Investigation of Neglected Areas of Asymmetric Carbonyl Allylboration Chemistry

by

Urmi Bhusan Bhakta

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry
University of Alberta

Abstract

Asymmetric allylboration is a very useful and potent method for the synthesis of chiral homoallylic alcohols, a structural motif present in many natural products and biologically relevant molecules. B/Si double-allylation reagents have also been reported that can lead to chiral homoallylic alcohols with an allylsilane unit. These molecules can then be exploited in the construction of more complex structures. Various total syntheses of important natural products have been achieved exploiting these methods. However, there are a number of areas of allylboration chemistry that have not received much attention. This thesis is aimed towards these areas. Chapter 2 of this thesis is designated for the application of a hydrobenzoin-based chiral synthetic diol (known as vivol)•$SnCl_4$-complex catalyzed allylboration towards the synthesis of chiral homoallylic propargylic alcohols, a structural moiety abundant in natural products. Despite of its importance, there are very few catalytic methods for the synthesis of these compounds and a vivol•$SnCl_4$ asymmetric allylboration methodology has been utilized effectively for this task. Chapter 3 discusses the application of a B/Si double-allylation reagent in imine allylboration to form synthetically useful chiral homoallylic amine. Although B/Si double-allylation reagents have been applied frequently in aldehyde allylation, there is almost no example of imine allylation before this study. Chapter 4 describes the attempted synthesis of a 3-fluoro and 3-trifluoromethyl allylboronate reagent. Had these reagents been prepared successfully, they would have generated chiral α-fluoro and α-trifluoromethyl homoallylic alcohol under vivol•$SnCl_4$-catalyzed allylboration conditions. Despite of the tremendous growth of the field of fluorination and trifluoromethylation chemistry, there is almost no method known towards the synthesis of such building blocks which can be easily manipulated into more useful compounds. Chapter 5 addresses the synthetic attempts towards a stable B/B bidirectional double- allylation reagent, which can afford chiral 1,5-diols present in various natural products. The only known reagent of this kind is an unstable dialkylborane based one, which needs to be prepared and reacted *in situ*. Having access to a more stable and user-friendly reagent would enable easy synthesis of chiral 1,5-diol building blocks. Future plans regarding these research areas are described in chapter 6.

Preface

Some of the research work described in Chapter 2 of this thesis was achieved in collaboration with Dr. Erin Sullivan (PhD in Chemistry, University of Alberta, 2011) led by Professor Dr. Dennis G. Hall. The data analysis described in this chapter on pages 44-53 is my work. This research was published in the journal Tetrahedron ("Catalytic enantioselective allylboration of propargylic aldehydes" *Tetrahedron* **2014**, *70*, 678.) with Prof. Hall as the supervisory author. I was responsible for part of the data collection and manuscript preparation. However, the research described in Chapters 3, 4, and 5 were solely conducted by me.

This thesis is dedicated to my parents

Acknowledgements

First of all I would like to thank my supervisor Professor Dennis G. Hall for his help and support. I also thank my supervisory committee members for their suggestions. Then, I would also like to thank my fellow group members past and present for all their help throughout my graduate studies for insightful discussions and suggestions. I express my gratitude to all the department facilities including the mass spectrometry, NMR spectroscopy, and analytical/instrumental facilities. I am grateful to Hayley Wan and Nada Djokic. I am also grateful to my instructors and teachers past and present. Most importantly I would like to thank my family and friends, who without their love, support, encouragement and belief in me none of this would have been possible.

Table of Contents

Chapter 4: Synthetic studies towards fluoro and trifluoromethyl allylboronate

List of Tables

List of Schemes

List of Figures

List of Symbols and Abbreviations

Symbols /abbreviation	Definition
Ac	acetyl
allylBpin	4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane
aq	aqueous
br	broad
BINOL	1,1'-binaphthalene-2,2'-diol
BOM	benzyloxylmethoxy
Bpin	4,4,5,5-tetramethyl-1,3,2-dioxaborolane
n-Bu	*n*-butyl
t-Bu	*t*-butyl
CAN	ceric ammonium nitrate
ClBz	2-chlorobenzoate
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
DHQD	dihydroquinidine
DIBAL-H	diisobutylaluminum hydride
DMAP	dimethylaminopyridine
DMF	N,N-dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
dppf	1,1'-bis(diphenylphosphino) ferrocene
dt	doublet of triplets

ee	enantiomeric excess
EI	electron impact
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*i*so
^{d}Ipc	d-isopinocamphenyl
IR	infrared spectroscopy
J	coupling constant (in NMR spectroscopy)
L.A. or LA	Lewis Acid
m	multiplet or medium
Me	methyl
mmol	millimole
mol	mole
MS	mass spectrometry or molecular sieves
m/z	mass to charge ratio
NBS	N-bromosuccinimide
NFSI	N-fluorodibenzenesulfonimide
NIS	N-iodosuccinimide
NMR	nuclear magnetic resonance
OMe	methoxy

OTf	trifluoromethanesulfonate
Ph	phenyl
PHAL	1,4-phthalazinediyl
pin	pinacol
Pr	propyl
i-Pr	isopropyl
q	quartet
qt	quartet of triplets
R	generic alkyl group
Rf	retention factor
rt	room temperature
s	singlet or strong
t	triplet
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMP	tetramesitylporphyrin
TMS	trimethylsilyl
TRIP-PA	(*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-

	diyl hydrogenphosphate
Ts	toluenesulfonic acid
w	weak
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
λ	wavelength
μ	micro
δ	delta

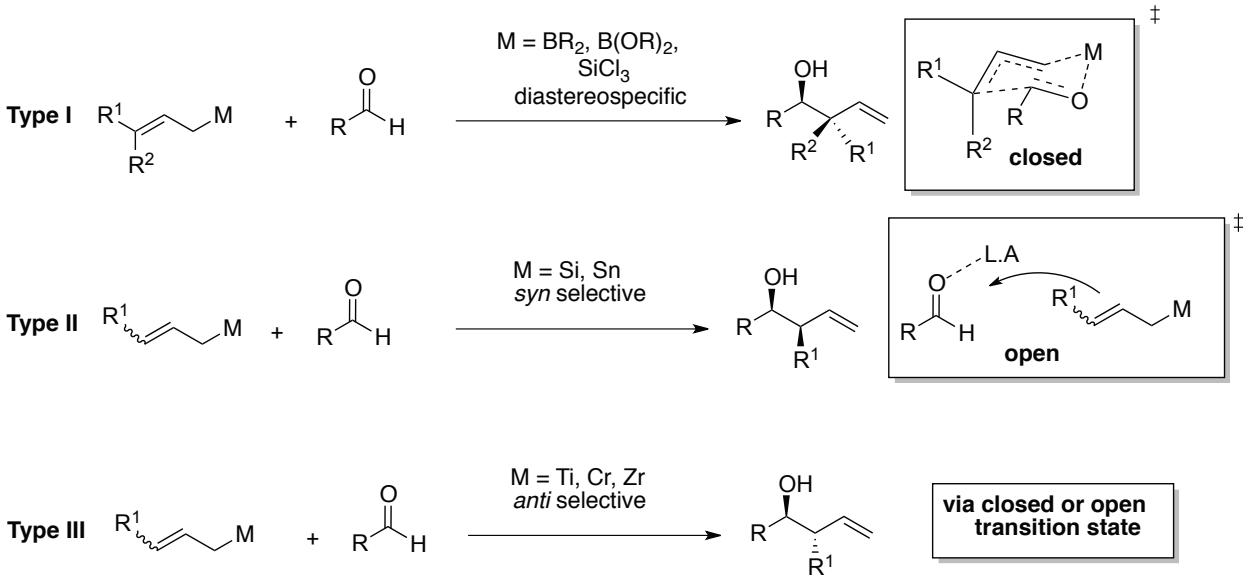
Chapter 1

Introduction: neglected areas of asymmetric carbonyl allylboration chemistry

1.1 Introduction: asymmetric allylboration

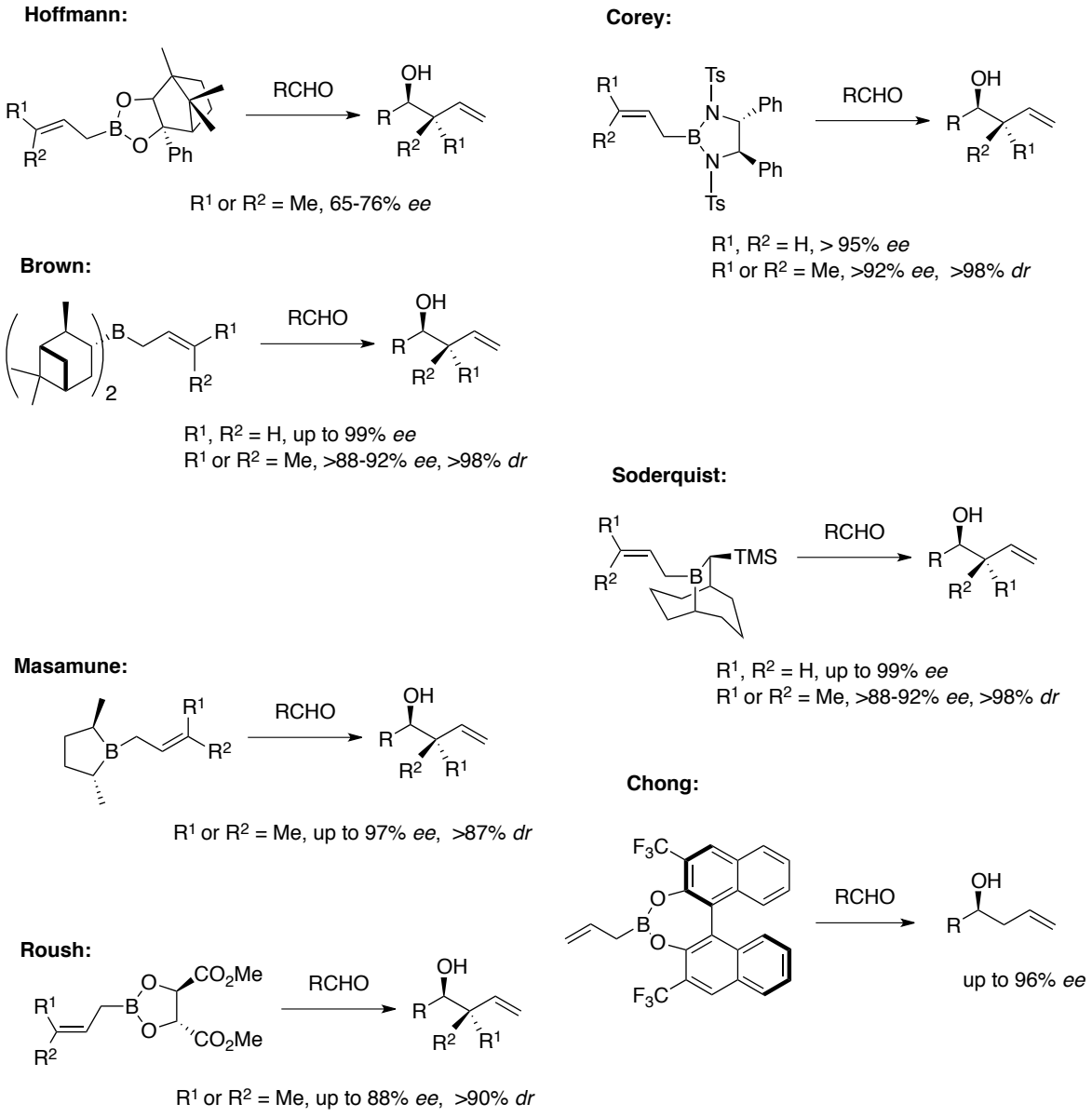
The addition of an allylmetal reagent onto an aldehyde has been a very successful method for the construction of continuous stereocentres. This method is very popular because of the many attractive features associated with this chemistry. These reactions are highly diastereoselective and enantioselective. Based on the nature of the metal, a diverse range of reagent reactivity can be achieved. Also, the final homoallylic alcohol product of the reaction is an extremely important building block with the possibility for different kinds of chemical modifications of the terminal olefin, including olefin methathesis.[1a,1b,1c]

Most of the allylation reagents are based on metals and metalloids such as silicon,[2] titanium,[3] chromium,[4] indium,[5] tin,[6] and zinc.[7] The reactivity of these reagents may vary depending on the nature of the metal and generally follow three distinct types of reactivity, namely Type-I, II, and III (Scheme 1.1). Although these methods are well investigated and useful, many of these reagents prepared from these heavy metals (Cr, Sn etc) suffer from potential toxicity problems. The other problem is the lack of methods to control enantioselectivity. Because of these reasons, allylboration has gained a lot of popularity. Boron-based compounds are stable, non-toxic, environmentally benign, and easy to handle. There are two sub-classes of allylboron reagents: the highly reactive dialkyl allyl– and crotyl boranes (containing one allylic and two alkyl groups on the boron atom) and allylic boronic esters, known as allylboronates (containing one allylic and two alkoxy groups on the boron atom). The latter class provides improved configurational stability and lower reactivity compared to the former.



Scheme 1.1. Type-I,II, and III reactivity in additions of allylmetal reagents to carbonyl compounds.

Ever since the publication of the first aldehyde allylboration reaction by Mikhailov and Bubnov in 1964[8] and enantioselective allylboration by a camphor derived allylboron reagent reported by Hoffmann in the late 70's,[9] several different groups such as Masamune, Brown, Roush, Hall, Corey, Soderquist, and Chong have published works on asymmetric allylboration methods with different chiral auxiliaries on the boron center.[10-15] Of these reagents, Brown's terpene-derived allylboranes have found application in the creation of absolute stereochemistry. Roush's tartrate-derived reagents have also become popular and were used frequently in simple and double diastereocontrolled allylation, where a chiral aldehyde is employed as a substrate (Scheme 1.2)

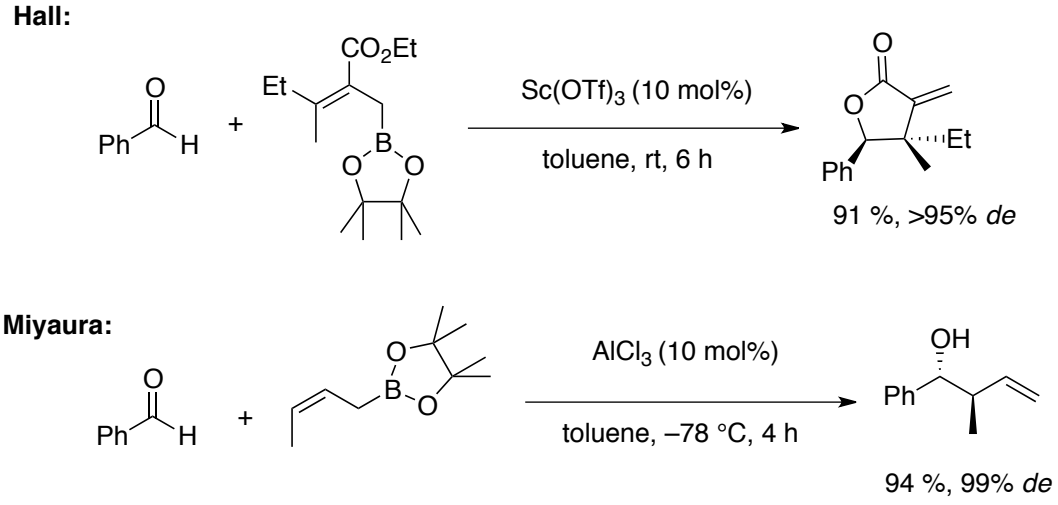


Scheme 1.2. Chiral allylboron reagents and their reactions with aldehydes.[10-15]

1.2 Catalytic racemic and asymmetric allylboration

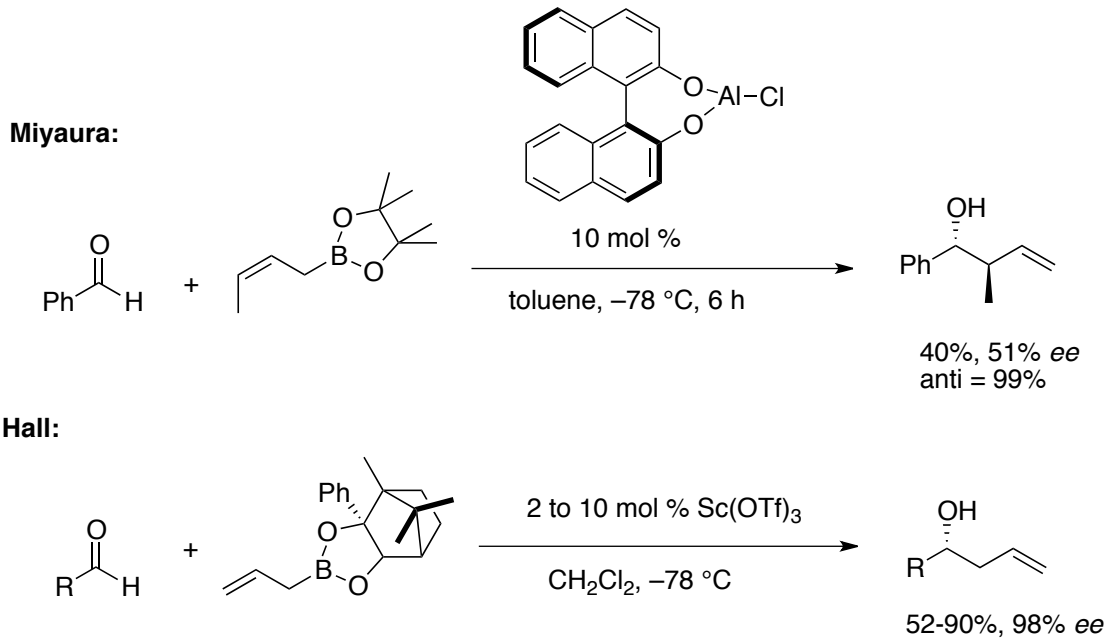
Although the first example of asymmetric allylboration was published decades ago and many such methods have been reported since then, there are very few examples of catalytic asymmetric methodologies known in the literature. One of the main reasons is the fact that many allylic boronic esters are hydrolytically labile and can form allylic boronic acids even in the presence of trace amount of

moisture. These factors, as revealed in the detailed and systematic study carried out by Brown and co-workers, can undergo a very rapid racemic background reaction with the carbonyl compound, along with the desired chiral reaction.[16] Allylboranes, on the other hand, are almost impossible for application in a catalytic enantioselective method because of their very rapid reaction with the carbonyl substrates. However, the main problem arises from the nature of the allylboration reactions. These reactions follow a Type-I mechanism via self-activation of the aldehyde substrate by the boron atom. Incorporation of any external catalyst, such as a Lewis acid, would sequester the carbonyl lone pairs and change the reaction to a Type-II, open transition state form. This would lead to the complete loss of the desired stereospecificity that is observed normally. Both of these problems have now been overcome. Hydrolytically stable and commercially available boronate reagents such as pinacol allylboronates can be used instead of the more labile allylboronate species. Hall and co-workers and later on Miyaura and co-workers have independently reported examples of catalytic allylboration with catalytic amounts of metal salts such as $Sc(OTf)_3$ and $AlCl_3$ (Scheme 1.3).[17,18]



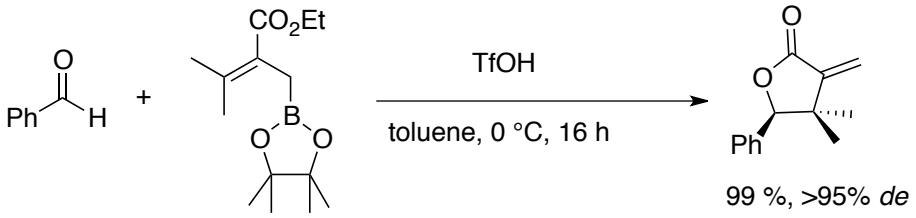
Scheme 1.3. Catalytic allylboration with metal salts.[17,18]

Later on, asymmetric versions of these methods were also reported by these groups. Miyaura and co-workers applied a catalytic amount of a BINOL-aluminum complex achieving 51 % *ee*. The Hall group, on the other hand, used a stoichiometric amount of camphor diol-derived chiral allylboronate in the presence of a catalytic amount of $Sc(OTf)_3$, obtaining *ee* values as high as 98% (Scheme 1.4).[19,20]



Scheme 1.4. Enantioselective allylboration with catalytic amounts of metal complexes.[19, 20]

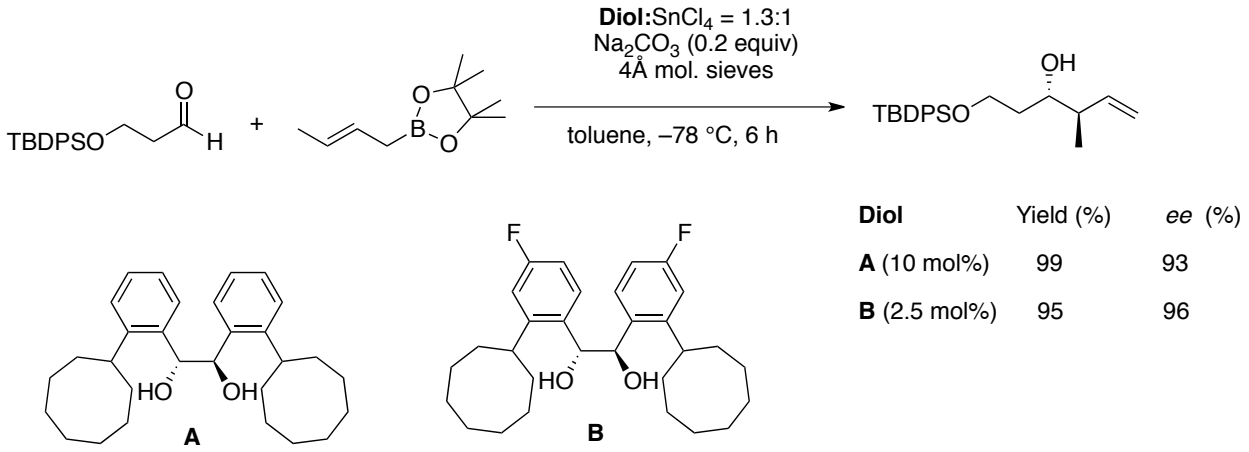
A major development in the field of catalytic allylboration was the application of TfOH as a Brønsted acid catalyst by Hall and co-workers. This catalyst proved to be much more efficient than their previously employed catalyst $Sc(OTf)_3$ (Scheme 1.5).[21]



Scheme 1.5. Triflic acid catalyzed allylboration.[21]

Inspired by the observation that a protic acid (Brønsted acid) can be employed as a catalyst for the allylboration reactions, the Hall group then decided to prepare a chiral protic acid which would be employed to induce chirality and at the same time can accelerate these reactions. Synthetic chiral diols (called vivol's) with saturated cycloalkyl rings substituted onto the diaryl backbone were prepared (p. 24, Figure 2.6; p. 33, Scheme 2.22). These diols, when treated with $SnCl_4$ produce a diol•$SnCl_4$ complex,

offers “chiral proton”-s which can drive the reactions.[22a] The cycloalkane units control stereoselectivity. It was observed that even more efficient diols can be prepared by adding strong electron withdrawing fluoride-substituents on the benzene ring. These diols are known as F-vivol’s. This methodology was extremely successful, affording excellent level of enantioselectivities and yields (see pp. 25-26). Total synthesies of important natural products have also been achieved by employing this method as one of the key steps (Scheme 1.6).[22b]



Diol	Yield (%)	*ee* (%)
A (10 mol%)	99	93
B (2.5 mol%)	95	96

Scheme 1.6. vivol•$SnCl_4$-catalyzed crotylboration of an aldehyde.[22]

A few years after the publication of the work from Hall and co-workers, Antilla and co-workers reported another asymmetric allylboration method employing a chiral BINOL-based phosphoric acid as a Brønsted acid catalyst.[23] Hu and co-workers reported a similar method employing a SPINOL-based phosphoric acid.[24] Despite of many advances in this area, there is one particular area which has not been addressed; specifically, the preparation of homoallylic propargylic alcohols. Chiral homoallylic propargylic alcohols constitute very useful structural scaffolds. Still, there are very few methods known in the literature regarding the catalytic asymmetric synthesis of these kinds of molecules. Hu and co-workers have exploited chiral phosphoric acid catalysis, however a thorough substrate scope study has not been carried out.

1.3 Double allylation reagents

One recent major development in the area of asymmetric allylboration was the introduction of the concept of double allylation methods. Stable, user-friendly reagents consisting of elements such as B, Si, Sn, are

designed in such a manner so that these elements together form a manifold which after performing one allylation reaction would still retain another allylmetal moiety. This remaining allylmetal unit would then perform another allylation reaction. The major contributor in this area is the Roush Group (reagents **I-VI**).[25] There are reports of such reagents from other groups as well, including one from our own, **XI** (Figure 1.1).[26]

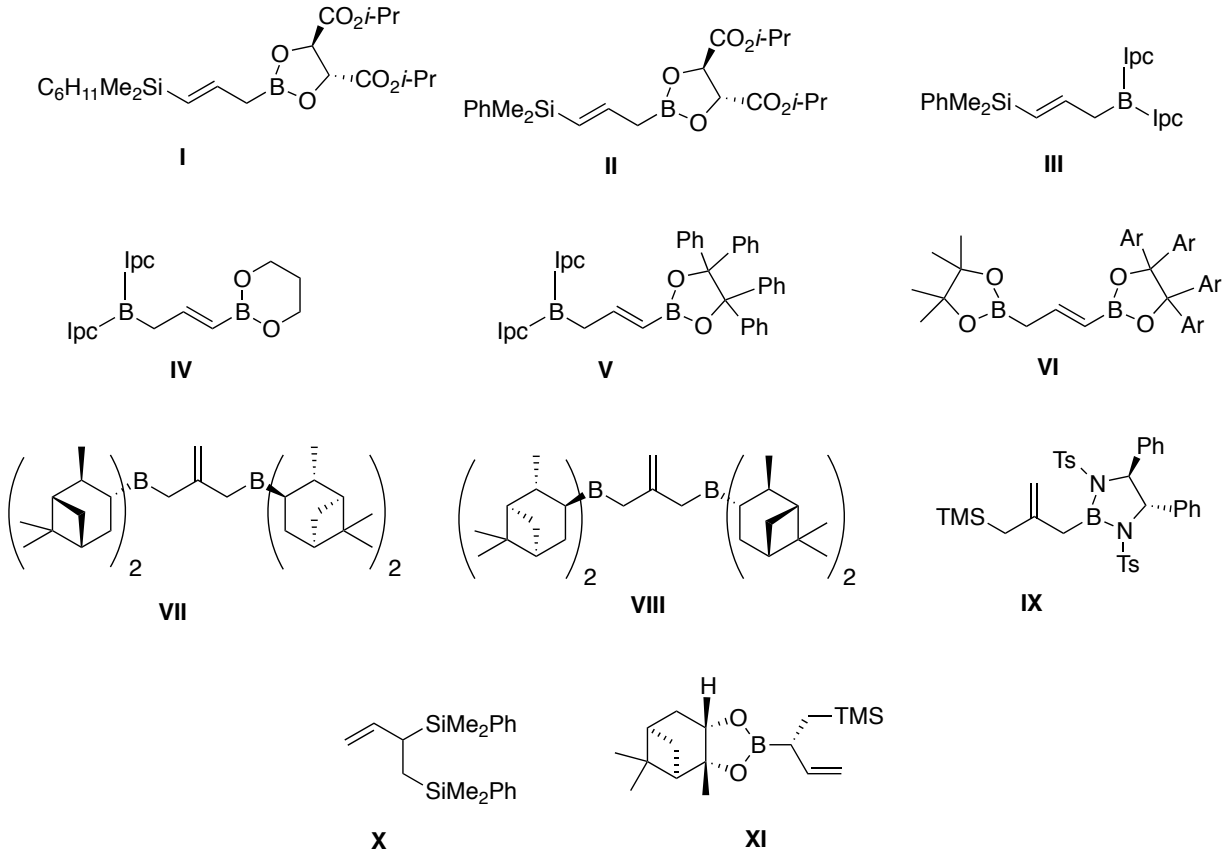
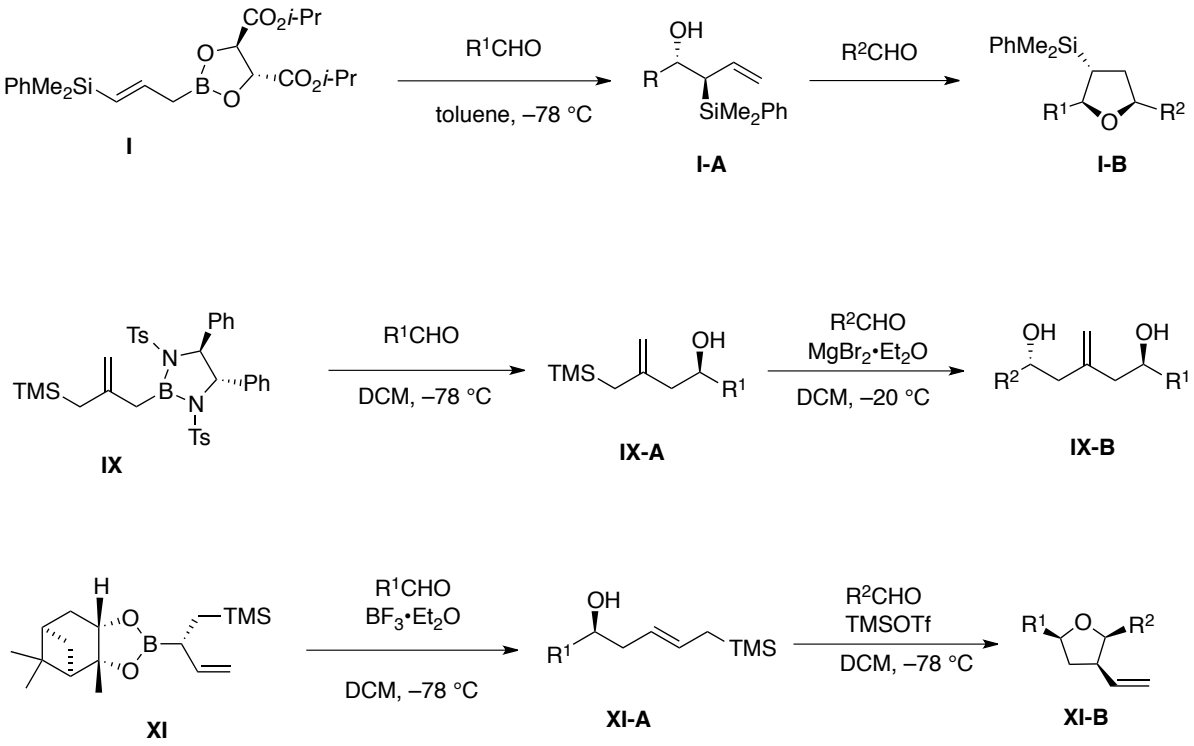


Figure 1.1. Various double allylation reagents reported in the literature.[25,26]

Very important building blocks can be prepared very easily in a maximum of two steps by employing these reagents in good yields and very high stereoselectivities. For example, 1,2,4-trisubstituted tetrahydrofurans (**IB** and **XI-B**) can be easily prepared from reagents **I** and **XI** in very good yields and excellent stereoselectivities. Reagent **IX** can yield 1,5-diols when treated with aldehydes (pp. 82-90). Many biologically and medicinally relevant molecules consisting of these structural motifs have been synthesized efficiently by applying these reagents (Scheme 1.7).[26,27]



Scheme 1.7. Application of various double allylation reagents.[26,27]

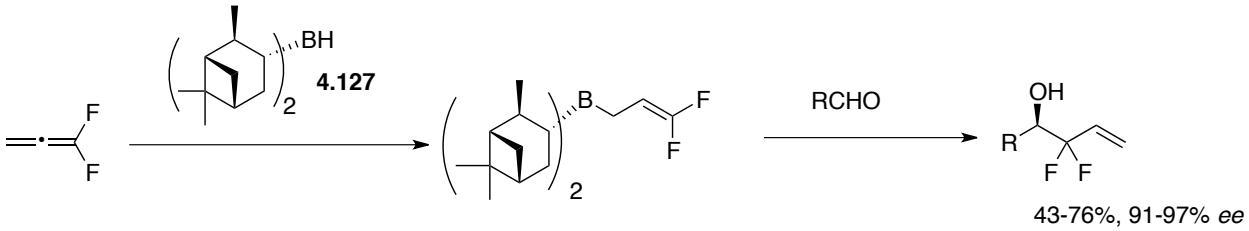
Although there are a lot of contributions in this area involving aldehyde allylation, there is hardly any example of a similar imine allylation. Imine allylation with one of these reagents would provide a chiral functionalized homoallylic amine. Chiral homoallylic amines are very useful building blocks present in many natural products. Apart from this, these functionalized homoallylic amines have the potential of being converted further into more diverse and complicated structures.

However, even in the field of aldehyde allylation, there is one particular class of reagent that has not been explored extensively. A boron based, stable bi-directional double-allylation reagent could be applied in the vivol•$SnCl_4$-catalyzed conditions to yield synthetically useful chiral 1,5-diols via two consecutive asymmetric allylborations. Such a process would be regarded as the first catalytic asymmetric double-allylboration. There is only one example of a reagent of this sort in the literature but it is an air sensitive dialkylborane, requiring immediate use after it has been prepared (p. 178).[25d]

1.4 3-Fluoro- and 3-trifluoromethyl allylboration

Fluorine containing organic molecules are of immense significance in medicinal chemistry, because of their increased lipophilicity, improved stability towards oxidative decompositions, and unique hydrogen

bonding abilities.[28a] There are many reported procedures for fluorination and trifluoromethylation.[28b] However, there is only one example of a fluoroallylborane to date (p. 152), reported by Ramachandran and co-workers, while no example of a trifluoromethylallylboronate is known (Scheme 1.8).[28c] Although it represents a significant contribution in this area, this method has a few shortcomings. The major one is the fact that it employs an unstable borane reagent and it is produced and reacted *in situ*. Also, the carbon bearing the fluorine atoms in the product is an achiral center. Instead, a γ-monofluoroallylboronic acid ester would not only be easy to handle and work with, it will also produce a fluorohomoallylic alcohol consisting of a stereogenic secondary carbon center bearing a fluorine atom. These kinds of molecules could be of great importance from a medicinal chemistry perspective. Clearly, fluoro- and trifluoromethylallylboronates are a neglected class of reagents which could be very useful.



Scheme 1.8. Synthesis and application of a 2,2-difluoroallylborane.[28c]

1.5 Research objectives: neglected areas of carbonyl allylboration chemistry

In spite of significant development in the area of asymmetric aldehyde and even ketone allylboration, there are certain areas which have not received the proper attention they deserve. These are:

a) Catalytic asymmetric allylation of propargylic aldehydes:

Chiral homoallylic propargylic alcohols are very important building blocks in organic synthesis. There have been many total syntheses involving this structure.[29] Yet, there are very few catalytic asymmetric allylation methods known in the literature that are effective for this class of substrates. Whereas allylboration is concerned, only two examples of known catalytic allylboration of propargylic aldehydes were published by Hu and co-workers with SPINOL-based phosphoric acid as the catalyst.[24] Thus, a catalytic enantioselective allylboration methodology for propargylic aldehyde is of great necessity. The vivol•$SnCl_4$ catalyzed allylboration reaction developed in our group can be exploited as a solution for this problem. A detailed optimization study is required to investigate the various details controlling this reaction. Then, a thorough examination of different propargylic aldehydes would be the next goal. Chapter 2 is dedicated towards this objective.

b) Imine allylation with B/Si-double allylation reagent:

As discussed earlier, there are hardly any examples of an imine allylboration involving a double allylation reagent. The products of this reaction sequence are functionalized chiral homoallylic amines which could be further transformed into useful end-products with biological applications. The B/Si-double allylation reagent developed in our group could be examined in the imine allylboration scheme. The goal of this particular project is twofold: a detailed optimization study for the imine allylation leading to chiral homoallylic amines with an allylsilane unit, followed by an attempt to exploit the amine product. Chapter 3 is aimed towards this objective.

c) Fluoro- and trifluoromethyl allylboration:

The immense importance and complete absence of a suitable method for the synthesis of chiral monofluorohomoallylic and trifluoromethylhomoallylic alcohols prompted us to consider the possibility of applying vivol•$SnCl_4$ catalysis conditions. For that to happen, we must find out an efficient synthesis of the corresponding allylboron reagents first. Because there is no example of the synthesis of these two boronates, suitable starting materials have to be identified which have the potential to be converted into the corresponding boronates. Chapter 4 describes all the attempts aimed towards the synthesis of these two reagents.

d) Boron based bidirectional double allylation:

Chiral 1,5-diols are very important building blocks and many natural products of biological relevance have been prepared by using these compounds as starting materials. To make these 1,5-diols, a stable double allylation reagent with two allylboronate units has to be prepared. No such reagent has ever been reported. So, a detailed investigation and application of various suitable synthetic methods would be necessary. Chapter 5 describes all the synthetic attempts towards the preparation of a boron-based double-allylation reagent.

1.6 References

1. a) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. b) Lachance, H.; Hall, D. G. *Org. React.* **2009**, *Vol. 73,* Ed. Denmark, S. E. c) Grubbs, R. H. *Adv. Synth. Catal.* **2007,** *349,* 34.
2. a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002,** *124,* 7920. b) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003,** *42,* 946. c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001,** *123,* 9488.
3. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothestreit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992,** *114,* 2321.
4. a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977,** *99,* 3179. b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995,** *60,* 5386. c) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996,** *118,* 12349. d) Bandini, M.; Cozzi, P.G.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **1999,** *38,* 3357. e) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006,** *128,* 2554.
5. Loh, T.-P.; Zhou, J.-R.; Yin. *Org. Lett.* **1999,** *1,* 1855.
6. a) Costa, A. L.; Piazza, M. G.; Tagliavini, E., Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993,** *115,* 7001. b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993,** *115,* 8467. c) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996,** *118,* 4723. d) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006,** *128,* 2554.
7. a) Pu. L.; Yu, H. -B. *Chem. Rev.* **2001,** *101,* 757. b) Hong, J. -H.; Tsai, Y. -C. *Angew. Chem. Int. Ed.* **1998,** 37, 468.
8. Mikhailov, B. M.; Bubhnov, Y. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1964,** 1874.
9. a) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979,** *20,* 4653. b) Hoffmann, R.W.; Zeiss, H. -J. *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 306.
10. Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989,** *111,* 1892.
11. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983,** *105,* 2092.
12. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985,** *107,* 8186.
13. Corey, E. J.; Yu, C. -M.; Kim, S. S. *J. Am. Chem. Soc.* **1989,** *111,* 5495.
14. Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005,** *127,* 8044.
15. Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2006,** *6,* 2701.
16. Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990,** *55,* 1868.
17. Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002,** *124,* 11586.
18. Shiyama, T.; Ahiko, T. -a.; Miyaura, N. *J. Am. Chem. Soc.* **2002,** *124,* 12414.
19. Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003,** *125,* 10160.
20. Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004,** 1290.

21. Yu, S. -H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005,** *127,* 12808.
22. a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. b) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.
23. Jain, P.; Antilla, J. *J. Am. Chem. Soc.* **2010,** *132,* 11884.
24. Xing, C. H.; Liao, Y.X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q. S. *Eur. J. Org. Chem.* **2012**, *6,* 1115.
25. a) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693. b) Roush, W. R., Gover, P. T.; Lin, X. *Tetrahedron. Lett.* **1990**, *31*, 7563. c) Roush, W. R., Gover, P. T. *Tetrahedron. Lett.* **1990**, *31*, 7567. d) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375. e) Williams, D. R.; Claeboe, C. D.; Bo, L.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866.
26. Peng, F. Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.
27. a) Roush, W. R., Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron. Lett.* **2000**, *41*, 9413. b) Micalizio, G. C., Roush, W. R. *Org. Lett.* **2000**, *2*, 461.
28. a) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100***,** 127. b) Ma, J-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. c) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.
29. a) Nicolaou, K.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. b) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.

Chapter 2

Catalytic enantioselective allylboration of propargylic aldehydes

2.1 Introduction: homoallylic propargylic alcohols

Homoallylic propargylic alcohols (**2.1**) are extremely important synthetic building blocks. This class of molecules possesses three functional groups: alcohol, alkene, and alkyne. Each of these functional groups has its own potential transformations; altogether making this moiety extremely useful as a synthetic intermediate. For example the alkyne sub-unit can be transformed into several different other building blocks as shown in Figure 2.1. This feature has led many synthetic chemists to exploit homoallylic propargylic alcohols in their syntheses of molecules of biological or medicinal importance.[1]

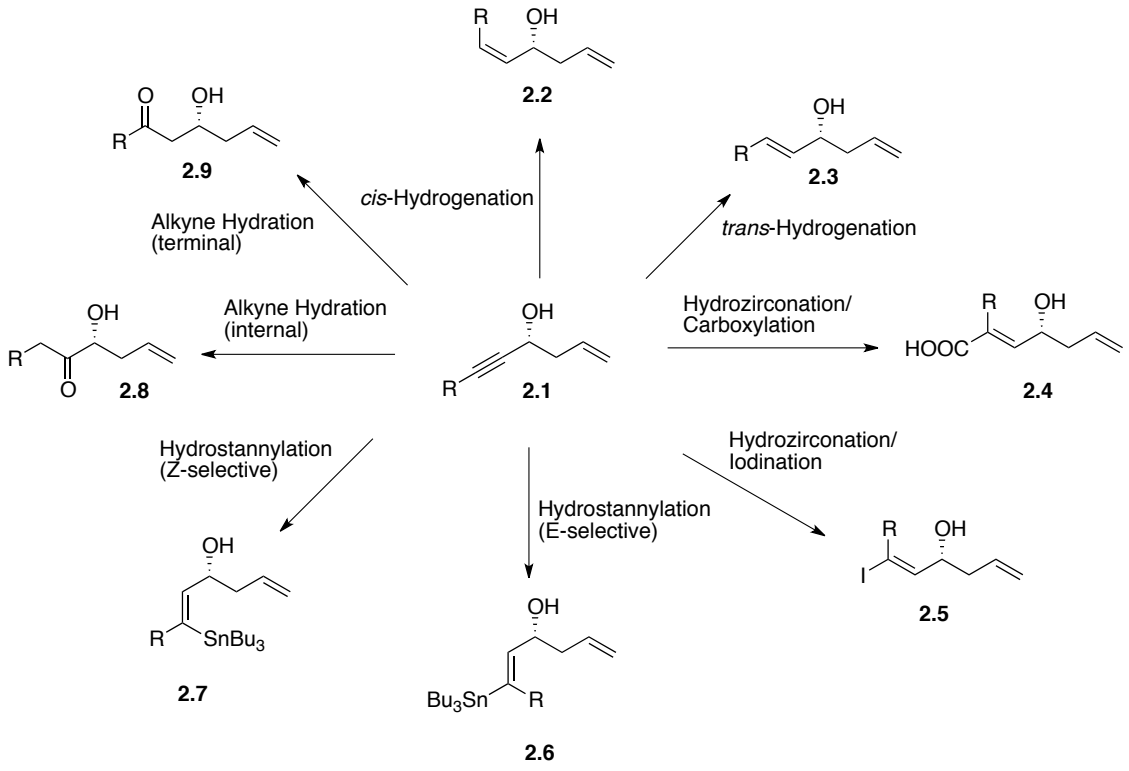
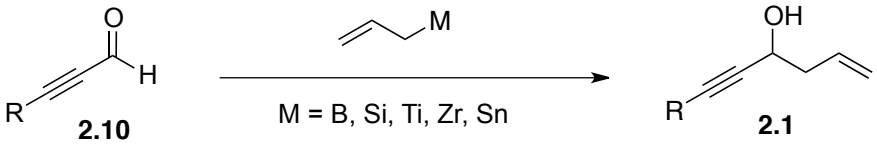


Figure 2.1. Synthetic manipulations of the alkyne functionality.

An alkyne can be converted into either a *cis*- or a *trans*- alkene (**2.2** and **2.3**).[2] Hydrozirconation of the alkyne sub-unit followed by the trapping of the intermediate organozirconium species with CO_2 or I_2 will yield vinyl carboxylic acid or vinyl iodide, respectively (**2.4** and **2.5**).[3] Similarly, hydrostanylation from different faces of the alkyne would lead to *cis*- and *trans*-alkenyltin species[4] ((**2.6** and **2.7**) which can be used as a coupling partners in Stille coupling. The alkyne can also undergo hydration to form a ketone in case of an internal hydration or an aldehyde when the hydration takes place terminally (**2.8** and **2.9**).[5] Easy manipulations of this unit makes it a very popular synthetic intermediate in the syntheses of molecules of biological and medicinal importance. Nicolaou's synthesis of both sanglifehrin and apoptolidin[6] had featured this backbone. Smith also exploited this backbone in the synthesis of macrolactin A.[7] Furstner used this sub-unit in his synthesis of sesquisabinene A.[8] A gold catalyzed cycloisomerization of an ester derivative from the homoallylic propargylic alcohol furnished a 3,5-fused bicylic ring structure present in the natural product. A common way to construct this building block is to treat an aldehyde with an allylmetal reagent (Scheme 2.1).



2.10 **2.1**

Scheme 2.1. Allylation of propargylic aldehydes.

Here the metal can be a main group element such as B, Si, or Sn or a transition metal such as Ti, Cr, or Zr. Each of these allylmetal reagents have a unique reactivity pattern. These reagents can be separated into three classes based on their mode of reactivity with the aldehyde (Figure 2.2). Allyl boranes, allylboronates and allyltrichlorosilanes have a Type-I aldehyde reactivity pattern. These kinds of allylmetal reagents undergo allylation via a six-membered Zimmermann-Traxler transition state where a dual activation mode operates. The metal, usually a good Lewis acid, interacts with the aldehyde making it more reactive towards allylation. These reactions usually display a very high diastereoselectivity because of the closed transition state they proceed through. Allylsilanes and allyltin reagents have a Type-II aldehyde reactivity pattern. These reagents undergo allylation via an open transition state, with the aldehyde being activated by another Lewis acid, which usually tends to favour the formation of *syn*- over *anti*-isomers. Reagents with Type-III aldehyde reactivity pattern include allyltitanium, allylchromium, and allylzirconium reagents and can undergo reaction via both open and closed transition states. These

reagents favour *anti*-isomer.

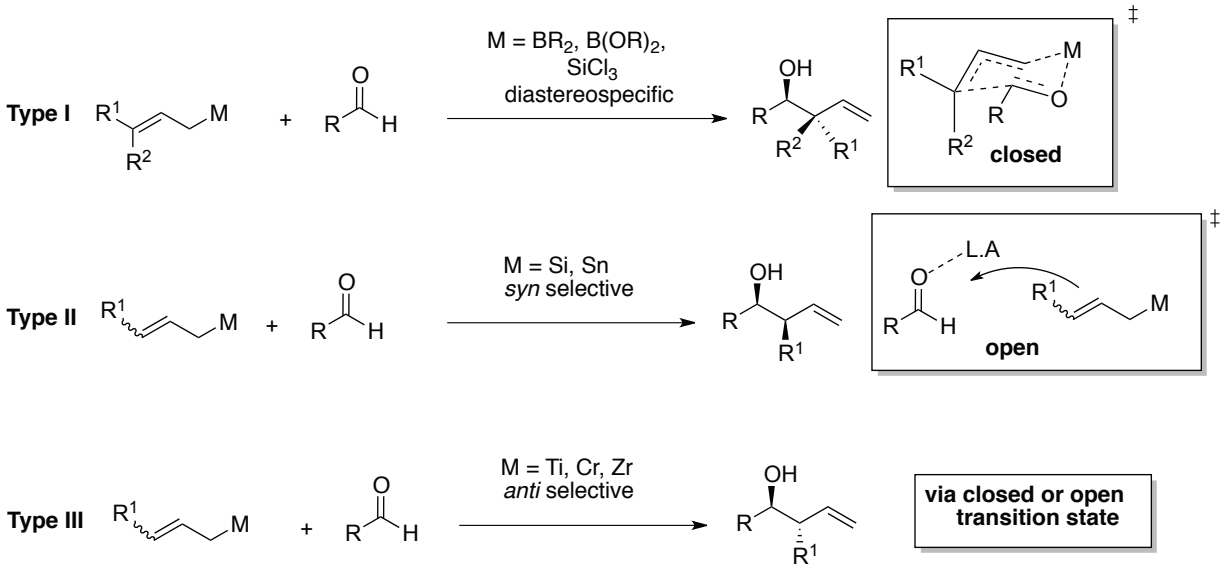
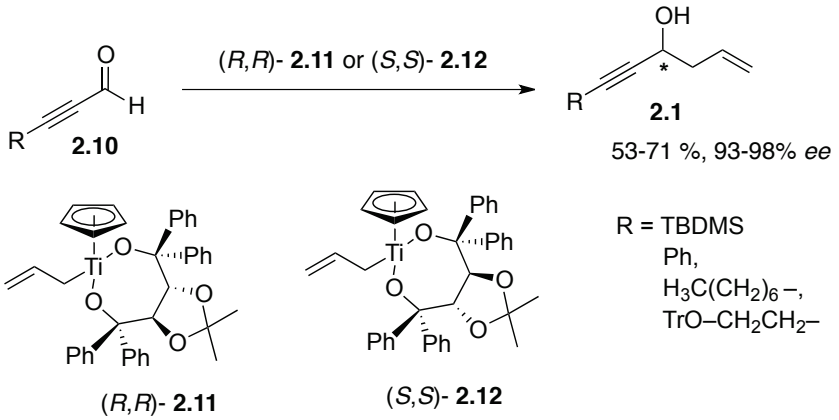


Figure 2.2. Different types of allylation mechanisms.

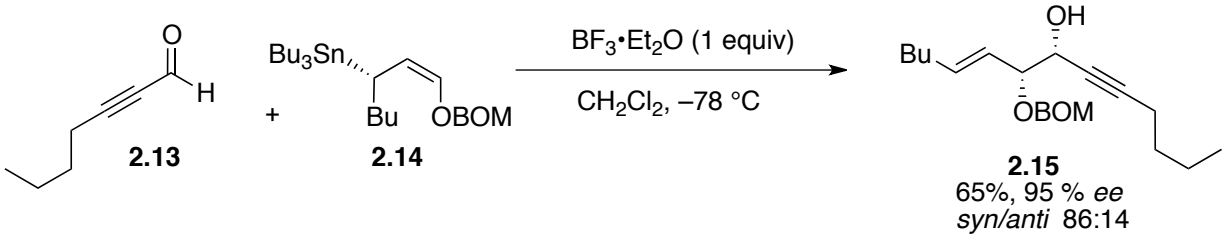
2.2 Allylation of propargylic aldehydes

There are quite a few examples of allylation of propargylic aldehydes in the literature. Bouzbouz and Cossy reported a reaction between propargylic aldehydes and a chiral allyltitanium reagent derived from TADDOL (Scheme 2.2).[9]



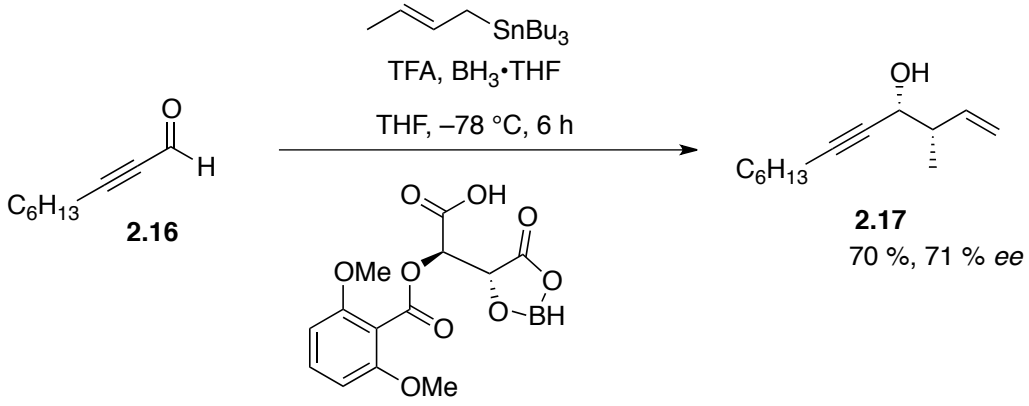
Scheme 2.2. Chiral allyltitanium mediated allylation of propargyl aldehydes.[9]

Marshall reported the first Lewis acid assisted allylation with a chiral allyltin reagent (Scheme 2.3).[10] The Lewis acid increases the rate of the reaction many-fold. The source of enantioselectivity was the stereogenic center of the molecule that bears the Sn atom in the molecule. The *syn*-isomer, which formed via an open transition state, was favoured over the *anti*-isomer.



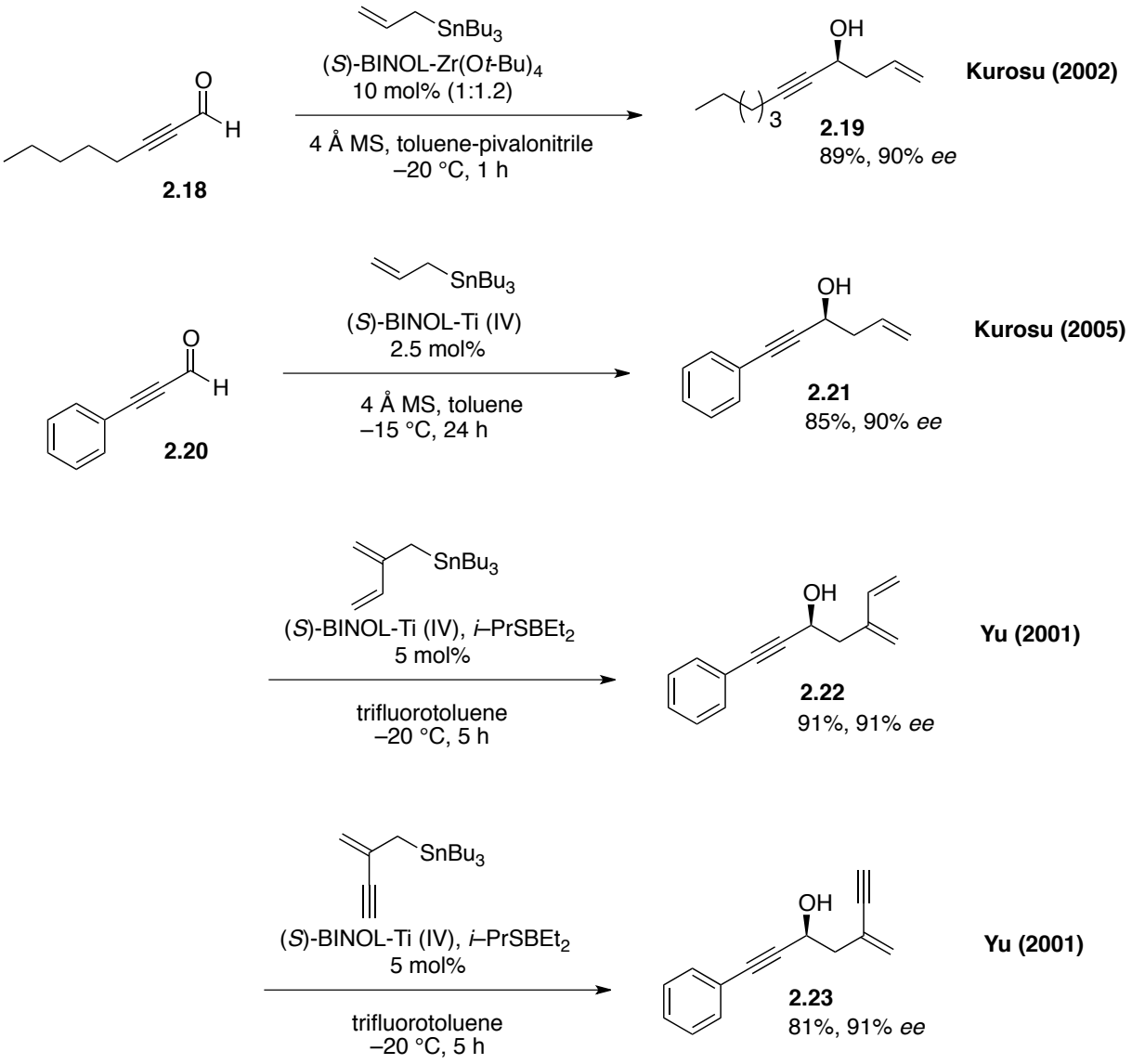
Scheme 2.3. Lewis acid mediated allylation with chiral allyltin reagent reported by Marshall.[10]

Later this group reported another allylstannation reaction in the presence of a chiral acyloxy(borane) derived from a tartrate derivative and BH_3•THF (Scheme 2.4).[11a] This kind of borane was first reported by Yamamoto.[11b] However the enantioselectivity of the homoallyl propargylic alcohol was only moderate.



Scheme 2.4. Chiral borane catalyzed allylation reported by Marshall.[11]

Many different asymmetric allylstannations similar to the previous one have been reported by other groups (Scheme 2.5). Kurosu reported a BINOL-Zr (IV) and BINOL-Ti (IV) catalyzed allylstannation of aldehydes.[12] Yu reported the dienyl and enynyl stannane additions of aldehydes catalyzed by a BINOL-Ti (IV) complex in the presence of *i*-PrSBEt$_2$ as an accelerating synergetic reagent.[13] Denmark reported a Lewis base activated Lewis acid catalysis approach in allyltin addition to aldehydes.[14]



Scheme 2.5. Asymmetric allylstannations with propargylic aldehydes reported by various groups.[12,13,14]

Although these procedures provide very good yields and enantioselectivities, they suffer from many drawbacks. One major problem is that all these methods employ stoichiometric amounts of toxic metals such as Sn, Cr, etc. Another problem is that not all of these methods are catalytic and hence often require stoichiometric amounts of chiral reagents. Therefore there is always a need for a catalytic enantioselective, and environmentally benign methodology towards the synthesis of homoallyl propargylic alcohols. Since organoborons are known to have very low or no adverse effect on the human body or on the environment, asymmetric allylboration can be a very attractive procedure to deal with toxicity problems.

2.3. Allylboration of carbonyl compounds

Mikhailov and Bubnov reported the first racemic allylboration reaction.[15] The first enantioselective allylboration was reported by Hoffmann.[16] Since then many asymmetric allylboration methods have been reported. These reagents can be subdivided into two categories: allylboranes and allylboronates (Figure 2.3):

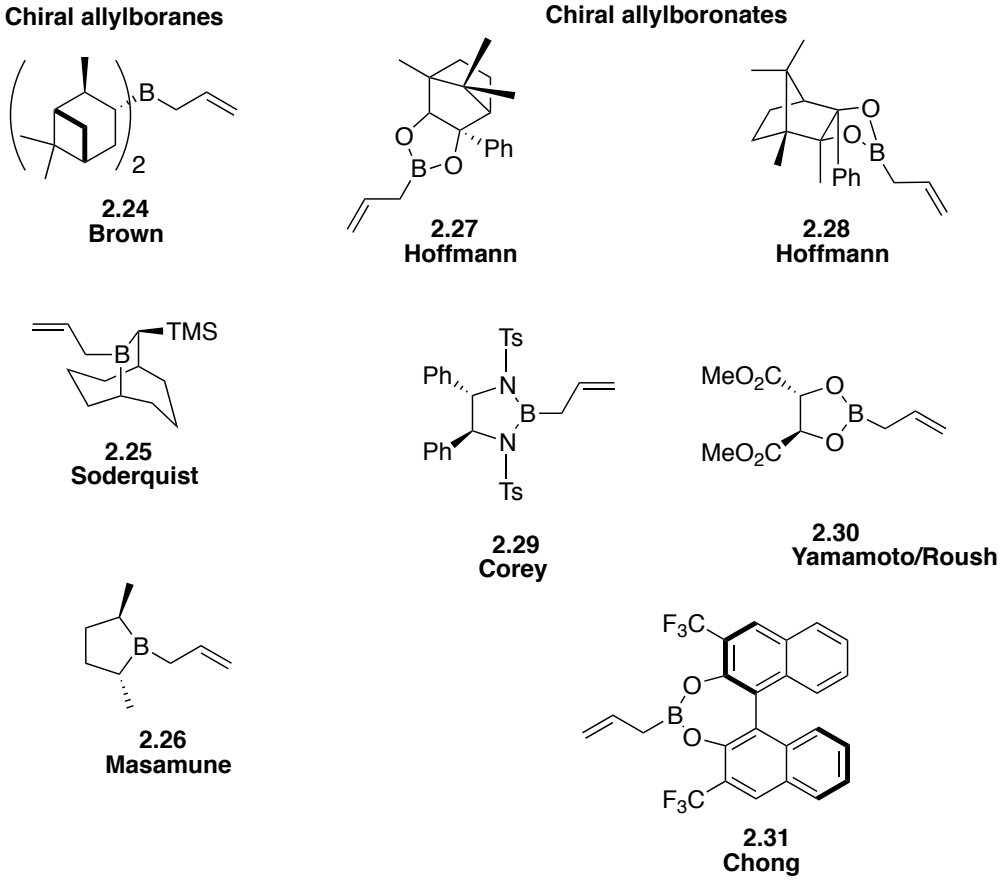


Figure 2.3. Different chiral allylboranes and allylboronates.

Allylboranes (**2.24** to **2.26**) present a few disadvantages compared to the use of allylboronates (**2.27** to **2.31**). They are far less stable towards air and moisture and have to be prepared and used immediately in reactions with carbonyl compounds. Allylboranes also tend to undergo reversible boratropic rearrangement, which leads to scrambling of olefin geometry and lower stereoselectivity with 3-substituted reagents such as the crotylboranes.[17] However, allylboranes are far more reactive than allylboronates. Allylboronates, on the other hand, are far more stable and less reactive (i.e less Lewis acidic) due to the partial donation of electrons from the oxygen atom or the nitrogen atom into the vacant

p orbital of boron. This effect makes allylboronates less susceptible towards moisture and air. All these reasons contribute in making allylic boronates preferred reagents compared to allylic boranes. Both allylboranes and allylboronates belong to the Type I category (Figure 2.2, Section 2.1). When reacting with the carbonyl compounds, most commonly with aldehydes, these reagents form a closed six membered chair-like Zimmermann-Traxler transition state with the reactant (Figure 2.4).[18] These reactions are spontaneous and require no external activation since the Lewis acidic boron atom of the reagent can itself activate the aldehyde for the reaction. The rate of the reaction depends both on the strength of the interaction between boron and the oxygen of aldehyde and the electron density of the olefin of the allylboronate reagent. Electron poor allylic boron reagents react slowly.

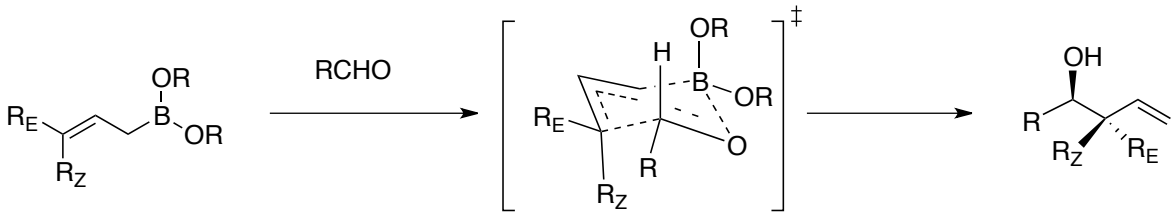
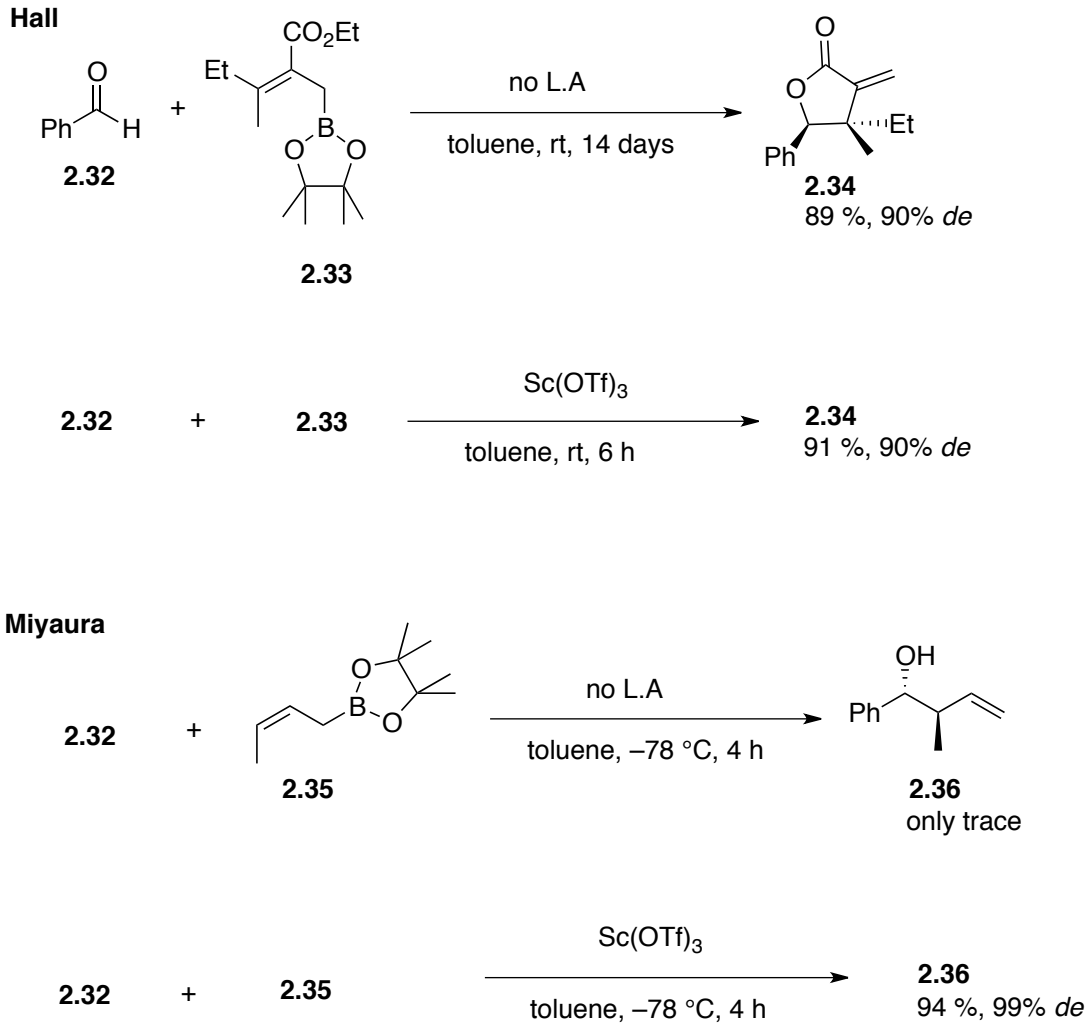


Figure 2.4. Allylation of an aldehyde with an allylboronate via a 6-membered transition state.[18]

The closed, organized transition state mechanism also ensures a high degree of stereoselectivity, which makes these reactions a popular methodology for synthetic chemists and these are often applied in the total synthesis of important natural products. Allylation proceeds with the retention of olefin geometry. The *E*-crotylboration (R_E= Me, R_Z= H, Figure 2.5) yields an *anti*-product and *Z*-crotylboration (R_E= H, R_Z= Me, Figure 2.5) gives a *syn*-product. Because allylborations proceed via a self-activated mechanism as described earlier, there would appear to be no advantage in using a Lewis acid or other such catalyst to catalyze the reaction. The other concern was that the external Lewis acid could bind with the lone pair of oxygen atoms of aldehyde switching off the original self-activation mechanism and initiating a Type II mechanism involving an open transition state and leading to lower diastereoselectivity. These are the main reasons behind the absence of literature examples of Lewis acid catalyzed allylboration. The first examples of using a Lewis acid to catalyze an allylboration were reported first by Hall and then Miyaura (Scheme 2.6).[19, 20] It was shown that by using $Sc(OTf)_3$ the reaction rate can be enhanced by more than 35 times. Thus whereas a 2-carboxyester (**2.33**) takes 14 days to complete the allylation of benzaldehyde, the same reaction is finished in 6 hours upon addition of $Sc(OTf)_3$ (Scheme 2.6).



Scheme 2.6. Lewis acid catalyzed allylboration reportedby Hall and Miyaura.[19,20]

Other control studies have shown that Lewis acids have no effect on the reactivity of dialkylallylboranes.[21] Based on these experiments, and theoretical studies by Omoto and Fujimoto, a chair-like transition structure similar to thermal additions can be proposed where the metal ion would preferably bind with the equatorial oxygen atom of the boronate (**A**) rather than the aldehyde oxygen atom (**B**). This latter possibility would lead to a higher energy transition state (Figure 2.5).[21,22]

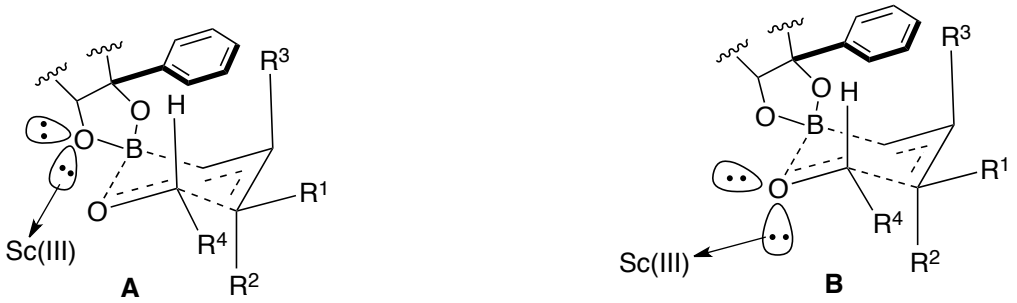
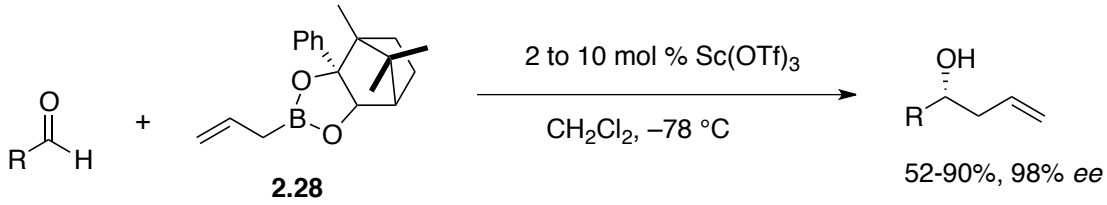


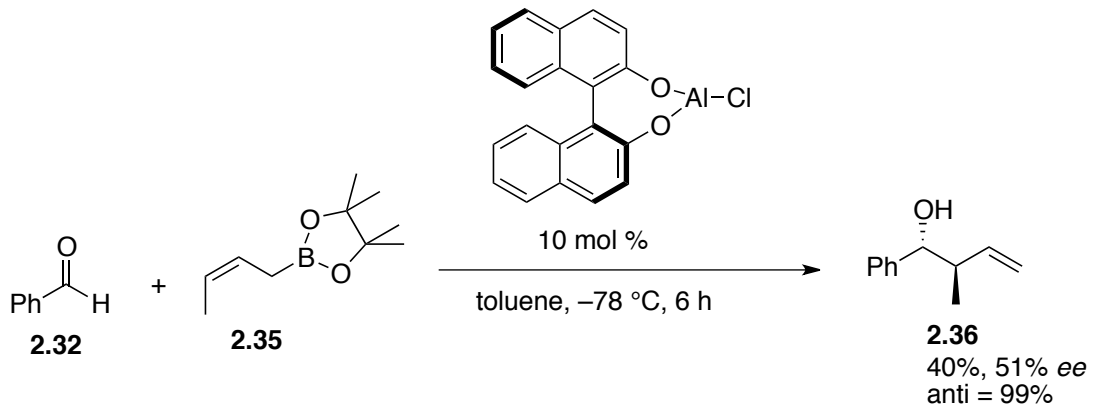
Figure 2.5. Transition state structure of a Lewis acid activated allylboration reaction.[21,22]

This coordination disrupts the delocalization of lone pairs on oxygen to the empty p-orbital of boron, thus increasing its Lewis acidity. The concept of a Lewis acid assisted activation of allylboronates was further exploited by the Hall group in enantioselective allylboration of aldehydes using the Hoffmann chiral diol derived allylboronate (Scheme 2.7).[23] This method provided a broad substrate scope with good to excellent yields and excellent enantio- and diastereoselectivities.



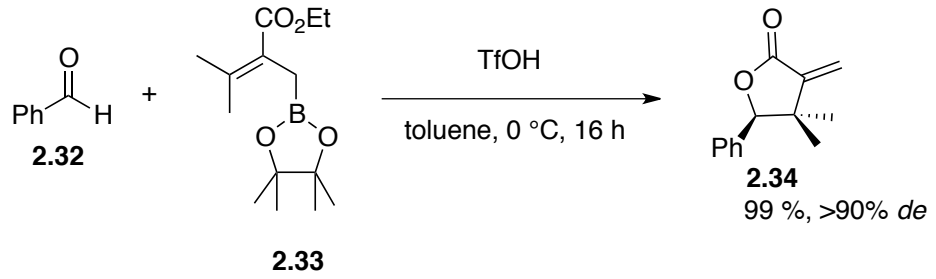
Scheme 2.7. Lewis acid assisted allylboration with Hoffmann's chiral diol derived allylboronate.[23]

Although it is a very useful methodology this reaction had one major drawback. The reaction needs a stoichiometric amount of an expensive chiral diol. A catalytic and enantioselective variation of this reaction would be of immense importance. Miyaura and coworkers were the first to demonstrate the application of a catalytic amount of chiral Lewis acid in allylboration. The chiral Lewis acid was derived from (*S*)-BINOL and Et_2AlCl. Unfortunately, it gave poor yield and enantioselectivity for the desired product (Scheme 2.8). [20]



Scheme 2.8. First catalytic asymmetric allylboration method reported by Miyaura.[20]

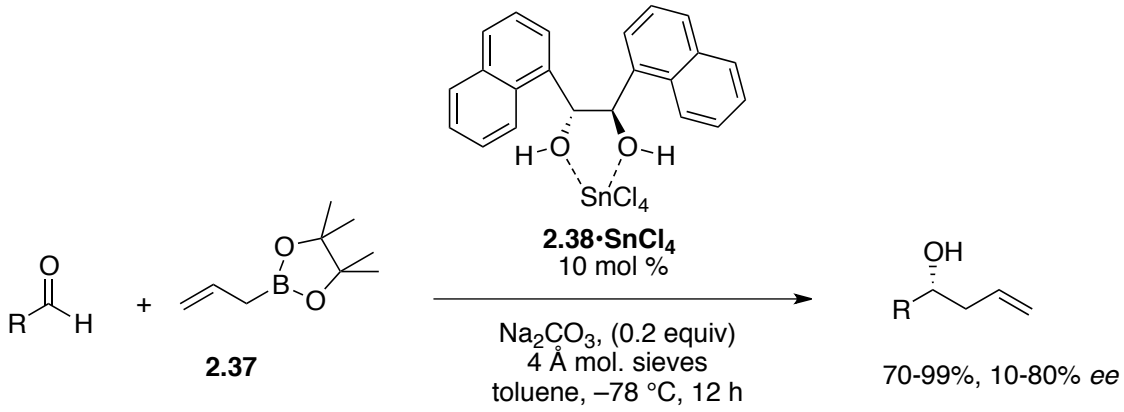
After the successful application of $Sc(OTf)_3$ as a catalyst, many other forms of activation were tried. In 2005 the Hall group reported the use of triflic acid as a catalyst in aldehyde allylboration (Scheme 2.9).[24a]



Scheme 2.9. Triflic acid catalyzed allylboration reported by Hall.[24a]

Around this time various novel ways of catalyzing reactions with a chiral Brønsted acid were being published.[24b] Yamamoto had exploited the known phenomenon of the enhanced acidity of an alcohol when bound to a metal salt into a new concept of catalysis called Lewis acid assisted Brønsted acid catalysis. Various chiral diols such as BINOL were treated with Lewis acidic metal salts to generate chiral Brønsted acids that were applied very effectively in many reactions.[25] These ideas along with the astounding observation of rate enhancement of allylboration reactions in the presence of $Sc(OTf)_3$ or TfOH inspired the possibility of developing an enantioselective allylboration methodology catalyzed by a chiral Brønsted acid, in other words a chiral "proton". This can be an effective and potent form of catalysis because of the tiny size and very high charge to size ratio of a proton. These properties would eliminate the possibility of a steric effect too which can cause a problem with bulky Lewis acids and would allow strong coordination with the oxygen atom of the boronate. In 2006, Rauniyar and Hall showed that a

complex between (*R*,*R*)-(+)-1,2-di(1-naphthyl)-1,2-ethanediol and $SnCl_4$ can be used as a Lewis acid assisted chiral Brønsted acid catalyst in aldehyde allylboration reactions. Although enantioselectivities up to 80 % could be achieved with some substrates, in most of the cases the *ee* was moderate. Unsaturated aldehydes had much lower enantioselectivities (Scheme 2.10).[26]



Scheme 2.10. Lewis acid assisted Brønsted acid catalyzed allylboration of aldehydes.[26]

Later on, a new class of novel chiral diols known as "vivol" were reported in 2008.[27] These diols performed very well and delivered very high yields and high enantioselectivities. The cycloalkyl rings on the benzene ring of these diols were important as they increased the energy difference between two competing transition states for the allylboration reaction. It was discovered that electron withdrawing groups added to the aryl substituents could furnish a more acidic and hence a more active diol, which can shorten the reaction time and help suppress the background racemic reaction. This background racemic reaction pathway was found to lead to loss of close to 4 % of the enantioselectivity. From the crystallographic data of the diol-$SnCl_4$ complex, it was rationalized that the substituents at the *para*-position of the phenol would least disrupt the catalyst's spatial arrangement. Thus fluorine atoms were placed in the *para*-positions of both phenyl groups. This new class of diols was named as "F-vivol", where F stands for fluorine substituition. Depending on the size of the cycloalkane ring, these diols are identified with names such as vivol- or F-vivol-7 (a cycloheptane ring), 8 (a cyclooctyl ring) etc. Thus, **2.39** is called vivol-8 and **2.40** is F-vivol-8 (Figure 2.6).[27]

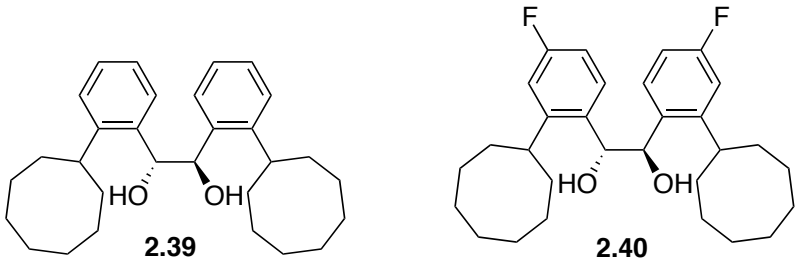
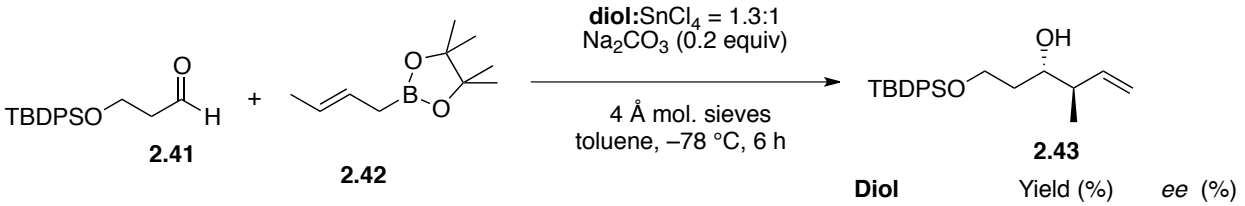


Figure 2.6. Second and third generation diols for catalytic asymmetric allylboration.[27]

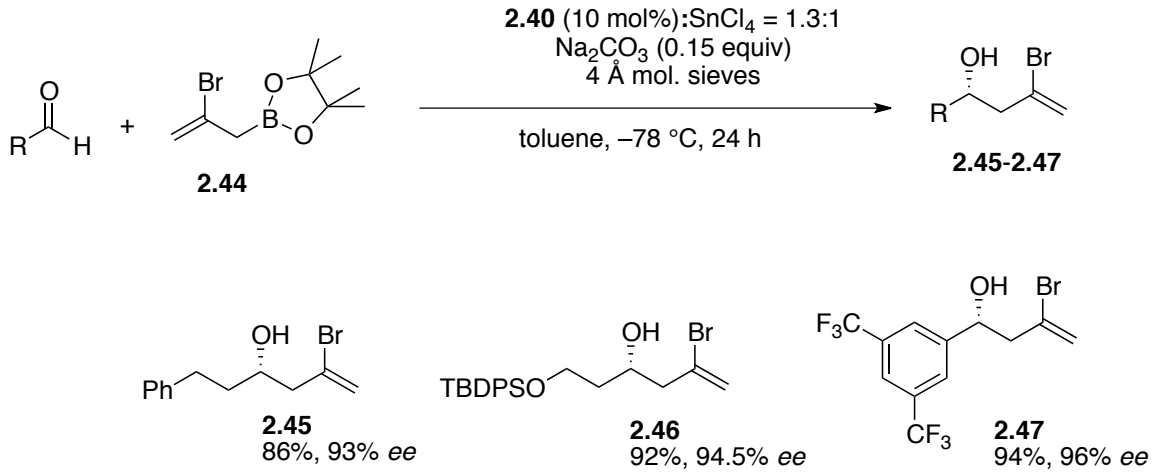
F-vivol-s performed even better compared to simple vivol-s and gave enantiomeric excess values (*ee*'s) as high as 97% (Scheme 2.11). Moreover, the catalyst loading could be reduced to 2.5 mol% without significant depletion in enantioselectivity. Although this catalyst displayed a broad range of substrate scope, α,β−unsaturated aldehydes did not perform well.



Diol	Yield (%)	*ee* (%)
2.39 (10 mol%)	99	93
2.40 (2.5 mol%)	95	96

Scheme 2.11. Comparison of vivol-8 and F-vivol-8•$SnCl_4$ complexes.[27]

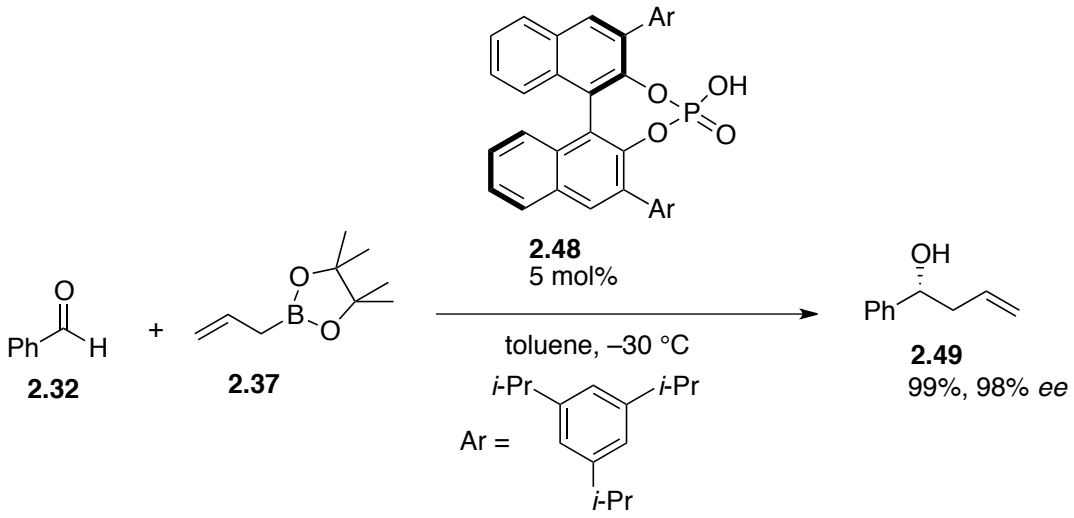
However, with F-vivol-8 (**2.40**) as a catalyst, high yield and enantiomeric excesses were achieved with electron deficient aromatic aldehydes (Scheme 2.12).[28]



Scheme 2.12. Broad substrate scope demonstrated by F-vivol-8•$SnCl_4$ complex.[28]

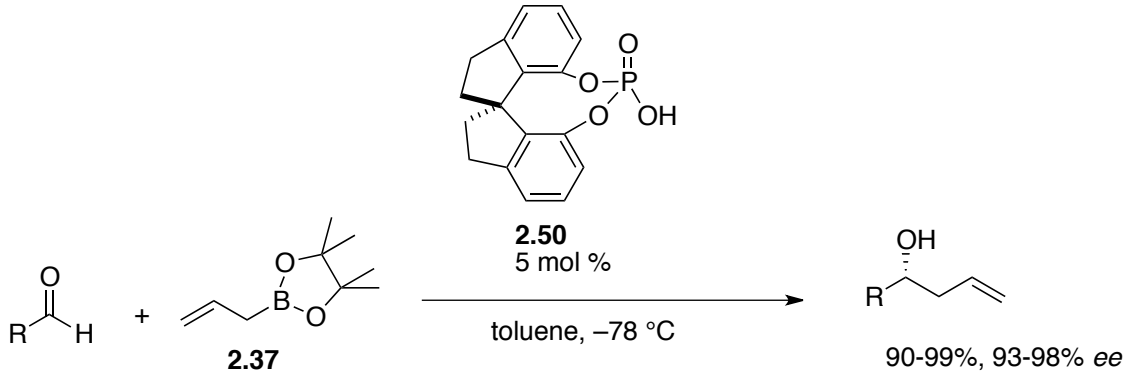
Other than F-vivol-s, CF_3-vivols were prepared too, which were not as effective as the F-vivol-s in terms of *ee* of the product. The Hall group applied the F-vivol•$SnCl_4$ complex catalyzed allylboration methodology in the synthesis of important natural products such as palmerolide A and (+)-dododeine.[28]

Over the past few years there has been an explosion in the number of publications in the area of organocatalysis. Highly substituted chiral phosphoric acids derived from substituted BINOL have been developed by many research groups with List[29], Terada[30] and Akiyama[31] leading in this area. Chiral phosphoric acids have been utilized in several different reactions. Recently Antilla reported an asymmetric allylboration method catalyzed by the chiral phosphoric acid 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**2.48**). Excellent levels of yield and enantioselectivity were observed with aromatic aldehydes (Scheme 2.13).[32]



Scheme 2.13. Chiral phosphoric acid catalyzed allylboration reported by Antilla.[32]

Hu and coworkers reported a novel diol (SPINOL) based chiral phosphoric acid (**2.50**) catalyzed allylboration (Scheme 2.14).[33]

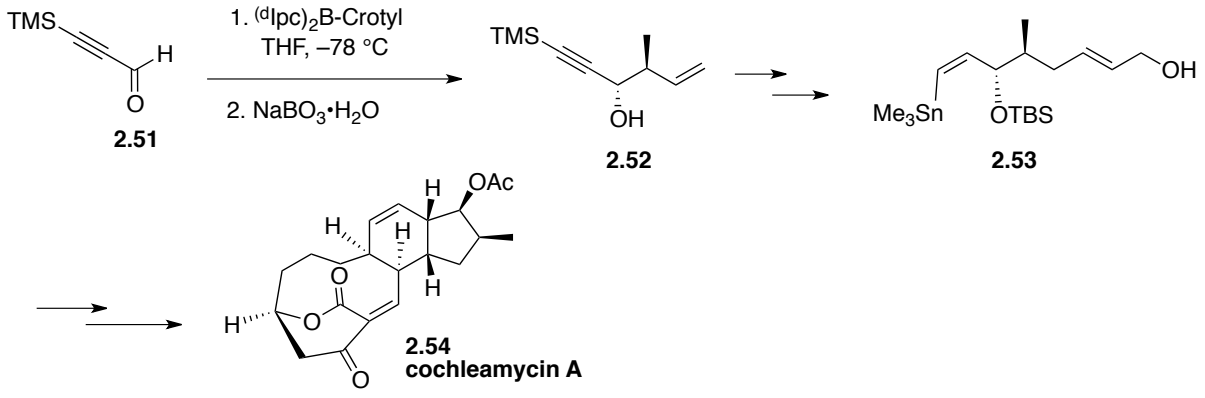


Scheme 2.14. SPINOL-phosphoric acid catalyzed allylboration reported by Hu.[33]

2.4 Allylboration of propargylic aldehydes

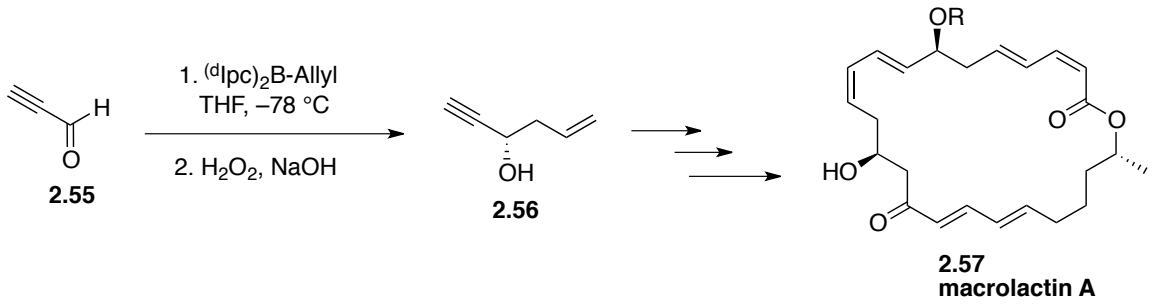
In the literature, there are only a few examples of allylboration reported for the preparation of chiral homoallylic propargylic alcohols. These examples involve both allyldialkylboranes and allyl- boronates. Brown's terpene-derived allylborane mediated allylation methodology of propargylic aldehyde has been

utilized by Roush in his total synthesis of cochleamycin A (Scheme 2.15).[1a,34]



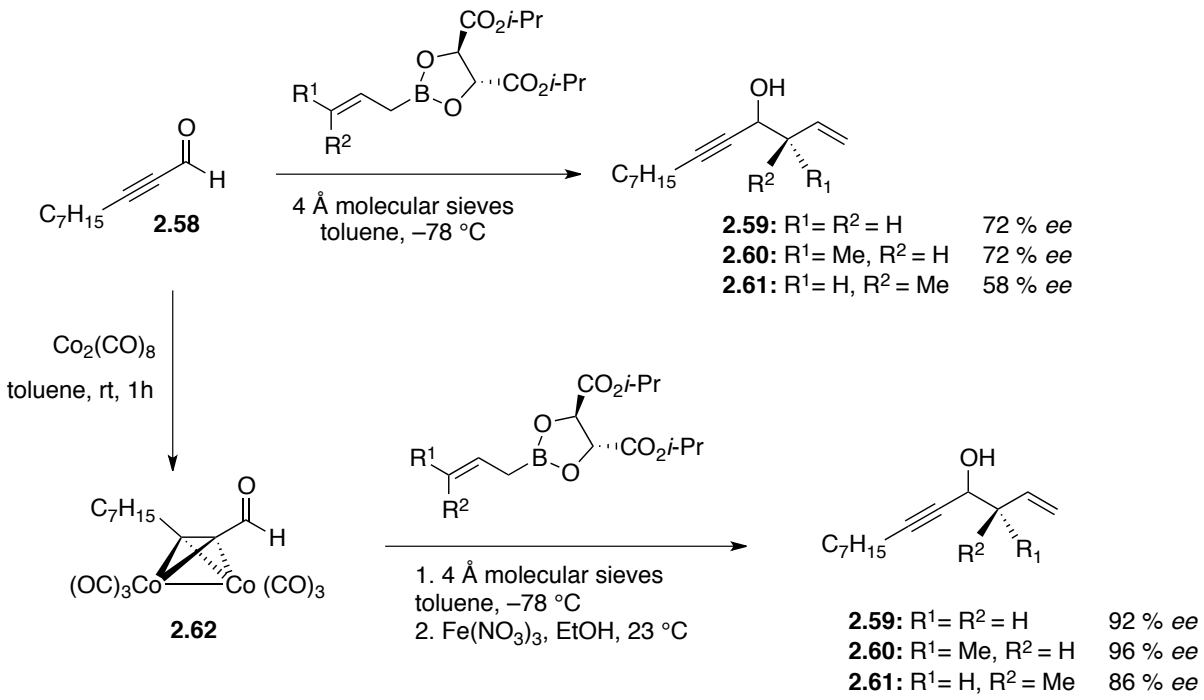
Scheme 2.15. Application of Brown's allylboration methodology with a propargylic aldehyde in the total synthesis of cochleamycin A.[1a,34]

Smith reported the total synthesis of macrolactin A which involves the methodology described earlier (Scheme 2.16).[7]



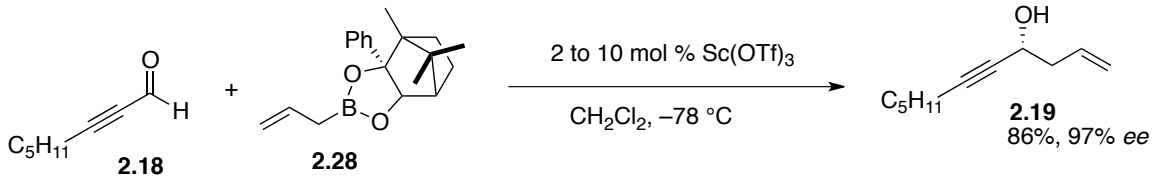
Scheme 2.16. Application of allylboration of a propargylic aldehyde in the total synthesis of macrolactin A.[7]

Roush has applied his tartrate-derived allyl and crotyl boronates in this regard too, resulting in moderate to good yields and enantioselectivities for the synthesis of homoallylic alcohols.[35] Intrigued by the observation that dicobalt hexacarbonyl complexes of propargylic aldehydes gave very high diastereoselectivities in aldol reactions,[36] Roush applied this concept in his allylboration method, starting with the cobalt carbonyl-propargylic aldehyde complex (**2.62**).[37] After the reaction the decomplexation could be achieved with an oxidative work-up with $Fe(NO_3)_3$ (Scheme 2.17).



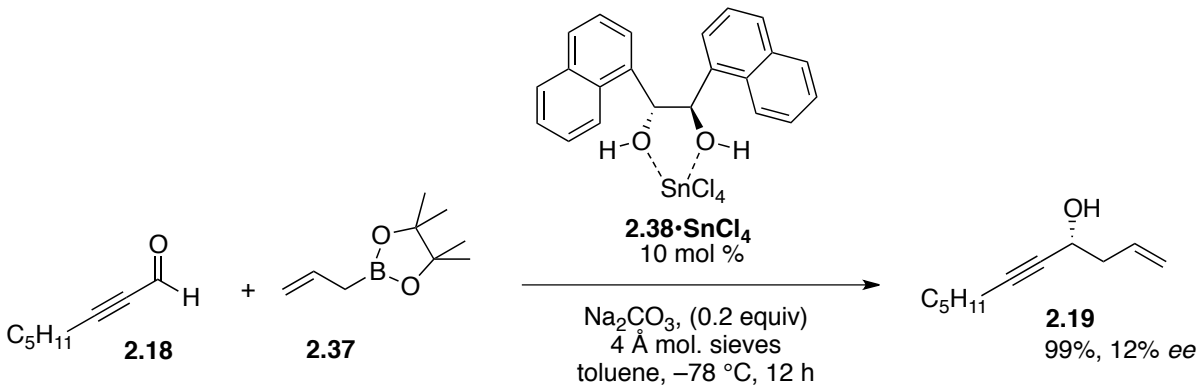
Scheme 2.17. Improved enantioselectivities with dicobalt-hexacarbonyl complexed propargylic aldehyde.[37]

During their substrate scope exploration in the $Sc(OTf)_3$ catalyzed allylation with Hoffmann's diol-derived allylboronate, the Hall group also reported an example involving a propargylic aldehyde. A very good yield and excellent enantioselectivity was observed (Scheme 2.18).[23]



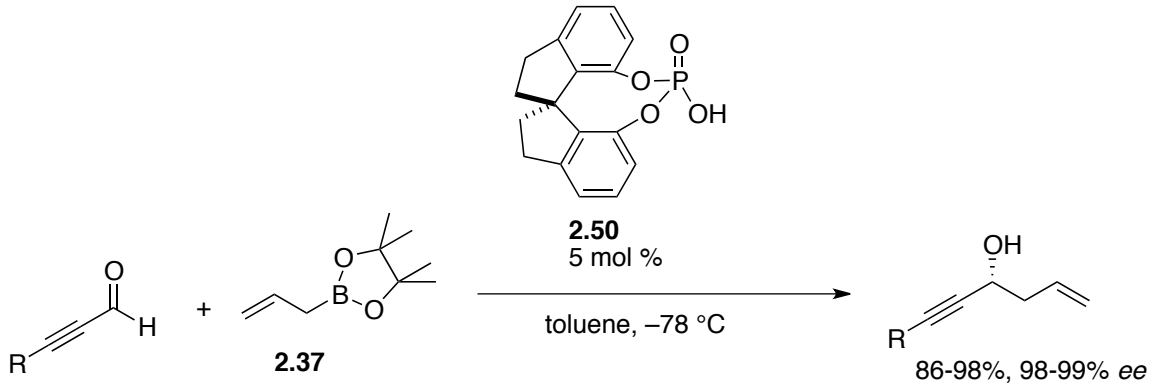
Scheme 2.18. Hall's Sc(III)-catalyzed allylboration of propargylic aldehyde.[23]

The Hall group also applied the Lewis acid assisted Brønsted acid catalysis concept in propargylic aldehyde allylation with their di(1-naphthyl)-1,2-ethanediol-$SnCl_4$ complex (**2.38**•$SnCl_4$) as the catalyst but the model aldehyde performed poorly yielding only 12% *ee* (Scheme 2.19).[26]



Scheme 2.19. Lewis acid assisted Brønsted acid system as a catalyst in allylboration of propargylic aldehydes.[26]

Hu's SPINOL-derived chiral phosphoric acid catalyzed allylboration method was also evaluated with propargylic aldehydes and afforded excellent yield and enantioselectivity (Scheme 2.20).[33]



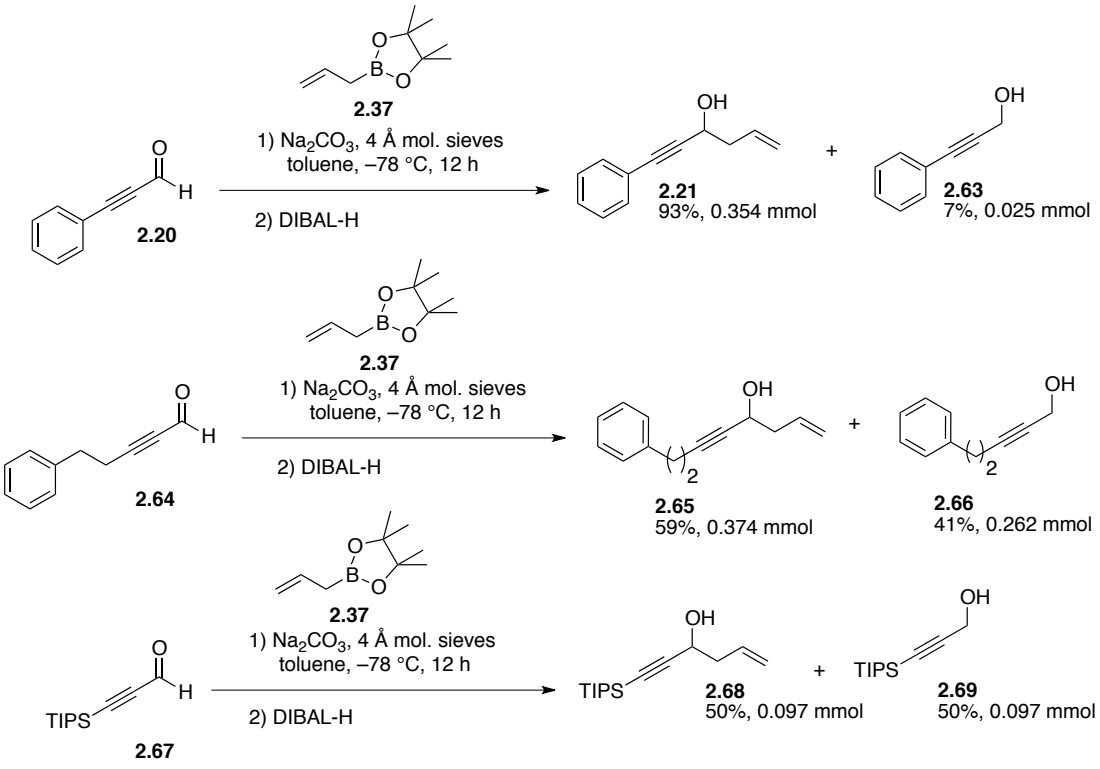
Scheme 2.20. SPINOL-based phosphoric acid catalyzed allylboration of propargylic aldehyde.[33]

Thus, we can see that although there are a few methods for the allylboration of propargylic aldehydes in the literature, most of them suffer from a number of drawbacks. These methodologies either use unstable allylboranes, or allylboronates with a stoichiometric amount of a chiral auxiliary. Sometimes special precautions and extra deprotection steps have to be employed. In the case of the SPINOL-based diol catalyzed allylboration method described above, although satisfactory results were obtained, a detailed substrate scope was not accomplished.[33]

2.5 Results and discussion

2.5.1 Study of the background reaction

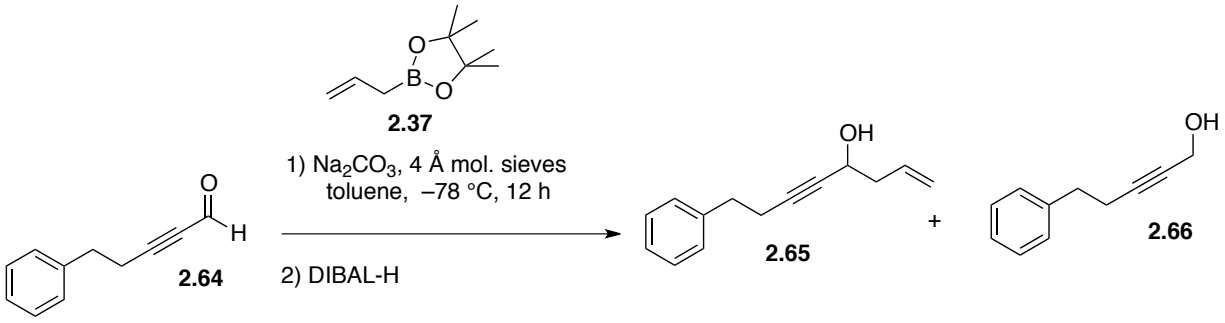
The occurrence of uncatalyzed reaction between an allylboronate and an aldehyde can never be neglected. The rate of this reaction is significant and reduces the overall enantiomeric excess of the final product by increasing the amount of racemic homoallylic alcohol product. To design a methodology for the catalytic asymmetric allylboration of propargylic aldehydes, factors that can influence the background reaction and lower its rate, must be taken into consideration. Control experiments were designed by a co-worker in the Hall group, Erin Sullivan, to explore the structural effect of the propargylic aldehyde on the uncatalyzed background reaction. The reaction conditions in the vivol•$SnCl_4$-catalyzed allyboration reaction of Rauniyar and Hall were utilized to test three different propargylic aldehydes (**2.20**, **2.64**, **2.67**). To this end, the propargylic aldehyde (0.2 to 0.64 mmol) was mixed with pinacol allylboronate (**2.37**) in 0.6 mL of toluene in the presence of Na_2CO_3; 4 A molecular sieves were added to ensure a moisture free environment. The reaction was run overnight at –78 °C and stopped by addition of DIBAL-H at this temperature (Scheme 2.21).



