Preparation of Optically Enriched Allylic Heterocyclic Organoboronates and Their Application in the Efficient Synthesis of Biologically Active Compounds

by

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Abstract

Organic chemistry is, has been, and will remain, a reliable tool for creating nearly any target molecule. Modern organic synthesis, however, is leaning towards the themes of efficiency, selectivity and strategy. In the midst of a potential energy crisis and global resource shortage, the primary goal of modern organic chemists is to access target molecules in an economically efficient and environmentally benign fashion. In this regard, organoboron reagents represent a promising solution to this challenge. These versatile compounds can be applied in a diverse range of chemical transformations to construct C−C or C−heteroatom bonds with efficacy. These reactions often exhibit high levels of chemo- and stereo-selectivity, allowing the desired products to be synthesized with little to no waste product. In addition to their attractive synthetic versatility, most organoboron derivatives present superior stability and environment-friendly features. In this thesis, efficient synthetic methods were developed to provide synthetically valuable chiral alkylboronates. These methods are based on an "early introduction" strategy, which applies established asymmetric synthetic protocols on substrates bearing a pre-installed boronyl unit. Subsequently, practical synthetic applications of novel chiral alkylboronates were also investigated, leading to a variety of biologically important natural products and pharmaceutical drugs.

As a class of newly emerged synthetic intermediates, chiral β-boronyl carbonyl compounds exhibit attractive synthetic utility in stereoselective C–C bond formation reactions and carbonyl modifications. In Chapters 2 and 3, catalytic

asymmetric conjugate reduction reactions of 3-boronyl-3-alkyl, aryl α,β-unsaturated esters with organosilane reagents were developed. As a novel approach to access this class of chiral alkylboronates, the methods also allowed the use of organosilanes as the nucleophilic hydride source, which has the advantage of being air-stable, inexpensive and environmentally friendly.

Along with exploring more efficient preparative methods for chiral alkylboronates, my studies also involved expanding their synthetic applications, including new bond formation methods with controlled regio-, stereoselectivities as well as asymmetric total syntheses of biologically active target molecules. In Chapter 4, through careful optimization, chiral dehydropiperidinyl boronates were accessed in gram-scale and high optical purity. This scaffold was then employed as the key intermediate for a concise enantioselective total synthesis of the antimalarial drug mefloquine. The absolute configuration and antimalarial activity of all resulting mefloquine stereoisomers and their analogues were also investigated. Moreover, efforts toward an asymmetric total synthesis of the more challenging alkaloid quinine were also initiated. These syntheses and their optimization are detailed at Chapter 4.

The ultimate challenge for the application of chiral allylic heterocyclic boronates would be their use in stereospecific Suzuki-Miyaura cross-coupling reactions, which has long been regarded as one of the last frontiers in cross-coupling chemistry. This challenge is not only due to the notorious restrictions imposed upon the Suzuki-Miyaura coupling of secondary alkylboronates, but also from the control of regio- and stereoselectivity. Upon careful examination of a chiral

catalytic system and other reaction conditions, a ligand controlled regiodivergent and enantiospecific cross-coupling of these chiral allylic heterocyclic boronates was achieved with high efficiency. It also found useful applications in the formal syntheses of the alkaloid (+)-anabasine and the antidepressant drug (+)-paroxetine. Detailed optimization, substrate scope, and synthetic applications will be described in Chapter 5.

Preface

Chapter 2 of this thesis has been published as Ding, J.; Hall, D. G. "Preparation of Chiral Secondary Boronic Esters *via* Copper-Catalyzed Enantioselective Conjugate Reduction of β-Boronyl-β-Alkyl α,β-Unsaturated Esters", *Tetrahedron* **2012**, *68*, 3428–3434. As the sole experimentalist, I was responsible for the reaction optimization, study of substrate scope, data collection and analysis. I also wrote the manuscript with assistance from Hall, D. G. Hall, D. G was the supervisory author and was involved with concept formation and project initiation.

Chapter 3 of this thesis has been published as Ding, J.; Lee, J. C. H.; Hall, D. G. "Stereoselective Preparation of β-Aryl-β-Boronyl Enoates and Their Copper-Catalyzed Enantioselective Conjugate Reduction", *Org. Lett.* **2012**, *14*, 4462–4465. I was responsible for the reaction optimization, study of substrate scope, data collection and analysis that involved the copper-catalyzed enantioselective conjugate reduction of β-aryl-β-boronyl enoates. My previous colleague Lee, J. C. H. was responsible for the reaction optimization, study of substrate scope, data collection and analysis that involved in the stereoselective preparation of β-aryl-β-boronyl enoate substrates. I also wrote the manuscript with assistance from Hall, D. G. and Lee, J. C. H. Hall, D. G was the supervisory author and was involved with concept formation and project initiation.

Chapter 4 of this thesis has been published as Ding, J.; Hall, D. G. "Concise Synthesis and Antimalarial Activity of All Four Mefloquine Stereoisomers Using a Highly Enantioselective Catalytic Borylative Alkene Isomerization", *Angew. Chem. Int. Ed.* **2013**, *52*, 8069–8073. As the sole chemistry experimentalist, I was responsible for the reaction optimization, syntheses of all mefloquine stereoisomers, data collection and analysis. The organization Medicines for Malaria Venture (MMV) was responsible for the study of antimalarial activity of mefloquine stereoisomers and anlogs. I also wrote the manuscript with assistance from Hall, D. G. Hall, D. G was the supervisory author and was involved with concept formation and project initiation.

Chapter 5 of this thesis has been accepted for publication as Ding, J.; Rybak, T.; Hall, D. G. "Merging Stereocontrol and Regiodivergent Selectivity in Suzuki-Miyaura Cross-Coupling of Heterocyclic Allylic Boronates", *Nature Comm*., **2014***, accepted*. My current colleague Rybak, T. was partly responsible for the study of substrate scope, data collection and analysis that involved the cross-coupling of chiral dihydropyranyl boronates, which is specified in Chapter 5. I was responsible for the rest of the experimental work. Hall, D. G was the supervisory author and was involved with concept formation and manuscript composition.

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I am also grateful for my Supervisory Committee and my PhD Examination Committee members: Professor Jeffrey Stryker, Professor Charles Lucy, Professor Derrick Clive, Professor Ravin Narain and Professor Paul Blakemore for their guidance and help throughout the thesis research. During my five-year PhD study, the annual progress report meetings with my Supervisory Committee members have always been stimulating. During the PhD candidacy examination, I also benefited greatly from their diverse opinions and suggestions.

The members of the Hall group, past and present, have provided great support to my professional and personal time at the University of Alberta. I am fortunate to have worked with such a fun group that is never lacking in good friendship, advice and collaboration. I am particularly grateful to Jack Lee, Hongchao Zheng, Ho-Yan Sun, Ed Fu, Dr. Nicolas Gernigon, and Dr. Jin-Yong Lu for their friendship and help. Outside of the Hall group, I thank my great friends that have continuously inspired me and patiently taught me both English and organic chemistry in the past five years: Colin Diner, Gaetano Stellacci, Anushka Jayasuriya, Mike Downey, Drew Hawranik, Terry Heidt, Yonghoon Kwon, and

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The research presented in this thesis would not have been possible without the assistance of various funding agencies. I would like to acknowledge the support of Novartis Pharmaceuticals Canada for providing me with a graduate scholarship. My gratitude also extends to the Natural Research and Engineering Research Council (NSERC) Canada and the University of Alberta for supporting my research. I am also thankful for the travel award administered by the Faculty of Graduate Studies and Research (FGSR) that allowed me attend the 17th International Symposia on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS) held at Fort Collins, United States.

Last but certainly not least, I would like to thank my fiancée Diana Hyui Sxin Tan, my family and her family for their love and encouragement. They are always there for me, especially during difficult times in my PhD pursuit, giving me support and optimism throughout my overseas study. Here I would like to express my sincere appreciation to all of them.

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List of Schemes

List of Abbreviations

Ac	Acetyl
acac	Acetylacetonyl
ACS	American Chemical Society
Ar	Aryl group
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
*t*Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
br	Broad
n-Bu	Normal Butyl
t-Bu	*tert*-Butyl
calcd	Calculated
cm^{-1}	Wavenumbers
COD	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether
PMHS	Polymethylhydrosiloxane
Cy	Cyclohexyl
dan	1,8-Diaminonaphthalene
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM	Dichloromethane
HDA	Hetero-Diels-Alder
IEDDA	Inverse electron-demand Diels-Alder
ACC	*N*-Amino cyclic carbamate
CD	Circular dichroism
ORD	Optical totatory dispersion
XRD	X-ray diffraction
PNBA	*p*-Nitrobenzoic acid
DIAD	Diisopropyl azodicarboxylate
DEAD	Diethyl azodicarboxylate
BQ	Benzoquinone
IBX	2-Iodoxybenzoic acid
TPAP	Tetrapropylammonium perruthenate
NMO	*N*-Methylmorpholine *N*-oxide
PCC	Pyridinium chlorochromate
DMP	Dess-Martin periodinane
DMA	*N,N*-Dimethyl aniline
dd	Doublet of doublets
ddd	Doublet of doublet of doublets

de	Diastereomeric excess
DFT	Density functional theory
DIPPF	Diisopropylphosphinoferrocene
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dq	Doublet of quartets
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact
eq	Equation
equiv	Equivalents
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour
HPLC	High performance liquid chromatography

HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MS	Molecular sieves
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
Ph	Phenyl
pin	Pinacolato
PMB	*p*-methoxybenzyl
PMHS	Polymethylhydrosiloxane
*i*Pr	Isopropyl
q	Quartet
qd	Quartet of doublets
qq	Quartet of quartets

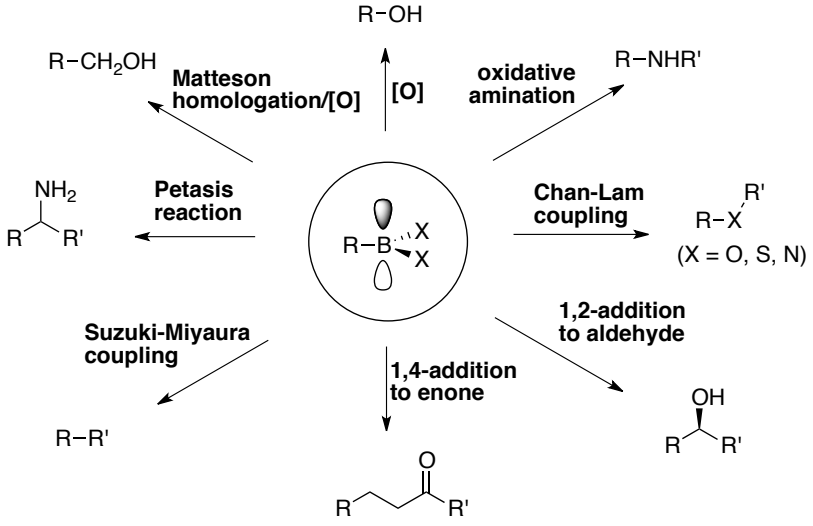
qt	Quartet of triplets
quint	Quintet
rt	Room temperature
SET	Single electron transfer
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
td	Triplet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
tol	Tolyl
Ts	*para*-Toluenesulfonyl
tt	Triplet of triplets
tq	Triplet of quartet

Chapter 1 Introduction: Preparation and Synthetic Applications of Chiral Alkylboronates

1.1 The unique aspects of organoboron reagents in organic synthesis

The commencement of modern organic synthesis was marked in 1828, when Friedrich Wöhler achieved the synthesis of urea from ammonium cyanate.[1] Since then, organic synthesis has experienced exponential growth to become a reliable tool in creating nearly any target molecule. It has found widespread applications in numerous scientific fields including pharmaceutical, petrochemical, agrochemical, food manufacture, fragrance etc. As we progress into the 21st century, in the midst of a potential energy crisis and global resource shortage, the primary objective facing organic chemists is to find new synthetic strategies that are economically efficient and environmentally benign.[2] In approaching this objective, organoboron compounds have made remarkable contributions, as evidenced by the two Nobel prizes awarded in this field.[3] The most significant advantage of these versatile compounds is their ubiquitous synthetic utility in regards to various bond formation methodologies under ambient conditions.[4] The unique electronic configuration of the boron atom results in a trivalent ground state geometry for organoboron compounds, which gives rise to an open coordination site for a variety of nucleophilic reactants. This interaction is the key for the prevalent chemical transformations involving organoboron reagents, providing either efficient cross-coupling strategies, or direct nucleophilic modification to access various chemical functionalities. As versatile synthetic intermediates, not only can these organoboron compounds be oxidized directly to access alcohols or amines, they are also involved in a wide variety of carbon-carbon bond formation reactions, including Matteson homologation, Petasis reaction, Suzuki-Miyaura cross-coupling, rhodium catalyzed 1,2- or 1,4- addition reactions, allylboration of carbonyl and imine compounds, among many others (Scheme 1-1).[4] Moreover, the copper catalyzed Chan-Lam coupling reaction

further expands the synthetic utility of organoboron compounds toward carbon-heteroatom bond formation. In addition to their attractive synthetic versatility, these organoboron reagents hold several other significant features. Unlike other organometallics such as Grignard reagents or organolithium compounds, most organoboron derivatives exhibit superior stability toward air and moisture, which allow ease of handling and milder reaction conditions. Furthermore, organoboron compounds are environmentally friendly because of their low toxicity and ultimate oxidation into boric acid. Owing to these attributes, research and development of organoboron chemistry has evolved as one of the frontiers in modern organic chemistry. Over the last few decades, tremendous progress has been witnessed in the development of the preparative methodologies and synthetic applications of organoboron compounds in both academic laboratories and the pharmaceutical industry.



Scheme 1-1: Representative examples of chemical transformations involving organoboron compounds.

1.2 Chiral organoboron compounds: classic applications and recent advances

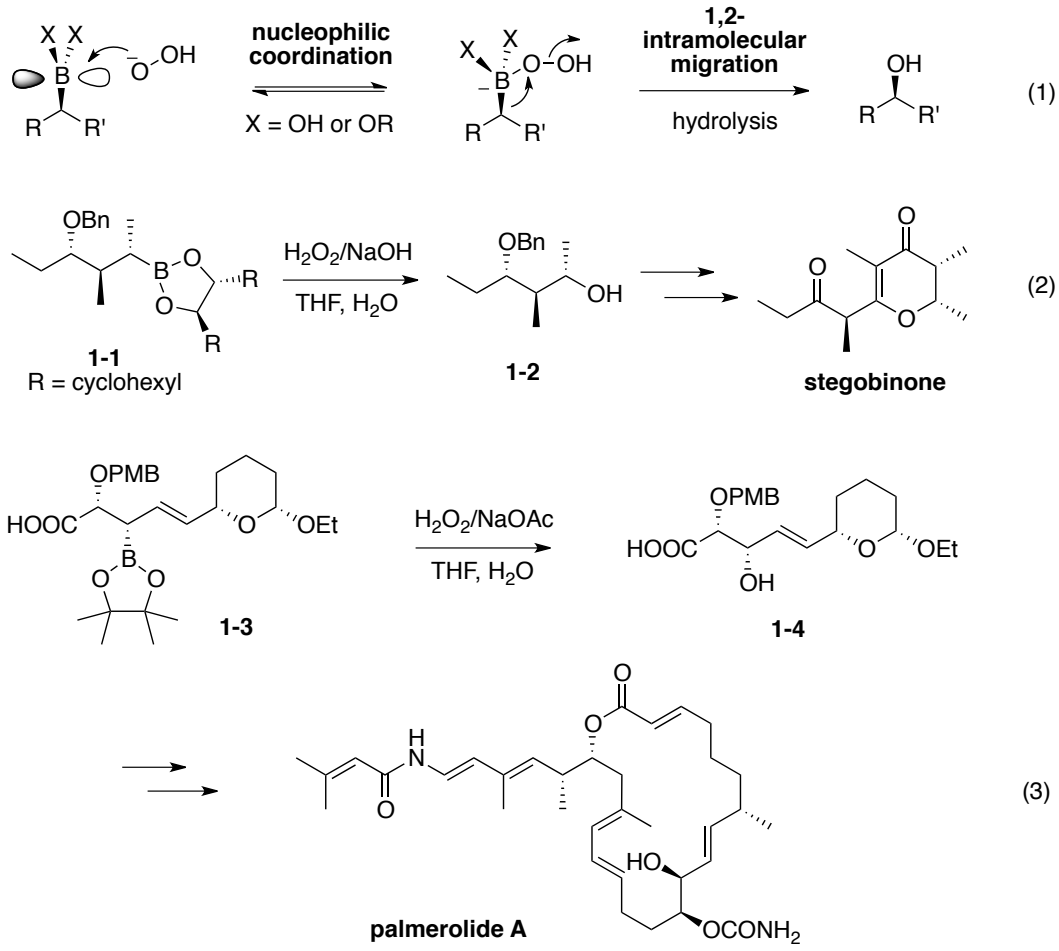
Since the introduction of asymmetric syntheses by Fisher and Marckwald more

than a century ago, the concept of chirality in organic chemistry has been long understood.[5] The significance of pure enantiomers in pharmaceutical chemistry, however, was not recognized until half of century ago.[6] Numerous clinical and pharmaceutical examples have shown that one enantiomer often has different biological activity and therapeutic effect than its non-superimposable mirror image.[6,7] Therefore, enantioselective synthesis is now of great importance in the pharmaceutical industry. Chiral organoboron compounds demonstrate great advantages in this sense, due to their wide range of synthetic utilities and recognized "greenness". Besides the fact that these optically enriched organoboron compounds can easily be functionalized as chiral surrogates, they are also involved in a diverse range of carbon-carbon and carbon-heteroatom bond formation reactions that usually occur with preservation of stereochemistry. Representative examples of asymmetric transformation of chiral organoboron compounds will be presented in the following sections.

1.2.1 Oxidation of chiral organoboronates to optically enriched alcohols

Oxidation of organoboron compounds with hydrogen peroxide was first reported in the 1930s when aryl and alkyl boronic acids were oxidized to give the corresponding alcohols.[8] Since then, organoboronic acids and their derivatives have become one of the most commonly used precursors of alcohol. The oxidation mechanism is accepted to be nucleophilic coordination to the boron center followed by intramolecular 1,2-migration of the carbon center (Scheme 1-2, Equation 1).[4] When chiral alkylboronates are subjected to this oxidation process, this migration proceeds stereospecifically with retention of stereochemistry. In Scheme 1-2, optically pure alkylboronate **1-1** was oxidized by alkaline hydrogen peroxide to give chiral secondary alcohol **1-2** with enantiomeric retention, which eventually lead to the completed synthesis of natural sex pheromone stegobinone (Scheme 1-2, Equation 2).[9] Another example was recently demonstrated in the Hall Group for the asymmetric synthesis of the anticancer macrolide palmerolide

A, in which the highly functionalized chiral boron pinacolate **1-3** was oxidized in the same manner to yield the corresponding alcohol **1-4** without any erosion of stereochemistry (Scheme 1-2, Equation 3).[10]

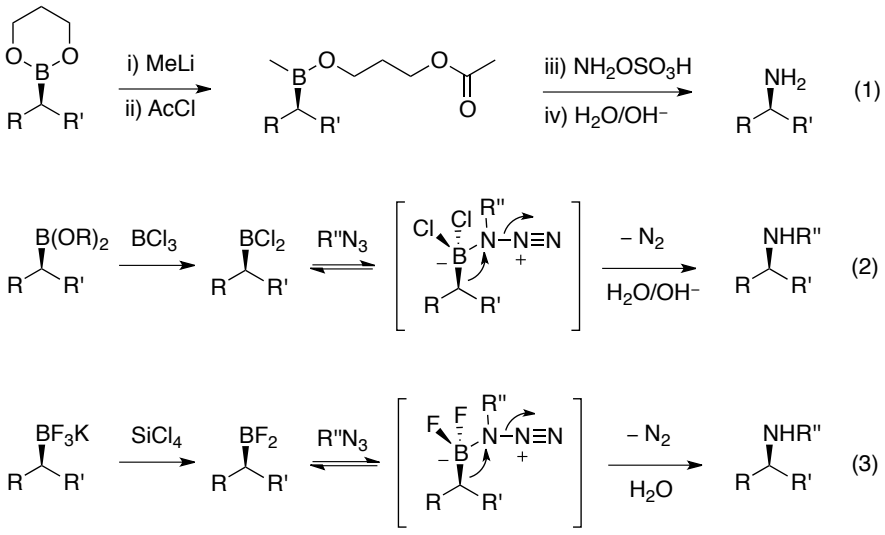


Scheme 1-2: General mechanism and selected examples of stereoselective oxidation of chiral alkylboronates.

1.2.2 Stereospecific transformation of chiral alkylboronates to amines

Compared to the well-established stereoselective oxidation of organoboronates, the nitrogen replacement of boron occurs under restricted conditions, which therefore have limited synthetic applications. Organoboronic acids and their ester derivatives are not electrophilic enough to initiate the oxidative

coordination/migration process depicted in Scheme 1-2 (Equation 1). Conventional solutions require the conversion of boronic acids or esters to the corresponding, more electrophilic borinic esters or dihaloboranes prior to treatment with an electrophilic amine source. For example, chiral secondary propanediol boronates can be subjected to sequential treatment of methyllithium and acetyl chloride to afford the corresponding borinic esters. These intermediates are electrophilic enough to undergo stereospecific amination when reacted with the hydroxylamine-*O*-sulfonic acid (Scheme 1-3, Equation 1).[11] Alternatively, chiral alkylboronates can be treated with the highly Lewis acidic boron trichloride. The resulting dichloroboranes can successfully react with alkylazides, leading to chiral secondary amines with full stereoretention. This successful transformation results from the strong migratory character of boron-ate complex (Scheme 1-3, Equation 2).[12]

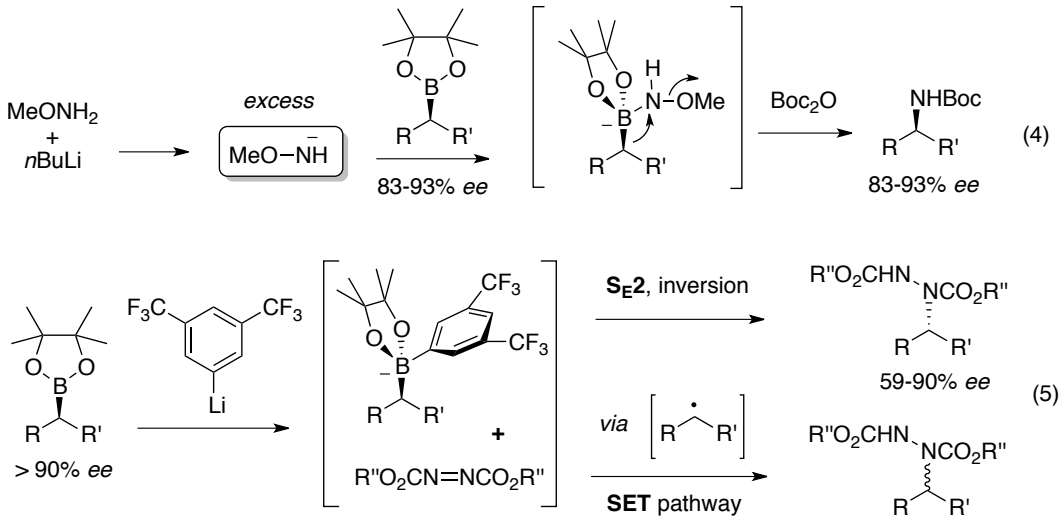


Scheme 1-3: Classic methods for stereospecific electrophilic amination.

Inspired by this strategy, Matteson and coworkers converted the highly stable chiral potassium trifluoroborate salts to the corresponding difluroborane intermediates, which were electrophilic enough to react with alkylazides to access various chiral amines with preservation of configuration (Scheme 1-3, Equation

3).[13] In spite of the importance of stereospecific amination, harsh reaction conditions, such as highly reactive organolithium reagents or the use of strong Lewis acids as shown above, are often required to activate chiral alkylboronates prior to the introduction of amines. As a result, these amination strategies have very limited functional group tolerance and are seldom applied in organic synthesis.

Milder and more efficient stereospecific amine displacement methods are under development. In 2012, the Morken Group demonstated the first example of direct transformation of highly stable chiral pinacol boronates to amines with complete retention of stereochemistry (Scheme 1-4, Equation 4).[14] This direct stereospecific amination was facilitated by the use of methoxyl amide anion, generated *in situ* from excess methoxyamine and *n*-butyllithium. This highly nucleophilic species can coordinate with the sterically hindered boron pinacolates at low temperature and promote sequential 1,2-migration/Boc protection, directly leading to protected chiral amines without loss of optical purity. Instead of relying on the nucleophilicity of amine sources, the Aggarwal Group recently found that chiral boron pinacolates could be preactivated in the presence of an optimized aryllithium reagent.[15] The resulting chiral boron ate complexes showed good nucleophilicity to react with different electrophiles, affording enantioenriched coupling products with inversion of stereochemistry in a S_E2 mechanism (Scheme 1-4, Equation 5). In addition, the aryl group coordinated boron ate complexes could also undertake single electron transfer (SET) pathways, resulting in undesired scrambling of stereochemistry. By reasoning that an electron-deficient aromatic coordination group on boron might surpress the SET pathway, different aryllithium reagents were screened and 3,5-$(CF_3)_2C_6H_3Li$ maximized the degree of stereochemical retention. Although the efficiency of stereospecific amination has been greatly improved in the above examples, the requirement for highly basic and nucleophilic activation reagents continues to limit its practical application in organic synthesis.

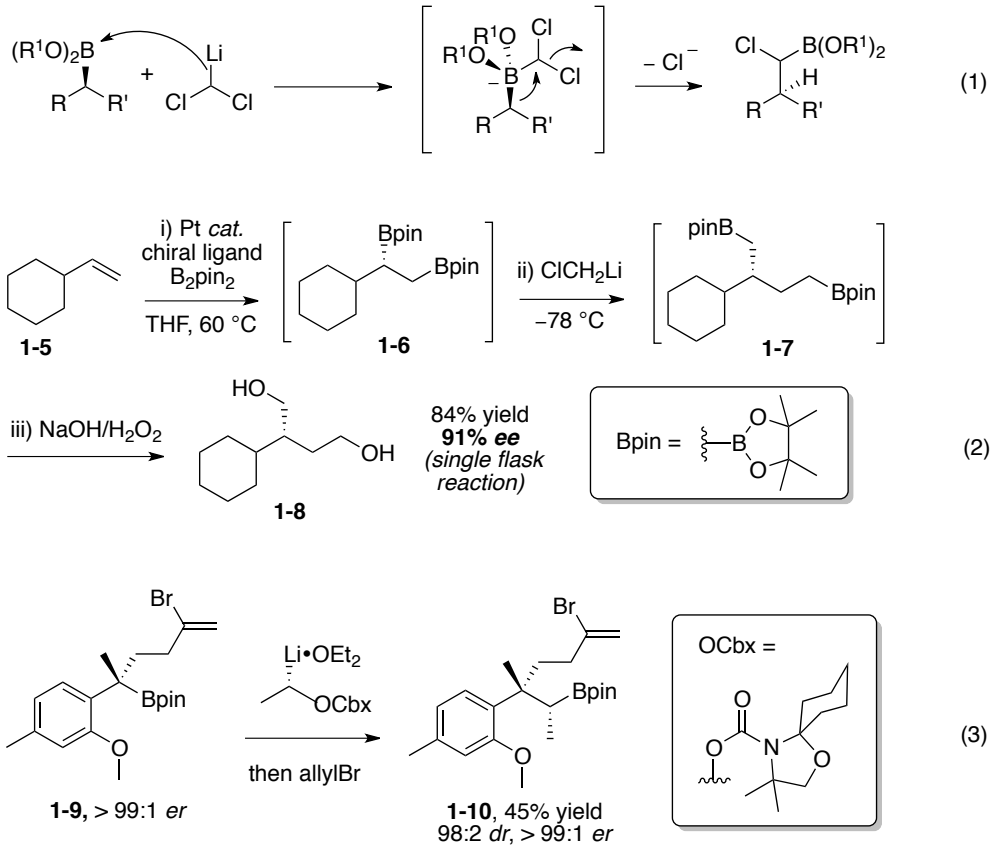


Scheme 1-4: Recent advances in stereospecific amination of chiral alkylboronates.

1.2.3 Asymmetric Matteson homologation

Another powerful transformation of chiral alkylboronates is the asymmetric Matteson homologation, in which the nucleophilic addition of α-haloalkyl carbanions to the boron centers leads to a 1,2-rearrangement and constitutes a formal one-carbon homologation with complete retention of stereochemistry (Scheme 1-5, Equation 1).[16] This elegant methodology has resulted in widespread applications in organic synthesis, especially in many mutli-component reactions. In 2009, the Morken Group presented an asymmetric Matteson homologation/oxidation of chiral diboron compound **1-6**, which was generated in the same flask from a Pt-catalyzed enantioselective diboration of 1-octene **1-5**.[17] The resulting homologated diol **1-8** was obtained in one-pot with high yield and very good enantiomeric excess (Scheme 1-5, Equation 2). In addition to secondary alkylboronates, this stereoselective homologation approach was also applied to chiral tertiary alkylboronates. Recently, the Aggarwal Group successfully constructed a chiral boron pinacolate **1-10** through a nucleophilic addition of lithiated carbamate on the optically pure tertiary boron pinacolate **1-9**. [18] The homologation occurred in a stereospecific manner with high

diastereoselectivity. It is notable that the high diastereoselectivity is due to the use of allyl bromide, which can effectively trap the leaving carbamate anion, and prevent its re-addition to the boronic ester.

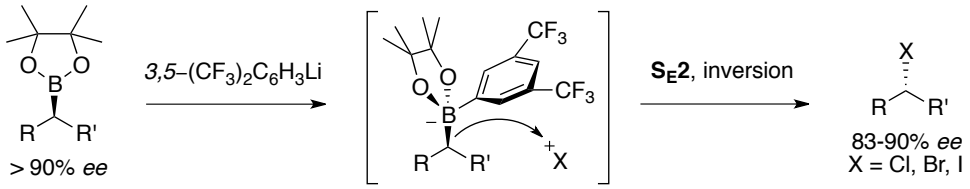


Scheme 1-5: Asymmetric Matteson homologation (Equation 1) and recent advances (Equation 2 and 3).

1.2.4 Stereospecific halogenation, alkenylation, arylation and protodeboronation

Halodeboronation of phenylboronic acid was first reported in 1930 for the syntheses of ipso-substituted phenyl halides by using cuprous halide or aqueous halogen.[19] Alkylboronic acids, however, show no reactivity under the same conditions.[20] As discussed in Section 1.2.2, the Aggarwal Group presented a new class of nucleophilic chiral boron-ate complexes that could react with

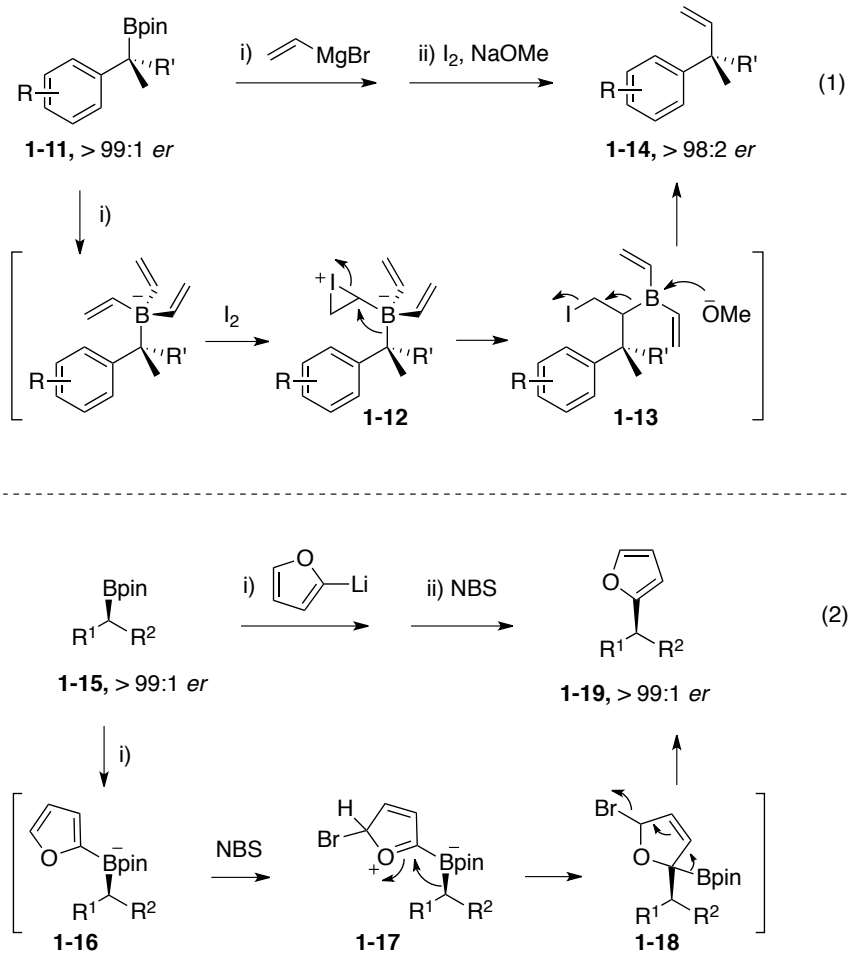
electrophilic azodicarboxylates to access chiral amine derivatives *via* a S_E2 pathway. Using the same strategy, the scope of electrophiles was expanded to electrophilic halogen sources, affording enantioenriched secondary halide with inversion of stereochemistry (Scheme 1-6).[15]



Scheme 1-6: Stereospecific halogenation of chiral alkylboronates.

Alkenylation of organoboron compounds was pioneered by Zweifel and coworkers in the 1960s, and it helped turn organoboronates into useful building blocks for olefin synthesis.[21] This protocol was recently improved by the Aggarwal Group, where stereospecific oxidative alkenylation was achieved from tertiary chiral boronates **1-11** (Scheme 1-7, Equation 1).[22] Based on their proposed mechanism, the nucleophlic attack of excess vinyl magnesium bromide and subsequent iodine oxidation could provide the iodonium species **1-12**, which was confirmed by ^{11}B NMR analysis. This electron-enriched boron-ate complex could initiate a stereoretentive 1,2-rearrangement of tertiary alkyl groups. The addition of the methoxide anion then promoted the elimination of boron and iodine atoms, giving the optically pure quaternary alkyl products **1-14**. In light of this success, the same group recently applied a similar strategy for the first example of enantiospecific arylation.[23] Instead of vinyl magnesium bromide, the 2-furyllithium reagent was initially applied for the nucleophilic addition of chiral secondary boronates **1-15**. Upon screening of different oxidants, *N*-Bromosuccinimide (NBS) was optimal to selectively oxidize the furyl group of the anionic boron complex **1-16**. The resulting intermediate **1-17** could trigger a stereospecific 1,2-migration of the chiral alkyl group to afford the intermediate **1-18**, which finally lead to the arylation products **1-19** though an

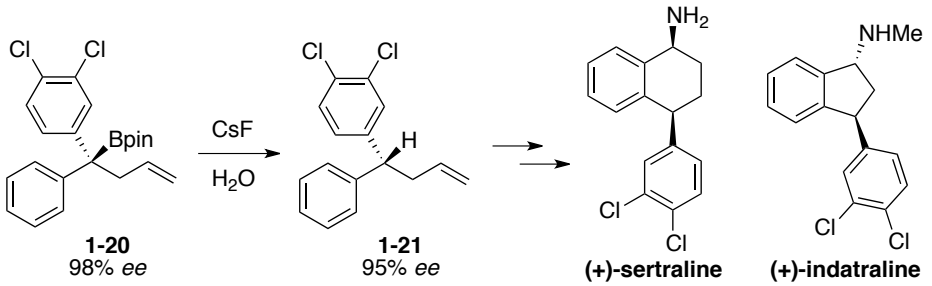
elimination/rearomatisation process (Scheme 1-7, Equation 2). The scope of both coupling partners was studied and great efficiency was obtained for the coupling of electron-rich aromatic/heteroaromatic compounds with various chiral alkylboronates. The restriction of electron-rich aryl or heteroaryl reagents possibly results from the obligatory oxidative activation.



Scheme 1-7: Stereospecific vinylation and arylation of chiral alkylboronates.

It was recently recognized that the C–B bond of tertiary boronic esters could be converted into a C–H bond with retention of configuration. Aqueous fluoride anion source, such as CsF-H_2O or TBAF•$3H_2O$, was the optimal activation reagent for this stereospecific protodeboronation process (Scheme 1-8).[24] This

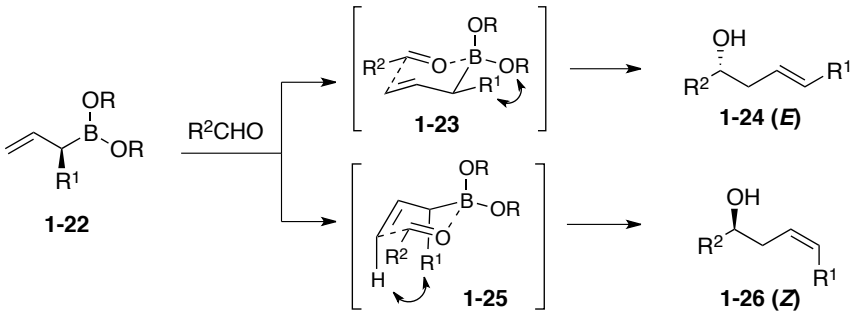
methodology was applied in the enantioselective syntheses of therapeutically important molecules (+)-sertraline and (+)-indatraline.



Scheme 1-8: Stereospecific protodeboronation of chiral tertiary boronates.

1.2.5 Enantioselective and diastereoselective carbonyl allylboration

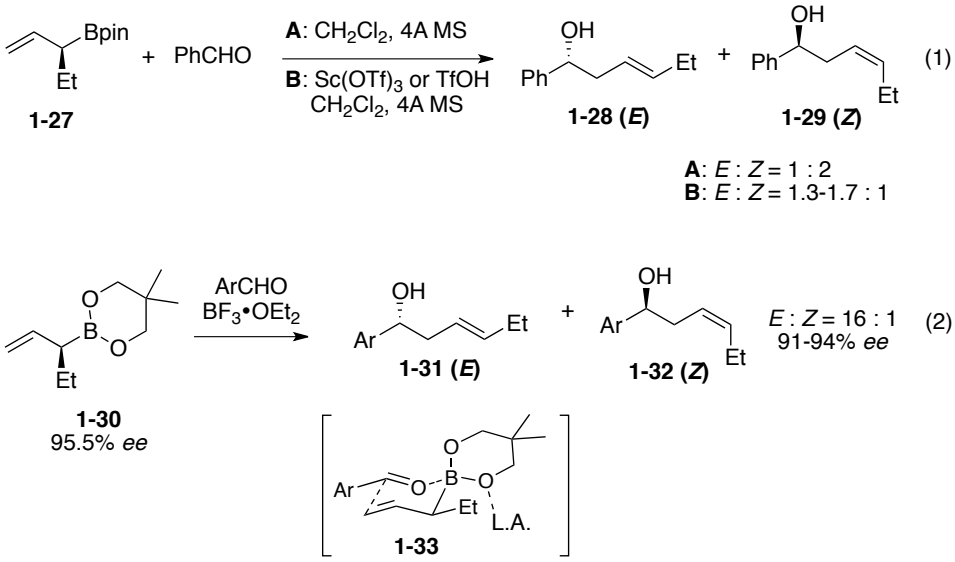
The allylation reaction between allylic boronates and aldehydes was first discovered in 1974.[25] Since then, this chemistry has found remarkable application in the total synthesis of optically pure natural products and pharmaceutical drugs.[26] The ubiquitous application of carbonyl allylation results from the advantage of its great stereocontrol, which is established by a closed chair-like Zimmerman-Traxler transition state.[27] Past work in this field favored allylic boranes due to their high electron-deficiency and the selectivity associated in the transition state. Organoboranes, however, are too reactive to be easily handled as synthetic intermediates, which diminish their practical synthetic value. Organoboronic ester, on the other hand, is a stable convenient alternative, despite suffering lower reactivity. In 2002, this low reactivity was independently addressed by the groups of Hall and Miyaura who discovered that the reactivity and stereoselectivity of allylboronates was dramatically enhanced though the introduction of catalytic amounts of a Lewis acid.[28]



Scheme 1-9: Proposed two competing transition states in the allylboration of aldehydes with α-substituted allylic boronates.

The effect of the α-substituent R^1 and the boronate group of chiral allylboronates **1-22** on the allylation stereoselectivity was extensively studied by Hoffmann (Scheme 1-9).[29] Two diastereomers **1-24** (*E* configuration) and **1-26** (*Z* configuration) were formed respectively through two putative transition states **1-23** and **1-25**. The competition between these two transition states depends on the electronic and steric nature of R^1 and the boronate group, which in turn determines the diastereomeric ratio of two homoallylic alcohol products. Compared to the conventional thermal uncatalyzed allylboration reactions, the Hall Group recently found that an opposite stereoselectivity of allylboration was achieved by use of a catalytic amount of Lewis acid.[30] In Scheme 1-10, a ratio of 1:2 was obtained between the *E*-configured product **1-28** and the corresponding *Z*-configured **1-29** under thermal conditions (**A**), while the ratio was reversed to 1.3-1.7:1 with the addition of a catalytic amount of triflic acid or scandium (III) triflate (Scheme 1-10, Equation 1). Hall and coworkers postulated that the coordination of Lewis acid to the oxygen atom of boron pinacolates increases the electron-deficiency of the boron atom, resulting in a closer bonding between boron and the carbonyl oxygen atom along with a longer boron-carbon bond, in which case the streric interaction between the R^1 substituent and the boronate is relieved. This effect favors a more advanced transition state (similar to the intermediate **1-33**), ultimately leading to the formation of *E*-configured products.

Through continuous fine-tuning of the Lewis acidity and steric strain imposed by the boron masking group, the same group later discovered that the diastereomeric ratios were significantly improved by employing the less sterically demanding neopentyl glycol boronate (**1-30**) and more oxyphilic Lewis acid BF_3•OEt_2 (Scheme 1-10, Equation 2).[31] Owing to the reduced strain between the α-subtituted ethyl group and the less bulky neopentyl glycol boronate,[32] the transition state favoring the *E*-configured isomer **1-33** was predominant, exclusively providing enantioenriched product **1-31** with high preservation of stereochemical integrity.



Scheme 1-10: Diastereoselective allylboration of aldehydes with chiral α-substituted allylic boronates.

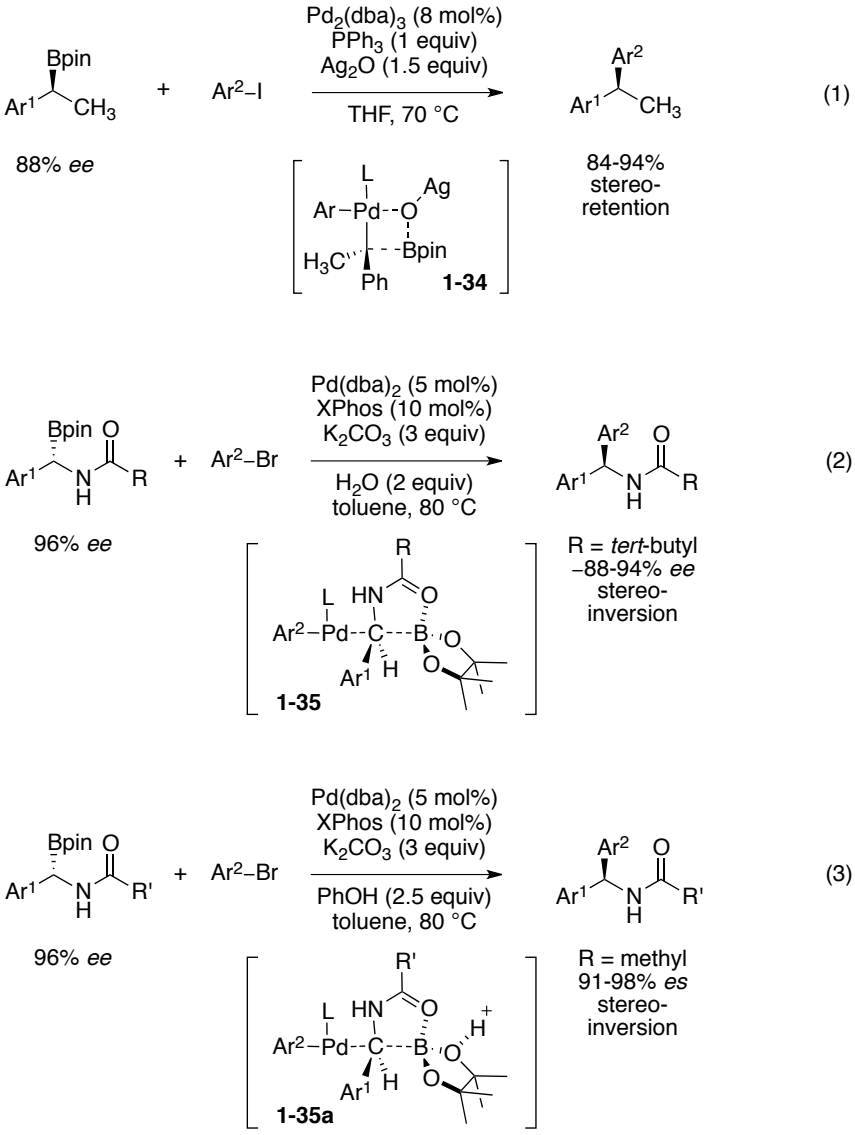
1.2.6 Suzuki-Miyaura cross-coupling of chiral alkylboronates

As one of the Nobel Prize-winning palladium-catalyzed cross-coupling reactions, the Suzuki-Miyaura reaction employs environmentally benign organoboron compounds as the cross-coupling partners and has been demonstrated as one of the most powerful methods for $C(sp^2)$-$C(sp^2)$ bond formation. In addition to organic synthesis, the significance of this reaction has been recognized by various

interdisciplinary research areas such as medicinal chemistry, chemical biology, materials and nanotechnology.[33] As cross-coupling partners, these versatile organoboron compounds afford several advantages over other organometallic reagents: 1) availability of thousands of commercially available boronic acids and derivatives; 2) superior stability when exposed to air, water and heat; and 3) ultimate degradation to non-toxic borate by-products. These attractive features allow Suzuki-Miyaura cross-coupling reactions to tolerate various functional groups and generate non-toxic boron by-products.[34]

Whereas $C(sp^2)$-$C(sp^2)$ bond formation has been the main focus within the realm of Suzuki-Miyaura cross-coupling reactions, the coupling of sp^3-hybridized organoboron compounds remains notoriously challenging. The struggle for this type of cross-coupling is attributable to the slower transmetallation, which is one of the key steps involved in transition metal catalysis.[33] The slow transmetallation is often accompanied by several side reactions such as β-hydride elimination, reinsertion and irreversible protodeboronation, leading to a mixture of side products. When using chiral alkylboronates as coupling partners, these issues are further compounded by the control of stereoselectivity as well as the uncooperative relationship between nucleophilicity and configurational stability.[35] Despite all these challenges, in 2009 the Crudden Group reported the first example of stereoselective Suzuki-Miyaura cross-coupling between enantiopure benzyl boron pinacolate and aryl iodide (Scheme 1-11, Equation 1).[36] The coupling procceded with high retention of optical purity without any loss of regiochemistry. The addition of silver(I) oxide proved to be crucial. The silver(I) oxide is believed to serve as an optimal activator to dramatically enhance the transmetallation rate, which was previously demonstrated in Pd-catalyzed cross-coupling reaction by the Kishi and Mori groups.[37] The retention of stereo chemical integrity may result from the four-membered ring transition state **1-34** occurring during the transmetallation step, as originally suggested by the Soderquist Group.[38] This closed transition state would in principle lead to

optically enriched products with retention of configuration after rapid reductive elimination, which usually occurs with preservation of stereochemistry.[33]



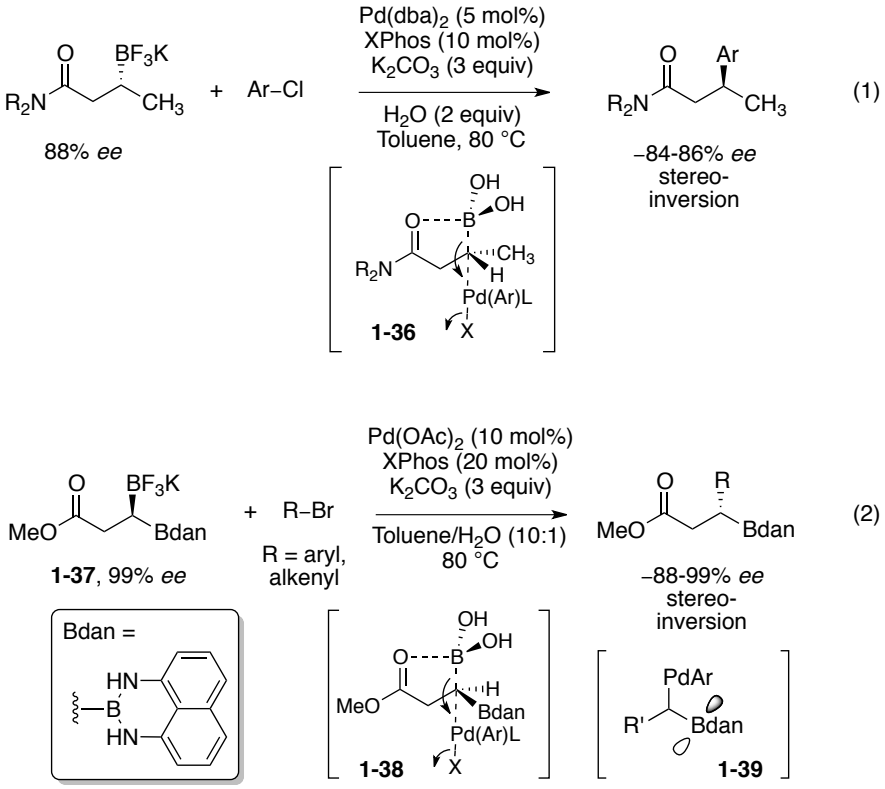
Scheme 1-11: Stereoselective Suzuki-Miyaura cross-coupling reactions of chiral secondary alkylboronates.

Alternatively, inversion of configuration was observed when chiral α-(acylamino)benzylboronic esters were employed as the coupling partners, as established by the Ohmura and Suginome Group in 2010 (Scheme 1-11, Equation

2).[39] The unique structure of the α-(acylamino)benzylboronic ester allowed for an intramolecular interaction between the amide oxygen and the boron atom. To rationalize this novel stereochemical outcome, based on prior studies on a variety of transition metal catalyzed cross-coupling reactions,[40] the authors proposed an open transition state **1-35** at the transmetallation stage, where the palladium complex favored a backside attack at the benzylic carbon atom resulting from this strong intramolecular coordination. This transition state thus afforded the stereoinverted coupling product after rapid reductive elimination. After extensive optimization studies on different ligands and bases, the bulky XPhos ligand with K_2CO_3 as base were found to be optimal, providing the best yield and enantiospecificity (*es*). To further improve the enantiospecificity, modification of the R substituents was also attempted and up to 96.5% *es* was achieved by the use of the highly sterically demanding *tert*-butyl group. More recently, the same group found that the use of phenol as a mild Brønsted acid can provide further enhancement of enantiospecificity for this stereospecific cross-coupling.[41] The authors reasoned that phenol could selectively bind to one of the oxygen atoms of the boronate unit to strengthen the intramolecular interaction between the amide oxygen and the boron atom (**1-35a**), which could in turn accelerate the transmetallation step. Owing to this enhanced binding effect, less sterically demanding methyl group can be used as the R' substituent, which is also more synthetically accessible (Scheme 1-11, Equation 3).

In both examples discussed above, the chiral alkylboron substrates were benzylic boronates, since their coupling is known to be facile. To expand the scope of stereospecific Suzuki-Miyaura cross-coupling chemistry, the Molander Group recently investigated the optically enriched β-trifluoroboratoamide as the first nonbenzylic organoboron coupling partner (Scheme 1-12, Equation 1).[42] These chiral acyclic trifluoroborates feature a strongly coordinating β-amide group, which cross-coupled with different aryl chlorides in high yields and high stereoselectivities. Similar to Suginome's stereochemical result, an inversion of

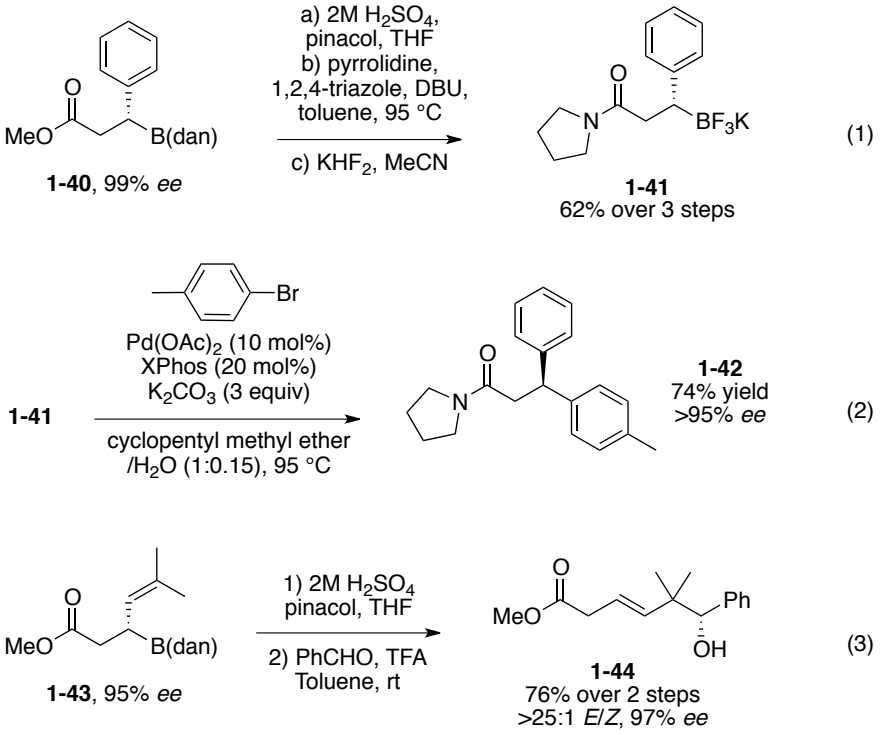
configuration was observed. Accordingly, Molander and coworkers proposed a similar intramolecular coordination between the amide oxygen and the boron atom (**1-36**). This unique interaction was advantageous, in that other competing side reactions, such as protodeboronation and β-hydride elimination, were suppressed. From this remote interaction the authors concluded that: 1) the transmetalation process was accelerated in the same manner as discussed in the above cases; 2) the conformational restriction of this diorganopalladium complex likely prevented the formation of a syn-coplanar conformer required for the undesired β-hydride elimination; 3) the interaction between the metal and a β-hydrogen, which is the prerequisite for β-hydride elimination, was inhibited by this carbonyl coordination (Scheme 1-12, Equation 1).



Scheme 1-12: Stereoselective Suzuki-Miyaura cross-coupling reactions of β-boronyl carbonyl compounds.

More recently, the Hall Group reported the first enantioselective preparation of a highly optically enriched 1,1-diboron compound, **1-37**.[43] This uniquely designed compound exhibited remarkable synthetic advantages, for it could couple with both aryl and alkenyl electrophiles in a chemo- and stereoselective fasion, affording synthetically prized chiral benzylic or allylic boronates (Scheme 1-12, Equation 2). The authors proposed two features for these advantageous cross-coupling reactions: 1) the strong internal stabilization effect from the α-boronyl-Pd(II) complex (**1-39**), as previously demonstrated by Shibata and co-workers;[44] and 2) the selective intramolecular carbonyl coordination towards the pinacol boronyl unit (**1-38**), as revealed by X-ray crystallographic analysis. These two distinctive activation factors allowed the use of more synthetically accessible methyl ester (**1-37**) and further expand the scope of stereoselective Suzuki-Miyaura cross-coupling reactions.

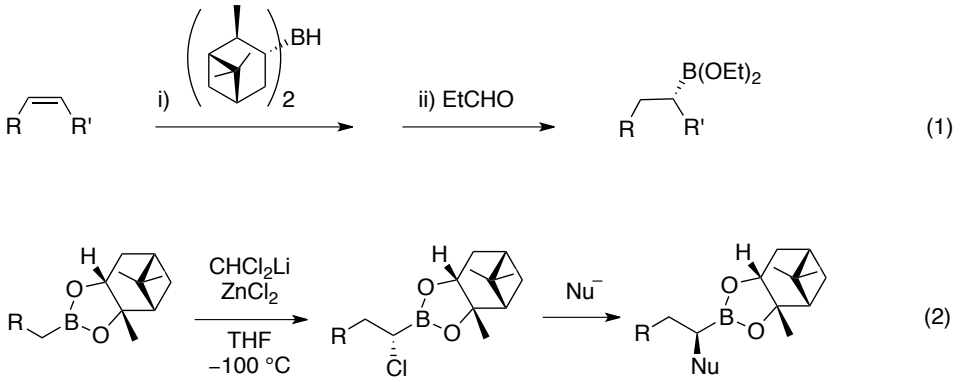
These highly enantioenriched mono cross-coupling products also demonstrated intriguing advantages in asymmetric synthesis (Scheme 1-13). When the mono boronyl product was benzylic boronate **1-40**, upon easy modification of carbonyl group and boron masking group, the second boronyl unit was again available for a subsequent stereoselective coupling with another aryl halide (Scheme 1-13, Equation 1). The resulting chiral trifluoroborate **1-41** could finally lead to the enantioenriched diarylmethane derivative **1-42**, which belongs to an important class of pharmacophore units (Scheme 1-13, Equation 2). When allylic boronate **1-43** was the coupling product, after a switch of boron protecting group, a Lewis acid catalyzed stereoselective allylboration reaction can be facilitated, providing the enantiopure homoallylic alcohol **1-44** whose motif is commonly found in bioactive natural products (Scheme 1-13, Equation 3).



Scheme 1-13: Applications of mono cross-coupling products.

1.3 Preparative strategies towards chiral alkylboronates

As dicussed in Section 1.2, chemical transformations involving chiral alkylboronates often occur with preservation of stereochemical integrity, which has made them versatile precursors for a diverse range of chiral functionalities in asymmetric synthesis. This significance has encouraged the development of novel and efficient methodologies to access these chiral surrogates. Previous contributions in this field include Brown's asymmetric hydroboration[45] and Matteson's stereoselective homologation (Scheme 1-14).[16] Both examples feature the utilization of stoichiometric chiral auxiliaries to generate new stereocenters.



Scheme 1-14: Conventional stoichiometric strategies for the preparation of chiral alkylboronates.

Recent efforts in the preparation of chiral alkylboronates have largely focused on the more atom-economical methods of asymmetric catalysis, which can be classified in two distinct approaches: 1) late stage asymmetric borylation of pre-functionalized organic compounds; and 2) early stage borylation followed by an asymmetric modification (Figure 1-1).

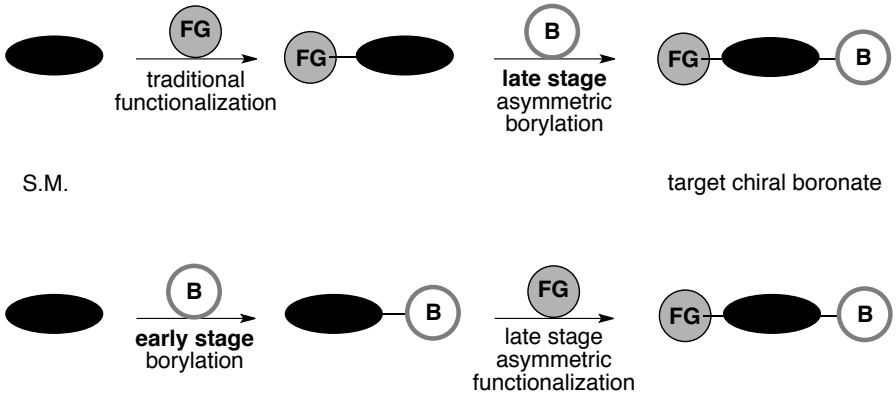


Figure 1-1: Two synthetic approaches towards the syntheses of chiral alkylboronates.

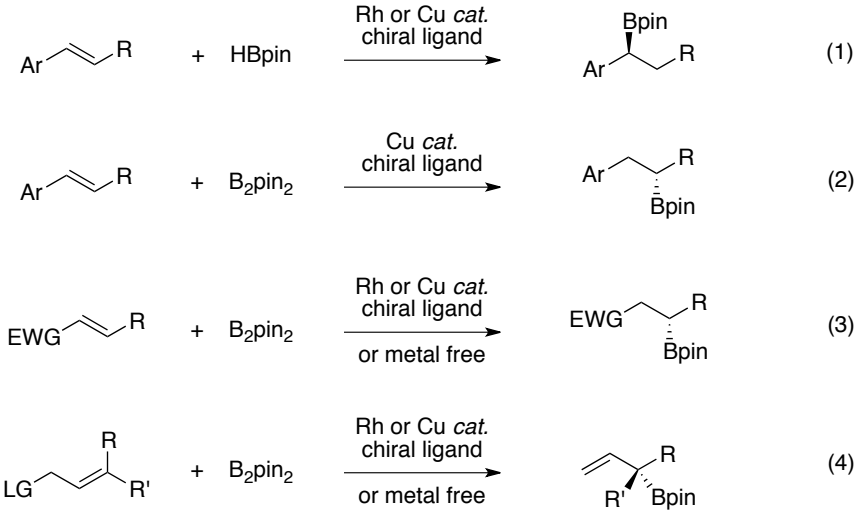
Conceptually, the late stage borylation strategy can access the target chiral alkylboronates with no concern for the deboronation issues. This strategy, however, is dependent on a limited selection of enantioselective borylation

protocols. On the other hand, with boronyl units pre-installed, the strategy of late asymmetric functionalization affords many options of well-establlished enantioselective, catalytic methodologies,[46] although only those that are compatible with boron-containing substrates can be exploited successfully. Herein, both strategies for the preparation of chiral alkylboronates will be summarized.

1.3.1 Late stage asymmetric borylation

Alkene hydroboration was first reported by Herbert C. Brown in 1959.[47] It features a *syn*-addition of hydroborane, where the borane unit was added on the least hindered alkene carbon with high regio- and stereoselectivity. The resulting boranes could either be directly oxidized to produce *anti*-Markovnikov alcohols, or act as nucleophiles in various carbon-carbon bond formation reactions such as the Suzuki-Miyaura cross-coupling. Recent progress in this field has utilized more efficient enantioselective transition metal catalysis to access the chiral alkylboronates, and the more convenient bis(pinacolato)diboron or pinacolborane is often empolyed as the boron source. Through the fine-tuning of asymmetric catalytic reaction conditions, both *anti*-Markovnikov and Markovnikov selectivities can be achieved with high enantiomeric purities (Scheme 1-15, Equations 1-2).[48] Alternatively, when activated with bases, the bis(pinacolato)diboron can act as a soft nucleophile under transition metal catalyzed conditions, which shows consistent reactivity towards various Michael acceptors *via* 1,4-addition. This behavior has been applied as an alternative asymmetric borylation strategy. In 2009, the Yun Group found that the addition of MeOH could significantly accelerate the rate of conjugate borylation. This discovery has motivated the development of enantioselective conjugate borylation of α,β-unsaturated ketones, esters and amides (Scheme 1-15, Equation 3).[49] More recently, the groups of Fernandez and Hoveyda presented the metal-free organocatalytic variants where chiral tertiary phosphorus compounds or enantiomerically pure N-heterocyclic carbenes were applied as the

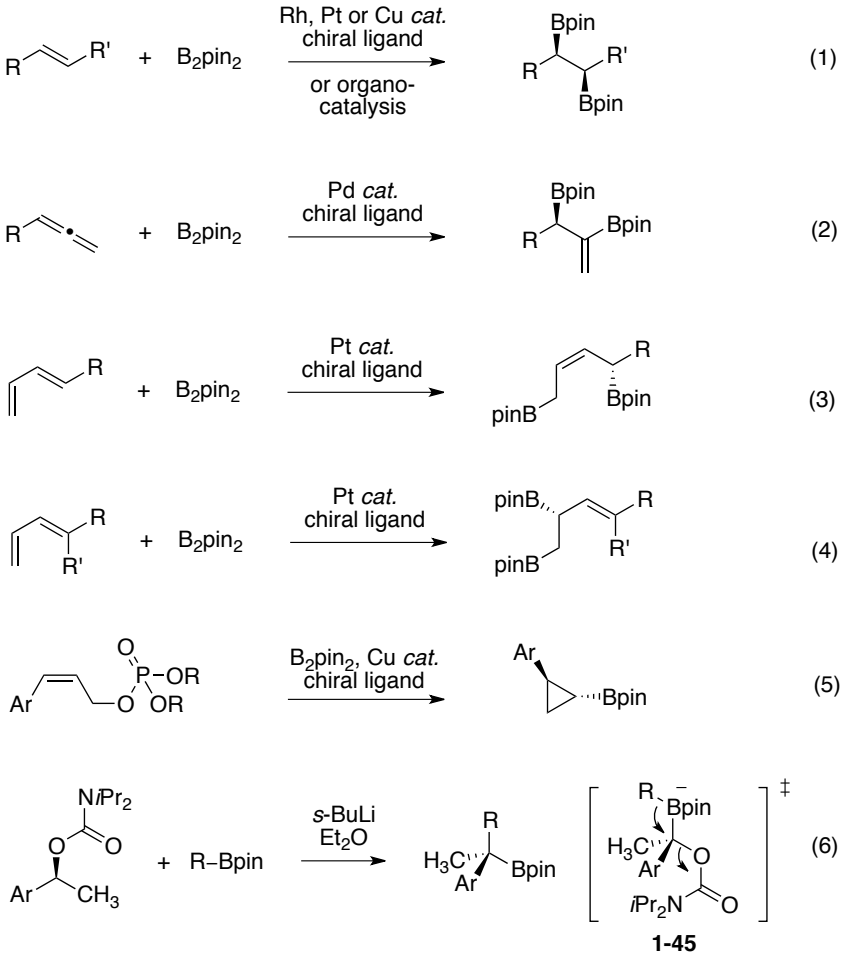
enantioselective organocatalysts.[50] These advances avoid use of expensive, toxic or less abundant transition metals and thus allow the synthesis of chiral alkylboronate to occur in a "greener" manner. Similarly, the bis(pinacolato)diboron reagent can also react with allylic electrophiles enantioselectively in an S_N2' fashion *via* either asymmetric transition metal catalysis or organocatalysis. The resulting enantiopure allylic boronates can be directly oxidized to chiral allylic alcohols in one-pot, or undergo diastereoselective carbonyl allylboration reactions to access chiral homoallylic alcohols (Scheme 1-15, Equation 4).[51]



Scheme 1-15: Early stage asymmetric hydroboration and conjugate borylation approaches.

Enantioselective diboration can also be achieved through either asymmetric transition metal catalysis or metal-free catalysis, where two boronyl units are simultaneously installed on unsaturated substrates such as alkenes,[52] allenes,[53] or dienes[54] (Scheme 1-16, Equations 1-4). These chiral diboron compounds present important synthetic utility that has been demonstrated in many regio-/stereoselective tandem processes such as direct oxidation, carbonyl allylboration, and Suzuki-Miyaura cross-coupling. Additionally, the Sawamura Group recently

found that chiral cyclopropyl boronates can be accessed when aryl substituted allylic phosphonates were employed as the electrophiles (Scheme 1-16, Equation 5).[55] Instead of the typical allylic borylation products as previously discussed (Scheme 1-15, Equation 4), these cyclopropylboronates were obtained with high yields and diastereo- and enantioselectivities. This unusual reactivity was due to the preferential attack of the nucleophilic copper(I)/boron system to the central carbon of the allylic electrophile instead of the terminal sites.



Scheme 1-16: Synthetic strategies towards enantiopure diboron compounds, cyclopropyl boronates and tertiary alkylboronates.

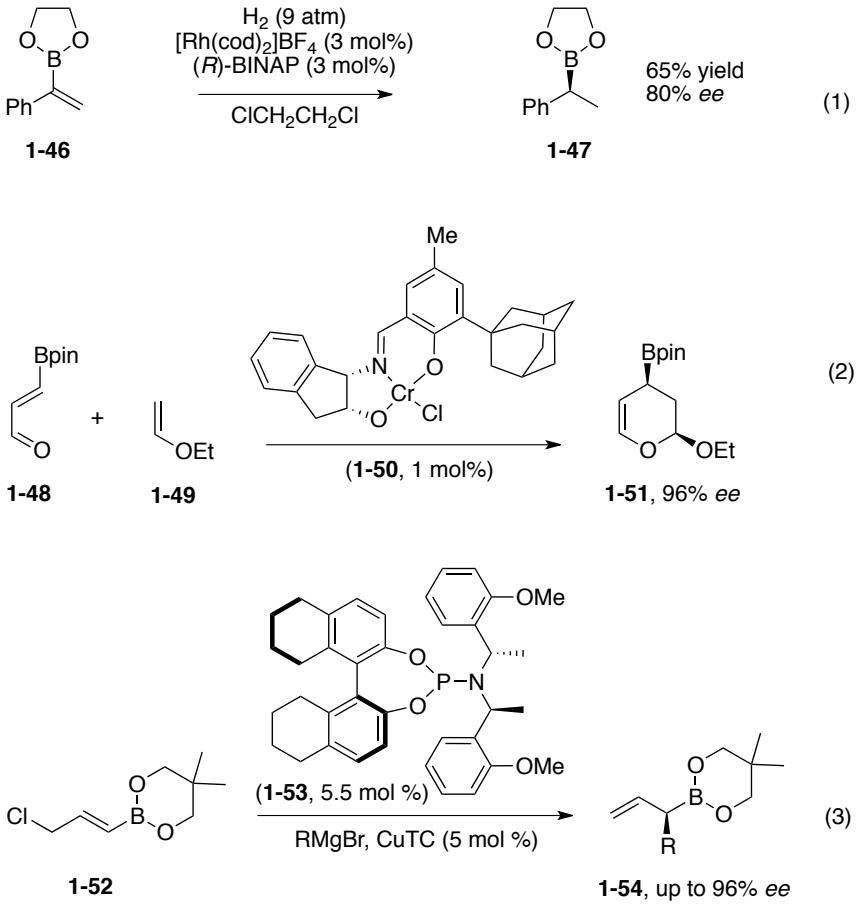
In addition to the above enantioselective syntheses of chiral secondary

alkylboronates, the Aggarwal Group achieved stereoselective syntheses of chiral tertiary alkylboronates from enantiomerically pure secondary carbamates (Scheme 1-16, Equation 6).[56] Inspired by the pioneering work of Hoppe[57] and Matteson,[16] the key processes of this protocol engaged a stereospecific deprotonation of the chiral carbamate by *s*-BuLi followed by a nucleophilic coordination towards the empty p-orbitals of the boronate. The resulting anionic boron-ate complex (**1-45**) can facilitate a 1,2-migration and afford the corresponding chiral tertiary alkylboronate with preservation of stereochemistry.

1.3.2 Early stage asymmetric borylation

One of the first representative examples for the early stage asymmetric borylation strategy was described by the Miyaura Group in the synthesis of chiral benzylic boronate **1-47**, which was achieved though a conventional Rh-catalysed asymmetric hydrogenation of the prochiral α-boronyl styrene **1-46** (Scheme 1-17, Equation 1).[58] This main challenge associated with this early introduction strategy is the compatibility of the pre-installed boronate groups under the subsequent asymmetric functionalization conditions. In Miyaura's example, the undesired rhodium insertion into B-C bond could result in many side reactions, and thus had to be avoided. This challenge has been addressed in the Hall Group as demonstrated by various successful examples of early stage asymmetric borylation (Scheme 1-17, Equations 2-5). In 2003, the Hall Group[59] demonstrated the first example of a diastereo- and enantioselective inverse electron demand Diels-Alder (IEDDA) reaction between 3-boronoacrolein **1-48** and ethyl vinyl ether **1-49** catalyzed by Jacobsen's chiral Cr(III) salen complex **1-50**.[60] The resulting allylic boronate **1-51** could subsequently react with various aldehydes in a multicomponent cascade process, affording the synthetically valuable α-hydroxyalkyl pyrans with excellent diastereoselectivity and complete preservation of enantiomeric purity. This elegant three-component methodology has demonstrated great utility in the total syntheses of several natural products,

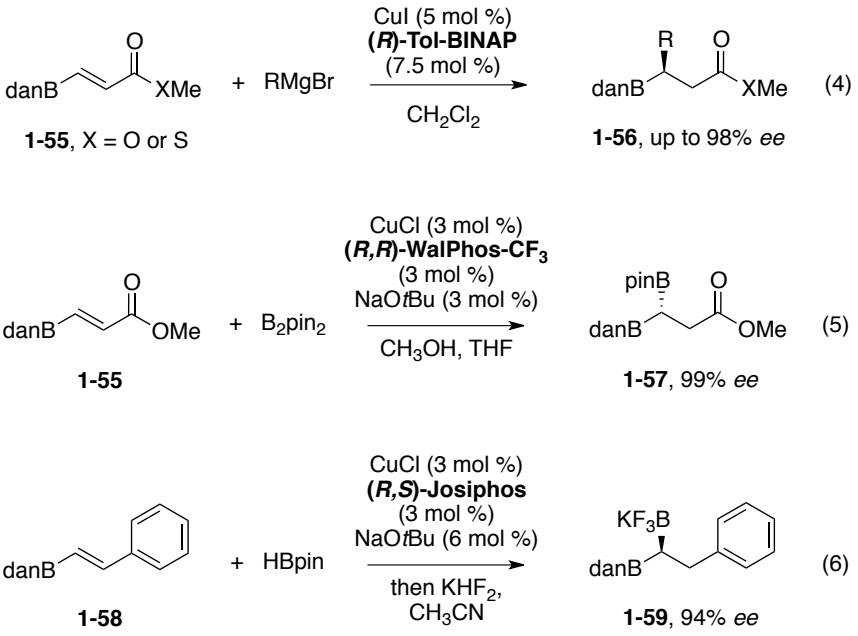
including the antibacterial marine nature product thiomarinol[61] and the complex macrolide palmerolide A.[10] In addition to the [4+2] cycloaddition, the same group later described a Cu-catalyzed enantioselective synthesis of the chiral acyclic allylic boronate *via* a regio- and stereoselective S_N2' addition of Grignard reagents to the (*E*)-3-chloropropenylboronate **1-52** (Scheme 1-17, Equation 3).[31]



Scheme 1-17: Representative early-stage borylation examples for catalytic asymmetric syntheses of chiral alkylboronates.

To continue exploring the advantages of the asymmetric early boronyl introduction strategy, the Hall Group also developed a highly efficient Cu-catalyzed enantioselective conjugate addition methodology employing Grignard reagents and 3-boronyl acrylate derivatives (Scheme 1-18, Equation 4).[62] Through

screening a variety of boron masking groups, the 1,8-diaminonaphthalene (dan) unit was found to be the most compatible one, resulting in chiral alkylboronates with high yields and high enantiomeric purities. This provided an attractive alternative from the mainstream borylative conjugate addition methodologies (such as Scheme 1-15, Equation 3).



Scheme 1-18: Representative early-stage borylation examples for catalytic asymmetric syntheses of chiral alkylboronates.

More recently, the same group designed a catalytic asymmetric synthesis of the unprecedented 1,1-organodiboron compound **1-57** as a single enantiomer (Scheme 1-18, Equation 5), which displays attractive synthetic utilities (as shown in Scheme 1-12, Equation 2, and Scheme 1-13, Equation 1-3).[43] Inspired from this pioneering work, the Yun Group recently reported an alternative synthesis of chiral 1,1-diboron compound **1-59** through an optimized regio- and enantioselective Cu-catalyzed hydroboration of borylalkenes (Scheme 1-18, Equation 6).[63] However, due to the lack of a carbonyl unit as the intramolecular activation group (as presented in **1-57**), this class of chiral diboron compound

showed a reduced reactivity in the stereospecific Suzuki-Miyaura cross-coupling reactions.

1.4 Thesis research objectives

Chiral alkylboronates constitute a very attractive class of building blocks in modern organic synthesis, owing to their versatility as chiral precursors and their benign impact on the environment. Regardless of their synthetic advantages, current classes of chiral alkylboronates that are readily available to organic chemists remain limited. Moreover, their synthetic utility is still restricted in many aspects such as the stereoselective amination, regio-/stereocontrol in Suzuki-Miyaura cross-coupling reactions, and application in the atom/step economical synthesis of pharmaceutical drugs and natural products. To address these challenges, the general objective of this research was to develop novel and efficient methodologies towards the syntheses of chiral alkylboronates and to explore their synthetic applications.

Encouraged by the great achievements on the development of early-stage borylation methods in our group, especially the recent success in the asymmetric conjugate addition of β-boronyl enoates (Section 1.3.2), my studies were initiated by proposing a corresponding Cu-catalyzed enantioselective conjugate reduction of the prochiral β-boronyl-β-alkyl enoates, where mild sources of hydride can be applied as the nucleophiles instead of unstabilized organometallic reagents. This proposal posed several inevitable challenges, including the search for a general synthetic route to access the β-boronyl-β-alkyl enoates, a compatible asymmetric catalytic system, a suitable boron-protecting group and hydride source to prevent the undesired protodeboronation process. All of these challenges will be addressed in detail in Chapter 2.[64]

To further expand the scope of possible substituents at the β position of the enoate, the asymmetric reduction of β-boronyl-β-aryl enoates was also examined.[65] These

novel substrates were synthesized by the former Hall Group member Jack Chang Hung Lee *via* a diastereoselective Heck coupling of β-boronyl enoates and aryl halides, which will also be briefly discussed in Chapter 3.

