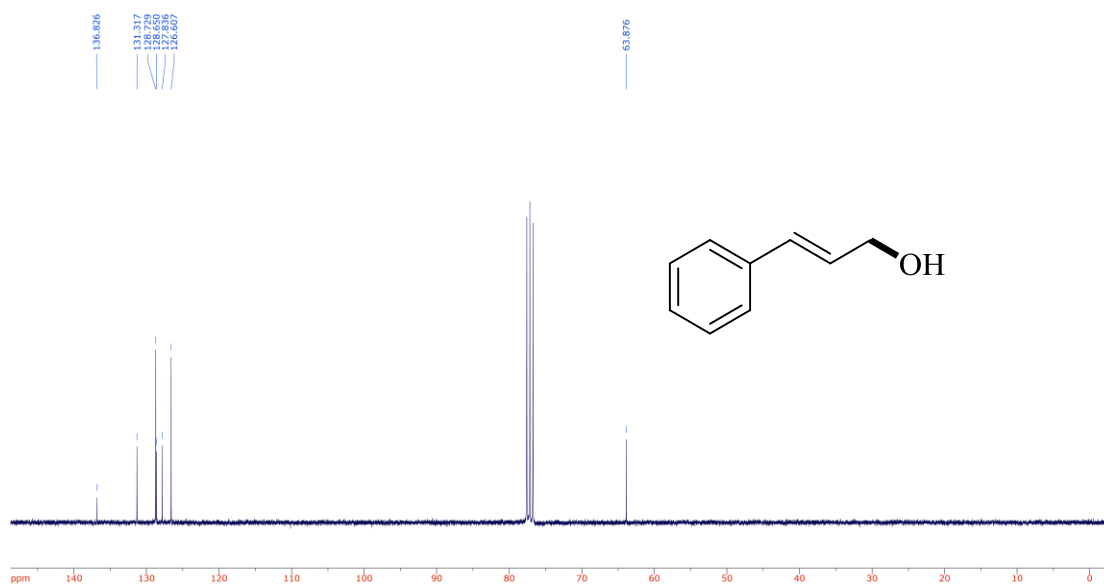


Figure S206. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 4-37 (75 MHz, CDCl_3).

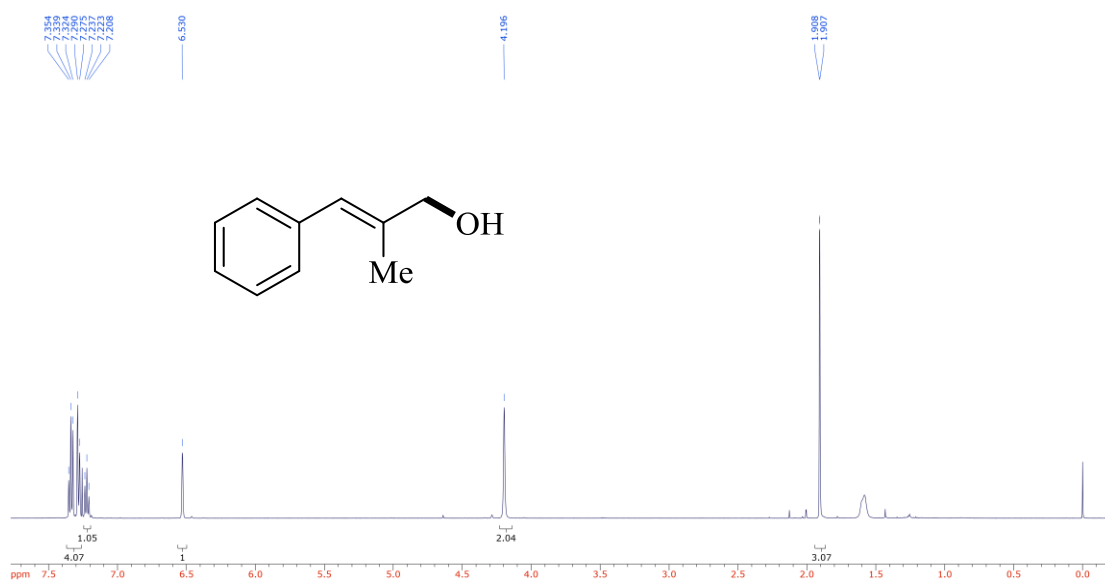


Figure S207. ^1H NMR spectrum of 4-38 (500 MHz, CDCl_3).

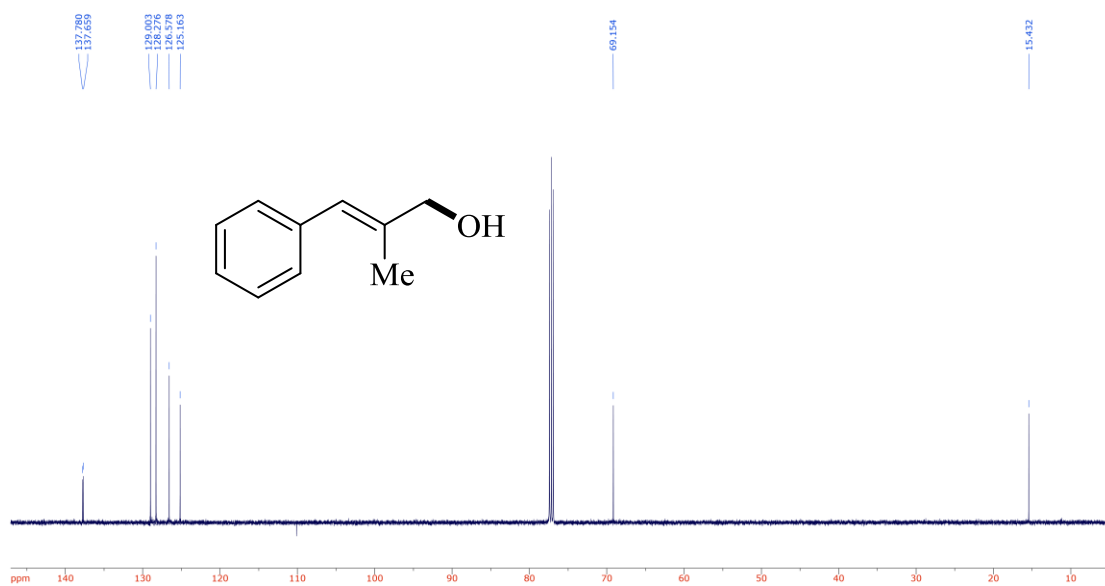


Figure S208. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 4-38 (125 MHz, CDCl_3).

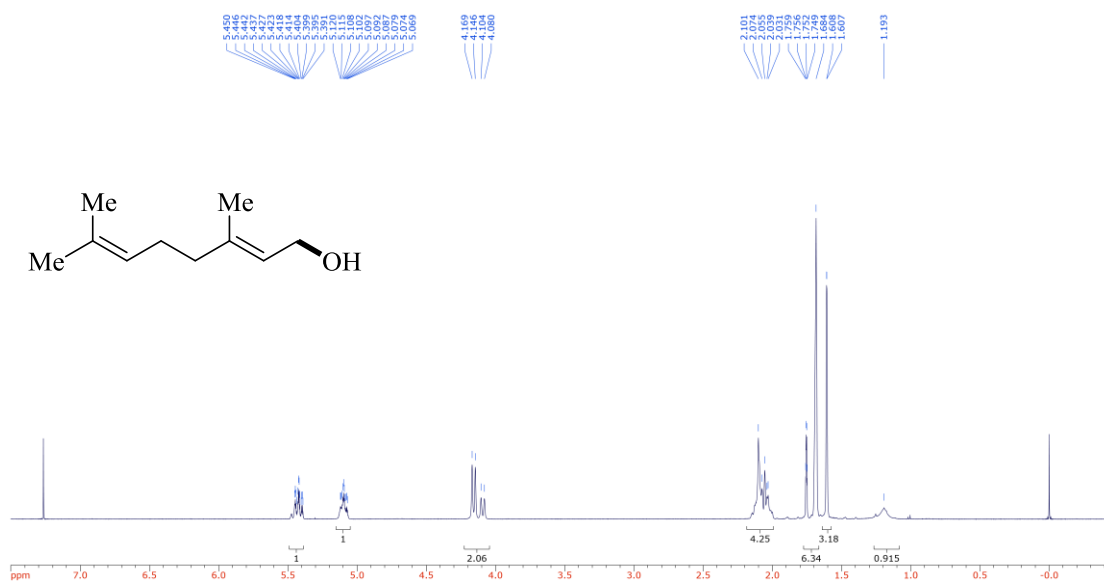


Figure S209. ^1H NMR spectrum of **4-39** (300 MHz, CDCl_3).

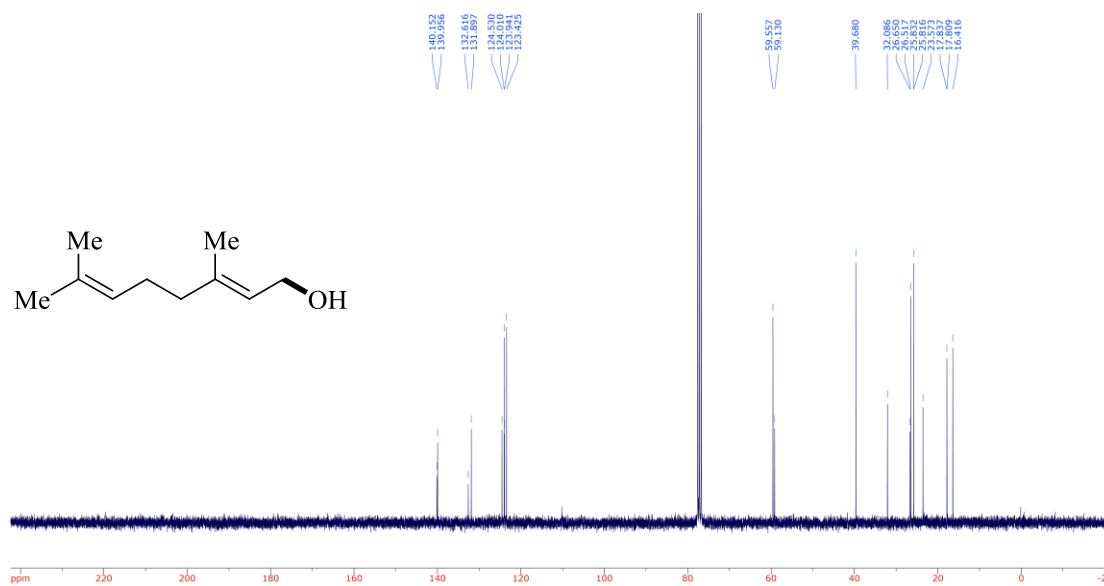


Figure S210. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-39** (75 MHz, CDCl_3).

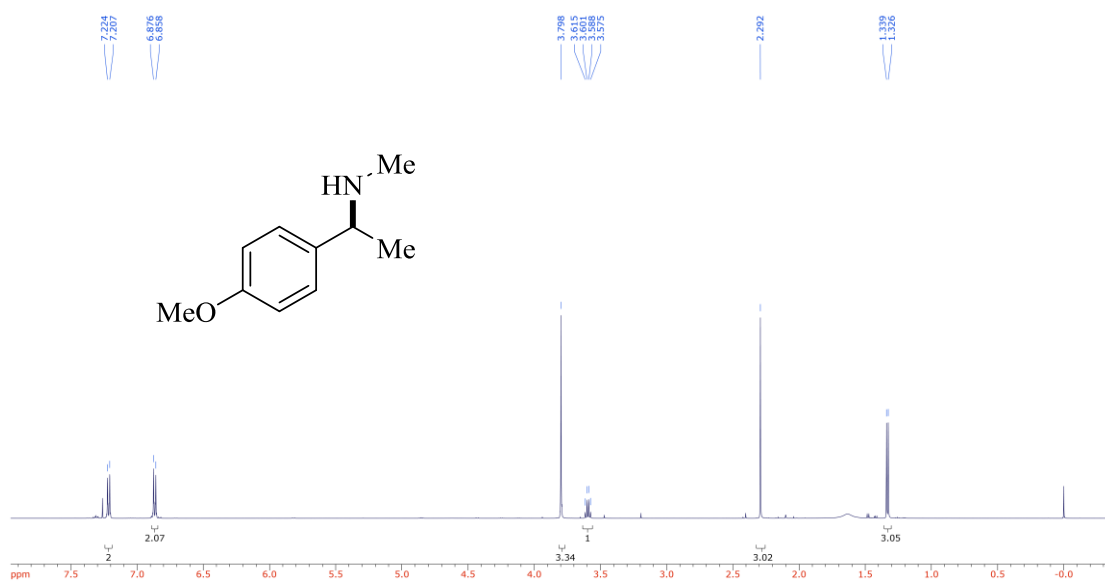


Figure S211. ^1H NMR spectrum of 4-43 (500 MHz, CDCl_3).