Scheme 2.21. Comparison of background reactions of different propargylic aldehydes.

Based on the final amounts of the reduced starting materials it was deduced that the uncatalyzed background rate of allylboration of propargylic aldehydes was the fastest with the more conjugated aldehyde phenylpropynal (**2.20**) and slowest with 3-triisopropylsilyl-2-pentynal (**2.67**). However, 3-phenyl-2-pentynal **2.64** had the second slowest rate of background allylboration after **2.67**, with a comparatively higher rate of the formation of the desired homoallylic alcohol product than **2.67**. Thus, this can be considered as a more suitable substrate for optimization studies because it is a more "balanced" substrate. Therefore, aldehyde **2.64** was employed as a substrate for further control studies. Thus, it was subjected to another round of control study to estimate the effect of its concentration on the speed of the background reaction. The same reaction as shown in Scheme 2.21 was now performed in four different concentrations of **2.64** (1 mmol) starting from 0.83 M to 2.2 M (Table 2.1). It was observed that the background reaction was the fastest at a 2.2 M concentration of **2.64**. At 1.67 M of **2.64** the background reaction slowed significantly giving 13% less of the racemic homoallylic alcohol product compared to what was obtained at 2.0 M. However, when the solvent concentration was reduced further to 0.83 M of the starting aldehyde, the rate diminished significantly.

Table 2.1: Effect of solvent concentration on the apparent rate of the background allylboration reaction.



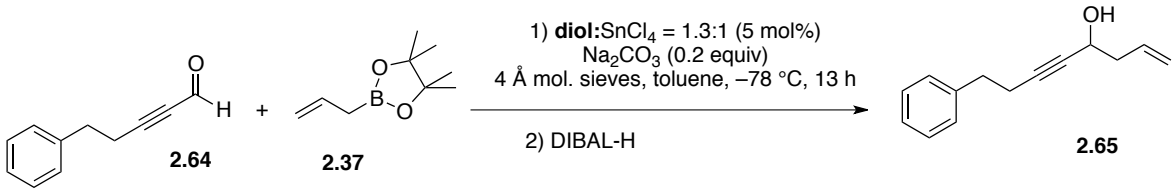
Solvent amount	Concentration	Time	% Conversion	% Conversion/h
0.45 mL	2.2 M	6 h	43	7
0.50 mL	2.0 M	10 h	59	6
0.60 mL	1.67 M	12 h	46	3.8
1.2 mL	0.83 M	9 h	23	2.6

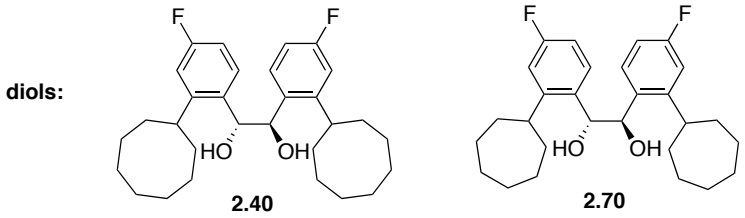
Thus, relatively concentrated solutions (such as 2.2 M or 2.0 M) or relatively dilute solutions (such as 0.83 M) of the aldehyde for the reaction should be avoided to keep both the overall reaction rate and the background reaction at a satisfactory, compromised level. Thus, the reaction concentration was set at 1.67 M for the next optimization studies.

2.5.2 F-Vivol•$SnCl_4$ catalyzed asymmetric allylboration of propargylic aldehydes

After a suitable substrate for the control experiments was selected and the effect of aldehyde concentration on the background reaction was determined, it was time to try the actual catalytic asymmetric conditions reported by Rauniyar and Hall.[29] To this end, Sullivan treated a 1.67 M solution of aldehyde, 5-phenyl-2-pentynal (1 mmol, **2.64**), with 5 or 10 mol% of F-vivol-8•$SnCl_4$ and F-vivol-7•$SnCl_4$ (**2.70**) in toluene at –78 °C in the presence of Na_2CO_3 and molecular sieves (Table 2.2).

Table 2.2: Catalytic asymmetric allylboration of propargylic aldehyde **2.64**.





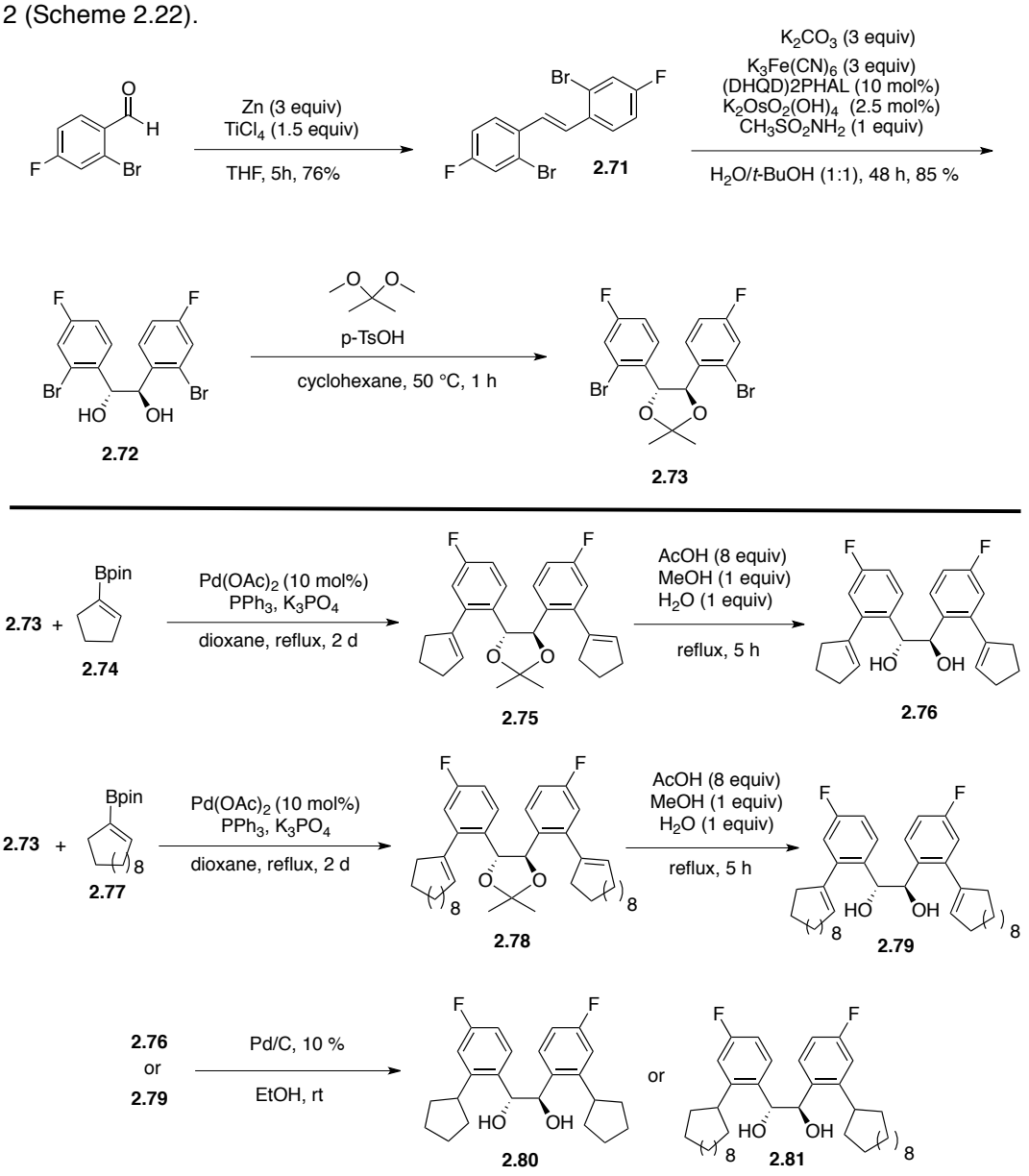
diol	Catalyst loading	Yield (%)[a]	*ee* (%)[b]
F-vivol-8 (**2.40**)	5 mol%	87	63
F-vivol-7 (**2.70**)	5 mol%	93	60
F-vivol-8 (**2.40**)	10 mol%	89	73
F-vivol-7 (**2.70**)	10 mol%	94	76

a) Isolated yields.

b) *ee* was determined by chiral HPLC analysis.

Thus, in the allylboration of propargylic aldehyde **2.64**, F-vivol-8 afforded a slightly better *ee* than F-vivol-7 at a catalyst loading of 5 mol%. Then, the catalyst loading was increased to 10 mol% to see what kind of effect an increased catalyst loading would have on the yield and enantioselectivity of the reaction. This time, F-vivol-7 performed better by affording an *ee* of 76%, proving quite unsurprisingly that a higher catalyst loading is preferable for this reaction. However, the difference in *ee* between the two diols at this loading was not significant at all. Since the difference in enantioselectivity between the two diols at two different loadings was not high and one catalyst outperformed the other in two different sets of conditions, it is difficult to draw any conclusion about the overall effect of these catalysts on the reaction and to select

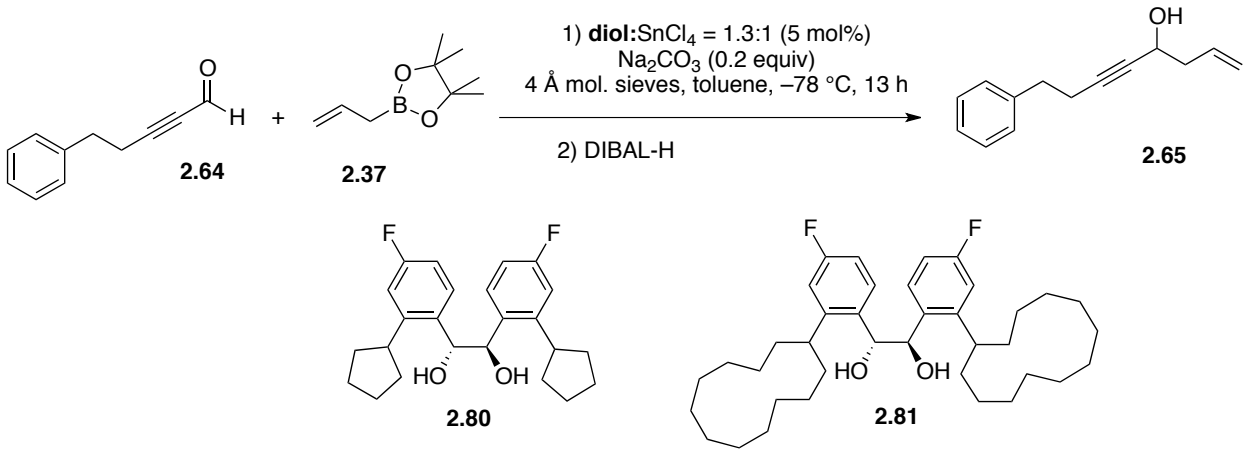
one of them for further studies. Hence it was decided to investigate the effect of vivol-diols with small and very large ring sizes on the phenyl ring. To this end, Sullivan prepared F-vivol-5 and F-vivol-12 by following the same procedure as that of the other two vivol-diols. The first step was a McMurry coupling of aldehydes (2-bromo-5-fluorobenzaldehyde) followed by a Sharpless asymmetric dihydroxylation resulting in the formation of a chiral diol, **2.72**. This diol was then protected by treating with 1,2-dimethoxypropane. Then, a Suzuki-Miyaura coupling between the resulting aryl compound (**2.73**) with cyclopentenylpinacol boronate (**2.74**) or cyclododecenylpinacol boronate (**2.77**) provided the precursors **2.75** and **2.78** for the two new vivol-diols. Deprotection of these precursors followed by hydrogenation afforded F-vivol-5 and F-vivol-12 (Scheme 2.22).



Scheme 2.22. Synthesis of F-vivol-5 and F-vivol-12.

The allylboration of propargylic aldehydes using the F-vivol-5 and F-vivol-12 based catalysts were planned in the same manner as with F-vivol-7 and F-vivol-8 with 10 mol% of the diol being used and a reaction concentration of 1.67 M (Table 2.3).

Table 2.3: Catalytic asymmetric allylboration of the propargylic aldehyde **2.64** employing F-vivol-5 and F-vivol-12.



Entry	Diol	Yield (%)[a]	*ee* (%)[b]
1	F-vivol-5 (**2.80**)	60	27
2	F-vivol-12 (**2.81**)	74	23

a) Isolated yields.

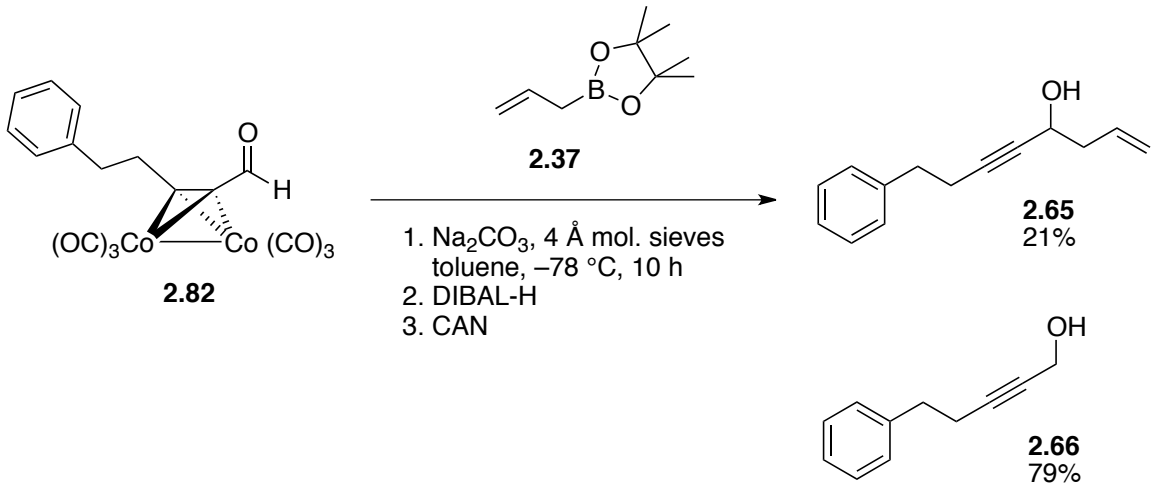
b) *ee* was determined by chiral HPLC analysis.

Table 2.3 shows that F-vivol-5 and F-vivol-12 proved to be less selective than the 7- and 8-membered F-vivols yielding only 27 and 23% *ee* for the 5- and 12-membered F-vivols respectively.

2.5.3 Application of cobalt hexacarbonyl complex

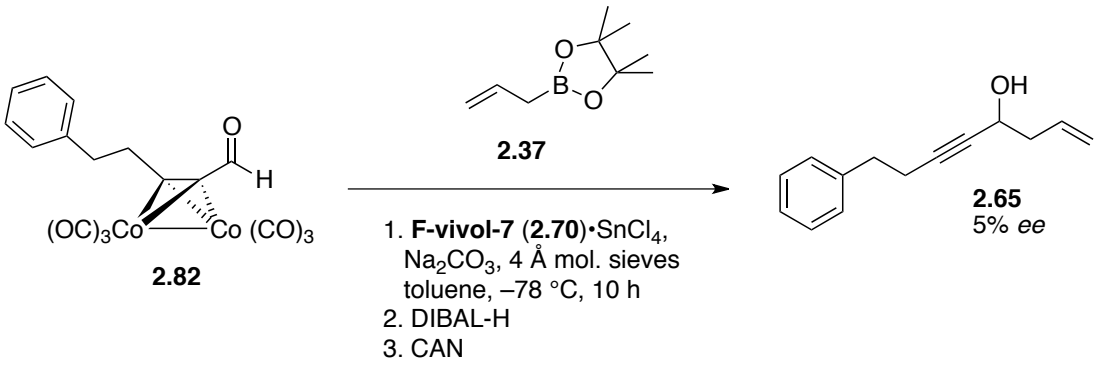
The application of a cobalt complex in the allylboration of propargylic aldehydes by Roush was discussed in Section 2.4.[37] It was expected that this method could be helpful for the vivol•$SnCl_4$ catalyzed asymmetric allylboration of propargylic aldehydes. To apply the propargylic aldehyde–cobalt complex in the vivol•$SnCl_4$-catalyzed asymmetric allylboration method, it was necessary to determine whether the complex formation between the aldehyde and the cobalt would affect the rate of the background reaction or not. Thus, Sullivan subjected the aldehyde-cobalt carbonyl complex to the similar kind of reaction

conditions described in Section 2.5.1 (Scheme 2.23).



Scheme 2.23. Study of the background allylation of cobalt-propargylic aldehyde complex.

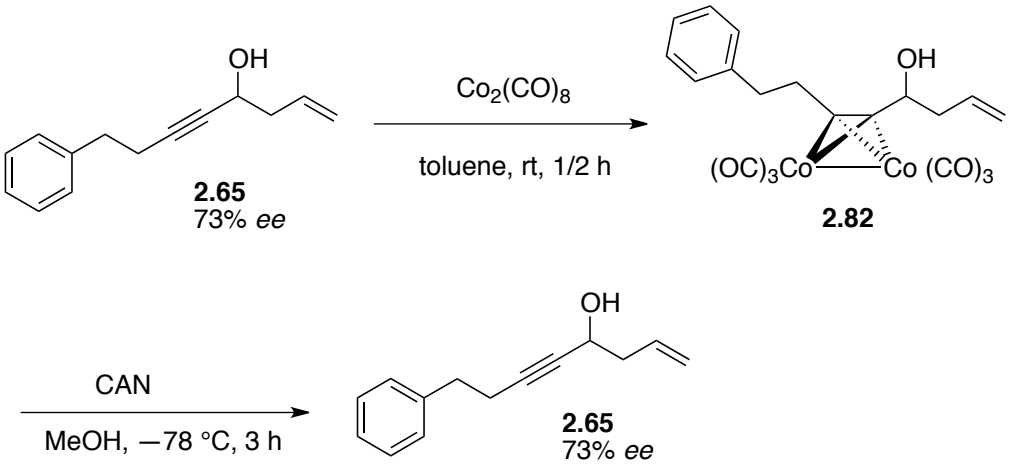
The results were encouraging because the speed of the background reaction was significantly lower than that observed in previous control studies (Figure 2.11 and Table 2.1) as revealed by the yields of the isolated homoallylic propargylic alcohol product and the reduced starting material. However, the lower yield of the homoallylic alcohol product might indicate a slower rate for the desired reaction, too. We decided to go ahead and perform the asymmetric vivol•$SnCl_4$-catalyzed reaction. Unfortunately, the asymmetric allylboration between the cobalt carbonyl-propargylic aldehyde complex and the allylboronate in the presence of F-vivol-7•$SnCl_4$ as a catalyst, afforded only 5% *ee* (Scheme 2.24).



Scheme 2.24. F-vivol-7•$SnCl_4$ catalyzed allylboration of a cobalt-propargylic aldehyde complex.

However, there were doubts regarding the reason behind such low enantioselectivity. At first it was presumed that there might be erosion in *ee* through epimerization during the oxidative decomplexation of

the cobalt complex. In order to establish whether or not the oxidative decomplexation was responsible for the low *ee*, a control study was planned. Homoallylic propargylic alcohol **2.65** with an *ee* of 73% (Table 2.2) prepared by F-Vivol-8•$SnCl_4$ catalyzed allylboration was transformed into the corresponding cobalt complex by treating the alcohol with cobalt carbonyl in toluene. No loss in enantioselectivity was noticed after ceric ammonium nitrate mediated decoupling (Scheme 2.25).



2.65
73% *ee*

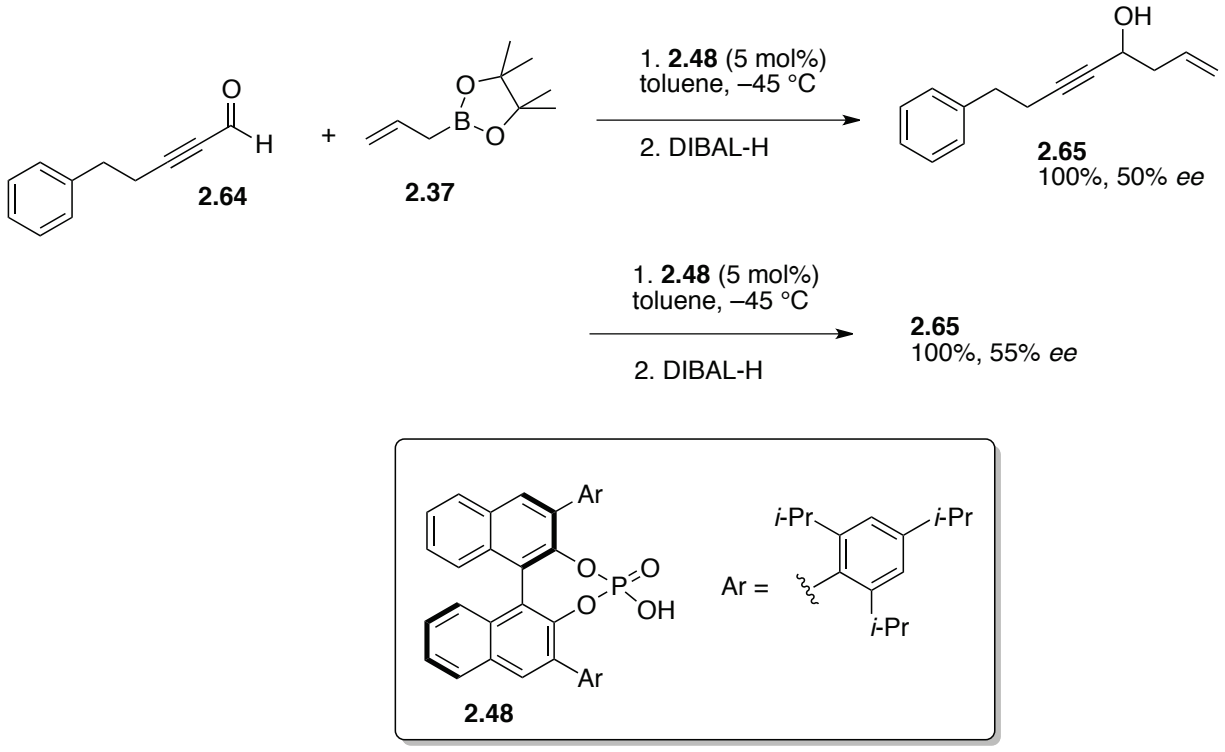
2.82

2.65
73% *ee*

Scheme 2.25. Examination of complexation and decomplexation of the homoallylic propargylic alcohol-cobalt carbonyl complex to determine the possibility of epimerization.

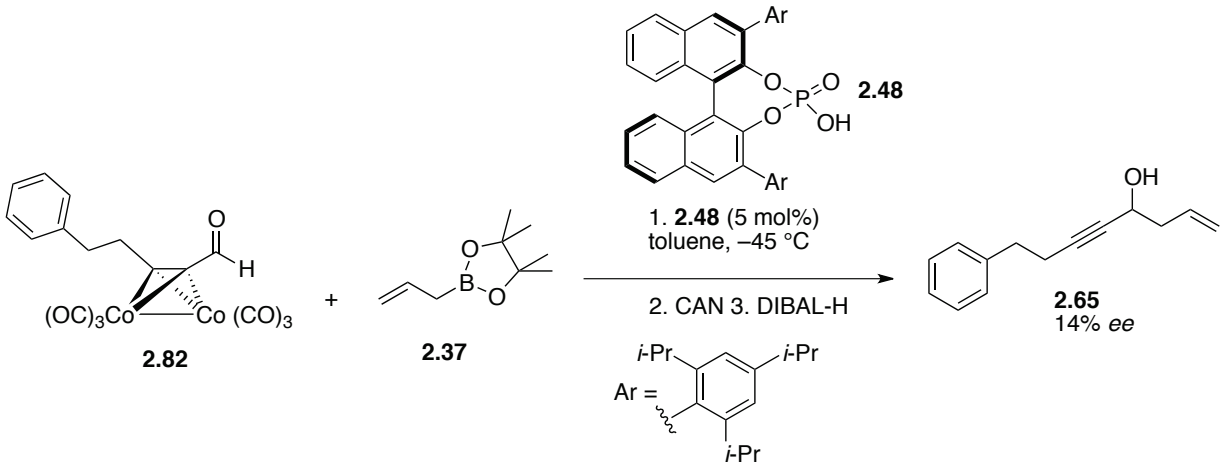
2.5.4 Application of chiral phosphoric acid catalysis

As discussed in Section 2.3, chiral phosphoric acid catalysis has been applied successfully in asymmetric allylboration. Encouraged by the success of Antilla's group with 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**2.48**), we attempted a similar reaction with propargylic aldehyde **2.64**. Unfortunately the *ee* was only 50% although the reaction was complete after 12 h. Increasing the catalyst loading to 10% and lowering down the temperature did not make any significant difference (Scheme 2.26).



Scheme 2.26. Chiral phosphoric acid catalyzed allylboration method applied to propargylic aldehydes with 5 and 10% catalyst loading.

The cobalt-aldehyde complex **2.82** was subjected to phosphoric acid catalysis too, but only afforded 14% *ee* (Scheme 2.27).



Scheme 2.27. Chiral phosphoric acid catalysis with cobalt-propargylic aldehyde complex.

2.5.5 Evaluation of different allylboronic esters

Brown and co-workers showed that the rate of the allylboration reaction depends on the nature of the diol unit that constitutes the boronic ester, along with solvent polarity.[38] Inspired by this work it was decided to try different allylboronates other than allylboronic acid pinacol boronate (**2.37**). These allylboronates were prepared by Sullivan by treating allylboronic acid with different diols (Figure 2.7).

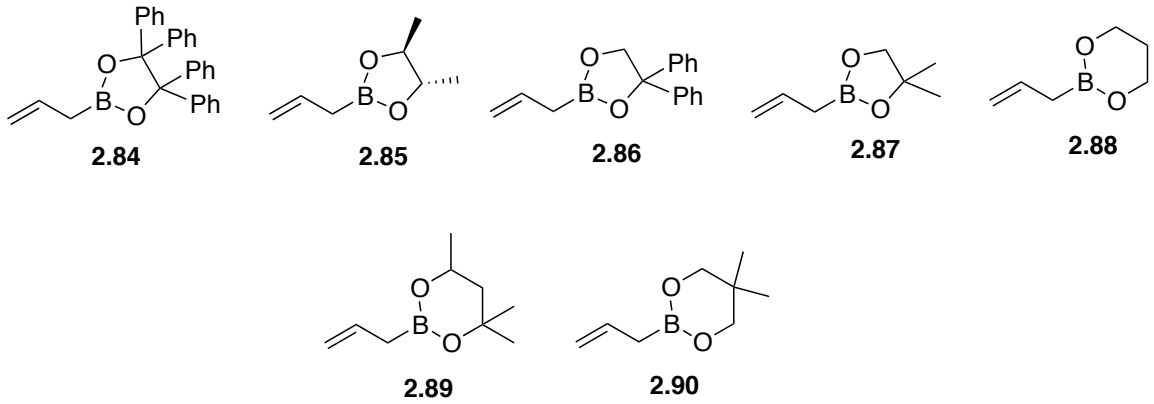
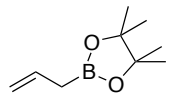
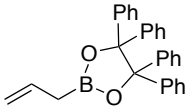
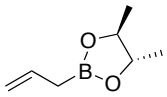
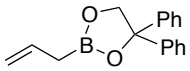
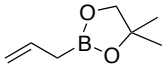
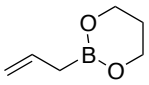
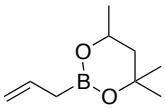
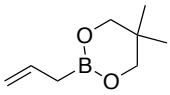


Figure 2.7. Allylboronates prepared for optimization of allylboration reaction.

Sullivan subjected these allylboronates to a racemic reaction with the aldehyde **2.64** under the same conditions described in section 2.5.1. Yields of isolated product and reduced starting materials are shown in Table 2.4.

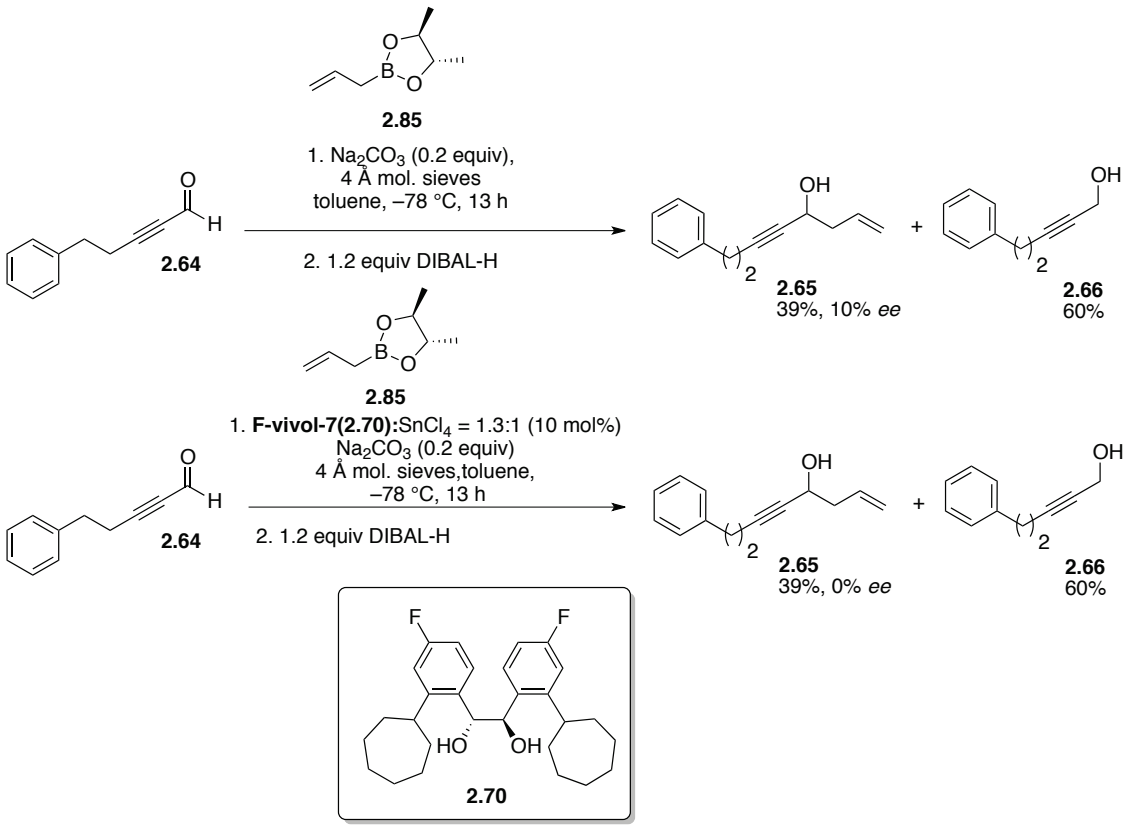
Table 2.4: Sullivan's study of the background allylboration reaction with various allylboronic esters.[a]

Allylboronate	Time (h)	Yield (%)[b]	Reduced S.M (%)[c]	% Yield/h
 **2.37**	12	59	41	4.9
 **2.84**	16	43	57	2.7
 **2.85**	5	18	82	3.6
 **2.86**	7	18	82	2.6
 **2.87**	7	35	65	5.0
 **2.88**	5	25	75	5.0
 **2.89**	9	4	96	0.44
 **2.90**	9	26	74	2.9

a) All reactions were carried out at 1.67 M concentration at –78 °C with 1.0 mmol of aldehyde and 1.2 mmol of allylboronate in 0.6 mL of toluene. b) Isolated yields. c) 1.2 equiv DIBAL-H was added at the end to stop any further reaction.

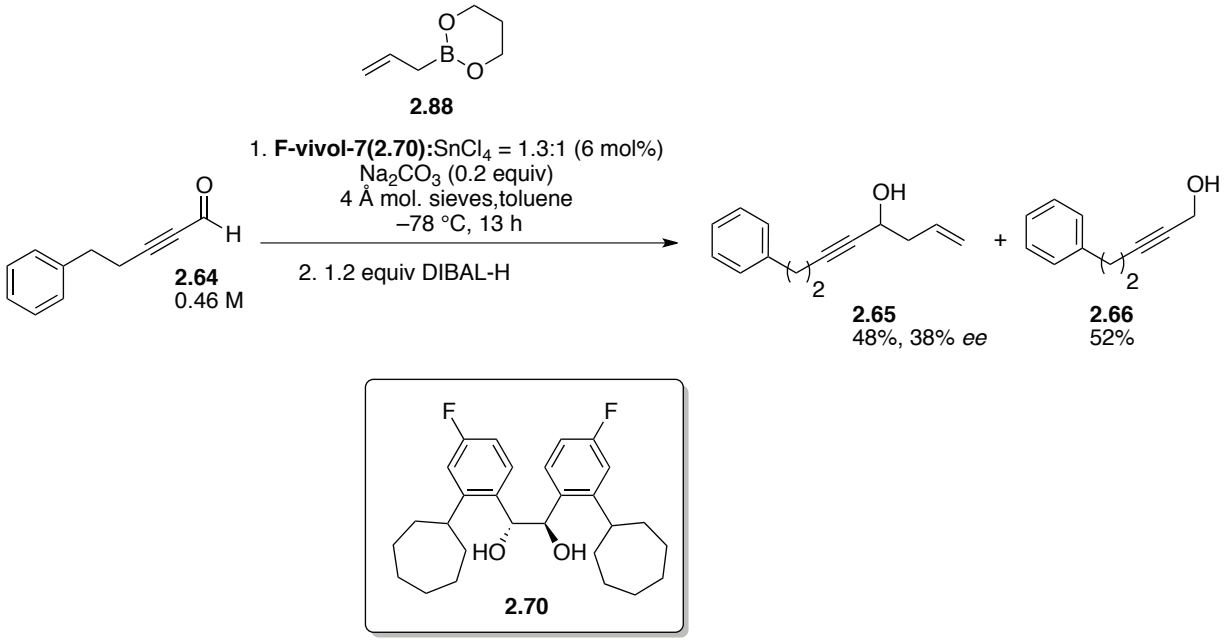
Sterically congested allylboronate **2.84** was slower to react with the aldehyde compared to allylBpin (**2.37**). This boronate, however, was very difficult to prepare. Some of the boronates prepared had congestion in one side that blocked one boronate oxygen allowing only the other oxygen to coordinate with the proton of the vivol•$SnCl_4$ complex. Allylboronate **2.87** had similar conversion rate/h to that of allylBpin but it was very difficult to prepare because of its unstability and decomposed into the boronic acid upon conatact with air and moisture. Allylboronate **2.85** was also closer in reactivity (conversion rate/h: 3.6) to allylBpin (**2.37**, conversion rate/h: 4.9). Allylboronates with six membered rings were tested too. Allylboronate **2.88** was similar in reactivity when compared to allylBpin. Allylboronate **2.89** was too bulky and the slowest of all the boronates. Allylboronate **2.90** displayed a very encouraging reactivity with a slower background reaction while still maintaining some reactivity. Thus **2.85**, **2.88** and **2.90** have very good potential to become suitable allylating agents in this reaction. Also, it was important to see whether there is any possibility of a

dramatic improvement in reaction rate under the vivol•$SnCl_4$-catalyzed conditions with allylboronate **2.89**, which had a very slow rate of background reaction. Since allylboronate **2.85** was made from a chiral diol it was expected to undergo asymmetric allylboration with the aldehyde. However, when Sullivan ran the reaction of this allylboronate **2.85** with a model aldehyde under similar conditions to the vivol•$SnCl_4$-catalyzed reaction without the chiral catalyst, she obtained only 10% *ee*. Surprisingly, adding optically pure 10 mol% of F-vivol-7•$SnCl_4$ diminished the enantioselectivity even more. This probably results from a "mismatch" situation; that is, if the other enantiomer of the diol was used instead, an enhanced *ee* might be expected. However, that reaction would require the use of a stoichiometric amount of the chiral diol (*S*,*S*-1,2 dimethylethanediol) in that case. The goal here was to find out a purely catalytic enantioselective method instead (Scheme 2.28).



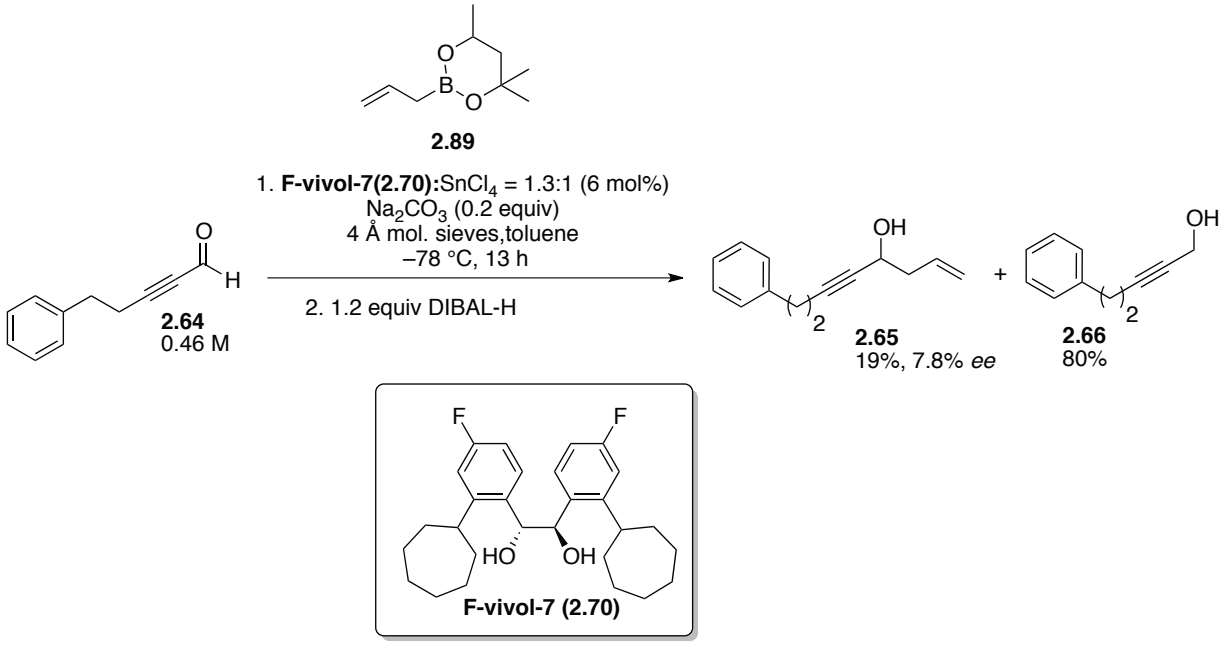
Scheme 2.28. Sullivan's allylboration attempts with allylboronate **2.85** derived from a chiral 1,2-diol.

Next, Sullivan explored allylboronates with six membered rings. Allylboronate **2.88** was reacted with aldehyde **2.64** under F-vivol-7•$SnCl_4$ catalyzed conditions. At this point she also decided to modify the concentration of this reaction a bit to see whether the change in concentration can improve the enantioselectivity. The concentration of aldehyde was reduced from 1.67 M to 0.46 M. Unfortunately the reaction was very sluggish and afforded only 48% of the desired product with an *ee* of 38% (Scheme 2.29). However, further optimization reactions performed at 0.46 M of aldehyde led to encouraging results (Schemes 2.30 onwards).



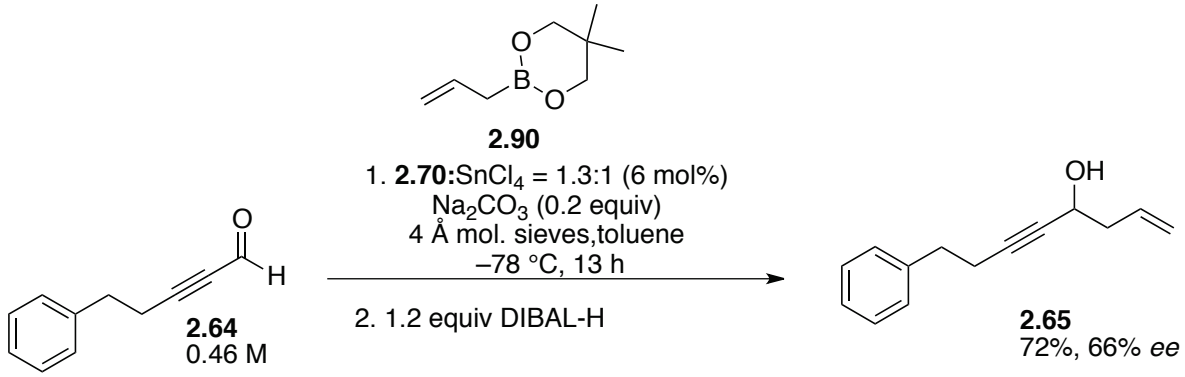
Scheme 2.29. Allylboration of aldehyde **2.64** with **2.88**.

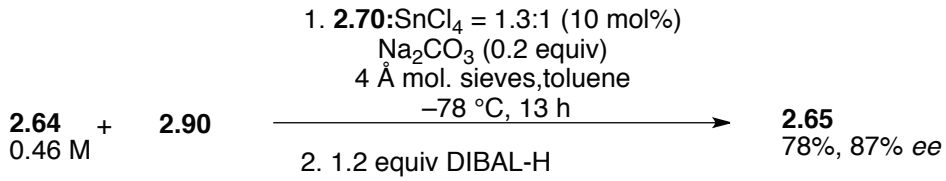
When Sullivan treated allylboronate **2.89** with aldehyde **2.64** under F-vivol-7•$SnCl_4$ catalyzed conditions, she observed only 7.8% *ee* with 19% yield along with 80% of reduced starting material after treatment with DIBAL-H (Scheme 2.30).

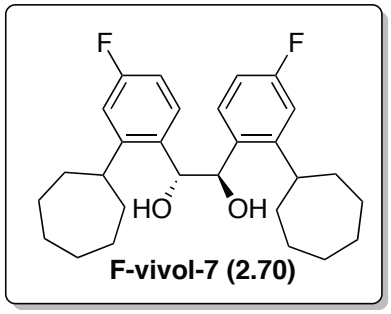


Scheme 2.30. Allylboration with bulky allylboronate **2.89**.

Sullivan then decided to employ allylboronate **2.90** with aldehyde **2.64** under F-vivol-7•$SnCl_4$ catalyzed conditions with 6 mol% of the diol being used. Although the starting material was fully consumed after 13 h, only 66% *ee* of the desired product was achieved. It is at this point that I took over the project and decided to increase the amount of F-vivol-7 up to 10 mol%. This increased the yield to 78% and the *ee* improved to the high 80s for the first time (Scheme 2.31).

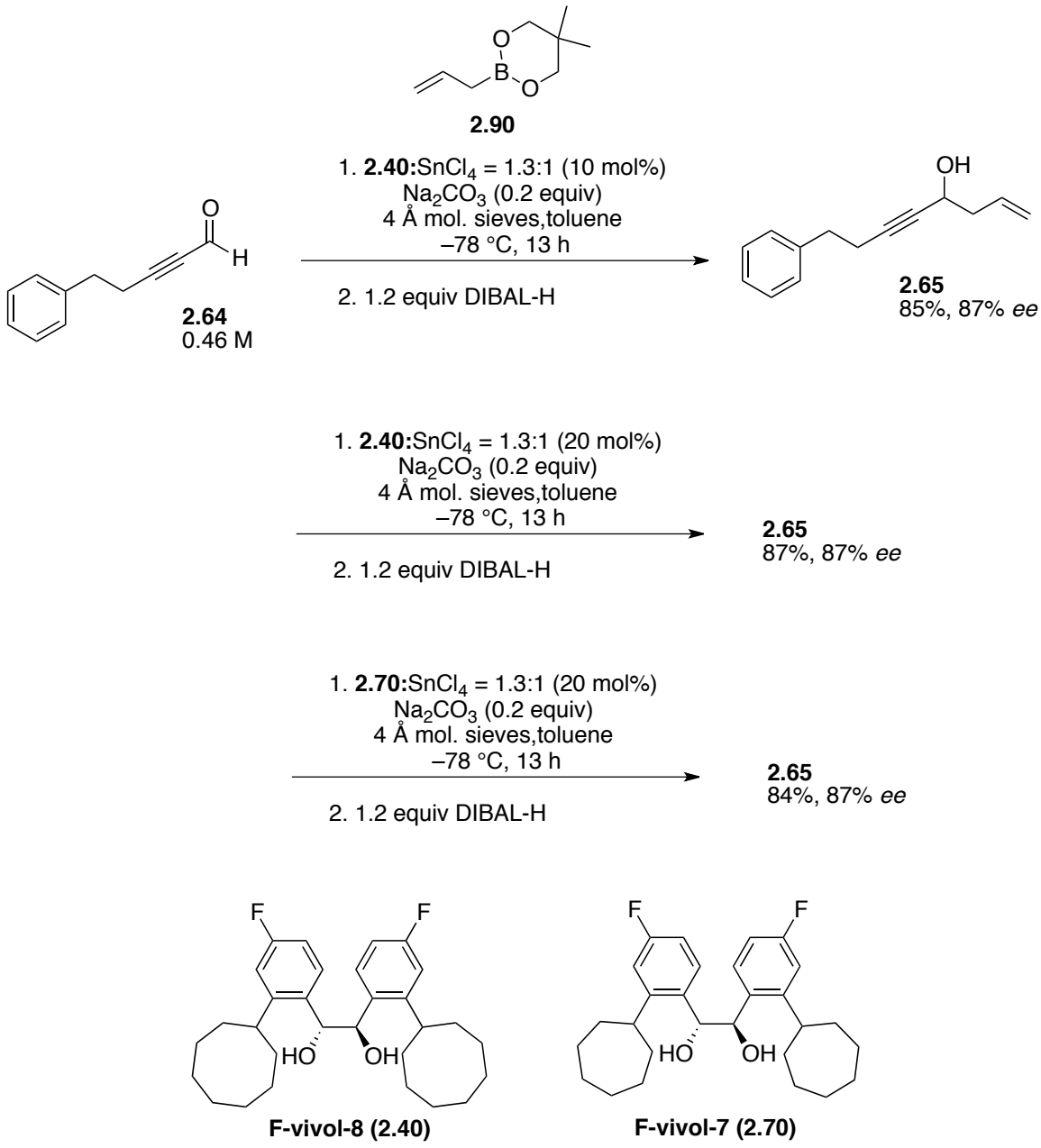






Scheme 2.31. Allylboration of **2.64** with allylboronate **2.90** with 6 and 10 mol% of F-vivol-7•$SnCl_4$.

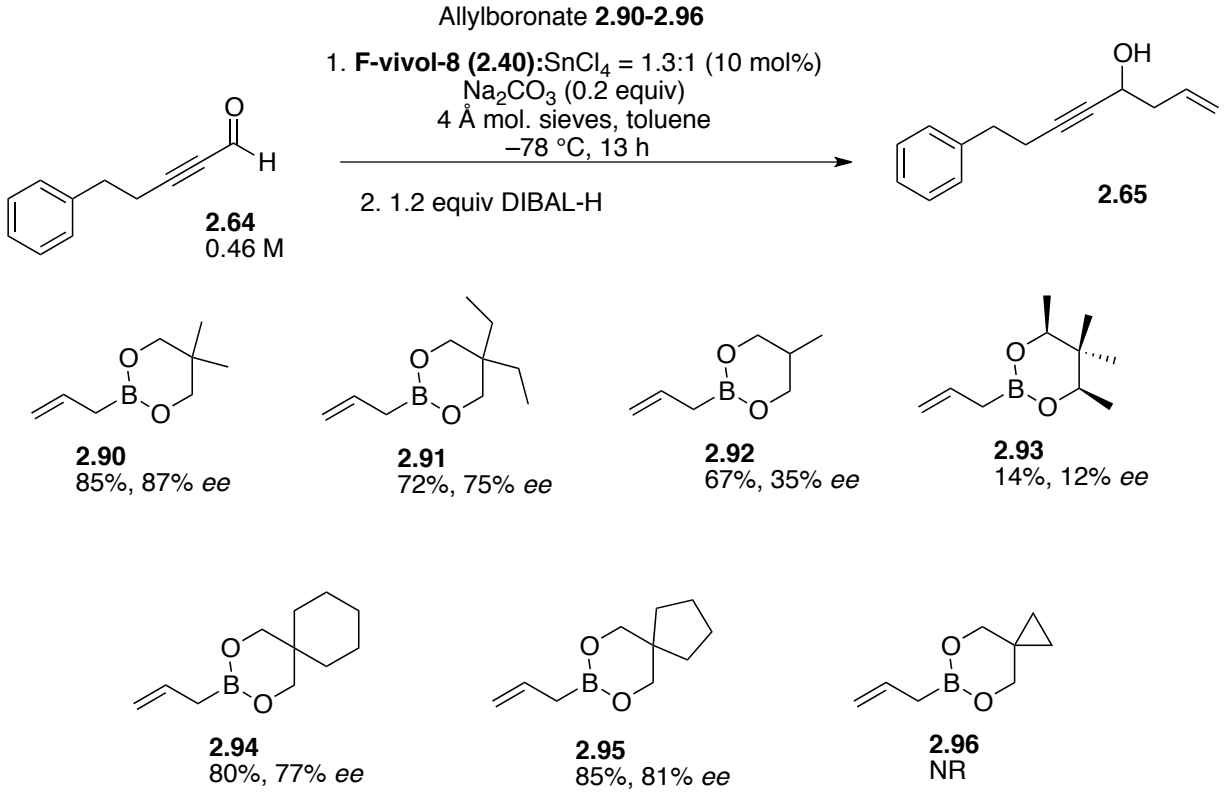
The reaction conditions were further optimized by changing the diol this time, using F-vivol-8 instead of F-vivol-7. This modification increased the yield to 85% without any change in enantioselectivity. Further increasing the catalyst loading to 20 mol% did not change the enantioselectvity. Similarly no improvement in *ee* was noticed with 20 mol% F-vivol-7•$SnCl_4$ (Scheme 2.32).



Scheme 2.32. Allylboration of **2.64** with allylboronate **2.90** in presence of 10 and 20 mol% F-vivol-8•$SnCl_4$ or F-vivol-7•$SnCl_4$.

Because allylboronate **2.90** gave the highest yield and *ee* in the reaction with **2.64**, it was postulated that allylboronates with substituents different from Me on the central carbon atom of the boronate's diol unit could possibly improve the outcome. Thus, a series of allylboronates with different substituents were prepared and reacted with aldehyde **2.64** under the conditions described in Section 2.5.1, as shown in Scheme 2.33. The performance of these boronates varied depending on the steric nature of the diol unit

of the boronate. Thus, boronates with rings on the central carbon atom instead of alkyl groups (**2.94** and **2.95**) performed better than the other boronates. Surprisingly, allylboronate **2.96** with a cyclopropane ring as a substituent on the central carbon atom did not react at all. On the other hand, changing the substitution pattern to diethyl (**2.91**) from dimethyl, reduced both yield and enantioselectivity whereas the boronate with just one methyl group (**2.92**) gave only 35% *ee*. Boronate **2.93** was the least effective of all, and steric congestion can be held responsible for that outcome (Scheme 2.33). Although, the exact reasons behind all these outcomes are not entirely clear at this moment, it can be assumed that the varying steric demand of the indivudual diol on the boronate may be playing a role.

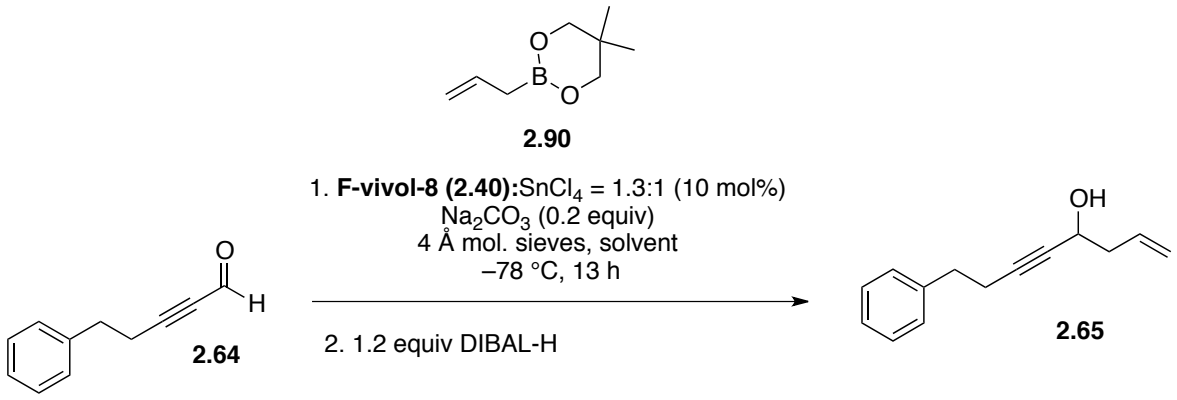


Scheme 2.33. Optimization study with allylboronates **2.90**-**2.96** in presence of F-vivol-8•$SnCl_4$ as the catalyst.

Since none of these allylboronates were proved to be better than **2.90**, further optimizations were conducted with the same allylboronate **2.90**. So far all the reactions had been carried out in toluene; it would be interesting to see the effect of solvent polarity on the reactivity. Thus a series of solvents and solvent combinations were attempted with the hope that the product yield and *ee* could be improved

(Table 2.5).

Table 2.5: Solvent scope optimization for vivol•$SnCl_4$ catalyzed asymmetric allylboration.[a]

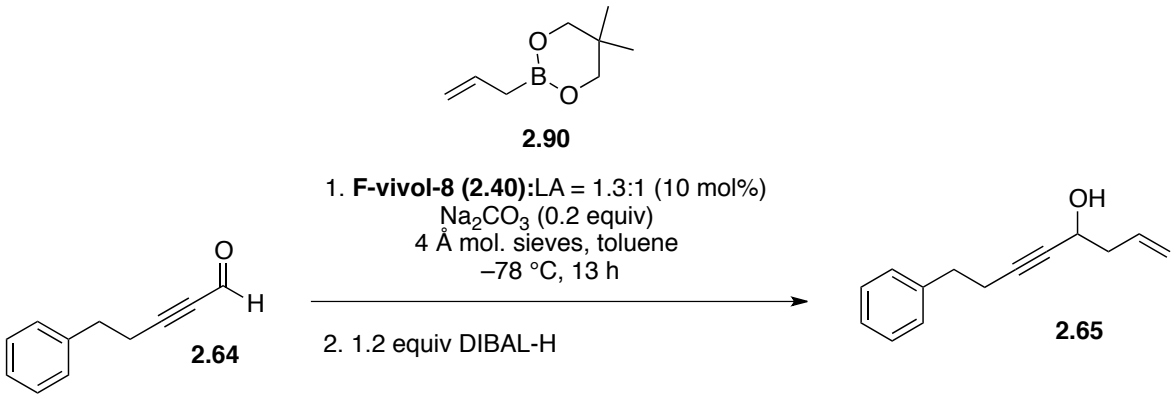


Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	toluene	85	87
2	1:1 toluene / DCM	78	81
3	1:1 toluene/DCM, (–100 °C)	82	81
4	DCM	74	75
5	PhF (– 25 °C)	68	72
6	*o*-xylene (– 25 °C)	65	64
7	$PhCF_3$ (– 25 °C)	58	52
8	Methylcyclohexane	85	82
9	Methylcyclopentane	85	83

a) Reactions were performed with 0.28 mmol of aldehyde and 0.32 mmol of allylboronate in 0.6 mL toluene; temperature was kept at –78 °C except for the indicated entries. b) Isolated yields. c) *ee*'s were determined by chiral HPLC.

The reactivity pattern matched well with the nature of the solvent. The tol:DCM combination afforded 81% *ee*, which is lower than what was achieved with toluene only as a solvent. It appears that the presence of polar DCM (ε=8.93) drove the background racemic reaction faster resulting in lower *ee*. Lowering the temperature to – 100 °C did not change the scenario whereas reaction in DCM only gave much lower *ee* suggesting that the rate of the background uncatalyzed reaction might have been enhanced. Changing to less polar solvents (entries 5-9) did not result in any dramatic improvement, with only methylcyclohexane (ε=2.02) and methylcyclopentane (ε=2.0) giving results close to toluene (ε=2.38). Since no other solvents proved to be better than toluene in terms of enantioselectivity, toluene continued to be the solvent of choice for this reaction. Similarly different Lewis acids were substituted for $SnCl_4$ but all of them were thoroughly underproductive (Table 2.6).

Table 2.6: Evaluation of Lewis acid partner for the asymmetric allylboration.[a]



Entry	Lewis acids	Yield (%)[b]	*ee* (%)[c]
1	$Yb(OTf)_3$	9	5
2	$La(OTf)_3$	12	9
3	SnF_4	14	8
4	$TiCl_4$	11	5
5	$ZrCl_4$	7	3

a) Reactions were performed with 0.28 mmol of aldehyde and 0.32 mmol of allylboronate in 0.6 mL toluene; temperature was kept at –78 °C except for the indicated entries. b) Isolated yields. c) *ee*'s were determined by chiral HPLC.

The reasons behind the lack of reactivity of the aldehyde after treatment with Lewis acids other than $SnCl_4$ could be explained by a combinations of different factors such as lack of solubility in toluene, and the formation of alkoxides generated through the reaction between the Lewis acids used and the vivol ligand. However the actual reasons are not clear at this stage.

2.5.6 Substrate scope investigation for the allylation of propargylic aldehydes

Once the optimized conditions were reached we decided to investigate the scope of substrates that would provide good yields and enantioselectivity. The goal of this effort was to see how general this method is. We were also interested to see the effect of different functional groups on the reactivity and selectivity under the vivol•$SnCl_4$-catalyzed conditions. Different propargylic aldehydes were synthesized with groups that had different functionalities by following a known procedure (Figure 2.8).[40-46] Details regarding the synthesis of these aldehydes are described in the experimental section (pp. 58-61).

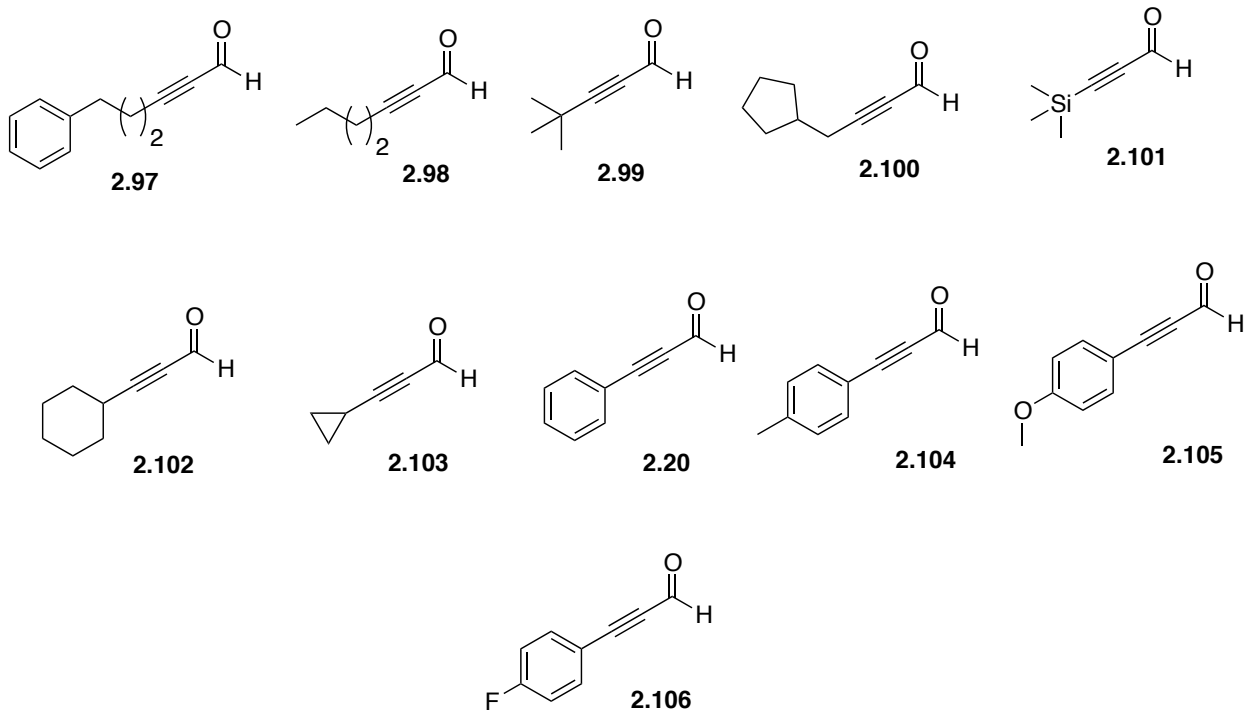
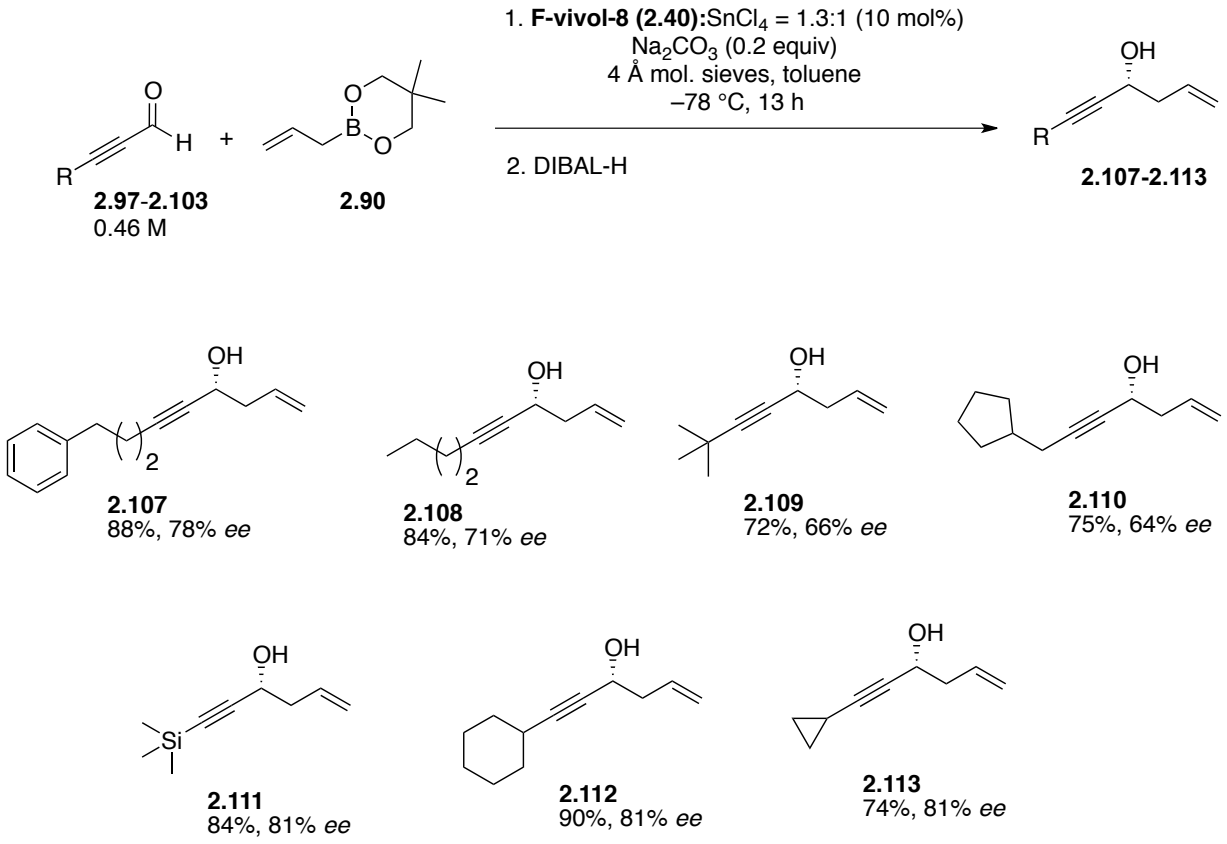


Figure 2.8. Propargylic aldehydes for a substrate scope study.

In the first round of the substrate scope study, aldehydes prepared with aliphatic side chains attached to the alkyne carbon (**2.20**-**2.106**) were subjected to the allylboration conditions described in Section 2.5.1 (Scheme 2.34).

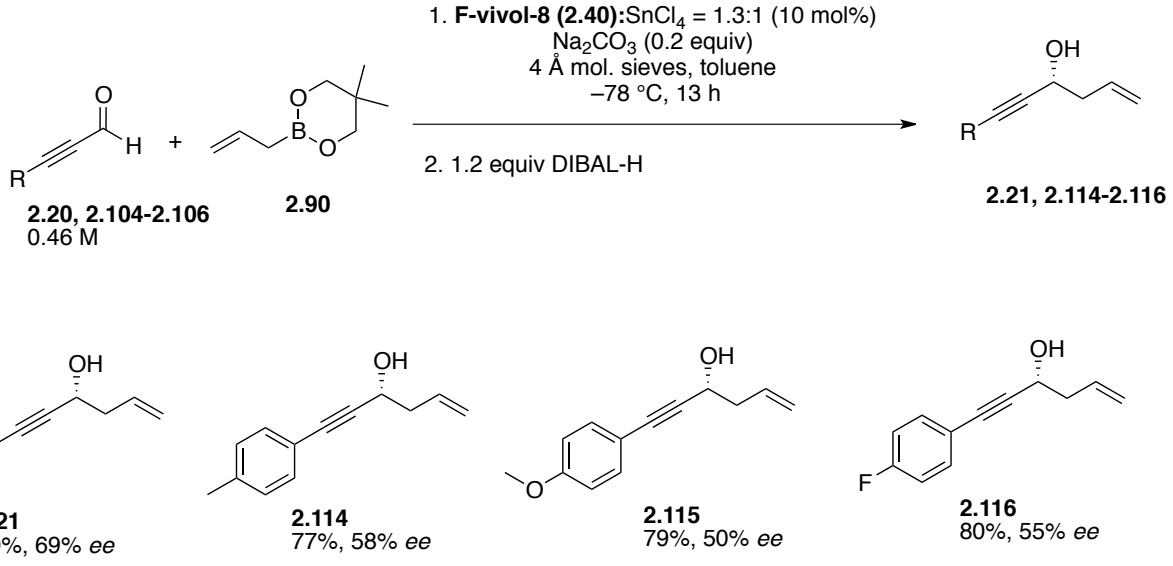


Scheme 2.34. Allylboration of propargylic aldehydes; each aldehyde has an aliphatic chain on the alkyne carbon.

All of these aldehydes worked well although none of them was better than aldehyde **2.64** in terms of *ee*. Propargylic aldehyde **2.97** with a side chain just one carbon longer than **2.64** gave an *ee* of 78% (alcohol **2.108**) compared to 87% *ee* observed with **2.65**. Reactions with aldehydes with both cyclohexyl or cyclopropyl rings directly attached to the alkyne carbon (**2.102** and **2.103**) afforded homoallylic propargylic alcohol products **2.112** and **2.113** with 81% *ee* each. Although aldehyde **2.101** with a trimethylsilyl group on the alkyne carbon worked pretty well (alcohol **2.111**, 81% *ee*), another aldehyde **2.99** with similar structure gave a homoallylic alcohol product **2.109** with much lower *ee*. The homoallylic propargylic alcohol **2.111** is a very useful building block and has been exploited numerous times in various total syntheses.[7]

Next we tried the aldehydes (**2.20**-**2.106**) with an aromatic ring directly bonded to the alkyne carbon. Unfortunately none of them proved to be superior in *ee* to the allylboration of aldehyde **2.64**. During our optimization studies it was observed that conjugated propargylic aldehydes such as **2.20** undergo a higher rate of background reaction than aldehydes with an aliphatic chain (Figure 2.21). That is probably the reason why conjugated propargylic aldehydes were less enantioselective. Electron-donating groups

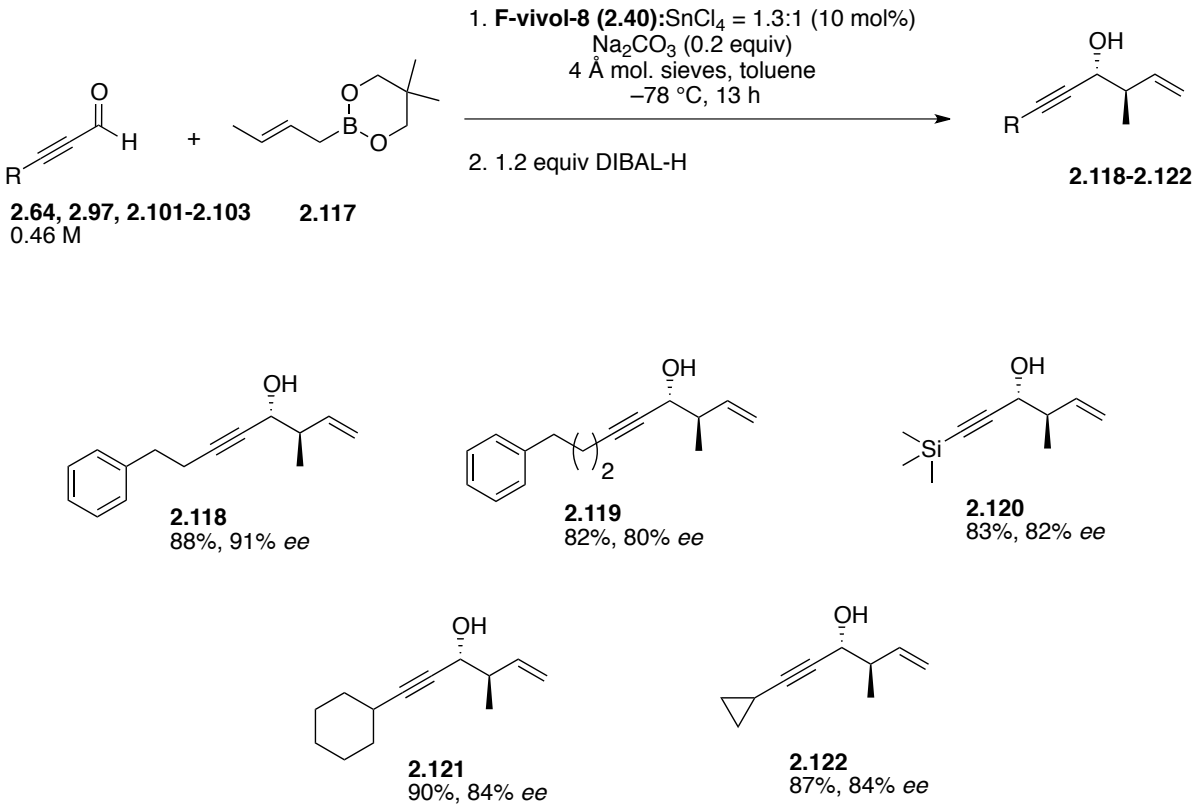
such as –Me or –OMe on the phenyl ring (aldehydes **2.104** and **2.105**) gave homoallylic alcohols **2.114** and **2.115** with even lower enantiomeric excess than aldehydes with just a phenyl ring. An electron-withdrawing group such as –F in aldehyde **2.106** pushed the *ee* cosiderably higher compared to what was obtained with aldehyde **2.105** with –OMe substitution, affording alcohol **2.116** with 55 % *ee*; but the *ee* was was still slightly lower compared with product **2.114** from aldehyde **2.104**. However, as it can be observed, none of the three other substrates performed better than aldehyde **2.20** in terms of the *ee* of alcohol product **2.21** (Scheme 2.35).



Scheme 2.35. Allylboration of propargylic aldehydes with an aromatic chain on an alkyne.

2.5.7 Substrate scope investigation for the crotylation of propargylic aldehydes

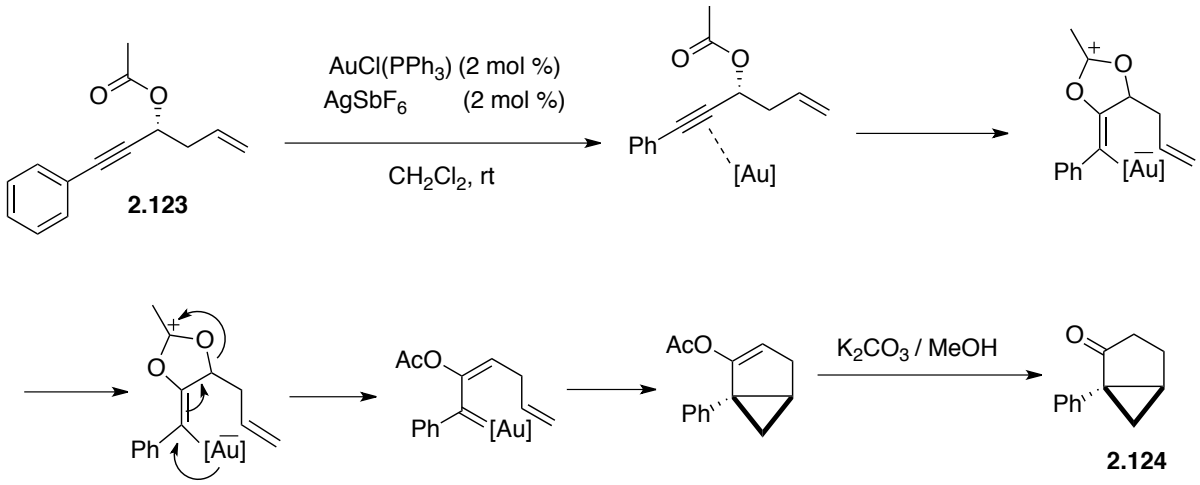
The *trans*-crotylboration of some of the aldehydes (**2.64**, **2.97**, **2.101**, **2.102,** and **2.103**) was performed. Aldehydes that gave comparatively higher *ee*'s in the allylboration reaction with allylboronate **2.90** were chosen. Reactions with all these aldehydes went smoothly. Although, the yields and ee's of the products of these reactions were numerically higher compared to their simple allylation variants, they were quite comparable. Homoallylic propargylic alcohol product **2.118** obtained from aldehyde **2.64** gave the highest *ee* of 91%. All the other alcohols (**2.119**-**2.122**) were observed to have percentage *ee*'s in the 80's (Scheme 2.36). The *Z*-crotylboration was not attempted because we wanted to avoid the use of the expensive gas *cis*-2-butene required as a starting material in the synthesis of the *Z*-crotylboronate .



Scheme 2.36. *Trans*-crotylboration of propargylic aldehydes.

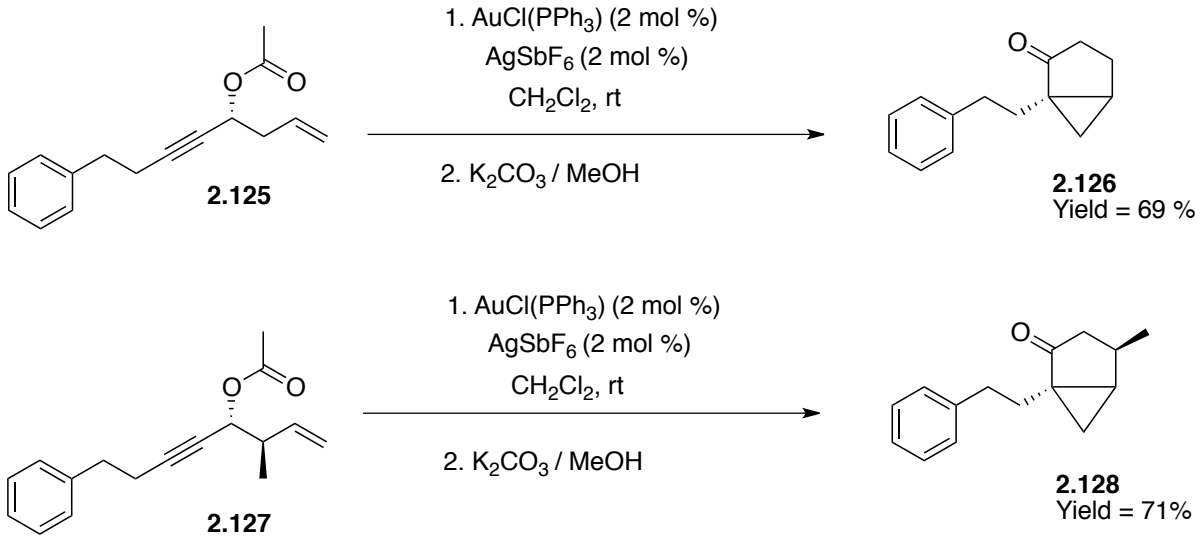
2.5.8 Gold catalyzed cycloisomerization of chiral homoallylic propargylic alcohol acetates

Gold catalyzed cycloisomerization of acetate esters of eneyne alcohols (Scheme 2.37) is a very powerful and useful method for constructing (3,5)-fused bicyclic rings and has been exploited in the synthesis of sesquisabinene A by Fürstner.[8,39]



Scheme 2.37. Au/Ag-catalyzed cycloisomerization of an eneyne system reported by Fürstner.[8,39]

With an intent of demonstrating the utility of the synthesizsed homoallylic propargylic alcohol products, two alcohols **2.65** and **2.118** were converted into acetate esters (**2.125** and **2.127**, respectively) and then were subjected to Au/Ag catalyzed conditions; yields of 69% and 71%, respectively were obtained for the bicyclic products **2.126** and **2.128** (Scheme 2.39).



Scheme 2.38. Au/Ag-catalyzed cycloisomerization of acetate esters derived from homoallylboration and crotylboration products.

2.6 Conclusion

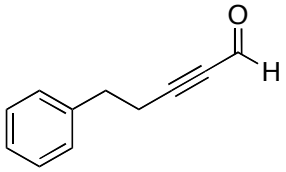
To conclude, a novel catalytic asymmetric allylboration methodology of propargylic aldehydes based on Lewis acid assisted Brønsted acid catalysis, was accomplished. Optimization studies revealed the importance of the nature of diol unit of the allylboronate partner. The allylboronate derived from 2,2-dimethylpropanediol displayed the lowest rate of background reaction and hence was the most effective. Two novel vivol diols, F-vivol-5 and F-vivol-12 were prepared and tested but both of them were found to be inferior to F-vivol-8 in terms of the enantioselectivity of the alcohol product that was formed. Several Lewis acid partners other than stannic chloride were tried and all of them resulted in poor yield and selectivity. This methodology worked well with a variety of aldehydes affording high yields and moderate to very good *ee*'s. However, propargylic aldehydes with aromatic rings attached to the terminal alkyne carbon afforded much lower enantioselectivities. Crotylboration of five aldehydes were also performed and very good yields and selectivities were obtained. Finally, the product homoallylic propargylic alcohol derivatives were successfully subjected to gold catalyzed cycloisomerization to form bicylic products.

2.7 Experimental details: general Information

All reactions were performed in standard, flame-dried glassware under an inert atmosphere of nitrogen. Unless otherwise specified, reagents were bought from commercial suppliers and used without further purification. Solvents were dried either by distillation or by using a solvent system purchased from MBRAUN. Anhydrous Na_2SO_4 or $MgSO_4$ were used as the drying agent after aqueous workup. All substrates were purified by silica gel chromatography before use. Evaporation and concentration *in vacuo* were accomplished at water aspirator pressure. Reaction products were purified by column chromatography using silica gel-60 (230-400 mesh). Reactions were monitored by thin layer chromatography with precoated glass plates covered with 0.2 mm silica gel . The spots were visualized by UV light, $KMnO_4$ or anisaldehyde stain. IR spectra were obtained with a Nicolet Magna-IR-750 spectrometer (cm^{-1}, cast film or neat). ^1H, ^{11}B, ^{13}C NMR spectra were obtained on a Varian Inova-300, 400 or Varian Unity-500 instruments, at 27 $^{\circ}C$ in $CDCl_3$. Residual solvent peaks (7.26 ppm for ^1H and 77.0 ppm for ^{13}C) were employed as reference. Accuracy for coupling constants (*J*-values) is estimated to be +/– 0.2 Hz. EI MS (m/z) was measured in a Kratos MS50 instrument. Optical rotation as recorded using a Perkin Elmer 241 polarimeter using the Sodium D line (589 nm) with a cell length of 10.002 cm. Optical purities of the products were measured by chiral HPLC using Chiralcel OD or Chiralpak AS column. Absolute configuration of alcohols **2.108**, **2.111**, **2.21** were assigned by comparing specific rotations of reported compounds.[55, 57, 14]

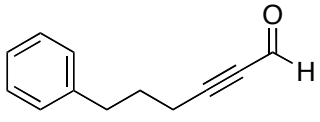
Preparation of Aldehydes:

5-Phenylpent-2-ynal (2.64):



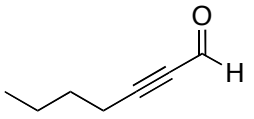
5-Phenylpent-2-ynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[40]

6-Phenyl-2-hexynal (2.97):



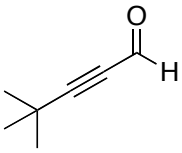
6-Phenyl-2-hexynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published. [40,41]

Butyl-2-propynal (2.98):



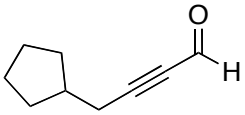
Butyl-2-propynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[40,42]

3,3-Dimethyl-1-butynal (2.99):



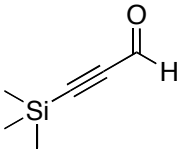
3,3-Dimethyl-1-butyne was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[43]

4-Cyclopentyl-2-butynal (2.100):



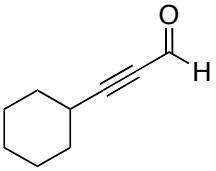
4-Cyclopentyl-2-butynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[43]

3-(Trimethylsilyl)propynal (2.101):



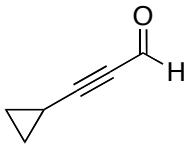
3-(Trimethylsilyl)propynal was purchased from Sigma-Aldrich.[44]

3-Cyclohexyl-2-propynal (2.102):



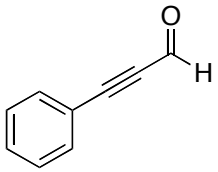
3-Cyclohexyl-2-propynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[45]

3-Cyclopropyl-2-propynal (2.103):



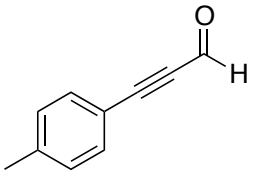
3-Cyclopropyl-2-propynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[46]

3-Phenylprop-2-ynal (2.20):



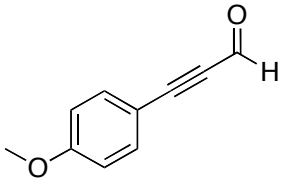
3-Phenylprop-2-ynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[46]

3-(4-Methylphenyl)-2-propynal (2.104):



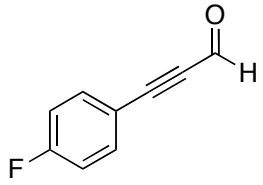
3-(4-Methylphenyl)-2-propynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[46]

3-(4-Methoxyphenyl)propynal (2.105):



3-(4-Methoxyphenyl)propynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[46]

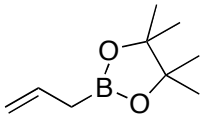
3-(4-Fluorophenyl)-2-propynal (2.106):



3-(4-Fluorophenyl)-2-propynal was prepared according to the published procedure. Spectral data for this compound matched with that previously published.[46]

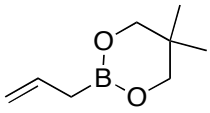
Preparation of allylboronates:

4,4,5,5-Tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane (2.37):



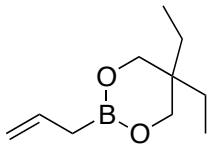
4,4,5,5-Tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane was synthesized according to the published procedure and data matched with that previously reported.[47]

5,5-Dimethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane (2.90):



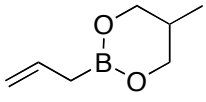
5,5-Dimethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure published procedure and data matched with that previously reported.[47,48]

5,5-Diethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane (2.91):



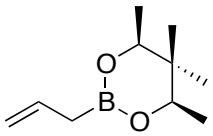
5,5-Diethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure and data matched with that previously reported.[47,49]

5-Methyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane (2.92):



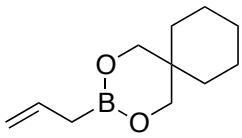
5-Methyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure.[47] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92-5.81 (m, 1H), 4.95-4.85 (m, 2H), 4.0 (dd, *J* = 11.0, 3.8 Hz, 2H), 3.58 (dd, *J* = 11.0, 10.6 Hz, 2H), 2.0 (m, 1H), 1.70 (d, *J* = 7.2 Hz, 2H), 0.90 (d, *J* = 7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 113.5, 67.3, 30.8, 12.2. ^{11}B NMR (159 MHz, $CDCl_3$) δ 28.8. EI HRMS calcd. for $C_7H_{13}BO_2$ 139.9908, found 139.9917.

4,4,5,5-Tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane (2.93):



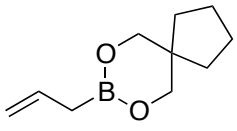
4,4,5,5-Tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane was synthesized according to the published procedure.[47,50] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92-5.83 (m, 1H), 4.97-4.85 (m, 2H), 3.78 (q, *J* = 7.0 Hz, 2H), 1.70 (d, *J* = 7.2 Hz, 2H), 1.20 (d, *J* = 7.0 Hz, 6H), 0.85 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 113.5, 70.8, 25.1, 19.3, 12.3. ^{11}B NMR (159 MHz, $CDCl_3$) δ 29.7. EI HRMS calcd. for $C_{10}H_{19}BO_2$ 182.0702, found 182.0705.

5-Cyclohexyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane (2.94):



5-Cyclohexyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure and matched with the previously reported one.[47,49] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94-5.85 (m, 1H), 4.98-4.88 (m, 2H), 3.74 (s, 4H), 1.73 (s, 4H), 1.70 (d, *J* = 7.2 Hz, 2H), 1.44 (s, 4H), 0.98 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 113.9, 71.3, 43.9, 32.7, 25.1, 12.3. ^{11}B NMR (159 MHz, $CDCl_3$) δ 29.0. EI HRMS calcd. for $C_{11}H_{19}BO_2$ 194.0805, found 194.0808.

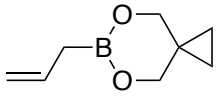
5-Cyclopentyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane (2.95):



5-Cyclopentyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure.[47,49] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93-5.84 (m, 1H), 4.97-4.86 (m, 2H), 3.75 (s, 4H), 1.71 (s, 4H), 1.70 (d, *J* = 7.2 Hz, 2H), 1.4 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 113.9, 71.0, 43.6, 32.7,

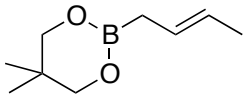
25.1. ^{11}B NMR (159 MHz, $CDCl_3$) δ 29.1. EI HRMS calcd. for $C_{10}H_{17}BO_2$ 180.0502, found 180.0507.

5-Cyclopropyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane (2.96):



5-Cyclopropyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure.[47] ^{1}H NMR (500 MHz, $CDCl_3$)) δ 5.91-5.80 (m, 1H), 4.94-4.85 (m, 2H), 3.70 (s, 4H), 1.70 (d, *J* = 7.2 Hz, 2H), 0.55 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 113.8, 69.1, 25.5, 8.9. ^{11}B NMR (159 MHz, $CDCl_3$) δ 29.0. EI HRMS calcd. for $C_8H_{13}BO_2$ 152.0002, found 152.0007.

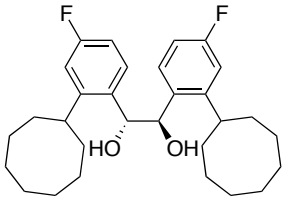
5,5-Dimethyl-2-(but-2-en-1-yl)-1,3,2-dioxaborinane (2.117):



5,5-Dimethyl-2-(but-2-en-1-yl)-1,3,2-dioxaborinane was synthesized according to the published procedure.[51] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50-5.43 (m, 1H), 5.39-5.31 (m, 1H), 3.58 (s, 4H), 1.63-1.61 (m, 3H), 1.56 (d, *J* = 7.0 Hz, 2H), 0.94 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.1, 124.4, 72.1, 31.6, 21.7, 18.0. ^{11}B NMR (159 MHz, $CDCl_3$) δ 29.0. EI HRMS calcd. for $C_9H_{17}BO_2$ 168.0438, found 168.0427.

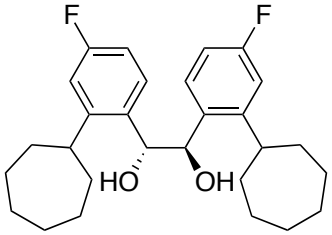
Synthesis of vivol diols:

(1*R*, 2*R*)-1,2-Bis(2-cyclooctyl-4-fluorophenyl)ethane-1,2-diol (F-vivol-8, 2.40):



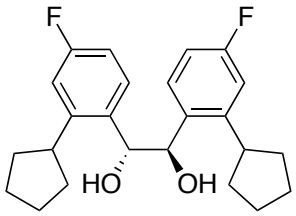
(1*R*,2*R*)-1,2-Bis(2-cyclooctyl-4-fluorophenyl)ethane-1,2-diol was synthesized according to the published procedure and spectral data matched with that of the reported.[52]

(1*R*, 2*R*)-1,2-Bis(2-cycloheptyl-4-fluorophenyl)ethane-1,2-diol (F-vivol-7, 2.70):

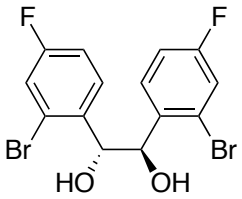


(1*R*, 2*R*)-1,2-Bis(2-cycloheptyl-4-fluorophenyl)ethane-1,2-diol was synthesized according to the published procedure and spectral data matched with that of the reported one.[53]

(1*R*, 2*R*)-1,2-Bis(2-cyclopentyl-4-fluorophenyl)ethane-1,2-diol (F-vivol-5, 2.80):

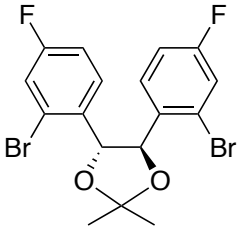


(4*R*,5*R*)-4,5-Bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane (2.72):



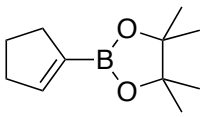
(4*R*,5*R*)-4,5-Bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane was synthesized according to the published procedure.[52]

(4*R*,5*R*)-4,5-Bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane (2.73):



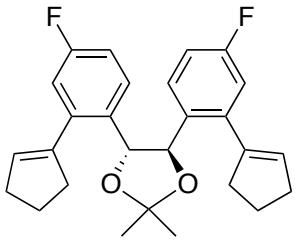
(4*R*,5*R*)-4,5-Bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane was synthesized according to the published procedure.[52]

2-(Cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.74):



2-(Cyclopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesized in a similar procedure to the published Shapiro protocol.[52] In a 250 mL round bottom flask equipped with a condenser, *p*-tolylsulfonyl hydrazide (18.0 g, 96.0 mmol, 1.0 equiv) was dissolved in 100% EtOH (20 mL). Cyclopentanone (8.6 mL, 8.1 g, 96 mmol, 1.0 equiv) was added and the reaction heated to reflux at 100 °C. After 5 min the suspension dissolved, and after another 15 min, a white solid appeared. After refluxing for 1.5 h the reaction flask was cooled to 0 °C and the resulting solid was then collected by filtration and washed with ice-cold EtOH. After drying under reduced pressure, the hydrazone was isolated as a white powder in a quantitative yield. The cyclopentanone *p*-tolylsulfonyl hydrazone (1.62 g, 5.40 mmol, 1.00 equiv) and 20 mL dry hexane was added to a flame dried 250 mL round bottom flask equipped with a septum and magnetic stirbar. To this mixture anhydrous TMEDA (20 mL) was added and the reaction was cooled to –78 °C, where it was maintained for 15 min, after which 2.5 M n-BuLi (10 mL, 25 mmol, 4.6 equiv) was added. The reaction mixture was then stirred at –78 °C for 1 h and then warmed to room temperature and stirred for 1.5 h at this temperature during this time N_2 gas was eliminated from the reaction and after the allotted time the reaction was cooled down to –78 °C and maintained for 15 min, after which pinacol isopropyl borate (5.5 mL, 4.5 g, 24 mmol, 4.4 equiv) was added. The reaction mixture was stirred at –78 °C for 1 h, and then the dry ice bath was removed and the mixture was stirred at room temperature for 3 h, before being quenched via the addition of 10% HCl (50 mL) and extracted with Et_2O (4 × 50 mL), (10% HCl was used instead of saturated NH_4Cl, to increase the acidity on work–up. By increasing the acidity, this reduced the amount of an emulsion and allowed for easier work-up). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified via column chromatography (95:5 hexanes/EtOAc) to give the desired compound (0.90 g, 86%) as a faint yellow oil. Spectral and analytical properties of this compound were in accordance with the literature.[52]

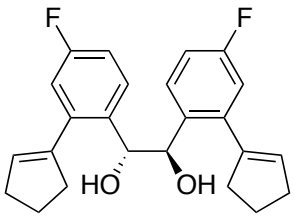
(4*R*,5*R*)-4,5-Bis[2-(cyclopent-1-en-1-yl)-4-fluorophenyl]-2,2-dimethyl-1,3-dioxolane (2.75) :



In a 250 mL round bottom flask equipped with a stir bar was charged cyclopentenylboronate (2.66 g, 13.7 mmol, 3.17 equiv), (4*R*,5*R*)-4,5-bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane (1.94 g, 4.33 mmol, 1.00 equiv), $Pd(OAc)_2$ (126 mg, 0.550 mmol, 0.127 equiv), PPh_3 (720 mg, 2.8 mmol, 0.64 equiv),

and K_3PO_4 (7.0 g, 33 mmol, 7.6 equiv). To this mixture was added 60 mL of anhydrous dioxane and 6 mL of degassed distilled water. The round bottom flask was then equipped with a condenser and then subjected to three freeze–pump–thaw cycles (to remove any dissolved oxygen) and heated at 111 ^{o}C for 2 days. The reaction mixture was brought to room temperature and poured into a 250 mL separatory funnel and the residue in the flask was further rinsed with Et_2O (100 mL), and transferred into the separatory funnel. The combined organic layer was then washed with saturated aqueous NH_4Cl (30 mL), separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The dark oily residue was purified by a sillica plug rinsed with hexanes and recrystallization with methanol (1.51 g, 84% yield). $[\alpha]^{22}_{D}$ = 65.3 (c = 0.49, $CHCl_3$). R_f = 0.45 (10:1 hexanes/EtOAc). IR (cast film, $CHCl_3$): 3044 (w), 2983 (m), 2953 (m), 2933 (m), 2847 (m), 1611 (m), 1585 (m), 1236 (s), 1055 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 9.0, 6.0 Hz, 2H), 6.99 (dt, *J* = 8.5, 3.0 Hz, 2H), 6.71 (dd, *J* = 9.5, 3.0 Hz, 2H), 4.99 (s, 2H), 4.75 (quintet, *J* = 2.0 Hz, 2H), 2.37–2.16 (m, 6H), 1.92–1.69 (m, 6H), 1.65 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 ($J_{C\text{-}F}$ = 247 Hz), 141.7 ($J_{C\text{-}F}$ = 8.0 Hz), 140.5, 130.5, 129.3 ($J_{C\text{-}F}$ = 3 Hz), 129.1 ($J_{C\text{-}F}$ = 9 Hz), 114.6 ($J_{C\text{-}F}$ = 21 Hz), 114.1 ($J_{C\text{-}F}$ = 21 Hz), 108.6, 81.4, 37.7, 33.5, 27.4, 23.5. EIMS *m/z* 422.2 (M+1,1), 232.1 ($C_{15}H_{17}FO$, 89), 189.1 ($C_{12}H_{10}FO$, 100). EI HRMS calcd. for $C_{27}H_{28}F_2O_2$ (M+) 422.2058, found 422.2055.

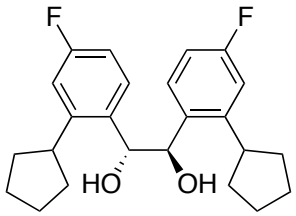
(1*R*,2*R*)-1,2-Bis[2-(cyclopent-1-en-1-yl)-4-fluorophenyl]ethane-1,2-diol (2.76) :



To a 100 mL round bottom flask equipped with a stir bar was added **2.75** (1.47 g, 3.48 mmol, 1.0 equiv), acetic acid (16 mL, 0.28 mol, 80 equiv), MeOH (2 mL) and H_2O (2 mL). The flask was equipped with a reflux condenser and the reaction was heated to 100 ^{o}C for 13 h. The resulting mixture was added to a separatory funnel along with $NaHCO_3$ (30 mL) and the organic layer was extracted with Et_2O (4 × 30 mL) dried over $MgSO_4$, filtered, and the solvent removed *in vacuo.* The crude mixture was purified by flash chromatography (3:1 hexanes/EtOAc) and the resulting product was recrystallized from CH_2Cl_2/hexanes to give the product (1.27 g, 95%) as white crystals. $[\alpha]^{22}_{D}$ = 140 (c = 0.50, $CHCl_3$). R_f = 0.58 (3:2 hexanes/EtOAc). IR (cast film, $CHCl_3$): 3271 (strong-broad), 3046 (w), 2954 (m), 2891 (m), 2844 (m), 1889 (w), 1612 (s), 1583 (s), 1500 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 6.0, 8.5 Hz, 2H), 6.89 (dt, *J* = 8.5, 2.5 Hz, 2H), 6.66 (dd, *J* = 10.0, 2.5 Hz, 2H), 5.23 (quintet, *J* = 2.0 Hz, 2H), 5.04 (m, 2H), 2.81 (t *J* = 1.5 Hz, 2H), 2.53–2.38 (m, 6H), 2.00–1.82 (m, 6H). ^{13}CNMR (125 MHz, $CDCl_3$) δ 161.9 ($J_{C\text{-}F}$ = 246 Hz), 141.2 ($J_{C\text{-}F}$ = 8 Hz), 141.1, 133.0 ($J_{C\text{-}F}$ = 3 Hz), 130.5, 129.3 ($J_{C\text{-}F}$ = 9 Hz), 114.5 ($J_{C\text{-}F}$ = 21 Hz),

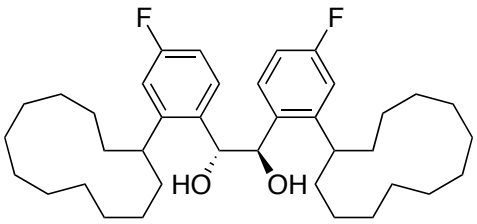
113.7 ($J_{C\text{-}F}$ = 21 Hz), 74.1, 37.5, 33.5, 23.6. EIMS *m/z* 382.2 (M+, 1), 191.1 ($C_{12}H_{10}FO$, 100). EI HRMS calcd. for $C_{24}H_{24}F_2O_2$ (M+) 382.1744, found 382.1740.

