Optimization and Applications of the Catalytic Enantioselective Borylative Migration of Functionalized Piperidines

by

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Abstract

The catalytic enantioselective borylative migration developed in 2009 by our laboratory is a convenient, single-step method that provides enantiomerically enriched heterocyclic allylboronates. However, this chemistry occasionally provided lower yields and enantioselectivity when used with piperidinyl precursor. Because piperidine derivatives are of great importance in the pharmaceutical industry due to their prevalence in biologically active molecules, we focused on the re-optimization of the reaction conditions for the catalytic enantioselective borylative migration, to identify an economical, industry-friendly procedure that could provide piperidine derivatives in a multi-gram scale. The following parameters were examined: the nature of the alkenylsulfonate and the *N*-protecting group of the substrate, the source and stoichiometry of palladium and diphosphine ligand, solvent, reaction concentration, temperature, and time.

With a more robust and industry-friendly procedure in hand, applications of this chemistry were explored to functionalize piperidine derivatives further. First, aldehyde allylboration was re-optimized and subsequently exploited in the intramolecular Heck reaction to furnish tricyclic α-hydroxyalkyl dehydropiperidine. Suzuki-Miyaura cross-coupling conditions to yield [3,4]-biaryl piperidine derivatives were also attempted. Finally, some mechanistic studies were conducted to validate the previously proposed mechanism for this chemistry.

Another synthetic target of interest explored in this thesis was *β*-borono-nitroethylene, which could be used as a novel precursor for the synthesis of pharmaceutically relevant chiral *β*-amino alcohols. Due to the lack of literature precedents for the synthesis of *β*-borono-nitro-olefin derivatives, several established procedures for the formation of olefins or nitro-olefins were attempted: metal-mediated nitration of alkenyl boronates; cross-metathesis or transmetalation of nitro-olefin derivatives; nucleophilic addition of nitromethane to halogenated boronates; copper-catalyzed conjugate borylation of nitro-olefins; lanthanum-catalyzed asymmetric Michael addition;

and Miyaura borylation of (2-bromo-2-nitrovinyl)benzene.

Preface

Chapter 2 of this thesis has been accepted for publication as Y. Kim and D. G. Hall. “Optimization and Multigram Scalability of a Catalytic Enantioselective Borylative Migration for the Synthesis of Functionalized Chiral Piperidines”, *Org. Biomol. Chem.,* **2016**, DOI: 10.1039/c6ob00685j. I was responsible for the experimental work and spectral data collection/analysis. Prof. D. G. Hall was the supervisory author and was involved with concept formation and manuscript composition.

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List of Abbreviations

ACPAs	2-arylcyclopropylamines
Ar	aryl
aq	aqueous
9-BBN	9-borabicyclo(3.3.1)nonane
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINOL	2,2′-dihydroxy-1,1′-dinaphthyl
Bn	benzyl
t-Boc	*tert*-butyloxycarbonyl
B_2pin_2	bis(pinacolato)diboron
br	broad
^{n}BuLi	normal butyllithium
^{s}BuLi	*sec*-butyllithium
Bz	benzoate
calcd	calculated
cat	catalyzed
cataCXium A-Pd-G2	chloro[(di(1-adamantyl)-n-butylphosphine)-2-(2-aminobiphenyl)]palladium(ii)
Cbz	carbobenzyloxy
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
CM	cross metathesis
DAN	1,8-diaminonaphthalene

Dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
de	diastereomeric excess
DIPEA	n,n-diisopropylethylamine
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
DMBQ	2,6-dimethylbenzoquinone
DMF	n,n-dimethylformamide
DMSO	dimethyl sulfoxide
DPPF	1,1’-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
equiv	equivalents
ESI	electrospray ionization
EWG	electron withdrawing group
FG	functional group
g	gram
gem	geminal
G-H II	grubbs-hoveyda catalyst 2nd generation
h	hour

HBpin	pinacolborane
HMBC	heteronuclear multiple-bond correlation spectroscopy
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infrared spectroscopy
L	ligand
L*	chiral ligand
L.A	lewis acid
LDA	lithium diisopropylamide
LG	leaving group
LiHMDS	lithium hexamethyldisilazide
μw	microwave
m	multiplet
3,4,7,8-Me_4phen	3,4,7,8-tetramethylphenanthroline
MHz	megahertz
MIDA	n-methyliminodiacetic acid
min	minute
mol	mole
mmol	millimole
MS	molecular sieves
Nf	perfluorobutanesulfonyl
NfF	perfluorobutanesulfonyl fluoride
NMR	nuclear magnetic resonance

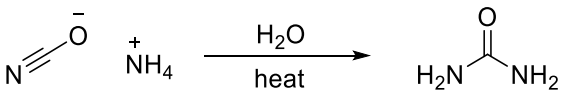
NSM	nitro(phenylsulfonyl)methane
Nu	nucleophile
PEPPSI	pyridine-enhanced precatalyst preparation, stabilization, and initiation
Ph	phenyl
pin	pinacolato
i-Pr	isopropyl
pyr	pyridine
RCM	ring-closing metathesis
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
rt	room temperature
s	singlet
sec	second
SET	single electron transfer
p-tol	*para*-tolyl
TBAF	tetra-n-butylammonium fluoride
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t	triplet
Taniaphos	(dimethylamino)[2-(diphenylphosphino)phenyl]methyl]-2-(diphenylphosphino)ferrocene

td	triplet of doublets
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
UV	ultraviolet

Chapter 1. Formation of Pharmaceutically Relevant Molecules

1.1. Organic synthesis in the pharmaceutical industry

The first account of modern organic synthesis was by the German chemist, Friedrich Wöhler, who accomplished the synthesis of urea from ammonium cyanate in 1828.[1] This work was named after its inventor and referenced to be one of the first syntheses of organic compounds (Scheme 1-1).[1] The field of organic synthesis has advanced tremendously since then; presently, organic synthesis has become vital in a variety of scientific fields including cosmetics, agriculture, petrochemicals, and pharmaceuticals.[2]



ammonium cyanate **urea**

Scheme 1-1. Wöhler synthesis: formation of urea from ammonium cyanate

Advancements in organic synthesis have provided significant progress in the formation of biologically active molecules via newly developed synthetic methodologies.[2] Syntheses of numerous drug candidates and commercial drugs have become possible, which has led to a huge growth in the pharmaceutical industry; this accounts for the tremendous increase in the life expectancy of humans over the past century.[2]

1.2. Chirality in pharmaceutically relevant molecules

1.2.1. Definition of chirality

A molecule is considered to be “chiral” when its two mirror images, enantiomers, are not superimposable with each other (Figure 1-1).[3] In an achiral environment, enantiomers have the same physical properties such as boiling point, melting point, and retention factor, with the

exception of the optical rotation as they rotate the plane of polarized light in opposite directions.[3] The interaction of enantiomers with other chiral molecules is often quite different; and this fact contributes to the reason why enantiomers have different characteristics in materials and biological systems.[4] Hence, the chemical and biological activities of a molecule often depend heavily on its absolute stereochemistry.[4]

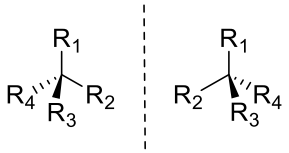


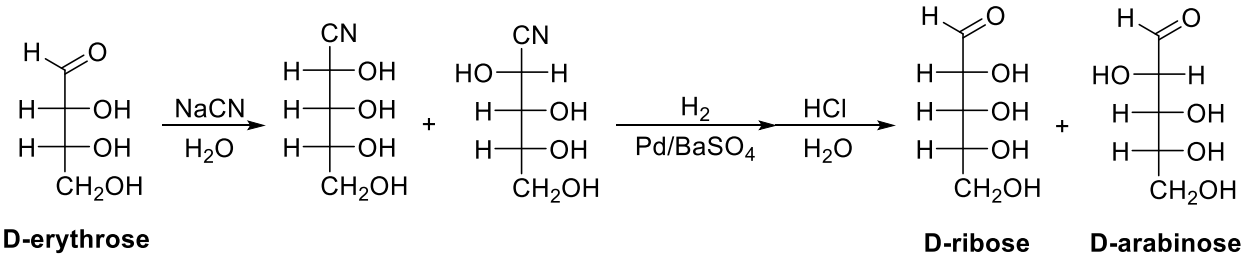
Figure 1-1. Enantiomers: stereoisomers that are non-superimposable mirror images

1.2.2. The origin of the concept of chirality

The history of chirality began in 1815 when the French physicist, Jean-Baptiste Biot, demonstrated that certain chemicals could rotate the plane of polarized light.[5] In 1848, based on the mechanical separation of tartrate enantiomers and crystallographic studies, the French chemist, Louis Pasteur, proposed that the nature behind this property is a molecular desymmetry.[6] One year later, the term "chirality" was coined by the Irish physicist, Lord Kelvin, and defined as "*…any geometrical figure, or groups of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself*".[7] The origin of chirality still remained a mystery until 1874 when the Dutch chemist, Jacobus Henricus van't Hoff, and the French chemist, Joseph Le Bel, independently proposed the origin of chirality to be the tetrahedral geometry of a carbon atom.[8]

1.2.3. The beginning of enantioselective synthesis

The pioneers of stereoselective synthesis were the German chemists, Hermann Emil Fischer and Willi Marckwald.[9] In 1894, Fischer started the field of stereoselective organic synthesis with his work on the interconversions in the sugar series, and together with the German chemist, Heinrich Kiliani, he developed a reaction that could elongate sugars stereoselectively.[9,10] This process was named after its inventors; and the Kiliani-Fischer synthesis is regarded as the first example of stereoselective synthesis (Scheme 1-2).[9,10] Fischer's contributions to carbohydrate chemistry were later recognized with his awarding of the Nobel Prize in Chemistry in 1902.[11]



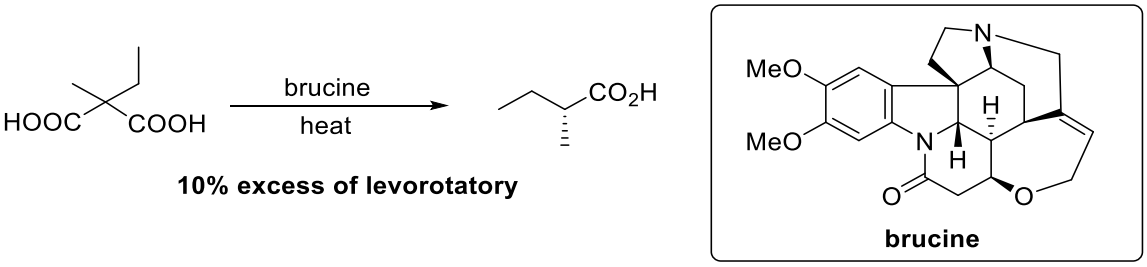
Scheme 1-2. Kiliani-Fischer synthesis of D-erythrose to D-ribose and D-arabinose

Unlike Fischer, Marckwald developed an asymmetric synthesis with an unnatural, achiral starting material in 1904.[10] The brucine salt of 2-ethyl-2-methylmalonic acid was subjected to a decarboxylation under heat to provide a slight excess of the levorotatory form of 2-methylbutyric acid (Scheme 1-3).[10] This reaction is of particular historical importance in the field of enantioselective synthesis as the belief of vitalism, which includes a scientific hypothesis that chirality could only exist in natural compounds, was prevalent in the early 1900s.[12]

1.2.4. Importance of enantioselective synthesis in the pharmaceutical industry

The relevance of pure enantiomers in the pharmaceutical industry was demonstrated in the early 20th century by the commercial drug, hyoscyamine, as one enantiomer possessed a

greater biological activity in controlling symptoms associated with disorders of the gastrointestinal tract (Figure 1-2).[12] Since then, numerous clinical studies have proven that the biological effect and pharmacokinetics of a chiral molecule differ from those of its enantiomer.[4,13] Today, most newly developed drugs and drug candidates consist of pure enantiomers.[13] Thus, enantioselective preparations of molecules with biological activities hold a significant importance in the pharmaceutical industry.[13]



Scheme 1-3. Marckwald's synthesis of 2-methylbutyric acid from 2-ethyl-2-methylmalonic acid

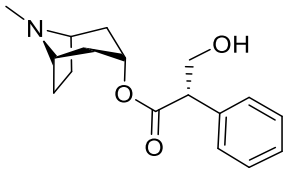


Figure 1-2. Structure of the commercial drug, hyoscyamine

Perhexiline, a racemic drug used to treat abnormal heart rhythms, illustrated the importance of using pure enantiomers in drugs (Figure 1-3).[13] One enantiomer of perhexiline was found to have a much longer half-life than its enantiomer, which led to an accumulation of gram quantities of the enantiomer in the body.[13] Consequently, this racemic drug caused a number of deaths with people who were administered the drug for prolonged periods of time.[13]

Another example is thalidomide, which was first marketed in 1957 as Contergan® from the German drug company, Chemie Grunenthal (Figure 1-4).[14] This racemic drug was prescribed to pregnant women for treating insomnia.[14] However, soon after its commercialization, the drug was

identified as the cause of an increasing number of infants born with phocomelia syndrome, and it was withdrawn in 1961.[14,15] By then, more than 5,000 infants from 46 countries had been born with phocomelia syndrome due to this drug.[14] Clinical tests later reported that the '*S*' enantiomer of thalidomide is a teratogen whereas the '*R*' enantiomer provides the desired sedative effect.[14,15]

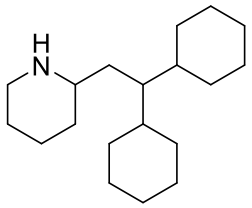
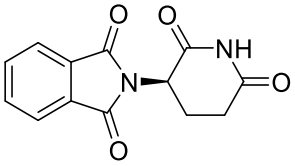
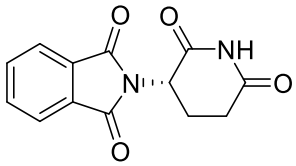


Figure 1-3. Structure of the racemic drug, perhexiline



(*R*)-thalidomide

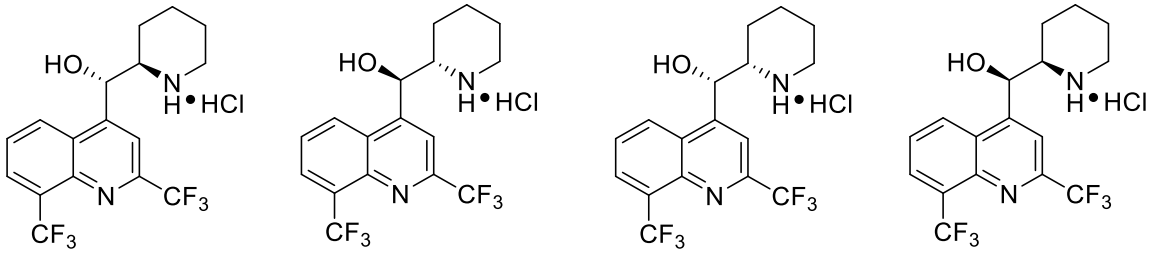


(*S*)-thalidomide

Figure 1-4. Structures of (*R*)- and (*S*)-thalidomide

A current example of the importance of enantiomerically pure drugs is the antimalarial agent, mefloquine, which is marketed as Lariam® from the Swiss pharmaceutical company, Roche.[16] Structurally, mefloquine embeds an *α*-hydroxyalkyl piperidine backbone with two stereogenic centres, which account for four possible stereoisomers (Figure 1-5).[16] Each stereoisomer exhibits various biological activities.[16] Studies have discovered that (−)-*erythro*-mefloquine binds to the adenosine receptor in the central nervous system causing severe psychotropic effects. This off-target activity can be problematic because Lariam® is formulated with racemic *erythro*-mefloquine.[16-18] Specifically, it may explain the severe neurotoxic side effects of the drug demonstrated throughout several clinical trials, which led to its withdrawal as the primary antimalarial drug in the U.S. military.[16-18]

As shown by the above examples, the use of a pharmaceutically active molecule in its enantiomerically pure form can lead to an increase in the potency of the drug as well as a reduction of severe side effects. Therefore, searching for new synthetic methodologies that can access molecules with biological activities in enantiomerically pure forms has become a crucial goal in the pharmaceutical industry.[13-18]



(+)-*erythro*-mefloquine **(–)-*erythro*-mefloquine** **(+)-*threo*-mefloquine** **(–)-*threo*-mefloquine**

Figure 1-5. Four stereoisomers of mefloquine

1.3. Use of chiral organoboron reagents in enantioselective synthesis

1.3.1. Advantages of using organoboron reagents in organic chemistry

When selecting synthetic strategies to form the target drug molecules, the main considerations for the pharmaceutical industry are cost-effectiveness and environmental friendliness.[19,20] In this regard, the use of organoboron compounds as precursors is highly beneficial in comparison to that of other traditional reagents because organoboron compounds, boronic acids in particular, are stable to air and water; relatively safe and environmentally friendly due to low toxicity and ultimate oxidation to boric acid; reactive under mild reaction conditions; and readily available.[20] Due to these aforementioned advantages, synthetic methodologies involving organoboron intermediates have found their applications in natural product synthesis, catalysis, chemical biology, and medicinal chemistry (Figure 1-6).[20] The contributions of organoboron compounds in organic chemistry have been recognized with the prestigious Nobel

Prize in Chemistry: Herbert C. Brown was cited in 1979 "*for [his] development of the use of boron-containing … compounds into important reagents*"; and Akira Suzuki shared the Prize in 2010 "*for palladium-catalyzed cross couplings in organic synthesis*" using boronic acids as coupling partners.[11]

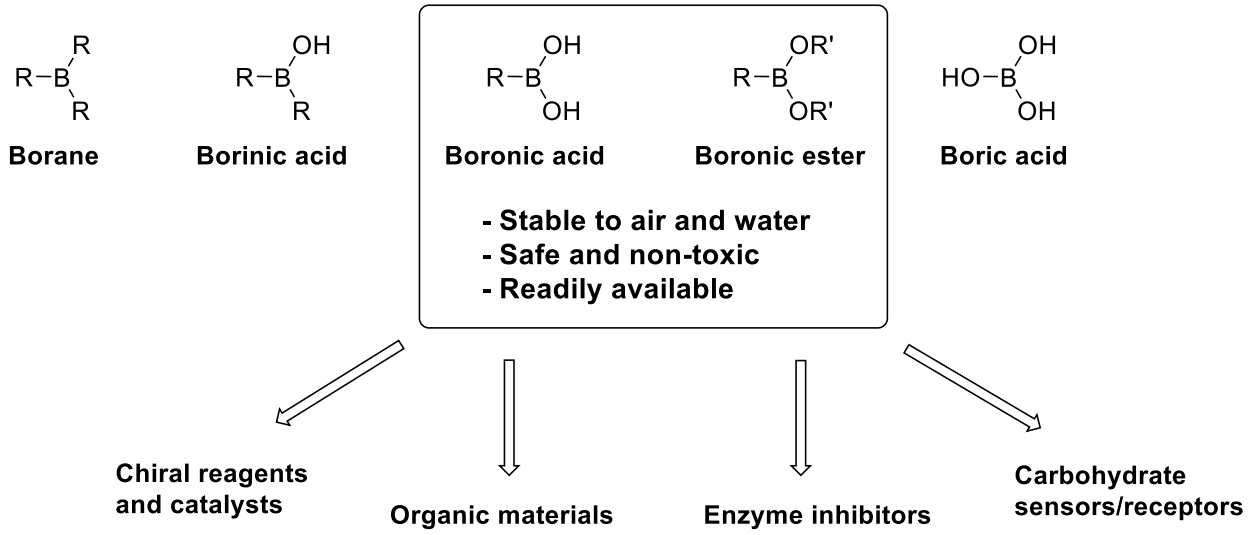
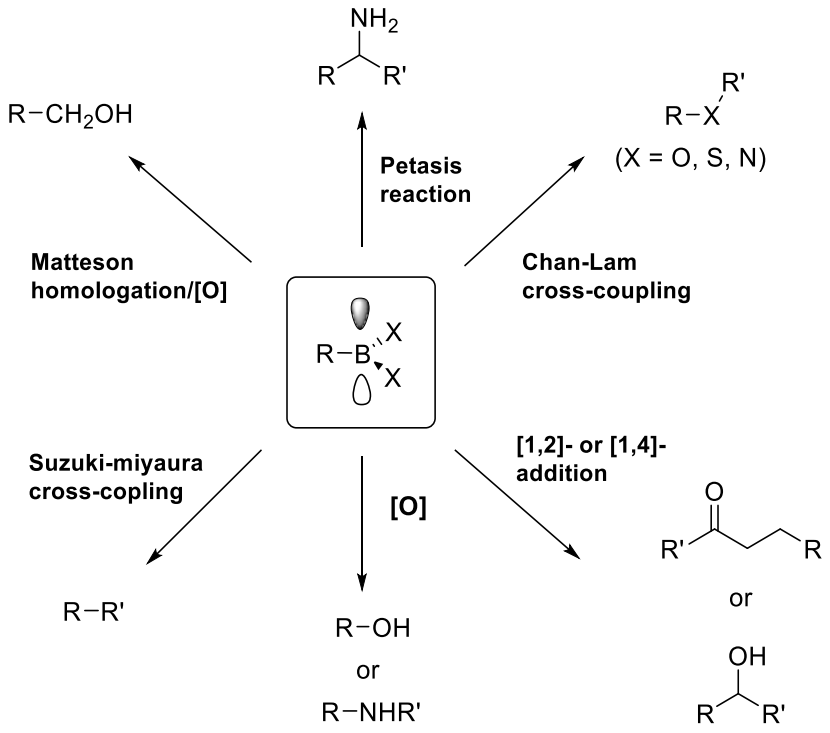


Figure 1-6. Applications of organoboron reagents in a variety of scientific fields

Perhaps the greatest advantage of using organoboron intermediates from the standpoint of organic chemists is its synthetic utility in a variety of bond-forming methodologies under mild or ambient conditions.[20] The versatility of organoboron compounds comes from the electronic configuration of the boron atom, which features a trivalent ground state geometry that results in an open coordination site, giving its Lewis acid property.[20] Some of the synthetic transformations involving organoboron intermediates include a direct oxidation to alcohols or amines, Matteson homologation, [1,2]- or [1,4]-addition on carbonyl compounds, Petasis reaction, and cross-coupling reactions such as the Suzuki-Miyaura and Chan-Lam reactions (Scheme 1-4).[20-32]

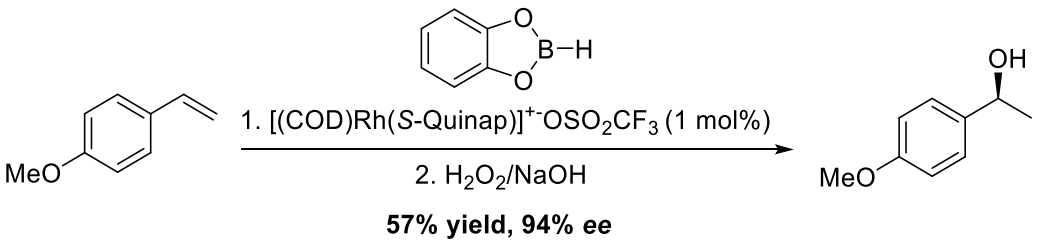


Scheme 1-4. Selected synthetic transformations involving organoboron intermediates

1.3.2. Applications of chiral organoboron compounds in enantioselective synthesis

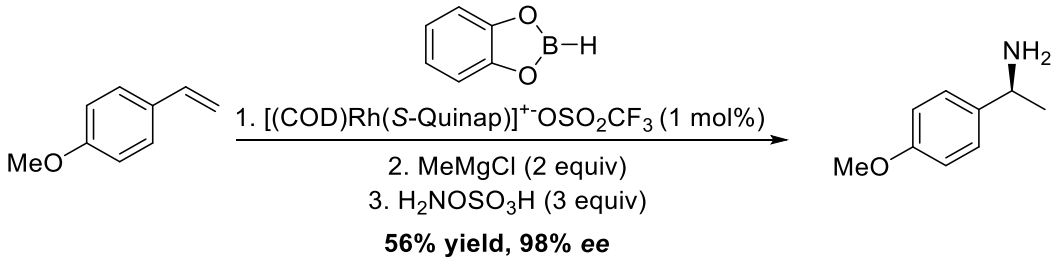
Due to the attributes mentioned in the previous section, organoboron chemistry has made significant progress in a range of different scientific fields over the past few decades.[20] The use of an organoboron intermediate is particularly valuable in enantioselective synthesis because chiral organoboron compounds can easily be transformed to desired chiral surrogates due to their versatility.[20]

Chiral organoboronates can be directly oxidized to form enantiomerically enriched alcohols.[21] In 1993, an asymmetric hydroboration of styrene derivatives employing a rhodium complex of (*S*)-Quinap as a catalyst was reported.[21] This hydroboration was followed by a standard oxidation with hydrogen peroxide to furnish a chiral, enantiomerically enriched alcohol (Scheme 1-5).[21]



Scheme 1-5. Rh-catalyzed asymmetric hydroboration-oxidation to form a chiral alcohol

The same rhodium complex was employed to catalyze an asymmetric hydroboration-amination reaction of styrene derivatives (Scheme 1-6).[22] Chiral organoboronates were directly transformed to enantiomerically enriched amines.[22]

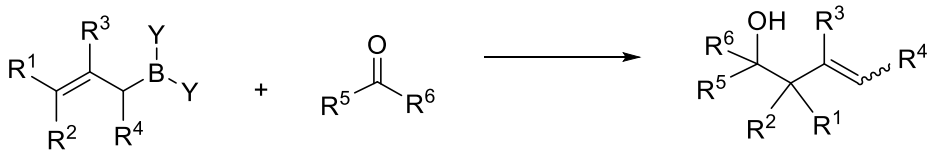


Scheme 1-6. Rh-catalyzed asymmetric hydroboration-amination to form a chiral amine

Chiral organoboronates are widely used in C-C bond-forming reactions such as the carbonyl allylboration reaction.[23-26] Since its discovery in 1966, the carbonyl allylboration reaction between an allylic borane and an aldehyde has made a significant impact, especially in the total syntheses of natural products.[23-26] The asymmetric version of this reaction forms a stereoselective homoallylic alcohol with up to two new stereogenic centres.[26] This reaction features a high control of diastereoselectivity due to a closed chair-like Zimmerman-Traxler transition state.[26] Pioneering studies in this field involved an organoborane as a chiral boron source, which is often hard to handle due to its high reactivity (Scheme 1-7A).[26] In an effort to find a more convenient substrate, an organoboronic ester has been employed as a practical alternative, although it often suffers from low reactivity.[24,25] In 2002, our laboratory and the Miyaura Group independently reported the

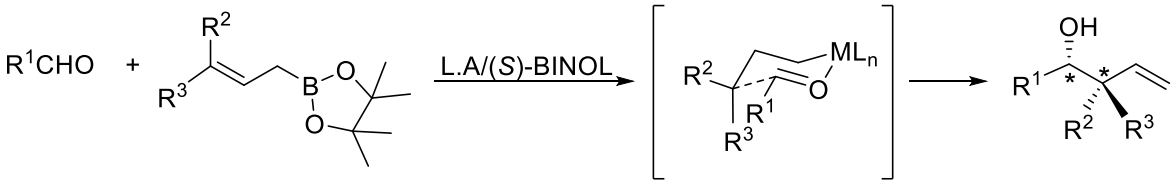
use of a catalytic Lewis acid such as scandium (III) triflate to enhance the reactivity of an organoboronic ester in the carbonyl allylboration reaction (Scheme 1-7B).[24,25]

A. Use of an organoborane in the uncatalyzed carbonyl allylboration reaction[23,26]



R^1 to R^6 = alkyl or H
Y = alkyl

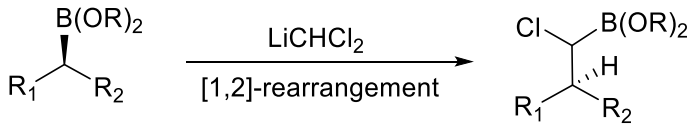
B. Lewis acid catalyzed asymmetric carbonyl allylboration reaction[24,25]



R^1 = alkyl
R^2, R^3 = alkyl or H

Scheme 1-7. General schemes for the carbonyl allylboration reaction

Starting from the early 1980s, Matteson has been the main pioneer in the field of homologation reactions involving organoboronates as precursors.[20] He used the lithium salt of *α*,*α*-dichloroalkyl carbanion as a nucleophile to provide [1,2]-rearrangement of the boron centre, which led to a formal one-carbon homologation with a retention of the stereochemistry (Scheme 1-8).[27] This homologation reaction was named after Matteson, and has been used extensively in a variety of applications in organic synthesis.[20]



Scheme 1-8. Asymmetric Matteson homologation reaction of chiral organoboronates

The most famous and widely used C-C bond-forming cross-coupling reaction involving organoboronates is the Nobel Prize winning Suzuki-Miyaura cross-coupling reaction.[20] Some of the advantages in using organoboronic acids and derivatives as cross-coupling partners include their wide availability; stability to air, water, and heat; low environmental impact and relatively low toxicity.[20] Traditional conditions for the Suzuki-Miyaura cross-coupling reaction allows the formation of sp^2-sp^2 C-C bonds; however, recent advances of this reaction have made the formation of sp^2-sp^3 and sp^3-sp^3 C-C bonds possible.[20]

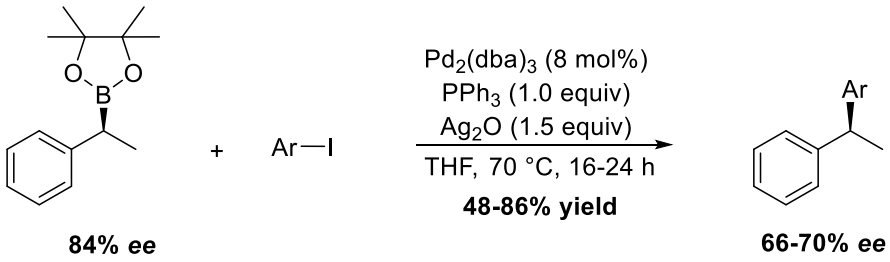
Compared to the cross-coupling reactions employing alkenyl or aryl boronates as cross-coupling partners, those with alkyl boronates are more difficult due to a slower transmetalation and possible side-reactions such as *β*-hydride elimination and protodeboronation.[20] The use of chiral secondary alkyl boronates as cross-coupling partners adds another complication in the form of stereocontrol. Despite these challenges, the stereoselective sp^2-sp^3 Suzuki-Miyaura cross-coupling has made significant progress over the past few years, starting with a key report in 2009 by Crudden and co-workers (Scheme 1-9A).[28] In 2010, the Suginome Group presented stereoinvertive cross-coupling reactions of *α*-(acylamino)benzylboronic esters (Scheme 1-9B).[29] However, the substrate scope of both of the aforementioned methods are limited to benzylic substrates.

Subsequently, Molander reported the first case of the use of non-benzylic secondary alkyltrifluoroborate salt as substrates for the stereoinvertive cross-coupling reaction in 2010 (Scheme 1-9C).[30] This research field was further advanced by Biscoe and co-workers; the starting materials for their reaction do not involve any boron-coordinating group (Scheme 1-9D).[31]

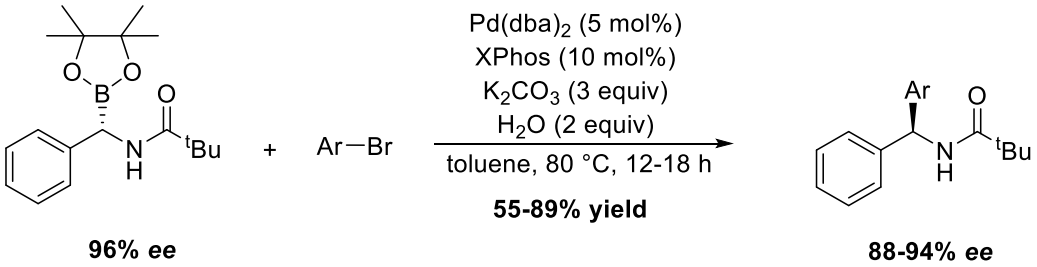
Our laboratory has also contributed to the asymmetric Suzuki-Miyaura cross-coupling reaction. Inspired by the previously reported chemoselective cross-coupling reactions of 1,1-diboronylalkanes with aryl halides accomplished by Shibata and co-workers, the first

stereoselective cross-coupling reaction with chiral 1,1-diboronyl compounds was achieved in 2011 (Scheme 1-9E).[32,33]

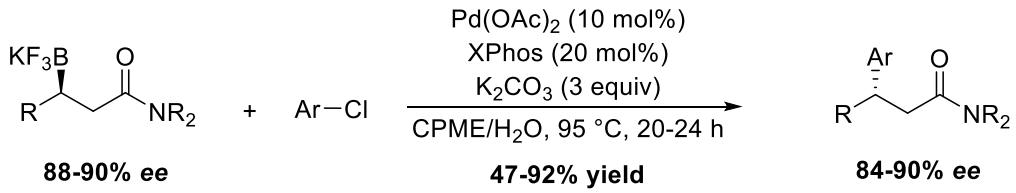
A. Crudden and co-workers in 2009[28]



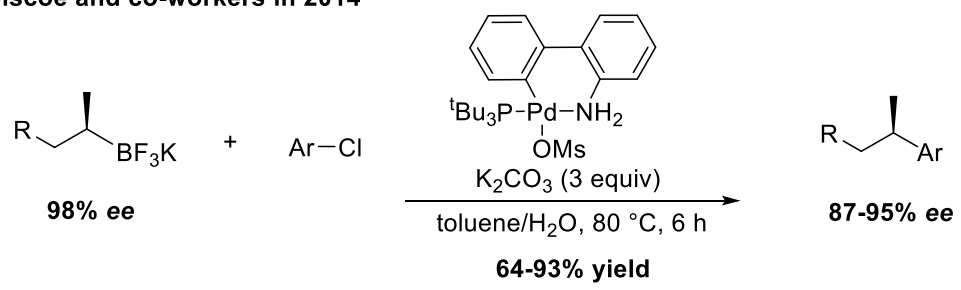
B. Suginome and co-workers in 2010[29]



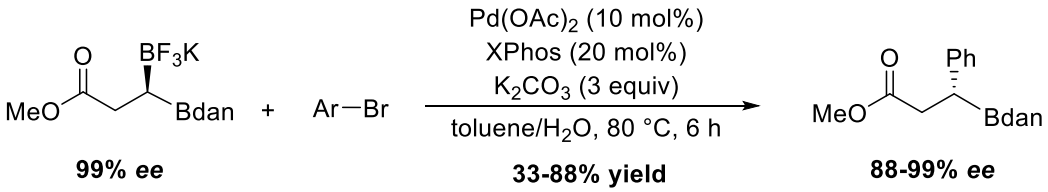
C. Molander and co-workers in 2010[30]



D. Biscoe and co-workers in 2014[31]



E. Hall and co-workers in 2011[33]



Scheme 1-9. Suzuki-Miyaura cross-coupling reactions involving chiral secondary organoboronates

1.4. Piperidine derivatives as “privileged” compounds in the pharmaceutical industry

1.4.1. Piperidine derivatives in biologically active molecules

Chiral non-aromatic *N*-heterocycles such as chiral piperidine derivatives are considered as a “privileged” class of compounds in drug discovery due to their prevalence in pharmaceutically active compounds.[34-36] They possess a wide range of biological activities such as antidepressant and antimalarial.[34-36] A few selected examples of pharmaceutical drugs and natural products embedding a piperidine subunit are depicted in Figure 1-7.

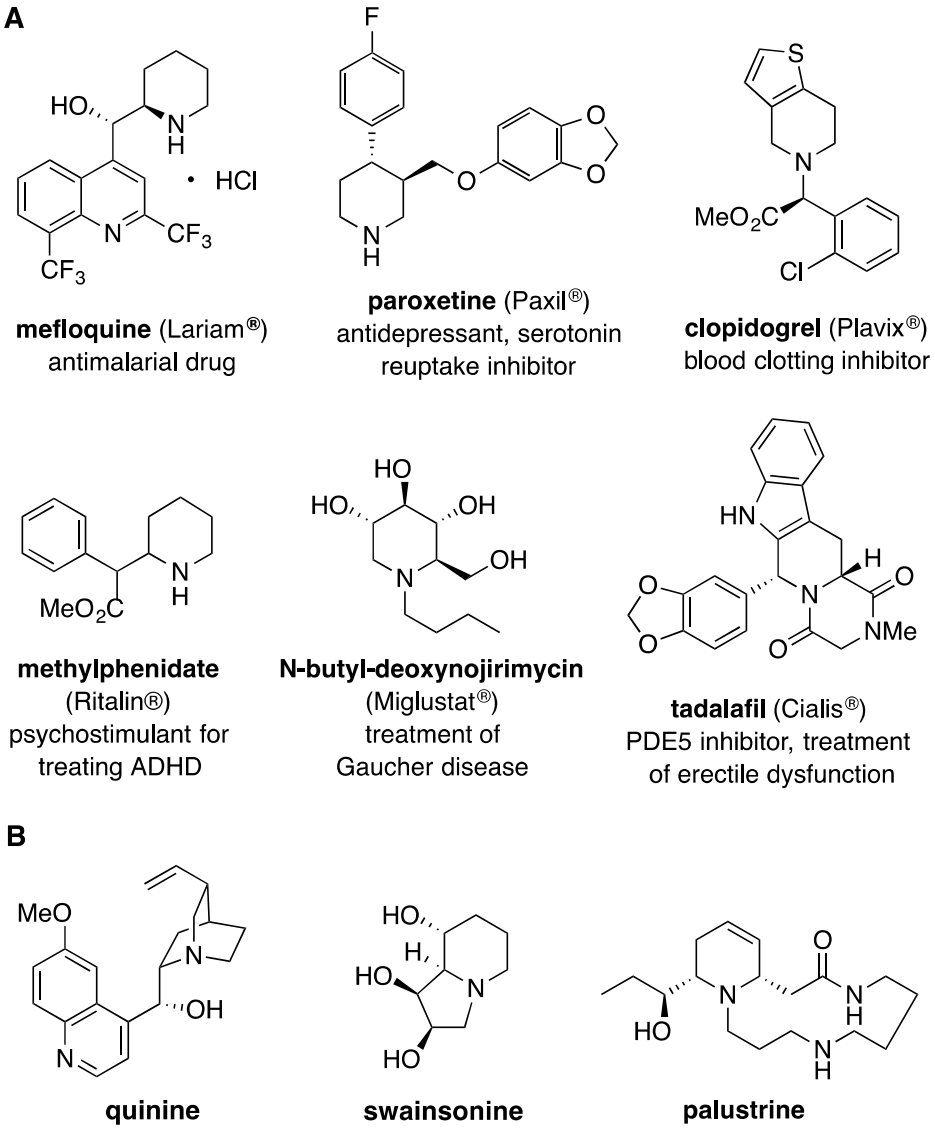
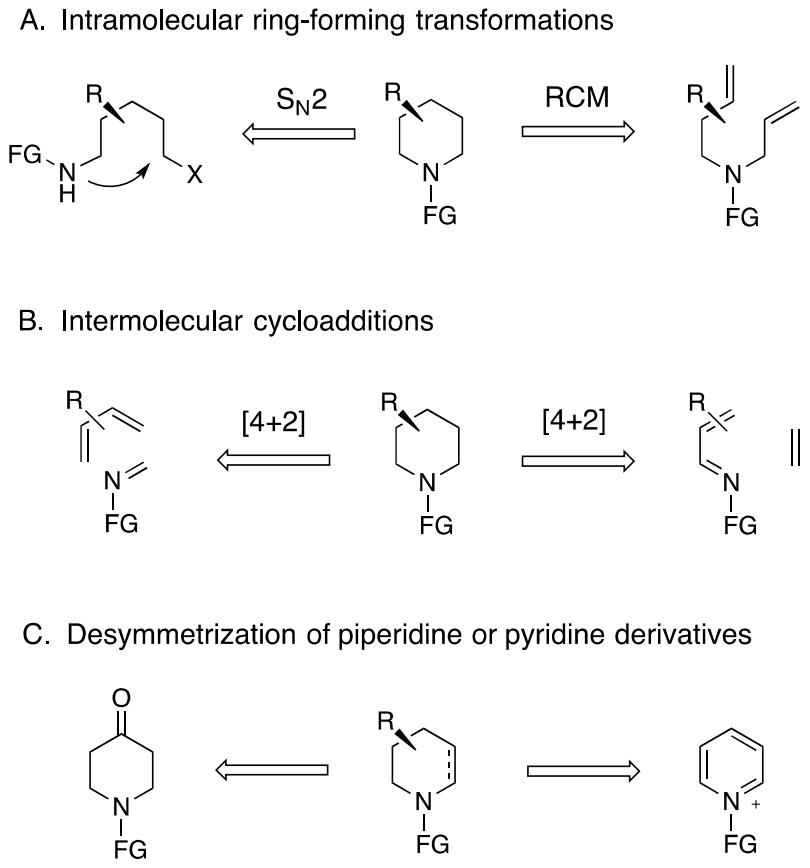


Figure 1-7. Examples of piperidine-containing (A) pharmaceutical drugs and (B) natural products

1.4.2. Conventional preparations of piperidine derivatives

Three general synthetic approaches can be considered to synthesize these chiral piperidine derivatives: intramolecular ring-forming transformations, intermolecular [4+2] cycloadditions, and desymmetrization of a readily available piperidine precursor (Scheme 1-10).[37-47]



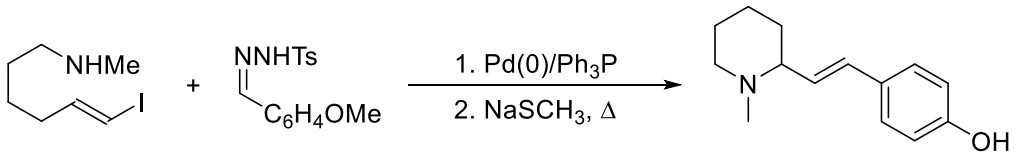
Scheme 1-10. General synthetic strategies to form chiral piperidine derivatives

Hydroamination is the addition of a nucleophilic nitrogen across a C-C multiple bond and was first described by the American chemist, Tobin J. Marks, in 1989.[37-39] This reaction has found its application in the synthesis of piperidine derivatives via an intramolecular addition of nucleophilic amines to olefins.[37-39] A selected novel application of the hydroamination reaction is

the synthesis of the natural product, (±)-caulophyllumine B, which is a piperidine alkaloid, commonly used as a dietary supplement for regulation of a menstrual cycle (Scheme 1-11A).[38]

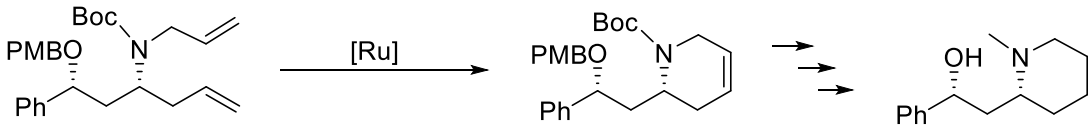
Another popular intramolecular cyclization method to form piperidine derivatives is the ring closing metathesis (RCM) reaction.[39] RCM is a convenient methodology that allows the synthesis of 5- to 30-membered cyclic alkenes.[39] For example, the cyclization step in the synthesis of the natural product, (+)-sedamine, proceeded efficiently via RCM (Scheme 1-11B).[39]

A. Hydroamination for the synthesis of (±)-caulophyllumine B[38]



(±)-caulophyllumine B

B. RCM for the synthesis of (+)-sedamine[39]

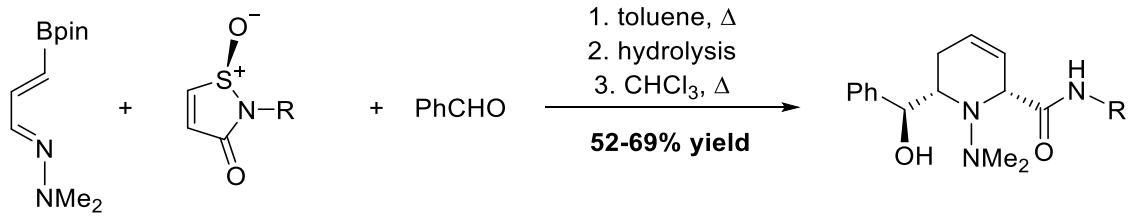


(+)-sedamine

Scheme 1-11. Intramolecular ring-forming transformations for natural product synthesis

However, the intramolecular cyclization via hydroamination or RCM requires pre-functionalized acyclic substrates, which are normally synthesized via a multi-step sequence.[37-39] In this regard, intermolecular [4+2] cycloaddition can be performed more conveniently, although the control of stereoselectivity can be challenging and fewer methods exist for the catalytic control of enantioselectivity with this approach. [40-43] In 2004, our laboratory reported a novel three-component sequential intermolecular aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene reaction to provide substituted piperidine derivatives (Scheme 1-12).[41]

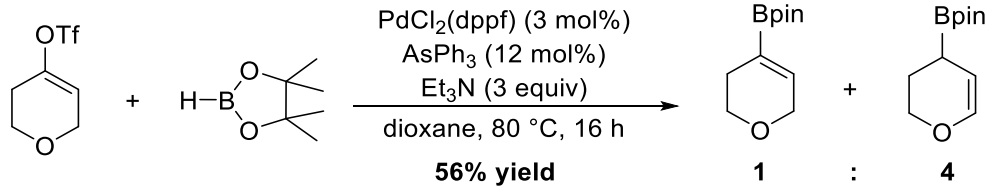
Hall and co-workers in 2004[41]



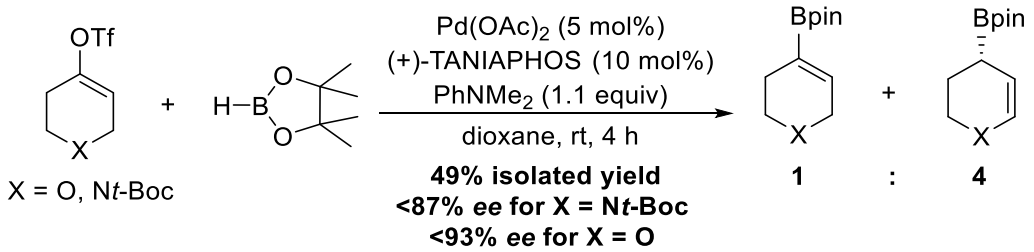
Scheme 1-12. Three-component sequential aza[4+2] cycloaddition/allylboration/retro-sulfinyl-ene reaction

A synthetic strategy that overcomes such aforementioned issues is the desymmetrization of a simple, prochiral piperidine substrate that provides an enantiomerically enriched piperidine derivative via a single-step.[44-47] Surprisingly, to the best of our knowledge, only a few methods exist for the desymmetrization of readily available piperidine precursors. Our laboratory has been one of the main contributors in this field. In 2009, the Hall Group reported the catalytic enantioselective borylative migration reaction of pyranyl and piperidinyl alkenyl triflates,[47] which was inspired by a report in 2000 on the palladium-catalyzed borylation of pyranyl alkenyl triflate from the Masuda Group (Scheme 1-13).[48]

Masuda and co-workers in 2000[48]



Lessard and Hall in 2009[47]

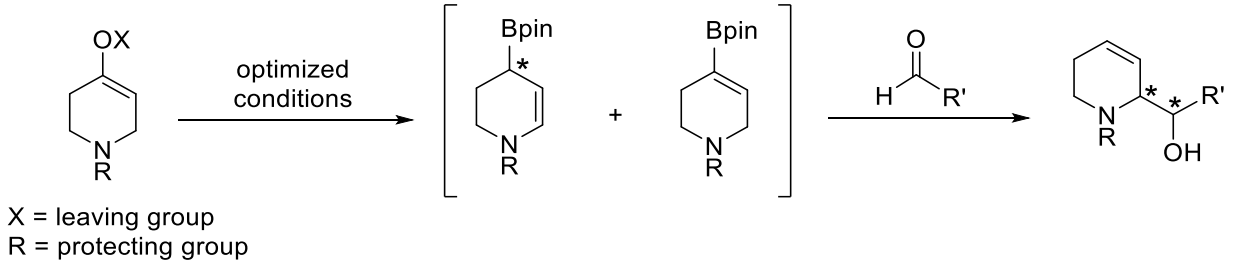


Scheme 1-13. Early development of the catalytic enantioselective borylative migration

1.5. Thesis objectives

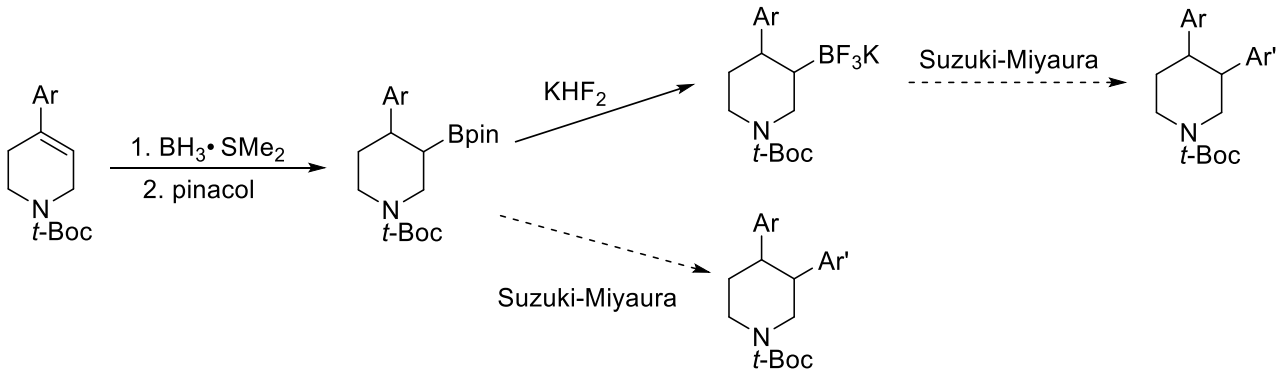
As described in Section 1.4, compounds embedding a piperidine backbone are of a significant importance in drug discovery due to their prevalence in biologically active molecules. In this regard, developing an industry-friendly procedure to form piperidine derivatives is highly desirable in the pharmaceutical industry.