Along with exploring more efficient preparative methods towards chiral alkylboronates, my studies also involved expanding their synthetic applications, including asymmetric total synthesis of biologically important natural products and pharmaceutical drugs as well as new stereospecific bond formation methods. In light of the synthesis of the unique chiral allylic heterocyclic boronates previously developed in our group,[66] a concise enantioselective total synthesis of the antimalarial drug mefloquine and the famed natural product quinine was proposed. The key step involved an optimized enantioselective Pd-catalyzed borylative alkene isomerization and subsequent diastereoselective allylboration. Through altering chiral ligands during this key step and inverting stereochemistry of the resulting secondary alcohols, all four mefloquine stereoisomers were obtained and their antimalarial activities were also studied.[67] Encouraged by this success, efforts toward an asymmetric total synthesis of the more challenging alkaloid quinine was also initiated. These syntheses and their optimizations will be detailed in Chapter 4.

The ultimate challenge for the application of the above chiral allylic heterocyclic boronates is their use in stereospecific Suzuki-Miyaura cross-coupling reactions. This challenge is not only due to the notorious restrictions of Suzuki-Miyaura coupling of secondary alkylboronates (see Section 1.2.6), but also from the complementary control of regio- and stereoselectivities. Upon careful examination of chiral catalytic system and other reaction conditions, a ligand controlled regiodivergent and enantiospecific cross-coupling of these chiral allylic heterocyclic boronates was achieved with high efficiency. Additionally, the resulting 2- and 4-substituted dehydro piperidines found useful applications in the formal syntheses of the alkaloid (+)-anabasine and the antidepressant drug (+)-

paroxetine.[68] Detailed optimization, substrate scope, and synthetic applications will be described in Chapter 5.

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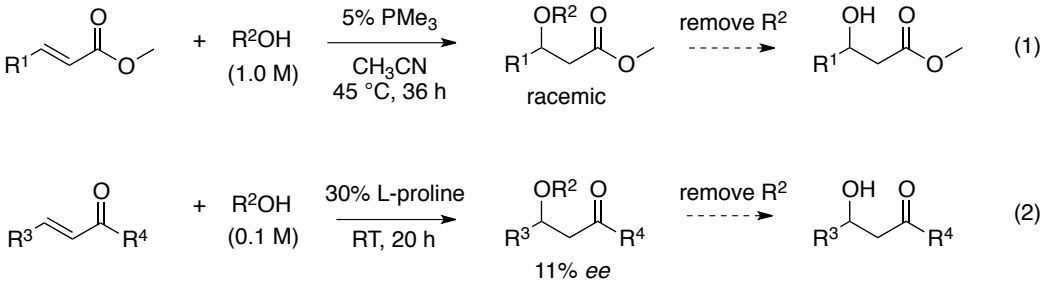
Chapter 2 Preparation of Chiral Alkylboronates via Cu-Catalyzed Enantioselective Conjugate Reductions*

2.1 Introduction

As discussed in Chapter 1, the emergence of boronic acids and their derivatives as a versatile class of synthetic intermediates has spurred the development of new methods to prepare chiral organoboronate derivatives in optically enriched form. These intermediates can be used as precursors of chiral alcohols and amines following a stereospecific B–C bond oxidation (see Section 1.2 for detailed discussions and references). In this regard, the boronate group may be viewed as a chiral surrogate for oxygen-containing nucleophiles in asymmetric conjugate addition reactions. The conventional oxy-Michael methods are notoriously difficult. They often require excess amounts of alcohol, prolonged reaction time and may require additional extra deprotection steps to reveal the alcohol product (Scheme 2-1, Equations 1-2).[69]



Scheme 2-1: Examples of conventional oxy-Michael reactions for the synthesis of β-hydroxy carbonyl compounds.

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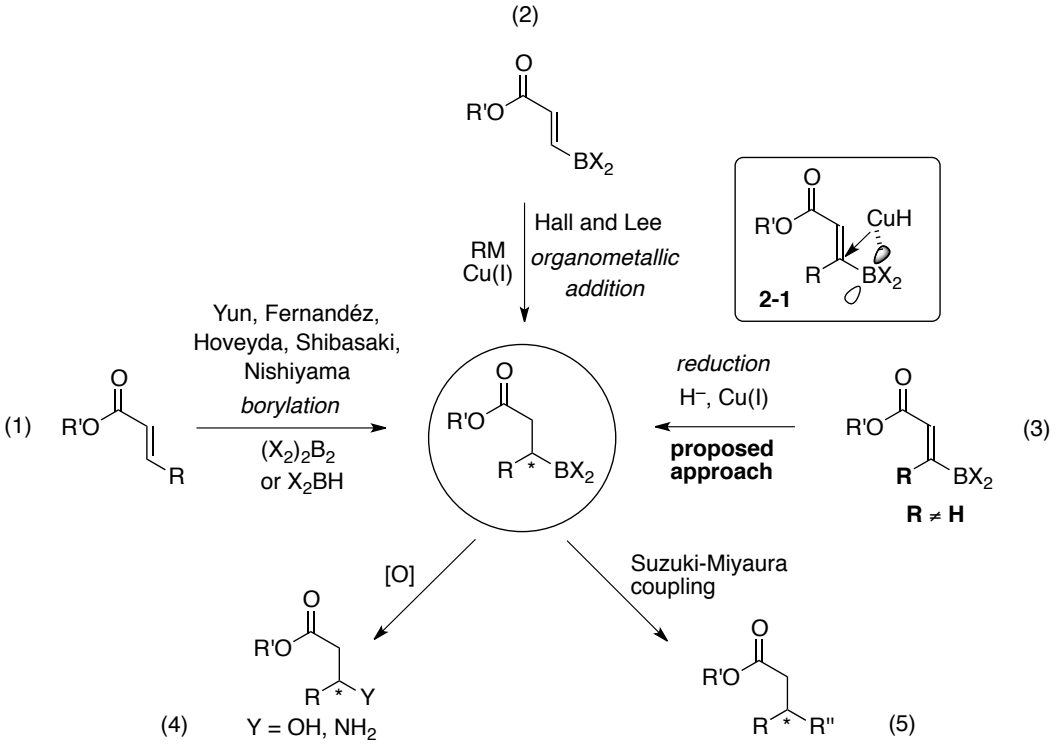
* A version of this chapter has been published. Ding, J.; Hall, D. G. *Tetrahedron* **2012**, *68*, 3428–3434.

Therefore, borylative conjugate additions[70] provide an attractive alternative, as recently demonstrated by the groups of Yun,[71] Fernandéz,[72] Hoveyda,[73] Shibasaki,[74] Nishiyama[75] and others[76] (Scheme 2-2, Equation 1). Recently, the Hall Group proposed a complementary approach (Section 1.3, Chapter 1) wherein the boronate unit was pre-installed on a single α,β-unsaturated ester substrate, which was then employed in a catalytic asymmetric conjugate addition with unstabilized carbanions (Scheme 2-2, Equation 2).[77] When using chiral biphosphine ligands, the copper-catalyzed enantioselective addition of organomagnesium reagents yielded products with enantiomeric excesses of up to 98%. As part of an ongoing search for new ways to access chiral secondary boronate derivatives, we reasoned that the corresponding copper-catalyzed enantioselective conjugate reduction of β-boronyl-β-alkyl α,β-unsaturated esters would provide a useful alternative method for the synthesis of these compounds (Scheme 2-2, Equation 3).

Most existing copper-catalyzed enantioselective conjugate reduction methods, however, employ enone substrates that are significantly more electrophilic than α,β-unsaturated esters.[78] With an electron-deficient boronyl unit installed at the β-position of the enoate, we predicted that the incoming soft copper hydride would interact with boron's empty *p*-orbital, resulting in enhanced reactivity of the Micheal acceptor (**2-1**, Scheme 2-2). This complementary approach to access chiral β-boronyl esters avoids the tedious preparation of different starting β-substituted enoates for every different β-boronyl ester product in the late-stage borylation strategy (Scheme 2-2, Equation 1). This method also prevents the use of unstabilized carbanions as nucleophiles, which often require *in situ* preparation (Scheme 2-2, Equation 2). Instead, various organosilanes can be applied as mild nucleophilic hydride sources, which are often readily available, inexpensive and environmentally benign. In addition, upon stereospecific oxidation or amination, the resulting chiral secondary alkylboronates could be easily converted into chiral β-hydroxy or β-amino acid derivatives, which are important motifs in natural

products and pharmaceutical drugs (Scheme 2-2, Equation 4). Alternatively, these chiral boronates can be subjected to stereospecific Suzuki-Miyaura cross-coupling reactions for the formation of carbon-carbon bonds (Scheme 2-2, Equation 5).



Scheme 2-2: Proposal for synthesizing chiral organoboronates through asymmetric conjugate reductions.

Since the groundbreaking emergence of Stryker's reagent in 1988,[79] this remarkable phosphine-stabilized hexamer $[(Ph_3P)CuH]_6$ has become a versatile tool in modern organic synthesis, especially in the highly regio- and enanoselective conjugate reduction of various Michael acceptors.[78] Reactions involving the Stryker's reagent often feature mild reaction conditions, improved functional group compatibilities and outstanding overall reaction efficiency. Accordingly, this mild hydride source was soon awarded the Fluka "Reagent of the Year" prize in 1991. To efficiently generate CuH, silanes are the most commonly used stoichiometric hydride sources. One of the frequently used silane

hydride sources is polymethylhydrosiloxane (PMHS),[80] which feature inexpensive, highly stable and environmentally friendly merits. When nonracemic bis-phosphines are employed as the chiral ligands, the *in situ* generated chiral copper hydride species can promote conjugate reduction reactions in a diastereo- and enantioselective fashion.[78] Representative examples of chiral ligands that can ligate with CuH asymmetrically include BIPHEP, [81] SEGPHOS [82] and JOSIPHOS [83] (Figure 2-1). These commercially available biaryl ligands or ferrocenyl bis-phosphines shown in Scheme 2-3 present not only remarkable discriminatory structural features but also high catalytic turnover numbers. One drawback, however, is the requirement for an oxygen-free environment such as a glovebox to avoid oxidation of the phosphine. More recently, to overcome the drawback of *in situ* generation of these reactive chiral CuH species, the Lipshutz Group presented a unique chiral SEGPHOS ligated copper hydride **2-2** (Figure 2-1), the so-called "CuH-in-a-Bottle", which exhibits exceptional stability and reactivity.[84]

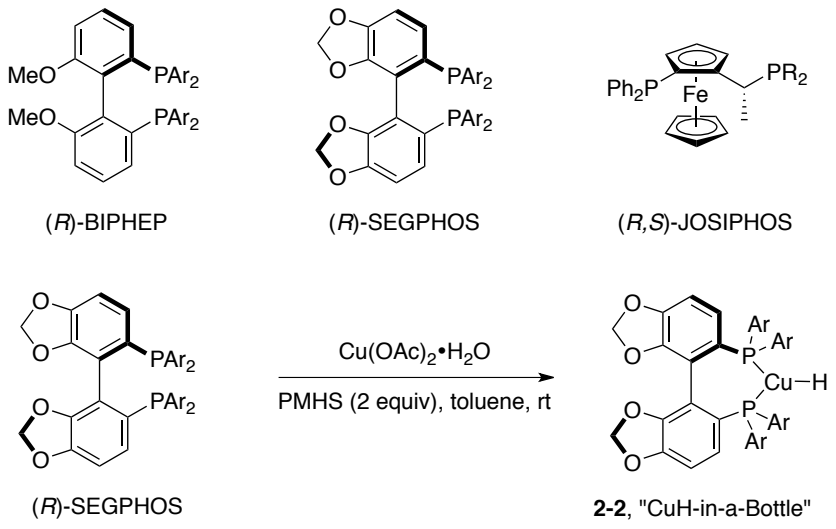


Figure 2-1: Bis-phosphines used for enantioselective CuH catalyzed reactions.

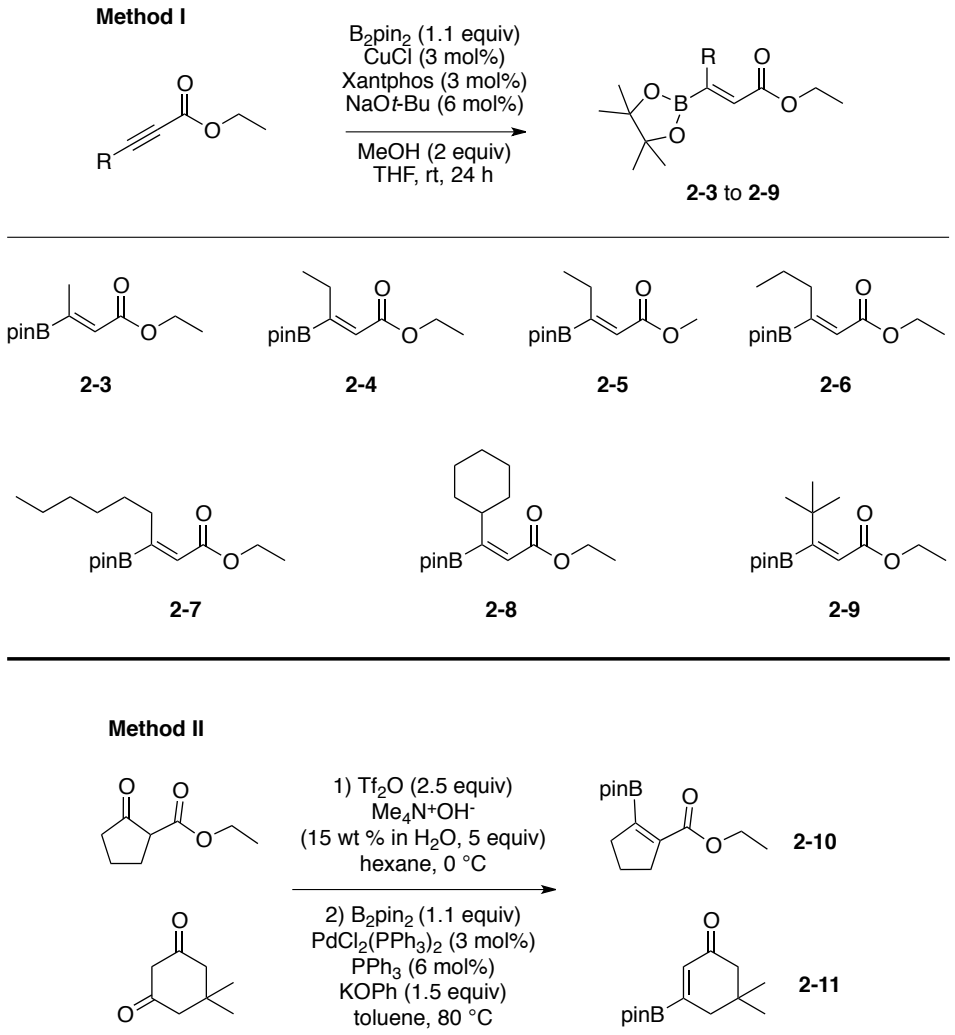
In spite of the advances as stated above, the proposed asymmetric conjugate reduction of prochiral β-boronyl-β-alkyl enoates with chiral CuH species posed

several challenges: 1) the need for a general synthetic route to access the β-boronyl-β-alkyl enoates; 2) a boronyl-compatible asymmetric copper-hydride catalytic system, which may require a suitable boron-protecting group and a hydride source to prevent the undesired protodeboronation process. These challenges will be addressed in detail in the following sections.

2.2 Screening of various asymmetric conjugate addition conditions

2.2.1 Stereoselective preparation of β-boronyl-β-alkyl carbonyl compounds 2-3 to 2-11

Prior to the development of an asymmetric conjugate reduction method, a series of prochiral β-boronyl-β-alkyl carbonyl derivatives were synthesized. The requisite acyclic substrates **2-3** to **2-9** were prepared in one step from ynoates according to the method developed by Yun and co-workers[85] (Scheme 2-3, method I). Alternatively, cyclic substrates **2-10** to **2-11** were prepared in two steps from β-ketoesters using the method of Miyaura and co-workers[86] (Scheme 2-3, method II). Both methods afforded the desired β-boronyl-β-alkyl carbonyl derivatives in good yield.

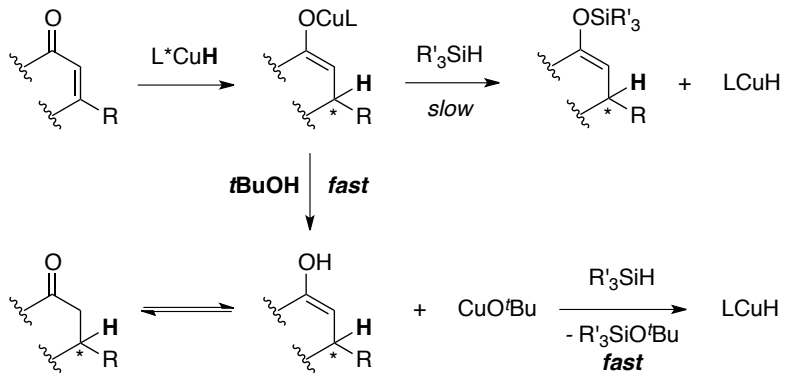


Scheme 2-3: Two methods for the preparation of acyclic substrates **2-3** to **2-9** and cyclic substrates **2-10**, **2-11**.

2.2.2 Optimization of reaction conditions for Cu-catalyzed asymmetric conjugate reduction of 2-3

Although there were lots of precedents on non-borylated substrates,[78] there have been no reported examples of catalytic conjugate reduction on β-borylated α,β-unsaturated carbonyl compounds. We anticipated that the chemical compatibility of the boronate substituent could be a major challenge in the design and optimization of this reaction. Possible undesired pathways include insertion into

the B–C bond leading to deboronative processes.



Scheme 2-4: CuH-catalyzed conjugate reduction in the presence of alcohols.

With various β-alkyl-β-boryl carbonyl compounds readily accessible (see Section 2.2.1), the first round of yield optimization employed β-methyl-β-boryl enoate **2-3** as a model substrate under conditions described by Lipshutz and co-workers.[87] These conditions were selected as a starting point because they featured an impressively low catalyst loading (substrate-to-ligand ratio of 7700:1), affording both cyclic and acylic carbonyl products with superior *ee*'s (95–99% range, Figure 2-2).

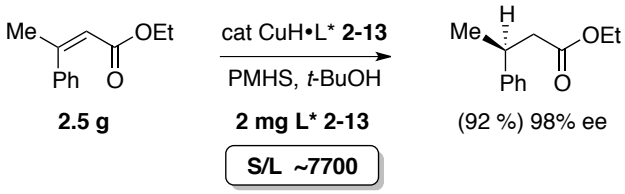


Figure 2-2: CuH-catalyzed asymmetric conjugate reduction condtions reported by the Lipshutz Group.[87a]

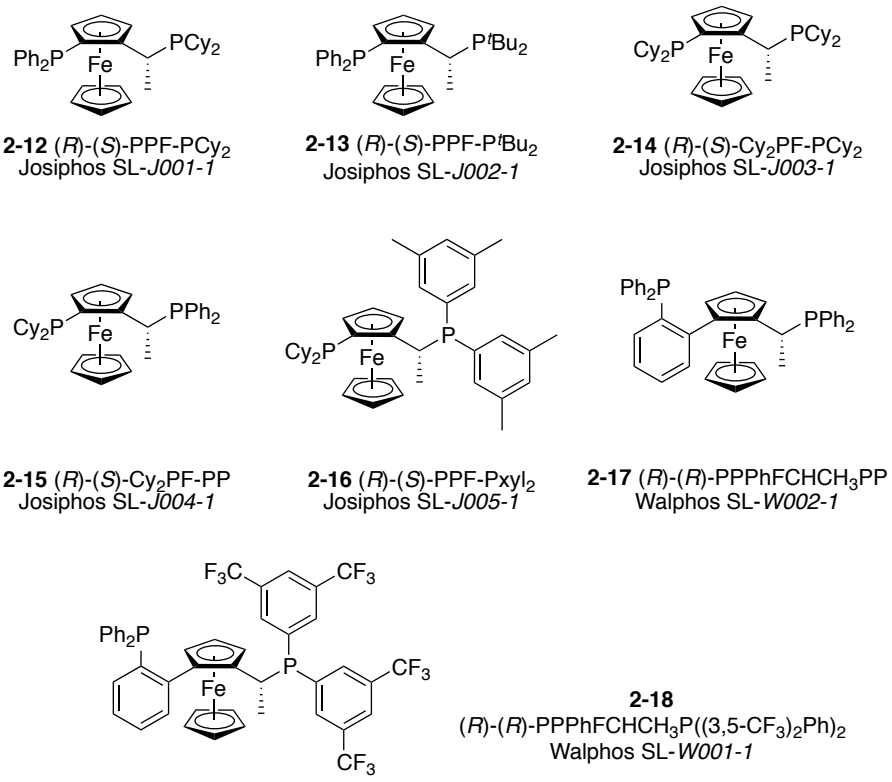
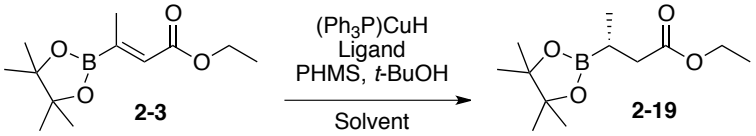


Figure 2-3: Structures of chiral ferrocenyl bis-phosphine ligands evaluated in the conjugate reduction of **2-3**.

In addition, another key advantage to their success was the use of a bulky alcohol, such as *t*BuOH (Scheme 2-4), which was proven to enhance the overall reaction rates. The role of the bulky alcohol is believed to be the promotion of a faster quenching of the copper enolate intermediate. In the presence of excess silane, the resulting copper *tert*-butoxide is also presumed to be an excellent precursor for the rapid re-generation of the reactive CuH species. In light of this pioneering work, various chiral ferrocenyl bisphosphines[78,83] (Figure 2-3) were evaluated with substoichiometric amounts of the Stryker reagent $[(Ph_3P)CuH]_6$. Polymethylhydrosiloxane (PMHS) was applied as the stoichiometric hydride source along with the bulky alcohol *t*-butanol as the rate-accelerating additive (Scheme 2-4). The first round of optimization employed toluene as the solvent at 0 °C (entries 1-7, Table 2-1).



Entry[a]	Ligand	Solvent	Temp.	Time (h)	Yield (%)	ee (%)[d]
1	**2-12**	toluene	0 °C	36	44	-
2	**2-13**	toluene	0 °C	36	34	-
3	**2-14**	toluene	0 °C	36	24	-
4	**2-15**	toluene	0 °C	24	92	92
5	**2-16**	toluene	0 °C	48	0	-
6	**2-17**	toluene	0 °C	36	13	-
7	**2-18**	toluene	0 °C	36	16	-
8	**2-15**	toluene	0 °C	24	95[b]	94
9	**2-15**	toluene	0 °C	16	94[c]	95
10	**2-15**	toluene	rt	24	91[b]	91
11	**2-15**	THF	0 °C	48	0[b]	-
12	**2-15**	THF	rt	48	0[b]	-
13	**2-15**	CH_2Cl_2	0 °C	24	93[b]	96
14	**2-15**	CH_2Cl_2	rt	24	94[b]	92

[a] Reaction conditions: **2-3** (1.0 mmol), 0.4 mol% $(Ph_3P)CuH$ (0.4 μmol), 0.2 mol% ligand (0.2 μmol), *t*-BuOH (1.1 mmol), PMHS (2.0 mmol), solvent (1 mL). [b] 0.8 mol% $(Ph_3P)CuH$, 0.4 mol% ligand **2-15**. [c] 1.6 mol% $(Ph_3P)CuH$, 0.8 mol% ligand **2-15**. [d] Measured by chiral HPLC after oxidation, see experimental section (Section 2.5) for details.

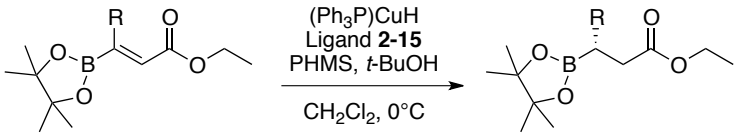
Table 2-1: Optimization of reaction conditions for conjugate reduction of β-methyl-β-boryl enoate **2-3**.

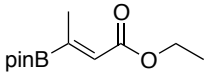
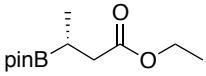
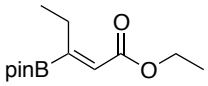
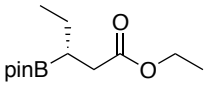
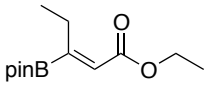
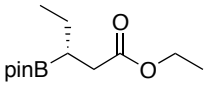
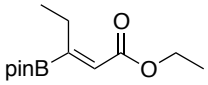
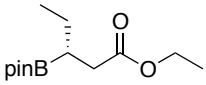
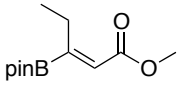
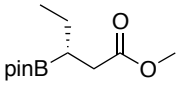
The reaction was relatively slow, requiring as long as 36 hours. Under these conditions, a high yield and excellent enantiomeric excess was obtained when JOSIPHOS **2-15** was used as the ligand (entry 4, Table 2-1). The enantiomeric excess value of the corresponding β-methyl-β-boryl ester **2-19** could not be directly measured by chiral HPLC due to its poor UV sensitivity. Accordingly, further substrate derivatization was applied for the incorporation of more UV sensitive functional groups (see Section 2.5.4 for details). Absolute configuration of the reduction product **2-19** was assigned by comparison with optical rotation of

a known compound (see Section 2.5.3.1 for details).[77] Fine-tuning of the catalyst loading revealed that less than 1 mol% of copper catalyst was sufficient for an efficient reaction (entry 8, Table 2-1). Using the optimal ligand and loading of catalyst, the influence of the solvent and temperature on the yield and enantioselectivity was examined next (entries 10-14, Table 2-1). When tetrahydrofuran was used as solvent, none of the desired product was obtained at either 0 °C or room temperature (entries 11-12, Table 2-1). This outcome is presumably due to solvent coordination to the copper center, resulting in depressed catalyst reactivity. In the end, methylene chloride was the most suitable solvent at 0 °C, leading to a high yield and the highest enantiomeric excess of 96% (entry 13, Table 2-1).

2.2.3 Substrate scope with the (PPh_3)CuH method (Method A)

Using the optimal conditions of Table 2-1 (entry 13), we then initiated the study of the scope for various β-boronyl-β-alkyl carbonyl substrates (Table 2-2). Surprisingly, substrate **2-4** did not give a level of enantioselectivity as high as expected compared to **2-3** (entry 2, Table 2-2). As a result, using **2-4** as a model substrate, further optimization was planned through varying the copper catalyst/bisphosphine ligand ratio and their catalyst loading (entries 3-4, Table 2-2). Even though an increase in the catalyst loading up to 1.6 mol% (Ph_3P)CuH, 0.8 mol% JOSIPHOS (entry 3, Table 2-2) shortened the reaction time, the enantiomeric excess did not improve. Adjusting the catalyst/ligand ratio to 1:1 (0.8 mol% (Ph_3P)CuH, 0.8 mol% JOSIPHOS) again did not increase the enantiomeric excess (entry 4, Table 2-2). It can be concluded that the catalyst/ligand ratio and their catalyst loading do not play a crucial role. At this point, the influence of steric effect from the ester on the enantiomeric excess was studied. The methyl ester **2-5** was reacted under the same reaction conditions (entry 5, Table 2-2). Unfortunately, the enantiomeric excess still did not improve significantly by using a smaller carboxyester.



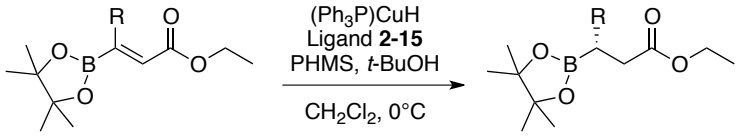
Entry[a]	Substrates		Product		Time (h)	Yield (%)	ee (%)[e]
1		**2-3**		**2-19**	24	95	96
2		**2-4**		**2-20**	24	91	75
3		**2-4**		**2-20**	12[b]	93[b]	74[b]
4		**2-4**		**2-20**	33[c]	92[c]	72[c]
5		**2-5**		**2-21**	16	95	81

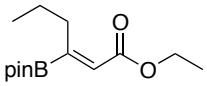
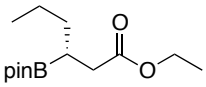
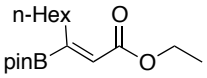
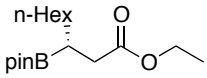
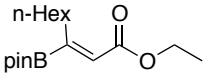
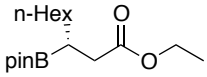
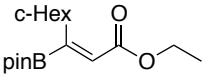
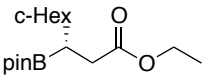
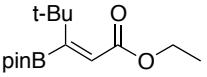
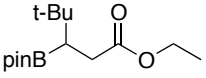
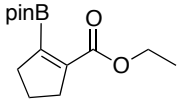
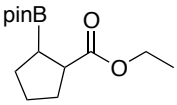
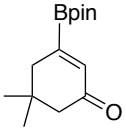
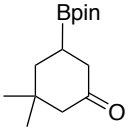
[a] Reaction conditions: substrate (0.5 mmol), 0.8 mol% $(Ph_3P)CuH$ (0.4 μmol), 0.4 mol% ligand (0.2 μmol), *t*-BuOH (0.55 mmol), PMHS (1.0 mmol), CH_2Cl_2 (0.5 mL) [b] 1.6 mol% $(Ph_3P)CuH$, 0.8 mol% ligand **2-15**. [c] 0.8 mol% $(Ph_3P)CuH$, 0.8 mol% ligand **2-15**. [d] 0.8 mol% $(Ph_3P)CuH$, without using any chiral ligands. [e] Measured by chiral HPLC after oxidation, see experimental section (Section 2.5) for details.

Table 2-2: Futher optimization of catalytic enantioselective conjugate reduction of β-boronyl-β-alkyl enoates (Method A).

A number of β-alkyl substituted substrates with longer chains were also tested, and lower enantiomeric excesses were obtained (entries 1-2, Table 2-3). Clearly, the enantioselection is very sensitive to the size of the β-alkyl substituent. Whereas the β-methyl enoate gave 96% *ee*, the β-ethyl and β-*n*-propyl enoates **2-20** to **2-22** provided *ee*'s around 80%. To investigate the cause of this drop in enantioselectivity, a background reaction without chiral ligand **2-15** was performed (entry 3, Table 2-3). The conjugate reduction of β-*n*-hexyl enoate **2-23**

occurred smoothly without the assistance of a diphosphine ligand, albeit with longer reaction time and lower yield (entry 3, Table 2-3).

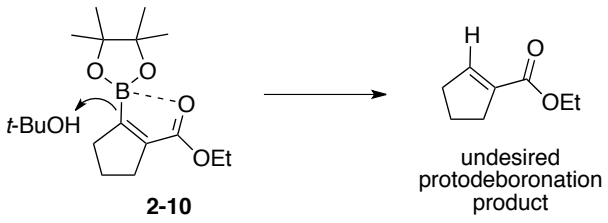


Entry[a]	Substrates		Product		Time (h)	Yield (%)	ee (%)[c]
1		**2-6**		**2-22**	36	92	79
2		**2-7**		**2-23**	48	88	71
3[b]		**2-7**		**2-23**	72[c]	81[c]	-
4		**2-8**		**2-24**	48	85	66
5		**2-9**		**2-25**	48	0	-
6		**2-10**		**2-26**	48	0	-
7		**2-11**		**2-27**	48	0	-

[a] Reaction conditions: substrate (0.5 mmol), 0.8 mol% $(Ph_3P)CuH$ (0.4 μmol), 0.4 mol% ligand (0.2 μmol), *t*-BuOH (0.55 mmol), PMHS (1.0 mmol), CH_2Cl_2 (0.5 mL). [b] 0.8 mol% $(Ph_3P)CuH$, without using any chiral ligands. [c] Measured by chiral HPLC after oxidation, see experimental section (Section 2.5) for details.

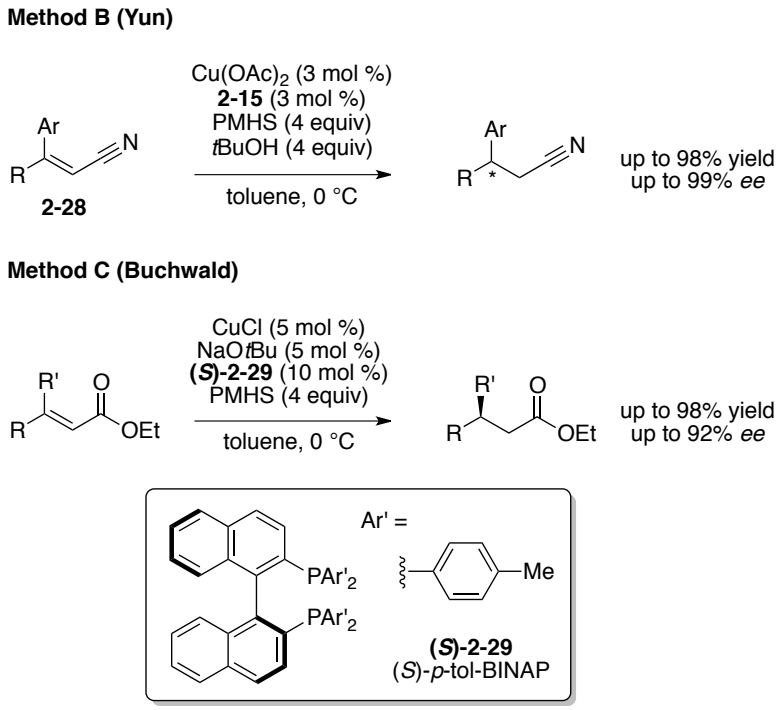
Table 2-3: Scope of β-boronyl-β-alkyl carbonyl compounds for the catalytic enantioselective conjugate reduction (Method A).

Thus, presumably the bisphosphine-less background reaction competes with the enantioselective reaction for the bulky substrates, leading to diminished enantioselectivity. A further drop of selectivity was observed with the β-cyclohexyl enoate **2-8** (entry 4, Table 2-3), and the bulkier β-*t*-butyl enoate **2-9** was unreactive (entry 5, Table 2-3). Unfortunately, under the conditions attempted, the cyclic substrates **2-10** and **2-11** failed to provide the desired conjugate reduction products (entries 6-7, Table 2-3). Instead, protodeboronation products were isolated. This result indicates that the optimal conditions obtained in Table 2-1 are not suitable with cyclic substrates. Further optimization with cyclic substrates, such as **2-10**, as the model substrate would be desirable. A possible mechanism was proposed for the protodeboronation process (Scheme 2-5). The boronic acid pinacol ester, which is *cis* to the carboxylate, could coordinate to the ester oxygen. This coordination would activate the boronyl unit towards protodeboronation. In order to surpress the undesired protodeboronation process could be beneficial to conduct further optimization of copper catalysts and ligands, such as NHC ligand which has been demonstrated to be efficient to promote the conjugate reduction of cyclic substrates.[89b] Alternatively, we could use the corresponding thioester as more reactive substrates, a strategy that was proven successful in previous work from our group.[77]



Scheme 2-5: Proposed pathway for protodeboronation for the cyclic substrates.

2.2.4 Alternative systems with *in situ* generation of copper(I) hydride (Methods B and C)

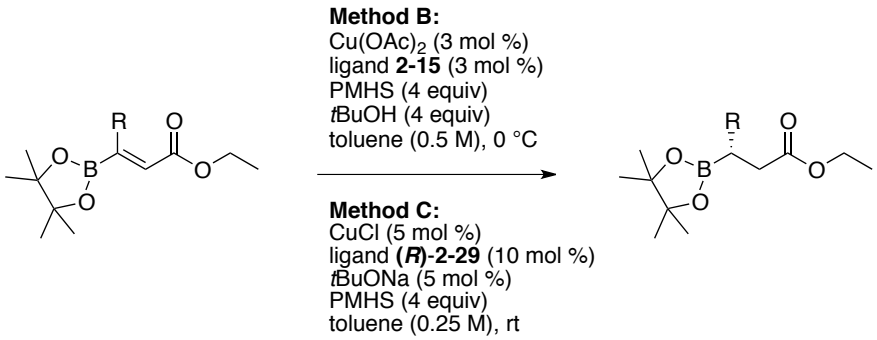


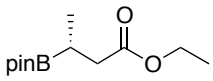
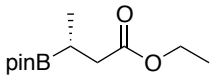
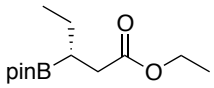
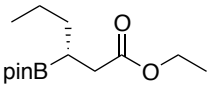
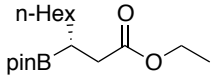
Scheme 2-6: Asymmetric conjugate reduction using *in situ* generated chiral CuH catalytic systems.

As discussed above, the low enantioselectivity for substrates **2-4** to **2-8** is presumably due to the steric hindrance at the β position as well as the competitive background reaction when Stryker's reagent[78,79] was used as the copper hydride source. Therefore, to avoid the background reaction, alternative copper(I) catalytic systems that can generate copper(I) hydride *in situ* without the use of triphenylphosphine were explored. For this purpose, Yun's (Method B, Scheme 2-6)[88] and Buchwald's (Method C, Scheme 2-6)[89] copper(I) catalyzed conjugate reduction systems were investigated. In Method B, the Yun Group applied reaction conditions similar to Lipshuz's (entry 4, Table 2-1) for the enantioselective conjugate reduction of α,β-unsaturated nitriles **2-28**, expect in

this case copper(II) acetate was used as the catalyst instead of the racemic triphenylphosphine ligated Stryker's reagent. Whereas in Method C, Buchwald and coworkers employed *in situ* generation of a bisphosphine-stabilized chiral copper hydride species with CuCl as the copper source, NaO*t*Bu as the base and (*S*)-*p*-tol-BINAP **2-29** as the chiral ligand. Both methods feature mild conditions and wide applicability, and the desired chiral β,β-disubstituted carbonyl derivatives were obtained with high yields and excellent enantioselectivities.

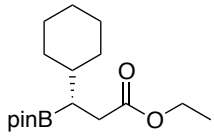
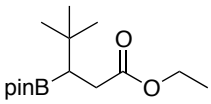
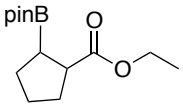
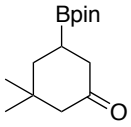
In Table 2-4, both Method B and Method C showed no background reaction (entry 1). In addition, compared to Method A (Table 2-2 and Table 2-3), both methods B and C showed higher catalytic reactivity, as indicated by the equally high yields obtained within a shorter reaction time for substrates **2-3** to **2-7** (entries 2-5, Table 2-4). In terms of enantioselectivity, method C was the most efficient in most cases. Both catalytic Method B and Method C, however, showed the same substrate limitations as Lipshutz's method (Method A, Table 2-2 and Table 2-3). High enantioselectivities are still limited to the less sterically hindered primary β-alkyl substituents (entries 2-4, Table 2-4), while the enantioselectivity for a secondary β-alkyl substituent (entry 1, Table 2-5) dropped significantly. Additionally, like Method A (Table 2-2 and Table 2-3), both Yun's and Buchwald's copper(I) catalytic systems are ineffective towards tertiary β-alkyl substitution and cyclic substrates (entries 2-4, Table 2-5). In spite of this limitation, Method C represents an effective alternative for enantioselective conjugate reduction of β-boronyl-β-alkyl α,β-unsaturated esters.



Entry	Product	Time (h)		Yield (%)		*ee* [d] (%)	
		Method B[a]	Method C[b]	Method B[a]	Method C[b]	Method B[a]	Method C[b]
1[c]	 **2-19**	24	24	0	0	-	-
2	 **2-19**	7	5	93	92	70	97
3	 **2-20**	12	17	92	95	76	96
4	 **2-22**	12	17	91	94	80	96
5	 **2-23**	14	17	82	90	68	94

[a] **Method B**: 3 mol% $Cu(OAc)_2$, 3 mol% ligand **2-15**, 4 equiv of PMHS and *t*-BuOH in toluene (0.5 M) at 0° C. [b] **Method C**: 4 equiv of PMHS, 5 mol% CuCl, 5 mol% NaO*t*-Bu, and 10 mol% (*R*)-**2-29** in toluene (0.25 M) at room temperature. [c] Background reaction (without using phosphine ligands). [d] Measured by chiral HPLC after oxidation, see experimental section (Section 2.5) for details.

Table 2-4: Scope of β-boronyl-β-alkyl carbonyl compounds under two other catalytic systems (Method B and Method C).

Entry	Product	Time (h)		Yield (%)		*ee* [c] (%)	
		Method B[a]	Method C[b]	Method B[a]	Method C[b]	Method B[a]	Method C[b]
1	 **2-24**	14	48	80	79	48	81
2	 **2-25**	72	72	0	0	-	-
3	 **2-26**	72	72	0	0	-	-
4	 **2-27**	72	72	0	0	-	-

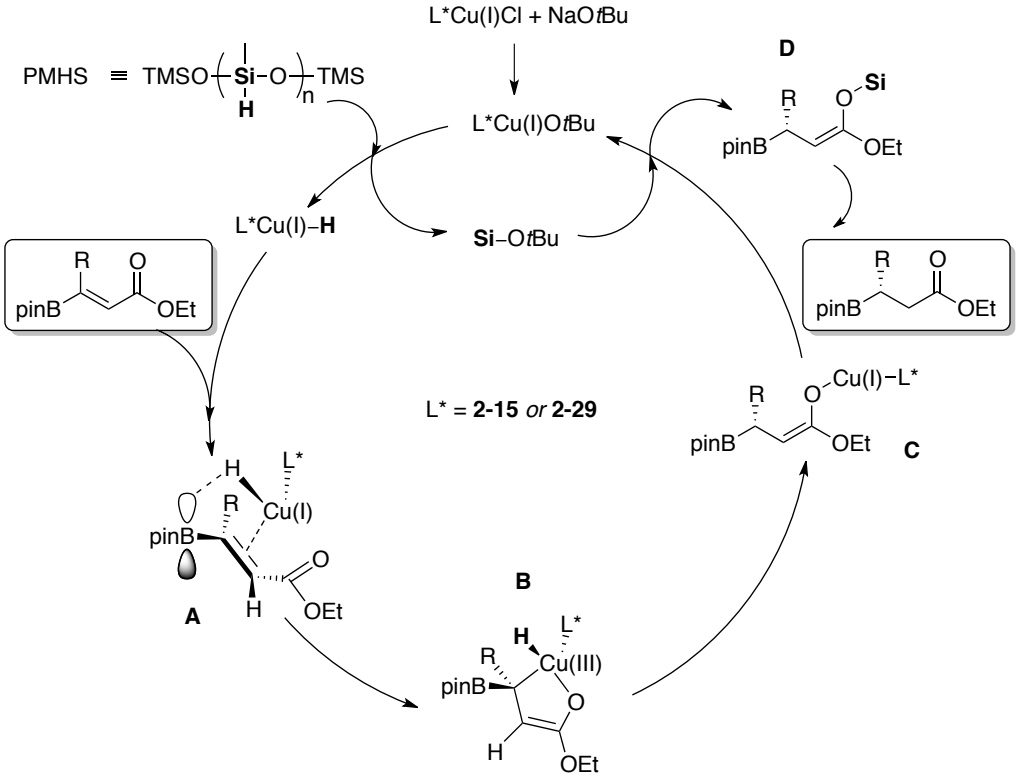
[a] **Method B**: 3 mol% $Cu(OAc)_2$, 3 mol% ligand **2-15**, 4 equiv of PMHS and *t*-BuOH in toluene (0.5 M) at 0° C. [b] **Method C**: 4 equiv of PMHS, 5 mol% CuCl, 5 mol% NaO*t*-Bu, and 10 mol% (*R*)-**2-29** in toluene (0.25 M) at room temperature. [c] Measured by chiral HPLC after oxidation, see experimental section (Section 2.5) for details.

Table 2-5: Scope of other challenging β-boronyl-β-alkyl carbonyl compounds under two other catalytic systems (Method B and Method C).

2.3 Proposed mechanism for the asymmetric conjugate reduction of β-boronyl-β-alkyl carbonyl compounds

Based on the proposed mechanism by Buchwald and coworkers[89] as well as the substrate scope observed in our study, a probable reaction pathway for the copper(I)-catalyzed conjugate reduction of β-boronyl-β-alkyl α,β-unsaturated esters can be proposed. In Scheme 2-7, after ligand exchange with the electron-

rich chiral bisphosphine ligand JOSIPHOS **2-15** or (*R*)-*p*-tol-BINAP **2-29**, a more nucleophilic copper(I) hydride complex is formed. It then reacts with the enoate to give the corresponding copper(I) complex **A**, which allows the asymmetric conjugate reduction to take place to form a proposed five membered copper(III) intermediate **B**.[90]



Scheme 2-7: Proposed mechanism for the copper(I)-catalyzed conjugate reduction of β-boronyl-β-alkyl α,β-unsaturated esters.

In the complex **A**, this conjugate reduction could be facilitated by the interaction between the electron-rich copper hydride and the empty *p*-orbitals of the boronyl group installed in the β-position. Upon reductive elimination of **B**, the copper(I) enolate **C** is subsequently formed. Regeneration of the copper hydride complex with PMHS affords the silylketene acetal intermediate **D**, which then undergoes σ-bond metathesis followed by tautomerization to give the enantioenriched

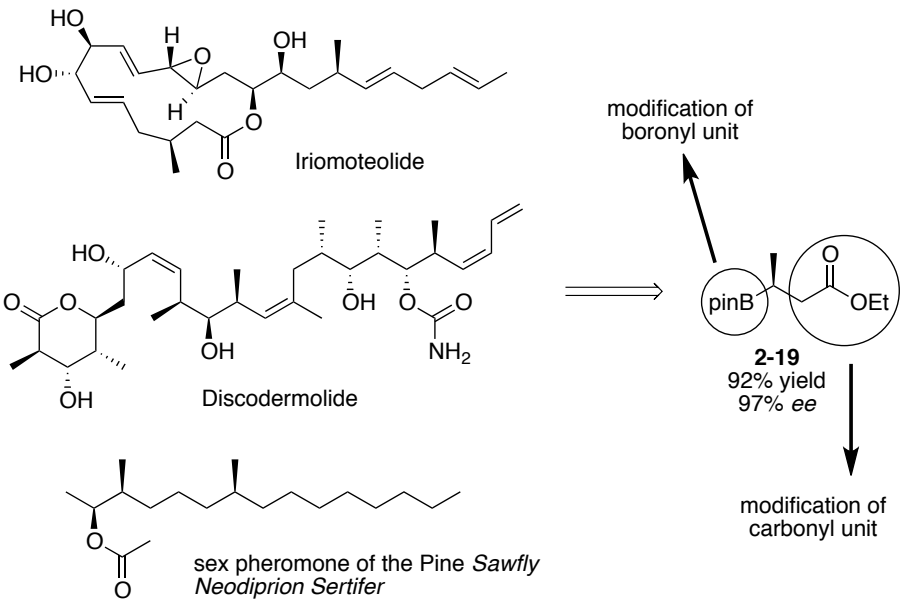
reduced product. In intermediate **A**, the delivery of hydride is strongly influenced by the bulkiness at the β-position. As a result, the smaller achiral triphenylphospine copper(I) hydride can approach the β-carbon more efficiently in the case of bulky β-alkyl substituted substrates, leading to a faster background reaction and thus a lower enantioselectivity.

2.4 Summary

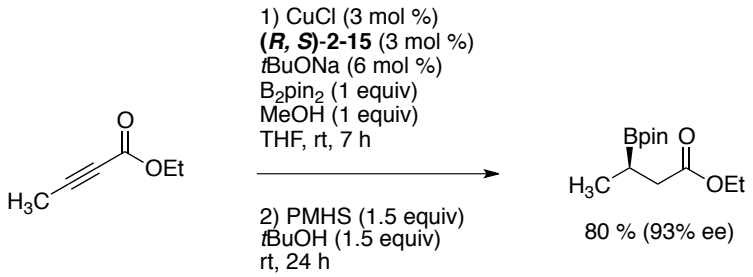
In conclusion, an alternative approach to access synthetically valuable secondary boronate derivatives through copper(I)-catalyzed enantioselective conjugate reductions of β-boronyl-β-alkyl α,β-unsaturated esters was successfully developed. Three copper(I) catalytic systems for enantioselective conjugate reduction were explored. In the beginning, Method A (modified Lipshutz's catalytic system, Tables 2-1, 2-2 and 2-3) was investigated for the optimization of reaction conditions and a substrate scope study was realized using this method. Due to strict limitations of β-substitution in the enoate substrate observed in Method A, alternative copper(I) catalytic systems that generate copper(I) hydride *in situ* were explored (Method B and C, Tables 2-4 and 2-5). Although the same substrate scope was observed, Method C, based on conditions developed by Buchwald and co-workers, was the most efficient, giving excellent yields and high enantiomeric excesses for all cases of β-primary alkyl substrates. As discussed in the previous chapter, these chiral secondary boronate derivatives could act as important building blocks in asymmetric synthesis, which can either be directly functionalized to form the corresponding chiral alcohols and amines, or be subjected to stereospecific Suzuki-Miyaura cross-coupling reactions for various carbon-carbon bond formation.

With respect to applications in natural product synthesis, it is noteworthy that the β-boronyl-β-methyl product **2-19**, obtained in 92% yield and 97% *ee* using our method, constitutes a potentially very useful synthon for the construction of

propionate units and other methylated natural products (Scheme 2-8). Additionally, the chiral methyl group has found widespread applications in determining the steric course of many biological pathways.[91] Furthermore, the easy modification of both the boronyl unit and the carboxyester makes product **2-19** an attractive synthetic building block.



Scheme 2-8: Selected examples for the methylated natural products.



Scheme 2-9: One-pot borylation/asymmetric reduction.

Soon after the above work was published, the Yun Group reported a convenient one-pot borylation/asymmetric reduction of α,β-unsaturated alkynoates *via* a similar copper catalyzed asymmetric conjugate reduction strategy (Scheme 2-9).[92]

The desired reduction product could be obtained in high overall yield and excellent enantioselectivity.

2.5 Experimental

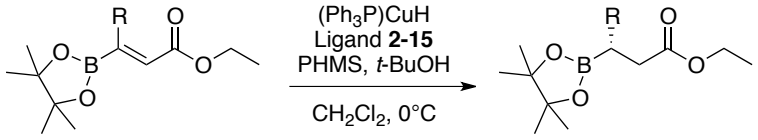
2.5.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were obtained from a MBraun MB SPS* solvent system prior to use. $(Ph_3P)CuH$ was purchased form Acros Organics, +97%; chiral ligands **2-12** to **2-18** were generously provided by Solvias AG. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron (^{11}B) NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is 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; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) ion source with double focussing sector analyzer (Kratos Analytical MS-50G) or electrospray (ESI) ion source with orthogonal acceleration TOF analyzer (Agilent Technologies 6220 oaTOF). Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD (4.6 × 250 mm, length × inner diameter; particle size 5 μm) or Chiralpak-AS (4.6 × 250 mm, length × inner diameter; particle size 5 μm) columns with UV detection. Acyclic

substrates **2-3** to **2-9**[85] and cyclic substrates **2-10** to **2-11**[86] were prepared according to the literature procedures.

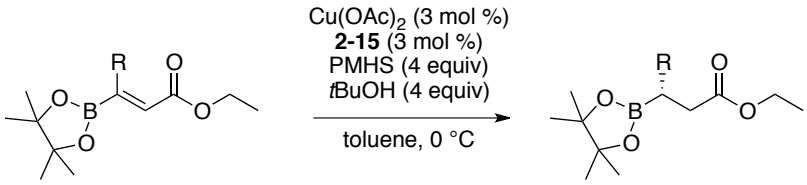
2.5.2 Preparation of chiral β-borylated esters

2.5.2.1 General procedure for the asymmetric conjugate reduction of enoates using Lipshutz's catalytic system (Method A, Tables 2-2 and 2-3)



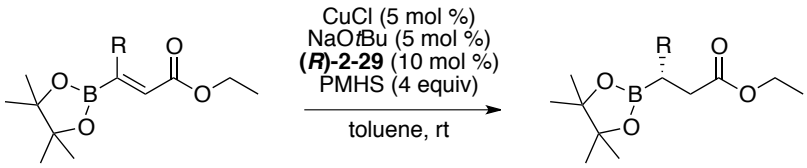
To a 15 mL Schlenk tube, flame dried and purged with nitrogen, was added $(Ph_3P)CuH$ (1.7 mg, 5.0 μmol) and (*R*)-(*S*)-JOSIPHOS **2-15** (1.7 mg, 2.5 μmol). Methylene chloride (0.5 mL) was added and the solution cooled to 0 °C. PMHS (66 μL, 1.0 mmol) was introduced via syringe followed by *t*-BuOH (54 μL, 0.55 mmol) and enoate (0.5 mmol) by syringe. The mixture was stirred at 0 °C until the reaction was deemed complete by TLC (eluent: 10% ethyl acetate/hexane). The reaction was quenched by pouring into aqueous sat. $NaHCO_3$, diluted with Et_2O/H_2O, and then stirred for 1 h at room temperature. The aqueous layer was extracted twice with Et_2O and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered through a pad of silica gel and rinsed with Et_2O until no product remained on the silica gel by TLC. The filtrate was then concentrated by rotary evaporation. The crude oil was purified by silica gel flash chromatography (10% ethyl acetate/hexane) to afford the product as a clear oil.

2.5.2.2 General procedure for the asymmetric conjugate reduction of enoates 1 using Yun's catalytic system (Method B, Tables 2-4 and 2-5)



To a 15 mL Schlenk tube, flame dried and purged with nitrogen, was added $Cu(OAc)_2$ (2.7 mg, 0.015 mmol) and (*R*)-(*S*)-JOSIPHOS **2-15** (10 mg, 0.015 mmol). PMHS (0.12 mL, 2.0 mmol) and toluene (0.5 mL) were added under nitrogen. The reaction mixture was stirred for 5 min at 0 °C and then the enoate (0.5 mmol) was added by syringe, followed by *t*-BuOH (0.19 mL, 2.0 mmol). The reaction tube was washed with toluene (0.5 mL) and sealed, and the reaction mixture was stirred until no starting material was detected by TLC (eluent: 10% ethyl acetate/hexane). The work up and purification procedure is the same as Section 2.5.2.1.

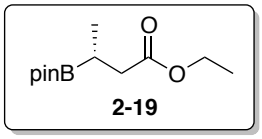
2.5.2.3 Modified procedure for the asymmetric conjugate reduction of enoates 1 using Buchwald's catalytic system (Method C, Tables 2-4 and 2-5)



To a 15 mL Schlenk tube, flame dried and purged with nitrogen, was added CuCl (2.7 mg, 0.027 mmol), (*R*)-*p*-tol-BINAP **(*R*)-2-29** (37 mg, 0.054 mmol) and NaO*t*-Bu (2.7 mg, 0.027 mmol). Toluene (1 mL) was added under nitrogen, and the resulting solution was stirred for 10 min. PMHS (0.12 mL, 2.0 mmol) was added, and the reaction mixture was stirred for another 10 min, followed by addition of enoate **1** (0.5 mmol). The reaction tube was washed with toluene (1

mL) and sealed, and the reaction mixture was stirred until no starting material was detected by TLC (eluent: 10% ethyl acetate/hexane). The work up and purification procedure is the same as Section 2.5.2.1.

2.5.2.4 (*R*)-Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate 2-19



2-19

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **2-19** (115 mg, 95 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (app q, *J* = 7.2 Hz, 2H), 2.45 (dd, *J* = 16.3, 7.7 Hz, 1H), 2.38 (dd, *J* = 16.3, 6.7 Hz, 1H), 1.40 (m, 1H), 1.29-1.23 (m, 15H), 1.02 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 83.1, 60.1, 37.7, 24.8, 24.6, 15.1, 14.3.

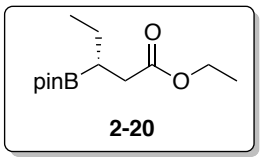
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.9.

IR (microscope, cm^{-1}) 2979, 2935, 2876, 1735.

HRMS (EI) for $C_{12}H_{23}BO_4$: calcd. 242.16895; found 242.16863.

$[\alpha]_D^{20}$: −8.66 (c = 1.36, $CHCl_3$) (Table 2-2, Method A); −4.3 (c = 0.79, $CHCl_3$) (Table 2-4, Method B); −7.7 (c = 0.82, $CHCl_3$) (Table 2-4, Method C).

2.5.2.5 (*R*)-Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate 2-20



2-20

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **2-20** (117 mg, 91 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (AB of ABX_3, app q, J = 7.2 Hz, 2H), 2.46 (A of ABX, m, 1H), 2.39 (B of ABX, m, 1H), 1.53-1.36 (m, 2H), 1.32-1.27 (m, 1H), 1.27-1.22 (m, 15H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 83.1, 60.1, 35.5, 24.8, 24.7, 23.5, 14.3, 13.2.

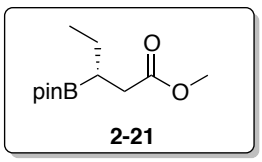
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.9.

IR (microscope, cm^{-1}) 2979, 2934, 2875, 1735.

HRMS (EI) for $C_{13}H_{25}BO_4$: calcd. 256.1846; found 256.1846.

$[\alpha]_D^{20}$: −2.80 (c = 1.00, $CHCl_3$) (Table 2-2, Method A); −2.6 (c = 0.92, $CHCl_3$) (Table 2-4, Method B); −6.3 (c = 0.82, $CHCl_3$) (Table 2-4, Method C).

2.5.2.6 (*R*)-Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate 2-21

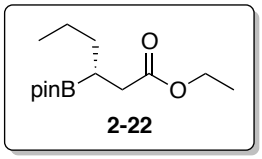


2-21

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **2-21** (115 mg, 95% yield) as a colourless oil. The characterization data for this compound matched that of a previous report.[77]

$[\alpha]_D^{20}$: −1.1 (c = 0.56, $CHCl_3$).

2.5.2.7 (*R*)-Ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanoate 2-22



2-22

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **2-22** (124 mg, 92% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16-4.10 (AB of ABX_3, m, 2H), 2.42 (A of ABX, m, 1H), 2.37 (B of ABX, m, 1H), 1.46-1.28 (m, 5H), 1.27-1.22 (m, 15H), 0.88 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 82.7, 59.7, 35.4, 32.4, 24.4, 24.3, 21.5, 13.9, 13.8.

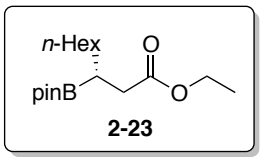
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.9.

IR (microscope, cm^{-1}) 2979, 2931, 2873, 1735.

HRMS (EI) for $C_{14}H_{27}BO_4$: calcd. 270.2002; found 270.2003.

$[\alpha]_D^{20}$: −2.38 (c = 1.00, $CHCl_3$) (Table 2-3, Method A); −2.7 (c = 0.65, $CHCl_3$) (Table 2-4, Method B); −6.3 (c = 0.82, $CHCl_3$) (Table 2-4, Method C).

2.5.2.8 (*R*)-Ethyl 3-*n*-hexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) propanoate 2-23



2-23

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **2-23** (137 mg, 88% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17-4.10 (AB of ABX_3, m, 2H), 2.45 (A of ABX, m, 1H), 2.39 (B of ABX, m, 1H), 1.50-1.20 (m, 26H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 83.1, 60.1, 35.8, 31.8, 30.6, 29.4, 28.7, 24.8, 24.7, 22.6, 14.3, 14.1.

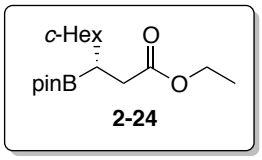
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8.

IR (microscope, cm^{-1}) 2978, 2959, 2928, 2857, 1735.

HRMS (EI) for $C_{17}H_{33}BO_4$: calcd. 312.2472; found 312.2474.

$[\alpha]_D^{20}$: –2.6 (c = 1.80, $CHCl_3$) (Table 2-3, Method A); –2.1 (c = 0.79, $CHCl_3$) (Table 2-4, Method B); –4.71 (c = 1.20, $CHCl_3$) (Table 2-4, Method C).

2.5.2.9 (*R*)-Ethyl 3-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) propanoate 2-24



2-24

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **2-24** (132 mg, 85 % yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18-4.07 (AB of ABX_3, m, 2H), 2.46 (dd, *J* = 16.4, 10.6 Hz, 1H), 2.37 (dd, *J* = 16.5, 5.6 Hz, 1H), 1.76-1.63 (m, 5H), 1.46-1.01 (m, 22H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 83.1, 60.1, 39.2, 33.7, 32.5, 32.2, 26.7, 25.0, 24.7, 14.3.

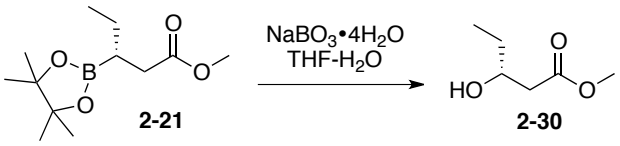
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.7.

IR (microscope, cm^{-1}) 2979, 2926, 2853, 1735.

HRMS (EI) for $C_{17}H_{31}BO_4$: calcd. 310.2315; found 310.2323.

$[\alpha]_D^{20}$: −2.9 (c = 0.70, $CHCl_3$) (Table 2-3, Method A); −1.1 (c = 0.76, $CHCl_3$) (Table 2-5, Method B); −4.10 (c = 1.00, $CHCl_3$) (Table 2-5, Method C).

2.5.3 Determination of absolute stereochemistry

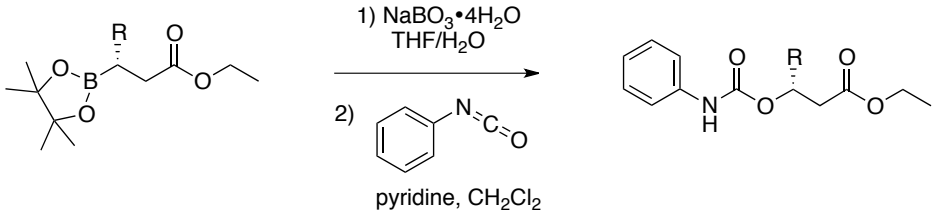


The title alcohol was prepared independently using the reported procedure (62 mg, 92 % yield).[93] The characterization data for the title compound **2-30** matched that of a previous report.[94]

The $[\alpha]_D^{20}$ of this compound was measured to be −23.2 (c = 1.00, chloroform), the same to the reported for the (*R*)-isomer (–37.2, c = 1.00, chloroform). The lower absolute value is presumably due to the lower enantiomeric excess. Thus,

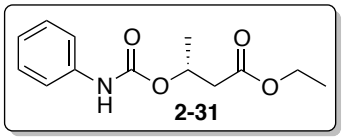
this proves that the compounds synthesized using our procedure from (*R*)-(-)-JOSIPHOS **2-15** as the ligand have the *R*-configuration on the stereogenic centre.

2.5.4 Enantiomeric excess measurement of the oxidized product



To measure the enantiomeric excess of the oxidized products, the title compound was prepared using the reported procedures.[77]

2.5.4.1 (*R*)-Ethyl 3-(phenylcarbamoyloxy)butanoate 2-31



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 2H), 7.33-7.26 (m, 2H), 7.06 (m, *J* = 7.3, 1.2 Hz, 1H), 6.67 (br s, 1H), 5.35-5.24 (m, 1H), 4.15 (app q, *J* = 7.2 Hz, 2H), 2.69 (dd, *J* = 15.4, 7.4 Hz, 1H), 2.55 (dd, *J* = 15.3, 5.7 Hz, 1H), 1.37 (d, J = 6.3 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 152.2, 137.4, 128.6, 123.0, 118.2, 68.0, 60.3, 40.8, 19.8, 13.8.

IR (microscope, cm^{-1}) 3367, 3061, 2984, 2937, 2877, 1737, 1600, 1541, 1502.

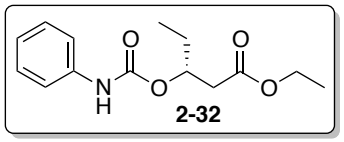
HRMS (ESI) for $C_{13}H_{17}NO_4$: calcd. 251.1158; found 251.1159.

$[\alpha]_D^{20}$: –5.9 (c = 0.58, chloroform) for 96% *ee* (Table 2-2, Method A); –1.9 (c = 0.8, chloroform) for 70% ee (Table 2-4, Method B); –6.5 (c = 1.0, chloroform) for

97% ee (Table 2-4, Method C).

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 41.9 min, T_{minor} = 31.6 min, *ee* = 96% (Table 2-2, Method A); 70% (Table 2-4, Method B); 97% (Table 2-4, Method C).

2.5.4.2 (*R*)-Ethyl 3-(phenylcarbamoyloxy)pentanoate 2-32



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.36 (m, 2H), 7.34-7.29 (m, 2H), 7.10-7.45 (m, 1H), 6.63 (br s, 1H), 5.23-5.16 (m, 1H), 4.20-4.12 (AB of ABX_3, m, 2H), 2.67 (dd, *J* = 15.3, 7.5 Hz, 1H), 2.61 (dd, *J* = 15.3, 5.3 Hz, 1H), 1.75 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.9, 137.9, 129.0, 123.4, 118.5, 72.8, 60.7, 39.2, 27.2, 14.2, 9.4.

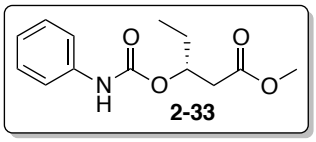
IR (microscope, cm^{-1}) 3336, 3060, 2976, 2938, 2881, 1737, 1600, 1541, 1502.

HRMS (ESI) for $C_{14}H_{19}NO_4$: calcd. 265.1314; found 265.1315.

$[\alpha]_D^{20}$: –3.4 (c = 0.75, chloroform) for 75% ee (Table 2-2, Method A); –3.9 (c = 0.70, chloroform) for 76% ee (Table 2-4, Method B); –6.30 (c = 1.20, chloroform) for 96% ee (Table 2-4, Method C).

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 280 nm, T_{major} = 15.4 min, T_{minor} = 17.5 min, ee = 75% (Table 2-2, Method A); 76% (Table 2-4, Method B); 96% (Table 2-4, Method C).

2.5.4.3 (*R*)-Methyl 3-(phenylcarbamoyloxy)pentanoate 2-33

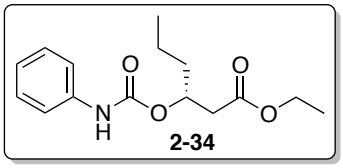


The characterization data for this compound matched that of a previous report.[77]

$[\alpha]_D^{20}$: –3.6 (c = 0.78, chloroform) for 83% *ee*.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 254 nm, T_{major} = 17.9 min, T_{minor} = 24.0 min, ee = 83%.

2.5.4.4 (*R*)-Ethyl 3-(phenylcarbamoyloxy)hexanoate 2-34



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.36 (m, 2H), 7.34-7.29 (m, 2H), 7.10-7.45 (m, 1H), 6.63 (br s, 1H), 5.23-5.16 (m, 1H), 4.16 (app q, *J* = 7.1 Hz, 2H), 2.67 (dd, *J* = 15.3, 7.5 Hz, 1H), 2.61 (dd, *J* = 15.3, 5.4 Hz, 1H), 1.75-1.60 (m, 2H), 1.50-1.36 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.9, 138.0, 129.0, 123.4, 118.6, 71.4, 60.7, 39.6, 36.4, 18.5, 14.2, 13.9

IR (microscope, cm^{-1}) 3338, 3060, 2962, 2935, 2874, 1737, 1600, 1541, 1502.

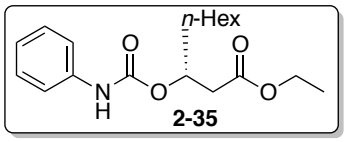
HRMS (ESI) for $C_{15}H_{21}NO_4$: calcd. 279.1471; found 279.1476.

$[\alpha]_D^{20}$: –2.19 (c = 1.39, chloroform) for 79% ee (Table 2-2, Method A); –3.1 (c = 1.0, chloroform) for 80% ee (Table 2-4, Method B); –4.3 (c = 0.80, chloroform)

for 96% ee (Table 2-4, Method C).

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 280 nm, T_{major} = 13.0 min, T_{minor} = 16.8 min, *ee* = 79% (Table 2-2, Method A); 80% (Table 2-4, method B); 96% (Table 2-4, method C).

2.5.4.5 (*R*)-Ethyl 3-*n*-hexyl-3-(phenylcarbamoyloxy)propanoate 2-35



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.36 (m, 2H), 7.35-7.30 (m, 2H), 7.10-7.45 (m, 1H), 6.58 (br s, 1H), 5.27-5.20 (m, 1H), 4.20-4.12 (AB of ABX_3, m, 2H), 2.67 (A of ABX, m, 1H), 2.61 (B of ABX, m, 1H), 1.77-1.62 (m, 2H), 1.46-1.22 (m, 11H), 0.90 (t, *J* = 6.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.8, 137.9, 129.0, 123.4, 118.6, 71.7, 60.7, 39.6, 34.3, 31.7, 29.1, 25.1, 22.6, 14.2, 14.1.

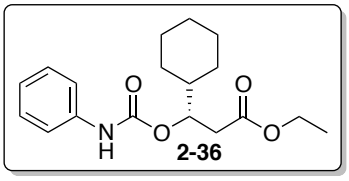
IR (microscope, cm^{-1}) 3338, 3060, 2957, 2931, 2859, 1738, 1601, 1541, 1502.

HRMS (ESI) for $C_{18}H_{27}NO_4$: calcd. 321.1940; found 321.1935.

$[\alpha]_D^{20}$: –1.8 (c = 0.59, chloroform) for 71% ee (Table 2-2, Method A); –1.3 (c = 0.90, chloroform) for 68% ee (Table 2-4, Method B); –5.30 (c = 1.00, chloroform) for 94% ee (Table 2-4, Method C).

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 254 nm, T_{major} = 12.1 min, T_{minor} = 16.4 min, *ee* = 71% (Table 2-2, Method A); 68% (Table 2-3, Method B); 94% (Table 2-3, Method C).

2.5.4.6 (*R*)-Ethyl 3-cyclohexyl-3-(phenylcarbamoyloxy)propanoate 2-36



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 2H), 7.34-7.26 (m, 2H), 7.08-7.02 (m, 1H), 6.57 (br s, 1H), 5.16-5.07 (m, 1H), 4.20-4.12 (AB of ABX_3, m, 2H), 2.64-2.56 (AB of ABX, m, 2H), 1.84-1.52 (m, 6H), 1.32-1.00 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 152.9, 138.0, 129.0, 123.3, 118.5, 75.2, 72.2, 60.7, 41.6, 37.1, 28.7, 28.2, 26.4, 26.1, 14.2.

IR (microscope, cm^{-1}) 3367, 3061, 2984, 2937, 2877, 1737, 1600, 1541, 1502.

HRMS (ESI) for $C_{18}H_{25}NO_4$: calcd. 319.1783; found 319.1783.

$[\alpha]_D^{20}$: −1.5 (c = 0.58, chloroform) for 66% ee (Table 2-2, Method A); −0.92 (c = 0.60, chloroform) for 48% ee (Table 2-3, Method B); −3.8 (c = 0.75, chloroform) for 81% ee (Table 2-3, Method C).

HPLC (Chiralcel OD): 3:97 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 280 nm, T_{major} = 24.0 min, T_{minor} = 26.6 min, ee = 66% (Table 2-2, Method A); 48% (Table 2-5, Method B); 81% (Table 2-5, Method C).

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Chapter 3 Stereoselective Preparation of β-Aryl-β-Boronyl Enoates and Their Copper-Catalyzed Enantioselective Conjugate Reduction*

3.1 Introduction

As discussed in the previous chapters, optically enriched chiral organoboronate derivatives are important synthetic intermediates,[95,96] which may be employed in cross-coupling chemistry or as precursors of alcohols and amines following a C−B bond oxidation. Borylative conjugate addition[97] provides an attractive methodology to access chiral alkylboronates, as recently demonstrated by many research groups[98] (also see Scheme 2-2, Equation 1). Our group has developed a complementary conceptual approach where the boronate group is pre-installed on a universal α,β-unsaturated ester substrate, which is then subjected to a catalytic asymmetric conjugate addition with unstabilized carbanions or to an asymmetric conjugate borylation that provides optically enriched alkylboronates[99] (also see Scheme 2-2, Equation 2). As part of our ongoing search for new ways to access chiral secondary alkylboronates, we reasoned that the corresponding copper-catalyzed enantioselective conjugate reduction of β-alkyl-β-boronyl α,β-unsaturated esters would provide a useful alternative.

The Buchwald[100] and Lipshutz[101] groups have independently developed efficient copper-catalyzed enantioselective methods for conjugate reduction of α,β-unsaturated compounds with PMHS as a mild hydride source. Recently, the Hall Group applied these methods for the catalytic asymmetric synthesis of chiral secondary alkylboronates from β-alkyl-β-boronyl

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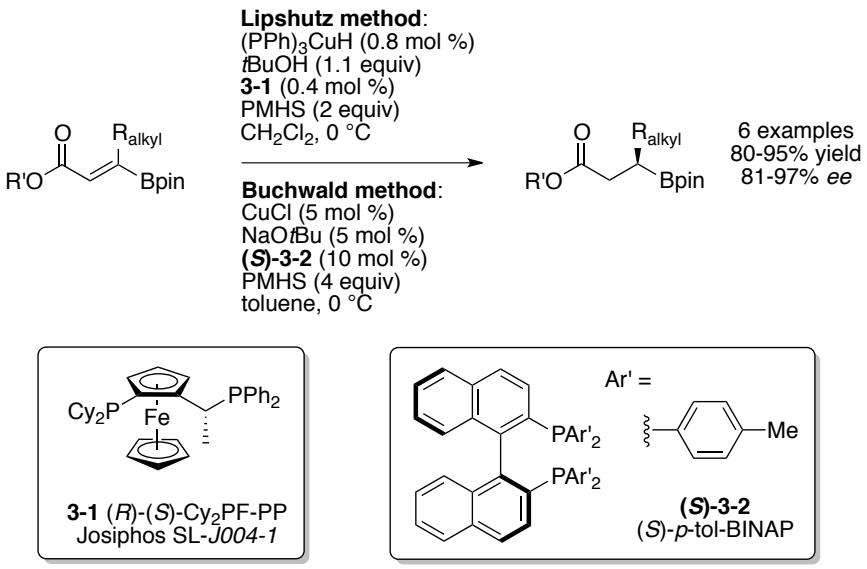
* A version of this chapter has been published: Ding, J.; Lee, J. C. H.; Hall, D. G. *Org. Lett.* **2012**, *14*, 4462−4465.

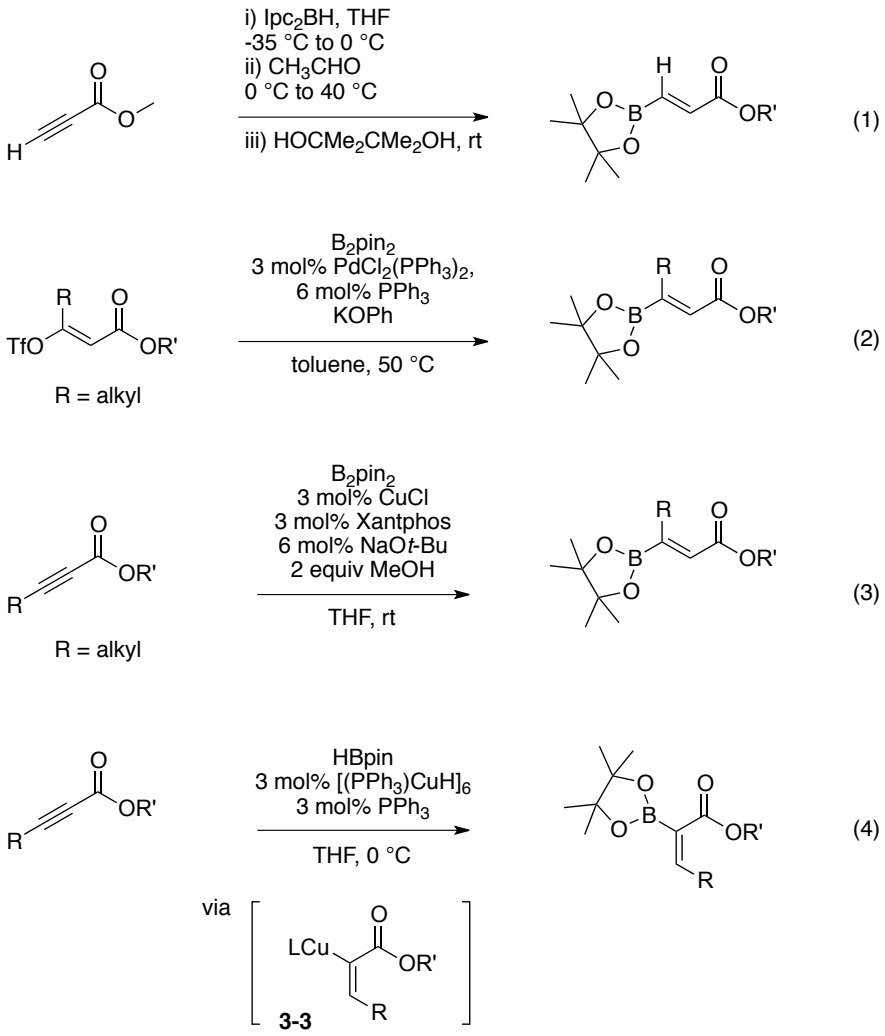
α,β-unsaturated esters (Scheme 3-1).[102] Various chiral secondary boronate derivatives were accessed in excellent yields and good to high enantioselectivity. With this method, however, the β-R group on the enoate substrate was limited to alkyl substituents because established methods for the preparation of the substrates did not permit the use of β-aryl groups (Scheme 3-2).