(1*R*,2*R*)-1,2-Bis(2-cyclopentyl-4-fluorophenyl)ethane-1,2-diol (F-vivol-5, 2.80)

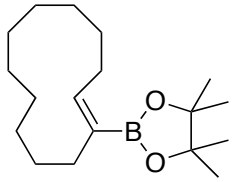


Into a round bottom flask was charged with 897 mg of diol, (1*R*,2*R*)-1,2-Bis[2-(cyclopent-1-en-1-yl)-4-fluorophenyl]ethane-1,2-diol (2.32 mmol) and absolute EtOH (45 mL). The resulting solution was degassed and purged with argon. At this point, Pd/C (10 wt%, 0.90 g) was carefully added to the reaction flask. (Caution!! Since this is a high loading of flammable palladium, the addition should take place strictly under argon). After the completion of addition of Pd/C, the sidewalls of the flask were washed with EtOH (2.0 mL) and the reaction mixture was degassed and purged with hydrogen. This cycle was repeated three times, after which the reaction was let to stir for 17 h at rt. After the elapsed time, the reaction was tested for completion using ^{1}H NMR spectroscopy of a small aliquot. The reaction was judged complete, and the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* and the crude product was purified by flash chromatography (10-20% EtOAc/hexanes) and to give the title compound (903 mg, quantitative) as white crystals. $[\alpha]^{22}_D$ = 7.9 (c = 0.30, $CHCl_3$). R_f = 0.6 (3:2 hexanes/EtOAc). m.p = 207-209 °C. IR (cast film, $CHCl_3$): 3333 (strong broad), 2962 (s), 2873 (m), 1896 (w), 1613 (m), 1590 (s), 1501 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.8, 6.0 Hz, 2H), 6.88 (dt, *J* = 8.8, 2.8 Hz, 2H) 6.79 (dd, *J* = 10.8, 2.8 Hz, 2H), 5.30 (s, 2H), 2.86 (s, 2H), 2.73–2.62 (m, 2H), 2.00–1.91 (m, 2H), 1.73–1.24 (m, 10H), 0.98–0.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 ($J_{C\text{-}F}$ = 244 Hz), 147.6 ($J_{C\text{-}F}$ = 7 Hz), 133.1, 129.0 ($J_{C\text{-}F}$ = 8 Hz), 112.8 ($J_{C\text{-}F}$ = 15 Hz), 112.6 ($J_{C\text{-}F}$ = 15 Hz), 74.2, 40.5, 35.9, 34.2, 25.8, 25.6. ESI MS *m/z* 409.2 ([M + Na]+, 100). ESI HRMS calcd. for $C_{24}H_{28}F_2NaO_2$ ([M + Na]+) 409.1951, found 409.1950.

(1*R*,2*R*)-1,2-Bis(2-cyclododecyl-4-fluorophenyl)ethane-1,2-diol (F-vivol-12, 2.81):

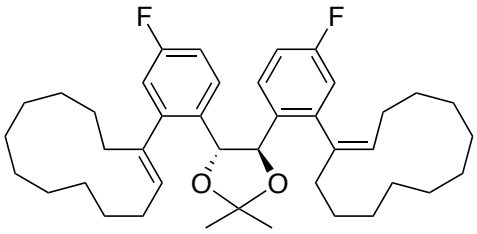


2-[(1*Z*)-Cyclododec-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.77):



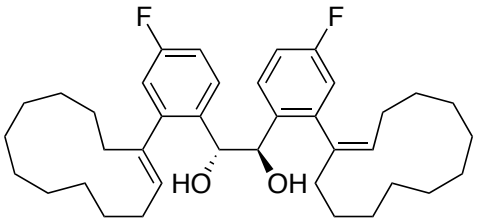
2-[(1*Z*)-Cyclododec-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesized in a similar procedure to the published Shapiro protocol. In a 250 mL round bottom flask *p*-tolylsulfonyl hydrazide (18.0 g, 96.0 mmol, 1.0 equiv) was combined with 100% EtOH (20 mL). Cyclododecanone (19.0 mL, 17.5 g, 96.0 mmol, 1.0 equiv) was added and the reaction heated to reflux at 100 °C. After 5 min the suspension dissolved, and after another 15 min, a white solid appeared. After refluxing for 1.5 h the reaction was cooled to 0 °C and the resulting solid was then collected by filtration and washed with ice-cold EtOH, After drying under reduced pressure the hydrazone was isolated as a white powder in a quantitative yield. The cyclododecanone *p*-tolylsulfonyl hydrazone (4.56 g, 13.0 mmol, 1.00 equiv) and 20 mL of dry hexanes was added to a flame dried 250 mL round bottom flask equipped with a septum and magnetic stirbar. To this mixture, anhydrous TMEDA (40 mL) was added and the reaction cooled to –78 °C, where it was maintained for 15 min, after which 2.5 M n-BuLi (21.0 mL, 53.0 mmol, 4.10 equiv) was added, turning the solution dark red in colour. The reaction mixture was then stirred at –78 °C for 1 h and then allowed to warm to room temperature and stirred for 1.5 h. During this time N_2 was extruded from the reaction and after the allotted time the reaction was cooled back down to –78 °C and maintained for 15 min, after which pinacol isopropyl borate (12.4 mL, 10.1 g, 54.0 mmol, 4.20 equiv) was added. The reaction mixture was stirred at –78 °C for 1 h, and then at room temperature for 3 h, before being quenched via the addition of 10% HCl (50 mL) and extracted with Et_2O (4 × 50 mL), (10% HCl was used instead of saturated NH_4Cl, to increase the acidity on work-up. By increasing the acidity, this reduced the amount of an emulsion and allowed for easier work-up). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude product was purified via column chromatography (20:1 hexanes/EtOAc) to give the desired compound (1.94 g, 51%) as a colorless oil. Spectral and analytical properties of this compound were in accordance with the literature.[52]

(4*R*,5*R*)-4,5-Bis{2-[(1*E*)-cyclododec-1-en-1-yl]-4-fluorophenyl}-2,2-dimethyl-1,3-dioxolane (2.78) :



In a 250 mL round bottom flask equipped with a stirbar was charged cyclododecenylboronate (2.00 g, 6.84 mmol, 3.07 equiv), (4*R*,5*R*)-4,5-bis(2-bromo-4-fluorophenyl)-2,2-dimethyl-1,3-dioxolane (1.00 g, 2.23 mmol, 1.00 equiv), $Pd(OAc)_2$ (56 mg, 0.25 mmol, 0.10 equiv), PPh_3 (315 mg, 1.20 mmol, 0.54 equiv), and K_3PO_4 (3.00 g, 14.1 mmol, 6.32 equiv). To this mixture was added anhydrous dioxane (30 mL) and degassed distilled water (4 mL). The round bottom flask was then equipped with a condenser and then subjected to three freeze thaw cycles (to remove any dissolved oxygen) and heated at 111 °C for 3 days. The reaction mixture was brought to room temperature and poured into a 250 mL separatory funnel and the residue in the flask was further rinsed with Et_2O (100 mL), and transferred into a separatory funnel. The combined organic layer was then washed with saturated aqueous NH_4Cl (30 mL), separated, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The oily residue was purified by flash chromatography (2% EtOAc/hexanes) and recrystallized with methanol to afford 1.15 g, 1.86 mmol (83%) of product as clear crystals. R_f = 0.55 (10:1 hexanes/EtOAc). $[\alpha]^{22}_D$ = 106 (c = 1.25, $CHCl_3$). IR (cast film, $CHCl_3$): 3017 (w), 2981 (m), 2929 (s), 2858 (m), 1610 (m), 1584 (m), 1494 (m) 1220 (m), 1050 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.5, 6.0 Hz, 2H), 6.96 (dt, *J* = 8.5, 3.0 Hz, 2H), 6.63 (dd, *J* = 9.5, 2.5 Hz, 2H) 5.02 (s, 2H), 4.45 (broad singlet, 2H), 2.17–2.03 (m, 6H), 1.80–1.60 (m, 8H), 1.45–1.30 (m, 25H), 1.22–1.00 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7 ($J_{C\text{-}F}$ = 247 Hz), 146.8 ($J_{C\text{-}F}$ = 4 Hz), 137.9, 131.9, 129.4, 129.0, 115.9 ($J_{C\text{-}F}$ = 19 Hz), 113.9 ($J_{C\text{-}F}$ = 21 Hz), 108.6, 81.1, 28.3, 27.5, 26.8, 25.0, 24.9, 24.8, 24.7, 24.6, 24.4, 24.3, 22.4. EIMS *m/z* 618.4 (M+, 1), 330.2 ($C_{22}H_{31}FO$, 77), 272.2 ($C_{19}H_{25}F$, 100). EI HRMS calcd. for $C_{41}H_{56}F_2O_2$ (M+) 618.4249, found 618.4242.

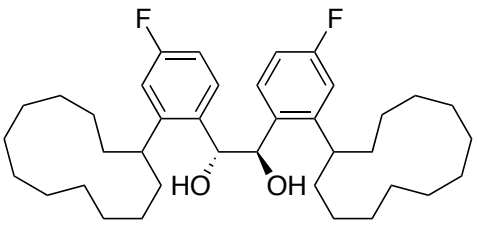
(1*R*,2*R*)-1,2-Bis{2-[(1*E*)-cyclododec-1-en-1-yl]-4-fluorophenyl}ethane- 1,2-diol (2.79):



To a 100 mL round bottom flask equipped with a stirbar was added (4*R*,5*R*)-4,5-bis{2-[(1*E*)-cyclododec-1-en-1-yl]-4-fluorophenyl}-2,2- dimethyl-1,3-dioxolane (400 mg, 0.646 mmol), acetic acid (16 mL, 0.28 mol, 80 equiv), MeOH (2 mL) and H_2O (2 mL). The flask was equipped with a reflux condenser and the reaction was heated to 100 °C for 5 days. The resulting mixture was added to a separatory funnel along with $NaHCO_3$ (30 mL) and the organic layer was extracted with Et_2O (4 × 30 mL) dried over $MgSO_4$, filtered, and the solvent was evaporated *under vacuo.* The crude mixture was purified by flash chromatography (3:1 hexanes/EtOAc) and the resulting product was recrystallized from MeOH/CH_2Cl_2 to

give the product (328 mg, 88%) as white crystals. R_f = 0.7 (3:2 hexanes/EtOAc). $[\alpha]^{22}_D$ = 101 (c = 2.88, $CHCl_3$). m.p = 232-234 °C. IR (cast film, $CHCl_3$): 3353 (m, broad), 2928 (s), 2855 (s), 2673 (w), 1726 (w), 1609 (m), 1584 (m) 1489 (m), 1468 (m) 1446 (m) cm^{-1}. ^1H NMR (300, $CDCl_3$) δ 7.43 (dd, *J* = 9.0, 6.0 Hz, 2H), 6.88 (dt, *J* = 8.4, 2.7 Hz, 2H), 6.58 (dd, *J* = 9.6, 2.7 Hz, 2H), 4.92 (s, 2H), 4.58 (broad singlet, 2H), 3.48 (s, 2H), 2.79 (s, 2H), 2.54–2.08 (m, 4H), 1.96–1.80 (m, 2H), 1.56–1.45 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 ($J_{C\text{-}F}$ = 247 Hz), 146.2 ($J_{C\text{-}F}$ = 7 Hz), 138.5, 132.9, 132.3, 129.4 ($J_{C\text{-}F}$ = 9 Hz), 116.4 ($J_{C\text{-}F}$ = 20 Hz), 113.4 ($J_{C\text{-}F}$ = 21 Hz), 73.8, 28.4, 26.8, 25.2, 24.85, 24.79, 24.7, 24.5, 24.0, 22.6, 22.2. EIMS *m/z* 578.4 (M+, 0.3), 560.4 ([M–H_2O]+, 10), 272.2 ($C_{16}H_{27}F_2O_2$, 100). EI HRMS calcd. for $C_{38}H_{52}F_2O_2$ (M+) 578.3936, found 578.3923.

(1*R*,2*R*)-1,2-Bis(2-cyclododecyl-4-fluorophenyl)ethane-1,2-diol (F-vivol-12, 2.81):



Into a round bottom flask was charged 210 mg of diol, (1*R*,2*R*)-1,2-bis{2-[(1*E*)-cyclododec-1-en-1-yl]-4-fluorophenyl}ethane-1,2-diol and absolute EtOH (25 mL). The resulting solution was degassed and purged with argon. At this point, Pd/C (10 wt%, 210 mg) was carefully added to the reaction flask. (Caution!! Since this is a high loading of flammable palladium, the addition should take place strictly under argon). After the completion of addition of Pd/C, the sidewalls of the flask were washed with EtOH (2.0 mL) and the reaction mixture was degassed and purged with hydrogen. This cycle was repeated twice, after which the reaction was let to stir for 17 h at rt. After the elapsed time, the reaction was tested for completion using ^1H NMR spectroscopy of a small aliquot and deemed complete. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* and the crude product was purified by flash chromatography (CH_2Cl_2) to give the product (210 mg, quant) as a small white crystalline powder. R_f = 0.8 (3:2 hexanes/EtOAc). $[\alpha]^{22}_D$ = –2.6 (c = 0.30, $CHCl_3$). IR (cast film, $CHCl_3$): 3382 (broad, m), 2930 (s), 2862 (m), 1653 (w), 1612 (m), 1589 (m), 1495 (m), 1470 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.4, 6.0 Hz, 2H), 6.89 (dt, *J* = 8.4, 2.4 Hz, 2H), 6.75 (dd, *J* = 11.2, 2.4 Hz, 2H), 5.08 (s, 2H), 2.85 (s, 2H), 2.59–2.54 (m, 2H), 1.55–1.27 (m, 32H), 1.20–0.98 (m, 10H), 0.86–0.76 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 ($J_{C\text{-}F}$ = 245 Hz), 148.0 ($J_{C\text{-}F}$ = 7.0 Hz), 133.3, 128.9 ($J_{C\text{-}F}$ = 9 Hz), 113.4 ($J_{C\text{-}F}$ = 21 Hz), 113.2 ($J_{C\text{-}F}$ = 21 Hz), 73.5, 35.3, 30.8, 29.2, 24.8, 24.49, 24.46, 23.5, 23.1, 22.9, 22.5, 21.2. EIMS *m/z* 582.4 (M+, 0.3), 292.2 ($C_{19}H_{29}FO$, 94), 291.2 ($C_{19}H_{28}FO$, 100). EI HRMS calcd. for $C_{38}H_{56}F_2O_2$ (M+) 582.4249, found 582.4271.

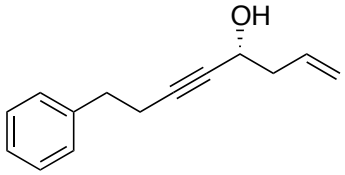
General procedure for the F-vivol · $SnCl_4$ catalyzed asymmetric allylboration reaction:

In a flame dried 10 mL round bottom flask equipped with a stirbar, the corresponding F-vivol catalyst (0.056 mmol, 0.10 equiv), anhydrous Na_2CO_3 (0.2 equiv) and 4 Å molecular sieves (90 mg, pre-dried under vacuum overnight and then stored in an oven) were added. The flask was equipped with a rubber septum and charged with nitrogen, then dry toluene (1.2 mL) was added. The mixture was stirred for 2 min and $SnCl_4$ (1.0 M in CH_2Cl_2, 38.5 µL, 0.0385 mmol, 0.078 equiv) was added. After stirring for 5 min at rt the reaction was cooled to –78 °C where it was maintained for 15 min. Allylboronic acid ester (0.8 mmol, 1.4 equiv) was added dropwise, followed 30 min later by the addition of the aldehyde (0.56 mmol, 1.0 equiv). The reaction was stirred at –78 °C until TLC analysis no longer showed the presence of the aldehyde starting material. Then, DIBAL-H (1.5 M volume in toluene, 2.0 equiv) was cooled to –78 °C and cannulated into the reaction flask. The reaction temperature was maintained the reaction at –78 °C. After all the remaining aldehyde was reduced (ca. 30-50 min), the excess DIBAL-H was quenched by the addition of 10% HCl (4.0 mL). The reaction was slowly warmed to rt over 1 h and stirred for an additional 30 min. The reaction mixture was then extracted with Et_2O (5 × 10 mL) and the combined organic extracts were extracted with saturated aq NaCl, dried over Na_2SO_4, filtered and concentrated *in vacuo.* Column chromatography (silica gel, 5–30% EtOAc in hexanes) gave the corresponding product. The chiral diol could not be recovered.

Crotylboration was also achieved in the same way and in the same scale.

Characterization of enantioselective allylboration products:

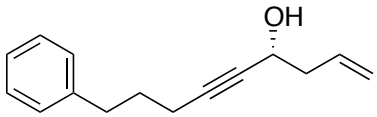
8-Phenyloct-1-en-5-yn-4-ol (2.65):



Collected as an oil. A 87% *ee* was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 7.8 min, T_{minor} = 11.3 min. $[\alpha]^{22}_D$ = 22.8 (c = 1.30, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3375 (broad, m), 3076 (m), 3063 (m), 3027 (m), 2978 (w), 2924 (s), 2859 (m), 2226 (w), 1641 (m), 1496 (m), 1453 (w), 1032 (s), 698 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.24–7.21 (m, 3H), 5.90–5.80 (m, 1H), 5.20–5.15 (m, 2H), 4.39 (tt, *J* = 6.0, 2.0 Hz, 1H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.52 (td, *J* = 7.6, 2.0 Hz, 2H), 2.45–

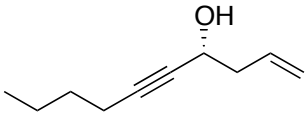
2.41 (m, 2H), 1.94 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 133.2, 128.4, 128.3, 126.3, 118.7, 85.1, 81.4, 61.7, 42.4, 35.0, 20.8. EIMS *m/z* 200.1 (M+, 0.2), 199.1 ([M–H]+, 1), 182.1 ($C_{14}H_{14}$, 6), 159.1 ($C_{11}H_{11}O$, 73). EI HRMS calcd. for $C_{14}H_{14}$+ ([M–H_2O]+) 182.1096, found 182.1093.

9-Phenylnon-1-en-5-yn-4-ol (2.107):



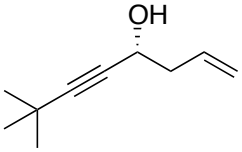
Collected as an oil. A 78% *ee* was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 11.9 min, T_{minor} = 14.6 min. $[\alpha]^{22}_D$ = 19.9 (c = 1.30, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3359 (broad, m), 3078 (m), 3063 (m), 3026 (m), 2979 (w), 2939 (s), 2860 (m), 2229 (w), 1642 (m), 1603(m), 1496 (m), 1454 (m), 1431 (m), 1032 (s), 699 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 2H), 7.22–7.18 (m, 3H), 5.91 (ddt, *J* = 17, 10, 7.5 Hz, 1H), 5.23–5.17 (m, 2H), 4.43-4.44 (m, 1H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.45-2.49 (m, 2H), 2.24 (td, *J* = 7.0, 2.0 Hz, 2H), 2.0 (d, *J* = 5.5 Hz,1H), 1.84 (app. quintet, *J* = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 133.3, 128.5, 128.3, 125.9, 118.7, 85.4, 81.2, 61.8, 42.5, 34.8, 30.2, 18.1. EI HRMS calcd. for $C_{15}H_{18}ONa$ 237.1250, found 237.1247

(4*R*)-Dec-1-en-5-yn-4-ol (2.108):



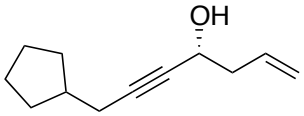
Collected as an oil. This was converted into the carbamate derivative[54] and a 71% *ee* was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 9.0 min, T_{minor} = 16.9 min. $[\alpha]^{22}_D$ = 27.6 (c = 1.1, $CHCl_3$). The absolute configuration was determined to be *R* by comparing with the specific rotation value (–26.3) of reported compound.[55] Spectral and analytical properties of the product were in accordance with the literature.[56]

7,7-Dimethyloct-1-en-5-yn-4-ol (2.109):



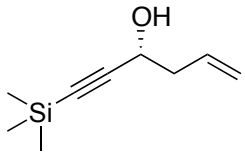
Collected as an oil. This was converted into the carbamate derivative[54] and a 66% *ee* was determined by HPLC analysis (Chiralcel OD column, 15% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 13.10 min, T_{minor} = 8.0 min. $[\alpha]^{22}_{D}$ = 32.8 (c = 1.1, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3347 (broad, m), 3078 (m), 2969 (w), 2928 (s), 2867 (m), 2239 (w), 1642 (m), 1476 (m), 1457 (m), 1434 (m), 1362(m), 1264(s), cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 17.1, 10.2, 7.1, Hz, 1H), 5.21-5.14 (m, 2H), 4.40 (t, *J* = 6.1 Hz, 1H), 2.46-2.44 (m, 2H), 1.99 (br. s., 1H), 1.22 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 118.5, 94.2, 79.0, 61.7, 42.6, 30.9, 27.3. EI HRMS calcd. for $C_{10}H_{15}ONa$, 174.2200 found 174.2202.

7-Cyclopentylhept-1-en-5-yn-4-ol (2.110):



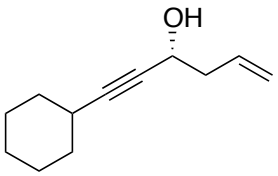
Collected as an oil. This was converted into the carbamate derivative[54] and a 64% *ee* was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 17.2 min, T_{minor} = 9.0 min. $[\alpha]^{22}_{D}$ = 34.3 (c = 2.2, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3351(broad, m), 3078 (m), 3011 (m), 2980 (w), 2914 (m), 2866 (w), 2240 (m), 1641 (m), 1429 (m), 1358 (m), 1052 (s), 1030 (s), 813 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 17.0, 10.4, 7.2 Hz, 1H), 5.19–5.13 (m, 2H), 4.40-4.38 (m, 1H), 2.46-2.41 (m, 2H), 2.20 (dd, *J* = 7.0, 2.0 Hz, 2H) 2.06-1.96 (m, 2H), 1.80-1.72 (m, 2H), 1.66-1.48 (m, 4H), 1.30-1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 118.1, 84.9, 80.2, 61.4, 42.2, 38.5, 31.5, 24.8, 24.0. EI HRMS calcd. for $C_{12}H_{17}ONa$ 200.2520 found 200.2531.

(4*R*)-1-Trimethylsilylhex-1-en-5-yn-4-ol (2.111):



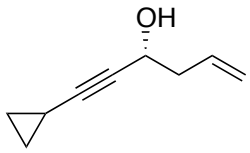
Collected as an oil. This was converted into the carbamate derivative[54] and a 81% *ee* was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 16.85 min, T_{minor} = 8.97 min. $[\alpha]^{22}_{D}$ = 56.9 (c = 6.4, $CHCl_3$). The absolute configuration was determined to be *R* by comparing with the specific rotation value (27.4, c= 3.6, CH_2Cl_2) of reported compound.[57] Spectral and analytical properties of the product were in accordance with the literature.[58]

1-Cyclohexylhex-5-en-1-yn-3-ol (2.112):



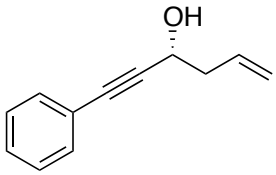
Collected as an oil. This was converted into the carbamate derivative[54] and a 81% *ee* was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 19.9 min, T_{minor} = 10.4 min. $[\alpha]^{22}_{D}$ = 58.7 (c = 1.15, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3338 (broad, m), 3077 (w), 3006 (w), 2979 (w), 2930 (s), 2854 (s), 2229 (w), 1642 (m), 1448 (m), 1338 (w), 1035 (s), 861(s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddt, *J* = 17.0, 10, 7.5 Hz, 1H), 5.18–5.13 (m, 2H), 4.40 (ddd, *J* = 11.5, 6.0, 2.0 Hz, 1H), 2.46-2.41 (m, 2H), 2.40-2.34 (m, 1H), 1.97-1.94 (m, 1H), 1.80-1.73 (m, 2H), 1.71-1.64 (m, 2H), 1.51-1.47 (m, 1H), 1.44-1.37 (m, 2H), 1.31-1.24 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.4, 118.5, 90, 80.5, 61.8, 42.6, 32.6, 28.9, 25.8, 24.8. EI HRMS calcd. for $C_{15}H_{18}ONa$ 201.1257, found 201.1254.

1-Cyclopropylhex-5-en-1-yn-3-ol (2.113):



Collected as an oil. This was converted into the carbamate derivative[54] and a 81% *ee* was determined by HPLC analysis (Chiralcel OD column, 10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 24.4 min, T_{minor} = 13.4 min. $[\alpha]^{22}_{D}$ = 71.1 (c = 1.05, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3351(broad, m), 3078 (m), 3011 (m), 2980 (w), 2914 (m), 2866 (w), 2240 (m), 1641 (m), 1429 (m), 1358 (m), 1052 (s), 1030 (s), 813 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.88-5.8 (m, 1H), 5.16–5.11 (m, 2H), 4.36-4.32 (m, 1H), 2.41-2.38 (m, 2H), 2.04-2.02 (m, 1H), 1.25-1.2 (m, 1H), 0.72-0.76 (m, 2H), 0.66-0.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.3, 118.5, 89.0, 75.7, 61.7, 42.5, 8.2, -0.6. EI HRMS calcd. for $C_9H_{12}ONa$ 159.0785, found 159.0777.

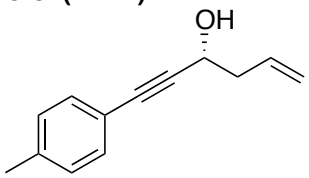
(3*S*)-1-Phenylhex-5-en-1-yn-3-ol (2.21):



Collected as an oil. A 69% *ee* was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in

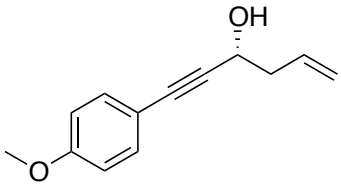
hexanes, 0.5 mL/min, λ = 210 nm, column temperature = 25 °C). T_{major} = 7.3 min, T_{minor} = 9.3 min. $[\alpha]^{22}_{D}$ = 26.0 (c = 0.36, $CHCl_3$). The absolute configuration was determined to be *S* by comparing with the specific rotation value (–5.63) of reported compound.[14] Spectral and analytical properties of the product were in accordance with the literature.[14]

1-(4-Methylphenyl)hex-5-en-1-yn-3-ol (2.114):



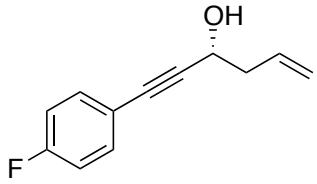
Collected as an oil. A 58% *ee* was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 6.9 min, T_{minor} = 8.3 min. $[\alpha]^{22}_{D}$ = 22.6 (c = 1.2, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3375 (broad, m), 3078 (s), 3029 (s), 2980 (s), 2921(m), 2860 (s), 2202 (m), 1666 (m), 1643 (m), 1606 (m), 1510(s), 1440 (m), 1038 (s), 817 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.11 (m, 2H), 5.96 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.25–5.19 (m, 2H), 4.64 (t, *J* = 6.0 Hz, 1H), 2.58-2.55 (m, 2H), 2.3 (s, 3H), 2.0 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 133.1, 131.6, 129.0, 119.4, 118.9, 88.7, 85.3, 62.1, 42.3, 21.4. EI HRMS calcd. for $C_{13}H_{14}ONa$ 209.0937, found 209.0939.

1-(4-Methoxyphenyl)hex-5-en-1-yn-3-ol (2.115):



Collected as an oil. A 50% *ee* was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 10.9 min, T_{minor} = 7.4 min. $[\alpha]^{22}_{D}$ = 16.1 (c = 1.4, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3384 (broad, m), 3075 (m), 3006 (m), 2935 (m), 2913 (m), 2837 (m), 2228 (m), 1642 (m), 1606 (s), 1463 (m), 1441 (m), 1031 (s), 1030 (s), 831 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 2H), 6.83 (m, 2H), 5.96 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.26–5.20 (m, 2H), 4.65-4.62 (m, 1H), 3.80 (s, 3H), 2.58-2.55 (m, 2H), 2.13 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 132.8, 118.5, 114.2, 113.6, 113.5, 87.6, 84.7, 61.7, 54.9, 41.9. EI HRMS calcd. for $C_{13}H_{14}O_2Na$ 225.0886, found 225.0885.

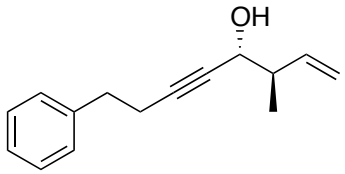
1-(4-Fluorophenyl)hex-5-en-1-yn-3-ol (2.116):



Collected as an oil. A 55% *ee* was determined by HPLC analysis (Chiralcel OD column, 50% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 9.3 min, T_{minor} = 10.9 min. $[\alpha]^{22}_{D}$ = 15.6 (c = 1.4, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3363 (broad, m), 3078 (s), 2980 (s), 2921(m), 2860 (s), 2232 (m), 1642 (s), 1602 (s), 1507(s), 1232 (s), 1440 (m), 1031 (m), 835 (s) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H), 7.05-7.0 (m, 2H), 5.98 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.29–5.24 (m, 2H), 4.65-4.61 (m,1H), 2.57-2.54 (m, 2H), 2.2 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (d, *J* = 250 Hz, 1C), 133.6 (d, *J* = 8.5 Hz, 2C), 132.9, 119.1, 118.6 (d, *J* = 3.4 Hz, 2C), 115.5 (d, *J* = 22 Hz, 2C), 89.1, 84.1, 62.0, 42.2. EI HRMS calcd. for $C_{12}H_{11}FONa$ 213.0686, found 213.0690.

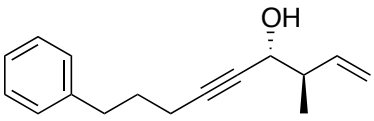
Characterization of enantioselective crotylboration products:

Methyl-7-phenyloct-5-en-1-yn-3-ol (2.118):



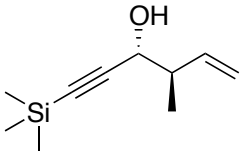
Collected as an oil. A 91% *ee* was determined by HPLC analysis (Chiralcel OD column, 40% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 7.63 min, T_{minor} = 11.26 min. $[\alpha]^{22}_{D}$ = 24.2 (c = 1.3, $CHCl_3$). IR (film cast, $CHCl_3$): 3400 (broad, m), 3064 (s), 2965 (s), 2928 (m), 2861 (s), 2229 (m), 1640 (s), 1603 (s), 1496 (s), 1454 (s), 1440 (m), 1429 (m), 1419 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.34 (m, 2H), 7.24-7.2 (m, 3H), 5.84-5.74 (m, 1H), 5.18–5.12 (m, 2H), 4.22-4.17 (m, 1H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.55 (dt, *J* = 7.2 Hz, 1.6 Hz, 2H), 2.45-2.37 (m, 1H), 1.92 (d, *J* = 5.2 Hz, 1H), 1.1(d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 139.5, 128.4, 128.3, 126.3, 116.5, 85.7, 80.3, 66.3, 44.5, 35.0, 20.9, 15.2. EI HRMS calcd. for $C_{15}H_{18}ONa$ 237.1250, found 237.1245.

Methyl-9-Phenylnon-1-en-5-yn-4-ol (2.119):



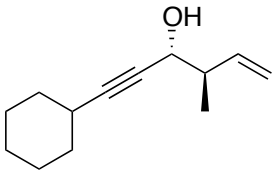
Collected as an oil. A 80% *ee* was determined by HPLC analysis (Chiralcel OD column,10% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 11.3 min, T_{minor} = 12.7 min. $[\alpha]^{22}_D$ = 15.3 (c = 1.8, $CHCl_3$). IR (film cast, $CHCl_3$): 3371 (broad, m), 3064 (s), 2964 (s), 2932 (m), 2862 (s), 2238 (m), 1640 (s), 1602 (s), 1496 (s), 1454 (s), 1430 (m), 1419 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 - 7.19 (m, 5H), 5.91 (ddd, *J* = 17.9, 10.4, 7.5 Hz, 1H), 5.24 - 5.15 (m, 2H), 4.26 (d, *J* = 5.5 Hz, 1H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.52 - 2.44 (m, 1H), 2.28 (dt, *J* = 7.0, 2.0 Hz, 2H), 1.91 (br. s., 1H), 1.88-1.87 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 139.6, 128.5, 128.3, 125.9, 116.5, 86.0, 80.1, 66.4, 44.7, 34.8, 30.3, 18.2, 15.3. EI HRMS calcd. for $C_{16}H_{20}ONa$ 251.1406, found 251.1402.

Methyl-1-Trimethylsilylhex-1-en-5-yn-4-ol (2.120):



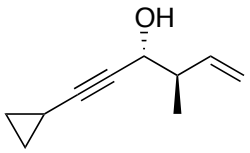
Collected as an oil. A 81 % *ee* was determined by Mosher ester analysis.[59] $[\alpha]^{22}_D$ = –0.38 (c = 4.1, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3367 (broad, m), 3080 (w), 2963 (w), 2933 (s), 2173 (w), 1641 (m), 1456 (m), 1251 (s), 1030 (s), cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ d = 5.83 (ddd, *J* = 17.1, 10.5, 7.7 Hz, 1H), 5.21 - 5.15 (m, 2H), 4.23 - 4.19 (m, *J* = 5.5 Hz, 1H), 2.51 - 2.43 (m, *J* = 1.1 Hz, 1H), 1.90 (d, *J* = 6.0 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.19 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 116.7, 105.0, 90.5, 66.6, 44.4,15.3, –0.1. EI HRMS calcd. for $C_{10}H_{17}ONa$ 204.3227, found 204.3218.

Methyl-1-cyclohexylhex-5-en-1-yn-3-ol (2.121):



Collected as an oil. This alcohol was converted into the carbamate derivative[54] and a 84% *ee* was determined by HPLC analysis (Chiralcel OD column, 1.5% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 29.9 min, T_{minor} = 26.2 min. $[\alpha]^{22}_D$ = 49.3 (c = 1.2, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3366 (broad, m), 3078 (w), 2932 (w), 2854 (s), 2232 (w), 1640 (m), 1449 (m), 1348 (w), 1024 (s), cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 5.19 - 5.11 (m, 2H), 4.22 (t, *J* = 4.4 Hz, 1H), 2.48 - 2.38 (m, 2H), 1.90 (d, *J* = 4.8 Hz, 1H), 1.83 - 1.75 (m, 2H), 1.74 - 1.66 (m, 2H), 1.55 - 1.40 (m, 3H), 1.36 - 1.27 (m, 3H), 1.13 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 116.3, 90.6, 79.4, 66.4, 44.7, 32.6, 28.9, 25.8, 24.7, 15.2. EI HRMS calcd. for $C_{13}H_{20}ONa$ 215.1406, found 215.1400.

Methyl-1-cyclopropylhex-5-en-1-yn-3-ol (2.122):



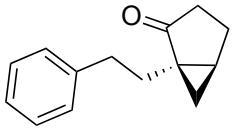
Collected as an oil. This was converted into the carbamate derivative[54] and a 84% *ee* was determined by HPLC analysis (Chiralcel OD column, 1.5% *i*-PrOH in hexanes, 0.5 mL/min, λ = 254 nm, column temperature = 25 °C). T_{major} = 16.5 min, T_{minor} = 18.4 min. $[\alpha]^{22}_{D}$ = 56.3 (c = 1.0, $CHCl_3$). R_f = 0.1 (hexanes/EtOAc 10:1). IR (film cast, $CHCl_3$): 3318 (broad, m), 3081 (m), 3011 (m), 2970 (w), 2931 (m), 2248 (m), 1601 (m), 1540 (s), 1444 (m), 1313 (m), 1221(s), 1051 (s), 1027 (s), cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 16.9, 10.6, 7.6 Hz, 1H), 5.17 - 5.12 (m, 2H), 4.17 (dd, *J* = 6.2, 1.5 Hz, 1H), 2.45 - 2.37 (m, 1H), 1.87 (br. s., 1H), 1.27 (dddd, *J* = 12.5, 9.0, 5.0, 2.0 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.78 (s, 2H), 0.70 - 0.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 116.4, 89.6, 74.7, 66.3, 44.7, 15.2, 8.2, -0.6. EI HRMS calcd. for $C_{10}H_{14}ONa$ 173.0937, found 173.0931.

Cycloisomerization of homoallyl propargylic alcohols:

Cycloisomerization of homoallyl propargylic alcohols were achieved by following the reported method.[39]

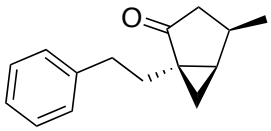
Characterization of cycloisomerization products:

1-Phenylethyl-bicyclo[3.1.0]hexan-2-one (2.126):



Collected as an oil. Spectral properties of similar compound has been reported.[39] $[\alpha]^{22}_{D}$ = –0.22 (c = 4.0, $CHCl_3$). IR (film cast, $CHCl_3$): 3061 (w), 3026 (w), 2941 (m), 2874 (m), 1719 (s), 1603 (m), 1496 (m), 1454 (m), 1416 (m), 1379 (m), 1313 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.20-7.17 (m, 3H), 2.80 - 2.68 (m, 2H), 2.23-2.16 (m, 1H), 2.14-2.03 (m, 2H), 2.0-1.87 (m, 2H), 1.77- 1.74 (m, 1H), 1.69-1.62(m, 1H), 1.04-1.01 (m, 1 H), 0.98 (apt t, *J* = 5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 142, 128.4, 128.2, 125.8, 36.6, 33.3, 32.5, 31, 27.7, 21.7, 19.3. MS (EI) : *m/z* (rel intensity) : 200 (15), 105 (24), 96 (26), 91 (100), 81 (26), 79 (24), 65 (29).

3-Methyl-1-phenylethyl-bicyclo[3.1.0]hexan-3-one (2.128):



Collected as an oil. Spectral properties of similar compound has been reported.[39] $[\alpha]^{22}_{D} = -3.6$ (c = 4.8, $CHCl_3$). IR (film cast, $CHCl_3$): 3062 (w), 3026 (w), 3001 (m), 2923 (m), 2866 (m), 1719 (s), 1603 (m), 1496 (m), 1454 (m), 1377 (m), 1328 (m) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.20-7.17 (m, 3H), 2.80 - 2.67 (m, 2H), 2.41-2.28 (m, 2H), 2.21-2.12(m, 1H), 1.78- 1.72 (m, 1H), 1.71-1.62 (m, 1H), 1.07-1.05 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 141.9, 128.46, 128.39, 128.31, 128.28 125.8, 41.2, 40.2, 36.7, 35.1, 33.4, 33.3, 30.89, 30.81, 28.9, 28.4, 22.3, 20.4, 18. MS (EI) : *m/z* (rel intensity) : 214 (56), 123 (28), 110(23), 105 (48), 95 (23), 91 (100).

2.8 References

1. a) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043. b) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865. c) Fátima, D.; Pilli, R. A. *Tetrahedron Lett.* **2003**, *44*, 872. d) Madec, D.; Férézou, J.-P. *Eur. J. Org. Chem.* **2006**, 92. e) Jung, W.-H.; Guyenne, S.; Riesco-Fagundo, C.; Mancuso, J.; Nakamura, S.; Curran, D. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1130.
2. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
3. Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.
4. a) Zweifel, G.; Steele, R. *J. Am. Chem. Soc.* **1967**, *89*, 5085. b) Zweifel, G.; Steele, R. *J. Am. Chem. Soc.* **1967**, *89*, 2754.
5. a) Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863. b) Chemin, D.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron* **1992**, *48*, 4369. c) Zhang, H.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. d) Russel, G. A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1985**, *26*, 4975. e) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044. f) Brown, H. C.; Ravindran, N.; Kulkarni, S. *J. Org. Chem.* **1980**, *45*, 384. g) Sayo, N.; Nakai, E.; Nakai, T. *Chem. Lett.* **1985**, 1723.
6. Nicolaou, K.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433.
7. Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.
8. Fürstner, A.; Schlecker, A. *Chem.–Eur. J.* **2008**, *14*, 9181.
9. Bouzbouz, S.; Pradaux, F.; Cossy, J.; Ferroud, C.; Falguières, A. *Tetrahedron Lett.* **2000**, *41*, 8877.
10. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 2183.
11. a) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 4381. b) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett.* **1991,** 561.
12. a) Kurosu, M.; Lorca, M. *Tetrahedron Lett.* **2002**, *43*, 1765. b) Kurosu, M.; Lorca, M. *Synlett* **2005**, 1109.
13. Yu, C. M.; Jeon, M.; Lee, J. Y.; Jeon, J. *Eur. J. Org. Chem.* **2001**, 1143.
14. Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.
15. Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1964,** 1874.
16. a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem. Int. Ed.* **1979,** *18,* 306. b) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979,** *20,* 4653.
17. Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis and Medicine;* Wiley-VCH: Weinheim, 2nd edition **2011**.
18. Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236.
19. Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002,** *124,* 11586.
20. Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002,** *124,* 12414.

21. Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004,** *126,* 4518.
22. Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331.
23. Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003,** *125,* 10160.
24. a) Yu, H. Y.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. b) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.
25. a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. b) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120.
26. Rauniyar, V.; Hall, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2426.
27. Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.
28. Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.
29. Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006,** *128,* 1086.
30. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126,* 5356.
31. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004,** *43,* 1566.
32. Jain, P.; Antilla, J. *J. Am. Chem. Soc.* **2010,** *132,* 11884.
33. Xing, C. H.; Liao, Y.X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q. S. *Eur. J. Org. Chem.* **2012**, *6,* 1115.
34. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105,* 2092.
35. Roush, W. R.; Hoong, L. K. Palmer, M. A. J. Park, J. C. *J. Org. Chem.* **1990,** *55,* 4109.
36. Ju, J.; Reddy, B.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1989,** *54,* 5426.
37. Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990,** *55,* 1143.
38. Brown, H. C.; Racherla, U.S.; Pellechia, P.J. *J. Org. Chem.* **1990**, *55*, 1868.
39. Mamane, V.; Gress, T.; Krause, H.; Furstner, A. *J. Am. Chem. Soc.*, **2004**, *126*, 8654.
40. Asikainen, M.; Lewis, W.; Blake, A. J.; Woodward, S. *Tetrahedron Lett*. **2010**, *51*, 6454.
41. Kawasaki, Y.; Ishikawa, Y.; Igawa, K.; Katsuhiko,T. *J. Am. Chem. Soc.* **2011**, *133*, 20712.
42. Rooke, D. A.; Ferreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3225.
43. Geyer, M.; Bauer, J.; Burschka, C.; Kraft, P.; Tacke, R. *Eur. J. Inorg. Chem.* **2011**,*17*, 2769.
44. Sigma-Aldrich Product no: 687170.
45. Shen, Y.-L.; Wu, W.-T.; Liu, Q.; Wu, G.-L.; Wu, L.-M. *J. Chem. Res.* **2006**, *8*, 545.
46. Romanov-Michailidis, F.; Besnard, C.; Alexakis, A. *Org. Lett*. **2012**, *14*, 4906.
47. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.
48. Malgorzata, M.; Heise; G.; Walsh, J. D. *Tetrahedron Lett.* **2012**, *53*, 2937.
49. Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Frohlich, J.; Kirchner, K. *Organometallics* **2005**, *24,* 3957.
50. Osamu, I.; Naoki, I.; Toshihide, S.; Hiroaki, K.; Yoshiki, F.; Yoshinori, H.; Toshio, S.; Katsuhiko, I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 177.

51. Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, *14*, 2293.
52. Rauniyar, V.; Zhai, H.; Hall, D. G. *Synth. Commun.* **2008**, *38*, 3984.
53. Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.
54. Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5913.
55. Hartley, R.C.; Lamothe, S.; Chan, T.H. *Tetrahedron Lett*. **1993**, *34*, 1449.
56. Wzorek, J.; Troutman, A.; Allegue, K.; Mitzel, T. *J. Org. Chem.* **2007**, *72*, 3042.
57. Robles, O.; McDonald, F. E. *Org. Lett.* **2009**, *11*, 5498.
58. Burova, S.A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188.
59. Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protocols.* **2007**, *2*, 2451.

Chapter 3

Application of B/Si double-allylation reagent in imine allylation

3.1 Introduction

Complex molecules of pharmaceutical and biological relevance can be produced by organic synthesis. An ideal organic synthesis takes into account the ideas of redox, atom and step economy.[1] The basic goal of redox economy is to minimize non-strategic oxidations and reductions in order to achieve a synthesis. Atom economy describes the conversion efficiency of a chemical process in terms of all atoms involved. In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. The precepts of step economy deals with the fact that minimizing the number of steps leads to an efficient multistep synthesis in terms of cost and time expended to obtain the desired target. Chemists attempt to reduce the number of these issues in a synthesis. That objective can be achieved by the application of multifunctional reagents which allow the formation of complex structures in high yield and high selectivity in a minimum number of operations. Among all the possible multifunctional reagents, double-allylation reagents are of special interest. These reagents can react with simple starting materials such as aldehydes and ketones and can generate multisubstituted complex molecules and natural products. There are various kinds of carbonyl double-allylation reagents known in the literature. They can be divided into four different types depending on the relative position of the metal or metalloid atoms (Figure 3.1).

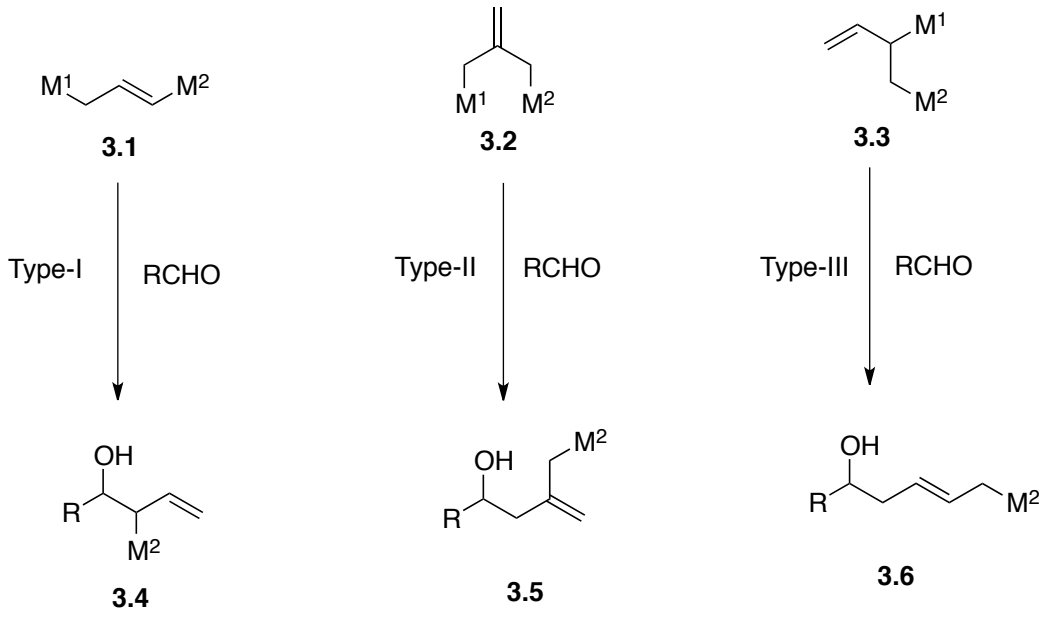


Figure 3.1. Different types of double-allylation reagents, shown here with a mono allylation.

3.2 Type-I reagents

Type-I reagents (**3.1**) have been reported frequently by Roush and co-workers.[2] There are both di-boron and boron-silicon versions of this class of reagent (Figure 3.2).

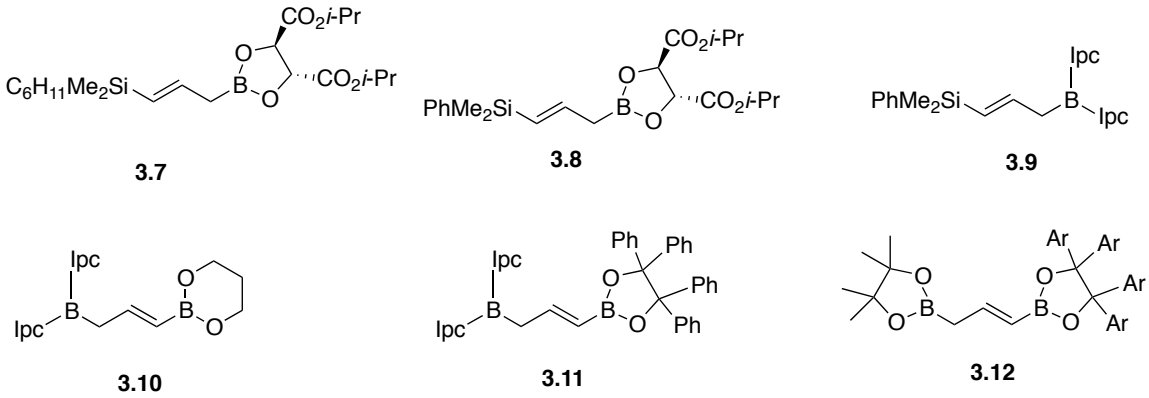
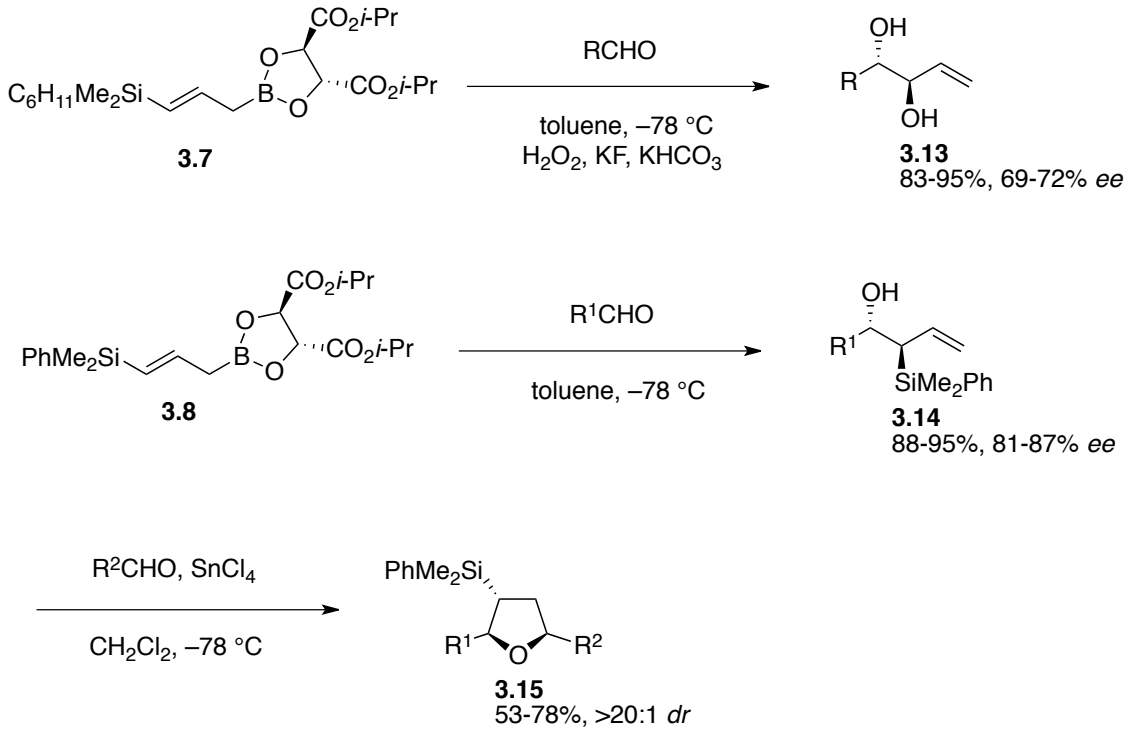


Figure 3.2. Examples of Type-I double-allylation reagents.[2]

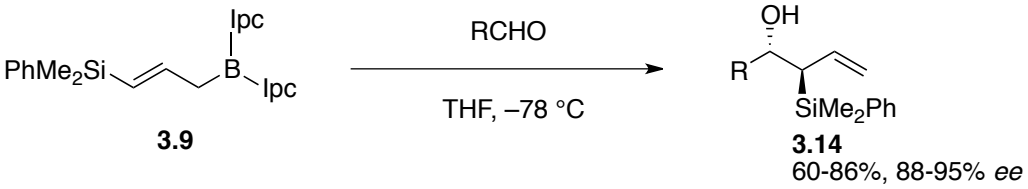
Reagents **3.7** and **3.8** were the first reported double-allylation reagents belonging to this class. In these reagents, the silicon atom is placed on the γ-position of an allylboronate. The stereoselectivity in carbonyl additions originates from the tartaric acid derived boronate. These reagents were exploited for the

preparation of 1,2-*anti*-diols and polysubstituted tetrahydrofurans (Scheme 3.1).[3,4]



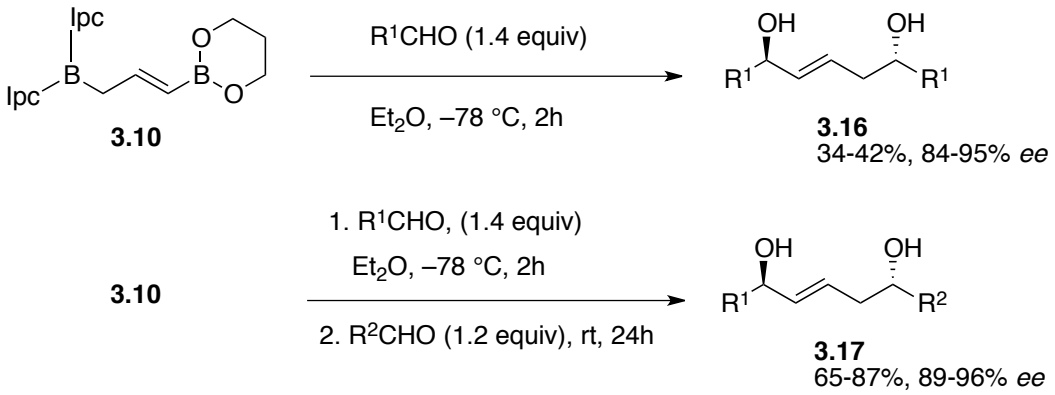
Scheme 3.1. Applications of Type-I B/Si double-allylation reagents.[3,4]

Later on, a total synthesis of the natural product (+)-bullatacin was reported. The trisubstituted tetrahydrofuran ring of this natural product was synthesized by applying this method.[5] Although these reagents exhibited a vast substrate scope, the inability to induce high enantioselectivity lessened their appeal. Another reagent belonging to this class is the γ-silyl allylboronate **3.9** (Figure 3.2). This reagent reacted with the aldehydes affording very good yields and enantioselectivities. However, the boron partner of this reagent is the allyldialkylborane which was prepared *in situ* and reacted with the aldehyde right away without prior isolation.[2,4,6] Thus the instability and difficulty in handling the allylborane makes this reagent less desirable (Scheme 3.2).



Scheme 3.2. Reaction of a Type-I B/Si double-allylation reagent with an allyldialkylborane.[2,4,6]

The Roush Group also reported B/B-reagents belonging to this class. These reagents, **3.10**, **3.11**, and **3.12** consist of two boron atoms with one of them sitting on the γ-position of an allylborane (Figure 3.2). This family of reagents has been utilized in the synthesis of 1,5-*anti* diols. Although the yields of these reactions were moderate, excellent enantioselectivities could be achieved (Scheme 3.3).[7,8]



Scheme 3.3. Applications of Type-I B/B double-allylation reagents.[7,8]

These reagents have found applications in the total synthesis of the two natural products of biological importance amphidinol and tetrafibricin.[9,10]

3.3 Type-II reagents

Barrett and co-workers were the first to report an example of a double-allylation reagent of this class (**3.2**). Reagents **3.18** and **3.19** possess borylmethyl groups at the β-position of an allylborane derived from 2-methylpropene (Figure 3.3).

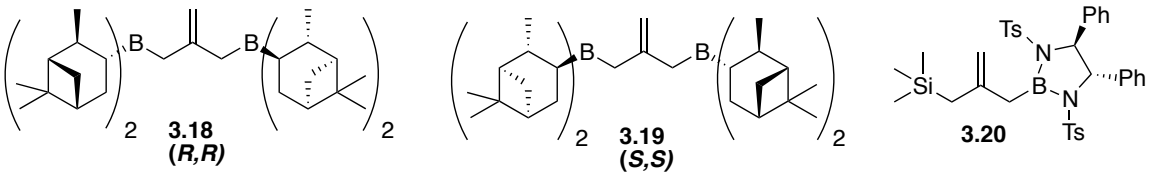
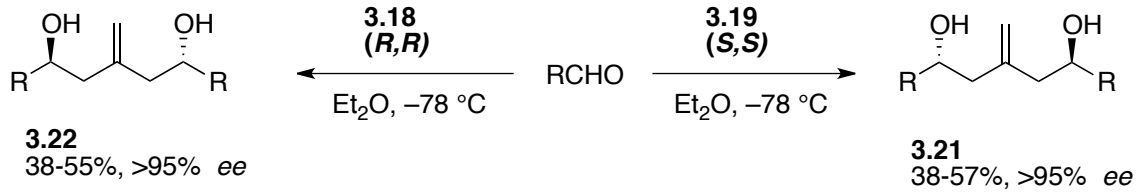


Figure 3.3. Examples of Type-II double-allylation reagents.

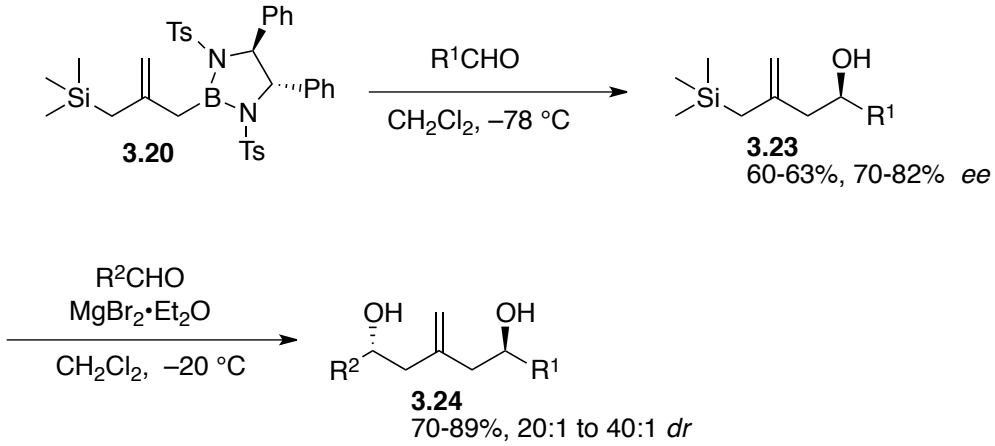
Upon treatment with aldehydes this reagent can produce 1,5-*anti*-diols in moderate yields and selectivities

(Scheme 3.4). This methodology has been further applied in the synthesis of C_2-symmetric spiroketals.[11]



Scheme 3.4. Applications of Type-II B/B double-allylation reagents.[11]

Another Type-II reagent is **3.20** reported by Williams and co-workers (Figure 3.3). This reagent was derived through a very facile transmetalation of an allylstannane; it has a silylmethyl group at the β-position and a chiral borane. When treated with an aldehyde this reagent resulted in a homoallylic alcohol (**3.23**), with very good enantioselectivity with the allylborane unit reacting more readily than the allylsilane moiety. After that, the allylsilane unit can react with an aldehyde when treated with a Lewis acid resulting in a 1,5-diol with excellent enantioselectivity (**3.24**, Scheme 3.5). This chemistry saw further application in the form of a total synthesis of the natural product peloruside.[12]

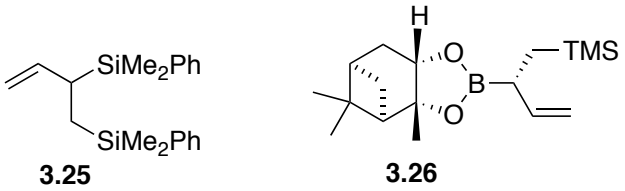


Scheme 3.5. Applications of a Type-II B/Si double-allylation reagent.[12]

3.4 Type-III reagents

Sarkar and co-workers reported the first example of a reagent (**3.3**) belonging to this class. The disilane

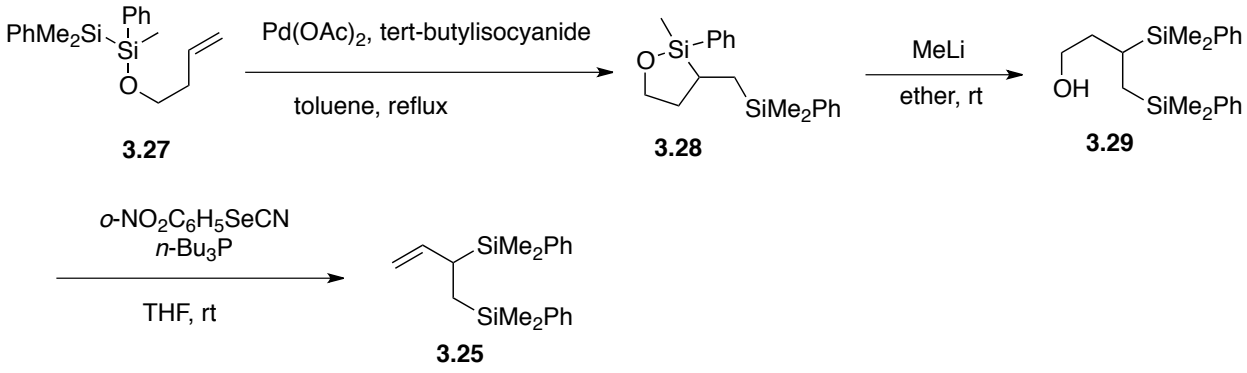
reagent **3.25** is a racemic compound with one silicon atom in the β-position of an allylsilane (Figure 3.4).[13]



3.25 **3.26**

Figure 3.4. Type-III double-allylation reagents.[13]

Reagent **3.25** is prepared from a disilyl ether of a homoallylic alcohol (**3.27**). Upon treatment with $Pd(OAc)_2$ it formed a five membered ring which upon treatment with MeLi formed an alcohol (**3.29**). This alcohol underwent a Grieco elimination to give the desired product (Scheme 3.6).

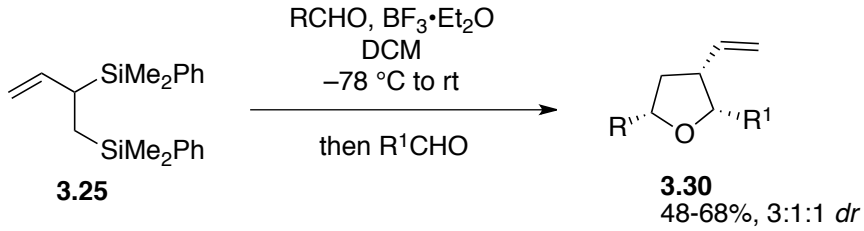


3.27 **3.28** **3.29**

3.25

Scheme 3.6. Preparation of Type-III Si/Si double-allylation reagent.[13]

Upon treatment of **3.25** with an aldehyde in the presence of a Lewis acid in dichloromethane good yields of different polysubstituted tetrahydrofurans were produced but lower diastereoselectivity was observed (Scheme 3.7).



3.25 **3.30**
48-68%, 3:1:1 *dr*

Scheme 3.7. Application of Type-III Si/Si double-allylation reagent to produce a polysubstitutedtetrahydrofuran.[13]

Chiral variants of this reagent (**3.32** and **3.34**) have also been reported but they are only specialized reagents with no substrate scope having been explored to this date (Figure 3.5).[14,15]

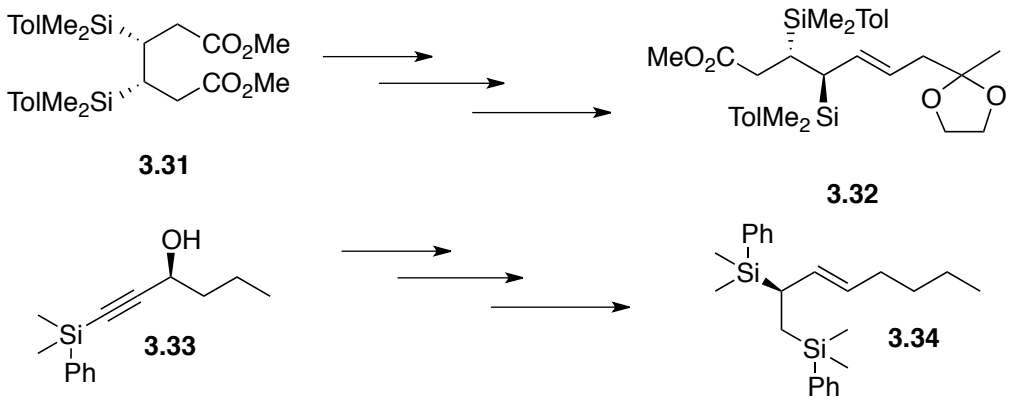
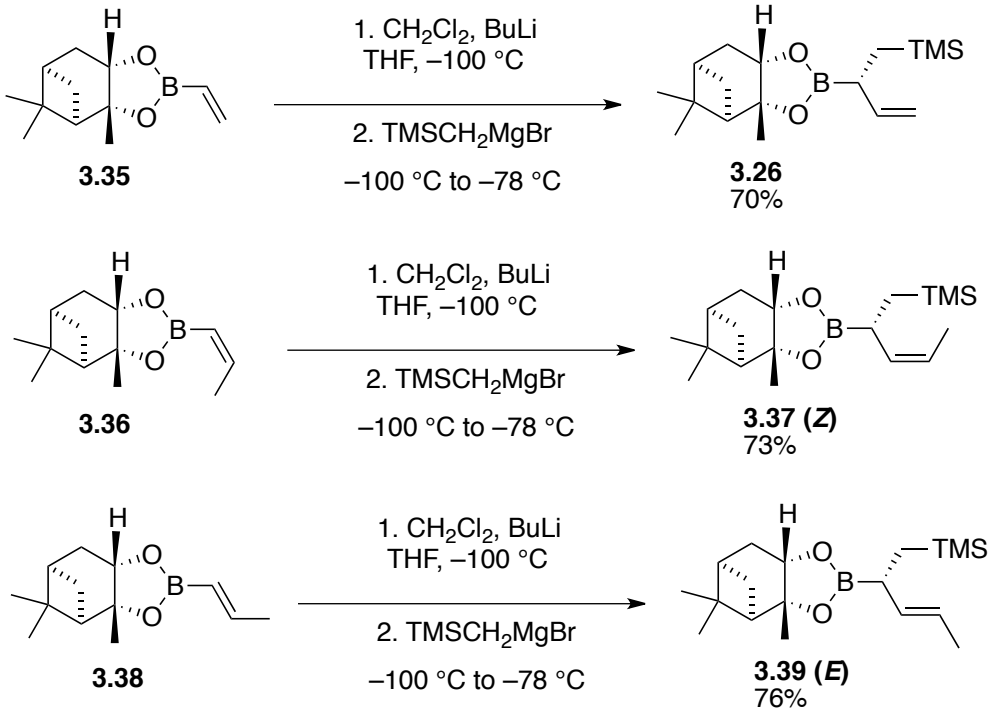


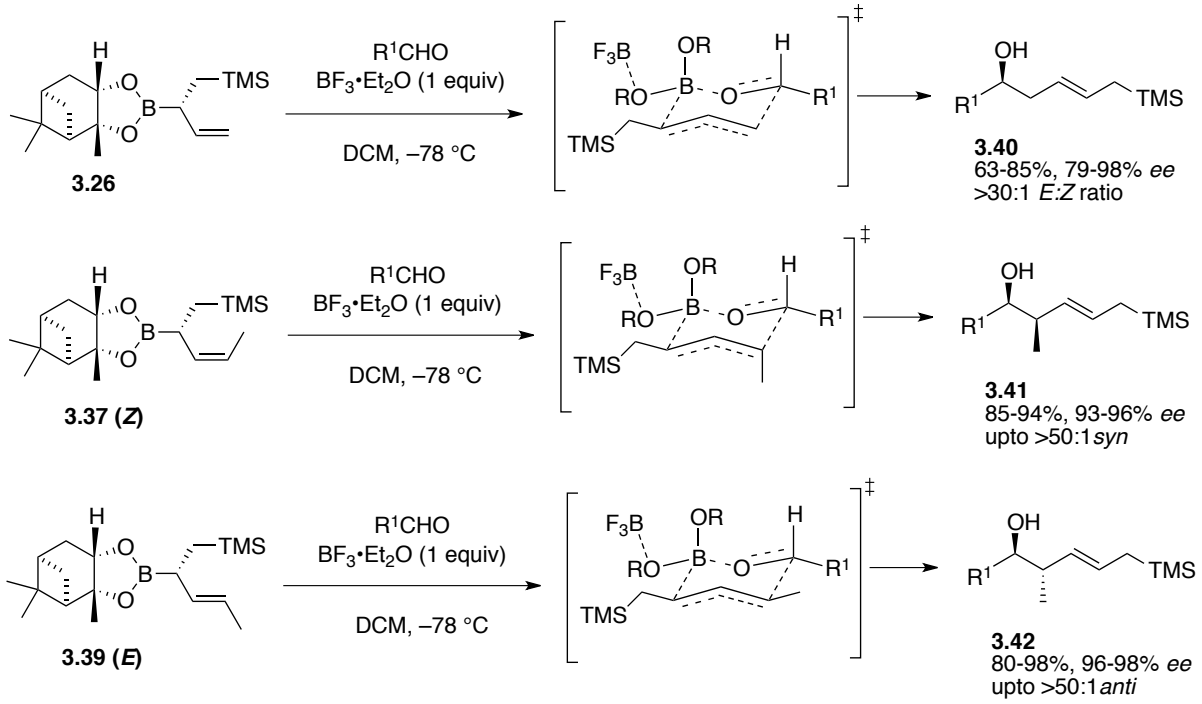
Figure 3.5. Chiral variants of Type-III Si/Si double-allylation reagent.[14,15]

Hall and co-workers reported the first Type-III enantiomeric B/Si-reagent, **3.26** (Figure 3.4). It was prepared using a simple Matteson homologation of pinanedioxy ethyleneboronic ester, followed by *in situ* addition of trimethylsilylmethyl-MgBr. High yield and excellent diastereoselectivity were observed for the simple allyl reagent (**3.26**) along with the *Z* and *E* crotyl boronate versions, **3.37** and **3.39** (Scheme 3.8).[16]



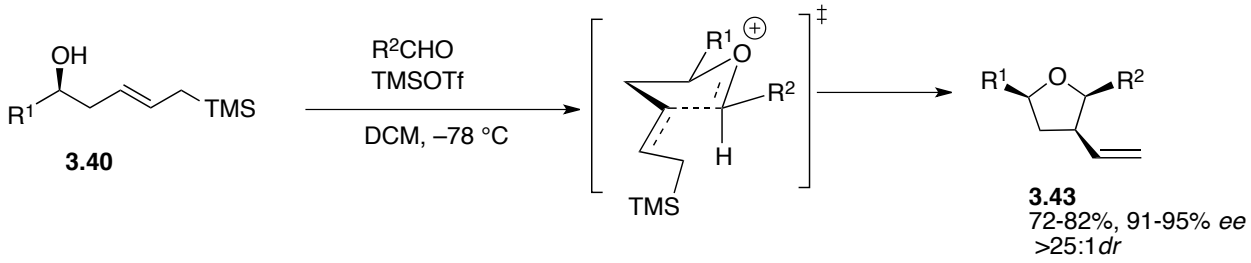
Scheme 3.8. Preparation of Type-III B/Si double-allylation reagents, **3.26**, **3.37**, **3.39**.[16]

With reagent **3.26** in hand the authors tested various aldehydes in asymmetric allylboration. Gratifyingly all of them produced the desired homoallylic alcohols in high yield and excellent enantioselectivity. The *E/Z* ratio of the olefin in the product was found to be outstanding. Similarly, the crotylation of aldehydes was performed and both the *Z* and *E* crotyl reagents (**3.37** and **3.39)** gave excellent levels of both enantio- and diastereoselection while maintaining a high *E/Z* ratio of the olefin product. This reaction was proposed to proceed via a closed and tight 6-membered Zimmerman-Traxler type transition state where the Lewis acid additive would bind to the O atom of the boronate enhancing the reactivity of this reagent. The high level of enantio- and diastereoselection as well as excellent *E/Z* ratio of the olefin can be ascribed to this tight transition state structure (Scheme 3.9).



Scheme 3.9. Applications of Type-III B/Si double-allylation reagents **3.26**, **3.37**, **3.39**.[16]

After the successful allylation and crotylation experiments the alcohol product was subjected to an intramolecular Sakurai reaction with the oxonium intermediate formed between the homoallylic alcohol product and another aldehyde, which afforded many polysubstituted tetrahydrofuran rings in very high yield and excellent enantio- and diastereoselectivity. The sterochemical outcome of this reaction can be predicted by a 5-membered envelope-like transition state where all the bulky groups occupy pseudo-equatorial positions to minimize various steric interactions (Scheme 3.10).

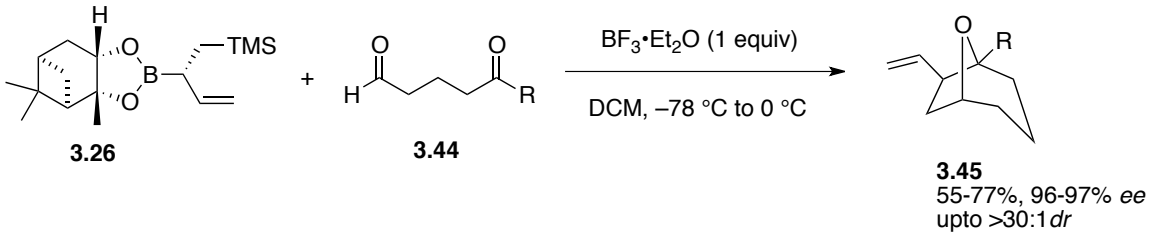


Scheme 3.10. Tetrahydrofuran ring synthesis from homoallyl alcohols.[16]

The Sakurai reaction was also attempted in a one-pot procedure under which conditions the desired product was obtained in acceptable yield and excellent enantioselectivity. The only drawback of this

process was its inferior diastereoselection compared to the stepwise reaction.

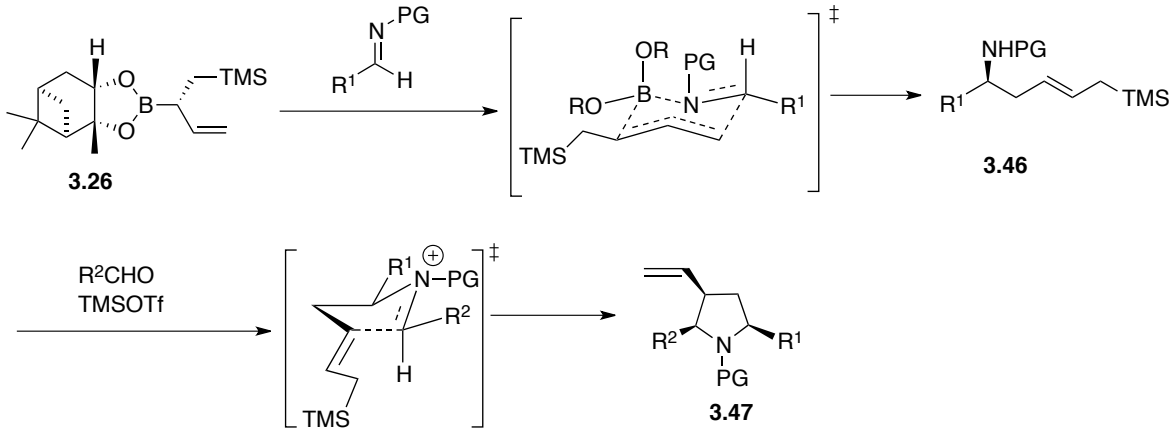
This reagent was shown also to transform 1,5-dicarbonyl compounds into oxabicyclic rings in good yields and excellent selectivities (Scheme 3.11).



Scheme 3.11. Synthesis of oxabyclic rings with reagent **3.26**.[16]

3.5 Project plan

The double-allylation reagent (**3.26**) developed in our group has so far been applied in aldehyde allylation to afford homoallyl alcohols with an allylsilane subunits. The allylic silane intermediate has further been manipulated into polysubstituted tetrahydrofuran. A similar reaction with an imine derivative would give a homoallylamine with an allylsilane subunit. This product **3.46** could then be transformed into a polysubstituted pyrrolidine with an aldehyde in either a stepwise or a one-pot manner (Scheme 3.12).



Scheme 3.12. Proposed synthesis of chiral homoallylic amines and pyrrolidine rings (PG = protecting group).

Both **3.46** and **3.47** of these products are immensely important building blocks and privileged sub-structures found in many natural products and drugs such as perindopril, an ACE inhibitor used to treat high blood pressure (Figure 3.6).[17]

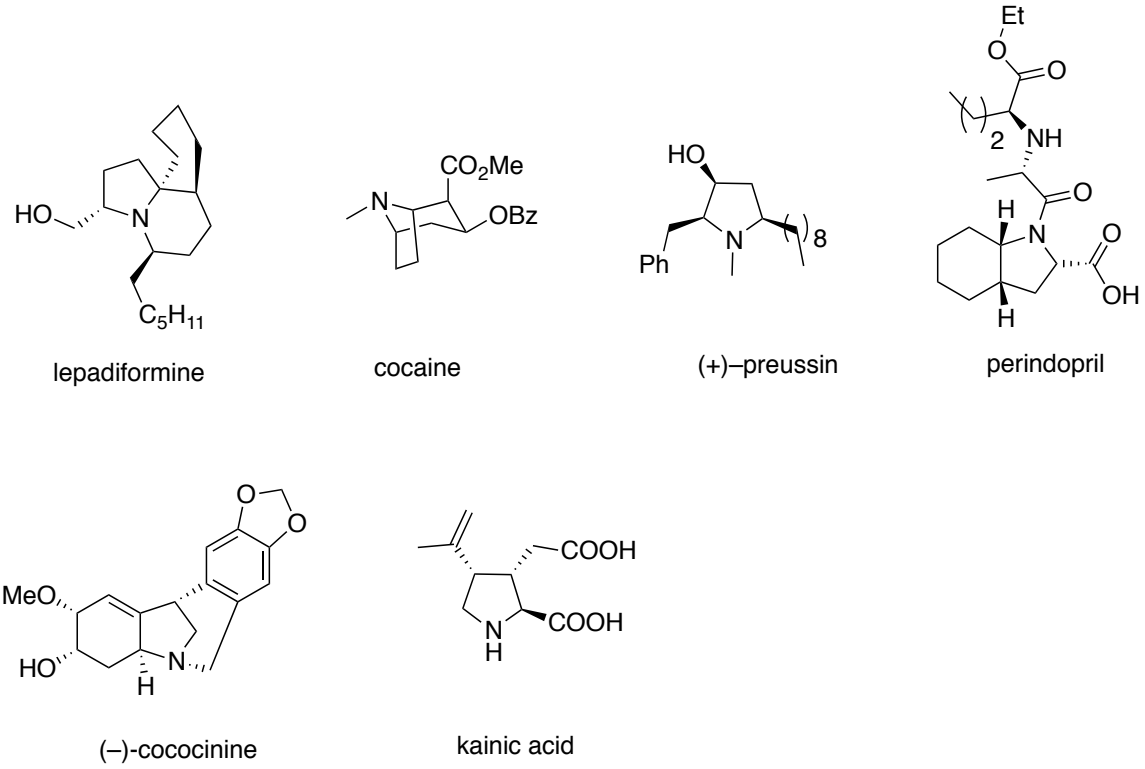
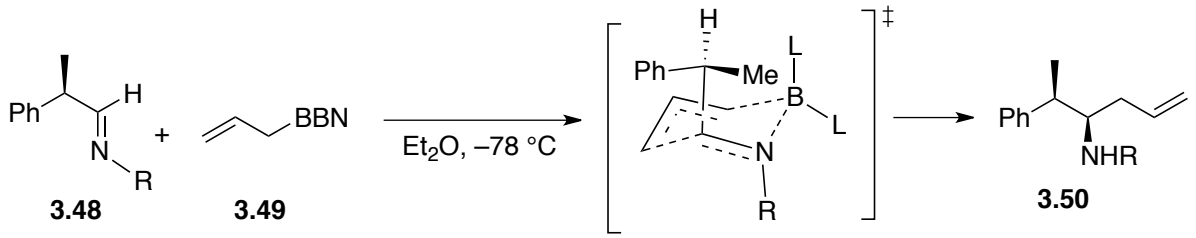


Figure 3.6. Natural products with pyrrolidine rings.[17]

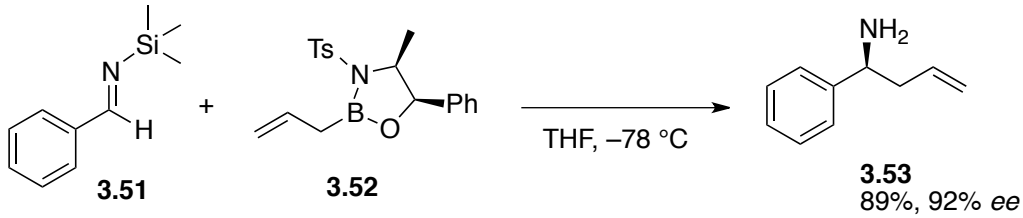
3.6 Imine allylboration

Despite the lesser reactivity of imine derivatives and their tendency towards degradation, there are a number of publications in the area of imine allylboration. Yamamoto and co-workers reported allylboration of an imine with a stereogenic α-carbon (Scheme 3.13).[18] The allylation reagent is an allylborane, and the reaction proceeds via a chair-like transition state and gives almost exclusively the Cram addition product.



Scheme 3.13. Imine allylboration reported by Yamamoto's group.[18]

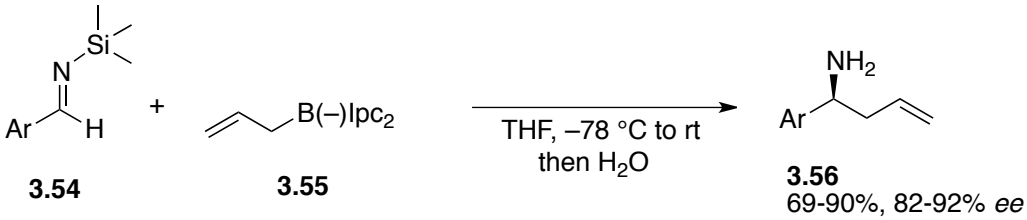
Itsuno and co-workers reported the asymmetric allylation of N-trimethylsilylimines with a chiral B-allyloxazaborolidine, which was generated *in situ* from triallylborane and N-sulfonylaminoalcohols (Scheme 3.14).[19]



3.51 **3.52** **3.53**
89%, 92% *ee*

Scheme 3.14. Asymmetric imine allylboration reported by Itsuno's group.[19]

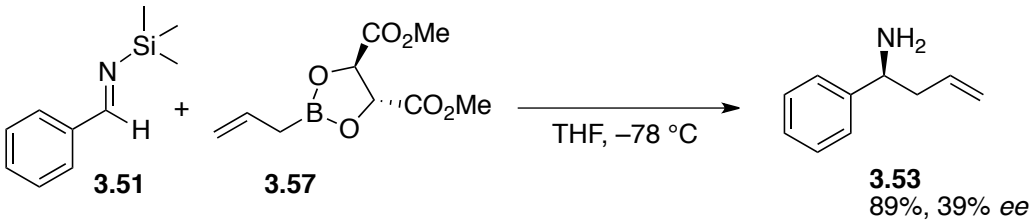
Brown and coworkers reported a methodology similar to the one utilized by Itsumo's group by employing B–(–)-allyldiisopinocampheylborane to the same class of imines. The silyl group is removed and the unmasked imine is thus generated *in situ* by the addition of a stoichiometric amount of water into the reaction mixture, which then reacts with the generated imine (Scheme 3.15).[20]



3.54 **3.55** **3.56**
69-90%, 82-92% *ee*

Scheme 3.15. Asymmetric imine allylboration reported by Brown's group.[20]

Itsuno reported the same methodology by using an allylboronate derived from tartaric acid but it afforded a much lower enantioselectivity (Scheme 3.16).[21]



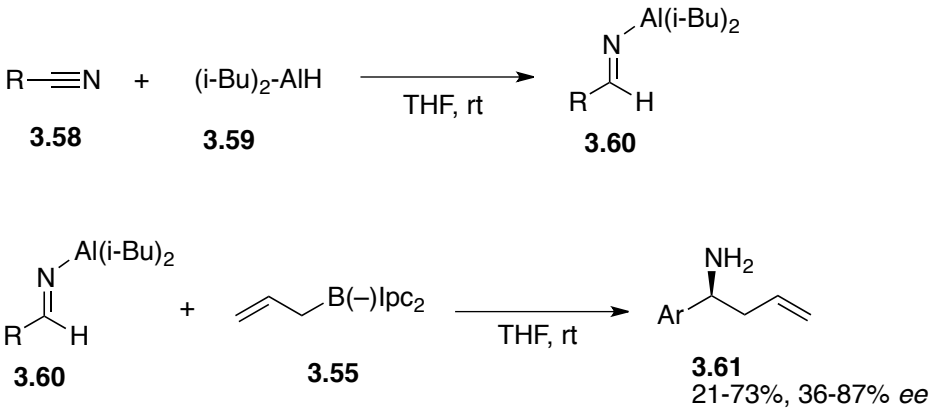
3.51 **3.57** **3.53**
89%, 39% *ee*

Scheme 3.16. Imine allylboration with tartrate derived allylboronate reported by Itsuno's group.[21]

Notably, water is used as an additive only in Scheme 3.15, although N-silylimine is used both in Scheme 3.14 and 3.16, and the reason for this is not explained in those two reports.

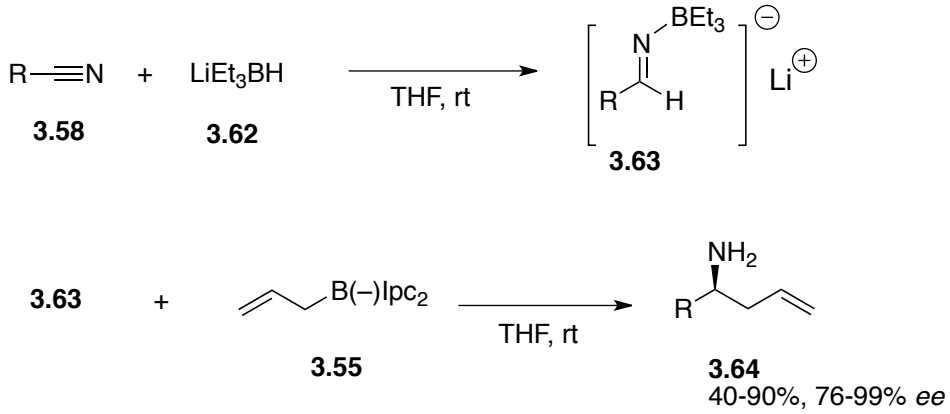
The Itsuno group has also reported a similar methodology involving an imine generated *in situ* through the

DIBAL reduction of nitriles and an allylborane (Scheme 3.17).[22]



Scheme 3.17. Imine allylboration with imine derived from nitrile reduction reported by Itsuno's group.[22]

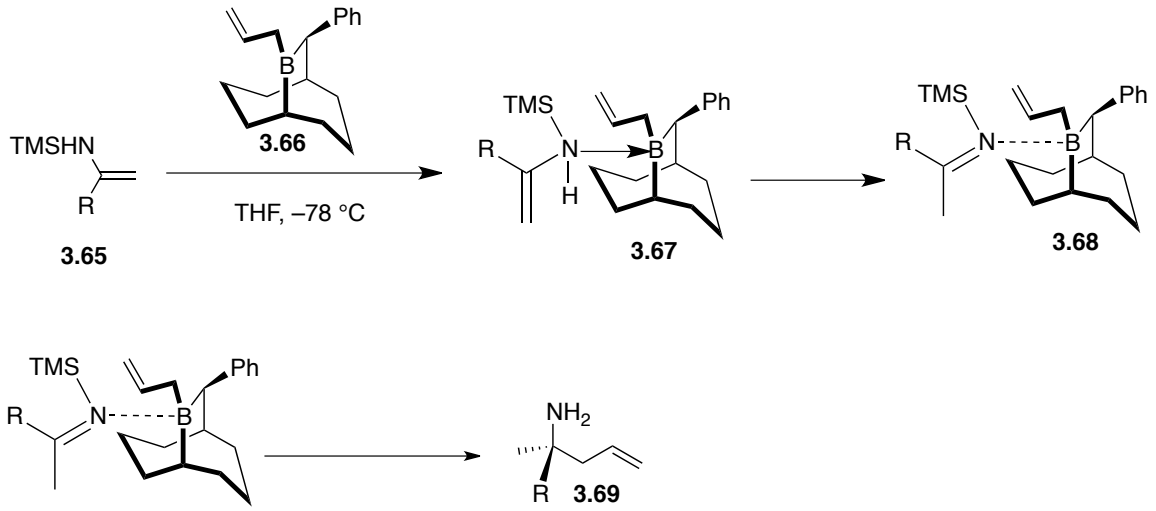
Later, Ramachandran and coworkers also published examples of imine allylborations employing B-allyldiisopinocampheylborane (**3.55**) and imines generated through the borohydride reduction of nitriles, **3.58** (Scheme 3.18). This method was employed to synthesize γ–butyric acid analogues.[23]



Scheme 3.18. Imine allylboration with imine derived from nitrile reduction reported by Ramachandran's group.[23]

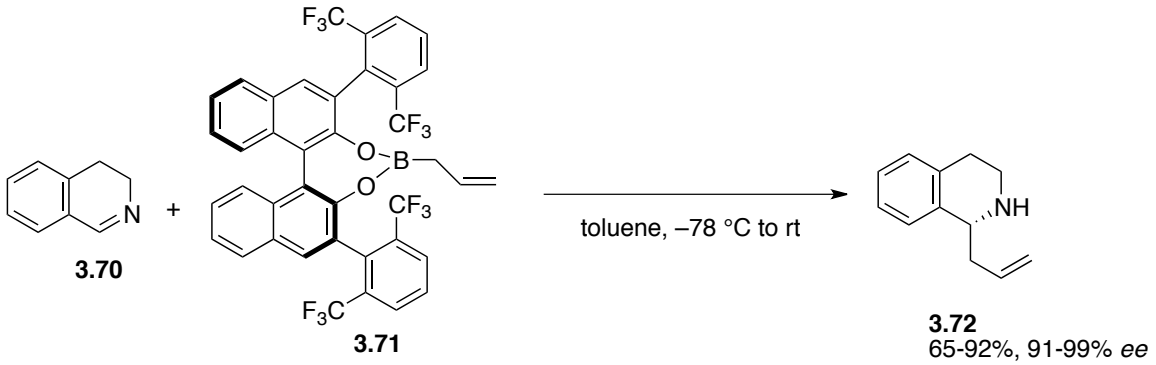
Soderquist and co-workers reported an example of imine allylboration with N-silylimine and B-allyl-10-phenyl-9-borabicyclo[3.3.2]-decanes, **3.66** (9-BBD-s).[24] In this case the imines are generated *in situ* from N-silylenamines (**3.65)** with the allylborane, and then can undergo the allylation in very good yield and enantioselectivity (Scheme 3.19). Although excellent yields and enantioselectivities are observed with all

these methods, the use of highly reactive and unstable allylic boranes, poses serious limitations.



Scheme 3.19. Asymmetric imine allylboration reported by Soderquist's group.[24]

A very useful and important methodology involving 3,3'-disubstituted binaphthol modified allylboronates with cyclic (*Z*)-imines was reported by Chong and co-workers. Phenyl ring fused cyclic imines (dihydroisoquinolines) as well as aliphatic cyclic imines gave excellent yield and enantioselectivity, thus displaying the broad scope of this methodology (Scheme 3.20).[25]



Scheme 3.20. Asymmetric imine allylboration reported by Chong's group.[25]

These cyclic (*Z*)-imines underwent very facile allylboration even at –78 °C through a 6-membered transition state without any assistance from any kind of Lewis acid or Brønsted acid. Substitution at 3 and 3' positions of the BINOL unit on the allylboronate was crucial for the selectivity while smaller or no substituents gave lower selectivity (Figure 3.7).

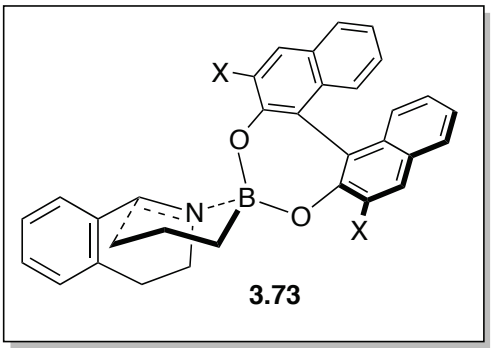
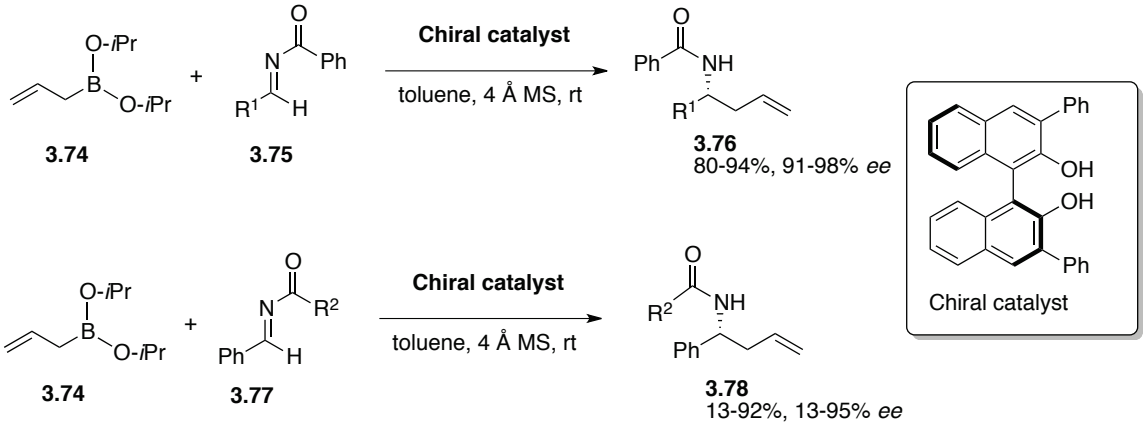


Figure 3.7. Most favoured transition state for asymmetric imine allylation with BINOL-allylboronate.[25]

The authors further applied this chemistry in the total synthesis of ent-corynantheidol, *R*-(–)–coniine, and (+)-crispine A. [25]

Schaus and co-workers reported a very versatile catalytic asymmetric imine allylboration methodology involving allyldiisopropoxyborane with a variety of N-benzylidene derivatives under BINOL-catalyzed conditions (Scheme 3.21).[26]

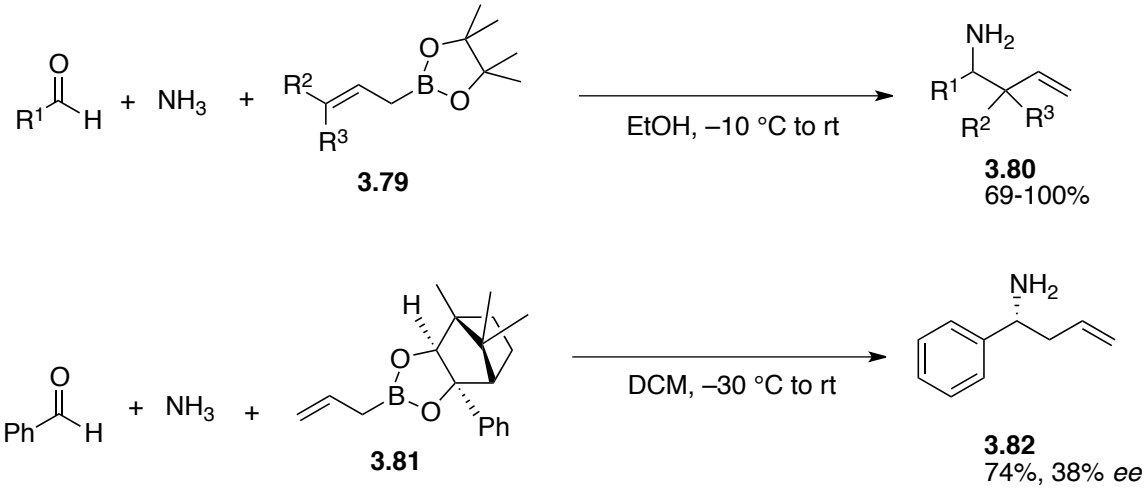


Scheme 3.21. BINOL-catalyzed asymmetric imine allylboration reported by the Schaus Group.[26]

Mechanistic investigations using ^{1}H NMR spectroscopy and ESI-MS revealed the formation of a dissymmetrical boronate complex between the 3,3'-disubstituted BINOL catalyst and allyldiisopropoxyborane, which then reacts with the N-acyl imine through a 6-membered transition state to give very high yield and selectivity.

Because the corresponding aldimines are not stable, an important development in imine allylboration

methodology was the direct use of ammonia for multicomponent couplings. Another advantage of this approach is that aldehydes or ketones can be used directly in the reaction with the imine being formed *in situ* which can then react with the boronate. In 2004, Kobayashi and co-workers reported the multicomponent coupling of aldehydes, ammonia and allylpinacolboronate to give homoallylic amines. Under these reaction conditions, a negligible amount of homoallylic alcohol was observed from the reaction of untransformed aldehyde and allylboronate. Allylations occurred in modest to excellent yields (69% to quant.) and with high chemoselectivity for the *in situ* generated imine over the aldehyde. However, only modest chiral induction (34% *ee*) was observed for an allylation reaction involving a chiral allylboronate reagent (Scheme 3.22).[27]

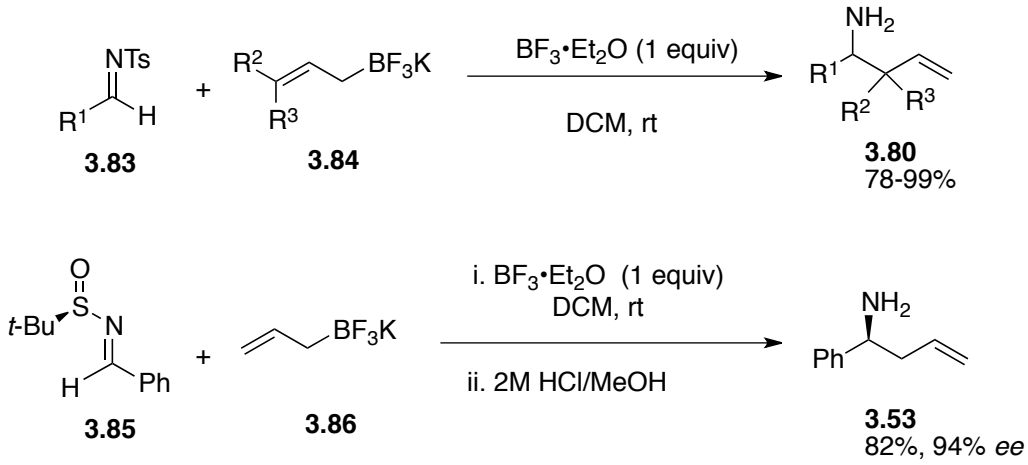


Scheme 3.22. Allylboration of imines generated *in situ,* reported by Kobayashi's group.[27]

In addition, crotylations with (*E*)- and (*Z*)-crotylpinacolboronate occurred in good to excellent yields and with excellent diastereoselectivities [(*E*)-crotyl: 79–92% yield, 92–93% *anti*; (*Z*)-crotyl: 85–90% yield, >99% *syn*]. Very high diastereoselectivities were also noted for the allylations of chiral α-alkoxyaldehydes, without concomitant epimerization at the α-position even in the presence of excess ammonia.

