DEVELOPING NEW SYNTHETIC METHODS INVOLVING ORGANOSILANE REAGENTS AND REACTANTS

By

Maria del Rosario Ivette Amado Sierra

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Chemistry – Doctor of Philosophy

2015

ABSTRACT

DEVELOPING NEW SYNTHETIC METHODS INVOLVING ORGANOSILANE REAGENTS AND REACTANTS

By

Maria del Rosario Ivette Amado Sierra

A novel green method for the reduction of imines to amines by a $Pd(OAc)_2$/PMHS/KF_{aq} system was developed and studied. The optimization studies confirmed the crucial role of the fluoride in activating the PMHS. The addition of PMHS to a $Pd(OAc)_2$ solution results in the formation of polysiloxane encapsulated Pd-nanoparticles, and we were able to confirm the existence of these nanoparticles using transmission electron microscopy (TEM). Additionally ^{29}Si NMR and ^{19}F NMR data obtained from our catalyst system gave some insight into the possible mechanism. Furthermore, the one-pot preparation of several amides via reduction of imines followed by addition of an electrophile was achieved.

We were able to develop a new one-pot allylation-hydrostannation sequence of alkynals where the tin byproduct, from the BF_3•OEt_2–promoted allylation step, was successfully recycled by the introduction of PMHS and catalytic $B(C_6F_5)_3$ to form Bu_3SnH in situ; that was used on the hydrostannation reaction. In addition, our studies were the first to follow BF_3•OEt_2 mediated allylation by ^{119}Sn and ^{11}B NMR.

Finally a new carbon-to-carbon [1,2]-silyl migration was discovered. This migration was triggered by epoxidation using *m*-CPBA, the cyclopentanones formed have not been reported and contain a silyl group at the α position of the carbonyl unit.

ACKNOWLEDGMENTS

The work described in this dissertation would not have been possible without the guidance, advice and scientific support of my research advisor, Professor. Robert E. Maleczka, Jr. His strong work ethic and passion for science helped me evolve both as person and as a scientist.

I would also like to thank the members of my thesis committee Dr. Babak Borhan, Dr. William D. Wulff and Dr. Merlin L. Bruening, for always taking time to assist me with my scientific endeavors. A note of appreciation goes to the Chemistry Department and staff at MSU, for providing me with this excellent educational opportunity. I particularly want to thank Dr. Dan Holmes, for his help and suggestions related to the NMR experiments. I am especially indebted to the Dr. Maleczka Research Group, for the late nights working together and their support in the lab. Especially I want to thank Luis S., Luis M., Monica, Damith, Suzi and Aaron for their friendship. I would also like to thank Dr. Jun Tang for his mentorship during my one year internship at GSK.

Last but certainly not least, I would like to thank my friends and family, for their unconditional love and prayers during the years. Thanks to the Latin community for helping me feel at home, especially the Parchecito group. My parents Teresa and Marino have been exceptionally supportive; without their help I would have never made it through graduate school. I also thank my sister Magaly and my aunt Julia, for being great friends and always believing in me. Finally, I want to thank my husband Ian, for all his tolerance and encouragement. I also thank him for his support and changing my life for the better. I cannot express how deeply I appreciate everything that he has done for me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

KEY TO ABBREVIATIONS

Ac	Acetate
Acac	Acetylacetonate
aq	Aqueous
$B(C_6F_5)_3$	tris(pentafluorophenyl)borane
BF_3•OEt_2	boron trifluoride diethyl ether
Boc	*tert*-butoxycarbonyl
Bu_3SnH	tributyltin hydride
CH_2Cl_2	dichloromethane
$Cl_2Pd(PPh_3)_2$	dichlorobis(triphenylphosphine)palladium(II)
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCC	N,N-dicyclohexylcarbodimide
DMF	N,N-dimethylformamide
EDS	energy dispersive spectroscopy
ee	enantiomeric excess
equiv	Equivalent
EtOAc	ethyl acetate
EtOH	Ethanol
Et_3N	triethylamine

Et_2O	diethyl ether
g	gram(s)
h	hour(s)
KF	potassium fluoride
HMPA	hexamethylphosphoramide
Hz	Hertz
m-CPBA	3-chloroperbenzoic acid
min	Minutes
M	Molar
mg	Milligram
mL	Milliliter
mmol	Millimole
Me	Methyl
MeO	Methoxy
n-BuLi	*n*-butyllithium
Naph	Naphtyl
NMR	Nuclear Magnetic Resonance
$Pd(OAc)_2$	palladium (II) acetate
Ph	Phenyl
PMHS	polymethylhydrosiloxane
r.b.	round bottom
RCM	ring-closing metathesis

r.t.	room temperature
sec-BuLi	*sec*-butyllithium
$SiEt_3$	Triethylsilyl
$SiMe_2Ph$	phenyldimethylsilyl
TBAF	tetrabutylammonium fluoride
TEM	transmission electron microscopy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatrography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluromethane sulfonate
Ts	Tosyl

CHAPTER 1: INTRODUCTION

1.1 Silicon: basic properties

Silicon (Si) belongs to the same periodic group as carbon (C) and shares its ability to form four bonds (tetravalent). Conversely, silicon has some unique properties that make organosilicon chemistry a rapidly growing field. Three of the major difference are silicon's bond strengths to other elements (Table 1.1), Si is less electronegative (1.90) than carbon (2.55) and the ability to extend its coordination to the so-called hypervalent silicon compounds.[1]

Table 1.1 Average bond dissociation energies and bond lengths[1]

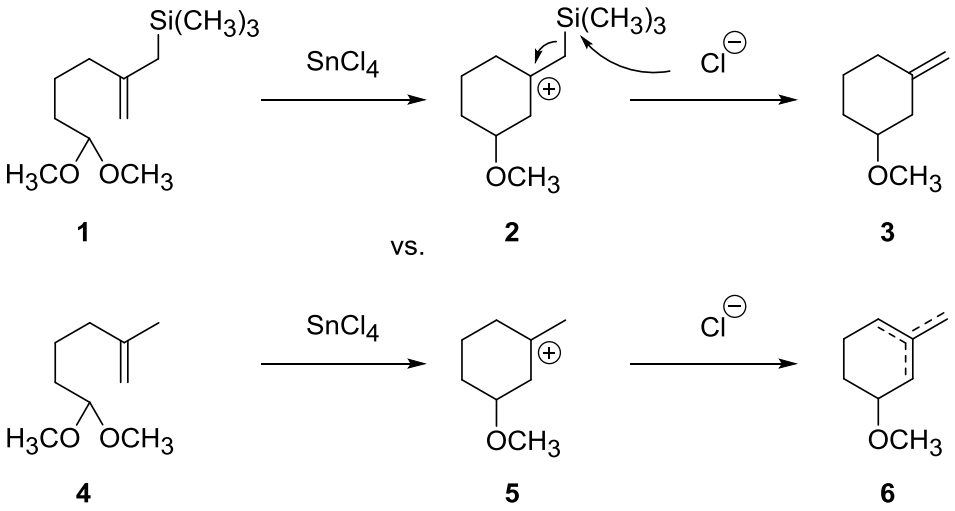
Entry	Bond strength (kcal/mol)	Bond length (Å)
Si-H	75	1.48
C-H	99	1.09
Si-C	76	1.85
C-C	83	1.54
Si-O	110	1.63
C-O	85.5	1.43
Si-F	135	1.60
C-F	116	1.35

Table 1.1 shows that silicon forms stronger bonds to oxygen and fluorine than to carbon and hydrogen. In addition, Si bonds have longer bond lengths in comparison to carbon bonds because the silicon atom is 1.5 times larger than the carbon atom.[2] Due to the lower electronegativity of silicon the Si-H and Si-C bond are polarized (Figure 1.1) giving particular properties to these bonds. For example, organosilicon hydrides (at least one Si-H bond) have the ability to serve as mild air and water-stable sources of hydride.[3]

Figure 1.1 Silicon bonds polarized

In the case of the Si-C bond, the polarization allows for nucleophilic attack at the Si center, breaking the bond heterolytically in a way that would be difficult with a C-H bond.[1] Early evidence of this rapid nucleophilic attack was reported in 1976 by Fleming.[4] In this study the β-trimethylsilyl carbenium species (**2**) is attacked by the nucleophile to generate only one isomer (**3**) in a short time. With species that lacked the trimethylsilyl group (**4**), the reaction was slower and not selective, thus formation of different isomers (**6**) was observed (Scheme 1.1).[4]

This polarization of the Si-C bond also generates two important properties of silicon, the stabilization of the negative charge at the adjacent carbon (α anions) and the stabilization of a positive charge at the β position (β silicon effect).



Scheme 1.1 Evidence for rapid nucleophilic attack

The α-stabilization effect has been attributed to overlap between the antibonding σ* level of the C-Si bond and the adjacent filled p-orbital of the carbanion, highly polarized carbon-metal bond (Figure 1.2). This interaction is favorable due to the difference in electronegativity between the Si and C, thus the antibonding σ* level of the C-Si bond has a relatively high coefficient on the silicon increasing the overlap.[1,2]

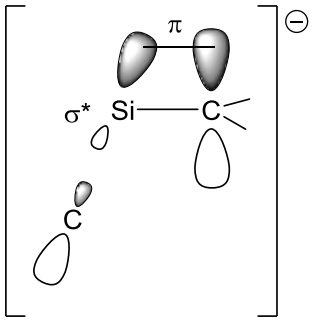


Figure 1.2 The α-anion (σ*- p)π overlap

The β-stabilization effect arises from the interaction between the bonding σ level of the C-Si bond and the adjacent empty p-orbital of the carbonium ion (Figure 1.3). The

electronegativity of Si gives a higher charge density to the carbon in the C-Si bond, which facilitates the hyperconjugative stabilization of the empty p-orbital. This stabilization is maximum when the empty p-orbital and the C-Si bond are coplanar to each other.[5]

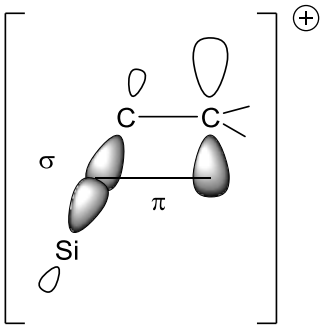


Figure 1.3 The β-stabilization effect (σ- p)π overlap

The basic properties highlighted on the previous pages allow organosilicon compounds to be more moisture- and air-stable than other organometallic reagents. They can also be prepared from a wide range of often cheap starting materials and usually present low toxicity.[1,2] Some of the most common reactions of these organosilicon compounds are described in the following pages of this chapter.

1.2 Allylsilanes

Allylsilanes have been extensively used in organic chemistry due to the weak polarization of the C-Si bond, which permits an easy handling and better stability of these organometallic-type reagents.[6] One the major applications of allylsilanes is the Lewis acid-catalyzed addition to aldehydes (Figure 1.4). In this process the Lewis acid activates the aldehyde toward nucleophilic attack. In cases where a chiral Lewis acid is employed, enantioselective addition is possible.[7]

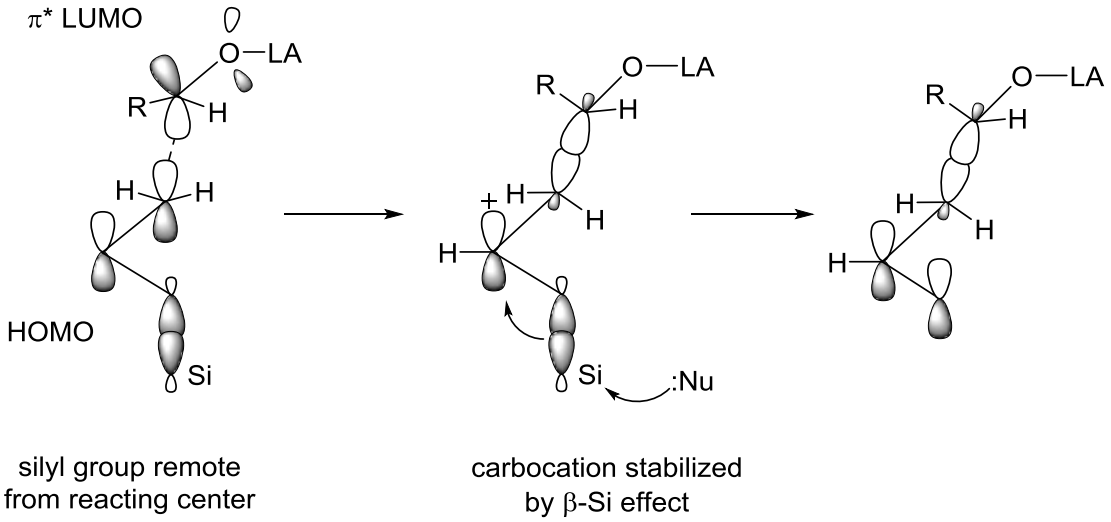


Figure 1.4 Lewis acid-catalyzed addition to aldehydes

The addition of allylic silanes to electrophiles has been shown to be a stepwise process.[8] In the first step the addition of the silane to an activated aldehyde forms a carbocation, which is stabilized by the β-effect of the C-Si bond (Figure 1.4). Furthermore, this reaction usually proceeds through an anti S_E2' reaction pathway (Figure 1.5).[9] The initial step of addition occurs at the γ-terminus carbon, thus the orientation of the double bond and the location of the silicon group in the transition state define the stereochemical outcome of the final substitution reaction. The most stable open transition state demands an *anti*-addition to the electrophile, where the silicon group is located away from the electrophile in an antiperiplanar orientation.[9]

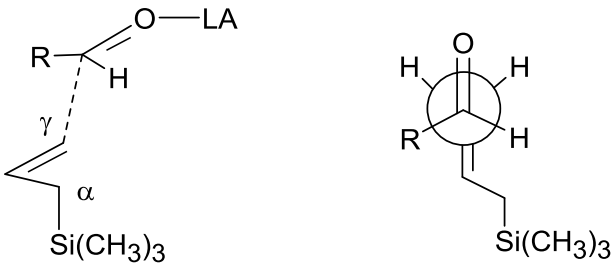
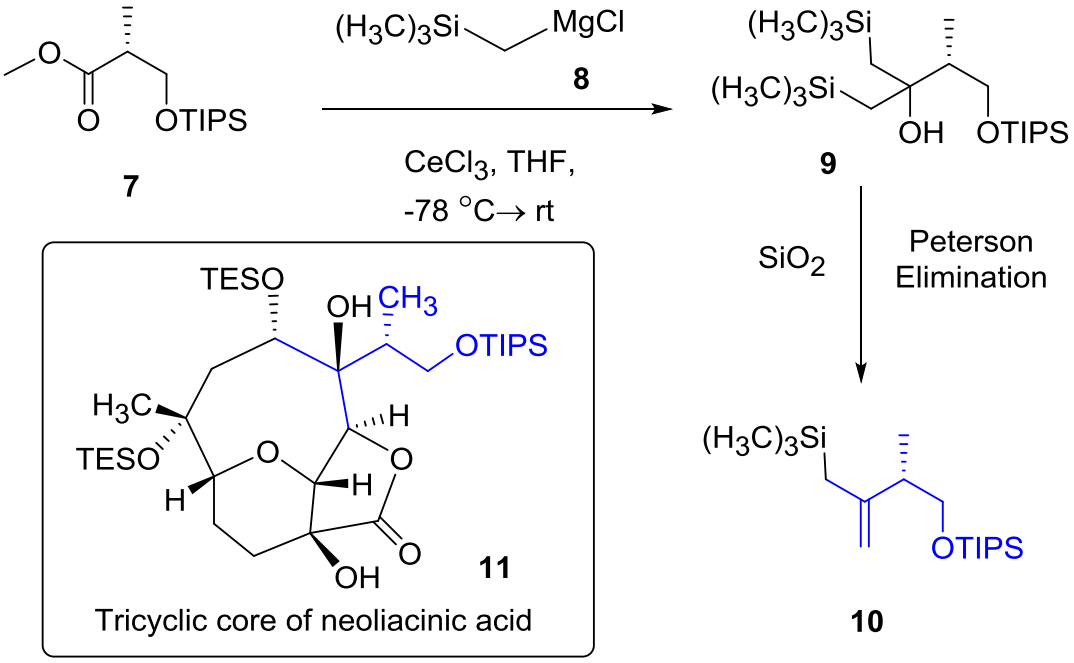


Figure 1.5 Reaction pathway of allylsilanes addition to aldehydes

One recent example of the utility of allylsilanes is in the preparation of a key allylic intermediate for the synthesis of the tricyclic core of neoliacinic acid (**11**).[10] The allylsilane (**10**) was prepared by treatment of the triisopropylsilyl-protected ester (**7**) with an organocerium reagent generated by the reaction of trimethylsilylmethylmagnesium chloride (**8**) with anhydrous cerium chloride. This reaction generated a double Grignard addition of the $TMSCH_2^{\delta-}$, then the product formed (**9**) undergoes the Peterson elimination after the work up upon exposure to silica gel, giving the desired allylic silane (**10**) (Scheme 1.2).

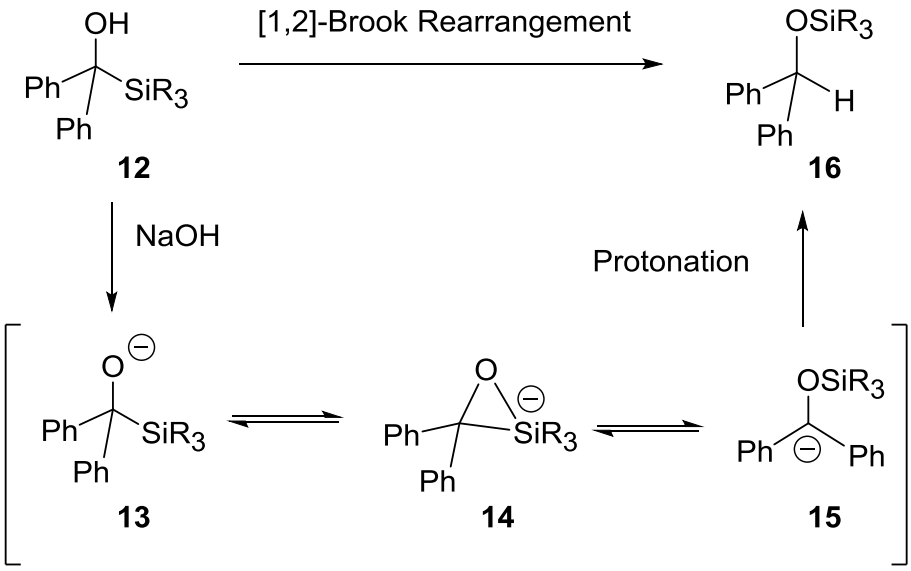


Scheme 1.2 Allylsilane intermediate towards the synthesis of lactone **11**

1.3 Brook rearrangement

Another common transformation of silicon containing molecules is the Brook rearrangement. Due to the stronger affinity of Si to oxygen (O), as explained previously, Si

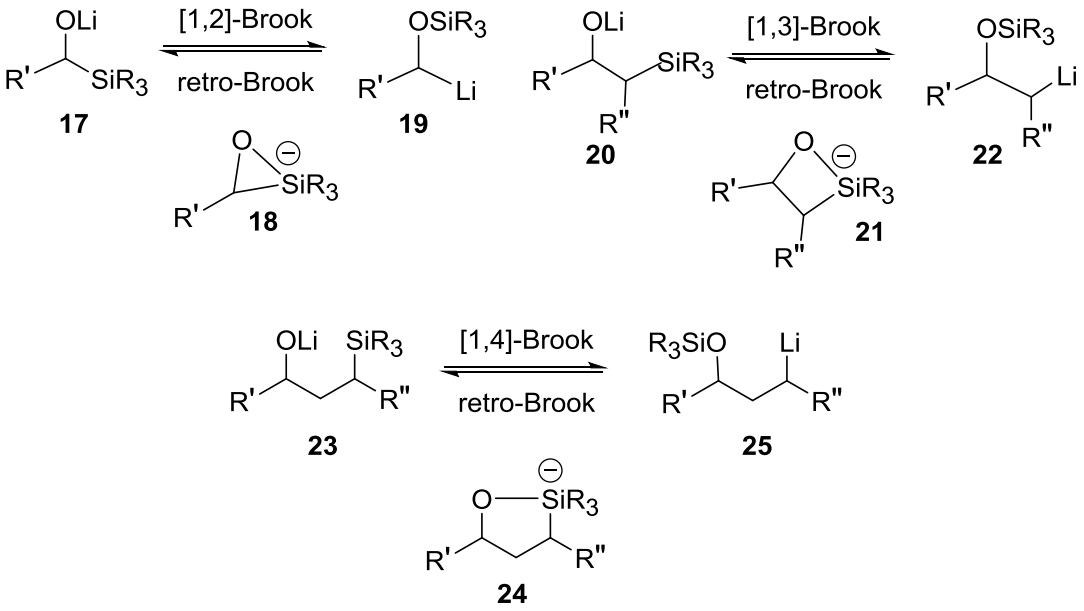
bonds to O have greater strength than those to C (see Table 1.1). This allows the formation of carbanions from alkoxides through the [1,2]-Brook rearrangement (Scheme 1.3).[11]



Scheme 1.3 First reported [1,2]-Brook rearrangement

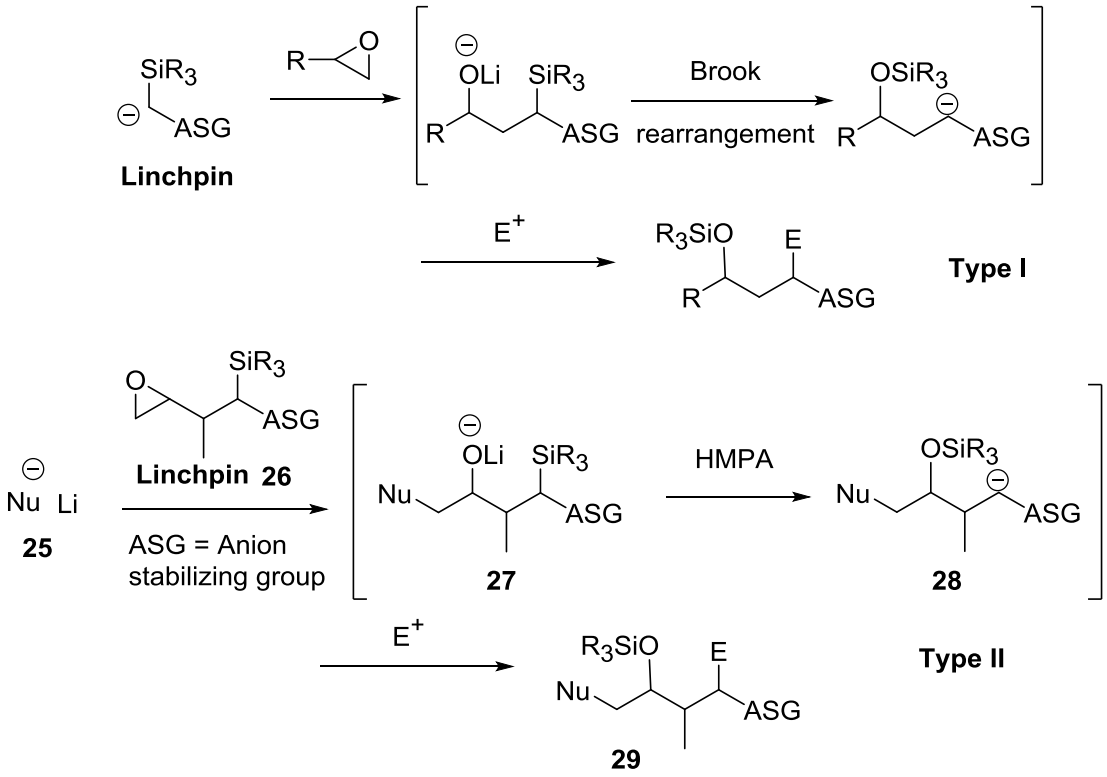
The nucleophilic attack of the oxygen to the α-silicon atom requires the presence of a base to promote the required electron density on the oxygen atom. This rearrangement is reversible and which side of the equilibrium is more stable depends on several factors. Some of them are i) the strength of the oxygen-metal ion pairing that stabilize the alkoxide, ii) how the carbon substituents can stabilize the negative charge of the carbanion, and iii) solvent polarity.[12]

Previous studies indicated that the silyl migration usually occurs with retention of configuration at the silicon and inversion of configuration at the carbon.[12a] Although the initial rearrangement was known for a 1,2 shift of Si, it was extended to a range of [1,3], [1,4] and [1,5]-silyl group to oxygen migrations (Scheme 1.4)[12b,13]



Scheme 1.4 Different Brook rearrangements

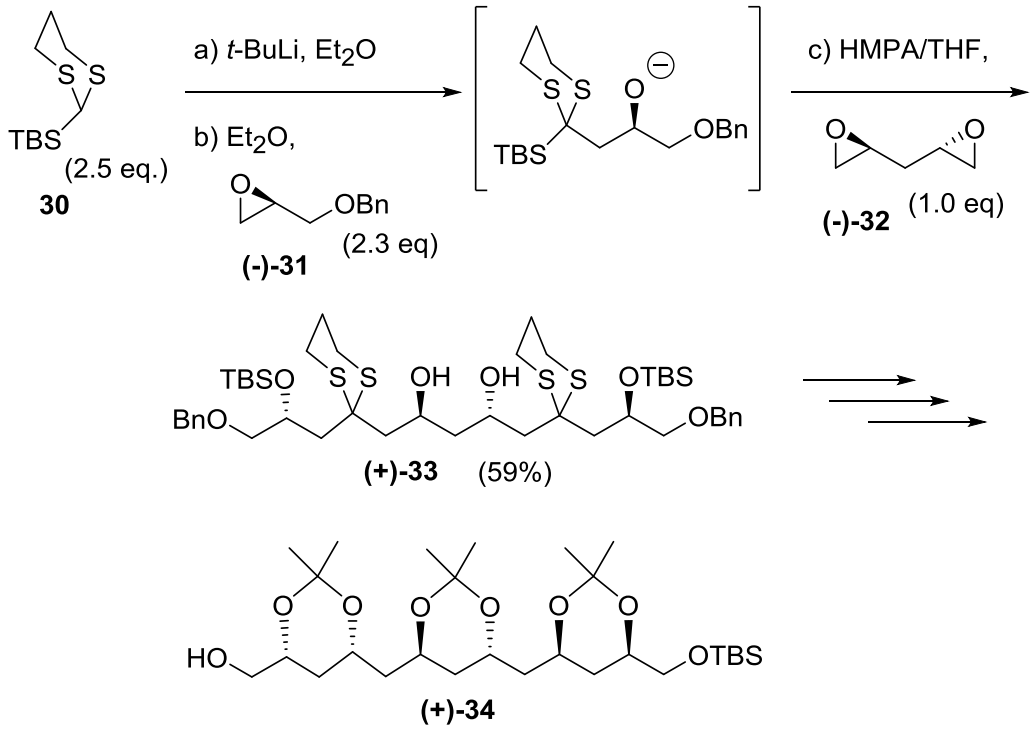
One excellent development of the Brook rearrangement is its application in Anion Relay Chemistry (ARC) elaborated by the Smith group.[14] Here an anion stabilizing group (ASG) located on the same carbon bearing a trialkyl silyl group, stabilizes the charge of the carbanion formed after the [1,4] Brook rearrangement takes place. The new reactive anion is available to react with a new electrophile generating a series of sequence reactions defined as "linchpin process" by the Smith group (Scheme 1.5).[14]



Scheme 1.5 Anion relay chemistry (ARC)

The ARC is basically divided in two groups regarding the charge migration, the latter could be "through-bonds" or "through-space". In the first scenario the transfer of the negative charge occurs like in a 1,4 addition reaction to enone, in which the negative charge is transfered via the unsaturated π-system. Conversely, in the second group the charge is "carried" from an alkoxide to the carbon atom by silyl migration like in the Brook rearrangement. This second group "through-space" can be divided in two types. Type I, where after addition of HMPA the negative charge is relayed back to the original location on the nucleophile (**linchpin**) and type II where an external nucleophile is needed to generated an anion, that with the aid of a transfer agent the negative charge is relayed to a new position on the molecule after rearrangement

(Scheme 1.5).[14] One application of the type 1 ARC in natural product synthesis is the preparation of an important intermediate (**34**) employed in the total synthesis of mycoticin (Scheme 1.6)[15]



Scheme 1.6 Five-component coupling using Type I ARC

1.4 Silanes in cross-coupling chemistry

Due to their low toxicity, stability, and availability organosilicon compounds are considered excellent reagents for cross-coupling reactions, acting as the nucleophilic partners for various organic halides.[16] Reactions that employ palladium (Pd) or nickel (Ni) catalyzed coupling of organohalides or triflates with organosilanes are called Hiyama couplings.[17] Due to their lower reactivity, organosilanes traditionally needs to be activated by a fluoride source upon

heating, giving a more reactive pentacoordinated intermediate that is more capable in transmetalations (Figure 1.6).

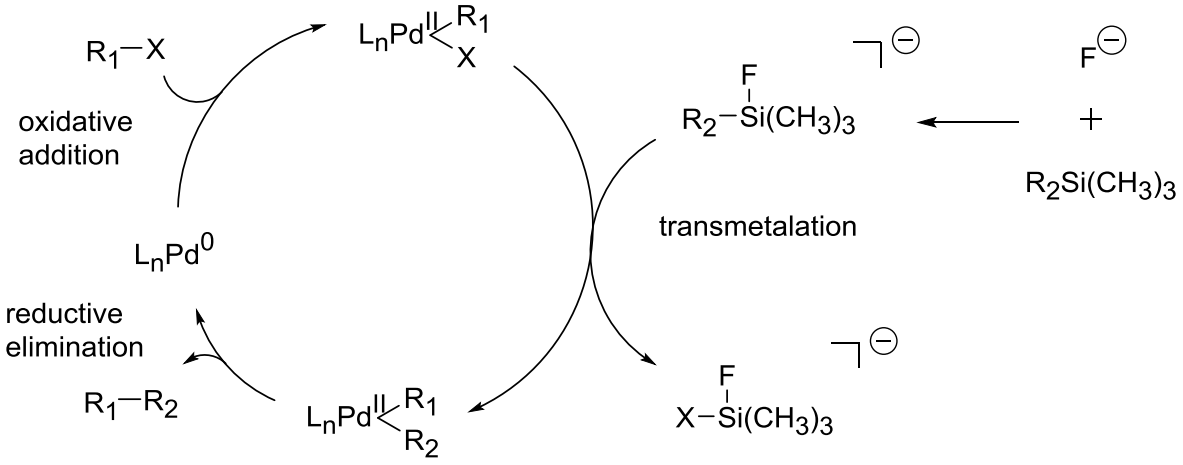


Figure 1.6 Hiyama cross-coupling mechanism

An improvement of this coupling reaction by Denmark involves the employment of organosilanols that do not require the use of a fluoride source for activation of the silicon species (Figure 1.7). However, this Brønsted base-promoted reaction depends on the steric and electronic properties of the silicon center.[18]

Kinetics studies of these base mediated Hiyama couplings, indicated that the intermediates are not only a hypercoordinate Si species. Instead Denmark invokes first the formation of complex **I** (Figure 1.7) that contains a silicon-oxygen-palladium bond and the reaction proceed via an intramolecular transmetallation of a tetracoordinate Pd^{II} species **II**.[18a,19]

Some applications of these coupling reactions include the synthesis of particularly challenging aryl heterocycles (Scheme 1.7). Treatment of *N*-Boc-dimethyl(2-indolyl)silanol (**35**) with NaH generates the active intermediate sodium *N*-Boc-dimethyl(2-indolyl)silanolate (**36**).

The latter is an active reagent for cross coupling with aryl iodides containing nitriles, ethers and esters substituents.[20]

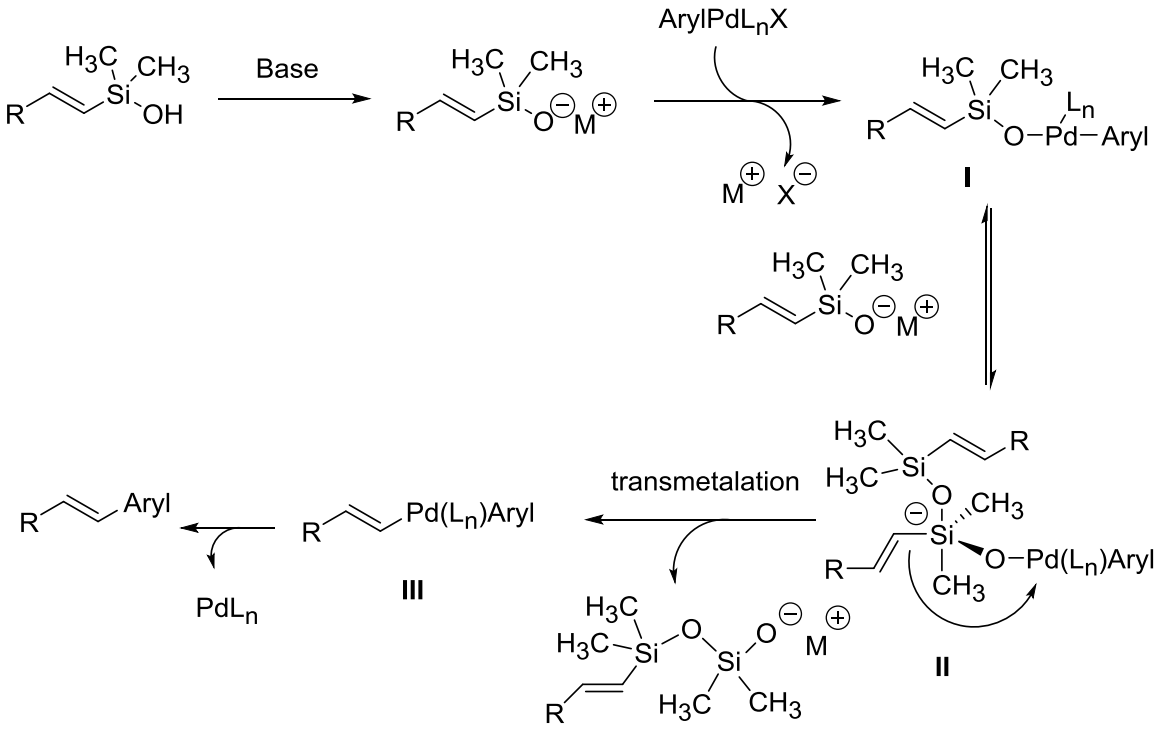
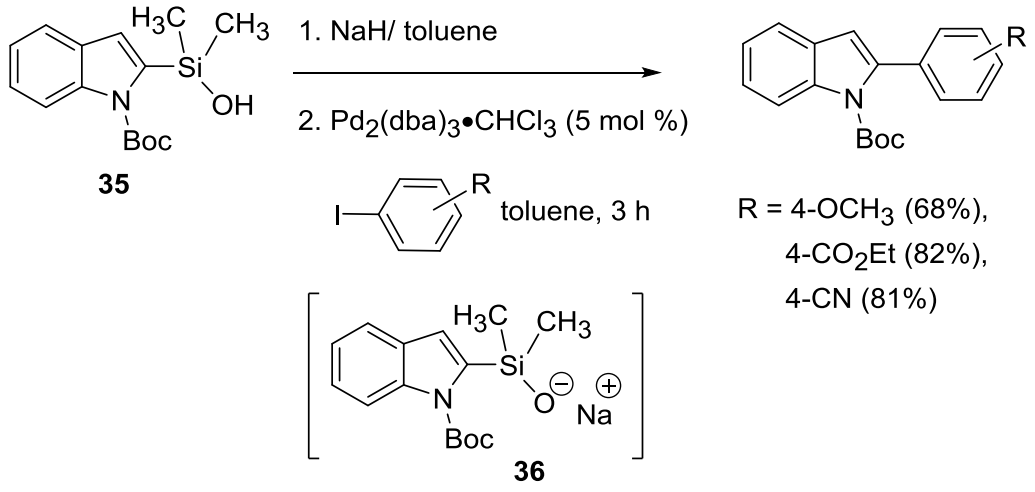


Figure 1.7 Mechanism of the non-fluoride activated palladium-catalyzed coupling



Scheme 1.7 Biaryl synthesis using organosilanols

The purpose of this introductory chapter was to highlight some of the unique properties of silicon as well as some of its important applications related to Pd- catalyzed reactions, allylations of aldehydes, and 1,2 shifts of silicon. These three areas will be subjects in the following chapters where the development of new methodologies in a quest to increase the use of silicon in the preparation of new intriguing organic molecules is described.

REFERENCES

REFERENCES

(1) (a) Colvin, E. W. *Silicon Reagents in Organic Synthesis;* Academic Press: San Diego, 1988: Chapter 1. (b) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry;* Wiley: New York, 2000: Chapter 1, 2 and 4.

(2) (a) Corey, J. Y. *Historical Overview and Comparison of Silicone with Carbon*, In *The Chemistry of Organic Silicon Compounds, Part 1;* Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1989.

(3) (a) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry;* Wiley: New York, 2000: Chapter 7. (b) Larson, G. L.; Fry, J. L. *Ionic and Organometallic-Catalyzed Organosilane Reductions,* in *Organic Reactions;* Wiley: New York, 2008; Vol. 71, Chapter 1 pp 5–75.

(4) Fleming, I.; Pearce, A; Snowden. R. L. *J.C.S. Chem. Comm.* **1976**, 182–183.

(5) (a) Jorgensen, W. L.; Chandrasekhar, J.; Wierschke, S. G. *J. Am. Chem. Soc.* **1985**, *107*, 1496–1500. (b) Lambert, J. B.; Wang, G.-T.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838–7845.

(6) (a) Fleming, I. *Allylsilanes, Allylstannanes and Related Systems,* in *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 563–593. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375–1408.

(7) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793. (b) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, *15*, 3173–3199.

(8) Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1421–1423.

(9) (a) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130–5132. (b) Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, *2*, 749–769.

(10) Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040–1055.

(11) (a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, *80*, 1886–1889. (b) Brook, A. G.; Warner, C, M.; McGriskin, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 981–983. (c) Brook, A. G.; Iachia, B. *J. Am. Chem. Soc.* **1961**, *83*, 827–831.

(12) (a) Brook. A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84. (b) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065–2084. (c) West, R.; Lowe, R.; Steward, H. F.; Wright, A. *J. Am. Chem. Soc.* **1971**, *93*, 282–283.

(13) (a) Hoffmann, R.; Bruckner, R. *Chem. Ber*. **1992**, *125*, 2731–2739.(b) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1995**, *60*, 4213–4227. (c) Smith, A. B., III; Xian, M.; Kim, W.-S.; Kim, D.-S. *J. Am. Chem. Soc.* **2006**, *128*, 12368–12369.

(14) (a) Smith, A. B., III; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66–67. (b) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883–5895.

(15) Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001–2004.

(16) (a) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem* **2002**, *219*, 61–85. (b) Denmark , S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835–846.

(17) Hatanaka. Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.

(18) (a) Denmark, S. E.; Neuville, L.; Christy, M. E. L.; Tymonko, S. A. *J. Org. Chem.* **2006**, *71*, 8500–8509. (b) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486–1499.

(19) (a) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865–4875. (b) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876–4882.

(20) Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem.* **2008**, *73*, 1440–1455.

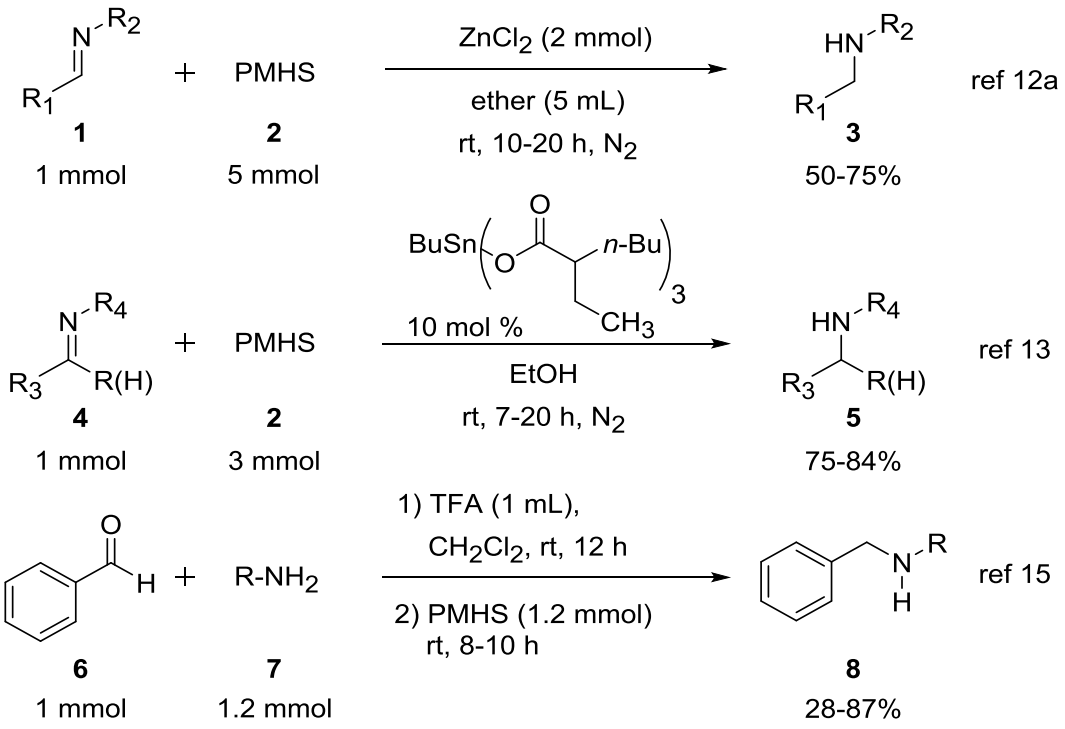
CHAPTER 2: IMINE REDUCTIONS

2.1 Introduction

The importance of the amino functionality in the pharmaceutical industry is considerable. Secondary amines are vital building blocks for alkaloid and pharmaceutical drug syntheses.[1] One of the most noteworthy pathways for the synthesis of these nitrogen-containing building blocks is their preparation from imine compounds. Conventional approaches to obtain secondary amines by reduction of imines often requires reagents that are difficult to handle or lack chemoselectivity (e.g. $NaBH_4$,[2] $LiAlH_4$,[3] $BH_3(CH_3)_2NH/CH_3COOH$ (glacial),[4] Ra-Ni/aluminum isopropoxide/iPr-OH,[5] NH_3/Ra-Ni,[6] $BH_3S(CH_3)_2$.[7]) These protocols also tend to generate copious waste and involve difficult work up to isolate the desired amine.

An alternative route applied towards imine reduction is the use of silanes and siloxanes as reducing reagents. Different methods have employed triethylsilane in combination with Zn,[8] Mo,[9] Ti[10a-b] catalysts or metal free conditions.[11] In the quest for environmentally friendly and inexpensive procedures, polymethylhydrosiloxane (PMHS) represents a safe and economic hydride source. Consequently several protocols have been reported using PMHS in combination with Zn,[12] Sn,[13] Ti,[10a-d] In,[14] and Cd[14] catalysts, in addition to metal free conditions wherein PMHS is activated only by trifluoroacetic acid[15] (Scheme 2.1). Noteworthy of the latter example, as well as in two recent publications[16] one-pot reductive amination is achieved. Several efforts have also been extended to the development of asymmetric syntheses of secondary amines using chiral catalysts and ligands by reductive amination.[10a-c,14,17] Applications of

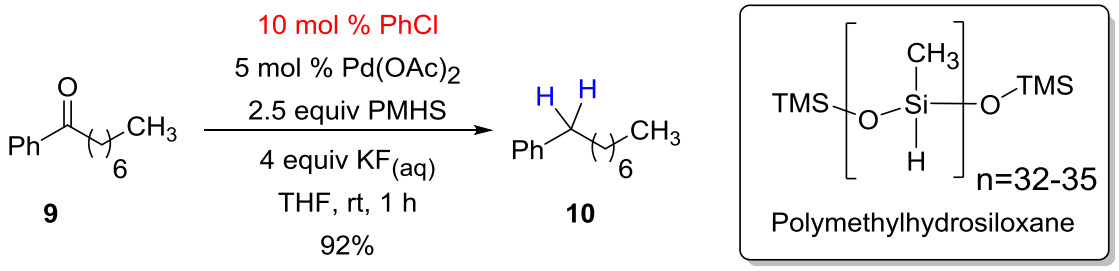
reductive amination in both academic research and chemical industries[1,18] highlight once again the importance of imines as key intermediates that can provide direct access to chiral amines.



Scheme 2.1 Previous examples of reduction of imines with PMHS

2.2 PMHS applications and background

PMHS is a powerful reagent that can perform a wide range of reactions, such as dehalogenation,[19] deoxygenations,[20] opening of aziridines,[21] reduction of ketones,[22] double bonds,[23] carboxylic esters,[24] carboxamides,[25] and organotin halides and oxides.[26] It is a byproduct of the silicon industry's synthesis of cyclic siloxanes, so it is inexpensive (approximately $7.2 per mol of hydride).[27] Moreover, PMHS is air and moisture stable (can be stored on the bench for years); and is assumed to be non-toxic (Scheme 2.2).



Scheme 2.2 Recent application in deoxygenations reaction[20] and PMHS structure

PMHS was first synthesized by Sauer[28] in 1946 but its utility in synthesis has only been exploited in the last decades.[29] A search in SciFinder® highlights, that over the past 22 years the use of PMHS has grown dramatically (Figure 2.1).[29b] One of the most cited papers that used PMHS for the enantioselective reduction of ketones in the presence of chiral zinc catalysts, has been cited 191 times up to now.[29c] Several protocols using PMHS in combination with Ti,[10,24] Pd,[21,23,30] Zn,[22a-b,31] Cu,[22c-d] Sn,[22e,26a,32] Zr,[24] Ru,[25] Fe,[33] and I_2[34] are reported. It is also known that PMHS can be activated to a hypercoordinate species with a fluoride source.[22f,26b,35,36] Maleczka and co-workers[36] showed that the combination of KF and PMHS, in ethereal solution, yielded tributyltin hydride from the corresponding tributyltin chloride.