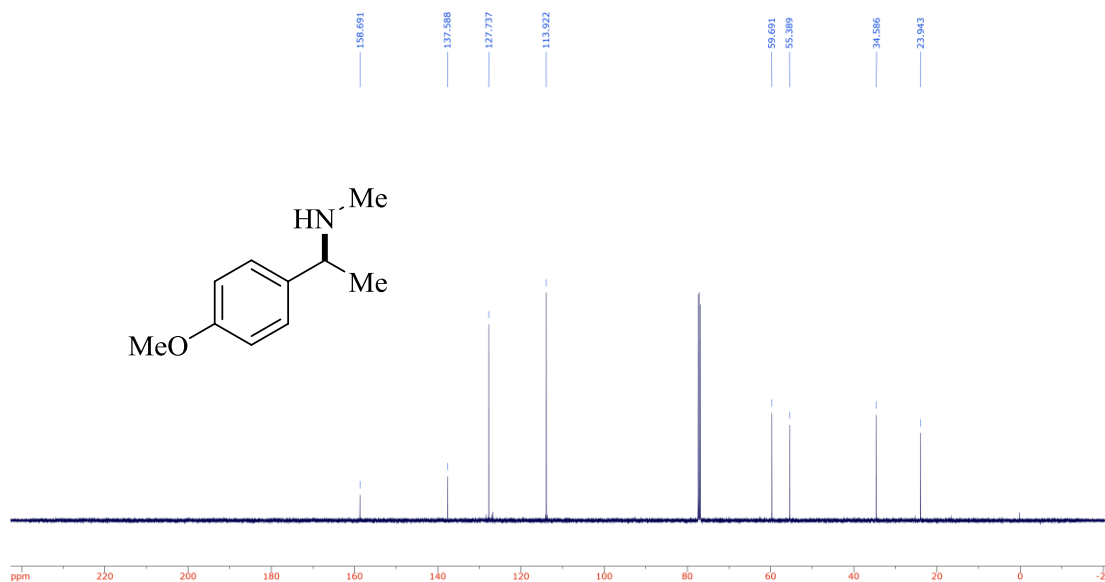


Figure S212. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of 4-43 (125 MHz, CDCl_3).

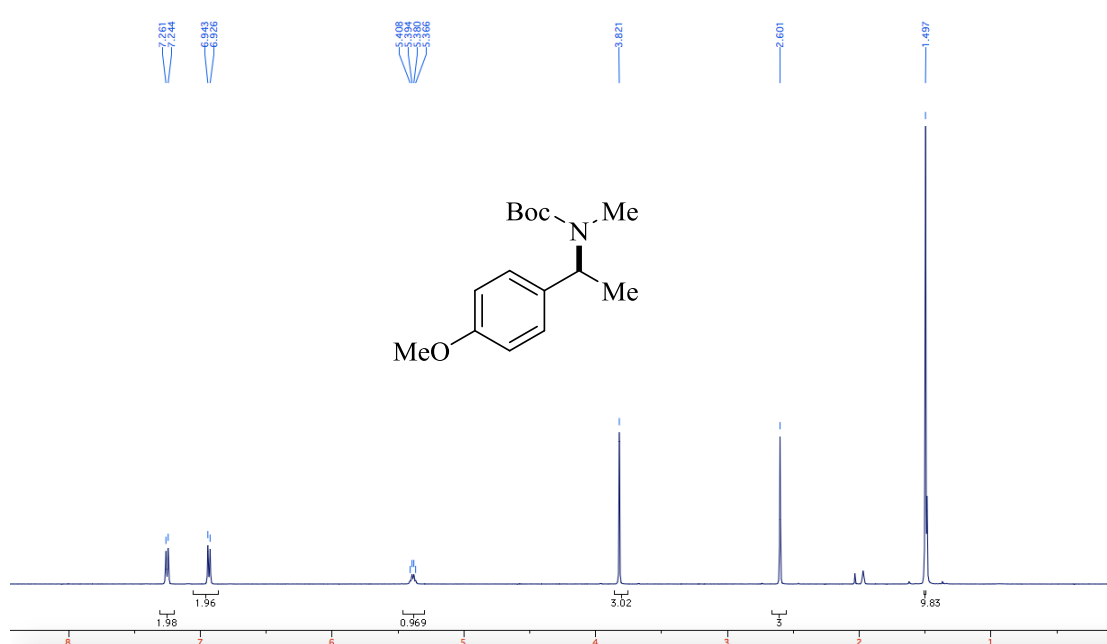


Figure S213. ^1H NMR spectrum of **4-43-Boc** (500 MHz, acetonitrile- d_3 at 338 K).

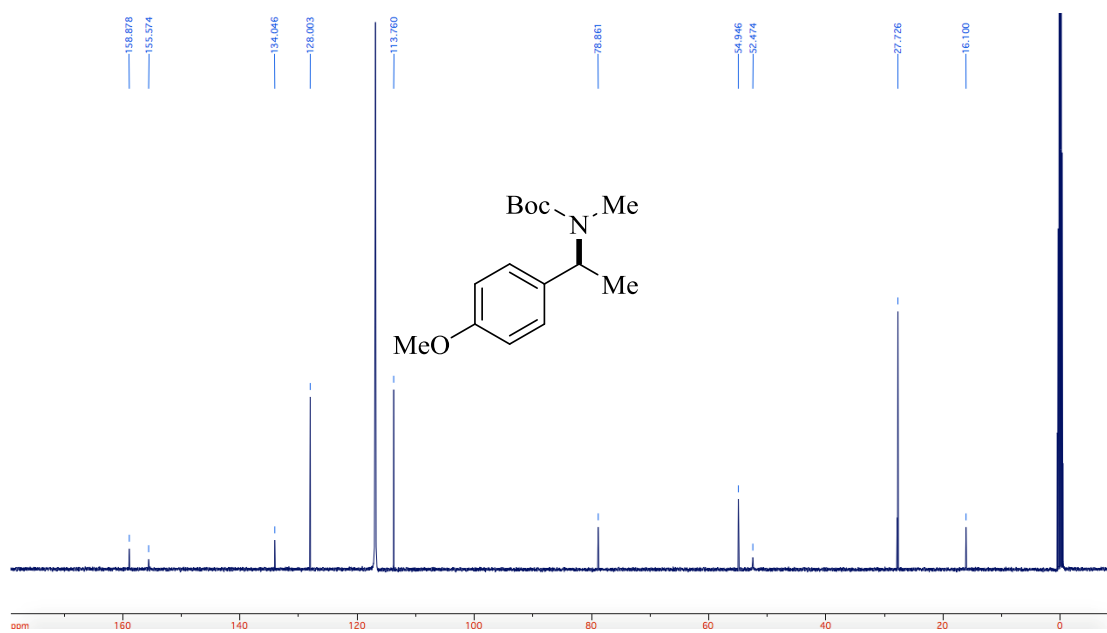


Figure S214. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-43-Boc** (125 MHz, acetonitrile- d_3 at 338 K).

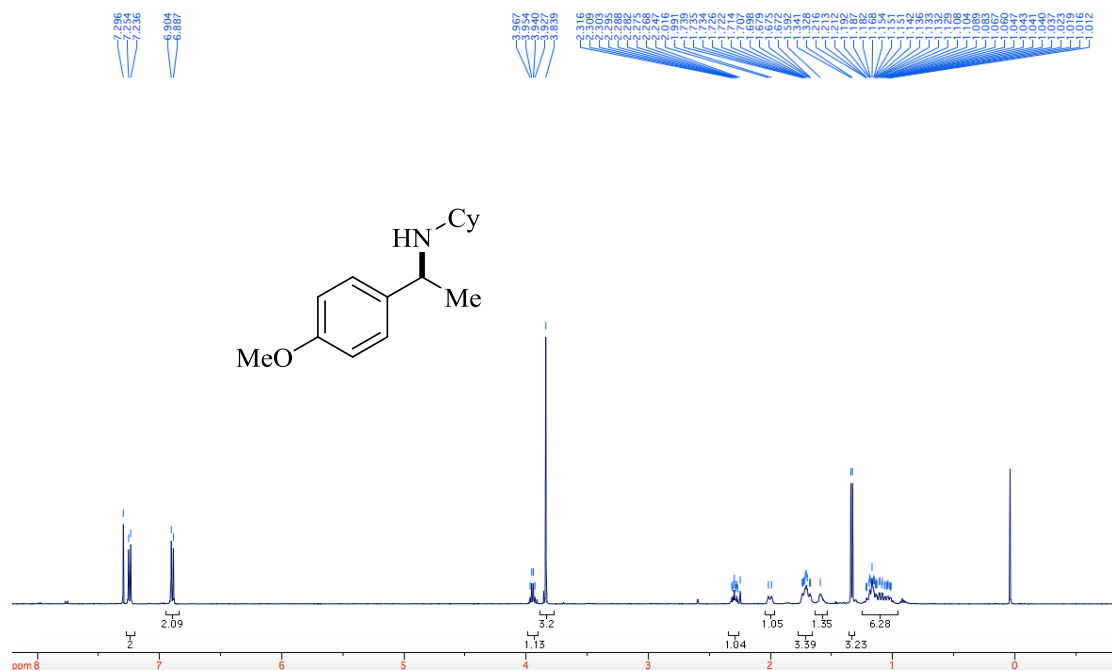


Figure S215. ^1H NMR spectrum of 4-44 (500 MHz, CDCl_3).

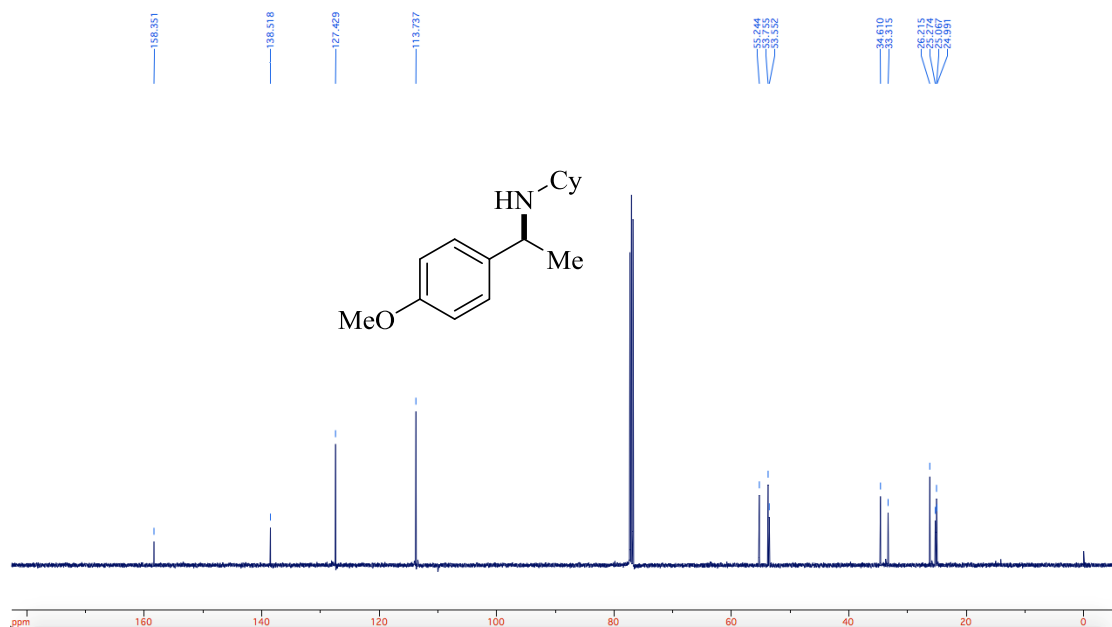


Figure S216. ^{13}C $\{^1\text{H}\}$ NMR spectrum of 4-44 (125 MHz, CDCl_3).

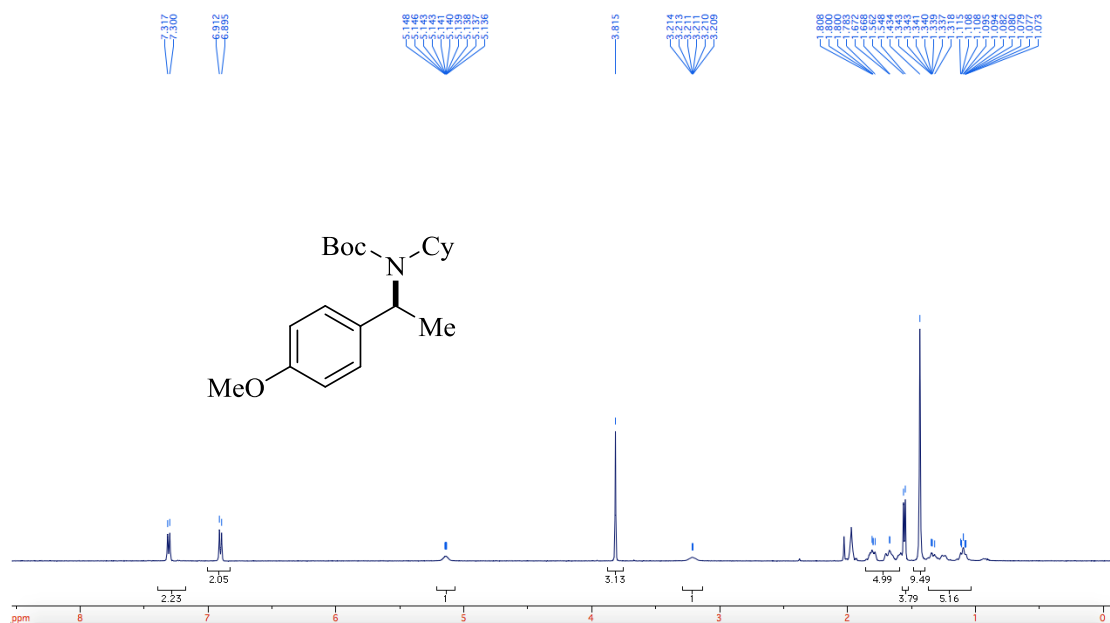


Figure S217. ^1H NMR spectrum of **4-44-Boc** (500 MHz, acetonitrile- d_3 at 338 K).