Chapter 2 describes a thorough optimization of the previously developed catalytic enantioselective borylative migration[47] for the piperidinyl substrates (Scheme 1-14). Throughout the optimization process, our main focus was to identify an economical, industry-friendly procedure that can provide piperidine derivatives in a multi-gram scale. In addition, some mechanistic studies were conducted to validate the proposed mechanism for this reaction reported in 2009.[47] In the same chapter, the attempts to form [3,4]-biaryl-piperidine derivatives via the sequential Suzuki-Miyaura cross-coupling reactions are presented (Scheme 1-15).

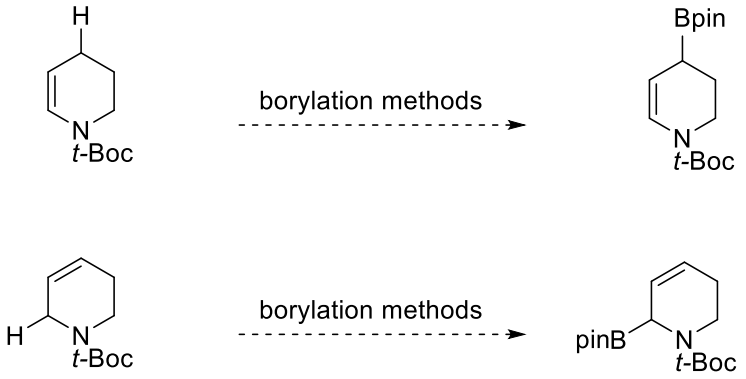


Scheme 1-14. General scheme of the catalytic enantioselective borylative migration

Although our laboratory's catalytic enantioselective borylative migration procedure offers a single-step preparation of enantiomerically enriched piperidinyl allylic boronate from a simple piperidinyl alkenyl triflate or nonaflate (Chapter 2), we explored alternative approaches that could utilize other convenient piperidine precursors. Chapter 3 reports attempted borylation of simple, commercial dehydropiperidines (Scheme 1-16).

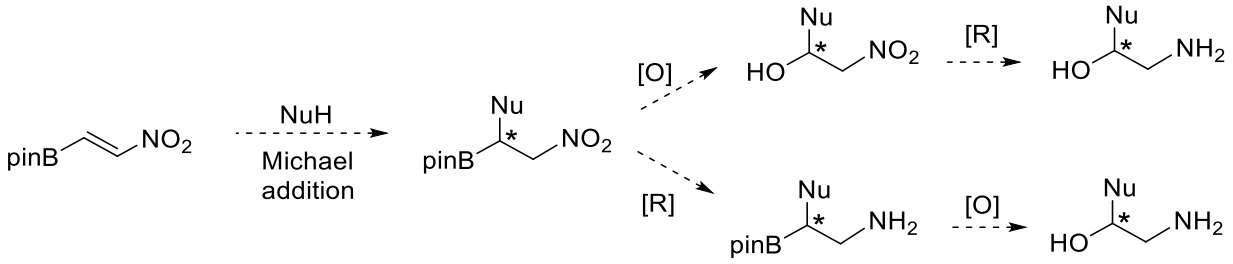


Scheme 1-15. Proposed synthesis of [3,4]-biaryl-piperidine derivatives via the sequential Suzuki-Miyaura cross-coupling reactions



Scheme 1-16. Borylation of simple, commercial dehydropiperidines

Our next synthetic target of interest was a chiral *β*-amino alcohol, which is a component of numerous pharmaceutical drugs.[50] To achieve this objective, we considered employing a chiral nitro-alkylboronate as a universal precursor, which could be synthesized using *β*-borono-nitroethylene as a novel precursor. Chapter 4 describes an attempted synthesis of *β*-borono-nitroethylene. Due to the lack of literature precedent on the synthesis of *β*-borono-nitroalkene derivatives, several conventional procedures for the formation of nitro-olefins were examined.



Scheme 1-17. Proposed synthesis of chiral *β*-amino alcohol using *β*-borono-nitroethylene

1.6. References

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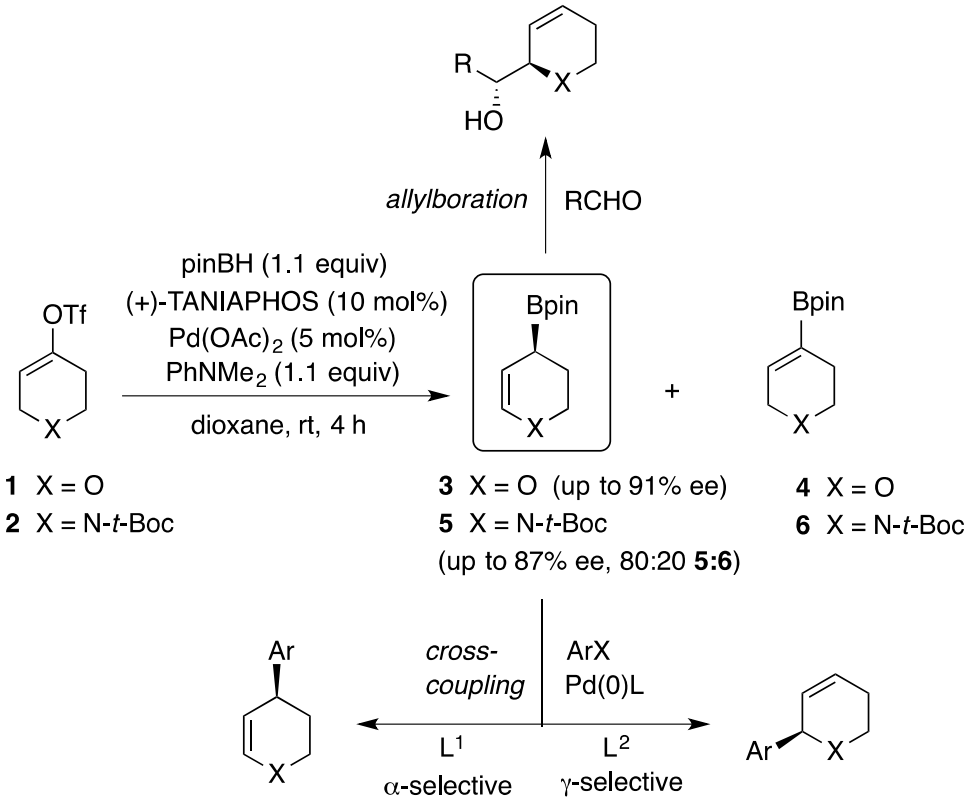
Chapter 2. Optimization and Applications of the Catalytic Enantioselective Borylative Migration of Functionalized Piperidines

2.1. Introduction and objectives

Development of efficient and convenient syntheses of pharmaceutically relevant piperidine derivatives is of great interest in the pharmaceutical industry.[1-3] As discussed in Chapter 1, the Hall Group previously developed the catalytic enantioselective borylative migration of a piperidinyl alkenyl triflate, which could provide the corresponding allylic boronate via a single-step. This allylic boronate can serve as a precursor for further transformations, such as carbonyl allylboration or the Suzuki-Miyaura cross-coupling reaction, leading to functionalized, optically enriched piperidines.

A detailed reaction scheme and synthetic applications of the catalytic enantioselective borylative migration of pyranyl and piperidinyl alkenyl triflates **1** and **2** are illustrated in Scheme 2-1.[3-5] This method was inspired by the work from the Masuda Group on the palladium-catalyzed borylation of a variety of alkenyl triflate derivatives to form the corresponding alkenyl boronates. When using a pyranyl triflate **1** as a substrate, however, the authors isolated allylic boronate **3** as a major product instead of the expected alkenyl boronate **4**.[6] This unusual observation was intriguing because modification of this chemistry could lead to a preparative isolation of allylic boronate. In 2009, our laboratory achieved the synthesis of optically enriched allylic boronates **3** and **5** by using a wide bite-angle, chiral diphosphine ligand, (+)-Taniaphos (Figure 2-1).[7]

In the search for applications of this chemistry in drug discovery, allylic boronate **5** was employed for the syntheses of several natural and synthetic products, such as (+)-*β*-conhydrine and mefloquine, via a highly diastereoselective carbonyl allylboration with corresponding aldehydes (Scheme 2-1, Figure 2-2).[5]



Scheme 2-1. Synthetic applications of heterocyclic allylic boronates prepared from the catalytic enantioselective borylative migration

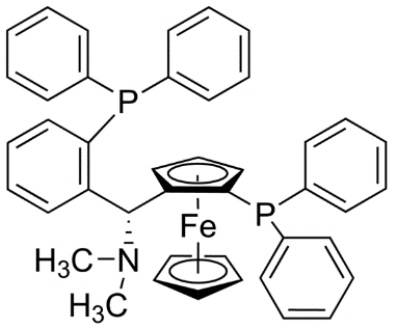
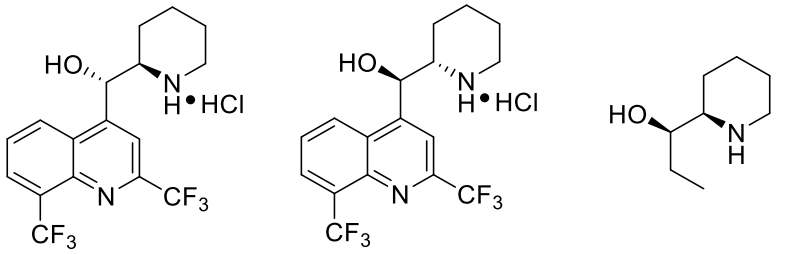


Figure 2-1. Structure of a wide bite-angle diphosphine ligand, (+)-Taniaphos

In 2014, our laboratory also accomplished a stereospecific, catalyst-controlled, and regiodivergent sp^2-sp^3 allylic Suzuki-Miyaura cross-coupling process between sp^2-organohalides and allylic boronates **3** or **5** (Scheme 2-1).[3] This cross-coupling methodology was applied to the efficient synthesis of the commercial drug, (3*R*, 4*S*)-paroxetine, as a pure enantiomer (Figure 2-3).[3]



(+)-*erythro*-mefloquine **(–)-*erythro*-mefloquine** **(+)-β-conhydrine**

Figure 2-2. Biologically active compounds synthesized via the catalytic enantioselective borylative migration-allylboration sequence

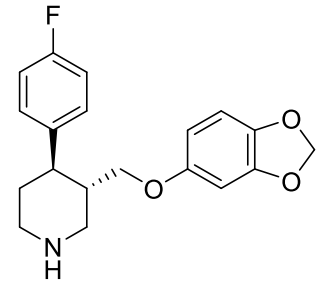
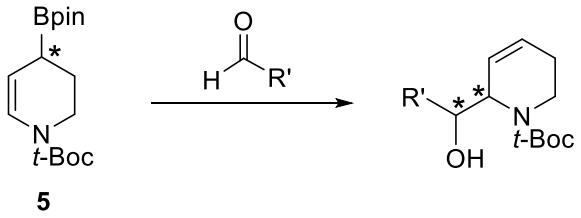


Figure 2-3. Enantioselective synthesis of the commercial drug, (3*R*, 4*S*)-paroxetine, via the catalytic enantioselective borylative migration-Suzuki-Miyaura cross-coupling sequence

The catalytic enantioselective borylative migration developed in 2009, however, occasionally provided lower yields and enantioselectivity. Possible detrimental effects include: the presence of peroxide in dioxane, insufficiently pure reagents, and partially oxidized ligand. In this regard, further fine-tuning of the current reaction conditions was deemed necessary. We decided to re-optimize the reaction conditions for a piperidinyl alkenyl substrate as the current reaction conditions were optimized solely based on pyranyl alkenyl triflate **1**. Our main focus was to identify an economical, industry-friendly procedure that could provide piperidine derivatives in a multi-gram scale since enantiomerically enriched piperidine derivatives are an important class of scaffolds in the pharmaceutical industry.[1-3]

After identifying the optimal reaction conditions for the borylative migration, our next objective was to employ allylic boronate **5** to briefly optimize a subsequent carbonyl allylboration

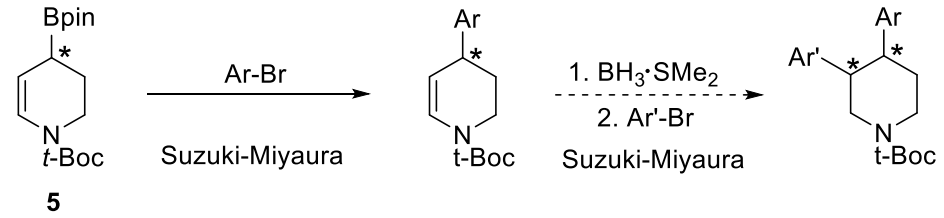
reaction with several different classes of substrates including aromatic, heteroaromatic, and acylic aldehydes (Scheme 2-2).



Scheme 2-2. General scheme of the aldehyde allylboration with allylic boronate **5**

Moreover, a number of mechanistic studies were conducted to validate the reaction mechanism for the catalytic enantioselective borylative migration proposed in 2009.[4]

Finally, the allylic boronate **5** was subjected to a variety of established Suzuki-Miyaura cross-coupling conditions in an effort to synthesize [3,4]-biaryl-piperidine derivatives (Scheme 2-3).



Scheme 2-3. Proposed synthesis of [3,4]-biaryl-piperidine derivatives via the sequential Suzuki-Miyaura cross-coupling reactions

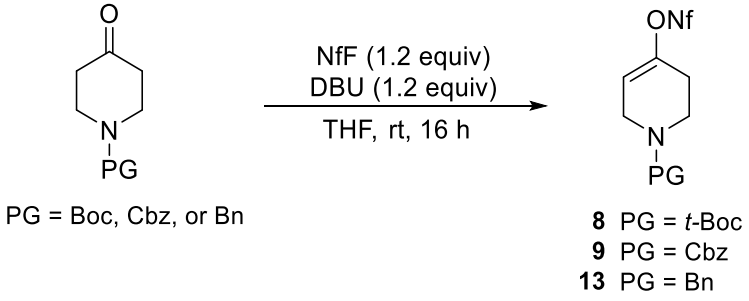
2.2. Optimization of catalytic enantioselective borylative migration

The current reaction conditions of the catalytic enantioselective borylative migration developed in 2009 presented several limitations: lower than desired *ee* and yields, use of peroxide-forming dioxane as the solvent, higher than desired catalyst loading (5 mol%), low reaction concentration (0.063 M), and reproducibility issues. In addition, compared to a pyranyl

analogue (90-91% *ee*), the piperidinyl alkenyl triflate **2** afforded a lower level of enantioselectivity (86-87% *ee*).[4] Several parameters, including the nature of the alkenylsulfonate and the *N*-protecting group of the substrate, the source and stoichiometry of palladium and diphosphine ligand, solvent, reaction concentration, temperature, and time, were examined in order to troubleshoot these aforementioned limitations and identify a more robust, industry-friendly reaction procedure.

2.2.1. Screening of substrates

The original reaction procedure for the catalytic enantioselective borylative migration reported in 2009 was performed solely on the piperidinyl alkenyl triflate **2**.[4] In this regard, we wondered whether another sulfonate derivative or *N*-protecting group would provide a higher yield and/or *ee*. Thus, we prepared piperidinyl alkenyl nonaflates **8**, **9**, and **13** according to the literature (Scheme 2-4).[8]



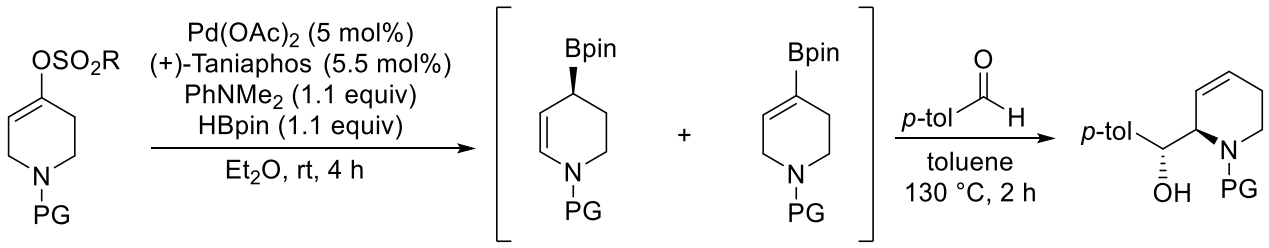
Scheme 2-4. Preparation of piperidinyl alkenyl nonaflates **8**, **9**, and **13**

With these new substrates in hand, the suitability of substrates **2**, **8**, **9**, and **13** was examined by comparing the regioselectivity ratio of desired allylic boronate (**5**, **10**, or **14**) to alkenyl boronate side-product (**6**, **11**, or **15**) (Table 2-1). The original reaction conditions reported in 2009 with slight modifications including a 1:1.1 Pd:ligand ratio and diethyl ether as the solvent were used for this screening. As previously shown, allylic boronates tend to decompose when exposed

to air or silica gel for prolonged periods of time; therefore, the yield and *ee* were measured indirectly using corresponding stable allylboration product (**7**, **12**, or **16**).[4]

Use of substrate **8**, which embeds an alkenyl nonaflate in lieu of an alkenyl triflate, did not provide an increase in *ee*; however, substrate **8** did lead to a higher yield of the desired allylic boronate **5**, compared to that of substrate **2** (entries 1-2). Moreover, compared to that of substrate **2**, the preparation of substrate **8** was higher-yielding and more cost-effective because perfluorobutanesulfonyl fluoride is less expensive than phenyl triflimide. In addition, the chromatographic purification of substrate **8** was more convenient.

Table 2-1. Optimization of the reaction substrate[a]



allylic boronate alkenyl boronate

2	R = CF_3, PG = *t*-Boc	**5**	+	**6**	PG = *t*-Boc	**7** PG = *t*-Boc
8	R = $(CF_2)_3CF_3$, PG = *t*-Boc	**5**	+	**6**	PG = *t*-Boc	**7** PG = *t*-Boc
9	R = $(CF_2)_3CF_3$, PG = Cbz	**10**	+	**11**	PG = Cbz	**12** PG = Cbz
13	R = $(CF_2)_3CF_3$, PG= Bn	**14**	+	**15**	PG = Bn	**16** PG = Bn

Entry	Substrate	R	PG	Proportion of 6, 11, 15 (%)[b]	Product	Yield (%)[c]	*ee* (%)[d]
1	**2**	CF_3	*t*-Boc	10-15%	**7**	66	91
2	**8**	$(CF_2)_3CF_3$	*t*-Boc	10-15%	**7**	76	91
3	**9**	$(CF_2)_3CF_3$	Cbz	<5%	**12**	60	90
4	**13**	$(CF_2)_3CF_3$	Bn	nr[e]	**16**	0	nr[e]

[a] Scale of reactions: 0.5 mmol. [b] Separable by flash chromatography. [c] Isolated yield of **7** or **12** after flash chromatography. [d] Determined by chiral HPLC of **7** or **12**. [e] nr = no reaction.

Subsequently, we screened the *N*-protecting groups. Compared to a *N*-Cbz group, which is cleaved by catalytic hydrogenation, removal of a *N*-Boc protecting group is orthogonal to that

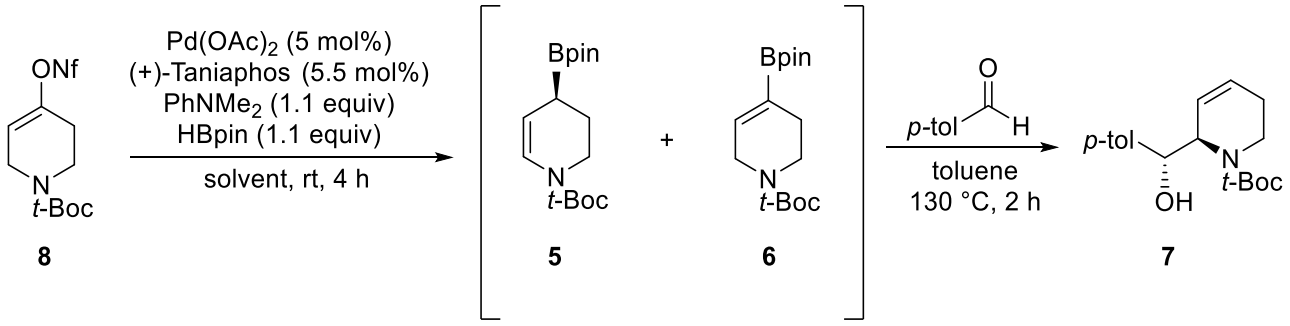
of the alkene present in the allylboration products. Therefore, although *N*-Cbz substrate **9** provided a lower proportion of undesired alkenyl boronate (entry 3), it was decided to employ substrate **8** for subsequent optimization. The reaction with substrate **13**, embedding a *N*-Bn protecting group, did not provide any conversion to the desired allylic boronate **16** (entry 4).

2.2.2. Optimization of solvent and reaction temperature

The original reaction conditions employ peroxide-forming dioxane as the reaction solvent.[4,9] Use of dioxane presents a significant limitation towards the adoption of this borylative migration in a multi-gram scale or in a process setting. In hopes of identifying a safer, more efficient, and greener solvent, we screened several solvents with an exploratory scale of 0.5 mmol of substrate **8**. The results of this study are shown in Table 2-2.

Our laboratory's original screening of solvents reported in 2009, employing pyranyl triflate **1** as a substrate, identified both toluene and dioxane as optimal solvents. It was therefore surprising to find that toluene and chlorobenzene were ineffective with alkenyl nonaflate **8** (entries 1-2). Many ethereal solvents, however, were found to be suitable, including diethyl ether (entry 4) and the green solvents, methyl *t*-butyl ether (MTBE) and cyclopentyl methyl ether (CPME) (entries 9-10).[9] Much to our delight, compared to the previously optimal solvent, dioxane, these green solvents provided higher and reproducible *ee*'s of 90-91% (entry 3). The use of lower temperatures (–10, 0 °C) did not provide significantly higher *ee*'s; unfortunately, the product yields were lower due to incomplete conversion even after 16 hours (entries 11-12). Lowering the temperature further to –35°C did not lead to any conversion due to solubility issues. Based on these results, we decided to continue the optimization process using ethereal solvents (e.g., diethyl ether and CPME) at ambient temperature.

Table 2-2. Broad evaluation of solvents in the catalytic borylative migration of **8**[a]



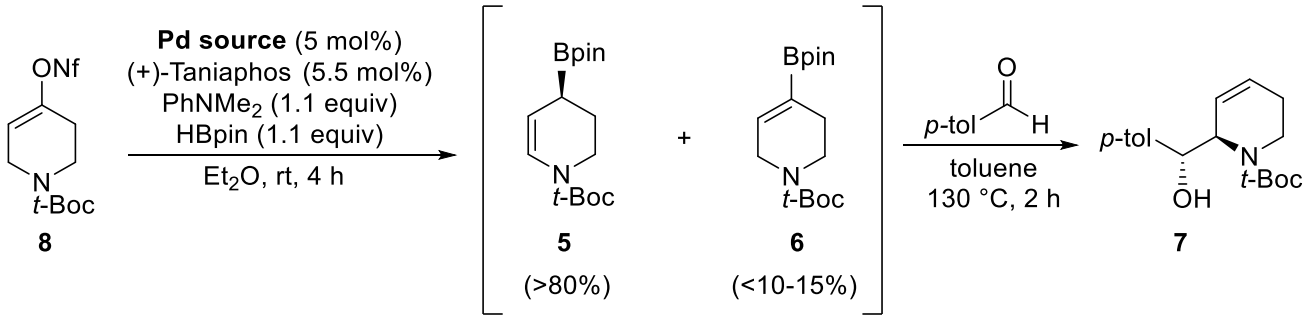
Entry	Solvent	Yield (%)[b]	*ee* (%)[c]
1	toluene	<5	-
2	chlorobenzene	<5	-
3	dioxane	78	86
4	diethyl ether	70	91
5	THF	0[e]	-
6	2-MeTHF	0[e]	-
7	dibutyl ether	0[e]	-
8	diglyme	0[e]	-
9	MTBE	60	90
10	CPME	63	90
11	CPME (0 °C)	60[d]	92
12	CPME (–10 °C)	50[d]	93
13	CPME (–35 °C)	0[e]	-

[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of **7** after flash chromatography. Accompanied with 10-15% of alkenylboronate **6**, separable by flash chromatography. [c] Determined by chiral HPLC of **7**. [d] Reactions failed to reach completion even after a 16 h reaction time. [e] nr = no reaction

2.2.3. Optimization of the palladium source

Although the source of palladium was examined previously,[4] we re-examined this important parameter with the new nonaflate substrate **8** (Figure 2-4). We confirmed that both Pd(0) and Pd(II) sources were suitable for this chemistry. Although several other Pd complexes were competent, including $Pd_2(dba)_3$, $[PdCl(allyl)]_2$, $[PdCl(cinnamyl)]_2$, and XPhos-Pd-G2, $Pd(OAc)_2$ was chosen for further optimization because of its stability to air and relatively lower cost.

Throughout this study, we noticed the importance of employing an ultrapure grade of $Pd(OAc)_2$ (99.95+%). A detrimental effect on the *ee* of product **7** was observed when using a lower grade $Pd(OAc)_2$ (98+%) as the palladium source.



Pd source:	
$Pd(OAc)_2$	70%, 91% *ee*
Pd_2dba_3	70%, 91% *ee*
$[PdCl(allyl)]_2$	ND, 90% *ee*
$[PdCl(cinnamyl)]_2$	ND, 90% *ee*
XPhos-Pd-G_2	ND, 90% *ee*

Figure 2-4. Examination of Pd source in the catalytic borylative migration of **8**

2.2.4. Optimization of the chiral ligand

In attempts to further increase the *ee* of the product with the newly optimized conditions in diethyl ether, we re-evaluated a small number of common chiral diphosphines and other ligands (Figure 2-5).

During this study, we found that relatively wide bite-angle and chelate size of the ligand seemed crucial in promoting the desired enantioselective reaction. Most of the attempted ligands failed to provide conversion of substrate **8**. The amine-containing diphosphine, Taniaphos, remained the most effective ligand. As described above (Table 2-2), this ligand also provided a significant improvement of *ee* when diethyl ether, MTBE, and CPME were employed as solvents compared to the previously optimal solvent, dioxane.

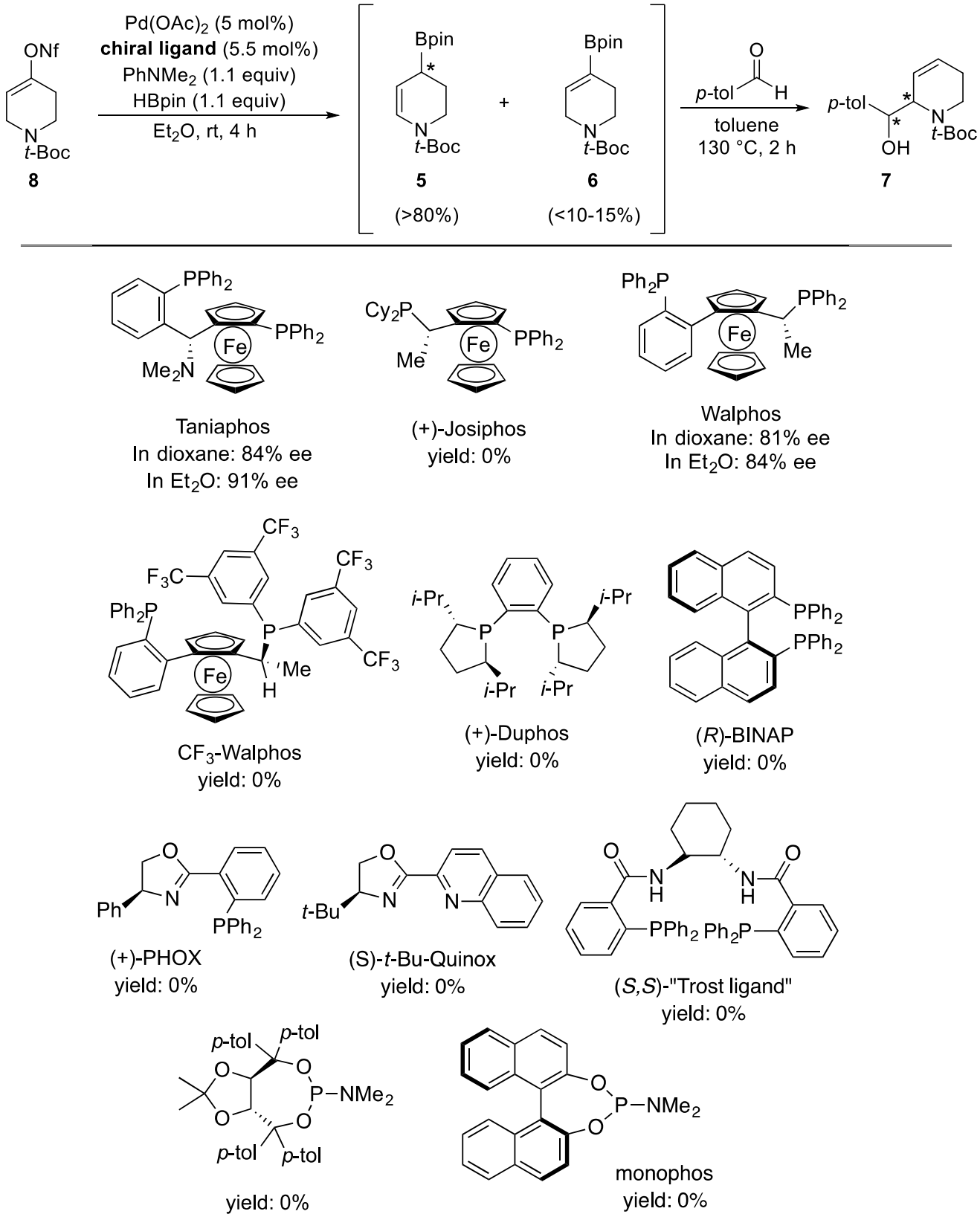
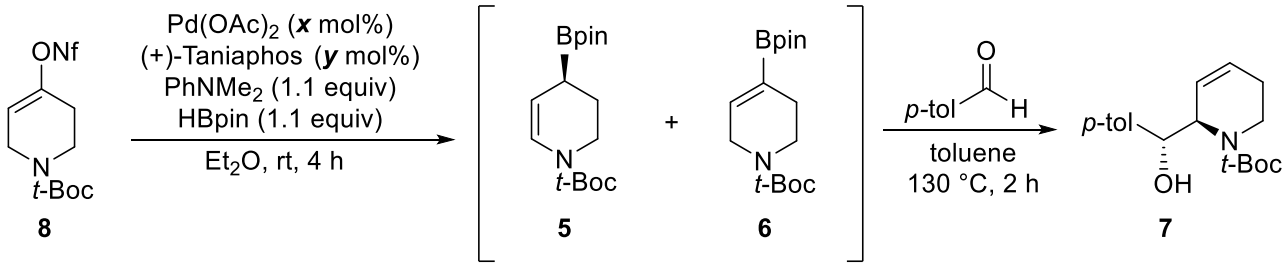


Figure 2-5. Selected chiral ligands evaluated in the catalytic borylative migration of **8**

2.2.5. Optimization of catalyst stoichiometry and reaction concentration

A lower catalyst loading and a higher reaction concentration would make this borylative migration more economically appealing to the pharmaceutical industry. In this regard, we examined the impact of varying these important parameters using diethyl ether as the model solvent (Table 2-3).

Table 2-3. Examination of catalyst stoichiometry and reaction concentration[a]



Entry	Pd loading (*x* mol%)	Ligand loading (*y* mol%)	Pd conc. (mM)	Conc. of 8 (M)	Yield (%)[b]	*ee* (%)[c]
1	5	10	1.9	0.063	70	91
2	5	7	1.9	0.063	70	91
3	5	5.5	1.9	0.063	72	91
4	3	3.3	1.9	0.063	35[d]	90
5	5	5.5	3.1	0.063	70	91
6	3	3.3	3.1	0.10	50[d]	91
7	3	3.3	4.7	0.16	65[d]	90
8	3	3.3	10	0.33	66[d]	90
9	3	3.3	10	0.33[e]	73	90
10	2	2.2	3.1	0.16[f]	64[g]	90
11	2	2.2	6.7	0.33[f]	64[g]	90
12[h]	5	5.5	1.9	0.063	70	91
13[h]	3	3.3	10	0.33[e]	71	92

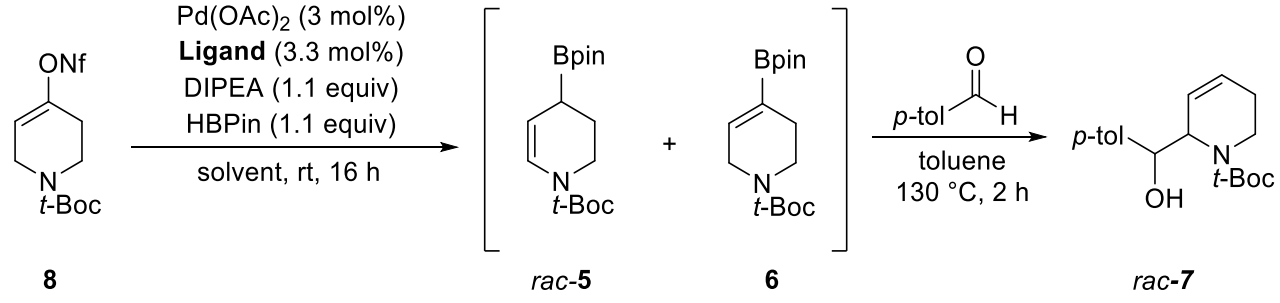
[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of **7** after flash chromatography. Accompanied with 10-15% of alkenylboronate **6**, separable by flash chromatography. [c] Determined by chiral HPLC of **7**. [d] Reactions failed to reach completion after a 4 h reaction time. [e] Stirred for 16 h, instead of 4 h. [f] Stirred for 24 h, instead of 4 h. [g] Reactions failed to reach completion after a 24 h reaction time. [h] CPME was used as the reaction solvent.

The previously optimized conditions from 2009 employed a 1:2 Pd:ligand ratio.[4] Using the same reaction conditions with diethyl ether as the solvent, a 70% yield of product **7** was obtained with a 91% *ee* (entry 1). We were delighted to find that decreasing the Pd:ligand ratio did not affect the yield or *ee* (entries 2-3); while maintaining a slight excess of the ligand to prevent Pd black out, the Pd:ligand ratio could be decreased to near equimolar (entry 3). Although decreasing the catalyst loading to 3 mol% led to a lower yield (entry 4), increasing the reaction concentration made up for this loss (entries 6-7). The aforementioned conditions utilize approximately one third of the originally reported amount of expensive chiral diphosphine ligand,[4] however, at a relatively low concentration of substrate **8**. In order to make this procedure more suitable for multi-gram scale applications, we attempted to increase the reaction concentration. We found it possible to run this borylative migration at a substrate concentration of 0.33 M, leading to substantial solvent economy (entries 8-9). Because a reduced Pd loading of 3 mol% led to an incomplete conversion with a reaction time of 4 h, the reaction was stirred for 16 h to assure completion of the reaction (entry 9). Unfortunately, further attempts to decrease the catalyst loading to 2 mol% led to incomplete conversions even after an extended reaction time of 24 h (entries 10-11). Finally, we were delighted to find that these optimal conditions with diethyl ether as the solvent were also suitable with the greener alternative, CPME, providing comparable yield and *ee* (entries 12-13).

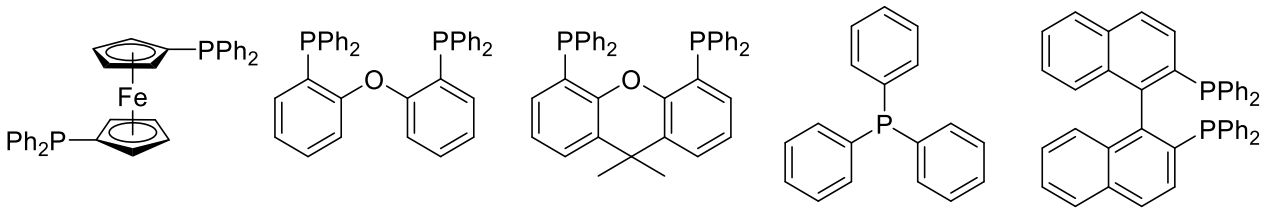
2.2.6. Optimization of racemic reaction conditions

For the purpose of optimizing chiral HPLC separations and other situations where optically enriched allylic boronate **5** was not required, we briefly optimized a racemic variant of the catalytic borylative migration (Table 2-4). Several common achiral diphosphines were screened. Using racemic Taniaphos as a standard (entry 1), we employed DPPF as it embeds a ferrocene backbone; however, it failed to provide any conversion of substrate **8** (entry 2).

Table 2-4. Selected achiral ligands evaluated in the catalytic borylative migration of **8**[a]



8 *rac*-**5** **6** *rac*-**7**



DPPF **DPEPhos** **XantPhos** **PPh_3** **BINAP**

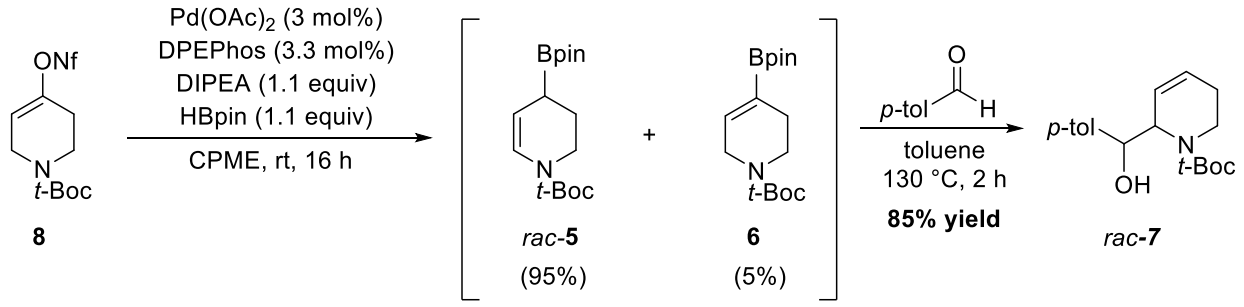
Entry	Ligand	Solvent	Proportion of 5	Proportion of 6	Yield (%)[b]
1	Taniaphos	dioxane	80	20	80
2	DPPF	dioxane	nr[c]	nr[c]	0
3	DPEPhos	dioxane	95	5	87
4	XantPhos	dioxane	90	10	40[d]
5	BINAP	dioxane	nr[c]	nr[c]	0
6	PPh_3	Et_2O	nr[c]	nr[c]	0
7	Taniaphos	CPME	80	20	75
8	DPEPhos	CPME	95	5	85

[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of *rac*-**7** after flash chromatography. Accompanied with 10-15% of alkenylboronate **6**, separable by flash chromatography. [c] nr = no reaction. [d] protodeborylated product was detected leading to the observed lower yield

Readily available and cheap diphosphines such as DPEPhos, BINAP, and PPh_3 were then examined. DPEPhos provided a higher regioselectivity and yield compared to those of the standard (entry 3). Encouraged by this result, Xantphos was employed as it features the same backbone as DPEPhos; however, a significant proportion of protodeborylated side-product was

observed, leading to a lower yield (entry 4). BINAP and PPh_3 did not provide any conversion of substrate **8** (entries 5-6).

In an effort to replace peroxide-forming dioxane, the greener alternative, CPME, was used as a reaction solvent with DPEPhos as a ligand (entry 8). As seen previously during the optimization of chiral reaction conditions (Table 2-2), CPME provided a comparable yield with that of the standard. Therefore, the racemic reaction was best achieved with DPEPhos as the achiral diphosphine ligand and CPME as the solvent (Scheme 2-5).

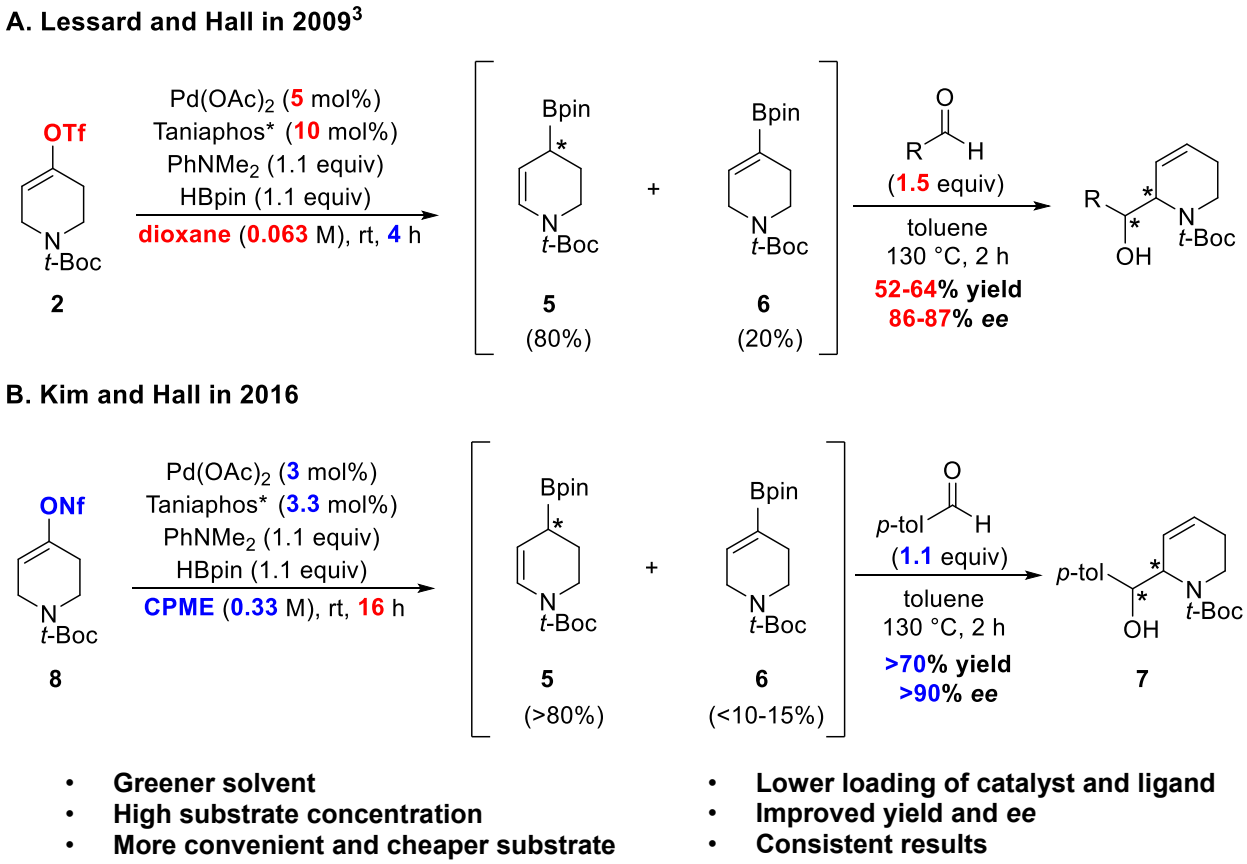


Scheme 2-5. Optimal conditions for the racemic catalytic borylative migration of **8**

2.2.7. Summary

We optimized a Pd-catalyzed enantioselective borylative migration of an alkenyl nonaflate derivative of the simple precursor, *N*-Boc-4-piperidone. An overview of the optimized conditions compared to the previous, un-optimized process is depicted in Scheme 2-6. This optimized reaction procedure is now more industry-friendly, featuring the following improvements: use of a greener solvent, high substrate concentration, cost-effectiveness (use of a cheaper substrate and lower loadings of catalyst and ligand), and reproducible results with improved yield and *ee*. These reaction conditions were also suitable for a multi-gram scale reaction, which is discussed in Section 2-5.

Piperidinyl allylic boronate **5** prepared by this fully optimized borylative migration reaction can be employed in further transformations, such as aldehyde allylboration (Section 2-5), the intermolecular Heck reaction (Section 2-5), and sequential Suzuki-Miyaura cross-coupling reactions (Section 2-6) to provide functionalized dehydropiperidines related to numerous pharmaceutical agents.