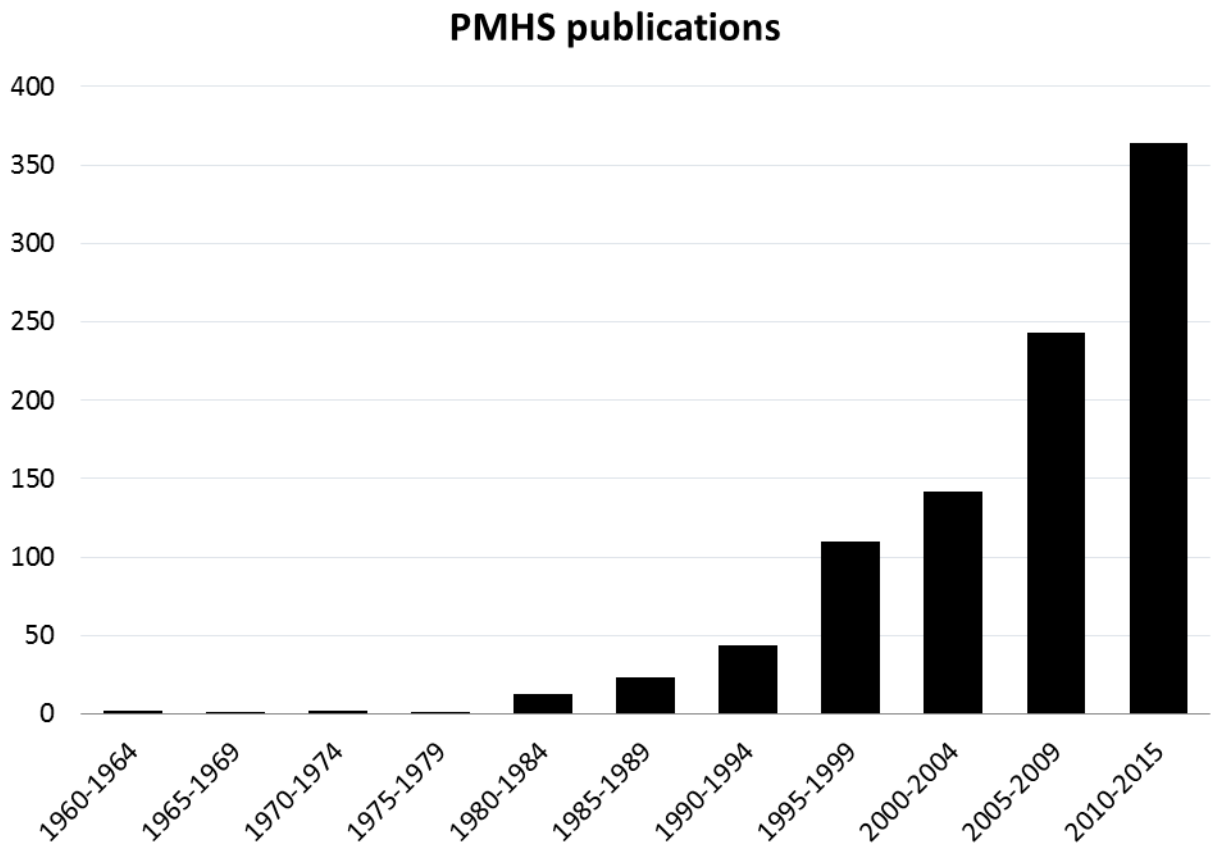
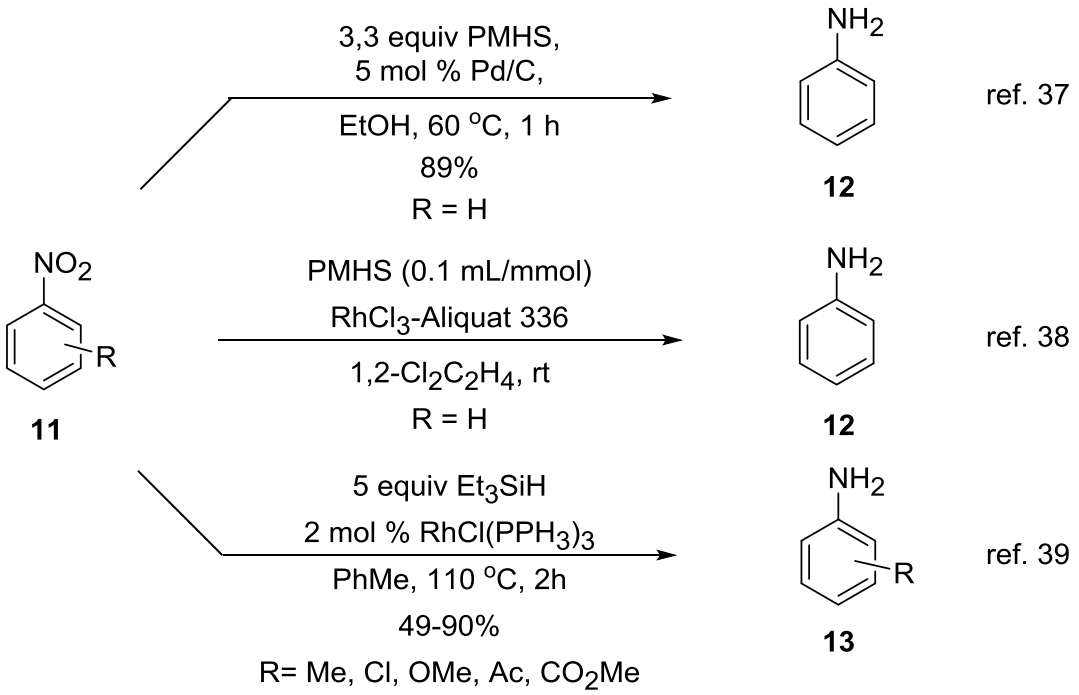


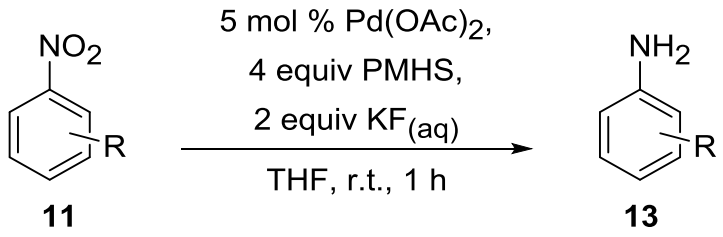
Figure 2.1 Reported publications using PMHS through the years[29b]

Another important application of PMHS is in nitro reductions. An attractive route for those reductions involves the use of silanes and siloxanes as hydride source. Early examples by Lipowitz and Bowman[37] recounted the use of PMHS with a Pd/C catalyst towards the reduction of nitrobenzene to aniline. Almost 20 years later, Blum and Volhardt[38] highlighted again the use of PMHS to reduce nitrobenzene using a rhodium catalyst for this transfer hydrogenation reaction (Scheme 2.3). Another successful methodology was reported years later by Brinkman and Miles,[39] who employed triethylsilane with Wilkinson's catalyst for the reduction of several nitrobenzenes.



Scheme 2.3 Previous examples of nitroarenes reductions using silyl hydrides

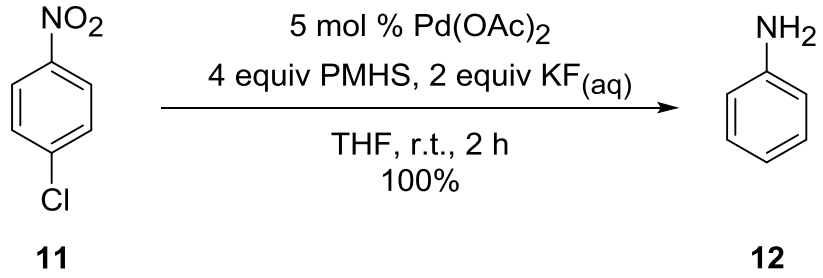
Encouraged by these results, the Maleczka group developed a methodology that facilitates the reductions of nitrogen-containing functional groups under milder conditions and shorter reaction times based on Pd-catalyzed reductions using PMHS in presence of aqueous KF[40] (Scheme 2.4).



Scheme 2.4 Reduction of nitro compounds with Pd/PMHS/$KF_{(aq)}$ at room temperature

The combination of these reagents was initially tested on the hydrodehalogenation of aryl chlorides.[19b] During those chlorodehalogenation studies, the reduction of the nitro group in 1-

chloro-4-nitrobenzene was also observed (Scheme 2.5). Therefore, nitrobenzene was subjected to the optimized dehalogenation conditions to yield the desired amine.[40a]

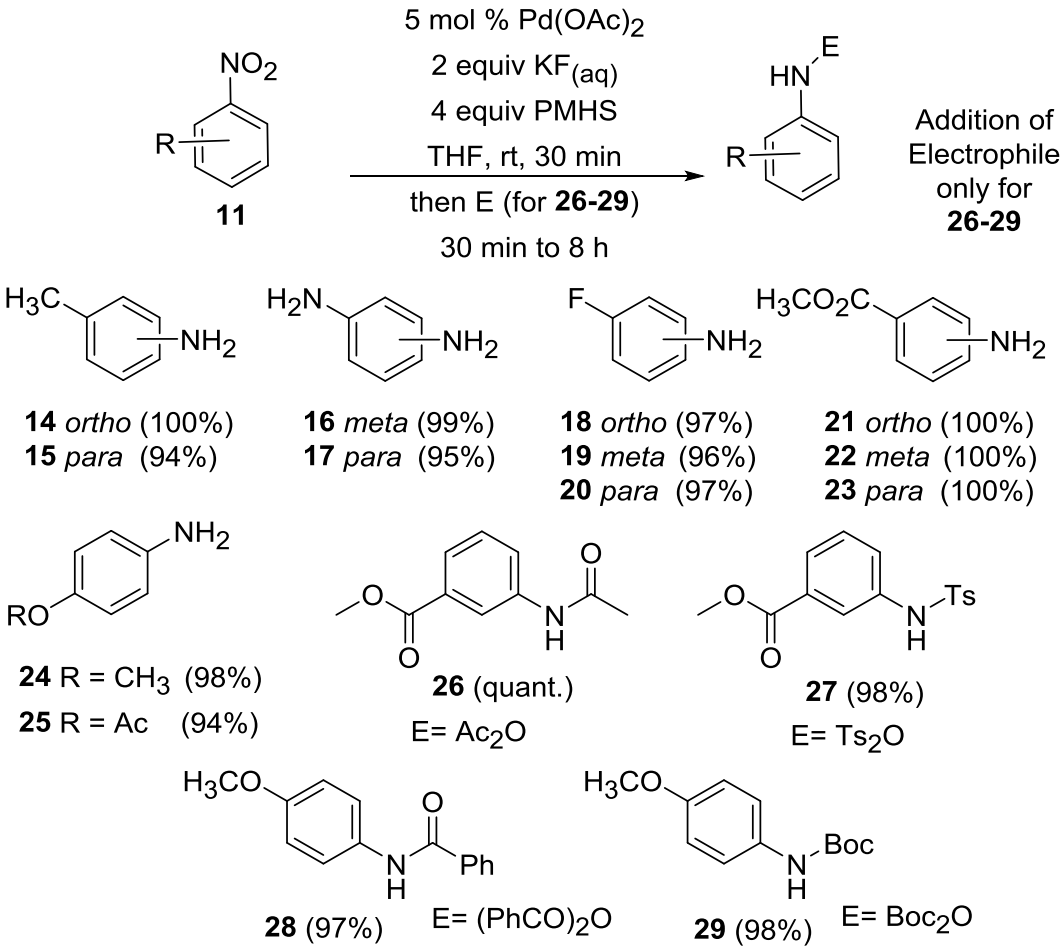


11 **12**

Scheme 2.5 Preliminary $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ nitro reduction

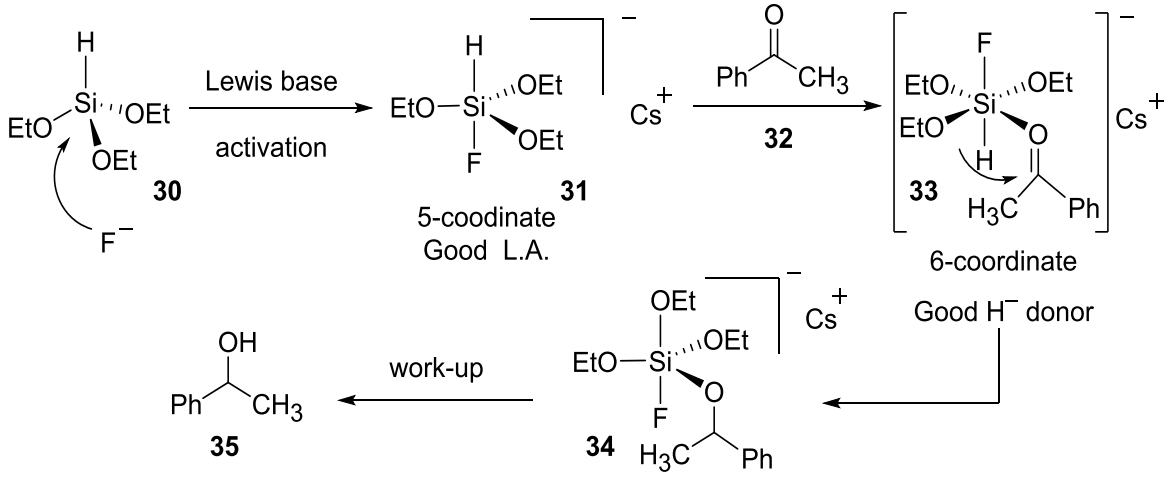
In order to optimize this nitro reduction; different palladium catalysts, fluoride sources, and siloxanes/silanes were screened using 2-nitrotoluene as the control substrate.[40a] It was found that the combination of $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ gave the highest yields and shortest reaction times.

This methodology displayed a broad substituent group (EDG and EWG) tolerance independent of their ring position affording the aniline products in quantitative yield. Chemoselective reductions of the nitro group were also observed, in which carboxylic acids, esters, amides, and fluoro substituents survive; however ketones, nitriles, bromo, chloro, olefins and triple bonds gave side products. Exceptions to the broad reactivity are substrates containing sulfur, which are assumed to poison the catalyst.[40] This methodology was extended to heteroaromatic[40] and aliphatic nitro compounds[40] giving the corresponding anilines and N-hydroxylamines. In the second case the optimization conditions required exchange of PMHS for a non-polymeric silicon hydride such as triethylsilane and removal of the fluoride source. Furthermore, one-pot reductive conversion of nitroarenes to amides, carbamates or sulfonamides was also reported by the Maleczka group[41] (Scheme 2.6).



Scheme 2.6 Application of $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ system[41]

It is important to mention that these results demonstrate the significance of the fluoride source to activate the PMHS.[22f,26b,35,36] The preference of the silicon atom to form pentacoordinate species activated by the presence of anionic ions had been reported.[42,43] Previous examples reported on hydrosilylation catalyzed by fluoride salts proposed that the F^- ion coordinate to the Si atom making the Si-H bond weaker. Indeed, this pentacoordination make the Si center more electrophilic, therefore reaction towards nucleophiles followed by delivery of the hydride takes place faster and a mechanism via Lewis base catalysis is suggested (Scheme 2.7).[43]



Scheme 2.7 Lewis base catalysis

In our catalyst system the presence of Pd suggested a different scenario due to the formation of Pd nanoparticles, as reported by Chauhan;[44] when $Pd(OAc)_2$ and PMHS were combined (Figure 2.2). The formation of this highly activated palladium nanoparticles, seems to influence the selectivity of these reductions.

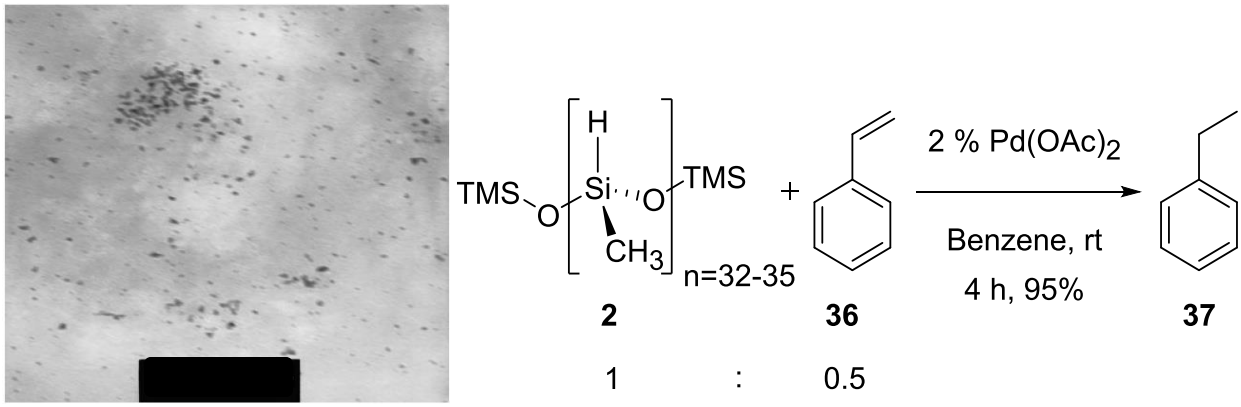


Figure 2.2. Palladium encapsulated nanoparticles reported by Chauhan and selective reduction of conjugates aromatic alkenes by "Pd-PMHS" nanocomposite.[44]

2.3 Application of $Pd(OAc)_2/PMHS/KF_{(aq)}$ system in the reduction of imines.

The successful studies on the reduction of nitro compounds using the Pd/PMHS/KF system sparked our interest to further investigate its application to the synthesis of secondary amines from the direct reduction of imines. To the best of our knowledge there has been no report of using $Pd(OAc)_2/PMHS/KF_{(aq)}$ for this reduction. Therefore, the study of the reduction of aromatic imines using this catalyst system was undertaken.[45]

The goal of this chapter is to report our results on imine reductions as well as their advantages of short reaction times, low catalyst loadings and own establishment of the formation of Pd nanoparticles.

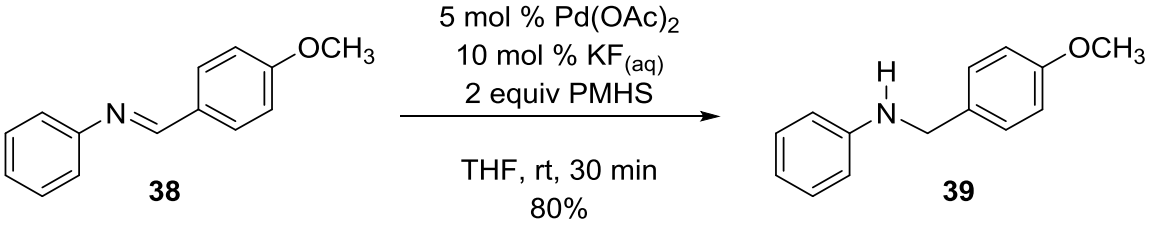
2.3.1 Optimization of the $Pd(OAc)_2/PMHS/KF_{(aq)}$ system

Initially *N*-phenyl-4-methoxybenzylideneamine was selected as a model substrate and it was prepared in quantitative yield following standards procedures.[46] Then the freshly synthesized imine was subjected to our reduction methodology in 1 mmol scale (Scheme 2.8). The first experiment with 5 mol % of $Pd(OAc)_2$, 2 equiv of PMHS and 10 mol% of KF gave complete conversion in just 30 min (Table 2.1, entry 1). Following attempts to reduce the $Pd(OAc)_2$ loads to 2.5 mol % and 1 mol % still showed traces of starting material at 30 min as monitored by ^1H NMR (Table 2.1, entry 2 and 3). Absence of Pd shutdown the reaction and no conversion was observed after 24 h (Table 2.1, entry 4). This result indicated that PMHS in the presence of aqueous KF does not hydrolyze the imine. When PMHS was not added to the

reaction vial no reduction of the imine was observed after 12 hours while using lower quantities of PMHS increased the reaction time (Table 2.1, entries 5 and 6).

It is worth noting that in the absence of $KF_{(aq)}$ the reaction does take place. However, such reaction cannot be driven to complete conversion even after 24 h (Table 2.1, entry 7). Therefore, the addition of KF as additive to activate the PMHS presumably via a pentacoordinate species was necessary to accelerate the delivery of the hydride. When only 5 mol % of KF was employed traces of imine can be observed at 30 min (Table 2.1, entry 8). Increasing the quantities of $KF_{(aq)}$ to 15 mol % furnished the desired product in 30 min, however at higher loads gel formation was occasional observed. It is reported that PMHS can form hydroxysiloxanes in the presence of a H_2O/THF solvent mixture catalyzed by Pd,[47] therefore adding more aqueous KF can promote the formation of hydrosiloxanes that would generate a difficult isolation of the product.

Finally we were able to confirm that the initial quantities of 5 mol % $Pd(OAc)_2$, 2 equiv of PMHS and 10 mol % of KF employed gave us the best results for this imine reduction. The order of addition was important in that mixing the $Pd(OAc)_2$ with the imine solution in THF/KF(aq) followed by addition of PMHS insured shorter reaction times.



Scheme 2.8 Reduction of *N*-phenyl-4-methoxybenzylideneamine with Pd/PMHS/KF system

Table 2.1 Control experiments with the $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ system

Entry	$Pd(OAc)_2$	PMHS	KF	Time	Result (ratio **38**/**39**)[a]
1	5 mol %	2 equiv	10 mol %	30 min	0:1
2	2.5 mol %	2 equiv	10 mol %	30 min	0.2:1
3	1 mol %	2 equiv	10 mol %	30 min	0.1:1
4	---	2 equiv	10 mol %	24 h	No reaction
5	5 mol %	---	10 mol %	12 h	No reaction
6	5 mol %	1 equiv	10 mol %	30 min	0.1:1
7	5 mol %	2 equiv	---	24 h	1:1
8	5 mol %	2 equiv	5 mol %	30 min	0.2:1
9	5 mol %	2 equiv	15 mol %	30 min	0:1

[a]Reactions were perform in a 1 mmol scale, at room temperature and using THF as solvent. Ratios were calculated by ^1H NMR of crude mixture.

These preliminary results indicated that the presence of the fluoride ion is necessary to accelerate the reaction. At this point a question needs to be addressed: Does changing the F^- source for a stronger base like tetrabutylammonium fluoride (TBAF) improve this reduction even more? Using 5 mol % of TBAF, but keeping the same quantities of imine (1 mmol), $Pd(OAc)_2$ (5 mol %) and PMHS (2 equiv), just 30% of conversion was detected at 30 min. Even after 24 h no more than 50 % conversion was reached (imine/secondary amine ratio 1:1). Increasing the TBAF up to 10 mol % generated a polymer like substance that shutdown the reaction. Therefore, until now the combination of Pd/PMHS/KF gave us the best results for this reduction.

In order to confirm that $Pd(OAc)_2$ was the best catalyst for these reductions, we tested different Pd catalysts under the same reaction conditions of PMHS/$KF_{(aq)}$ previously established (Table 2.2). Using 5 mol % of each catalyst and 1 mmol of *N*-phenyl-4-methoxybenzylideneamine, control reactions were performed and monitored by ^{1}H-NMR between 30 min and 2 hours. In the first two attempts using $Pd(Cl)_2$ and $Pd(CN)_2$ (Table 2.2, entries 1 and 2) the ^{1}H NMR spectrum of the crude reaction mixture displayed only the signals of the starting material. Therefore we continued both reactions for an additional 30 min, however, no conversion was observed and the palladium precipitated after 2 hours in both cases.

When phosphine ligands were employed (entries 3 and 4), no conversion to the desired amine was observed after 30 min, instead hydrolysis of the imine generated a complicated mixture as judged by ^{1}H NMR. The same result was observed when $Pd(NH_3)_2Cl_2$ was used as a catalyst (entry 5). On the other hand, when $Pd_2(dba)_3$, $Pd(OH)_2$/C, Pd black, and Pd/C activated were employed, partial reduction of the imine was observed at 30 min. The secondary amine to imine ratio was 1:1; complete conversion was observed by ^{1}H NMR after 1 hour (entries 6 to 9). However, in the last two cases we observed a Pd black and Pd/C batch dependence even when new bottles of these catalysts were used. Using a different bottle of Pd black, no conversion was observed even after 24 h; for the latter case a mixture of secondary amine and imine (2:1) was obtained after leaving the reaction overnight. The last catalyst tested, $Pd(acac)_2$, gave a higher conversion in 30 min. The ratio of secondary amine to imine was 4 to 1 and the reaction was complete after 45 min. In summary, these findings confirmed that $Pd(OAc)_2$ was the best catalyst, giving complete conversion in as little as 30 min.

Table 2.2 Screening of different Pd catalysts for imine reduction

Entry	Catalyst	Time	% conversion	Observation
1	$Pd(Cl)_2$	30 min	0	Pd precipitation
2	$Pd(CN)_2$	30 min	0	Pd precipitation
3	$Pd(PPh_3)_2(C_6H_5)Cl$	30 min	0	Hydrolysis
4	$Pd(PPh_3)_2Cl_2$	30 min	0	Hydrolysis
5	$Pd(NH_3)_2Cl_2$	30 min	0	Hydrolysis
6	$Pd_2(dba)_3$	30 min	50	Done in 1 h
7	$Pd(OH)_2/C$	30 min	50	Done in 1 h
8	Pd black	30 min	50	Done in 1 h
9	Pd/C activated	30 min	50	Done in 1 h
10	$Pd(acac)_2$	30 min	80	Done in 45 min
11	$Pd(OAc)_2$	30 min	100	Done in 30 min

With these results in hand, we next analyzed the substrate scope. Several imines were prepared not only to study reductive aminations, but also to further investigate the chemoselectivity of this reduction in the presence of other functional groups such as alkenes, alkynes, ketones, esters, nitriles, halogens and nitro substituents.

2.3.2 Substrate scope and chemoselectivity studies

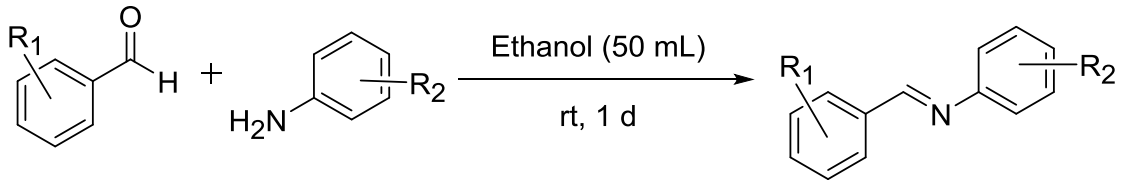
The synthesis of the starting materials is indicated on Table 2.3. From entries 1 to 8 different imines with electron donating groups (EDG) or electron withdrawing groups (EWG)

incorporated into their structure were prepared. The second part of this table was prepared in order to investigate the possible chemoselective reduction of the imine in the presence of other functionalities. Furthermore, imines with more than one substituent on the benzaldehyde or aniline core, as well as some imines derived from benzylamine, cinnamaldehyde and 2-napthaldehyde were synthesized (Scheme 2.9).

Using the previously established reaction conditions of 5 mol % $Pd(OAc)_2$, 2 equiv of PMHS and 10 mol % of KF in a 1 mmol scale of each starting material; the reductions were complete after 15 min to 2 hours and the secondary amine yield ranged from 23 to 93% (Table 2.4 and Scheme 2.10). The products were identified by ^{1}H-NMR and isolated after acid/base work up. The ^{1}H-NMR spectrum usually display an imine proton (RN=C**H**) around 8.4 ppm for the starting material. After reduction, this signal disappears and a new peak for the methylene protons (RNH-C$\mathbf{H}_2$R) of the secondary amine is observed around 4.3 ppm.

As previously mentioned, the second part of Table 2.4 showcases the reactivity of the imine in the presence of other functional groups. Previous studies of this methodology in the presence of halogen substituents showed dehalogenation as a side reaction. However, under the optimized imine reduction conditions no dehalogenated products where observed in the case of F (imine **44a**) and Cl (**43a** and **46a**) containing substrates.

Table 2.3 Synthesis of starting materials



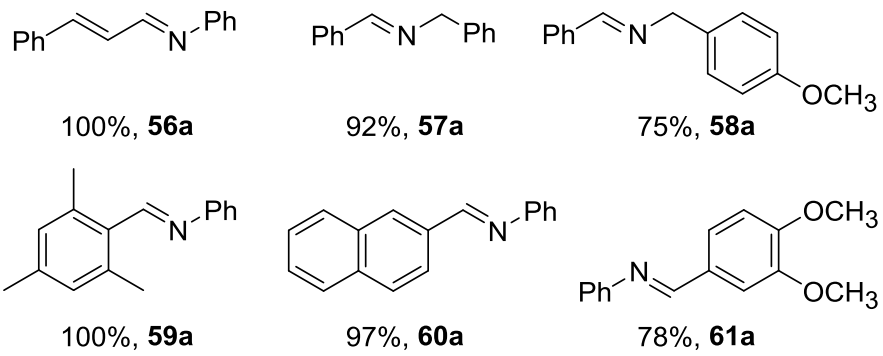
10 mmol 10 mmol **a**

Entry	R1	R2	Products	Yield[a]
1	H	H	**40a**	80%
2	p-OCH_3	H	**41a**	100%
3	H	p-OCH_3	**42a**	96%
4	H	p-Cl	**43a**	97%
5	H	p-F	**44a**	100%
6	p-Br	H	**45a**	98%
7	p-Cl	H	**46a**	97%
8	p-CF_3	H	**47a**	99%
9	H	p-NO_2	**48a**	94%
10	p-NO_2	H	**49a**	87%
11	H	m-NO_2	**50a**	97%
12	m-NO_2	H	**51a**	91%
13	p-CN	H	**52a**	90%
14	H	p-$COOCH_3$	**53a**	89%
15	H	p-$COCH_3$	**54a**	98%
16	p-C≡CH	H	**55a**	99%

[a]Yields refer to spectroscopically pure products unless otherwise noted.

On the other hand, the imine reduction with Br containing substrate (**45a**) displayed a complicated mixture in the ^{1}H NMR spectrum, where four different compounds could be

identified: two secondary amines (**40b**, **45b**) and two imines (**40a**, **45a**) as a consequence of dehalogenation.



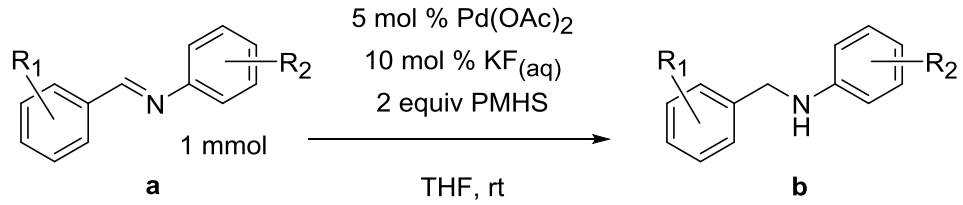
Scheme 2.9 Additional imines prepared

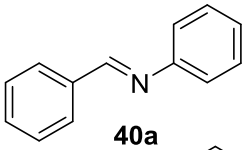
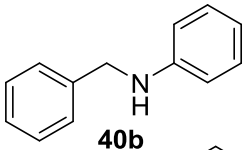
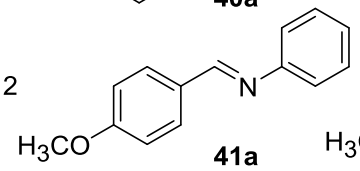
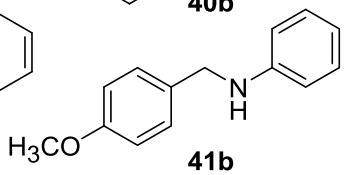
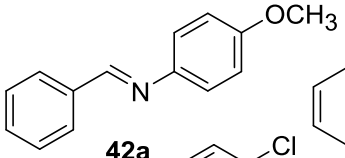
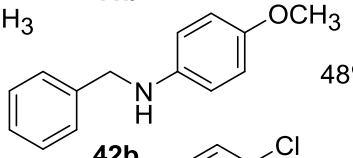
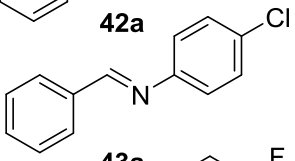
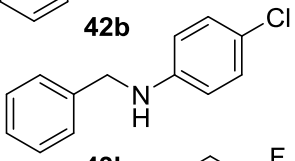
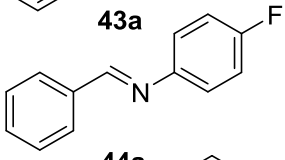
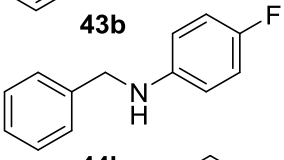
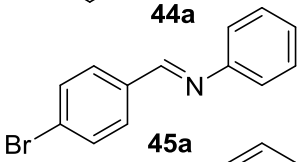
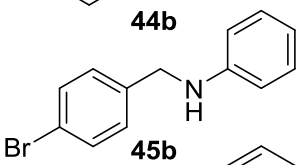
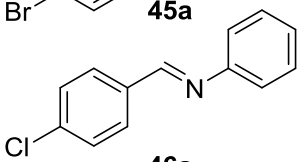
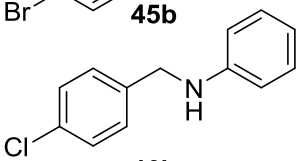
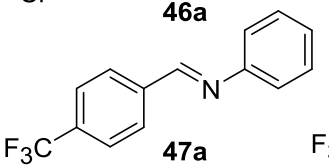
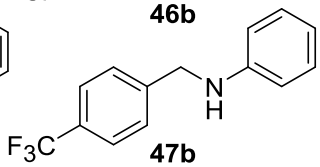
The initial work up for the *N*-phenyl-4-methoxybenzylideneamine reduction included addition of ether, which precipitated the catalyst upon stirring. A quick filtration of the Pd through a plug of Celite (top layer) and neutral alumina (bottom layer) gave a high recovery of crude product; however the yield of product after column chromatography was <50% and some contamination with PMHS was observed by ^{1}H NMR. To circumvent this problem, a new work up was attempted in which a mixture of H_2O/Et_2O (1:1) was added to the crude reaction mixture. After stirring, the organic phase was separated, dried with $MgSO_4$, filtered and concentrated. The crude product was dissolved in EtOAc and treated with a 3M HCl solution. The white solids that formed were filtered, washed with EtOAc and dried overnight to give the desired secondary amine as a hydrochloride salt. The salt was dissolved in a H_2O/methanol (1:1) mixture and $NaHCO_3$ (sat) solution was added. The solution was concentrated under reduced pressure to a minimum volume, and then extracted with EtOAc. The organic layers were dried and

concentrated to give the secondary amine in 65% yield. Optimization of the work up with a shorter acid/base procedure increased the yield of *N*-(4-methoxybenzyl)phenylamine to 80%. In this work up a mixture of Et_2O/1M HCl (1:1) was added and stirred for 10 min. The organic phase was separated and washed with 1M HCl. Then the aqueous layers were combined, made basic with addition of $KOH_{(s)}$, and extracted with EtOAc. Finally, the combined organic layers were dried, filtered and concentrated.

The next substrates selected from Table 2.4 contained NO_2 groups in the para and meta position of the aniline or benzaldehyde ring. Better chemoselectivity was observed when the nitro substituent was at the para position (**48a** and **49a**). Regardless of whether the p-NO_2 group was on an aniline or benzaldehyde ring, the nitro group survived the reduction conditions and no over reduced product was observed within one hour of reaction, however some starting imine remained. Conversely, leaving the mixture for longer time reduced the yield of the target secondary amine and increased the formation of the amino derivative (Table 2.4, entries 9 and 10). When the electron withdrawing group was on the meta position, reduction of both functionalities was observed in 1 hour. In the case of m-NO_2 anilines (imine **50a**), only the over reduction product (**50c**) was observed. In contrast m-NO_2 benzaldehydes (imine **51a**) gave a 1:1 mixture of the nitro secondary amine (**51b**) and the over reduction product (**51c**).

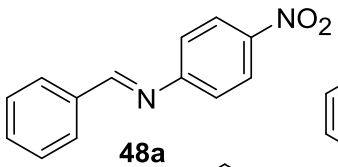
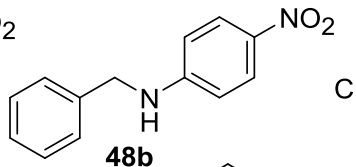
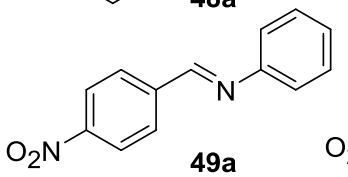
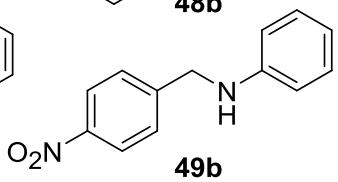
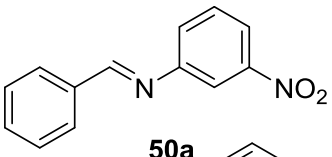
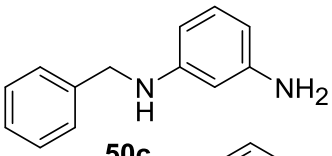
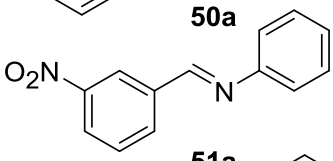
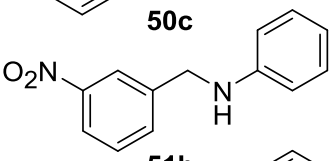
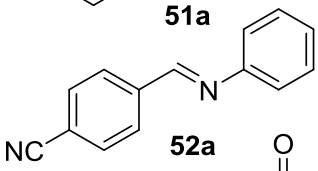
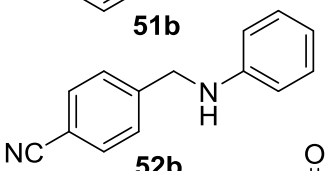
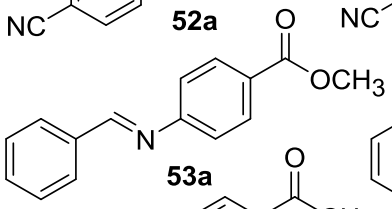
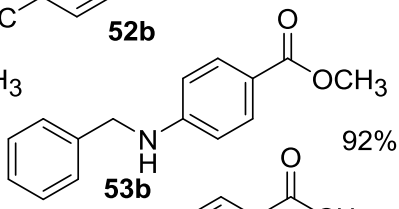
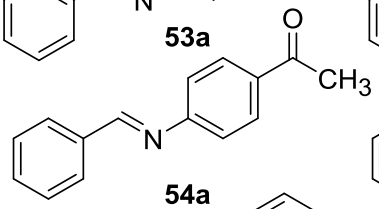
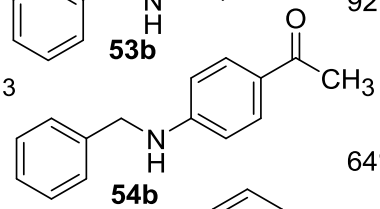
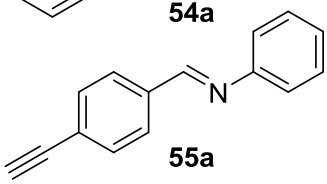
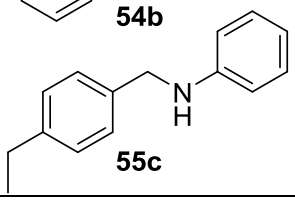
Table 2.4 Imine reductions using the $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ system



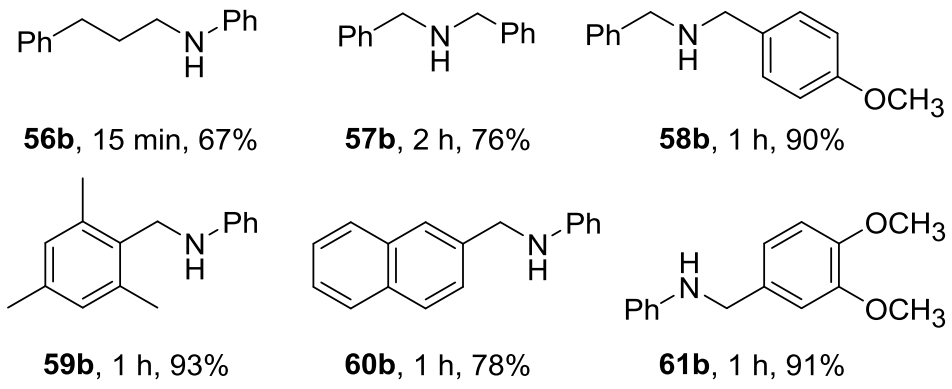
Entry	Starting Imine	Product	Yield (%)[a]	Time
1	 **40a**	 **40b**	90%	2 h
2	 **41a**	 **41b**	80%	30 min
3	 **42a**	 **42b**	48%	30 min
4	 **43a**	 **43b**	50%	1 h
5	 **44a**	 **44b**	69%	1 h
6	 **45a**	 **45b**	C.M.[b]	30 min
7	 **46a**	 **46b**	55%	2 h
8	 **47a**	 **47b**	90%	1 h

[a]Yields shown are a two-run average. [b]Compex mixture of **45a/45b** and **40a/40b** (debromination).

Table 2.4 (cont'd)

Entry	Starting Imine	Product	Yield (%)[a]	Time
9	 **48a**	 **48b**	C.M.[c]	1 h
10	 **49a**	 **49b**	28%	1 h
11	 **50a**	 **50c**	52%[d]	1 h
12	 **51a**	 **51b**	84%[e] (1/1)	1 h
13	 **52a**	 **52b**	72%	2 h
14	 **53a**	 **53b**	92%	1 h
15	 **54a**	 **54b**	64%	30 min[f]
16	 **55a**	 **55c**	23%[g]	1 h

[a]Yields shown are a two-run average. [b]Complex mixture of **45a/45b** and **40a/40b** (debromination). [c]Complex mixture of **48b**, and p-Nitroaniline. [d]Nitro group was also reduced to give NH_2. [e]Mixture of **51b** and **51c** (Imine and nitro group were both reduced). [f]Conversion of ketone to alcohol was observed. [g]Alkyne was reduced to alkane.



Scheme 2.10 Additional secondary amines obtained

To our delight, a different set of results were observed with nitrile (**52a**) and ester (**53a**) substituents where chemoselective reduction of the imines were obtained in high yields (Table 3, entry 13 and 14). Unfortunately a limitation of this methodology was observed in the presence of conjugated double (**56a**) and triple bonds (**55a**). In the former case, the presence of the conjugated double bond accelerates the reaction, yielding complete reduction in only 15 min (Scheme 2.3, **56b**). An important observation was that the complete formation of the secondary amine (**56b**) was detected even before the typical bubbling and color change could be observed. On the other hand, normal reaction conditions were observed for the triple bond containing substrate imine **55a**, however in only 1 h the alkyne was reduce to the alkane (Table 2.4, entry 16). Further analysis of this substrate by following the reaction by ^{1}H NMR proved interesting. It was observed that the reduction of the triple bond occurred first without reduction of the imine, and only after consumption of the triple bond was the imine reduced. This type of reaction has been reported before for β,γ-alkynyl α-imino esters in the presence of a Brønsted acid, both functional groups were reduced to afford an alkenyl α-amino ester. An investigation of the

reaction mechanism indicated that the reduction of the C-C triple bond to alkene was faster than the reduction of the imine bond.[48]

Continuing our studies on chemoselectivity, reductions of imines in the presence of ketones (imine **54a**) were carried out. ^{1}H NMR analysis of the crude material after 30 min indicated a mixture of selective imine reduction **54b** and the over reduced product (conversion of ketone to alcohol and imine reduction) in a ratio 1:0.3. The usual work up developed for the isolation of the secondary amines allowed us to obtain **54b** (64% yield); however the alcohol product did not survive these conditions.

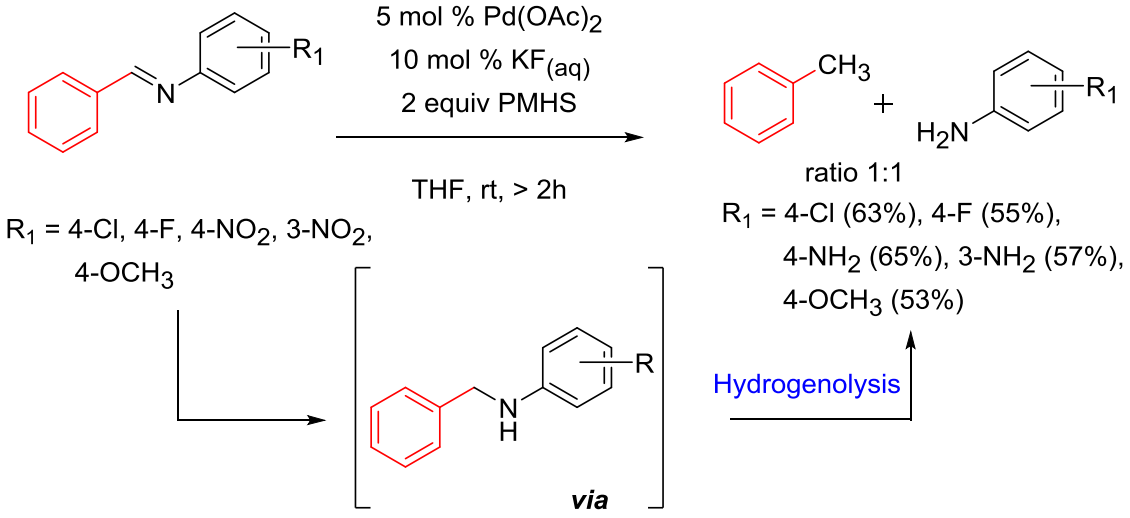
2.3.3 Hydrogenolysis results: substituent effects

A different result was obtained when *N*-benzylidene-4-methoxyaniline (imine **42a**) was subjected to the reduction conditions. At 30 min, the target secondary amine **42b** was observed by ^{1}H NMR, along with 4-methoxyaniline as an impurity (Table 2.5). The presence of small quantities of starting imine **42a** led us to leave the reaction for another 30 min. Surprisingly, another compound was detected in the crude mixture but after purification and concentration of the solvent, only the secondary amine **42b**, imine **42a** and 4-methoxyaniline were recovered. In a batch that was left for 5 hours, the desired product **42b** was not detected. Instead, toluene and 4-methoxyaniline were the major components in the mixture, along with a small percent of starting material. Leaving the reaction overnight led to the complete consumption of **42b** and **42a**, yielding only toluene and 4-methoxyaniline (Table 2.5).

Table 2.5 Hydrogenolysis of the secondary amine **42b** with time

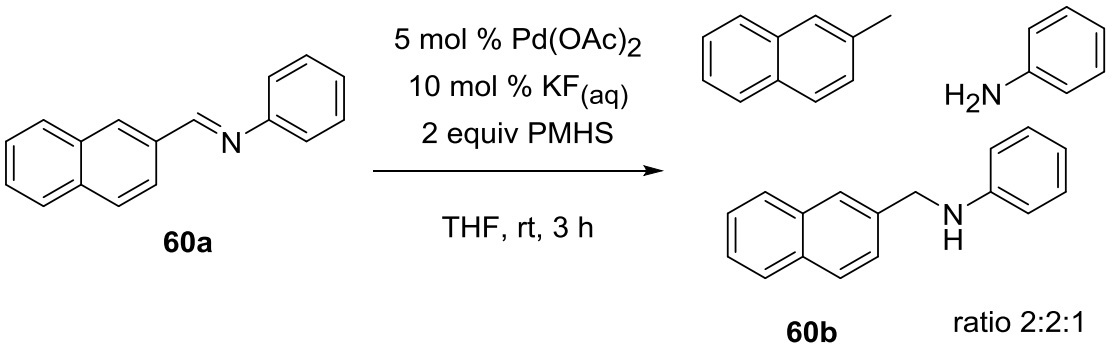
Entry	NMR Crude	N-benzylidene-4-methoxyaniline **42a**	Secondary amine **42b**	Toluene	4-Methoxyaniline
1	at 30 min	5.8%	44%	9.8%	39.6%
2	at 1 h	5.1%	37.8%	16%	41.2%
3	at 5 h	3.7%	---	43.6%	52.7%
4	at 21 h	---	---	46.8%	53.2%

During these studies, we observed that for those imines that did not have substituents on the benzaldehyde ring, running the reductions for longer times led to consumption of the secondary amines. In all cases hydrogenolysis of the benzylic C–N bond and formation of toluene was observed (Scheme 2.11). As we had previously established that PMHS in the presence of aqueous KF does not hydrolyze the imine (discussed on part 2.3.1), this reduction is almost certainly the result of hydrogenolysis. The secondary amines were complete consumed after 20 hours.



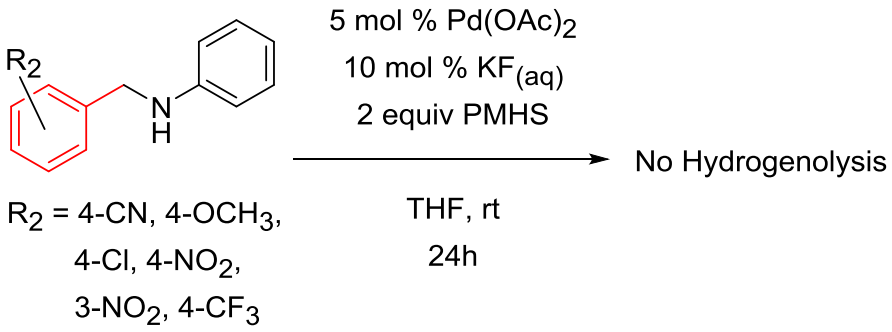
Scheme 2.11 Hydrogenolysis of secondary amines with time

Furthermore, reduction of the imine derived from 2-napthaldehyde (**60a**) afforded, after 3 hours of exposure to the Pd-catalyzed reduction conditions, a 2:2:1 ratio of the fully reduced products and the secondary amine (Scheme 2.12).



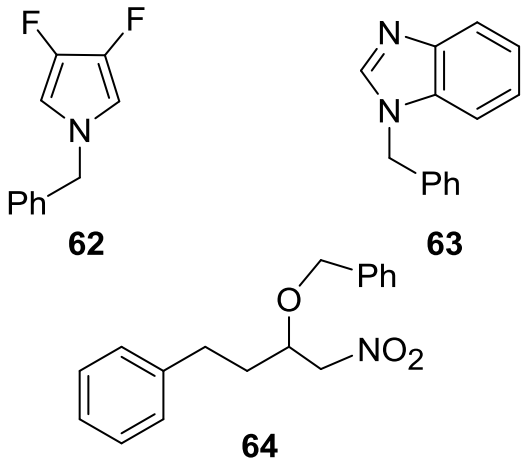
Scheme 2.12 Hydrogenolysis of imine **60a**

On the other hand, we observed that for imines with substituents on the benzaldehyde ring once the secondary amines was formed, no further hydrogenolysis products could be detected. The secondary amines obtained were isolated and after purification were subjected to our Pd-catalyzed conditions again without further conversion (Scheme 2.13). This second group of imines substrates were subjected to the hardest conditions in attempt to promote hydrogenolysis, however neither increasing the reaction time, raising the temperature to 60 ^{o}C, nor using chlorobenzene (as a additive previously employed in the nitro reduction) yielded the hydrogenolysis products. Our hydrogenolysis conditions appear to be selective for benzylated anilines since in the case of N-(4-methoxybenzyl)-benzylamine (**58b**) no hydrogenolysis was observed (Scheme 2.13).



Scheme 2.13 No hydrogenolysis: Substituent effect

Turning back into the literature we found a previous reference where starting from a secondary benzylamine using ethanol as a solvent and H_2 in Pd/C at room temperature, the cleavage of the N-benzyl linkage was possible only for a unsubtituted benzyl group.[49] This paper suggested that any substituent on the benzyl core stabilizes the ring preventing the cleavage of the benzylic C-N to occur. As a result heating to 75 $^{\circ}$C was required to remove the benzyl group with p-OMe or p-OH substituents. They also highlighted that the only group more labile than the unsubstituted benzyl was the naphthyl group that is easily removed at room temperature. Based on these results we decided to explore our conditions for the selective removal of a benzyl or a napthyl protective group on amines and alcohols. We decided to start with some N-benzylated heterocycles and one protected alcohol (Scheme 2.14).



