SEQUENTIAL INTERMOLECULAR HYDROAMINATION OF ALKYNES WITH AMINES TOWARDS THE SYNTHESIS OF NITROGEN-CONTAINING COMPOUNDS

by

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Sequential Intermolecular Hydroamination of Alkynes with Amines Towards the Synthesis of Nitrogen-Containing Componds

submitted by Erica Kwei Jen Lui in partial fulfillment of the requirements

the degree of Doctor of Philosophy

in Chemistry

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Abstract

This thesis details the development of sequential intermolecular hydroamination of alkynes with amines followed by other reactions for the synthesis nitrogen-containing compounds, such as amines and heterocycles. The main feature of this thesis is the use of a bis(amidate)bis(amido)titanium complex, also known as the Schafer titanium catalyst, for the catalytic intermolecular hydroamination of terminal and internal alkynes.

The catalytic synthesis of linear secondary amines using the Schafer titanium catalyst was accomplished through an intermolecular hydroamination of terminal alkynes followed by a Pd/C hydrogenation. The clean formation of products allowed for a facile synthesis and isolation of 23 examples of secondary amines in yields of 33-99%. The developed methodology allows for the synthesis of a variety of secondary amines containing aryl or alkyl substituents within a few hours and without the need for column chromatography.

The selective *anti*-Markovnikov hydroamination of alkynes and ammonia remains a challenge. The first example of a hydroamination reaction with *N*-silylamine as an ammonia surrogate is disclosed in this thesis. Synthesis of anhydrous *N*-silylamine was accomplished using gaseous ammonia and *tert*-butyldimethylchlorosilane, which was then reacted with a variety of terminal and internal alkynes, leading to the synthesis of 25 examples of *N*-silylenamines in yields of 54-99%. The synthesis of primary amines (9 examples) was also accomplished upon treatment of the reaction mixture with palladium on carbon (Pd/C) and H_2. The isolation and characterization of key organometallic titanium-imido complexes was performed to probe the mechanism of the hydroamination reaction. Computational studies were also performed to study the preference of the *N*-silylenamine over the *N*-silylimine tautomer.

Upon the remark that *N*-silylenamines were observed exclusively in the majority of cases, it was reasoned that such synthons could be used towards the synthesis of pyridines. Following the reported hydroamination reaction, a large variety of pyridines were formed with the addition of α,β-unsaturated followed by an oxidation event. This methodology allowed for the synthesis of 47 examples of mono-, di-, tri-, tetra-, and penta-substituted pyridines in yields of 11-96%.

Lay Summary

Nitrogen-containing compounds are ubiquitous in all aspects of life. Biologically, for example, both DNA and proteins contain nitrogen in their structures. Furthermore, in the pharmaceutical and chemical companies, nitrogen-containing compounds are also commonly found. In fact 84% of the U.S. Food and Drug Administration approved small molecules by 2014 contained nitrogen in their structure. It is therefore not surprising that efficient and facile methods to make nitrogen-containing compounds are important.

This thesis describes the synthesis of amines and pyridines using a titanium metal catalyst. In particular, the amines synthesized in this thesis are structurally similar to a family of neurotransmitters called trace amines, which includes adrenaline and dopamine, for example. A methodology for the synthesis of a pyridine motif, which is found in nicotine, is also disclosed in this thesis.

Preface

In collaboration and consultation with my supervisor Prof. Dr. Laurel L. Schafer, I designed and conducted all of the experiments described herein, except for specific instances described below. I have written the text of this document entirely with input and suggestions from my supervisor Prof. Dr. Laurel L. Schafer, except for specific instances described below.

A version of the data contained in Chapter 2 has been published: **Lui, E. K. J.**; Schafer, L. L. *Adv. Synth. Catal.* **2016**, *358*, 713-718. I performed this work (experimental and otherwise) in its entirety. This publication was written with input and suggestions from Prof. Schafer.

A version of Chapter 3 has been published: **Lui, E. K. J.**; Brandt, J. W.; Schafer, L. L. *J. Am. Chem. Soc.* **2018**, *140*, 4973-4976. This work (experimental and otherwise) was done in collaboration with former Schafer group colleague Dr. Jason W. Brandt. Dr. Brandt contributed to the synthesis of the (*N*-*tert*-butyldimethylsilyl)amine, to the refinement of the single-crystal molecular structures of titanium complexes **3.1a-c** and to the calculations and conclusions reported in Section 3.2.4. I designed and performed all the other reactions reported in Chapter 3. This publication was written with input and suggestions from Dr. Brandt and Prof. Schafer.

A version of Chapter 4 has been accepted for publication: **Lui, E. K. J.**; Hergesell, D.; Schafer, L. L. *Org. Lett.* **2018**, *Just Accepted Manuscript* (DOI: ol-2018-02703f). This work was done in collaboration with former Schafer group visiting student Daniel Hergesell. While I designed the experiments, Mr. Hergesell contributed experimentally to the screening of reaction conditions listed on Table 4-3 (**4.3b**) and Table 4-4 (**4.4b**, **4.4h-l**, **4.4p**, **4.4r-u**) as well as to the synthesis of compounds **4.1a-e**, **4.1g-i**, **4.1k-o** and **4.1q**. All other screening reactions and substrate scope was performed by me. This publication was written with input and suggestions from Prof. Schafer.

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List of Schemes

List of Symbols

Symbol	Description
°	degree
°C	degrees Celsius
Å	angstrom
δ	chemical shift in ppm
Δ	reflux
ΔG_{calc}	calculated change in Gibbs energy
η^x	eta, denotes hapticity of x atoms
${}^nJ(A,B)$	n-bond coupling constant between atoms A and B (spectral)
κ^x	kappa, denotes denticity of x atoms
μ^x	mu, denotes bridging of ligand to x metal centers

List of Abbreviations

Abbreviation	Description
Ac	acetyl
ACS	American Chemical Society
Alk	generic alkyl group
Ar	generic aryl group
atm	standard atmosphere
bar	metric unit of pressure
Bn	benzyl
BQ	1,4-benzoquinone
Bu	butyl
Calc'd	calculated
cat.	catalyst
CI	chemical ionization
Cl-BQ	tetrachloro-1,4-benzoquinone
Cp	cyclopentadienyl
Cp*	η^5-1,2,3,4,5-pentamethylcyclopentadienyl
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet (spectral)
DCM	dichloromethane
dd	doublet of doublets (spectral)

DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT	density functional theory
DMF	dimethylformamide
dmpa	di(pyrrolyl-α-methyl)methylamine
DMSO	dimethylsulfoxide
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
(*E*)-/(*Z*)-	entgegen ("opposite") / zusammen ("together") (isomers)
EA	elemental analysis
EI	electron impact
ESI	electrospray ionization
equiv.	equivalents
Et	ethyl
et. al	and others
FDA	Food and Drug Administration
FLP	Frustrated Lewis Pair
g	gram
G	Gibbs free energy
GC-MS	gas chromatography mass spectrometry
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz

^{i}Pr	isopropyl
Ind	indenyl
K	kelvin
kcal	kilocalorie
LC	liquid chromatography
LED	light emitting diode
LP	lone pair
LRMS	low resolution mass spectrometry
M	molarity
m	multiplet (spectral)
m-	meta
mm	millimeter
Me	methyl
mL	milliliter
mmol	millimole
MS	molecular sieves
m/z	mass-to-charge ratio
$NaBAr_4^F$	sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
N.D.	not determined
NHC	*N*-heterocycliccarbene
NMR	nuclear magnetic resonance
[O]	oxidation

o-	ortho
ORTEP	Oakridge thermal ellipsoid plot
OTf	triflate
p-	para
p-cymene	1-isopropyl-4-methylbenzene, 4-isopropyltoluene
PET	positron emission tomography
Ph	phenyl
Pr	propyl
py	pyridine
q	quartet (spectral)
quint	quintet (spectral)
RT	room temperature
rac	racemic
s	singlet (spectral)
sec	second
sept	septet (spectral)
t	triplet (spectral)
TASF	tris(dimethylamido)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDMS	tert-butyldimethylsilyl
^{t}Bu	tert-butyl

Tf	triflyl
THF	tetrahydrofuran
tert-	tertiary
temp	temperature
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TMS-	trimethylsilyl (group)
TLC	thin layer chromatography
Tol	toluene (molecule)
Tol-	tolyl (group)
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate

Acknowledgements

I would like to thank my advisor Prof. Dr. Laurel L. Schafer for guiding and supporting me over the years. Graduate school, let alone a Ph.D. degree, would not have been possible without your support, even before I joined the Schafer lab. Thank you for your commitment and dedication in shaping me into becoming the best scientist I could be and for sharing your knowledge and personal experiences with me, which taught me that with perseverance and hard word, I can achieve anything I want.

Many thanks to my former and current colleagues of the Schafer group and around the department for their assistance both in chemistry and non-chemistry areas. Special thanks to my collaborators Dr. Jason W. Brandt and Mr. Daniel Hergesell for fast tracking the projects we worked on together. I would also like to thank the Love lab, which has been my go to refuge when needed. Thank you Weiling Chiu for your friendship and for listening to me whenever I needed to talk.

Thank you to the faculty members that have helped me get to the point I am currently. I would like to thank my committee members, Prof. Dr. Chris Orvig, Prof. Dr. Glenn M. Sammis, and Prof. Dr. Martin E. Tanner for their time and patience throughout the years. I am very thankful to Prof. Dr. Jason E. Hein, Prof. Dr. Jennifer A. Love and Prof. Dr. Glenn M. Sammis for all the encouragement and counseling they have given me.

I would like to thank the many members of the shops and services at the UBC Chemistry department. In particular, I would like to thank Ken Love for his passion and efficiency in fixing and maintaining the various equipments that were used throughout my Ph.D degree. I would also like to thank Dr. Maria Ezhova for her help with a variety of NMR experiments that were crucial for this thesis to be completed. Thank you to Brian Ditchburn for making the necessary

glassware to perform the reactions, specially the ones needed for the liquid ammonia reactions and Milan Coschizza for keeping impeccable notes on the gloveboxes, so that problems could be fixed in a timely fashion.

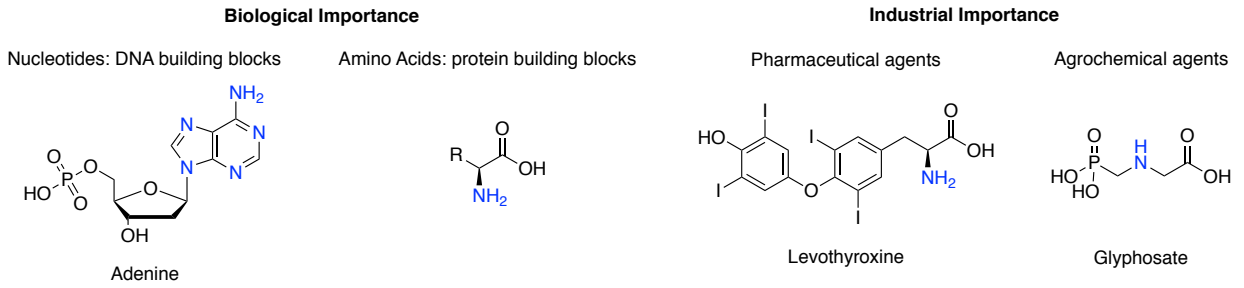
Finally, I would not be where I am today without the support of my family and my boyfriend Jason W. Brandt. Special thanks are owed to my parents, in special my dad Lui Pak Kam who has supported me throughout my years of education, both morally and financially. While a Ph.D. degree was not in the original plans, I hope my mom Perng Shwu Yuh Lui (who passed away years ago, but is always, and will forever be, in my heart) is proud of my achievements.

Dedication

I dedicate this thesis to my parents and my boyfriend Jason.

Chapter 1: Introduction

Nitrogen-containing compounds play an important role in many aspects of biological and industrial processes (Scheme 1.1). Not only are they found in all living organisms, such as the nucleotides and amino acids, but they are also found in a wide variety of pharmaceutical and agrochemical agents. For example, 84% of unique small-molecules approved by the U.S. Food and Drug Administration (FDA) by 2014 were *N*-containing drugs.[1] Furthermore, 90% of heterocycles synthesized by medicinal chemists contains a nitrogen molecule.[2] It is therefore not surprising that continuous research towards more efficient methods of incorporating nitrogen have been reported throughout the years.



Scheme 1.1 Importance of Nitrogen-Containing Compounds

In medicinal chemistry, *N*-substitution or *N*-arylation of alkyl-/aryl-halides and reductive amination remain preferred methods for the construction of C-N bonds.[2] Extensive air and moisture exclusion are usually not necessary for *N*-substitution or reductive amination reactions and thus the reaction set-up is typically straightforward. However, all three methodologies suffer from the production of by-products and/or stoichiometric amounts of waste.

One of the major drawbacks of the substitution reaction is over-alkylation, which delivers complex reaction mixtures of primary, secondary and tertiary amines as well as quaternary ammonium salts. On the other hand, while the condensation of carbonyl functional groups with

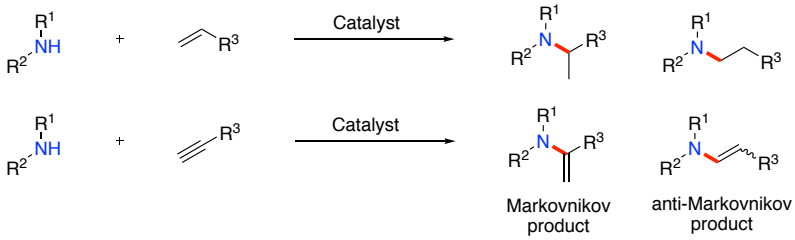
amines could deliver similar products selectively, reductive aminations often involve the use of stoichiometric hydride sources, consequently forming stoichiometric amounts of waste. Furthermore, carbonyl-containing compounds are usually derived from feedstock chemicals, such as alkenes and alkynes. Thus several steps are required to access target amine products.

1.1 Efforts Towards Sustainable Chemistry

1.1.1 Catalysis

In efforts to develop more selective and efficient C-N bond formation protocols, extensive advances in transition metal catalysis have been achieved. Palladium-catalyzed C-N cross coupling, for example, has emerged as a powerful tool for the synthesis of aryl amines.[3] While exceptionally efficient catalytic conditions have been developed, due to the requirement of a halogen or pseudo-halogen starting materials, the reaction inherently produces stoichiometric amounts of waste.

On the other hand, hydrofunctionalization reactions are atom economical. The direct addition of an N-H bond from an amine across an unsaturated C-C bond, also known as hydroamination, is among the various synthetic approaches developed in the past two decades to minimize waste production (Scheme 1.2).[4-5]



Scheme 1.2 General Alkene and Alkyne Hydroamination Reactions

Although the intermolecular hydroamination of alkenes deliver amines directly, its substrate scope remains a significant challenge, even with the recent contribution from the

Knowles research group. Knowles and co-workers reported an intermolecular hydroamination of unactivated alkenes with secondary alkylamines, which delivered 50 examples of tertiary amines with a variety of different substitutents.[6] The transformation was accomplished using an iridium catalyst and a thiol additive, under a blue LED light. Mechanistically, the authors propose that an aminium radical cation intermediate is formed via an electron transfer between an excited state photocatalyst and an amine substrate, which then undergoes a C-N bond formation and quenching of the radical to deliver the desired products.[6]

Alternatively, the intermolecular hydroamination of alkynes has been well developed and a wide range of amines and alkynes can be employed.[4-5, 7-9] To date, some highly selective catalysts deliver either the Markovnikov or the *anti*-Markovnikov product from terminal alkynes. Likewise, the reaction with internal alkynes has also been well studied, although few catalysts are able to perform the intermolecular hydroamination of unsymmetrical alkynes selectively.

For the intermolecular hydroamination of alkynes, depending on the starting materials used, the imine/enamine products formed could be moisture sensitive. Thus, instead of a traditional stepwise synthetic approach, the reactions are commonly incorporated into sequential transformations, as well as one-pot methodologies.

1.1.2 Cascade, Domino, Sequential and Tandem Reactions

The development of methodologies that elaborate simple precursors into more complex structures in more than one step is highly desirable due to the minimization of waste produced by the absence of work-up/purification between various steps.[10-11] While terminology is not used uniformly, there are four major terms used in literature: cascade, domino, sequential and tandem transformations.[12-15] In all cases, the process involves two or more bond-forming events and the

subsequent reactions can only transpire as a consequence of the functionality formed in the preceding steps.

In cascade/domino and tandem transformations all the reagents or catalysts required are added at the onset of the reaction. Meanwhile, in sequential transformations, addition of other reagents or catalysts is usually necessary for the latter reactions to occur. The intermediates in cascade/domino transformations are generally not isolable, which is in contrast with the products formed in the first step of the tandem or sequential reactions. In fact, in the development of sequential reactions, the individual reactions are usually established separately and then attempted in a sequential fashion.[12-15]

Among the reactions commonly performed after an intermolecular hydroamination of alkynes are reductions to form higher molecular amines and cyclizations to form *N*-heterocycles.

1.2 Sequential Reactions Involving Catalytic Intermolecular Hydroamination of Alkynes Towards the Synthesis of Nitrogen-Containing Small Molecules and Heterocycles

Reactions using alkoxyamines, amides, carbonates, hydrazine, sulfonamides, and ureas, as well as formal hydroamination reactions, where the nitrogen and hydrogen source comes from different starting materials, will not be discussed in this chapter. The hydroamination of highly activated substrates that could occur through an aza-Michael reaction will also not be included.

In the case of intermolecular hydroamination of alkynes, two potential regioisomers are possible, Markovnikov and *anti*-Markovnikov. The regioselectivity of the reaction is highly dependent on the catalyst as well as the starting materials used. While no regioisomeric ratios will be provided in this section, a single isomer will be drawn for highly selective reactions, while both isomers will be shown for reactions providing a mixture of products. In this section, "Alk^x" will be used as an abbreviation for alkyl substituents, while "Ar^x" will be used as an

abbreviation for aryl substituents. In cases where more than one functional group is represented, "R^x" will be used as the abbreviation.

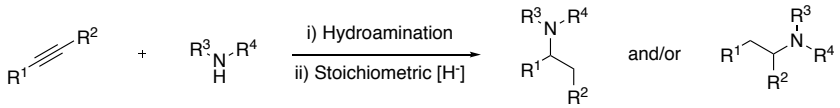
1.2.1 Amine Synthesis

The use of intermolecular alkyne hydroamination for the synthesis of secondary amines has been well established, with procedures that deliver high yields and great selectivity.[4-5, 7-9] In contrast, the synthesis of primary and tertiary amines has not been studied as extensively due to the limited number of catalysts that are able to catalyzed the hydroamination of alkynes using ammonia or secondary amines.

While some sequential hydroamination/reduction reactions implemented stoichiometric amounts of reductant,[16-56] in the past decade, groups have shifted their focus to the employment of catalytic reduction routes, such as metal-catalyzed hydrogenation using H_2,[18, 24, 35-36, 57-61] frustrated Lewis pair hydrogenation,[62] and more recently transfer hydrogenation.[63] Other nucleophiles, such as organolithium reagents,[64-65] trimethylsilyl cyanide,[66-67] and metal-acetylides,[68-71] have also been added to the hydroamination intermediate products to access more complex amine products.

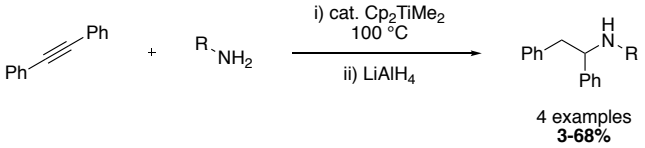
1.2.1.1 Using Stoichiometric Reductants

The ease of using stoichiometric hydride sources to reduce imine/enamine hydroamination intermediates products allowed for the easy isolation of a variety of amines (Scheme 1.3).



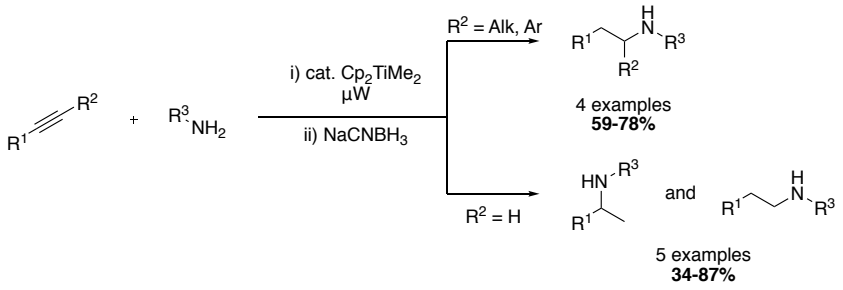
Scheme 1.3 General Sequential Hydroamination/Addition of Hydride Reactions Toward the Synthesis of Amines

In 1999, Doye and co-workers reported the intermolecular hydroamination of diphenylacetylene, which was catalyzed by dimethyltitanocene, followed by reduction with lithium aluminum hydride to synthesize 4 examples of secondary amines (Scheme 1.4).[16] A wide variety of 2-arylethylamines were synthesized regioselectively using dimethyltitanocene-catalyzed hydroamination of unsymmetrical aryl/alkyl alkynes. The yields of the secondary amines after reduction using sodium cyano-borohydride varied from 19-87%.[17]



Scheme 1.4 Doye (1999) – Dimethyltitanocene-Catalyzed Hydroamination Reaction Toward the Synthesis of Secondary Amines

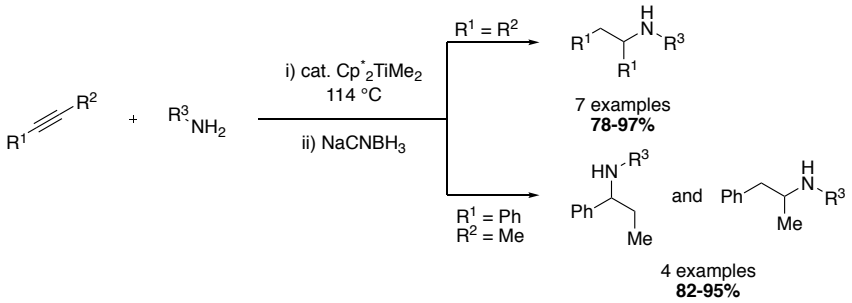
A follow-up paper explored the reaction using microwave technology, which significantly reduced the reaction times for the dimethyltitanocene-catalyzed hydroamination reaction (Scheme 1.5).[18] In this case, while internal alkynes delivered a single product in moderate to good yields, terminal alkynes delivered a mixture of Markovnikov and *anti*-Markovnikov products.



Scheme 1.5 Doye (2001) – Microwave-Assisted Dimethyltitanocene-Catalyzed Hydroamination Reaction Toward the Synthesis of Secondary Amines

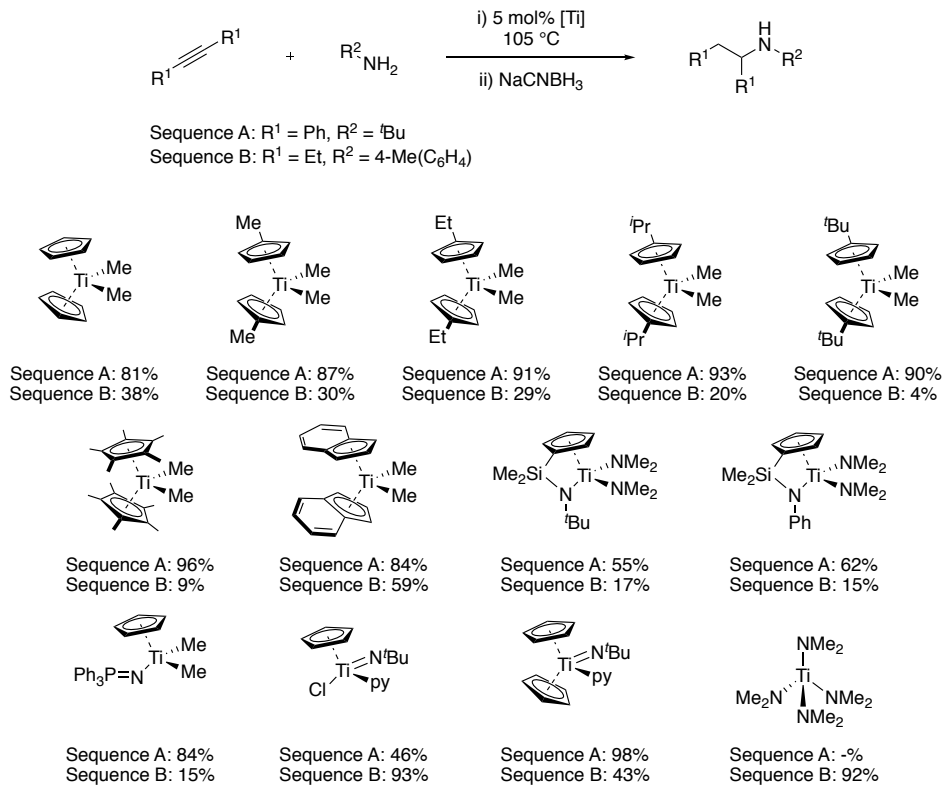
Heutling and Doye also showed that the hydroamination reaction of internal alkynes and amines was possible with a derivative of dimethyltitanocene, dipentamethylcyclopentadienyl

dimethyl titanium (Scheme 1.6).[19] Unfortunately, in the case of unsymmetrical aryl/alkyl alkynes, a mixture of regioisomers was obtained.



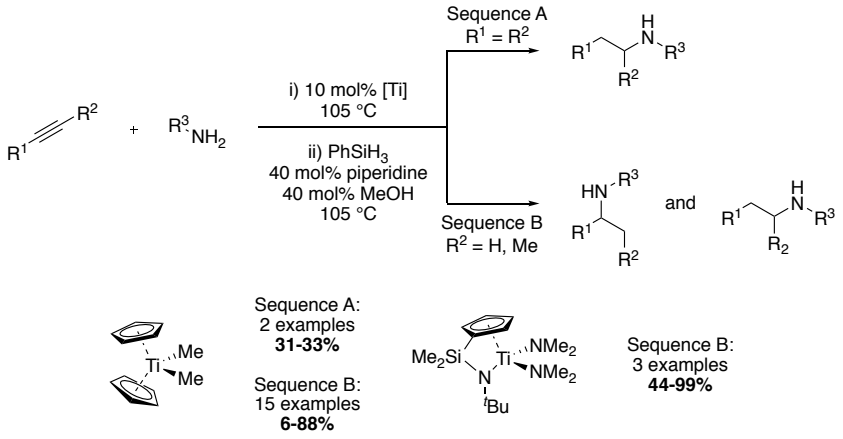
Scheme 1.6 Doye (2002) – Titanium-Catalyzed Hydroamination Reaction Toward the Synthesis of Secondary Amines

A variety of titanium-catalysts were used to study two hydroamination reactions (Scheme 1.7).[20] Sequence A focused on the reaction between diphenylacetylene and *tert*-butyl amine, while sequence B focused on the reaction with hex-3-yne. In all cases, the reactivity of the catalyst for one sequence was opposite as that for the other sequence. For example, in the case of dimethyltitanocene, 81% yield was obtained for sequence A, while only 38% was obtained for sequence B. On the other hand, tetrakis(dimethylamido)titanium did not react in sequence A, while 92% yield was obtained for sequence B.



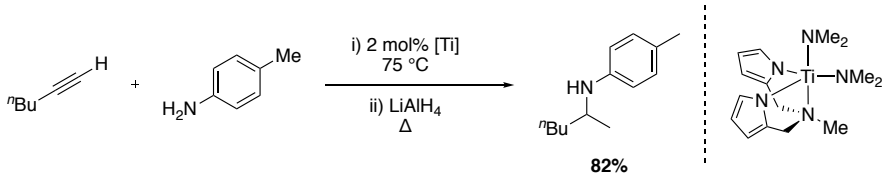
Scheme 1.7 Doye (2002) – Fifteen Titanium Catalysts Studied for the Hydroamination Reaction Toward the Synthesis of Secondary Amines

Instead of the traditional boron and aluminium-based reductants, Doye also reported that phenylsilane could be used to reduce hydroamination products by hydrosilylation (Scheme 1.8).[21]



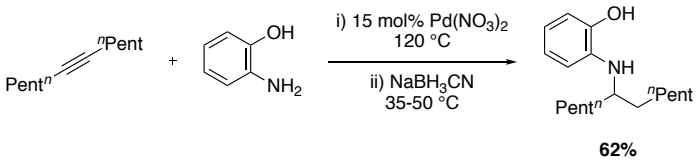
Scheme 1.8 Doye (2005) – Titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

Odom and co-workers published a single example of a Markovnikov selective hydroamination of hex-1-yne and *p*-toluidine, which was reduced with lithium aluminum hydride to afford the desired secondary amine in 82% yield (Scheme 1.9).[22]



Scheme 1.9 Odom (2001) – Titanium Pyrrolyl Complex-Catalyzed Hydroamination Reaction Towards the Synthesis of a Secondary Amine

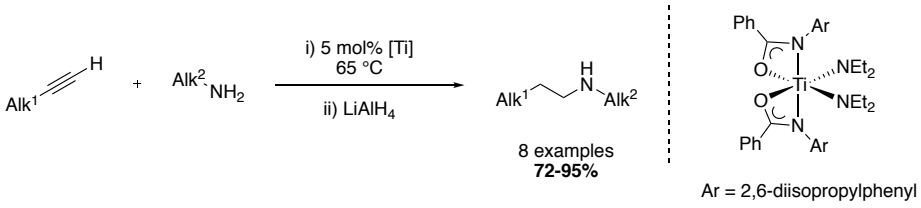
Up until the early 2000's, all of the catalysts reported for the sequential intermolecular hydroamination reactions of alkynes followed by stoichiometric reduction of the imine intermediates were titanium based. However, in 2002, Yamamoto and co-workers reported an example of a palladium-catalyzed hydroamination reaction of dodec-6-yne and *ortho*-aminophenol, which delivered the reduced product in 62% yield (Scheme 1.10).[23]



Scheme 1.10 Yamamoto (2002) – Palladium-Catalyzed Hydroamination Reaction Towards the Synthesis of a Secondary Amine

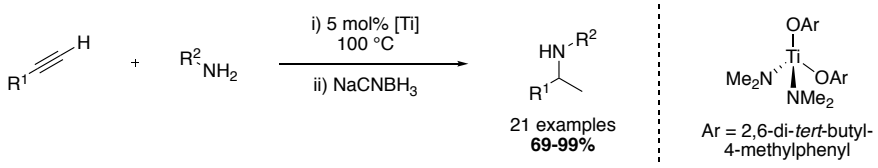
A follow-up publication demonstrated that by changing the palladium source to $[Pd(dppe)(H_2O)_2](OTf)_2$, they were able to perform the reaction using diphenylacetylene and aniline to deliver 48% of the desired secondary amine.[24] In both cases, oxygen or water exclusion were not necessary due to the stability of the palladium catalysts, which was in great contrast to the early transition metal work.

In 2003, Schafer and co-workers reported an bis(amidate)bis(amido)titanium catalyzed *anti*-Markovnikov hydroamination of terminal alkyl-alkynes followed by lithium aluminium hydride reduction to deliver 8 examples of linear secondary amines in 72-95% yields (Scheme 1.11).[25] In follow-up publications, the substrate scope was increased to include terminal aryl-alkynes as well as symmetrical and unsymmetrical internal alkynes.[26-27] The Schafer group also showed that by changing the phenyl group on the amide ligand to a penta-fluorophenyl group, the Markovnikov and *anti*-Markovnikov selectivity ratios change according to the different substrates used.[28]



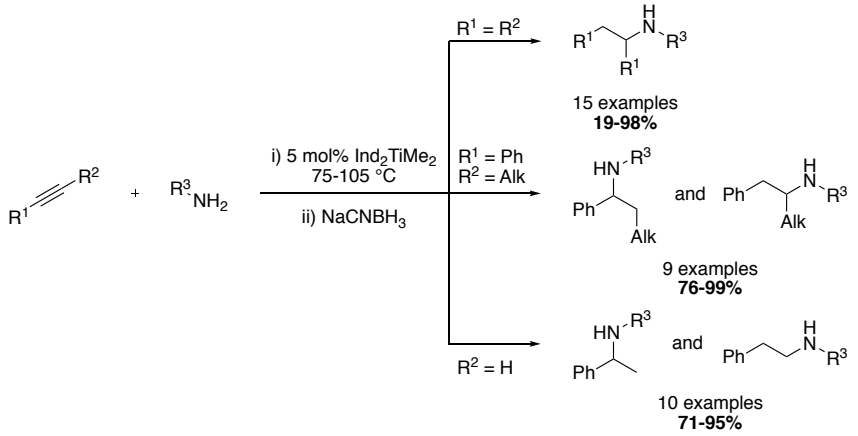
Scheme 1.11 Schafer (2003) – Bis(amidate)bis(amido)titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Linear Secondary Amines

Using an aryloxotitanium complex, a Markovnikov regioselective hydroamination of terminal alkynes was reported by Beller and co-workers (Scheme 1.12).[29] Upon reduction of the reaction mixture using sodium cyano-borohydride, 21 examples of the desired secondary amine were obtained.



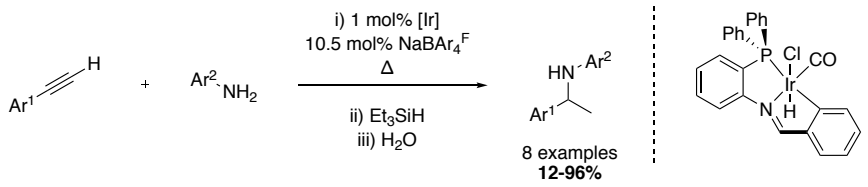
Scheme 1.12 Beller (2003) – Ayloxotitanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

Evolving from the dimethyltitanocene work, three separate publications were reported by Doye and co-workers on the diindenyldimethyltitanium-catalyzed hydroamination of alkynes (Scheme 1.13).[30-32] Unfortunately, the reaction was not regioselective when unsymmetrical aryl/alkyl alkynes and terminal alkynes were used as substrates. Notably, methyl- and ethyl-amine gases were successfully employed to deliver the respective secondary amines after reduction.[32]



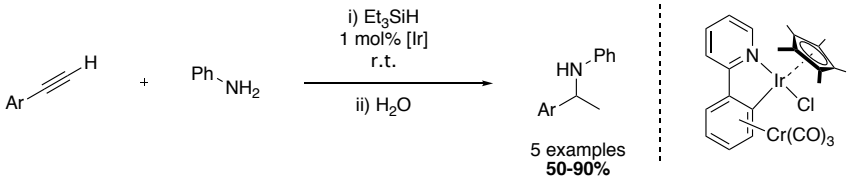
Scheme 1.13 Doye (2004) – Diindenyldimethyltitanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

The combination of a phosphine-imine iridium complex with sodium tetrakis(3,5-trifluoromethylphenyl)borate was shown to be catalytically active for the Markovniokv intermolecular hydroamination of aryl terminal alkynes with aniline derivatives, which upon hydrosilylation and hydrolysis afforded 8 examples of secondary amines in poor to excellent yields (Scheme 1.14).[33]



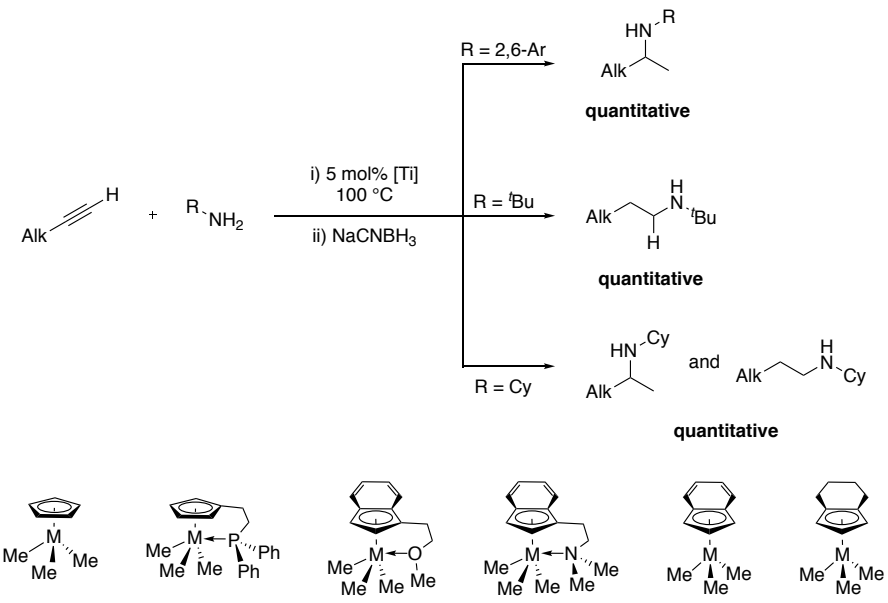
Scheme 1.14 Liu (2007) – Iridium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

It has also been shown that tricarbonylchromium-bound iridacycles can be used as the catalyst for a one-pot tandem hydroamination/hydrosilylation transformation, as reported by the Djukic group (Scheme 1.15).[34]



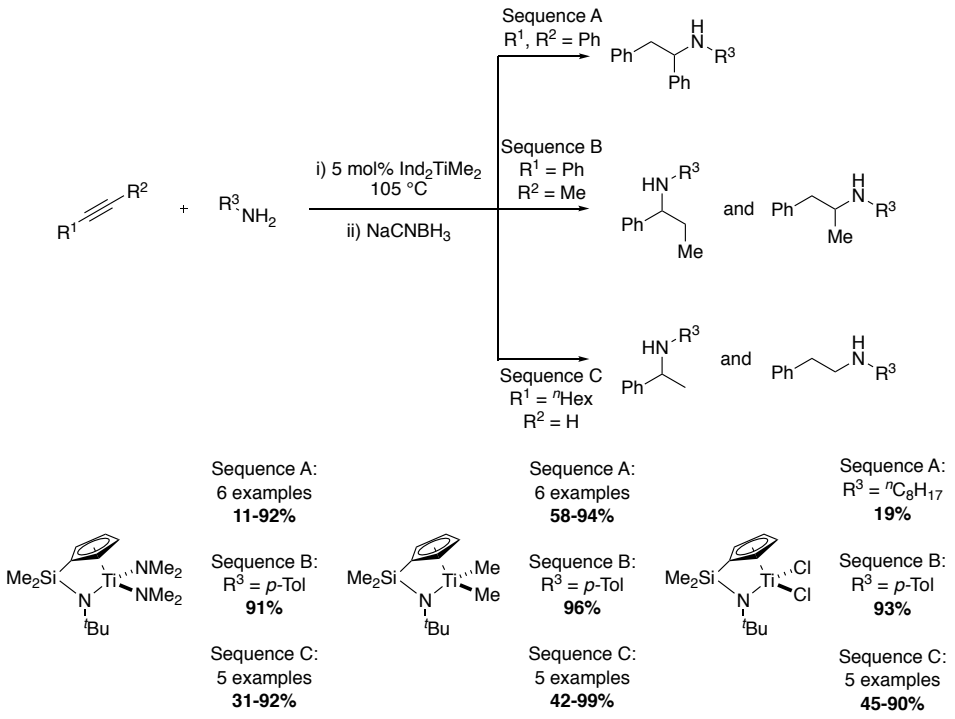
Scheme 1.15 Djukic (2012) – Tricarbonylchromium-Bound Iridium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

The Esteruelas group has focused their study on the intermolecular hydroamination of alkynes catalyzed by a variety of half-sandwich alkyl-titanium complexes (Scheme 1.16).[35-36] The selectivity that they observe is intrinsically related to the substrates that are used for the reactions. If the amine used is an aromatic amine with *ortho*-disubstitution, the Markovnikov product is obtained. However, an inversion in the regioselectivity occurs if the amine used is *tert*-butylamine. Furthermore, using cyclohexylamine leads to a mixture of the two regioisomers.



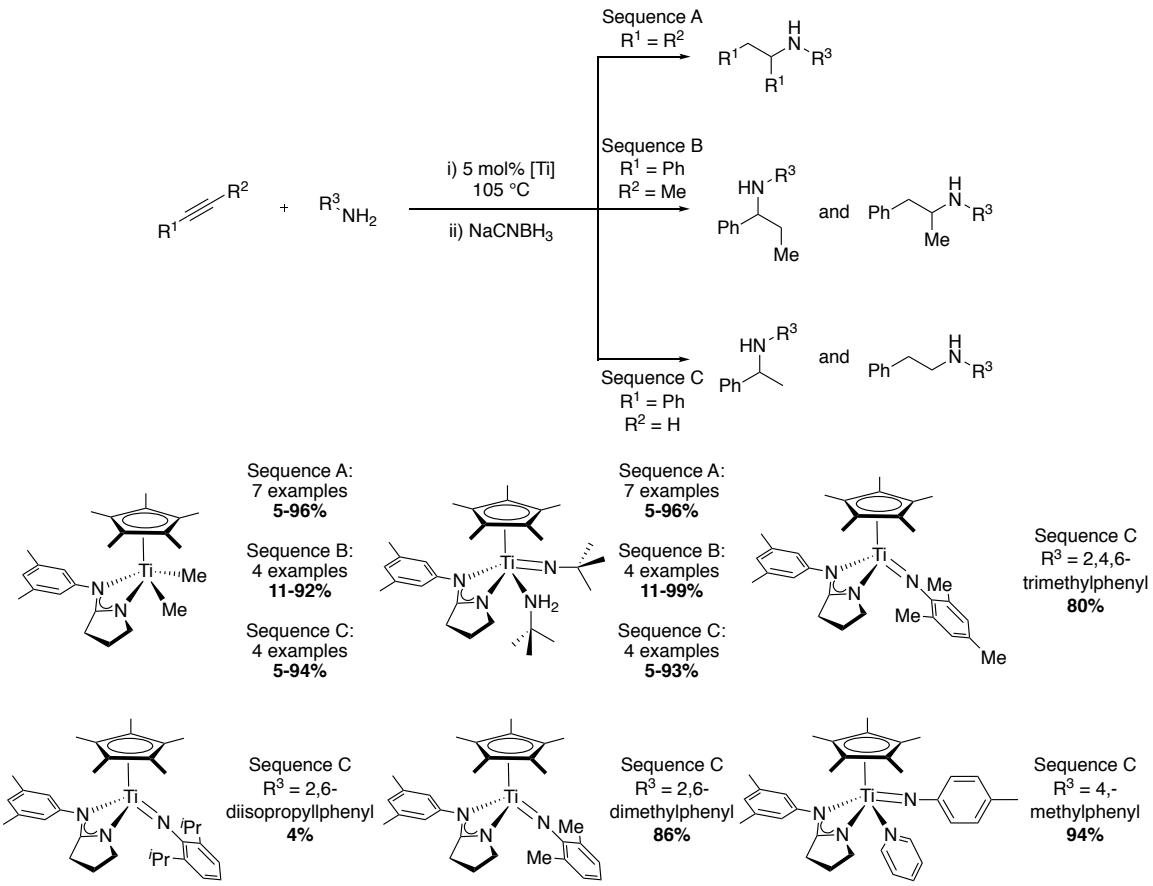
Scheme 1.16 Esteruelas (2006, 2007) – Half-Sandwich Alkyl Titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

Doye and co-workers also studied similar complexes to that reported by Esteruelas and co-workers. In their case, the titanium complexes featured the common constrained geometry ligand $[\eta^5\text{-}(C_5H_4)\text{-}SiMe_2\text{-}N^tBu]^{2-}$ together with two X ligands (Scheme 1.17).[37] Similarly to other Doye hydroamination systems, the reaction with unsymmetrical aryl/alkyl and terminal alkynes leads to a mixture of Markovnikov and *anti*-Markovnikov products.



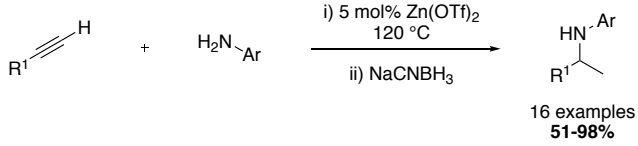
Scheme 1.17 Doye (2008) – Neutral Titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

Other half-sandwich titanium complexes containing Cp* and 2-aminopyrrolinato ligands were also reported by Gade and co-workers (Scheme 1.18).[38] Not surprisingly, their reactions were also not selective when it came to unsymmetrical aryl/alkyl and terminal alkynes.



Scheme 1.18 Gade (2009) – Half-Sandwich Titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

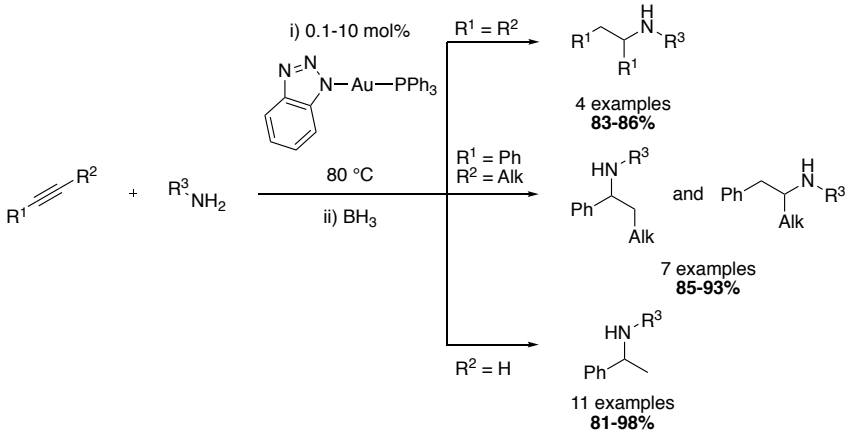
Beller and co-workers were able to perform the intermolecular hydroamination of terminal alkynes and aniline derivatives using zinc triflate as the catalyst to afford 16 examples of α-methylated amines in 51-98% yields (Scheme 1.19).[39]



Scheme 1.19 Beller (2008) – Zinc Triflate-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

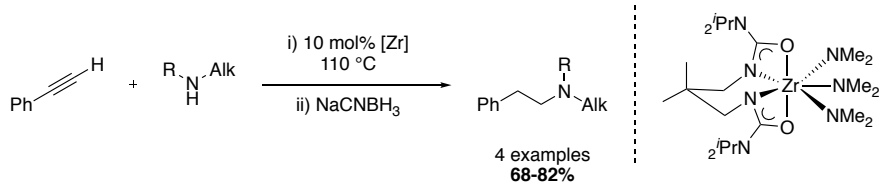
A triazole-gold complex was shown by the Shi group to be catalytically active for the hydroamination of alkynes (Scheme 1.20).[40] While a mixture of products was obtained with the

use of unsymmetrical aryl/alkyl alkynes, the reactions with terminal alkynes were selective for the Markovnikov product.



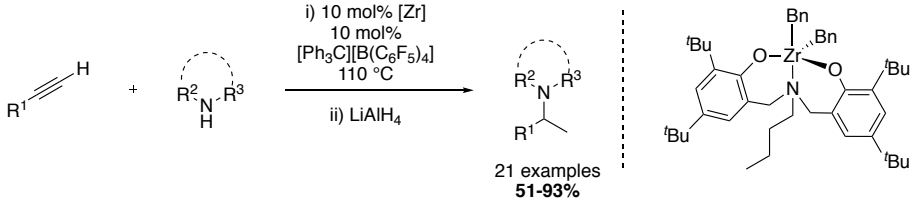
Scheme 1.20 Shi (2009) – Gold-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

While titanium complexes have been widely studied for the intermolecular hydroamination of alkynes, zirconium-complexes have not received as much attention, although they have been shown to be catalytically active for the hydroamination reaction if sterically demanding amines are used. In 2009, Schafer and co-workers reported a tethered bis(ureate)tris(dimethylamido)zirconium species that was competent for the hydroamination of terminal alkynes using secondary amines to deliver linear tertiary amines after reduction with sodium cyano-borohydride (Scheme 1.21).[41] This was the first neutral group 4 example to show significant reactivity towards secondary amines for the intermolecular hydroamination of alkynes, this would only be possible with a change in mechanism. The authors proposed that the reaction does not go through an imido species followed by a [2+2] cycloddition, but through a nucleophilic attack of the bound secondary amido ligand to a coordinated alkyne substrate.



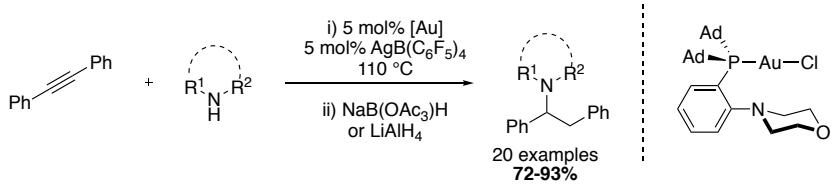
Scheme 1.21 Schafer (2009) – Bis(ureate)tris(dimethylamido)Zirconium-Catalyzed Hydroamination Reaction Towards the Synthesis of Tertiary Amines

In 2015, Yao and co-workers disclosed a cationic zirconium-complex that was competent for the hydroamination of alkynes using secondary amines (Scheme 1.22).[42] In their case however, the reaction delivered the Markovnikov product selectively for terminal alkynes. A follow up report by the same authors showed that similar cationic zirconium-complexes also work with primary amines.[43]



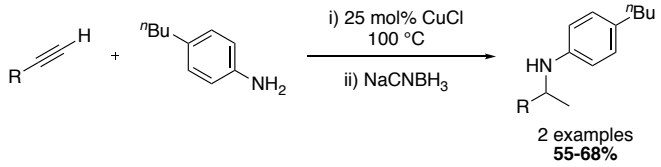
Scheme 1.22 Yao (2015) – Cationic Zirconium-Catalyzed Hydroamination Reaction Towards the Synthesis of Tertiary Amines

Complementary to the zirconium publications, Stradiotto and co-workers reported a gold catalyst competent for the hydroamination of internal alkynes using secondary amines to deliver 20 examples of tertiary amines in good to excellent yields (Scheme 1.23).[44]



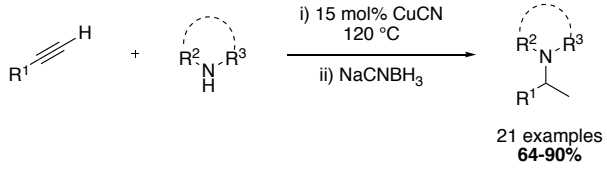
Scheme 1.23 Stradiotto (2010) – Gold-Catalyzed Hydroamination Reaction Towards the Synthesis of Tertiary Amines

Robbins and Hartwig demonstrated two examples of Markovnikov selective intermolecular hydroamination of terminal alkynes using copper chloride as the catalyst (Scheme 1.24).[45] Moderate yields of the final secondary amine products were obtained by reducing the hydroamination reaction mixture with sodium cyanoborohydride.



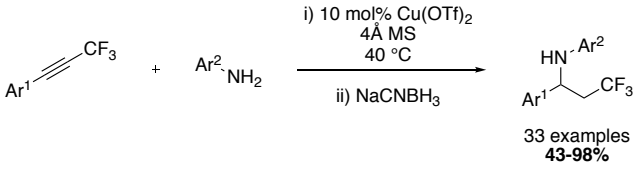
Scheme 1.24 Hartwig (2011) – Copper-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

Copper-catalysis was also demonstrated to be successful for the synthesis of tertiary amines (Scheme 1.25).[46] Monnier and co-workers reported using copper cyanide as the catalyst for the hydroamination of terminal alkynes with secondary amines, followed by reduction with sodium cyanoborohydride to deliver 21 examples of tertiary amines in 64-90% yields.



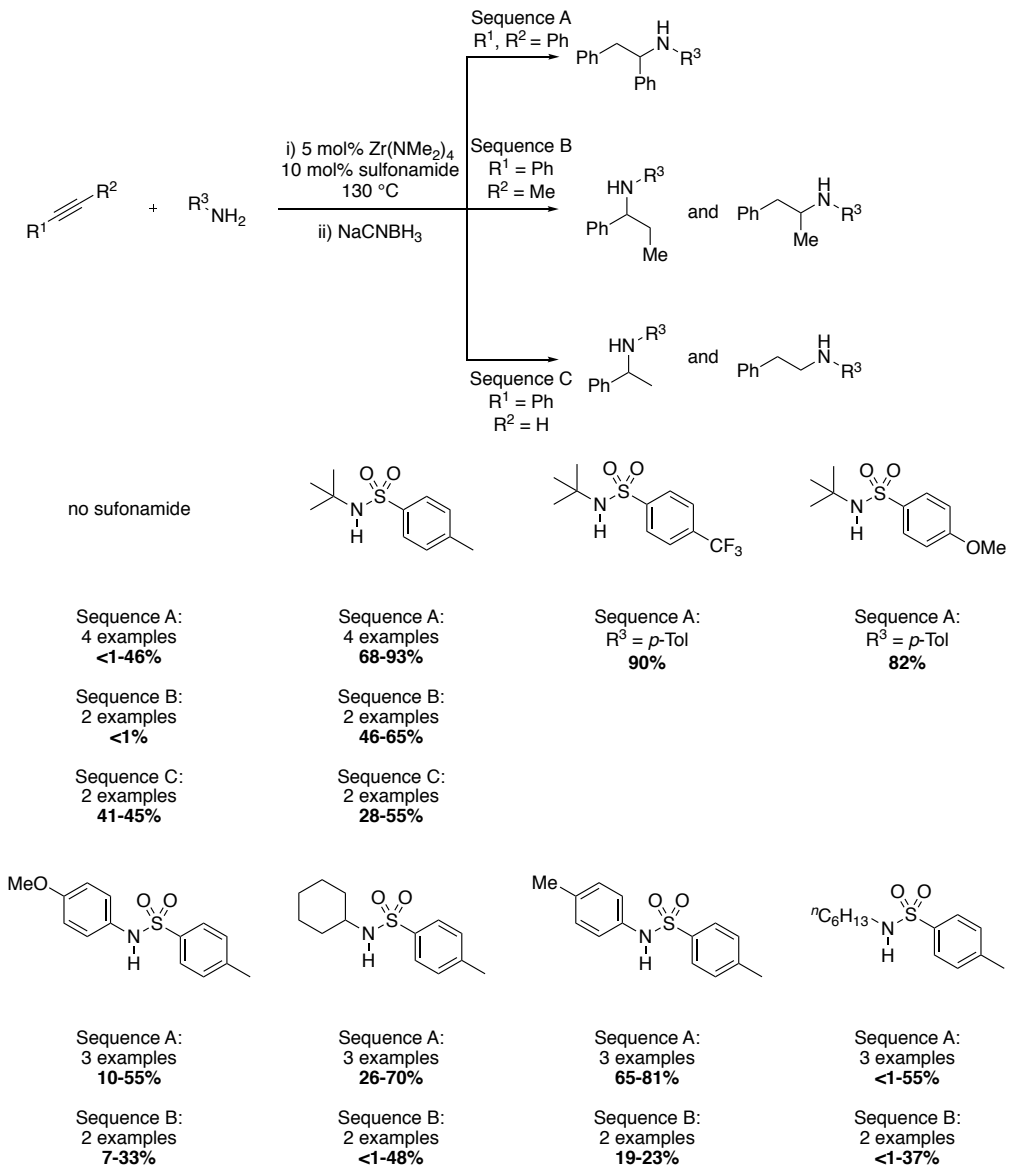
Scheme 1.25 Monnier (2015) – Copper-Catalyzed Hydroamination Reaction Towards the Synthesis of Tertiary Amines

Furthermore, Kawatsura and co-workers reported a methodology towards the synthesis of β-trifluoromethyl substituted secondary and tertiary amines using catalytic amounts of copper triflate (Scheme 1.26).[47] The hydroamination reaction with aryl and trifluoromethyl substituted internal alkynes was accomplished with 10 mol% copper triflate, while the reduction was performed with sodium cyanoborohydride to afford 33 examples of secondary and 3 examples of tertiary amines if moderate to excellent yields.



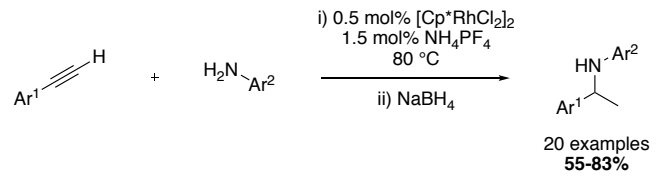
Scheme 1.26 Kawatsura (2016) – Copper-Catalyzed Hydroamination Reaction Towards the Synthesis of β-Trifluoromethyl Substituted Secondary Amines

In 2012, Born and Doye reported a zirconium-catalyzed intermolecular hydroamination (Scheme 1.27).[48] The catalyst used was generated *in situ* from the combination of tetrakis(dimethylamido)zirconium and a sulfonamide ligand. The type of sulfonamide ligand significantly influenced the regioselectivity of the reactions using unsymmetrical aryl/alkyl and terminal alkynes.



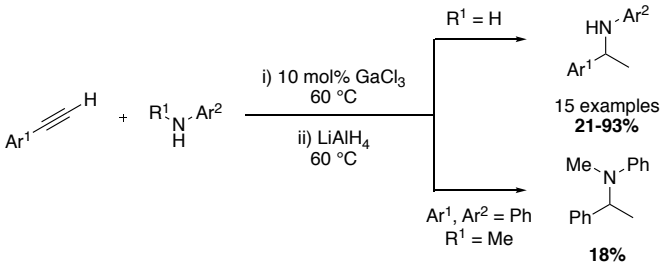
Scheme 1.27 Doye (2012) – Zirconium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

The readily available $[Cp^*RhCl_2]_2$ was shown to be a good catalyst for the Markovnikov hydroamination of terminal aryl-alkynes and aniline derivatives, delivering 20 examples of the reduced product in yields of 55-83% (Scheme 1.28).[49] Experimental and computational evidence led to the proposal of a reaction pathway involving cationic intermediates.



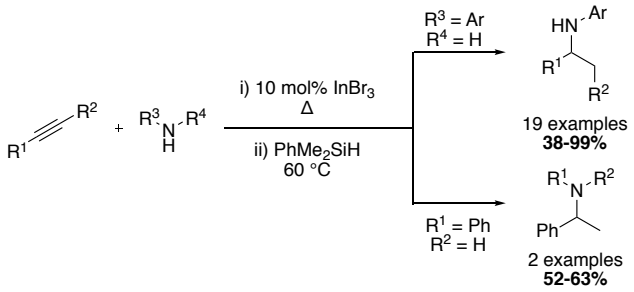
Scheme 1.28 Leong (2012) – Rhodium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

Using gallium trichloride as the catalyst allowed for the synthesis of Markovnikov products using both, primary and secondary amines as substrates (Scheme 1.29).[50] In their system, however, trace amounts of the *anti*-Markovnikov products were also observed by GC-MS for some of the substrates attempted.



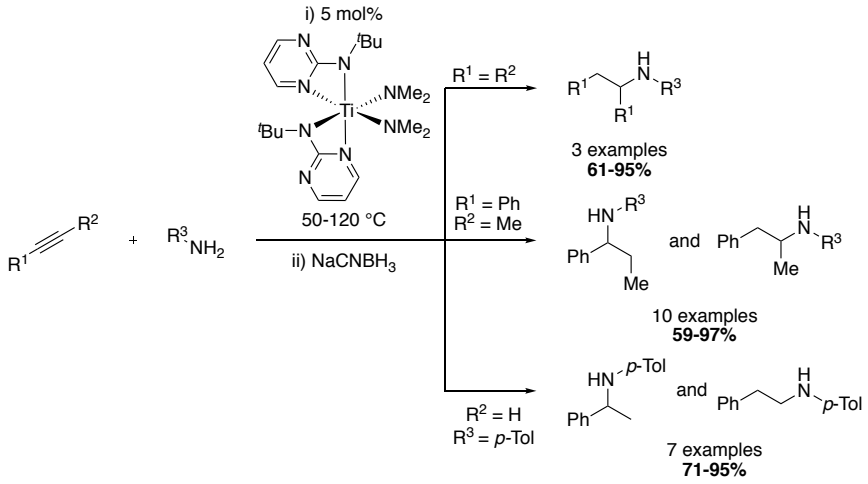
Scheme 1.29 Li (2012) – Gallium Trichloride Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary and Tertiary Amines

Similarly, indium tribromide was also shown to perform the intermolecular hydroamination of alkynes with primary and secondary amines (Scheme 1.30).[51] Upon hydrosilylation, secondary and tertiary amines were synthesized in 38-99% yields.



Scheme 1.30 Sakai (2014) – Indium Tribromide Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary and Tertiary Amines

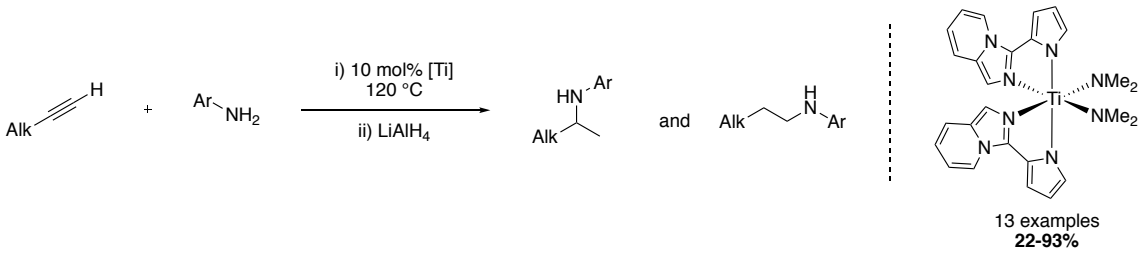
Moving away from titanium complexes containing a cyclopentadienyl group, Doye and co-workers reported an (aminopyrimidinato)titanium catalyst that delivered high *anti*-Markovnikov regioselectivity for unsymmetrical aryl/alkyl and terminal alkynes (Scheme 1.31).[52] They also reported an (aminopyridinato)titanium catalyst that was competent for the intermolecular hydroamination of alkynes and amines, although the selectivity of the reaction was highly dependent on the substrates used.[53]



Scheme 1.31 Doye (2013) – (Aminopyridiminato)Titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

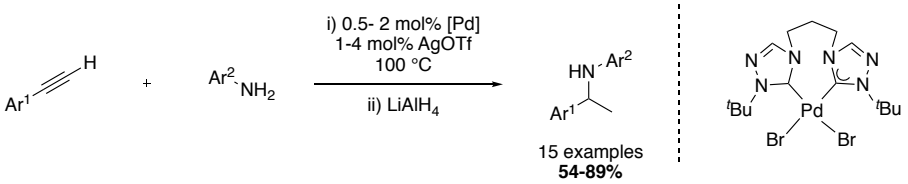
Similar titanium complexes containing amino-heteroaromatic ancillary ligands were reported by the Doye group and others. Liu and co-workers, for example, reported a couple of

imidazo[1,5-*a*]pyridine-containing pyrrolyl titanium complexes that were competent for the hydroamination of alkyl-alkynes and aniline derivatives (Scheme 1.32).[54] While the Markovnikov selectivity was favoured, the majority of reactions attempted delivered mixtures of two products.



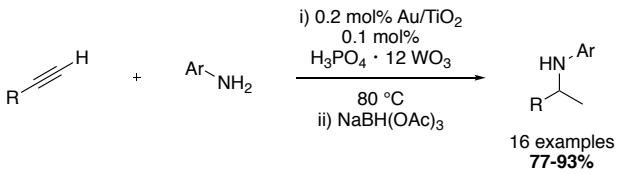
Scheme 1.32 Liu (2015) – Imidazo[1,5-*a*]pyridine-Containing Pyrrolyl Titanium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

In 2013, Cao and co-workers reported an *N*-heterocyclic carbene-palladium complex that was selective for the Markovnikov regioisomer (Scheme 1.33).[55] While their reaction was limited to aromatic terminal alkynes and aromatic amines, the catalyst used could be recovered through precipitation using diethyl ether and re-used 3 times without loss of reactivity.



Scheme 1.33 Cao (2013) – (*N*-Heterocyclic Carbene)Palladium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

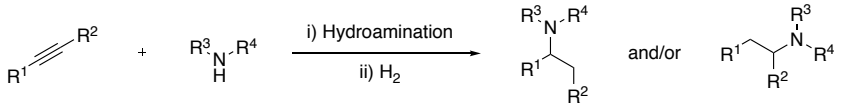
Commercially available gold nanoparticles supported on titanium oxide was also found to be a recyclable and efficient catalyst for the Markovnikov intermolecular hydroamination of terminal alkynes and aniline derivatives (Scheme 1.34).[56] Filtration and washing of the Au/TiO_2 with toluene allowed for the catalyst to be reused 5 times with no loss of catalytic activity.



Scheme 1.34 Hammond (2016) – Gold Nanoparticles Supported on Tititanium Oxide Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

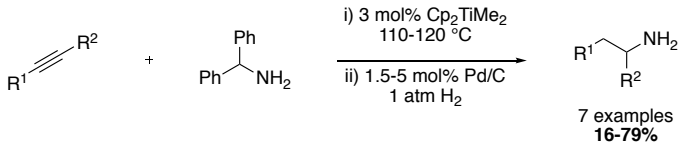
1.2.1.2 Using Catalytic Hydrogenation

It is undeniable that reduction using hydrogen (H_2) gas is the ideal scenario for a truly catalytic and atom-economical synthesis of amines using sequential hydroamination/reduction reactions (Scheme 1.35). Thus, it is not surprising that such approaches have been successfully carried out with both homogeneous and heterogeneous catalyts.



Scheme 1.35 General Sequential Hydroamination/Hydrogenation Reactions Toward the Synthesis of Amines

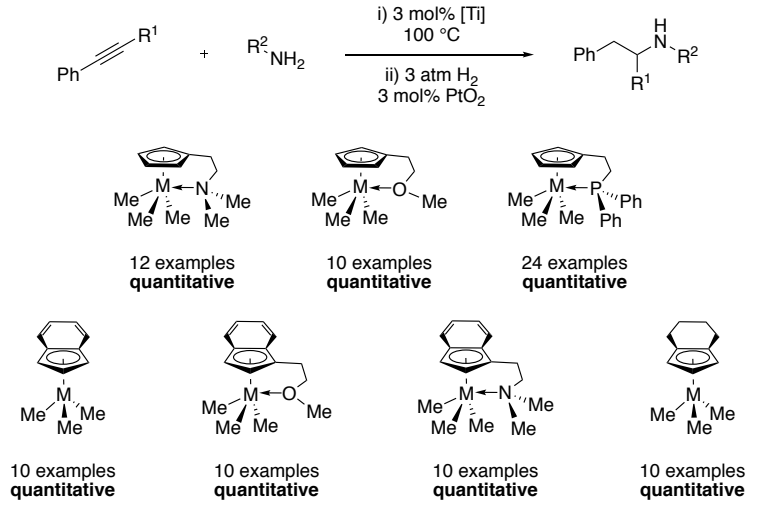
Notably, the development of methodologies towards the synthesis of primary amines using hydroamination has been limited. To date, only two approaches have been previously explored.[57, 72] The first approach, reported by Doye and co-workers, makes use of a titanium-catalyzed hydroamination reaction of alkynes and diphenylmethanamine.[57] Upon exposure of the hydroamination product to palladium on carbon (Pd/C) and H_2 gas, the imine/enamine double bond was reduced and the C-N bond of diphenylmethanamine underwent hydrogenolysis to deliver 7 examples of the desired primary amines (Scheme 1.36). They also showed a few examples of secondary amines being synthesized using the same hydroamination followed by Pd/C hydrogenation.[18]



Scheme 1.36 Doye (2000) – Dimethyltitanocene-Catalyzed Hydroamination Reaction Toward the Synthesis of Primary Amines

The second, more challenging, approach was reported by Bertrand and co-workers, in which gaseous ammonia was used as their nitrogen source.[72] Although no primary amines were isolated, they report the formation of H-substituted imines, which in theory could be hydrogenated using H_2 gas to afford a 100% atom-economical and catalytic synthesis of primary amines from ammonia feedstocks.

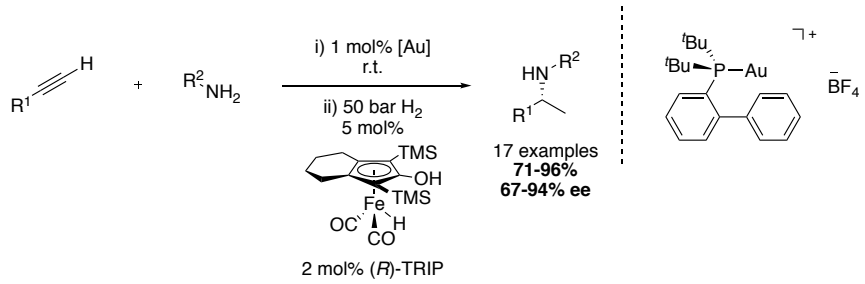
Platinum dioxide has also been show to be a good hydrogenation catalyst for the synthesis of secondary amines as reported by Esteruelas and co-workers (Scheme 1.37).[35-36, 58-59]



Scheme 1.37 Esteruelas (2005, 2006, 2007) – Half-Sandwich Alkyl Titanium-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Secondary Amines

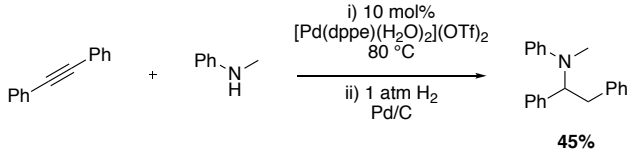
In 2012, Beller and co-workers reported an enantioselective synthesis of secondary amines through a sequential hydroamination/hydrogenation reaction (Scheme 1.38).[60] The Markovnikov selectivity for the hydroamination reaction was obtained using a gold-phosphine

complex, and the enantioselectivity of the final product was obtained using an iron-catalyst in addition to (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, (*R*)-TRIP, under 50 bar of H_2 gas.



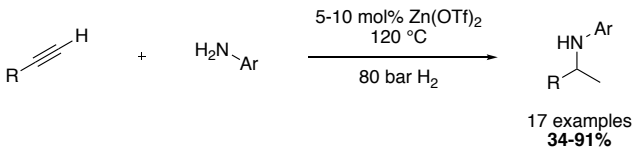
Scheme 1.38 Beller (2012) – Gold-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Enantioselective Secondary Amines

Yamamoto and co-workers demonstrated a single example of a palladium-catalyzed hydroamination of alkynes with *N*-methylaniline, followed by Pd/C hydrogenation to deliver 45% of the desired tertiary amine (Scheme 1.39).[24]



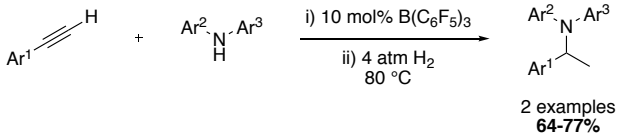
Scheme 1.39 Yamamoto (2005) – Palladium-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Tertiary Amines

Beller and co-workers were able to perform the intermolecular hydroamination and the hydrogenation reactions using zinc triflate as the catalyst for both transformations.[61] At catalytic loadings of 5 to 10 mol% of zinc, under 80 bar of hydrogen gas, 17 examples of α-methylated secondary amines were synthesized in 34-91% yields (Scheme 1.40). A single example was also reported for the synthesis of *N*-methyl-*N*-(1-phenylethyl)aniline, which was accomplished in 69% yield.



Scheme 1.40 Beller (2008) – Zinc Triflate-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Secondary Amines

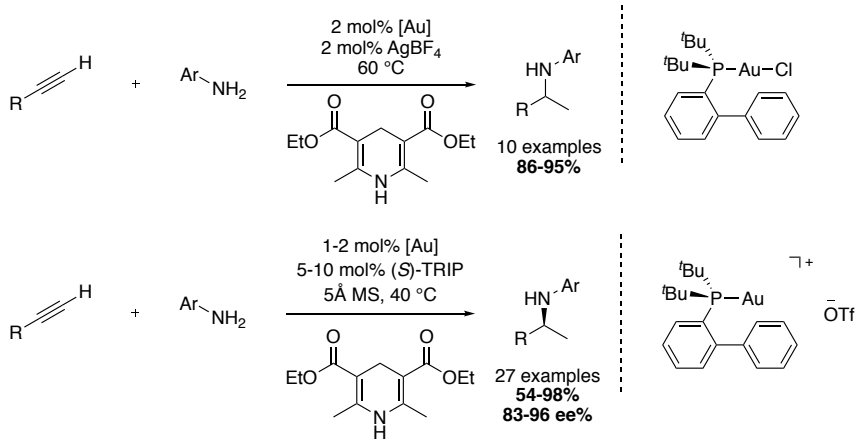
Frustrated-Lewis pair (FLP) chemistry with $B(C_6F_5)_3$ was reported to be catalytically active for the intermolecular hydroamination of aryl terminal alkynes and secondary amines to afford Markovnikov selective products (Scheme 1.41).[62] Interestingly, the FLP-catalyst is also capable of performing the hydrogenation step when the reaction solution it is exposed to 4 atm of H_2 gas.



Scheme 1.41 Stephan (2013) – Frustrate-Lewis Pair-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Tertiary Amines

1.2.1.3 Using Transfer Hydrogenation

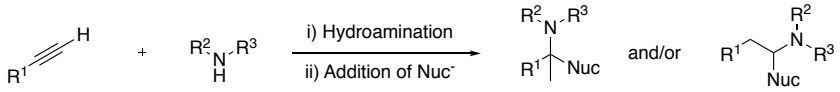
To date, only one example of transfer hydrogenation has been applied to the sequential hydroamination of alkyne/reduction to synthesize amines (Scheme 1.42).[63] Not only were Che and co-workers able to synthesized racemic secondary amines through a tandem gold-catalyzed hydroamination followed by a transfer hydrogenation using Hantzsch ester, they were also able to synthesize highly enantioselective chiral amines by adding (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, (*S*)-TRIP, to the reaction mixture.



Scheme 1.42 Che (2009) – Gold-Catalyzed Hydroamination Reaction Towards the Synthesis of Enantioselective Secondary Amines

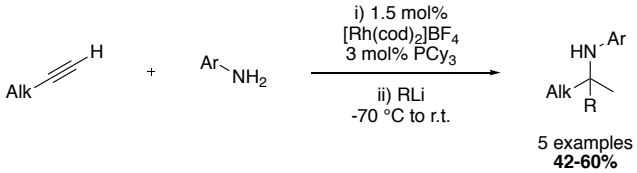
1.2.1.4 Using Nucleophilic Addition

Hydrides are not the only nucleophiles that have been used in sequential hydroamination/reduction reactions. Other carbon- or nitrogen-nucleophiles have also been added to give α-substituted amines (Scheme 1.43).



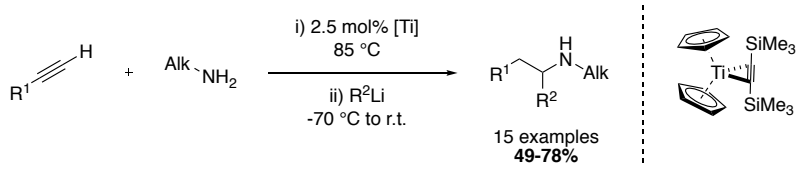
Scheme 1.43 General Sequential Hydroamination/Addition of Nucleophile Reactions Toward the Synthesis of Amines

The first rhodium-catalyzed intermolecular hydroamination of alkynes was performed with $[Rh(cod)_2]BF_4$ and tricyclohexylphosphine (Scheme 1.44).[64] Following the Markovnikov selective imine formation, secondary amines were synthesized in a one-pot fashion by the addition of organolithium reagents to the hydroamination product mixtures. Due to the selectivity of the rhodium-catalyst, 5 examples of amines containing α-quaternary centers were synthesized in moderate yields.



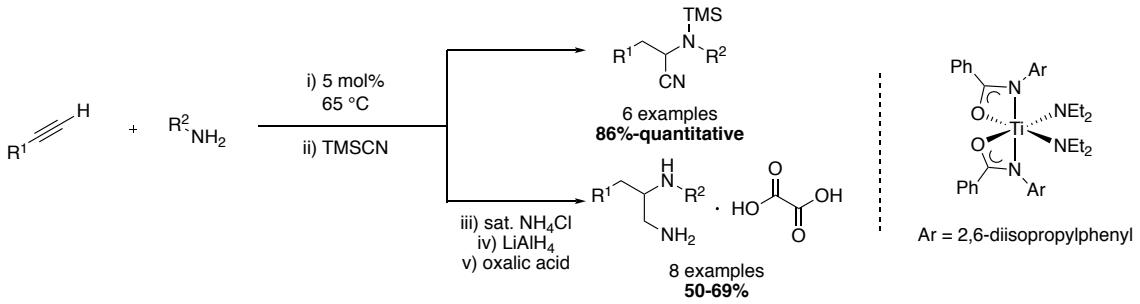
Scheme 1.44 Beller (2001) – Rhodium-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Secondary Amines Containing a α-Quaternary Centre

Beller and co-workers also reported a similar approach to synthesize α-substituted phenethylamines (Scheme 1.45).[65] In this case, however, instead of using a rhodium-catalyst in the hydroamination step, Rosenthal's catalyst was used. Complementary to the previous approach, the change in catalyst led to the formation of *anti*-Markovnikov products, which upon addition of organolithium reagents delivered 15 examples of amines in 49-78% yields.



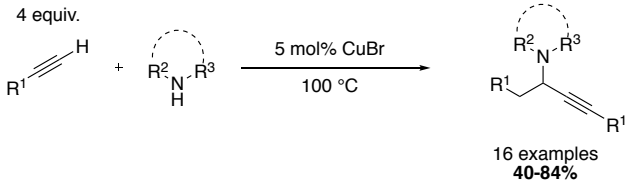
Scheme 1.45 Beller (2003) – Titanium-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Secondary Amines

Instead of adding organolithium reagents to the hydroamination reaction, Schafer and co-workers showed that trimethylsilyl cyanide could be used as the nucleophilic source (Scheme 1.46).[66-67] Since the hydroamination reaction delivers imines, and such intermediates are invoked in the Strecker reaction, by combining these two reactions, a one-pot synthesis of α-cyanoamines was developed. Further transformations could be performed sequentially to afford unsymmetrical vicinal diamines in moderate yields.



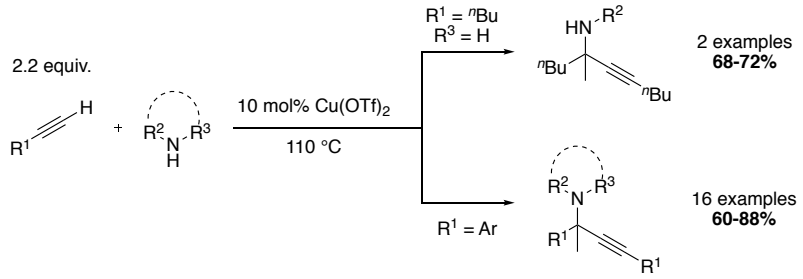
Scheme 1.46 Schafer (2006, 2009) – Titanium-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of α-Cyanoamines and Vicinal Diamines

Propargylamines can be readily synthesized from a tandem hydroamination and alkyne addition as shown by Li and co-workers (Scheme 1.47).[68] Copper bromide was used as the catalyst to perform both the *anti*-Markovnikov hydroamination reaction as well as the alkyne addition to the formed imine.



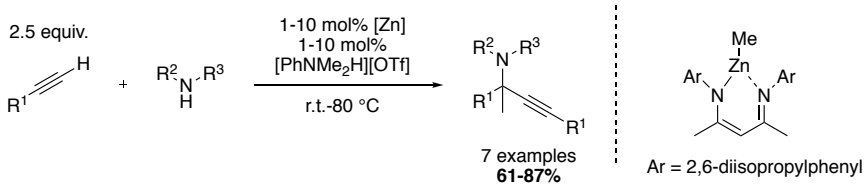
Scheme 1.47 Li (2009) – Copper-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Propargylamines

Interestingly, if the reaction is performed under neat conditions and copper triflate was the catalyst used, the Markovnikov imine was formed, thus allowing for the synthesis of quaternary propargyl amines, as shown by Larsen and co-workers (Scheme 1.48).[69-70]



Scheme 1.48 Larsen (2013) – Copper-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Propargylamines Containing a Quaternary Centre

Similar products can also be synthesized using a zinc β-diiminate-complex in the presence of a triflate co-catalyst (Scheme 1.49).[71]



Scheme 1.49 Blechert (2010) – Zinc-Catalyzed Hydroamination Reaction Towards the Catalytic Synthesis of Propargylamines

1.2.1.5 Conclusion

The synthesis of amines through a sequential intermolecular hydroamination of alkynes followed by reduction of the imine/enamine product mixtures has been well established. However, further work is required to increase the scope of primary amines synthesized through this methodology. Currently, in order to obtain good yields of primary amines, the scope is mainly limited to internal alkynes. Although remarkable progress has been made towards the synthesis of secondary amines through sequential hydroamination/reduction transformations, a selective, practical and broad methodology has been underdeveloped. Furthermore, the synthesis of enantiopure amines *via* the sequential transformations has been limited.

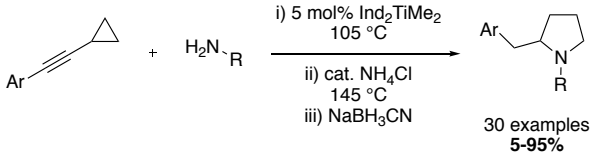
1.2.2 Heterocycle Synthesis

The intermolecular hydroamination of alkynes can also be employed to construct more sophisticated *N*-containing heterocycles, which includes 5-,[73-88] 6-,[25-26, 89-108] or 7-membered[109-110] rings and may contain one or more heteroatoms.

1.2.2.1 Formation of 5-Membered *N*-Heterocycles

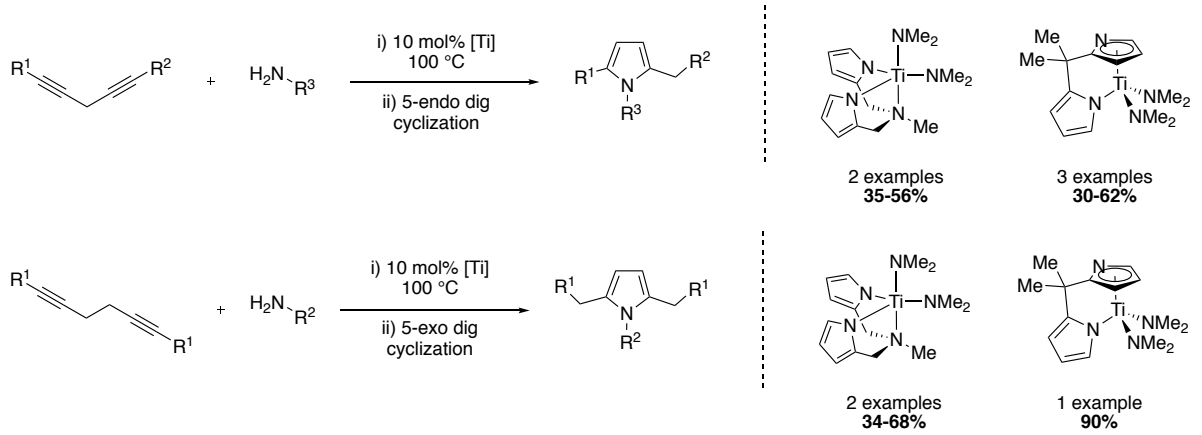
1.2.2.1.1 Pyrrolidine and Pyrrole

Doye and co-workers reported a one-pot methodology for the synthesis of 30 examples of *N*-substituted-2-(arylmethyl)pyrrolidines through a titanium catalyzed intermolecular hydroamination of alkynes followed by a cyclopropylimine rearrangement and sodium cyano-borohydride reduction (Scheme 1.50).[73]



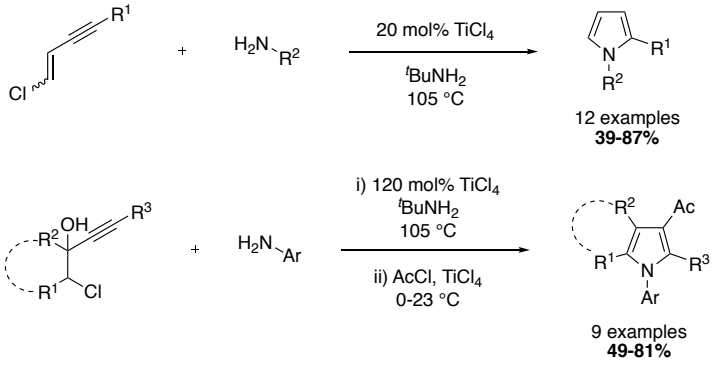
Scheme 1.50 Doye (2009) – Sequential Titanium-Catalyzed Hydroamination, Cyclopropylimine Rearrangement and Reduction Reactions Towards the Synthesis of Pyrrolidines

Starting from 1,4- and 1,5-diynes, 1,2,5-trisubstituted pyrroles can be accessed *via* a titanium-catalyzed hydroamination followed by an *in situ* 5-endo-dig or a 5-exo-dig cyclization (Scheme 1.51).[74] Interestingly, the titanium complexes used were chosen depending on the substrates used, for example, if terminal alkynes were present, the tridentate titanium-complex was used, while for internal alkynes, the bidentate titanium-complex was used.



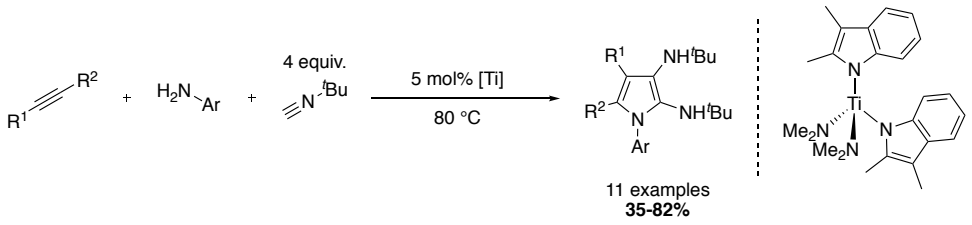
Scheme 1.51 Odom (2004) – Sequential Double Titanium-Catalyzed Hydroamination Reactions Towards the Synthesis of Pyrroles

Pyrroles could also be synthesized in one-pot using (*E*/*Z*)-haloenynes (Scheme 1.52).[75] In 2009, Ackermann and co-workers reported a regioselective method for the synthesis of mono-substituted pyrroles using 20 mol% of tetrachlorotitanium as the catalyst in the presence of stoichiometric amounts of *tert*-butylamine. Upon formation of the hydroamination product, an intramolecular nucleophilic substitution occurs to form the pyrrole ring. Fully substituted pyrroles could also be synthesized by the addition of acetyl chloride and excess titanium chloride to the hydroamination reaction mixture to deliver the desired product in 49-81% yields.



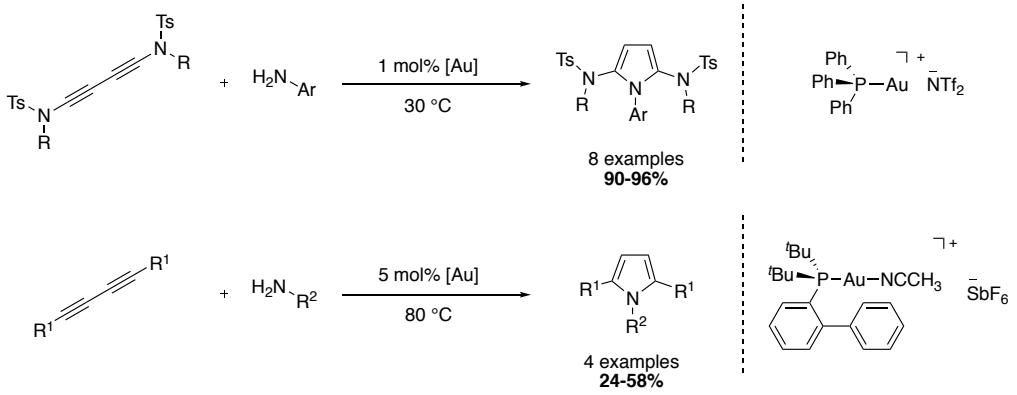
Scheme 1.52 Ackermann (2009) – Sequential Titanium-Catalyzed Hydroamination/Cyclization Reactions Towards the Synthesis of Pyrroles

The synthesis of 2,3-diaminopyrroles was accomplished from a four-component coupling of 2 equivalents of isonitrile, 1 equivalent of arylamine and 1 equivalent of alkyne using a diindolylbis(dimethylamido)titanium complex (Scheme 1.53).[76] The transformation from starting materials to products is proposed to occur through a hydroamination reaction followed by insertion of two isonitriles and finally a nucleophilic attack to form the pyrrole.



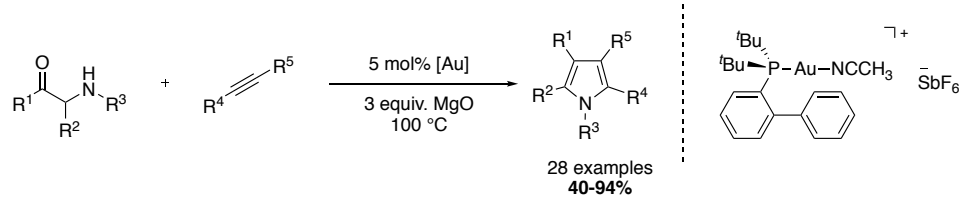
Scheme 1.53 Odom (2009) – Sequential Titanium-Catalyzed Hydroamination/Iminoamination/Cyclization Reactions Towards the Synthesis of Pyrroles

By using 1,3-diynes, 2,5-disubstitutedpyrroles could be synthesized using a cationic gold-complex (Scheme 1.54).[77] Different substrates demanded different cataysts, for example, 1 mol% of [bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold complex was used for the synthesis of 8 examples of 2,5-diaminopyrrole in 90-96% yields, while 5 mol% of (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold hexafluoroantimonate was used for the synthesis of 4 examples of 2,5-disubstituted pyrroles in 24-58% yields. In both cases, product formation occurs through a double hydroamination of the starting materials.



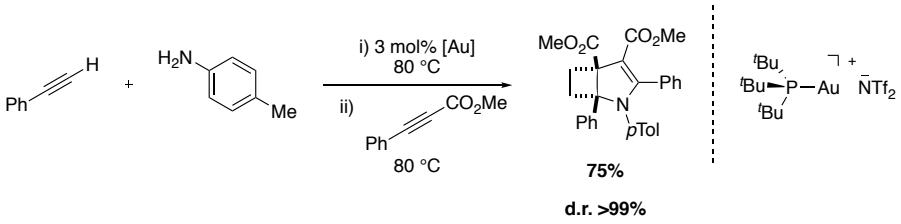
Scheme 1.54 Skrydstrup (2010) – Sequential Gold-Catalyzed Double Hydroamination Reactions Towards the Synthesis of Pyrroles

Liu and co-workers, used the same (acetonitrile)[(2-biphenyl)di-tert-butylphosphine]gold hexafluoroantimonate complex to synthesize 28 examples of pyrroles (Scheme 1.55).[78] Starting from an intermolecular hydroamination of alkynes with α-amino ketones, following a cyclization and aromatization events, a variety of di-, tri- and tetra-substituted pyrroles were synthesized in moderate to excellent yields.



Scheme 1.55 Liu (2015) – Sequential Gold-Catalyzed Hydroamination/Cyclization Reaction Towards the Synthesis of Pyrroles

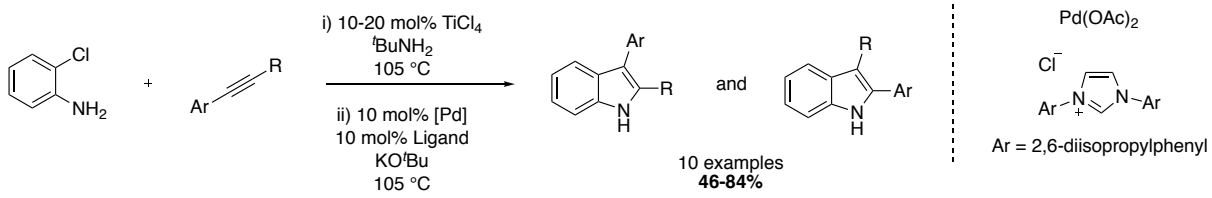
Similarly, Corma and co-workers also used a gold-complex to synthesize a single example of a fused cyclobutapyrrolidine compound in 75% yield and greater than 99% diastereoselectivity (Scheme 1.56).[79] In this case, hydroamination of two phenylacetylene molecules to *p*-toluidine formed a bis(enamine) intermediate, which was reacted with dimethylacetylenedicarboxylate to form the final product.



Scheme 1.56 Corma (2010) – Sequential Gold-Catalyzed Hydroamination/ Reaction Towards the Synthesis of Cyclobutapyrrolidine

1.2.2.1.2 Indole

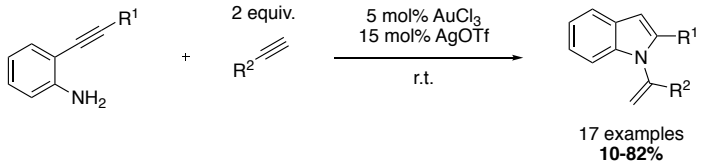
The intermolecular hydroamination of alkynes and *ortho*-chloroaniline derivatives was combined with a 5-endo Heck cyclization to afford a variety of indoles regioselectively (Scheme 1.57).[80-81] After titanium-catalyzed hydroamination, 10 mol% of palladium acetate and 10 mol% of the *N*-heterocyclic carbene ligand were added to the reaction mixture to afford 10 examples of indoles in 46-84% yields.[80] By changing the ligand for the second step to tricyclohexylphosphine, the scope of the reaction could be improved to allow for further substitution on other positions of the *ortho*-chloroaniline.[81]



Scheme 1.57 Ackermann (2008) – Sequential Titanium-Catalyzed Hydroamination/Palladium-Catalyzed Heck Reactions Towards the Synthesis of Indoles

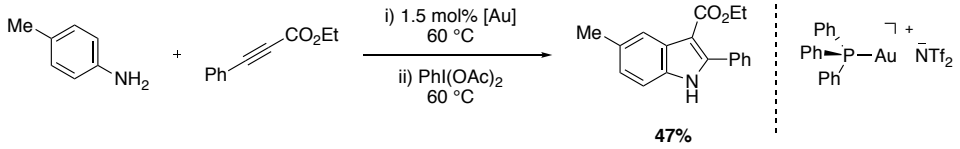
The synthesis of *N*-vinylindoles was performed through a double hydroamination of terminal alkynes with *ortho*-alkynylanilines to deliver 17 examples of the desired product in varying yields (Scheme 1.58).[82] The first hydroamination is an intermolecular reaction between the aniline and the terminal alkyne, while the second hydroamination is an intramolecular reaction between the formed imine and the alkyne. Both reactions are performed in the presence

of 5 mol% of gold trichloride and 15 mol% of silver triflate. The Markovnikov regioselectivity is exclusively formed in the first step of the reaction for the majority of cases demonstrated, except in the case where the terminal alkyne used is hex-1-yne.



Scheme 1.58 Li (2007) – Sequential Gold-Catalyzed Double-Hydroamination Reactions Towards the Synthesis of *N*-Vinylindoles

The hydroamination of methyl 3-phenylpropiolate and *p*-toluidine was performed with catalytic amounts of [bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold complex. The newly formed *N*-arylenamine was then cyclized to the indole under oxidizing conditions with (diacetoxyiodo)benzene (Scheme 1.59).[83]

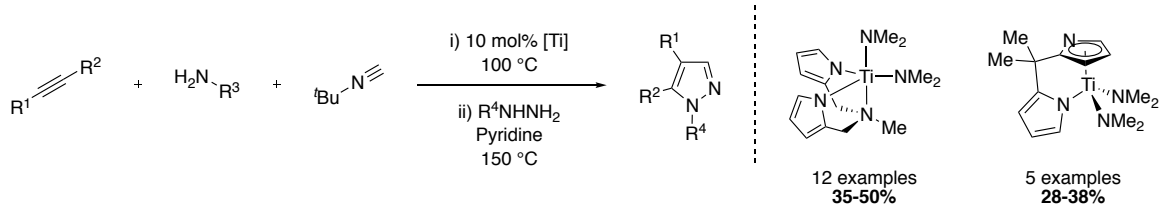


Scheme 1.59 Skrydstrup (2009) – Sequential Gold-Catalyzed Hydroamination/Cyclization Towards the Synthesis of an Indole

1.2.2.2 Formation of 5-Membered *N,N*- or *N,O*-Heterocycles

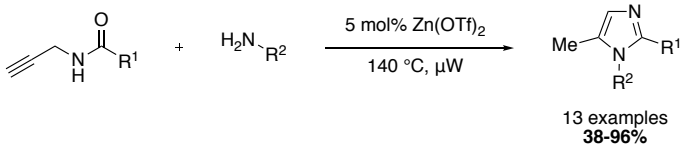
1.2.2.2.1 Pyrazole and Imidazole

Odom and co-workers also reported a four-component synthesis of 17 examples of pyrazoles (Scheme 1.60).[84] Through a titanium-catalyzed coupling of 1 equivalent of isonitrile, 1 equivalent of amine and 1 equivalent of alkyne, 1,3-diimines were generated, which underwent an *in situ* cyclization with hydrazine and derivatives to produce pyrazoles in moderate yields.



Scheme 1.60 Odom (2009) – Sequential Titanium-Catalyzed Hydroamination/Iminoamination/Hydrazine Addition Reactions Towards the Synthesis of Pyrazoles

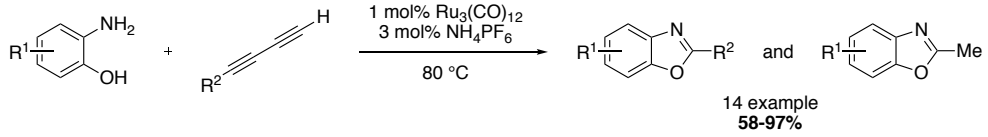
Zinc triflate was reported for the catalytic synthesis of 13 examples of imidazoles in moderate to great yields (Scheme 1.61).[85] After the zinc-catalyzed intermolecular hydroamination of propargylamides, a cyclization between the formed imine and the amide group occurs, which is followed by a dehydration event to afford the imidazoles. While the majority of examples demonstrated delivers 1,2,5-trisubstituted imidazoles, a single example of a 2,5-disubstituted imidazole was shown using ammonia as the nitrogen source.



Scheme 1.61 Beller (2011) – Sequential Zinc-Catalyzed Hydroamination/Cyclization/Dehydration Reactions Towards the Synthesis of Imidazoles

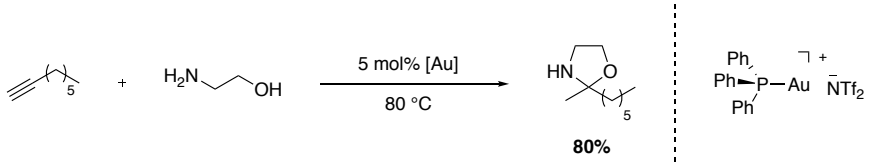
1.2.2.2.2 Oxazolidine, Oxazole and Others

Benzoxazoles can be synthesized from the intermolecular hydroamination of 1,3-diynes and *ortho*-aminophenol derivatives (Scheme 1.62).[86] The reaction mechanism reported by Yamamoto and co-workers starts from a double hydroamination of the diyne, followed by a C-C bond cleavage to form the desired products and ketone by-products. Unfortunately, the transformation reported delivers a mixture of two regioisomers.



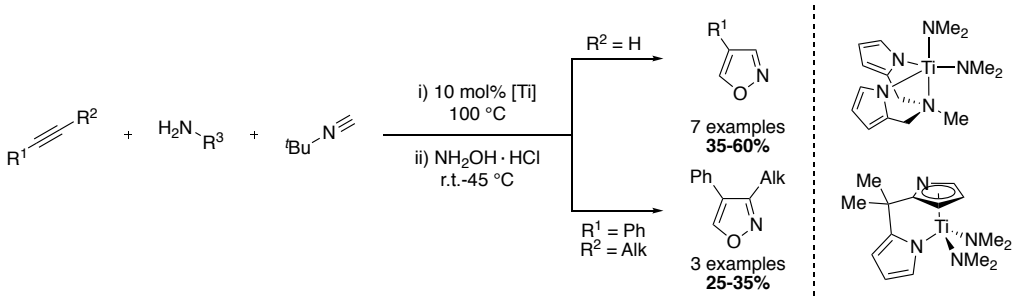
Scheme 1.62 Yamamoto (2003) – Sequential Ruthenium-Catalyzed Double Hydroamination/C-C Bond Cleavage Reactions Towards the Synthesis of Benzoxazoles

Leyva and Corma demonstrated a single example of an oxazolidine being synthesized through a [bis(trifluoromethanesulfonyl)imidate](triphenylphosphine) gold-complex catalyzed hydroamination of oct-1-yne and 2-aminoethan-1-ol (Scheme 1.63).[87] The chemoselectivity of the gold catalyst to perform hydroamination over hydroalkoxylation was crucial for the transformation to deliver a single product after the nucleophilic attack of the hydroxyl group to the newly formed imine.



Scheme 1.63 Corma (2009) – Sequential Gold-Catalyzed Hydroamination/Cyclization Reactions Towards the Synthesis of a Oxazolidine

Odom's four-component strategy could be applied to synthesize 4-substituted isoxazoles from terminal alkynes and 3,4-disubstituted isoxazoles from internal alkynes, albeit the yields were modest (Scheme 1.64).[88] The methodology involved a one-pot titanium-catalyzed multicomponent coupling reaction followed by the addition of hydroxylamine. The choice of titanium-catalyst used was dependent on the starting materials used, for example, for all the phenylacetylene derivatives, the tridentate titanium complex was used, while for all the internal alkynes, the bidentate titanium scomplex was used.

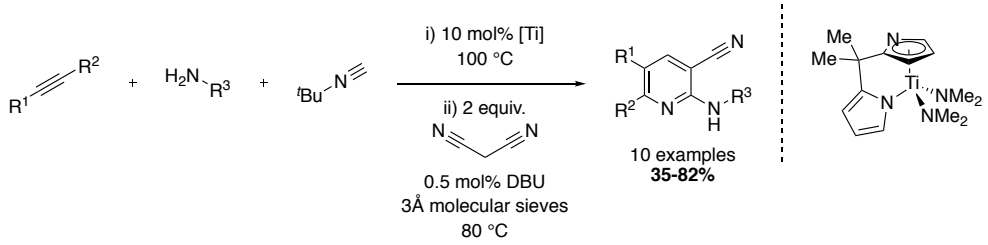


Scheme 1.64 Odom (2012) – Sequential Titanium-Catalyzed Hydroamination/Iminoamination/Hydroxylamine Addition Reactions Towards the Synthesis of Mono- and Di-Substituted Isoxazoles

1.2.2.3 Formation of 6-Membered *N*-Heterocycles

1.2.2.3.1 Dihydropyridine and Pyridine

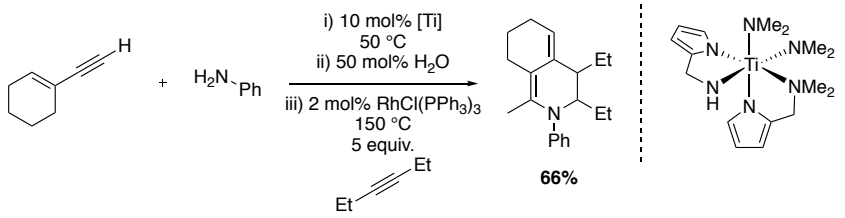
The strategy of forming 1,3-diimides through intermolecular hydroamination of alkynes followed by iminoamination was also implemented towards the synthesis of 2-amino-3-cyanopyridines in a one-pot procedure in moderate to good yields (Scheme 1.65).[89] According to studies performed by the authors, a Dimroth rearrangement occurs upon treatment of the reaction mixture with base and malononitrile to afford a single isomer of the final product and *tert*-butylamine as a side product.



Scheme 1.65 Odom (2014) – Sequential Titanium-Catalyzed Hydroamination/Iminoamination/Dimroth Rearrangement Reactions Towards the Synthesis of 2-Amino-3-Cyanopyridines

Odom and co-workers also demonstrated an example of a tandem intermolecular hydroamination of 1-ethynylcyclohexene with aniline followed by a C-H activation/insertion and

a 6-π electrocyclization to afford a dihydropyridine in 66% yield (Scheme 1.66).[90] The authors disclosed that in order for the one-pot reaction to be successful, prior to the addition of Wilkinson's catalyst, 50 mol% of water had to be added to decompose the titanium catalyst, which was thought to interfere with the second reaction.

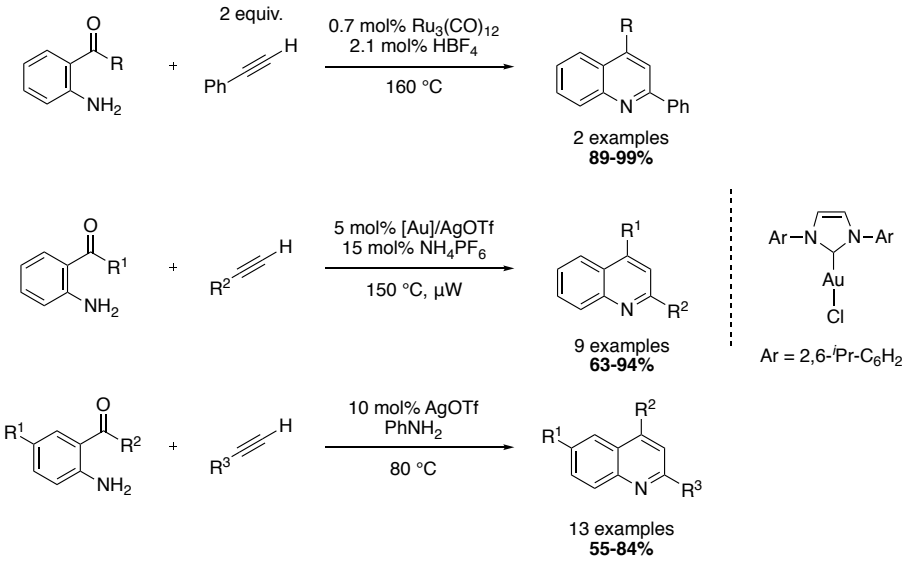


Scheme 1.66 Odom (2004) – Sequential Titanium-Catalyzed Hydroamination/C-H Activation/Electrocyclization Reactions Towards the Synthesis of a Dihydropyridine

1.2.2.3.2 Dihydroquinoline, Quinoline, Tetrahydroquinoline, Tetrahydroisoquinoline and Naphthyridine

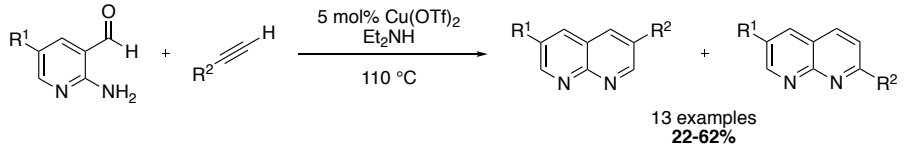
Wakatsuki and co-workers reported that catalytic amounts of triruthenium dodecarbonyl and tetrafluoroboric acid could be used to synthesize 2,4-disubstituted quinolines (Scheme 1.67 – top).[91] After the intermolecular hydroamination of alkynes with 2-amino aromatic ketones, a nucleophilic attack on the ketone occurs from the enamine formed, thus forming the bicyclic-core. Upon dehydration, 2 examples of quinolines were synthesized in excellent yields. This transformation has also been shown to be feasible using an NHC-gold complex, which delivered 9 examples of the desired quinoline in moderate to great yields (Scheme 1.67, middle).[92] Furthermore, Li and co-workers have demonstrated that silver triflate is also competent towards the synthesis of 2,4,6-trisubstituted quinolines following a similar approach (Scheme 1.67 – bottom).[93] In their report, however, aniline was used as a mediator for the reaction to occur. The mechanism proposed by the authors started from the hydroamination of the terminal alkyne with aniline to form a silver enaminyl species. Nucleophilic attack to the ketone functional group,

followed by intramolecular cycloaddition leads to the release of aniline. Finally, aromatization delivered the quinoline product in 55-84% yields. Palladium bromide in the presence of acetic or pivalic acid has also been shown to be a competent catalyst for the synthesis of 2,3,4-trisubstituted quinolines from internal alkynes and 2-amino aromatic ketones.[94]



Scheme 1.67 Wakatsuki (1999), Che (2007), Li (2011) – Sequential Metal-Catalyzed Hydroamination/Cyclization Reactions Towards the Synthesis of Quinolines

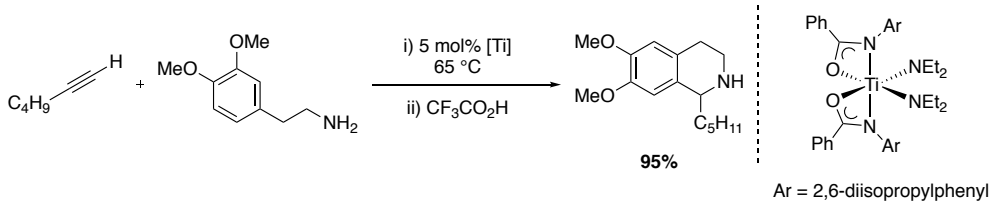
A similar approach was reported for the synthesis of naphthyridines (Scheme 1.68).[95] Peshkov and co-workers used catalytic amounts of copper triflate and stoichiometric amounts of diethylamine to synthesize 13 examples of 1,8-naphthyridines in moderate yields of up to 62%.



Scheme 1.68 Peshkov (2016) – Sequential Copper-Catalyzed Hydroamination/Cyclization Reactions Towards the Synthesis of Naphthyridines

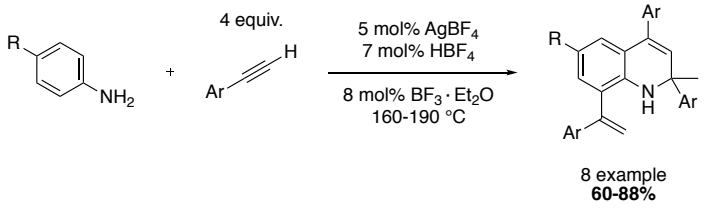
In 2003, Zhang and Schafer showed the synthesis of a dihydroisoquinoline substrate in 95% yield (Scheme 1.69).[25] A hydroamination reaction using a bis(amidate)bis(amido)titanium

catalyst was performed first, followed by the addition of trifluoroacetic acid, which triggered a Pictet-Spengler type reaction to afford the desired product. In a following publication, the substrate scope of the reaction was increased to accommodate aryl alkyne starting materials.[26]



Scheme 1.69 Schafer (2003) – Sequential Titanium-Catalyzed Hydroamination/Pictet-Spengler Reactions Towards the Synthesis of a Tetrahydroisoquinoline

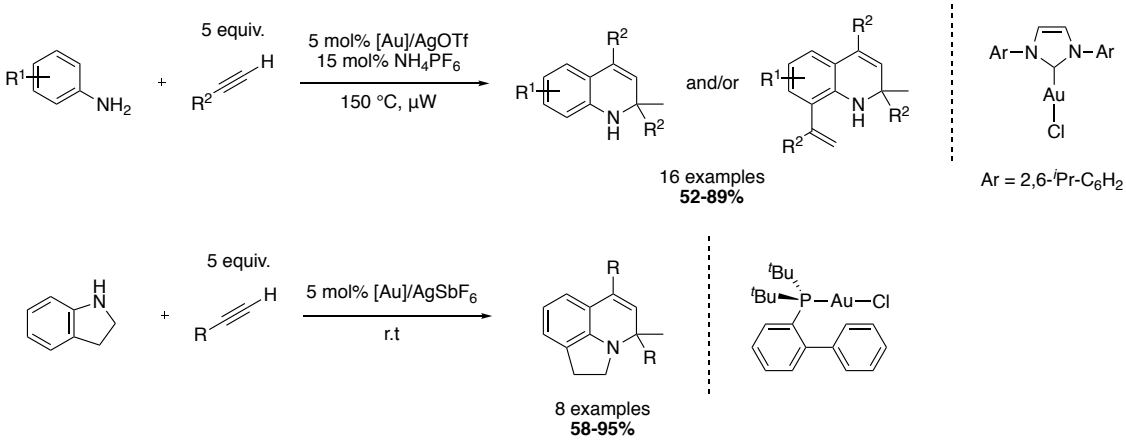
Poly-substituted 1,2-dihydroquinoline derivatives were synthesized in a one-pot domino process in the presence of catalytic amounts of silver tetrafluoroborate, tetrafluoroboric acid and boron trifluoride (Scheme 1.70).[96] The transformation occurs through an intermolecular hydroamination, followed by an alkyne addition to the formed imine, intramolecular hydroarylation and then a second intermolecular hydroarylation of a third molecule of alkyne.



Scheme 1.70 Li (2005) – Sequential Silver-Catalyzed Hydroamination/Alkyne Addition/Hydroarylation Reactions Towards the Synthesis of Dihydroquinolines

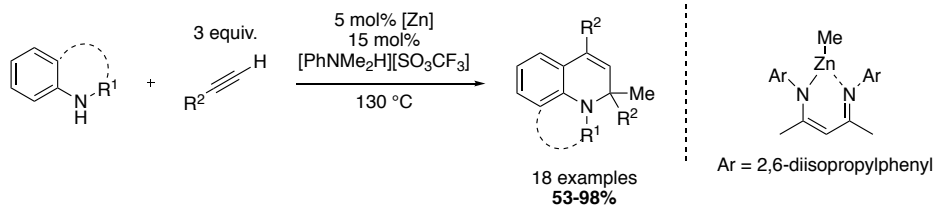
A variety of gold-complexes have been used for the tandem hydroamination/alkyne addition/hydroarylation reactions towards the synthesis dihydroquinolines and quinolines (Scheme 1.71).[92, 97-98] Che and co-workers showed that in the majority of cases, using aryl amine derivatives and excess terminal alkynes in the presence of catalytic amounts of an NHC-gold complex, a single hydroarylation reaction occurs to deliver 1,2-dihydroquinolines in moderate to

great yields. However, in 3 examples due to the occurrence of a second hydroarylation reaction, a mixture of products is formed. Additionally, the reaction with a phosphine-based gold complex was also successful using indoline instead of aniline to produce 8 examples of tricyclic *N*-heterocycles in 58-95% yields. Pentamethylcyclopentadienylrhodium chloride dimer has also been used as a catalyst to synthesize 1,2-dihydroquinolines from terminal alkynes and anilines in yields of 34-89%.[99] In the report by Kumaran and Leong, a second intermolecular hydroarylation was not stated.



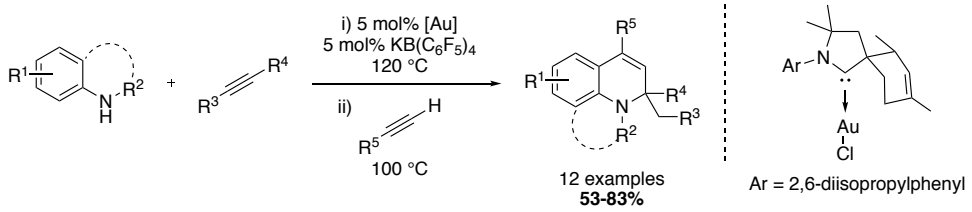
Scheme 1.71 Che (2007) – Sequential Gold-Catalyzed Hydroamination/Alkyne Addition/Hydroarylation Reactions Towards the Synthesis of Dihydroquinolines

Catalytic amounts of zinc β-diiminate-complex and *N*,*N*-dimethylaniline hydrotrifluoromethyl sulfonate have been identified as a catalyst for the synthesis of 1,2-dihydroquinolines (Scheme 1.72).[100]



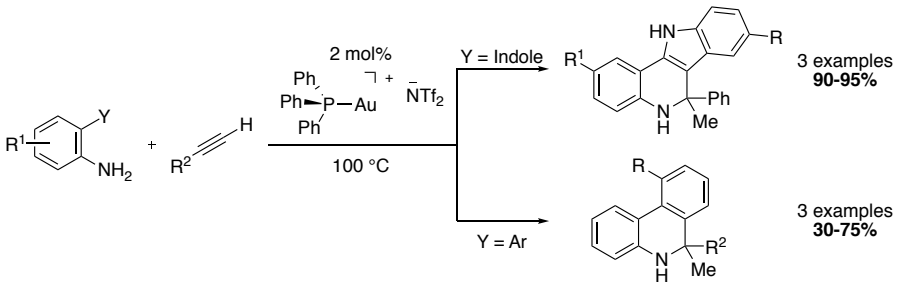
Scheme 1.72 Blechert (2012) – Sequential Zinc-Catalyzed Hydroamination/Alkyne Addition/Hydroarylation Reactions Towards the Synthesis of Dihydroquinolines

The scope of 1,2-dihydroquinolines synthesized using a one-pot three-component approach was greatly improved when internal alkynes were reported to be viable starting materials (Scheme 1.73).[97] Bertrand and co-workers were able to synthesize 12 examples of 1,2-dihydroquinolines containing a variety of substitutions in 53-83% yield. The reported methodology not only allowed for the use of internal alkynes in the first reaction, but it also allowed for a different alkyne to be used in the second step, thus further increasing the scope of the products synthesized.



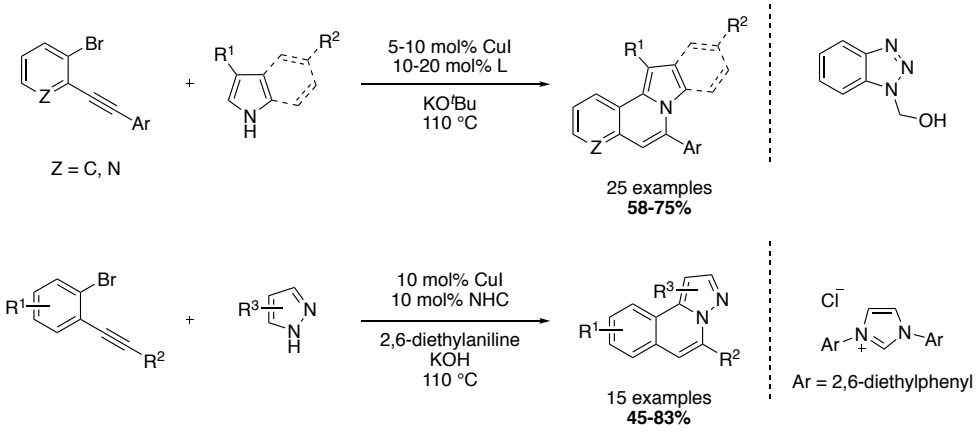
Scheme 1.73 Bertrand (2009) – Sequential Gold-Catalyzed Hydroamination/Alkyne Additon/Hydroarylation Reactions Towards the Synthesis of Dihydroquinolines

Patil and co-workers demonstrated that a [bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold complex can be used to synthesize fused-tetrahydroquinolines (Scheme 1.74).[98] Following the hydroamination reaction, hydroarylation of the *ortho*-substitutent on the aniline forms the final product.