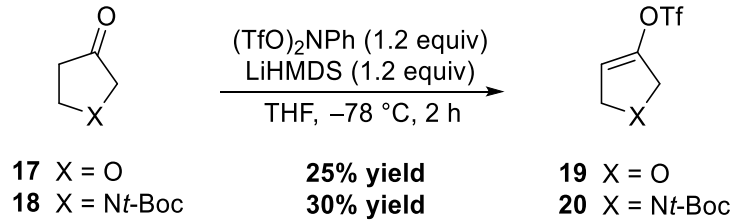


Scheme 2-6. Summary of the optimized catalytic enantioselective borylative migration-aldehyde allylboration sequence for the synthesis of piperidine derivatives

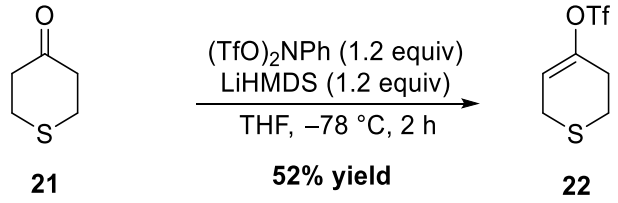
2.3. Exploring other heterocycles for catalytic enantioselective borylative migration

Employment of new classes of substrates of varying ring sizes and different heterocyclic backbones for the catalytic enantioselective borylative migration would be tremendously useful in

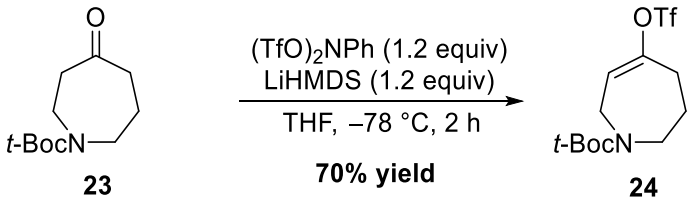
the pharmaceutical industry.[10-11] In hopes of expanding the substrate scope of the borylative migration to 5-membered ring heterocycles, the starting 5-membered alkenyl triflates **19** and **20** were synthesized from the corresponding ketones **17** and **18** under kinetic deprotonation conditions according to the literature (Scheme 2-7).[12,13] These 5-membered alkenyl triflate heterocyclic species are known to be quite unstable and volatile; therefore, they were subjected to the catalytic borylative migration directly upon their purification.[12] We also prepared an alkenyl triflate of a thiane derivative **22** to test the suitability of a sulfur-containing substrate under the borylative migration conditions (Scheme 2-8).[14] In addition, a 7-membered ring heterocycle, an alkenyl triflate of an azepane derivative **24**, was prepared for evaluation (Scheme 2-9).[15]



Scheme 2-7. Synthesis of 5-membered alkenyl triflates **19** and **20**

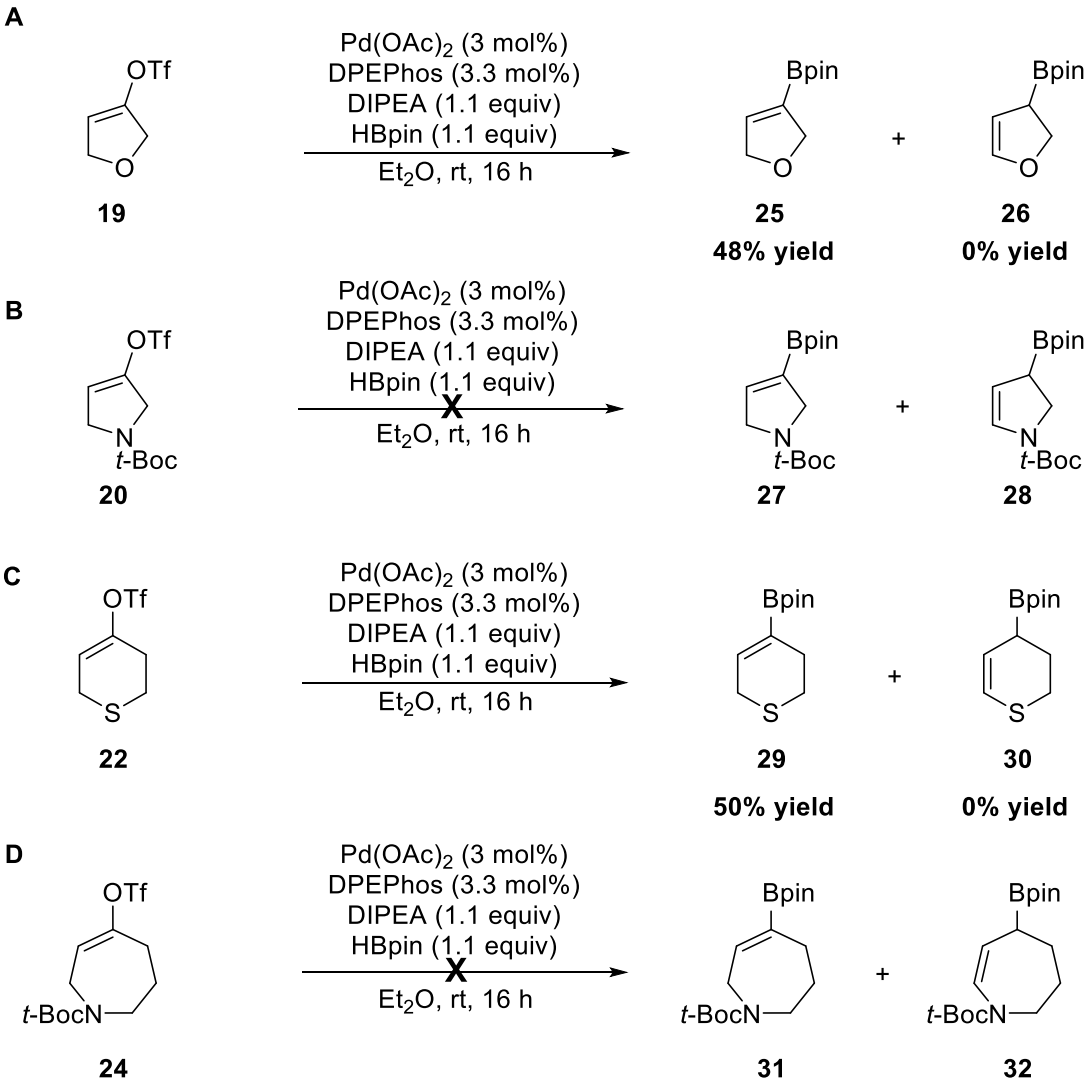


Scheme 2-8. Synthesis of an alkenyl triflate of a thiane derivative **22**



Scheme 2-9. Synthesis of an alkenyl triflate of an azepane derivative **24**

Borylative migration reactions with a tetrahydrofuran derivative **19** or a thiane derivative **22** provided the formation of corresponding alkenyl boronates **25** and **29**, respectively, rather than the desired allylic boronates **26** and **30** (Scheme 2-10A and D).[13,15] Therefore, these substrates tend to undergo the competing Pd(0)-catalyzed Miyaura borylation instead of the desired borylative migration reaction.[16] Unfortunately, both of a pyrrolidine derivative **20** and an azepane derivative **24** did not convert under these catalytic borylative migration conditions (Scheme 2-10B and C).

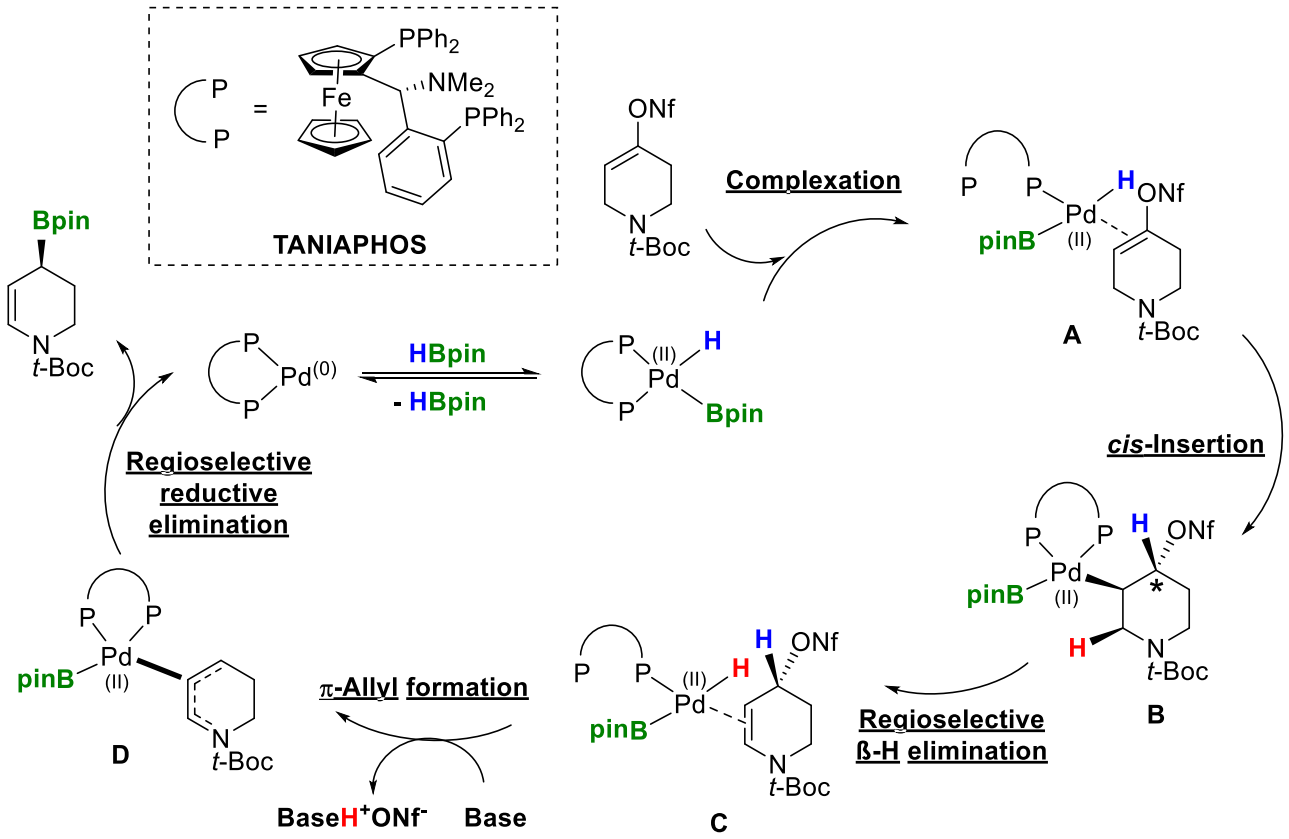


Scheme 2-10. Borylative migration of (A) tetrahydrofuran derivative **19**; (B) pyrrolidine derivative **20**; (C) thiane derivative **22**; and (D) azepane derivative **24**

2.4. Mechanistic studies of the catalytic enantioselective borylative migration

2.4.1. Previously proposed mechanism of the catalytic enantioselective borylative migration

The proposed mechanism for the catalytic enantioselective borylative migration is depicted in Scheme 2-11.[4] The formation of a pinB-Pd(II)-H complex by insertion of HBpin to Pd(0) is considered the beginning of the catalytic cycle. This *in situ* generated metal hydride is complexed with the substrate to form complex **A,** which undergoes a *cis*-insertion to provide complex **B**. *β*-Hydride elimination of the most hydridic C-H of complex **B** gives complex **C**. This is followed by a base-mediated elimination of nonaflate to yield complex **D** via π-allyl formation. Finally, complex **D** undergoes a regioselective reductive elimination to furnish the formation of the product and regeneration of the catalyst.

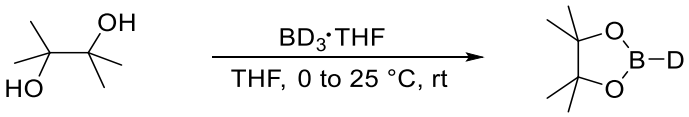


Scheme 2-11. Proposed mechanism of the catalytic enantioselective borylative migration

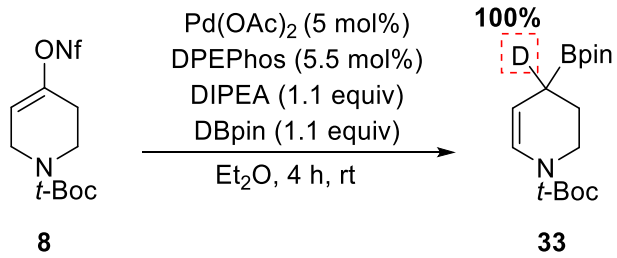
2.4.2. Mechanistic studies to validate the proposed mechanism

Extensive NMR studies to detect the intermediate complexes **A** to **D** were not successful. The ^{1}H NMR spectra of the reaction monitored every 15 min for a 16 h reaction time presented a clear disappearance of the peaks corresponding to the alkenyl nonaflate **8**, with an appearance of the peaks from the product. No other peaks were detected.

In this regard, we attempted to gain support for the formation of complex **A** by reviewing literature precedents. There is a literature example of a Pd-catalyzed hydroboration, which reports the formation of boryl-palladium hydride.[17] The following *cis*-insertion step leading to complex **B** was validated by a deuterium labelling study using deuterated pinacolborane synthesized according to the method described in Scheme 2-12.[18] This study revealed a 100% deuterium incorporation at the *α*-position to the boron in the resulting allylic boronate **33** (Scheme 2-13).



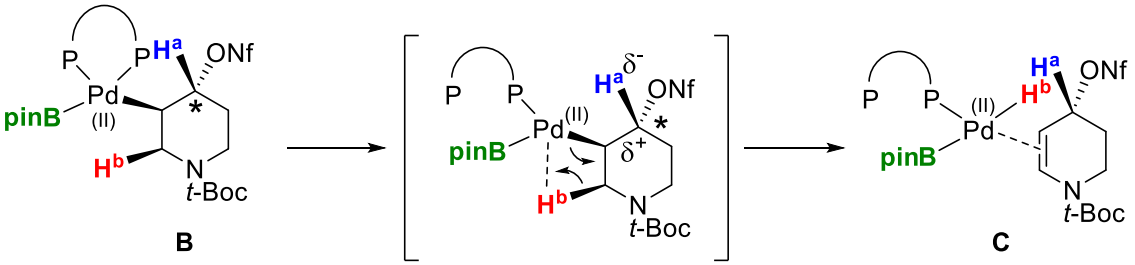
Scheme 2-12. Synthesis of deuterated pinacolborane



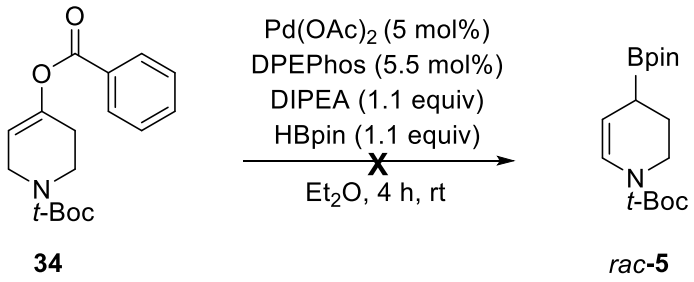
Scheme 2-13. Deuterium labelling study of alkenyl nonaflate **8** using deuterated pinacolborane

The regioselective *β*-hydride elimination can be explained by the strong electron-withdrawing nature of the nonaflate group compared to a *N*-Boc group, making H^{a} less hydridic than H^{b} (Scheme 2-14). This idea is supported by the fact that the reaction did not provide any conversion when a benzoate group was used as a leaving group (Scheme 2-15). We believe that

this benzoate substrate **34** still undergoes a *cis*-insertion to afford the corresponding complex **B**; however, because a benzoate group has a less electron-withdrawing nature compared to the nonaflate group, H^a is now more hydridic than H^b. The result of this *β*-hydride elimination would be the regeneration of the alkenyl benzoate **34**, leading to the lack of conversion under borylative migration conditions.

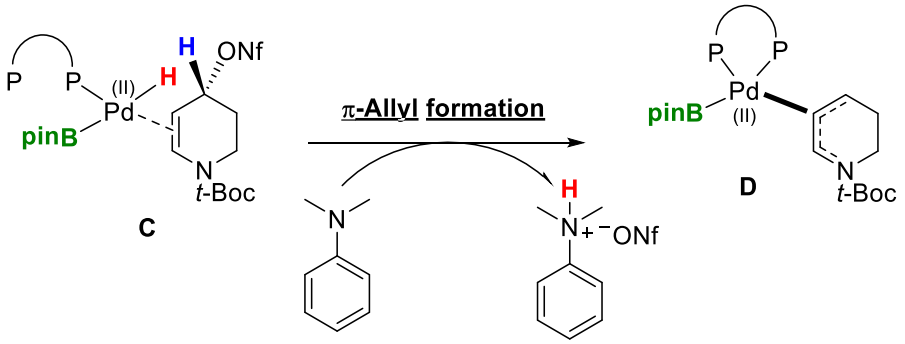


Scheme 2-14. Regioselective *β*-hydride elimination of complex **B** leading to complex **C**



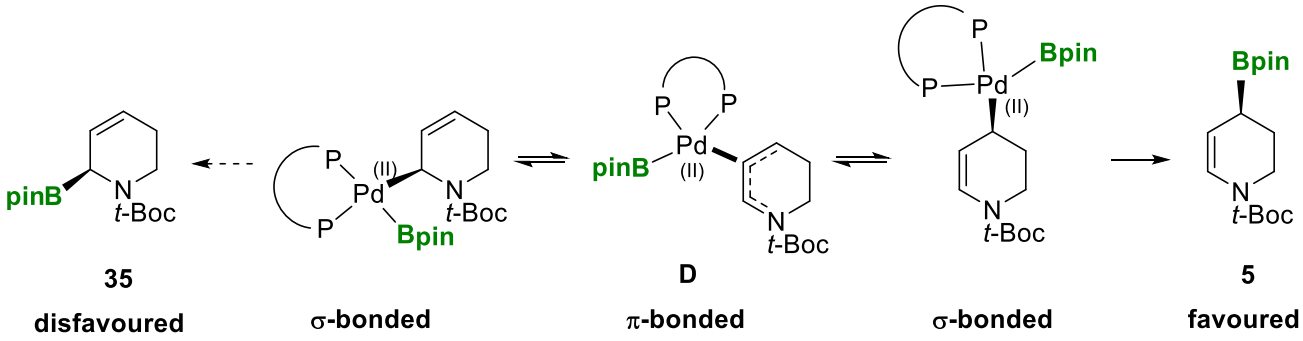
Scheme 2-15. Borylative migration of an alkenyl benzoate **34** as a probe substrate

During the NMR study, a peak at 11.2 ppm slowly appeared simultaneously as the peaks of the alkenyl nonaflate correspondingly disappeared. Integration of this peak was 1 H after a full conversion of the starting material. This observation implies the presence of a protonated base salt, which is consistent with our proposed mechanism (Scheme 2-16). A sample containing only the base and triflic acid was independently prepared as a standard (observed chemical shift *δ*10.5 ppm) to confirm that this peak at 11.2 ppm indeed corresponds to the protonated base salt.



Scheme 2-16. The role of base in the π-allyl formation step

The final regioselective reductive elimination step can be explained by the following: the σ-bonded form leading to the product is thought to be higher in energy and thus, reacts more quickly to form the observed product according to the Curtin-Hammett principle (Scheme 2-17).[19] The energy of the σ-bonded form of each regioisomer will be calculated by computational studies in collaboration with Prof. Claude Legault from the University of Sherbrooke to support the experimental results. The presence of the other regioisomer was not detected by the ^{1}H NMR spectrum of the crude reaction mixture.

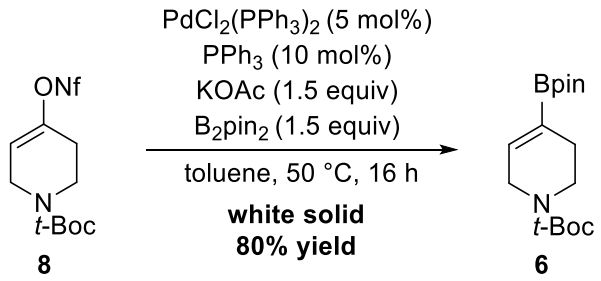


Scheme 2-17. Regioselective reductive elimination of complex **D** leading to the formation of **5**

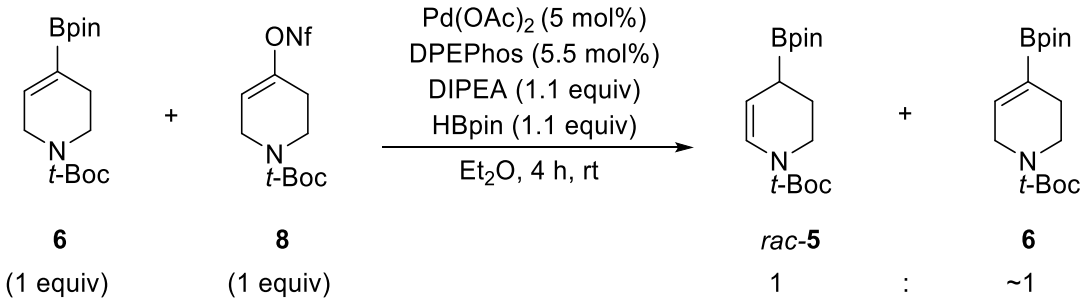
2.4.3. Attempts to identify reaction intermediates

With the aim to identify the possible reaction intermediates, the major side-product, alkenyl boronate **6**, was prepared separately to be used as a substrate. Pure alkenyl boronate **6** was

obtained as a white solid in 80% yield via the Miyaura borylation reaction (Scheme 2-18).[16] The 1:1 mixture of synthesized alkenyl boronate **6** and alkenyl nonaflate **8** was subjected to the standard borylative migration conditions; however, the reaction provided almost a 1:1 ratio of allylic boronate *rac*-**5** to alkenyl boronate **6**, suggesting that the alkenyl boronate **6** is not involved as an intermediate in the borylative migration (Scheme 2-19).

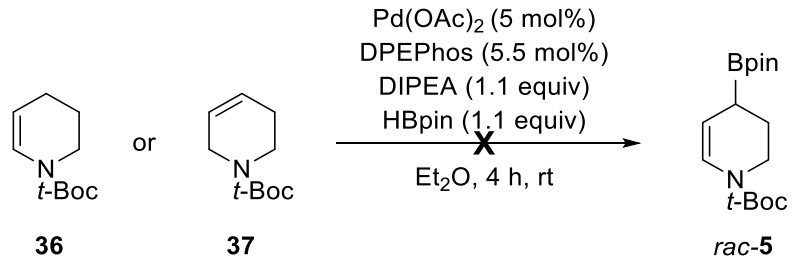


Scheme 2-18. Synthesis of alkenyl boronate **6** via the Miyaura borylation



Scheme 2-19. Examination of reactivity of alkenyl boronate **6** under the borylative migration conditions

Alkenyl piperidine derivatives **36** and **37** were also examined as possible substrates under standard borylative migration conditions (Scheme 2-20). According to the ^{1}H NMR spectra of the crude reaction mixtures, they did not provide any conversion, suggesting that they are not likely to be the reaction intermediates.

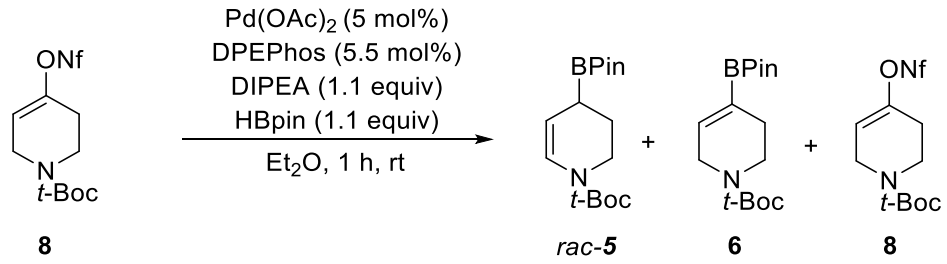


Scheme 2-20. Borylative migration of dehydropiperidines **36** and **37** as substrates

2.4.4. Measuring kinetic isotope effects of natural ^{13}C abundance

The concept behind the measurement of natural ^{13}C abundance for the purpose of a mechanistic study is the competitive reactivity of isotopically labeled substances in reactions.[20] Theoretically, a reaction would favour to proceed at lighter carbons, resulting in a preference of ^{12}C over ^{13}C. During the course of a reaction, the carbon sites that are involved in the rate-determining step of a reaction would become fractionally enriched in the lighter isotopic components, as ^{12}C would be reacted before ^{13}C. Therefore, the carbons involved in the reaction mechanism could be identified by comparing ^{13}C enrichment of the recovered starting material to that of unreacted starting material.

This method was employed to identify the carbons involved in the rate-determining step of our borylative migration. The reaction was stopped after one hour for the purpose of recovering the starting material **8** (Scheme 2-21). While setting the internal standard as the carbons of the *t*-Boc group, all of the peaks in the ^{13}C NMR spectra were compared. Unfortunately, this borylative migration occurred rather unselectively; there was no difference in the peaks of the ^{13}C NMR spectra between the recovered and unreacted starting materials. Therefore, we were unable to determine the carbons involved in the rate-determining step using this method.



8 *rac-**5*** **6** **8**

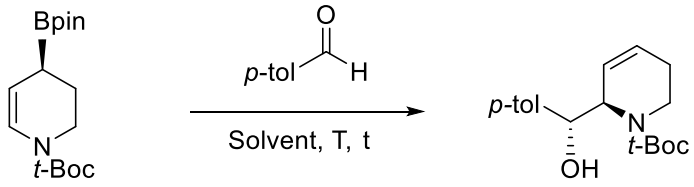
Scheme 2-21. Borylative migration for the purpose of ^{13}C natural abundance study

2.5. Fine-tuning the aldehyde allylboration reaction

2.5.1. Optimization of thermal aldehyde allylboration conditions

Piperidinyl congeners react with aldehydes more sluggishly in comparison to pyranyl allylic boronates. The original reaction conditions for the aldehyde allylboration reported in 2009 required the use of microwave heating at 130 °C in toluene (0.2 M) for 2 hours in a sealed vessel.[4] The resulting product yields were moderate, ranging between 50 to 65%.[4] We suspected that these disappointing yields were caused by an incomplete conversion of the allylboration reaction. Indeed, by continuous monitoring of the model reaction via TLC, we found that a significant proportion of the allylic boronate **5** was left unreacted after 2 hours (entries 1-5; Table 2-5); hence the reaction time was re-examined. We found it necessary to increase the reaction time to 5 hours in order to obtain a full conversion and a higher isolated yield of the allylboration product **7** (entry 6).

Table 2-5. Optimization of the aldehyde allylboration of **5**[a]



5 **7**

Entry	Solvent	Heat source	Conc. (M)	T (°C)	t (h)	Yield[c] (%)	*ee*[d] (%)
1[b]	chlorobenzene	μw	0.2	160	0.5	75	-
2[b]	chlorobenzene	μw	0.2	160	2	84	-
3	toluene	μw	0.2	130	1	79	90
4	toluene	μw	0.2	130	2	80	90
5	toluene	oil bath	0.2	130	2	81	91
6	toluene	μw	0.2	130	5	86	91
7	toluene	oil bath	0.2	130	5	85	90
8	neat	N/A	N/A	rt	16	85	92

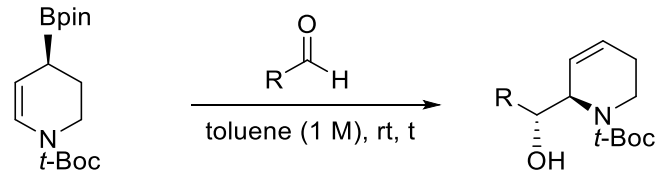
[a] Scale of reactions: 0.5 mmol. [b] Entry 1 and 2 used racemic allylboronate. [c] Isolated yield of **7** after flash chromatography. [d] Determined by chiral HPLC of **7**. [e] Allylic boronate **5** was fully purified prior to the allylboration reaction, leading to higher yields in comparison to the reported yields utilizing pre-purified **5**.

The carbonyl allylboration reaction is considered highly diastereoselective (>96% *de*) as it occurs through a closed chair-like Zimmerman-Traxler transition state with bond formation on the same face as the C–B bond.[21] Indeed, no diastereomer was observed in this allylboration reaction. The allylic boronate **5** should not be prone to thermally induced epimerization or allylic migration because the thermal boratropic [1,3]-rearrangement of allylic pinacol esters is known to occur only at elevated temperatures over 150 °C.[21] As expected, the heat source did not affect the yield or *ee* of the product **7** (entries 4-7). Our next objective was to decrease the reaction temperature. Much to our delight, the reaction underwent a full conversion at rt after 16 h, however, only under neat conditions (entry 8).

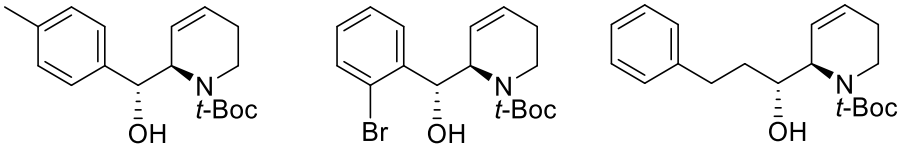
Because the use of solvent is essential with solid aldehyde substrates, the scope of aldehydes at a substrate concentration of 1 M in toluene was investigated (Table 2-6). Under these conditions, allylboration with the model aldehyde gave a full conversion at ambient temperature after 16 h (entry 1). The same reaction conditions were successfully applied to provide product **38** (entry 2). When compared to the results obtained using the previous, un-optimized borylative migration procedure, allylborations with hydrocinnamaldehyde and *trans*-cinnamaldehyde gave improved yields and *ee*'s (entries 3-4).[4,13] Encouraged by these positive

results, we examined heteroaromatic aldehydes. To our satisfaction, these reactions required a shorter time to achieve full conversion (entries 5-6). Overall, the newly optimized conditions consistently led to higher yields under lower reaction temperature and a reduced amount of solvent compared to the previously optimized conditions.[4]

Table 2-6. Substrate scope of the aldehyde allylboration of **5**[a,d]



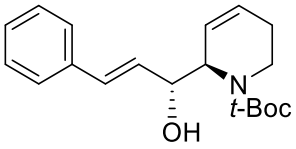
5 **7, 38-42**



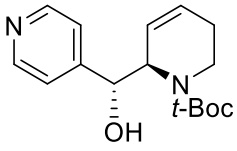
7

38

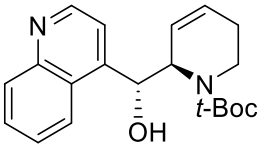
39



40



41



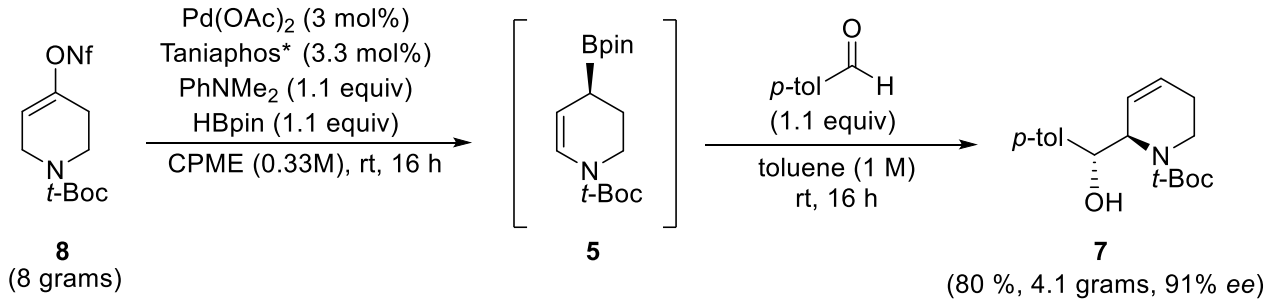
42

Entry	Reaction time (h)	Product	Yield[b] (%)	*ee*[c] (%)
1	16	**7**	70	92
2	16	**38**	70	90
3	16	**39**	70	90
4	16	**40**	71	90
5	3	**41**	70	94
6	3	**42**	72	91

[a] Scale of reactions: 0.5 mmol. [b] Isolated yield of **7**, **38**−**42** after flash chromatography. [c] Determined by chiral HPLC of **7**, **38**−**42**. [d] *de*'s of **7, 38**−**42** were >96% and determined by crude ^{1}H NMR.

With this newly optimized thermal aldehyde allylboration in hand, we attempted a multi-gram scale sequence of the catalytic enantioselective borylative migration-aldehyde allylboration

(Scheme 2-22). Using eight grams (17 mmol) of alkenyl nonaflate **8** and 3 mol% of the catalyst, product **7** was obtained in 4.1 grams (80% yield) with an *ee* of 91%, which was comparable to that obtained on much smaller reaction scales (0.25 to 1 mmol). The purification process of the large scale reaction was identical to that of the small scale reaction: the allylic boronate **5** was quickly pre-purified via a filtration through a short pad of silica gel, followed by concentration of solvent. The resulting residue was immediately subjected to the aldehyde allylboration reaction to avoid decomposition. The crude product **7** was then purified directly via silica column chromatography. During this purification, the major side-product, alkenyl boronate **6**, was easily removed to give the desired pure product **7**.



8
(8 grams)

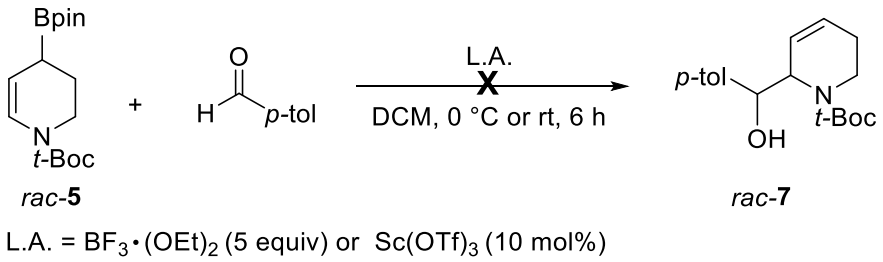
5

7
(80 %, 4.1 grams, 91% *ee*)

Scheme 2-22. Multi-gram scale catalytic enantioselective borylative migration-aldehyde allylboration sequence

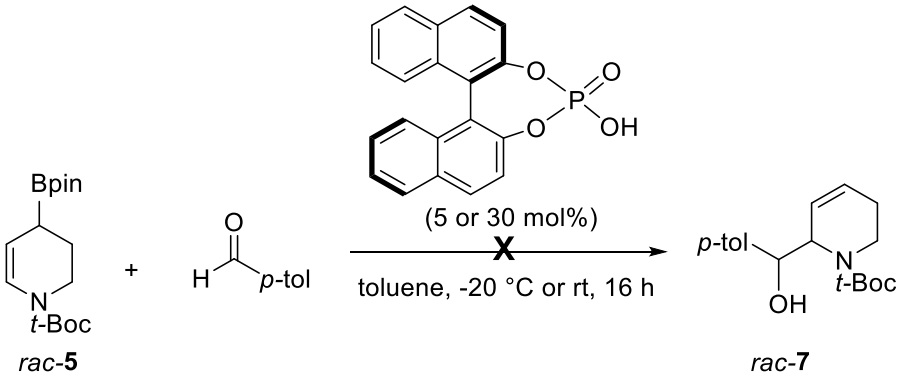
2.5.2. Aldehyde allylboration with alternative conditions

In an effort to identify alternative conditions that can afford the allylboration products in even higher yields, we decided to screen several reagents which are commonly used as catalysts in allylboration reactions.[21-25] The use of Lewis acid catalysts, such as $BF_3{\cdot}(OEt)_2$ and $Sc(OTf)_3$, was attempted either at 0 or 25 °C (Scheme 2-23).[22,23] As seen previously by our laboratory's former student, Stéphanie Lessard, these Lewis acid conditions led to decomposition of the starting allylic boronate *rac*-**5**.[13]



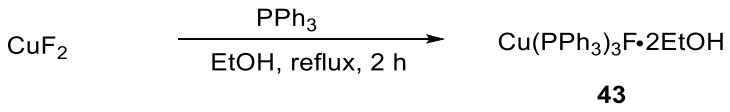
Scheme 2-23. Aldehyde allylboration with Lewis acid catalysis

Brønsted acid catalysis using (*R*)-BINOL phosphoric acid was also examined.[24] However, this type of catalysis was ineffective towards our aldehyde allylboration; allylic boronate *rac*-**5** remained unreacted even with the addition of 30 mol% (*R*)-BINOL phosphoric acid (Scheme 2-24).

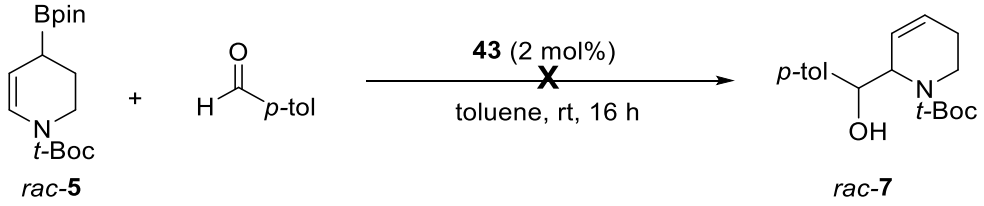


Scheme 2-24. Aldehyde allylboration with (*R*)-BINOL phosphoric acid as a Brønsted acid catalyst

Finally, the copper-catalyzed allylboration conditions developed by Shibasaki and co-workers in 2004 were attempted for our aldehyde allylboration.[25] Synthesis of the copper catalyst **43** was reproduced smoothly according to the literature (Scheme 2-25).[25] Unfortunately, this copper catalyst did not induce allylboration with our rather unreactive allylic boronate *rac*-**5** (Scheme 2-26).



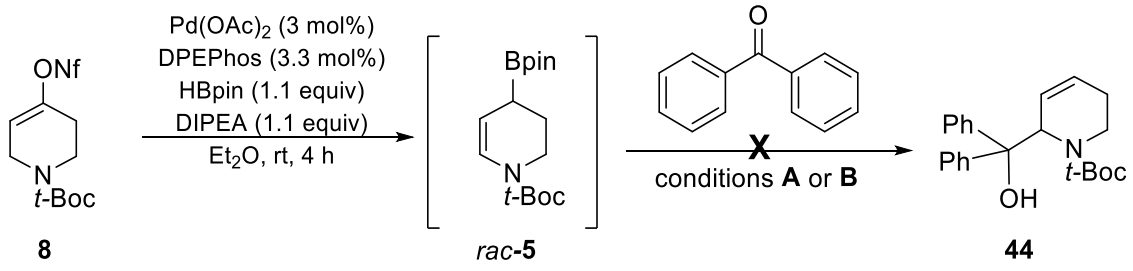
Scheme 2-25. Synthesis of copper catalyst **43** for aldehyde allylboration



Scheme 2-26. Copper-catalyzed aldehyde allylboration of allylic boronate *rac*-**5**

2.5.3. Preliminary attempts of the ketone allylboration reaction

Expanding the allylboration partner to ketones would make our allylic boronate substrate even more appealing in drug discovery. Because piperidinyl allylic boronate *rac*-**5** was believed to be insufficiently reactive for allylboration reactions with ketones; therefore, we decided to attempt this reaction with either an extended reaction time under heat or Brønsted acid catalysis (Scheme 2-27).[26] Unfortunately, allylic boronate *rac*-**5** did not react with benzophenone even after 2 d of heating at 100 °C under neat conditions. Treatment with (*R*)-BINOL did not lead to any conversion of the starting *rac*-**5**.



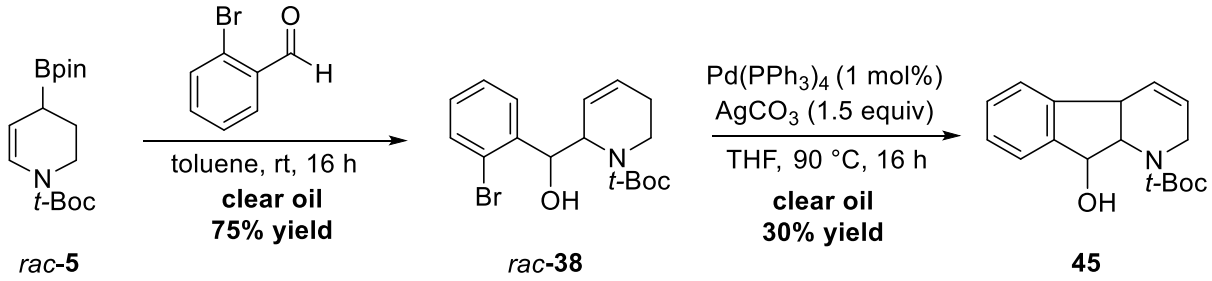
conditions **A** = neat, 100 °C, 2 d
conditions **B** = (R)-BINOL, ^{t}BuOH, 100 °C, 2 d

Scheme 2-27. Ketone allylboration of allylic boronate *rac*-**5** with benzophenone

2.5.4. Further application of the aldehyde allylboration reaction

While seeking for a further application of the catalytic borylative migration-aldehyde allylboration sequence, we realized the possibility of an intramolecular Heck reaction of the allylboration product **38** (Scheme 2-28). This product was subjected to standard Heck reaction conditions to afford the desired tricyclic *α*-hydroxyalkyl dehydropiperidine **45** as a clear oil in 30% yield.[27]

This preliminary work will be examined further in the future for yield optimization and an expansion of substrate scope. In addition, chiral, optically enriched **38** will be employed for the formation of the corresponding enantiomerically enriched tricyclic *α*-hydroxyalkyl dehydropiperidine.



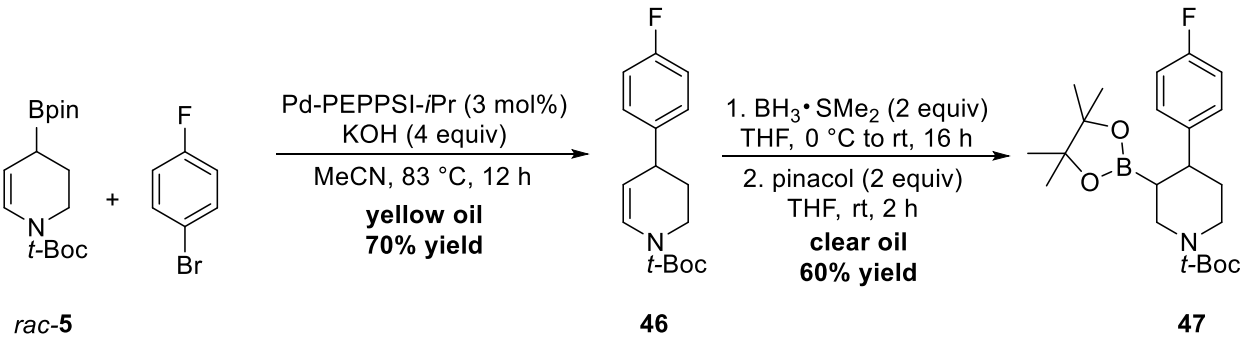
Scheme 2-28. Borylative migration-aldehyde allylboration-intramolecular Heck sequence for the formation of tricyclic *α*-hydroxyalkyl dehydropiperidine **45**

2.6. Synthesis of [3,4]-biaryl-piperidine derivatives via sequential Suzuki-Miyaura cross-coupling reactions

Transition-metal catalyzed cross-coupling reactions are one of the most versatile methods for the formation of a new C-C bond, comprising over 60% of all C-C bond forming reactions performed by medicinal chemists.[28] In this class of processes, the Suzuki-Miyaura cross-coupling reaction has become a fundamental method in drug industry due to the following advantages:

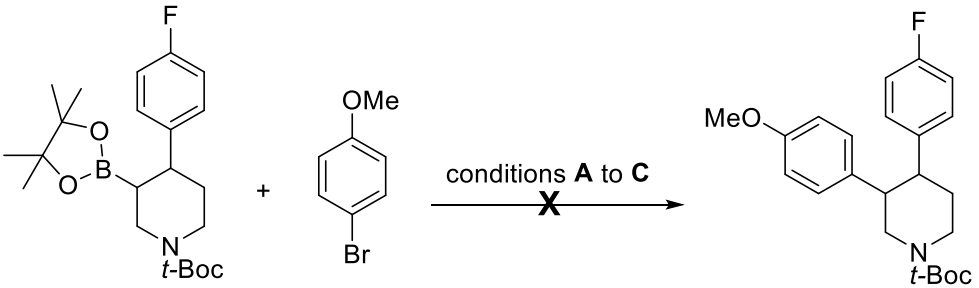
mild reaction conditions, good functional group tolerance, and use of stable reagents.[29]

In 2014, our laboratory reported the synthesis of (+)-paroxetine via the Suzuki-Miyaura cross-coupling using chiral allylic boronate **5** prepared from the catalytic enantioselective borylative migration.[3] Inspired by this process, we envisioned the installment of another aryl group via a subsequent Suzuki-Miyaura cross-coupling reaction to obtain [3,4]-biaryl-piperidine derivatives. To test our idea, we first synthesized the starting material **46** from racemic allylic boronate *rac*-**5**, which was then subjected to Suzuki-Miyaura cross-coupling conditions, followed by a standard hydroboration (Scheme 2-29).



Scheme 2-29. Synthesis of the starting material **47** for the sequential Suzuki-Miyaura cross-coupling reactions

The synthesized pinacol boronate **47** was subjected to several established Suzuki-Miyaura reaction conditions: conditions **A** developed by Crudden and co-workers in 2009, utilizing Ag_2O as a base;[30] conditions **B** reported by Organ and co-workers in 2012 with their signature Pd-PEPPSI-*i*Pr catalyst;[31] and conditions **C** reported in 2009 by Molander and co-workers,[32] and subsequently adapted by the Huang Group in 2014 (Scheme 2-30).[33] Unfortunately, none of these conditions afforded the desired [3,4]-biaryl product. This outcome was somewhat expected due to the challenges associated with secondary alkyl cross-coupling reactions, such as facile *β*-hydride elimination and slow transmetalation.[28] Substrate **47** may be too sterically crowded to be functionalized vicinal to the existing aryl group.