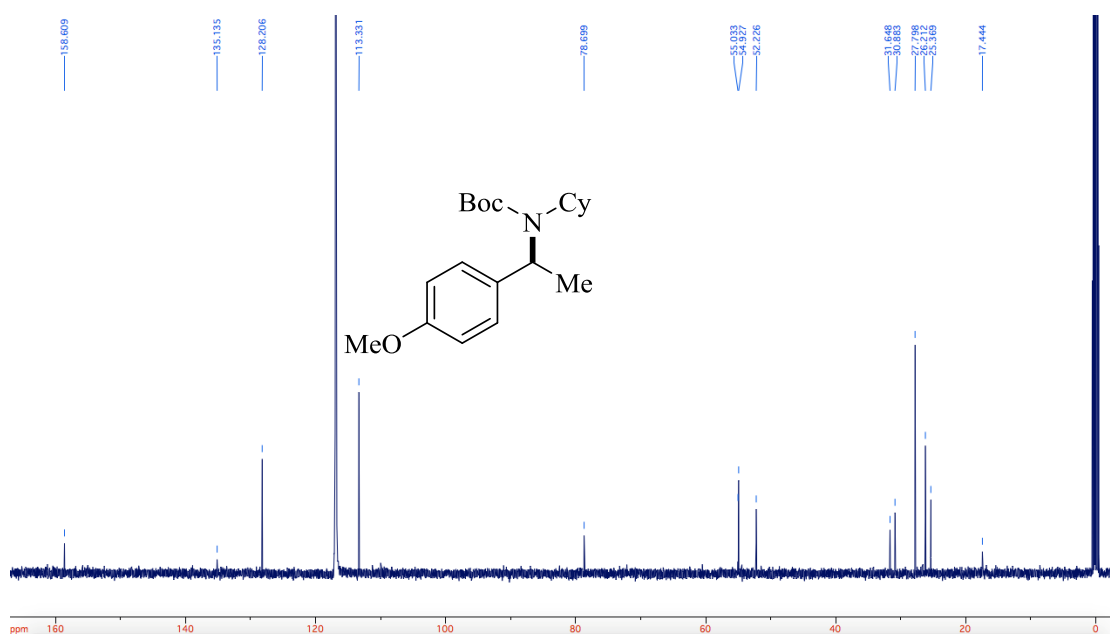
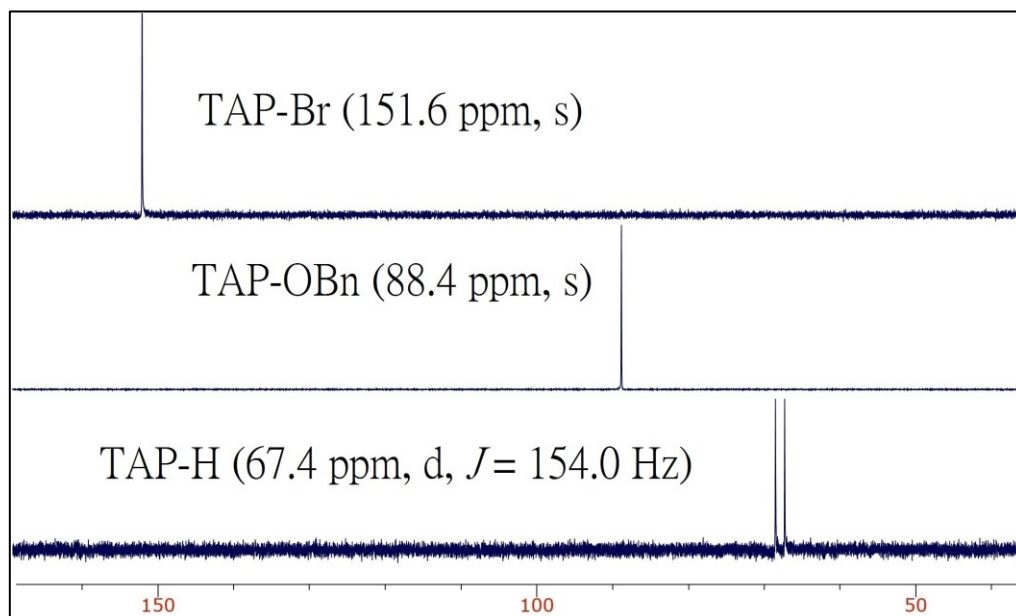


Figure S218. $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of **4-44-Boc** (125 MHz, acetonitrile- d_3 at 338 K).

Appendix B: NMR Mechanistic Studies

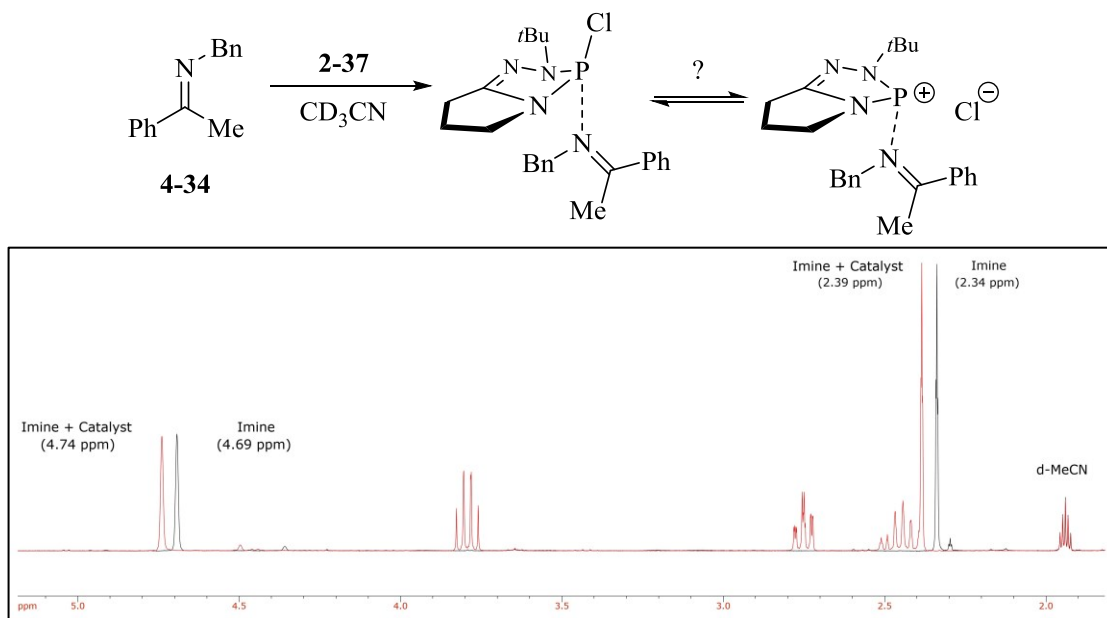
P-H observation: Compounds **2-32** and **2-45** were synthesized according to the synthetic procedure. In the glovebox, compound **2-45** (0.005 g, 0.011 mmol, 1.0 equiv.) was dissolved in CD₃CN (0.5 mL), and HB(cat) (0.011 mL, 0.110 mmol, 10.0 equiv.) was added. The mixture was transferred into an NMR tube and the cap sealed with PTFE tape, then the NMR spectrum was recorded on a Bruker AV-500 NMR spectrometer within 5 minutes of the addition of the borane.



Scheme S1. Observation of TAP-H from TAP-OBn.

Coordination: In the glovebox, **4-34** (9.5 mg, 0.046 mmol, 1.0 equiv.) was dissolved in CD₃CN (0.5 mL), then the mixture was transferred into an NMR tube and the cap sealed with PTFE tape. The NMR spectrum was recorded on a Bruker AV-300 NMR spectrometer. The NMR tube was taken back into the glovebox, and **2-37** (10 mg,

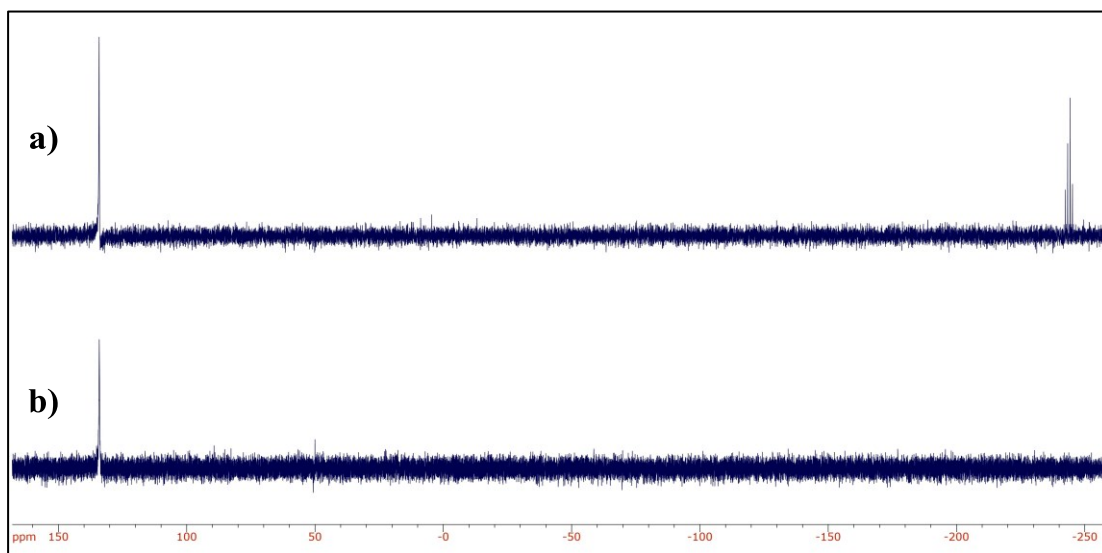
0.046 mmol, 1.0 equiv.) was added, then the mixture was transferred back into the NMR tube and the cap sealed with PTFE tape. The NMR spectrum was recorded on a Bruker AV-300 NMR spectrometer within 10 minutes of addition of **2-37**.



Scheme S2. Observation of coordination behaviour between **2-37** and **4-34**.

Interaction between 2-37 and HB(pin), (a) with or (b) without 4-34: (a) In the glovebox, HB(pin) (0.007 mL, 0.046 mmol, 1.0 equiv.) was added to a mixture of **4-34** (9.5 mg, 0.046 mmol, 1.0 equiv.) and **2-37** (10 mg, 0.046 mmol, 1.0 equiv.) in CD₃CN (0.5 mL). The mixture was transferred into an NMR tube and the cap sealed with PTFE tape. The NMR spectrum was recorded on a Bruker AV-300 NMR spectrometer within 5 minutes of addition of the borane. (b) In the glovebox, HB(pin) (0.007 mL, 0.046 mmol, 1.0 equiv.) was added to a solution of **2-37** (10 mg, 0.046 mmol, 1.0 equiv.) in CD₃CN (0.5 mL), then the mixture was transferred into an NMR tube and the cap sealed

with PTFE tape. Insoluble materials begin to crash out of solution after 30 minutes of addition of the borane, then the NMR spectrum was recorded on a Bruker AV-500 NMR spectrometer.



Scheme S3. Interactions between **2-37** and HB(pin) **a)** with **4-34** or **b)** without **4-34**.

Appendix C: HPLC Traces

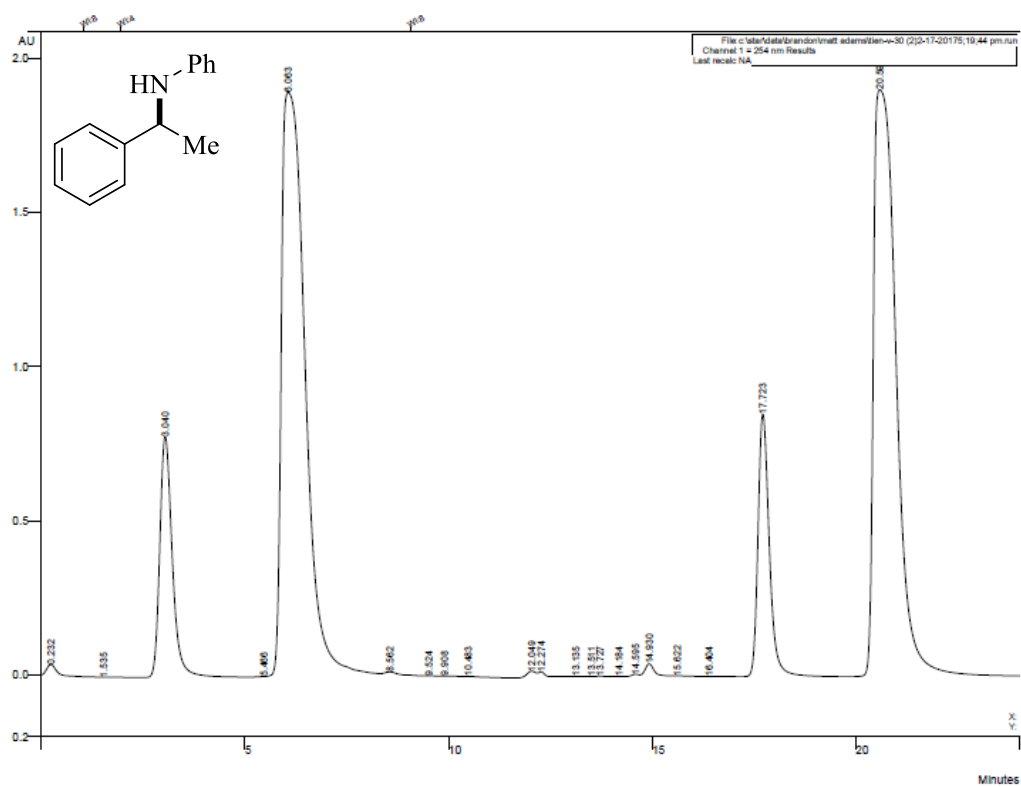


Figure S219. HPLC trace of **4-7** synthesized *via* **3-50**-catalyzed hydroboration (Astec Cellulose DMP column, 99% *n*-hexane and 1% *i*PrOH, 0.55 mL/min).