Scheme 3-1: Asymmetric conjugate reduction of β-alkyl-β-boronyl enoates.

β-Boronyl α,β-unsaturated esters are important synthetic intermediates since these compounds hold a variety of reactive sites that can be functionalized regio- and stereoselectively.[103] To date, several synthetic methodologies have been reported for the preparation of this class of compounds (Scheme 3-2). In 1992, the Vaultier Group developed a regio- and stereoselective hydroboration approach for the installation of boronates onto methyl propiolate (Scheme 3-2, Equation 1).[104] The Hall Group later demonstrated that the corresponding boronic acid analogue could also be accessed using this protocol.[105] This method, however, is limited to hydroboration of ynoates bearing terminal alkynes, and thus only gives access to simple disubstituted β-boronyl enoates. In 2003, the Miyaura Group described a palladium-catalyzed borylation of alkenyl triflates with bis(pinacolato)diboron,

which could afford trisubstituted β-boronyl enoates stereoselectively (Scheme 3-2, Equation 2).[106] Similar adducts can also be prepared through a copper-catalyzed conjugate borylation with various β-substituted ynoates, as recently demonstrated by the Yun Group (Scheme 3-2, Equation 3).[107] Both of these approaches, however, are limited to precursors bearing alkyl substituents, while the synthesis of aryl variants till now remained an unsolved problem (Scheme 3-2, Equations 2 and 3).



Scheme 3-2: Known methods for the preparation of boronyl enoates.

In addition to these synthetic methods for the installation of boronate units to the

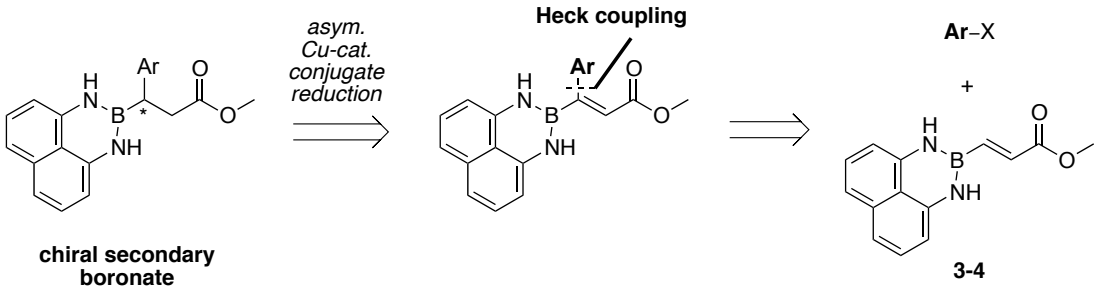
β-position of enoates, the Lipshutz Group has recently developed a CuH catalyzed conjugate reduction/transmetallation protocol for the incorporation of boronyl groups to the α-position (Scheme 3-2, Equation 4).[108] Upon addition of CuH as the nucleophilic catalyst, the authors found that catalytic chemo- and stereoselective 1,2-additions of CuH to acetylenic esters could be achieved, providing the resulting α-cuprio enoate **3-3** stereoselectively. Subsequent facile *in situ* transmetallation with pinacolborane successfully yields the α-boronyl enoates with stereoretention.

3.2 Objectives

As mentioned in the above section, the known literature methods for synthesizing trisubstituted β-boronyl enoates are limited to aliphatic substituents at the β-position, while the preparation for β-aryl-β-boronyl enoates has not yet been reported. Due to the prevalent synthetic applications associated with these boron compounds and the α,β-unsaturated carbonyl motif, a new method for the preparation of β-aryl-β-boronyl α,β-unsaturated esters would be valuable. The Hall Group previously demonstrated that β-boronyl compound **3-4** can be compatible with a variety of transition metal-catalyzed reaction conditions.[99] Accordingly, we surmised that the synthesis of trisubstituted alkenes could be accessed from β-boronyl enoate **3-4** through a Heck cross coupling reaction (Scheme 3-3, Equation 1). The Heck cross-coupling reaction has become a ubiquitous tool in organic synthesis for the formation of C−C bonds.[109] Owing to its important synthetic utility in both academic laboratories and the pharmaceutical industry, Richard Heck was jointly awarded the 2010 Nobel Prize with Akira Suzuki and Ei-ichi Negishi for their contribution to the development of palladium-catalyzed cross-coupling reactions. We anticipated that the proposed Heck reaction approach in Scheme 3-3 would encounter difficulty due to the possibility of undesired transmetalation with the sp^2 C−B bond of substrate **3-4**. As demonstrated by the Suginome and Hall groups,[110] however, the pre-installed

boronyl unit, which features the use of 1,8-diaminonaphthalene (dan) as the boron masking-group, should be stable towards transmetallation, which would allow the desired cross-coupling reaction to be realized.

While the first objective was to prepare β-aryl-β-boronyl α,β-unsaturated esters *via* a proposed Heck reaction (Scheme 3-3), work that was mainly conducted by former Hall Group member Jack Chang Hung Lee, the second objective was to access chiral β-aryl-β-boronyl esters [111] *via* a copper-catalyzed asymmetric conjugate reduction (Scheme 3-3).

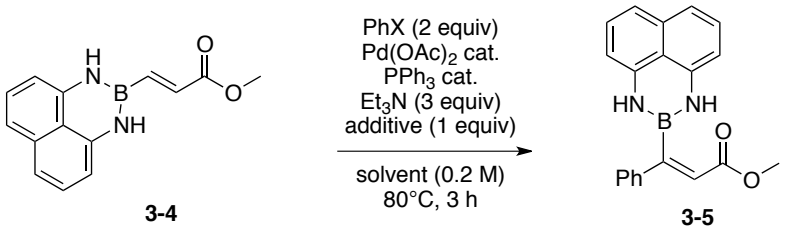


Scheme 3-3: Proposed approach for the synthesis of β-aryl-β-boronyl enoate and their subsequent application in conjugate reduction.

3.3 Reaction optimization for the Heck reaction

Optimal conditions were first sought for the Heck coupling reaction, and 1,8-diaminonaphthalene (dan) adduct **3-4** was used as a test substrate (Table 3-1). This part of the work was conducted by former Hall Group member Jack Chang Hung Lee.[112] In Table 3-1, when 5 mol% $Pd(OAc)_2$ was applied as the catalyst with 10 mol% PPh_3 as the ligand, the desired coupling product **3-5** was obtained in a decent yield as a single *E* stereoisomer (entry 1). Considering the possibility of partial decomposition of the β-boronyl enoate **3-4** under the reaction conditions, a slight excess of the boron compound **3-4** was employed relative to iodobenzene. The yield of the desired transformation, however, further decreased (entry 2, Table 3-1), which suggests that the substrate **3-4** is fairly stable under the cross-

coupling reaction conditions. Further fine-tuning of the catalyst loading found that an excess amount of phosphine was unnecessary. Instead, only a small catalytic amount of phosphine ligand was required to afford a decent yield for the desired Heck reaction (entry 3, Table 3-1).



entry[a]	X	catalyst loading (mol%)	additive	solvent	yield (%)[b]
1	I	5% $Pd(OAc)_2$, 10% PPh_3	–	DMF	52
2[c]	I	5% $Pd(OAc)_2$, 10% PPh_3	–	DMF	24
3	I	10% $Pd(OAc)_2$, 6% PPh_3	–	DMF	58
4	I	10% $Pd(OAc)_2$, 6% PPh_3	Bu_4NHSO_4	DMF	63
5	I	10% $Pd(PPh_3)_4$	–	DMF	20
6	Br	10% $Pd(OAc)_2$, 6% PPh_3	–	DMF	55
7	Br	10% $Pd(OAc)_2$, 6% PPh_3	Bu_4NHSO_4	DMF	75
8	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	DMF	76
9[d]	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	DMF	75
10	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	toluene	61
11	Br	5% $Pd(OAc)_2$, 3% PPh_3	Bu_4NHSO_4	MeCN	74

[a] Reaction conditions: **3-4** (1.0 mmol), PhX (2.0 mmol), Et_3N (3.0 mmol), additive (1.0 mmol), solvent (5 mL), 80 °C for 10 h. [b] Isolated yield of products after flash colum chromatography, E/Z > 98% by ^{1}H-NMR analysis. [c] PhI (1 equiv) and **3-4** (1.5 equiv) [d] 1 M instead of 0.2 M

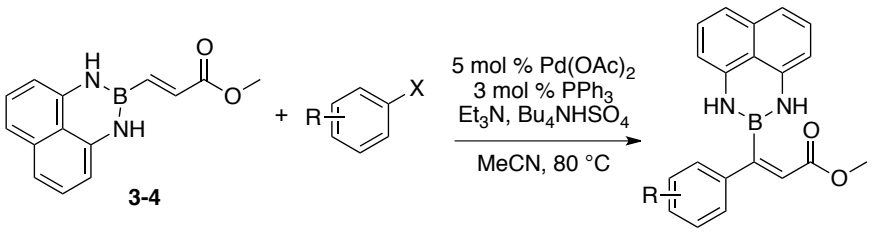
Table 3-1: Optimization of reaction conditions for the synthesis of substrate **3-4** (conducted by former Hall group member Jack Chang Hung Lee).[112]

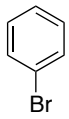
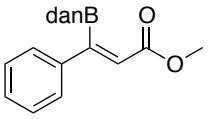
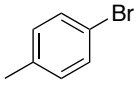
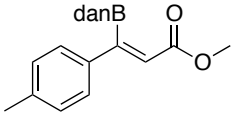
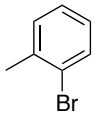
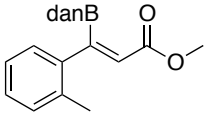
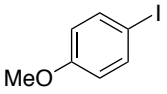
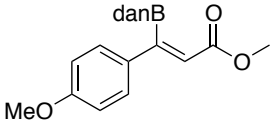
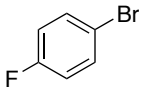
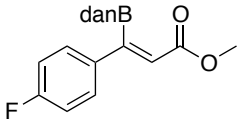
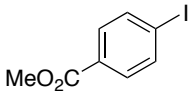
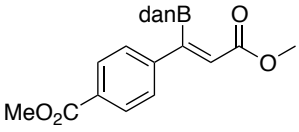
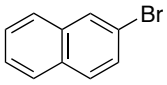
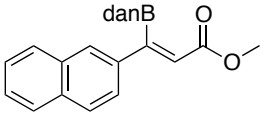
Further optimization revealed that the additive Bu_4NHSO_4 was highly beneficial, allowing better conversions and yields of the desired products to be afforded (entry 4, Table 3-1). This key additive[109a] could play several roles during the reaction: 1) the bisulfate anion can activate the palladium centre to accelerate the

oxidative addition step; and 2) the anion can also stabilize the palladium catalyst through the formation of a more stable neutral or anionic complex owing to Coulombic interactions, which can prolong the lifetime of the catalyst.[113] When bromobenzene instead of iodobenzene was employed as the aryl halide substrate, an improved yield was observed (entry 7, Table 3-1). In terms of the reaction solvent, DMF and acetonitrile were found to be optimal, while other solvents such as toluene afforded lower yields (entries 9-11, Table 3-1). Overall, the reaction conditions shown in entry 11 were optimal for the preparation of the prototype β-aryl-β-boronyl enoate **3-5**.

3.4 Scope of aryl halides in Heck reaction

The scope of aryl halides toward the preparation of β-aryl-β-boronyl α,β-unsaturated esters was examined under the optimal reaction conditions of entry 11 (Table 3-1). This part of the work was also conducted by Jack Chang Hung Lee.[112] In Table 3-2, while bromobenzene and 4-bromotoluene can be used as coupling partners to afford the desired coupling products **3-6** and **3-7** with good yields, coupling of 2-bromotoluene failed to occur (entries 1-3, Table 3-2). Presumably, steric hindrance from the ortho-substituent inhibits the desired coupling. In terms of electronic effects, both electron rich and electron deficient aryl halides afforded the desired β-aryl-β-boronyl α,β- unsaturated esters as single stereoisomers with good yields (entries 4-6, Table 3-2). An oligoaryl substituent such as 2-bromonaphthalene was also tolerated, providing the desired enoate **3-12** with good efficiency (entry 7, Table 3-2). In a few cases, aryl iodides must be employed presumably to accelerate the rate of oxidative addition (**3-9** and **3-11**, Table 3-2).



entry[a]	Ar–X	product		yield (%)[b]
1			**3-6**	76
2			**3-7**	72
3			**3-8**	0
4			**3-9**	76
5			**3-10**	77
6			**3-11**	80
7			**3-12**	68

[a] Reaction conditions: **3-4** (1.0 mmol) and ArX (2.0 mmol) in MeCN (1 M) with 5 mol % $Pd(OAc)_2$, 3 mol % PPh_3, 3 equiv of Et_3N and 1 equiv of Bu_4NHSO_4 (1.0 mmol) at 80 °C for 10 h. [b] Isolated yield, E/Z > 98% by ^{1}H-NMR analysis

Table 3-2: Scope of aryl halides in the Heck reaction of boronyl compound **3-4** (conducted by the former Hall Group member Jack Chang Hung Lee).[112]

3.5 Determination of the absolute stereochemistry of the coupling product

To determine the absolute stereochemistry of the double bond formed from the Heck coupling process (Table 3-2), a T-ROESY experiment[114] of the cross-coupled product **3-6** was performed. The correlation in Figure 3-1 was observed between the alkenyl proton H_e and the *ortho* protons H_a of the phenyl substituent. This strong through-space coupling interaction is only prone to occur in the corresponding (*E*)-isomer where the two hydrogen atoms are within 5Å distance. On the other hand, this type of coupling interaction cannot exist in the corresponding (*Z*)-adduct **3-13**, which was not observed in the Heck reaction. The *E/Z* ratio is over 98% as indicated by ^{1}H-NMR analysis.

3.6 Asymmetric conjugate reduction of β-boronyl-β-aryl enoates

3.6.1 Optimization of asymmetric conjugate reduction conditions

As discussed in Chapter 2, the Buchwald[100] and Lipshutz[101] groups have developed alternative copper-catalyzed enantioselective methods for conjugate reduction of α,β-unsaturated compounds with PMHS as a mild hydride source (Scheme 3-1). Recently, for the first time, our group applied these methods to the reduction of β-alkyl-β-boronyl α,β-unsaturated esters to access various chiral secondary alkylboronates in excellent yields and good to high enantioselectivity.[102a] To further expand this methodology, we decided to explore the scope of asymmetric conjugate reduction on β-aryl-β-boronyl enoate substrates.

With a variety of β-aryl-β-boronyl enoates now in hand (**3-6** to **3-12**, Table 3-2), their subsequent copper-catalyzed asymmetric conjugate reductions were then tested. To begin with, we attempted the optimal condtions previously employed for the enantioselective conjugate reduction of β-alkyl-β-boronyl enoate substrates (Chapter 2).[102a] With JOSIPHOS as the chiral ligand,[115] both $(Ph_3P)CuH$[101] and $Cu(OAc)_2$[116] can be used as the copper salts to give the desired

product **3-14** with decent yields and enantioselectivities (entries 1-2, Table 3-3). When CuCl was used as the copper source, slightly higher reactivity and enantioselectivity were obtained (entry 3, Table 3-3). In terms of chiral ligands, (*R*)-tol-BINAP was optimal, while JOSIPHOS and WALPHOS ligands provided relatively lower enantiomeric excesses (entries 3-5, Table 3-3). The asymmetric conjugate reduction was equally efficient at room temperature (entry 6, Table 3-3). As the reaction solvent, both dichloromethane and toluene were effective, but no product was obtained when tetrahydrofuran was employed as the solvent (entries 6-8, Table 3-3). Interestingly, even though β-Bdan-β-phenyl enoate **3-6** can be reduced to the chiral β-Bdan ester **3-14** with good yield and enantiomeric excess, the corresponding β-Bpin-β-phenyl enoate showed no reactivity under the same reaction conditions and the starting material was recovered instead (entry 9, Table 3-3). Thus, the reaction conditions of entry 8 were optimal to explore the substrate scope.

To establish the stereochemical outcome of the optimized asymmetric conjugate reduction conditions (entry 8, Table 3-3), oxidation of the chiral β-Bdan-β-phenyl ester **3-14** was conducted by following the reported procedure (Scheme 3-4).[117] The corresponding alcohol product **3-14a** is a known compound, and its characterization data matched that of a previous report.[118] The $[\alpha]_D^{20}$ of the alcohol **3-14a** was −48.3 (c = 0.320, CH_3Cl, 85% *ee*), the same as that reported for the (*S*)-isomer (–51.3, c = 1.30, CH_3Cl, 93% *ee*). Thus, this proves that the compounds synthesized using the optimal conditions with (*R*)-tol-BINAP **3-2** as the ligand (entry 8, Table 3-3), have the *S*-configuration on the stereogenic centre.

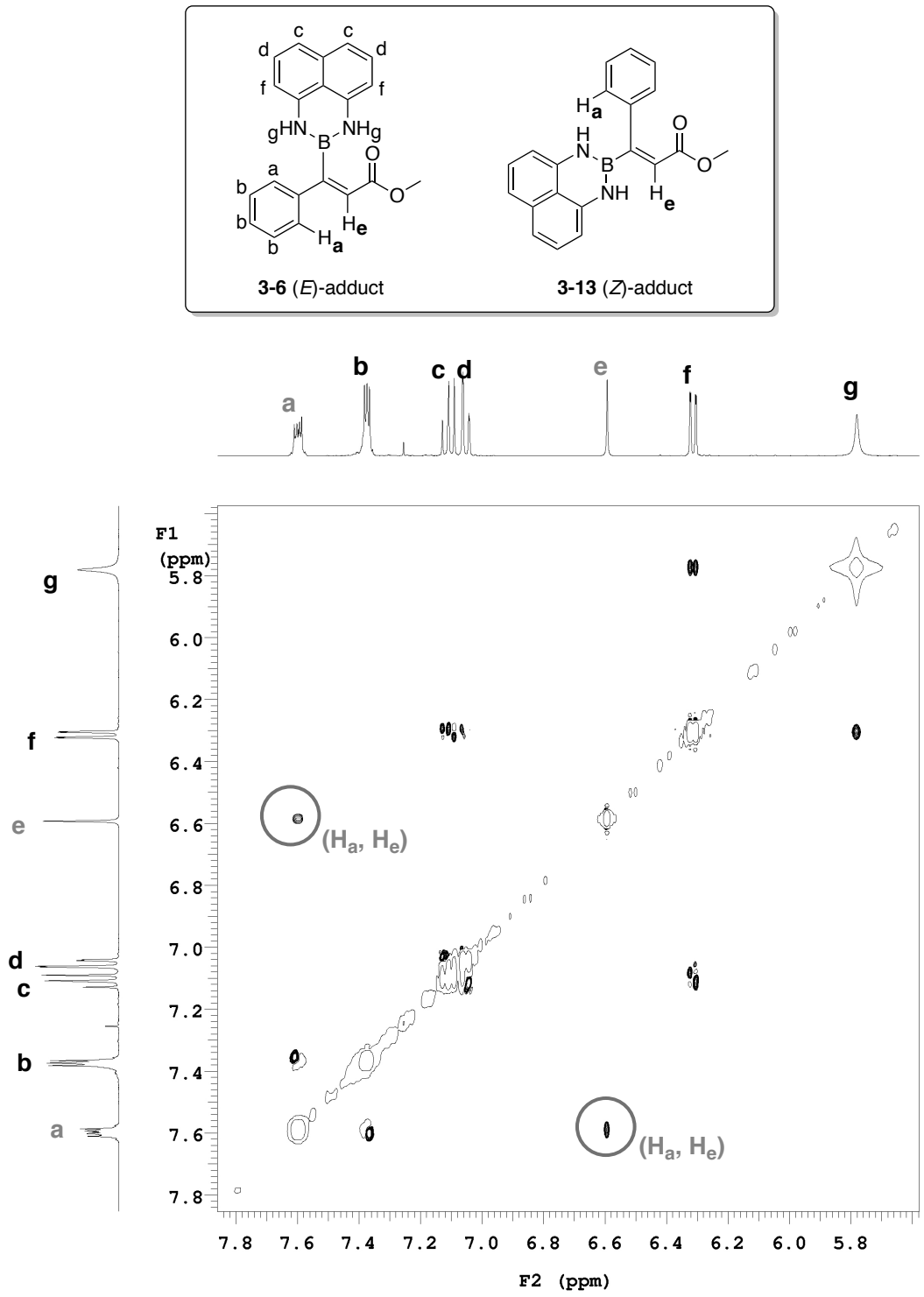
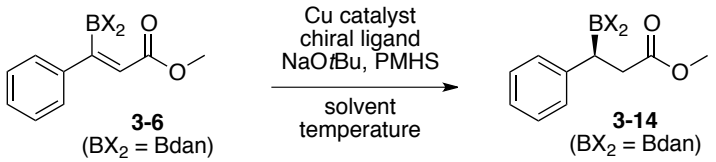
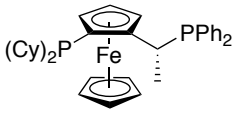


Figure 3-1: TROESY experiment to determine the stereochemistry of Heck coupling product **3-6**.

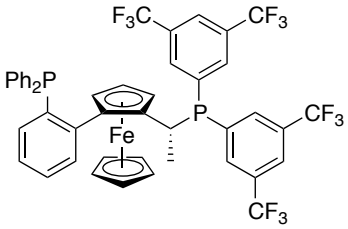


entry[a]	X_2	Cu catalyst	ligand	temperature	solvent	yield (%)[b]	*ee* (%)[c]
1	dan	$(Ph_3P)CuH$	**3-1**	0 °C	toluene	67	71
2	dan	$Cu(OAc)_2$	**3-1**	0 °C	toluene	71	70
3	dan	CuCl	**3-1**	0 °C	DCM	83	75
4	dan	CuCl	**3-15**	0 °C	DCM	83	72
5	dan	CuCl	**(*R*)-3-2**	0 °C	DCM	87	85
6	dan	CuCl	**(*R*)-3-2**	rt	DCM	88	84
7	dan	CuCl	**(*R*)-3-2**	rt	THF	0	–
8	dan	CuCl	**(*R*)-3-2**	rt	toluene	88	85
9	pin	CuCl	**(*R*)-3-2**	rt	toluene	0	–

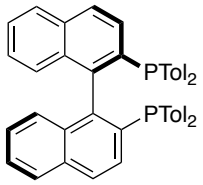
[a] Reaction conditions: 0.25 M **3-6** (1.0 mmol) in solvent with 4 equiv of PMHS, 5 mol % catalyst, 10 mol % ligand and 5 mol % NaO*t*Bu. [b] Isolated yields. [c] Measured by chiral HPLC.



3-1 (*R*)-(*S*)-Cy_2PF-PP
Josiphos

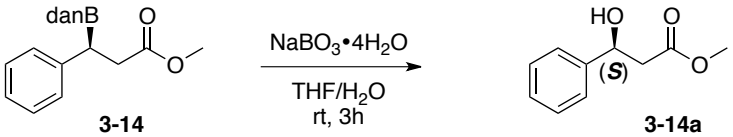


3-15 (*R*)-(*R*)-PPPhFCHCH$_3$P
$((3,5\text{-}CF_3)_2Ph)_2$ Walphos



(*R*)-3-2
(*R*)-tol-BINAP

Table 3-3: Possible conjugate addition approaches to chiral secondary boronates.

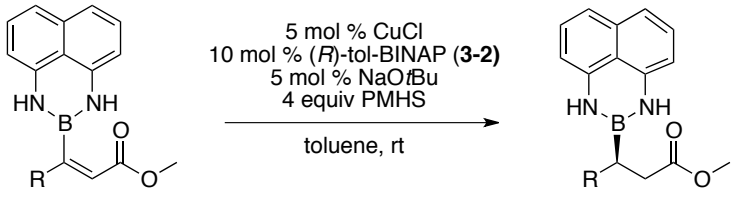


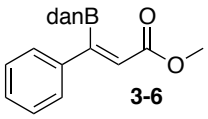
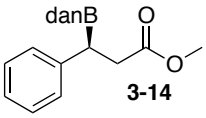
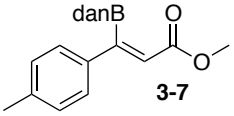
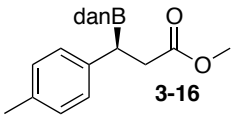
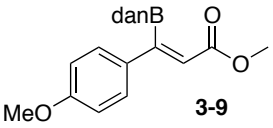
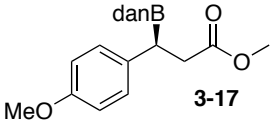
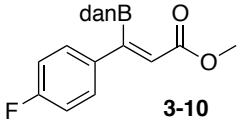
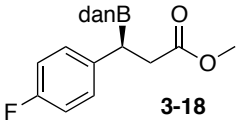
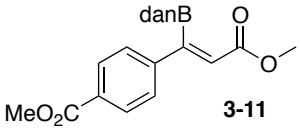
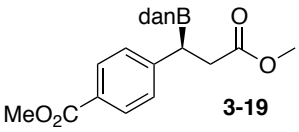
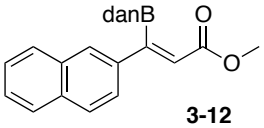
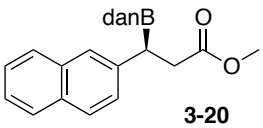
$[\alpha]_D^{20}$ measured: –48.3 (c = 0.320, $CHCl_3$)
lit. data:[22] –51.3 (c = 1.30, $CHCl_3$)

Scheme 3-4: Oxidation of β-Bdan-β-phenyl ester **3-14** for the confirmation of the absolute configuration assignment.

3.6.2 Scope for the copper-catalyzed enantioselective conjugate reduction

By applying the optimal conditions previously identified (entry 9, Table 3-3), the scope for the preparation of chiral β-aryl-β-boronyl esters was examined. In Table 3-4, both electron rich and electron poor substrates (prepared by Jack Chang Hung Lee, see Table 3-2) afforded the desired products with moderate to high yields and moderate enantiomeric excesses. Substrates bearing β-aryl groups, however, provided lower yields with lower enantiomeric excesses (entries 2-4, Table 3-4). Product **3-16** could not be well resolved by chiral HPLC for the enantiomeric excess measurement. Further modification of the Bdan unit was applied, and the detailed operation was shown in Section 3.8.5 of the experimental information. Carbomethoxy-substituted β-aryl substrate **3-11** (entry 5, Table 3-4) afforded the corresponding protodeboronation product. On the other hand, naphthyl substituted substrate **3-12** led to excellent enantioselectivity (entry 6, Table 3-4), possibly due to its highly conjugated planar structure, which can lead to enhanced interactions with the catalyst.



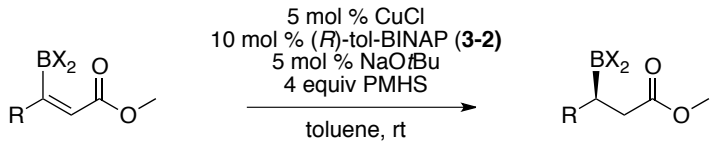
entry[a]	enoates	product	yield (%)[b]	*ee* (%)[c]
1	 **3-6**	 **3-14**	88	85
2	 **3-7**	 **3-16**	72	51
3	 **3-9**	 **3-17**	77	65
4	 **3-10**	 **3-18**	85	66
5	 **3-11**	 **3-19**	0[d]	–
6	 **3-12**	 **3-20**	65	98

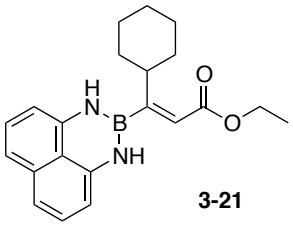
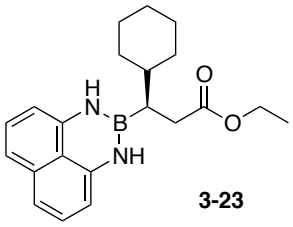
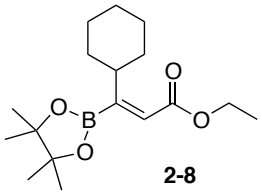
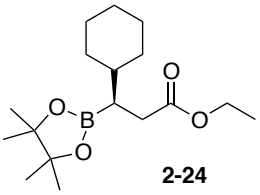
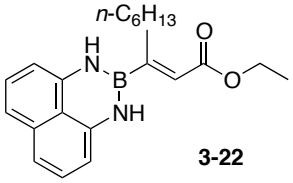
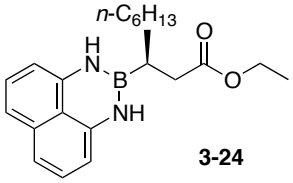
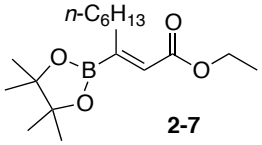
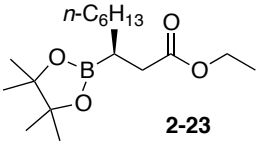
[a] Reaction conditions: 0.25 M of enoates (1.0 mmol) in toluene with 4 equiv of PMHS, 5 mol % CuCl, 5 mol % NaO*t*-Bu, and 10 mol % **3-2** at room temperature. [b] Isolated yield. [c] Measured by chiral HPLC. Absolute configuration assigned by comparison with optical rotation of known compound. [d] The protodeboronation product was obtained exclusively.

Table 3-4: Substrate scope for the copper-catalyzed asymmetric conjugate reduction of β-aryl-β-boronyl enoates.

3.6.3 The effect of boron protecting groups on the reactivity and enantioselectivy of copper-catalyzed asymmetric conjugate reduction

To study the influence of boron protecting groups on the reactivity and enantioselectivity of the copper-catalyzed asymmetric conjugate reduction, the 1,8-diaminonaphthalene (dan) protecting group was compared with the pinacol (pin) protecting group, which was previously reported for the enantioselective reduction of alkyl-substituted substrates[102] (entries 1-4, Table 3-5). Similar to the results observed for the β-Bdan-β-phenyl enoate **3-6** (entries 8-9, Table 3-3), an improvement for the Bdan substrates was also observed for β-Bdan-β-cyclohexyl enoate **3-21** compared to the corresponding β-Bpin substrate **2-8** (entries 1-2, Table 3-5). The key for the improved reactivity and enantioselectivity in the reduction of these substrates is the use of 1,8-diaminonaphthalene as a planar masking group over the bulky pinacol protecting group. The same level of reactivity and enantioselectivity were obtained for β-Bdan-β-(*n*-hexyl) enoate **3-22**[16] (entries 3-4, Table 3-5).



entry[a]	enoates	product	yield (%)[b]	*ee* (%)[c]
1	 **3-21**	 **3-23**	87	97
2	 **2-8**	 **2-24**	79	81
3	 **3-22**	 **3-24**	80	94
4	 **2-7**	 **2-23**	82	91

[a] Reaction conditions: 0.25 M of enoates (1.0 mmol) in toluene with 4 equiv of PMHS, 5 mol % CuCl, 5 mol % NaO*t*-Bu, and 10 mol % **3-2** at room temperature. [b] Isolated yield. [c] Measured by chiral HPLC.

Table 3-5: The effect of boron protecting group on the reactivity and enantioselectivity.

3.7 Summary

A new and efficient approach was successfully developed to access synthetically valuable β-boronyl β-aryl enoates through Heck coupling, and the subsequent copper(I)-catalyzed enantioselective conjugate reduction of these enoates to produce various chiral secondary alkylboronate derivatives. This method constitutes the first general approach for synthesizing β-boronyl β-aryl enoates in very high *E/Z* selectivity. In addition, these substrates could be asymmetrically reduced with moderate to excellent enantiomeric excesses, affording the desired optically enriched secondary alkylboronates with substantially improved reactivity and selectivity compared to our previously reported conditions. These improvements are attributed to the utilization of the planar 1,8-diaminonaphthalene as a superior boron-masking group over the bulky pinacolate unit. Accordingly, with chiral boronic acid derivatives emerging as important and versatile functional groups in organic synthesis, I believe that the synthetic methods reported herein are valuable tools to access a variety of important optically enriched intermediates in asymmetric synthesis.

3.8 Experimental

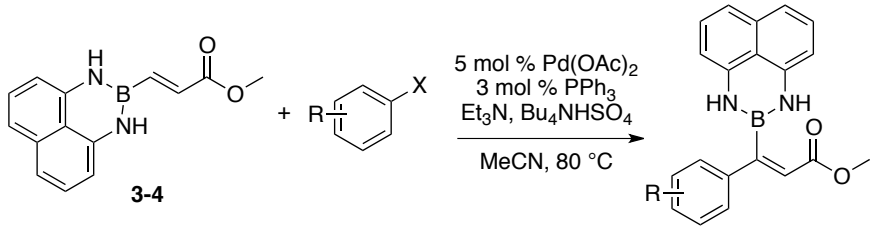
3.8.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were obtained from a MBraun MB SPS* solvent system prior to use. $(Ph_3P)CuH$ was from Acros Organics, +97%; chiral ligands **3-1** and **3-15** were generously provided by Solvias AG. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal references.

Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is 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; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. The error of coupling constants from ^1H NMR analysis is estimated to be ±0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) ion source with double focussing sector analyzer (Kratos Analytical MS-50G) or electrospray (ESI) ion source with orthogonal acceleration TOF analyzer (Agilent Technologies 6220 oaTOF). Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 cm^{-1}. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD (4.6 × 250 mm, inner diameter × length; particle size 5 μm) or Chiralpak-AS (4.6 × 250 mm, inner diameter × length; particle size 5 μm) columns with UV detection. Compound **3-4**[99a] was synthesized according to the literature procedure.

3.8.2 Preparation of β-boronyl-β-aryl α,β-unsaturated esters

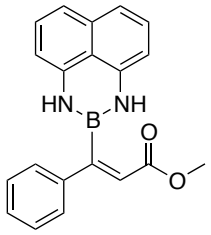
3.8.2.1 General procedure for the preparation of β-boronyl-β-aryl α,β-unsaturated esters (By Jack Chang Hung Lee from the Hall Group, included for the comprehensiveness of this Chapter)



To a mixture of enoate **3-4** (1.0 mmol), aryl halide (2.0 mmol), $Pd(OAc)_2$ (0.050

mmol), PPh_3 (0.030 mmol), and Et_3N (3.0 mmol) was added acetonitrile (1 mL). The solution was stirred for 10 hours at 80 °C before it was allowed to cool down to room temperature. The reaction mixture was then concentrated *in vacuo*, and the crude product was purified with flash silica column chromatography to afford the pure product.

3.8.2.2 (*E*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenyl acrylate 3-6



3-6

The title compound was prepared using the general procedure for Heck couplings between **3-4** and phenyl bromide. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **3-6** (249 mg, 76 % yield) as an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.40-7.38 (m, 3H), 7.12 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.06 (dd, *J* = 8.3, 1.1 Hz, 2H), 6.60 (s, 1H), 6.32 (dd, *J* = 7.2, 1.1 Hz, 2H), 5.79 (br s, 2H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 140.4, 138.7, 136.0, 129.2, 128.5, 127.3, 127.1, 124.3, 119.3, 117.4, 105.7, 51.5. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

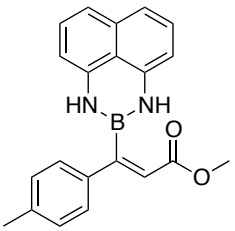
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0.

IR (microscope, cm^{-1}) 3388, 3054, 2949, 1706, 1627, 1601, 1508.

HRMS (ESI) for $C_{20}H_{17}BN_2O_2$: calcd. 328.1383; found 328.1383.

M.P.: 152-153 °C.

3.8.2.3 (*E*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(*p*-tolyl) acrylate 3-7



3-7

The title compound was prepared using the general procedure for Heck reaction between **3-4** and 4-bromotoluene. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **3-7** (246 mg, 72 % yield) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.08 (dd, *J* = 8.4, 1.0, 2H), 6.60 (s, 1H), 6.35 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.77 (br s, 2H), 3.78 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 140.9, 140.0, 136.4, 136.1, 129.6, 127.7, 127.5, 123.5, 119.7, 117.7, 106.1, 51.8, 21.3. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

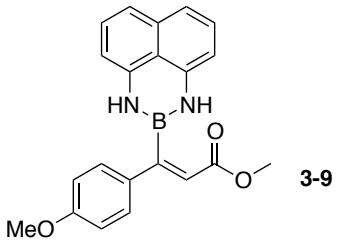
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7.

IR (microscope, cm^{-1}) 3416, 3386, 3050, 3025, 2953, 2921, 1707, 1625, 1604, 1513.

HRMS (ESI) for $C_{21}H_{19}BN_2O_2$: calcd. 342.1540; found 342.1534.

M.P.: 177-180 °C.

3.8.2.4 (*E*)-Methyl 3-(4-methoxyphenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diaza borinin-2(3*H*)-yl)acrylate 3-9



3-9

The title compound was prepared using the general procedure for Heck reaction between **3-6** and 1-iodo-4-methoxybenzene. Flash silica column chromatography (hexanes/EtOAc = 8:2) yielded **3-9** (272 mg, 76 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.9 Hz, 2H), 7.14 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.09 (dd, *J* = 8.2, 0.7 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.56 (s, 1H), 6.34 (dd, *J* = 7.2, 0.8 Hz, 2H), 5.77 (br s, 2H), 3.85 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 161.0, 140.9, 136.4, 131.2, 129.4, 127.6, 121.8, 119.7, 117.7, 114.3, 106.1, 55.4, 51.8. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

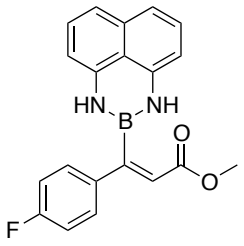
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7.

IR (microscope, cm^{-1}) 3382, 3052, 2947, 1698, 1626, 1599, 1509.

HRMS (ESI) for $C_{21}H_{19}BN_2O_3$: calcd. 358.1489; found 358.1491.

M.P.: 75-76 °C (dec.).

3.8.2.5 (*E*)-Methyl 3-(4-fluorophenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diaza borinin-2(3*H*)-yl) acrylate 3-10



3-10

The title compound was prepared using the general procedure for Heck reaction between **3-4** and 1-bromo-4-fluorobenzene. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **3-10** (266 mg, 77 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.13 (m, 2H), 7.14 (m, 2H), 7.09 (m, 4H), 6.57 (s, 1H), 6.35 (dd, *J* = 7.2, 0.9 Hz, 2H), 5.80 (br s, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 163 (*J* = 250 Hz), 136.4, 135.1, 129.7, 127.6, 124.3, 119.7, 117.9, 116.1, 115.9, 106.2, 51.9. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

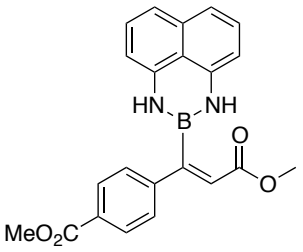
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0.

IR (microscope, cm^{-1}) 3391, 3054, 2950, 1709, 1628, 1602.

HRMS (ESI) for $C_{20}H_{16}BN_2O_2F$: calcd. 346.1289; found 346.1291.

M.P.: 104 °C.

3.8.2.6 (*E*)-Methyl 4-(3-methoxy-1-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-oxoprop-1-en-1-yl)benzoate 3-11



3-11

The title compound was prepared using the general procedure for Heck reaction between **3-4** and methyl 4-iodobenzoate. Flash silica column chromatography (hexanes/EtOAc = 8:2) yielded **3-11** (309 mg, 80 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.14 (m, 2H), 7.09 (m, 2H), 6.64 (s, 1H), 6.35 (dd, *J* = 7.2, 0.7 Hz, 2H), 5.87 (br s, 2H), 3.95 (s, 3H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.5, 143.6, 140.7, 136.4, 131.1, 130.8, 130.1, 127.6, 127.5, 119.8, 118.0, 106.2, 52.3, 52.0. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

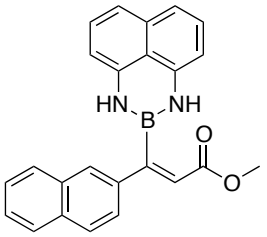
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7.

IR (microscope, cm^{-1}) 3427, 3400, 3054, 3006, 2951, 2845, 1726, 1716, 1626, 1603, 1509.

HRMS (ESI) for $C_{22}H_{19}BN_2O_4$: calcd. 386.1438; found 386.1448.

M.P.: 167 °C (dec.).

3.8.2.7 (*E*)-Methyl 3-(naphthalen-2-yl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diaza borinin-2(3*H*)-yl)acrylate 3-12



3-12

The title compound was prepared using the general procedure for Heck reaction between **3-4** and 2-bromonaphthalene. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **3-12** (257 mg, 68 % yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.04 (m, 1H), 7.86-7.82 (m, 3H), 7.73-7.70 (m, 1H), 7.53-7.48 (m, 2H), 7.13 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.07 (dd, *J* = 8.4, 1.1 Hz, 2H), 6.73 (s, 1H), 6.34 (dd, *J* = 7.2, 1.2 Hz, 2H), 5.83 (br s, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 140.9, 136.4, 136.3, 133.8, 133.3, 128.8, 128.7, 128.6, 127.6, 127.5, 127.1, 126.7, 124.8, 124.0, 119.8, 117.8, 106.2, 51.9. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

^{11}B NMR (128 MHz, $CDCl_3$) δ 30.8.

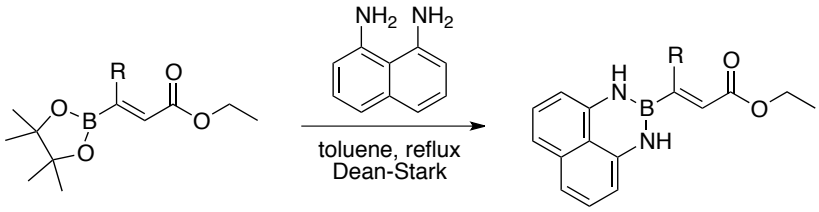
IR (microscope, cm^{-1}) 3409, 3054, 2948, 1706, 1625, 1601, 1504.

HRMS (ESI) for $C_{24}H_{19}BN_2O_2$: calcd. 378.1540; found 378.1541.

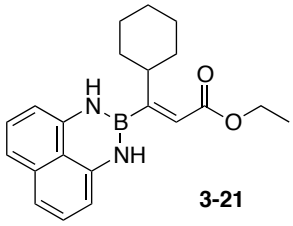
M.P.: 180-181 °C.

3.8.3 Preparation of β-boronyl-β-alkyl α,β-unsaturated esters (3-21 and 3-22, Table 3-5)

The β-Bdan-β-alkyl α,β-unsaturated esters **3-21** and **3-22** were prepared from the corresponding β-Bpin-β-alkyl α,β-unsaturated esters using the reported procedure.[99a]



3.8.3.1 (*Z*)-Ethyl 3-cyclohexyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl) acrylate 3-21



3-21

The title compound was prepared using the general procedure for the preparation of β-boronyl-β-alkyl α,β-unsaturated esters to yield **3-21** (173 mg, 63 % yield) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.11 (m, 2H), 7.10-7.05 (m, 2H), 6.34 (dd, *J* = 5.7, 0.9 Hz, 2H), 5.99 (d, *J* = 0.6 Hz, 1H), 5.68 (br s, 2H), 4.22 (q, *J* = 5.4 Hz, 2H), 3.57-3.48 (m, 1H), 1.80-1.73 (m, 5H), 1.48-1.16 (m, 8H).

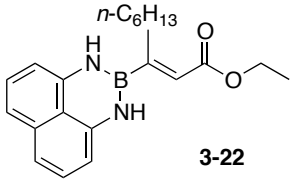
^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 140.1, 135.9, 127.2, 122.8, 119.4, 117.6, 105.7, 59.5, 40.1, 32.6, 25.9, 25.6, 14.0. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.4

IR (microscope, cm^{-1}) 3386, 3054, 2980, 2926, 2850, 1702, 1628, 1599, 1504.

HRMS (EI) for $C_{21}H_{25}BN_2O_2$: calcd.348.2009; found 348.2005.

3.8.3.2 (*Z*)-2-(1-Ethoxynon-2-en-3-yl)-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2] diazaborinine 3-22



3-22

The title compound was prepared using the general procedure for the preparation of β-boronyl-β-alkyl α,β-unsaturated esters to yield **3-22** (128 mg, 72 % yield) as a purple oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.10 (m, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.35 (d, *J* = 7.2 Hz, 2H), 6.18 (br s, 1H), 5.79 (br s, 2H), 4.25-4.20 (q, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 1.50-1.32 (m, 11H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 140.2, 135.9, 127.2, 124.5, 119.4, 117.7, 105.8, 59.6, 31.3, 30.0, 29.4, 29.2, 22.2, 13.9, 13.7. (The boron-bound carbon was not detected due to extensive broadening caused by quadrupolar relaxation).

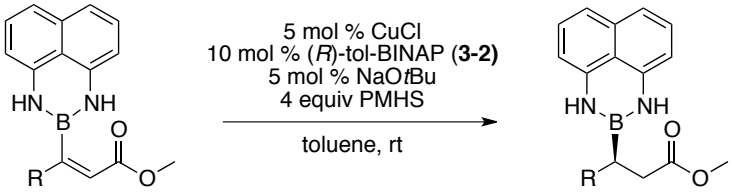
^{11}B NMR (160 MHz, $CDCl_3$) δ 28.9.

IR (microscope, cm^{-1}) 3386, 3054, 2955, 2927, 2856, 1703, 1629, 1601, 1509.

HRMS (EI) for $C_{21}H_{27}BN_2O_2$: calcd.350.2166; found 350.2157.

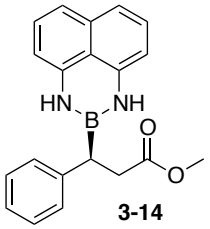
3.8.4 Preparation of chiral β-boronyl carboxyesters

3.8.4.1 General procedure for the asymmetric conjugate reduction of enoates (Table 3-4)



To a 15 mL Schlenk tube, flame dried and purged with nitrogen, was added CuCl (2.7 mg, 0.027 mmol), (*R*)-*p*-tol-BINAP **3-2** (37 mg, 0.054 mmol) and NaO*t*-Bu (2.7 mg, 0.027 mmol). Toluene (1 mL) was added under nitrogen, and the resulting solution was stirred for 10 min. PMHS (0.12 mL, 2.0 mmol) was added, and the reaction mixture was stirred for another 10 min, followed by addition of the enoate (0.5 mmol). The reaction tube was washed with toluene (1 mL) and sealed, and the reaction mixture was stirred until no starting material was detected by TLC (eluent: 10% ethyl acetate/hexane). The reaction mixture was directly subjected to silica gel flash silica column chromatography (10% ethyl acetate/hexane) to afford the title product.

3.8.4.2 (*S*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenyl propanoate 3-14



3-14

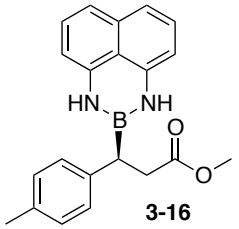
The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-14** (145 mg, 88 % yield) as a yellow oil.

The characterization data for this compound matched that of a previous report.[99a]

$[\alpha]_D^{20}$: −0.61 (c = 0.56, $CHCl_3$) for 85% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 29.6 min, T_{minor} = 36.0 min, ee = 85%.

3.8.4.3 (*S*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(*p*-tolyl) propanoate 3-16



3-16

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-16** (124 mg, 72 % yield) as a yellow oil.

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.17 (d, *J* = 7.9 Hz, 2H), 7.10 (m, 4H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.27 (d, *J* = 7.3 Hz, 2H), 5.70 (s, 2H), 3.68 (s, 3H), 2.96-2.75 (m, 3H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 140.9, 139.5, 136.2, 135.5, 129.7, 129.5, 127.7, 127.5, 117.7, 105.9, 51.9, 36.8, 21.0. (The boron-bound carbon was not detected due to quadrupolar relaxation).

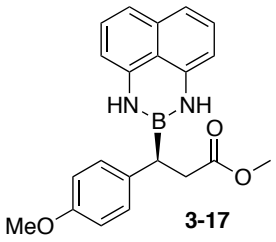
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6.

IR (microscope, cm^{-1}) 3398, 3051, 2950, 2922, 1727, 1628, 1601, 1509.

HRMS (EI) for $C_{21}H_{21}BN_2O_2$: calcd. 344.1696; found 344.1694.

$[\alpha]_D^{20}$: 1.3 (c = 1.0, $CHCl_3$) for 51% ee.

3.8.4.4 (*S*)-Methyl 3-(4-methoxyphenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diaza borinin-2(3*H*)-yl)propanoate 3-17



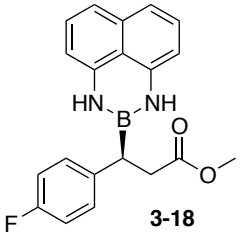
3-17

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-17** (139 mg, 77 % yield) as a yellow oil. The characterization data for this compound matched that of a previous report.[99b]

$[\alpha]_D^{20}$: 13.0 (c = 0.59, $CHCl_3$) for 65% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 34.2 min, T_{minor} = 38.3 min, ee = 65%.

3.8.4.5 (*S*)-Methyl 3-(4-fluorophenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diaza borinin-2(3*H*)-yl)propanoate 3-18



3-18

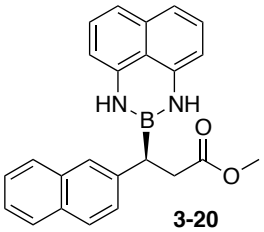
The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-18** (133 mg, 85 % yield) as a yellow oil. The characterization data for this compound matched that of a previous report.[14]

$[\alpha]_D^{20}$: 7.60 (c = 0.56, $CHCl_3$) for 66% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm,

T_{major} = 35.3 min, T_{minor} = 42.2 min, ee = 66%.

3.8.4.6 (*S*)-Methyl 3-(naphthalen-2-yl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diaza borinin-2(3*H*)-yl)propanoate 3-20



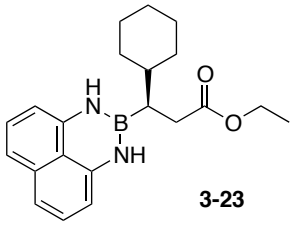
3-20

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-20** (124 mg, 65 % yield) as a yellow oil. The characterization data for this compound matched that of a previous report.[99a]

$[\alpha]_D^{20}$: −8.70 (c = 0.56, $CHCl_3$) for 98% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 79.1 min, T_{minor} = 88.1 min, ee = 98%.

3.8.4.7 (*S*)-Methyl 3-cyclohexyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanoate 3-23



3-23

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-23** (151 mg, 87 % yield) as a colourless oil.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.10 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.00 (dd, *J* = 8.3,

0.9 Hz, 2H), 6.31 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.75 (d, *J* = 0.2 Hz, 2H), 4.11 (app q, *J* = 7.1 Hz, 2H), 2.54 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.40 (dd, *J* = 15.9, 9.8 Hz, 1H), 1.80-1.72 (m, 5H), 1.46-1.37 (m, 1H), 1.27-1.19 (m, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 140.6, 135.9, 127.1, 119.3, 117.0, 105.2, 60.0, 39.3, 33.6, 32.5, 32.0, 26.3, 26.0, 13.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.9.

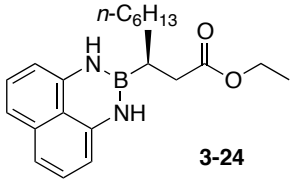
IR (microscope, cm^{-1}) 3392, 3053, 2979, 2923, 2850, 1718, 1629, 1601, 1508.

HRMS (EI) for $C_{21}H_{27}BN_2O_4$: calcd.350.2166; found 350.2158.

$[\alpha]_D^{20}$: −0.89 (c = 0.47, $CHCl_3$) for 98% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{minor} = 23.3 min, T_{major} = 25.2 min, ee = 98%.

3.8.4.8 (*R*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)nonanoate 3-24



3-24

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **3-24** (139 mg, 80 % yield) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.10 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.31 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.76 (d, *J* = 0.3 Hz, 2H), 4.13 (app q, *J* = 7.1 Hz, 2H), 2.44-2.41 (m, 2H), 1.47-1.21 (m, 14H), 0.92-0.86 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 140.7, 135.9, 127.1, 119.3, 117.0, 105.3,

60.1, 36.3, 31.4, 31.3, 29.1, 28.5, 22.2, 13.9, 13.7.

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.5.

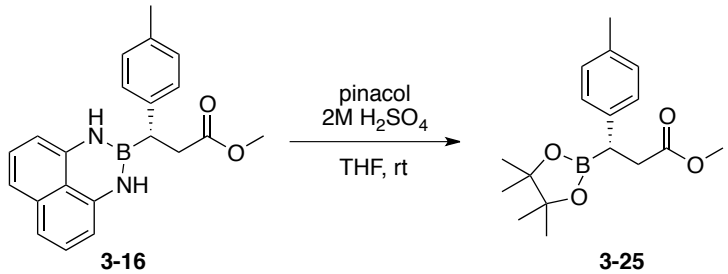
IR (microscope, cm^{-1}) 3392, 3054, 2955, 2925, 2854, 1719, 1629, 1602, 1510.

HRMS (EI) for $C_{21}H_{29}BN_2O_4$: calcd. 352.2322; found 352.2316.

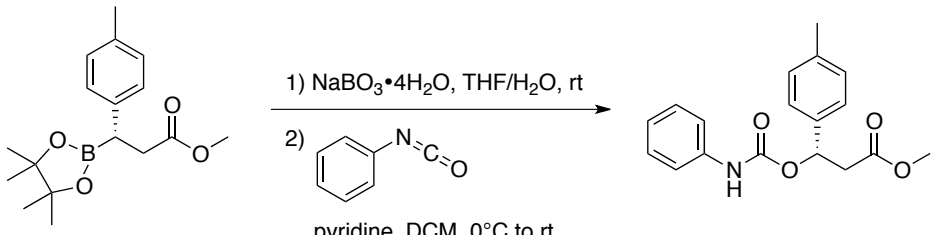
$[\alpha]_D^{20}$: –4.39 (c = 0.36, $CHCl_3$) for 93% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{minor} = 24.5 min, T_{major} = 26.5 min, ee = 93%.

3.8.5 Enantiomeric excess measurement of the oxidized product



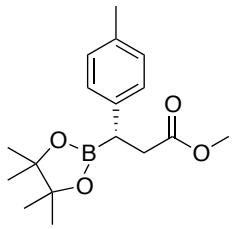
3-16 **3-25**



3-25 **3-26**

To measure the enantiomeric excess of **3-16**, the oxidized derivative **3-26** (12 mg) was prepared using the reported procedures[99b] with 33% overall yield over three steps.

3.8.5.1 (*S*)-Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*p*-tolyl) propanoate 3-25



3-25

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.06 (m, 4H), 3.65 (s, 3H), 2.87 (dd, *J* = 15.6, 9.5 Hz, 1H), 2.63 (A of ABX, m, 1H), 2.69 (B of ABX, m, 1H), 2.30 (s, 3H), 1.21 (s, 6H), 1.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 138.2, 135.1, 129.2, 128.1, 83.5, 51.5, 37.3, 29.7, 24.6, 21.0.

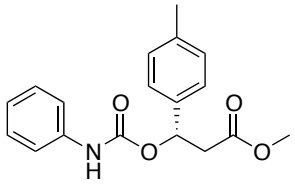
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.1.

IR (microscope, cm^{-1}) 2978, 2952, 2926, 2857, 1738, 1513.

HRMS (ESI) for $C_{17}H_{25}BO_4$: calcd. 304.1846; found 304.1842.

$[\alpha]_D^{20}$: 5.90 (c = 0.58, chloroform)

3.8.5.2 (*S*)-Methyl 3-((phenylcarbamoyl)oxy)-3-(*p*-tolyl)propanoate 3-26



3-26

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.37-7.25 (m, 5H), 7.17 (d, *J* = 7.9 Hz, 2H),

7.07-7.01 (m, 2H), 6.70 (br s, 1H), 6.16 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.69 (s, 3H), 3.03 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.81 (dd, *J* = 15.6, 5.2 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 152.3, 138.3, 137.7, 136.3, 129.4, 126.4, 123.5, 118.6, 115.1, 73.1, 52.0, 41.4, 21.2.

IR (microscope, cm^{-1}) 3335, 3137, 3029, 2953, 2924, 1740, 1600, 1541, 1501.

HRMS (ESI) for $C_{18}H_{19}NO_4$: $(M+Na)^+$ *m/z* calcd. 336.1206, found 336.1206; $(M+K)^+$ *m/z* calcd. 352.0946, found 352.0949.

$[\alpha]_D^{20}$: 30.0 (c = 2.3, chloroform) for 51% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{minor} = 13.9 min, T_{minor} = 25.8 min, ee = 51%.

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Chapter 4 Chiral Allylic Heterocyclic Boronates as Valuable Intermediates in Enantioselective Total Syntheses of Pharmaceutical Drugs and Natural Products*

4.1 Introduction

A variety of biologically important natural products and synthetic drugs are constituted of non-aromatic oxygen and nitrogen containing heterocycles bearing an α-hydroxyalkyl substituent.

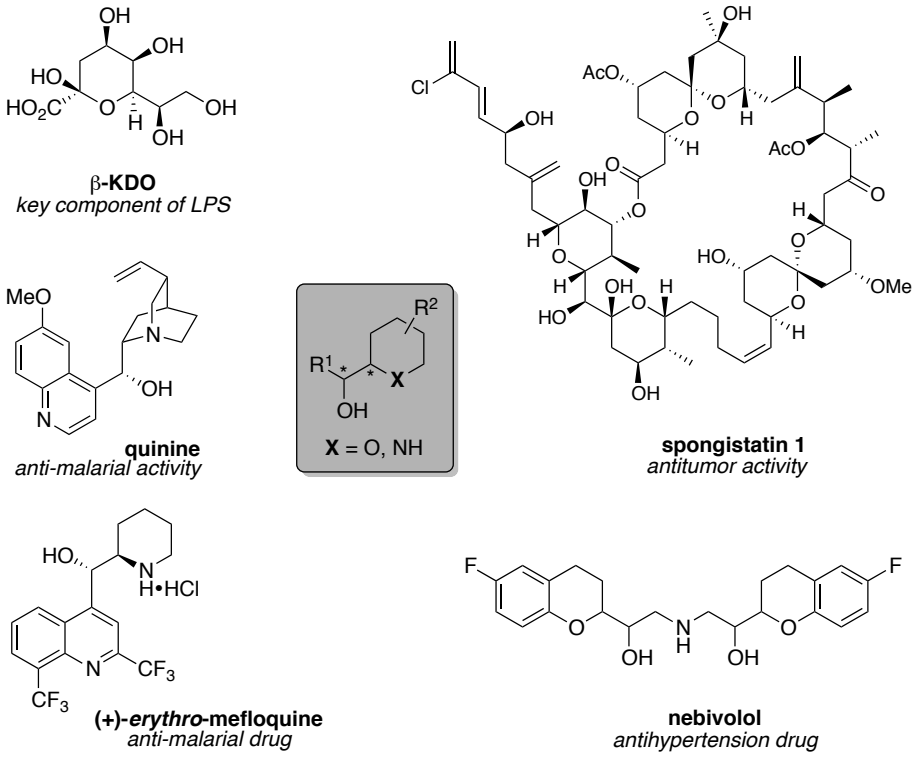

Figure 4-1: Selected examples of natural products and synthetic drugs containing α-hydroxyalkyl pyran or piperidine heterocycles.

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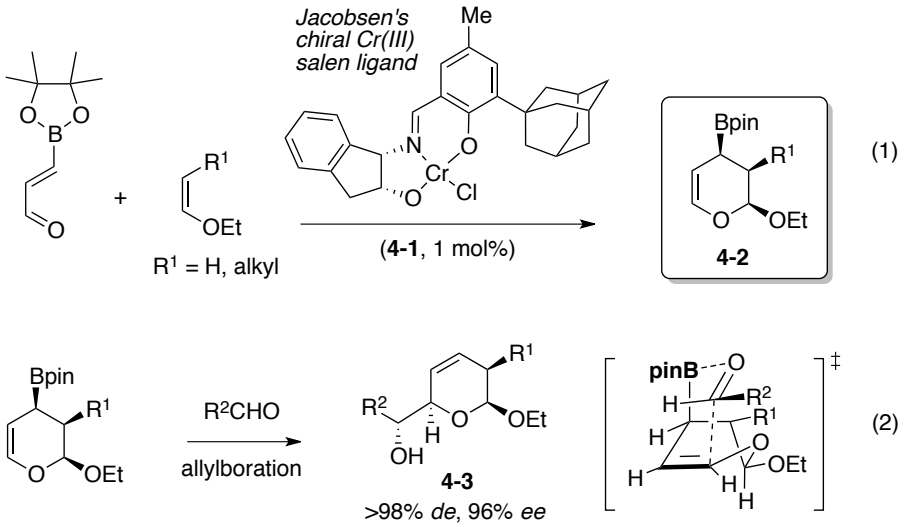
* A version of this chapter has been published. Ding, J.; Hall, D. G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8069–8073.

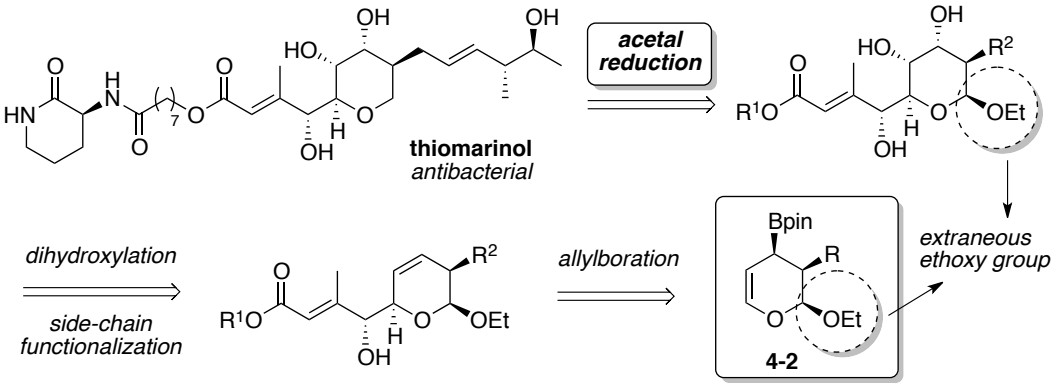
Representative examples of pyran-containing substances include higher order sugars such as β-KDO, which is an essential component of lipopolysaccharides (LPS) that is expressed by Gram-negative bacteria.[119] Other notable examples include many piperidine alkaloids, marine oligopyrans, and the antihypertension drug nebivolol (Figure 4-1).[120] As a result, rapid access to these biologically important chiral α-hydroxyalkyl pyran or piperidine core units is highly desirable.



Scheme 4-1: Preparation of chiral heterocyclic allylic boronates **4-2** *via* catalytic asymmetric hetero [4+2] cycloaddition (Equation 1) and its application in the preparation of α-hydroxyalkyl dihydropyrans *via* allylboration of aldehydes (Equation 2).

Accordingly, in 2002 the Hall Group reported a novel catalytic asymmetric preparation of the chiral heterocylic allylic boronate **4-2** *via* an inverse electron-demand Diels-Alder (IEDDA) reaction[121] catalyzed by Jacobsen's chiral Cr(III) salen complex[122] (**4-1**) (Scheme 4-1, Equation 1).[123] Without a change of solvent, the resulting enantiopure allylic boronate **4-2** could react with various aldehydes in a multicomponent cascade process, affording the α-hydroxyalkyl pyrans in a diastereoselective and stereospecific manner (Scheme 4-1, Equation 2). This elegant three-component [4+2] cycloaddition/allylboration relay reaction has

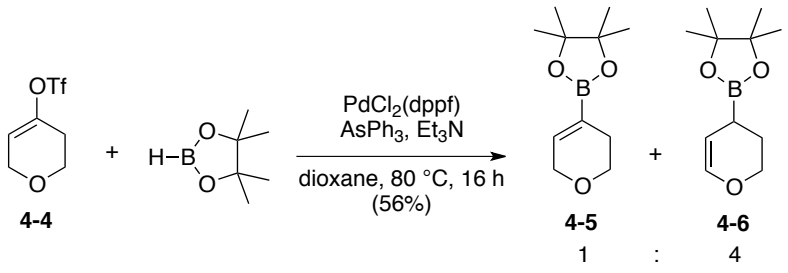
demonstrated great utility in the total syntheses of several natural products, including the antibacterial marine natural product thiomarinol (Scheme 4-2)[124] and the complex macrolide palmerolide A.[125]



Scheme 4-2: Retrosynthesis of thiomarinol from chiral allylic boronate **4-2**.

In Scheme 4-2, the successful asymmetric total synthesis of thiomarinol could be, in large part, attributed to the use of the chiral allylic boronate **4-2** as the key intermediate. In spite of its high efficiency, this synthesis highlighted that the residual ethoxy group on the highly functionalized chiral boronate **4-2** can be extraneous. Not only are additional steps required for the removal of the undesired ethoxy substituent (Scheme 4-2), its presence can also impact on the reactivity of the dihydropyran ring system and thus limit its synthetic modification. Recognizing this limiting feature, the Hall Group sought for an alternative method for the preparation of unsubstituted chiral pyranyl allylic boronates.

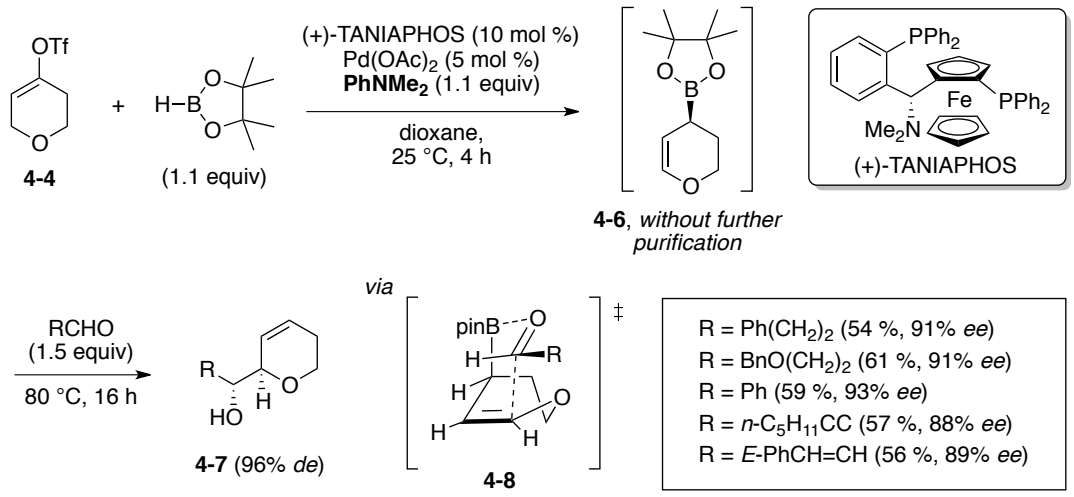
In that regard, Hall and co-workers were intrigued by a report by the Masuda Group involving the development of a new procedure for palladium-catalyzed borylation of alkenyl triflates (Scheme 4-3).[126] Instead of affording the corresponding alkenylboronate **4-5**, the unexpected alkene isomerization product, allylic boronate **4-6**, was obtained as the major product.



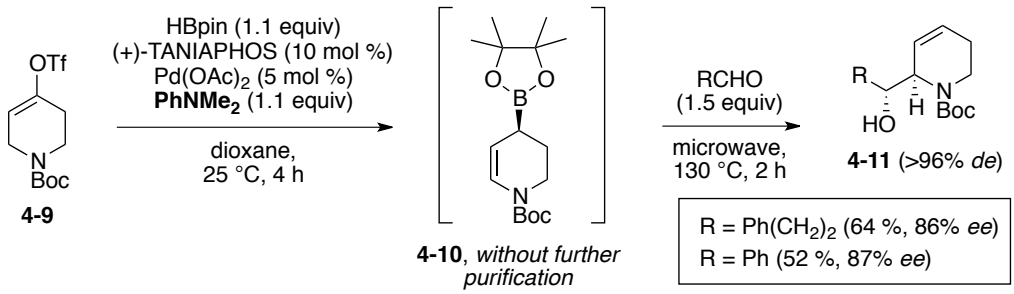
Scheme 4-3: Undesired isomerization product **4-6** in the palladium-catalyzed borylation of alkenyl triflate **4-4** by Masuda and co-workers.[126]

Inspired from this unexpected result (Scheme 4-3), the Hall Group set out to explore optimal conditions towards the selective formation of chiral allylic boronate **4-6**.[127] Upon extensive optimization of the chiral diphosphine ligands and fine tunning of other reaction parameters, the chiral unsubstituted pyranyl allylic boronate **4-6** could be accessed in high enantioselectivity. Without further purification, the chiral pyranyl allylic boronate **4-6** can be subjected to a diastereoselective allylboration with various aromatic and aliphatic aldehydes *via* chairlike transition state **4-8** (Scheme 4-4). The desired α-hydroxyalkyl dihydropyrans **4-7** were accessed in high enantio-, diastereoselectivities and free from the acetal substituent found in analogue **4-3** (Scheme 4-1).

By altering the alkenyl triflate to **4-9**, one that bears a dihydropiperidine motif, the substrate underwent a similar catalytic enantioselective borylative alkene isomerization for the selective formation of the corresponding chiral piperidyl boronate **4-10**.[127] The subsequent allylboration reaction was facilitated through the use of microwave conditions, which allows for shorter reaction times at higher reaction temperatures (Scheme 4-5). Both aromatic and aliphatic aldehydes were compatible with these reaction conditions. The resulting α-hydroxyalkyl dihydropiperidines **4-11** were obtained with high diastereo- and enantioselectivities (Scheme 4-5).



Scheme 4-4: Catalytic enantioselective borylative alkene isomerization for the preparation of α-hydroxyalkyl dihydropyrans **4-7**.[127]



Scheme 4-5: Catalytic enantioselective borylative alkene isomerization for the preparation of α-hydroxyalkyl dihydropiperidines **4-11**.[127]

4.2 Objectives

As discussed above, chiral α-hydroxyalkyl piperidine ring systems are present as core structures in many biologically important natural products or synthetic drugs. One such examples are the important antimalarial drug mefloquine and the natural alkaloid quinine that also features important antimalarial activity (Figure 4-1). With methods available for the rapid construction of α-hydroxyalkyl dihydropiperidines **4-11** (Scheme 4-5), we proposed to demonstrate its utility with the asymmetric total syntheses of mefloquine and quinine. In Figure 4-2, we

envisioned that mefloquine, which contains a piperidine ring with an α-hydroxyalkyl substituent, could be accessed in a few steps. When the palladium-catalyzed enantioselective borylative alkene isomerization/allylboration (Scheme 4-5) is applied as the key step, the corresponding alkenyl triflate **4-9**, pinacol borane and quinoline aldehyde **4-12** can be efficiently incorporated to assemble the core structure of mefloquine. In this way, the two stereogenic centers can be established diastereo- and enantioselectively in the early stage of the synthesis. Using the same process as the key step involving **4-13** for the aldehyde allylboration, we presumed that the main skeleton of quinine could also be constructed with high efficiency, although further construction of the bridged bicyclic piperidine moiety could certainly be difficult (Figure 4-2).

In spite of the advances stated above, these proposed asymmetric total syntheses of mefloquine and quinine posed several challenges: 1) further optimization of the catalytic enantioselective borylative alkene isomerization (Scheme 4-5) is needed to obtain the key intermediate **4-10** in gram-scale and higher enantiopurity; and 2) since the stereochemical integrity is established in the early stage of the synthesis, further synthetic modification requires a careful selection of reaction conditions to avoid erosion of enantiomeric purity. These challenges will be addressed in detail in the following sections.

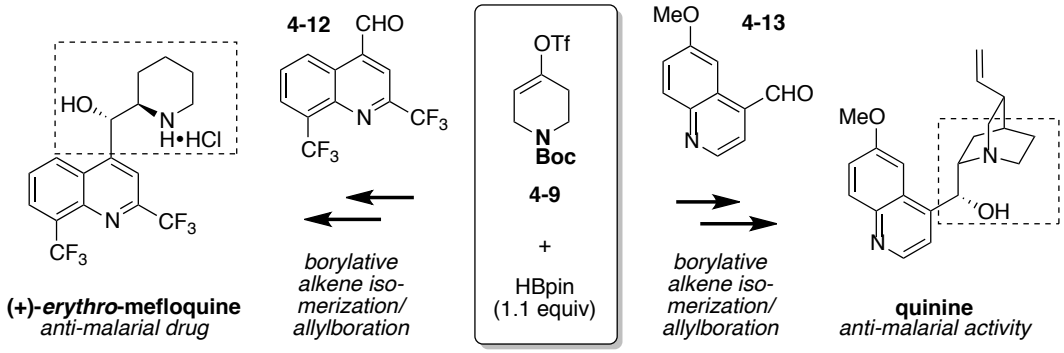


Figure 4-2: Proposed syntheses of quinine and mefloquine.

4.3 Consise synthesis of all four stereoisomers of mefloquine

4.3.1 The significance of synthesizing all mefloquine stereoisomers in antimalarial drug discovery

Malaria is a mortal disease caused by *Plasmodium* parasites, which are spread to humans by infected mosquitoes. According to the latest estimates, almost half of the world's population[128] − over three billion inhabitants − are in danger of contracting malaria. In 2010, there were approximately 216 million clinical cases of malaria and approximately 655,000 resultant deaths.[128] Currently, a number of effective antimalarial drugs and treatments are available, but drug resistance remains a continuing problem due to the rapid evolution and adaptation of malaria parasites. Moreover, current antimalarial drugs are unaffordable for underdeveloped countries where people are most vulnerable. Therefore, novel and economical alternative treatments are needed.[129]

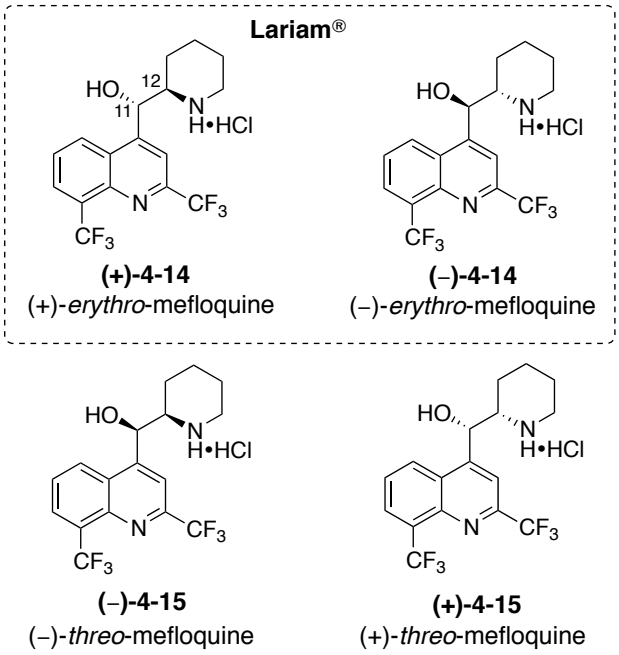


Figure 4-3: All four stereoisomers of mefloquine.

A leading antimalarial drug, mefloquine was formulated in the 1970s, and was

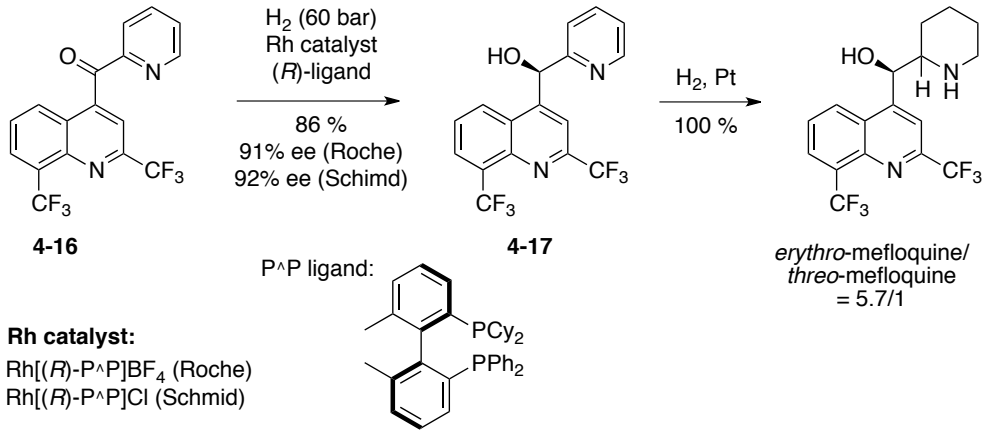
soon developed and marketed under the name Lariam®, the Roche branded formulation. Mefloquine remains effective against all human malaria parasites, including the recently identified fifth species, *Plasmodium knowlesi*.[130] Additionally, mefloquine shows a longer half-life compared to other antimalarial drugs, and thus allows for less frequent administration making patient compliance less problematic.[131] The clinical utility of mefloquine as a prophylactic antimalarial drug, however, is plagued with the risk for severe neurotoxic side effects.[132] As a result, the U.S. military withdrew mefloquine as their primary antimalarial drug in 2009.[132] Recent reports allege that upon returning from foreign missions, many Canadian soldiers were suffering from adverse side effects from taking mefloquine.[133] Regardless, mefloquine is still widely prescribed in many countries.