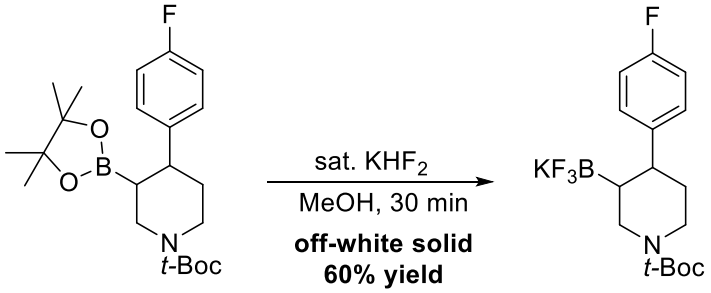


47 **48**

conditions **A** = $Pd_2(dba)_3$, PPh_3, Ag_2O
conditions **B** = Pd-PEPPSI-*i*Pr, KOH
conditions **C** = $Pd(OAc)_2$, RuPhos, KO^tBu

Scheme 2-30. Suzuki-Miyaura cross-coupling reactions of pinacol boronate **47**

Afterwards, pinacol boronate **47** was converted to the corresponding alkyltrifluoroborate salt **49** to try the more recently reported Suzuki-Miyaura cross-coupling conditions (Scheme 2-31).[28,32,34,35,36]

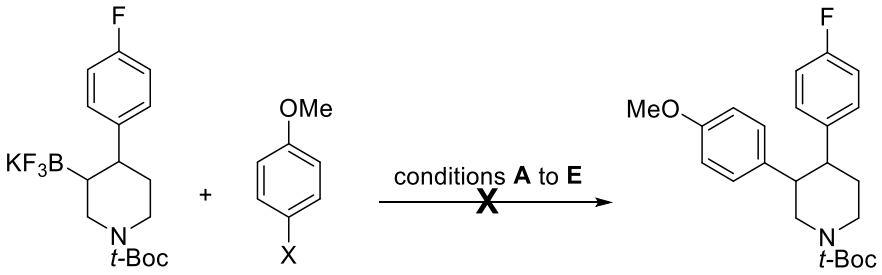


47 **49**

Scheme 2-31. Conversion of pinacol boronate **47** to alkyltrifluoroborate salt **49**

The resulting alkyltrifluoroborate salt **49** was subjected to a number of reported Suzuki-Miyaura cross-coupling conditions by Molander and co-workers: conditions **A** were standard conditions reported in 2003;[34] conditions **B** reported in 2009 featured the use of RuPhos as a ligand;[32] and conditions **C** utilized a more advanced catalyst, CataCXium A-Pd-G2 (conditions **A-C**, Scheme 2-32).[35] In 2015, Molander and co-workers reported an Ir-induced single-electron-mediated alkyl transfer for Ni(0)-catalyzed cross-coupling reactions of secondary alkyltrifluoroborate salts with aryl bromides (conditions **D**, Scheme 2-32).[28] This method was the

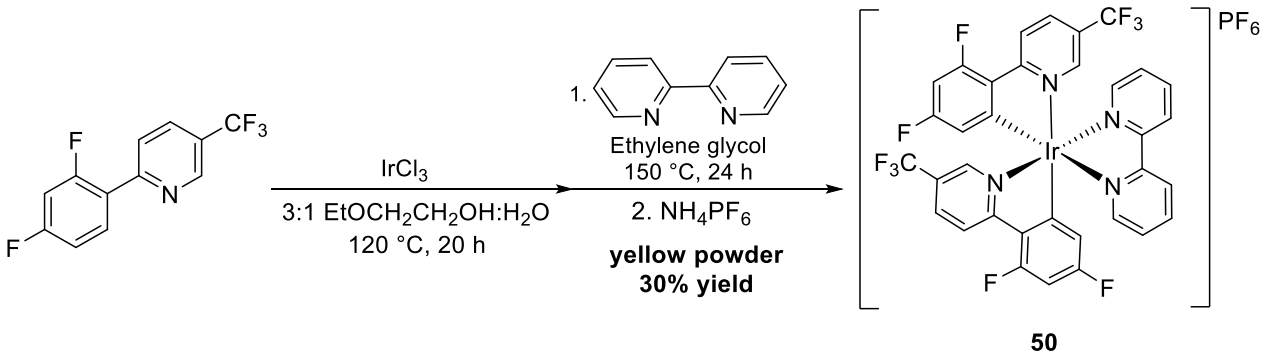
most promising because radical chemistry should be more suitable for our hindered substrate **49**. Prior to cross-coupling reaction, Ir-photoredox catalyst **50** was first synthesized as described in Scheme 2-33.[28] Finally, a method reported by Biscoe and co-workers in 2014 was attempted with our substrate **49** (conditions **E**, Scheme 2-32).[36] This method described a stereospecific Pd-catalyzed cross-coupling reaction of secondary alkylboron nucleophiles with aryl chlorides.[36] The authors employed the Buchwald precatalyst **51**, which was activated by K_2CO_3 under heat. Synthesis of **51** is described in Scheme 2-34.[36] Unfortunately, this and other cross-coupling conditions reported by Molander and co-workers were not effective towards our substrate **49**, which remained unreactive under all of the above reaction conditions. These failures highlight some of the continuing challenges in the area of sp^2-sp^3 Suzuki-Miyaura cross-coupling reactions.



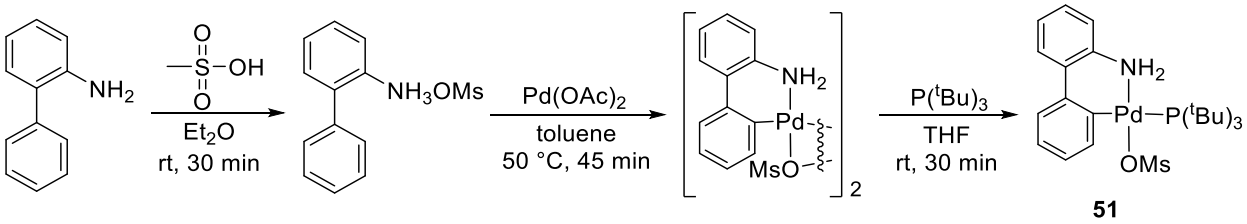
49 X = Cl or Br **48**

conditions **A** = $PdCl_2(dppf)$, Cs_2CO_3
conditions **B** = $Pd(OAc)_2$, RuPhos, K_2CO_3
conditions **C** = CataCXium A-Pd-G2, $CsOH{\bullet}H_2O$
conditions **D** = Ir-photocatalyst **50**, $NiCl_2{\bullet}$DME/dtbbpy, Cs_2CO_3
conditions **E** = Buchwald pre-catalyst **51**, K_2CO_3

Scheme 2-32. Suzuki-Miyaura cross-coupling reactions of alkyltrifluoroborate salt **49**



Scheme 2-33. Synthesis of Ir-photoredox catalyst **50**



Scheme 2-34. Synthesis of Buchwald precatalyst **51**

2.7. Conclusions

Chapter 2 describes the extensive optimization of the Pd-catalyzed enantioselective borylative migration of an alkenyl nonaflate derivative of the simple precursor, *N*-Boc-4-piperidone. The current reaction conditions of the catalytic enantioselective borylative migration developed in 2009[4] presented several limitations: lower than desired *ee* and yields, use of peroxide-forming dioxane as the solvent, higher than desired catalyst loading (5 mol%), low reaction concentration (0.063 M), and reproducibility issues. Several parameters, including the nature of the alkenylsulfonate and the *N*-protecting group of the substrate, the source and stoichiometry of palladium and diphosphine ligand, solvent, reaction concentration, temperature, and time, were examined in order to troubleshoot these aforementioned limitations and identify a more robust, industry-friendly reaction procedure. As a result, enantiomerically enriched allylboration product **7** was provided reliably on a multi-gram scale in 80% yield, 91% *ee*.

Mechanistic studies were conducted in an effort to validate the previously proposed mechanism of the borylative migration reported in 2009.[4] To support the experimental observations, computational work by a collaboration with Prof. Claude Legault from the University of Sherbrooke is ongoing.

Finally, the following applications of the borylative migration were explored: aldehyde allylboration, intramolecular Heck reaction, and the sequential Suzuki-Miyaura cross-coupling reactions.

2.8. Experimental

2.8.1. General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF and toluene were purified using a MBraun MB SPS* solvent system. Dioxane was distilled over sodium. Diethyl ether (Et_2O) was distilled over sodium/benzophenone ketyl. Anhydrous chlorobenzene, cyclopentyl methyl ether (CPME), methyl *tert*-butyl ether (MTBE), dibutyl ether, 2-methyltetrahydrofuran (2-MeTHF), and diglyme were purchased from Sigma-Aldrich and used as received. *N,N*-Diisopropylethylamine (DIPEA) and *N,N*-dimethylaniline (DMA) were purchased from Sigma-Aldrich and distilled over potassium hydroxide prior to use. Pinacolborane and 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) were purchased from Oakwood Products and Sigma-Aldrich, respectively, and were used without further purification. 1-*tert*-Butoxycarbonyl-4-piperidone, 1-carbobenzoxy-4-piperidone, 1-benzyl-4-piperidone, and perfluorobutanesulfonyl fluoride (NfF) were purchased from Combi-Blocks Inc. and were used without further purification. All aldehydes were purified by a bulb-to-bulb distillation under reduced pressure. Palladium(II) acetate, allylpalladium(II) chloride dimer, tris(dibenzylideneacetone)dipalladium(0), DPEphos, Taniaphos, and Walphos were purchased from Strem Chemicals. All other palladium catalysts and ligands were purchased from Sigma-

Aldrich. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and visualized with UV light, p-anisaldehyde stain, and $KMnO_4$ stain. Flash column chromatography was performed on ultra-pure silica gel 230-400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 or INOVA-500 instruments. The residual solvent protons (^1H) and the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; app s, apparent singlet; t, triplet; app t, apparent triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. Reported *J*-values are deemed accurate within ± 0.3 Hz. NMR data were processed either using VnmrJ from Agilent Technologies or MestReNova from Mestrelab Research. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electrospray ionization (ESI) method. Infrared spectra were obtained from a Nicolet Magna-IR machine with frequencies expressed in cm^{-1}. Optical rotations were measured using a 1 mL cell with a 1 dm length on a P.E. 241 polarimeter. Regioselectivity of alkenyl to allyl boronate and the diastereomeric ratios for chiral compounds were determined by integration of relevant signals on the crude ^1H NMR spectra. The enantiomeric excess ratios for optically enriched compounds were determined using a HPLC Agilent instrument with a Chiralcel-OD or IB or IC column as specified in the following individual procedures.

2.8.2. Experimental details of the borylative migration reaction

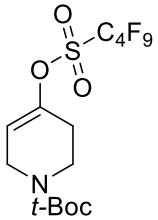
Pinacolborane received in a bottle was transferred to a round bottom flask under a nitrogen atmosphere and stored in a freezer. DIPEA and DMA were distilled over potassium hydroxide under a nitrogen atmosphere and stored in a refrigerator. The synthesized alkenyl nonaflates were transferred to vials after purification and stored in a refrigerator. Prior to the borylative

migration reaction, pinacolborane, the base, and the alkenyl nonaflate were allowed to warm up to room temperature (ca. 20 min). Ultrapure (99.95+%) $Pd(OAc)_2$ was used. All of the phosphine ligands were checked for oxidation via ESI-ToF technique prior to use. Palladium and ligand were weighed out carefully and transferred to a reaction flask, which was evacuated and back-filled with nitrogen three times. Due to its instability to a prolonged exposure to air and silica gel, freshly-made crude allylic boronate was filtered through a silica plug (silica gel to crude product, 100/1, w/w) very quickly (ca. 30 seconds) and subjected to the allylboration reaction directly after concentration of solvent. The major side product, alkenyl boronate, was removed during the purification of final products, α-hydroxyalkyl dehydropiperidines.

2.8.3. General procedure and spectral data for piperidinyl alkenyl nonaflates

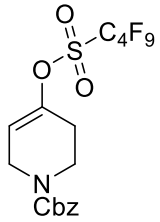
N-Protected piperidone (10 mmol, 1.0 equiv) was dissolved in THF (50 mL) under a nitrogen atmosphere. The mixture was cooled in an ice-water bath (0 °C) and stirred for 5 min. DBU (1.8 mL, 12 mmol, 1.2 equiv) and perfluorobutanesulfonyl fluoride (2.2 mL, 12 mmol, 1.2 equiv) were added respectively and the resulting solution was stirred for 10 min. The reaction was then allowed to warm up to rt and stirred for 16 h. The reaction was quenched with a slow addition of water (50 mL) and extracted with EtOAc (3 × 60 mL). The organic layers were combined and washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The brown oil was then purified by flash column chromatography (50% Et_2O/pentane or 10% EtOAc/hexane).

tert-Butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dhydropyridine-1(_2H_)-carboxylate (8)



A colorless oil (4.6 g, 95% yield) was obtained according to the general procedure using 1-(*tert*-butoxycarbonyl)-4-piperidone (2.0 g, 10 mmol, 1.0 equiv) as a substrate. Spectral data correspond to that reported.[8]

Benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (9)



A light-yellow oil (4.6 g, 89% yield) was obtained according to the general procedure using 1-carbobenzoxy-4-piperidone (2.3 g, 10 mmol, 1.0 equiv) as a substrate.

R_f = 0.41 (15% EtOAc/hexane);

^{1}H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 7.39 – 7.32 (m, 5 H), 5.82 – 5.75 (m, 1 H), 5.16 (s, 2 H), 4.14 (app s, 2 H), 3.72 (app s, 2 H), 2.47 (app s, 2 H);

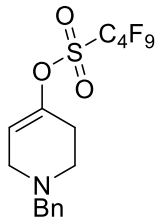
^{13}C NMR (100 MHz, $CDCl_3$, ^{19}F decoupled, 60 °C) *δ* (ppm) 155.1, 147.0, 136.5, 128.7, 128.3, 128.1, 115.8, 115.4, 114.5, 110.1, 108.7, 67.8, 42.1, 40.8, 28.2;

^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled, 60 °C) –80.8, –109.4, –120.6, –125.5;

IR (Microscope, cm^{-1}) 3035, 2957, 1711, 1423, 1353, 1280;

HRMS (ESI-ToF) for $C_{17}H_{14}F_9NNaO_5S$ ($M + Na^+$): calcd. 538.0341; found 538.0337;

1-(Benzyl)-4-[(nonafluorobutanesulfonyl)oxy]-1,2,3,6-tetrahydropyridine (13)



A yellow oil (4.3 g, 91% yield) was obtained according to the general procedure using 1-benzyl-4-piperidone (1.9 mL, 10 mmol, 1.0 equiv) as a substrate.

R_f = 0.56 (15% EtOAc/hexane);

^{1}H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 7.35 – 7.27 (m, 5 H), 5.75 – 5.73 (m, 1 H), 3.64 (s, 2 H), 3.15 – 3.13 (m, 2 H), 2.73 (t, *J* = 5.7 Hz, 2 H), 2.46 – 2.45 (m, 2 H);

^{13}C NMR (100 MHz, $CDCl_3$, ^{19}F Dec) *δ* (ppm) 147.5, 137.7, 129.0, 128.5, 127.4, 117.1, 116.3, 114.2, 109.9, 108.5, 61.3, 50.5, 49.1, 28.4;

^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled) –80.8, –110.1, –121.1, –126.0;

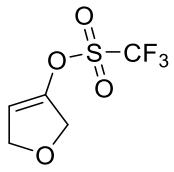
IR (Microscope, cm^{-1}) 3031, 2926, 2806, 1699, 1454, 1421;

HRMS (ESI-ToF) for $C_{16}H_{15}F_9NO_3S$ $(M + H)^+$: calcd. 472.0623; found 472.0618;

2.8.4. General procedure and spectral data for piperidinyl alkenyl triflates

Ketone (1.0 mmol, 1.0 equiv) was dissolved in THF (5 mL) under a nitrogen atmosphere. The mixture was cooled in an acetone/dry-ice bath (−78 °C) and stirred for 5 min. LiHMDS (1 M in THF) (1.2 mL, 1.2 mmol, 1.2 equiv) and phenyl triflimide (0.43 g, 1.2 mmol, 1.2 equiv) were added respectively and the resulting solution was stirred for 2 h. The reaction was quenched with a slow addition of water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic layers were combined and washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The brown oil was then purified by flash column chromatography (50% Et_2O/pentane or 10% EtOAc/hexane).

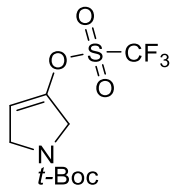
2,5-Dihydrofuran-3-yl-trifluoromethanesulfonate (19)



The title compound (**19**) was synthesized by the general procedure using 3-oxotetrahydrofuran

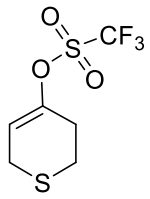
(86 mg, 1.0 mmol, 1.0 equiv). The product was obtained as a clear oil (55 mg, 25% yield) after flash column chromatography. Spectral data correspond to that reported.[12]

***tert*-Butyl 3-(trifluoromethanesulfonyloxy)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (20)**



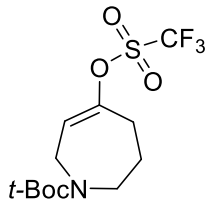
The title compound (**20**) was synthesized by the general procedure using *N*-Boc-3-pyrrolidinone (185 mg, 1.00 mmol, 1.00 equiv). The product was obtained as a clear oil (95 mg, 30% yield) after flash column chromatography. Spectral data correspond to that reported.[13]

3,6-Dihydro-2*H*-thiopyran-4-yl-trifluoromethanesulfonate (22)



The title compound (**22**) was synthesized by the general procedure using tetrahydro-4*H*-thiopyran-4-one (116 mg, 1.00 mmol, 1.00 equiv). The product was obtained as a yellow oil (129 mg, 52% yield) after flash column chromatography. Spectral data correspond to that reported.[14]

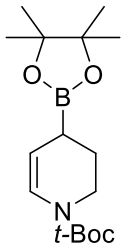
***tert*-Butyl 5-(trifluoromethanesulfonyloxy)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (24)**



The title compound (**24**) was synthesized by the general procedure using *N*-Boc-hexahydro-1*H*-azepin-2-one (213 mg, 1.00 mmol, 1.00 equiv). The product was obtained as a clear oil (242 mg, 70% yield) after flash column chromatography. Spectral data correspond to that reported.[15]

2.8.5. Experimental procedure for racemic allylic boronate

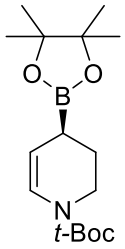
***tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(*2H*)-carboxylate (*rac*-5)**



Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and DPEPhos (18 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with N_2 three times. Et_2O (3 mL) was added and the mixture was stirred for 15 min. DIPEA (192 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (25% Et_2O/pentane or 5% EtOAc/hexane) providing a colorless oil (155 mg, 56% yield). Spectral data correspond to that reported.[4] Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ^1H NMR spectrum was 15:85.

2.8.6. Experimental procedure and spectral data for optically enriched allylic boronate

(4*S*)-*tert*-Butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(*2H*)-carboxylate (5)



Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and purified by flash column chromatography (25% Et_2O/pentane or 5% EtOAc/hexane) providing a colorless oil (155 mg, 50% yield). Spectral data correspond to that reported.[4] Regioselectivity of alkenyl to allyl boronic ester determined by integration of relevant signals on the crude ^{1}H NMR spectrum was 1:4.

2.8.7. General procedure for racemic α-hydroxyalkyl dehydropiperidines

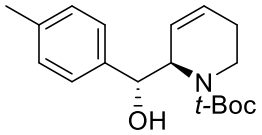
Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and DPEPhos (18 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 15 min. DIPEA (192 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The

mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and transferred to a pre-dried 5 mL round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under a nitrogen atmosphere for 3 or 16 h as specified in the following individual procedures. The mixture was purified directly by flash column chromatography.

2.8.8. General procedure and spectral data for optically enriched α-hydroxyalkyl dehydropiperidines

Palladium (II) acetate (6.7 mg, 0.030 mmol, 0.030 equiv) and (+)-TANIAPHOS (23 mg, 0.033 mmol, 0.033 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar, which was then evacuated and backfilled with nitrogen three times. Et_2O (3 mL) was added and the mixture was stirred for 30 min. DMA (140 µL, 1.10 mmol, 1.10 equiv), pinacolborane (160 µL, 1.10 mmol, 1.10 equiv), and alkenyl nonaflate (1.0 mmol, 1.0 equiv) were respectively added. The mixture was stirred at rt for 16 h. The solvent was concentrated *in vacuo*, followed by a quick filtration through a silica plug (100% Et_2O). The resulting mixture was concentrated *in vacuo* and transferred to a pre-dried 5 mL round bottom flask using dry toluene (1 mL). The flask was flushed with nitrogen and aldehyde (1.1 mmol, 1.1 equiv) was added. The solution was stirred at rt under nitrogen for 3 or 16 h. The mixture was purified directly by flash column chromatography.

(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(*p*-tolyl)methyl]-5,6-dihydropyridine-1(2*H*)-carboxylate (7)



The title compound (**7**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00

equiv) and *p*-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (213 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane or 10 % EtOAc/hexane).

R_f = 0.50 (20% EtOAc/hexane);

$[\alpha]^{20}_D$ + 135.0 (*c* 1.00, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) rotamers are present: *δ* (ppm) 7.25 – 7.23 (m, 2 H), 7.17 – 7.15 (m, 2 H), 5.89 – 5.81 (m, 1 H), 5.34 – 5.17 (m, 1 H), 4.63 – 4.53 (m, 2 H), 4.18 – 3.85 (m, 1 H), 3.04 – 2.78 (m, 1 H), 2.34 (s, 3 H), 2.22 – 2.17 (m, 1 H), 1.95 – 1.90 (m, 1 H), 1.49 (s, 9 H);

^{1}H NMR (400 MHz, $CDCl_3$, 65 °C) *δ* (ppm) 7.24 (d, *J* = 8.0 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 5.85 – 5.81 (m, 1 H), 5.30 – 5.28 (m, 1 H), 4.63 – 4.62 (m, 2 H), 4.13 – 4.09 (m, 1 H), 2.92 – 2.86 (m, 1 H), 2.34 (s, 3 H), 2.18 – 2.14 (m, 1 H), 1.95 – 1.89 (m, 1 H), 1.49 (s, 9 H);

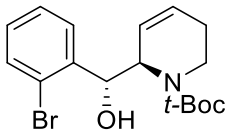
^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) *δ* (ppm) 156.8, 138.6, 137.6, 129.1, 127.1, 125.1, 80.5, 76.4, 58.5, 37.9, 28.5, 24.8, 21.1;

IR (Microscope, cm^{-1}) 3060, 2975, 2930, 1644, 1611, 1512, 1250;

HRMS (ESI-ToF) for $C_{18}H_{25}NNaO_3$ $(M + Na)^+$: calcd. 326.1727; found 326.1724;

HPLC (Chiralcel OD): 3.8% *i*-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 19.6 min, T_{minor} = 17.3 min; 92% *ee*; >96% *de*;

(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(*o*-bromophenyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (38)



The title compound (**38**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 2-bromobenzaldehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed

for 16 h. The product was obtained as a colorless oil (258 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane or 10 % EtOAc/hexane).

R_f = 0.49 (20% EtOAc/hexane);

$[\alpha]^{20}_D$ + 50.5 (*c* 1.42, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$, 65 °C) *δ* (ppm) 7.57 (app d, *J* = 7.7 Hz, 1 H), 7.51 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.33 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.13 (app td, *J* = 7.7, 1.8 Hz, 1 H), 5.97 – 5.91 (m, 1 H), 5.41 – 5.35 (m, 1 H), 5.25 (d, *J* = 6.7 Hz, 1 H), 4.73 – 4.72 (m, 1 H), 4.21 – 4.14 (m, 1 H), 3.16 – 3.09 (m, 1 H), 2.21 – 2.19 (m, 1 H), 2.01 – 1.94 (m, 1 H), 1.39 (s, 9 H);

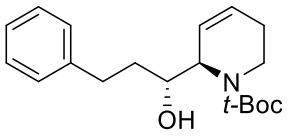
^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) *δ* (ppm) 156.0, 140.7, 132.7, 129.1, 129.0, 128.0, 127.7, 124.7, 123.3, 80.3, 75.1, 57.5, 38.2, 28.4, 24.8;

IR (Microscope, cm^{-1}) 3427, 3028, 2976, 2929, 1670, 1592, 1454;

HRMS (ESI-ToF) for $C_{17}H_{23}BrNO_3$ $(M + H)^+$: calcd. 368.0856; found 368.0850;

HPLC (Chiralcel OD): 3.8% *i*-PrOH/hexane, 6 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 26.5 min, T_{minor} = 19.3 min; 90% *ee*; >96% *de*;

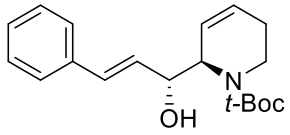
(*R*)-*tert*-Butyl 2-[(*R*)-1-hydroxy-3-phenylpropyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (39)



The title compound (**39**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and hydrocinnamaldehyde (145 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a yellow oil (222 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane or 10 % EtOAc/hexane). Spectral data correspond to that reported.[4]

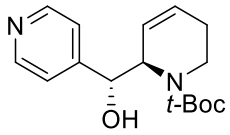
HPLC (Chiralcel OD): 10% *i*-PrOH/hexane, 25 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 12.2 min, T_{minor} = 9.4 min; 90% *ee*, >96% *de*;

***trans*-(*R*)-*tert*-Butyl 2-[(1*R*)-hydroxy-3-phenylallyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (40)**



The title compound (**40**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and hydrocinnamaldehyde (145 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a yellow oil (224 mg, 71% yield) after flash column chromatography (50% Et_2O/pentane or 10 % EtOAc/hexane). Spectral data correspond to that reported.[12]

(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(4-pyridyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (41)



The title compound (**41**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 4-pyridinecarboxaldehyde (104 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (206 mg, 71% yield) after flash column chromatography (100% EtOAc).

R_f = 0.27 (100% EtOAc);

$[\alpha]^{20}_D$ + 131.6 (*c* 1.07, $CHCl_3$);

^{1}H NMR (400 MHz, DMSO-d_6) rotamers are present: δ (ppm) 8.48 – 8.47 (m, 2 H), 7.25 – 7.23 (m, 2 H), 5.91 – 5.88 (m, 1 H), 5.71 – 5.66 (m, 2 H), 4.77 (app t, J = 4.8 Hz, 1 H), 4.52 – 4.41 (m, 1 H), 3.94 – 3.68 (m, 1 H), 2.71 – 2.62 (m, 1 H), 1.94 – 1.83 (m, 2 H), 1.33 – 1.21 (m, 9 H);

^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ (ppm) 8.48 (d, J = 5.8 Hz, 2 H), 7.25 (d, J = 5.8 Hz, 2 H), 5.89 – 5.88 (m, 1 H), 5.71 – 5.68 (m, 1 H), 5.45 – 5.43 (m, 1 H), 4.78 (app t, J = 4.8 Hz, 1 H), 4.51 (app s, 1 H), 3.87 – 3.83 (m, 1 H), 2.64 – 2.57 (m, 1 H), 1.96 – 1.91 (m, 1 H), 1.83 – 1.78 (m, 1 H), 1.32 (s, 9 H);

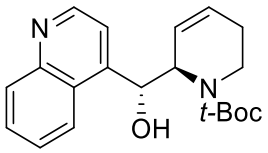
^{13}C NMR (100 MHz, DMSO-d_6, 80 °C) δ (ppm) 153.6, 151.0, 148.6, 126.7, 124.6, 121.8, 78.3, 72.5, 56.3, 37.2, 27.6, 23.7;

IR (Microscope, cm^{-1}) 3402, 3189, 2976, 2929, 1691, 1603, 1477, 1455;

HRMS (ESI-ToF) for $C_{16}H_{23}N_2O_3$ $(M + H)^+$: calcd. 291.1703; found 291.1707;

HPLC (Chiralcel IC): 50% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 254 nm, T_{major} = 6.3 min, T_{minor} = 14.2 min; 94% *ee*; >96% *de*;

(*R*)-*tert*-Butyl 2-[(*R*)-hydroxy(4-quinolinyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (42)



The title compound (**42**) was synthesized by the general procedure using *tert*-butyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**8**) (481 mg, 1.00 mmol, 1.00 equiv) and 4-quinolinecarboxaldehyde (173 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 3 h. The product was obtained as a colorless oil (245 mg, 72% yield) after flash column chromatography (100% EtOAc).

R_f = 0.44 (100% EtOAc);

$[\alpha]^{20}_D$ + 51.4 (*c* 1.56, $CHCl_3$);

^{1}H NMR (500 MHz, DMSO-d_6) rotamers are present: δ (ppm) 8.85 – 8.82 (m, 1 H), 8.26 – 8.11 (m, 1 H), 8.04 – 7.98 (m, 1 H), 7.74 – 7.71 (m, 1 H), 7.59 – 7.50 (m, 2 H), 5.98 – 5.80 (m, 2 H), 5.69 – 5.60 (m, 2 H), 4.71 – 4.59 (m, 1 H), 3.99 – 3.95 (m, 1 H), 3.18 – 3.12 (m, 1 H), 1.93 – 1.86 (m, 2 H), 1.30 – 0.67 (m, 9 H);

^{1}H NMR (500 MHz, DMSO-d_6, 115 °C) δ (ppm) 8.83 (d, J = 4.4 Hz, 1 H), 8.21 (d, J = 8.4 Hz, 1 H), 8.02 (d, J = 8.4 Hz, 1 H), 7.70 (dt, J = 7.6, 0.91 Hz, 1 H), 7.56 – 7.51 (m, 2 H), 5.92 – 5.89 (m, 1 H), 5.75 – 5.72 (m, 1 H), 5.59 (app t, J = 4.5 Hz, 1 H), 5.39 (app s, 1 H), 4.74 (app s, 1 H), 3.85 – 3.84 (m, 1 H), 2.73 (br s, 1 H), 2.01 – 1.93 (m, 1 H), 1.83 – 1.80 (m, 1 H), 1.12 (s, 9 H);

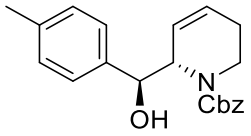
^{13}C NMR (125 MHz, DMSO-d_6, 115 °C) δ (ppm) 153.5, 149.0, 147.5, 147.4, 129.1, 127.9. 126.5, 125.7, 125.2, 125.0, 123.1, 119.0, 77.9, 69.4, 56.0, 36.9, 27.2, 23.5;

IR (Microscope, cm^{-1}) 3405, 3180, 3041, 2976, 2930, 1687, 1477;

HRMS (ESI-ToF) for $C_{20}H_{25}N_2O_3$ $(M + H)^+$: calcd. 341.1860; found 341.1863;

HPLC (Chiralcel IC): 50% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 280 nm, T_{major} = 6.1 min, T_{minor} = 13.2 min; 90% *ee*; >96% *de*;

(*S*)-Benzyl 2-[(*R*)-hydroxy(*p*-tolyl)methyl]-5,6-dihydropyridine-1(*2H*)-carboxylate (12)



The title compound (**12**) was synthesized by the general procedure (modification: use of (−)-TANIAPHOS instead of (+)-TANIAPHOS) using benzyl-4-(nonafluorobutylsulfonyloxy)-5,6-dihydropyridine-1(*2H*)-carboxylate (**9**) (515 mg, 1.00 mmol, 1.00 equiv) and *p*-tolualdehyde (130 µL, 1.10 mmol, 1.10 equiv); allylboration was performed for 16 h. The product was obtained as a colorless oil (202 mg, 60% yield) after flash column chromatography (50% Et_2O/pentane or 10 % EtOAc/hexane).

R_f = 0.41 (20% EtOAc/hexane);

[α]$^{20}_{D}$ –109.1 (*c* 0.32, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) *δ* (ppm) 7.38 – 7.31 (m, 5 H), 7.31 – 7.12 (m, 4 H), 5.89 – 5.82 (m, 1 H), 5.41 – 5.38 (m, 1 H), 5.23 – 5.11 (m, 2 H), 4.70 – 4.67 (m, 2 H), 4.22 – 3.46 (m, 1 H), 3.03 – 2.83 (m, 1 H), 2.34 (s, 3 H), 2.23 – 2.20 (m, 1 H), 1.97 – 1.93 (m, 1 H);

^{1}H NMR (400 MHz, $CDCl_3$, 65 °C) *δ* (ppm) 7.39 – 7.29 (m, 5 H), 7.23 (app d, *J* = 7.9 Hz, 2 H), 7.14 (app d, *J* = 7.9 Hz, 2 H), 5.89 – 5.84 (m, 1 H), 5.36 – 5.34 (m, 1 H), 5.18 (s, 2 H), 4.68 – 4.66 (m, 2 H), 4.21 – 4.16 (m, 1 H), 2.98 – 2.90 (m, 1 H), 2.35 (s, 3 H), 2.27 – 2.17 (m, 1 H), 1.97 – 1.90 (m, 1 H);

^{13}C NMR (100 MHz, $CDCl_3$, 65 °C) *δ* (ppm) 156.8, 138.3, 137.8, 136.9, 129.2, 128.6, 128.1, 128.0, 127.1, 124.9, 76.2, 67.6, 58.7, 38.0, 24.8, 21.2;

IR (Microscope, cm^{-1}) 3438, 3031, 2921, 1697, 1515, 1431, 1391;

HRMS (ESI-ToF) for $C_{21}H_{23}NNaO_3$ $(M + Na)^+$: calcd. 360.1570; found 360.1567;

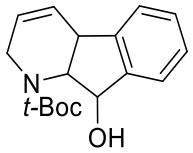
HPLC (Chiralcel IB): 5% *i*-PrOH/hexane, 20 °C, 0.5 mL/min, λ = 210 nm, T_{major} = 15.8 min, T_{minor} = 18.9 min; 90% *ee*; >96% *de*;

*2.8.9. Synthesis of the catalyst **43** for copper-catalyzed ketone allylboration*

$Cu(PPh_3)_3F•2EtOH$

A white powder (50 mg, 9% yield) was obtained according to the literature.[25] Spectral data correspond to that reported.[25]

*2.8.10. Experimental procedure for intramolecular Heck reaction of **38***



Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.100 mmol, 0.100 equiv), Ag_2CO_3 (414 mg, 1.50 mmol, 1.50 equiv), and *rac*-**38** (368 mg, 1.00 mmol, 1.00 equiv) were added to a pre-dried 25 mL round bottom flask. The apparatus was flushed with nitrogen. THF (10 mL) was added and the mixture was brought to a reflux and stirred for 24 h. The reaction was then cooled to rt and diluted with pentane (10 mL). The mixture was filtered through a silica plug (100% Et_2O), followed by concentration *in vacuo*. The yellow residue was purified by flash column chromatography (25% Et_2O/pentane). The title compound (**38**) was obtained as a clear oil (86 mg, 30% yield).

R_f = 0.51 (20% EtOAc/hexane);

^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ (ppm) 7.57 (app d, J = 9.7 Hz, 1 H), 7.51 (dd, J = 8.0, 1.2 Hz, 1 H), 7.33 (td, J = 7.6, 1.1 Hz, 1 H), 7.13 (app td, J = 7.8, 1.8 Hz, 1 H), 5.97 – 5.91 (m, 1 H), 5.24 (d, J = 6.7 Hz, 1 H), 4.73 – 4.72 (m, 1 H), 4.21 – 4.14 (m, 1 H), 3.16 – 3.09 (m, 1 H), 2.21 – 2.19 (m, 1 H), 2.01 – 1.94 (m, 1 H), 1.39 (s, 9 H);

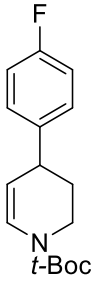
^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ (ppm) 156.0, 140.7, 132.7, 129.2, 129.0, 127.7, 124.7, 123.2, 80.2, 75.0, 57.5, 38.0, 28.4, 24.8;

IR (Microscope, cm^{-1}) 3423, 3029, 2976, 1689, 1671, 1454, 1423, 1391;

HRMS (ESI-ToF) for $C_{17}H_{21}NNaO_3$ $(M + Na)^+$: calcd. 310.1414; found 310.1408;

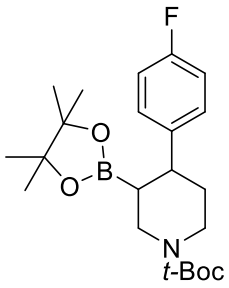
2.8.11. Syntheses of the starting materials and catalysts for sequential Suzuki-Miyaura cross-coupling reactions

***tert*-Butyl 4-(4-fluorophenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (46)**



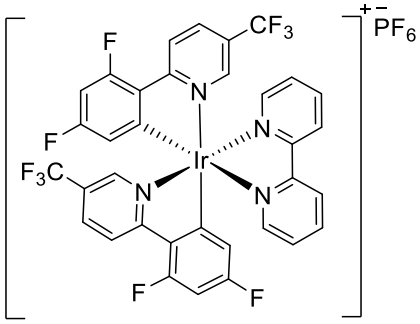
The title compound (**46**) was prepared according to the literature.[3] The product was obtained as a yellow oil (159 mg, 70% yield) after flash column chromatography (50% Et_2O/pentane). Spectral data correspond to that reported.[3]

***tert*-Butyl 4-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-piperidine-1-carboxylate (47)**



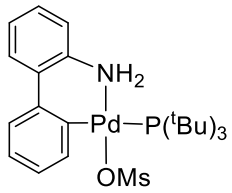
The title compound (**47**) was prepared according to the literature.[3] The product was obtained as a clear oil (243 mg, 60% yield) after flash column chromatography (50% Et_2O/pentane). Spectral data correspond to that reported.[3]

Ir-photoredox catalyst (50)



A yellow powder (115 mg, 30% yield) was obtained according to the literature.[28] Spectral data correspond to that reported.[28]

Buchwald precatalyst (51)



A yellow solid (310 mg, 68% yield) was obtained according to the literature.[36] Spectral data correspond to that reported.[36]

2.9. References

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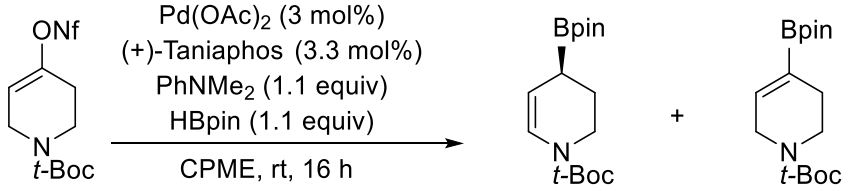
Chapter 3. Borylation of Alkenyl Dehydropiperidines

3.1. Introduction and objectives

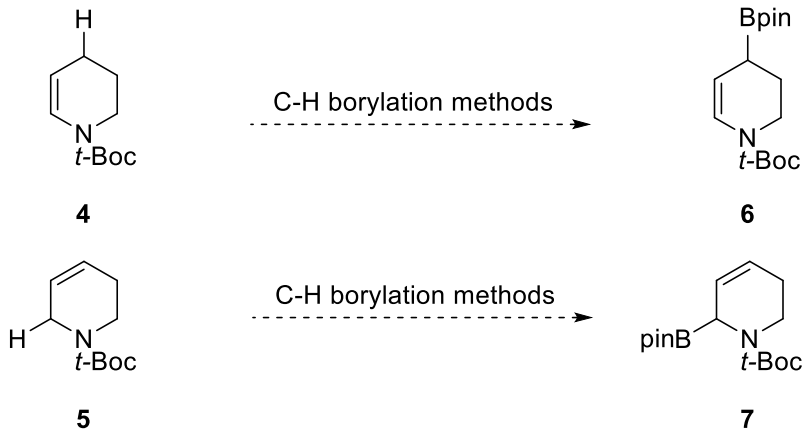
As discussed in Chapter 2, enantiomerically enriched piperidinyl allylic boronate **2** is a convenient precursor leading to chiral, optically enriched functionalized piperidine derivatives via several chemical transformations such as aldehyde allylboration or regio-controlled Suzuki-Miyaura cross-coupling.[1-3] Developing a more practical preparation of such piperidinyl allylic boronates is highly desirable in the pharmaceutical industry because piperidine derivatives are one of the most common heterocyclic units found in commercial pharmaceutical drugs.[4,5]

Although our laboratory's catalytic enantioselective borylative migration procedure re-optimized in Chapter 2 offers a single-step, industry-friendly preparation of enantiomerically enriched piperidinyl allylic boronate **2** from a simple piperidinyl alkenyl nonaflate **1** (Scheme 3-1),[1] we aimed to explore alternative approaches that could utilize other convenient piperidine precursors.



Scheme 3-1. Synthesis of enantiomerically enriched piperidinyl allylic boronate **2** via the catalytic enantioselective borylative migration

We envisaged the use of simple, commercial dehydropiperidines **4** and **5** as potential substrates towards forming piperidinyl allylic boronates **6** and **7** (Scheme 3-2). One of the possible synthetic transformations allowing the installation of a boryl group onto **4** and **5** is an allylic sp^3 C-H borylation process.

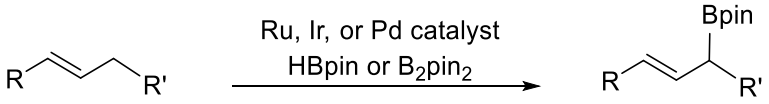


4 **6**

5 **7**

Scheme 3-2. Synthesis of **6** and **7** via borylation of simple dehydropiperidine precursors **4** and **5**

Transition metal-catalyzed C-H borylation is a step-economical synthetic approach leading to the formation of organoboronates (Scheme 3-3).[6-8] This method features relatively mild reaction conditions with high regioselectivity and utilizes commercially available pinacolborane (HBpin) or bis(pinacolato)diboron (B_2pin_2) as the boron source.[7] Relative to the field of sp^2 C-H borylation of aromatic and alkene precursors, sp^3 C-H borylation of alkyl precursors is rather under-developed, although there has been an increased number of publications in recent years.[7] Allylic sp^3 C-H borylation is particularly challenging because the desired allylic boronates easily rearrange to more thermodynamically stable alkenyl boronates. Attempts to convert dehydropiperidine precursors **4** and **5** to the corresponding borylated species using this method are described in Section 3-2.

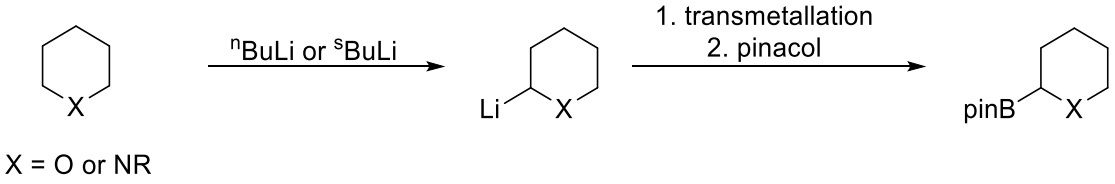


R, R' = alkyl

Scheme 3-3. General scheme of allylic sp^3 C-H borylation

Another borylation method considered was a sequential lithiation-transmetalation approach (Scheme 3-4).[9,10] This synthetic transformation is a formal two-step reaction:

deprotonation of the most acidic proton by a strong, organolithium base such as ^{n}BuLi or ^{s}BuLi,[9] followed by transmetalation with an organoborate reagent such as trimethyl borate.[10] Following hydrolytic work-up, the resulting boronic acid is condensed with pinacol to provide the desired organoboronate.[10] Attempts to use this chemistry to borylate the dehydropiperidine precursors **4** and **5** are described in Section 3-3.

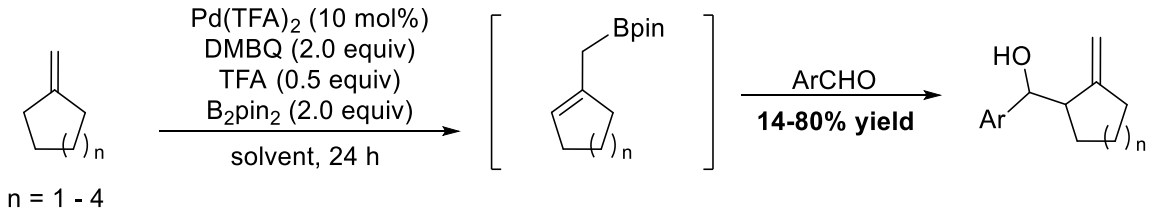


Scheme 3-4. General scheme of sequential lithiation-transmetalation of six-membered heterocycle

3.2. Synthesis of piperidinyl allylic boronate via C-H borylation methods

A recent example of C-H borylations of sp^3 substrates was reported by Szabo and co-workers in 2014 (Scheme 3-5).[7] Their substrates of choice, exocyclic alkene derivatives, were subjected to Pd-catalyzed sp^3 allylic C-H borylation conditions with air-stable, commercial B_2pin_2 as the boron source, followed by a subsequent addition onto aldehyde to afford the desired homoallylic alcohols.[7]

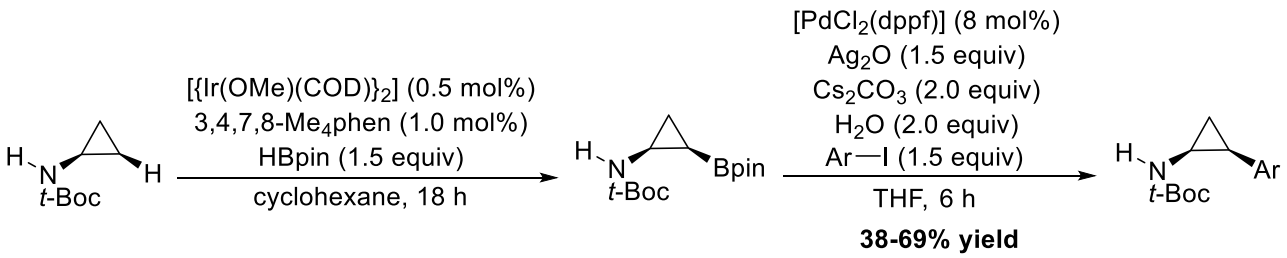
Szabo and co-workers in 2014[7]



Scheme 3-5. One-pot Pd-catalyzed allylic sp^3 C-H borylation of exocyclic alkene-addition onto aldehyde

An alternative to this Pd-catalyzed C-H borylation procedure is the Ir-catalyzed C-H borylation method reported by Itami and co-workers in 2015 (Scheme 3-6).[8] The authors employed this borylation method to afford borylated cyclopropylamines, which were transformed to biologically active 2-arylcyclopropylamines (ACPAs) via the Suzuki-Miyaura cross-coupling process.[8]

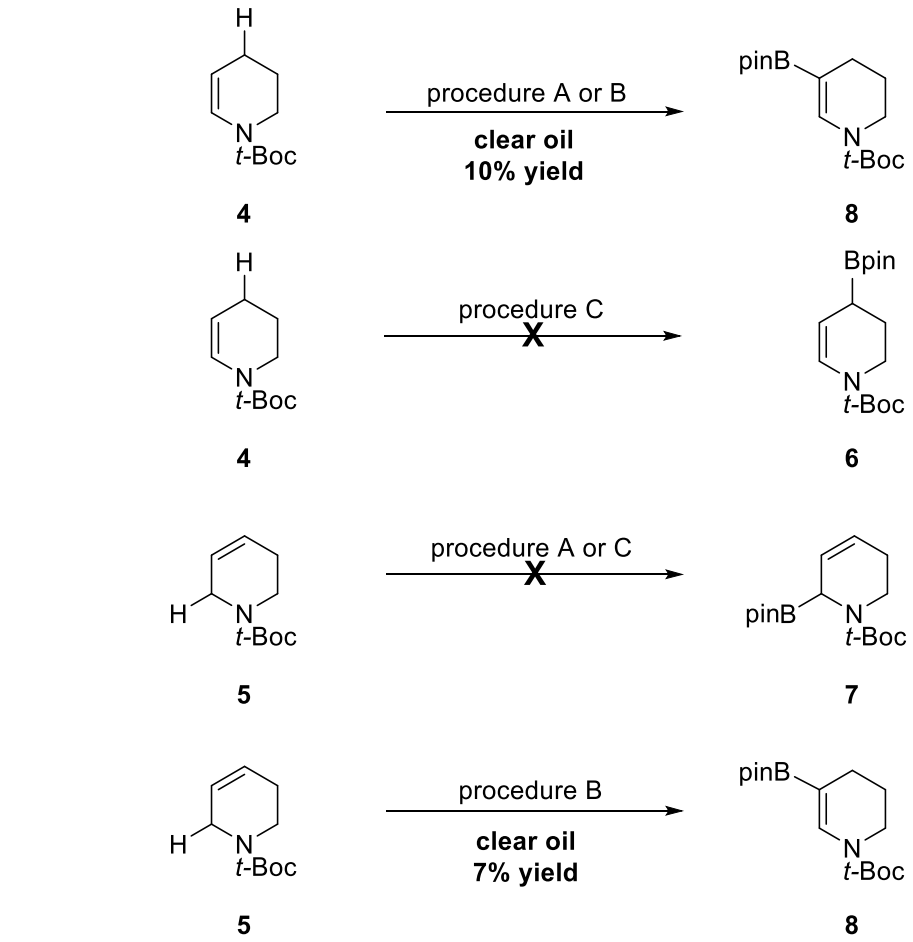
Itami and co-workers in 2015[8]



Scheme 3-6. Ir-catalyzed *cis*-selective C-H borylation of cyclopropylamines, followed by the Suzuki-Miyaura cross-coupling to form ACPAs

Both of the aforementioned C-H borylation methods were attempted for the syntheses of allylic boronates **6** and **7** from simple, commercial dehydropiperidine precursors **4** and **5** (Scheme 3-7). The original reaction conditions from the Szabo Group were used directly for this C-H borylation (procedure A, Scheme 3-7).[7] The conditions reported by the Itami Group were used either directly without modification (procedure B, Scheme 3-7),[8] or with a change of the boron source from HBpin to B_2pin_2 (procedure C, Scheme 3-7).[8]

Unfortunately, the desired allylic boronates **6** and **7** were not obtained under any of these attempted procedures. Instead, the undesired alkenyl boronate **8** was obtained from substrate **4** via procedure A and B as well as from substrate **5** via procedure B. A possible mechanism of the formation of **8** is shown in Scheme 3-8. Substrates **4** and **5** remained unreacted under procedure C.