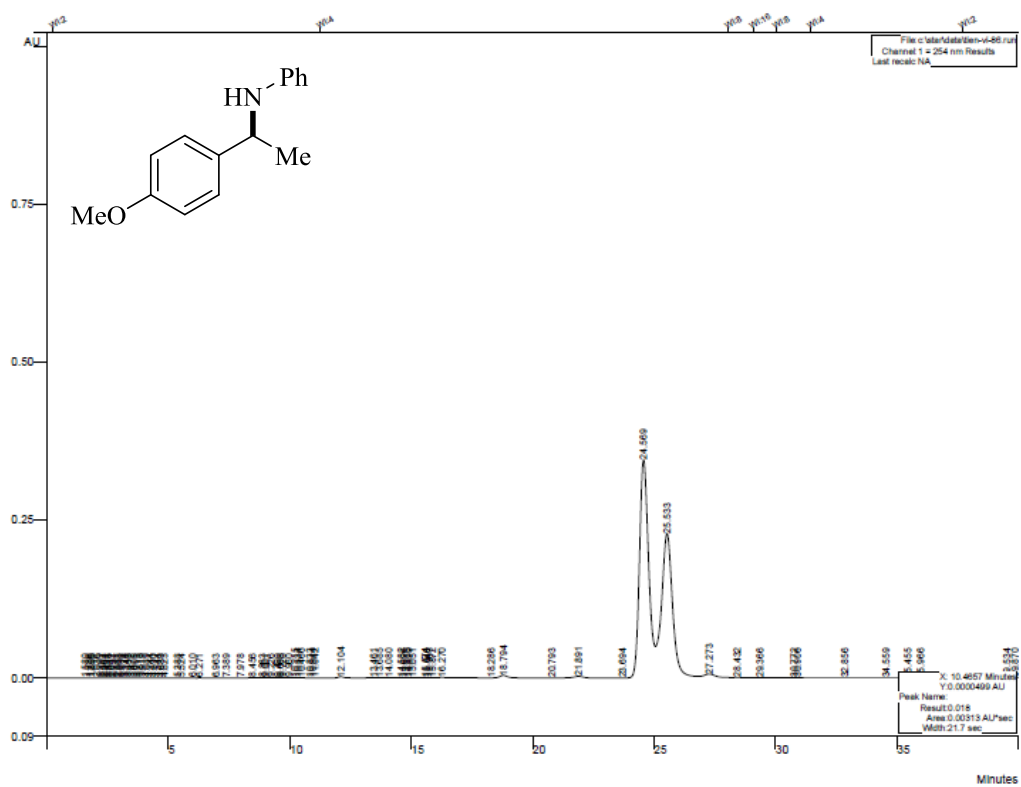


Figure S220. HPLC trace of **4-8** synthesized *via* **4-2**-catalyzed hydroboration (Astec Cellulose DMP column, 99% *n*-hexane and 1% *i*PrOH, 0.55 mL/min).

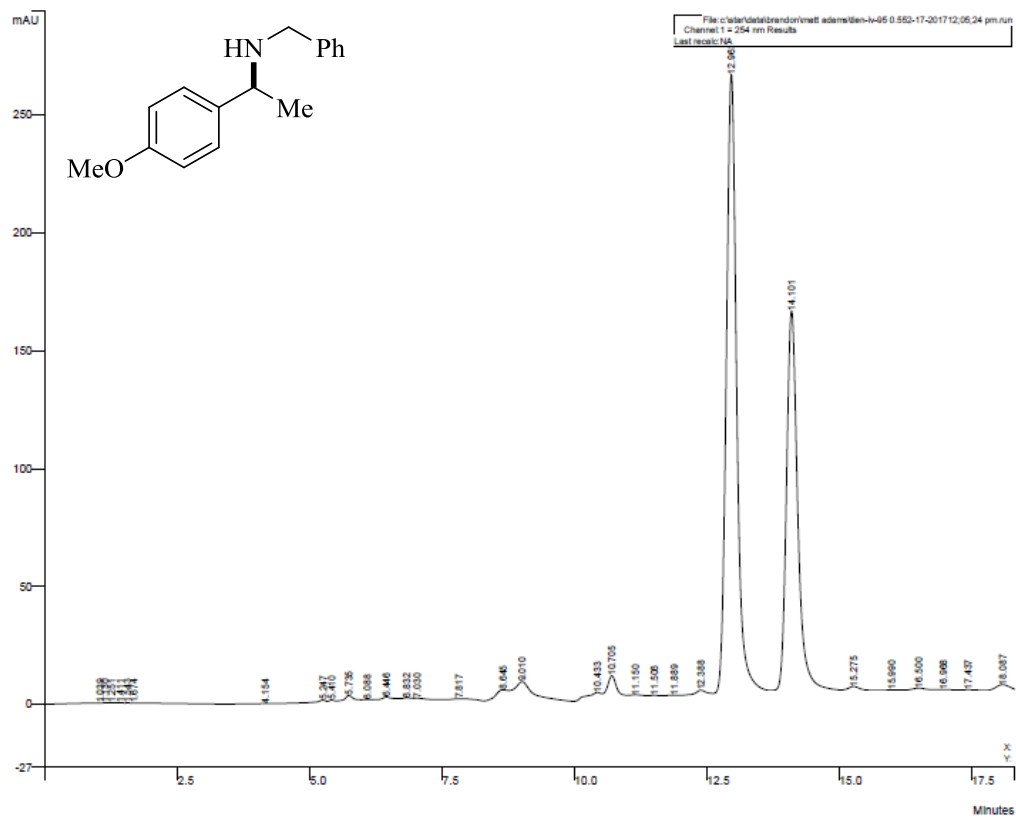


Figure S221. HPLC trace of **4-14** synthesized *via* **3-50**-catalyzed hydroboration (Astec Cellulose DMP column, 99% *n*-hexane and 1% *i*PrOH, 0.55 mL/min).

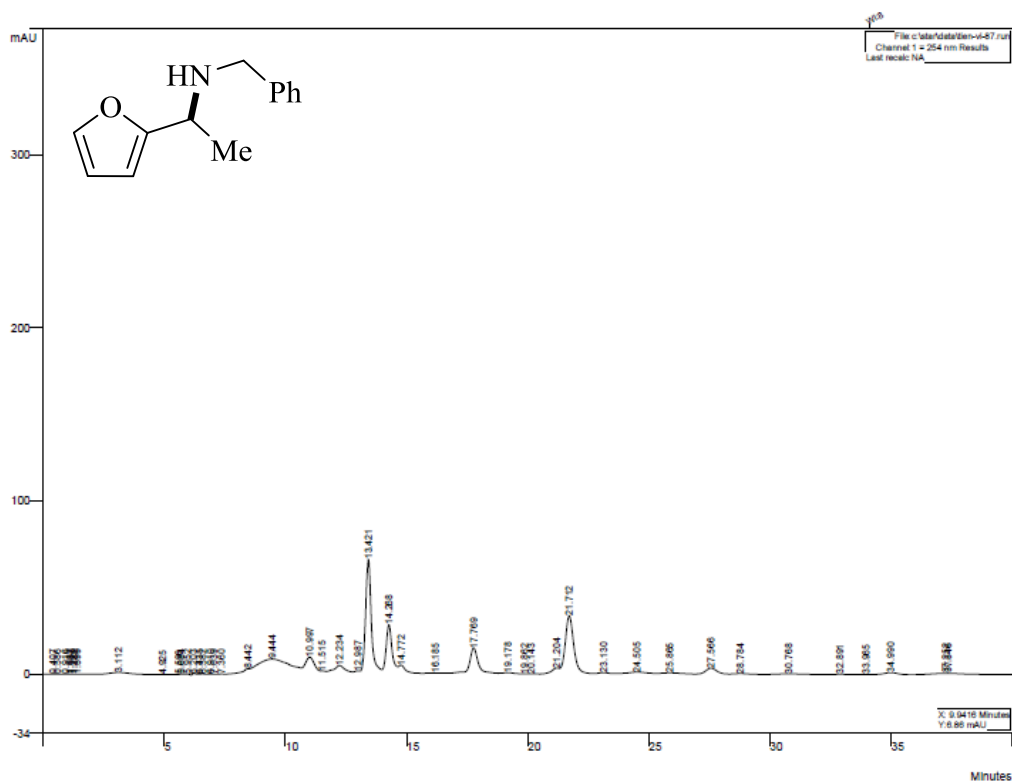


Figure S222. HPLC trace of **4-20** synthesized *via* **4-2**-catalyzed hydroboration (Astec Cellulose DMP column, 99% *n*-hexane and 1% *i*PrOH, 0.55 mL/min).

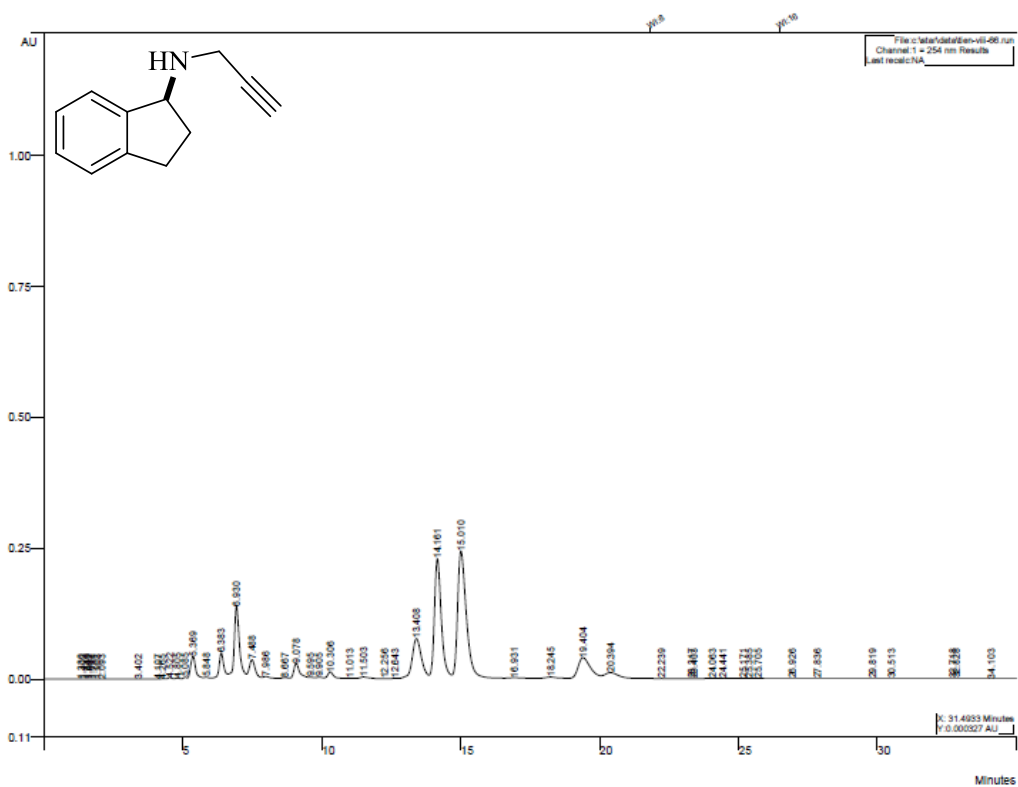


Figure S223. HPLC trace of **4-21** synthesized *via* **3-44**-catalyzed hydroboration (Chiralpak ADH column, 99% *n*-hexane and 1% *i*PrOH, 0.75 mL/min)

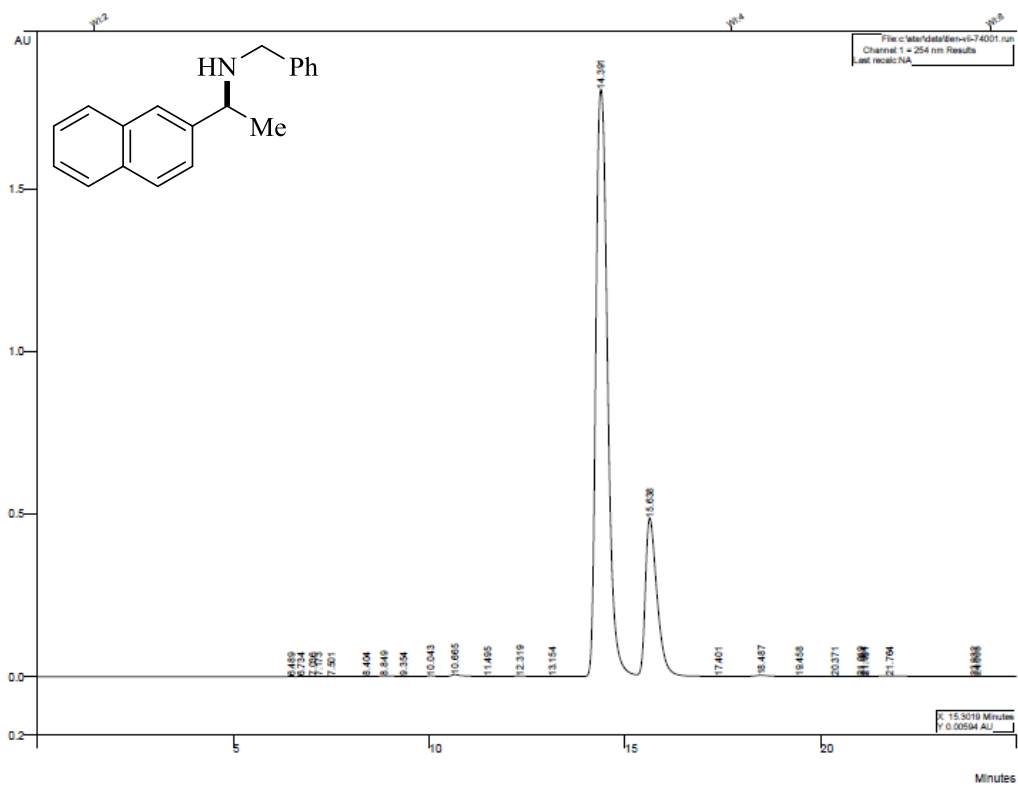


Figure S224. HPLC trace of **4-23** synthesized *via* **4-2**-catalyzed hydroboration (Chiralpak ADH column, 99% *n*-hexane and 1% *i*PrOH, 0.75 mL/min).