Structurally, mefloquine is an α-hydroxyalkyl piperidine with two contiguous stereogenic centres, and thus may exist as four stereoisomers (Figure 4-3). These stereoisomers possess various biological activities.[134,135a] (+)-*erythro* and *threo* mefloquine ((+)-**4-14** and (+)-**4-15**) have similar IC_{50} against *Plasmodium* parasites, and they are 1.7 to 2.0 times more active than their respective enantiomers ((−)-**4-14** and (−)-**4-15**).[135a] On the other hand, (−)-*erythro* mefloquine ((−)-**4-14**) binds with the adenosine receptor in the central nervous system, which can cause severe psychotropic effects.[135] Furthermore, due to its higher plasma concentrations, the half-life of (−)-*erythro* mefloquine ((−)-**4-14**) is 2.5 times longer than that of the (+)-*erythro* enantiomer ((+)-**4-14**).[136] Lariam® is constituted of racemic (±)-*erythro* mefloquine (Figure 4-3), and thus contains both active and harmful forms of the drug. To the best of our knowledge, use of the *threo* enantiomers **4-15** has never been explored for treating malaria, which may be due to a more difficult synthetic access. Thus far, the four stereoisomers have only been obtained by HPLC separation using a chiral stationary phase.[135a] Enantioselective synthetic access to all mefloquine isomers is an unmet challenge, and its successful realization could be beneficial in the global fight against

malaria parasites.[137] This Chapter describes a concise and scalable synthesis of six mefloquine analogues, including all four stereoisomers, using a carefully optimized Pd-catalyzed asymmetric borylative alkene isomerization in tandem with stereoselective aldehyde allylboration.

4.3.2 Previous asymmetric syntheses of (+)-*erythro*-mefloquine and the debate about its absolute configuration

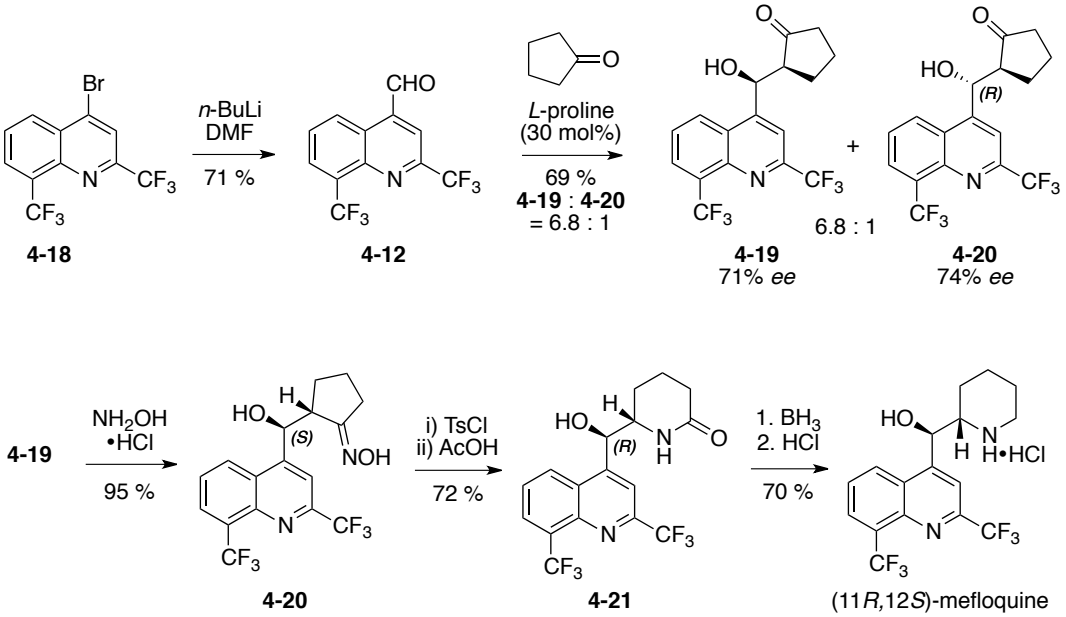
As discussed in the Section 4.3.1, while the *threo*-mefloquine enantiomers display promising antimalarial properties, several research groups focused instead on developing selective syntheses of (+)-*erythro*-mefloquine.



Scheme 4-6: Synthesis of (+)-*erythro*-mefloquine *via* asymmetric hydrogenation.

The first enantioselective synthesis of (+)-*erythro*-mefloquine was completed in 1993 by Roche's chemists[138] using a Rh-catalyzed enantioselective hydrogenation of 2-pyridyl-2,8-bis(trifluoromethyl)-quinolineketone **4-16**, which was obtained *via* a three-step synthesis[139] from commercial sources (Scheme 4-6). The corresponding chiral secondary alcohol **4-17** was obtained in 86 % yield and 91% *ee*. To further improve the enantioselectivity, Schmid and co-workers[140] later screened several other Rh catalysts and chiral ligands, and found the unsymmetrical ligand containing one dicyclohexylphosphino and one

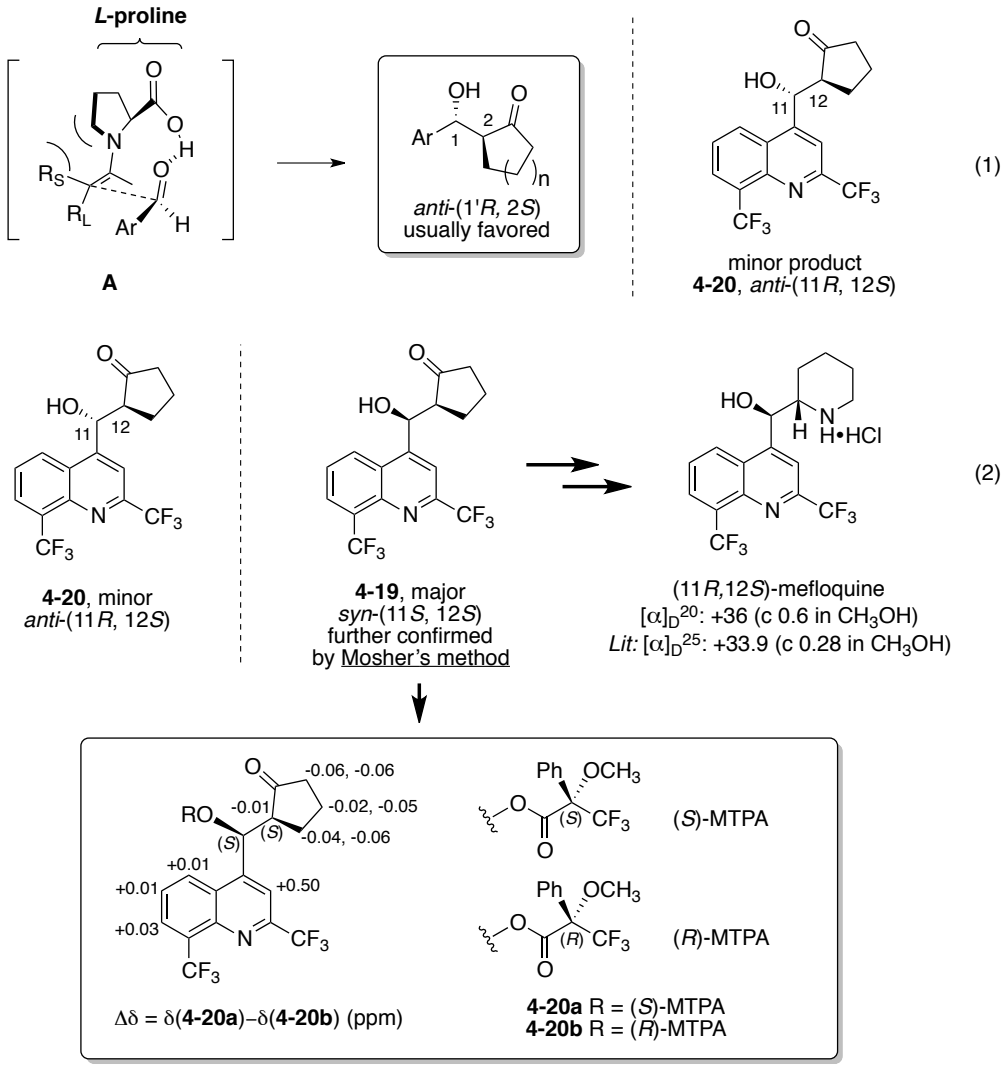
diphenylphosphino moiety remained optimal. In the following pyridine hydrogenation, however, both research groups obtained a 5.7:1 diastereomeric mixture of (11*R*,12*S*)-*erythro*-mefloquine and (11*R*,12*R*)-*threo*-mefloquine with quantitative yields (Scheme 4-6). In both cases, the stereochemistry of (+)-*erythro*-mefloquine was assigned arbitrarily by following its first assignment in 1974, to be (11*R*,12*S*),[135a] while no conclusive evidence was provided.



Scheme 4-7: Synthesis of (+)-*erythro*-mefloquine *via* an organocatalytic aldol addition and a Beckmann rearrangement.

In 2003, Xie and co-workers[141] applied an organocatalytic aldol addition and a Beckmann rearrangement as key steps for the asymmetric total synthesis of (+)-*erythro*-mefloquine. In Scheme 4-7, the aldehyde **4-12** was afforded through formylation of 4-bromoquinoline **4-18** in the presence of *n*-BuLi and DMF. With 30 mol% loading of *L*-proline as the organocatalyst, the key asymmetric aldol reaction was initiated through the reaction of aldehyde **4-12** with cyclopentanone. The corresponding *syn*-aldol product **4-19** and *anti*-aldol product **4-20** were obtained as a mixture with a diastereomeric ratio of 6.8:1, which could, however,

be separated using silica gel flash column chromatography. The purified *syn*-aldol **4-19** was then reacted with hydroxylamine for the formation of oxime **4-20**, which underwent a Beckmann rearrangement upon treatement with TsCl. Upon acidic work-up, the δ-lactam **4-21** was obtained in good yield. Further reduction of the lactam was achieved through treatment with borane dimethylsulfide. Finally, the subsequent addition of concentrated HCl afforded the putative (11*R*,12*S*)-mefloquine hydrochloride in good yield (Scheme 4-7).

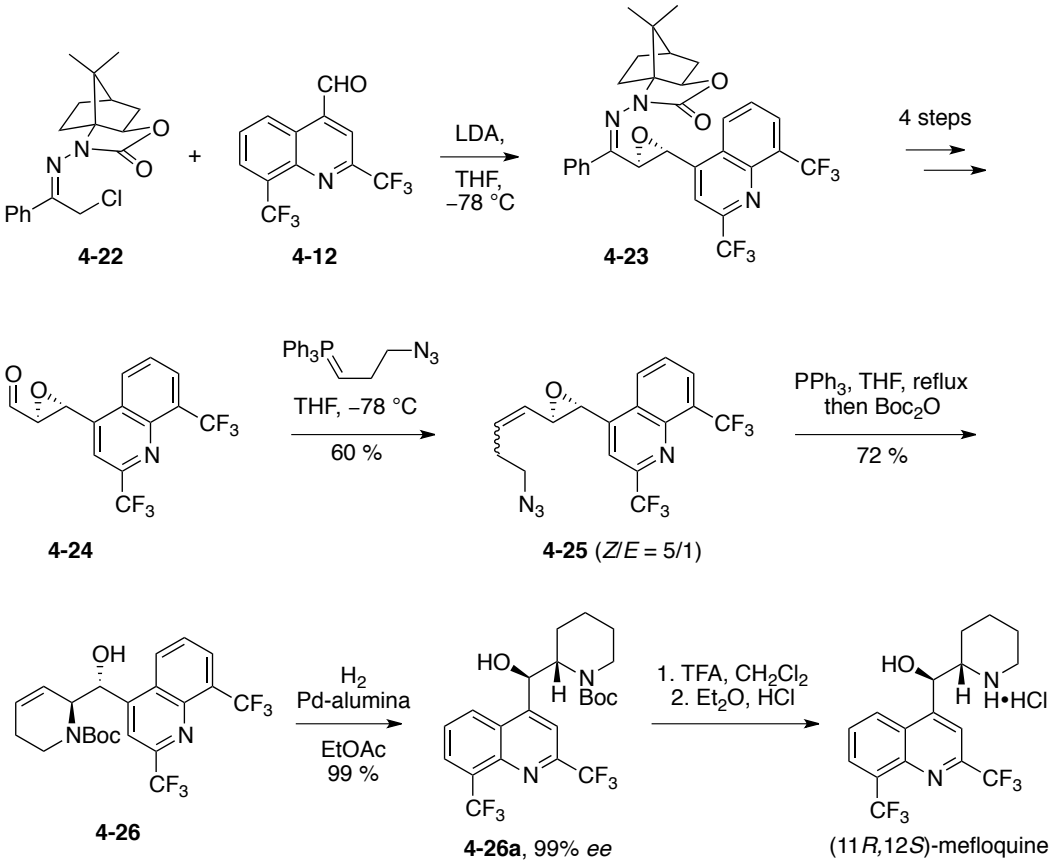


Scheme 4-8: Absolute stereochemistry assignment of **4-20** through correlation with literature.

To assign the stereochemistry of the final product (+)-mefloquine, Xie and co-workers's investigated the stereochemical outcome of the asymmetric aldol reaction where the two stereogenic centers were established. Since its discovery in 2000,[142] the *L*-proline-catalyzed asymmetric aldol reaction has been well studied, and its stereochemical outcome has become reliable.[143] A variety of literature results indicated that the *anti*-(1*R*,2*S*) enantiomers are usually favored in the *L*-proline-catalyzed asymmetric aldol reaction between aldehydes and cyclic ketones (Scheme 4-8, Equation 1).[144] The transition state **A** controls both the enantioselectivity and diastereoselectivity, especially in the case of cyclic ketones where only *E* enamine geometry is possible. Through this correlation, Xie and coworkers assigned the absolute configuration of the *anti*-aldol **4-20** to be (11*R*,12*S*), despite the fact that it is the minor diastereomer. Based on this assignment, the authors proposed the stereochemistry of the major product *syn*-aldol to be (11*S*,12*S*). This was further confirmed by the Mosher's method,[145] although the chemical shift differences were quite insignificant. In this manner, the stereochemistry of the final product (+)-*erythro*-mefloquine was assigned rather inconclusively to be (11*R*,12*S*) (Scheme 4-8, Equation 2).

Recently, using an asymmetric Darzens reaction[146] as the key step, another enantioselective total synthesis of (+)-*erythro*-mefloquine was completed by Coltart and co-workers.[147] In Scheme 4-9, with the *N*-amino cyclic carbamate (ACC) as the chiral auxiliary, an asymmetric Darzens reaction of ACC hydrazone **4-22** and aldehyde **4-12** affords the desired *trans*-α,β-epoxy hydrazone **4-23** as the key intermediate in good yield, high diastereo- and enantioselectivity. In this regard, the stereochemistry was established in the early stage of this synthesis of (+)-*erythro*-mefloquine. After removal of the chiral auxiliary and further modification of the carbonyl group, the aldehyde **4-24** was obtained in four steps. In the final stages of the synthesis, the aldehyde **4-24** was first subjected to a Wittig reaction to give olefins **4-25** as a *Z*/*E* mixture with a ratio of 5:1. This transformation was followed by a cascade azide reduction/epoxide ring opening

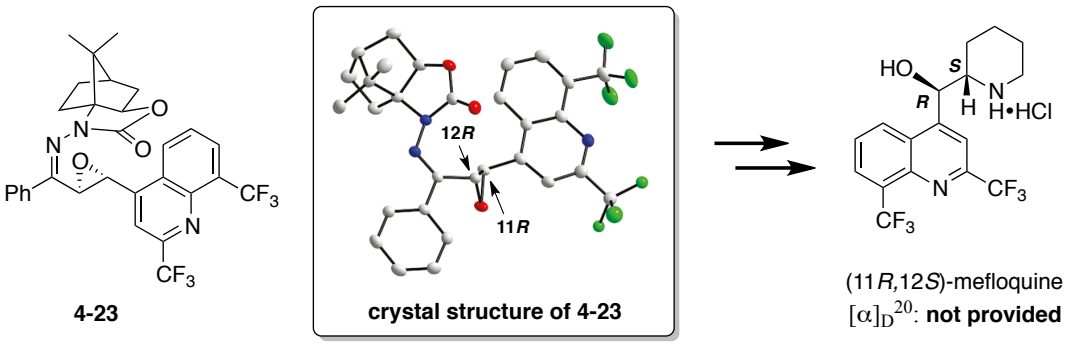
sequence when the azide compound **4-25** was treated with triphenylphosphine in wet THF. Without further purification, the resulting amino alcohol was directly converted to the *N*-Boc protected compound **4-26** through an *in situ* addition of Boc_2O. The resulting dehydro-mefloquine **4-26** was subjected to a palladium-catalyzed olefin hydrogenation reaction, providing the mefloquine precusor **4-26a** in 99% *ee*, which was measured by the chiral HPLC. Finally, the desired (11*R*,12*S*)-mefloquine hydrochloride was obtained after Boc removal and amine protonation.



Scheme 4-9: Synthesis of (+)-*erythro*-mefloquine *via* a key step of the asymmetric Darzens reaction.

To assign the absolute configuration of the product (+)-mefloquine, Coltart and coworkers examined the stereochemical outcome of the asymmetric Darzens

reaction, which determined the stereochemistry for the rest of the synthesis. For this purpose, a crystal structure of the key intermediate **4-23** was obtained. Based on X-ray crystal-structure analysis and the known absolute stereochemistry of the ACC chiral auxiliary, its absolute configuration was confirmed to be (11*R*,12*R*) (Scheme 4-10). In principle, further synthetic modifications towards the final product mefloquine did not affect the stereochemical integrity of C11, while that of C12 should be inverted during the azide reduction/epoxide ring opening step (Scheme 4-9). Strangely, the authors did not address the debate of the absolute configuration of (+)-mefloquine. Instead, they arbitrarily agreed with the Xie Group for its stereochemistry assignment to be (11*R*,12*S*), while no optical rotation data was provided to further exclude the possible formation of (–)-*erythro*-mefloquine.



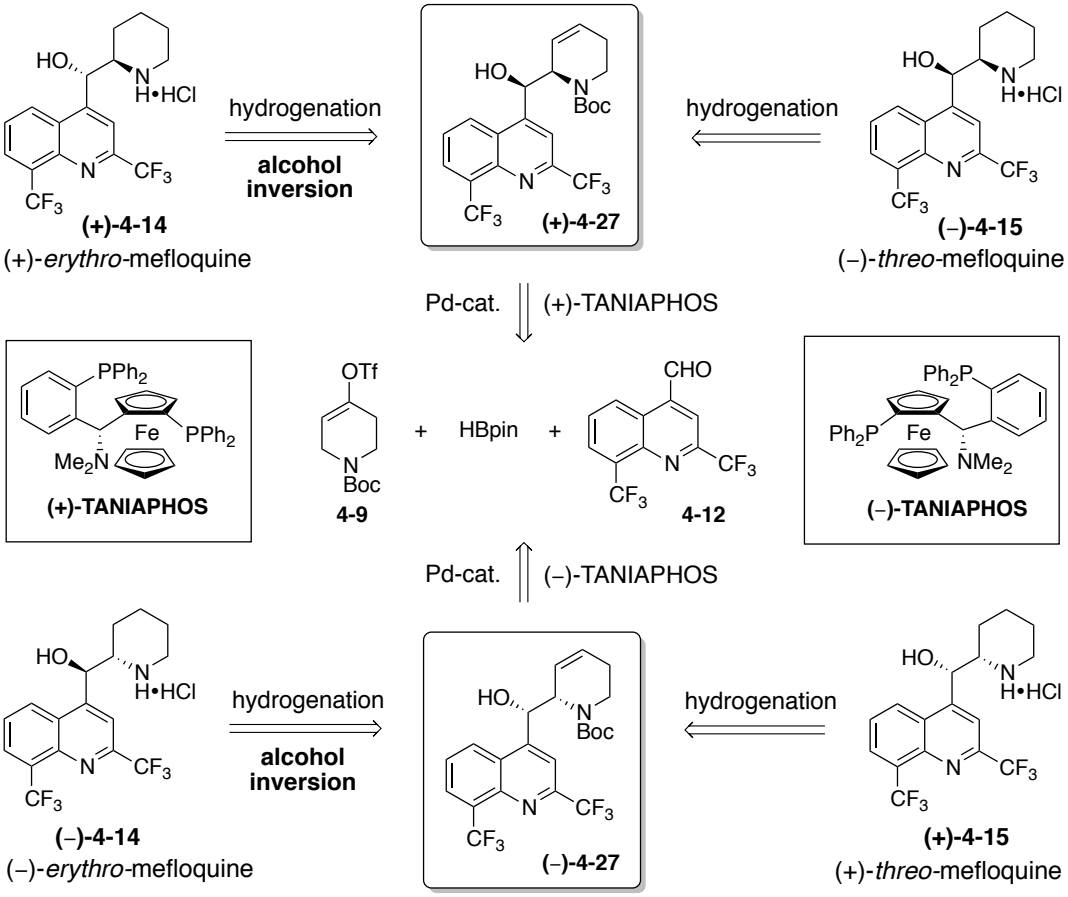
Scheme 4-10: Absolute configuration of *erythro*-mefloquine assigned by Coltart and co-workers.[147]

As discussed above, with respect to the absolute configuration of (+)-*erythro*-mefloquine, all three syntheses conformed with its first assignment, in 1974, to be (11*R*,12*S*), which was based on circular dichroism (CD) and empirical rules.[135a] This original assignment, however, was reversed in 2002 by Karle and co-workers on the basis of X-ray Diffraction (XRD) studies.[148] More recently, Schmidt and co-workers[149] confirmed the absolute configuration to be (11*S*,12*R*) based on the combined analyses of NMR with optical rotatory dispersion (ORD) and circular

dichroism (CD) measurement.

4.3.3 Retrosynthetic plan towards all four stereoisomers of mefloquine

In spite of the recent developments for the synthesis of (+)-*erythro*-mefloquine as discussed above, further exploration of this important antimalarial drug remains limited owing to the lack of synthetic route to the *threo* mefloquine enantiomers and the conflicting assignment for the absolute configuration of (+)-*erythro*-mefloquine.



Scheme 4-11: Unified retrosynthetic scheme for all four mefloquine stereoisomers.

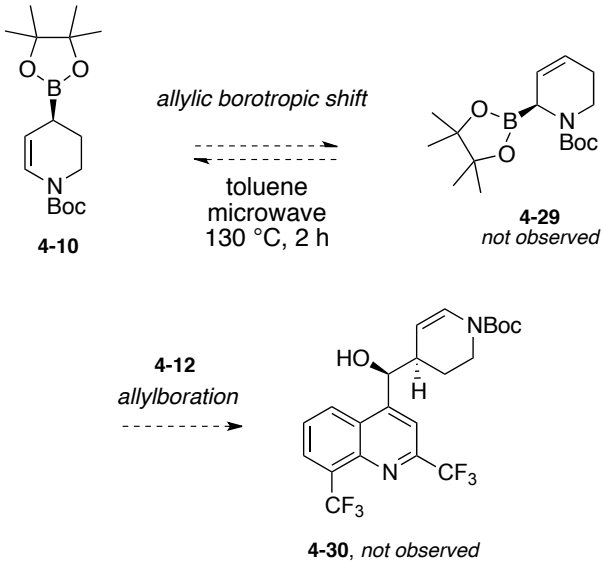
In this regard, a new and unified synthetic strategy was designed to access all four stereoisomers of mefloquine. In the retrosynthetic plan (Scheme 4-11), (+)-*erythro*-mefloquine (+)-**4-14** could be prepared from the key dehydropiperidine intermediate (+)-**4-27** through hydrogenation and alcohol inversion. Without the alcohol inversion, its diastereomer (−)-*threo*-mefloquine (−)-**4-15** could be afforded directly. The synthesis of optically pure (+)-**4-27** could be achieved by optimizing the Pd-catalyzed asymmetric borylative isomerization/aldehyde allylboration process previously examined in a preliminary study by our group (Scheme 4-5). Both alkenyl triflate **4-9**[127] and aldehyde **4-12**[141,147] can be synthesized in gram-scale from cheap starting materials in only two steps. Utilizing the same approach, the two other mefloquine stereoisomers (−)-**4-14** and (+)-**4-15** could be accessed from (−)-**4-27**, using (−)-TANIAPHOS as the chiral ligand (Scheme 4-11).

4.3.4 Optimization of reaction conditions for the Pd-catalyzed asymmetric borylative isomerization/allylboration with aldehyde 4-12

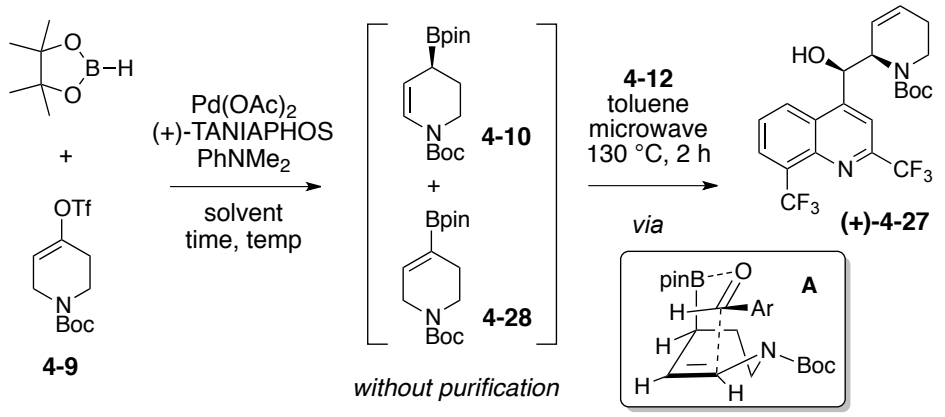
We first attempted the Pd-catalyzed asymmetric borylative isomerization/ allylboration using (+)-TANIAPHOS[150] as the chiral ligand. The previously developed conditions[127] exclusively afforded the diastereomer (+)-**4-27** in moderate yield and enantioselectivity (entry 1, Table 4-1). The relative *threo* stereochemistry of (+)-**4-27** can be rationalized by the usual chairlike 6-membered transition structure **B** of carbonyl allylboration reactions. Moreover, when this step was run on gram-scale, poor selectivity of **4-10**/**4-28** was observed (entry 2, Table 4-1). Thus, to become effective and practical, this key transformation required significant optimization. Alternative solvents (entries 3-5, Table 4-1) and different temperatures (entries 6-7, Table 4-1) were attempted, which gave either low selectivities or low conversions for the borylative isomerization product **4-10**. Upon further optimization, we found that the enantioselectivity could be enhanced reproducibly by using a higher grade of $Pd(OAc)_2$ and by deoxygenation of the

solvent dioxane, as detailed in the legend of Table 4-1 (entry 8, Table 4-1). To make the key step more economical, a lower catalytic loading was attempted, which unfortunately resulted in lower conversion and enantioselectivity (entry 9, Table 4-1). Further adjustment of catalytic loading identified the use of 3 mol% of $Pd(OAc)_2$/6 mol% ligand as being the optimal stoichiometry (entry 10, Table 4-1). To our satisfaction, these optimized conditions worked efficiently on a gram-scale (entry 11, Table 4-1).

1,3-borotropic rearrangement of allylic boronic esters is prone to occur at elevated temperature.[151] Accordingly, we reasoned that an allylic borotropic arrangement of chiral allylic boronate **4-10** could occur under the high-temperature, microwave-assisted allylboration conditions. In principle, the allylic borotropic shift should be stereospecific and preserve the configuration of chiral allylic boronate **4-10**.[152] We have not, however, observed the rearranged product **4-29** or the corresponding carbonyl allylboration adduct **4-30** under our reaction conditions (Scheme 4-12).



Scheme 4-12: Proposed allylic borotropic shift of chiral allylic boronate **4-10** and corresponding allylboration of the regioisomer **4-29.**



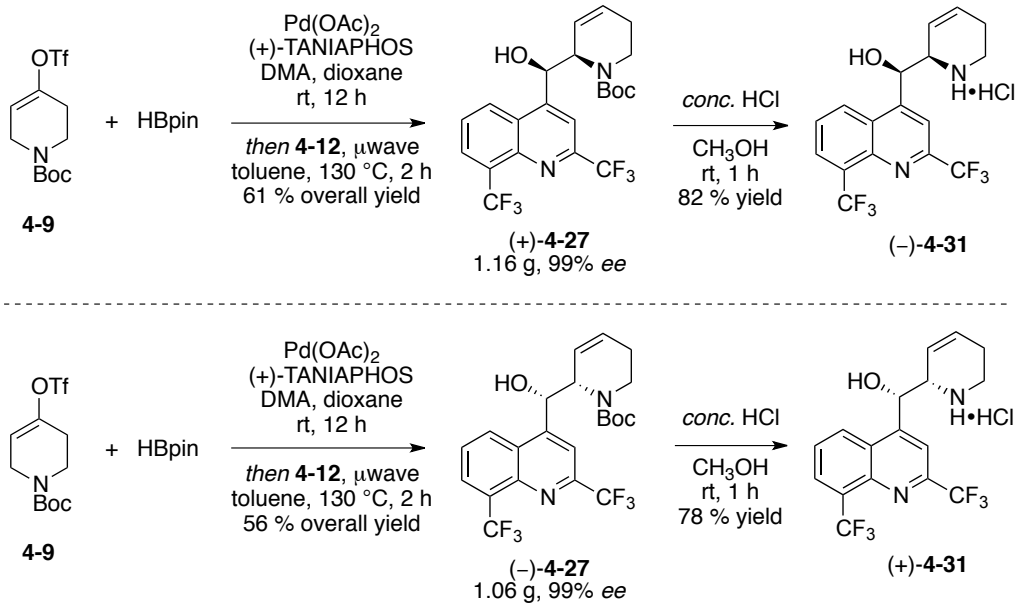
entry[a]	cat. loading $Pd(OAc)_2$/L	solvent	temp, time	**4-10** : **4-28**[b]	(+)-**4-27**[c]
1	5 mol%/10 mol%	dioxane	25°C, 4h	3 : 1	56%, 83% *ee*
2[d]	5 mol%/10 mol%	dioxane	25°C, 4h	1 : 1	-
3	5 mol%/10 mol%	THF	25°C, 4h	2 : 1	-[e]
4	5 mol%/10 mol%	toluene	25°C, 4h	1.3 : 1	-[e]
5	5 mol%/10 mol%	DCM	25°C, 4h	2 : 1	38%, 85% *ee*
6	5 mol%/10 mol%	dioxane	0°C, 24h	-[d]	-
7	5 mol%/10 mol%	dioxane	50°C, 1h	1 : 1.5	-
8[f]	5 mol%/10 mol%	dioxane	25°C, 4h	4 : 1	58%, 99% *ee*
9[f]	1 mol%/2 mol%	dioxane	25°C, 4h	2 : 1	42%, 91% *ee*
10[f]	3 mol%/6 mol%	dioxane	25°C, 12h	4 : 1	63%, 99% *ee*
11[d,f]	**3 mol%/6 mol%**	**dioxane**	**25°C, 12h**	**3 : 1**	**59%, 99% *ee***

[a] Reaction conditions: **4-9** (1.33 g, 4.00 mmol), $Pd(OAc)_2$ (27 mg, 0.20 mmol), (+)-TANIAPHOS (165 mg, 0.400 mmol), HBpin (640 μL, 4.40 mmol), $PhNMe_2$ (592 μL, 4.40 mmol) in dioxane (96 mL), rt, 12 h; after a quick filtration and solvent evaporation, toluene was added (15 mL), **4-12** (1.8 g, 6.0 mmol), in a Biotage™ microwave reactor, 130 °C, 2 h. [b] Ratio determined by ^{1}H-NMR. [c] Yield over two steps; *ee* determined by chiral HPLC. [d] Reaction on gram-scale. [e] Low conversion. [f] Using ≥99.9% $Pd(OAc)_2$; commercial dry dioxane was deoxygenated under dry nitrogen for three hours before use.

Table 4-1: Pd-catalyzed asymmetric borylative isomerization/allylboration using (+)-TANIAPHOS as the chiral ligand.

4.3.5 Asymmetric synthesis of dehydro-mefloquine analogs in gram-scale

Conducting the key step on a gram scale (Scheme 4-13), the unsaturated piperidine derivative (+)-**4-27** was accessed as a single enantiomer with a good overall yield without purification of the borylative isomerization intermediate **4-10**, which was subjected to the thermal allylboration with aldehyde **4-12** after a quick filtration, evaporation and solvent change. A high reaction temperature of 130 °C is crucial to the high enantioselectivity of this sequence, and quite remarkably, allylic boronate **4-10** preserves its stereochemical integrity under these conditions. The other key intermediate (−)-**4-27** was also obtained with high efficiency using (−)-TANIAPHOS as the chiral ligand.

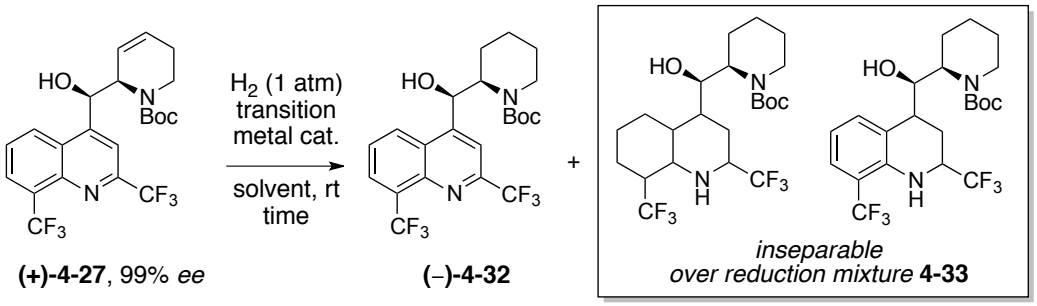


Scheme 4-13: Asymmetric synthesis of dehydro-mefloquine analogs (+)-**4-31** and (−)-**4-31**.

With both key intermediates (+)-**4-27** and (−)-**4-27** in hand, the optically pure dehydro-mefloquine analogs (−)-**4-31** and (+)-**4-31** were respectively obtained as hydrochloride salts, in good yields, following a N-Boc deprotection/protonation step with methanolic HCl.

4.3.6 Asymmetric synthesis of (+)-, and (−)-*threo*-mefloquine

To prepare the *threo*-mefloquine enantiomers, hydrogenation conditions for the selective olefin hydrogenation of (+)-**4-27** were first screened. Several transition metal catalyzed hydrogenation methods were initially screened (entries 1-4, Table 4-2). In most cases, however, undesired reduction of the quinoline ring was prone to happen, resulting in a mixture of inseparable reduction products **4-33** as major products. In further investigation of hydrogenation conditions, a conventional diimide reduction[153] was promising, leading to the exclusive formation of desired olefin reduction product **(+)-4-32** in high yield, although partial enantiomeric erosion was observed (entry 5, Table 4-2). The undesired minor racemization presumably resulted from the harsh, basic diimide reduction conditions, which required a treatment with hydrazine monohydrate and refluxing under oxygen in ethanol for 24 hours (entry 5, Table 4-2). Other milder catalytic diimide reduction conditions were also examined. Catalysts tested included $CuCl_2$,[154] guanidine nitrate[155] and modified riboflavin,[156] which often promote efficient diimide reductions at lower temperatures (entries 6-8, Table 4-2). None of these catalytic conditions, however, gave results nearly as good as that of entry 5 (Table 4-2). Eventually, Crabtree's catalyst was attempted for the homogeneous hydrogenation of **4-27**, since it is efficient for selective hydrogenation of hindered olefins especially in the presence of a coordinating hydroxyl group.[157] To our delight, the desired olefin hydrogenation product **(+)-4-32** was obtained in decent yield without any loss of enantiomeric purity (entry 9, Table 4-2). Further optimization found that a 5 mol% catalyst loading of Crabtree's catalyst and prolonged reaction time can lead to the desired hydrogenation product **(+)-4-32** in exellent yield and 99% *ee* (entry 11).

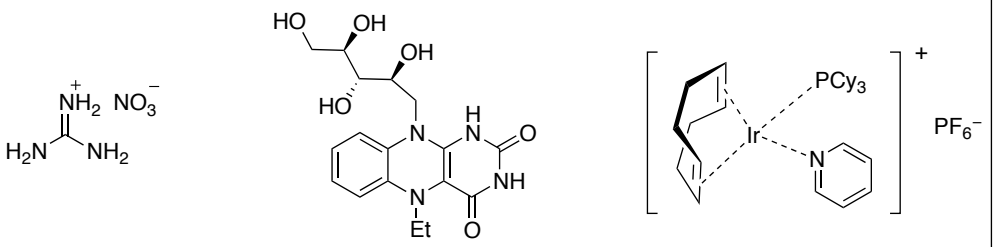


(+)-4-27, 99% *ee*

(–)-4-32

inseparable
over reduction mixture **4-33**

entry	catalyst	additives, solvent, time, temp	(–)-**4-32 : 4-33**[a]	(–)-**4-32**[b]
1	Pd/C, 10 mol%	EtOAc, 24 h, rt	1 : 10	-
2	Ru/Al, 5 mol%	EtOAc, 24 h, rt	1 : 12	-
3	Pd/Al, 10 mol%	EtOAc, 24 h, rt	1 : 1.5	-
4	Pd/C, 10 mol%	DCM, 24 h, rt	1 : 10	-
5	-	$NH_2NH_2 \bullet H_2O$, O_2 EtOH, 24 h, reflux	>98%	94%, 82% *ee*
6	$CuCl_2$, 10 mol%	$NH_2NH_2 \bullet H_2O$, O_2 EtOH, 24 h, 55 °C	SM recovered	-
7	Guanidine nitrate, 20 mol%	$NH_2NH_2 \bullet H_2O$, O_2 EtOH, 24 h, rt	SM recovered	-
8	**4-34**, 20 mol%	$NH_2NH_2 \bullet H_2O$, O_2 EtOH, 24 h, rt	>98 %	30%
9	**4-35**, 2.5 mol%	DCM, 24 h, rt	>98 %	60%, 99% *ee*
10	**4-35**, 2.5 mol%	DCM, 48 h, rt	>98 %	80%, 99% *ee*
11	**4-35**, **5 mol%**	**DCM, 48 h, rt**	**>98 %**	**95%, 99% *ee***



Guanidine nitrate

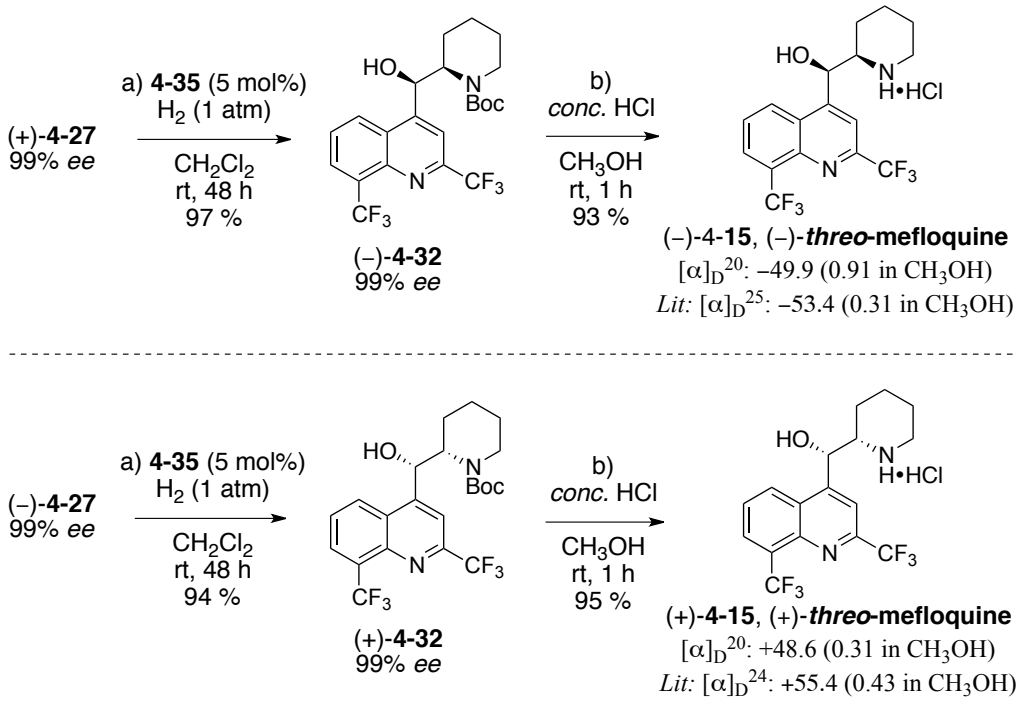
4-34, modified Riboflavin

4-35, Crabtree's catalyst

[a] Ratio determined by ^{1}H-NMR. [b] Isolated yield; *ee* was determined by chrial HPLC

Table 4-2: Screening of hydrogenation conditions towards the selective olefin reduction of (+)-**4-27**.

Using Crabtree's catalyst **4-35**, hydrogenation of the β-hydroxy alkene of (+)-**4-27** afforded the desired saturated product (−)-**4-32** in excellent yield without any apparent enantiomeric erosion (Scheme 4-14). The resulting optically pure piperidine (−)-**4-32** was then deprotected to provide (−)-*threo*-mefloquine hydrochloride (−)-**4-15** in excellent yield. The (+)-*threo*-mefloquine hydrochloride (+)-**4-15** was also obtained efficiently using the same sequence of reactions. This is the first isolation of the two *threo*-mefloquine enantiomers *via* stereoselective total synthesis.



Scheme 4-14: Asymmetric synthesis of *threo*-mefloquine enantiomers (+)-**4-15** and (−)-**4-15.**

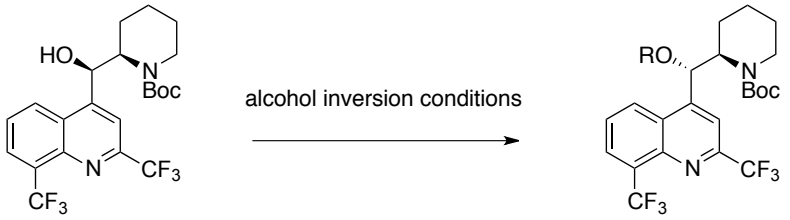
4.3.7 Asymmetric synthesis of (+)- and (−)-*erythro*-mefloquine

4.3.7.1 Attempts for the alcohol inversion of intermediate 4-32 *via* Mitsunobu reaction and other stoichiometric alcohol activation protocols

To achieve the synthesis of *erythro*-mefloquine enantiomers (+)-**4-14** and (−)-**4-**

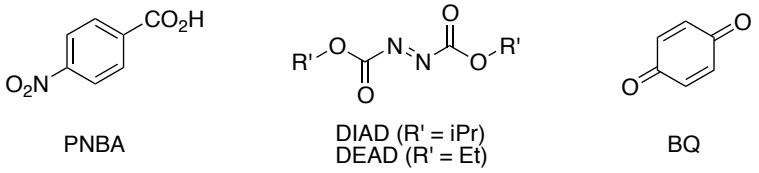
15, the stereochemistry of the secondary carbinol derivatives (−)-**4-32** and (+)-**4-32** needed to be inverted. For this purpose, various Mitsunobu reaction conditions[158] were initially attempted. A careful optimization of a series of reaction parameters was conducted, including carboxylic acids, azodicarboxylate reagents, the order of addition of different reactants, solvent, temperature, *etc* (entries 1-8, Table 4-3). Most of these attempted conditions, however, constantly gave complex mixtures. Mass spectrometric analysis of reaction mixtures indicated that the corresponding elimination products were the major side products, while no or little desired esterification product **4-36** with inverted stereochemistry was observed.

With various Mitsunobu reaction conditions failing to proceed, alternative methods for the alcohol inversion were investigated. In this regard, mesylation of the secondary alcohol **4-32** was performed under basic conditions. The resulting mesylate was then subjected to a stereoinvertive S_N2 process by the treatment of nucleophilic carboxylate anion (entry 9, Table 4-3). Unfortunately, decomposition was again observed. Another important alternative for the secondary alcohol inversion was developed by the Mukaiyama Group in 2003,[159] which features the use of *n*BuLi as strong base and benzoquinone as oxidant for the stoichiometric alcohol activation. These conditions, however, resulted in complex mixtures when the alcohol **4-32** was applied (entry 10, Table 4-3).



4-32 *rac* **4-36**

entry	alcohol inversion conditions	temp, time	**4-36**[a]
1	PPh_3, DIAD, PNBA, THF	25 °C, 24 h	decomp.
2	PPh_3, DEAD, $PhCO_2H$, toluene	25 °C, 4 h	decomp.
3	PPh_3, DIAD, $PhCO_2H$, THF	0→25 °C, 4 h	SM recovered
4	PPh_3, DIAD, CH_3OTs, THF	−10→25 °C, 18 h	decomp.
5	PPh_3, DEAD, PNBA, THF	0→25 °C, 2 h	decomp.
6	PPh_3, DIAD, PNBA, benzene	25 °C, 24 h	decomp.
7	PPh_3, DIAD, PNBA, toluene/THF (1/1)	−20→25 °C, 24 h	SM recovered
8	PPh_3, DIAD, propionic acid, THF	25°C , 14h	SM recovered
9	i) MsCl, pyridine (base and solvent) ii) CsOAc, 18-C-6, toluene	i) 0→25 °C, 12 h ii) reflux, 12 h	decomp.
10	i) *n*-BuLi, Ph_2PCl, THF ii) PNBA, BQ, DCM	i) 0→25 °C, 1 h ii) rt, 12 h	decomp.



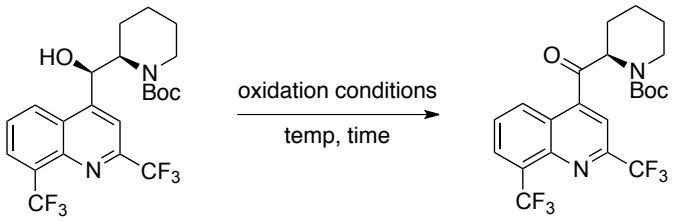
[a] Conversion was determined by ^{1}H-NMR. PNBA: *p*-nitrobenzoic acid; DIAD: diisopropyl azodicarboxylate; DEAD: diethyl azodicarboxylate; BQ: benzoquinone.

Table 4-3: Attempts for the alcohol inversion of **4-32**.

4.3.7.2 Oxidation/reduction protocol for the alcohol inversion of 4-32

With various Mitsunobu reaction conditions and several stoichiometric alcohol activation protocols failed (Table 4-3), we proposed an oxidation/reduction

sequence[160] for the alcohol inversion of **4-32**. Accordingly, optimization of oxidation conditions of the secondary alcohol **4-32** was first conducted. As shown in Table 4-4, a variety of alcohol oxidation conditions were screened. While several conventional oxidation conditions gave low product yield or decomposition (entries 1-4, Table 4-4), the PCC (pyridium chlorochromate) oxidation afforded the desired ketone **4-37** with a promising conversion. Several attempts at the reproduction of PCC oxidation found that their isolated yields were not consistent, which varied between 62% and 85% (entry 5, Table 4-4). The irreproducible yields presumably resulted from the tedious work-up and removal of the chromium-containing byproducts.[161] Eventually, the mild Dess-Martin periodinane[162] oxidation was highly efficient, consistently affording the desired ketone **4-37** with excellent yield (entry 6, Table 4-4).



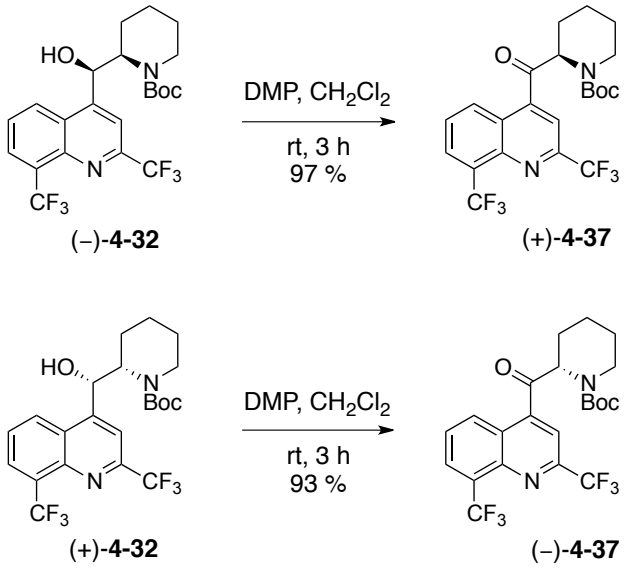
4-32 *rac* **4-37**

entry	oxidation conditions	temp, time	**(+)-4-37**[a]
1	IBX, THF/DMSO	0 °C to rt, 12 h	decomp.
2	$(COCl)_2$, DMSO, Et_3N, DCM	–78 °C to rt, 5 h	35 %
3	SO_3•Py, DMSO, Et_3N, DCM	0 °C, 12 h	SM recovered
4	TPAP, NMO, DCM	rt, 24 h	45 %
5	PCC, DCM	rt, 5 h	62-85 %
6	**DMP, DCM**	**rt, 12 h**	**92 %**

[a] Isolated yield. IBX: 2-iodoxybenzoic acid; TPAP: tetrapropylammonium perruthenate; NMO: *N*-methylmorpholine *N*-oxide; PCC: pyridinium chlorochromate; DMP: Dess-Martin periodinane.

Table 4-4: Optimization of oxidation of alcohol **4-32**.

Accordingly, Dess-Martin periodinane promoted oxidation of the alcohols (−)-**4-32** and (+)-**4-32** led to the ketones (+)-**4-37** and (−)-**4-37** respectively in excellent yields (Scheme 4-15). Unfortunately, the enantiomeric excesses of the resulting ketones could not be directly determined by chiral HPLC due to a difficult separation. The alcohol (+)-**4-32** from the subsequent reduction of ketone (−)-**4-37** (Table 4-5), however, was well resolved by chiral HPLC, and its enantiomeric excess was 99 %. This indicated that no enantiomeric erosion occurred during the Dess-Martin periodinane oxidation reactions.

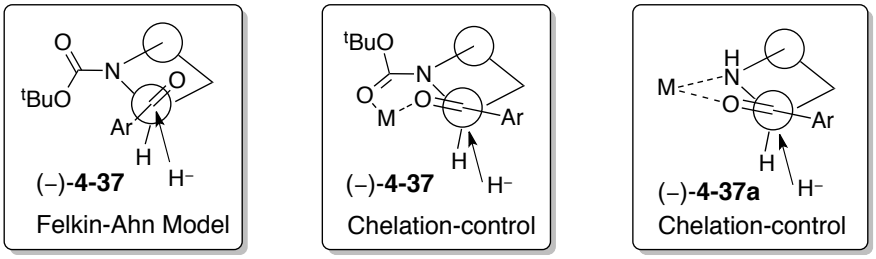


Scheme 4-15: DMP oxidation of chiral secondary alcohols (–)-**4-32** and (+)-**4-32**.

With optically pure ketones (+)-**4-37** and (−)-**4-37** in hand, a diastereoselective reduction could implement the desired alcohol inversion of chiral alcohols (−)-**4-32** and (+)-**4-32**. Hence, the optimization of reduction conditions was conducted by using the α-amino ketone (−)-**4-37** as the model substrate. Most reducing agents showed poor diastereoselectivities, in which the desired inverted alcohol (−)-**4-38** was obtained as the minor diastereomer (entries 1-6, Table 4-5). A

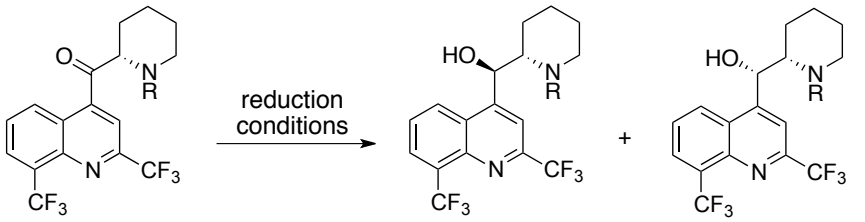
Felkin-Ahn model (Figure 4-4, **A**) can be proposed to rationalize this outcome. The chelation-control model (Figure 4-4, **B**), however, would be expected to provide the opposite, desired diastereoselectivity. In entry 7, the Luche conditions [163] showed modest diastereoselectivity in favor of **(−)-4-38** with excellent yield.

Additionally, a few more chelation-controlled reducing reagents [164] were attempted (entries 8-10, Table 4-5), but only poor yields and diastereoselectivities were achieved. Other reducing reagents such as PMHS[165] and SmI_2,[166] which are known for reducing α-amino ketones in anti-selective manner, were also teseted, but no successful results were achieved (entries 11-12, Table 4-5). The reduction under Luche conditions after removal of the bulky Boc protecting group, however, showed promising diastereoselectivity (entry 13, Table 4-5). Presumably, chelation between the ketone carbonyl and the Boc carbonyl requires formation of a thermodynamically unfavored seven-membered complex (Figure 4-4, **B**). It was surmised that after removal of the Boc group, the 1,2-chelation between the ketone oxygen and the nitrogen atom would be more efficient (Figure 4-4, **C**). Upon further optimization, the one-pot Boc deprotection/ketone reduction was achieved, affording the desired stereoinverted alcohol (−)-**4-38a** in excellent yield and high diastereoselectivity (entry 14, Table 4-5).



A (Table 4-5, Entries 1-6) **B** (Table 4-5, Entry 7) **C** (Table 4-5, Entry 14)

Figure 4-4: Diastereoselective reduction models for ketone (–)-**4-37**.



(–)-**4-37** (R = Boc)
(–)-**4-37a** (R = H)

(–)-**4-38** (R = Boc)
(–)-**4-38a** (R = H)

(+)-**4-32** (R = Boc)
(+)-**4-32a** (R = H)

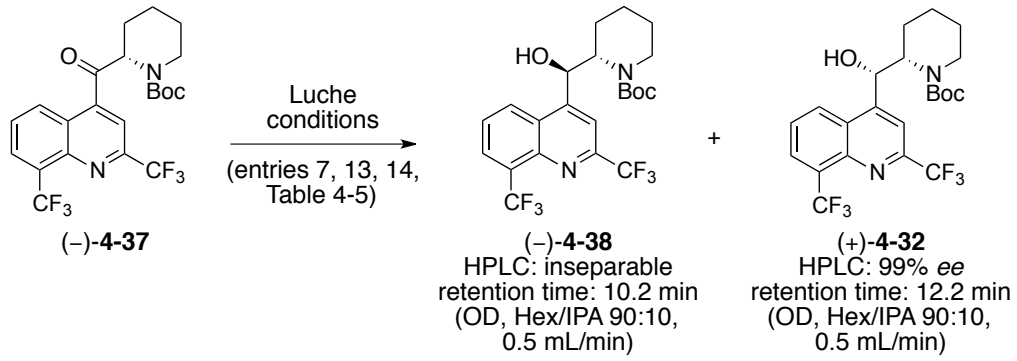
entry	reducing reagent	reaction condition	(–)-**4-38(a)** : (+)-**4-32(a)**[a]	conversion[b]
1	$NaBH_4$	–78°C, EtOH	1 : 3	99%
2	$LiBH_4$	–78°C, THF	1 : 3	75%
3	Red-Al	0°C, EtOH	-	0
4	$LiH(OtBu)_3$	–78°C, Et_2O	1 : 2	80%
5	L-selectride	–78°C, THF	1 : 1	65%
6	$LiEt_3BH$	–78°C, THF	1 : 5	80%
7	**$NaBH_4$, $CeCl_3$**	**–78°C, EtOH**	**2 : 1**	**99%**
8	BH_3•THF	–78°C, THF	1 : 10	45%
9	9-BBN	–78°C, EtOH	1 : 2	30%
10	$ZnBH_4$	–78°C, THF	1 : 3	80%
11	PMHS, TBAF	0°C, THF	1 : 1	30%
12	SmI_2, MeOH	0°C, THF	-	0
13[c]	$NaBH_4$, $CeCl_3$	–78°C, EtOH	6 : 1	80%
14[c,d]	$NaBH_4$, $CeCl_3$	**–78°C, EtOH**	**10 : 1**	**99%[e]**

[a] Ratio determined by ^{1}H-NMR. [b] Conversion determinted by ^{1}H-NMR. [c] Reduction after Boc deprotection. [d] Reduction after Boc deprotection in one-pot. [e] The enantiomeric excess of (–)-**4-38** could not be determined by chrial HPLC, while that of (+)-**4-32** was determined to be 99% *ee*. L-selectride = lithium tri-*sec*-butylboro hydride. 9-BBN = 9-borabicyclo(3.3.1)nonane, PMHS = polymethylhydrosiloxane, TBAF = tetra-*n*-butylammonium fluoride.

Table 4-5: Optimization of diastereoselective reduction of ketone (–)-**4-37**.

To exclude the possibility of undesired enantiomeric erosion that could occur *via* enolization of C12 under the Luche reduction conditions (Table 4-5, entries 7, 13 and 14), the two optically pure diastereomers (−)-**4-38** and (+)-**4-32** were separated by flash column chromatography and subjected to chiral HPLC measurement. The enantiomeric excess of the resulting diastereomer (−)-**4-38**,

however, could not be determined by chiral HPLC due to a difficult separation, even through different HPLC conditions were screened, including the ones applied by the Coltart Group.[147] The resulting diatereomer (+)-**4-32** was determined to be 99% *ee* with retention time of 12.2 min, while its enantiomer (−)-**4-32** has a retention time of 15.5 min (Chiralcel-OD chiral column; volume ratio of hexane/isopropanol 90:10; flow rate 0.5 mL/min). Under the same HPLC conditions, the racemic compound **4-38**, which showed as a single peak due to overlapping of enantiomer peaks, had the retention time of 10.2 min. Therefore, the reduction of optically pure ketone (−)-**4-37** under the Luche conditions gave rise to the diastereomer (+)-**4-32** with 99% *ee* and different retention time as that of the other diastereomer (−)-**4-38** (Scheme 4-16).



Scheme 4-16: HPLC indication of no enantiomeric erosion for the reduction of the single stereoisomer (−)-**4-37** under the Luche conditions.

Moreover, a co-injection of racemic compounds **4-38** and **4-32** showed three well-separated peaks with distinct retention times (Figure 4-5), which further excluded any possible overlapping among (±)-**4-38** (11.0 min), (+)-**4-32** (13.3 min) and (−)-**4-32** (16.3 min). These results indicate that the Luche conditions do not cause any enantiomeric erosion.

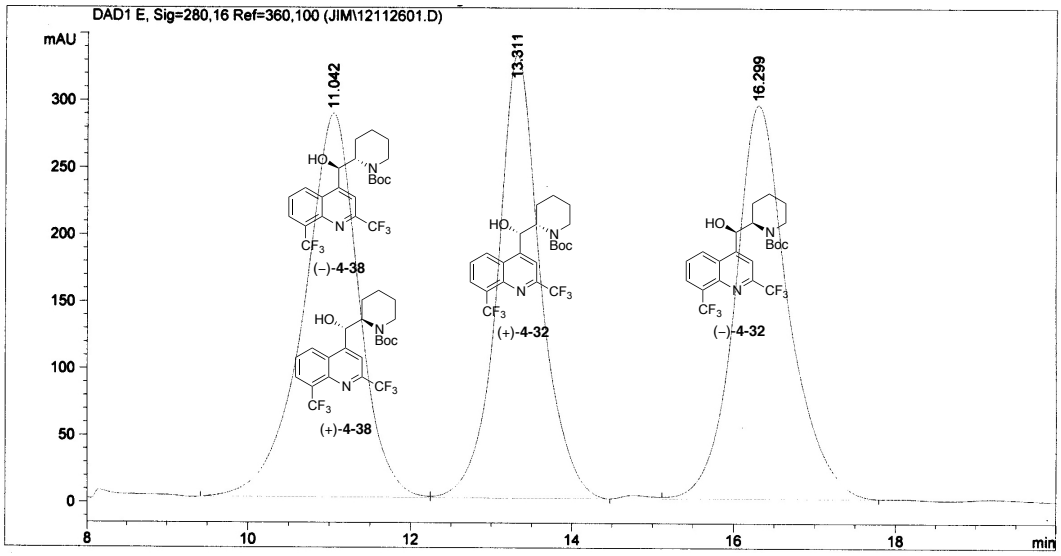
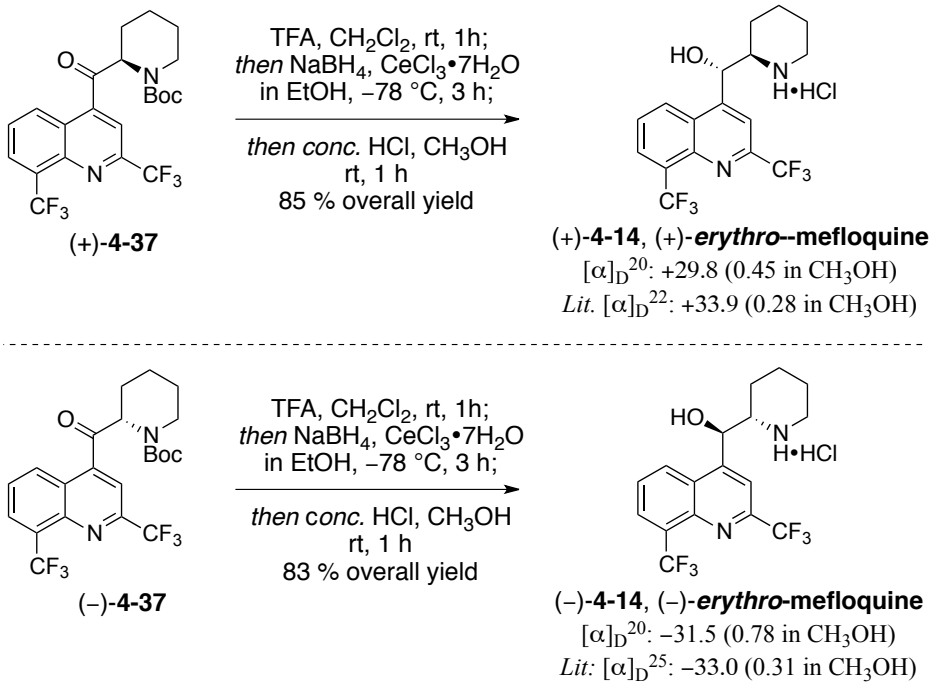


Figure 4-5: The HPLC co-injection of racemic compounds **4-38** (left peak) and **4-32** (middle and right peaks).

4.3.7.3 Asymmetric synthesis of *erythro*-mefloquine enantiomers (+)-4-14 and (−)-4-14

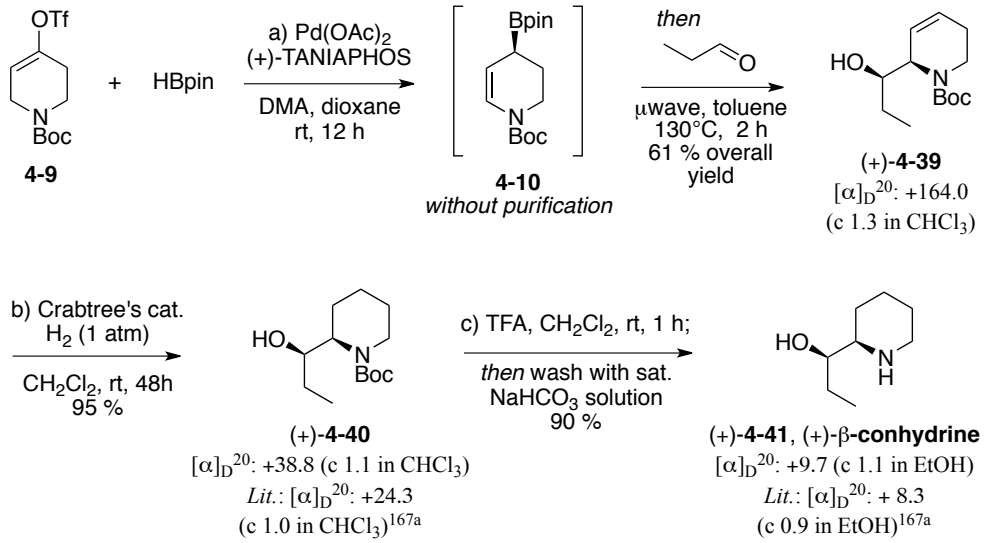
The optimal reduction conditions (entry 14, Table 4-5) were applied to the diastereoselective reduction of both (+)-**4-37** and (−)-**4-37**. Further optimization showed that the Boc deprotection/ketone reduction/HCl protonation sequence could be achieved in one-pot, thus affording *erythro*-mefloquine enantiomers directly without any purification. In Scheme 4-14, ketone (+)-**4-37** was treated with trifluoroacetic acid (TFA, 3 equiv) for the Boc removal, followed by slow addition of a solution of $CeCl_3$ (6 equiv) and $NaBH_4$ (6 equiv) in EtOH at −78°C. After aqueous work-up, the desired α-amino alcohol was obtained as the main diastereomer, which was directly protonated without any further purification to provide (+)-*erythro*-mefloquine hydrochloride salt ((+)-**4-14**) in good yield. The other enantiomer (−)-**4-14** was also obtained with high efficiency using the same sequence (Scheme 4-17).



Scheme 4-17: Synthesis of *erythro*-mefloquine enantiomers (+)-**4-14** and (−)-**4-14**.

4.3.8 Confirmation of the absolute configuration of all mefloquine stereoisomers *via* a total synthesis of (+)-β-conhydrine

As discussed in Section 4.2.2, the absolute configuration of (+)-*erythro*-mefloquine has been debated since 1974, when it was first assigned to be (11*R*,12*S*). To address this problem and further determine the absolute configuration of all mefloquine stereoisomers, we conducted a total synthesis of (+)-β-conhydrine ((+)-**4-41**, Scheme 4-18) *via* the same synthetic strategy applied in the total synthesis of the mefloquine stereoisomers.



Scheme 4-18: Total synthesis of (+)-β-conhydrine (+)-**4-41**.

In contrast to the conflicting assignment for the stereochemistry of (+)-*erythro*-mefloquine, the absolute stereochemistry of (+)-β-conhydrine ((+)-**4-41**) has been well established through numerous total syntheses.[167] Using a similar borylative isomerization/allylboration reaction of the alkenyl triflate **4-9**, with (+)-TANIAPHOS as the chiral ligand, the dehydro-conhydrine (+)-**4-39** was synthesized with good efficiency. After hydrogenation using Crabtree's catalyst, the *N*-Boc-conhydrine (+)-**4-40** was prepared in excellent yield without any enantiomeric erosion. Eventually, following with Boc deprotection, the total synthesis of optically pure (+)-β-conhydrine ((+)-**4-41**) was achieved in three steps with 52% overall yield, which is the most efficient enantioselective synthesis of (+)-β-conhydrine thus far. The observed optical rotation value of (+)-β-conhydrine ($[\alpha]_D^{20}$ = +9.7 (c 1.1 in EtOH)) matches the reported value for (+)-β-conhydrine ($[\alpha]_D^{20}$ = +8.0 (c 0.85 in EtOH))[167a] Accordingly, the known absolute stereochemistry for (+)-β-conhydrine provides strong evidence for the absolute stereochemistry assignment of all the mefloquine stereoisomers reported herein. Hence, this work constitutes the first chemical proof of absolute stereochemistry of (+)-mefloquine and thus confirms the (11*S*,12*R*) assignment claimed in the

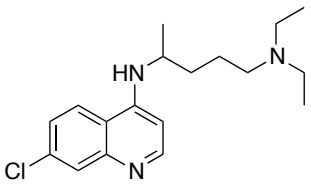
Karle[148]/Schmidt[149] revision.

4.3.9 Antimalarial activity of mefloquine stereoisomers and analogs

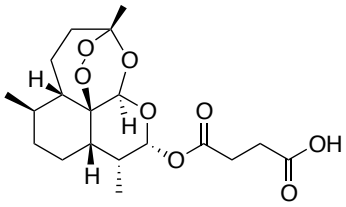
With all four optically pure mefloquine stereoisomers and two dehydro-mefloquine analogs in hand, their antimalarial activity against *Plasmodium falciparum* NF54 was evaluated by our collaborator Dr. Xavier Ding from Medicines for Malaria Venture (MMV).

samples	EC_{50} (nM)[a]	IC_{50} (nM)[b]
	Tested against: *Plasmodium falciparum* NF54	Tested against: Sierra Leone and the Indochina *Plasmodium falciparum* clones
(–)-**dehydro-mefloquine**	23.5	N/A
(+)-**dehydro-mefloquine**	9.2	N/A
(+)-***threo*-mefloquine**	7.6	13.0 ± 6.5
(–)-***threo*-mefloquine**	82.7	22.5 ± 8.6
(–)-***erythro*-mefloquine**	12.9	42.3 ± 7.2
(+)-***erythro*-mefloquine**	14.5	23.4 ± 3.8
chloroquine[c]	19.6	N/A
artesunate[c]	5.9	N/A

[a] Data from Medicines for Malaria Venture (MMV). [b] Previous data reported by Karle and co-workers.[148a] [c] From commercial sources provided by MMV.



chloroquine



artesunate

Table 4-6: Antimalarial activity of mefloquine stereoisomers and analogs.

In Table 4-6, all samples showed great potency against the malaria parasite,

except for (−)-**4-15** (EC_{50} = 82.7 nM). The EC_{50} values of (+)-**4-15**, (+)-**4-14**, (−)-**4-14** match quite well with IC_{50} values previously reported by Karle and co-workers[135a] on samples purified by chiral HPLC. It is interesting to note that the most potent stereoisomer in both assays is the (+)-*threo*-mefloquine isomer ((+)-**4-15**), not the commercial (+)-*erythro* isomer (+)-**4-14**, and it matches closely the potency of artesunate, a common herbal-based antimalarial drug. To our satisfaction, the two novel *threo*-dehydromefloquine enantiomers (−)-**4-31** and (+)-**4-31**, which were prepared with great efficiency in only two steps from known substrates (Scheme 4-11), are also very potent and thus have potential to be developed as alternative antimalarial drugs.

4.3.10 Summary

In summary, we have optimized a highly enantioselective catalytic borylative alkene isomerization strategy for the stereoselective synthesis of the antimalarial drug mefloquine. All four mefloquine stereoisomers and analogs were accessed in 2-4 steps on gram scale from known substrates with high optical purities. The absolute configuration of these compounds was confirmed for the first time using a chemical approach, which unraveled almost 40-year debate for the absolute stereochemistry of (+)-*erythro*-mefloquine. It was further confirmed that the configurational assignments in the recent revisions by Karle and Schmidt are correct. Soon after the above results were published, two research groups independently reported asymmetric syntheses of mefloquine using alternative synthetic pathways. Chen and co-workers[168] reported a four-step synthesis of (−)-*erythro*-mefloquine hydrochloride from the commercial (*S*)-(−)-1-Boc-2-piperidinecarboxylic acid and determined its absolute configuration to be (11*R*,12*S*). Additionally, the Griesinger Group [169] also demonstrated an asymmetric synthesis of all four stereoisomers of mefloquine *via* a domino Sonogashira-6π-electrocyclization as the key step. Both syntheses further confirmed our own stereochemical assignment.

The *threo* enantiomers and the two novel dehydromefloquine enantiomers displayed potent antimalarial activities against *Plasmodium falciparum* NF54, which highlights their potential to be developed as alternative antimalarial drugs. With an outstanding level of enantioselectivity now achievable on gram scale, this work demonstrates that the borylative alkene isomerization/aldehyde allylboration process can be applied with high efficiency to the preparation of various drugs and natural products containing a piperidine core.

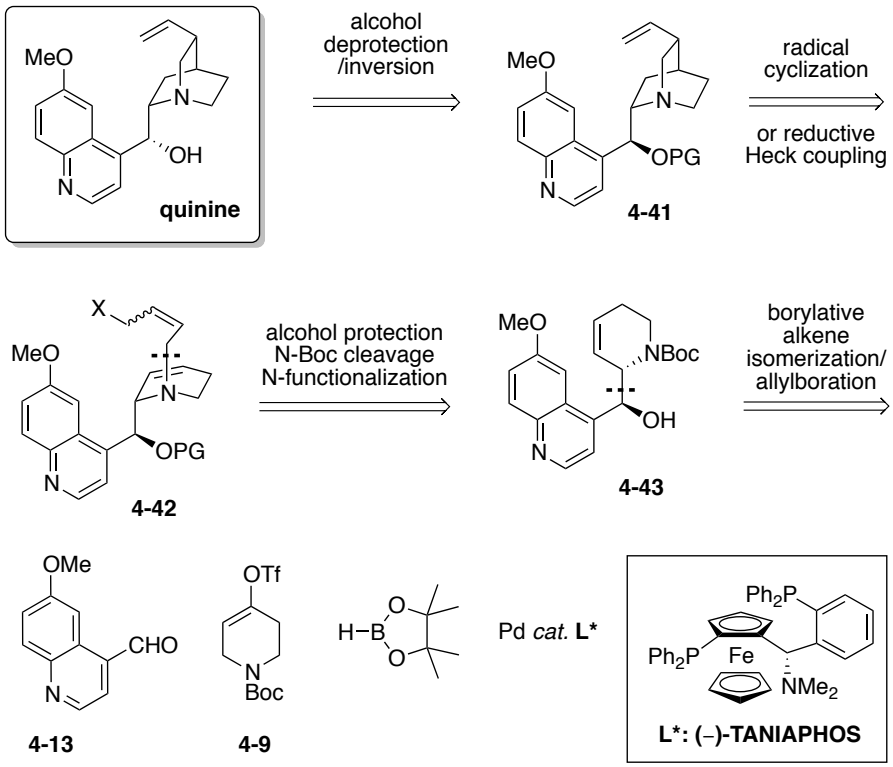
4.4 Efforts towards a total synthesis of quinine

4.4.1 Retrosynthetic plan for a concise asymmetric total synthesis of quinine

As one of the earliest anti-malaria drugs, the famed alkaloid quinine is still commonly used for malaria treatment among countries with low rates of drug resistance.[170] In addition to its biologically importance, quinine is also synthetically challenging.[171] Although its asymmetric synthesis has received increasing interest since the beginning of the 20th century, the first enantioselective total synthesis of quinine was not achieved until 2001.[172]

In light of the successful enantioselective total synthesis of all four stereoisomers of mefloquine, we envisioned that quinine, as an important analogue of mefloquine, could also be efficiently constructed using the borylative alkene isomerization/allylboration strategy. In Scheme 4-19, the optically pure α-hydroxyalkyl dihydropiperidine intermediate **4-43** could be synthesized with high diastereo- and enantioselectiviy *via* the optimized palladium-catalyzed asymmetric borylative alkene isomerization with (–)-TANIAPHOS as the chiral ligand and sequential allylboration with aldehyde **4-13**. Upon alcohol protection of the chiral compound **4-43**, removal of the Boc protecting group and *N*-alkylation, the key intermediate **4-42** would be established. With the core structure of chiral piperidyl compound **4-42** set up with an allylic electrophile, a radical allylic cyclization or reductive Heck coupling could give rise to the

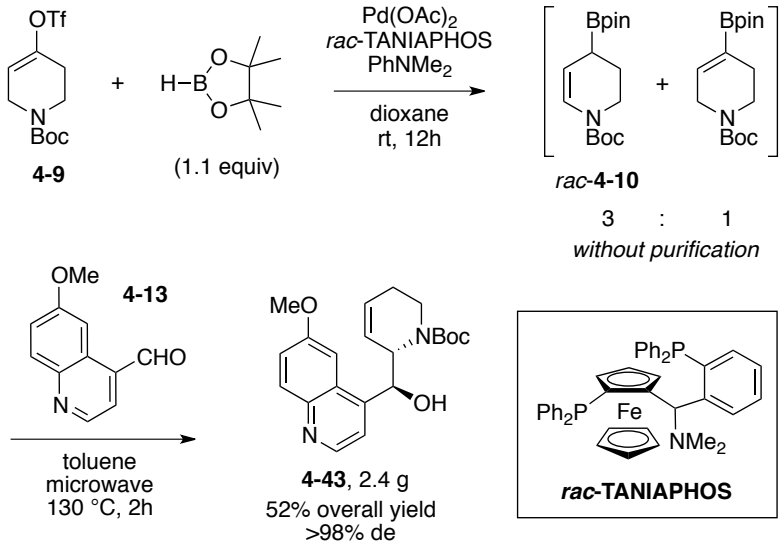
bridged bicyclic piperidine moiety in compound **4-41**. Completed by an alcohol deprotection and stereoinversion, the synthetically challenging and biologically important target quinine could be accessed (Scheme 4-19).



Scheme 4-19: Retrosynthetic plan for a concise asymmetric synthesis of quinine.