Scheme 1.74 Patil (2010) – Sequential Gold-Catalyzed Hydroamination/Hydroarylation Reactions Towards the Synthesis of Tetrahydroquinolines

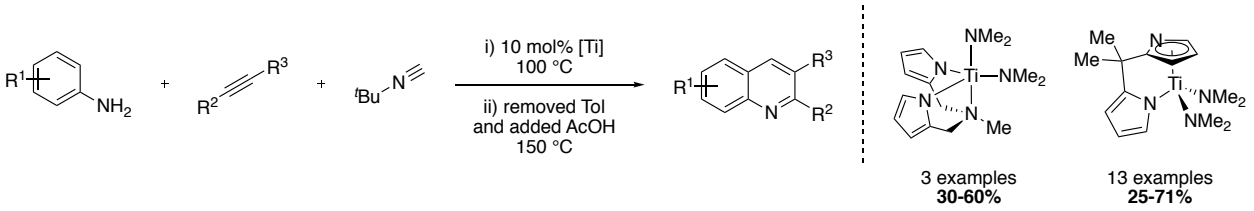
The groups of Verma and Wu disclosed two copper-catalyzed tandem hydroamination/arylation reactions towards the synthesis of multi-fused isoquinolines starting from *ortho*-bromoarylalkynes and *N*-heterocyles, such as pyrroles and pyrazoles (Scheme 1.75).[101-102] In both cases, copper iodide was used as the metal source and potassium alkoxide/hydroxide were used as the base. However, while Verma and co-workers reported the use of a triazole derivative as their ligand, Wu and co-workers reported the use of an NHC compound. Overall, the substrate scope presented and yields obtained were comparable between the two methodologies. A follow-up publication using microwave technology was also disclosed by Verma and co-workers, although no significant improvement on the yields were observed.[103]



Scheme 1.75 Verma (2012), Wu (2013) – Sequential Copper-Catalyzed Hydroamination/Arylation Reactions Towards the Synthesis of Multi-Fused Isoquinolines

A three-component strategy could be applied to synthesize quinolines from aniline, alkyne and *tert*-butylisonitrile (Scheme 1.76).[104] The methodology involves the synthesis of *N*-aryl-1,3-diimines through hydroamination/iminoamination followed by a Brönstead acid-catalyzed intramolecular electrophilic attack on the pendant aromatic ring, which triggers the release of *tert*-butylamine and aromatization of the nitrogen heterocycle. The tridentate pyrrolyl

titanium complex was chosen as the catalyst when terminal alkynes were used, while the bidentate pyrrolyl titanium complex was chosen for internal alkynes.

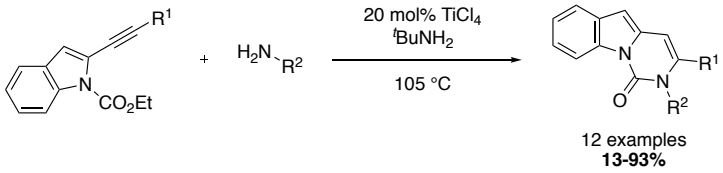


Scheme 1.76 Odom (2009) – Sequential Titanium-Catalyzed Hydroamination/Iminoamination/Cyclization Reactions Towards the Synthesis of Quinolines

1.2.2.4 Formation of 6-Membered *N,N*- or *N,O*-Heterocycles

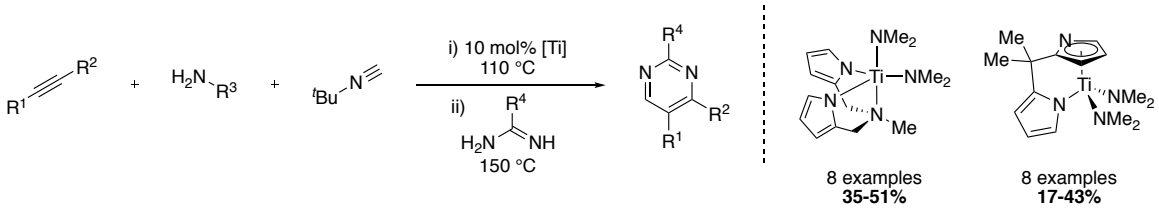
1.2.2.4.1 Tetrahydropyrimidine, Pyrimidine and Quinoxaline

Through a titanium-catalyzed hydroamination of *N*-ethoxycarbonyl-2-alkynylindole, followed by the nucleophilic attack of the enamine to the ester functional group, 12 examples of pyrimido[1,6-α]indolones were synthesized in a wide range of yields (Scheme 1.77).[105]



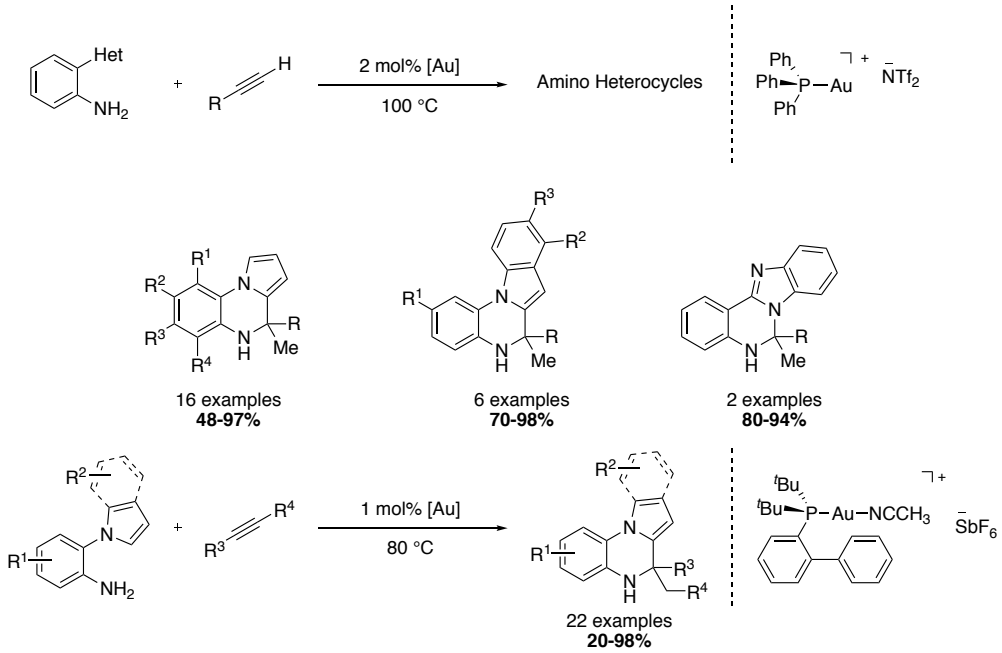
Scheme 1.77 Rossi (2009) – Sequential Titanium-Catalyzed Hydroamination/Cyclization Reactions Towards the Synthesis of Pyrimido[1,6-α]Indolones

Substituted pyrimidines can be accessed *via* a one-pot procedure through the formation of 1,3-diimides followed by the addition of amidines (Scheme 1.78).[106] While the yields obtained were poor, the transformation was reported to be regioselective depending on the titanium catalyst employed.



Scheme 1.78 Odom (2010) – Sequential Titanium-Catalyzed Hydroamination/Iminoamination/Amidine Addition Reactions Towards the Synthesis of Pyrimidines

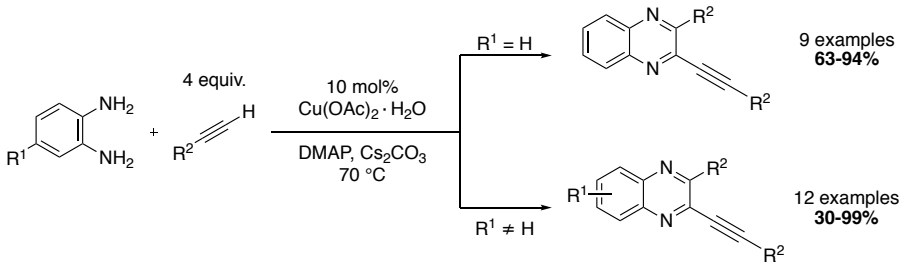
Starting from anilines containing an *N*-heterocycle on the *ortho*-position and alkynes, a variety of fused-quinoxalines and fused-quinazolines were reported in two separate publications (Scheme 1.79).[98, 107] While both methodologies make use of phophine-bound gold complexes, which have been shown to perform tandem hydroamination/hydroarylation reactions, Patil and co-workers were limited to the use of terminal alkynes.



Scheme 1.79 Patil (2010), Liu (2011) – Sequential Gold-Catalyzed Hydroamination/Hydroarylation Reactions Towards the Synthesis of Fused-Quinoxalines

Chen and co-workers reported a copper-catalyzed synthesis of quinoxaline starting from benzene-1,2-diamine and terminal alkyne (Scheme 1.80).[108] While a single product was obtained

with unsubstituted diamines in moderate to great yields, a mixture of regioisomers were obtained with 4-substituted benzene-1,2-diamines. Mechanistically, the authors propose that an intermolecular *anti*-Markovnikov alkyne hydroamination occurs, followed by a cyclization of the *ortho*-nitrogen on to the formed enamine. Attack of a second equivalent of alkyne and oxidation leads to the formation of product.



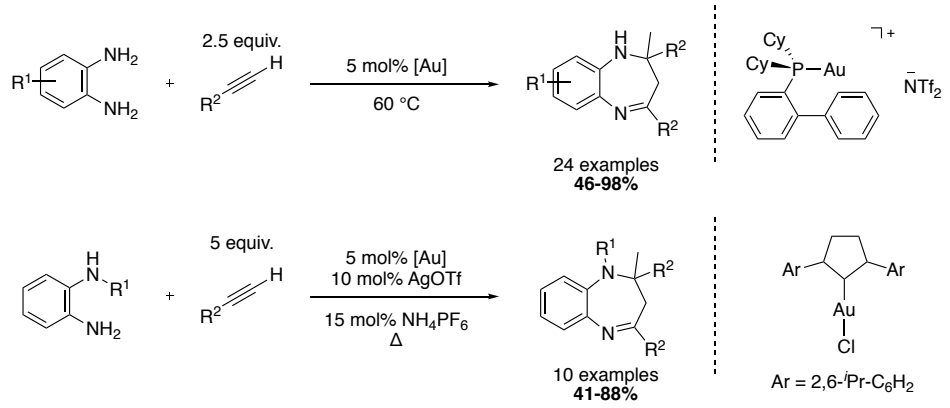
Scheme 1.80 Chen (2011) – Sequential Copper-Catalyzed Hydroamination/Cyclization/Alkyne Additon Reactions Towards the Synthesis of Quinoxalines

1.2.2.5 Formation of 7-Membered *N,N*- or *N,O*-Heterocycles

1.2.2.5.1 Dihydrobenzodiazapine and Benzodiazepine

The synthesis of dihydrobenzodiazapine from benzene-1,2-diamine and terminal alkynes can be accomplished using gold catalysts (Scheme 1.81).[109-110] While the groups of Liu and Xu focused on a phosphine-based gold complex,[109] Luo and co-workers showcased their methodology using an NHC-gold complex.[110] The main difference between the two methodologies reported was the starting diamine. In the former report, primary benzene-1,2-diamines were used as the starting material and in the latter report, mixed primary/secondary benzene-1,2-diamines were used. Overall the yield of the dihydrobenzodiazapines obtained is comparable in the two systems. The proposed mechanism for both reports begins with double hydroamination of the benzene-1,2-diamine to form an dienamine intermediate, which can

readily tautomerize to an enamine-ketimine intermediate. Then, the 7-membered cycle is formed upon an intramolecular addition of the enamine to the ketimine.



Scheme 1.81 Xu (2012), Luo (2014) – Sequential Gold-Catalyzed Double Hydroamination/Cyclization Reactions Towards the Synthesis of Dihydrobenzodiazapines

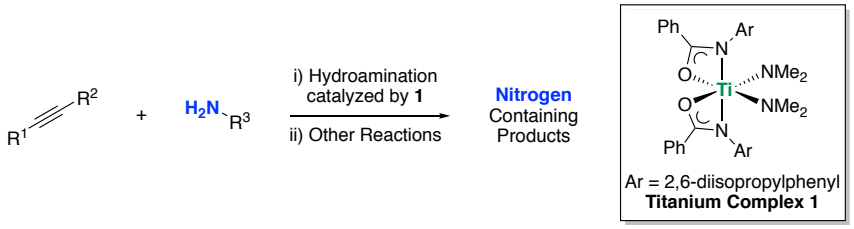
1.2.2.6 Conclusion

A wide variety of *N*-heterocycles have been synthesized through sequential hydroamination followed by another reaction. By far, indoles and multi-fused heterocycles have received the greatest amount of attention. The development of new synthons through hydroamination could help increase the targeted heterocyclic compounds. For example, there is currently a single methodology towards the synthesis of pyridines starting from an intermolecular hydroamination of alkynes, even though pyridines were the second most common motif in U.S. FDA nitrogen containing heterocycle approved drugs.

1.3 Scope of Thesis

The development of sequential methods featuring the bis(amidate)bis(amido)titanium-catalyzed intermolecular hydroamination of alkynes, followed by other reactions is the focus of this thesis (Scheme 1.82). Among the reactions attempted after the hydroamination reaction were catalytic hydrogenation (Chapter 2 and 3) and *N*-heterocycle formation (Chapter 4).

Stoichiometric work was also performed towards the isolation of organometallic intermediates (Chapter 3).



Scheme 1.82 Overview of Scope of Thesis

Chapter 2 focuses on the catalytic synthesis of secondary amines using a previously reported bis(amidate)bis(amido)titanium complex. While the Schafer group has extensively studied the hydroamination of alkynes using this titanium complex, the formation of amines from the imine intermediates relied heavily on the use of stoichiometric reductants, such as sodium borohydride and lithium aluminum hydride. To access a more sustainable synthesis of amines, the intermolecular hydroamination process was further examined, which led to the reduction of catalyst loading. The minimization of waste produced was also accomplished with the change from stoichiometric hydride sources for the reduction step, to the use of catalytic amounts of palladium on carbon (Pd/C) and hydrogen (H_2) gas. Due to the great regioselectivity of the first step and clean hydrogenation of products to the amines, a facile synthesis and isolation of 23 examples of secondary amines was accomplished.

The formation of primary amines through an intermolecular hydroamination of alkynes has been reported only once and it made use of diphenylmethanamine as the nitrogen source. An alternative ammonia surrogate that has received some attention in the past 10 years has been *N*-silylated amines. While the intermolecular hydroamination of alkynes and *N*-silylamines has been attempted in the past, no successful reports prior to this work had been published. Thus,

Chapter 3 focuses on the study of this reaction using the same titanium complex as above. Under our reaction conditions, the reaction was successful and allowed for the synthesis of 25 examples of *N*-silylenamines. Upon treatment of the hydroamination mixture with Pd/C and H_2 gas, 9 examples of primary amines were obtained. Stoichiometric work was also performed to isolate a series of relevant organometallic complexes.

The tautomerization of the enamine to the imine products formed from the hydroamination reaction was not as readily achieved in the case with silicon substitution on the nitrogen as compared to the case with carbon substitution on the nitrogen. This observation showed that a primary enamine surrogate could be reliably obtained. This new synthon inspired the synthesis of pyridines, which is the focus of Chapter 4. After the hydroamination reaction, in the presence of α,β-unsaturated carbonyls, molecular sieves, catalytic amounts of tetra-butylammonium fluoride, and oxidant, a large variety of pyridines were formed. This methodology allowed for the synthesis of mono-, di-, tri-, tetra-, and penta-substituted pyridines in moderate to good yields.

Finally, in Chapter 5, several preliminary results that further exploit the use of our preferred titanium hydroamination catalyst allow for further research projects within the Schafer group. Conclusions to the research presented in this thesis will also be presented.

Chapter 2: Facile Synthesis and Isolation of Secondary Amines via a Sequential Titanium(IV)-Catalyzed Hydroamination and Palladium-Catalyzed Hydrogenation

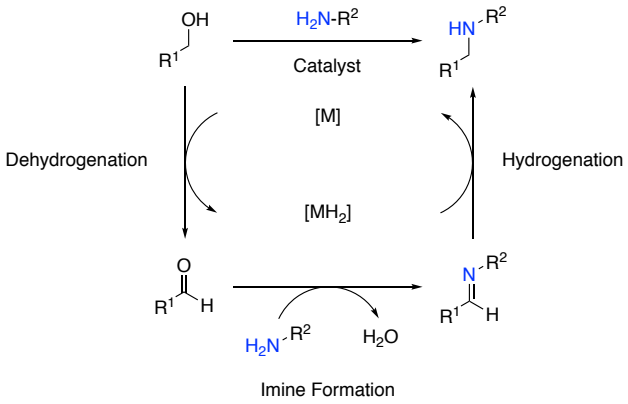
2.1 Introduction

The synthesis of secondary amines from primary amines has been the topic of intense investigation. In order to develop selective syntheses, the formation of by-products, such as tertiary amines or quaternary ammonium salts has to be suppressed, either through the implementation of protecting groups or through the modification of starting material and/or product reactivity. In the former case, the introduction of protecting groups adds two steps to the synthesis. Therefore, it is not surprising that efforts have been applied towards the development of methodologies in which unprotected amines can be used. Among the catalytic syntheses developed for the selective formation of secondary amines, this section will focus on the amination of alcohols, C-N cross-coupling, hydroaminomethylation and hydroamination.

2.1.1 Amination of Alcohols

Reductive amination is a facile transformation that allows for the synthesis of secondary amines starting from a carbonyl moiety, a primary amine and a hydride source. The synthesis of a carbonyl functional group can be derived from feedstocks through a variety of transformations. For example, aldehydes and ketones can be formed from alkenes through ozonolysis, hydroformylation, or hydration followed by oxidation and from alkynes through hydration followed by tautomerization. The development of methodologies, which use pre-carbonyl starting materials, would be desirable to reduce the synthetic steps required.

The reaction between an alcohol and a primary amine in the presence of a catalyst can lead to the synthesis of secondary amines through a hydrogen borrowing strategy (Scheme 2.1).[111-112] The amination of alcohols starts from the *in situ* formation of a carbonyl group by dehydrogenation, which in the presence of a primary amine forms an imine. This imine can then be hydrogenated to deliver the desired secondary amine. Among the advantages of this methodology is the formation of water as the only by-product of the reaction as well as the minimization of side reactions that can occur in reductive amination, such as aldol condensations. On the other hand, the reactions usually require extensive heating at temperatures that are either at or above the boiling point of the solvent, which requires extra caution.

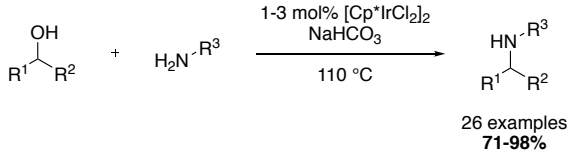


Scheme 2.1 General Amination of Alcohols Towards the Synthesis of Secondary Amines

While heterogeneous catalysts for the amination of alcohols have been known since the early 20th century and are used industrially for the synthesis of lower alkyl amines, the first homogeneous catalysts for this transformation were only reported in the 80s. Simultaneous research by Grigg *et. al*[113] and Watanabe *et. al*[114] was disclosed in 1981. While Grigg's study included the use of ruthenium, rhodium and iridium as catalysts, and the amination of alcohols was performed with primary and secondary amines,[113] Watanabe's study focused on the dichlorotris(triphenylphosphine)ruthenium catalyzed amination of alcohols with aniline.[114] In

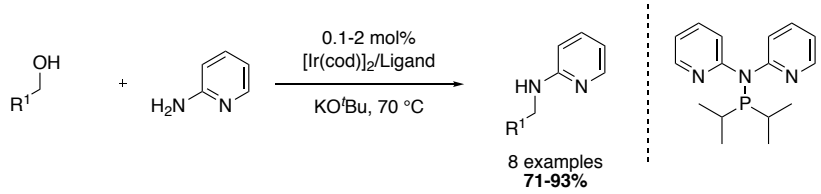
both cases, substrate scope was limited to simple alcohols, such as methanol and ethanol, and the reaction conditions required high temperatures of up to 180 °C.

In recent years, a more diverse substrate scope and milder reaction conditions have been realized. Fujita *et. al* demonstrated that a catalytic system consisting of di-μ-chloro-bis[chloro(pentamethylcyclopentadienyl)iridium(III)] and sodium bicarbonate could perform the amination reaction with alcohols containing a variety of substituents, which included nitro-, cyano-, and ester-substituents (Scheme 2.2 – top).[115] The same research group also showed that the reaction can be accomplished in water in an air atmosphere using a water-soluble iridium catalyst.[116]



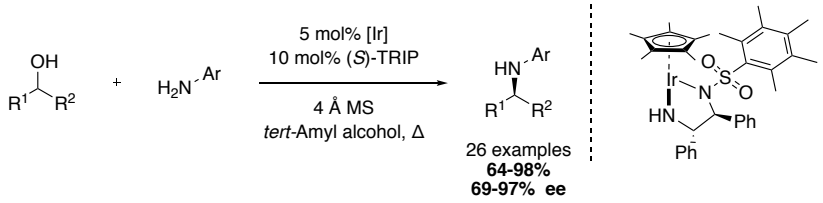
Scheme 2.2 Yamaguchi (2008, 2011) – Iridium-Catalyzed Amination of Alcohols Towards the Synthesis of Secondary Amines

In 2009, Kempe and co-workers disclosed a P,N-ligand stabilized iridium complex that showed high reactivity, which allowed for the amination reactions to be accomplished with low catalyst loading of 0.1 mol% and at comparatively mild temperature (70 °C) (Scheme 2.3 – top).[117] The same catalyst system was used towards the synthesis of diamines starting from aminoalcohols (Scheme 2.3 – bottom).[118]



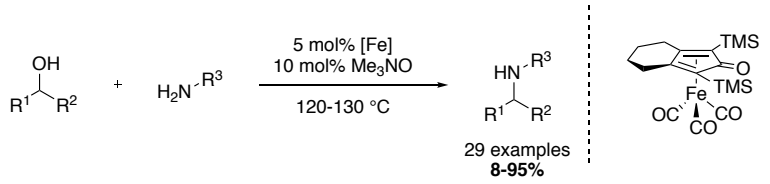
Scheme 2.3 Kempe (2009) – Iridium-Catalyzed Amination of Alcohols Towards the Synthesis of Secondary Amines

Up until Zhao and co-workers disclosed an enantioselective amination of alcohols in 2014, no asymmetric examples had been reported. Using cooperative catalysis between an iridium catalyst and a chiral phosphoric acid, the authors were able to synthesize 26 examples of secondary amines in 64-98% yields and up to 97% of enantiomeric excess (Scheme 2.4).[119] Following a similar procedure, Zhao and co-workers also reported a dynamic kinetic asymmetric amination starting from a mixture of four isomers to deliver enantiopure α-branched amines.[120] Dual-enzyme catalysis has also been reported to deliver secondary amines from alcohol in up to 96% yield and 99% enantiomeric excess.[121]



Scheme 2.4 Zhao (2014) – Cooperative Iridium/Chiral-Phosphoric Acid Catalyzed Enantioselective Amination of Alcohols Towards the Synthesis of Secondary Amines

Another area of improvement has been the shift towards the implementation of cheaper metals, such as iron.[122-126] While Singh and co-workers showed that iron phthalocyanine was able to perform the amination of alcohols, their substrate scope was limited to heterocyclic amines.[122] On the other hand, Barta and co-workers reported an iron-catalyzed amination of a wide range of alcohols with aryl and benzyl amines delivering 29 examples of secondary amines.[123]



Scheme 2.5 Barta (2014) – Iron-Catalyzed Amination of Alcohols Towards the Synthesis of Secondary Amines

While improvements have been reported on the amination of alcohols, some goals remain unsolved. The development of more active catalysts could help increase the substrate scope to include a wider range of alcohols and amines as well as decrease the need for heating at or above boiling point temperatures.

2.1.2 C-N Cross-Coupling Reactions

Traditional cross-coupling reactions refer to the formation of a C-C bond through a metal catalyzed oxidative addition, transmetallation and reductive elimination steps. The cross-coupling field is of such importance that the 2010 Nobel Prize in Chemistry was awarded to Professors Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their work in the development of palladium-catalyzed cross coupling reactions.[127]

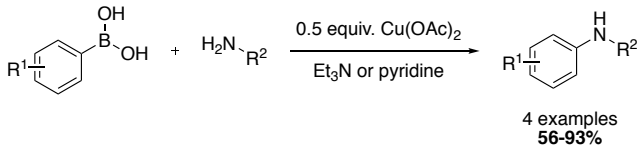
Just as significant, is the research on the C-N cross-coupling reaction, which includes the copper-mediated or catalyzed Ullmann-Goldberg reaction and Chan-Evans-Lam reaction as well as the palladium-catalyzed Buchwald-Hartwig coupling.[3, 128-129] While the copper reactions are more robust, in the sense that water and oxygen exclusion are not necessary for the reaction to occur, the substrate scope is usually limited. On the other hand, the scope of the palladium-catalyzed reactions is wide, but palladium is comparatively expensive and toxic and usually requires ligands to tune the reactivity.[130] In both cases, numerous reports are available and thus

the focus of this section will be to give a historical perspective while highlighting the important advancements towards the synthesis of secondary amines in particular.

2.1.2.1 Copper-Mediated or Catalyzed C-N Cross Coupling

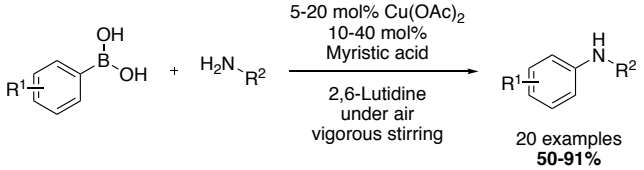
The Ullmann reaction is a copper-mediated nucleophilic aromatic substitution between an aryl amine and an aryl halide.[131] The addition of potassium carbonate allows for the reaction to be performed with catalytic amounts of copper, which is known as the Ullmann-Goldberg reaction.[132] While the Ullmann-Goldberg reaction has been known since the early 20th century, the requirement for reflux conditions of over 260 °C limited the scope of the reaction and thus the practicality of the transformation. Recent advances in copper catalysis towards the synthesis of C-N bonds include the development of reactive copper-complexes[133-136] or the utilization of other coupling agents, which include organoboron,[137-139] organosilicon,[140] organolead,[141-142] organotin[143-144] and organobismuth.[145-146]

In 1998, the groups of Chan,[137] and Lam[138] independently reported a general protocol for a copper-mediated arylation of a wide variety of nitrogen nucleophiles, which was accomplished at room temperature using boronic acids (Scheme 2.6). While Chan and co-workers were able to use alkyl/aryl amines, amides, imides, ureas, sulfonamides and carbamates as their nitrogen source, Lam and co-workers focused on heterocyclic amines. In both cases, however, sub- or super-stoichiometric amounts of copper ranging from 0.5 to 1.5 equivalents were necessary.



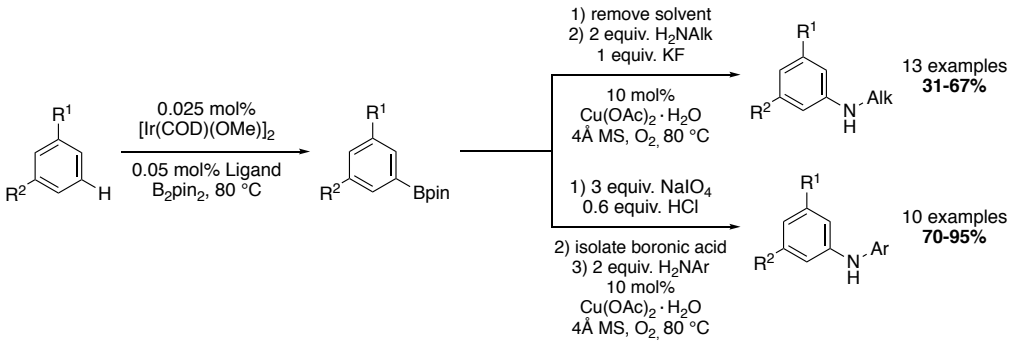
Scheme 2.6 Chan (1998) – Copper-Mediated Arylation of Amines Towards the Synthesis of Secondary Amines

Shortly after, the catalytic version of the reaction was accomplished by Collman and Zhong using catalytic amounts of di-μ-hydroxo-bis[(N,N,N′.N′-tetramethylethylenediamine)copper] chloride, albeit the nitrogen source studied was limited to imidazoles.[147] A more general copper-catalyzed C-N cross-coupling of aryl boronic acids with simple primary amines to deliver secondary amines was reported by Antilla and Buchwald in 2001 (Scheme 2.7).[148] The coupling was accomplished at room temperature under catalytic copper acetate/myristic acid using 2,6-lutidine as the base. Examples of monoaryl and diaryl secondary amines were synthesized in 50-91% yields.



Scheme 2.7 Buchwald (2003) – Copper-Catalyzed Arylation of Amines Towards the Synthesis of Secondary Amines

In 2006, Hartwig and co-workers disclosed a sequential iridium-catalyzed borylation followed by a copper-catalyzed C-N bond formation (Scheme).[149] The reported methodology allowed for the synthesis of secondary aryl/alkyl-amines starting from arenes in moderate yields without the isolation of the organo-boron species. While the yields for the synthesized diarylamines was higher, extra steps were required as the boronic ester had to be converted to the boronic acid and isolated prior to the C-N bond formation.

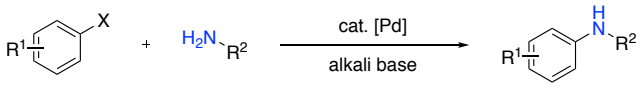


Scheme 2.8 Hartwig (2006) – Sequential Iridium-Catalyzed Borylation/Copper-Catalyzed C-N Cross-Coupling Reactions Towards the Synthesis of Secondary Amines

The copper-mediated/catalyzed C-N cross-coupling reaction has come a long way since it's first discovery in 1903. The substrate scope has increased dramatically and the applicability of the transformation has been applied in the synthesis of natural products.[150] The overall understanding of the reaction mechanism is still being investigated, as evidenced by the 2017 report from Watson and co-workers on the spectroscopic studies of the Chan-Lam amination.[151]

2.1.2.2 Palladium-Catalyzed C-N Cross Coupling

A few years before the emergence of the Chan-Lam reaction, Buchwald and Hartwig concurrently reported the C-N cross-coupling using phosphine/palladium complexes (Scheme 2.9).[152-153] The initial catalyst reported by both groups was a tri-*o*-tolylphosphine palladium complex, which in the presence of alkali metals, such as sodium *tert*-butoxide or lithium (bistrimethylsilyl)amide was able to catalyze the C-N bond formation between aryl bromides and amines.

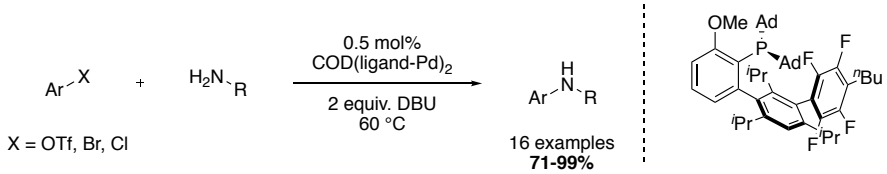


Scheme 2.9 General Palladium-Catalyzed C-N Cross-Coupling Towards the Synthesis of Secondary Aryl-Amines

While copper amination reactions traditionally do not require ligands, in palladium catalysis, the presence and type of ligand are crucial to the reactivity of the complex.[154] For example, in the initial communications by Buchwald and Hartwig, tri-*o*-tolylphosphine was used as the ligand and minimal formation of products was observed when primary amines were attempted. However, by changing the ligand from a monodentate phosphine to a bidentate phosphine (DPPE[155] or BINAP[156-157]), the reaction with primary amines delivered the arylated products in yields of up to 98%.

The importance of the ligand on the palladium-complex is not related only to the reactivity of the amine starting materials but also to the coupling reagents used. Currently, the Buchwald-Hartwig amination works with aryl iodides,[155, 158] bromides,[152-153] chlorides,[159-160] triflates,[161-162] mesylates,[163-164] and tosylates.[159] Depending on the ligand used, the reaction can be selective for the synthesis of secondary amines.

For over 30 years, the need for alkali bases was one of the major drawbacks in the product scope of the reaction. In 2018, Buchwald and co-workers were able to perform the reaction in the presence of 1,8- diazabicyclo[5.4.0]undec-7-ene (DBU), which is a mild soluble organic base (Scheme 2.10). Starting from aryl (pseudo)halides and amines, 16 examples of secondary amines were synthesized in great yields. While the change in base seems like a minor improvement to a well-established transformation, the new methodology allows for the use of functional groups, such as alkyl halides, which were not tolerated with previous reaction conditions.



Scheme 2.10 Buchwald (2018) – Palladium-Catalyzed Arylation of Amines Towards the Synthesis of Secondary Amines

The usefulness of the Buchwald-Hartwig amination reaction can be seen in the synthesis of a wide range of heterocycles and natural products.[3] Furthermore, the reaction has also been applied in medicinal and process chemistry as well as in material and biological chemistry.[3]

Despite the improvements and efficiency of both copper- and palladium-catalyzed C-N cross-coupling, the starting materials used in the reaction still require pre-activation and the products formed are largely arylated amines. Thus, the development of other methodologies is required.

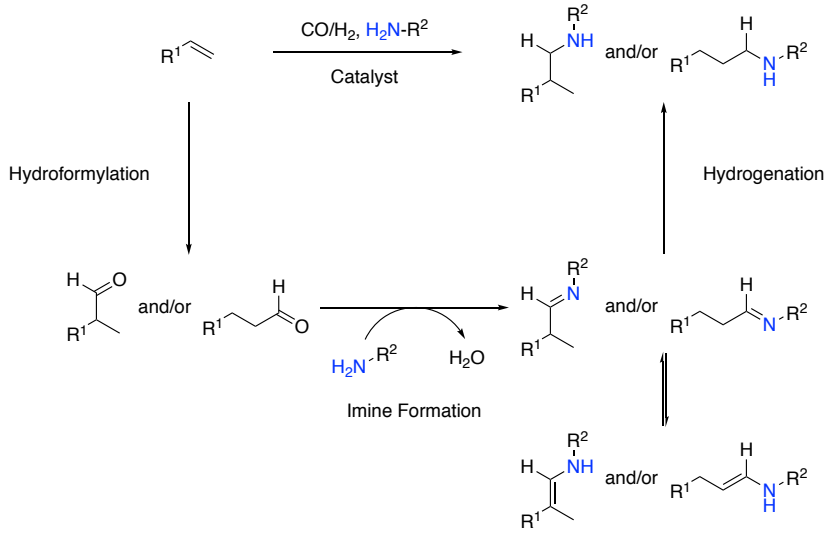
2.1.3 Hydrofunctionalization Reactions

The functionalization of inexpensive feedstock materials such as alkenes and alkynes represents an advance towards the development of efficient amine syntheses. The minimization of the steps required to manufacture the starting materials required, in addition to the atom-economic nature of hydrofunctionalization reactions make the development of versatile and selective synthetic routes of fundamental importance. Among the different types of hydrofunctionalization reactions, the focus will be on hydroaminomethylation and hydroamination reactions.

2.1.3.1 Hydroaminomethylation

Hydroaminomethylation is a one-pot, tandem reaction that involves an alkene, an amine and syngas, which is a gas mixture consisting of carbon monoxide and hydrogen (Scheme

2.11).[165-167] The reaction starts with the hydroformylation of the alkene, followed by the addition of the amine to the newly formed aldehyde. The imine/enamine mixture is then reduced through hydrogenation to deliver the desired amine.

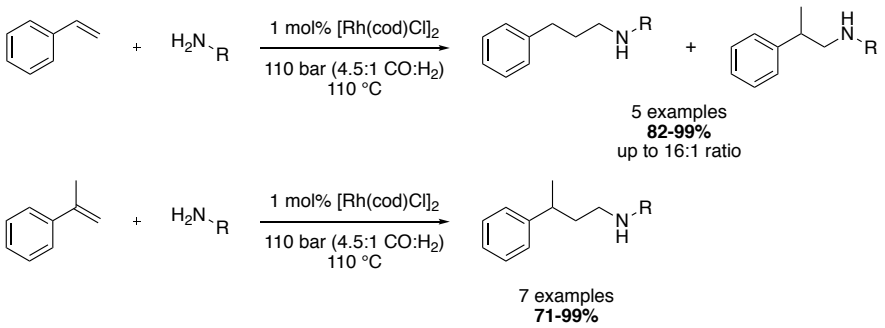


Scheme 2.11 General Hydroaminomethylation of Alkenes Towards the Synthesis of Secondary Amines

In 1949, the first account of this reaction was reported by Reppe and Vetter, who were able to synthesize amine products from acetylene, carbon monoxide, ammonia and water using stoichiometric amounts of pentacarbonyliron.[168] Since then, rhodium has become the metal of choice for the hydroaminomethylation transformation,[166] although recently, some ruthenium catalysts have been developed.

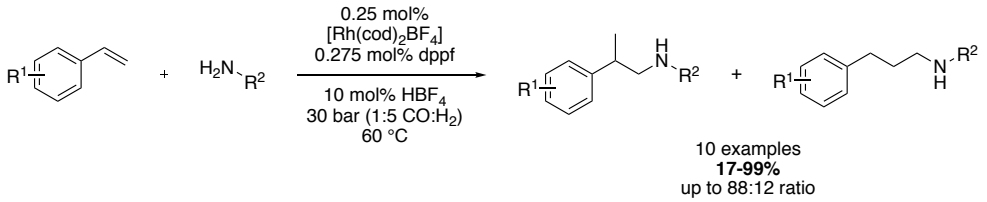
Chemo- and regio-selectivity are among the challenges in the development of this reaction. Due to the presence of hydrogen gas at the onset of the reaction, formation of alkane and alcohol by-products can occur through the hydrogenation of the starting alkene and formed aldehyde. In addition, the hydroformylation reaction can form linear and/or branched aldehydes, thus leading to the formation of two similar amines, which could be difficult to separate.

The group of Eilbracht was a big contributor to the development of hydroaminomethylation methodologies towards the synthesis of nitrogen containing products.[169-185] Eilbracht and co-workers reported the first hydroaminomethylation reaction of styrenes. In the presence of catalytic amounts of $[Rh(cod)Cl]_2$ and syngas, 12 examples of secondary amines were synthesized in high yields (Scheme 2.12).[169]



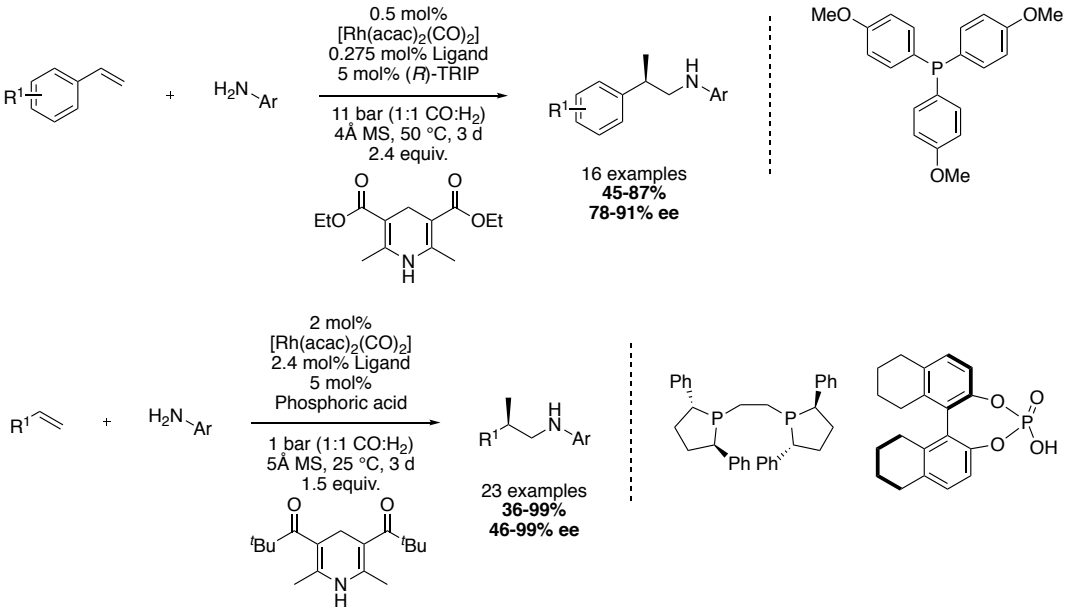
Scheme 2.12 Eilbracht (1997) – Rhodium-Catalyzed Hydroaminomethylation Reaction Towards the Synthesis of Secondary Amines

Milder reaction conditions (60 °C of heating and 30 bar of pressure) for the hydroaminomethylation of styrenes were obtained by Beller and co-workers using $[Rh(cod)_2BF_4]$ and 1,1'- bis(diphenylphosphanyl)ferrocene (dppf) ligand.[186] In the Beller case, however, the selectivity was favoured towards the branched product with the best ratio between products being 88:12.



Scheme 2.13 Beller (2005) – Rhodium-Catalyzed Hydroaminomethylation Reaction Towards the Synthesis of Secondary Amines

Due to the tautomerization between imines and enamines, an asymmetric variant for the synthesis of amines using hydroaminomethylation has not been successfully developed[187-189] without the addition of a secondary chiral catalyst (Scheme 2.14).[190-191] Both the Xiao and Han reports had similar reaction conditions, which included a rhodium catalyst, phosphine ligand, chiral phosphoric acid, and 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. In both cases, the substrate scope was limited to aryl amine derivatives, although in the Han example, the alkene starting material was expanded beyond styrene derivatives to include electron-withdrawing aliphatic alkenes (Scheme 2.14 – bottom).



Scheme 2.14 Xiao (2015), Han (2017) –Asymmetric Hydroaminomethylation Reaction Towards the Synthesis of Secondary Amines

The separation of two amine products containing similar physical proprieties is non-trivial. Thus, the development of selective hydroaminomethylation reaction conditions for either the branched or linear amines is crucial. In particular, the selective synthesis of linear amines has been well studied. Beller and co-workers have demonstrated that linear amines can be obtained

through the hydroaminomethylation reaction using both internal[192] and terminal alkenes.[193] Unfortunately, only a handful of secondary amine examples were accomplished in either publication.

Hydroaminomethylation is an atom-economic reaction that produces nitrogen-containing products from alkenes. While improvements have been made towards the chemo- and regio-selectivity of this transformation, further advances are required to broaden the scope of the reaction. The substrate scope, for example, is still highly reliant on styrene derivatives and amino-heterocycles. Furthermore, the isomerization of internal alkenes to terminal alkenes under catalytic conditions prevents the development of the selective synthesis of β,γ-branched amines from internal alkenes.

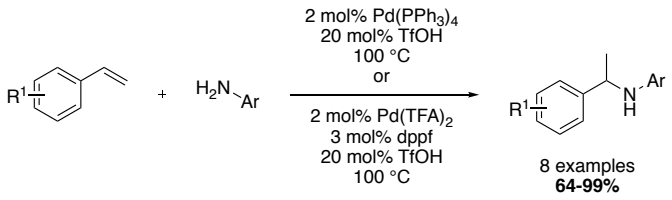
2.1.3.2 Hydroamination

Similarly to hydroaminomethylation, hydroamination is a hydrofunctionalization reaction in which nitrogen-containing compounds can be synthesized. The main difference between the two methodologies is the fact that in hydroamination, the C-N bond is formed in a single step. Similarly, however, is the need for regio-selective catalysts in order to obtain the Markovnikov or *anti*-Markovikov amines selectively. For hydroamination, both alkenes and alkynes can be used, and in fact the latter case is the more established methodology for the synthesis of amines (Scheme 1.2).[4-5] Chapter 1 addresses the synthesis of amines through the intermolecular hydroamination of alkynes, thus, this section will focus on the intermolecular hydroamination of alkenes for the synthesis of secondary amines.

The first example of hydroamination in the academic literature was reported in 1953 and it demonstrated that alkali metals were able to perform the hydroamination reaction of olefins under high temperature (up to 200 °C) and pressure (800-1000 atm).[194] Since then, a wide range

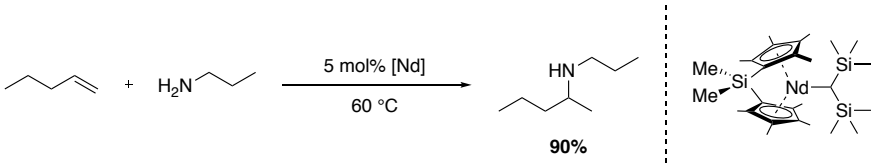
of catalysts has been developed to perform the C-N bond formation under milder reaction conditions.

Traditionally, the intermolecular hydroamination of olefins is usually performed with highly activated alkenes, such as styrenes,[195] norbornenes,[196] allenes,[197] and dienes.[198] The nitrogen source is also typically performed with heterocyclic amines.[199] On the other hand, very few examples use primary amines, thus the formation of secondary amines has not been broadly explored.[195, 200] In 2000, Kawatsura and Hartwig reported a palladium catalyzed Markovnikov selective intermolecular hydroamination of styrene derivatives with aryl amines, which delivered 8 examples of secondary amines in 64-99% yields (Scheme 2.15).[195] The same publication also attempted the reaction asymmetrically using 4-trifluoromethylstyrene and aniline with 10 mol% [Pd((R)-binap)$(OTf)_2$], which gave products with a yield of 80% in 81% ee.



Scheme 2.15 Hartwig (2000) – Palladium-Catalyzed Hydroamination Reaction Towards the Synthesis of Secondary Amines

In the past 10 years, attempts at performing intermolecular hydroamination with simple alkyl alkenes have been successful using specific heterocyclic amines.[201-203] However, a general synthesis of secondary amines by hydroamination of alkenes with primary amines remains a challenge. Marks and co-workers showed one example of a dialkyl amine synthesis using pent-1-ene and propan-1-amine in the presence of a lanthanide-complex (Scheme 2.16).[200]



Scheme 2.16 Marks (2003) – Neodymium-Catalyzed Hydroamination Reaction Towards the Synthesis of a Secondary Amine

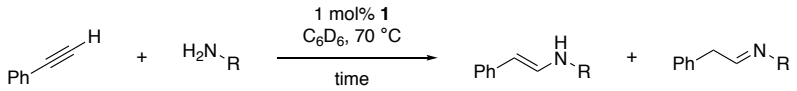
While the asymmetric synthesis of secondary amines has been tried using an intermolecular hydroamination of alkenes with alkyl amines, the enantiomeric excesses are usually moderate of up to 61%.[204]

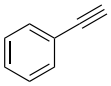
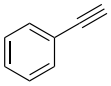
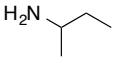
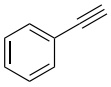
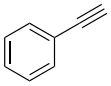
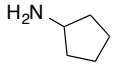
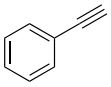
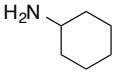
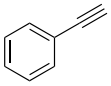
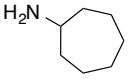
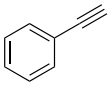
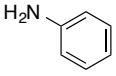
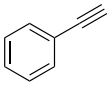
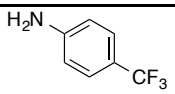
2.2 Results and Discussion

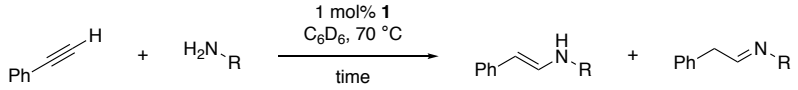
In Chapter 1, it was shown that a wide variety of complexes were competent for the intermolecular hydroamination of alkynes with primary amines, which upon reduction of the hydroamination product led to the formation of secondary amines. A synthetic approach to linear secondary amines that minimizes waste generation and reduces the amount of solvent required for product purification is disclosed in this section of Chapter 2. An optimized intermolecular alkyne hydroamination methodology with a reduced catalyst loading of only 1 mol% of pre-catalyst has been developed. Subsequent hydrogenation of the enamine/imine mixture is achieved using easily removed Pd/C catalyst. Finally, a streamlined work-up procedure has been established which features filtration protocols, and avoids purification by column chromatography in most cases. As a demonstration of utility, secondary amines have been prepared and isolated on multigram scale in 5 - 10 h from commercially available terminal alkyne and primary amine starting materials.

2.2.1 Optimization of Reaction Conditions

To optimize reaction conditions, the hydroamination reaction with **1** was monitored by ^{1}H NMR spectroscopy to determine substrate dependent reaction times (30 min to 6 h) giving TOFs of 1.3 to 200 h^{-1} at 70 °C (Table 2-2 and Table 2-2). A variety of alkyl and aryl amines and alkynes of different electronic and steric nature were successfully employed in the hydroamination step.



Entry	Alkyne	Amine	Time	E:I Ratio	TOF (h^{-1})
2.1a			30 min	91:9	200
2.1b			30 min	83:17	200
2.1c			1h	97:3	100
2.1d			1h	42:58	100
2.1e			1h	74:26	100
2.1f			2h	69:31	50
2.1g			30 min	82:18	200
2.1h			30 min	49:51	200



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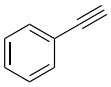
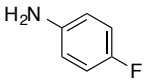
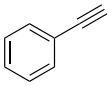
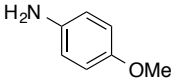
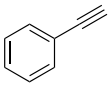
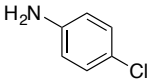
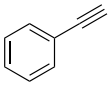
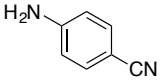
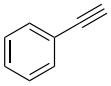
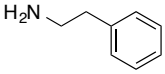
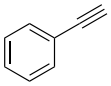
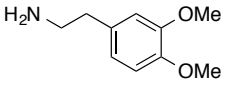
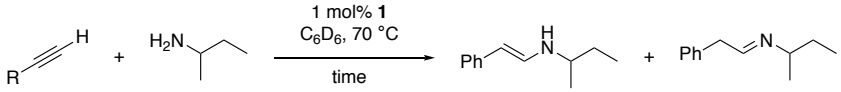
2.1i			1h	67:33	100
2.1j			1h	57:43	100
2.1k			1h	82:18	100
2.1l			3h	100:0	33
2.1m			5h	54:46	20
2.1n			6h	60:40	17

Table 2-1 Optimization of the Hydroamination Reactions Using Ethynylbenzene



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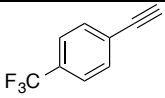
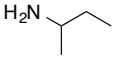
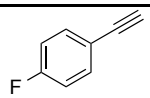
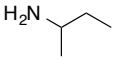
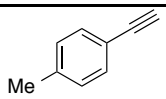
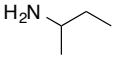
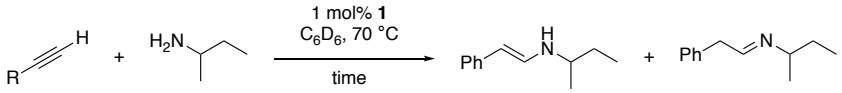
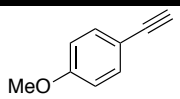
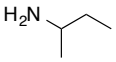
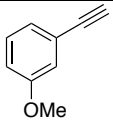
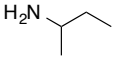
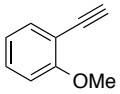
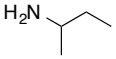
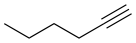
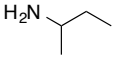
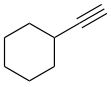
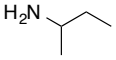
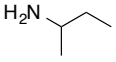
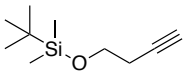
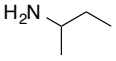
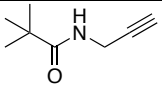
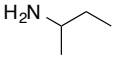
2.2a			30 min	69:31	200
2.2b			1h	75:25	100
2.2c			1h	60:40	100



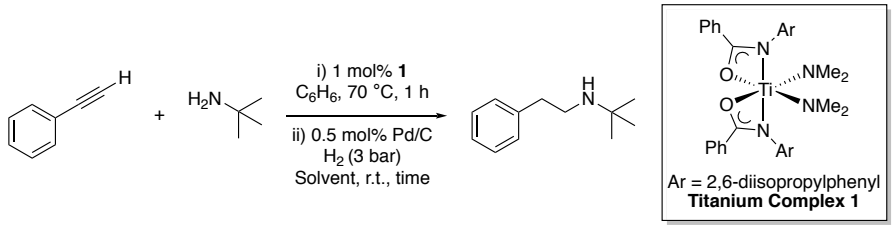
Entry	Alkyne	Amine	Time	E:I Ratio	TOF (h^{-1})
2.2d			1h	84:16	100
2.2e			1h	64:36	100
2.2f			3h	63:37	33
2.2g			2h	58:42	50
2.2h			3h	7:93	33
2.2i[a]			6h	1:99	1.7
2.2j[b]			30 min	55:46	80
2.2k[b]			1h	31:69	40

[a] 10 mol% of the titanium complex was required. [b] 2.5 mol% of the titanium complex was required.

Table 2-2 Optimization of the Hydroamination Reactions Using *Sec*-Butylamine

Initial studies on the feasibility of performing a sequential hydroamination/hydrogenation reaction were performed using ethynylbenzene and *tert*-butylamine as model substrates (Table 2-3). The hydroamination reaction was set-up in a scintillation vial in an inert atmosphere glovebox using dried and distilled starting materials. The reaction mixture was removed from the

glovebox and was stirred at 70 °C for 1 h before transferring the reaction mixture by syringe to the Fischer-Porter® tube used for hydrogenation. Reduction of the hydroamination product was first performed at 1 bar of H_2 over 3 days, yielding 65% of the desired product (Entry 1). In an attempt to shorten the reaction time, the pressure of H_2 was increased to 3 bar resulting in a reaction time of only 3 h and an improved yield (Entry 2). Although different solvents delivered similar yields, methanol was selected as the solvent of choice due to its favorable environmental and health hazard profile.[205]



Entry	Solvent	Time (hours)	Yield (%)[a]
2.3a[b]	MeOH	72	65
2.3b	MeOH	3	98
2.3c	THF	3	96
2.3d	^{i}PrOH	3	96
2.3e	Benzene	3	92

[a)] Reported yield percentages refer to obtained yield after work-up conditions. [b)] Hydrogenation reaction was performed at 1 bar.

Table 2-3 Optimization of the Sequential Reaction Conditions

In addition to developing optimized hydrogenation conditions, an easy work-up procedure was established to afford the desired amine (Figure 2.1). Due to the lack of by-products formed in this reaction sequence and the low solubility of the ligand in hexanes, simple filtration of the crude reaction mixture through Celite® removed the titanium and palladium metal residues, while the addition of cold hexanes followed by a second filtration allowed for full recovery of the amide proligand. Using this protocol, no column chromatography was required to

obtain clean products (>95% purity as established by ^{1}H NMR spectroscopy) and thus, all reported yields are crude, unless stated otherwise.

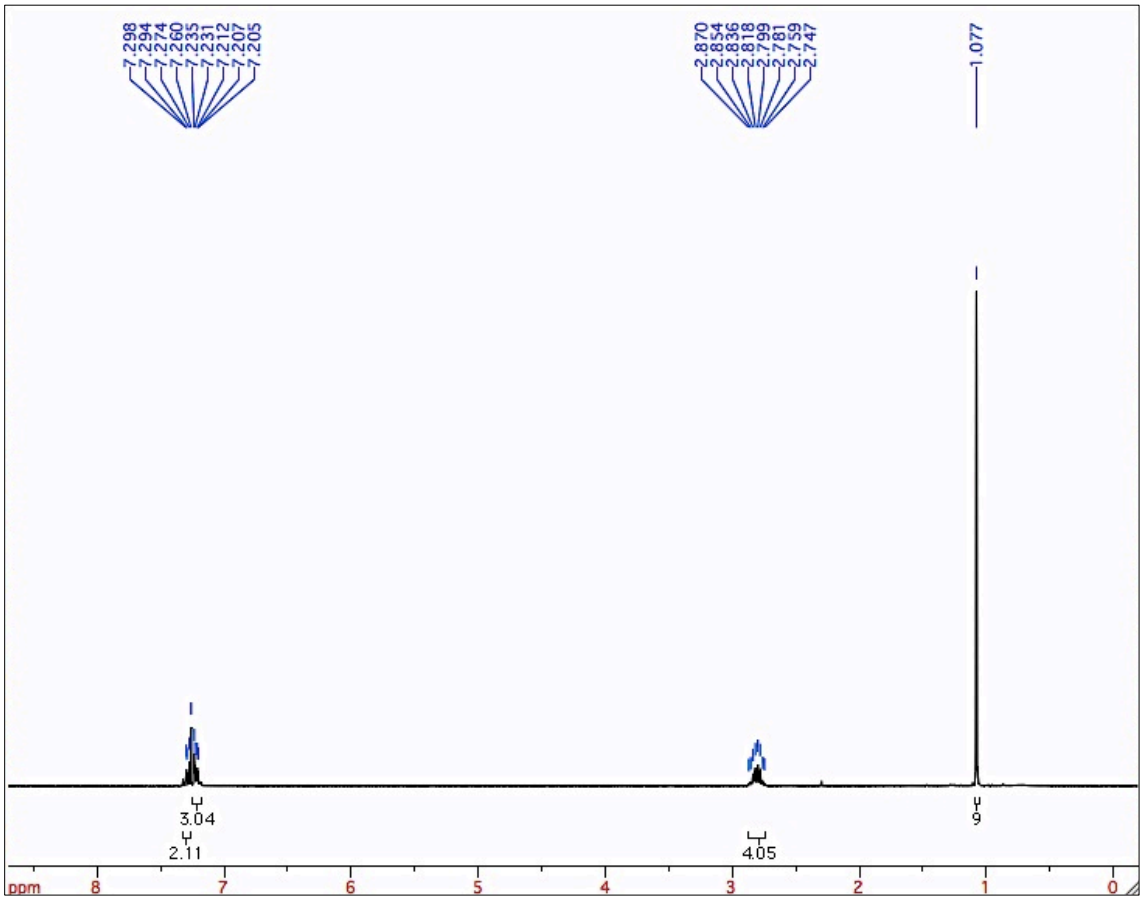
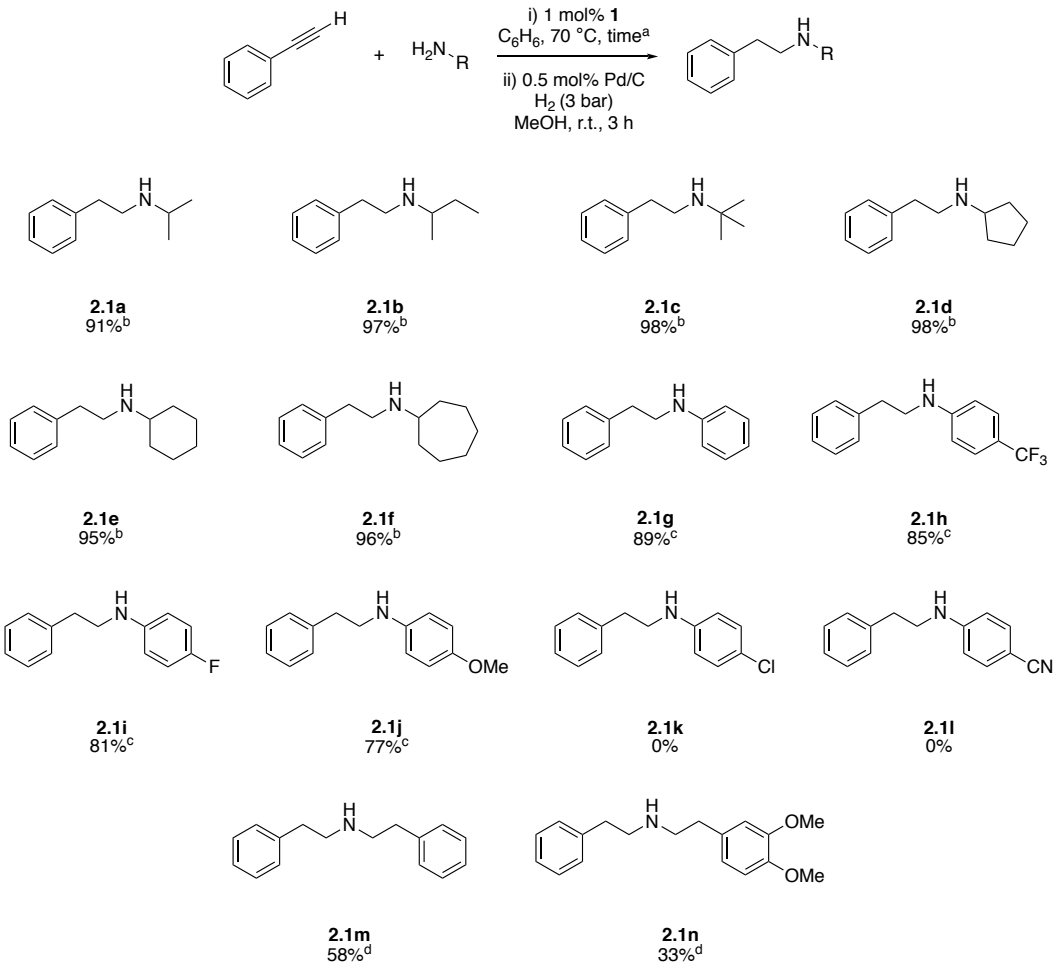


Figure 2.1 ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 298 K) for the Crude Sequential Hydroamination/Hydrogenation Reaction of Ethynylbenzene and *Tert*-Butylamine

2.2.2 Substrate Scope of Sequential Hydroamination/Hydrogenation Transformation Towards Linear Secondary Amines

In order to investigate the scope and limitations of the sequential procedure, we first examined the reaction of ethynylbenzene with a wide variety of amines (Scheme 2.17). Alkyl amines, both acyclic (**2.1a-c**) and cyclic (**2.1d-f**), deliver excellent yields of enamine/imine intermediates in an hour or less. More sterically demanding substituents require longer reaction

intermediates in an hour or less. More sterically demanding substituents require longer reaction times (**2.1c-f**). Aryl amines (**2.1g-j**), including aryl amines with both electron-withdrawing (eg. **2.1h**) and electron-donating substituents (eg. **2.1j**) are also compatible with these low catalyst loadings.



[a)] Refer to Table 2-1 for hydroamination reaction times. [b)] Reported yield percentages refer to obtained yield after work-up conditions, unless otherwise stated. [c)] Isolated yield percentages after column chromatography. [d)] Isolated yield percentages after back-extraction.

Scheme 2.17 Effect of Amine Modification on Reaction with Ethynylbenzene

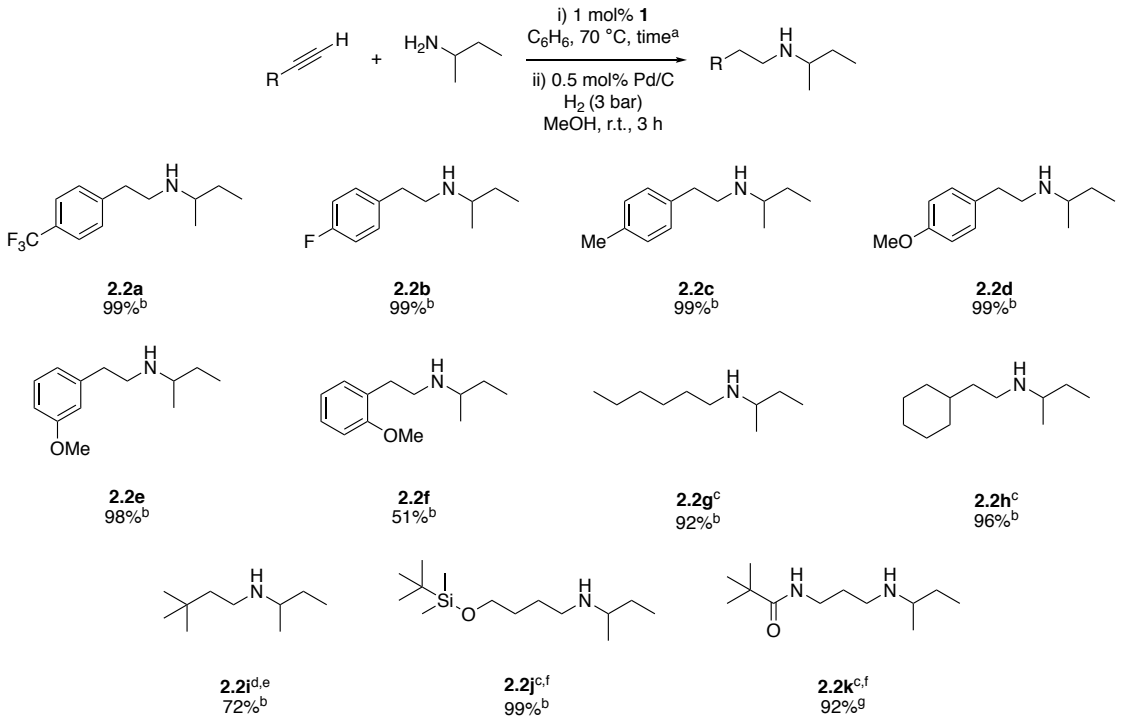
Although the aforementioned work-up procedure was transferrable towards all alkyl amines screened (**2.1a-f**), aryl amines (**2.1g-j**) required further purification to remove minor,

unidentified impurities. Unfortunately, chloro- (**2.1k**) and cyano- (**2.1l**) substituted aniline derivatives were incompatible with the hydrogenation step. In the case of diphenethylamine derivatives (**2.1m,n**), this protocol affords the desired products quantitatively; however, the insolubility of these amines in hexanes complicates isolation. In these cases column chromatography could not be used effectively to separate impurities from the desired secondary amine products. Thus, to obtain the amine in pure form, the optimized work-up procedure required isolation of the amine-HCl salt product derivative followed by re-basification and extraction.

The reaction of *sec*-butylamine with a variety of terminal alkynes was also examined (Scheme 2.2). Both electron-withdrawing and -donating para-substituted ethynylbenzenes (**2.2a-d**) were successfully synthesized in excellent yields. Meta- (**2.2e**) and ortho-substituted (**2.2f**) ethynylbenzenes were also tolerated, though the latter was obtained in lower yield, presumably due to steric bulk. Such steric hinderance has not been observed to dramatically impact hydroamination, but could hinder palladium-catalyzed hydrogenation. More importantly, less electronically and sterically biased alkyl alkynes also smoothly reacted in a regioselective manner with the amine in the hydroamination step (**2.2g**, **2.2h**). To the best of our knowledge, catalyst **1** is the only highly regioselective catalyst using such alkyl alkynes and alkyl amines as substrates. In the hydrogenation step of alkyl substituted imines (**2.2g-i**) a higher catalyst loading of 1 or 5 mol % of Pd/C and slightly prolonged reaction times were necessary to realize full hydrogenation of these unactivated species. In all instances presented in Scheme 3, no further purification was required beyond the established filtration protocol to afford pure products.

We have previously shown[25-27] that the hydroamination of alkynes containing protected alcohols, esters, or amides can be tolerated, notably these substrates are not compatible with the

low catalyst loading and short reaction times targeted here. However, by increasing the loading of **1**, the streamlined one-day process could also be achieved with alkynes containing silylether (**2.2j**) and amide (**2.2k**) functionalities.



[a)] Refer to Table 2-2 for hydroamination reaction times. [b)] Reported yield percentages refer to obtained yield after work-up conditions; [c)] 1 mol% of Pd/C and 5 hours were required. [d)] 10 mol% of 1 was required. [e)] 5 mol% of Pd/C and 4 hours were required. [f)] 2.5 mol% of 1 was required. [g)] Isolated yield percentages after back-extraction.

Scheme 2.18 Effect of Alkyne Modification on Reaction with *sec*-Butylamine

2.2.3 Large Scale and One-Pot Transformations

With the potential synthetic relevance of our methodology in mind, larger-scale reactions of 25 mmol were performed in a 100 mL round bottomed flask. Following the general procedure for the sequential approach and simplified filtration work-up protocol, 4.3g (97% yield) of 2-methyl-*N*-phenethylpropan-2-amine and 3.3g (83% yield) of *N*-(*sec*-butyl)hexan-1-amine was

obtained with the same degree of purity as that obtained for the smaller scale reactions (Figure 2.2).

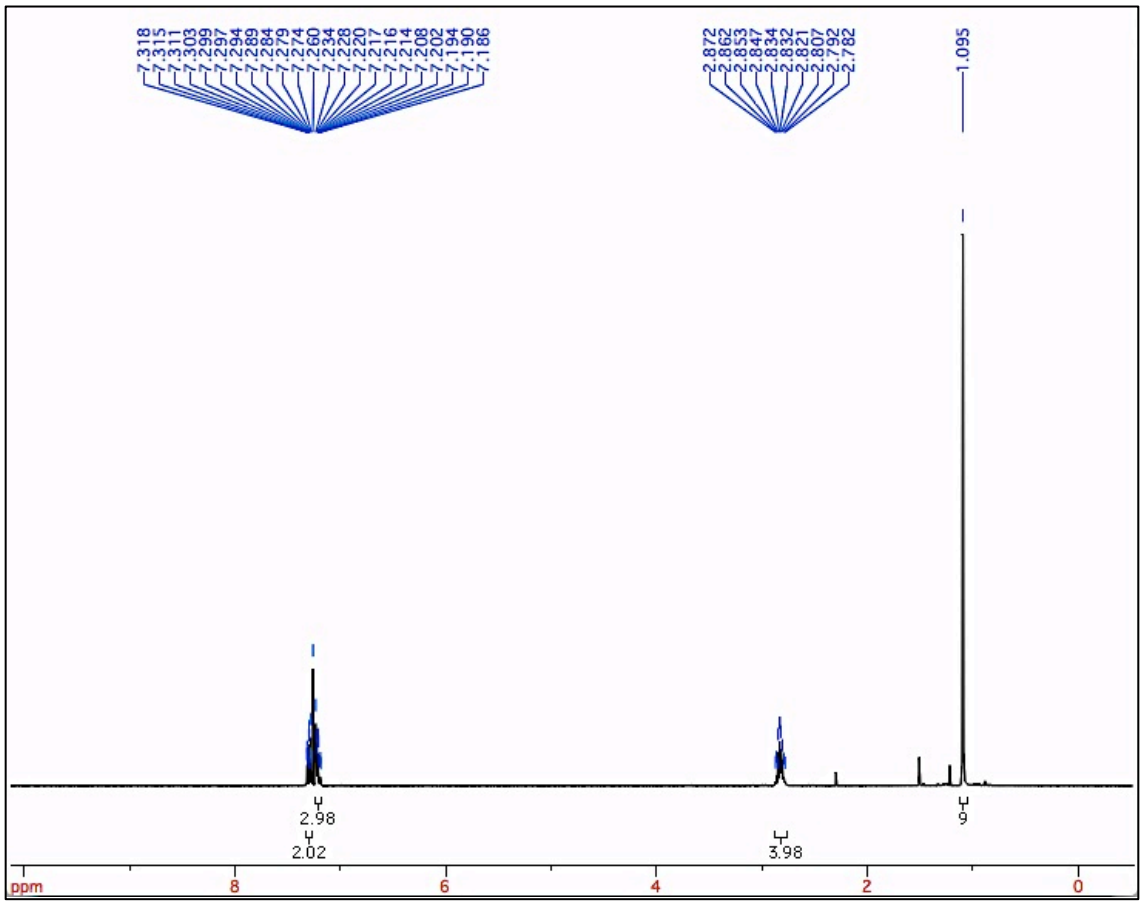
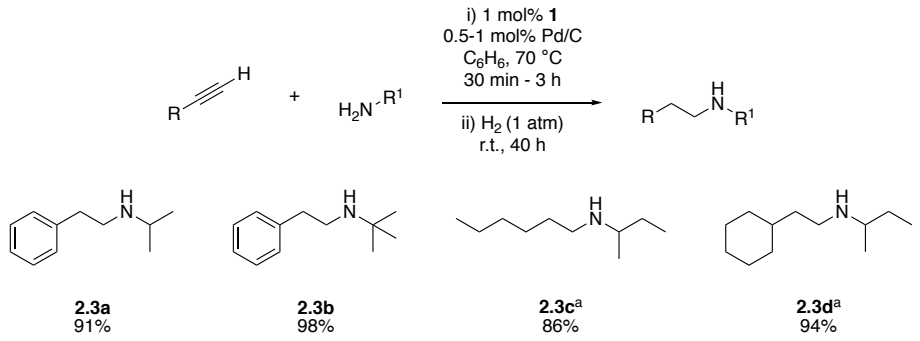


Figure 2.2 ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 298 K) for the Crude Large-Scale Sequential Hydroamination/Hydrogenation Reaction of Ethynylbenzene and *Tert*-Butylamine

With this facile procedure in hand, we next developed a one-pot approach to further simplify our methodology. Experiments confirmed that palladium does not affect the desired hydroamination transformation that is mediated by titanium and a control experiment confirmed that Pd/C does not catalyze the hydroamination reaction itself.

Varied selections of substrates were synthesized using the one-pot approach (Scheme 2.19). In this case, both Ti catalyst **1** and Pd/C were loaded into a scintillation vial in the

glovebox. Benzene, amine and alkyne were added before removing the reaction vessel from the glovebox. After stirring and heating the hydroamination reaction mixture for the previously determined optimized reaction times, a hydrogen-filled balloon was attached to the reaction vial. Upon reaction completion our optimized reaction protocol was used to obtain yields comparable to those of the sequential approach. Only minor impurities can be observed in the baseline of the ^{1}H NMR spectra (Figure 2.3).



[a)] 1 mol% of palladium on carbon was required. [b)] Refer to Table 2-1 and Table 2-2 for hydroamination reaction times. [c)] Reported yield percentages refer to obtained yield after work-up conditions.

Scheme 2.19 One-Pot Approach Towards the Synthesis of Secondary Amines

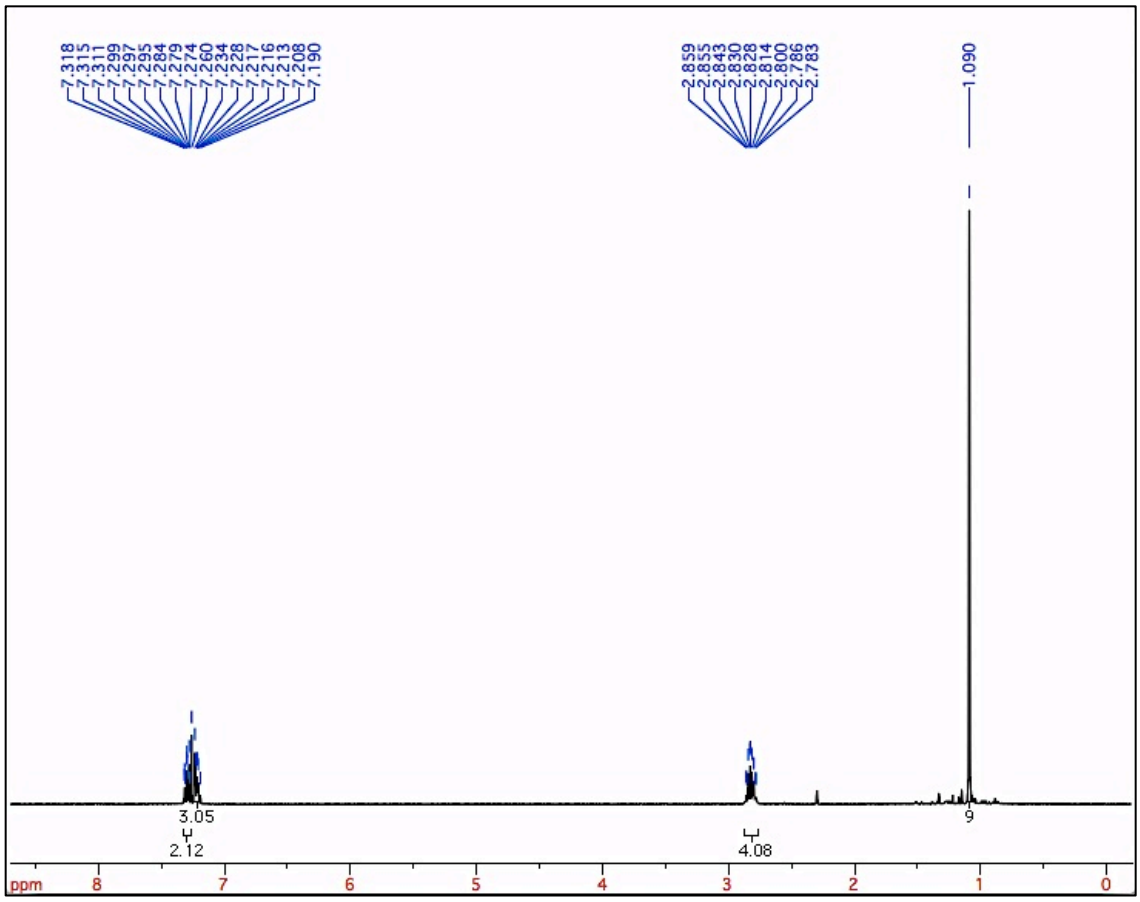


Figure 2.3 ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz, 298 K) for the Crude One-Pot Hydroamination/Hydrogenation Reaction of Ethynylbenzene and *Tert*-Butylamine

2.3 Conclusion

In summary, this chapter describes an alternative to reductive amination for the synthesis of primary and secondary amines, using terminal or internal alkynes and amines as starting materials. Titanium-catalyzed regioselective, intermolecular alkyne hydroamination can be performed quantitatively at low catalyst loading (1 mol %). The resultant intermediate mixtures can then undergo quantitative hydrogenation with a commonly available Pd/C catalyst to give amine products. These products can typically be isolated cleanly using a simple filtration protocol to give a variety of alkyl- and aryl-substituted secondary amine product, or using

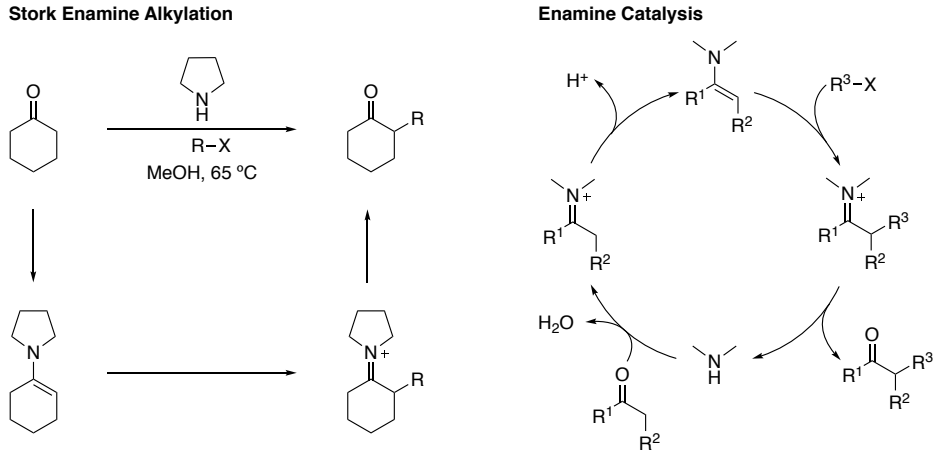
sublimation to give a variety of primary amine products. This sequential reaction affords clean products that typically avoid the need for column chromatography. Most importantly, we have demonstrated that this protocol can be carried out on multigram scale, and is suitable for general laboratory use.

Future directions for this chapter will include expanding the scope of the secondary amines synthesized by using internal alkynes and optimizing the homogenous hydrogenation conditions towards the synthesis of enantiopure amines. Chapter 5 will have a more detailed background and overview of the future directions of this research project.

Chapter 3: Regio- and Stereoselective Hydroamination of Alkynes Using an Ammonia Surrogate: Synthesis of *N*-Silylenamines as Reactive Synthons

3.1 Enamines in Organic Chemistry

The first few reports on the reactivity of enamines were published in the late 19th century and the beginning of the 20th century.[206-208] However, it was only after Stork and co-workers demonstrated that *N*-alkylenamines could be used for C-alkylation (Scheme 3.1– left) and C-acylation that great attention was focused on the synthetic applications of enamines.[209] Presently, chemistry involving enamines revolves around the topic of organocatalysis, where the enamine is formed catalytically (Scheme 3.1– right).[210]

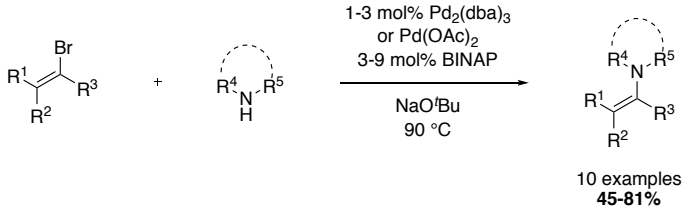


Scheme 3.1 General Stork Enamine Alkylation Reaction and Enamine Catalysis

3.1.1 Synthesis of Enamines

Traditionally, the synthesis of enamines occurs through the condensation of secondary amines to carbonyls, such as aldehydes or ketones, in the presence of a water scavanger.[206-207, 211] The requirement for secondary amines arises from the fact that enamine-imine tautomerization readily occurs for enamines that contain one or two hydrogen substituents.[211]

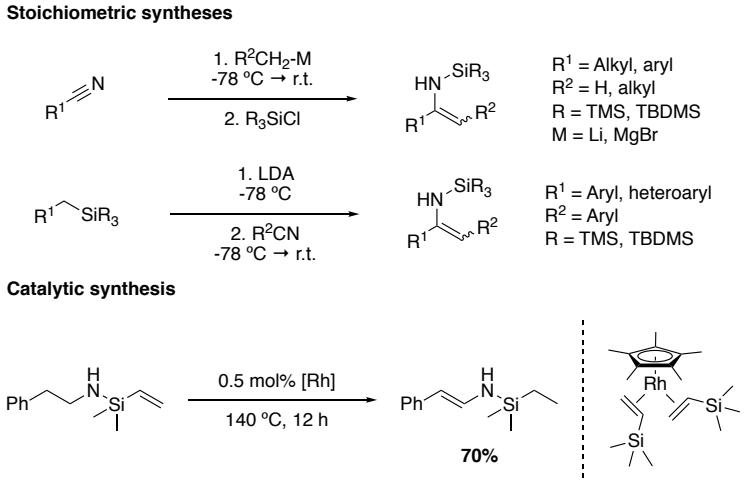
Catalytically, the synthesis of enamines can be accomplished through the amination of alkenyl (pseudo)halides with secondary or *N*-heterocycles.[212] Barluenga and co-workers reported the first example of a palladium catalyzed amination of alkenyl bromides in 2002 (Scheme 3.2).[213] Since then, other similar methodologies have been developed using alkenyl chlorides[214] and triflates[215]. Copper-catalyzed variants have also been studied using alkenyl boronic acids[216] and alkenyl bromides.[217]



Scheme 3.2 Barluenga (2002) – Palladium-Catalyzed Amination of Alkenyl Bromides Towards the Synthesis of Enamines

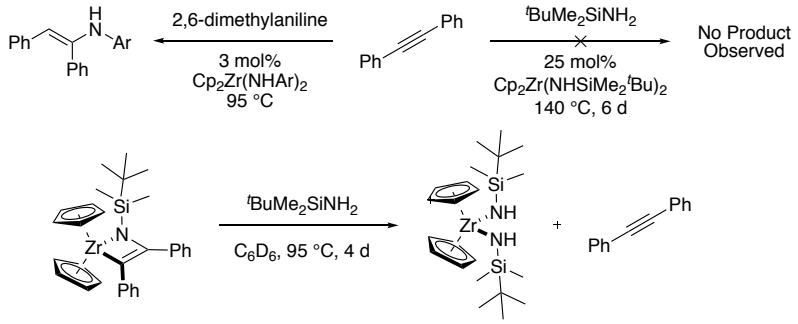
3.1.2 Synthesis of *N*-Silylenamines

Although *N*-alkyl substituted enamines are commonly used in synthesis, use[218-227] of related *N*-silylenamines are limited, largely due to their laborious syntheses. The preparation of *N*-silylenamines is typically achieved by the stoichiometric addition of highly active carbon nucleophiles to aromatic cyanide groups followed by trapping with either silylchloride[218-219, 222, 226-229] (Scheme 3.3 – top) or an intramolecular silyl-migration[229-235] (Scheme 3.3 – middle). A Rh-catalyzed route was reported by Brookhart and co-workers, which employed intramolecular transfer hydrogenation of vinylaminosilane, to give *N*-silylenamine in 70% yield (Scheme 3.3 – bottom).[236]



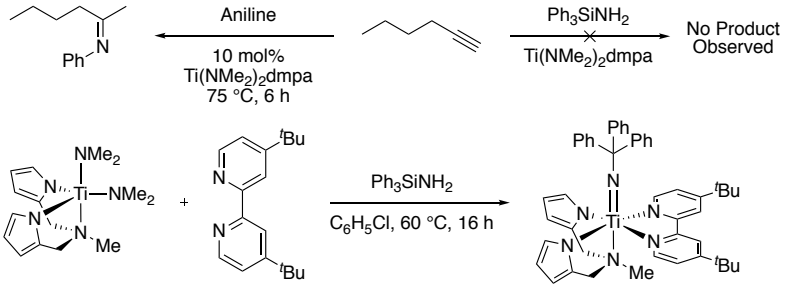
Scheme 3.3 Stoichiometric and Catalytic Syntheses of *N*-Silylenamines

Over the past 25 years, no example of *N*-silylenamine synthesis by hydroamination has been reported, even though the reaction has been previously attempted with catalysts that are known to catalyze the hydroamination of alkynes with typical carbon substituted amines.[197, 237] For example, Bergman and co-workers showed that bis(cyclopentadienyl)bis(amido)zirconium complexes could be used as catalysts for the generation of enamines with anilines. However when the reaction was performed with *N*-silylamine, no enamine formation was observed. Furthermore, when isolated zircona-(*N*-silyl)-azametallacycle was reacted with excess *N*-silylamine, only the products resulting from cycloreversion, free diphenylacetylene and Cp_2Zr-bis(silyl)amide, were recovered (Scheme 3.4).[197]



Scheme 3.4 Bergman (1992) – Catalytic and Stoichiometric Bis(Cyclopentadienyl)Zirconium Chemistry

In 2001, Odom and co-workers showed that the catalytic hydroamination reaction of hex-1-yne and aniline was successful using their titanium-pyrrolyl complex.[22] A few years after, the hydroamination reaction was attempted using (*N*-triphenylsilyl)amine as the substrate and no product was observed. The Odom group was able to prepare an (*N*-triphenylsilyl)imido titanium complex supported by pyrrole ligands (Scheme 3.5).[237]



Scheme 3.5 Odom (2001, 2005) – Catalytic and Stoichiometric Bis(Pyrrolyl)Titanium Chemistry

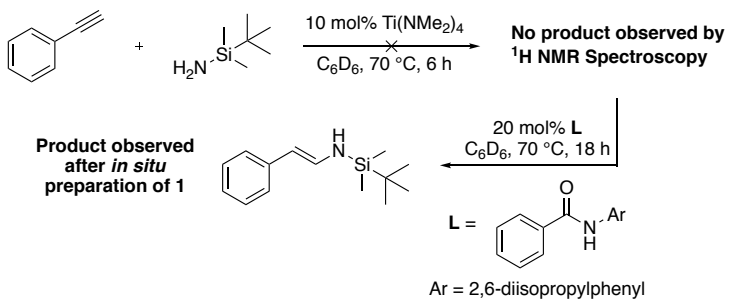
The Schafer group's bis(amidate)bis(amido)-Ti(IV) catalyst (**1**) has high activity and excellent anti-Markovnikov selectivity for the hydroamination of alkynes. Inspired by other transition-metal catalyzed reactions that utilize silylated amines as ammonia surrogates for the generation of primary amines, such as (*N*-triphenylsilyl)amine in Pd-catalyzed Buchwald-Hartwig cross-coupling,[238-247] we envisioned utilizing *N*-silylamines, H_2NSiR_3, as ammonia surrogates for the hydroamination of alkynes. In this chapter, we disclose the regioselective hydroamination of a variety of alkynes to give a broad range of (*E*)-*N*-silylenamines. The use of these products as reactive enamine intermediates is demonstrated and a mechanistic proposal invoking catalytically active Ti-silylimido is presented.

3.2 Results and Discussion

3.2.1 Reaction Conditions and Controls

Our studies toward the catalytic hydroamination of alkynes with *N*-silylamines began by using commercially available (*N*-triphenylsilyl)amine, ethynylbenzene, and the commercialized Ti catalyst **1**. In an NMR tube scale reaction the *N*-silylenamine product was observed exclusively after 18 hours at 70 °C using 2.5 mol% of **1**. The anti-Markovnikov product was assigned as the *E*-isomer on the basis of the observed 13.7 Hz coupling between the vicinal olefinic hydrogens (δ 6.99, 5.61 ppm). With this successful reaction in hand we also sought to use a trialkylsilylamine variant. Thus, (*N*-*tert*-butyldimethylsilyl)amine was prepared in 82% yield from ammonia and *tert*-butyldimethylchlorosilane. Subsequent hydroamination of ethynylbenzene with the synthesized *N*-silylamine gave the anti-Markovnikov (*E*)-*N*-silylenamine product using only 1 mol% catalyst loading at 70 °C over 6 hours.

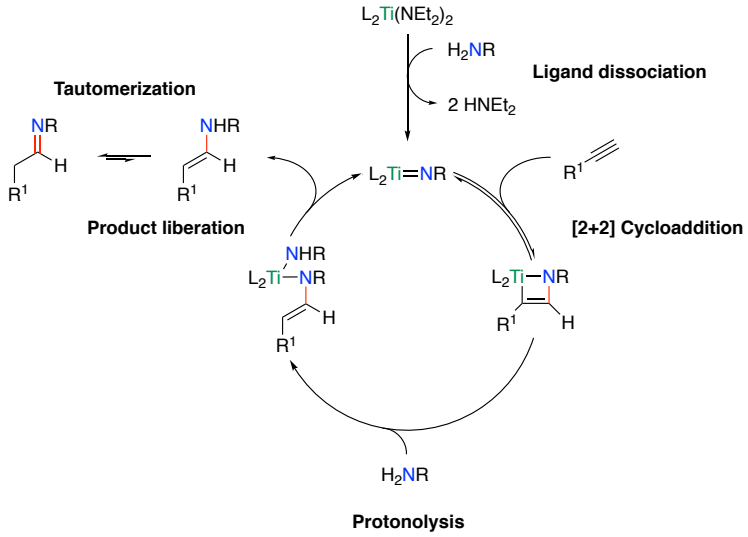
Tetrakis(dimethylamido)titanium is known to catalyze the hydroamination of alkynes.[248] However, when this complex was tested as a potential catalyst, no *N*-silylenamine formation could be observed (Scheme 3.6). By adding the amide proligand (**L**) to the unreacted reaction mixture, catalyst **1** was formed *in situ* and full conversion to the desired product was achieved. This experiment demonstrates the importance of the bis(amidate) ligand environment to promote hydroamination with silylamine substrates (*vide infra*).



Scheme 3.6 Testing the Importance of Amidate Ligands

3.2.2 Stoichiometric Studies

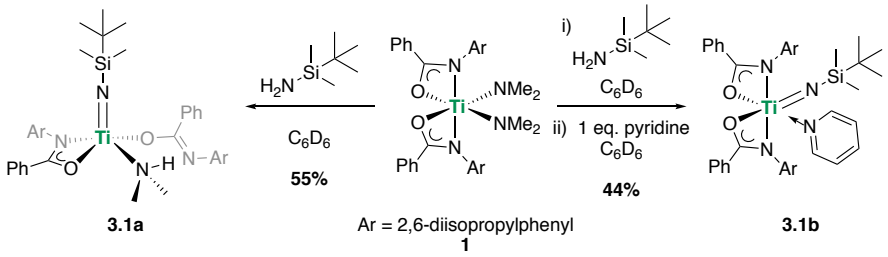
The accepted mechanism for Ti-catalyzed hydroamination invokes the formation of an imido reactive intermediate, thereby limiting reactivity to primary amine substrates (Scheme 3.7).[249-251] Consistent with this mechanistic proposal, when the reaction was attempted with bis(trimethylsilylamine), a secondary amine, no product was observed by ^{1}H NMR spectroscopy.



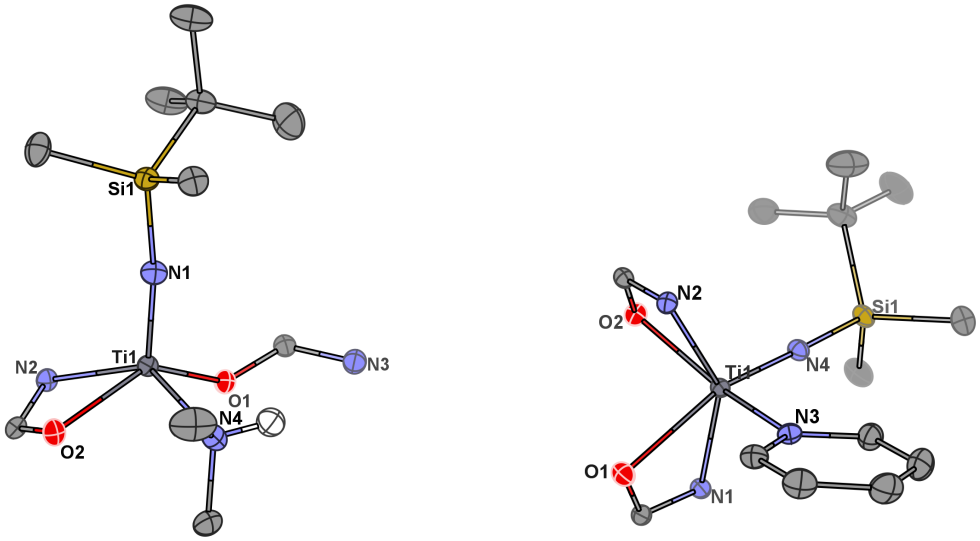
Scheme 3.7 Proposed Mechanism for the Titanium-Catalyzed Hydroamination of Alkynes

To further probe the role of intermediate imido complexes, we synthesized and characterized silylimido species from **1**. The generation of imido complex **3.1a** was obtained by reacting one equivalent of (*N-tert*-butyldimethylsilyl)amine with one equivalent of Ti complex **1** (Scheme 3.8, Figure 3.1). Recrystallization afforded the desired silylimido species in 55% yield.

Attempts to remove the neutral dimethyl amine donor under vacuum proved unsuccessful. However, the addition of excess pyridine resulted in ligand exchange to give complex **3.1b** in 44% recrystallized yield from complex **1**.



Scheme 3.8 Synthesis of *N*-Silylimido-Titanium Species 3.1a and 3.1b



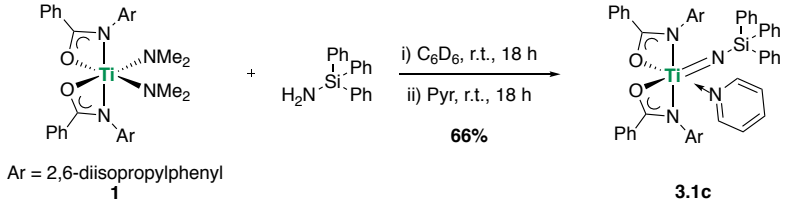
Thermal ellipsoids are shown at 50% probability. Phenyl and 2,6-diisopropylphenyl groups of the ligand and hydrogen atoms are omitted for clarity.

Figure 3.1 Single-Crystal Molecular Structures of 3.1a (left) and 3.1b (right)

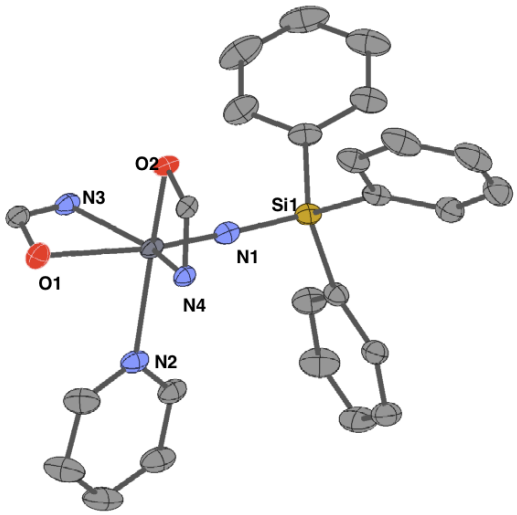
Importantly, **3.1a** can catalyze the reaction between ethynylbenzene and (*N-tert*-butyldimethylsilyl)amine at 1 mol% Ti with full conversion of starting materials to the desired enamine product in 6 h at 70 °C. This strongly suggests that catalysis described here follows the previously proposed mechanism involving a Ti–imido species.[249-251] Furthermore, we have

previously proposed the hemi-lability of amidate ligands to play a significant role in the reactivity and selectivity of complex **1**.[27]

Interestingly, complexes **3.1a** and **3.1b** display different coordination of the ancillary amidate ligand due to change in donor ligand. In **3.1a** one of the amidate ligands is bound in a κ^1-*O* fashion, giving in a 5-coordinate pseudo-square based pyramidal complex with an axial *N*-silylimido ligand. Substitution of the dimethylamine ligand with a pyridine ligand results in a 6-coordinate, distorted octahedral complex **3.1b**, with both amidate ligands in a κ^2-*N*,*O* binding mode. We attribute this coordination variation to the slight steric differences in the dimethylamine and pyridine neutral ligands. The *N*-sp^3 hybridized dimethylamine, with a comparatively shorter Ti–N bond length of 2.1780(18) Å, imparts a greater steric parameter at the Ti center (**2a**) than the planar, *N*-sp^2 hybridized pyridine, with a comparatively longer bond length of 2.2140(13) Å (**3.1b**). We additionally attempted the analogous reaction with (*N*-triphenylsilyl)amine, however, recrystallization was only possible as the pyridine complex resulting in complex **3.1c**, in 66% yield (Scheme 3.9, Figure 3.2).



Scheme 3.9 Synthesis of *N*-Silylimido-Titanium Species 3.1c



Thermal ellipsoids are shown at 50% probability. Phenyl and 2,6-diisopropylphenyl groups of the ligand and hydrogen atoms are omitted for clarity.

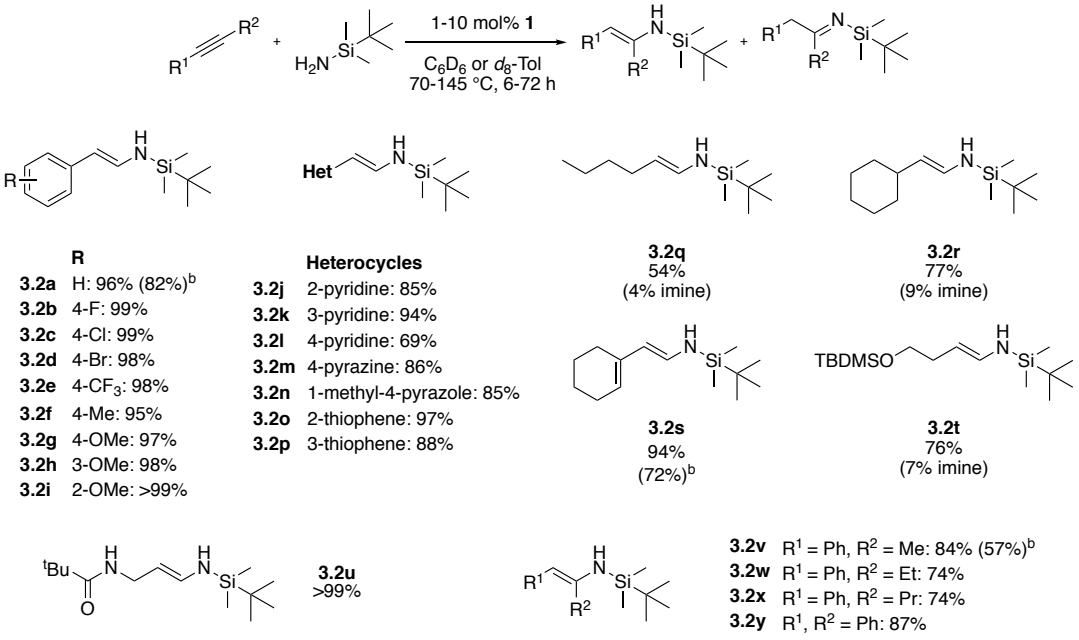
Figure 3.2 Single-Crystal Molecular Structures of 3.1c

The Ti–N bond lengths and Ti–N–Si bond angles observed in the silylimido ligands observed in **3.1a** (1.7030(16) Å, 170.70(9)°), **3.1b** (1.7196(12) Å, 168.92(8)°), and **3.1c** (1.724(3) Å, 168(2)°) are comparable to the known bis(amidate)*tert*-butylimidopyridine Ti(IV) complex (1.1711(2) Å, 172.3(2)°),[26] and the previously mentioned Ti complex reported by Odom and co-workers (1.718(4) Å, 168.9(3)°).[237]

3.2.3 Substrate Scope of the Intermolecular Hydroamination of Alkynes and *N*-Silylamine

The scope of the hydroamination reaction was studied with a variety of terminal and internal alkynes (Scheme 3.9). Due to the moisture sensitivity of the products, ^{1}H NMR spectroscopy was used to determine reaction yields *in situ* using trimethoxybenzene as an internal standard. In all cases, full consumption of starting materials was observed and only the anti-Markovnikov product was formed. The yields obtained for the hydroamination of a range of ethynylbenzene derivatives (**3.2a-i**) were excellent, independent of the arene substitution pattern.

Even substrates with sterically demanding and potentially chelating *ortho*-methoxy substituents (**3.2i**) could be accomodated. Good yields were also obtained using alkynes with nitrogen and sulfur containing heterocycles (**3.2j-p**). In all cases where conjugated products result, only the enamine tautomer could be observed. Interestingly, when using alkyl substituted alkynes such as 1-hexyne (**3.2q**) or 1-ethynylcyclohexane (**3.2r**) a minor amount of imine tautomer can be observed. Notably, the conjugated 1-ethynylcyclohex-1-ene delivered the enamine product exclusively (**3.2s**). Other functional groups, such as silylether (**3.2t**) and amide (**3.2u**) were also compatible with catalyst **1**. Internal alkynes were employed successfully (**3.2v-y**) to give products regioselectively and in high yield.



a) ^{1}H NMR yields obtained quantitatively by using 1,3,5-trimethoxybenzene as internal standard. b) Reactions were performed on a 5 mmol scale using nondeuterated toluene, and products were purified by vacuum distillation under heat.

Scheme 3.10 Scope of Alkyne Hydroamination Towards the Synthesis of *N*-Silylenamines

Three examples of *N*-silylenamines (**3.2a, 3.2s, 3.2v**) were purified and isolated by vaccum distillation under heat. It is worth noting that for the majority of substrates synthesized,

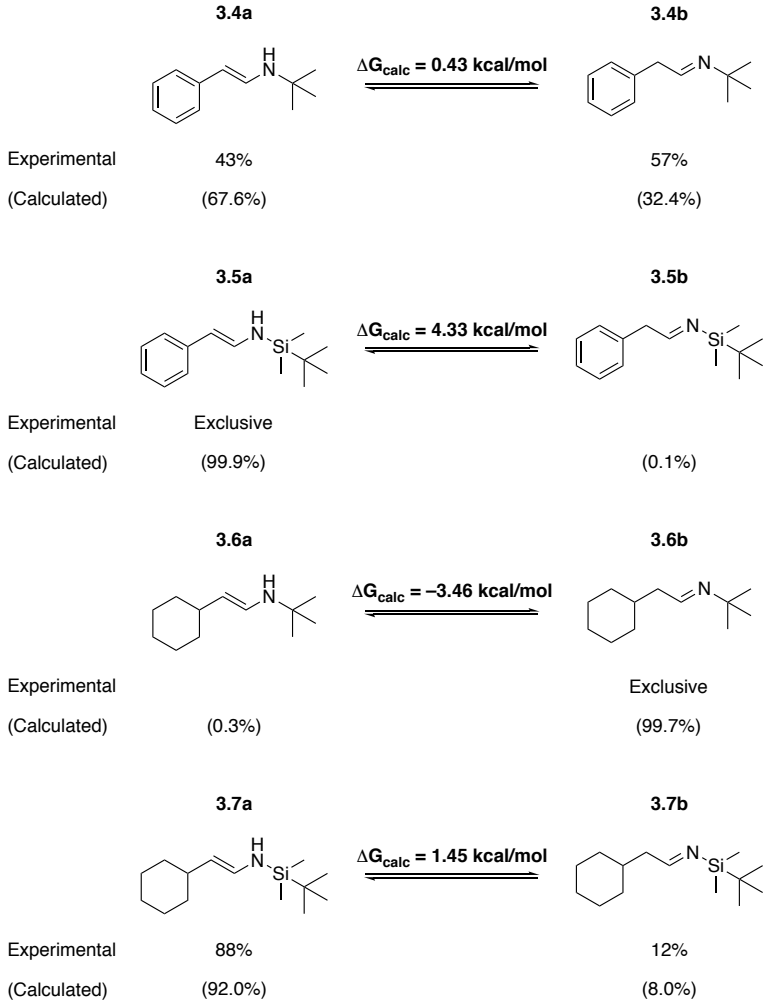
the (*E*)-isomer was the sole product obtained. However, a mixture of (*E*)- and (*Z*)-isomers were observed in certain cases (**3.2j**, **3.2m**, **3.2u-y**). Furthermore, analogous to the initial reaction using (*N*-triphenylsilyl)amine, it was observed that the enamine tautomer was prevalent and exclusive in all cases, except for the alkyl substituted derivatives (**3.2q-r** and **3.2t**), where minor amounts of the imine tautomer is observed due to the absence of extended conjugation. In the generally accepted mechanism for titanium-catalyzed hydroamination of alkynes, the formation of the more thermodynamically stable imine occurs *via* the tautomerization of the enamine product. Thus, the preference for the enamine tautomer when the nitrogen is silylated warranted further investigation.

3.2.4 Computational Studies – DFT Calculations

The observation of the preferential formation of enamine products when using silylamines is in contrast to reactivity trends observed with primary alkyl amine substrates which furnish imine products upon reaction completion.[27] In order to further understand the preference of *N*-silylenamines over the *N*-silylimine tautomer, DFT calculations (B3LYP/6-311g(d,p)) were performed by Dr. Jason W. Brandt. These results were evaluated in comparson to experimental results obtained.

Calculated tautomer ratios correlated well with experimentally determined equilibria (Scheme 3.11). For example, the calculated and observed tautomeric ratios for the hydroamination reaction using ethynylcyclohexane showed that when N is alkylated, the observed imine:enamine ratio is 100:0 (DFT calc. 99.7:0.3), yet when N is silylated the observed imine:enamine ratio is reversed at 12:88 (DFT calc. 8:92).

The NBO calculations show a change in bond polarity between the N-alkyl and N-silyl cases, such that the electropositive Si affords a more electron rich N. This results in significant stabilization of the N lone pair by donation into the π* of the enamine double bond. Although this interaction exists in both N-alkyl and N-silyl enamines, NBO analysis estimates the N_{LP} to $\pi^*_{C=C}$ stabilization to be ~9 kcal/mol greater in the enamine with N-$SiMe_2{}^tBu$ over N-CMe_3 (Figure 3.3). These insights highlight the different electronic features accessible in N-silylenamines as readily accessible reactive intermediates.



Scheme 3.11 Experimental and Calculated Data for Enamine and Imine Tautomerization Experiments

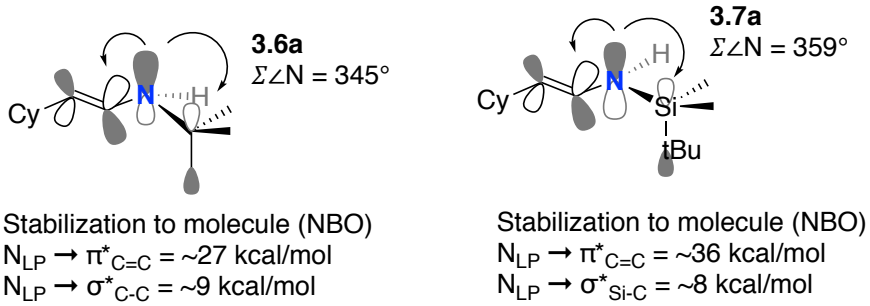
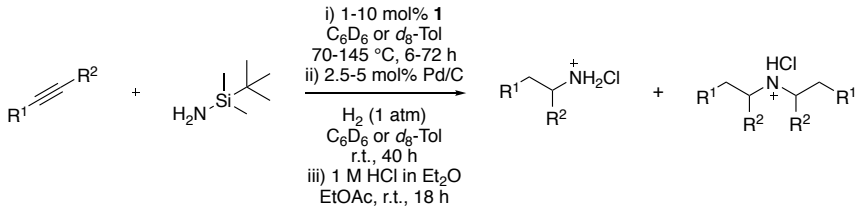


Figure 3.3 Frontier Molecular Orbital Analysis Based on Natural Bond Order Calculations

3.2.5 Substrate Scope of Sequential Hydroamination/Hydrogenation Transformation To Access Primary Amines

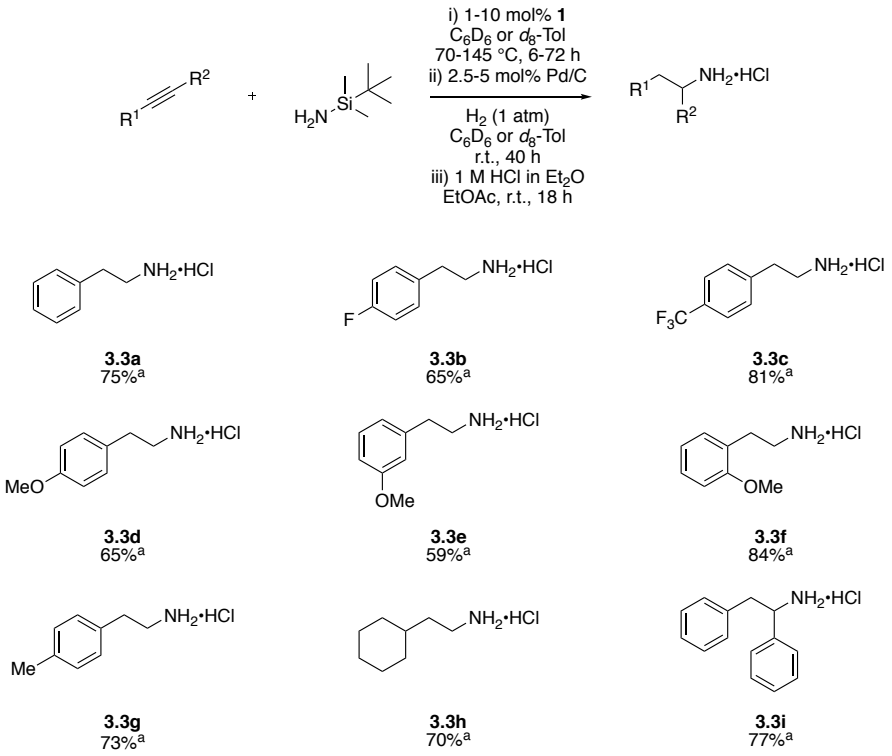
As an illustration of the use of *N*-silylenamines as in situ generated reactive intermediates and a demonstration of the use of *N*-silylamines as ammonia surrogates for hydroamination, primary amine products were prepared using this sequential catalytic approach. First, the hydroamination reaction was performed and the reactive *N*-silylenamine intermediate was then exposed to catalytic Pd/C and H_2. The salt of the crude amine product could be isolated by filtration following treatment with 1M hydrochloric acid.

In some cases, unwanted secondary amine byproducts were formed during the hydrogenation reaction (Table 3-1). The formation of secondary amines could occur through the exchange of silicon between the starting enamine and the reduced product, leading to the formation of an unsubstituted imine, which could be attacked by another amine. Gratifyingly, the salt of the primary amine product can be isolated by sublimation. Various terminal alkynes and one internal alkyne could be used in this tandem sequential approach (Scheme 3.12).



Compound Number	Ratio of Primary to Secondary Amines	Combined Yield (%)[a]
3.3a	95:5	82
3.3b	92:8	71
3.3c	>99:1	81
3.3d	95:5	70
3.3e	74:26	84
3.3f	>99:1	85
3.3g	96:4	90
3.3h	>99:1	70
3.3i	>99:1	77

Table 3-1 Ratio of Primary to Secondary Amines After Hydrogenation and Salt Formation Reactions



a) Isolated yields after purification by sublimation.

Scheme 3.12 Sequential Catalysis for the Synthesis of Primary Amines from Alkynes and *N*-Silylamine

3.3 Conclusion

In summary, a regio- and stereoselective hydroamination with *N*-silylamine substrates using bis(amidate)bis(amido)titanium catalyst **1** has been realized. The diverse array of (*E*)-*N*-silylenamines accessible represents a high yielding and atom-economic route for the *in situ* preparation of a useful class of organic synthons, which are otherwise hard to access through alternative methods. To test the [2+2] cycloaddition mechanistic hypothesis for the hydroamination reaction with silylamines, catalytically active silylimido species were isolated. Characterization by X-ray crystallography provided insights regarding the hemi-labile nature of the 1,3-*N,O*-chelating amidate ligands that support this unique reactivity. As a demonstration of the use of *N*-silylamine as a viable ammonia surrogate, a tandem sequential catalytic route was

used to prepare primary amines from alkynes in good yields. On-going work focuses on the application of selectively prepared (*E*)-*N*-silylenamines as reactive intermediates in the preparation of *N*-heterocycles, which will be further discussed in Chapter 5.

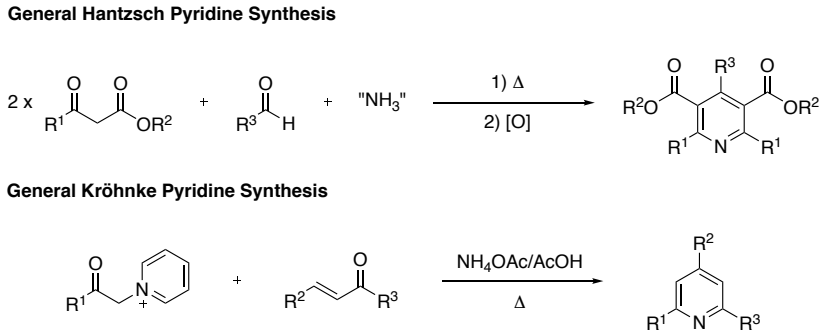
Chapter 4: *N*-Silylenamines as Reactive Intermediates. Hydroamination for the Modular Synthesis of Selectively Substituted Pyridines

4.1 Introduction

A wide variety of pyridines, can be found in numerous natural products[252] and pharmaceutical agents.[1, 253] Thus, significant effort has been employed toward their efficient preparation. In order to access pyridines with selected substitution patterns, two approaches are commonly employed: laborious, stepwise functionalization of the pyridine core,[254-256] or formation of the 6-membered aromatic ring through condensation, cycloisomerization or cycloaddition.[257-260]

Selective functionalization of the pyridine core is an attractive methodology, albeit in the cases of multi-substituted pyridines, it can be material and labour intensive. On the other hand, combining two or more simple molecules via thermal or metal-catalyzed reactions can readily assemble substituted pyridines.[258-260] For example, established condensation methods using 1,3- or 1,5-dicarbonyl derivatives are procedurally easy to set up, but offer restricted substitution patterns. For example, the Hantzsch pyridine synthesis reacts 1,3-dicarbonyls, an aldehyde and an ammonia source in one-pot to typically form substituted pyridines with specifically electron-withdrawing substituents in the 3- and/or 5-positions (Scheme 4.1 – top).[261] The Kröhnke synthesis, on the other hand, starts with a pyridinium salt and a α,β-unsaturated carbonyl to form a 1,5-dicarbonyl intermediate, which can then react with ammonium acetate to deliver 2,4,6-trisubstituted pyridines selectively (Scheme 4.1 – bottom).[262-263] However, yields can be problematic as dicarbonyls are prone to side-reactions, such as intra- or inter-molecular condensations, especially in cases where aldehydes are required to make pyridines without ortho-

substituents. Thus, a flexible and selective approach for the rapid assembly of a library of pyridines with diverse substitution patterns would allow for the modular assembly of such important substituted pyridine products and building blocks.



Scheme 4.1 General Hantzsch (top) and Kröhnke (bottom) Pyridine Syntheses

Previously, *N*-silylated enamines had been used to construct select substituted pyridines,[221, 264-265] although reported results were limited in substrate scope due to the difficult preparation and handling of moisture sensitive *N*-silylenamines using traditional stoichiometric approaches. However, as described in Chapter 3, a regioselective catalytic alkyne hydroamination with *N*-silylamines enables reliable and efficient *in situ* access to a wide range of mono-silylated enamines.[266] Such reactive nucleophilic synthons allow for subsequent reaction with a broad range of α,β-unsaturated carbonyls to access very diverse substitution patterns using a single synthetic protocol. Among these pyridine motifs, we disclose the synthesis of 3-mono-, 2,5-di-, 3,4-di-, 2,3,5-tri-, 2,4,5-tri-, 2,3,4,5-tetra-, 2,3,4,6-tetra- and even 2,3,4,5,6-penta-substituted pyridines. In this chapter, 47 examples of substituted pyridines are disclosed, including 30 examples of 2,4,5-trisubstituted pyridines. This specific substitution pattern is known to be of importance for the development of a new class of NK_1 receptor antagonists,[267] the preparation of radiolabels for PET imaging,[268] and the synthesis of alkaloids, such as flavocarpine and dihydrovincarpine.[269] However, there are very few general syntheses of such

2,4,5-trisubstituted pyridines,[221, 270-275] and even fewer where the substituent at the 5-position is something other than methyl.[270-273, 275] Here we highlight how 1) the anti-Markovnikov regioselectivity of our hydroamination reaction with terminal alkynes, followed by 2) 6-membered ring formation via addition to an α,β-unsaturated aldehyde or ketone and (3) oxidation, affords a range of selectively substituted pyridines, including 2,4,5-substituted pyridines with various substituents.