Boronates often display instability towards air and moisture. Organotrifluoroborate salts have been demonstrated to be air- and water-stable equivalents to the corresponding organoboronic acids or esters and can be stored for many months without decomposition. These compounds have found widespread utility in organic synthesis in recent times. Potassium allyl- and crotyltrifluoroborate salts have been developed by Batey and co-workers for addition reactions to carbonyl compounds using Lewis acid, phase-transfer, or Montmorillonite K10 catalysis, or through the use of stoichiometric or catalytic indium metal.[28] Subsequent to these studies, Batey and co-workers reported the allylation of N-sulfonylaldimines to form homoallylic N-sulfonylamines in high yields using potassium allyltrifluoroborate with a catalytic

quantity of boron trifluoride-diethyl ether complex. Crotylations were also performed with either potassium (*E*)- or (*Z*)-crotyltrifluoroborate to afford the desired products in high yields and excellent diastereoselectivities. It was also demonstrated that chiral benzaldehyde-derived N-sulfinylimine could be allylated to form chiral homoallylic amine with excellent enantioselectivity (94% *ee*) (Scheme 3.23).[29]

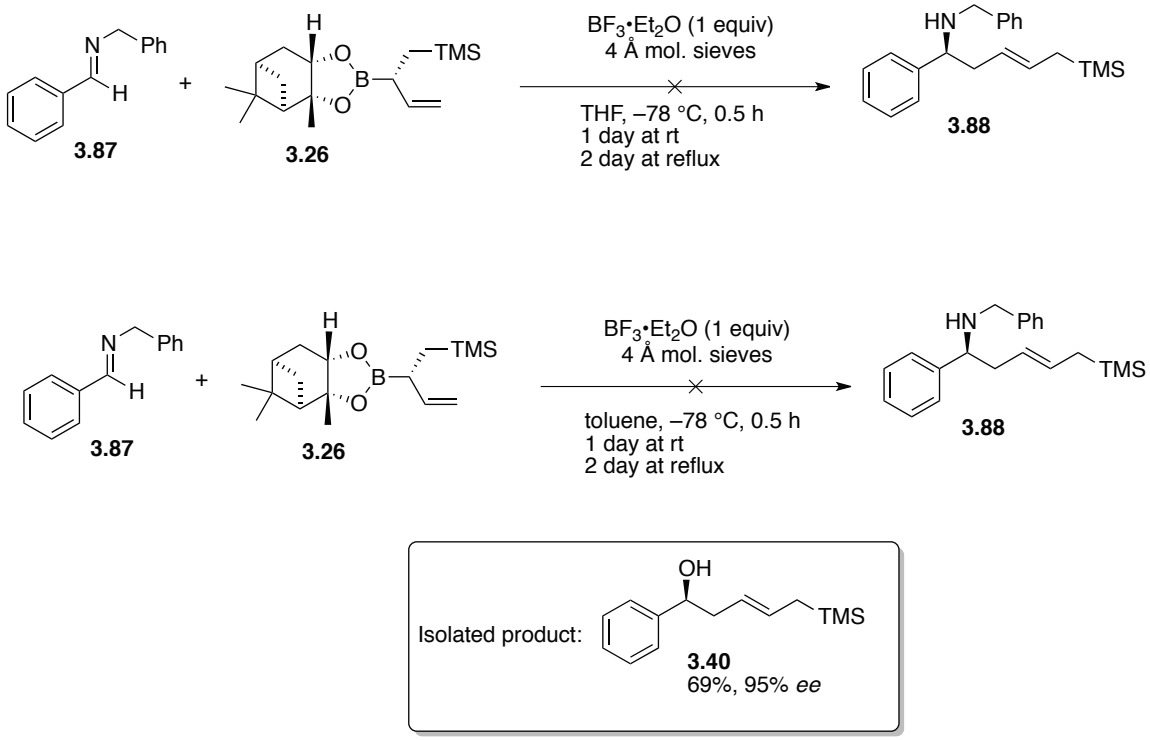


Scheme 3.23. Allylboration of N-tosylaldimines with allylic trifluoroborate salt reported by the Batey group.[29]

3.7 Results and discussion

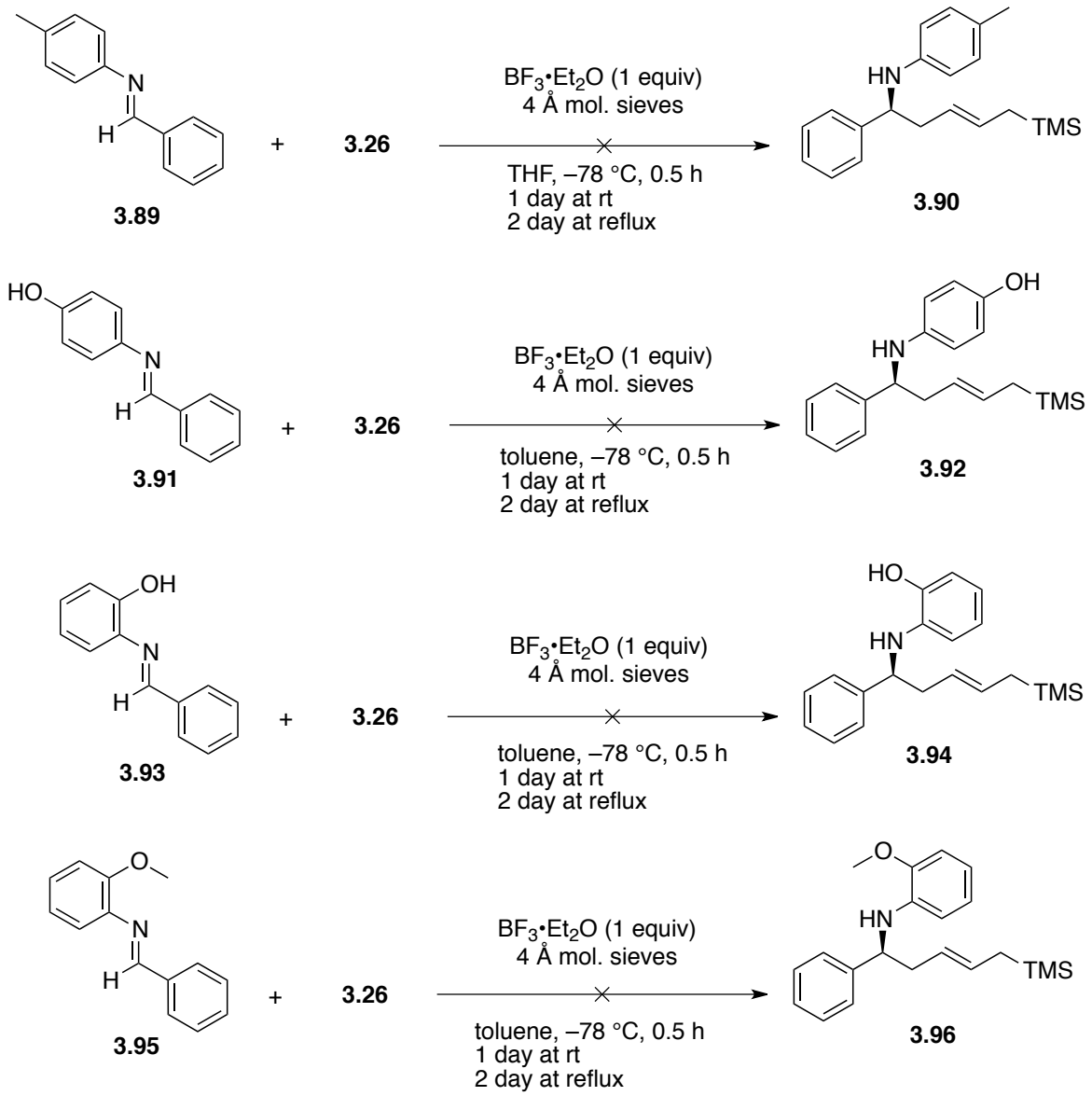
As discussed in Section **3.5**, the first goal of the project was to identify and optimize suitable conditions for the asymmetric allylboration of imines with the double-allylation reagent (**3.26**) previously developed in our group for carbonyl additions (Scheme 3.12). To initiate a search for promising reaction conditions, N-benzylidinebenzylamine (**3.87**) was chosen as the imine partner. This imine is very stable and does not possess any substituents on the two benzene rings that might exert any significant electronic effects. Reactions were first conducted in the solvent THF. Molecular sieves were added to remove any moisture and to suppress any possible decomposition of the imine. Boron trifluoride as a Lewis acid was used to increase the reactivity of the boronate reagent. Boron trifluoride was added at –78 °C and the reaction mixture was held at that temperature for 0.5 h, and then it was stirred at room temperature for one day. After 24 h at room temperature the presence of imine starting material was revealed by thin layer chromatography. The reaction was then heated at reflux temperature for two days. Unfortunately, this led to the formation of homoallylic alcohol (**3.40**) as side products instead of the desired homoallylic amine.

Replacing THF with toluene and refluxing again was unsuccessful as well, and yielded the undesired side product of aldehyde allylation **3.40** (Scheme 3.24).



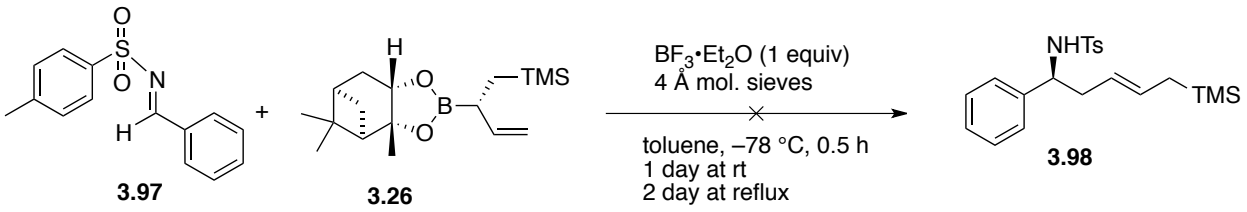
Scheme 3.24. Attempted allylboration of N-benzylidineaniline with B/Si double-allylation reagents using THF or toluene as solvents.

In another round of optimization studies, imines with different substituents on the nitrogen were tried with the idea that one of them would give better reactivity with the double-allylation reagent. All the selected imines had one particular feature; they had an electron-rich aromatic substituent on the N atom of the imine, which should facilitate the coordination of the boron atom in the double allylation reagent. This in turn should speed up the reaction rate. As well, the products would be oxidatively deprotectable to reveal the primary amine. Unfortunately, even these attempts failed to give any product and both the starting materials were recovered (Scheme 3.25).



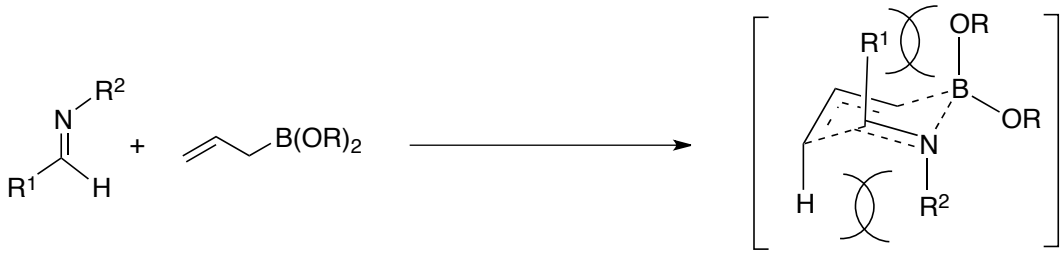
Scheme 3.25. Attempted allylborations of electron-rich imines.

Because electron-donating groups on the nitrogen atom did not lead to any improvement, it was anticipated that imines with electron-withdrawing groups might enhance the reactivity. An increase in the electrophilicity of the imine carbon would make it more reactive toward a nucleophillic attack from the allylboron unit. A tosyl-substituted imine was employed in the allylboration reaction but even this attempt failed to produce an allylboration product and the starting materials were recovered (Scheme 3.26).



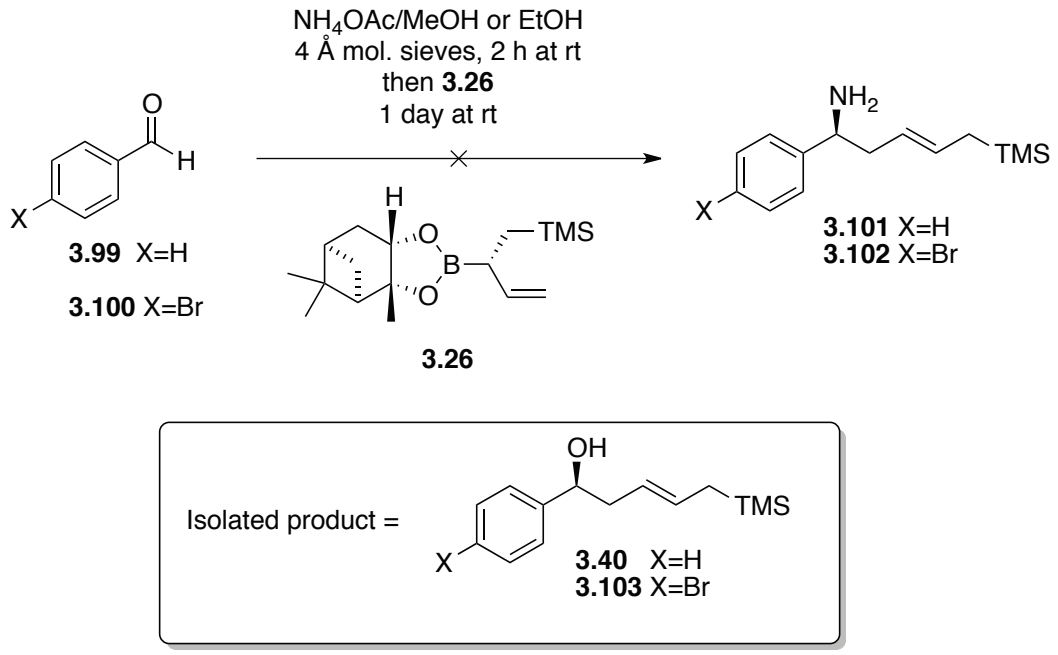
Scheme 3.26. Attempted allylboration of an electron-poor imine.

The failure of these allylborations of the indicated imines might be explained by the fact that all the imine substrates tested are substituted and are thus thermodynamically more stable in the *E*-configuration. Substituted imines would be more likely than unsubstituted imines to undergo steric interactions with an incoming nucleophile (such as the allylboronate in this case). These pseudo-diaxial interactions can significantly increase the activation energy barrier of the allylboration reaction, making it slower (Scheme 3.27).



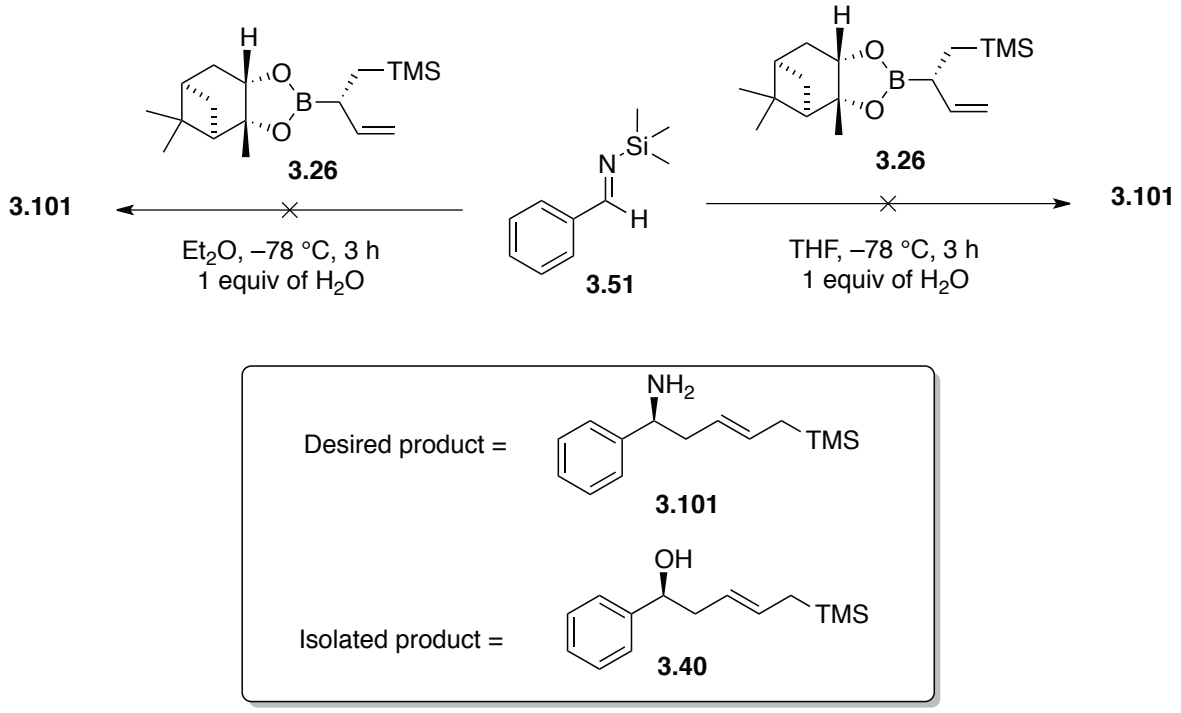
Scheme 3.27. Possible steric interactions with substituted imines.

A possible solution for this problem would be to make non-substituted primary imines in situ from the aldehydes. Non-substituted primary imines would be free of the bulky groups that tend to increase their stability and lifetime. Thus the reactivity of the imines would be improved. To achieve this objective two different aldehydes were treated with ammonium acetate in ethanol and methanol, and stirred for two hours to let the imines form. Then, the double-allylation reagent was added into the reaction mixture as a solution in either ethanol or methanol.[27] The product of this reaction was the corresponding homoallylic alcohol and there was no sign of the desired homoallylamine (Scheme 3.28).



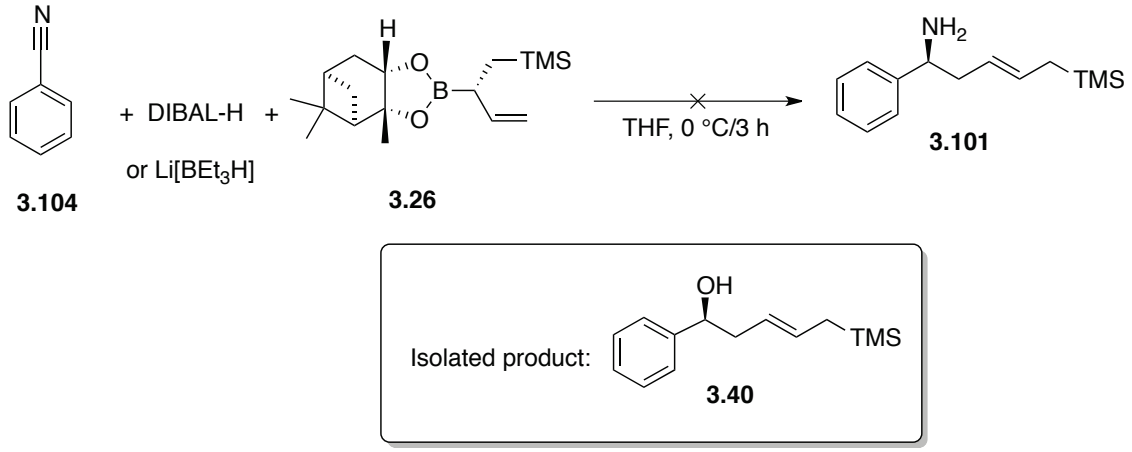
Scheme 3.28. Attempted allylation with *in situ* generated primary imines generated from aldehyde and ammonia.

A similar approach was taken in which an unsubstituted imine was generated from the corresponding N-silylimine by treating it with water or methanol followed by reaction with the double-allylation reagent.[20] Similarly to previous attempts, a homoallylic alcohol product formation was observed (Scheme 3.29).



Scheme 3.29. Attempted allylation with primary imines generated *in situ* from N-silylimine.

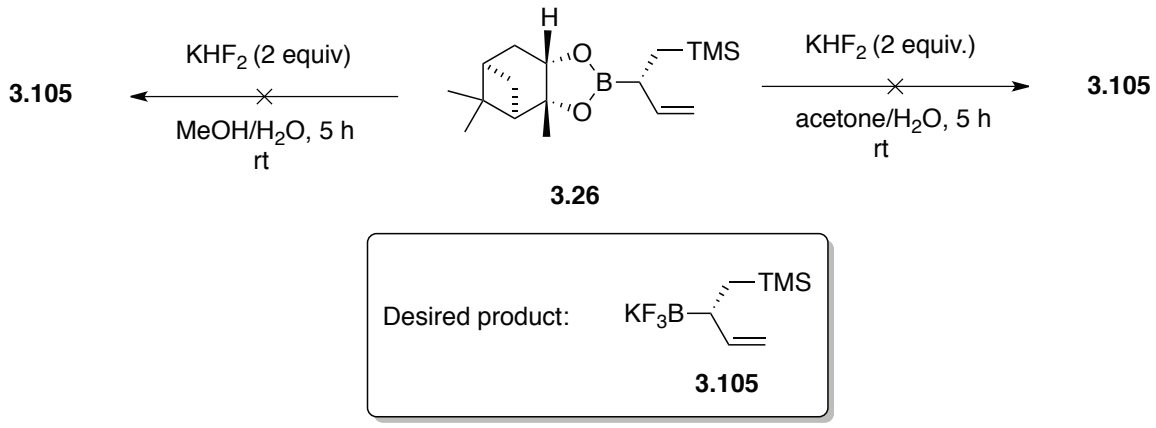
Another approach taken was to make the desired imines from nitriles through reduction with DIBAL or lithium triethylborohydride (Super Hydride®) and then trying to capture the imine with the boron reagent. Even this attempt failed and afforded only the undesired homoallylic alcohol (Scheme 3.30).



Scheme 3.30. Attempted allylation with N-substituted primary imines generated *in situ* from nitrile reduction.

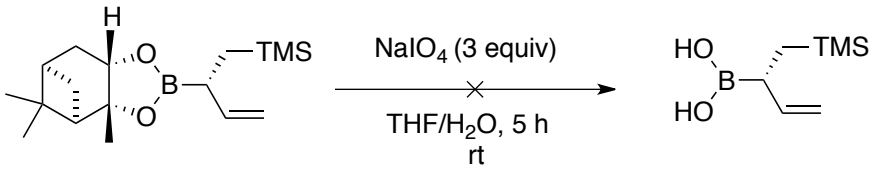
The failures noted above might be explained by the fact that the allylboronate reagent reacts very slowly, even with unsubstituted imines, because of the steric repulsion caused by the bulky pinanediol auxiliary. The imine, which is unstable and prone towards hydrolysis can revert back to the parent aldehyde. This aldehyde reacts much faster with the reagent giving the homoallylic alcohol as the product instead of the desired homoallylic amine. Thus, attempts were made to change the bulky pinanedioxy group on boron and to replace it with a less sterically demanding scaffold. As described in previous studies it is noteworthy that the pinanediol moiety of this reagent has very little influence on the stereochemical induction into the homoallylic alcohol or amine.[16] It is the stereogenic center α to the boron atom that guides the stereochemical outcome. However, all these attempts to transesterify the boronate proved to be ineffective and either the starting material was recovered or the reaction led towards complete decomposition of the starting allylboronate reagent beyond recovery.

At first, efforts were made to convert the reagent (**3.26**) to the corresponding trifluoroborate salt (**3.105**) by known procedures.[30] This would replace the bulky pinanediol unit with small F-atoms which perhaps would impart low steric influence. But treatment of **3.26** with KHF_2 in two different solvents yielded only the starting material back (Scheme 3.31).



Scheme 3.31. Attempted synthesis of trifluoroborate salts.

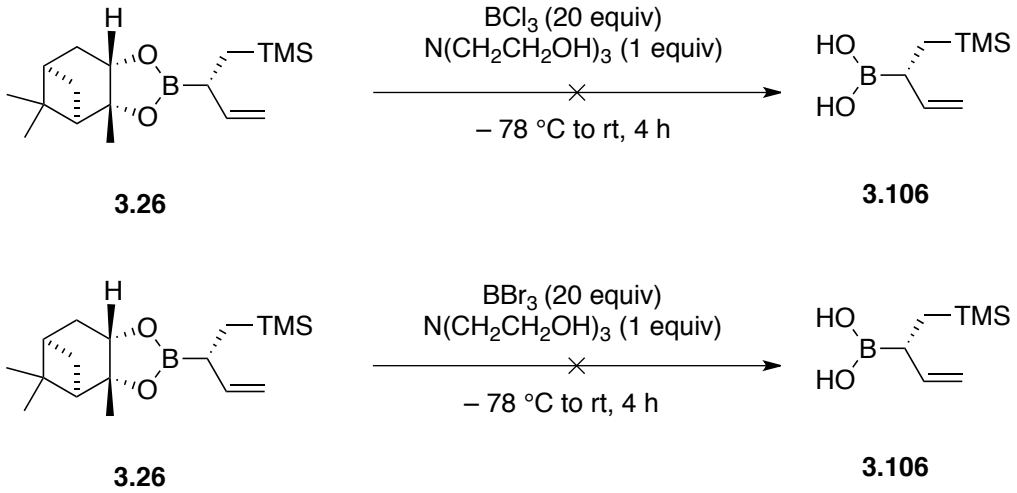
Then efforts were made to convert the boronic ester into the corresponding boronic acid. Boronic acids are far more reactive than their corresponding esters.[31a] Also, these acids can be transformed into less sterically demanding boronate esters if required. However, known procedures for oxidative cleavage of boronate esters using $NaIO_4$ proved to be ineffective (Scheme 3.32).[31b]



3.26 **3.106**

Scheme 3.32. Attempted oxidative cleavage of double-allylation reagent.

When the methods described above did not produce the desired homoallylamine, harsher methods were implemented. BCl_3 and BBr_3 were used to hydrolyse the boronate and triethanolamine was added to capture the boronic acid. It was expected that triethanolamine would form a complex with the boronic acid and the solid complex would precipitate. However, no solid complex was formed (Scheme 3.33).



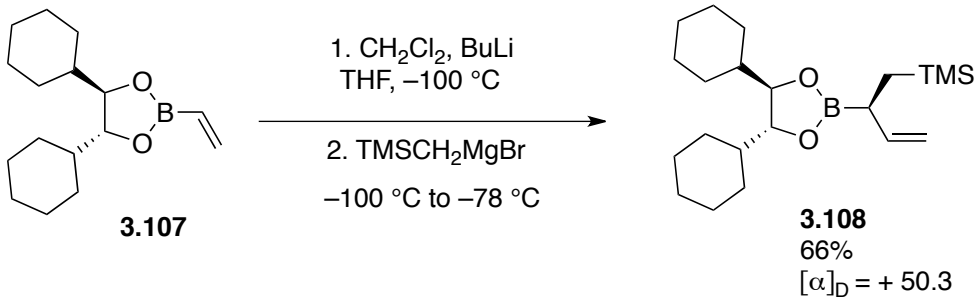
3.26 **3.106**

3.26 **3.106**

Scheme 3.33. Attempted hydrolysis of the boronate unit of **3.26**.

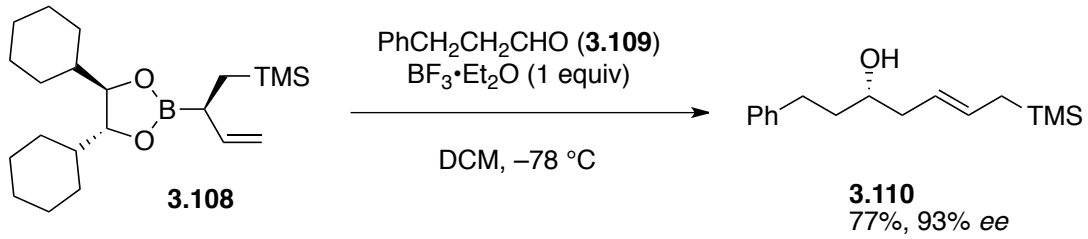
Since none of these methods could remove the pinanediol moiety, we moved to identify a chiral auxiliary that would be an efficient stereoinducer, but is at the same time sterically less encumbering than the pinanediol moiety. One such auxiliary is (*R*,*R*)–DICHED (1,2-dicyclohexylethane-1,2-diol), which has been exploited by the Matteson group in asymmetric synthesis of alkylboronic esters.[32]

The new reagent **3.108** was prepared by following the same procedure previously used in the synthesis of the pinanediol derived double allylation reagents (Section 3.4, Scheme 3.8) (Scheme 3.34). The stereochemistry of the reagent was assigned based on Matteson's work.



Scheme 3.34. Synthesis of new double allylation reagent derived from (*R*,*R*)-DICHED.

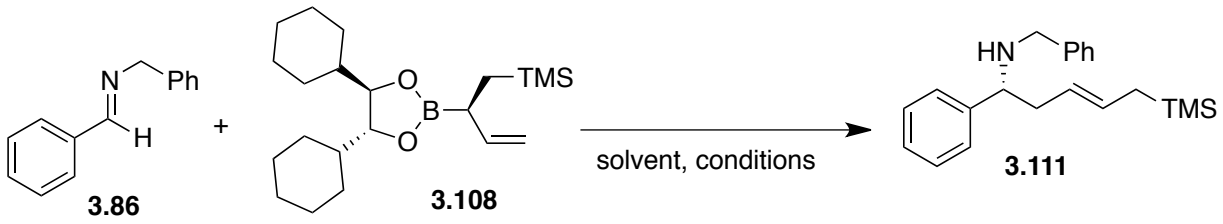
This reagent **3.108** afforded a homoallylic alcohol in good yield and excellent *ee* when subjected to an allylboration reaction with an aldehyde (Scheme 3.35).



Scheme 3.35. Allylboration of an aldehyde with a double allylation reagent derived from *R*,*R*-DICHED.

With the new allylation reagent **3.108** in hand, we decided to optimize the conditions for our desired imine allylboration reaction. N-benzylidinebenzylamine (**3.86**) was chosen again as the imine partner. At first solvents were optimized (Table 3.1).

Table 3.1: Conditions and outcomes of the allylboration of **3.86** with **3.108** in different solvents.[a]



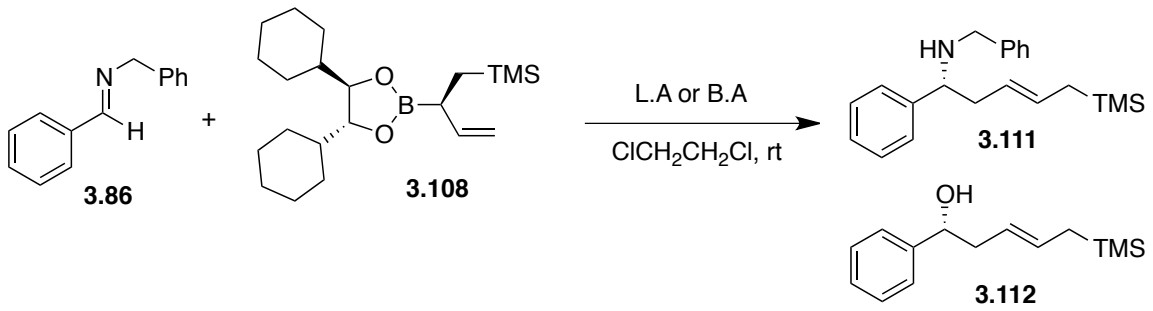
Solvent	Conditions	Outcome (yield/*ee*)[b]
Toluene	reflux/6 days	45% yield
CH_2Cl_2	reflux/6 days	40% yield
$ClCH_2CH_2Cl$	reflux/5 days	60% yield, >95%
Chloroform	reflux/5 days	52% yield
Diethylether	reflux/7 days	Negligible

a) 0.2 mmol of imine was reacted with 0.25 mmol of B/Si-reagent in the presence of 4 Å mol. sieves in 3 mL of solvent.

b) All yields are isolated yields; *ee*'s were measured by chiral HPLC

Dichloroethane (DCE) proved to be the best solvent for the allylboration of **3.86** with **3.108**, affording 60% yield and >95% *ee*. Enantioselectivity was determined only for the reaction with the best yield. The success of the allylboration reaction in DCE can be ascribed to a combination of factors such as the comparatively higher polarity of DCE (ε_{Tol} = 2.38, ε_{DCM}= 8.93, ε_{DCE}= 10.36, ε_{CHCl3}= 4.81, ε_{ether}= 4.33) and the relatively high boiling point of DCE that allowed a much facile reaction, among other factors.[33] The reaction in ether afforded a lower conversion because of the capability of ether to bind with the Lewis acidic boron atom, which would render reagent **3.108** less reactive. It was subsequently attempted to enhance the rate of the allylboration of **3.86** with **3.108** by employing various Lewis and Brønsted acids (Table 3.2).

Table 3.2: Conditions and outcomes of the allylboration of **3.86** with **3.108** in the presence of different Lewis and Brønsted acids.[a]



Lewis acid	Time	Product	Yield (%)
BBr_3	5 days	**3.111**	44
$TiCl_4$	5 days	**3.111** + **3.112**	12 + 65
$SnCl_4$	5 days	**3.111** + **3.112**	14 + 70
$ZnCl_2$	5 days	**-**	N/A
$Sc(OTf)_3$	5 days	**-**	N/A
$La(OTf)_3$	5 days	**-**	N/A
TsOH	2 days	**3.112**	82

a) 0.2 mmol of imine was reacted with 0.25 mmol of B/Si-reagent in the presence of 0.2 mmol of acid and 4 Å mol. sieves in 3 mL of solvent.

Although different Lewis acids and Brønsted acids were attempted, none of them were observed to be useful. In the presence of $TiCl_4$ and $SnCl_4$, a mixture of products were obtained. It is assumed that the imine had been hydrolysed into an aldehyde in the presence of those acids and had then undergone the allylboration to afford the homoallylic alcohol side product. The source of adventitious water is not clear at this stage; however, it can be hypothesized that it may come from the Lewis acids. The possibility of the solvent as the source of moisture is less likely but can not be completely ruled out.

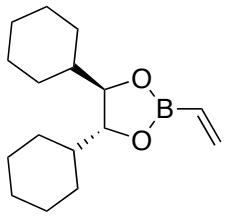
3.8 Conclusion

To conclude, a detailed investigation of the imine allylboration with B/Si-double allylation reagent **3.108** was performed. The reagent derived from (*R*,*R*)-pinanediol (**3.26**) failed to yield any desired homoallylic amine product. Steric repulsion from bulky pinanediol unit of this reagent may be the reason behind the failure. A less sterically demanding reagent prepared from (*R*,*R*)-dicyclohexylethanediol, **3.108** proved to be effective, affording moderate yield and good enantioselectivity.

3.9 Experimental details: general Information

All reactions were performed in standard, flame-dried glassware under an inert atmosphere of nitrogen. Unless otherwise specified, reagents were bought from commercial suppliers and used without further purification. Solvents were dried either by distillation or by using a solvent system purchased from MBRAUN. Anhydrous Na_2SO_4 or $MgSO_4$ were used as the drying agent after aqueous workup. All substrates were purified by silica gel chromatography before use. Evaporation and concentration *in vacuo* were accomplished at water aspirator pressure. Reaction products were purified by column chromatography using silica gel-60 (230-400 mesh). Reactions were monitored by thin layer chromatography with precoated glass plates covered with 0.2 mm silica gel . The spots were visualized by UV light, $KMnO_4$ or anisaldehyde stain. IR spectra were obtained with a Nicolet Magna-IR-750 spectrometer (cm^{-1}, cast film or neat). ^1H, ^{11}B, ^{13}C NMR spectra were obtained on a Varian Inova-300, 400 or Varian Unity-500 instruments, at 27 $^{\circ}C$ in $CDCl_3$. Residual solvent peaks (7.26 ppm for ^1H and 77.0 ppm for ^{13}C) were employed as reference. Accuracy for coupling constants (J-values) is estimated to be +/- 0.2 Hz. EI MS (m/z) was measured in a Kratos MS50 instrument. Optical rotation as recorded using a Perkin Elmer 241 polarimeter using the Sodium D line (589 nm) with a cell length of 10.002 cm. Optical purities of the products were measured by chiral HPLC using Chiralcel OD or Chiralpak AS column.

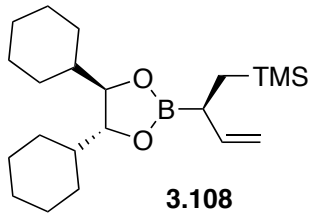
Preparation of vinylboronic acid ester (3.107):



Vinylmagnesium bromide (15 mL, 1.0 M solution in THF) was added dropwise to a THF (20 mL) solution of $B(OCH_3)_3$ (12 mmol) at –78 °C. After stirring this mixture for 3 hours, the reaction mixture was added to a 2.0 M solution of HCl and ice. After that the organic layer was extracted with diethyl ether. The combined organic layers were dried over anhydrous Na_2SO_4. All the sodium sulfate salts were removed by filtration. After removing the solvent the crude product was mixed with *R*,*R*-DICHED (1,2-dicyclohexylethane-1,2-diol, 10 mmol)[34] in ether in the presence of anhydrous $MgSO_4$ (40 mmol). This mixture was stirred for 12 hours. Then all the $MgSO_4$ salts were removed by filtration. The product was then purified by a flash chromatography on silica gel (5 % ether in pentane). Yield: 82%, collected as a colourless liquid. $[\alpha]^{22}_D$ = + 46.0 (c = 1.90, $CHCl_3$). IR (cast film, $CHCl_3$): 2926, 2853, 1618, 1449, 1433,

1253, 1223 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 19.6, 4.4 Hz, 1H), 6.0 (dd, *J* = 13.8, 4.4 Hz, 1H), 5.87 (dd, *J* = 19.6, 13.8 Hz, 1H), 3.9 (m, 2H), 1.83-1.59 (m, 11H), 1.43–0.96 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 83.4, 43.0, 28.3, 27.3, 26.4, 26.0, 25.9. ^{11}B NMR (159 MHz, $CDCl_3$) δ 29.3. EI HRMS calcd. for $C_{16}H_{27}BO_2$ (M+) 262.2001, found 262.2017.

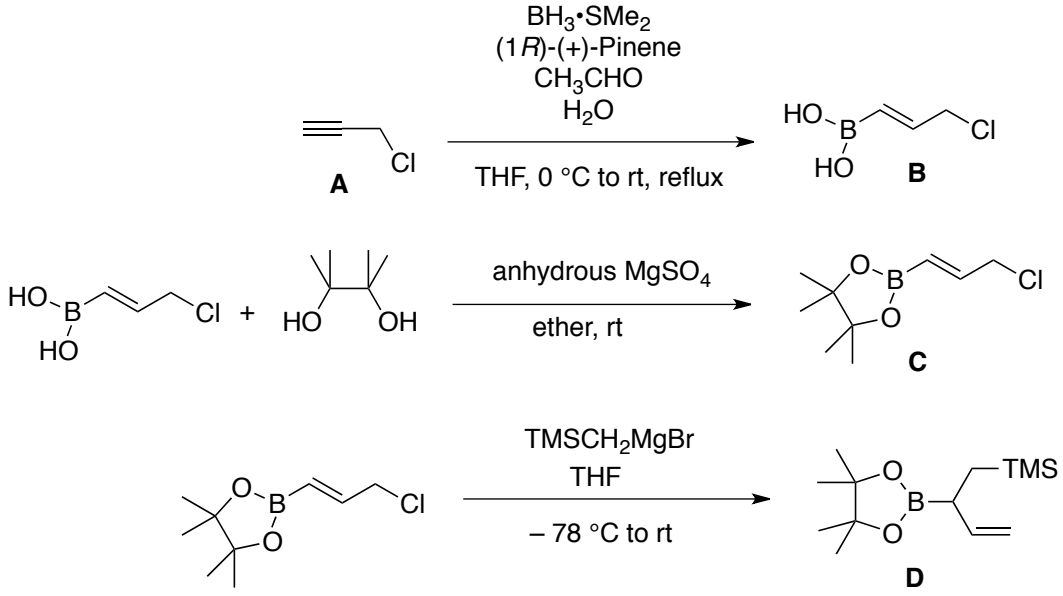
Preparation of B/Si-double allylation reagent ([(*R*,*R*)]-1,2-dicyclohexyl 2[(trimethylsilyl)methyl]-2-propen-1-yl, 1,3,2-dioxaborolane, 3.108):



3.108

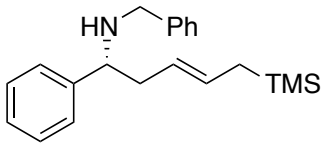
A solution of dichloromethane (8 mmol, 0.52 mL) in 10 mL of anhydrous THF was cooled to –100 °C (liquid N_2/ethanol bath). *n*-BuLi (5mmol) was added by dripping on the inside wall of the flask over a period of 6 minutes. After that the reaction mixture was stirred for 30 minutes and the vinylboronic acid ester, **3.107** (5 mmol) in 5 mL of THF was added in one portion. After keeping at this temperature for 5 minutes, the reaction mixture was warmed up to 0 °C and stirred at that temperature for 45 minutes. The homologation occurred at this time period and the mixture changed from colourless to grey. At this stage, the reaction mixture was cooled down to –78 °C and a freshly prepared solution of $TMSCH_2MgBr$ (5 mmol) in 6 mL THF was added slowly over a period of 2 minutes. The mixture was stirred for 6 h at that temperature. After that, a saturated aqueous NH_4Cl solution was added to the reaction mixture and allowed to warm up to room temperature. The product was extracted with ether and the organic layers were combined and dried over anhydrous $MgSO_4$. After filtering off all the $MgSO_4$, the solvent was removed and the grey liquid was subjected to column purification (1-4% diethyl ether in pentane). Yield: 70%, collected as a colourless liquid. $[\alpha]^{22}_{D}$ = +50.3 (c = 1.60, $CHCl_3$). IR (cast film, $CHCl_3$): 2926, 2854, 1627, 1450, 1392, 1351, 1246 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 18.0, 9.5, 9.0 Hz, 1H), 5.0 (ddd, *J* = 18.0, 2.0, 1.5 Hz, 1H), 4.9 (ddd, *J* = 9.5, 2.0, 1.0 Hz, 1H), 3.84-3.80 (m, 2H), 1.99-1.95 (m, 1H), 1.83-1.59 (m, 11H), 1.43–0.96 (m, 11H), 0.87 (dd, *J* = 15, 7.5 Hz, 1H), 0.70 (dd, *J* = 15, 7.5 Hz, 1H), 0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.3, 112.1, 83.4, 43.0, 28.3, 27.5, 26.5, 26.4, 26.0, 17.0, -0.9. ^{11}B NMR (159 MHz, $CDCl_3$) δ 33.0. EI HRMS calcd. for $C_{21}H_{39}BO_2Si$ (M+) 362.4310, found 262.4258.

Preparation of racemic-B/Si-double allylation reagent (4,4,5,5-tetramethyl-2[(trimethylsilyl)methyl]-2-propen-1-yl,1,3,2-dioxaborolane, D):



Intermediates **B** and **C** were prepared by following the procedure reported by Hall and co-workers.[35] A freshly prepared solution of $TMSCH_2MgBr$ (11 mmol) in THF was added drop wise into a 15 mL THF solution of **C** (10 mmol) at –78 °C over a period of 15 minutes. The mixture was stirred at that temperature for 4 hours and then was allowed to warm up to room temperature. After 1 day, the reaction was quenched by the addition of NH_4Cl. The product was extracted with diethyl ether, dried over anhydrous Na_2SO_4, filtered, evaporated and purified by column chromatography (2% diethyl ether in pentane). Yield: 83%, collected as a colourless liquid. IR (cast film, $CHCl_3$): 2923, 2851, 1619, 1442, 1410, 1389, 1347, 1229 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.8, 9.4, 8.6 Hz, 1H), 5.0 (ddd, *J* = 17.5, 1.8, 1.2 Hz, 1H), 4.9 (ddd, *J* = 9.4, 1.8, 1.0 Hz, 1H), 3.84-3.80 (m, 2H), 1.92 (q, *J* = 8 Hz, 1H), 1.2 (s, 12H), 0.85 (dd, *J* = 15, 7.5 Hz, 1H), 0.70 (dd, *J* = 15, 7.5 Hz, 1H), 0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 112.2, 83.0, 24.6, 16.6, -0.9. ^{11}B NMR (159 MHz, $CDCl_3$) δ 33.2. EI HRMS calcd. for $C_{12}H_{21}BO_5$ (M+) 256.1000, found 256.0870.

Procedure for the asymmetric imine allylboration with B/Si-double allylation reagent (N-(phenyl)-[(2*E*)-4-trimethylsilyl)-2-buten-1-yl]-benzenemethanamine, 3.111):



Molecular sieves (30 mg, 4 Å) were added into a solution of N-benzylidinebenzylamine (0.2 mmol) and B/Si-double allylation reagent (0.25 mmol) in 3 mL of dry DCE. The mixture was refluxed for 5 days. After that the reaction mixture was purified by silica gel chromatography (5-15% ethyl acetate in hexane) directly without any workup. The product (**3.111**) was then converted into the corresponding trifluoroacetamide derivative by treating the amine with trifluoroacetic anhydride (2 equiv) in the presence of triethylamine (4 equiv). This derivative was a mixture of rotamers and was used for chiral HPLC analysis.[36] Yield: 60%, collected as a pale yellow liquid. $[\alpha]^{22}_{D}$ = +22.9 (c = 1.20, $CHCl_3$). IR (cast film, $CHCl_3$): 3062, 3026, 2953, 2900, 2834, 1602, 1493, 1453, 1247, 1154, 852 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.4 - 7.3 (m, 10H), 5.5-5.4 (m, 1H), 5.2-5.12 (m, 1H), 3.83 - 3.72 (m, 2H), 3.61 - 3.58 (m, 1H), 2.45 - 2.35 (m, 2H), 1.9 (brs, 1H), 1.46 (d, *J* = 8 Hz, 2H), 0.0 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 140.7, 129.9, 128.4, 128.3, 128.2, 127.4, 126.9, 126.8, 125.1, 62.5, 51.7, 42.4, 22.9, -1.9. EI HRMS calcd. for $C_{21}H_{29}NSi$ (M+) 324.2142, found 324.2141. HPLC : Chiralcel OD, 2.5% *i*-PrOH/Hexane, 0.5 mL/minute, mixture of rotamers, major peak at 8.14 min., minor peak at 7.25 min., >95% *ee*.

3.10 References

1. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
2. Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693.
3. a) Roush, W. R., Gover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563. b) Roush, W. R., Gover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567.
4. a) Roush, W. R., Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413. b) Micalizio, G. C., Roush, W. R. *Org. Lett.* **2000**, *2*, 461.
5. Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245.
6. Micalizio, G. C., Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.
7. a) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644. b) Li, F.; Roush, W. R. *Org. Lett.* **2009**, *11*, 2932.
8. a) Winbush, S.A.M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 4344.
9. a) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509. b) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411. c) Hicks, J. D.; Roush, W. R. *Org. Lett.* **2008**, *10*, 681.
10. Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 533.
11. Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375.
12. Williams, D. R.; Claeboe, C. D.; Bo, L.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866.
13. Sarkar, T.K.; Haque, S.A.; Basak, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1417.
14. Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1.* **1998**, 2733.
15. a) Peng, Z.-H. Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379. b) Peng, Z.-H. Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675.
16. Peng, F. Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.
17. a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, *17*, 2815. b) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339.
18. Yamamoto, Y.; Nishii, S.; Kazuhiro, M.; Komatsu, T.; Wataru I. *J. Am. Chem. Soc.* **1986**, *108*, 7778.
19. Itsuno, S.; Katsuhiro,W.; Koichi, I.; El-Shehawy, A. A.; Ali, A. S. *Angew. Chem. Int. Ed.* **1997**, *36*, 109.
20. Chen, G.M.; Ramachandran, P.V.; Brown, H.C. *Angew. Chem. In. Ed.* **1999**, *38*, 825.
21. Katsuhiro,W.; Koichi, I.; Itsuno, S.*Tetrahedron Asym.* **1995**, *6*, 1531.
22. Katsuhiro,W.; Kuroda, S.; Yokoi, A.; Koichi, I.; Itsuno, S. *J. Organometallic Chem.* **1999**, *581*, 103.
23. Ramachandran, P. V.; Biswas, D. *Org. Lett.* **2007**, *9*, 3025.
24. Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712.
25. Wu, T.R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.
26. Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.

27. Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182.
28. Ramadhar, T. R.; Batey, R. A. *Synthesis* **2011**, 1321.
29. Li, S-W.; Batey, R. A. *Chem. Commun.* **2004**, *12*, 1382.
30. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.
31. a) Brown, H. C.; Racherla, U.S.; Pellechia, P.J. *J. Org. Chem.* **1990**, *55*, 1868. b) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.*, **2007**, *9*, 757.
32. a) Matteson, D. S.; Soundararajan, R.; Ho, O. C.; Gatzweiler, W. *Organometallics*. **1996**, *15*, 152. b) Matteson, D. S.; Singh, R. P.; Schafman, B.; Yang, J. *J. Org. Chem.* **1998**, *63*, 4466. c) Matteson, D. S.; Man, H-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560.
33. *depts.washington.edu/eooptic/linkfiles/dielectric_chart[1].pdf*
34. Scott, M. S.; Lucas, A. C.; Luckhurst, C.A.; Prodger, J. C.; Dixon, D. J. *Org. Biomol. Chem.* **2006**, *4*, 1313.
35. Gravel, M., Toure, B. B., Hall, D. G. *Org. Prep. Proc. Intl.* **2004**, *36*, 573.
36. Fernandes, R. A.; Nallasivam, J. L. *Org. Biomol. Chem.*, **2012**, *10*, 7789.

Chapter 4

Synthetic studies towards fluoro and trifluoromethyl allylboronate

4.1: Introduction: fluorinated organic molecules

Although fluorine is present in nature in many forms such as fluoride, fluoroapatite, and cryolite, there have been only close to a dozen organic compounds possessing fluorine atom found in nature to date (Figure 4.1).[1] Despite of its scarcity in natural sources, huge number of compounds with fluorine atoms or fluorinated groups have been synthesized and reported. Fluorinated organic compounds possess unique properties that are often unmatched by compounds containing other elements.

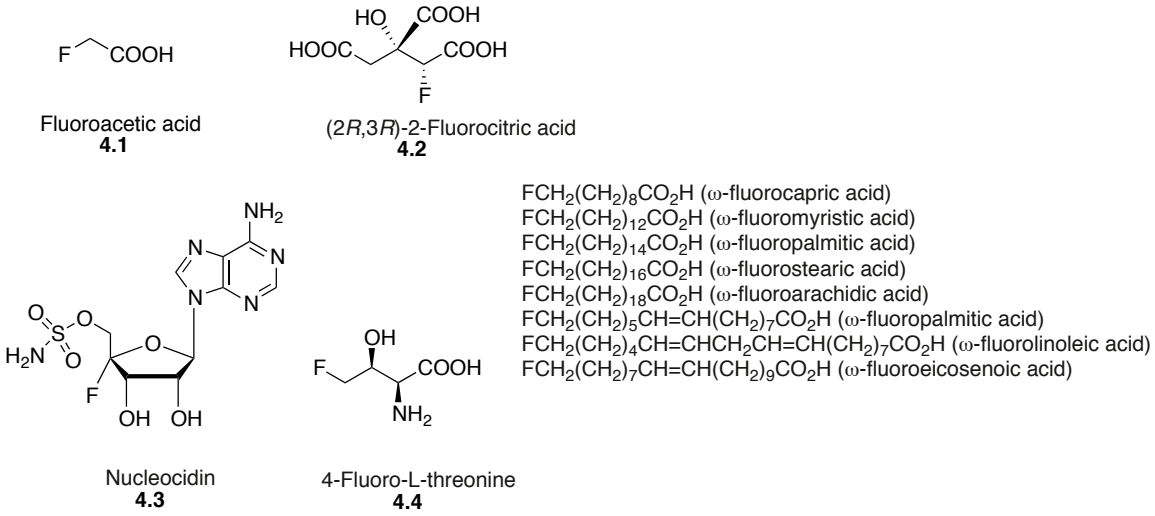


Figure 4.1. Naturally occurring fluorine-containing molecules.[1]

The following section presents a brief discussion on the various properties of organofluorine compounds.

4.2: Mimic effect and block effect

Table 4.1 represents major physical properties of fluorine in comparison with other elements. As it is shown, the van der Waals radius of fluorine is 1.47 Å compared to 1.20 Å for hydrogen, the only element similar in size. It is much smaller compared to other elements (*e.g*, Cl and Br are 46% and 54% larger than hydrogen, respectively).[1, 2] Similarly, the C–F bond length is 0.295 Å longer than the C–H bond when compared between CH_3F and CH_4. Furthermore it is 0.403 and 0.551 Å shorter than the C–Cl and C–Br bonds, respectively. Because of the similarity in size, fluorine can "mimic" hydrogen. Microorganisms and enzymes often can not differentiate between these two.

Table 4.1: Comparison of physical properties of hydrogen and other group XVII elements.

Properties	H	C	O	**F**	Cl	Br
Electronegativity[1]	2.20	2.55	3.44	**3.98**	3.16	2.96
van der Waals radius[2]	1.20	1.70	1.52	**1.47**	1.75	1.85
CH_3–X bond length[2]	1.08	1.53	1.42	**1.38**	1.78	1.93
CH_3–X bond energy[3]	103.1	88.0	90.2	**108.1**	81.1	67.9
Ionization potential[3]	313.9	259.9	314.3	**402.2**	299.3	272.7
Electron affinity[3]	17.42	29.1	3.7	**78.5**	83.4	77.6

1) Measured in electron volts.

2) Measured in Å

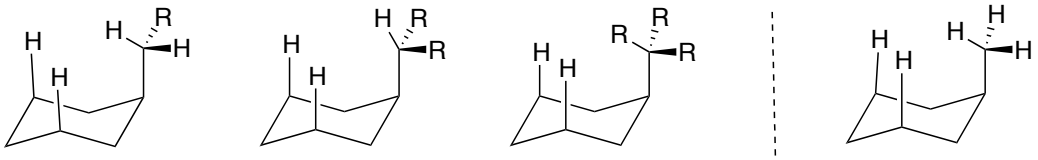
3) Measured in kcal/mol

Also the CH_3–F bond is stronger than that of CH_3–H by 5.0 kcal/mol. This explains why C–F bonds are resistant towards hydroxylation by the cytochrome P-450 family of enzymes, which is a very facile and common observation with C–H bonds. This feature is known as the "block effect". This strategy has been employed in several occasions to prevent deactivation of biologically active substances *in vivo.* For example, it was found that the hydroxylation of the methylene moiety at the side-chain of vitamin D_3 could

lead to deactivation before being excreted. In contrast when a difluoromethylene group was incorporated into the molecule, the undesired hydroxylation reaction at that site was prevented which led to better activity.[1,3,4]

4.3: Steric effect of fluorine and fluorine containing groups

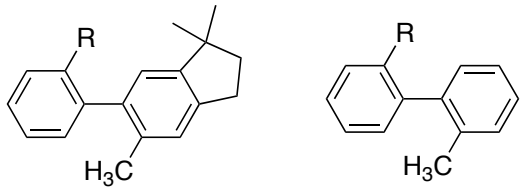
Usually the sizes of the fluorine containing groups are larger than the corresponding variants with hydrogen atom. Introduction of the fluorine atoms in a methyl group generally increases the steric bulk. Thus CH_2F is 20% bigger than CH_3. In the same way CHF_2 is 50% and CF_3 is 90% bigger compared to CH_3.[1,5a] A well-known representation of steric bulk is "*A*" value. *A* values are numerical figures which determine the most stable orientation of atoms in a molecule.[1,5b] Groups or atoms with higher *A* values present higher steric demands. In cyclohexane derivatives, substituents with higher *A* values prefer to occupy the equatorial positions to avoid steric repulsion from other substituents or hydrogen atoms. An interesting case is noted when the *A* values of fluorinated compounds are taken into consideration. As discussed earlier, CH_2F is bigger in size compared to CH_3 and hence should have a higher *A* value and higher preference for equatorial positioning. Instead, it displays an increased preference for the axial position. Likewise, CHF_2 should have a much bigger *A* value because of its size but it causes a rather small increment in *A* value. These observations can be explained by taking into consideration a specific conformation of the axial conformers of monosubstituted cyclohexanes bearing these substituents. As shown in Figure 4.2, the C–H of CH_2F and CHF_2 substituents occupies the *endo* position and bulkier fluorine atoms occupy *exo* positions to minimize 1,3-diaxial strain. However, when a CF_3 group is the substituent, the C–F has no other option but to take the *endo* position, which leads to greater 1,3-diaxial strain. This is reflected in the *A* value difference between CF_3 and CHF_2, which is much larger than that between CHF_2 and CH_2F. The same trend is observed for CH_3, CH_2CH_3, $CH(CH_3)_2$, and $C(CH_3)_3$ (Figure 4.2). *A* values for other F-containing substituents have recently been reported: C_2F_5 (2.67), CF_3S (1.18), CF_3O (0.79), and CH_3O (0.49).[1,6]



	4.5/4.6	**4.7/4.8**	**4.9/4.10**	**4.11**
R=F	1.59	1.85	2.37	1.70
CH_3	1.75	2.15	4.89	

Figure 4.2. Comparison of *A* values with 1,3-diaxial strains between fluorinated and non- fluorinated analogues of cyclohexane derivatives.[1,6]

Based on the comparison of rotational barriers along the biphenyl axis, the bulkiness of a CF_3 group was estimated. It was found that a CF_3 group is similar to that of a $(CH_3)_2CH$ group in terms of bulkiness (Figure 4.3).[1,7,8]



4.12 (R=CH_3, 338.2 kcal/mol)
4.13 (R=$(CH_3)_2CH$, 388.7 kcal/mol)
4.14 (R=CF_3, 384.6 kcal/mol)
4.15 (R=$(CH_3)_2CH$, 456.5 kcal/mol)
4.16 (R=CF_3, 459.0 kcal/mol)

Figure 4.3. Energy barriers for rotation of nonfluorinated substituted biphenyls and their fluorinated analogues.[1,7,8]

4.4: Lipophilicity of fluorine and fluorine containing groups

The two factors that control the distribution and absorption of a drug molecule in a body are lipophilicity and hydrophilicity. The correct balance between these two maintains the desired level of activity. Increased lipophilicity leads to enhanced blood-brain barrier permeability. On the other hand, change in pK_a values of functional groups results in favorable partition between polar media and less-polar binding sites. Usually, incorporation of fluorine or fluorinated groups increases the lipophilicity of organic compounds, especially aromatic compounds. Lipophilicity is expressed by Hansch π_X parameters. It has

been found that for monosubstituted benzenes, fluorobenzene has slightly higher π_X value compared to benzene, making it more lipophilic. On the other hand, it is interesting to note that chlorobenzene is much more lipophilic compared to benzene. In the same way, CF_3-Ph is 57% more lipophilic than CH_3Ph. When compared between CF_3-Y-Ph and CH_3-Y-Ph (Y = O, CO, CONH, SO_2), CF_3-Y-Ph is found to be substantially more lipophilic than CH_3-Y-Ph. In the former case, strongly electron-withdrawing CF_3 groups reduce the electron density on Y which in turn significantly reduces its H-bonding capability leading towards enhanced lipophilicity. Along the same lines, CF_3-arenes with amine, alcohol, ether, carbonyl, and amide substituents display diminished hydrogen-bond accepting capability in an aqueous phase, which leads to increased hydrophobicity and thus lipophilicity. However, the introduction of fluorine into aliphatic compounds results in a slight decrease in lipophilicity. Amines with fluorine substitution near the amino groups exhibit a large enhancement in lipophilicity due to the reduced amine basicity through the inductive effect of fluorine, leading towards the increase in the amount of the neutral amine component as opposed to the ammonium ion in equilibrium.[1,9,10]

4.5: Inductive effect of fluorine and fluorine containing groups

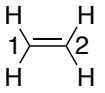
Due to the strong electron-withdrawing effect of fluorine and fluorinated groups, pK_a values of carboxylic acids, alcohols, or amines are significantly changed which drastically affect their physiological properties. Thus, binding affinity for the receptors or target enzymes, biological activities, and pharmacokinetics of fluorinated versions of bioactive compounds are radically changed. It has been observed that halogen substitution at the 2-position of acetic acid decreases the pK_a values in the order Br > Cl > F, which is qualitatively parallel to electronegativity (see Table 4.2). Fluorine, with the highest electronegativity, exerts the strongest effect (ΔpK_a = –2.17 compared to 4.76 for acetic acid) compared to non-fluorinated analogues. Further substitutions with two fluorines and three fluorines at this position increase the acidity even more (ΔpK_a = –3.43 and –4.26 respectively). Although introduction of a methylene group between CF_3 and CO_2H moieties diminishes the natural inductive effect of the CF_3 group, the pK_a of 3,3,3-trifluoropropanoic acids (3.06) is still substantially higher than propanoic acid (pK_a = 4.87) (ΔpK_a = –1.81). Introduction of strongly electron-withdrawing CF_3 groups to methanol dramatically increases the acidity of the resulting alcohols. Thus, pK_a values of CF_3CH_2OH, $(CF_3)_2CHOH$ and $(CF_3)_3COH$ are 12.39, 9.3 and 5.4, respectively. However, the decrease in pK_a value with the number of CF_3 groups reaches its limit with $(CF_3)_3COH$ which is only 0.7 larger than that of acetic acid.[1,11]

Table 4.2: Comparisons of pKa values of various compounds and their fluorinated analogues

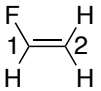
Compound	pK_a	Compound	pK_a	Compound	pK_a
CH_3CO_2H	4.76	$CH_3CH_2CO_2H$	4.87	$(CH_3)_2CHOH$	17.1
CH_2FCO_2H	2.59	$CF_3CH_2CO_2H$	3.06	$(CF_3)_2CHOH$	9.3
CH_2ClCO_2H	2.87	$C_6H_5CO_2H$	4.21	$(CH_3)_3COH$	19.0
CH_2BrCO_2H	2.90	$C_6F_5CO_2H$	1.7	$(CF_3)_3COH$	5.4
CHF_2CO_2H	1.33	CH_3CH_2OH	15.93	C_6H_5OH	9.99
CF_3CO_2H	0.50	CF_3CH_2OH	12.39	C_6F_5OH	5.5

Similarly, perfluorination of benzoic acid and phenol leads towards the increment in their acidity by 2.5 and 4.5 pKa units, respectively (Table 4.2). In these cases, the strong electronic repulsion between the lone pairs of five fluorine atoms on the ring forces the π-electrons in these perfluorinated arenes to the center of the ring. With the amines, on the other hand, the bioavailability and lipophilicty increases with the introduction of fluorine (s) due to the diminished basicity. A linear decrease in the pK_a values of ethylamines is observed upon successive fluorine introductions: $CH_3CH_2NH_2$ (10.7), $FCH_2CH_2NH_2$ (9.0), $F_2CHCH_2NH_2$ (7.3), and $F_3CCH_2NH_2$ (5.8).

An interesting feature of fluorinated olefins is the change in charge distribution among atoms. Carbon bearing fluorine atom (C^1) in a fluorinated olefin carries a significant amount of cationic charge, while C^2 atom experiences a substantial amount of negative charge (**4.18** and **4.19**). The strong electronic repulsion between the π-electrons of the carbon–carbon double bond and the lone pairs of fluorine can be considered the reason behind this phenomenon which is unique to fluoroethenes (**4.18** and **4.19**). The corresponding dichloroethenes (**4.20**), on the other hand, show much weaker "p–π repulsion" due to the lack of proper interaction between the 3p lone pairs of Cl and the $2p_z$ olefinic π-electrons along with the longer C–Cl bond (1.744 Å for **4.20** vs. 1.326 Å for **4.19**). Also, the unusually small F–C^1–F bond angle (109.5°) of **4.19**, which is 10.5° smaller than the angle observed generally for the sp^2 hybridization, points towards the significant amount of contribution of an $F^{(+)}$=C(F)–$^{(-)}$CH resonance structure along with the attractive electronic interaction between $F^{(+)}$ and F (Figure 4.4).[1,12,13]

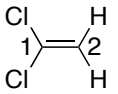


4.17
C¹ : –0.366
C² : –0.366
H-C¹-H bond angle : 116.5°



4.18
C¹ : 0.261
C² : –0.475
F-C¹-H bond angle : 111.5°

4.19
C¹ : 0.781
C² : –0.562
F-C¹-F bond angle : 109.5°



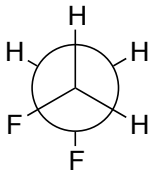
4.20
C¹ : –0.118
C² : –0.414
Cl-C¹-Cl bond angle : 114.2°

Figure 4.4. Charges on carbons in ethylenes and its fluoro analogues as estimated by *ab initio* calculations.[1,12,13]

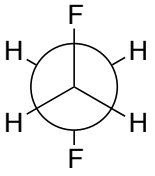
4.6: Gauche effect

Due to the lower-lying molecular orbitals owing to the strong electronegativity of fluorine, a C–F bond is a very good acceptor of electrons to its vacant $\sigma^*_{C\text{-}F}$ orbital from a vicinal electron-donating orbital, while it is a poor electron donor. These factors play very important roles in determining the three-dimensional structure of molecules. 1,2-Difluoroethane has two possible conformations, *gauche* and *anti*. It can be assumed that ***anti*-4.22** should be more stable, with two electron rich fluorine atoms away from each other, than *gauche*-**4.21** from both steric and electrostatic points of view. However, based on various spectroscopic analyses and computational modeling studies it as been concluded that the latter is stable by 1.0 kcal/mol.[1,14,15] This stabilization is achieved through the donation of electrons from the neighboring $\sigma_{C\text{-}H}$ orbital to the lower-lying vacant $\sigma^*_{C\text{-}F}$ orbital, which is only possible in the corresponding *gauche* isomer. For the *anti*-isomer, on the other hand, the corresponding donor orbital is a poor donor $\sigma_{C\text{-}F}$ (Figure 4.5). This phenomenon is known as the "*gauche effect*". However, such stabilizations are not observed with other vicinal 1,2-dihaloethanes as the increasing steric hindrance caused by two bigger halogens in the *gauche* geometry outweighs the energy gain through orbital interaction involving $\sigma^*_{C\text{-}Halogen}$. For example, 1-fluoro-2-chloroethane prefers the *anti* conformation over the *gauche* to avoid steric repulsion, as revealed by the computational analysis as well as experimental results.[1,16] Similar interaction of the $\sigma^*_{C\text{-}F}$ orbital with the lone pairs of fluorine is observed in fluorinated derivatives too. While the C–H bond length in these compounds is almost constant regardless of the number of fluorines in a molecule, the C–F bond length decreases as the number of fluorines increases due to substantial n_F–

σ^*_{C-F} interaction mentioned above. This, together with the strong positive charge developed on carbon may play a key role in strengthening C–F bonds in an electrostatic manner.[1,17]



4.21



4.22

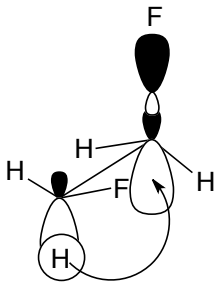


Figure 4.5. Preferred conformation of 1,2-difluoroethane and the orbital interaction.[1,14, 15]

4.7: Other electronic effects of fluorine related to the gauche effect

Just like the *gauche* effect discussed earlier, similar interaction of an electron-rich bond with the lower-lying vacant orbital of a polarized neighboring C–F bond (σ*C–F), has been clearly observed in $[(CH_3)_3N]_3S^+CF_3O^-$ (**4.23**) (Figure 4.6).[1,18] But in this case the oxygen atom of the counter-anion, CF_3O^-, of **4.23** plays the role of the donor as revealed by the significantly short C–O bond (1.227Å). The C–F bonds (1.390 and 1.397Å) were observed to be longer. This phenomenon point towards the effective orbital interaction of the electron rich n_O orbital with a lower-lying σ*C–F orbital, a phenomenon called "negative hyperconjugation".[1,19]

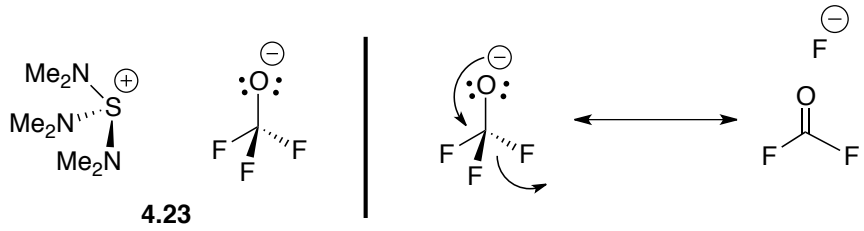
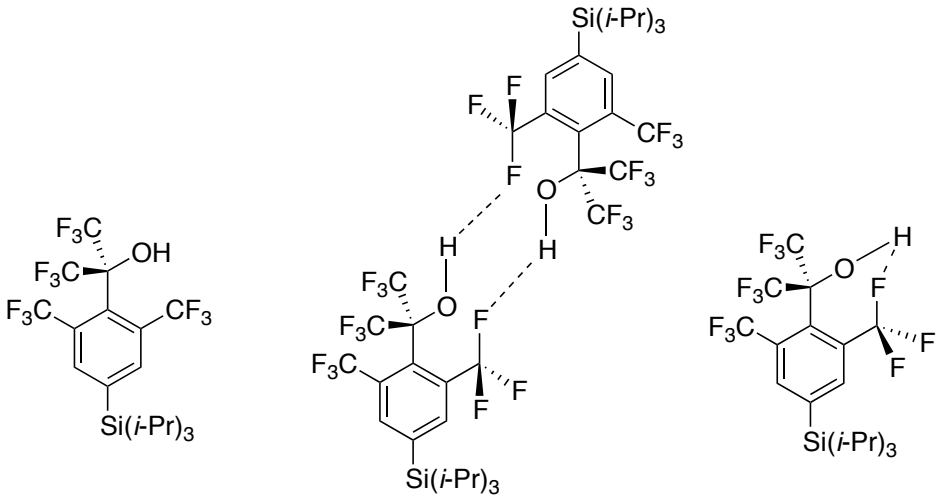


Figure 4.6. Negative hyperconjugation in CF_3–O^- anion.[1,18,19]

4.8: Hydrogen bonding

Fluorine with three sets of lone-pair electrons can participate in hydrogen bonding with different electron-deficient atoms intramolecularly or intermolecularly with relatively acidic hydrogens bonded to heteroatoms. In addition, perfluoroalkyl groups can change the hydrogen bonding abilities by increasing the acidity of functional groups such as alcohol, amine, amide, and carboxylic acid. For example, CF_3-containing benzylic alcohol **4.24** is a very suitable substrate for hydrogen bonding due to its acidity which is as high as or higher than that of phenol (Table 4.2 for hexafluoro-2-propanol). Apart from its acidity, its increased anionic character by negative hyperconjugation (Section 4.7) makes it a very good substrate for H-bonding too as revealed by the X-ray crystallographic analysis which shows the formation of a dimeric structure in the solid state through two strong intermolecular hydrogen bonds (H···F distance is 2.01 Å). The strength of this hydrogen bond can be explained by taking into consideration of the fact that the sum of the van der Waals radii of H and F (2.67 Å) is much higher than the observed H···F length (2.01 Å).[1,20] The same compound forms an intramolecular hydrogen bond in hexane solution (Figure 4.7).[1,21]



4.24 **Solid state**

Figure 4.7. Intermolecular and intramolecular H···F hydrogen bonding **4.24** in solid state and solution.[1,20,21]

4.9: Fluorine containing molecules as isosteres

Peptides, both natural and synthetic, are exploited as pharmaceutical drugs and bioactive agents due to their diverse range of biological properties. One major problem with these peptides are that they are often rendered inactive through key amide bond cleavage by various enzymes. However, if a key amide bond could be replaced with a non-cleavable bond, maintaining the characteristics and properties of the amide functionality, such inactivity can be avoided. One example, due to the substantial contribution of the imidate like zwitter ionic resonance structure **4.25B**, the free rotation around the C–N bond of peptide such as **4.25A** is partially restricted. Thus it might be possible to replace an amide linkage with a group of atom/atoms with similar molecular shape, volume, valence electron or electronic distribution but maintaining similar physical and biological properties. These groups of atom/atoms are known as isosteres or bioisosteres. Initially a *trans*-olefin unit was attempted as the "peptide isostere" of enkephalin but it failed to give a desirable effect.[1,22] The computational analysis of a model amide, N-methylacetamide (**4.26**) and its isosteres revealed that the fluoroolefin **4.28** (isoelectronic with **4.26**) resembled **4.26** much more closely than **4.27** (not isoelectronic). The oxygen atom of the model amide, **4.26** bears a significant amount of negative charge while the carbonyl carbon is highly positive. Also it consists of a highly negative nitrogen atom along with a very positive NH hydrogen. On the other hand, **4.27** has a non-polarized C=C bond with CH hydrogen carrying weakly positive charge. Thus there is very little electronic similarity between **4.27** and **4.26**. **4.28** on the other hand, has an appropriately polarized

C=C double bond, a negative fluorine atom in place of the oxygen atom of amide **4.26**, and a positive CH in place of the NH moiety of amide **4.26**. Thus, **4.28** indeed mimics **4.26** electronically. Another structure which can mimic **4.26** is **4.29** with a non-polarized C=C bond, a modestly positive CH hydrogen, and three negative fluorine atoms. However, sterically the CF_3 group is much bulkier than an oxygen atom and not isoelectronic either. Hence it does not qualify as a suitable isostere (Figure 4.8).[1,23]

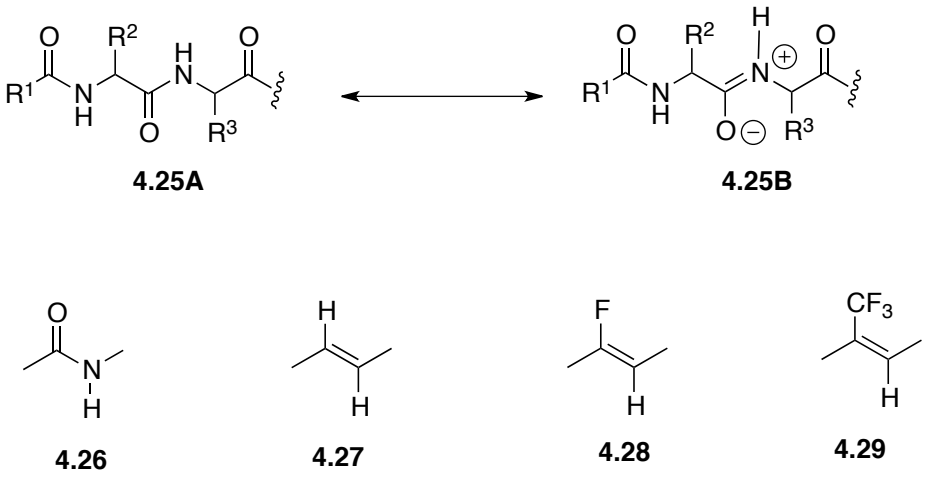


Figure 4.8. Peptide **4.25**, its resonance form, amide **4.26**, and different alkene isosteres.[1,23]

4.10: Applications of fluorinated organic molecules

Because of these unique range of properties just discussed, organofluorines have been heavily exploited in industry. Many fluorinated molecules are used as drugs and pharmaceutical agents. In fact, 20% of the drugs today have at least one fluorine atom present (Figure 4.9).[24]

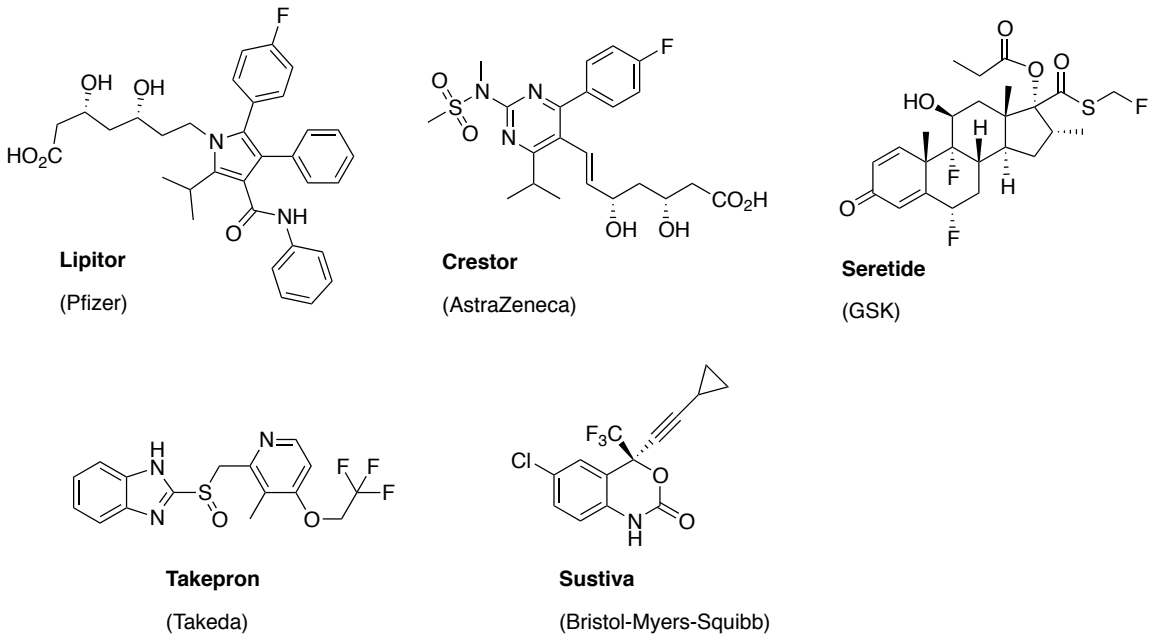


Figure 4.9. Structures of pharmaceutical drugs with fluorine atom/atoms.[24]

Apart from being used as drugs, many organofluorine compounds are used as extremely useful materials (Figure 4.10). Teflon® and Gore-Tex® are two popular commercial materials containing flurorine atoms.[25]

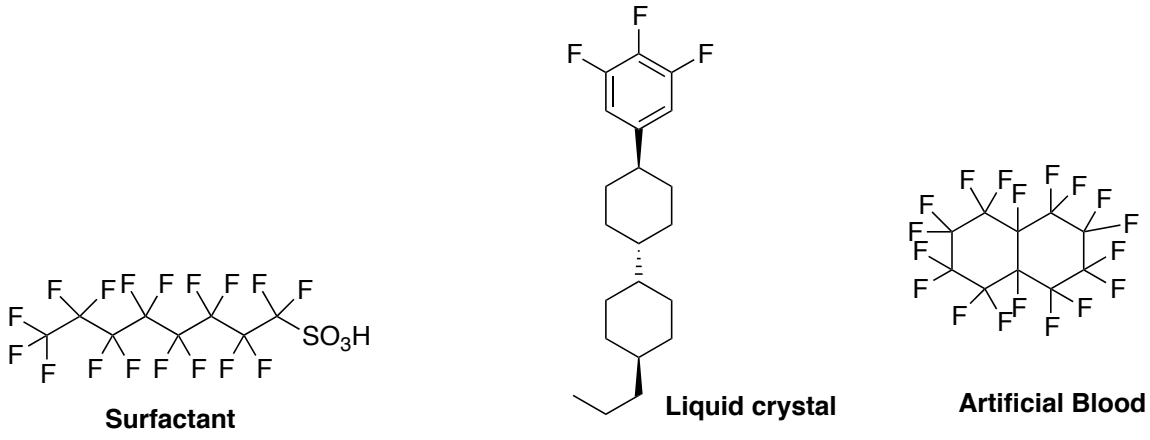


Figure 4.10. Important fluorine-containing materials.[25]

Apart from these applications, fluorinated molecules are also heavily employed in PET imaging, an area which is becoming very popular in cancer treatment.[26] Due to all these reasons discussed above, synthetic methodologies for fluorinated organic molecules are in high demand. There are many reported fluorinating reagents and procedures. A brief discussion of various fluorination and trifluoromethylation

methods is described in the next section.

4.11: Synthetic methods for fluorination

The various methods of synthesizing fluorinated molecules can be divided into four major classes:

1) Electrophilic fluorination.

2) Nucleophilic fluorination.

3) Electrochemical fluorination.

4) Metal catalyzed fluorination.

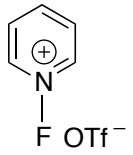
There are several fluorinating reagents known in the literature which can be employed to incorporate fluorine atom/atoms in a molecule (Figure 4.11).

Inorganic reagents: AgF_2, CoF_3, $CsSO_4F$, HgF_2, $PbF_2(OAc)_2$

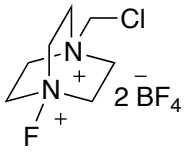
Ammonium fluorides: $Et_3N{\cdot}3HF$ (TREAT-HF), (HF)x.Pyr (PPHF, Olah's reagent)

Hypofluorites: CH_3COOF, CF_3COOF, CF_3OF

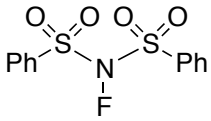
N-Fluoro reagents:



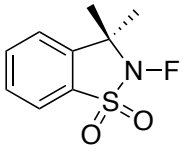
4.30



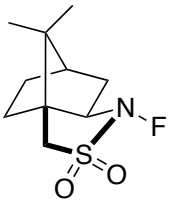
4.31



4.32 (NFSI)



4.33



4.34

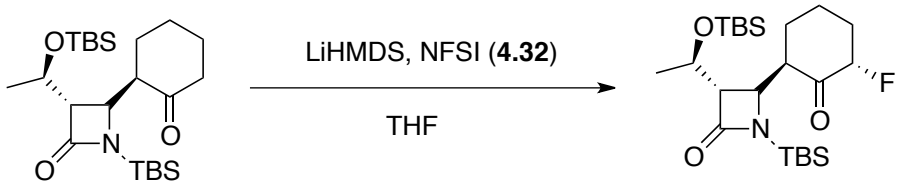
Fluoroaminosulfuranes: $(Me_2N)_3S(Me)_3SiF_2$ (TASF)

Other Reagents: $PhIF_2$, BF_3 , XeF_2

Figure 4.11. Important flurorination reagents.

4.12: Electrophilic fluorination

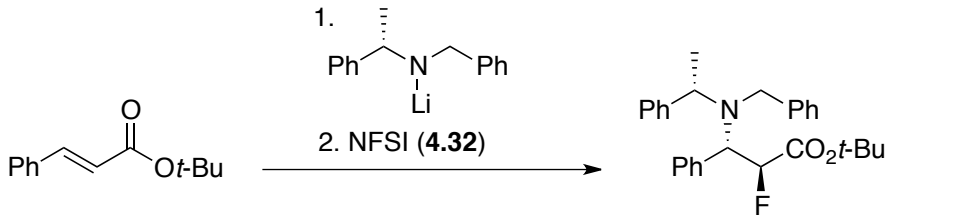
There are many reported fluorination methods in the literature. The most common strategy is to treat an enolate with an electrophilic fluorinating reagent such as **4.30**, **4.31**, **4.32**, and **4.34**. Here the racemic electrophilic fluorination will be discussed first. Poss and coworkers reported the first selective γ-fluorination of various steroids as exemplified on 4-cholesten-3-one.[27] A fluorinated member of a new family of β-lactam antibiotics was prepared by fluorination of the lithium enolate of **4.35** with NFSI (**4.32**, N–fluorobenzenesulfonimide). This method, reported by Perboni, gave very high yield but lower distereoselectivity (Scheme 4.1).[28]



4.35 **4.36** 95%, 40% *de*

Scheme 4.1. Fluorination of a β-lactam derivative reported by Perboni.[28]

Duggan and co-workers reported the synthesis of β-amino-α-fluoro ester **4.38** by the tandem conjugate addition of a chiral lithium amide on a cinnamate derivative followed by electrophilic fluorination with NFSI. This method afforded almost quantitative yield with moderate diastereoselectivity (Scheme 4.2).[29]

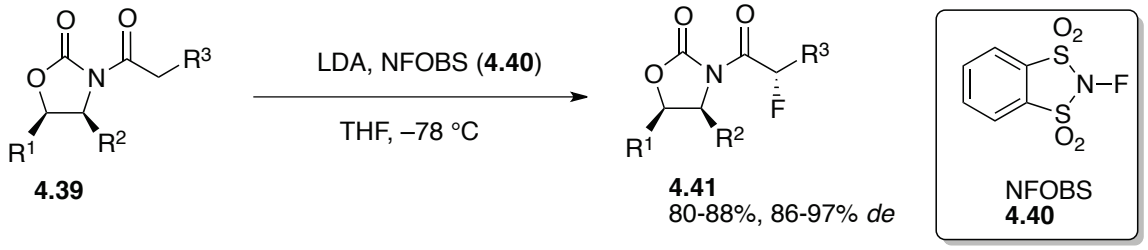


4.37 **4.38** quantitative, 64% *de*

Scheme 4.2. Fluorination of cinnamate ester via conjugate addition reported by Duggan.[29]

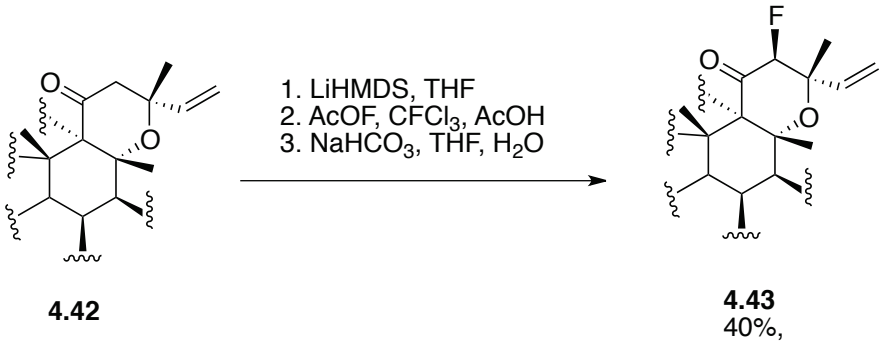
A chiral auxiliary based approach with Evans' oxazolidinone was reported by Davis and co-workers.[30]

Good to excellent diastereoselectivities were obtained when the fluorinating agent, NFOBS (**4.40**, N-fluoro-*o*-benzenedisulfonimide) approached the less hindered *si*-face of the chiral imide enolate (Scheme 4.3). However, when attempts were made to remove the auxiliary by treating with LiOH, some amount of racemization was observed due to the enhanced acidity of the proton close to the fluorine atom.



Scheme 4.3. Evans chiral auxiliary based fluorination reported by Davis.[30]

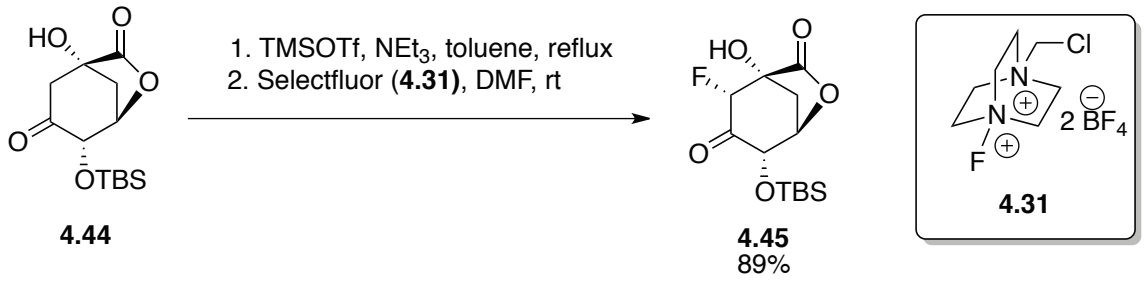
Other than NFSI and NFOBS, there are applications of many other electrophilic fluorinating reagents reported in the literature. Shutske reported the synthesis of 12-fluoroforskolin, in which the intermediate **4.43** was obtained by fluorination of the enolate with acyl hypofluorite (Scheme 4.4).[31]



Scheme 4.4. Fluorination with hypofluorite reported by Shutske.[31]

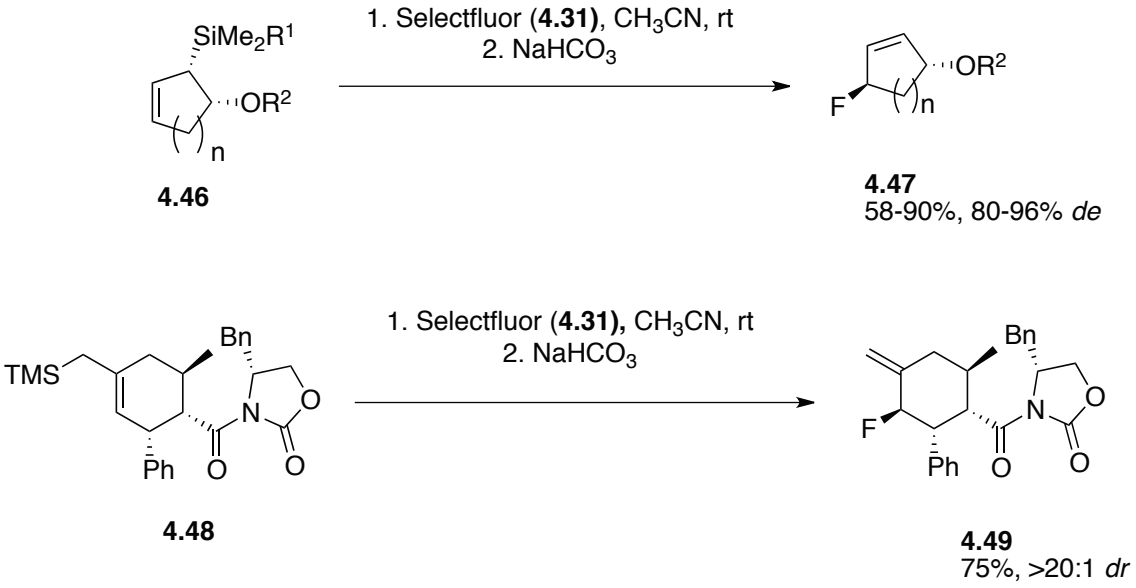
Other than acyl hypofluorite, N-fluoropyridinium triflate (**4.30**) has also been utilized. Dauben and coworkers reported the application of N-fluoropyridinium triflate in the synthesis of the precursors of fluorinated vitamin-D_3 leading towards low yields and selectivities along with nonfluorinated side products.[32] A very common and effective fluorinating reagent is Selectfluor®(**4.31**). This is a colourless salt derived from the heterocycle DABCO and was first described by Banks.[33] It has since been commercialized by many companies. In their synthesis of 2-(*R*)-fluorodehydroquinic acid, Abell and co-workers used Selectfluor® for the fluorination of the enolate derived from the precursor **4.44** (Scheme

4.5).[34]



Scheme 4.5. Synthesis of fluorodehydroquinic acid precursor by fluorination with Selectfluor® reported by Abell.[34]

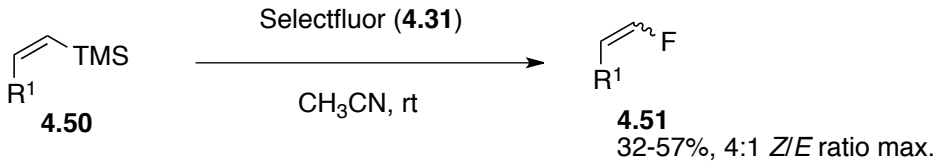
Allylsilanes are very popular substrates in organofluorine chemistry. γ-Fluorination of allylsilanes occurs smoothly thanks to the β-silicon effect.[35] Gouverneur and co-workers reported a series of papers on the synthesis of fluorinated carbocyles employing fluorodesilylation method of various cyclic allylsilanes, **4.46** and **4.48** affording good to excellent yields and diastereoselectivities (Scheme 4.6).[36]



Scheme 4.6. Synthesis of fluorocarbocycles from cyclic allylsilanes reported by Gouverneur.[36]

A relatively less explored fluorodesilylation method was reported by the Gouverneur Group, where in

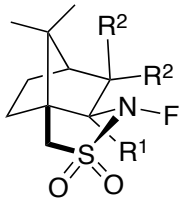
alkenyl silanes were converted into very valuable building blocks such as alkenyl fluorides. Although an important methodology, it suffered from quite a few drawbacks such as low yields, poor *E*/*Z*-selectivities and narrow substrate scope (Scheme 4.7).[37]



Scheme 4.7. Fluorodesilylation of alkenyl silanes reported by Gouverneur.[37]

4.13: Enantioselective electrophilic fluorination

Enantioselective fluorination leading towards a stereogenic center bearing a fluorine atom is of extreme importance from drug discovery point of view. Various chiral fluorinating reagents have been developed. Other than these reagents, applications of achiral fluorinating reagents along with chiral ligands or metal complexes have become popular. The pioneering work of Differding and Lang followed by Davis led to the development of the N-fluorocamphorsultams as chiral fluorinating reagents (**4.34-A**, **4.34-B**, **4.34-C**, and **4.34-D**; Figure 4.12).[38]



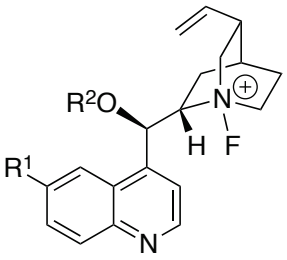
4.34-A: R^1=R^2=H (Differding and Lange)
4.34-B: R^1=CH_3, R^2=H (Differding and Lange)
4.34-C: R^1=H, R^2=Cl (Davis)
4.34-D: R^1=H, R^2=OMe (Davis)

Figure 4.12. Chiral N-fluorocamphorsultams.[38]

These reagents have been employed in electrophilic fluorination of various metal enolates, derived either from cyclic keto-esters or cyclic ketones, affording poor to moderate yields and low enantioselectivities, along with a limited substrate scope. Lower enantioselectivity often was a result of base-mediated racemization of the product compound due to enhanced acidity through fluorine incorporation.[39]

A major breakthrough was the introduction of a new class of reagents derived from naturally occurring cinchona alkaloids. Cahard and Shibata reported simultaneously a number of enantioselective fluorination reagents prepared from cinchona alkaloids and Selectfluor®. These reagents have been utilized in

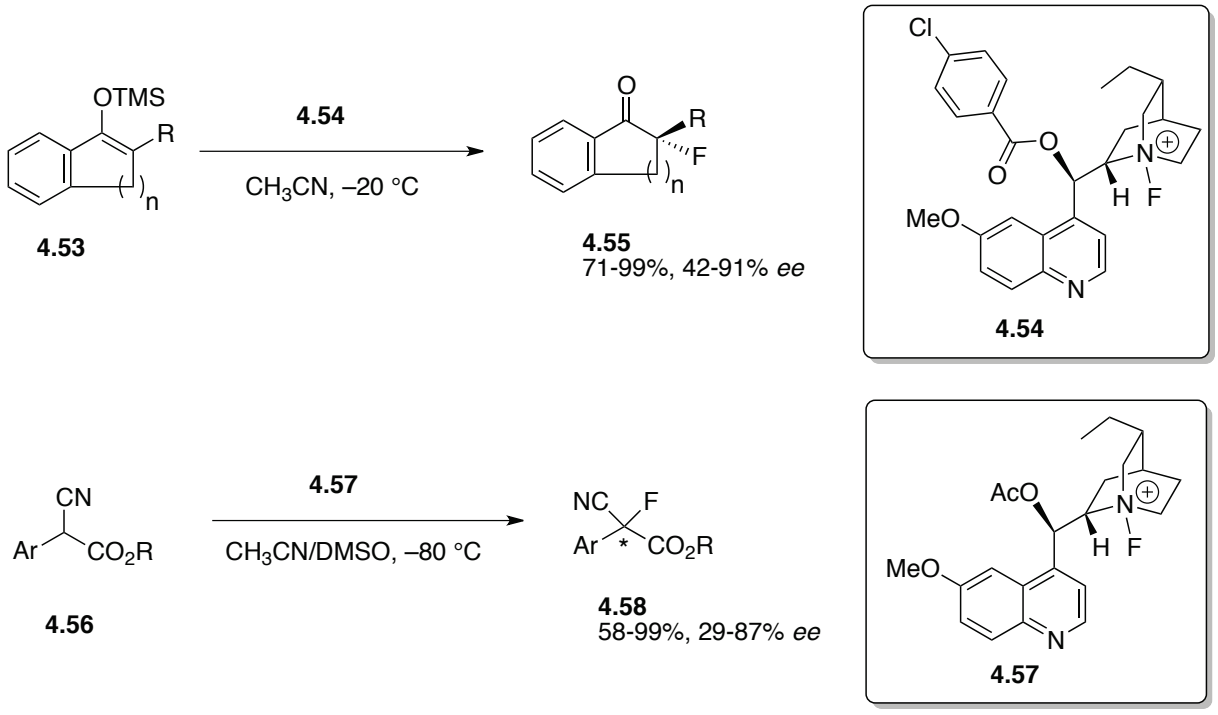
enantioselective fluorination of metal enolates affording high yield and moderate *ee* (Figure 4.13).[40, 41]



4.52-A: R^1=R^2=H
4.52-B: R^1=OMe,R^2=*p*-ClBz
4.52-C: R^1=OMe,R^2=2-naphthoic

Figure 4.13. Cinchona derived chiral fluorination reagents applied by Cahard and Shibata.[40, 41]

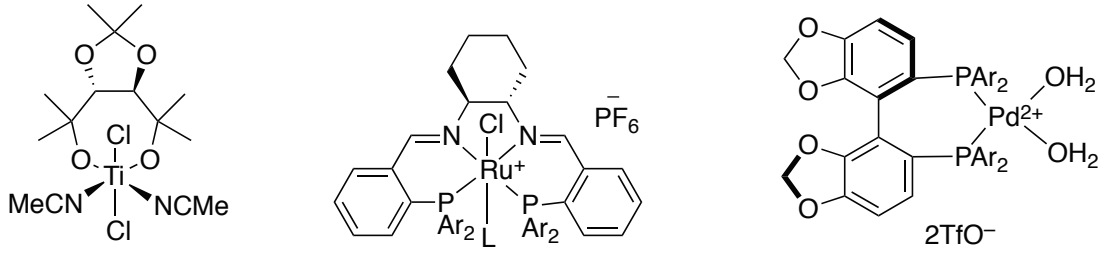
These groups then went on to report reagents with minor modifications, **4.54** and **4.57**. Upon reactions with the enolates, these reagents gave good to excellent yields and moderate to very good levels of enantioselectivities (Scheme 4.8).[42]



Scheme 4.8. Application of quinine-based chiral fluorination reagents.[42]

One very popular method of enantioselective fluorination is by employing a combination of a known achiral fluorinating reagent with a chiral metal catalyst. Togni reported an enantioselective fluorination of β-keto esters with Selectfluor® and a catalytic amount of a TADDOL-derived titanium complex, **4.59**. Their

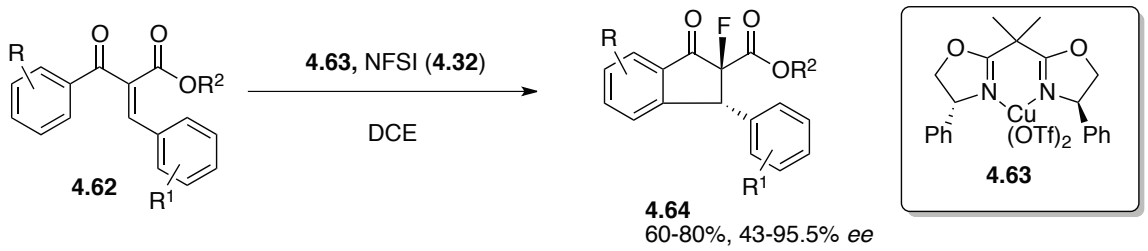
group also reported a catalytic methodology involving a ruthenium complex (**4.60**) and NFSI. The Sodioka group reported an enantioselective fluorination process with a palladium complex (**4.61**) as a catalyst along with NFSI as fluorinating reagent. Both of these groups reported products with high yields and very good *ee* (Figure 4.14).[43, 44]



4.59 **4.60** L= OEt_2 **4.61**

Figure 4.14. Transition metal catalysts applied by Togni and Sodioka.[43, 44]

A rather indirect approach of making fluorinated molecules was attempted by Ma's group, who exploited Nazarov cyclization-electrophilic fluorination to afford fluorine containing 1-indanone derivatives. This reaction, catalyzed by a Cu(II)-bis(oxazoline) complex, gave good yields and moderate to excellent enantioselectivities (Scheme 4.9).[45]

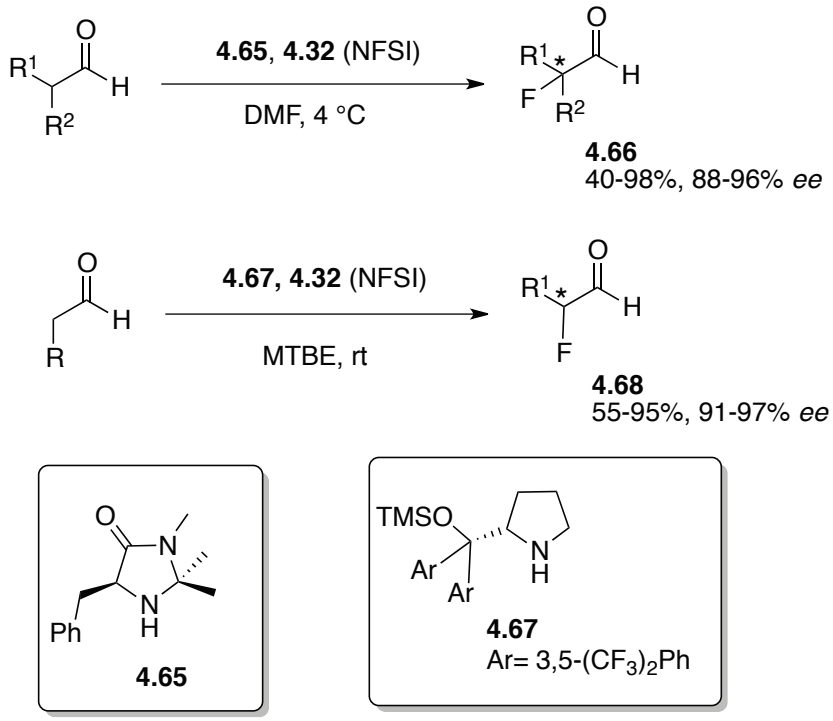


Scheme 4.9. Enantioselective Nazarov cyclization-electrophilic fluorination catalyzed by copper-bisoxazoline complex reported by Ma.[45]

Organocatalysis is another approach towards enantioselective electrophilic fluorination. Small organic molecules have been used effectively in a wide range of reactions including electrophilic fluorination. Enders and co-workers reported the first enantioselective organocatalytic fluorination of aldehydes and ketones with *L*-proline as the catalyst in the presence of Selectfluor®. Unfortunately, both yields and

enantiomeric excesses were poor with the highest *ee* only 36%.[46]

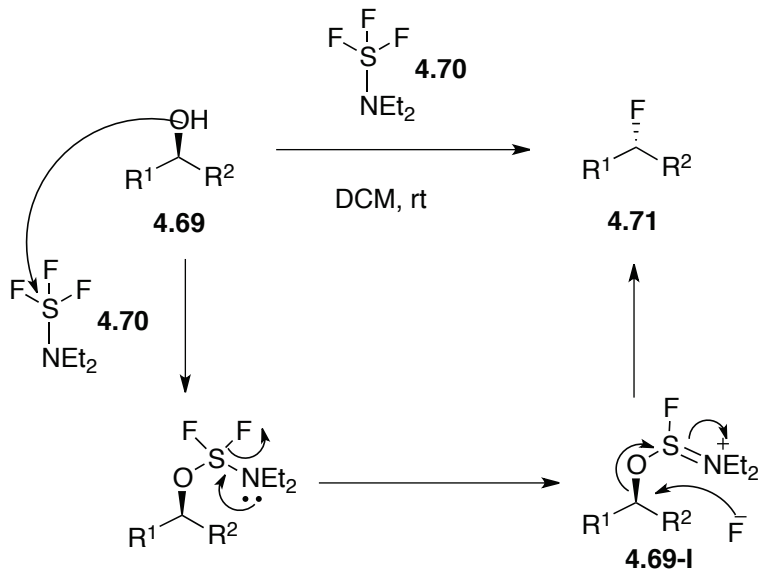
Then the Barbas group reported an asymmetric organocatalytic fluorination of linear and branched aldehydes with imidazolidinone based organocatalyst, **4.65**. Jørgensen and co-workers have reported a direct asymmetric fluorination with NFSI in the presence of prolinol-based organocatalyst, **4.67**. This sterically encumbered catalyst was very effective in blocking one face of the enolate derived from the aldehyde. Both of these methodologies displayed a broad substrate scope and very high yields and *ee*'s were obtained with almost all the substrates (Scheme 4.10).[47, 48]



Scheme 4.10. Organocatalytic enantioselective fluorination reported by Barbas and Jørgensen.[47,48]

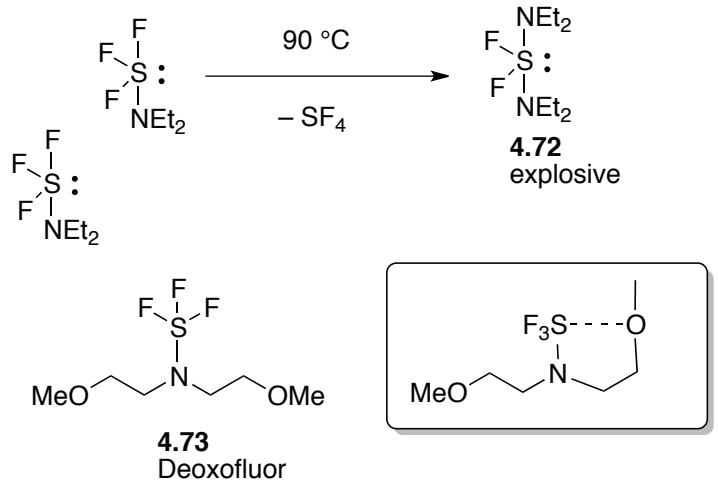
4.14: Nucleophilic fluorination

Another alternative method of making a C–F bond is by nucleophilic fluorination. Aminosulfurtrifluorides have been used extensively in this regard. One such reagent, **4.70** or "DAST", mainly reacts with alcohols. Upon reaction with the hydroxyl group, it forms intermediates such **4.69-I**, which is then attacked by the fluoride anion. In this way the configuration is reversed at the carbon bearing the hydroxyl group (Scheme 4.11). Apart from this transformation, DAST is also known to convert a ketone into a *gem*-difluoride.[49]



Scheme 4.11. Diaminosulfurtrifluoride in nucleophilic fluorination.[49]

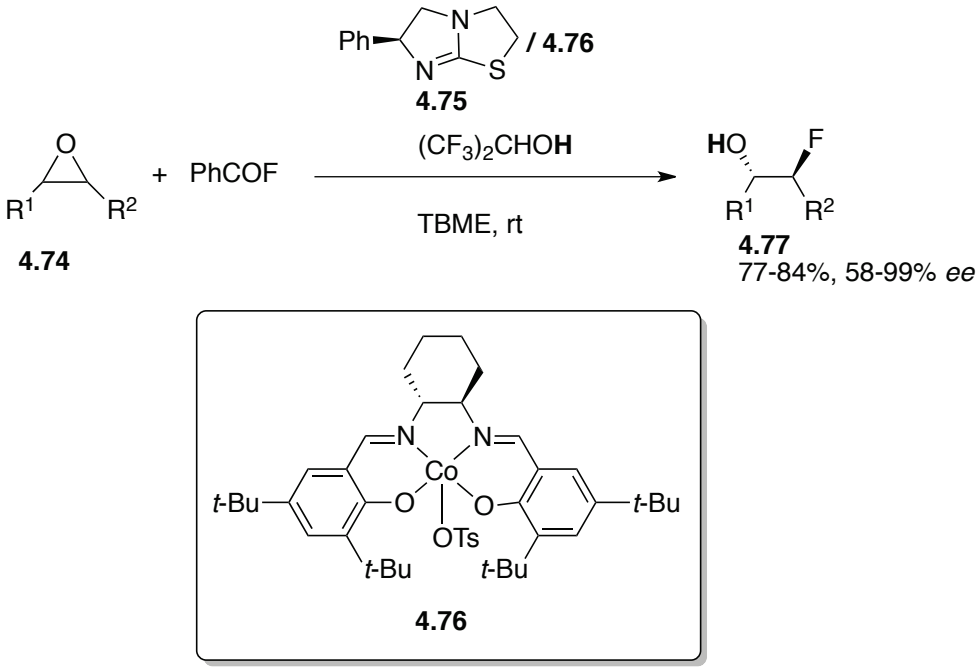
Although a very potent and effective fluorinating reagent, DAST suffers from one major problem. This reagent is unstable and forms an explosive intermediate (**4.72**) when heated.[50] To overcome this problem, a new generation of DAST reagent (Deoxofluor®, **4.73**) has been prepared which owes its stability to the formation of an intramolecular coordination bond between the O atom and the S atom (Scheme 4.12).[51]



Scheme 4.12. Stability problem of DAST, and Deoxofluor® as a DAST-analogue.[50, 51]

4.15: Enantioselective nucleophilic fluorination

Haufe and co-workers reported the first asymmetric ring-opening of *meso*-epoxides with a hydrofluorinating reagent mediated by Jacobsen's Salen–Cr(III)-complex, leading to good yields and moderate *ee*'s, along with chlorohydrin side products in non-negligible amounts.[52] A similar enantioselective ring-opening of epoxides has been reported by Doyle and co-workers exploiting a variant of Jacobsen's complex. This group has shown that by employing a combination of a thioguanidene-based organocatalyst (tetramisole, **4.75**) and a Salen-Co(III) metal complex (**4.76**) as a cooperative catalytic system, very high levels of enantiomeric excesses can be achieved along with excellent yields (Scheme 4.13).[53] Benzoyl fluoride and 1,1,1,3,3,3-hexafluoroisopropanol generates HF, which then formed a HF–chiral amine salt that led to the desired enantioselective process.