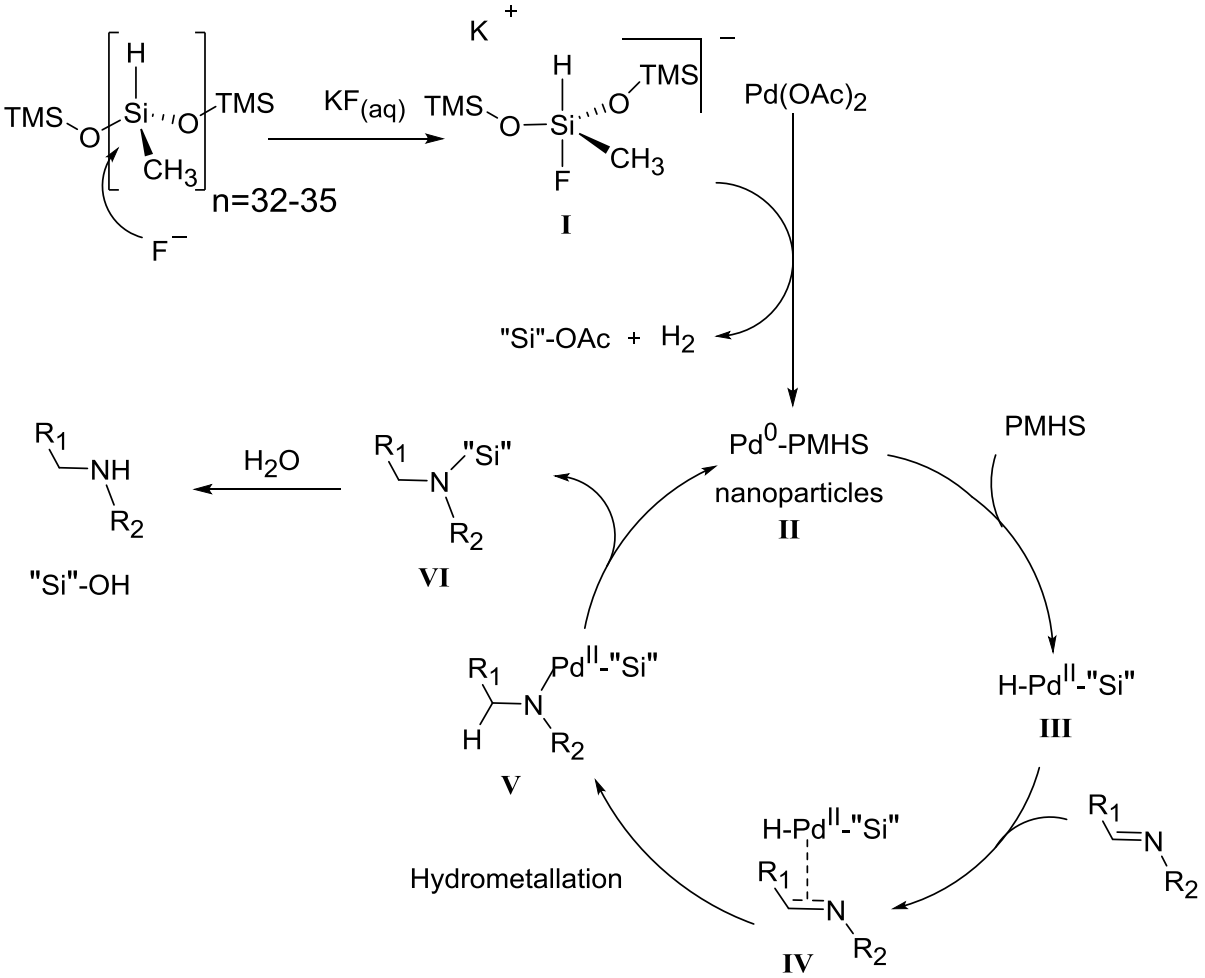
Scheme 2.14 Model compounds for debenzylation reactions

We subjected **62**, **63** and **64** to our reduction methodology. Unfortunately increasing the temperature, using chlorobenzene and leaving the reaction for longer time proved to be futile as only the starting materials were recovered.

2.3.4 Mechanistic studies

As we discussed in the optimization of our catalyst system, the presence of fluoride is essential for accelerating the reaction. Therefore, we suggested that in this first step the Si center of the PMHS is activated by the fluoride source (**I**). Then the active catalyst is generated when $Pd(OAc)_2$ reacts with PMHS/KF forming the Pd^0-PMHS nanoparticles (**II**), evidence of the formation of related encapsulated Pd-siloxane nanoparticles was reported previously by Chauhan.[44] Excess PMHS will form the hydrido-silyl complex (**III**) that coordinates later across the double bond of the imine (**IV**). From here the complex **IV** can undergo migratory insertion of the imine into the Pd-H bond (hydrometallation) to give the amine-silyl species (**V**). Reductive

elimination will give the hydrosilylation product **VI**, which is hydrolyzed to the amine during the acid/base work-up (Scheme 2.15).



Scheme 2.15 Proposed imine reduction catalytic cycle

We decided to analyze the mixture of PMHS (2 mmol) and KF (10 mol %) by ^{29}Si NMR and ^{19}F NMR with the purpose of probing the formation of the presumed pentacoordinate Si species **I**. In the ^{19}F NMR we were able to observe the signal of a Si-F bond at -159 ppm, the usual area assigned for pentacoordinate Si species. On the other hand, in the ^{29}Si NMR, we observed the signals for Si-H (-34.7 ppm), Si-OH (-65.63 ppm) and SiO_2 (-110 ppm)

characteristic for polymeric materials.[50] Finally the ^{1}H NMR spectrum of this mixture showed a broad peak near zero due to the "TMS" units and broad peak around 4.6 ppm for the Si-H bond. Preparing a similar mixture but now adding 5 mol% of Pd (same quantities employed for imine reduction) did not change the signals previously observed. In order to probe the suggested oxidative addition of the activated PMHS to the Pd nanoparticles, an equimolar mixture of Pd/PMHS/KF was prepared. To our delight, in the ^{1}H NMR and ^{29}Si NMR spectra the signal for Si-H disappeared suggesting the oxidative addition to Pd. These results support our initial proposed mechanism.

2.3.5 Palladium nanoparticles: TEM and EDS studies

We observed that the addition of PMHS to a $Pd(OAc)_2$ solution generates polysiloxane encapsulated Pd-nanoclusters, related to those previously reported in the literature.[44] Using Transmission Electron Microscopy (TEM) to explore the morphology of the catalyst medium, we were able to confirm the existence of the Pd-nanoparticles (Figure 2.3). The presence of these nanoparticles could explain the selectivity of this reaction system, however, the stability and exact composition of these Pd-nanoparticles remains unexplored.

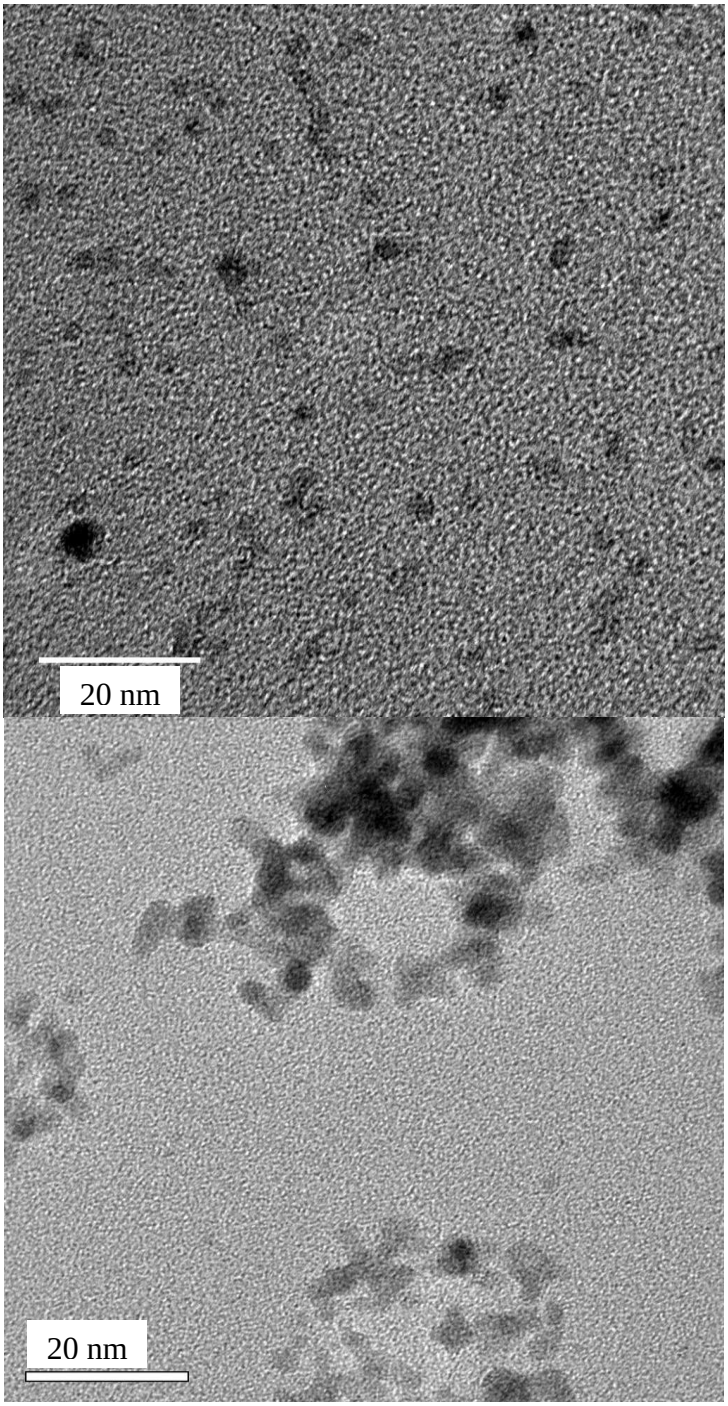


Figure 2.3 TEM images of Pd nanoparticles using Gatan Digital MSC camera [51]

Samples were prepared under the same reaction conditions without the substrate. One hour after the addition of PMHS to a solution of $Pd(OAc)_2/KF_{(aq)}$ in THF, an aliquot was taken

from the reaction mixture and added dropwise to a coated copper grid (carbon film support). The concentration of the sample is about 0.7 mM of the catalyst. Using tweezers, we dispersed the sample on the grid, but in some areas saturation was observed. TEM images of the catalyst at high resolution displayed Pd nanoparticles with an average size between 2 to 4 nm (Figure 2.3). One important finding in this project was the crucial role of the additive KF. When the samples were prepared without KF solution, agglomeration of the Pd-nanoparticles was observed (Figure 2.4). Finally, X-ray energy dispersive spectroscopy (EDS) gave the chemical composition highlighting the presence of K, Si, O and Pd. The spectrum collected at different locations confirmed that the darker particles were the Pd-nanoparticles (Figure 2.5).

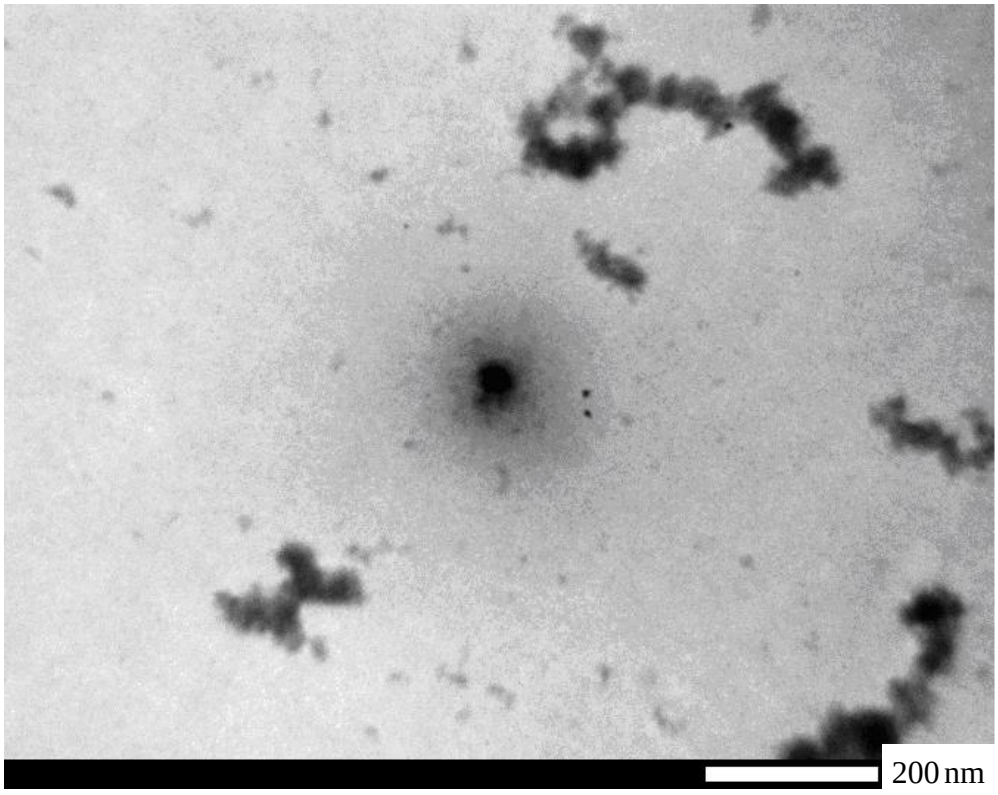


Figure 2.4 TEM image of reaction mixture of $Pd(OAc)_2$/PMHS in THF/H_2O without $KF_{(aq)}$ at X80k magnification

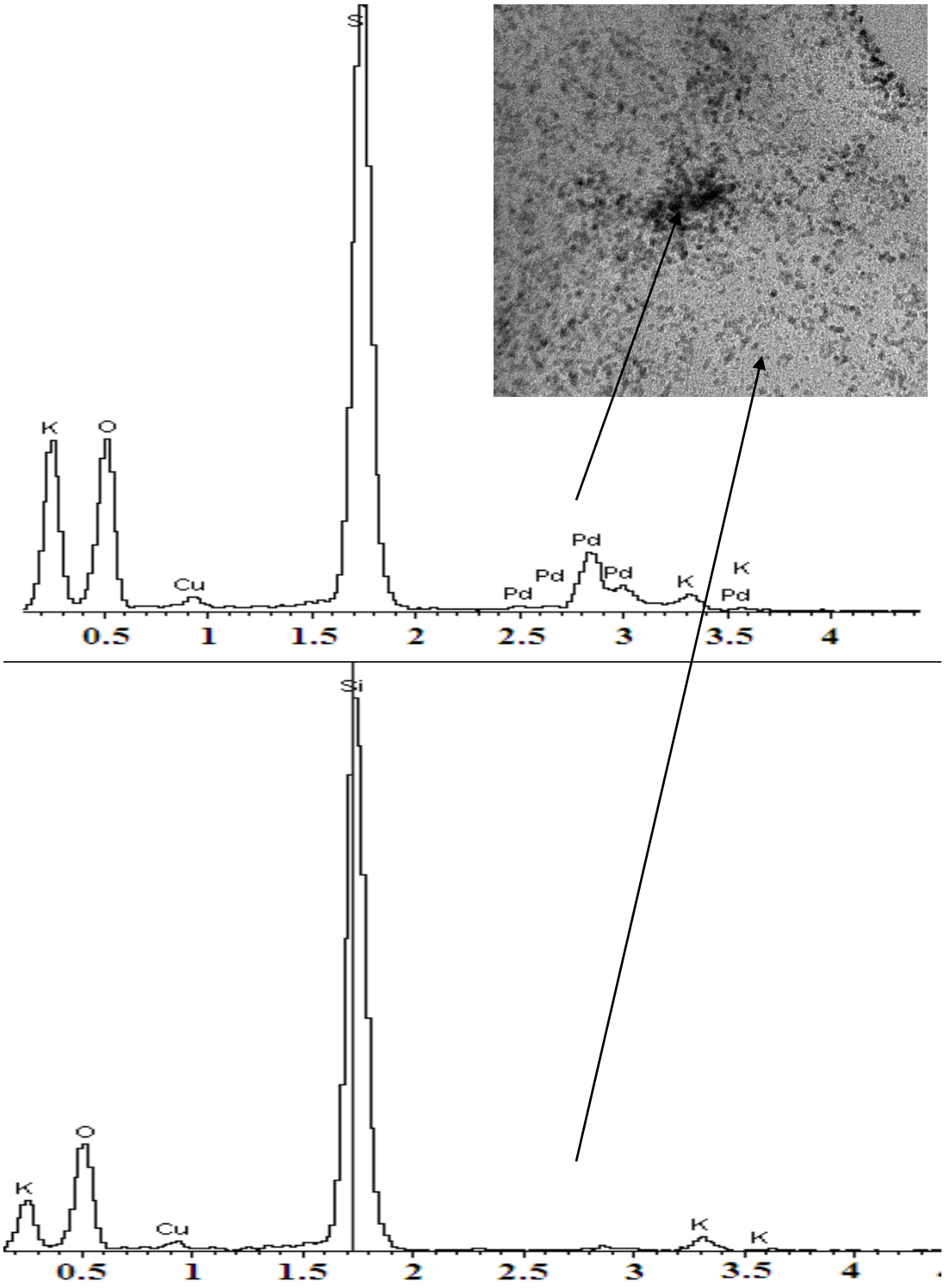
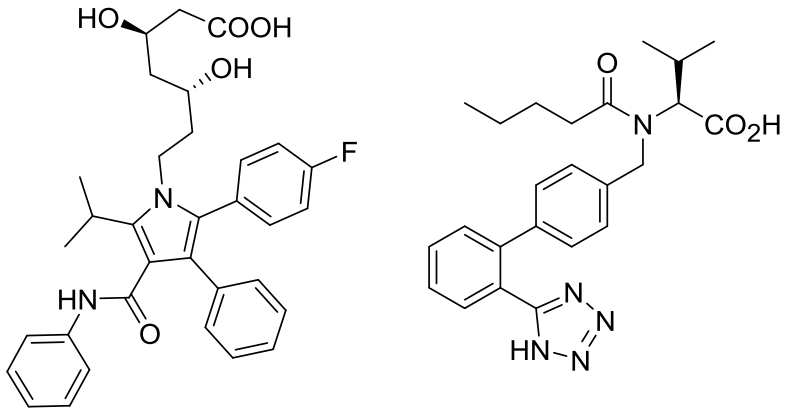


Figure 2.5 EDS of normal sample (spectrum top). EDS of coated film without selecting darker particles (spectrum bottom)

2.4 One-Pot synthesis of amides

2.4.1. Background

Amide bond formation is one of the most useful reactions in organic chemistry, not only for being part of biological active compounds but also for their presence in around 25% of top-selling drugs.[52] Examples of drugs containing amides bonds are Atorvastatin (**65**), the generic name of Lipitor® a cholesterol-lowering drug of Pfizer;[53] and Valsartan (**66**) the generic name of Diovan®, made by Novartis commonly used for high blood pressure and heart failure[54] (Scheme 2.16). An analysis of drug candidates made for leading pharmaceutical companies like GlaxoSmithKline, Pfizer and AstraZeneca indicated that the amide bond formation was employed in the synthesis of 66% of the drug candidates that required acylation reactions.[55]

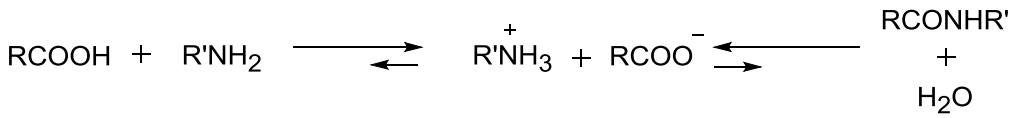


65 Atorvastatin **66** Valsartan

Scheme 2.16 Examples of top selling drugs containing an amide bond

The formation of an amide bond[56] typically involves the reaction of a carboxylic acid and an amine, however when mixing these two functional groups an acid-base reaction occurs to form a stable salt (Scheme 2.17) and the direct condensation can only take place at high

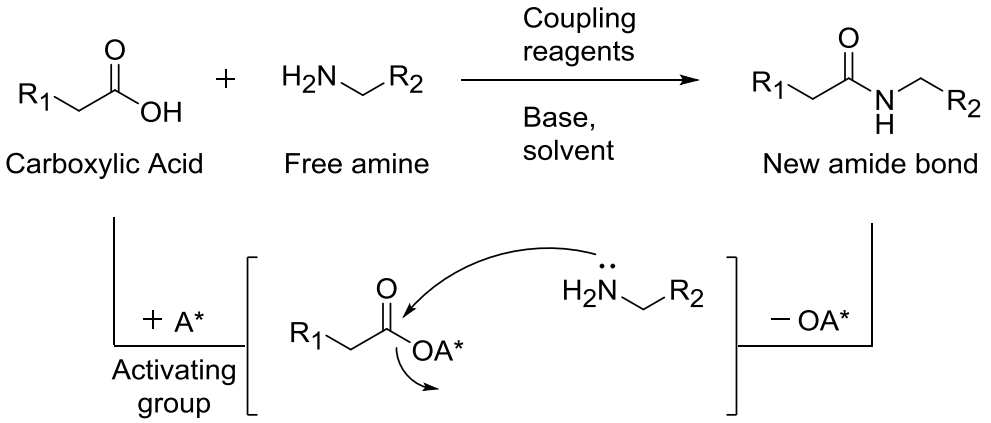
temperatures (160-180 ^{o}C),[57] limiting the reaction only to substrates that can survive such harsh conditions.



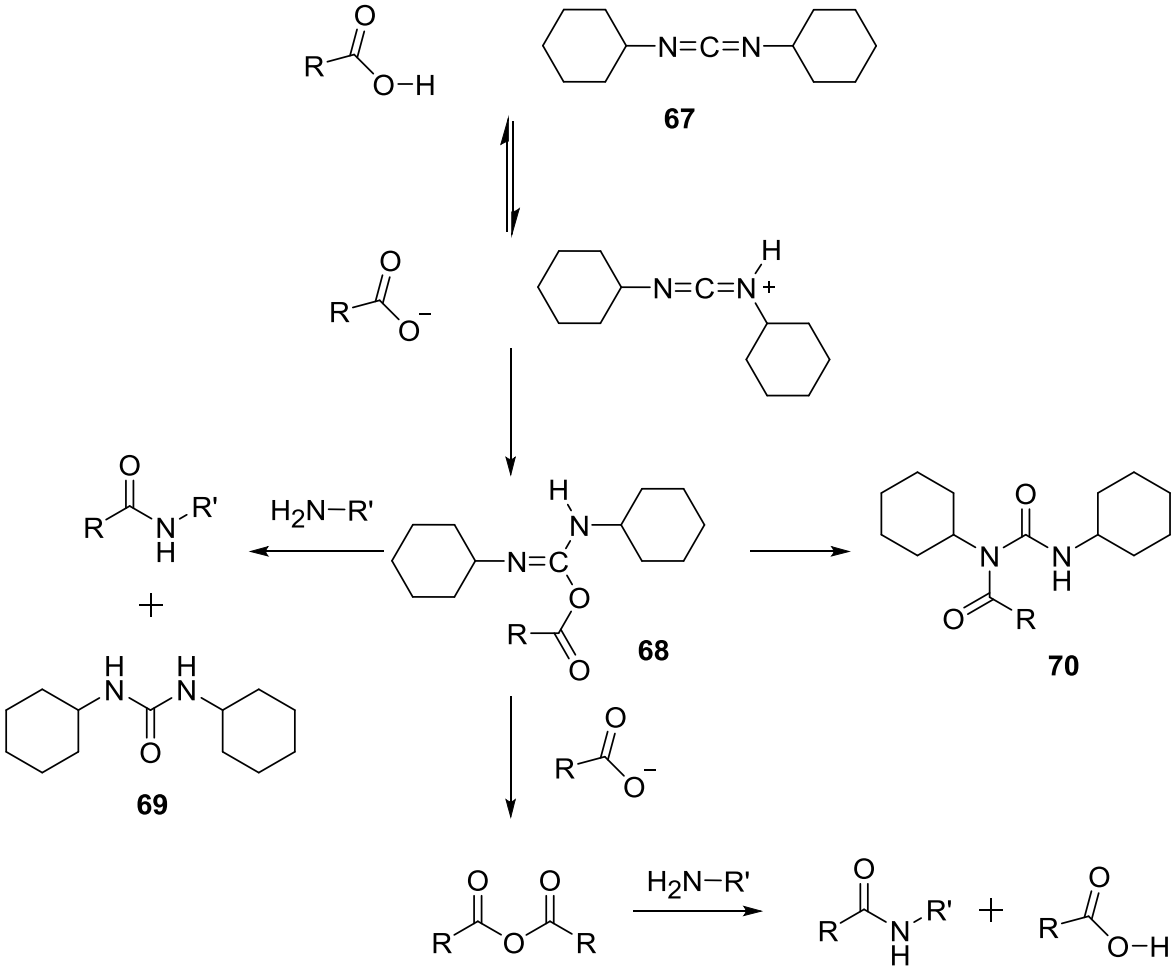
Scheme 2.17 Amide bond formation against thermodynamics

Therefore the activation of the acid with a good leaving group at the acyl carbon of the acid is usually the method used to allow amine bond formation (Scheme 2.18). These reagents included acid halides, aryl azides, anhydrides, mixed anhydrides, active esters, etc.[56,58] Acylation of amines with activated carboxylic acids is the most common method employed in the pharmaceutical industry for the preparation of drug candidates containing amides bonds.[59] Some new promising methods for amide bond formation include the use of boronic acids as coupling reagents,[60] generation of activated carboxylates from functionalized aldehydes using N-heretocyclic carbenes (NHC) as catalyst,[61] and the direct coupling of an alcohol and amine under ruthenium catalysis.[62] This chapter will focus on the acylation of amines with carboxylic acid derivatives.

One of the first coupling reagents employed was dicyclohexylcarbodiimide (DCC)[63] and the mechanism is highlighted on Scheme 2.19. However, the formation of byproducts like DCU (**69**) and N-acyl urea (**70**) as well the requirement of 2 equiv of the acid are some of the disadvantages of this method.

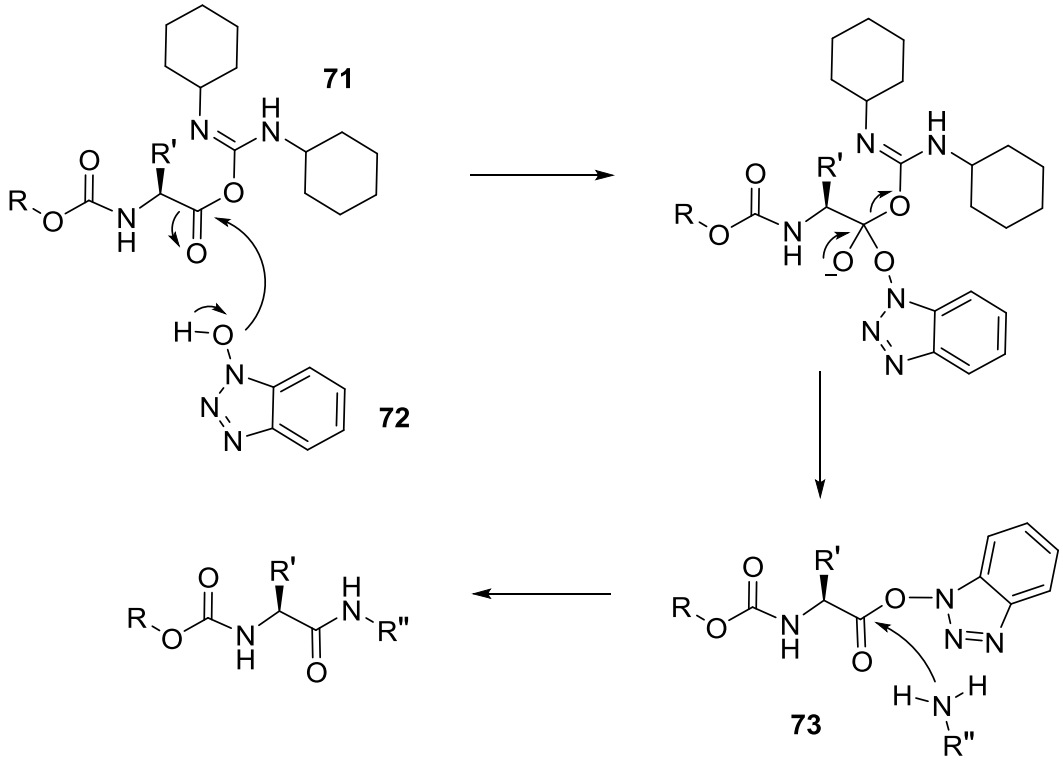


Scheme 2.18 Acid activation and amide bond formation

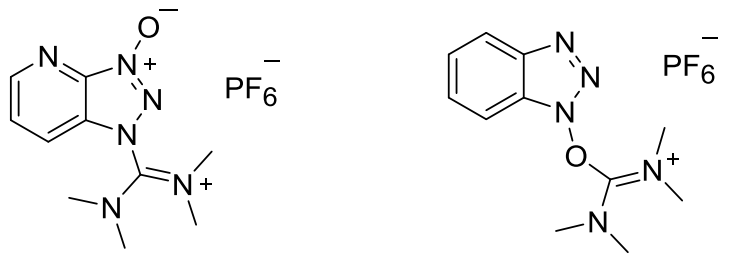


Scheme 2.19 Amide formation reaction using DCC as coupling reagent

Subsequently, the use of additives to increase the yield of the reaction and reduce epimerization was achieved with 1-hydroxy-1*H*-benzotriazole (HOBt),[64] which react with the O-acylurea (**71**) to give a more active ester OBt (**73**). It is believe that this active ester enhances the reactivity via hydrogen bonding with the amine (Scheme 2.20). Therefore several coupling reagents based on 1*H*-benzotriazole salts have being prepared including aminium, phosphonium and immonium salts.[58a] The more reactive salts frequently used are HATU (**74**) and HBTU (**75**), however a critical issue regarding this 1*H*-benzotriazole salts is their potential explosive properties (Scheme 2.21).[65]

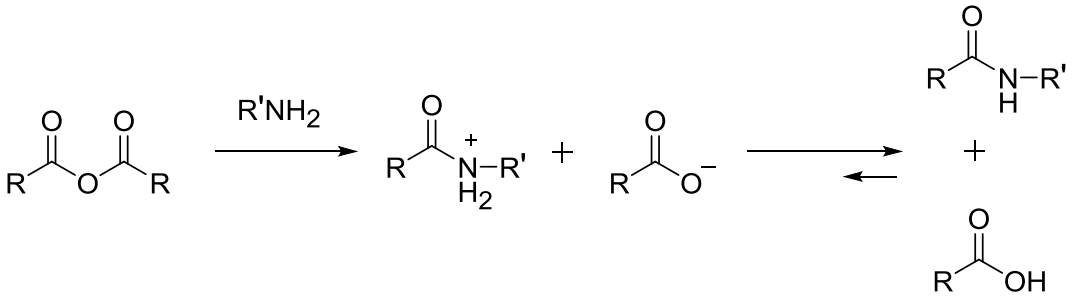


Scheme 2.20 Mechanism of activation by HOBt (**72**) when used as an additive



Scheme 2.21 Most commonly used 1*H*-benzotriazole salts

A similar approach involves starting from the commercially available anhydride or a mixed anhydride, which has de advantage of being less expensive. Direct reaction of the selected anhydride with the amine would form the desired amide. In this scenario the presence of base is not required due to the formation in situ of a carboxylate anion, which is promptly protonated (Scheme 2.22).[56] This method is one of the most efficient and mild, however in terms of atom economy one half of the anhydride is wasted. One way to overcome this waste problem is using mixed anhydrides, where the second carboxylic moiety could come from a cheap reagent and should be easy to couple.[56]

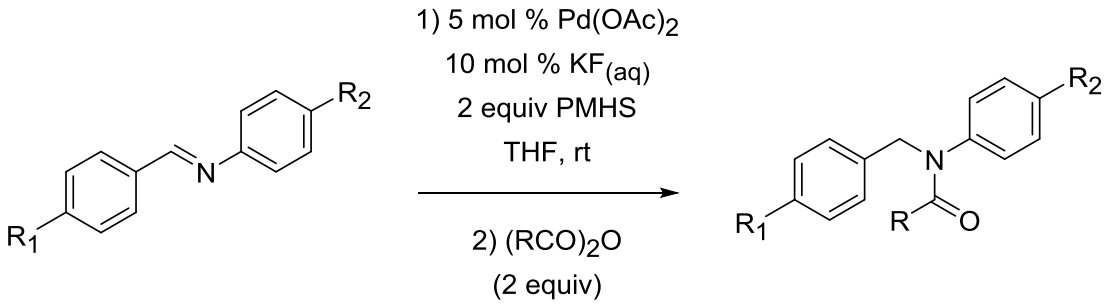


Scheme 2.22 Anhydride coupling with amines

Conversely, most of the preparation methods for amides are expensive, require the used of toxic or corrosive reagents and produce large quantities of hazardous waste. As consequence, in 2007 the ACS GCIPR (American Chemical Society Green Chemistry Institute Pharmaceutical

Round-table) voted as a top research priority, that the amide bond formation reaction was in urgent need for better reagents because most of them avoid the so called atom economy.[66]

Therefore in the search for a more environmentally friendly and non-expensive route on the synthesis of amides, we proposed a one-pot synthesis of tertiary amides starting from aromatic imines. In our synthesis the imines were reduced by our $Pd(OAc)_2$/PMHS/$KF_{(aq)}$ methodology (as explained before in part 2.3 of this chapter) then upon addition of the selected anhydride the tertiary amides were obtained (Scheme 2.23).



Scheme 2.23 General procedure for one-pot synthesis of amides

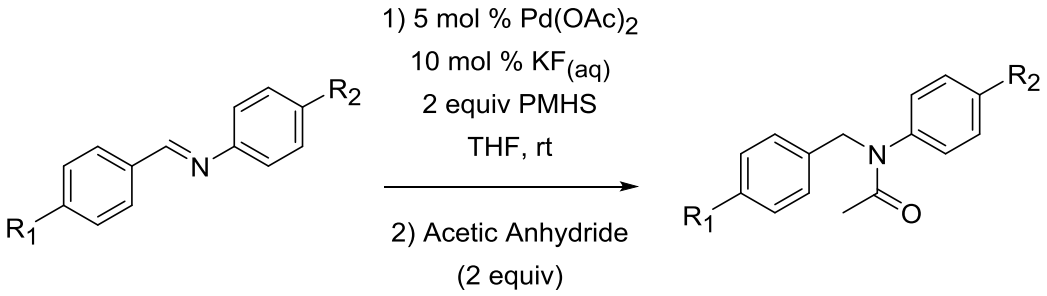
2.4.2 Substrate scope

Searching in the literature for the use of imines as a source for amides synthesis only few examples are reported (Table 2.7). One of the earliest studies employs catalytic quantities of cobalt carbonyl and phase-transfer catalysis conditions for the diacylation of the imines.[67] A second paper reported the oxidation of the imines to amides using m-CPBA and BF_3•OEt_2.[68] The third one, involves the reaction of imines with isocyanates using $TaCl_5$/Zn.[69] A few years ago a group reported the first synthesis of amides via a transition metal catalyzed hydrosilylation of imines.[70] Using an Et_3SiH/Zn system, Ghaffarzadeh *et.al.*[70] published a simple and efficient approach for the direct synthesis of amides using imines and acyl chlorides. As was explained in the introduction part of this chapter (see part 2.1 page 16), metal catalyzed hydrosilylation of

imines to amines has been reported over the years. However using this methodology for the direct conversion of imines to amides was not reported before.

Although our methodology is not the first reported hydrosilylation of imines to amides, it is still the first study using a palladium catalyst with PMHS as silicon based reducing agent. Here we report our preliminary results with the synthesis of 11 tertiary amides using 3 different anhydrides. Reaction times vary between 2 and 5 hours and yields were between 40% up to 87%. The common work up involves quick filtration through a plug with celite/neutral alumina to get rid of Pd and PMHS, followed by concentration of the crude reaction mixture and a final purification by flash column chromatography. Full characterization of each amide is indicated in the appendix.

Table 2.6 Synthesis of amides using acetic anhydride



Entry	R1	R2	Product	Yield	Time
1	OCH_3	H	**76**	86%	2 h
2	CF_3	H	**77**	58%	4 h
3	CN	H	**78**	56%	3 h
4	H	F	**79**	60%	3 h
5	Cl	H	**80**	40%	2 h
6	F	H	**81**	55%	2 h

Furthermore, most of these structures are new as only one was reported (amide **76**) on the previous synthetic method that used a Zn/Et_3SiH system.[70] In this communication a shorter reaction time of 30 min and slightly lower yield in comparison to our methodology was reported. Ghaffarzadeh *et.al.*[70] made a comparison of the efficiency of previous methods reported for the synthesis of amides from imines, highlighting that their method was the simplest and more efficient (Table 2.7). Including our methodology results in the last row of Table 2.7, our synthesis can be classified as well as one of the simplest and efficient. In addition, the Zn/Et_3SiH system[70] maybe faster than our reaction system but they only report methyl or ethyl groups at the acyl position. Our methodology is clearly open to different substituents at the acyl position, because our starting material is an anhydride which tend to be more stable and easier to handle than an acyl chlorides.

Consequently, the second anhydride used in our methodology was benzoic anhydride, commercially available at low cost (100 g/ $32.70)[71] and used without further purification. The two amides prepared (see Table 2.8) were obtained in less than 5 h with high yields. Three more examples in where R_1=Cl/R_2=H, R_1=CN/R_2=H and R_2=F/R_1=H were explored; these reactions were done in 2 hours. However after purification by column, the ^{1}H NMR analysis showed the benzoic acid by-product as a minor contaminant. Improving our purification methods should give us access to these three new amides.

Table 2.7 Different methods for amide synthesis using imines.

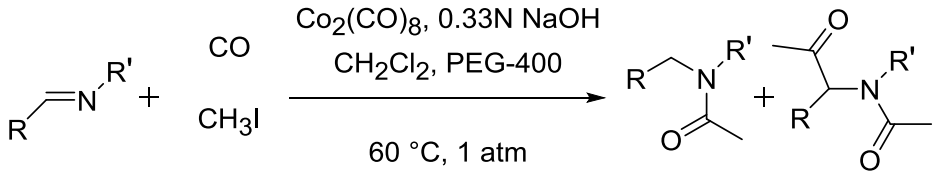
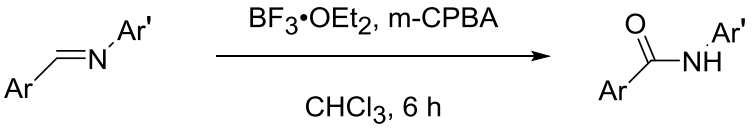
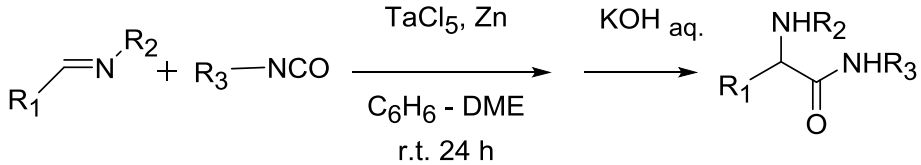
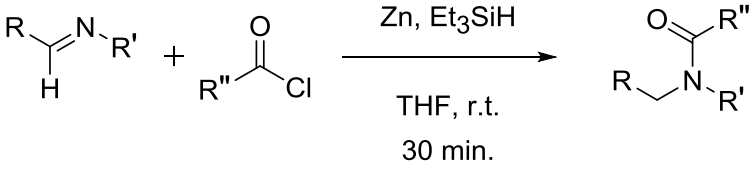
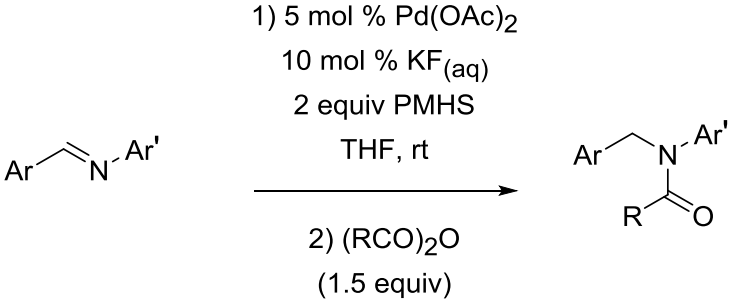
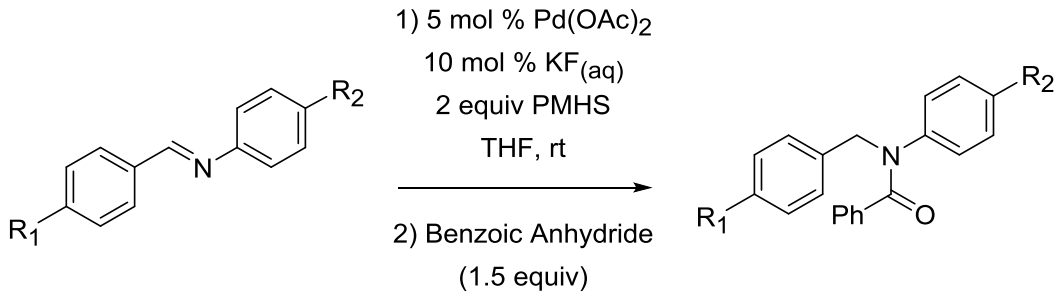
Methodology	Yield (%)	Ref.
	10 – 48%	**[67]**
	39 – 91%	**[68]**
	59 – 93%	**[69]**
	70 – 85%	**[70]**
	40 – 87%	**This work**

Table 2.8 Synthesis of amides using benzoic anhydride

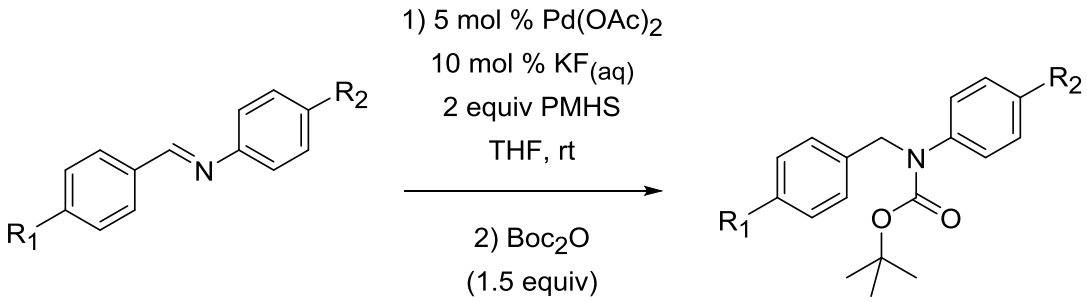


Entry	R_1	R_2	Product	Yield	Time
1	OCH_3	H	**82**	74%	2 h
2	CF_3	H	**83**	73%	5 h

The last anhydride used was di-tert-butyl dicarbonate (Boc anhydride), it is commercially available and was used without further purification. Three new amides were prepared (see Table 2.9) using 1.5 equiv of the Boc anhydride with reaction times between 2 to 5 hours and an average yield 60-70%. As in previous examples these amides are new structures that were obtained after a quick plug filtration and flash column chromatography.

This methodology could be further improved as mentioned before by using mixed anhydrides, as well using several of the substituted imines prepared for us on table 2.3 and scheme 2.9.

Table 2.9 Synthesis of amides using Boc anhydride



Entry	R_1	R_2	Product	Yield	Time
1	OCH_3	H	**84**	60 %	2 h
2	CF_3	H	**85**	70 %	5 h
3	H	F	**86**	60 %	3 h

2.5 Conclusions

A novel green method for the reduction of imines to amines by a $Pd(OAc)_2$/PMHS/KF_{aq} system was developed and studied. The optimization studies confirmed the crucial role of the fluoride ion in activating the PMHS. With only 5 mol % of $Pd(OAc)_2$, 2 equiv of PMHS and 10 mol % of KF reduction times for a variety of imines ranged between 15 min to 2 hours.

This methodology is selective and can operate in the presence of nitriles, ester, fluoride, chloride and p-nitro substituents yielding the target secondary amine in short reaction times at room temperature. With ketone substituents, their reduction was slower than the imine functionality thus reactions of these substrates must be stopped after 30 min to avoid over reduction to the alcohol derivative. Unfortunately double bonds, triple bonds and bromide do not survive under the optimized conditions established for imine reduction. Furthermore,

hydrogenolysis of secondary amines was observed after longer reaction times. These reductions appears to be highly selective for benzyl (and napthyl) protected anilines.

The ^{29}Si NMR and ^{19}F NMR obtained from our catalyst system gave us some insights into the possible mechanism. A hydrosilylation catalytic cycle seems consistent with the data obtained during our NMR studies. However, taking into account the formation of Pd-PMHS nanoparticles gave us a different scenario that probably surface chemistry studies could explain.

Finally, the one-pot preparation of several amides via reduction of imines followed by addition of an electrophile were achieved. These reactions were run at room temperature for 2 to 5 hours and average of 40% to 87% yield. This methodology is the first reported hydrosilylation of imines to amides using a palladium catalyst with PMHS as silicon based reducing agent. Furthermore, such amides can be prepared using mixed anhydrides.

2.6 Experimental section

General Materials and Methods

All starting materials were used as received, unless otherwise stated. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone under nitrogen. Toluene was distilled from calcium hydride. All reactions were carried out in oven-dried or flame dried glassware under nitrogen atmosphere, unless otherwise stated. All reactions were performed with magnetic stirring and monitored by ^{1}H-NMR and GC-FID. Palladium (II) acetate purchased from Strem, anhydrous A.C.S. grade potassium fluoride and polymethylhydrosiloxane (PMHS) purchased from Sigma-Aldrich were used without purification. Flash chromatography was performed with silica gel 60 Å (230-400 mesh) purchased from Silicycle, monitored by thin-

layer chromatography using 0.25-nm pre-coated silical gel aluminum plates and developed with uv and/or phosphomolybdeneic acid. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR, ^{13}C NMR spectra were recorded on Varian spectrometers: Inova-300 (300.11 MHz for ^{1}H and 75.47 MHz for ^{13}C), Varian VXR-500 (499.74 MHz for ^{1}H and 125.67 MHz for ^{13}C), Varian Inova-600 (599.89 MHz for ^{1}H and 150.84 MHz for ^{13}C). ^{29}Si NMR and ^{19}F NMR were recorded on the last two spectrometers. Chemical shifts are reported relative to the residue peaks of solvent $CDCl_3$ (δ 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C), TMS-$CDCl_3$ (δ 0.00 ppm for ^{29}Si) and 0.05% Trifluorotoluene in Benzene- d_6 (-63.73 ppm for ^{19}F). TEM sample were acquired at the Michigan State University Center for Advanced Microscopy using a JEOL 2200FS TEM microscope. Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected.

General procedure for imine formation:

Method A: a dried r.b. flask was charged with the corresponding aromatic aldehyde (1.0 mmol), the appropriate aniline (1.0 mmol) and 10 mL of Ethanol. The reaction mixture was stirred at room temperature and checked by ^{1}H-NMR until the reaction was finished (usually 24 h). Then the solvent was removed under reduced pressure and the pure imine was obtained without an additional purification. For some imines recrystallization was required and it was indicated in each case.

Method B: a dried r.b. flask was charged with the corresponding aromatic aldehyde (1.0 mmol), the appropriate aniline (1.0 mmol) and 50 mL of Toluene. The reaction mixture was refluxed at

120 °C for 24 hours using a Dean Strak apparatus. Then the solvent was evaporated in reduce pressure and the pure imine was obtained.

General procedure for the reduction of aromatic imines to amines:

A dry 25 mL round bottom flask was charged with $Pd(OAc)_2$ (0.05 mmol, 0.011g), an imine (1 mmol) and 5 mL of freshly distilled THF. The flask was sealed, and placed under nitrogen while stirring. Then a $KF_{(aq)}$ solution (0.1 mmol, 0.1 mL) was added via syringe. This aqueous solution was previously degassed using vacuum and liquid N_2. The nitrogen outlet was replaced by a balloon filled with N_2. After 5 min PMHS (2 mmol, 0.12 mL, 1 mmol is equal to 0.06 mL) was added dropwise via syringe. Bubble formation is observed and the mixture turns black. The reaction was stirred for 30 min or until completed conversion as judged by NMR or GC analysis. Three different work-up procedures were employed.

Alternate work up procedure I

The reaction mixture was diluted with ether (5 mL). The organic phase was filtrated through a plug with celite (top layer) and neutral alumina (bottom layer) in a 1 cm diameter column by flushing with EtOAc. The mixture was then dried over $MgSO_4$ and concentrated. Finally the crude was purified by silica gel column chromatography.

Alternate work up procedure II

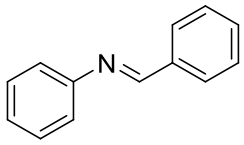
A mixture of 10 mL H_2O/Et_2O (1:1) was added to the crude, the layers were separated, and the aqueous layer back extracted with Et_2O. After stirring the organic phase was separated, dried with $MgSO_4$, filter and concentrated. The crude was dissolved in EtOAc and treated with a 3M

HCl solution. The white solids formed were filtered, washed with EtOAc and dried over night to give the desired secondary amine as hydrochloride salt. The latter was dissolved in a H_2O/methanol (1:1) mixture and $NaHCO_3$ (sat) solution was added. The volume was reduced to the minimum and extracted with EtOAc (4 x 10 mL), dried and concentrated.

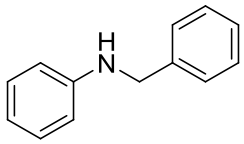
Alternate work up procedure III

Upon addition of 10 mL Et_2O/1M HCl (1:1) and stirring for 10 min, the organic phase was separated and extracted with 1M HCl (3 x 10 mL). Then the aqueous layers were combined, made basic with addition of $KOH_{(s)}$, and extracted with EtOAc (4x 15 mL). Finally, the organic layers were dried, filtered and concentrated.