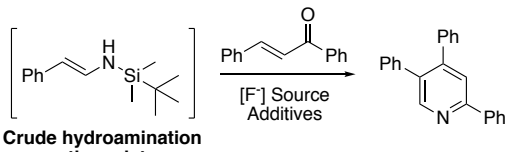
Alkynes and α,β-unsaturated carbonyls, are both commercially available and have been previously used in pyridine syntheses, although not concurrently in the same procedure. The intermolecular synthesis of pyridines using unactivated alkynes is commonly performed using late transition metals with coupling partners such as nitriles,[273, 275-280] halovinylimines,[281-282] enamides,[283-285] α,β-unsaturated imines[286] and α,β-unsaturated ketoximes,[287-291] which often have to be pre-synthesized. While, α,β-unsaturated carbonyls are readily available, they have been most typically applied toward the synthesis of 2,4,6-trisubstituted pyridines[292-296] or pyridines containing electron-withdrawing groups (amide, cyano, ester and ketone groups) at the 3-position,[297-302] with few examples that reach beyond these limitations.[221, 264, 274, 303-307] Here we show how alkynes and α,β-unsaturated carbonyls can be used together to access a broad range of selectively substituted pyridines in moderate to excellent yields.

4.2 Results and Discussion

4.2.1 Optimization of Pyridine Formation Step

Preliminary studies on the feasibility of synthesizing substituted pyridines using a sequential hydroamination followed by addition of an α,β-unsaturated carbonyl approach were performed using ethynylbenzene and (*N*-tert-butyldimethylsilyl)amine for the hydroamination step to generate the reactive N-silylenamine synthon in situ. Subsequently *trans*-chalcone was

added for the development of optimized conditions for the second step of the reaction (Table 4-1). While the reaction does occur in the absence of additives at 100 °C, the 11% yield was unsatisfactory. The addition of catalytic amounts a fluoride source helped activate the N-Si bond. For example, by adding 0.05 eq. of CsF the yield of the desired product was raised to 43%. Further optimization conditions were attempted with 10 mol% of CsF (Table 4-2). By changing the fluoride source to TBAF, the yield was not improved, however, a 1M solution of TBAF in THF is procedurally easier to handle. Other fluoride sources were also attempted, albeit no improvement on the yield was obtained (Table 4-3). The addition of 3 Å molecular sieves further increased the yield to 62% (Entry **4.1d**). Finally, addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidant allowed for the isolation of the desired product in 78% yield (Entry **4.1e**). Further screening of stoichiometric and catalytic oxidant sources were attempted to no improvements in yield could be obtained (Table 4-4). A slight improvement on the yield was obtained using dimethysulfoxide (DMSO) as the solvent (Entry 6). Furthermore, a 5-mmol scale of the reaction was also performed to synthesize over a gram of the desired pyridine (Entry **4.1f**, yield in parenthesis). If desired, the intermediate *N*-silylenamine can be purified by vacuum distillation. The use of the isolated intermediate affords the same yield as the case using in situ prepared intermediate, suggesting that the titanium and amide ligand present no deleterious effect on pyridine formation (Entry **4.1g**). The reaction can also be achieved by using commercially available *N*-triphenylsilylamine instead of the (*N*-tert-butyldimethylsilyl)amine although a somewhat diminished yield results (65% , Entry **4.1h**).

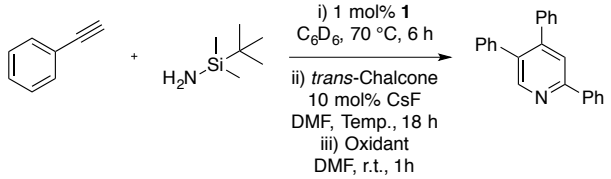


Crude hydroamination reaction mixture

Entry	Fluoride Source	Additive	Yield [%][a]
4.1a	-	-	11[b]
4.1b	0.05 equiv. CsF	-	43[c]
4.1c	0.1 equiv. TBAF	-	43
4.1d	0.1 equiv. TBAF	3 Å MS	62
4.1e	0.1 equiv. TBAF	3 Å MS; 1 equiv. DDQ	78
4.1f	0.1 equiv. TBAF	3 Å MS; 1 equiv. DDQ	85[d] (74)[e]
4.1g	0.1 equiv. TBAF	3 Å MS; 1 equiv. DDQ	83[f]
4.1h	0.1 equiv. TBAF	3 Å MS; 1 equiv. DDQ	65[g]

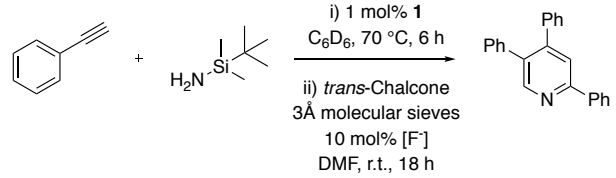
[a)] Isolated yields. [b)] Heated to 100 °C. [c)] Heated to 50 °C; d DMSO as solvent. [e)] 5 mmol scale. [f)] Using isolated *N*-silylenamine. [g)] Commercially available Ph_3SiNH_2.

Table 4-1 Optimization of Conditions for the Pyridine Formation Steps



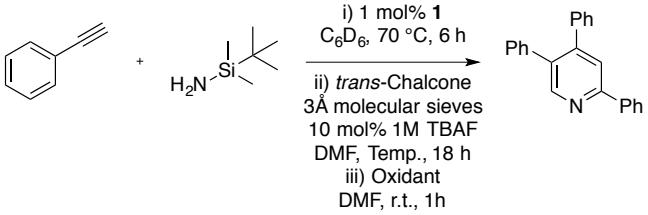
Entry	Temp (°C)	Oxidant	Yield (%)	Notes
4.2a	25	-	46	
4.2b	25	-	40	25 mol% CsF
4.2c	25	-	51	50 mol% CsF
4.2d	25	-	52	1 equiv. CsF
4.2e	50	-	43	5 mol% CsF
4.2f	50	Air	47	
4.2g	50	10 mol% CuCl Under air	24	Solvent was DMSO
4.2h	80		46	
4.2i	25	-	40	0.5 equiv. chalcone
4.2j	25	-	38	2 equiv. chalcone
4.2k	25	-	29	3Å molecular sieves

Table 4-2 Optimization of Pyridine Synthesis Using 10 mol% Cesium Fluoride



Entry	[F⁻]	Yield (%)	Notes
4.3a	1M TBAF in THF	43	
4.3b	CuF_2	30	
4.3c	TASF	39	
4.3d	TBAT	31	

Table 4-3 Optimization of Pyridine Synthesis Using 10 mol% of Other Fluoride Sources and 3Å molecular sieves



Entry	Temp.	Oxidant	Yield	Notes
4.4a	50	-	21	5 mol% 1M TBAF no molecular sieves THF was used as solvent
4.4b	25	-	52	2 equiv. chalcone
4.4c	25	-	49	1.2 equiv. *N*-silylamine
4.4d	25	-	62	
4.4e	50	-	71	
4.4f	75	-	61	
4.4g	100	-	62	
4.4h	25	-	57	1 equiv. 1M TBAF
4.4i	25	-	67	1 equiv. 1M TBAF 0.4000g of molecular sieves
4.4j	25	10 mol% $Cu(OAc)_2$	63	Oxidant allowed to react for 18 h
4.4k	25	10 mol% $Cu(OAc)_2$	62	Oxidant added after 3 h and allowed to react for 18 h
4.4l	25	20 mol% $Cu(OAc)_2$	70	Oxidant added after 30 min and allowed to react for 18 h

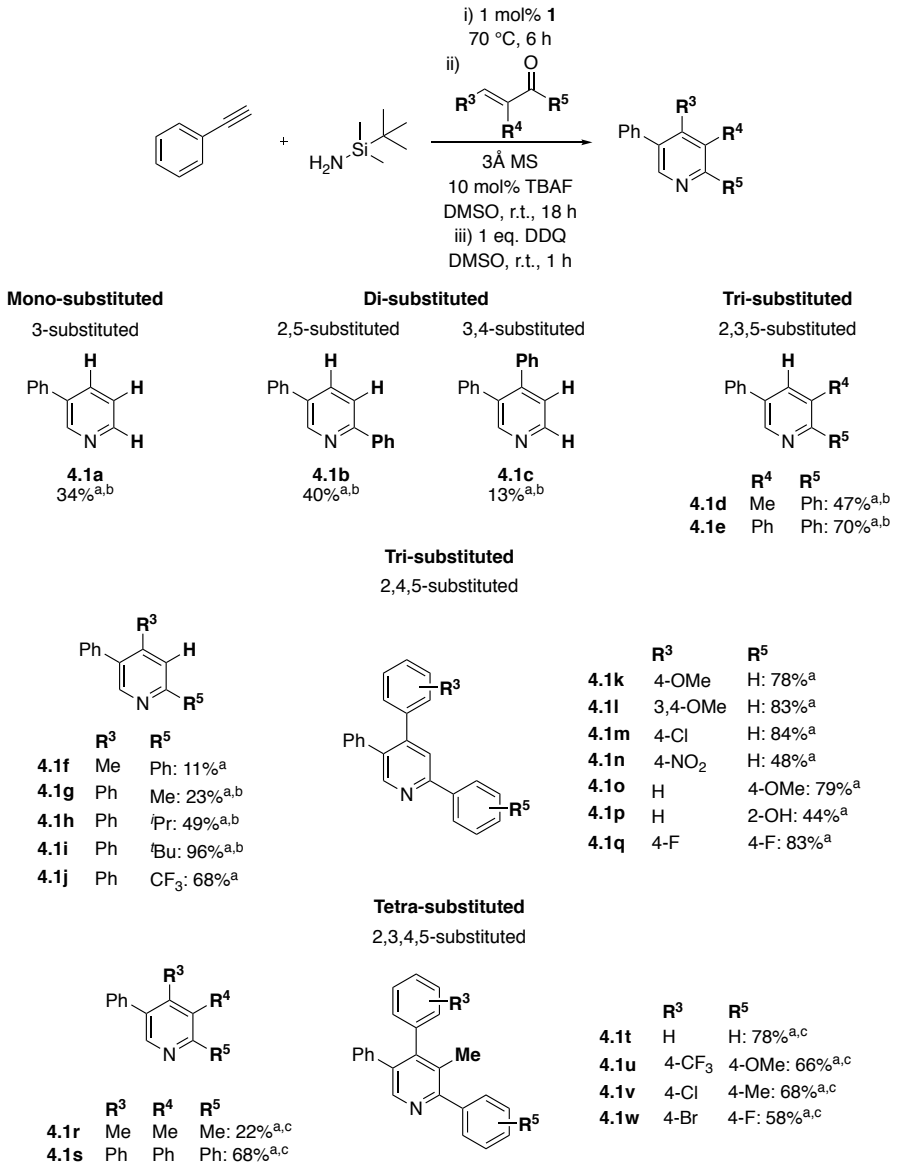
Entry	Temp.	Oxidant	Yield	Notes
4.4m	25	1 equiv. MnO_2	53	Oxidant added after 3 h and allowed to react for 18 h
4.4n	25	10 equiv. MnO_2	53	Oxidant allowed to react for 18 h
4.4o	25	1 equiv. $KMnO_4$	64	Oxidant allowed to react for 18 h
4.4p	25	1 equiv. I_2 in MeOH	67	
4.4q	25	1 equiv. I_2 in MeOH	25	Oxidant added after 3 h and allowed to react for 18 h
4.4r	25	1 equiv. I_2 in MeOH	77	Oxidant allowed to react for 18 h
4.4s	25	1 equiv. I_2 in MeOH	74	Oxidant allowed to react for 3 h
4.4t	25	10 equiv. activated carbon Under air	56	Oxidant added after 1.5 h and allowed to react for 18 h
4.4u	25	10 equiv. activated carbon 1 atm O_2	54	Oxidant added after 3 h and allowed to react for 18 h
4.4v	25	1 equiv. DDQ	74	Oxidant added after 3 h
4.4w	25	1 equiv. BQ	54	Oxidant added after 3 h
4.4x	25	1 equiv. Cl-BQ	63	Oxidant added after 3 h
4.4y	25	1 equiv. DDQ	65	Oxidant added after 1 h
4.4z	25	1 equiv. DDQ	78	
4.4aa	25	1 equiv. DDQ	41	0.0 mL DMF was used
4.4ab	25	1 equiv. DDQ	80	0.25 mL DMF was used
4.4ac	25	1 equiv. DDQ	78	1 mL DMF was used
4.4ad	25	1 equiv. DDQ	84	2.5 mL DMF was used
4.4ae	25	1 equiv. DDQ	77	5 mL DMF was used
4.4af	**25**	**1 equiv. DDQ**	**85**	**0.25 mL DMSO was used**

Table 4-4 Optimization of Pyridine Synthesis Using 10 mol% of 1M Tetra-Butylammonium Fluoride in THF and 3Å molecular sieves

4.2.2 Substrate Scope

With optimized conditions in hand, the scope and limitations of the sequential procedure were investigated (Scheme 4.2). We first examined the reaction of a terminal alkyne,

ethynylbenzene, with a variety of α,β-unsaturated aldehydes and ketones, which were commercially available or easily synthesized through aldol condensation.[308-310] By reacting the hydroamination product mixture with prop-2-enal, an example of a mono-substituted pyridine was obtained in 34% yield (**4.1a**). By using a mono-substituted α,β-unsaturated carbonyl substrate, di-substituted pyridines, with 2,5- or 3,4-substitution patterns were obtained in 40 and 13% yields, respectively (**4.1b** and **4.1c**). The reduced yields observed for the reactions using aldehydes is likely due to ill-defined side reactions of these substrates in the presence of the Lewis acidic titanium catalyst. Regardless, of note is the fact that currently 2,5-diphenylpyridine is commonly prepared via a double Suzuki coupling.[311-317] However, the synthesis of 2,5-disubstituted pyridines with different substituents would demand sequential and chemospecific reaction conditions to distinguish between (pseuso)halogens. As for 3,4-diphenylpyridine only 6 procedures have been disclosed, all of which require multi-step procedures.[318-323] Meanwhile our approach is completely regioselective and uses a common reaction protocol in all cases.



a) Isolated yields. b) One-pot reaction: hydroamination reaction performed under neat conditions followed by addition of α,β-unsaturated carbonyl. c) Second step performed at 80 °C.

Scheme 4.2 Various α,β-Unsaturated Carbonyl Substrates can be Incorporated into this Sequential Reaction

Similarly, disubstituted α,β-unsaturated ketones can be used to access tri-substituted pyridines with excellent regioselectivity for either the 2,3,5- or 2,4,5-positions. These variably substituted products were synthesized in a variety of yields ranging from 11-96% (**4.1d-q**). In

medicinal chemistry, a trifluoromethyl group can drastically change the physical and biological properties of heterocycles.[324] Thus a noteworthy example is pyridine **4.1j**, which contains a trifluoromethyl group at the 2-position. This desirable motif was synthesized in 68% yield from 1,1,1-trifluoro-4-phenylbut-3-en-2-one.[325] The resulting regioselectivity of pyridine formation was confirmed by X-ray diffraction of crystalline product **4.1m** (Figure 4.1).

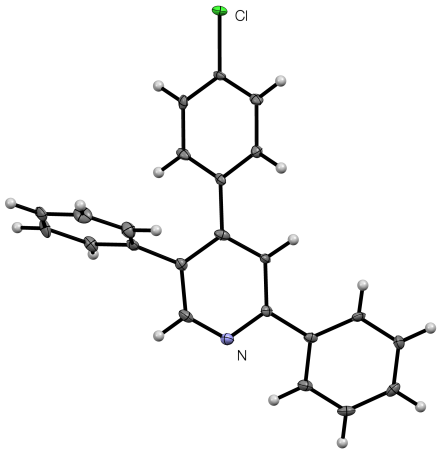
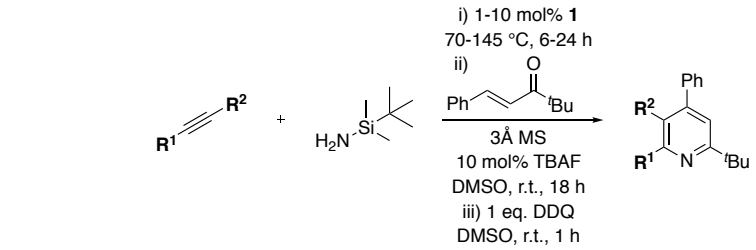


Figure 4.1 X-ray Crystallography of Pyridine 4.1m

Finally, the synthesis of 2,3,4,5-tetrasubstituted pyridines could also be readily accessed using trisubstituted α,β-unsaturated ketones. Notably, this transformation features symmetrical and unsymmetrical α,β-unsaturated ketones in yields of up to 78% (**4.1r-w**). Notably, 4 of the 5 examples of 2,3,4,5-tetrasubstituted pyridines reported here are new compounds, which suggests that routine methods for these more highly substituted pyridines are underdeveloped. Compound **4.1s** has been recently synthesized by Chen and co-workers.[275] In their synthesis, an alkenylation of nitriles with vinyliodonium salts is performed. While the reaction occurs in a single step, the vinyliodonium salts have to be pre-synthesized.

Next the effect of different alkyne-substituents on the sequential reaction was examined using 4,4-dimethyl-1-phenylpent-1-en-3-one as a consistent α,β-unsaturated carbonyl substrate

(Scheme 4.3). In all cases, full consumption of starting materials in the hydroamination step is observed for the hydroamination reaction and the ^{1}H NMR yields for the synthesized *N*-silylenamines vary between 69-99%.[266] Halogenated *para*-substituted ethynylbenzenes (**4.2a-c**) were successfully employed in 81-88% yields. The presence of chloro- and bromo-substituents could allow for further cross-coupling transformations to be performed. Other *para*-substituted ethynylbenzenes bearing electron-donating and electron-withdrawing substituents were used to give products (**4.2d-f)** in great yields. The *meta*- (**4.2g**) and *ortho*-substituted (**4.2h**) ethynylbenzenes were also tolerated with no decrease in pyridine yield.



Tri-substituted

2,4,5-substituted

	R
4.2a	4-F: 81%[a]
4.2b	4-Cl: 88%[a]
4.2c	4-Br: 85%[a]
4.2d	4-CF_3: 77%[a]
4.2e	4-Me: 82%[a]
4.2f	4-OMe: 85%[a]
4.2g	3-OMe: 90%[a]
4.2h	2-OMe: 78%[a]

	Heterocycles
4.2i	2-pyridine: 70%[a]
4.2j	3-pyridine: 72%[a]
4.2k	4-pyridine: 60%[a]
4.2l	4-pyrazine: 72%[a]
4.2m	1-methyl-4-pyrazole: 63%[a]
4.2n	2-thiophene: 82%[a]
4.2o	3-thiophene: 75%[a]

4.2p 78%[a]

4.2q 27%[a,b]

4.2r 26%[a,b]

Tetra-substituted

2,3,4,6-substituted

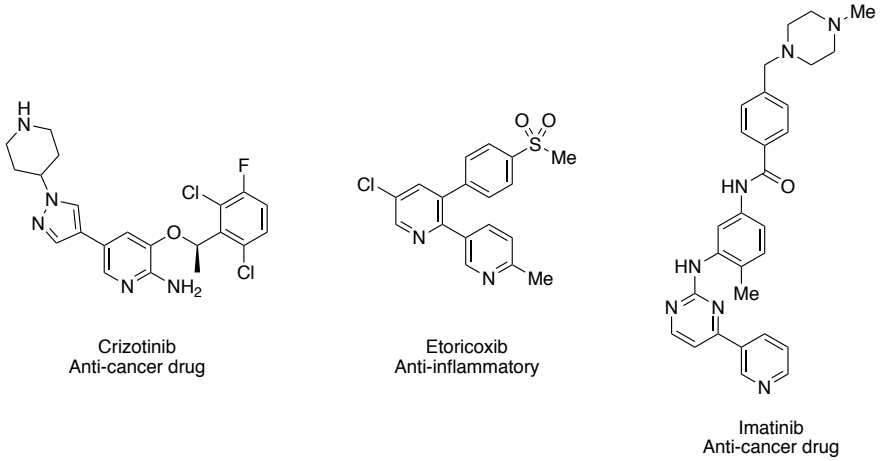
	R^1	R^2
4.2s	Me	Ph: 79%[a,c]
4.2t	Et	Ph: 72%[a,c]
4.2u	Pr	Ph: 67%[a,c]
4.2v	Ph	Ph: 64%[a,c]

[a)] Isolated yields. [b)] Second step performed at 50 °C. [c)] Second step performed at 80 °C.

Scheme 4.3 Effect of Alkyne-Substituents on Sequential Reaction for Pyridine Synthesis

The synthesis of pyridines containing other heterocycles on the 3- or 5-positions is important, as seen by the presence of such motifs in current commercial pharmaceutical drugs such as Crizotinib, Etoricoxib and Imatinib (Scheme 4.4). Using our developed methodology, alkynes containing various nitrogen- or sulfur-heterocycles (**4.2i-o**) were also compatible with these reaction conditions and the resultant pyridines could be synthesized and isolated in good yields (60-82%).

Currently Approved Drugs Containing 3-Heterocyclic Pyridine Motifs

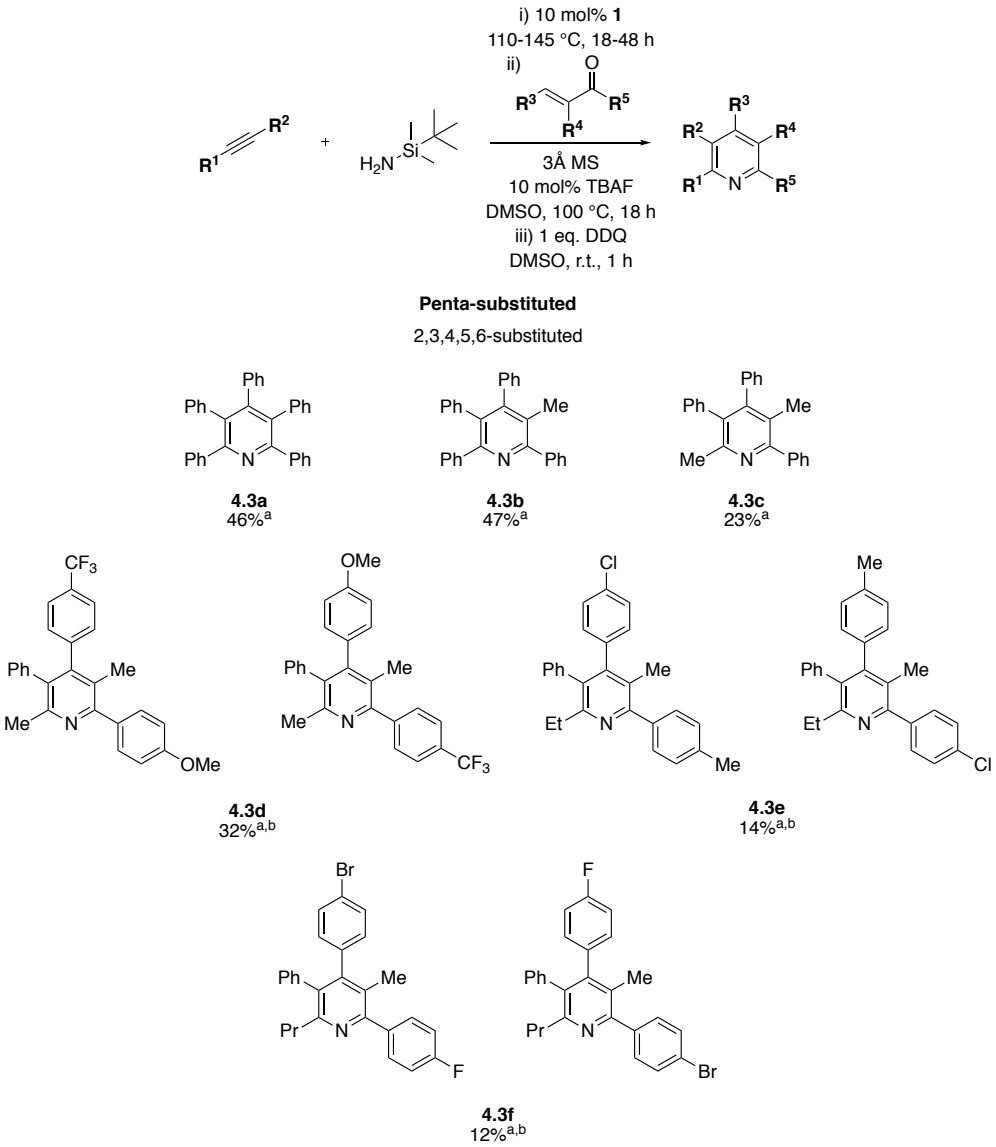


Scheme 4.4 Importance of 3-Heterocyclic Pyridine Motif

Importantly, our reaction conditions are not limited to arylalkyne substrates, as shown with an enyne precursor (**4.2p**), as well as the use of an alkylamide to give product (**4.2q**) and silylether to furnish pyridine (**4.2r**). While these different derivatives were tolerated, the latter two were noted to be lower yielding. The incorporation of alkyl substituents on the 5-position presents a challenge. For example, there are no examples of 2,4,5-trisubstituted pyridines containing a methylene-spaced pivalamide substituent on the 5-position and only a single example containing a propanol substituent on the 5-position.[326]

Finally, internal alkynes could be used in combination with disubstituted α,β-unsaturated ketones to give 2,3,4,6-tetrasubstituted pyridines in 64-79% yields (**4.2s-v**). In the case of unsymmetrical aryl-alkyl internal alkynes, the regioselective hydroamination reaction allowed for the selective synthesis of tetra-substituted pyridines containing an alkyl group at the 2-position and an aryl group on the 3-position (**4.2s-u**). None of these examples have been reported previously.

The synthesis of penta-substituted pyridines is a synthetic challenge, particularly in cases where the pyridine core contains five-carbon substitutents.[272, 286-289, 327-330] However, using the developed sequential methodology, penta-substituted pyridines can be assembled in yields of 23-47% (**4.3a-c**) using the same 3 step sequential protocol (Scheme 4.5). Unfortunately, when the reaction was attempted with aryl-alkyl alkynes and unsymmetrical α,β-unsaturated ketones, a mixture of 2 regioisomers were obtained in ratios ranging from 65:35 to 78:22 (**4.3d-f**). Since the hydroamination using **1** is known to be regioselective for the addition of the amine to the alkyl side of the alkyne, the formation of regioisomers could hint to a change in mechanism for the formation of the 6-membered ring.



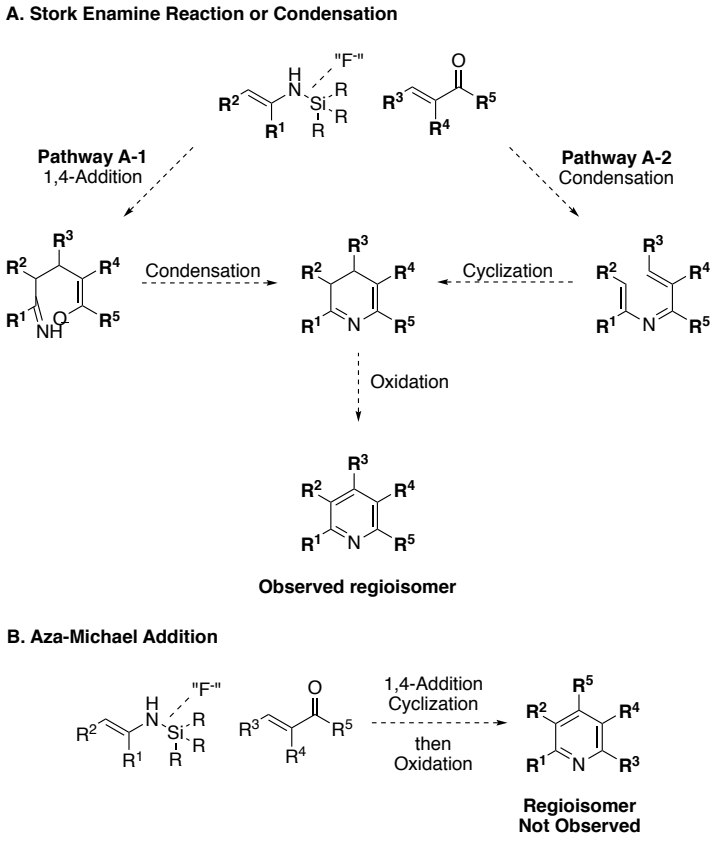
[a)] Isolated yields. [b)] Combined yields.

Scheme 4.5 Synthesis of Penta-Substituted Pyridines

4.2.3 Proposed Mechanism for the Formation of Pyridines

Analysis of the substitution pattern obtained for product **4.1m** provides a hint as to the mechanistic path for the cycloaddition step for pyridine formation (Scheme 4.6). As observed, R^3 is located in the 4-position, which would be consistent with a Stork enamine reaction, where the

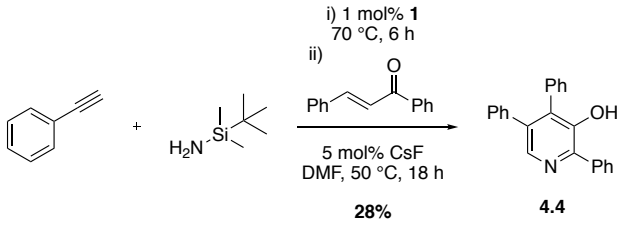
β-carbon of the enamine attacks the α,β-unsaturated carbonyl in a 1,4-addition fashion. Another pathway that could not be ruled out was the condensation reaction, followed by a cyclization event, which would also deliver the correct regioisomer. After condensation or cyclization and oxidation, the pyridine regioisomer obtained through these mechanisms would be in agreement with the isolated product. An alternative pathway considered was an aza-Michael addition, where the nitrogen of the enamine nucleophilically attacks the β-position of the α,β-unsaturated carbonyl. The product of this mechanism, however, would not furnish the observed regioisomer. Carbon-based enamines are known to react through the β-carbon of the enamine moiety. However, as shown from our previous study on *N*-silylenamines,[266] which were notably resistant to tautomerization, in contrast to their carbon-substituted variants, the reactivity of enamines containing silicon-based substituents can be different from enamines containing carbon-based substituents. Thus, further investigation on the nucleophilicity of mono-silylated enamines is necessary to confirm the mechanistic pathway of this reaction.



Scheme 4.6 Potential Mechanisms for the Formation of Pyridines

4.2.4 Isolation of 2,4,5-Triphenylpyridin-3-ol By-Product

In the initial stages of the optimization screening for the formation of pyridines, a common spot not corresponding to the product retention factor was observed by TLC. Separation of the unknown spot by column chromatography lead to the isolation of hydroxypyridine **4.4** in 28% yield (Scheme 4.7). The molecular structure of **4.4** was characterized by X-ray diffraction of the crystalline product (Figure 4.2). Preliminary efforts at optimizing the reaction towards the synthesis of **4.4** were attempted, but unsuccessfully.



Scheme 4.7 Reaction that Lead to the Isolation of By-Product 4.4

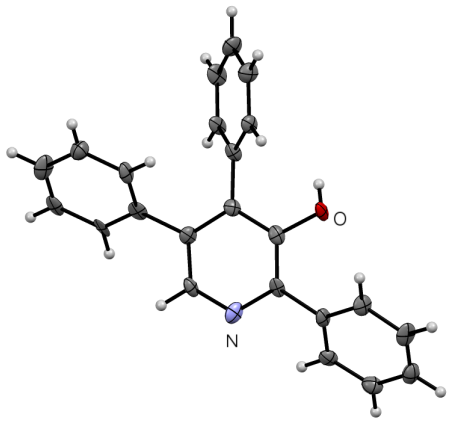


Figure 4.2 X-ray Crystallography of Hydroxypyridine 4.4

4.3 Conclusion

In conclusion, a simple, modular method to prepare mono-, di-, tri-, tetra-, and pentasubstituted pyridines has been disclosed in this chapter. The method developed employs a sequential regioselective hydroamination of alkynes with *N*-silylamine followed by the addition of an α,β-unsaturated carbonyl substrate to give a 6-membered nitrogen-containing ring intermediate that can undergo oxidation to afford pyridines. A broad range of targeted products could be isolated in a wide range of isolated yields. The generality of the transformation is demonstrated by using a wide scope of both alkyne and α,β-unsaturated carbonyl substrates. Notably, both of these starting materials are commercially available and/or easily synthesized. An aza-Michael reaction mechanism for N-silylenamine nucleophilic attack of the α,β-unsaturated carbonyl has been ruled out. A Stork enamine 1,4-addition would furnish the

observed selectively substituted pyridine products. Mechanistic investigations and applications in the synthesis of selectively substituted pharmaceutically relevant pyridine compounds are the natural progression for the continuation of this chapter.

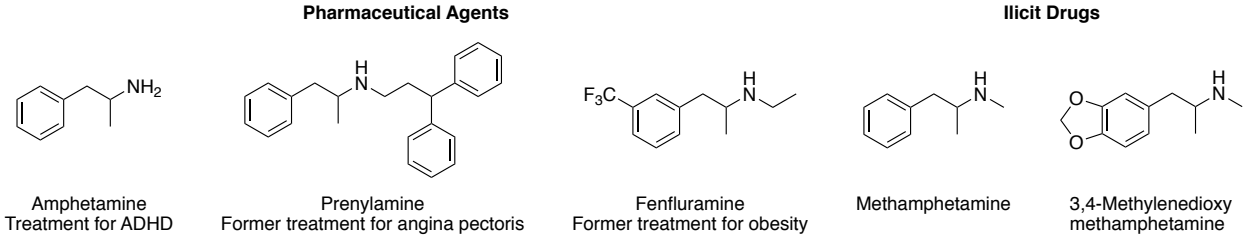
Chapter 5: Future Directions and Conclusions

5.1 Future Directions

The use of the Schafer, bis(amidate)bis(amido) titanium, complex has been studied extensively.[25-27, 66-67, 266, 331-338] However, as clearly demonstrated by the work within this thesis, there are numerous new synthetic opportunities that can be explored using this complex.

5.1.1 Synthesis of Secondary Amines Containing α- and β-Substituents *via* a Sequential Hydroamination of Alkynes Followed by Reduction

For several decades, amphetamine and its derivatives have been used as pharmaceutical agents, both medicinally and illicitly (Scheme 5.1).[339-340] As such, the synthesis of such motifs is of significant interest to the pharmacology community. Titanium complex **1** has been shown to be regioselective for the hydroamination of unsymmetrical aryl/alkyl internal alkynes to give the correct regioisomer towards the synthesis of α-alkyl and β-aryl substituted amines. A logical continuation of the work performed in Chapter 2 would be to expand the substrate scope to include internal alkynes.

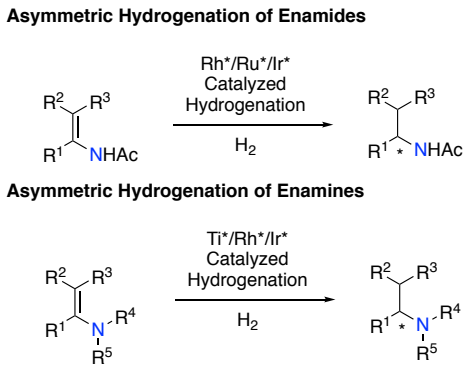


Scheme 5.1 Uses of Amphetamine and Derivatives

Furthermore, there is currently no sequential hydroamination of alkynes followed by asymmetric hydrogenation strategy for the synthesis of enantiopure α-substituted phenethylamines. The only example of an asymmetric reduction after a hydroamination reaction

was accomplished using transfer hydrogenation.[63] In the methodology developed by Che and co-workers, however, the hydroamination reaction delivered the Markovnikov regioisomer.

The challenge for the synthesis of enantiopure amines, via alkyne hydroamination, lies within the asymmetric reduction step. The asymmetric hydrogenation of enamides (*N*-acetyl enamines) using late-transition metal complexes, in particular rhodium,[341] has been well studied, with systems delivering high yields and enantiomeric excesses. Consequently, the required *N*-acyl group is generally not easily cleaved (Scheme 5.2 – top).[342-345]

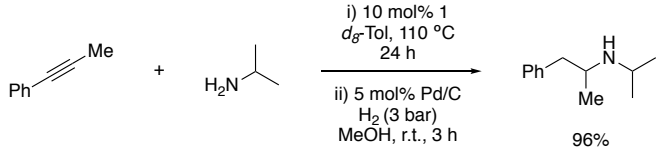


Scheme 5.2 General Asymmetric Hydrogenation of Enamides and Enamines

On the other hand, the asymmetric hydrogenation of alkyl enamines has only been reported a few times, with a compromise between high enantiomeric excess and broad substrate scope (Scheme 5.2 – bottom).[346-357] Furthermore, the asymmetric hydrogenation of unactivated imines has only been successful in cases where the substrate is cyclic, or has an aryl substituent on the nitrogen or on the α-position of the imine.[342, 344, 358] The difficulty in the asymmetric hydrogenation of unactivated enamines stems from the fact that these enamines lack the ability to form a stable bis-chelate that the related enamides are proposed to form, which occurs through chelation of the alkene and oxygen of the carbonyl prior to insertion into the metal-hydride.

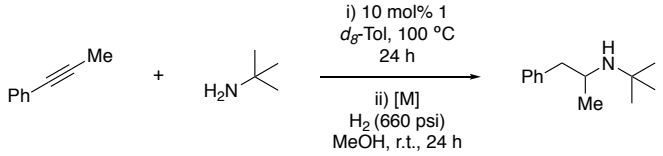
5.1.1.1 Preliminary Results

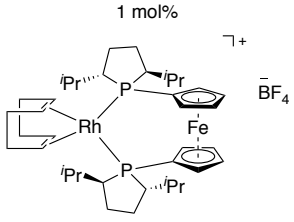
The hydroamination of internal alkynes with complex **1** followed by Pd/C hydrogenation was successful with one example. Following the same procedure as developed for terminal alkynes discussed in Chapter 2, prop-1-yn-1-ylbenzene was reacted with *iso*-propylamine in the presence of 10 mol% of titanium complex **1** and then reacted with Pd/C and H_2 gas at 3 bar to deliver 96% yield of *N*-isopropyl-1-phenylpropan-2-amine (Scheme 5.3).



Scheme 5.3 Sequential Hydroamination/Hydrogenation Towards the Synthesis of *N*-isopropyl-1-phenylpropan-2-amine

The synthesis of enantiopure secondary amines using homogeneous hydrogenation catalysts were attempted (Table 5-1). The reaction mixtures were analyzed using mass spectrometry, but isolation of the final products have yet to be performed.



Entry	[M]	Observation by GC-MS
2.4a		Mass corresponding to hydrolyzed starting material observed. **LRMS** (CI) m/z calc'd for $C_9H_{10}O$ [M+H$^+$]: 134.07; found: 135.0. Trace amounts of product observed.

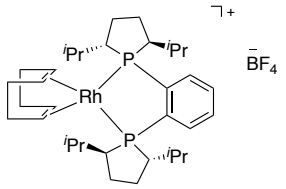
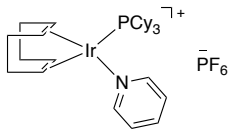
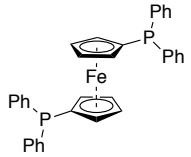
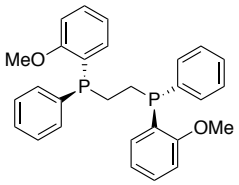
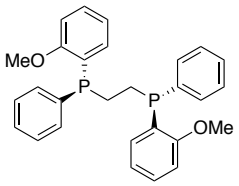
Entry	[M]	Observation by GC-MS
2.4b	1 mol% 	Mass corresponding to hydrolyzed starting material observed. **LRMS** (CI) m/z calc'd for $C_9H_{10}O$ [M+H$^+$]: 134.07; found: 135.0. Trace amounts of desired product observed.
2.4c	0.5 mol% 	Mass corresponding to product observed. **LRMS** (CI) m/z calc'd for $C_{13}H_{21}N$ [M+H$^+$]: 191.17; found: 192.0. Yield: N.D.
2.4d	0.5 mol% $[Ir(cod)Cl]_2$ 1 mol% 	Mass corresponding to product observed. **LRMS** (CI) m/z calc'd for $C_{13}H_{21}N$ [M+H$^+$]: 191.17; found: 192.0. Yield: N.D. Enantiomeric excess %: N.D.
2.4e	0.5 mol% $[Ir(cod)Cl]_2$ 1 mol% 	Mass corresponding to product observed. **LRMS** (CI) m/z calc'd for $C_{13}H_{21}N$ [M+H$^+$]: 191.17; found: 192.0. Yield: N.D. Enantiomeric excess %: N.D.
2.4f	0.5 mol% $[Ir(cod)Cl]_2$ 1 mol%  1 mol% $NaBF_4$	Trace amounts of desired product observed.

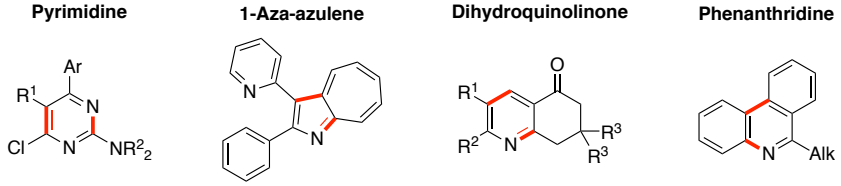
Table 5-1 Preliminary Results of the Homogeneous Hydrogenation Towards α-Substituted Secondary Amines

By examining the results in hand, it seems that rhodium catalysts are not as reactive as iridium catalysts towards the hydrogenation of the hydroamination reaction mixtures. However,

other reaction conditions, such as addition of acids, could still be attempted with rhodium catalysts.

5.1.2 Synthesis of *N*-Heterocycles Using *N*-Silylenamine as a Reactive Intermediate

Mono-silylated enamines have been used in the synthesis of very few *N*-heterocycles, which range from a single ring to multi-fused systems (Scheme 5.4).[219, 223, 225-226] Due to the limited synthetic methodologies available towards the synthesis of *N*-silylenamines, in all previous cases, an α-substituent was required. In Chapter 3, however, it was demonstrated that linear *N*-silylenamines could be synthesized through a titanium-catalyzed hydroamination of alkynes with *N*-silylamines. Furthermore, a modular synthesis of mono-, di-, tri-, tetra- and penta-substituted pyridines using *N*-silylenamines as a reactive synthon was described in Chapter 4. Thus, the synthesis of other *N*-heterocycles would be a reasonable extension to showcase the applicability of *N*-silylenamines.



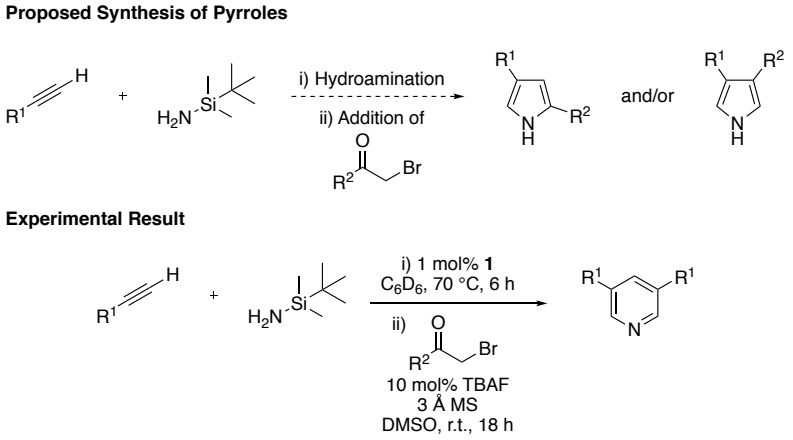
Highlighted in red are the bonds formed between the *N*-silylenamine and the other starting material.

Scheme 5.4 Synthesis of *N*-Heterocycles Using *N*-Mono-Silylated Enamines

5.1.2.1 Reactivity of α-Haloketones with *N*-Silyenamines

Due to the diverse biological activity shown by molecules containing a pyrrole motif, it is not surprising that the syntheses of such compounds have been widely studied.[359-361] The synthesis of pyrroles through an intermolecular hydroamination of alkynes has been accomplished four times.[74-77] However, in all cases reported to date, no examples of pyrroles

without an *N*-substituent has been demonstrated. Since the cleavage of an N-Si bond can be be readily achieved, it was envisioned that the synthesis of pyrroles could occur through the addition of an α-haloketone to the *N*-silylenamine product (Scheme 5.5 – top). However, when the reaction was performed, 3,5-disubstituted pyridines were obtained (Scheme 5.5 – bottom). The pyridine product was unexpected, as both the starting materials are two-carbon fragments, suggesting either the cleavage of a C-C bond or methyl abstraction from the DMSO solvent.



Scheme 5.5 Proposed Sequential Hydroamination/Addition of α-Haloketone Towards the Synthesis of Pyrroles and General Scheme for Experimentally Obtained Results

When the reaction was performed with 2-bromo-1-phenylethan-1-one, 3,5-diphenylpyridine was isolated in 20% yield (Table 5-2, Entry 3.2a). By changing the α-haloketone to 1-bromo-3,3-dimethylbutan-2-one, the mass corresponding to 3,5-diphenylpyridine was obtained by GC-MS. On the other hand, by changing the *N*-silylenamine fragment but maintaining the α-haloketone as 2-bromo-1-phenylethan-1-one, the mass corresponding to 3,5-bis(4-(trifluoromethyl)phenyl)pyridine was obtained by GC-MS.

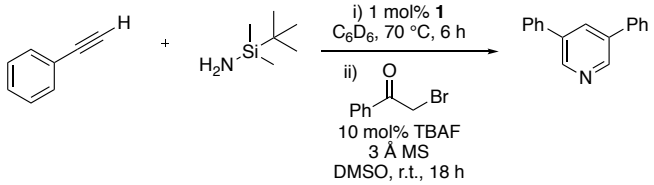
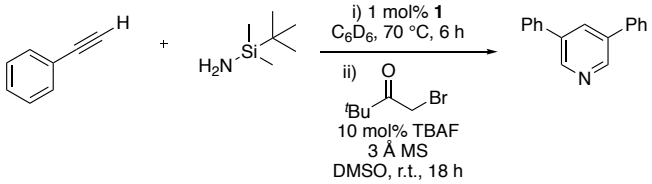
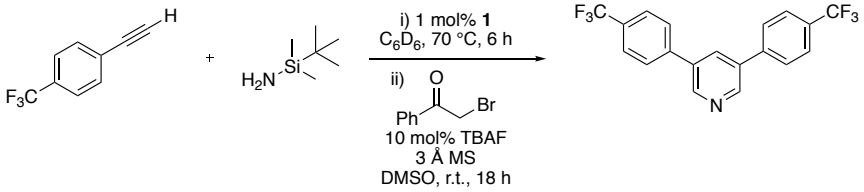
Entry	Reaction (Notes)
3.2a	 (20% isolated yield. Product obtained was confirmed by X-ray crystallography.)
3.2b	 (Yield: N.D. Mass corresponding to depicted product was observed by GC-MS. **LRMS** (CI) m/z calc'd for $C_{17}H_{13}N$ [M+H$^+$]: 231.30; found: 232.1.)
3.2c	 (Yield: N.D. Mass corresponding to depicted product was observed by GC-MS. **LRMS** (CI) m/z calc'd for $C_{19}H_{11}F_6N$ [M+H$^+$]: 367.08; found: 368.0.)

Table 5-2 Preliminary Results of Sequential Hydroamination/Addition of α-Haloketone Reactions

Considered together, it is reasonable to propose that 2 equivalents of *N*-silylenamine and a yet unidentified one-carbon source are reacting to form the observed 3,5-disubstituted pyridines. While we do not have evidence that dimethylsulfoxide is involved in the reaction, it has been previously shown that dimethylsulfoxide can act as a one-carbon source.[362-363] In most cases reduction of dimethylsulfoxide to dimethylsulfide is necessary before it can be used as a –CH– source. Other control reactions, which include performing the reaction in the absence of α-

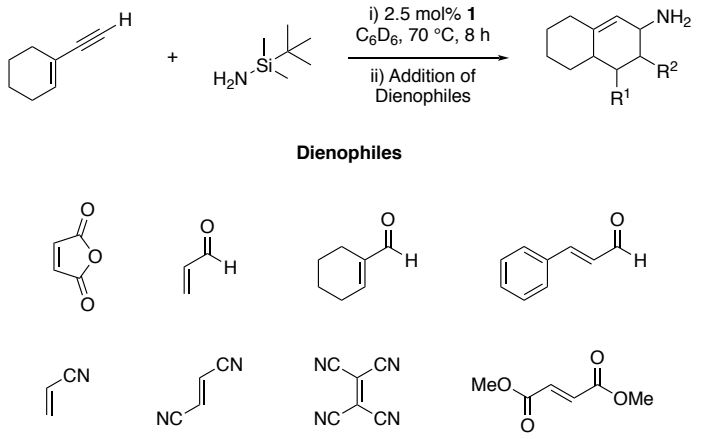
haloketone and performing the reaction in various solvents, are needed to further understand the formation of 3,5-disubstituted pyridines.

5.1.2.2 Synthesis of *N*-Silyl-1-Amino-1,3-Diene and Reactivity with Dienophiles

The syntheses of linear dienes containing a nitrogen group at the 1-position are usually limited to *N*-acylated,[364-366] *N*-Boc protected[367] or secondary amine[368-370] containing dienes. Such 1-amino-1,3-dienes are reactive towards dienophiles to give aminocyclohexenes *via* a Diels-Alder transformation.[364, 366, 371-376] Through the methodology developed in Chapter 3, *N*-silyl-1-amino-1,3-dienes could be easily synthesized in a single step starting from an enyne and a *N*-silylamine. Furthermore, primary aminocyclohexenes could be targeted.

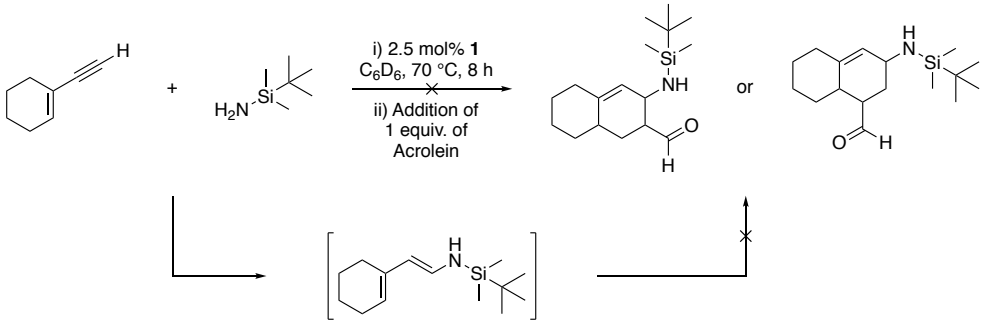
Other than traditional Diels-Alder reactions, aminocyclohexenes can be synthesized through the hydroamination of 1,3-dienes,[377] allylic substitution of cyclic allyl carbonates with amines,[378] hydrogenation of cyclic enamides,[379] and isomerization of ynamides and allenamides.[380]

After performing the hydroamination of 1-ethynylcyclohex-1-ene with *N*-silylamine, a variety of dienophiles were added to the reaction mixture (Scheme 5.6). Although the consumption of starting materials was observed by ^{1}H NMR spectroscopy, the isolation of the final desired products remains unsuccessful and thus further work towards the isolation of product would be a priority.



Scheme 5.6 Dienophiles Attempted Towards the Synthesis of Aminocyclohexenes

In the case when acrylaldehyde was added to the hydroamination mixture (Scheme 5.7), full consumption of both starting materials (*N*-silylenamine and acrolein) and appearance of new peaks were observed by ^{1}H NMR spectroscopy (Figure 5.1). However, attempted purification and isolation of the product by column chromatography was not successful. Decomposition of the product appears to occur as evidenced by the appearance of several compounds by TLC.



Scheme 5.7 Sequential Hydroamination/Addition of Acrolein

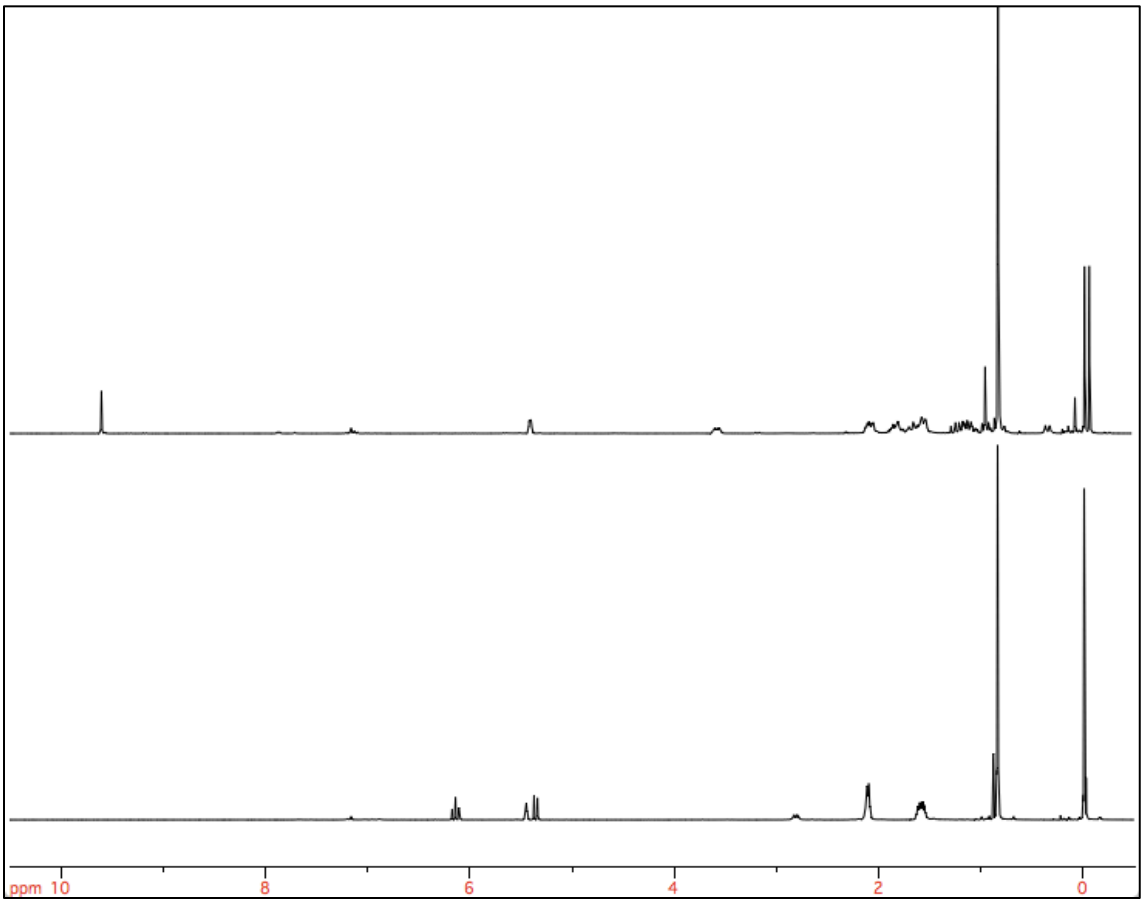


Figure 5.1 ^{1}H NMR Spectra (C_6D_6, 300 MHz, 298 K) for the Crude Hydroamination Reaction Product Between 1-Ethynylcyclohex-1-ene and *N*-*Tert*-Butyldimethylsilylamine (top) and for the Crude Reaction depicted in Scheme 5.7 (bottom)

5.2 Summary

This thesis has demonstrated that titanium complex **1** is a useful catalyst towards the synthesis of nitrogen-containing small molecules and heterocycles, including primary and secondary amines, and pyridines.

An atom economical and catalytic route for the synthesis of aryl- and alkyl-substituted secondary amines was disclosed in Chapter 2. Using the titanium complex **1**, the hydroamination of terminal alkynes with a range of amines resulted in the selective formation of the anti-

Markovnikov hydroamination product. The crude enamine/imine mixtures were effectively hydrogenated using palladium on carbon (Pd/C) and H_2 to afford the corresponding secondary amine in excellent yields. Simple work-up procedures allowed for the isolation of pure compounds while avoiding purification *via* column chromatography. Further work into the hydroamination of internal alkynes for the synthesis of asymmetric α-substituted amines is required.

In Chapter 3, an anti-Markovnikov selective hydroamination of alkynes with *N*-silylamines to afford *N*-silylenamines was reported. The reaction was also catalyzed by complex **1** and was compatible with a variety of terminal and internal alkynes. Stoichiometric mechanistic studies and computational calculations were also performed. This method easily afforded interesting *N*-silylenamine synthons in good to excellent yields and the easily removable silyl protecting group enabled the catalytic synthesis of primary amines after reduction using Pd/C and H_2. The applicability of the *N*-silylenamine synthon still requires further exploration.

Finally, a modular and selective synthesis of mono-, di-, tri-, tetra- and penta-substituted pyridines is reported in Chapter 4. Addition of α,β-unsaturated carbonyls to the crude mixtures of hydroamination reactions followed by oxidation affords 47 examples of pyridines in yields of up to 96%. This disclosed synthetic route allows for the synthesis of diverse pyridines containing different substitution patterns in three sequential reactions, which can be carried out using a one-pot protocol. Expansion of the substrate scope and improvement of the yield for the penta-substituted pyridines would be a great contribution to the field as very limited methodologies are available for the synthesis of such motifs.

5.3 Concluding Remarks

In conclusion, the findings of this thesis allows for the synthesis of nitrogen-containing compounds using an easily synthesized titanium-catalyst **1**. The natural abundance of titanium in addition to the ability of using catalytic loadings of 1 mol% are important features towards the development of more sustainable methodologies. Furthermore, the straightforward synthesis of *N*-silylenamines broadens the potential applicability to the synthesis of other *N*-heterocycles.

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Appendices

Appendix A

This appendix is for the supporting information pertaining the research conducted in Chapter 2.

A.1 General Considerations

All air and moisture sensitive reactions were performed using a MBraun LABmaster glovebox filled with a N_2 atmosphere. All pieces of glassware were dried for at least 4 hours in a 160 °C oven before being transferred into the glovebox. All stirring was done with appropriately sized Teflon coated magnetic stir bars dried for at least 4 hours in a 160 °C oven. Benzene and hexanes were passed over activated alumina columns into Teflon sealed Straus flasks and stored therein until use. d_6-Benzene was dried over sodium metal, distilled, degassed, and stored in Teflon sealed Schlenk flasks prior to use. Hydrogenations were performed using a Fischer-Porter tube. Experiments conducted on NMR tube scale were performed in J-Young NMR tubes (8" x 5 mm) sealed with screw-type Teflon caps. Thin layer chromatography (TLC) was set-up on EMD Silica gel 60 F254 plates. Visualization was achieved under a 254 nm UV light source and/or by staining with potassium permanganate or ninhydrin solutions. Flash chromatography was set-up using SiliaFlash F60 silica gel (230-400 mesh) (Silicycle) and glass columns, with ACS grade solvents (Sigma-Aldrich).

A.2 Materials

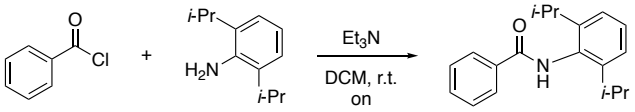
$Ti(NMe_2)_4$ (Sigma-Aldrich) and 10 wt% Pd/C (Sigma-Aldrich) were used as received. All amines and alkynes were purchased from commercial sources, dried over CaH_2 and distilled prior to use. Hydrogen gas (PP 4.5) was purchased from Praxair and used without further purification.

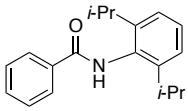
A.3 Instrumentation

NMR spectra were recorded as dilute solutions in deuterated chloroform or benzene on a Bruker Avance 300, 400 or 600 MHz spectrometer at ambient temperature. ^{1}H chemical shift data are given in units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm and δ (C_6D_6) = 7.16 ppm, while ^{13}C chemical shift data are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.16 ppm and δ (C_6D_6) = 128.06 ppm. High-resolution mass spectra were measured by the mass spectrometry and microanalysis service at the Department of Chemistry, University of British Columbia. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC spectrometer using electrospray ionization source. Fragment signals are given in mass per charge number (*m/z*).

A.4 Synthesis and Compound Characterization

N-(2,6-diisopropylphenyl)benzamide

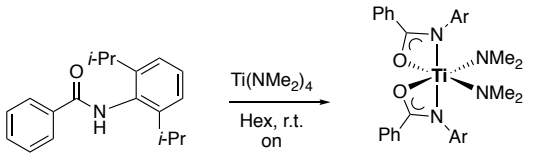




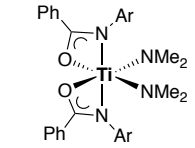
The amide was synthesized following a procedure adapted from literature.[381] Benzoyl chloride (5.10 mL, 44 mmol, 1.1 equiv.) was added to a solution of 2,6-diisopropylaniline (7.54 mL, 40 mmol, 1 equiv.) and triethylamine (7.21 mL, 52 mmol, 1.3 equiv.) in dichloromethane (267 mL, 0.15M). The reaction solution was stirred at room temperature overnight. Upon completion, the reaction mixture was washed with 1M HCl (x3), 1M NaOH (x3) and brine (x1). The organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to afford a pale pink solid. Subsequent re-crystallizations afforded the title compound as white needles in 89% yield. The analytical data was consistent with literature.[382] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.95-7.92 (m, 2H), 7.61-7.56 (m, 1H), 7.52 (m,

2H), 7.34 (m, 1H), 7.30 (s, 1H), 7.23 (m, 2H), 3.15 (7, *J* = 6.9 Hz, 2H), 1.23 (d, *J* = 6.9 Hz, 12H). **^{13}C NMR** (100 MHz; $CDCl_3$): δ 167.1, 146.5, 134.7, 131.8, 131.3, 128.9, 128.6, 127.3, 123.7, 29.0, 23.8.

Bis(*N*-2,6-diisoprpylphenylbenzamidate)bis(dimethylamido)titanium (IV)



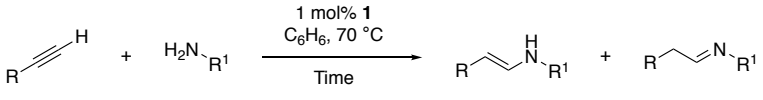
Ar = 2,6-diisopropylphenyl
Titanium Complex 1



Ar = 2,6-diisopropylphenyl
Titanium Complex 1

The titanium complex was synthesized following a procedure adapted from literature.[25] Inside an inert atmosphere box, tetrakis(dimethylamido)titanium (IV) (0.6728 g, 3 mmol, 1 equiv.) was added to a solution of *N*-(2,6-diisopropylphenyl)benzamide (1.6871 g, 6 mmol, 2 equiv.) in hexanes. The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction solution was concentrated under reduced pressure to afford the title compound as a red powder in quantitative yield. The crude compound was subsequently used without further purification. ^{1}H NMR (400 MHz; C_6H_6): δ 7.75-7.73 (m, 4H), 7.20 (s, 6H), 6.95-6.86 (m, 6H), 3.71-3.61 (m, 4H), 3.33 (s, 12H), 1.35 (d, *J* = 6.8 Hz, 12H), 0.98 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (100 MHz; C_6D_6): δ 177.2, 142.7, 142.5, 133.1, 131.5, 130.3, 128.0, 126.0, 124.1, 47.8, 28.2, 24.7, 24.4.

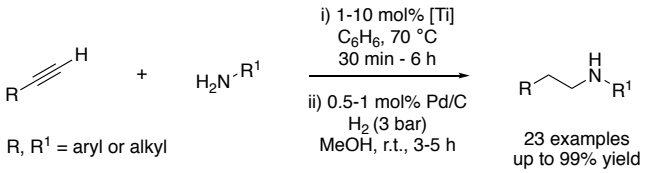
General Procedure for the Time Optimization of the Hydroamination Reaction



Inside an inert atmosphere box, benzene (0.3 mL) was added to the titanium complex (0.01 mmol, 1 mol% Ti) in a 5-dram vial. The solution was then transferred to a J-Young tube. The amine (1 mmol, 1 equiv.) and alkyne (1 mmol, 1 equiv.) were pre-weighed to separate 5-dram

vials and transferred to the J-Young tube. The remaining benzene (0.7 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction tube. The J-Young tube was sealed, taken out of the inert atmosphere box and a time zero ^{1}H NMR spectrum was obtained. The reaction solution was heated at 70 °C and after every hour of heating, a ^{1}H NMR spectrum was obtained until full consumption of starting materials was observed. For reactions that required more than 1 hour of heating, a second reaction was set-up, in which no hourly stoppages occurred. Other than the time zero ^{1}H NMR spectrum, only the ^{1}H NMR spectrum at the expected completion time was obtained.

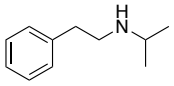
General Procedure for the Sequential Hydroamination/Hydrogenation Synthesis of Secondary Amines



Inside an inert atmosphere box, benzene (3 mL) was added to the titanium complex (0.05 mmol, 1 mol% Ti) in a 5-dram vial. The solution was then transferred to a scintillation vial. The amine (5 mmol, 1 equiv.) and alkyne (5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the reaction vessel. The remaining benzene (2 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction vessel. The mixture was sealed, taken out of the inert atmosphere box and stirred at 70 °C for 0.5 to 6 hours, depending on the substrate. Half an hour prior to the completion of the hydroamination step, an oven dried Fischer-Porter tube was cooled under N_2. Under a N_2 flow, palladium on carbon (0.25 mmol, 0.5 mol% Pd or 0.5 mmol, 1 mol% Pd) and methanol (2 mL) were added to the vessel, which was then pressurized and vented with H_2 five times. After allowing the hydroamination reaction mixture to cool down, the solution was added to the Fischer-Porter tube using a 5 mL syringe.

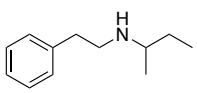
An additional 3 mL of methanol was used to rinse the vial containing the first step, and this liquid was also added to the Fischer-Porter tube. The tube was then sealed and pressurized to 3 bar. The reaction was allowed to proceed at room temperature for 3 to 5 hours depending on the substrate. The crude compound was concentrated under reduced pressure and filtered through a short plug of Celite using hexanes. The filtrate was concentrated under reduced pressure, affording a mixture of ligand and product. The mixture was chilled in the fridge for at least 30 minutes. Cold hexanes were added to the concentrated oil and the suspension formed was filtered using filter paper and a funnel. Unless otherwise stated, concentration of filtrate under reduced pressure afforded the desired secondary amine in high purity.

***N*-phenethylpropan-2-amine (2.1a)**



According to the general procedure, propan-2-amine (0.2956 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 30 minutes. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a pale yellow oil in 91% yield. The analytical data was consistent with literature.[383] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.30-7.28 (m, 2H), 7.23-7.19 (m, 3H), 2.91-2.87 (m, 2H), 2.82 (m, 3H), 1.06 (d, J = 6.3 Hz, 6H).^{13}C NMR (101 MHz; $CDCl_3$): δ 140.3, 128.8, 128.6, 126.3, 49.0, 48.7, 36.7, 23.0.

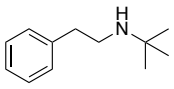
***N*-phenethylbutan-2-amine (2.1b)**



According to the general procedure, butan-2-amine (0.3657 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 30 minutes. Upon

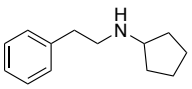
completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a yellow oil in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 2H), 7.23-7.19 (m, 3H), 2.95-2.78 (m, 4H), 2.60-2.52 (m, 1H), 1.51-1.43 (m, 1H), 1.33-1.28 (m, 1H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 128.8, 128.6, 126.2, 54.6, 48.8, 36.8, 29.7, 20.0, 10.4. HRMS (ESI+) m/z calc'd for $C_{12}H_{20}N$ [M+H$^+$]: 178.1596; found: 178.1597.

2-methyl-*N*-phenethylpropan-2-amine (2.1c)



According to the general procedure, 2-methyl-propan-2-amine (0.3657 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a yellow oil in 98% yield. The analytical data was consistent with literature.[58] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.32-7.27 (m, 2H), 7.23-7.19 (m, 3H), 2.86-2.82 (m, 2H), 2.80-2.76 (m, 2H), 1.08 (s, 9H).^{13}C NMR (101 MHz; $CDCl_3$): δ 140.4, 128.8, 128.5, 126.2, 50.4, 44.3, 37.4, 29.1.

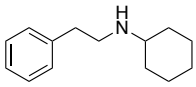
***N*-phenethylcyclopentanamine (2.1d)**



According to the general procedure, cyclopentanamine (0.4258 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the

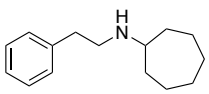
title compound as a pale yellow oil in 98%. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31-7.28 (m, 2H), 7.22-7.19 (m, 3H), 3.12-3.06 (m, 1H), 2.90-2.80 (m, 4H), 1.88-1.81 (m, 2H), 1.70-1.63 (m, 2H), 1.56-1.49 (m, 2H), 1.36-1.27 (m, 2H). ^{13}C NMR (101 MHz; $CDCl_3$) δ 140.3, 128.8, 128.6, 126.2, 59.9, 50.1, 36.7, 33.3, 24.2. HRMS (ESI+) m/z calc'd for $C_{13}H_{20}N$ [$M+H^+$}: 190.1596; found: 190.1591.

***N*-phenethylcyclohexanamine (2.1e)**



According to the general procedure, cyclohexanamine (0.4959 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 2 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a pale yellow oil in 95% yield. The analytical data was consistent with literature.[58] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 2.92-2.88 (m, 2H), 2.81-2.78 (m, 2H), 2.43 (m, 1H), 1.89-1.83 (m, 2H), 1.74-1.68 (m, 2H), 1.63-1.57 (m, 1H), 1.29-1.20 (m, 2H), 1.18-1.12 (m, 1H), 1.10-1.00 (m, 2H).^{13}C NMR (101 MHz; $CDCl_3$) δ 140.4, 128.8, 128.6, 126.2, 56.9, 48.4, 36.8, 33.7, 26.3, 25.2.

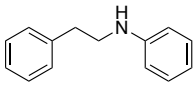
***N*-phenethylcycloheptamine (2.1f)**



According to the general procedure, cycloheptanamine (0.5660 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 2 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a pale yellow oil in 96% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31-7.27 (m,

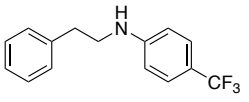
2H), 7.22-7.18 (m, 3H), 2.90-2.86 (m, 2H), 2.83-2.79 (m, 2H), 2.67-2.62 (m, 1H), 1.85-1.79 (m, 2H), 1.67-1.60 (m, 2H), 1.56-1.47 (m, 4H), 1.44-1.36 (m, 4H).[13]C NMR (101 MHz; $CDCl_3$) δ 140.4, 128.8, 128.6, 126.2, 59.2, 49.0, 36.7, 35.0, 28.4, 24.6. HRMS (ESI+) m/z calc'd for $C_{15}H_{24}N$ [$M+H^+$}: 218.1909; found: 218.1911.

***N*-phenethylaniline (2.1g)**



According to the general procedure, aniline (0.0.4656 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 30 min. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Purification by column chromatography (95:5 Hex/Et_2O + 0.1% Et_3N) afforded the title compound as a yellow oil in 89% yield.[384] The analytical data was consistent with literature.[x] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.26-7.22 (m, 3H), 7.21-7.17 (m, 2H), 6.74-6.69 (m, 1H), 6.64-6.61 (m, 2H), 3.67 (s, 1H), 3.41 (t, *J* = 7.0 Hz, 2H), 2.93 (t, *J* = 7.0 Hz, 2H).[13]C NMR (101 MHz; $CDCl_3$): δ 148.1, 139.4, 129.4, 128.9, 128.7, 126.6, 117.6, 113.1, 45.2, 35.7.

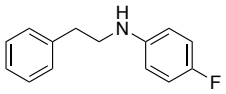
***N*-phenethyl-4-(trifluoromethyl)aniline (2.1h)**



According to the general procedure, 4-(trifluoromethyl)aniline (0.8056 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Purification by column chromatography (95:5 Hex/Et_2O + 0.1% Et_3N) afforded the title compound as a yellow oil in 85% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.35-7.31 (m, 2H), 7.28-7.21

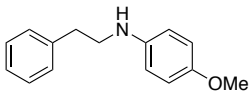
(m, 3H), 6.65 (d, *J* = 8.5 Hz, 2H), 3.44 (t, *J* = 7.0 Hz, 2H), 2.94 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (151 MHz; $CDCl_3$): δ 150.4, 138.9, 128.9, 128.8, 126.8 (q, $^3J(C,F)$ = 3.6Hz),125.1 (q, $^1J(C,F)$ = 270.2Hz), 119.1 (q, $^2J(C,F)$ = 32.7Hz), 112.2, 44.8, 35.3. HRMS (ESI+) m/z calc'd for $C_{15}H_{15}NF_3$ [M+H$^+$}: 266.1157; found: 266.1150.

_N_-phenethyl-4-fluoroaniline (2.1i)



According to the general procedure, 4-fluoroaniline (0.5556 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Purification by column chromatography (95:5 Hex/Et_2O + 0.1% Et_3N) afforded the title compound as a pale yellow oil in 81% yield.[384] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H), 6.93-6.88 (m, 2H), 6.63-6.59 (m, 2H), 3.37 (t, *J* = 7.1 Hz, 2H), 2.93 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 156.0 (d, $^1J(C,F)$ = 235.9Hz), 139.3, 128.9, 128.8, 126.6, 115.8 (d, $^2J(C,F)$ = 22.4Hz), 114.1 (d, $^3J(C,F)$ = 6.5Hz), 45.9, 35.5.

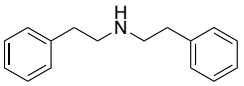
4-methoxy-_N_-phenethylaniline (2.1j)



According to the general procedure, 4-metoxyaniline (0.6158 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Purification by column chromatography (9:1 Hex/EtOAc + 0.1% Et_3N) afforded the title compound as a yellow oil in 77% yield.[384] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.31 (m, 2H), 7.25-7.21 (m, 3H), 6.81-6.79 (m,

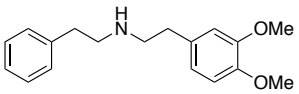
2H), 6.67 (m, 2H), 3.75 (s, 3H), 3.37 (t, J = 7.1 Hz, 2H), 2.93 (t, J = 7.1 Hz, 2H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 152.5, 142.1, 139.5, 128.9, 128.7, 126.5, 115.1, 114.7, 55.9, 46.3, 35.7.

Diphenethylamine (2.1k)



According to the general procedure, 2-phenylethan-1-amine (0.6059 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex in benzene. The reaction mixture was stirred at 70 °C for 5 hours. Upon completion the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Purification by formation and isolation of HCl salt and re-basification to the free amine afforded the title compound as a pale orange solid in 58% yield.[385] ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.30-7.26 (m, 4H), 7.22-7.16 (m, 6H), 2.96-2.92 (m, 4H), 2.86-2.83 (m, 4H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 139.9, 128.8, 128.6, 126.3, 51.1, 36.3.

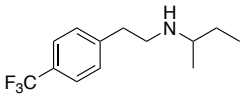
***N*-(3,4-dimethoxyphenethyl)-2-phenylethan-1-amine (2.1l)**



According to the general procedure, 2-(3,4-dimethoxyphenyl)ethan-1-amine (0.9062 g) and ethynylbenzene (0.5107 g) were added to a solution of the titanium complex in benzene. The reaction mixture was stirred at 70 °C for 6 hours. Upon completion the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Purification by formation and isolation of HCl salt and re-basification to the free amine afforded the title compound as a pale yellow solid in 33% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.29-7.25 (m, 1H), 7.22-7.15 (m, 3H), 6.78-6.76 (m, 1H), 6.70 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 2.97-2.79 (m, 8H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 149.1, 147.7, 139.1, 131.7, 128.7, 128.6, 126.5,

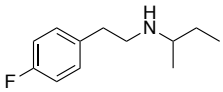
120.6, 112.0, 111.4, 56.0, 55.9, 50.5, 50.4, 35.3, 34.9. HRMS (ESI+) m/z calc'd for $C_{18}H_{23}NO_2$ [M+H$^+$]: 286.1807; found: 286.1805.

***N*-(4-(trifluoromethyl)phenethyl)butan-2-amine (2.2a)**



According to the general procedure, butan-2-amine (0.3657 g) and 1-ethynyl-4-(trifluoromethyl)benzene (0.8506 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 30 minutes. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a yellow oil in 99% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.95-2.84 (m, 4H), 2.58 (m, 1H), 1.52-1.45 (m, 1H), 1.35-1.28 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz; $CDCl_3$): δ 144.3, 129.0, 128.6 (q, ^{2}J(C,F) = 32.4Hz) 125.4 (q, ^{3}J(C,F) = 3.7Hz), 124.3 (q, ^{1}J(C,F) = 271.8Hz), 54.5, 48.2, 36.4, 29.4, 19.7, 10.2. HRMS (ESI+) m/z calc'd for $C_{13}H_{19}NF_3$ [M+H$^+$]: 246.1470; found: 246.1465.

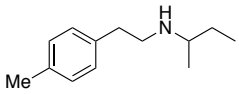
***N*-(4-fluorophenethyl)butan-2-amine (2.2b)**



According to the general procedure, butan-2-amine (0.3657 g) and 1-ethynyl-4-fluorobenzene (0.6006 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a yellow oil in 99% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.34-7.30 (m, 2H), 7.24-7.20 (m, 3H), 6.93-6.88 (m, 2H), 6.63-6.59 (m, 2H), 3.37 (t, *J* = 7.1 Hz, 2H), 2.93 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 161.5 (d, ^{1}J(C,F) = 244.0Hz), 135.9, 130.2(d, ^{3}J(C,F) =

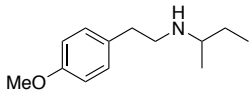
7.6Hz), 115.3 (d, $^{2}J(C,F)$ = 20.1Hz), 54.6, 48.8, 35.9, 29.6, 19.9, 10.4. HRMS (ESI+) m/z calc'd for $C_{12}H_{19}NF$ [$M+H^{+}$]: 196.1502; found: 196.1503.

***N*-(4-methylphenethyl)butan-2-amine (2.2c)**



According to the general procedure, butan-2-amine (0.3657 g) and 1-ethynyl-4-methylbenzene (0.5808 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a pale yellow oil in 99% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.10 (s, 4H), 2.93-2.75 (m, 4H), 2.57 (m, 1H), 2.32 (s, 3H), 1.53-1.43 (m, 1H), 1.36-1.26 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 137.2, 135.7, 129.2, 128.7, 54.6, 48.9, 36.3, 29.7, 21.1, 19.9, 10.4. HRMS (ESI+) m/z calc'd for $C_{13}H_{22}N$ [$M+H^{+}$}: 192.1752; found: 192.1747.

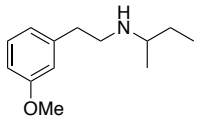
***N*-(4-methoxyphenethyl)butan-2-amine (2.2d)**



According to the general procedure, butan-2-amine (0.3657 g) and 1-ethynyl-4-methoxybenzene (0.6608 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a yellow oil in 99% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.15-7.11 (m, 2H), 6.86-6.82 (m, 2H), 3.79 (s, 3H), 2.91-2.72 (m, 4H), 2.59-2.51 (m, 1H), 1.50-1.43 (m, 1H), 1.33-1.26 (m, 1H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 158.1, 132.3, 129.7, 114.0, 77.5, 77.2, 76.8, 55.4, 54.6,

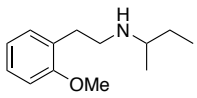
48.9, 35.7, 29.6, 19.9, 10.4. HRMS (ESI+) m/z calc'd for $C_{13}H_{22}NO$ [M+H$^+$]: 208.1701; found: 208.1703.

***N*-(3-methoxyphenethyl)butan-2-amine (2.2e)**



According to the general procedure, butan-2-amine (0.3657 g) and 1-ethynyl-3-methoxybenzene (0.6608 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% of palladium (0.0266 g) in 3 hours. Subsequent filtrations afforded the title compound as a pale yellow oil in 98% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.21 (td, *J* = 7.7, 0.7 Hz, 1H), 6.81 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.78-6.74 (m, 2H), 3.80 (s, 3H), 2.94-2.76 (m, 4H), 2.60-2.52 (m, 1H), 1.51-1.44 (m, 1H), 1.35-1.26 (m, 1H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 159.8, 142.0, 129.5, 121.2, 114.5, 111.6, 55.3, 54.6, 48.6, 36.8, 29.7, 19.9, 10.4. HRMS (ESI+) m/z calc'd for $C_{13}H_{22}NO$ [M+H$^+$}: 208.1701; found: 208.1704.

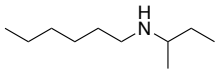
***N*-(2-methoxyphenethyl)butan-2-amine (2.2f)**



According to the general procedure, butan-2-amine (0.3657 g) and 1-ethynyl-2-methoxybenzene (0.6608 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 3 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 0.5 mol% in 3 hours. Subsequent filtrations afforded the title compound as an orange oil in 51% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.21-7.15 (m, 2H), 6.91-6.84 (m, 2H), 3.82 (s, 3H), 2.88-2.81 (m, 4H), 2.63-2.55 (m, 1H), 1.51-1.44 (m, 1H), 1.34-1.27 (m, 1H), 1.03 (d, *J* = 6.3 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H).^{13}C NMR (101 MHz; $CDCl_3$): δ 157.7, 130.4, 128.8,

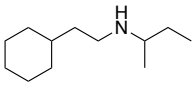
127.5, 120.5, 110.5, 55.4, 54.5, 47.3, 31.2, 29.7, 19.9, 10.4. HRMS (ESI+) m/z calc'd for $C_{13}H_{22}NO$ [M+H$^+$}: 208.1701; found: 208.1700.

_N_-(_sec_-butyl)hexan-1-amine (2.2g)



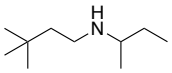
According to the general procedure, butan-2-amine (0.3657 g) and hex-1-yne (0.4108 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 2 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 1 mol% of palladium (0.0532 g) in 5 hours. Subsequent filtrations afforded the title compound as a clear oil in 92% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.66-2.49 (m, 3H), 1.52-1.42 (m, 3H), 1.30-1.26 (m, 7H), 1.03 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 77.5, 77.2, 76.8, 54.8, 47.6, 32.0, 30.6, 29.8, 27.3, 22.8, 20.0, 14.2, 10.4. HRMS (ESI+) m/z calc'd for $C_{10}H_{24}N$ [M+H$^+$]: 158.1909; found: 158.1904.

_N_-(2-cyclohexylethyl)butan-2-amine (2.2h)



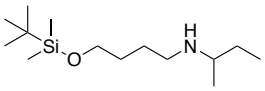
According to the general procedure, butan-2-amine (0.3657 g) and ethynylcyclohexane (0.5409 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction mixture was stirred at 70 °C for 3 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 1 mol% of palladium (0.0532 g) in 5 hours. Subsequent filtrations afforded the title compound as a clear oil in 96% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.68-2.53 (m, 3H), 1.73-1.60 (m, 5H), 1.56-1.45 (m, 1H), 1.41-1.15 (m, 8H), 1.03 (d, J = 6.3 Hz, 3H), 0.96-0.87 (m, 5H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 77.5, 77.2, 76.8, 54.9, 45.2, 38.3, 36.0, 33.6, 33.6, 29.7, 26.8, 26.5, 20.0, 10.5. HRMS (ESI+) m/z calc'd for $C_{12}H_{26}N$ [M+H$^+$]: 184.2065; found: 184.2062.

***N*-(*sec*-butyl)-3,3-dimethylbutan-1-amine (2.2i)**



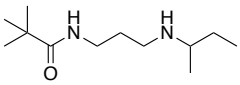
According to the general procedure, butan-2-amine (0.3657 g) and 3,3-dimethylbut-1-yne (0.4108 g) were added to a solution of the titanium complex (0.3484 g) in benzene. The reaction mixture was stirred at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 5 mol% of palladium (0.2660 g) in 4 hours. Subsequent filtrations afforded the title compound as a clear oil in 72% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.64-2.49 (m, 3H), 1.53-1.43 (m, 1H), 1.39-1.34 (m, 2H), 1.32-1.25 (m, 1H), 1.01 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.86 (d, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ 55.0, 44.6, 43.5, 30.0, 29.8, 20.0, 10.4. HRMS (ESI+) m/z calc'd for $C_{10}H_{24}N$ [M+H$^+$]: 158.1909; found: 158.1908.

***N*-(*sec*-butyl)-4-((*tert*-butyldimethylsilyl)oxy)butan-1-amine (2.2j)**



According to the general procedure, butan-2-amine (0.3657 g) and (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (0.9218 g) were added to a solution of the titanium complex (0.0871 g) in benzene. The reaction mixture was stirred at 70 °C for 30 minutes. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 1 mol% of palladium (0.0532 g) in 5 hours. Subsequent filtrations afforded the title compound as a clear oil in 99% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.62 (m, 2H), 2.67-2.50 (m, 3H), 1.57-1.45 (m, 5H), 1.30 (m, 1H), 1.02 (d, J = 6.3 Hz, 3H), 0.90-0.86 (m, 13H), 0.04 (s, 6H). ^{13}C NMR (101 MHz; CDCl3): δ 63.3, 54.7, 47.4, 30.9, 29.8, 27.0, 26.1, 20.0, 18.5, 10.4, -5.1. HRMS (ESI+) m/z calc'd for $C_{14}H_{33}NOSi$ [M+H$^+$]: 260.2410; found: 260.2418.

***N*-(3-(*sec*-butylamino)propyl)pivalamide (2.2k)**



According to the general procedure, butan-2-amine (0.3657 g) and *N*-(prop-

2-yn-1-yl)pivalamide (0.6960 g) were added to a solution of the titanium complex (0.0871 g) in benzene. The reaction mixture was stirred at 70 °C for 1 hour. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 1 mol% of palladium (0.0532 g) in 5 hours. Purification by formation of HCl salt and re-basification to the free amine afforded the title compound as a yellow oil in 92% yield. ^{1}H NMR (400 MHz; $CDCl_3$): δ 3.41-3.29 (m, 2H), 2.77-2.67 (m, 2H), 2.57-2.49 (m, 1H), 1.68-1.62 (m, 2H), 1.55-1.45 (m, 1H), 1.32 (m, 1H), 1.18 (s, 9H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz; CDCl3): δ 178.5, 55.0, 46.5, 39.9, 38.7, 29.6, 29.4, 27.8, 20.0, 10.3. HRMS (EI+) m/z calc'd for $C_{12}H_{26}N_2O$ [$M+H^+$]: 214.20451; found: 214.20430.

General Procedure for the One-Pot Hydroamination/Hydrogenation Synthesis of Secondary Amines

Inside an inert atmosphere box, benzene (3 mL) was added to the titanium complex (0.05 mmol, 1 mol% Ti) in a 5-dram vial. The solution was transferred to a scintillation vial containing pre-weighed palladium on carbon (0.25 mmol, 0.5 mol% or 0.5 mmol, 1 mol% Pd). The amine (5 mmol, 1 equiv.) and alkyne (5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the reaction vessel. The remaining benzene (2 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction vessel. The mixture was sealed, taken out of the inert atmosphere box and stirred at 70 °C for 0.5 to 3 hours, depending on the substrate. Upon completion of the hydroamination reaction, the mixture was allowed to cool down and a balloon filled with hydrogen gas was attached to the reaction vessel. The reaction was allowed to proceed at room temperature for 40 hours. The crude compound was concentrated under reduced pressure and filtered through a short plug of Celite using hexanes. The filtrate was concentrated under reduced pressure, affording a mixture of ligand and product.

The mixture was chilled in the fridge for at least 30 minutes. Cold hexanes were added to the concentrated oil and the suspension formed was filtered using filter paper and a funnel. Unless otherwise stated, concentration of filtrate under reduced pressure afforded the desired secondary amine in high purity.

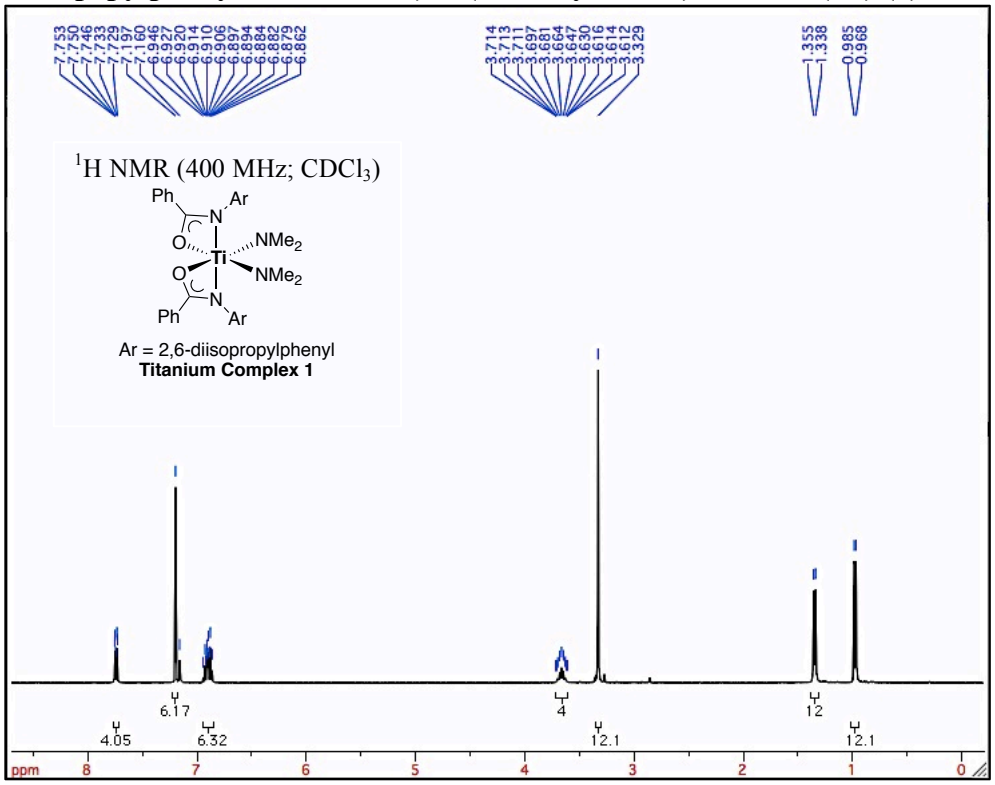
General Procedure for the Large Scale Sequential Hydroamination/Hydrogenation Synthesis of Secondary Amines

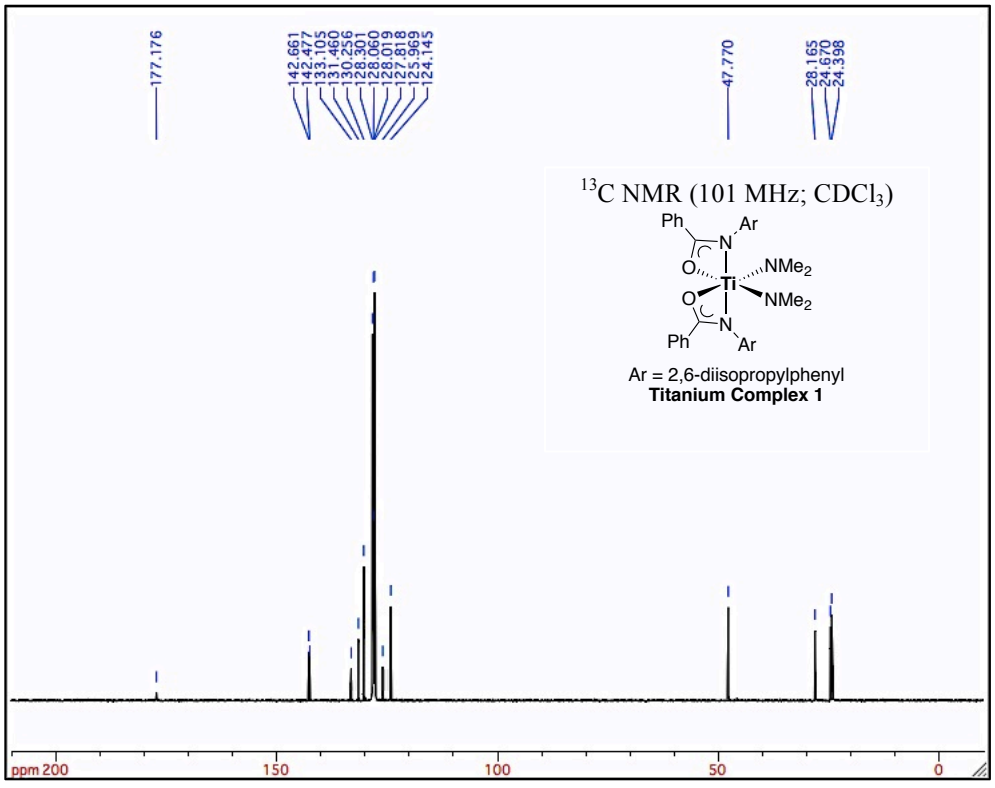
Inside an inert atmosphere box, benzene (20 mL) was added to the titanium complex (0.25 mmol, 1 mol% Ti) in a 5-dram vial. The solution was then transferred to a 100 mL round bottom flask. The amine (25 mmol, 1 equiv.) and alkyne (25 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the reaction vessel. The remaining benzene (5 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction vessel. The mixture was sealed, taken out of the inert atmosphere box and stirred at 70 °C for 1 to 2 hours, depending on the substrate. Half an hour prior to the completion of the hydroamination step, an oven dried Fischer-Porter tube was cooled under N_2. Under a N_2 flow, palladium on carbon (0.125 mmol, 0.5 mol% Pd or 0.25 mmol, 1 mol% Pd) and methanol (10 mL) were added to the vessel, which was then pressurized and vented with H_2 five times. After allowing the hydroamination reaction mixture to cool down, the solution was added to the Fischer-Porter tube using a 10 mL syringe. An additional 15 mL of methanol was used to rinse the vial containing the first step, and this liquid was also added to the Fischer-Porter tube. The tube was then sealed and pressurized to 3 bar. The reaction was allowed to proceed at room temperature for 3 to 5 hours depending on the substrate. The crude compound was concentrated under reduced pressure and filtered through a short plug of Celite using hexanes. The filtrate was concentrated under reduced pressure, affording a mixture of ligand and product. The mixture was

chilled in the fridge for a few hours. Cold hexanes were added to the concentrated oil and the suspension formed was filtered using filter paper and a funnel. Unless otherwise stated, concentration of filtrate under reduced pressure afforded the desired secondary amine in high purity.

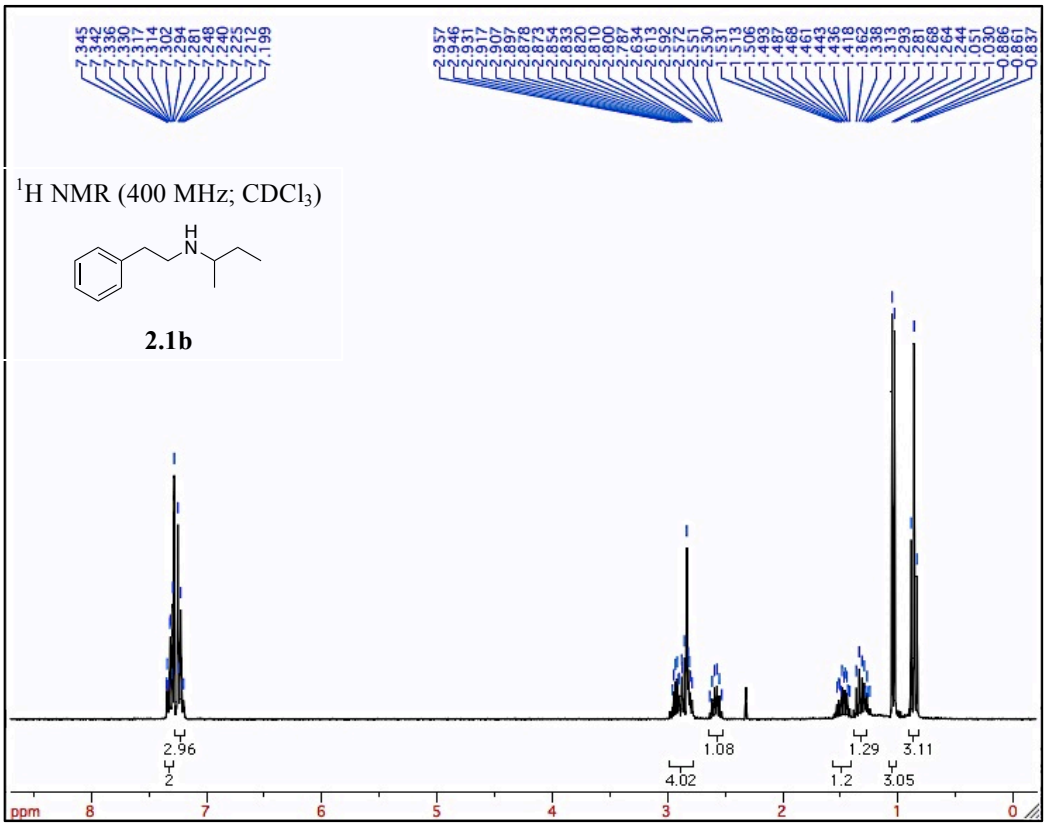
A.5 NMR Spectra

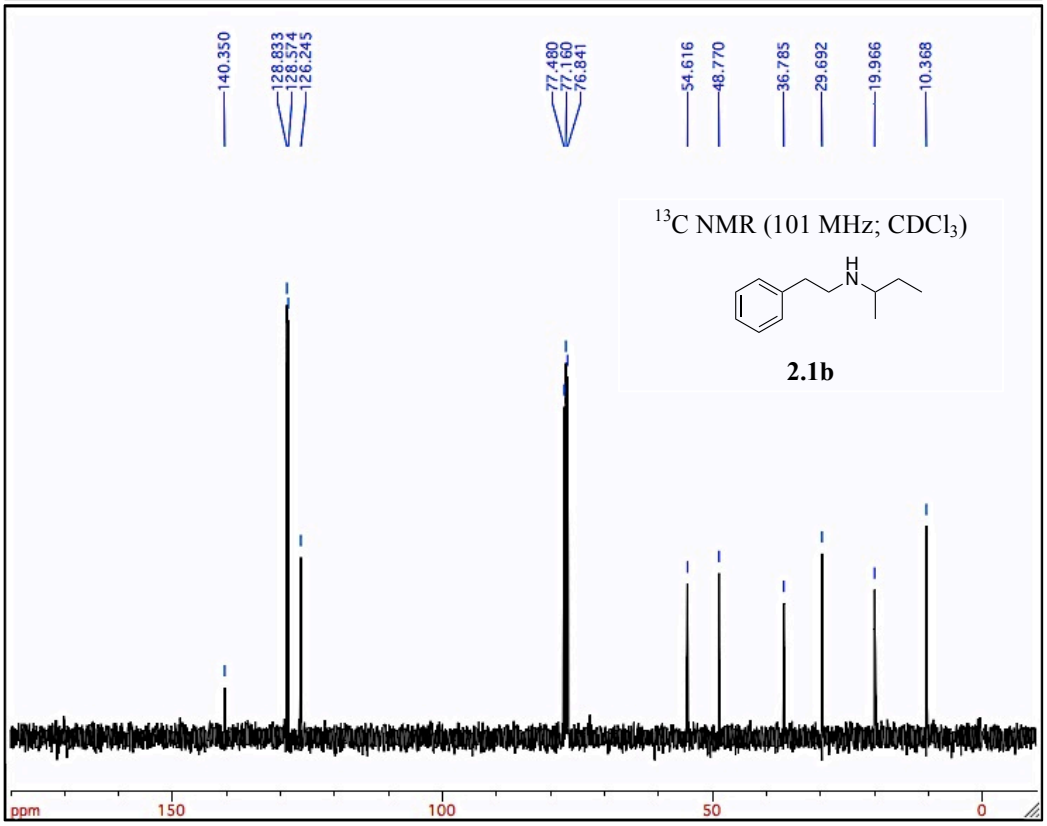
Bis(*N*-2,6-diisoprpylphenylbenzamidate)bis(dimethylamido)titanium (IV) (1)



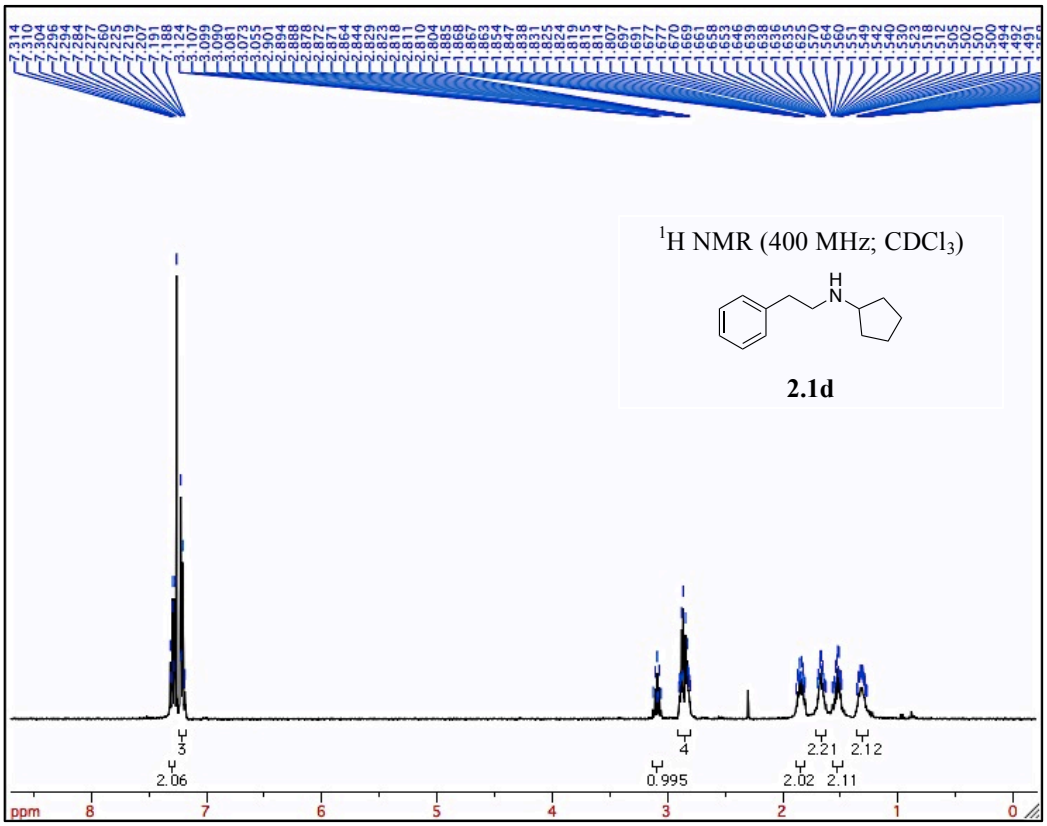


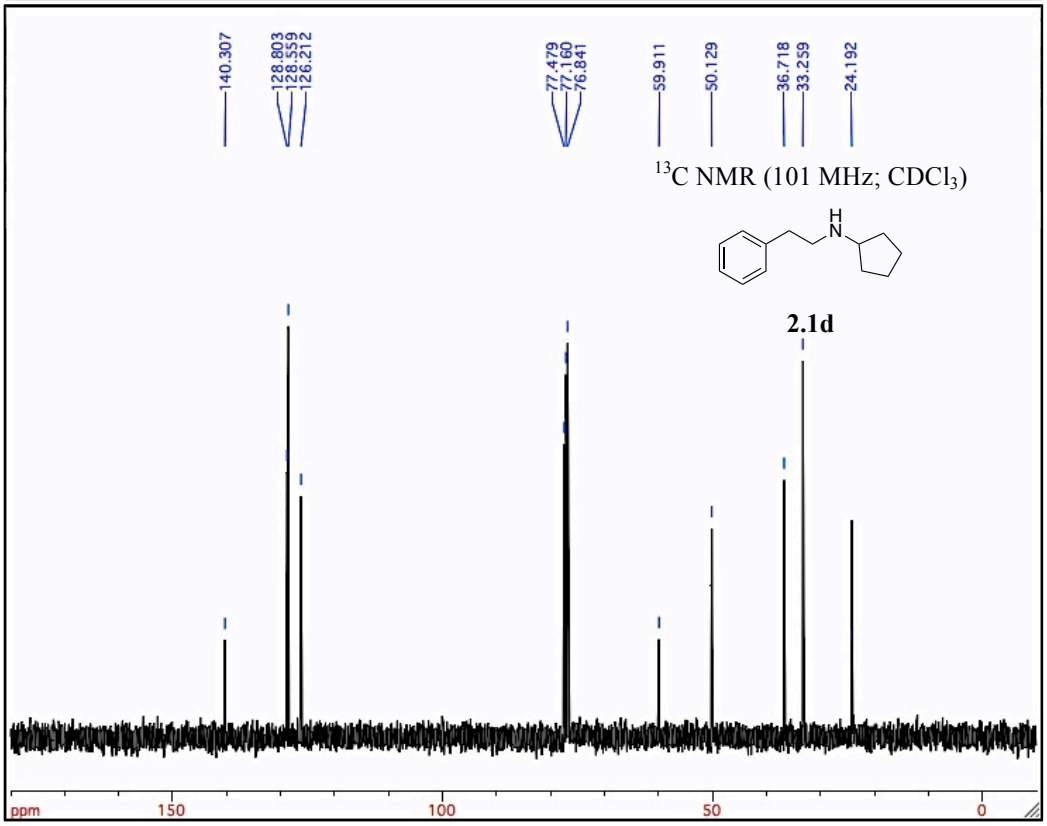
N-phenethylbutan-2-amine (2.1b)



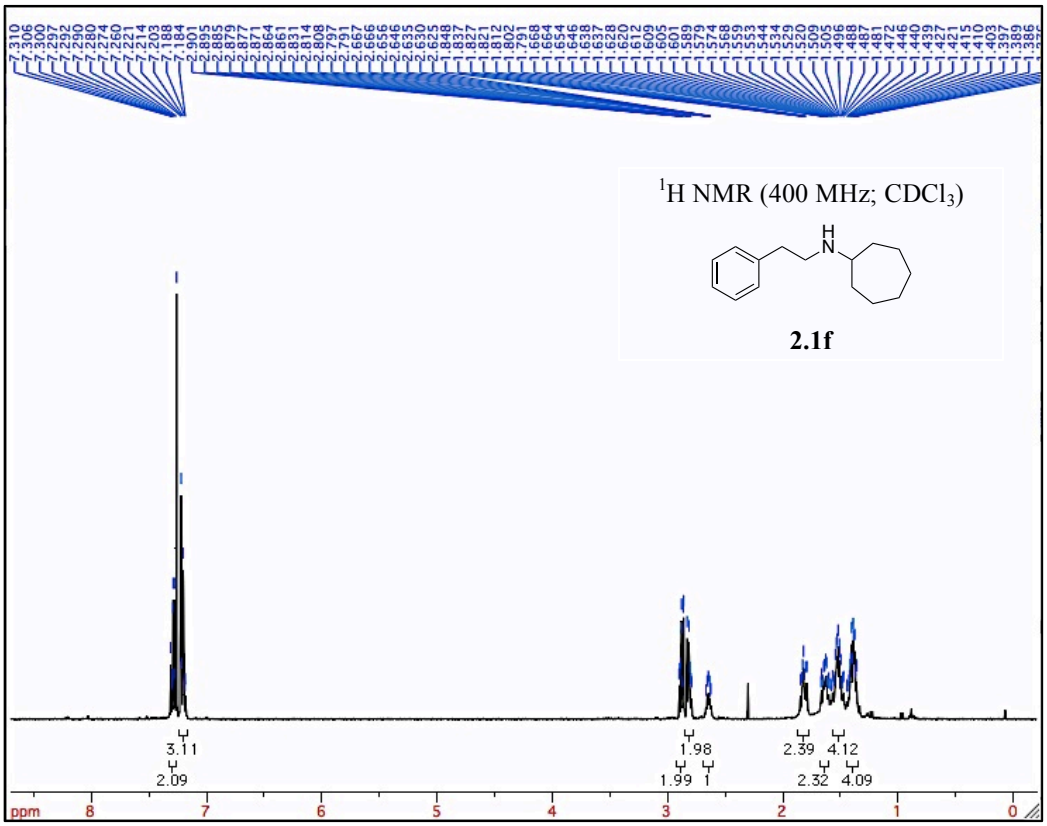


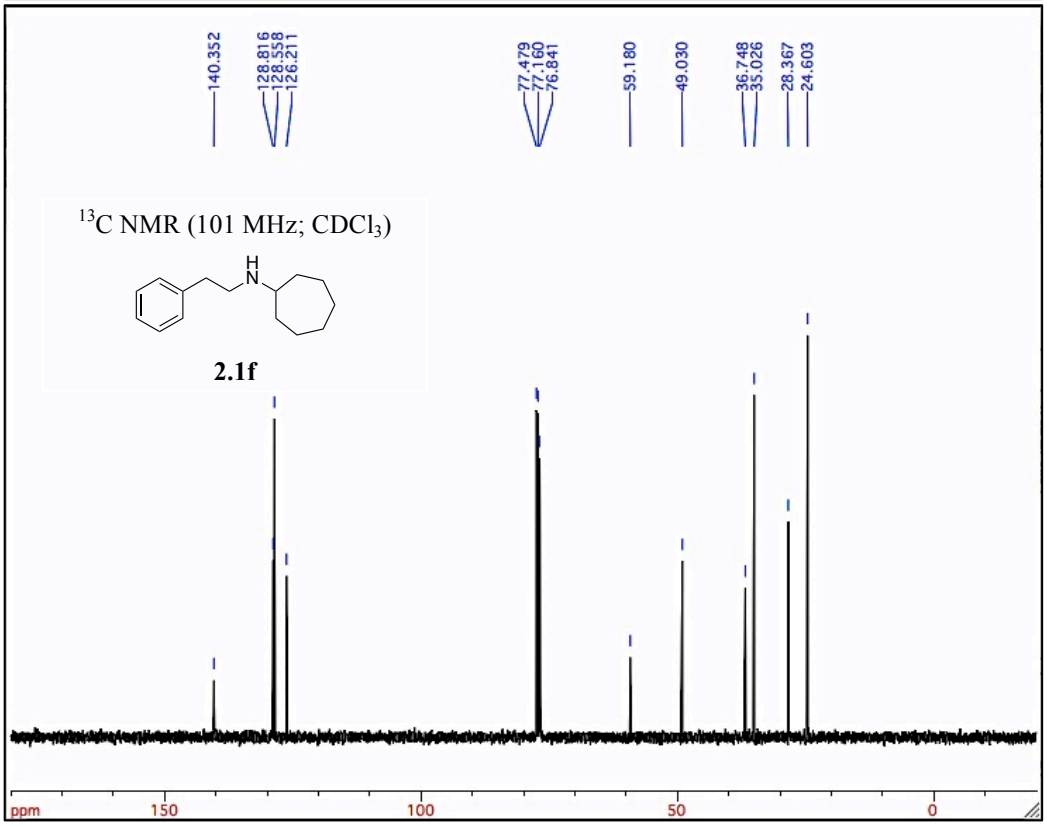
N-phenethylcyclopentanamine (2.1d)



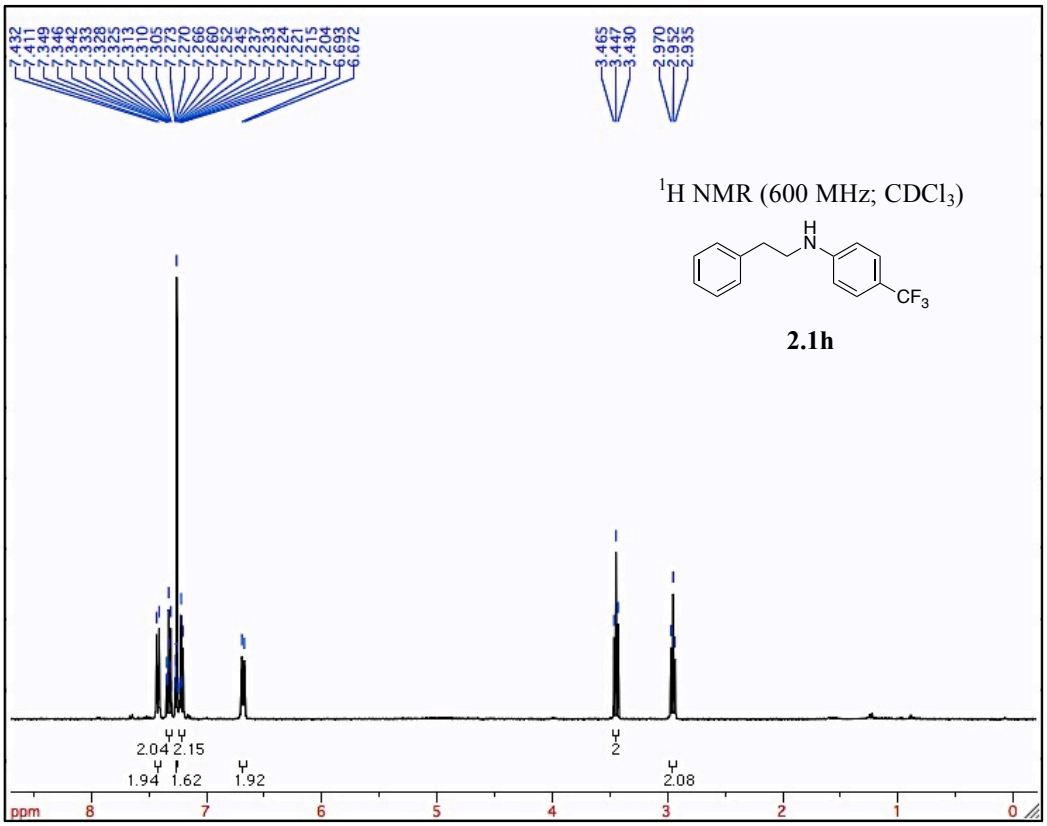


N-phenethylcycloheptamine (2.1f)



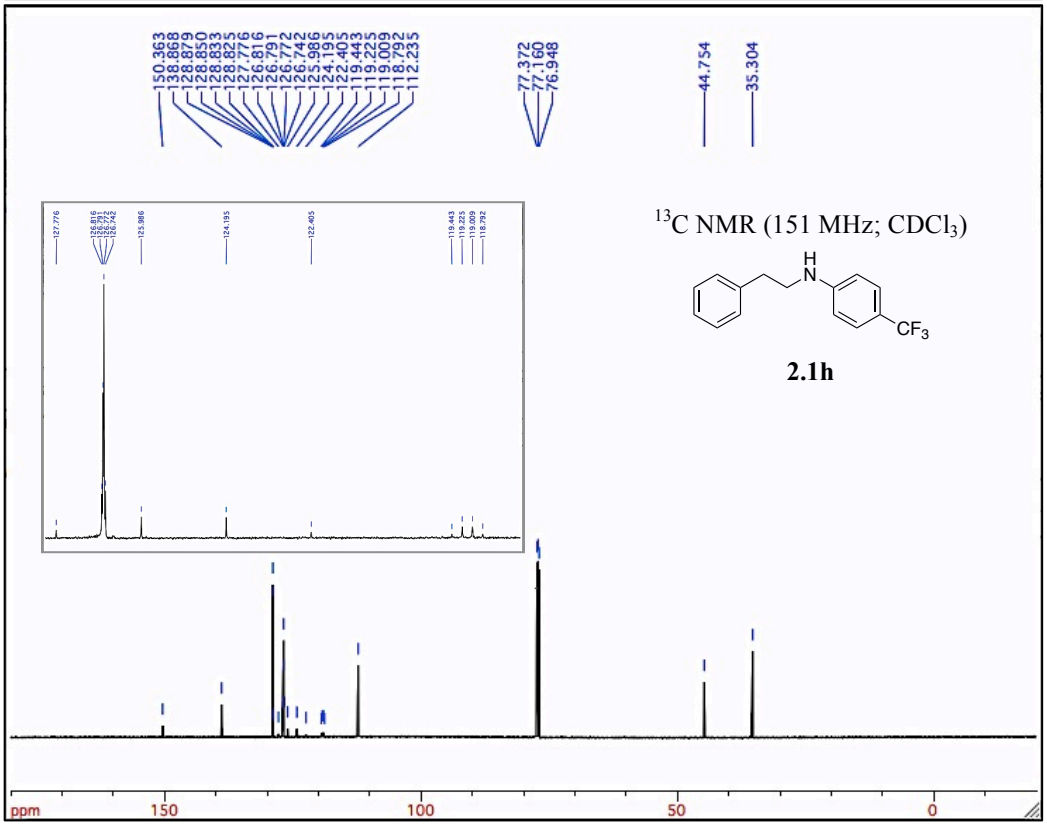


***N*-phenethyl-4-(trifluoromethyl)aniline (2.1h)**



^{1}H NMR (600 MHz; $CDCl_3$)