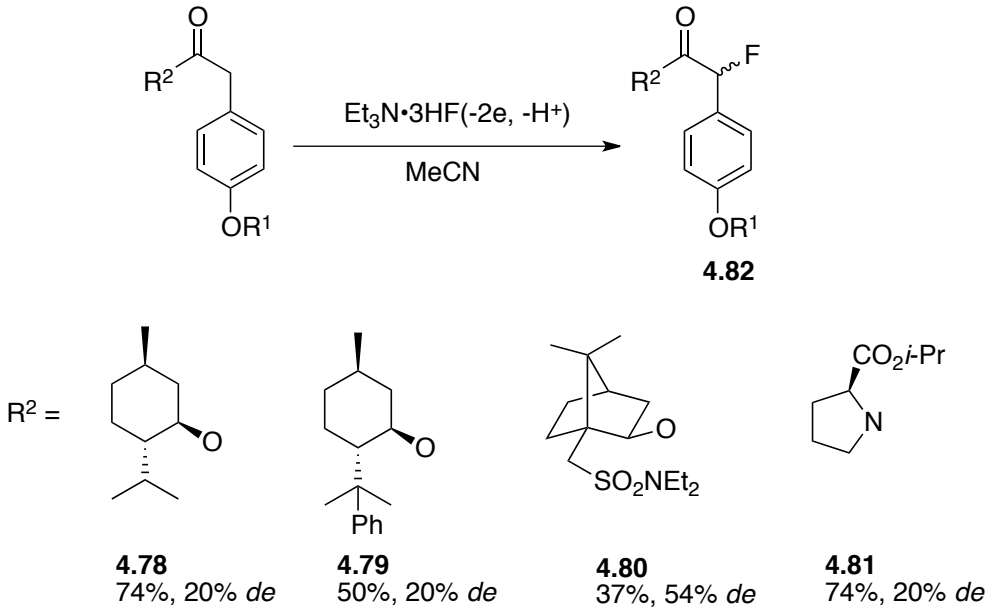


Scheme 4.13. Enantioselective ring-opening of epoxides under cooperative catalysis conditions reported by Doyle using a Salen-Co complex.[53]

4.16: Electrochemical fluorination

Electrochemistry has made a significant contribution in the area of fluorination of organic compounds with the development of the Simmons process.[54] By this process, it is possible to make perfluorinated

compounds. In the last few years, the electrochemical partial fluorination was used to achieve highly selective fluorinations by introduction of either one fluorine atom or fluorinated groups in an organic molecule. Fluorination with chemical methods using fluorinated reagents often lead to many undesired side products due to their high reactivities. Many of these reagents are hazardous, difficult to handle and costly. Electrochemical methods, on the other hand, can overcome these problems. The use of hydrofluoric acid is often necessary for this process. However, this is a volatile and highly corrosive acid in nature. To overcome this problem, various complexes of HF with various N-donor bases have been studied. Reagents such as $Et_3N{\bullet}3HF$ and $Py{\bullet}(HF)_x$ (Olah's reagent) have been studied in different solvents with MeCN being the most common one. Laurent's group and Fuchigami's group independently reported the first examples of selective fluorination of organosulfur compounds. Several functional groups such as ester, nitrile, ketone, and amide were tolerated.[55, 56] Apart from these examples, there are few asymmetric electrolytic fluorination examples in the literature. However, asymmetric electrolytic fluorination is generally very difficult due to the small size of the fluoride ion and the use of polar solvents for the electrical conductivity. The Laurent group observed a diastereoselective fluorination at the benzylic position of aromatic compounds containing chiral auxiliaries (**4.78** to **4.81**). Only moderate diastereomeric excesses were recorded (Scheme 4.14).[57]



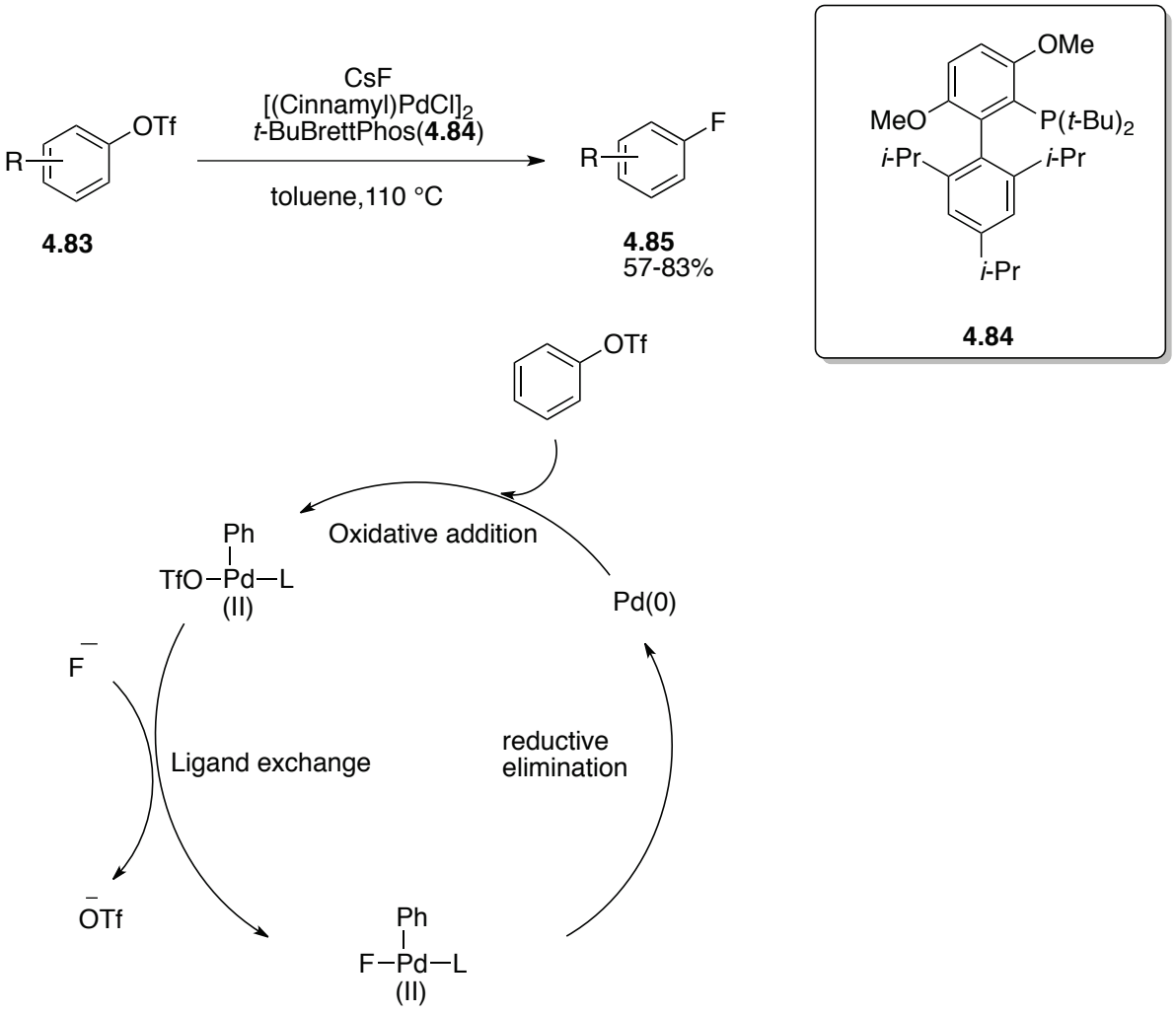
Scheme 4.14. Diastereoselective electrochemical fluorination with a chiral auxiliary approach.[57]

After Laurent published his pioneering work, Fuchigami and co-workers reported several works on diastereoselective fluorination including N-protected thiazolidines derived from L-cysteine in moderate

yields and high diastereoselectivities.[58]

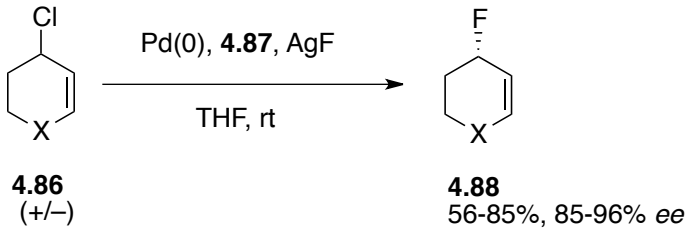
4.17: Metal catalyzed fluorination

In recent years, transition metal catalyzed fluorination of organic compounds has received much attention. Pioneering studies from the Grushin group have demonstrated that the reductive elimination of aryl-Pd (II)(F)- intermediates is quite challenging.[59] Buchwald and co-workers have overcome this challenge and reported a palladium-catalyzed cross-coupling reaction of aryl triflates with CsF to afford fluoroarenes. In this reaction, the sterically hindered phosphine ligand *t*-BuBrettphos, **4.84** plays an important role in promoting the reductive elimination from L_nPd^{II}(Aryl)F. A diverse range of substrates responded, giving moderate to very good yields (Scheme 4.15).[60]



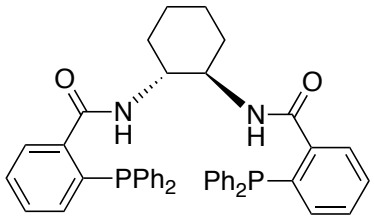
Scheme 4.15. Palladium catalyzed fluorination of aryl triflates.[60]

As discussed earlier, C–F bond formation by reductive elimination from ArPd(II)F intermediate, generated from Pd(II) precursor with nucleophilic F-reagent, has proven more challenging. Doyle and co-workers identified another distinct mechanism in which the nucleophilic attack of fluoride on an electrophilic Pd(II)-allyl intermediate can generate allylfluorides. Treatment of racemic allylic chlorides such as **4.86** with a palladium complex in the presence of commercially available Trost ligand **4.87** formed allyl fluorides in moderate to good yields and high *ee*'s. It was proposed that the use of AgF as fluoride source can provide a significant amount of driving force through generation and precipitation of AgCl (Scheme 4.16).[61]



4.86
(+/–)

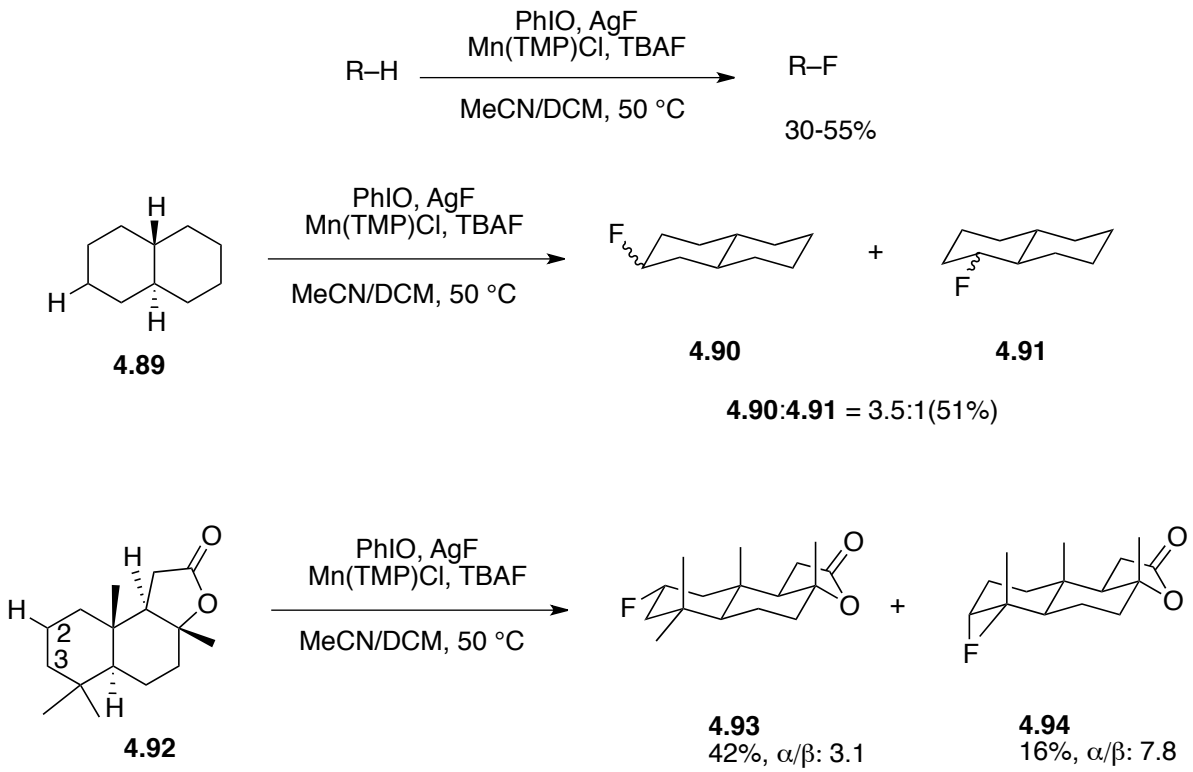
4.88
56-85%, 85-96% *ee*



4.87

Scheme 4.16. Asymmetric palladium catalyzed fluorination of allylic chlorides.[61]

An oxidative aliphatic C–H activation/fluorination catalyzed by a Mn(III)-porphyrin complex was reported by Groves and co-workers. Substrates with different functional groups responded well affording yields up to 55% with minor side products formed through fluorination at other sites (Scheme 4.17). The site-selectivity depends on both the steric and electronic nature of the C–H bond. Electron rich sites are preferentially fluorinated over the electron poor ones (sites adjacent to functional groups such as carbonyl). Sterically conjested rings are avoided. The higher preference for the α position over the β position in the fluorinated product (**4.92**) can be attributed to the bent π*–approach trajectory of the Mn–O π* orbitals of the oxoMn^{V} complex formed during the reaction.[62]



Scheme 4.17. A Mn(III)-porphyrin complex catalyzed C–H activation/fluorination.[62]

4.18: Trifluoromethylation reactions

In recent years, trifluoromethyl-substituted molecules have gained significant interest. The introduction of a strong electron-withdrawing group such as trifluoromethyl can bring dramatic changes in the properties of molecules as discussed before.

The synthetic trifluoromethylation processes can be divided into four categories:

1) Nucleophilic trifluoromethylation.

2) Electrophilic trifluoromethylation.

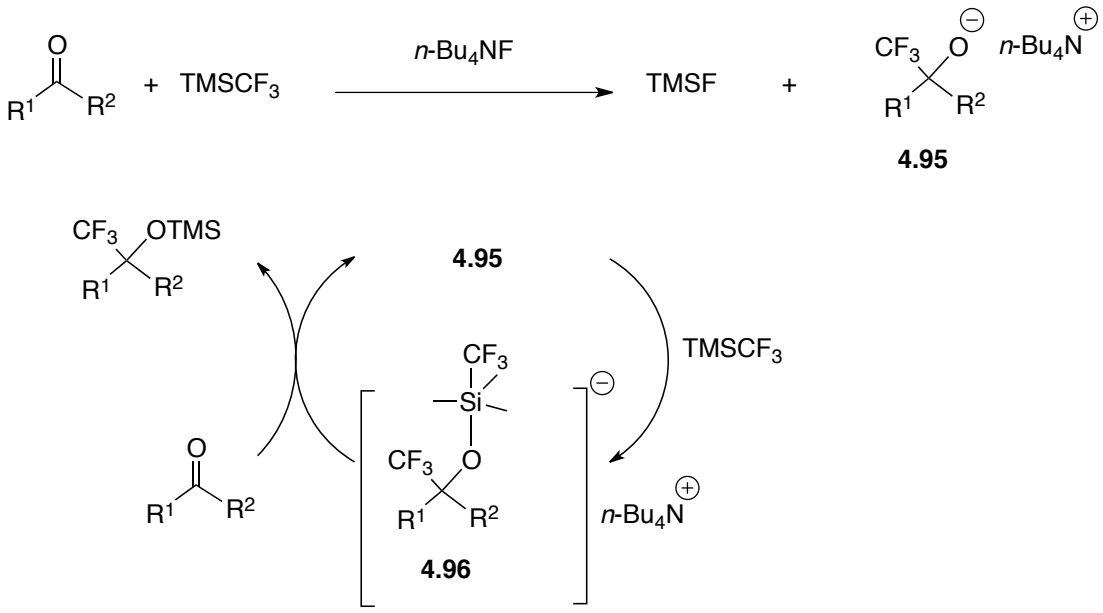
3) Radical trifluoromethylation.

4) Metal catalyzed trifluoromethylation methods.

4.19: Nucleophilic trifluoromethylation reactions

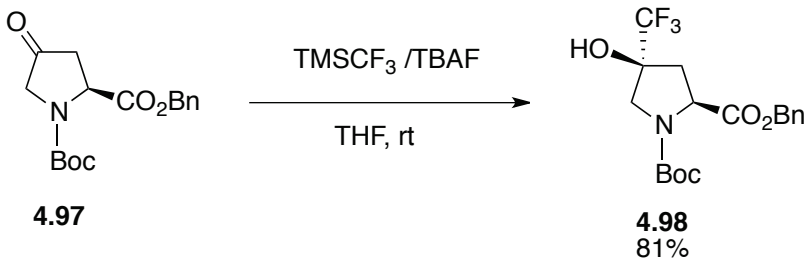
One of the reagents that has been heavily exploited in nucleophilic trifluoromethylation and whose chemistry has been studied in details, is trifluoromethyltrimethylsilane (TMS)CF_3. This reagent, known as

the Rupert-Prakash reagent, was first reported by Prakash and co-workers.[63] Since then, many groups have reported various examples of nucleophilic trifluoromethylation with this reagent. $(TMS)CF_3$ is used a precursor to the trifluoromethide anion (CF_3^-), which is generated by activation with a fluoride anion source (nucleophilic initiator) like TBAF. Upon addition of a catalytic amount of TBAF to the reaction mixture of a carbonyl compound and $(TMS)CF_3$, the process starts with the formation of TMSF and alkoxide adduct **4.95**. This adduct then reacts with $(TMS)CF_3$ to generate a pentavalent complex **4.96** followed by the transfer of the CF_3 group to the electrophilic carbon of the carbonyl group (Scheme 4.18).[64]



Scheme 4.18. Trifluoromethylation of carbonyl compounds with the Rupert-Prakash reagent.[64]

One of the earliest examples in this category was reported by Qing and co-workers who performed the trifluoromethylation of proline derivative **4.97** with $(TMS)CF_3$ in the presence of a catalytic amount of TBAF to afford a good yield of product **4.98** (Scheme 4.19).[65]

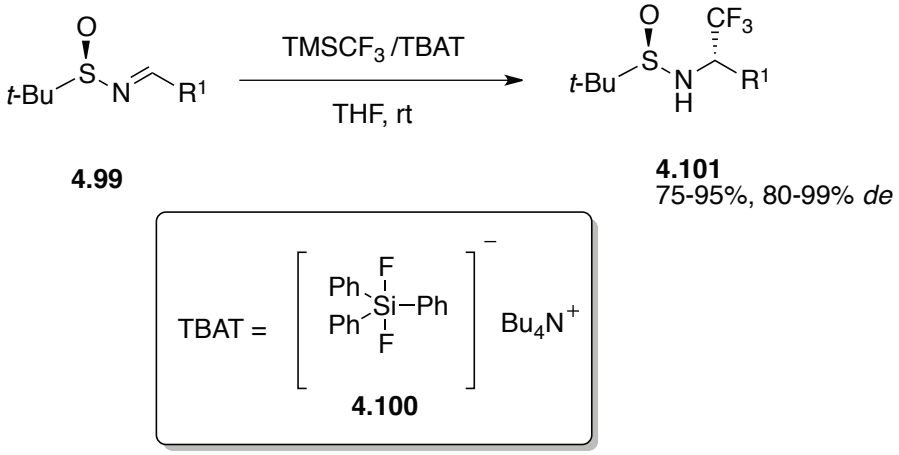


4.97 **4.98** 81%

Scheme 4.19. Trifluoromethylation of proline derivative **4.97** with the Rupert-Prakash reagent.[65]

This reagent was effective with other carbonyl containing functional groups except amide. Anker and co-workers observed that this reagent shows selectivity towards a lactone unit in the presence of amide functional group.[66]

Trifluoromethylated chiral amines are important building blocks for pharmaceutical research. Direct asymmetric synthesis of trifluoromethylated amines was recently achieved by Prakash and co-workers. The reactivity and selectivity of the reaction are dependent on the fluoride source. Chiral sulfinimines of type **4.99** reacted with $(TMS)CF_3$ in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT, **4.100**) to give the desired products with high yields and diastereoselectivities (Scheme 4.20).[67,68]



4.99 **4.101** 75-95%, 80-99% *de*

4.100

Scheme 4.20. Diastereoselective nucleophilic trifluoromethylation of chiral sulfinimines reported by Prakash and co-workers.[67]

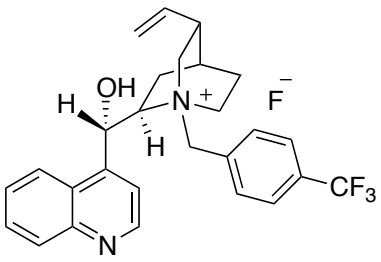
Another trifluoromethylating reagent which is relatively less explored under nucleophilic

trifluoromethylation conditions is trifluoromethyl iodide. In this case, the trifluoromethide anion is generated by treatment with metallic Zn in DMF.[68]

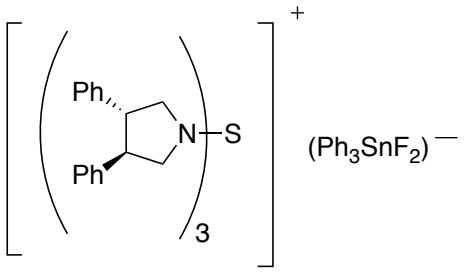
4.20: Nucleophilic enantioselective trifluoromethylation reactions

Enantiopure trifluoromethylated compounds are extremely important in medicinal chemistry, agrochemistry, electronics and optics.[69] This demand has led to several investigations dealing with attempts of enantioselective nucleophilic trifluoromethylation of carbonyls primarily with $(TMS)CF_3$. As discussed in Section 4.19, the mechanism of this reaction suggests (Scheme 4.18) that the ammonium cation is closely associated with the alkoxy adduct during the reaction. Thus, there is a possibility of inducing enantioselectivity if a chiral ammonium cation is used.

Prakash and co-workers were the first to report the application of *N*-benzylquinidium fluoride to allow enantioselective trifluoromethylation of 9-anthraldehyde in excellent *ee*. However a detailed substrate scope was not explored.[70] Iseki and co-workers employed a catalytic amount of *N*-[4-(trifluoromethyl)benzyl]cinchonium fluoride (**4.102**) as an effective catalyst for the asymmetric introduction of the CF_3 group in high yields, however with low enantiomeric excesses. This group also developed the chiral triaminosulfonium salt (**4.103**), which acts as Lewis base catalyst in the enantioselective trifluoromethylation of aldehydes with $(TMS)CF_3$ leading to low to moderate *ee*'s (Figure 4.15).[71]



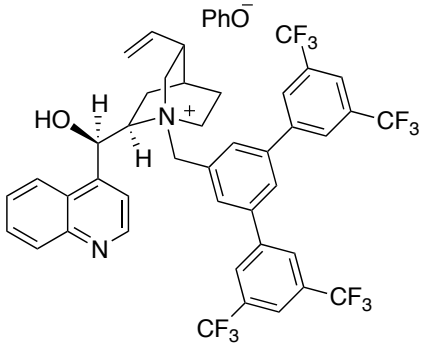
4.102



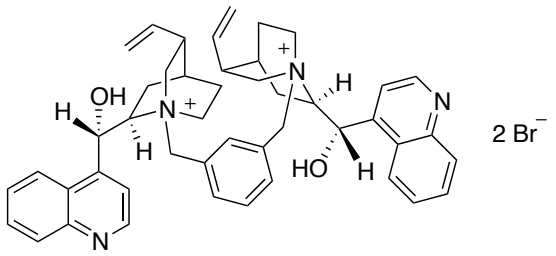
4.103

Figure 4.15. Cinchonium-based catalyst and chiral triaminosulfonium salt as Lewis base catalyst in enantioselective nucleophilic trifluoromethylation reported by Iseki and co-workers.[71]

Similar cinchonium salts were also applied by the Mukaiyama and Shibata laboratories independently (Figure 4.16).[72] This chemistry was applied with both ketones and keto-esters leading to very high yields and moderate to excellent *ee*'s for the corresponding trifluoromethylated products.



4.104 (Mukaiyama)
Highest *ee* 87%

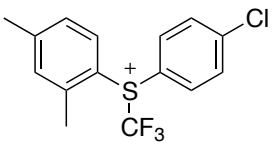


4.105 (Shibata)
Highest *ee* 94%

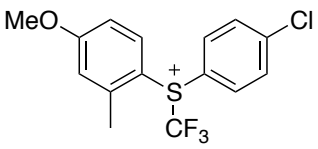
Figure 4.16. Cinchonidine-derived ammonium salts reported by Mukaiyama and Shibata for the enantioselective nucleophilic trifluoromethylation of ketones and keto-esters.[72]

4.21: Electrophilic racemic and enantioselective trifluoromethylation reactions

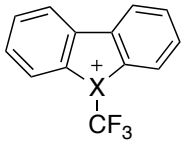
Unlike nucleophilic trifluoromethylation, electrophilic trifluoromethylation developed relatively slowly. Yagupol'skii reported the first electrophilic trifluoromethylating reagents (**4.106**, **4.107**; Figure 4.17), which showed low reactivity.[73] Then Umemoto and co-workers reported a series of dibenzoheterocyclic salts as trifluoromethylating reagents (**4.108**, Figure 4.17).[74]



4.106



4.107



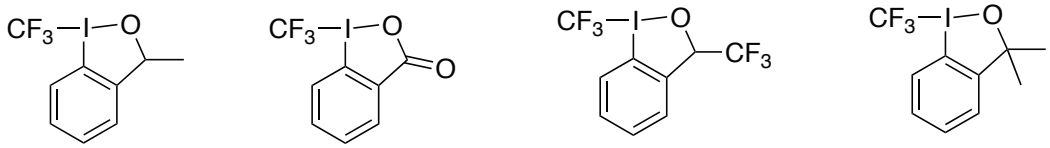
4.108
X=S, Se, Te, O

Figure 4.17. Electrophilic trifluoromethylation reagents.[73, 74]

Despite its importance, there are very few examples of enantioselective electrophilic trifluoromethylation reactions. The most successful method so far was reported by Cahard and co-workers on 1-oxo-indan-2-carboxylic acid methyl ester by employing catalytic amounts of cinchona alkaloid and **4.108** (X=S) as a trifluoromethylating reagent which resulted in a highest *ee* of only 71%.[75]

The new hypervalent iodine (III)–CF_3 reagents (**4.109**–**4.112**, Figure 4.18) reported by Togni and co-

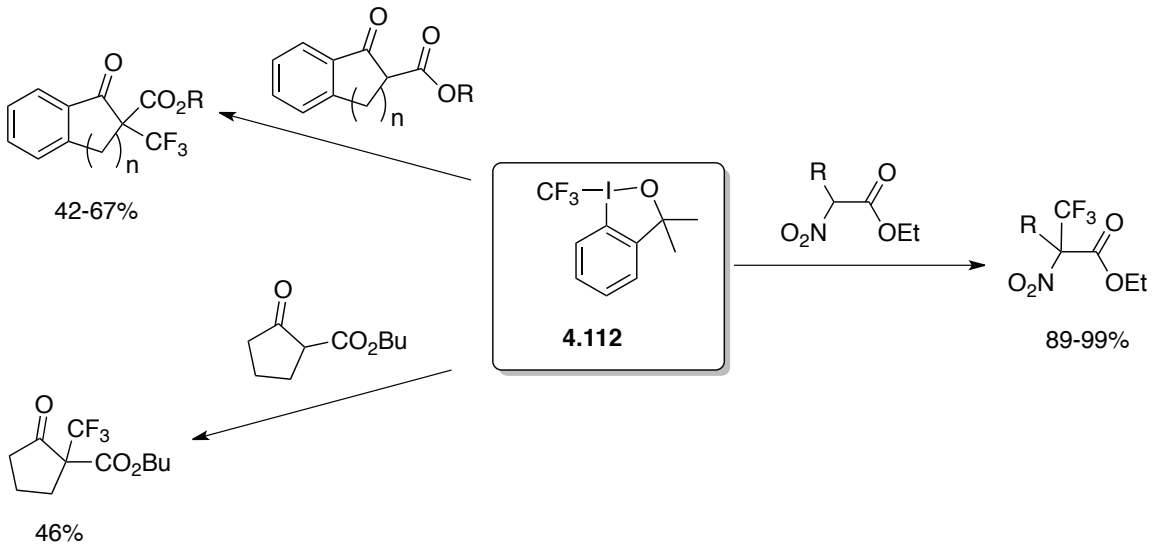
workers have also been exploited heavily and many publications have emerged on the application of these reagents in electrophilic trifluoromethylation.[76]



4.109 **4.110** **4.111** **4.112**

Figure 4.18. Hypervalent iodine based trifluoromethylating reagents reported by Togni.[76]

Substrates capable of forming enolates underwent smooth reactions with the reagent to afford trifluoromethylated compounds in moderate to very high yields (Scheme 4.21).[77]

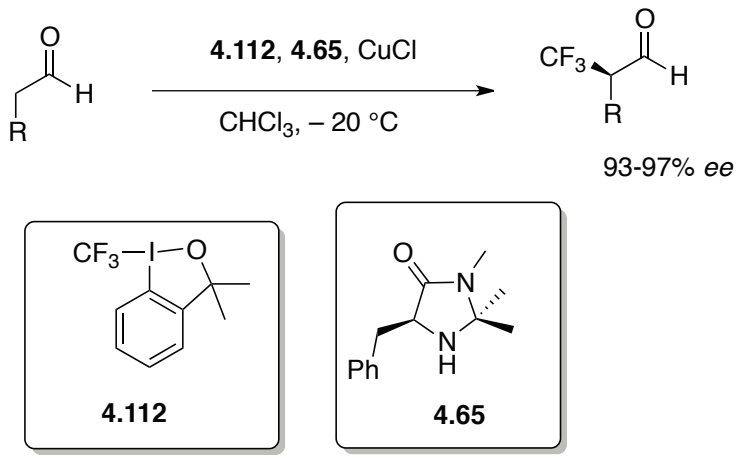


Scheme 4.21. Electrophilic trifluoromethylation of enolates with Togni's reagent.[77]

These reagents have also been used to trifluoromethylate various thiols including highly functionalized carbohydrate and amino acid derivatives. Togni's reagent was also applied with alcohols but the yields were much lower compared to thiols, which could be due to the lower nucleophilicity of alcohols.[78]

The first highly enantioselective electrophilic trifluoromethylation of aldehydes has only recently been reported by MacMillan and co-workers by employing a combination of Togni's reagent and

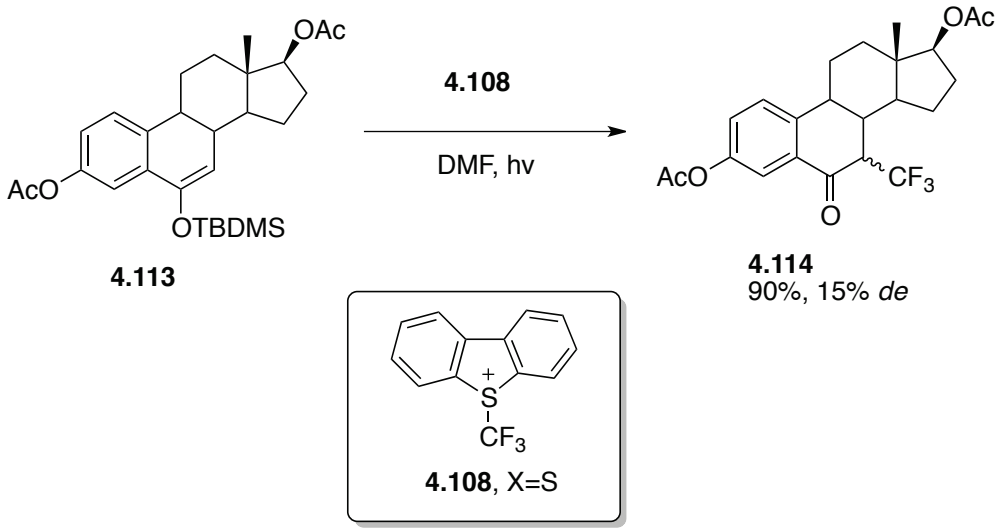
organocatalysis. Very high enantioselectivities were obtained in the range 93-97% *ee*.[79] The scope of this reaction is limited to aldehydes, which afford much higher enantioselectivities when compared to other carbonyl containing compounds such as β-ketoesters (Scheme 4.22).



Scheme 4.22. Enantioselective organocatalytic electrophilic trifluoromethylation of aldehydes by MacMillan.[79]

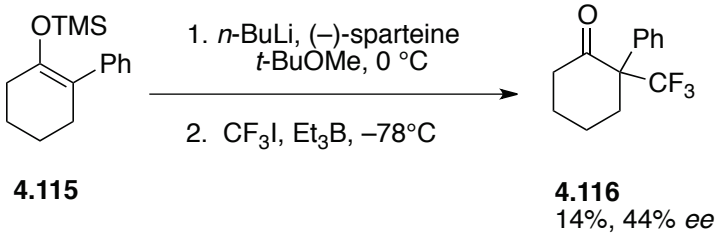
4.22: Radical trifluoromethylation reactions

Blazejewski and co-workers developed an approach for direct introduction of the trifluoromethyl group by reaction of silyl enol ether (**4.113**) of a steroidal ketone with Umemoto's reagent (**4.108**). Under usual thermal conditions the yield was low. However, UV-irradiation of the reaction mixture led to an excellent yield but in lower selectivity (Scheme 4.23).[80]



Scheme 4.23. Trifluoromethylation of silyl enol under UV-irradiation.[80]

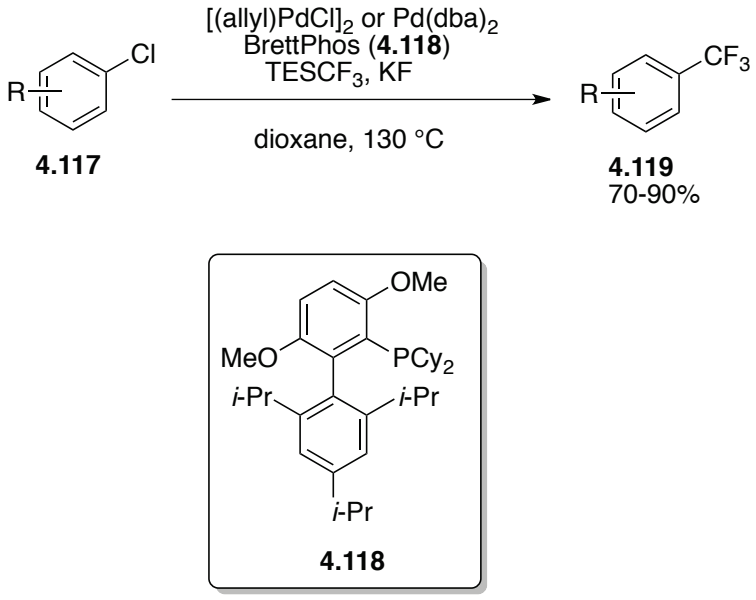
The only example of enantioselective radical trifluoromethylation has been reported by Mikami and co-workers. The radical trifluoromethylation was achieved at the α–position of 2-phenylcyclohexane through the corresponding silyl enol ether (**4.115**). A bidentate ligand, (–)-sparteine, was added to induce asymmetric radical trifluoromethylation. However, only low yield and low *ee* was obtained (Scheme 4.24).[81] No explanation about the stereochemical induction was provided in the paper.



Scheme 4.24. Enantioselective radical mediated trifluoromethylation of silyl ether.[81]

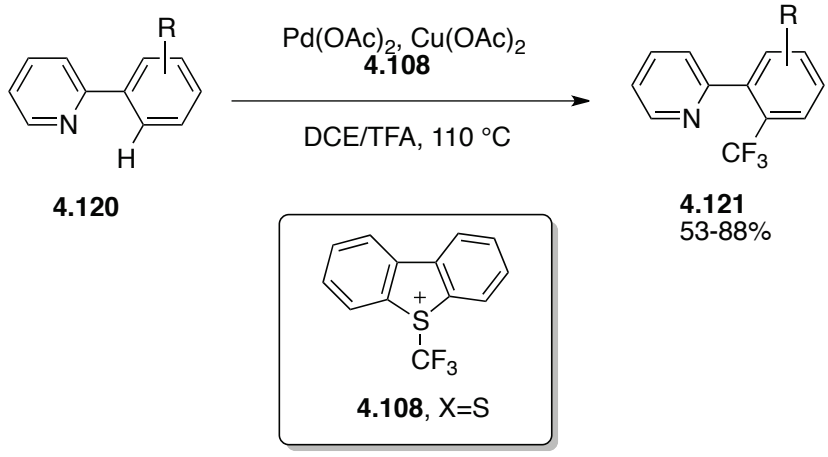
4.23: Metal catalyzed trifluoromethylation reactions

Buchwald and co-workers reported a palladium catalyzed cross-coupling method towards the synthesis of trifluoromethylated aromatic rings from aromatic chlorides. A bulky ligand such as BrettPhos (**4.118**) and high temperature were necessary to promote the important reductive elimination step. Various functional groups including heterocycles worked well affording moderate to high yields of the corresponding trifluoromethylated benzenes (Scheme 4.25).[82]



Scheme 4.25. Palladium catalyzed trifluoromethylation of aromatic halides.[82]

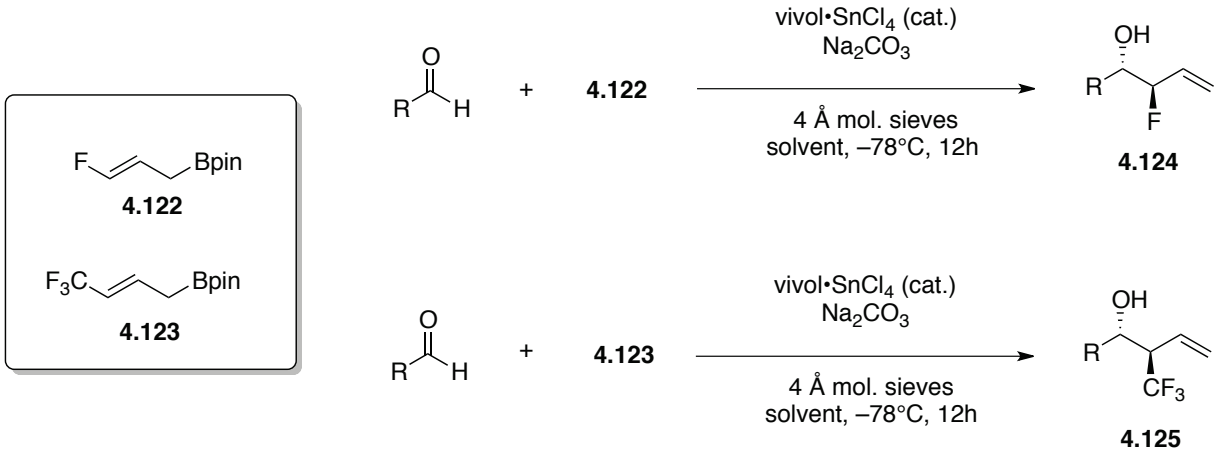
Another palladium catalyzed trifluoromethylation method involving C–H activation was reported by Yu and co-workers using Umemoto's reagent (**4.108**) as a trifluoromethylating reagent. In this method, a stoichiometric amount of copper (II) salt is added to enhance catalyst turnover and is proposed to work probably both as a Lewis acid and oxidant for Pd(0). Although a broad substrate scope was observed, a directing atom such as N in the form of a heterocycle was necessary (Scheme 4.26).[83]



Scheme 4.26. Palladium catalyzed trifluoromethylation of aromatic C–H bond.[83]

4.24: Project plan

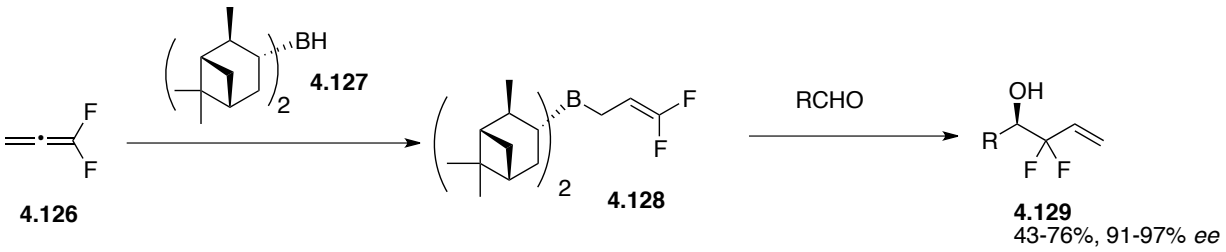
Despite of the presence of so many fluorinating methods and trifluoromethylation methodologies in the literature, one particular approach has been overlooked. There is either no example or very few examples in the literature of fluorinated and trifluoromethyl substituted allyl boronate reagents (**4.122** and **4.123**) along with their resulting chiral fluoro and trifluoromethyl homoallylic alcohol products (e.g. **4.124** and **4.125**). The plan was to develop a preparation of fluorinated and trifluoromethyl substituted allyl boronate reagents and then utilize the vivol•$SnCl_4$ catalyzed allylboration methodology with these boronates (Scheme 4.27).



Scheme 4.27. Research plan: synthesis and application of fluorinated and trifluoromethyl substituted allylboronates.

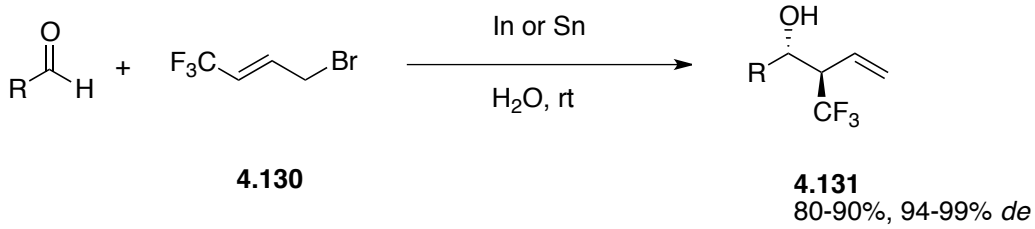
4.25: Literature examples of fluorine and trifluoromethyl substituted allylboronate reagents and homoallyl alcohols

The only example of a flurorine substituted allylboronate was reported by Ramachandran and co-workers. They prepared a *B*-(3,3-difluoroallyl)-diisopinocampheylborane (**4.127**) reagent via the hydroboration of 1,1-difluoroallene (**4.126**). This reagent when treated with aldehydes provides chiral 2,2-gem-difluorinated homoallylic alcohols in good yields and 91–97% *ee*'s (Scheme 4.28).[84]



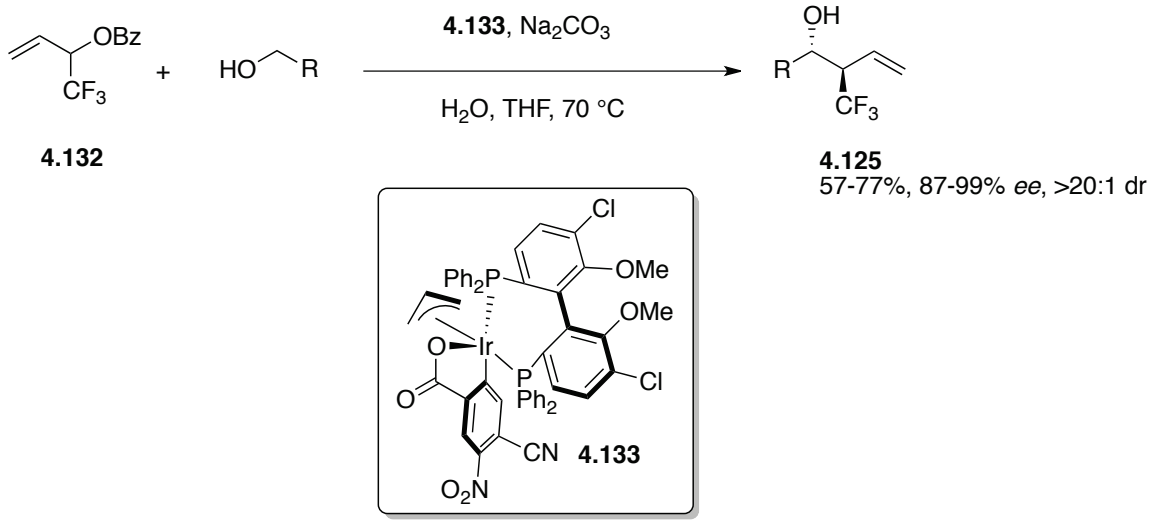
Scheme 4.28. Synthesis of *B*-(3,3-difluoroallyl)-diisopinocampheylborane and chiral 2,2-gem-difluorinated homoallylic alcohols.[84]

On the other hand, there is no known example of a trifluoromethylallylboronate reagent of our interest. The corresponding homoallylic alcohol product, however, is known. Loh and co-workers reported a metallic tin and indium mediated racemic allylation of aldehydes with 4-bromo-1,1,1-trifluorobut-2-ene (**4.130**) prepared in two steps from ethyl 4,4,4-trifluorocrotonate (Scheme 4.29).[85]



Scheme 4.29. Tin and indium mediated trifluoromethyl-allylation of aldehydes in water.[85]

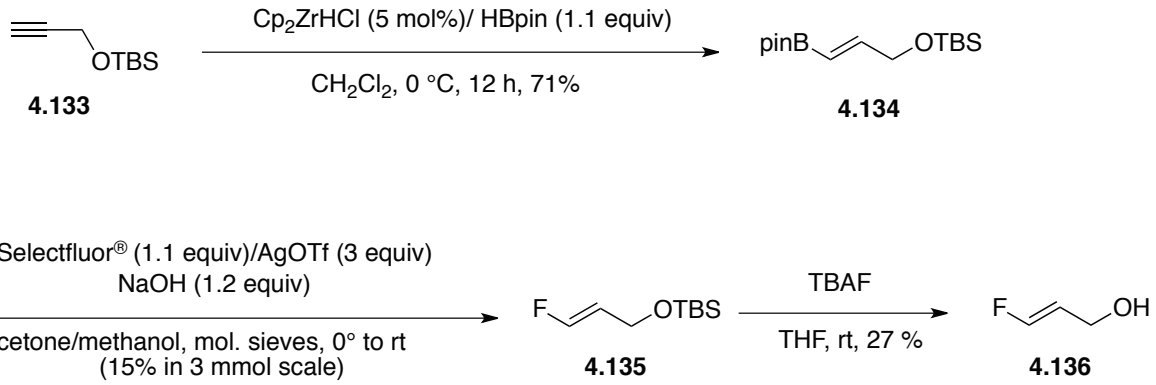
Krische and co-workers adopted a different approach. They took the advantage of carbonyl allylation protocols recently developed in their laboratory, wherein primary alcohol dehydrogenation triggers reductive generation of allyliridium nucleophiles, thus enabling carbonyl allylation from the alcohol oxidation level. A novel iridium catalyst (**4.133**) was employed and excellent levels of enantioselectivities and diastereoselectivities were observed (Scheme 4.30).[86]



Scheme 4.30. Iridium catalyzed carbonyl (α-trifluoromethyl)allylation.[86]

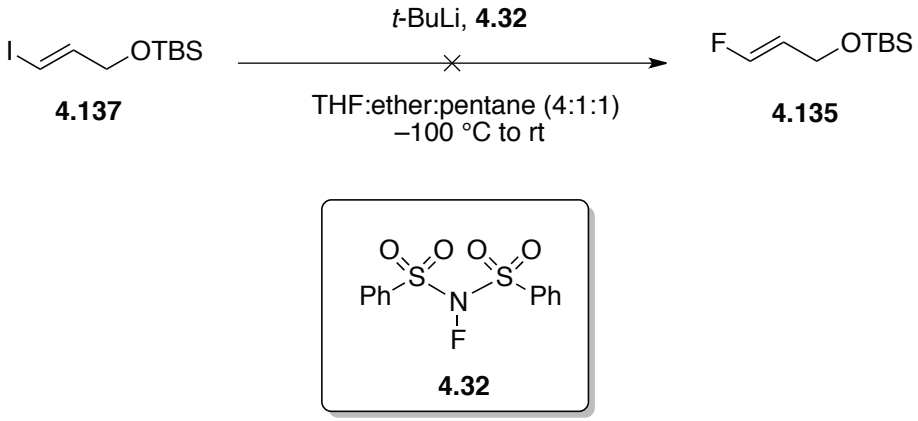
4.26: Results and discussion: synthetic attempts towards a fluoro allylboronate 4.122

At first, a method reported by Szabo and Aggarwal was adopted. These two research groups together reported a very simple and effective one-step method for synthesizing allyl and crotyl boronates from the corresponding allyl or crotyl alcohol in the presence of catalytic amounts of *p*-toluenesulfonic acid and a commercially available bridged palladium complex.[87] To this end, the corresponding allyl alcohol was prepared by the following method. The first step involved hydrozirconocene catalyzed borylation of the terminal alkyne. After that, the alkenyl boronate was subjected to a fluorination method reported by Ritter and co-workers.[88a] The reaction worked but only afforded a low yield. When it was performed on a larger scale (>1 mmol), the yield dropped even more. The deprotection step led to the desired fluoroallylic alcohol **4.136** in just 27 % yield (Scheme 4.31). Protodeborylation of the alkenyl boronate intermediate product (**4.134**) was a major problem as indicated by the isolation of the corresponding product (*i.e*, allyl alcohol *tert*-butyldimethylsilyl ether) along with some other side products.



Scheme 4.31. Synthesis of fluoroallyl alcohol **4.136**.

Disappointed by the overall yield, an alternative method for the synthesis of the intermediate **4.135** was attempted. Lithium halogen exchange of an alkenyl iodide (**4.137**) followed by treatment with NFSI (**4.32**) in a 4:1:1 mixture of THF/ether/pentane led only to a complete decomposition instead of the desired vinyl fluoride (**4.135**) (Scheme 4.32).[88b]

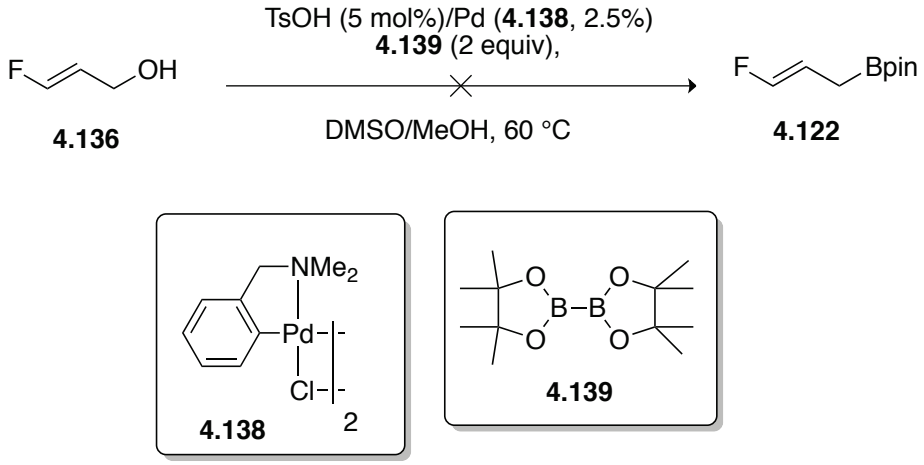


Scheme 4.32. Attempted fluorination of vinyl iodide alkenyl iodide **4.137**.

Although the reasons for this failure is not understandable at this stage, it can be postulated that the possibility of a deprotonation of the acidic methylene protons adjacent to the –OTBS may lead to many unwanted side reactions.

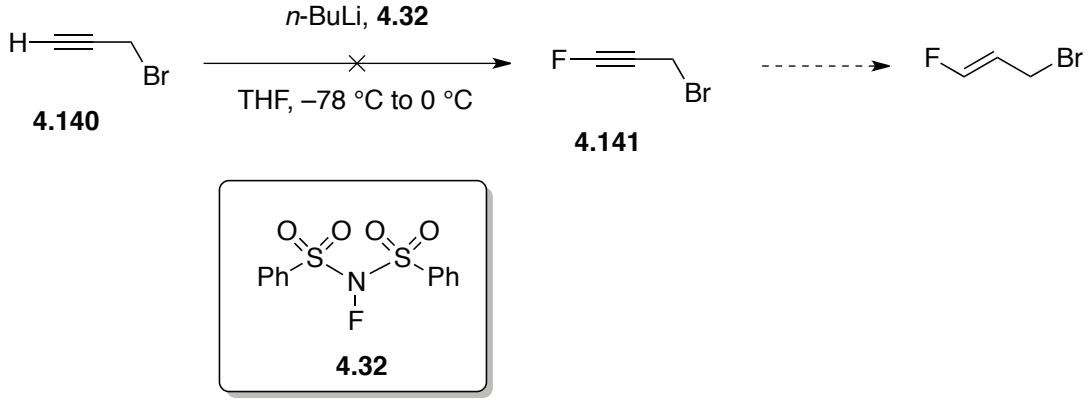
Then, the fluoroallylic alcohol **4.136**, obtained as described in Scheme **4.31**, was subjected to a borylation method reported by Aggarwal and Szabo.[87] Although trial reactions repeated on literature examples were successful, unfortunately no desired product was obtained when a similar reaction was attempted with the fluoroallylic alcohol **4.136** and trace amount of starting material was recovered (Scheme 4.33). Keeping in mind that this reaction may go via an allyl carbocationic intermediate, the strong electron withdrawing

effect of the fluorine atom may render the substrate ineffective towards the generation of such species.



Scheme 4.33. Attempted borylation of fluoroallyl alcohol **4.136** using Szabo's method.[87]

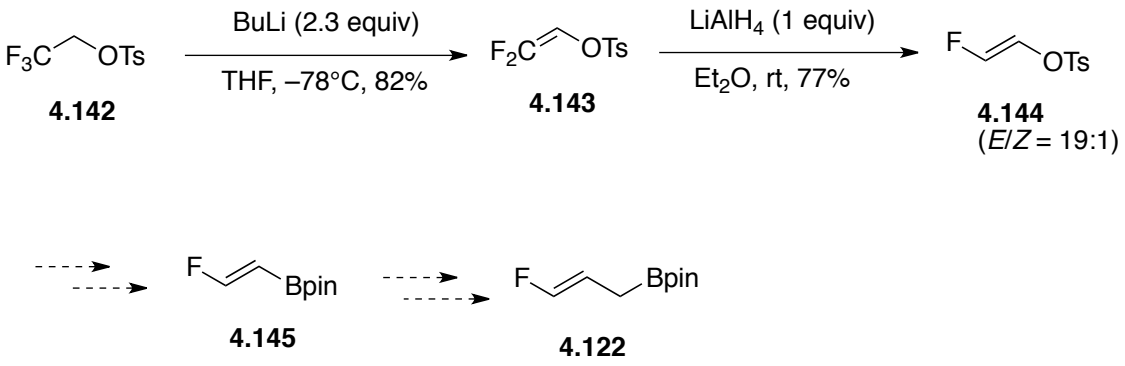
In an attempt to make fluoroallyl bromide, a potential precursor for the desired boronate, propargyl bromide was subjected to *n*-BuLi with the hope that it would lead to deprotonation of the terminal alkyne which then can be captured with NFSI. Unfortunately a complete decomposition of the starting material was observed (Scheme 4.34). Although the exact reason for this failure is not clear at this moment, it is assumed that there may be a possibility of lithium-Br exchange that may lead to many other unexpected side reactions.



Scheme 4.34. Attempted synthesis of fluoropropargyl bromide.

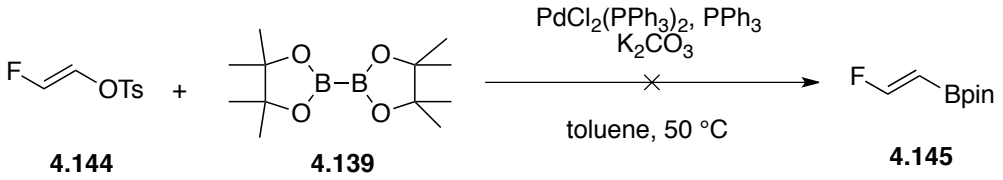
Another alternative approach that was applied involved the application of 2-fluorovinyl tosylate (**4.144**), prepared from 2,2,2-trifluorotosylate (**4.143**) via an addition-elimination pathway, in which the Li from LAH

coordinates with fluoride making it more susceptible towards elimination than the tosylate. The very high configurational selectivity (*E*/*Z* =19:1) of the 2-fluorovinyl tosylate (**4.144**) product can be explained by taking into consideration of the fact that the reaction with LAH proceeds via a transition state in which the steric repulsion between the tosylate and the fluoride plays a crucial role. The transition state leading to the *Z* isomer involves a steric interaction between the fluoride and the tosylate, making it less favourable. Xiao and co-workers have utilized this substrate as cross-coupling partner for the synthesis of terminal alkenyl fluorides.[89] In our case, the substrate (**4.144**) could be subjected to metal catalyzed borylation instead. If successful, it would furnish the desired 2-fluoroethylene boronate (**4.145**). In turn, **4.145** could be transformed into the desired fluroroallylboronate by a simple homologation (Scheme 4.35).

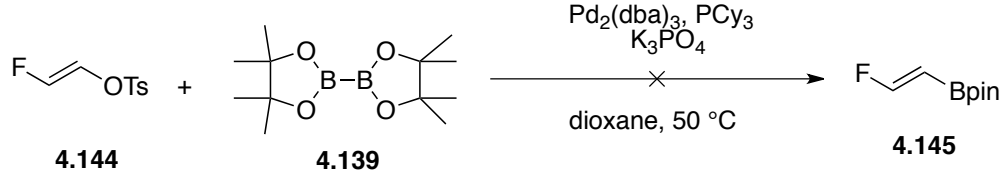


Scheme 4.35. Synthesis of fluorovinyl tosylate and the intended transformation towards **4.145** and **4.122**.

Unfortunately, when palladium catalyzed borylation was applied to the fluorovinyltosylate **4.144**, the starting material remained unchanged even after hours and almost all of the starting material was recovered (Scheme 4.36).



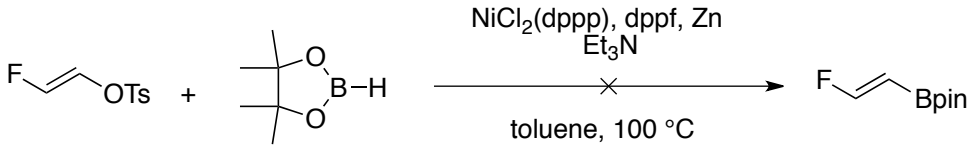
4.144 **4.139** **4.145**



4.144 **4.139** **4.145**

Scheme 4.36. Attempted borylation of fluorovinyl tosylate **4.144**.

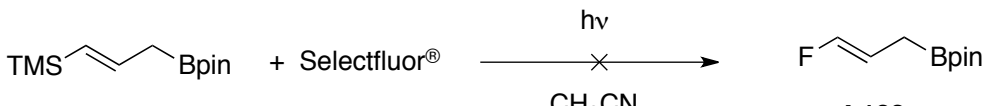
Inspired by the observations of Percec and co-workers, nickel catalyzed borylation method was employed with the fluorovinyl tosylate **4.144**.[90] A mixed ligand–catalytic system ($NiCl_2$(dppp)/dppf), pinacolborane (**4.146**) as boron coupling partner with a stoichiometric amount of Zn metal were used. Even after heating the mixture in toluene for 12 h, only starting material was observed (Scheme 4.37). Reasons for this failure is not clear at this stage.



4.144 **4.146** **4.145**

Scheme 4.37. Attempted nickel catalyzed borylation of fluorovinyl tosylate **4.144**.

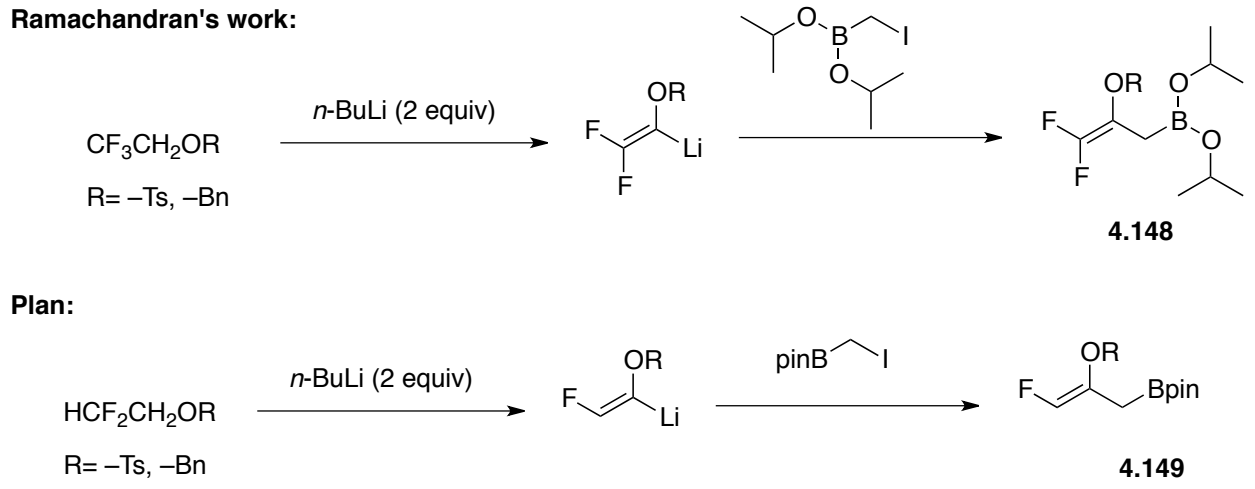
Intrigued by the findings of Governeur and co-workers that alkenyl silanes can be converted into alkenyl fluorides, an alternative plan was adopted. This time, B/Si reagent **4.147** was subjected to fluorination with Selectfluor® under microwave conditions, hoping that the C–Si bond would be replaced by a C–F bond. Unfortunately a large amount of decomposition was observed (Scheme 4.38).



4.147 **4.122**

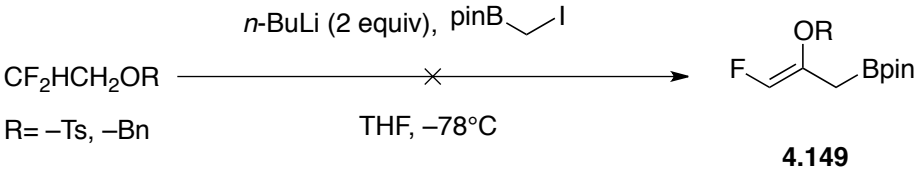
Scheme 4.38. Attempted fluorination of alkenyl silane **4.147**.

Encouraged by the success of Ramachandran and co-workers in generating γ,γ-difluoroallylboronates **4.148** from trifluoroethanol tosylate and benzyl ethers, a similar plan was adopted to synthesize γ-fluoroallylboronate **4.149** (Scheme 4.39).[91]



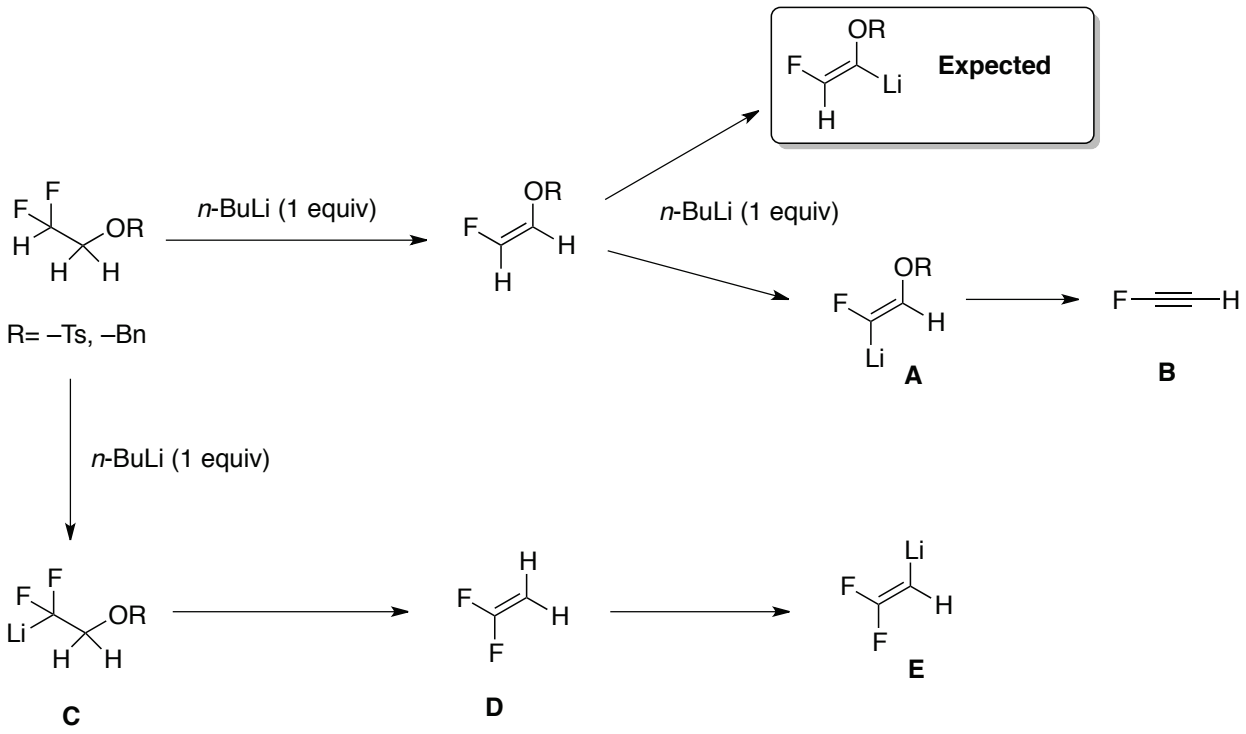
Scheme 4.39. Synthesis of 2-alkoxydifluoroallylboronates and monofluoroallylboronates.

Upon treatment with the base followed by the addition of the iodomethyl pinacolboronate, the corresponding tosylate and benzyl ethers of difluoroethanol form a black mixture. TLC analysis showed a complete decomposition of the starting materials (Scheme 4.40).



Scheme 4.40. Attempted synthesis of 2-alkoxymonofluoroallylboronate from difluoroethanol tosylate and difluoroethanol benzyl ether.

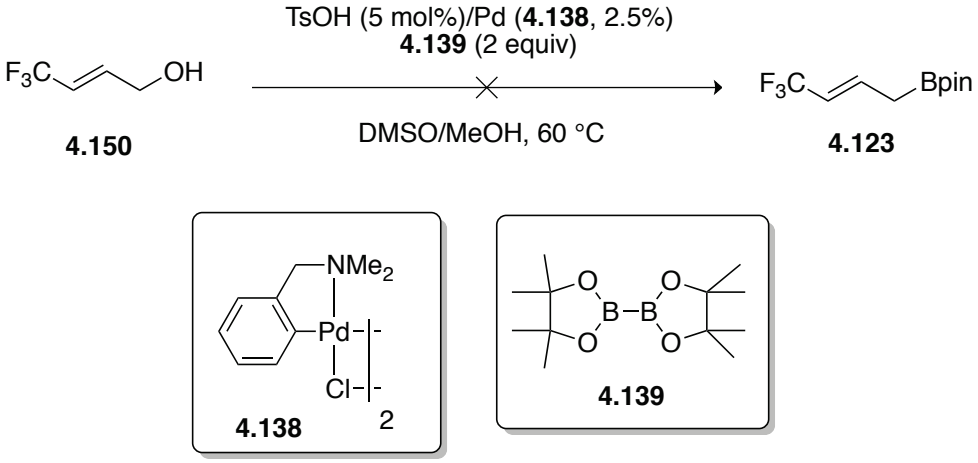
Although the exact reasons for this outcome is not clear at this stage, it can be postulated that the substrate upon treatment with 2 equivalents of base can form various intermediates (A-F) which could lead to various side products (Scheme 4.41)



Scheme 4.41. Various probable side reactions of difluoroethyl tosylate and difluoroethyl benzyl ether.

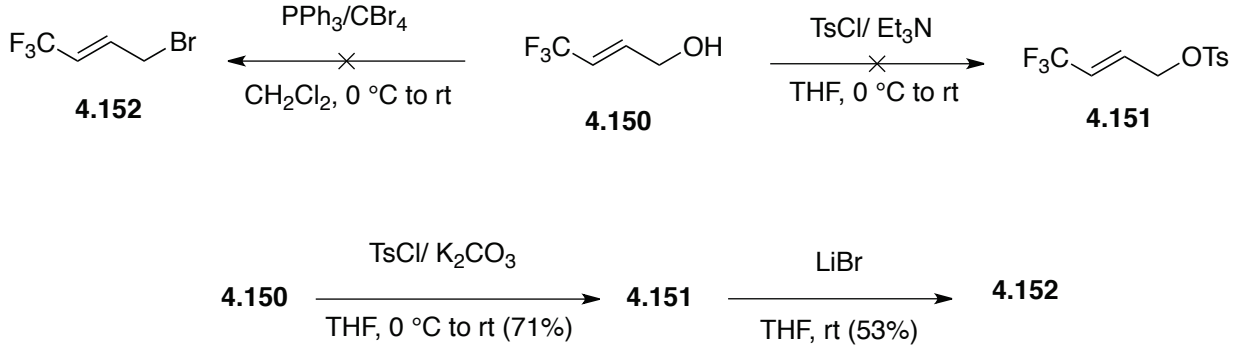
4.27: Results and discussion: synthetic attempts towards a 3-trifluoromethyl allylboronate (4.123)

Just like the attempted fluoroallylboronate synthesis described before (Scheme 4.33), the first approach towards the preparation of a trifluoromethylallylboronate involved the chemistry developed by Aggarwal and Szabo as discussed earlier. The starting alcohol (**4.150**) was both commercially available as well as easy to prepare. However, upon treatment of this alcohol under the conditions described earlier, no change was observed and the starting material was recovered (Scheme 4.42).



Scheme 4.42. Attempted synthesis of 3-trifluoromethylallylboronate from the corresponding allyl alcohol using the method of Szabo and Aggarwal.[87]

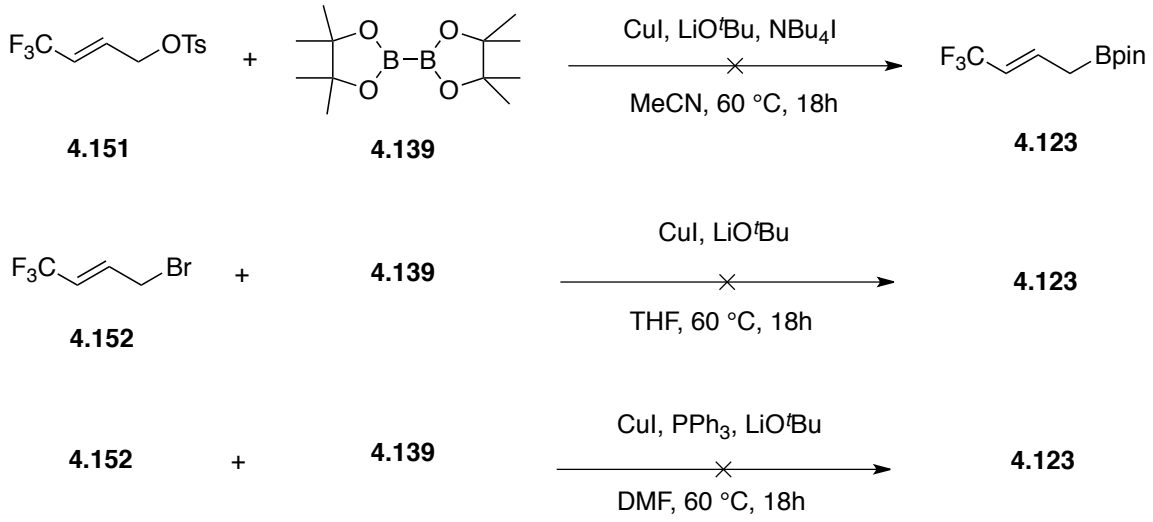
Following the unsuccessful attempt, the alcohol **4.150** was converted into a tosylate (**4.151**) or a bromide (**4.152**) with the intent of using these derivatives as the precursors. However, it was not easy as simple tosylation and bromination procedures such as the Appel reaction did not work at all. A much stronger base had to be used for the tosylation step and an indirect approach was taken via the tosylate for the conversion into the bromide (Scheme 4.43).



Scheme 4.43. Synthesis of 3-trifluoromethylallyl tosylate and bromide from the corresponding allyllic alcohol.

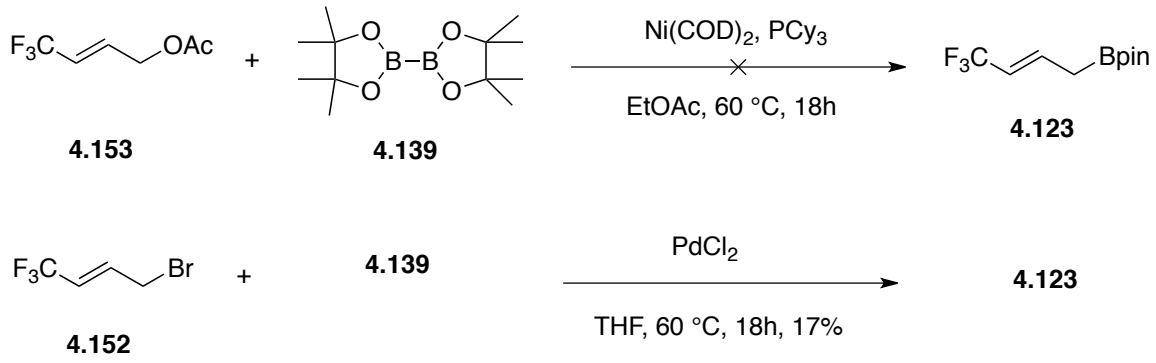
Once the tosylate **4.151** and bromide **4.152** were in hand, different borylation procedures were attempted. Conditions similar to the ones reported by Marder and co-workers were first tried.[93] Tetrabutylammonium iodide was added with the reaction mixture containing the tosylate to convert the substrate into the more

reactive iodide. However, only starting material was recovered after the reaction. The bromide, which is expected to be more reactive than the tosylate as observed by the Marder Group, remained unreacted too. Changing the solvent did not alter the outcome (Scheme 4.44). Two examples reported in the paper were successfully reproduced under the same conditions, hinting to the delicate nature of these particular substrates.[93]



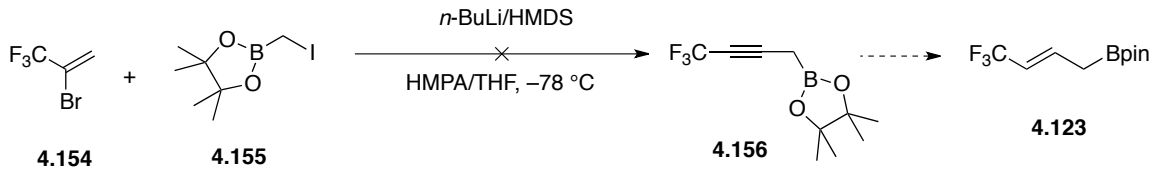
Scheme 4.44. Attempted synthesis of 3-trifluoromethylallylboronate using Marder's method.[92]

With the failure of these borylation methods, we decided to apply the borylation conditions developed by Morken and co-workers.[93] One method involved a nickel catalyzed borylation of the acetate in presence of a phosphine ligand. But despite of all the attempts, starting material remained unconsumed even after hours. The other method, involving palladium catalysis, worked only once. This reaction was difficult to reproduce and yielded many side products too, resulting in poor yield (Scheme 4.45).



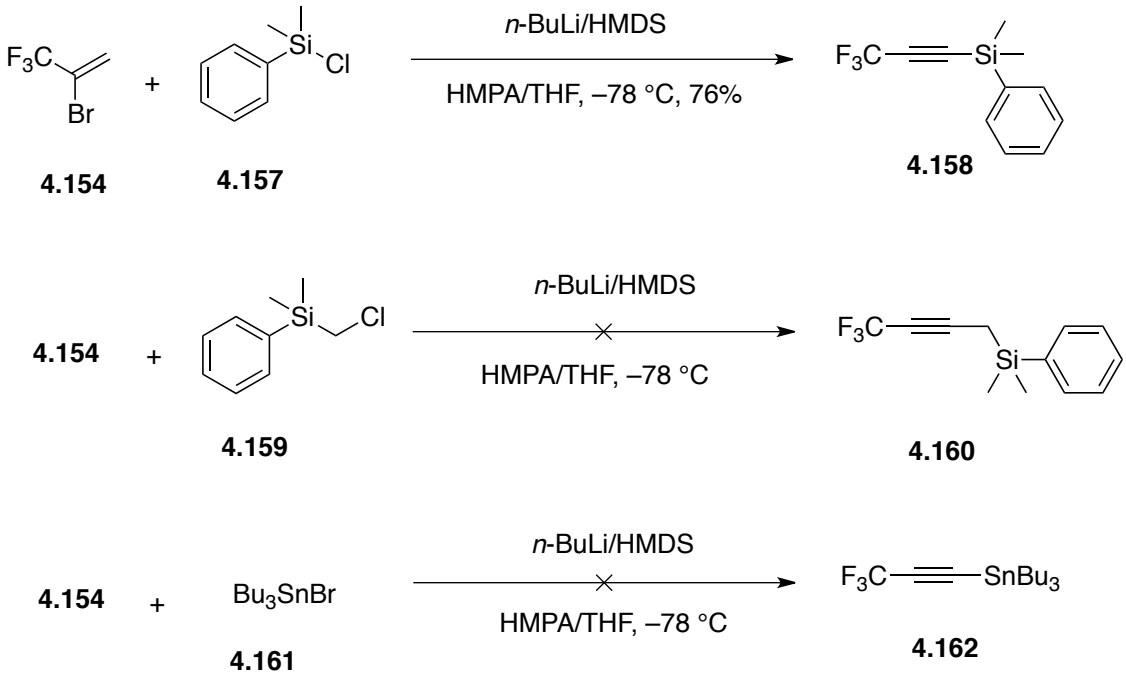
Scheme 4.45. Attempted synthesis of 3-trifluoromethylallylboronate using Morken's borylation method.[93]

With the intent of identifying a much higher yielding method, we decided to explore a few other procedures. Intrigued by the finding of Hanamoto and co-workers that 2-bromo-3,3,3-trifluoropropene can generate a trifluoromethylacetylide carbanion when treated with a base, we decided to adopt this idea as another alternative route towards the synthesis of the desired allylboronate.[94] Thus 2-bromo-3,3,3-trifluoropropene (**4.154**) was treated with BuLi followed by iodomethylpinacolboronate addition. However, with great disappointment, it was observed that the reaction did not go at all and starting iodomethylpinacolboronate was recovered (Scheme 4.46). The strong electron withdrawing effect of the trifluoromethyl group may decrease the reactivity of the intermediate acetylide nucleophile.



Scheme 4.46. Attempted synthesis of 3-trifluoromethylpropargylboronate using Hanamoto's method.

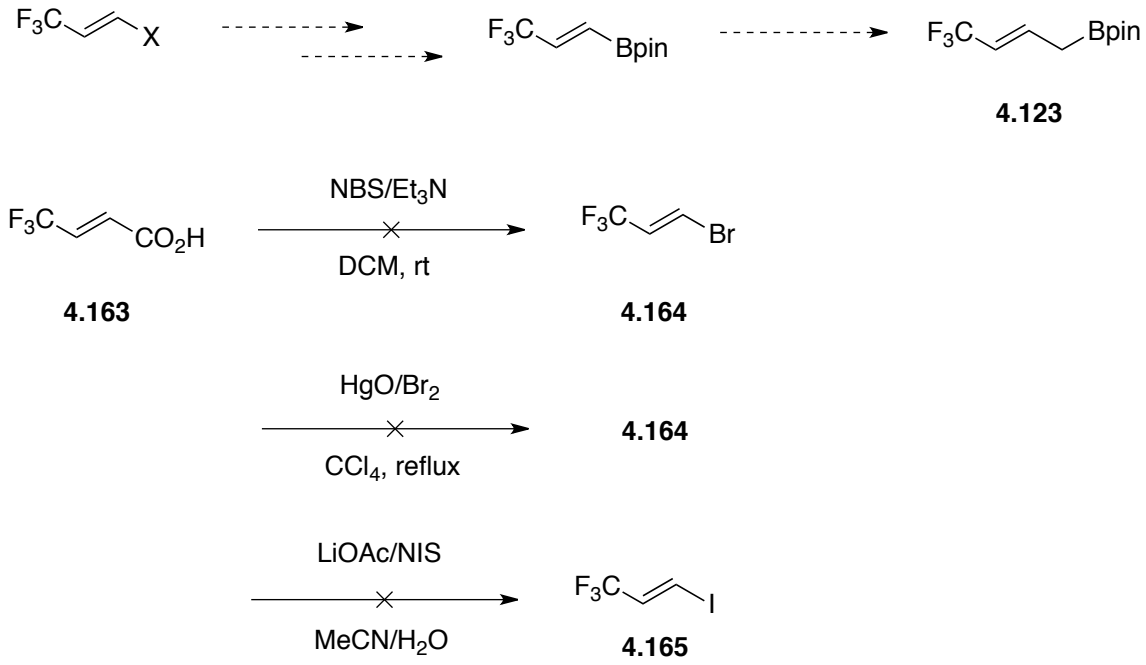
A silicon containing electrophile (**4.157**), however, worked smoothly. But the moment the electrophilic partner was changed into another silicon-containing electrophile but with one extra carbon atom (**4.159**), no reaction was observed. A tin-containing electrophile (**4.161**) did not work either (Scheme 4.47). All these observations clearly show that this particular method is very limited.



Scheme 4.47. Reactions with different electrophile partners.

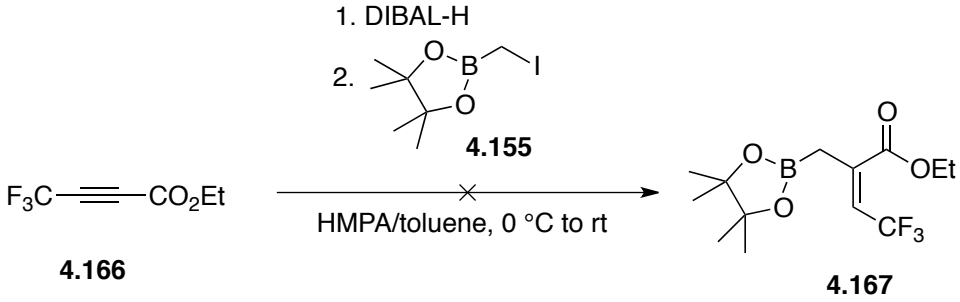
In an attempt to synthesize 2-trifluoromethylethylene halide, known literature methods of converting an alkenyl carboxylic acid into alkenyl bromide were applied.[95] The 2-trifluoromethylethylene halides would enable lithium halogen exchange/borylation or cross-coupling methods towards the ultimate goal. However, all the attempts towards the synthesis of 2-trifluoromethylethylene halides were unsuccessful. 2-trifluoromethylethylene carboxylic acid, prepared from the corresponding ester, was subjected to various modified Borodin-Hunsdiecker reaction conditions, affording only decomposition products (Scheme 4.48).

Plan:



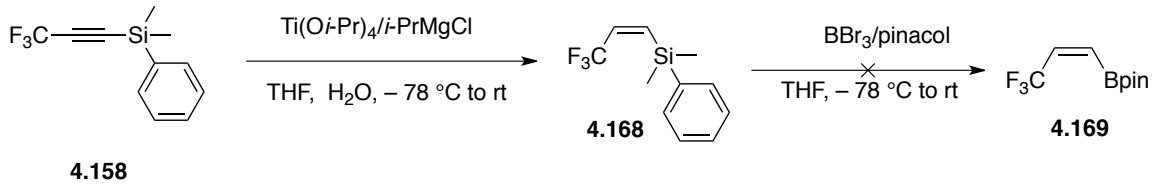
Scheme 4.48. Attempted synthesizes of 2-trifluoromethylethylene halides as precursors for trifluoromethylvinyl boronate.

Since none of these methods was productive, a slightly different approach was taken which if successful would lead to a reagent similar to what is being planned to achieve. This reagent, (**4.167**), although not exactly what is desired, could still be extremely valuable. These kinds of reagents have many potential applications including the synthesis of biologically relevant structures such as γ-lactone.[96] In an attempt to make this reagent, the corresponding propargylic ester (**4.166**) was subjected to reported procedures. After addition of DIBAL-H into a mixture of the ester (**4.166**) in HMPA and toluene, reagent **4.155** was added. In the usual conditions, the alkenyl aluminum species that is formed after the DIBAL-H addition captures the boron reagent, furnishing the desired product. Unfortunately, with substrate **4.166** only the starting materials were recovered and no desired product was observed (Scheme 4.49).



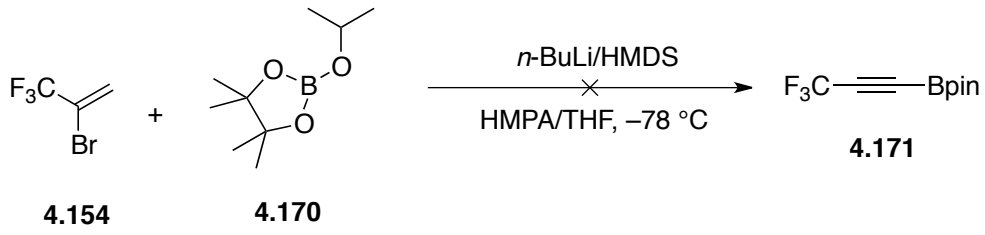
Scheme 4.49. Attempted synthesis of reagent **4.167**.

A desilylation/borylation method was also adopted towards the synthesis of 2-trifluoromethylvinyl boronate **4.169**, a potential precursor for the desired allylboronate. The vinyl silane precursor (**4.168**) was synthesized from the corresponding alkyne (**4.158**), whose preparation has been shown in Scheme 4.47.[94] The alkenyl silane **4.168** was treated with boron tribromide followed by pinacol. Unfortunately a complex mixture was obtained after the reaction (Scheme 4.50).



Scheme 4.50. Attempted synthesis of 2-trifluoromethylvinyl boronate.[94]

A more direct approach was taken by attempting to convert **4.154** into alkynyl boronate **4.171**, which then can be reduced to the desired vinyl boronate, **4.169**. Thus **4.154** was treated with butyllithium followed by the addition of isopropoxypinacolboronate (**4.170**). Unfortunately, no desired product was obtained (Scheme 4.51).



Scheme 4.51. Attempted synthesis of trifluoromethylalkynyl boronate.

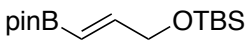
4.28: Conclusion

To conclude, a detailed investigation for the synthesis of 3-fluoroallylboronate and 3-trifluoromethylallylboronate was planned. Various processes, such as the Szabo method, the Miyaura borylation, fluoro desilylation, Ramachandran's method, Marder's procedure and Morken's method were applied. Most of these attempts were unsuccessful except the Morken's borylation method which afforded less than 20% yield along with many side products. Also, it was difficult to reproduce. The reasons for these failures are not clear at this stage. The lack of reactivity can be assigned to the presence of strong electron withdrawing groups such as –F and $–CF_3$ in these substrates, which significantly alters the electronic nature of the starting substrates making them less responsive towards those methods. However, other alternative methods towards the synthesis of the desired chiral α-fluorohomoallylic alcohol can be applied. All of these alternative methods have been discussed in the final chapter.

4.29: Experimental details: general Information

All reactions were performed in standard, flame-dried glassware under an inert atmosphere of nitrogen. Unless otherwise specified, reagents were bought from commercial suppliers and used without further purification. Solvents were dried either by distillation or by using a cartridge purification solvent system. Anhydrous Na_2SO_4 or $MgSO_4$ were used as the drying agent after aqueous workup. All substrates were purified by silica gel chromatography before use except the ones which were purchased. Evaporation and concentration *in vacuo* were accomplished at water aspirator pressure. Reaction products were purified by column chromatography using silica gel-60 (230-400 mesh). Reactions were monitored by thin layer chromatography with precoated glass plates covered with 0.2 mm silica gel. The spots were visualized by UV light, $KMnO_4$ or anisaldehyde stain. IR spectra were obtained with a Nicolet Magna-IR-750 spectrometer (cm^{-1}, cast film or neat). ^1H, ^{11}B, ^{13}C, and ^{19}F NMR spectra were obtained on a Varian Inova-300, 400 or Varian Unity-500 instruments, at 27 $^{\circ}C$ in $CDCl_3$. Residual solvent peaks (7.26 ppm for ^1H and 77.0 ppm for ^{13}C) were employed as reference. Accuracy for coupling constants (J-values) is estimated to be +/- 0.2 Hz. EI MS (m/z) was measured in a Kratos MS50 instrument. Alkenyl fluoride (**4.135**) was synthesized by following the procedure reported by Ritter and co-workers.[88a] The trifluoromethylallyl bromide (**4.152**) was synthesized by following the procedure reported by Loh and co-workers.[85]

Synthesis of alkenyl boronate 4.134



4.134

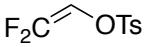
Pinacolborane (1.50 mL, 10.4 mmol) was added at 0 °C to a solution of 3-(*tert*-butyldimethylsilyloxy)-1-propyne (4.133, 2.00 mL, 9.86 mmol) in CH_2Cl_2 (8 mL). After stirring for 5 min, the resulting mixture was transferred via canula to a cooled (0 °C) suspension of $Cp_2ZrH(Cl)$ (136 mg, 0.493 mmol) in CH_2Cl_2 (4 mL) and the resulting mixture stirred at ambient temperature for 24 h. The reaction was quenched by slow addition of H_2O (causes foaming) and diluted with Et_2O (100 mL). Extractions with ether followed by flash chromatography gave alkenylboronate, **4.134** as a colorless oil (2.06 g, 71%). The compound is prone to undergo slow hydrolysis but can be stored under inert atmosphere at –20°C for extended periods of time. IR (film cast, $CHCl_3$): = 2979, 2930, 2896, 2857, 1645, 1472, 1340, 1320, 1257, 1146, 1109, 974, 838, 777; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.65 (dt, *J* = 17.9, 3.5 Hz, 1H), 5.74 (dt, *J* = 17.9, 2.1 Hz, 1H), 4.23 (dd, *J* = 3.5, 2.1 Hz, 2H), 1.25 (s, 12H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.1, 83.1, 64.5, 25.9, 24.7, 18.4, –5.4; ^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.8 ppm; MS (EI): m/z(%): 298 (1) $[M]^+$, 283 (7), 241 (42), 199 (1), 183 (2), 159 (4), 141 (100), 117 (5), 101 (28), 83 (39).