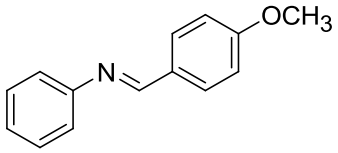
Experimental details and spectroscopic data:



***N*-Phenylbenzylideneamine (40a):** Using the general procedure for imine formation (Method A) a light white solid was obtained after recrystallization from hexanes. Yield: 80%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1 H, CH-imine), 7.94 (m, 2 H, Ar-H), 7.51–7.50 (m, 3 H, Ar-H), 7.45–7.41 (m, 2 H, Ar-H), 7.28–7.24 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 152.1, 136.3, 131.4, 129.2, 128.8, 128.7, 125.9, 120.8. mp = 51 °C. Spectroscopic data were consistent with those previously reported.[72]

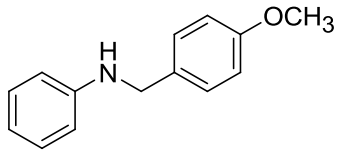


***N*-Phenylbenzylamine (40b):** *N*-Phenylbenzylideneamine (181 mg, 1 mmol) was reduced following the general procedure for imine reduction (2 h reaction time). After work up procedure I, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a yellow oil. Yield: 90%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39–7.33 (m, 4 H, Ar-H), 7.27 (t, *J* = 7.0 Hz, 1 H, Ar-H), 7.18 (t, *J* = 7.0 Hz, 2 H, Ar-H), 6.72 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.68 (d, *J* = 8.5 Hz, 2 H, Ar-H), 4.27 (s, 2 H, Ar-CH_2), 4.07 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 139.4, 129.2, 128.6, 127.5, 127.2, 117.5, 112.8, 48.3. Spectroscopic data were consistent with those previously reported.[72a]

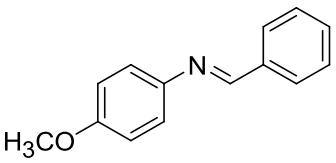


***N*-Phenyl-4-methoxybenzylideneamine (41a):** Using the general procedure for imine formation (Method A) a white solid was obtained after recrystallization from hexanes. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1 H, CH-imine), 7.84 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.38–7.34 (m, 2 H, Ar-H), 7.21–7.16 (m, 3 H, Ar-H), 6.97 (d, *J* = 8.5 Hz, 2 H, Ar-H), 3.86 (s, 3 H, Ar-

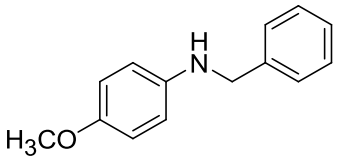
OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 159.7, 152.4, 130.5, 129.3, 129.1, 125.5, 120.9, 114.1, 55.4. mp = 56 °C. Spectroscopic data were consistent with those previously reported.[72]



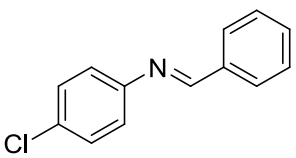
***N*-(4-methoxybenzyl)phenylamine (41b):** *N*-Phenyl-4-methoxybenzylideneamine (211 mg, 1 mmol) was reduced in 30 min, following the general procedure for imine reduction. After work up procedure III, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a light brown oil. Yield: 80%. ^1H-NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 9.0 Hz, 2 H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2 H, Ar-H), 6.90 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.74 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.65 (d, *J* = 9.0 Hz, 2 H, Ar-H), 4.26 (s, 2 H, Ar-CH_2), 4.00 (br s, 1 H, -NH), 3.81 (s, 3 H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 148.2, 131.3, 129.2, 128.7, 117.4, 113.9, 112.7, 55.2, 47.7. Spectroscopic data were consistent with those previously reported.[72a]



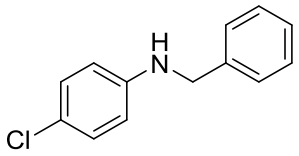
***N*-(4-methoxyphenyl)benzylideneamine (42a):** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1 H, CH-imine), 7.91–7.89 (m, 2 H, Ar-H), 7.48–7.47 (m, 3 H, Ar-H), 7.26 (d, *J* = 6.5 Hz, 2 H, Ar-H), 6.96 (d, *J* = 7.0 Hz, 2 H, Ar-H), 3.86 (s, 3 H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 144.9, 136.4, 130.9, 128.7, 128.5, 122.1, 114.3, 55.4. mp = 70 °C. Spectroscopic data were consistent with those previously reported.[72]



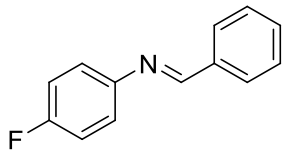
***N*-benzyl-(4-methoxyphenyl)amine (42b):** *N*-(4-Methoxyphenyl)benzylideneamine (211 mg, 1 mmol) was reduced in 30 min, following the general procedure for imine reduction. After work up procedure III, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a yellow oil. Yield: 48%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41–7.35 (m, 4 H, Ar-H), 7.30–7.27 (m, 1 H, Ar-H), 6.81 (d, *J* = 7.0 Hz, 2 H, Ar-H), 6.63 (d, *J* = 7.0 Hz, 2 H, Ar-H), 4.31 (s, 2 H, Ar-CH_2), 3.86 (s, 1 H, -NH), 3.76 (s, 3 H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.0, 142.4, 139.6, 128.6, 127.5, 122.2, 114.8, 114.1, 55.7, 49.2. Spectroscopic data were consistent with those previously reported.[72a]



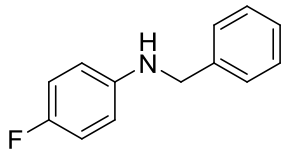
***N*-(4-Chlorophenyl)-benzylideneamine (43a):** Using the general procedure for imine formation (Method A) a light yellow solid was obtained after recrystallization from hexane. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1 H, CH-imine), 7.88–7.86 (m, 2 H, Ar-H), 7.48–7.45 (m, 3 H, Ar-H), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.14 (d, *J* = 7.0 Hz, 2 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 150.5, 135.9, 131.6, 131.4, 129.2, 128.9, 128.8, 122.1. mp = 59 °C. Spectroscopic data were consistent with those previously reported.[72b,73]



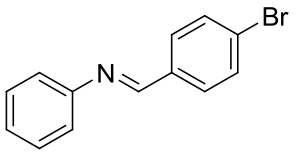
***N*-benzyl-(4-chlorophenyl)amine (43b):** *N*-(4-Chlorophenyl)benzylideneamine (215 mg, 1 mmol) reduced in 1 h, following the general procedure for imine reduction. After work up procedure I, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a light brown oil. Yield: 50%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28–7.26 (d, 2 H, *J* = 2.0 Hz, Ar-H), 7.07–7.03 (td, *J* = 2.0, 6.5 Hz, 4 H, Ar-H), 6.48–6.45 (td, *J* = 2.0, 6.8 Hz, 3 H, Ar-H), 4.56 (s, 2 H, Ar-CH_2), 4.08 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 138.9, 129.1, 128.7, 127.5, 127.4, 122.1, 113.8, 48.3. Spectroscopic data were consistent with those previously reported.[74]



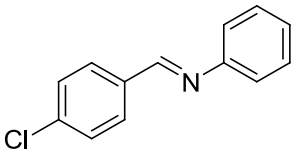
***N*-(4-Fluorophenyl)-benzylideneamine (44a):** Using the general procedure for imine formation (Method A) a brown solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1 H, CH-imine), 7.88–7.86 (m, 2 H, Ar-H), 7.47-7.44 (m, 3 H, Ar-H), 7.19–7.17 (m, 2 H, Ar-H), 7.08–7.04 (m, 2 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 160.1, 148.5, 136.5, 131.4, 128.7, 122.3, 122.2, 115.9, 115.7. mp = 60 °C. Spectroscopic data were consistent with those previously reported.[75]



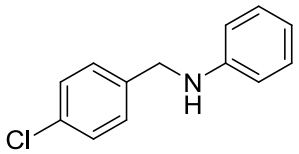
***N*-benzyl-(4-Fluorophenyl)amine (44b):** *N*-(4-Fluorophenyl)-benzylideneamine (199 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure II, the crude material was purified by column chromatography (7:3 hexanes/EtOAc) which afforded the amine as a brown oil. Yield: 69%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.39 (m, 4 H, Ar-H), 7.35–7.32 (m, 1 H, Ar-H), 6.95–6.90 (m, 2 H, Ar-H), 6.62–6.59 (m, 2 H, Ar-H), 4.33 (s, 2 H, Ar-CH_2), 3.96 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 144.4, 139.2, 128.6, 127.4, 115.7, 115.4, 113.6, 48.8. Spectroscopic data were consistent with those previously reported.[74]



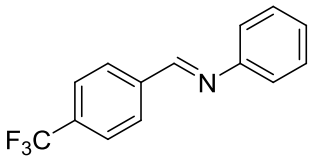
***N*-phenyl-4-bromobenzylideneamine (45a):** Using the general procedure for imine formation (Method A) a white solid was obtained. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1 H, CH-imine), 7.80 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.63 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.42 (t, *J* = 8.5 Hz, 2 H, Ar-H), 7.28–7.22 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 151.6, 135.1, 132.0, 130.1, 129.1, 126.2, 125.8, 120.8. mp = 73 °C. Spectroscopic data were consistent with those previously reported.[72b,73]



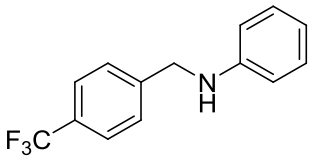
***N*-phenyl-4-chlorobenzylideneamine (46a):** Using the general procedure for imine formation (Method A) a light yellow solid was obtained. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1 H, CH-imine), 7.88 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.48 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.43 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.29–7.27 (m, 1 H, Ar-H), 7.24 (d, *J* = 8.5 Hz, 2 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 151.6, 137.3, 134.7, 129.9, 129.1, 129.0, 126.1, 120.8. mp = 62 °C. Spectroscopic data were consistent with those previously reported.[72]



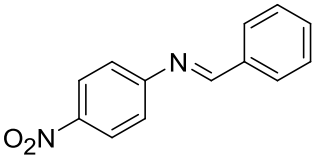
***N*-(4-chlorobenzyl)phenylamine (46b):** *N*-Phenyl-4-chlorobenzylideneamine (215 mg, 1 mmol) was reduced in 2 h, following the general procedure for imine reduction. After work up procedure I, the crude material was purified by column chromatography (7:3 hexanes/EtOAc) which afforded the amine as a brown oil. Yield: 55%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.18–7.13 (m, 4 H, Ar-H), 6.75–6.59 (m, 3 H, Ar-H), 6.61 (d, *J* = 8.0 Hz, 2 H, Ar-H), 4.29 (s, 2 H, Ar-CH_2), 4.05 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 138.0, 131.6, 129.3, 128.8, 128.7, 117.7, 112.8, 47.5. Spectroscopic data were consistent with those previously reported.[72a]



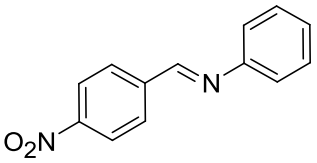
***N*-Phenyl-4-trifluoromethylbenzylideneamine (47a):** Using the general procedure for imine formation (Method A) a white solid was obtained. Yield: 99%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.54 (s, 1 H, CH-imine), 8.05 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.76 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.46–7.43 (m, 2 H, Ar-H), 7.31–7.26 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 151.3, 139.2, 132.0, 129.2, 128.9, 126.5, 125.7 (q, J_{C-F} = 3.8 Hz), 120.8. mp = 79 °C. Spectroscopic data were consistent with those previously reported.[46a,76]



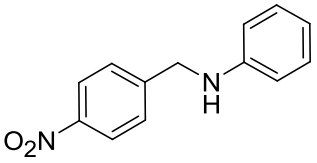
***N*-(4-trifluoromethylbenzyl)phenylamine (47b):** *N*-Phenyl-4-trifluoromethylbenzy- idene amine (252 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction After work up procedure III, the amine was obtained as a light brown oil. Yield: 90%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.47 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.15 (td, *J* = 7.5, 1.0 Hz, 2 H, Ar-H), 6.72 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.59 (dt, *J* = 9.0, 1.0 Hz, 2 H, Ar-H), 4.39 (s, 2 H, Ar-CH_2), 4.00 (br s, 1 H, -NH) ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 143.7, 129.3, 127.4, 125.5 (q, $J_{C–F}$ = 3.8 Hz), 117.9, 112.8, 47.7. Spectroscopic data were consistent with those previously reported.[77]



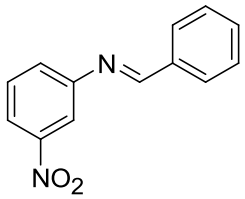
***N*-(4-nitrophenyl)-benzylideneamine (48a):** Using the general procedure for imine formation (Method B) a yellow solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1 H, CH-imine), 8.30 (d, *J* = 9.5 Hz, 2 H, Ar-H), 7.96–7.94 (m, 2 H, Ar-H), 7.58–7.54 (m, 3 H, Ar-H), 7.27 (d, *J* = 9 Hz, 2 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 157.9, 146.0, 135.4, 132.4, 129.2, 128.9, 125.0, 121.2. mp = 138 °C. Spectroscopic data were consistent with those previously reported.[78]



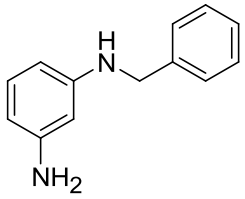
***N*-phenyl-4-nitrobenzylideneamine (49a):** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 87%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1 H, CH-imine), 8.36 (d, *J* = 8.5 Hz, 2 H, Ar-H), 8.11 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.46 (t, *J* = 8 Hz, 2 H, Ar-H), 7.34–7.27 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 150.9, 141.6, 129.4, 129.3, 127.0, 124.0, 120.9, 105.0. mp = 89 °C. Spectroscopic data were consistent with those previously reported.[79]



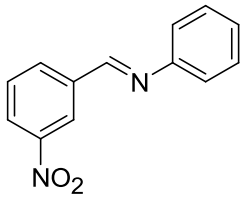
***N*-(4-nitrobenzyl)phenylamine (49b):** *N*-Phenyl-4-nitrobenzylideneamine (226 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a brown oil. Yield: 33%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.55 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2 H, Ar-H), 6.76 (t, *J* = 8.4 Hz, 1 H, Ar-H), 6.60 (d, *J* = 8.5 Hz, 2 H, Ar-H), 4.49 (s, 2 H, Ar-CH_2), 4.25 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4, 147.2, 129.3, 129.2, 127.6, 123.8, 118.1, 112.8, 47.5. Spectroscopic data were consistent with those previously reported.[80]



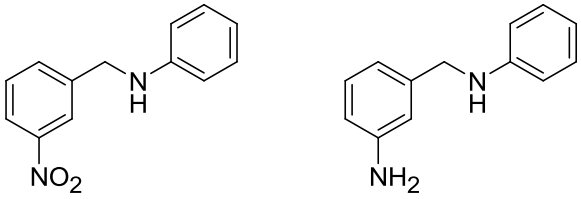
***N*-(3-nitrophenyl)-benzylideneamine (50a):** Using the general procedure for imine formation (Method A) a white-yellow solid was obtained. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.47 (s, 1 H, CH-imine), 8.07 (td, *J* = 2.0, 7.5 Hz, 1 H, Ar-H), 8.22 (t, *J* = 2.0 Hz, 1 H, Ar-H), 7.91 (dd, *J* = 2.0, 6.5 Hz, 2 H, Ar-H), 7.55–7.47 (m, 5 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 153.1, 148.9, 135.4, 132.1, 129.8, 129.1, 128.9, 127.5, 120.4, 115.3. mp = 70 °C. Spectroscopic data were consistent with those previously reported.[78c]



***N*-benzyl-(3-aminophenyl)amine (50b):** *N*-(3-Nitrophenyl)-benzylideneamine (226 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the amine was obtained as a light brown oil. Yield: 52%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.39–7.34 (m, 5 H, Ar-H), 6.98 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.15–6.09 (m, 2 H, Ar-H), 6.00–5.99 (m, 1 H, Ar-H), 4.31 (s, 2 H, Ar-CH_2), 3.60 (br s, 3 H, -NH, -NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.0, 147.5, 140.0, 130.1, 128.6, 127.5, 127.1, 105.1, 104.0, 99.4, 48.2. Spectroscopic data were consistent with those previously reported.[81]

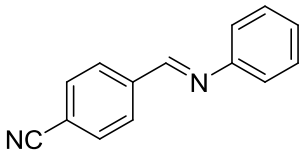


***N*-phenyl-3-nitrobenzylideneamine (51a):** Using the general procedure for imine formation (Method A) a brown solid was obtained. Yield: 91%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.80 (s, 1 H, CH-imine), 8.59 (s, 1 H, Ar-H), 8.38 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.30 (d, *J* = 7.8 Hz, 1 H, Ar-H), 7.71 (t, *J* = 8.1 Hz, 1 H, Ar-H), 7.48 (t, *J* = 7.8 Hz, 2 H, Ar-H), 7.36–7.29 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1, 150.8, 148.7, 137.8, 134.0, 129.7, 129.2, 126.8, 125.5, 123.4, 120.9. mp = 64 °C. Spectroscopic data were consistent with those previously reported.[82]

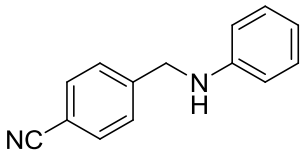


***N*-(3-nitrobenzyl)phenylamine (51b) and *N*-(3-aminobenzyl)phenylamine (51c):** *N*-Phenyl-3-nitrobenzylideneamine (226 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the crude material was purified by column chromatography (4:1 hexanes/EtOAc) which afforded the amines as orange oils. Compound **12b** was obtained as a mixture 1:1 with **12c** Yield: 84% of crude material. **12b**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1 H, Ar-H), 8.14 (dd, *J* = 2.5, 8.5 Hz, 1 H, Ar-H), 7.74 (dt, *J* = 1.0, 7.5 Hz, 1 H, Ar-H), 7.52 (t, *J* = 8 Hz, 1 H, Ar-H), 7.21–7.17 (m, 2 H, Ar-H), 6.77 (dt, *J* = 1.0, 7.5 Hz, 1 H,

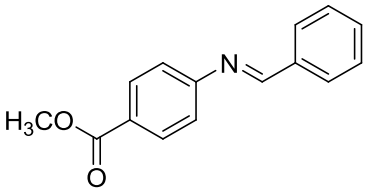
Ar-H), 6.75–6.61 (m, 2 H, Ar-H), 4.48 (s, 2 H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.1, 141.8, 133.2, 129.5, 129.4, 129.3, 122.3, 122.1, 118.3, 113.1, 47.6. Spectroscopic data were consistent with those previously reported.[12a] **12c**: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.16 (t, *J* = 10 Hz, 2 H, Ar-H), 7.10 (t, *J* = 10 Hz, 1 H, Ar-H), 6.72 (m, 3 H, Ar-H), 6.63 (d, *J* = 7.5 Hz, 2 H, Ar-H), 6.58 (d, *J* = 7.5 Hz, 1 H, Ar-H), 4.22 (s, 2 H, Ar-CH_2), 3.90 (br s, 1 H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.6, 140.5, 129.5, 129.2, 117.8, 117.7, 114.1, 114.0, 113.0, 53.5, 48.5. Spectroscopic data were consistent with those previously reported.[8]



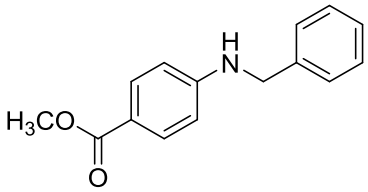
***N*-phenyl-4-nitrilebenzylideneamine (52a):** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 90%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1 H, CH-imine), 8.03 (d, *J* = 6.5 Hz, 2 H, Ar-H), 7.78 (d, *J* = 7.5, 2 H, Ar-H), 7.44 (t, *J* = 8.0 Hz, 2 H, Ar-H), 7.32–7.25 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 151.0, 139.9, 132.5, 129.2, 129.1, 126.8, 120.9, 118.4, 114.4. mp = 87 °C. Spectroscopic data were consistent with those previously reported.[75b,83]



***N*-(4-nitrilebenzyl)phenylamine (52b):** *N*-Phenyl-4-nitrilebenzylideneamine (206 mg, 1 mmol) was reduced in 2 h, following the general procedure for imine reduction. After work up procedure I, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a light yellow oil. Yield: 72%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.51 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.20 (t, *J* = 7.5 Hz, 2 H, Ar-H), 6.77 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.61 (d, *J* = 8.0 Hz, 2 H, Ar-H), 4.41 (s, 2 H, Ar-CH_2), 4.30 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 145.3, 132.4, 129.3, 127.6, 118.8, 118.1, 112.8, 110.9, 47.9. Spectroscopic data were consistent with those previously reported.[84]

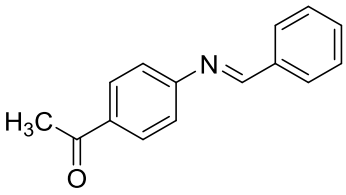


Methyl 4-(benzylideneamino)benzoate (53a): Using the general procedure for imine formation (Method B) a white solid was obtained. Yield: 89%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1 H, CH-imine), 8.06 (dt, *J* = 2.0, 8.5 Hz, 2 H, Ar-H), 7.89 (dt, *J* = 2.0, 6.5 Hz, 2 H, Ar-H), 7.51–7.45 (m, 3 H, Ar-H), 7.19 (dt, *J* = 2.0, 9.0 Hz, 2 H, Ar-H), 3.90 (s, 2 H, $ArCOOCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.7, 161.6, 156.2, 131.8, 130.8, 129.0, 128.9, 128.8, 127.3, 120.6, 52.0. mp = 104 °C. Spectroscopic data were consistent with those previously reported.[85]



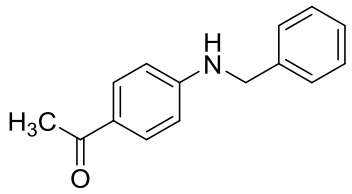
Methyl 4-(benzylamino)benzoate (53b): Methyl 4-(benzylideneamino)benzoate (239 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the amine was obtained as a light yellow solid. Yield: 92%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 2.0, 6.8 Hz, 2 H, Ar-H), 7.37–7.36 (m, 4 H, Ar-H), 7.32 (m, 1 H, Ar-H), 6.61 (dd, *J* = 2.0, 7.0 Hz, 2 H, Ar-H), 4.40 (s, 2 H, Ar-CH_2), 3.85 (s, 3 H, Ar-$COOCH_3$), 3.82 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ =167.3, 151.8, 138.4, 131.6, 128.7, 127.5, 127.4, 118.6, 111.6, 51.5, 47.6. mp = 125 °C. Spectroscopic data were consistent with those previously reported.[86]

.

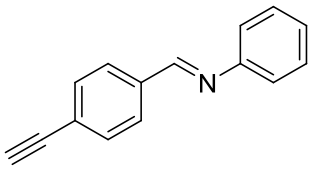


4-(N-benzylideneaminoacetophenone (54a): Using the general procedure for imine formation (Method B) a white solid was obtained. Yield: 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1 H, CH-imine), 7.99 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.90 (dd, *J* = 1.5, 8.0 Hz, 2 H, Ar-H), 7.50–7.48 (m, 3 H, Ar-H), 7.21 (d, *J* = 9.0 Hz, 2 H, Ar-H), 2.60 (s, 2 H, Ar-$COCH_3$). ^{13}C NMR (125 MHz,

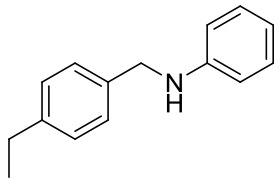
$CDCl_3$): δ 197.2, 161.7, 156,4, 135.7, 134.6, 131.9, 129.7, 129.1, 128.8, 120.8, 26.57. mp = 94 °C. Spectroscopic data were consistent with those previously reported.[87]



4-(*N*-benzylamino)acetophenone (54b): 4-(*N*-Benzylideneaminoacetophenone (223 mg, 1 mmol) was reduced in 30 min, following the general procedure for imine reduction. After work up procedure III, the crude material was purified by column chromatography (4:1 hexanes/EtOAc) which afforded the amine as a light orange solid. Yield: 64%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, *J* = 1.5, 7.5 Hz, 2 H, Ar-H), 7.36–7.32 (m, 4 H, Ar-H), 7.30–7.27 (m, 1 H, Ar-H), 6.58 (dd, *J* = 1.5, 7.0 Hz, 2 H, Ar-H), 4.60 (s, br 1 H, NH), 4.39 (d, *J* = 5.5 Hz, 2 H, Ar-CH_2), 2.47 (s, 3 H, Ar-$COCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.2, 151.9, 138.2, 130.7, 128.8, 127.5, 127.3, 127.0, 111.6, 47.6, 26.0. mp = 77 °C. Spectroscopic data were consistent with those previously reported.[86b,88]

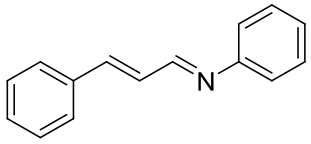


***N*-(4-ethynylbenzylidene)amine (55b):** Using the general procedure for imine formation (Method A) a yellow solid was obtained. Yield: 99%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.46 (s, 1 H, CH-imine), 7.88 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.60 (d, *J* = 8.0, 2 H, Ar-H), 7.42 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.27–7.22 (m, 3 H, Ar-H), 3.23 (s, 1 H, C≡CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 151.1, 136.3, 132.5, 129.2, 128.6, 126.2, 124.9, 120.8, 83.2, 79.4. mp = 67 °C. Spectroscopic data were consistent with those previously reported.[89]

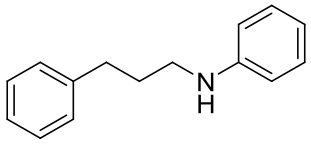


***N*-(4-ethylbenzyl)phenylamine (55c):** *N*-(4-Ethynylbenzylidene)amine (205 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction After work up procedure III, the crude material was purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amine as a orange oil. Yield: 23%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.24–7.18 (m, 4 H, Ar-H), 7.14 (d, *J* = 2.0 Hz, 1 H, Ar-H), 6.74 (td, *J* = 1.0, 6.0 Hz, 1 H, Ar-H), 6.67 (dd, *J* = 1.0, 8.5 Hz, 2 H, Ar-H), 4.31 (s, 2 H, Ar-CH_2N), 4.00 (br s, 1 H, -NH), 2.69 (q, *J* = 7.5 Hz, 2 H, Ar-**CH_2**CH_3), 1.26 (t, *J* = 7.5 Hz, 3 H, Ar-CH_2**CH_3**). ^{13}C NMR (125 MHz,

$CDCl_3$): δ 143.3, 138.0, 129.2, 128.1, 127.6, 127.5, 117.5, 112.8, 48.1, 28.5, 15.6. Spectroscopic data were consistent with those previously reported.[90]

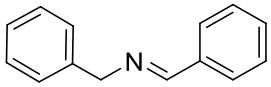


***N*-1, 3-diphenyl-(E)-2-propenimine (56a):** Using the general procedure for imine formation (Method A) an orange solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 6.5 Hz, 1 H, CH-imine), 7.58 (d, *J* = 7.5 Hz, 2 H, CH=CH), 7.43–7.40 (m, 5 H, Ar-H), 7.30–7.18 (m, 5 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 151.7, 143.9, 135.5, 129.5, 129.1, 128.8, 128.5, 127.4, 126.1, 120.8. mp = 102 °C. Spectroscopic data were consistent with those previously reported.[91]

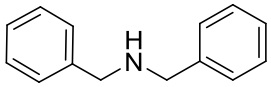


***N*-1-[(E)-3-phenyl-2-propenyl]phenylamine (56b):** *N*-1,3-Diphenyl-(*E*)-2-propenimine (207 mg, 1 mmol) was reduced in 15 min, following the general procedure for imine reduction. After work up procedure III, the amine was obtained as a brown oil. Yield: 67%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2 H, Ar-H), 7.27–7.16 (m, 5 H, Ar-H), 6.72–6.69 (m, 1 H, Ar-H), 6.59 (d, *J* = 8.5 Hz, 2 H, Ar-H), 3.64 (s, 1 H, -NH), 3.17 (t, *J* = 7.5 Hz, 2 H, -N-CH_2), 2.75 (t, *J* = 7.5

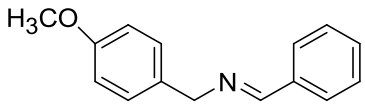
Hz, 2 H, Ar-CH_2), 2.01-1.94 (m, 2 H, -CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 141.6, 129.2, 128.4, 126.0, 117.1, 115.0, 112.7, 43.3, 33.3, 31.0. Spectroscopic data were consistent with those previously reported.[92]



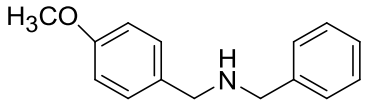
***N*-benzylbenzylideneamine (57a):** Using the general procedure for imine formation (Method A) a yellow oil was obtained. Yield: 92%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1 H, CH-imine), 7.83–7.81 (m, 2 H, Ar-H), 7.47–7.44 (m, 3 H, Ar-H), 7.39-7.37 (m, 4 H, Ar-H), 7.31–7.28 (m, 1 H, Ar-H), 4.87 (s, 2 H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 139.1, 130.7, 128.6, 128.5, 128.3, 128.0, 127.0, 65.0. Spectroscopic data were consistent with those previously reported.[93]



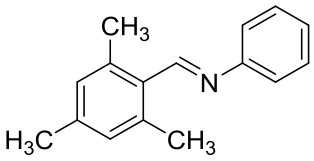
Dibenzylamine (57b): *N*-Benzylbenzylideneamine (195 mg, 1 mmol) was reduced in 2 h, following the general procedure for imine reduction. After work up procedure I, the amine was obtained as a yellow oil. Yield: 76%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.35 (m, 8 H, Ar-H), 7.31–7.28 (m, 2 H, Ar-H), 3.85 (s, 4 H, Ar-CH_2), 1.80 (br s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.2 (2C), 128.4 (2C), 128.1 (2C), 126.9 (2C), 53.1 (2C). Spectroscopic data were consistent with those previously reported.[94]



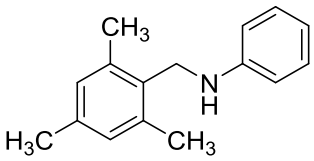
***N*-(4-methoxybenzyl)-benzylideneamine (58a):** Using the general procedure for imine formation (Method A) a yellow oil was obtained. Yield: 75%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.41 (s, 1 H, CH-imine), 7.85–7.84 (m, 2 H, Ar-H), 7.47–7.46 (m, 3 H, Ar-H), 7.33 (d, *J* = 8.3 Hz, 2 H, Ar-H), 6.95 (d, *J* = 8.5 Hz, 2 H, Ar-H), 4.83 (s, 2 H, Ar-CH_2), 3.83 (s, 3 H, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 158.6, 136.1, 131.2, 130.5, 129.1, 128.4, 128.1, 113.7, 64.2, 55.1. Spectroscopic data were consistent with those previously reported.[95]



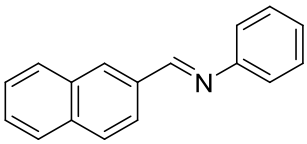
***N*-(4-methoxybenzyl)benzylamine (58b):** *N*-(4-Methoxybenzyl)-benzylideneamine (225 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the amine was obtained as a brown oil. Yield: 90%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.22 (m, 4 H, Ar-H), 7.13 (t, *J* = 8.5 Hz, 3 H, Ar-H), 6.76 (d, *J* = 7.0 Hz, 2 H, Ar-H), 3.67 (br s, 7 H, CH_2NCH_2, Ar-OCH_3), 1.40 (s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 139.8, 131.9, 129.2, 128.3, 128.1, 126.8, 113.7, 55.0, 52.7, 52.2. Spectroscopic data were consistent with those previously reported.[96]



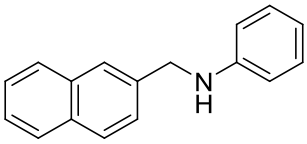
***N*-Phenyl-2,4,6-trimethylbenzylideneamine (59a):** Using the general procedure for imine formation (Method A) a light yellow solid was obtained. Yield: 100%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.80 (s, 1 H, CH-imine), 7.46–7.42 (m, 2 H, Ar-H), 7.27–7.23 (m, 1 H, Ar-H), 7.21–7.18 (m, 2 H, Ar-H), 6.95 (s, 2 H, Ar-H), 2.56 (s, 6 H, Ar-CH_3), 2.34 (s, 3 H, Ar-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 153.1, 139.8, 138.6, 130.5, 129.7, 129.1, 125.5, 120.7, 21.2, 21.0. mp = 50 °C. Spectroscopic data were consistent with those previously reported.[97]



***N*-(2,4,6-trimethylbenzyl)phenylamine (59b)**: *N*-Phenyl-2,4,6-trimethylbenzyl ideneamine (223 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the amine was obtained as a orange oil. Yield: 93%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37–7.33 (m, 2 H, Ar-H), 7.03 (s, 2 H, Ar-H), 6.86 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.79 (d, *J* = 7.5 Hz, 2 H, Ar-H), 4.32 (s, 2 H, Ar-CH_2), 3.4 (s, 1 H, -NH), 2.48 (s, 6 H, Ar-CH_3), 2.42 (s, 3 H, Ar-CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 137.4, 137.2, 132.1, 129.2, 129.0, 117.1, 112.3, 42.2, 20.8, 19.3. Spectroscopic data were consistent with those previously reported.[98]

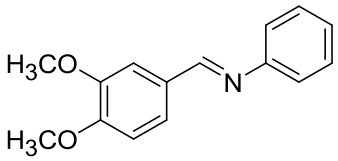


N-phenyl-1-napthylideneamine (60a): Using the general procedure for imine formation (Method A) a white solid was obtained. Yield: 97%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1 H, CH-imine), 8.22 (s, 1 H, Ar-H), 8.19 (d, *J* = 8.5 Hz, 1 H, Ar-H), 7.95 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.90 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.60–7.54 (m, 2 H, Ar-H), 7.46–7.42 (m, 2 H, Ar-H), 7.30–7.27 (m, 3 H, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 152.0, 135.0, 133.9, 133.0, 131.2, 129.1, 128.7, 128.6, 127.9, 127.5, 126.6, 125.9, 123.9, 120.9. mp = 114 °C. Spectroscopic data were consistent with those previously reported.[72b]

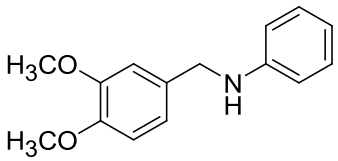


N-(1-napthylmethyl)-phenylamine (60b): *N*-Phenyl-1-napthylideneamine (231 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure I, the crude material was purified by column chromatography (4:1 hexanes/EtOAc) which afforded the amine as a light orange solid. Yield: 78%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.85–7.83 (m, 4 H, Ar-H), 7.52–7.46 (m, 3 H, Ar-H), 7.19 (t, *J* = 7.5 Hz, 2 H, Ar-H), 6.74 (t, *J* = 8.0 Hz, 1 H, Ar-H), 6.70 (t, *J* = 8.0 Hz, 2 H, Ar-H), 4.52 (s, 2 H, Ar-CH_2), 4.15 (s, 1 H, -NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 136.9, 133.5, 132.8, 129.3, 128.4, 127.8, 127.7, 126,1,

125.9, 125.8, 125.7, 117.6, 112.9, 48.7. mp = 60 °C. Spectroscopic data were consistent with those previously reported.[99]



***N*-Phenyl-3,4-dimethoxybenzylideneamine (61a):** Using the general procedure for imine formation (Method A) a brown solid was obtained. Yield: 78%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1 H, CH-imine), 7.60 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.36 (t, *J* = 8.0 Hz, 2 H, Ar-H), 7.29 (dd, *J* = 2.0, 7.0 Hz, 1 H, Ar-H), 7.19–7.17 (m, 3 H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 1 H, Ar-H) 3.94 (s, 3 H, -OCH_3), 3.93 (s, 3 H, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 152.3, 152.0, 149.5, 129.6, 129.1, 125.6, 124.4, 120.8, 110.5, 108.9, 56.1, 56.0. mp = 80 °C. Spectroscopic data were consistent with those previously reported.[100]



N*-(3,4-dimethoxybenzyl)phenylamine(61b):N*-Phenyl-3,4-dimethoxybenzylideneamine (241 mg, 1 mmol) was reduced in 1 h, following the general procedure for imine reduction. After work up procedure III, the amine was obtained as a light brown solid. Yield: 91%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.21 (t, *J* = 7.5 Hz, 2 H, Ar-H), 6.95–6.94 (m, 2 H, Ar-H), 6.86 (d, *J* = 9.0 Hz, 1 H, Ar-H), 6.76 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.68 (d, *J* = 7.5 Hz, 2H), 4.28 (s, 2 H, Ar-CH_2),

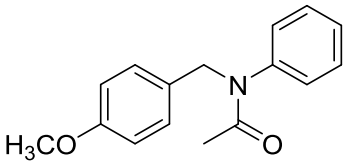
3.90 (s, 3 H, -OCH_3), 3.89 (br s, 4 H, -NH, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.1, 148.3, 148.2, 131.9, 129.2, 119.7, 117.6, 112.9, 111.2, 110.7, 55.9, 55.8, 48.2. mp = 73 °C. Spectroscopic data were consistent with those previously reported.[101]

General procedure for the one-pot synthesis of amides:

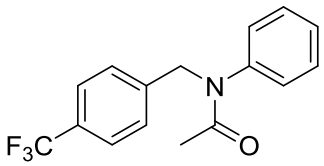
A dry 25 mL round bottom flask was charged with $Pd(OAc)_2$ (0.05 mmol, 0.011g), an imine (1 mmol) and 5 mL of freshly distilled THF. The flask was sealed, and placed under nitrogen while stirring. Then a $KF_{(aq)}$ solution (0.1 mmol, 0.1 mL) was added via syringe. This aqueous solution was previously degassed using vacuum and liquid N_2. The nitrogen outlet was replaced by a balloon filled with N_2. After 5 min PMHS (2 mmol, 0.12 mL, 1 mmol is equal to 0.06 mL) was added dropwise via syringe. Bubble formation is observed and the mixture turns black. The reaction was stirred for 30 min or until completed imine reduction as judged by NMR or GC analysis. Then the appropriated anhydride (between 5 mmol to 2 mmol) was added via syringe.

Once the amide formation was detected by ^1H NMR (between 2 and 5 hours) the reaction mixture was diluted with ether (5 mL). The organic phase was filtrated through a plug with celite (top layer) and neutral alumina (bottom layer) in a 1 cm diameter column by flushing with EtOAc. The mixture was then dried over $MgSO_4$ and concentrated. Finally the crude was purified by silica gel column chromatography.

Experimental details and spectroscopic data:

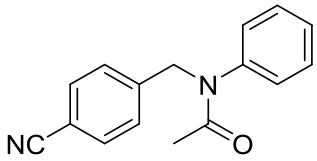


***N*-(4-methoxybenzyl)-*N*-phenylacetamide (76):** *N*-Phenyl-4-methoxybenzylidene- amine (211 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of acetic anhydride (0.19 mL, 2 mmol), amide formation was observed in 2 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amide as a colorless oil. Yield: 86%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.29–7.26 (m, 3H, Ar-H), 7.08 (d, *J* = 8.5 Hz, 2 H, Ar-H), 6.94 (d, *J* = 7.5 Hz, 2 H, Ar-H), 6.75 (d, *J* = 9.0 Hz, 2 H, Ar-H), 4.79 (s, 2 H, Ar-CH_2), 3.72 (s, 3 H, Ar-OCH_3), 1.83 (s, 3 H, CH_3CO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 158.8, 142.7, 130.1, 129.4, 128.3, 127.8, 113.8, 113.6, 55.1, 52.1, 22.7.

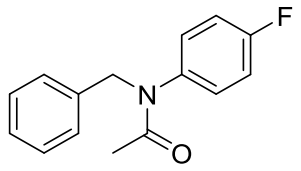


***N*-(4-trifluoromethylbenzyl)- *N*-phenylacetamide (77) :** *N*-Phenyl-4-trifluoromethyl-benzylideneamine (249 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of acetic anhydride (0.19 mL, 2 mmol), amide formation was

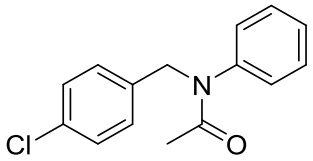
observed in 4 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (8:2 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 58%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.49 (d, J = 8.0 Hz, 2 H, Ar-H), 7.34–7.29 (m, 5 H, Ar-H), 6.98 (d, J = 7.0 Hz, 2 H, Ar-H), 4.91 (s, 2 H, Ar-CH_2), 1.88 (s, 3 H, CH_3CO) ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 146.2, 141.5, 129.7, 128.9, 128.1, 127.9, 125.3 (q, J_{C-F} = 3.0 Hz), 123.0, 52.4, 22.6.



***N*-(4-nitrilebenzyl)-*N*-phenylacetamide (78):** *N*-phenyl-4-nitrilebenzylideneamine (206 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of acetic anhydride (0.19 mL, 2 mmol), amide formation was observed in 3 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (8:2 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 56%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 8.0 Hz, 2 H, Ar-H), 7.34–7.29 (m, 5 H, Ar-H), 6.97 (d, J = 7.5 Hz, 2 H, Ar-H), 4.89 (s, 2 H, Ar-CH_2), 1.87 (s, 3 H, CH_3CO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 142.7, 142.3, 132.1, 129.6, 129.1, 128.1, 127.7, 118.5, 111.0, 52.44, 22.4.

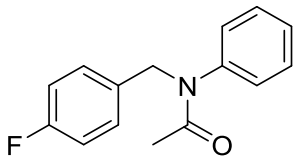


***N*-benzyl-*N*-(4-fluorophenyl)acetamide (79):** *N*-(4-fluorophenyl)-benzylideneamine (199 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of acetic anhydride (0.19 mL, 2 mmol), amide formation was observed in 3 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (7:3 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 60%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.26–7.21 (m, 3 H, Ar-H), 7.16 (d, *J* = 7.5 Hz, 2 H, Ar-H), 6.97 (t, *J* = 8.2 Hz, 2 H, Ar-H), 6.92–6.90 (m, 2 H, Ar-H), 4.84 (s, 2 H, Ar-CH_2), 1.85 (s, 3 H, CH_3CO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 162.6, 137.1, 129.8, 128.6, 128.7, 127.3, 116.3, 116.2, 52.6, 22.5.

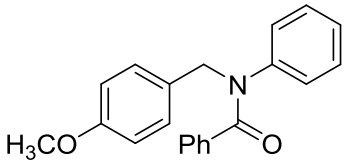


***N*-(4-chlorobenzyl)-*N*-phenylacetamide (80):** *N*-phenyl-4-chlorobenzylideneamine (215 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of acetic anhydride (0.19 mL, 2 mmol), amide formation was observed in 2 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (7:3 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 40%; ^{1}H-NMR (500 MHz, $CDCl_3$): ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36–7.30 (m, 3 H, Ar-H), 7.21 (d, *J* = 8.5 Hz, 2 H, Ar-

H), 7.14–7.08 (m, 2 H, Ar-H), 6.96 (d, J = 7.5 Hz, 2 H, Ar-H), 4.83 (s, 2 H, Ar-CH_2), 1.86 (s, 3 H, CH_3CO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 142.6, 136.0, 133.1, 130.2, 129.6, 128.5, 128.1, 128.0 52.1, 22.8.

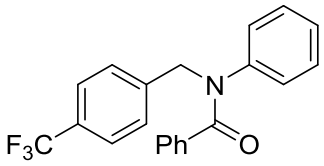


***N*-(4-fluorobenzyl)-*N*-phenylacetamide (81):** *N*-phenyl-4-fluorobenzylideneamine (199 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of acetic anhydride (0.19 mL, 2 mmol), amide formation was observed in 2 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 55%; ^{1}H-NMR (500 MHz, $CDCl_3$): ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.30–7.25 (m, 3 H, Ar-H), 7.15–7.10 (m, 2 H, Ar-H), 6.93–6.86 (m, 4 H, Ar-H), 4.80 (s, 2 H, Ar-CH_2), 1.83 (s, 3 H, CH_3CO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 160.9, 142.4, 133.2, 130.3, 129.4, 127.8, 115.0, 114.8, 51.8, 22.49.

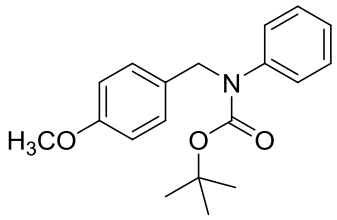


***N*-(4-methoxybenzyl)-*N*-phenylbenzamide (82):** *N*-Phenyl-4-methoxybenzylidene- amine (211 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after

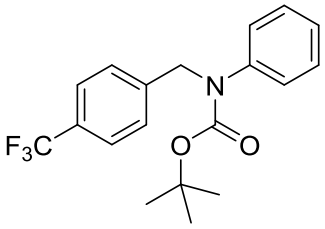
addition of benzoic anhydride (0.34 g, 1.5 mmol), amide formation was observed in 2 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (7:3 hexanes/EtOAc) which afforded the amide as a colorless oil. Yield: 74%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.5 Hz, 2 H, Ar-H), 7.25–7.20 (m, 3H, Ar-H), 7.15–7.06 (m, 5H, Ar-H), 6.91 (d, *J* = 8.0 Hz, 2 H, Ar-H), 6.81 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.09 (s, 2 H, Ar-CH_2), 3.72 (s, 3 H, Ar-OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 158.6, 143.0, 135.7, 133.1, 129.8, 129.6, 128.7, 128.1, 127.7, 127.5, 126.4, 113.6, 54.8, 53.0.



***N*-(4-trifluoromethylbenzyl)-*N*-phenylbenzamide (83):** *N*-Phenyl-4-trifluoromethyl-benzylideneamine (249 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of benzoic anhydride (0.34 g, 1.5 mmol), amide formation was observed in 5 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amide as a colorless oil. Yield: 73%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.50–7.43 (m, 3 H, Ar-H), 7.33 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.25 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.20–7.12 (m, 5 H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.18 (s, 2 H, Ar-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 143.2, 135.4, 133.7, 130.1, 129.9, 129.2, 128.8, 128.6, 128.4, 127.8, 127.5, 126.9, 125.4 (q, J_{C-F} = 3.8 Hz), 53.5.

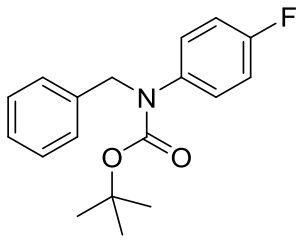


***N*-(4-methoxybenzyl)-*N*-(phenyl) *tert*-butyl carbamate (84):** *N*-Phenyl-4-methoxy benzylideneamine (211 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of Boc anhydride (0.33 g, 1.5 mmol), amide formation was observed in 2 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 60%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.20–7.14 (m, 5H, Ar-H), 6.84 (d, *J* = 8.5 Hz, 2 H, Ar-H), 4.78 (s, 2 H, Ar-CH_2), 3.77 (s, 3 H, Ar-OCH_3), 1.43 (s, 9 H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 154.8, 142.7, 130.1, 128.9, 128.6, 126.8, 125.8, 113.7, 80.3, 55.1, 53.3, 28.3.



***N*-(4-trifluoromethylbenzyl)-*N*-(phenyl) *tert*-butyl carbamate (85):** *N*-Phenyl-4-trifluoromethylbenzylideneamine (249 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of Boc anhydride (0.33 g, 1.5 mmol), amide

formation was observed in 5 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 70% ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.38 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.30 (t, *J* = 8.0 Hz, 2 H, Ar-H), 7.25–7.17 (m, 3 H, Ar-H), 4.90 (s, 2 H, Ar-CH_2), 1.44 (s, 9 H, *t*-Bu) ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 142.7, 129.4, 129.3, 129.2, 128.7, 126.1, 125.3 (q, J_{C-F} = 3.8 Hz), 123.0, 80.8, 53.6, 28.2.



***N*-benzyl-*N*-(4-fluorophenyl) *tert*-butyl carbamate (86):** *N*-(4-fluorophenyl)-benzyl-ideneamine (199 mg, 1 mmol) was reduced following the general procedure for imine reduction. Then after addition of Boc anhydride (0.33 g, 1.5 mmol), amide formation was observed in 3 h. Finally it was isolated using the general work up procedure for amides and purified by column chromatography (9:1 hexanes/EtOAc) which afforded the amide as a yellow oil. Yield: 60%; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.32–7.22 (m, 5 H, Ar-H), 7.07 (br, 2 H, Ar-H), 6.95 (t, *J* = 8.75 Hz, 2 H, Ar-H), 4.80 (s, 2 H, Ar-CH_2), 1.43 (s, 9 H, *t*-Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 159.6, 154.8, 138.3, 128.5, 128.4, 127.2, 115.5, 115.3, 80.8, 54.0, 28.2.

REFERENCES

REFERENCES

(1) (a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753–819. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.

(2) (a) Varma, R. S.; Dahiya, R. *Tetrahedron* **1998**, *54*, 6293–6298. (b) Kazemi, F.; Kiasat, A. R.; Sarvestani, E. *Chin. Chem. Lett.* **2008**, *19*, 1167–1170. (c) Cho, B. T.; Kang, S. K. *Synlett* **2004**, *9*, 1484–1488. (d) Varala, R.; Enugala, R.; Ponnamanemi, V. K.; Adapa, S. R. *Chin. J. Chem.*, **2006**, *24*, 807–810.