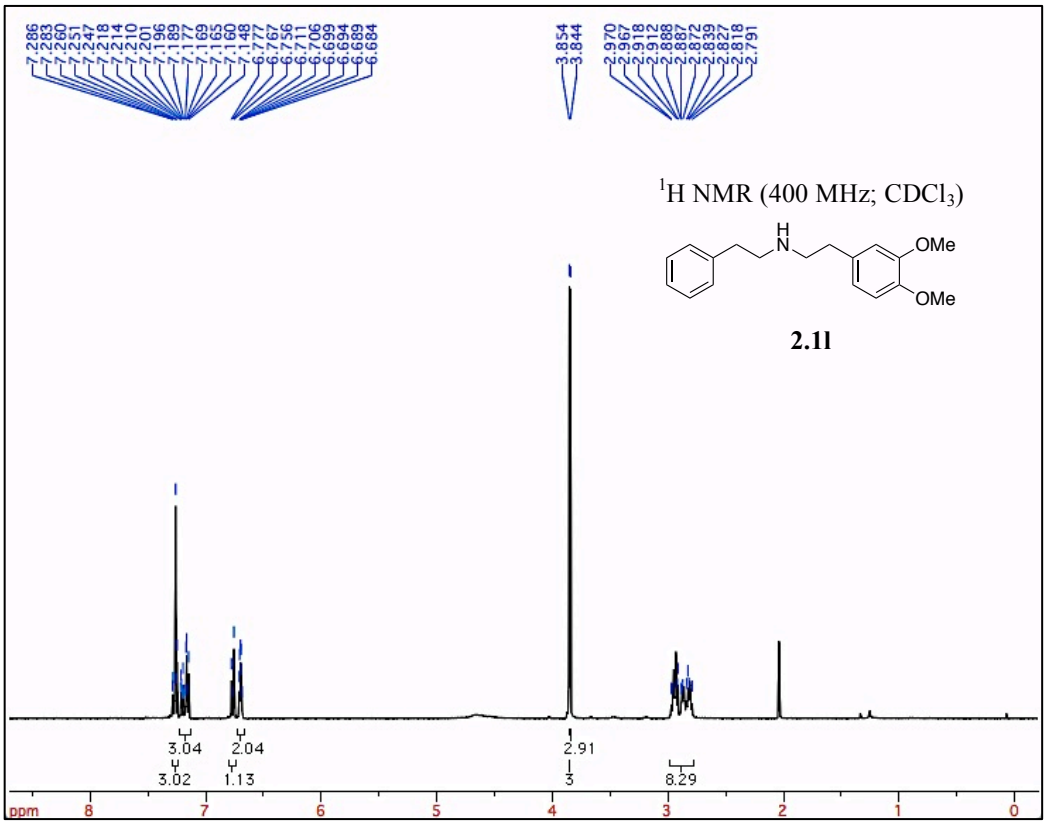
2.1h

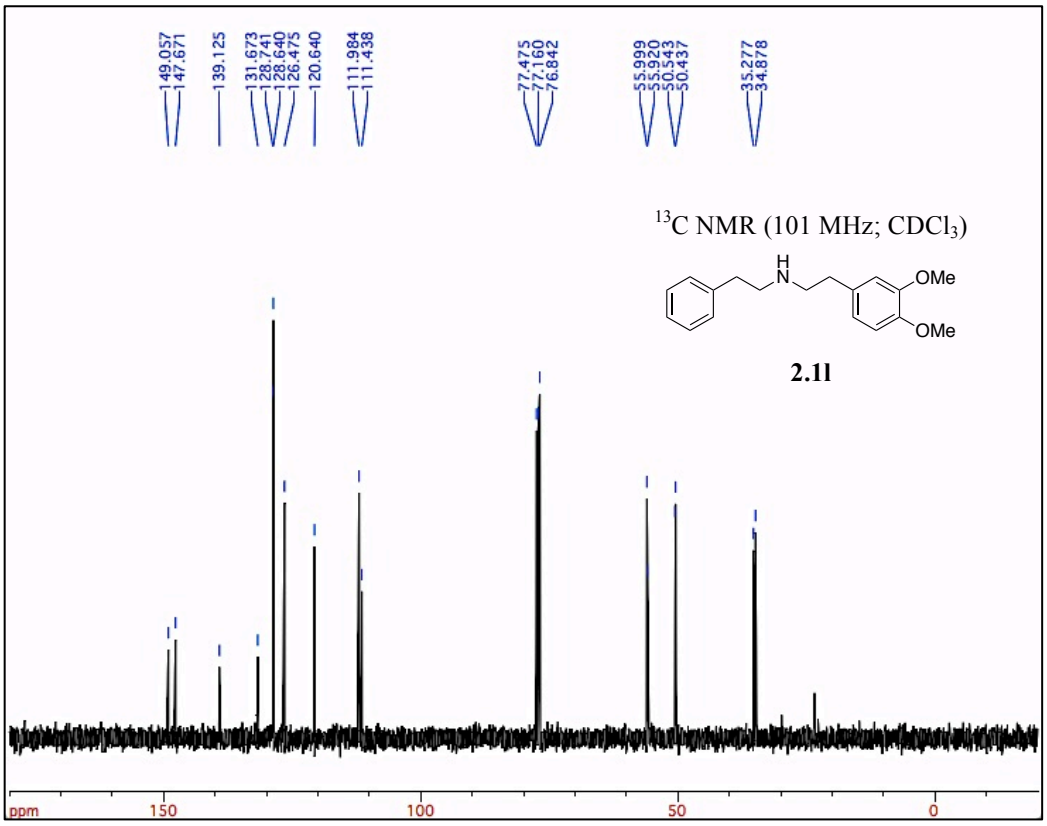


^{13}C NMR (151 MHz; $CDCl_3$)

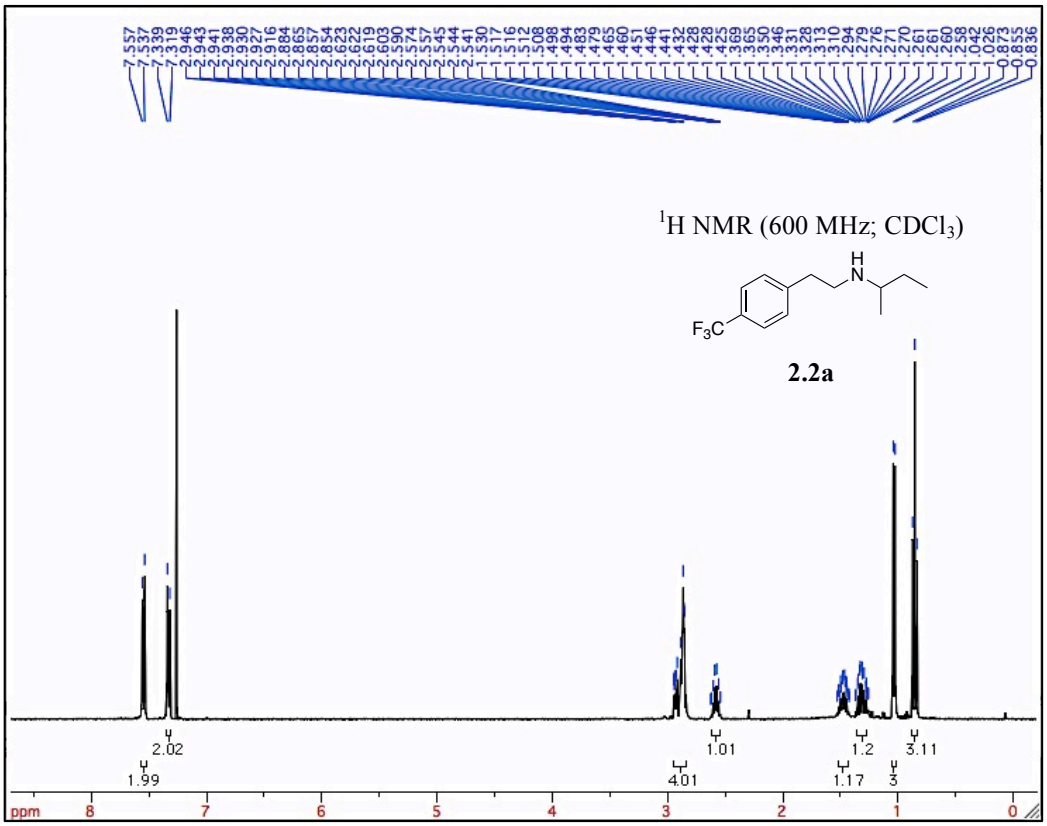
2.1h

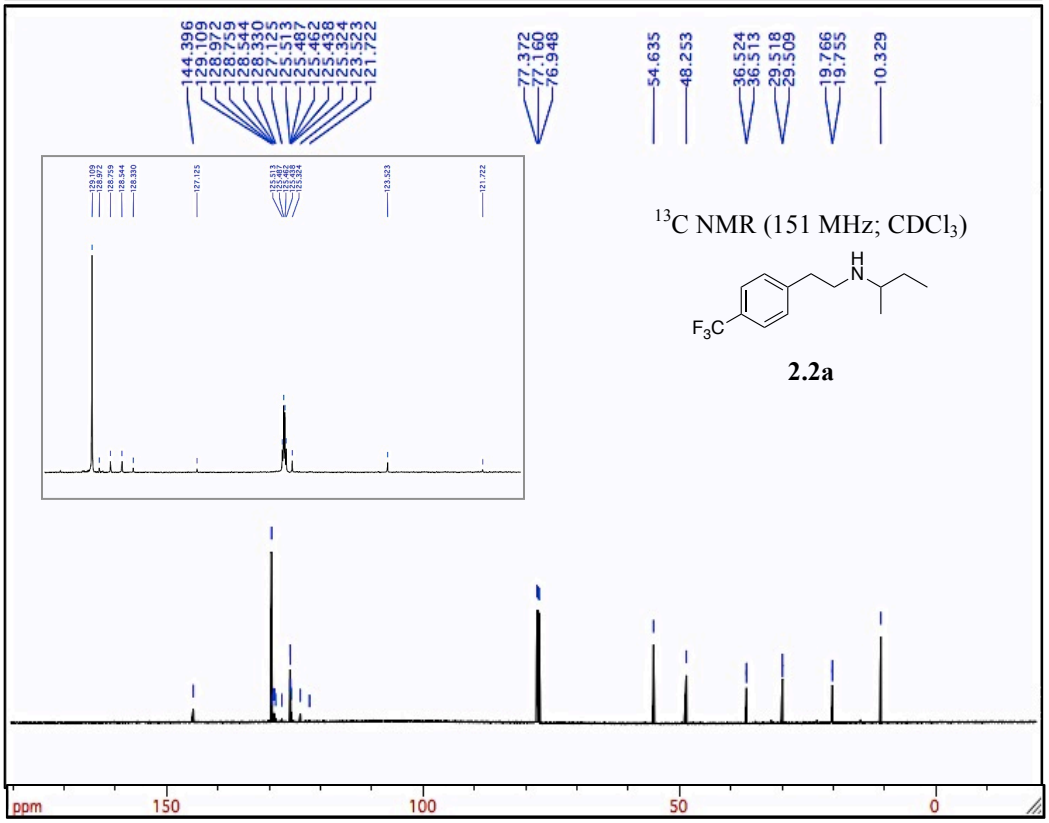
***N*-(3,4-dimethoxyphenethyl)-2-phenylethan-1-amine (2.11)**



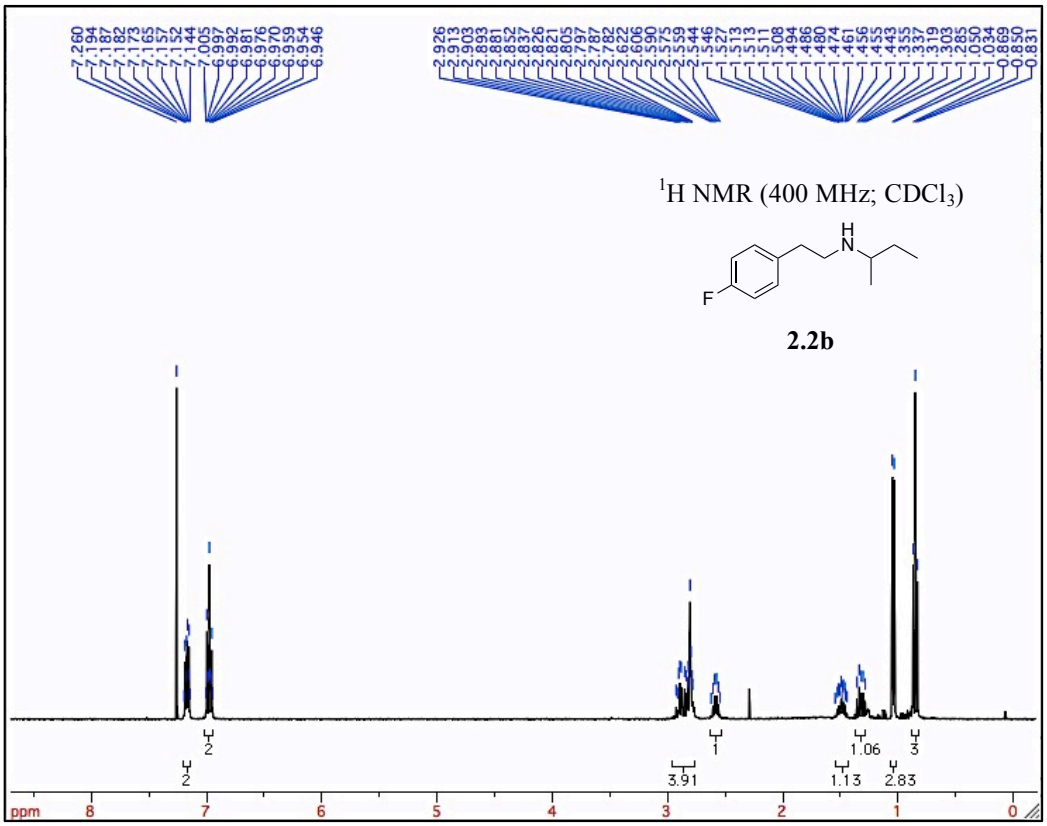


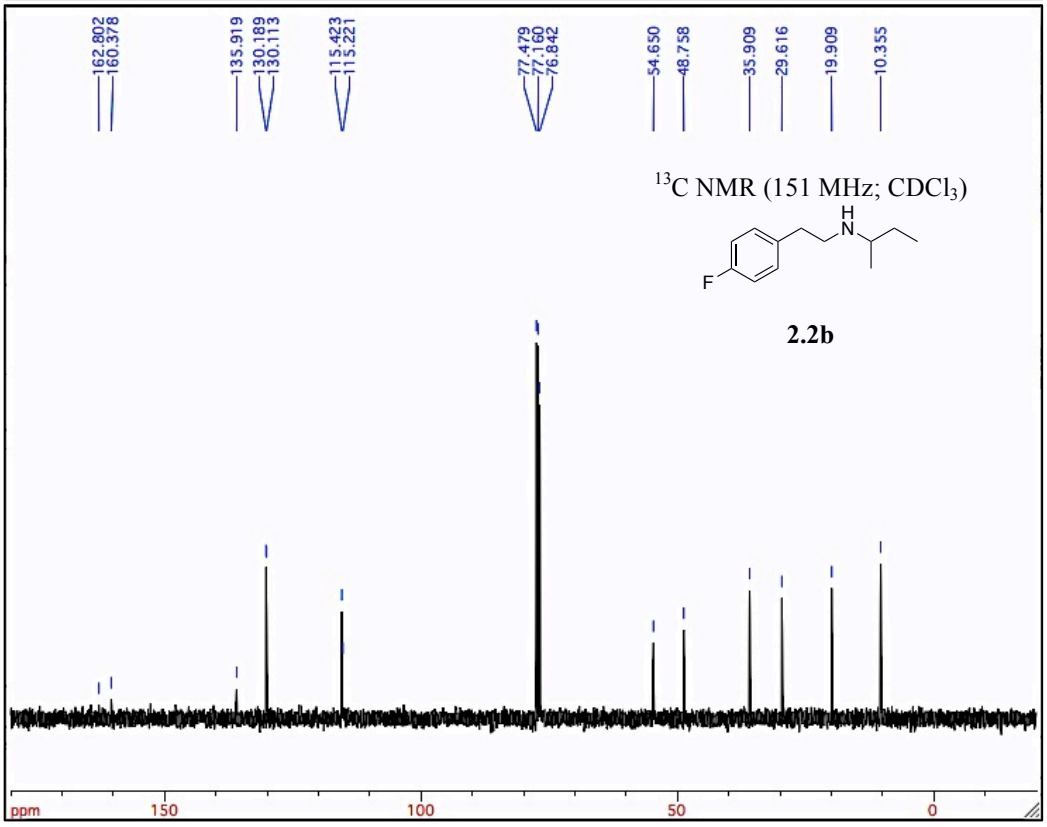
N-(4-(trifluoromethyl)phenethyl)butan-2-amine (2.2a)



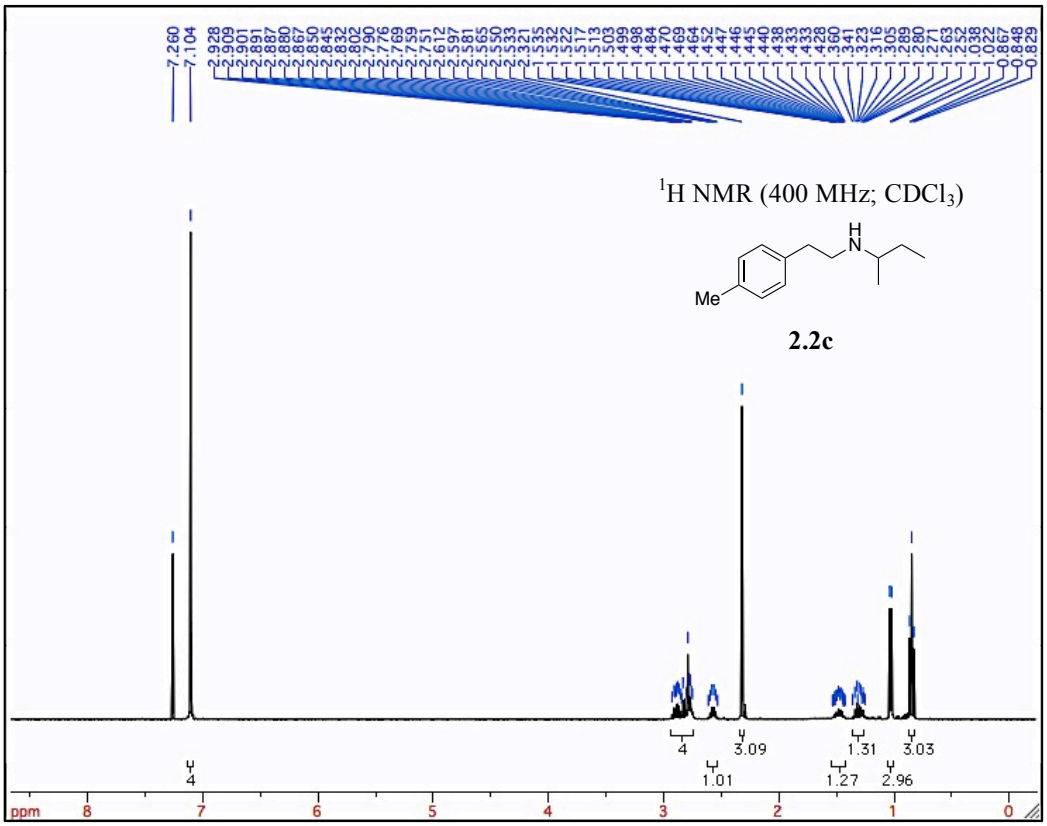


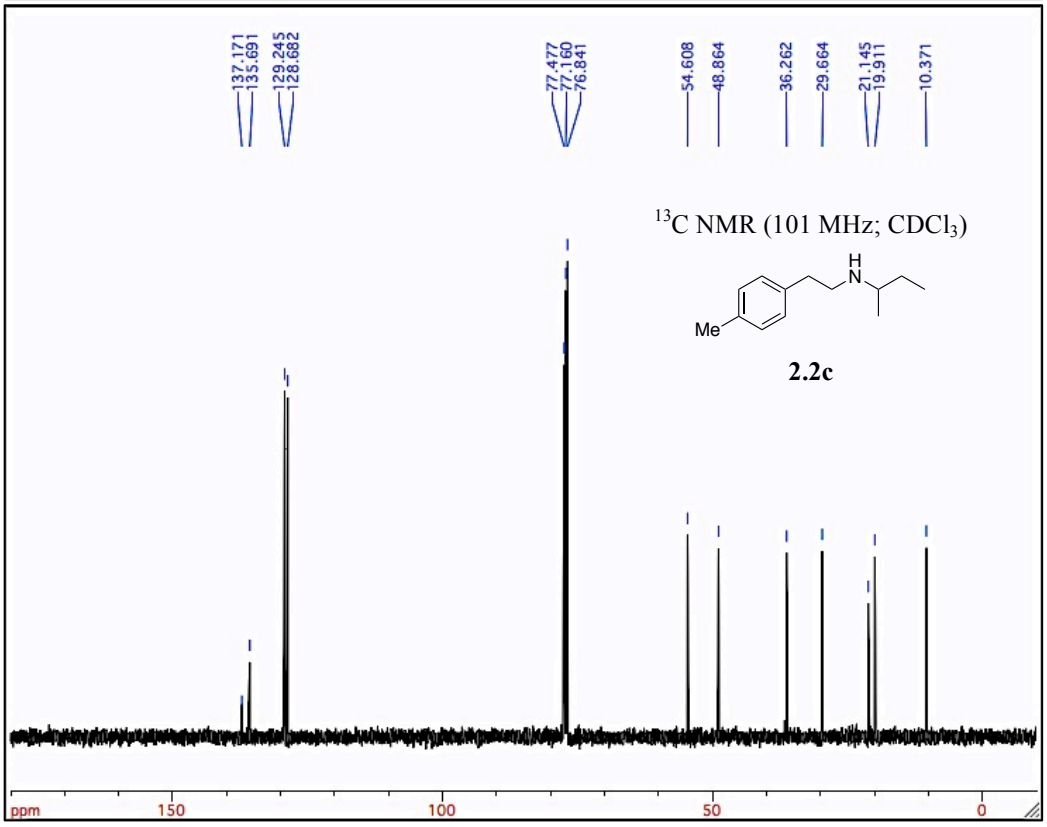
N-(4-fluorophenethyl)butan-2-amine (2.2b)



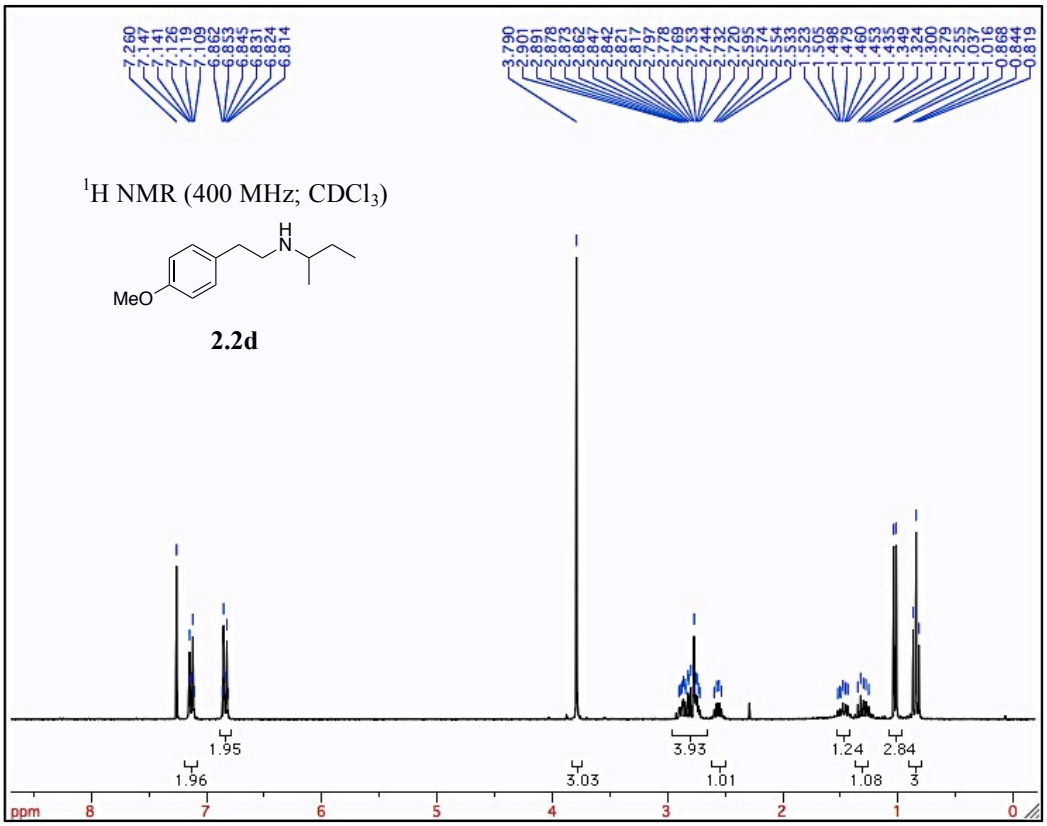


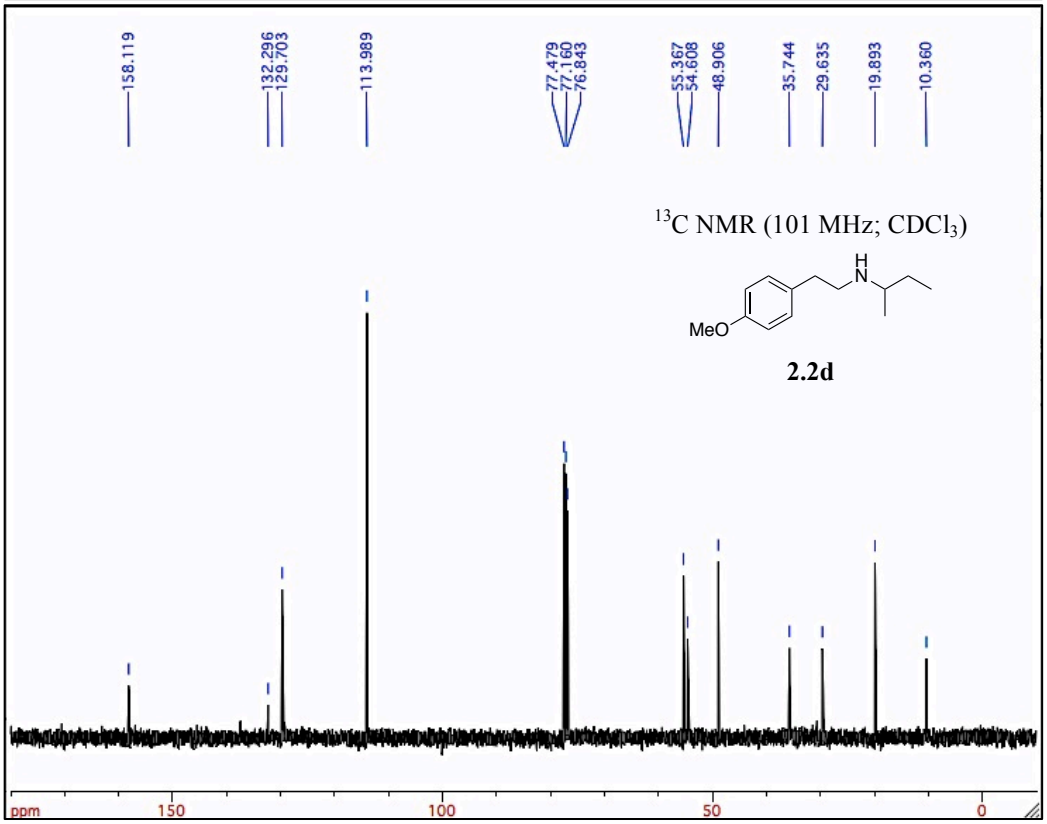
N-(4-methylphenethyl)butan-2-amine (2.2c)



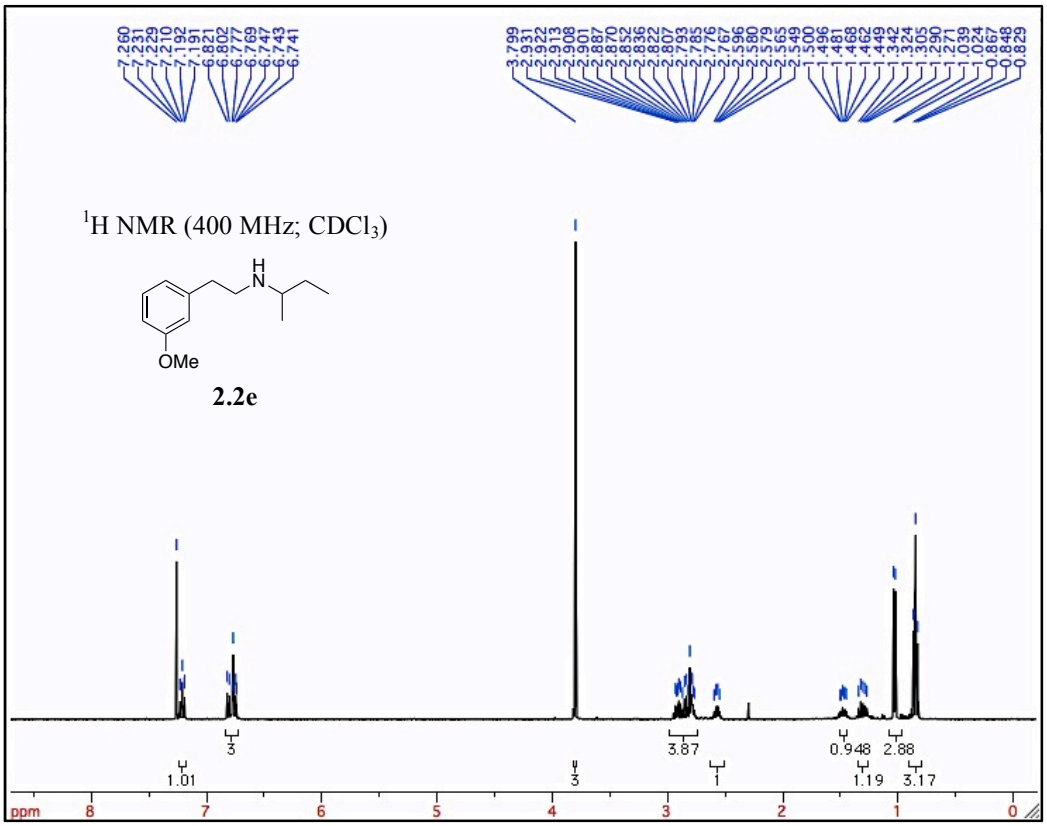


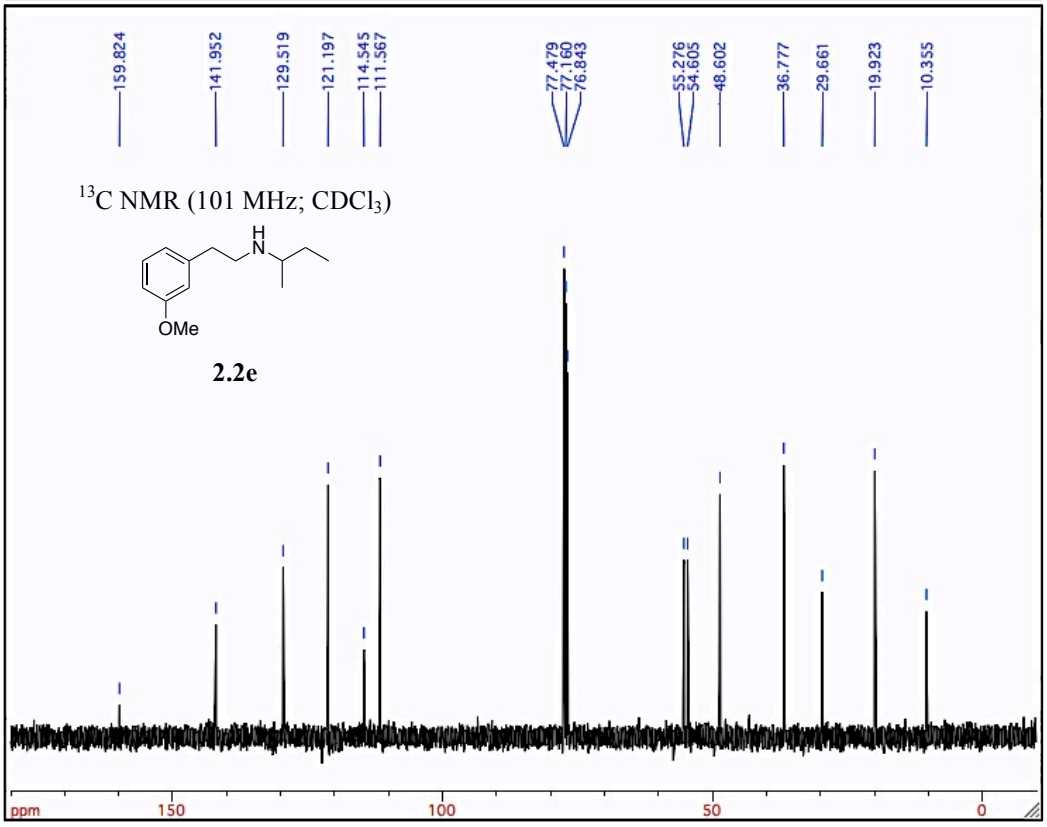
N-(4-methoxyphenethyl)butan-2-amine (2.2d)



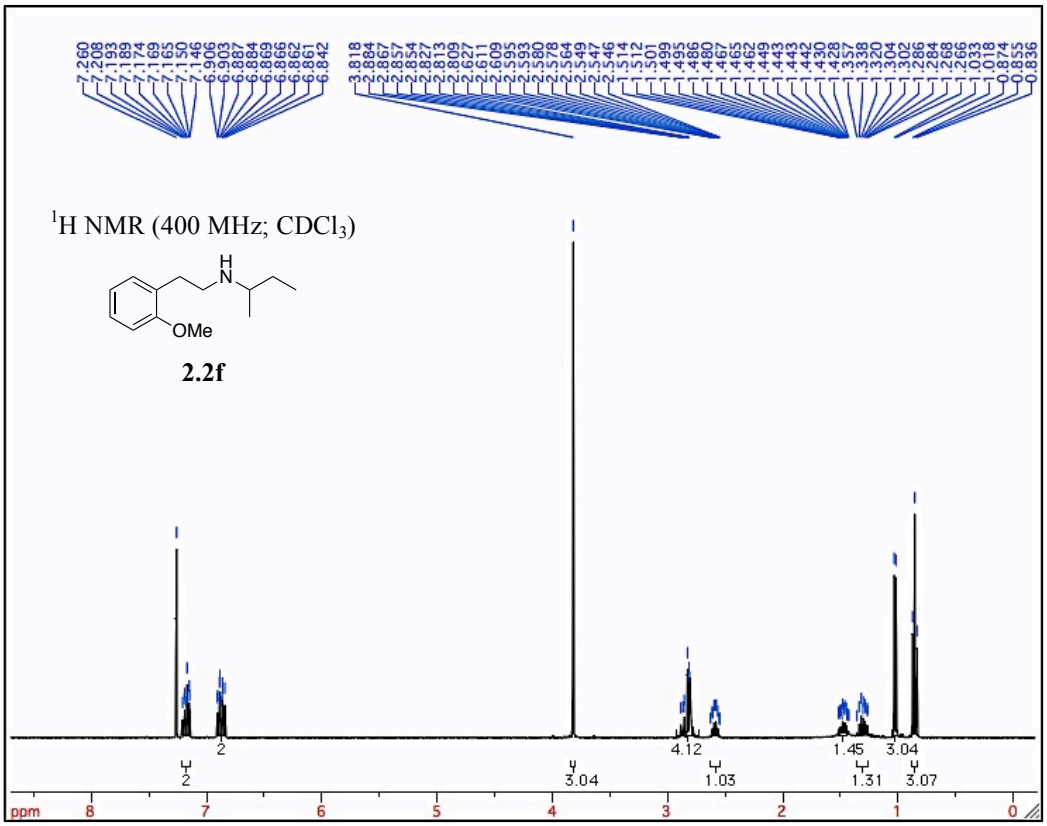


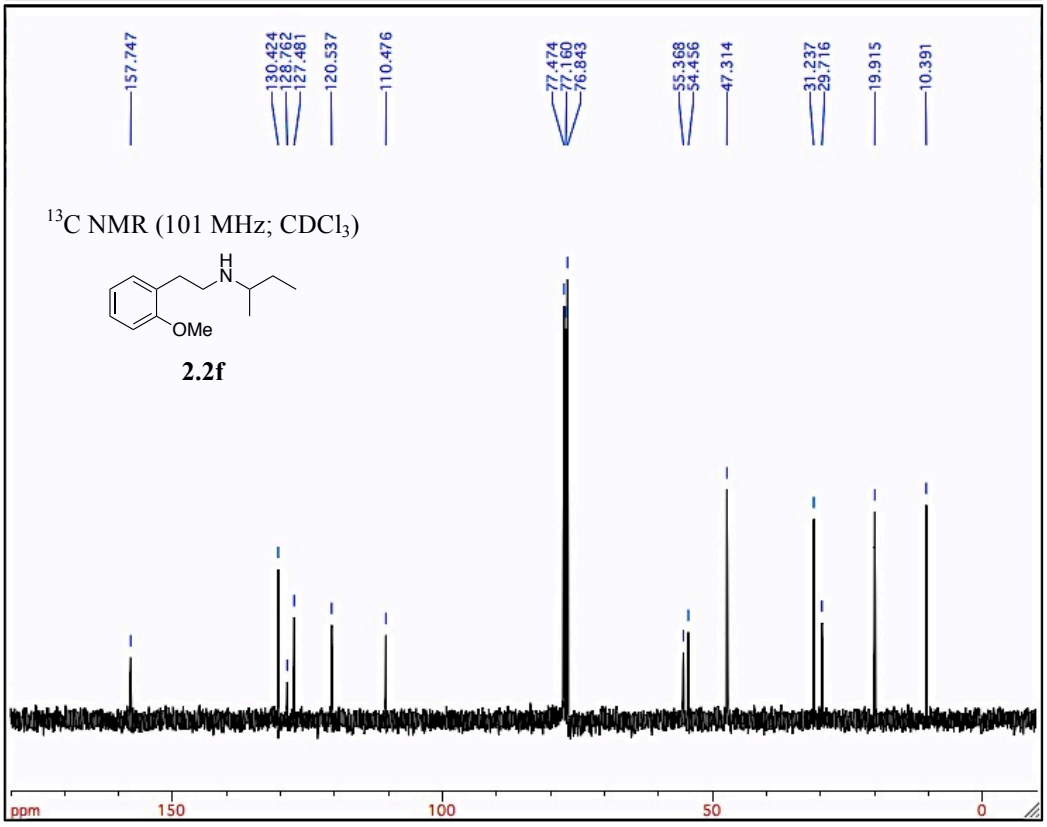
N-(3-methoxyphenethyl)butan-2-amine (2.2e)



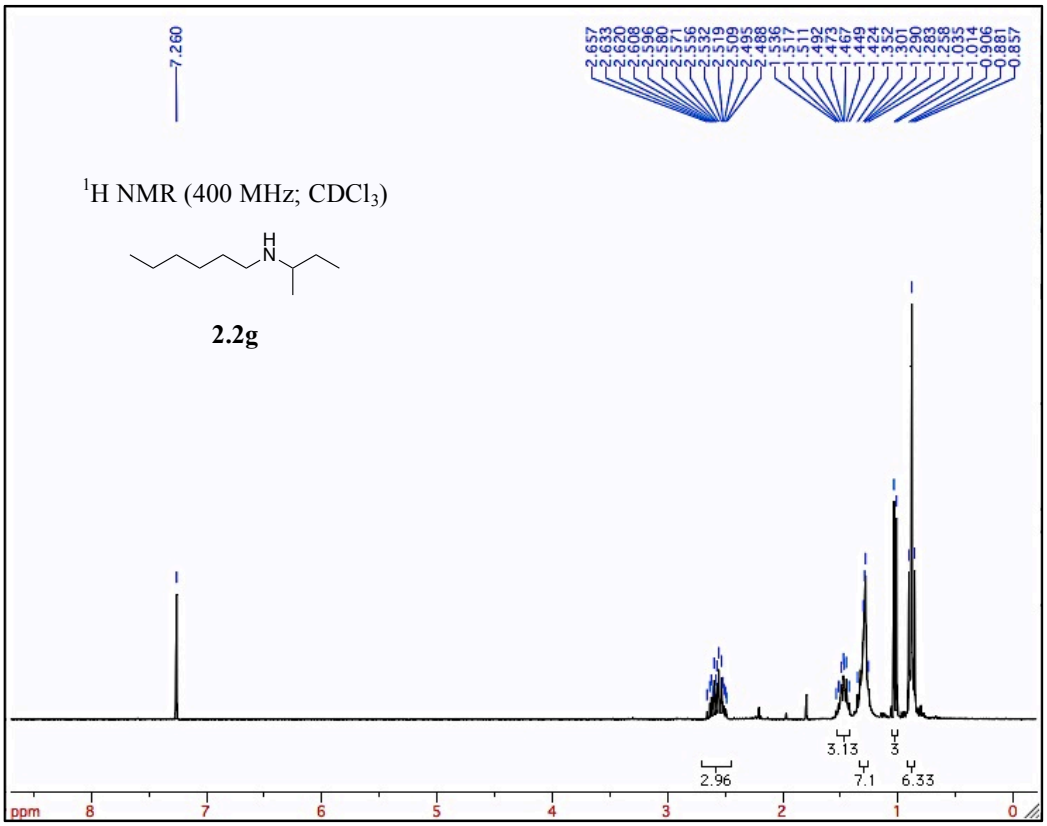


N-(3-methoxyphenethyl)butan-2-amine (2.2f)



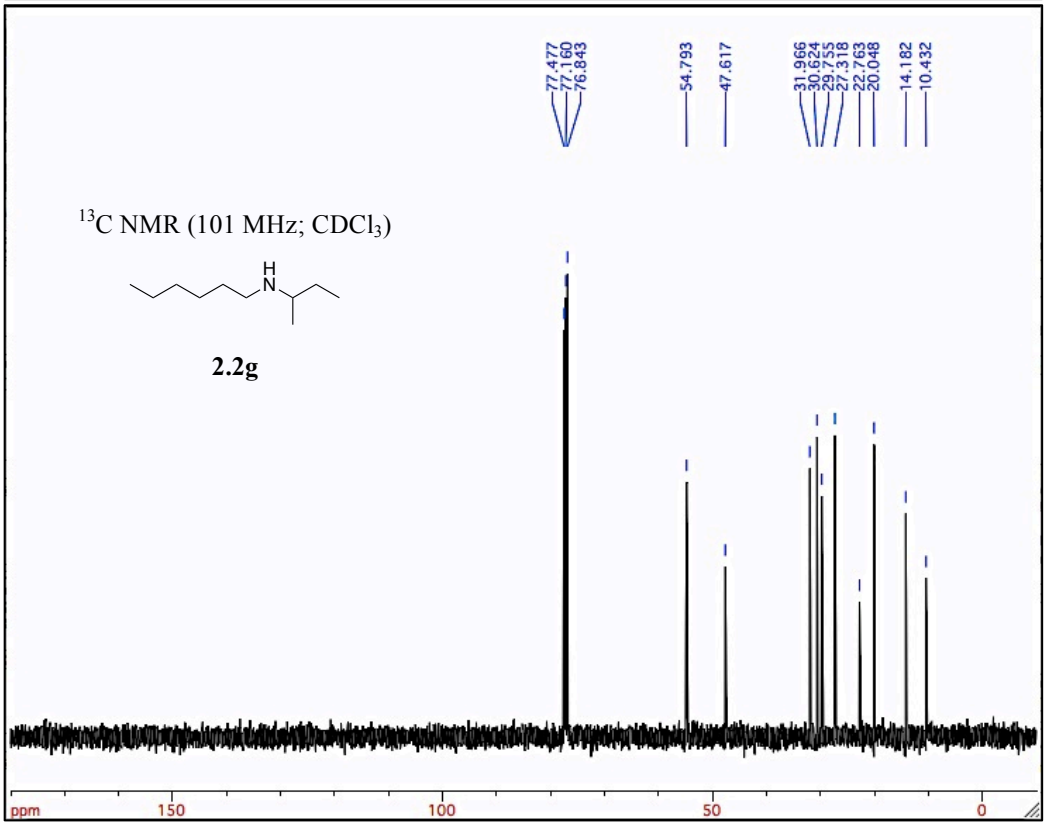


***N*-(*sec*-butyl)hexan-1-amine (2.2g)**



^{1}H NMR (400 MHz; $CDCl_3$)

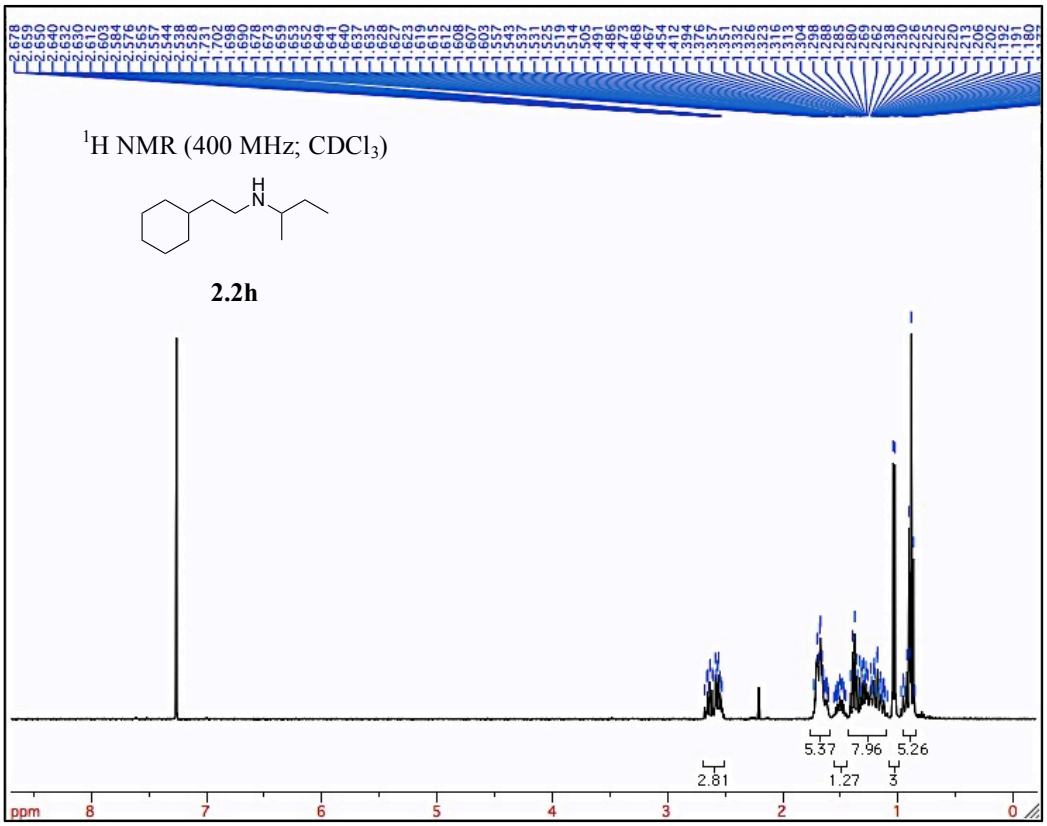
2.2g

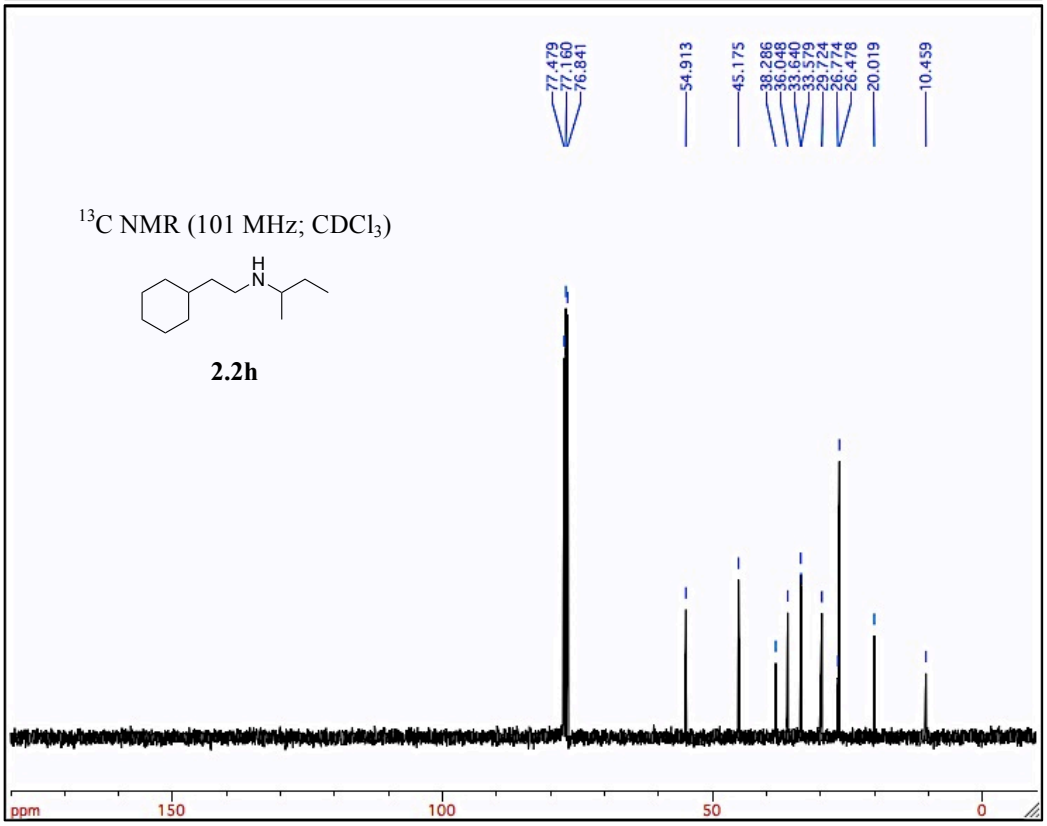


^{13}C NMR (101 MHz; $CDCl_3$)

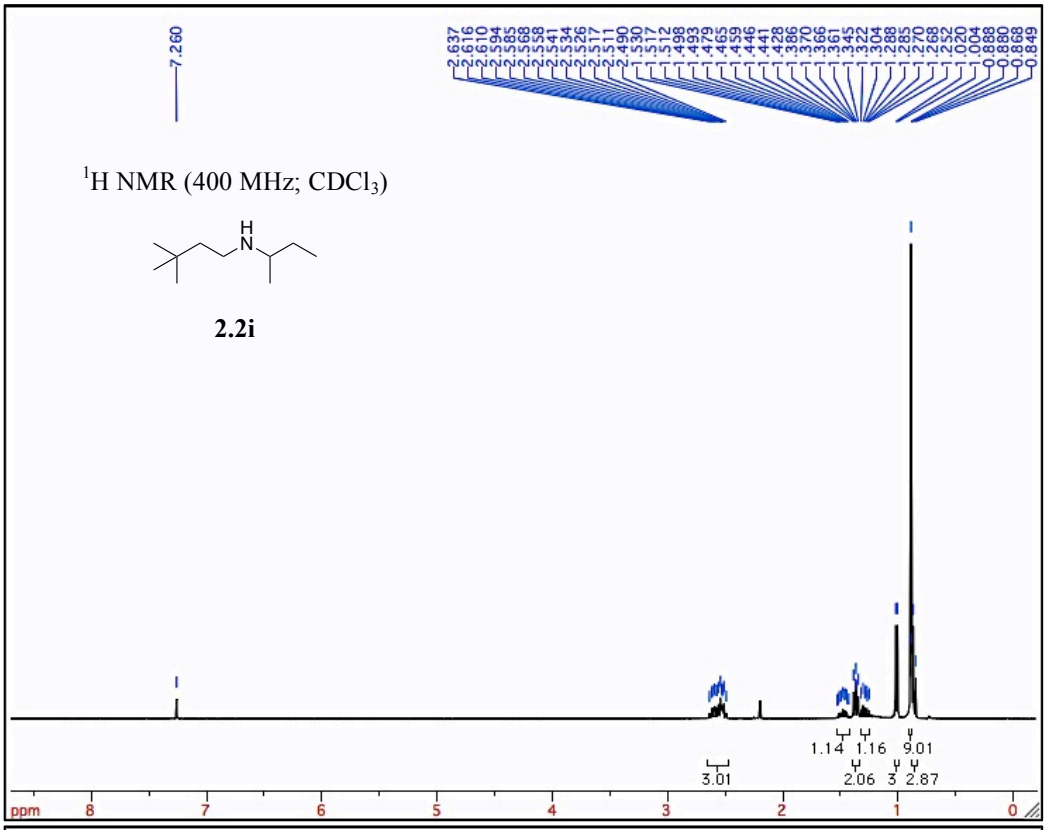
2.2g

N-(2-cyclohexylethyl)butan-2-amine (2.2h)



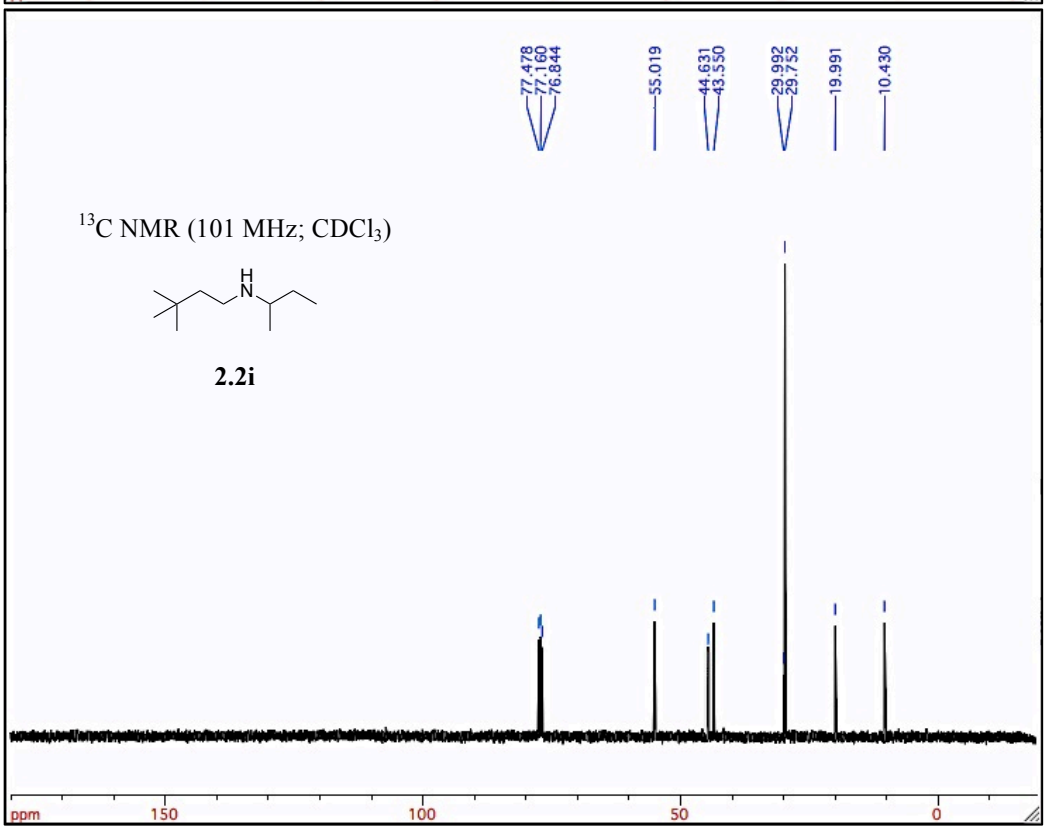


***N*-(*sec*-butyl)-3,3-dimethylbutan-1-amine (2.2i)**



^{1}H NMR (400 MHz; $CDCl_3$)

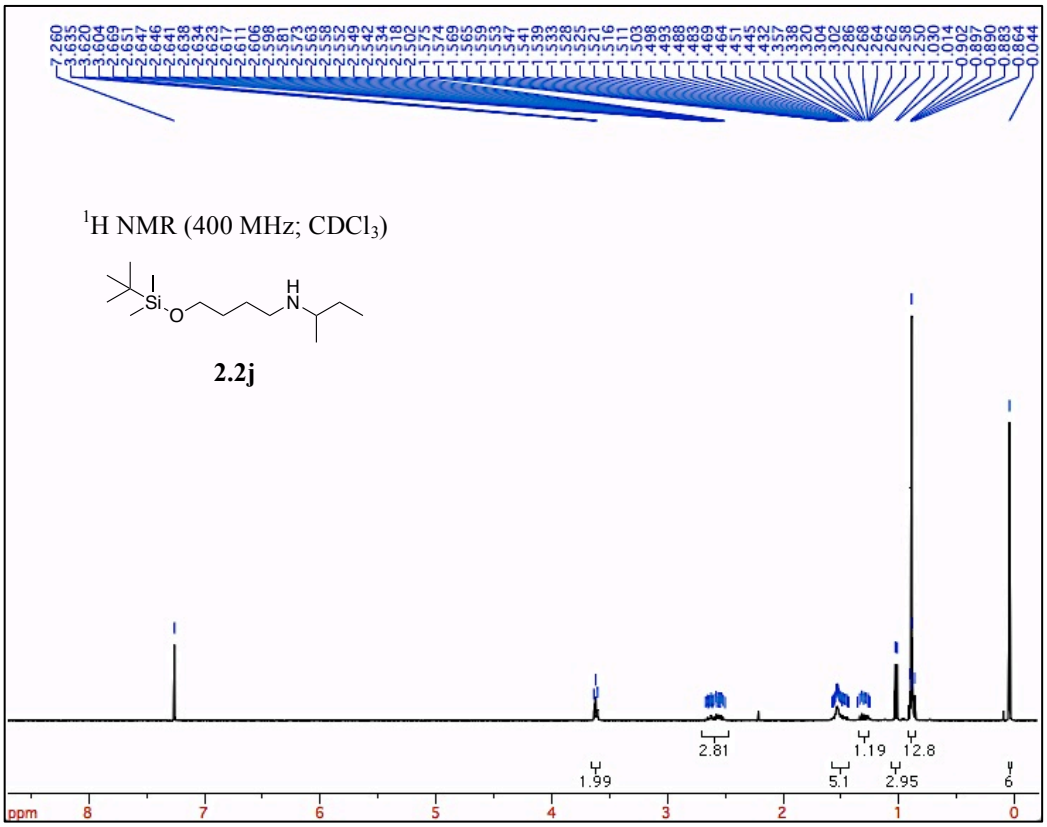
2.2i

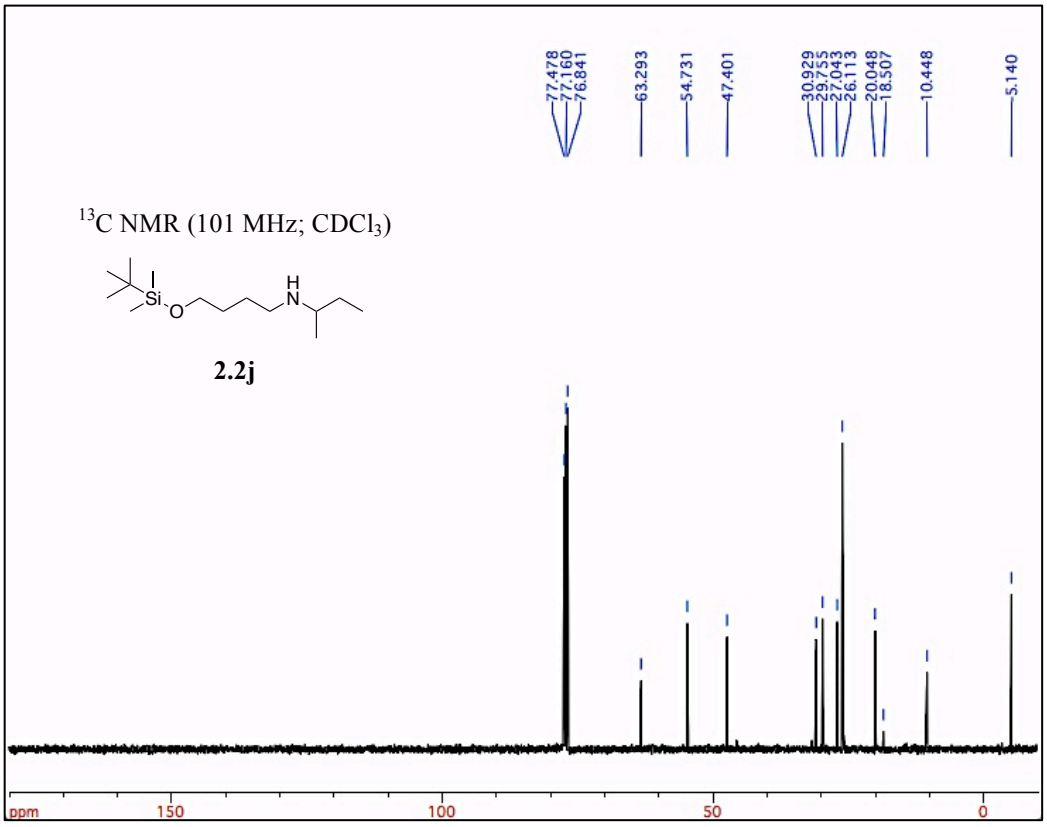


^{13}C NMR (101 MHz; $CDCl_3$)

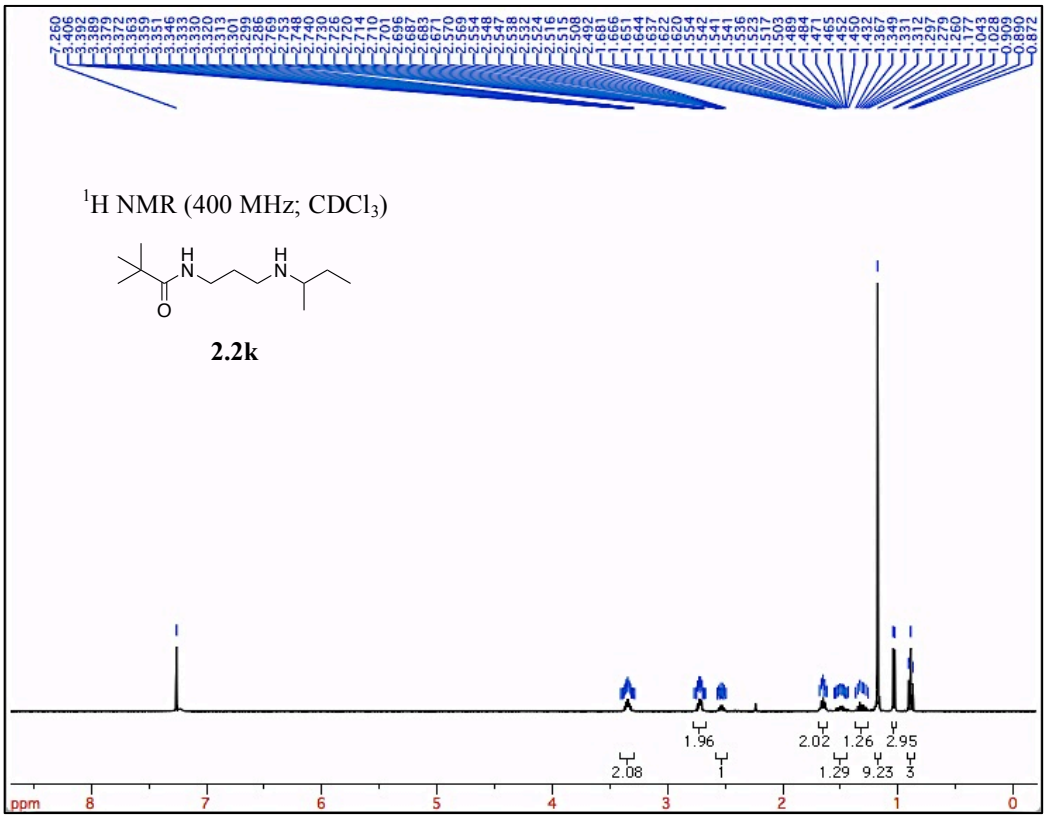
2.2i

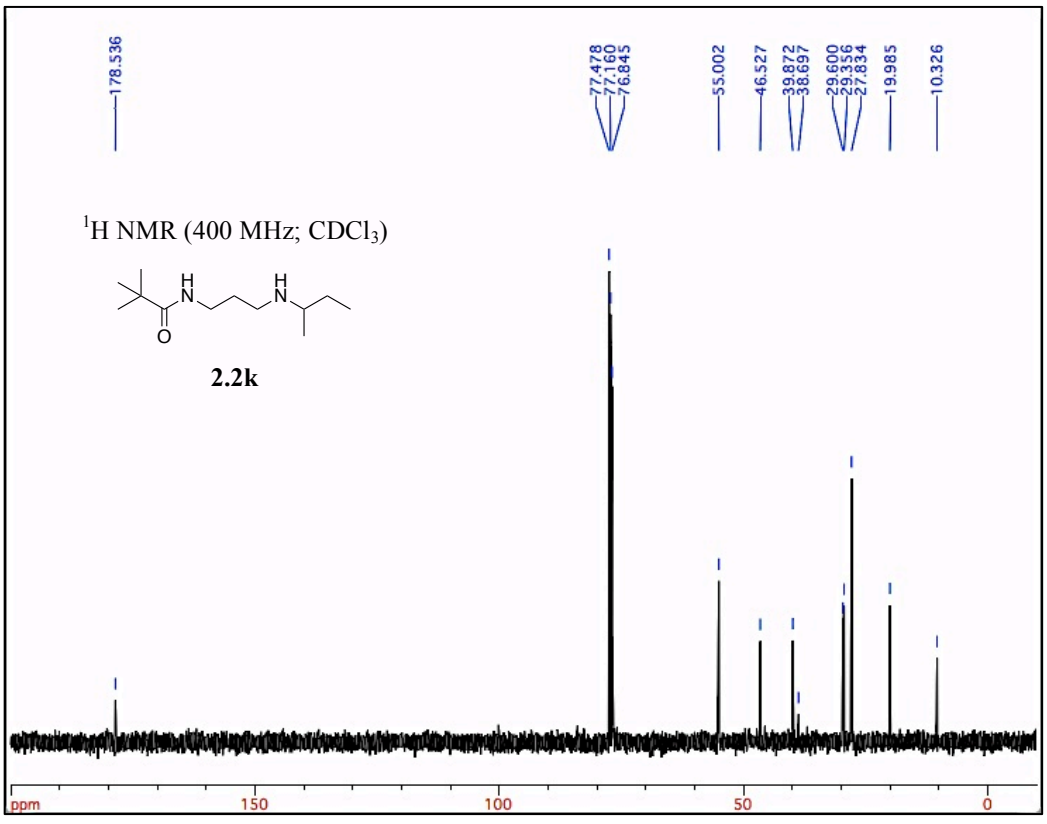
_N_-(_sec_-butyl)-4-((_tert_-butyldimethylsilyl)oxy)butan-1-amine (2.2j)





N-(3-(*sec*-butylamino)propyl)pivalamide (2.2k)





Appendix B

This appendix is for the supporting information pertaining the research conducted in Chapter 3.

B.1 General Considerations

All air and moisture sensitive reactions were performed using a MBraun LABmaster glovebox filled with a N_2 atmosphere. All pieces of glassware were dried for at least 4 hours in a 160 °C oven before being transferred into the glovebox. All stirring was done with appropriately sized Teflon coated magnetic stir bars dried for at least 4 hours in a 160 °C oven. Benzene and hexanes were passed over activated alumina columns into Teflon sealed Straus flasks and stored therein until use. d_6-Benzene was dried over sodium metal, distilled, degassed, and stored in Teflon sealed Schlenk flasks prior to use. Hydrogenations were performed using a Radley's parallel reactor tube. Experiments conducted on NMR tube scale were performed in J-Young NMR tubes (8" x 5 mm) sealed with screw-type Teflon caps. Internal standard used for quantitative ^{1}H NMR experiments was 1,3,5-trimethoxybenzene and the chemical shifts associated with it are the following: **^{1}H NMR** (400 MHz; C_6D_6): δ 6.25 (s, 1H), 3.32 (s, 3H). **^{13}C NMR** (101 MHz; C_6D_6): δ 162.3, 93.5, 54.9.

B.2 Materials

$Ti(NMe_2)_4$ (Sigma-Aldrich) and 10 wt% Pd/C (Sigma-Aldrich) were used as received. All amines and alkynes were purchased from commercial sources, dried over CaH_2 and distilled prior to use. Hydrogen gas (PP 4.5) was purchased from Praxair and used without further purification.

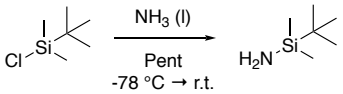
B.3 Instrumentation

NMR spectra were recorded as dilute solutions in deuterated chloroform or benzene on a Bruker Avance 300, 400 or 600 MHz spectrometer at ambient temperature. ^{1}H chemical shift data are

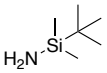
given in units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm and δ (C_6D_6) = 7.16 ppm, while ^{13}C chemical shift data are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.16 ppm and δ (C_6D_6) = 128.06 ppm. High-resolution mass spectra were measured by the mass spectrometry and microanalysis service at the Department of Chemistry, University of British Columbia. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC spectrometer using electrospray ionization source. Fragment signals are given in mass per charge number (*m/z*).

B.4 Synthesis and Compound Characterization

Tert-butyldimethylsilanamine



82%



The *tert*-butyldimethylsilanamine was synthesized following a procedure adapted from literature.[386] Inside an inert atmosphere box, sublimed *tert*-butyldimethylchlorosilane (15.072g, 100 mmol, 1 equiv.) was added to the glassware depicted below and diluted with 50 mL of pentane. The glassware was sealed and taken out of the inert atmosphere box. Connection to an Schlenk line occurred through the middle ground-joint (hidden behind the Teflon tap). The tubing was evacuated and refilled with N_2 (x3) and then both sides of glassware were cooled to -78 °C. Anhydrous ammonia gas (excess) was introduced to the system and condensed on left side of the glassware prior to the addition of sodium pieces. Upon the ammonia solution turning blue in colour, the system was carefully closed and the ammonia was transferred to the right side of the glassware, which contained the *tert*-butyldimethylchlorosilane solution. After transfer, the reaction solution was stirred at -78 °C for an hour and then warmed to room temperature with a vent. The salts formed during the reaction were removed *via* filter cannula to an Schlenk flask

and the pentane was distilled off from the product. Careful evacuation of the remainder of the pentane afforded the desired product as a white solid in 82% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 0.90 (s, 9H), -0.01 (s, 6H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 26.2, 17.9, -3.4.

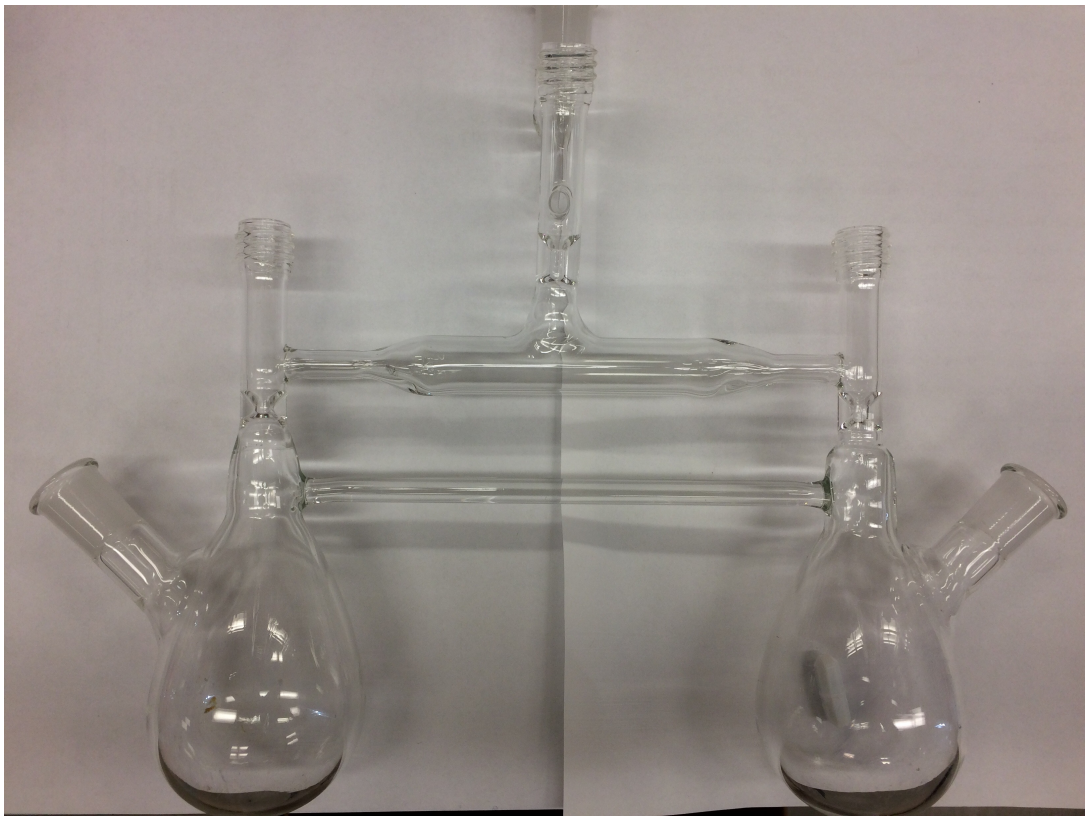
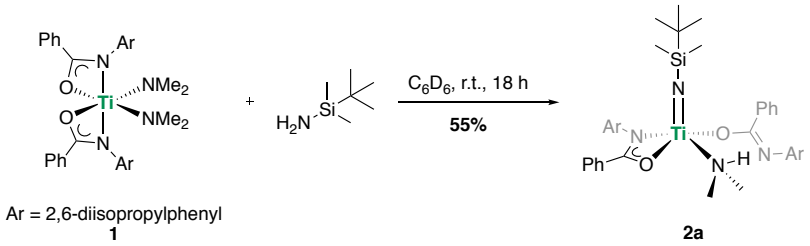
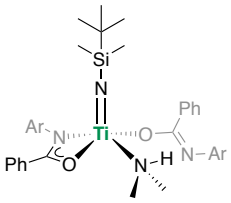


Figure B.1 Glassware Used for the Synthesis of *Tert*-Butyldimethylsilanamine

Bis(*N*-2,6-diisopropylphenylbenzamidate)(*tert*-butyldimethylsilylimido)(dimethylamido) titanium (IV) (3.1a)

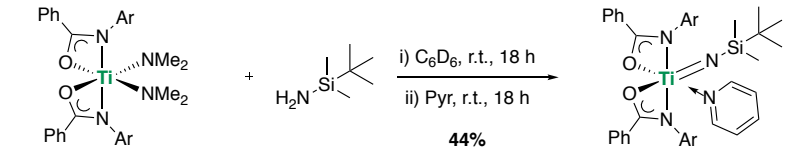




Ar = 2,6-diisopropylphenyl
3.1a

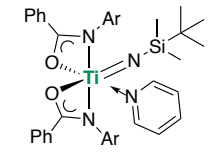
Inside an inert atmosphere box, toluene (0.15 mL) was added to the titanium complex **1** (0.3484 g, 0.5 mmol, 1 equiv.) in a 5-dram vial and the solution was transferred to a scintillation vial. The silylamine (0.0656 g, 0.5 mmol, 1 equiv.) was also pre-weighed to a separate 5-dram vial and transferred to the same scintillation vial using the remainder of the solvent (0.35 mL). The reaction flask was sealed and the reaction solution was stirred for 18 h at room temperature. The volatiles were removed under reduced pressure and recrystallization of the solid compound from hexanes afforded complex **3.1a** as yellow crystals in 55% yield. **^{1}H NMR** (300 MHz; C_6D_6): δ 8.37 (s, 1H), 7.73-7.63 (m, 2H), 7.31-7.18 (m, 4H), 7.13-7.00 (m, 6H), 6.95-6.83 (m, 4H), 3.97-3.74 (m, 2H), 3.23-3.14 (m, 1H), 2.59 (d, *J* = 5.9 Hz, 3H), 2.33-2.25 (m, 1H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.51-1.42 (m, 9H), 1.28 (d, *J* = 6.7 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 9H), 0.80 (d, *J* = 6.0 Hz, 3H), 0.04 (s, 3H), -0.10 (s, 3H). **MS** (EI) m/z: calc'd for $C_{46}H_{66}N_4O_2SiTi$ $[M - C_9H_{13}N]^+$: 680; found: 680. **Elemental Analysis** calc'd for $C_{46}H_{66}N_4O_2SiTi$: C 70.56, H 8.50, N 7.16; found: C 70.21, H 8.63, N 6.80.

Bis(*N*-2,6-diisopropylphenylbenzamidate)(*tert*-butyldimethylsilylimido)(pyridino) titanium (IV) (3.1b)



Ar = 2,6-diisopropylphenyl
1

2b

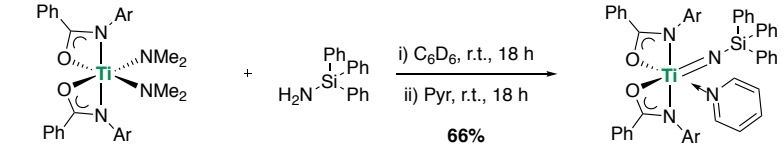


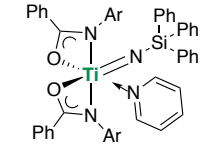
Ar = 2,6-diisopropylphenyl
3.1b

Titanium complex **3.1b** was synthesized following a procedure adapted from literature.[1] Inside an inert atmosphere box, hexanes (0.15 mL) were added to the titanium complex **1** (0.3484 g, 0.5 mmol, 1 equiv.) in a 5-dram vial and the solution was transferred to a scintillation vial. The silylamine (0.0656 g,

0.5 mmol, 1 equiv.) was also pre-weighed to a separate 5-dram vial and transferred to the same scintillation vial using the remainder of the solvent (0.35 mL). The reaction flask was sealed and the reaction solution was stirred for 18 h at room temperature. The volatiles under reduced pressure and due to the lack of crystallinity, pyridine (0.0395 g, 0.5 mmol, 1 equiv.) was added to the scintillation vial and the reaction mixture was once again stirred for 18 h at room temperature. The volatiles were once again removed under reduced pressure. Recrystallization of the solid compound from toluene and hexanes afforded complex **3.1b** as orange crystals in 44% yield. **^{1}H NMR** (300 MHz; C_6D_6): δ 9.31 (d, *J* = 4.9 Hz, 2H), 7.82-7.79 (m, 4H), 7.18 (s, 5H), 6.92-6.89 (m, 7H), 6.73-6.66 (m, 1H), 6.49-6.44 (m, 2H), 4.29-4.23 (m, 2H), 3.70-3.60 (m, 2H), 1.42-1.38 (m, 12H), 1.23-1.19 (m, 9H), 1.12-1.09 (m, 12H), -0.08 (s, 9H). **MS** (EI): m/z: calc'd for $C_{49}H_{64}N_4O_2SiTi$ $[M - C_9H_{13}N]^+$: 680; found: 680. **Elemental Analysis** calc'd for $C_{49}H_{64}N_4O_2SiTi$: C 72.03, H 7.90, N 6.86; found: C 72.24, H 7.98, N 6.77.

Bis(*N*-2,6-diisopropylphenylbenzamidate)(triphenylsilylimido)(pyridino) titanium (IV) (3.1c)

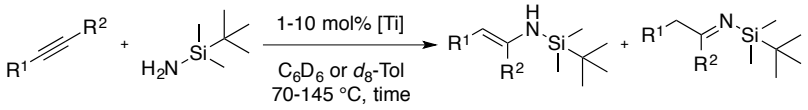




Titanium complex **3.1c** was synthesized following a procedure adapted from literature.[1] Inside an inert atmosphere box, hexanes (0.15 mL) were added to the titanium complex **1** (0.3484 g, 0.5 mmol, 1 equiv.) in a 5-dram vial and the solution was transferred to a scintillation vial. The silylamine (0.1377 g, 0.5 mmol, 1 equiv.) was also pre-weighed to a separate 5-dram vial and transferred to the same scintillation vial using the remainder of the solvent (0.35 mL). The reaction flask was sealed and

the reaction solution was stirred for 18 h at room temperature. The volatiles under reduced pressure and due to the lack of crystallinity, pyridine (0.0395 g, 0.5 mmol, 1 equiv.) was added to the scintillation vial and the reaction mixture was once again stirred for 18 h at room temperature. The volatiles were once again removed under reduced pressure. Recrystallization of the solid compound from toluene and hexanes afforded complex **3.1c** as yellow crystals in 66% yield. **^{1}H NMR** (300 MHz; C_6D_6): δ 9.08 (d, *J* = 4.9 Hz, 2H), 7.80-7.75 (m, 9H), 7.14-7.00 (m, 18H), 6.96-6.93 (m, 4H), 6.69-6.63 (m, 1H), 6.36-6.31 (m, 2H), 4.02-3.99 (m, 2H), 3.67-3.63 (m, 2H), 1.29 (d, *J* = 5.8 Hz, 6H), 1.02-0.95 (m, 12H), 0.73 (d, *J* = 5.8 Hz, 6H). **MS** (EI): m/z: calc'd for $C_{61}H_{64}N_4O_2SiTi$ $[M - C_5H_5N]^+$: 881; found: 881. **Elemental Analysis** calc'd for $C_{61}H_{64}N_4O_2SiTi$: C 76.23, H 6.71, N 5.83; found: C 75.87, H 7.03, N 5.80.

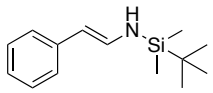
General Procedure for the Hydroamination Reaction



Inside an inert atmosphere box, 1,3,5-trimethoxybenzene solution was added to a J-young tube. Then, *d_6*-benzene (0.15 mL) was added to the titanium complex (0.005-0.05 mmol, 1-10 mol% Ti) in a 5-dram vial and the solution was transferred to a J-Young tube. The amine (0.5 mmol, 1 equiv.) and alkyne (0.5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the J-Young tube. The remaining benzene (0.35 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction tube. The J-Young tube was sealed, taken out of the inert atmosphere box and a time zero ^{1}H NMR spectrum was obtained. The reaction solution was heated at 70-145 °C depending on the starting materials used. A ^{1}H NMR spectrum was obtained after 6-72 hours of heating and full consumption of

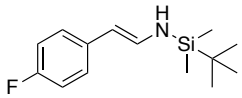
starting materials was observed. Quantitative ^{1}H NMR yields were obtained by integrating the starting materials and products to the internal standard.

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-styrylsilanamine (3.2a)



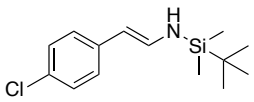
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 96%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.21 (m, 4H), 6.99 (m, 1H), 6.69 (dd, *J* = 13.7, 13.4 Hz, 1H), 5.47 (d, *J* = 13.7 Hz, 1H), 3.02 (d, *J* = 13.4 Hz, 1H), 0.81 (s, 9H), -0.03 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 139.8, 133.8, 128.9, 124.3, 124.3, 105.3, 26.1, 18.4, -5.3

(*E*)-1-*tert*-butyl-*N*-(4-fluorostyryl)-1,1-dimethylsilanamine (3.2b)



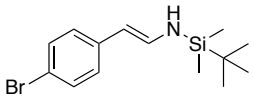
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-fluorobenzene (0.0601 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 99%. Characterization was performed *in situ* - ^{1}H NMR (400 MHz; C_6D_6): δ 6.99-6.95 (m, 2H), 6.86-6.82 (m, 2H), 6.53 (dd, *J* = 13.8, 13.5 Hz, 1H), 5.35 (d, *J* = 13.5 Hz, 1H), 3.01 (d, *J* = 13.8 Hz, 1H), 0.82 (s, 9H), -0.02 (s, 6H). ^{13}C NMR (101 MHz; C_6D_6): δ 160.9 (d, ^{1}J(C,F) = 274.4Hz), 135.9, 133.6, 125.3 (d, ^{3}J(C,F) = 7.7Hz), 115.6 (d, ^{2}J(C,F) = 21.4Hz), 104.0, 26.1, 18.3, -5.3. ^{19}F NMR (282 MHz; C_6D_6): δ -119.7.

(*E*)-1-*tert*-butyl-*N*-(4-chlorostyryl)-1,1-dimethylsilanamine (3.2c)



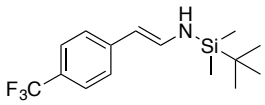
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-chloro-4-ethynylbenzene (0.0683 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 99%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.14-7.10 (m, 2H), 6.94-6.91 (m, 2H), 6.57 (dd, *J* = 14.0, 13.5 Hz, 1H), 5.29 (d, *J* = 13.5 Hz, 1H), 3.06 (d, *J* = 14.0 Hz, 1H), 0.80 (s, 9H), -0.03 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 138.4, 134.5, 129.2, 128.9, 125.3, 103.9, 26.1, 18.3, -5.3.

(*E*)-1-*tert*-butyl-*N*-(4-chlorostyryl)-1,1-dimethylsilanamine (3.2d)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-bromo-4-ethynylbenzene (0.0905 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 98%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.28-7.25 (m, 2H), 6.88-6.85 (m, 2H), 6.58 (dd, *J* = 14.0, 13.5 Hz, 1H), 5.27 (d, *J* = 13.5 Hz, 1H), 3.06 (d, *J* = 14.0 Hz, 1H), 0.80 (s, 9H), -0.04 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 138.8, 134.6, 131.8, 125.7, 117.0, 103.9, 26.1, 18.3, -5.3

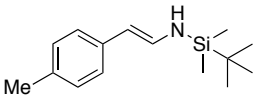
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(4-(trifluoromethyl)styryl)silanamine (3.2e)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-(trifluoromethyl)benzene (0.0851 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 98%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz;

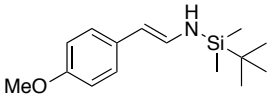
C_6D_6): δ 7.37 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.68 (dd, *J* = 14.2, 13.5 Hz, 1H), 5.28 (d, *J* = 13.5 Hz, 1H), 3.16 (d, *J* = 14.2 Hz, 1H), 0.80 (s, 9H), -0.03 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 143.7, 136.5, 125.8 (q, ^{3}J(C,F) = 3.8Hz), 125.6 (q, ^{1}J(C,F) = 271.0Hz), 125.5 (q, ^{2}J(C,F) = 32.2Hz), 123.8, 103.7, 25.9, 18.2, -5.5. **^{19}F NMR** (282 MHz; C_6D_6): δ -119.7.

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(4-methylstyryl)silanamine (3.2f)



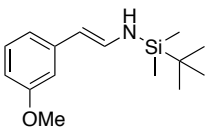
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-methylbenzene (0.0581 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 95%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.69 (dd, *J* = 13.8, 13.6 Hz, 1H), 5.51 (d, *J* = 13.6 Hz, 1H), 3.01 (d, *J* = 13.8 Hz, 1H), 2.19 (s, 3H), 0.83 (s, 9H), -0.01 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 137.0, 133.3, 133.0, 129.6, 124.3, 105.3, 26.2, 21.2, 18.4, -5.2.

(*E*)-1-*tert*-butyl-*N*-(4-methoxystyryl)-1,1-dimethylsilanamine (3.2g)



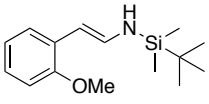
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 97%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.16-7.14 (m, 3H), 6.82-6.80 (m, 2H), 6.61 (dd, *J* = 13.7, 13.6 Hz, 1H), 5.52 (d, *J* = 13.6 Hz, 1H), 3.41 (s, 3H), 3.03 (d, *J* = 13.7 Hz, 1H), 0.85 (s, 9H), 0.01 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 157.4, 132.5, 132.1, 125.3, 114.5, 104.9, 54.9, 26.2, 18.4, -5.2.

(*E*)-1-*tert*-butyl-*N*-(3-methoxystyryl)-1,1-dimethylsilanamine (3.2h)



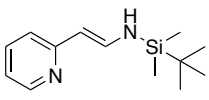
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-3-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 98%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.12 (m, 1H), 6.91-6.88 (m, 2H), 6.74 (dd, *J* = 13.5, 13.5 Hz, 1H), 6.57 (m, 1H), 5.48 (d, *J* = 13.5 Hz, 1H), 3.43 (s, 3H), 3.13 (d, *J* = 13.5 Hz, 1H), 0.81 (s, 9H), -0.02 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 160.7, 141.3, 134.2, 129.7, 117.0, 110.5, 109.5, 105.2, 54.7, 26.1, 18.3, -5.3.

(*E*)-1-*tert*-butyl-*N*-(2-methoxystyryl)-1,1-dimethylsilanamine (3.2i)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-2-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was >99%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.34 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.98 (td, *J* = 7.9, 1.7 Hz, 1H), 6.94-6.87 (m, 2H), 6.62 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.01 (d, *J* = 13.6 Hz, 1H), 3.44 (s, 3H), 3.16 (d, *J* = 14.0 Hz, 1H), 0.83 (s, 9H), -0.01 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 155.7, 134.8, 128.9, 124.8, 121.2, 111.1, 111.0, 100.7, 55.1, 26.2, 18.4, -5.3.

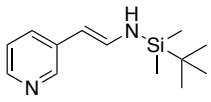
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyridin-2-yl)vinyl)silanamine (3.2j)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 2-ethynylpyridine (0.0516 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 8 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield

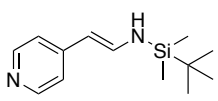
was 85% (81% of (*E*)-isomer and 4% of (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 8.43 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 7.76 (dd, *J* = 14.8, 12.9 Hz, 1H), 7.11 (ddd, *J* = 7.9, 7.4, 1.9 Hz, 1H), 6.71 (ddd, *J* = 7.9, 1.1, 0.8 Hz, 1H), 6.55 (ddd, *J* = 7.4, 4.8, 1.1 Hz, 1H), 5.64 (d, *J* = 12.9 Hz, 1H), 3.93 (d, *J* = 14.8 Hz, 1H), 0.80 (s, 9H), -0.01 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 158.7, 149.5, 139.5, 135.8, 119.2, 118.4, 104.7, 26.1, 18.3, -5.3.

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyridin-3-yl)vinyl)silanamine (3.2k)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 3-ethynylpyridine (0.0516 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 18 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 94%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 8.66 (s, 1H), 8.32 (d, *J* = 4.2 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 7.8, 4.2 Hz, 1H), 6.71 (dd, *J* = 13.8, 13.6 Hz, 1H), 5.35 (d, *J* = 13.6 Hz, 1H), 3.87 (d, *J* = 13.8 Hz, 1H), 0.82 (s, 9H), -0.01 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 146.5, 145.3, 136.1, 135.6, 129.6, 123.5, 100.8, 26.1, 18.4, -5.3.

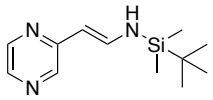
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyridin-4-yl)vinyl)silanamine (3.2l)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 4-ethynylpyridine (0.0516 g) were added to a solution of the titanium complex (0.0348 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 18 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 69%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 8.41 (s, 2H), 6.96 (dd, *J* = 13.4, 13.2 Hz, 1H), 6.84 (d, *J* = 2.7 Hz, 2H), 5.34 (d, *J* = 13.4 Hz, 1H), 4.50 (d, *J* =

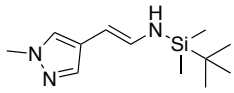
13.2 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 150.1, 147.5, 139.0, 118.5, 102.1, 26.0, 18.3, -5.4

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyrazin-2-yl)vinyl)silanamine (3.2m)



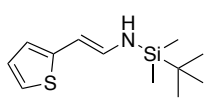
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 2-ethynylpyrazine (0.0521 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 18 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 86% (69% of (*E*)-isomer and 17% of (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 8.21 (s, 1H), 8.05 (s, 1H), 7.92 (s, 1H), 7.70 (dd, *J* = 14.9, 12.9 Hz, 1H), 5.43 (d, *J* = 12.9 Hz, 1H), 4.14 (d, *J* = 14.9 Hz, 1H), 0.87 (s, 3H), 0.78 (s, 9H), 0.03 (s, 2H), -0.03 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 154.5, 144.0, 141.7, 139.3, 100.5, 94.8, 26.0, 18.2, -5.4.

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(1-methyl-1*H*-pyrazol-4-yl)vinyl)silanamine (3.2n)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 4-ethynyl-1-methyl-1*H*-pyrazole (0.0531 g) were added to a solution of the titanium complex (0.0087 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 18 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 85%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 7.55 (s, 1H), 6.73 (s, 1H), 6.47 (dd, *J* = 14.1, 13.7 Hz, 1H), 5.37 (d, *J* = 13.7 Hz, 1H), 3.33 (s, 3H), 3.25 (d, *J* = 14.1 Hz, 1H), 0.86 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 135.9, 132.3, 124.7, 121.6, 94.8, 38.3, 26.2, 18.5, -5.2.

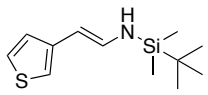
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(thiophen-2-yl)vinyl)silanamine (3.2o)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g)

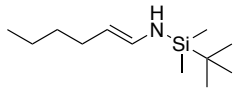
and 2-ethynylthiophene (0.0541 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 18 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 97%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 6.77 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.68-6.61 (m, 3H), 5.61 (d, *J* = 13.4 Hz, 1H), 2.97 (d, *J* = 13.6 Hz, 1H), 0.79 (s, 9H), -0.06 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 144.4, 134.4, 127.5, 120.1, 119.3, 99.3, 26.1, 18.3, -5.4.

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(thiophen-3-yl)vinyl)silanamine (3.2p)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 3-ethynylthiophene (0.0541 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 18 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 88%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 6.95 (d, *J* = 2.1 Hz, 2H), 6.60 (t, *J* = 2.1 Hz, 1H), 6.54 (dd, *J* = 13.7, 13.5 Hz, 1H), 5.48 (d, *J* = 13.5 Hz, 1H), 2.94 (d, *J* = 13.7 Hz, 1H), 0.82 (s, 9H), -0.02 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 141.1, 133.9, 125.4, 124.7, 114.8, 100.5, 26.2, 18.4, -5.2.

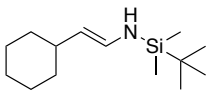
(*E*)-1-*tert*-butyl-*N*-(hex-1-en-1-yl)-1,1-dimethylsilanamine (3.2q)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and hex-1-yne (0.0411 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 24 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 63% (55% of enamine and 8% of imine). Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 5.95-5.88 (ddt, *J* = 13.2, 12.5, 1.0 Hz, 1H), 4.50 (dt, *J* = 13.2, 7.0 Hz, 1H), 2.64 (d, *J* = 12.5 Hz, 1H), 2.02-1.97 (m, 2H), 1.40-1.33 (m, 4H), 1.04-0.94 (m, 3H), 0.85 (s, 9H), -

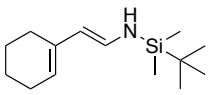
0.01 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 132.1, 103.4, 34.1, 30.4, 26.7, 26.3, 22.6, 14.3, -5.1. Note: other isomers could be present in the reaction mixture, which could explain the convoluted ^{1}H NMR and ^{13}C NMR spectra.

(*E*)-1-*tert*-butyl-*N*-(2-cyclohexylvinyl)-1,1-dimethylsilanamine (3.2r)



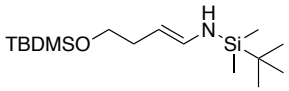
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylcyclohexane (0.0541 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 24 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 77% (68% of enamine and 9% imine). Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 6.02 (ddd, *J* = 13.3, 13.2, 0.9 Hz, 1H), 4.59 (dd, *J* = 13.3, 7.3 Hz, 1H), 2.71 (d, *J* = 13.2 Hz, 1H), 2.03-1.67 (m, 9H), 1.43-1.14 (m, 8H), 0.96 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 130.2, 110.3, 39.3, 35.4, 27.0, 26.8, 26.8, 26.8, 26.4, 18.7, -5.1. Note: other isomers could be present in the reaction mixture, which could explain the convoluted ^{1}H NMR and ^{13}C NMR spectra.

(*E*)-1-*tert*-butyl-*N*-(2-(cyclohex-1-en-1-yl)vinyl)-1,1-dimethylsilanamine (3.2s)



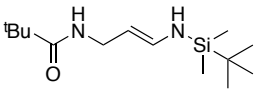
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynylcyclohex-1-ene (0.0531 g) were added to a solution of the titanium complex (0.0087 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 8 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 94%. Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 6.15 (dd, *J* = 13.5, 13.4 Hz, 1H), 5.46 (t, *J* = 3.6 Hz, 1H), 5.37 (d, *J* = 13.5 Hz, 1H), 2.82 (d, *J* = 13.4 Hz, 1H), 2.14-2.09 (m, 4H), 1.64-1.53 (m, 4H), 0.84 (s, 9H), -0.00 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 135.2, 129.9, 119.3, 110.2, 26.3, 26.2, 25.5, 23.6, 23.4, 18.6, -5.2.

(*E*)-1-*tert*-butyl-*N*-(4-((*tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)-1,1-dimethylsilanamine (3.2t)



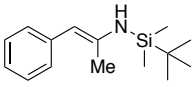
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (0.0922 g) were added to a solution of the titanium complex (0.0087 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 8 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 76% (69% of enamine and 7% of imine). Characterization was performed *in situ* - **^{1}H NMR** (400 MHz; C_6D_6): δ 5.92 (dd, *J* = 13.3, 13.1 Hz, 1H), 4.48 (dt, *J* = 13.3, 7.0 Hz, 1H), 3.56 (t, *J* = 7.0 Hz, 2H), 2.69 (d, *J* = 13.1 Hz, 1H), 2.24-2.17 (m, 2H), 0.97 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), -0.03 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 133.7, 99.2, 65.0, 34.5, 26.3, 26.3, 18.6, 18.6, -4.9, -5.1.

(*E*)-*N*-(3-((*tert*-butyldimethylsilyl)amino)allyl)pivalamide (3.2u)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and *N*-(prop-2-yn-1-yl)pivalamide (0.0696 g) were added to a solution of the titanium complex (0.0087 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 3 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was >99% (85% of (*E*)-isomer and 14% (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 6.05 (dd, *J* = 14.4, 7.7 Hz, 1H), 5.97 (t, *J* = 5.9 Hz, 1H), 5.27 (d, *J* = 14.4 Hz, 1H), 4.30 (q, *J* = 7.7 Hz, 1H), 3.80 (dd, *J* = 7.7, 5.9 Hz, 2H), 1.06 (s, 9H), 0.94 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 178.2, 136.7, 96.5, 38.6, 34.7, 27.8, 26.3, 18.5, -5.1.

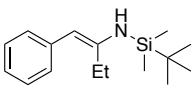
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(1-phenylprop-1-en-2-yl)silanamine (3.2v)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g)

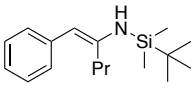
and prop-1-yn-1-ylbenzene (0.0581 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 110 °C for 6 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 84% (82% of (*E*)-isomer and 2% (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 7.26-7.21 (m, 4H), 7.07-7.03 (m, 1H), 5.75 (s, 1H), 2.49 (s, 1H), 1.81 (s, 3H), 0.94 (s, 9H), 0.20 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 142.3, 140.3, 128.8, 128.4, 124.4, 104.0, 26.7, 20.5, 18.2, -3.8. Note: by heating the reaction solution for extended time at 110 °C, the conversion between (*E*)- and (*Z*)-isomer occurs and the (*Z*)-isomer can be characterized. (*Z*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 7.39-7.37 (m, 2H), 7.20-7.19 (m, 2H), 7.00-6.96 (m, 1H), 5.24 (s, 1H), 4.46 (s, 1H), 1.86 (s, 3H), 0.83 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 141.7, 139.7, 129.1, 128.1, 124.9, 102.3, 26.5, 23.6, 17.7, -2.5.

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(1-phenylbut-1-en-2-yl)silanamine (3.2w)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and prop-1-yn-1-ylbenzene (0.0651 g) were added to a solution of the titanium complex (0.0348 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 110 °C for 24 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 74% (73% of (*E*)-isomer and <1% (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 7.34-7.28 (m, 4H), 7.15-7.10 (m, 1H), 5.84 (s, 1H), 2.44 (s, 1H), 2.29 (q, *J* = 7.6 Hz, 2H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.04 (s, 9H), 0.30 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 147.6, 140.1, 131.9, 128.6, 128.5, 124.6, 103.6, 26.8, 18.2, 13.4, -4.0.

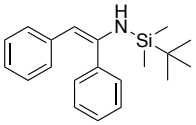
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(1-phenylpent-1-en-2-yl)silanamine (3.2x)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and pent-1-yn-1-ylbenzene (0.0721 g) were added to a solution of the titanium

complex (0.0348 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 110 °C for 24 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 74% (72% of (*E*)-isomer and 2% (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; C_6D_6): δ 7.21-7.19 (m, 4H), 7.05-6.99 (m, 1H), 5.77 (s, 1H), 2.39 (s, 1H), 2.21-2.17 (m, 2H), 1.51-1.45 (m, 2H), 0.94 (s, 9H), 0.91-0.88 (m, 3H), 0.21 (s, 6H). **^{13}C NMR** (101 MHz; C_6D_6): δ 146.2, 140.1, 128.8, 128.4, 124.6, 104.1, 35.4, 26.8, 22.1, 18.2, 14.0, -4.0.

(*E*)-1-*tert*-butyl-*N*-(1,2-diphenylvinyl)-1,1-dimethylsilanamine (3.2y)



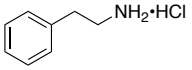
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1,2-diphenylethyne (0.0891 g) were added to a solution of the titanium complex (0.0348 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 145 °C for 48 hours. Upon full disappearance of starting material, the obtained ^{1}H NMR yield was 87% (79% of (*E*)-isomer and 8% (*Z*)-isomer). Characterization was performed *in situ* – (*E*)-isomer: **^{1}H NMR** (400 MHz; d_8-Tol): δ 7.39-7.37 (m, 2H), 7.08-7.06 (m, 3H), 6.97-6.93 (m, 4H), 6.86-6.83 (m, 1H), 5.97 (s, 1H), 2.83 (s, 1H), 0.93 (s, 9H), 0.19 (s, 6H). **^{13}C NMR** (101 MHz; d_8-Tol): δ 145.8, 141.3, 131.8, 129.6, 128.7, 128.6, 128.3, 128.0, 124.3, 105.5, 26.6, 18.0, -4.1.

General Procedure for the Sequential Hydroamination/Hydrogenation Synthesis of Primary Amines

Inside an inert atmosphere box, d_6-benzene (0.15 mL) was added to the titanium complex (0.005-0.05 mmol, 1-10 mol% Ti) in a 5-dram vial and the solution was transferred to a J-Young tube. The amine (0.5 mmol, 1 equiv.) and alkyne (0.5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the J-Young tube. The remaining benzene (0.35 mL) was used to

rinse the vials containing amine and alkyne, which were also transferred to the reaction tube. The J-Young tube was sealed, taken out of the inert atmosphere box and a time zero ^{1}H NMR spectrum was obtained. The reaction solution was heated at 70-145 °C depending on the starting materials used. A ^{1}H NMR spectrum was obtained after 6-72 hours of heating and full consumption of starting materials was observed. The reaction tube was cooled and brought into the inert atmosphere box, where the reaction solution was transferred to a Radley's parallel reactor tube using d_6-benzene (0.5 mL). Pd/C (0.0125 mmol, 2.5 mol% Pd) was added to the reaction tube, which was then sealed with the Radley's parallel reactor cap. The system was removed from the inert atmosphere box and attached to a Schlenk line. After evacuating and refilling the tubing with N_2, H_2 was introduced to the reaction flask at 1 atm. The reaction was allowed to proceed at room temperature for 40 hours. The crude compound was filtered through a short plug of Celite using ethyl acetate. To the filtrate was added 1M HCl in ether (1 mmol, 2 equiv.) and the hydrochloride amine salts were filtered using a Büchner funnel. If a mixture of primary to secondary amine were obtained, sublimation under reduced pressure was performed to isolate the primary amine salt.

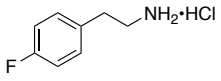
2-phenylethan-1-amine hydrochloride salt (3.3a)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of palladium (0.0133 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, a mixture of 95:5 of primary to secondary amine was obtained in 82% yield. Purification by sublimation afforded the title

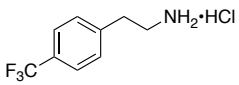
compound as a colourless powder in 75% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.46-7.41 (m, 2H), 7.39-7.31 (m, 3H), 3.30 (t, *J* = 7.3 Hz, 2H), 3.02 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 136.7, 129.1, 128.9, 127.4, 40.6, 32.8. **HRMS** (ESI+) m/z calc'd for $C_8H_{12}N$ [$M+H^+$]: 122.0970; found: 122.0964.

2-(4-fluorophenyl)ethan-1-amine hydrochloride salt (3.3b)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-fluorobenzene (0.0601 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of palladium (0.0133 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, a mixture of 92:8 of primary to secondary amine was obtained in 71% yield. Purification by sublimation afforded the title compound as a colourless powder in 65% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.36-7.31 (m, 2H), 7.18-7.12 (m, 2H), 3.28 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 1612.0 (d, $^{1}J(C,F)$ = 242.4 Hz), 132.4 (d, $^{3}J(C,F)$ = 3.0 Hz), 130.6, 130.5, 115.7 (d, $^{2}J(C,F)$ = 21.6 Hz), 40.6, 32.0. **HRMS** (ESI+) m/z calc'd for $C_8H_{11}NF$ [$M+H^+$]: 140.0876; found: 140.0881.

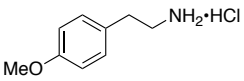
2-(4-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride salt (3.3c)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-(trifluoromethyl)benzene (0.0851 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of

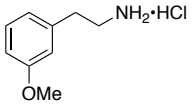
palladium (0.0133 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, a mixture of >99:1 of primary to secondary amine was obtained in 81%. Purification by sublimation afforded the title compound as a colourless powder in 81% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.1 Hz, 2H), 3.33 (t, *J* = 7.4 Hz, 2H), 3.09 (t, *J* = 7.4 Hz, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 141.0, 129.4, 128.8 (q, $^{2}J(C,F)$ = 32.2Hz), 125.8 (q, $^{3}J(C,F)$ = 3.7Hz), 124.2 (q, $^{1}J(C,F)$ = 250.3Hz), 40.2, 32.6. **HRMS** (ESI+) m/z calc'd for $C_9H_{11}NF_3$ [M+H$^+$]: 190.0844; found: 190.0846.

2-(4-methoxyphenyl)ethan-1-amine hydrochloride salt (3.3d)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of palladium (0.0133 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, a mixture of 95:5 of primary to secondary amine was obtained in 70%. Purification by sublimation afforded the title compound as a colourless powder in 65% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 3.25 (t, *J* = 7.3 Hz, 2H), 2.95 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 158.0, 130.2, 129.1, 114.5, 55.4, 40.7, 31.9. **HRMS** (ESI+) m/z calc'd for $C_9H_{14}NO$ [M+H$^+$]: 152.1075; found: 152.1081.

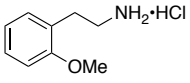
2-(3-methoxyphenyl)ethan-1-amine hydrochloride salt (3.3e)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-3-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel

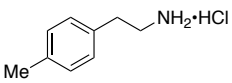
was heated at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of palladium (0.0133 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, a mixture of 74:26 of primary to secondary amine was obtained in 84% yield. Purification by sublimation afforded the title compound as a colourless powder in 59% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.40-7.34 (m, 1H), 6.98-6.94 (m, 3H), 3.84 (s, 3H), 3.29 (t, *J* = 7.3 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 159.2, 138.4, 130.3, 121.7, 114.6, 112.8, 55.4, 40.5, 32.8. **HRMS** (ESI+) m/z calc'd for $C_9H_{14}NO$ [$M+H^+$]: 152.1075; found: 152.1071.

2-(2-methoxyphenyl)ethan-1-amine hydrochloride salt (3.3f)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-2-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of palladium (0.0133 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, a mixture of >99:1 of primary to secondary amine was obtained in 85% yield. Purification by sublimation afforded the title compound as a colourless powder in 84% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.37 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.09 (dd, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 7.5, 7.4 Hz, 1H), 3.87 (s, 3H), 3.25 (t, *J* = 7.0 Hz, 2H), 3.00 (t, *J* = 7.0 Hz, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 157.5, 130.9, 129.1, 124.8, 121.2, 111.5, 55.4, 39.7, 27.9. **HRMS** (ESI+) m/z calc'd for $C_9H_{14}NO$ [$M+H^+$]: 152.1075; found: 152.1077.

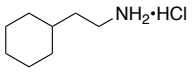
2-(*p*-tolyl)ethan-1-amine hydrochloride salt (3.3g)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g)

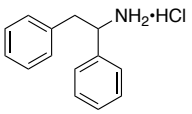
and 1-ethynyl-4-methylbenzene (0.0581 g) were added to a solution of the titanium complex (0.0035 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 6 hours. Upon completion and salt formation using hydrochloric acid, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 2.5 mol% of palladium (0.0133 g) in 40 hours. Upon deprotection, a mixture of 96:4 of primary to secondary amine was obtained in 90% yield. Purification by sublimation afforded the title compound as a colourless powder in 73% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.25 (q, *J* = 6.3 Hz, 4H), 3.26 (t, *J* = 7.4 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 2.33 (s, 3H). **^{13}C NMR** (101 MHz; D_2O): δ 137.5, 133.5, 129.7, 128.9, 40.7, 32.4, 20.1. **HRMS** (ESI+) m/z calc'd for $C_9H_{14}N$ [$M+H^+$]: 136.1126; found: 136.1128.

2-cyclohexylethan-1-amine hydrochloride salt (3.3h)



According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylcyclohexane (0.0541 g) were added to a solution of the titanium complex (0.0174 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 70 °C for 24 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 5 mol% of palladium (0.0266 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, the title compound was obtained as a colourless powder in 70% yield. **^{1}H NMR** (400 MHz; D_2O): δ 3.09-3.05 (m, 2H), 1.75-1.57 (m, 7H), 1.44-1.18 (m, 4H), 1.03-0.94 (m, 2H). **^{13}C NMR** (101 MHz; D_2O): δ 37.7, 34.4, 34.2, 32.4, 26.1, 25.8. **HRMS** (ESI+) m/z calc'd for $C_8H_{11}NF$ [$M+H^+$]: ; found:.

1,2-diphenylethan-1-amine hydrochloride salt (3.3i)

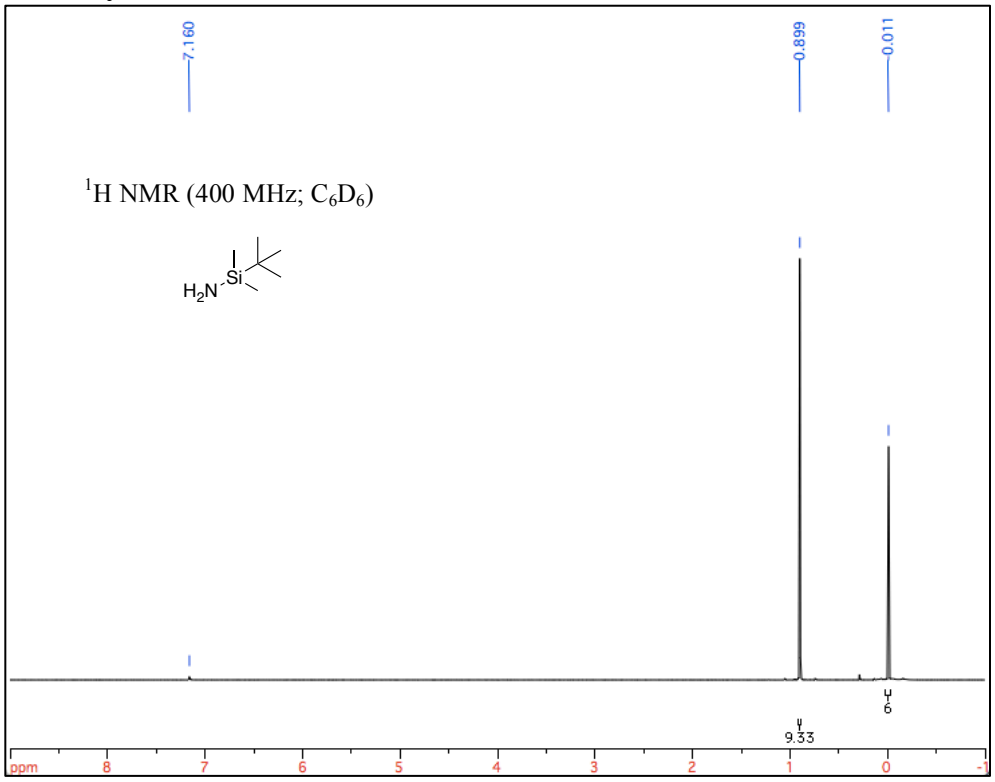


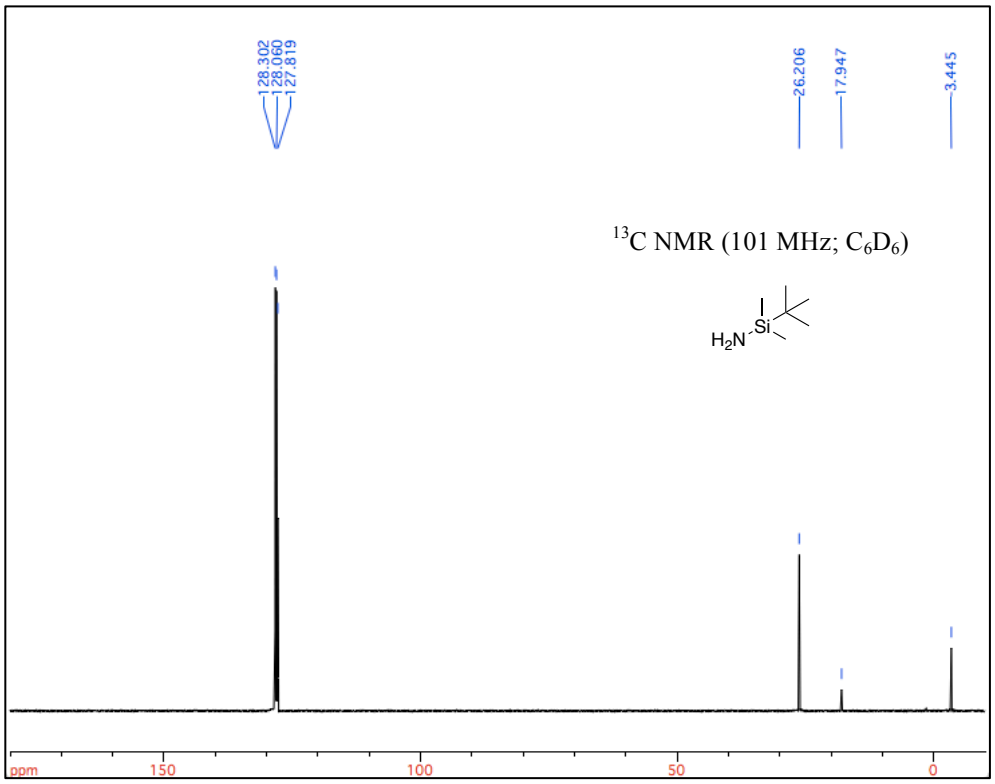
According to the general procedure, *tert*-butyldimethylsilanamine (0.0656 g) and 1,2-diphenylethyne (0.0891 g) were added to a solution of the titanium

complex (0.0348 g) in benzene and transferred to a J-Young tube. The reaction vessel was heated at 145 °C for 48 hours. Upon completion, the hydrogenation was set-up following the general procedure. Fully hydrogenated product was obtained using 5 mol% of palladium (0.0266 g) in 40 hours. Upon deprotection and salt formation using hydrochloric acid, the title compound was obtained as a colourless powder in 77% yield. **^{1}H NMR** (400 MHz; D_2O): δ 7.46-7.39 (m, 5H), 7.34-7.26 (m, 3H), 7.22-7.19 (m, 2H), 4.65 (dd, *J* = 8.6, 7.0 Hz, 1H), 3.37 (dd, *J* = 13.8, 7.0 Hz, 1H), 3.30 (dd, *J* = 13.8, 8.6 Hz, 1H). **^{13}C NMR** (101 MHz; D_2O): δ 135.7, 135.6, 129.4, 129.3, 129.2, 128.9, 127.4, 127.3, 56.7, 39.8. **HRMS** (ESI+) m/z calc'd for $C_{14}H_{16}N$ $[M+H^+]$: 198.1283; found: 198.1281.