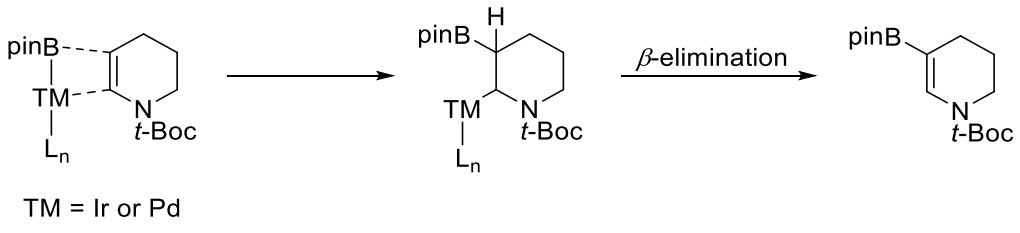


procedure A[7] = $Pd(TFA)_2$ (10 mol%), DMBQ (2.0 equiv), TFA (0.5 equiv), B_2pin_2 (2.0 equiv)

procedure B[8] = [{Ir(OMe)(COD)}$_2$] (0.5 mol%), 3,4,7,8-Me_4phen (1.0 mol%), B_2pin_2 (1.5 equiv)

procedure C[8] = [{Ir(OMe)(COD)}$_2$] (0.5 mol%), 3,4,7,8-Me_4phen (1.0 mol%), HBpin (1.5 equiv)

Scheme 3-7. C-H borylation of dehydropiperidine precursors **4** and **5** for the syntheses of **6** and **7**



TM = Ir or Pd

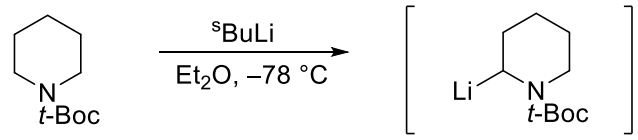
Scheme 3-8. Possible mechanism for the formation of alkenyl boronate **8**

3.3. Synthesis of piperidinyl allylic boronate via lithiation-transmetalation methods

Conventional lithiation methods providing lithiated heterocycles, followed by transmetalation with boron species could be useful for the borylation of dehydropiperidines. In this regard, we attempted a sequential lithiation-transmetalation approach on our dehydropiperidine precursor **5**.

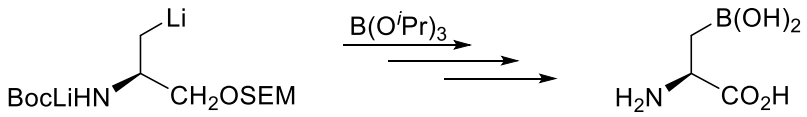
As shown in Scheme 3-9, Beak and co-workers obtained the corresponding lithiated products from piperidine precursors.[9] These lithiated species could undergo transmetalation with borates to provide the desired borylated products (Scheme 3-10).[10]

Beak and co-workers in 1993[9]



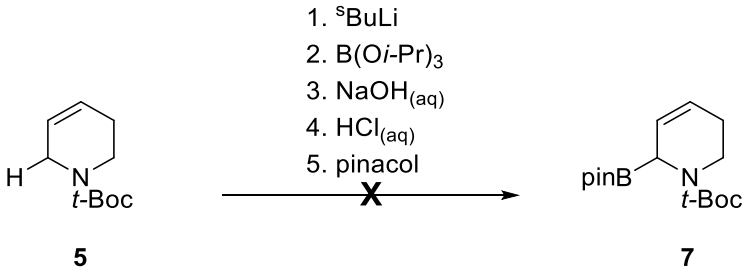
Scheme 3-9. Lithiation of piperidine precursor using ^{s}BuLi

Taylor and co-workers in 2004[10]



Scheme 3-10. Transmetalation of lithiated substrate with borate

When attempted with dehydropiperidine precursor **5**, this sequential lithiation-transmetalation approach did not lead to the formation of the desired product **7** (Scheme 3-11). The starting dehydropiperidine **5** was fully consumed; however, the resulting side products could not be isolated for characterization.



5 **7**

Scheme 3-11. Sequential lithiation-transmetalation of dehydropiperidine **5**

3.4. Conclusions

Enantiomerically enriched piperidinyl allylic boronate **2** is a convenient precursor leading to the formation of chiral, optically enriched functionalized piperidine derivatives, which are prevalent in biologically active molecules.[1-5] Thus, developing a more practical preparation of piperidinyl allylic boronates is highly desirable in the pharmaceutical industry. In this regard, we examined existing methods such as C-H borylation[7,8] and sequential lithiation-transmetalation[9,10] for the synthesis of piperidinyl allylic boronates from simple, commercial dehydropiperidine precursors. Unfortunately, both of the aforementioned approaches to achieve the synthesis of piperidinyl allylic boronates were ineffective. These failures underline the synthetic challenges associated with the formation of heterocyclic allylic boronates.

3.5. Experimental

3.5.1. General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF was purified using a MBraun MB SPS* solvent system. Et_2O was distilled over sodium/benzophenone ketyl. Cyclohexane was purified by a bulb-to-bulb distillation. Anhydrous benzotrifluoride, ^{s}BuLi, $Pd(TFA)_2$, $B(O\textit{i}\text{-}Pr)_3$, 2,6-dimethyl benzoquinone, 3,4,7,8-

tetramethylphenanthroline, and TFA were purchased from Sigma-Aldrich and used as received. 1-Boc-1,2,3,6-tetrahydropyridine, 1-Boc-3,4-dihydropyridine, HBpin, and B_2pin_2 were purchased from Combi-Blocks Inc. and were used without further purification. [{Ir(OMe)(COD)}$_2$] was purchased from Strem Chemicals. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and visualized with UV light, p-anisaldehyde stain, and $KMnO_4$ stain. Flash column chromatography was performed on ultra-pure silica gel 230-400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 or INOVA-500 instruments. The residual solvent protons (^{1}H) and the solvent carbons (^{13}C) were used as internal standards. ^{1}H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electrospray ionization (ESI) method. Infrared spectra were obtained from a Nicolet Magna-IR machine with frequencies expressed in cm^{-1}.

3.5.2. General C-H borylation procedures

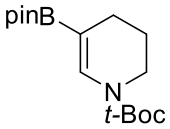
Procedure A: C-H borylation procedure adapted from the Szabo Group[7]

Dehydropiperidine (0.10 mmol, 1.0 equiv), B_2pin_2 (51 mg, 0.20 mmol, 2.0 equiv), TFA (4 µL, 0.05 mmol, 0.5 equiv), 2,6-dimethyl benzoquinone (35 mg, 0.20 mmol, 2.0 equiv), and $Pd(TFA)_2$ (3.4 mg, 0.010 mmol, 0.10 equiv) were added to a pre-dried 10 mL round bottom flask equipped with a stir-bar. The flask was flushed with N_2. Benzotrifluoride (0.5 mL) was added to the flask. The mixture was stirred at rt for 24 h. The solvent was concentrated *in vacuo* and the crude residue was purified by flash column chromatography (25% EtOAc/hexane).

Procedure B: C-H borylation procedure adapted from the Itami Group[8]

3,4,7,8-Tetramethylphenanthroline (2.4 mg, 0.010 mmol, 0.010 equiv) and [{Ir(OMe)(COD)}$_2$] (3.4 mg, 0.0050 mmol, 0.0050 equiv) were added to a pre-dried 15 mL Schlenk flask equipped with a stir-bar. The flask was flushed with N_2. Cyclohexane (0.18 mL) was added and the mixture was stirred at rt for 15 min. Dehydropiperidine (1.0 mmol, 1.0 equiv), HBpin (0.22 ml, 1.5 mmol, 1.5 equiv), and cyclohexane (1.4 mL) were added to the flask. The mixture was stirred at 80 °C for 18 h. The reaction was cooled to rt and the solvent was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (25% EtOAc/hexane).

tert-Butyl 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate (8)



The title compound (**8**) was synthesized either by procedure A using 1-Boc-3,4-dihydropyridine (20 µL, 0.10 mmol, 1.0 equiv) or procedure B using 1-Boc-3,4-dihydropyridine (191 µL, 1.00 mmol, 1.00 equiv) or 1-Boc-1,2,3,6-tetrahydropyridine (191 µL, 1.00 mmol, 1.00 equiv). The product was obtained as a clear oil and the yields were 10% (1.8 mg) using procedure A and 7% (1.3 mg) using procedure B. Spectral data correspond to that reported.[11]

3.6. References

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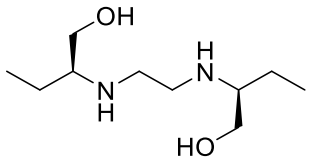
11. Reed, M. A.; Wood, T. K.; Banfield, S. C.; Barden, C. J.; Yadav, A.; Lu, E.; Wu, F. *Preparation of anti-amyloid compounds containing benzofurazan.* U.S. Patent, US 61,945,697. February 27, 2014.

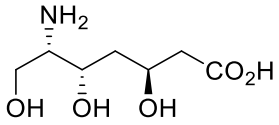
Chapter 4. Synthesis of Chiral β-Amino Alcohols via Highly Functionalized Organoboron Intermediates

4.1. Chiral β-amino alcohols in biologically active molecules

Chiral β-amino alcohols are components of numerous pharmaceutical drugs; and they are also commonly used as versatile intermediates in the syntheses of unnatural amino acids and biologically active natural compounds.[1] Chiral β-amino alcohol derivatives exhibit a wide range of biological activities including antifungal, antimicrobial, and antibacterial, as well as immunosuppressive properties (Figure 4-1).[2,3] Several commercially available antibiotics and β-blocker drugs for cardiac arrhythmias contain chiral β-amino alcohols as pure enantiomers.[1-3]



Ethambutol
Treatment of tuberculosis

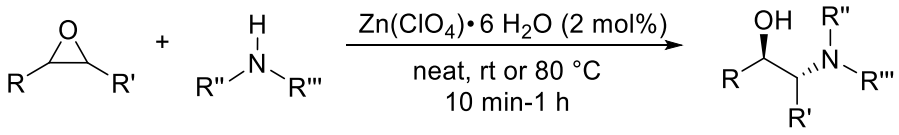


Galantinic acid
Antibacterial and antifungal activities

Figure 4-1 Examples of biologically active chiral β-amino alcohols

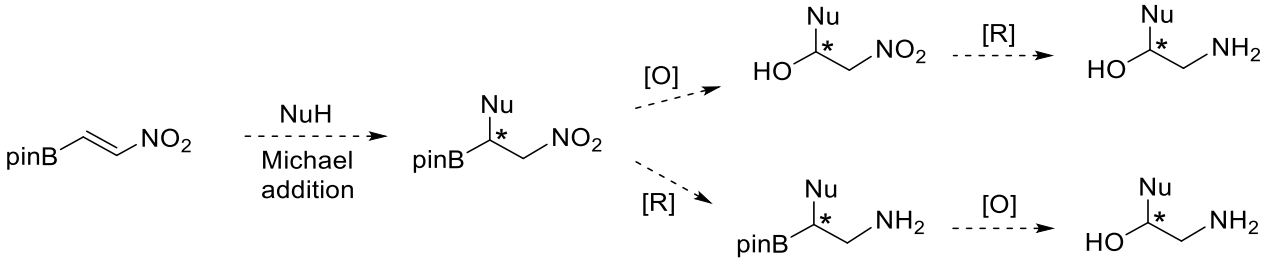
The important roles of chiral β-amino alcohols in both synthetic organic chemistry and the pharmaceutical industry have led to a rise in demand for convenient methodologies to synthesize these molecules. One of the most well-known classical methods to form chiral β-amino alcohols is the nucleophilic ring opening of epoxides with excess amines.[1] This conventional reaction is still used to date and has numerous variants; a recent example is a zinc-catalyzed epoxide ring cleavage by an amine, providing a chiral β-amino alcohol as the product (Scheme 4-1).[4] However, several drawbacks are associated with this traditional method: a lack of stereoselectivity, use of high temperature, use of excess amine, and the necessity for activation of the epoxides.[1]

Chakraborti and co-workers in 2007



Scheme 4-1 Zinc-catalyzed epoxide ring cleavage by amine

In order to develop a methodology that overcomes the aforementioned limitations, we considered employing a chiral nitro-alkylboronate as a universal precursor, which could be synthesized using *β*-borono-nitroethylene as a novel reagent (Scheme 4-2). The advantages of the use of *β*-borono-nitroethylene will be discussed in Section 4.2.



Scheme 4-2. Proposed synthesis of chiral *β*-amino alcohol using *β*-borono-nitroethylene

4.2. *β*-Borono-nitroethylene as a nitro-olefin source

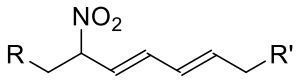
4.2.1. Synthetic importance and utility of nitro-olefins

The nitro group holds a significant synthetic importance due to its abundance in biological molecules with antifungal, antibacterial, and anti-inflammatory properties (Figure 4-2A).[5-7] Several commercialized natural and synthetic drugs contain a nitro group, including nitrofurantoin for the treatment of urinary tract infections and nilutamide for the treatment of prostate cancer (Figure 4-2B).[8-10]

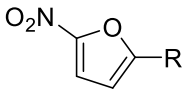
Furthermore, the nitro-olefin is one of the most frequently used nitro group-containing functionalities in organic synthesis.[11] Due to its strong electron-withdrawing nature, a nitro-olefin

is a powerful electrophile that can serve as a versatile intermediate in a range of synthetic methodologies.[11] A few selected examples include Michael addition reaction, Morita-Baylis-Hillman reaction, Diels-Alder reaction, Barton-Zard reaction, and reduction to nitroalkanes (Scheme 4-3).[12-16]

A. Biologically active compounds containing a nitro group

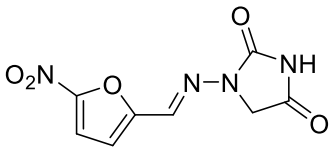


Nitro fatty acids
Anti-inflammatory lipid mediators

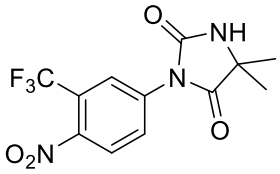


Nitrofuran derivatives
Antibiotic and/or antifungal

B. Commercial drugs containing a nitro group



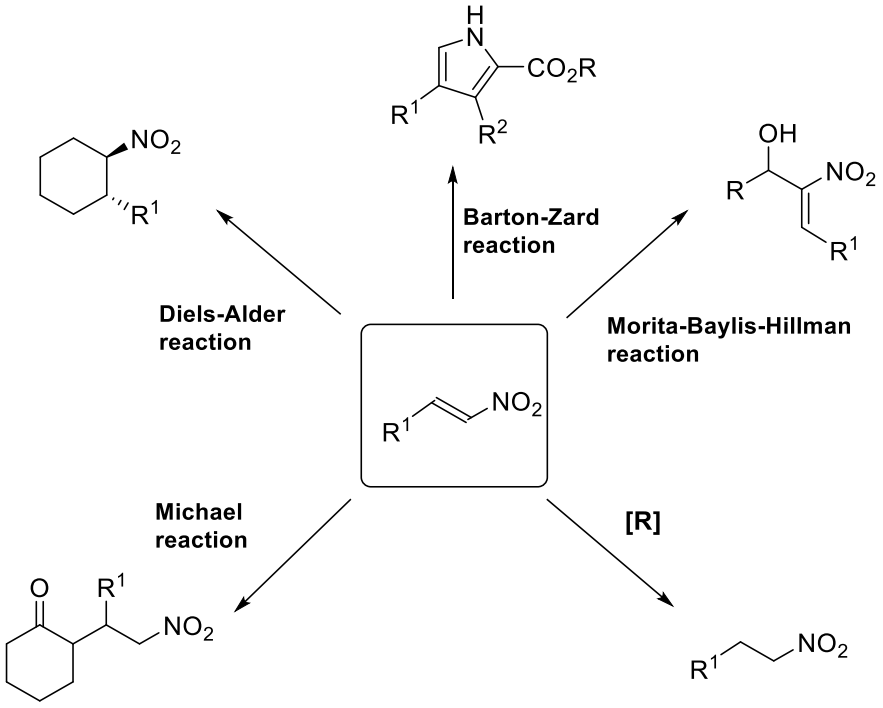
Nitrofurantoin
Antibiotics for urinary tract infections



Nilutamide
Treatment of prostate cancer

Figure 4-2. Nitro group-containing (A) compounds with biological activities and (B) commercial drugs

The Michael reaction, discovered in 1887 by the American chemist, Arthur Michael, is a [1,4]-conjugate addition reaction of resonance-stabilized carbanions.[12] In this reaction, a nitro-olefin can serve as an excellent Michael acceptor owing to its ability to stabilize the incoming negative charge via resonance.[12] In the Morita-Baylis-Hillman reaction, an activated nitro-olefin forms a resonance-stabilized nucleophilic carbanion *in situ*, under amine catalysis, and the carbanion attacks an aldehyde to form an allylic alcohol as the product.[13]



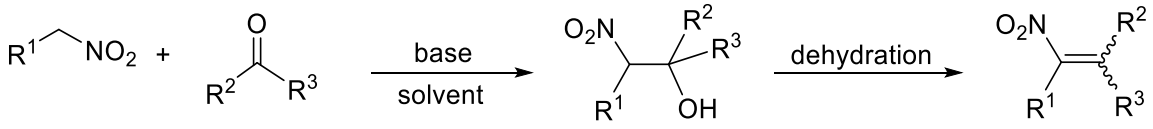
Scheme 4-3. Selected synthetic transformations involving a nitro-olefin precursor

The Diels-Alder reaction utilizes a nitro-olefin as an activated dienophile.[14] Due to the electron-withdrawing nature of the nitro substituent, the energy of the alkene's LUMO is significantly lowered, hence its superior reactivity as a dienophile.[14]

A nitro-olefin also finds its application in the synthesis of pyrrole derivatives; the Barton-Zard reaction utilizes a nitro-olefin as an electrophile and an *α*-isocyanoacetate as a nucleophile under base catalysis.[15] The addition of an *in-situ* generated nucleophile to a nitro-olefin is followed by a 5-endo-dig cyclization and a base-catalyzed elimination of the nitro group, respectively.[15] The resulting intermediate is re-aromatized via [1,5]-sigmatropic rearrangement to provide a pyrrole derivative as the final product.[15]

In addition, a nitro-olefin can be reduced to a nitroalkane.[16] Palladium-catalyzed hydrogenation reactions are known to be efficient for the reduction of nitro-olefins to provide nitroalkanes.[16]

The most commonly used preparation of nitro-olefins is the Henry reaction, which is a C-C bond-forming reaction between a carbonyl compound and a nitroalkane, discovered in 1895 by the Belgian chemist, Louis Henry; the resulting *β*-nitro-alcohol is then subjected to a dehydration reaction to provide the desired nitro-olefin (Scheme 4-4).[6]

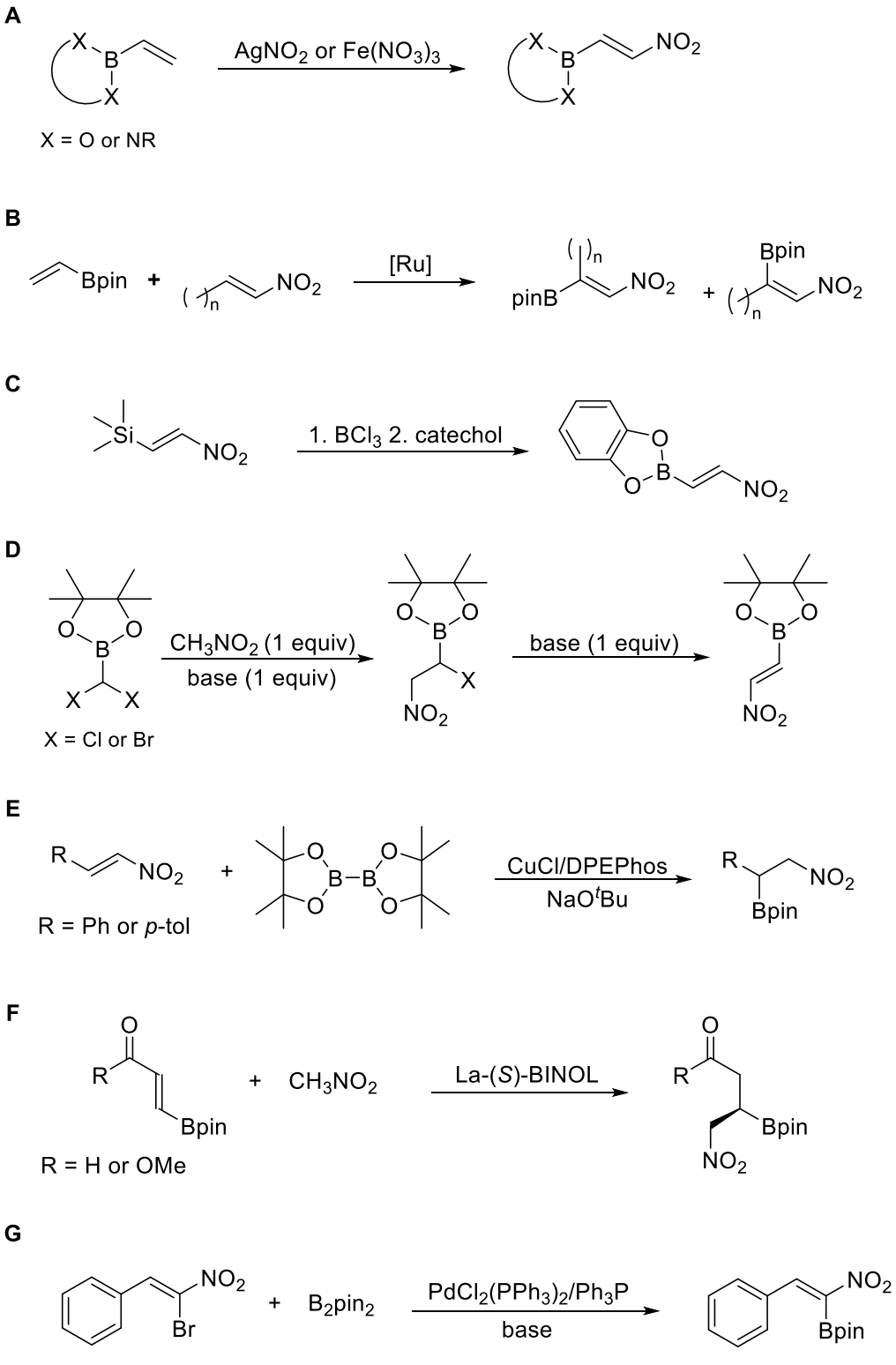


Scheme 4-4. Formation of nitro-olefins via the Henry reaction followed by dehydration

4.2.2. Overview of proposed synthetic approaches towards β-borono-nitroethylene

As discussed previously, a nitro-olefin backbone holds a significant importance in organic chemistry due to its synthetic utility as a precursor for many organic reactions.[5] However, conventional preparations of nitro-olefins pose severe limitations including harsh and complex reaction conditions, narrow substrate scope, and low regio- and stereoselectivity.[5] In this regard, *β*-borono-nitroethylene could serve as a nitro-olefin precursor, providing complex nitro-olefin compounds via the highly stereoselective, convenient, and mild Suzuki-Miyaura cross-coupling process.[17]

However, to the best of our knowledge, there is no reported synthesis of *β*-borono-nitroethylene. Therefore, we approached this objective through the modification of several established procedures for generating nitro-olefins (Scheme 4-5): **A**. metal-mediated nitration of alkenyl boronates (Section 4.3); **B**. cross-metathesis between alkenyl boronate and nitro-olefin (Section 4.4); **C**. transmetalation of *β*-nitro-vinyltrimethylsilane with BCl_3 (Section 4.5); **D**. nucleophilic addition of nitromethane to halogenated boronates (Section 4.6); **E**. copper-catalyzed conjugate borylation of nitro-olefins (Section 4.7); **F**. lanthanum-catalyzed asymmetric Michael addition (Section 4.8); and **G**. Miyaura borylation of (2-bromo-2-nitrovinyl)benzene (Section 4.9).



Scheme 4-5. Overview of synthetic approaches to form *β*-borono-nitroethylene

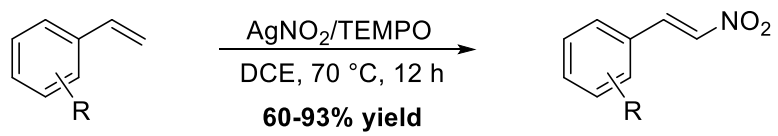
4.3. Metal-mediated nitration of alkenyl boronates

4.3.1. Silver-mediated nitration of alkenyl boronates

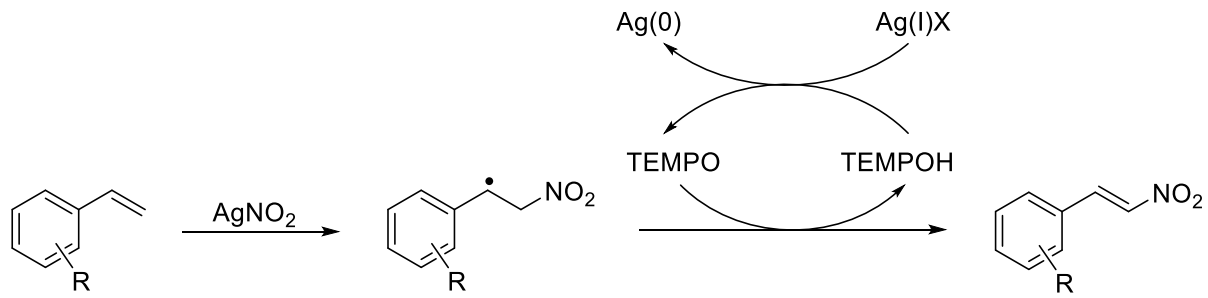
Efficient regio- and stereoselective nitration of styrene derivatives was demonstrated by Maiti and co-workers in 2013 (Scheme 4-6A).[5] The mechanism of this nitration method was proposed to be an addition of a nitro radical from $AgNO_2$ to the substrate, followed by a H-atom abstraction by TEMPO (Scheme 4-6B). The product of this chemistry was exclusively (*E*)-*β*-nitrostyrene derivatives.[5]

Maiti and co-workers in 2013[5]

A

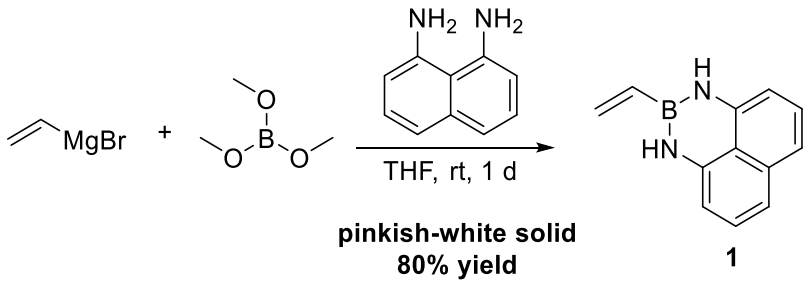


B



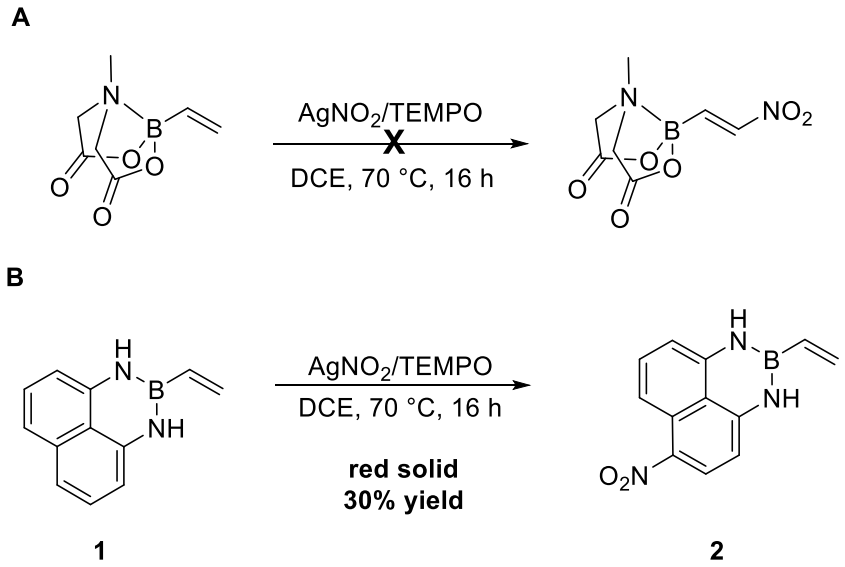
Scheme 4-6. (A) Silver-mediated nitration of styrene derivatives; (B) Proposed mechanism of this reaction

Preliminary results from our laboratory's former student, Jinyue Ding, suggested that this silver-mediated nitration method may be applicable to vinylboronic esters leading to the desired *β*-borono-nitroethylene. His substrate of choice was vinylboronic acid 1,8-diaminonaphthalene (1,8-DAN) ester **1**, which is stable to air and robust under harsh conditions. The synthesis of **1** was reproduced as described in Scheme 4-7.[17]



Scheme 4-7. Synthesis of vinylboronic acid 1,8-DAN ester **1**

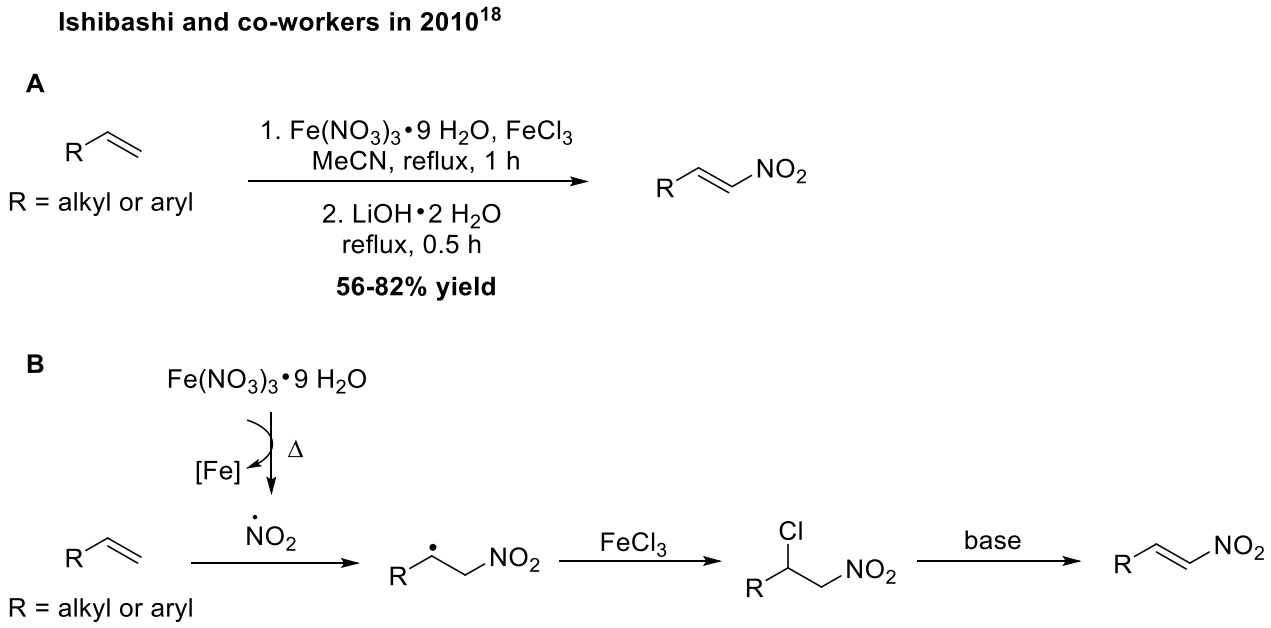
Both of the commercial vinylboronic acid MIDA ester and the above in-house synthesized boronate **1** were subjected to silver(I)-mediated nitration conditions. The former did not lead to any conversion under these reaction conditions; a nitration of the latter was observed, although it occurred at the *para*-position of the naphthalene ring of **1** (Scheme 4-8). The product **2** was initially misinterpreted as the (*Z*)-*β*-nitroalkenyl boronate due to similar coupling constants; further 2D NMR studies such as ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC revealed the correct identity of this compound.



Scheme 4-8. Ag(I)-mediated nitration of (A) vinylboronic acid MIDA ester and (B) vinylboronic acid 1,8-DAN ester **1**

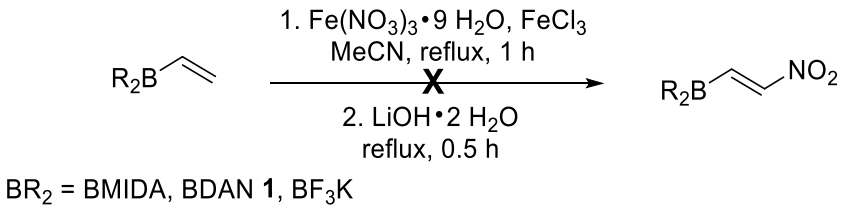
4.3.2. Iron-mediated nitration of alkenyl boronates

The use of iron reagents is attractive due to its relative low-toxicity and cost-effectiveness.[18] Although rather unexplored, iron reagents have been used in several nitration reactions. A recent example is the radical halo-nitration of alkenes using iron(III) nitrate nonahydrate reported in 2010 by the Ishibashi Group (Scheme 4-9A).[18] This chemistry is a formal three-step reaction; the first step is a nitration of the alkenyl substrate by a nitrogen dioxide free radical generated from the thermal decomposition of the iron(III) reagent. This step is followed by a radical trapping by a chlorine atom from the iron chloride complex. Lastly, the resulting intermediate undergoes an elimination reaction to give the nitro-olefin product (Scheme 4-9B).[18]



Scheme 4-9. (A) Iron-mediated nitration of alkene derivatives; (B) Proposed mechanism of this reaction

We decided to try this chemistry with our organoboronate substrates: vinylboronic acid MIDA ester, vinylboronic acid 1,8-DAN ester **1**, and potassium vinyltrifluoroborate salt (Scheme 4-10).[18,19] However, none of these boronates were converted under the described reaction conditions. Interestingly, the nitration of a naphthalene ring of the 1,8-DAN protecting group was not observed, as seen with the previously attempted silver(I)-nitration method.



Scheme 4-10. Fe(III)-mediated nitration of alkenyl boronates

4.4. Cross-metathesis between alkenyl boronate and nitro-olefin

Cross-metathesis (CM) is an effective and convenient method to provide functionalized olefins from simple olefin precursors.[20] The use of this chemistry could form a C-C bond of the obvious disconnection found in the *β*-borono-nitroethylene. However, nitro-olefins are normally categorized as "type IV" olefins, which are defined as "o*lefins [that are] inert to CM, but do not deactivate [the] catalyst (spectator)*".[20]

To the best of our knowledge, there is no reported "type IV" categorization of nitro-olefins with the newer catalyst, Hoveyda-Grubbs catalyst 2nd generation (Figure 4-3); consequently, the use of this catalyst was attempted for the CM reaction between alkenyl boronates and nitro-olefins.

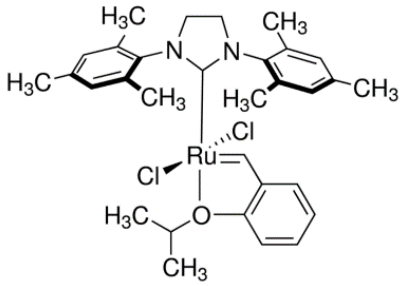
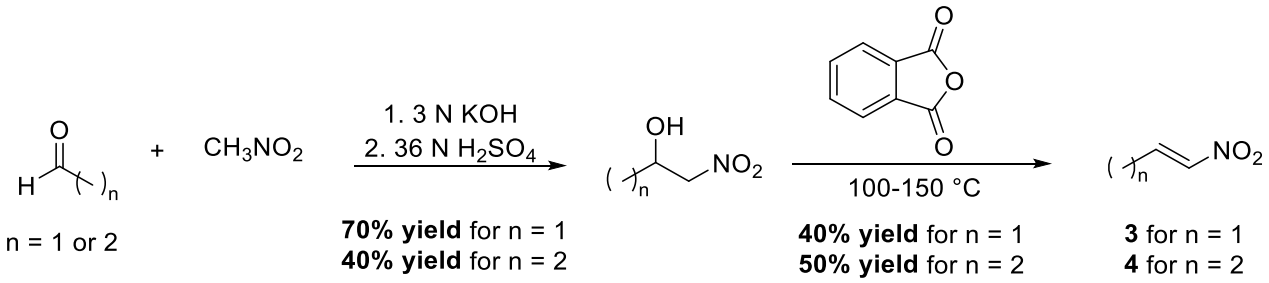


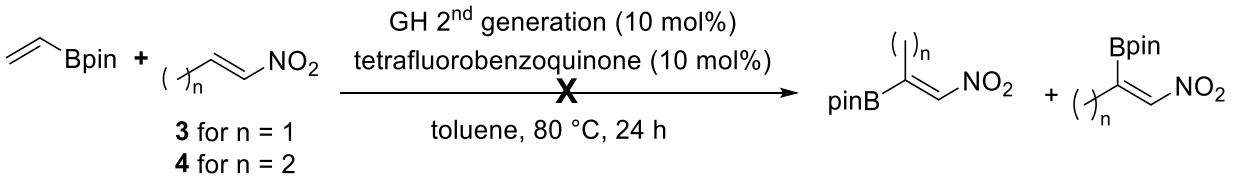
Figure 4-3. Structure of the Hoveyda-Grubbs catalyst 2nd generation

Prior to the CM reaction, the substrates **3** and **4** were prepared by the Henry reaction, followed by a dehydration (Scheme 4-11).[23] Freshly synthesized **3** and **4** were then subjected to CM reaction conditions with vinylboronic acid pinacol ester as a CM partner (Scheme 4-12). The CM reaction conditions that had been used for the formation of a C-C bond between an alkene

and a vinylboronic acid pinacol ester were attempted.[21] The additive, tetrafluorobenzoquinone, was employed to prevent olefin isomerization.[22]



Scheme 4-11. Synthesis of nitro-olefins **3** and **4** from the corresponding nitro-alcohols



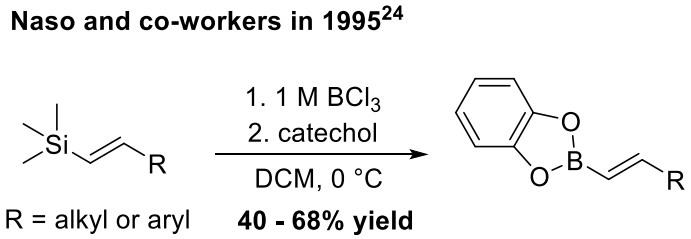
Scheme 4-12. CM reactions of vinylboronic acid pinacol ester with nitro-olefins **3** and **4**

The two starting materials remained unreacted according to the ^{1}H NMR spectrum of the crude reaction mixture. It was clear that nitro-olefins **3** and **4** were spectators under these CM conditions.

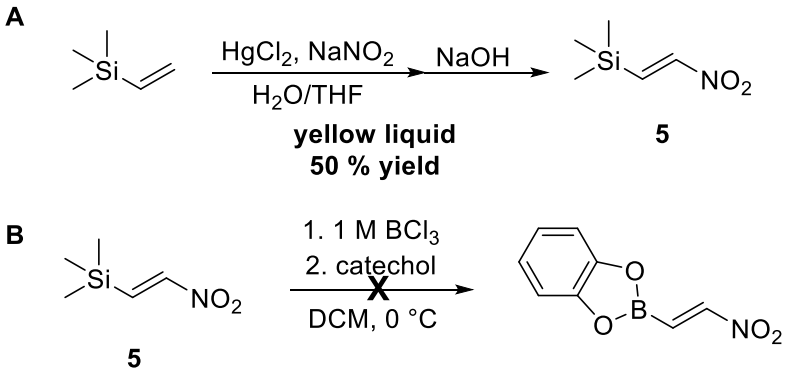
4.5. Transmetalation of *β*-nitro-vinyltrimethylsilane with BCl_3

The Naso Group achieved the first example of a simple, rapid conversion of vinyltrimethylsilane derivatives into alkenyl boronates in 1995 (Scheme 4-13).[24] Inspired by this method, we planned to obtain the desired *β*-borono-nitroethylene via a transmetalation of *β*-nitro-vinyltrimethylsilane with BCl_3. The synthesis of *β*-nitro-vinyltrimethylsilane **5** was first conducted through a two-step reaction: nitromercuration of the starting vinyltrimethylsilane, followed by a base-mediated elimination (Scheme 4-14A).[25] The product **5** was successfully formed as a yellow liquid in 50% yield, and subjected to a transmetalation with BCl_3. The reaction was subsequently

quenched by excess catechol (Scheme 4-14B). However, attempted transmetalation conditions did not lead to any conversion of **5**, according to the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 4-13. Transmetalation of vinyltrimethylsilane derivatives with alkenyl boronates



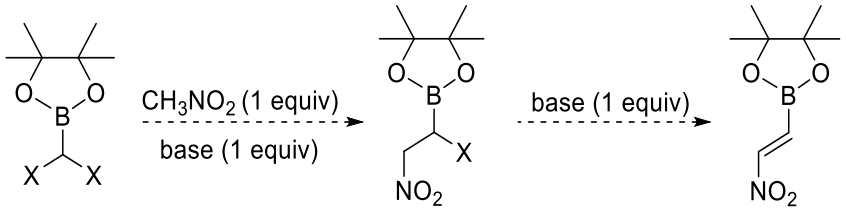
Scheme 4-14. (A) Synthesis of starting *β*-nitro-vinyltrimethylsilane, **5**; (B) Transmetalation of **5** with BCl_3

4.6. Nucleophilic addition of nitromethane to halogenated boronates

4.6.1. Overview of the strategy

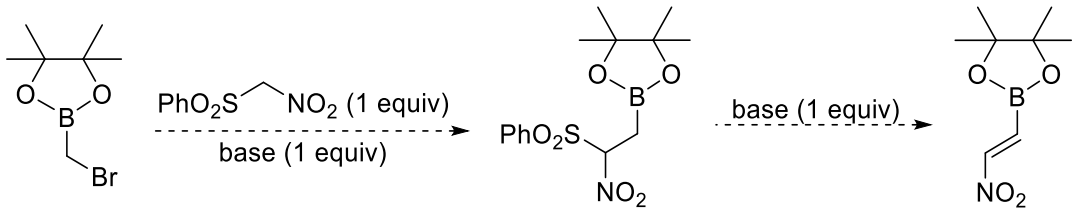
The first synthesis of *α,α*-dihaloboronates is dated back to the 1970s.[26,27] Since then, this compound was used extensively in the Matteson homologation reaction.[28] We reasoned that these dihalogenated boronates could serve as electrophiles in nucleophilic substitution reactions as they contain good leaving groups, either chloride or bromide. The nucleophile in this reaction would be the *in situ* generated carbanion of nitromethane leading to the formation of *β*-borono-*β*-

halo-nitroalkane.[26,27,29] The resulting nitroalkane could be subjected to a base-mediated elimination to furnish the desired *β*-borono-nitroethylene. An overview of this strategy is depicted in Scheme 4-15.



Scheme 4-15. Proposed strategy of nucleophilic addition of nitromethane to *α,α*-dihaloboronates

We also planned to use an *α*-brominated boronate as an electrophile for this nucleophilic substitution reaction. The nucleophile was nitro(phenylsulfonyl)methane (NSM).[30,31] A general scheme of this nucleophilic substitution reaction is illustrated in Scheme 4-16.

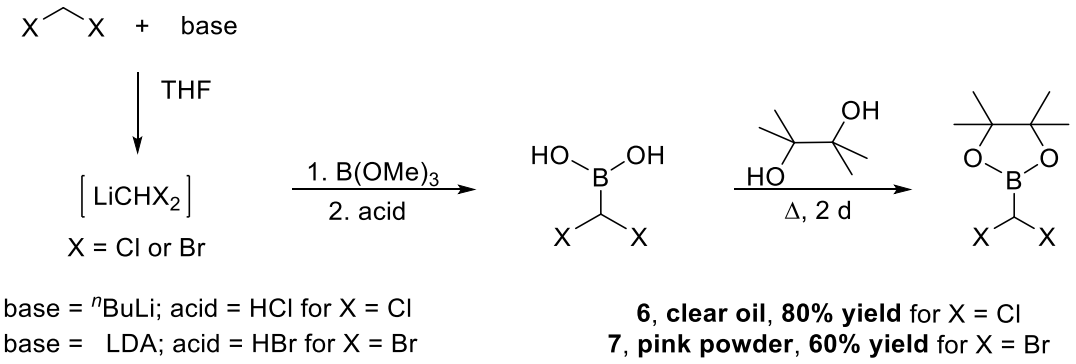


Scheme 4-16. Proposed strategy of nucleophilic addition of NSM to *α*-brominated boronate

4.6.2. Mono-alkylation of α,α-dihaloboronate with nitromethane

The syntheses of 2,2-(dichloro-) and 2,2-(dibromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes, **6** and **7**, respectively, were reproduced smoothly according to the literature (Scheme 4-17).[26,27,29] The chemistry to form these boronates is a formal three-step reaction: lithium-dihalomethane is carefully generated *in situ* using either dichloro- or dibromomethane under treatment with a lithiated base. Subsequently, the boronic acid is obtained via transmetalation of lithium to boron, followed by quenching the reaction with an acid. Finally, the

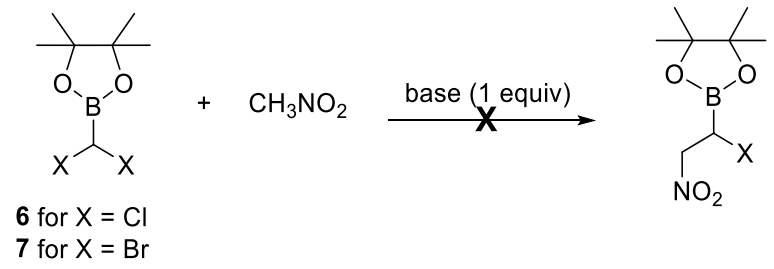
resulting boronic acid was condensed with excess pinacol in a Dean-Stark apparatus to furnish the desired *α,α*-dihaloboronate **6** or **7**.[26,27,29]



Scheme 4-17. Synthesis of *α,α*-dihaloboronates **6** and **7**

The nucleophilic carbanion of nitromethane was required to be generated *in situ* for the mono-alkylation of *α,α*-dihaloboronate **6** or **7**. The Brønsted acidity of nitromethane (pK_a 10.2) allows for easy deprotonation.[32] Several established procedures of the Henry reaction were adapted and modified for this chemistry with a number of different classes of bases: traditional hydroxide and alkoxide bases such as KO^{t}Bu, NaOMe, NaOH, and KOH;[33-36] mild ammonium salt base, NH_4OAc,[37] under microwave heating; standard amine bases such as DBU[38] and TEA;[39] and finally, lithiated bases including LDA[33] and ^{n}BuLi[40] (Scheme 4-18).