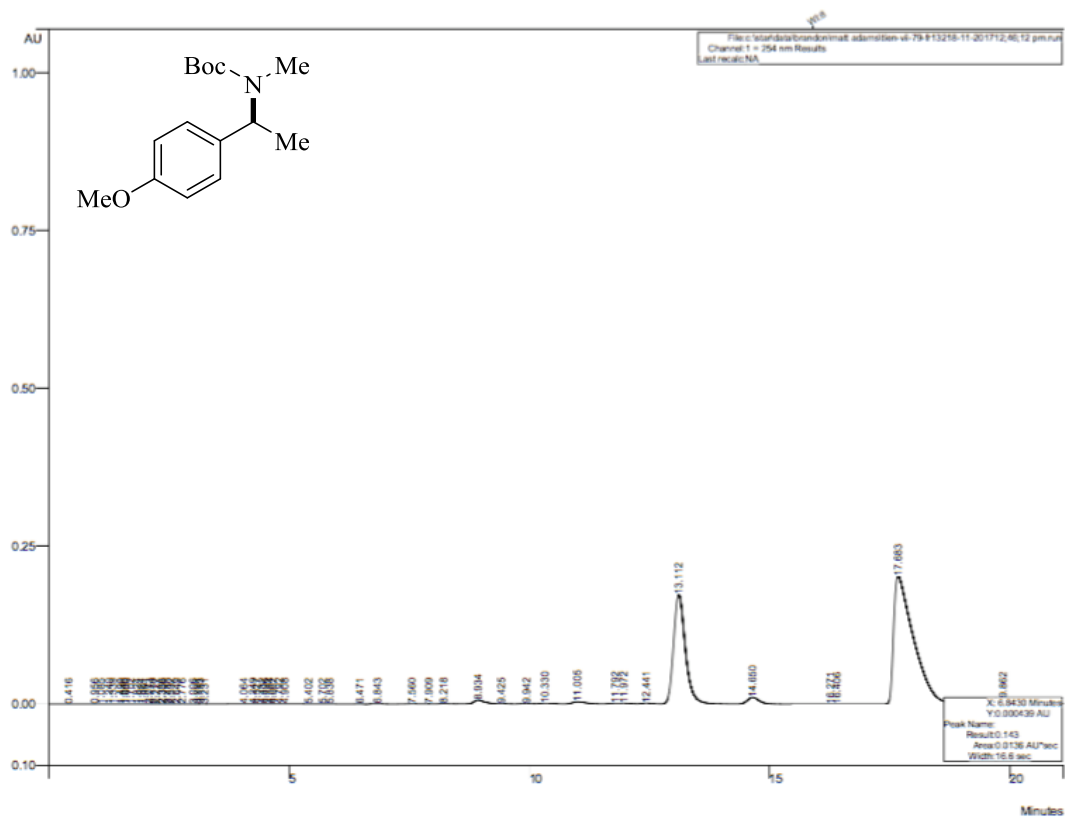


Figure S225. HPLC trace of **4-43-Boc** synthesized *via* **4-2**-catalyzed hydroboration (Chiralpak ADH column, 99% *n*-hexane and 1% *i*PrOH, 0.75 mL/min).

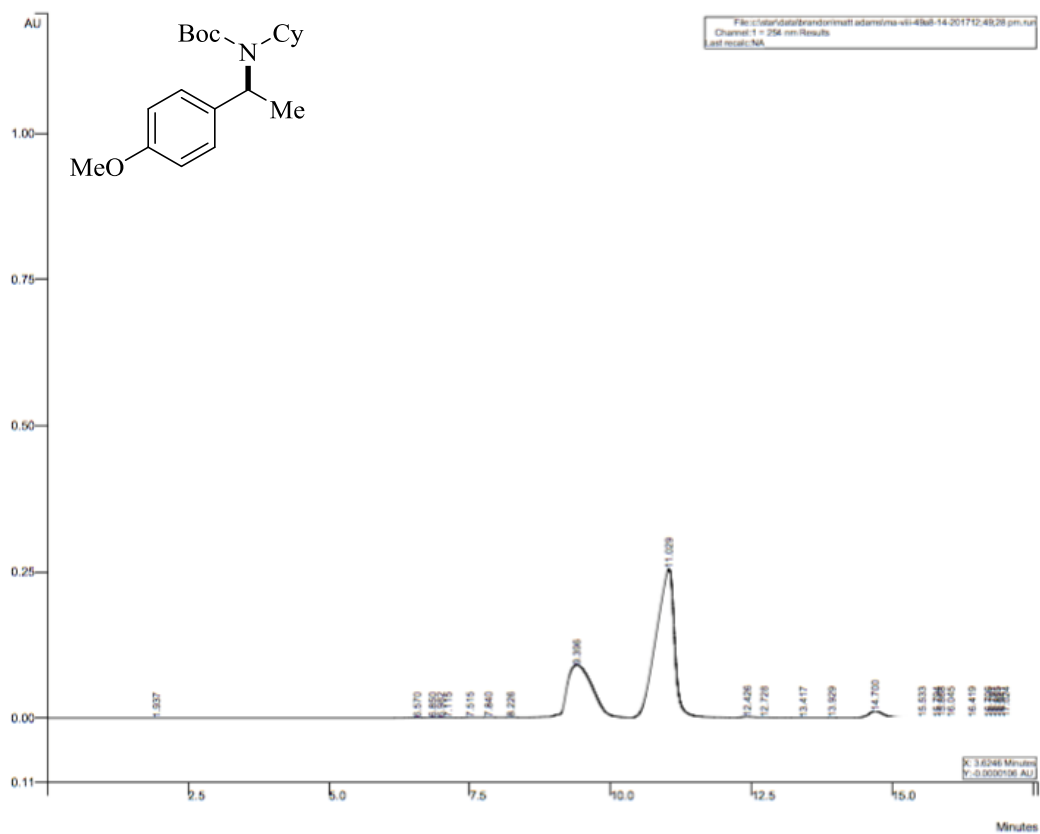


Figure S226. HPLC trace of **4-44-Boc** synthesized *via* **4-2**-catalyzed hydroboration (Chiralpak ADH column, 99% *n*-hexane and 1% *i*PrOH, 0.75 mL/min).

Appendix D: X-Ray Crystallographic Data

3-Bromo-5-(*tert*-butyl)-4-(2,6-diisopropylphenyl)-2-phenyl-1,2,4,3-triaza-

phospholene (2-32):

A. Crystal Data

| | |
|---|--|
| Formula | C ₂₃ H ₃₁ BrN ₃ P |
| Formula weight | 460.39 |
| Crystal dimensions (mm) | 0.33 × 0.30 × 0.10 |
| Crystal system | triclinic |
| Space group | $P\bar{1}$ (No. 2) |
| Unit cell parameters | |
| a (Å) | 9.1345 (4) |
| b (Å) | 14.6643 (7) |
| c (Å) | 18.0325 (8) |
| α (deg.) | 92.0230 (6) |
| β (deg.) | 96.2988 (6) |
| γ (deg.) | 105.0315 (6) |
| V (Å ³) | 2313.62 (18) |
| Z | 4 |
| ρ_{calcd} (g cm ⁻³) | 1.322 |
| μ (mm ⁻¹) | 1.859 |

B. Data Collection and Refinement Conditions

| | |
|----------------------------|---|
| Diffractionmeter | Bruker D8/APEX II CCD |
| Radiation (λ [Å]) | graphite-monochromated Mo K α (0.71073) |

| | |
|--|--|
| Temperature (°C) | -100 |
| Scan type | ω scans (0.3°) (20 s exposures) |
| Data collection 2θ limit (deg.) | 55.15 |
| Total data collected | 20857 ($-11 \leq h \leq 11$, $-18 \leq k \leq 19$, $-23 \leq l \leq 23$) |
| Independent reflections | 10603 ($R_{\text{int}} = 0.0187$) |
| Number of observed reflections (<i>NO</i>) | 8601 [$F_o^2 \geq 2\sigma(F_o^2)$] |
| Structure solution method | intrinsic phasing (<i>SHELXT-2014</i>) |
| Refinement method | full-matrix least-squares on F^2 (<i>SHELXL-2014</i>) |
| Absorption correction method | Gaussian integration (face-indexed) |
| Range of transmission factors | 0.5982 - 0.4348 |
| Data/restraints/parameters | 10603 / 0 / 505 |
| Goodness-of-fit (<i>S</i>) [all data] | 1.044 |
| Final <i>R</i> indices | |
| R_1 [$F_o^2 \geq 2\sigma(F_o^2)$] | 0.0318 |
| wR_2 [all data] | 0.0795 |
| Largest difference peak and hole | 0.586 and -0.511 e Å ⁻³ |

3-Bromo-4*H*-2-phenyl-5-(2-pyridyl)-1,2,4,3-triazaphospholene (2-33):

A. Crystal Data

| | |
|-------------------------|--|
| Formula | C ₁₂ H ₁₀ BrN ₄ P |
| Formula weight | 321.12 |
| Crystal dimensions (mm) | 0.28 × 0.24 × 0.16 |
| Crystal system | triclinic |
| Space group | $P\bar{1}$ (No. 2) |

Unit cell parameters

| | |
|---|--------------|
| a (Å) | 8.2714 (11) |
| b (Å) | 8.3791 (11) |
| c (Å) | 9.3486 (13) |
| α (deg.) | 88.2606 (16) |
| β (deg.) | 78.6579 (16) |
| γ (deg.) | 81.3977 (15) |
| V (Å ³) | 628.12 (15) |
| Z | 2 |
| ρ_{calcd} (g cm ⁻³) | 1.698 |
| μ (mm ⁻¹) | 3.386 |

B. Data Collection and Refinement Conditions

| | |
|---|---|
| Diffractometer | Bruker PLATFORM/APEX II CCD |
| Radiation (λ [Å]) | graphite-monochromated Mo K α (0.71073) |
| Temperature (°C) | -80 |
| Scan type | ω scans (0.3°) (15 s exposures) |
| Data collection 2θ limit (deg.) | 56.61 |
| Total data collected | 5436 ($-11 \leq h \leq 11$, $-11 \leq k \leq 11$, $-12 \leq l \leq 12$) |
| Independent reflections | 3044 ($R_{\text{int}} = 0.0171$) |
| Number of observed reflections (NO) | 2590 [$F_o^2 \geq 2\sigma(F_o^2)$] |
| Structure solution method | Patterson/structure expansion (<i>DIRDIF-2008</i>) |
| Refinement method | full-matrix least-squares on F^2 (<i>SHELXL-2014</i>) |
| Absorption correction method | Gaussian integration (face-indexed) |

| | |
|---|------------------------------------|
| Range of transmission factors | 0.6447 - 0.5053 |
| Data/restraints/parameters | 3044 / 0 / 163 |
| Goodness-of-fit (<i>S</i>) [all data] | 1.072 |
| Final <i>R</i> indices | |
| $R_1 [F_o^2 \geq 2\sigma(F_o^2)]$ | 0.0531 |
| wR_2 [all data] | 0.1747 |
| Largest difference peak and hole | 1.326 and -0.784 e Å ⁻³ |

3-Bromo/Iodo-4-cyclohexyl-2-phenyl-5-thiomethyl-1,2,4,3-triazaphospholene

(2-39):