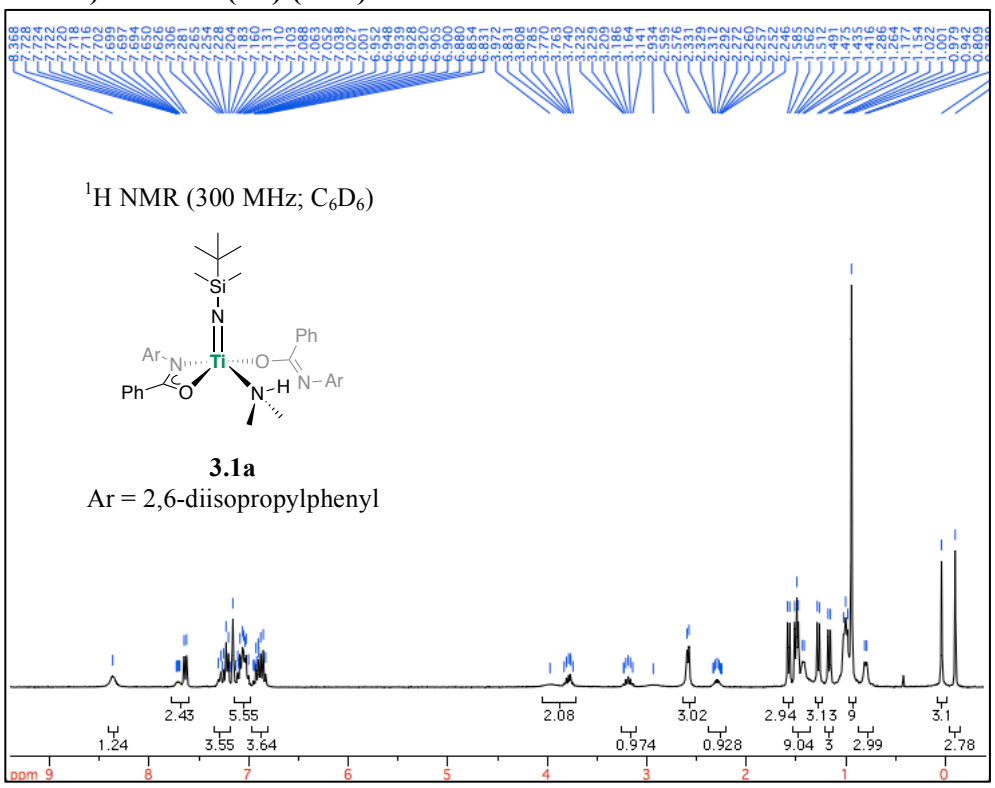
B.5 NMR Spectra

Tert-butyldimethylsilanamine





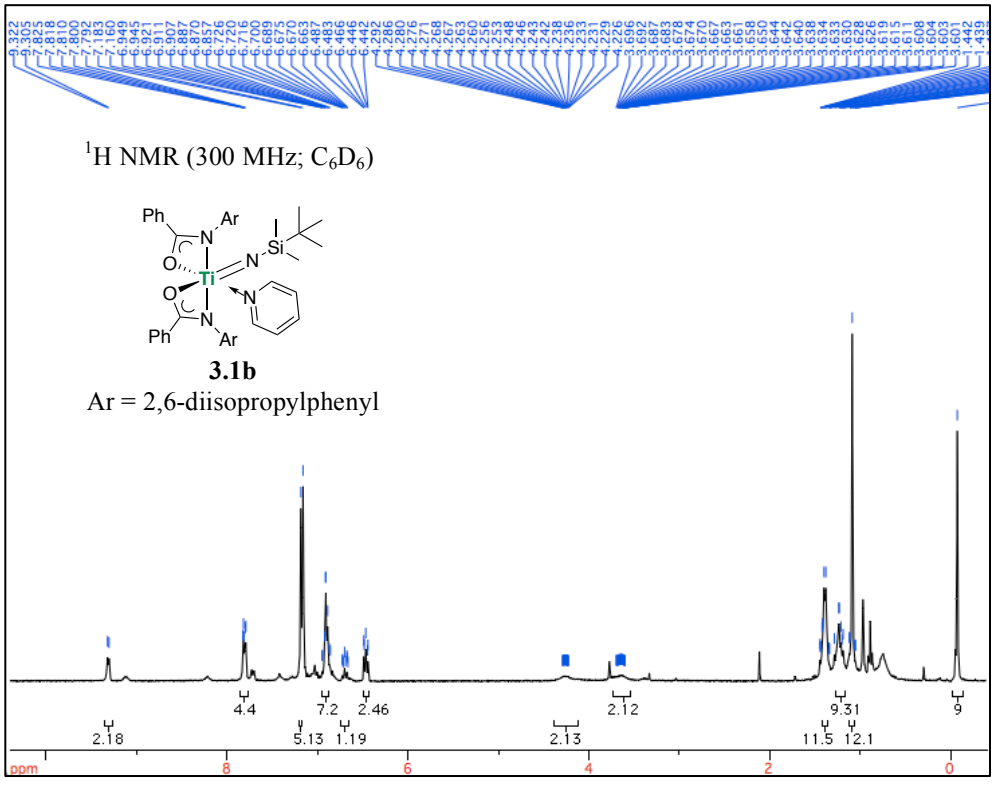
Bis(*N*-2,6-diisopropylphenylbenzamidate)(*tert*-butyldimethylsilylimido) (dimethylamido)titanium (IV) (3.1a)



3.1a

Ar = 2,6-diisopropylphenyl

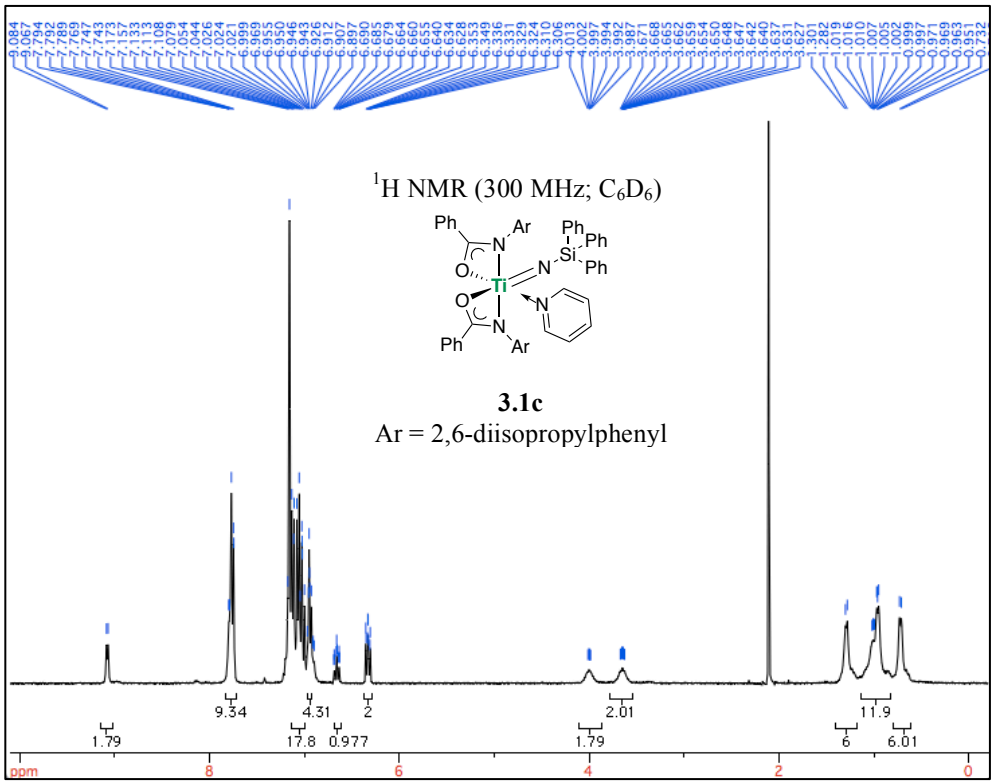
Bis(*N*-2,6-diisopropylphenylbenzamidate)(*tert*-butyldimethylsilylimido)(pyridino) titanium (IV) (3.1b)



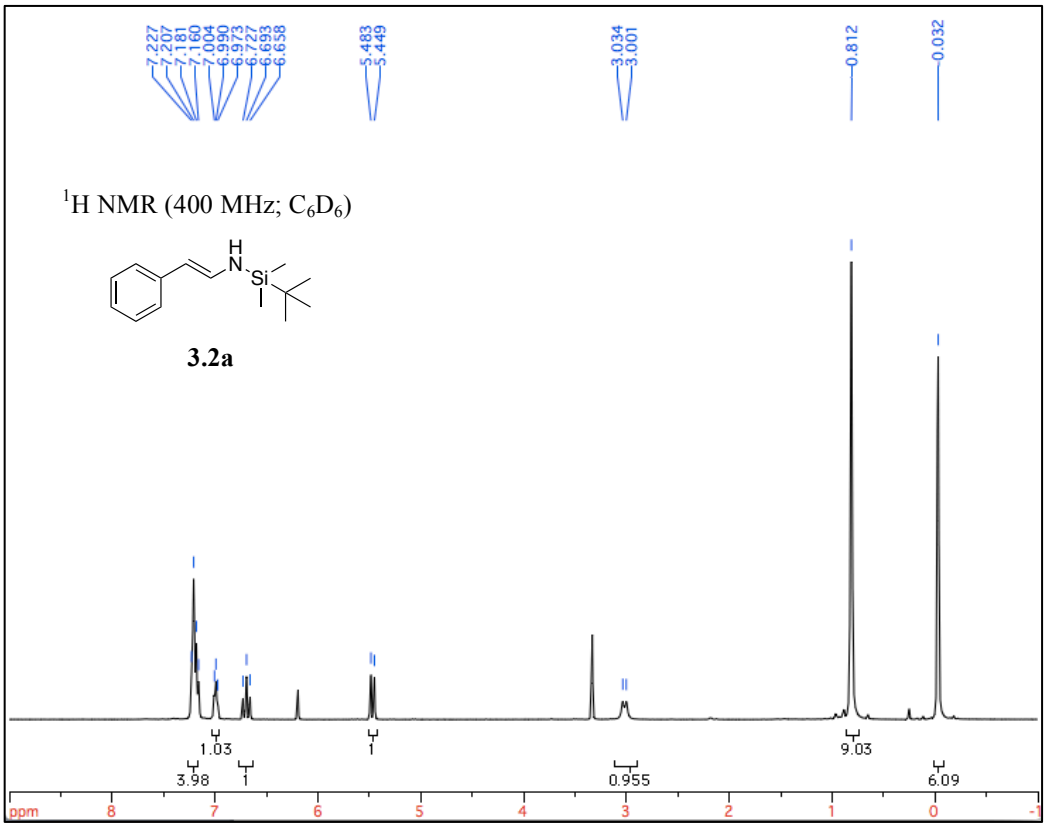
3.1b

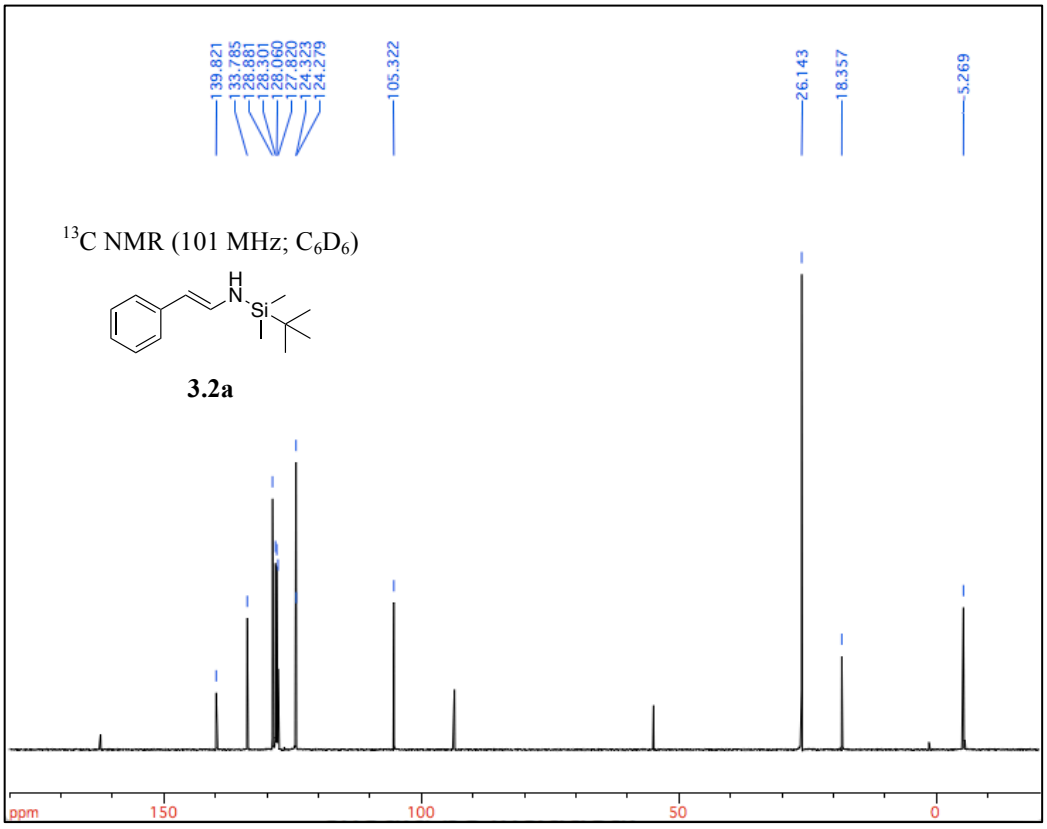
Ar = 2,6-diisopropylphenyl

Bis(*N*-2,6-diisopropylphenylbenzamidate)(triphenylsilylimido)(pyridino) titanium (IV) (3.1c)

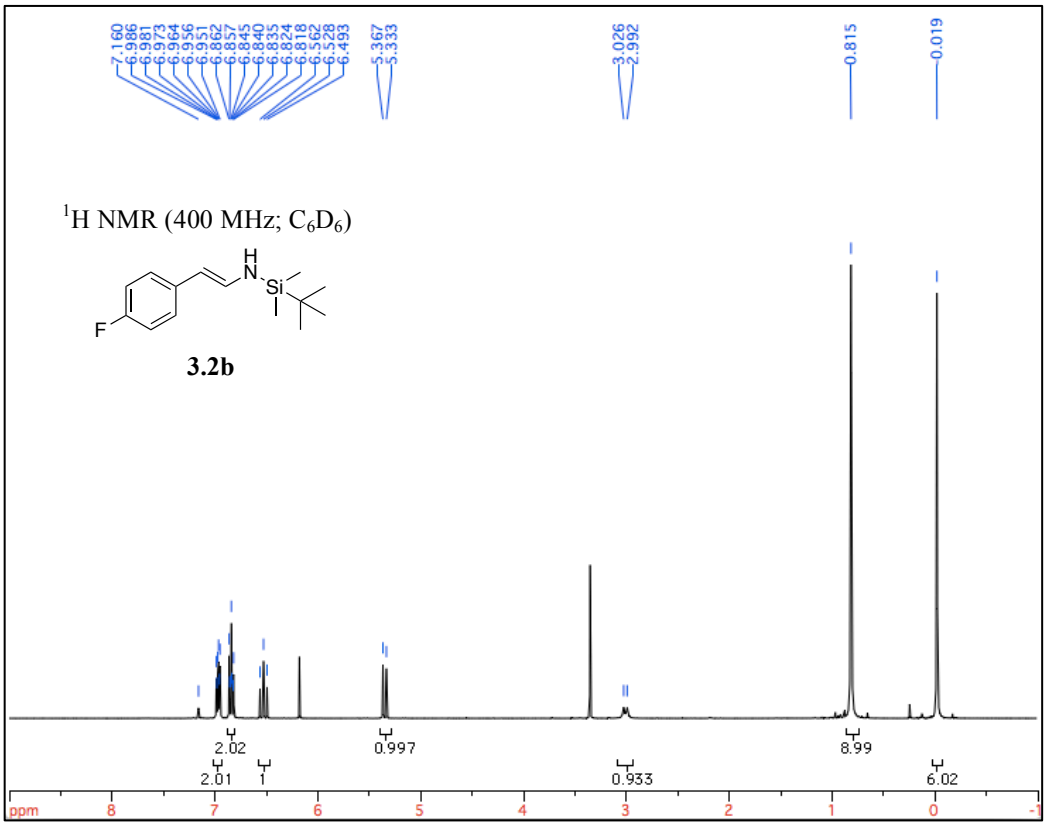


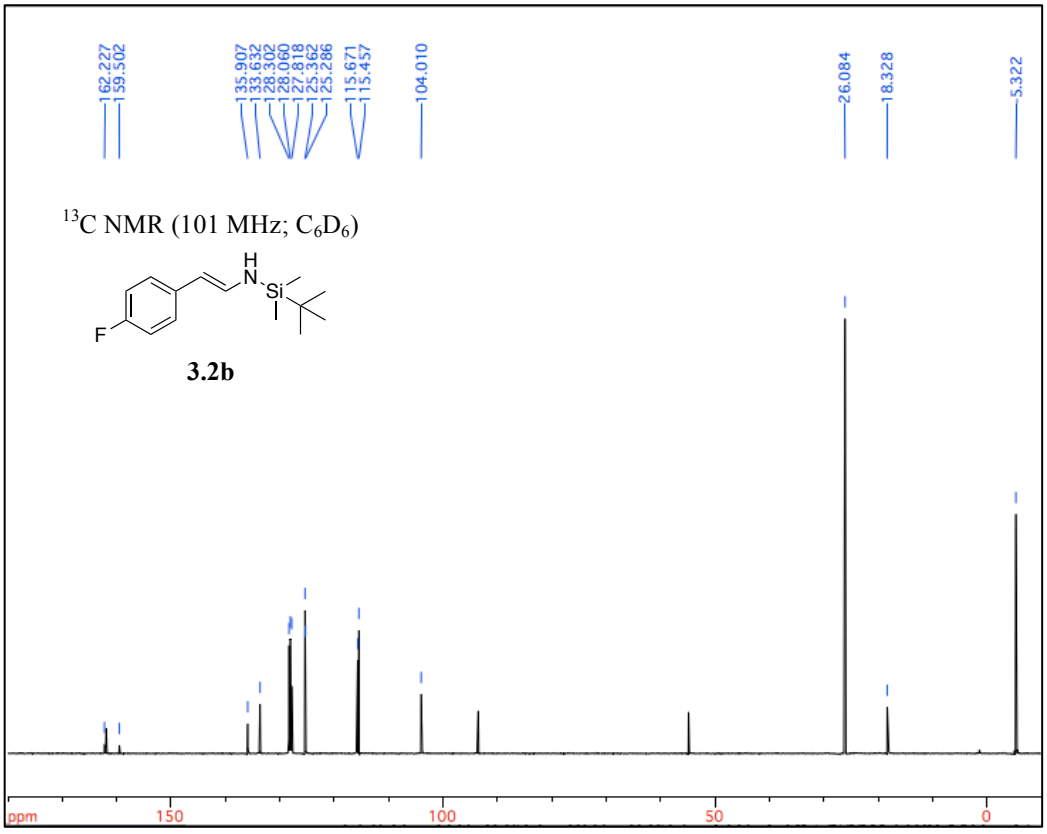
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-styrylsilanamine (3.2a)



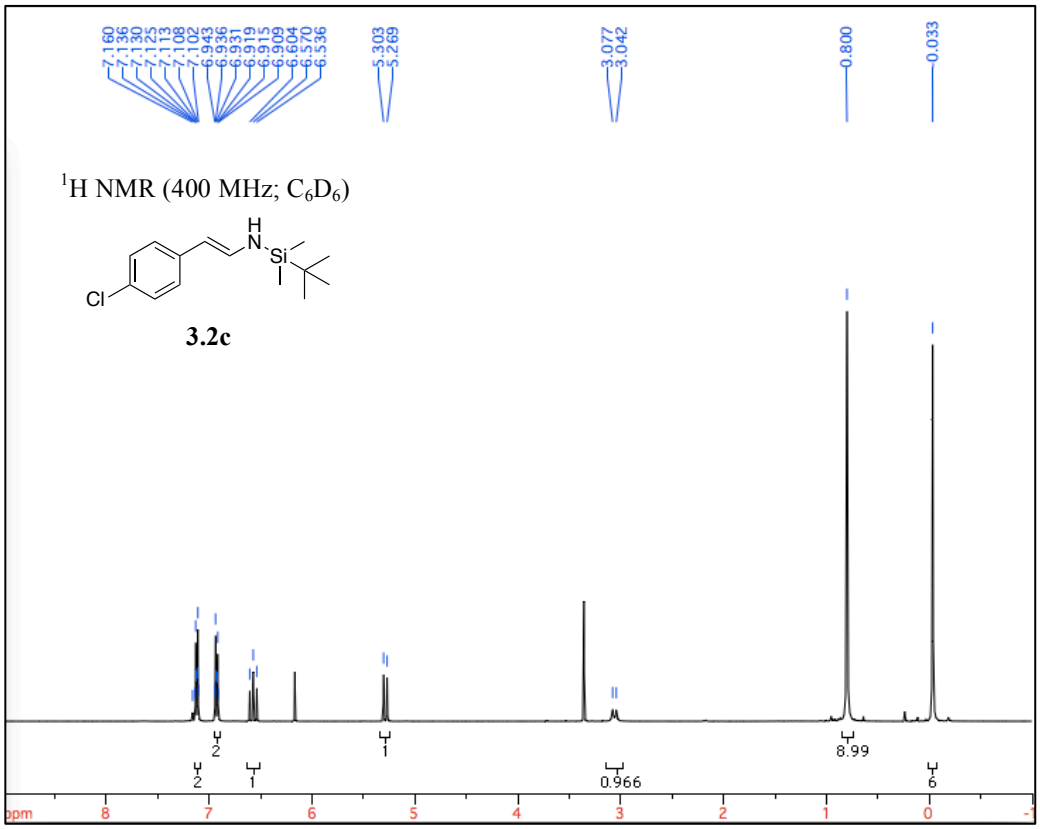


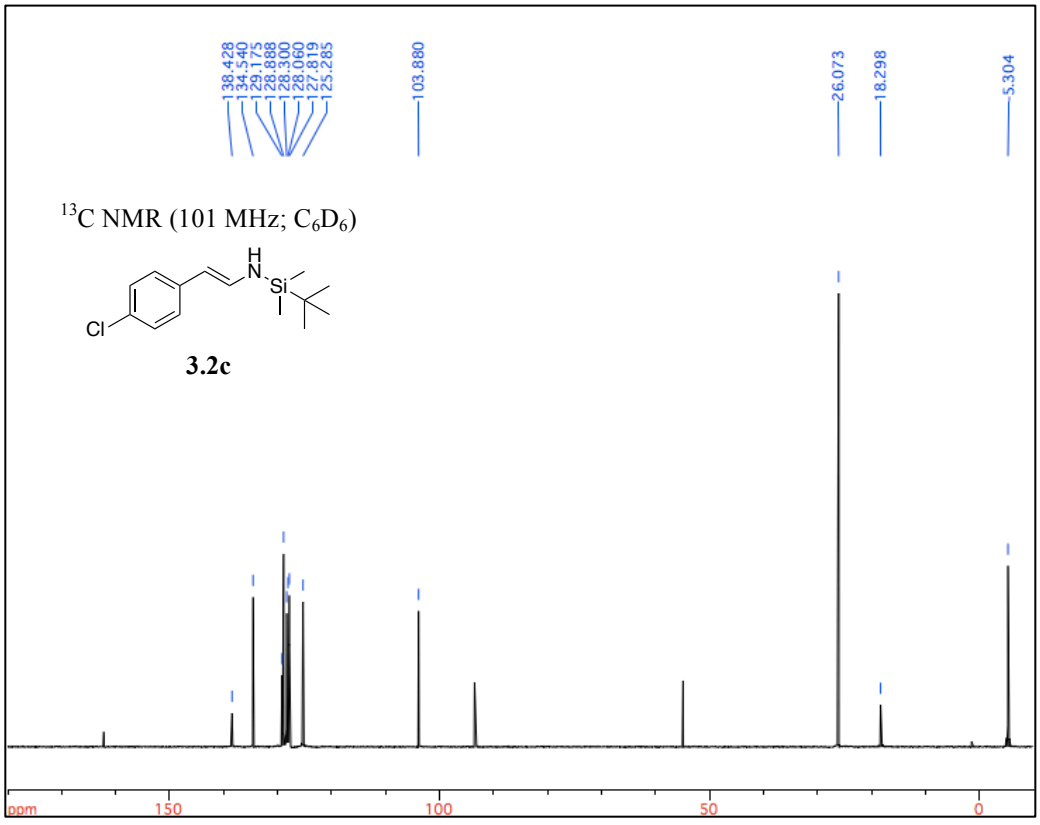
(*E*)-1-*tert*-butyl-*N*-(4-fluorostyryl)-1,1-dimethylsilanamine (3.2b)



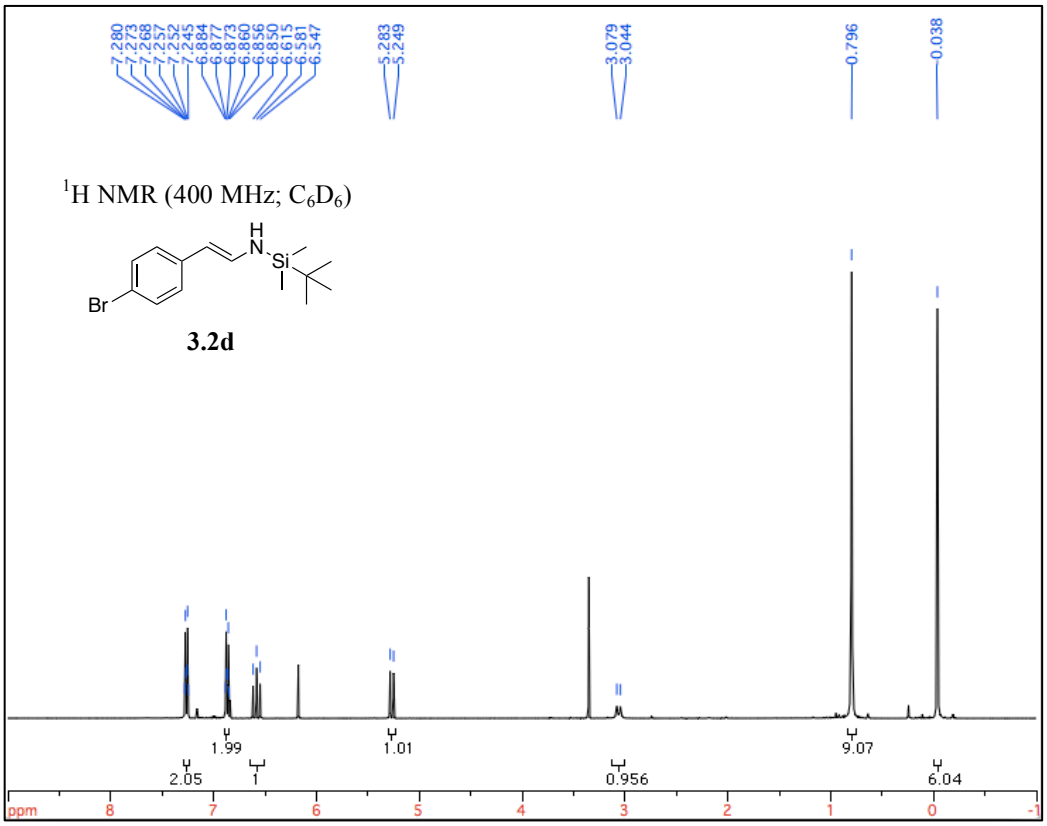


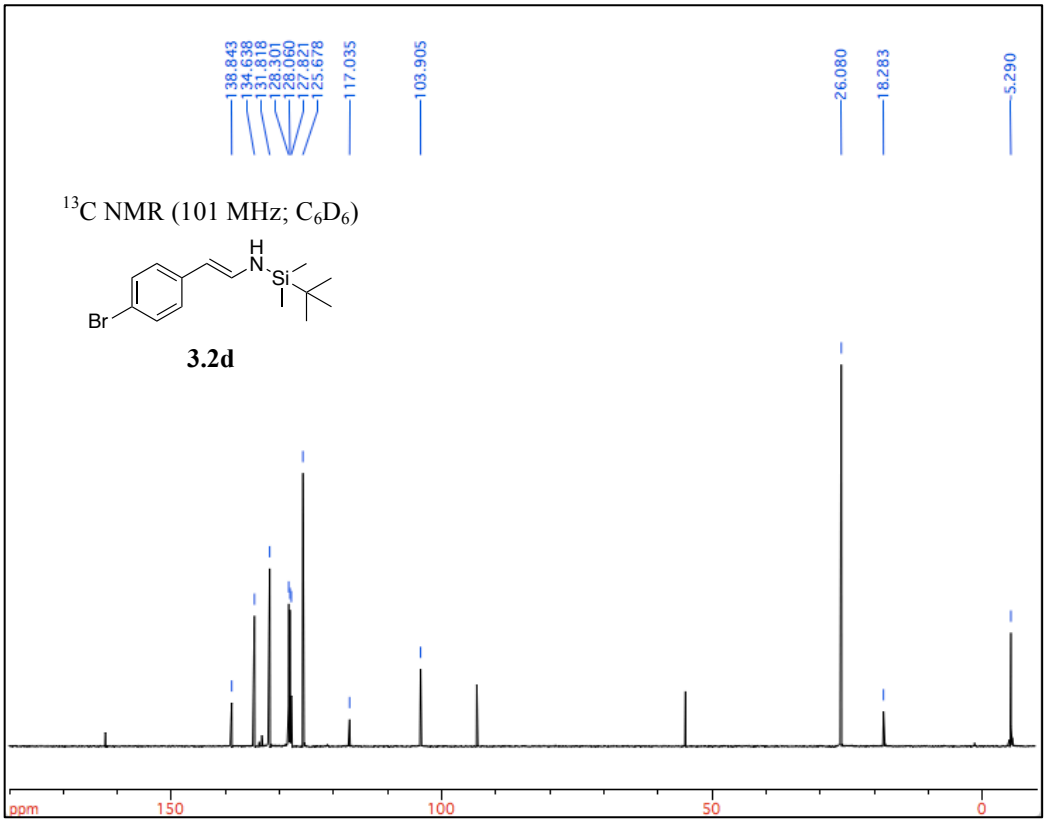
(*E*)-1-*tert*-butyl-*N*-(4-chlorostyryl)-1,1-dimethylsilanamine (3.2c)



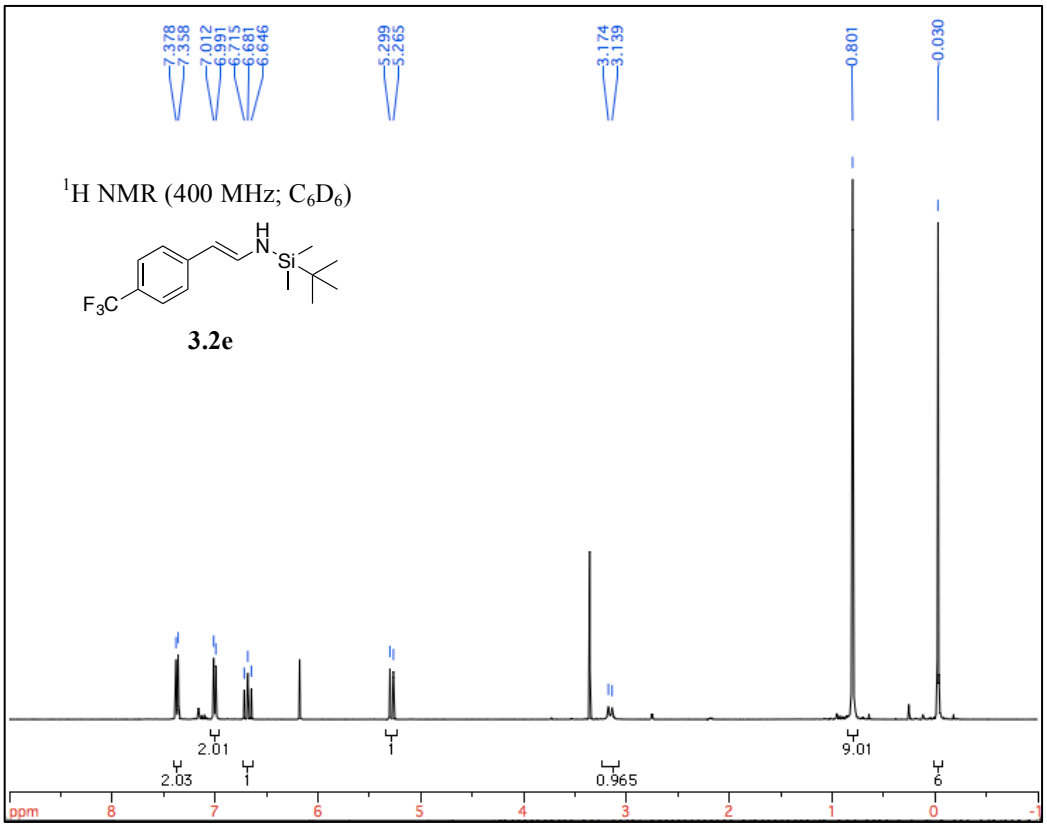


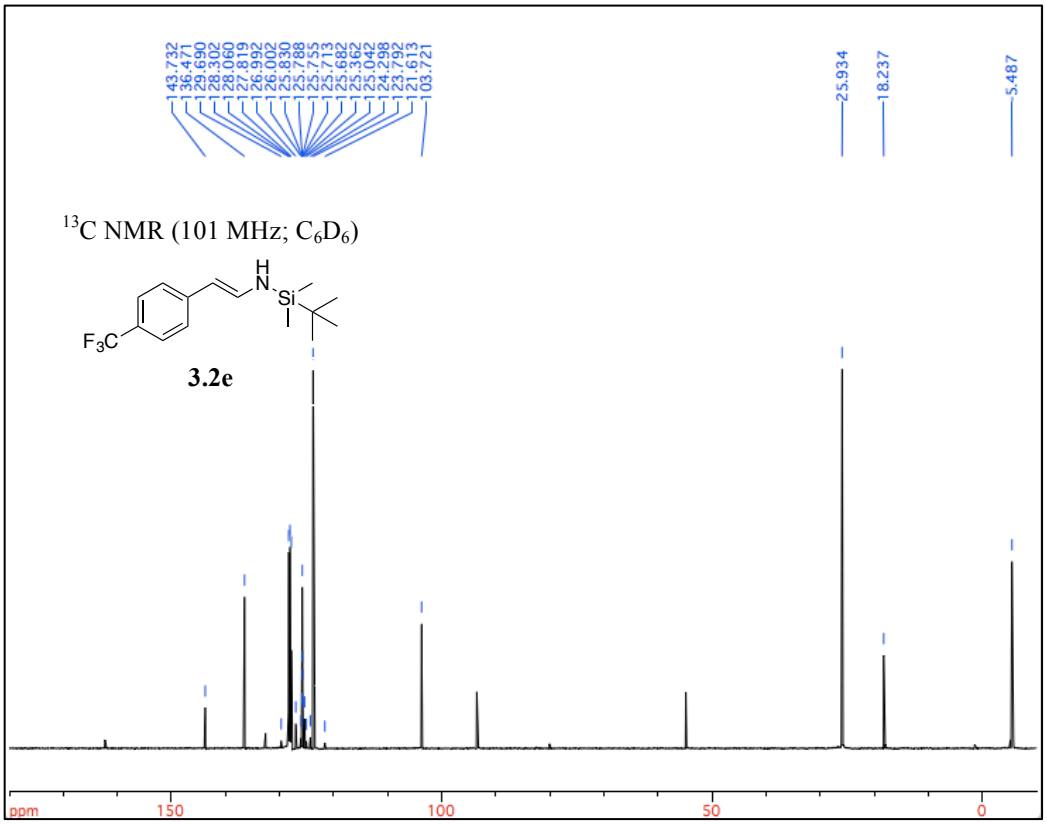
(*E*)-1-*tert*-butyl-*N*-(4-chlorostyryl)-1,1-dimethylsilanamine (3.2d)



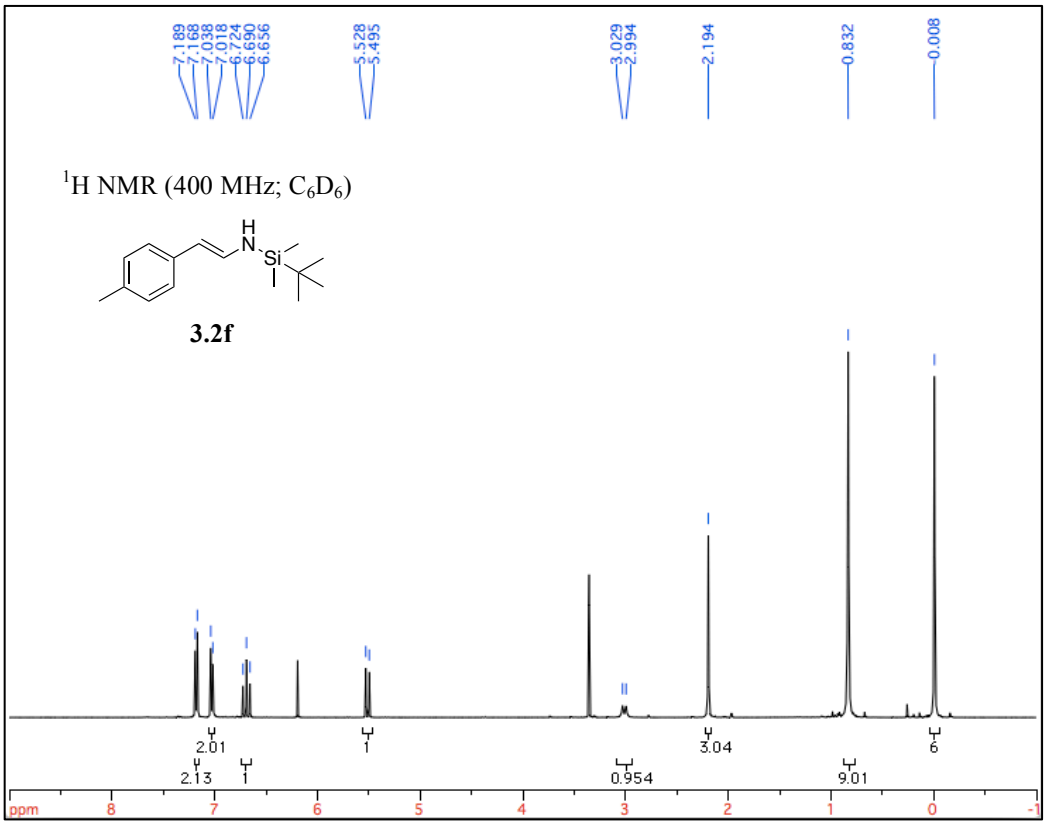


(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(4-(trifluoromethyl)styryl)silanamine (3.2e)



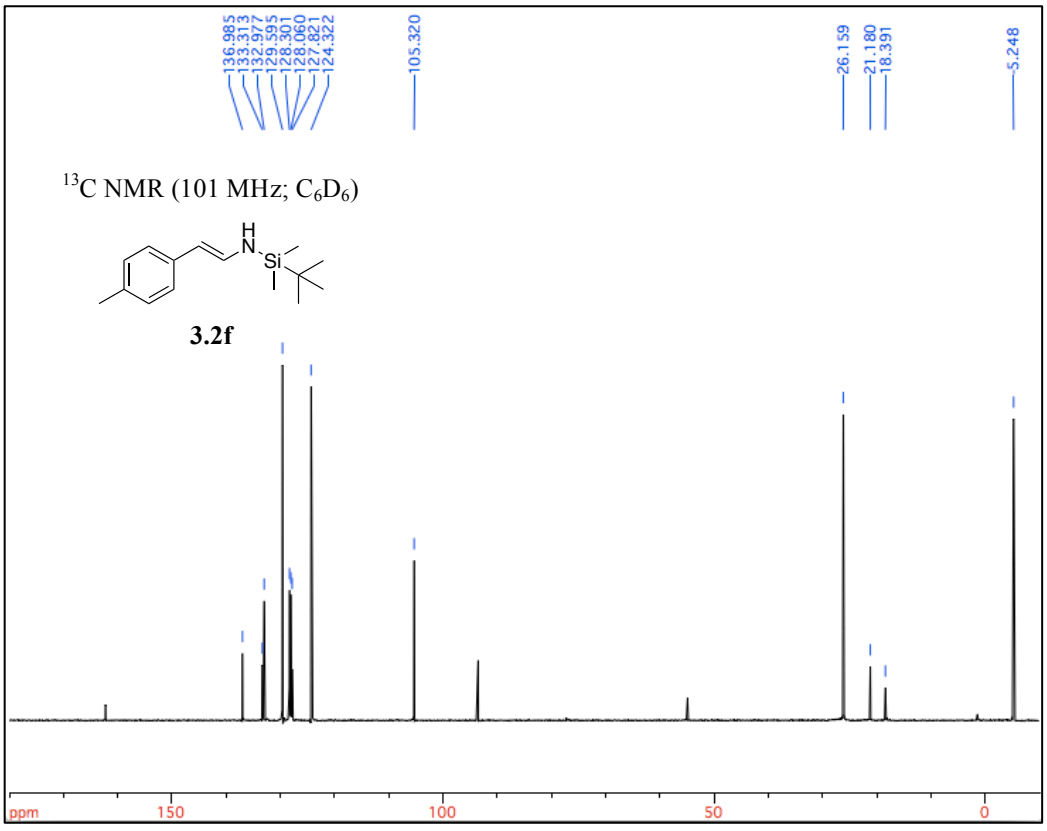


(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(4-methylstyryl)silanamine (3.2f)



^{1}H NMR (400 MHz; C_6D_6)

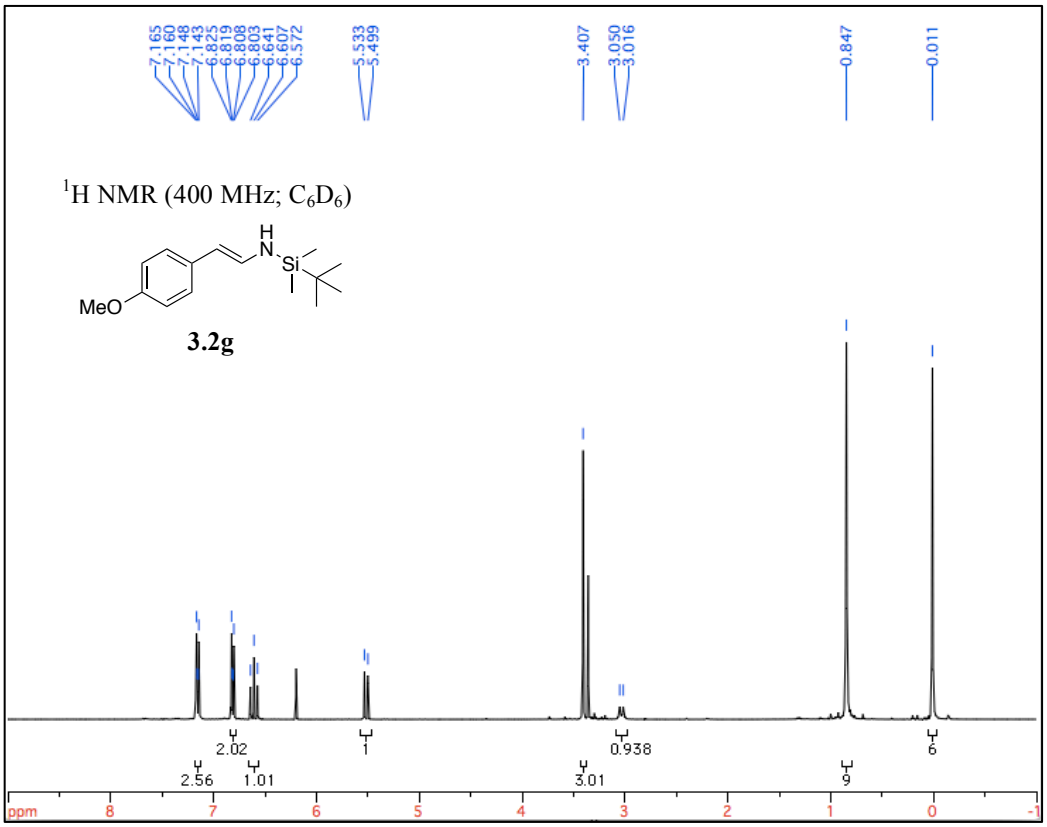
3.2f

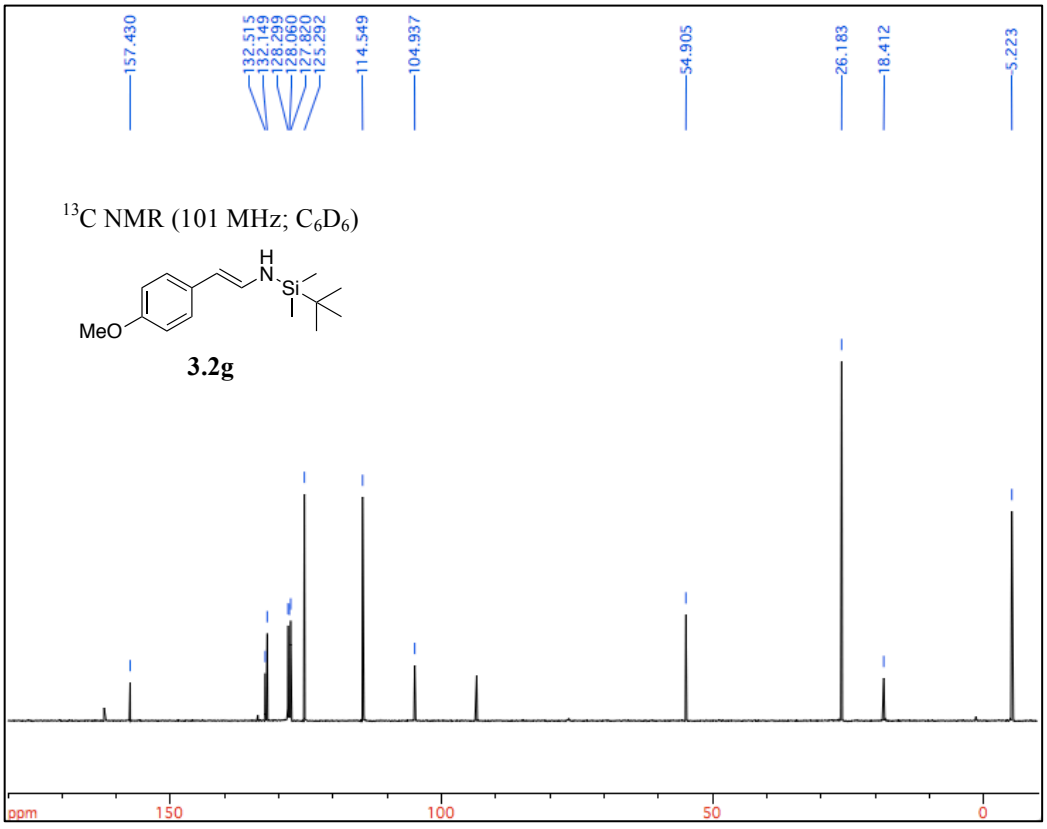


^{13}C NMR (101 MHz; C_6D_6)

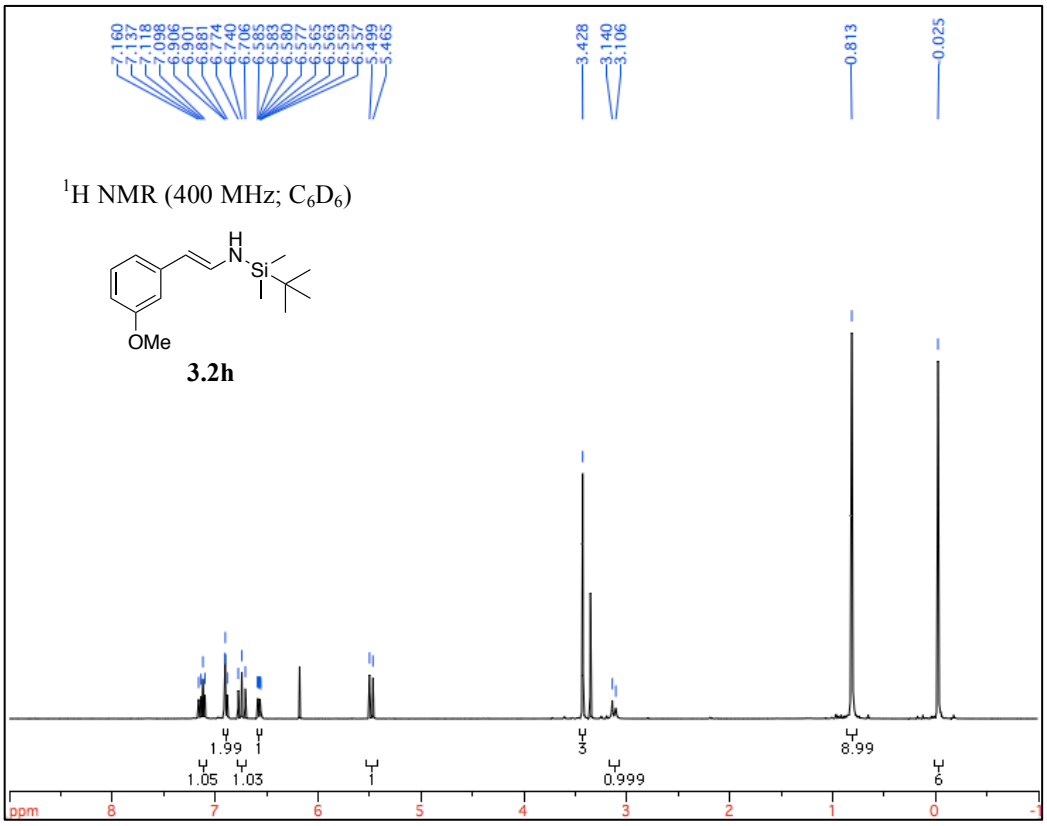
3.2f

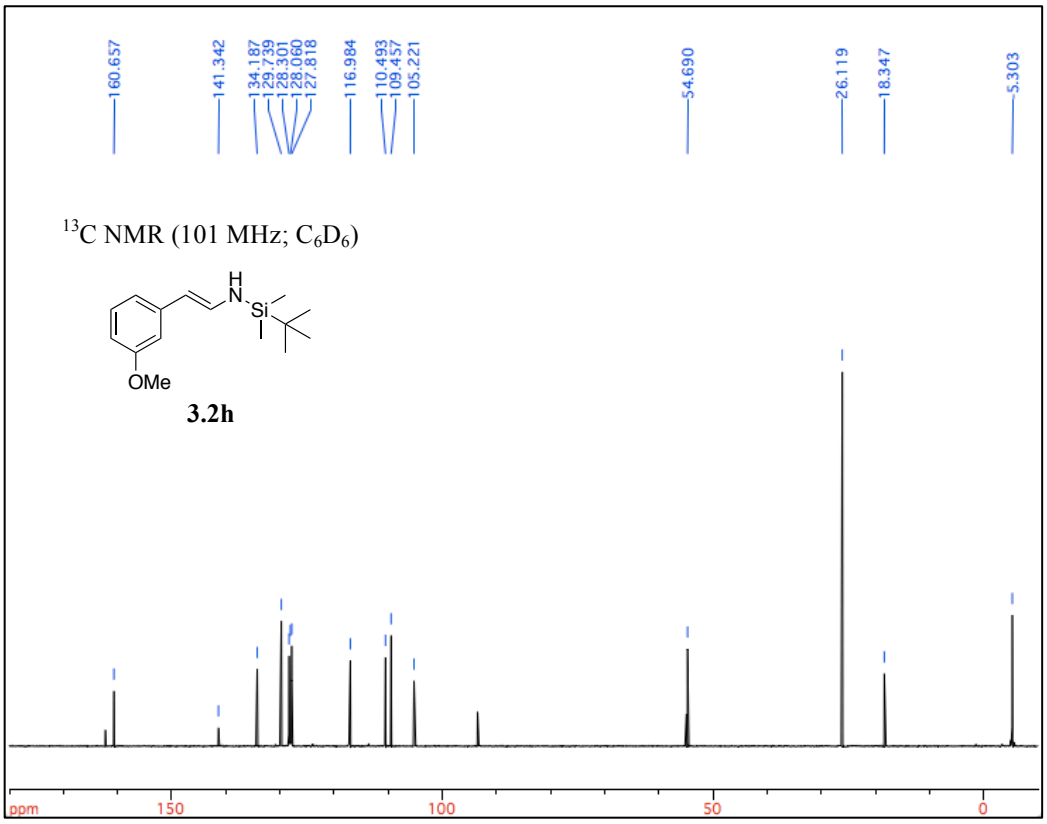
(*E*)-1-*tert*-butyl-*N*-(4-methoxystyryl)-1,1-dimethylsilanamine (3.2g)



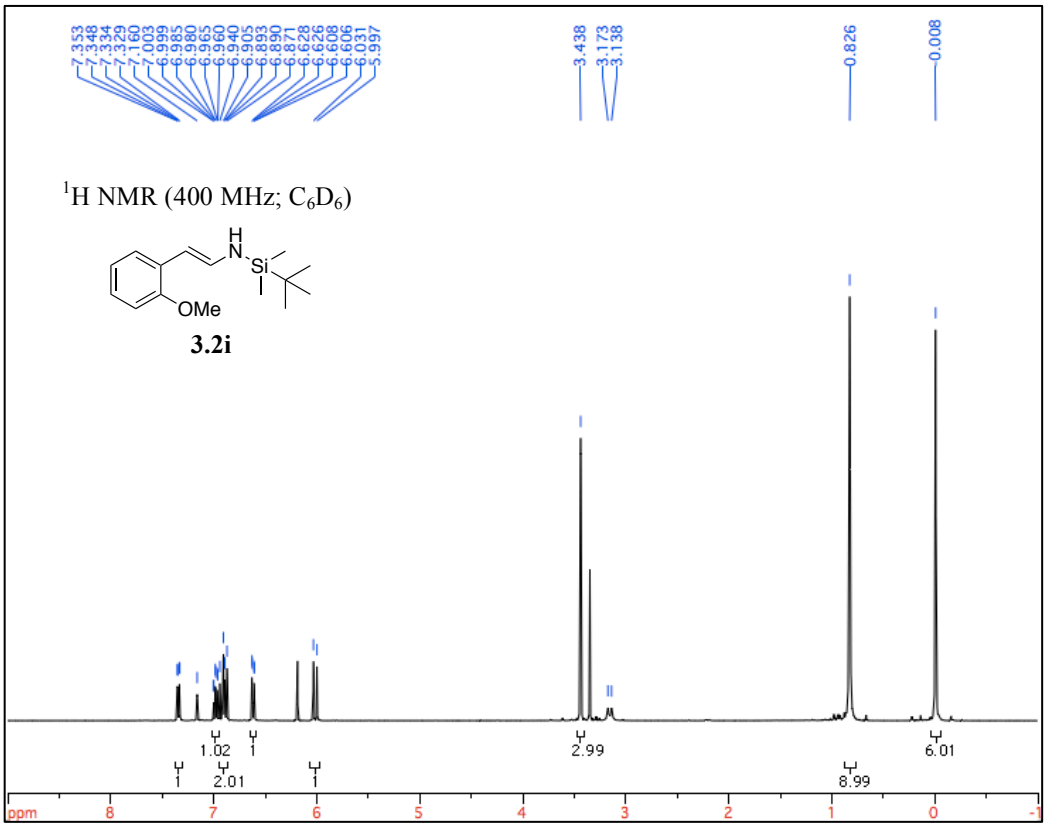


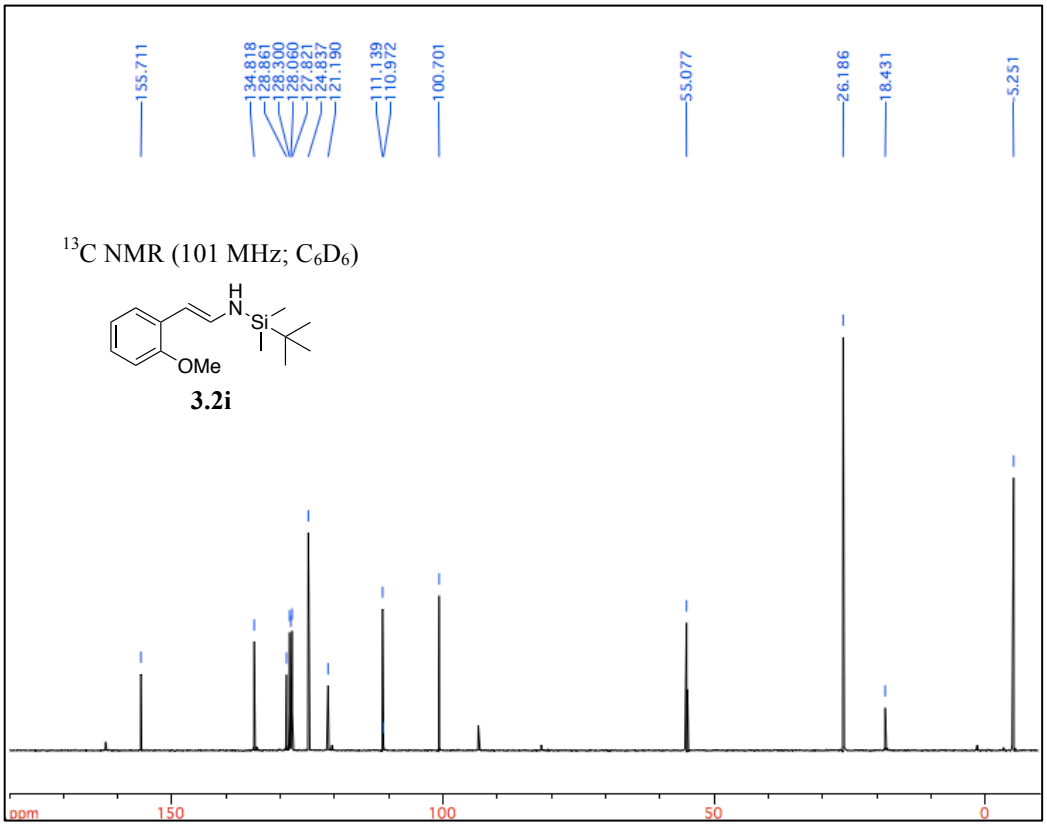
(*E*)-1-*tert*-butyl-*N*-(3-methoxystyryl)-1,1-dimethylsilanamine (3.2h)



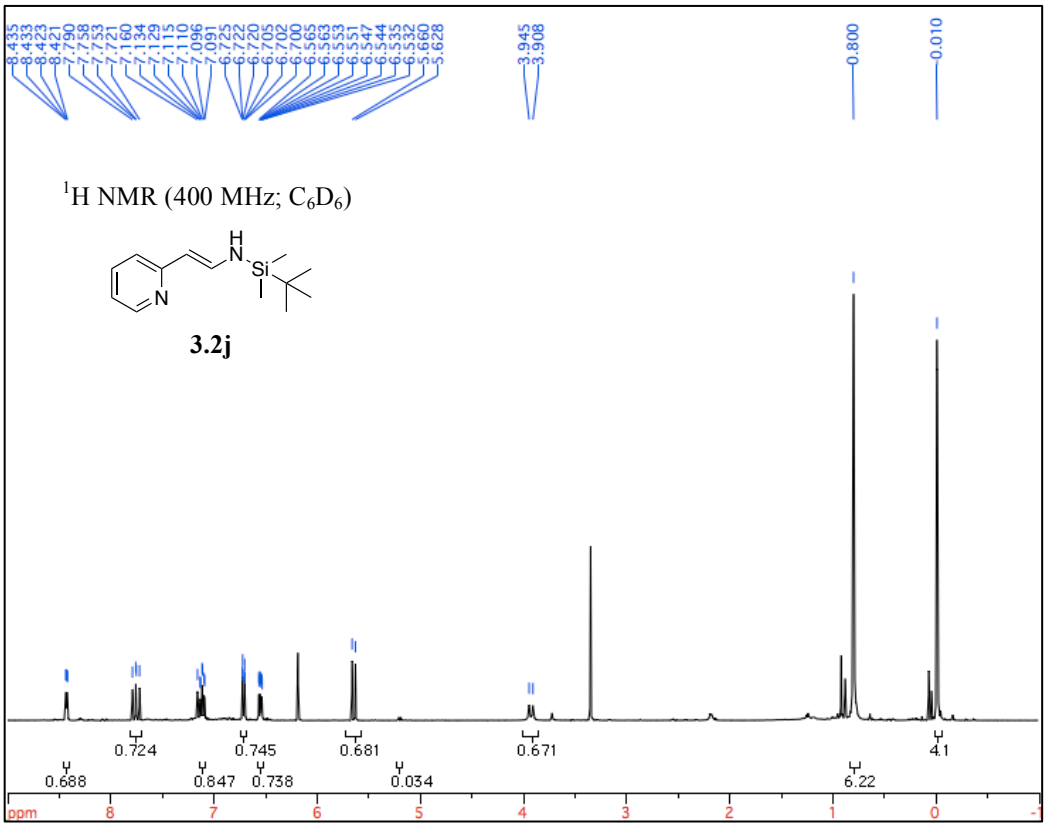


(*E*)-1-*tert*-butyl-*N*-(2-methoxystyryl)-1,1-dimethylsilanamine (3.2i)



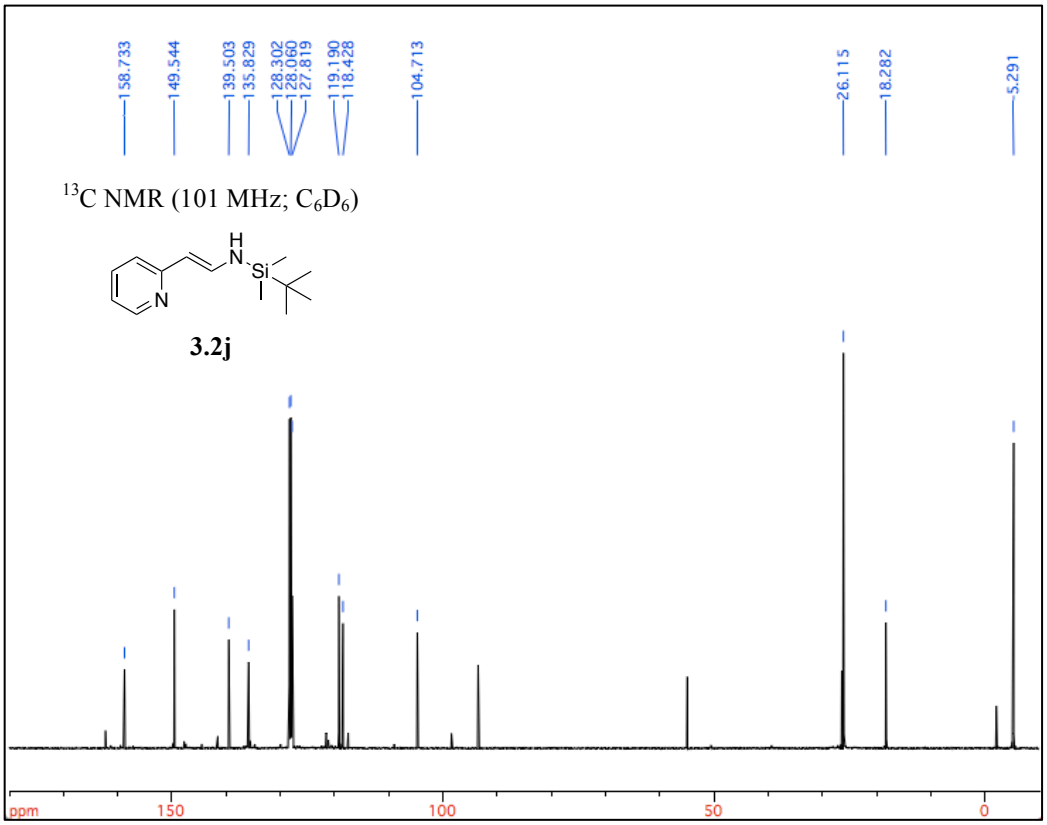


(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyridin-2-yl)vinyl)silanamine (3.2j)



^{1}H NMR (400 MHz; C_6D_6)

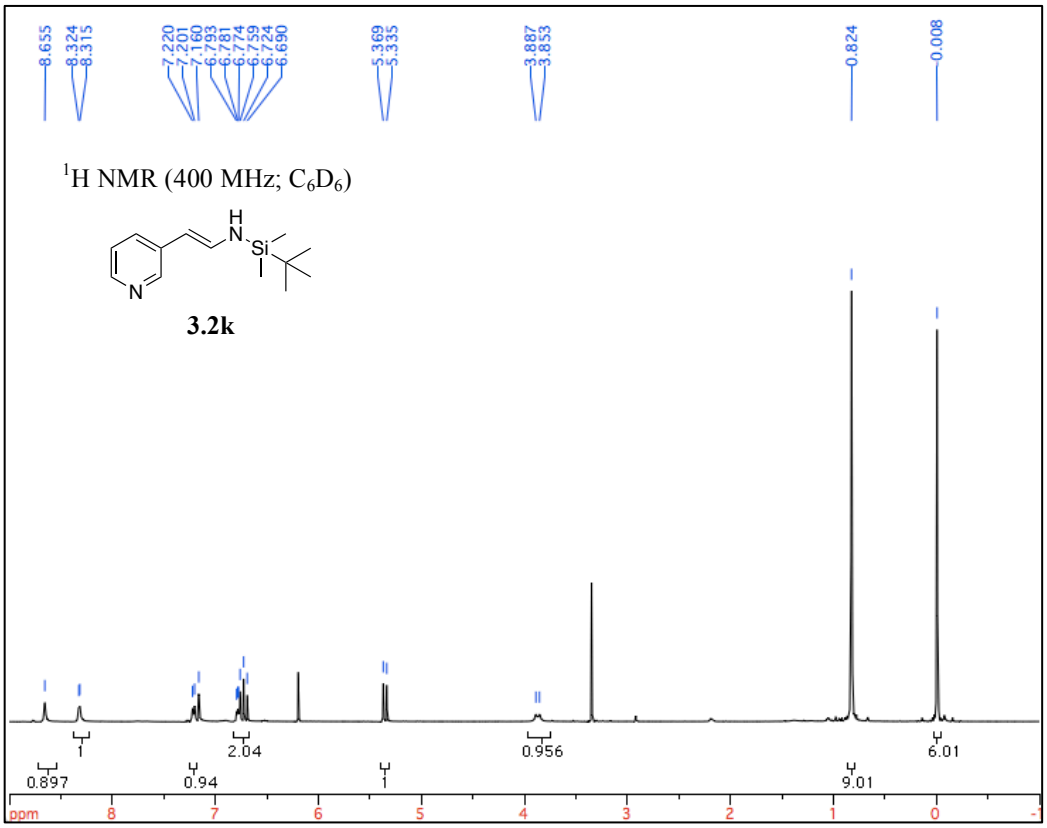
3.2j

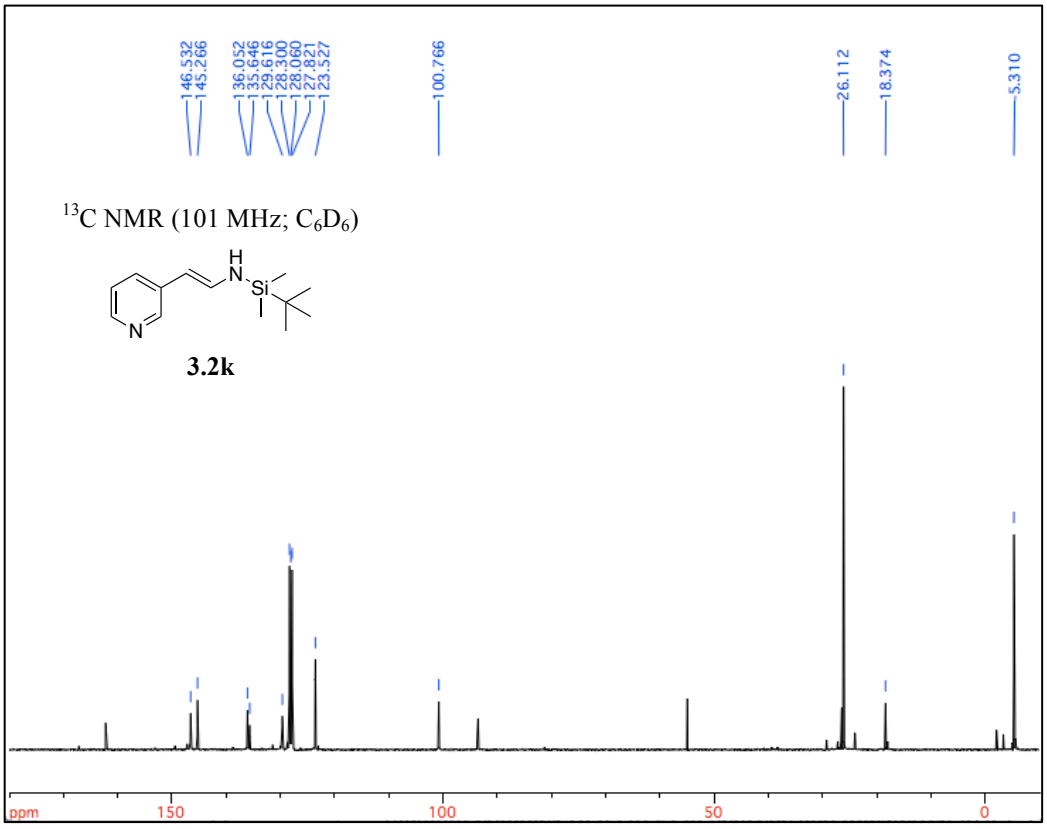


^{13}C NMR (101 MHz; C_6D_6)

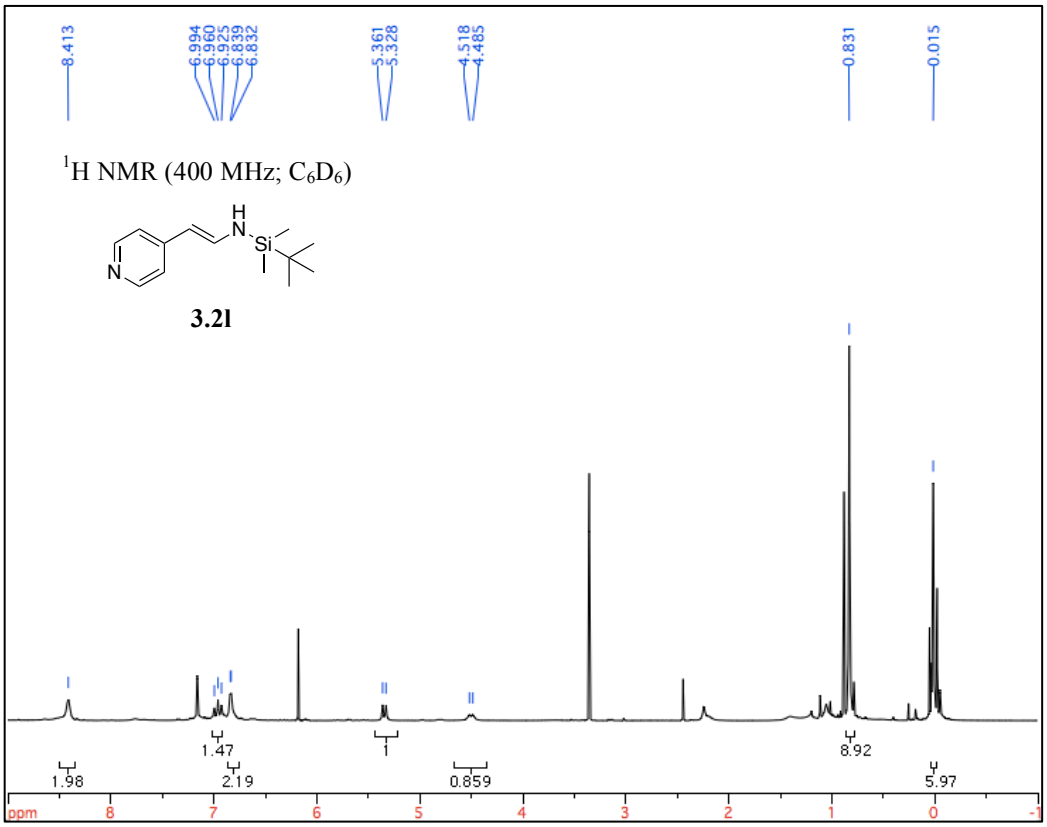
3.2j

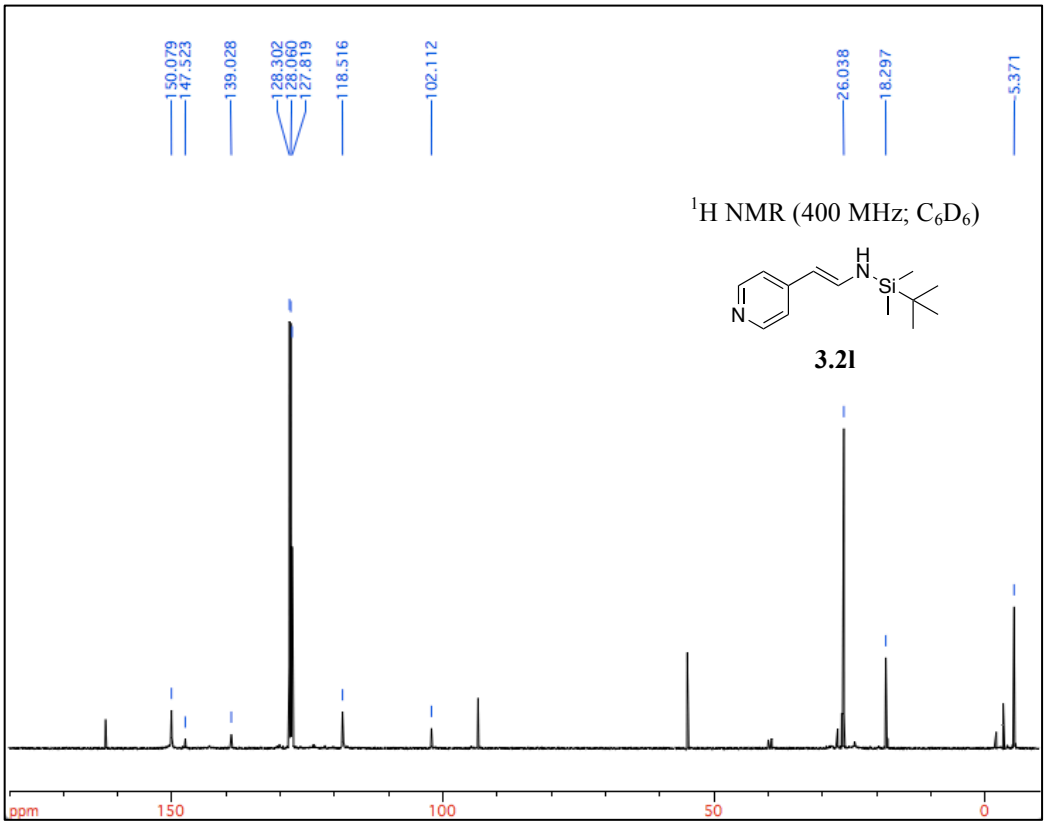
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyridin-3-yl)vinyl)silanamine (3.2k)



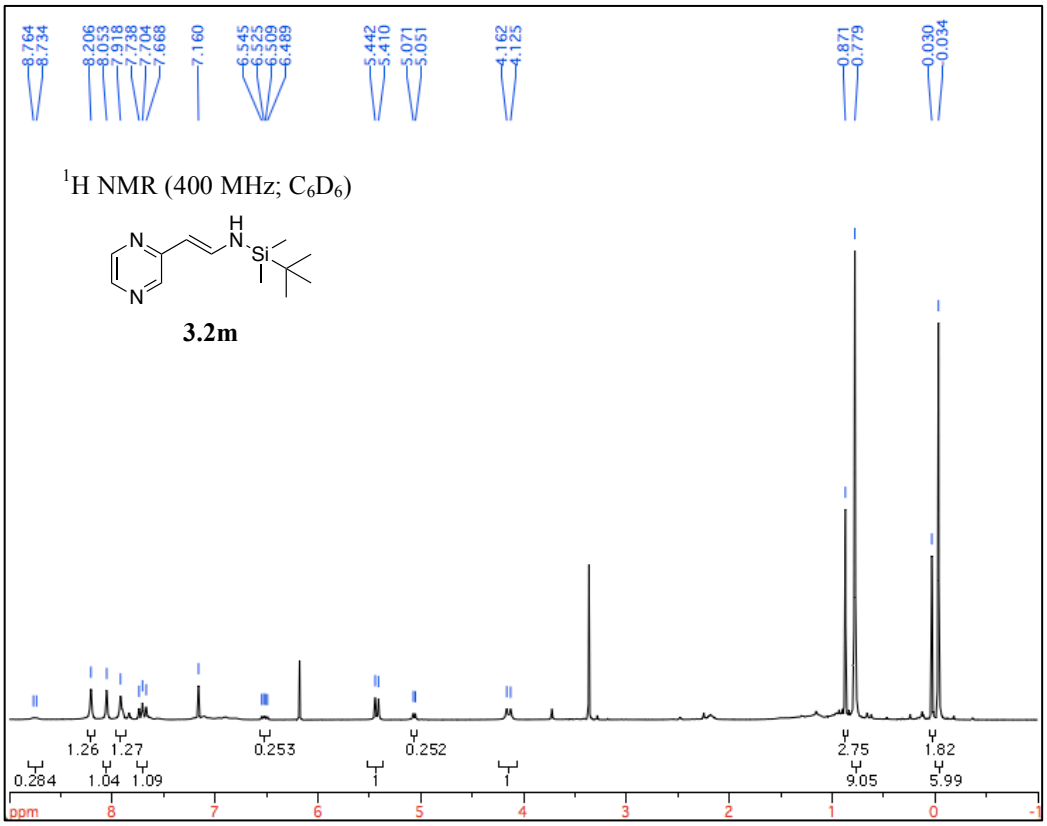


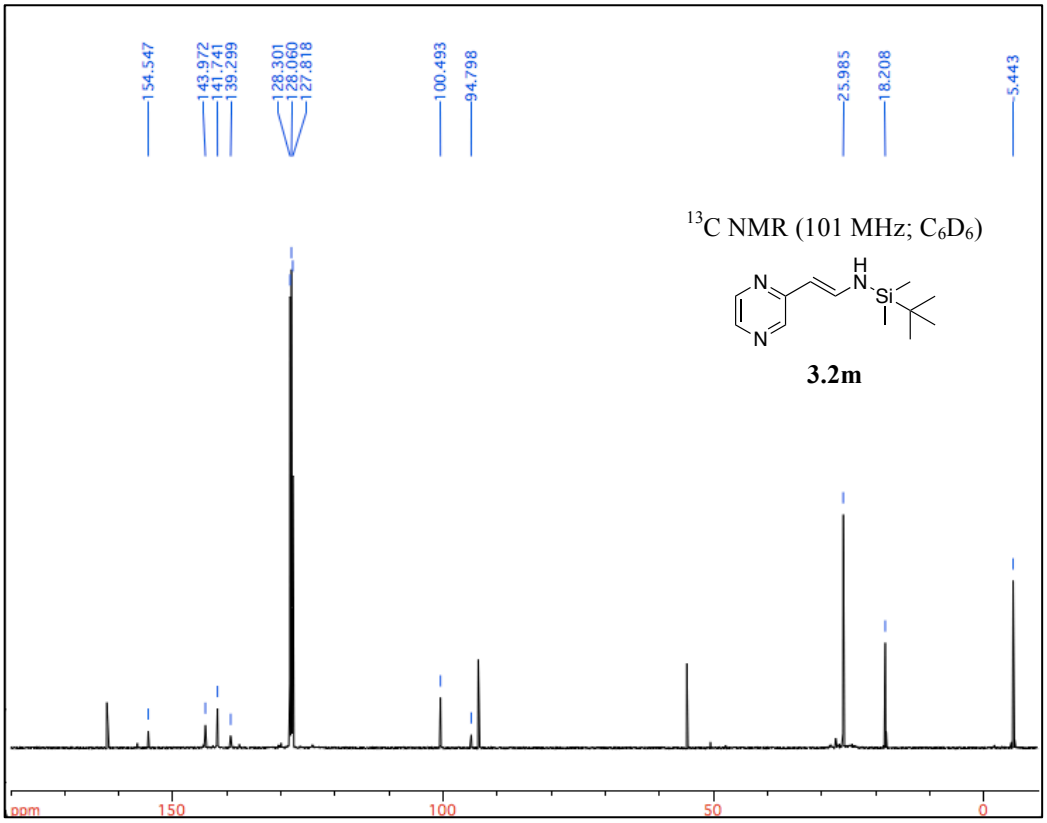
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyridin-4-yl)vinyl)silanamine (3.2l)



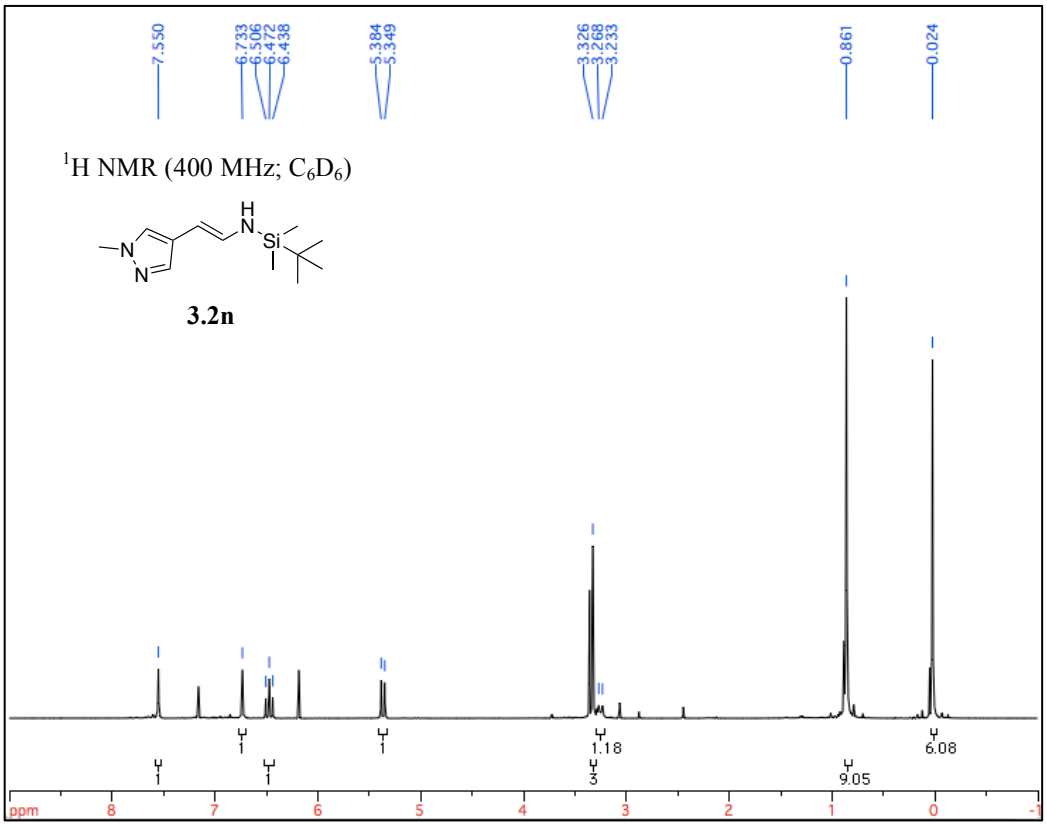


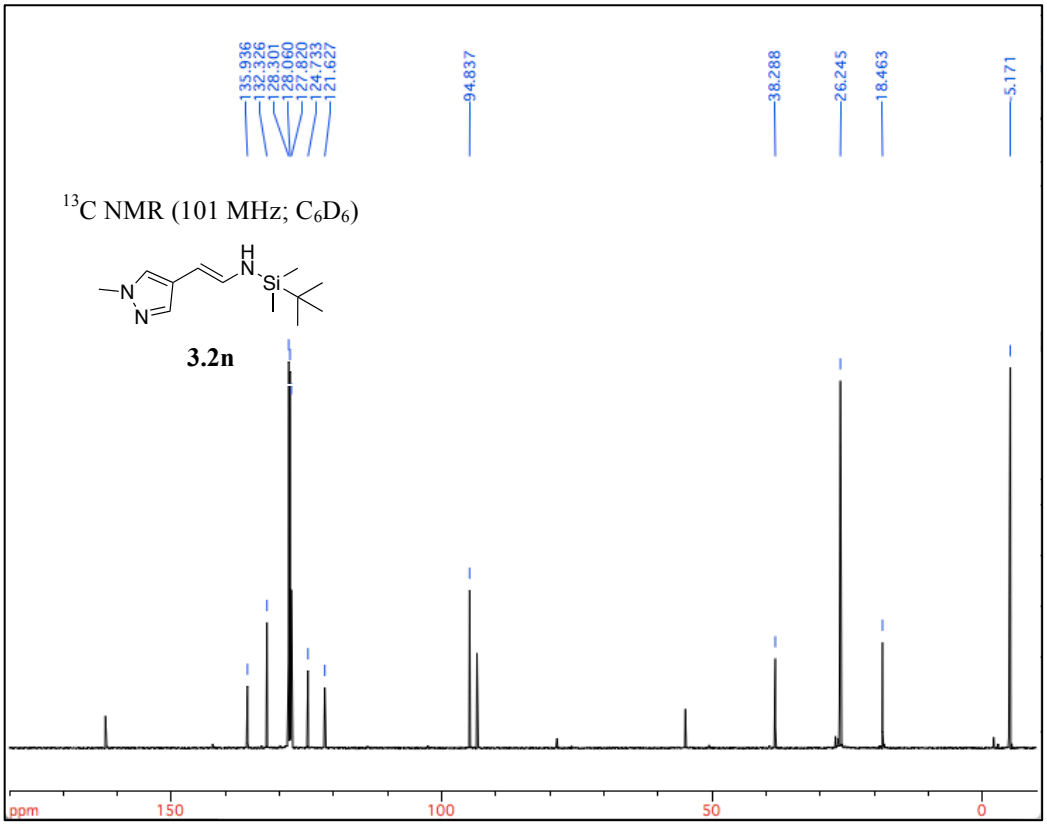
(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(pyrazin-2-yl)vinyl)silanamine (3.2m)



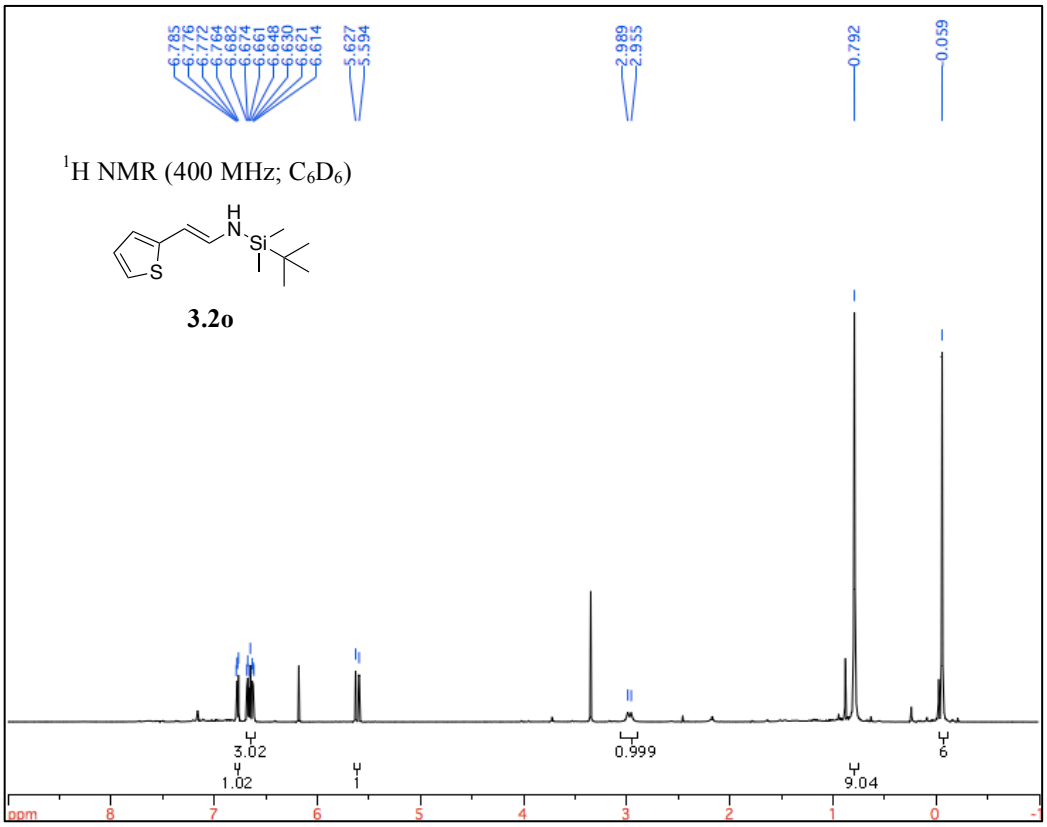


(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(1-methyl-1*H*-pyrazol-4-yl)vinyl)silanamine (3.2n)



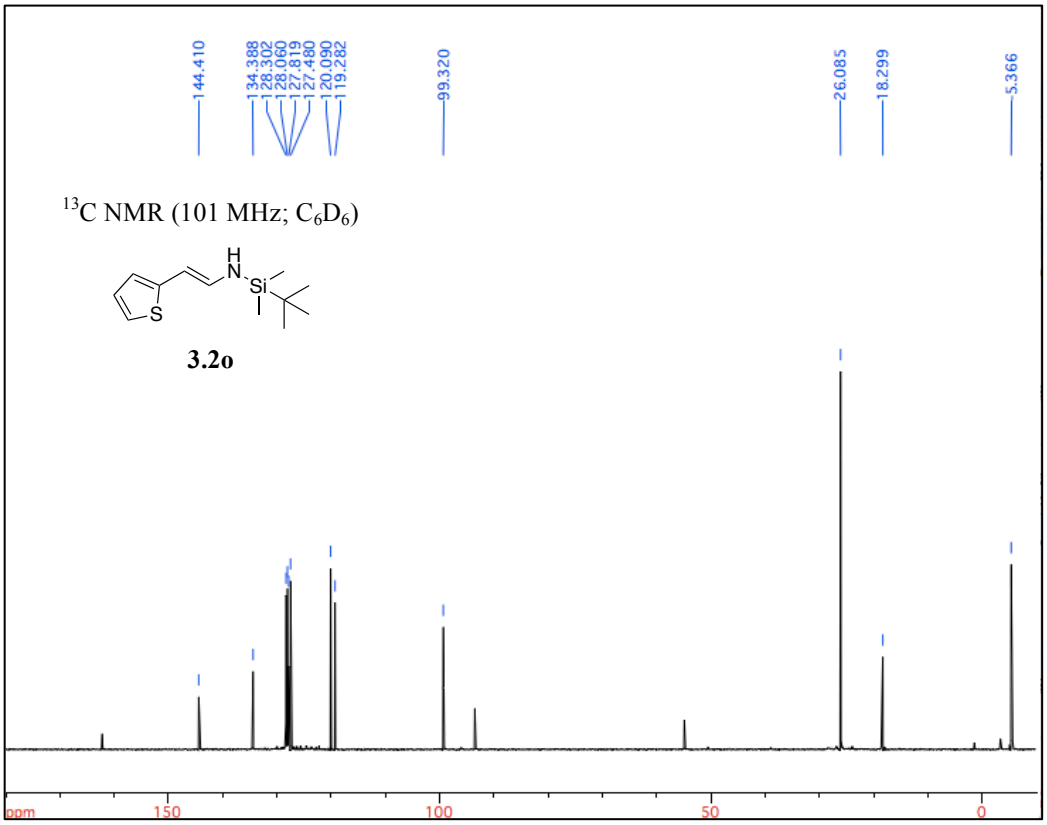


(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(thiophen-2-yl)vinyl)silanamine (3.2o)



^{1}H NMR (400 MHz; C_6D_6)

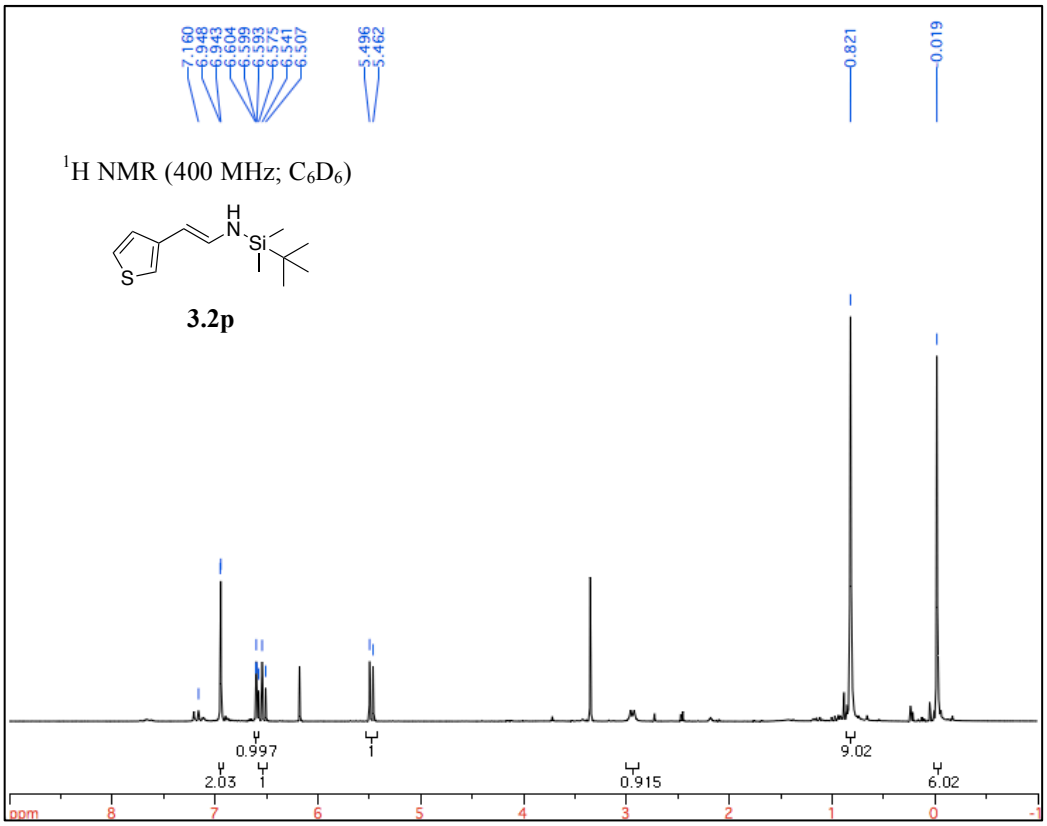
3.2o



^{13}C NMR (101 MHz; C_6D_6)

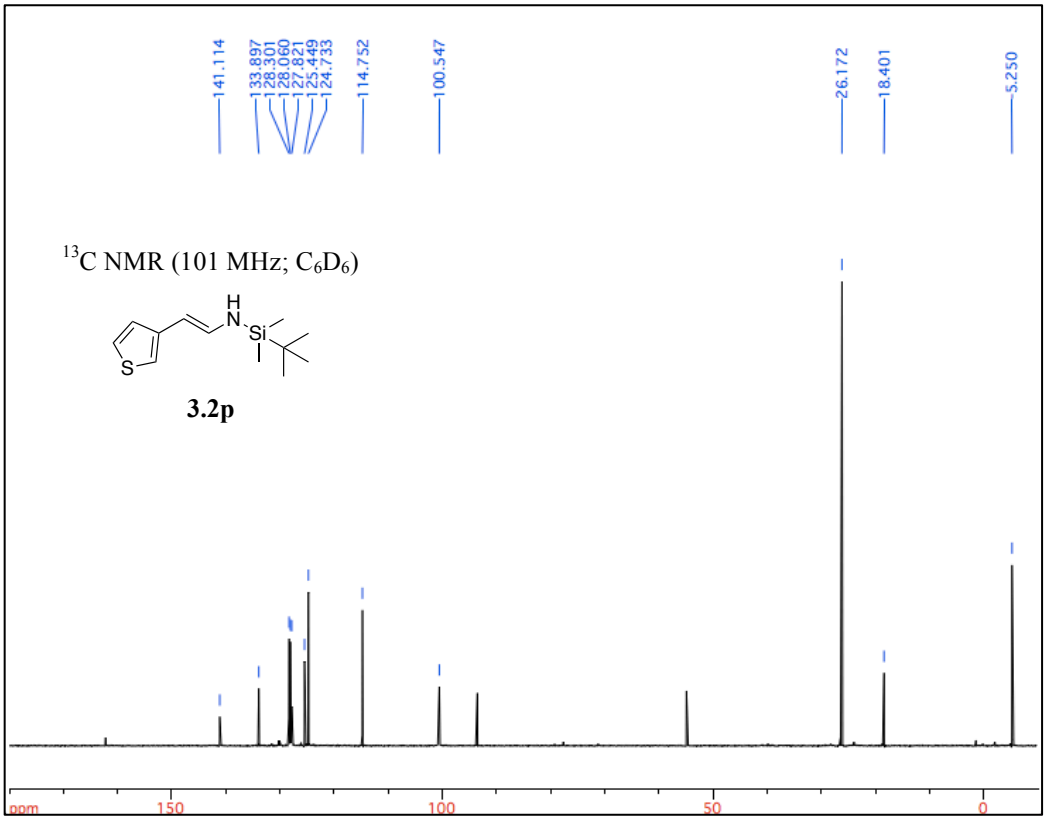
3.2o

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(2-(thiophen-3-yl)vinyl)silanamine (3.2p)



^{1}H NMR (400 MHz; C_6D_6)

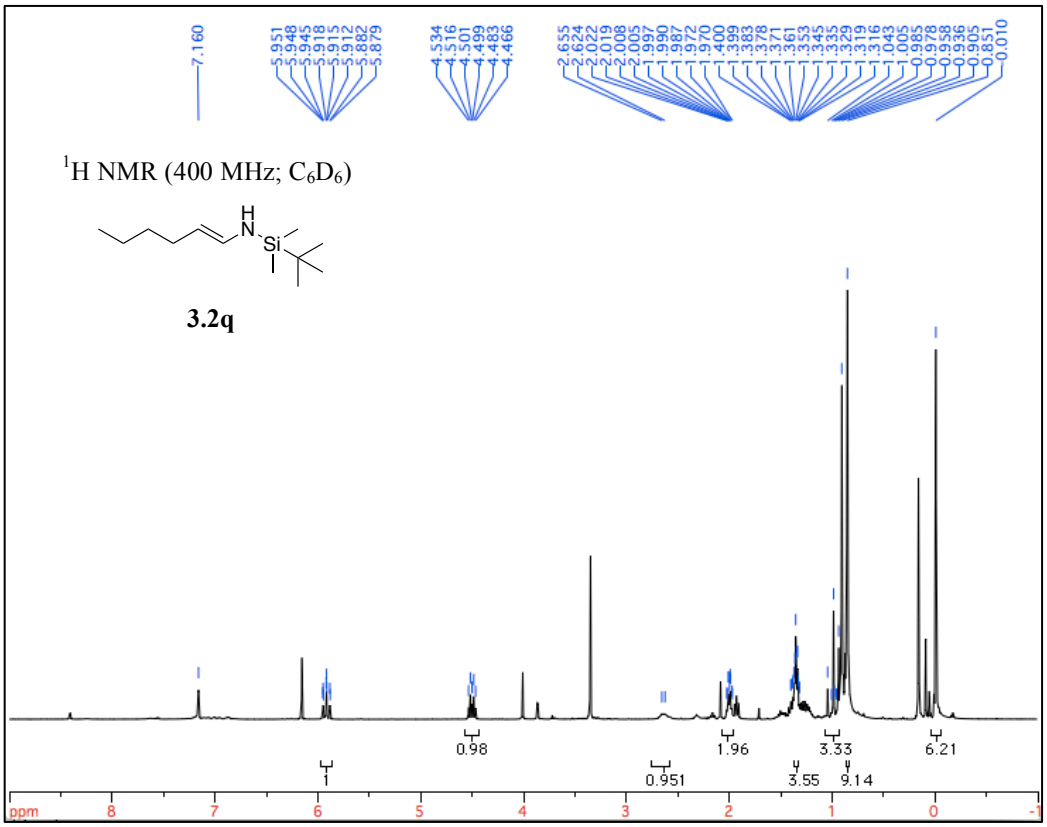
3.2p

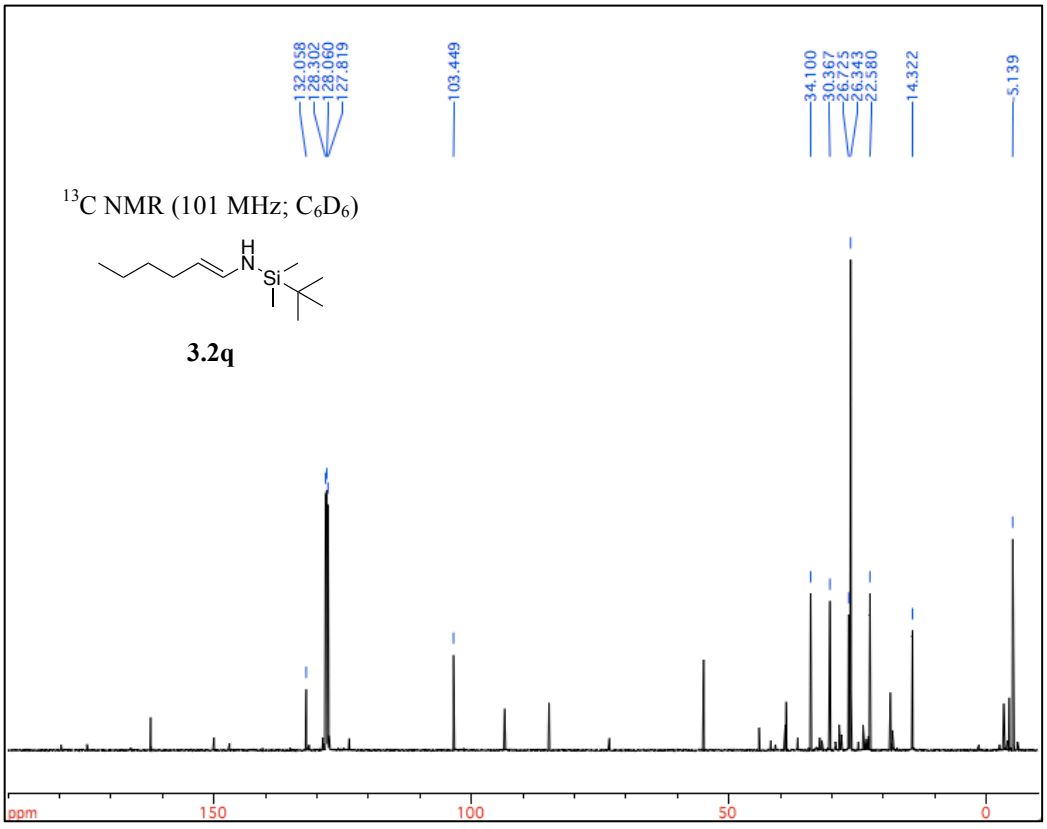


^{13}C NMR (101 MHz; C_6D_6)

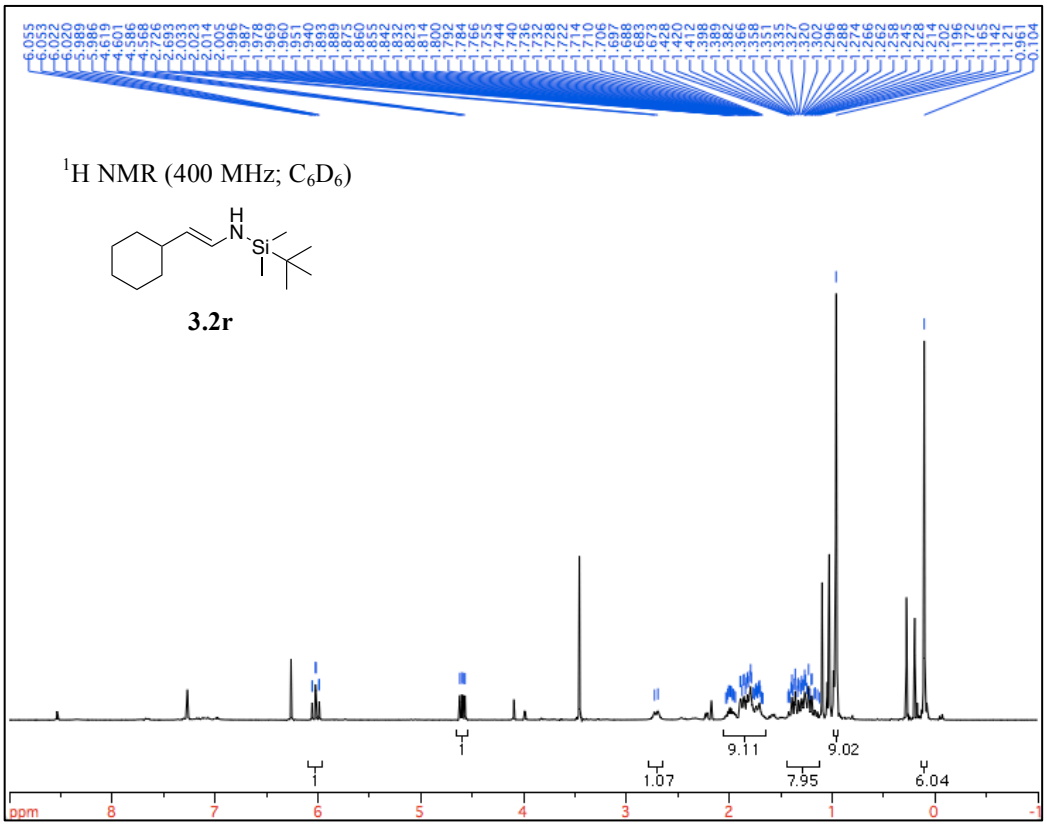
3.2p

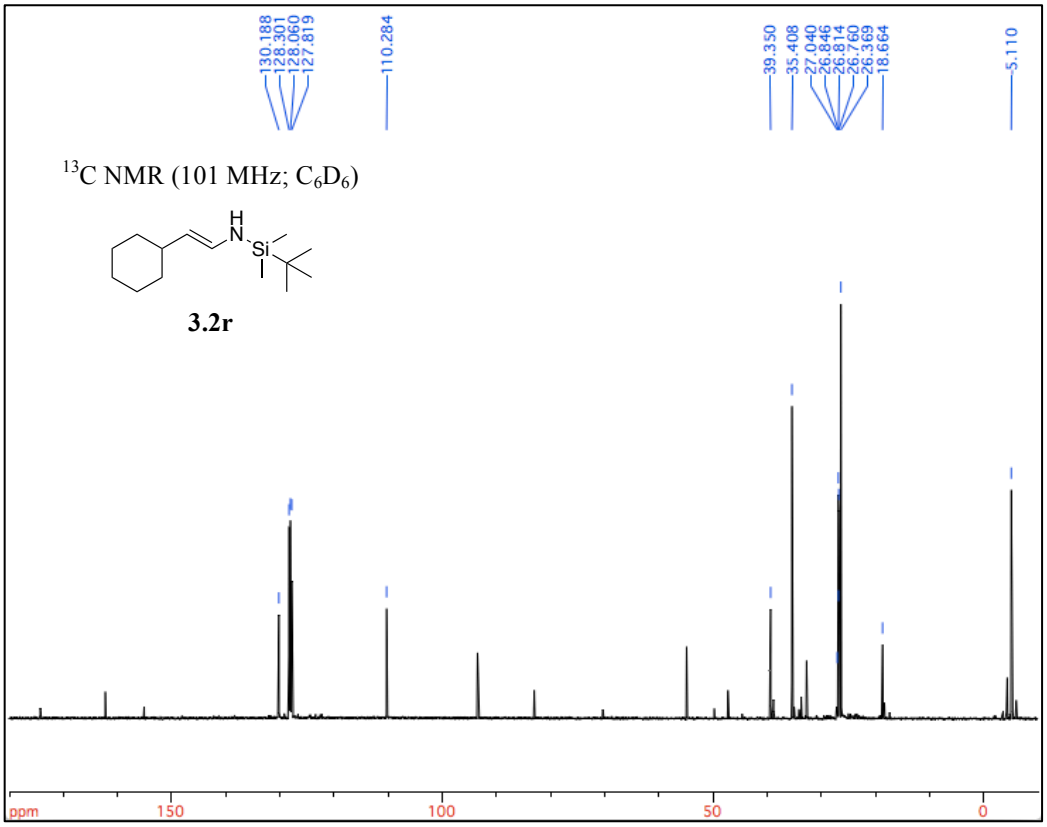
(*E*)-1-*tert*-butyl-*N*-(hex-1-en-1-yl)-1,1-dimethylsilanamine (3.2q)



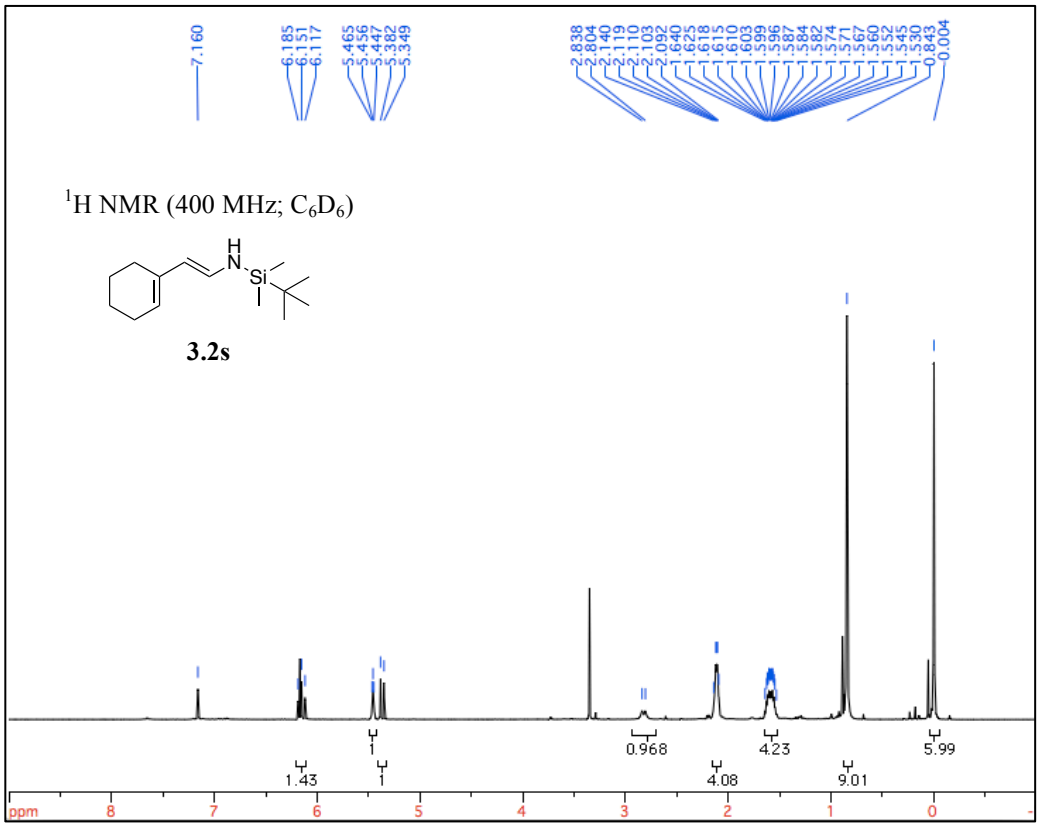


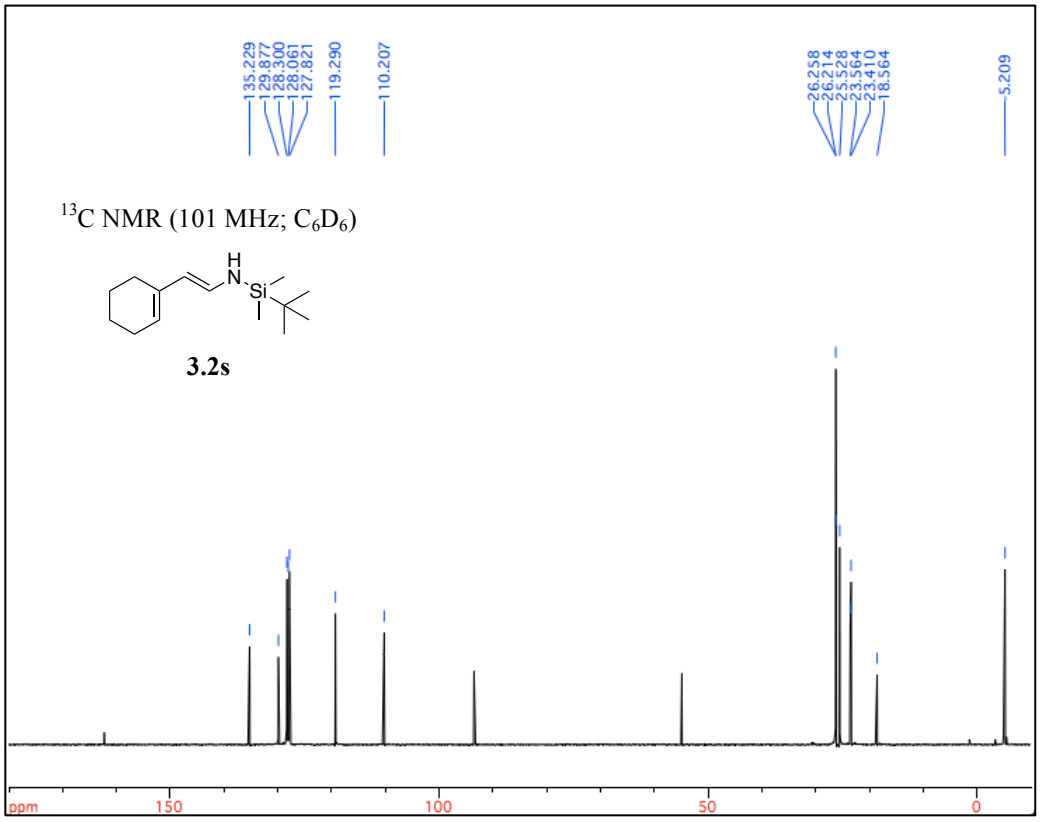
(*E*)-1-*tert*-butyl-*N*-(2-cyclohexylvinyl)-1,1-dimethylsilanamine (3.2r)



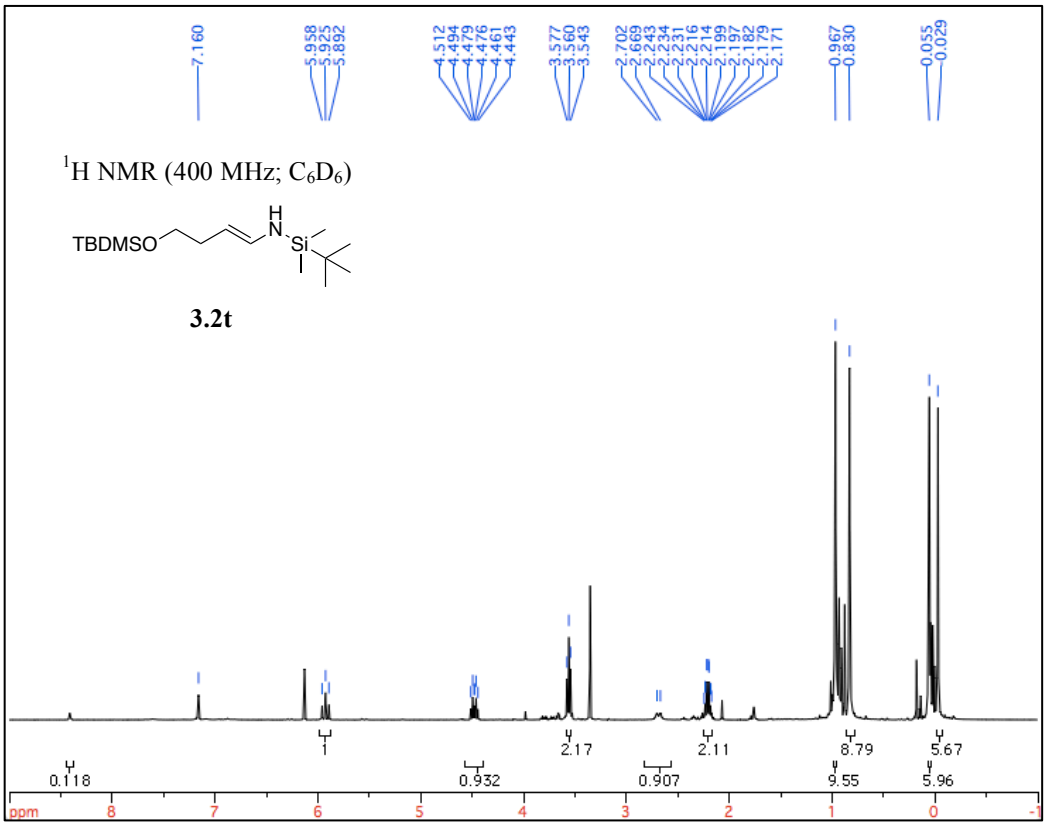


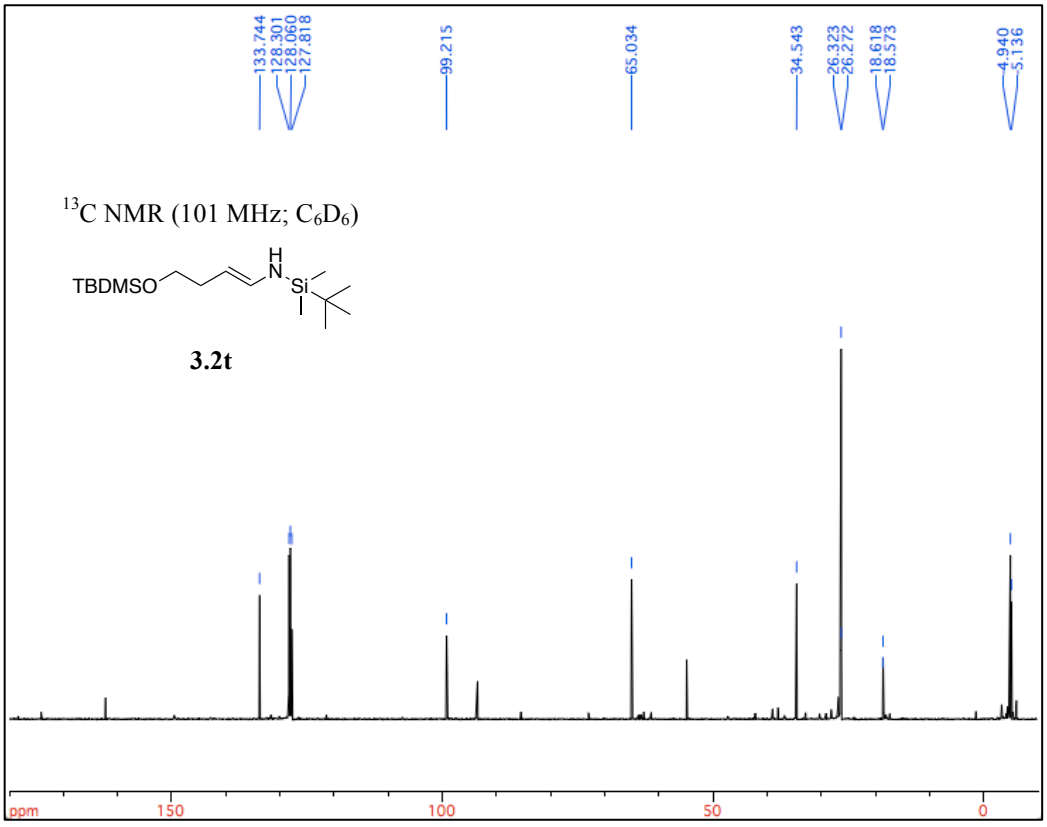
(*E*)-1-*tert*-butyl-*N*-(2-(cyclohex-1-en-1-yl)vinyl)-1,1-dimethylsilanamine (3.2s)