(3) Hutchins, R. O.; Hutchins, M. K. *Comprehensive Organic Synthesis;* Pergamon Press: Oxford, 1991; Vol. 8, pp 25–78.

(4) McDowell, J. W.; Billman, J. H. *J. Org. Chem.* **1961**, *26*, 1437–1440.

(5) Botta, M.; De Angelis, F.; Gambacorta, A.; Labbiento, L.; Nicoletti, R. *J. Org. Chem.* **1985**, *50*, 1916–1919.

(6) Haskelberg, L. *J. Am. Chem. Soc.* **1948**, *70*, 2811–2812.

(7) Tokizane, M.; Sato, K.; Sakami, Y.; Imori, Y.; Matsuo, C.; Ohta, T; Ito, Y. *Synthesis* **2010**, *1*, 36–42.

(8) Kumar, K. A.; Sreelekha, T. S.; Shivakumara, K. N.; Prakasha, K. C.; Gowda, D. C. *Synth. Commun.* **2009**, *39*, 1332–1341

(9) Fernandes, A. C.; Romao, C. C. *Tetrahedron Lett.* **2005**, *46*, 8881–8883.

(10) (a) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640–5644. (b) Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103–1107. (c) Hansen, M.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713–715. (d) Chandrasekhar, S.; Reddy, Ch. R.; Ahmed, M. *Synlett* **2000**, *11*, 1655–1657.

(11) Guizzetti, S.; Benaglia, M.; Biaggi, C.; Celentano, G. *Synlett* **2010**, *1*, 134–136. (b) Guizzetti, S.; Benaglia, M.; Rossi, S. *Org. Lett.* **2009**, *11*, 2928–2931.

(12) (a) Chandrasekhar, S.; Reddy, M. V.; Chandraiah, L. *Synth. Commun.* **1999**, *29*, 3981–3987. (b) Enthaler, S. *Catal. Lett.* **2010**, *140*. Online First™, 21 October 2010.

(13) Lopez, R. M.; Fu, G.C. *Tetrahedron* **1997**, *53*, 16349–16354.

(14) Ireland, T.; Fontanet, F.; Tchao, G.-G. *Tetrahedron Lett.* **2004**, *45*, 4383–4387.

(15) Patel, J. P.; Li, A.-H.; Dong, H.; Korlipara, V.; Mulvihill, M. *Tetrahedron Lett.* **2009**, *50*, 5975–5977.

(16) (a) Enthaler, S. *Catal. Lett* **2011**, *141*, 55–61. (b) Enthaler, S. *Chem Cat Chem.* **2010**, *2*, 1411–1415.

(17) (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86. (b) Wang, C.; Pettman, A.; Basca, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

(18) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037–1057.

(19) (a) Maleczka, R. E. Jr.; Rahaim, R. J. Jr.; Teixeira, R. R. *Tetrahedron Lett.* **2002**, *43*, 7087–7090. (b) Rahaim, R. J. Jr.; Maleczka, R. E. Jr. *Tetrahedron Lett.* **2002**, *43*, *8823–8826*.

(20) Rahaim, R. J. Jr.; Maleczka, R. E. Jr. *Org. Lett.* **2011**, *13*, *584–587*.

(21) Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, *40*, 9325–9327.

(22) (a) Chandrasekhar, S.; Reddy, Y. R.; Ramarao, C. *Synthetic Commun.* **1997**, 27, 2251–2254. (b) Bette, V.; Mortreux, A.; Lehmann, C. W.; Carpentier, J.-F. *Chem. Commun.* **2003**, 332–333. (c) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045–4048. (d) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111–4113. (e) Lawrence, N. J.; Bushell, S. M. *Tetrahedron Lett.* **2000**, *41*, 4507–4512. (f) Kobayashi, Y.; Takahisa, E.; Nakano, M.; Watani, K. *Tetrahedron.* **1997**, *53*, 1627–1634.

(23) Fowley, L. A.; Michos, D.; Luo, X.-L.; Crabtree, R. H. *Tetrahedron Lett.* **1993**, *34*, 3075–3078.

(24) Breeden, S. W.; Lawrence, N. J. *Synlett* **1994**, 833–835.

(25) Motoyama, Y.; Mitsui, K.; Ishida, T.; Nagashima, H. *J. Am. Chem. Soc.* **2005**, *127*, 13150–13151.

(26) (a) Maleczka, R. E. Jr.; Lavis, J. M.; Clark, D. H.; Gallagher, W. P. *Org. Lett.* **2000**, *2*, 3655–3658. (b) Gallagher, W. P.; Maleczka, R. E. Jr. *J. Org. Chem.* **2005**, *70*, 841–846.

(27) PMHS was purchased from Aldrich Chemical Company, Inc. (250g bottle/ $32.90).

(28) Sauer, R. O.; Scheiber, W. J.; Brewer, S. D. *J. Am. Chem. Soc.* **1946**, *68*, 962–963.

(29) (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans 1*. **1999**, 3381–3391. (b) Lavis, J. M.; Maleczka, R. E. Jr. *Polymethylhydrosiloxane (PMHS),* In *EROS-Electronic Encyclopedia of Reagents for Organic Synthesis;* Paquette, L. A.; Crich, D.; Fuchs, P. L.; Wipf, P., Eds.; Wiley: New York, 2003, [Online]. (b) SciFinder® search based on publications that used PMHS since 1960. This search was done using Polymethylhydrosiloxane as "research topic", then analized by publication year. This search includes all type of publications. https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf (accessed on 08/26/2015) (c) Mimoun, H.; De Saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158–6166.

(30) (a) Chandrasekhar, S.; Reddy, Ch. R.; Rao, R. J. *Synlett* **2001**, *10*, 1561–1562. (b) Chandrasekhar, S.; Babu, B. N.; Reddy, Ch. R. *Tetrahedron Lett.* **2003**, *44*, 2057–2059. (c) Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, *48*, 3545–3548. (d) Chandrasekhar, S.; Reddy, M. V.; Chandraiah, L. *Synlett* **2000**, *9*, 1351–1353. (e) Mori, A.; Suguro, M. *Synlett* **2001**, *6*, 845–847.

(31) Chandrasekhar, S.; Reddy, Ch. R.; Rao, R. J. *Tetrahedron.* **2001**, *57*, 3435–3438.

(32) Maleczka, R. E. Jr.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 5958–5965.

(33) (a) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9507–9510. (b) Zotto, C. D.; Virieux, D.; Campagne, J.-M. *Synlett* **2009**, *2*, 276–278.

(34) Yadav, J. S.; Reddy, B. V. S.; Shankar, K. S.; Swamy, T. *Tetrahedron Lett.* **2010**, *51*, 46–48.

(35) Gallagher, W. P.; Maleczka, R. E. Jr. *J. Org. Chem.* **2003**, *68*, 6775–6779.

(36) Terstiege, I.; Maleczka, R. E. Jr. *J. Org. Chem.* **1999**, *64*, 342–343.

(37) Lipowitz, J.; Bowman, S. A. *J. Org. Chem.* **1973**, *38*, 162–165.

(38) Blum, J.; Bitan, G.; Marx, S.; Vollhardt, K. P. C. *J. Mol. Catal.* **1991**, *66*, 313–319.

(39) Brinkman, H. R.; Miles, W. H.; Hilborn, M. D.; Smith, M. C. *Synth. Commun.* **1996**, *26*, 973–980.

(40) (a) Rahaim, R. J. Jr. *Application of Palladium Nanoparticles in the Reduction of Organic Functional Groups.* Doctoral Dissertation, Michigan State University 2006. (b) Rahaim, R. J. Jr.; Maleczka, R. E. Jr. *Org. Lett.* **2005**, *7*, 5087–5090.

(41) Rahaim, R. J. Jr.; Maleczka, R. E. Jr. *Synthesis* **2006**, *19*, 3316–3340.

(42) Demmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, 1560−1638.

(43) (a) Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron*. **1983**, *39*, 999−1009. (b) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem Rev*. **1993**, *93*, 1371−1448.

(44) Chauhan, B. P. S.; Rathore, J. S.; Glloxhani, N. *Appl. Organometal. Chem.* **2005**, *19*, 542−550.

(45) Amado Sierra, M. R. I. *PALLADIUM-CATALYZED PMHS REDUCTIONS OF IMINES* Master Thesis, Michigan State University 2011.

(46) (a) Garcia, J. L.; Aleman, J.; Alonso, I.; Parra, A.; Marcos, V.; Aguirre, J. *Chem. Eur. J.* **2007**, *13*, 6179−6195. (b) Yu-Lu, Z.; Xiao-Dong, J.; Rui, L.; Bing, H.; Long-Min, W. *Chin. J. Chem.* **2007**, *25*, 422−425. (c) Neuvonen, K.; Fulop, F.; Neuvonen, H.; Koch, A.; Kleinpeter, E.; Pihlaja, K. *J. Org. Chem.* **2003**, *68*, 2151−2160. (d) Ankersen, M.; Hansen, B. S. *Eur. J. Med. Chem.* **1997**, *32*, 631−635.

(47) Uchida, H.; Kabe, Y.; Yoshino, K.; Kawamanta, A.; Tsumuraya, T.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*¸ 7077−7079.

(48) You, S-L.; Zhao, Z-A.; Kang, Q. *Org. Lett.* **2008**, *10*, 2031−2034.

(49) Baltzly, R.; Buck, J. S. *J. Am. Chem. Soc.* **1943**, *65*, 1984−1992.

(50) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry;* Wiley: New York, 2000: Chapter 1, 4, 5 and 7.

(51) Gatan Image software, version 3.4, was used for microscope operation. High resolution images were taken using Gatan Digital Multi-Scan Camera (MSC)

(52) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*¸ 55−68.

(53) *www.lipitor.com* Pfizer (accessed on 06/10/2015).

(54) *www.pharma.us.novartis.com/product/pi/pdf/diovan.pdf* Novartis Pharmaceutical (accessed on 06/10/2015)

(55) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*¸ 2337−2347.

(56) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*¸ 10827−10852.

(57) Jursic, B. S.; Zdravkovski, Z. *Synth. Commun.* **1993**, *23*¸ 2761−2770.

(58) (a) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*¸ 606–631. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*¸ 471–479. (c) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453–7465.

(59) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*¸ 3451–3479.

(60) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*¸ 4196–4197.

(61) Bode. J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*¸ 13798–13799.

(62) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*¸ 790–792.

(63) Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*¸ 1067–1068.

(64) Koening, W.; Geiger, R. *Chem. Ber.* **1970**, *103*¸ 788–798.

(65) Malow, M.; Wehrstedt, K. D.; Neuenfeld, S. *Tetrahedron Lett.* **2007**, *48*¸ 1233–1235.

(66) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*¸ 411–420.

(67) Vasapollo, G.; Alper, H. *Tetrahedron Lett.* **1988**, *29*¸ 5113–5116.

(68) An, G.; Kim, M.; Kim, J. Y.; Rhee, H. *Tetrahedron Lett.* **2003**, *44*¸ 2183–2186.

(69) Shimizu, H.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*¸ 7593–7595.

(70) (a) Ghaffarzadeh, M.; Joghan, S. S.; Faraji, F. *Tetrahedron Lett.* **2012**, *53*¸ 203–206. (b) Ghaffarzadeh, M.; Heidarifard, S.; Faraji, F.; Joghan, S. S. *Appl. Organometal. Chem.* **2012**, *26*¸ 103–107.

(71) *www.sigmaaldrich.com* Benzoic Anhydride product information on Sigma-Aldrich website. (accessed on 06/10/2015)

(72) (a) Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 5547–5557. (b) Naka, H.; Koseki, D.; Kondo, Y. *Adv. Synth. Catal.* **2008**, *350*, 1901–1906.

(73) Donthiri, R. R.; Patil, R. D.; Adimurthy, S. *Eur. J. Org. Chem.* **2012**, *24*, 4457–4460.

(74) Sreedhar, B.; Surendra Reddy, P.; Keerthi Devi, D. *J. Org. Chem.* **2009**, *74*, 8806–8809.

(75) (a) Sadownik, J. W.; Philp, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 9965–9970. (b) Kumar, A.; Samuelson, A. G. *J. Organomet. Chem.* **2010**, *695*, 338–345.

(76) Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Isihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175–3178.

(77) Zhao, Y.; Foo, S. W.; Suito, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3006–3009.

(78) (a) Xue, Z.; Mazumdar, A.; Hope-Weeks, L. J.; Mayer, M. F. *Tetrahedron Lett.* **2008**, *49*, 4601–4603. (b) Akaba, R.; Sukaragi, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.*, **1985**, *58*, 1186–1195. (c) Naeimi, H.; Sharghi, H.; Salimi, F.; Rabiei, K. *Heteroatom Chem.* **2008**, *19*, 43–47.

(79) Chen, C.-W; Tseng, M.-C.; Hsiao, S.-K.; Chen, W.-H.; Chu, Y.-H. *Org. Biomol. Chem.* **2011**, *9*, 4188–4193.

(80) Zhang, M.; Yang, H.; Zhang, Y.; Zhu, Ch.; Li, W.; Cheng, Y. Hu, H. *Chem. Commun* **2011**, *47*, 6605–6607.

(81) Saha, A.; Ranu, B. *J. Org. Chem.* **2008**, *73*, 6867–6870.

(82) Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2005**, *61*, 11148–11155.

(83) Smith, J. G.; Ho, I. *J. Org. Chem.* **1973**, *38*, 2776–2779.

(84) Sousa, S. C. A.; Fernandes, A. C. *Adv. Synth. Catal.* **2010**, *352*, 2218–2226.

(85) Marshall, R. L.; Muderawan, I. W.; Young, D. J. *J. Chem. Soc., Perkin Trans. 2.* **2000**, 957–962.

(86) (a) Huang, Y.-B; Yang, C.-T.; Yi, J.; Deng, X.-J.; Fu, Y.; Liu, L. *J. Org. Chem.* **2011**, *76*, 800–810. (b) Baelen, G. V.; Maes, B. U. W. *Tetrahedron* **2008**, *64*, 5604–5619.

(87) (a) Wang, J.-R.; Fu, Y.; Zhang, B.-B.; Cui, X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2006**, *47*, 8293–8297. (b) Montgomery, J. A.; Roe, A. *J. Am. Chem. Soc.* **1953**, *75*, 910–912.

(88) Zhang, Y.; Yang, X.; Yao, Q.; Ma, D. *Org. Lett.* **2012**, *14*, 3056–3059.

(89) Karim, S. M. A.; Nomura, R.; Masuda, T. *Polymer Bulletin* **1999**, *43*, 305–310.

(90) Prakash, G. K. S.; Do, C.; Mathew, T.; Olah, G. A. *Catal. Lett.* **2010**, *137*, 111–117.

(91) (a) Haak, E. *Eur. J. Org. Chem.* **2007**, 17, 2815–2824. (b) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K.-I. *J. Org. Chem.* **2001**, *66*, 7051–7054.

(92) Kubiak, R.; Prochnow, I.; Doye, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 2626–2629.

(93) Pérez, J. M.; Cano, R.; Yus, M.; Ramón, D. J. *Eur. J. Org. Chem.* **2012**, *24*, 4548–4554.

(94) Cheng, C.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 11304–11307.

(95) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051.

(96) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. *Chem. Eur. J.* **2011**, *17*, 2587–2591.

(97) (a) Da Silva-Filho, L. C.; Lacerda Jr., V.; Constantino, M. G.; Jóse Da Silva, G. V. *Synthesis* **2008**, *16*, 2527–2536. (b) Grammaticakis. *Bull. Soc. chim. Fr.* **1951**, 965–966.

(98) Miecznikowski, J. R.; Crabtree, R. H. *Polyhedron* **2004**, *23*, 2857–2872.

(99) Cano, R.; Yus, M.; Ramón, D. J. *Tetrahedron Lett.* **2011**, *67*, 8079–8085.

(100) (a) Xu, J.; Zhuang, R.; Bao, L.; Tang, G.; Zhao, Y. *Green Chem.* **2012**, *14*, 2384–2387. (b) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 327–330.

(101) Moreno, I.; Tellitu, I.; Etayo, J.; SanMartín, R.; Domínguez, E. *Tetrahedron* **2001**, *57*, 5403–5411.

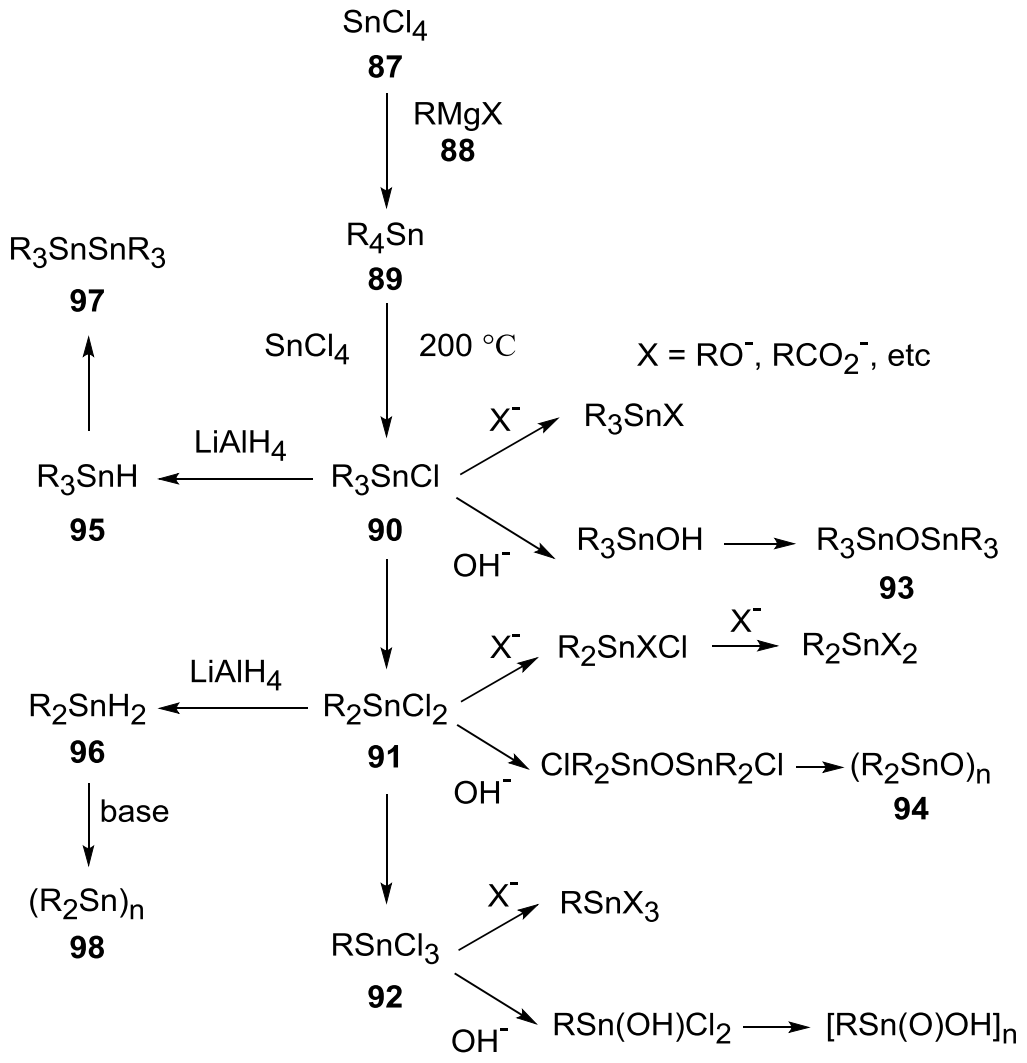
CHAPTER 3: MECHANISTIC STUDIES TOWARDS THE DEVELOPMENT OF ONE-POT ALLYLATION HYDROSTANNATION INVOLVING RECYCLING OF TIN WASTE

3.1 Introduction

Tin (Sn) belongs to the same periodic group as silicon, with four electrons in the outer electronic shell and have common properties like the "β effect" (stabilization of the positive charge on the β-carbon, see page 4), as well as better stability than other organometallics compounds.[1] Although the Sn-C bond is weaker than the C-C or Si-C, it is relatively non-polar so it is stable in the presence of air and moisture. Therefore the reactivity and application of organotin compounds R_nSnX_{4-n} (n=3, 2 or 1) depends on the stability of the Sn-C bond, the lability of the anion X and the impact of hypercoordination (similar to silicon).[2]

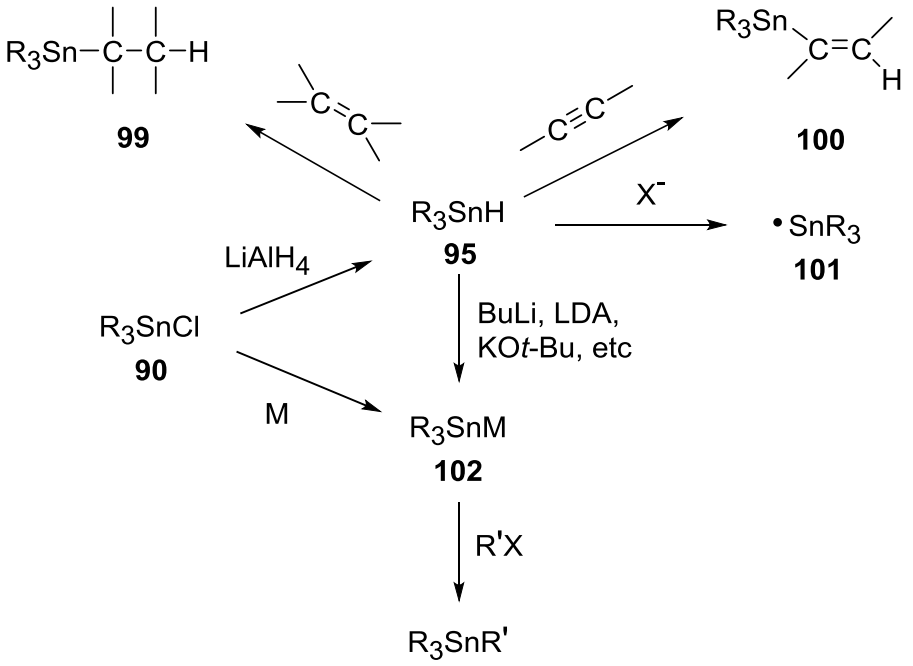
Scheme 3.1 highlights the major routes into the principal groups of organotin (IV) compounds via the nucleophilic alkylation of tin tetrachloride (**87**) with an organometallic reagent, most commonly a Grignard reagent (**88**).[2] This reaction usually gives the tetraorganotin compound (**89**), which then is heated with tin tetrachloride to yield organotin chlorides R_nSnCl_{4-n} (n= 3, 2 or 1). The latter ones are obtained by redistribution of the R and Cl groups via the Kocheshkov reaction.[2] The chlorides can then be replaced by nucleophiles (X = RO^-, RCO_2^-, etc) to give the derivatives R_nSnX_{4-n} by anion exchange. Hydrolysis of the organotin chlorides (**90 and 91**) with OH^- yields the hydroxides, which are often unstable and dehydrate to give the oxides $R_3SnOSnR_3$ (**93**) or $(R_2SnO)_n$ (**94**).[2]

One of the most important reactions is the reduction of the tin halides with a metal hydride such as lithium aluminium hydride, sodium borohydride or by employing our own methodology using PMHS to obtain the corresponding organotin hydride **95**.[3] Later these hydride donors can reduce the tin halides to tin hydrides (hydrostannolysis), which react with alkenes or alkynes (hydrostannation products **99** and **100**) after radical chain reactions, involving $R_3Sn\bullet$ (**101**) radicals to provide another way of forming Sn-C bonds (Scheme 3.2).[2]



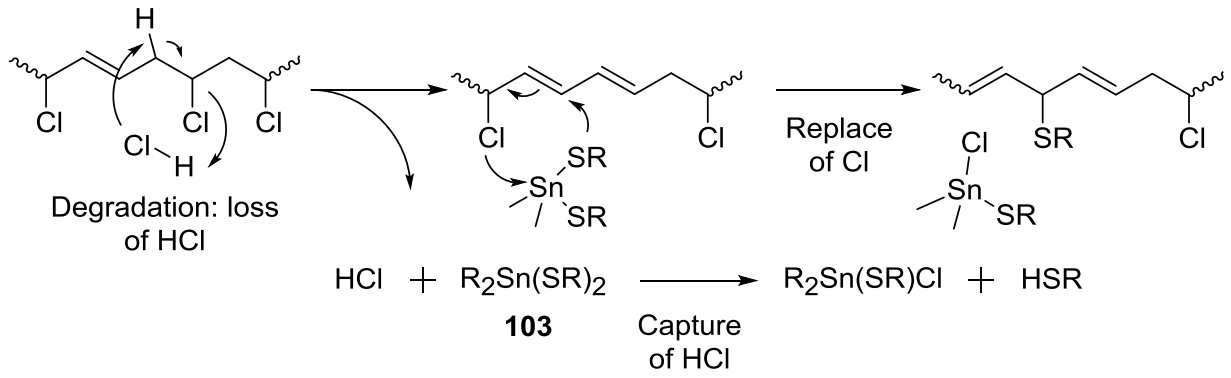
Scheme 3.1 Organotin synthesis based on the Grignard and Kocheshkov reactions

Furthermore, the organotin hydrides (**95**) and dialkyltin dihydrides (**96**) eliminate hydrogen, under the presence of a base, to give distannanes **97** (R_3SnSnR_3) and oligostannanes **98** $(R_2Sn)_n$. Finally the tin halides (**90**) and hydrides (**95**) can react with alkali metals (M) to give R_3SnM (**102**) metallic derivatives, which can react with alkyl halides giving access to another route for Sn-C bond formation (Scheme 3.2).[2]



Scheme 3.2 Organotin synthesis based on reactions of tin hydrides and R_3SnM

One of the major industrial applications of organotin compounds is as stabilizers of polyvinyl chloride (PVC). While working with PVC, high temperatures are required. At these conditions degradation occurs through progressive loss of HCl, leading to a system of conjugated double bonds that results in the loss of physical properties. The organotin stabilizers (**103**) trap the HCl released reducing the degradation and also replace the labile chloride atoms by SR groups that are less prone to undergo elimination (Scheme 3.3).[1,4]



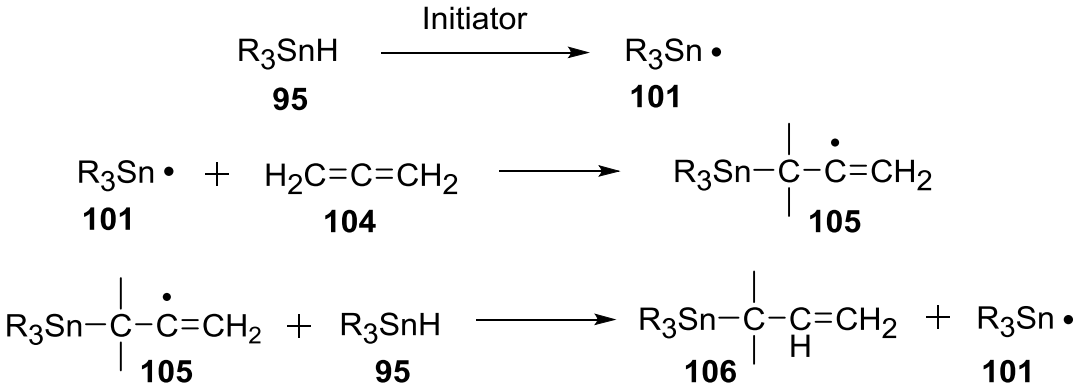
Scheme 3.3 Stabilization of PVC

This chapter is based on the hydrostannation reaction and the addition of allylstannanes to aldehydes. The chemistry involved in the preparation and the reaction mechanism of the addition of allylstannanes will be discussed.

3.2 Allylation reactions with allylstannanes

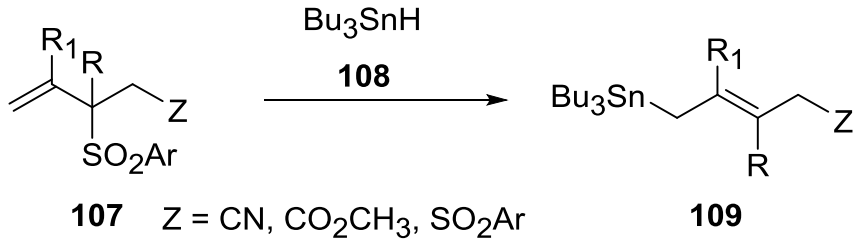
3.2.1 Preparation of allylstannanes

As mention before one of the principal methods to form Sn-C bonds is the hydrostannation of alkenes or alkynes (Scheme 3.2). As a result, allylstannanes **106** can also be prepared by the radical reaction of an organotin hydride with allenes **104** (Scheme 3.4).[5] Another conventional route to allylstannanes is the reaction of an allylmetallic compound with a tin halide or the reaction of stannylmetallic compound with an allyl halide.[6]



Scheme 3.4 Hydrostannations by radical mechanism

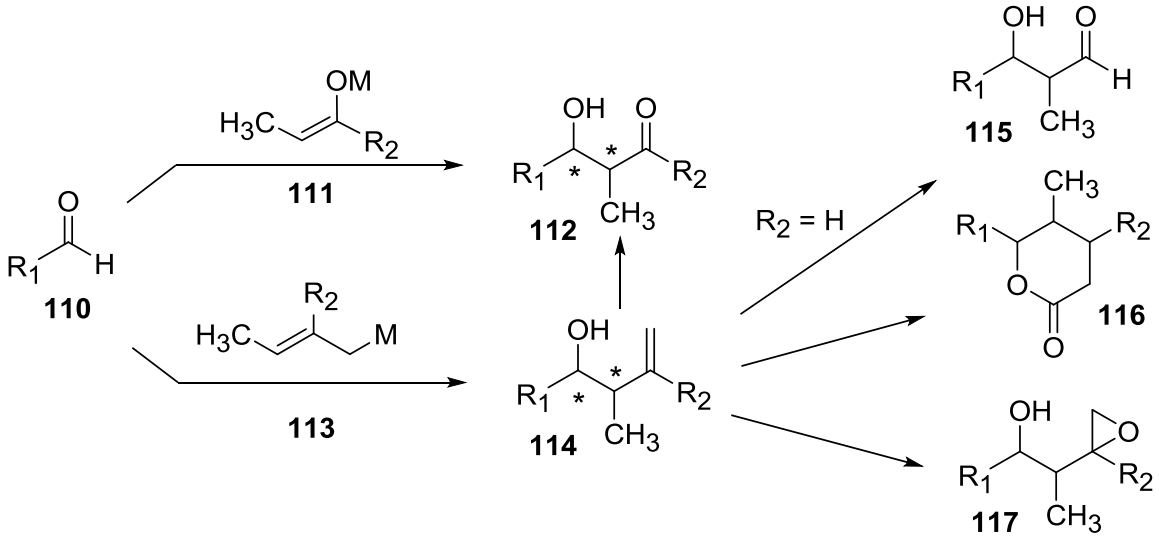
Various allylstannanes bearing functional groups **109** (e.g. CN, CO_2CH_3 or SO_2Ar) can be prepared as well by the radical-chain reaction of allyl sulfones **107** with tributyltin hydride **108** in refluxing benzene (Scheme 3.5)[7]



Scheme 3.5 Allylstannane preparation

Among the extensive uses of allylstannanes in organic and organometallic synthesis,[6] one of the most noteworthy applications is the electrophilic addition reaction with aldehydes.[8] In the quest for a controlled construction of open-chain systems bearing sequences of stereocenters (acyclic stereocontrol), the addition of allylstannanes to aldehydes is one of the most efficient strategies giving control of diastereo- and enantioselectivity.[8] Allylstannane reactions are synthetically analogous to the aldol reaction since the resulting homoallyl alcohol (**114**) can be

converted to the aldol product (**112**). Another advantage of allymetal additions is that the homoallylic alcohol can be converted to hydroxyaldehydes (**115**) via olefin cleavage,[9] or δ-lactones (**116**)[10] via hydroformylation, or can be epoxidized (**117**)[11] to introduce a third chiral center, making this reaction ideal for synthetic planning (Scheme 3.6).[8b] The mechanism of allystannane additions to aldehydes is intriguing and differs with the conditions used, e.g thermal,[12] high pressure,[13] Lewis acid[14] or transition-metal catalyzed.[15]

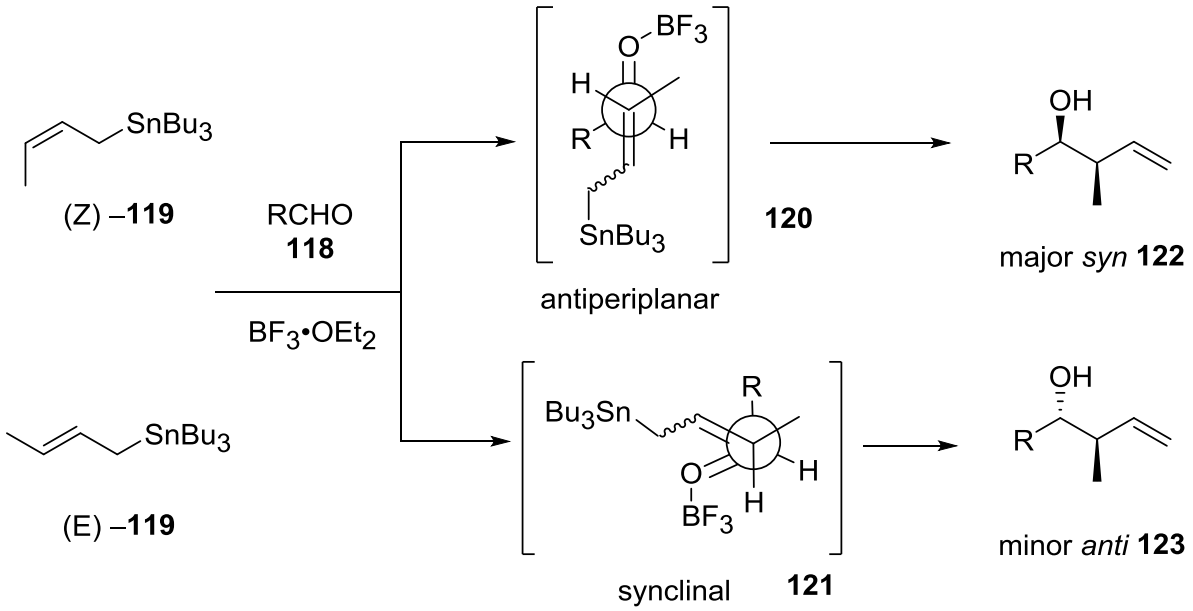


Scheme 3.6 Aldol reaction and allylmetal aldehyde condensation

3.2.2 Reaction with aldehydes in the presence of Lewis acids

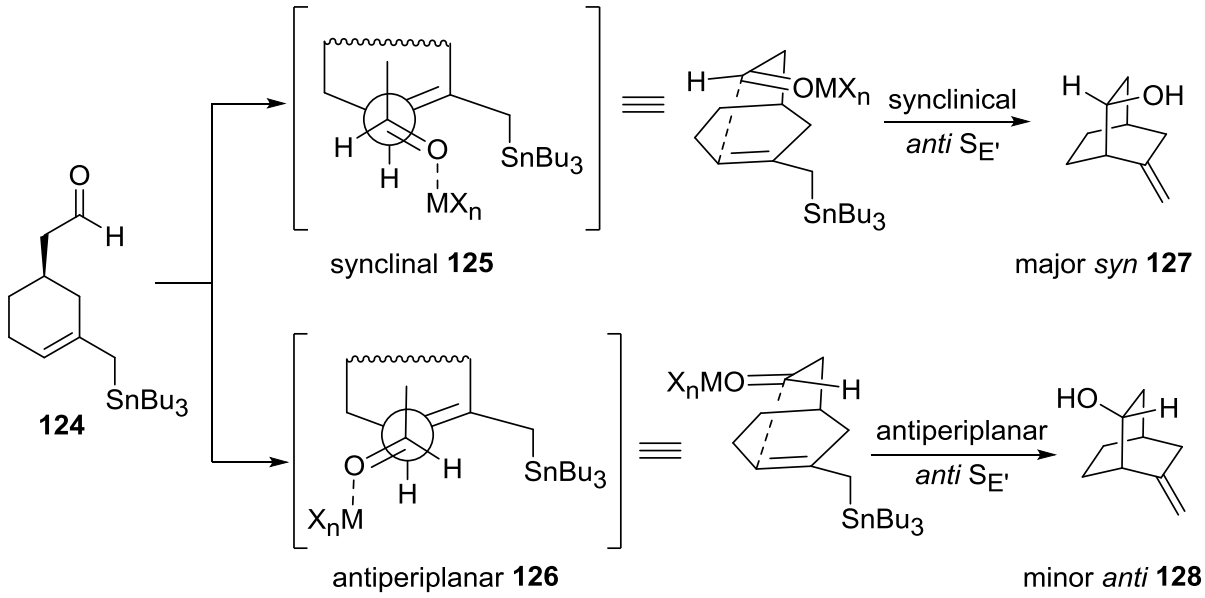
In 1980 Yamamoto report a new approach to the stereoselective addition of crotyl tributylstannanes (E)- and (Z)-(**119**) to aldehydes (**118**) induced by Lewis acids.[16] In this early report it was highlighted that BF_3•OEt_2 promoted addition of **119** to benzaldehyde to afford >90% of the syn homoallylic alcohol **122**. This result was not affected at all by the geometry of the but-2-enyl unit, as either cis or trans reagents gave the same result (Scheme 3.7). Due to this

result they proposed an acyclic transition state in which the Lewis acid coordinates to the oxygen atom preventing the coordination of the Sn atom. Furthermore, they proposed that the antiperiplanar transition state (**120**) is the most stable conformation leading to the syn alcohol.[14b,17]



Scheme 3.7 Stereochemical outcome of allylstannane addition to aldehydes

Once this reaction pathway was proposed a controversy began related to the putative transition state. Denmark[14c,18] studied a model system **124** (Scheme 3.8) to evaluate which transition state is more stable, the synclinal geometry **125** or antiperiplanar **126** as proposed by Yamamoto.[14b,17] Contrary to Yamamoto's results, Denmark's studies indicated that the most stable conformation is the synclinal orientation of the double bond concluding that the alcohol (**127**) is obtained through the synclinal transition state (**125**) via anti-S_E' substitution (Scheme 3.8).



Scheme 3.8 Model studies on the reaction of allylstannanes with aldehydes

It was proposed that the possible origins for this synclinal preference could be due to a Coulombic attraction effect and secondary orbital interactions.[18] The first effect is based on the charge accumulation in the transition state (**129**). Because the reactions are done in non-polar solvents, Denmark argued that charge separation should be energetically disfavored (Scheme 3.10). The second effect is related to the HOMO of the allylmetal and the LUMO of the complexed aldehyde. In the favored synclinal orientation there is an overlap between the oxygen and the metal-bearing carbon (**131**), which is absent on the antiperiplanar orientation (**130**) (Figure 3.1)[18,14a]

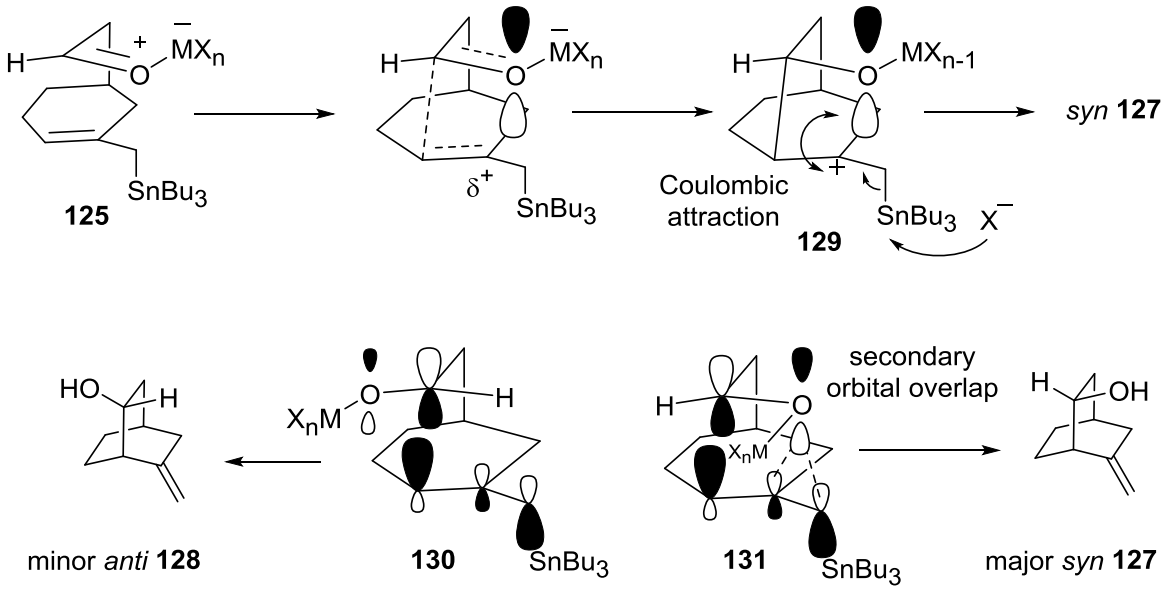
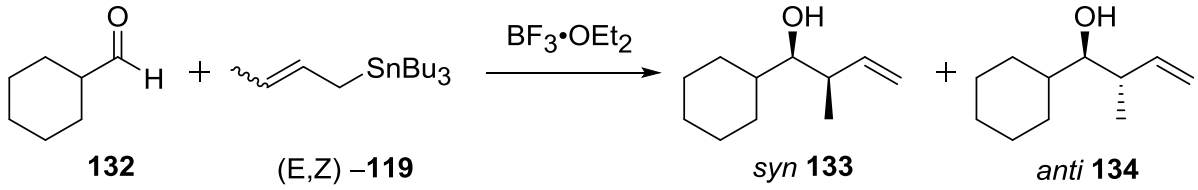


Figure 3.1 Favoring effect towards the synclinal transition state

Finally, studies performed by Keck[14a,19] with enriched mixtures of E and Z-2-butenylstannanes (**119**) and various simply aldehydes like **132** indicate the preference for the synclinal conformation. These reactions were also selective for the syn homoallylic alcohol. Diastereoselectivity was increased when the (E)-stannane was present in a higher percent (Scheme 3.9).



E:Z
90:10
74:26
12:88

syn:anti	
94: 6	(88%)
86:14	(80%)
58:42	(82%)

Scheme 3.9 Crotylstannanes reaction with cyclohexanecarboxaldehyde

The stability of the different conformations leading to the products depends also on the bulkiness of the Lewis acid-aldehyde complex (the steric and electronic effects present within the substituents on the aldehyde and the Lewis acid), the stoichiometry of the reactants, the order of addition and the reaction conditions all may favor either the synclinal transition state or the antiperiplanar arrangement.[6]

3.2.3 Palladium catalyzed reaction of allylstannanes with aldehydes

A different approach for the allylation of aldehydes with allylstannanes is the use of transitions metals complexes.[20] One important study was done by Yamamoto using Pd (II) and Pt (II) complexes to catalyzed the reaction of allystannanes with aldehydes.[15] The findings of this study indicated that the bis-π-allylpalladium complex (**141**) would be the key intermediate for the allylation reaction (Figure 3.2). The reasoning behind the formation of this key intermediate **141** was based on ^{1}H NMR studies and experimental results. When allylstannane (**135**) was mixed with the Pd(II) catalyst (**136**) a π-allylpalladium chloride complex (**138**) was formed along with PPh_3 (**139**) and tributylstannyl chloride (**140**), all detected by ^{1}H NMR. Initially it was assumed that the π-allylpalladium chloride complex (**138**) could be the key intermediate however addition of benzaldehyde to **138** or to the mixture of **138** with PPh_3 and Bu_3SnCl did not produce the homoallylic alcohol. Conversely, when allylstannane (**135**) was added to the mixture of benzaldehyde with **138** (or the mixture including PPh_3 and Bu_3SnCl) the allylation reaction took place quickly. This proved that the bis-π-allylpalladium complex (**141**) formed was the key intermediate and the one able to react directly with benzaldehyde (Figure 3.2). Conversely, when the addition of benzaldehyde to **141** was monitored by ^{1}H NMR the

signals of the bis-π-allylpalladium complex disappeared, suggesting that **141** rearranges in the presence of the benzaldehyde to afford a π-allyl(alkoxy)palladium complex (**142**), which would be the actual species reacting with the aldehyde.[15]

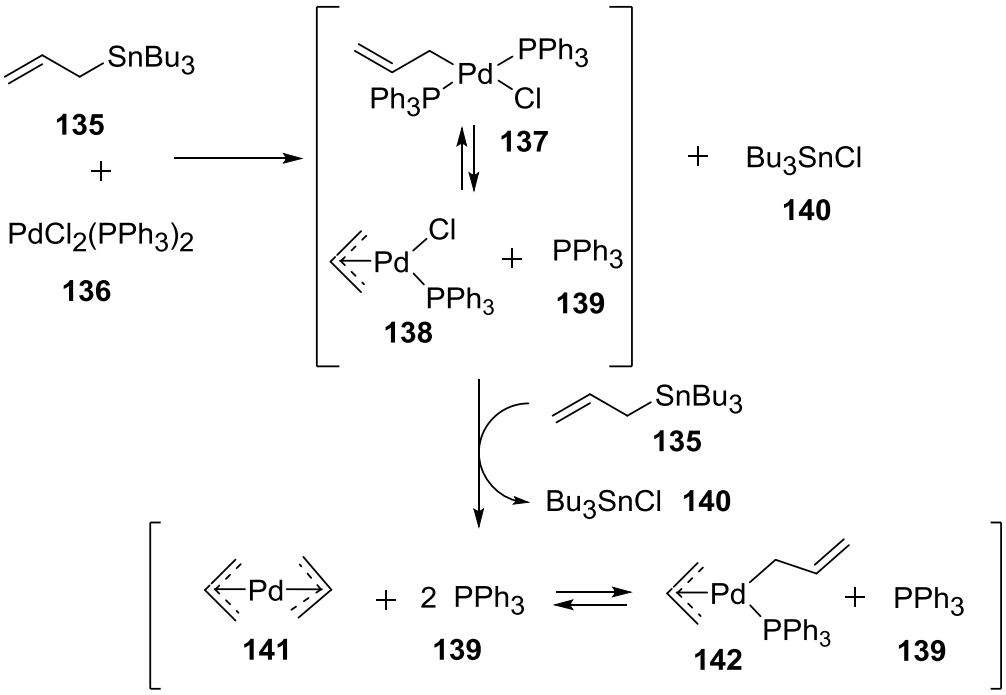


Figure 3.2 Preparation of bis-π-allylpalladium complex (**141**)

The catalytic cycle proposed starts from the π-allyl(alkoxy)palladium complex (**142**) reacting with the aldehyde to give the π-allyl-σ-allyl palladium complex (**144**). The latter may produce the homoallyloxy palladium (**145**) that finally reacts with allylstannane (**135**) to yield the homoallyloxystannane **146** and **142** (Figure 3.3).[15]

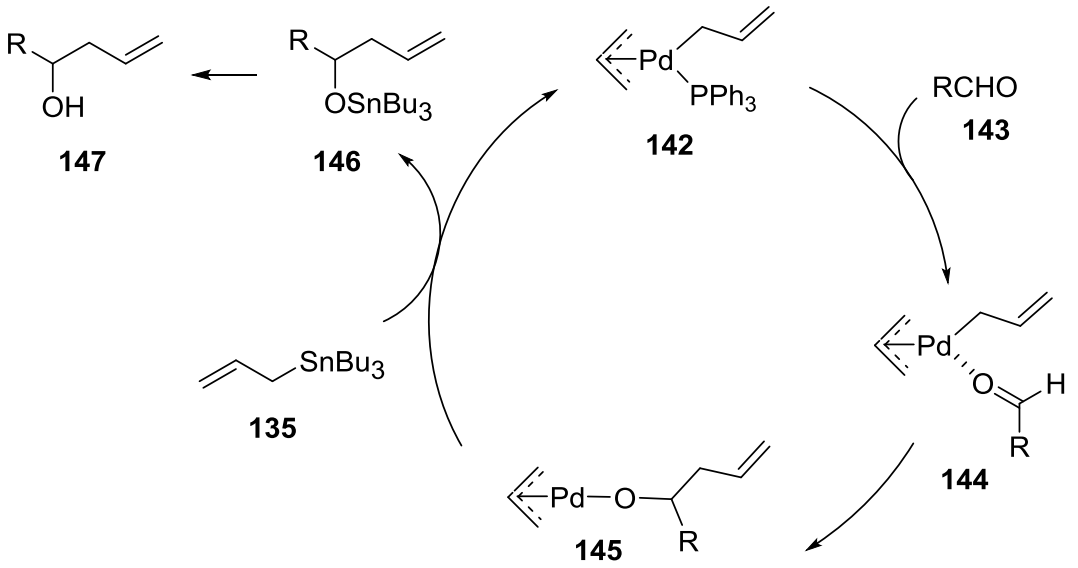
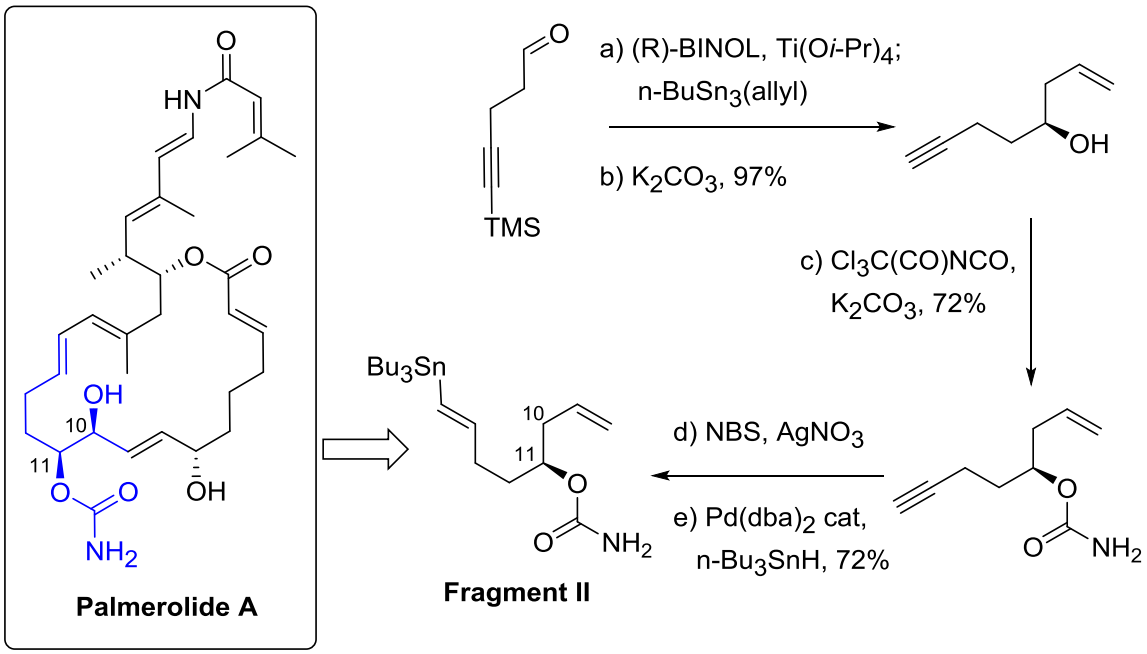


Figure 3.3 Proposed Pd catalyzed mechanism of allystannanes addition to aldehydes

Among the different applications of allylation chemistry, one particular synthesis caught our attention. The synthesis of palmerolide A analogues by Nicolaou and co-workers,[21] requires the preparation of a vinyl stannane fragment **II** via an aldehyde allylation followed by an alkyne hydrostannation (Scheme 3.10).