A. Crystal Data

| | |
|----------------------------|--|
| Formula | C ₁₄ H ₁₉ Br _{0.50} I _{0.50} N ₃ PS |
| Formula weight | 395.76 |
| Crystal dimensions (mm) | 0.25 × 0.18 × 0.15 |
| Crystal system | triclinic |
| Space group | $P\bar{1}$ (No. 2) |
| Unit cell parameters | |
| <i>a</i> (Å) | 8.8228 (9) |
| <i>b</i> (Å) | 9.4847 (10) |
| <i>c</i> (Å) | 10.7342 (11) |
| α (deg.) | 82.0904 (12) |
| β (deg.) | 89.7754 (13) |
| γ (deg.) | 67.7915 (11) |
| <i>V</i> (Å ³) | 822.57 (15) |
| <i>Z</i> | 2 |

| | |
|---|-------|
| ρ_{calcd} (g cm ⁻³) | 1.598 |
| μ (mm ⁻¹) | 2.441 |

B. Data Collection and Refinement Conditions

| | |
|--|---|
| Diffractometer | Bruker D8/APEX II CCD |
| Radiation (λ [Å]) | graphite-monochromated Mo K α (0.71073) |
| Temperature (°C) | -100 |
| Scan type | ω scans (0.3°) (15 s exposures) |
| Data collection 2θ limit (deg.) | 57.05 |
| Total data collected | 8232 ($-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $-14 \leq l \leq 14$) |
| Independent reflections | 4170 ($R_{\text{int}} = 0.0217$) |
| Number of observed reflections (<i>NO</i>) | 4170 [$F_o^2 \geq 2\sigma(F_o^2)$] |
| Structure solution method | intrinsic phasing (<i>SHELXT-201c</i>) |
| Refinement method | full-matrix least-squares on F^2 (<i>SHELXL-2014</i>) |
| Absorption correction method | Gaussian integration (face-indexed) |
| Range of transmission factors | 0.8049 - 0.6610 |
| Data/restraints/parameters | 4170 / 0 / 185 |
| Goodness-of-fit (<i>S</i>) [all data] | 1.027 |
| Final <i>R</i> indices | |
| R_1 [$F_o^2 \geq 2\sigma(F_o^2)$] | 0.0297 |
| wR_2 [all data] | 0.0701 |
| Largest difference peak and hole | 0.691 and -0.335 e Å ⁻³ |

3-Benzyl-2-(*tert*-butyl)-3-oxo-5-(2-pyridyl)-2*H*-1,2,4,3-triazaphosphole • 1.5

MeCN (2-55):*A. Crystal Data*

| | |
|---|---|
| Formula | C ₂₀ H _{25.5} N _{5.5} OP |
| Formula weight | 389.93 |
| Crystal dimensions (mm) | 0.35 × 0.31 × 0.03 |
| Crystal system | trigonal |
| Space group | $P\bar{3}$ (No. 147) |
| Unit cell parameters | |
| <i>a</i> (Å) | 16.4238 (3) |
| <i>c</i> (Å) | 14.0340 (4) |
| <i>V</i> (Å ³) | 3278.38 (15) |
| <i>Z</i> | 6 |
| ρ_{calcd} (g cm ⁻³) | 1.185 |
| μ (mm ⁻¹) | 1.272 |

B. Data Collection and Refinement Conditions

| | |
|--|--|
| Diffractometer | Bruker D8/APEX II CCD |
| Radiation (λ [Å]) | Cu K α (1.54178) (microfocus source) |
| Temperature (°C) | -100 |
| Scan type | ω and ϕ scans (1.0°) (5/5/10 s exposures) |
| Data collection 2θ limit (deg.) | 147.66 |
| Total data collected | 22407 ($-20 \leq h \leq 20$, $-20 \leq k \leq 20$, $-17 \leq l \leq 16$) |
| Independent reflections | 4446 ($R_{\text{int}} = 0.0525$) |
| Number of observed reflections (<i>NO</i>) | 3759 [$F_o^2 \geq 2\sigma(F_o^2)$] |
| Structure solution method | direct methods/dual space (<i>SHELXD</i>) |

| | |
|---------------------------------------|--|
| Refinement method | full-matrix least-squares on F^2 (<i>SHELXL-2014</i>) |
| Absorption correction method | Gaussian integration (face-indexed) |
| Range of transmission factors | 1.0000 - 0.7278 |
| Data/restraints/parameters | 4446 / 0 / 213 |
| Extinction coefficient (x) | 0.00030(9) |
| Goodness-of-fit (S) [all data] | 1.033 |
| Final R indices | |
| R_1 [$F_o^2 \geq 2\sigma(F_o^2)$] | 0.0341 |
| wR_2 [all data] | 0.0975 |
| Largest difference peak and hole | 0.250 and -0.403 e \AA^{-3} |

**1-Bromo-2-(*tert*-butyl)-2,4,6,10b-tetrahydro-1*H*,5a*H*-indeno[2,1-*b*][1,2,4,3]-
triazaphospholo[4,5-*d*][1,4]oxazine (3-39):**

A. Crystal Data

| | |
|-------------------------|--------------------------------|
| Formula | $C_{15}H_{19}BrN_3OP$ |
| Formula weight | 368.21 |
| Crystal dimensions (mm) | $0.51 \times 0.27 \times 0.12$ |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ (No. 19) |
| Unit cell parameters | |
| a (\AA) | 8.6900 (5) |
| b (\AA) | 9.6005 (5) |
| c (\AA) | 19.7725 (11) |
| V (\AA^3) | 1649.59 (16) |

| | |
|---|--|
| Z | 4 |
| ρ_{calcd} (g cm ⁻³) | 1.483 |
| μ (mm ⁻¹) | 2.591 |
| <i>B. Data Collection and Refinement Conditions</i> | |
| Diffractometer | Bruker D8/APEX II CCD |
| Radiation (λ [Å]) | graphite-monochromated Mo K α (0.71073) |
| Temperature (°C) | -100 |
| Scan type | ω scans (0.3°) (20 s exposures) |
| Data collection 2θ limit (deg.) | 56.58 |
| Total data collected | 15513 ($-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $-26 \leq l \leq 26$) |
| Independent reflections | 4061 ($R_{\text{int}} = 0.0199$) |
| Number of observed reflections (<i>NO</i>) | 3716 [$F_o^2 \geq 2\sigma(F_o^2)$] |
| Structure solution method | direct methods/dual space (<i>SHELXD</i>) |
| Refinement method | full-matrix least-squares on F^2 (<i>SHELXL-2014</i>) |
| Absorption correction method | Gaussian integration (face-indexed) |
| Range of transmission factors | 0.7831–0.4349 |
| Data/restraints/parameters | 4061 / 0 / 191 |
| Flack absolute structure parameter | 0.008(7) |
| Goodness-of-fit (<i>R</i>) [all data] | 1.104 |
| Final <i>R</i> indices | |
| R_1 [$F_o^2 \geq 2\sigma(F_o^2)$] | 0.0225 |
| wR_2 [all data] | 0.0573 |
| Largest difference peak and hole | 0.474 and -0.304 e Å ⁻³ |

Appendix E: Optimized Cartesian Coordinates for Scheme 4.7

4-34

C,0,-1.2361152691,1.2208676911,-0.1543346931
C,0,-2.4752912821,0.3650087132,-0.0250693216
C,0,-2.4129632622,-0.9533378188,0.407448902
C,0,-3.7188333575,0.920365189,-0.3160537049
C,0,-3.5746871777,-1.7023221792,0.5478065928
C,0,-4.8102052042,-1.14268233,0.2583171931
C,0,-4.8792747042,0.1752594221,-0.1756538451
H,0,-1.4425552703,-1.3868647634,0.624725033
H,0,-3.7790171684,1.9511788335,-0.6598696276
H,0,-3.5111384015,-2.7329635958,0.885725211
H,0,-5.7171314236,-1.7303897008,0.3671668966
H,0,-5.8410724591,0.6230414619,-0.4093940449
N,0,-0.0192127988,0.4445322217,-0.1330307764
H,0,-1.2394890929,1.9621956978,0.6579131723
H,0,-1.2994794592,1.7923355883,-1.0913516386
C,0,4.5905555981,-1.4496143882,-0.0063797773
C,0,1.1044992289,1.0375440352,-0.0883909025
C,0,4.6455255873,-0.1695984842,0.5243486666
C,0,3.4052099245,-1.9132982053,-0.5646820983
C,0,3.5236828608,0.6473835923,0.4883051656
C,0,2.2834289214,-1.102005729,-0.5897025776
C,0,2.3313351752,0.1891061272,-0.0660854824
H,0,5.4700776556,-2.0865561686,0.0142396615
H,0,3.356505665,-2.9139366964,-0.9842409822
H,0,5.5656108064,0.1977389632,0.9693340007
H,0,3.5808984452,1.6436867149,0.917117116
H,0,1.3493969563,-1.4519568458,-1.0166881234
C,0,1.2690743098,2.5369481232,-0.0486640019
H,0,0.5308315109,3.0245711176,-0.689453631
H,0,2.2607440929,2.8439821743,-0.3823969494
H,0,1.1181905923,2.9130972388,0.969530567

Complex I

C,0,-1.9810253794,-1.155292023,-1.9390959549

C,0,-3.1225892702,-0.4339911724,-1.2610911412
C,0,-3.8753704269,0.5064347056,-1.9568588791
C,0,-3.4508817738,-0.7204787661,0.0621551994
C,0,-4.9415591195,1.1495416133,-1.3421494854
C,0,-5.2617044534,0.8607860439,-0.0225467589
C,0,-4.5146459718,-0.0767172605,0.6789222487
H,0,-3.6290842535,0.737461376,-2.9903787769
H,0,-2.8735497152,-1.4558209501,0.6176989713
H,0,-5.5229836339,1.8795549343,-1.8967511077
H,0,-6.0952250493,1.363243598,0.4582323214
H,0,-4.7651383212,-0.311968695,1.7089779967
N,0,-0.8326991735,-1.2137914677,-1.0485925411
H,0,-1.6860130446,-0.6020274083,-2.8375952417
H,0,-2.3046775527,-2.1460600623,-2.2701699649
C,0,2.6906989414,-2.333903391,2.3493368457
C,0,-0.3378276533,-2.3271948025,-0.6609373329
C,0,2.8268450547,-3.1530265646,1.2333195272
C,0,1.5888054297,-1.4976327177,2.465506747
C,0,1.8526272372,-3.1510677425,0.2473979872
C,0,0.6235500252,-1.4801984624,1.4687441702
C,0,0.7459309521,-2.3071940534,0.3560427509
H,0,3.4416432578,-2.3558426884,3.1332062641
H,0,1.4756572276,-0.8593449524,3.3361338377
H,0,3.6869035855,-3.8088615616,1.1407768713
H,0,1.9568069562,-3.8097241687,-0.61102598
H,0,-0.2489054988,-0.8415598235,1.5632312496
C,0,-0.824779711,-3.6761067312,-1.1271314608
H,0,-0.7418351051,-3.7802079062,-2.2125393986
H,0,-1.8770016777,-3.8106823575,-0.8591055854
H,0,-0.2617956113,-4.4799442139,-0.6544793254
H,0,4.2053919652,1.1529682777,-1.8482299388
H,0,0.1660532353,4.4777547274,0.737383997
H,0,4.2533379744,1.3149134435,0.5515532322
H,0,2.2959233279,0.2529666462,-2.9539973398
C,0,3.8068351984,0.2669205213,-1.3466012404
H,0,-1.784121095,3.4425713811,-0.5168101774

C,0,-0.149589206,3.9241491612,1.6264021709
C,0,3.5695831022,0.5706109491,0.1417848085
P,0,-0.0771470054,1.1054142173,-1.0275149068
N,0,1.5340667576,0.6944730563,-1.0316905455
C,0,2.4194483837,-0.0630315895,-1.9171019536
H,0,0.7205283129,3.7638228089,2.2651097213
H,0,-0.8732566819,4.5353145555,2.1715010536
C,0,2.1562093648,1.0425653494,0.1394458648
N,0,0.18722513,1.8252591932,0.4415938053
C,0,-2.0287574831,2.852401455,0.3725291667
N,0,1.4277786515,1.6675088983,0.9946205017
H,0,4.5110822721,-0.5513780835,-1.5016726289
C,0,-0.802230282,2.6021578181,1.2379941354
H,0,-2.7579986926,3.4203992484,0.9544897401
H,0,3.6367842144,-0.3328014872,0.755473619
H,0,2.1797353493,-1.126904453,-1.8341994291
H,0,-2.5193488525,1.9237251852,0.065985994
C,0,-1.1729417469,1.7860315064,2.470669426
H,0,-0.2794940008,1.5191739081,3.0409296488
H,0,-1.8277093306,2.3749587376,3.1179273817
H,0,-1.7106651346,0.8763022397,2.1874798394

HB(pin)

B,0,-1.2904551115,-0.0434616812,0.0111092987
C,0,0.8131619734,0.7739062445,-0.0687601399
C,0,0.8439666467,-0.7786284734,0.0700864155
O,0,-0.5622962169,1.0252224861,-0.4298464323
O,0,-0.5170970136,-1.0830458452,0.4446170721
H,0,-2.4799160756,-0.0665530643,0.0169204026
C,0,1.0585118653,1.4961127849,1.2495998361
C,0,1.1041872782,-1.4909915064,-1.250773695
C,0,1.7152343001,1.3357098414,-1.1501940863
C,0,1.7777415856,-1.3048417897,1.1424793581
H,0,0.4413726495,-1.1209538639,-2.0379371284
H,0,0.9107517497,-2.5582786794,-1.1189485815
H,0,2.1399866144,-1.3638203037,-1.5769407732
H,0,1.449831595,0.948447696,-2.1349890935
H,0,2.761994321,1.0912118975,-0.9445908575