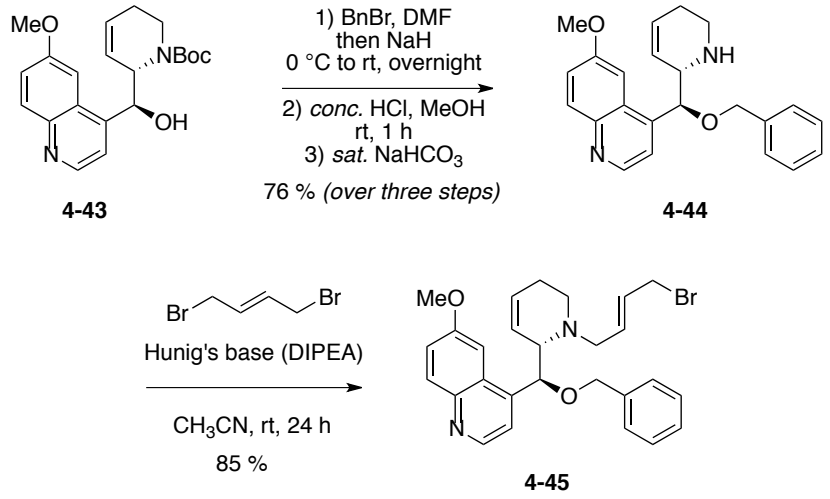
4.4.2 Efforts towards a total synthesis of quinine

With the above retrosynthetic analysis in mind (Scheme 4-19), we first set out to conduct the racemic synthesis of the quinine precursor **4-43** *via* the optimized palladium-catalyzed borylative alkene isomerization with *rac*-TANIAPHOS as the ligand. In Scheme 4-19, the racemic piperidyl allylic boronate **4-10** was obtained as the major product, which without further purification, was subjected to sequential allylboration with aldehyde **4-13** under microwave thermal conditions. The resulting racemic α-hydroxyalkyl dihydropiperidine **4-43** was afforded in gram scale with good overall yield and excellent diastereoselectivity.

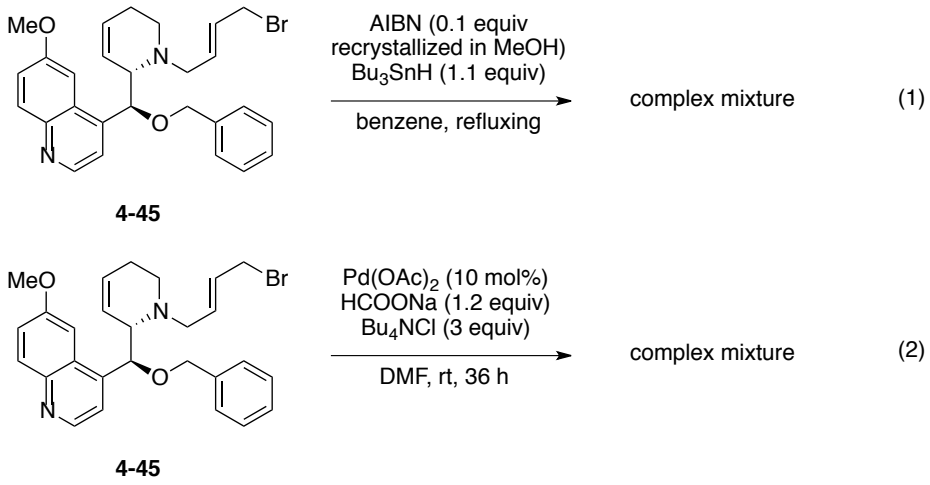


Scheme 4-20: Racemic synthesis of the quinine precursor **4-43**.

With the quinine precursor **4-43** accessible in gram scale, the free hydroxyl group was first protected by the treatment of benzyl bromide under basic conditions (Scheme 4-21). Without purification, the resulting crude mixture was subjected to the *N*-Boc deprotection with methanolic HCl and subsequent basic work up, affording compound **4-44** in good yield over three steps. Further *N*-alkylation from the secondary amine **4-44**, however, encountered some difficulties, which often resulted in either the corresponding quaternary ammonium salts or a mixture of the desired tertiary amine and the starting secondary amine.[173] The selection of bases was the key for the desired formation of tertiary amine. In this regard, Hunig's base, *N*,*N*-diisopropylethylamine, is often recognized to be a good base but a poor nucleophile owing to its sterically bulky alkyl branches.[174] The Soloshonok Group[175] demonstrated that the use of this unique base was efficient for the selective mono-*N*-alkylation of secondary amines. Accordingly, in the presence of Hunig's base and acetonitrile as the solvent, the desired tertiary amine **4-45** was successfully synthesized in excellent yield (Scheme 4-21).



Scheme 4-21: Synthesis of the key intermediate **4-45**.

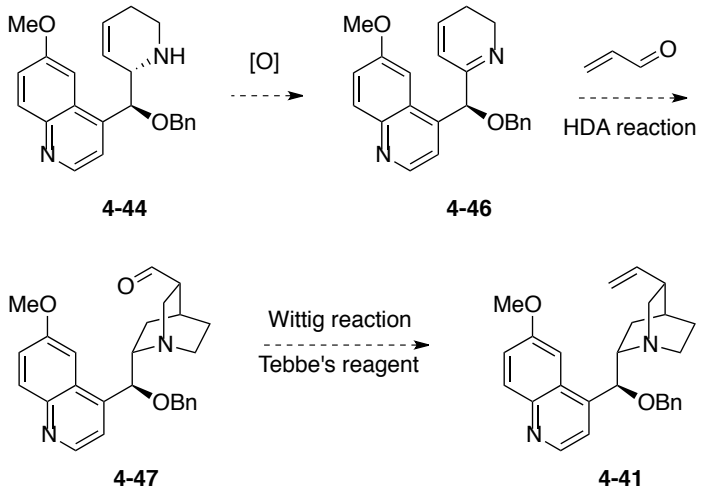


Scheme 4-22: Attempts towards the construction of the bridged bicyclic piperidine moiety *via* allylic radical cyclization and reductive Heck coupling reaction (selected examples).

With the key intermediate **4-45** in hand, based on the retrosynthetic analysis of Scheme 4-19, a cyclization of the allylic electrophile and subsequent alcohol inversion would give rise to the end product quinine, which would accomplish the shortest synthesis of quinine thus far. Motivated by this synthetic plan, several methods of radical cyclization[176] were initially attempted to build the bridged

bicyclic piperidine moiety. A selection of representative allylic radical cyclization conditions are shown in Scheme 4-22. Complex mixtures, however, were often obtained, while the desired cyclization product was not observed based on the mass spectral analysis (Scheme 4-22, Equation 1). Alternatively, a series of reductive Heck coupling conditions[177] were also attempted, which again afforded unresolved complex mixtures (Scheme 4-22, Equation 2).

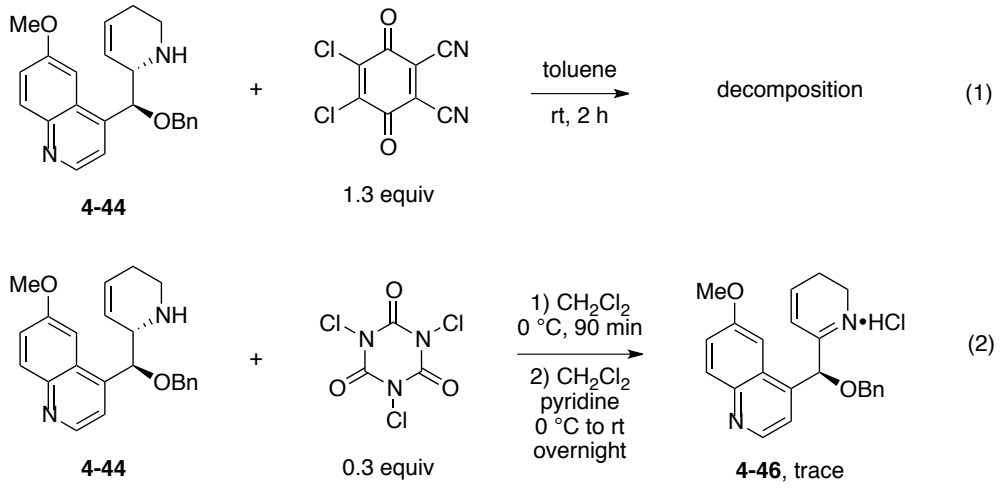
While searching for the optimal conditions for the allylic radical cyclization or reductive Heck coupling reaction, we proposed a hetero-Diels-Alder (HDA) reaction for the establishment of the bridged bicyclic moiety. In Scheme 4-23, we foresaw that the hetero diene compound **4-46** could be accessed *via* an oxidative imine formation. Upon the treatment of acrolein as the dienophile, a HDA reaction could be used to give the bridged compound **4-47**. A Wittig reaction or Tebbe olefination could lead to the formation of the quinine precursor **4-41**.



Scheme 4-23: Proposed hetero-Diels-Alder (HDA) reaction for the construction of the bridged bicyclic moiety of quinine.

To synthesize the hetero diene compound **4-46**, a variety of oxidation conditions were screened. In Scheme 4-24, while DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation[178] of the dehydropiperidine compound **4-44** resulted in

its decomposition (Scheme 4-24, Equation 1), a TCCA (trichloroisocyanuric acid) oxidation[179] gave a trace amount of the desired hetero diene compound **4-46** as the HCl salt (Scheme 4-24, Equation 2). The low yield probably resulted from the poor stability of product **4-46** under the oxidation conditions.

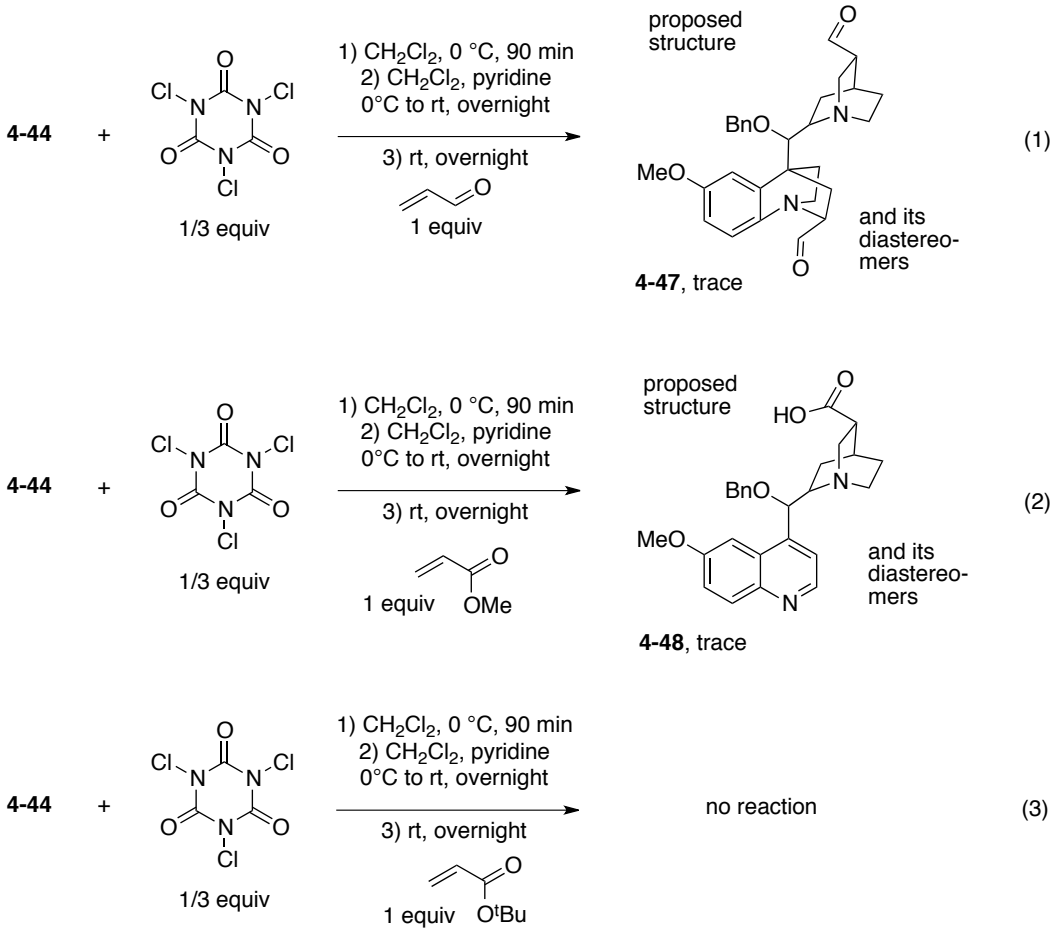


Scheme 4-24: Synthesis of heterodiene compound **4-46**.

In this regard, we attempted the sequential addition of several dienophiles to react with the *in situ* generated reactive hetero diene compound. As the dienophile acrolein was too reactive, the product was proposed to be a mixture of the double HDA reaction product **4-47** and its diastereomers, based on the mass spectrum analysis (Scheme 4-25, Equation 1). The product structure could not be confirmed due to the extremely low yield (lower than 1 mg quantity).

The less reactive dienophiles were thus applied. As a result, methyl acrylate was applied, which indeed gave the desired mono HDA reaction product **4-48**. However, the yield, regio- and diastereoselectivity was too low to be applicable (Scheme 4-25, Equation 2). Based on these results, we anticipated that *tert*-butyl acrylate, as a more sterically demanding dienophile, could increase the regio- and diastereoselectivity of the desired HDA reaction.[180] Unfortunately, no reactivity was observed when *tert*-butyl acrylate was employed (Scheme 4-25, Equation 3).

As part of the future work, the inverse electron demand Diels–Alder reaction (IEDDA) could be investigated, which would involve the use of electron rich dienophile such as enol ethers.



Scheme 4-25: Multicomponent oxidative imine formation/HDA reaction.

4.4.3 Conclusions and future perspectives

As discussed in Section 4.3 for the enantioselective synthesis of all stereoisomers of mefloquine, this success is mainly attributed to the use of an optimized palladium-catalyzed asymmetric borylative alkene isomerization and sequential aldehyde allylboration. Additionally, the same strategy again proved to be promising during the attempts towards the synthesis of the biologically important

natural alkaloid quinine, in which the gram scale synthesis of the key intermediate **4-52** was achieved in good yield and excellent diastereoselectivity. Although various approaches were endeavored for the further modification of the key intermediate, the total synthesis of quinine could not be completed. Nevertheless, significant progress has been made through a rapid construction of a partial skeleton of quinine.

The late stage establishment of the bridged bicyclic moiety proved to be challenging. To overcome this challenge, further ring closing methods need to be pursued, including alternative radical cyclization, intramolecular Heck coupling, intramolecular ene cyclization, etc. Overall, motived by the diastero, enantioselective, gram-scale synthesis of mefloquine and the key intermediates of quinine, we are looking forward to exploring the efficient synthesis of other biologically important natural products and synthetic drugs containing a piperidine core.

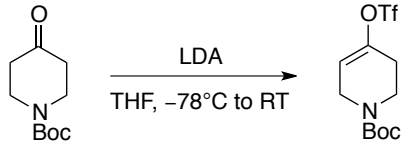
4.5 Experimental

4.5.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were from a MBraun MB SPS* solvent system. The anhydrous 1,4-dioxane was from Sigma-Aldrich, 99.8%, and it was deoxygenated with dry nitrogen for 3 hours before use. $Pd(OAc)_2$ was purchased from Sigma-Aldrich, ≥99.9% purity; chiral ligands (+)-TANIAPHOS and (−)-TANIAPHOS were synthesized on gram-scale respectively according to the literature procedure.[150] Chloroquine and artesunate were provided by Medicines for Malaria Venture (MMV). Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent

carbons (^{13}C) were used as internal standards. ^{1}H NMR data is 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; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) ion source with double focussing sector analyzer (Kratos Analytical MS-50G) or electrospray (ESI) ion source with orthogonal acceleration TOF analyzer (Agilent Technologies 6220 oaTOF). Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD (4.6 × 250 mm, inner diameter × length; particle size 5 μm) or Chiralpak-AS (4.6 × 250 mm, inner diameter × length; particle size 5 μm) columns. Even when the other enantiomer was not detected, we reported a conservative enantiomeric excess of 99%.

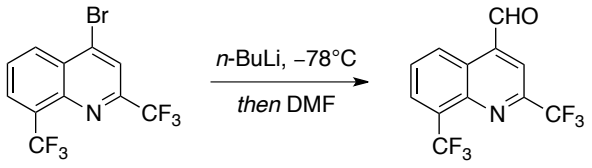
4.5.2 *tert*-Butyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (4-9)



4-9, *15 grams*

Compound **4-9** was synthesized according to a known literature procedure from the Boc-protected piperidone.[181] Spectral data match those previously reported.[181]

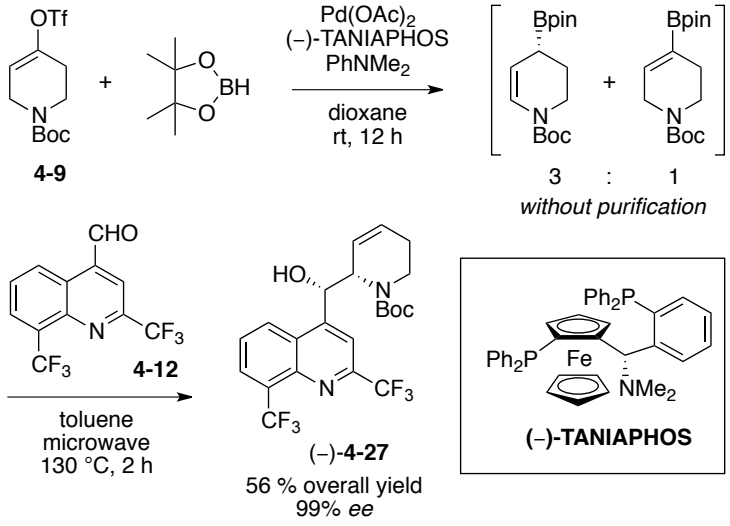
4.5.3 2,8-Bis(trifluoromethyl)quinoline-4-carbaldehyde (4-12)



4-12, *10 grams*

Compound **4-12** was prepared from 4-bromo-2,8-bis(trifluoromethyl)quinoline, *n*-butyllithium, and *N,N*-dimethylformamide according to the literature procedure.[141,146] Spectral data match those previously reported.[141,146]

4.5.4 (*R*)-*tert*-Butyl 2-((*R*)-(2,8-bis(trifluoromethyl)quinolin-4-yl) (hydroxy)methyl)-5,6 -dihydropyridine-1(*2H*)-carboxylate ((+)-4-27)



$Pd(OAc)_2$ (27 mg, 0.20 mmol) and (+)-TANIAPHOS (0.17 g, 0.40 mmol) were added in a flamed-dried round bottom flask, which was then flushed with nitrogen. The deoxygenated dioxane (32 mL) was added and the mixture was stirred for 10 minutes. N,N-Dimethylaniline (0.60 mL, 4.4 mmol), dioxane (32 mL), pinacolborane (0.64 mL, 4.4 mmol) and vinyl triflate **4-9** (1.3 g, 4.0 mmol) in dioxane (32 mL) solution were respectively added in the indicated order. The reaction mixture was then stirred at room temperature for 12 hours. The crude

reaction mixture was filtered through silica gel and rinsed with ether. The solvents were evaporated and the residue was diluted in dry toluene (15 mL) and aldehyde **4-12** (1.8 g, 6.0 mmol) was added to the flask. The solution was sealed and heated at 130 ºC for 2 hours in a Biotage^{TM} microwave oven (Absorption level: high. Pre-stirring: 10 sec). The mixture was allowed to cool down to room temperature, then the solvent was evaporated to yield a crude yellow oil, which was directly subjected to silica gel flash chromatography (50% ethyl acetate/hexane) to afford the title product (+)-**4-27** as a colorless oil (1.16 g, 61% overall yield and 99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$, 25°C) δ 8.40-8.35 (m, 1H), 8.22-8.13 (m, 1H), 8.11-7.95 (m, 1H), 7.77-7.67 (m, 1H), 6.18-5.82 (m, 1H), 5.68-5.35 (m, 1H), 5.20-4.82 (m, 1H), 4.80-4.45 (m, 1H), 4.34-4.02 (m, 1H), 3.14-2.83 (m, 1H), 2.30-2.12 (m, 1H), 2.07-1.95 (m, 1H), 1.54-1.36 (m, 6H), 1.21-0.99 (m, 3H). (Rotamers present at room temperature).

^{13}C NMR (100 MHz, $CDCl_3$, 25°C) δ 157.1, 150.2, 148.3 (q, $J_{C\text{-}F}$ = 35.4 Hz), 143.8, 129.3 (q, $J_{C\text{-}F}$ = 32.9 Hz), 129.0, 128.8 (q, $J_{C\text{-}F}$ = 5.3 Hz), 127.9, 127.5, 126.9, 123.5 (q, $J_{C\text{-}F}$ = 273.6 Hz), 123.4, 121.2 (q, $J_{C\text{-}F}$ = 275.6 Hz), 116.3, 81.4, 72.8, 57.8, 38.6, 28.3, 24.6. (Rotamers present at 25°C; only signals from the major rotamer were listed).

^{1}H NMR (400 MHz, $C_6D_5CD_3$, −30°C) δ 8.15 (s, 0.7H), 8.04-7.98 (m, 1.4H), 7.67-7.61 (m, 1.2H), 7.11 (s, 1H), 5.87 (s, 0.4H), 5.66-5.60 (m, 1H), 5.47-5.37 (m, 1.4H), 5.15-5.07 (m, 0.7H), 4.98-4.90 (m, 0.6H), 4.63-4.56 (m, 0.6H), 4.30-4.24 (m, 0.4H), 3.49-3.40 (m, 1H), 2.92-2.81 (m, 0.5H), 1.89-1.75 (m, 1.4H), 1.28 (s, 7H), 1.07 (m, 2H). (Rotamers present at −30 °C).

^{1}H NMR (400 MHz, $C_6D_5CD_3$, 100°C) δ 8.11 (d, J = 6.8 Hz, 1H), 7.89 (s, 1H), 7.78 (d, J = 5.9 Hz, 1H), 7.14 (dd, J = 5.9, 6.8 Hz, 1H), 5.57-5.53 (m, 1H), 5.23 (d, J = 6.0 Hz, 1H), 5.12 (dddd, J = 10.2, 3.8, 2.7, 1.2 Hz, 1H), 4.75 (br s, 1H), 3.89-3.80 (m, 1H), 2.95-2.62 (br m, 1H), 2.53-2.45 (m, 1H), 1.84-1.74 (m, 1H), 1.43-

1.36 (m, 1H), 1.22-1.15 (s, 9H). (Shown as single rotamer at 100 °C).

^{19}F NMR (376 MHz, $CDCl_3$, 25°C) δ −60.3, −67.9.

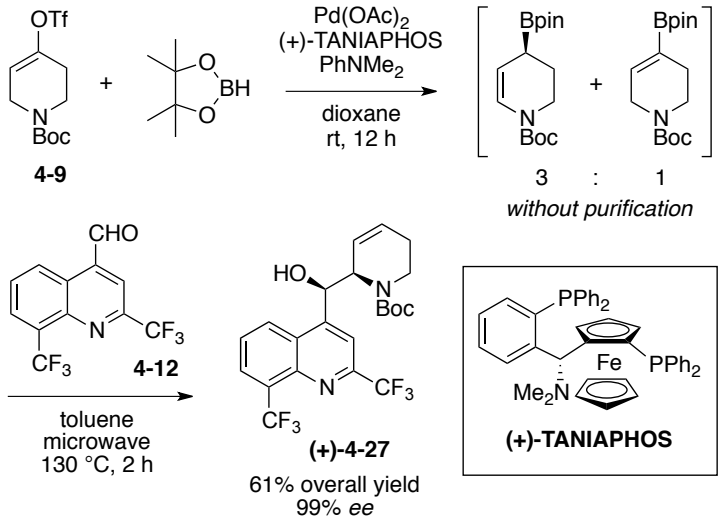
IR (microscope, cm^{-1}) 3409, 3025, 2982, 2935, 1670, 1603, 1585.

HRMS (ESI) for $(M+Na)^+$ $C_{22}H_{22}F_6N_2NaO_3$: calcd. 499.1427; found 499.1425.

$[\alpha]_D^{20}$: +66.4 (c = 0.56, $CHCl_3$) for 99% *ee*.

HPLC (Chiralcel OD): 2.5:97.5 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 254 nm, T_{major} = 32.1 min, T_{minor} = 36.7 min, *ee* = 99%.

4.5.5 (*S*)-*tert*-Butyl 2-((*S*)-(2,8-bis(trifluoromethyl)quinolin-4-yl) (hydroxy) methyl)-5,6 -dihydropyridine-1(*2H*)-carboxylate ((−)-4-27)



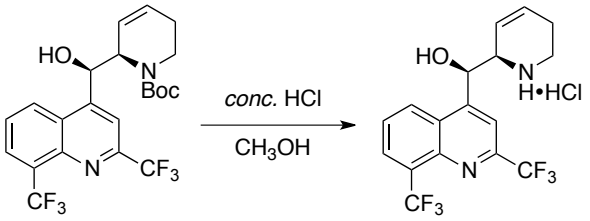
The title compound (−)-**4-27** was prepared with (−)-TANIAPHOS as the chiral ligand, utilizing the same procedure as for (+)-**4-27** mentioned above. Silica gel flash column chromatography (50% ethyl acetate/hexane) yielded **(+)-4-27** (1.06 g, 56% overall yield, 99% *ee*) as a colorless oil.

The **^{1}H-**, **^{13}C-**, **^{19}F-NMR**, **IR** and **HRMS** data were identical to that of (+)-**4-27**.

$[\alpha]_D^{20}$: −67.6 (c = 0.17, $CHCl_3$) for 99% *ee*.

HPLC (Chiralcel OD): 2.5:97.5 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 36.1 min, *ee* = 99%.

4.5.6 (*R*)-(2,8-Bis(trifluoromethyl)quinolin-4-yl)((*R*)-1,2,5,6-tetrahydro pyridin-2-yl)methanol hydrochloride salt (−)-4-31



(+)-4-27 **(–)-4-31**

The purified compound (+)-**4-27** (476 mg, 1.0 mmol) was dissolved in MeOH (10 mL), and *conc.* HCl solution (900 μL, 10 mmol) was added to the solution dropwise. The resulting mixture was stirred for one hour. The solvents were removed under *vacuo*, affording the title compound (−)-**4-31** as a white solid without any further purification (338 mg, 82 % yield).

^{1}H NMR (400 MHz, CD_3OD) δ 8.62-8.52 (m, 1H), 8.33-8.27 (m, 1H), 8.232 (s, 1H), 7.96-7.89 (m, 1H), 6.02-6.06 (m, 1H), 5.76 (br s, 1H), 5.46-5.41 (m, 1H), 4.31-4.25 (br s, 1H), 3.51-3.45 (m, 1H), 3.22-3.15 (m, 1H), 2.58-2.50 (m, 1H), 2.39-2.33 (m, 1H). (OH resonance absent due to H/D exchange with CD_3OD).

^{13}C NMR (126 MHz, CD_3OD) δ 149.4, 148.0 (q, $J_{C\text{-}F}$ = 35.1 Hz), 143.7, 129.3 (q, $J_{C\text{-}F}$ = 5.0 Hz), 129.0 (q, $J_{C\text{-}F}$ = 30.4 Hz), 128.2, 128.1, 128.0, 126.8, 123.6 (q, $J_{C\text{-}F}$ = 273.3 Hz), 121.3, 121.2 (q, $J_{C\text{-}F}$ = 274.8 Hz), 115.9, 68.4, 58.2, 40.0, 21.4.

^{19}F NMR (376 MHz, CD_3OD) δ −60.0, −67.9.

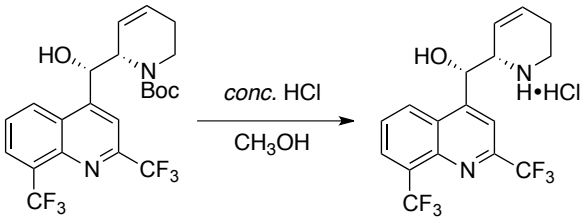
IR (microscope, cm^{-1}) 3221, 2922, 2851, 1674, 1602, 1585, 1309.

HRMS (ESI) for $(M+H)^+$ $C_{17}H_{15}F_6N_2O$: calcd. 377.1083; found 377.1077.

$[\alpha]_D^{20}$: −24.6 (c = 0.93, CH_3OH) for 99% *ee*.

M.P.: 254-256 °C (dec.)

4.5.7 (*S*)-(2,8-Bis(trifluoromethyl)quinolin-4-yl)((*S*)-1,2,5,6-tetrahydro pyridin-2-yl)methanol hydrochloride salt (+)-4-31



(−)-4-27 (+)-4-31

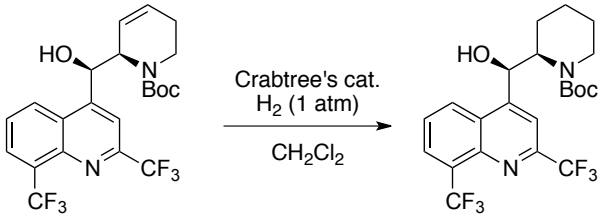
The title compound (+)-**4-31** was prepared from (−)-**4-27**, utilizing the same N-Boc deprotection/HCl protonation procedure as for (−)-**4-31** mentioned above (322 mg, 78% yield).

The **^{1}H-**, **^{13}C-**, **^{19}F-NMR**, **IR** and **HRMS** data were identical to that of (−)-**4-31**.

$[\alpha]_D^{20}$: +22.1 (c = 0.35, $CHCl_3$) for 99% *ee*.

M.P.: 254-255 °C (dec.)

4.5.8 (*R*)-*tert*-Butyl 2-((*R*)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy) methyl) piperidine-1-carboxylate (−)-4-32



(+)-**4-27** 99% *ee* (−)-**4-32** 99% *ee*

Compound (+)-**4-27** (476 mg, 1.00 mmol) and Crabtree's catalyst (40 mg, 0.050 mmol) were mixed in a flame-dried round bottom flask. Dichloromethane (20 mL) was added, and a balloon containing hydrogen gas was applied. The resulting mixture was stirring for 48 hours at room temperature. The solvent was then evaporated to yield a crude yellow oil, which was directly subjected to silica gel flash chromatography (50% ethyl acetate/hexane) to afford the title product (−)-**4-32** as a colorless oil (464 mg, 97% yield, 99% *ee*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 7.2 Hz, 1H), 7.92 (br s, 1H), 7.74 (dd, *J* = 8.4, 7.2 Hz, 1H), 5.70-5.57 (m, 1H), 4.65 (br s, 1H), 4.38-3.95 (m, 2H), 3.25-2.98 (m, 2H), 1.78-1.47 (m, 13H), 1.24-1.08 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 150.9, 148.3 (q, $J_{C\text{-}F}$ = 35.1 Hz), 144.2, 129.6 (q, $J_{C\text{-}F}$ = 30.4 Hz), 129.0 (q, $J_{C\text{-}F}$ = 5.3 Hz), 128.1, 127.5, 127.2, 123.5 (q, $J_{C\text{-}F}$ = 273.8 Hz), 121.2 (q, $J_{C\text{-}F}$ = 275.6 Hz), 116.5, 81.2, 56.7, 41.3, 28.4, 25.2, 24.7, 19.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ −60.4, −67.9.

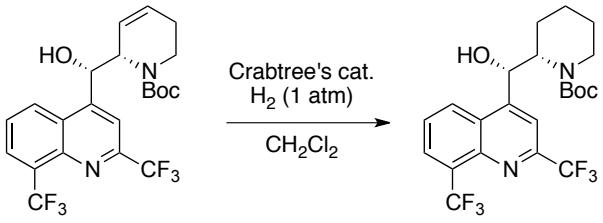
IR (Microscope, cm^{-1}) 3404, 2936, 2869, 1663, 1603, 1585, 1309.

HRMS (ESI) for $(M+H)^+$ $C_{22}H_{25}F_6N_2O_3$: calcd. 479.1764; found 479.1763; for $(M+Na)^+$ $C_{22}H_{24}F_6N_2NaO_3$: calcd. 501.1583; found 501.1581.

$[\alpha]_D^{20}$: −43.3 (c = 0.42, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 15.45 min, *ee* = 99%.

4.5.9 (*S*)-*tert*-Butyl 2-((*S*)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy) methyl) piperidine-1-carboxylate (+)-4-32



(–)-**4-27** 99% *ee* (+)-**4-32** 99% *ee*

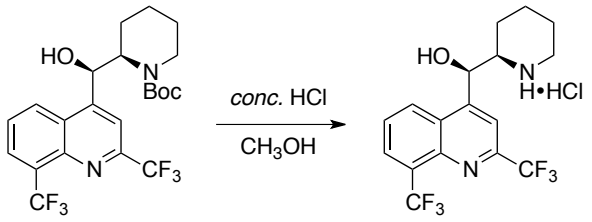
The title compound (+)-**4-32** was prepared from (–)-**4-27**, utilizing the same procedure as for (−)-**4-32** mentioned above (449 mg, 94% yield).

The **^{1}H-**, **^{13}C-**, **^{19}F-NMR**, **IR** and **HRMS** data were identical to that of (−)-**4-32**.

$[\alpha]_D^{20}$: +44.9 (c = 0.30, CH_3OH) for 99% *ee*.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 12.16 min, *ee* = 99%.

4.5.10 (−)-*threo*-Mefloquine (–)-4-15



(–)-4-32 99% *ee* (–)-**4-15**

Compound (−)-**4-15** was prepared from (−)-**4-32**, utilizing the same N-Boc deprotection/HCl protonation procedure as for (−)-**4-31** mentioned above (273 mg, 93% yield, 99% *ee*).

^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (d, *J* = 8.4 Hz, 1H), 8.31 (d, *J* = 7.2 Hz, 1H), 8.17 (s, 1H), 7.93 (dd, *J* = 8.4, 7.2 Hz, 1H), 5.58 (d, *J* = 6.8 Hz, 1H), 3.53 (ddd, *J*

= 10.0, 6.8, 2.8 Hz, 1H), 3.42-3.35 (m, 1H), 2.94 (dt, J = 12.8, 2.8 Hz, 1H), 1.90-1.63 (m, 4H), 1.63-1.39 (m, 2H). (OH resonance absent due to H/D exchange with CD_3OD).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 148.0 (q, $J_{C\text{-}F}$ = 35.4 Hz), 143.7, 129.3 (q, $J_{C\text{-}F}$ = 5.3 Hz), 129.0 (q, $J_{C\text{-}F}$ = 30.1 Hz), 128.1, 127.9, 127.0, 123.6 (q, $J_{C\text{-}F}$ = 272.8 Hz), 121.3 (q, $J_{C\text{-}F}$ = 274.8 Hz), 115.9, 69.6, 61.0, 44.7, 25.7, 21.9, 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ −61.6, −69.5.

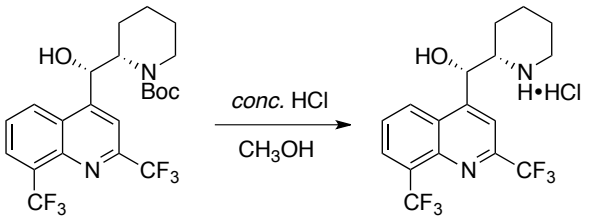
IR (microscope, cm^{-1}) 3323, 3080, 2959, 2939, 2860, 2819, 1668, 1601, 1584, 1313.

HRMS (ESI) for $(M+H)^+$ $C_{17}H_{17}F_6N_2O$: calcd. 379.1240; found 379.1232; for $(M+Cl)^-$ $C_{17}H_{17}Cl_2F_6N_2O$: calcd. 449.0628; found 449.0636.

$[\alpha]_D^{20}$: −49.9 (c = 0.91, CH_3OH) for 99% ee.

M.P.: 250-251 °C.

4.5.11 (+)-*threo*-Mefloquine (+)-4-15



(+)-4-32 99% *ee* (+)-**4-15**

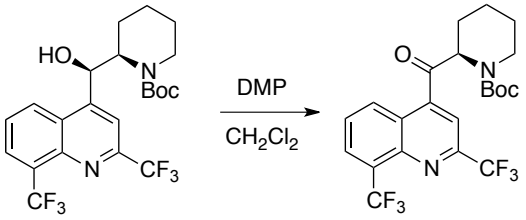
Compound (+)-**4-15** was prepared from (+)-**4-32**, utilizing the same N-Boc deprotection/HCl protonation procedure as for (−)-**4-31** mentioned above (233 mg, 95% yield, 99% *ee*).

The **^{1}H-**, **^{13}C-**, **^{19}F-NMR**, **IR** and **HRMS** data were identical to that of (−)-**4-15**.

$[\alpha]_D^{20}$: +48.6 (c = 0.31, $CHCl_3$) for 99% ee.

M.P.: 251-253 °C.

4.5.12 (*R*)-*tert*-Butyl 2-(2,8-bis(trifluoromethyl)quinoline-4-carbonyl) piperidine-1-carboxylate (+)-4-37



(–)-**4-32** 99% *ee* (+)-**4-37**

To a flame-dried round bottom flask, Dess–Martin periodinane (2.0 mmol, 0.8 g) and CH_2Cl_2 (20 mL) were added. The flask was then flushed with nitrogen. In another flame-dried round bottom flask, the compound (−)-**4-32** (1.0 mmol, 0.5 g) was dissolved in 10 mL CH_2Cl_2, and the mixture was slowly added into the Dess–Martin periodinane solution at 0°C. The reaction mixture was warmed up to room temperature over 3h. The solvent was evaporated to yield a crude yellow oil, which was dissolved in diethyl ether (20 mL) and washed with *sat.* aqueous $NaHSO_3$ solution (20 mL) and *sat.* aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried over anhydrous Na_2SO_4. The solid was filtered and the filtrate was concentrated in *vacuo*. The residue was subjected to silica gel flash chromatography (20% ethyl acetate/hexane) to afford the title compound (+)-**4-37** as a colorless oil (423 mg, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$, RT) δ 8.48 (d, *J* = 8.5 Hz, 0.7H), 8.43-8.36 (m, 0.3H), 8.31-8.24 (m, 1H), 8.11 (s, 0.7H), 8.00-7.96 (m, 0.3H), 7.83 (dd, *J* = 10.1, 5.7 Hz, 1H), 5.61-5.54 (m, 0.7H), 5.54-5.49 (m, 0.3), 4.17-4.10 (m, 0.3H), 3.95-3.87 (m, 0.7H), 3.08-2.93 (m, 1H), 2.22-2.13 (m, 0.8H), 2.08-1.98 (m, 0.5H), 1.87-1.73 (m, 2H), 1.73-1.63 (m, 1H), 1.51 (s, 3H), 1.46 (s, 6H). (Rotamers present at room temperature).

^{1}H NMR (400 MHz, $C_6D_5CD_3$, −30°C) δ 8.35 (d, *J* = 8.5 Hz, 0.7H), 8.0 (d, *J* = 8.5 Hz, 0.3H), 7.94 (s, 0.7H), 7.66 (s, 0.2H), 7.49 (d, *J* = 7.0 Hz, 0.3H), 7.44 (d, *J* = 7.1 Hz, 1H), 5.18 (br s, 0.7H), 5.08-5.05 (m, 0.3), 4.23 (d, *J* = 13.4 Hz, 0.3H), 3.68 (d, *J* = 13.3 Hz, 0.7H), 3.04-2.94 (m, 0.2H), 2.86-2.76 (m, 0.7H), 1.68-1.60 (m, 0.7H), 1.40 (s, 2H), 1.25 (s, 7H), 1.22-1.01 (m, 5H). (Rotamers present at −30°C).

^{1}H NMR (400 MHz, $C_6D_5CD_3$, +100°C) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.1 Hz, 1H), 5.18-5.12 (m, 1H), 3.81-3.66 (m, 1H), 2.97-2.88 (m, 1H), 1.78-1.66 (m, 1H), 1.41-1.09 (m, 14H). (Shown as single rotamer at 100°C.)

^{13}C NMR (127 MHz, $CDCl_3$, 25°C) δ 203.2, 155.6, 148.0 (q, $J_{C\text{-}F}$ = 35.9), 145.3, 144.4, 129.5, 129.3, 128.9, 128.6, 125.5, 123.4 (q, $J_{C\text{-}F}$ = 273.6), 120.9 (q, $J_{C\text{-}F}$ = 275.6), 115.3, 80.9, 59.5, 43.3, 28.2, 24.9, 24.8, 20.7 (Rotamers present at 25°C; only signals from the major rotamer were listed).

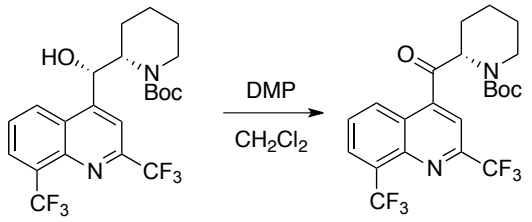
^{19}F NMR (376 MHz, $CDCl_3$, 25°C) δ −60.3, −67.8.

IR (microscope, cm^{-1}) 2943, 2865, 1685, 1597, 1584, 1514, 1313.

HRMS (ESI) for $(M+H)^+$ $C_{22}H_{23}F_6N_2O_3$: calcd. 477.1607; found 477.1613; for $(M+Na)^+$ $C_{22}H_{22}F_6N_2NaO_3$: calcd. 499.1427; found 499.1427.

$[\alpha]_D^{20}$: +33.9 (c = 0.62, $CHCl_3$).

4.5.13 (*S*)-*tert*-Butyl 2-(2,8-bis(trifluoromethyl)quinoline-4-carbonyl) piperidine-1-carboxylate (−)-4-37



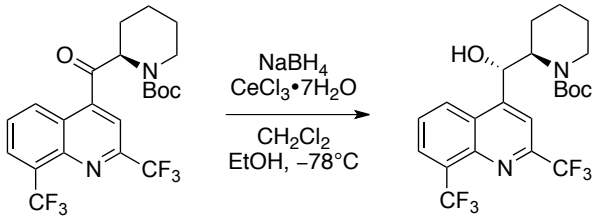
(+)-**4-32** 99% *ee* (−)-**4-37**

The compound (−)-**4-37** was prepared from (+)-**4-32**, utilizing the same DMP oxidation procedure as for (+)-**4-37** mentioned above (447 mg, 94% yield).

The **^{1}H-**, **^{13}C-**, **^{19}F-NMR**, **IR** and **HRMS** data were identical to that of (+)-**4-37**.

$[\alpha]_D^{20}$: −35.7 (c = 0.72, $CHCl_3$).

4.5.14 (*R*)-*tert*-Butyl 2-((*S*)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy) methyl) piperidine-1-carboxylate (+)-4-38



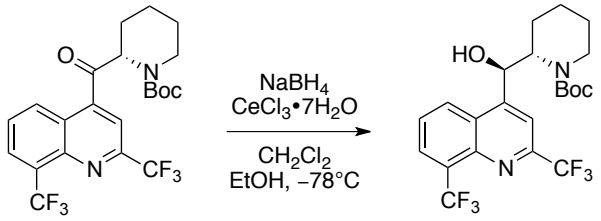
(+)-**4-37** (+)-**4-38**, 65%

Compound (+)-**4-38** was prepared from the ketone (+)-**4-37** according to the literature reported procedure (200 mg, 65% yield).[163]

Spectral data match those previously reported.[147]

$[\alpha]_D^{20}$: +14.8 (c = 0.87, $CHCl_3$).

4.5.15 (*S*)-*tert*-Butyl 2-((*R*)-(2,8-bis(trifluoromethyl)quinolin-4-yl)(hydroxy) methyl) piperidine-1-carboxylate (−)-4-38



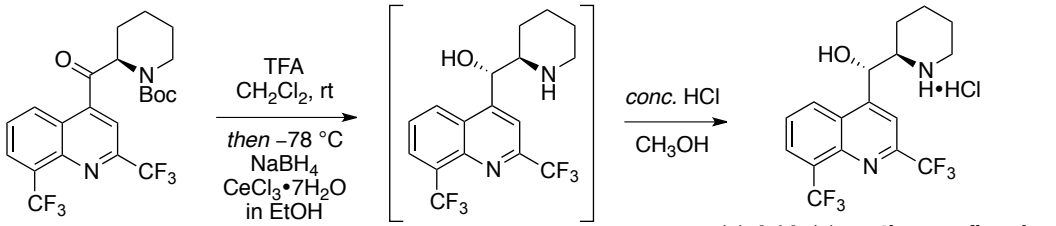
(−)-**4-37** (−)-**4-38**, 68%

Compound (−)-**4-38** was prepared from the ketone (−)-**4-37** according to the literature reported procedure (209 mg, 68% yield).[163]

Spectral data match those previously reported.[147]

$[\alpha]_D^{20}$: −13.7 (c = 1.00, $CHCl_3$).

4.5.16 (+)-*erythro*-Mefloquine (+)-4-14



(+)-**4-37** *withou purification* (+)-**4-14**, (+)-***erythro*-mefloquine**
$[\alpha]_D^{20}$: +29.83 (0.45 in CH_3OH)

Compound (+)-**4-37** (1.00 mmol, 476 mg) was dissolved in CH_2Cl_2 (10 mL) in a flame-dried round bottom flask, followed by the addition of TFA (3.00 mmol, 230 μL). The reaction mixture was stirred for one hour at room temperature, then cooled down to −78 °C. $CeCl_3$•$7H_2O$ (6.0 mmol, 2.3 g) was dissolved in EtOH (10 mL), and the solution was added at −78 °C. After stirring for 10 minutes, $NaBH_4$ (6.00 mmol, 228 mg) in EtOH (10 mL) solution was added over one hour. After another two hours, the reaction was quenched with H_2O and the mixture was allowed to warm to room temperature. The aqueous layer was extracted with

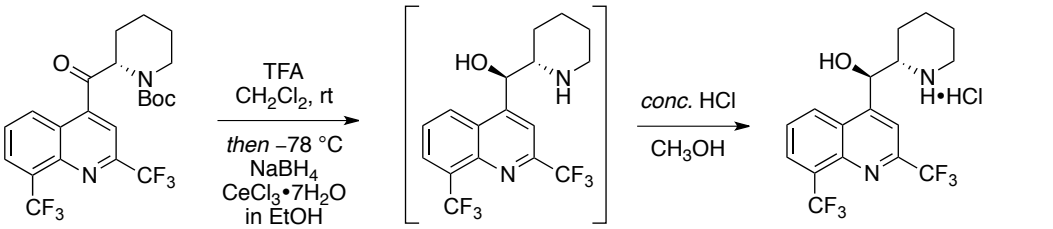
CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a crude material. Without further purification, the crude was dissolved into CH_3OH (15 mL), which was followed by slow addition of *conc.* HCl solution (900 μL, 10.0 mmol). The resulting mixture was stirred for one hour at room temperature. The solvents were then removed under *vacuo*, affording the (+)-*erythro*-mefloquine (+)-**4-14** as a white salt without any purification (323 mg, 85% yield).

Spectral data match those previously reported.[141]

$[\alpha]_D^{20}$: +29.8 (c = 0.45, CH_3OH).

M.P.: 279-280 °C.

4.5.17 (−)-*erythro*-Mefloquine (−)-4-14



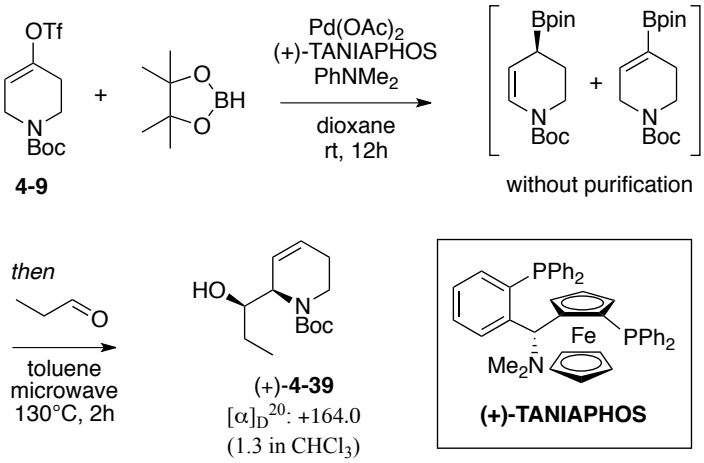
The compound (−)-**4-14** was prepared from (−)-**4-37**, utilizing the same one-pot procedure as described for the preparation of (+)-**4-14** (322 mg, 83% yield).

Spectral data match those previously reported.[141]

$[\alpha]_D^{20}$: −31.5 (c = 0.78, CH_3OH).

M.P.: 278-280 °C.

4.5.18 (*R*)-*tert*-Butyl 2-((*R*)-1-hydroxypropyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (+)-4-39



The compound (+)-**4-39** was prepared utilizing the same one-pot procedure as mentioned for the preparation of (+)-**4-27** (378 mg, 61% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01-5.98 (m, 1H), 5.71-5.62 (m, 1H), 4.48-3.98 (m, 2H), 3.61 (dt, *J* = 7.9, 3.3 Hz, 1H), 3.11-2.92 (m, 1H), 2.32-2.14 (m, 1H), 1.99-1.91 (m, 1H), 1.73-1.61 (m, 1H), 1.52-1.41 (m, 10H), 1.03 (t, *J* = 7.4 Hz, 3H). (Rotamers present at room temperature).

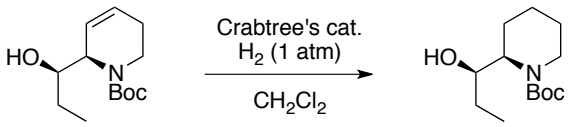
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 127.5, 125.2, 80.2, 74.9, 56.5, 38.4, 28.5, 26.8, 24.8, 9.5. (Rotamers present at room temperature; only singles from the major rotamer were listed).

IR (Microscope, cm^{-1}) 3462, 3035, 2975, 2932, 2879, 1692, 1674, 1421, 1173.

HRMS (ESI) for $(M+Na)^+$ $C_{13}H_{23}NNaO_3$: calcd. 264.1570; found 264.1566.

$[\alpha]_D^{20}$: +164.0 (c = 1.30, $CHCl_3$).

4.5.19 (*R*)-*tert*-Butyl 2-((*R*)-1-hydroxypropyl)piperidine-1-carboxylate (+)-4-40



(+)-**4-39** (+)-**4-40**

$[\alpha]_D^{20}$: +38.8 (c 1.1 in $CHCl_3$)

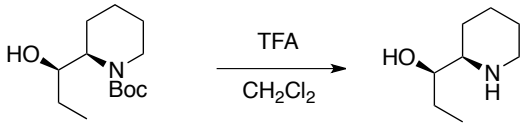
Lit.: $[\alpha]_D^{20}$: +24.3 (c 1.0 in $CHCl_3$)

The *N*-Boc-conhydrine (+)-**4-40** was prepared from the compound (+)-**4-39**, utilizing the same hydrogenation procedure as mentioned for the preparation of (−)-**4-32** (210 mg, 95% yield).

Spectral data match those previously reported.[167]

$[\alpha]_D^{20}$: +38.8 (c = 1.10, $CHCl_3$). (*Lit.* [167] : +24.3, c 1.0 in $CHCl_3$).

4.5.20 (+)-β-Conhydrine (+)-4-41



(+)-**4-40** (+)-**4-41**, (+)-β-**conhydrine**

$[\alpha]_D^{20}$: +9.7 (c 1.1 in EtOH)

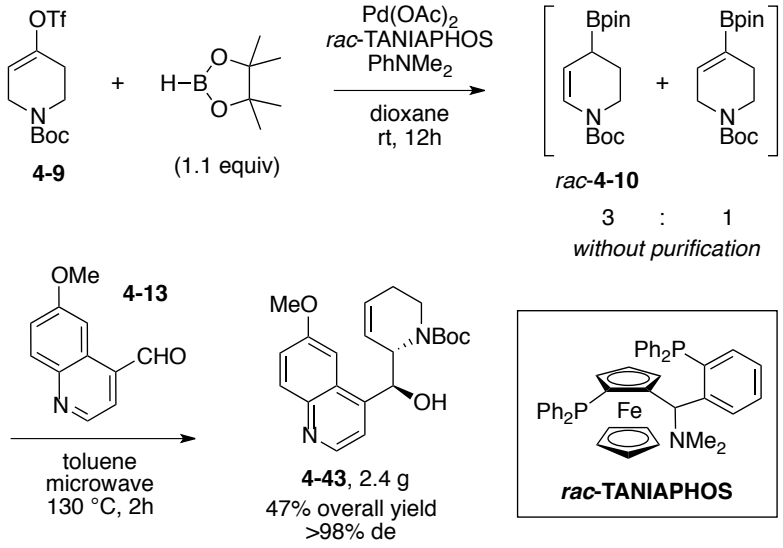
Lit.: $[\alpha]_D^{20}$: +8.3 (c 0.9 in EtOH)

The (+)-β-conhydrine (+)-**4-41** was prepared from compound (+)-**4-40**, according to the literature reported procedure (68 mg, 90% yield). [167]

Spectral data match those previously reported. [167]

$[\alpha]_D^{20}$: +9.7 (c = 1.1 in EtOH). (*Lit.* [167]: +8.3, c 0.9 in EtOH).

4.5.21 Racemic (*S*)-*tert*-butyl 2-((*S*)-hydroxy(6-methoxyquinolin-4-yl)methyl)-5,6-dihydropyridine-1(2*H*)-carboxylate 4-43



The title compound **4-43** was prepared utilizing the same one-pot procedure as mentioned for the preparation of (+)-**4-27**. (2.4 g, 52 % overall yield)

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 8.73-8.66 (m, 1H), 8.20-7.94 (m, 1H), 7.54-7.40 (m, 1.5H), 7.36-7.29 (m, 1H), 7.22-7.13 (m, 0.5H), 6.09-5.74 (m, 1H), 5.64-5.28 (m, 1.5H), 5.13-4.41 (m, 1.5H), 4.30-4.00 (m, 1H), 3.89 (s, 3H), 3.75-3.40 (m, 1H), 3.08-2.95 (m, 1H), 2.23-2.12 (m, 1H), 2.03-1.90 (m, 1H), 1.63-1.34 (m, 5H), 1.18-0.85 (m, 4H). (Rotamers present at 25 °C)

^{1}H NMR (500 MHz, DMSO-d6, 110 °C) δ 8.68 (d, 1H, J = 4.4 Hz), 7.94 (d, 1H, J = 9.3 Hz), 7.53 (s, 1H), 7.48 (d, 1H, J = 4.6 Hz), 7.39 (dd, 1H, J = 2.8, 9.2 Hz), 5.96-5.87 (m, 1H), 5.81-5.69 (m, 1H), 5.54-5.45 (m, 1H), 5.39 (s, 1H), 4.76 (s, 1H), 3.95-3.84 (m, 3H), 3.10-2.78 (m, 2H), 2.04-1.95 (m, 1H), 1.88-1.81 (m, 1H), 1.22-0.94 (m, 9H).

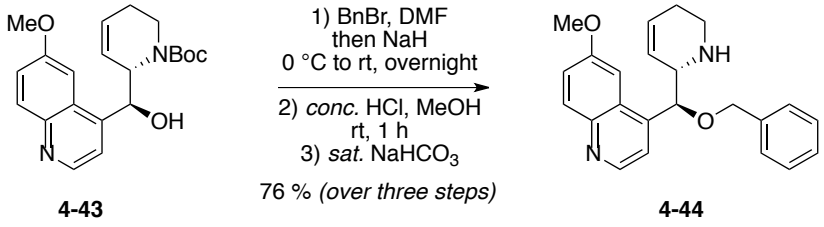
^{13}C NMR (125 MHz, DMSO-d6, 110 °C) δ 156.7, 153.5, 146.6, 146.3, 143.5, 130.5, 126.7, 126.4, 125.3, 120.0, 119.2, 102.8, 77.9, 70.1, 55.9, 55.1, 37.1, 27.2,

23.6.

IR (Microscope, cm^{-1}) 3374, 3188, 3005, 2975, 2930, 2854, 1688, 1622, 1510, 1417, 1243, 1170.

HRMS (ESI) for $(M+H)^+$ $C_{21}H_{26}N_2O_4$: calcd. 371.1965; found 371.1961.

4.5.22 Racemic 4-((*S*)-(benzyloxy)((*S*)-1,2,5,6-tetrahydropyridin-2-yl)methyl)-6-methoxyquinoline 4-44



4-43 **4-44**

Compound **4-43** (1.00 mmol, 370 mg) was dissolved in DMF (10 mL) in a flame-dried round bottom flask, followed by the addition of benzyl bromide (1.50 mmol, 257 mg). The reaction mixture was stirred for 30 min at room temperature, then cooled down to 0 °C. Sodium hydride (2.0 mmol, 80 mg, 60 % dispersion in mineral oil) was added in three portions. The resulting mixture was allowed to warm up to room temperature overnight. The reaction was cooled backed to 0 °C before quenched with a slow addition of H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 three times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to give a crude material. Without further purification, the crude was dissolved into CH_3OH (15 mL), which was followed by slow addition of *conc.* HCl solution (900 μL, 10.0 mmol) at room temperature. The resulting mixture was stirred for one hour at room temperature before quenched by a slow addition of saturated $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with ethyl acetate (10 mL) three times. The combined organic extracts were washed by brine (10 mL) and dried over anhydrous sodium sulfate. After filtration and

solvent removal under *vacuo*, a crude oil was obtained, which was subjected to silica gel flash column chromatography (50 % EtOAc/hexane) for purification. The pure compound **4-44** was finally obtained as a clear oil (274 mg, 76 % overall yield).

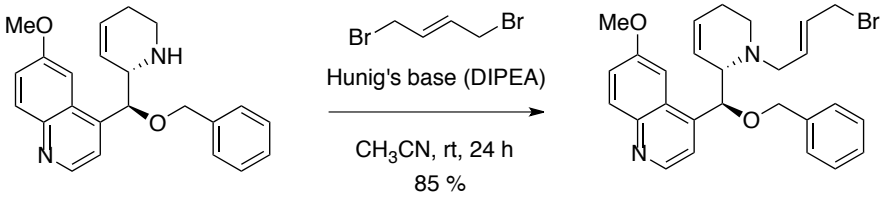
^{1}H NMR (498 MHz, CD_2Cl_2) δ 8.78 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 4.4 Hz, 1H), 7.47 (d, *J* = 2.4 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.36-7.29 (m, 5H), 5.76-5.72 (m, 1H), 5.02 (d, *J* = 8.6 Hz, 1H), 4.96-4.93 (m, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 3.88 (s, 3H), 3.84-3.82 (m, 1H), 3.10-3.06 (m, 1H), 2.90-2.85 (m, 2H, overlap with NH), 2.21-2.14 (m, 1H), 2.08-2.01 (m, 1H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 157.6, 147.6, 144.8, 143.1, 137.9, 131.6, 128.3, 128.2, 128.1, 127.8, 125.3, 121.7, 120.5, 102.2, 80.2, 71.0, 58.9, 55.5, 40.5, 29.7, 25.5.

IR (microscope, cm^{-1}) 3063, 3031, 3004, 2918, 2850, 2833, 1620, 1589, 1570.

HRMS (ESI) for $(M+H)^+$ $C_{23}H_{25}N_2O_3$: calcd. 361.1911; found 361.1906.

4.5.23 4-((*S*)-(Benzyloxy)((*S*)-1-((*E*)-4-bromobut-2-en-1-yl)-1,2,5,6-tetrahydropyridin-2-yl)methyl)-6-methoxyquinoline 4-45



4-44 **4-45**

Compound **4-44** (0.50 mmol, 180 mg) was dissolved in CH_3CN (5 mL) in a flame-dried round bottom flask, followed by the addition of Hunig's base *N*,*N*-diisopropylethylamine (1.0 mmol, 130 mg) at room temperature. This was followed by the addition of (*E*)-1,4-dibromobut-2-ene (0.60 mmol, 130 mg), and

the resulting mixture was allowed to stir for 24 min at room temperature. Upon conventional acid-base wash, the crude product was obtained as a dark brown oil, which was subjected to silica gel flash column chromatography (25 % EtOAc/hexane) for purification. The desired pure tertiary amine **4-45** was finally obtained as a clear oil (210 mg, 85 % overall yield).

^{1}H-NMR (400 MHz, acetone-d6) δ 8.72 (d, *J* = 4.4 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 2.8 Hz, 1H), 7.51 (d, *J* = 4.4 Hz, 1H), 7.37-7.30 (m, 5H), 7.28-7.24 (m, 1H), 5.84-5.75 (m, 2H), 5.60-5.54 (m, 1H), 5.35-5.29 (m, 2H), 4.48 (s, 2H), 3.88 (s, 3H), 3.86-3.83 (m, 2H), 3.58-3.55 (m, 1H), 3.38-3.32 (m, 1H), 3.28-3.22 (m, 1H), 3.04-2.97 (m, 1H), 2.64-2.58 (m, 1H), 2.10-2.05 (m, 1H), 1.70-1.64 (m, 1H).

^{13}C NMR (126 MHz, acetone-d6) δ 157.3, 147.3, 144.7, 138.7, 134.1, 131.4, 129.4, 128.3, 128.1, 127.51, 127.44, 127.32, 126.1, 121.2, 120.7, 102.7, 80.5, 71.1, 62.3, 56.0, 55.0, 45.1, 32.5, 21.1.

IR (microscope, cm^{-1}) 3030, 3004, 2927, 2856, 1620, 1587.

HRMS (ESI) for $(M+H)^+$ $C_{27}H_{30}BrN_2O_2$: calcd. 493.1485; found 493.1478.

4.6 References

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Chapter 5 Ligand-Controlled Regiodivergent and Stereospecific Suzuki-Miyaura Cross-Coupling of Chiral Heterocyclic Allylic Boronates to Access Chiral Heterocycles*

5.1 Introduction

As discussed in Chapter 4, chiral heterocylic allylic boronates belong to a class of valuable synthetic intermediates, especially in creating biologically important target molecules. In addition to those common attractive features of organoboronates discussed in Chapter 1, the structurally unique characteristics of chiral heterocyclic allylic boronates highlight several advantages: 1) chiral boronate moieties can be involved in many chemical transformations with excellent chemo- and stereoselectivity; 2) chiral heterocyclic units constitute the core structures in many biologically important natural products and pharmaceutical drugs; and 3) these structurally unique chiral heterocyclic allylic boronates are accessible in gram scale with high enantiomeric purity.[182,183] These advances have been demonstrated in practical applications such as the asymmetric total synthesis of several targets with important antimalarial activities, including the efficient total synthesis of all four stereoisomers of mefloquine[183] as well as the rapid construction of the quinine precursor **4-45** (Figure 5-1). In spite of these advantages, applications of chiral heterocyclic allylic boronates have been limited to aldehyde allylboration reactions. As a result, these intriguing chiral boronates can only be used to construct α-hydroxyalkyl heterocycles (Figure 5-1). To expand their scope of applications, we decided to investigate other synthetic transformations of these chiral heterocyclic allylic boronates. In this regard, we

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set out to examine other representative stereospecific transformations that involve chiral alkylboronates.

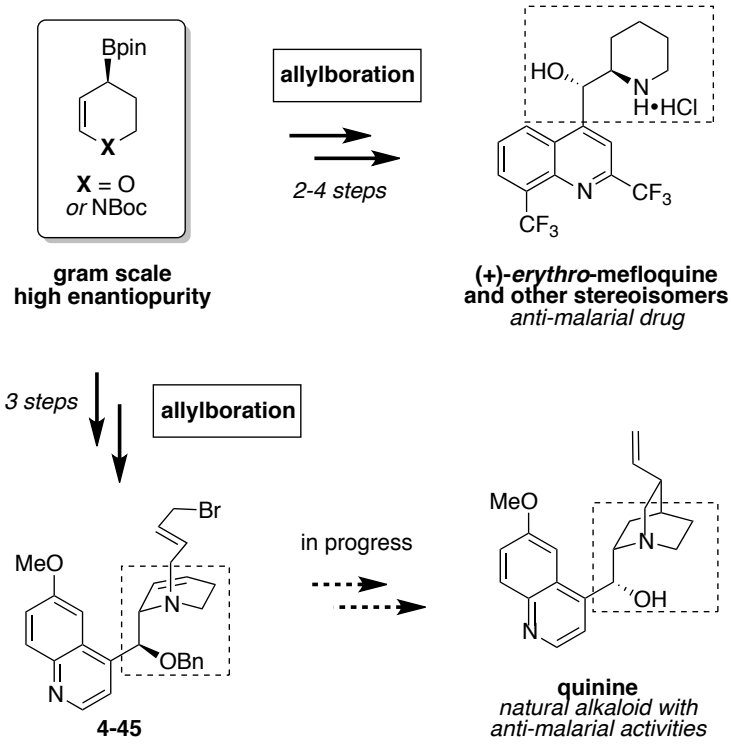


Figure 5-1: Applications of chiral heterocyclic allylic boronates in the asymmetric total synthesis of natural products and pharmaceutical drugs.

As discussed in Chapter 1, $C(sp^2)$-$C(sp^2)$ bond formation has been the main focus within the realm of Suzuki-Miyaura cross-coupling reactions. The coupling of sp^3-hybridized organoboron compounds, however, remains notoriously challenging (Section 1.2.6). As shown in the general catalytic cycle for the palladium catalyzed Suzuki-Miyaura cross-coupling of secondary alkylboronates (Figure 5-2), in theory the typical oxidative addition/transmetallation/reductive elimination sequence would give rise to the desired $C(sp^3)$-$C(sp^2)$ bond formation. There are, however, several pitfalls associated with the use of alkylboronates. The transmetallation step involving the alkylboronates is slow.[184] The slow transmetallation is also accompanied by several side reactions such as β-hydride

elimination, reinsertion and irreversible protodeboronation, potentially leading to a mixture of side products. When using chiral secondary alkylboronates as coupling partners, these issues are further compounded by the control of stereoselectivity as well as the uncooperative relationship between nucleophilicity and configurational stability.[185]

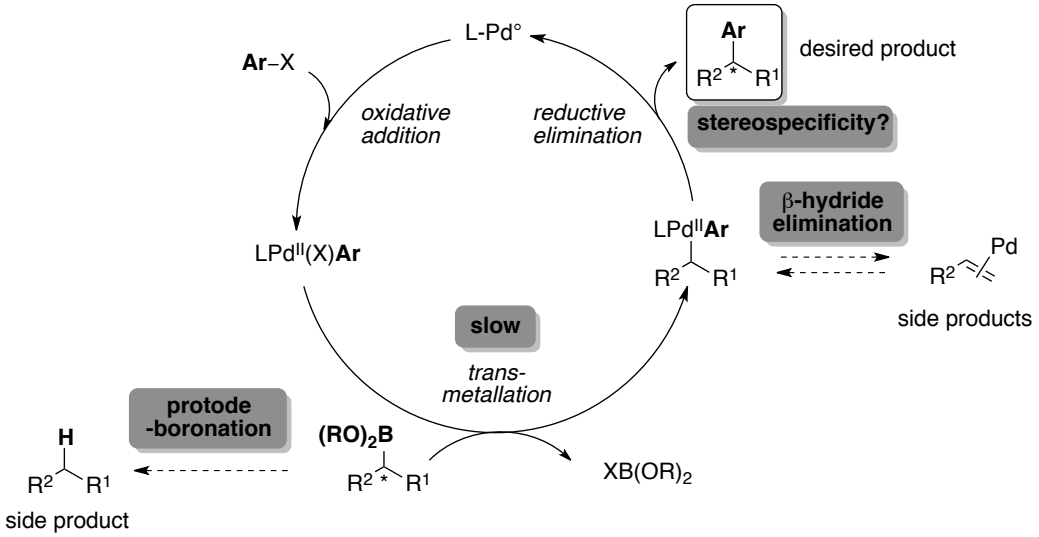


Figure 5-2: Proposed catalytic cycle for the Suzuki-Miyaura cross-coupling of sp^3-hybridized organoboronates.

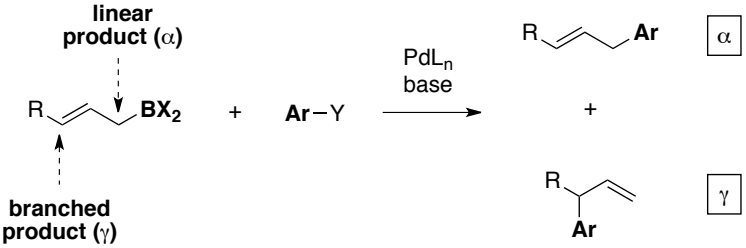
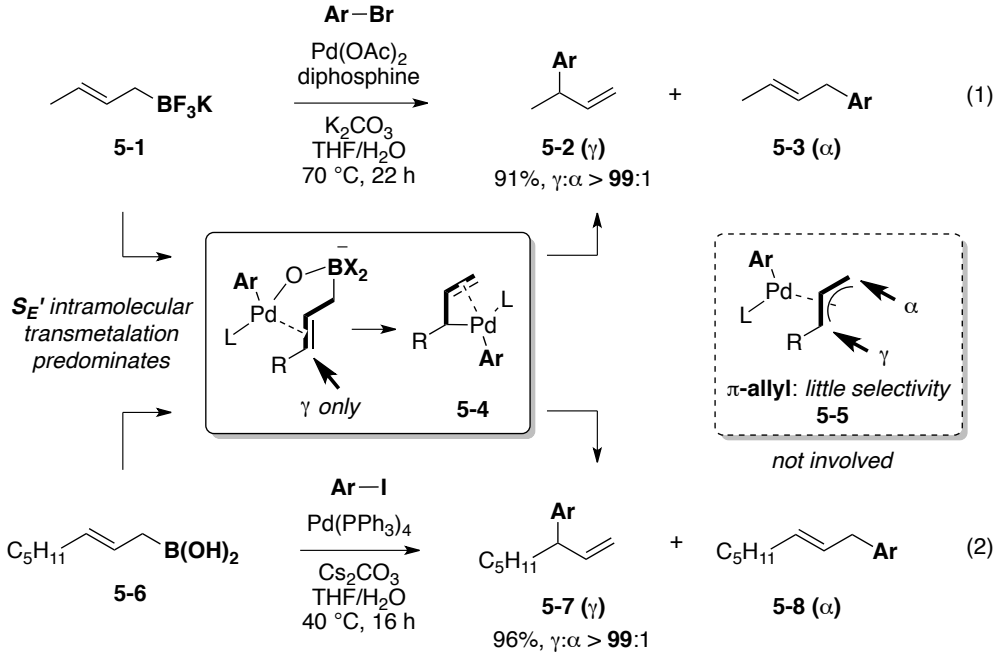


Figure 5-3: Regiochemistry issue in the Suzuki-Miyaura reaction of allylic boronates.

Although some progress has been realized in recent years (see Section 1.2.6),[186] control of stereoselectivity is indeed viewed as one of the final frontiers in the Suzuki-Miyaura reaction.[187] With allylic boronates, the challenge is further

aggravated by the possibility of forming branched (γ) and linear (α) regioisomers (Figure 5-3).

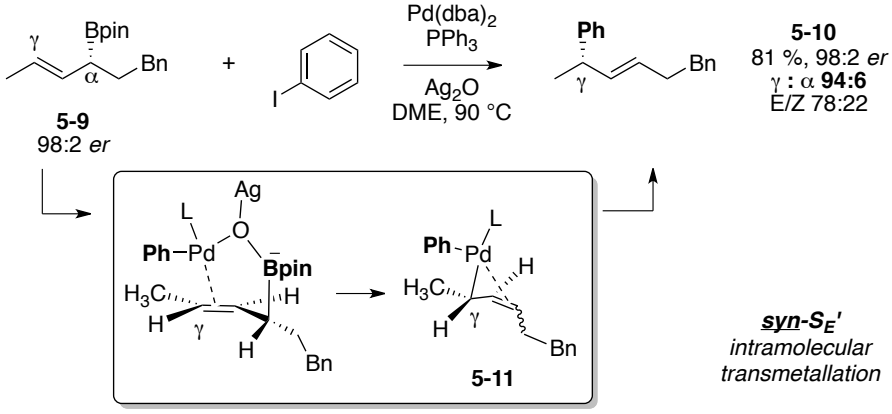


Scheme 5-1: γ-Selective Suzuki-Miyaura reaction of primary allyl boron compounds.

To address this challenge, Miyaura and co-workers[188] demonstrated a γ-selective Suzuki-Miyaura reaction of potassium allyltrifluoroborates (**5-1**) with arylbromides catalyzed by a Pd(0)/diphosphine complex (Scheme 5-1, Equation 1). The γ regioisomer (branched product **5-2**) was obtained with high yield and up to 99:1 regioselectivity. Alternatively, the Szabó Group[189] applied allyl boronic acid (**5-6**) as the nucleophilic cross-coupling partner and triphenylphosphine-ligated palladium as the catalyst, which gave rise to the same level of reactivity and regioselectivity in the formation of γ regioisomer **5-7** (Scheme 5-1, Equation 2). In both examples, the predominance of the branched/γ regioisomer suggested an alkene-directed S_E' intramolecular transmetallation mechanism (with allylic rearrangement, **5-4**). The formation of η^3 π-allyl complex (**5-5**) is not likely

involved, which would otherwise lead to the formation of a mixture of both γ and α regioisomers with none or little regioselectivity (Scheme 5-1).

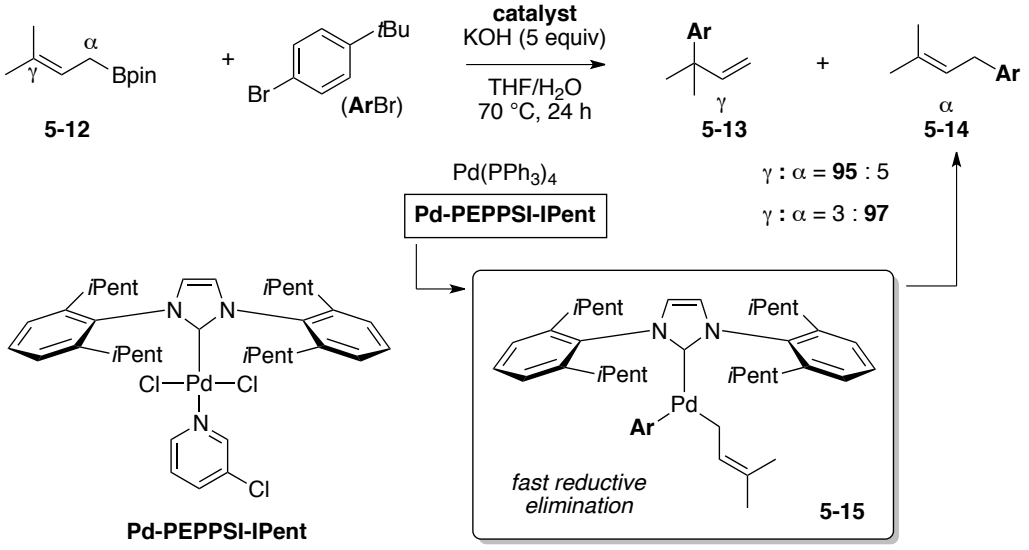
Recently, Crudden, Aggarwal and co-workers[190] described the first stereospecific Suzuki-Miyaura cross-coupling of chiral secondary allylic boron substrates (**5-9**), where they applied a triphenylphosphine-ligated palladium complex as the catalyst and silver oxide as the base. In Scheme 5-2, despite the low *E*/*Z* selectivity, high γ-regioselectivity (γ:α = 94:6) and high retention of optical purity (98:2 *er*) were observed for the corresponding allylation product **5-10**. Mechanistic studies were also conducted by the same authors, which further supported the alkene-directed S_E' intramolecular transmetallation mechanism (**5-4**). Additionally, the stereoretentive outcome of the cross-coupling also indicated that the S_E' transmetallation proceeds in a *syn* fashion, as shown in the intermediate **5-11** (Scheme 5-2).



Scheme 5-2: γ-Selective Suzuki-Miyaura reaction of enantioenriched secondary allylic boronic esters.

While the groups of Szabó, Miyaura (Scheme 5-1), Crudden and Aggarwal (Scheme 5-2) demonstrated the remarkable γ-regioselectivity for the Suzuki-Miyaura reaction of allyl boron nucleophiles, the Organ Group[191] developed the first complementary approach for the exclusive formation of α-regioisomers using

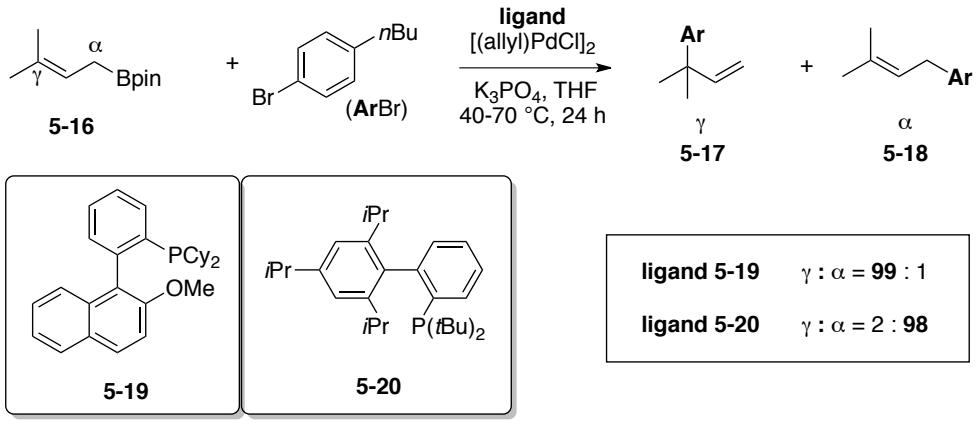
the carbene-ligated Pd-PEPPSI-IPENT as the catalyst (Scheme 5-3). In agreement with the regioselectivities observed by the Szabó Group (Scheme 5-1, Equation 2) when a triphenylphosphine-ligated palladium was used as the catalyst, the Suzuki-Miyaura cross-coupling reaction of allyl boron pinacolate **5-12** and arylbromide provided the γ-regioisomer **5-13** exclusively. In contrast, when using the NHC-ligated palladium complex (Pd-PEPPSI-IPENT) as the catalyst, the corresponding α-regioisomer **5-14** was afforded exclusively. The authors suggested that this unprecedented α-regioselectivitity was attributed to the bulky nature of the NHC ligand, which could facilitate a fast reductive elimination (intermediate **5-15**), while neither the alkene-directed S_E' intramolecular transmetallation (intermediate **5-4**) nor the formation of η^3 π-allyl complex (intermediate **5-5**) were involved.