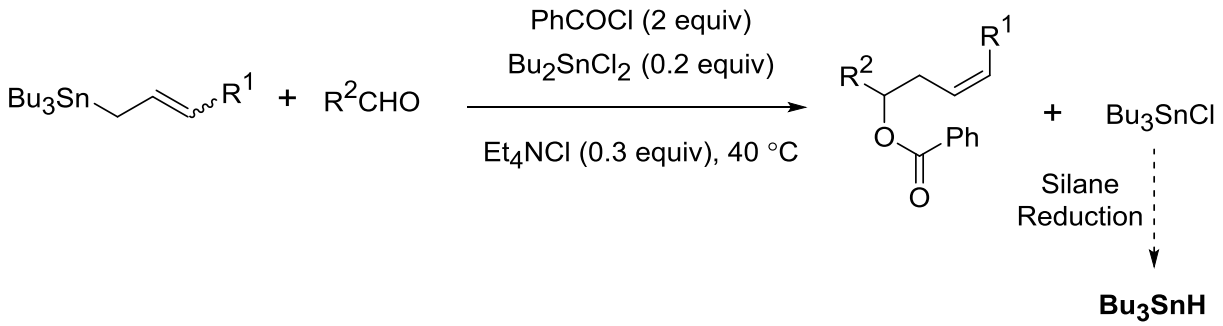


Scheme 3.10 Total synthesis of Palmerolide A analogues

We became interested in the development of a one-pot allylation-hydrostannation sequence, where the tin waste from the allylation reaction could be converted to an organotin hydride that could perform the hydrostannation reaction. This combined process would help in minimize the use of tin reagents employed in synthesis in comparison with those protocols in where the two steps are performed separately.[22,23]

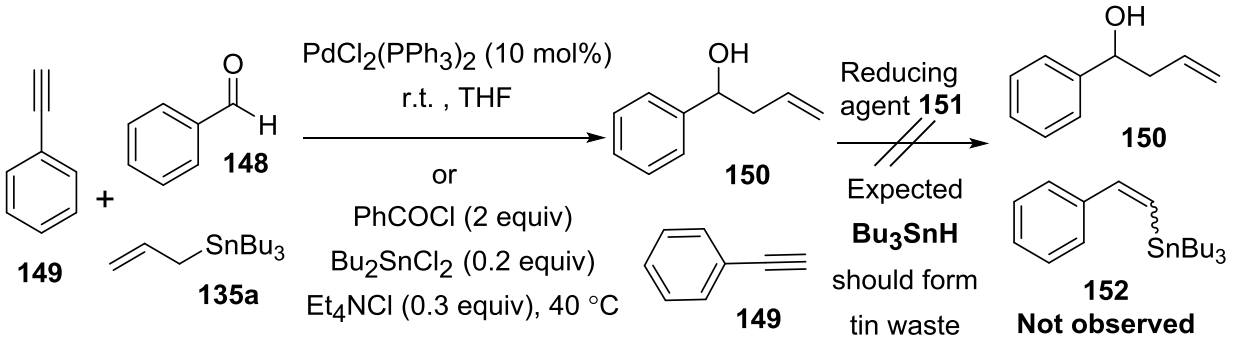
3.3 One-pot allylation-hydrostannation protocol

In the quest for a simpler method for an allylation-hydrostannation sequence, we were able to develop a one-pot allylation and hydrostannation of alkynals where the tin byproduct formed in the first step of the reaction was recycled and used in the second step of the sequence.[24] Our initial thinking was that the stannyl ether intermediates **146** observed by Yamamoto on the Pd-catalyzed allylation (Figure 3.3),[15] or either the byproduct Bu_3SnCl (observed by Baba and co-workers[25] on the allylation of aldehydes with allyltributylstannane and catalytic amounts of Bu_2SnCl_2) could be reduced in situ to Bu_3SnH (Scheme 3.11).[26]



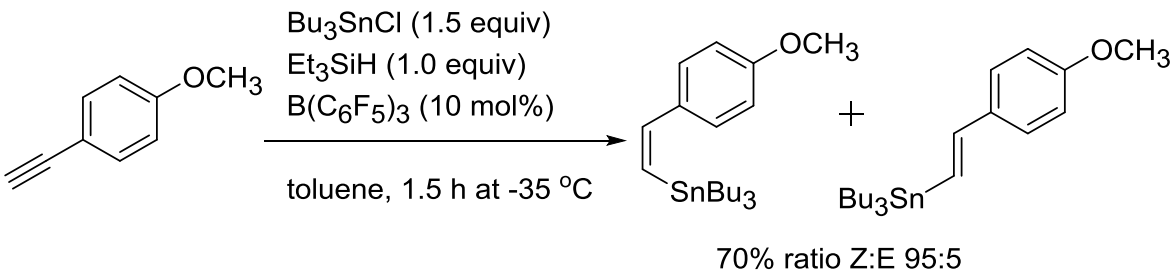
Scheme 3.11 Allylation of aldehydes using Bu_2SnCl_2 as additive and proposed Bu_3SnH generation in situ.

However, attempts to react a mixture of **135**, **148**, and **149** under the conditions of these two methodologies, which in theory would be followed by the hydrostannation of **149** via the addition of PMHS, PMHS/TBAF, or Et_3SiH as the reducing agent (**151**) with Pd or Pt as the hydrostannation catalyst failed (Scheme 3.12). That said only the allylation of **148** to **150** (Yamamoto's protocol) or the benzoyl derivative of **150** (Baba's protocol) were observed. Neither of these methods could be made to work for a one-pot allylation-hydrostannation sequence, therefore we decided to explore BF_3•OEt_2 induced allylations.[16] However the tin intermediates formed in these reactions are not fully characterized and are matter of controversy.[27]



Scheme 3.12 Initial attempts of allylation-hydrostannation sequence

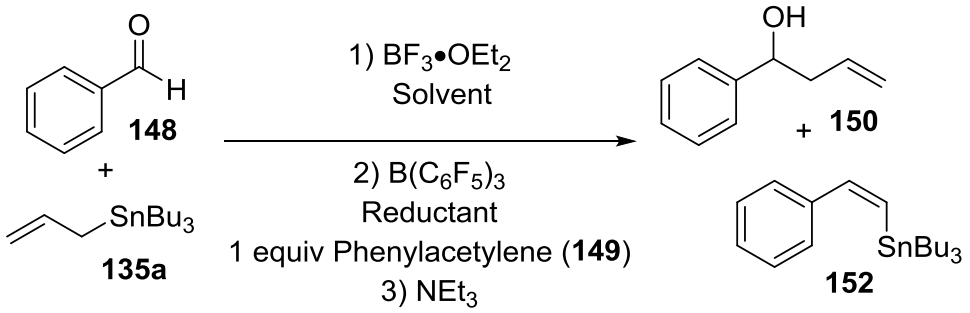
Thinking that a common hydrostannation catalyst like $PdCl_2(PPh_3)_2$[26b] or $MoBI_3$[28] would not survive in the presence of BF_3•OEt_2, we decide to explore Lewis acid mediated hydrostannations. $B(C_6F_5)_3$ was chosen as the hydrostannation catalyst.[26a,29] A report of the use of $B(C_6F_5)_3$ catalyzed hydrostannation was reported by Yamamoto.[26a] In this protocol they found that 10 mol % of $B(C_6F_5)_3$ effectively catalyzed the hydrostannation of alkynes with Bu_3SnH generated in situ from Bu_3SnCl and Et_3SiH as the hydride source (Scheme 3.13).



Scheme 3.13 Yamamoto hydrostannation reaction

After significant optimization of the reaction conditions[24] were explored different sources of reducing agents (Et_3SiH, PMHS, and PMHS/TBAF) for the one-pot allylation-hydrostannation sequence (Table 3.1), we found that 1.05 equiv of BF_3•OEt_2, 20 mol % of $B(C_6F_5)_3$ and 2 equiv of PMHS in toluene at -35 °C followed by quenching with 1.4 equiv of NEt_3 produced the highest combined yield of the expected homoallylic alcohol **150** (78%) and vinylstannane **152** (100%) as monitored by NMR using $(CH_3)_3SiOSi(CH_3)_3$ as internal standard (Table 3.1 entry 15).[24] After isolation 71% of **150** and 99% of **152** were recovered. Yamamoto[26a] tried to do hydrostannation reaction with Bu_3SnH generated in situ from the reduction of tributyltin oxide with PMHS, under the Lewis acid catalyzed conditions using $B(C_6F_5)_3$ as a catalyst, however no hydrostannations products were detected, presumably due to a strong affinity of the Lewis acid for the oxygen. Contrary to Yamamoto's observations,[26a] in our results PMHS is not inhibited by $B(C_6F_5)_3$ as a catalyst for the hydrostannation reaction and the reaction proceeds smoothly (Table 3.1).

Table 3.1 Optimization of one-pot allylation-hydrostannation sequence



Entry	BF_3•OEt_2 (equiv)	Solvent	Temp (°C)	$B(C_6F_5)_3$ (mol%)	Reductant[b] (equiv)	**150**[c] (%)	**152**[c] (%)
1	2	DCM	0	10	**A** (1)	56	32
2	2	DCM	0	20	**A** (1)	60	55
3	2	toluene	0	20	**A** (1)	72	65
4	2	toluene	0	100	**A** (1)	12	-
5	2	toluene	0	20	**A** (1.5)	63	85
6	2	toluene	0	0	**A** (1.5)	71	8
7	2	toluene	0	20	**A** (2)	46	76
8	2	toluene	0	30	**A** (2)	62	35
9	2	toluene	0	20	**B** (1) + **C** (cat.)	75	62
10	2	toluene	0	20	**B** (2) + **C** (cat.)	71	86
11	2	toluene	0	20	**B** (3) **+ C** (cat.)	38	52
12	2	toluene	-35	20	**B**(2) + **C** (cat.)	73	92
13	3	toluene	-35	20	**B** (2)	61	99
14[a]	1.05	toluene	-35	20	**B** (2)	74	93
15[a]	1.05	toluene	-35	20	**B** (2)	78	100

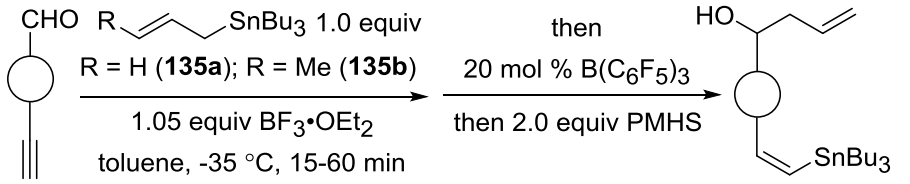
[a]Entries 1-14 were quenched with 2.2 equiv of Et_3N, and entry 15 was quenched with 1.4 equiv of Et_3N. [b]**A** = Et_3SiH, **B** = PMHS, **C** = TBAF. [c]Determined using $Me_3SiOSiMe_3$ as internal standard.

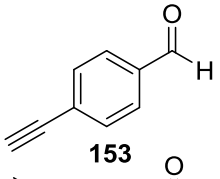
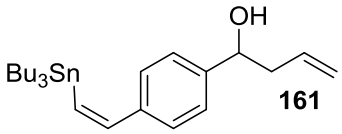
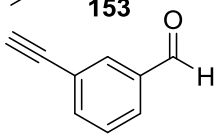
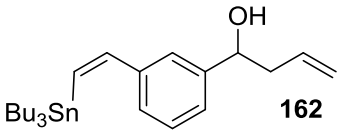
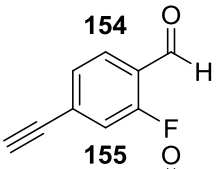
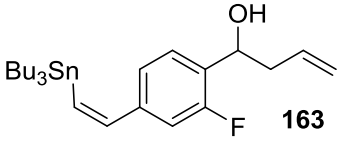
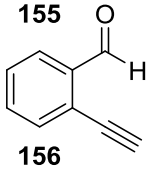
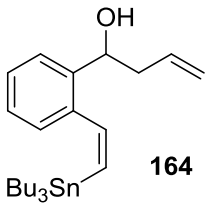
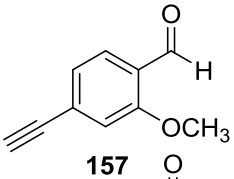
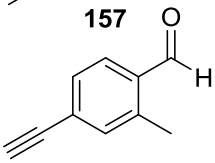
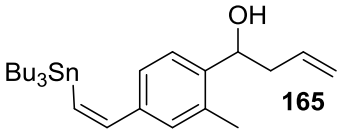
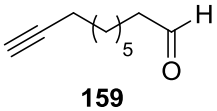
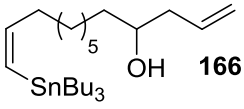
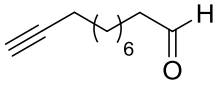
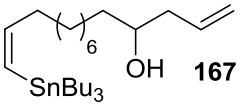
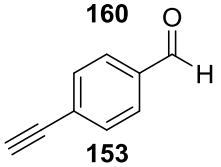
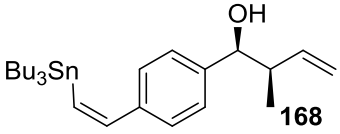
Once this new one-pot allylation hydrostannation sequence was achieved where the aldehyde and alkyne moieties were in separated molecules, we wanted to demonstrate that this sequence could be applied to alkynals like **153-160**. The synthesis of alkynals **154, 155, 157, 158, 159,** and **160** are explained in detail in our recent publication Gosh *et al.*[24]

The results described in Table 3.2 highlight that (Z)-vinylstannanes were the exclusive or predominant product of these Lewis acid catalyzed reactions as reported earlier by Yamamoto.[29] Furthermore, the allylation step tends to be fast (usually between 15 to 60 min, except for entry 9), however the second step was influenced by sterics and electronic effects of the starting materials. For example, we observed that the reaction of **153** under our one-pot allylation hydrostannation conditions only takes 1 h (Table 3.2, entry 1), however when the ethynyl moiety was moved closer to the aldehyde the reaction became slower (14 h for **154** and 1 day for **156**). When an electron-withdrawing group was introduced the reaction was finally completed only after 3 days (Table 3.2, entry 3). When an electron-donating group was present the hydrostannation step was inhibited (Table 3.2, entry 5 and 6). On the other hand, for aliphatic alkynals **159** and **160** yields were lower in comparison with the aromatic alkynals, and the second step was the slowest at 3 days (Table 3.2, entry 7 and 8).

Finally, on the crotylation of **153** with (E)-crotylstannane (**135b**) the allylation step was slower than other substrates (90 min, entry 9).[24] In addition, most of the alkynals selected favorably undergo the allylation-hydrostannation sequence, however the yields were moderated. Therefore, in order to understand this drawback on the final product yields a stepwise analysis of the sequence was deemed necessary.

Table 3.2 One-pot allylation-hydrostannation protocol of alkynals



Entry	Alkynal	Stannylating agent	Product	Yield (%)[a]
1	 **153**	**135a**	 **161**	51
2	 **154**	**135a**	 **162**	48
3	 **155**	**135a**	 **163**	50
4	 **156**	**135a**	 **164**	57
5[b]	 **157**	**135a**	—	—
6	 **158**	**135a**	 **165**	<7
7	 **159**	**135a**	 **166**	41
8	 **160**	**135a**	 **167**	43
9[c]	 **153**	**135b**	 **168**	38

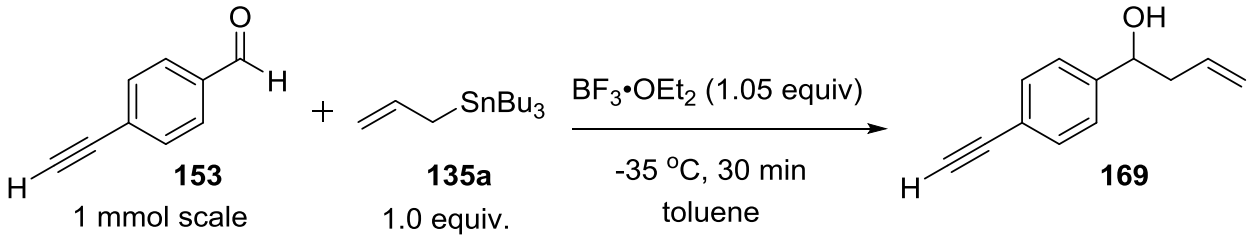
[a]Yields shown are a two-run average. [b]Allylation-hydrostannation product was not observed.
[c]90 min allylation reaction time, *erythro/threo* = 7/1 based on NMR of crude material.

3.4 Stepwise analysis of one-pot allylation hydrostannation

Searching for a better understanding of this allylation hydrostannation protocol a stepwise analysis was performed. The reactivity and stability of the proposed intermediates were studied under different combinations of the reagents used in this methodology, either by excluding one of the reagents or by resubmitting the products to the reaction conditions.

3.4.1 Stepwise allylation and hydrostannation reaction of 4-ethynylbenzaldehyde

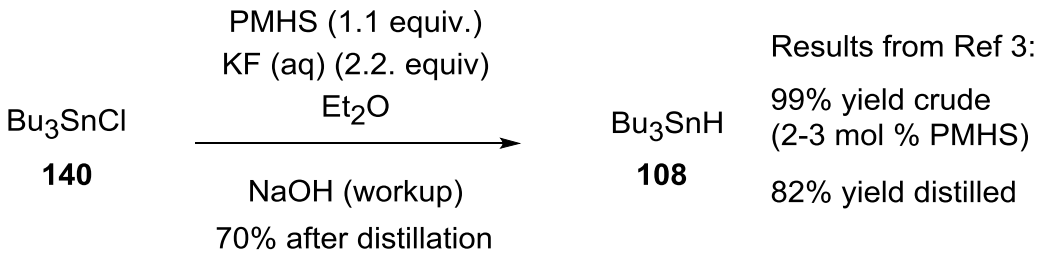
As explained on the beginning of this chapter the allylation of aldehydes with allylstannanes can be achieved in the presence of Lewis acids.[24] Following the order of addition for our one-pot allylation hydrostannation protocol, we expect the formation of 1-(4-ethynylphenyl)but-3-en-1-ol as intermediate upon treatment of 4-ethynylbenzaldehyde (**153**) with allylstannane (**135a**) in the presence of BF_3•OEt_2. As expected in this first step, the allylic alcohol (**169**) was isolated after 30 min at -35 °C in toluene. Purification after column chromatography yielded 86% of **169** (Scheme 3.14).



Scheme 3.14 Allylation of 4-ethynylbenzaldehyde

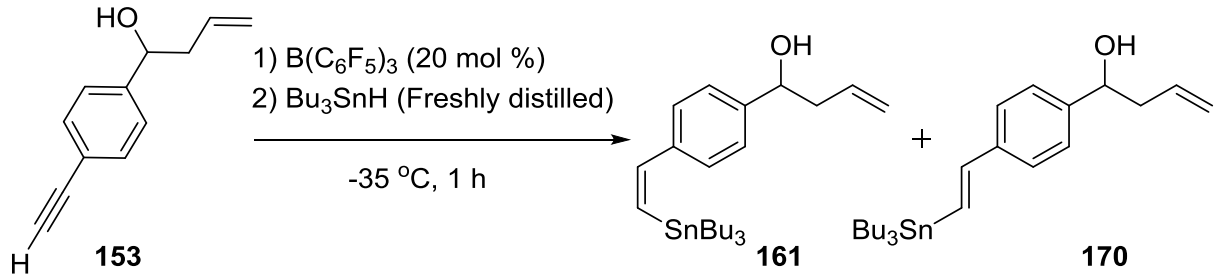
The next step involved submitting the homoallylic alcohol (**169**) to the hydrostannation step in the presence of $B(C_6F_5)_3$ followed by addition of tributyltin hydride. Initial attempts did

not work and only homoallylic alcohol **169** was recovered. We previously mentioned Yamamoto's[26a] results highlighting that $B(C_6F_5)_3$ can be used as hydrostannation catalyst in the presence of Bu_3SnH formed in situ (Scheme 3.13). Knowing that this reaction should work, it was decided to prepare fresh tributyltin hydride following the method developed by our lab[3] (Scheme 3.15), expecting that this would reverse the previous negative results.



Scheme 3.15 Preparation of tributyltin hydride

Upon using this freshly distilled Bu_3SnH in the presence of $B(C_6F_5)_3$ the hydrostannate products **161** and **170** were isolated in 42% yield as a mixture of Z/E isomers in a ratio 1.4:1, along with 36% of starting material and other tin impurities (Scheme 3.16).



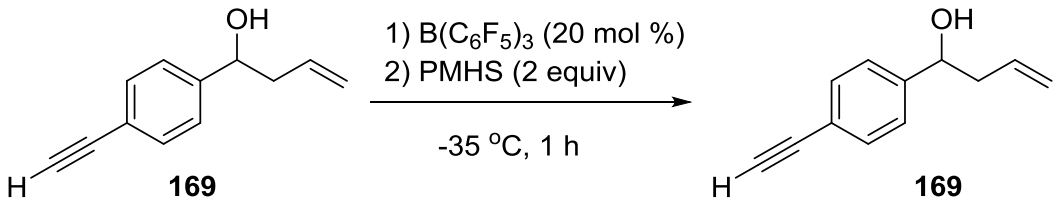
Scheme 3.16 Hydrostannation reaction of 1-(4-ethynylphenyl)but-3-en-1-ol

This result highlights that the formation of hydrostannation products via the in situ generation of Bu_3SnH is possible, and also shows an advantage of the one-pot protocol in that only the Z product was detected. On the other hand, when the reaction is done one step at a time,

an Z/E mixture is observed. Even though, Yamamoto reported a Z:E ratio of 95:5 with 70% yield (Scheme 3.13), in our hands the same substrate reacted with fresh Bu_3SnH and $B(C_6F_5)_3$ yielding 69% of a Z:E mixture in a 1:1 ratio.

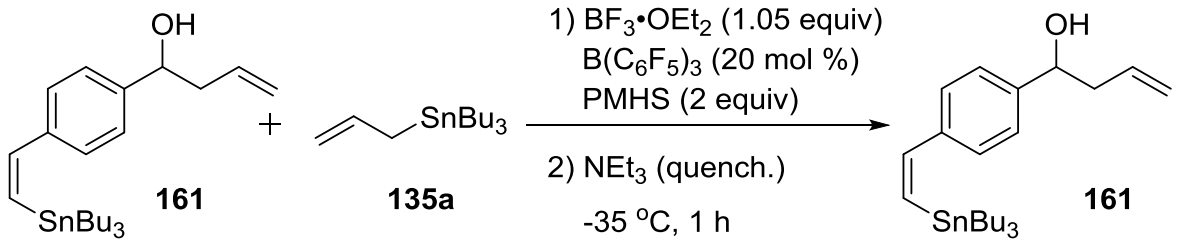
3.4.2 Study of the stability of the allylation and allylation-hydrostannation product of 4-ethynylbenzaldehyde in the reaction media

Next we wanted to study the stability of the homoallylic alcohol (**169**) under the reaction conditions, but in the absence of tributyltin hydride. Even after 1 hour under the reaction conditions at -35 °C in toluene, only starting material was detected. After column chromatography 71.4% of **169** was recovered as a clear oil (Scheme 3.17).



Scheme 3.17 Stability of 1-(4-ethynylphenyl)but-3-en-1-ol in the reaction media without Bu_3SnH

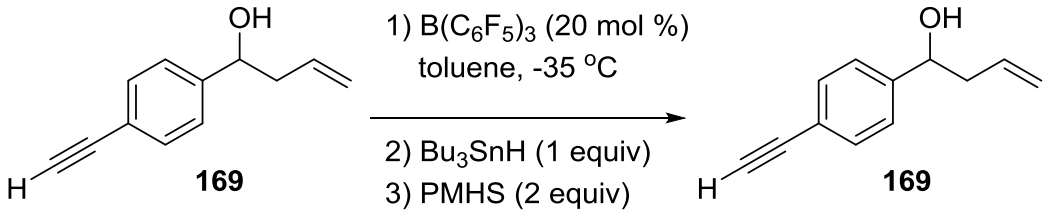
This result indicated that degradation of the alkynol **169** under our reaction conditions cannot fully explain the moderate yields observed for the final products in Table 3.2. Therefore, we decide to look into the stability of the final products in the reaction media. When we resubmitted product **161** to the reaction conditions, and purified the final crude by column chromatography, only 40% of **161** was recoverd as a clear oil (Scheme 3.18). This indicated that the degradation of the final product **161** in the reaction mixture is consistent with the moderated yields observed in our one-pot allylation-hydrostannation protocol.



Scheme 3.18 Stability of **161** in the reaction media

3.4.3 $B(C_6F_5)_3$-catalyzed hydrostannation of 1-(4-ethynylphenyl)but-3-en-1-ol with tributyltin hydride in presence of PMHS

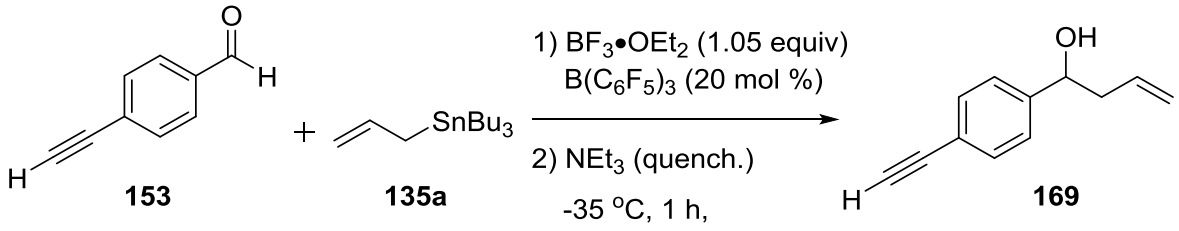
We next studied the hydrostannation of homoallylic alcohol **169** in the presence of 20 mol % of $B(C_6F_5)_3$, 2 equiv of PMHS and 1 equiv of freshly Bu_3SnH. Even after 1 hour under these reaction conditions at -35 °C in toluene, only **169** was isolated after column chromatography (79% yield) and only traces amounts of (Z)-stannane **161** were observed by ^1H NMR (Scheme 3.19). These results indicated that only the in situ formed Bu_3SnH is involved in the hydrostannation step under our reaction conditions.



Scheme 3.19 Hydrostannation attempt of 1-(4-ethynylphenyl)but-3-en-1-ol

3.4.4 One-pot allylation-hydrostannation of 4-ethynylbenzaldehyde without PMHS

Finally we wanted to confirm that the presence of PMHS was necessary for the in situ formation of Bu_3SnH. In the absence of PMHS only homoallylic alcohol **169** was obtained in high yield 93% (Scheme 3.20). This proved that PMHS is involved in the generation of Bu_3SnH.



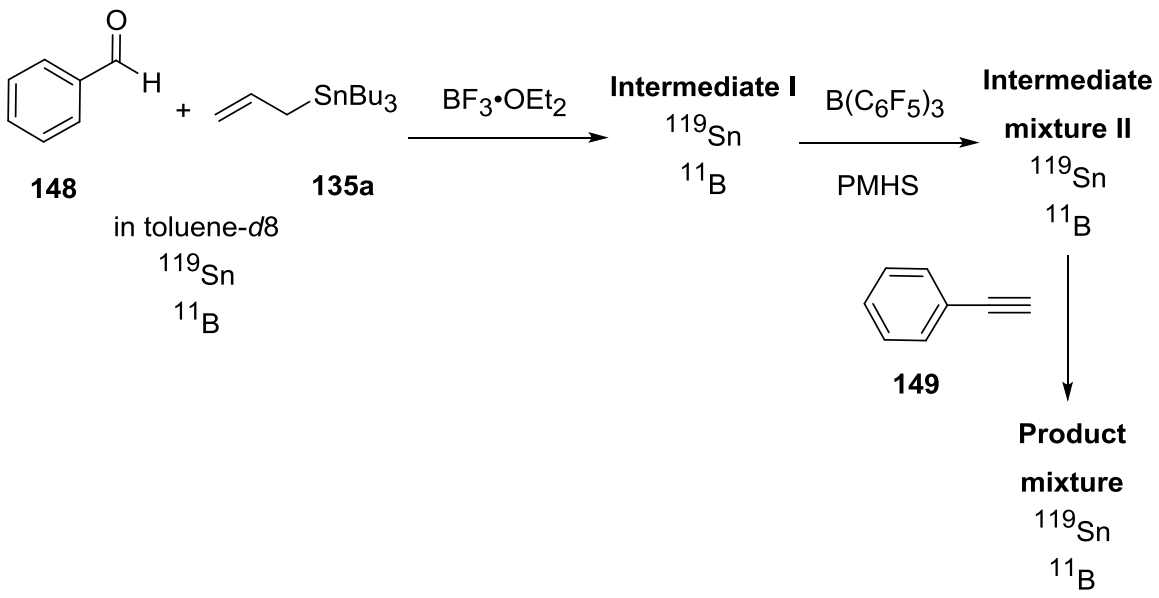
Scheme 3.20 Hydrostannation attempt of 4-ethynylbenzaldehyde without PMHS

3.5 NMR studies (^{119}Sn, ^{19}F and ^{11}B)

Along with the reaction analyses just described, NMR studies were performed in order to probe the intermediates of the allylation hydrostannation protocol. ^{119}Sn, ^{11}B and ^{19}F NMR were obtained after addition of each reagent to the crude reaction mixture allowing us to confirm the in situ generation of Bu_3SnH.

Following Scheme 3.21, in the absence of BF_3•OEt_2, the reaction mixture of benzaldehyde (0.04 mL, 0.375 mmol) and stannane (0.12 mL, 0.375 mmol) only showed the characteristic peak for allyltributylstannane (-17 ppm) by ^{119}Sn NMR.[30] When the Lewis acid BF_3•OEt_2 (0.05 mL, 0.393 mmol) (**Intermediate I**) was added a doublet at 164 ppm slowly grew as the peak corresponding to allyltributylstannane decayed (Figure 3.4). The coupling constant (*J*) of this doublet was found to be in the range of 1430 Hz. Such a large coupling constant is

consistent with many Sn–F species.[31] Both of the peaks at -17 ppm and 164 ppm appeared broad. These broad peaks suggest that these species are not monomeric and may be aggregates.



Scheme 3.21 ^{119}Sn NMR study of one-pot allylation-hydrostannation protocol

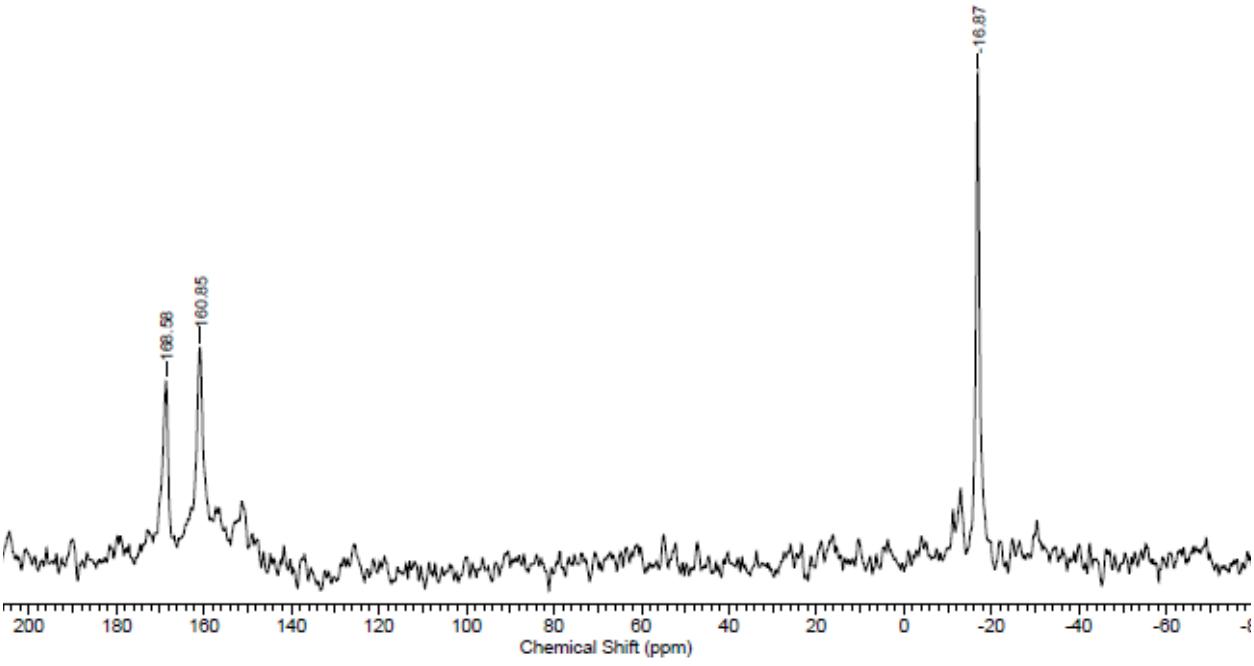


Figure 3.4 ^{119}Sn NMR spectrum of Intermediate I

A ^{11}B NMR study of the same mixture (**Intermediate I**) showed two peaks at 0.14 and –1.22 ppm respectively. The peak at 0.14 ppm is attributed to unreacted $BF_3 \cdot OEt_2$. The peak at -1.22 ppm is consistent with formation of an oxygen bound BF_3 (Figure 3.5).[32] These boron-oxygen interactions were observed before by Denmark and co-workers, in the spectroscopic investigation of the addition of allylstannanes to aldehydes induced by Lewis acid.[27b] Using ^{13}C NMR they were able to identified the formation of boron ethers species while no stannyl ethers were observed when $BF_3 \bullet OEt_2$ was used as a Lewis acid (pathway A on Scheme 3.20). Instead when $SnCl_4$ was employed as the Lewis acid they found evidence of an interaction between the Lewis acid and the allylic stannane before reacting with the aldehyde (pathway B on Scheme 3.22).[27b] The latter involves a transmetallation of the allylstannane (metathesis) with the Lewis acid to form a new reagent species **174**. This scenario is not observed under our reaction conditions.

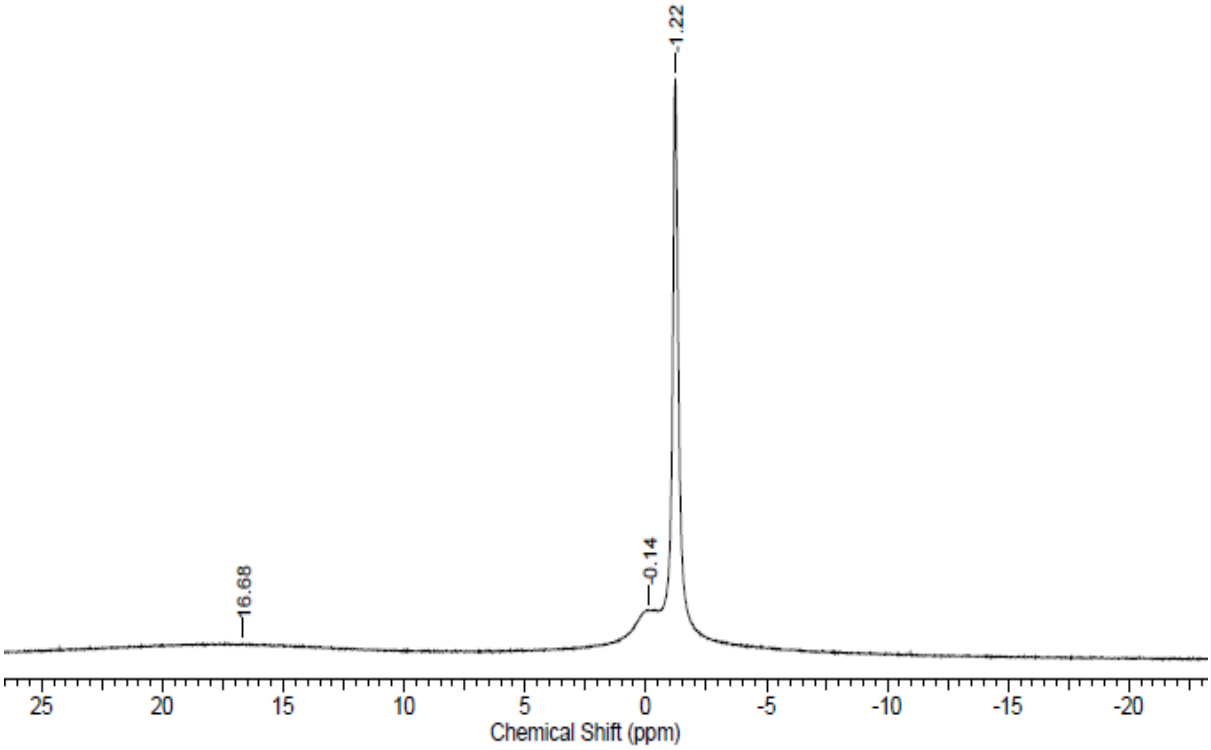
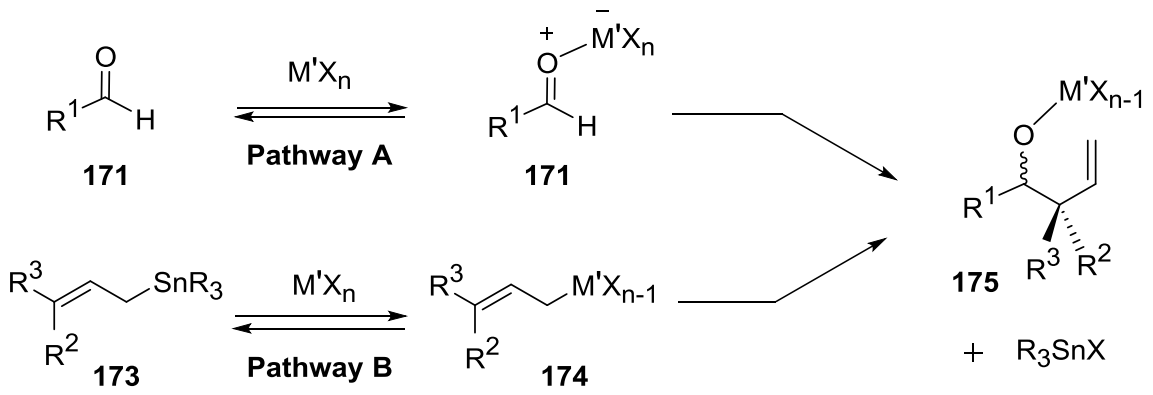


Figure 3.5 ^{11}B NMR spectrum of Intermediate I



Scheme 3.22 Normal Lewis acid reaction vs. transmetallation of allylstannane (metathesis) with Lewis acid

The next step involved the addition of $B(C_6F_5)_3$ (38 mg, 20 mol %) to reaction mixture followed by PMHS (0.05 mL) (**Intermediate mixture II**). A significant change in ^{119}Sn NMR was observed as a new peak could be seen at -88 ppm that is a characteristic peak for tributyltin hydride.[30] The doublet peak slightly shifted to 165 ppm and the coupling constant (*J*) of this doublet increased to 1538 Hz. (Figure 3.6). As noted earlier, this transformation was slow and needed precision in reagent addition and mixing. If the tin hydride is not produced, the reaction will not proceed to the desired product. Chandrasekar and co-workers demonstrated that $B(C_6F_5)_3$ functions as a PMHS activator.[33] We anticipate that $B(C_6F_5)_3$ serves a similar role in our reactions. Thus, it is likely that $B(C_6F_5)_3$ activates PMHS to reduce the Sn-F species to tributyltin hydride during the course of the reaction. Furthermore, the ^{11}B NMR study of the **Intermediate mixture II** (Figure 3.7) showed, two peaks slightly shifted to 0.23 and –1.36 ppm. The dominant ^{11}B species in the reaction mixture are oxygen coordinated BF_3, since BF_3 is used stoichiometrically, whereas only 20 mol % $B(C_6F_5)_3$ is used.

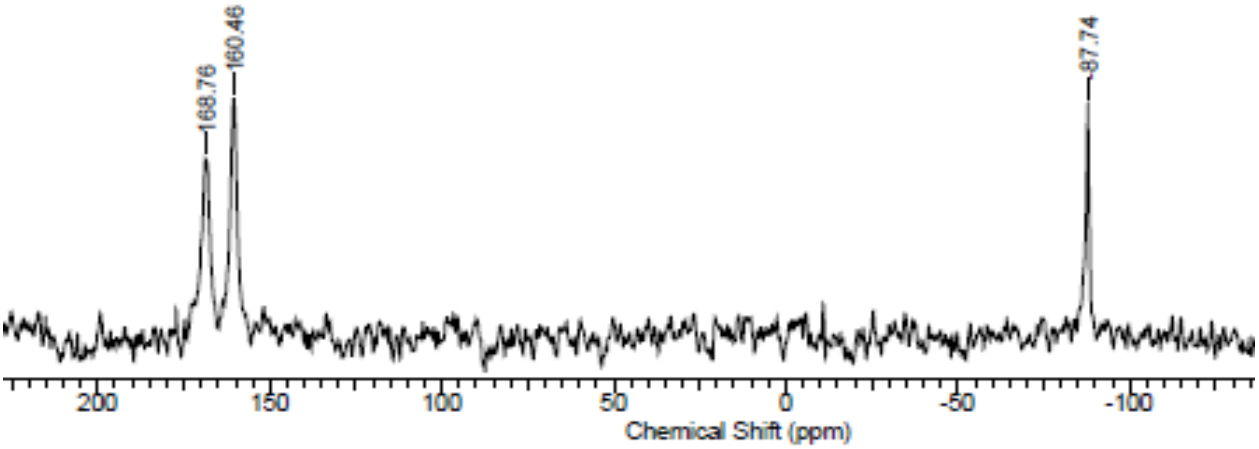


Figure 3.6 ^{119}Sn NMR spectrum of Intermediate mixture II

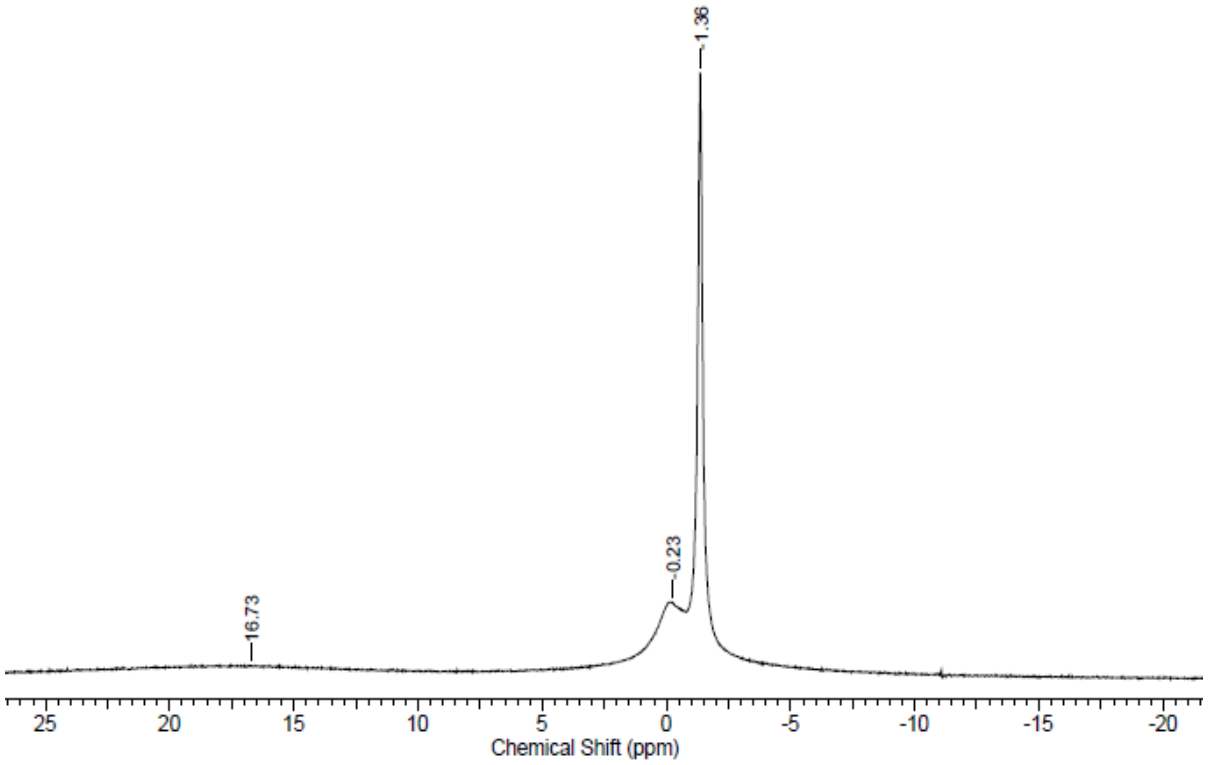


Figure 3.7 ^{11}B NMR spectrum of Intermediate mixture II

To confirm that the splitting of the peak at 165 ppm in the ^{119}Sn NMR spectrum was due to fluorine scalar coupling, we performed a fluorine-decoupled ^{119}Sn NMR spectrum of the mixture. Since the peaks span 32500 Hz, broadband fluorine decoupling is not feasible. We, therefore, performed a band-selective decoupling on the region around -194 ppm. This region was selected based on a doublet at -193 ppm having a scalar coupling similar to that observed in the ^{119}Sn spectrum.[34] The doublet collapsed in the ^{119}Sn NMR to a singlet upon the selective decoupling (Figure 3.8). This result conclusively demonstrates that a Sn-F species is produced during the reaction.

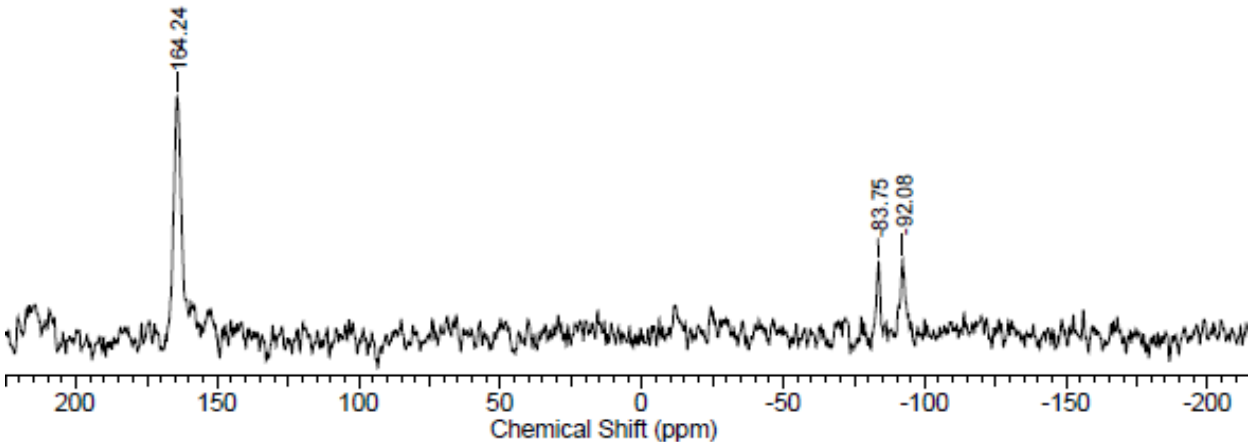


Figure 3.8 ^{19}F-decoupled ^{119}Sn NMR spectrum of Intermediate mixture II.