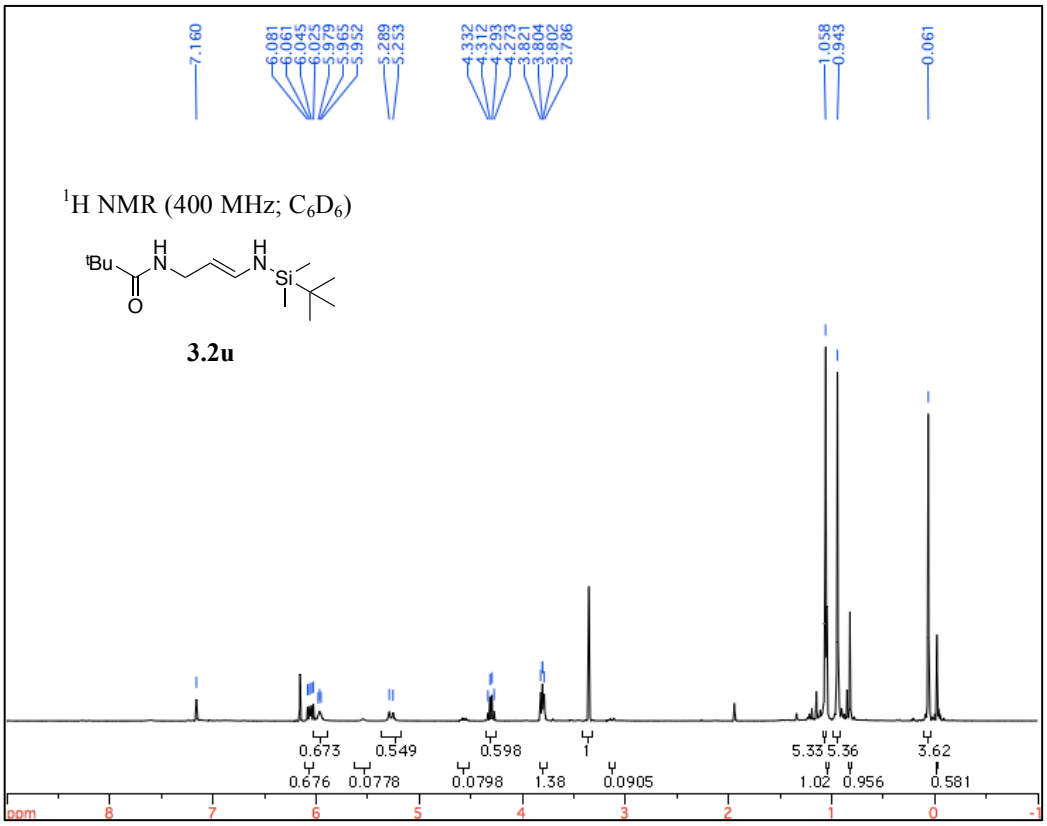


(*E*)-1-*tert*-butyl-*N*-(4-((*tert*-butyldimethylsilyl)oxy)but-1-en-1-yl)-1,1-dimethylsilanamine (3.2t)



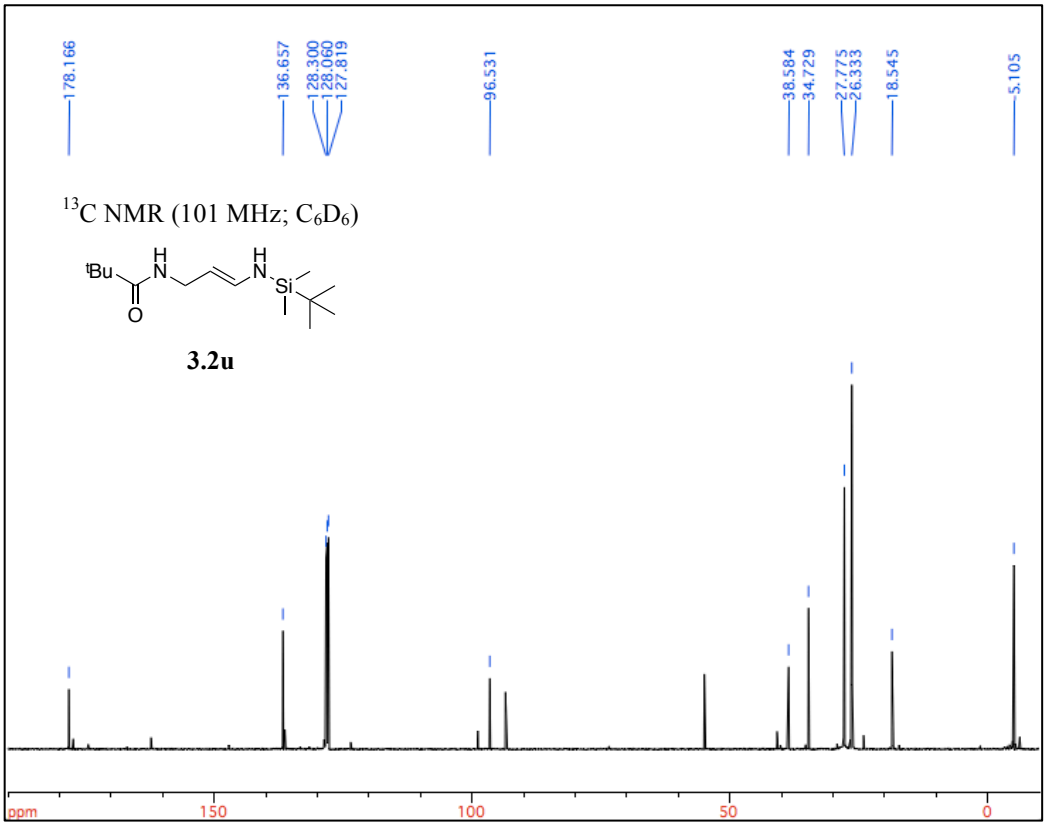


(*E*)-*N*-(3-((*tert*-butyldimethylsilyl)amino)allyl)pivalamide (3.2u)



^{1}H NMR (400 MHz; C_6D_6)

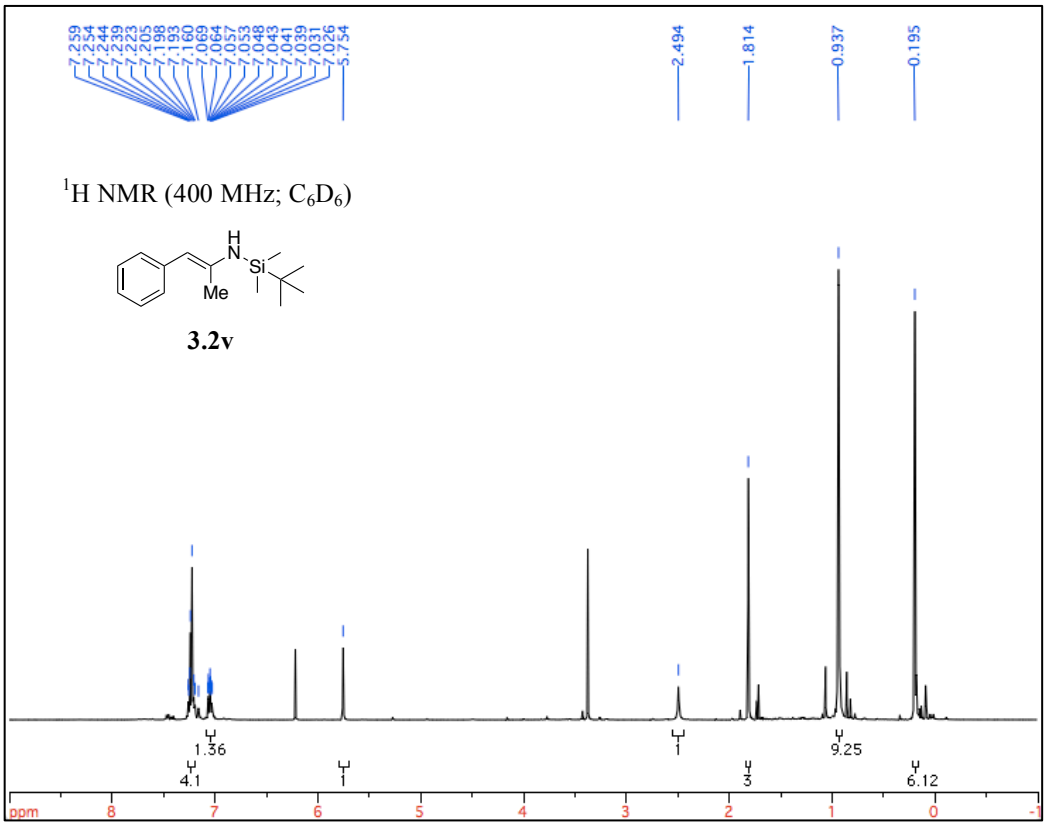
3.2u



^{13}C NMR (101 MHz; C_6D_6)

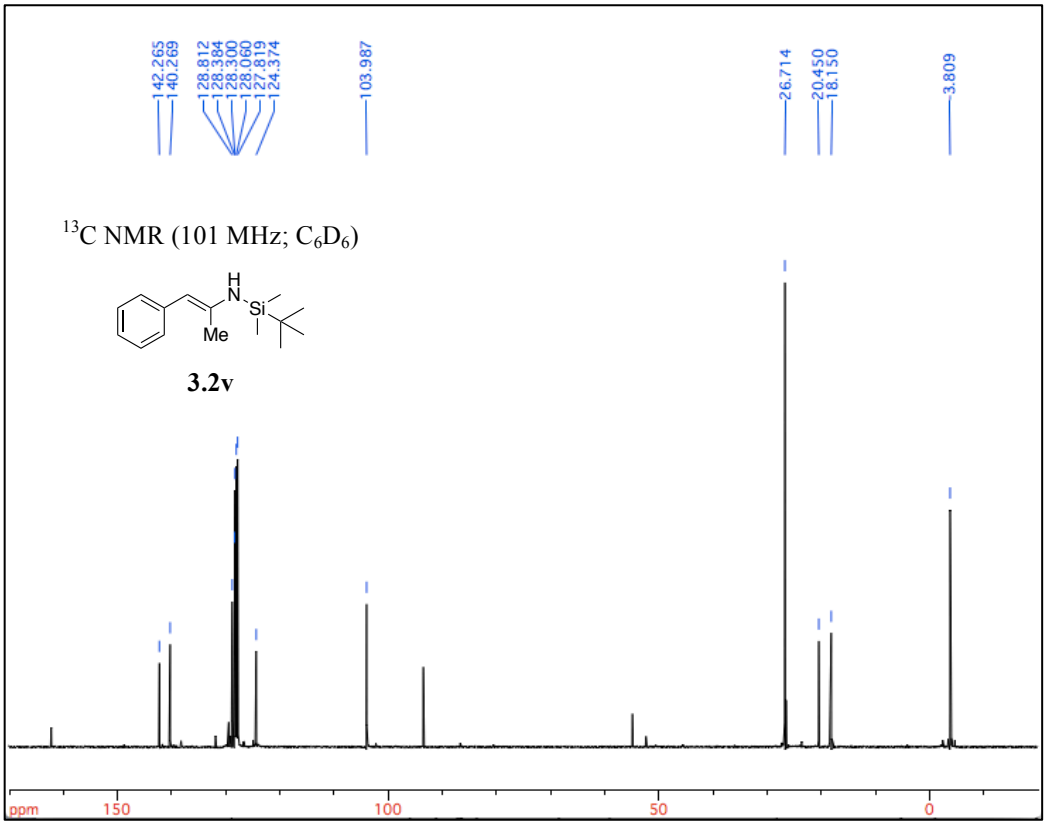
3.2u

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(1-phenylprop-1-en-2-yl)silanamine (3.2v)



^{1}H NMR (400 MHz; C_6D_6)

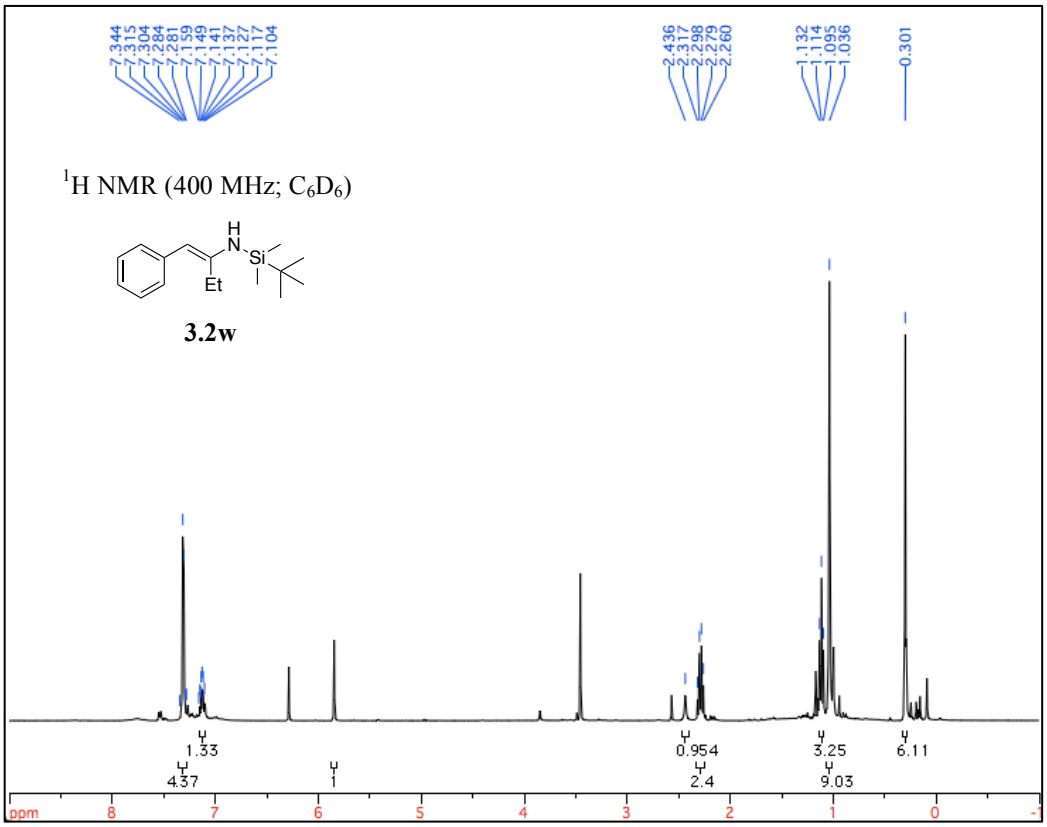
3.2v

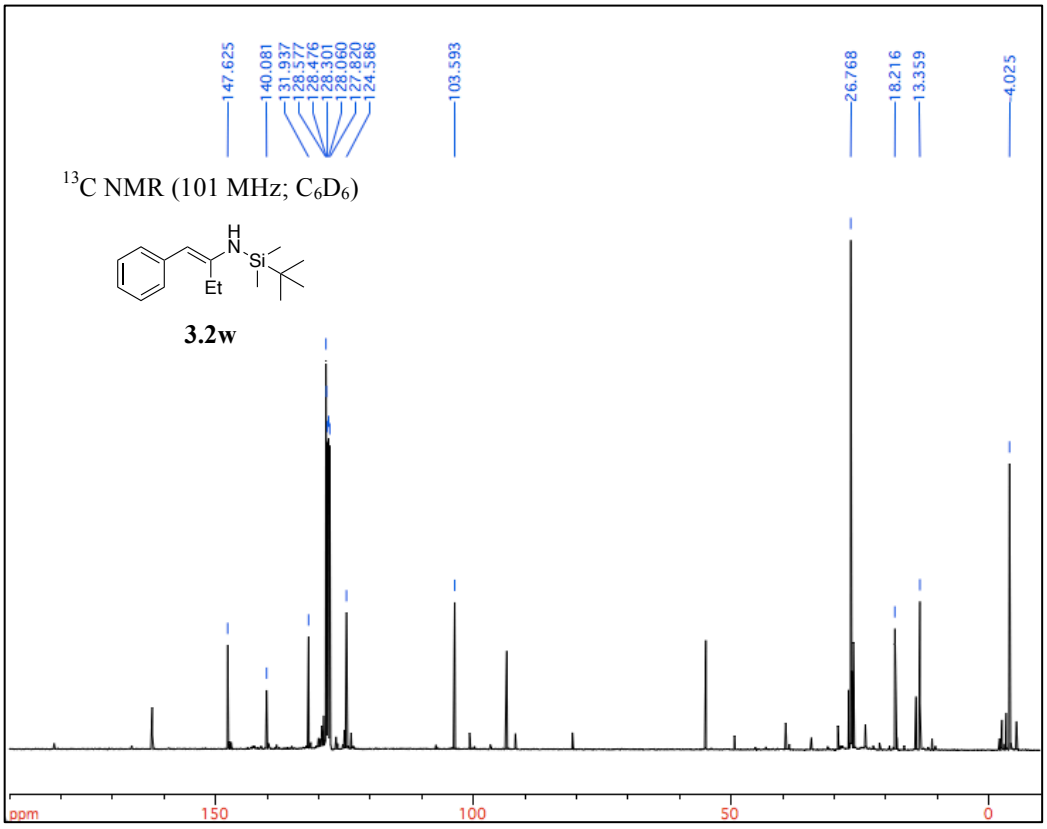


^{13}C NMR (101 MHz; C_6D_6)

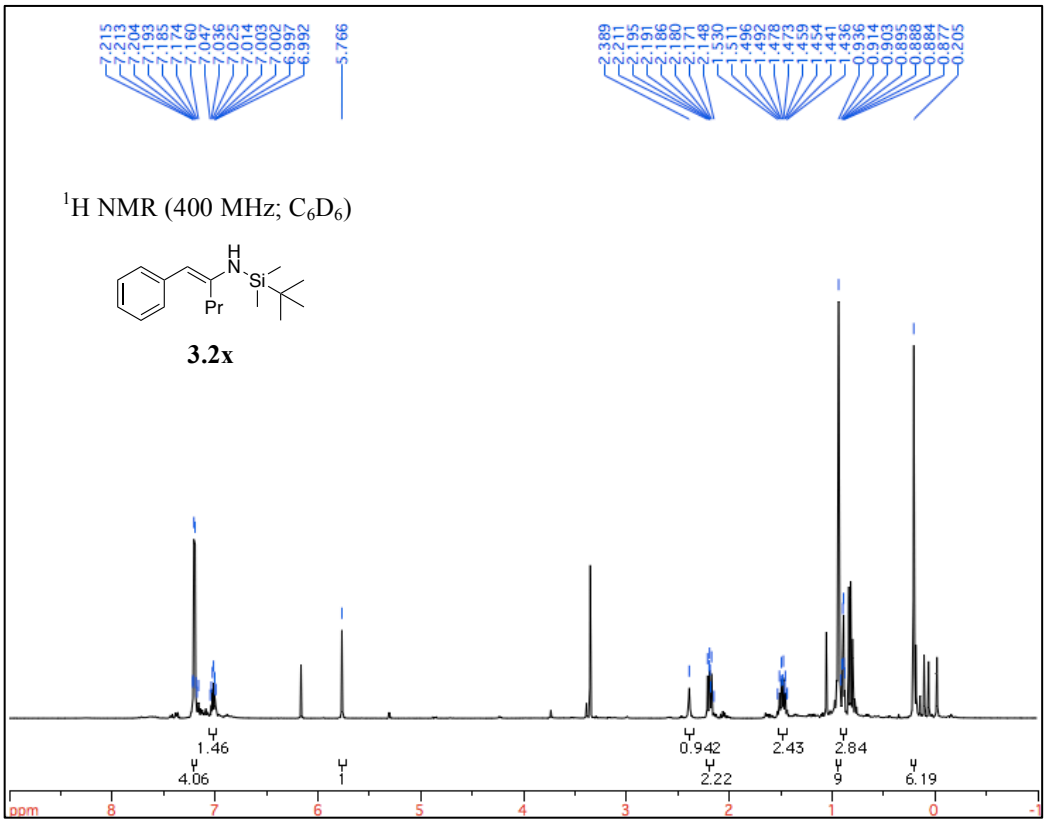
3.2v

(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(1-phenylbut-1-en-2-yl)silanamine (3.2w)



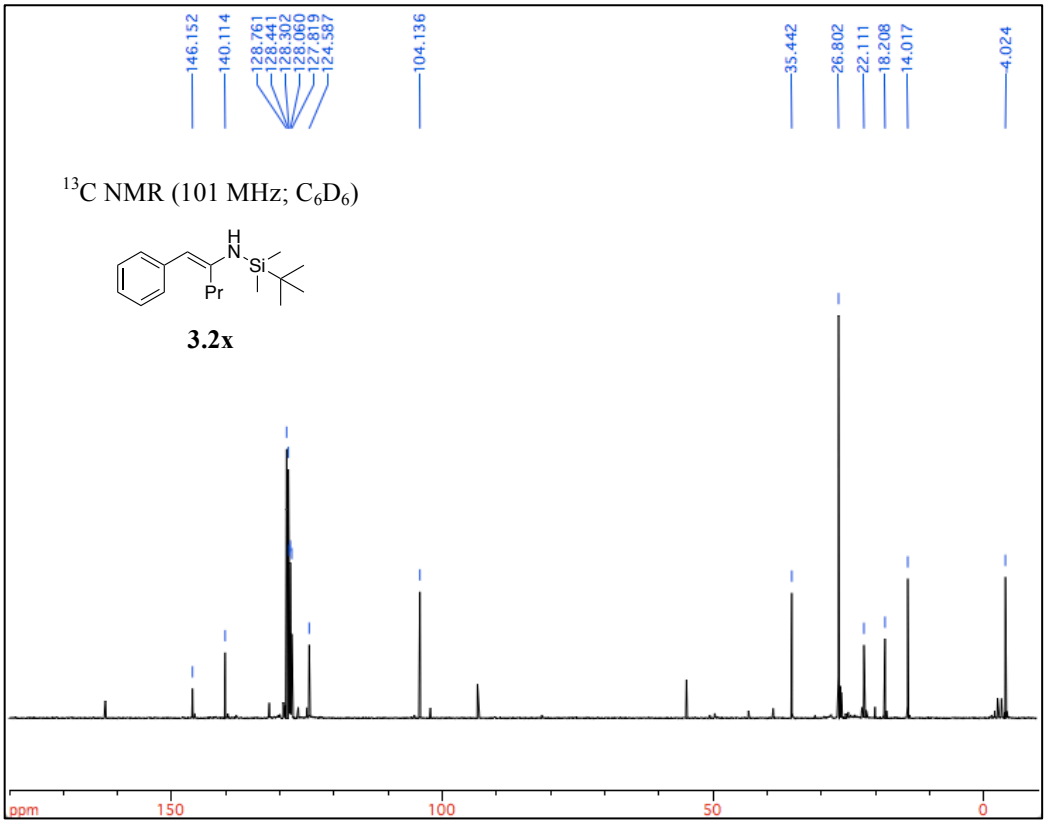


(*E*)-1-*tert*-butyl-1,1-dimethyl-*N*-(1-phenylpent-1-en-2-yl)silanamine (3.2x)



^{1}H NMR (400 MHz; C_6D_6)

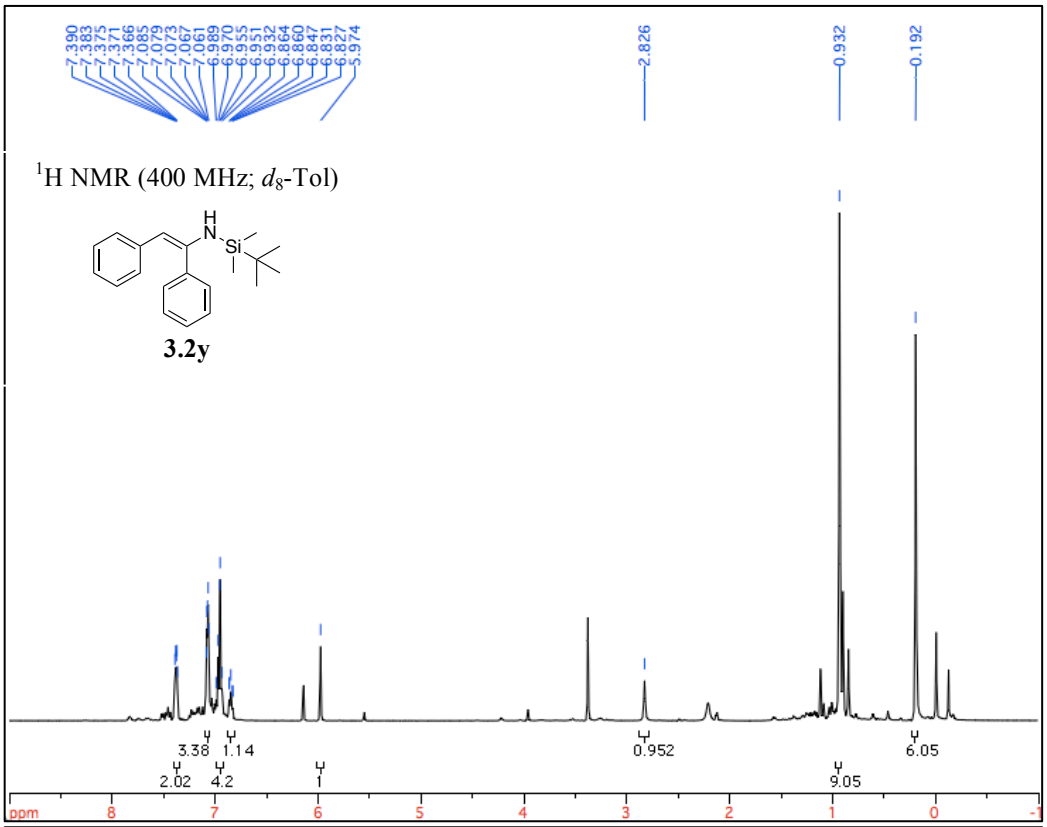
3.2x

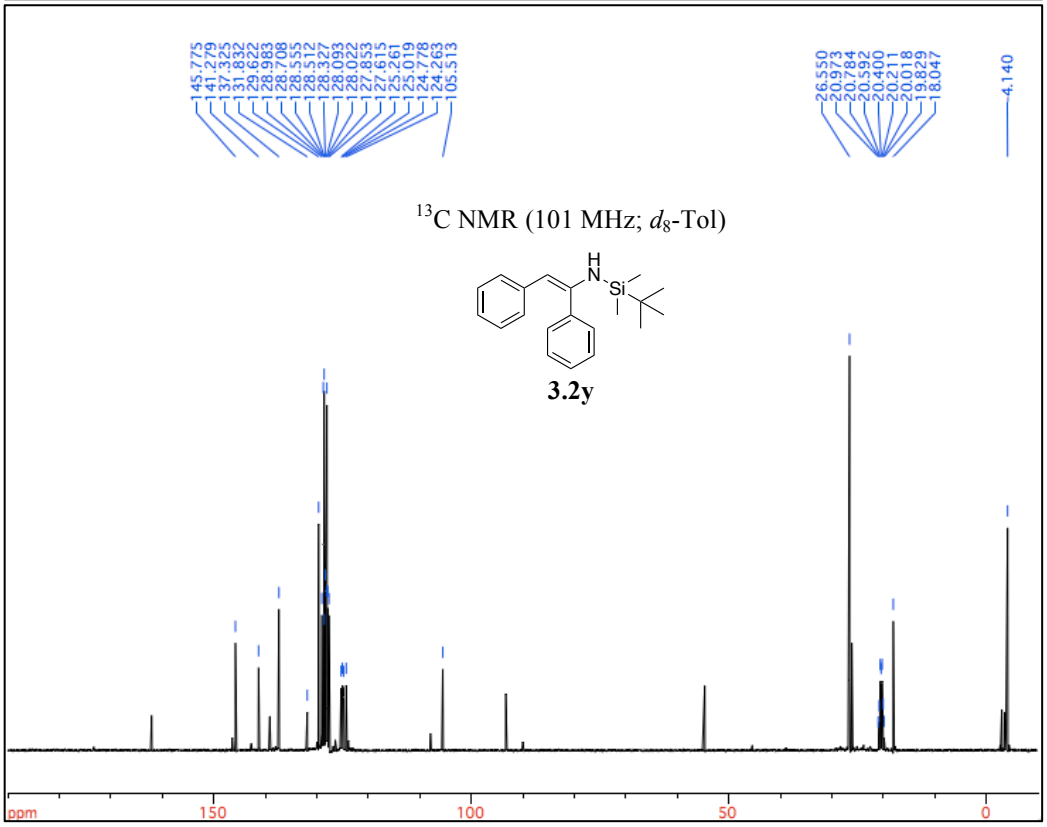


^{13}C NMR (101 MHz; C_6D_6)

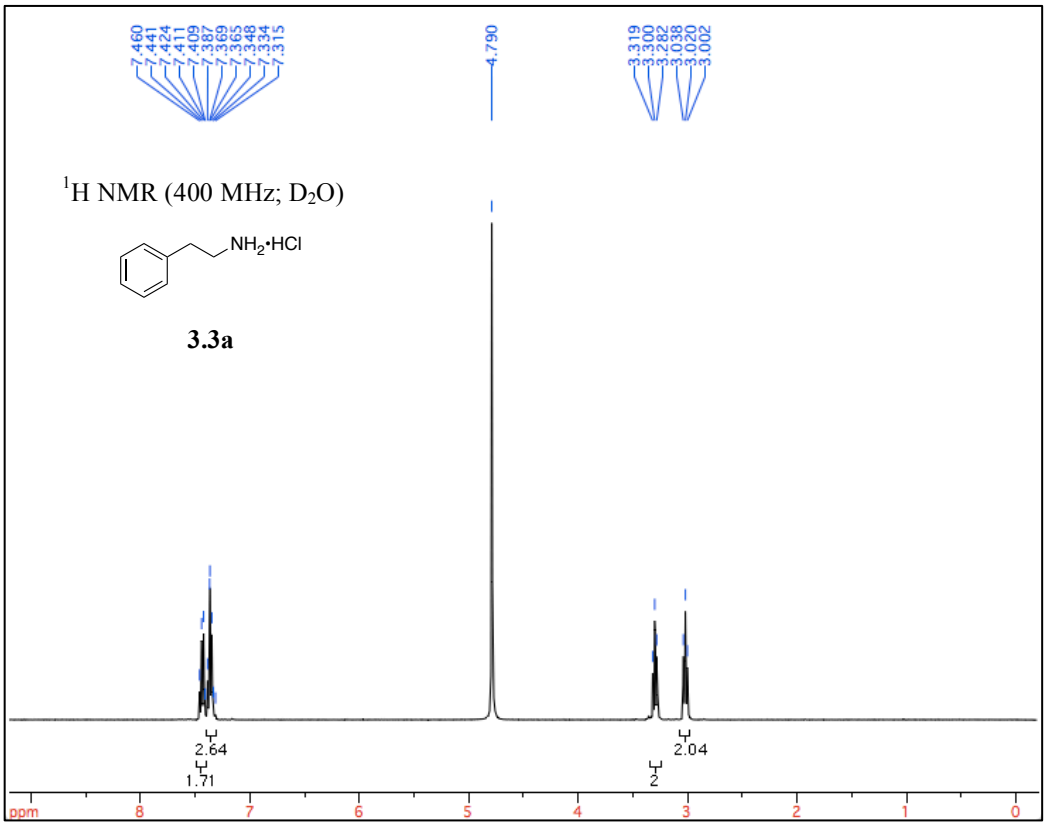
3.2x

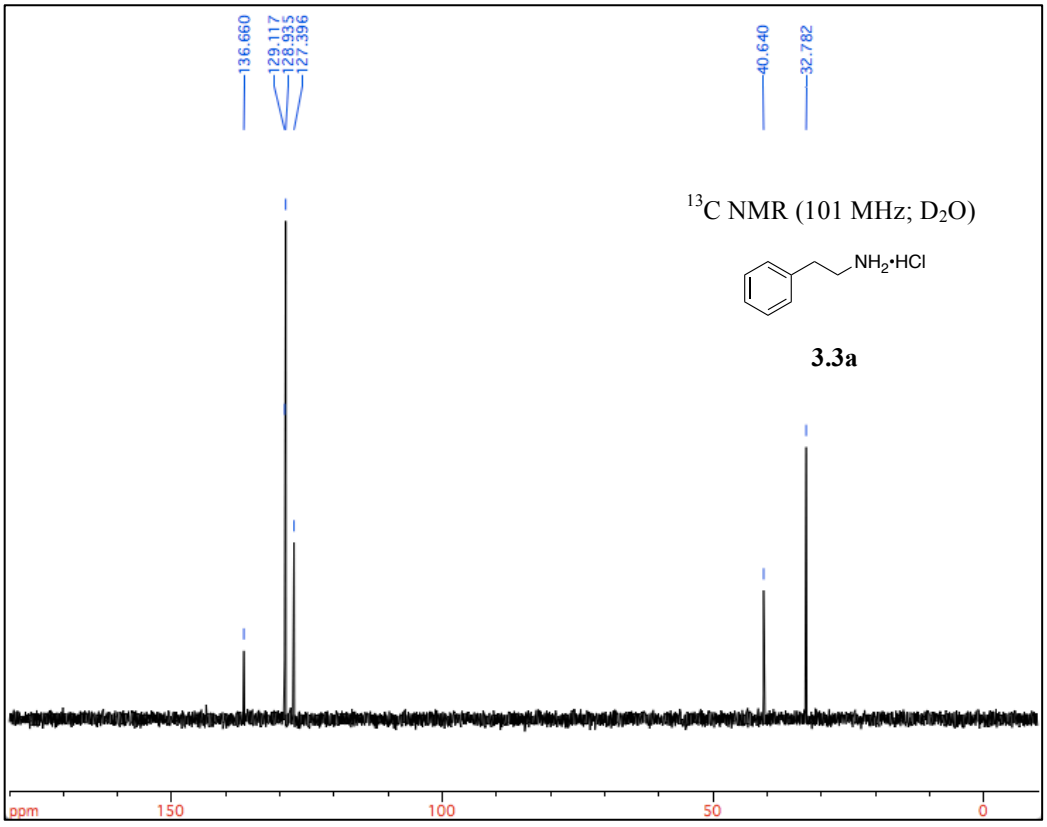
(*E*)-1-*tert*-butyl-*N*-(1,2-diphenylvinyl)-1,1-dimethylsilanamine (3.2y)



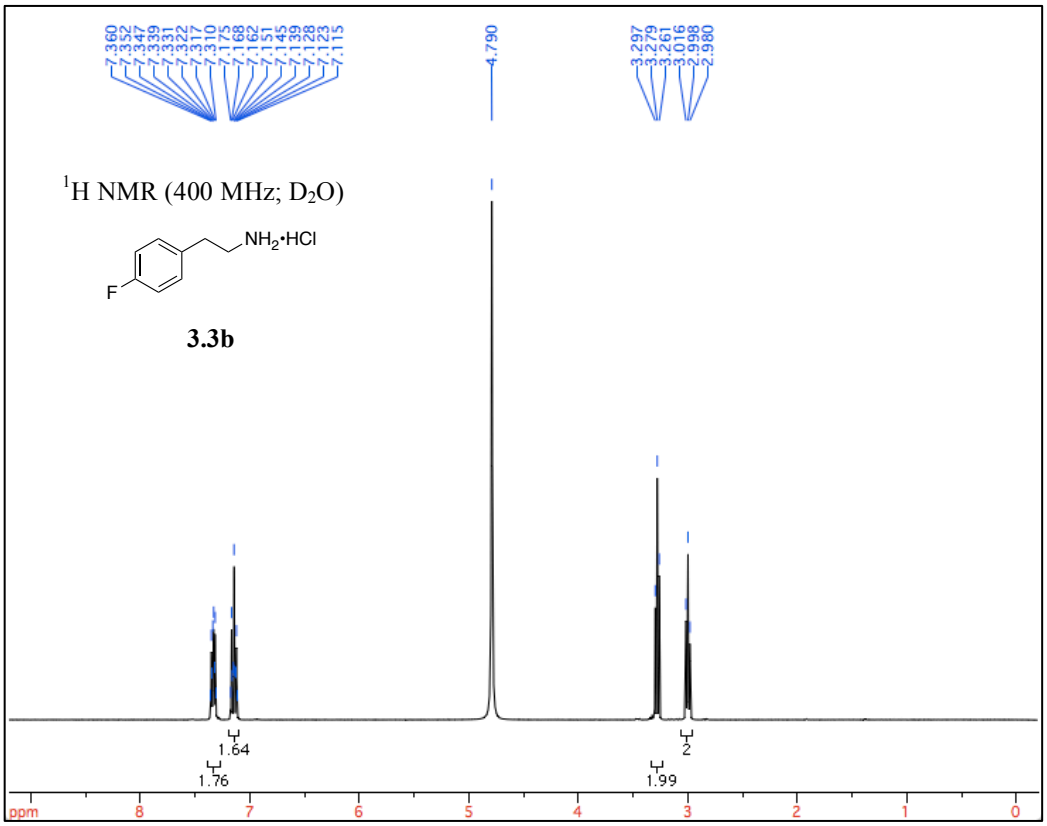


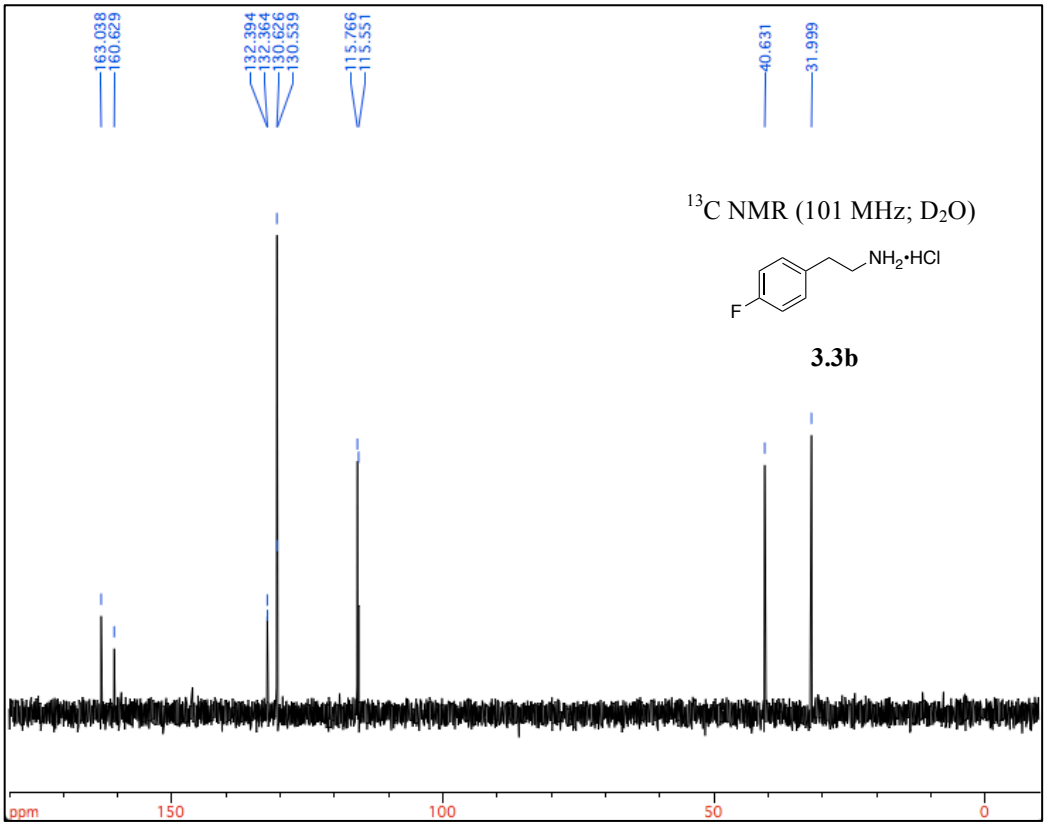
2-phenylethan-1-amine hydrochloride salt (3.3a)



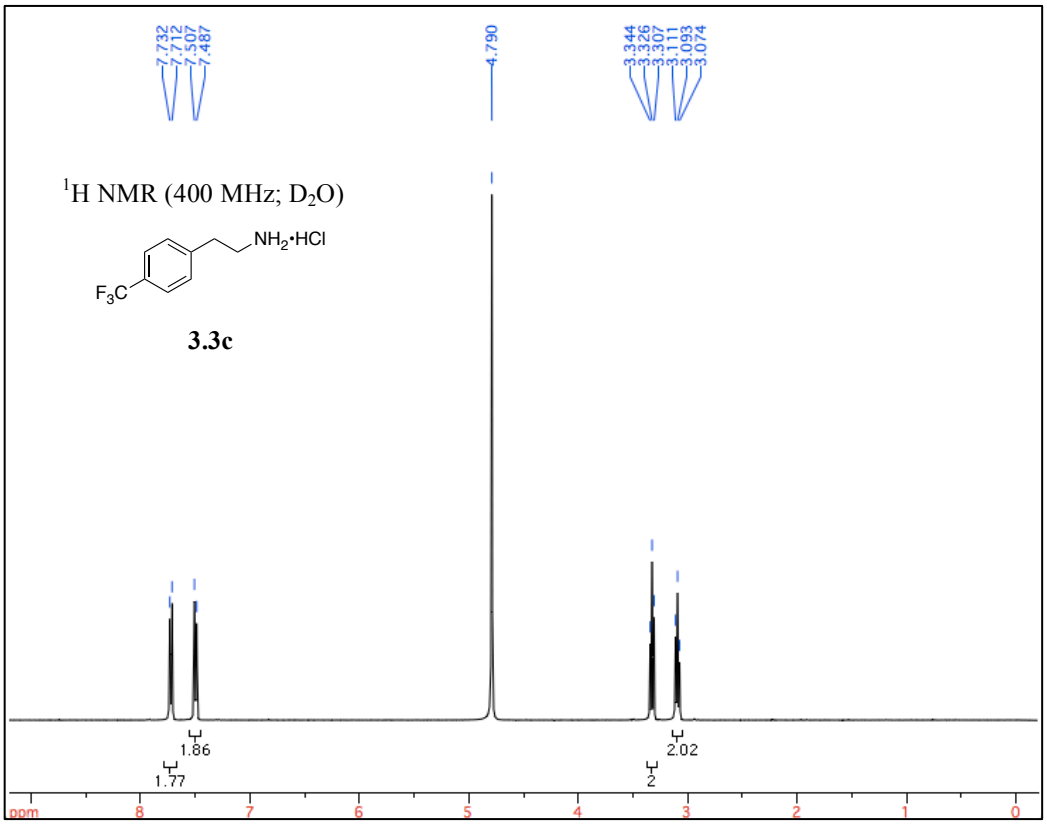


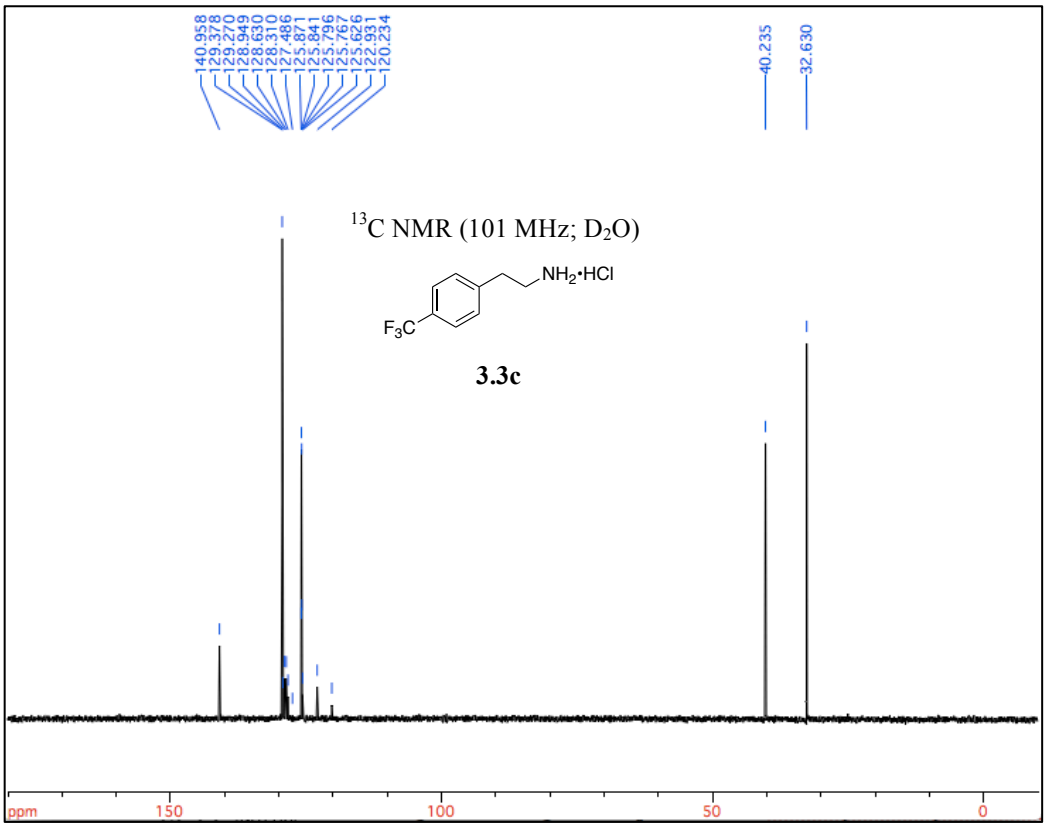
2-(4-fluorophenyl)ethan-1-amine hydrochloride salt (3.3b)



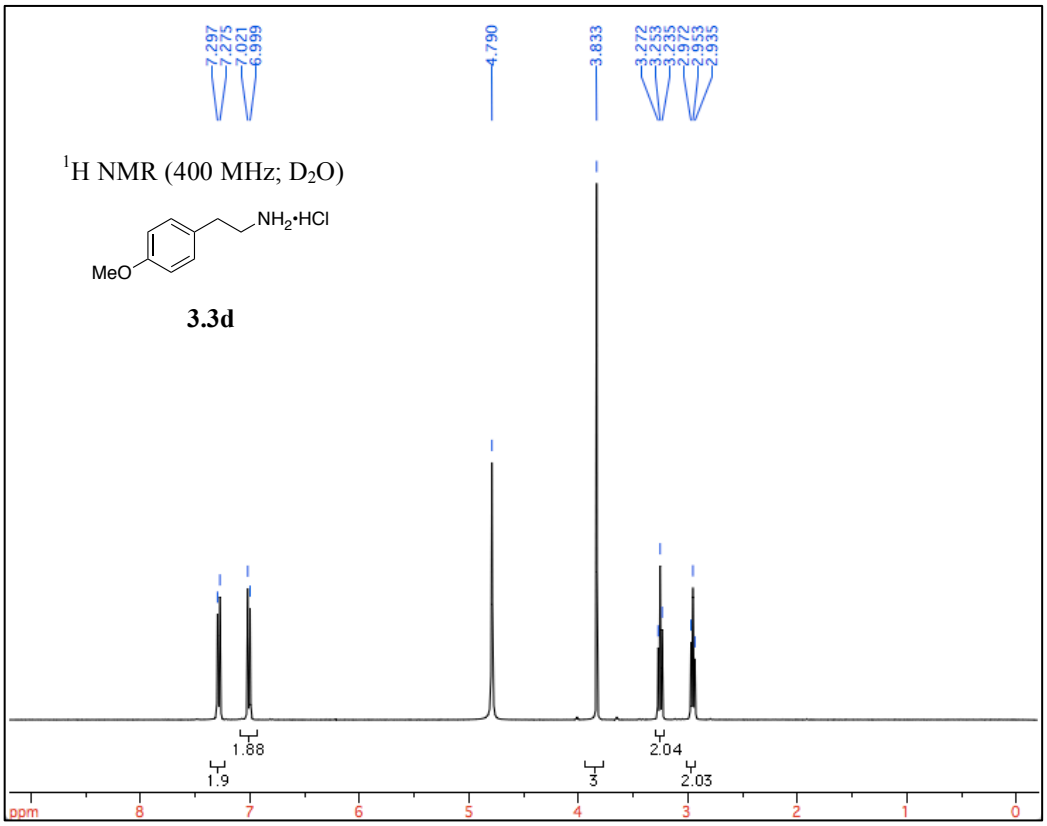


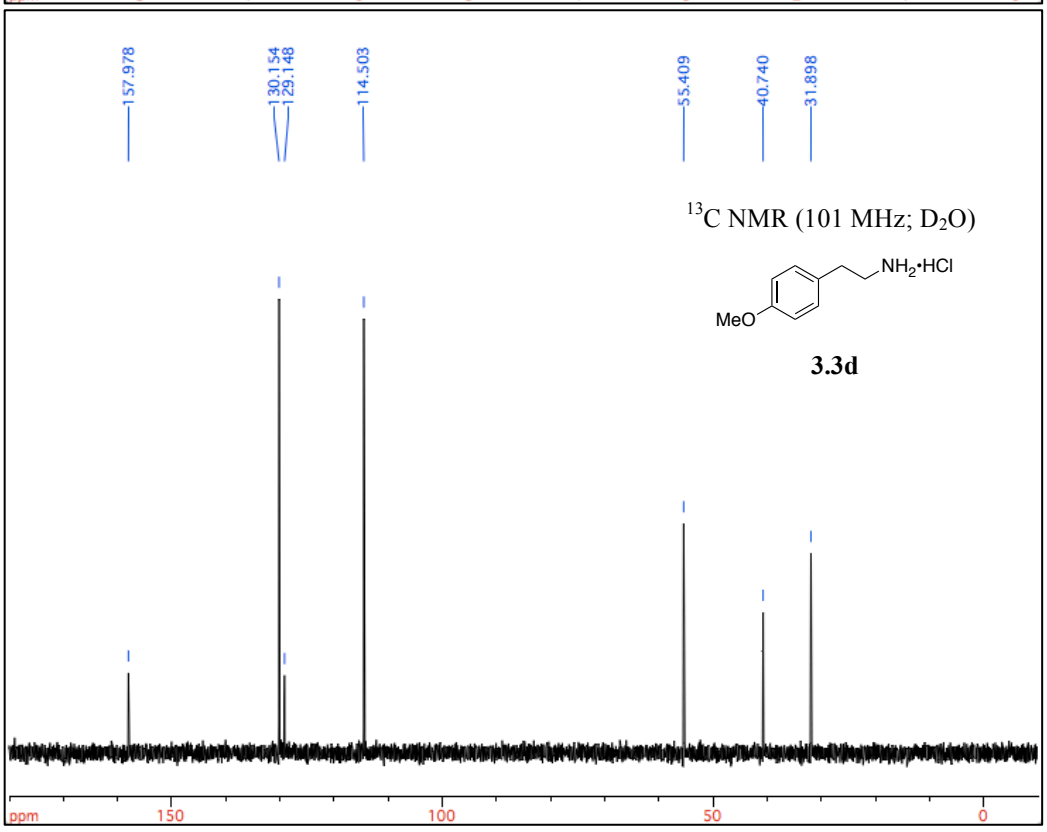
2-(4-(trifluoromethyl)phenyl)ethan-1-amine hydrochloride salt (3.3c)



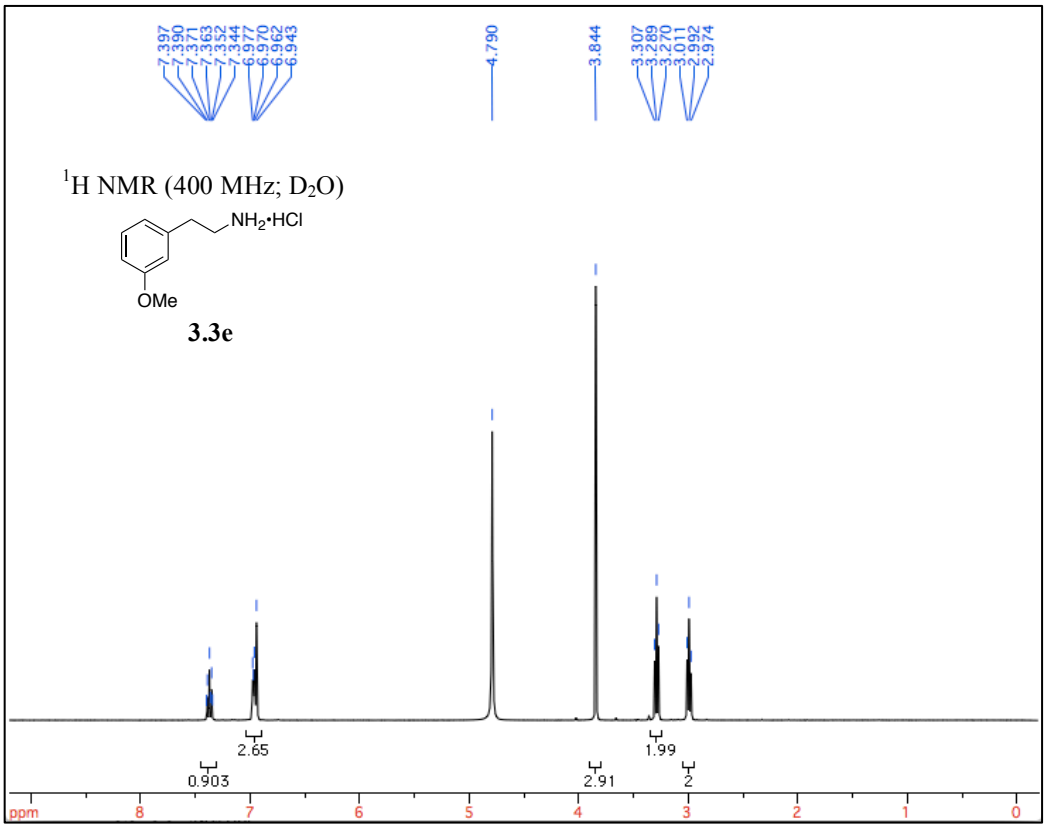


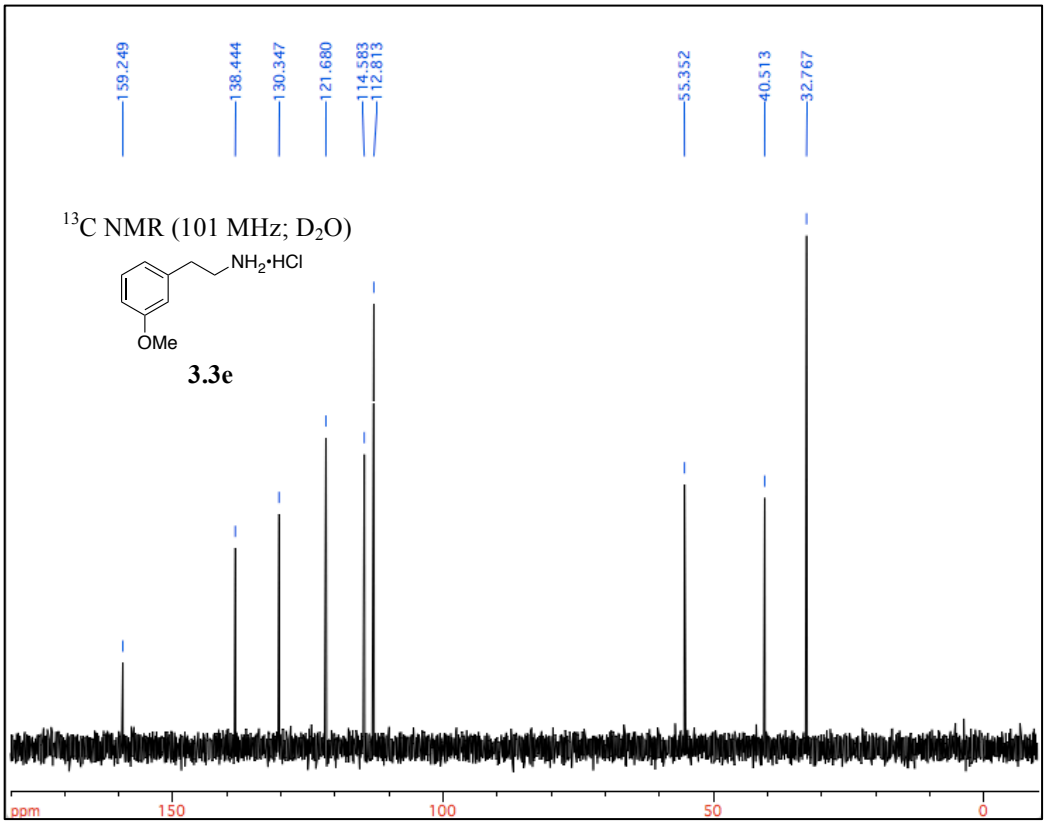
2-(4-methoxyphenyl)ethan-1-amine hydrochloride salt (3.3d)



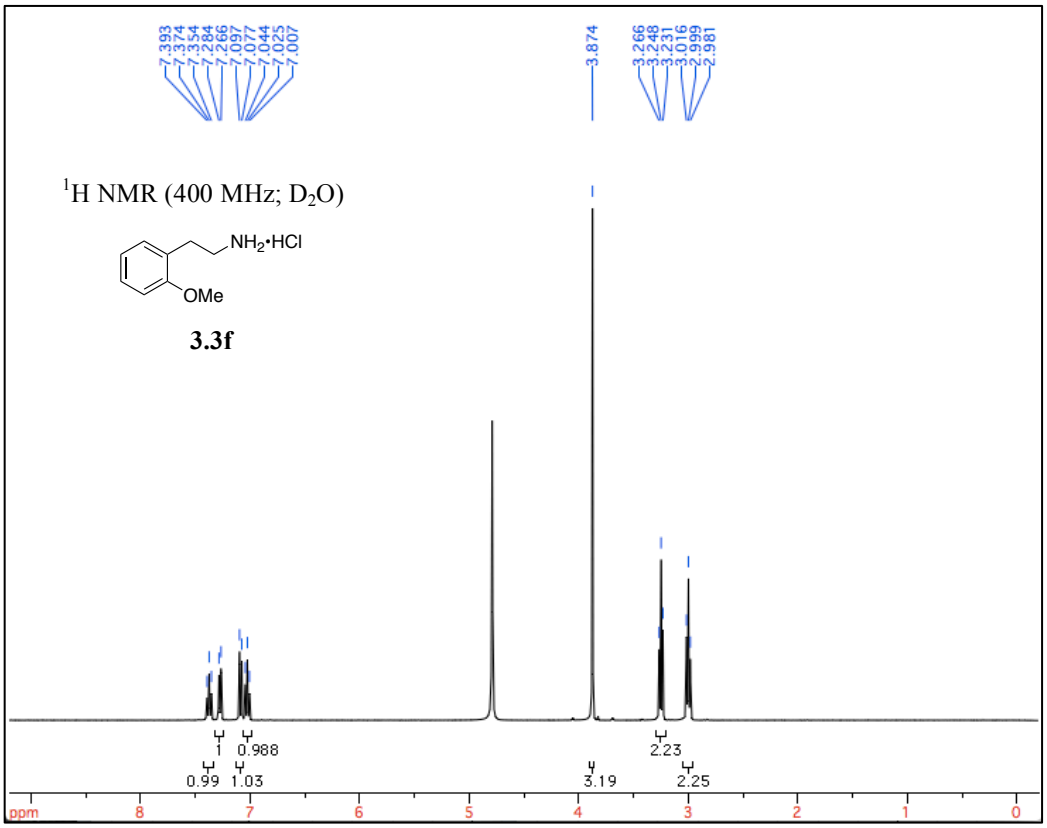


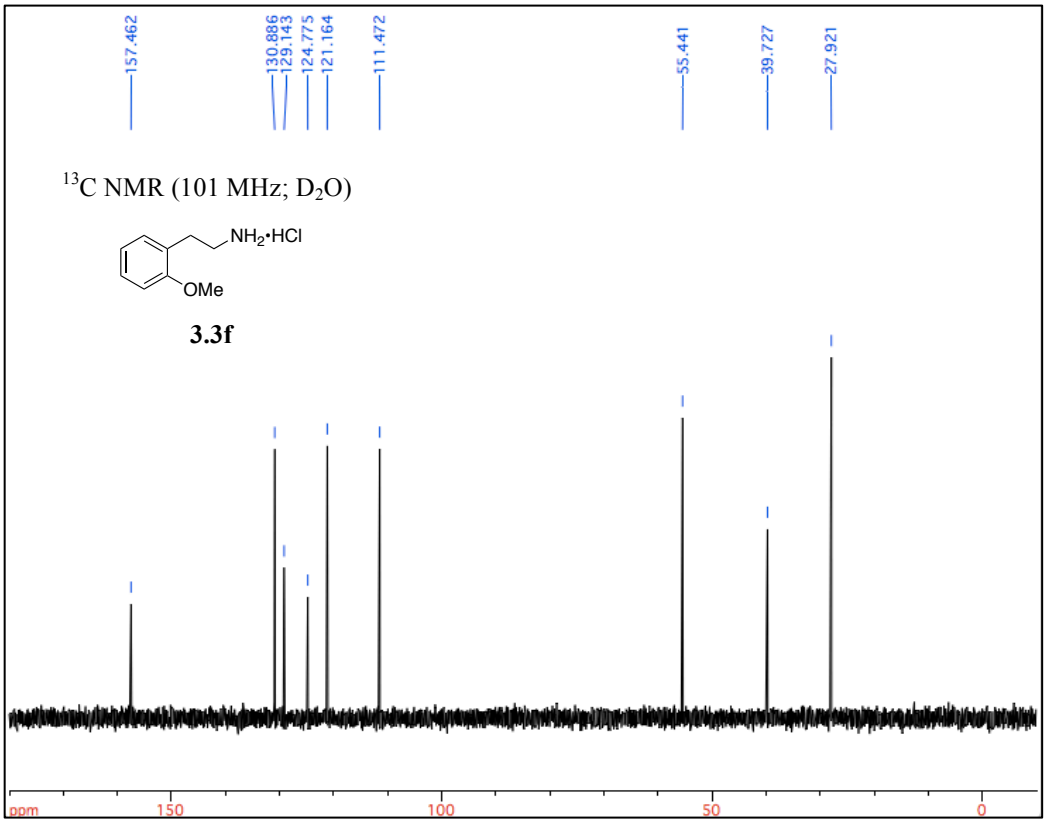
2-(3-methoxyphenyl)ethan-1-amine hydrochloride salt (3.3e)



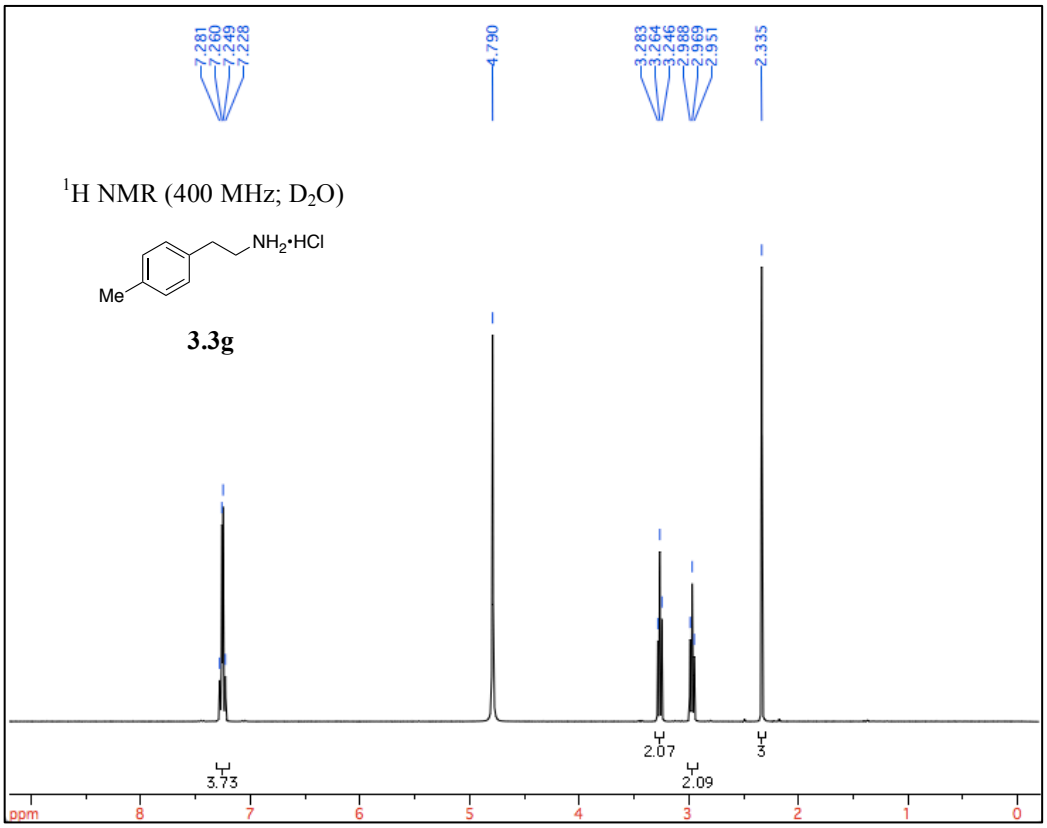


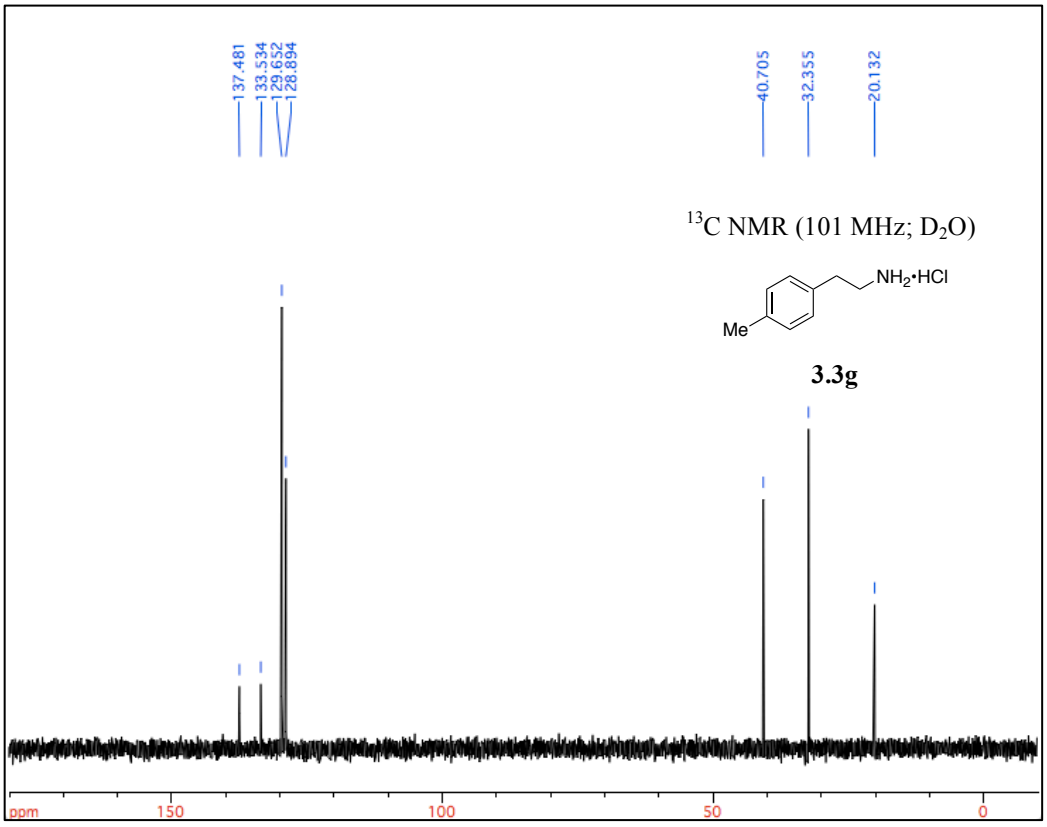
2-(2-methoxyphenyl)ethan-1-amine hydrochloride salt (3.3f)



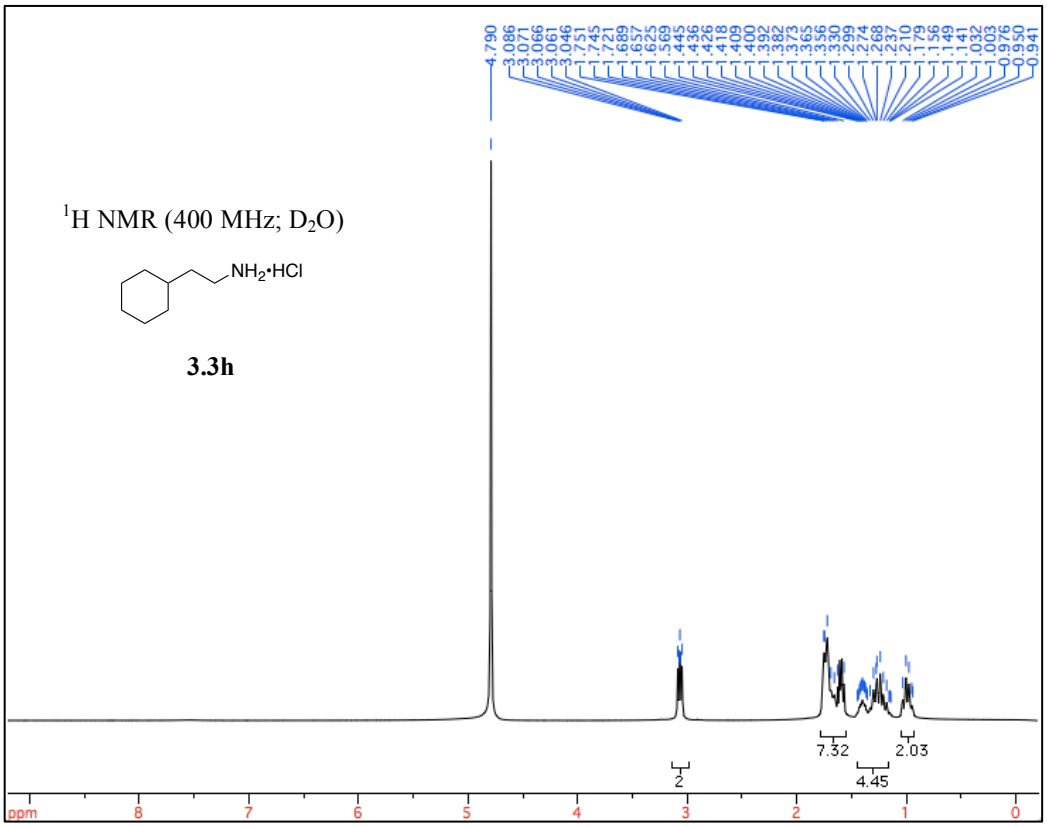


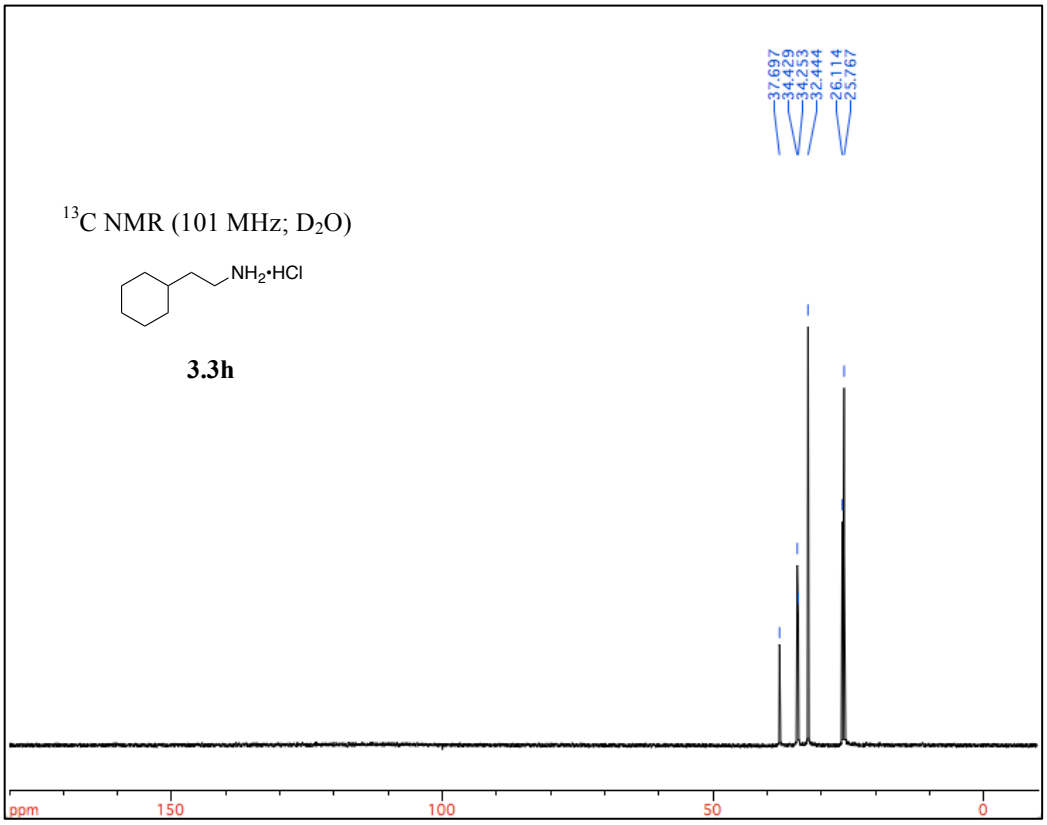
2-(*p*-tolyl)ethan-1-amine hydrochloride salt (3.3g)



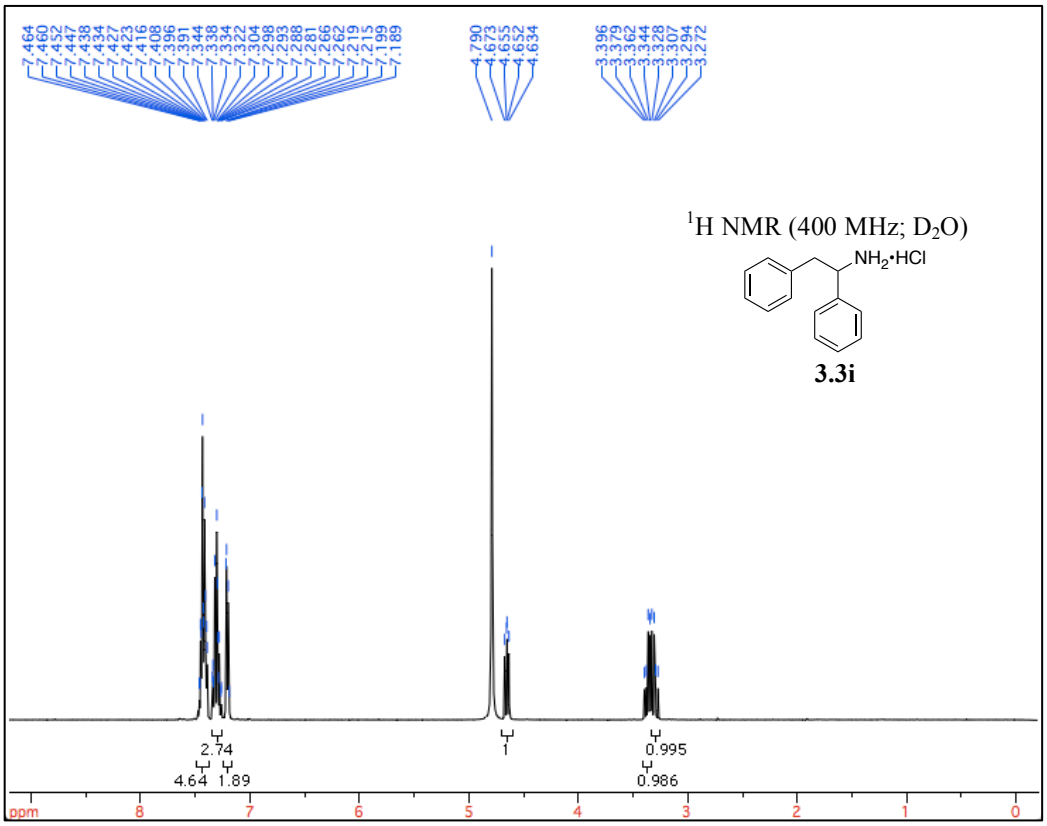


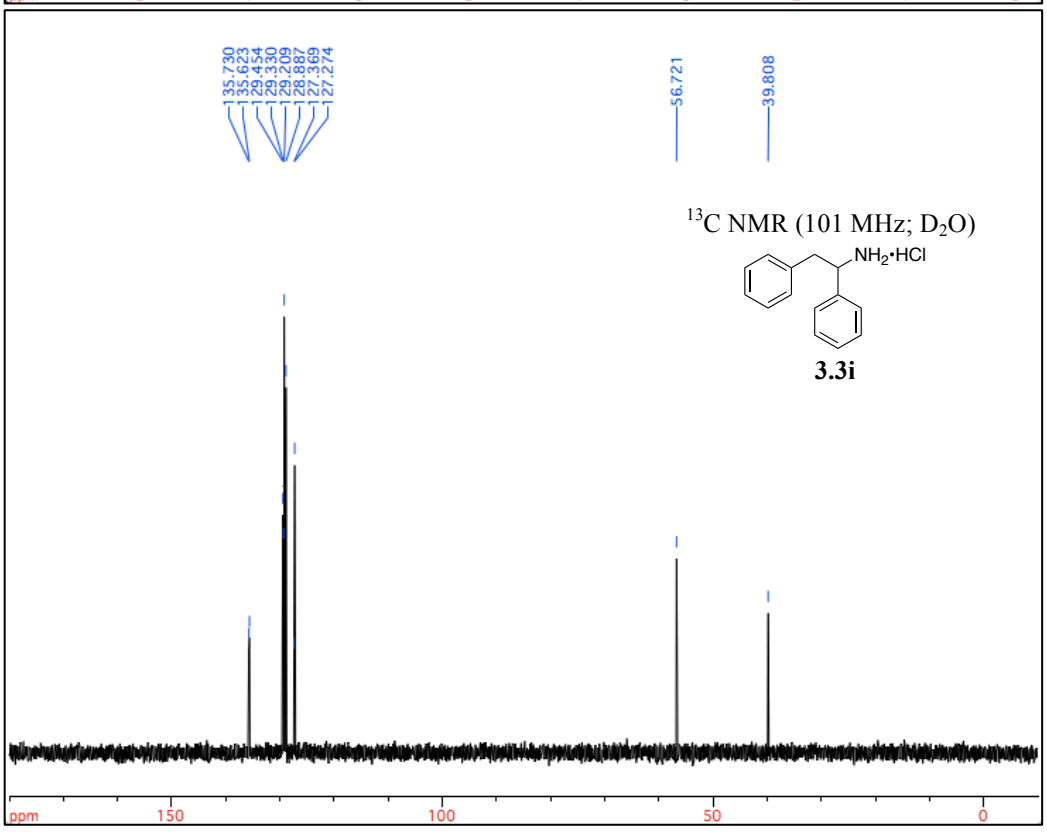
2-cyclohexylethan-1-amine hydrochloride salt (3.3h)





1,2-diphenylethan-1-amine hydrochloride salt (3.3i)





B.6 Solid State Molecular Structures and X-Ray Crystallographic Data

Single crystal X-ray structure determinations were performed at the X-ray crystallography lab at the Department of Chemistry, University of British Columbia on either a Bruker X8 APEX or Bruker APEX DUO diffractometer using graphite-monochromated Mo Kα radiation (λ=0.71073 Å). Unless otherwise noted, data integration was performed using Bruker SAINT (v.8.34A),[387] absorption correction was performed using Bruker SADABS (2014/5),[387] structures were solved using direct methods using SIR2004 or SHELXS,[388,389] and refinement (including modelling of disorder) was performed using SHELXL (2014/7)[390] using the OLEX2[391] interface.

Compound **LS590**: Disorder was modelled for a single benzamidate benzene ring (of the four present in the asymmetric unit). This group was split into two parts using the SIMU constraint, with each part being assigned a free variable and refined freely. Electron density from disordered solvent molecules was masked using OLEX2.

	Complex **3.1a (LS648)**	Complex **3.2b (LS599)**	Complex **3.3c (LS590)**
formula	$C_{46}H_{66}N_4O_2SiTi$	$C_{52}H_{71}N_4O_2SiTi$	$C_{244}H_{256}N_{16}O_8Si_4Ti_4$
F_w	783.01	860.11	3844.59
crystal size (mm)	0.58 x 0.51 x 0.46	0.28 x 0.26 x 0.24	0.42 x 0.32 x 0.17
color, habit	yellow, prism	orange, prism	yellow, prism
crystal system	Monoclinic	Monoclinic	Triclinic
space group	$P2_1/n$	$P2_1/n$	P-1
T (K)	90	90	100
a (Å)	12.4428(12)	12.8621(10)	812.843
b (Å)	27.623(3)	21.1899(17)	20.558
c (Å)	13.2015(12)	18.8390(15)	23.390
α (Å)	90	90	72.79
β (Å)	92.073(2)	104.842(2)	77.72
γ (Å)	90	90	72.76
V (Å^3)	4534.4(7)	877.79(15)	5580.9
Z	4	4	1

ρ_{calcd} (g cm^{-3})	1.147	1.151	1.144
F(000)	1688.0	1852.0	2040.0
μ (Mo$_{K\alpha}$) (mm^{-1})	0.254	0.238	0.219
$2\theta_{max}$ (°)	54.36	60.124	60.126
total no. of reflns	70628	59876	124636
no. of unique reflns	10001	14512	32571
R_1 (F^2, all data)	0.0470	0.0605	0.0556
wR_2 (F^2, all data)	0.0939	0.1155	0.1046
R_1 (F, $I > 2\sigma(I)$)	0.0376	0.0427	0.0396
wR_2 (F, $I > 2\sigma(I)$)	0.0886	0.1056	0.0965
goodness of fit	1.049	1.012	1.028

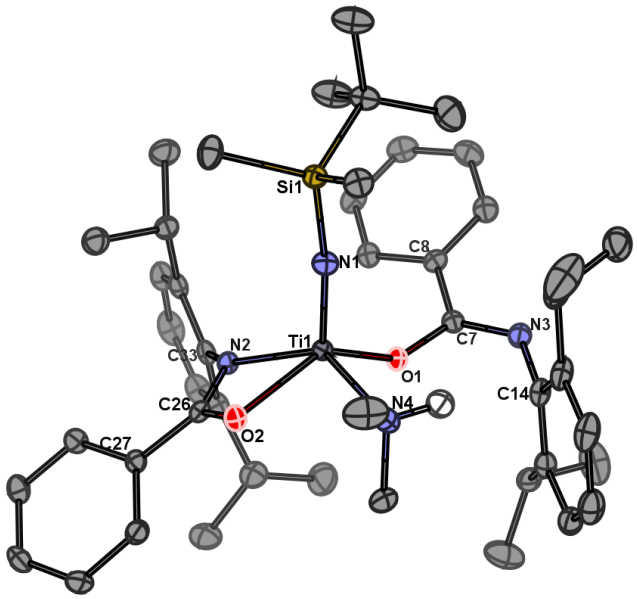


Figure B.2 Single crystal molecular structure of complex 3.1a

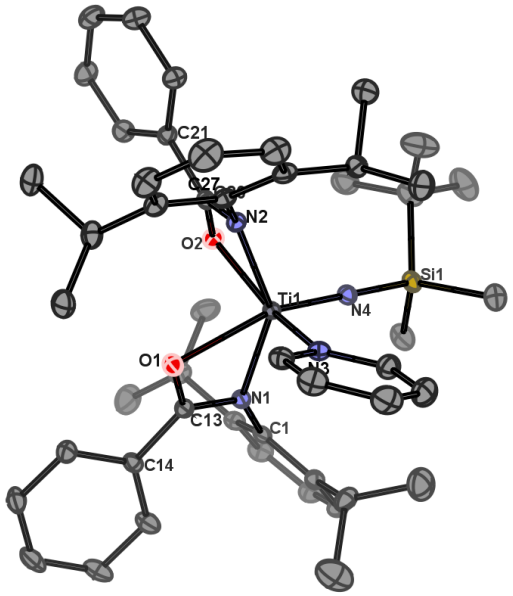


Figure B.3 Single crystal molecular structure of complex 3.1b

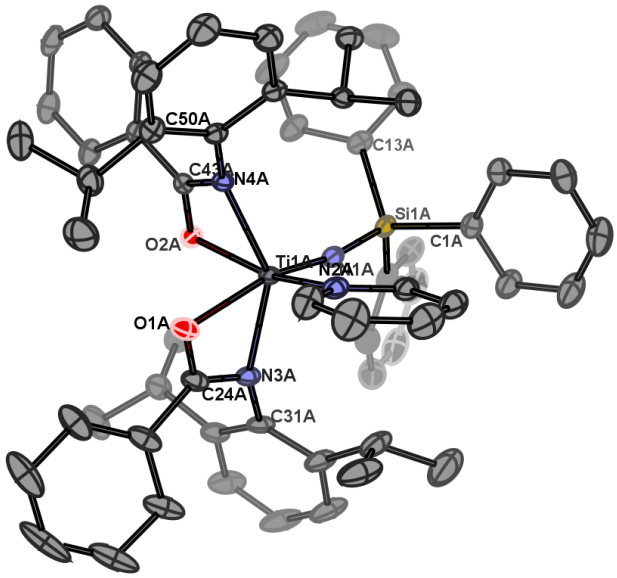


Figure B.4 Single crystal molecular structure of complex 3.1c

B.7 Computational Data and Details

Geometry optimizations and single point frequency calculations were performed with Gaussian 09 (Revision E.01)[392] at the B3LYP/6-311g(d,p) level of theory.[393-396] NBO calculations were performed with the NBO 6.0 program,[397] linked to through the Gaussian software. Frequency calculations showed no negative frequencies for all structures ensuring the calculated structures were at a minimum. Solvation effects were accounted for using the PCM model (solvent = benzene),[398] however, these results differed significantly from experiment. The PCM model was not used given the strong agreement with experiment (as shown below) without the model.

Optimized geometry for **3.4a**

N	1.93552300	-0.50785900	-0.56611500
H	2.00346100	-1.50911000	-0.69998000
C	3.21517300	1.57401100	-0.21758500
H	2.40732500	2.13006200	0.26377500
H	4.15703600	1.97936500	0.16026400
H	3.16490900	1.75501100	-1.29361400
C	3.12288500	-0.17716500	1.60144200
H	3.08760000	-1.24825600	1.82086800
H	4.01708000	0.23724500	2.07631500
H	2.24653500	0.28716900	2.06087400
C	0.65566100	-0.07049800	-0.29002800
C	-0.46301200	-0.82185500	-0.35221400
H	0.58739600	0.98516700	-0.05157700
H	-0.35589300	-1.88871900	-0.53988300
C	-1.83360000	-0.34295200	-0.17719800
C	-2.86571000	-1.27561100	0.03397500
C	-2.19261500	1.01843700	-0.20998400
C	-4.18304700	-0.87234600	0.22335500
H	-2.62144000	-2.33308000	0.05530900
C	-3.50754000	1.42125500	-0.01234600
H	-1.43881600	1.77039700	-0.41501200
C	-4.51431000	0.48072300	0.20717300
H	-4.95383200	-1.61848000	0.38475600
H	-3.75218700	2.47778900	-0.04419000
H	-5.54041800	0.79828700	0.35278700
C	3.13699300	0.06726100	0.07872400
C	4.34487400	-0.63736600	-0.55632500
H	4.30562600	-1.71724100	-0.37821100
H	4.36429700	-0.46873000	-1.63559000
H	5.27814100	-0.26523200	-0.12800600

Optimized geometry for **3.4b**

N	-1.71184100	-0.21726300	-0.63169600
C	-0.72258300	-0.80471300	-0.10750600
H	-0.65908700	-1.05619100	0.95932900
C	1.74868900	-0.50573200	-0.44884400
C	2.73530200	-1.20473200	0.25137500
C	1.93809600	0.86128000	-0.68458000
C	3.88568100	-0.55901600	0.70272900
H	2.60630100	-2.26607000	0.43916100
C	3.08618300	1.50850800	-0.23764400
H	1.17775200	1.41712600	-1.22339800
C	4.06470400	0.79980200	0.45871000
H	4.64215100	-1.11933300	1.24116400
H	3.21900900	2.56678000	-0.43412600
H	4.95989800	1.30344700	0.80575600
C	0.48418900	-1.19358700	-0.93062000
H	0.27432700	-0.94138700	-1.97240300
H	0.61885000	-2.27946000	-0.86754100
C	-2.89748000	0.17803500	0.15362800
C	-3.02814100	1.70269000	-0.02350100
H	-3.04431800	1.95857200	-1.08481400
H	-3.94788800	2.06869800	0.44149500
H	-2.18083800	2.21787700	0.43724800
C	-2.85686600	-0.17063100	1.65057400
H	-2.77555000	-1.24912100	1.81387200
H	-2.02088500	0.31779700	2.15925000
H	-3.77834100	0.16690700	2.13144100
C	-4.09436300	-0.52504500	-0.51412500
H	-5.03591700	-0.19947300	-0.06295600
H	-4.11742300	-0.29663000	-1.58146200
H	-4.01560900	-1.60984200	-0.40130700

Optimized geometry for **3.5a**

N	0.67143500	-0.49708500	0.21620200
H	0.75131100	-1.49756200	0.34923900
Si	2.13145100	0.47976900	0.41607700
C	1.79780900	2.16555800	-0.35532800
H	1.04817000	2.72480700	0.21182200
H	2.71056400	2.76853800	-0.35655200
H	1.44931700	2.08449600	-1.38783000
C	2.52468900	0.70882400	2.24858000
H	2.72799500	-0.24327200	2.74696200
H	3.39206700	1.35795000	2.40176000
H	1.67245500	1.16803600	2.75857400
C	3.55559300	-0.45314500	-0.47171100
C	4.89320300	0.27423800	-0.21431200
H	5.70730900	-0.23422500	-0.74519500
H	4.87403900	1.30947200	-0.56924200
H	5.15600200	0.28814600	0.84732000
C	3.28982800	-0.49897500	-1.99088000
H	4.08261300	-1.06268100	-2.49803100
H	2.33712300	-0.98310600	-2.22284000
H	3.27028100	0.50231100	-2.43064700
C	3.66777200	-1.89826300	0.06049700
H	4.50953900	-2.41286900	-0.41886300
H	3.84049600	-1.93090600	1.14056300
H	2.77199600	-2.48835100	-0.15842700
C	-0.63969600	-0.06467500	0.10232700
C	-1.73867700	-0.84312400	0.15628900
H	-0.74046500	1.00531700	-0.04739700
H	-1.60343600	-1.90677200	0.34484700
C	-3.12473300	-0.39866800	0.01134900
C	-4.16583500	-1.29174800	0.32396000

C	-3.49189000	0.88664400	-0.43254300
C	-5.50175600	-0.91967600	0.21632200
H	-3.91506800	-2.29227200	0.66225800
C	-4.82600600	1.25958400	-0.53463200
H	-2.72674100	1.60029900	-0.71708300
C	-5.84337800	0.36134700	-0.21015100
H	-6.27855700	-1.63407400	0.46749400
H	-5.07555700	2.25737200	-0.88000300
H	-6.88336000	0.65464700	-0.29581500

Optimized geometry for **3.5b**

N	0.51419000	-0.20651300	0.43974900
C	1.77421100	0.41463600	-2.26213200
H	0.85385000	0.87971100	-2.62925400
H	2.60961200	0.93485500	-2.73991800
H	1.78494800	-0.62016700	-2.61574700
C	1.86060700	2.36269700	0.11528000
H	1.84030200	2.48171800	1.20116500
H	2.73267000	2.89935000	-0.26993300
H	0.96816500	2.85038900	-0.28825600
C	3.45381600	-0.34708300	0.28790000
C	4.71912200	0.22818900	-0.38262700
H	5.61434500	-0.27090100	0.00905200
H	4.71427900	0.08064900	-1.46686500
H	4.83617600	1.29929500	-0.18983600
C	3.36594900	-1.85778200	-0.01410000
H	4.25301500	-2.37318700	0.37513700
H	2.48886500	-2.31229100	0.45485600
H	3.31880300	-2.06190300	-1.08850800
C	3.55524200	-0.14971400	1.81533100
H	4.42582800	-0.69017900	2.20840300
H	3.67824700	0.90385700	2.08360000
H	2.66608300	-0.52448100	2.32824400
C	-0.50075000	-0.72666300	-0.10351800
H	-0.64723600	-0.77244600	-1.19844900
C	-2.95831200	-0.62908800	0.38380500
C	-3.86351700	-1.15221200	-0.54418100
C	-3.26766600	0.58490200	1.00819300
C	-5.04998300	-0.48331400	-0.84052900
H	-3.64237400	-2.09585000	-1.03305400
C	-4.45330700	1.25346100	0.71713300

H	-2.57273000	1.00485900	1.72795100
C	-5.34869700	0.72151000	-0.20971300
H	-5.74228500	-0.90704600	-1.55969900
H	-4.67994600	2.18972100	1.21524800
H	-6.27310700	1.24106200	-0.43538800
C	-1.64712500	-1.32867100	0.68685200
H	-1.39830200	-1.26273700	1.74770600
H	-1.73119900	-2.38899900	0.42048200
Si	1.89036600	0.54393600	-0.37723800

Optimized geomtry for **3.6a**

C	-0.92574300	0.32444800	0.04190800
H	-0.92196400	0.32447900	1.12823100
C	1.58073800	0.08835300	0.04979300
C	2.29719700	-1.22707700	-0.33000500
C	2.49031300	1.29623800	-0.27275500
H	1.42190200	0.07730600	1.13787600
C	3.68338100	-1.34977700	0.31863400
H	2.40307000	-1.26713500	-1.42285000
H	1.66682400	-2.07667100	-0.04892000
C	3.87685400	1.17527500	0.37594800
H	2.60478700	1.36887600	-1.36296200
H	1.99598500	2.21818100	0.04887200
C	4.56953900	-0.13972700	-0.00682600
H	4.16965200	-2.27569800	-0.00627000
H	3.56570900	-1.42646500	1.40763700
H	4.50008500	2.02976000	0.09140700
H	3.76930700	1.22022500	1.46775600
H	5.53331400	-0.22483100	0.50612100
H	4.78842300	-0.13235400	-1.08273000
C	0.23543300	0.19923700	-0.61546200
H	0.23273800	0.19731100	-1.70628400
N	-2.17974000	0.54316300	-0.52502900
H	-2.16946400	0.44735900	-1.53355400
C	-3.40594700	-0.03916000	0.06628600
C	-4.57179700	0.41700000	-0.82351600
H	-4.44988300	0.04692800	-1.84715600
H	-5.52206700	0.03435400	-0.44375200
H	-4.62240900	1.50775400	-0.85853000
C	-3.34440600	-1.58025900	0.10077400
H	-3.22207900	-1.98394600	-0.90876200

H	-2.49780500	-1.92279000	0.70127900
H	-4.25850700	-2.00415900	0.52724100
C	-3.60774500	0.51535300	1.48627300
H	-3.59969700	1.60755200	1.47286400
H	-4.56675200	0.17793700	1.88776200
H	-2.82989300	0.17445800	2.17360800

Optimized geometry for **3.6b**

N	-1.91762000	-0.36109400	-0.51688900
C	-0.98560200	-0.73910600	0.25076300
H	-1.05731000	-0.69650600	1.34751000
C	0.30654700	-1.29541500	-0.28356800
H	0.26169800	-1.28232800	-1.37626700
H	0.37633500	-2.34647500	0.03017200
C	1.56322800	-0.55651500	0.21900100
C	2.84324400	-1.31294700	-0.17923400
C	1.62253900	0.89753600	-0.28277900
H	1.52397000	-0.53053400	1.31883800
C	4.11516100	-0.59364700	0.29167300
H	2.86752700	-1.41508300	-1.27269000
H	2.81360900	-2.33045400	0.22648900
C	2.89008100	1.62236500	0.19227900
H	1.59664600	0.89082800	-1.38083300
H	0.73120700	1.44474900	0.03959900
C	4.16038600	0.85814300	-0.20478400
H	5.00185300	-1.13917200	-0.04744000
H	4.14717600	-0.60037600	1.38905200
H	2.91532100	2.63806500	-0.21567500
H	2.85903000	1.72764000	1.28476800
H	5.04787000	1.36540800	0.18741000
H	4.25613500	0.86242300	-1.29838400
C	-3.19911500	0.15979700	-0.00339900
C	-4.28505600	-0.78335000	-0.55567400
H	-4.18043000	-1.78397100	-0.12730200
H	-5.28361200	-0.40781500	-0.31459300
H	-4.19293300	-0.86831500	-1.64021700
C	-3.32285500	0.25548000	1.52663900
H	-3.22974200	-0.72346600	2.00562400

H	-2.56635400	0.91999400	1.95406600
H	-4.30342700	0.65918800	1.79119200
C	-3.36639300	1.55854000	-0.62673000
H	-3.25931900	1.50141000	-1.71167800
H	-4.35052800	1.97268500	-0.38995200
H	-2.60436900	2.24447800	-0.24659900

Optimized geometry for **3.7a**

C	-2.18374600	0.62282900	2.14801200
H	-1.45749900	1.38533500	2.44431900
H	-3.12667300	0.87203600	2.64345800
H	-1.84083200	-0.33717700	2.54125500
C	-2.81715100	2.33030400	-0.31697900
H	-2.98222700	2.36904800	-1.39755100
H	-3.70910400	2.73397900	0.17182000
H	-1.98324900	3.00188300	-0.09064500
C	-3.79667000	-0.64076900	-0.25269700
C	-5.16529900	-0.12751500	0.24402600
H	-5.95800400	-0.83184200	-0.03703000
H	-5.19538200	-0.02582100	1.33335100
H	-5.42259900	0.84241400	-0.19110700
C	-3.53009400	-2.03501600	0.35159700
H	-4.29992600	-2.74513200	0.02432000
H	-2.55850800	-2.43125300	0.04397900
H	-3.55012000	-2.01443600	1.44525200
C	-3.84417500	-0.76305600	-1.79141900
H	-4.65816600	-1.43421200	-2.09246500
H	-4.02132500	0.20062600	-2.27863000
H	-2.92017600	-1.18472100	-2.20028500
C	0.38540400	0.13780400	0.06492900
H	0.42930000	0.48890700	1.09279800
C	2.89779700	0.00536600	0.02783800
C	3.63216200	-1.35254500	0.11436600
C	3.76721000	1.02493300	-0.74236400
H	2.77811300	0.38125900	1.05439100
C	5.04338500	-1.22064400	0.70480900
H	3.69891500	-1.78094500	-0.89511400
H	3.03299700	-2.05066100	0.70735600

C	5.17897700	1.15791800	-0.15375300
H	3.84039000	0.70295900	-1.79024700
H	3.26366300	1.99674100	-0.75176700
C	5.88883800	-0.20029100	-0.06909600
H	5.53957900	-2.19696100	0.71368300
H	4.96661800	-0.90241500	1.75292900
H	5.77052100	1.85909700	-0.75204700
H	5.11095700	1.59086700	0.85302700
H	6.87191400	-0.08693500	0.39993200
H	6.06933100	-0.57730400	-1.08442300
C	1.52789800	-0.13377300	-0.57950100
H	1.48722700	-0.48715500	-1.61065700
N	-0.91043100	0.00135200	-0.43402500
H	-0.93384700	-0.32394400	-1.39189400
Si	-2.41257800	0.58164400	0.27725400

Optimized geometry for **3.7b**

N	-0.74351300	-0.18512900	-0.28741000
C	-2.26142800	1.09232900	2.02711400
H	-1.41186600	1.73074000	2.28956000
H	-3.17003100	1.64914300	2.27469500
H	-2.22688700	0.21279600	2.67606400
C	-2.29375600	2.22497800	-0.83339000
H	-2.21198900	2.01069400	-1.90160300
H	-3.22340600	2.77668700	-0.66581300
H	-1.46416700	2.88599600	-0.56482400
C	-3.66902400	-0.54617900	-0.25563300
C	-5.02150100	0.09565300	0.11904200
H	-5.84552100	-0.57971200	-0.14335600
H	-5.09828400	0.29872900	1.19154700
H	-5.19293000	1.03621300	-0.41390400
C	-3.51116100	-1.87255900	0.51716700
H	-4.32612400	-2.56033500	0.25847400
H	-2.56939600	-2.37187300	0.27289100
H	-3.54440300	-1.72511500	1.60133100
C	-3.65320500	-0.84723100	-1.76893400
H	-4.45402400	-1.55428900	-2.02089200
H	-3.81599700	0.05500500	-2.36606700
H	-2.70321500	-1.28794400	-2.08074500
C	0.24221200	-0.48272900	0.44710000
H	0.28179200	-0.23220600	1.52593300
C	1.46252800	-1.21835200	-0.04595100
H	1.36409000	-1.37436200	-1.12395200
H	1.46350300	-2.20838700	0.43271600
Si	-2.22768400	0.64240300	0.18775700
C	2.79157500	-0.51544900	0.29355600
C	3.99469800	-1.43047100	0.00273000

C	2.94601200	0.82437400	-0.44968200
H	2.79341800	-0.30244700	1.37357600
C	5.33346100	-0.74909200	0.31952800
H	3.97461000	-1.71529700	-1.05788900
H	3.90036300	-2.35972500	0.57555500
C	4.28179300	1.51151800	-0.13142700
H	2.88153400	0.63643900	-1.52984000
H	2.11235300	1.49081800	-0.20585800
C	5.47480300	0.58944200	-0.41821300
H	6.16311800	-1.41502600	0.06091300
H	5.40146000	-0.57357700	1.40107300
H	4.37140200	2.43848600	-0.70698600
H	4.29612400	1.80094600	0.92749600
H	6.41164800	1.08097000	-0.13664700
H	5.53294600	0.40151100	-1.49821800

Appendix C

This appendix is for the supporting information pertaining the research conducted in Chapter 4.

C.1 General considerations

All air and moisture sensitive reactions were performed using a MBraun LABmaster glovebox filled with a N_2 atmosphere. All pieces of glassware were dried for at least 4 hours in a 160 °C oven before being transferred into the glovebox. All stirring was done with appropriately sized Teflon coated magnetic stir bars dried for at least 4 hours in a 160 °C oven. Benzene and hexanes were passed over activated alumina columns into Teflon sealed Straus flasks and stored therein until use. d_6-Benzene was dried over sodium metal, distilled, degassed, and stored in Teflon sealed Schlenk flasks prior to use. Experiments conducted on NMR tube scale were performed in J-Young NMR tubes (8" x 5 mm) sealed with screw-type Teflon caps. Thin layer chromatography (TLC) was set-up on EMD Silica gel 60 F254 plates. Visualization was achieved under a 254 nm UV light source and/or by staining with potassium permanganate or ninhydrin solutions. Flash chromatography was set-up using SiliaFlash F60 silica gel (230-400 mesh) (Silicycle) and glass columns, with ACS grade solvents (Sigma-Aldrich).

C.2 Materials

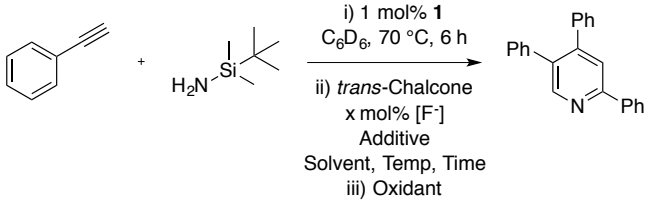
Commercially available terminal and internal alkynes were dried over CaH_2 and distilled or sublimed prior to use. Synthesized terminal and internal alkynes were made following previously reported conditions[399] and were also dried prior to use. Commercially available α,β-unsaturated carbonyls were dried over CaH_2 and distilled or sublimed prior to use. Synthesized α,β-unsaturated carbonyls were made following previously reported conditions[308-310, 325] and were also dried prior to use. The oxidant, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (Combi-Blocks), was used as received.

C.3 Instrumentation

NMR spectra were recorded as dilute solutions in deuterated chloroform or benzene on a Bruker Avance 400, 400 or 600 MHz spectrometer at ambient temperature. ^{1}H chemical shift data are given in units δ relative to the residual protic solvent where δ ($CDCl_3$) = 7.26 ppm and δ (C_6D_6) = 7.16 ppm, while ^{13}C chemical shift data are given in units δ relative to the solvent where δ ($CDCl_3$) = 77.16 ppm and δ (C_6D_6) = 128.06 ppm. High-resolution mass spectra were measured by the mass spectrometry and microanalysis service at the Department of Chemistry, University of British Columbia. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC spectrometer using electrospray ionization source. Fragment signals are given in mass per charge number (*m/z*).

C.4 Synthesis and Compound Characterization

General Procedure for the Optimization of the Pyridine Synthesis



Inside an inert atmosphere box, benzene (0.15 mL) was added to the titanium complex (0.005 mmol, 1 mol% Ti) in a 5-dram vial. The solution was then transferred to a J-Young tube. The amine (0.5 mmol, 1 equiv.) and alkyne (0.5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the J-Young tube. The remaining benzene (0.35 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction tube. The J-Young tube was sealed, taken out of the inert atmosphere box and heated at 70 °C for 6 hours. The reaction vessel was re-introduced into the inert atmosphere box, where the reaction solution was transferred with hexanes (0.5 mL) to a Radley's parallel reactor tube containing pre-weighed

trans-chalcone (0.5 mmol, 1 equiv.) and 3Å molecular sieves (0.1000 g). Outside the inert atmosphere box, the Radley's tube was connected to a Radley's parallel reactor. The tubing was evacuated and purged with nitrogen gas three times before the solvent inside the reaction mixture was removed under reduced pressure. Under nitrogen, the new solvent (0.5 mL) was introduced using a syringe and needle. If a solid fluoride source (0.05 mmol, 10 mol% F) was used, it was introduced inside the glovebox together with the *trans*-chalcone, however, if 1M TBAF in THF (0.05 mmol, 10 mol% F) was used, it was added after the addition of new solvent using a syringe and needle. The reaction mixture was allowed to stir at a specific temperature and time. In some cases, oxidants were subsequently added to the reaction mixture. Upon completion, the solvents were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the desired compound as a colourless solid.

General Procedure A: Procedure for the Synthesis of Poly-Substituted Pyridines Using High Boiling α,β-Unsaturated Carbonyls

Inside an inert atmosphere box, d_6-benzene or d_8-toluene (0.15 mL) was added to the titanium complex (0.005 mmol, 0.0125 mmol or 0.025 mmol, 1 mol% Ti, 2.5 mol% Ti or 5 mol% Ti) in a 5-dram vial. The solution was then transferred to a J-Young tube. The amine (0.5 mmol, 1 equiv.) and alkyne (0.5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the J-Young tube. The remaining benzene or toluene (0.35 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction tube. The J-Young tube was sealed, taken out of the inert atmosphere box and heated at 70 °C, 110 °C or 145 °C for a specific time. The reaction vessel was re-introduced into the inert atmosphere box, where the reaction solution was transferred with hexanes (0.5 mL) to a Radley's parallel reactor tube containing pre-weighed α,β-unsaturated carbonyl (0.5 mmol, 1 equiv.) and 3Å molecular

sieves (0.1000 g). Outside the inert atmosphere box, the Radley's tube was connected to a Radley's parallel reactor. The tubing was evacuated and purged with nitrogen gas three times before the solvent was evacuated under reduced pressure. The DMSO (0.25 mL or 0.50 mL) was introduced using a syringe and needle. After the addition of solvent, 1M TBAF in THF (0.05 mmol 10 mol% F) was also added using a syringe and needle. The reaction mixture was allowed to stir at room temperature, 50 °C, 80 °C or 100 °C for 18 hours. Upon completion, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.5 mmol, 1 equiv.) and more DMSO (0.25 mL or 0.50 mL) were added to the reaction mixture, which was allowed to react for 1 hour. The volatiles were removed under reduced pressure and purification by column chromatography afforded the desired compounds.

General Procedure B: Procedure for the Synthesis of Poly-Substituted Pyridines Using Low Boiling α,β-Unsaturated Carbonyls

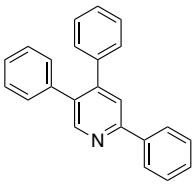
Inside an inert atmosphere box, d_6-benzene or d_8-toluene (0.15 mL) was added to the titanium complex (0.005 mmol, 1 mol% Ti) in a 5-dram vial. The solution was then transferred to a J-Young tube. The amine (0.5 mmol, 1 equiv.) and alkyne (0.5 mmol, 1 equiv.) were pre-weighed to separate 5-dram vials and transferred to the J-Young tube. The remaining benzene or toluene (0.35 mL) was used to rinse the vials containing amine and alkyne, which were also transferred to the reaction tube. The J-Young tube was sealed, taken out of the inert atmosphere box and heated at 70 °C for a specific time. The reaction vessel was re-introduced into the inert atmosphere box, where the reaction solution was transferred with hexanes (0.5 mL) to a Radley's parallel reactor tube. The solvent was removed under reduced pressure and then the α,β-unsaturated carbonyl (0.5 mmol, 1 equiv.) and 3Å molecular sieves (0.1000 g) were added to the reaction mixture. Outside the inert atmosphere box, the Radley's tube was connected to a

Radley's parallel reactor. The tubing was evacuated and purged with nitrogen gas three times before DMSO (0.25 mL) was introduced using a syringe and needle. After the addition of solvent, 1M TBAF in THF (0.05 mmol 10 mol% F) was also added using a syringe and needle. The reaction mixture was allowed to stir at room temperature for 18 hours. Upon cooling, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.5 mmol, 1 equiv.) and more DMSO (0.50 mL) were added to the reaction mixture, which was allowed to react for 1 hour. The volatiles were removed under reduced pressure and purification by column chromatography afforded the desired compounds.

General Procedure C: One-Pot Procedure for the Synthesis of Poly-Substituted Pyridines

Inside an inert atmosphere box, the titanium complex (0.005 mmol, 1 mol% Ti) was weighed into a Teflon sealed reaction vessel. The amine (0.5 mmol, 1 equiv.) and alkyne (0.5 mmol, 1 equiv.) were also weighed into the reaction vessel. The vessel was sealed, taken out of the inert atmosphere box and heated at 70 °C for 3 hours. The reaction vessel was re-introduced into the inert atmosphere box. The α,β-unsaturated carbonyl (0.5 mmol, 1 equiv.) and 3Å molecular sieves (0.1000 g) were then added to the reaction mixture. Outside the inert atmosphere box, the reaction vessel was evacuated and purged with nitrogen gas three times before DMSO (0.25 mL) was introduced using a syringe and needle. After the addition of solvent, 1M TBAF in THF (0.05 mmol 10 mol% F) was also added using a syringe and needle. The reaction mixture was allowed to stir at room temperature, 80 °C or 100 °C for 18 hours. Upon cooling, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.5 mmol, 1 equiv.) and more DMSO (0.50 mL) were added to the reaction mixture, which was allowed to react for 1 hour. The crude mixture was filtered through a Celite pad and the Celite was rinsed with ethyl acetate. The volatiles were then removed under reduced pressure. Purification by column chromatography afforded the desired compounds.

2,4,5-Triphenylpyridine



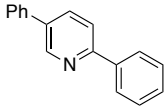
According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, chalcone (0.1041 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 85% yield. The analytical data were consistent with literature.[270] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.73 (s, 1H), 8.10-8.07 (m, 2H), 7.79 (s, 1H), 7.53-7.49 (m, 2H), 7.44 (m, 1H), 7.32-7.27 (m, 6H), 7.24-7.18 (m, 4H).**^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.4, 150.8, 148.8, 139.04, 138.92, 137.6, 134.4, 129.9, 129.4, 129.2, 128.9, 128.43, 128.40, 128.0, 127.4, 127.1, 121.8.

3-phenylpyridine (4.1a)

According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, prop-2-enal (0.0280 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (85:15 Hex/EtOAc) afforded the title compound as a colourless solid in 34% yield. The analytical data were consistent with literature.[400] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.61 (d, J = 2.7 Hz, 1H), 7.94-7.90 (m,

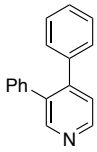
1H), 7.61-7.57 (m, 2H), 7.52-7.46 (m, 2H), 7.45-7.38 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.32, 148.21, 137.8, 136.9, 134.7, 129.2, 128.3, 127.3, 123.8.

2,5-diphenylpyridine (4.1b)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 1-phenylprop-2-en-1-one (0.0661 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (75:25 Hex/EtOAc) afforded the title compound as a colourless solid in 40% yield. The analytical data were consistent with literature.[401] **^{1}H NMR** (400 MHz, $CDCl_3$) 8.94 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.06-8.03 (m, 2H), 7.96 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.82 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.66-7.63 (m, 2H), 7.52-7.49 (m, 4H), 7.46-7.40 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.3, 148.2, 139.1, 137.8, 135.22, 135.04, 129.24, 129.13, 128.94, 128.2, 127.14, 126.97, 120.5.

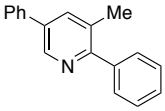
3,4-diphenylpyridine (4.1c)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, cinnamaldehyde (0.0661 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (85:15 Hex/EtOAc)

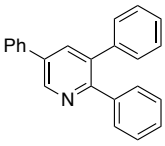
afforded the title compound as a colourless solid in 13% yield.[319] The analytical data were consistent with literature. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.63 (d, *J* = 5.0 Hz, 1H), 7.34 (d, *J* = 5.0 Hz, 1H), 7.28-7.26 (m, 6H), 7.17-7.14 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.5, 148.5, 148.2, 138.5, 137.6, 136.2, 129.9, 129.4, 128.5, 128.1, 127.6, 124.9.

3-methyl-2,5-diphenylpyridine (4.1d)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 2-methyl-1-phenylprop-2-en-1-one (0.0731 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 47% yield. The analytical data were consistent with literature.[402] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 2.1 Hz, 1H), 7.81 (d, *J* = 1.9 Hz, 1H), 7.65-7.62 (m, 2H), 7.60-7.57 (m, 2H), 7.52-7.46 (m, 4H), 7.44-7.40 (m, 2H), 2.45 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 145.5, 140.5, 137.9, 137.1, 135.1, 130.8, 129.18, 129.13, 128.3, 128.1, 127.2, 20.3.

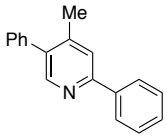
2,3,5-triphenylpyridine (4.1e)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 1,2-diphenylprop-2-en-1-one (0.1041 g) and molecular sieves (0.1000 g) were added following

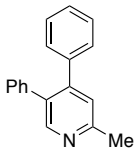
general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 70% yield. The analytical data were consistent with literature.[403] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.3 Hz, 1H), 7.93 (d, *J* = 2.3 Hz, 1H), 7.70-7.67 (m, 2H), 7.53-7.49 (m, 2H), 7.45-7.38 (m, 3H), 7.32-7.29 (m, 3H), 7.27-7.24 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.0, 146.8, 140.01, 139.96, 137.5, 137.0, 136.1, 135.1, 130.0, 129.7, 129.3, 128.5, 128.3, 128.03, 127.93, 127.5, 127.2.

4-methyl-2,5-diphenylpyridine (4.1f)



According to general procedure B, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 1-phenylbut-2-en-1-one (0.0731 g) and molecular sieves (0.1000 g) were added following general procedure B. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 11% yield. The analytical data were consistent with literature.[401] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.04-8.02 (m, 2H), 7.64 (s, 1H), 7.51-7.46 (m, 4H), 7.44-7.36 (m, 4H), 2.38 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.3, 150.0, 145.3, 139.4, 138.0, 136.4, 129.5, 128.96, 128.87, 128.6, 127.7, 127.0, 122.2, 20.3.

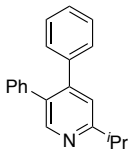
2-methyl-4,5-diphenylpyridine (4.1g)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a

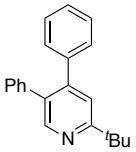
sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 4-phenylbut-3-en-2-one (0.0731 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 23% yield. The analytical data were consistent with literature.[273] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.27-7.24 (m, 6H), 7.21 (s, 1H), 7.16-7.12 (m, 4H), 2.64 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 150.3, 148.2, 138.9, 137.8, 133.2, 129.9, 129.4, 128.3, 128.3, 127.8, 127.2, 124.3, 24.1.

2-isopropyl-4,5-diphenylpyridine (4.1h)



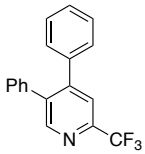
According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 4-methyl-1-phenylpent-1-en-3-one (0.0871 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 49% yield. The analytical data were consistent with literature.[273] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.30-7.27 (m, 6H), 7.20-7.15 (m, 4H), 3.21 (7, J = 6.9 Hz, 1H), 1.42 (d, J = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4, 150.2, 148.4, 139.3, 138.0, 133.4, 129.9, 129.4, 128.3, 128.3, 127.8, 127.2, 121.7, 36.2, 22.8.

2-(*tert*-butyl)-4,5-diphenylpyridine (4.1i)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 96% yield. The analytical data were consistent with literature.[273] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.37 (s, 1H), 7.28-7.24 (m, 6H), 7.18-7.13 (m, 4H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5, 149.9, 148.0, 139.6, 138.1, 132.9, 130.0, 129.5, 128.34, 128.32, 127.8, 127.1, 120.2, 37.4, 30.4.

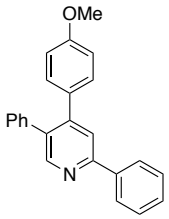
4,5-diphenyl-2-(trifluoromethyl)pyridine (4.1j)



According to general procedure B, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 1,1,1-trifluoro-4-phenylbut-3-en-2-one (0.1001 g) and molecular sieves (0.1000 g) were added following general procedure B. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 68% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.74 (s, 1H), 7.35-7.27 (m, 6H), 7.18-7.15 (m, 4H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.4, 149.4, 147.3 (q, $^{2}J(C,F)$ = 34.6Hz), 138.7,

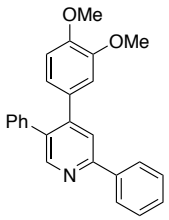
137.6, 136.5, 129.8, 129.4, 128.68, 128.66, 128.2, 121.83 (q, $^{1}J(C,F)$ = 274.1Hz), 121.67 (q, $^{3}J(C,F)$ = 2.7Hz). **^{19}F NMR** (282 MHz; $CDCl_3$): δ -67.7. **HRMS** (ESI+) m/z calc'd for $C_{18}H_{13}NF_3$ [M+H$^+$]: 400.1000; found: 400.1006.

4-(4-methoxyphenyl)-2,5-diphenylpyridine (4.1k)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (0.1191 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (85:15 Hex/EtOAc) afforded the title compound as a colourless solid in 78% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.09-8.06 (m, 2H), 7.76 (s, 1H), 7.53-7.48 (m, 2H), 7.46-7.42 (m, 1H), 7.33-7.28 (m, 3H), 7.23-7.20 (m, 2H), 7.17-7.14 (m, 2H), 6.84-6.81 (m, 2H), 3.81 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.6, 156.5, 101.0, 148.4, 138.0, 134.4, 131.3, 130.7, 129.9, 129.2, 128.9, 128.5, 127.4, 127.1, 121.7, 113.9, 55.4. **HRMS** (EI+) m/z calc'd for $C_{24}H_{19}NO$ [M+H$^+$]: 337.14666; found: 337.14624.