Scheme 5-3: α-Selective Suzuki-Miyaura reaction of primary allylic boronic esters.

More recently, the Buchwald Group [192] developed a complementary set of palladium-catalyzed, ligand-controlled regiodivergent Suzuki-Miyaura cross-coupling conditions for primary allylic boronic esters. In Scheme 5-4, the use of ligand **5-19** lead to the exclusive formation of γ-regioisomer **5-17**. Alternatively,

the *t*-BuXPhos derived bulky ligand **5-20** displayed high selectivity for the production of α-regioisomer **5-18**, which again suggests that ligand's steric bulkiness plays a positive role in the enhancement of α-regioselectivity. In particular, these regiodivergent Suzuki-Miyaura cross-coupling protocols feature a broad substrate scope for both aryl and heteroaryl halides.



Scheme 5-4: Ligand-controlled regiodivergent Suzuki-Miyaura reaction of primary allylic boronic esters.

As discussed above, important progress has been achieved for the regioselective Suzuki-Miyaura cross-coupling of allylic boronates. Still, there are limitations. As summarized in Figure 5-4, Miyaura and co-workers[188] demonstrated notable γ-regioselectivities for the Suzuki-Miyaura reaction of potassium allyltrifluoroborates. Successively, the Organ[191] and Buchwald[192] groups independently achieved regiodivergent control for the formation of both γ and α regioisomers with high selectivity. The allylic boronate substrates employed by all three research groups, however, are limited to a simple primary allylboronate devoid of any stereochemistry (**5-16**). To this extend, Crudden and Aggarwal[190] reported highly stereoretentive coupling with optically enriched acyclic secondary allylboronates, however limited to the formation of γ branched regioisomers along with low E/Z selectivity (Figure 5-4).

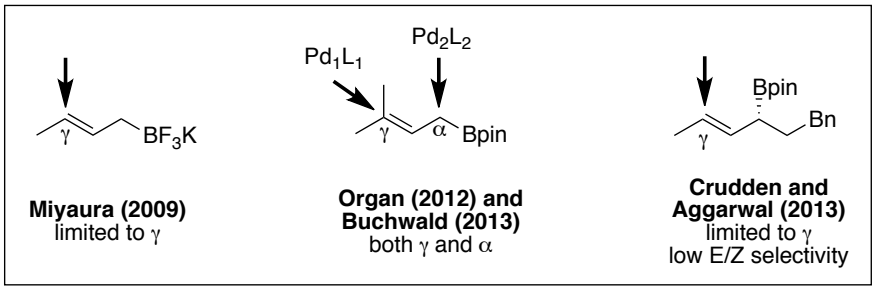


Figure 5-4: Recent advances and limitations of the Suzuki-Miyaura reaction of allylic boronates.

5.2 Objectives

Based on the recent advances and limitations in Suzuki-Miyaura reactions of allylic boronates (Figure 5-4), we aimed to develop a regiodivergent and stereospecific Suzuki-Miyaura cross-coupling of chiral heterocyclic allylic boronates, which would produce the 2- or 4-functionalized, optically pure piperidine or pyran-containing heterocycles (Figure 5-5).

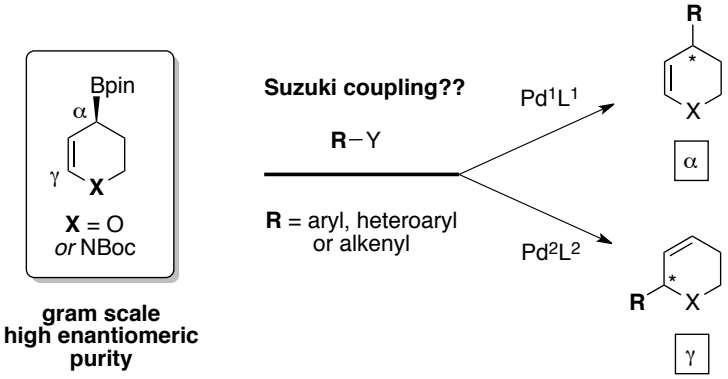


Figure 5-5: Proposed Suzuki-Miyaura cross-coupling reactions of chiral heterocyclic allylic boronates.

Chiral piperidine or pyran ring systems have been recognized as one of the most important pharmacophore units in many biologically active natural products and pharmaceutical drugs.[193] In Figure 5-6, a series of biologically important

compounds, to list just a few, could be accessed within a few steps if the chiral heterocyclic allylic boronates are employed as the Suzuki-Miyaura cross-coupling partners. In addition to these attractive synthetic applications, this study would further expand the realm of conventional Suzuki-Miyaura reactions and help understand the mechanism of regio- and stereoselectivity in these palladium-catalyzed sp^3-sp^2 carbon-carbon bond formation reactions.

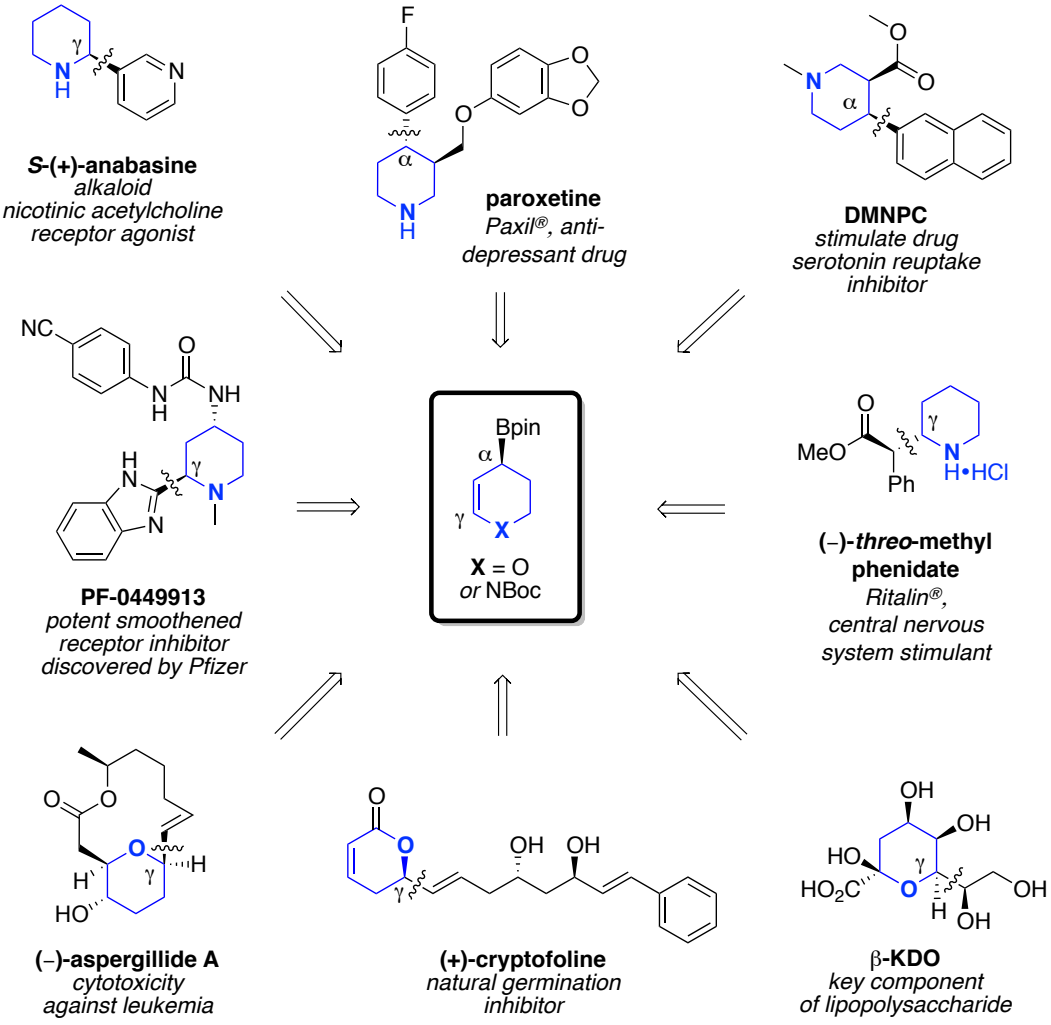


Figure 5-6: Representative examples of piperidine and pyran-containing natural products and pharmaceutical drugs.

In spite of the advances stated above, the proposed Suzuki-Miyaura cross-

coupling reactions of chiral heterocyclic allylic boronates posed several challenges: (1) the selection of palladium catalysts and ligands for a complementary set of regiodivergent protocols; (2) the control of stereospecificity with the possible outcomes of stereochemical inversion, retention or enantiomeric erosion; and (3) the scope of a diverse range of electrophilic cross-coupling partners including aryl, heteroaryl or alkenyl halides. These challenges will be addressed in detail in the following sections.

5.3 Optimization of regioselective Suzuki-Miyaura coupling of heterocyclic allylic boronates

5.3.1 Optimization of yield and regioselectivity in the model Suzuki-Miyaura coupling of dihydropyranyl boronate with 4-haloanisole

To achieve the objective described in Section 5-2, the first step consisted in the development of a highly efficient catalytic enantioselective borylative isomerization of heterocyclic alkenyl triflates to afford pyranyl and piperidinyl allylic boronates.[182,183] In Figure 5-7, by making use of antipodes of the chiral ligand TANIAPHOS in the catalytic enantioselective borylation step, both enantiomers of **4-6** and **4-10** can be obtained in high selectivity from the achiral enol triflates **4-4** and **4-9** respectively. The resulting chiral allylic boronates **4-6** and **4-10** could then lead to either α or γ-selectivity in a Suzuki-Miyaura cross-coupling with organohalide electrophiles (R–Y). The controlled, selective formation of both regioisomers using different catalysts or conditions would provide a powerful and conceptually novel methodology to access optically enriched 2- or 4-substituted heterocycles such as aryl-piperidines that are generally considered a class of privileged structures in drug discovery.[194]

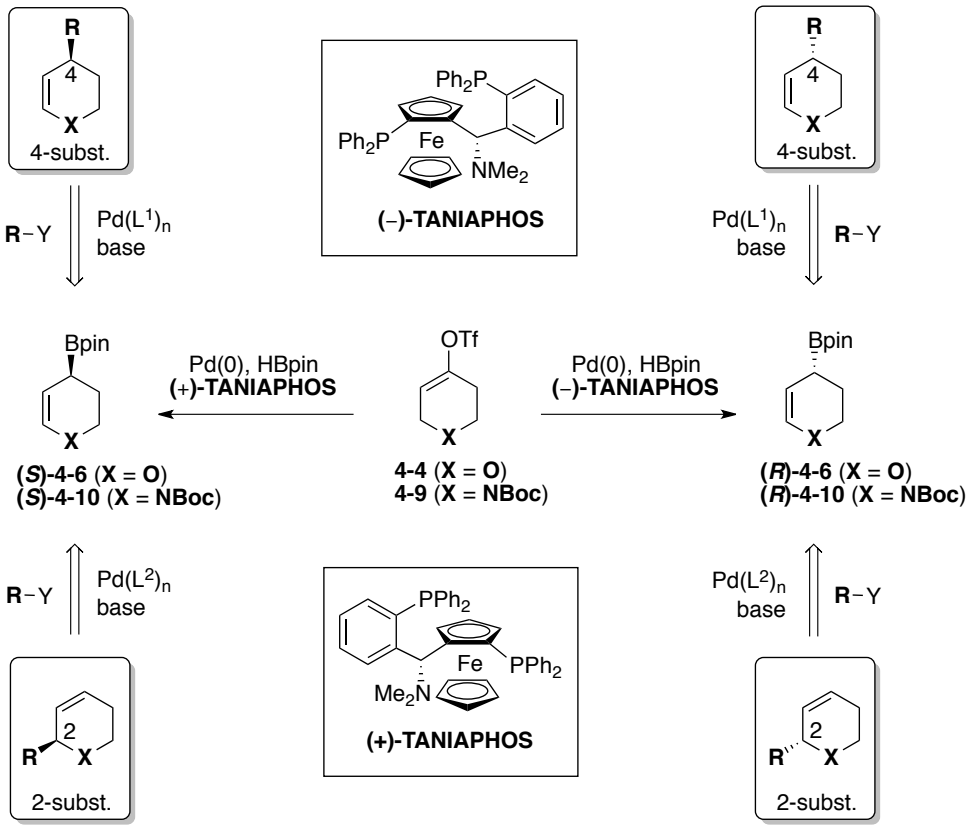
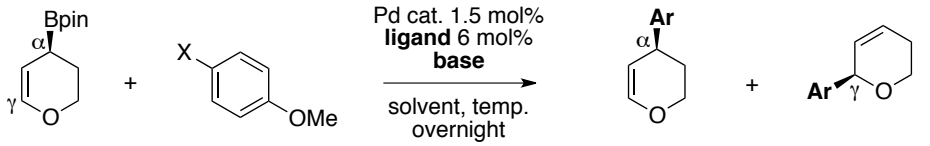


Figure 5-7: Regioselective Suzuki-Miyaura cross-coupling of heterocylic allylic boronates **4-6** and **4-10** to access all four possible isomeric piperidine and pyran products from achiral enol triflates **4-4** and **4-9**.

As discussed in Section 5.1, the regioselectivity of allylic Suzuki-Miyaura cross-couplings is tied to the mechanistic nature of the transmetallation step and whether it occurs with or without allylic rearrangement (see intermediates **5-4**, **5-5**, **5-11**, **5-15** and related discussion). Initial optimization of the regioselectivity was conducted on the racemic dihydropyranyl boronate **4-6** with 4-haloanisole as the electrophile (Table 5-1). At the onset, we planned to test out conditions and catalysts known to be particularly favorable for promoting allylic Suzuki-Miyaura cross-coupling reactions. Although the use of silver(I) oxide as the base has been proven to be crucial for the allylic Suzuki-Miyaura cross-couplings by the Crudden group[190], it showed no reactivity for the coupling of dihydropyranyl

boronate **4-6** (entries 1-2, Table 5-1). A series of Pd(II) complexed, as precurcors of Pd(0) to promote oxidative addition, were further optimized, which identified that the use of $[(allyl)PdCl]_2$ showed slight reactivity towards the formation of γ-product **5-22** (entry 3, Table 5-1), while other palladium catalysts failed to produce either α or γ coupling products (entry 5-6, Table 5-1).



rac-**4-6** (**Ar**X) **5-21** (α) **5-22** (γ)

entry[a]	X	**Pd cat.**	**ligand**	**base**	**solvent, T**	**yield[b] γ (5-22) + α (5-21)**
1	Br	$Pd(OAc)_2$	PPh_3	Ag_2O	THF, 70°C	0
2	Br	$Pd_2(dba)_3$	PPh_3	Ag_2O	THF, 70°C	0
3	Br	$[(allyl)PdCl]_2$	XPhos	Ag_2O	THF, 40°C	8% γ + 0% α
4	Br	$[(allyl)PdCl]_2$	XPhos	K_2CO_3	THF, 40°C	0
5	Br	$Pd(OAc)_2$	XPhos	K_3PO_4	THF, 40°C	0
6	Br	$Pd_2(dba)_3$	XPhos	K_3PO_4	THF, 40°C	0
7	Br	$[(allyl)PdCl]_2$	$PtBu_3$	K_3PO_4	THF, 40°C	70% γ + 0% α
8	Br	$[(allyl)PdCl]_2$	tBuXPhos	K_3PO_4	THF, 40°C	85% γ + 0% α
9	Br	$[(allyl)PdCl]_2$	$(2\text{-thiophen})_3P$	K_3PO_4	THF, 40°C	0
10	Br	$[(allyl)PdCl]_2$	$(2\text{-furyl})_3P$	K_3PO_4	THF, 40°C	0
11	**Br**	$[(allyl)PdCl]_2$	**XPhos**	**K_3PO_4**	**THF, 40°C**	**92% γ + 0% α**
12	Cl	$[(allyl)PdCl]_2$	XPhos	K_3PO_4	THF, 40°C	26% γ + 0% α

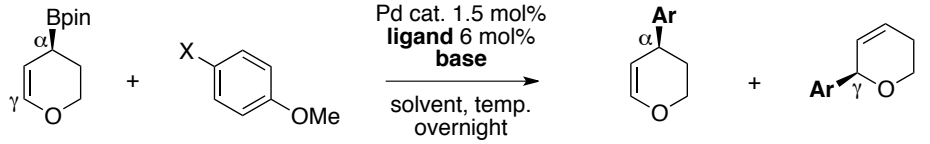
[a] Reaction scale: *rac*-**4-6** (0.30 mmol, 1.2 equiv), 4-haloanisole (0.25 mmol, 1.0 equiv), Pd catalyst (3.8 μmol, 1.5 mol%), ligand (15 μmol, 6 mol%), base (1.3 mmol, 5 equiv). [b] Isolated yields.

Table 5-1: Optimization of γ-regioselectivity and yield in the model Suzuki-Miyaura coupling between racemic allylic boronate **4-6** and 4-haloanisole.

Subsequently, strong σ-donor alkylphosphine ligands such as XPhos (Figure 5-8) and tri-tertbutylphosphine were also examined using different sources of palladium and bases (entries 7-11, Table 5-1). To our delight, when using $[(allyl)PdCl]_2$/XPhos as the catalytic system and K_3PO_4 as the base, the desired 2-substituted coupling product **5-22** was obtained in high yield and excellent γ-regioselectivity (entry 11, Table 5-1). The use of aqueous base K_3PO_4 is presumably to promote the formation of *oxo*-palladium complex *via* the coordination towards palladium center after oxidative addition (*i.e.*, formation of $Ar–PdL_2–OH$ from $Ar–PdL_2–X$), which is known to accelerate the transmetallation step.[195] Under the same optimal conditions, the corresponding aryl halide congener 4-chloroanisole, however, showed reduced cross-coupling reactivity (entry 12, Table 5-1).

With optimal conditions established to favor the γ-regioselectivity (entry 11, Table 5-1), the optimization of α-regioselectivity was also conducted using the same model Suzuki-Miyaura coupling between racemic boronate **4-6** and 4-haloanisole. Accordingly, phosphine ligands with different steric and electronic characteristics were screened. Compared to the electron-rich trialkylphosphine ligand (entry 1, Table 5-2), the relatively weak σ-donating ligand triarylphosphine led to promising α-regioselectivity in spite of the low yields (entries 2-3, Table 5-2). A reexamination of the reaction solvent identified acetonitrile as being optimal in affording a high yield of product (entry 4, Table 5-2). Further fine-tuning of the steric and electronic parameters of different phosphine ligands was attempted (entries 7-11, Table 5-2). Eventually, we found that an excellent regioselectivity over 17:1 was observed in favor of the α regioisomer **5-21** when using a weaker σ-donating phosphine, tri(4-fluoromethylphenyl)phosphine (entry 9, Table 5-2). Use of Organ's Pd-PEPPSI-IPr catalyst,[191] a N-heterocyclic carbene complex (Figure 5-8), afforded similar regioselectivity (entries 12-13, Table 5-2), with the base potassium hydroxide providing a slight increase of the yield of α regioisomer

5-21 (entry 13, Table 5-2). On the other hand, the corresponding 4-chloroanisole as the electrophile again showed a decreased reactivity (entries 14-15, Table 5-2).



rac-**4-6** (**Ar**X) **5-21** (α) **5-22** (γ)

entry[a]	X	Pd cat.	ligand	base	solvent, T	yield[b] γ (5-22) + α (5-21)
1	Br	$[(allyl)PdCl]_2$	PCy_3	K_3PO_4	THF, 40°C	0
2	Br	$[(allyl)PdCl]_2$	PPh_3	K_3PO_4	THF, 40°C	3% γ + 26% α
3	Br	$[(allyl)PdCl]_2$	$(o\text{-Tolyl})_3P$	K_3PO_4	THF, 40°C	4% γ + 26% α
4	Br	$[(allyl)PdCl]_2$	PPh_3	K_3PO_4	CH_3CN, 70°C	7% γ + 63% α
5	Br	$[(allyl)PdCl]_2$	PPh_3	K_3PO_4	dioxane, 70°C	6% γ + 41% α
6	Br	$[(allyl)PdCl]_2$	PPh_3	K_3PO_4	DMF, 70°C	2% γ + 10% α
7	Br	$[(allyl)PdCl]_2$	$(p\text{-Tolyl})_3P$	K_3PO_4	CH_3CN, 70°C	21% γ + 74% α
8	Br	$[(allyl)PdCl]_2$	no ligand	K_3PO_4	THF, 40°C	1% γ + 6% α
9	**Br**	$[(allyl)PdCl]_2$	**$(p\text{-}CF_3Ph)_3P$**	**K_3PO_4**	**CH_3CN, 70°C**	**4%** γ + **75%** α
10	Br	$[(allyl)PdCl]_2$	$(p\text{-F-Ph})_3P$	K_3PO_4	CH_3CN, 70°C	0% γ + 35% α
11	Br	$[(allyl)PdCl]_2$	$(1\text{-naphth})_3P$	K_3PO_4	CH_3CN, 70°C	74% γ + 16% α
12	Br	Pd-PEPPSI-IPR [c]		K_3PO_4	CH_3CN, 70°C	10% γ + 58% α
13	Br	Pd-PEPPSI-IPR [c]		KOH	THF, 70°C	3% γ + 63% α
14	Cl	$[(allyl)PdCl]_2$	$(p\text{-}CF_3Ph)_3P$	K_3PO_4	CH_3CN, 70°C	0% γ + 32% α
15	Cl	Pd-PEPPSI-IPR [c]		K_3PO_4	CH_3CN, 70°C	2% γ + 42% α

[a] Reaction scale: *rac*-**4-6** (0.30 mmol, 1.2 equiv), 4-haloanisole (0.25 mmol, 1.0 equiv), Pd catalyst (3.8 μmol, 1.5 mol%), ligand (15 μmol, 6 mol%), base (1.3 mmol, 5 equiv). [b] Isolated yields. [c] PEPPSI ligand (3.0 mol%).

Table 5-2: Optimization of α-regioselectivity and yield in the model Suzuki-Miyaura coupling between racemic allylic boronate **4-6** and 4-haloanisole.

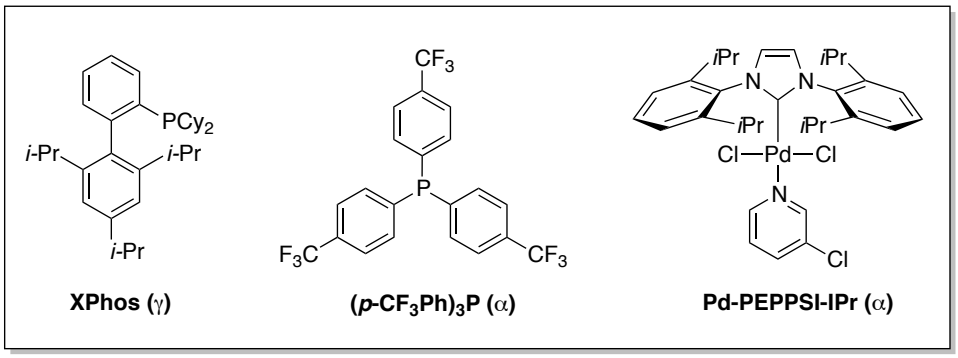
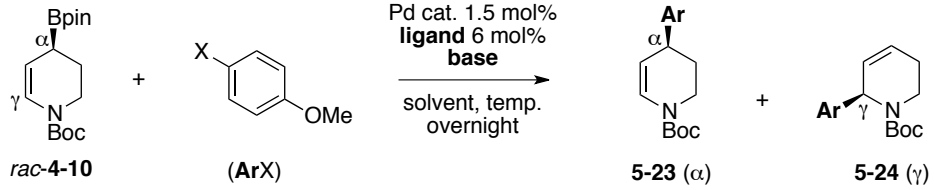


Figure 5-8: Optimal ligands for the regiodivergent Suzuki-Miyaura cross-coupling between racemic dihydropyranyl boronate **4-6** and 4-bromoanisole.

5.3.2 Optimization of yield and regioselectivity in the model Suzuki-Miyaura coupling of dehydropiperidyl boronate and 4-haloanisole

To examine the scope of heterocyclic allylic boronates, the optimal conditions for the regiodivergent Suzuki-Miyaura coupling of dihydropyranyl boronate **4-6** were also applied for the couplings of the dehydropiperidyl boronate **4-10**.

Initially, the γ-selective conditions optimized for dihydropyran substrate **4-6** were initially tested on the dehydropiperidyl boronate **4-10**. In Table 5-3, the desired γ-regioisomer **5-24** was produced exclusively, the yield, however, was significantly lower compared to the results of γ-selective coupling of dihydropyran substrate **4-6** (entry 1, Table 5-3). Further alterations on the selection of bases, solvents and reaction temperatures were sought. Eventually, a switch to potassium hydroxide as the stronger base and tetrahydrofuran as the solvent at elevated temperature, a protocol that demonstrated great efficiency by the Organ Group for the regioselective Suzuki-Miyaura cross-coupling of branched allylic boronate **5-12** (Scheme 5-3),[191] led to an improved yield of the desired 2-substituted dehydropiperidine **5-24** (entries 2-3, Table 5-3).



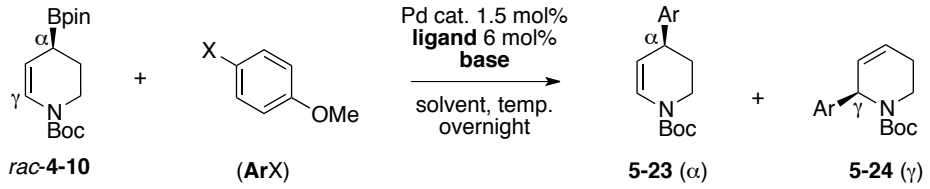
entry[a]	X	Pd cat.	ligand	base	solvent, T	yield[b] γ (5-23) + α (5-24)
1	Br	$(AllylPdCl)_2$	XPhos	K_3PO_4	THF, 40°C	62% γ + 0% α
2	Br	$(AllylPdCl)_2$	XPhos	K_3PO_4	CH_3CN, 70°C	65% γ + 0% α
3	Br	$(AllylPdCl)_2$	XPhos	**KOH**	**THF, 70°C**	**92%** γ + **0%** α

[a] Reaction scale: *rac*-**4-10** (0.38 mmol, 1.5 equiv), 4-bromoanisole (0.25 mmol, 1.0 equiv), Pd catalyst (3.8 μmol, 1.5 mol%), ligand (15 μmol, 6 mol%), base (1.3 mmol, 5 equiv). [b] Isolated yields.

Table 5-3: Optimization of γ-regioselectivity and yield in the model Suzuki-Miyaura coupling between racemic allylic boronate **4-10** and 4-bromoanisole.

On the other hand, preparation of the 4-substituted dehydropiperidyl product **5-23** *via* an α-selective coupling proved to be more challenging. The optimal conditions identified for dihydropyranyl boronate **4-6**, using tris(4-fluoromethylphenyl)phosphine as the ligand, provided a low yield (entry 1, Table 5-4). Thus, to further improve the reactivity, the reaction conditions for the α-selective cross-coupling of dehydropiperidyl boronate **4-10** needed to be further tuned. For this purpose, optimizaton of various halide electrophiles was initially attempted. Neither 4-chloro- nor iodoanisole, however, showed any improvement on the α-selective cross-coupling reactivities (entries 2-3, Table 5-4), which suggested that the oxidative addition is not the rate-limiting step in this system. Further adjustment to the steric and electronic parameters of different triarylphosphine ligands was also conducted, which unfortunately did not lead to any promising results (entries 4-6, Table 5-4). Switching to the Pd-PEPPSI-IPr catalyst (Figure 5-8), however resulted in a significantly higher yield of the α-product with excellent regioselectivity (entry 7, Table 5-4). The yield and α-

regioselectivity were further improved by slightly increasing the reaction temperature with potassium hydroxide as the base (entry 9, Table 5-4). Contrary to the work of Organ and co-workers,[191] the corresponding Pd-PEPPSI-IPent catalyst was found to be less selective (entry 10, Table 5-4).



entry[a]	X	Pd cat.	ligand	base	solvent, temp.	yield[b] γ (5-23) + α (5-24)
1	Br	$(AllylPdCl)_2$	$(p\text{-}CF_3Ph)_3P$	K_3PO_4	CH_3CN, 70°C	2% γ + 30% α
2	Cl	$(AllylPdCl)_2$	$(p\text{-}CF_3Ph)_3P$	K_3PO_4	CH_3CN, 70°C	0% γ + 15% α
3	I	$(AllylPdCl)_2$	$(p\text{-}CF_3Ph)_3P$	K_3PO_4	CH_3CN, 70°C	5% γ + 3% α
4	Br	$(AllylPdCl)_2$	PPh_3	K_3PO_4	CH_3CN, 70°C	25% γ + 22% α
5	Br	$(AllylPdCl)_2$	$(3,5\text{-}diCF_3\text{-}Ph)_3P$	K_3PO_4	CH_3CN, 70°C	4% γ + 25% α
6	Br	$(AllylPdCl)_2$	$(C_6F_5)_3P$	K_3PO_4	CH_3CN, 70°C	2% γ + 14% α
7	Br	Pd-PEPPSI-IPR [c]		K_3PO_4	CH_3CN, 70°C	11% γ + 58% α
8	Br	Pd-PEPPSI-IPR [c]		KOH	THF, 70°C	12% γ + 80% α
9	**Br**	**Pd-PEPPSI-IPR [c]**		**KOH**	**CH_3CN, 85°C**	**6% γ + 82% α**
10	Br	Pd-PEPPSI-IPENT [c]		KOH	CH_3CN, 85°C	35% γ + 63% α

[a] Reaction scale: *rac*-**4-10** (0.38 mmol, 1.5 equiv), 4-bromoanisole (0.25 mmol, 1.0 equiv), Pd catalyst (3.8 μmol, 1.5 mol%), ligand (15 μmol, 6 mol%), base (1.3 mmol, 5 equiv). [b] Isolated yields. [c] PEPPSI catalyst (3.0 mol%).

Table 5-4: Optimization of α-regioselectivity and yield in the model Suzuki-Miyaura coupling between racemic allylic boronate **4-10** and 4-haloanisole.

5.4 Substrate scope for the regioselective and stereospecific Suzuki-Miyaura coupling of chiral heterocyclic allylic boronates

With two complementary sets of reaction conditions available for the coupling of both dihydropyranyl and dehydropiperidinyl substrates (Table 5-1 to Table 5-4), we set out to examine the regioselectivity and stereospecificity of the Suzuki-Miyaura coupling between chiral heterocyclic allylic boronates and a variety of sp^2-hybridized electrophiles.

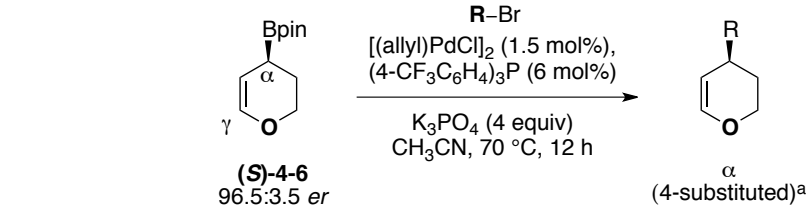
5.4.1 Substrate scope for the regioselective and stereospecific Suzuki-Miyaura coupling of optically pure dehydropyranyl boronate (*S*)-4-6

A preliminary examination of the scope of suitable coupling partners for the optically enriched dihydropyranyl boronate (*S*)-**4-6** was performed (Scheme 5-5 and Scheme 5-6). The chiral allylic boronate (*S*)-**4-6** was obtained in gram scale and high enantiomeric purity (96.5:3.5 *er*) *via* the Pd-catalyzed enantioselective borylative alkene isomerization reaction with (+)-TANIAPHOS as the chiral ligand (Figure 5-7). Part of the substrate scope was conducted by my colleague Taras Rybak, as indicated specifically in the legend of Scheme 5-5 and Scheme 5-6, which was included for the comprehensiveness of this chapter.

Initially, the optimal conditions that favor the α coupling products (Table 5-2) were applied by using tris-4-trifluoromethylphenyl phosphine as a weak σ-donor ligand. A diverse range of sp^2-hybridized electrophiles was investigated, including aryl and heteroaryl halides with both electron-donating and electron-withdrawing substituents. As shown in Scheme 5-5, all electrophiles were successfully coupled in good to high yields, producing the 4-substituted regioisomers **5-21** and **5-25** to **5-29** with regioselectivity ratios ranging from 5:1 to 15:1. The regioselectivity appeared to be lower for the cross-coupling of the sterically congested aryl bromide (**5-25**, α/γ = 5:1) and the electron-deficient aryl bromide (**5-28**, α/γ = 6:1). All regioisomers can be easily separated by flash column chromatography. It is

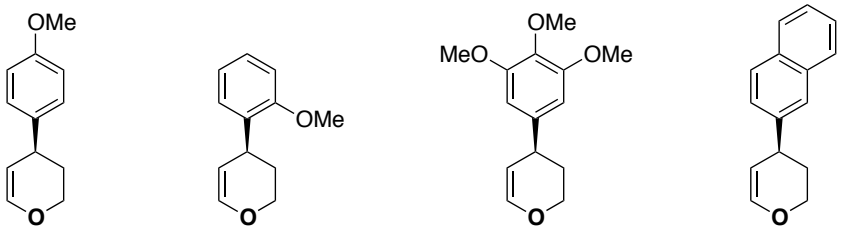
remarkable that near or full preservation of optical purity was observed for all of these examples, as verified by the excellent enantiomeric ratios for all coupling products. The enantiomeric ratios of all products were measured directly by chiral HPLC, except for the products **5-25**, **5-29** to **5-31**, which could not be resolved despite that different HPLC conditions were attempted. Thus, further chemical derivatization of these non-resolved products was conducted, and the details will be outlined in Section 5.8.4 of the experimental section.

Additionally, as shown with the formation of **5-30** and **5-31** (Scheme 5-5), both 1- and 2-substituted alkenyl halides are suitable electrophiles, leading to the formation of enantioenriched 4-alkenyl dihydropyran products with excellent yields and very good regioselectivities. It is noteworthy that the coupling product (*E*)-**5-31** was prepared from a mixture of *E*/*Z* (80/20) stereoisomers of β-bromostyrene. Only the 80% (*E*)-β-bromostyrene was reactive under the α coupling conditions, while the 20% (*Z*)-isomer was recovered intact after the reaction. This is probably because that the oxidative insertion of the (*Z*)-isomer is more sterically hindered.



(*S*)-4-6
96.5:3.5 *er*

α

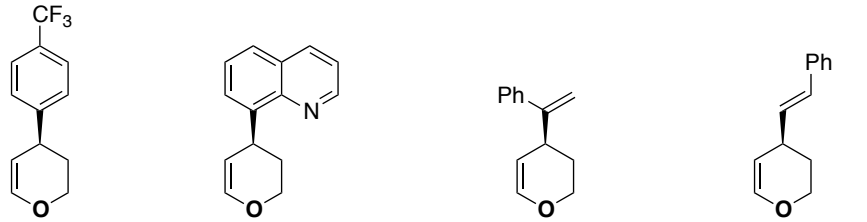


5-21 (78%)[b]
α/γ = 15:1[c]
95:5 *er*[d]

5-25 (71%)[b]
α/γ = 5:1[c]
95:5 *er*[e]

5-26 (76%)[b]
α/γ = 9:1[c]
95:5 *er*[d]

5-27 (70%)[b]
α/γ = 7:1[c]
96:4 *er*[d]



5-28 (72%)[b,f]
α/γ = 6:1[c]
95:5 *er*[d]

5-29 (93%)[b,f]
α/γ = 10:1[c]
96.5:3.5 *er*[e]

5-30 (86%)[b,f]
α/γ = 7:1[c]
95:5 *er*[e]

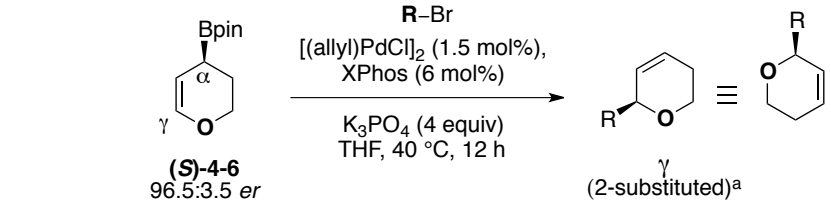
5-31 (78%)[b,f]
α/γ = 9:1[c]
96:4 *er*[e]

[a] $[(allyl)PdCl]_2$ (1.4 mg, 3.8 μmol), $(4\text{-}CF_3C_6H_4)_3P$ (7.0 mg, 15.0 μmol) (*S*)-**4-6** (63.0 mg, 0.30 mmol), R-Br (0.25 mmol) and K_3PO_4 (2.5M in H_2O, 2.5 mL, 1.0 mmol) in dry CH_3CN (2.5 mL) at 70 °C. [b] Isolated yields of the major, separated regioisomers. [c] Regioisomer ratio (α/γ) was measured from the ^1H NMR spectra of crude products. [d] The enantiomeric ratio (*er*) was obtained directly from the pure coupling product by chiral HPLC analysis with a conservative error of 2%. [e] *er* was measured after chemical derivatization as outlined in the Section 5.8.4. [f] Reaction was conducted by my colleague Taras Rybak, which was included for the comprehensiveness of this chapter.

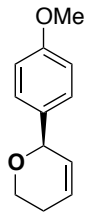
Scheme 5-5: Scope of electrophiles in the α-selective stereospecific Suzuki-Miyaura cross-coupling with chiral dihydropyranyl boronate (*S*)-**4-6**.

The substrate scope for the γ-selective Suzuki-Miyaura coupling of chiral dihydropyranyl boronate (*S*)-**4-6** was also examined with the same set of sp^2-hybridized electrophiles as the coupling partners. Thus, the optimal conditions favoring the γ coupling products (Table 5-1) were applied by using the sterically bulky, electron-rich XPhos as the ligand. As shown in Scheme 5-6, even better regioisomeric control was achieved under the optimal γ coupling conditions. Electrophilic coupling partners, involving both electron-donating and electron-withdrawing aryl halides as well as heteroaryl halides, were successfully coupled with the chiral dihydropyranyl boronate (*S*)-**4-6**. The resulting optically pure 2-substituted pyran products **5-22** and **5-32** to **5-36** were obtained with good to excellent yields, in excellent enantiomeric ratios and over 98:2 regioisomeric ratios. All enantiomeric ratios of the coupling products were measured directly by chiral HPLC, however, the product **5-33** cannot be resolved. Therefore, further chemical derivatization of **5-33** was conducted, and the details will be outlined in Section 5.8.4 of the experimental section.

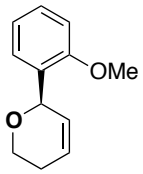
In addition, as shown with the formation of **5-37** and **5-38**, both 1- and 2-substituted alkenyl halides again are suitable electrophiles, leading to the formation of enantioenriched 2-substituted alkenyl dihydropyran products with excellent yields despite a lower regioselectivity (γ/α = 3/1). Furthermore, the coupling product (*E*)-**5-38** was also prepared from a mixture of *E*/*Z* (80/20) stereoisomers of β-bromostyrene, while only the (*E*)-β-bromostyrene was reactive under the γ coupling conditions. The (*Z*)-β-bromostyrene again showed no reactivity, presumably due to steric reasons.



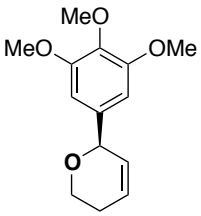
γ



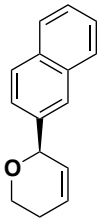
5-22 (92%)[b]
γ/α = >98:2[c]
95:5 *er*[d]



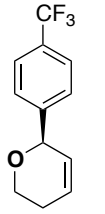
5-32 (74%)[b]
γ/α = >98:2[c]
96:4 *er*[d]



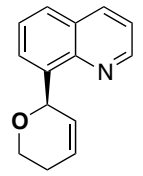
5-33 (71%)[b]
γ/α = >98:2[c]
96:4 *er*[e]



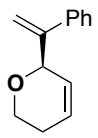
5-34 (98%)[b]
γ/α = >98:2[c]
96.5:3.5 *er*[d]



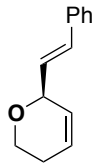
5-35 (98%)[b,f]
γ/α = >98:2[c]
95:5 *er*[d]



5-36 (86%)[b,f]
γ/α = >98:2[c]
96.5:3.5 *er*[d]



5-37 (65%)[b,f]
γ/α = 3:1[c]
95.5:4.5 *er*[d]



5-38 (74%)[b,f]
γ/α = 3:1[c]
96:4 *er*[d]

[a] [(allyl)PdCl]$_2$ (1.4 mg, 3.8 μmol), XPhos (7.2 mg, 15 μmol), (*S*)-**4-6** (63.0 mg, 0.30 mmol), R-Br (0.25 mmol) and K_3PO_4 (2.5M in H_2O, 2.5 mL, 1.0 mmol) in dry THF (2.5 mL) at 40 °C. [b] Isolated yields of the major, separated regioisomers. [c] Regioisomer ratio (α/γ) was measured from the ^{1}H NMR spectra of crude products. [d] The enantiomeric ratio (*er*) was obtained directly from the pure coupling product by chiral HPLC analysis with a conservative error of 2%. [e] *er* was measured after chemical derivatization as outlined in the Section 5.8.4. [f] Reaction was conducted by my colleague Taras Rybak, which was included for the comprehensiveness of this chapter.

Scheme 5-6: Scope of electrophiles in the γ-selective stereospecific Suzuki-Miyaura cross-coupling with chiral dihydropyranyl boronate (*S*)-**4-6**.

5.4.2 Substrate scope for the regioselective and stereospecific Suzuki-Miyaura coupling of optically pure dehydropiperidyl boronate (*S*)-4-10

Due to the importance of piperidines as a prominent class of saturated heterocycles in medicinal chemistry, it was gratifying to observe a wide scope of aryl, heteroaryl and alkenyl coupling partners for the piperidylboronate (*R*)- or (*S*)-**4-10** (Scheme 5-7 and Scheme 5-8). The chiral allylic boronate (*S*)-**4-10** was obtained in gram scale and high enantiomeric purity (97.5:2.5 *er*) *via* the Pd-catalyzed enantioselective borylative alkene isomerization reaction with (+)-TANIAPHOS as the chiral ligand, while its enantiomer (*R*)-**4-10** was prepared in the same efficiency with (–)-TANIAPHOS as the chiral ligand (Figure 5-7).

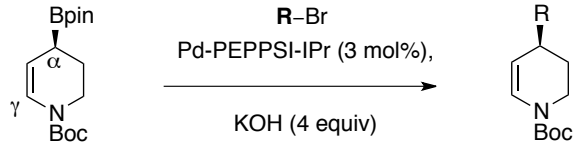
Initially, as shown in Scheme 5-7, a broad range of sp^2-hybridized electrophiles was examined as coupling partners in the optimal α-selective conditions of Table 5-4 with Pd-PEPPSI-IPr as the catalyst. The resulting 4-substituted regioisomers were obtained with excellent yields and up to >98:2 α regioselectivity. Starting from optically enriched boronate (*R*)- or (*S*)-**4-10** with an optical purity of 97.5:2.5 enantiomeric ratio (*er*), coupling products **5-23** and **5-39** to **5-45** were all obtained with little or no erosion of enantiomeric purity with selectivities over 95:5 *er*. All enantiomeric ratios of the coupling products were measured directly by chiral HPLC, however, the product **5-39** cannot be resolved. Accordingly, further chemical derivatization of **5-39** was conducted, and the details will be outlined in Section 5.8.4 of the experimental section.

Moreover, as shown with the formation of **5-44** (from (*R*)-**4-10**) and **5-45** (from (*S*)-**4-10**), both 1- and 2-substituted alkenyl halides are suitable coupling partners, leading to the formation of enantioenriched 4-alkenyl dehydropiperidine products with good yields despite a slightly lower regioselectivity (α/γ = 7/1). It is noteworthy that the pure coupling product (*E*)-**5-38** was again prepared from a mixture of *E*/*Z* (80/20) stereoisomers of β-bromostyrene, between which only the

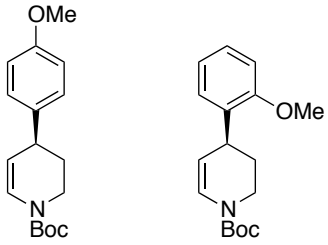
(*E*)-β-bromostyrene was selectively coupled and the (*Z*)-isomer was completely recovered (Scheme 5-7).

The substrate scope for the γ-selective Suzuki-Miyaura coupling of optically pure piperidinyl boronate (*R*)- or (*S*)-**4-10** was also examined with the same set of sp^2-hybridized electrophiles as the coupling partners. Thus, the optimal conditions favoring the γ coupling products (Table 5-3) were applied by using the sterically bulky, electron-rich XPhos as the ligand. To our delight, the regioselective and stereospecific cross-coupling reaction proved to be extremely effective, providing 2-substituted dehydropiperidines **5-24** and **5-46** to **5-52** in regioselectivities ranging from 15:1 to >98:2 and *er's* over 95.5:4.5 (Scheme 5-8). In two cases (**5-48**, **5-49**), within measurement error, no erosion of enantiomeric purity was detected and coupled products were isolated with a 97.5:2.5 *er*. The enantiomeric ratios of all products were measured directly by chiral HPLC, except for the products **5-49**, **5-50** to **5-51**, which could not be resolved despite that different HPLC conditions were attempted. As a result, further chemical derivatization of these non-resolved products was conducted, and the details will be outlined in Section 5.8.4 of the experimental section.

Additionally, as shown with the formation of **5-51** (from (*R*)-**4-10**) and **5-52** (from (*S*)-**4-10**), both 1- and 2-substituted alkenyl halides can be efficiently coupled, producing the corresponding enantioenriched 2-alkenyl dehydropiperidine products with very good yields and excellent γ-selectivities. As indicated before, the pure coupling product (*E*)-**5-52** was prepared from a mixture of *E*/*Z* (80/20) stereoisomers of β-bromostyrene, in which only the (*E*)-β-bromostyrene demonstrated cross-coupling reactivity (Scheme 5-8).

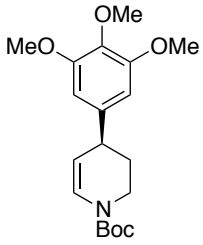


α

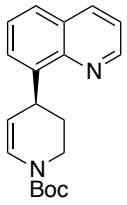


5-23 (83%)[b]
α/γ = 14:1[c]
97:3 *er*[d]

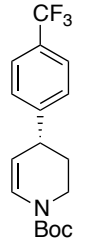
5-39 (75%)[b]
α/γ = 15:1[c]
96:4 *er*[d,e]



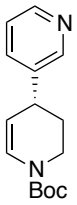
5-40 (81%)[b]
α/γ = 17:1[c]
96.5:3.5 *er*[d]



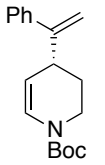
5-41 (70%)[b]
α/γ = >98:2[c]
95:5 *er*[d]



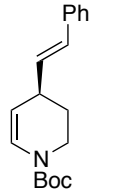
5-42 (66%)[b]
α/γ = 11:1[c]
95:5 *er*[d,f]



5-43 (72%)[b]
α/γ = 11:1[c]
96:4 *er*[e,f]



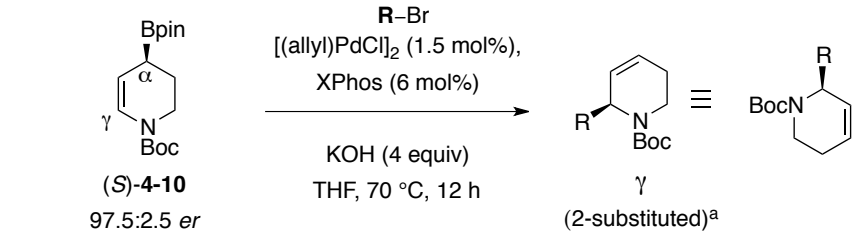
5-44 (74%)[b]
α/γ = 7:1[c]
95.5:4.5 *er*[e,f]



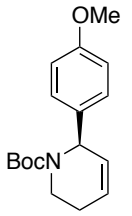
5-45 (60%)[b]
α/γ = 7:1[c]
95.5:4.5 *er*[d]

[a] Pd-PEPPSI-*i*Pr (5.1 mg, 7.5 μmol), (*S*)-**4-10** (117.5 mg, 0.38 mmol, unless indicated otherwise), R-Br (0.25 mmol) and KOH (5M in H_2O, 250 μL, 1.25 mmol) in dry CH_3CN (2.5 mL). [b] Isolated yields of the major, separated regioisomers. [c] Regioisomer ratio (α/γ) was measured from the ^1H NMR spectra of crude products. [d] The enantiomeric ratio (*er*) was obtained directly from the pure coupling product by chiral HPLC analysis with a conservative error of 2%. [e] *er* was measured after chemical derivatization as outlined in Section 5.8.4. [f] Product was prepared from (*R*)-**4-10**.

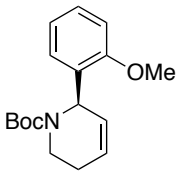
Scheme 5-7: Scope of electrophiles in the α-selective stereospecific Suzuki-Miyaura cross-coupling with chiral dehydropiperidinyl boronate (*S*)-**4-10**.



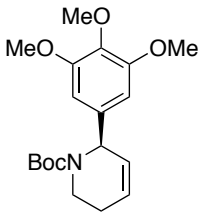
γ



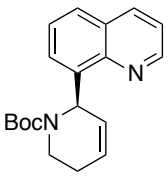
5-24 (91%)[b]
γ/α = >98:2[c]
97:3 *er*[d]



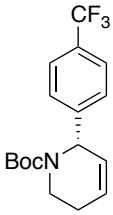
5-46 (91%)[b]
γ/α = >98:2[c]
96:4 *er*[d]



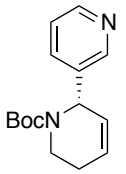
5-47 (96%)[b]
γ/α = >98:2[c]
95.5:3.5 *er*[d]



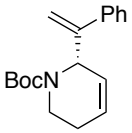
5-48 (80%)[b]
γ/α = >98:2[c]
97.5:2.5 *er*[d]



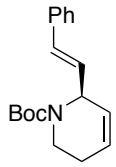
5-49 (68%)[b]
γ/α = >98:2[c]
97.5:2.5 *er*[e,f]



5-50 (66%)[b]
γ/α = 15:1[c]
96:4 *er*[e,f]



5-51 (78%)[b]
γ/α = 15:1[c]
96:4 *er*[e,f]



5-52 (88%)[b]
γ/α = >98:2[c]
95.5:5.5 *er*[d]

[a] $[(allyl)PdCl]_2$ (1.4 mg, 3.8 μmol), XPhos (7.2 mg, 15 μmol), (*S*)-**4-10** (117.5 mg, 0.38 mmol, unless indicated otherwise), R-Br (0.25 mmol) and KOH (5M in H_2O, 250 μL, 1.25 mmol) in dry THF (2.5 mL). [b] Isolated yields of the major, separated regioisomers. [c] Regioisomer ratio (α/γ) was measured from the ^1H NMR spectra of crude products. [d] The enantiomeric ratio (*er*) was obtained directly from the pure coupling product by chiral HPLC analysis with a conservative error of 2%. [e] *er* was measured after chemical derivatization as outlined in the Section 5.8.4. [f] Product was prepared from (*R*)-**4-10**.

Scheme 5-8: Scope of electrophiles in the γ-selective stereospecific Suzuki-Miyaura cross-coupling with chiral dehydropiperidinyl boronate (*S*)-**4-10**.

Based on the alkene directed *syn*-S_E2' intramolecular transmetallation mechanism proposed by the Crudden and Aggarwal groups (Scheme 5-2),[190] the stereochemical integrity of the above described coupling reactions is presumably preserved (*i.e.*, configurational retention). To verify this assumption, further derivatization of selected substrates was conducted. The optical rotation values of resulting derivatives were then compared with those of previously reported compounds. These experiments will be discussed in detail in Section 5.5.3.

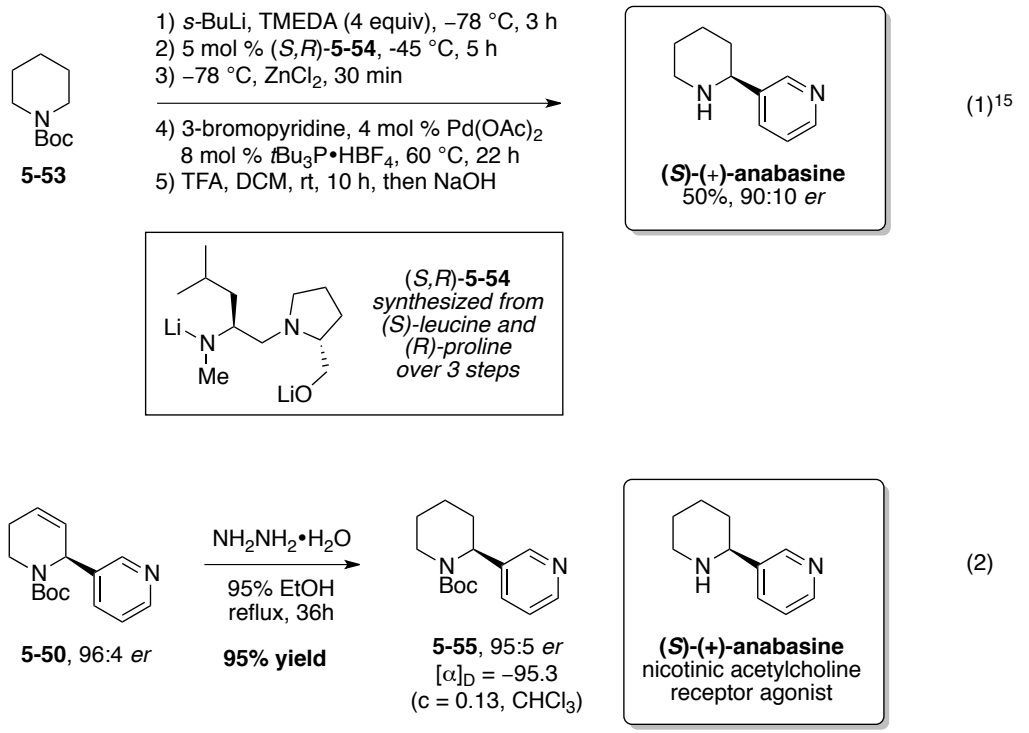
5.5 Application of regiodivergent and stereospecific Suzuki-Miyaura cross-coupling products in the preparation of synthetic drugs and natural products

To demonstrate the practical usefulness of this methodology in the selective preparation of synthetic drug intermediates and natural products, we applied the regiodivergent couplings to the preparation of two neurologically active piperidine-containing substances, (*S*)-(+)-anabasine and (+)-paroxetine (Figure 5-6).

5.5.1 Asymmetric formal synthesis of (+)-anabasine

(*S*)-(+)-Anabasine is a class of tobacco alkaloid, which was formerly used as a botanical insecticide.[196] The most recent synthesis was achieved by the Gawley Group,[197] which applied a methodology involving regioselective asymmetric arylation of the simple *N*-Boc-piperidine **5-53**. As shown in Scheme 5-8 (Equation 1), upon 2-lithiation of **5-53**, catalytic dynamic resolution (CDR) using (*S*,*R*)-**5-54** as the chiral source, transmetallation with zinc chloride, Pd-catalyzed Negishi coupling, Boc removal and aqueous base wash, the end product (*S*)-(+)-anabasine was accessed over 5 steps with decent yield and moderate enantiomeric ratio. This synthesis represented the shortest asymmetric synthesis of (*S*)-(+)-anabasine thus far. The pratical value of this synthesis, however, is diminished by the use of highly basic and nucleophilic reagent *s*-BuLi. Additionally, the chiral ligand (*S*,*R*)-**5-54** requires a three-step synthesis from (*S*)-leucine and (*R*)-

proline.[198] On the other hand, starting from the optically pure γ coupling product **5-50** (96:4 *er*, Scheme 5-8), we envisioned a shorter and more straightforward asymmetric synthesis of (*S*)-(+)-anabasine. As illustrated in Scheme 5-9 (Equation 2), the olefin of **5-50** was hydrogenated with diimide[199] without affecting the stereochemical integrity, providing the *N*-Boc-protected anabasine **5-55** in 95% yield and 95:5 enantiomeric ratio. The latter can be transformed in a single high-yielding step to (*S*)-(+)-anabasine (Scheme 5-9).

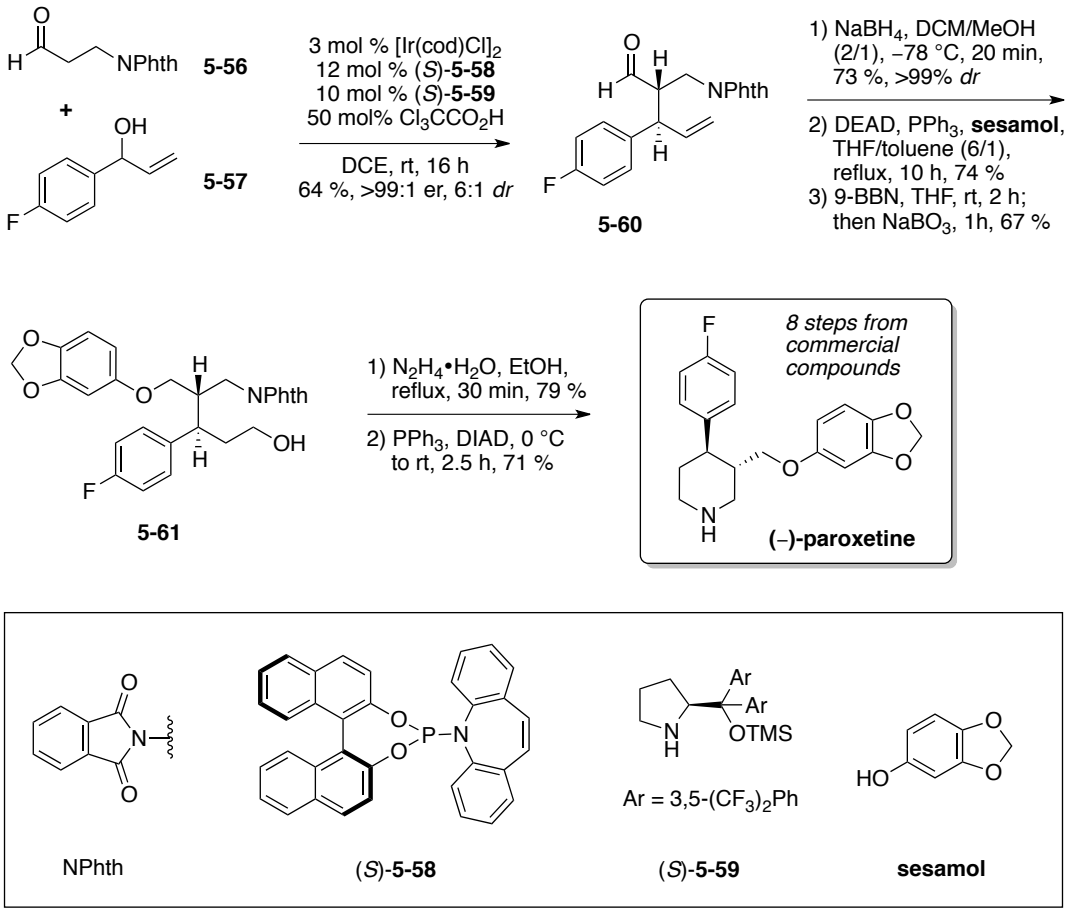


Scheme 5-9: Formal synthesis of (*S*)-(+)-anabasine from **5-50**.

5.5.2 Asymmetric formal synthesis of (+)-paroxetine

Paroxetine (Figure 5-6) is a highly prescribed antidepressant drug belonging to the class of selective serotonin reuptake inhibitors (SSRI). It is commonly used for the clinical treatment of depression, anxiety, and panic disorders.[200] Due to its biological and pharmacologic importance, a number of asymmetric syntheses of

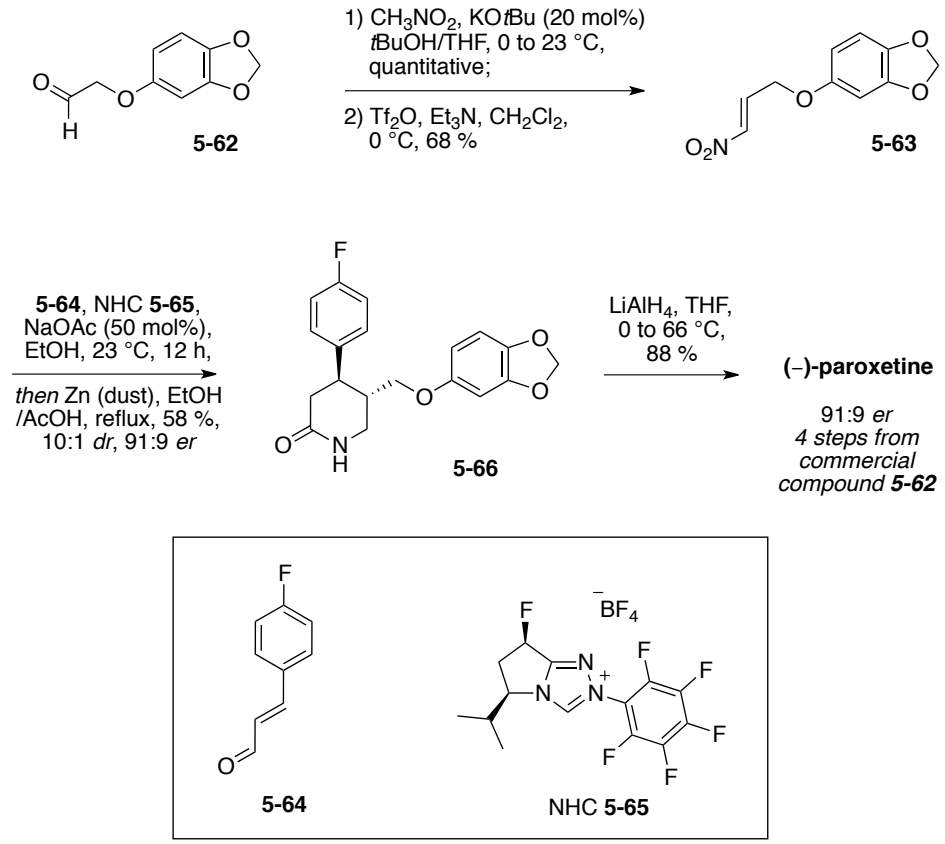
paroxetine have been reported.[201] The recent synthesis of (−)-parocetine that achieved by the Carreira Group in 2014 represented one of the shortest asymmetric syntheses to date (Scheme 5-10).[201i] Carreira and co-workers employed a novel stereodivergent, dual catalytic α-allylation of β-amino aldehyde **5-56** with 4-fluorophenyl vinyl carbinol **5-57**, where a combination of highly enantioselective Ir/(*S*)-**5-58** and (*S*)-**5-59** amine catalysis was applied.



Scheme 5-10: Recent synthesis of (−)-paroxetine by the Carreira Group.[201i]

As a result, the γ,δ-unsaturated aldehyde **5-60** was afforded as the major diastereomer in 64 % yield, in over 99:1 *er* and 6:1 *dr*. The diastereomers were separable after being subjected to $NaBH_4$ reduction. The resulting primary alcohol was then displaced by sesamol under Mitsunobu conditions. Regioselective

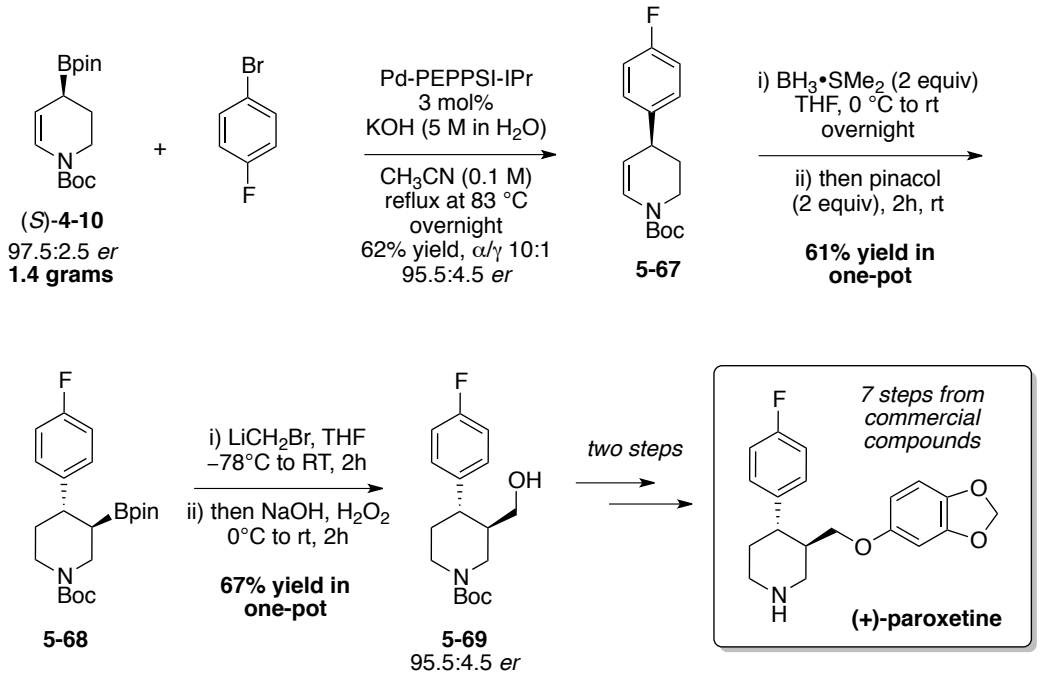
hydroboration of the terminal alkene and sequential oxidation afforded the alcohol **5-61**. Eventually, cleavage of the phthalimide followed by *N*-cyclization furnished (−)-paroxetine. As the starting β-amino aldehyde **5-56** required a two-step synthesis from the commercial γ-amino alcohol,[202] a total of 8 steps was counted for the concise synthesis of (−)-paroxetine recently achieved by the Carreira Group.



Scheme 5-11: Recent synthesis of (−)-paroxetine by the Rovis Group.[201j]

Other representative examples for the asymmetric synthesis of (−)-paroxetine include a 15-step synthesis reported by the Park and Jew groups in 2010[201h] *via* an enantioselective phase-transfer catalytic monoalkylation of malonamide ester. As this chapter was drafted, a 4-step synthesis of (−)-paroxetine, despite a low enantioselectivity, was published by the Rovis Group[201j] *via* an N-heterocyclic

carbene (NHC) catalyzed homoenolate **5-64** addition to nitroalkene **5-63** (Scheme 5-11). The desired nitroalkene **5-63** was first synthesized from the commercially available aldehyde **5-62** in 68% yield over two steps, where a Henry reaction with nitromethane followed by elimination with trifluoroacetic anhydride was performed. As the key step for the synthesis of (−)-paroxetine, the reaction of the resulting nitroalkene **5-63** and enal **5-64** was facilitated through an optimized NHC-catalyzed homoenolate addition and *in situ* nitroester reduction/lactam formation protocol previously reported by the same group.[203] The use of the fluorinated NHC catalyst **5-65** was found to be optimal, providing the key intermediate *trans* 3,4-disubstituted piperidone **5-66** in 91:9 *er*, 10:1 *dr*, and 58% yield. Upon the treatment of lithium aluminium hydride (LAH), the (−)-paroxetine was finally obtained in 88% yield.



Scheme 5-12: Concise synthesis of (+)-paroxetine from Suzuki-Miyaura coupling of (*S*)-**4-10**.

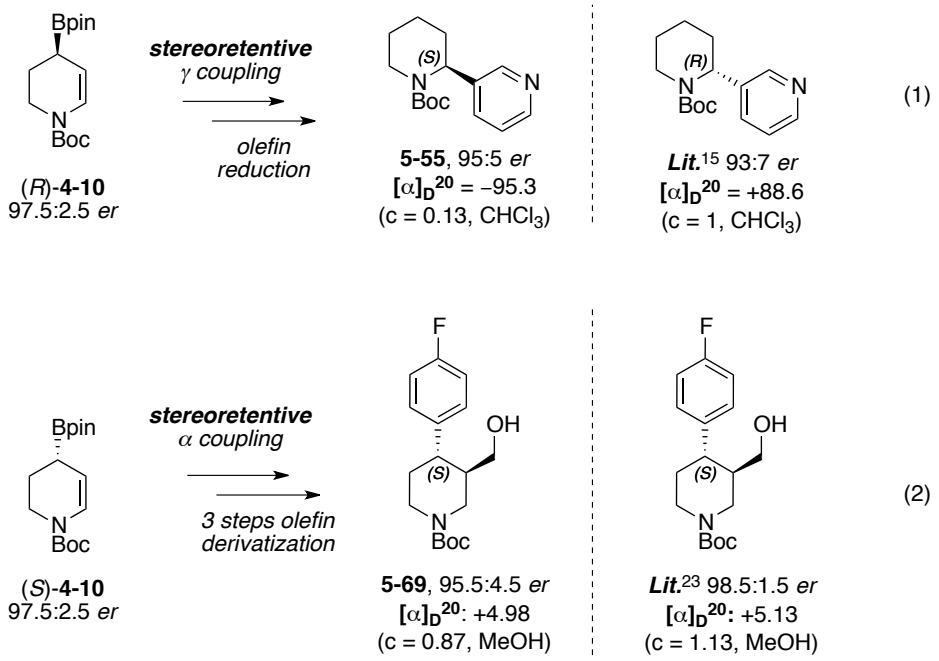
We undertook a de novo catalytic enantioselective synthesis of (3*S*,4*R*)-(+)-paroxetine from 4-aryl dehydropiperidine **5-67**, which was obtained exclusively through an α-regioselective (α/γ = 11:1, separable) and stereospecific cross-coupling between boronate (*S*)-**4-10** and 4-fluorophenyl bromide (Scheme 5-12). Notably, this key cross-coupling step was performed on a gram-scale. Subsequently, a highly regio- and diastereoselective hydroboration of **5-67** afforded secondary boronate **5-68**,[204] which was subjected to a Matteson homologation[205] to afford, after an oxidative work-up, the alcohol intermediate **5-69**. Because the latter is a known, advanced intermediate to paroxetine,[206] this sequence constitutes a formal synthesis of (+)-paroxetine that can be accomplished in only 7 steps from commercial *t*-Boc 4-piperidinone. Additionally, this synthesis features two high-yielding one-pot processes with no significant enantiomeric erosion, which demonstrates efficient protocols for the further modifications of the cyclic enamide moiety carried in the γ-coupling product.

The above-described syntheses of (+)-anabasine and (+)-paroxetine highlight how the use of a different catalyst/ligand in the Suzuki-Miyaura cross-coupling provides a regiodivergent access to optically enriched piperidine derivatives of great utility in medicinal chemistry. Moreover, as shown in the synthesis of paroxetine (Scheme 5-12), the residual unsaturation in the dehydro heterocyclic products offers numerous other opportunities to transform both the α and γ coupling products into more complex targets.

5.5.4 Verification of stereoretentive coupling of chiral heterocyclic allylic boronates

As discussed in Section 5.1, based on the *syn*-S_E2' intramolecular transmetallation mechanism demonstrated by the Crudden and Aggarwal groups (Scheme 5-2),[190] we anticipated that both γ- and α-selective Suzuki-Miyaura coupling of chiral heterocyclic allylic boronates would proceed in a stereoretentive fashion. To support this assumption, the above asymmetric formal syntheses of (+)-anabasine

and (+)-paroxetine provided strong chemical proof of absolute stereochemistry of both γ- and α-coupling products. As shown in the Equation 1 of Scheme 5-13, upon γ-coupling of (*R*)-**4-10** with 3-bromopyridine and sequential olefin reduction, the optically pure γ-product **5-55** was obtained. The latter is a known compound with established stereochemistry. By comparing the measured optical rotation value of **5-55** with that of a previously reported sample,[197] the absolute configuration of **5-55** was confirmed to be *S*, which further supports the assumption that the γ-coupling is stereoretentive.



Scheme 5-13: Verification of stereoretentive coupling through the asymmetric formal syntheses of (+)-anabasine and (+)-paroxetine.

On the other hand, upon α-coupling of (*S*)-**4-10** followed by the 3-step olefin derivatization (Scheme 5-13, Equation 2), the enantiopure α-product **5-69** was isolated. This intermediate is a previously reported compound with known stereochemistry. Through comparison of optical rotation values, the absolute stereochemistry of **5-69** was assigned to be *S*,[206] which confirmed that the α-

coupling proceeds with retention of stereochemistry.

5.6 Mechanistic proposal

This cross-coupling methodology demonstrates an unprecedented level of regiochemical control with a near-perfect level of retention of stereochemistry. Three different catalyst-ligand systems, through extensive optimization (Tables 5-1 to 5-4), have been identified to give rise to this level of control in the regiodivergent formation of α and γ regioisomers. As an attempt to rationalize these outcomes, Figure 5-9 proposes a unifying mechanism for all three ligand systems: N-heterocyclic carbene (Pd-PEPPSI-IPr), XPhos, and $(4\text{-}CF_3\text{-}C_6H_4)_3P$ (see structures in Figure 5-8). Under the aqueous base conditions employed, oxidative addition of the electrophile provides the hydroxyl-Pd(II) complex **A**.[195] The subsequent transmetallation may occur through either an S_E or S_E' transmetallation mechanism. The S_E' mode of transmetallation is thought to be prevalent with phosphine-ligated Pd(II) species.[188,190] Consequently, in these conditions both XPhos and $(4\text{-}CF_3\text{-}C_6H_4)_3P$ are expected to first provide σ-bonded allylic Pd(II) complex **B** *via* a *syn*-S_E' pathway made favorable through coordination of the electron-deficient Pd(II) to the electron-rich alkene. From complex **B**, the bulky strong σ-donor phosphine ligand XPhos provides the steric effect to encourage a fast reductive elimination that yields the γ regioisomer product.[192,207] Being smaller and less conducive of reductive elimination, it is possible that the weaker, more labile σ-donor phosphine $(4\text{-}CF_3\text{-}C_6H_4)_3P$ promotes slippage of the η^1 σ-bonded complex **B** to the η^3 π-allyl intermediate **C** (*i.e.*, $K\sigma\text{–}\pi > K_{RE}$). The latter could now undergo π–σ equilibration between the two regioisomeric σ-bonded complexes **B** and **D**, which is presumed to favor **D** as the thermodynamic isomer due to heteroatom conjugation with the olefin.[187] Accordingly, reductive elimination on complex **D** affords the α regioisomer. The NHC ligated catalyst Pd-PEPPSI-IPr appears to behave differently. This class of catalysts was previously alleged to transmetallate efficiently with simple

allylboronic esters by a S_E mechanism to give α substitution to the σ-bonded complex **D** directly.[191] This type of NHC complex is suspected to undergo a fast reductive elimination, and thus provide the α regioisomeric product with high selectivity. The reasons for its preference for a S_E transmetallation are unclear, but it may be attributed to the bulk and nondissociative character of the NHC ligand that disfavors an alkene-directed S_E' mechanism. Because the C–B bond in complex **A** is "locked" on a specific face of the allyl unit, the reaction is enantiospecific regardless of the three pathways described above. The observed retention of configuration is the outcome of a stereoretentive transmetallation followed by a stereoretentive reductive elimination.[208] Whereas the occurrence of enantiomeric erosion is possible in reactions of chiral π-allyl palladium complexes,[209] it is observed only to a minimal extent in these sp^3-sp^2 cross-couplings.

Although it requires experimental evidence, the above mechanistic proposal satisfactorily rationalizes the ligand-controlled regiodivergence in the formation of α and γ cross-coupling products. Additionally, it highlights the important role of the heteroatom in providing a strong π-donating alkene that favors the S_E' pathway when using XPhos or $(4\text{-}CF_3\text{-}C_6H_4)_3P$ as ligands, and in favoring the most stable σ-bonded Pd(II) complex **D** when using $(4\text{-}CF_3\text{-}C_6H_4)_3P$. In contrast, the electronic properties of the alkene in heterocyclic allylboronates **4-6** and **4-10** should not play a determinant role when using the NHC liganded catalyst.