Considering the possibility that the Sn-F species contains Sn-O bonds and, as such, could react with PMHS to form the reactive organotin hydride,[35,36] we decided to reverse the order of addition of $B(C_6F_5)_3$ and PMHS. When PMHS was added to a mixture of benzaldehyde, allylstannane, and BF_3•OEt_2 no change in the multiplicity of the doublet in the ^{119}Sn spectrum was observed, even after an hour, and no formation of organotin hydride was evident. The chemical shift of the doublet, however, moved ~ 6 ppm downfield, possibly due to coordination between Sn and the oxygen atoms of PMHS (Figure 3.9). The peak corresponding to tributyltin hydride only formed when $B(C_6F_5)_3$ was added before the PMHS. This is further evidence that $B(C_6F_5)_3$ is involved in the reduction of the Sn-F species to tributyltin hydride. Since PMHS cleaves Sn-O bonds without any assistance from $B(C_6F_5)_3$ generating organotin hydrides (even at –35 °C as we have observed)[35] and ^{119}Sn chemical shifts for oxygen bound tins are typically observed in the range of 70-150 ppm (our tin doublet appears at ~ 165 ppm), we do not believe that species containing F-Sn-O- are intermediates in our reaction.[30,36] It is also clear that the Sn-F species observed during our reaction is not polymeric tributyltin fluoride, which typically

appears far upfield (~ -10 ppm in hexane solution) as a triplet with a coupling constant of ~1350 Hz.[37]

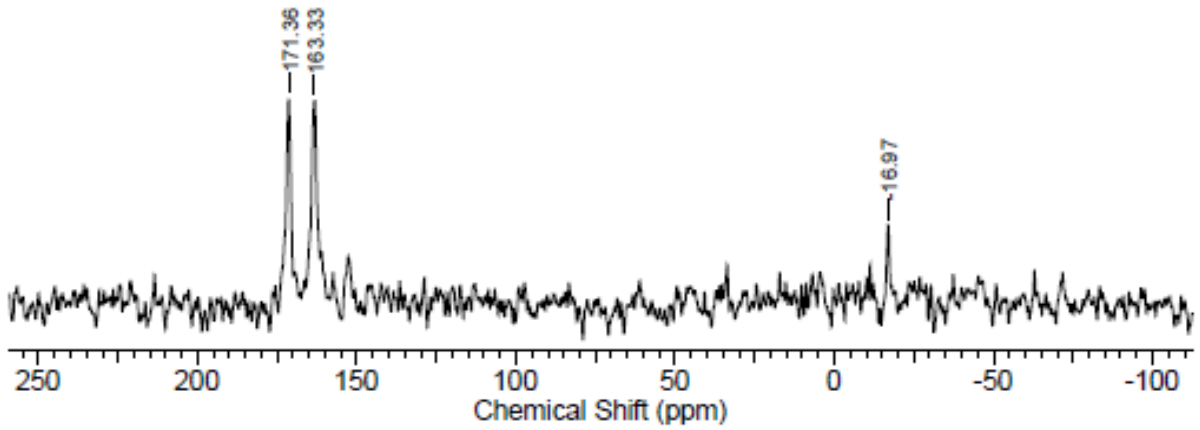


Figure 3.9 ^{119}Sn NMR spectrum of crude reaction after addition of PMHS before $B(C_6F_5)_3$

Addition of $B(C_6F_5)_3$ and PMHS not only results in the formation of the tributyltin hydride, there is evidence from the ^{19}F NMR spectral data that silicon bound fluorides are produced. Figure 3.10 shows an expansion region of change for the ^{19}F NMR spectrum prior to (top) and after (bottom) $B(C_6F_5)_3$ and PMHS addition. The new resonances at -146.0 and -145.4 ppm are consistent with fluorine bound to silicon.[38] Therefore once the tributyltin hydride is produced, a Si-F species is also generated in the reaction mixture.

Finally, when phenyl acetylene (0.04 mL, 0.375 mmol) was added to a solution of **Intermediate mixture II**, the tributyltin hydride and the tin doublet disappeared and the corresponding peak of the vinylstannane species appeared at – 55.4 ppm (Figure 3.11) (^{119}Sn NMR of purified vinylstannane showed a sharp singlet at -56 ppm). ^{11}B NMR of the crude product showed two peaks at 0.13 and -1.40 ppm (Figure 3.12).[39]

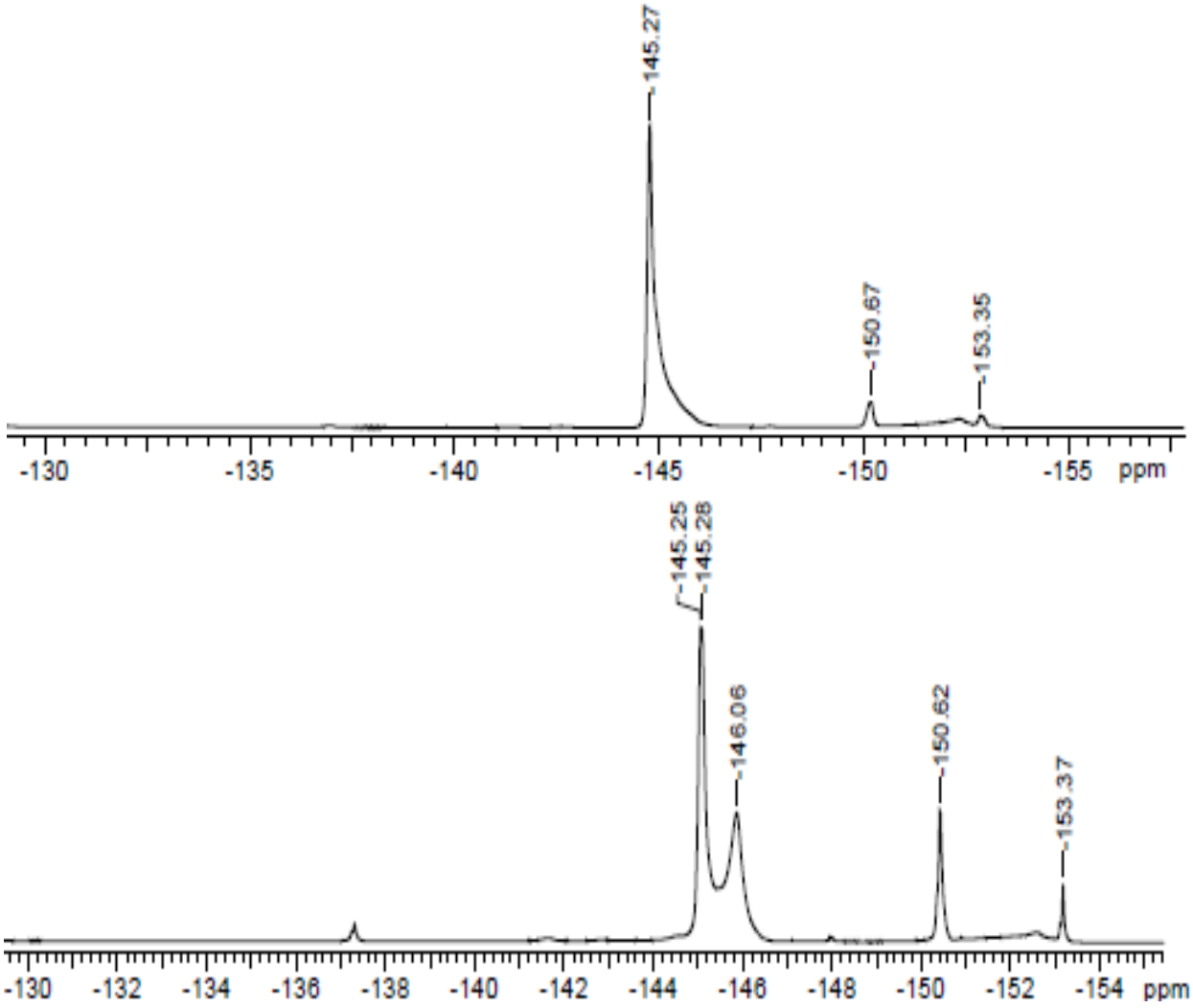


Figure 3.10 Expansion of ^{19}F spectra prior to (top) and after (bottom) addition of $B(C_6F_5)_3$ and PMHS.

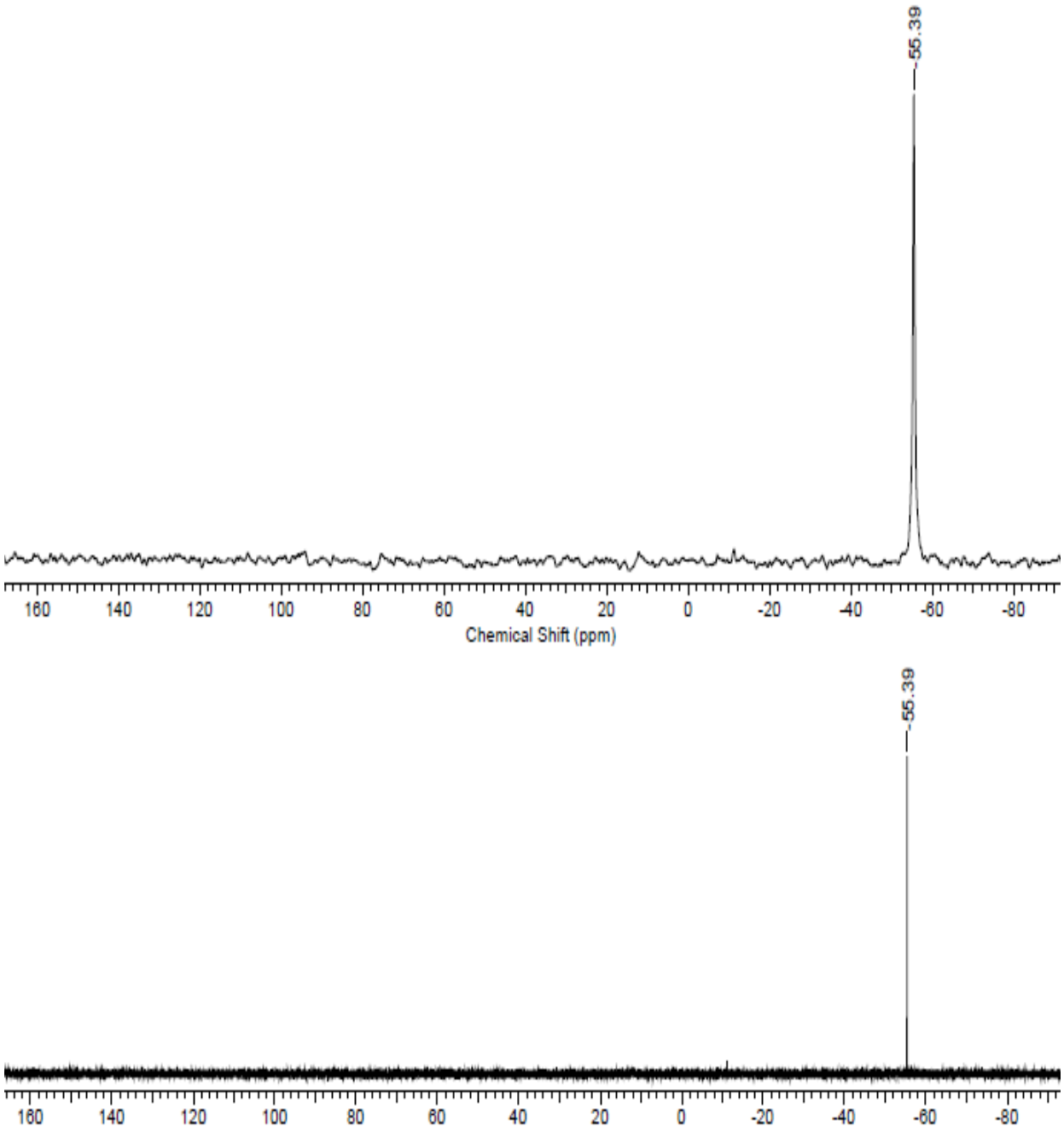


Figure 3.11 ^{119}Sn NMR spectra of crude product mixture with exponential multiplication set to 100 Hz (i.e. lb=100) (top). With lb=10 (bottom).

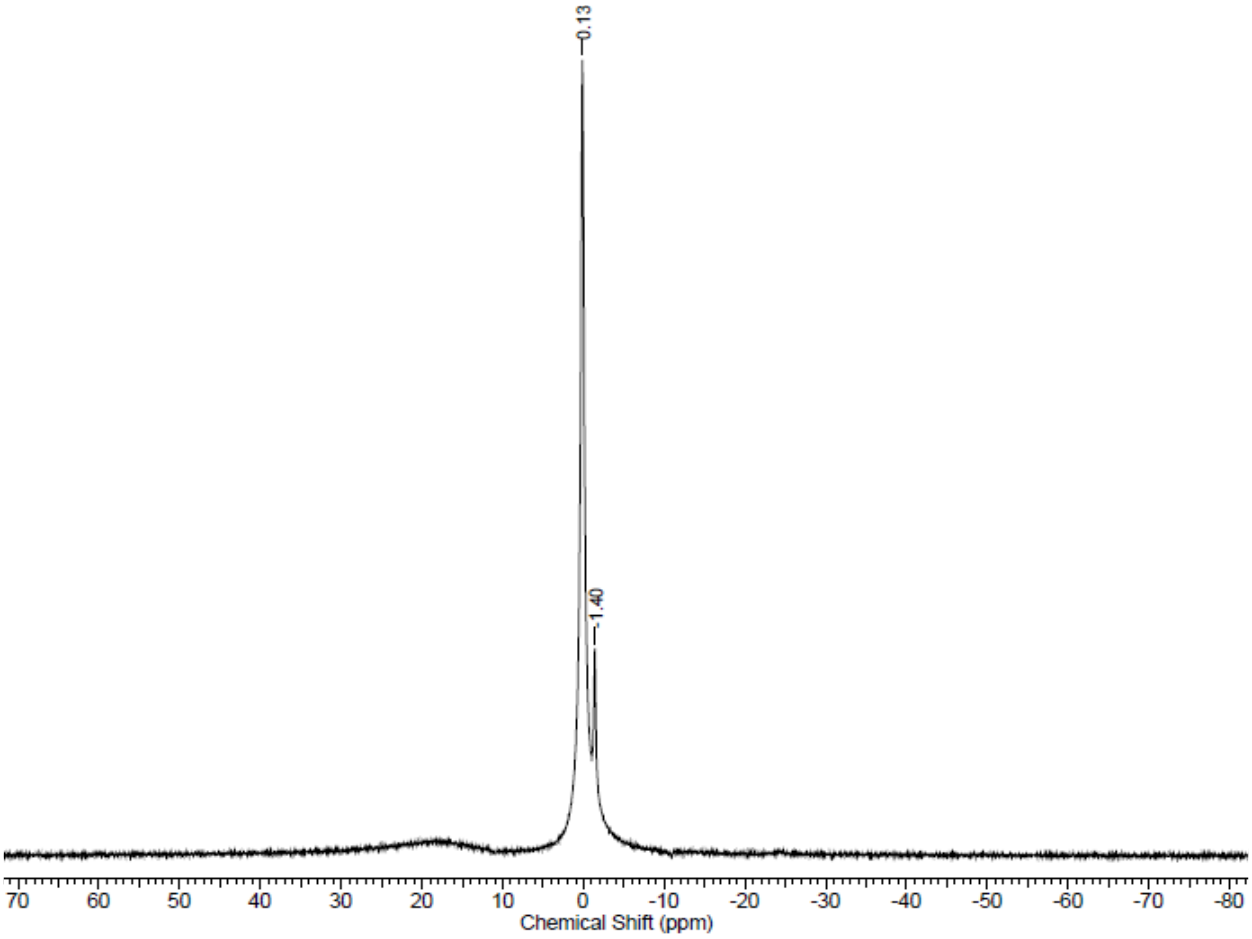


Figure 3.12 ^{11}B NMR spectra of crude product mixture[39]

After all this NMR analysis we proposed a mechanism described in Figure 3.13 that is supported by ^{119}Sn and ^{11}B NMR spectra after addition of each reagent. Furthermore, in order to eliminate the possibility of Bu_3SnF involvement, reactions were performed with premade tributyltin fluoride for 3 h (exact same time as our typical hydrostannation step for phenyl acetylene in our optimized allylation-hydrostannation protocol). We obtained a different result using Bu_3SnF (**177**), as (*Z*)-**152** and (*E*)-**176** vinylstannanes were produced in almost equal amounts with a combined 11% yield. Finally, from mass spectrometry experiments done in our lab, it was known that Bu_3SnF can undergo a boron to tin ligand exchange reaction, thus this erosion of yield is not unexpected (Scheme 3.23). Non-selective product formation and the low

yield obtained in the reaction further indicates that it is unlikely for Bu_3SnF to be involved in our allylation-hydrostannation reaction.

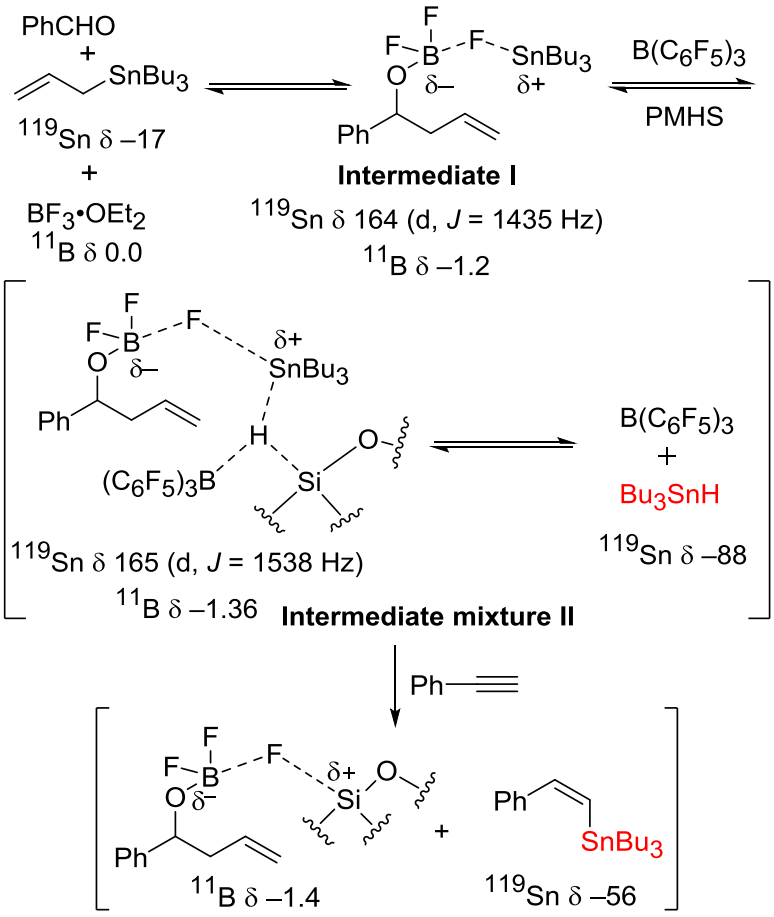
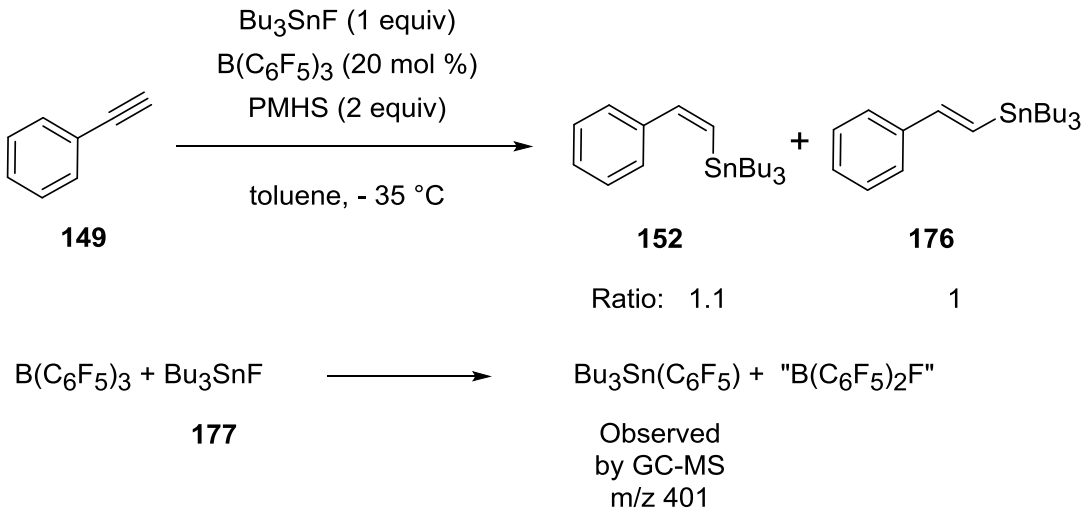


Figure 3.13 Mechanistic rationale of one-pot allylation hydrostannation reaction



Scheme 3.23 Hydrostannation of phenylacetylene by Bu_3SnF

3.6 Conclusions

We were able to develop a new one-pot allylation-hydrostannation sequence of alkynals where the tin byproduct, from the BF_3•OEt_2–promoted allylation step, was successfully recycled by the introduction of PMHS and catalytic $B(C_6F_5)_3$ to form Bu_3SnH in situ; that was used on the hydrostannation reaction.

The stepwise analysis of this methodology highlights that degradation of the final product in the reaction mixture was consistent with the moderate yields observed in our one-pot protocol. Our one-pot was more efficient than carrying out an allylation and hydrostannation of an alkynal in two separate steps. The latter stepwise reaction gave us 42% yield of a 1.4 /1 mixture of (Z)- and (E)-stannanes, while the one-pot reaction yield 51% of only (Z)-stannane. Furthermore, we confirm that the presence of PMHS is crucial for the formation in situ of Bu_3SnH, as without PMHS activated by $B(C_6F_5)_3$ only allylic alcohol **169** was obtained.

In addition, our studies were the first BF_3•OEt_2 mediated allylation being followed by ^{119}Sn and ^{11}B NMR, although such studies have been described for $SnCl_4$[27f] and solvent mediated[27g] allylstannations. The only reports for BF_3•OEt_2 mediated allylation done by Denmark[27b] were followed by ^{13}C NMR. Therefore, following the reaction by ^{119}Sn and ^{11}B NMR revealed that a Sn-F intermediate is formed during the BF_3•OEt_2 mediated reaction between the aldehyde and allyltributylstannane. Later the Sn-F intermediate is reduced to Bu_3SnH by $B(C_6F_5)_3$–activated PMHS. In our one-pot protocol $B(C_6F_5)_3$ also acts as a catalyst for the subsequent hydrostannation.

3.7 Experimental section

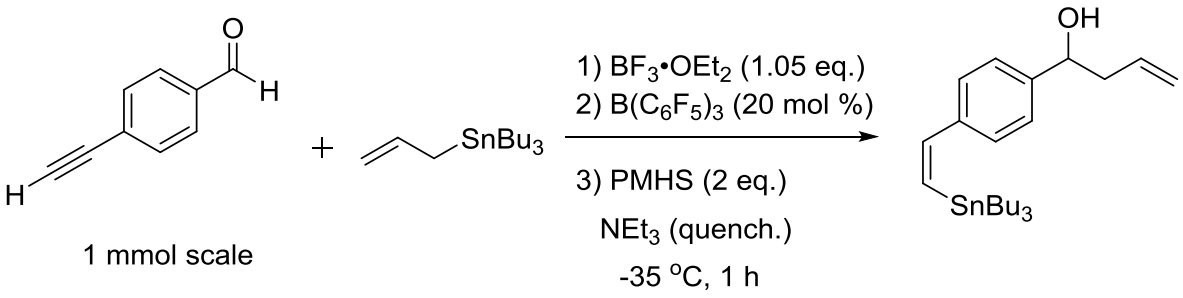
General Materials and Methods

All reactions were carried out in oven or flame-dried glassware under nitrogen in round bottom flasks or in sealed tubes unless otherwise noted. All commercial reagents were used without purification except benzaldehyde (**148**) and phenylacetylene (**149**) that were purchased from Sigma-Aldrich and often freshly distilled before reactions. allylstannane (**135a**), polymethylhydrosiloxane, BF_3•OEt_2 and alkynes **153**, and **156** were purchased from Sigma-Aldrich and used as received. Tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) was purchased from Sigma-Aldrich and Strem chemicals. All solvents were reagent grade. Dichloromethane and toluene were freshly distilled from calcium hydride under nitrogen. Tetrahydrofuran was distilled from sodium and benzophenone under nitrogen. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin-layer chromatography with 0.25-mm pre-coated silica

gel plates and developed with uv or phosphomolybdic acid or potassium permanganate solutions. Flash chromatography was performed with silica gel 60 Å (230–400 mesh ASTM). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise mentioned. ^{1}H, ^{11}B, ^{13}C, ^{19}F, and ^{119}Sn NMR spectra were recorded on Varian spectrometers: Inova-300 (300.11 MHz for ^{1}H and 75.47 MHz for ^{13}C), Varian UnityPlus-500 (499.74 MHz for ^{1}H, 470.169 MHz for ^{19}F, 186.357 MHz for ^{119}Sn, 160.335 MHz for ^{11}B, and 125.67 MHz for ^{13}C).

Experimental

Synthesis of (*Z*)-1-[4-(2-(tributylstannyl)vinyl)phenyl]but-3-en-1-ol (161):



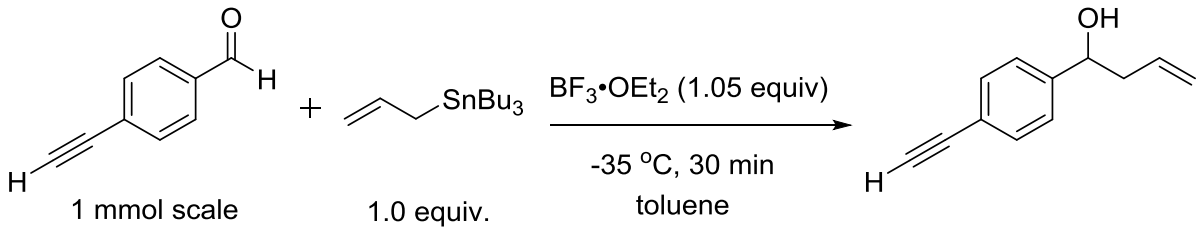
4-Ethynylbenzaldehyde (**153**) (130 mg, 1 mmol) was dissolved in toluene (2 mL) in a round-bottom flask and the mixture was cooled to –35 °C. Allylstannane (**135a**) (0.31 mL, 1 mmol) was added followed by BF_3•OEt_2 (0.13 mL, 1.05 equiv). The reaction was monitored until complete (15 minutes). At this point, $B(C_6F_5)_3$ (103 mg, 20 mol %) was added to the solution under N_2 (glove bag) and it was cooled to –35 °C. PMHS (0.12 mL, 2 equiv) was added and the reaction was run for 1 h. NEt_3 was added to quench the reaction. The crude mixture was passed through a short silica plug (1´´), buffered with 1% NEt_3, with 4:1 hexane/EtOAc solution (200

mL) The solution was concentrated and subjected to column chromatography [silica gel; 80:20 hexane:EtOAc, 1% Et_3N] to afford **161** (232 mg, 50%) as an oil.

Data for **161**: IR (neat): 3386 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) = 0.74-0.96 (m, 15H), 1.17-1.32 (m, 6H), 1.35-1.51 (m, 6H), 2.12 (br s, 1H), 2.46-2.52 (m, 2H), 4.70-4.75 (m, 1H), 5.10-5.18 (m, 2H), 5.71-5.84 (m, 1H), 6.18 (d, *J* = 13.7, 1H), 7.22-7.30 (m, 4H), 7.59 (d, *J* = 13.7, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) = 10.8, 13.6, 27.2, 29.0, 43.8, 73.1, 118.4, 125.6, 127.1, 132.8, 134.3, 141.0, 142.9, 146.9. HRMS (EI) m/z calcd for $C_{20}H_{31}O^{116}Sn$ $[M\text{-}Bu]^+$, 403.1392; found: 403.1406.

Control experiments:

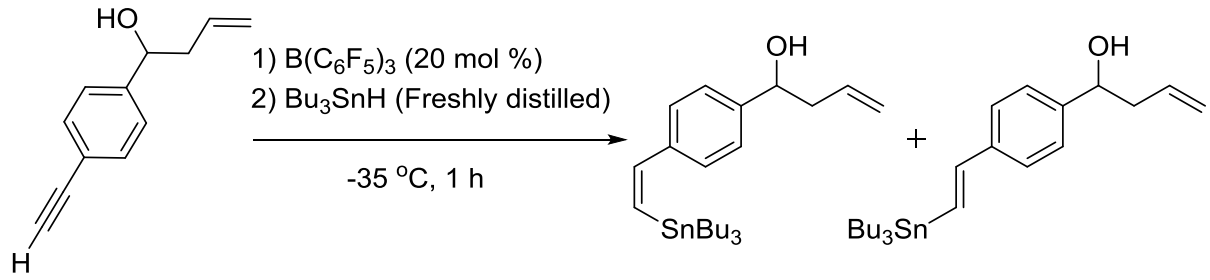
(a) Step-wise allylation and hydrostannation reaction of 4-ethynylbenzaldehyde (153)



4-Ethynylbenzaldehyde (**153**) (130 mg, 1 mmol) was dissolved in toluene (1 mL) in a round-bottom flask and the mixture was cooled to –35 °C. Allylstannane (**135a**) (0.31 mL, 1 mmol) was added followed by BF_3•OEt_2 (0.13 mL, 1.05 equiv). The reaction was monitored until complete (30 minutes). 2 mL of water were added to quench the reaction. The organic phase was

separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). Organic phase were combined, dried with $MgSO_4$ and evaporated using a rotavap. The crude product was subjected to column chromatography [silica gel; 80:20 hexane/EtOAc, 1% Et_3N] to afford 1-(4-ethynylphenyl)but-3-en-1-ol (**169**) (148.4 mg, 86%) as a clear oil.

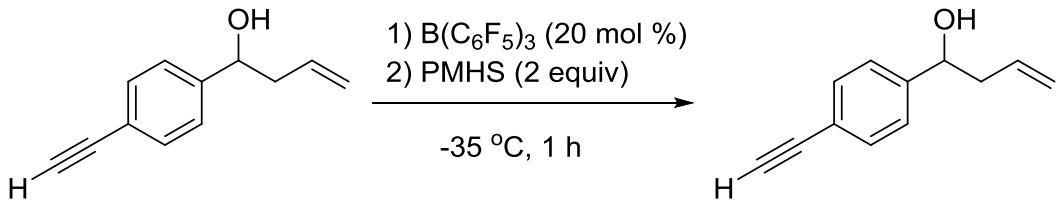
Data for **169**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) = 7.46–7.44 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.29–7.27 (d, *J* = 8.5 Hz, 2 H, Ar-H), 5.79–5.70 (m, 1 H, C*H*=CH_2), 5.15–5.11 (m, 2 H, CH=C*H*$_2$), 4.71–4.68 (dd, *J* = 5.0, 8.0 Hz, 1 H, C*H*OH), 3.05 (s, 1 H, C≡C*H*), 2.49–2.41 (m, 2 H, CHC*H*$_2$), 2.20 (s, br, 1H, O*H*). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) = 144.5, 133.9, 132.1, 125.7, 121.1, 118.7, 83.4, 77.1, 72.7, 43.6.



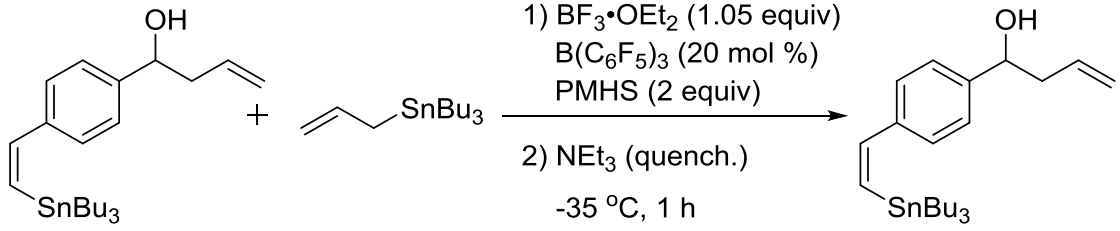
1-(4-Ethynylphenyl)but-3-en-1-ol **(169)** (107.1 mg, 0.62 mmol) was dissolved in toluene in a round-bottom flask. Then $B(C_6F_5)_3$ (63 mg, 20 mol %) was added to the solution under N_2 (glove bag) and it was cooled to –35 °C. Freshly prepared tributyltin hydride (0.167 mL, 1 equiv) was added and the reaction was run for 1 h. NEt_3 was added to quench the reaction. The crude was passed through a short celite plug (**1´´**) buffered with 1% NEt_3 with hexanes (200 mL). The solution was concentrated and subjected to column chromatography [silica gel; 90:10 hexane/EtOAc, 1% Et_3N] to recover a mixture of Z (**161**) and *E* (**170**) ratio 1.4: 1 (121.4 mg,

42%) as yellow oils. 36% of the starting 1-(4-ethynylphenyl)but-3-en-1-ol **(169)** was also recovered.

(b) Study of the stability of the allylation and allylation-hydrostannation product of 4-ethynylbenzaldehyde (6) in the reaction media



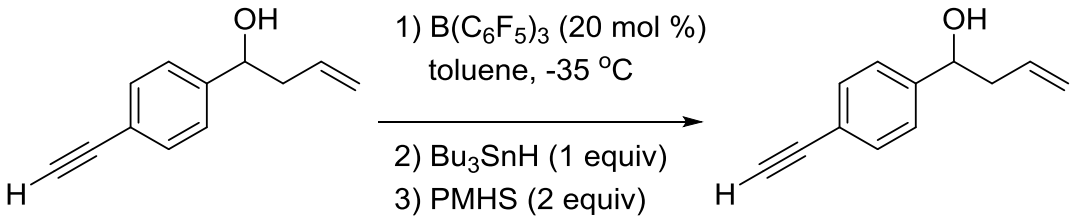
1-(4-Ethynylphenyl)but-3-en-1-ol **(169)** (70 mg, 0.41 mmol) was dissolved in toluene in a round-bottom flask. Then $B(C_6F_5)_3$ (42 mg, 20 mol %) was added to the solution under N_2 (glove bag) and it was cooled to –35 °C. Then PMHS (0.04 mL, 2 equiv) was added dropwise. Finally the reaction was run for 1 h. NEt_3 was added to quench the reaction. The crude was passed through a short celite plug (1´´) buffered with 1% NEt_3 with hexanes (150 mL). The solution was concentrated and subjected to column chromatography [silica gel; 90:10 hexane/EtOAc, 1% Et_3N] to recover the starting material **169** (50 mg, 71%) as a clear oil.



(*Z*)-1-(4-(2-(tributylstannyl)vinyl)phenyl)but-3-en-1-ol (**161**), 100 mg, 0.22 mmol) was dissolved in toluene in a round-bottom flask and the mixture was cooled to –35 °C.

Allylstannane (**135a**) (0.07 mL, 1 equiv) was added followed by BF_3•OEt_2 (0.03 mL, 1.05 equiv). After 15 min $B(C_6F_5)_3$ (22 mg, 20 mol %) was added to the solution under N_2 (glove bag) and it was cooled to –35 °C. PMHS (0.03 mL, 2 equiv) was added and the reaction was run for 1 h. NEt_3 was added to quench the reaction. The crude was passed through a short celite plug (1´´) buffered with 1% NEt_3 with 4:1 hexane/EtOAc solution (200 mL) The solution was concentrated and subjected to column chromatography [silica gel; 80:20 hexane/EtOAc, 1% Et_3N] to afford the starting material **161** (40 mg, 40%) as clear oil.

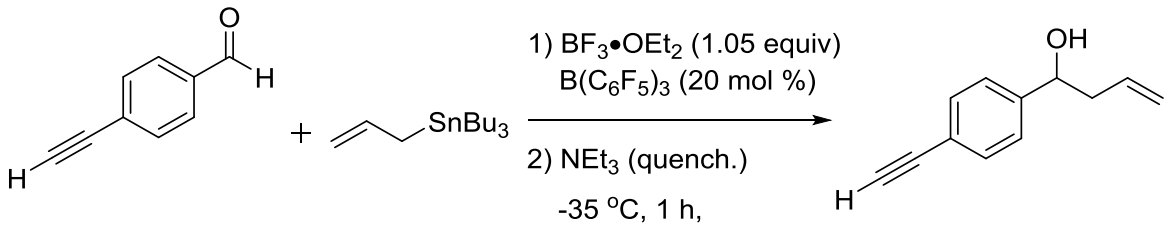
(c) $B(C_6F_5)_3$-catalyzed hydrostannation of 1-(4-ethynylphenyl)but-3-en-1-ol (169) with tributyltin hydride in presence of PMHS



1-(4-ethynylphenyl)but-3-en-1-ol **(169)** (52 mg, 0.30 mmol) was dissolved in toluene in a round-bottom flask. Then $B(C_6F_5)_3$ (31 mg, 20 mol %) was added to the solution under N_2 (glove bag) and it was cooled to –35 °C. Freshly prepared tributyltin hydride (0.08 mL, 1 equiv) was added followed by addition of PMHS (0.04 mL, 2 equiv) dropwise. Finally the reaction was run for 1 h. NEt_3 was added to quench the reaction. The crude was passed through a short celite plug (1´´) buffered with 1% NEt_3 with hexanes (150 mL). The solution was concentrated and subjected to

column chromatography [silica gel; 90:10 hexane/EtOAc, 1% Et_3N] to recover the starting material **169** (41 mg, 79%) and trace amount of *Z*-stannane as clear oils.

(d) One-pot allylation-hydrostannation of 4-ethynylbenzaldehyde without PMHS



4-ethynylbenzaldehyde (**153**) (130 mg, 1 mmol) was dissolved in toluene in a round-bottom flask and the mixture was cooled to –35 °C. Allylstannane (**135a**) (0.31 mL, 1 mmol) was added followed by BF_3•OEt_2 (0.13 mL, 1.05 equiv). The reaction was monitored until complete (15 minutes). At this point, $B(C_6F_5)_3$ (102 mg, 20 mol %) was added to the solution under N_2 (glove bag) and it was cooled to –35 °C. The reaction was run for 1 h. NEt_3 was added to quench the reaction. The crude was passed through a short celite plug (1´´) buffered with 1% NEt_3 with 4:1 hexane/EtOAc solution (200 mL) The solution was concentrated and subjected to column chromatography [silica gel; 80:20 hexane/EtOAc, 1% Et_3N] to afford 1-(4-ethynylphenyl)but-3-en-1-ol (**169**) (160.5 mg, 93%) as a clear oil.

NMR Studies Experimental

^{119}Sn NMR, ^{19}F NMR and ^{11}B NMR study of one-pot allylation/hydrostannation protocol: It should be noted that monitoring this reaction mixture using NMR proved to be very challenging due to the viscosity, heterogeneity, and difficulties in transferring reaction mixtures from reaction flasks to NMR tubes. Performing the entire experiment in an NMR tube without transfer was also problematic most likely due to inefficient mixing. With either method, thorough mixing, careful temperature control, and accurate reagent addition were essential to success. In all cases, if the Sn-F species was not observed, the reaction would not produce the desired product. Temperature of a reaction bath was maintained at –35 °C by dry ice and a mixture of ethanol (30%) and ethylene glycol (70%). All ^{119}Sn and ^{11}B NMR spectra were acquired with a 500 MHz NMR instrument kept at –35 °C. To an NMR tube under nitrogen, in the reaction bath, containing toluene-d_8, were dissolved benzaldehyde (**148**) (0.04 mL, 0.375 mmol) and allyltributylstannane (**135a**) (0.12 mL, 0.375 mmol) and vortexed. The NMR tube containing the reaction mixture was transferred to the spectrometer, at -35 °C, and ^{119}Sn NMR was recorded. The NMR tube was returned to the cold bath, BF_3•OEt_2 (0.05 mL, 0.393 mmol) was added, the tube returned to the instrument, and ^{119}Sn NMR was observed again. $B(C_6F_5)_3$ (38 mg, 20%) was added in a glove bag under N_2 followed by addition of PMHS (0.05 mL) and ^{119}Sn NMR was recorded again. Finally, phenyl acetylene (**149**) was added (0.04 mL, 0.375 mmol) and ^{119}Sn NMR was recorded. These steps were repeated for acquiring the ^{19}F NMR and ^{11}B NMR spectra at the same stages.

REFERENCES

REFERENCES

(1) Davies, A. G. *J. Chem. Res.* **2010**, *Vol 34*, No 4, 181–190.

(2) (a)Davies, A. G; *Organotin Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004: Chapter 1 and 2. (b) Harrison, P. G., in *Chemistry of Tin,* 2nd ed.; Smith. P. J. Ed.; Blackie: London, 1998. Chapter 1 and 2.

(3) Terstiege, I.; Maleczka, R. E. Jr. *J. Org. Chem.* **1999**, *64*, 342–343.

(4) Arkis, E.; Balkoese, D. *Polym. Degrad. Stab.* **2005**, *88*, 46–51.

(5) (a) Kuivila, H. G.; Rahman, W.; Fish, R. H. *J. Am. Chem. Soc.* **1965**, *87*, 2835–2840. (b) Mitchell, T. N.; Schneider, U. *J. Organomet. Chem.*, **1991**, *405*, 195–199. (c) Koerber, K.; Gore, J.; Vatele, J. –M. *Tetrahedron Lett.* **1991**, *32*, 1187–1190.

(6) (a)Davies, A. G; *Organotin Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004: Chapter 9. (b) Wardell, J. L., in *Chemistry of Tin,* 2nd ed.; Smith. P. J. Ed.; Blackie: London, 1998. Chapter 4.

(7) Uneo, Y.; Ohta, M.; Okawara, M. *J. Organomet. Chem.*, **1980**, *197*, C1–C4.

(8) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31–47.

(9) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357–386.

(10) Wuts, P. G. M.; Obrzut, M. L. *Tetrahedron Lett.* **1984**, *25*, 4051–4054.

(11) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229–3231

(12) Pratt, A. J.; Thomas, E. J.; *J. Chem. Soc., Chem. Commun*, **1982**, 1115–1117.

(13) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.* **1983**, 489–490

(14) (a) Keck, G. E.; Salvin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889–7896. (b) Yamammoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243–249, (c) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970–7971.

(15) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647.

(16) Yamamoto, Y.; Yatagai, H.; Naruta, Y. Maruyama, K. *J. Am. Chem. Soc*. **1980**, *102*, 7107-7109.

(17) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239–2246.

(18) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053–1065.

(19) Keck, G. E.; Dougherty, S. M.; Savin, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 6210–6223.

(20) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem* **1983**, *48*, 4634–4642. (b) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408–422. (c) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586.

(21) Nicolaou, K. C.; Leung, G. Y. C.; Dethe, D. H.; Guduru, R.; Sun, Y.-P.; Lim, C. S.; Chen, D. Y. -K. *J. Am. Chem. Soc.* **2008**, *130*, 10019–10023.

(22) For allylation/ alkyne hydrostannation sequences with stoichiometric amounts of tin, see: (a) Fliegel, F.; Beaudet, I.; Quintard, J.-P. *J. Organomet. Chem*. **2001**, *624*, 383–387. (b) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873–8876. (c) Chakraborty, T. K.; Pulukuri, K. K.; Sreekanth, M. *Tetrahedron Lett*. **2010**, *51*, 6444–6446. (d) Kerric, G.; Grognec, E. L.; Fargeas, V.; Zammattio , F.; Quintard, J.-P.; Biesemans, M.; Willem, R. *J. Organomet. Chem*. **2010**, *695*, 1414–1424. (e) Candy, M.; Tomas, L.; Parat, S.; Heran,V.; Bienayme, H.; Pons, J.-M.; Bressy, C. *Chem. Eur. J.* **2012**, *18*, 14267–14271.

(23) For an allylation/allene hydrostannation see Chang, H.-M.; Cheng, C.-H. *Org. Lett*. **2000**, *2*, 3439–3442.

(24) Ghosh, B.; Amado-Sierra, M. I.; Holmes, D.; Maleczka, R. E. Jr. *Org. Lett.* **2014**, *16*, 2318–2321.

(25) Yano, K.; Baba, A.; Matsuda, H. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 66–70.

(26) (a) Gervorgyan, V.; Liu, J.-X.; Yamamoto, Y. *Chem. Commun*. **1998**, 37–38. (b) Maleczka, R. E. Jr.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem*. **1999**, *64*, 5958–5965.

(27) (a) Boaretto, A.; Morton, D.; Tagliavini, G.; Ganis, P. *J. Organomet. Chem.* **1987**, *321*, 199–207. (b) Denmark, S. E.; Wilson, T.;Willson, T. M. *J. Am. Chem. Soc*. **1988**, *110*, 984–986. (c) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett*. **1989**, *30*, 7349–7352. (d) Harston, P.; Wardell, J. L.; Marton, D.; Tagliavini, G.; Smith, P. J. *Inorg. Chim. Acta* **1989**, *162*, 245–250. (e) Marshall, J. A.; Gill, K. *J. Organomet. Chem*. **2001**, *624*, 294–299. (f) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136-

8141. (g) Cokley, T. M.; Harvey, P. J.; Marshall, R. L.; McCluskey. A.; Young, D. J. *J. Org. Chem*. **1997**, *62*, 1961–1964.

(28) (a) Kazmaier, U.; Schauss, D.; Pohlman, M. *Org. Lett.* **1999**, *1*, 1017–1019. (b) Maleczka, R. E., Jr.; Ghosh, B.; Gallagher, W. P.; Baker, A. J.; Muchnij, J. A.; Szymanski, A. L. *Tetrahedron* **2013**, *69*, 4000–4008.

(29) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 1071–1087.

(30) Davies, A. G; *Organotin Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004: Chapter 2.

(31) Dakternieks, D.; Zhu,H.; *Organometallics*, **1992**, *11*, 3820–3825. b) Al-Juaid, S. S.; Dhaher, S. M.; Eaborn, C.; Hitchcock, P. B.; Smith, J. D. *J. Organomet. Chem*. **1987**, *325*, 117–127. c) Plass, W.; Verkade, J. G. *Inorg. Chem.* **1993**, *32*, 5153–5159. d) Dean, P.A.W.; Evans, D.F. *J. Chem. Soc. (A)* **1968**, 1154–1166.

(32) a) Carbillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Org. Lett.* **2001**, *3*, 1165–1167. b) Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds Containing Two-, Three-, and Four-Coordinate Boron*. In Annual Reports on NMR Spectroscopy; Webb, G.A., Ed.; Academic Press: London, **1988**; Vol. 20; p 61.

(33) Chandrasekhar, S.; Reddy, C. R.; Babu, B. N. *J. Org. Chem*. **2002**, *67*, 9080–9082.

(34) The coupling is ~1450 Hz. Accurate measurement of these couplings is difficult due to the broadness of the peaks.

(35) Note: In fact, $(Bu_3Sn)_2O$, an oxygen bound tin species, reacts with PMHS at –35 °C to form tributyltin hydride, albeit, at a much slower rate compared to that observed at room temperature. The rate at which $(Bu_3Sn)_2O$ forms tributyltin hydride at –35 °C increases a great deal when $B(C_6F_5)_3$ was added.

(36) Lawrence, N. J.; Drew, M. D. Bushell, S. M. *J. Chem. Soc., Perkin Trans*. *1*, **1999**, 3381–3391.

(37) Kim, Y. W.; Labouriau, A.; Taylor, C. M.; Earl, W. L.; Weberlow, L. G. *J. Phys. Chem.* **1994**, *98*, 4919–4922.

(38) a) Feher, F.J.; Soulivong, D.; Lewis, G.T. *J. Am. Chem. Soc.* **1997**, *119*, 11323–11324. b) For a bridging fluoride, see Panisch, R.; Bolte, M.; Müller, T. *J. Am. Chem. Soc.* **2006**, *128*, 9676–9682.

(39) This last ^{11}B NMR was obtained from a kinetic experiment perform by Dr. Ghosh.