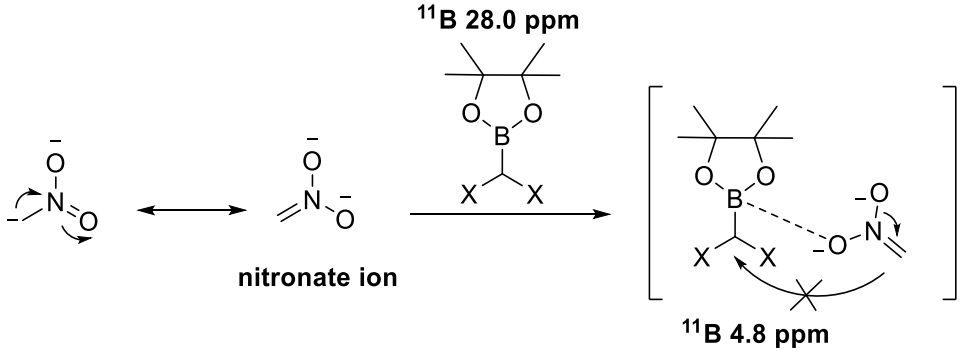
Unfortunately, the ^{1}H NMR spectra of the crude reaction mixtures suggested that none of the aforementioned conditions afforded the desired product, nor the dialkylated side-product. Although the ^{1}H NMR spectra did not provide much information, other than the presence of unreacted starting materials, a peak at 4.8 ppm in the ^{11}B NMR spectrum suggested that the boron atoms from *α,α*-dihaloboronate **6** and **7** were coordinated to a Lewis base, mostly likely the oxygen anion from an *in situ* generated nitronate ion. It is possible that this coordination led to a more electron rich electrophile, interfering with the S_N2 reaction (Scheme 4-19). Spectral data from mass spectrometry confirmed the presence of unreacted starting materials in the crude reaction mixtures.



6 for X = Cl
7 for X = Br

A. base = KO^tBu, NaOMe, KOH, or NaOH[33-36]
B. base = NH_4OAc[37]
C. base = DBU[38] or TEA[39]
D. base = LDA[33] or ^nBuLi[40]

Scheme 4-18. Mono-alkylation of *α,α*-dihaloboronates **6** and **7** with nitromethane using various bases

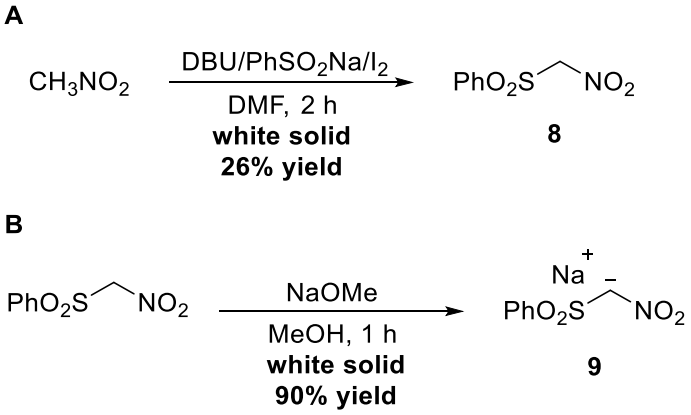


Scheme 4-19. Possible explanation for the lack of conversion observed in the nucleophilic substitution reaction

4.6.3. Alkylation of α-brominated boronate with NSM

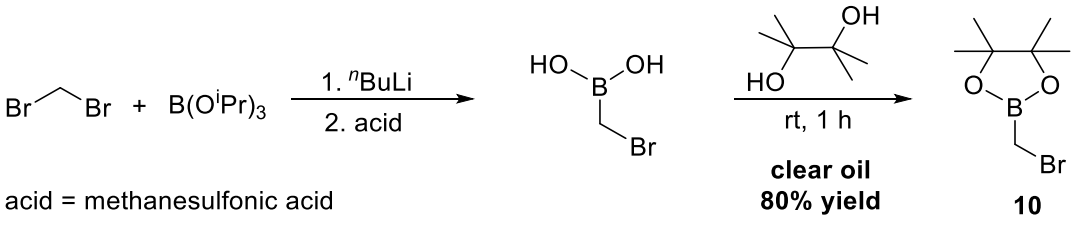
The syntheses of the starting materials, **8**, **9**, and **10** were reproduced successfully according to the literature (Schemes 4-20 and 4-21).[30,31] The activated nitroalkane **8** was synthesized by the following simple nucleophilic addition reaction: nitromethane was deprotonated by DBU, forming an *in-situ* generated nucleophilic carbanion, which added to an *in-situ* generated electrophile, $PhSO_2$−I (Scheme 4-20A).[30] It can also be converted to a sodium salt

9 upon treatment with sodium methoxide (Scheme 4-20B).[36] This sodium salt is convenient in a nucleophilic substitution reaction as it does not require pre-treatment with base.



Scheme 4-20. Syntheses of (A) NSM **8** and (B) sodium salt of NSM **9**

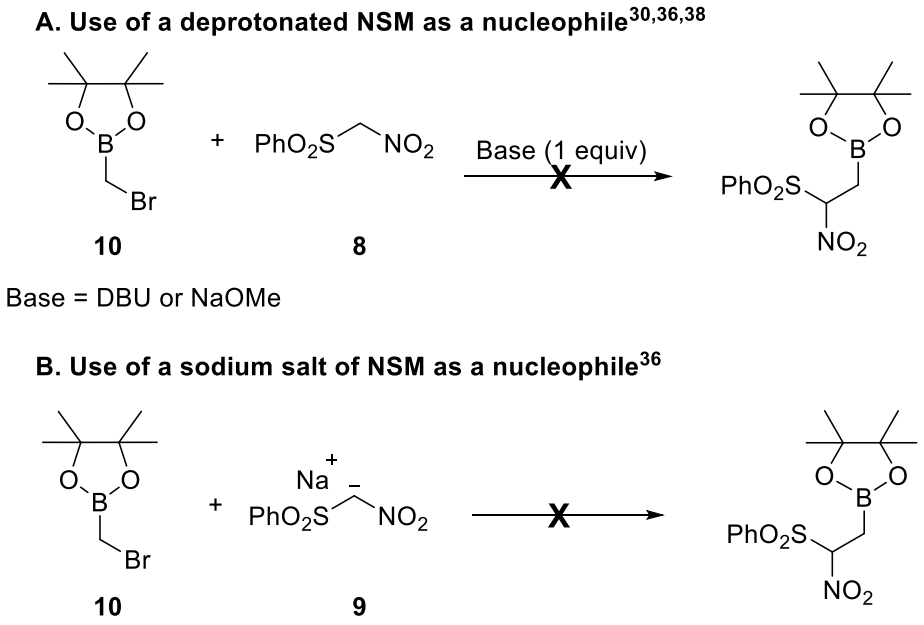
Formation of the electrophile, *α*-brominated boronate **10**, was achieved by the following sequence of reactions: treatment of a mixture of triisopropyl borate and dibromomethane with ^{n}BuLi, followed by quenching with methanesulfonic acid provided *α*-brominated boronic acid; subsequently, condensation with pinacol yielded the product **10** (Scheme 4-21).[31]



Scheme 4-21. Synthesis of 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **10**

Relatively milder bases, DBU or NaOMe, were employed for an *in situ* generation of a nucleophile, the carbanion of **8**, which was subsequently added to **10** to furnish the desired functionalized nitroalkane (Scheme 4-22A).[30,36,38] In the case of **9** as a nucleophile, the starting materials were mixed directly (Scheme 4-22B).[36] However, this class of functionalized nitroalkanes did not provide the desired product; the starting materials remained unreacted under

described reaction conditions according to the ^{1}H NMR spectra of the crude reaction mixtures. A peak at 4.5 ppm in the ^{11}B NMR spectrum was observed, which was consistent with the previous results seen in the monoalkylation of *α,α*-dihaloboronates **6** and **7**.

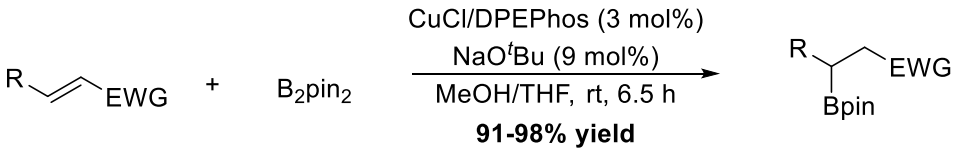


Scheme 4-22. Alkylation of *α*-brominated boronate **10** using **8** or **9** as a nucleophile

4.7. Copper-catalyzed conjugate borylation of nitro-olefins

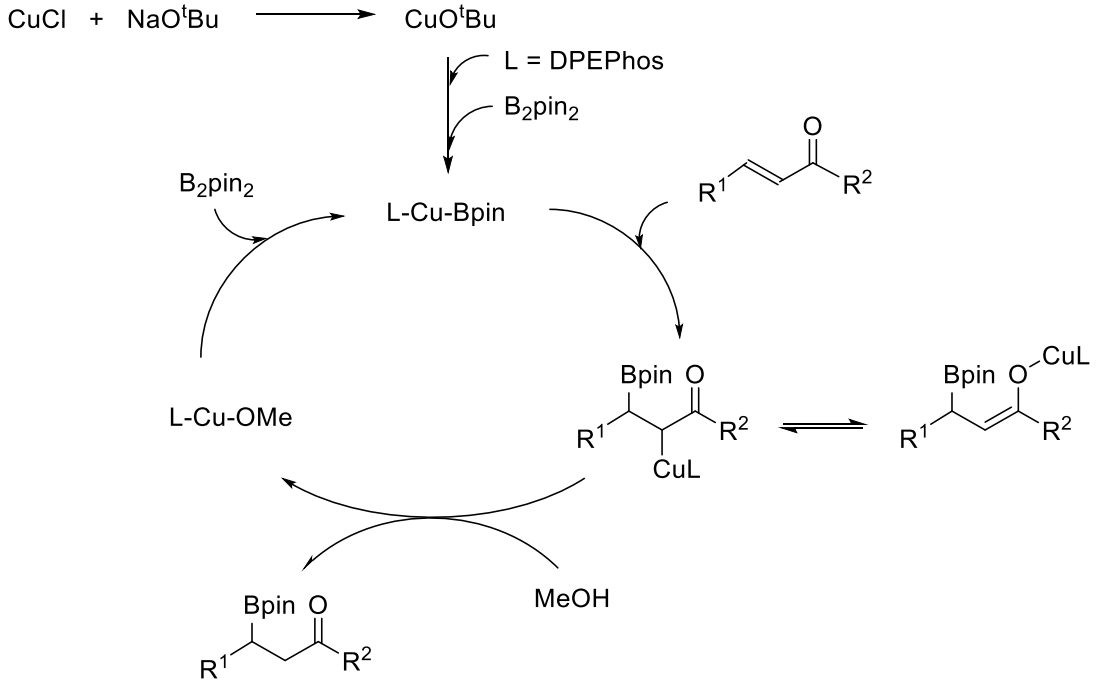
Copper-catalyzed conjugate borylation of *α,β*-unsaturated carbonyl compounds was reported by Yun and co-workers in 2006 (Scheme 4-23).[41] The authors observed that the use of xanthene-based ligands such as DPEPhos increased the nucleophilic reactivity of copper complexes. The proposed mechanism of this chemistry is depicted in Scheme 4-24; a diphosphine-ligated, copper-boryl complex adds to the starting *α,β*-unsaturated carbonyl compound. The resulting organocopper species undergoes an exchange with methanol to form the protonated product.

Yun and co-workers in 2006[41]



R = H, alkyl, aryl
EWG = -C(O)R', -C(O)OEt, -CN, -P(O)OEt$_2$

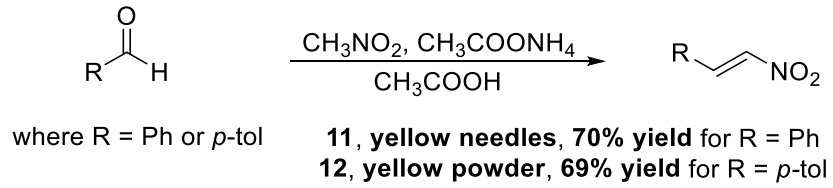
Scheme 4-23. Copper-catalyzed conjugate borylation of *α,β*-unsaturated carbonyl compounds



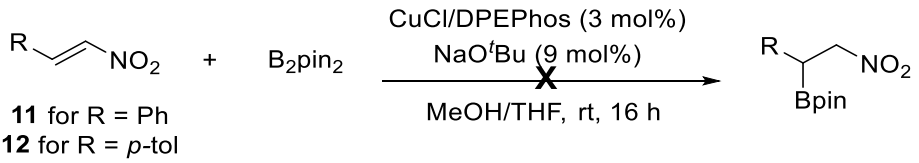
Scheme 4-24. Proposed mechanism for the copper-catalyzed conjugate borylation

Because this chemistry was achieved with a variety of substrates with different electron withdrawing groups with an exception of a nitro group, we envisioned transferring this chemistry to the synthesis of *β*-borono-nitrostyrene derivatives. To explore this idea, the starting materials, *β*-nitrostyrene derivatives **11** and **12**, were synthesized according to the literature (Scheme 4-25).[42] Subsequently, they were subjected to described conjugate borylation conditions (Scheme 4-26).

Conjugate borylation of **11** or **12** with B_2pin_2, however, did not lead to the desired *β*-borono-nitrostyrene derivatives; decomposition of **11** and **12** were observed under these conditions.



Scheme 4-25. Synthesis of the starting *β*-nitrostyrene derivatives **11** and **12**



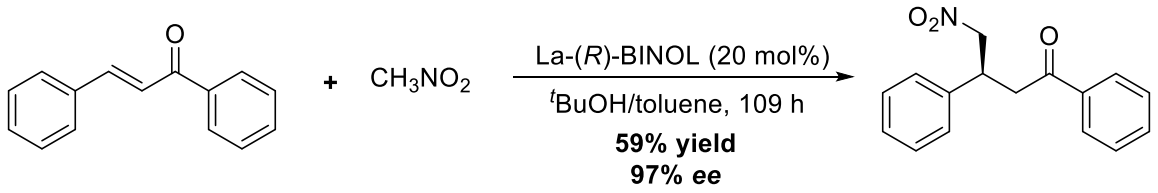
Scheme 4-26. Copper-catalyzed conjugate borylation of *β*-nitrostyrene derivatives **11** and **12** with B_2pin_2

The ^{11}B NMR spectrum of the crude reaction mixture displayed two peaks: one at 30.4 ppm and the other at 22.2 ppm. The former is attributed to the starting B_2pin_2; the latter peak may be a result of an oxidation of B_2pin_2 under the reaction conditions. Since we successfully reproduced the borylation of cinnamonitrile following the procedure outlined by Yun and co-workers,[41] it is highly likely that our nitro-containing starting materials **11** and **12** were not compatible with this procedure.

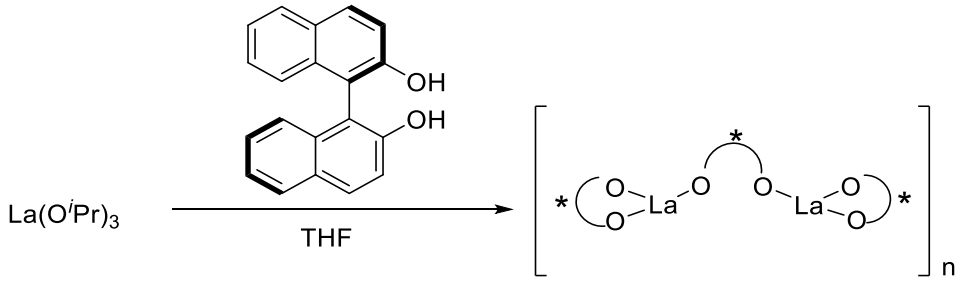
4.8. Lanthanum-catalyzed asymmetric Michael addition

Lanthanum-catalyzed asymmetric Michael addition was reported by Shibasaki and co-workers in 1994 (Scheme 4-27).[43] Synthesis of the active catalyst, La-(*R*)-BINOL, is illustrated in Scheme 4-28. Nitromethane is deprotonated by the catalyst to be activated as the Michael donor, which adds to the Michael acceptor to furnish the Michael adduct.

Shibasaki and co-workers in 1994[43]

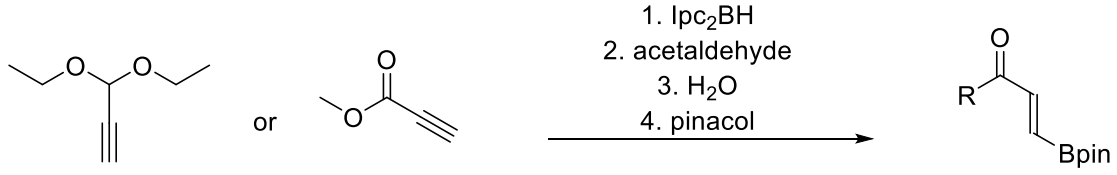


Scheme 4-27. Lanthanum-catalyzed asymmetric Michael addition



Scheme 4-28. Synthesis of the active catalyst, La-(*R*)-BINOL

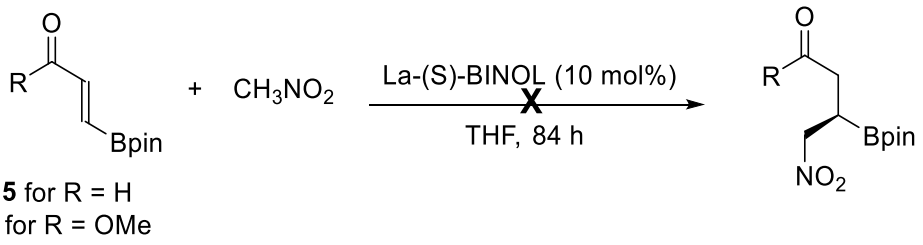
We employed this chemistry for the asymmetric Michael addition of nitromethane to alkenyl boronates to provide *β*-borono-nitroalkane derivatives. In order to attempt this reaction, we first synthesized the starting *trans*-alkenyl pinacol boronates **15** and **16** according to literature procedures (Scheme 4-29).[44] However, attempts to convert **15** and **16** to the corresponding Michael adducts were unsuccessful. Therefore, our starting materials, **15** and **16**, were not compatible with this procedure.



13 **14**

15, **white powder**, **48% yield** for R = H
16, **white powder**, **69% yield** for R = OMe

Scheme 4-29. Synthesis of the starting *trans*-alkenyl pinacol boronates **15** and **16**



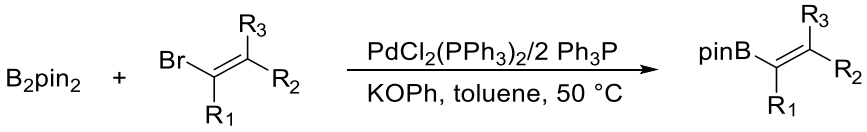
15 for R = H
16 for R = OMe

Scheme 4-30. Lanthanum-catalyzed Michael addition of nitromethane to **15** and **16**

4.9. Miyaura borylation for the synthesis of (2-borono-2-nitrovinyl)benzene

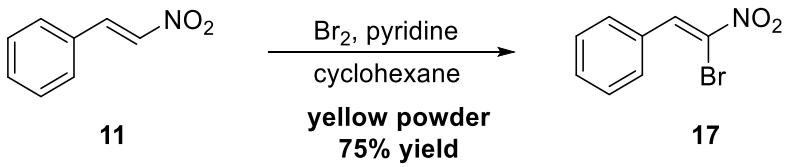
The Miyaura borylation is a process that affords sp^2-boronates by the cross-coupling of sp^2-halides with B_2pin_2 (Scheme 4-31).[45,46] The most important consideration regarding this reaction is to suppress the competing Suzuki-Miyaura cross-coupling. The Miyaura Group reported that the use of KOAc or KOPh affords a preference for the Miyaura borylation over the Suzuki-Miyaura cross-coupling.[45,46]

Miyaura and co-workers in 2002[45]

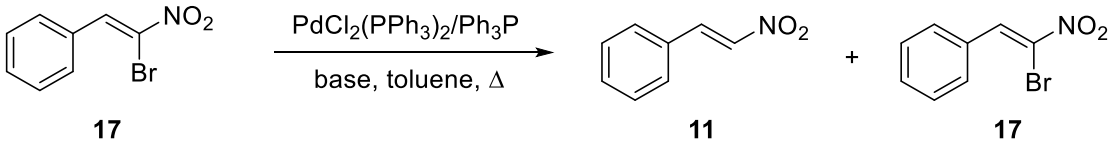


Scheme 4-31. Synthesis of alkenyl boronates via the Miyaura borylation

We saw potential in the above reaction for the synthesis of (2-borono-2-nitrovinyl)benzene via the borylation of (2-bromo-2-nitrovinyl)benzene **17**. To test this idea, we synthesized **17** according to the literature,[47] and subsequently subjected this substrate to several established Miyaura borylation conditions (Schemes 4-32 and 4-33).[46-48]



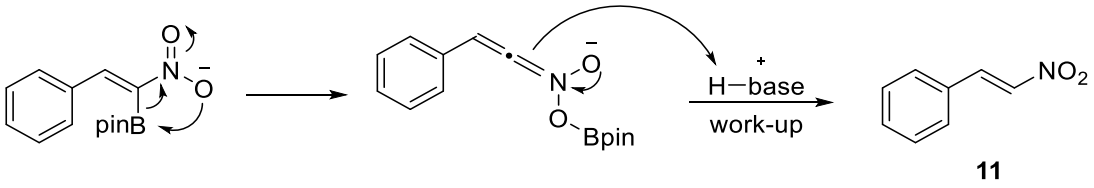
Scheme 4-32. Synthesis of the starting (2-bromo-2-nitrovinyl)benzene **17**



base = KOPh[45], KOAc[46], K_2CO_3[48]

Scheme 4-33. Miyaura borylation of **17** for the synthesis of (2-borono-2-nitrovinyl)benzene

As illustrated in Scheme 4-33, the starting materials were recovered along with 2-nitrostyrene **11**. Formation of **11** suggested that the borylation of **17** occurred; however, protoborylation of the desired product may have followed. Speculation of this phenomenon is illustrated in Scheme 4-34.



Scheme 4-34. Speculation for the formation of **11** under the Miyaura borylation conditions

4.10. Conclusions

A nitro-olefin backbone holds a significant importance in organic chemistry due to its synthetic utility as a precursor for several organic reactions. However, conventional preparative methods pose severe limitations including harsh and complex reaction conditions, narrow substrate scope, and low regio- and stereoselectivity. Developing an alternative synthetic pathway that can overcome the aforementioned limitations is highly desirable regarding the importance of

a nitro-olefin in synthetic organic chemistry.

In this regard, *β*-borono-nitroethylene as a novel nitro-olefin precursor could provide more complex nitro-olefin compounds via the highly stereoselective, convenient, and mild Suzuki-Miyaura cross-coupling process. However, there is no reported synthesis of *β*-borono-nitroethylene.

To achieve this objective, several established procedures for the synthesis of nitro-olefins were attempted to furnish *β*-borono-nitroethylene: metal-mediated nitration of alkenyl boronates; cross-metathesis or transmetalation of nitro-olefin derivatives; nucleophilic addition of nitromethane to halogenated boronates; copper-catalyzed conjugate borylation of nitro-olefins; lanthanum-catalyzed asymmetric Michael addition; and Miyaura borylation of (2-bromo-2-nitrovinyl)benzene.

Unfortunately, all of the aforementioned approaches to achieve the synthesis of *β*-borono-nitroethylene were ineffective. It remains an elusive target, thus highlighting the continuing challenges in the synthesis of functionalized nitro-olefins.

4.11. Experimental

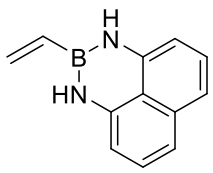
4.11.1. General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF, DCM, methanol, DMF, and toluene were purified using a MBraun MB SPS* solvent system. Dioxane was distilled over sodium. Dichloroethane was purified by a bulb-to-bulb distillation. Silver nitrite, lanthanum (III) isopropoxide, mercury (II) chloride, TEMPO, and Hoveyda-Grubbs catalyst 2nd generation were purchased from Sigma-Aldrich and used as received. Nitromethane, phthalic anhydride, sodium nitrite, boron trichloride, catechol, vinyltrimethylsilane, ^{n}BuLi, and trimethyl borate were purchased from Sigma-Aldrich and used

without further purification. DBU and sodium *p*-toluenesulfinate were purchased from Alfa Aesar and used without further purification. Pinacol, (*R*)-BINOL, and bis(pinacolato)diboron were purchased from Combi-Blocks, Inc. and used without further purification. All aldehydes were purchased from Sigma-Aldrich and purified by a bulb-to-bulb distillation under reduced pressure. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} plates and visualized with UV light, p-anisaldehyde stain, and $KMnO_4$ stain. Flash column chromatography was performed on ultra-pure silica gel 230-400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded on INOVA-400 or INOVA-500 instruments. The residual solvent protons (^1H) and the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; app s, apparent singlet; t, triplet; app t, apparent triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet. Reported *J*-values are deemed accurate within ± 0.3 Hz. NMR data were processed either using VnmrJ from Agilent Technologies or MestReNova from Mestrelab Research. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using electrospray ionization (ESI) or electron impact (EI) method. Infrared spectra were obtained from a Nicolet Magna-IR machine with frequencies expressed in cm^{-1}.

*4.11.2. Experimental procedure and spectral data for vinylboronic ester **1***

Vinylboronic acid 1,8-diaminonaphthalene ester (1)



Trimethyl borate (22 mmol, 1.2 equiv, 2.5 mL) was dissolved in THF (15 mL) in a three-necked round bottom flask charged with a stir-bar under a nitrogen atmosphere. The mixture was cooled in an acetone/dry-ice bath (−78 °C). Vinylmagnesium bromide (1 M in THF) (18 mmol, 1.0 equiv, 18 mL) was added dropwise into the mixture and the resulting solution was stirred for 30 min. The reaction was warmed up to rt, and stirred for 1 h. The solution was then cooled in an ice-water bath (0 °C), followed by addition of 1,8-DAN (22 mmol, 1.2 equiv, 3.5 g). The reaction was warmed up to rt, and stirred for 20 min. The reaction was then quenched with a slow addition of NH_4Cl (60 mL) and extracted with EtOAc (3 × 60 mL). The organic layers were combined and washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The pinkish oil was then purified by flash column chromatography (15% EtOAc/Hexane). The title compound (**1**) was obtained as a pinkish-white solid (2.8 g, 80% yield).

R_f = 0.75 (50% EtOAc/hexane);

^{1}H NMR (400 MHz, CD_2Cl_2) *δ* (ppm) 7.11 (dd, *J* = 8.3, 7.3 Hz, 2 H), 7.01 (dd, *J* = 8.4, 1.0 Hz, 2 H), 6.36 (dd, *J* = 7.4, 1.0 Hz, 2 H), 6.10 – 5.92 (m, 3 H), 5.86 (br s, 2 H);

^{13}C NMR (100 MHz, CD_2Cl_2) *δ* (ppm) 142.1, 136.3, 130.8, 127.6, 119.8, 117.4, 105.7;

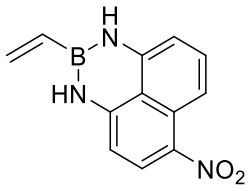
^{11}B NMR (128 MHz, CD_2Cl_2) *δ* (ppm) 27.6;

IR (Microscope, cm^{-1}) 3410, 3053, 2962, 1629, 1600, 1506, 1463;

HRMS (EI) for $C_{12}H_{11}BN_2$ (m/z): calcd. 194.1015; found 194.1016;

*4.11.3. Experimental procedure for silver-mediated nitration and spectral data for **2***

Vinylboronic acid 1,8-diamino-4-nitronaphthalene ester (2)



The synthesized compound **1** (1.00 mmol, 1.00 equiv, 194 mg), $AgNO_2$ (3.00 mmol, 3.00 equiv, 462 mg), TEMPO (0.400 mmol, 0.400 equiv, 62.5 mg), 4 Å molecular sieves (150 mg), and dichloroethane (2 mL) were added to a 10 mL round bottom flask charged with a stir-bar under a nitrogen atmosphere. The vial was sealed. The mixture was heated at 70 °C and stirred for 17 hr. The reaction was cooled to rt and filtered through a pad of celite with EtOAc as an eluent. The reaction was then quenched with a slow addition of NH_4Cl (60 mL) and extracted with EtOAc (3 × 60 mL). The resulting solution was then concentrated *in vacuo*. The crude was then purified by flash column chromatography (25% EtOAc/Hexane). The title compound (**2**) was obtained as a red solid (167 mg, 30% yield).

R_f = 0.12 (15% EtOAc/hexane);

^{1}H NMR (400 MHz, CD_2Cl_2) *δ* (ppm) 10.57 (br s, 1 H), 7.99 (d, *J* = 9.5 Hz, 1 H), 7.45 (t, *J* = 7.9 Hz, 1 H), 7.09 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.97 (d, *J* = 9.7 Hz, 1 H), 6.75 (dd, *J* = 7.7, 0.9 Hz, 1 H), 6.63 (br s, 1 H), 6.27 – 6.09 (m, 3 H);

^{13}C NMR (100 MHz, CD_2Cl_2) *δ* (ppm) 144.0, 142.6, 138.0, 133.7, 132.2, 126.0, 122.7, 118.9, 118.3, 118.2, 110.2;

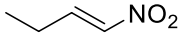
^{11}B NMR (128 MHz, CD_2Cl_2) *δ* (ppm) 27.6;

IR (Microscope, cm^{-1}) 3338, 2926, 2852, 1630, 1604, 1591, 1445;

HRMS (EI) for $C_{12}H_{10}O_2BN_3$ (m/z): calcd. 239.0866; found 239.0866;

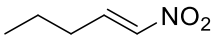
4.11.4. Synthesis of the starting materials for CM between alkenyl boronate and nitro-olefin

1-Nitro-1-butene (3)



A yellow oil (10.1 g, 40% yield) was prepared according to the literature.[23] Spectral data correspond to that reported.[23]

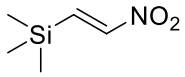
1-Nitro-1-pentene (4)



A yellow oil (288 mg, 50% yield) was prepared according to the literature.[23] Spectral data correspond to that reported.[23]

*4.11.5. Synthesis of the starting material **5** for transmetalation of β-nitro-vinyltrimethylsilane with BCl_3*

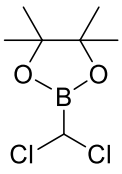
(*E*)-2-Nitrovinyltrimethylsilane (5)



A yellow oil (726 mg, 50% yield) was prepared according to the literature.[25] Spectral data correspond to that reported.[25]

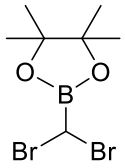
4.11.6. Synthesis of the starting materials for nucleophilic addition of nitromethane to halogenated boronates

2,2-(Dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes (6)



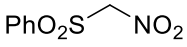
A clear oil (16.9 g, 80% yield) was prepared according to the literature.[26,27] Spectral data correspond to that reported.[27]

2,2-(Dibromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolanes (7)



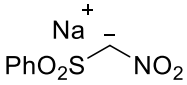
A pink powder (8.6 g, 60% yield) was prepared according to the literature.[29] Spectral data correspond to that reported.[29]

Nitro(phenylsulfonyl)methane (8)



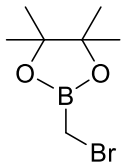
A white solid (1.2 g, 26% yield) was prepared according to the literature.[30] Spectral data correspond to that reported.[30]

Sodium nitro(phenylsulfonyl)methane (9)



A white solid (2.0 g, 90% yield) was prepared according to the literature.[36] Spectral data correspond to that reported.[36]

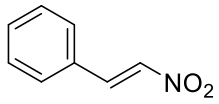
2-(Bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10)



A clear oil (1.9 g, 80% yield) was prepared according to the literature.[31] Spectral data correspond to that reported.[31]

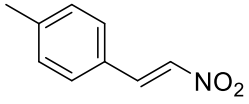
4.11.7. Synthesis of the starting materials for copper-catalyzed conjugate borylation of nitro-olefins

(2-Nitrovinyl)benzene (11)



Yellow needles (5.9 g, 70% yield) were prepared according to the literature.[42] Spectral data correspond to that reported.[42]

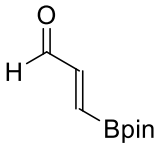
1-Methyl-4-(2-nitrovinyl)benzene (12)



A yellow powder (1.8 g, 69% yield) was prepared according to the literature.[42] Spectral data correspond to that reported.[42]

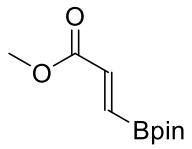
4.11.8. Synthesis of the starting materials for lanthanum-catalyzed asymmetric Michael addition

(*E*)-3-Boroacrolein pinacolate (15)



A white powder (708 mg, 48% yield) was prepared according to the literature.[44] Spectral data correspond to that reported.[44]

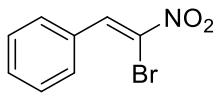
(*E*)-2-(Methoxycarbonyl)ethyl-1-enylboronic acid pinacol ester (16)



A white powder (365 mg, 69% yield) was prepared according to the literature.[44] Spectral data correspond to that reported.[44]

4.11.9. Synthesis of the starting materials for Miyaura borylation of (2-bromo-2-nitrovinyl)benzene

(2-Bromo-2-nitrovinyl)benzene (17)



A yellow powder (855 mg, 75% yield) was prepared according to the literature.[47] Spectral data correspond to that reported.[47]

4.12. References

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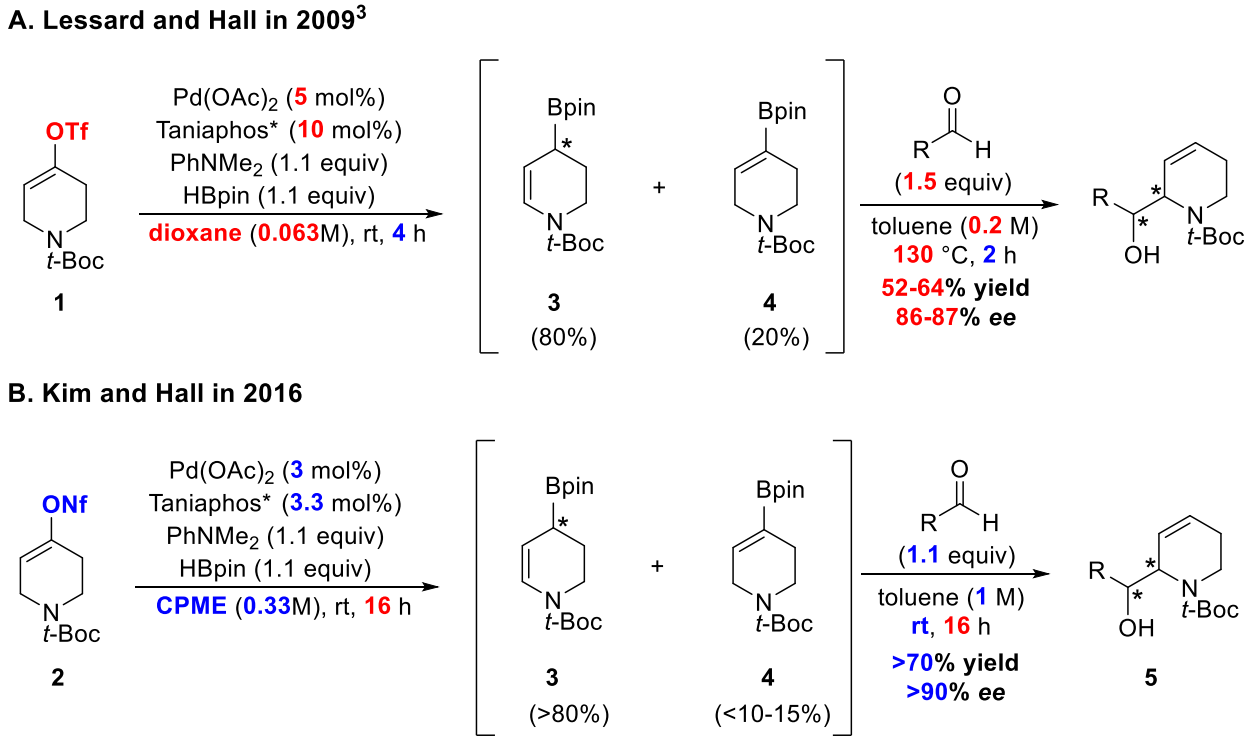
Chapter 5. Thesis Conclusions

5.1. Conclusions

This thesis focuses on the formation of chiral, optically enriched piperidine derivatives, which are deemed a "privileged" class of compounds in drug discovery due to their prevalence in pharmaceutically active compounds.[1,2] An introduction to their importance in the pharmaceutical industry and conventional preparative methods are described in Chapter 1.

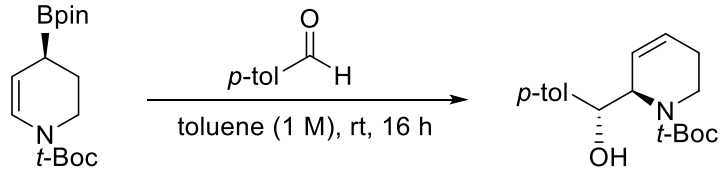
Chapter 2 describes the optimization of the catalytic enantioselective borylative migration and its applications. Catalytic enantioselective borylative migration reported by our laboratory in 2009 is a single-step preparation of enantiomerically enriched piperidinyl allylic boronate **5**,[3] which can lead to the formation of chiral, optically enriched piperidine derivatives via aldehyde allylboration or the Suzuki-Miyaura cross-coupling reaction (Scheme 5-1A).[4,5] This convenient synthetic transformation, however, had not been thoroughly optimized and presented several limitations: lower than desired *ee* and yields, use of peroxide-forming dioxane as the solvent, high catalyst loading (5 mol%), low reaction concentration (0.063 M), and reproducibility issues. To overcome the aforementioned limitations and make this procedure more appealing to the pharmaceutical industry, we fine-tuned the original reaction conditions by screening the following parameters: the nature of the alkenylsulfonate and the *N*-protecting group of the substrate, the source and stoichiometry of palladium and diphosphine ligand, solvent, reaction concentration, temperature, and time. The improvements of the re-optimized conditions are highlighted in Scheme 5-1B in comparison to the original conditions reported in 2009.[3] With the re-optimized, industry-friendly procedure in hand, we explored the applications of this chemistry, which include aldehyde allylboration, the intramolecular Heck reaction, and the sequential Suzuki-Miyaura cross-coupling reactions (Scheme 5-2). The original reaction conditions of aldehyde allylboration reported in 2009[3] were briefly re-examined to achieve an industry-friendly procedure featuring a

significant solvent economy under ambient temperature (Scheme 5-2A). Using 2-bromobenzaldehyde as the aldehyde precursor, synthesized allylboration product *rac*-**6** was subjected to the intramolecular Heck reaction conditions to afford the tricyclic *α*-hydroxyalkyl dehydropiperidine **7** (Scheme 5-2B). This preliminary work will be examined further in the future for yield optimization, and expansion of the substrate scope. Finally, the sequential Suzuki-Miyaura cross-coupling reactions of functionalized piperidine precursor **8** were attempted for the synthesis of [3,4]-biaryl-piperidine derivative **9** (Scheme 5-2C). Unfortunately, all of the attempted Suzuki-Miyaura cross-coupling conditions were ineffective towards our substrate **8**.



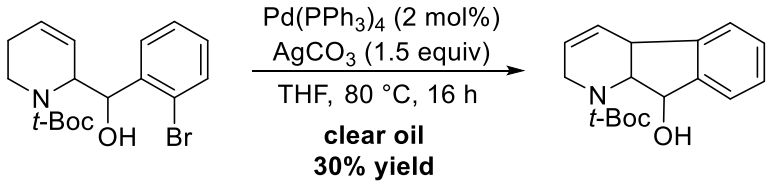
Scheme 5-1. Summary of the optimized catalytic enantioselective borylative migration-aldehyde allylboration sequence for the synthesis of piperidine derivatives

A. Re-optimized aldehyde allylboration



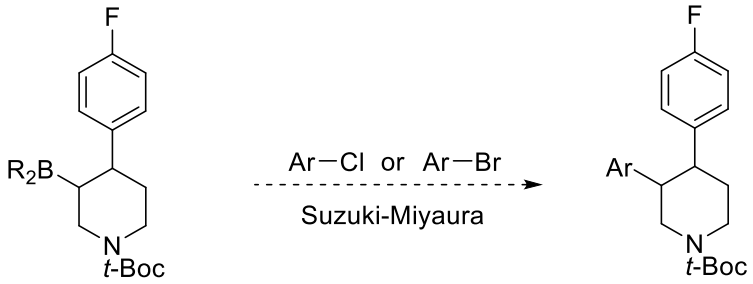
3 **5**

B. Intramolecular Heck reaction of allylboration product, *rac*-6



rac-**6** **7**

C. Sequential Suzuki-Miyaura cross-couplings



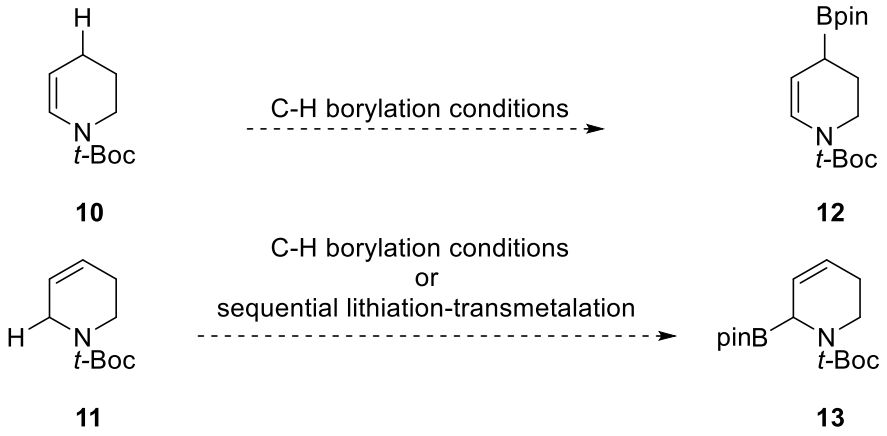
8 **9**

BR_2 = Bpin or BF_3K

Scheme 5-2. Applications of the catalytic enantioselective borylative migration: (A) Aldehyde allylboration; (B) Intramolecular Heck reaction; (C) Sequential Suzuki-Miyaura cross-coupling reactions

Chapter 3 describes attempts to synthesize enantiomerically enriched piperidinyl allylic boronates via alternative synthetic approaches to the catalytic enantioselective borylative migration. Existing methods such as C-H borylation and sequential lithiation-transmetalation were examined using simple, commercial dehydropiperidine precursors **10** and **11** (Scheme 5-3). However, both of the aforementioned approaches to achieve the synthesis of piperidinyl allylic

boronate **12** and **13** were ineffective. These failures underline the synthetic challenges associated with the formation of heterocyclic allylic boronates.



Scheme 5-3. Synthesis of **12** and **13** via borylation of simple dehydropiperidine precursors **10** and **11**

Finally, efforts to synthesize another synthetic target of interest, *β*-borono-nitroethylene, are described in Chapter 4. *β*-Borono-nitroethylene could be used as a novel reagent to synthesize chiral *β*-amino alcohols, which are an important class of compounds in the pharmaceutical industry because they exhibit a wide range of biological activities including antifungal, antimicrobial, and antibacterial. In an effort to furnish *β*-borono-nitroethylene, several established procedures for the synthesis of nitro-olefins were attempted: metal-mediated nitration of alkenyl boronates; cross-metathesis or transmetalation of nitro-olefin derivatives; nucleophilic addition of nitromethane to halogenated boronates; copper-catalyzed conjugate borylation of nitro-olefins; lanthanum-catalyzed asymmetric Michael addition; and Miyaura borylation of (2-bromo-2-nitrovinyl)benzene (Figure 5-1). Unfortunately, all of the aforementioned approaches to prepare *β*-borono-nitroethylene derivatives were ineffective, thus highlighting the continuing challenges in the synthesis of functionalized nitro-olefins.