H,0,1.6177217822,2.4238077658,-1.1768938855
H,0,1.7227884469,-2.3959001807,1.169883453
H,0,1.5071959284,-0.9280267282,2.1299228276
H,0,2.8121578825,-1.0199437989,0.9266675442
H,0,2.1016106201,1.409258234,1.5655703722
H,0,0.4182896832,1.1008374935,2.0431678779
H,0,0.8225694957,2.5550714714,1.1198502153

Complex II

C,0,0.3867369133,-0.5034887256,-0.7982269624
C,0,1.7496251994,-1.0914387537,-1.0793410959
C,0,1.9082160765,-2.4710509195,-0.9722049074
C,0,2.8333023466,-0.3170556556,-1.4779358506
C,0,3.1267305499,-3.0657579599,-1.2641851163
C,0,4.2079747332,-2.2849114973,-1.6547470369
C,0,4.0586101981,-0.9097790856,-1.759560374
H,0,1.0708065007,-3.0831917405,-0.6468533487
H,0,2.7332603422,0.7617864556,-1.5709819461
H,0,3.2347361274,-4.1427143465,-1.1790130816
H,0,5.1631843904,-2.7486611055,-1.8799894019
H,0,4.8966822909,-0.2934752572,-2.0711175177
N,0,0.4436994091,0.8624154214,-0.2869603948
C,0,0.6909125508,5.7869684919,0.5541860907
C,0,0.2561965539,1.8757083878,-1.060192669
C,0,-0.4974308702,5.419684719,-0.066041535
C,0,1.7442839004,4.8868397427,0.6336113492
C,0,-0.6345286564,4.1536455641,-0.6123148916
C,0,1.6014033606,3.6090712481,0.1137522403
C,0,0.4088464751,3.237329099,-0.5017210251
H,0,0.799181774,6.7848118824,0.9672841819
H,0,2.6798672422,5.1816074466,1.0981908401
H,0,-1.3177331657,6.127053432,-0.13223152
H,0,-1.5607239074,3.8700444598,-1.1051322192
H,0,2.4304207999,2.9069857969,0.1538738529
C,0,-0.0688249347,1.7459005397,-2.5165910938
H,0,-0.9897500465,1.1774618033,-2.676961921
H,0,0.7343467324,1.2071659394,-3.0296121094
H,0,-0.1643157471,2.7307820221,-2.9722508322

H,0,4.2875828175,-0.1461591596,3.5833535105
H,0,-1.0331602881,-0.2136909373,4.7622158691
H,0,3.3811079567,-2.3270114732,3.0676482962
H,0,3.601732001,1.7741635427,2.3495713678
C,0,4.1899639853,-0.3421155636,2.5118619033
H,0,-1.9441106802,1.4943226301,3.1555873362
C,0,-1.4912119976,-0.9993852397,4.1540544283
C,0,3.2983088421,-1.5725155035,2.2847202111
P,0,0.5382457197,1.0940938215,1.7406069056
N,0,2.0458087028,0.3954592993,1.9731430383
C,0,3.4364454681,0.8190304302,1.8470208544
H,0,-0.922363275,-1.9213943171,4.2912228764
H,0,-2.5103233804,-1.1638811224,4.514160954
C,0,1.9407583649,-0.9581697493,2.2312402282
N,0,-0.1237577404,-0.3523930027,2.2451589256
C,0,-2.3146166214,0.6927389614,2.50911129
N,0,0.7586004459,-1.4181575044,2.3884928225
H,0,5.1917718713,-0.4652159634,2.0980191077
C,0,-1.5178864136,-0.5940953936,2.6833882078
H,0,-3.356516259,0.5039573366,2.7784362795
H,0,3.5131496536,-2.0471797641,1.3218971987
H,0,3.7056055767,0.9142314957,0.7898755768
H,0,-2.3082056881,1.0420893277,1.4708261602
C,0,-2.1215135665,-1.7063528375,1.832123987
H,0,-1.4964404046,-2.6020169663,1.8694806212
H,0,-3.1165388154,-1.963112052,2.2045922271
H,0,-2.233714079,-1.3869157171,0.7924979055
H,0,-0.1143626843,-1.1094323544,-0.0410020172
H,0,-0.2401990927,-0.5387478477,-1.6921688658
H,0,-2.9776033445,0.8951151911,-0.8740535273
H,0,-2.2194548285,-2.7812028149,-1.2290038665
H,0,-4.4088608169,-3.4649167453,-1.018418113
C,0,-2.2162647407,-2.8559982304,-2.3202626481
H,0,-2.5377619477,-3.8632143334,-2.5960970266
H,0,-1.190900196,-2.7206168928,-2.6757529186
C,0,-5.0527809015,-3.0712670305,-1.8064652534
O,0,-4.3754899322,-0.8320572197,-1.2271371629
B,0,-3.2916873438,-0.068472747,-1.5046163667

H,0,-6.0526106018,-2.9332443878,-1.3887841908
H,0,-5.1199177567,-3.8105501472,-2.6100283745
C,0,-4.5426582278,-1.7479629457,-2.3401897688
O,0,-2.5605035726,-0.5074129501,-2.5741139065
C,0,-3.1086880446,-1.7990579566,-2.9561641393
C,0,-5.5713215355,-1.1166626732,-3.2669977793
C,0,-3.0673288372,-1.9174907438,-4.4661348036
H,0,-6.4902146376,-0.9384031473,-2.7040209489
H,0,-2.0287586036,-1.9374988212,-4.8059063086
H,0,-3.5466786111,-2.8455379006,-4.7907527228
H,0,-5.8051044964,-1.7729986885,-4.1089216031
H,0,-5.2228540011,-0.1568636832,-3.6587744978
H,0,-3.5677645804,-1.0778369129,-4.9500729837

TS I

C,0,1.4331596568,-0.6071242212,-1.6709508222
C,0,2.9163884542,-0.4567388936,-1.4530860312
C,0,3.6891669456,-1.6033181078,-1.2925897739
C,0,3.5408053627,0.7855807301,-1.4444610616
C,0,5.0611207895,-1.5094345968,-1.1066680389
C,0,5.675419613,-0.2636722482,-1.0746407236
C,0,4.9127782147,0.8829583342,-1.2488512512
H,0,3.2116893607,-2.5802308499,-1.3183856224
H,0,2.9559527269,1.688776065,-1.5949450308
H,0,5.6530872345,-2.4116128208,-0.9860152732
H,0,6.7476639839,-0.1877080632,-0.9244266949
H,0,5.3887399323,1.8587793776,-1.2413895362
N,0,0.6692103613,0.5039970535,-1.0864476716
C,0,-1.3728213018,5.1318583289,-0.6271385917
C,0,-0.2627077591,1.1713871293,-1.7551525815
C,0,-2.3519825303,4.2321834066,-1.0340192439
C,0,-0.0458091271,4.7332786613,-0.5630139237
C,0,-2.005466152,2.9372689296,-1.3750617873
C,0,0.3037571577,3.4323647437,-0.8917839843
C,0,-0.6758206366,2.5246472858,-1.291294131
H,0,-1.64683633,6.1488164336,-0.3646316166
H,0,0.7225693069,5.4367356469,-0.2591299487
H,0,-3.3906438307,4.5422309251,-1.0840845804

H,0,-2.7729773662,2.2274147926,-1.6712455213
H,0,1.3448350186,3.1271336664,-0.8512706884
C,0,-0.611834763,0.8048405722,-3.1570350191
H,0,-0.7977240735,-0.2675879739,-3.2385694389
H,0,0.2193947924,1.0893048613,-3.8131219042
H,0,-1.48806544,1.366840579,-3.4779955569
H,0,2.7117559954,-1.5751436181,3.6677272777
H,0,-0.2216784607,1.2103435184,3.1072007918
H,0,1.5826761269,-3.4213755948,2.5919408408
H,0,2.9679652276,0.4774034546,2.5277637029
C,0,3.0066491177,-1.7193053548,2.6244921858
H,0,-1.9404165492,1.884838731,1.3051033717
C,0,-0.7821743109,0.2896839603,3.3011866012
C,0,2.0115766522,-2.6652921991,1.9343215812
P,0,0.4789834151,0.6746119717,0.6928573975
N,0,1.5677618914,-0.4670424789,1.2579793079
C,0,2.9018721869,-0.3872054376,1.8626700611
H,0,-0.0900286228,-0.5121818312,3.5727536011
H,0,-1.4062407383,0.4828044438,4.1770012792
C,0,0.9838232406,-1.7059960453,1.4389838311
N,0,-0.8543872164,-0.5775971391,0.9298767256
C,0,-2.5489563346,1.0701779112,1.7119262546
N,0,-0.2679998997,-1.8441481111,1.2627930173
H,0,4.0258466529,-2.1076792817,2.6174022541
C,0,-1.7027117991,-0.1183234707,2.1481855265
H,0,-3.069342664,1.4621482366,2.5895760971
H,0,2.4692836081,-3.1715146187,1.0788538828
H,0,3.662285745,-0.2927366733,1.0855569435
H,0,-3.2966852244,0.7755107995,0.9743651222
C,0,-2.5786260218,-1.2669795568,2.6394025315
H,0,-1.9768701368,-2.0690799544,3.0693555048
H,0,-3.2315034219,-0.8702612771,3.4220200136
H,0,-3.1976334882,-1.668281254,1.8408379033
H,0,1.0580700865,-1.5476083505,-1.2639255979
H,0,1.2189640182,-0.6375400937,-2.7390319047
H,0,-1.7496566609,0.4034488704,-0.9602514911
H,0,-1.8076609165,-3.6594540139,0.3279878965
H,0,-4.1222171237,-3.6183915173,0.1596254131

C,0,-1.6890240183,-3.9281731793,-0.7226410792
H,0,-2.2904711828,-4.8156495341,-0.9383824871
H,0,-0.6377311691,-4.1814382712,-0.8861795926
C,0,-4.4724856255,-3.1300179985,-0.7511039136
O,0,-3.1056000463,-1.2261209502,-0.2418021338
B,0,-1.7992032099,-0.7696919629,-0.512296132
H,0,-5.4006403102,-2.601637117,-0.5190017177
H,0,-4.6980441579,-3.8990443129,-1.4961262635
C,0,-3.4470851352,-2.1473983335,-1.2840568268
O,0,-1.1662966663,-1.6765695241,-1.4039393588
C,0,-2.0674574807,-2.7739553261,-1.6402157585
C,0,-4.0467408042,-1.3443850353,-2.4342349544
C,0,-1.9261654054,-3.2046760051,-3.0891681838
H,0,-4.8977753022,-0.7726636582,-2.0559235993
H,0,-0.9300099361,-3.6247072638,-3.253908454
H,0,-2.6595996887,-3.977502803,-3.3376416726
H,0,-4.3995367218,-1.9907885183,-3.2420817522
H,0,-3.3196251754,-0.6387112485,-2.8478144113
H,0,-2.0633119404,-2.3677527308,-3.7770435826

Intermediate III

C,0,0.7737689043,0.3571839614,-1.6070368379
C,0,2.1642954355,0.0397275244,-2.1053203977
C,0,2.3437447957,-1.0918979913,-2.8963854764
C,0,3.2583073782,0.8549308378,-1.8387723198
C,0,3.5941107728,-1.405299501,-3.411543333
C,0,4.6823323515,-0.586900116,-3.1396817251
C,0,4.5102664271,0.5443893278,-2.3538943244
H,0,1.4940324768,-1.7368414171,-3.1127668194
H,0,3.1359597916,1.7309679395,-1.2107800966
H,0,3.7178403913,-2.2900738578,-4.028856343
H,0,5.6610530607,-0.8281079167,-3.5424556568
H,0,5.3557173392,1.1915210775,-2.140104903
N,0,0.6846135369,1.0360945483,-0.3144101845
C,0,-0.4499223213,3.9649493335,3.6292931324
C,0,0.1188264631,2.4129833601,-0.3471375637
C,0,-1.5402435142,3.5804289983,2.864249061
C,0,0.8329812518,3.8610095576,3.1029995564