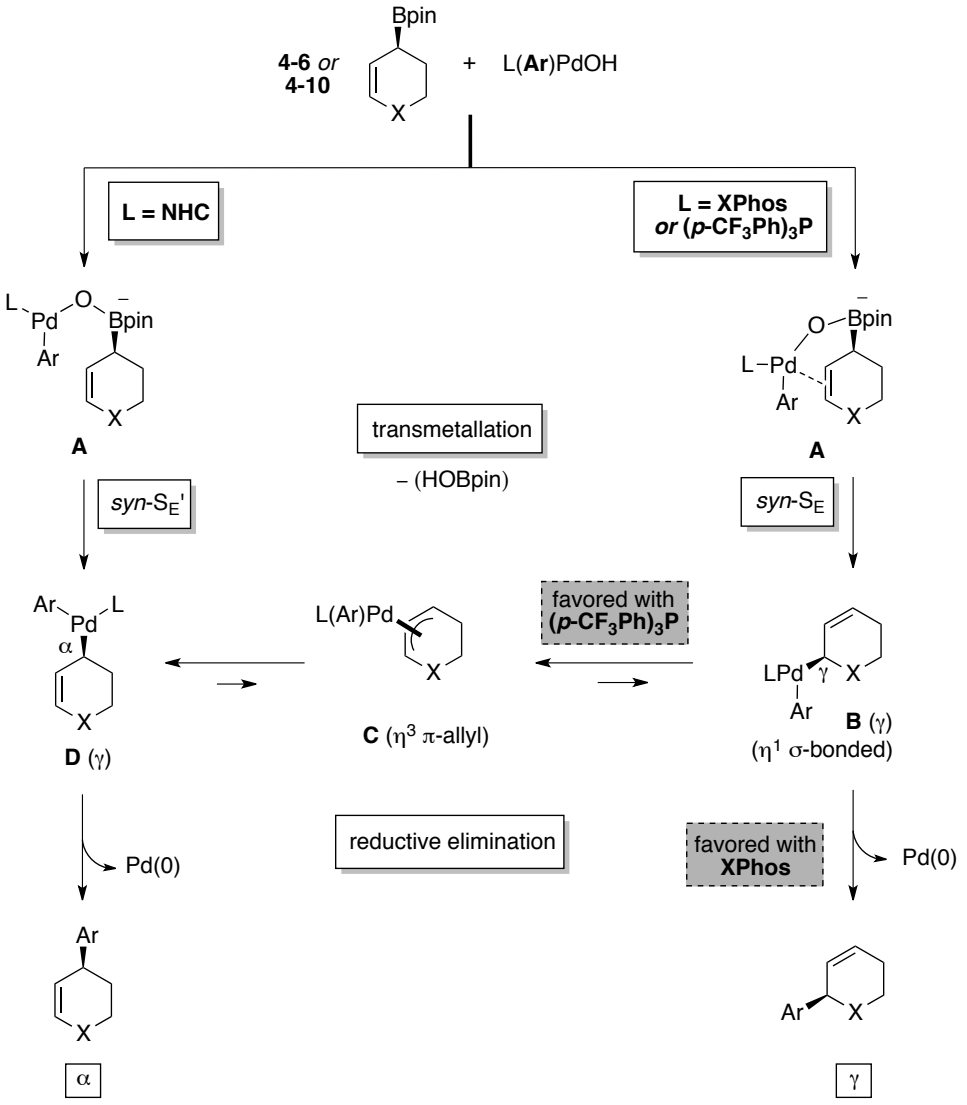
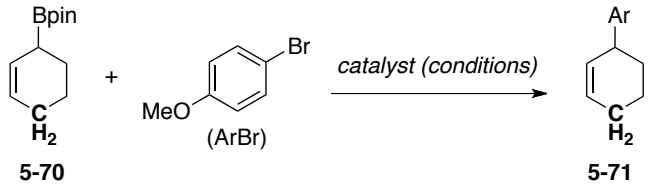


Figure 5-9: Proposed mechanistic paths for the ligand-controlled regioselective Suzuki-Miyaura cross-coupling of heterocyclic allylic boronates **4-6** and **4-10**.

To provide further evidence for the importance of the heteroatom, we conducted control experiments where the non-heteroatom conjugated allylboronate **5-70** was employed as the coupling partner. Indeed, as shown in Scheme 5-14, when using the carbocyclic analogue **5-70**, only the NHC catalyst Pd-PEPPSI-IPr was able to promote the coupling to form product **5-71**. On the other hand, the phosphine ligands XPhos and $(4\text{-}CF_3\text{-}C_6H_4)_3P$ showed no reactivity. This control experiment

supports the requirement for a strong π-donating alkene as found in the heteroatom-conjugated substrates **4-6** and **4-10**, as well as a S_E' transmetallation pathway associated with the phosphines XPhos and $(4\text{-}CF_3\text{-}C_6H_4)_3P$.



5-70 **5-71**

catalyst (conditions)	isolated yield
Pd-PEPPSI-IPr (Table 5-4, entry 9)	**46%**
Pd (0), XPhos (Table 5-3, entry 3)	0%
Pd (0), $(4\text{-}CF_3\text{-}C_6H_4)_3P$ (Table 5-2, entry 9)	0%

Scheme 5-14: Control experiment for the coupling of the non-heteroatom conjugated allylboronate **5-70**.

5.7 Summary

Overall, this study demonstrates that a careful choice of ligand for the palladium catalyst can successfully achieve a control of several levels of selectivity, notably, stereoselectivity and regioselectivity in the Suzuki-Miyaura cross-coupling reaction. Such an ability to merge stereocontrol with a divergent control of regioselectivity was achieved with a class of heterocyclic substrates of tremendous importance in the field of drug discovery. This methodology provides a conceptually novel and general way of synthesizing optically enriched 2- and 4-aryl, heteroaryl and alkenyl substituted piperidines and pyrans by direct sp^2-sp^3 coupling. These findings provide much anticipation for the role of transition metal catalysis to greatly expand its breadth of application from its resounding success in the coupling of "flat" sp^2-hybridized substrates, to now include the construction of stereochemically defined sp^3 carbon centers in biologically relevant molecules with a potential for improved clinical success.[210] It is envisioned that a series of

biologically important compounds, to name just a few in Figure 5-6, can be readily accessed within a few steps when the advantageous chiral heterocyclic allylic boronates are employed as the Suzuki-Miyaura cross-coupling partners.

5.8 Experimental

5.8.1 General information

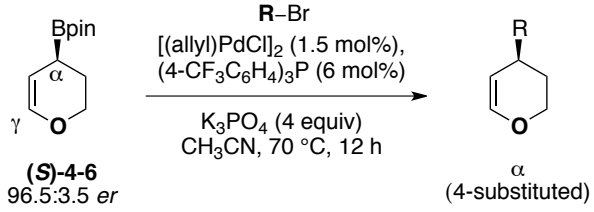
Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were obtained from a MBraun MB SPS* solvent system prior to use. The anhydrous 1,4-dioxane was purchased from Sigma-Aldrich, 99.8%, and it was deoxygenated with dry nitrogen for 3 hours before use. $Pd(OAc)_2$ was purchased from Sigma-Aldrich, ≥99.9%; chiral ligands (+)-TANIAPHOS and (−)-TANIAPHOS were synthesized on gram-scale respectively according to the literature procedure.[211] Other ligands and palladium catalysts were obtained from commercial sources. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data is 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; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets; dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) ion source with double focussing sector analyzer (Kratos Analytical MS-50G) or electrospray (ESI) ion source with orthogonal acceleration TOF analyzer (Agilent Technologies 6220 oaTOF). Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The

enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD (4.6 × 250 mm, inner diameter × length; particle size 5 μm), Chiralpak-AS (4.6 × 250 mm, inner diameter × length; particle size 5 μm), Chiralpak-IC (4.6 × 150 mm, inner diameter × length; particle size 5 μm) or Chiralpak-IB (4.6 × 150 mm, inner diameter × length; particle size 5 μm) columns.

Enol triflates **4-4** and **4-9**, as well as allylic boronates **4-6** and **4-10** were all prepared on gram-scale (0.5 mmol) following our previously published procedures.[182,183] Careful purification of both allylic boronates **4-6** and **4-10** was required prior to the cross-coupling reactions. When purified *via* silica gel flash chromatography, these air-sensitive allylic boronates tend to develop considerable affinity to the silica gel over time, resulting in a difficult purification, especially on a smaller scale (below 0.5 mmol). To obtain good purity without diminishing the isolated yield on a small scale, some important technical tips need to be considered: 1) after evaporating the solvent from the crude reaction, immediately run a quick silica gel flash chromatography; 2) use silica columns that are short and wide to avoid long elution times; 3) quantitate the silica gel (around 100/1, w/w, silica gel to crude compound ratio).

5.8.2 Experimental and spectral data for products of Schemes 5-5 and 5-6

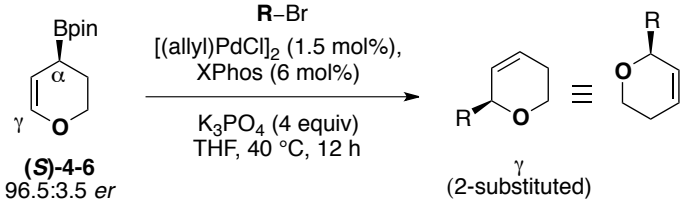
<u>General procedure A</u> towards 4-substituted pyrans (Scheme 5-5):



Complex $[(allyl)PdCl]_2$ (1.4 mg, 3.8 μmol) and $(4\text{-}CF_3C_6H_4)_3P$ (7.0 mg, 15 μmol) was added in a flamed-dried reaction tube, which was then flushed with nitrogen.

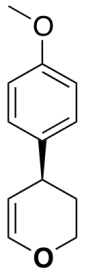
Dry acetonitrile (1.0 mL) was added and the mixture was stirred for 10 minutes. Allylic heterocyclic boronic ester (*S*)-**4-6** (0.30 mmol, 1.2 equiv) was added *via* syringe, which was washed three times with dry acetonitrile (0.5 mL portion). The organobromide (0.25 mmol) and aqueous K_3PO_4 solution (2.5 M in H_2O, 0.5 mL, 5 equiv) were added and the resulting reaction mixture was allowed to stir under nitrogen at 70 °C for 12 h. The mixture was allowed to cool down to room temperature, passed through a short pipette loaded with silica gel, and rinsed with 15 mL ethyl acetate. The solvents were then evaporated to yield a crude oil, which was subjected to silica gel flash chromatography (15% ethyl acetate/hexane, unless otherwise addressed) to afford the pure 4-substituted pyran product.

<u>General procedure B</u> towards 2-substituted pyrans (Scheme 5-6):



Complex $[(allyl)PdCl]_2$ (1.4 mg, 3.8 μmol) and XPhos (6.4 mg, 15 μmol) was added in a flamed-dried reaction tube, which was then flushed with nitrogen. Dry THF (1.0 mL) was added and the mixture was stirred for 10 minutes. Allylic heterocyclic boronic ester (*S*)-**4-6** (0.3 mmol, 1.2 equiv) was added *via* syringe, which was washed three times with dry THF (0.5 mL portion). The organobromide (0.25 mmol) and aqueous K_3PO_4 solution (2.5M in H_2O, 0.5 mL, 5 equiv) were then added, and the resulting reaction mixture was allowed to stir under nitrogen at 40 °C for 12 h. The mixture was allowed to cool down to room temperature, passed through a short pipette loaded with silica gel, and rinsed with 15 mL ethyl acetate. The solvents were then evaporated to yield a crude oil, which was subjected to silica gel flash chromatography (15% ethyl acetate/hexane, unless otherwise addressed) to afford the pure 2-substituted pyran product.

(*S*)-4-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyran (5-21)



By following the general procedure A, the title compound **5-21** was synthesized from (*S*)-**4-6** and the the corresponding aryl bromide. The crude product, containing **5-21** in a 15 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (37 mg, 78 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.67.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.23-7.20 (m, 2H), 6.90-6.87 (m, 2H), 6.57 (dd, J = 6.2, 2.0 Hz, 1H), 4.77 (apparent ddt, J = 6.3, 3.4, 0.8 Hz, 1H), 4.05-3.96 (m, 2H), 3.82 (s, 3H), 3.48-3.45 (m, 1H), 2.21-2.15 (m, 1H), 1.84 (dddd, J = 13.8, 6.9, 6.9, 3.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 158.1, 144.6, 137.8, 128.6, 113.8, 103.9, 63.8, 55.3, 35.4, 32.3.

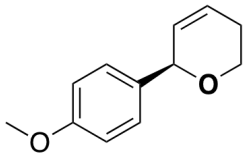
IR (microscope, cm^{-1}) 3034, 2958, 2924, 2836, 1612, 1586, 1513.

HRMS (EI) for $C_{12}H_{14}O_2$: calcd. 190.0994; found 190.0993.

$[\alpha]_D^{20}$: −2.8 (c = 0.15, $CHCl_3$).

HPLC (Chiralcel IC): 10:90 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 12.1 min, T_{minor} = 11.0 min, 95:5 *er*.

(*R*)-6-(4-Methoxyphenyl)-3,6-dihydro-2*H*-pyran (5-22)



By following the general procedure B, the title compound **5-22** was synthesized from (*S*)-**4-6** and the the corresponding aryl bromide. The crude product, containing **5-22** in a single regioisomer, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (44 mg, 92 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.60.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.34-7.31 (m, 2H), 6.92-6.89 (m, 2H), 6.04-6.00 (m, 1H), 5.82 (apparent dq, J = 10.3, 2.0 Hz, 1H), 5.12 (apparent quintet, J = 2.6 Hz, 1H), 4.01-3.97 (m, 1H), 3.83-3.79 (m, 3H), 2.40-2.32 (m, 1H), 2.13-2.06 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 159.3, 133.5, 129.6, 128.9, 125.2, 113.8, 75.6, 62.9, 55.3, 25.2.

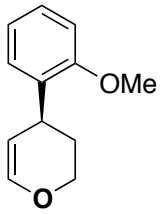
IR (microscope, cm^{-1}) 3058, 3028, 2953, 2930, 2873, 2835, 1643, 1610, 1583.

HRMS (EI) for $C_{12}H_{14}O_2$: calcd. 190.0994; found 190.0993.

$[\alpha]_D^{20}$: +4.8 (c = 0.08, $CHCl_3$).

HPLC (Chiralcel OD): 3:97 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 33.9 min, T_{minor} = 39.6 min, 95:5 *er*.

(*S*)-4-(2-Methoxyphenyl)-3,4-dihydro-2H-pyran (5-25)



By following the general procedure A, the title compound **5-25** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-25** in a 5 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (20% Et_2O/Hexane) to afford the title compound (34 mg, 71 % yield).

Clear oil; TLC (Et_2O:Hexane, 15:85 v/v): Rf = 0.51.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.32 (dd, J = 7.5, 1.7 Hz, 1H), 7.18 (ddd, J = 7.7, 7.5, 1.5 Hz, 1H), 6.95 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.87 (dd, J = 8.2, 0.8 Hz, 1H), 6.62 (dd, J = 6.3, 1.9 Hz, 1H), 4.72 (dd, J = 6.3, 3.8 Hz, 1H), 4.00 (ddd, J = 10.4, 7.2, 3.0 Hz, 1H), 3.93 (ddd, J = 10.9, 8.2, 2.9 Hz, 1H), 3.88 (dd, J = 3.8, 2.0 Hz, 1H), 3.85 (s, 3H), 2.20 (dddd, J = 14.6, 9.6, 3.2, 3.0 Hz, 1H), 1.82-1.73 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 156.9, 145.1, 133.6, 128.8, 127.3, 120.3, 110.1, 103.4, 63.8, 55.3, 29.9, 29.2.

IR (microscope, cm^{-1}) 3057, 2957, 2932, 2875, 2835, 1645, 1598, 1585.

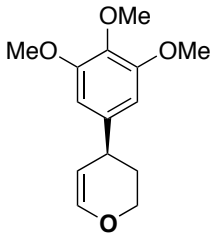
HRMS (EI) for $C_{12}H_{14}O_2$: calcd. 190.0994; found 190.0994.

$[\alpha]_D^{20}$: −31.9 (c = 0.32, $CHCl_3$).

Enantiomeric ratio of compound **5-25** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after

hydroboration/oxidation.

(*S*)-4-(3,4,5-Trimethoxyphenyl)-3,4-dihydro-2H-pyran (5-26)



By following the general procedure A, the title compound **5-26** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-26** in a 9 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/Hexane) to afford the title compound (47 mg, 76% yield).

Clear oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.50.

^{1}H NMR (498 MHz, $CDCl_3$, 25 °C) δ 6.57 (dd, J = 6.2, 1.9 Hz, 1H), 6.49 (s, 2H), 4.75 (dddd, J = 6.3, 3.2, 1.0, 0.7 Hz, 1H), 4.04-3.97 (m, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.43 (dddd, J = 6.4, 6.2, 4.0, 1.6 Hz, 1H), 2.24-2.13 (m, 1H), 1.89-1.82 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) δ 153.2, 145.0, 141.5, 136.5, 104.7, 103.6, 64.0, 60.9, 56.2, 36.6, 32.3.

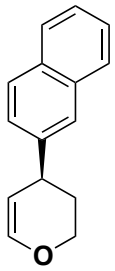
IR (microscope, cm^{-1}) 3056, 2938, 2876, 2836, 1643, 1588, 1506.

HRMS (EI) for $C_{14}H_{18}O_4$ (m/z): calcd. 250.1205; found 250.1202.

$[\alpha]_D^{20}$: −72.6 (c = 0.50, $CHCl_3$).

HPLC (Chiralcel IC): 10:90 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 210 nm, T_{major} = 18.8 min, T_{minor} = 17.3 min, 95:5 *er*.

(*S*)-4-(Naphthalen-2-yl)-3,4-dihydro-2H-pyran (5-27)



By following the general procedure A, the title compound **5-27** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-27** in a 7 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (20% Et_2O/Hexane) to afford the title compound (37 mg, 70% yield).

White waxy oil; TLC (Et_2O:Hexane, 20:80 v/v): Rf = 0.38.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.87-7.78 (m, 3H), 7.72 (d, J = 1.1 Hz, 1H), 7.52-7.38 (m, 3H), 6.66 (dd, J = 6.3, 1.9 Hz, 1H), 4.89 (dddd, J = 6.3, 3.6, 0.8, 0.8 Hz, 1H), 4.11-3.98 (comp m, 2H), 3.68 (dddd, J = 6.3, 6.2, 3.8, 2.0 Hz, 1H), 2.31-2.23 (dddd, J = 9.9, 6.3, 5.2, 4.8 Hz, 1H), 2.0-1.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 145.1, 143.1, 133.5, 132.3, 128.1, 127.7, 127.62, 126.3, 126.1, 126.1, 125.5, 103.5, 63.8, 36.3, 32.0.

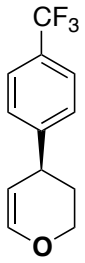
IR (microscope, cm^{-1}) 3055, 2948, 2928, 1644, 1600, 1506.

HRMS (EI) for $C_{15}H_{14}O$ (m/z): calcd. 210.1045; found 210.1044.

$[\alpha]_D^{20}$: −155.7 (c = 0.83, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.3 mL/minute, λ = 230 nm, T_{major} = 10.3 min, T_{minor} = 9.7 min, 96:4 *er*.

(*S*)-4-(4-(Trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran (5-28)



By following the general procedure A, the title compound **5-28** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-28** in a 6 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (5% Et_2O/Hexane) to afford the title compound (41 mg, 72% yield).

Clear oil; TLC (Et_2O:Hexane, 20:80 v/v): Rf = 0.55

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.57 (d, J = 8.0 Hz, 2H), 7.39 (dd, J = 8.0, 0.5 Hz, 2H), 6.60 (dd, J = 6.3, 1.9 Hz, 1H), 4.75 (dddd, J = 6.2, 3.4, 3.4, 0.5 Hz, 1H), 4.07-3.93 (m, 2H), 3.58-3.54 (m, 1H), 2.21 (dddd, J = 13.3, 6.6, 6.5, 3.0 Hz, 1H), 1.84 (dddd, J = 14.0, 7.2, 3.6, 3.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 149.7, 145.4, 128.0, 125.4, 125.4, 125.3, 125.3, 102.62, 63.7, 36.2, 32.0.

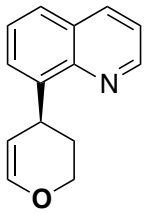
IR (microscope, cm^{-1}) 3062, 2932, 2877, 1645, 1618.

HRMS (EI) for $C_{12}H_{11}F_3O$ (m/z): calcd. 228.0762; found 228.0767.

$[\alpha]_D^{20}$: −53.3 (c = 0.50, $CHCl_3$).

HPLC (Chiralcel IB): 5:95 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 27.6 min, T_{minor} = 25.1 min, 95:5 *er*.

(*S*)-8-(3,4-Dihydro-2H-pyran-4-yl)quinolone (5-29)



By following the general procedure A, the title compound **5-29** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-29** in a 10 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (20% Et_2O/Hexane) to afford the title compound (48 mg, 91% yield).

Clear oil; TLC (EtOAc:Hexane, 20:80 v/v): Rf = 0.43

^{1}H NMR (498 MHz, $CDCl_3$, 25 °C) δ 8.94 (dd, J = 4.2, 1.8 Hz, 1H), 8.16 (dd, J = 8.2, 1.8 Hz, 1H), 7.71 (ddd, J = 9.5, 7.6, 1.3 Hz, 2H), 7.52 (dd, J = 8.0, 7.5 Hz, 1H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 6.74-6.67 (m, 1H), 4.92-4.82 (m, 2H), 4.10 (ddd, J = 10.3, 7.2, 3.0 Hz, 1H), 3.99 (ddd, J = 10.8, 7.9, 2.9 Hz, 1H), 2.53-2.40 (m, 1H), 1.92-1.87 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 149.4, 146.1, 145.4, 143.9, 136.5, 128.9, 128.2, 126.4, 126.3, 121.0, 103.9, 64.1, 30.9, 30.3.

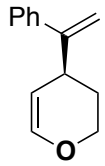
IR (microscope, cm^{-1}) 3054, 3001, 2964, 2873, 1644, 1612, 1596, 1574, 1497.

HRMS (EI) for $C_{14}H_{13}NO$ (m/z): calcd. 211.0997; found 211.0998.

$[\alpha]_D^{20}$: +60.4 (c = 0.33, $CHCl_3$).

Enantiomeric ratio of compound **5-29** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after hydroboration/oxidation.

(*S*)-4-(1-Phenylvinyl)-3,4-dihydro-2H-pyran (5-30)



By following the general procedure A, the title compound **5-30** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-30** in a 7 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (4% Et_2O/Hexane) to afford the title compound (40 mg, 86% yield).

Clear oil; TLC (Et_2O:Hexane, 10:90 v/v): Rf = 0.60

^{1}H NMR (498 MHz, $CDCl_3$, 25 °C) δ 7.41–7.28 (m, 4H), 6.54 (dd, J = 6.3, 1.8 Hz, 1H), 5.40 (d, J = 1.3 Hz, 1H), 5.18 (dd, J = 1.2, 1.0 Hz, 1H), 4.77 (ddd, J = 5.9, 3.9, 0.8 Hz, 1H), 3.98-3.90 (m, 2H), 3.42 (dd, J = 10.1, 4.7 Hz, 1H), 2.04-1.95 (m, 1H), 1.67-1.59 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 151.9, 144.8, 141.1, 128.4, 127.5, 126.6, 114.5, 102.9, 63.1, 34.5, 27.9.

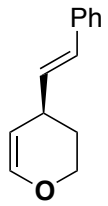
IR (microscope, cm^{-1}) 3079, 3058, 2951, 2928, 2874, 1646, 1624, 1598, 1493.

HRMS (EI) for $C_{13}H_{14}O$ (m/z): calcd. 186.1045; found 186.1047.

$[\alpha]_D^{20}$: −110.1 (c = 0.20, $CHCl_3$).

Enantiomeric ratio of compound **5-30** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after dihydroxylation.

(*R*,*E*)-4-Styryl-3,4-dihydro-2H-pyran (5-31)



By following the general procedure A, the title compound **5-31** was synthesized from (*S*)-**4-6** and corresponding alkenyl bromide. The crude sample, containing **5-31** in a 9 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (4% Et_2O/Hexane) to afford the title compound (36 mg, 78 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.35 (m, 2H), 7.32-7.29 (m, 2H), 7.23-7.20 (m, 1H), 6.48 (dd, J = 6.5, 2.0 Hz , 1H), 6.43 (d, J = 15.0 Hz , 1H), 6.17 (dd, J = 15.7, 7.0 Hz , 1H), 4.70 (dd, J = 6.0, 3.5 Hz , 1H), 4.01 (dd, J = 5.98 Hz , 2H), 3.05-3.00 (m, 1H), 2.09-2.05 (m, 1H), 1.79-1.75 (m, 1H).

Clear oil; TLC (Et_2O:Hexane, 2:98 v/v): Rf = 0.29.

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.41, 137.47, 133.85, 130.17, 128.58, 127.19, 126.16, 103.02, 63.58, 33.35, 29.14.

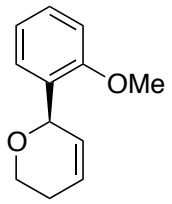
IR (microscope, cm^{-1}) 3058, 3026, 2955, 2924, 2853, 1644, 1600, 1493, 1451.

HRMS (EI) for $C_{13}H_{14}O$: calcd. 186.1045; found 186.1041.

$[\alpha]_D^{20}$: −306.8 (c = 0.41, $CHCl_3$).

Enantiomeric ratio of compound **5-31** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after dihydroxylation.

(*R*)-6-(2-Methoxyphenyl)-3,6-dihydro-2H-pyran (5-32)



By following the general procedure B, the title compound **5-32** was synthesized as a single regioisomer from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample was subjected to silica gel flash chromatography (20% Et_2O/Hexane) to afford the title compound (36 mg, 74% yield).

Clear oil; TLC (Et_2O:Hexane, 20:80 v/v): Rf = 0.38

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.43 (dd, J = 7.5, 1.7 Hz, 1H), 7.29-7.23 (m, 1H), 6.96 (ddd, J = 7.5, 7.2, 0.5 Hz, 1H), 6.89 (dd, J = 8.2, 0.6 Hz, 1H), 5.97 (dddd, J = 7.6, 7.5, 2.5, 2.5 Hz, 1H), 5.79 (dddd, J = 10.1, 4.0, 2.0, 2.0, 2.0 Hz, 1H), 5.63 (ddd, J = 5.1, 2.5, 2.5 Hz, 1H), 4.02 (ddd, J = 11.2, 4.7, 4.5 Hz, 1H), 3.88-3.78 (m, 4H), 2.40-2.28 (m, 1H), 2.14-2.03 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 156.8, 129.5, 129.3, 128.8, 128.1, 124.9, 120.5, 110.6, 69.9, 63.1, 55.5, 25.3.

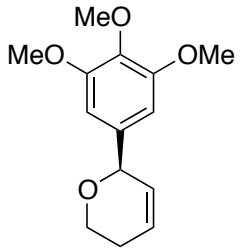
IR (microscope, cm^{-1}) 3035, 2999, 2958, 2922, 2853, 2836, 1720, 1601, 1589, 1491, 1463.

HRMS (EI) for $C_{12}H_{14}O_2$ (m/z): calcd. 190.0994; found 190.0997.

$[\alpha]_D^{20}$: +88.1 (c = 0.28, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 11.2 min, T_{minor} = 23.9 min, 96:4 *er*.

(*R*)-6-(3,4,5-Trimethoxyphenyl)-3,6-dihydro-2H-pyran (5-33)



By following the general procedure B, the title compound **5-33** was synthesized as a single regioisomer from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample was subjected to silica gel flash chromatography (50% Et_2O/Hexane) to afford the title compound (44 mg, 71% yield).

Clear oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.31

^{1}H NMR (498 MHz, $CDCl_3$, 25 °C) δ 6.61 (s, 2H), 6.0 (dddd, J = 7.0, 6.4, 5.0, 2.5 Hz, 1H), 5.81 (dddd, J = 10.6, 2.0, 2.0, 2.0 Hz, 1H), 5.06 (ddd, J = 4.7, 3.0, 2.5 Hz, 1H), 4.02 (ddd, J = 11.1, 5.5, 3.0 Hz, 1H), 3.93-3.74 (m, 8 H), 2.38 (dddd, J = 14.3, 11.3, 5.5, 2.6 Hz, 1H), 2.12-2.02 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ 153.3, 137.7, 137.0, 129.4, 125.6, 104.6, 63.4, 60.8, 56.1, 25.1.

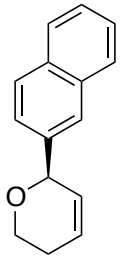
IR (microscope, cm^{-1}) 3032, 2994, 2958, 2937, 2837, 1591, 1506.

HRMS (EI) for $C_{14}H_{18}O_4$ (m/z): calcd. 250.1205; found 250.1201.

$[\alpha]_D^{20}$: +32.5 (c = 0.36, $CHCl_3$).

Enantiomeric ratio of compound **5-33** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after diimide reduction.

(*R*)-6-(Naphthalen-2-yl)-3,6-dihydro-2H-pyran (5-34)



By following the general procedure B, the title compound **5-34** was synthesized as a single regioisomer from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample was subjected to silica gel flash chromatography (10% Et_2O/Hexane) to afford the title compound (51 mg, 98% yield).

White solid (m.p.: 63.0–65.1 °C); TLC (Et_2O:Hexane, 20:80 v/v): Rf = 0.60

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.87-7.81 (m, 3H), 7.53 (dd, J = 8.5, 1.7 Hz, 1H), 7.50-7.45 (m, 2H), 6.06 (dddd, J = 10.1, 5.0, 2.7, 2.5 Hz, 1H), 5.92 (dddd, J = 10.2, 2.0, 2.0, 2.0 Hz, 1H), 5.32 (ddd, J = 2.6, 2.5, 2.5 Hz, 1H), 4.06 (ddd, J = 11.2, 5.4, 3.8 Hz, 1H), 3.87 (dddd, J = 11.3, 8.6, 4.2 Hz, 1H), 2.48-2.35 (m, 1H), 2.20-2.08 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 138.8, 133.3, 133.1, 129.5, 128.3, 128.1, 127.7, 126.3, 126.0, 125.9, 125.6, 125.5, 77.7, 76.2, 63.1, 25.3.

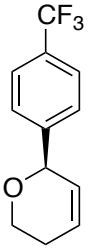
IR (microscope, cm^{-1}) 3055, 3034, 2960, 2921, 2856, 1688, 1646, 1600, 1508.

HRMS (EI) for $C_{15}H_{14}O$ (m/z): calcd. 210.1045; found 210.1044.

$[\alpha]_D^{20}$: +147.1 (c = 1.02, $CHCl_3$).

HPLC (Chiralcel IC): 2:98 *i*-PrOH/Hexane, 25 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 18.7 min, T_{minor} = 5.0 min, 96.5:3.5 *er*.

(*R*)-6-(4-(Trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran (5-35)



By following the general procedure B, the title compound **5-35** was synthesized as a single regioisomer from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample was subjected to silica gel flash chromatography (15% ethyl acetate/Hexane) to afford the title compound (55 mg, 97 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.57

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.61 (d, J = 8.1 Hz, 2H), 7.50 (d J = 8.1, 2H), 6.02 (dddd, J = 10.2, 5.0, 2.5, 2.0 Hz, 1H), 5.79 (dddd, J = 10.3, 2.0, 2.0, 2.0 Hz, 1H), 5.19 (ddd, J = 5.2, 3.0, 2.7 Hz, 1H), 4.01 (ddd, J = 11.4, 5.5, 3.5 Hz, 1H), 3.83 (ddd, J = 11.3, 8.9, 4.1 Hz, 1H), 2.42-2.32 (m, 1H), 2.14-2.05 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 145.5, 128.8, 127.6, 125.8, 125.5, 125.4, 125.4, 125.4, 77.3, 63.3, 25.1.

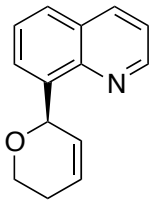
IR (microscope, cm^{-1}) 3039, 2966, 2926, 2858, 1645, 1619.

HRMS (EI) for $C_{12}H_{11}F_3O$ (m/z): calcd. 228.0762; found 228.0765.

$[\alpha]_D^{20}$: −8.7 (c = 0.12, $CHCl_3$).

HPLC (Chiralcel IB): 2:98 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 210 nm, T_{major} = 48.7 min, T_{minor} = 44.0 min, 95:5 *er*.

(*R*)-8-(5,6-Dihydro-2H-pyran-2-yl)quinolone (5-36)



By following the general procedure B, the title compound **5-36** was synthesized as a single regioisomer from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample was subjected to silica gel flash chromatography (20% Et_2O/Hexane) to afford the title compound (45 mg, 86% yield).

Yellow oil; TLC (Et_2O:Hexane, 20:80 v/v): Rf = 0.28

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.96 (dd, J = 4.2, 1.8 Hz, 1H), 8.15 (dd, J = 8.3, 1.8 Hz, 1H), 7.90 (dd, J = 7.0, 1.5 Hz, 1H), 7.76 (dd, J = 8.2, 1.4 Hz, 1H), 7.55 (dd, J = 8.0, 7.3 Hz, 1H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 6.53-6.52 (m, 1H), 6.05-5.94 (m, 2H), 4.15 (ddd, J = 11.2, 5.4, 3.0 Hz, 1H), 3.99 (ddd, J = 11.2, 9.2, 4.0 Hz, 1H), 2.51-2.38 (m, 1H), 2.19-2.05 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 149.7, 145.7, 139.3, 136.4, 130.2, 128.3, 127.5, 127.4, 126.4, 124.6, 121.0, 77.3, 71.1, 63.7, 25.4.

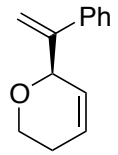
IR (microscope, cm^{-1}) 3037, 2957, 2919, 2852, 1615, 1596, 1577, 1498.

HRMS (EI) for $C_{14}H_{13}NO$ (m/z): calcd. 211.0997; found 211.0993.

$[\alpha]_D^{20}$: +129.4 (c = 0.81, $CHCl_3$).

HPLC (Chiralcel IB): 25:75 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 280 nm, T_{major} = 9.1 min, T_{minor} = 35.7 min, 96:4 *er*.

(*R*)-6-(1-Phenylvinyl)-3,6-dihydro-2H-pyran (5-37)



By following the general procedure A, the title compound **5-37** was synthesized from (*S*)-**3** and the corresponding aryl bromide. The crude sample, containing **5-37** in a 3 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (5% Et_2O/Hexane) to afford the title compound (30 mg, 65 % yield).

Clear oil; TLC (Et_2O:Hexane, 10:90 v/v): Rf = 0.45

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.51-7.47 (m, 2H), 7.36-7.27 (m, 3H), 5.94 (ddd, *J* = 10.2, 6.2, 3.8 Hz, 1H), 5.73 (ddd, *J* = 10.3, 4.2, 2.1 Hz, 1H), 5.50 (d, *J* = 1.4 Hz, 1H), 5.37 (app s, 1H), 5.13-5.08 (m, 1H), 4.00 (ddd, *J* = 11.1, 5.5, 5.0 Hz, 1H), 3.79 (ddd, *J* = 11.5, 7.0, 4.5 Hz, 1H), 2.29-2.21 (m, 1H), 2.16-2.05 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$, 25 °C) δ 147.6, 139.9, 128.5, 128.3, 127.6, 126.8, 125.5, 115.6, 77.3, 75.3, 62.2, 25.3.

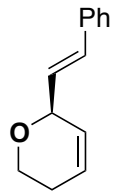
IR (microscope, cm^{-1}) 3081, 3055, 3033, 2961, 2922, 2855, 1628, 1600, 1574, 1494.

HRMS (EI) for $C_{13}H_{14}O$ (m/z): calcd. 186.1045; found 186.1040.

$[\alpha]_D^{20}$: +3.0 (c = 0.40, $CHCl_3$).

HPLC (Chiralcel IB): 1:99 *i*-PrOH/Hexane, 0 °C, 0.3 mL/minute, λ = 254 nm, T_{major} = 12.1 min, T_{minor} = 11.0 min, 95.5:4.5 *er*.

(*R*,*E*)-6-Styryl-3,6-dihydro-2H-pyran (5-38)



By following the general procedure A, the title compound **5-38** was synthesized from (*S*)-**4-6** and the corresponding aryl bromide. The crude sample, containing **5-38** in a 3 : 1 mixture of regioisomers, was subjected to silica gel flash chromatography (2% Et_2O/Hexane) to afford the title compound (33 mg, 70 % yield).

Clear oil; TLC (Et_2O:Hexane, 2:98 v/v): Rf = 0.27.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.32-7.29 (m, 2H), 7.25-7.22 (m, 1H), 6.62 (dd, *J* = 16.0, 0.5 Hz, 1H), 6.22 (dd, *J* = 15.7, 6.5 Hz, 1H), 5.97-5.93 (m, 1H), 5.74 (app. dq, *J* = 10.0, 2.5 Hz, 1H), 4.78-4.74 (m, 1H), 4.00 (ddd, *J* = 11.5, 5.0, 5.0 Hz, 1H), 3.77 (ddd, *J* = 11.9, 7.2, 4.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.83, 131.83, 128.92, 128.63, 128.57, 127.71, 126.59, 125.45, 62.43, 29.75, 25.20.

IR (cast film, cm^{-1}) 3082, 3029, 2960, 2922, 2855, 1599, 1577, 1494, 1460.

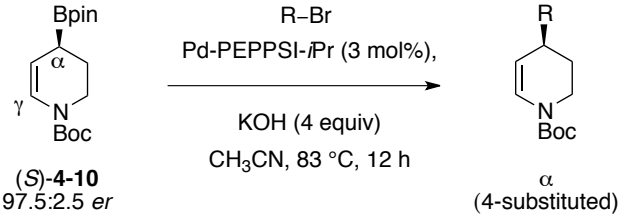
HRMS (EI) for $C_{13}H_{14}O$ (m/z): calcd. 186.10446; found 186.10417.

$[\alpha]_D^{20}$: +130.4 (c = 1.33, $CHCl_3$).

HPLC (Chiralcel IC): 2:98 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 280 nm, T_{major} = 9.8 min, T_{minor} = 11.6 min, 96:4 *er*.

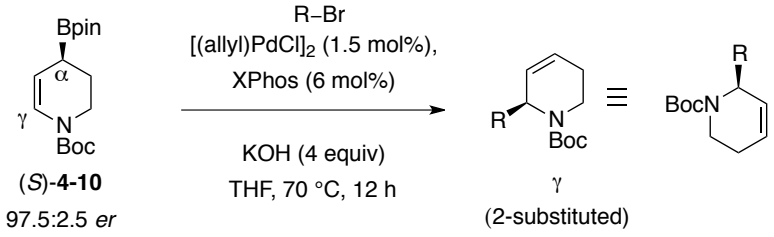
5.8.2 Experimental and spectral data for products of Schemes 5-7 and 5-8

<u>General procedure C</u> towards 4-substituted piperidines (Scheme 5-7):



Pd-PEPPSI-IPr (5.1 mg, 7.5 μmol) was added in a flamed-dried reaction tube, which was then flushed with nitrogen. Dry acetonitrile (1.0 mL) was added and the mixture was stirred for 10 minutes. Allylic heterocyclic boronic ester (*S*)-**4-10** (116 mg, 0.38 mmol, 1.5 equiv, unless otherwise addressed) was added *via* syringe, which was washed three times with dry acetonitrile (0.5 mL portion). The organobromide (0.25 mmol) and aqueous KOH solution (5 M in H_2O, 0.25 mL, 5 equiv) were then added, and the resulting reaction mixture was allowed to stir under nitrogen at 83 °C for 12 h. The mixture was allowed to cool down to room temperature, passed through a short pipette loaded with silica gel, and rinsed with 15 mL ethyl acetate. The solvents were then evaporated to yield a crude oil, which was subjected to silica gel flash chromatography (15% ethyl acetate/hexane, unless otherwise addressed) to afford the pure 4-substituted piperidine product.

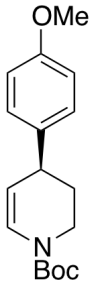
<u>General procedure D</u> towards 2-substituted piperidines (Scheme 5-8):



Complex [(allyl)PdCl]$_2$ (1.4 mg, 3.8 μmol) and XPhos (6.4 mg, 15 μmol) was added in a flamed-dried reaction tube, which was then flushed with nitrogen. Dry

THF (1.0 mL) was added and the mixture was stirred for 10 minutes. Allyllic heterocyclic boronic ester (*S*)-**4-10** (116 mg, 0.38 mmol, 1.5 equiv, unless otherwise addressed) was added *via* syringe, which was washed three times with dry THF (0.5 mL portion). The organobromide (0.25 mmol) and aqueous K_3PO_4 solution (5 M in H_2O, 0.25 mL, 5 equiv) were then added, and the resulting reaction mixture was allowed to stir under nitrogen at 70 °C for 12 h. The mixture was allowed to cool down to room temperature, passed through a short pipette loaded with silica gel, and rinsed with 15 mL ethyl acetate. The solvents were then evaporated to yield a crude oil, which was subjected to silica gel flash chromatography (15% ethyl acetate/hexane, unless otherwise addressed) to afford the pure 2-substituted piperidine product.

(*S*)-*tert*-Butyl 4-(4-methoxyphenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (5-23)



By following the general procedure C, the title compound **5-23** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-23** in a mixture of 14 : 1 regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (60 mg, 83% yield).

Clear oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.70.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.19-7.14 (m, 2H), 7.13-6.92 (m, 1H), 6.89 (d, J = 8.6 Hz, 2H), 5.04-4.84 (m, 1H), 3.83 (s, 3H), 3.68-3.50 (m, 2H), 3.50-3.45

(m, 1H), 2.17-2.05 (m, 1H), 1.84-1.75 (m, 1H), 1.55 (br s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 158.2, 152.2, 137.4, 128.6, 126.2, 113.8, 108.1, 80.4, 55.3, 39.6, 37.4, 31.3, 28.4. (Rotamers present at 25 °C).

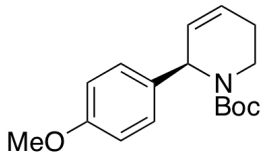
IR (microscope, cm^{-1}) 3034, 2976, 2933, 1702, 1650, 1583.

HRMS (EI) for $C_{17}H_{23}NO_3$: calcd. 289.1678; found 289.1674.

$[\alpha]_D^{20}$: −26.2 (c = 0.75, $CHCl_3$).

HPLC (Chiralcel OD): 2:98 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 13.7 min, T_{minor} = 12.2 min, 96.5:3.5 *er*.

(*R*)-*tert*-Butyl 2-(4-methoxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (5-24)



By following the general procedure D, the title compound **5-24** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-24** as a single regioisomer, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (67 mg, 93% yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.62.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.40-7.30 (m, 2H), 6.89-6.86 (m, 2H), 6.04-6.01 (m, 1H), 5.83-5.75 (m, 1H), 5.65-5.32 (m, 1H), 4.20-3.88 (m, 1H), 3.82 (s, 3H), 2.90 (ddd, *J* = 13.3, 11.9, 4.0 Hz, 1H), 2.36-2.29 (m, 1H), 2.07-2.02 (m,

1H), 1.49 (s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 158.9, 154.7, 133.4, 129.5, 127.3, 123.7, 113.6, 79.9, 55.3, 54.2, 36.5, 28.6, 25.0. (Rotamers present at 25 °C).

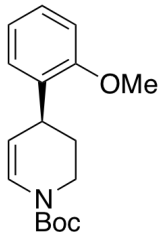
IR (microscope, cm^{-1}) 3034, 2975, 2931, 1692, 1611, 1584.

HRMS (EI) for $C_{17}H_{23}NO_3$: calcd. 289.1678; found 289.1677.

$[\alpha]_D^{20}$: +235.9 (c = 1.43, $CHCl_3$).

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexane, 20.0 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 11.2 min, T_{minor} = 9.4 min, 96.5:3.5 *er*.

(*S*)-*tert*-Butyl 4-(2-methoxyphenyl)-3,4-dihydropyridine-1(2H)-carboxylate (5-39)



By following the general procedure C, the title compound **5-39** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-39** in a mixture of 15 : 1 regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (54 mg, 75 % yield).

Clear oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.60.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.26-7.20 (m, 2H), 7.16-6.96 (m, 1H),

6.96-6.87 (m, 2H), 4.98-4.81 (m, 1H), 3.94-3.88 (m, 1H), 3.86 (br s, 3H), 2.20-2.07 (m, 1H), 3.62-3.43 (m, 2H), 1.80-1.72 (m, 1H), 1.52 (br s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ 156.8, 133.1, 128.6, 127.3, 126.6, 120.3, 110.2, 107.8, 80.7, 55.3, 39.5, 31.0, 28.8. (Rotamers present at 25 °C).

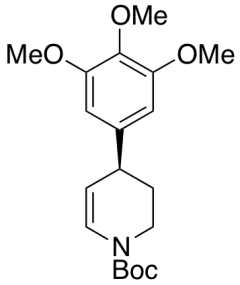
IR (microscope, cm^{-1}) 3063, 2976, 2933, 2837, 1704, 1649, 1598, 1586.

HRMS (ESI) for $(M+H)^+$ $C_{13}H_{16}NO_3$ (t-Bu loss): calcd. 234.1123; found 234.1125; for $(M+Na)^+$ $C_{17}H_2NNaO_3$: calcd. 312.1569; found 312.1570.

$[\alpha]_D^{20}$: −23.1 (c = 0.95, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 210 nm, T_{major} = 11.0 min, T_{minor} = 12.4 min, 96:4 *er*.

(*S*)-*tert*-Butyl 4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyridine-1(2H)-carboxylate (5-40)



By following the general procedure C, the title compound **5-40** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-40** in a mixture of 17 : 1 regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (71 mg, 81 % yield).

Clear oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.25.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.11-6.95 (m, 1H), 6.48 (br s, 2H), 4.99-4.87 (m, 1H), 3.89 (br s, 6H), 3.86 (br s, 3H), 3.74-3.63 (m, 1H), 3.55-3.53 (m, 1H), 3.48-3.44 (m, 1H), 2.15-2.12 (m, 1H), 1.85-1.83 (m, 1H), 1.53-1.50 (m, 9H). (Rotamers present at 25 °C).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 153.2, 141.1, 136.5, 126.5, 107.8, 104.6, 80.9, 60.9, 56.2, 40.9, 39.9, 38.6, 31.4, 28.4. (Rotamers present at 25 °C).

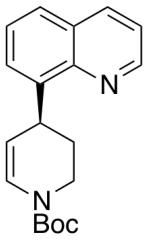
IR (microscope, cm^{-1}) 2974, 2935, 2839, 1702, 1648, 1588.

HRMS (ESI) for $[M+Na]^+$ $C_{19}H_{27}NNaO_5$: calcd. 372.1781, found 372.1781.

$[\alpha]_D^{20}$: +52.8 (c = 1.12, $CHCl_3$).

HPLC (Chiralcel OD): 2:98 *i*-PrOH/Hexane, 20.0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 26.3 min, T_{minor} = 30.5 min, 96.5:3.5 *er*.

(*S*)-*tert*-Butyl 4-(quinolin-8-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate (5-41)



By following the general procedure C, the title compound **5-41** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-41** as a single regioisomer, was subjected to silica gel flash chromatography (50% ethyl acetate/hexane) to afford the pure title compound (54 mg, 70 % yield).

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.21.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.73 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.25-7.08 (m, 1H), 5.13-5.01 (m, 1H), 4.95-4.94 (m, 1H), 3.76-3.66 (m, 1H), 3.60-3.51 (m, 1H), 2.42-2.38 (m, 1H), 1.92-1.89 (m, 1H), 1.54 (s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 152.4, 149.4, 146.0, 143.4, 136.5, 128.5, 128.1, 126.9, 126.4, 126.2, 121.0, 108.1, 80.7, 39.6, 32.0, 29.8, 28.4. (Rotamers present at 25 °C).

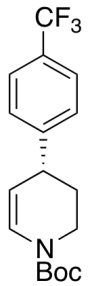
IR (microscope, cm^{-1}) 3042, 3003, 2975, 2929, 2872, 1698, 1650.

HRMS (EI) for $C_{19}H_{22}O_2N_2$: calcd. 310.1681; found 310.1690.

$[\alpha]_D^{20}$: +83.5 (c = 0.28, $CHCl_3$).

HPLC (Chiralcel OD): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 16.3 min, T_{minor} = 14.4 min, 95:5 *er*.

(*S*)-*tert*-Butyl 4-(4-(trifluoromethyl)phenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (5-42)



By following the general procedure C, the title compound **5-42** was synthesized

from (*R*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-42** in a mixture of 11 : 1 regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (54 mg, 66 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.63.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.60 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.16-7.00 (m, 1H), 4.97-4.85 (m, 1H), 3.68-3.54 (m, 3H), 2.21-2.18 (m, 1H), 1.86-1.79 (m, 1H), 1.55 (br s, 9H). (Rotamers present at 25 °C).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 152.1, 149.3, 128.8 (q, J = 32.4 Hz, 1C), 128.0 (m, 1C), 126.9 (m, 1C), 125.3 (q, J = 3.8 Hz, 1C), 123.2, 106.5, 81.0, 39.5, 38.1, 31.0, 28.3. (Rotamers present at 25 °C).

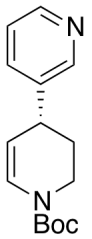
IR (microscope, cm^{-1}) 3065, 2979, 2934, 2879, 1707, 1649, 1618.

HRMS (EI) for $C_{17}H_{20}NO_2F_3$: calcd. 327.1446; found 327.1447.

$[\alpha]_D^{20}$: +34.9 (c = 0.42, $CHCl_3$).

HPLC (Chiralcel OD): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 9.0 min, T_{minor} = 10.0 min, 95:5 *er*.

(*R*)-*tert*-Butyl 3',4'-dihydro-[3,4'-bipyridine]-1'(2'*H*)-carboxylate (5-43)



By following the general procedure C, the title compound **5-43** was synthesized from (*R*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-43** as a mixture of 11 : 1 regioisomers, was subjected to preparative TLC purification (50% ethyl acetate/hexane) to afford the pure title compound (47 mg, 72 % yield).

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.15.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.55-8.53 (m, 2H), 7.59-7.55 (m, 1H), 7.29-7.26 (m, 1H), 7.16-7.00 (m, 1H), 4.98-4.81 (m, 1H), 3.67-3.54 (m, 3H), 2.20-2.17 (m, 1H), 1.83-1.82 (m, 1H), 1.55 (br s, 9H). (Rotamers present at 25 °C).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 152.1, 149.5, 147.9, 140.5, 135.1, 127.2, 123.4, 106.1, 81.1, 39.5, 35.9, 31.0, 28.3. (Rotamers present at 25 °C).

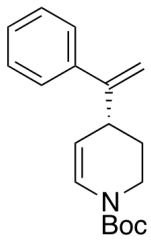
IR (microscope, cm^{-1}) 3058, 2976, 2931, 2874, 1705, 1648, 1574.

HRMS (EI) for $C_{15}H_{20}NO_2N_2$: calcd. 260.1525; found 260.1522.

$[\alpha]_D^{20}$: +48.9 (c = 0.38, $CHCl_3$).

The enantiomeric ratio of compound **5-43** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after hydroboration/oxidation.

(*S*)-*tert*-Butyl 4-(1-phenylvinyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (5-44)



By following the general procedure C, the title compound **5-44** was synthesized from (*R*)-**4-10** and corresponding alkenyl bromide. The crude product, containing **5-44** as a mixture of 7 : 1 regioisomers, was subjected to preparative TLC purification (15% ethyl acetate/hexane) to afford the pure title compound (53 mg, 74 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.65.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.43-7.31 (m, 5H), 7.10-6.90 (m, 1H), 5.40 (br s, 1H), 5.13 (br s, 1H), 5.04-4.87 (m, 1H), 3.72-3.57 (m, 1H), 3.47-3.37 (m, 2H), 1.97-1.86 (m, 1H), 1.72-1.61 (m, 1H), 1.54 (br s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 152.2, 151.4, 141.2, 128.4, 127.5, 126.6, 126.3, 114.4, 107.0, 80.0, 38.8, 36.4, 28.4, 26.9. (Rotamers present at 25 °C).

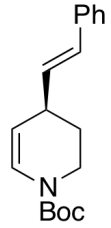
IR (microscope, cm^{-1}) 3058, 2977, 2932, 1703, 1599.

HRMS (ESI) for $[M+Na]^+$ $C_{18}H_{23}NNaO_2$: calcd. 308.1621; found 308.1619.

$[\alpha]_D^{20}$: +32.7 (c = 0.30, $CHCl_3$).

The enantiomeric ratio of compound **5-44** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after dihydoxylation.

(*R*,*E*)-*tert*-Butyl 4-styryl-3,4-dihydropyridine-1(2*H*)-carboxylate (5-45)



By following the general procedure C, the title compound **5-45** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-45** as a mixture of 7 : 1 regioisomers, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (39 mg, 55% yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.66.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.39-7.36 (m, 2H), 7.35-7.30 (m, 2H), 7.26-7.21 (m, 1H), 7.04-6.82 (m, 1H), 6.43 (d, J = 15.8 Hz, 1H), 6.17 (dd, J = 15.8, 7.2 Hz, 1H), 4.93-4.80 (m, 1H), 3.63-3.59 (m, 2H), 3.09-3.03 (m, 1H), 2.04-2.01 (m, 1H), 1.79-1.74 (m, 1H), 1.51 (s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 152.2, 137.4, 133.2, 130.2, 128.5, 128.3, 126.1, 125.9, 107.0, 80.8, 39.3, 35.2, 28.4, 28.1. (Rotamers present at 25 °C).

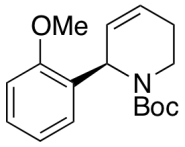
IR (microscope, cm^{-1}) 3058, 3028, 2977, 2931, 1701, 1599, 1577.

HRMS (ESI) for $[M+Na]^+$ $C_{18}H_{23}NNaO_2$: calcd. 308.1621; found 308.1618.

$[\alpha]_D^{20}$: −94.9 (c = 0.59, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 39.4 min, T_{minor} = 39.0 min, 95.5:4.5 *er*.

(*R*)-*tert*-Butyl 2-(2-methoxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (5-46)



By following the general procedure D, the title compound **5-46** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-46** as a single regioisomer, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (66 mg, 91 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.59.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.26-7.22 (m, 1H), 7.16 (dd, J = 7.6, 1.3 Hz, 1H), 6.95-6.90 (m, 2H), 6.01-5.70 (m, 3H), 4.38-4.24 (m, 1H), 3.83 (s, 3H), 3.18 (ddd, J = 12.9, 11.4, 3.9 Hz, 1H), 2.36-2.29 (m, 1H), 2.16-2.04 (m, 1H), 1.72-1.21 (m, 9H). (Rotamers present at 25 °C).

^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ 156.3, 155.1, 131.0, 127.8 (br s, 2C), 125.8, 124.4, 120.5, 110.5, 79.4, 55.3, 51.2, 28.3, 24.9. (Rotamers present at 25 °C).

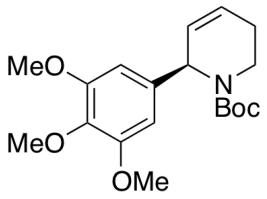
IR (microscope, cm^{-1}) 3074, 2977, 2934, 2840, 1694, 1652, 1600.

HRMS (ESI) for $[M+H]^+$ $C_{13}H_{16}NO_3$ (loss of *t*-Bu): calcd. 234.1125, found 234.112; for [M+H]+ $C_{17}H_{24}NO_3$: calcd. 290.1751, found 290.175; for $[M+Na]^+$ $C_{17}H_{24}NNaO_3$: calcd. 312.157, found 312.1568.

$[\alpha]_D^{20}$: −16.5 (c = 0.22, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 280 nm, T_{major} = 24.5 min, T_{minor} = 26.6 min, 96.5:3.5 *er*.

(*R*)-*tert*-Butyl 2-(3,4,5-trimethoxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (5-47)



By following the general procedure D, the title compound **5-47** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-47** as a single regioisomer, was subjected to silica gel flash chromatography (50% ethyl acetate/hexane) to afford the pure title compound (84 mg, 96% yield).

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.20.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.64 (br s, 2H), 6.09-6.06 (m, 1H), 5.80-5.90 (m, 1H), 5.80-5.35 (m, 1H), 3.90-4.30 (m, 1H), 3.88 (br s, 6H), 3.87 (br s, 3H), 2.92 (ddd, J = 13.2, 12.0, 3.9 Hz, 1H), 2.37-2.32 (m, 1H), 2.10-2.04 (m, 1H), 1.51 (br s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 154.5, 153.1, 137.3, 137.0, 127.0, 126.8, 105.0, 79.8, 60.9, 56.2, 53.4, 29.7, 28.6, 25.1. (Rotamers present at 25 °C).

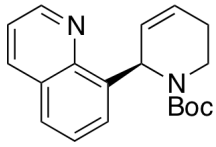
IR (microscope, cm^{-1}) 3033, 2974, 2934, 2836, 1692, 1653, 1590.

HRMS (ESI) for $[M+Na]^+$ $C_{19}H_{27}NNaO_5$: calcd. 372.1781; found 372.1780.

$[\alpha]_D^{20}$: −241.3 (c = 1.10, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 66.8 min, T_{minor} = 64.9 min, 96:4 *er*.

(*R*)-*tert*-Butyl 2-(quinolin-8-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (5-48)



By following the general procedure D, the title compound **5-48** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-48** as a single regioisomer, was subjected to silica gel flash chromatography (50% ethyl acetate/hexane) to afford the pure title compound (69 mg, 80% yield).

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.16.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.97 (dd, J = 4.1, 1.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.0 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.43 (dd, J = 8.1, 4.1 Hz, 1H), 6.68 (br s, 1H), 6.22-6.21 (m, 1H), 5.92-5.89 (m, 1H), 4.46 (br s, 1H), 3.38 (ddd, J = 12.8, 11.1, 3.7 Hz, 1H), 2.45-2.38 (m, 1H), 2.31-2.10 (m, 1H), 1.80-0.99 (m, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 155.4, 149.2, 145.4, 141.3, 136.2, 128.6, 126.6, 126.3, 124.47, 124.46, 124.0, 120.9, 79.4, 52.3, 38.9, 28.25, 28.23, 28.13, 28.12, 28.11, 25.08, 25.08, 25.07. (Rotamers present at 25 °C).

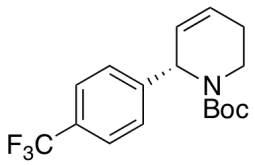
IR (microscope, cm^{-1}) 3040, 3003, 2975, 2928, 2870, 1694, 1652.

HRMS (EI) for $C_{19}H_{22}O_2N_2$: calcd. 310.1681; found 310.1684.

$[\alpha]_D^{20}$: −187.8 (c = 1.01, $CHCl_3$).

HPLC (Chiralcel OD): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 22.0 min, T_{minor} = 24.5 min, 97.5:2.5 *er*.

(*S*)-*tert*-Butyl 2-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (5-49)



By following the general procedure D, the title compound **5-49** was synthesized from (*R*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-49** as a single regioisomer, was subjected to silica gel flash chromatography (15% ethyl acetate/hexane) to afford the pure title compound (56 mg, 68% yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.55.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.62 (d, J = 8.2 Hz, 2H), 7.53 (br s, 2H), 6.11-6.08 (m, 1H), 5.95-5.78 (m, 1H), 5.75-5.40 (m, 1H), 4.35-3.90 (m, 1H), 2.95-2.89 (m, 1H), 2.39-2.33 (m, 1H), 2.12-2.08 (m, 1H), 1.48 (br s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 154.6, 145.4 (m, 1C), 129.4 (q, J = 32.3 Hz, 1C), 127.7 (m, 1C), 127.0, 126.5, 125.3 (q, J = 3.8 Hz, 1C), 123.1, 79.9, 52.2 (m, 1C), 36.5 (m, 1C), 28.5, 24.9.

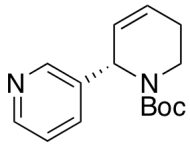
IR (microscope, cm^{-1}) 3039, 2978, 2931, 2876, 1696, 1654, 1685.

HRMS (EI) for $C_{17}H_{20}NO_2F_3$: calcd. 327.1446; found 327.1452.

$[\alpha]_D^{20}$: −237.3 (c = 1.00, $CHCl_3$).

The enantiomeric ratio of compound **5-49** could not be determined directly, due to the difficult HPLC separation. See Section 5.8.4 for *er* determination after diimide reduction.

(*S*)-*tert*-Butyl 5,6-dihydro-[2,3'-bipyridine]-1(2*H*)-carboxylate (5-50)



By following the general procedure D, the title compound **5-50** was synthesized from (*R*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-50** as a mixture of 15:1 regioisomers, was subjected to preparative TLC purification (50% ethyl acetate/hexane) to afford the pure title compound (43 mg, 66 % yield).

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.12.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.90-8.40 (m, 2H), 7.73 (br s, 1H), 7.31 (br s, 1H), 6.18-6.08 (m, 1H), 5.92-5.43 (m, 2H), 4.21-3.95 (m, 1H), 2.90 (ddd, J = 13.4, 11.8, 3.9 Hz, 1H), 2.42-2.30 (m, 1H), 2.20-2.15 (m, 1H), 1.49 (br s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 154.5, 149.3, 148.6, 136.5 (m, 1C), 134.7 (m, 1C), 127.3, 126.1, 123.5 (m, 1C), 80.3, 53.5 (m, 1C), 37.2 (m, 1C), 28.5, 24.9. (Rotamers present at 25 °C).

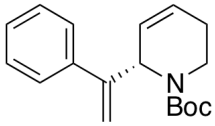
IR (microscope, cm^{-1}) 3034, 2977, 2929, 1695, 1655, 1589.

HRMS (EI) for $C_{15}H_{20}N_2O_2$: calcd. 260.1525; found 260.1529.

$[\alpha]_D^{20}$: −174.2 (c = 0.55, $CHCl_3$).

HPLC (Chiralcel OD): 5:95 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 22.3 min, T_{minor} = 26.9 min, 96:4 *er*.

(*S*)-*tert*-Butyl 2-(1-phenylvinyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (5-51)



By following the general procedure D, the title compound **5-51** was synthesized from (*R*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-51** as a mixture of 15:1 regioisomers, was subjected to preparative TLC purification (15% ethyl acetate/hexane) to afford the pure title compound (57 mg, 80 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.60.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.53-7.24 (m, 5H), 5.93-5.85 (m, 1H), 5.85-5.20 (m, 3H), 5.14 (br s, 1H), 4.20-3.95 (m, 1H), 2.99-2.85 (m, 1H), 2.38-2.22 (m, 1H), 2.08-1.93 (m, 1H), 1.52-1.30 (m, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 154.7, 148.3, 140.7, 128.2, 127.5, 127.2, 126.4, 126.1, 113.6, 79.7, 55.9, 36.5, 28.3, 25.0. (Rotamers present at 25 °C).

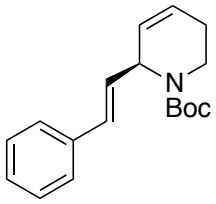
IR (microscope, cm^{-1}) 3082, 3052, 3002, 2976, 2929, 2838, 1697, 1654, 1413.

HRMS (ESI) for $[M+Na]^+$ $C_{18}H_{23}NNaO_2$: calcd. 308.1623; found 308.1621.

$[\alpha]_D^{20}$: −116.0 (c = 0.35, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 12.2 min, T_{minor} = 14.2 min, 96:4 *er*.

(*R*,*E*)-*tert*-Butyl 2-styryl-5,6-dihydropyridine-1(2*H*)-carboxylate (5-52)



By following the general procedure D, the title compound **5-52** was synthesized from (*S*)-**4-10** and the corresponding aryl bromide. The crude product, containing **5-52** as a single regioisomer, was subjected to preparative TLC purification (15% ethyl acetate/hexane) to afford the pure title compound (63 mg, 88 % yield).

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.62.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.39 (app d, J = 7.4 Hz, 2H), 7.33 (app t, J = 7.6 Hz, 2H), 7.25 (app t, J = 7.2 Hz, 1H), 6.48 (d, J = 15.9 Hz, 1H), 6.23-6.18 (m, 1H), 5.99-5.96 (m, 1H), 5.77-5.71 (m, 1H), 5.10-4.97 (m, 1H), 4.21-4.09 (m, 1H), 2.95-2.89 (m, 1H), 2.33-2.26 (m, 1H), 2.04-2.00 (m, 1H), 1.51 (s, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 154.7, 136.9, 130.9, 129.9, 128.6, 128.4, 127.6, 126.7, 126.4, 79.7, 53.8, 36.3, 28.5, 25.1. (Rotamers present at 25 °C).

IR (microscope, cm^{-1}) 3082, 3059, 3029, 3005, 2975, 2927, 1694, 1655, 1599, 1577.

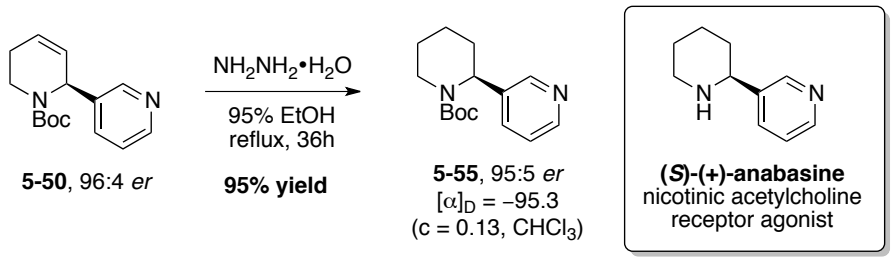
HRMS (EI) for $C_{18}H_{23}NO_2$: calcd. 285.1729; found 285.1732.

$[\alpha]_D^{20}$: +282.0 (c = 1.10, $CHCl_3$).

HPLC (Chiralcel IC): 2:98 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 14.6 min, T_{minor} = 13.5 min, 96:4 *er*.

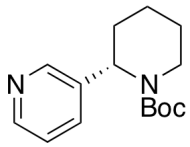
5.8.3 Formal syntheses of (+)-anabasine and (+)-paroxetine

5.8.3.1 Formal synthesis of (+)-anabasine



Procedure: Dehydropiperidine compound **5-50** (0.1 mmol) was dissolved in 95% ethanol (1.0 mL, 0.1 M) and hydrazine monohydrate (49 μL, 1.0 mmol) was added. The resulting mixture was refluxed under open air for 24 h. The reaction mixture was concentrated then directly subjected to silica gel flash column chromatography to afford the desired hydrogenated product in a quantitive yield.[199]

(*S*)-*tert*-Butyl 2-(pyridin-3-yl)piperidine-1-carboxylate 5-55



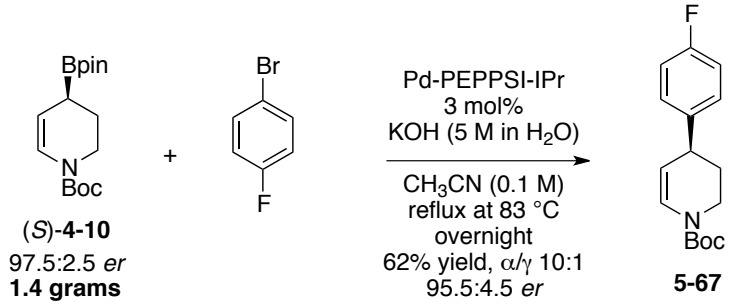
Compound **5-55** was obtained as a clear oil (26 mg, 98 % yield). Spectral data of compound **5-55** match those previously reported.[197]

$[\alpha]_D^{20}$: −95.3 (c = 0.13, $CHCl_3$). (*Lit.*: +93.1 (c = 1.00, MeOH), 86% *ee*).[197]

HPLC (Chiralcel IC): 20:80 *i*-PrOH/Hexane, 20.0 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 54.4 min, T_{minor} = 60.7 min, 95:5 *er*.

5.8.3.2 Formal synthesis of (+)-paroxetine

(*S*)-*tert*-Butyl 4-(4-fluorophenyl)-3,4-dihydropyridine-1(2H)-carboxylate (5-67)



By following the general procedure C, the 4-substituted piperidine compound **5-67** was obtained as a yellow oil (848 mg, 62 % yield) and α/γ 10:1 regioselectivity.

Yellow oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.75.

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.22-7.15 (m, 2H), 7.10-6.90 (m, 3H), 4.96-4.79 (m, 1H), 3.66-3.45 (m, 3H), 2.17-2.04 (m, 1H), 1.80-1.71 (m, 1H), 1.57-1.44 (m, 9H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 161.5 (d, J = 244.3 Hz), 152.0, 140.9 (d, J = 3.1 Hz), 129.1 (d, J = 7.8 Hz), 126.5, 115.1 (d, J = 21.2 Hz), 107.5, 80.9, 39.5, 37.5, 31.3, 28.4. (Rotamers present at 25 °C).

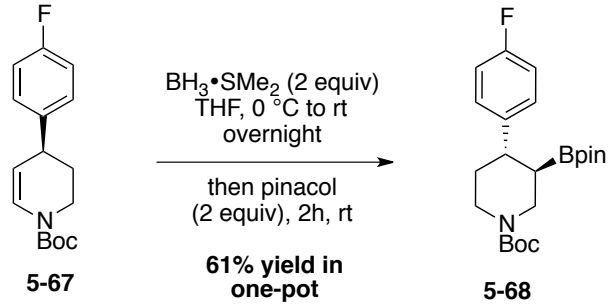
IR (microscope, cm^{-1}) 3068, 2977, 2932, 2879, 1706, 1650, 1604, 1509.

HRMS (EI) for $C_{16}H_{20}O_2NF$ (*m/z*): calcd. 277.1478; found 277.1479.

$[\alpha]_D^{20}$: −25.7 (c = 1.34, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 11.1 min, T_{minor} = 12.5 min, 95.5:4.5 *er*.

(3*R*,4*S*)-*tert*-Butyl 4-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (5-68)



Procedure[204]**:** The 4-substituted piperidine compound **5-67** (0.6 g, 2.2 mmol) was dissolved in dry THF (0.1 M, 2.2 mL) in a flame-dried reaction tube under nitrogen. The solution was cooled 0 °C in an ice bath, and BH_3•SMe_2 (417 μL, 4.4 mmol) was added dropwise *via* syringe. The resulting mixture was allowed to warm up to room temperature overnight. Pinacol (520 mg, 4.4 mmol) was then added, and reaction mixture was stirred for 2 hours at room temperature. After removal of the solvent, the residue was directly subjected to silica gel flash chromatography (EtOAc:Hexane, 15:85 v/v) to afford the desired boronate **5-68** as a clear oil (567 mg, 61% overall yield).

Clear oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.55.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.22-7.15 (m, 2H), 7.01-6.95 (m, 2H), 4.40-4.10 (m, 2H), 2.90-2.75 (m, 2H), 2.72 (apparent td, J = 12.1, 3.5 Hz, 1H), 1.79-1.73 (m, 1H), 1.53 (d, J = 5.8 Hz, 1H), 1.50 (br s, 9H), 1.44 (apparent td, J = 12.1, 3.8 Hz, 1H), 1.04 (s, 6H), 0.99 (s, 6H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 161.5 (d, J = 243.8 Hz), 154.7, 141.2 (d, J = 3.1 Hz), 128.9 (d, J = 7.9 Hz), 114.9 (d, J = 21.0 Hz), 83.2, 79.4, 46.0-43.5 (m), 44.2, 35.0-34.6 (m), 29.8-28.8 (m), 28.5, 24.5, 24.4. (Rotamers present at 25 °C).

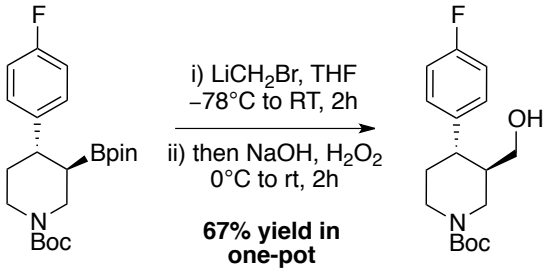
^{11}B NMR (160 MHz, $CDCl_3$, 25 °C): δ 33.0.

IR (microscope, cm^{-1}) 3043, 2978, 2931, 2856, 1694, 1605, 1511.

HRMS (ESI) for $[M+H]^+$ $C_{18}H_{26}BFNO_4$ (loss of *t*-Bu): calcd. 350.1935, found 350.1933; for $[M+H]^+$ $C_{22}H_{34}BFNO_4$: calcd. 406.2555, found 406.2559; for $[M+Na]^+$ $C_{22}H_{33}BFNNaO_4$: calcd. 428.2373, found 428.2379.

$[\alpha]_D^{20}$: +35.7 (c = 1.02, $CHCl_3$).

(3*R*,4*S*)-*tert*-Butyl 4-(4-fluorophenyl)-3-(hydroxymethyl)piperidine-1-carboxylate (5-69)



5-68 **5-69** 95.5:4.5 *er*

Matteson homologation/oxidation procedure:[205] Boronate **5-68** (567 mg, 1.40 mmol) was dissolved in dry THF (14 mL, 0.1 M), followed by the addition of CH_2Br_2 (dried with molecular sieves, 3.5 mmol, 245 μL). The solution was cooled to –78 °C and *n*BuLi (2.5 M in Hexane, 1.2 mL, 3.1 mmol) was added dropwise. The system was stirred at –78 °C for 10 min, then at room temperature for 2 hours. The reaction mixture was then cooled to 0 °C in an iced bath, and a mixture of NaOH (2N in H_2O, 10 mL) and H_2O_2 (30 wt % in H_2O, 5 mL) was added dropwise. This mixture was stirred at room temperature for 2 hours before diluted with H_2O (10 mL). The resulting biphasic mixture was extracted twice with EtOAc (2 x 20 mL), washed with brine (20 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash

chromatography (EtOAc:Hexane, 50:50 v/v) to afford the desired homologation product **5-69** as a clear oil (290 mg, 67 % yield).

Clear oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.25.

Spectral data matche those previously reported.[206]

$[\alpha]_D^{20}$: +4.98 (c = 0.87, MeOH). (*Lit.*: [206] +5.13 (c = 1.13, MeOH), 98.5:1.5 *er*).

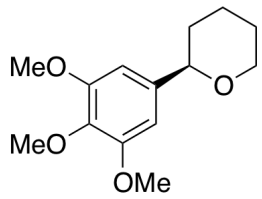
HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 62.0 min, T_{minor} = 58.6 min, 95.5:4.5 *er*.

5.8.4 Substrate derivatization for enantiomeric ratio determination

5.8.4.1 Diimide reduction

General procedure:[199] The unsaturated heterocyclic compound (0.1 mmol) was dissolved in 95% ethanol (1.0 mL, 0.1 M) and hydrazine monohydrate (49 μL, 1.0 mmol) was added. The resulting mixture was refluxed under open air for 24 h. The reaction mixture was concentrated then directly subjected to silica gel flash column chromatography to afford the desired hydrogenated product with a quantitive yield.

(*R*)-2-(3,4,5-Trimethoxyphenyl)tetrahydro-2*H*-pyran (5-33a)



The title compounds **5-33a** was obtained as the major diastereomer (24 mg, 95 % yield), by the following the general procedure for diimide reduction.

Clear oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.35.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.62 (s, 2H), 4.28 (dd, *J* = 10.6, 2.0 Hz, 1H), 4.19-4.15 (m, 1H), 3.90 (s, 6H), 3.85 (s, 3H), 3.64 (td, *J* = 11.7, 2.3 Hz, 1H), 1.98 (dt, *J* = 8.8, 2.3 Hz, 1H), 1.86 (dd, *J* = 12.3, 2.2 Hz, 1H), 1.75-1.59 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 153.2, 139.1, 137.1, 102.9, 80.3, 69.1, 60.8, 56.1, 34.0, 25.9, 24.0.

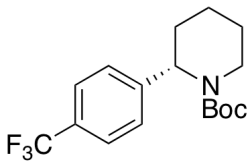
IR (microscope, cm^{-1}) 2937, 2841, 2734, 1591.

HRMS (EI) for $C_{14}H_{20}O_4$: calcd. 252.1362; found 252.1363.

$[\alpha]_D^{20}$: +22.3 (c = 0.15, $CHCl_3$).

HPLC (Chiralcel IC): 25:75 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 210 nm, T_{major} = 42.2 min, T_{minor} = 31.6 min, 95.5:4.5 *er*.

(*S*)-*tert*-Butyl 2-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (5-49a)



The title compounds **5-49a** was obtained as the major diastereomer (29 mg, 94 % yield), by following the general procedure for diimide reduction.

Clear oil; TLC (EtOAc:Hexane, 15:85 v/v): Rf = 0.68.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.36-7.34 (m, 2H), 5.47-5.43 (m, 1H), 4.11-4.07 (m, 1H), 2.77 (ddd, *J* = 13.5, 12.2, 3.8 Hz, 1H), 2.33-2.29 (m, 1H), 1.95 (dddd, *J* = 14.0, 13.3, 5.6, 3.8 Hz, 1H), 1.69-1.61 (m, 1H),

1.61-1.50 (m, 1H, overlap with H_2O peak), 1.50-1.44 (m, 9H), 1.44-1.33 (m, 2H). (Rotamers present at 25 °C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 155.5, 145.0, 128.8 (q, J = 32.3 Hz, 1C), 126.9, 125.5 (q, J = 3.9 Hz, 1C), 123.2, 79.9, 53.2, 40.3, 29.7, 28.4, 25.3, 19.3.

IR (microscope, cm^{-1}) 2977, 2938, 2866, 1693, 1619.

HRMS (ESI) for $[M+Na]^+$ $C_{17}H_{22}NNaO_2F_3$: calcd. 329.1603; found 329.1602.

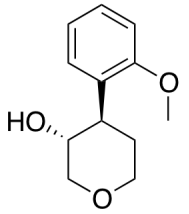
$[\alpha]_D^{20}$: −89.4 (c = 0.60, $CHCl_3$).