CHAPTER 4: CARBON-TO-CARBON [1,2]-SILYL MIGRATION IN ALPHA SILYL ALLYLIC ALCOHOLS TRIGGERED BY EPOXIDATION

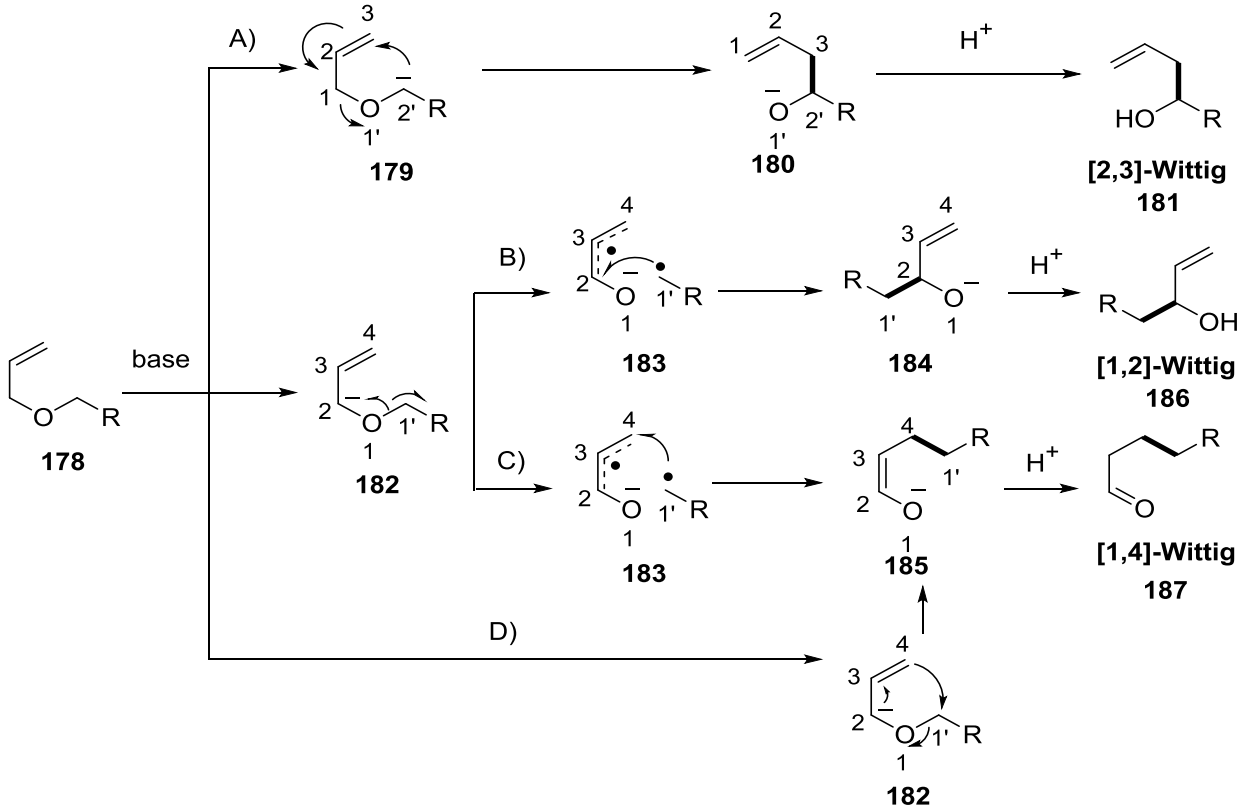
4.1 Introduction

Bond reorganization of α-metalated ethers are known as Wittig rearrangements.[1] These reactions can take place via different pathways depending on the nature of the substrate (e.g. symmetrical vs. unsymmetrical ethers, neighboring π-systems, etc). Wittig rearrangements can proceed through a concerted, orbital-symmetry allowed [2,3]-sigmatropic pathway (Scheme 4.1, route A),[2,3] or a stepwise radical/radical-anion pair [1,2]-migration (route B).[4] Deprotonation at the allylic position followed by rearrangement would provide the [1,2] and [1,4] product (**186** and **187**), whereas metalation at the benzylic position (if R = Ph in **179**) would lead to the [2,3] product **181**. Therefore, regioselectivity in the deprotonation step is an important factor in charting the synthetic course of Wittig rearrangements.

Preparation of substrates capable of efficient [1,2]-migration are limited perhaps by the required radical-stabilization groups (R in **183**) for facile C–O bond homolysis. Another problem is the regioselectivity issue after the radical formation of **183** species from **182** (scheme 4.1), where a mixture of products can be obtained for the competition between the [1,4]-migration and the [1,2]-shift.[5,6] This problem is not observed for the [2,3]-Wittig rearrangement, which has found more synthetic applications due to their remarkable features of regioselective carbon-carbon bond formation, generation of specific olefin geometries and transfer of chirality.[2]

The last two routes **C** and **D** (Scheme 4.1) highlight the [1,4]-wittig rearrangement as a unique pathway in the formation of stereodefined enolates.[7-9] There is evidence supporting a

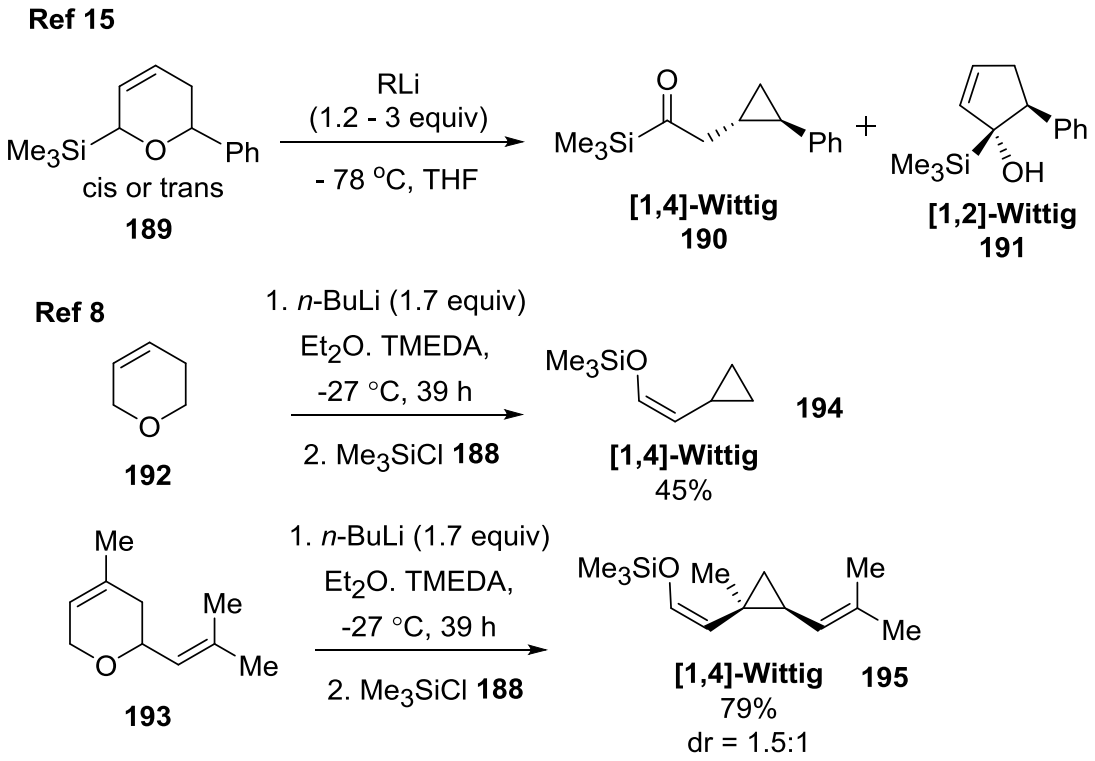
stepwise mechanishm (route C),[9,10] however if the orbitals are aligned on a cisoid conformation a concerted process is allowed in some substrates (route D).[1b] The critical factors that favor the [1,4] over the [1,2] pathways or vice versa, are not totally clear.[8,11-13] It is known that the [1,4]-shift is favored at lower temperatures, furthermore the nature of the base and base counterion also affect the final product distribution.[9] Conversely, the major influential factor seems to be the substrate type that can direct the rearrangement to one particular pathway preferentially over the other.[9,14] But, few studies have been done in order to fully address this substrate dependence.[9]



Scheme 4.1 Possible Wittig rearrangement pathways of **178**

In the quest for a better understanding of the selectivities in [1,4] vs [1,2] Wittig rearrangements from earlier studies done in our labs, we explored these rearrangements on small cyclic ethers (Scheme 4.2). We demonstrated that the transformation of these diastereomeric 2-

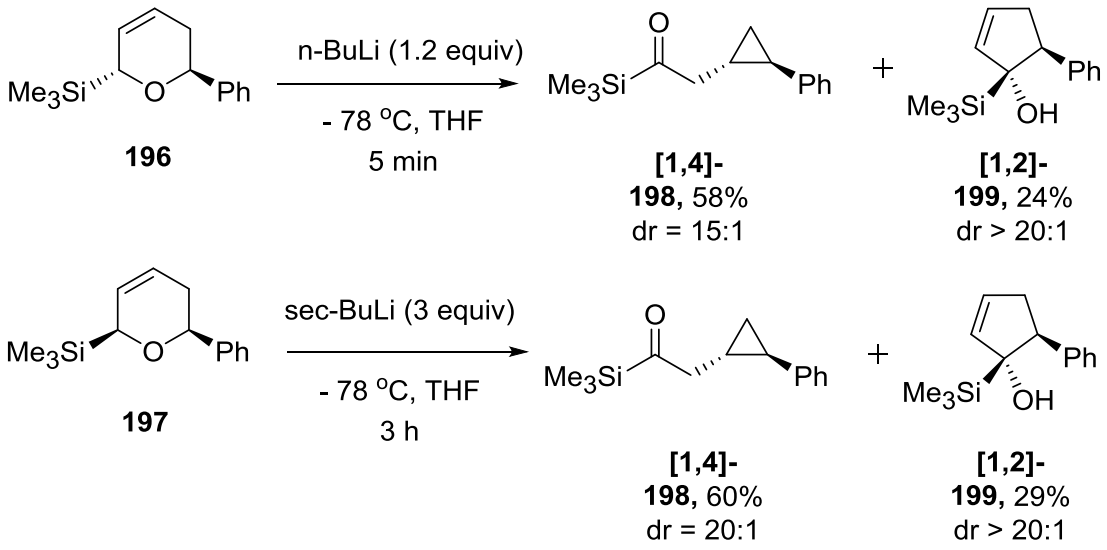
silyl-6-aryl-5,6-dihydro-(2*H*)-pyrans (**189**) was directed by electronic and steric factors.[15] The remarkable work done by Dr. Mori showed that the proper choice of the silyl group or selective olefin substitution, as well the appropriate electron-donating or electron-withdrawing group on the aromatic moiety allow one to direct this ring contractions toward the α-cyclopropyl acylsilanes **190** (via [1,4]-Wittig) or α-silyl cyclopentenols (via [1,2]-Wittig) **191** with excellent diastereselectivities and in a stereoconvergent fashion.



Scheme 4.2 Known Wittig rearrangements of dihydropyrans

Even though, the ring contraction of macrocyclic ethers via [1,2]- and [2,3]-Wittig rearrangements have been reported by Marshall[16-18] and Takahashi,[19-21-,22,23] the study of smaller cyclic ethers is limited to few examples.[8,24-28] In particular, the [1,4]-Wittig rearrangement of cyclic allylic ethers was limited to two examples reported by Rautenstrauch,[8]

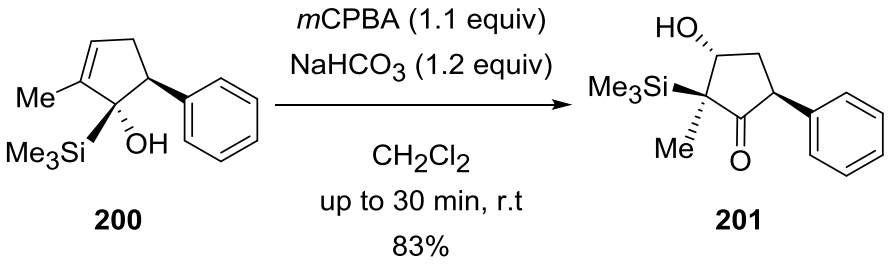
this study showed that isomerization of dihydropyran (**192**) and nerol oxide (**193**) occur to give the corresponding α-cyclopropyl acetaldehydes **194** and **195** (scheme 4.2). The work done by Dr. Mori not only gives us access to novel structures like **190** and **191**, it also shows us that it may be possible to tune this reaction towards the [1,4] or the [1,2] pathway and is what makes this research stand out. Further stereochemical experiments showed that both the [1,4]- and [1,2]-Wittig rearrangements of such cyclic ethers proceed with high retention of stereochemistry at the migrating center. Finally deuterium trapping experiments indicated the presence of a common intermediate, leading to the observed stereoconvergence of both isomerization pathways (Scheme 4.3).[15] It was concluded that the primary mechanism of the [1,4]-Wittig reaction in these substrates involves a stepwise process similar to the [1,2]-pathway.



Scheme 4.3 [1,4]- and [1,2]-Wittig rearrangements of model 2-silyldihydropyrans

As part of our studies on organosilicon compounds we decided to study a series of α-silyl allylic alcohols (**191**) of the type obtained from the [1,2]-Wittig rearrangements of allyl benzyl

ethers (**189**) with a silyl group at the α-allylic position[29] under epoxidizing conditions. Upon treatment of alcohol **200** with *m*-CPBA in the presence of sodium bicarbonate, an interesting rearrangement that involves a carbon-to-carbon [1,2]-silyl migration was triggered (Scheme 4.4). This novel migration generates α-silyl ketone **201** via a simple protocol.



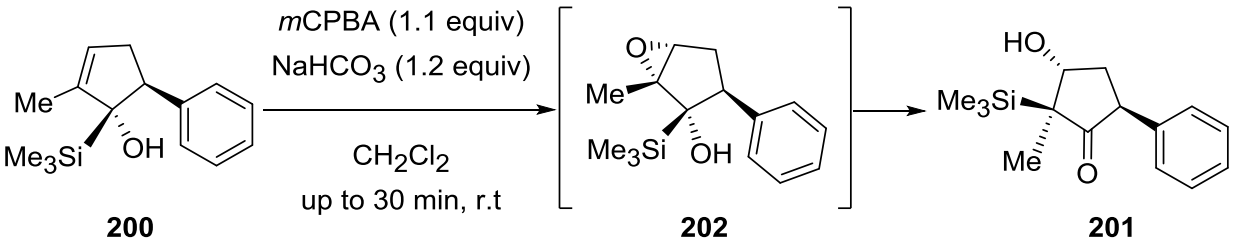
Scheme 4.4 Novel [1,2]-silyl migration in α-silyl allylic alcohols

4.2 Carbon-to-carbon [1,2]-silyl migration

The most common 1,2-shift of silicon it is the one involving the migration from C to O of the so called Brook rearrangement (see Chapter 1 page 7). A less common and often unexplored transformation is the 1,2-silyl migration from C to C. The literature examples of such 1,2-silyl migration are typically triggered by protic acids.[30] Other examples of 1,2-silyl migrations involve alkynyl silanes or silyl propagylic systems and are catalyzed by Lewis acids[31] and/or transitions metals.[32] However, to the best of our knowlegde 1,2-silyl migration of α-silyl allylic alcohols to generate α-silyl ketones **201** has not been reported. Therefore all the structures presented in this study are new organosilicon containing molecules.

Although the substrates employed in this novel protocol are racemic alcohols, it seems that the migration of the silyl group occurs in a *syn* fashion without epimerization of the benzylic

position. The stereoselective epoxidation of the double bond by *m*-CPBA could be guided by the intramolecular hydrogen bonding interaction with the tertiary alcohol (Scheme 4.5). Then the epoxide opening could be due to ring strain for the formation of an epoxide group next to the cyclopentane framework. This silyl migration appears to be triggered by the release of unfavorable ring strain and also by steric interactions between the bulky phenyl and trimethylsilyl groups that are *syn* to one another.



Scheme 4.5 Proposed mechanism for carbon-to-carbon [1,2]-silyl migration

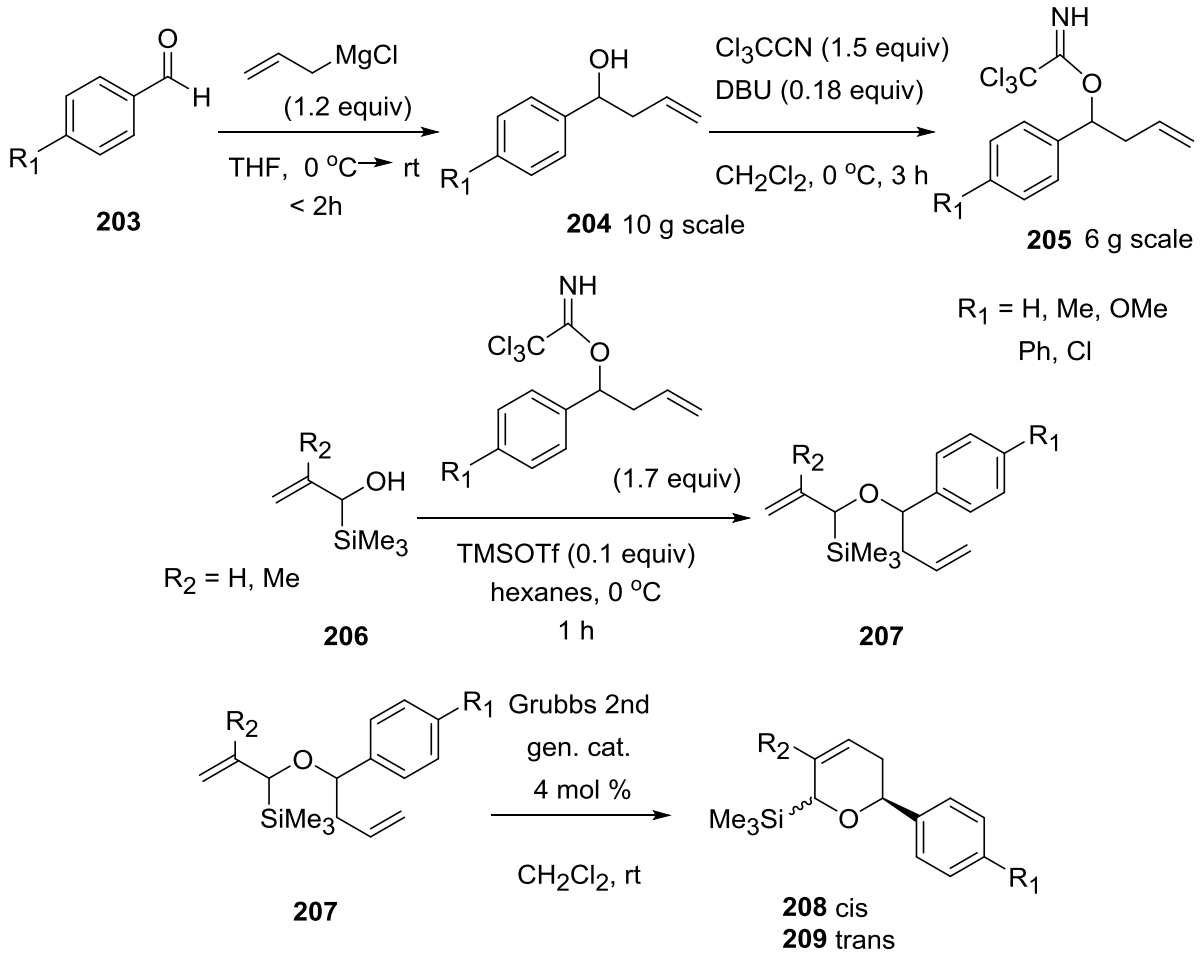
At this point it is unknown if this protocol proceeds though a concerted process (epoxide ring opening/silyl migration) or stepwise (epoxide ring opening to give a tertiary carbocation, then silyl migration). A concerted mechanism would involve an intramolecular S_N2 reaction at a quaternary center by a bulky silyl group, which seems unlikely. Therefore a stepwise process is more probable. As mentioned before previous reports on 1,2-silyl migration indicate the formation of a carbocation followed by 1,2-sillyl migration is usually triggered by protic acids.[30]

4.2.1 Synthesis of starting materials

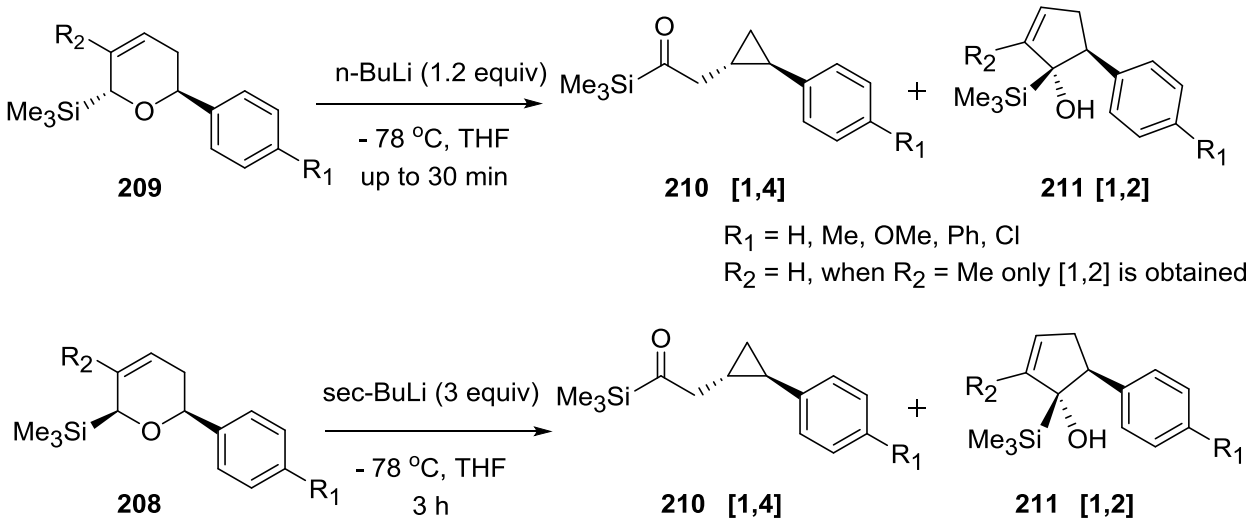
The preparation of the selected α-silyl allylic alcohols [1,2]-Wittig products, was developed and optimized by Dr. Mori.[15] This route was employed again for the preparation of our starting materials (Scheme 4.6). The synthesis of the cyclic ethers started with the addition of homoallylic alcohols to trichloroacetonitrile under basic conditions (**204** → **205**). Lewis acid-catalyzed etherification of α-silyl alcohols (**206**) with the homoallylic trichloroacetimidate (**205**) yield the bisallylic precursors **207**. The α-hydroxysilanes **206** were prepared by a retro-Brook rearrangement of the in situ generated O-silylated allylic alcohols. The dienes **207** were submitted to ring-closing metathesis using the Grubbs 2nd generation catalyst to afford the cyclic ethers cis **208** and trans **209** (Scheme 4.6).

The cyclic ethers were obtained as mixtures of cis/trans diastereomers from diastereomeric **207** or as a single diastereomer from either *syn* or *anti*-**207** via ring closing metathesis. The cis/trans cyclic ethers were completely separable by column chromatography. Finally the isolated cis **208** and trans **209** were subjected to the Wittig rearrangement conditions to yield the [1,4] (**210**) and [1,2] (**211**) products (Scheme 4.7).

As with previous examples[15] the trans cyclic ethers rearranged more quickly and efficiently than the cis. Also electron-donating groups on the aromatic moiety favored the [1,4]-shift (Entry 1, Table 4.1) while electron-withdrawing groups favored the [1,2]-pathway. Therefore all the substrates selected for these studies on silyl migration were those where the [1,2]-Wittig products were major (Entry 2 to 4, Table 4.1).

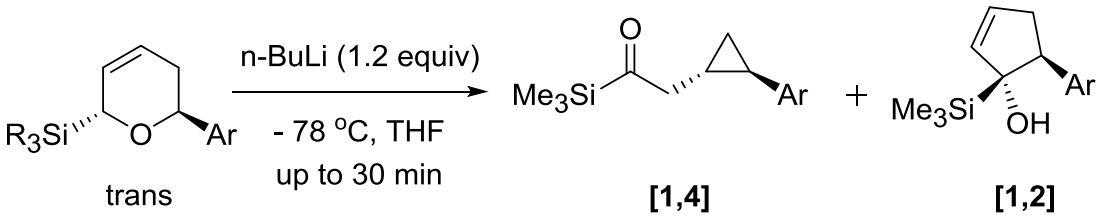


Scheme 4.6 Synthesis of cyclic ethers **208** and **209**



Scheme 4.7 Synthesis of [1,4] and [1,2]-Wittig rearrangement products

Table 4.1 Wittig rearrangement of trans-disubstituted pyrans for selected substrates[15]

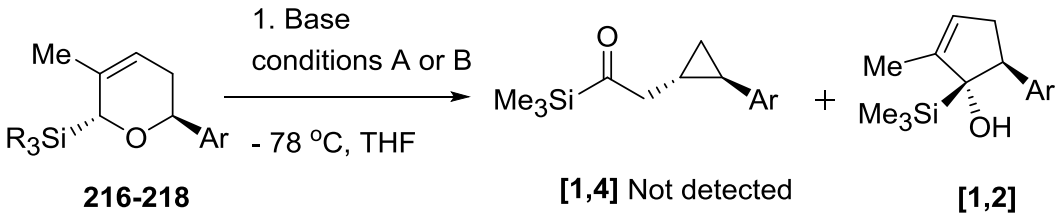


Entry	Substrate	SiR_3	Ar	[1,4]-Wittig[a]	dr [1,4][b]	[1,2]-Wittig[a,c]
1	**212**	$SiMe_3$	4-$MeOC_6H_4$	65%	15:1	--
2	**213**	$SiMe_3$	4-ClC_6H_4	28%	15:1	65%
3	**214**	$SiMe_3$	4-PhC_6H_4	4%	nd	59%
4	**215**	$SiEt_3$	2-Naph	16%	6:1	75%

[a]Isolated yields. [b]Determined from ^1H NMR spectra of isolated material.
[c]dr>>20:1 in all cases.

Placing an alkyl substituent on the double bond proximal to the silicon group afforded exclusively the [1,2]-Wittig products, even when *para* positioned electron-donating groups on the Ar moeity were present (Entries 3-6, Table 4.2).[15] This is in contrast to previous observations where R_2 = H, in which [1,4]-Wittig were favored in the presence of para electron-donating substituents.[15] Once again the trans diastereomers were more reactive and higher yielding than the cis isomers in these reactions. Thus some of these trans substrates were selected for the 1,2 silyl migrations studies.

Table 4.2 Effect of substitution at the double bond[15]

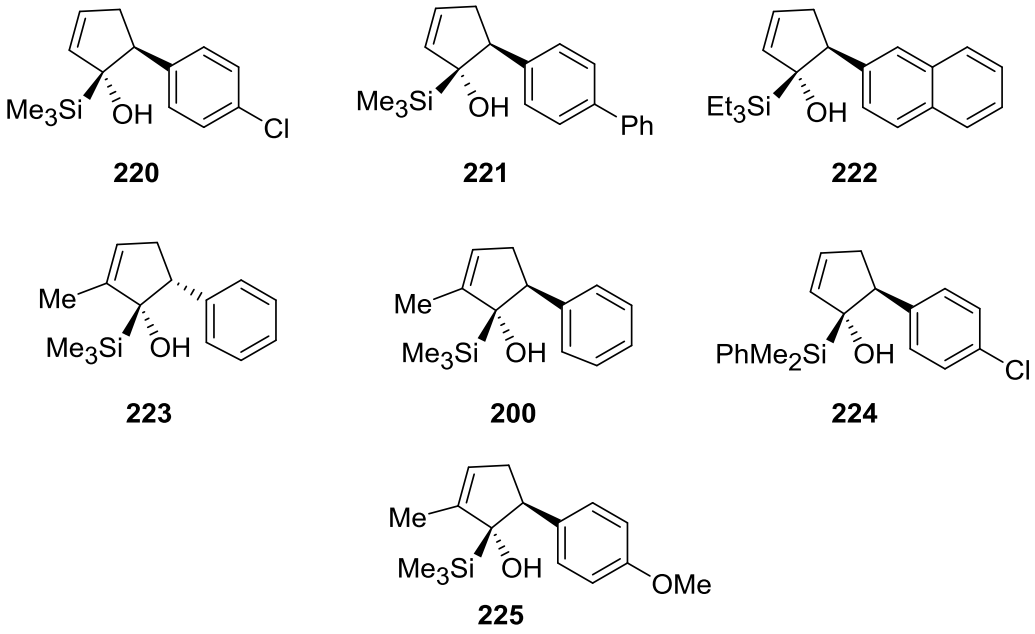


216-218 **[1,4]** Not detected **[1,2]**

Entry	Substrate	Ar	base[a]	Time	[1,2]-Wittig[b]
1	**216a**	Ph	*sec*-BuLi	7 h	79%
2	**216b**	Ph	*n*-BuLi	0.5 h	85%
3[c]	**217a**	4-$MeOC_6H_4$	*sec*-BuLi	7 h	26%
4	**217b**	4-$MeOC_6H_4$	*n*-BuLi	0.5 h	72%
5[d]	**218a**	4-MeC_6H_4	*sec*-BuLi	5.5 h	75%
6	**219b**	4-MeC_6H_4	*n*-BuLi	0.5 h	91%

[a] a cis substrates: 3 equiv of base, b trans substrates: 2 equiv of base. [b]dr = 99:1 [c]29% recovered starting material. [d]15% recovered starting material.

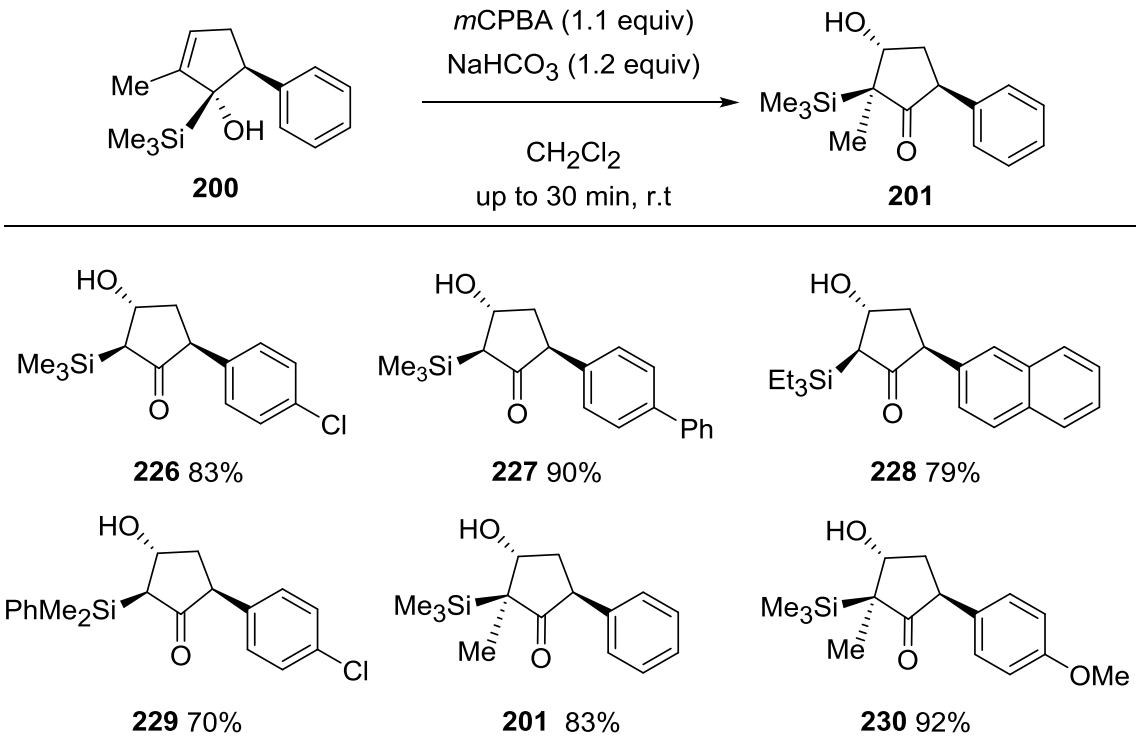
Finally the following starting materials were selected to undergo the 1,2-silyl migration (Scheme 4.8). As mention before they were obtained as the major product of the Wittig rearrangements and most of these compound were isolated as white solids. During the preparation of these substrates a crystal structure of the 2-napthyl derivative (**222**) was obtained, confirming our relative stereochemical assignment.[15]



Scheme 4.8 Selected starting materials for 1,2-silyl migration

4.3 Results and discussion

Scheme 4.9 shows the products obtained by this novel carbon-to-carbon [1,2]-silyl migration. Upon treatment of the selected [1,2]-Wittig products with *m*-CPBA in the presence of sodium bicarbonate, the cyclopentanone derivatives were obtained. The reactions were run for up to 30 min at room temperature using dichloromethane as a solvent. The yields ranged from moderated to high (70% to 92%) and in some cases purification by column chromatography was not necessary.



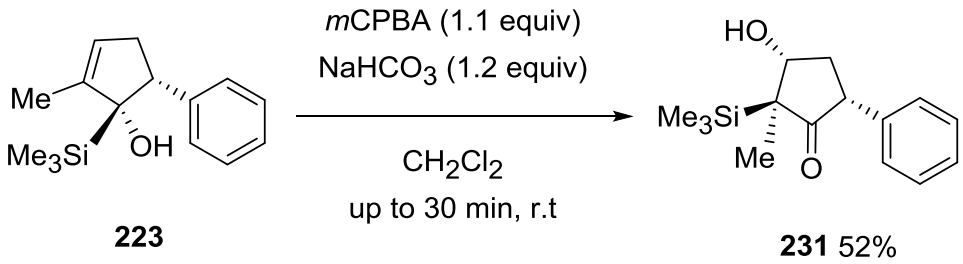
Scheme 4.9. Carbon-to-carbon [1,2]-silyl migration

Even though the cyclopentanone products contain a hydroxyl group and R_3Si unit next to each other on the cyclopentanone framework (β-hydroxysilanes), an expected loss of the silicon group via a Peterson olefination[33] was not observed. Usually under diluted acid conditions or Lewis acid these type of substrates undergo a stereospecific *anti*-elimination (E2) to afford an alkene. When the hydroxyl group and silyl moiety are *syn* to each other, basic conditions are required for a *syn*-elimination via the formation of an oxasiletadine intermediate.[33] The latter scenario is not possible for our substrates because the hydroxyl group and the R_3Si unit are *anti* to each other.

In our hands the cyclopentanone compounds were stable during purification and isolation. However several months after storage under freezing conditions, a ^1H NMR was

retaken in order to check the stability of the cyclopentanones products. Unfortunately loss of the SiR_3 was observed in all the products, and the NMR show complicated mixtures.

A notable case was the rearrangement of a cyclopentanol substrate where the silyl group was trans to the phenyl group (**223**). Even though the yield was lower than other examples, the substrate underwent the [1,2]-silyl migration and no epimerization was observed (scheme 4.10). This result suggested that the position of the phenyl group does not determine the stereochemistry of this reaction, instead the position of the tertiary allylic alcohol dominates this transformation promoting a stereoselective epoxidation presumably guided by intermolecular hydrogen bonding interaction.



Scheme 4.10 [1,2]-silyl migration of **223** as a single diastereomer

4.4 Conclusions

A novel carbon-to-carbon [1,2]-silyl migration was discovered. This migration was triggered by epoxidation of the olefin present in the [1,2]-Wittig product (1-silylcyclopent-2-en-1-ol structures). The new cyclopentanones obtained feature a silyl group located at the α position of the carbonyl. There are no reports of similar cyclic structures. Furthermore, substitution at the double bond leads to more stable materials, threfore the purification process of those products in some cases does not require column chromatography.

Finally this migration was not affected by the different SiR_3 groups employed (R = Me, Et or Me_2Ph) or by the aryl group being cis or trans to the silyl group. We believe that the stereochemistry of this reaction is determine by the position of the tertiary allylic alcohol, thus promoting a sterereoselective epoxidation guided by intermolecular hydrogen bonding interactions.

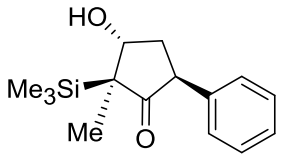
4.5 Experimental section

All reactions were run under a positive atmosphere of nitrogen in oven-dried or flame-dried round bottom flasks or disposable drum vials capped with rubber septa. Solvents were removed by rotary evaporation at temperatures lower than 45 ºC. Column chromatography was run on silica gel 60 Å (230–400 mesh ASTM). Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone under nitrogen; dichloromethane, benzene, diisopropylamine, triethylamine and trimethylsilyl chloride were distilled from calcium hydride. Hexane and cyclohexane were used as received. Triethylsilyl chloride and dimethylphenylsilyl chloride, were used as received. Methyllithium (1.4 M in diethyl ether), *n*-butyllithum (1.6 M in hexanes), *sec*-butyllithium (1.4 M in cyclohexane) were titrated with diphenylacetic acid (average of three runs). ^1H NMR spectra was collected in 500 MHz and 600 MHz instruments using $CDCl_3$ as solvent, which was referenced at 7.24 ppm (residual chloroform proton) and ^{13}C NMR spectra was collected in $CDCl_3$ at 126 MHz or 151 MHz and referenced at 77 ppm. Yield refer to chromatographically and spectroscopically pure compounds unless otherwise mentioned.

General conditions for [1,2]-silyl migration

To a solution of the corresponding α-silyl allylic alcohol (0.2 mmol) in dichloromethane (2 mL) was added $NaHCO_3$ (1.2 equiv) followed by *m*-CPBA (~77% w/w, 1.1 equiv). The reaction mixture was stir for 30 min at room temperature. The reaction was followed by TLC (typically 5% EtOAc in hexanes) using triethylamine pre-washed plates. After completion (typically 30 min), the reaction was diluted with CH_2Cl_2 (5 mL) and extracted twice with $NaHCO_3$ (2 x 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 mL). Combined organic extracts were washed with Brine, dried over $MgSO_4$, filtered and concentrated by rotary evaporation. Finally the residue was purified by silica gel column chromatography (typically 5% EtOAc in hexanes) buffered with ~1% triethylamine.

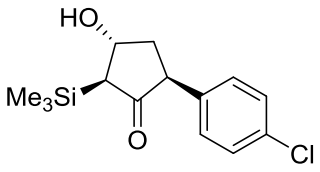
Experimental details and spectroscopic data:



201 83%

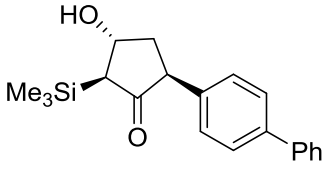
Following the general procedure to the α-silyl allylic alcohol **200** (15.7 mg, 0.064 mmol, 1 equiv), m-CPBA (77% w/w, 15.72 mg, 0.0701, 1.1 equiv) and $NaHCO_3$ (6.43 mg, 1.2 equiv) afforded after column chromatography (10% EtOAc in hexanes) 14 mg (83%) of **201** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 4 H), 7.21 (m, 1 H), 4.56 (m, 1 H), 3.76 (dd, *J* = 8.5, 12.5 Hz, 1 H), 2.50 (ddd, *J* = 1.2, 8.4, 13.8 Hz, 1 H), 2.40 (ddd, *J* = 4.2, 12.6, 13.8 Hz, 1

H), 1.73 (s, 1 H), 1.28 (s, 3 H), 0.04 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.0, 137.0, 128.4 (2 C), 127.8 (2 C), 126.7, 72.5, 50.7, 50.1, 36.7, 13.8, -2.3.



226 83%

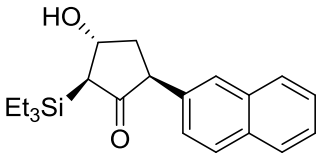
Following the general procedure to the α-silyl allylic alcohol **220** (40 mg, 0.150 mmol, 1 equiv), m-CPBA (77% w/w, 36.97 mg, 0.165 mmol, 1.1 equiv) and $NaHCO_3$ (15.12 mg, 1.2 equiv) afforded after column chromatography (20% EtOAc in hexanes) 35.3 mg (83%) of **226** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz 2 H), 7.17 (d, *J* = 8.5 Hz, 1 H), 4.71 (d, *J* = 4.0 Hz, 1 H), 3.81 (dd, *J* = 8.5, 12.2 Hz, 1 H), 2.51 (m, 1 H), 2.32 (m, 1 H), 2.28 (dt, *J* = 4.0, 13.5 Hz, 1 H), 1.26 (s, 1 H), 0.13 (s, 9 H).



227 90%

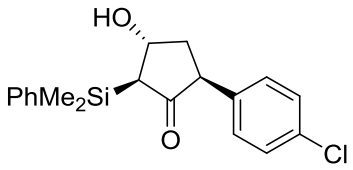
Following the general procedure to the α-silyl allylic alcohol **221** (26.5 mg, 0.086 mmol, 1 equiv), m-CPBA (77% w/w, 21.18 mg, 0.094, 1.1 equiv) and $NaHCO_3$ (8.66 mg, 1.2 equiv) afforded after column chromatography (20% EtOAc in hexanes) 25 mg (90%) of **227** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 5 H), 7.41 (t, *J* = 7.8 Hz, 2 H), 7.28 (m 2 H), 4.71

(d, *J* = 4.2 Hz, 1 H), 3.86 (dd, *J* = 8.4, 12.6 Hz, 1 H), 2.53 (m, 1 H), 2.36 (dt, *J* = 4.2, 13.2 Hz, 1 H), 2.31 (m, 1 H), 1.25 (s, 1 H), 0.15 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.7, 140.9, 139.8, 136.3, 128.7 (2C), 128.4 (2 C), 127.3 (2 C), 127.1, 127.0 (2 C), 70.5, 54.0, 51.0, 39.2, -1.5.



228 79%

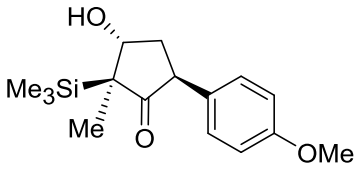
Following the general procedure to the α-silyl allylic alcohol **222** (25 mg, 0.077 mmol, 1 equiv), m-CPBA (77% w/w, 18.98 mg, 0.084 mmol, 1.1 equiv) and $NaHCO_3$ (7.76 mg, 1.2 equiv) afforded after column chromatography (20% EtOAc in hexanes) 20.7 mg (79%) of **228** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.82 (m, 3 H), 7.65 (s, 1 H), 7.5-7.40 (m, 3 H), 4.80 (m, 1 H), 3.80 (m, 1 H), 3.49 (m, 1 H), 2.62 (m, 1 H), 2.50 (m, 1 H), 1.80 (s. 1 H), 0.89 (t, *J* = 8.0 Hz, 9 H), 0.70 (dq, *J* = 1.5, 8.0 Hz, 6 H).



229 70%

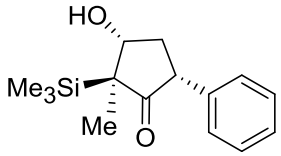
Following the general procedure to the α-silyl allylic alcohol **224** (15 mg, 0.046 mmol, 1 equiv), m-CPBA (77% w/w, 11.25 mg, 0.05 mmol, 1.1 equiv) and $NaHCO_3$ (4.60 mg, 1.2 equiv) afforded after column chromatography (20% EtOAc in hexanes) 11 mg (70%) of **229** as a white

solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (m, 3 H), 7.36 (m, 2 H), 7.18 (d, *J* = 8.0, 2 H), 6.75 (d, *J* = 8.0 Hz, 2 H), 4.70 (d, *J* = 3.5 Hz, 1 H), 3.71 (ddd, *J* = 1.8, 3.0, 6.5 Hz, 1 H), 3.50 (ddd, *J* = 1.2, 2.4, 6.5 Hz, 1 H), 2.49 (m, 1 H), 2.31 (m, 1 H), 1.96 (dt, *J* = 4.0, 13.5 Hz, 1 H), 1.56 (s, 1 H), 0.50 (s, 3 H), 0.46 (s, 3 H).



230 92%

Following the general procedure to the α-silyl allylic alcohol **225** (50 mg, 0.181 mmol, 1 equiv), m-CPBA (77% w/w, 44.62 mg, 0.199 mmol, 1.1 equiv) and $NaHCO_3$ (18.25 mg, 1.2 equiv) afforded after column chromatography (20% EtOAc in hexanes) 48.6 mg (92%) of **230** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.56 (d, *J* = 4.0 Hz, 1 H), 3.80 (s, 3H), 3.72 (dd, *J* = 8.5, 13 Hz, 1 H), 2.50 (ddd, *J* = 1.5, 8.9, 13.5 Hz, 1 H), 2.38 (ddd, *J* = 4.5, 10.5, 13 Hz 1 H), 1.30 (s, 3 H), 1.27 (s, 1H) 0.07 (s, 9 H).



231 52%

Following the general procedure to the α-silyl allylic alcohol **223** (40 mg, 0.163 mmol, 1 equiv), m-CPBA (77% w/w, 40.12 mg, 0.1790 mmol, 1.1 equiv) and $NaHCO_3$ (16.37 mg, 1.2 equiv) afforded after column chromatography (20% EtOAc in hexanes) 22.1 mg (52%) of **231** as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.34 (m, 2 H), 7.26 (m, 3 H), 4.59 (m, 1 H), 3.42

(dd, *J* = 8.5, 9.7 Hz, 1 H), 2.79 (ddd, *J* = 5.4, 9.7, 13.8 Hz, 1 H), 2.23 (ddd, *J* = 5.0, 8.5, 13.8 Hz, 1 H), 1.60 (s, 1 H), 1.27 (s, 3H), 0.17 (s, 9 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 218.1, 139.2, 128.6 (2 C), 128.5 (2 C), 126.7, 72.8, 53.9, 51.2, 38.6, 12.2, -3.6.

REFERENCES

REFERENCES

(1) (a) Mikami, H.; Nakai, T. *Org. React.* **1994**, *46*, 105–209. (b) Marshall, J. A. *In Comprehensive Organic Synthesis*; Pattenden, G., Ed.; Pergamon: London, **1991**; Vol. 3, pp 975–1014.

(2) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885-902.

(3) Nakai, T.; Tomooka, K. *Pure Appl. Chem.* **1997**, *69*, 595-600..

(4) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann. Recl.* **1997**, 1275-1281.

(5) Felkin, H.; Tambute, A. *Tetrahedron Lett.* **1969**, 821-822.

(6) Schöllkopf, U. *Angew. Chem., Int. Ed.* **1970**, *9*, 763-773.

(7) Briére, R.; Chérest, M.; Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1977**, *18*, 3489-3492.

(8) Rautenstrauch, V. *Helv. Chim. Acta* **1972**, *55*, 594-609.

(9) Schlosser, M.; Strunk, S. *Tetrahedron* **1989**, *45*, 2649-2664.

(10) Felkin, H.; Frajerman, C. *Tetrahedron Lett.* **1977**, *18*, 3485-3488.

(11) Tomooka, K.; Yamamoto, H.; Nakai, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4500-4502.

(12) Hodgson, D. M.; Tomooka, K.; Gras, E. *Top. Organomet. Chem.* **2003**, *5*, 217-250.

(13) Onyeozili, E. N.; Maleczka, R. E. *Chem. Commun.* **2006**, 2466-2468.

(14) Onyeozili, E. N.; Mori-Quiroz, L. M.; Maleczka, R. E. *Tetrahedron* **2013**, *69*, 849-860.

(15) Mori-Quiroz, L. M.; Maleczka, R, E., Jr. *J. Org. Chem.* **2015**, *80*, 1163–1191.

(16) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925-2931.

(17) Marshall, J. A.; Robinson, E. D.; Lebreton, J. *J. Org. Chem.* **1990**, *55*, 227-239.

(18) Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796-797.

(19) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315-4316.

(20) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499-5520.

(21) Doi, T.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 3465-3467.

(22) Audrain, H.; Skrydstrup, T.; Ulibarri, G.; Riche, C.; Chiaroni, A.; Grierson, D. S. *Tetrahedron* **1994**, *50*, 1469-1502.

(23) Tsubuki, M.; Takahashi, K.; Honda, T. *J. Org. Chem.* **2003**, *68*, 10183-10186.

(24) Mazaleyrat, J. P.; Welvart, Z. *Nouv. J. Chim.* **1983**, *7*, 491-497.

(25) Schmidt, R. R.; Beitzke, B. *Chem. Ber. Recl.* **1983**, *116*, 2115-2135.

(26) Verner, E. J.; Cohen, T. *J. Org. Chem.* **1992**, *57*, 1072-1073.

(27) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375-377.

(28) Soloshonok, V. A.; Ohkura, H.; Yasumoto, M. *J. Fluorine Chem.* **2006**, *127*, 708-711.

(29) (a) Maleczka, R. E. Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1115–1118. (b) Onyeozili, E. N.; Maleczka, R. E. Jr. *Tetrahedron Lett.* **2006**, *47*, 6565–6568

(30) (a) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1985**, *107*, 4260–4264. (b) Cunico, R. F. *Tetrahedron Lett.* **1986**, *27*, 4269–4272. (c) Pornet, J. *J. Organomet. Chem.* **1988**, *340*, 273–282. (d) Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Am. Chem. Soc.* **2000**, *122*, 11348–11357. (e) Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* **2000**, *2*, 385–388. (f) Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* **2002**, *67*, 6082–6090. (g) Miura, K.; Takahashi, T.; Hondo, T.; Hosomi, A. *Chirality*, **2003**, *15*, 41–52.

(31) (a) Mergardt, M.; Weber, K.; Adiwidjaja, G.; Schaumann, E. *Angew. Chem. Int. Ed.* **1991**, *30*, 1687–1688. (b) Sakaguchi, K.; Higashino, M.; Ohfune, Y. *Tetrahedron*, **2003**, *59*, 6647–6658.

(32) (a) Werner, H.; Baum, M.; Schneider, D.; Windmüller, B. *Organometallics*, **1994**, *13*, 1089–1097. (b) Katayama, H.; Ozawa, F. *Organometallics*, **1998**, *17*, 5190–5196. (c) Huang, D.; Streib, W. E.; Bollinger, J. C.; Caulton, K. G.; Winter, R. F.; Scheiring, T. *J. Am. Chem. Soc.*. **1999**, *121*, 8087–8097. (d) Katayama, H.; Wada, C.; Taniguchi, K.; Ozawa, F. *Organometallics*, **2002**, *21*, 3285–3291. (e) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050–12051. (f) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928. (g) Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924–5927.

(33) (a) Staden, L. F. V.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195–200. (b) Heo, J.-N.; Holson, E. B.; Roush, W, R. *Org. Lett.* **2003**, *5*, 1697–1700. (c) Hudrlik, P. F.; Gebreselassie, P.; Tafesse, L.; Hudrlik, A. M. *Tetrahedron. Lett.* **2003**, *44*, 3409–3412.