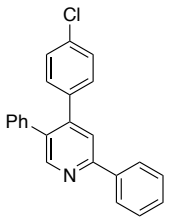
4-(3,4-dimethoxyphenyl)-2,5-diphenylpyridine (4.1l)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 3-(3,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one

(0.1341 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 83% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.10-8.07 (m, 2H), 7.81 (s, 1H), 7.54-7.49 (m, 2H), 7.47-7.43 (m, 1H), 7.34-7.29 (m, 3H), 7.23-7.21 (m, 2H), 6.94 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 2.0 Hz, 1H), 3.89 (s, 3H), 3.54 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6, 150.9, 149.0, 148.50, 148.40, 139.1, 138.1, 134.4, 131.4, 129.9, 129.2, 128.9, 128.5, 127.4, 127.1, 121.8, 121.4, 113.1, 111.1, 56.0, 55.7. **HRMS** (ESI+) m/z calc'd for $C_{25}H_{22}NO_2$ [$M+H^+$]: 368.1651; found: 368.1642.

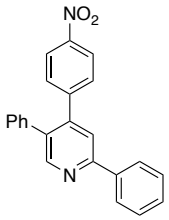
4-(4-chlorophenyl)-2,5-diphenylpyridine (4.1m)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (0.1214 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5-9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 84% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.08-8.06 (m, 2H), 7.74 (s, 1H), 7.53-7.49 (m, 2H), 7.47-7.43 (m, 1H), 7.34-7.26 (m, 5H), 7.21-7.14 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.7, 101.0, 147.5, 138.8, 137.51, 137.31, 134.33, 134.26, 130.8,

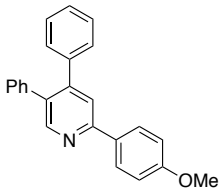
129.9, 129.3, 129.0, 128.74, 128.59, 127.6, 127.1, 121.4. **HRMS** (EI+) m/z calc'd for $C_{23}H_{16}NCl$ [M+H$^+$]: 341.09713; found: 341.09671.

4-(4-nitrophenyl)-2,5-diphenylpyridine (4.1n)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (0.1266 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 48% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.18-8.15 (m, 2H), 8.09-8.07 (m, 2H), 7.76 (s, 1H), 7.54-7.50 (m, 2H), 7.48-7.47 (m, 1H), 7.42-7.38 (m, 2H), 7.34-7.30 (m, 3H), 7.19-7.15 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.0, 101.3, 147.5, 146.3, 145.9, 138.6, 136.7, 134.3, 130.4, 129.9, 129.6, 129.1, 128.8, 128.0, 127.1, 123.7, 121.1. **HRMS** (ESI+) m/z calc'd for $C_{23}H_{17}N_2O_2$ [M+H$^+$]: 353.1290; found: 353.1295.

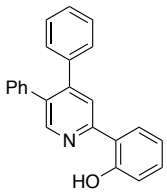
2-(4-methoxyphenyl)-4,5-diphenylpyridine (4.1o)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (0.1191 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

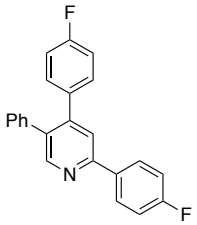
(0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 79% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.06-8.02 (m, 2H), 7.72 (s, 1H), 7.30-7.27 (m, 6H), 7.24-7.17 (m, 4H), 7.04-7.01 (m, 2H), 3.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7, 156.3, 150.9, 148.6, 139.3, 137.9, 133.7, 131.8, 129.9, 129.5, 128.41, 128.37, 128.32, 127.9, 127.3, 120.9, 114.3, 55.5. **HRMS** (EI+) m/z calc'd for $C_{24}H_{19}NO$ [M+H$^+$]: 337.14666; found: 337.14638.

2-(4,5-diphenylpyridin-2-yl)phenol (4.1p)



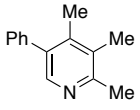
According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (0.1121 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 44% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 0.5 Hz, 1H), 7.94 (s, 1H), 7.87 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.36-7.27 (m, 7H), 7.25-7.21 (m, 2H), 7.20-7.15 (m, 2H), 7.07 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.92 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2, 156.8, 149.8, 147.1, 138.8, 137.1, 134.2, 131.6, 129.9, 129.4, 128.56, 128.52, 128.33, 127.7, 126.3, 120.2, 119.01, 118.85, 118.78. **HRMS** (ESI+) m/z calc'd for $C_{23}H_{18}NO$ [M+H$^+$]: 324.1388; found: 324.1379.

2,4-bis(4-fluorophenyl)-5-phenylpyridine (4.1q)



According to general procedure C, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to a solution of the titanium complex (0.0035 g) in a sealed reaction vessel. The reaction vessel was heated at 70 °C for 3 hours. Upon completion, 1,3-bis(4-fluorophenyl)prop-2-en-1-one (0.1221 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 83% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.09-8.04 (m, 2H), 7.70 (s, 1H), 7.31-7.30 (m, 3H), 7.21-7.17 (m, 6H), 7.01-6.96 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.8 (d, $^{1}J(C,F)$ = 248.8Hz), 162.6 (d, $^{1}J(C,F)$ = 248.0Hz), 155.7, 101.1, 147.7, 137.4, 135.19 (d, $^{4}J(C,F)$ = 3.0Hz), 135.00 (d, $^{4}J(C,F)$ = 3.6Hz), 134.4, 131.2 (d, $^{3}J(C,F)$ = 8.1Hz), 129.9, 128.9 (d, $^{3}J(C,F)$ = 8.5Hz), 128.6, 127.6, 121.2, 115.9 (d, $^{2}J(C,F)$ = 21.4Hz), 115.6 (d, $^{2}J(C,F)$ = 21.8Hz). **^{19}F NMR** (282 MHz; $CDCl_3$): δ -112.8, -113.6. **HRMS** (ESI+) m/z calc'd for $C_{23}H_{16}NF_2$ [M+H$^+$]: 344.1251; found: 344.1245.

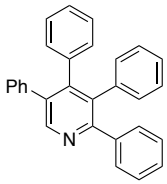
2,3,4-trimethyl-5-phenylpyridine (4.1r)



According to general procedure B, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 3-methylpent-3-en-2-one (0.0491 g) and molecular sieves (0.1000 g) were added following general procedure C. The reaction was heated and stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification

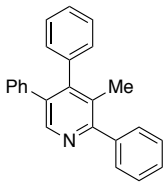
by column chromatography (6:4 Hex/EtOAc) afforded the title compound as a colourless solid in 22% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.46-7.42 (m, 2H), 7.40-7.35 (m, 1H), 7.29-7.26 (m, 2H), 2.60 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3, 146.4, 143.0, 139.1, 135.9, 130.3, 129.7, 128.4, 127.4, 23.4, 17.1, 15.4. **HRMS** (ESI+) m/z calc'd for $C_{14}H_{16}N$ [$M+H^+$]: 198.1283; found: 198.1275.

2,3,4,5-tetraphenylpyridine (4.1s)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 1,2,3-triphenylprop-2-en-1-one (0.1422 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 68% yield. The analytical data were consistent with literature.[275] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.34-7.30 (m, 2H), 7.23-7.18 (m, 6H), 7.15-7.11 (m, 2H), 7.04-6.97 (m, 6H), 6.89-6.85 (m, 2H), 6.82-6.79 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.2, 149.3, 148.4, 140.8, 138.18, 138.09, 137.5, 135.5, 135.1, 131.4, 130.6, 130.06, 129.98, 128.1, 127.74, 127.57, 127.50, 127.46, 127.1, 126.8, 126.5.

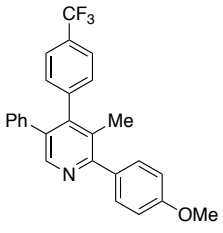
3-methyl-2,4,5-triphenylpyridine (4.1t)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon

completion, 2-methyl-1,3-diphenylprop-2-en-1-one (0.1111 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (85:15 Hex/EtOAc) afforded the title compound as a colourless solid in 78% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 0.4 Hz, 1H), 7.62-7.59 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.39 (m, 1H), 7.31-7.24 (m, 3H), 7.23-7.17 (m, 3H), 7.13-7.07 (m, 4H), 2.13 (d, *J* = 0.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6, 149.3, 147.5, 141.3, 138.35, 138.29, 135.3, 130.0, 129.7, 129.3, 129.0, 128.34, 128.28, 128.03, 128.00, 127.4, 127.0, 18.6. **HRMS** (ESI+) m/z calc'd for $C_{24}H_{20}N$ [$M+H^+$]: 322.1596; found: 322.1600.

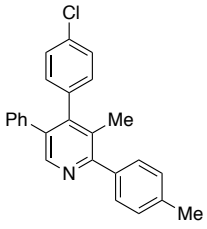
2-(4-methoxyphenyl)-3-methyl-5-phenyl-4-(4-(trifluoromethyl)phenyl)pyridine (4.1u)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 1-(4-methoxyphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (0.1601 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (8:2 to 7:3 Hex/EtOAc) afforded the title compound as a colourless solid in 66% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.58-7.54 (m, 4H), 7.24-7.19 (m, 5H), 7.08-7.06 (m, 2H), 7.04-7.00 (m, 2H), 3.88 (s, 3H), 2.13 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.8, 158.1, 148.3, 147.18, 147.17, 142.2, 137.5, 134.9, 132.7, 130.7,

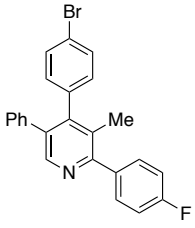
130.1, 129.87, 129.70 (q, $^{2}J(C,F)$ = 32.6Hz), 128.8, 128.3, 127.4, 125.3 (q, $^{3}J(C,F)$ = 3.7Hz), 124.1 (q, $^{1}J(C,F)$ = 272.1Hz), 113.9, 55.5, 18.9. **^{19}F NMR** (282 MHz; $CDCl_3$): δ -62.6. **HRMS** (ESI+) m/z calc'd for $C_{26}H_{21}NOF_3$ [M+H$^+$]: 420.1575; found: 420.1583.

4-(4-chlorophenyl)-3-methyl-5-phenyl-2-(*p*-tolyl)pyridine (4.1v)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 3-(4-chlorophenyl)-2-methyl-1-(*p*-tolyl)prop-2-en-1-one (0.1354 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 to 9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 68% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) 8.58 (d, *J* = 0.4 Hz, 1H), 7.50-7.47 (m, 2H), 7.30-7.25 (m, 5H), 7.24-7.20 (m, 3H), 7.10-7.08 (m, 2H), 7.05-7.01 (m, 2H), 2.43 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.7, 148.0, 147.5, 138.15, 138.01, 137.93, 136.9, 135.1, 133.4, 131.1, 129.9, 129.20, 129.04, 128.78, 128.59, 128.2, 127.2, 21.5, 18.7. **HRMS** (ESI+) m/z calc'd for $C_{25}H_{21}NCl$ [M+H$^+$]: 370.1363; found: 370.1360.

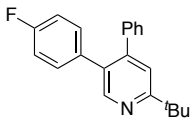
4-(4-bromophenyl)-2-(4-fluorophenyl)-3-methyl-5-phenylpyridine (4.1w)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and ethynylbenzene (0.0511 g) were added to the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 3-(4-bromophenyl)-1-(4-fluorophenyl)-2-methylprop-2-en-1-one

(0.1596 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 to 9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 58% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 0.3 Hz, 1H), 7.59-7.56 (m, 2H), 7.44-7.41 (m, 2H), 7.25-7.21 (m, 3H), 7.20-7.15 (m, 2H), 7.10-7.07 (m, 2H), 6.98-6.95 (m, 2H), 2.11 (d, *J* = 0.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (d, $^{1}J(C,F)$ = 246.7Hz), 157.6, 148.2, 147.6, 137.8, 137.15, 137.05 (d, $^{4}J(C,F)$ = 3.9Hz), 135.4, 131.6, 131.4, 131.1 (d, $^{3}J(C,F)$ = 9.1Hz), 129.9, 128.8, 128.3, 127.3, 121.8, 115.4 (d, $^{2}J(C,F)$ = 21.8Hz), 18.7. **^{19}F NMR** (282 MHz; $CDCl_3$): δ -113.8. **HRMS** (ESI+) m/z calc'd for $C_{24}H_{18}NBrF$ $[M+H^+]$: 418.0607; found: 418.0612.

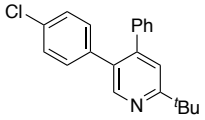
2-(*tert*-butyl)-5-(4-fluorophenyl)-4-phenylpyridine (4.2a)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-fluorobenzene (0.0601 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 81% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.37 (s, 1H), 7.30-7.27 (m, 3H), 7.16-7.13 (m, 2H), 7.12-7.08 (m, 2H), 6.97-6.93 (m, 2H), 1.45 (s, 9H). **^{13}C NMR**

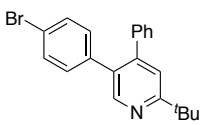
(101 MHz, $CDCl_3$) δ 168.7, 162.2 (d, $^1J(C,F)$ = 247.0Hz), 149.7, 148.1, 139.4, 134.0, 132.0, 131.5 (d, $^3J(C,F)$ = 7.6Hz), 129.5, 128.5, 127.9, 120.3, 115.4 (d, $^2J(C,F)$ = 21.5Hz), 37.5, 30.4. **^{19}F NMR** (282 MHz; $CDCl_3$): δ -115.4. **HRMS** (ESI+) m/z calc'd for $C_{21}H_{20}FN$ [M+H$^+$]: 306.1658; found: 306.1658.

2-(*tert*-butyl)-5-(4-chlorophenyl)-4-phenylpyridine (4.2b)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-chloro-4-ethynylbenzene (0.0683 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 88% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): 8.56 (s, 1H), 7.37 (s, 1H), 7.32-7.28 (m, 3H), 7.25-7.21 (m, 2H), 7.17-7.14 (m, 2H), 7.08-7.05 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 168.9, 149.7, 148.1, 139.3, 136.5, 133.4, 131.8, 131.2, 129.5, 128.61, 128.52, 128.0, 120.3, 37.5, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{21}H_{20}ClN$ [M+H$^+$]: 322.1363; found: 322.1371.

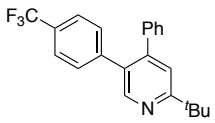
2-(*tert*-butyl)-5-(4-bromophenyl)-4-phenylpyridine (4.2c)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-bromo-4-ethynylbenzene (0.0905 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves

(0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 85% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.56 (s, 1H), 7.40-7.37 (m, 2H), 7.37 (s, 1H), 7.32-7.28 (m, 3H), 7.17-7.14 (m, 2H), 7.03-6.99 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$) δ 169.0, 149.6, 148.1, 139.2, 137.0, 131.8, 131.57, 131.53, 129.5, 128.6, 128.0, 121.6, 120.4, 37.5, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{21}H_{21}NBr$ [$M+H^+$]: 366.0857; found: 366.0859.

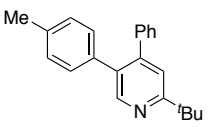
2-(tert-butyl)-4-phenyl-5-(4-(trifluoromethyl)phenyl)pyridine (4.2d)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-(trifluoromethyl)benzene (0.0851 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 77% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.59 (s, 1H), 7.53-7.50 (m, 2H), 7.40 (s, 1H), 7.31-7.25 (m, 5H), 7.15-7.13 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (151 MHz; $CDCl_3$): δ 169.4, 149.6, 148.3, 141.8, 138.9, 131.7, 130.2, 129.45, 129.31 (q, $^{2}J(C,F)$ = 32.4Hz), 128.6, 128.1, 125.3 (q, $^{3}J(C,F)$ = 3.7Hz), 124.3 (q, $^{1}J(C,F)$ = 272.1Hz), 120.5, 37.5, 30.4. **^{19}F NMR**

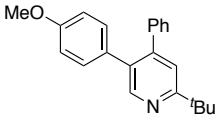
(282 MHz; $CDCl_3$): δ -62.5. **HRMS** (ESI+) m/z calc'd for $C_{22}H_{21}NF_3$ [M+H$^+$]: 356.1626; found: 356.1627.

2-(*tert*-butyl)-4-phenyl-5-(*p*-tolyl)pyridine (4.2e)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-methylbenzene (0.0581 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 82% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.59 (s, 1H), 7.35 (s, 1H), 7.30-7.26 (m, 3H), 7.19-7.16 (m, 2H), 7.07-7.02 (m, 4H), 2.32 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 168.2, 149.9, 147.9, 139.8, 136.8, 135.0, 132.9, 129.8, 129.5, 129.1, 128.3, 127.7, 120.3, 37.4, 30.4, 21.3. **HRMS** (ESI+) m/z calc'd for $C_{22}H_{24}N$ [M+H$^+$]: 302.1909; found: 302.1913.

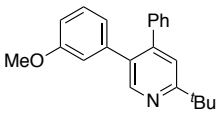
2-(*tert*-butyl)-5-(4-methoxyphenyl)-4-phenylpyridine (4.2f)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-4-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction

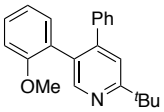
solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 85% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.58 (s, 1H), 7.35 (s, 1H), 7.30-7.27 (m, 3H), 7.20-7.16 (m, 2H), 7.08-7.04 (m, 2H), 6.81-6.77 (m, 2H), 3.79 (s, 3H), 1.45 (s, 9H).**^{13}C NMR** (101 MHz; $CDCl_3$) δ 168.1, 158.9, 149.8, 147.9, 139.8, 132.6, 131.0, 130.3, 129.5, 128.4, 127.7, 120.3, 113.9, 55.3, 37.4, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{22}H_{24}NO$ [M+H$^+$]: 318.1858; found: 318.1862.

2-(*tert*-butyl)-5-(3-methoxyphenyl)-4-phenylpyridine (4.2g)



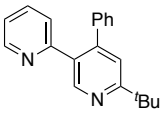
According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-3-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 90% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.61 (d, *J* = 0.5 Hz, 1H), 7.37 (d, *J* = 0.6 Hz, 1H), 7.29-7.27 (m, 3H), 7.20-7.17 (m, 3H), 6.79 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 6.75 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 1H), 6.66 (dd, *J* = 2.5, 1.6 Hz, 1H), 3.62 (s, 3H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$) δ 168.6, 159.4, 149.8, 148.0, 139.7, 139.4, 132.8, 129.44, 129.32, 128.4, 127.8, 122.4, 120.2, 115.3, 113.3, 55.2, 37.4, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{22}H_{24}NO$ [M+H$^+$]: 318.1858; found: 318.1853.

2-(*tert*-butyl)-5-(2-methoxyphenyl)-4-phenylpyridine (4.2h)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynyl-2-methoxybenzene (0.0661 g) were added to a solution of the titanium complex (0.0035 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (9:1 Hex/EtOAc) afforded the title compound as a colourless solid in 78% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.55 (s, 1H), 7.38 (s, 1H), 7.27 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 7.24-7.22 (m, 3H), 7.20 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.17-7.13 (m, 2H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.73 (dd, *J* = 8.2, 0.5 Hz, 1H), 3.32 (s, 3H), 1.46 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 168.4, 156.6, 150.2, 149.1, 140.6, 131.7, 129.8, 129.2, 128.5, 128.0, 127.5, 127.2, 120.8, 119.6, 111.0, 55.0, 37.4, 30.5. **HRMS** (ESI+) m/z calc'd for $C_{22}H_{24}NO$ [$M+H^+$]: 318.1858; found: 318.1858.

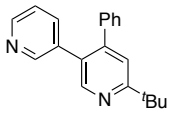
6'-(*tert*-butyl)-4'-phenyl-2,3'-bipyridine (4.2i)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 2-ethynylpyridine (0.0516 g) were added to a solution of the titanium complex (0.0174 g) in benzene. The reaction J-Young tube was heated at 70 °C for 8 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (6:4 Hex/EtOAc) afforded the title compound as a colourless solid in 70% yield.

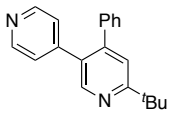
^{1}H NMR (400 MHz; $CDCl_3$): δ 8.81 (d, *J* = 0.6 Hz, 1H), 8.63 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.47 (td, *J* = 7.8, 1.8 Hz, 1H), 7.37 (d, *J* = 0.6 Hz, 1H), 7.31-7.26 (m, 3H), 7.19-7.13 (m, 3H), 6.97 (dt, *J* = 7.8, 1.0 Hz, 1H), 1.44 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 169.6, 156.8, 150.2, 149.8, 148.2, 139.5, 135.7, 132.0, 129.3, 128.5, 127.9, 125.3, 121.9, 120.0, 37.6, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{20}H_{21}N_2$ [M+H$^+$]: 289.1705; found: 289.1707.

6-(*tert*-butyl)-4-phenyl-3,3'-bipyridine (4.2j)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 3-ethynylpyridine (0.0516 g) were added to a solution of the titanium complex (0.0174 g) in benzene. The reaction J-Young tube was heated at 70 °C for 18 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (1:1 Hex/EtOAc) afforded the title compound as a colourless solid in 73% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.59 (d, *J* = 0.6 Hz, 1H), 8.50-8.46 (m, 2H), 7.42-7.39 (m, 2H), 7.31-7.28 (m, 3H), 7.19-7.13 (m, 3H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 169.6, 150.4, 149.7, 148.50, 148.39, 138.9, 137.2, 133.9, 129.51, 129.44, 128.6, 128.2, 123.1, 120.4, 37.6, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{20}H_{21}N_2$ [M+H$^+$]: 289.1705; found: 289.1699.

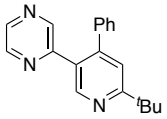
6-(*tert*-butyl)-4-phenyl-3,4'-bipyridine (4.2k)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 4-ethynylpyridine (0.0516 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction J-Young tube was heated at 70 °C for 18 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g)

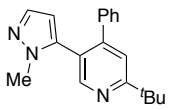
were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (1:1 Hex/EtOAc) afforded the title compound as a colourless solid in 60% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): 8.58 (d, *J* = 0.6 Hz, 1H), 8.49 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.40 (d, *J* = 0.6 Hz, 1H), 7.33-7.28 (m, 3H), 7.16-7.13 (m, 2H), 7.07 (dd, *J* = 4.5, 1.5 Hz, 2H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 170.1, 149.8, 149.4, 148.3, 146.2, 138.7, 130.3, 129.4, 128.7, 128.3, 124.7, 120.5, 37.6, 30.3. **HRMS** (ESI+) m/z calc'd for $C_{20}H_{21}N_2$ [M+H$^+$]: 289.1705; found: 289.1701.

2-(6-(*tert*-butyl)-4-phenylpyridin-3-yl)pyrazine (4.2l)



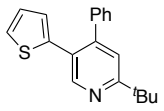
According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 2-ethynylpyrazine (0.0521 g) were added to a solution of the titanium complex (0.0174 g) in benzene. The reaction J-Young tube was heated at 70 °C for 18 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (7:3 Hex/EtOAc) afforded the title compound as a colourless solid in 78% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.84 (d, *J* = 0.5 Hz, 1H), 8.60 (dd, *J* = 2.5, 1.4 Hz, 1H), 8.41 (d, *J* = 2.5 Hz, 1H), 8.20 (d, *J* = 1.4 Hz, 1H), 7.41 (d, *J* = 0.5 Hz, 1H), 7.34-7.31 (m, 3H), 7.18-7.15 (m, 2H), 1.45 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 170.6, 152.8, 150.3, 148.6, 146.2, 144.4, 142.5, 138.8, 129.2, 128.88, 128.73, 128.4, 120.2, 37.7, 30.3. **HRMS** (ESI+) m/z calc'd for $C_{19}H_{20}N_3$ [M+H$^+$]: 290.1657; found: 290.1664.

2-(*tert*-butyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-4-phenylpyridine (4.2m)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 4-ethynyl-1-methyl-1*H*-pyrazole (0.0531 g) were added to a solution of the titanium complex (0.0087 g) in benzene. The reaction J-Young tube was heated at 70 °C for 18 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (1:1 Hex/EtOAc) afforded the title compound as a colourless solid in 63% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.65 (d, *J* = 0.6 Hz, 1H), 7.39-7.36 (m, 3H), 7.28-7.25 (m, 3H), 7.21 (d, *J* = 0.6 Hz, 1H), 6.98 (s, 1H), 3.80 (s, 3H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.6, 148.6, 147.5, 140.1, 138.8, 129.04, 128.95, 128.6, 128.1, 124.1, 120.3, 118.6, 39.1, 37.3, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{19}H_{22}N_3$ [$M+H^+$]: 292.1814; found: 292.1823.

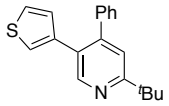
2-(*tert*-butyl)-4-phenyl-5-(thiophen-2-yl)pyridine (4.2n)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 2-ethynylthiophene (0.0541 g) were added to a solution of the titanium complex (0.0174 g) in benzene. The reaction J-Young tube was heated at 70 °C for 18 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 82%

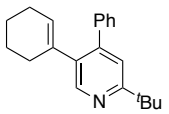
yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.72 (d, *J* = 0.6 Hz, 1H), 7.37-7.33 (m, 3H), 7.31 (d, *J* = 0.6 Hz, 1H), 7.28-7.26 (m, 1H), 7.26-7.25 (m, 1H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.80 (dd, *J* = 3.6, 1.2 Hz, 1H), 1.42 (s, 9H) **^{13}C NMR** (101 MHz; $CDCl_3$): δ 168.8, 149.7, 148.2, 139.56, 139.51, 129.3, 128.5, 128.1, 127.34, 127.25, 126.38, 126.27, 120.3, 37.5, 30.3. **HRMS** (ESI+) m/z calc'd for $C_{19}H_{20}NS$ [M+H$^+$]: 294.1315; found: 294.1314.

2-(*tert*-butyl)-4-phenyl-5-(thiophen-3-yl)pyridine (4.2o)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 3-ethynylthiophene (0.0541 g) were added to a solution of the titanium complex (0.0174 g) in benzene. The reaction J-Young tube was heated at 70 °C for 18 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 75% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.67 (d, *J* = 0.6 Hz, 1H), 7.34-7.31 (m, 4H), 7.23-7.20 (m, 2H), 7.17 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.07 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.71 (dd, *J* = 5.0, 1.3 Hz, 1H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 168.5, 149.5, 147.9, 139.8, 138.5, 129.2, 128.9, 128.4, 127.98, 127.95, 125.3, 123.5, 120.2, 37.4, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{19}H_{20}NS$ [M+H$^+$]: 294.1316; found: 294.1305.

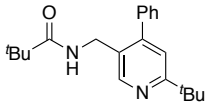
2-(*tert*-butyl)-5-(cyclohex-1-en-1-yl)-4-phenylpyridine (4.2p)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1-ethynylcyclohex-1-ene (0.0531 g) were added to a solution of the titanium complex (0.0087 g) in benzene. The reaction J-Young tube was heated at 70 °C for 6 hours.

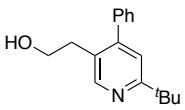
Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 71% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.40 (s, 1H), 7.46-7.37 (m, 5H), 7.24 (s, 1H), 5.79-5.76 (m, 1H), 2.16-2.11 (m, 2H), 1.76-1.71 (m, 2H), 1.57-1.53 (m, 2H), 1.48-1.44 (m, 2H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.8, 148.8, 147.0, 140.4, 136.2, 135.7, 128.8, 128.54, 128.37, 127.9, 119.7, 37.3, 30.4, 29.2, 25.9, 23.0, 22.0. **HRMS** (ESI+) m/z calc'd for $C_{19}H_{20}NS$ [M+H$^+$]: 294.1316; found: 294.1305.

***N*-((6-(*tert*-butyl)-4-phenylpyridin-3-yl)methyl)pivalamide (4.2q)**



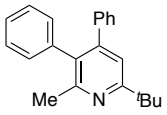
According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and *N*-(prop-2-yn-1-yl)pivalamide (0.0696 g) were added to a solution of the titanium complex (0.0087 g) in benzene. The reaction J-Young tube was heated at 70 °C for 3 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (1:1 Hex/EtOAc) afforded the title compound as a colourless solid in 27% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.56 (s, 1H), 7.49-7.41 (m, 3H), 7.36-7.33 (m, 2H), 7.23 (s, 1H), 5.67 (s, 1H), 4.46 (d, J = 5.4 Hz, 2H), 1.40 (s, 9H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 178.1, 168.9, 149.4, 148.8, 139.0, 128.9, 128.4, 128.0, 120.2, 39.5, 38.7, 37.4, 30.3, 27.5. **HRMS** (ESI+) m/z calc'd for $C_{21}H_{29}N_2O$ [M+H$^+$]: 325.2280; found: 325.2282.

2-(6-(*tert*-butyl)-4-phenylpyridin-3-yl)ethan-1-ol (4.2r)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (0.0922 g) were added to a solution of the titanium complex (0.0087 g) in benzene. The reaction J-Young tube was heated at 70 °C for 8 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (4:6 Hex/EtOAc) afforded the title compound as a colourless solid in 26% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 8.54 (s, 1H), 7.48-7.41 (m, 3H), 7.33-7.31 (m, 2H), 7.20 (s, 1H), 3.69 (t, J = 6.9 Hz, 2H), 2.89 (t, J = 6.9 Hz, 2H), 1.39 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.4, 150.3, 150.0, 139.7, 128.71, 128.61, 128.3, 128.0, 120.2, 63.0, 37.2, 33.3, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{18}H_{23}NO_2$ [M+H$^+$]: 286.1807; found: 286.1805. **HRMS** (ESI+) m/z calc'd for $C_{17}H_{22}NO$ [M+H$^+$]: 256.1701; found: 256.1703.

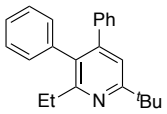
6-(*tert*-butyl)-2-methyl-3,4-diphenylpyridine (4.2s)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and prop-1-yn-1-ylbenzene (0.0581 g) were added to a solution of the titanium complex (0.0174 g) in benzene. The reaction J-Young tube was heated at 110 °C for 6 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. After 1 hour, the volatiles were removed under reduced

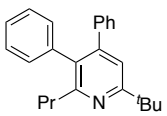
pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 79% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.25-7.15 (m, 7H), 7.08-7.04 (m, 4H), 2.40 (s, 3H), 1.43 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.4, 155.6, 148.8, 140.5, 139.1, 132.1, 130.5, 129.5, 128.1, 127.9, 127.1, 126.7, 117.6, 37.3, 30.4, 24.5. **HRMS** (ESI+) m/z calc'd for $C_{22}H_{24}N$ [M+H$^+$]: 302.1909; found: 302.1911.

6-(*tert*-butyl)-2-ethyl-3,4-diphenylpyridine (4.2t)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and but-1-yn-1-ylbenzene (0.0651 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction J-Young tube was heated at 110 °C for 24 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 72% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.24-7.18 (m, 3H), 7.17-7.15 (m, 4H), 7.08-7.04 (m, 4H), 2.66 (q, *J* = 7.5 Hz, 2H), 1.43 (s, 9H), 1.19 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.4, 159.9, 148.8, 140.7, 138.8, 131.5, 130.7, 129.5, 127.93, 127.80, 127.0, 126.7, 117.2, 37.5, 30.4, 29.4, 13.8. **HRMS** (ESI+) m/z calc'd for $C_{23}H_{26}N$ [M+H$^+$]: 316.2065; found: 316.2069.

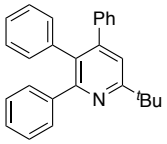
6-(*tert*-butyl)-3,4-diphenyl-2-propylpyridine (4.2u)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and pent-1-yn-1-ylbenzene (0.0721 g) were added to a solution of the titanium

complex (0.0348 g) in benzene. The reaction J-Young tube was heated at 110 °C for 24 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 67% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.24-7.18 (m, 3H), 7.17-7.14 (m, 4H), 7.07-7.03 (m, 4H), 2.63-2.59 (m, 2H), 1.75-1.66 (m, 2H), 1.43 (s, 9H), 0.85 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.2, 158.8, 148.8, 140.7, 138.9, 131.8, 130.8, 129.5, 127.90, 127.79, 127.0, 126.7, 117.1, 38.1, 37.5, 30.4, 22.6, 14.3. **HRMS** (ESI+) m/z calc'd for $C_{24}H_{28}N$ [M+H$^+$]: 330.2222; found: 330.2222.

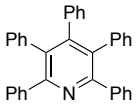
6-(*tert*-butyl)-2,3,4-triphenylpyridine (4.2v)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1,2-diphenylethyne (0.0891 g) were added to a solution of the titanium complex (0.0348 g) in toluene. The reaction J-Young tube was heated at 145 °C for 48 hours. Upon completion, 4,4-dimethyl-1-phenylpent-1-en-3-one (0.0941 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction mixture was stirred for 18 hours at 80 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (100 Hex to 97:3 Hex/EtOAc) afforded the title compound as a colourless solid in 64% yield. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.33-7.30 (m,

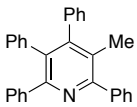
3H), 7.22-7.15 (m, 6H), 7.09-7.01 (m, 5H), 6.89-6.86 (m, 2H), 1.48 (s, 9H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 167.8, 156.4, 149.9, 141.4, 140.5, 138.5, 131.6, 131.2, 130.4, 129.5, 127.92, 127.76, 127.5, 127.21, 127.17, 126.5, 119.1, 37.7, 30.4. **HRMS** (ESI+) m/z calc'd for $C_{27}H_{26}N$ [$M+H^+$]: 364.2065; found: 364.2071.

2,3,4,5,6-pentaphenylpyridine (4.3a)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1,2-diphenylethyne (0.0891 g) were added to a solution of the titanium complex (0.0348 g) in toluene. The reaction J-Young tube was heated at 145 °C for 48 hours. Upon completion, 1,2,3-triphenylprop-2-en-1-one (0.1422 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 100 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 46% yield. The analytical data were consistent with literature.[329] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.44-7.39 (m, 4H), 7.21-7.15 (m, 6H), 7.02-6.97 (m, 6H), 6.95-6.89 (m, 7H), 6.80-6.76 (m, 2H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 156.5, 150.4, 141.0, 138.6, 138.3, 133.8, 131.5, 130.56, 130.37, 127.64, 127.52, 127.47, 127.1, 126.39, 126.32.

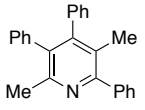
3-methyl-2,4,5,6-tetraphenylpyridine (4.3b)



According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and 1,2-diphenylethyne (0.0891 g) were added to a solution of the titanium complex (0.0348 g) in toluene. The reaction J-Young tube was heated at 145 °C for 48 hours. Upon completion, 2-methyl-1,3-diphenylprop-2-en-1-one (0.1111 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 100 °C. Upon

cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (95:5 Hex/EtOAc) afforded the title compound as a colourless solid in 47% yield. The analytical data were consistent with literature.[330] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.75-7.72 (m, 2H), 7.53-7.49 (m, 2H), 7.45-7.41 (m, 1H), 7.38-7.34 (m, 2H), 7.27-7.21 (m, 3H), 7.20-7.16 (m, 3H), 7.08-7.05 (m, 2H), 7.04-7.00 (m, 3H), 6.93-6.89 (m, 2H), 2.16 (s, 3H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 158.0, 154.8, 151.3, 141.4, 141.0, 139.1, 138.6, 133.8, 131.3, 130.2, 129.61, 129.51, 128.2, 127.98, 127.83, 127.63, 127.45, 127.2, 126.9, 126.3, 18.8.

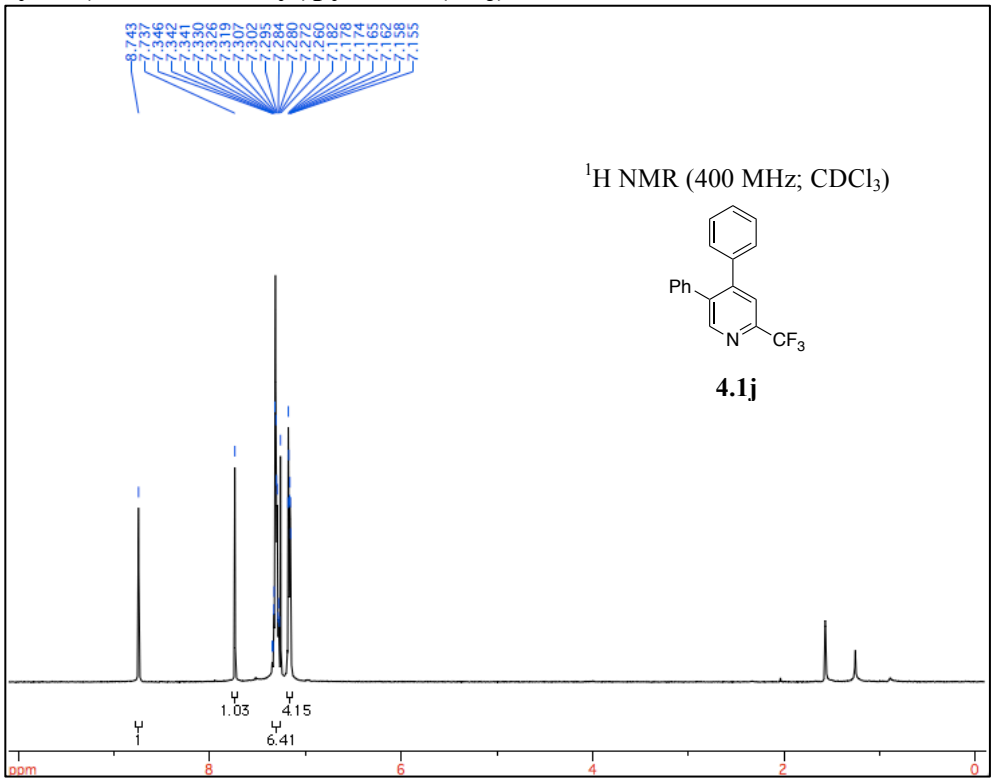
2,5-dimethyl-3,4,6-triphenylpyridine (4.3c)

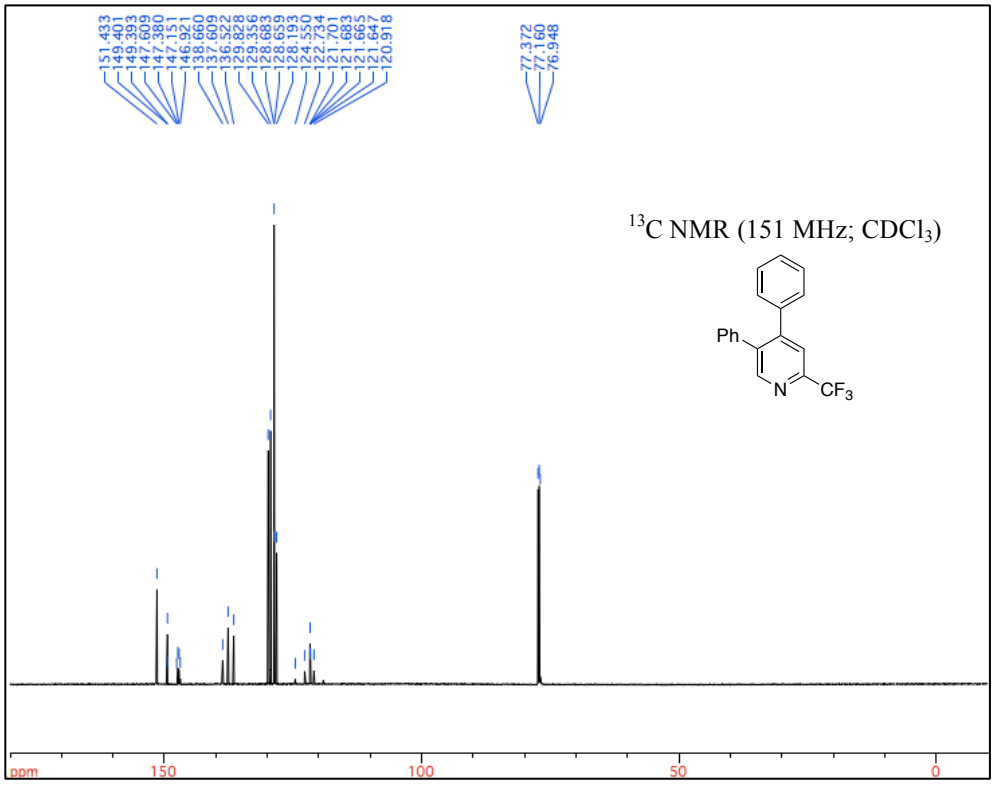


According to general procedure A, *tert*-butyldimethylsilanamine (0.0656 g) and prop-1-yn-1-ylbenzene (0.0581 g) were added to a solution of the titanium complex (0.0348 g) in benzene. The reaction J-Young tube was heated at 110 °C for 6 hours. Upon completion, 2-methyl-1,3-diphenylprop-2-en-1-one (0.1111 g) and molecular sieves (0.1000 g) were added following general procedure A. The reaction was heated and stirred for 18 hours at 100 °C. Upon cooling of the reaction mixture, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.1135 g) was added to the reaction solution. After 1 hour, the volatiles were removed under reduced pressure. Purification by column chromatography (85:15 Hex/EtOAc) afforded the title compound as a colourless solid in 23% yield.[404] **^{1}H NMR** (400 MHz; $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.49-7.44 (m, 2H), 7.41-7.37 (m, 1H), 7.21-7.16 (m, 4H), 7.15-7.10 (m, 2H), 7.03-6.97 (m, 4H), 2.39 (s, 3H), 2.02 (s, 3H). **^{13}C NMR** (101 MHz; $CDCl_3$): δ 157.7, 153.4, 150.3, 141.6, 139.08, 139.03, 134.8, 130.1, 129.32, 129.28, 128.3, 127.89, 127.86, 127.83, 126.8, 126.6, 126.2, 24.0, 18.2.

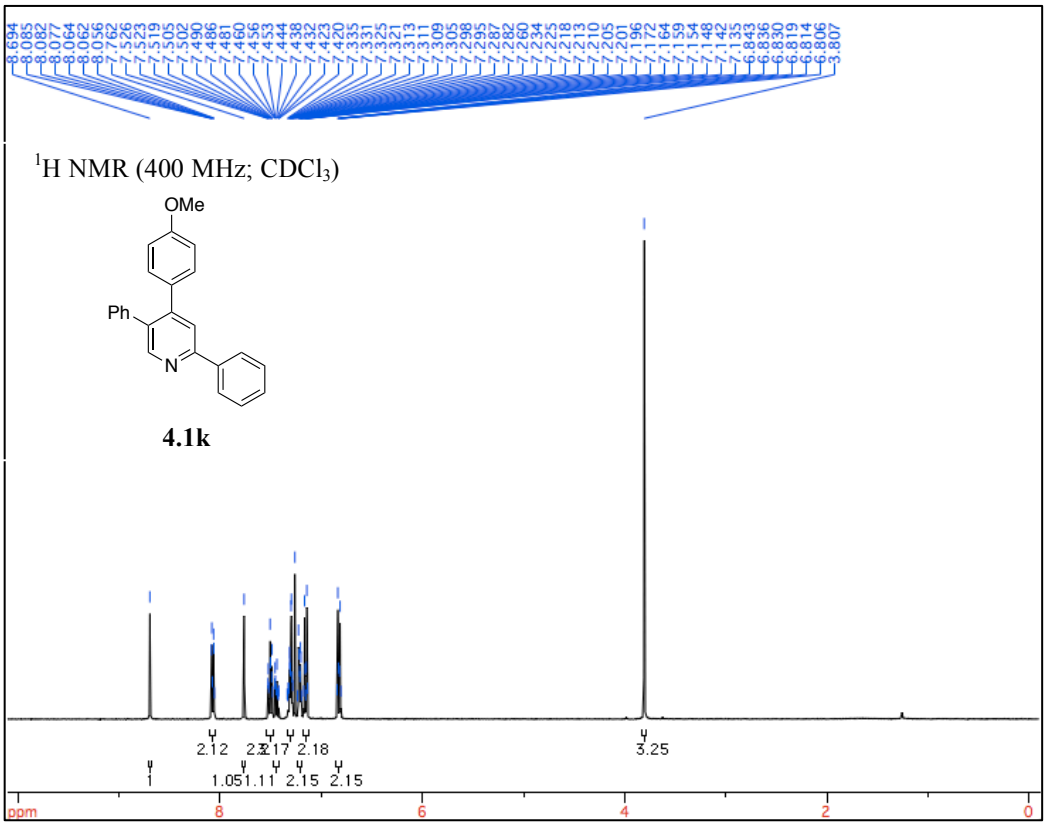
C.5 NMR Spectra

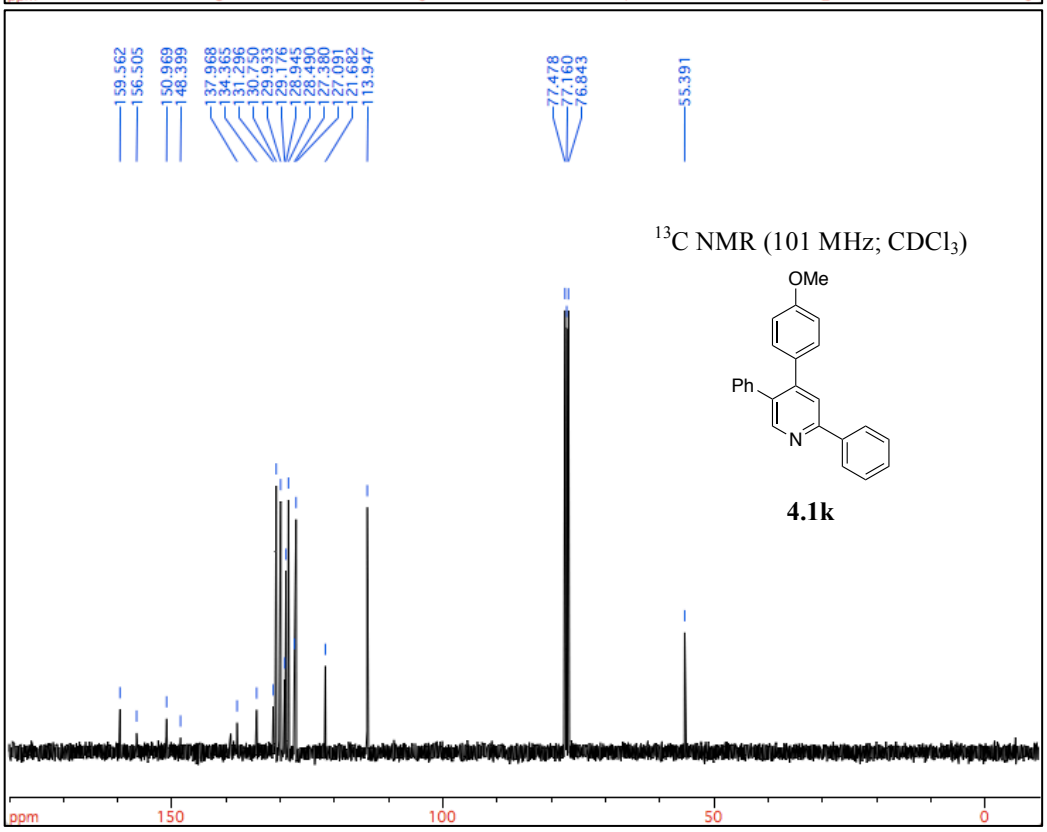
4,5-diphenyl-2-(trifluoromethyl)pyridine (4.1j)



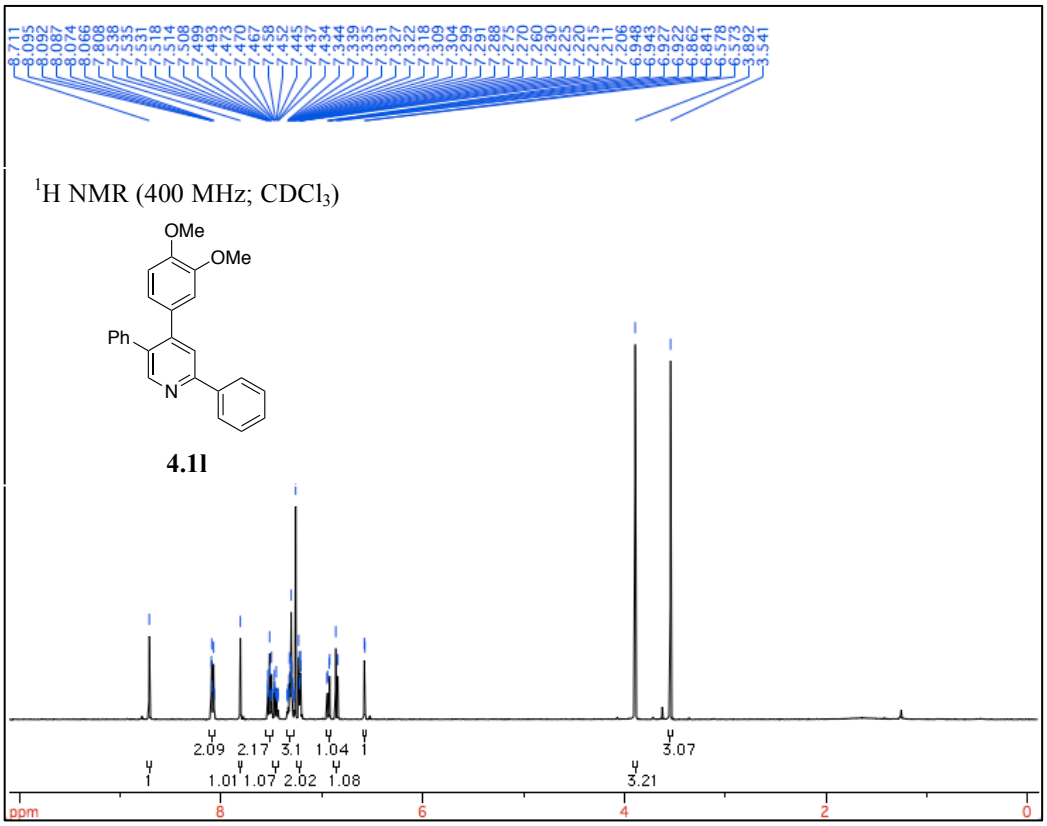


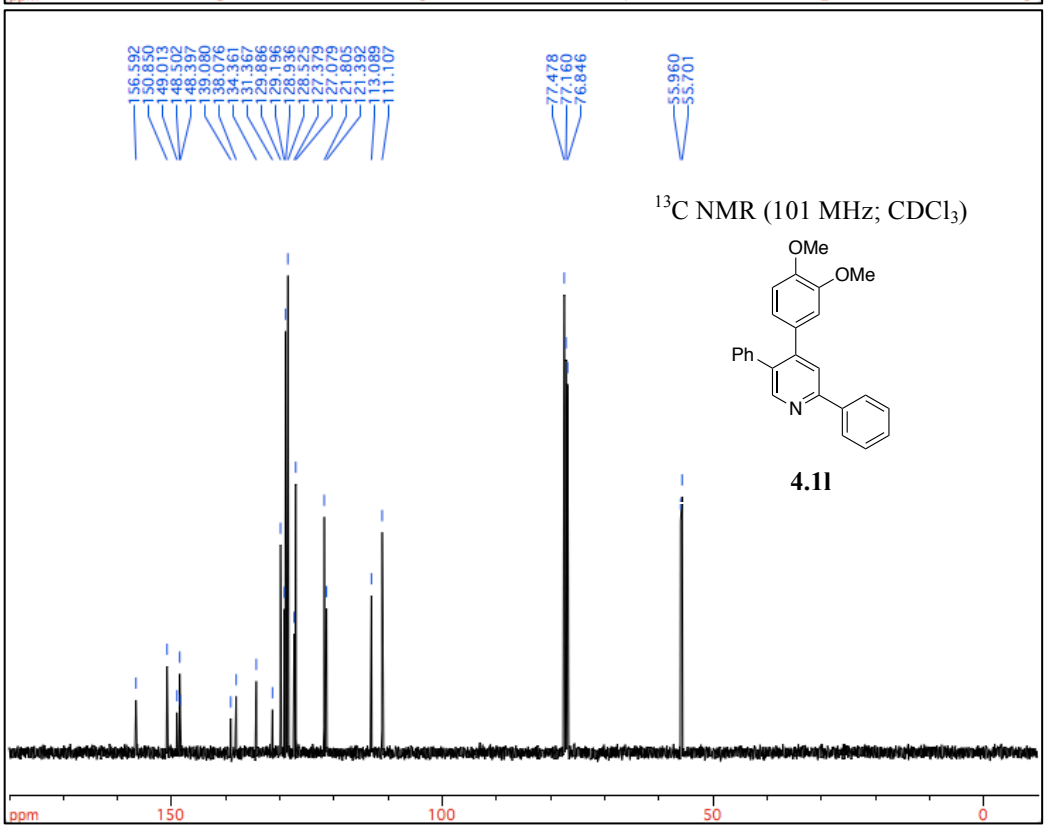
4-(4-methoxyphenyl)-2,5-diphenylpyridine (4.1k)



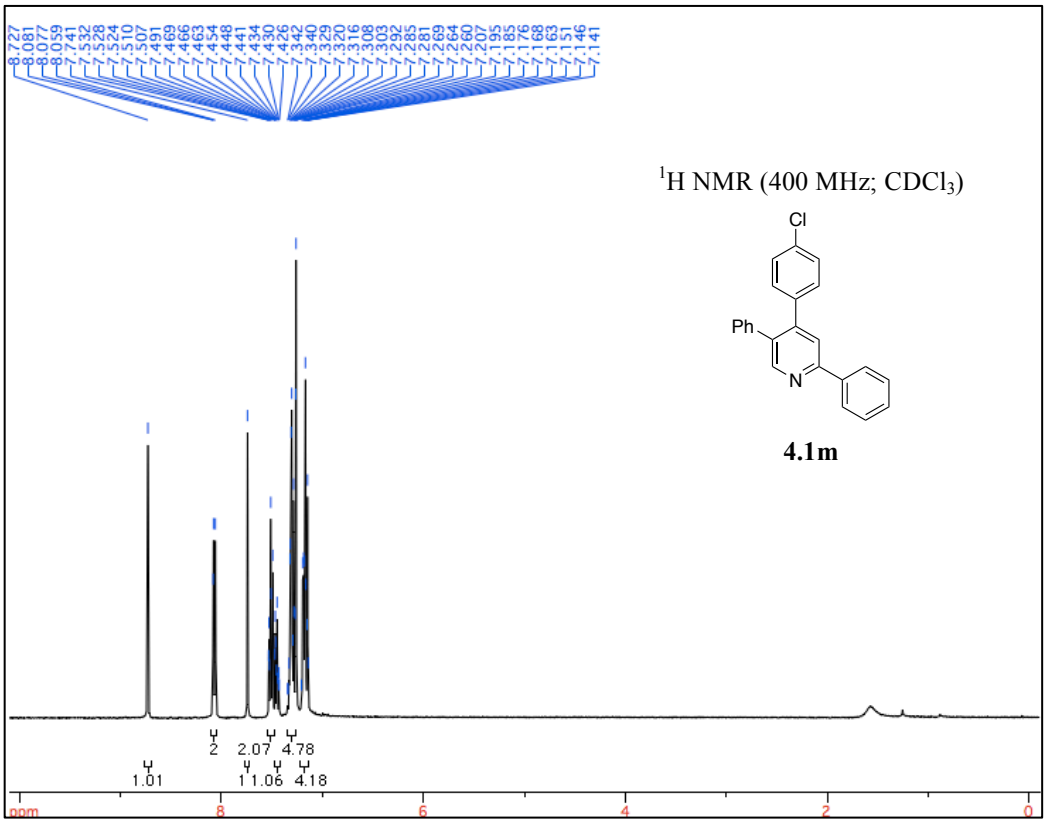


4-(3,4-dimethoxyphenyl)-2,5-diphenylpyridine (4.1l)



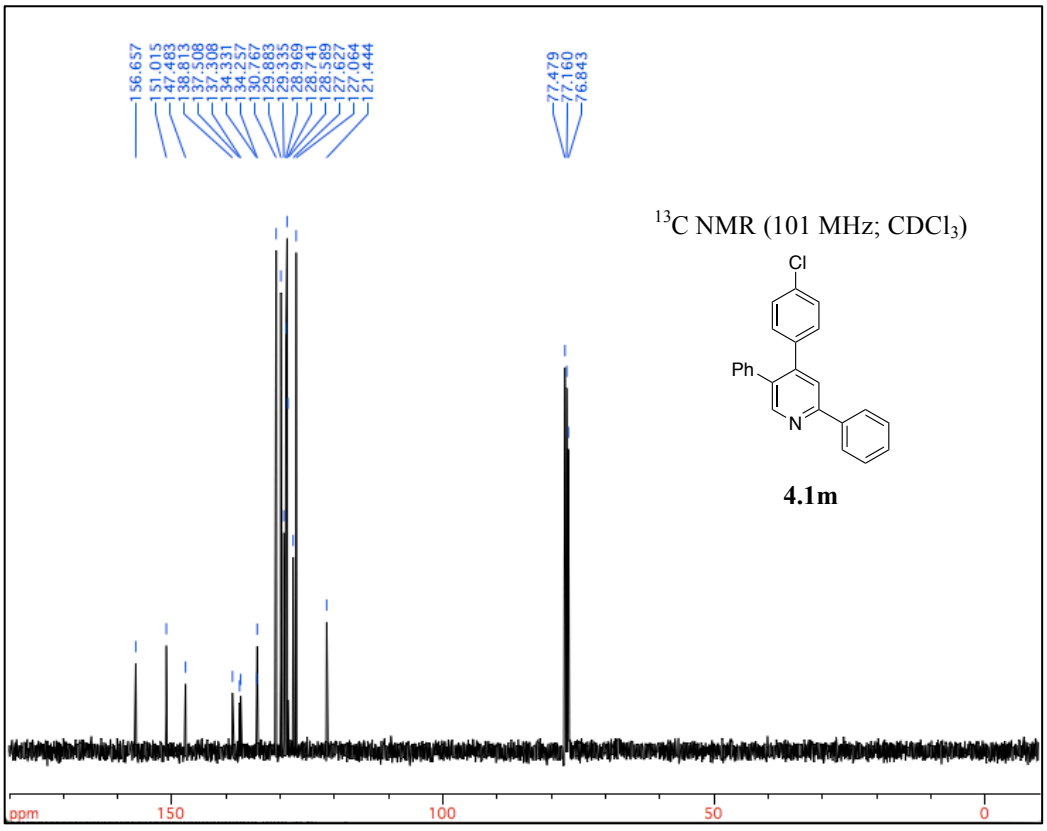


4-(4-chlorophenyl)-2,5-diphenylpyridine (4.1m)



^{1}H NMR (400 MHz; $CDCl_3$)

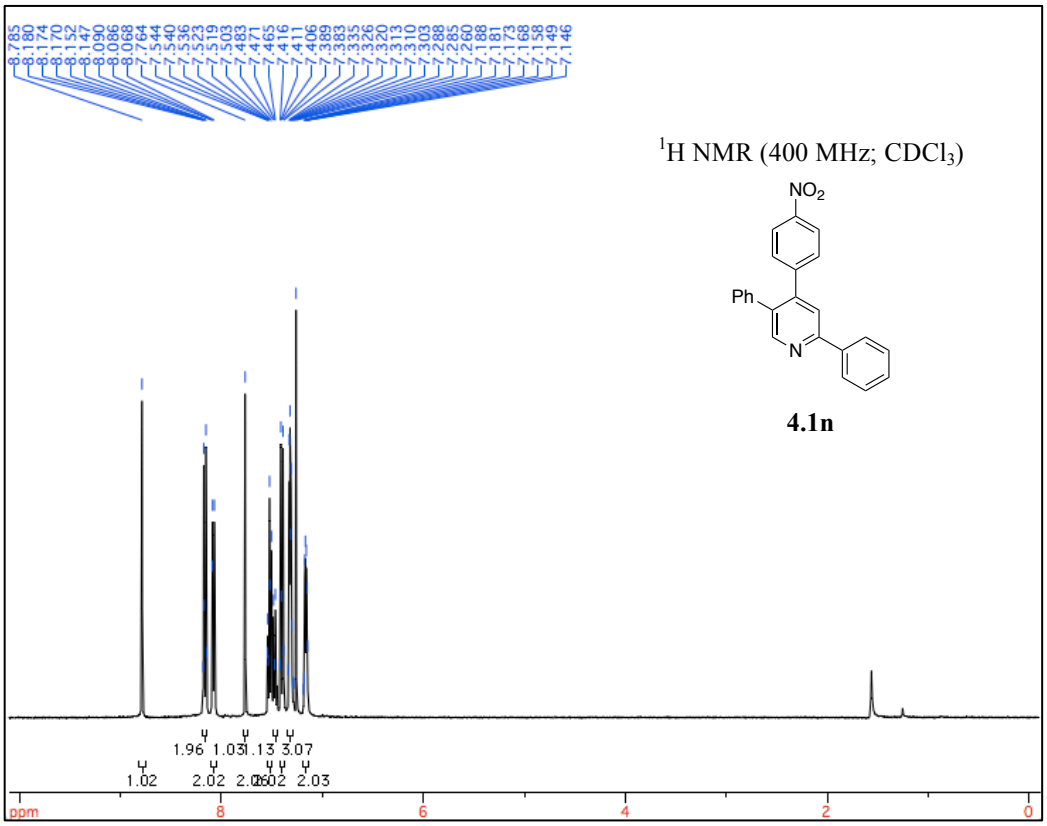
4.1m

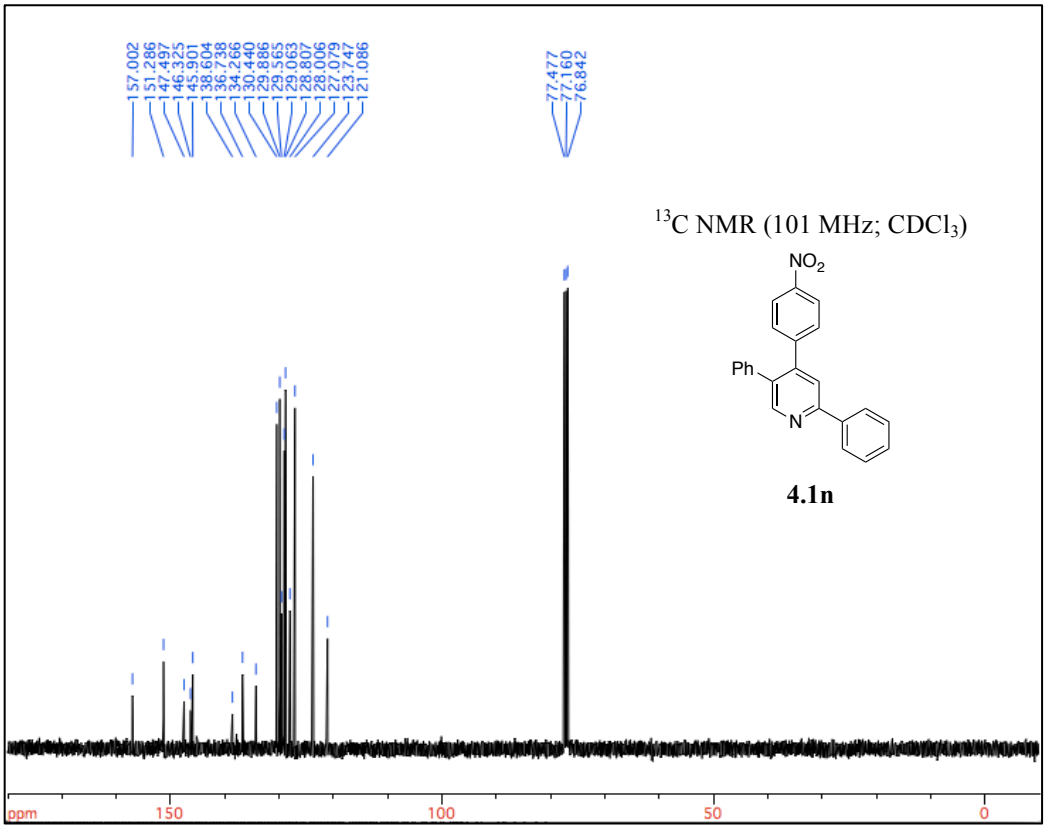


^{13}C NMR (101 MHz; $CDCl_3$)

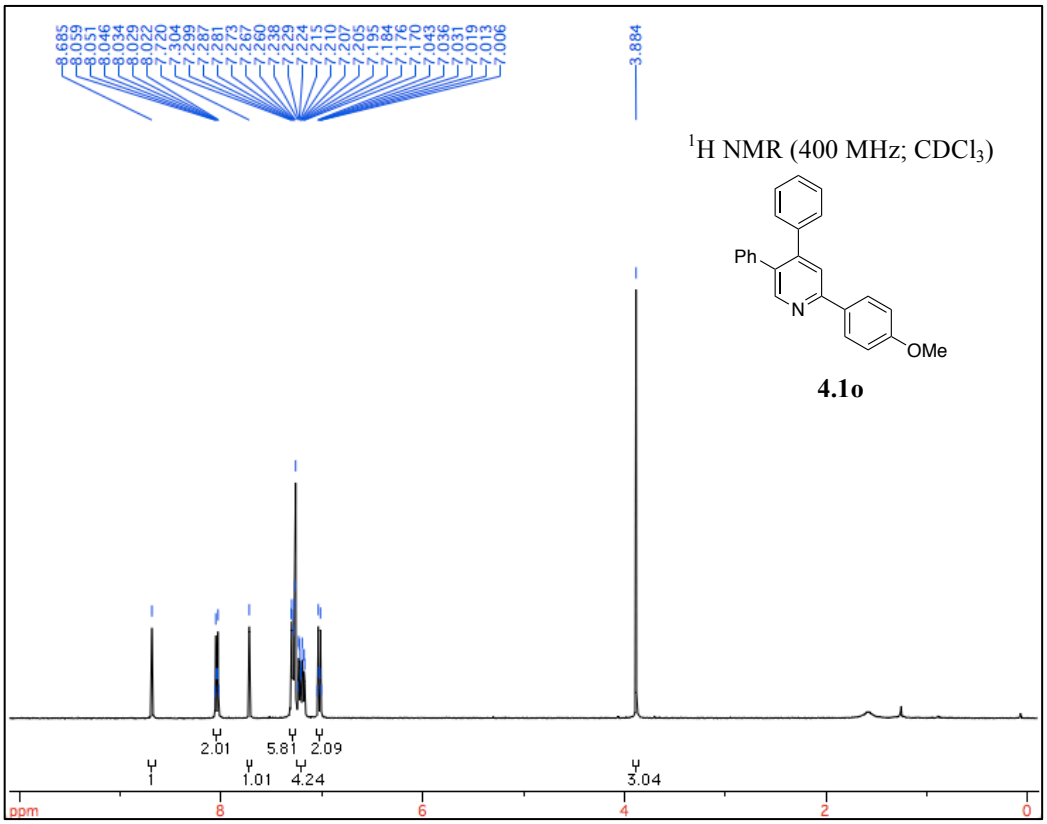
4.1m

4-(4-nitrophenyl)-2,5-diphenylpyridine (4.1n)



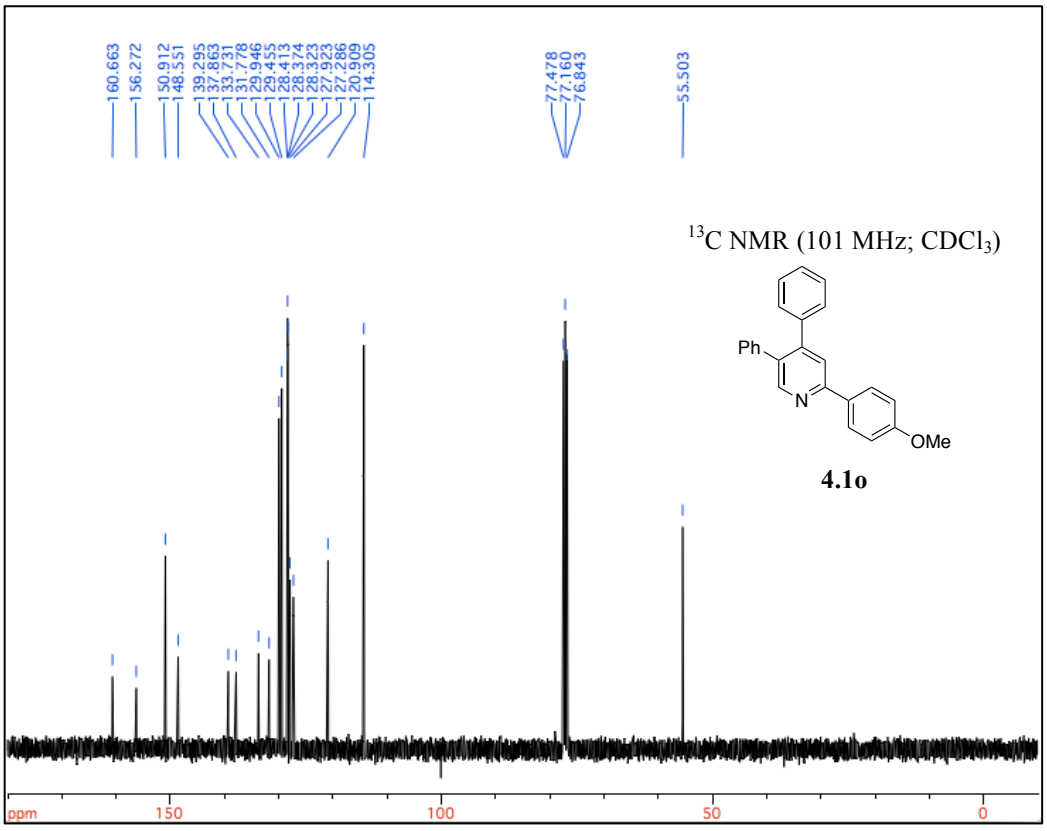


2-(4-methoxyphenyl)-4,5-diphenylpyridine (4.1o)



^{1}H NMR (400 MHz; $CDCl_3$)

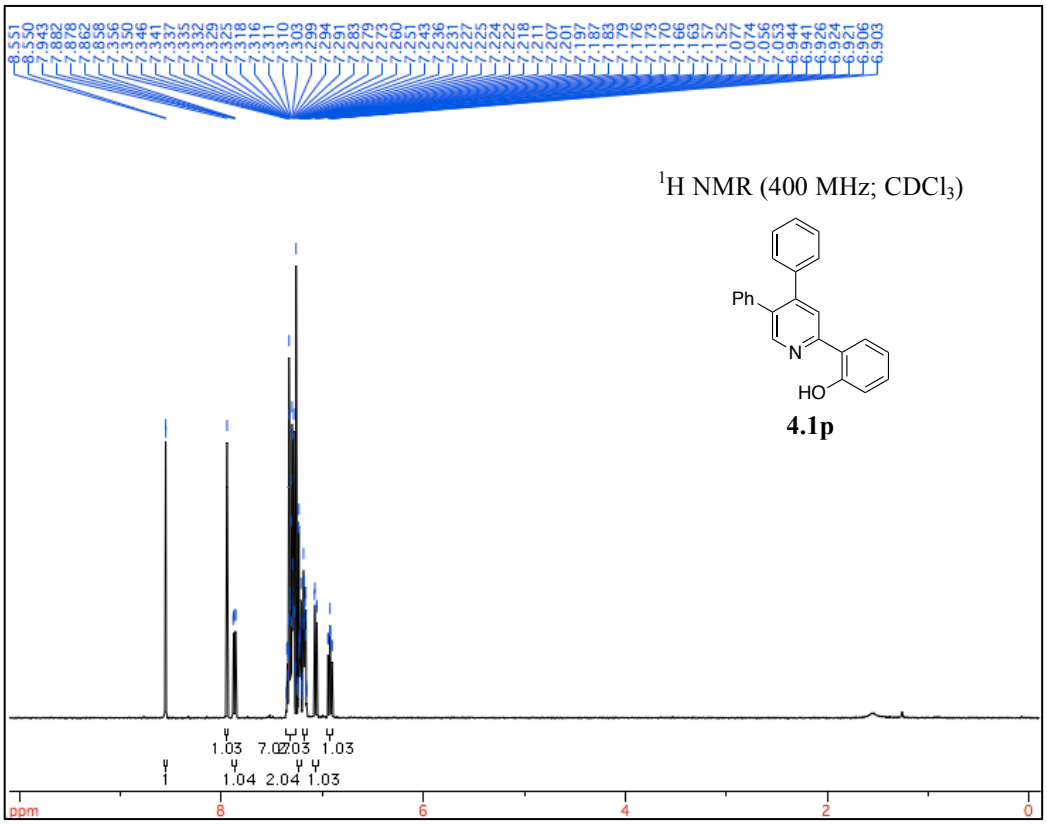
4.1o

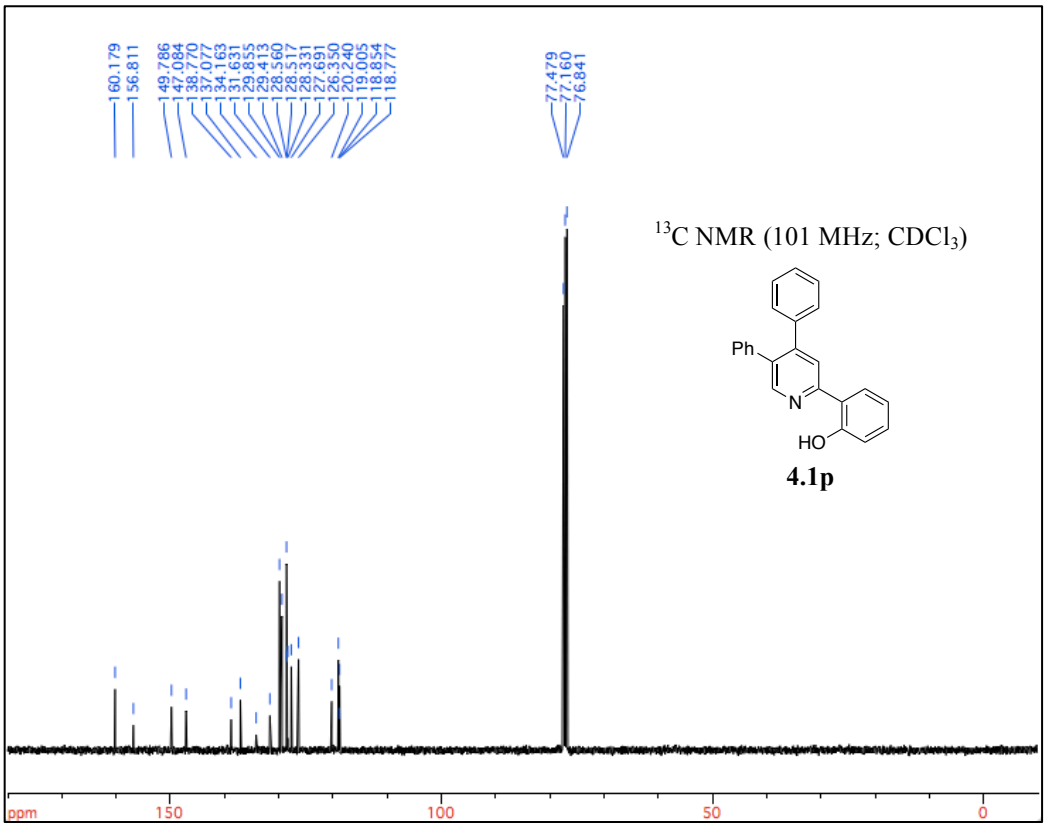


^{13}C NMR (101 MHz; $CDCl_3$)

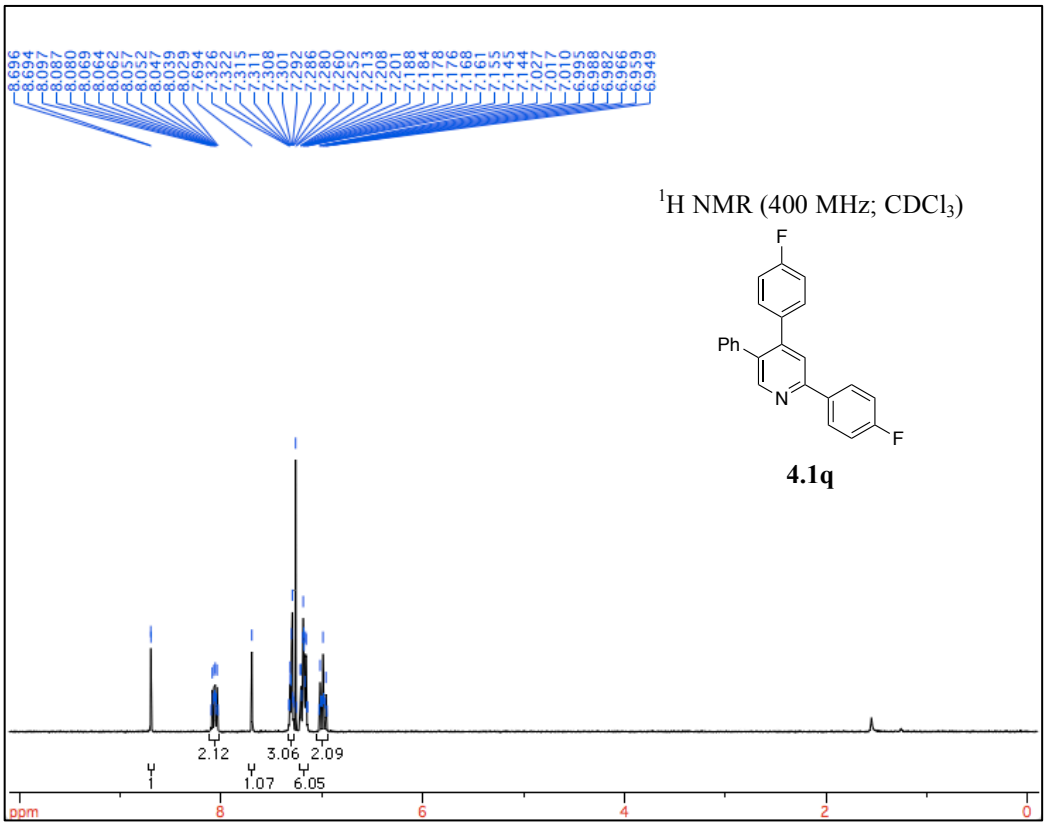
4.1o

2-(4,5-diphenylpyridin-2-yl)phenol (4.1p)



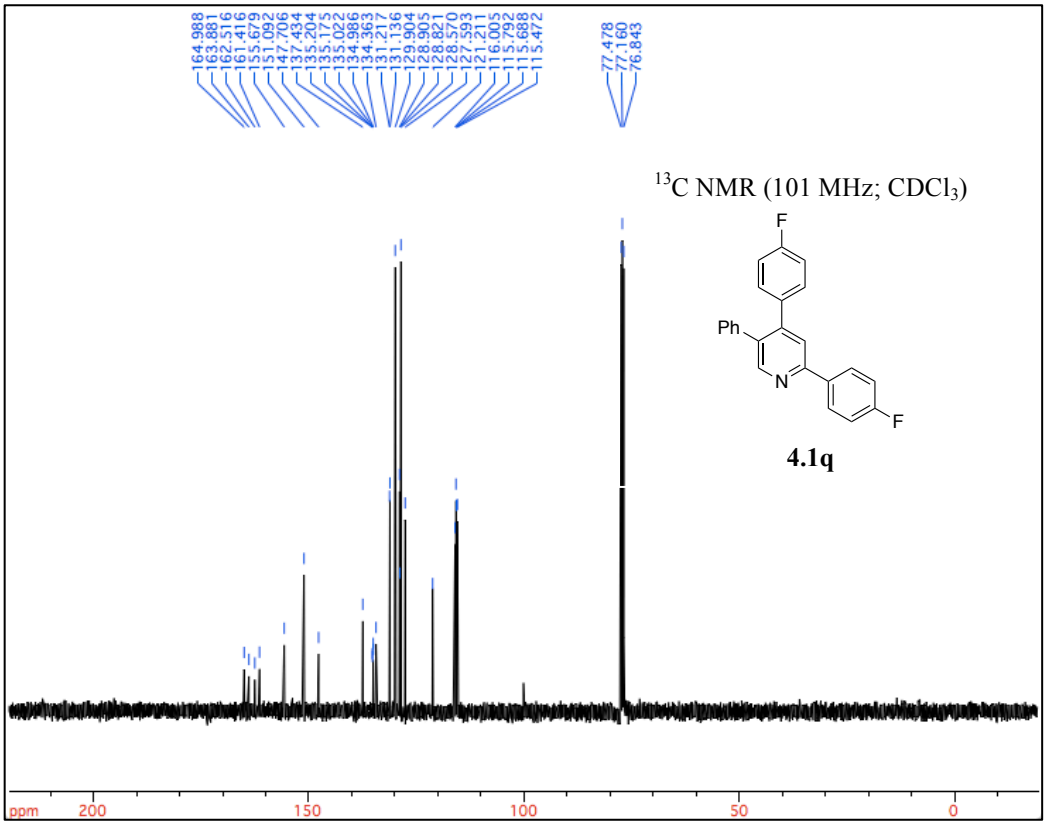


2,4-bis(4-fluorophenyl)-5-phenylpyridine (4.1q)



^{1}H NMR (400 MHz; $CDCl_3$)

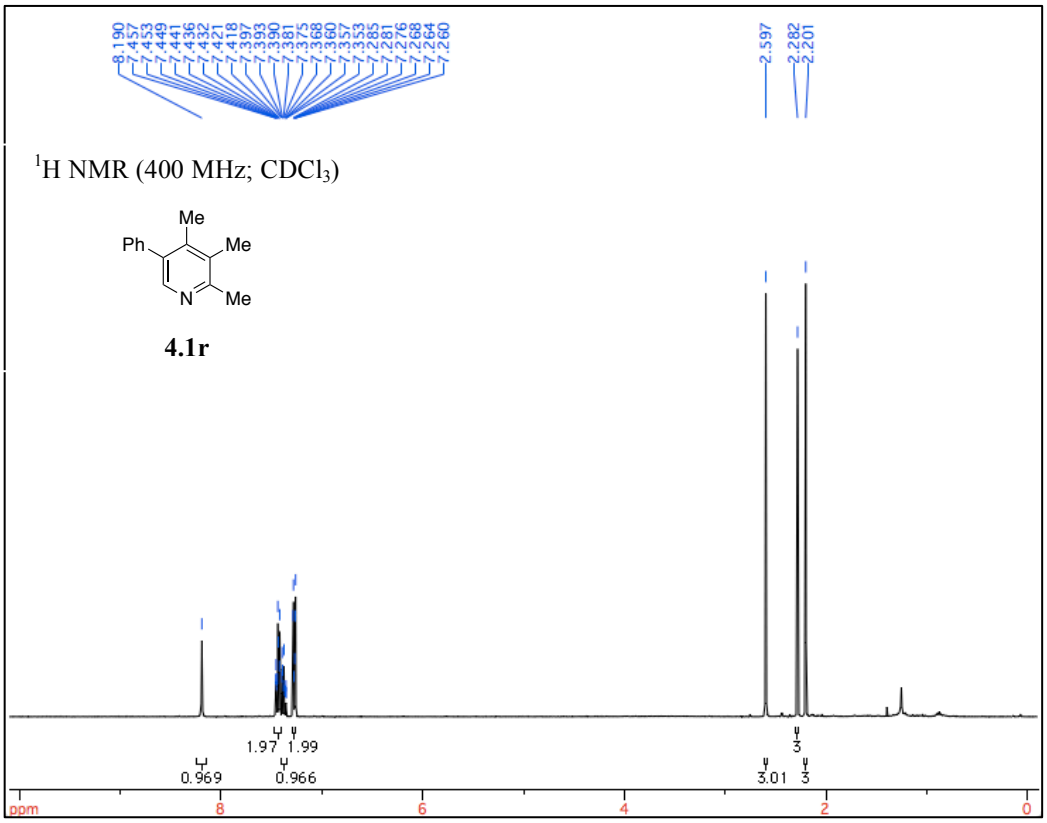
4.1q

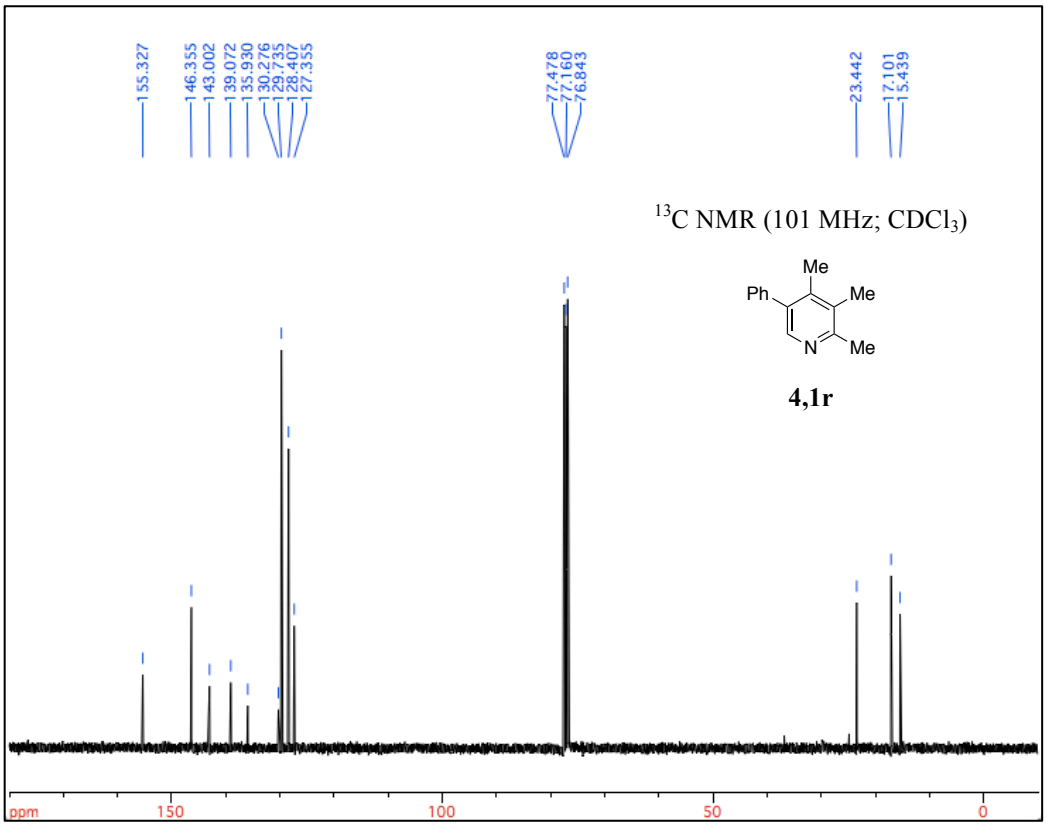


^{13}C NMR (101 MHz; $CDCl_3$)

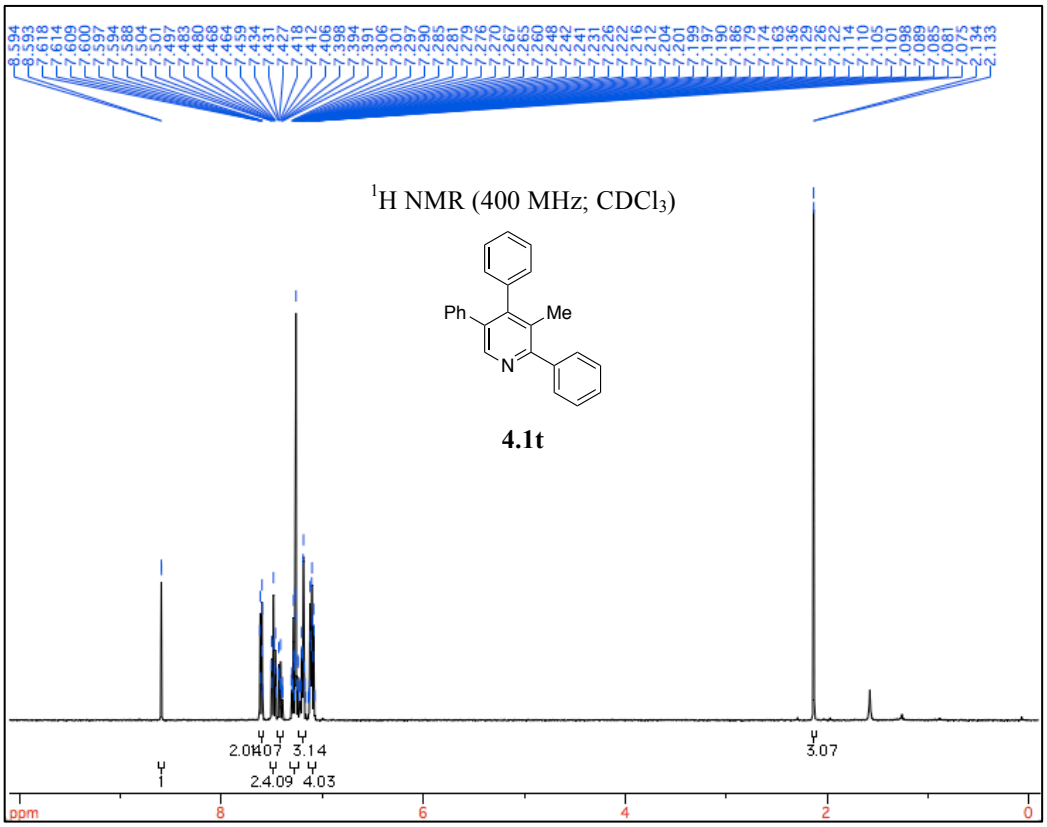
4.1q

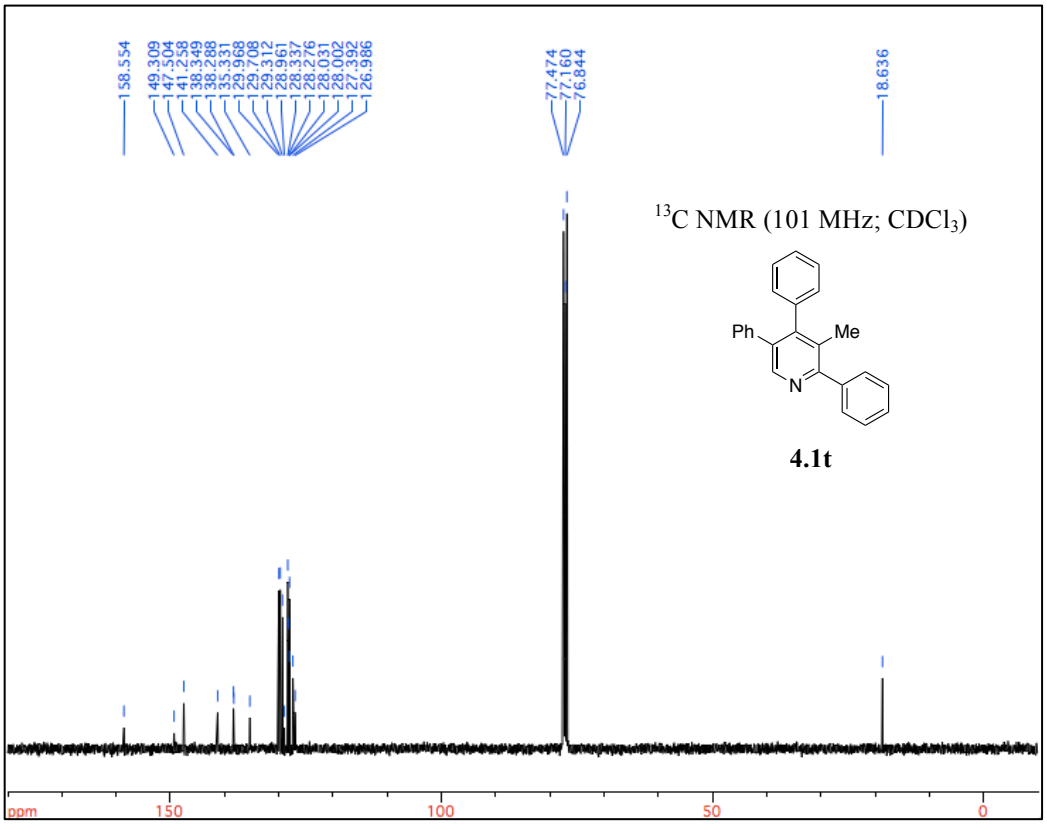
2,3,4-trimethyl-5-phenylpyridine (4.1r)



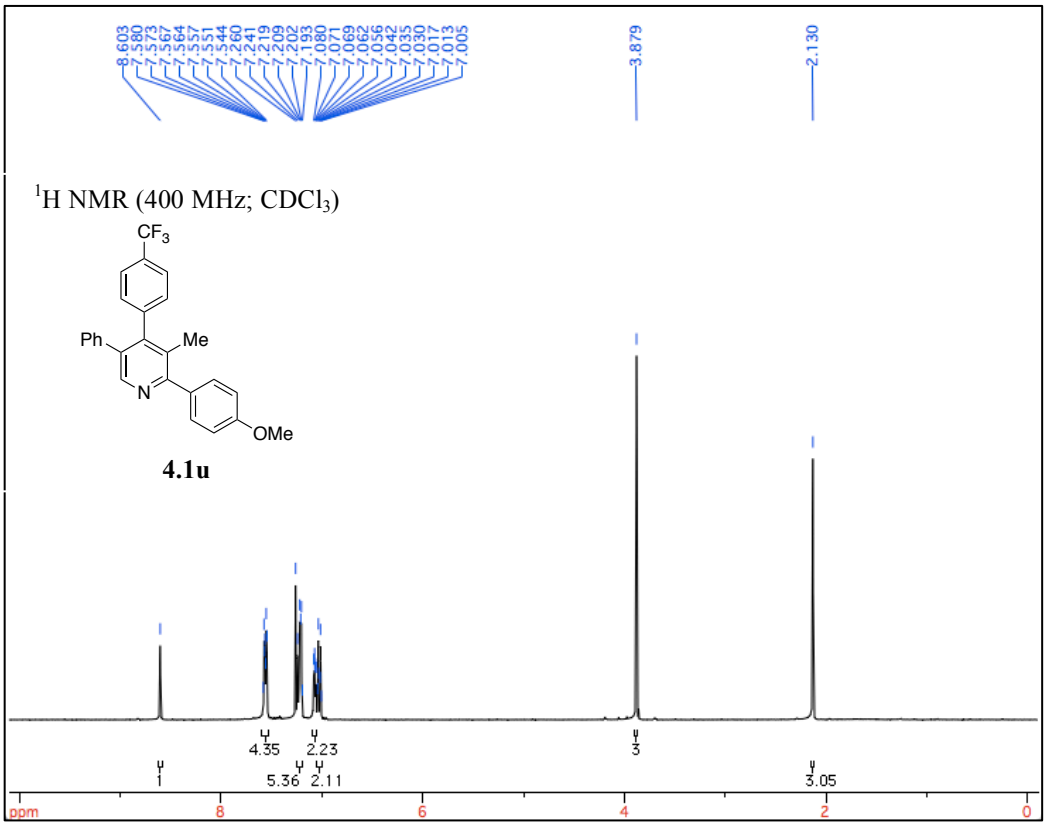


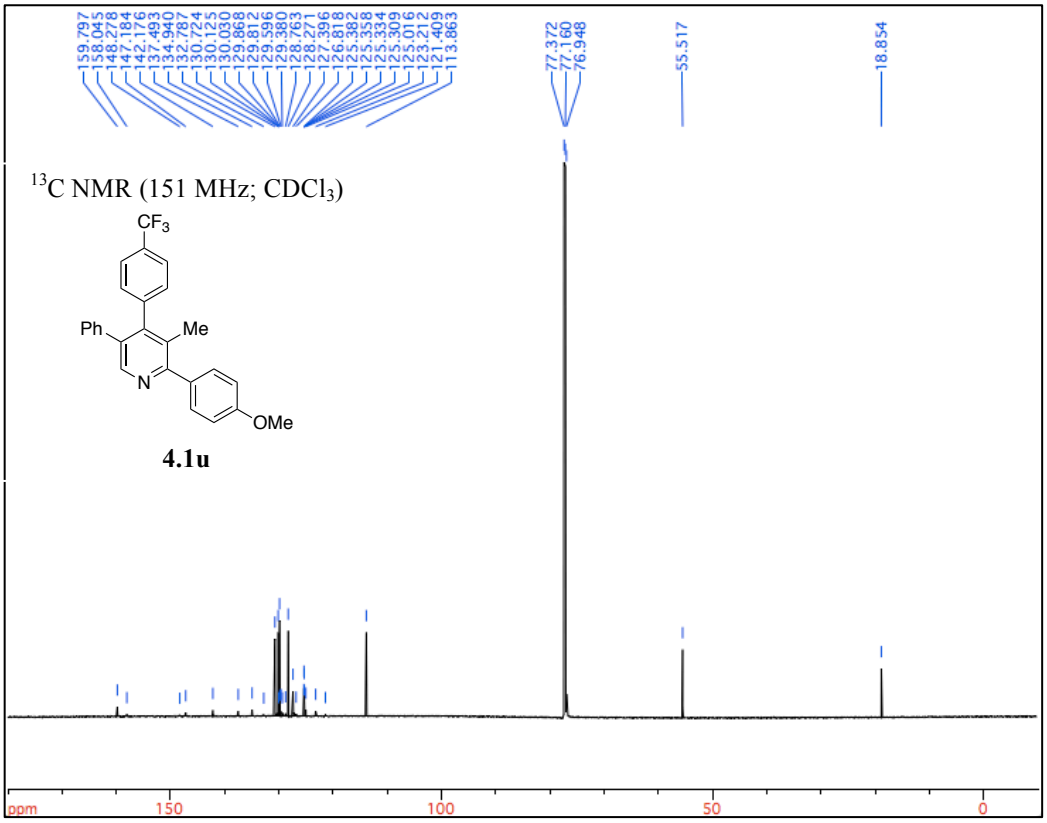
3-methyl-2,4,5-triphenylpyridine (4.1t)



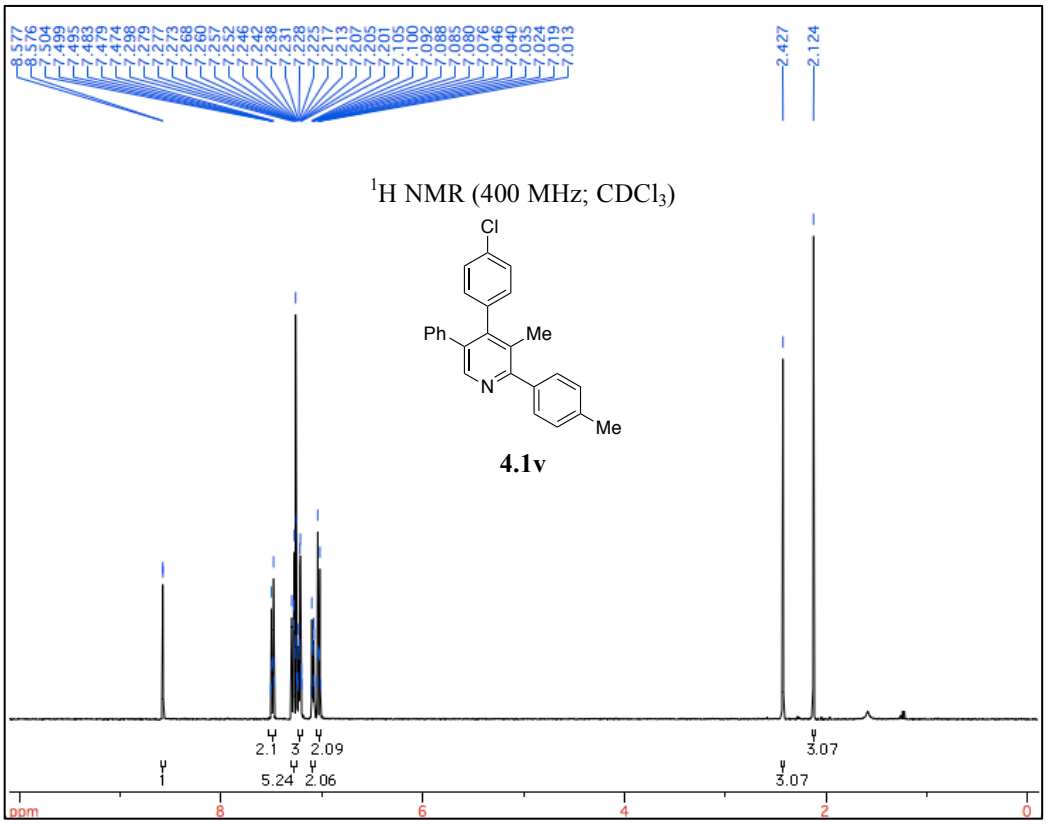


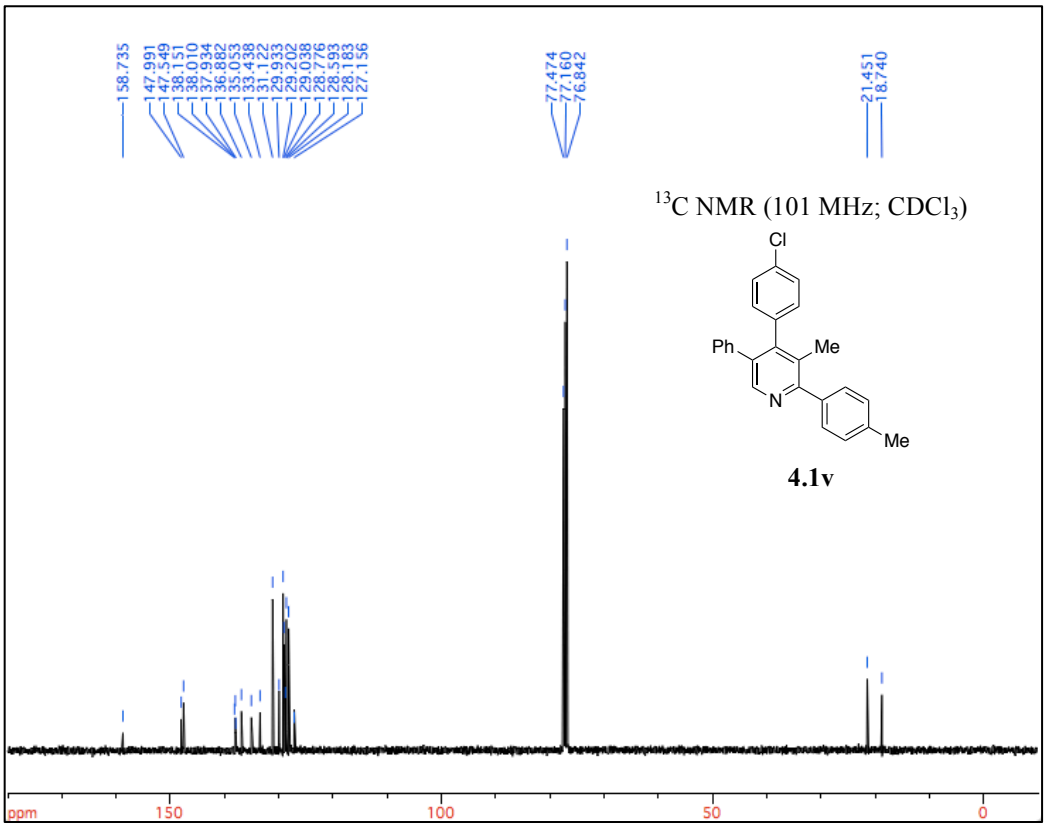
2-(4-methoxyphenyl)-3-methyl-5-phenyl-4-(4-(trifluoromethyl)phenyl)pyridine (4.1u)



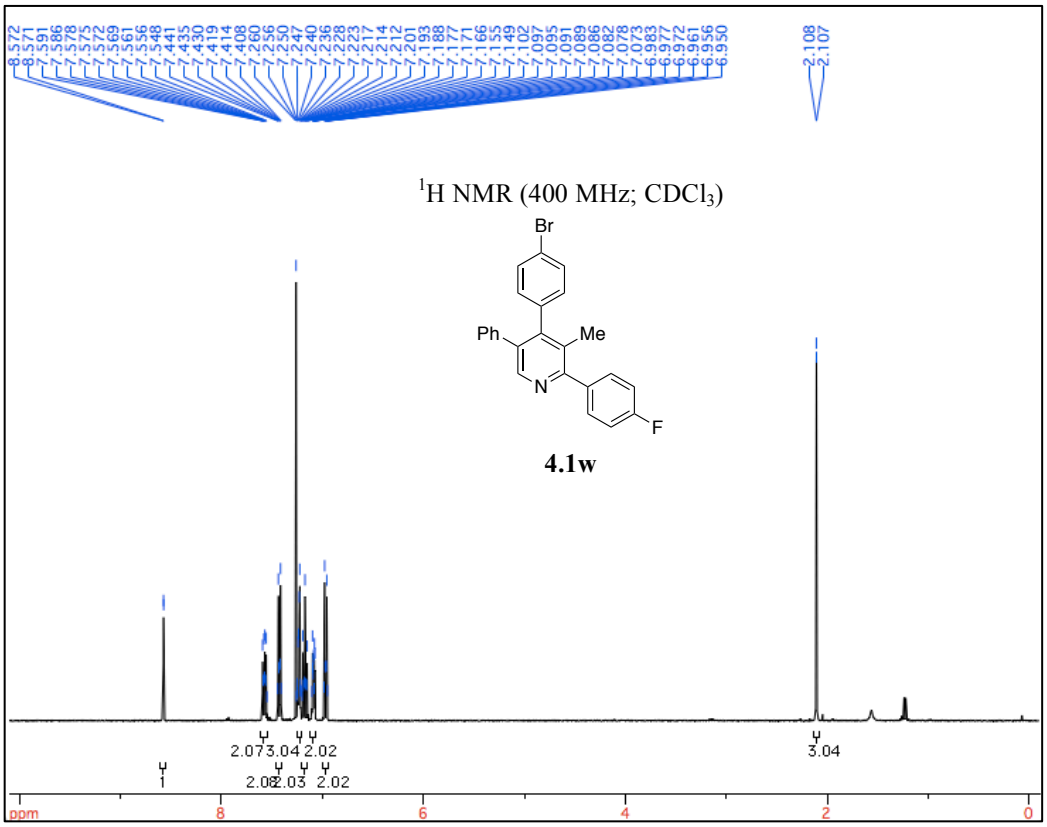


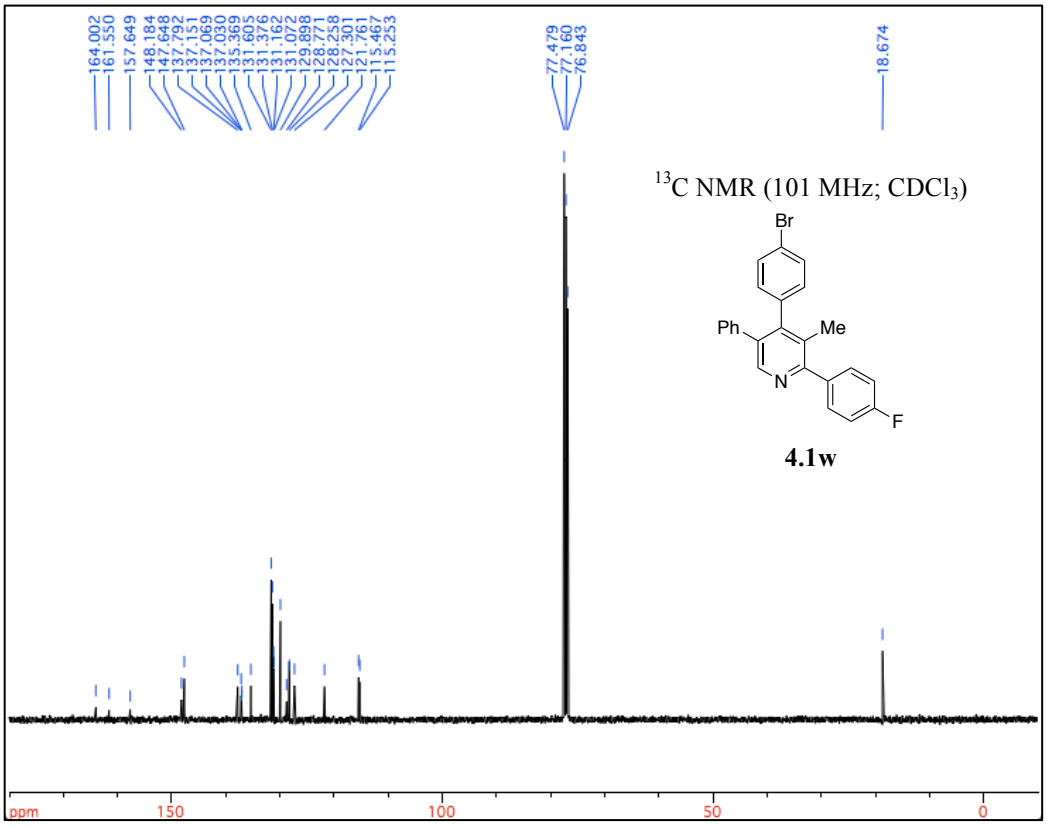
4-(4-chlorophenyl)-3-methyl-5-phenyl-2-(*p*-tolyl)pyridine (4.1v)



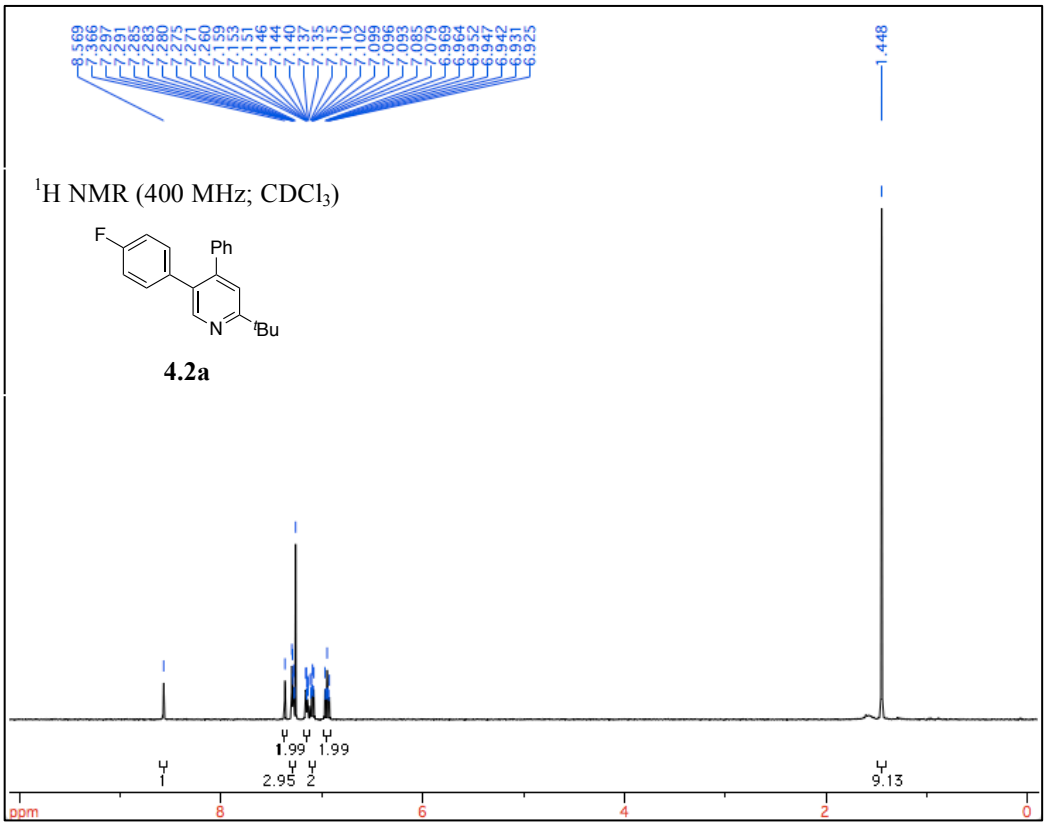


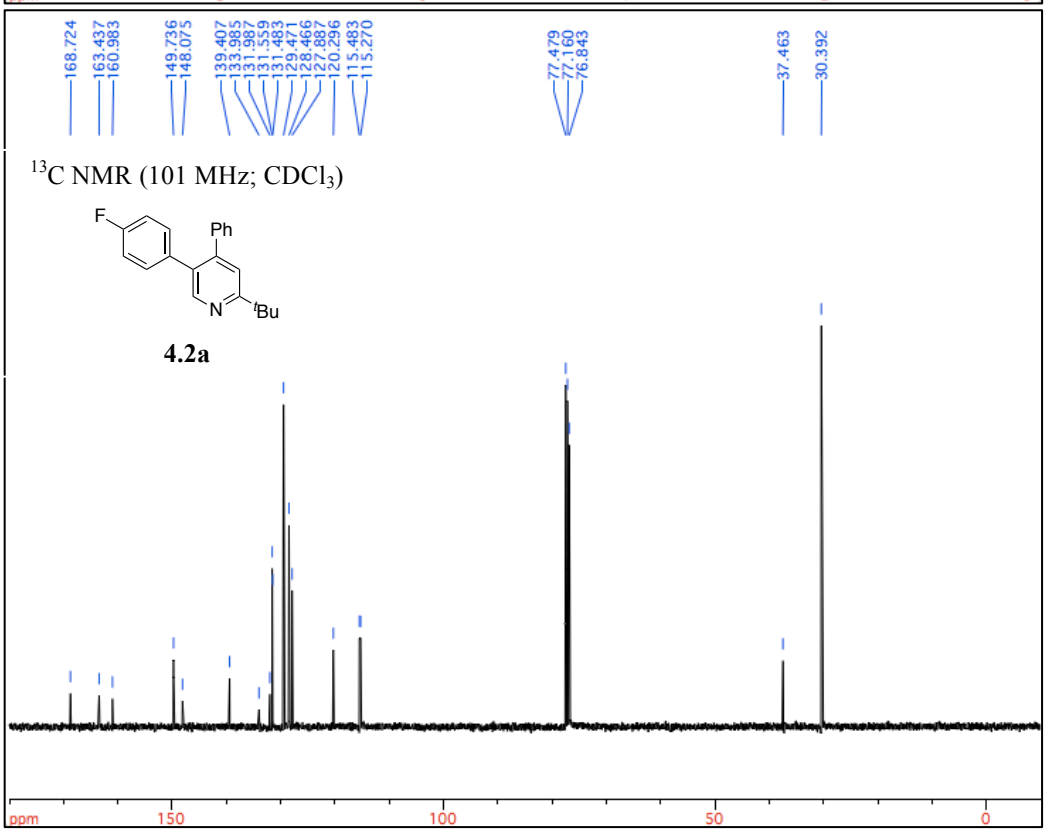
4-(4-bromophenyl)-2-(4-fluorophenyl)-3-methyl-5-phenylpyridine (4.1w)



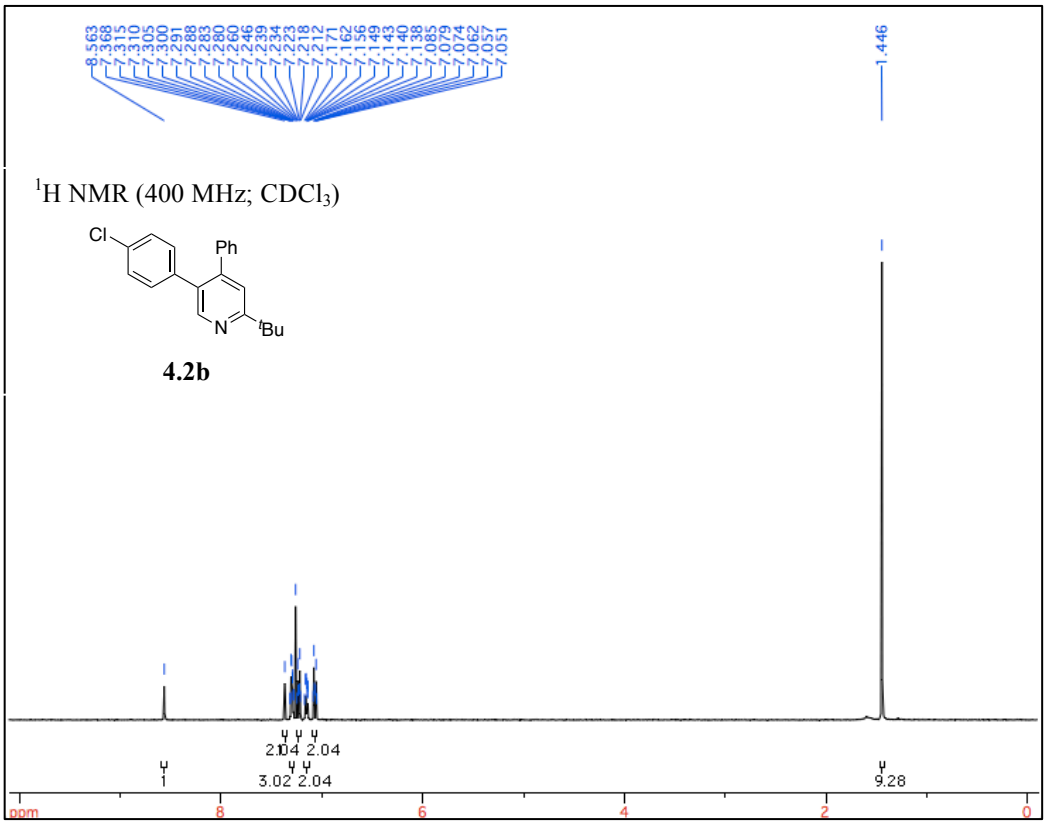


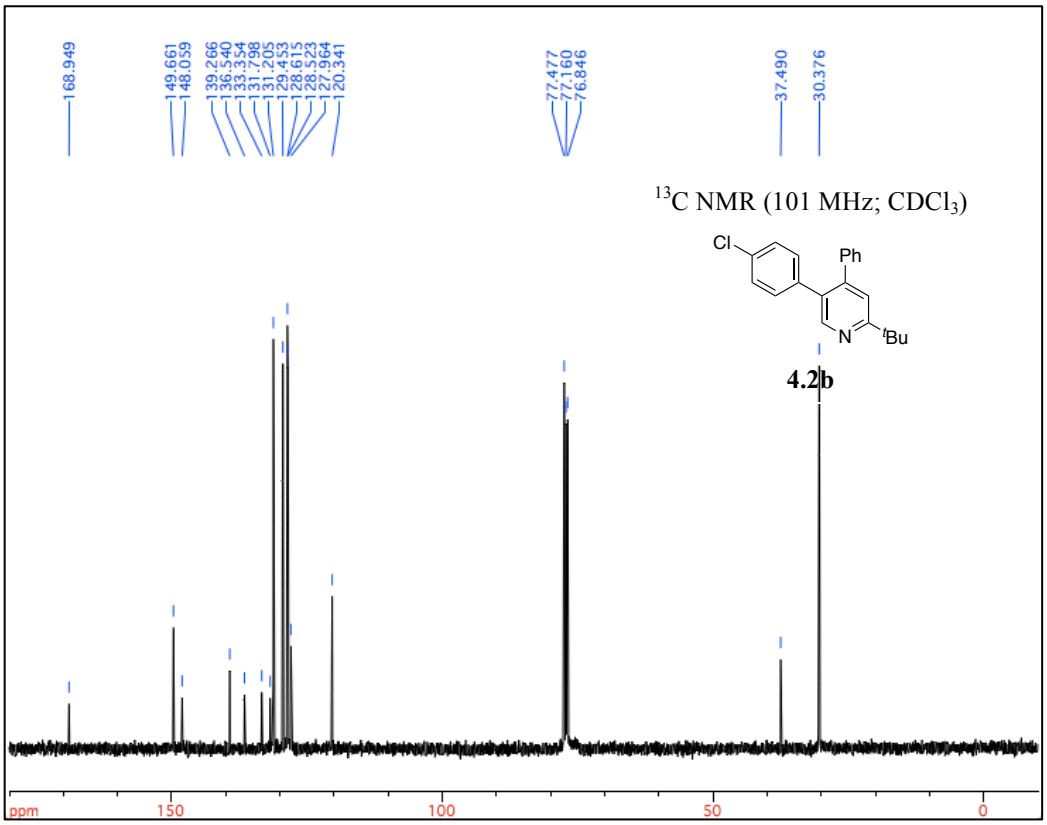
2-(*tert*-butyl)-5-(4-fluorophenyl)-4-phenylpyridine (4.2a)