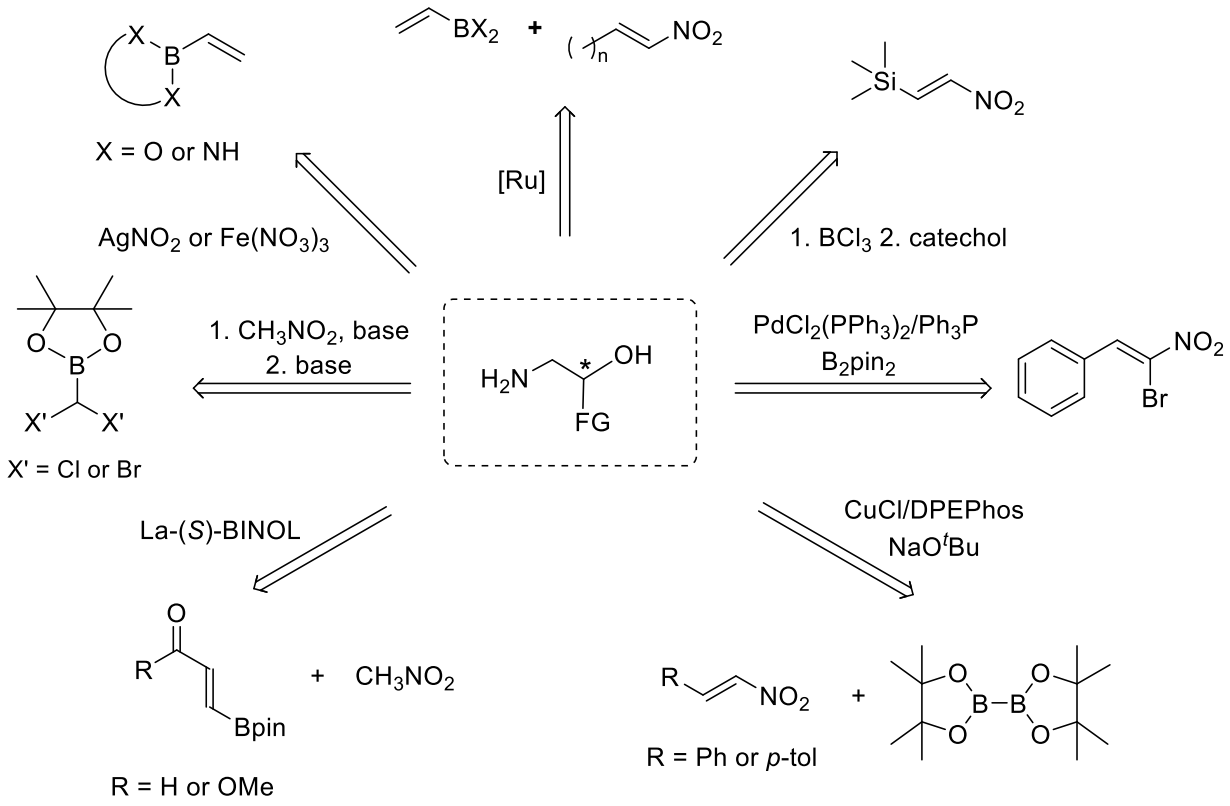


Figure 5-1. Overview of attempted retro-synthetic strategies to form chiral *β*-amino alcohols

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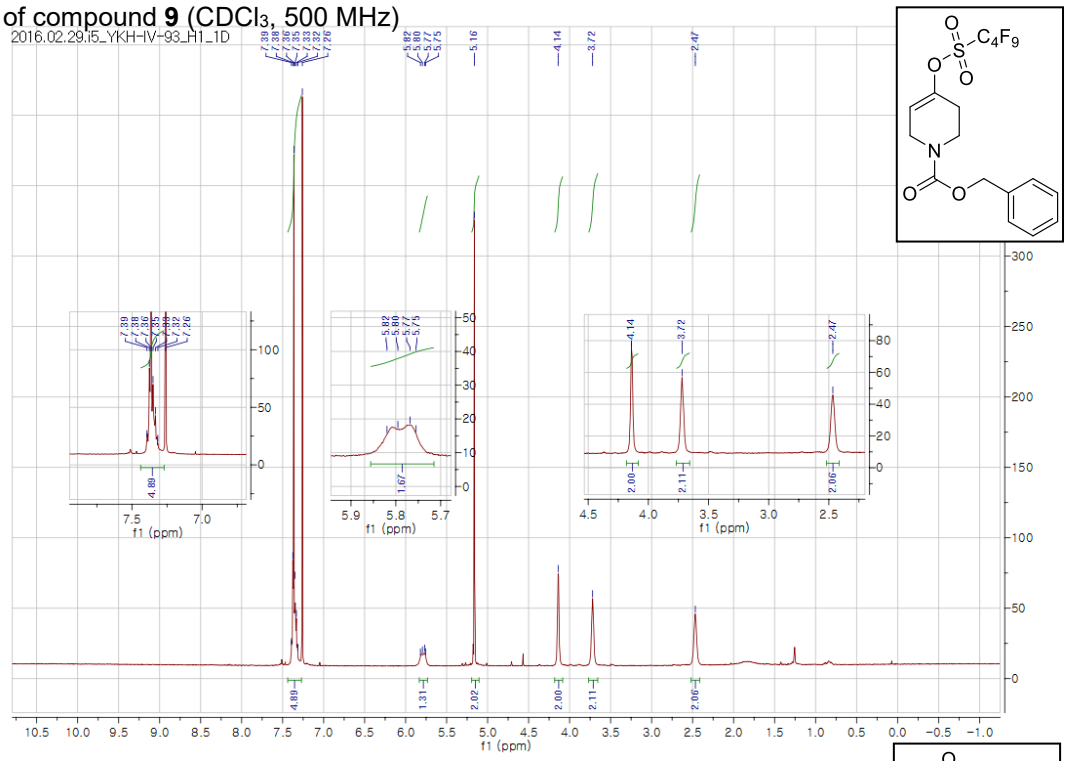
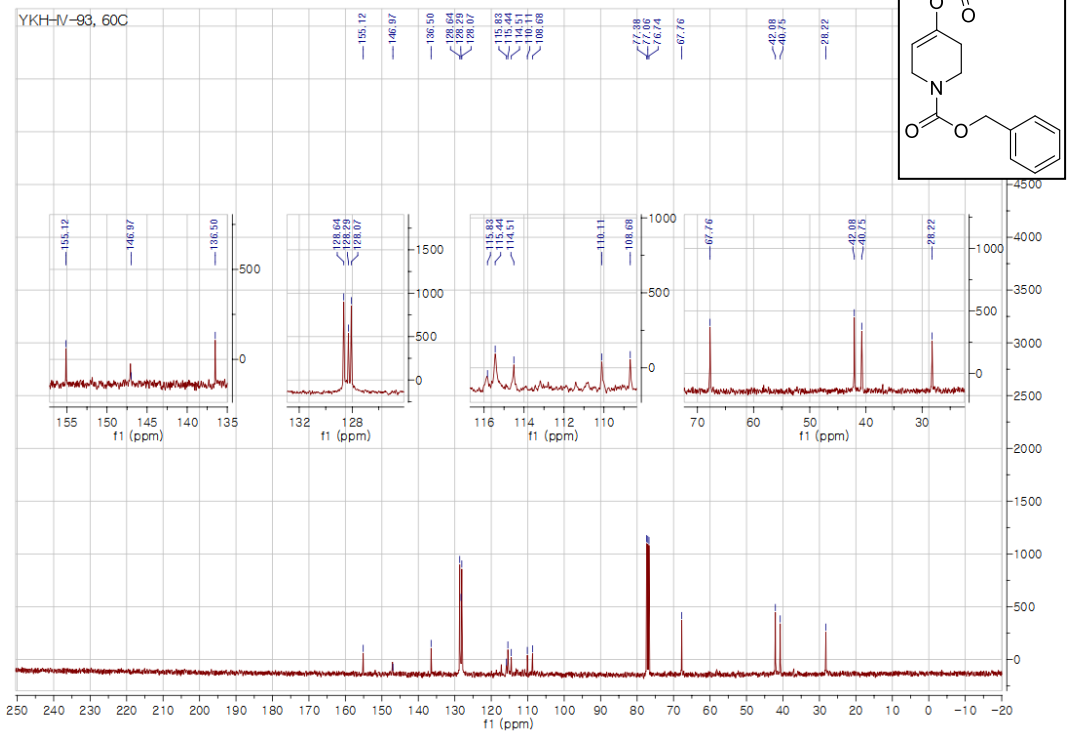
Appendices

Appendix 1: Selected copies of NMR spectra of compounds found in Chapter 2

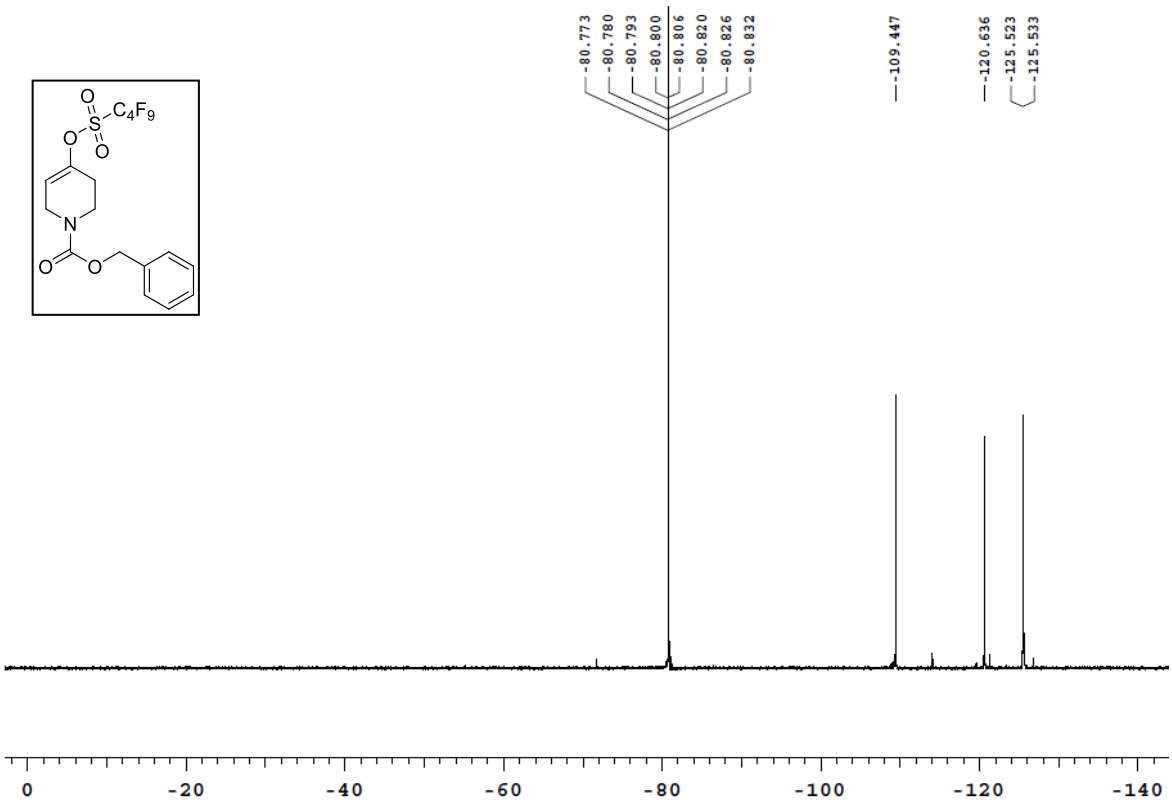
^{1}H NMR of compound **9** ($CDCl_3$, 500 MHz)



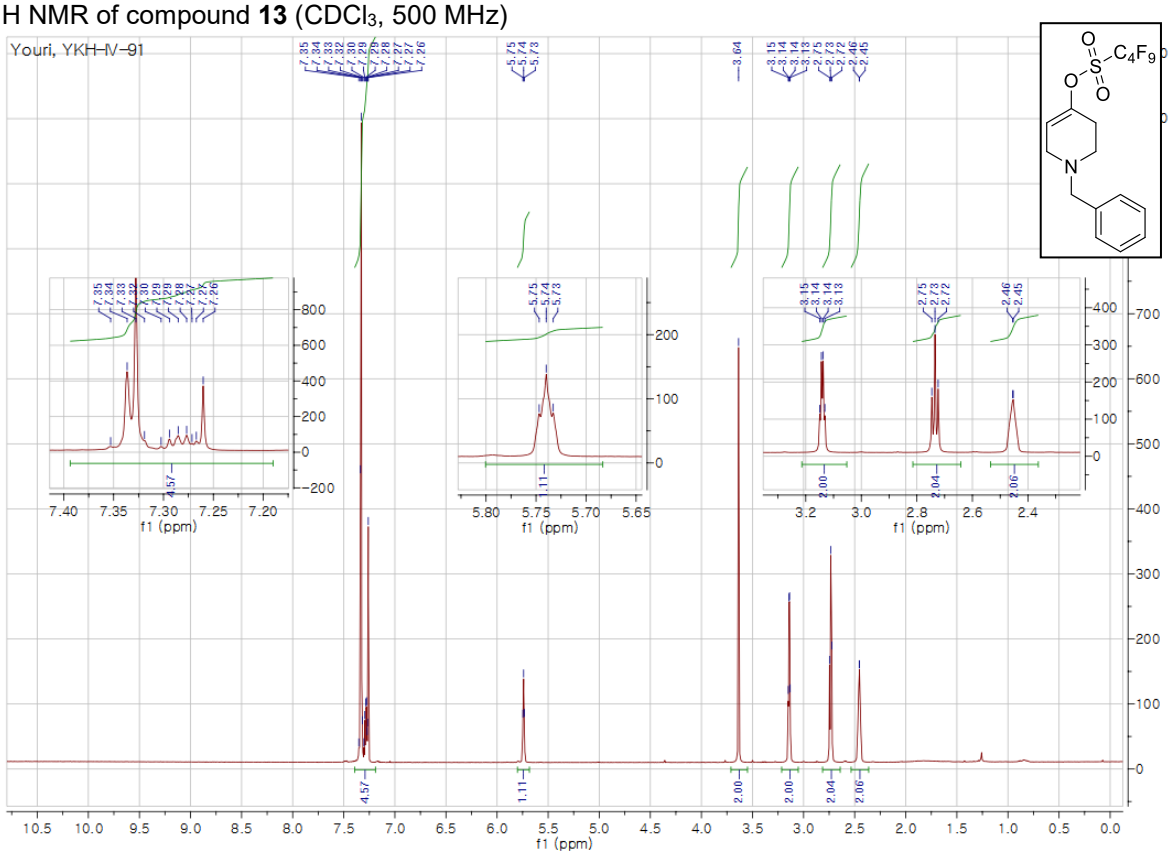
^{13}C NMR of compound **9** ($CDCl_3$, 100 MHz, ^{19}F decoupled, 60 °C)



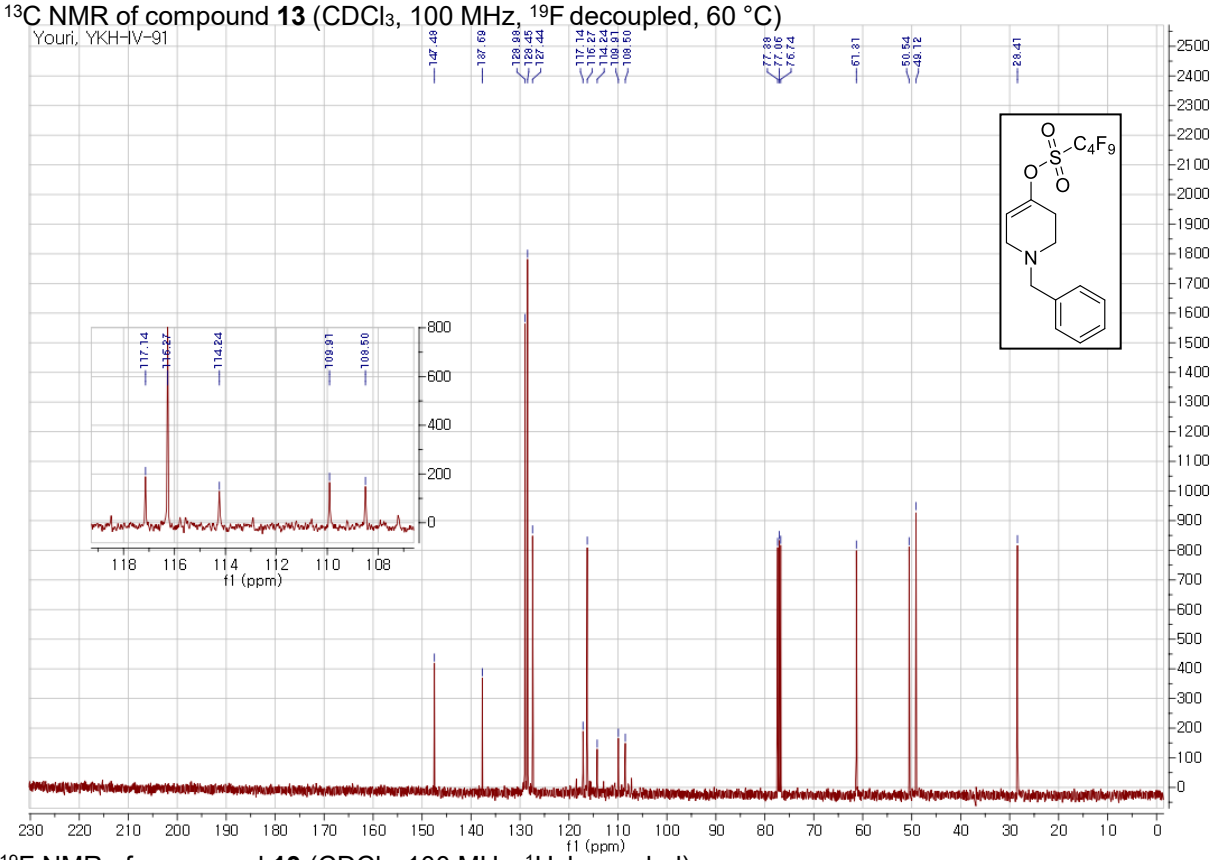
^{19}F NMR of compound **9** ($CDCl_3$, 100 MHz, ^{1}H decoupled, 60 °C)



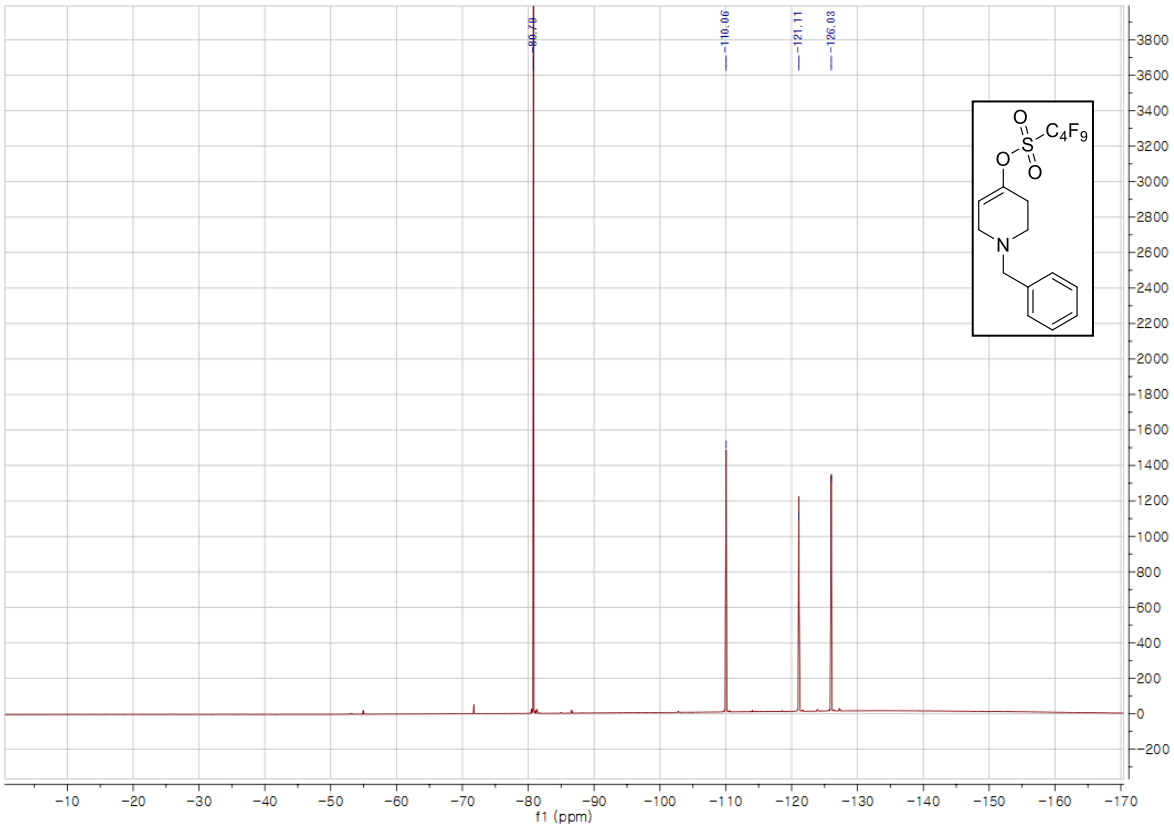
^{1}H NMR of compound **13** ($CDCl_3$, 500 MHz)



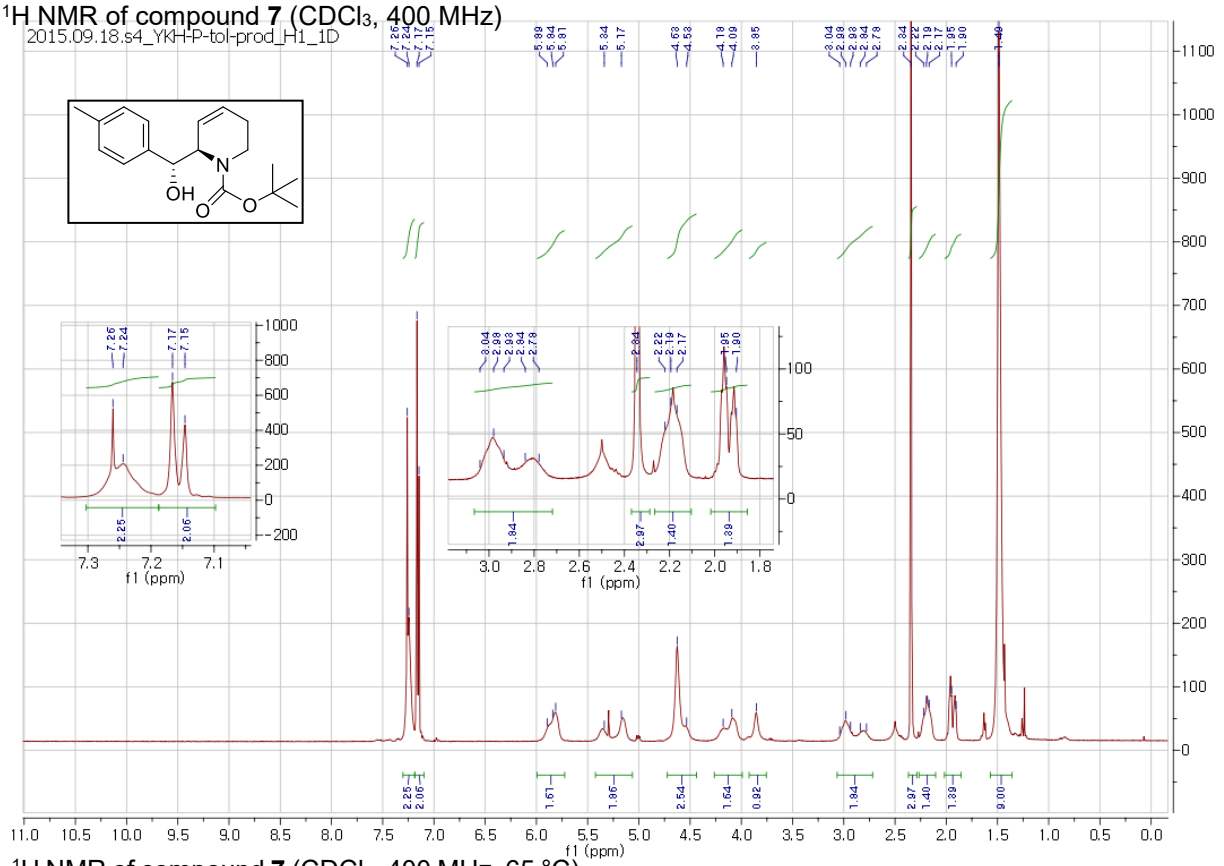
^{13}C NMR of compound **13** ($CDCl_3$, 100 MHz, ^{19}F decoupled, 60 °C)



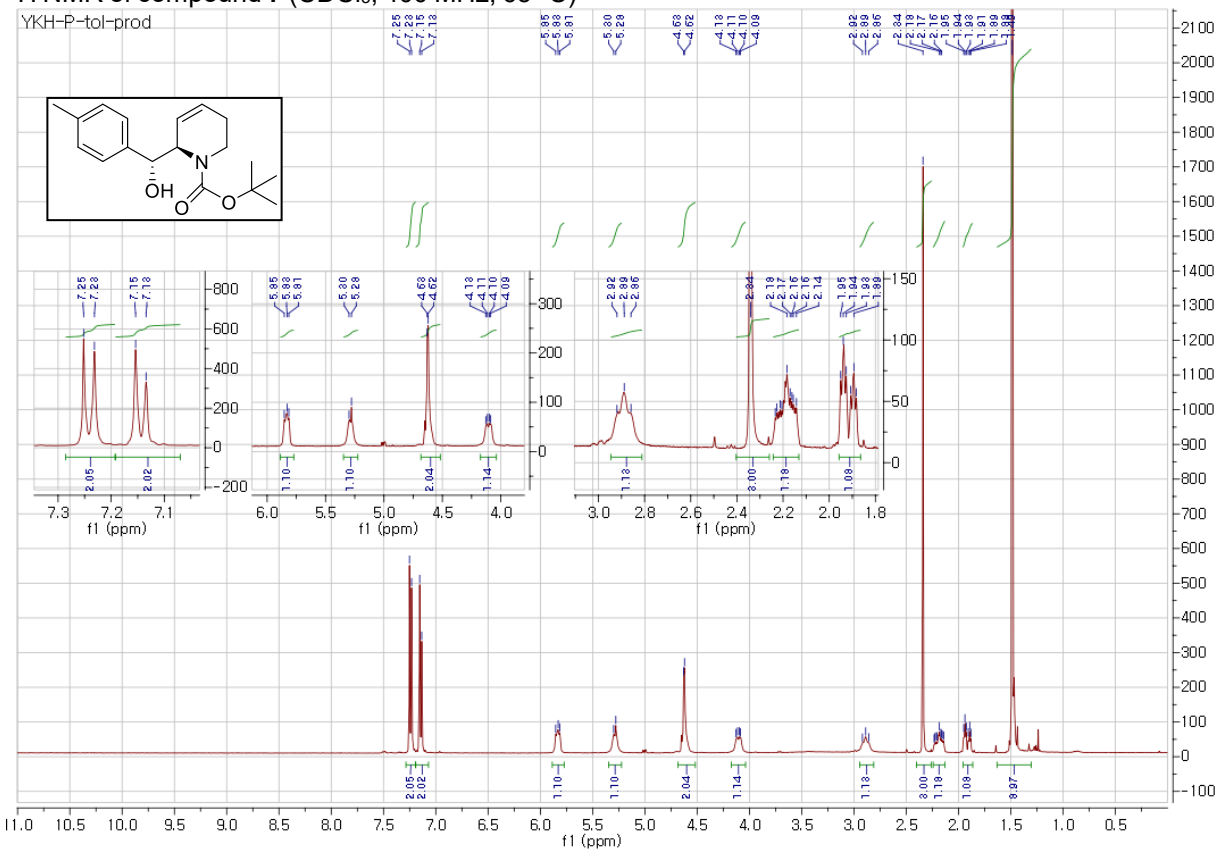
^{19}F NMR of compound **13** ($CDCl_3$, 100 MHz, ^{1}H decoupled)



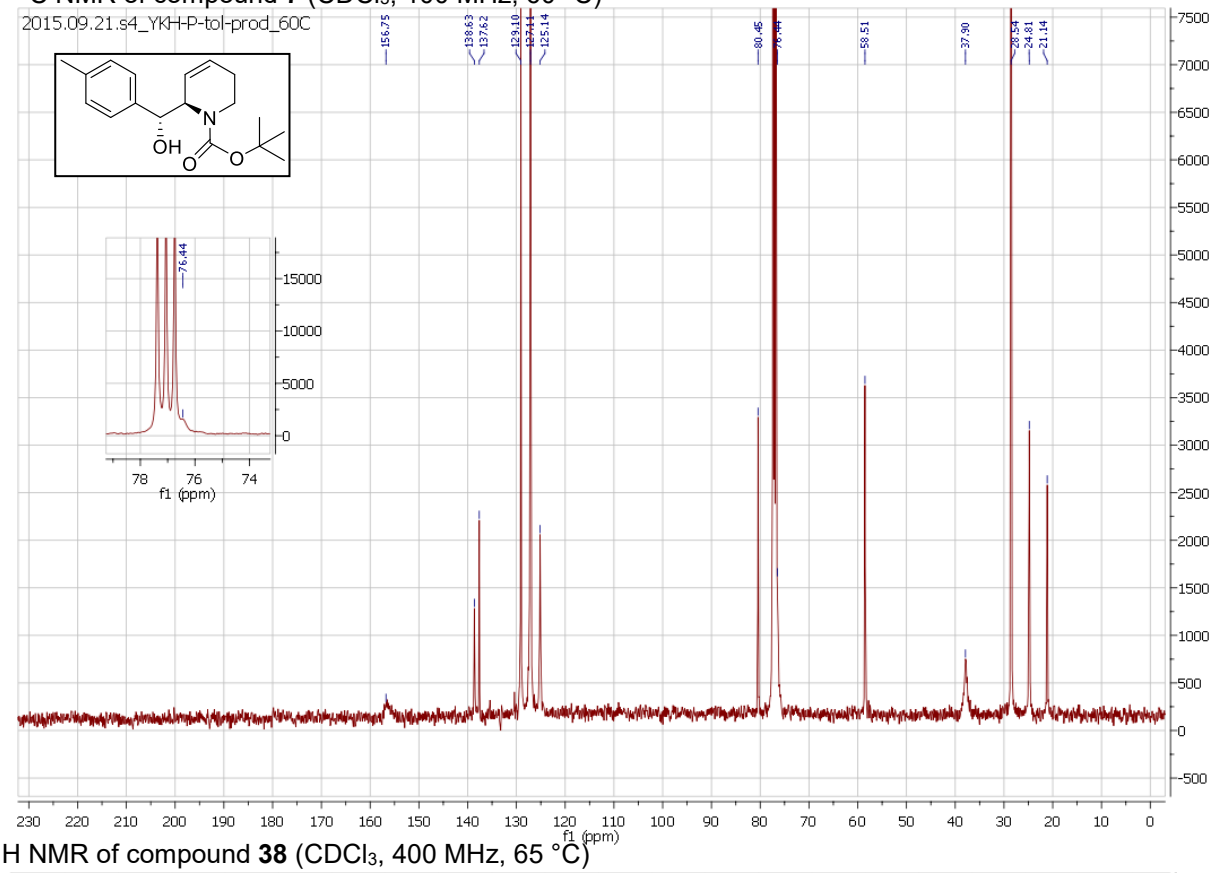
^{1}H NMR of compound **7** ($CDCl_3$, 400 MHz)



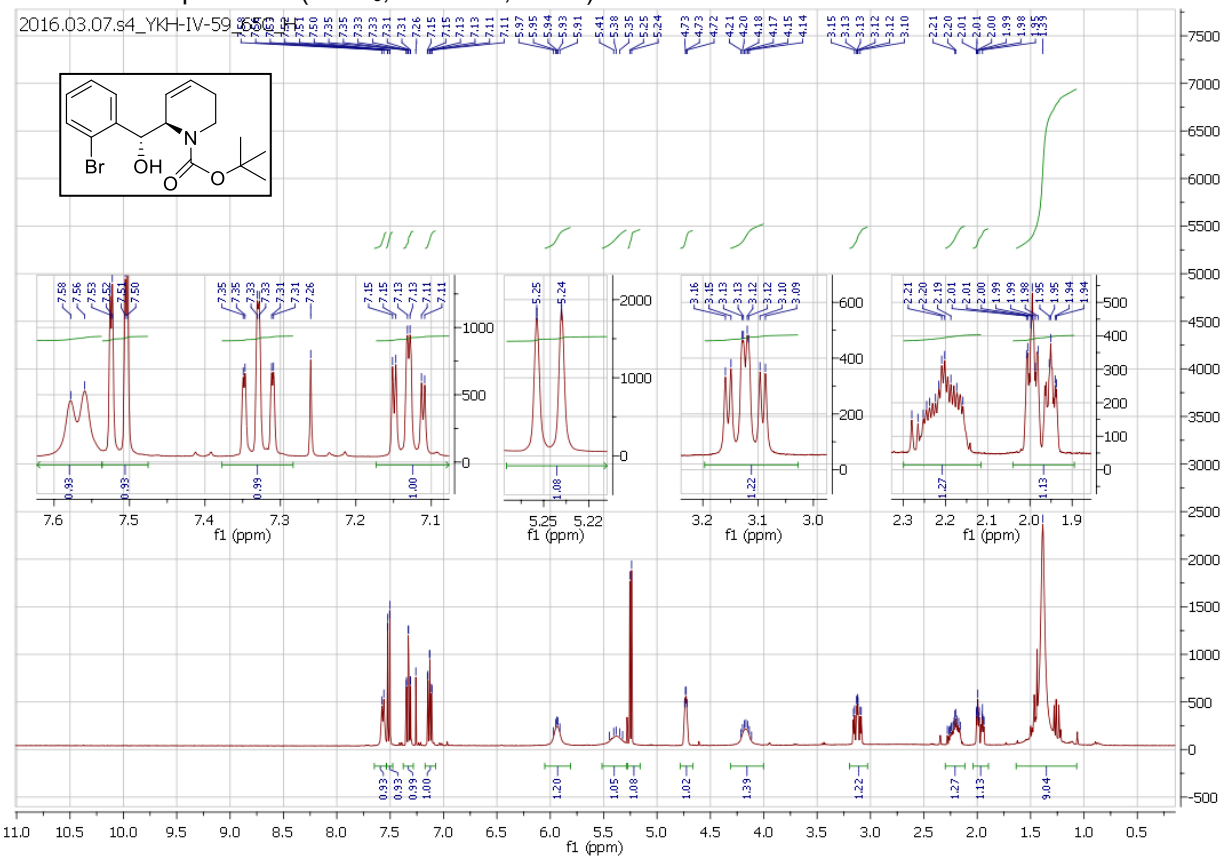
^{1}H NMR of compound **7** ($CDCl_3$, 400 MHz, 65 °C)



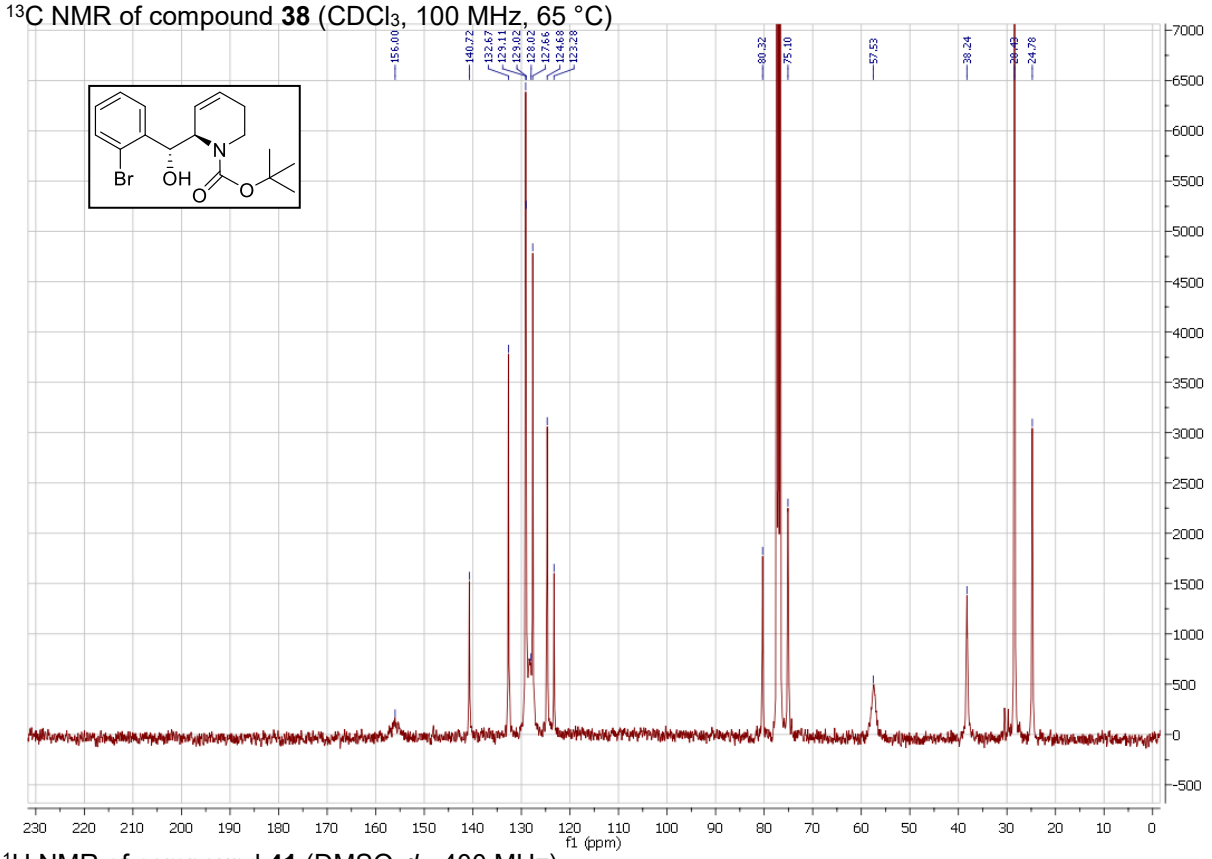
^{13}C NMR of compound **7** ($CDCl_3$, 100 MHz, 60 °C)



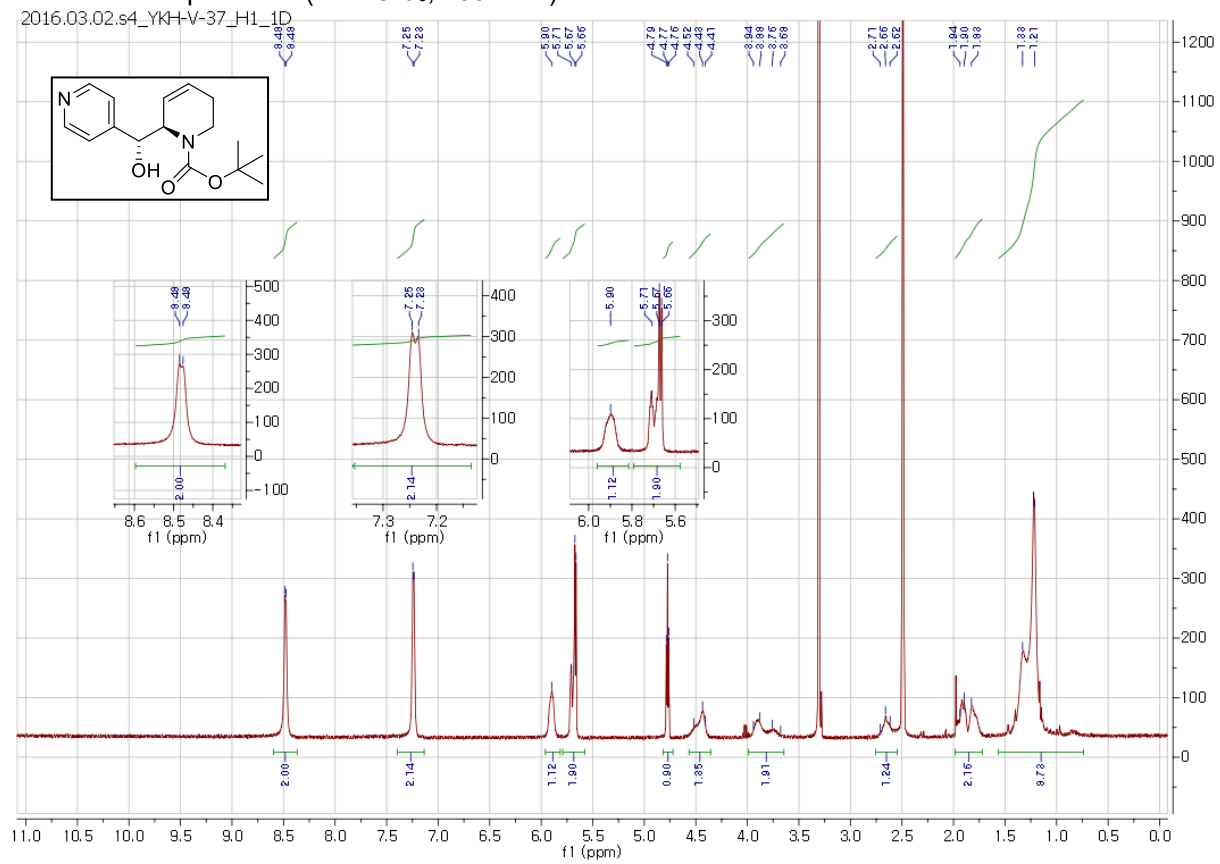
^{1}H NMR of compound **38** ($CDCl_3$, 400 MHz, 65 °C)



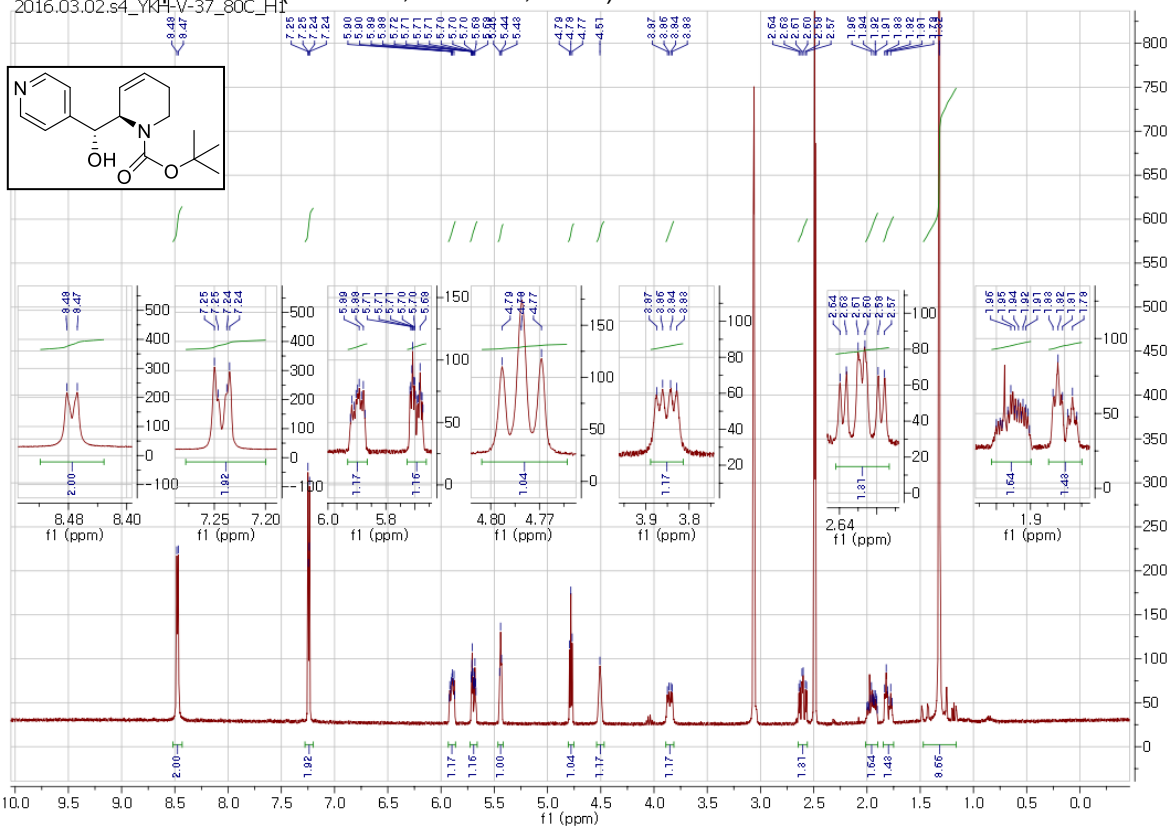
^{13}C NMR of compound **38** ($CDCl_3$, 100 MHz, 65 °C)



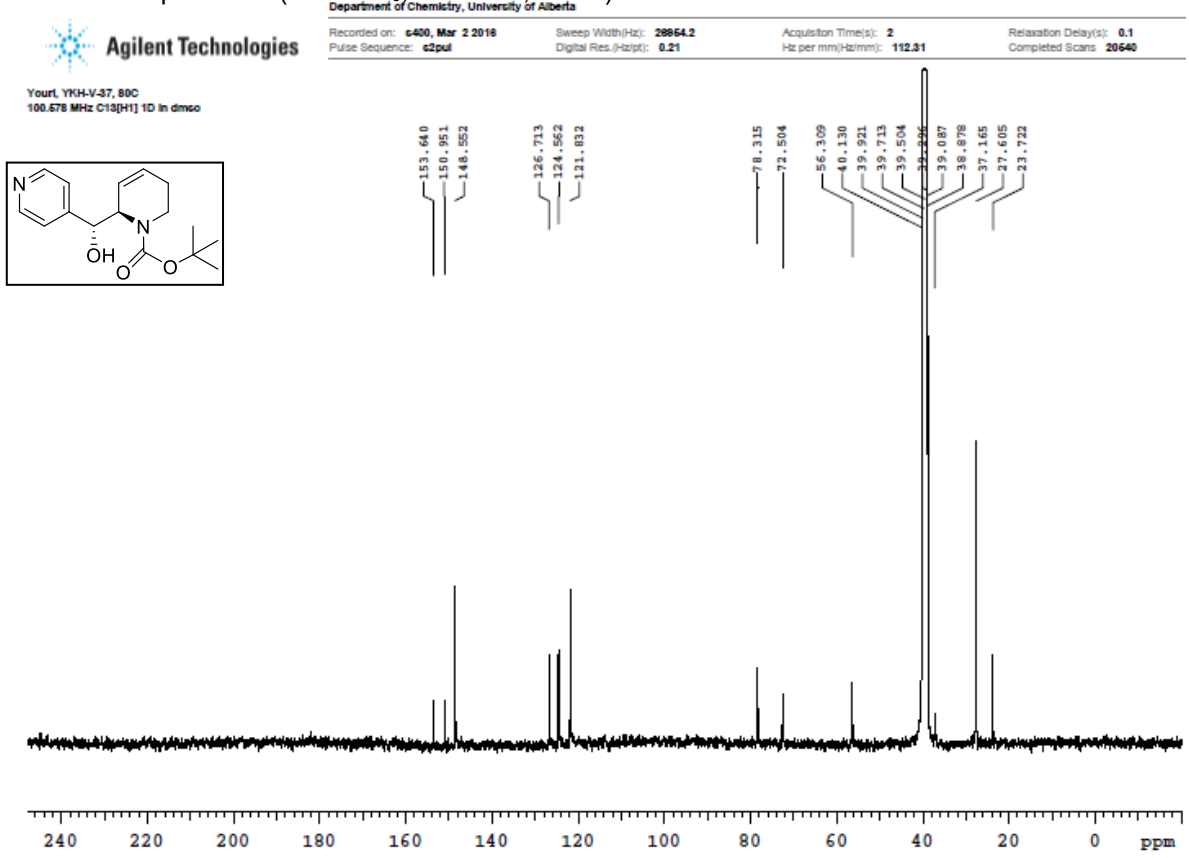
^{1}H NMR of compound **41** (DMSO-d_6, 400 MHz)



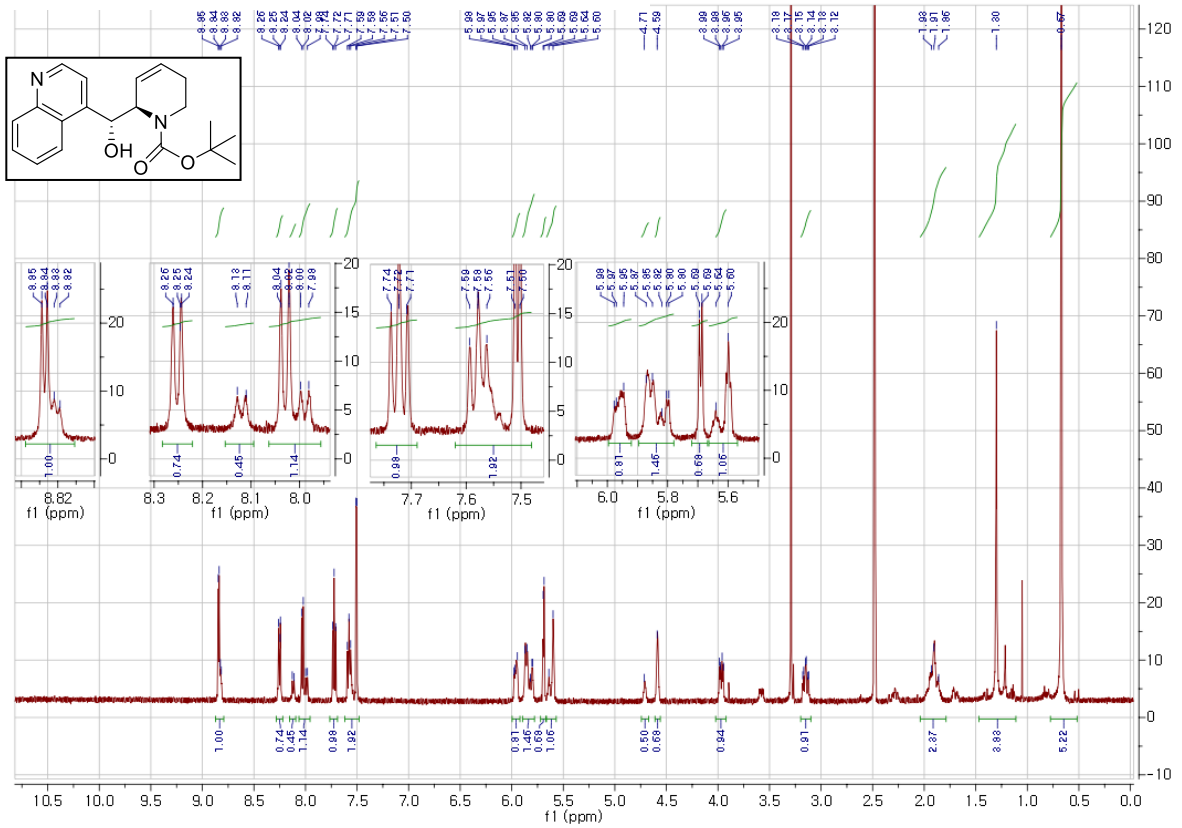
^{1}H NMR of compound **41** (DMSO-d_6, 400 MHz, 80 °C)