Synthesis of 2,2,2-trifluoroethyl tosylate (4.142)

4.142

A solution of 2,2,2-trifluoroethanol (10 mmol, 0.73 mL) and triethylamine (36 mmol, 5 mL) in CH_2Cl_2 (10 mL) was cooled to 0 °C. p-Toluenesulfonyl chloride (12 mmol, 2.3 g) was added, and the solution was stirred at that temperature for 1 h, then warmed to room temperature and stirred for a further 12 h. The organic layer was separated and washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated. Purification by flash chromatography on silica gel eluting with 10 % CH_2Cl_2 in hexane yielded **4.142** as a colorless solid (87 %). m.p: 38-39 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 4.36 (q, *J* = 7.9 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 131.9, 130.3, 128.2, 122.0 (q, *J*= 276 Hz), 64.6 (q, *J*= 37.8 Hz), 21.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.1; MS (EI): m/z: 254 $[M]^+$.

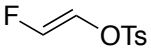
Synthesis of 2,2-difluorovinyl tosylate (4.143)



4.143

To a solution of 2,2,2-trifluoroethyltosylate (**4.142**, 8.7 mmol, 2.21 g) in THF (50 mL) at –78 °C was added dropwise 1.6 M *n*-butyllithium in hexane (20 mmol, 12.5 mL). After stirring under a nitrogen atmosphere at that temperature for 1 h, the solution was neutralized with a mixture of THF/H_2O (1:1, 30 mL). Water (20 mL) was added, and the organic phase was extracted with ether, dried over anhydrous sodium sulfate, filtered and evaporated. Purification by flash chromatography on silica gel eluting with 10 % CH_2Cl_2 in hexane yielded **4.143** as a colorless liquid (82 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.1 (dd, *J* = 14.3, 3.9 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2 (dd, *J*= 282.5, 293.2 Hz), 146.3, 131.5, 130.3, 128.5, 101.0 (dd, *J*= 59.5, 15.3 Hz), 21.9; ^{19}F NMR (282 MHz, $CDCl_3$): δ = –108.9 (dd, *J* = 50.6, 4.0 Hz, 1F), –90.3 (dd, *J* = 50.6, 14.3 Hz, 1F); MS (EI): m/z: 234 $[M]^+$.

Synthesis of (*E*)-2-fluorovinyl 4-methylbenzenesulfonate (4.144)

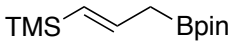


4.144

To a solution of 2,2-drifluorovinyl tosylate (**4.143**, 8.0 mmol, 1.9 g) in ether (50 mL) at 0 °C was added $LiAlH_4$ in hexane (8.0 mmol, 0.31 g) in one portion. The solution was warmed to room

temperature and stirred for 12 h. After cooling to 0 °C, the mixture was neutralized with an aqueous solution of NaOH (0.1 M, 1.0 mL), then filtered through a pad silica gel eluting with 10 % CH_2Cl_2 in hexane yielded **4.144** as a colorless oil (77 %). IR (neat) v = 3101, 2919, 1597, 1381, 1194, 1087, 893, 824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 2 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 7.00–6.77 (m, 2 H), 2.47 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.8 (d, *J* = 255.0 Hz), 145.9, 131.1, 130.0, 128.9 (d, *J* = 45.9 Hz), 128.4, 21.70; ^{19}F NMR (471 MHz, $CDCl_3$): δ = –161.95 to –161.69 (m); EI-MS: m/z (%): 91 (100), 155 (55.89), 65 (27.24), 92 (8.27), 89 (7.65), 63 (6.94), 156 (4.89), 51 (3.51).

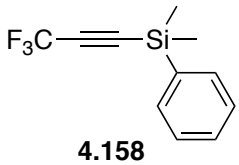
Synthesis of 4,4,5,5-tetramethyl-2-[(2*E*)-3-(trimethylsilyl)-2-propenyl]-1,3,2 dioxaboroline (4.147)



4.147

To a solution of 7.5 ml (50 mmol) of tetramethylethylenediamine in 30 ml of THF was added at –78 °C 43 ml (50 mmol) of a 1.16 M solution of *sec*-butyllithium in cyclohexane. Subsequently, 7.9 ml (50 mmol) of allyltrimethylsilane was added dropwise. The solution was stirred for 30 min at –30 °C) and recooled to –78 °C. This solution was added to a precooled solution of 9.30 g (50 mmol) of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 15 ml of THF. The mixture was allowed to reach room temperature over 12 h, then 100 ml of dichloromethane, 50 ml of saturated aqueous NH_4Cl solution, and 50 ml of 1 M hydrochloric acid were added sequentially. The organic phase was separated and extracted three times with 50 ml each of water. After drying with $MgSO_4$ and filtration and concentration, the residue was chromatographed on silica gel with ether/petroleum ether to give 7.48 g (62%) of **4.147** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.06 (dt, *J* = 18.4 , 7.1 Hz, 1 H), 5.61 (dt, *J* = 18.4, 1.5 Hz, 1H), 1.79 (d, *J* = 7.0 Hz, 2H), 1.23 (s, 12H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0, 130.6, 83.1, 24.7, –1.1; ^{11}B NMR (128.5 MHz, $CDCl_3$): = 30; MS (EI): m/z (%): 240.17 (100.0%), 239.18 (24.5%), 241.18 (13.6%), 241.17 (5.8%), 242.17

Synthesis of 3,3,3-trifluoro-1-(dimethylphenylsilyl) propyne (4.158)

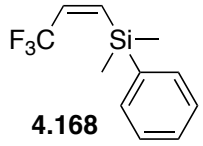


4.158

To a 100 mL three-neck flask equipped with a magnetic stir bar was charged with 10 mL of THF, followed by HMDS (8.43 mmol, 1.76 mL) and HMPA (0.517 mmol, 90 µL) respectively. Then *n*-BuLi (2.64 M in hexane solution, 8.45 mmol, 3.20 mL) was added dropwise at 0 °C. Another 25 mL two-neck

flask equipped with a magnetic stir bar was charged with 2-bromo-3,3,3-trifluoropropene (3.87 mmol, 0.40 mL) in 3 mL of THF under argon. After both the solutions were cooled at –78 °C, the second solution was transferred to the first solution via cannula while both the flasks were kept at —78 °C. After the solution was stirred for 30 min, chlorodimethylphenylsilane (3.51 mmol, 0.58 mL) was added. After the addition, the mixture was further stirred for 30 min. At this point, a large excess of hexane (70 mL) was added to the mixture and allowed to warm to room temperature. Finally a saturated aqueous solution of NH_4Cl (15 mL) was added to the mixture. After the organic layer was separated, additional extraction with hexane was repeated twice. The combined organic phases were dried over sodium sulfate, filtered, and evaporated. The solution was concentrated *in vacuo*, and the residual oil was quickly purified by short-path distillation (46-48 °C, 2 mm Hg) to give the desired product as a colorless oil in 76% of 4.158. IR (neat) v = 3075, 3050, 3025, 2975, 2200. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7-7.35 (5 H, m), 0.6-0.5 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.7, 133.0, 130.2, 128.2, 113.1 (q, *J* = 257.9 Hz), 92.3 (q, *J* = 6.0 Hz), 91.1 (q, *J* = 50.9 Hz), – 2.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ = 27.8 (s).

Synthesis of (*Z*)-3,3,3-trifluoro-1-(dimethylphenylsilyl) propene (4.168)



4.168

A 25 mL three-neck flask equipped with a magnetic stir bar was charged with 4.158 (0.396 mmol, 90.3 mg) and [Ti(O*i*-Pr)$_4$] (0.96 mmol, 0.3 mL) in ether (7 mL) under argon. To this solution was added *i*-PrMgCl (2.0 M in ether, 1.90 mmol, 0.95 mL) at –78 °C, and then the solution was warmed to – 50 °C over 30 min, during which time it turned dark red. After the mixture had been stirred at that temperature for 2 h, water (2.8 mmol) was added. After the mixture was stirred for 1 h, the reaction was quenched with 1 M HCl. After the organic layer was separated, additional extraction with hexane/ether (3:1) was repeated twice. The combined organic layers were concentrated in vacuo and the resultant oil was purified by column chromatography (hexane:ether = 10:1) to give **4.168** as a colourless oil (72 %). IR (neat) v = 3073, 2961, 1626, 1376, 1288, 1199, 1120; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.54 (2H, m), 7.41-7.35 (3 H, m), 6.50-6.32 (2 H, m), 0.6-0.5 (6 H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.3 (d, *J* = 5.6 Hz), 137.6, 133.6 (d, *J* = 35.1 Hz), 133.5, 129.3, 127.9, 122.9 (q, *J* = 271.5 Hz), – 2.0 (q, *J* = 2.5 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) –62.7 (d, *J* = 6.8 Hz); MS (EI): m/z (%): 215 [M^+ –15 (Me), 0.2], 171 (7), 153 (2), 133 (42), 115 (77), 91 (17), 77 (100).

4.30: References

1. a) Important review on the physical properties of organofluorine compounds: *Fluorine in Medicinal Chemistry and Chemical Biology*, Ojima, E., Ed.; Wiley–Blackwell: **2009**. b) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127. c) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
2. a) Peters, R.; Wakelin, R. W. *Proc R. Soc. Ser. B,* **1953**, *140*, 497. b) Lauble, H.; Kennedy, M. C.; Emptage, M. H.; Beinert, H.; Stout, C. D. *Proc. Natl. Acad. Sci. USA,* **1996**, *93*, 13699.
3. Kobayashi, Y.; Taguchi, T. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 1073.
4. Okamoto, S.; Tanaka, Y.; DeLuca, H. F.; Kobayashi, Y.; Ikekawa, N. *Am. J. Physiol.* **1983**, *244,* 159.
5. a) MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34,* 3553. b) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.
6. a) Carcenac, Y.; Diter, P.; Wakselman, C.; Tordeux, M. *New J. Chem.* **2006**, *30,* 442. b) Carcenac, Y.; Tordeux, M.; Wakselman, C.; Diter, P. *New J. Chem.* **2006**, *30,* 447.
7. Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102,* 5618.
8. Leroux, F. *ChemBioChem.* **2004**, *5,* 644.
9. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology,* John Wiley & Sons, Inc., Hoboken: **1979**.
10. a) Ganguly, T.; Mal, S.; Mukherjee, S. *Spectrochim. Acta. Part A* **1983**, *39A,* 657. b) Morgenthaler, M.; Schweizer, E.; Hoffmann-Roder, A.; Bennini, F.; Rainer, E. M.; Jaeshke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diedrich, F.; Kansay, M.; Muller, K. *ChemMedChem.* **2007**, *2,* 1100.
11. Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc. Perkin Trans 2.* **1989**, *2,* 699.
12. Smart, B. E. *Molecular Structure and Energetics,* F. Liebman and A. Greenberg Eds.; Wiley–VCH Verlag GbmbH, Weinheim.**1986**.
13. Bock, C. W.; George, P.; Mains, G. J.; Trachtman, M. *J. Chem. Soc., Perkin Trans.* **1979**, *2,* 814.
14. a) Klaboe, P.; Nielsen, J. R. *J. Chem. Phys.* **1960**, *33,* 1764. b) Hirano, T.; Nonoyama, S.; Miyajima, T.; Kurita, Y.; Kawamura, T.; Sato, H. *J. Chem. Soc., Chem. Commun.* **1986**, 606.
15. a) Fernholt, L.; Kveseth, K. *Acta Chem. Scand. A.* **1980**, *34,* 163. b) Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* **1980**, *102,* 3987. c) Dixon, D. A.; Matsuzawa, N.; Walker, S. C. *J. Phys. Chem.* **1992**, *96,* 10740.
16. a) Wiberg, K. B.; Keith, T. A.; Frisch, M. J.; Murcko, M. *J. Phys. Chem.* **1995**, *99*, 9072. b) Rablen, P. R.; Hoffmann, R. W.; Hrovat, D. A.; Borden, W. T. *J. Chem. Soc. Perkin Trans. 2,* **1999**, 1719.
17. Nicoletti, M.; O' Hagan, D.; Slawin, A . M. Z. *J. Am. Chem. Soc.* **2005**, *127,* 482.
18. Apeloig, Y. *J. Chem. Soc., Chem. Commun.* **1981***,* 396.

19. Farnham, W. B.; Smart, B. E.; Middleton, W. J.; Calabrese, J. C.; Dixon, D. *J. Am. Chem. Soc.* **1985**, *107,* 4565.
20. Barbarich, T. J.; Rithner, C. D.; Miller, S. M.; Anderson, O. P.; Strauss, S. H. *J. Am. Chem. Soc.* **1999**, *121,* 4280.
21. Bartolomé, C.; Espinet, P.; Martín-Alvarez, J. M. *Chem. Commun.* **2007***,* 4384.
22. Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc. Chem. Commun.* **1980**, 234.
23. Allmendinger, T.; Furet, P.; Hungerbuhler, E. *Tetrahedron Lett.* **1990**, *31,* 7297.
24. *MedAdNews 200 – World's Best-Selling Medicines, MedAdNews,* (http://en. wikipedia.org/wiki/List_of_top_selling_drugs).
25. Lewandowski, G.; Meissner, E.; Milchert, E. *J. Hazard. Mater.* **2006**, *136*, 385.
26. Patterson, J. C.; Mosley, M. L. *Mol. Imaging Biol.* **2005**, *7*, 197.
27. a) Ma, J-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. b) Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1995**, *36,* 4721.
28. Padova, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *J. Chem. Soc. Chem. Commun.* **1995**, 661.
29. Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A. M.; McCarthy, T. D. *Synlett.* **2004**, 791.
30. Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60,* 4730.
31. Shutske, G. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1544.
32. Dauben, W. G.; Greenfield, L. J. *J. Org. Chem.* **1992**, *57,* 1597.
33. Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc. Chem. Commun.* **1992**, 595.
34. Manthey, M. K.; Gonzalez-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 625.
35. Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.
36. a) Purser, S.; Odell, B.; Claridge, T. D. W.; Moore, P. R.; Gouverneur, V. *Chem. Eur. J.* **2006**, *12,* 9176. b) Purser, S.; Wilson, C.; Moore, P. R.; Gouverneur, V. *Synlett.* **2007**, 1166. c) Lam, Y.-h.; Bobbio, C.; Cooper, I. R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2007**, *46,* 5106.
37. Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233.
38. Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29,* 6087.
39. Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34,* 3971.
40. a) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2,* 3699. b) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122,* 10728.
41. a) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123,* 7001. b) Cahard, D.;

Audouard, C.; Plaquevent, J.-C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42,* 1867.

42. Baudequin, C.; Loubassou, J. F.; Plaquevent, J.-C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122,* 189
43. Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55,* 801.
44. Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46,* 1447.
45. Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9,* 3053.
46. Enders, D.; Hu¨ttl, M. R. M. *Synlett.* **2005**, 991.
47. Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44,* 3706.
48. Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44,* 3703.
49. Singh, R.; Shreeve, J. *Synthesis* **2002**, *17,* 2561.
50. Messina, P.; Mange, K.; Middleton, W. *J. Fluorine Chem.* **1989**, *42,* 137.
51. Lal, G.; Pez, G. P.; Pesresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64,* 7048.
52. Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104,* 247.
53. Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268.
54. Laurent, E. G.; Marquet, B.; Tardivel, R.; Thiebault, H. *Tetrahedron Lett.*, **1987**, *28*, 2359.
55. Fuchigami, T.; Shimojo, M.; Konno, A.; Nakagawa, K. *J. Org. Chem.* **1990**, *55*, 6074.
56. Lee, S. M.; Roseman, J. M.; Zartman, C. B.; Morrison, E. P.; Harrison, S. J.; Stankiewicz, C. A. W.; Middleton, J. *J. Fluorine Chem.,* **1996**, *77*, 65.
57. Kabore, L.; Chebli, S.; Faure, R.; Laurent, E.; Marquet, B. *Tetrahedron Lett.* **1990**, *31,* 3137.
58. Baba, D.; Ishii, H.; Higashiya, S.; Fujisawa, K.; Fuchigami, T. *J. Org. Chem.* **2001**, *66,* 7020.
59. Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
60. Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T. Buchwald, S. L. *Science* **2009**, *325*, 1661.
61. Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.
62. Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Godadard, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322.
63. Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111,* 393.
64. Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38,* 2252.
65. Qiu, X. L.; Qing, F. L. *J. Org. Chem.* **2002**, *67,* 7162.
66. Munier, P.; Picq, D.; Anker, D. *Tetrahedron Lett.* **1993**, *34,* 8241.
67. Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40,* 589.
68. Hanzawa, Y.; Uda, J.-I.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. *Chem. Pharm. Bull.* **1991**,

39, 2459.

69. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317,* 1981.
70. Prakash, G. K. S. 29th Western Regional Meeting of the American Chemical Society and 32nd Annual Meeting of the Southern California Section of the Society for Applied Spectroscopy, Pasadena, CA, October 19-23, **1993**.
71. Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35,* 3137.
72. a) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36,* 666. b) Nagao, H.; Kawano, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2007**, *80,* 2406. c) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707.
73. Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20,* 103.
74. a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31,* 3579. b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115,* 2156.
75. Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59,* 5692.
76. a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *9,* 2579. b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46,* 754.
77. Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575.
78. Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* **2009**, *48,* 4332.
79. Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132,* 4986.
80. Blazejewski, J.-C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11,* 335.
81. Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62,* 7199.
82. Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328,* 1679.
83. Wang, X.; Truesdale, L.; Yu, J. *J. Am. Chem. Soc.* **2010**, *132,* 3648.
84. Ramachandran, P. V.; Agnieszka, T-K.; Chatterjee, A. *J. Org. Chem.* **2012**, *77*, 9329.
85. Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, 1893.
86. Gao, X.; Yong, J. Z.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 4173.
87. Dutheuil, G.; Selander,N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis*, **2008**, 2293.
88. a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. b) Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *108,* 2445.
89. Zhang, H.; Zhou, C.-B.; Chen, Q.-Y.; Xiao, J.-C.; Hong, R. *Org. Lett.* **2011**, *13*, 560.
90. Wilson, D. A.; Wilson, C. J.; C. Moldoveanu, A.-M.; Resmerita, P.; Corcoran, L. M.; Hoang, B.; Rosen, M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 18000.
91. Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.

92. Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Czyzewska, Y.F. M.; Steel, P.G.; Marder, T.B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528.
93. Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1363.
94. Hanamoto,T.; Yamada, K. *J. Org. Chem.* **2009**, *74,* 7559.
95. Xu, R.-S.; Yue, L.; Pan, Y.-J. *Tetrahedron* **2012**, *68*, 5046.
96. Elford, T. G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G. D.; Hall, D. G. *J. Comb. Chem.* **2009**, *11,* 155.

Chapter 5

Studies towards the synthesis of a boron based bidirectional double-allylation reagent

5.1 Introduction

Although many double allylation reagents are reported and their applications in aldehyde allylation are thoroughly studied, boron based bidirectional double allylation reagents have not been explored extensively. These reagents, upon asymmetric allylation with aldehydes would generate chiral methylenepentane-1,5-diols. These diols are extremely important structural motifs and can be transformed into perhydrofurans and spiroketals; both structures are abundant in natural products (**5.1-5.4**, Figure 5.1).[1,2]

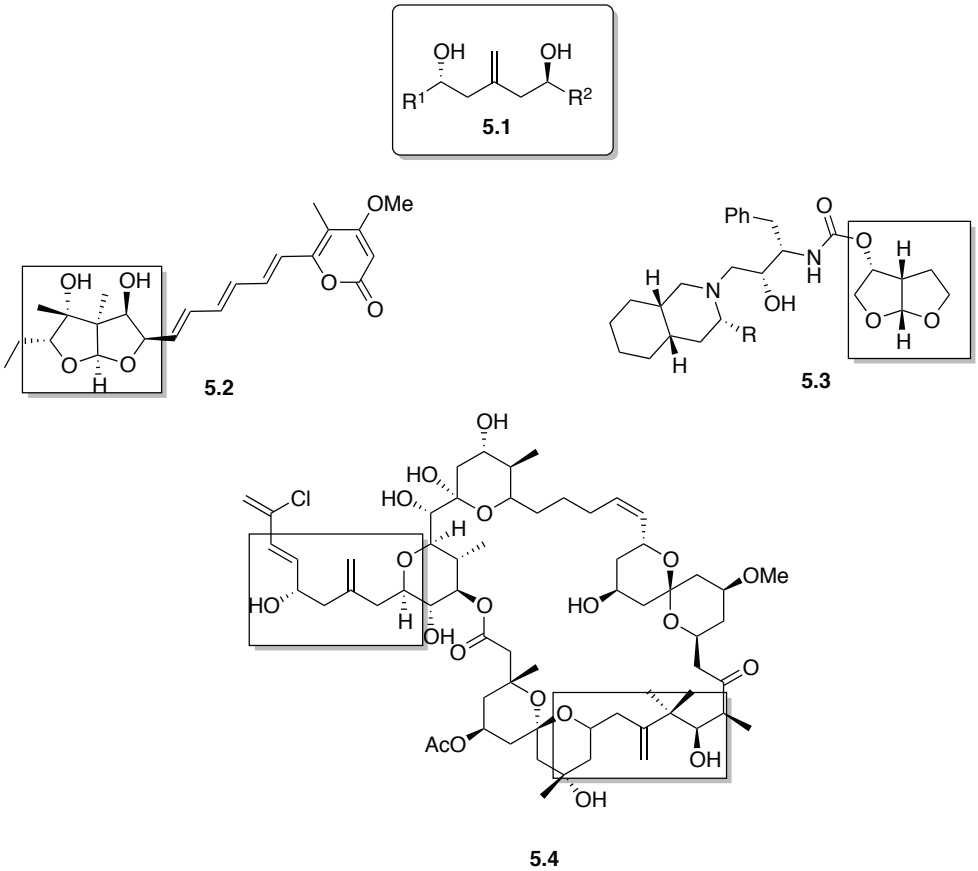


Figure 5.1. Chiral methylenepentane-1,5-diol and various natural products containing this unit.[1,2]

Despite of such immense potential, there are only two known boron-based bidirectional reagents in the literature. One example was reported by Barrett and co-workers. However, these reagents (**5.5** and **5.6**) is an unstable diborane and had to be prepared and reacted *in situ*.[1] The other reagent was a B/Si-based reagent (**5.7**), reported by Williams and co-workers, which also had to be prepared and reacted at once.[3] A detailed discussion about these reagents was included in Chapter 3 (Figure 5.2).

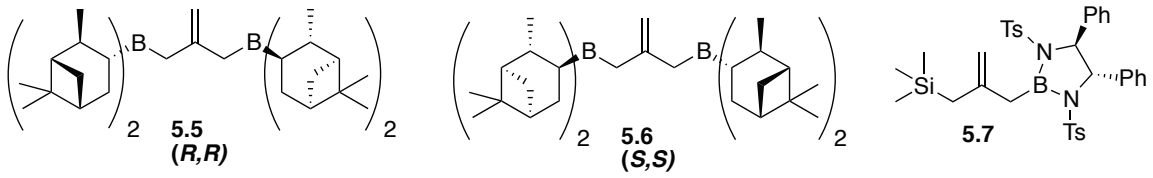
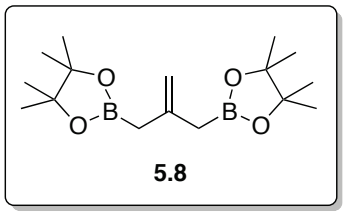
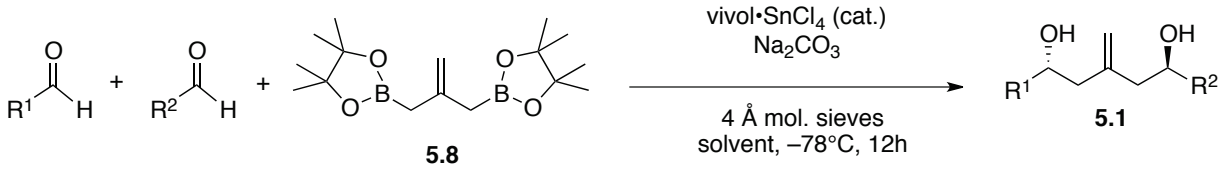


Figure 5.2. Chiral bidirectional reagents reported by Barrett and Williams.[1,3]

5.2 Project plan

There is a need for a stable and user friendly boron based bidirectional reagent **5.8**, which can be used in catalytic allylboration. The goal is to make the reagent from suitable starting materials and then to apply the reagent in the vivol•$SnCl_4$-catalyzed allylboration reaction (Scheme 5.1).

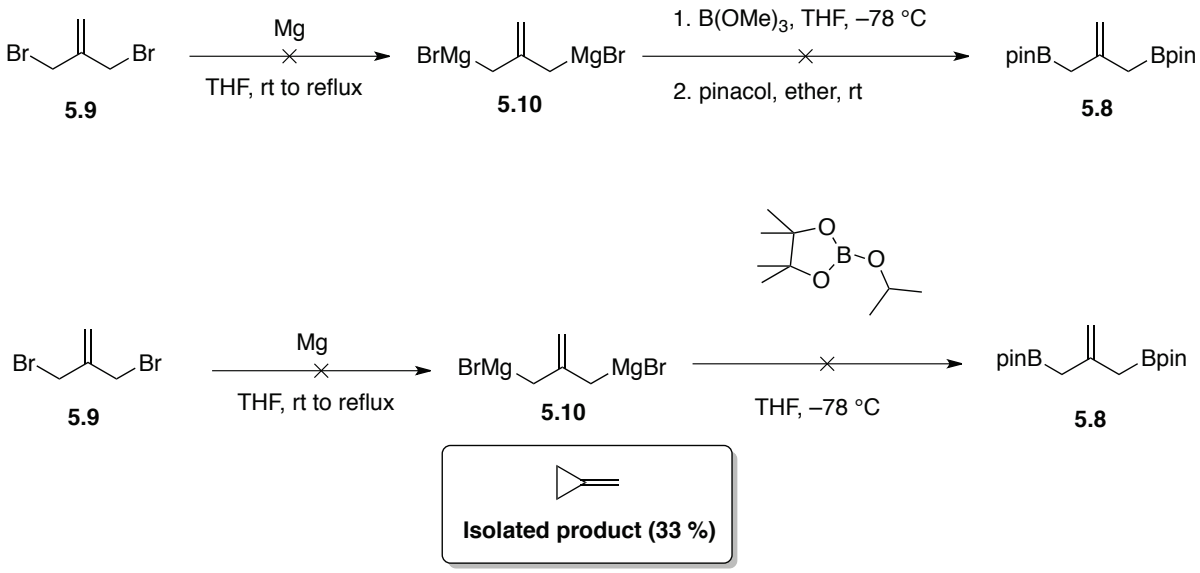




Scheme 5.1. B/B-bidirectional double-allylation reagent and its application in vivol•$SnCl_4$ catalyzed double-allylboration.

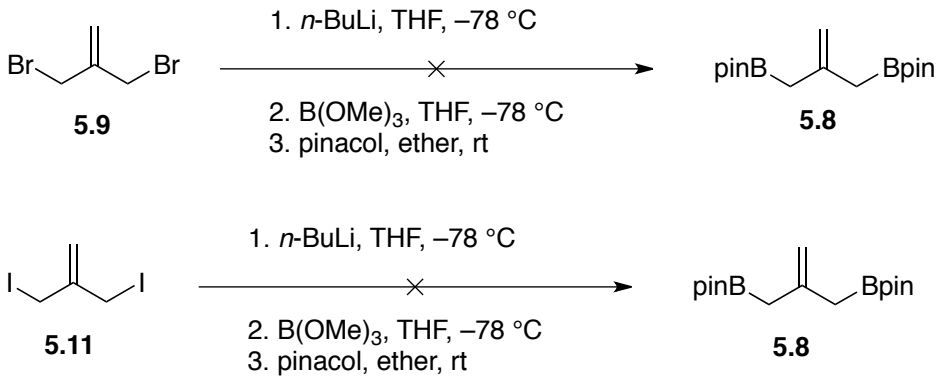
5.3 Results and discussion

The initial attempts towards the synthesis of the B/B-bidirectional double-allylation reagent involved the applications of Grignard and Li-halogen exchange reactions. The plan was to make a di-anion/di-metal species which would be treated with a suitable borylation reagent. When 3-bromo-2-(bromomethyl)-propene (**5.9**) was subjected to Grignard reaction conditions, a dark black solution formed, which was treated with $B(OMe)_3$ with the intent of forming the diboronic acid after acidic work-up. The obtained crude mixture was treated with pinacol afterwards. Another reaction was set-up where the dark solution obtained after the Grignard step was treated directly with isopropoxyboronic acid pinacol ester. Unfortunately, both reactions failed and a cyclopropane-based side product was obtained. Thus, it can be postulated that the initial Grignard reaction could not take place at all and instead underwent intramolecular cyclization (Scheme 5.2). Titration of the Grignard mixture indeed revealed that the desired Grignard reagent has not formed at all.



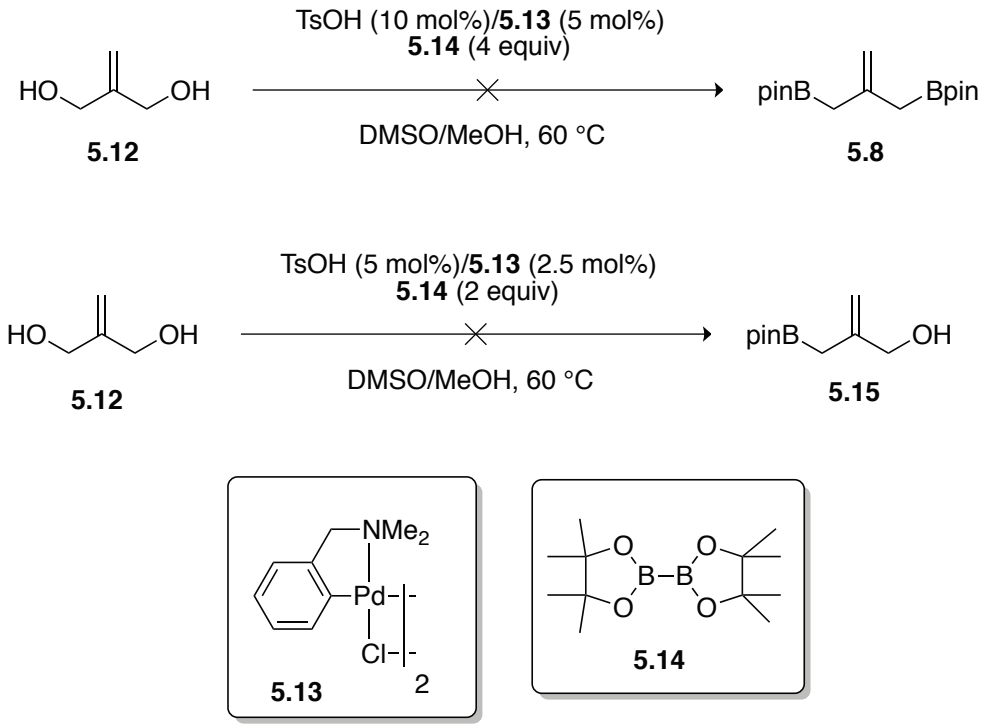
Scheme 5.2. Attempted synthesis of B/B-bidirectional double-allylation reagent via Grignard reactions.

Attempts were made to generate the desired di-anion/di-metal species via lithium-halogen exchange of 3-bromo-2-(bromomethyl)-propene (**5.9**). However, a complete decomposition was observed. Similar attempts with the iodo version (**5.11**) also led to many undesired side products (Scheme 5.3).



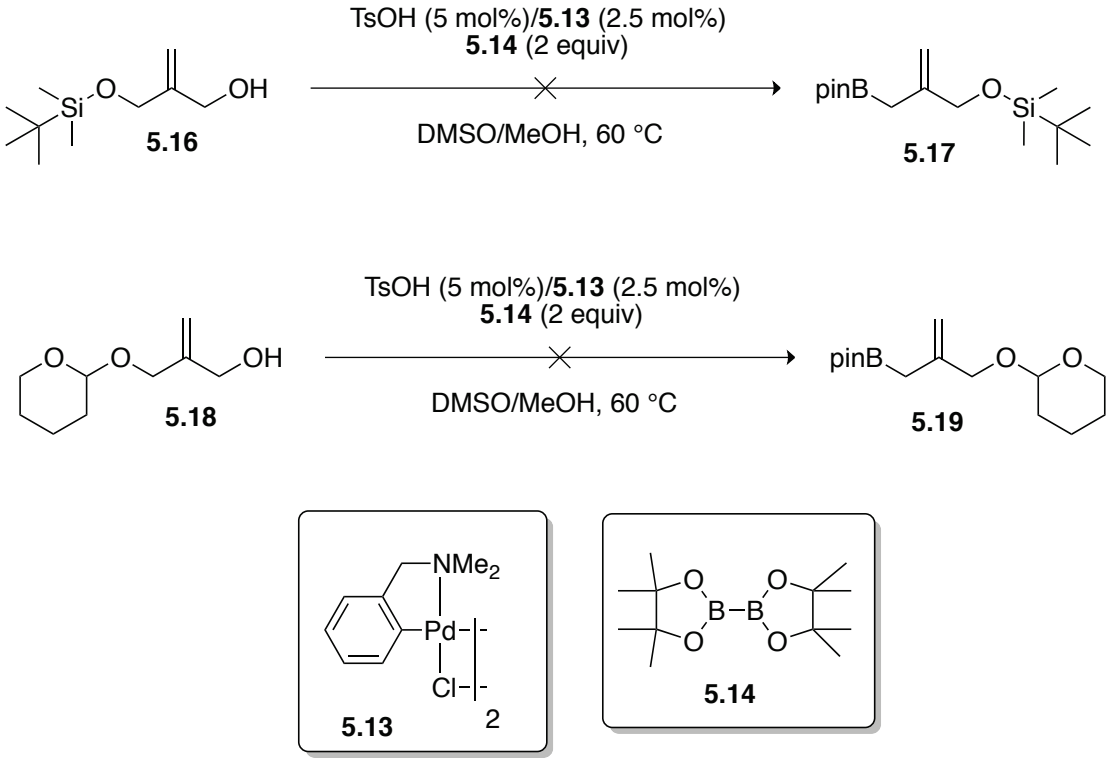
Scheme 5.3. Attempted synthesis of B/B-bidirectional double-allylation reagent via lithium-halogen exchange.

After the failure of the di-anion/di-metallic approach, borylation methods reported by Szabo and co-workers were adopted. Szabo and co-workers have successfully transformed allyl and crotyl alcohols into the corresponding allylboronates by treating them with bispinacolatodiboron (**5.16**) in the presence of bridged or pincer palladium complexes as catalysts.[4] In this reaction, two equivalents of bispinacolatodiboron are used for one equivalent of allyl or crotyl alcohol. 2-Methylene-1,3-propanediol (**5.12**) was chosen as the substrate which was subjected to the Szabo method in the presence of four equivalents of B_2pin_2 to allow borylation of both –OH groups. At the same time another reaction was set up with two equivalents of B_2pin_2 expecting to see a partial or monoborylation. Unfortunately both reactions failed to generate the desired products and starting materials were recovered in both cases (Scheme 5.4).



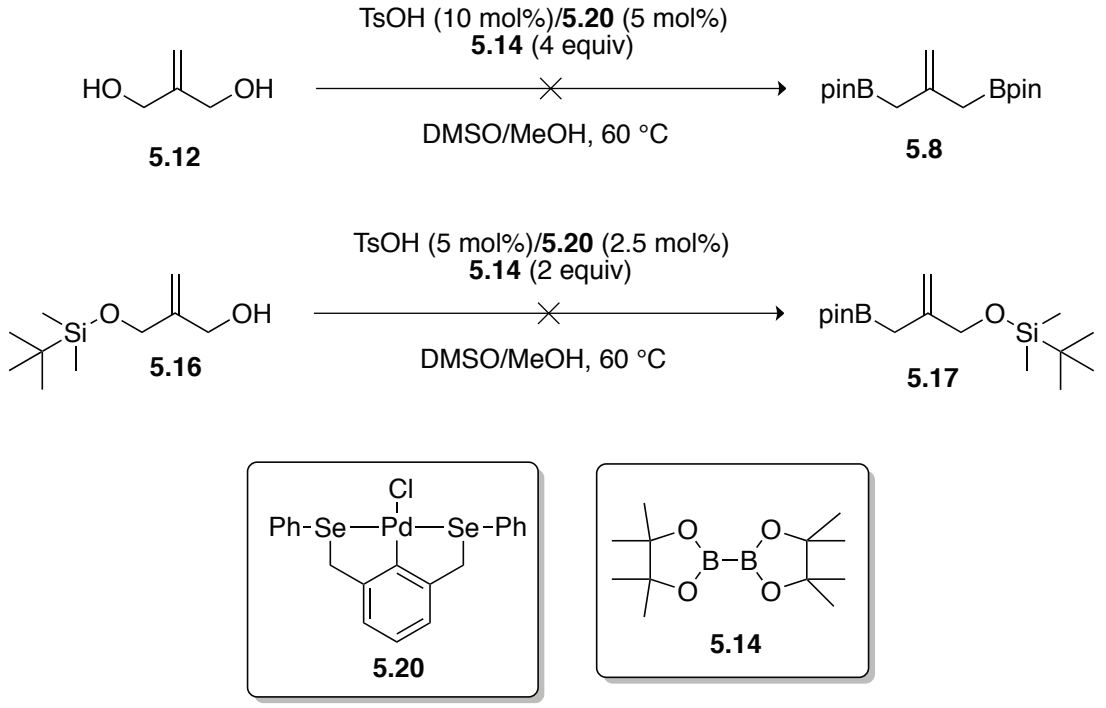
Scheme 5.4. Attempted synthesis of B/B-bidirectional double-allylation reagent via the Szabo's method.

Anticipating the possibility of interference from the second –OH group, one of the –OH groups was protected independently with TBDMS and THP groups. Both, of these substrates (**5.16** and **5.18**) were then subjected to the Szabo procedure employing two equivalents of B_2pin_2. However, none of these reactions were fruitful and the starting materials were recovered (Scheme 5.5).



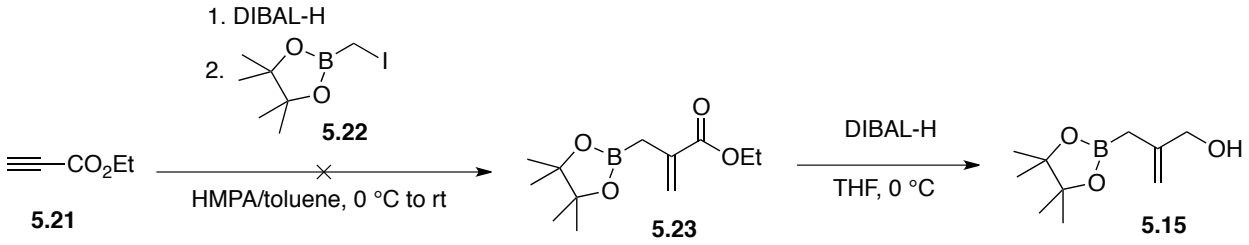
Scheme 5.5. Attempted synthesis of B/B-bidirectional double-allylation reagent from monoprotected diol via Szabo's method.

Using a Pd-pincer complex (**5.20**) as catalyst, exploited heavily by the Szabo Group in these kinds of reactions, did not change the outcome (Scheme 5.6).



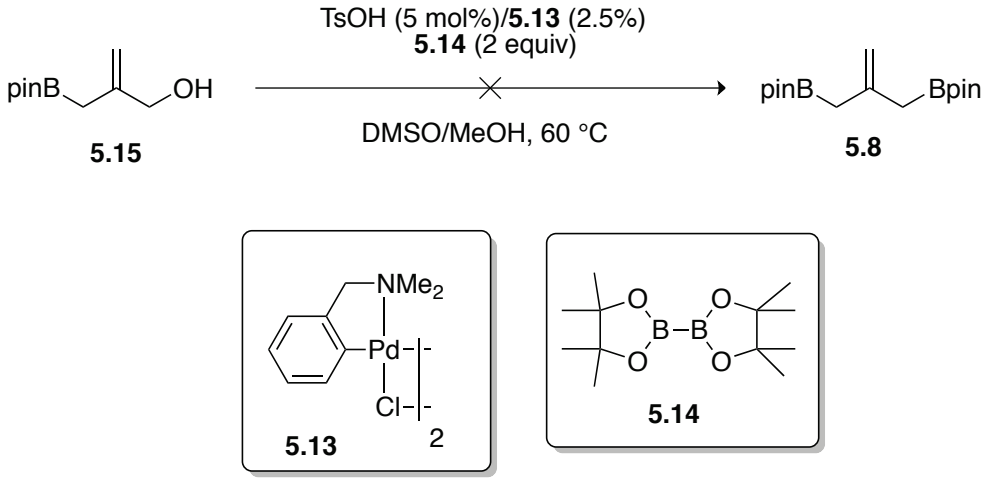
Scheme 5.6. Attempted synthesis of B/B-bidirectional double-allylation reagent using Pd-pincer complex as catalyst.

An alternative substrate (**5.24**) for the Szabo chemistry, already possessing an allylboronate unit, was prepared as shown in Scheme 5.7.



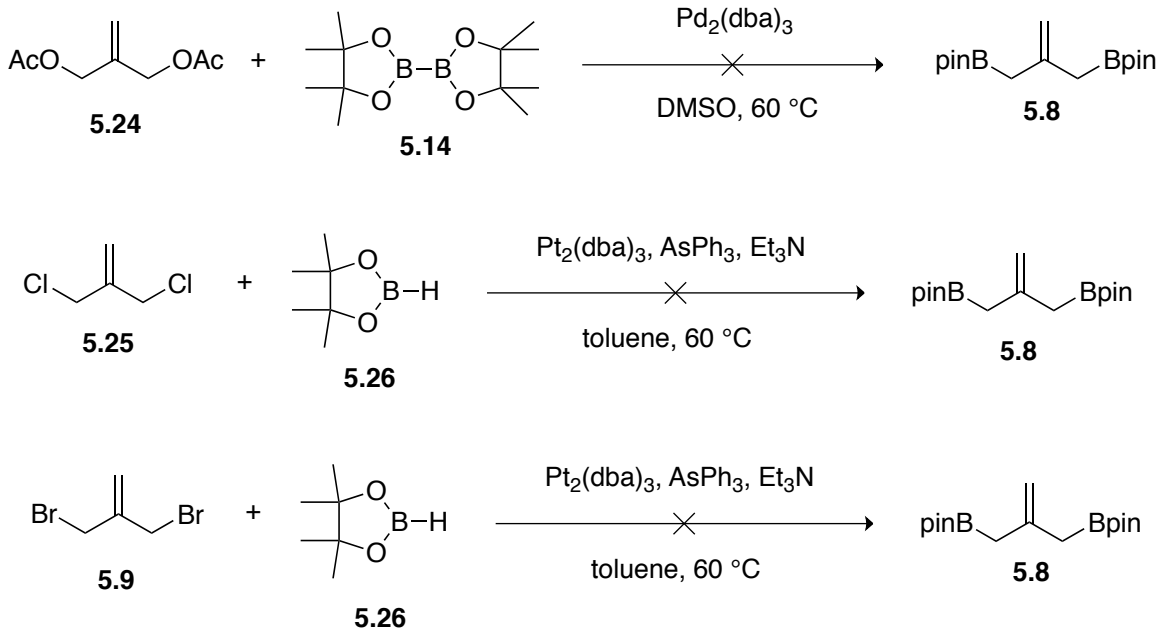
Scheme 5.7. Synthesis of the precursor **5.15** for Szabo's chemistry.

With this reagent in hand, the borylation method was applied with two equivalents of B_2pin_2. Unfortunately no desired product was formed and the starting material was fully recovered (Scheme 5.8).



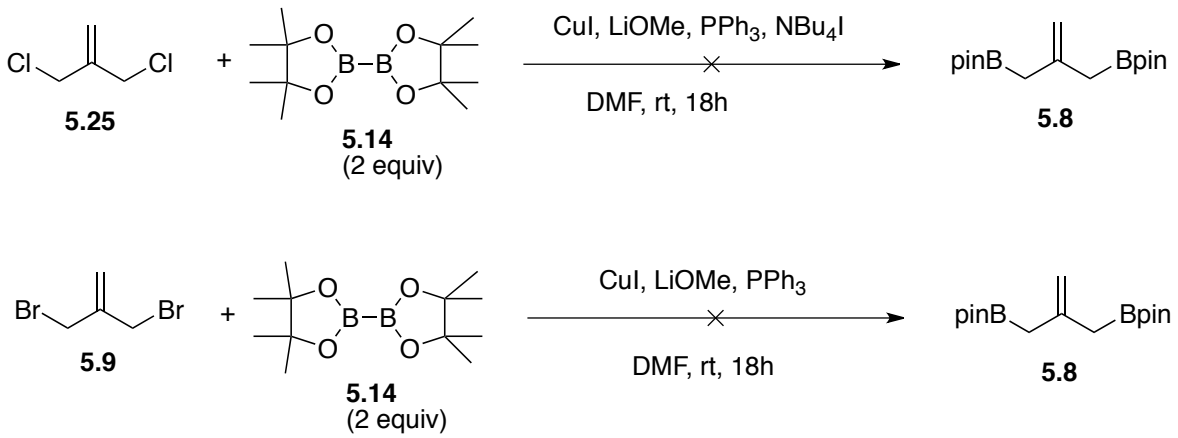
Scheme 5.8. Attempted borylation of alcohol **5.15**.

Since none of the above mentioned methods worked, the Szabo procedure was abandoned. Instead, palladium and platinum catalyzed cross-coupling methods of generating allylboronates from allylic acetates and halides reported by Miyaura and Masuda, were adopted.[5,6] Appropriate substrates were subjected to the Miyaura and Masuda methods using 1.1 equivalents of B_2pin_2 and 1.5 equivalents of pinacolborane respectively as borylating reagents. Unfortunately, both the reactions failed and the starting materials were recovered along with a few more unidentifiable side products (Scheme 5.9).



Scheme 5.9. Attempted synthesis of B/B-bidirectional double-allylation reagent by using the methods of Miyaura and Masuda.[5,6]

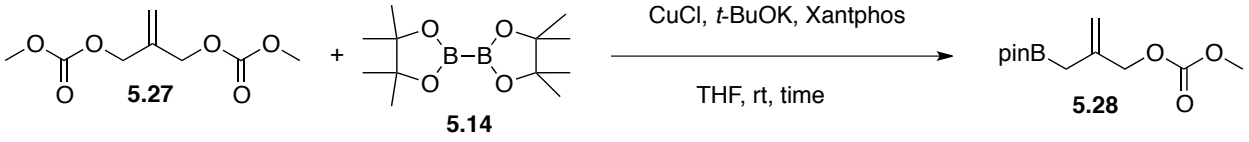
Copper (I) halide-catalyzed borylation methods reported by Marder and co-workers were attempted next.[7] Two dihalide substrates were subjected to the copper iodide catalyzed borylation conditions in the presence of triphenylphosphine as the ligand. Tetrabutylammonium iodide was employed for the dichloride substrate (**5.25**) to convert into a more reactive diiodide species *in situ* (Scheme 5.10). Unfortunately, neither of the substrates yielded the desired product. In view of this failure, and to ensure that all reagents were functional, a simpler substrate such as allyl bromide was successfully converted to the corresponding boronate under the same conditions.



Scheme 5.10. Attempted synthesis of B/B-bidirectional double-allylation reagent by using the method of Marder and co-workers.[7]

Ito and co-workers have reported a very useful and practical procedure for converting allylic carbonates into allylboronates by treating the former with two equivalents of bispinacolatodiboron in the presence of catalytic amounts of CuCl, Xantphos as the ligand and *t*-BuOK as the base.[8] Interestingly, when tried with the dicarbonate **5.27** a rather clean and smooth reaction took place but afforded only the monoborylated product (**5.28**). When the reaction was performed for a longer time period to push the second borylation, several decomposition products were observed during the TLC-analysis along with significant amounts of the monoborylated product **5.28**. Increasing the amount of B_2pin_2 only led to more decomposition along with the generation of the monoborylated product (Table 5.1).

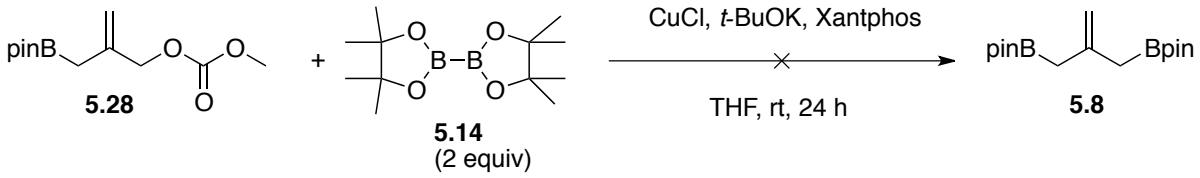
Table 5.1: Attempted synthesis of B/B-bidirectional double-allylation reagent by using the method reported by the Ito group.[8]



Equiv of **5.14**	Time	Yield[a]
4	3h	76%
4	24h	60%
6	3-24h	52%

a) all yields are isolated yields.

Attempts to convert **5.28** into the desired product **5.8** met with failure and about half of the starting material was recovered (Scheme 5.11).



Scheme 5.11. Attempted conversion of **5.28** to **5.8**.

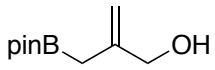
5.4 Conclusion

All the attempts towards the synthesis of the boron based bidirectional double-allylation reagent were unsuccessfull. Tradional methods of reacting the organometallic precursor with boron reagents did not work at all. Coupling methods also resulted in failure. Attempts to convert the allyl alcohols into the corresponding boronates were also unsuccessful. Method reported by Ito and co-workers was only partially successful, yielding only the monoborylated product.

5.5 Experimental details: general Information

All reactions were performed in standard, flame-dried glassware under an inert atmosphere of nitrogen. Unless otherwise specified, reagents were bought from commercial suppliers and used without further purification. Solvents were dried either by distillation or by using a cartridge purification solvent system. Anhydrous Na_2SO_4 or $MgSO_4$ were used as the drying agent after aqueous workup. All substrates were purified by silica gel chromatography before use except the ones which were purchased. Evaporation and concentration *in vacuo* were accomplished at water aspirator pressure. Reaction products were purified by column chromatography using silica gel-60 (230-400 mesh). Reactions were monitored by thin layer chromatography with precoated glass plates covered with 0.2 mm silica gel. The spots were visualized by UV light, $KMnO_4$ or anisaldehyde stain. IR spectra were obtained with a Nicolet Magna-IR-750 spectrometer (cm^{-1}, cast film or neat). ^1H, ^{11}B, ^{13}C, and ^{19}F NMR spectra were obtained on a Varian Inova-300, 400 or Varian Unity-500 instruments, at 27 $^{\circ}C$ in $CDCl_3$. Residual solvent peaks (7.26 ppm for ^1H and 77.0 ppm for ^{13}C) were employed as reference. Accuracy for coupling constants (*J*-values) is estimated to be +/– 0.2 Hz. EI MS (m/z) was measured in a Kratos MS50 instrument. **5.9**, **5.11**, **5.12, 5.13,** and **5.26** were purchased from Sigma-Aldrich. **5.16**, **5.18, 5.20, 5.23, 5.25,** and **5.28** were prepared by following procedures reported in the literature.[9,10,4,11,12,13]

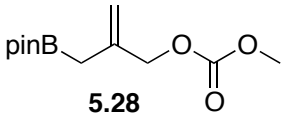
Synthesis of allyl boronate 5.15



5.15

DIBAL-H (16.0 mL in toluene, 16 mmol) was added drop wise at 0 °C to a solution of **5.23** (1.7 g, 7.1 mmol) in THF (20 mL). After stirring for 1.5 h, the reaction mixture was quenched slowly with MeOH first, then with 2M HCl solution. A thick slurry was formed. The mixture was passed through a pad of celite and a much clear mixture was obtained. The aqueous layer was extracted twice with diethyl ether, dried over anhydrous sodium sulfate, filtered, and evaporated. An oil was obtained after performing a flash chromatography with 20% EtOAc in hexane (1.0 g, 71%). ^1H NMR (400 MHz, $CDCl_3$): ^1H NMR (400 MHz, $CDCl_3$): δ = 5.1 (d, *J* = 1.5 Hz, 1H), 5.0 (d, *J* = 1.5 Hz, 1H), 4.53 (s, 2H), 1.80 (s, 2H), 1.20 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 117.9, 83.1, 54.2, 24.4; ^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.3 ppm.

Synthesis of allyl boronate 5.28



5.28

The procedure reported by Ito and co-workers was followed.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.1 (d, *J* = 1.5 Hz, 1H), 5.0 (d, *J* = 1.5 Hz, 1H), 4.60 (s, 2H), 3.80 (s, 3H), 1.80 (s, 2H), 1.20 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 137.1, 118.0, 83.2, 66.8, 55.2, 24.6; ^{11}B NMR (128 MHz, $CDCl_3$): δ = 30.5 ppm.

5.6 References

1. Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375.
2. Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 2187.
3. Williams, D. R.; Claeboe, C. D.; Bo, L.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866.
4. Dutheuil, G.; Selander,N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, 2293.
5. Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889.
6. Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **2000**, *41*, 5877.
7. Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Czyzewska, Y.F. M.; Steel, P.G.; Marder, T.B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528.
8. Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423.
9. Couladouros, E. A.; Konstantinos, D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430.
10. Yoon, Y.; Kang, T.; Lee, H-Y. *Chem. Asian J.* **2011**, *6*, 646.
11. Elford, T. G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G. D.; Hall, D. G. *J. Comb. Chem.* **2009,** *11,* 155.
12. Trost, B.M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492.
13. Dudley, G. B.; Salamone, S. G. *Org. Lett.* **2005**, *7*, 4443.

Chapter 6

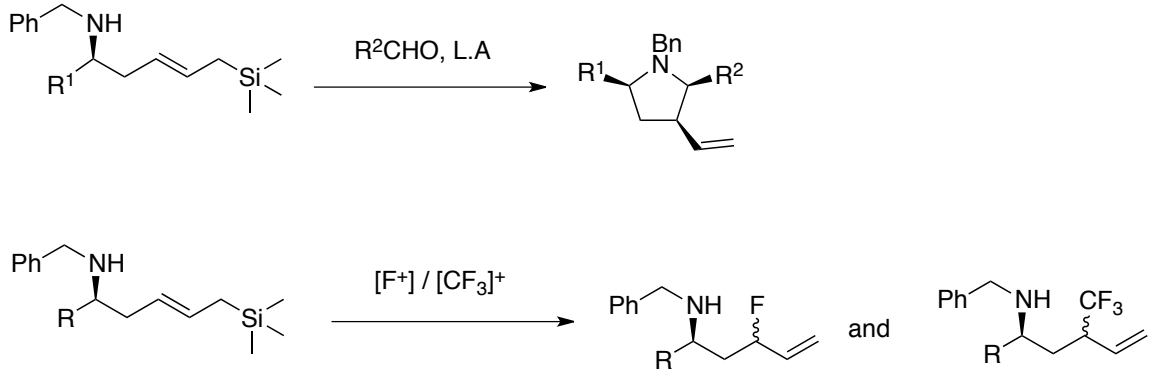
Future directions and conclusions

6.1 Future directions and conclusions

Three neglected areas of asymmetric allylboration were discussed and covered in the previous chapters. The outcomes of these investigations gave mixed results and a number of objectives have not been met.

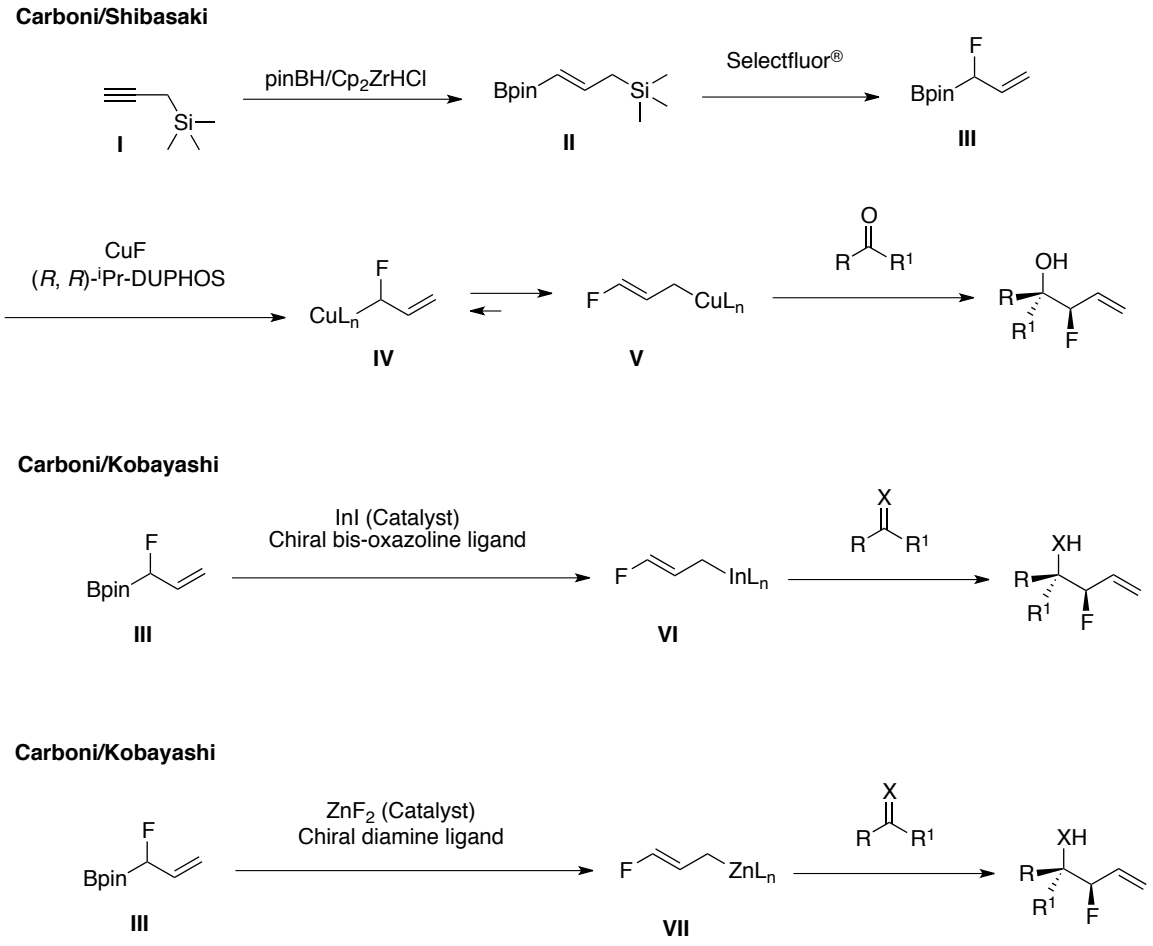
In Chapter 2, a detailed study of the vivol•$SnCl_4$–catalyzed asymmetric allylboration of propargylic aldehydes was discussed. Two new chiral diols, F-vivol-6 and F-vivol-12, were prepared and evaluated but both of them were proved to be inferior compared to F-vivol-8 both in terms of yield and selectivity. Once again the importance of solvent, concentration and Lewis acid partner was realized. The method worked for a variety of substrates affording very good yields and moderate to very good enantioselectivities. The next objective for this successful study would be to identify and synthesize a natural product where this method could be applied.

In Chapter 3, a chiral B/Si-double allylation reagent, previously described by our group, was subjected to imine allylation. The original pinanediol-based reagent did not react at all, prompting us to design a new reagent. Realizing that the steric repulsion from the pinanediol unit can be the reason behind the failure, a new less sterically demanding reagent prepared from (*R*,*R*)-DICHED was introduced. This variant reacted but slowly with the model imine affording good yield and very good enantioselectivity. Various conditions were attempted to improve the rate of the reaction but there was hardly any improvement. A detailed substrate scope should be carried out. The final homoallylic amine then can be converted into important structures. The acyclic homoallylic amine can be treated with an aldehyde in the presence of a Lewis acid to convert the amine into a pyrrolidine ring, a structure present in many important molecules. On the other hand, the amine can also be transformed into fluorinated and trifluoromethylated chiral amines by treating the reagent with either Selectfluor or Togni's reagent (Scheme 6.1).[1]



Scheme 6.1. Various possible applications of chiral homoallylic amine derived from imine allylation.

As discussed in chapter 4, all the synthetic attempts to synthesize the fluoro- and trifluoromethylallylboronate were unsuccessful. The procedure of converting allylic alcohols into allylboronates reported by Szabo, was tried to convert the fluorohomoallylic alcohols into the corresponding boronates. All of these attempts failed. Different coupling methods failed to achieve the desired products too. However, utility and importance of asymmetric fluorination and trifluoromethylation justifies continued efforts. Ideas developed by other research groups can be applied to address the problem. Recently Carboni and co-workers reported a procedure for converting silylborylalkenes into various α−substituted allylboronates including α−fluoroallylboronates (**III**).[2] This compound can be utilized along with other forms of catalysis methods reported. For example, this compound when treated with CuF in the presence of chiral phosphine ligand is expected to produce intermediate **V** preferably, similar to the observations made by Shibasaki and co-workers with α−substituted allylboronates. This intermediate can be reacted with the carbonyl compounds leading towards the desired products. Other procedures which can be exploited here are the methods reported by Kobayashi and co-workers. They observed that α−substituted allylboronates can undergo γ-addition/transmetallation when treated with InI or ZnF_2 in the presence of either chiral bis-oxazoline or diamine ligands producing crotylindium (**VI**) or crotylzinc intermediates (**VII**). These intermediates can react with carbonyl compounds (Scheme 6.2).[3, 4, 5] Similarly, the 3-trifluoromethylallylboronate can be prepared by following Carboni's procedure but with a source of CF_3^+, such as Togni's reagent. Then the same ideas discussed above can be applied with this reagent too.



Scheme 6.2. Possible alternatives for the synthesis of and fluorolallylboronate and its plausible application.

In chapter 5, a detailed study towards the synthesis of a boron based stable bidirectional reagent has been described. Most of the attempted approaches failed and resulted either in degradation of starting materials or formed unwanted side products.

To summarize, I was able to develop a methodology for the catalytic asymmetric allylboration of propargylic aldehydes. I also optimized conditions for the asymmetric imine allylboration with a versatile B/Si double allylation reagent. Unfortunately, despite of many attempts, the desired fluoroallylboronate and 3-trifluoromethylallylboronate could not be prepared. However, importance of fluorinated organic compounds justifies continued efforts.

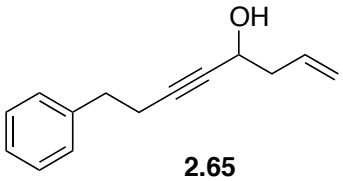
6.2 References

1. Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka M. *Angew. Chem. Int. Ed* **2012,** *51,* 4577.
2. Mace, A.; Tripoteau, F.; Zhao, Q.; Gayon, E.; Vrancken, E.; Campagne, J.; Carboni, B. Org. Lett. **2013**, *15*, 906.
3. Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004,** *126,* 8910.
4. Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2010,** *49,* 1838.
5. Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008,** *130,* 2914.

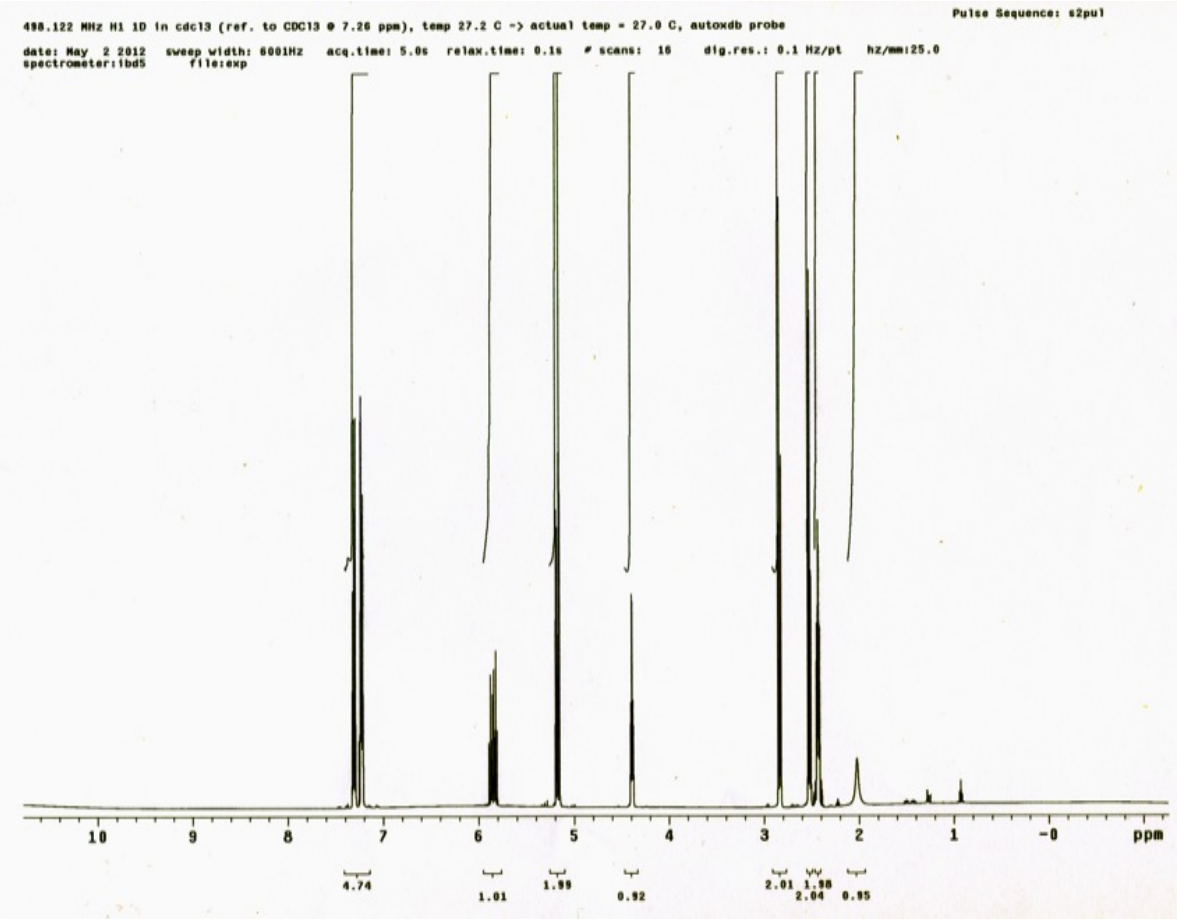
Appendix A: Supporting spectra

^{1}H NMR (500 MHz, $CDCl_3$)

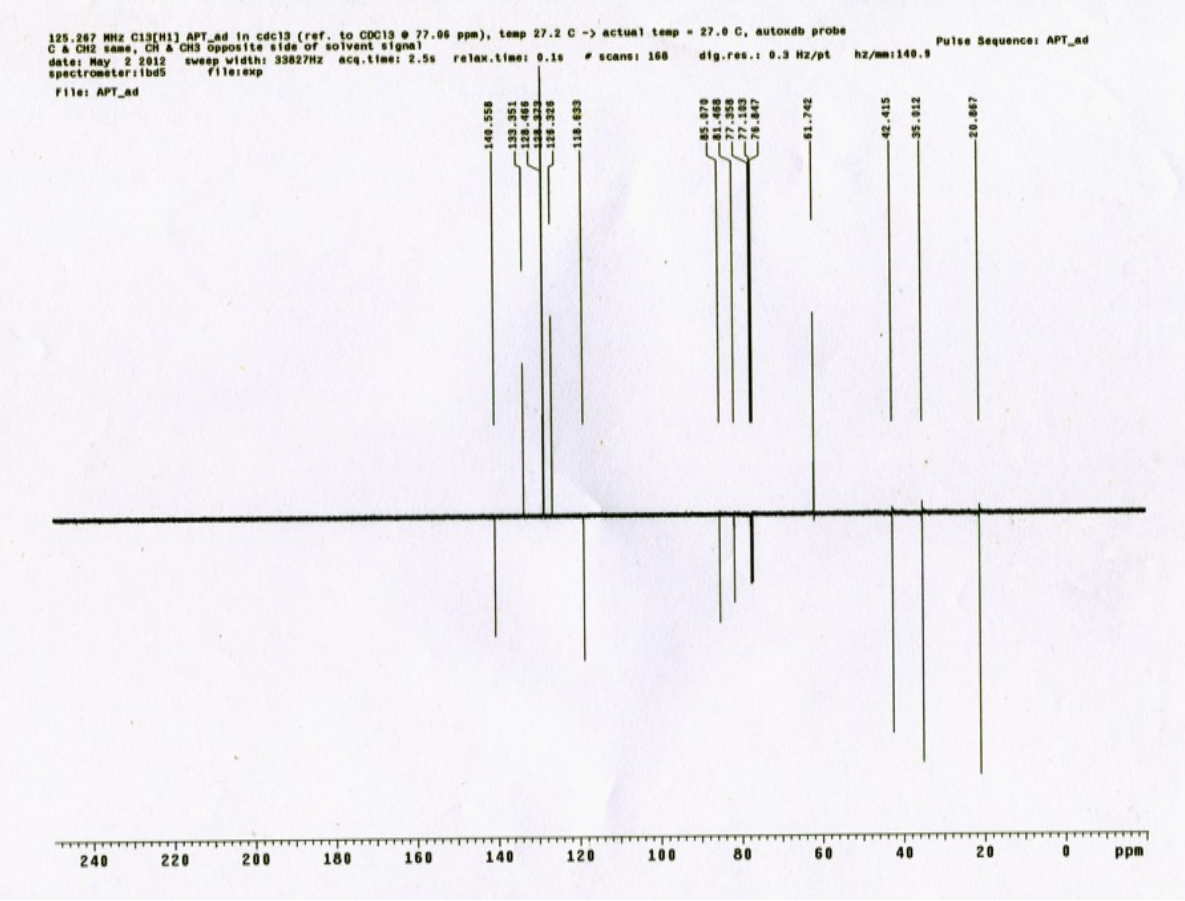
8-Phenyloct-1-en-5-yn-4-ol



2.65

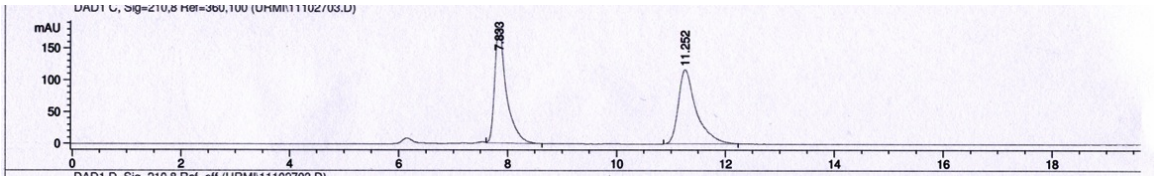


^{13}C NMR (125 MHz, $CDCl_3$)

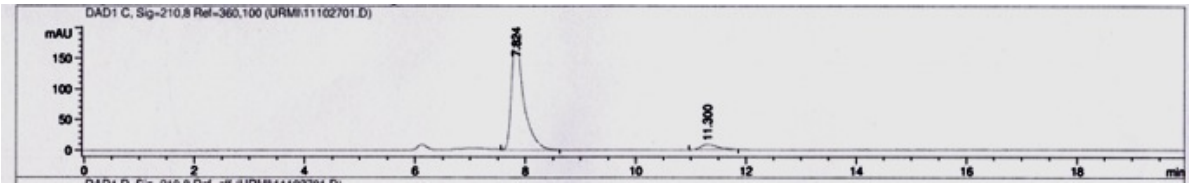


50% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



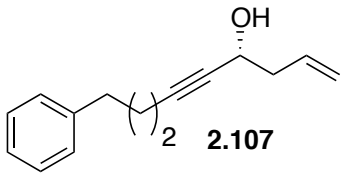
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.833	VB	0.2111	2680.46118	182.80658	49.7637
2	11.252	BB	0.3378	2705.91943	117.02294	50.2363
Totals :				5386.38062	299.82952	



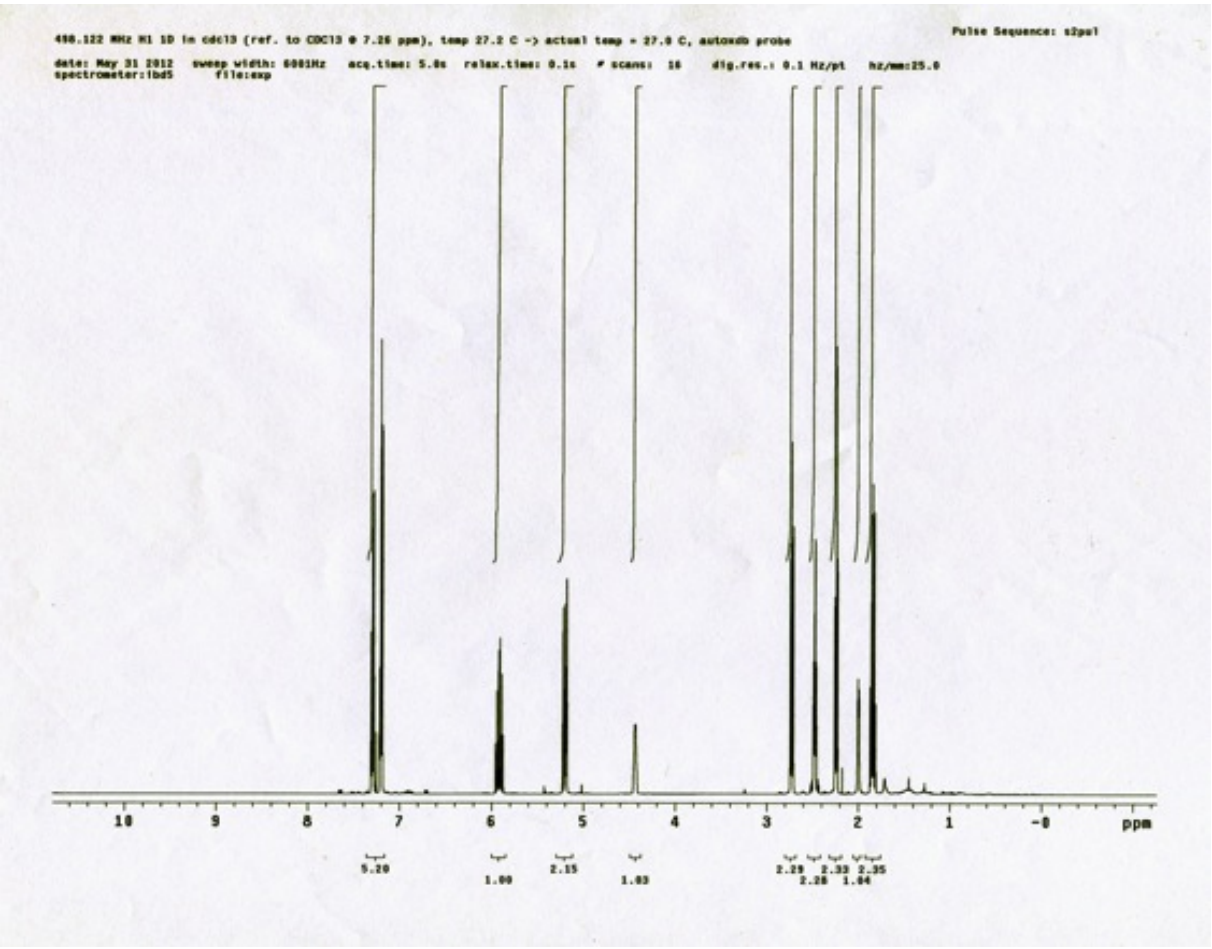
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.824	VB	0.2131	2798.97144	190.85179	93.4991
2	11.300	BB	0.3212	194.60892	9.03694	6.5009
Totals :				2993.58035	199.88873	

^{1}H NMR (500 MHz, $CDCl_3$)

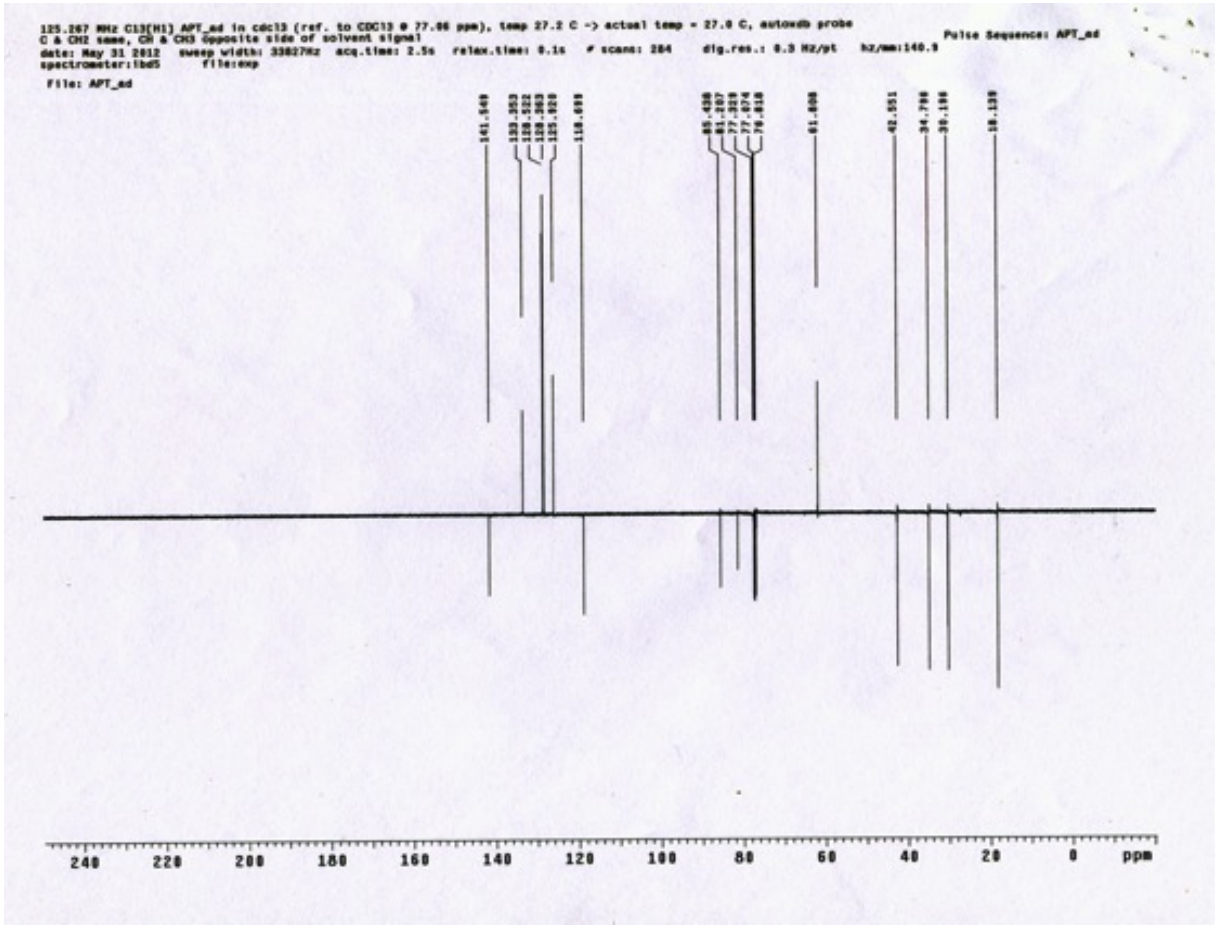
9-Phenylnon-1-en-5-yn-4-ol



2.107

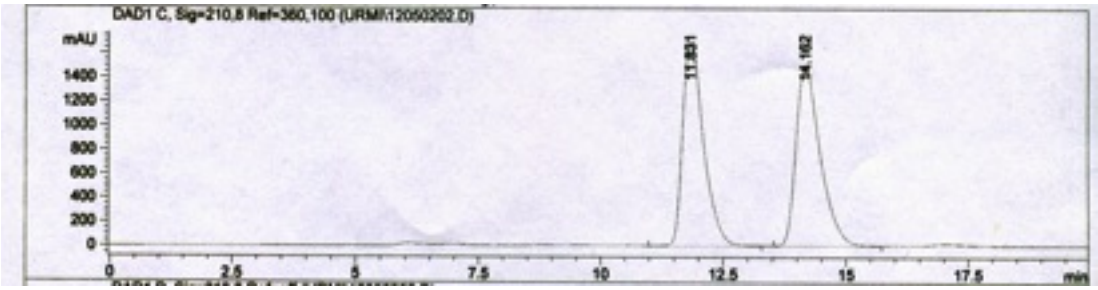


^{13}C NMR (125 MHz, $CDCl_3$)

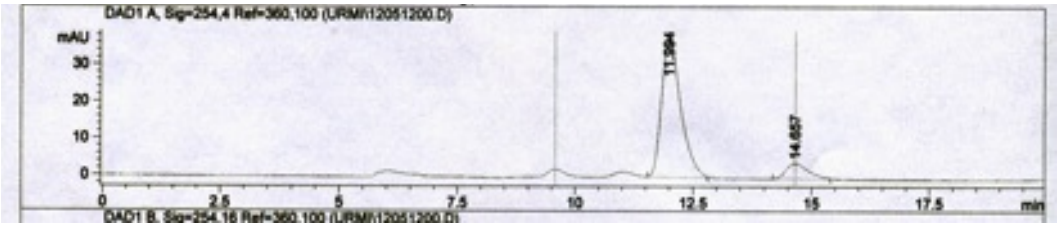


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



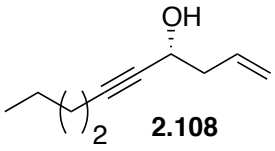
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.831	VB	0.4546	5.04581e4	1678.97974	49.5497
2	14.162	BB	0.5241	5.13752e4	1483.37183	50.4503
Totals :				1.01833e5	3162.35156	



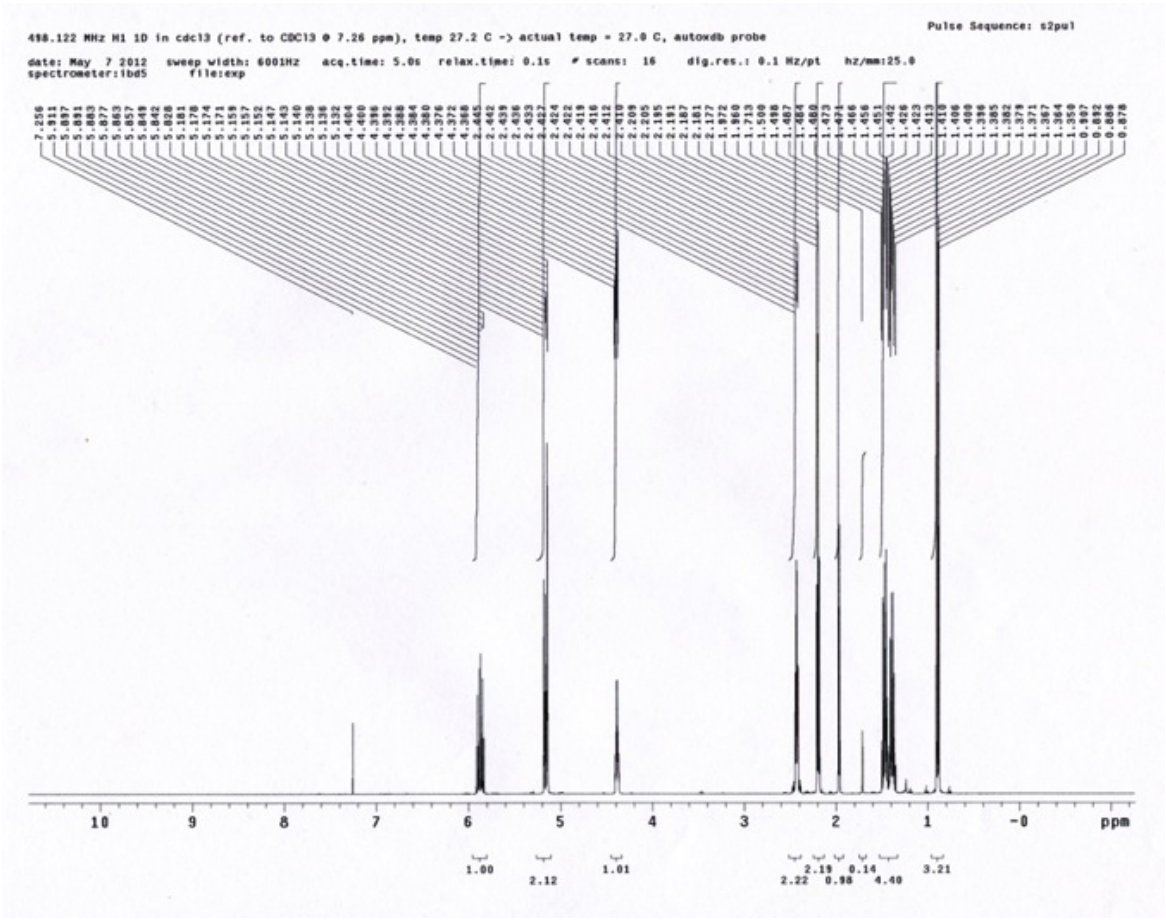
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.994	PB	0.4204	1058.78247	37.60895	88.6093
2	14.657	BB	0.4174	136.10609	4.18507	11.3907
Totals :				1194.88857	41.79401	

^{1}H NMR (500 MHz, $CDCl_3$)

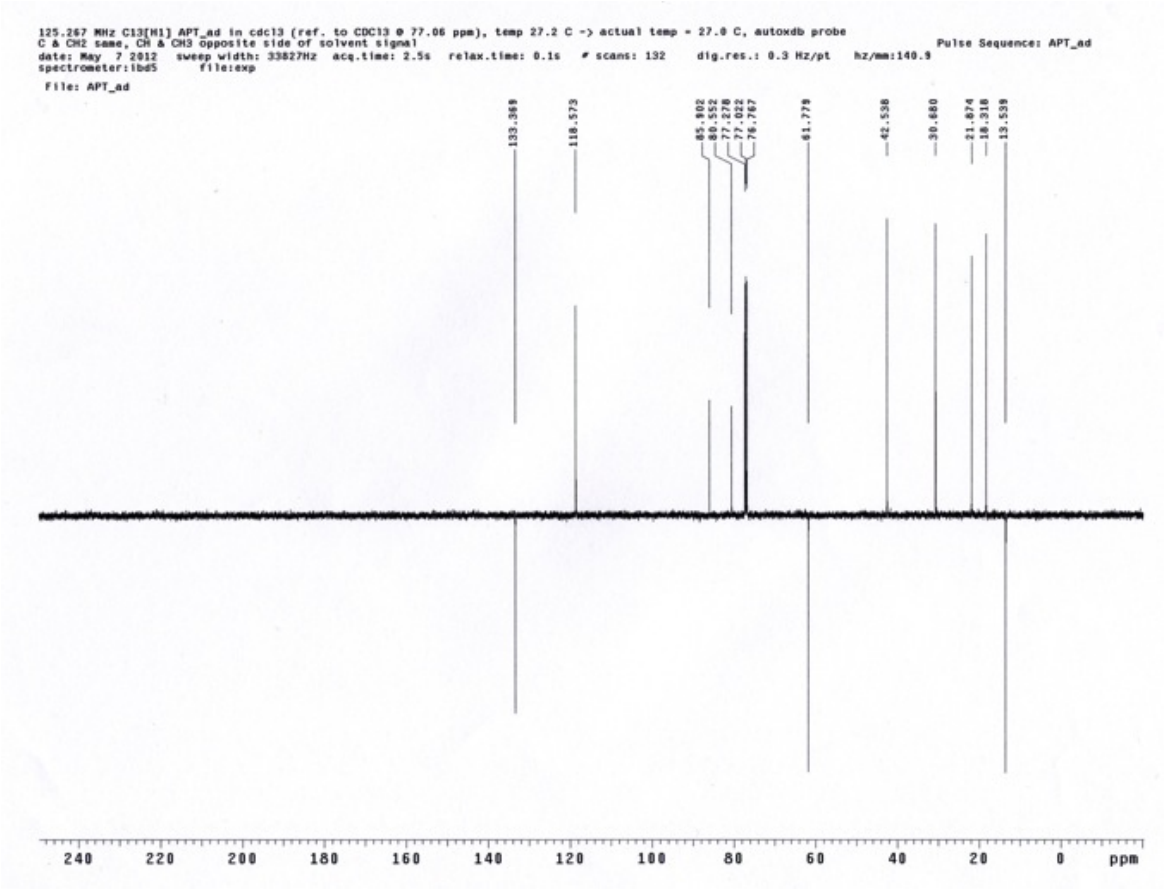
(4*R*)-Dec-1-en-5-yn-4-ol



2.108

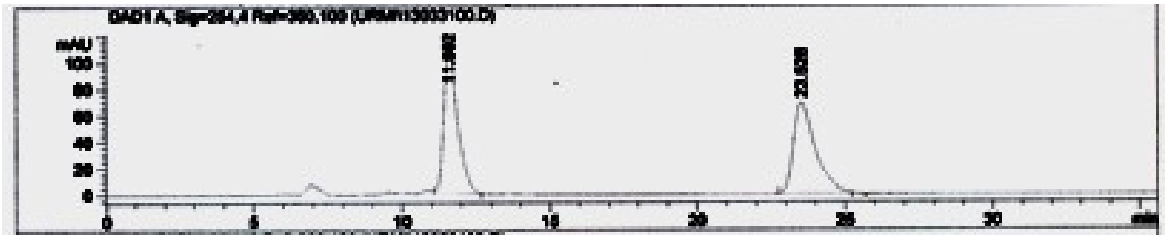


^{13}C NMR (125 MHz, $CDCl_3$)

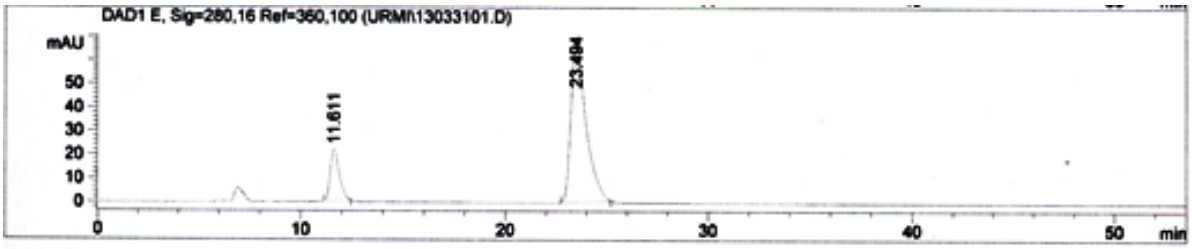


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



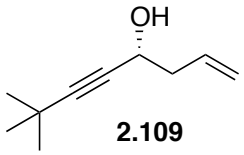
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.592	VB	0.4674	3620.06641	114.95699	50.5003
2	23.526	BB	0.7585	3548.33984	68.48298	49.4997
Totals :				7168.40625	183.43996	



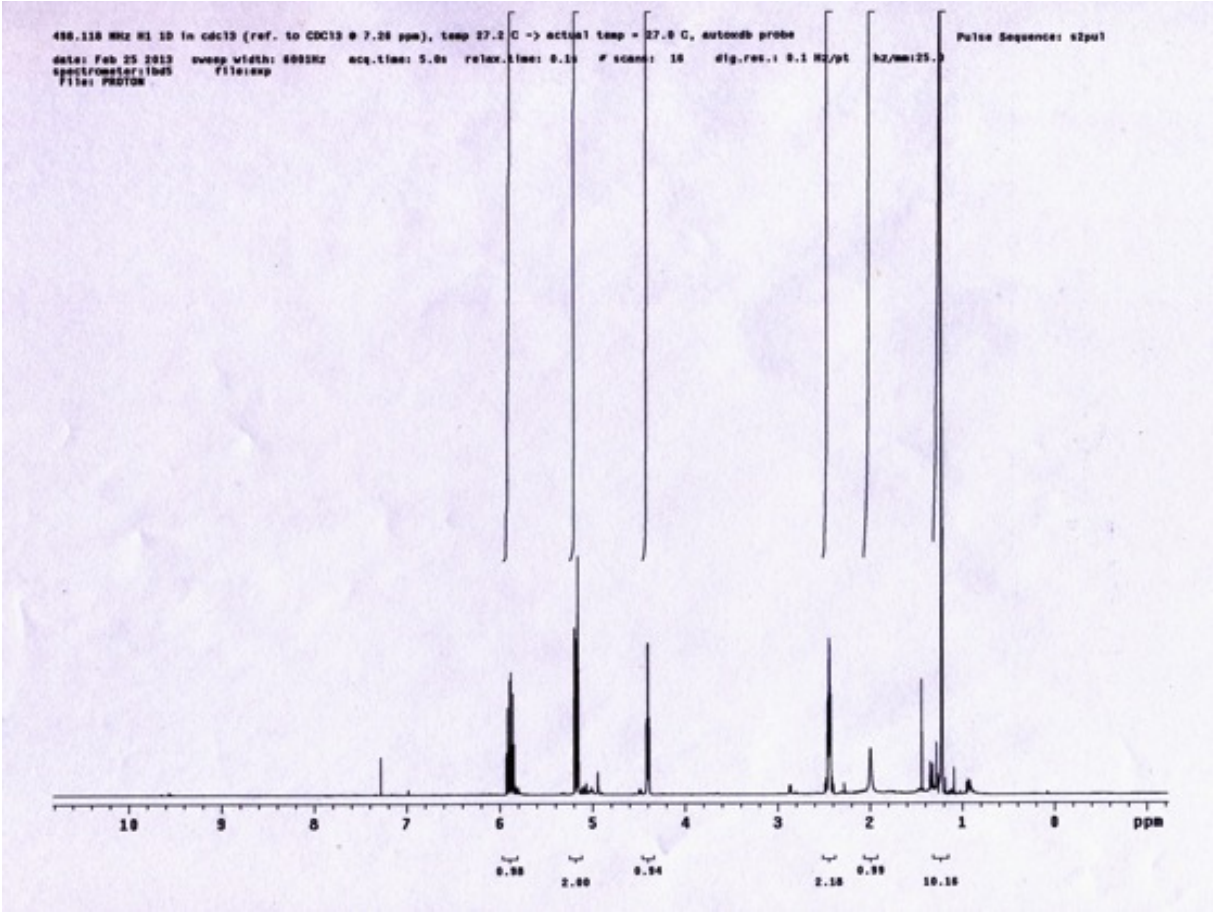
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.611	BB	0.4536	674.61700	22.00835	16.1498
2	23.494	BB	0.7757	3502.63257	67.02122	83.8502
Totals :				4177.24957	89.02957	

^{1}H NMR (500 MHz, $CDCl_3$)

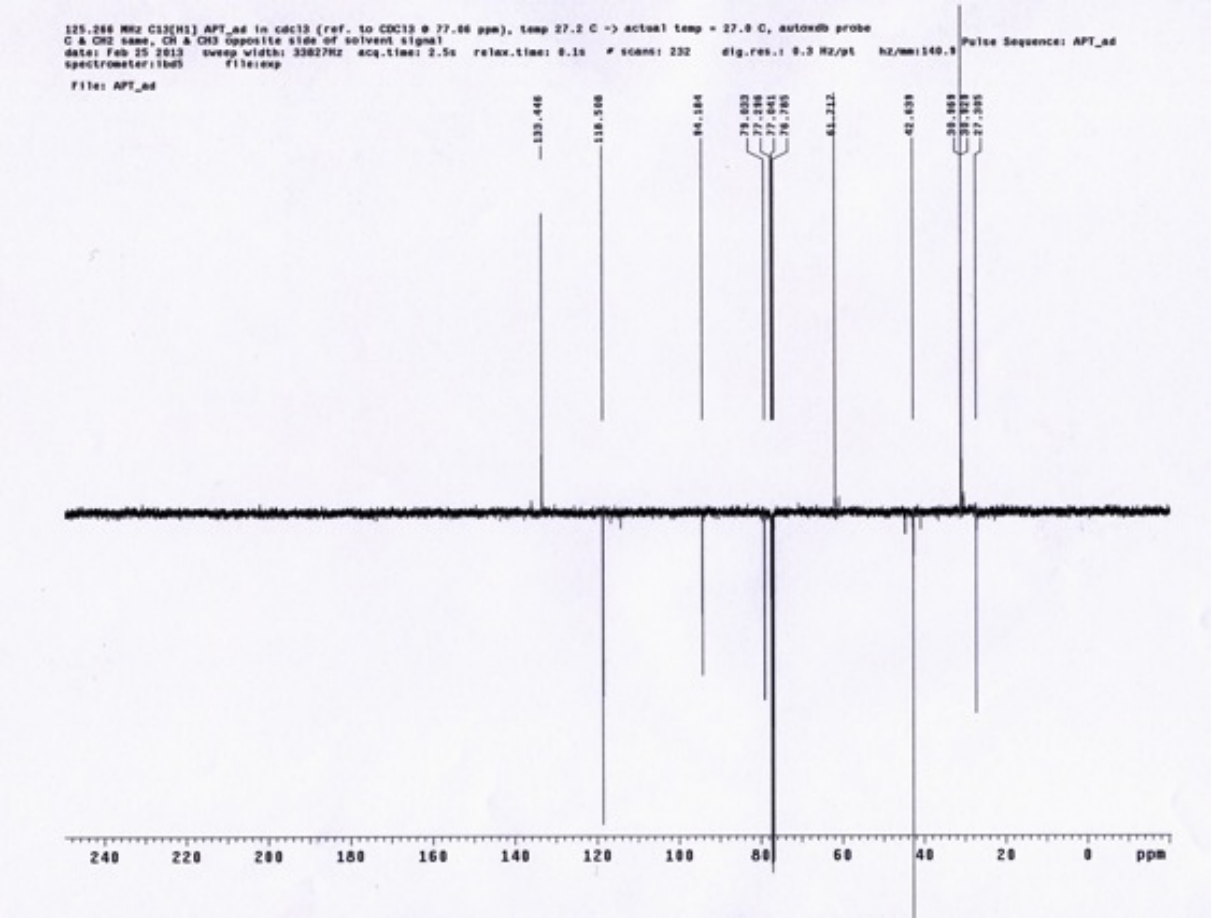
7,7-Dimethyloct-1-en-5-yn-4-ol



2.109

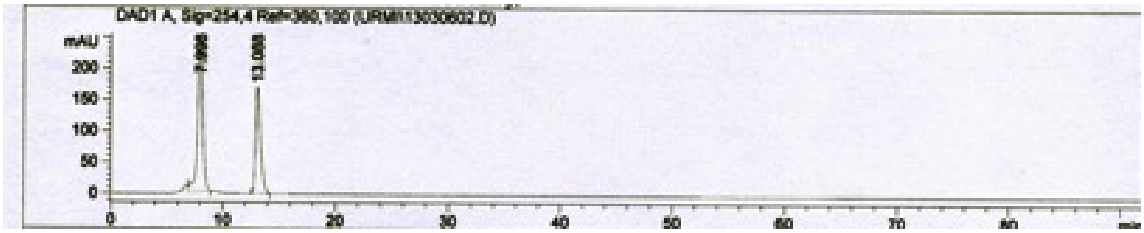


^{13}C NMR (125 MHz, $CDCl_3$)

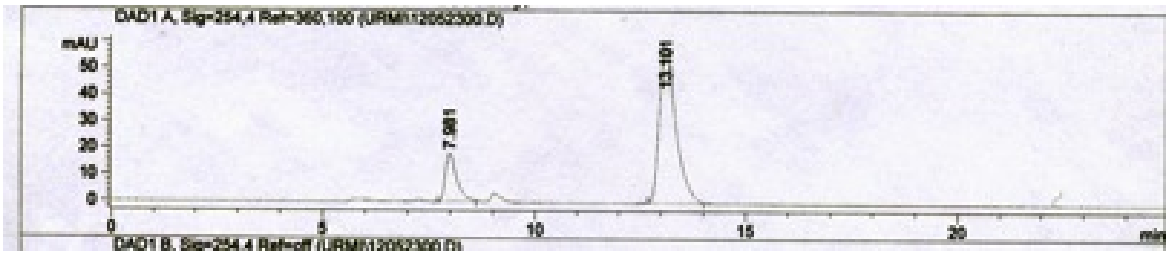


15% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



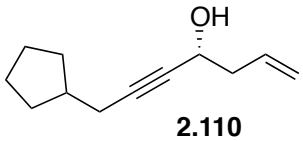
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.998	VB	0.4928	7823.57764	265.64420	49.7506
2	13.088	BB	0.4306	5057.12256	192.83624	50.2494
Totals :				1.28807e4	458.48044	