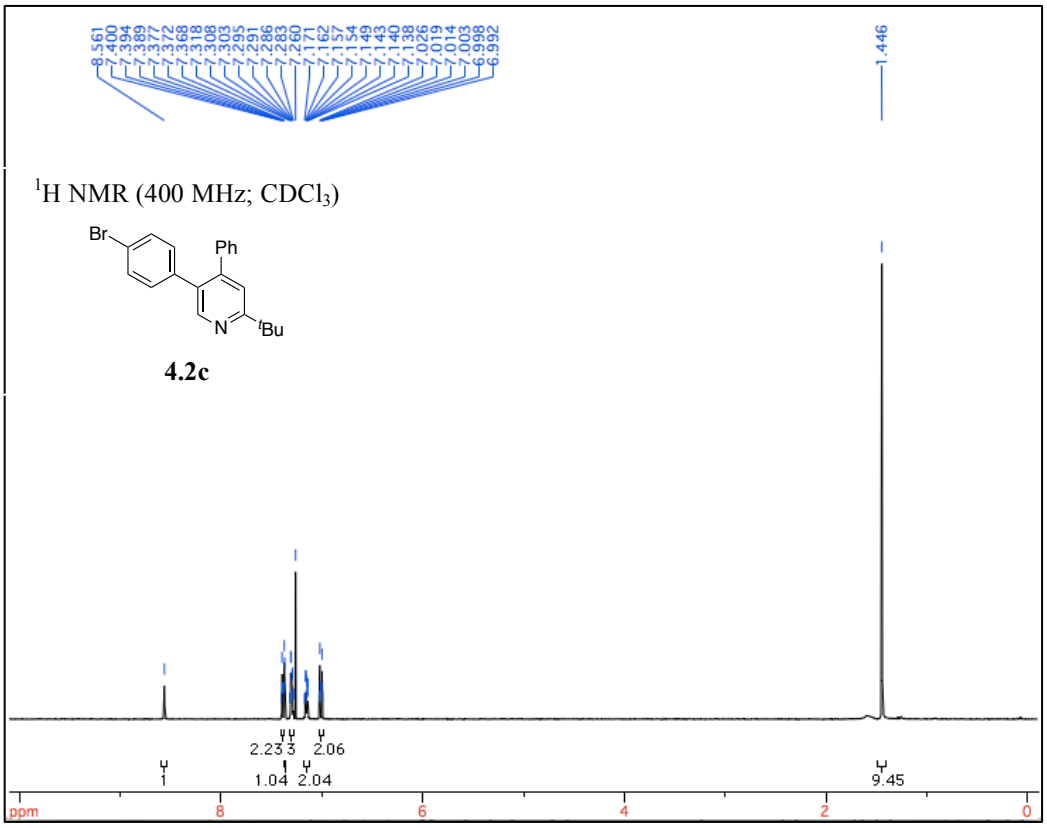


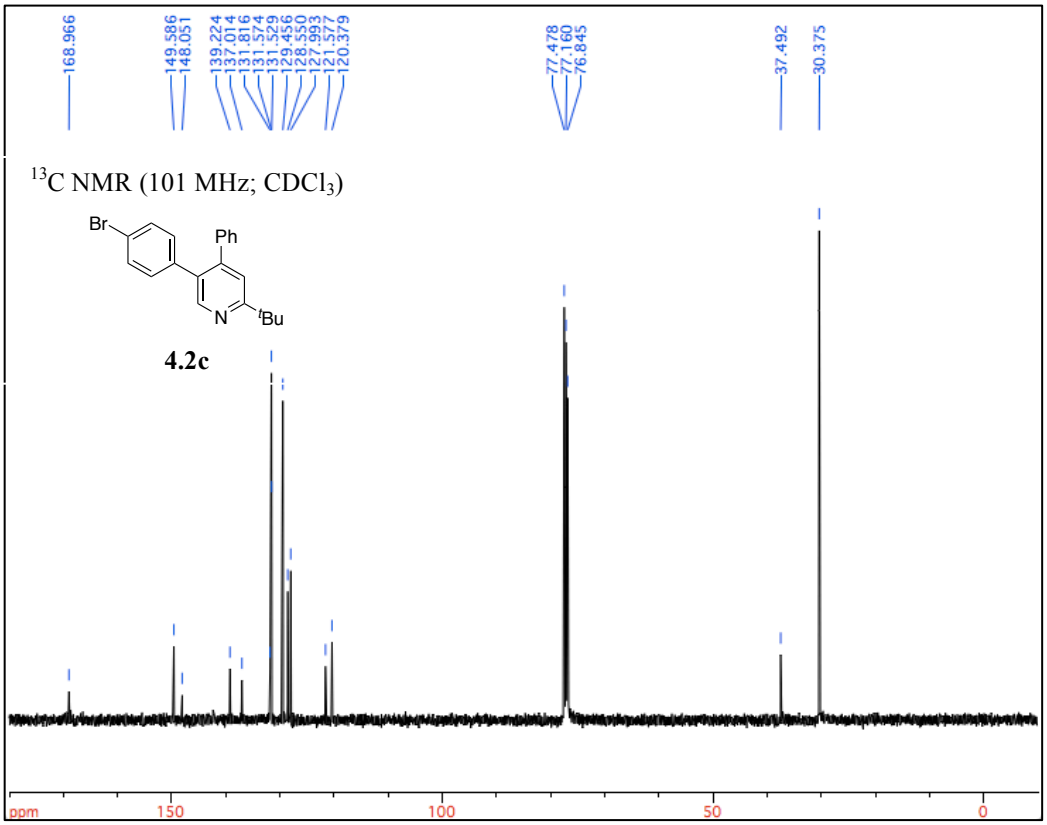
2-(*tert*-butyl)-5-(4-chlorophenyl)-4-phenylpyridine (4.2b)



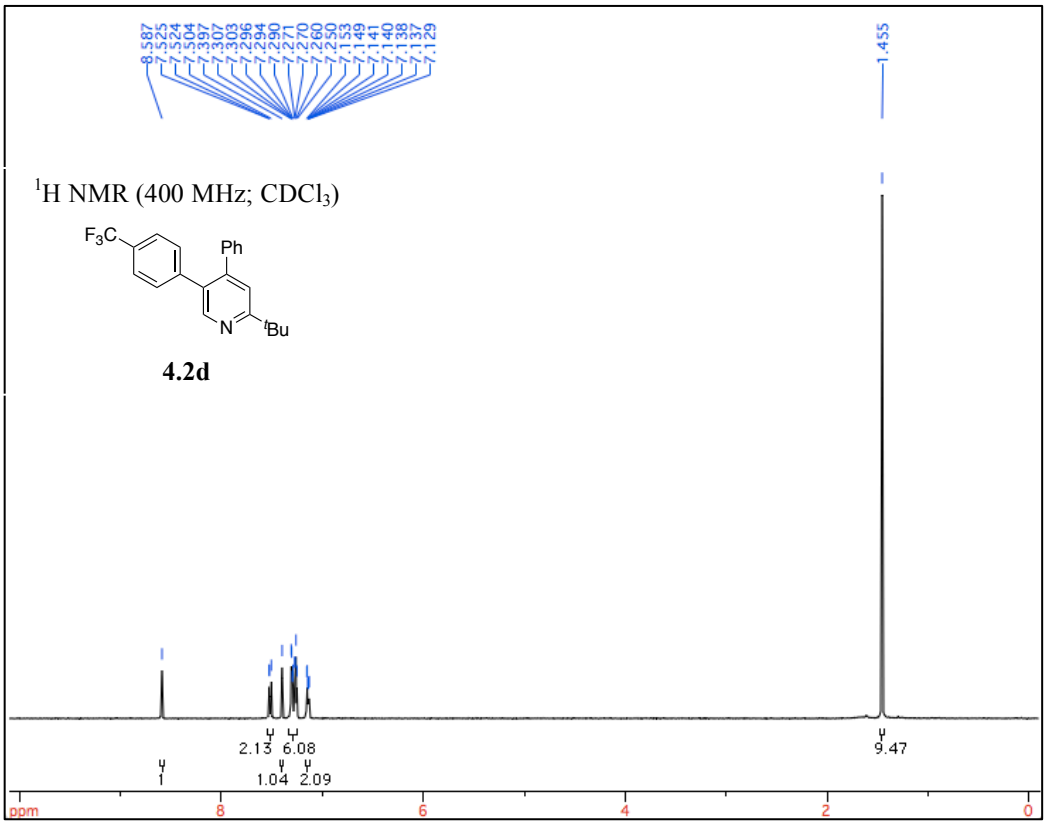


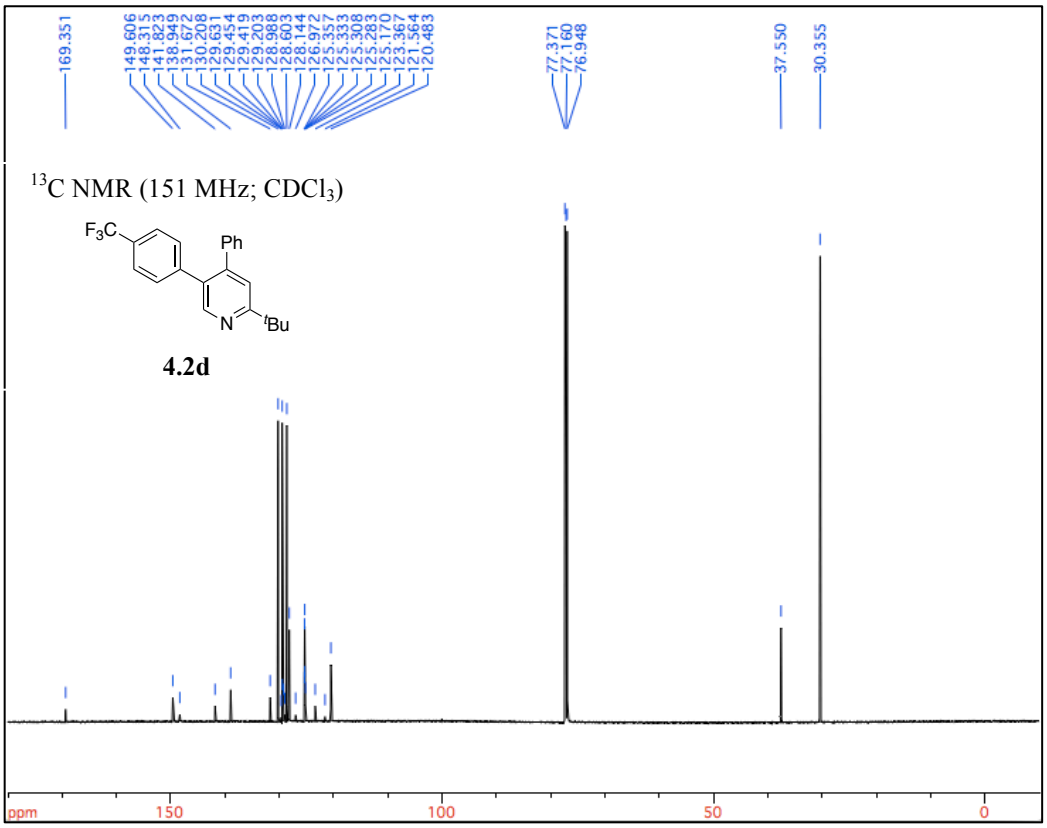
2-(*tert*-butyl)-5-(4-bromophenyl)-4-phenylpyridine (4.2c)



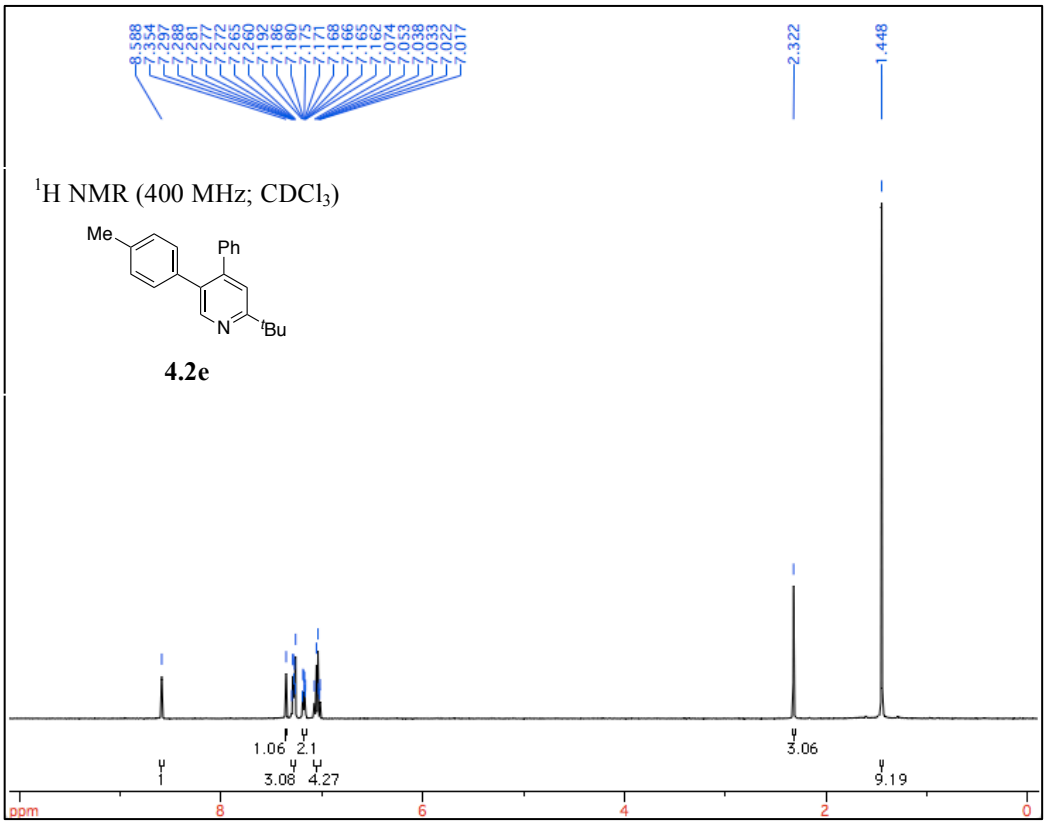


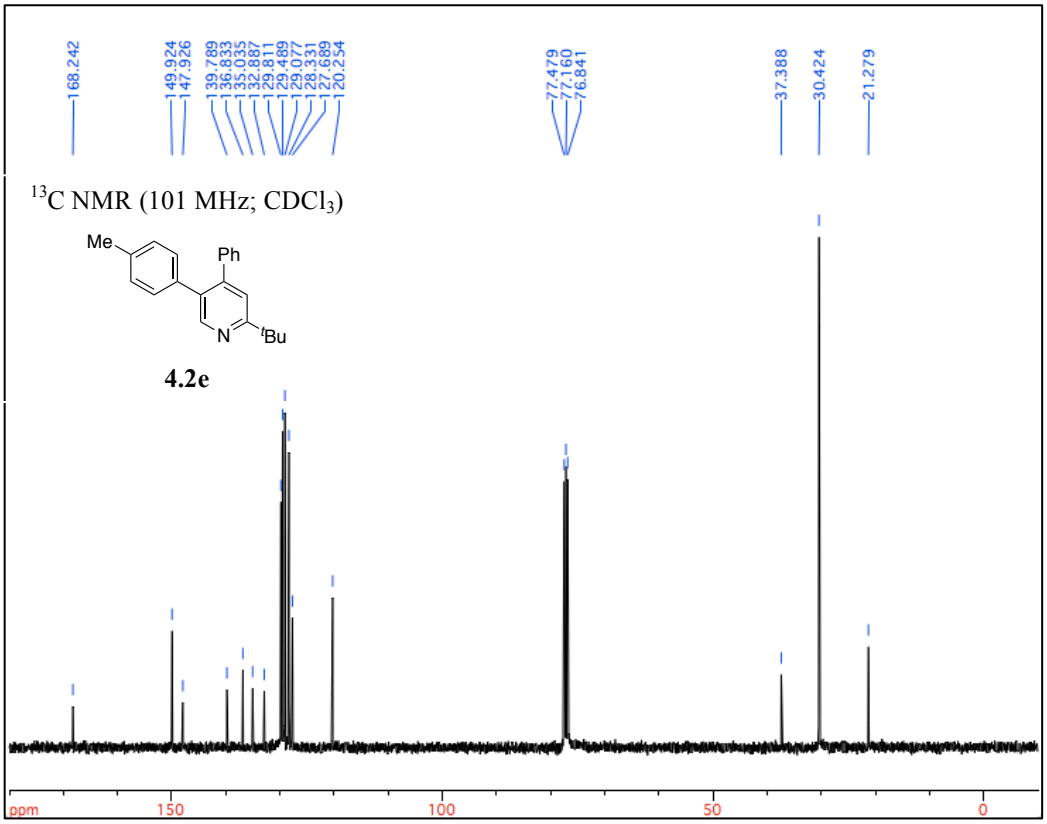
2-(tert-butyl)-4-phenyl-5-(4-(trifluoromethyl)phenyl)pyridine (4.2d)



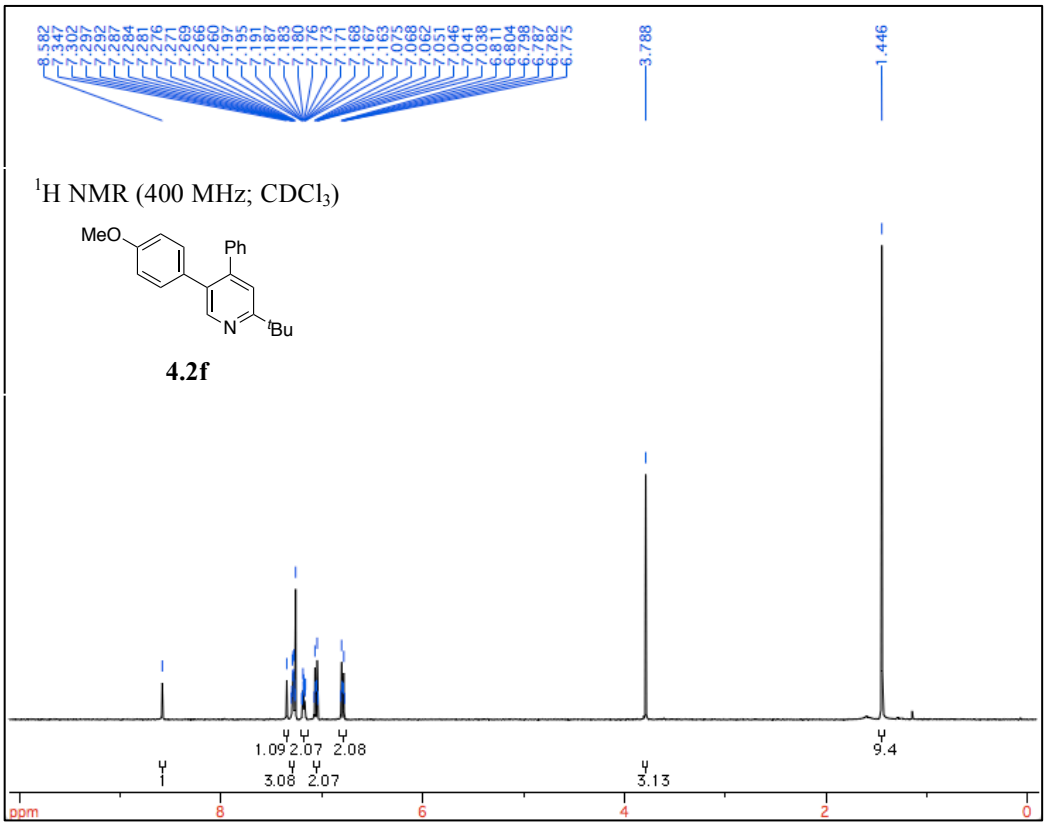


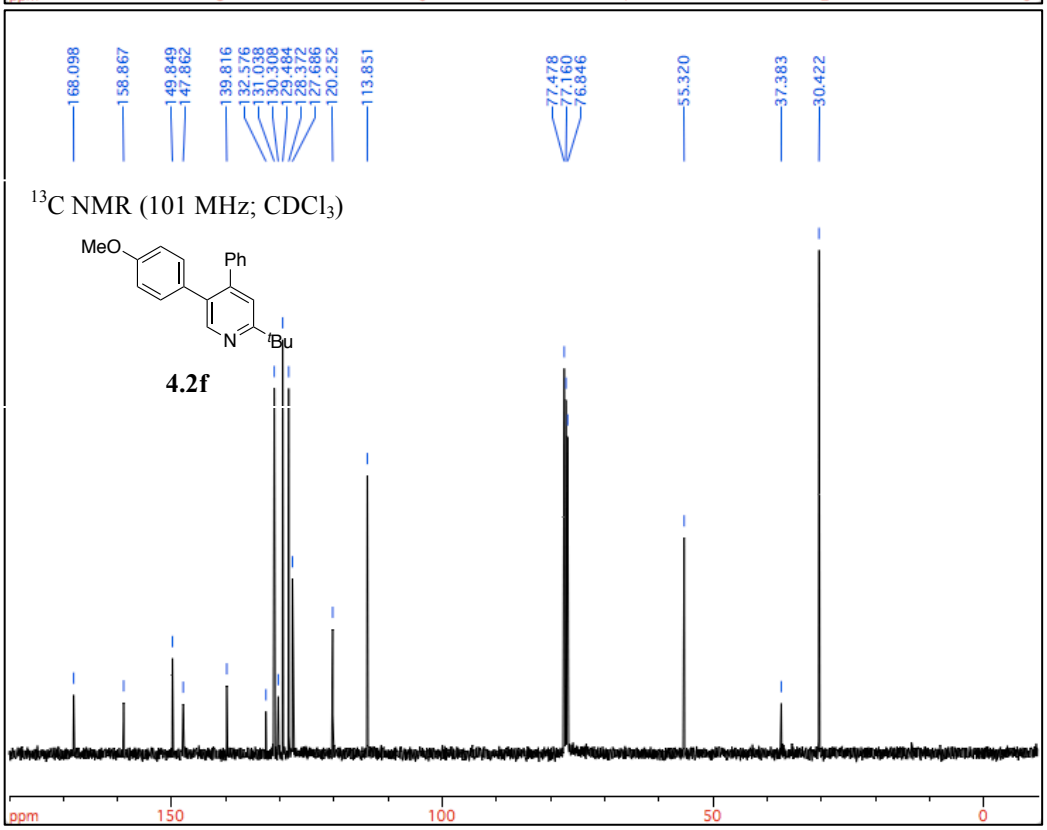
2-(*tert*-butyl)-4-phenyl-5-(*p*-tolyl)pyridine (4.2e)



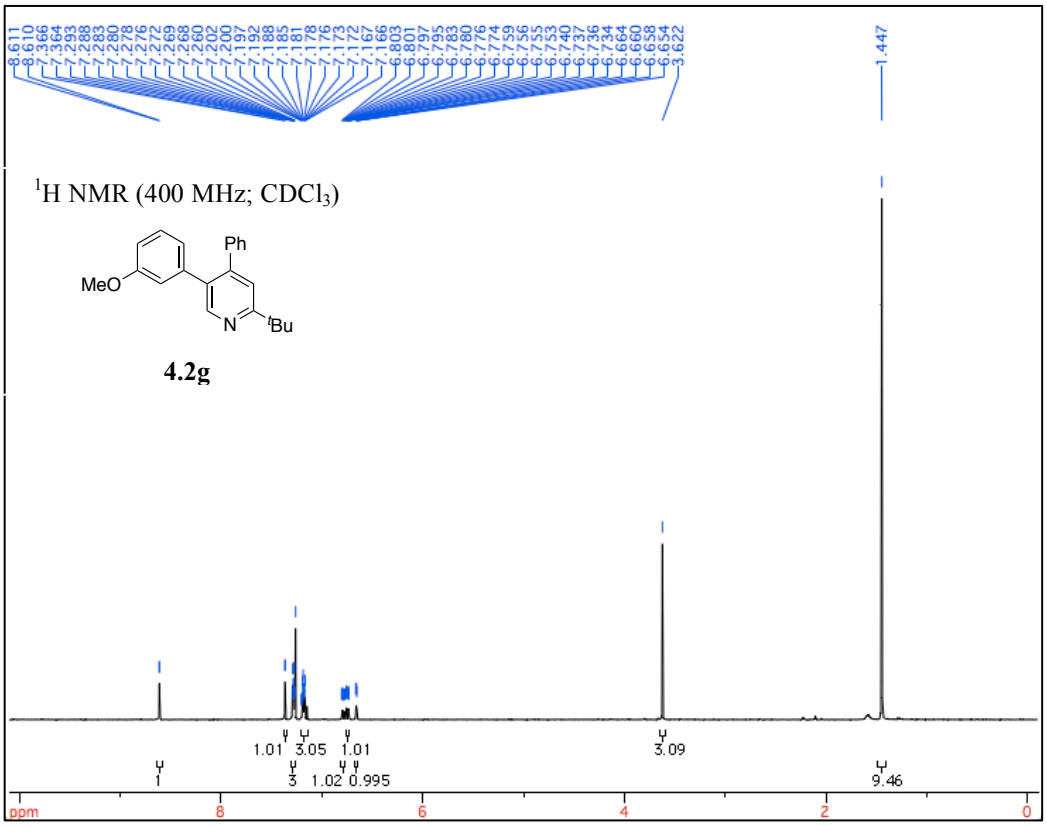


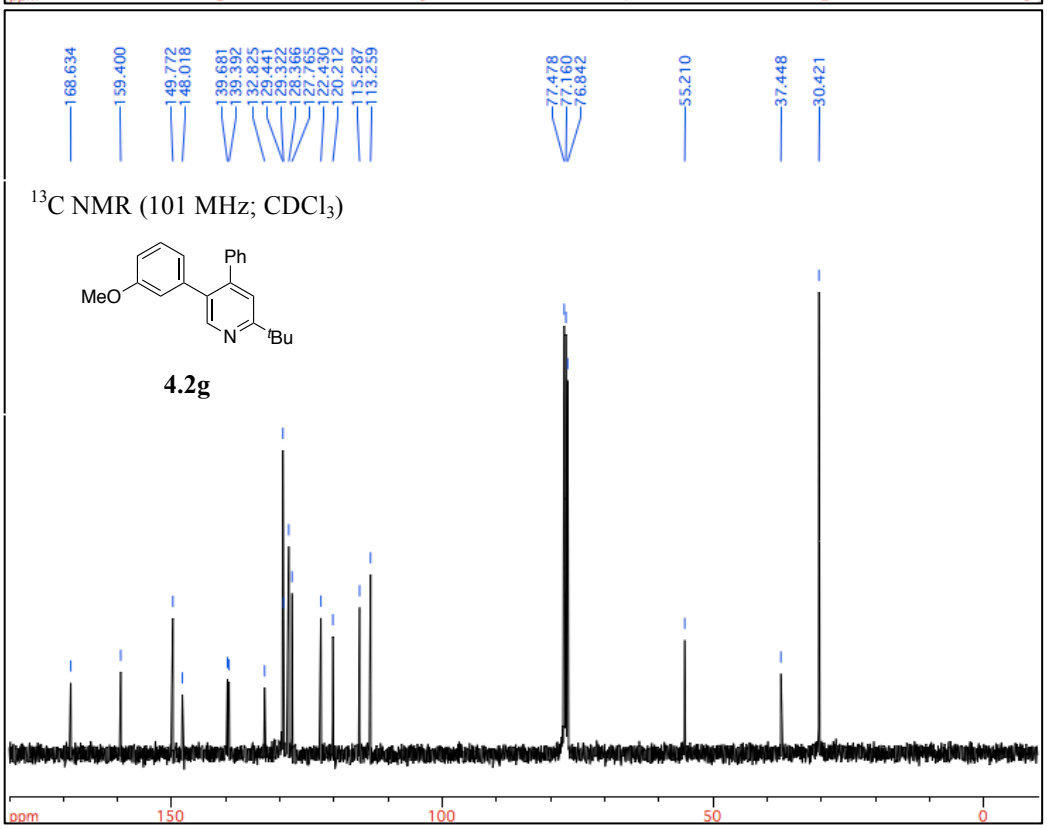
2-(*tert*-butyl)-5-(4-methoxyphenyl)-4-phenylpyridine (4.2f)



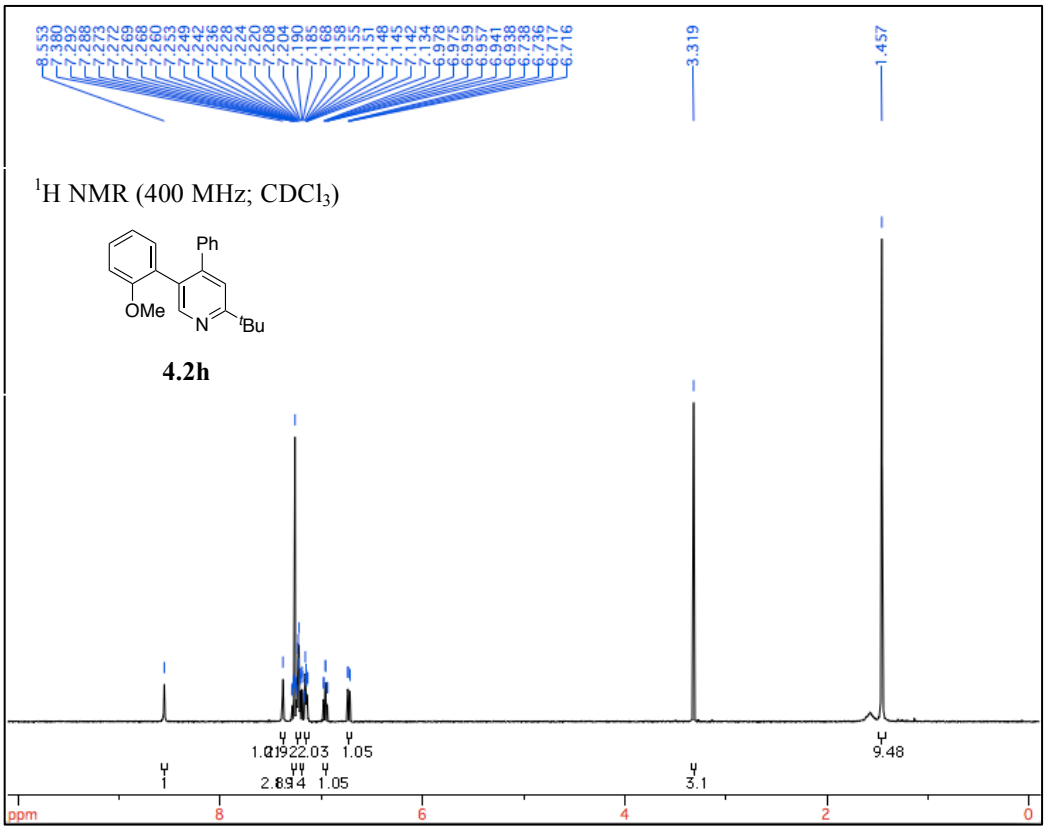


2-(*tert*-butyl)-5-(3-methoxyphenyl)-4-phenylpyridine (4.2g)



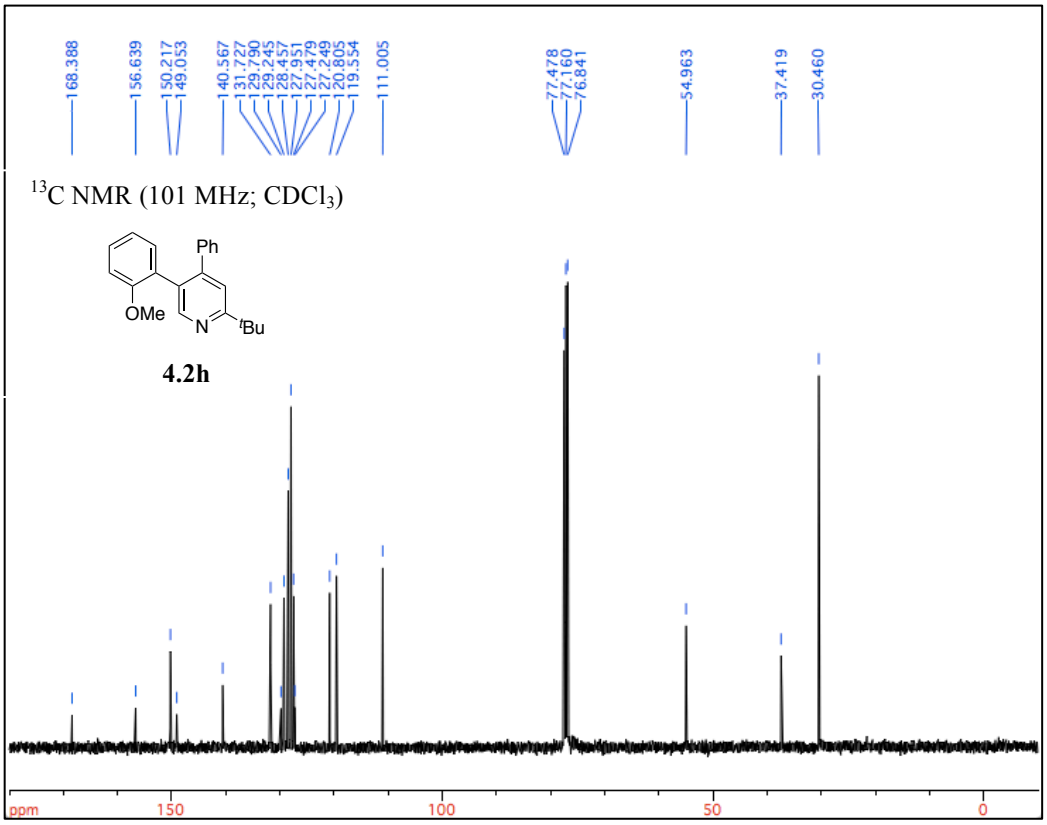


2-(*tert*-butyl)-5-(2-methoxyphenyl)-4-phenylpyridine (4.2h)



^{1}H NMR (400 MHz; $CDCl_3$)

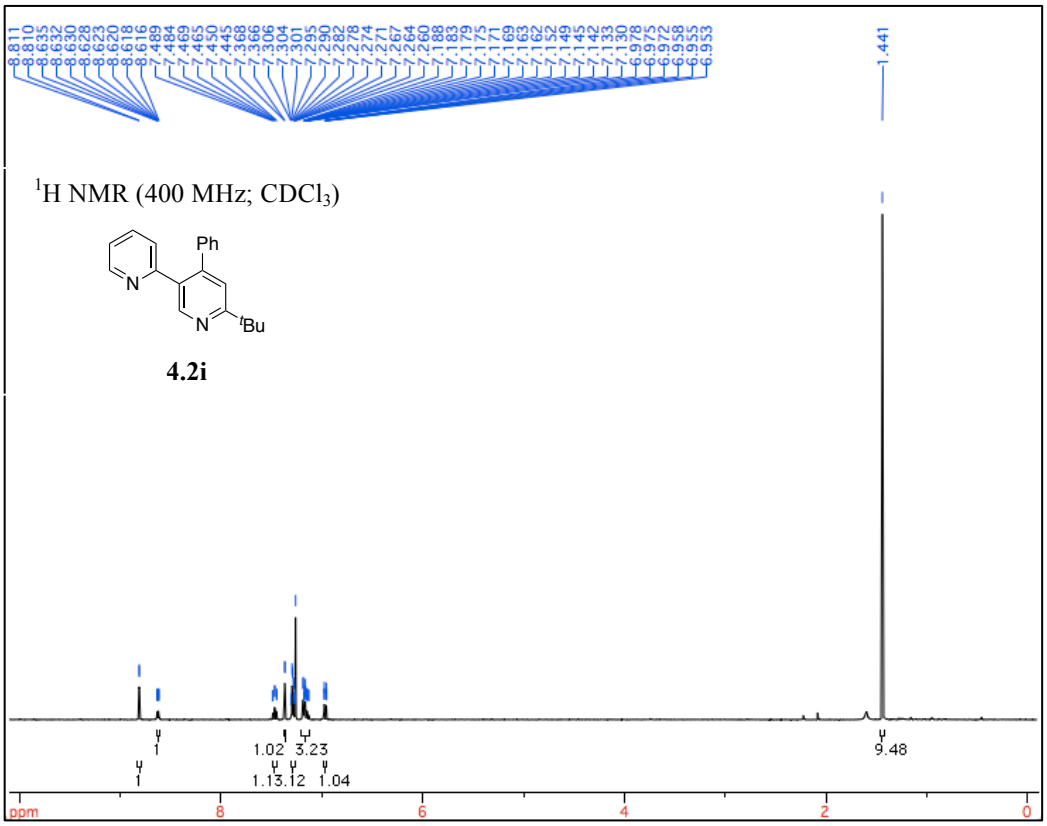
4.2h

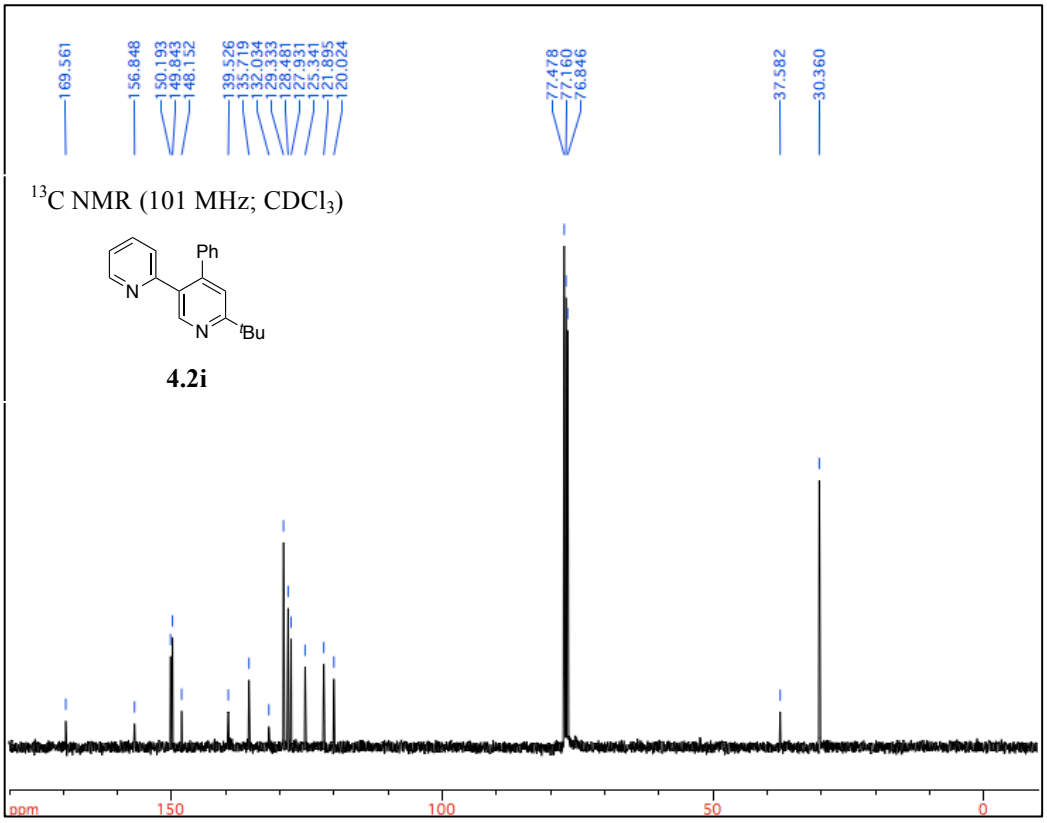


^{13}C NMR (101 MHz; $CDCl_3$)

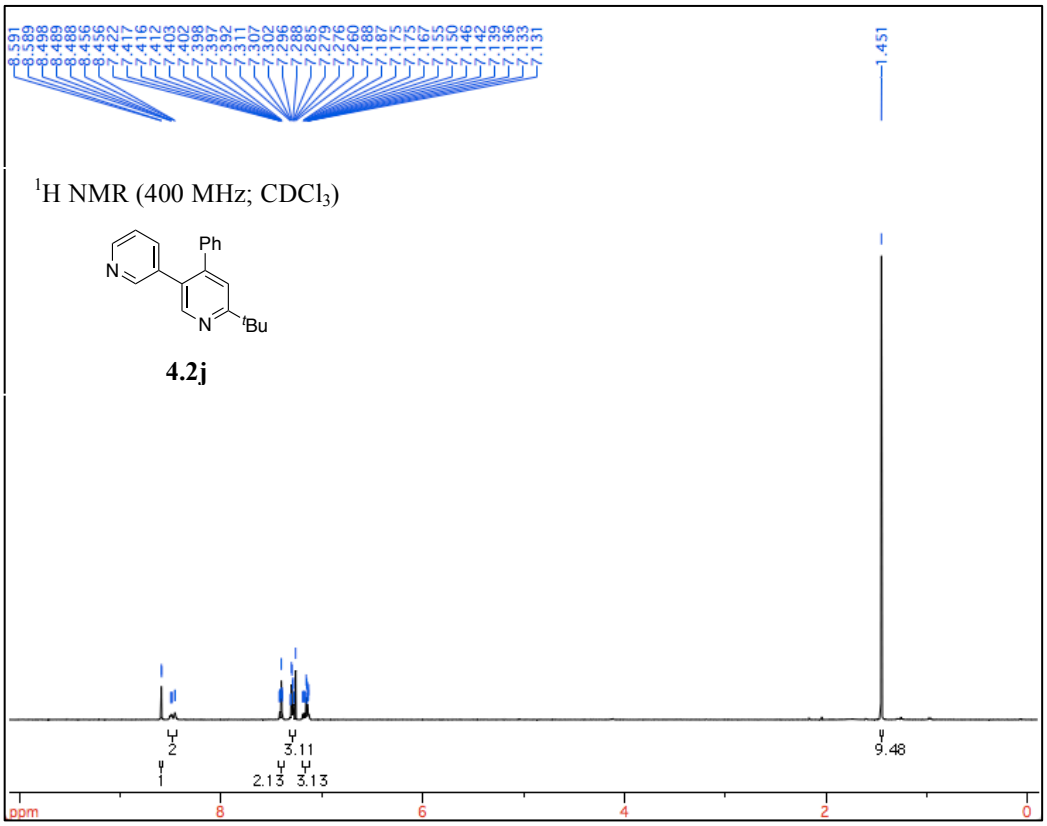
4.2h

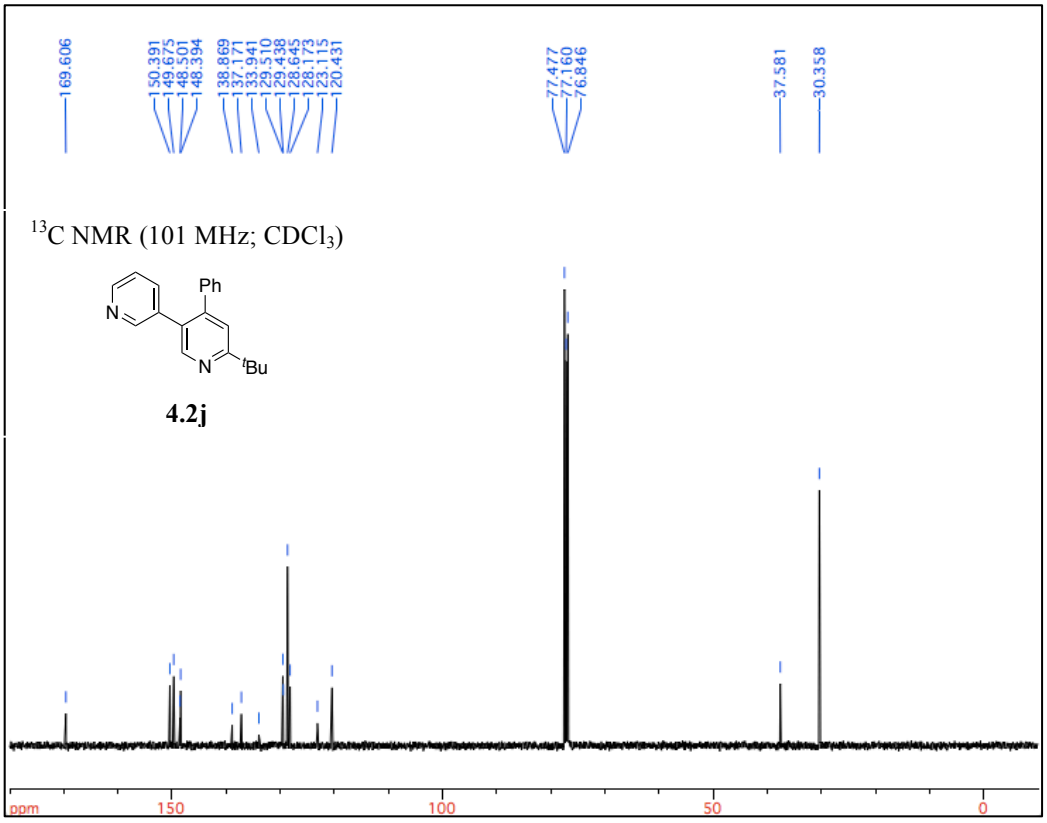
6'-(*tert*-butyl)-4'-phenyl-2,3'-bipyridine (4.2i)



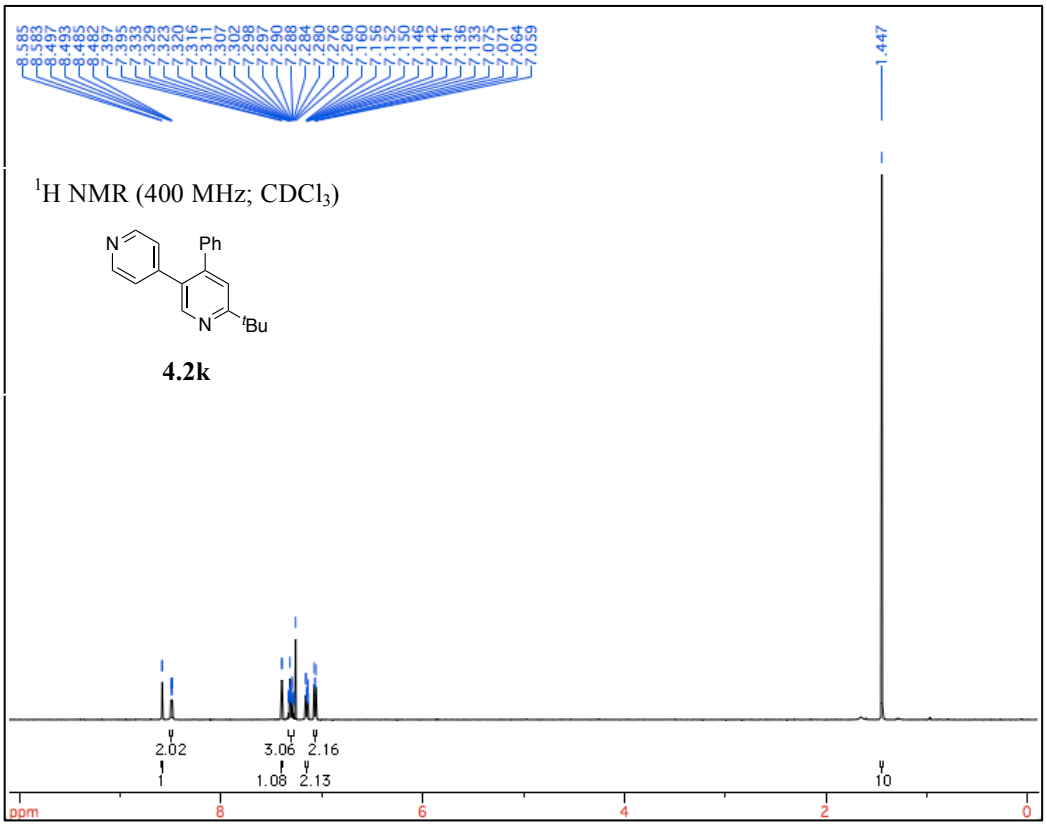


6-(*tert*-butyl)-4-phenyl-3,3'-bipyridine (4.2j)



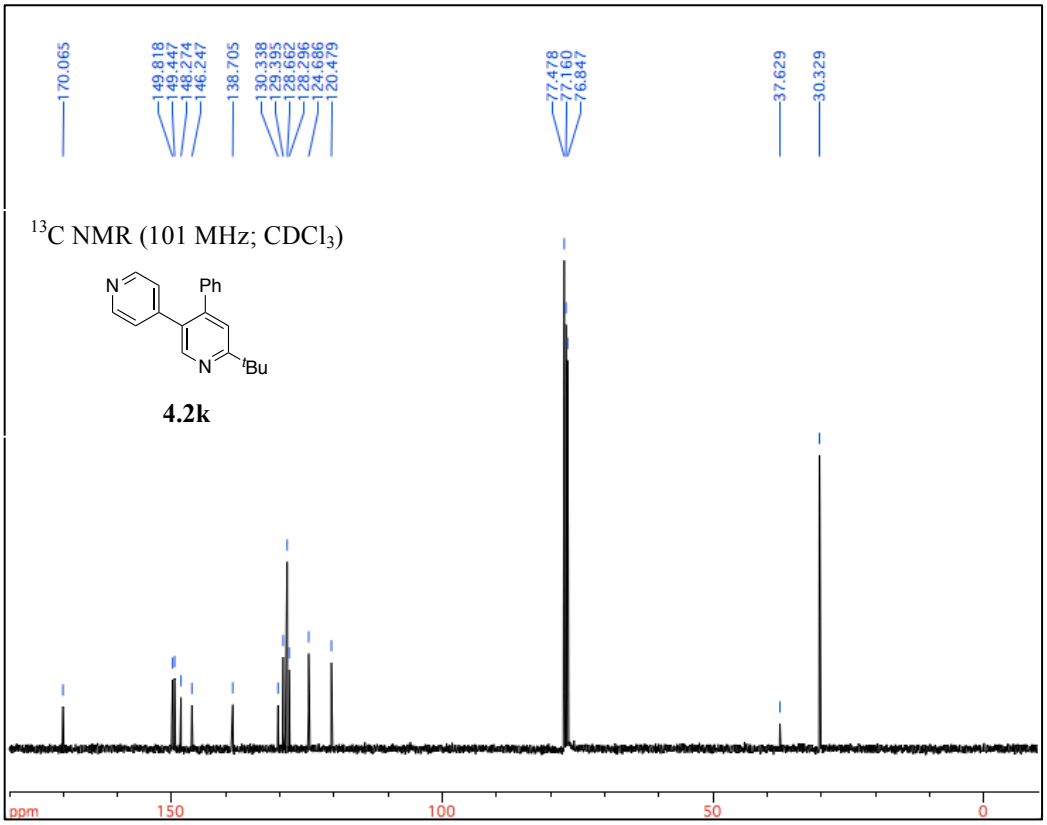


6-(*tert*-butyl)-4-phenyl-3,4'-bipyridine (4.2k)



^{1}H NMR (400 MHz; $CDCl_3$)

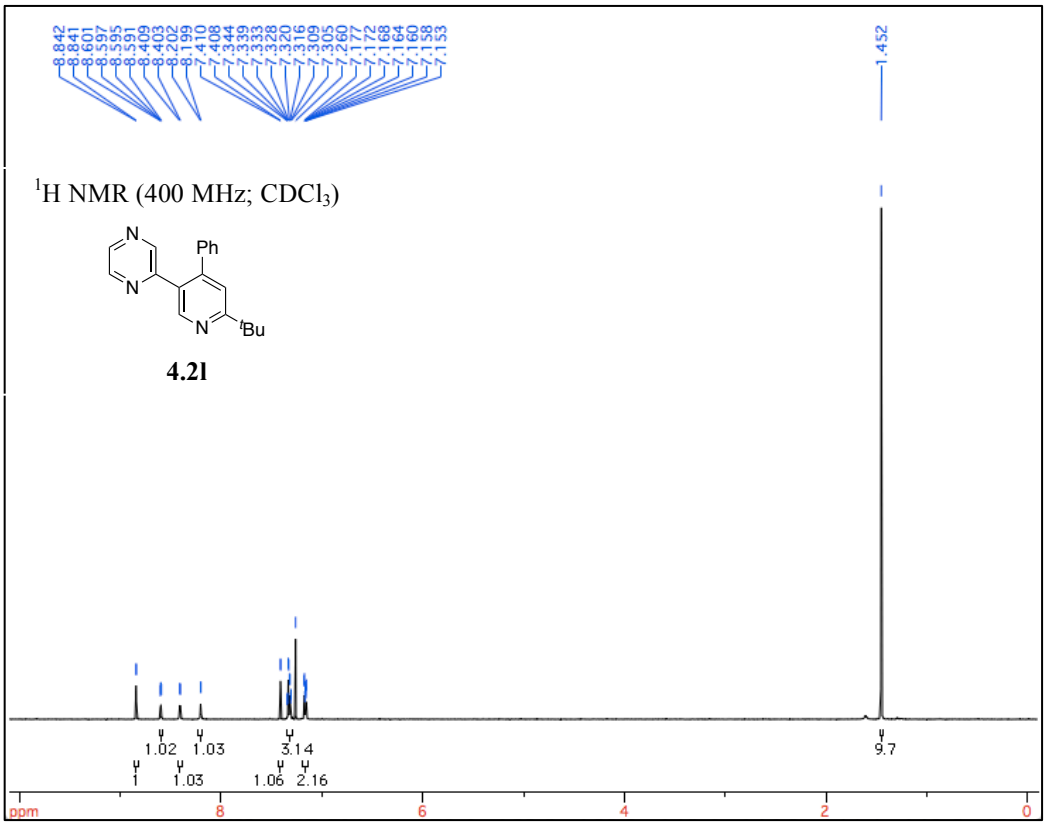
4.2k

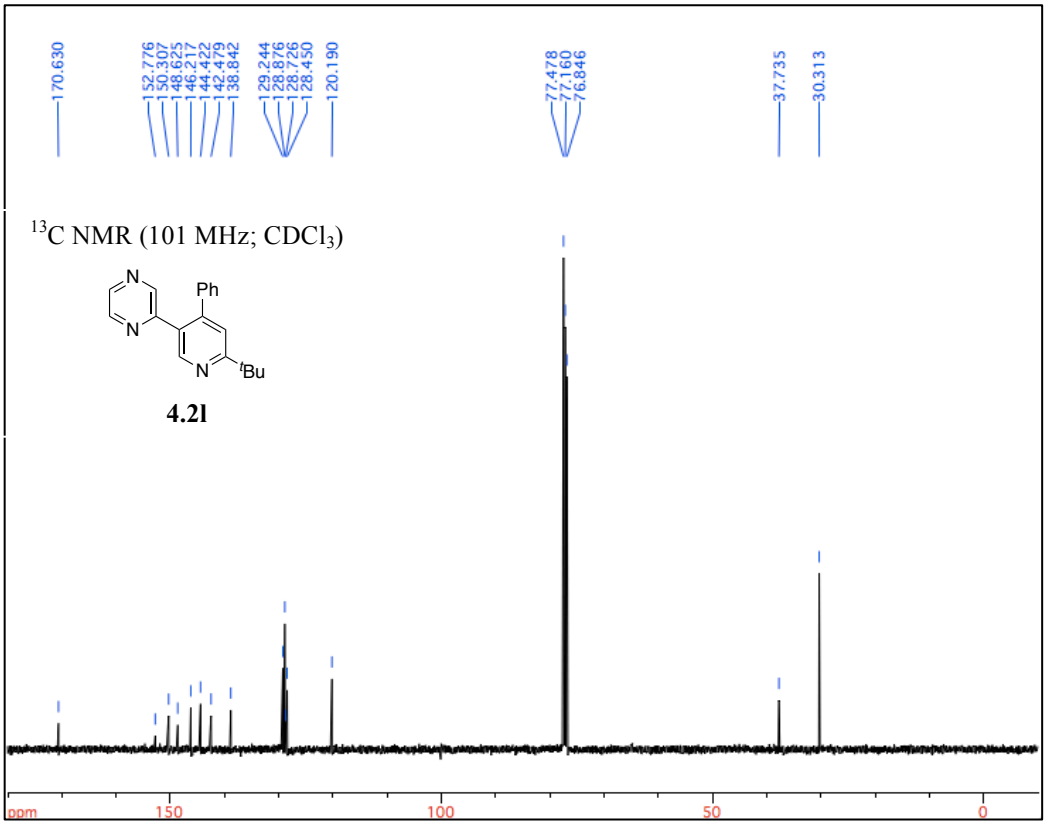


^{13}C NMR (101 MHz; $CDCl_3$)

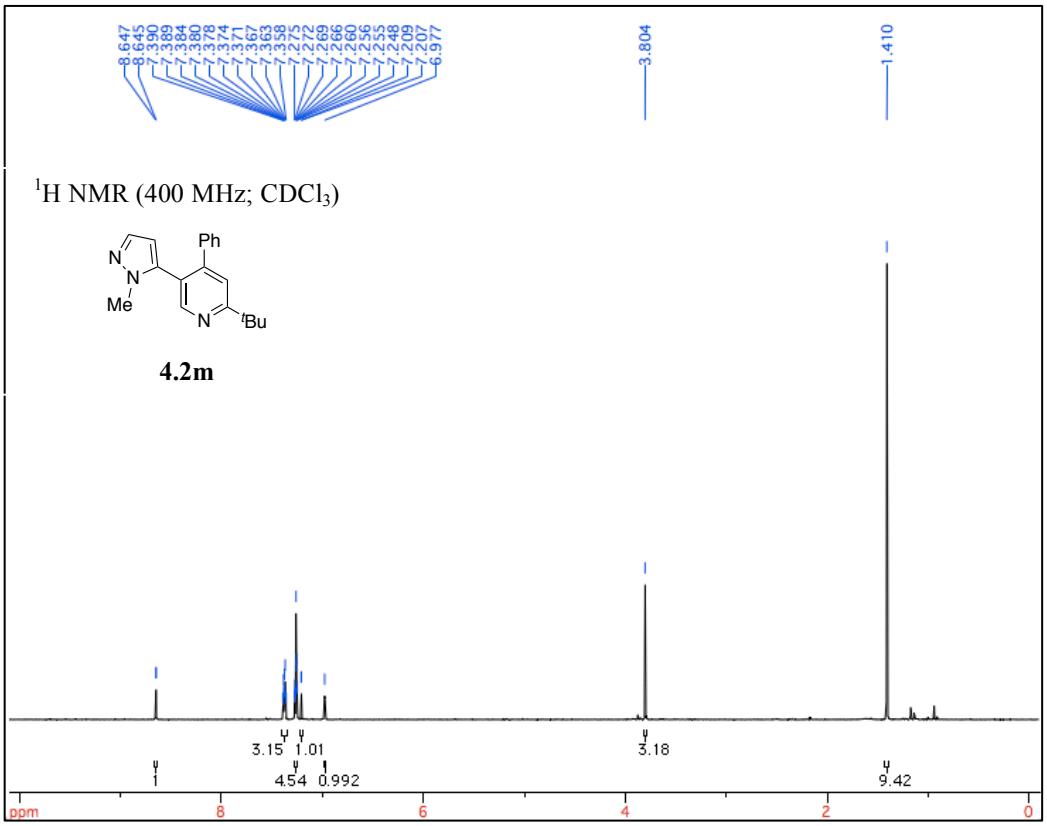
4.2k

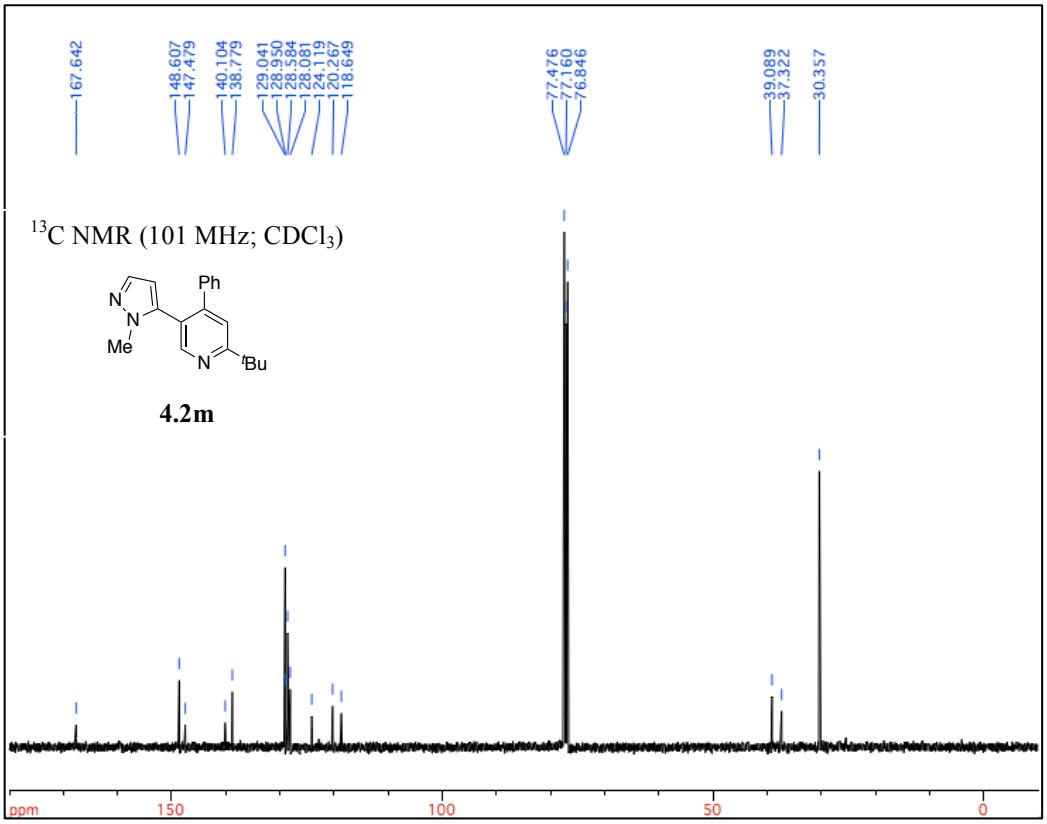
2-(6-(*tert*-butyl)-4-phenylpyridin-3-yl)pyrazine (4.2l)



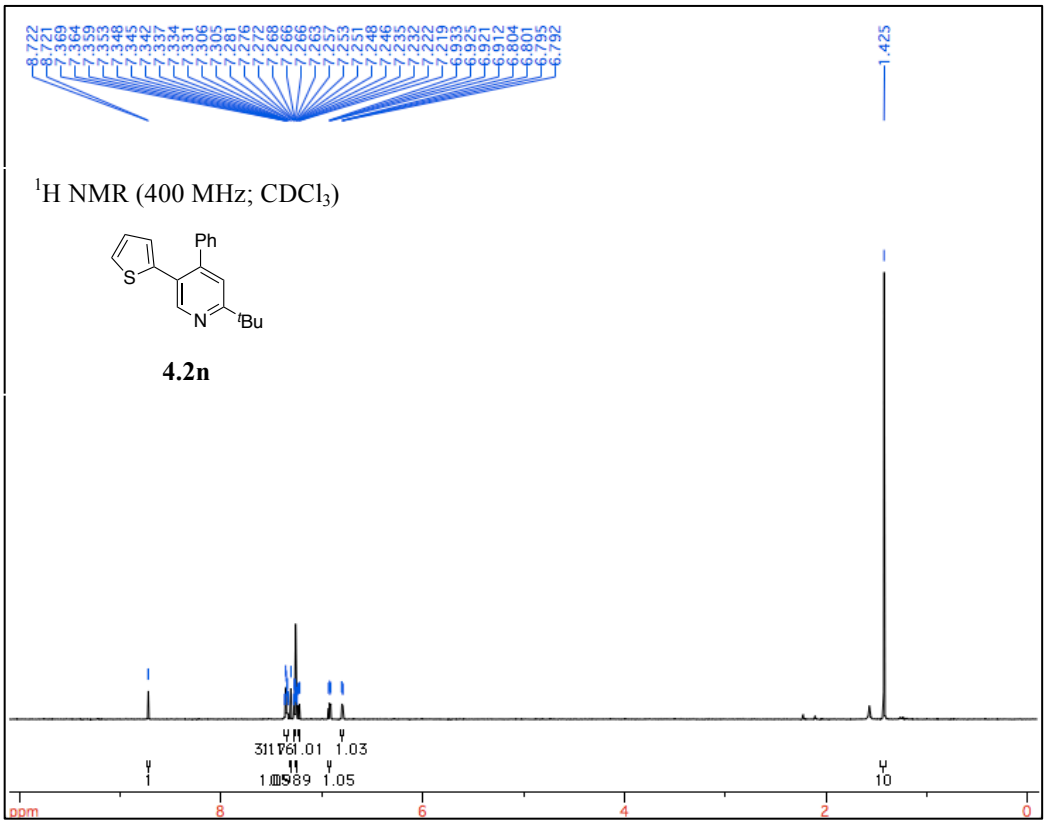


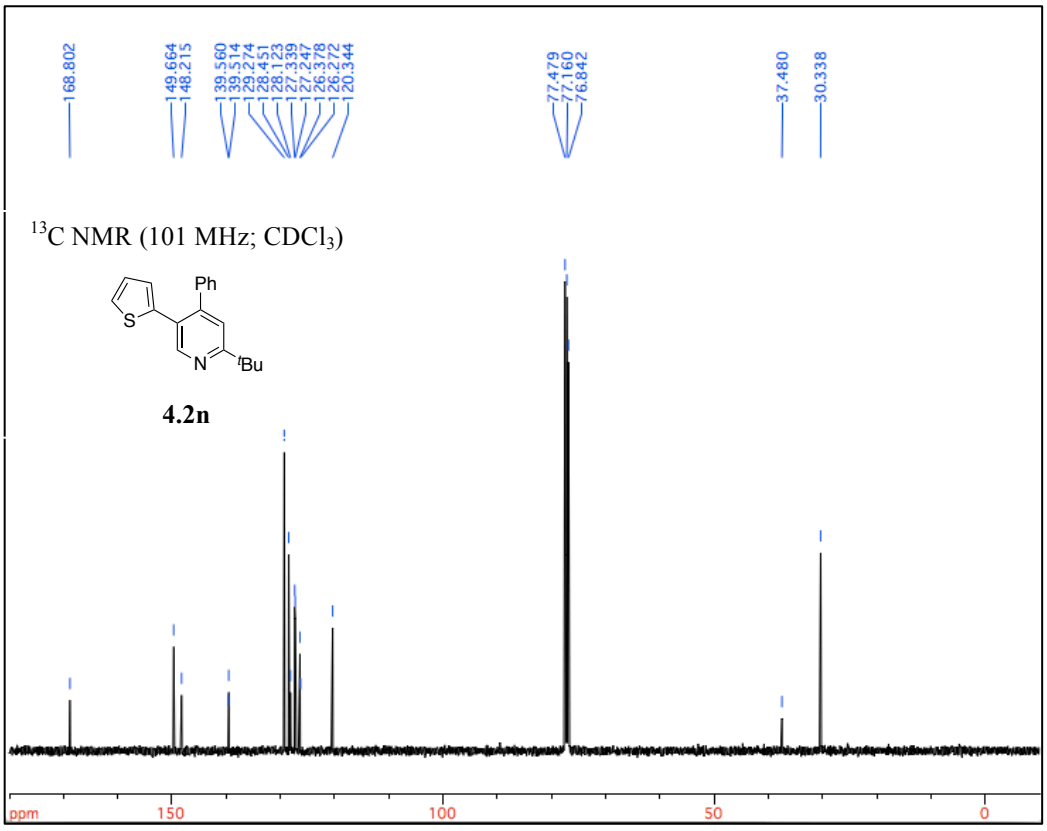
2-(*tert*-butyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-4-phenylpyridine (4.2m)



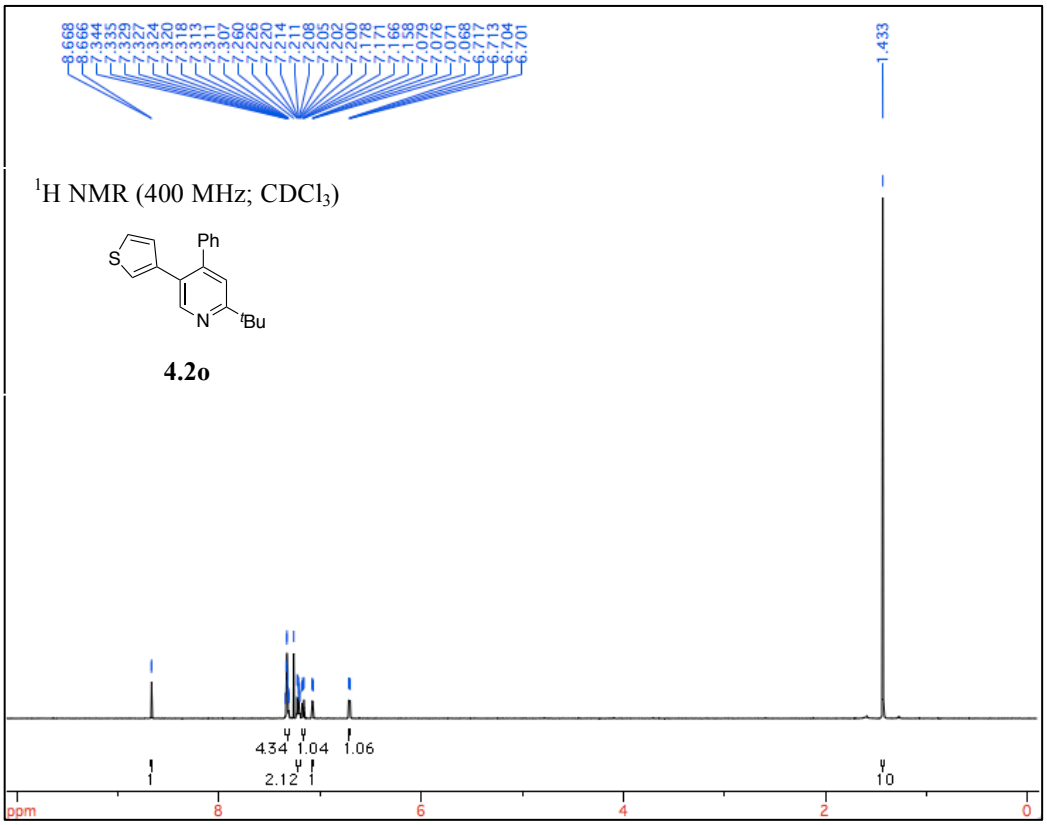


2-(*tert*-butyl)-4-phenyl-5-(thiophen-2-yl)pyridine (4.2n)

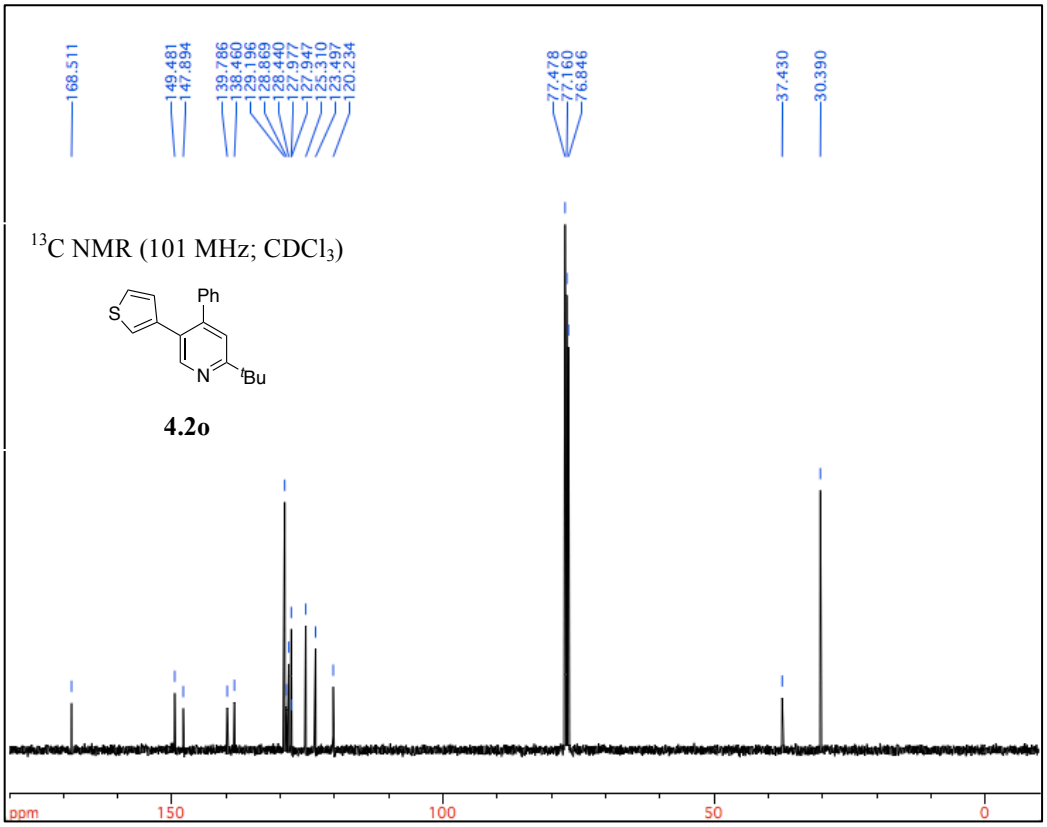




2-(*tert*-butyl)-4-phenyl-5-(thiophen-3-yl)pyridine (4.2o)

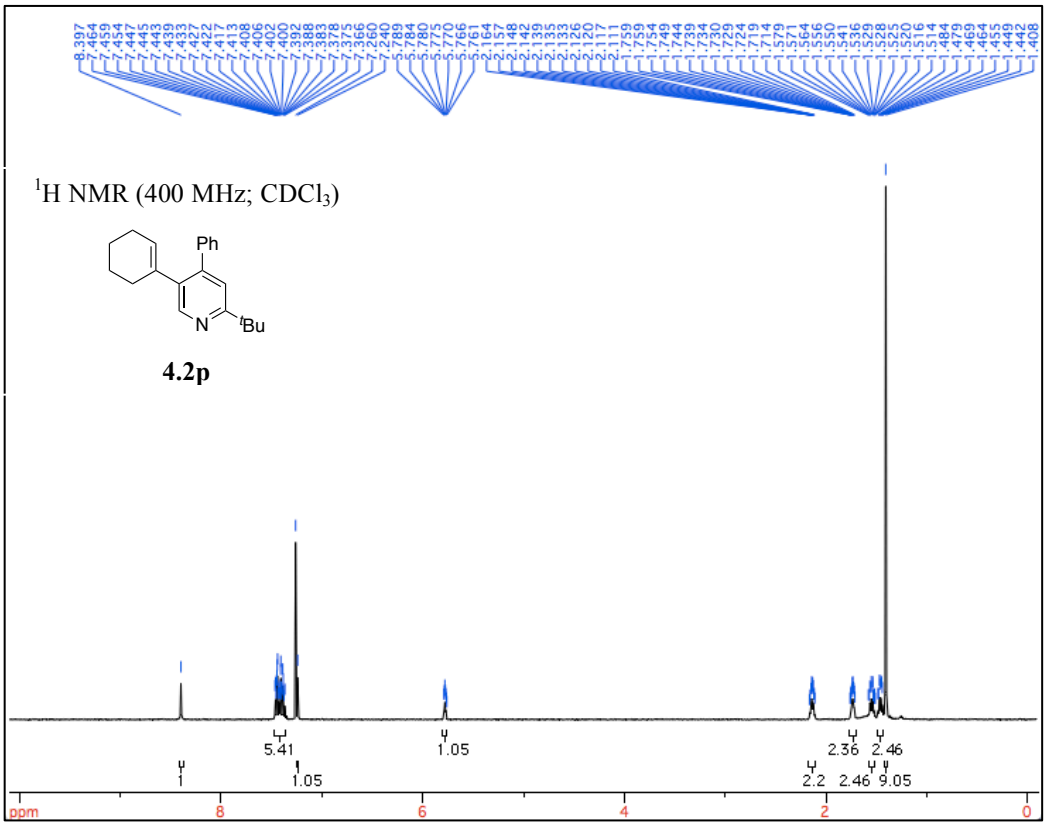


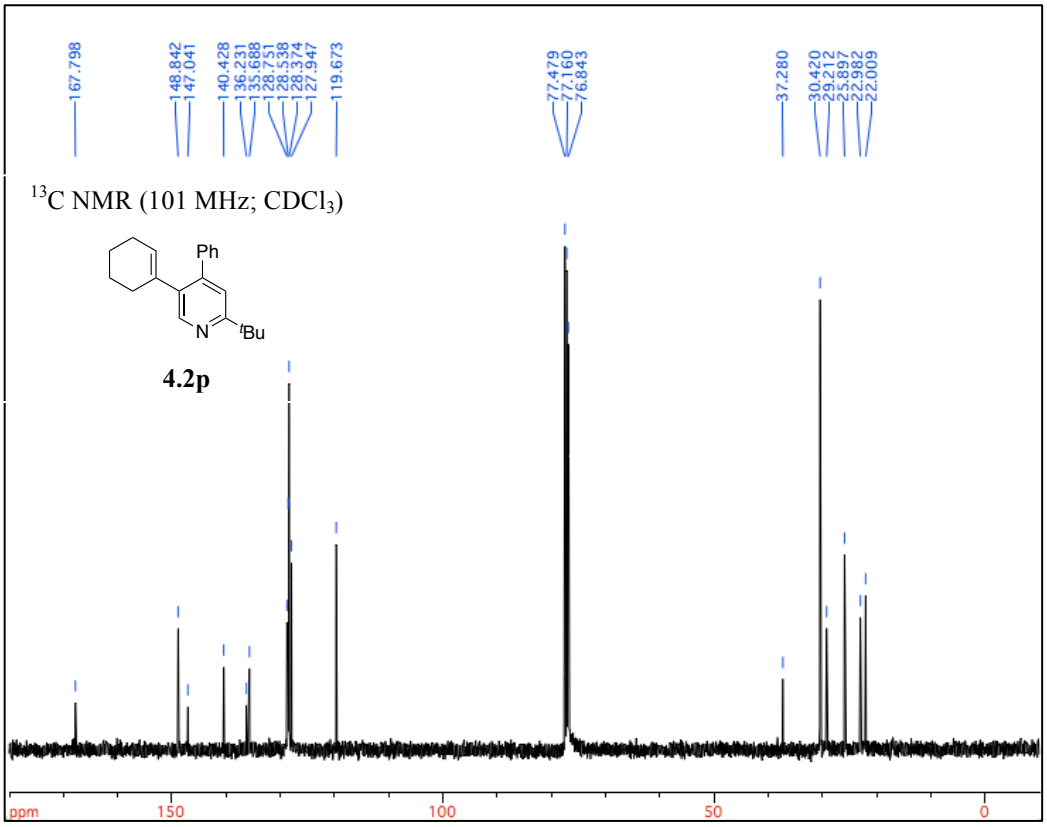
4.2o



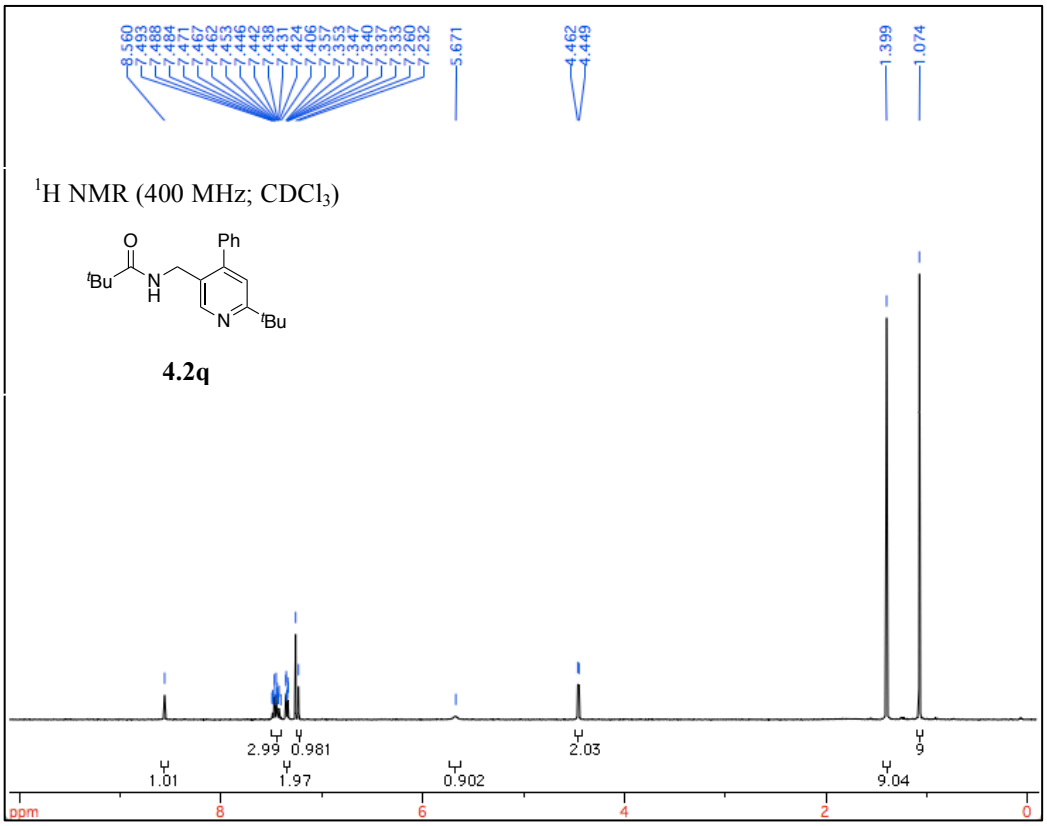
4.2o

2-(*tert*-butyl)-5-(cyclohex-1-en-1-yl)-4-phenylpyridine (4.2p)



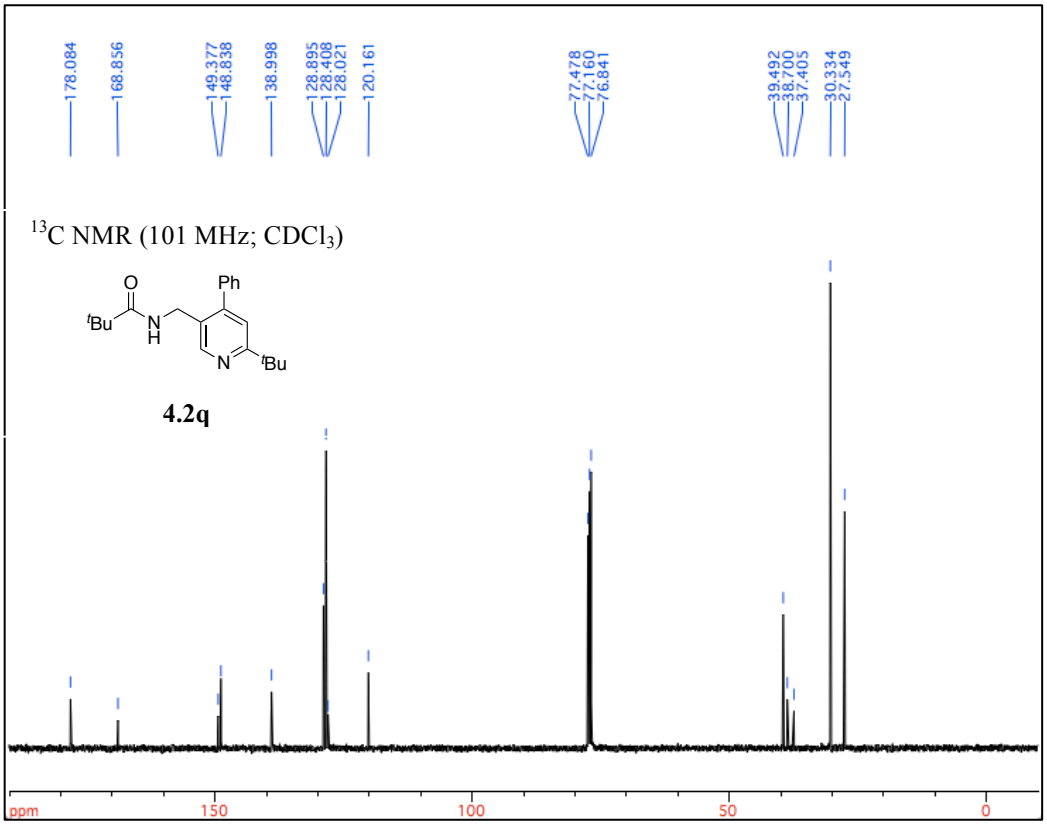


N-((6-(*tert*-butyl)-4-phenylpyridin-3-yl)methyl)pivalamide (4.2q)



^{1}H NMR (400 MHz; $CDCl_3$)

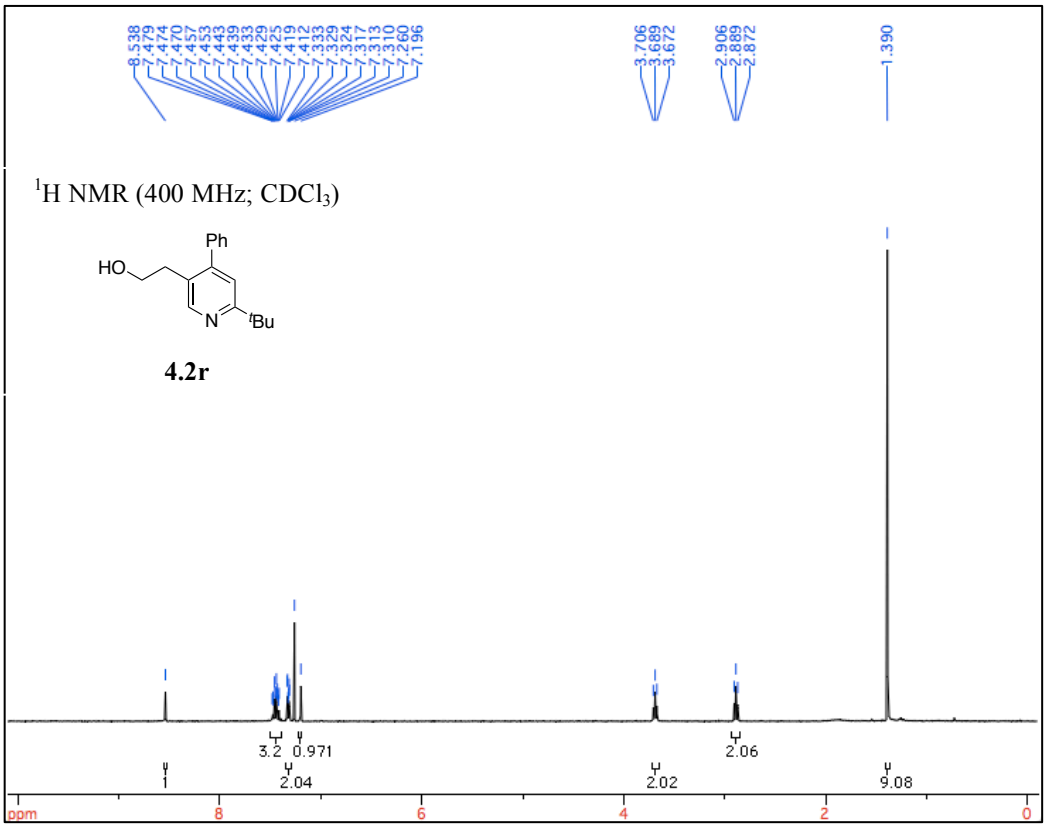
4.2q



^{13}C NMR (101 MHz; $CDCl_3$)

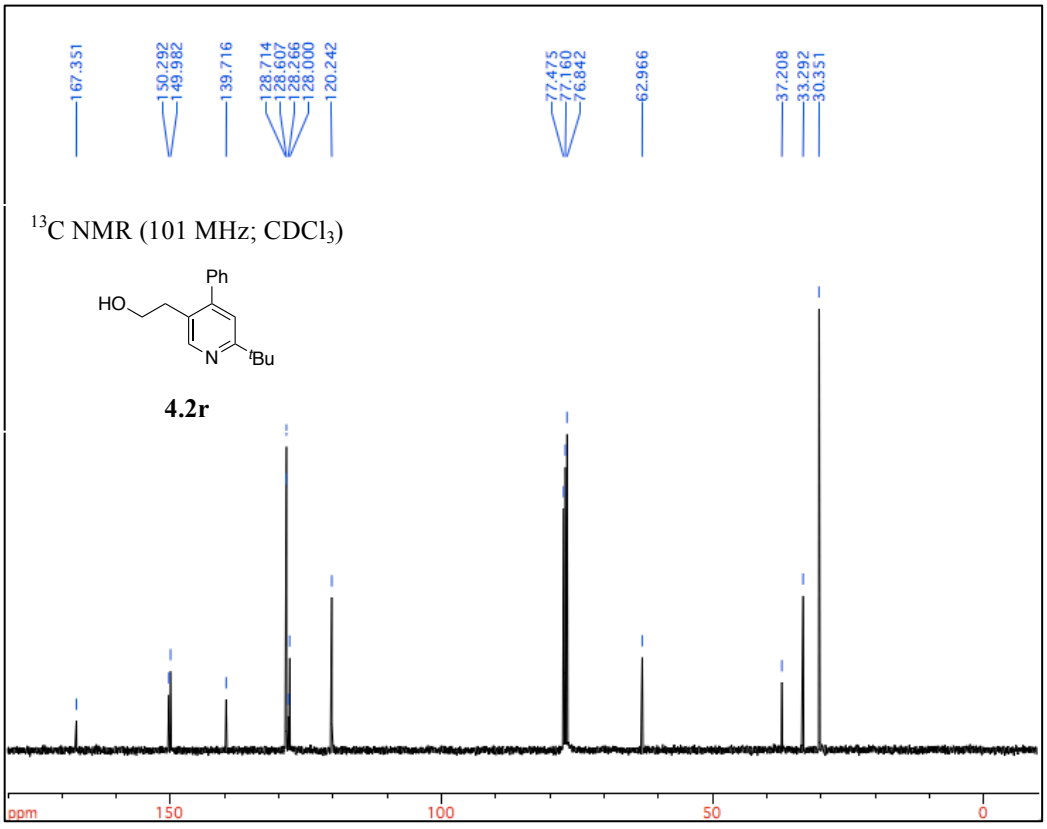
4.2q

2-(6-(*tert*-butyl)-4-phenylpyridin-3-yl)ethan-1-ol (4.2r)



^{1}H NMR (400 MHz; $CDCl_3$)

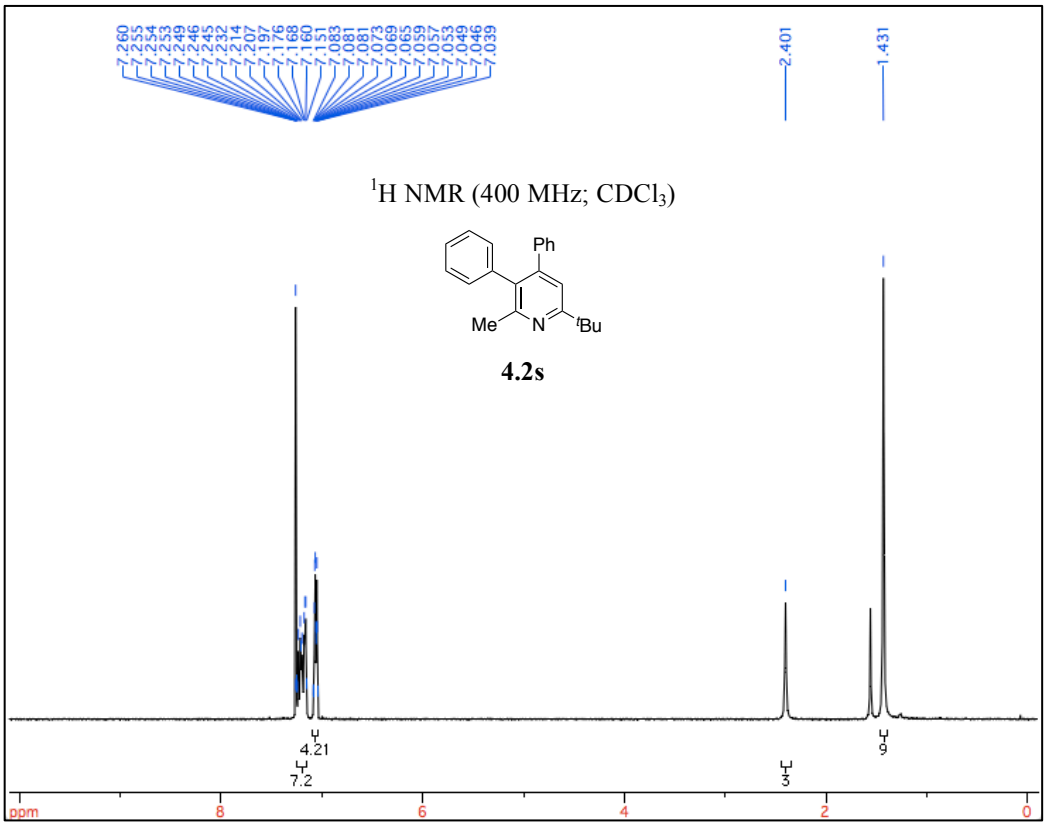
4.2r



^{13}C NMR (101 MHz; $CDCl_3$)

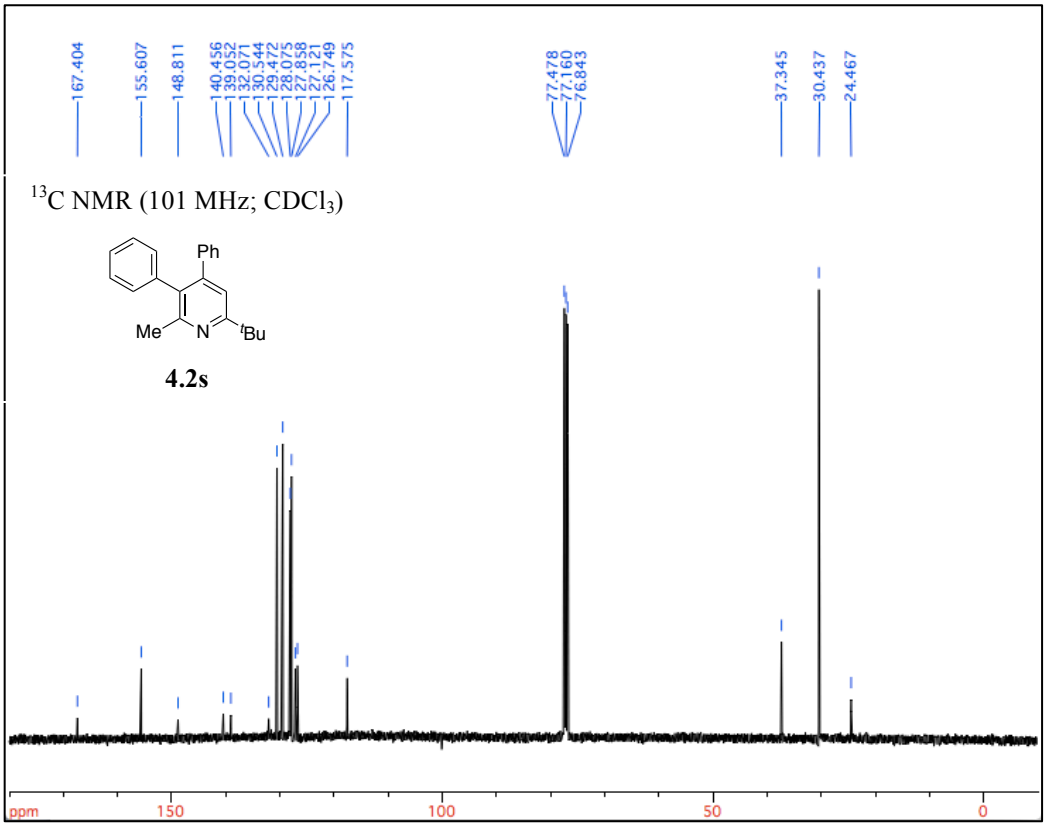
4.2r

6-(*tert*-butyl)-2-methyl-3,4-diphenylpyridine (4.2s)



^{1}H NMR (400 MHz; $CDCl_3$)

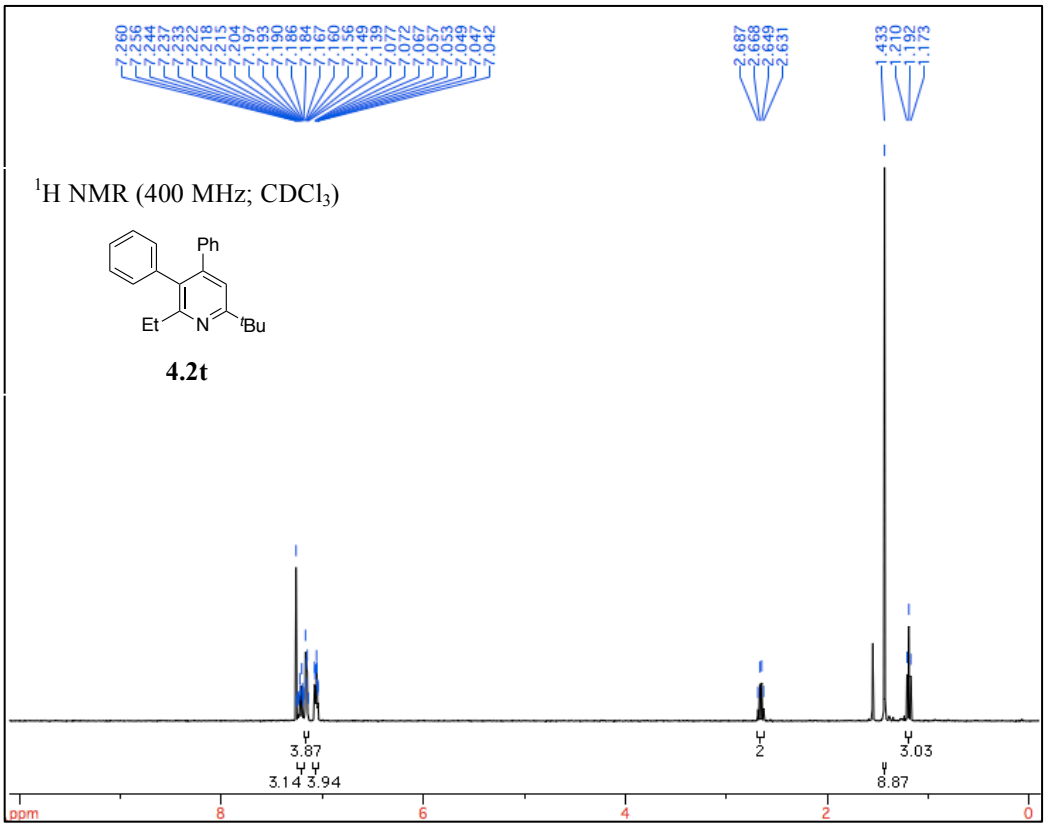
4.2s



^{13}C NMR (101 MHz; $CDCl_3$)

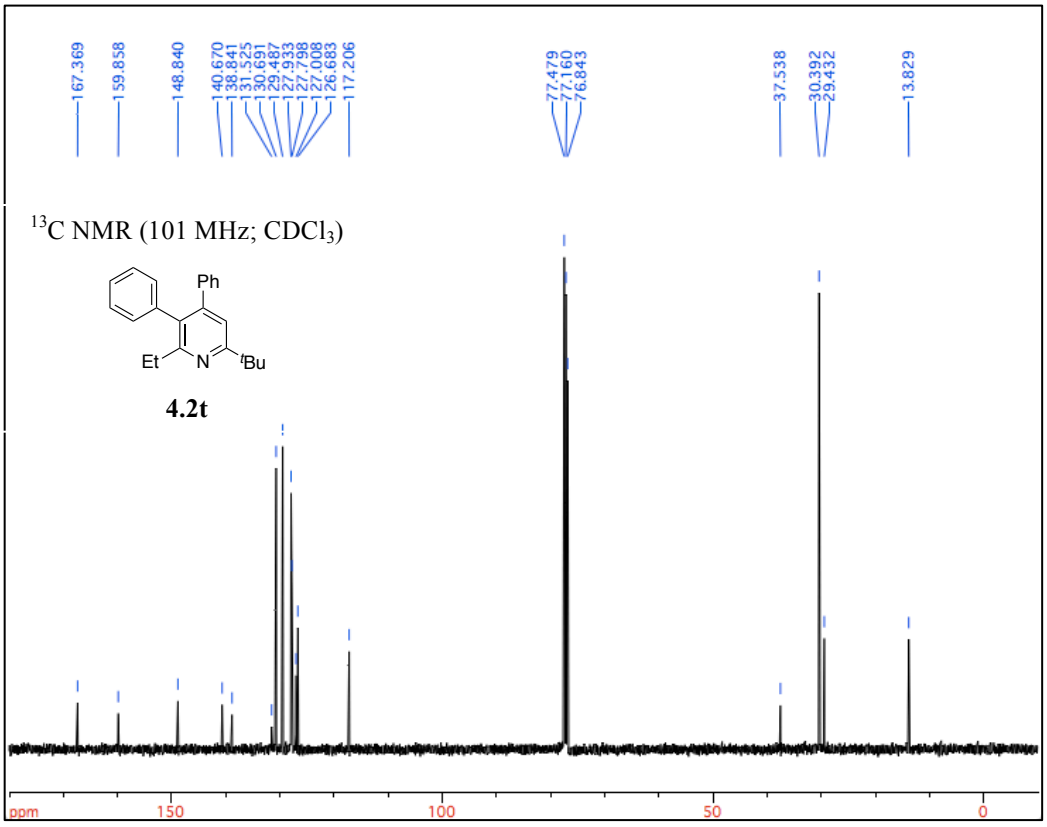
4.2s

6-(*tert*-butyl)-2-ethyl-3,4-diphenylpyridine (4.2t)



^{1}H NMR (400 MHz; $CDCl_3$)

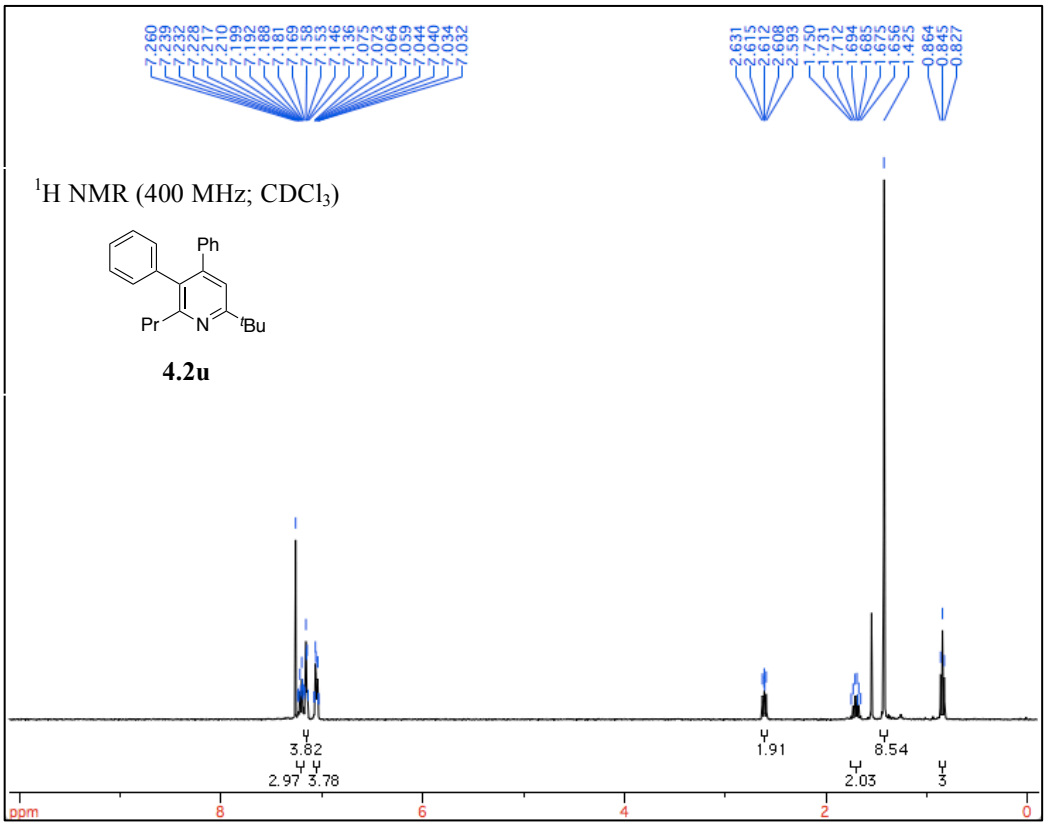
4.2t

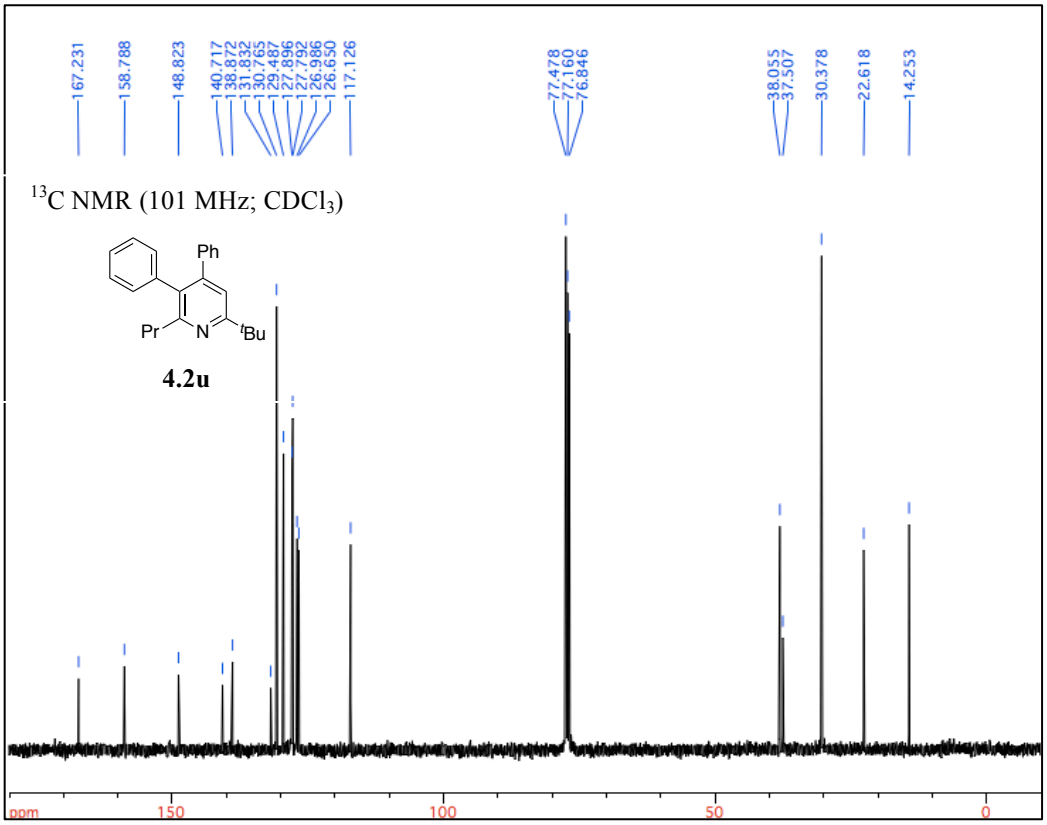


^{13}C NMR (101 MHz; $CDCl_3$)

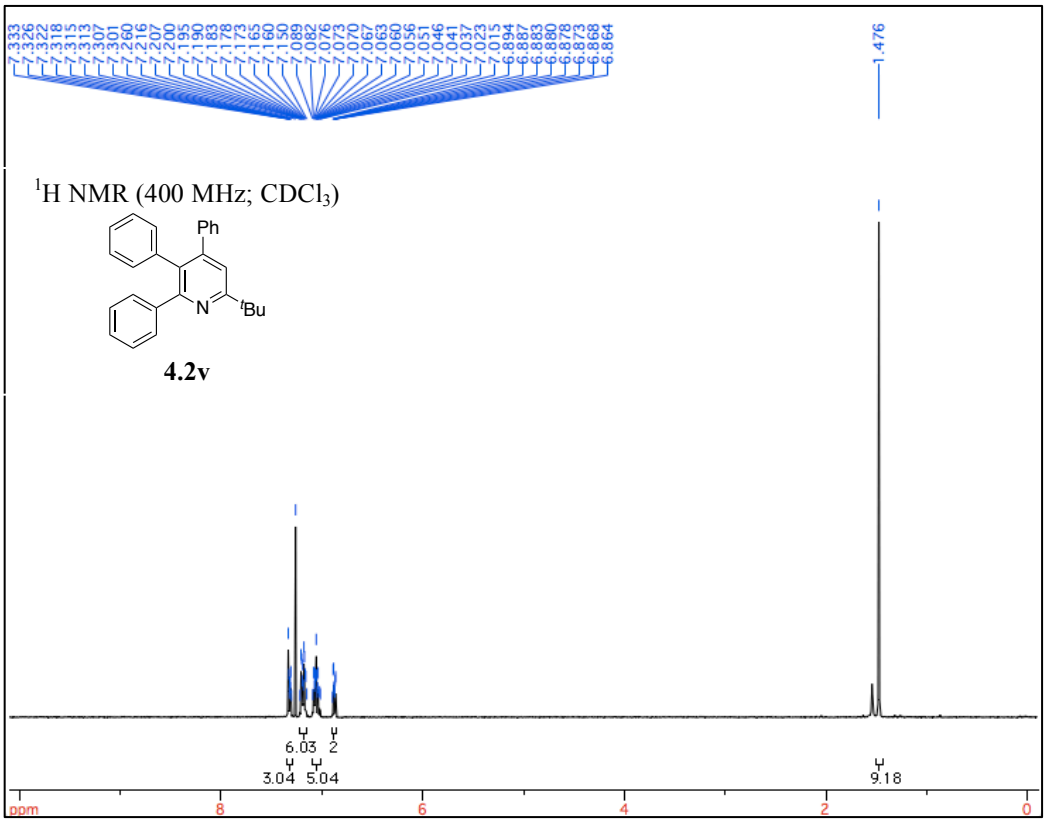
4.2t

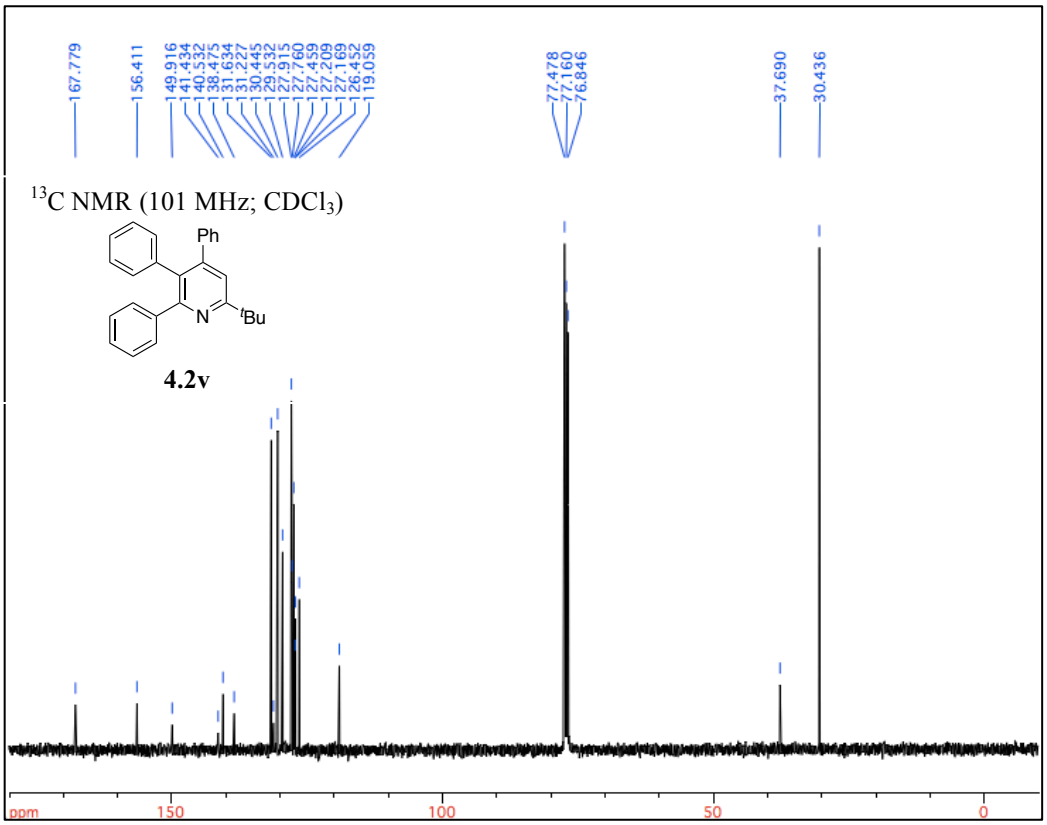
6-(*tert*-butyl)-3,4-diphenyl-2-propylpyridine (4.2u)





6-(*tert*-butyl)-2,3,4-triphenylpyridine (4.2v)





C.6 Solid State Molecular Structures and X-Ray Crystallographic Data

Single crystal X-ray structure determinations were performed at the X-ray crystallography lab at the Department of Chemistry, University of British Columbia on either a Bruker X8 APEX or Bruker APEX DUO diffractometer using graphite-monochromated Mo Kα radiation (λ=0.71073 Å). Unless otherwise noted, data integration was performed using Bruker SAINT (v.8.34A),[387] absorption correction was performed using Bruker SADABS (2014/5),[387] structures were solved using direct methods using SIR2004 or SHELXS,[388,389] and refinement (including modelling of disorder) was performed using SHELXL (2014/7)[390] using the OLEX2[391] interface.

	Pyridine **2m (LS707)**
formula	$C_{23}H_{16}ClN$
F_w	341.82
crystal size (mm)	0.523 × 0.223 × 0.065
color, habit	Colourless, prism
crystal system	Monoclinic
space group	$P2_1/c$
T (K)	100
a (Å)	12.6031(11)
b (Å)	5.7258(5)
c (Å)	24.106(2)
α (Å)	90
β (Å)	103.839(2)
γ (Å)	90
V (Å^3)	1689.1(3)
Z	4
ρ_{calcd} (g cm^{-3})	1.344
F(000)	712.0
μ ($Mo_{K\alpha}$) (mm^{-1})	0.230
$2\theta_{max}$ (°)	3.328 to 50.782
total no. of reflns	6383
no. of unique reflns	6383
R_1 (F^2, all data)	0.0700
wR_2 (F^2, all data)	0.0940

R_1 (F, $I > 2\sigma(I)$)	0.0450
wR_2 (F, $I > 2\sigma(I)$)	0.0847
goodness of fit	1.015

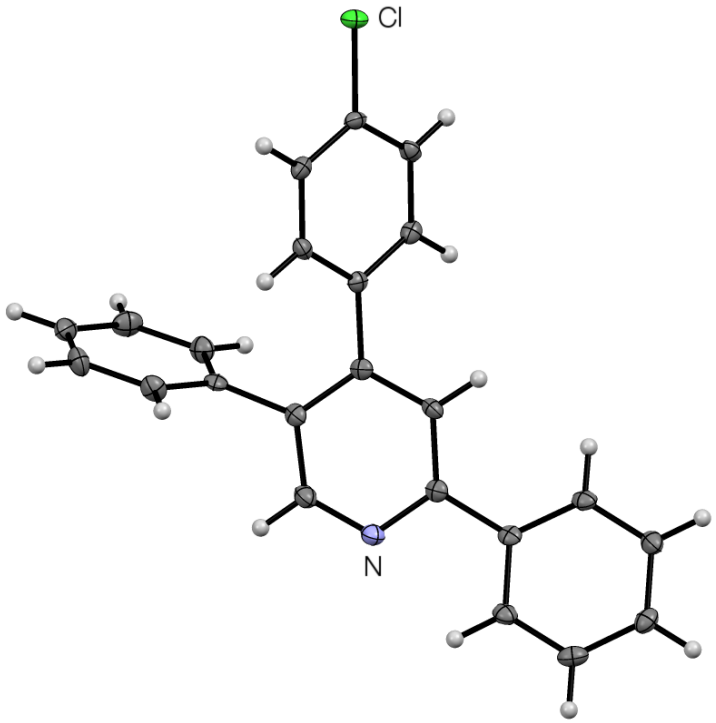


Figure C.1 Single Crystal Molecular Structure of Pyridine 4.1m