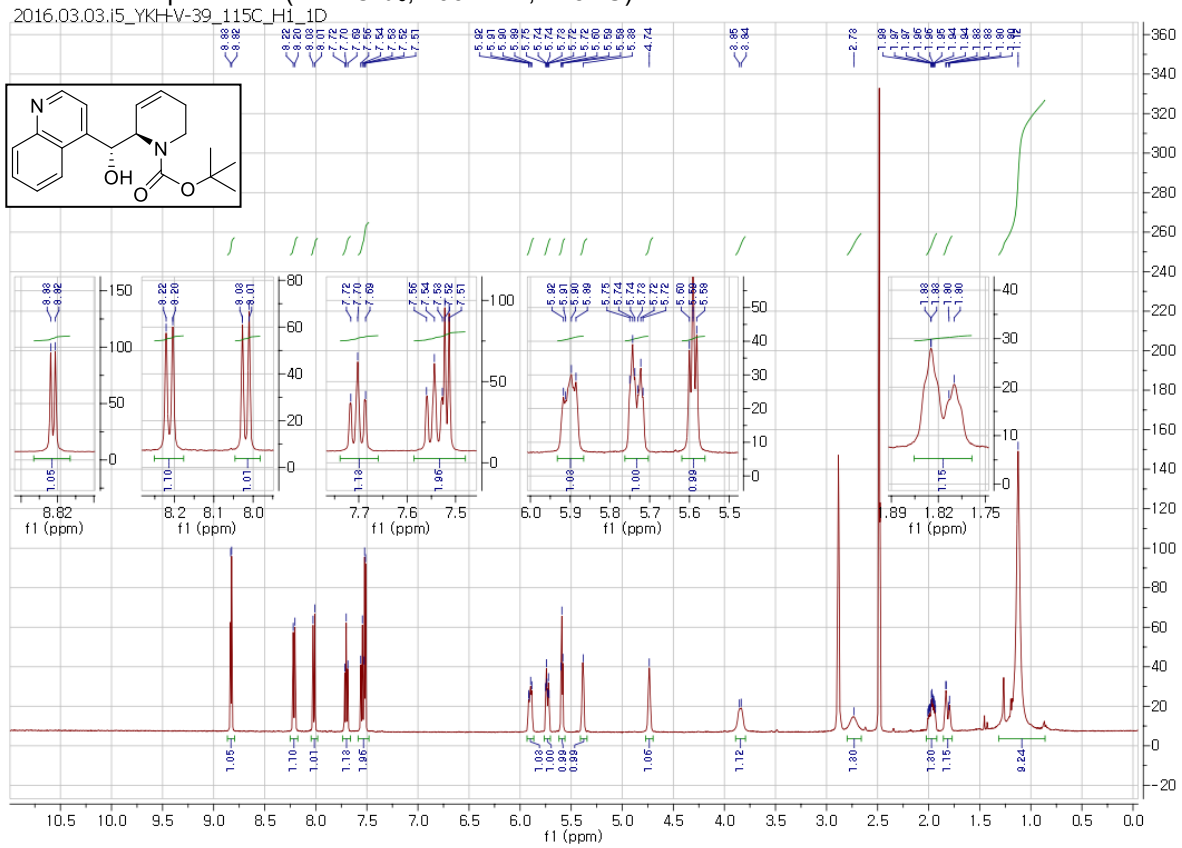
^{13}C NMR of compound **41** (DMSO-d_6, 100 MHz, 80 °C)



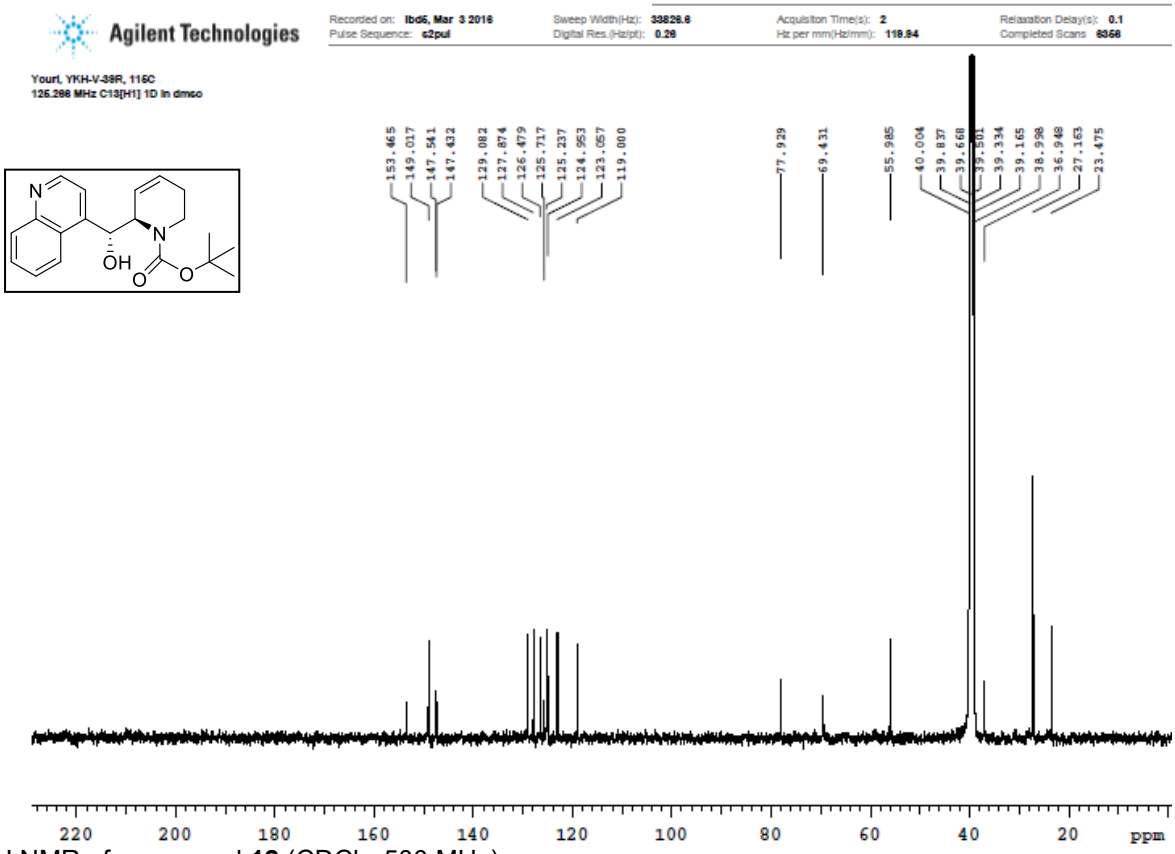
^{1}H NMR of compound **42** (DMSO-d_6, 400 MHz)



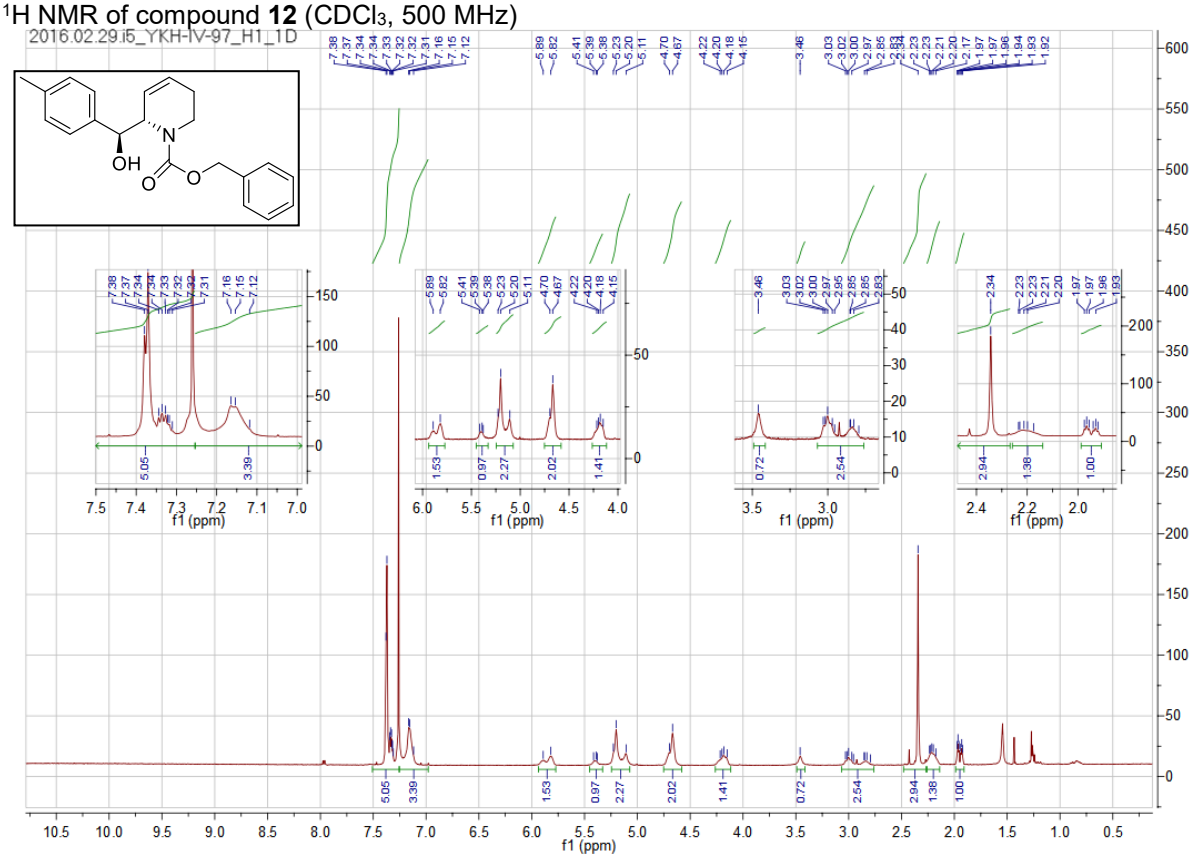
^{1}H NMR of compound **42** (DMSO-d_6, 400 MHz, 115 °C)



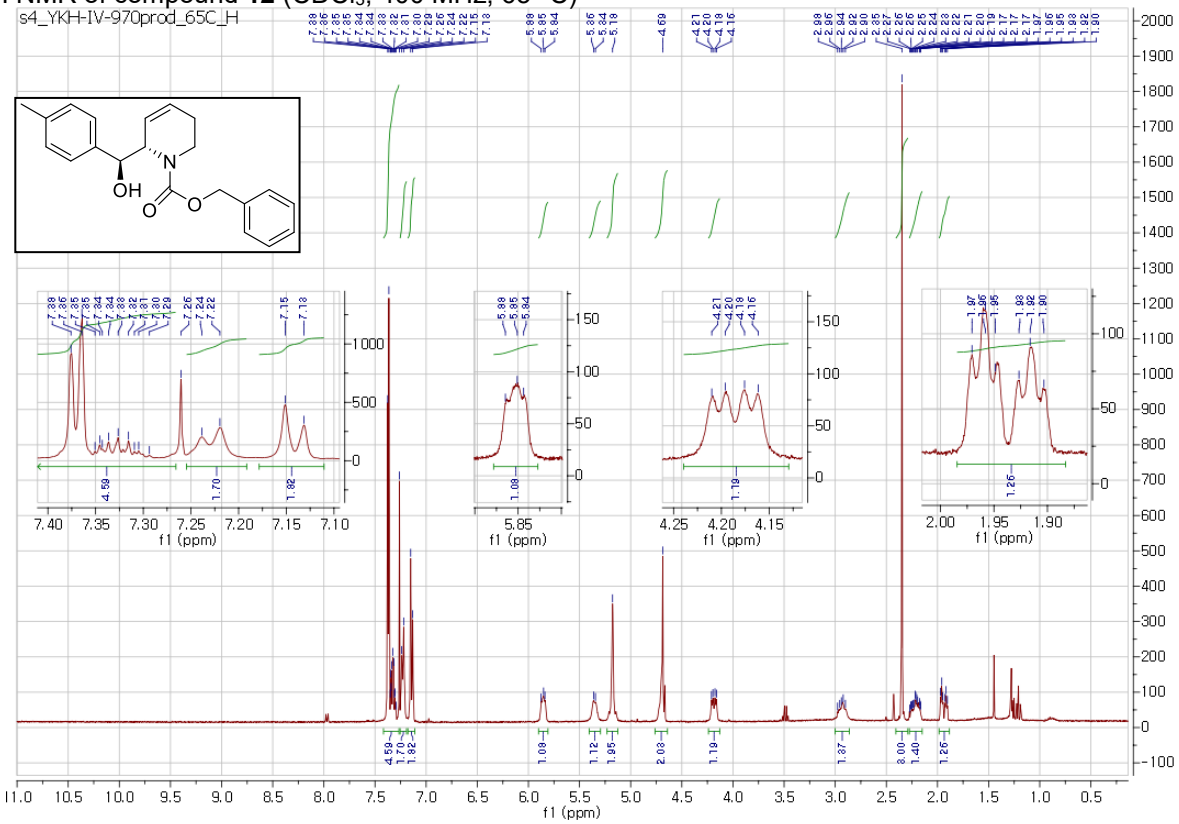
^{13}C NMR of compound **42** (DMSO-d_6, 100 MHz, 115 °C)



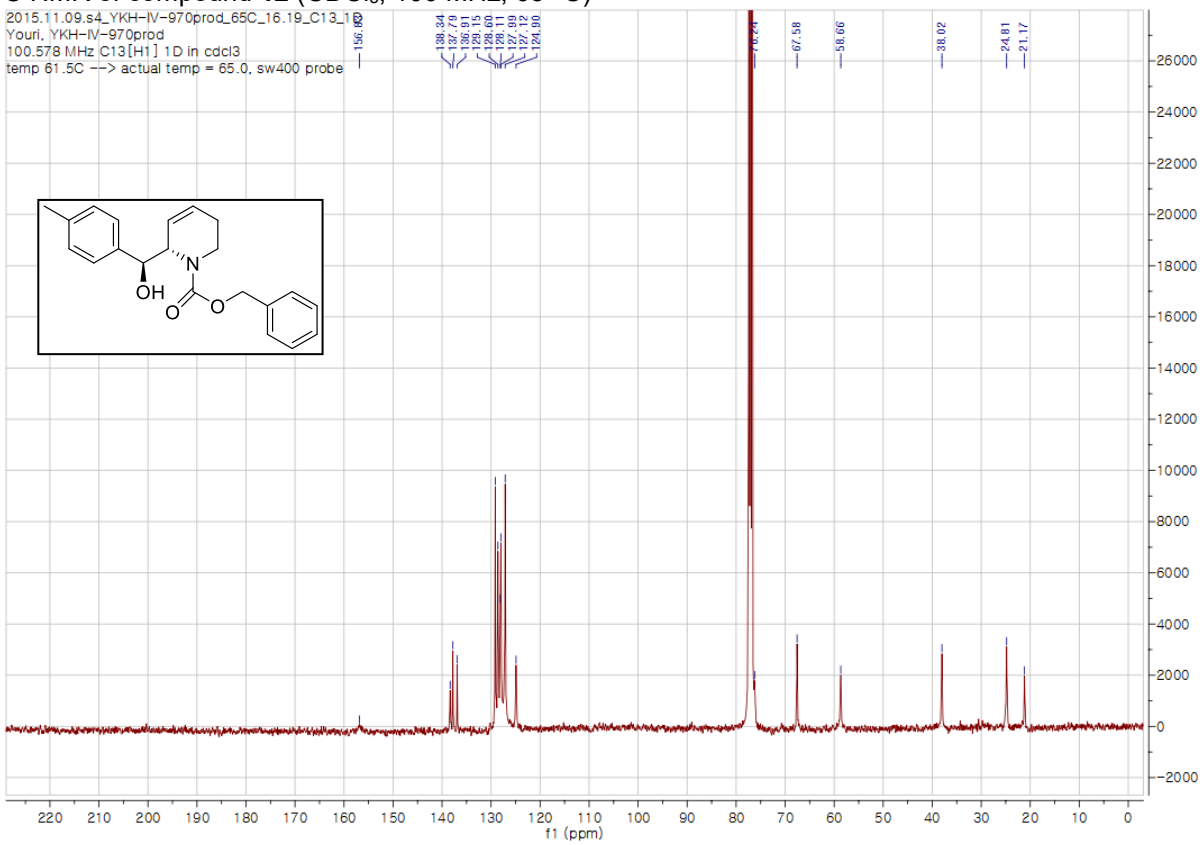
^{1}H NMR of compound **12** ($CDCl_3$, 500 MHz)



^{1}H NMR of compound **12** ($CDCl_3$, 400 MHz, 65 °C)

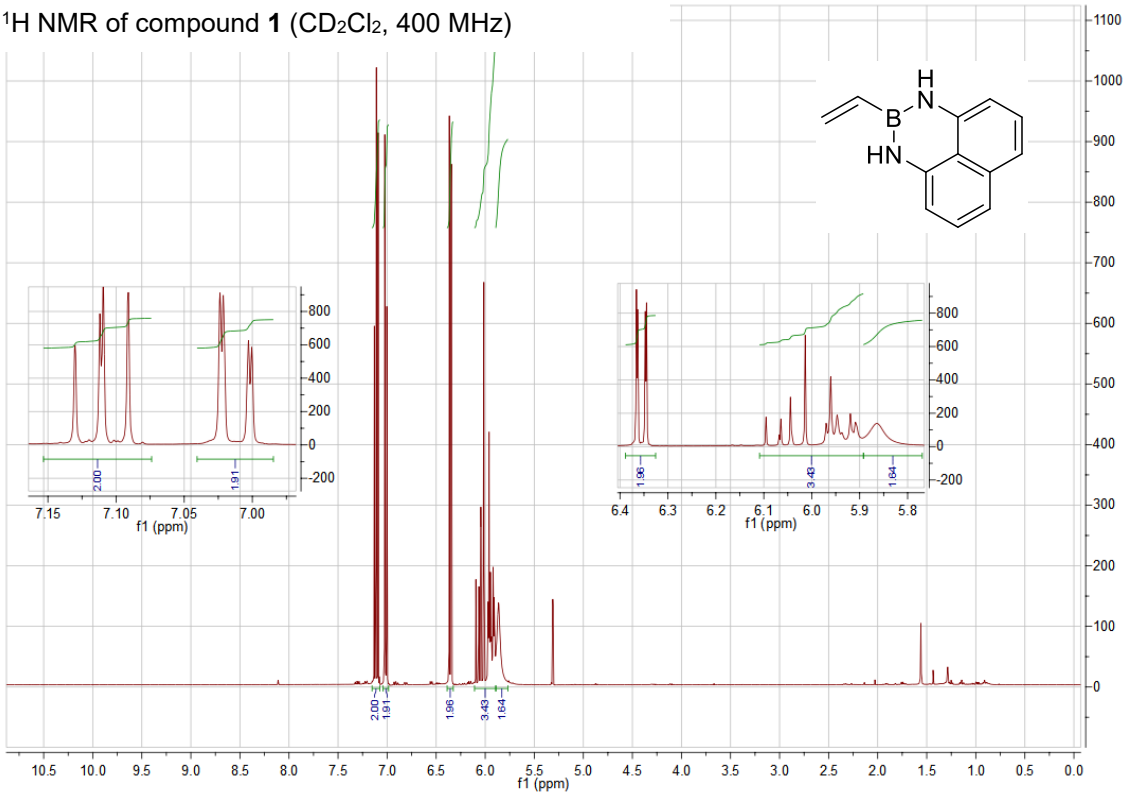


^{13}C NMR of compound **12** ($CDCl_3$, 100 MHz, 65 °C)

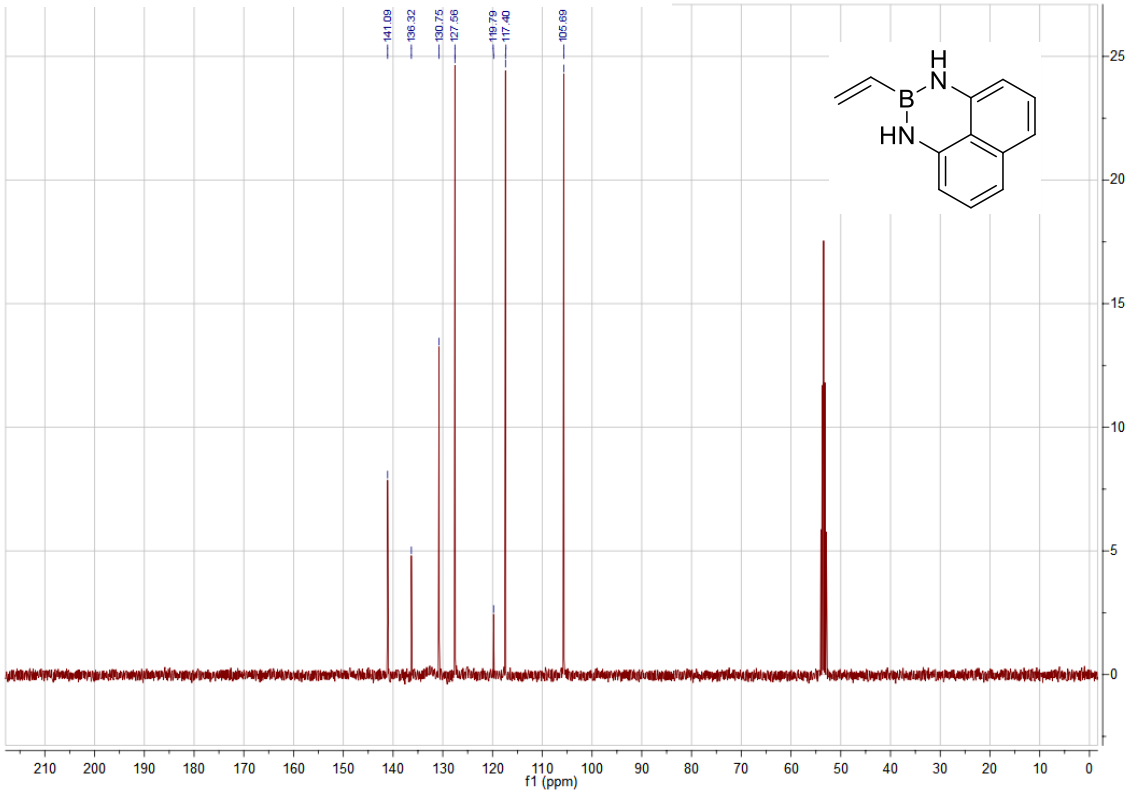


Appendix 2: Selected copies of NMR spectra of compounds found in Chapter 4

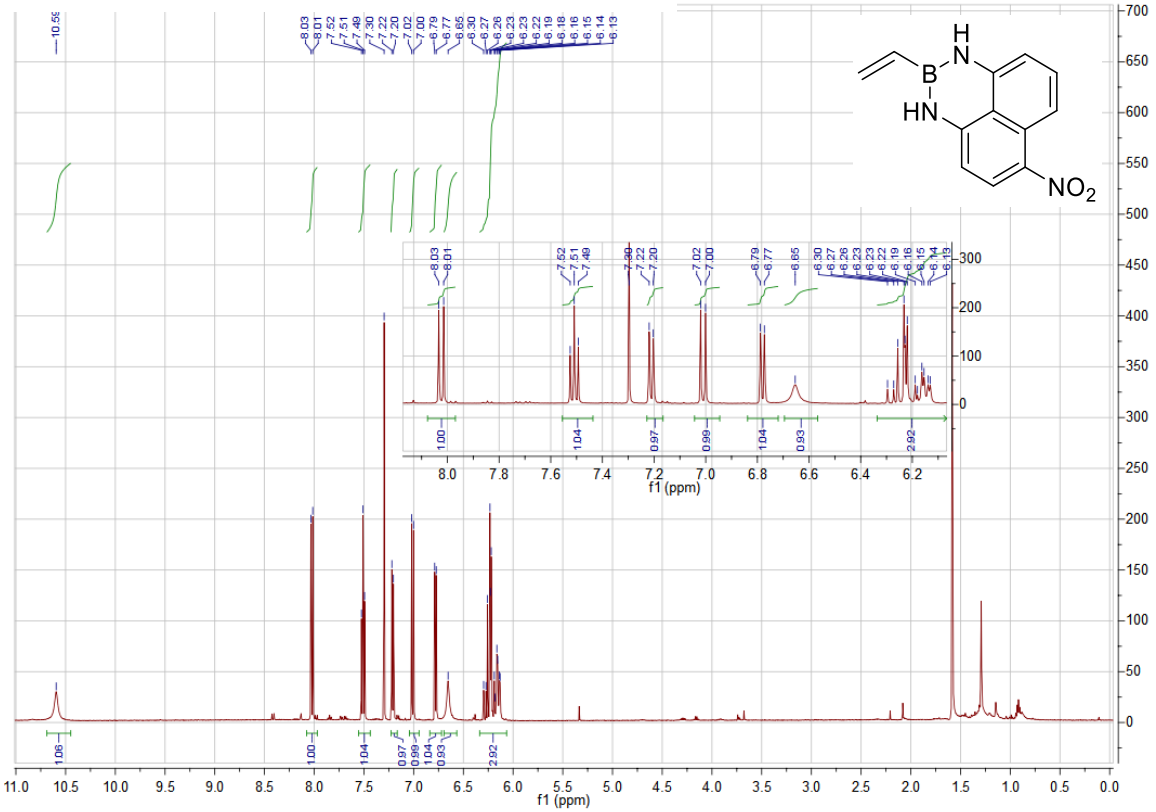
^{1}H NMR of compound **1** (CD_2Cl_2, 400 MHz)



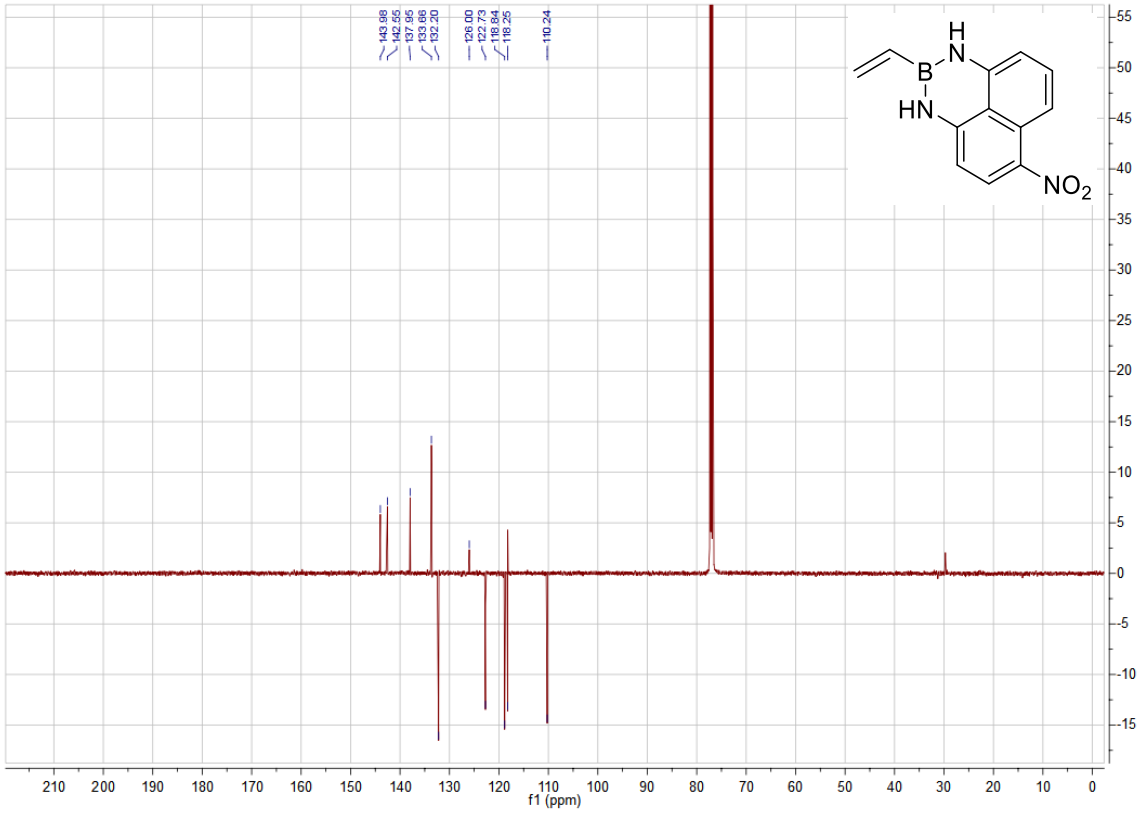
^{13}C NMR of compound **1** (CD_2Cl_2, 100 MHz)



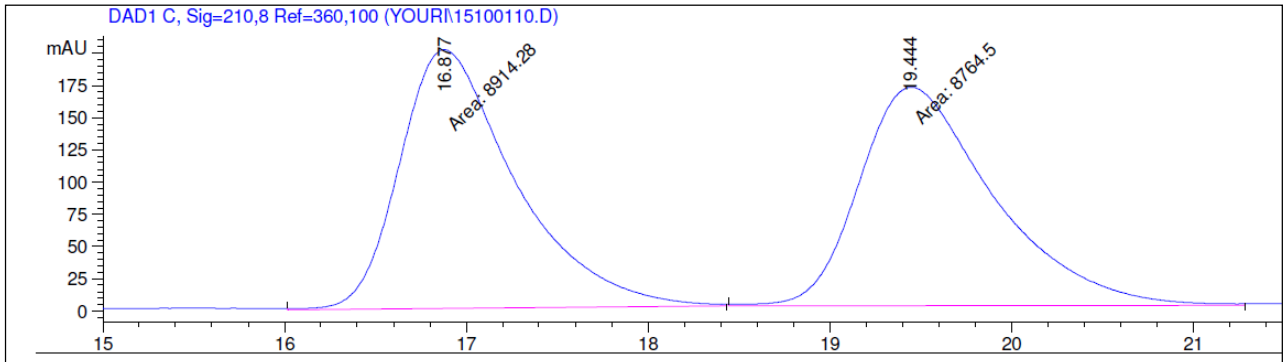
^{1}H NMR of compound **2** (CD_2Cl_2, 400 MHz)



^{13}C NMR of compound **2** (CD_2Cl_2, 100 MHz)



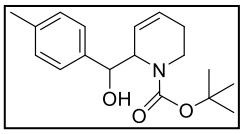
Appendix 3: Selected HPLC chromatograms of compounds found in Chapter 2 for enantiomeric excess measurements

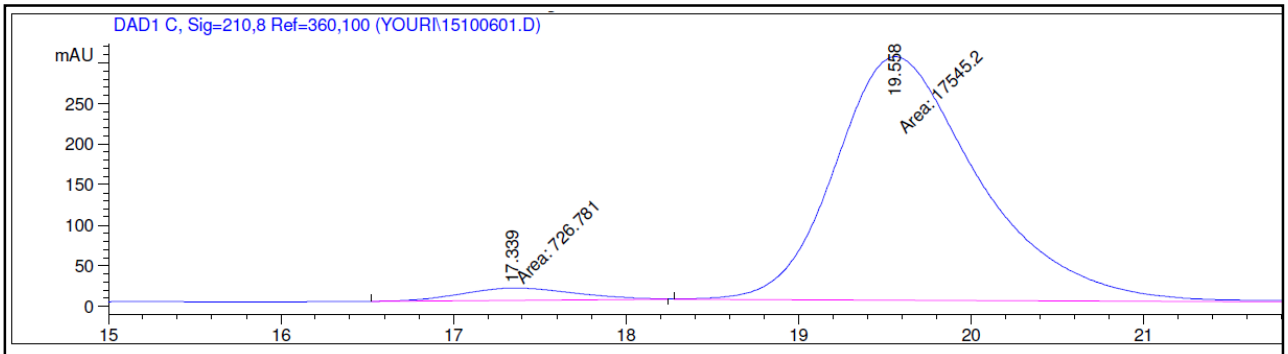


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.877	MM	0.7390	8914.28223	201.04823	50.4236
2	19.444	MM	0.8596	8764.49902	169.93340	49.5764
Totals :				1.76788e4	370.98163	

Compound *rac*-**7**

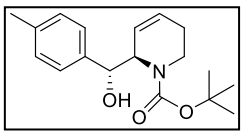


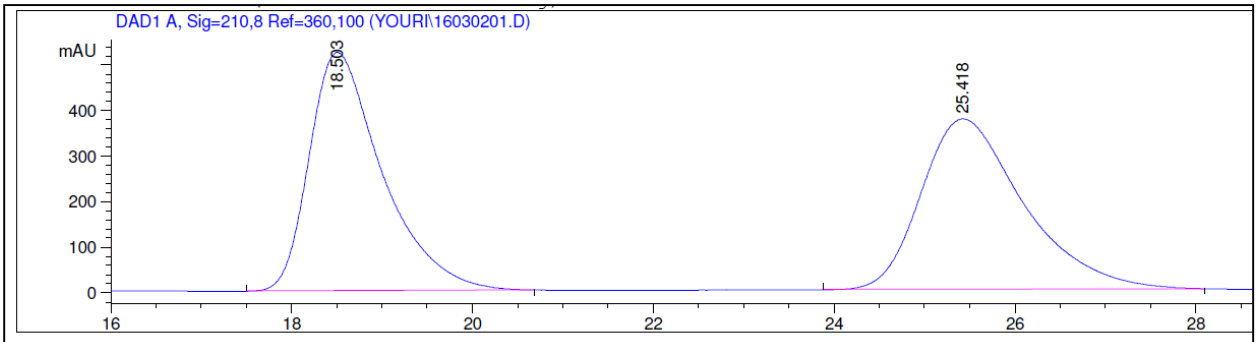


Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.339	MM	0.7780	726.78107	15.56991	3.9776
2	19.558	MM	0.9736	1.75452e4	300.34979	96.0224
Totals :				1.82719e4	315.91970	

Compound **7**

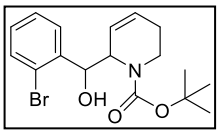


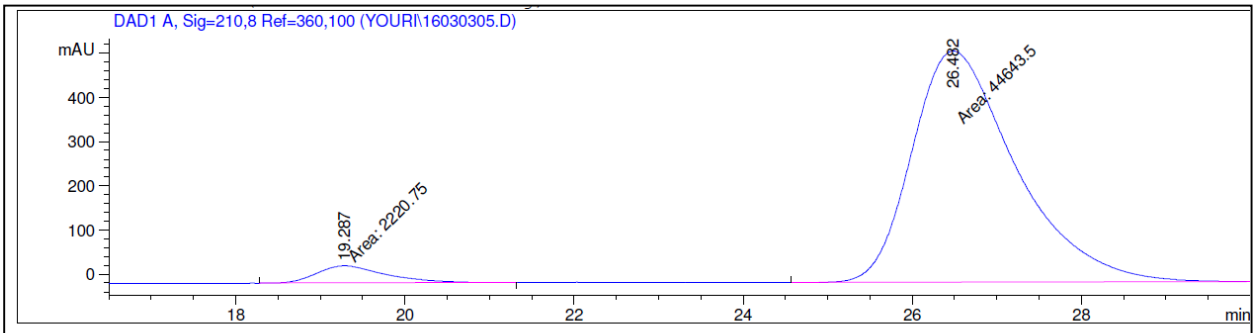


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.503	BB	0.8022	2.93236e4	522.92322	49.8967
2	25.418	BB	1.1548	2.94451e4	373.89606	50.1033

Compound *rac*-**38**

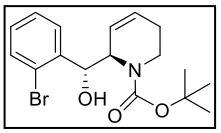


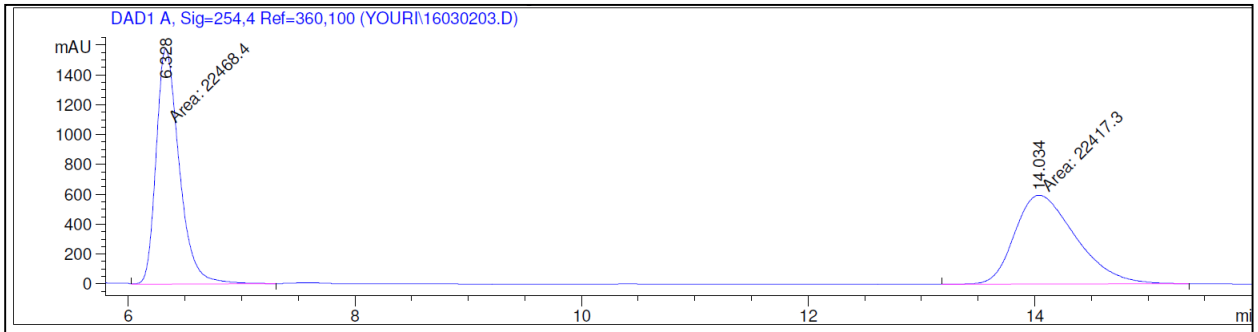


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.287	MM	0.9569	2220.74780	38.68064	4.7387
2	26.482	MM	1.4230	4.46435e4	522.87378	95.2613
Totals :				4.68643e4	561.55442	

Compound **38**

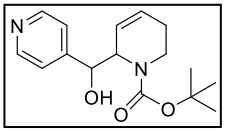


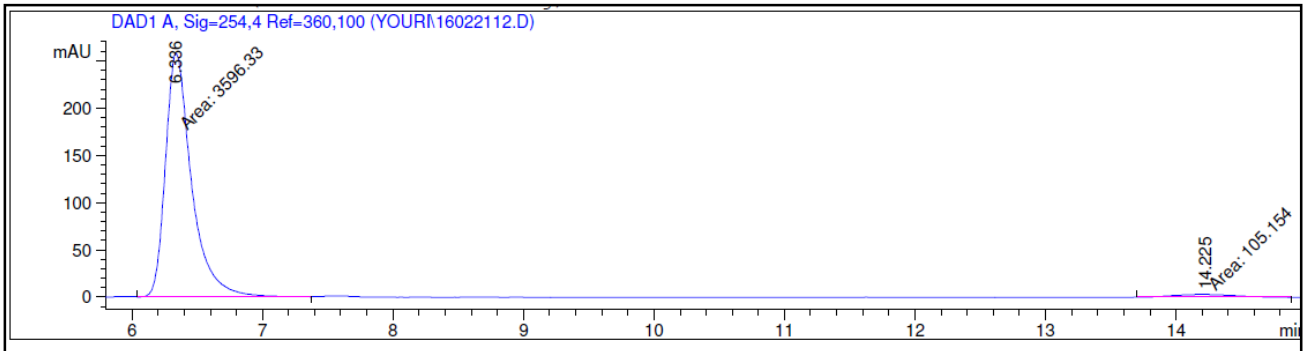


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.328	MM	0.2373	2.24684e4	1578.19604	50.0569
2	14.034	MM	0.6263	2.24173e4	596.55115	49.9431
Totals :				4.48857e4	2174.74719	

Compound *rac*-**41**

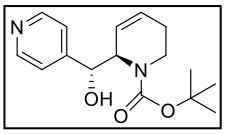


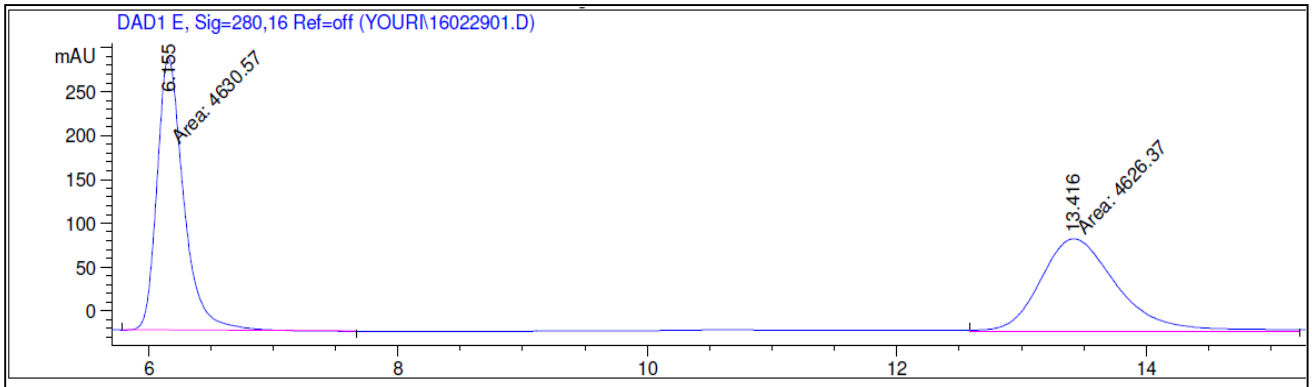


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.336	MM	0.2325	3596.32520	257.84659	97.1591
2	14.225	MM	0.5924	105.15359	2.95818	2.8409
Totals :				3701.47879	260.80477	

Compound **41**

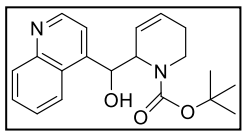


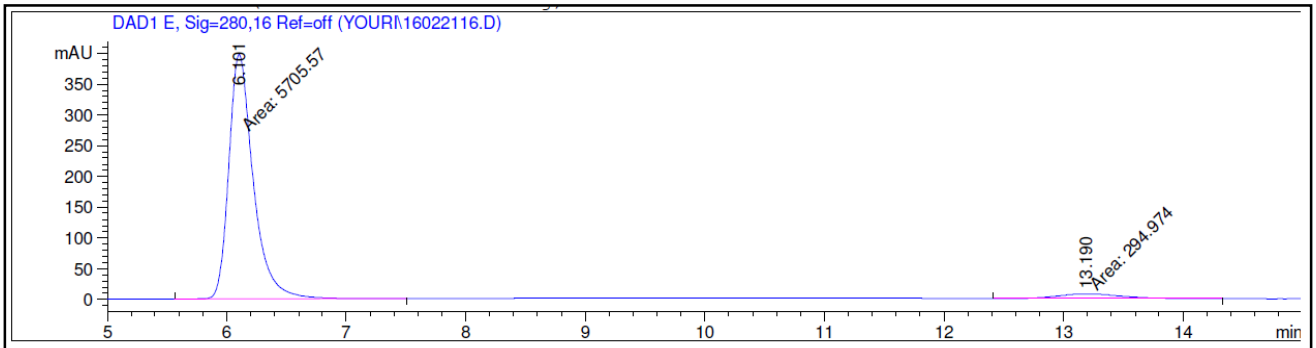


Signal 1: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.155	MM	0.2484	4630.56885	310.67099	50.0227
2	13.416	MM	0.7266	4626.36865	106.12547	49.9773
Totals :				9256.93750	416.79646	

Compound *rac*-**42**

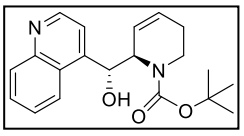


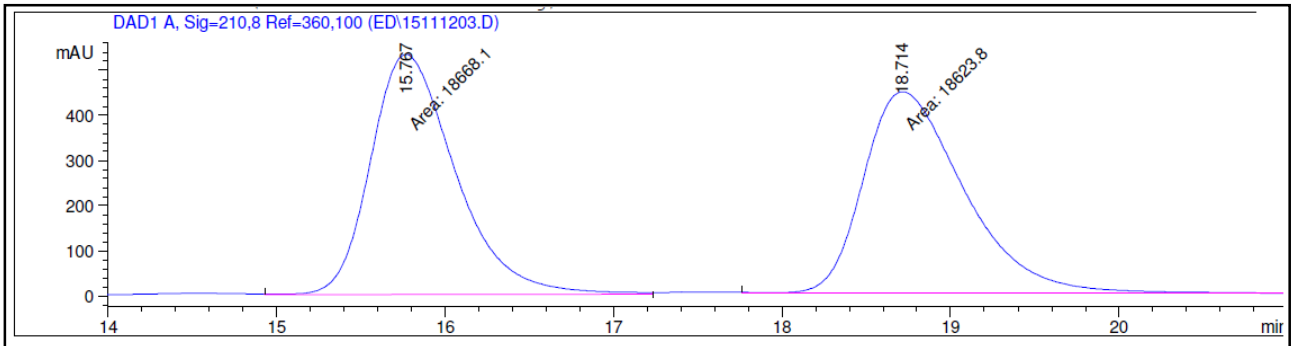


Signal 1: DAD1 E, Sig=280,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.101	MM	0.2390	5705.57324	397.95880	95.0842
2	13.190	MM	0.6482	294.97440	7.58408	4.9158
Totals :				6000.54764	405.54288	

Compound **42**

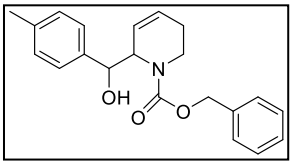


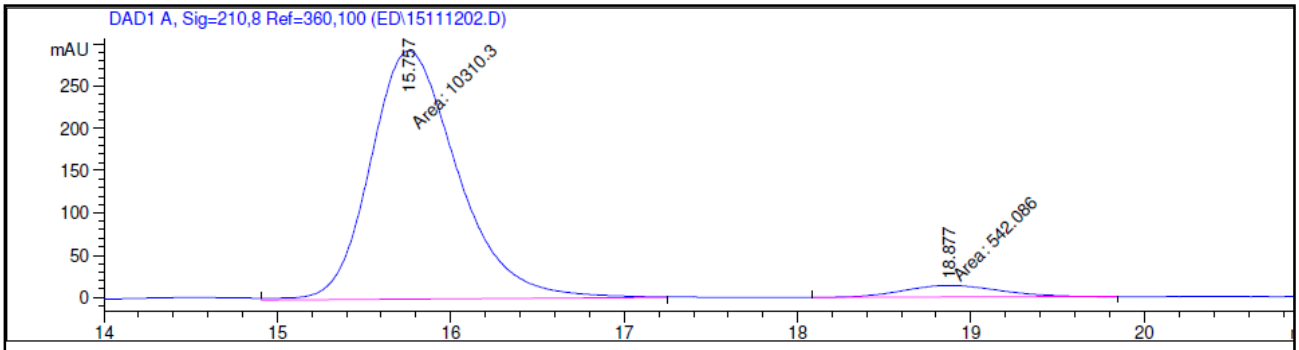


Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.767	MM	0.5848	1.86681e4	532.03448	50.0594
2	18.714	MM	0.6955	1.86238e4	446.32394	49.9406
Totals :				3.72918e4	978.35843	

Compound *rac*-**12**





Signal 1: DAD1 A, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.757	MM	0.5850	1.03103e4	293.73120	95.0049
2	18.877	MM	0.6506	542.08630	13.88588	4.9951
Totals :				1.08524e4	307.61708	

Compound **12**