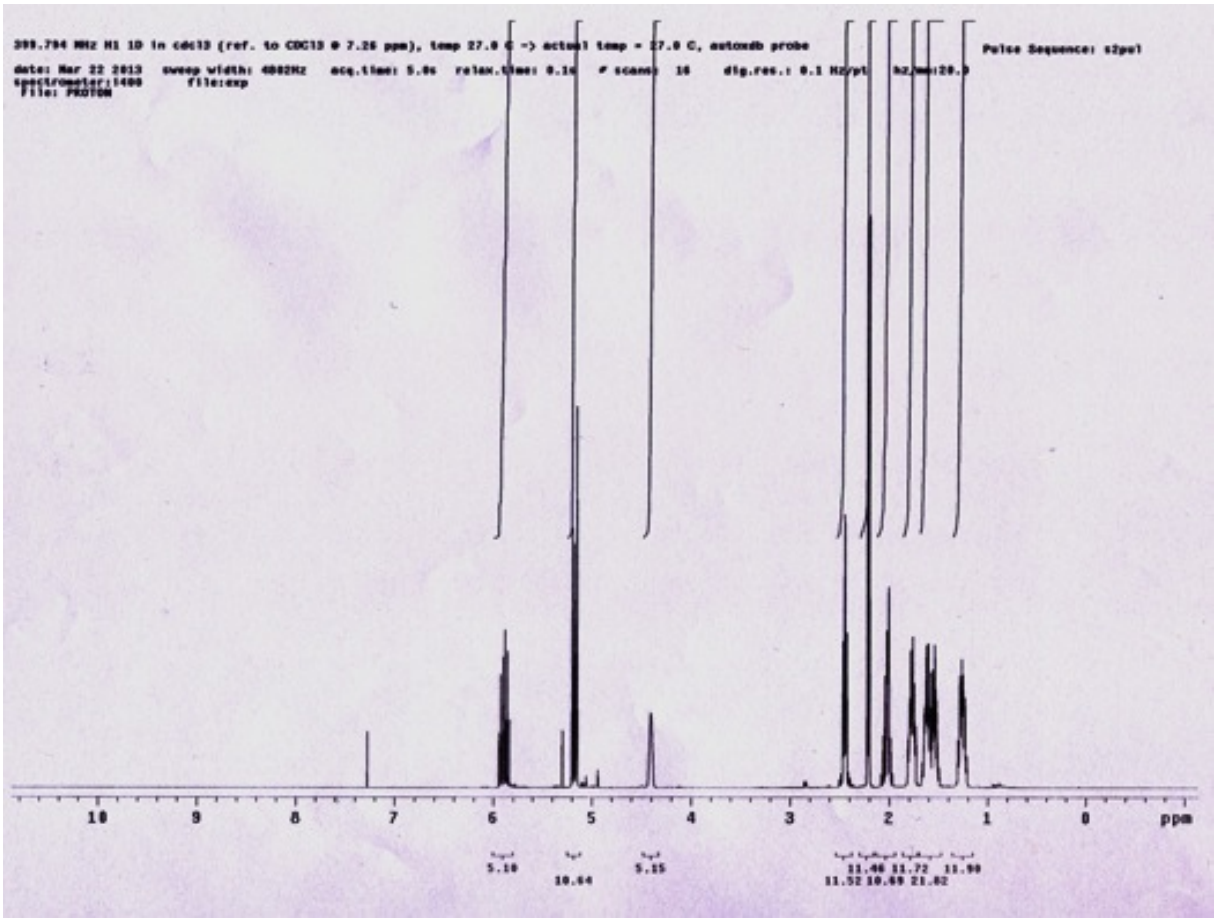
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.981	PB	0.2753	329.95639	17.87556	17.4150
2	13.101	BB	0.3914	1564.71067	58.62157	82.5850
Totals :				1894.67307	76.49713	

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

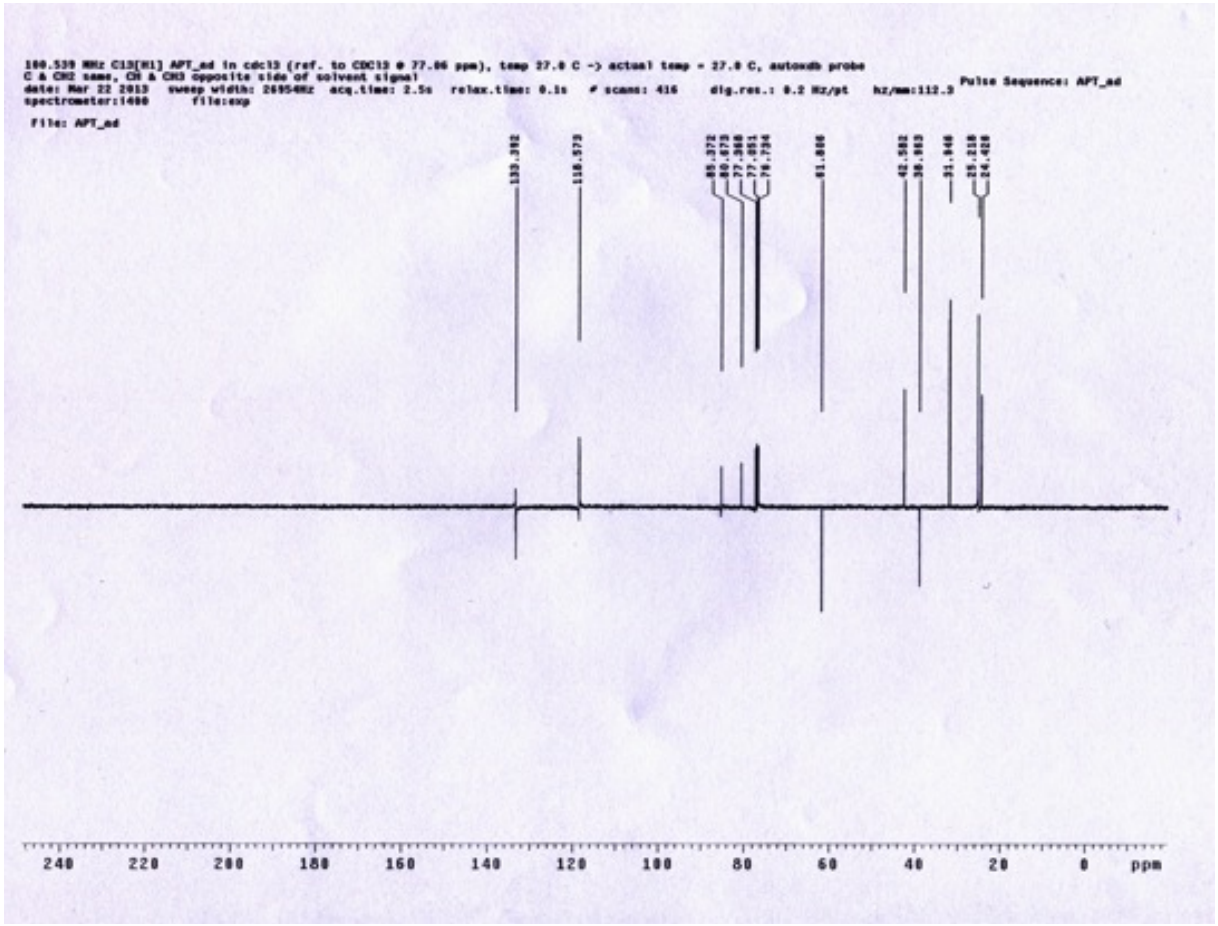
7-Cyclopentylhept-1-en-5-yn-4-ol



2.110

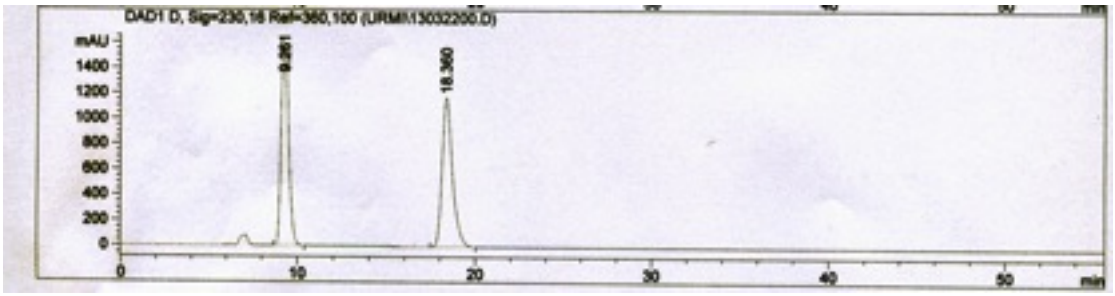


^{13}C NMR (100 MHz, $CDCl_3$)

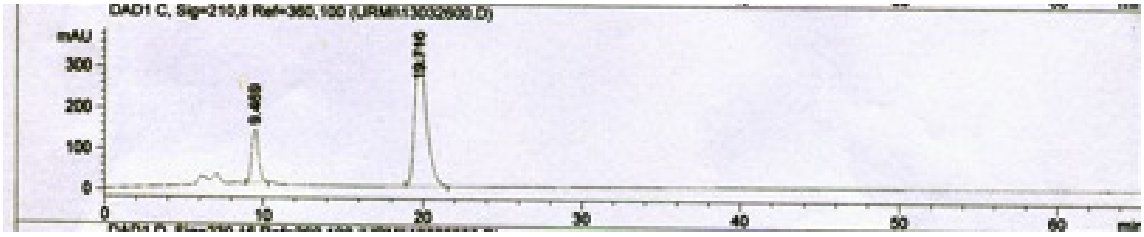


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



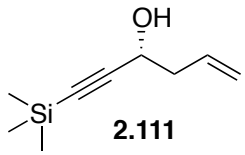
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.261	BB	0.4590	4007.18945	137.91737	50.0145
2	18.361	BB	0.5979	4004.87109	99.00205	49.9855
Totals :				8012.06055	236.91943	



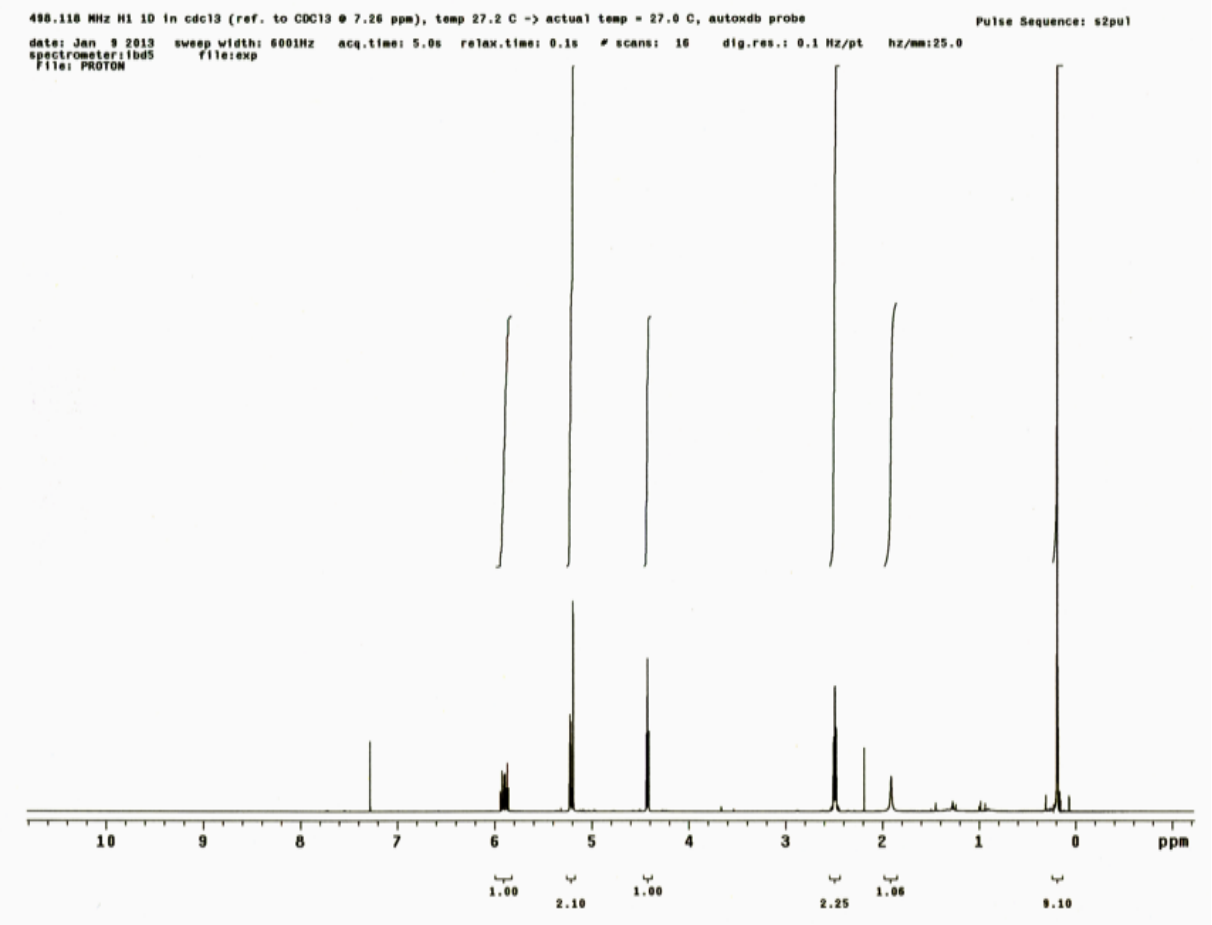
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.469	VB	0.4835	4026.56104	131.39328	18.6486
2	19.716	BB	0.7236	1.75652e4	359.74304	81.3514
Totals :				2.15918e4	491.13632	

^{1}H NMR (500 MHz, $CDCl_3$)

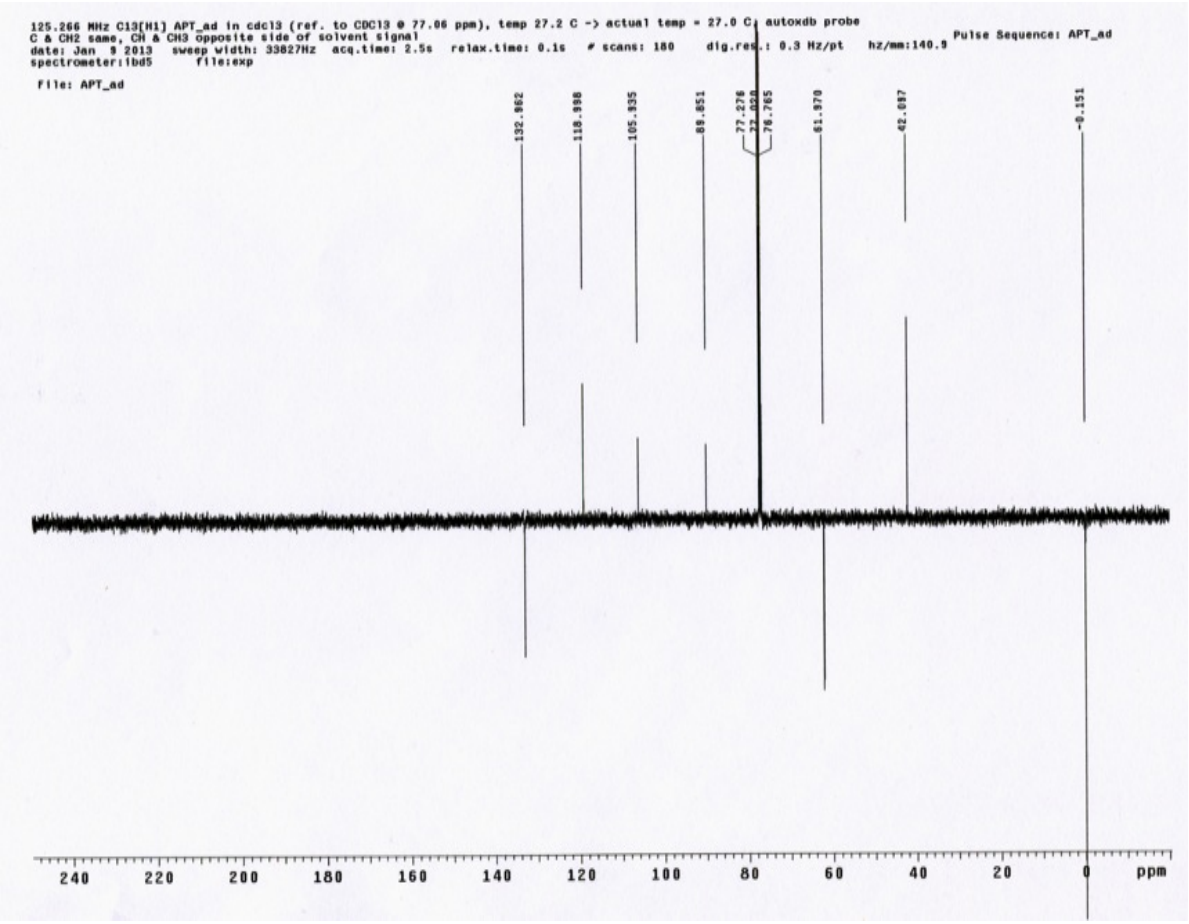
(4*R*)-1-Trimethylsilylhex-1-en-5-yn-4-ol



2.111

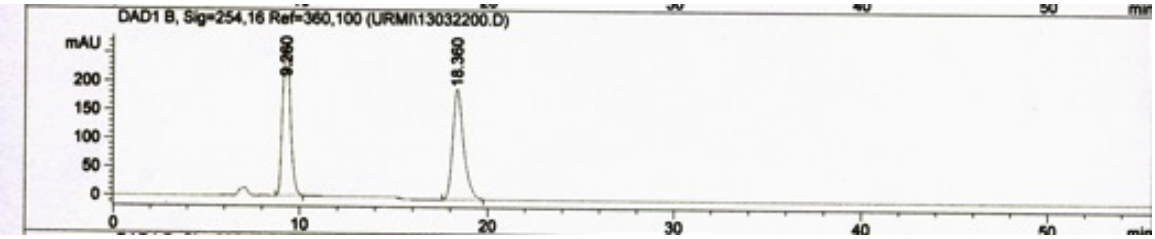


^{13}C NMR (125 MHz, $CDCl_3$)

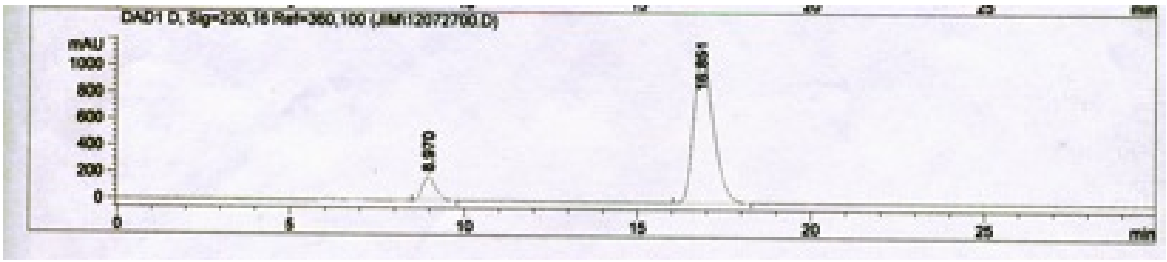


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



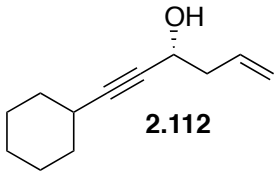
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.261	BB	0.4590	4007.18945	137.91737	50.0145
2	18.361	BB	0.5979	4004.87109	99.00205	49.9855
Totals :				8012.06055	236.91943	



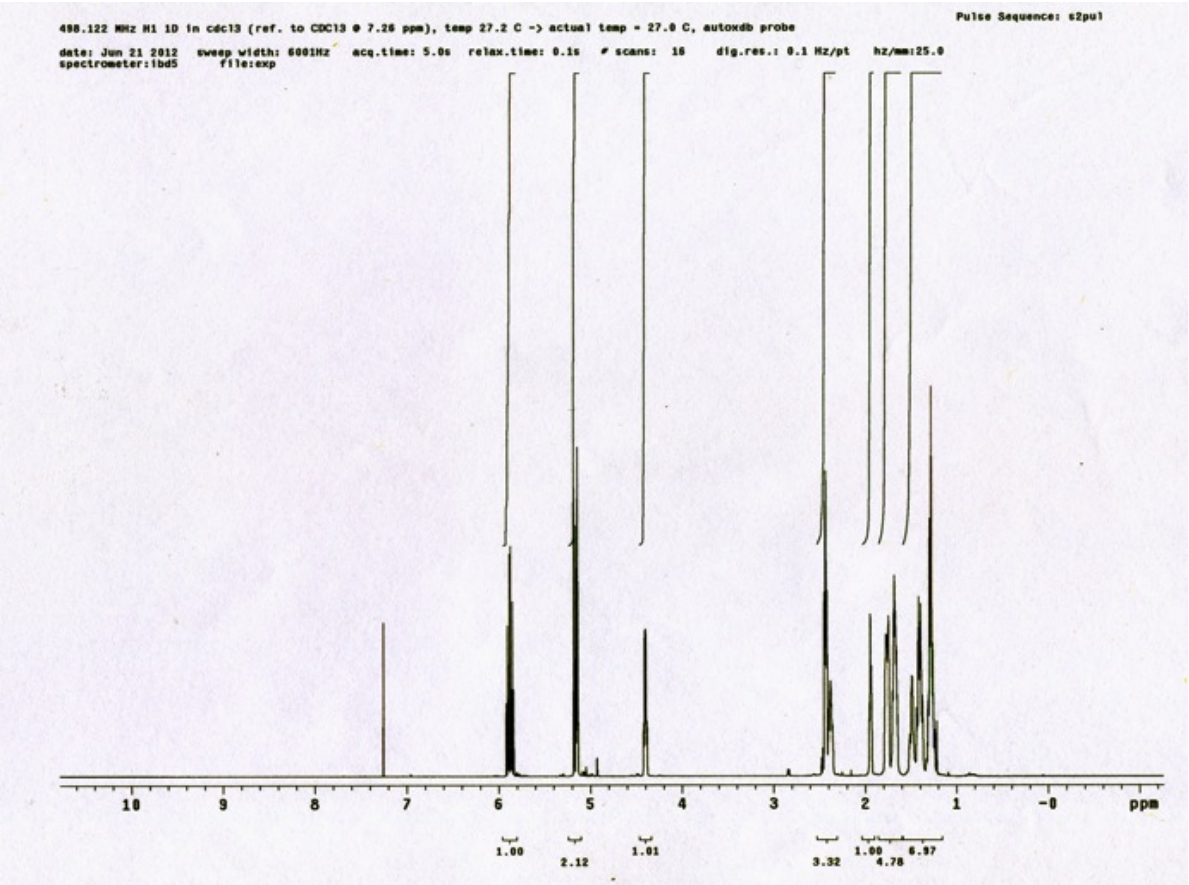
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.970	VB	0.4122	4628.58936	176.33551	9.4662
2	16.851	BB	0.5792	4.42676e4	1154.84546	90.5338
Totals :				4.88962e4	1331.18097	

^{1}H NMR (500 MHz, $CDCl_3$)

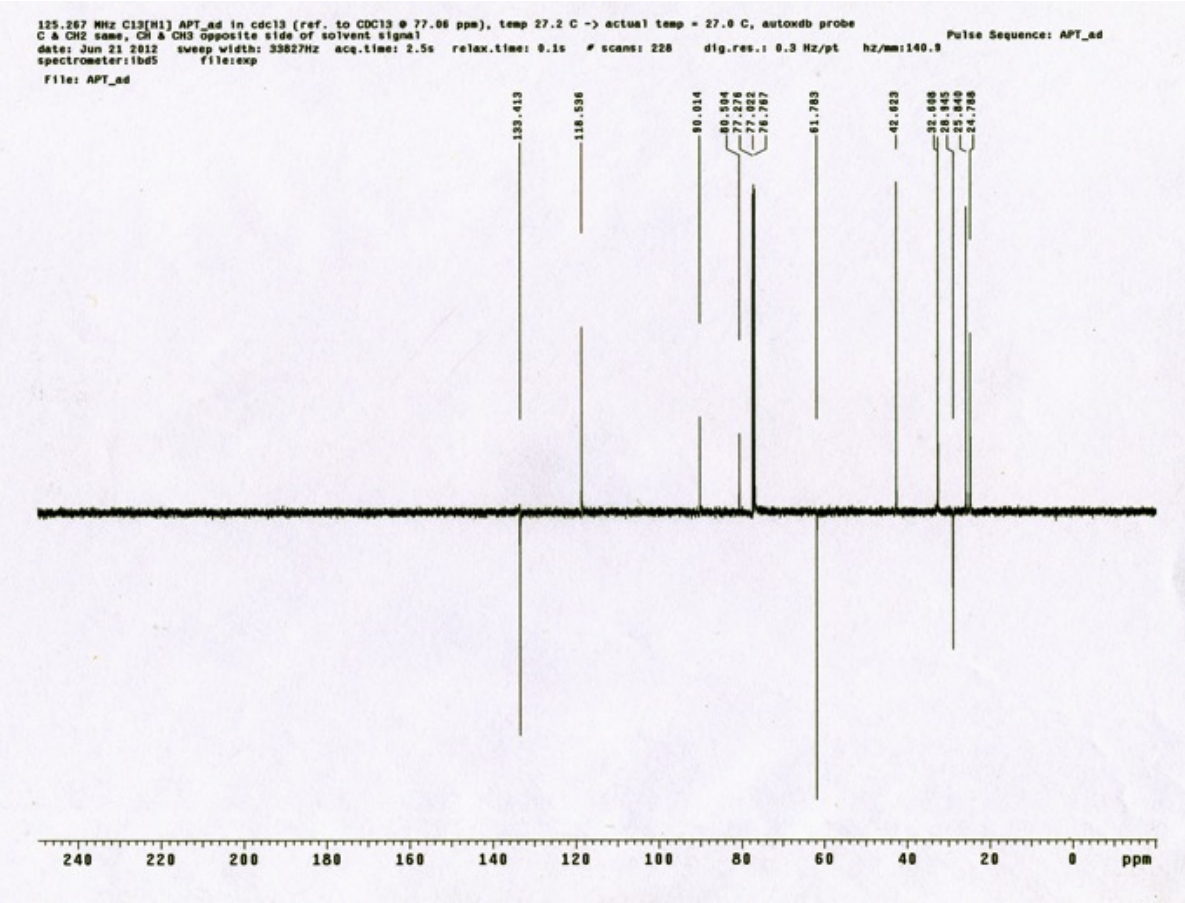
1-Cyclohexylhex-5-en-1-yn-3-ol



2.112

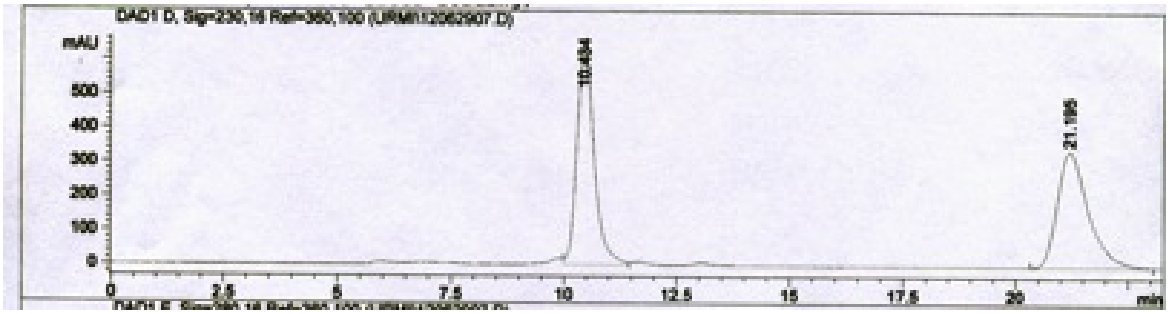


^{13}C NMR (125 MHz, $CDCl_3$)

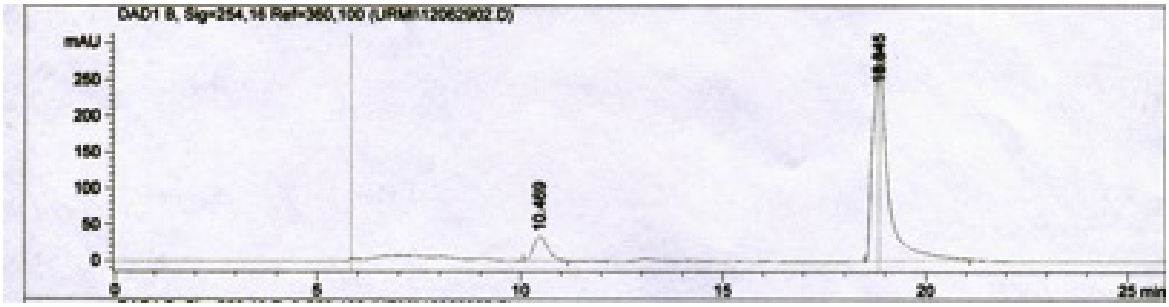


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



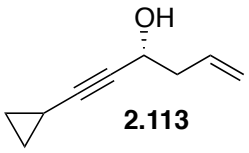
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.434	VV	0.4047	1.70041e4	634.39117	50.9206
2	21.195	BB	0.7250	1.63893e4	339.61819	49.0794
Totals :				3.33934e4	974.00937	



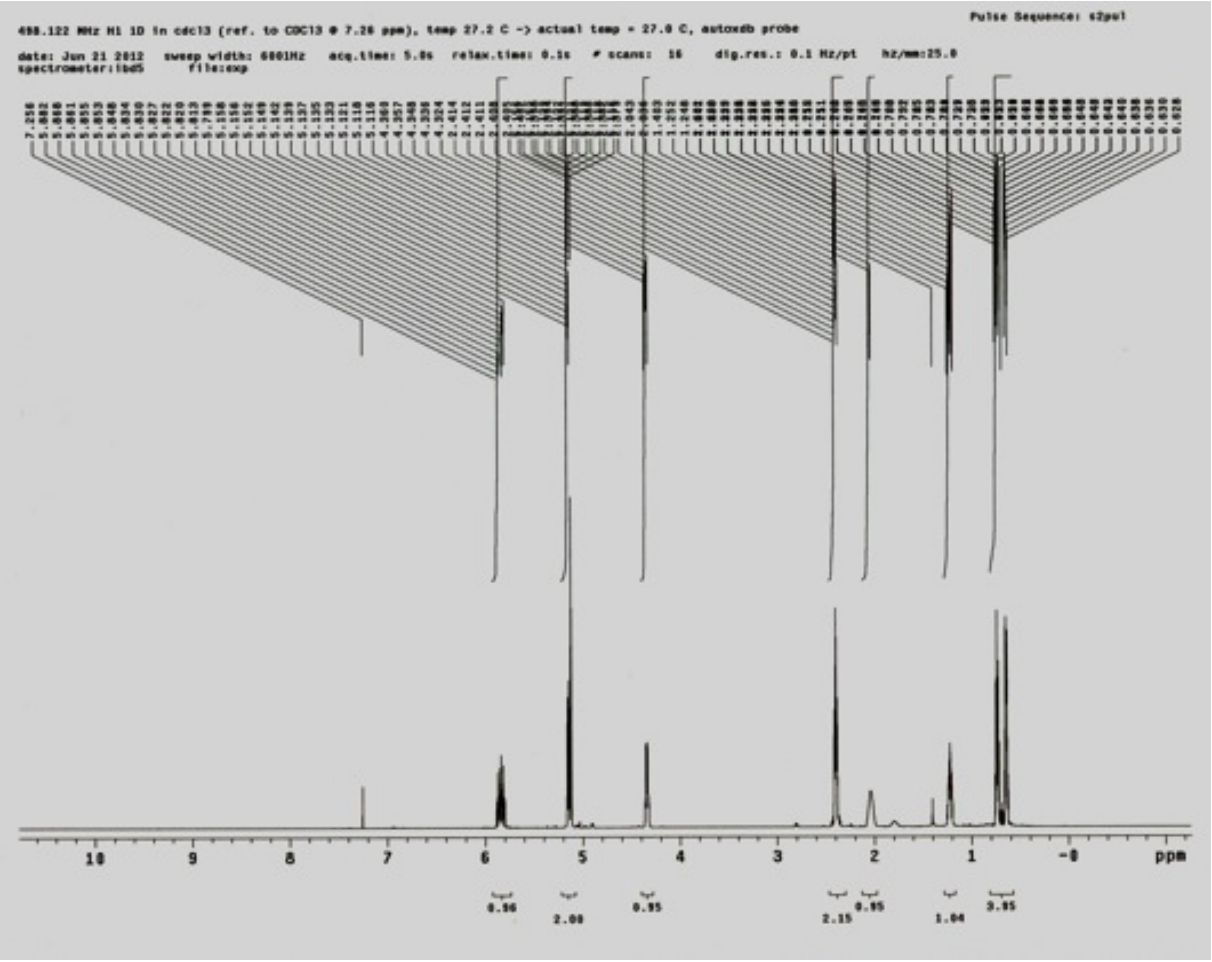
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.469	BB	0.3653	823.76923	33.92176	9.8786
2	18.845	BB	0.3323	7515.14844	299.96255	90.1214
Totals :				8338.91766	333.88432	

^{1}H NMR (500 MHz, $CDCl_3$)

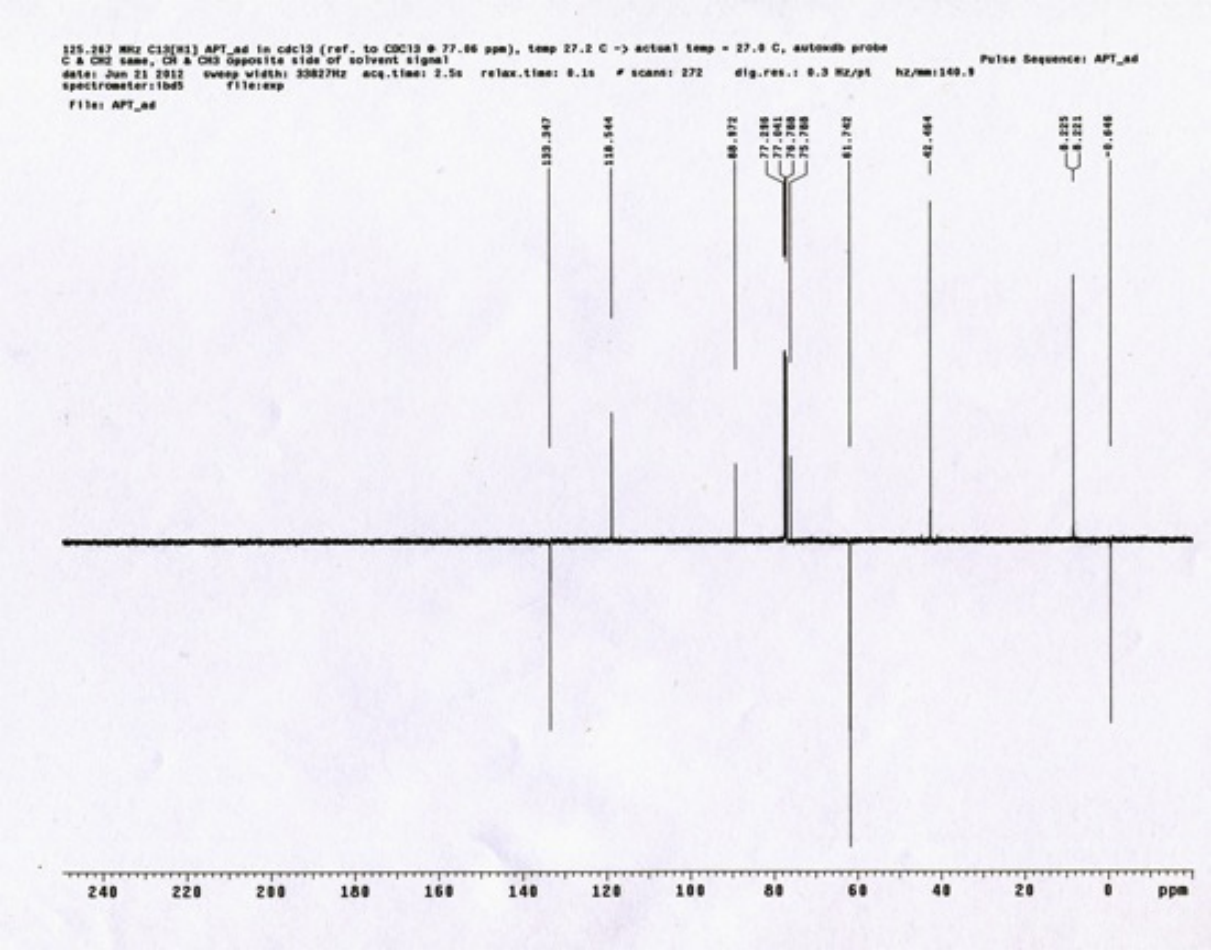
1-Cyclopropylhex-5-en-1-yn-3-ol



2.113

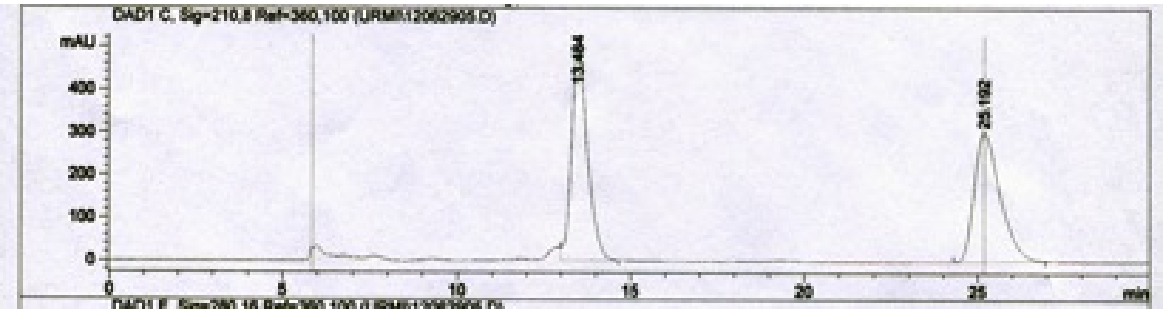


^{13}C NMR (125 MHz, $CDCl_3$)

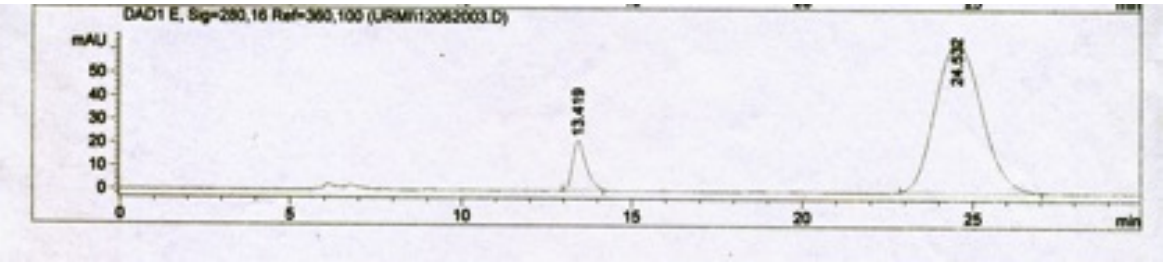


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



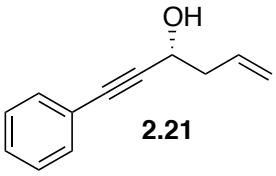
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.484	VB	0.4736	1.59780e4	501.67746	50.2613
2	25.192	BB	0.7501	1.58119e4	301.35764	49.7387
Totals :				3.17899e4	803.03510	



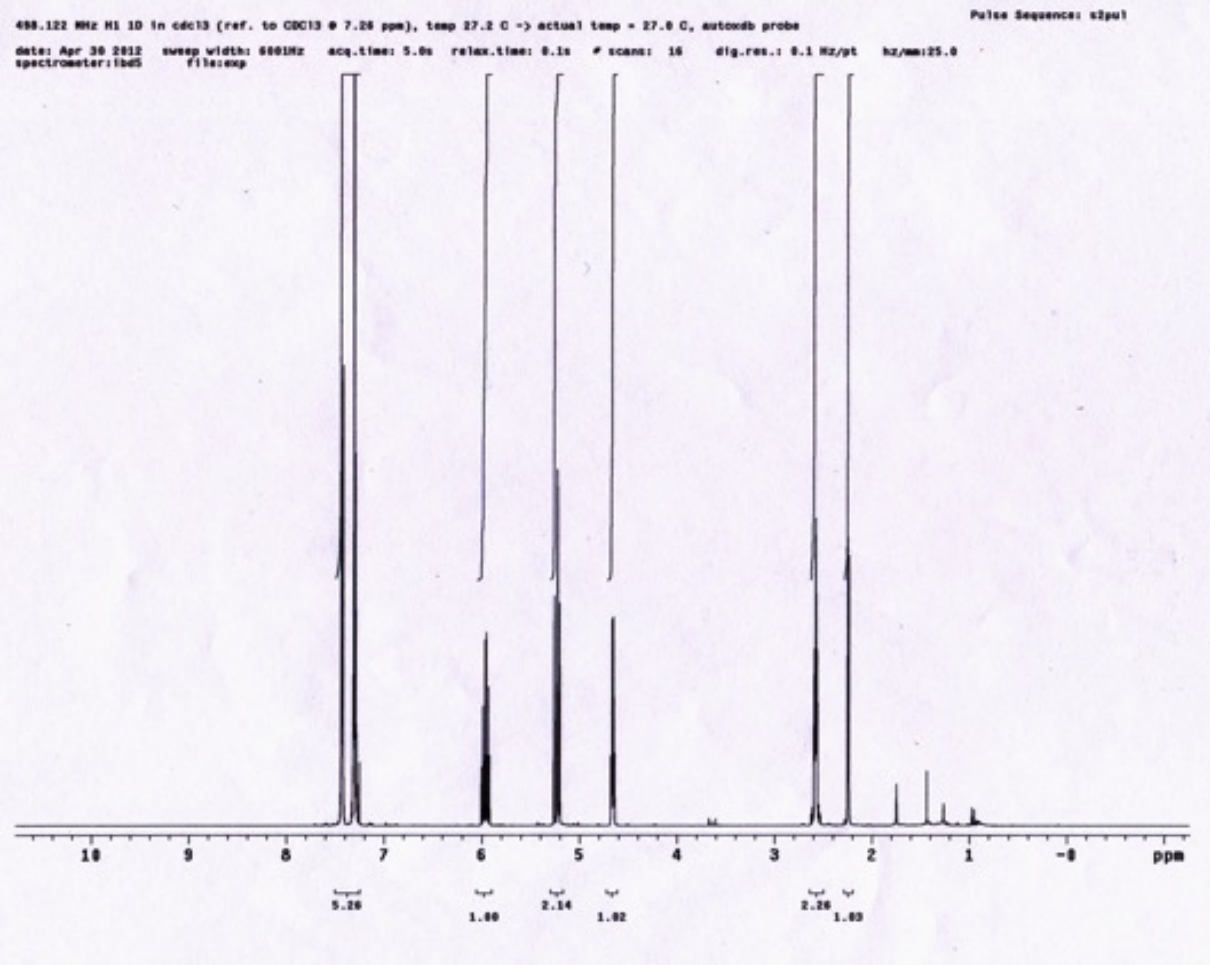
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.419	BB	0.4177	597.53107	21.40277	8.9883
2	24.532	BB	1.4207	6050.32959	63.43979	91.0117
Totals :				6647.86066	84.84256	

^{1}H NMR (500 MHz, $CDCl_3$)

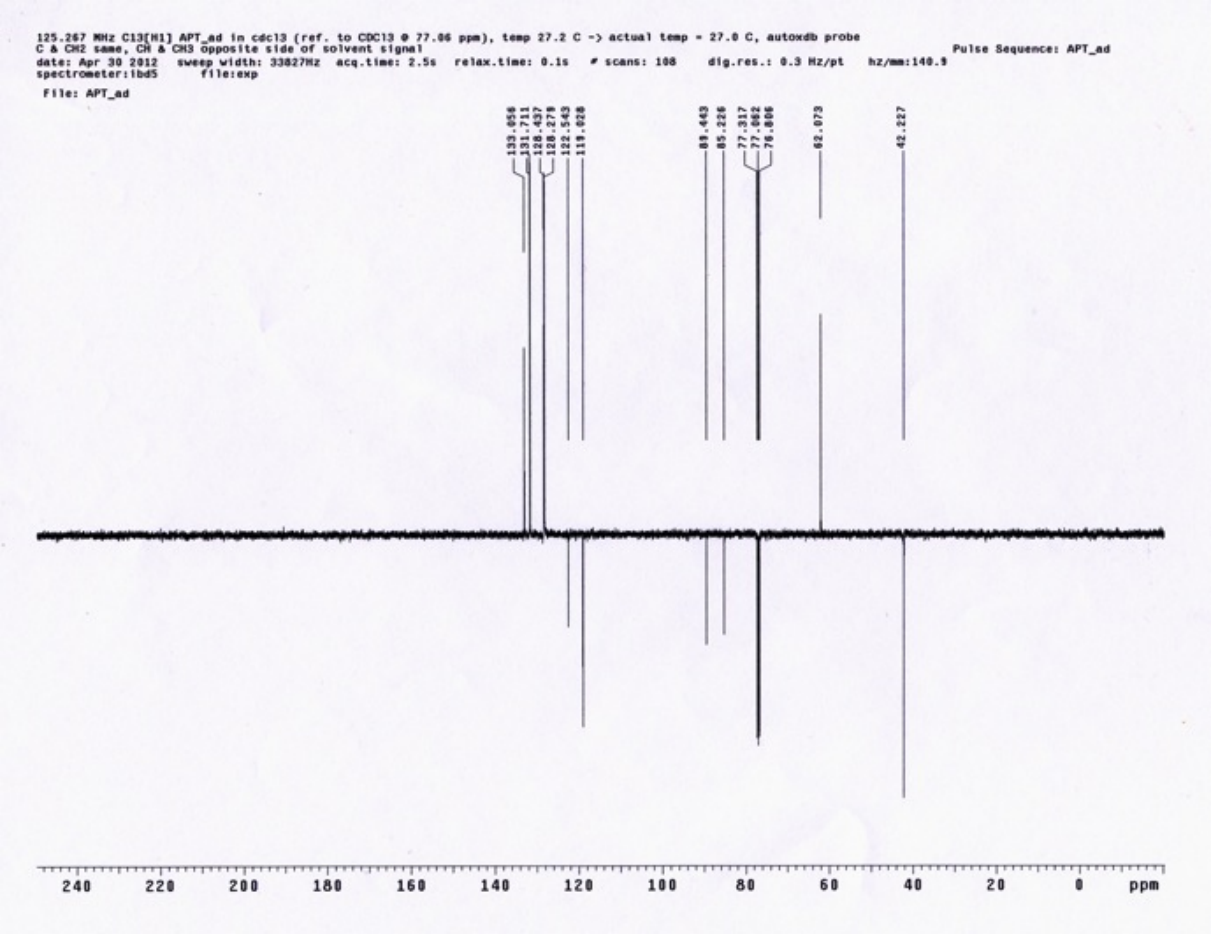
(3*S*)-1-Phenylhex-5-en-1-yn-3-ol



2.21



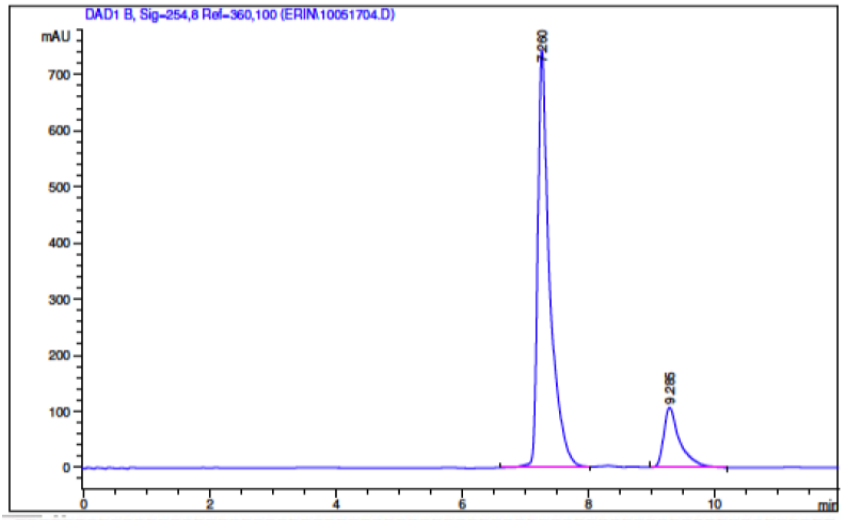
^{13}C NMR (125 MHz, $CDCl_3$)



50% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.010	BV	0.4392	6.29675e4	2316.29736	51.1484
2	8.918	VB	0.3660	6.01399e4	2487.66455	48.8516
Totals :				1.23107e5	4803.96191	

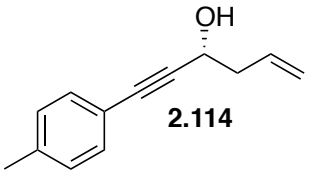


Area Percent Report

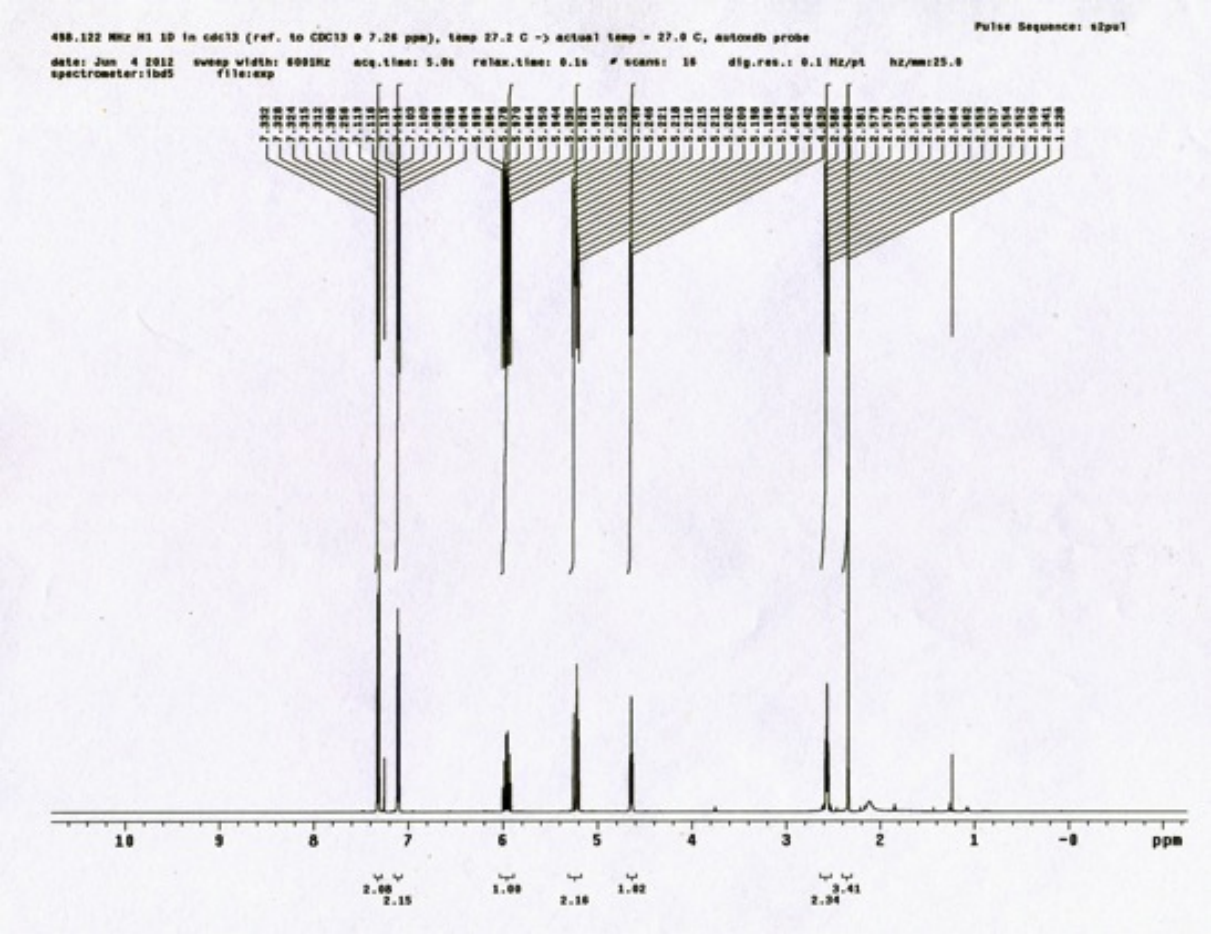
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.260	BB	0.1909	9888.65820	745.02399	83.8301
2	9.285	VB	0.2583	1907.41479	106.83940	16.1699

^{1}H NMR (500 MHz, $CDCl_3$)

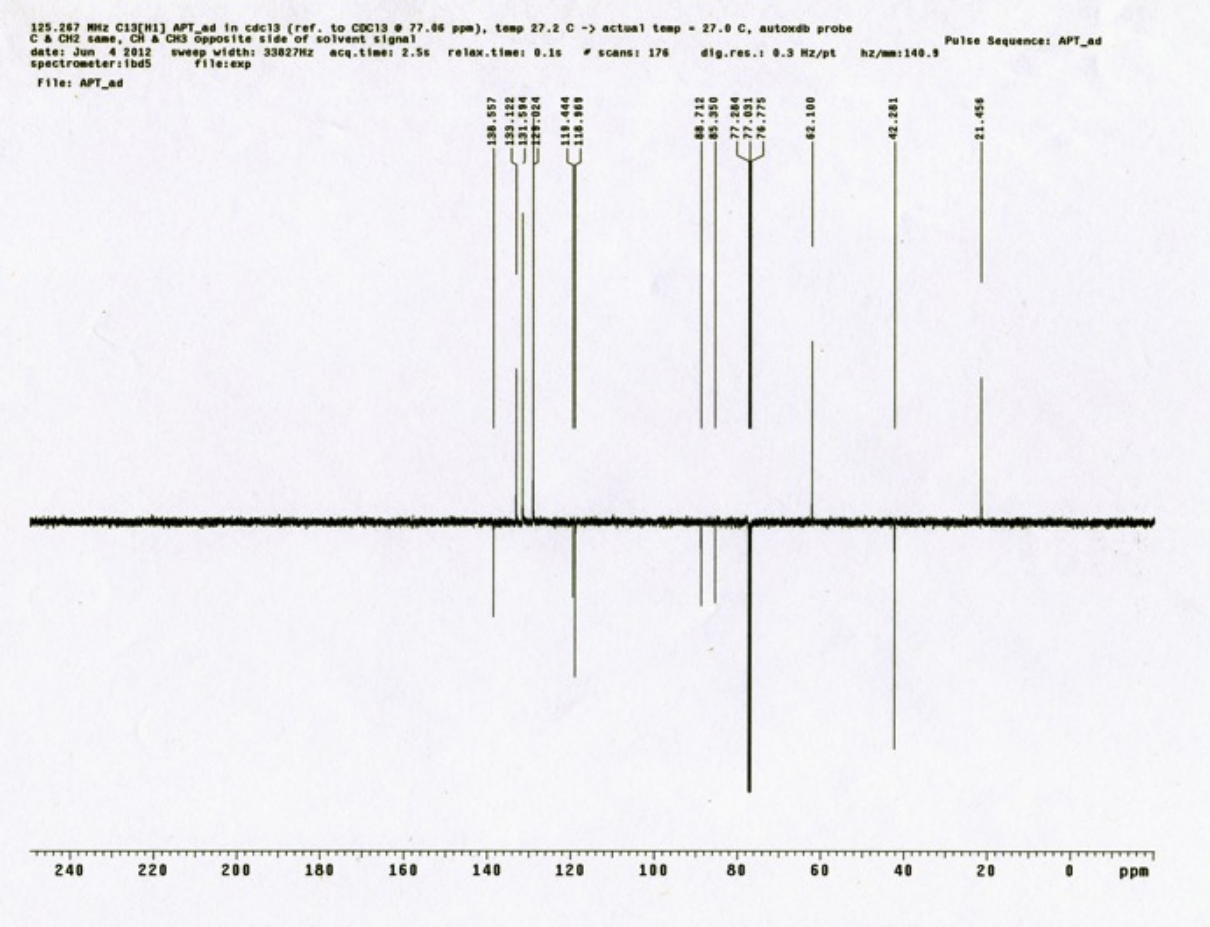
1-(4-Methylphenyl)hex-5-en-1-yn-3-ol



2.114

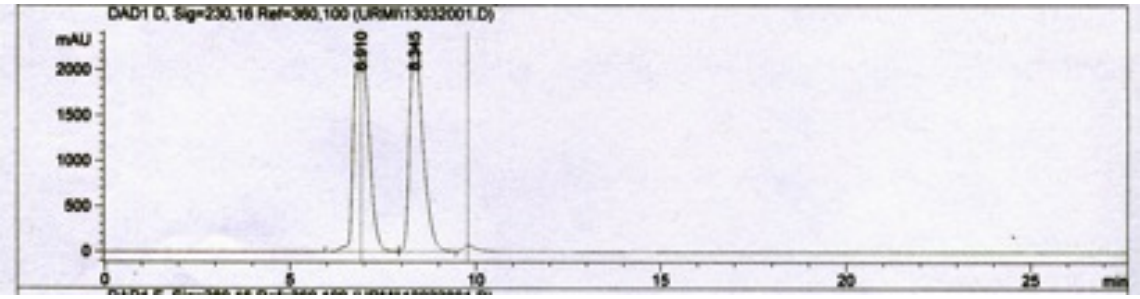


^{13}C NMR (125 MHz, $CDCl_3$)

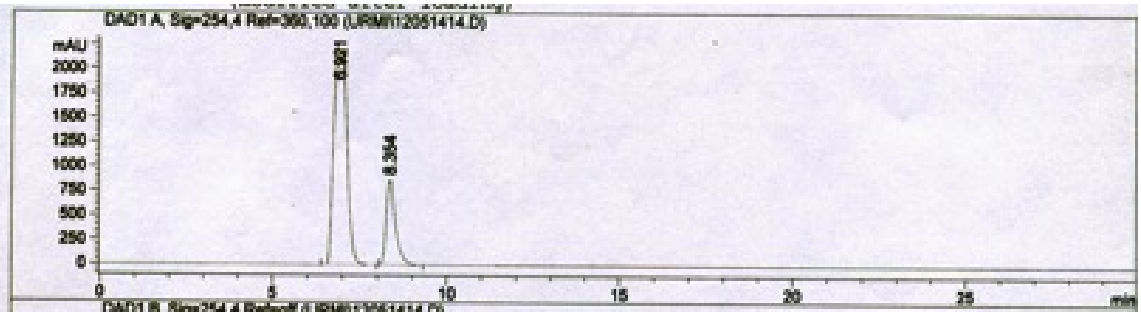


50% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



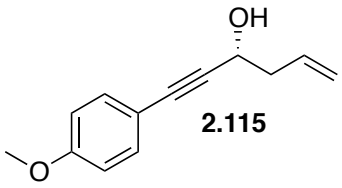
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.910	BV	0.4140	6.31094e4	2115.64868	52.1065
2	8.345	VV	0.3852	5.80067e4	2308.51172	47.8935
Totals :				1.21116e5	4424.16040	



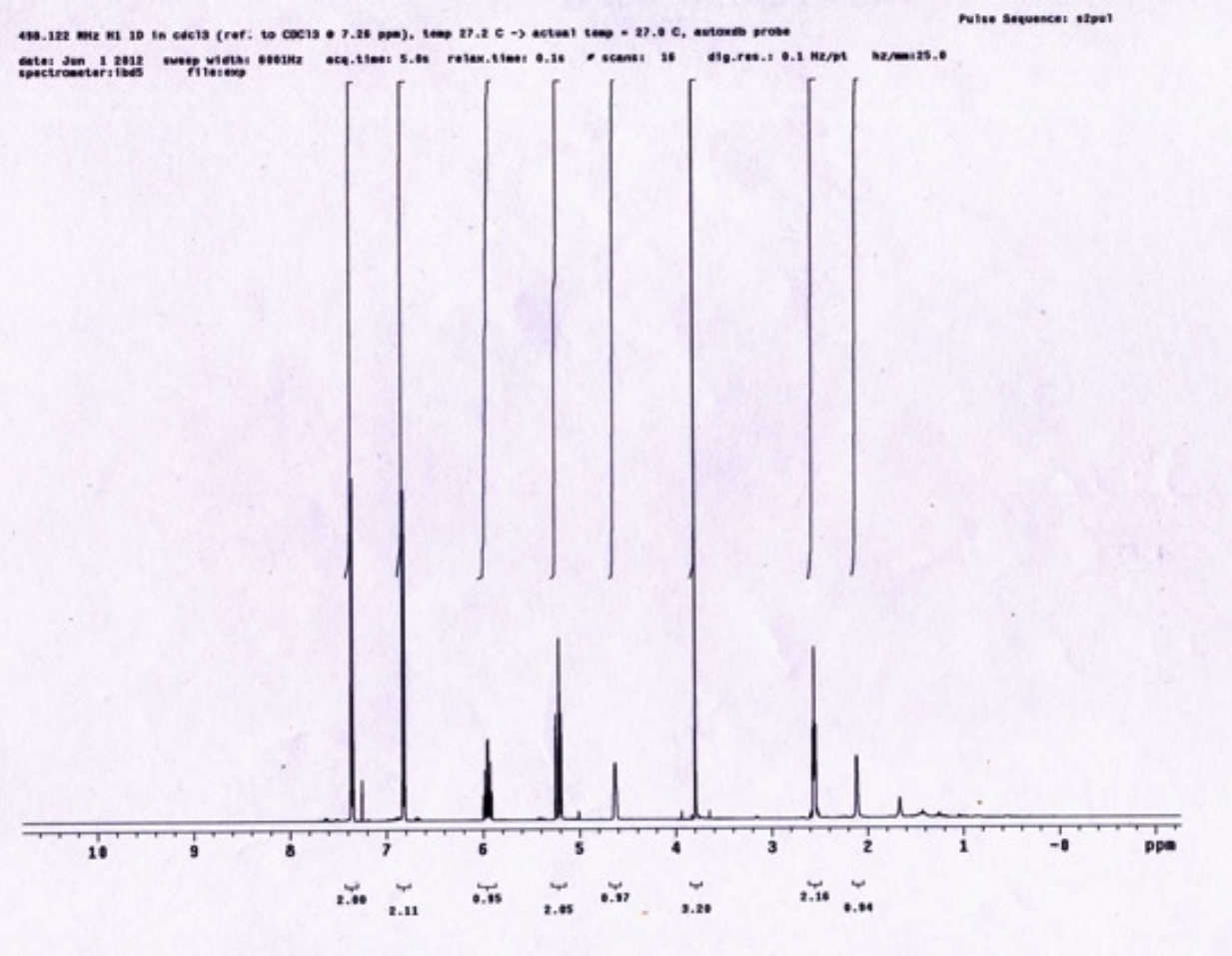
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.921	BB	0.4250	5.69755e4	2194.12622	78.8181
2	8.354	BB	0.2615	1.53110e4	869.23944	21.1819
Totals :				7.22873e4	3063.36566	

^{1}H NMR (500 MHz, $CDCl_3$)

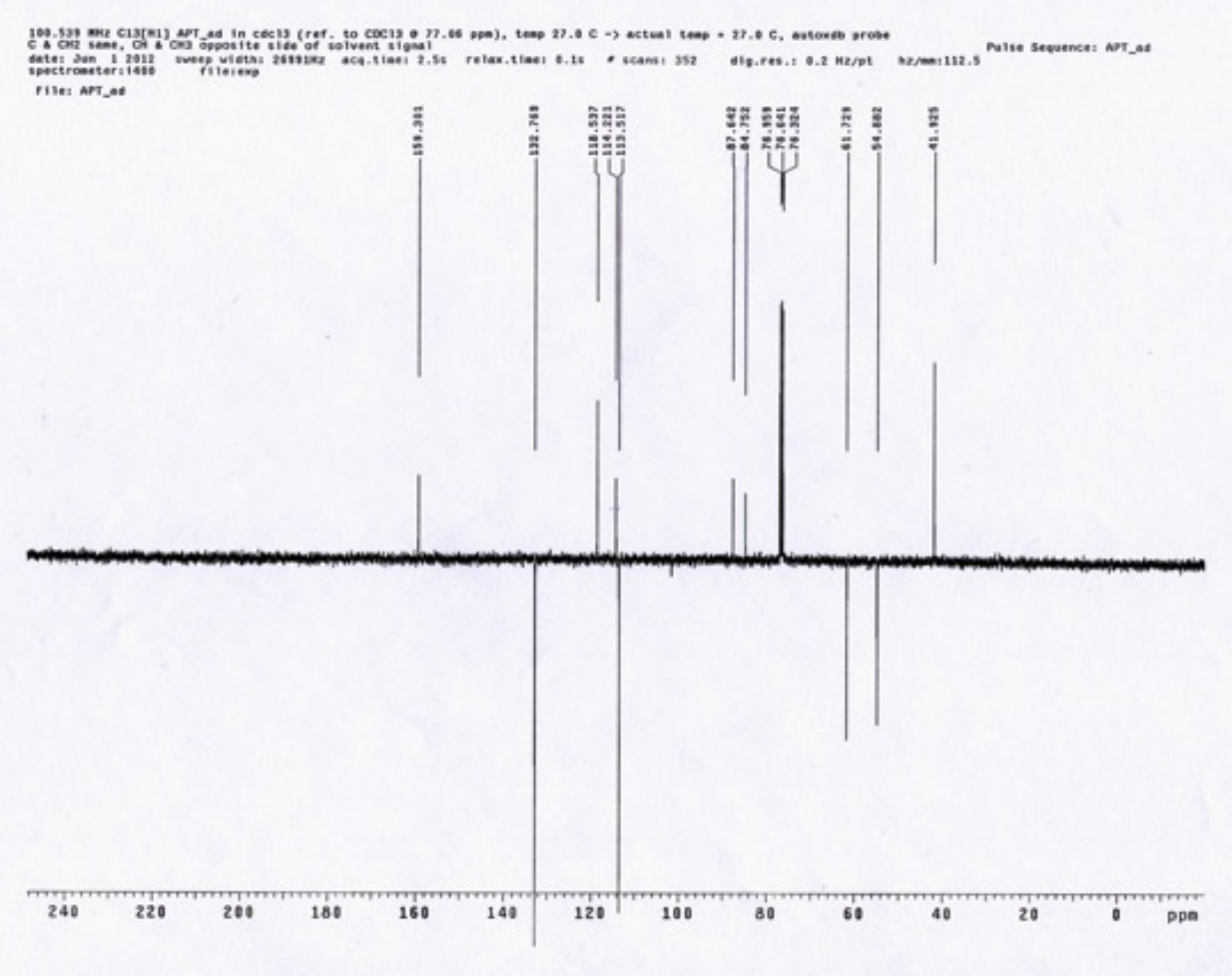
1-(4-Methoxyphenyl)hex-5-en-1-yn-3-ol



2.115

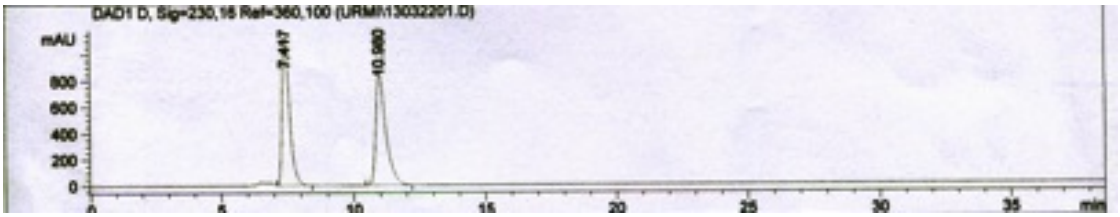


^{13}C NMR (100 MHz, $CDCl_3$)

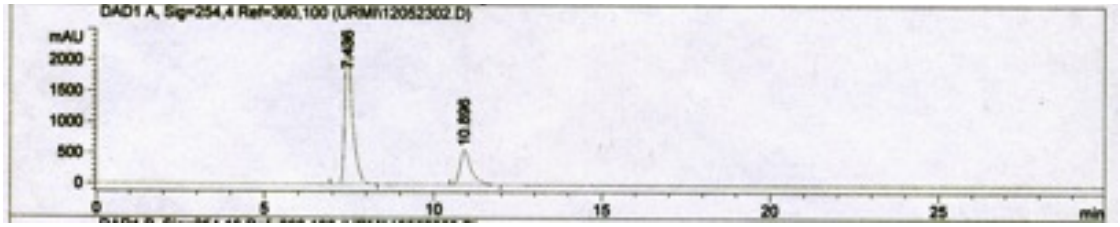


50% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



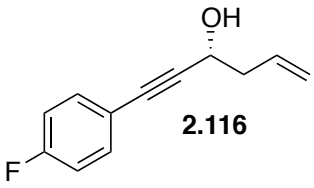
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.417	VB	0.3048	2.23493e4	1129.90625	49.8077
2	10.980	PB	0.3886	2.25219e4	857.02661	50.1923
Totals :				4.48711e4	1986.93286	



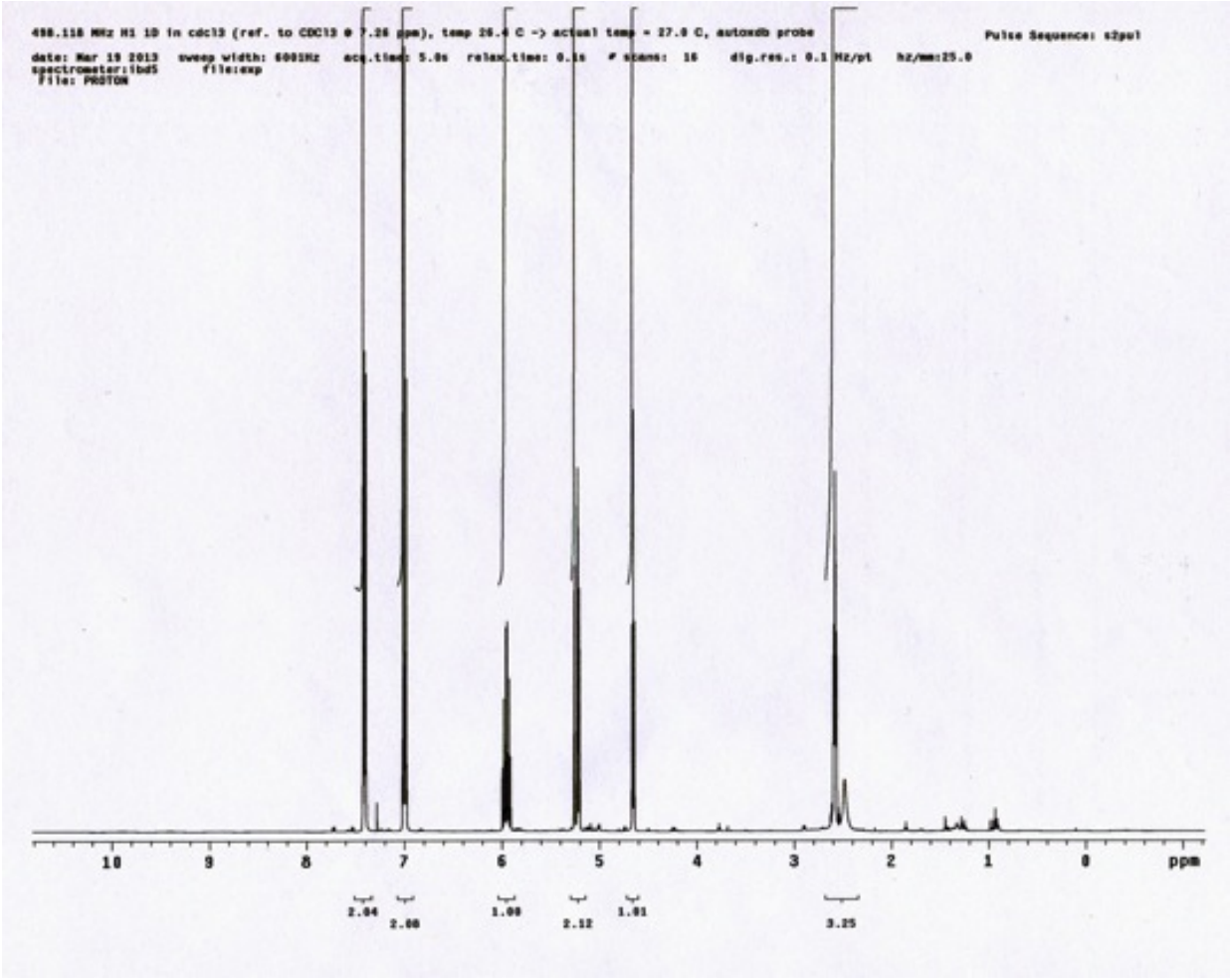
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.436	PB	0.2116	3573.17456	245.85811	75.6198
2	10.896	BB	0.3267	1152.00769	51.55431	24.3802
Totals :				4725.18225	297.41242	

^{1}H NMR (500 MHz, $CDCl_3$)

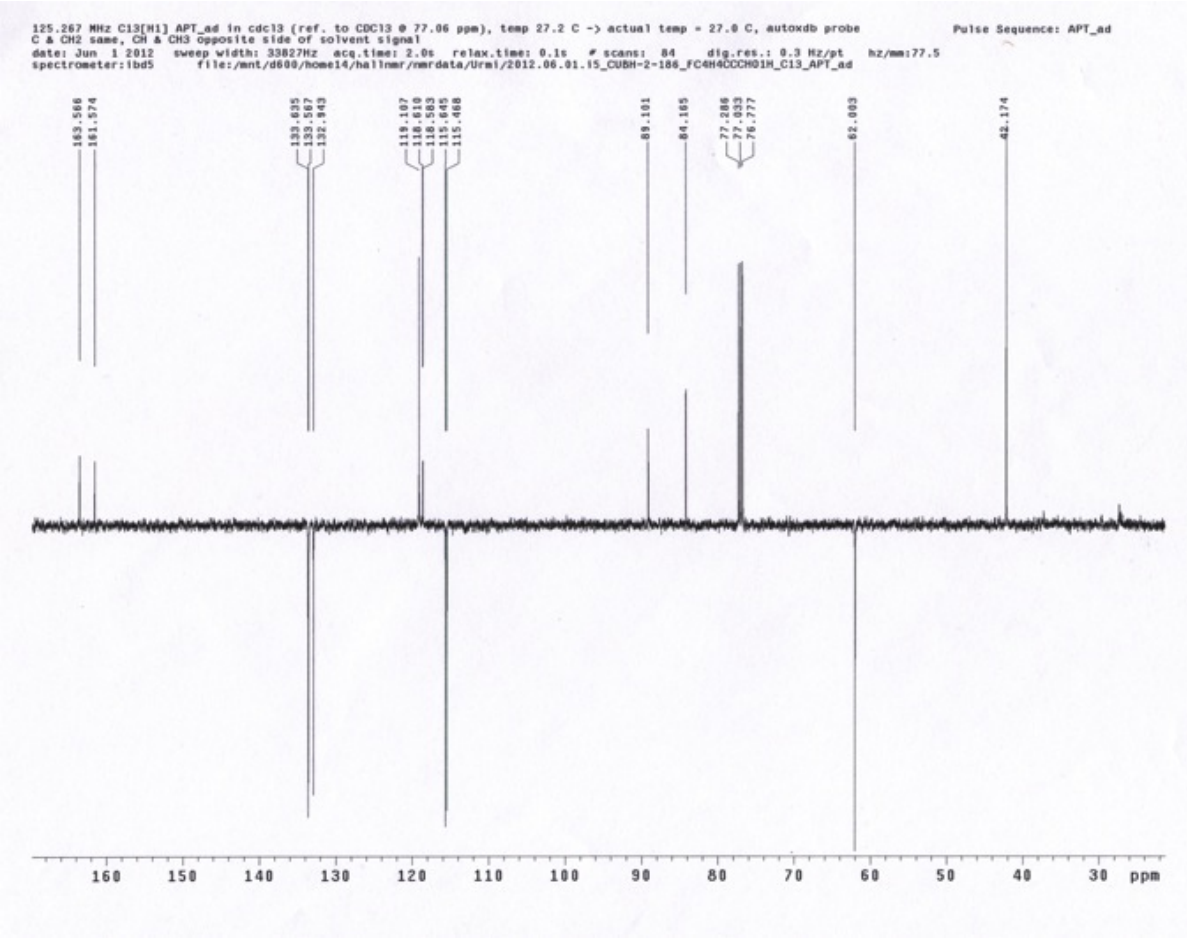
1-(4-Fluorophenyl)hex-5-en-1-yn-3-ol



2.116

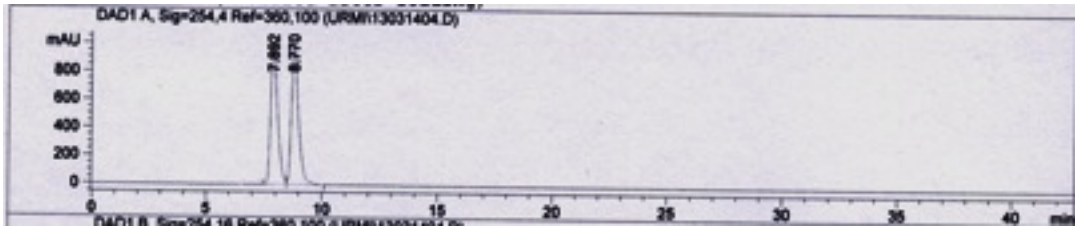


^{13}C NMR (125 MHz, $CDCl_3$)

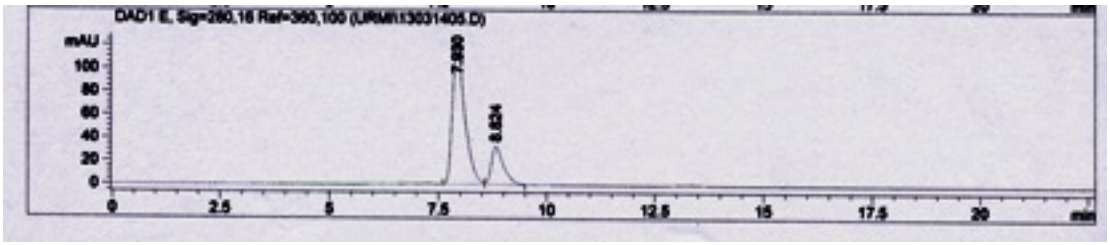


50% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



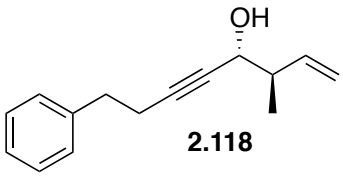
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.892	PV	0.3057	2.08021e4	1021.06262	49.6834
2	8.770	VB	0.3082	2.10673e4	998.22711	50.3166
Totals :				4.18694e4	2019.28973	



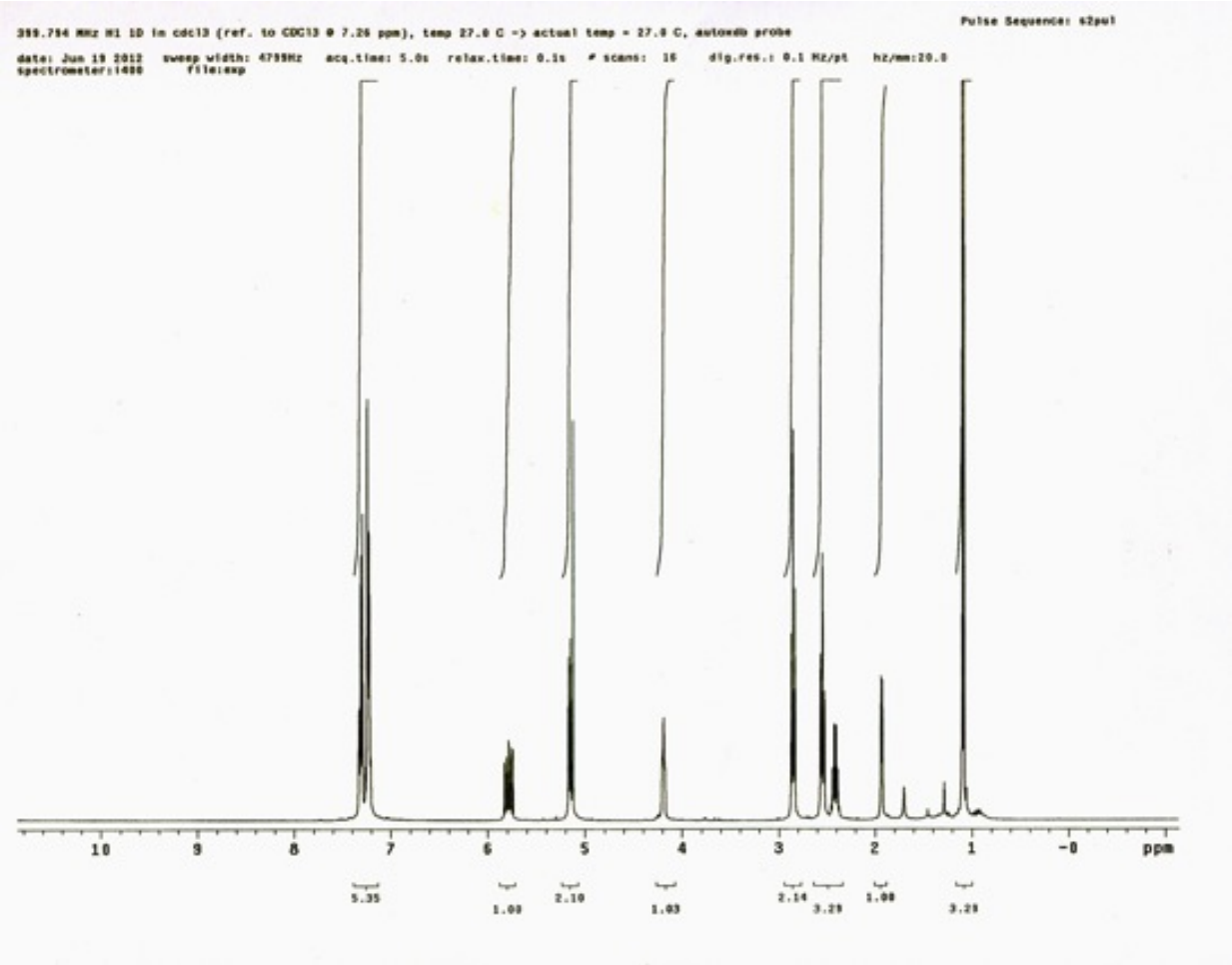
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.930	BV	0.2896	2381.45679	122.07830	78.4925
2	8.824	VB	0.2866	652.53510	33.29507	21.5075
Totals :				3033.99188	155.37337	

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

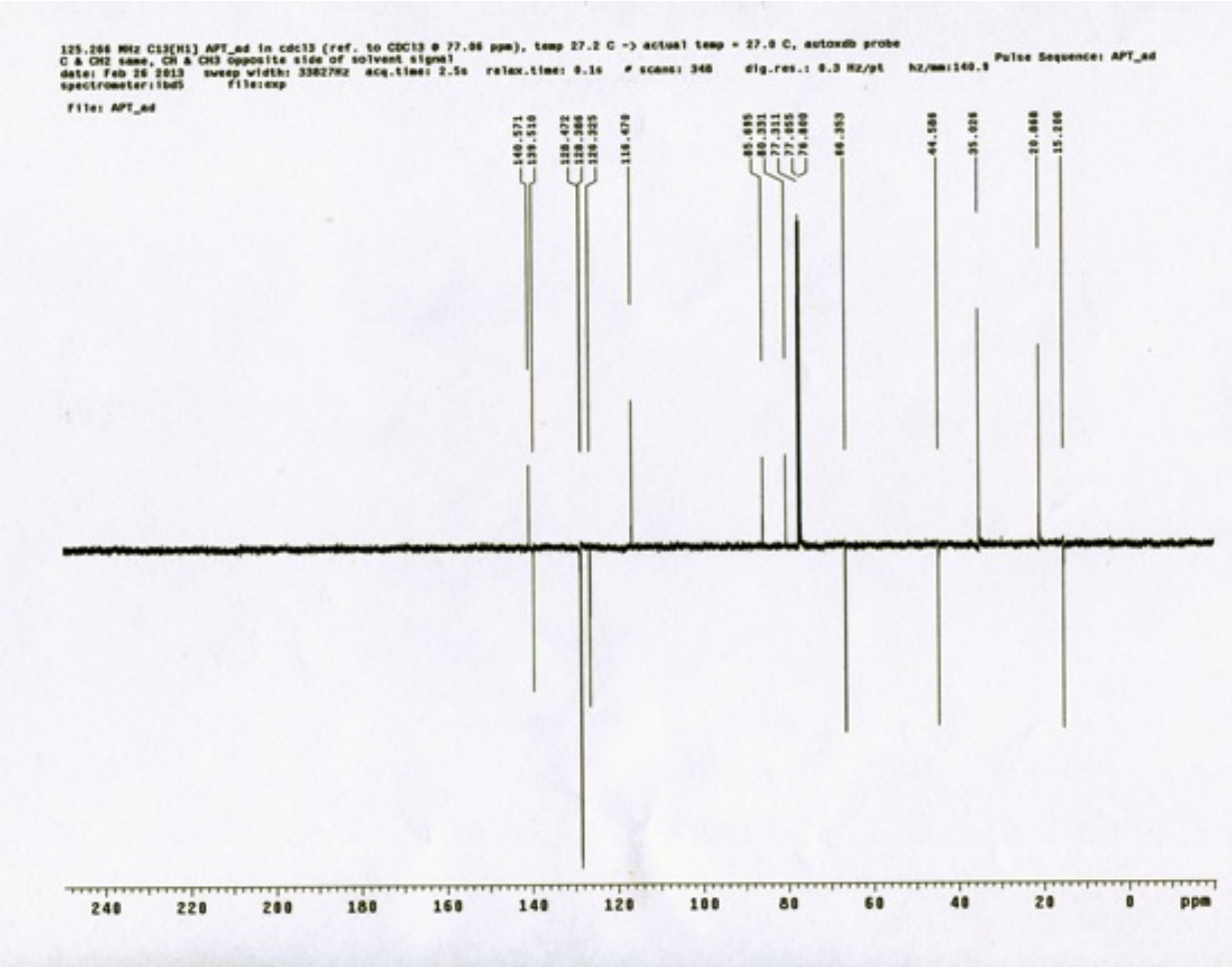
Methyl-7-phenyloct-5-en-1-yn-3-ol



2.118

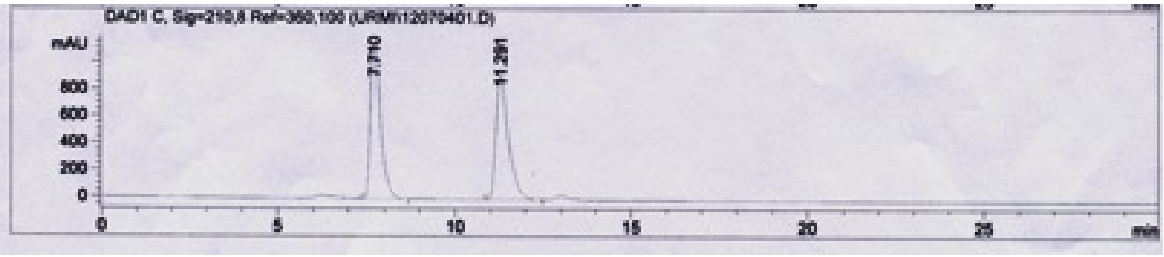


^{13}C NMR (125 MHz, $CDCl_3$)

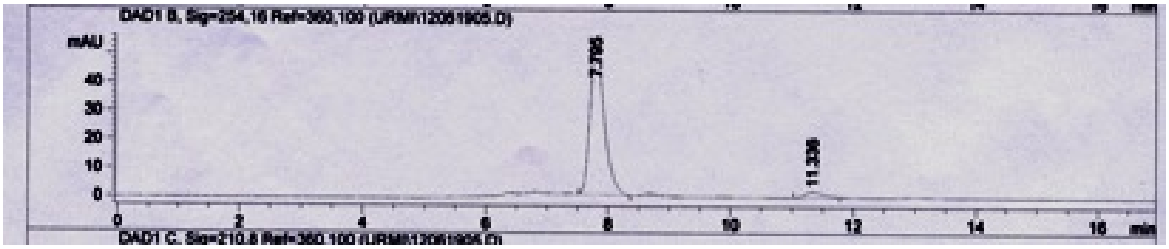


40% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



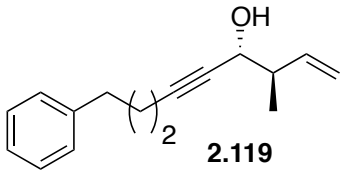
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.710	PB	0.3097	2.27748e4	1146.77161	50.4717
2	11.291	BB	0.3577	2.23491e4	919.22498	49.5283
Totals :				4.51239e4	2065.99658	



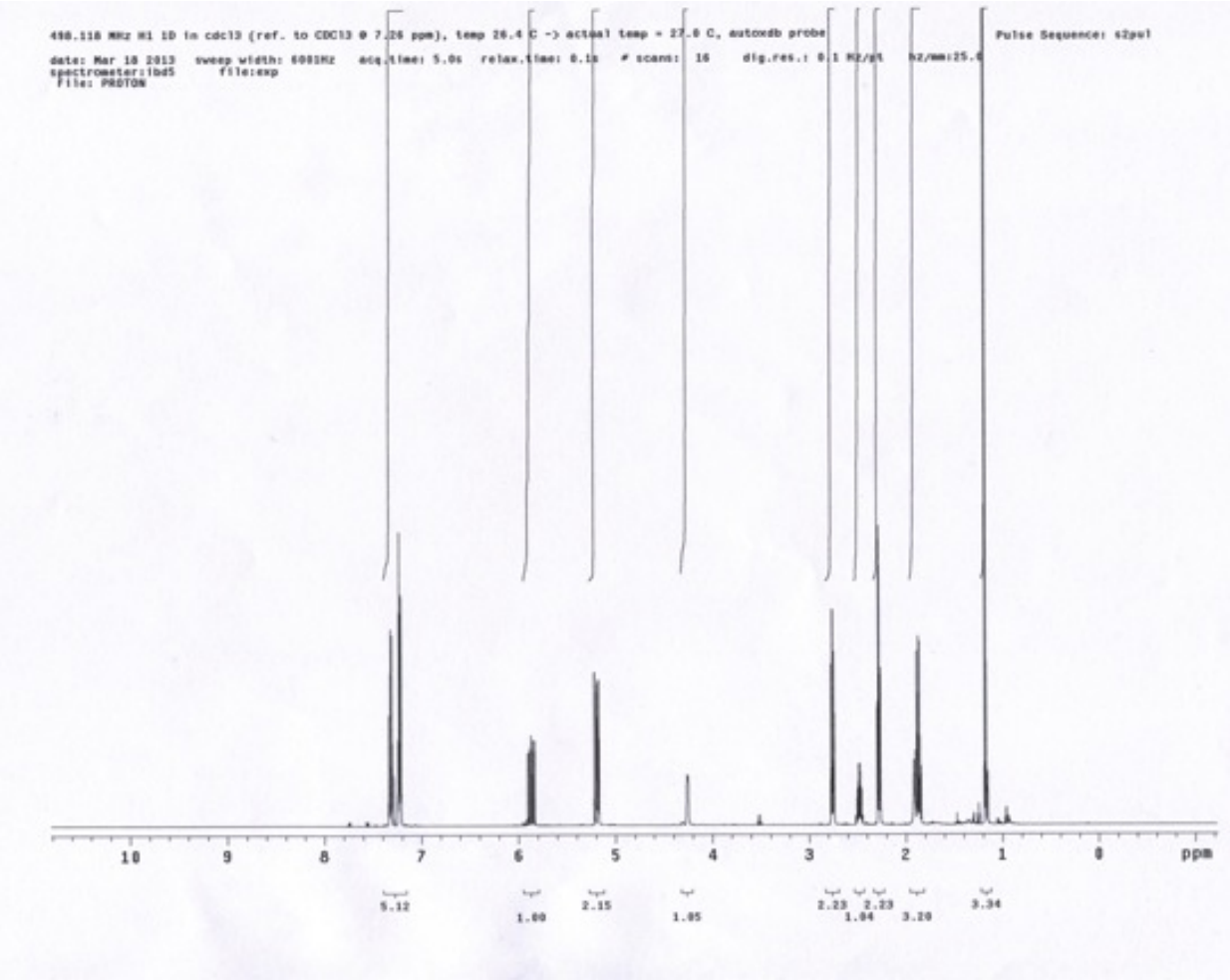
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.795	BP	0.2424	847.00665	52.44963	95.4074
2	11.336	PB	0.2814	40.77258	1.93811	4.5926
Totals :				887.77923	54.38774	

^{1}H NMR (500 MHz, $CDCl_3$)

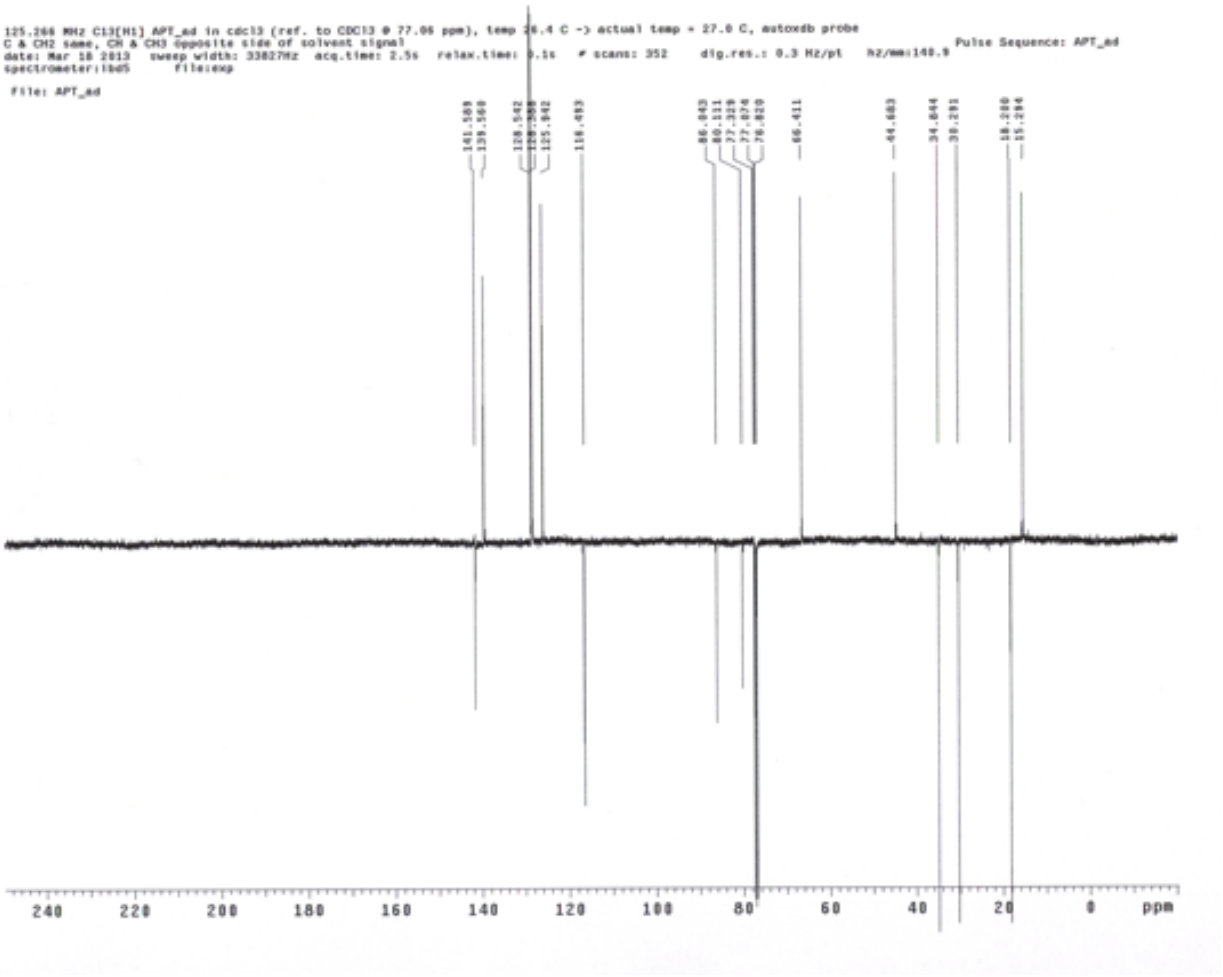
Methyl-8-Phenylnon-1-en-5-yn-4-ol



2.119

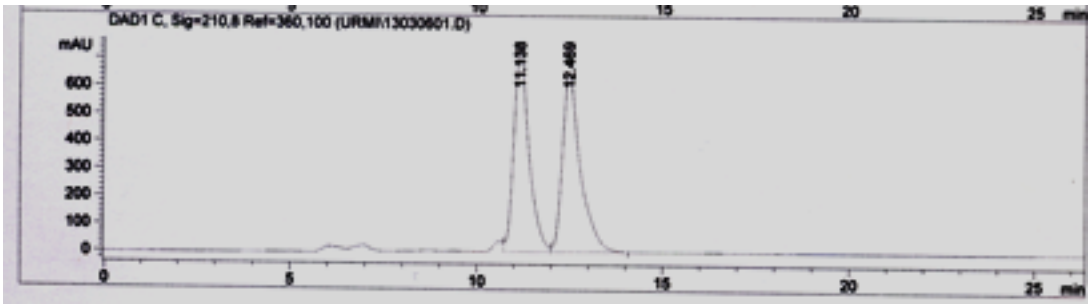


^{13}C NMR (125 MHz, $CDCl_3$)

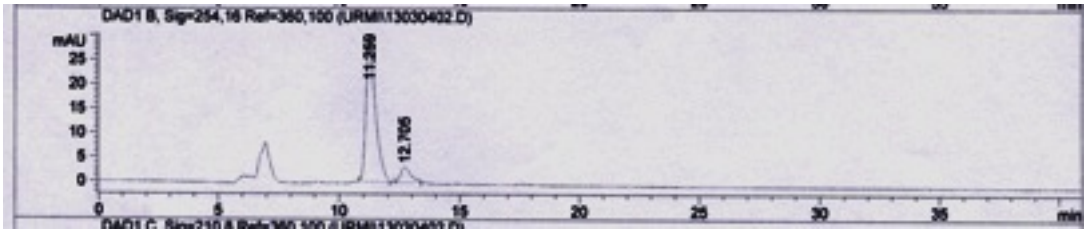


10% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



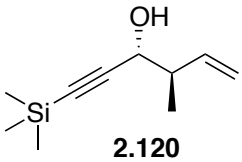
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.138	VV	0.4294	2.09903e4	725.86115	48.9056
2	12.469	VB	0.5001	2.19297e4	642.62201	51.0944