C,0,-1.3476536934,3.0823249312,1.5814753792
C,0,1.0203521472,3.3717518259,1.8207477765
C,0,-0.0687559873,2.9676868866,1.0491029218
H,0,-0.5968170076,4.3566294643,4.6311130982
H,0,1.6894288896,4.1723042285,3.6932842219
H,0,-2.5458390725,3.6722594538,3.2636969846
H,0,-2.2007459596,2.7713964061,0.9856997479
H,0,2.0290758286,3.2956241063,1.4230034086
C,0,0.9570408719,3.3500493568,-1.2073690011
H,0,1.1132033809,2.9627449601,-2.2176055428
H,0,1.9353663371,3.5445882797,-0.7637108409
H,0,0.4365298113,4.3070282462,-1.2937608493
H,0,3.5739575314,-3.0262392761,1.907607316
H,0,0.6314954399,-1.2323916322,3.3894254162
H,0,2.1814894262,-4.208973876,0.3143131746
H,0,3.5717174984,-0.6523670105,1.9404977401
C,0,3.5869399525,-2.5931982057,0.9032481259
H,0,-1.2592730732,0.4384728327,2.9908346638
C,0,-0.0699949758,-2.0466662112,3.1867462161
C,0,2.4390126797,-3.1783742013,0.0688909018
P,0,0.6922797217,0.1915010424,1.1179425663
N,0,1.8327881702,-1.0490806056,0.8093003304
C,0,3.2864920439,-1.0895908518,0.9802891636
H,0,0.4720749946,-2.9138898437,2.8049805859
H,0,-0.5147096906,-2.3319928697,4.1429323195
C,0,1.3273306293,-2.2321313841,0.3788896855
N,0,-0.593256207,-1.2517977453,0.86204284
C,0,-1.922255118,-0.4149619913,2.8321984749
N,0,0.0605861808,-2.4275822972,0.3227144895
H,0,4.5661855797,-2.7898966131,0.4651103809
C,0,-1.1978492878,-1.6250405163,2.2525250259
H,0,-2.3277198723,-0.7066394025,3.8043443851
H,0,2.6561398194,-3.1193388857,-1.0019040917
H,0,3.7736373984,-0.5322099163,0.177041548
H,0,-2.7564189955,-0.0887880587,2.2098848569
C,0,-2.1695538534,-2.7842534871,2.0615690884
H,0,-1.6886594315,-3.6313283431,1.5710120453
H,0,-2.5241219443,-3.1004210055,3.0456736514

H,0,-3.0437868614,-2.4975427378,1.4722954559
H,0,0.2078351642,-0.5823634396,-1.5805808164
H,0,0.2589966379,0.9883047738,-2.3386942976
H,0,-0.8750133072,2.3250985227,-0.7987181684
H,0,-4.8988086508,-2.2140223952,-0.9525102101
H,0,-4.5375654693,-0.6722137046,0.6568220519
C,0,-4.4703206282,-1.9381186323,-1.9168820909
H,0,-5.2281027052,-1.406569018,-2.4994683808
H,0,-4.2164653525,-2.8576212584,-2.4487510636
C,0,-4.5954843673,0.2042750712,0.005706792
O,0,-2.2219836014,0.3577173997,-0.1852703844
B,0,-1.7177074608,-0.8944667558,-0.1038601136
H,0,-4.5693283464,1.0986603209,0.633532847
H,0,-5.5566538263,0.1807866641,-0.5129336514
C,0,-3.4406620257,0.2535836702,-0.9823530212
O,0,-2.287938277,-1.8049178219,-0.9125449784
C,0,-3.2251068186,-1.0879304032,-1.7621622589
C,0,-3.5506450075,1.4865442191,-1.8553864798
C,0,-2.5446172915,-0.9117834119,-3.1101997618
H,0,-3.6758840783,2.3737602469,-1.2294521966
H,0,-2.2620181876,-1.8951677061,-3.4926819172
H,0,-3.2167792804,-0.4427668622,-3.8327672173
H,0,-4.4244229783,1.4130087815,-2.5087538588
H,0,-2.665919579,1.6270837082,-2.4785549993
H,0,-1.6410324051,-0.3033026883,-3.0353652535

TS II

C,0,1.1939077191,-0.7989324904,-1.359499966
C,0,2.5769439007,-0.2477637901,-1.6164987392
C,0,3.454452541,-1.0265688517,-2.3674882316
C,0,3.0292681727,0.9662526654,-1.1174430611
C,0,4.7511643287,-0.600885737,-2.6101863009
C,0,5.1915997338,0.6180562031,-2.1100017051
C,0,4.3257427869,1.4021607112,-1.3633026878
H,0,3.115998219,-1.9778065207,-2.7721522269
H,0,2.3656874849,1.602802667,-0.5363454829
H,0,5.4195892317,-1.2203975041,-3.2000778488
H,0,6.2039724361,0.9562371908,-2.3066180397

H,0,4.6564991222,2.3591000192,-0.9702950814
N,0,0.1682395016,0.1399274764,-0.871884576
C,0,-0.8783764489,5.0928872558,-0.2073426555
C,0,-0.3774340901,1.1477948502,-1.8715251801
C,0,-1.9428437805,4.2064459498,-0.2679121595
C,0,0.3579105527,4.7192361311,-0.720962888
C,0,-1.7606572757,2.9429770583,-0.8144327955
C,0,0.5347832069,3.4582395249,-1.2694376028
C,0,-0.5175369828,2.5437702931,-1.2955259754
H,0,-1.0153454888,6.0831803384,0.2158230997
H,0,1.1848605675,5.4228558514,-0.7106730696
H,0,-2.9209773513,4.501247408,0.1001621262
H,0,-2.598391318,2.2530712379,-0.8751504236
H,0,1.4976940152,3.1997098253,-1.6980132926
C,0,0.3376346307,1.1683212311,-3.2163391819
H,0,0.3272493037,0.1960707591,-3.7134560851
H,0,1.3717678411,1.5063975057,-3.154819277
H,0,-0.2061131146,1.8652702603,-3.8586917427
H,0,2.741426851,-0.7167191314,4.0090938222
H,0,-0.472134924,0.763723155,3.4887982807
H,0,1.909279607,-2.8943731693,3.30687421
H,0,2.8617492813,1.0792249572,2.4405441035
C,0,3.0905450773,-1.0340610928,3.0221615241
H,0,-2.0522731589,1.8007184502,1.7692904914
C,0,-1.2272637571,-0.022123114,3.6055721429
C,0,2.2350703854,-2.2079554157,2.5254563874
P,0,0.2631369867,0.6819438804,0.7912388694
N,0,1.5058262735,-0.2386361287,1.4884350321
C,0,2.8463302751,0.0809706701,1.9963036549
H,0,-0.7607312054,-0.9121412874,4.0305930379
H,0,-1.9630559683,0.3471988223,4.3236505236
C,0,1.0928983865,-1.483024757,1.9007575283
N,0,-0.8736581295,-0.7084475667,1.2524884585
C,0,-2.6978435656,0.9211192645,1.8374278379
N,0,-0.1324089879,-1.8203932253,1.8017602471
H,0,4.1483490417,-1.287028525,3.1046414951
C,0,-1.9438712976,-0.3213302212,2.2922867984
H,0,-3.4630513606,1.1362493628,2.5877846973

H,0,2.7553857989,-2.7845742822,1.7528984138
H,0,3.5695259893,0.0502934759,1.1785431384
H,0,-3.1980252467,0.7630701597,0.8829061828
C,0,-2.9052491826,-1.4877176112,2.4615828015
H,0,-2.3730104807,-2.4173048081,2.6699915819
H,0,-3.5675385575,-1.2734040685,3.3042136628
H,0,-3.5278723819,-1.6087500224,1.5733801345
H,0,1.2625166363,-1.6206962151,-0.6446078372
H,0,0.8028612752,-1.2688670973,-2.2633583079
H,0,-1.3963672799,0.8075103882,-2.0563202794
H,0,-3.1372952938,-3.4728154988,0.4494828827
H,0,-4.7264772657,-2.1658934364,-0.4636560369
C,0,-2.7827744113,-3.9303390633,-0.474939783
H,0,-3.6240881073,-4.42648627,-0.9653063964
H,0,-2.0443621365,-4.6892579301,-0.2068735937
C,0,-4.4962070319,-1.8531734653,-1.4828711406
O,0,-2.550485037,-0.6878385676,-0.7023621177
B,0,-1.3460989713,-1.1277116228,-0.2176446793
H,0,-5.0232881573,-0.9163513355,-1.6796253976
H,0,-4.8823486955,-2.6088737665,-2.1725466594
C,0,-3.0072454495,-1.6502096643,-1.6934933491
O,0,-0.9978433952,-2.3674364424,-0.6771521682
C,0,-2.1236514,-2.9146468145,-1.3969818557
C,0,-2.7751150904,-1.0601241326,-3.0761605753
C,0,-1.6008970458,-3.6265325583,-2.6318564666
H,0,-3.2806323103,-0.0933657047,-3.1473986087
H,0,-0.9728960492,-4.4651914201,-2.3225160012
H,0,-2.4261464707,-4.0257322716,-3.2281617531
H,0,-3.189520157,-1.7129843097,-3.8482011721
H,0,-1.7154579835,-0.9141278647,-3.2942218216
H,0,-1.0012653671,-2.9705302278,-3.2647708897

Product 4-11-(Bpin)

B,0,-0.9929185723,-0.4558673874,0.7256210401
C,0,-2.821612176,0.3700101157,-0.301768346
C,0,-2.7861443212,-1.1791895844,-0.4549498855
O,0,-1.9056244471,0.5811524925,0.781806535
O,0,-1.4289510527,-1.4874263776,-0.0898804232

N,0,0.2386924305,-0.3913168688,1.4087817332
C,0,-2.2558990446,1.0983196843,-1.5155303407
C,0,-3.6957492368,-1.8919131365,0.5373080037
C,0,-4.1734233957,0.941981514,0.0767930111
C,0,-3.0377815029,-1.6845720995,-1.8619827894
C,0,0.6753460323,0.9237553484,1.8718698449
C,0,1.1697221842,-1.4996990581,1.61142151
H,0,1.6931387095,-1.2888989681,2.5524594525
C,0,0.4650944698,-2.8381105591,1.7988005106
H,0,-0.0471789196,-3.1587664645,0.8912845503
H,0,-0.2734452281,-2.7670049728,2.6026124121
H,0,1.2021654076,-3.5999526248,2.0668728038
H,0,1.6750172003,0.8094188041,2.3042293276
H,0,0.0195537427,1.2758182109,2.676742264
C,0,0.0443141154,3.1798215426,0.9470657429
H,0,-0.5489874829,3.3382553954,1.8439698909
C,0,0.0861573059,4.1587357819,-0.0370248439
H,0,-0.4604659221,5.0874858366,0.100943547
C,0,0.7311495017,1.9819333961,0.79075336
C,0,0.8152321361,3.9446693045,-1.1979171322
C,0,1.467505891,1.7784865357,-0.3736406651
C,0,1.5060101602,2.7504825798,-1.362108855
H,0,0.8458972711,4.7052824014,-1.9728804267
H,0,2.0830068965,2.5746403581,-2.26569357
H,0,2.0085548052,0.8474292649,-0.51192946
C,0,3.5591953384,-1.3297449237,0.8070429487
H,0,3.8566297699,-1.1166599559,1.8315754602
C,0,4.5192337357,-1.3498147301,-0.1990298265
H,0,5.5599425296,-1.1537054457,0.0425766795
C,0,2.2218420052,-1.5692239172,0.5196414114
C,0,4.1452771059,-1.6141242757,-1.5067244719
C,0,1.8548992854,-1.8397374742,-0.7986983588
C,0,2.8084682554,-1.8611783582,-1.803051804
H,0,4.8909439019,-1.6273985959,-2.296344626
H,0,2.5089696983,-2.0682444806,-2.8266306266
H,0,0.8083861601,-2.0130756019,-1.0353672412
H,0,-2.9880606305,-2.7765596177,-1.8748294376
H,0,-2.2913524681,-1.301727751,-2.5598333736

H,0,-4.031372258,-1.3839311689,-2.2088425068
H,0,-3.5346992198,-1.5204182937,1.5532442737
H,0,-3.464824661,-2.9601346323,0.5235180696
H,0,-4.7509151896,-1.7628220471,0.2806057323
H,0,-4.5174036674,0.549537727,1.0352208254
H,0,-4.9205457266,0.7118211703,-0.6893085771
H,0,-4.096616415,2.0287904238,0.1629427466
H,0,-2.9387323155,1.0520551873,-2.3688172936
H,0,-1.2901900337,0.6795573069,-1.812775154
H,0,-2.0919441587,2.1458019897,-1.251609652

Complex IV

N,0,1.0909576476,0.1029229204,0.0076417245
N,0,0.6720974041,1.3737882121,0.0855513945
C,0,-0.6255990003,1.3770633171,0.0730879761
N,0,-1.2071538587,0.1485472885,-0.0080355519
C,0,-1.6481251764,2.4599877275,0.1164813236
C,0,2.5700399768,-0.1328816432,0.0188279096
C,0,-2.6794758977,0.24904006,-0.0483636013
C,0,2.8098814305,-1.6327041534,-0.0780075818
H,0,-3.0061810324,0.1199017538,-1.0834084736
H,0,-3.1327554273,-0.526297048,0.5697282408
P,0,-0.0782263152,-1.0698188959,-0.0788590842
H,0,2.4207952503,-2.0573096415,-1.0103597749
H,0,2.3921016824,-2.1775057028,0.7761859458
H,0,3.8868604216,-1.8134598235,-0.0726815773
C,0,3.1108528838,0.42376266,1.3306563837
C,0,3.1562114626,0.5932726797,-1.1862849672
H,0,2.7404215372,0.2068821871,-2.1214022582
H,0,4.2374575852,0.4382025754,-1.2047700215
H,0,2.9648055843,1.6666031645,-1.1289628386
H,0,2.6623445333,-0.0831575307,2.1900455377
H,0,2.9193208364,1.4956497495,1.4104850945
H,0,4.1910614637,0.2647169408,1.3673379212
H,0,-1.7173867425,2.9313130691,-0.8695739913
H,0,-1.3935462023,3.2345000267,0.841023073
C,0,-2.9199608645,1.6724657899,0.4755645645
H,0,-3.8212425586,2.1093849275,0.0445227433

H,0,-3.0458466238,1.6462793891,1.5611998889

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a) Copyright permission letter for the work on racemic TAPs:



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