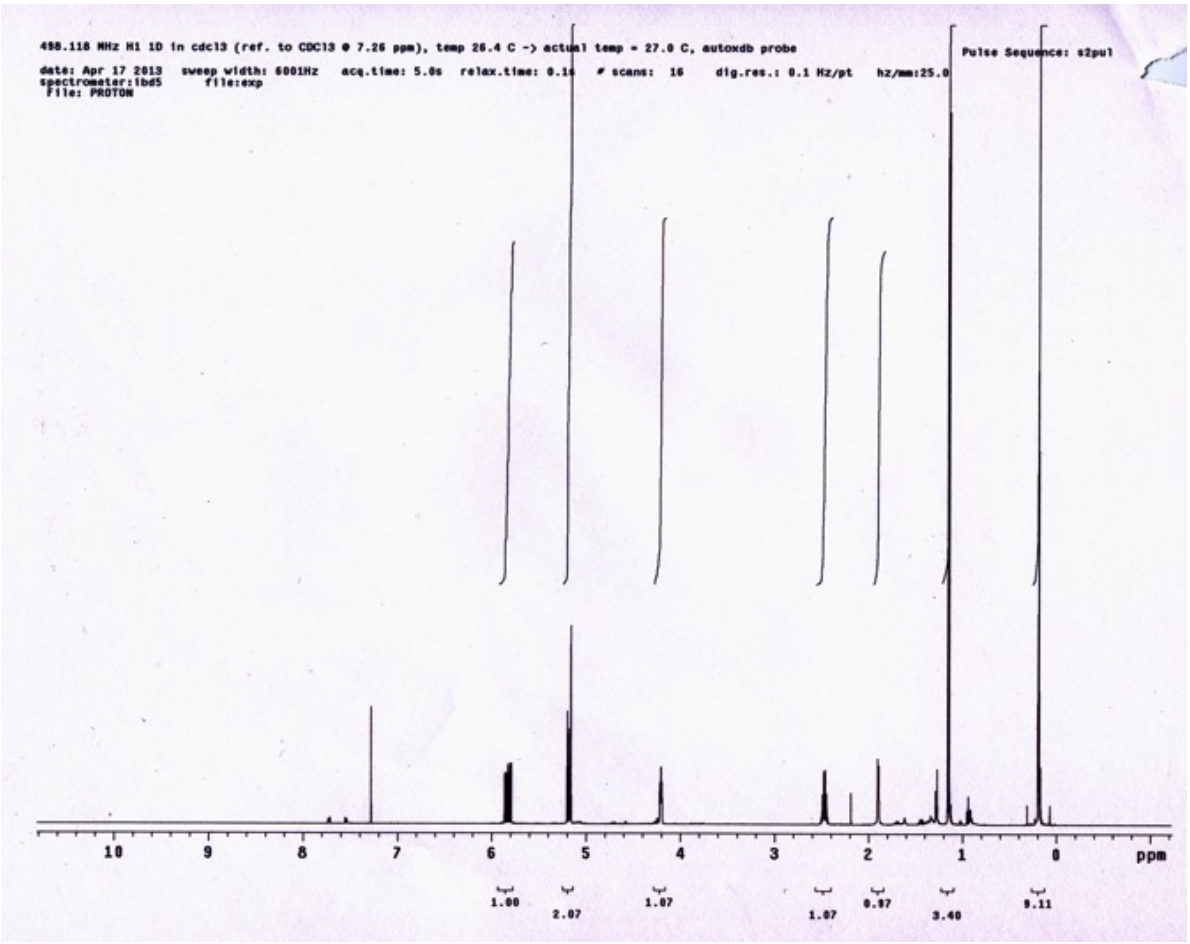
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.259	BB	0.4159	807.70795	28.91354	89.6938
2	12.705	PB	0.3862	92.80894	3.16440	10.3062
Totals :				900.51689	32.07794	

^{1}H NMR (500 MHz, $CDCl_3$)

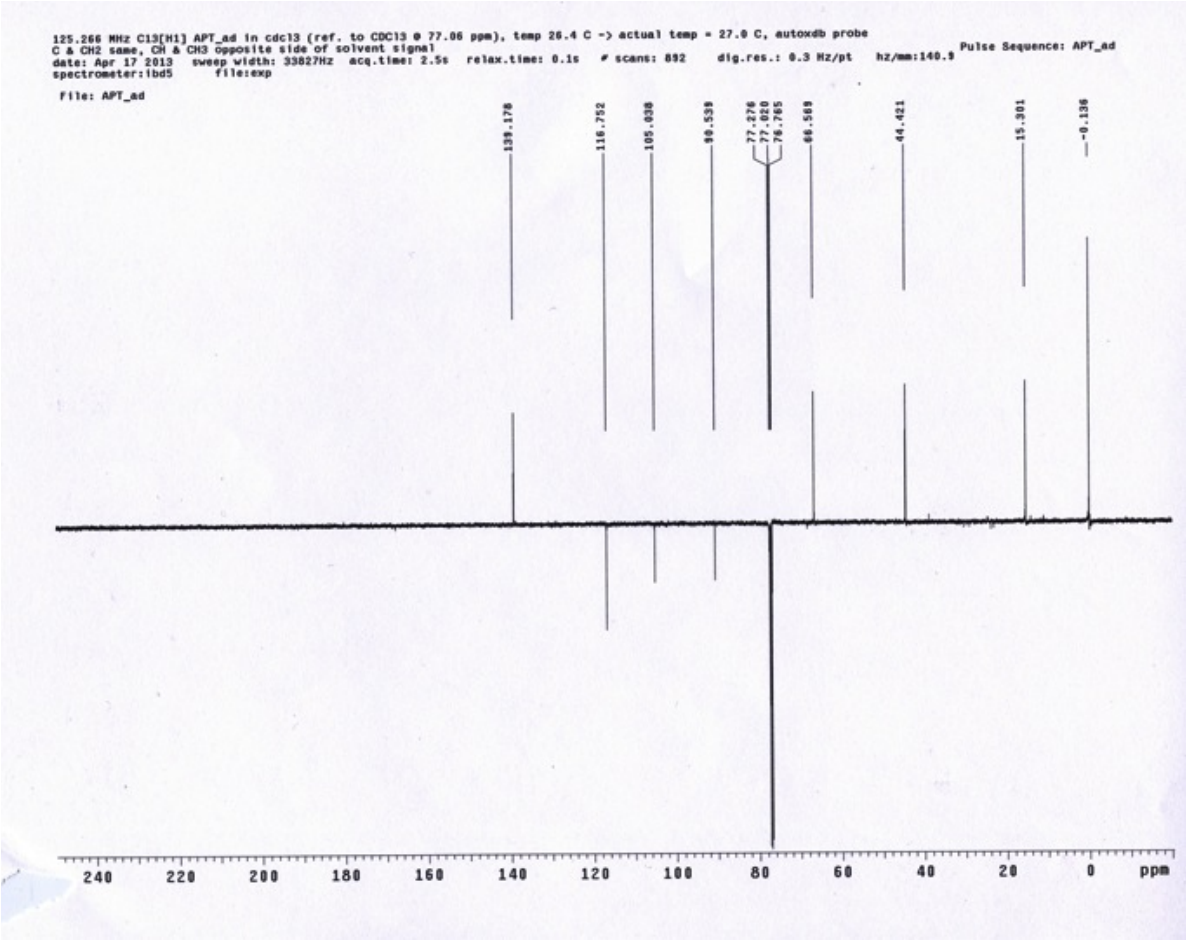
Methyl-1-Trimethylsilylhex-1-en-5-yn-4-ol



2.120

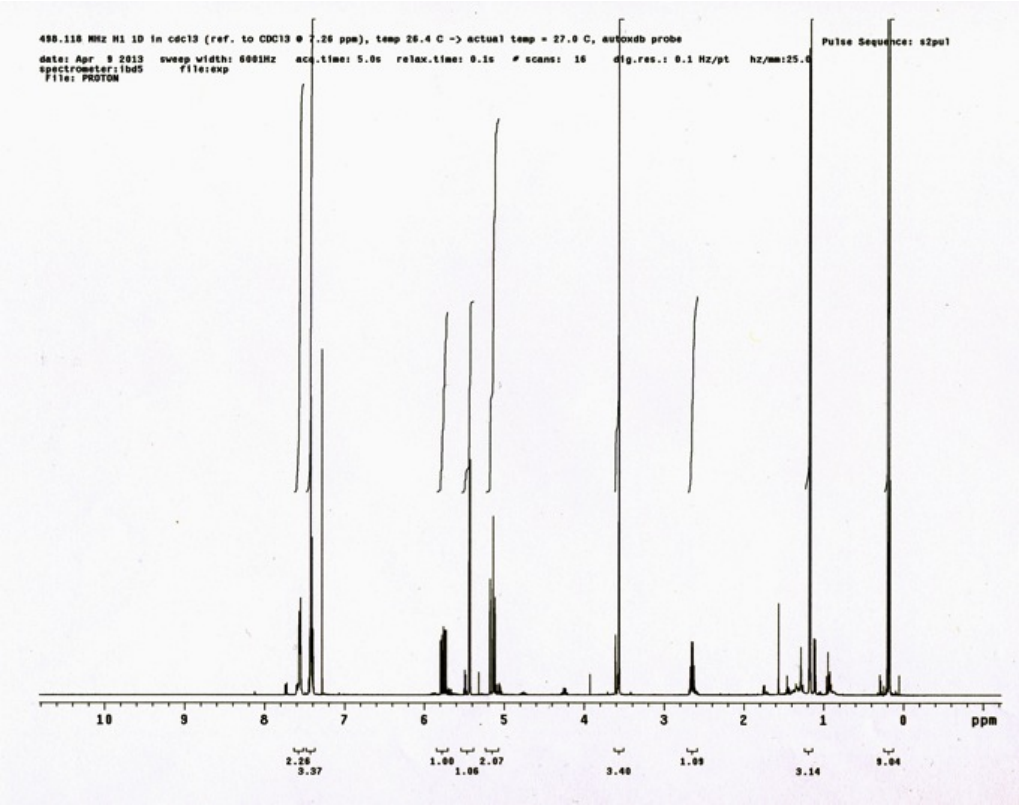


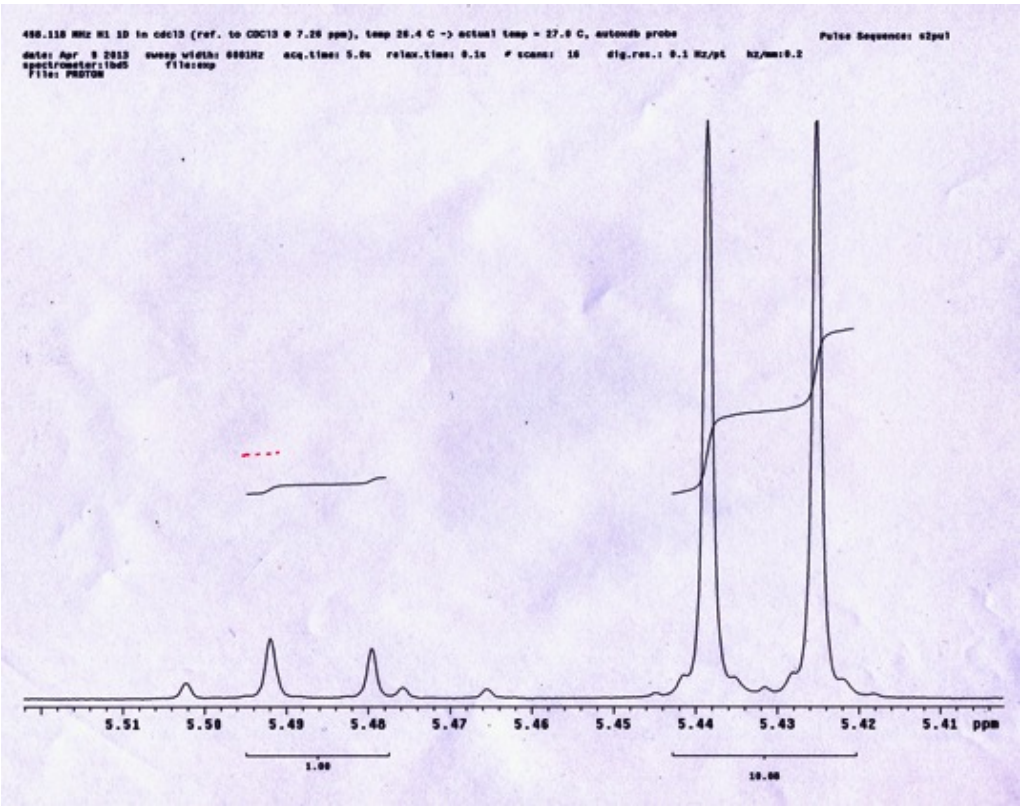
^{13}C NMR (125 MHz, $CDCl_3$)



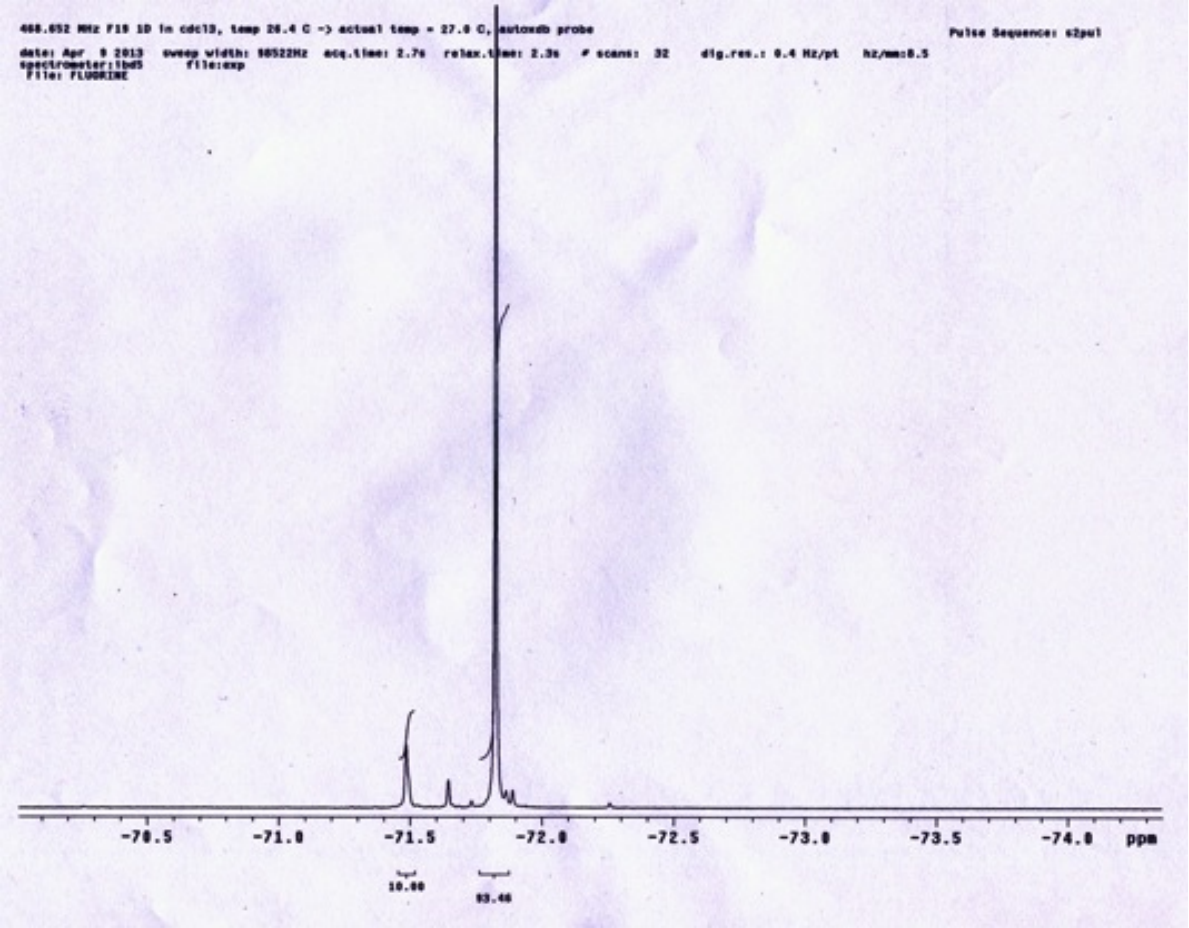
^{1}H NMR (500 MHz, $CDCl_3$)

Mosher ester



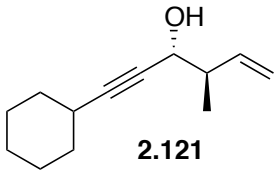

5.51
5.50
5.49
5.48
5.47
5.46
5.45
5.44
5.43
5.42
5.41
ppm
1.00
10.00

^{19}F NMR (500 MHz, $CDCl_3$)

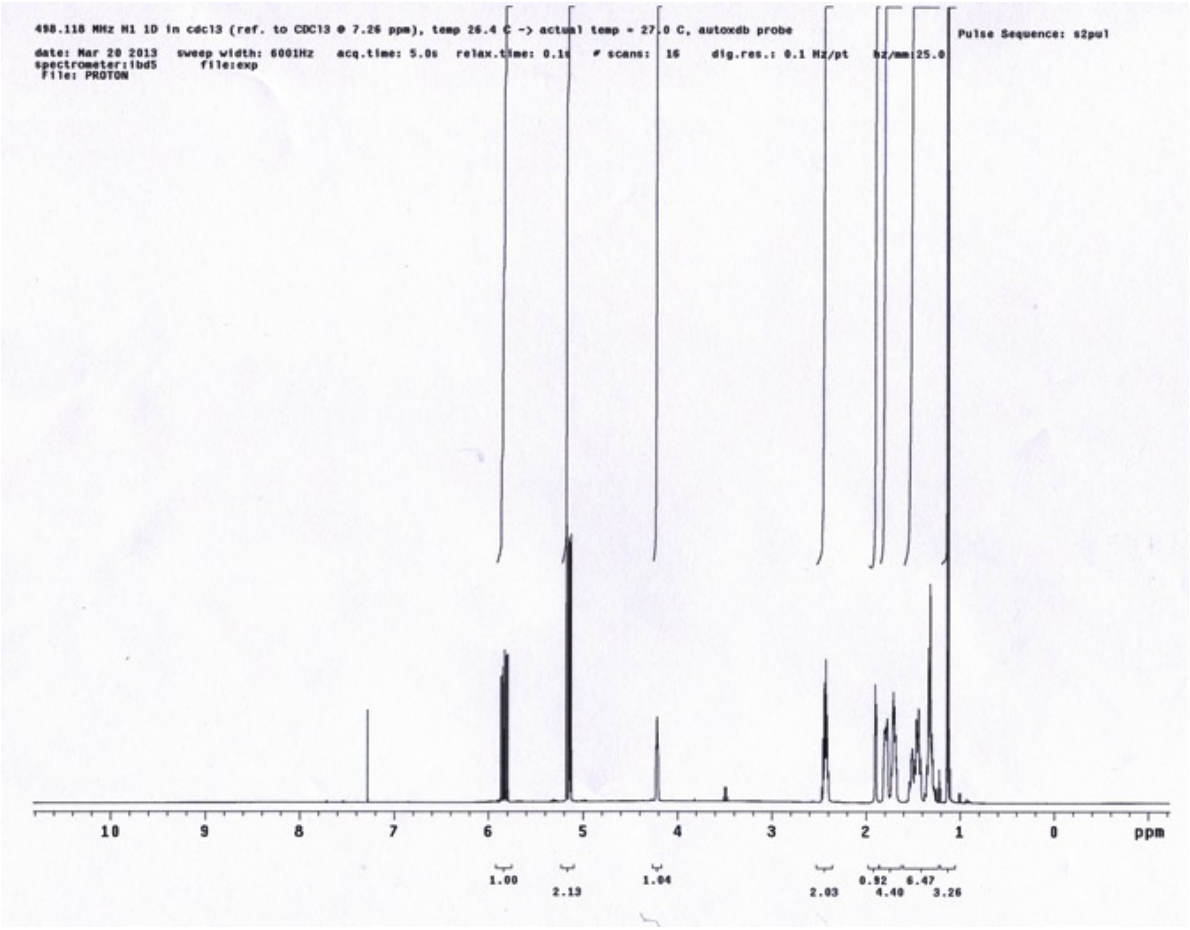


^{1}H NMR (500 MHz, $CDCl_3$)

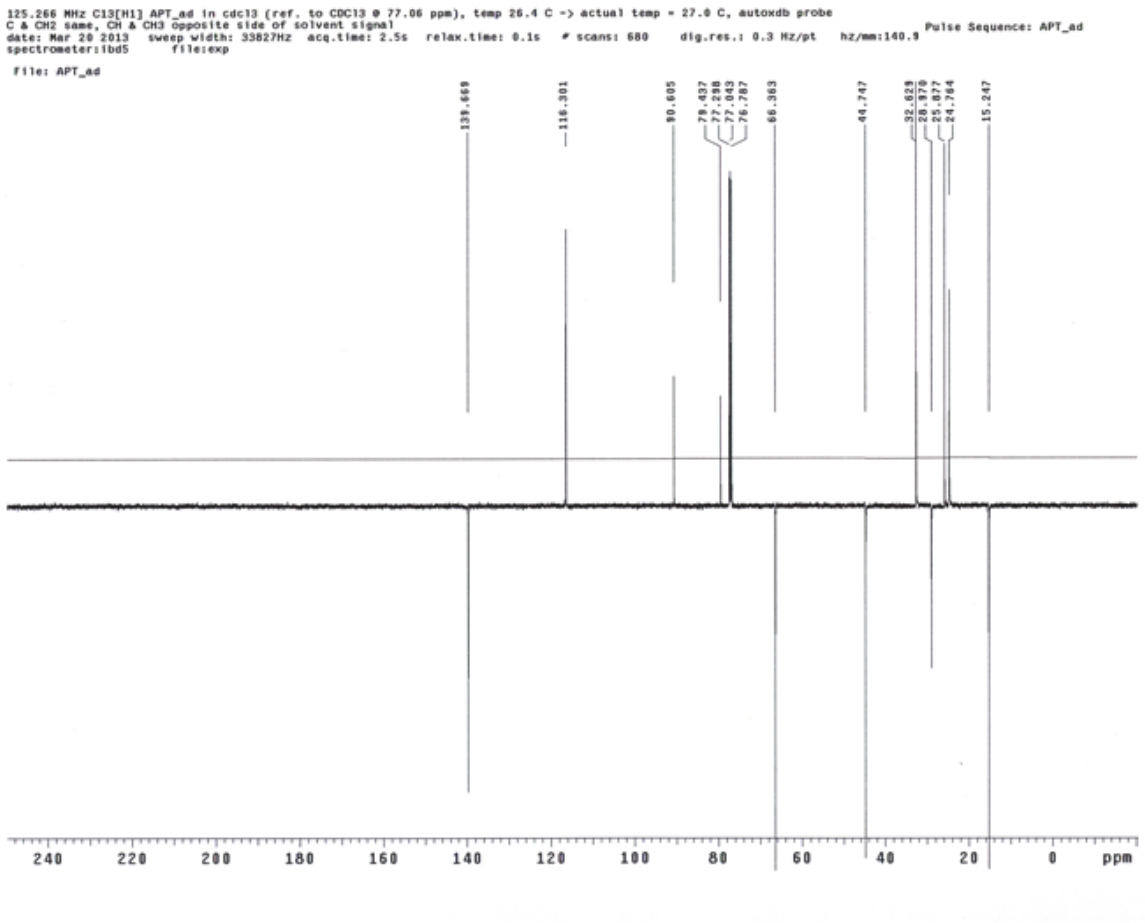
Methyl-1-cyclohexylhex-5-en-1-yn-3-ol



2.121

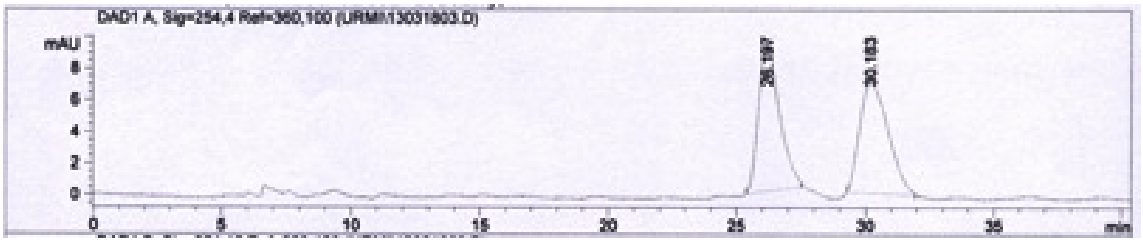


^{13}C NMR (125 MHz, $CDCl_3$)

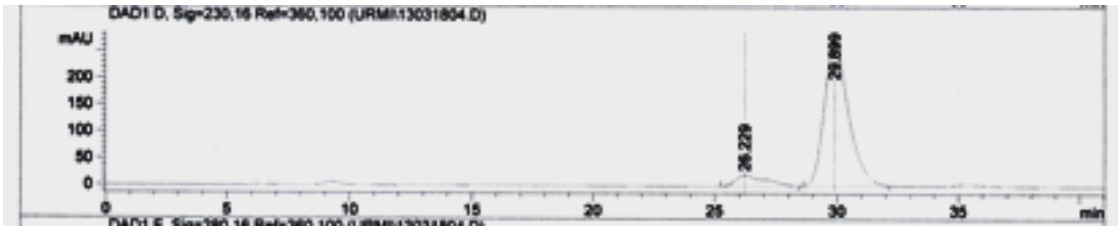


1.5% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



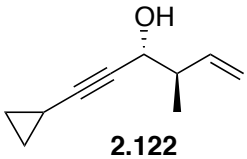
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.197	BB	0.6869	529.03870	9.31107	49.2601
2	30.183	BB	0.9052	544.93176	7.13378	50.7399
Totals :				1073.97046	16.44485	



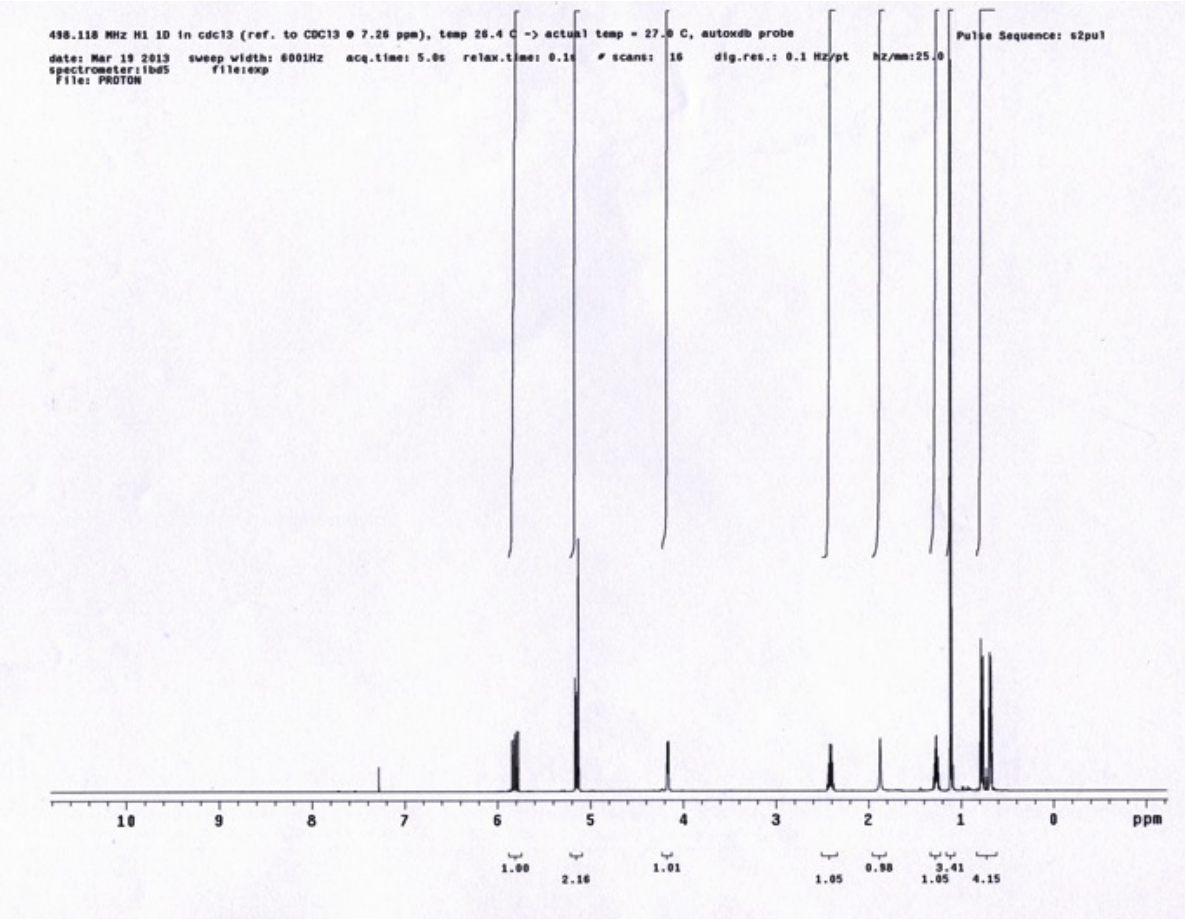
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.229	BB	1.1117	1708.07214	20.13564	8.4464
2	29.899	BB	1.0194	1.85143e4	272.25760	91.5536
Totals :				2.02224e4	292.39324	

^{1}H NMR (500 MHz, $CDCl_3$)

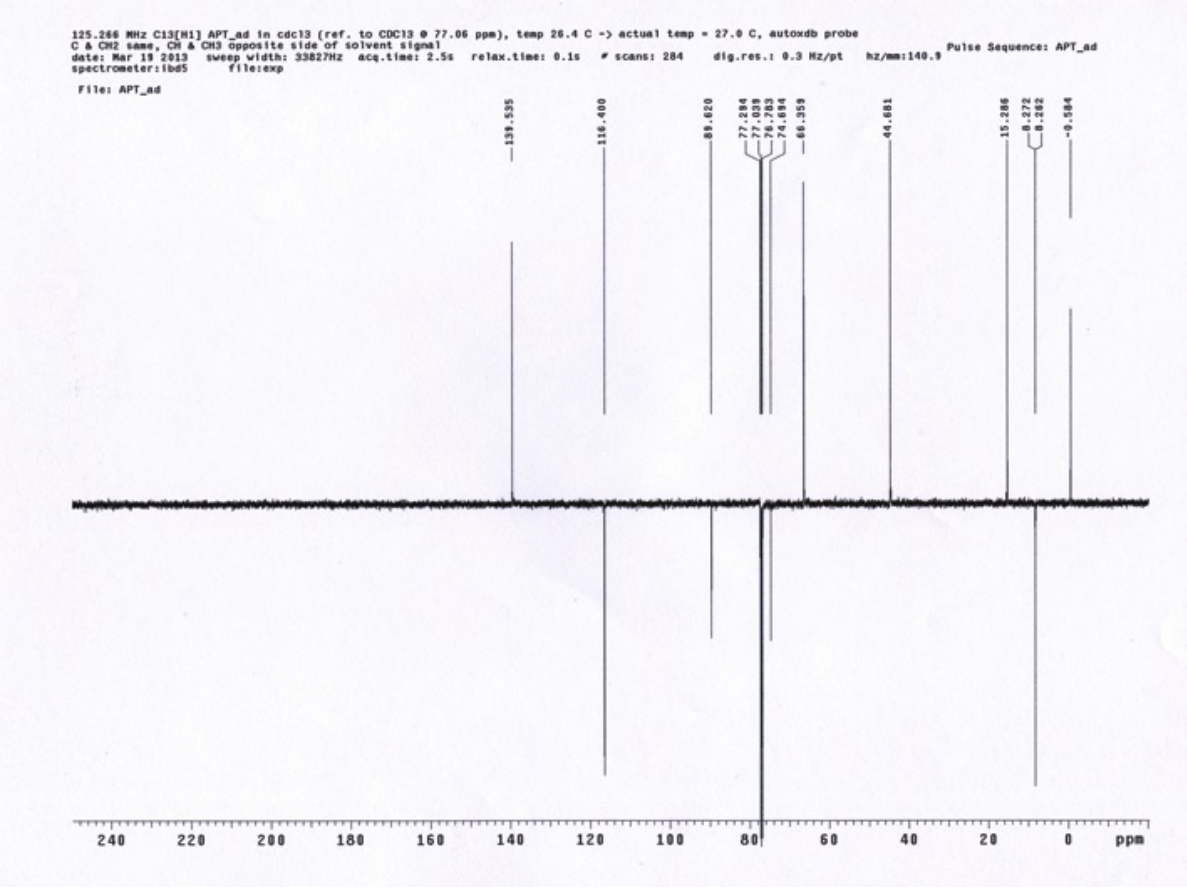
Methyl-1-cyclopropylhex-5-en-1-yn-3-ol



2.122

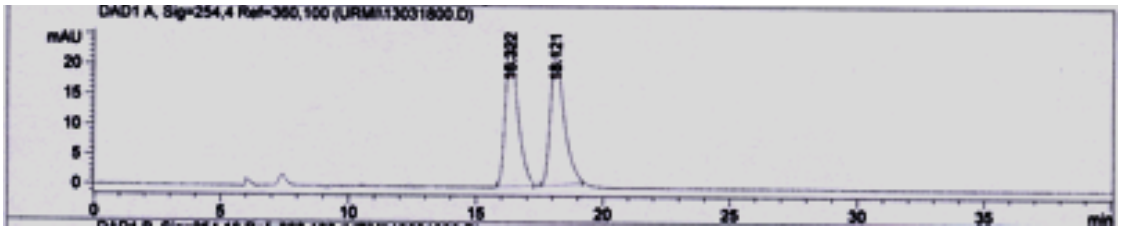


^{13}C NMR (125 MHz, $CDCl_3$)

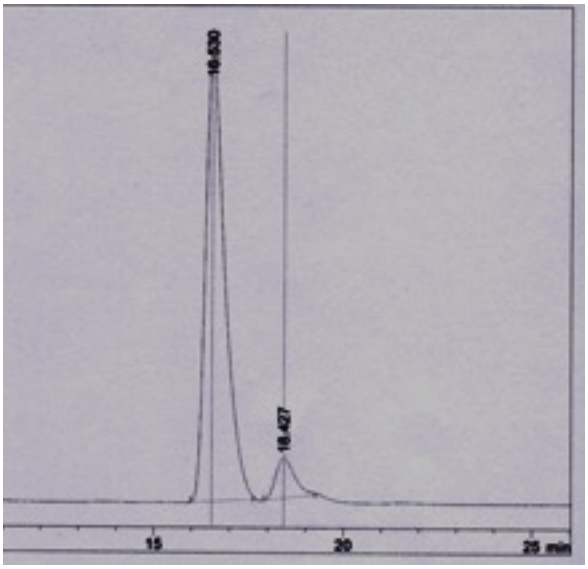


1.5% i-PrOH in hexanes

0.5 mL/min, λ = 254 nm



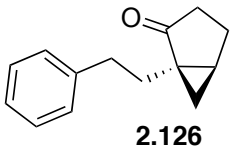
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.322	BB	0.5035	831.02032	24.39110	49.7400
2	18.121	PB	0.5526	839.70953	22.13193	50.2600
Totals :				1670.72986	46.52303	



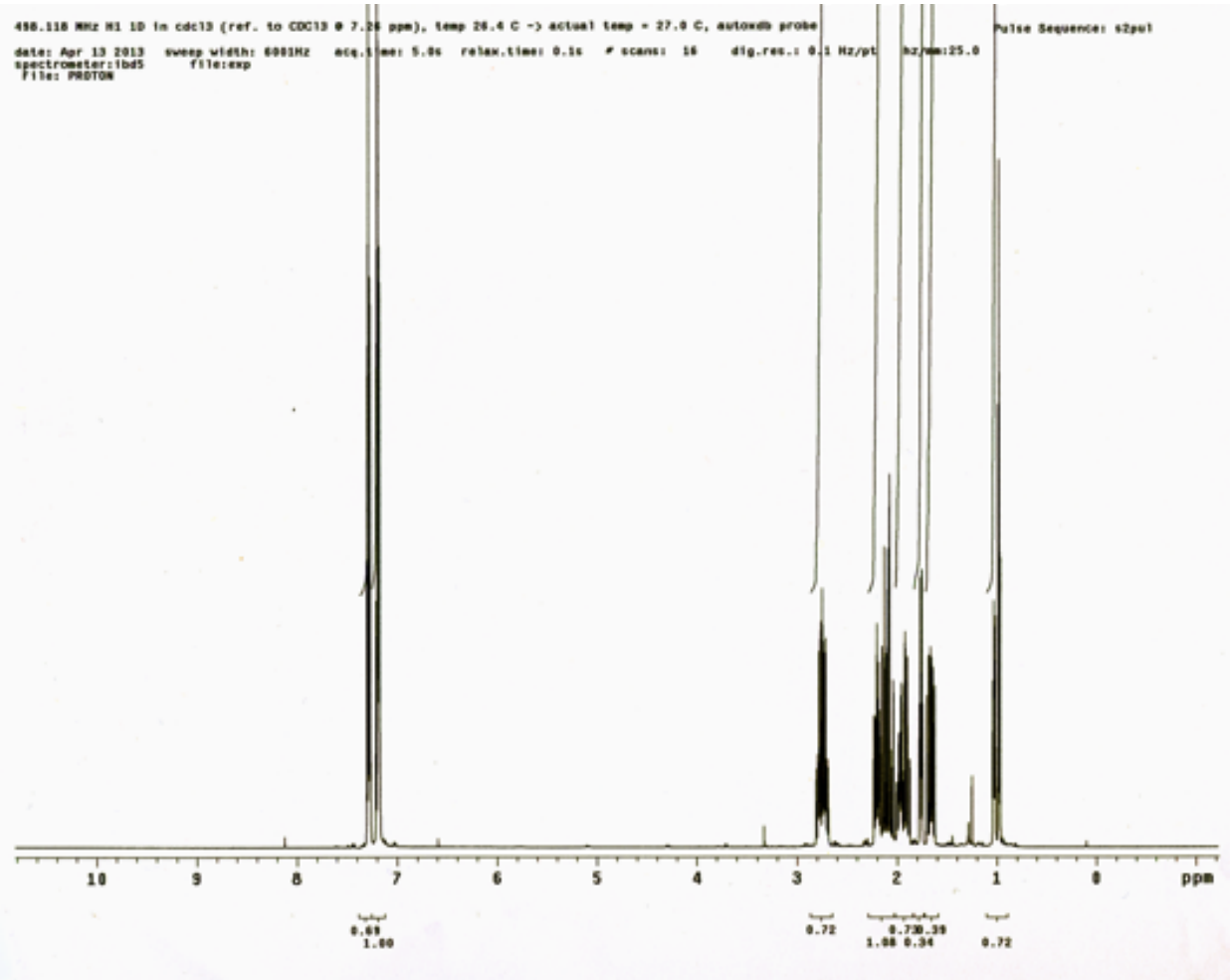
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.530	BB	0.5306	1737.67493	48.89178	91.8565
2	18.427	PB	0.4737	154.05345	4.45170	8.1435
Totals :				1891.72838	53.34348	

^{1}H NMR (500 MHz, $CDCl_3$)

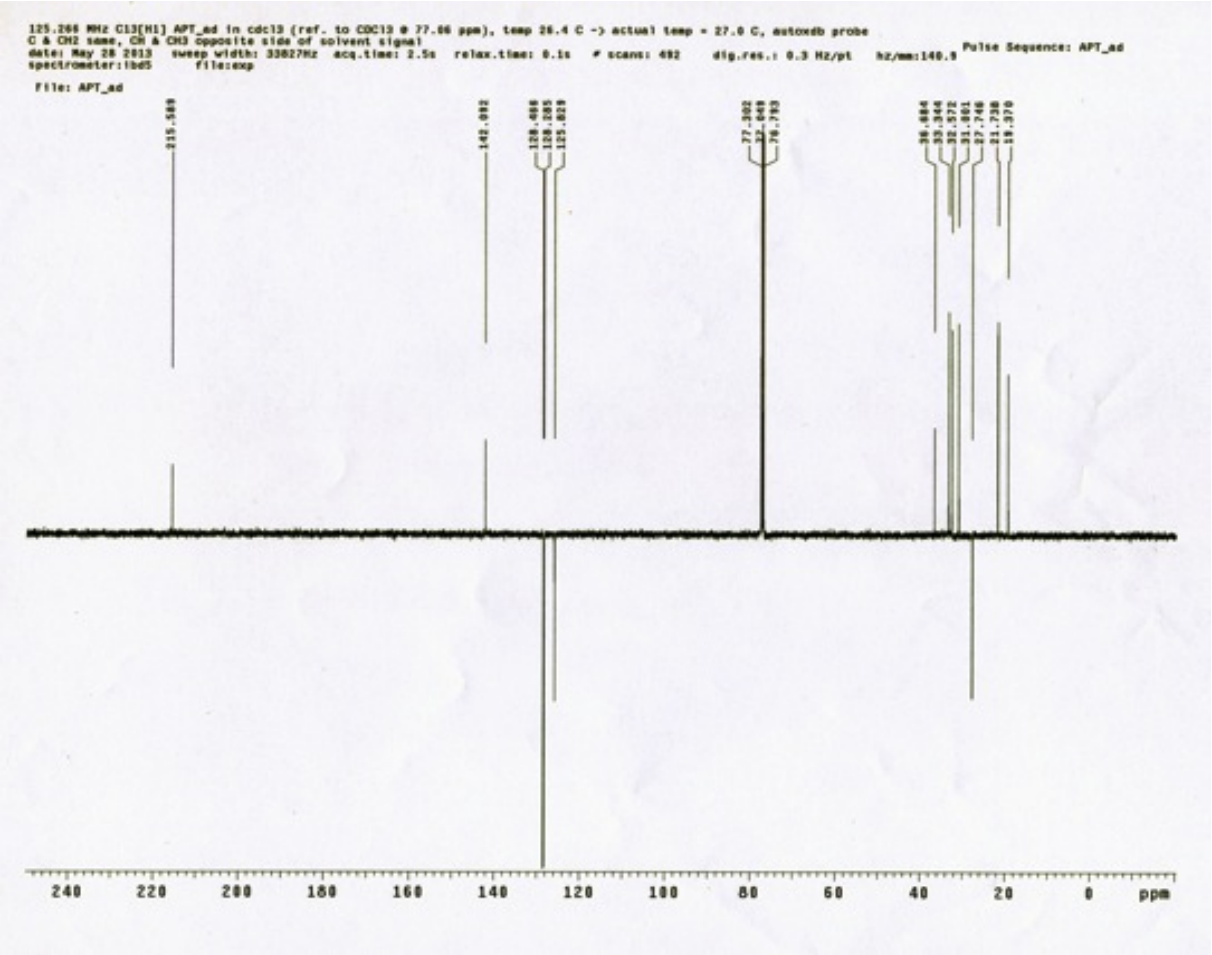
1-Phenylethyl-bicyclo[3.1.0]hexan-2-one



2.126

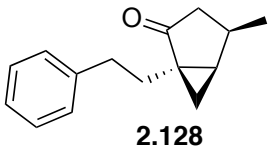


^{13}C NMR (125 MHz, $CDCl_3$)

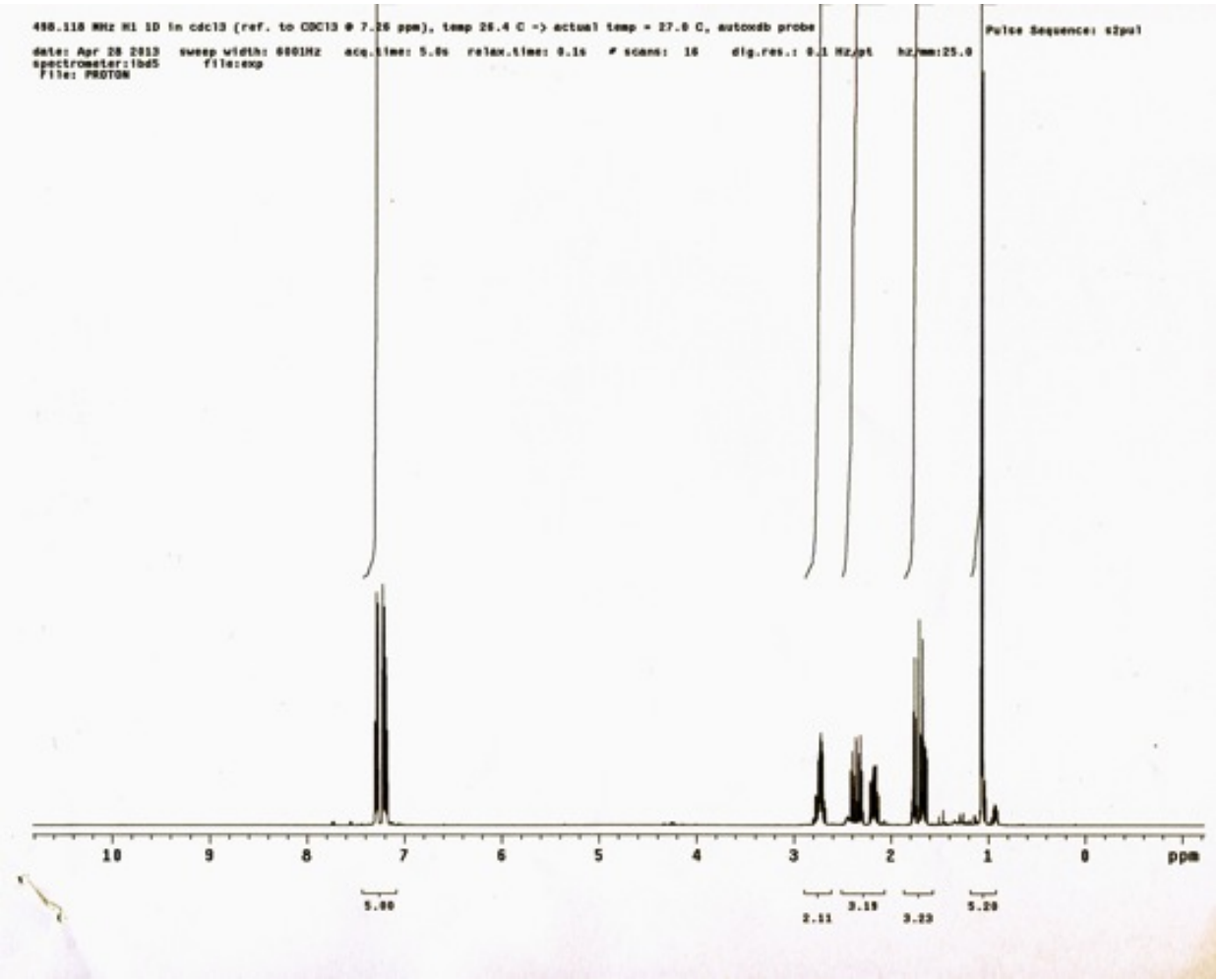


^{1}H NMR (500 MHz, $CDCl_3$)

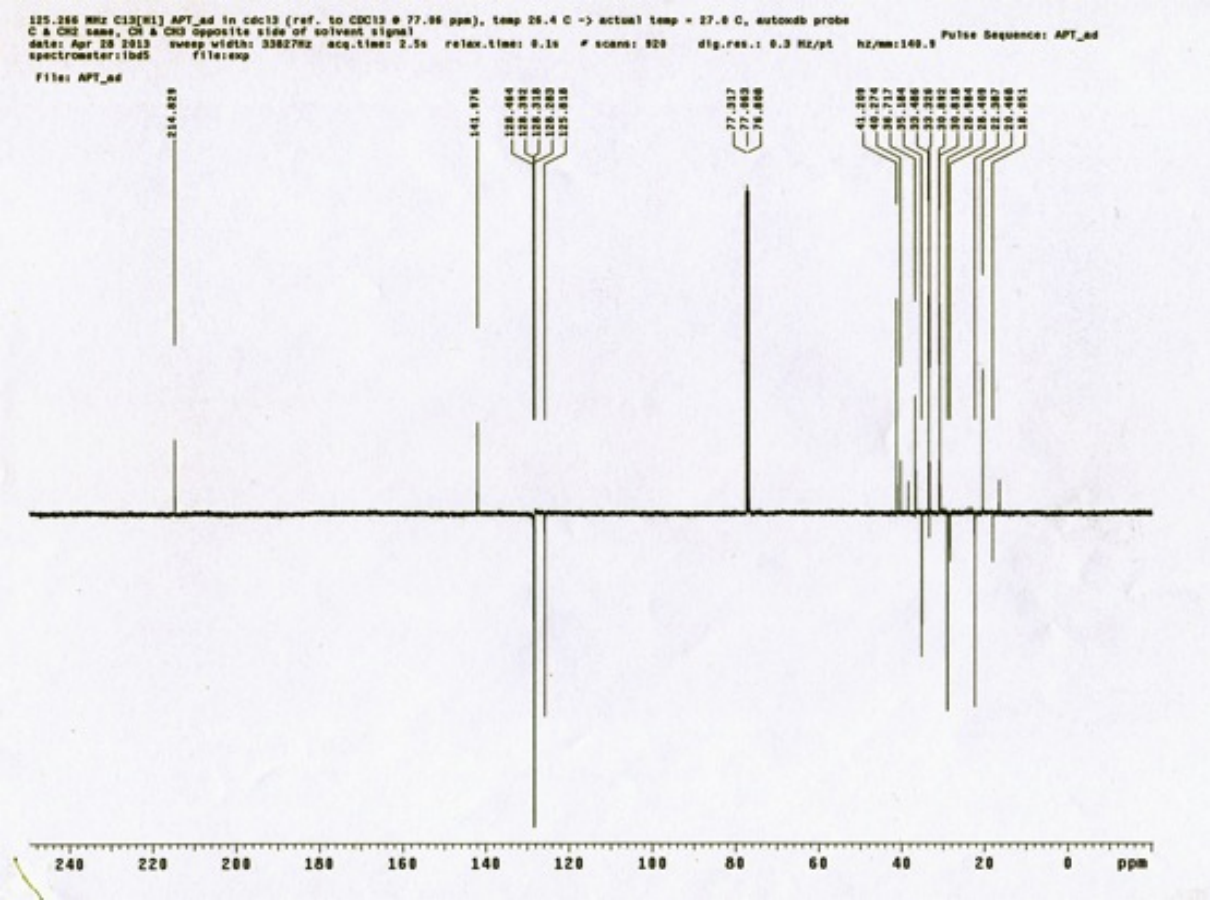
3-Methyl-1-phenylethyl-bicyclo[3.1.0]hexan-2-one



2.128

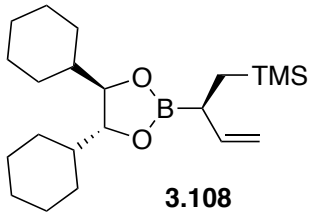


^{13}C NMR (125 MHz, $CDCl_3$)

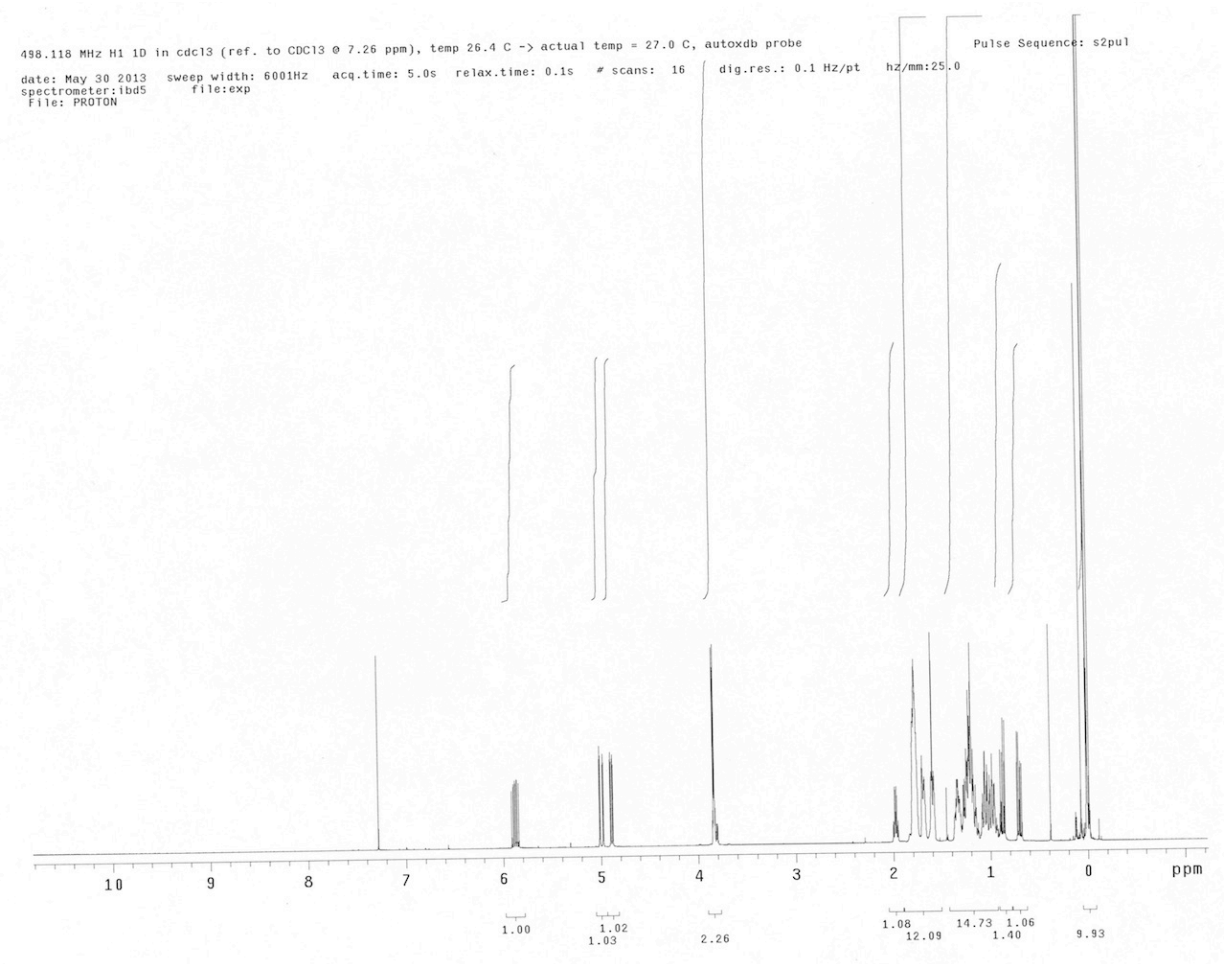


^{1}H NMR (500 MHz, $CDCl_3$)

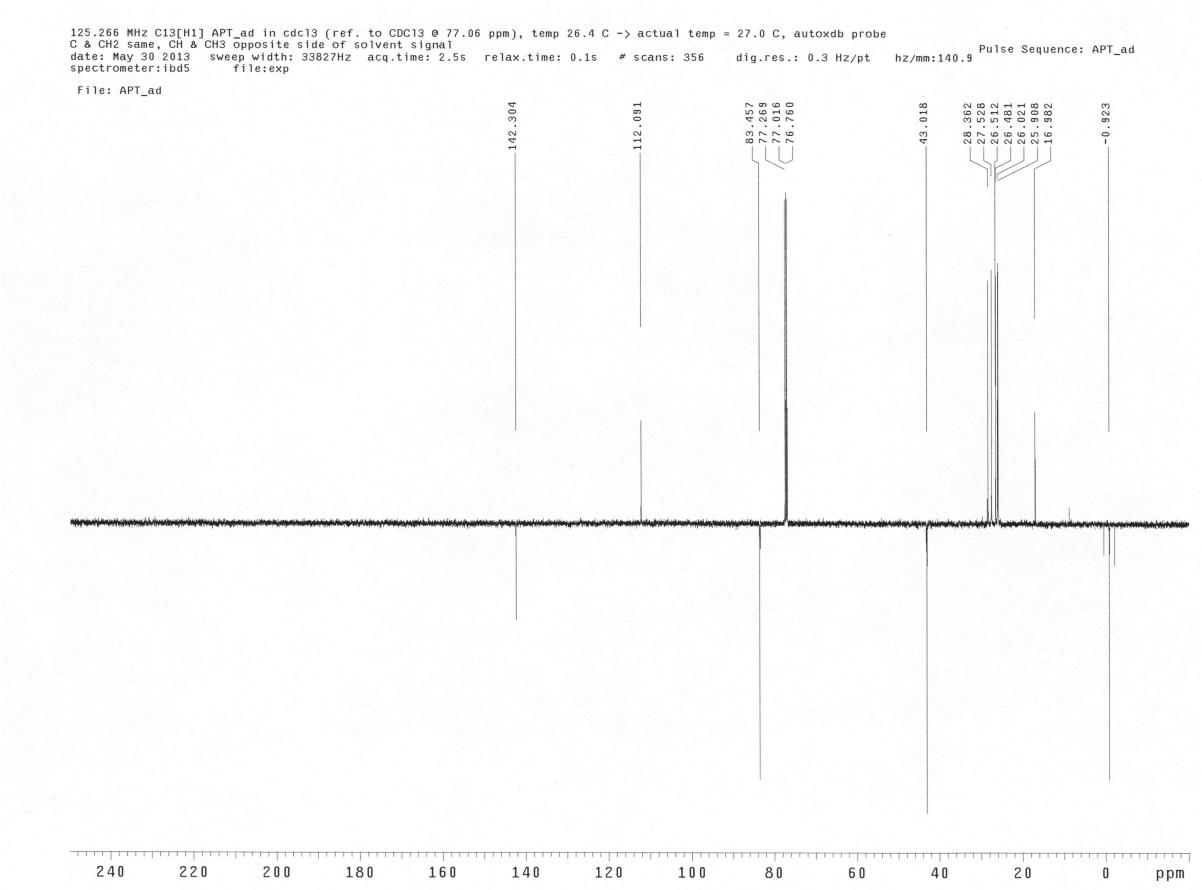
([(*R*,*R*)]-1,2-dicyclohexyl-2[(trimethylsilyl)methyl]-2-propen-1-yl-1,3,2-dioxaborolane



3.108

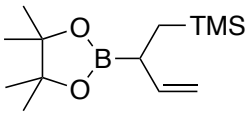


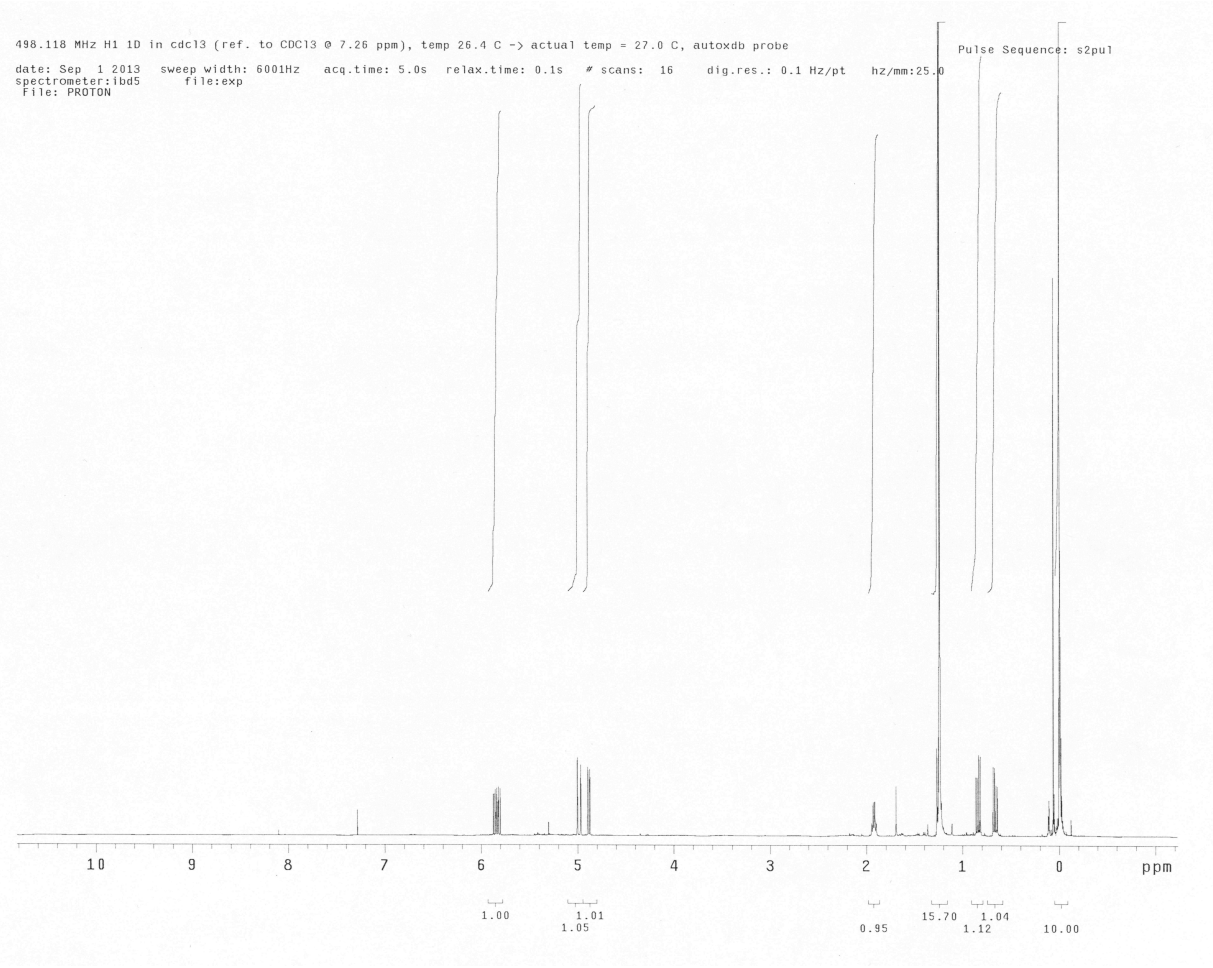
^{13}C NMR (125 MHz, $CDCl_3$)



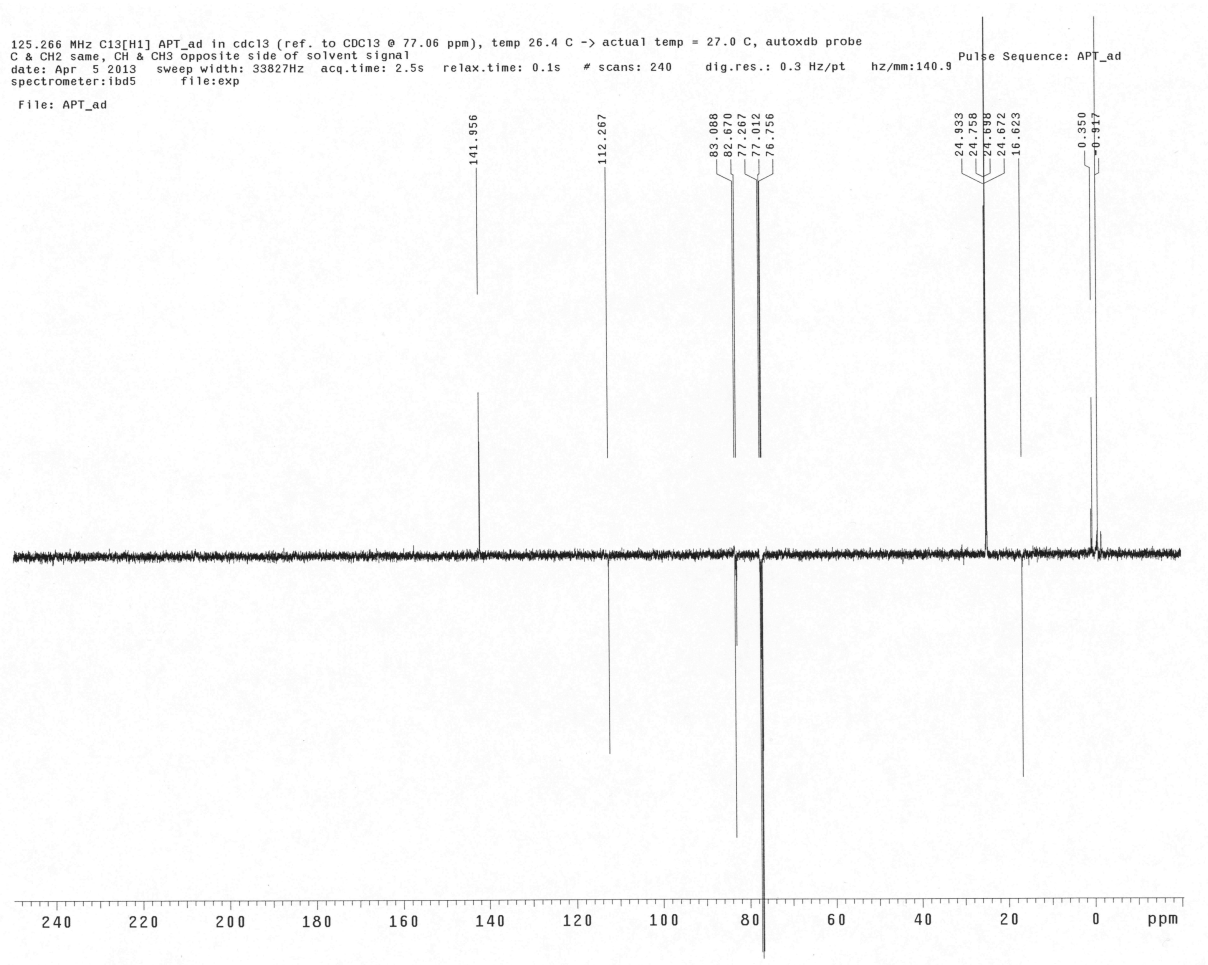
^{1}H NMR (500 MHz, $CDCl_3$)

4,4,5,5-tetramethyl-2[(trimethylsilyl)methyl]-2-propen-1-yl,1,3,2-dioxaborolane



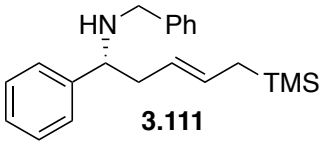


^{13}C NMR (125 MHz, $CDCl_3$)

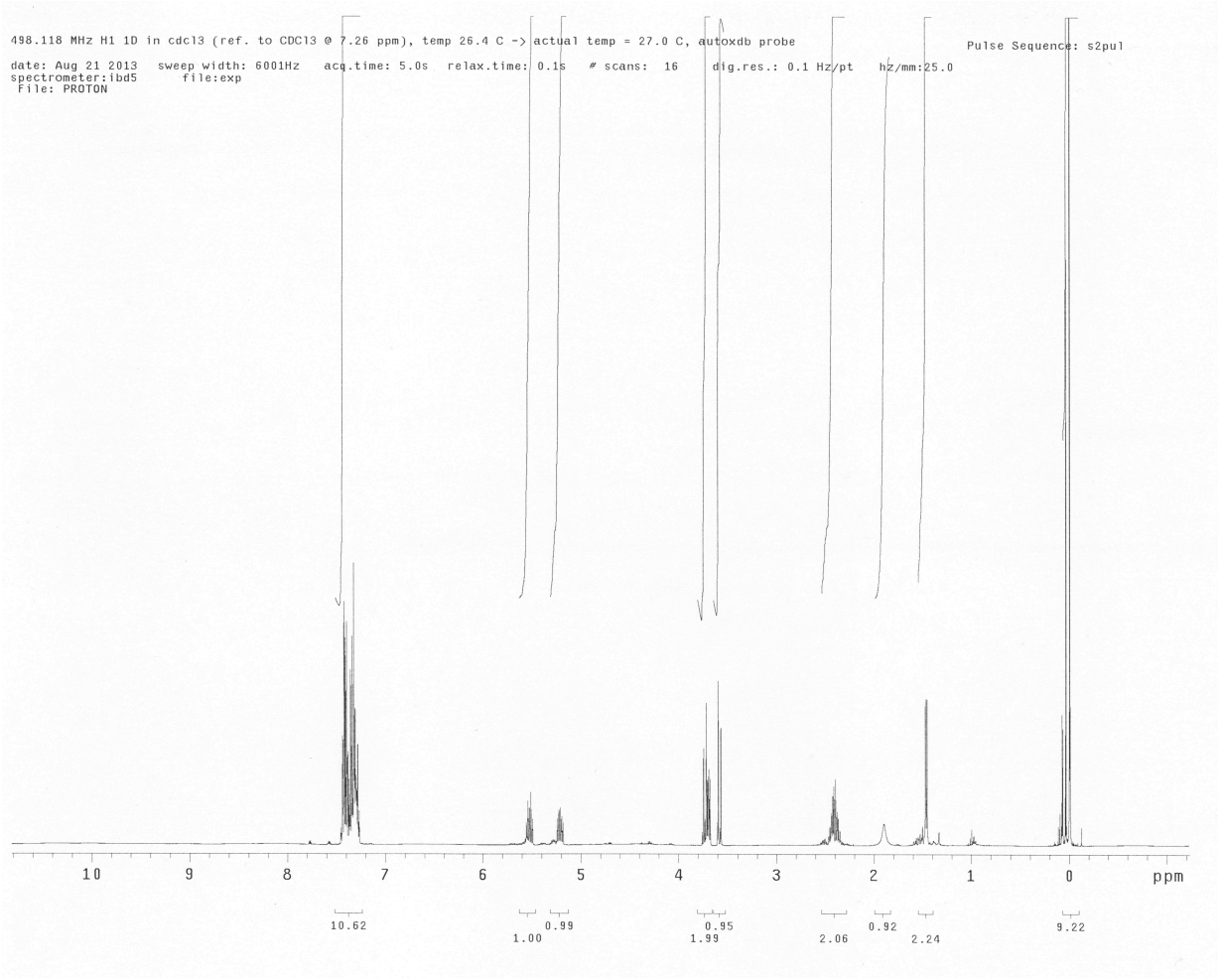


^{1}H NMR (500 MHz, $CDCl_3$)

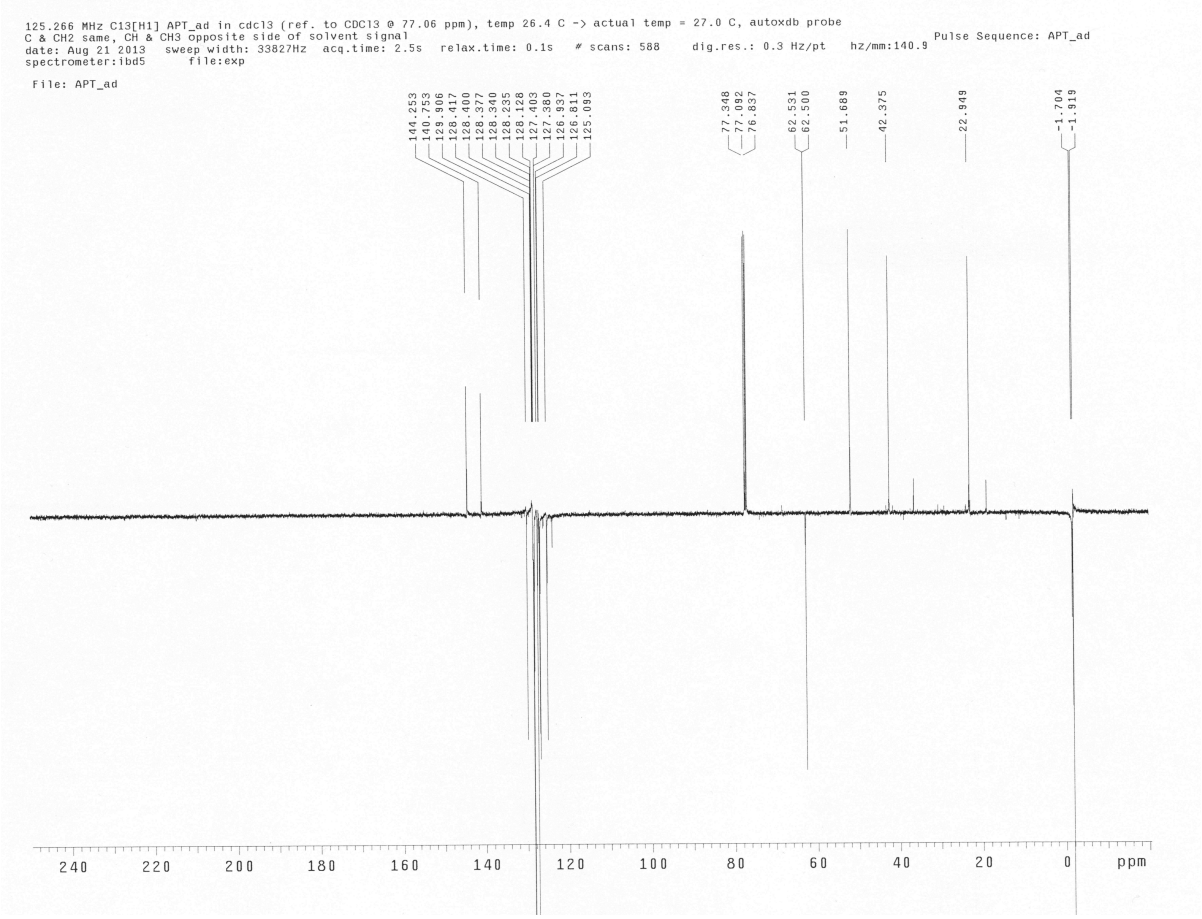
N-(phenyl)-[(2*E*)-4-trimethylsilyl)-2-buten-1-yl] benzenemethanamine



3.111

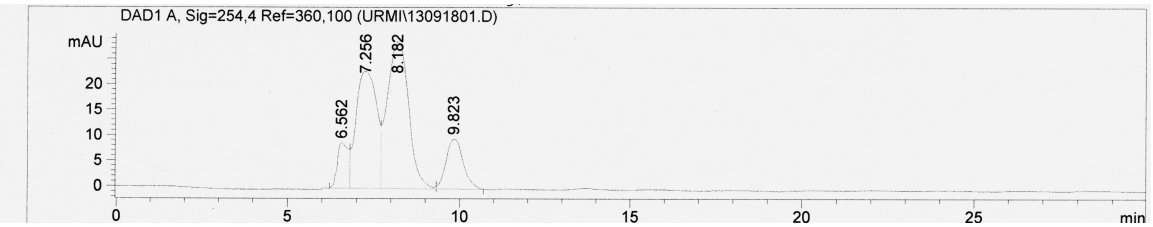


^{13}C NMR (125 MHz, $CDCl_3$)



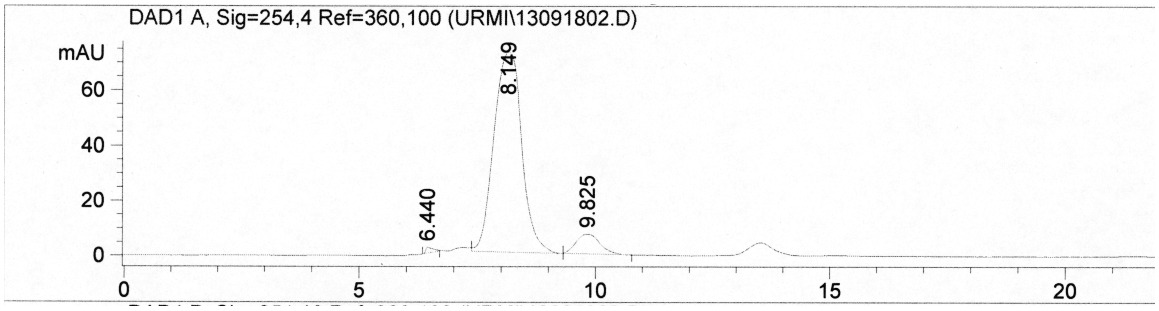
2.5% *i*-PrOH in hexanes

0.5 mL/min, λ = 254 nm



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.562	BV	0.3160	198.15121	8.89247	7.1997
2	7.256	VV	0.5114	959.55273	23.06209	34.8648
3	8.182	VB	0.6382	1250.67334	28.93812	45.4425
4	9.823	BB	0.4777	343.83331	9.79195	12.4930
Totals :				2752.21060	70.68463	



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.440	PB	0.1450	24.41084	2.27835	0.7461
2	8.149	BB	0.6538	2987.58618	72.65239	91.3122
3	9.825	BP	0.4288	259.83844	7.27295	7.9417
Totals :				3271.83547	82.20368	

Collective bibliography:

Chapter 1:

1. a) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. b) Grubbs, R. H. *Adv. Synth. Catal.* **2007,** *349,* 34.
2. a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002,** *124,* 7920. b) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003,** *42,* 946. c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001,** *123,* 9488.
3. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothestreit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992,** *114,* 2321.
4. a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977,** *99,* 3179. b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995,** *60,* 5386. c) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996,** *118,* 12349. d) Bandini, M.; Cozzi, P.G.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **1999,** *38,* 3357. e) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006,** *128,* 2554.
5. Loh, T.-P.; Zhou, J.-R.; Yin. *Org. Lett.* **1999,** *1,* 1855.
6. a) Costa, A. L.; Piazza, M. G.; Tagliavini, E., Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993,** *115,* 7001. b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993,** *115,* 8467. c) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996,** *118,* 4723. d) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006,** *128,* 2554.
7. a) Pu. L.; Yu, H. -B. *Chem. Rev.* **2001,** *101,* 757-824. b) Hong, J. -H.; Tsai, Y. -C. *Angew. Chem. Int. Ed.* **1998,** 37, 468.
8. Mikhailov, B. M.; Bubhnov, Y. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1964,** 1874.
9. a) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979,** *20,* 4653. b) Hoffmann, R.W.; Zeiss, H. -J. *Angew. Chem. Int. Ed. Engl.* **1979,** *18,* 306.
10. Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989,** *111,* 1892.
11. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983,** *105,* 2092.
12. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985,** *107,* 8186.
13. Corey, E. J.; Yu, C. -M.; Kim, S. S. *J. Am. Chem. Soc.* **1989,** *111,* 5495.
14. Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005,** *127,* 8044.
15. Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2006,** *6,* 2701.
16. Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990,** *55,* 1868.
17. Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002,** *124,* 11586.
18. shiyama, T.; Ahiko, T. -a.; Miyaura, N. *J. Am. Chem. Soc.* **2002,** *124,* 12414.

19. Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003,** *125,* 10160.
20. Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004,** 1290.
21. Yu, S. -H.; Ferguson, M. J.; McDonald, R.; Hall, D.G. *J. Am. Chem. Soc.* **2005,** *127,* 12808.
22. a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. b) Rauniyar, V.; Zhai, H.; Hall, D.G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.
23. Jain, P.; Antilla, J. *J. Am. Chem. Soc.* **2010,** *132,* 11884.
24. Xing, C. H.; Liao, Y.X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q. S. *Eur. J. Org. Chem.* **2012**, *6,* 1115.
25. a) Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693. b) Roush, W. R., Gover, P. T.; Lin, X. *Tetrahedron. Lett.* **1990**, *31*, 7563. c) Roush, W. R., Gover, P. T. *Tetrahedron. Lett.* **1990**, *31*, 7567. d) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375. e) Williams, D. R.; Claeboe, C. D.; Bo, L.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866.
26. Peng, F. Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.
27. a) Roush, W. R., Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron. Lett.* **2000**, *41*, 9413. b) Micalizio, G. C., Roush, W. R. *Org. Lett.* **2000**, *2*, 461.
28. a) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100***,** 127. b) Ma, J-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. c) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.
29. a) Nicolaou, K.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. b) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.

Chapter 2:

1. a) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043. b) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865. c) Fátima, D.; Pilli, R. A. *Tetrahedron Lett.* **2003**, *44*, 872. d) Madec, D.; Férézou, J.-P. *Eur. J. Org. Chem.* **2006**, 92. e) Jung, W.-H.; Guyenne, S.; Riesco-Fagundo, C.; Mancuso, J.; Nakamura, S.; Curran, D. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1130.
2. Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.
3. Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226.
4. a) Zweifel, G.; Steele, R. *J. Am. Chem. Soc.* **1967**, *89*, 5085. b) Zweifel, G.; Steele, R. *J. Am. Chem. Soc.* **1967**, *89*, 2754.
5. a) Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863. b) Chemin, D.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron* **1992**, *48*, 4369. c) Zhang, H.; Guibé, F.; Balavoine, G. *J. Org. Chem.*

1990, *55*, 1857. d) Russel, G. A.; Ngoviwatchai, P. *Tetrahedron Lett.* **1985**, *26*, 4975. e) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044. f) Brown, H. C.; Ravindran, N.; Kulkarni, S. *J. Org. Chem.* **1980**, *45*, 384. g) Sayo, N.; Nakai, E.; Nakai, T. *Chem. Lett.* **1985**, 1723.

6. Nicolaou, K.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433.
7. Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.
8. Fürstner, A.; Schlecker, A. *Chem.–Eur. J.* **2008**, *14*, 9181.
9. Bouzbouz, S.; Pradaux, F.; Cossy, J.; Ferroud, C.; Falguières, A. *Tetrahedron Lett.* **2000**, *41*, 8877.
10. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 2183.
11. a) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 4381. b) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett.* **1991,** 561.
12. a) Kurosu, M.; Lorca, M. *Tetrahedron Lett.* **2002**, *43*, 1765. b) Kurosu, M.; Lorca, M. *Synlett* **2005**, 1109.
13. Yu, C. M.; Jeon, M.; Lee, J. Y.; Jeon, J. *Eur. J. Org. Chem.* **2001**, 1143.
14. Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.
15. Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1964,** 1874.
16. a) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem. Int. Ed.* **1979,** *18,* 306. b) Hoffmann, R. W.; Ladner, W. *Tetrahedron Lett.* **1979,** *20,* 4653.
17. Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis and Medicine;* Wiley-VCH: Weinheim, 2nd edition 2011.
18. Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 1236.
19. Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002,** *124,* 11586.
20. Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002,** *124,* 12414.
21. Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004,** *126,* 4518.
22. Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331.
23. Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003,** *125,* 10160.
24. a) Yu, H. Y.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. b) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179.
25. a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. b) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120.
26. Rauniyar, V.; Hall, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2426.
27. Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481.
28. Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.
29. Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006,** *128,* 1086.
30. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004,** *126,* 5356.

31. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed.* **2004,** *43,* 1566.
32. Jain, P.; Antilla, J. *J. Am. Chem. Soc.* **2010,** *132,* 11884.
33. Xing, C. H.; Liao, Y.X.; Zhang, Y.; Sabarova, D.; Bassous, M.; Hu, Q. S. *Eur. J. Org. Chem.* **2012**, *6,* 1115.
34. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105,* 2092.
35. Roush, W. R.; Hoong, L. K. Palmer, M. A. J. Park, J. C. *J. Org. Chem.* **1990,** *55,* 4109.
36. Ju, J.; Reddy, B.; Khan, M.; Nicholas, K. M. *J. Org. Chem.* **1989,** *54,* 5426.
37. Roush, W. R.; Park, J. C. *J. Org. Chem.* **1990,** *55,* 1143.
38. Brown, H. C.; Racherla, U.S.; Pellechia, P.J. *J. Org. Chem.* **1990**, *55*, 1868.
39. Mamane, V.; Gress, T.; Krause, H.; Furstner, A. *J. Am. Chem. Soc.*, **2004**, *126*, 8654.
40. Asikainen, M.; Lewis, W.; Blake, A. J.; Woodward, S. *Tetrahedron Lett.* **2010**, *51*, 6454.
41. Kawasaki, Y.; Ishikawa, Y.; Igawa, K.; Katsuhiko,T. *J. Am. Chem. Soc.* **2011**, *133*, 20712.
42. Rooke, D. A.; Ferreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3225.
43. Geyer, M.; Bauer, J.; Burschka, C.; Kraft, P.; Tacke, R. *Eur. J. Inorg. Chem.* **2011**,*17*, 2769.
44. Sigma-Aldrich Product no: 687170.
45. Shen, Y.-L.; Wu, W.-T.; Liu, Q.; Wu, G.-L.; Wu, L.-M. *J. Chem. Res.* **2006**, *8*, 545.
46. Romanov-Michailidis, F.; Besnard, C.; Alexakis, A. *Org. Lett.* **2012**, *14*, 4906.
47. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.
48. Malgorzata, M.; Heise; G.; Walsh, J. D. *Tetrahedron Lett.* **2012**, *53*, 2937.
49. Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Frohlich, J.; Kirchner, K. *Organometallics* **2005**, *24,* 3957.
50. Osamu, I.; Naoki, I.; Toshihide, S.; Hiroaki, K.; Yoshiki, F.; Yoshinori, H.; Toshio, S.; Katsuhiko, I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 177.
51. Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, *14*, 2293.
52. Rauniyar, V.; Zhai, H.; Hall, D. G. *Synth. Commun.* **2008**, *38*, 3984.
53. Penner, M.; Rauniyar, V.; Kaspar, L. T.; Hall, D. G. *J. Am. Chem. Soc.* **2009**, *131*, 14216.
54. Carosi, L.; Hall, D. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 5913.
55. Hartley, R.C.; Lamothe, S.; Chan, T.H. *Tetrahedron Lett.* **1993**, *34*, 1449.
56. Wzorek, J.; Troutman, A.; Allegue, K.; Mitzel, T. *J. Org. Chem.* **2007**, *72*, 3042.
57. Robles, O.; McDonald, F. E. *Org. Lett.* **2009**, *11*, 5498.
58. Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188.
59. Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protocols.* **2007**, *2*, 2451.

Chapter 3:

1. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
2. Heo, J.-N.; Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1693.
3. a) Roush, W. R., Gover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563. b) Roush, W. R., Gover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567.
4. a) Roush, W. R., Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413. b) Micalizio, G. C., Roush, W. R. *Org. Lett.* **2000**, *2*, 461.
5. Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245.
6. Micalizio, G. C., Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.
7. a) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644. b) Li, F.; Roush, W. R. *Org. Lett.* **2009**, *11*, 2932.
8. a) Winbush, S.A.M.; Roush, W. R. *Org. Lett.* **2010**, *12*, 4344.
9. a) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509. b) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411. c) Hicks, J. D.; Roush, W. R. *Org. Lett.* **2008**, *10*, 681.
10. Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 533.
11. Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375.
12. Williams, D. R.; Claeboe, C. D.; Bo, L.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866.
13. Sarkar, T.K.; Haque, S.A.; Basak, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1417.
14. Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1.* **1998**, 2733.
15. a) Peng, Z.-H. Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379. b) Peng, Z.-H. Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675.
16. Peng, F. Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.
17. a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, *17*, 2815. b) Pearson, W. H. *Pure Appl. Chem.* **2002**, *74*, 1339.
18. Yamamoto, Y.; Nishii, S.; Kazuhiro, M.; Komatsu, T.; Wataru I. *J. Am. Chem. Soc.* **1986**, *108*, 7778.
19. Itsuno, S.; Katsuhiro,W.; Koichi, I.; El-Shehawy, A. A.; Ali, A. S. *Angew. Chem. Int. Ed.* **1997**, *36*, 109.
20. Chen, G.M.; Ramachandran, P.V.; Brown, H.C. *Angew. Chem. In. Ed.* **1999**, *38*, 825.
21. Katsuhiro,W.; Koichi, I.; Itsuno, S.*Tetrahedron Asym.* **1995**, *6*, 1531.
22. Katsuhiro,W.; Kuroda, S.; Yokoi, A.; Koichi, I.; Itsuno, S. *J. Organometallic Chem.* **1999**, *581*, 103.
23. Ramachandran, P. V.; Biswas, D. *Org. Lett.* **2007**, *9*, 3025.
24. Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712.
25. Wu, T.R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.

26. Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.
27. Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182.
28. Ramadhar, T. R.; Batey, R. A. *Synthesis* **2011**, 1321.
29. Li, S-W.; Batey, R. A. *Chem. Commun.* **2004**, *12*, 1382.
30. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.
31. a) Brown, H. C.; Racherla, U.S.; Pellechia, P.J. *J. Org. Chem.* **1990**, *55*, 1868. b) Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.*, **2007**, *9*, 757.
32. a) Matteson, D. S.; Soundararajan, R.; Ho, O. C.; Gatzweiler, W. *Organometallics*. **1996**, *15*, 152. b) Matteson, D. S.; Singh, R. P.; Schafman, B.; Yang, J. *J. Org. Chem.* **1998**, *63*, 4466. c) Matteson, D. S.; Man, H-W.; Ho, O. C. *J. Am. Chem. Soc.* **1996**, *118*, 4560.
33. *depts.washington.edu/eooptic/linkfiles/dielectric_chart[1].pdf*
34. Scott, M. S.; Lucas, A. C.; Luckhurst, C.A.; Prodger, J. C.; Dixon, D. J. *Org. Biomol. Chem.* **2006**, *4*, 1313.
35. Gravel, M., Toure, B. B., Hall, D. G. *Org. Prep. Proc. Intl.* **2004**, *36*, 573.
36. Fernandes, R. A.; Nallasivam, J. L. *Org. Biomol. Chem.*, **2012**, *10*, 7789.

Chapter 4:

1. a) Important review on the physical properties of organofluorine compounds: *Fluorine in Medicinal Chemistry and Chemical Biology*, Ojima, E., Ed.; Wiley–Blackwell: **2009**. b) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127. c) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.
2. a) Peters, R.; Wakelin, R. W. *Proc R. Soc. Ser. B,* **1953**, *140*, 497. b) Lauble, H.; Kennedy, M. C.; Emptage, M. H.; Beinert, H.; Stout, C. D. *Proc. Natl. Acad. Sci. USA,* **1996**, *93*, 13699.
3. Kobayashi, Y.; Taguchi, T. *J. Synth. Org. Chem. Jpn.* **1985**, *43*, 1073.
4. Okamoto, S.; Tanaka, Y.; DeLuca, H. F.; Kobayashi, Y.; Ikekawa, N. *Am. J. Physiol.* **1983**, *244,* 159.
5. a) MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34,* 3553. b) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.
6. a) Carcenac, Y.; Diter, P.; Wakselman, C.; Tordeux, M. *New J. Chem.* **2006**, *30,* 442. b) Carcenac, Y.; Tordeux, M.; Wakselman, C.; Diter, P. *New J. Chem.* **2006**, *30,* 447.
7. Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102,* 5618.
8. Leroux, F. *ChemBioChem.* **2004**, *5,* 644.
9. Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology,* John Wiley & Sons, Inc., Hoboken: **1979**.
10. a) Ganguly, T.; Mal, S.; Mukherjee, S. *Spectrochim. Acta. Part A* **1983**, *39A,* 657. b) Morgenthaler,

M.; Schweizer, E.; Hoffmann-Roder, A.; Bennini, F.; Rainer, E. M.; Jaeshke, G.; Wagner, B.; Fischer, H.; Bendels, S.; Zimmerli, D.; Schneider, J.; Diedrich, F.; Kansay, M.; Muller, K. *ChemMedChem.* **2007**, *2,* 1100.

11. Abraham, M. H.; Grellier, P. L.; Prior, D. V.; Duce, P. P.; Morris, J. J.; Taylor, P. J. *J. Chem. Soc. Perkin Trans 2.* **1989**, *2,* 699.
12. Smart, B. E. *Molecular Structure and Energetics,* F. Liebman and A. Greenberg Eds.; Wiley–VCH Verlag GbmbH, Weinheim.**1986**.
13. Bock, C. W.; George, P.; Mains, G. J.; Trachtman, M. *J. Chem. Soc., Perkin Trans.* **1979**, *2,* 814.
14. a) Klaboe, P.; Nielsen, J. R. *J. Chem. Phys.* **1960**, *33,* 1764. b) Hirano, T.; Nonoyama, S.; Miyajima, T.; Kurita, Y.; Kawamura, T.; Sato, H. *J. Chem. Soc., Chem. Commun.* **1986**, 606.
15. a) Fernholt, L.; Kveseth, K. *Acta Chem. Scand. A.* **1980**, *34,* 163. b) Friesen, D.; Hedberg, K. *J. Am. Chem. Soc.* **1980**, *102,* 3987. c) Dixon, D. A.; Matsuzawa, N.; Walker, S. C. *J. Phys. Chem.* **1992**, *96,* 10740.
16. a) Wiberg, K. B.; Keith, T. A.; Frisch, M. J.; Murcko, M. *J. Phys. Chem.* **1995**, *99*, 9072. b) Rablen, P. R.; Hoffmann, R. W.; Hrovat, D. A.; Borden, W. T. *J. Chem. Soc. Perkin Trans. 2,* **1999**, 1719.
17. Nicoletti, M.; O' Hagan, D.; Slawin, A . M. Z. *J. Am. Chem. Soc.* **2005**, *127,* 482.
18. Apeloig, Y. *J. Chem. Soc., Chem. Commun.* **1981***,* 396.
19. Farnham, W. B.; Smart, B. E.; Middleton, W. J.; Calabrese, J. C.; Dixon, D. *J. Am. Chem. Soc.* **1985**, *107,* 4565.
20. Barbarich, T. J.; Rithner, C. D.; Miller, S. M.; Anderson, O. P.; Strauss, S. H. *J. Am. Chem. Soc.* **1999**, *121,* 4280.
21. Bartolomé, C.; Espinet, P.; Martín-Alvarez, J. M. *Chem. Commun.* **2007***,* 4384.
22. Hann, M. M.; Sammes, P. G.; Kennewell, P. D.; Taylor, J. B. *J. Chem. Soc. Chem. Commun.* **1980**, 234.
23. Allmendinger, T.; Furet, P.; Hungerbuhler, E. *Tetrahedron Lett.* **1990**, *31,* 7297.
24. *MedAdNews 200 – World's Best-Selling Medicines, MedAdNews,* (http://en. wikipedia.org/wiki/List_of_top_selling_drugs).
25. Lewandowski, G.; Meissner, E.; Milchert, E. *J. Hazard. Mater.* **2006**, *136*, 385.
26. Patterson, J. C.; Mosley, M. L. *Mol. Imaging Biol.* **2005**, *7*, 197.
27. a) Ma, J-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. b) Poss, A. J.; Shia, G. A. *Tetrahedron Lett.* **1995**, *36,* 4721.
28. Padova, A.; Roberts, S. M.; Donati, D.; Marchioro, C.; Perboni, A. *J. Chem. Soc. Chem. Commun.* **1995**, 661.
29. Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A. M.; McCarthy, T. D. *Synlett.* **2004**, 791.

30. Davis, F. A.; Han, W.; Murphy, C. K. *J. Org. Chem.* **1995**, *60,* 4730.
31. Shutske, G. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1544.
32. Dauben, W. G.; Greenfield, L. J. *J. Org. Chem.* **1992**, *57,* 1597.
33. Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc. Chem. Commun.* **1992**, 595.
34. Manthey, M. K.; Gonzalez-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 625.
35. Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.
36. a) Purser, S.; Odell, B.; Claridge, T. D. W.; Moore, P. R.; Gouverneur, V. *Chem. Eur. J.* **2006**, *12,* 9176. b) Purser, S.; Wilson, C.; Moore, P. R.; Gouverneur, V. *Synlett.* **2007**, 1166. c) Lam, Y.-h.; Bobbio, C.; Cooper, I. R.; Gouverneur, V. *Angew. Chem. Int. Ed.* **2007**, *46,* 5106.
37. Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233.
38. Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29,* 6087.
39. Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34,* 3971.
40. a) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Roques, N. *Org. Lett.* **2000**, *2,* 3699. b) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122,* 10728.
41. a) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123,* 7001. b) Cahard, D.; Audouard, C.; Plaquevent, J.-C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42,* 1867.
42. Baudequin, C.; Loubassou, J. F.; Plaquevent, J.-C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122,* 189
43. Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55,* 801.
44. Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46,* 1447.
45. Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9,* 3053.
46. Enders, D.; Hu¨ttl, M. R. M. *Synlett.* **2005**, 991.
47. Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2005**, *44,* 3706.
48. Marigo, M.; Fielenbach, D.; Braunton, A.; Kjœrsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44,* 3703.
49. Singh, R.; Shreeve, J. *Synthesis* **2002**, *17,* 2561.
50. Messina, P.; Mange, K.; Middleton, W. *J. Fluorine Chem.* **1989**, *42,* 137.
51. Lal, G.; Pez, G. P.; Pesresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64,* 7048.
52. Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104,* 247.
53. Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268.
54. Laurent, E. G.; Marquet, B.; Tardivel, R.; Thiebault, H. *Tetrahedron Lett.*, **1987**, *28*, 2359.
55. Fuchigami, T.; Shimojo, M.; Konno, A.; Nakagawa, K. *J. Org. Chem.* **1990**, *55*, 6074.

56. Lee, S. M.; Roseman, J. M.; Zartman, C. B.; Morrison, E. P.; Harrison, S. J.; Stankiewicz, C. A. W.; Middleton, J. *J. Fluorine Chem.,* **1996**, *77*, 65.
57. Kabore, L.; Chebli, S.; Faure, R.; Laurent, E.; Marquet, B. *Tetrahedron Lett.* **1990**, *31,* 3137.
58. Baba, D.; Ishii, H.; Higashiya, S.; Fujisawa, K.; Fuchigami, T. *J. Org. Chem.* **2001**, *66,* 7020.
59. Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160.
60. Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T. Buchwald, S. L. *Science* **2009**, *325*, 1661.
61. Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 17402.
62. Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Godadard, W. A.; Groves, J. T. *Science* **2012**, *337*, 1322.
63. Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111,* 393.
64. Maggiarosa, N.; Tyrra, W.; Naumann, D.; Kirij, N. V.; Yagupolskii, Y. L. *Angew. Chem., Int. Ed.* **1999**, *38,* 2252.
65. Qiu, X. L.; Qing, F. L. *J. Org. Chem.* **2002**, *67,* 7162.
66. Munier, P.; Picq, D.; Anker, D. *Tetrahedron Lett.* **1993**, *34,* 8241.
67. Prakash, G. K. S.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40,* 589.
68. Hanzawa, Y.; Uda, J.-I.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. *Chem. Pharm. Bull.* **1991**, *39,* 2459.
69. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317,* 1981.
70. Prakash, G. K. S. 29th Western Regional Meeting of the American Chemical Society and 32nd Annual Meeting of the Southern California Section of the Society for Applied Spectroscopy, Pasadena, CA, October 19-23, **1993**.
71. Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35,* 3137.
72. a) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36,* 666. b) Nagao, H.; Kawano, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2007**, *80,* 2406. c) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707.
73. Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20,* 103.
74. a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31,* 3579. b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115,* 2156.
75. Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59,* 5692.
76. a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *9,* 2579. b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46,* 754.
77. Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575.
78. Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* **2009**, *48,* 4332.

79. Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132,* 4986.
80. Blazejewski, J.-C.; Wilmshurst, M. P.; Popkin, M. D.; Wakselman, C.; Laurent, G.; Nonclercq, D.; Cleeren, A.; Ma, Y.; Seo, H.-S.; Leclercq, G. *Bioorg. Med. Chem.* **2003**, *11,* 335.
81. Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62,* 7199.
82. Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328,* 1679.
83. Wang, X.; Truesdale, L.; Yu, J. *J. Am. Chem. Soc.* **2010**, *132,* 3648.
84. Ramachandran, P. V.; Agnieszka, T-K.; Chatterjee, A. *J. Org. Chem.* **2012**, *77*, 9329.
85. Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, 1893.
86. Gao, X.; Yong, J. Z.; Krische, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 4173.
87. Dutheuil, G.; Selander,N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis*, **2008**, 2293.
88. a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860. b) Lee, S. H.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *108,* 2445.
89. Zhang, H.; Zhou, C.-B.; Chen, Q.-Y.; Xiao, J.-C.; Hong, R. *Org. Lett.* **2011**, *13*, 560.
90. Wilson, D. A.; Wilson, C. J.; C. Moldoveanu, A.-M.; Resmerita, P.; Corcoran, L. M.; Hoang, B.; Rosen, M.; Percec, V. *J. Am. Chem. Soc.* **2010**, *132*, 18000.
91. Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.
92. Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Czyzewska, Y.F. M.; Steel, P.G.; Marder, T.B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528.
93. Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1363.
94. Hanamoto,T.; Yamada, K. *J. Org. Chem.* **2009**, *74,* 7559.
95. Xu, R.-S.; Yue, L.; Pan, Y.-J. *Tetrahedron* **2012**, *68*, 5046.
96. Elford, T. G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G. D.; Hall, D. G. *J. Comb. Chem.* **2009**, *11,* 155.

Chapter 5:

1. Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375.
2. Alonso, F.; Lorenzo, E.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 2187.
3. Williams, D. R.; Claeboe, C. D.; Bo, L.; Zorn, N.; Chow, N. S. C. *Org. Lett.* **2012**, *14*, 3866.
4. Dutheuil, G.; Selander,N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, 2293.
5. Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889.
6. Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **2000**, *41*, 5877.
7. Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Czyzewska, Y.F. M.; Steel,

P.G.; Marder, T.B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528.
8. Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423.
9. Couladouros, E. A.; Konstantinos, D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430.
10. Yoon, Y.; Kang, T.; Lee, H-Y. *Chem. Asian J.* **2011**, *6*, 646.
11. Elford, T. G.; Ulaczyk-Lesanko, A.; De Pascale, G.; Wright, G. D.; Hall, D. G. *J. Comb. Chem.* **2009,** *11,* 155.
12. Trost, B.M.; Schroeder, G. M.; Kristensen, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3492.
13. Dudley, G. B.; Salamone, S. G. *Org. Lett.* **2005**, *7*, 4443.

Chapter 6:

1. Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka M. *Angew. Chem. Int. Ed* **2012,** *51,* 4577.
2. Mace, A.; Tripoteau, F.; Zhao, Q.; Gayon, E.; Vrancken, E.; Campagne, J.; Carboni, B. Org. Lett. **2013**, *15*, 906.
3. Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004,** *126,* 8910.
4. Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2010,** *49,* 1838.
5. Fujita, M.; Nagano, T.; Schneider, U.; Hamada, T.; Ogawa, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2008,** *130,* 2914.