HPLC (Chiralcel IC): 1:99 *i*-PrOH/Hexane, 0 °C, 0.3 mL/minute, λ = 254 nm, T_{major} = 16.3 min, T_{minor} = 14.6 min, 97.5:2.5 *er*.

5.8.4.2 Hydroboration/oxidation

General procedure: The unsaturated heterocyclic compound (0.1 mmol) was added in a flame-dried reaction tube under nitrogen. Dry THF (0.1 M, 1 mL) was added and the resulting solution was cooled to 0 °C in an ice bath, followed by dropwise addition of BH_3•SMe_2 (0.2 mmol). The reaction mixture was slowly allowed to warm up to room temperature overnight. Sequentially, 5 equiv of $NaBO_3$•$4H_2O$ was added, and the reaction mixture was stirred vigorously at room temperature for 1 hour. The excess amount of borane was quenched though addition of 10 μL of H_2O. The resulting mixture was extracted twice with EtOAc (2 x 5 mL), washed with brine (5 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The resulting crude product was purified *via* preparative TLC (unless otherwise addressed) to give the desired secondary alcohol with high regioselectivity.

(3*R*, 4*R*)-4-(2-Methoxyphenyl)tetrahydro-2*H*-pyran-3-ol (5-25a)



The title compounds **5-25a** was obtained as the major diastereomer (9.6 mg, 46 % yield), by following the general procedure for hydroboration/oxidation.

Clear oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.12.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.31-7.26 (m, 2H, overlap with $CDCl_3$), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.95 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.17 (dd, *J* = 10.9, 4.8 Hz, 1H), 4.05-4.02 (m, 1H), 3.88-3.85 (m, 4H, overlap with CH_3), 3.52 (td, *J* = 11.8, 2.0 Hz, 1H), 3.27 (dd, *J* = 10.8, 10.0 Hz, 1H), 3.21 (ddd, *J* = 12.3, 10.3, 3.9 Hz, 1H), 2.03-1.94 (m, 2H), 1.80 (ddt, *J* = 13.6, 3.9, 1.9 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 157.6, 129.7, 127.9, 127.4, 121.3, 110.8, 72.8, 70.4, 68.2, 55.5, 43.0, 31.6.

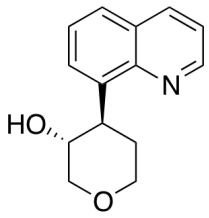
IR (microscope, cm^{-1}) 3411, 3062, 2954, 2923, 2839, 1600, 1585, 1494.

HRMS (EI) for $C_{12}H_{16}O_3$: calcd. 208.1099; found 208.1099.

$[\alpha]_D^{20}$: +19.0 (c = 0.10, $CHCl_3$).

HPLC (Chiralcel IC): 15:85 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 15.8 min, T_{minor} = 13.0 min, 95:5 *er*.

(3*R*, 4*R*)-4-(Quinolin-8-yl)tetrahydro-2*H*-pyran-3-ol (5-29a)



The title compound **5-29a** was obtained as the major diastereomer (21 mg, 86% yield), by the following the general procedure for hydroboration/oxidation. Flash chromatography was applied for the purification.

Clear oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.33.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.95 (d, J = 5.2 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 7.83-7.78 (m, 2H), 7.69 (t, J = 7.7 Hz, 1H), 7.56 (dd, J = 8.3, 5.3 Hz, 1H), 4.30 (dd, J = 11.3, 4.4 Hz, 1H), 4.24 (dd, J = 11.4, 4.1 Hz, 1H), 3.79 (td, J = 11.9, 1.7 Hz, 1H), 3.54 (t, J = 11.4 Hz, 1H), 3.11-3.06 (m, 1H), 2.37-2.32 (m, 1H), 1.80 (qd, J = 11.9, 4.5 Hz, 1H), 1.30-1.21 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 148.5, 140.98, 140.93, 140.5, 129.9, 128.1, 126.3, 120.1, 73.5, 68.3, 54.3, 41.9, 31.9.

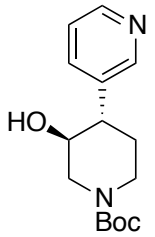
IR (microscope, cm^{-1}) 3381, 3064, 2941, 2839, 2746, 1613, 1593, 1513.

HRMS (EI) for $C_{15}H_{16}NO_2$: calcd. 242.2281; found 242.2281.

$[\alpha]_D^{20}$: −56.7 (c = 0.18, $CHCl_3$).

HPLC (Chiralcel IC): 50:50 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 13.7 min, T_{minor} = 35.4 min, 96.5:3.5 *er*.

(3*S*, 4*S*)-*tert*-Butyl 3-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate (5-43a)



The title compound **5-43a** was obtained as the major diastereomer (21 mg, 76 % yield), by the following the general procedure for hydroboration/oxidation.

Clear oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.18.

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 8.60-8.47 (m, 2H), 7.88-7.80 (m, 1H), 7.54-7.47 (m, 1H), 4.50-4.02 (m, 2H), 3.75-3.70 (m, 1H), 2.92-2.72 (m, 2H), 2.75-2.61 (m, 2H), 1.96-1.83 (m, 1H), 1.83-1.70 (m, 1H), 1.58-1.40 (br s, 9H). (Rotamers present at 25 °C).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 154.4, 147.2, 145.9, 140.4, 138.4, 125.1, 80.4, 70.5, 50.4, 44.3, 31.4, 29.7, 28.4. (Rotamers present at 25 °C).

IR (microscope, cm^{-1}) 3415, 3053, 2979, 2919, 2850, 1687, 1620.

HRMS (ESI) for $[M+H]^+$ $C_{15}H_{23}N_2O_3$: calcd. 279.1703; found 279.1703.

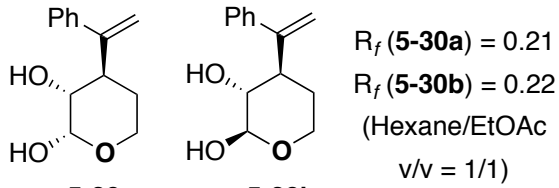
$[\alpha]_D^{20}$: +17.8 (c = 0.18, $CHCl_3$).

HPLC (Chiralcel IC): 5:95 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 22.4 min, T_{minor} = 26.9 min, 96:4 *er*.

5.8.4.3 Dihydroxylation

General procedure: The unsaturated heterocyclic compound (0.1 mmol) was dissolved in 1 mL of acetone and 250 μL of distilled water. The solution was cooled to 0 °C in an ice bath. *N*-Methylmorpholine *N*-oxide (50% w/w aq. soln., 40.7 μL, 0.2 mmol) and osmium(VIII) oxide (4% w/w aq. soln., 23.3 μL, 4 μmol) were added sequentially. The reaction mixture was slowly allowed to warm up to room temperature overnight. The resulting mixture was extracted twice with EtOAc (2 x 5 mL), washed with brine (5 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The resulting crude product was purified by flash chromatography to give the desired 1,2-diol with high regioselectivity.

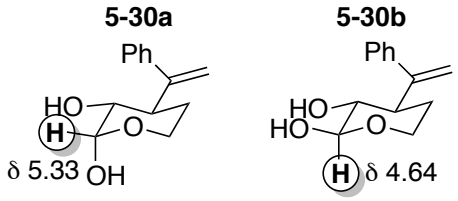
(2*S*,3*R*,4*R*)-4-(1-Phenylvinyl)tetrahydro-2*H*-pyran-2,3-diol (5-30a) and (2*R*,3*R*,4*R*)-4-(1-phenylvinyl)tetrahydro-2*H*-pyran-2,3-diol (5-30b)



5-30a **5-30b**

The title α,β-diol compounds **5-30a** and **5-30b** were obtained as a 1/1 ratio of an unseparable mixture (17 mg, 75% yield), by following the general procedure for dihydroxylation.

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.21 (**5-30a**), Rf = 0.22 (**5-30b**).



magnetic anisotropy effects

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.41-7.35 (m, 4H), 7.34-7.30 (m, 1H), 5.39-5.37 (m, 1H), 5.33-5.33 (m, 0.5H, **5-30a**, equatorial proton more deshielded due to magnetic anisotropy effects), 5.30-5.26 (m, 1H), 4.64 (dd, J = 7.1, 5.2 Hz, 0.5H, **5-30b** axial proton more shielded due to magnetic anisotropy effects), 4.06-3.98 (m, 1H), 3.81-3.77 (m, 0.5H), 3.64-3.57 (m, 1H), 3.54-3.51 (m, 0.5H), 3.12-3.10 (m, 0.5H), 3.10-3.05 (m, 0.5H), 2.80-2.80 (m, 0.5), 2.79-2.73 (m, 0.5H), 2.38-2.32 (br s, 0.5H), 2.10-2.01 (m, 0.5H), 1.82-1.73 (m, 1H), 1.73-1.62 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 150.0, 149.4, 142.08, 141.90, 128.30, 128.28, 127.52, 127.49, 127.00, 126.95, 113.9, 113.6, 99.1, 92.5, 74.3, 71.5, 65.5, 59.4, 47.1, 42.4, 32.5, 31.7. (22 carbon signals result from mixture of **5-30a** and **5-30b**)

IR (microscope, cm^{-1}) 3368, 3081, 3055, 3022, 2924, 2852, 1949 (overtone), 1884 (overtone).

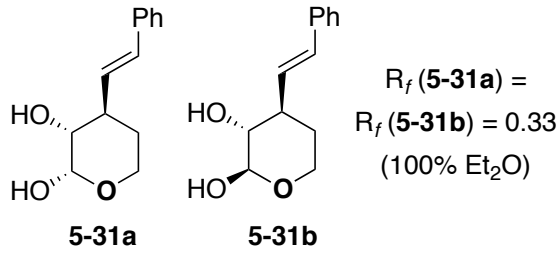
HRMS (EI) for $C_{13}H_{16}O_3$: calcd. 220.1099; found 220.1098.

$[\alpha]_D^{20}$: +17.7 (c = 0.14, $CHCl_3$).

HPLC of 5-30a (Chiralcel IC): 10:90 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 32.6 min, T_{minor} = 28.8 min, 95:5 *er*.

HPLC of 5-30b (Chiralcel IC): 10:90 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 230 nm, T_{major} = 11.8 min, T_{minor} = 17.5 min, 95:5 *er*.

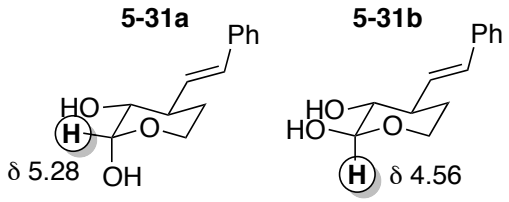
(2*S*,3*R*,4*R*)-4-((E)-Styryl)tetrahydro-2H-pyran-2,3-diol (5-31a) and (2*R*,3*R*,4*R*)-4-((E)-styryl)tetrahydro-2H-pyran-2,3-diol (5-31b)



5-31a **5-31b**

The title α,β-diol compounds **5-31a** and **5-31b** were obtained as a 1/1 ratio of an unseparable mixture (12 mg, 8 % yield), by following the general procedure for dihydroxylation. This reaction were conducted by my colleague Taras Ryback, which was included for the comprehensiveness of this chapter.

White solid (m.p.: 127.8–138.3 °C); TLC (Et_2O): Rf = 0.33 (**5-31a** and **5-31b**)



magnetic anisotropy effects

^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.39-7.29 (m, 4H), 4.24-7.21 (m, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.17 (ddd, J = 15.9, 8.0, 8.0 Hz, 1H), 5.27 (d, J = 2.5 Hz, 0.5H, 15a, equatorial proton more deshielded due to magnetic anisotropy effects), 4.56 (d, J = 7.5 Hz, 1H, 15b, axial proton more shielded due to magnetic anisotropy effects), 4.05-4.00 (m, 1H), 3.66-3.59 (m, 1H), 3.50-3.49 (m, 0.5H), 3.23 (dd, J = 10.0, 7.5 Hz, 0.5H), 3.09 (br s, 0.5H), 2.79 (br s, 0.5H), 2.72-2.73 (m, 0.5H), 2.46-2.39 (m, 0.5H), 2.28 (br s, 0.5H), 2.04-2.01 (m, 0.5H), 1.80-1.56 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0, 137.0, 131.9, 131.8, 130.4, 129.7, 128.6, 128.6, 127.6, 127.5, 126.3, 126.3, 126.2, 98.8, 98.7, 77.0, 76.9, 76.9, 76.8, 76.7, 76.7, 74.8, 71.9, 65.1, 60.4, 59.0, 45.1, 40.9, 31.2, 30.5, 30.4, 21.1, 14.2. (33 carbon signals result from mixture of **5-31a** and **5-31b**)

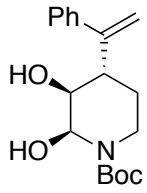
IR (cast film, cm^{-1}) 3376, 2957, 2885, 2853, 1598, 1493, 1447.

HRMS (ESI) for $[M+NH_4]^+$ $C_{13}H_{20}NO_3$: calcd. 238.1438; found 238.1436, $[M+Na]^+$ $C_{13}H_{16}NaO_3$: calcd. 243.0992; found 243.0989.

$[\alpha]_D^{20}$: +118.9 (c = 0.59, $CHCl_3$).

HPLC of 5-31a (Chiralcel IC): 5:95 *i*-PrOH/Hexane, 20 °C, 0.5 mL/minute, λ = 254 nm, T_{major} = 33.9 min, T_{minor} = 37.6 min, 96:5 *er*.

(2*S*,3*S*,4*S*)-*tert*-Butyl 2,3-dihydroxy-4-(1-phenylvinyl) piperidine-1-carboxylate (5-44a)



The title α,β-diol compounds **5-44a** were obtained as the major diastereomer (23 mg, 67 % yield), by following the general procedure for dihydoxylation.

Yellow oil; TLC (EtOAc:Hexane, 50:50 v/v): Rf = 0.27.

^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ 7.40-7.31 (m, 5H), 5.84-5.82 (br s, 1H), 5.38 (s, 1H), 5.27 (s, 1H), 3.87-3.82 (m, 1H), 3.74-3.70 (m, 1H), 3.16-3.10 (m, 1H), 3.02-2.97 (m, 1H), 2.83-2.50 (m, 1H), 2.27 (d, *J* = 6.4 Hz, 1H), 1.84-1.81 (m, 1H), 1.53-1.42 (m, 10H, overlap with Boc proton singles). (Rotamers present at

25°C)

^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 150.2, 142.0, 128.3, 127.6, 127.0, 113.9, 80.8, 72.0, 54.3, 43.0, 31.0, 29.7, 28.4.

IR (Microscope, cm^{-1}) 3414, 3081, 3055, 2926, 2855, 1700, 1678, 1599.

HRMS (ESI) for $[M+Na]^+$ $C_{18}H_{25}NNaO_4$: calcd. 342.1676; found 342.74.

$[\alpha]_D^{20}$: +5.7 (c = 0.12, $CHCl_3$).

HPLC (Chiralcel IC): 5:95 *i*-PrOH/Hexanes, 20°C, 0.5 mL/minute, λ = 230 nm, T_{major} = 53.3 min, T_{minor} = 58.2 min, 95.5:4.5 *er*.

5.9 References

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Chapter 6 Conclusions and Future Perspectives

As the science of organic chemistry progresses into the 21st century, in the midst of a potential energy crisis and a shortage of global resources, the primary goal facing organic chemists is to find new synthetic strategies that are economically efficient and environmentally benign. In this regard, as discussed throughout this thesis, chiral alkylboronates constitute a very attractive class of building blocks in modern organic synthesis, owing to their versatility as chiral precursors as well as their "green" characteristics. Despite these advantages, current synthetic methods for chiral alkylboronates remain limited. Moreover, their synthetic utility is still restricted in many aspects, especially in the control of chemo- and stereoselectivity. To address these challenges, the general objective of this thesis was to develop novel and efficient methods towards the syntheses of chiral alkylboronates (Chapters 2 and 3) and to explore their synthetic applications with control of all levels of selectivities to access biologically important target molecules (Chapters 4 and 5).

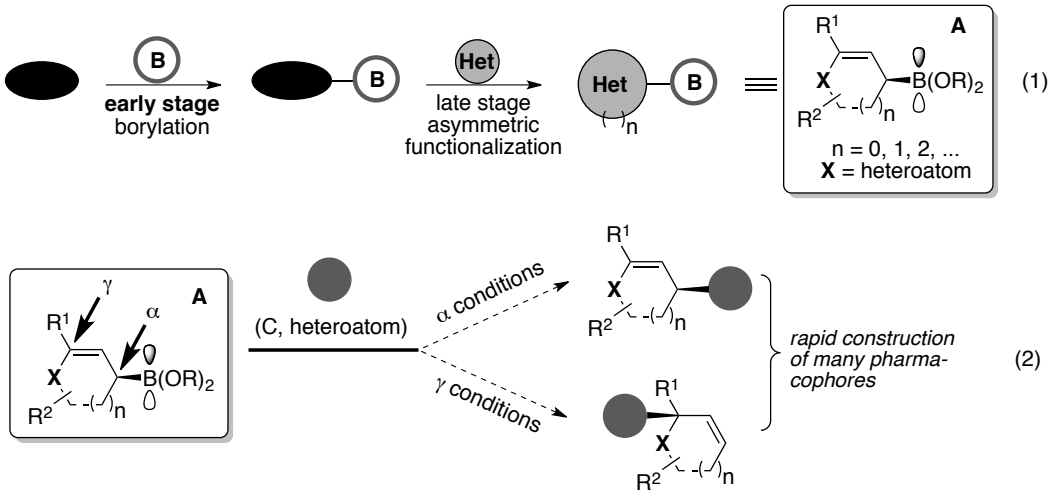
As detailed in Chapter 1, mainstream methods favor the "late introduction" of the boronyl unit, our group, however, has proven the validity of the "early introduction" strategy (Section 1.3.2). By applying well-established synthetic protocols on substrates bearing a pre-installed boronyl unit, novel organoboronates can be accessed with great efficiency and excellent control of selectivities. For example, as a class of newly emerged synthetic intermediates, chiral β-boronyl carbonyl compounds exhibited attractive synthetic applications in stereoselective C–C bond formation reactions and versatile carbonyl modification reactions (Chapter 2). In this thesis, these synthetically valuable compounds were obtained in high yields and good to high enantiomeric purity *via* a fine-tuned Cu-catalyzed enantioselective conjugate reduction of enoates with boronyl units pre-installed at the β position (Chapters 2 and 3). As a complementary approach to access this class of chiral alkylboronates (Chapter 1), the methods also allowed

the use of organosilane as the nucleophilic hydride source, which features air-stablity, low cost and environment-friendly nature.

The second part of this thesis focused on the exploration of new synthetic applications of chiral alkylboronates, including rapid synthesis of biologically active molecules and invention of new C–C bond formation methods with controlled regio- and stereoselectivity (Chapters 4 and 5). Through a careful optimization of the Pd-catalyzed borylative alkene isomerization method previously developed in our group, unique chiral heterocyclic allylic boronates were accessed in gram-scale with high enantiomeric purity (Chapter 4). Not only this class of chiral intermediates contain a versatile boronyl unit that can be applied in many C–C or C–heteroatom bond formation reactions with high chemo- and stereoselectivity, but they also enclose heterocyclic rings that are pharmacophore units in many biologically important natural products and pharmaceutical drugs. For instance, mefloquine is an important antimalarial drug that is intriguing both structurally and biologically (Sections 4.3.1 and 4.3.2). With the chiral piperidinyl allylic boronate as the key intermediate, all four mefloquine stereoisomers were obtained within 2-4 steps in gram-scale with high optical purities (Chapter 4). Additionally, this study opened an in-depth investigation into the absolute configurational assignment and antimalarial activities for all resulting stereoisomers of mefloquine and their analogues. Using a chemical approach (Section 4.3.8), our contribution towards the study of absolute configurations of all mefloquine compounds has helped unravel almost 40-year debate for the stereochemistry of (+)-*erythro*-mefloquine. The ultimate challenge for the application of the chiral allylic heterocyclic boronates would be their use in stereospecific Suzuki-Miyaura cross-coupling reactions, which has been recognized as one of the last frontiers of cross-coupling chemistry. This challenge is not only due to the notorious restrictions imposed upon the Suzuki-Miyaura coupling of secondary alkylboronates (Section 1.2.6), but also from the complementary control of regio- and stereoselectivities. Upon careful examination

of chiral catalytic system and other reaction conditions, a ligand-controlled regiodivergent and enantiospecific cross-coupling of these chiral allylic heterocyclic boronates was achieved with high efficiency (Chapter 5). Moreover, the usefulness of the resulting 2- and 4-substituted dehydropiperidines was highlighted in the successful, short formal syntheses of the botanical insecticide (+)-anabasine and the antidepressant drug (+)-paroxetine.

These studies not only illustrated the synthetic advantages of organoboronates *via* an "early introduction" strategy, but also opened doors towards a new direction of organoboron chemistry, i.e., incorporation of organoboron chemistry in aliphatic heterocyclic chemistry. In this thesis, two types of transformations of the chiral heterocyclic allylic boronates were demonstrated, including aldehyde allylboration and regio-/stereoselective Suzuki-Miyaura cross-coupling reactions. High levels of reactivity and selectivity were achieved in both cases.



Scheme 6-1: Two future perspectives for "non-racemic heterocyclic boron chemistry".

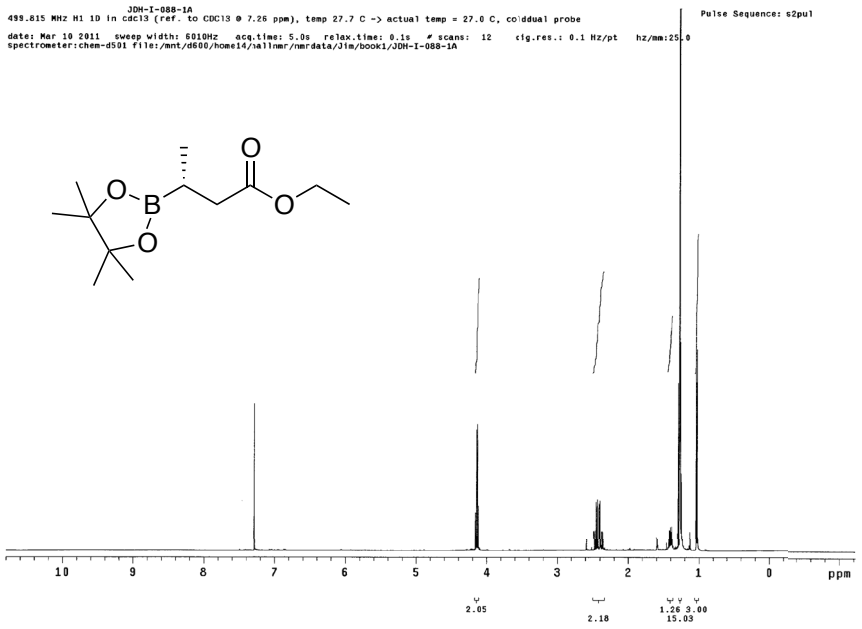
Based on these advances, this thesis could lead to at least two future branches in the direction of "non-racemic heterocyclic boron chemistry": (1) application of "early-stage borylation" strategies to access a series of chiral heterocyclic and

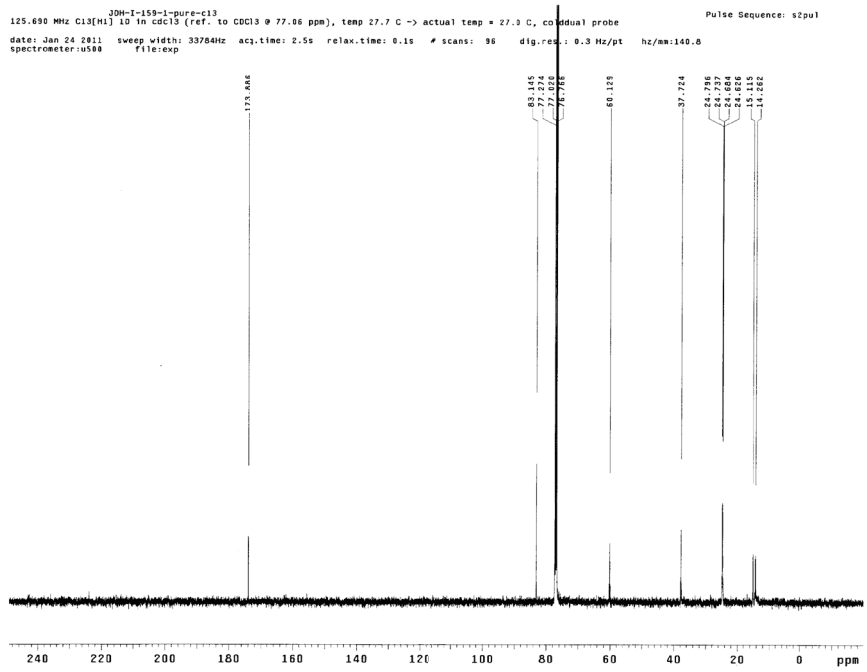
acyclic boronates with alternative size, substituents and heteroatoms (Scheme 6-1, Equation 1); (2) exploration of additional synthetic applications of these chiral heterocyclic boronates with controlled reactivity and selectivity, such as stereospecific C–C and C–heteroatom bond formation reactions (Scheme 6-1, Equation 2). These two future perspectives envision the regiodivergent and stereospecific construction of numerous biologically important small molecules, which are also economically efficient and environmentally benign reactions. Nevertheless, considering the significance of heterocycle synthesis in pharmaceutical research and the "green" nature of boron derivatives, the two proposed branches mentioned here only represent a minute fraction of potential future directions generated from this thesis. The author believes that the findings achieved in this thesis and their future perspectives provide much expectation for the practical role of organoboron chemistry in modern organic synthesis.

Appendices

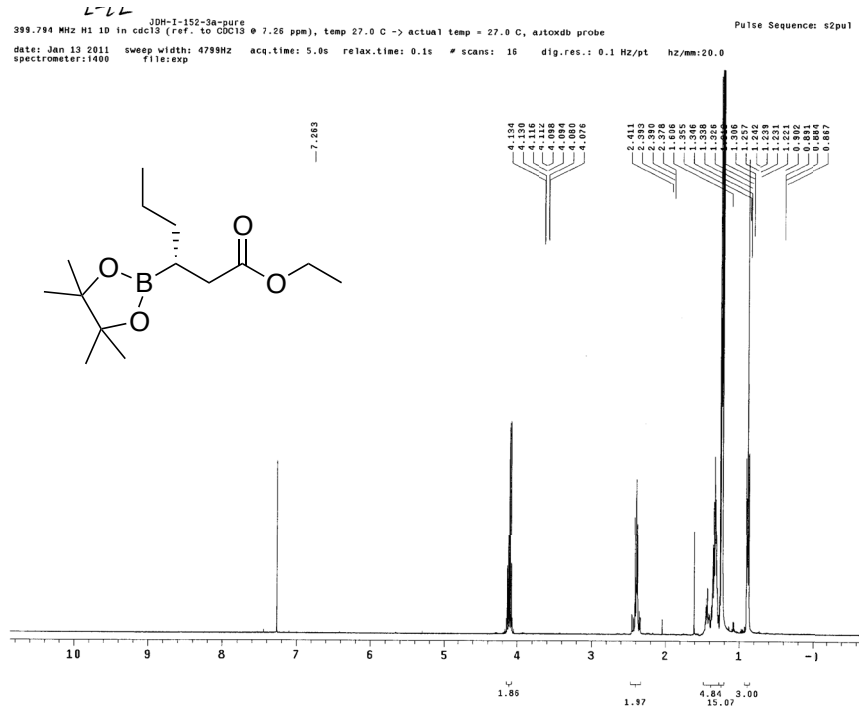
Appendix 1: Selected copies of NMR spectra

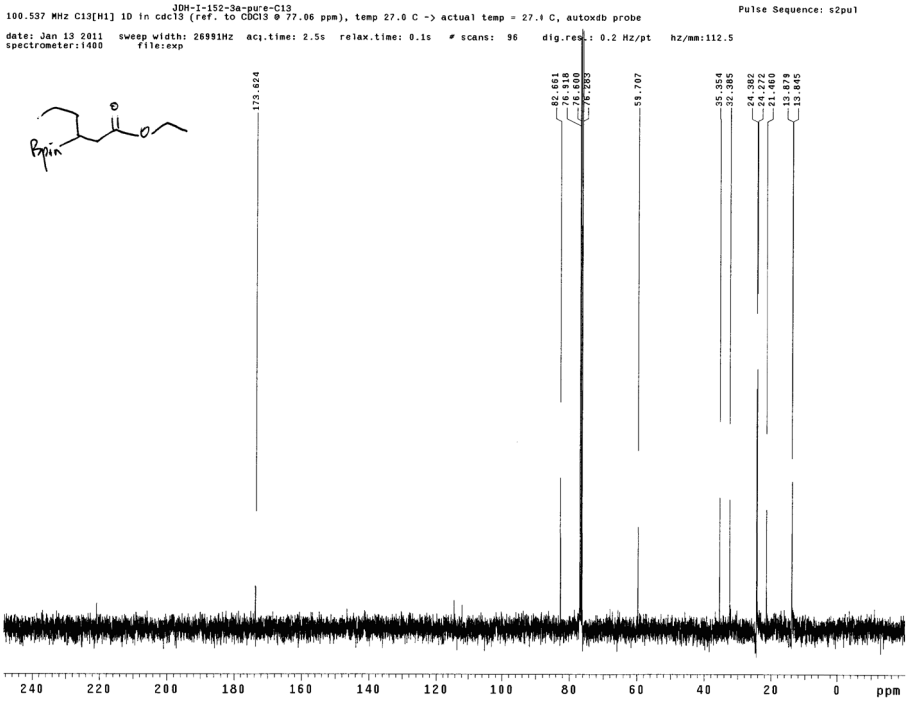
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 2-19 in $CDCl_3$ at 25 ^{o}C



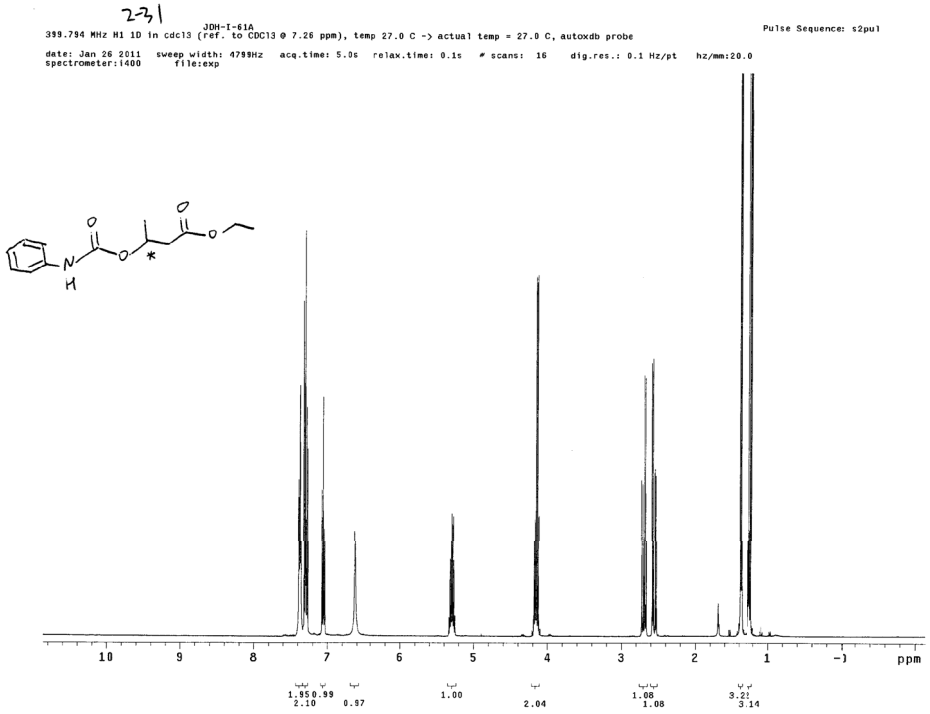


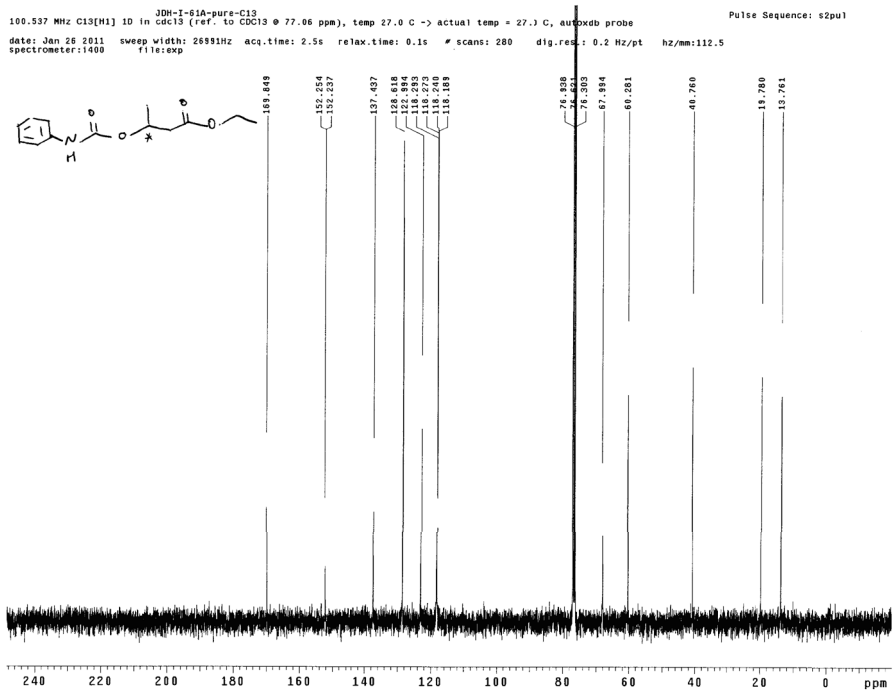
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of 2-22 in $CDCl_3$ at 25 ^{o}C



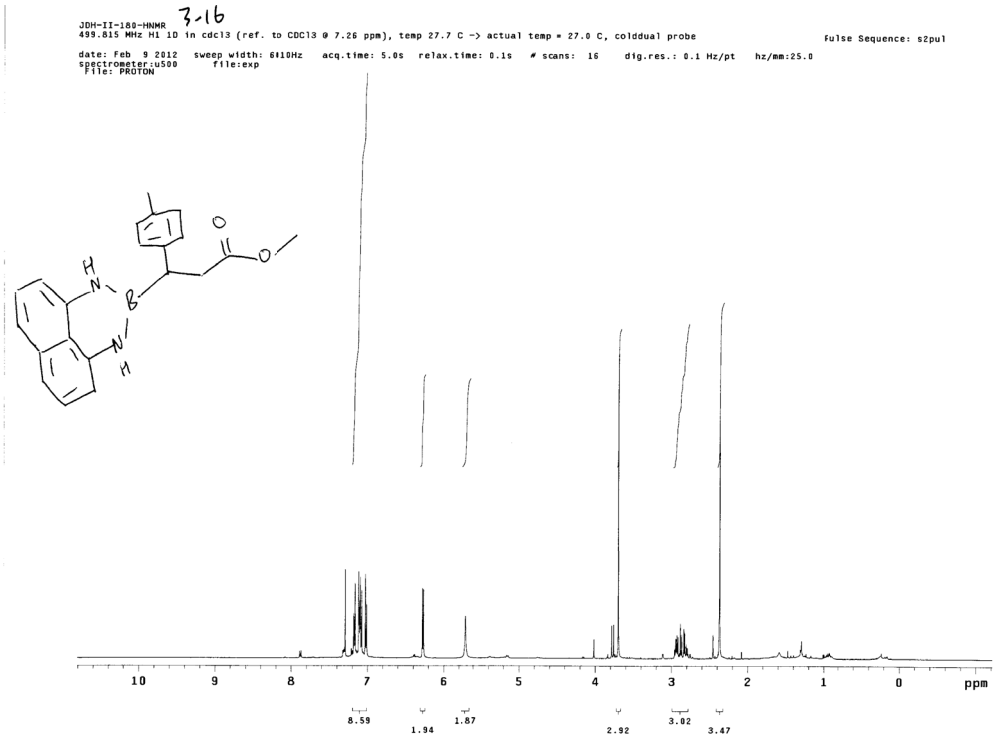


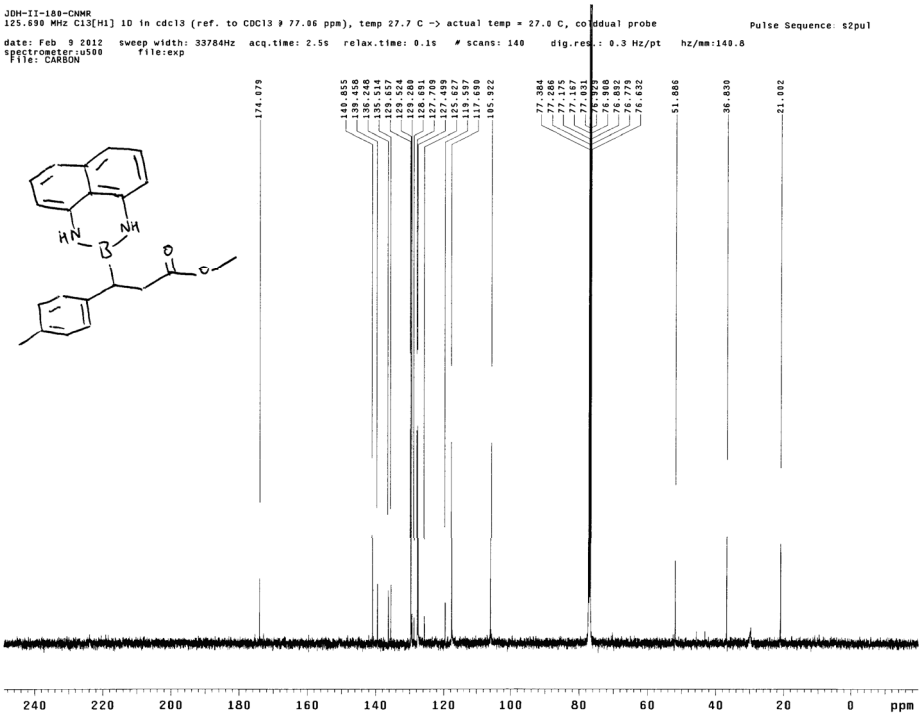
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of 2-31 in $CDCl_3$ at 25 ^{o}C



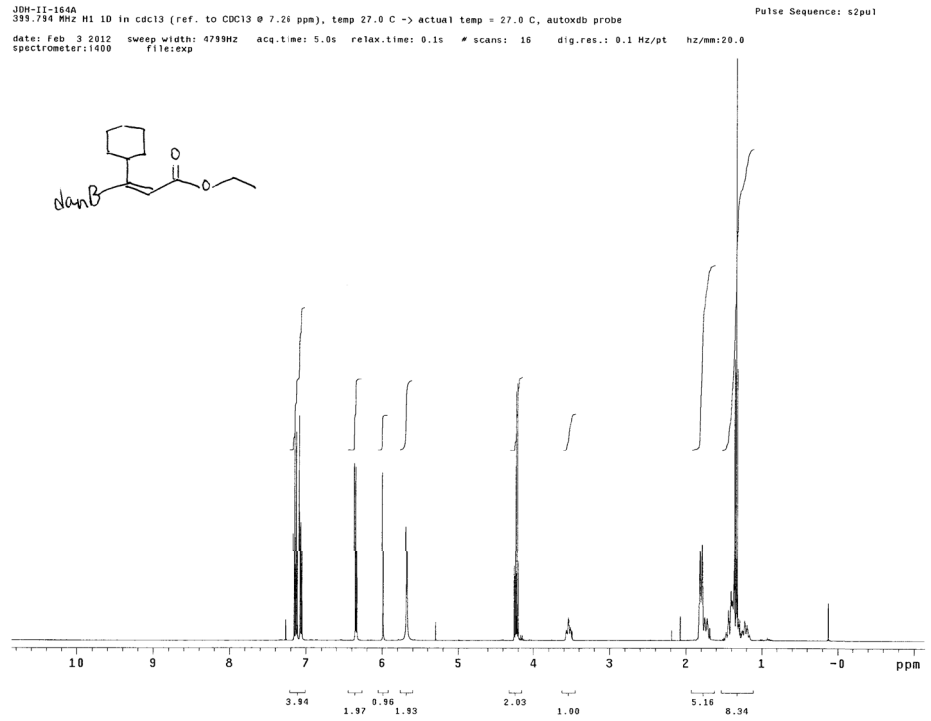


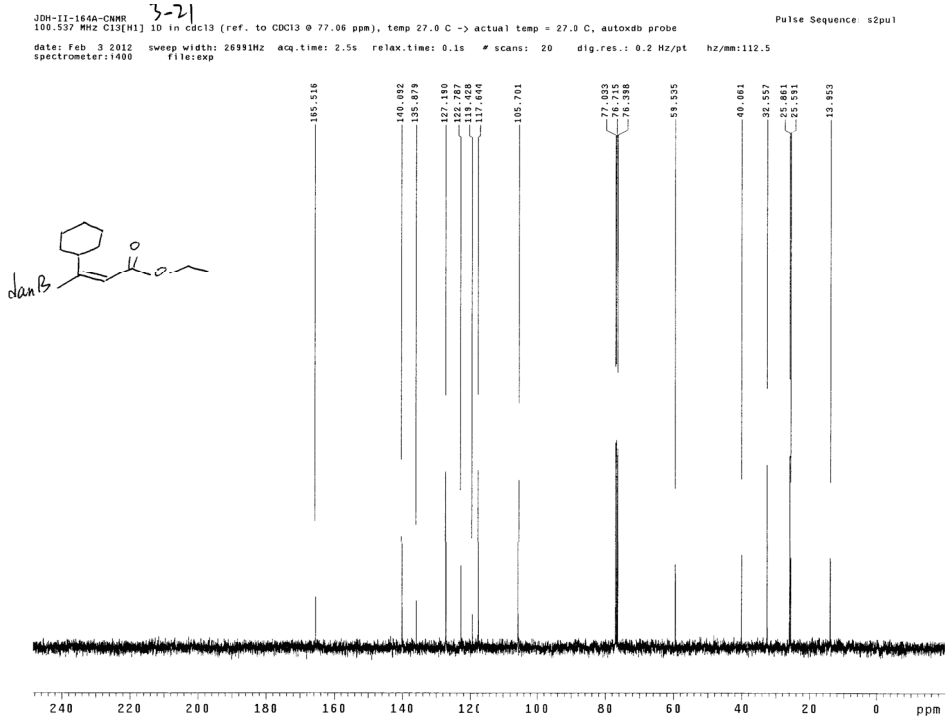
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of 3-16 in $CDCl_3$ at 25 ^{o}C



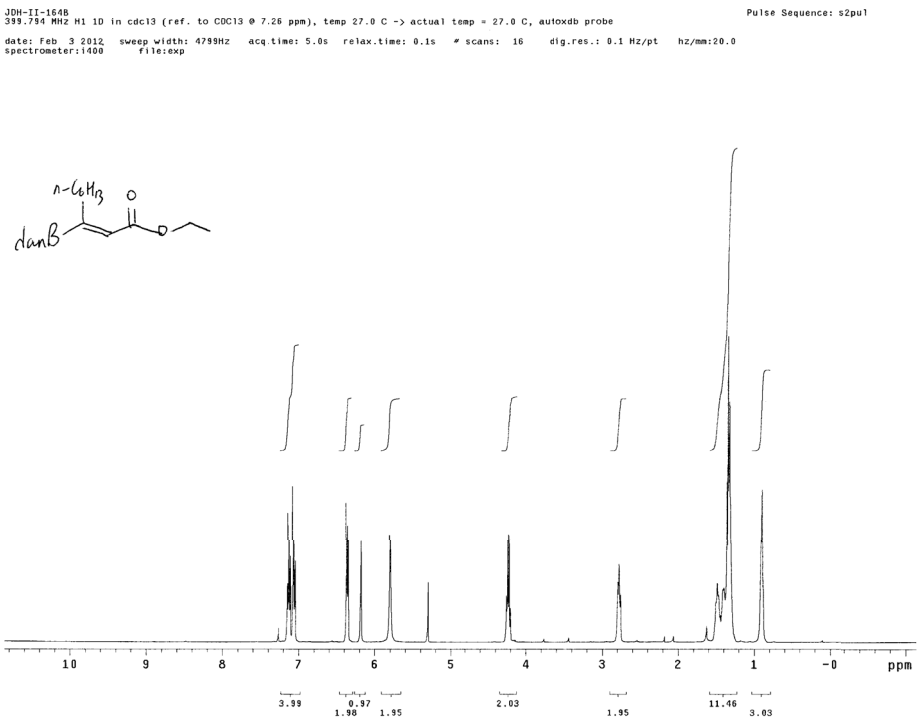


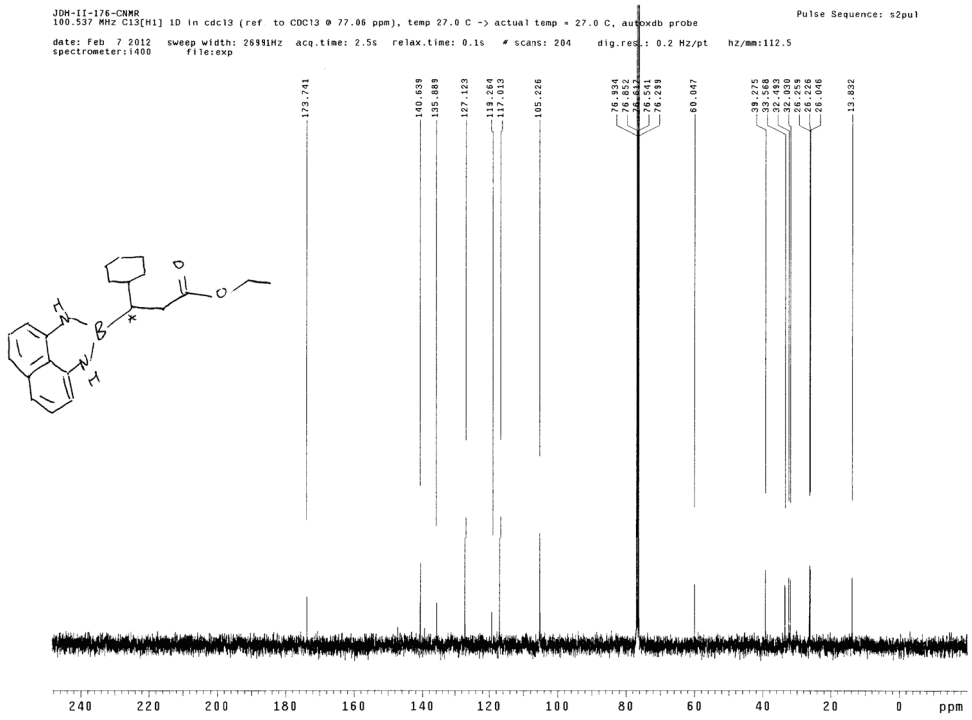
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR of 3-21 in $CDCl_3$ at 25 ^{o}C



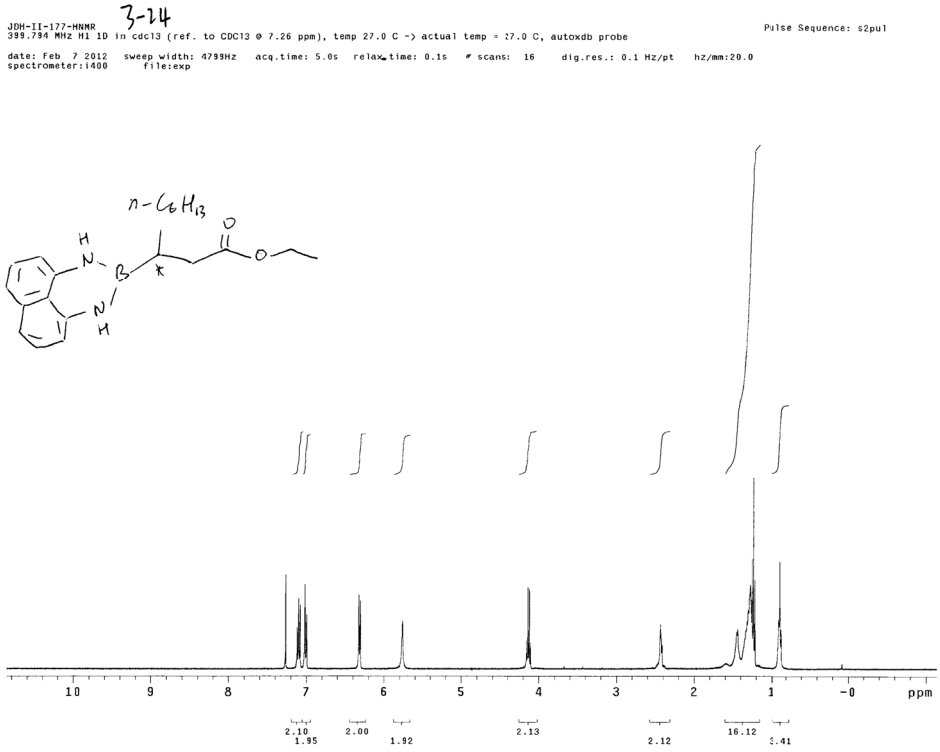


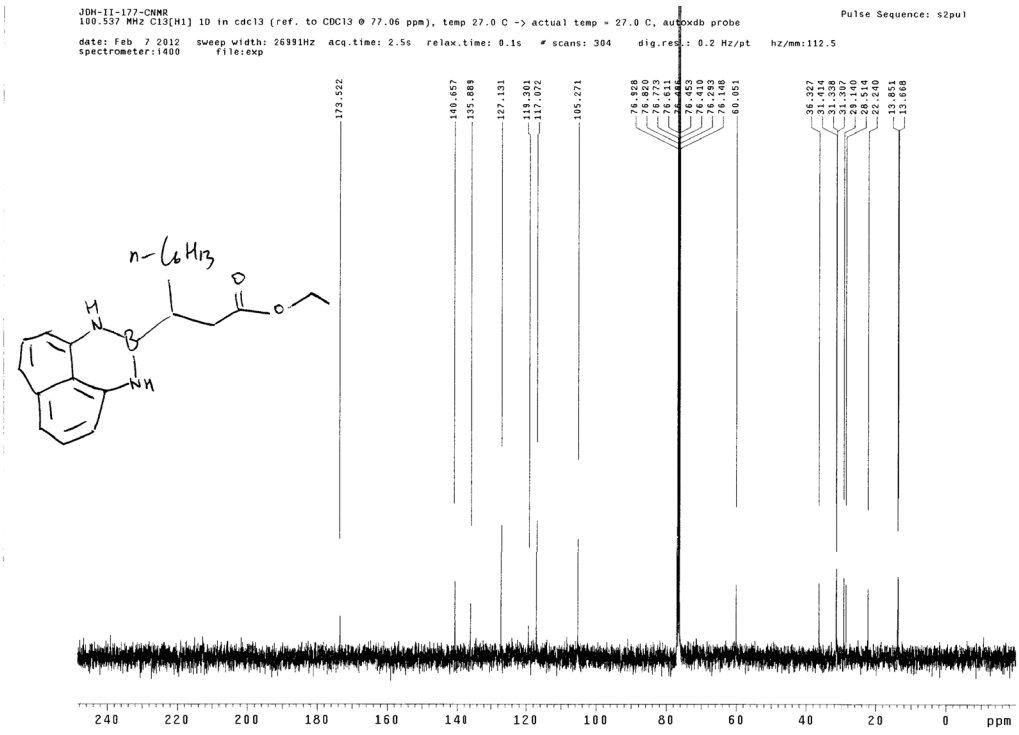
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of 3-23 in $CDCl_3$ at 25 ^{o}C



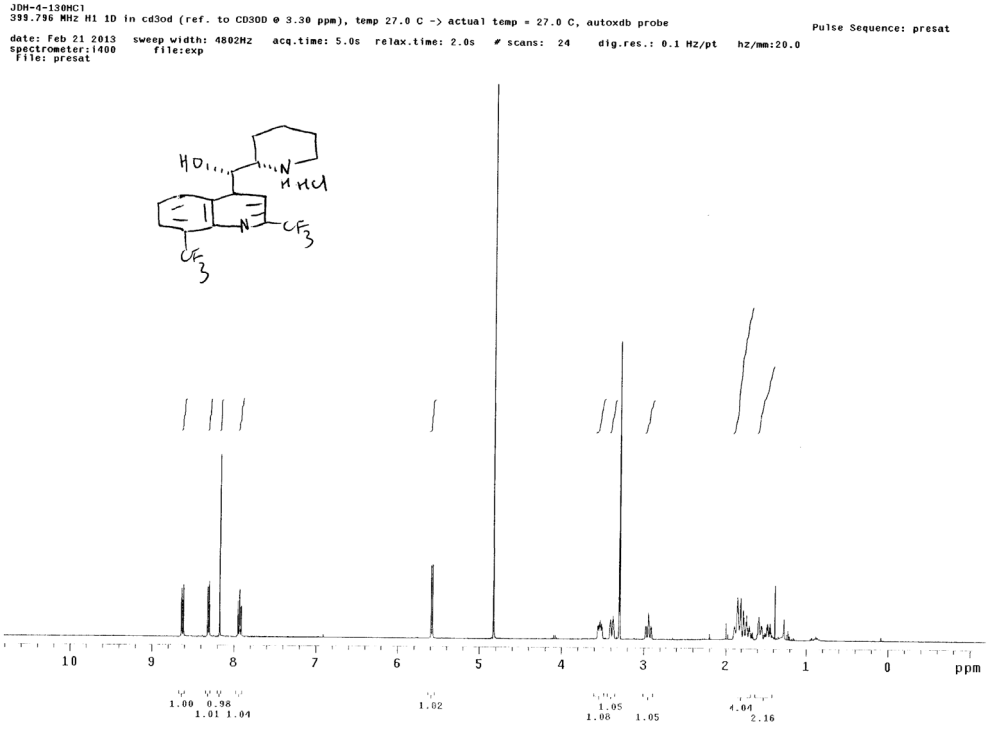


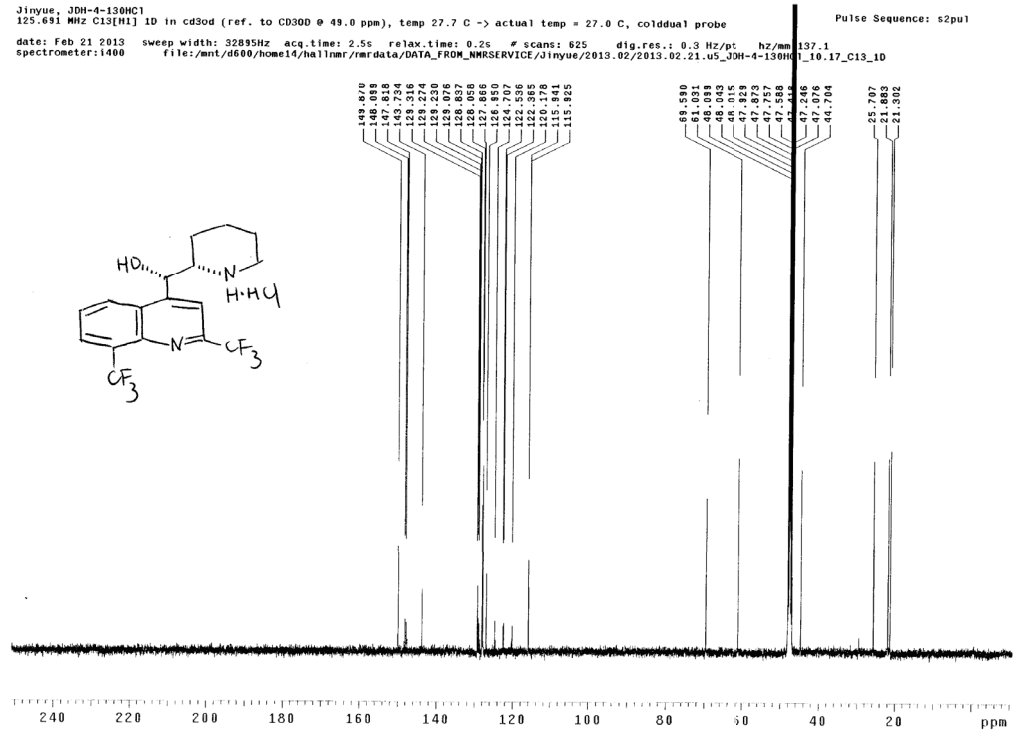
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of 3-24 in $CDCl_3$ at 25 ^{o}C



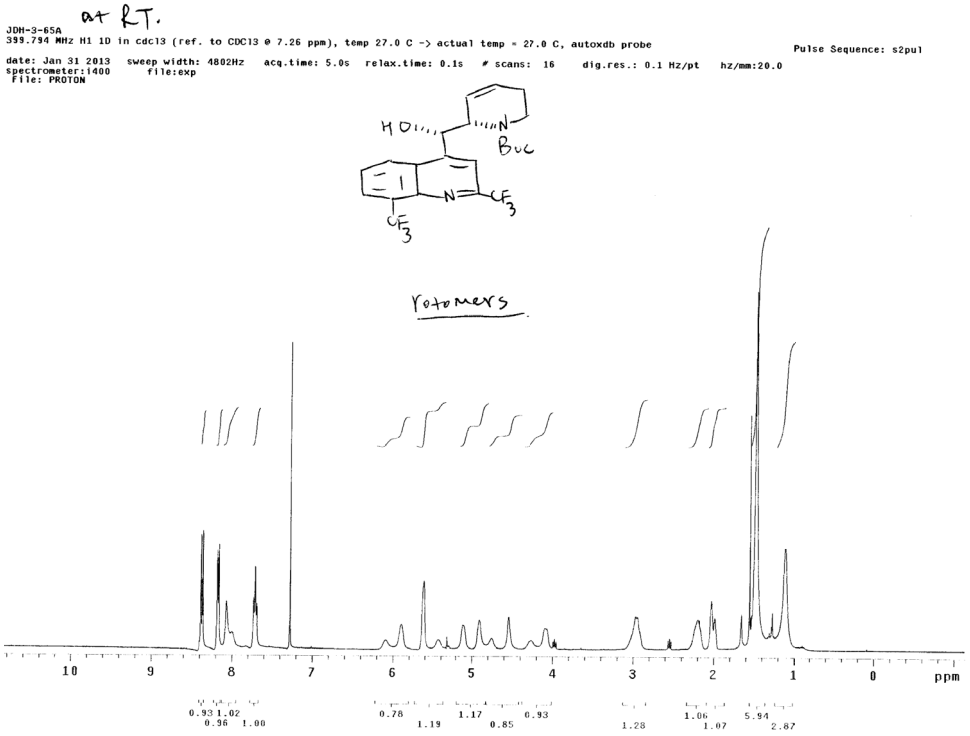


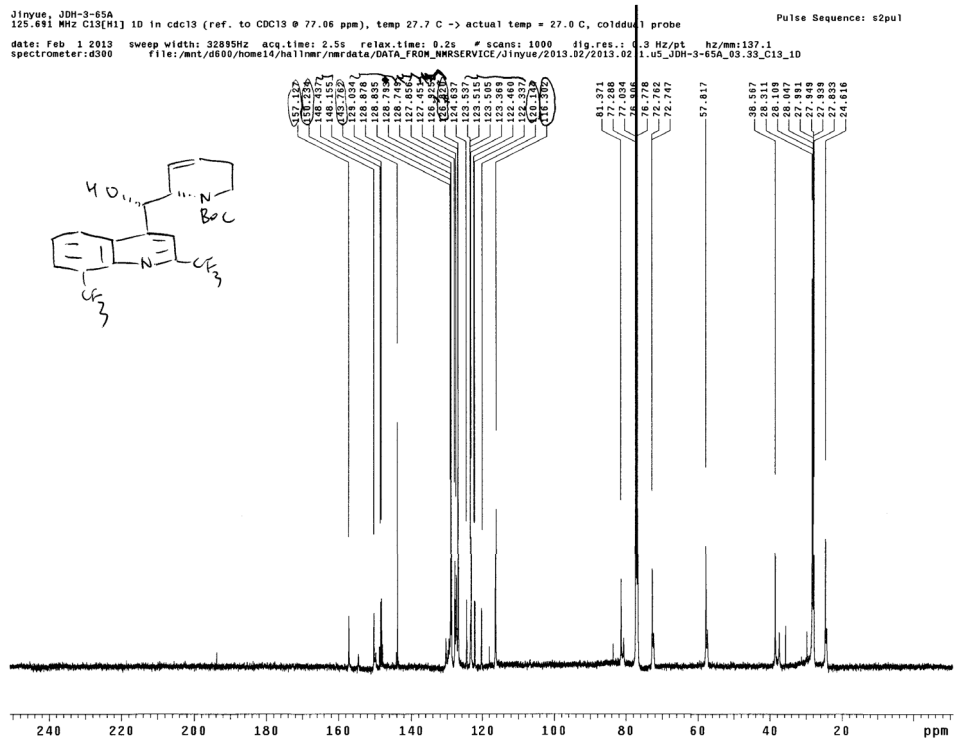
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of 4-15 in CD_3OD at 25 ^{o}C



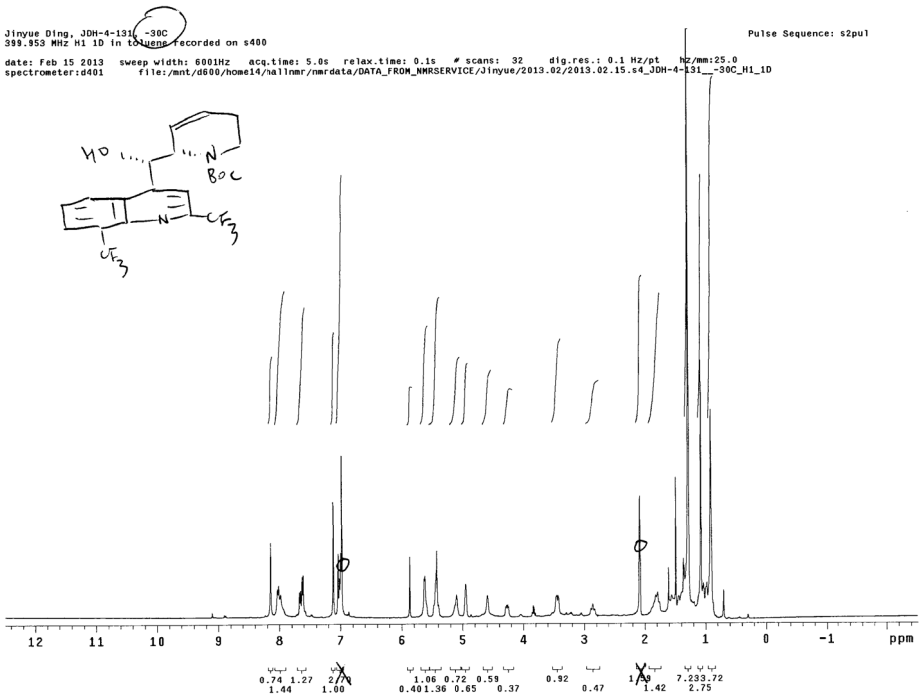


^{1}H (400 MHz) and ^{13}C (126 MHz) NMR of 4-27 in $CDCl_3$ at 25 ^{o}C

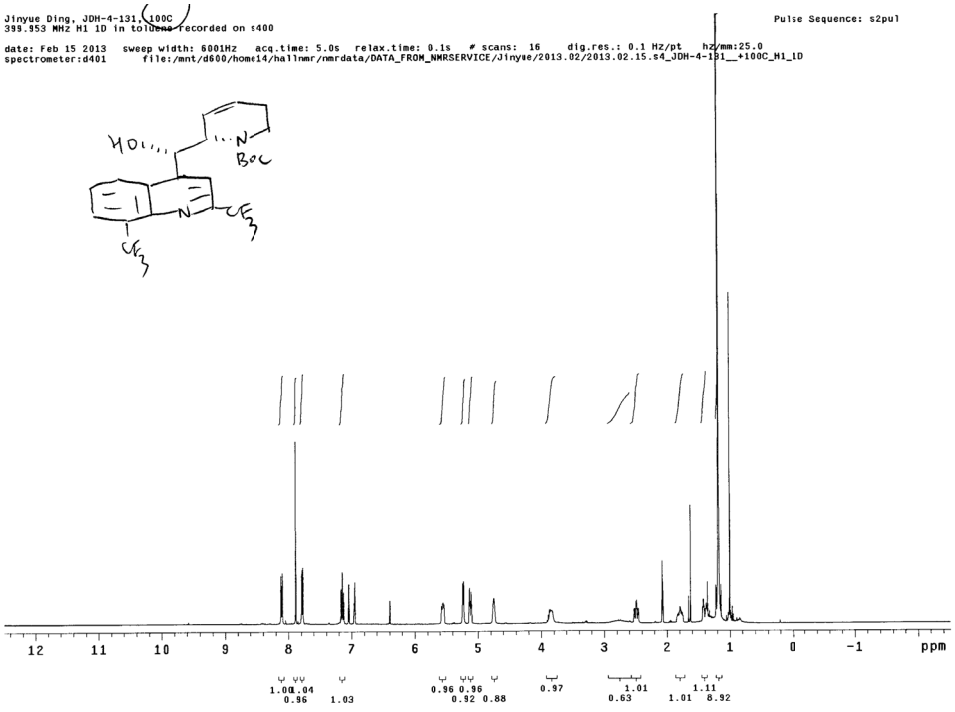




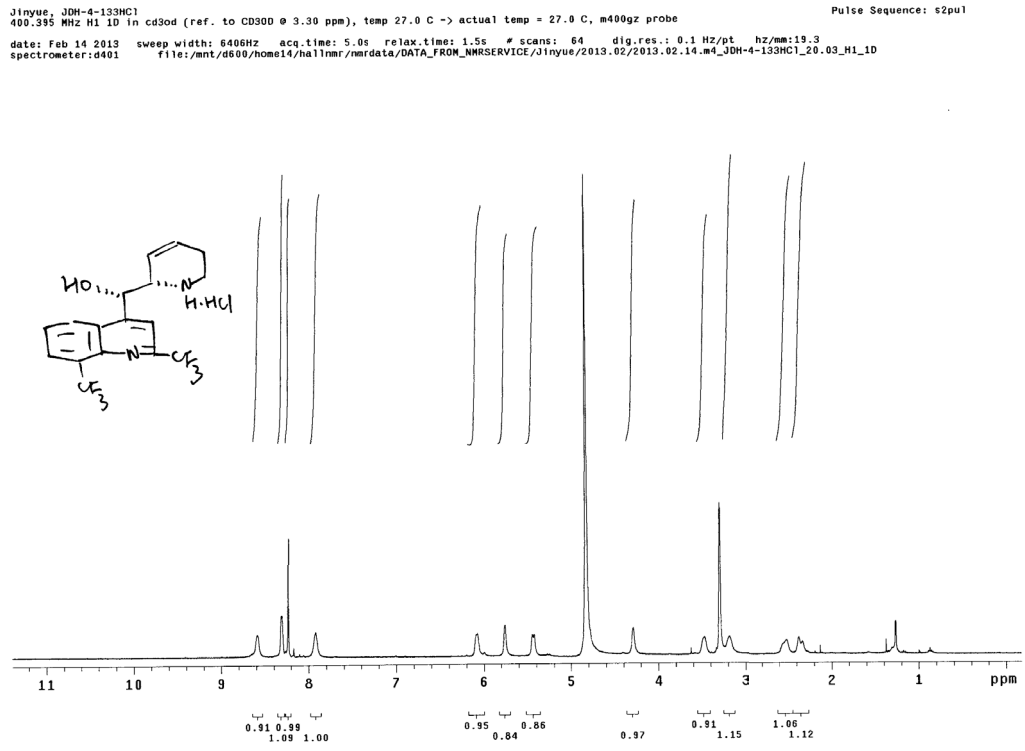
^{1}H (400 MHz) of 4-27 in $C_6D_5CD_3$ at −30 ^{o}C

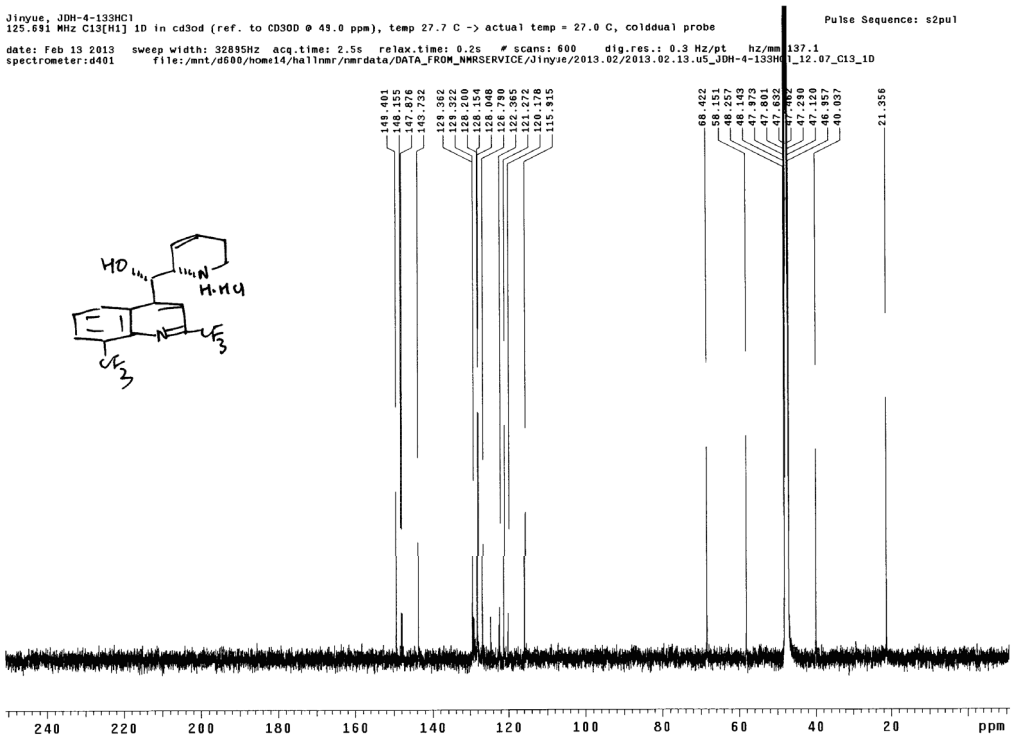


^{1}H (400 MHz) of 4-27 in $C_6D_5CD_3$ at 100 ^{o}C

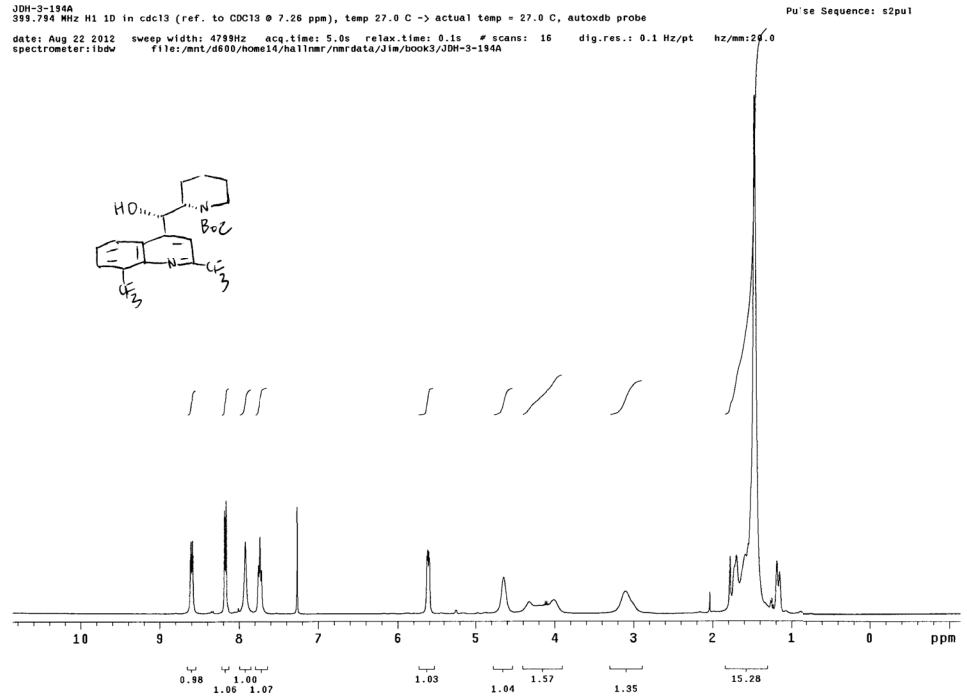


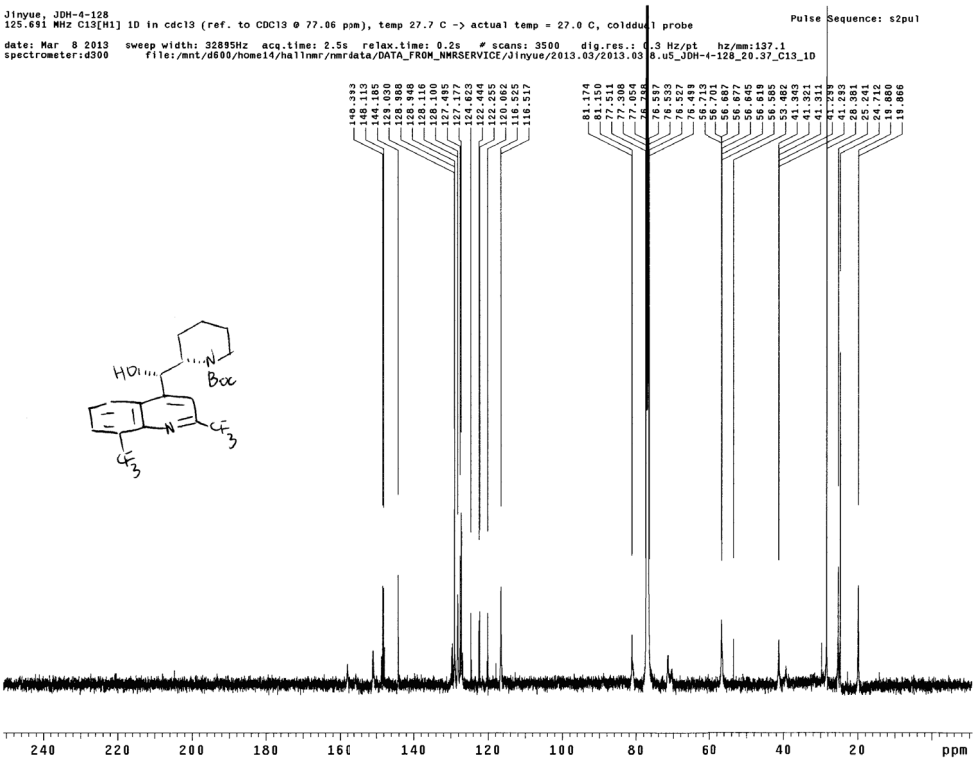
^{1}H (400 MHz) and ^{13}C (126 MHz) NMR of 4-31 in $CDCl_3$ at 25 ^{o}C



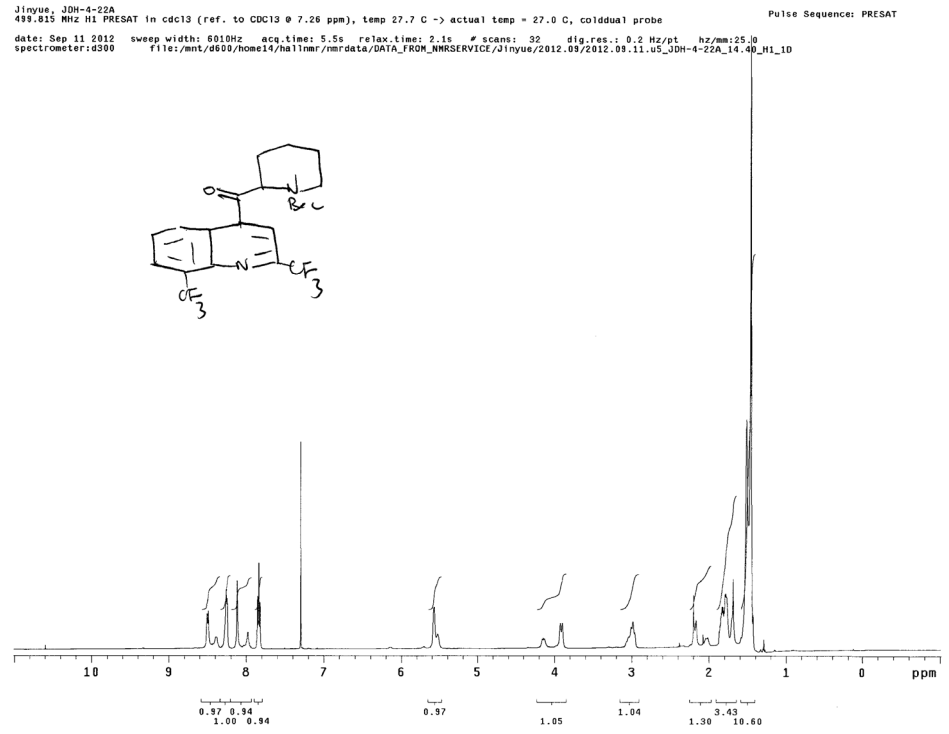


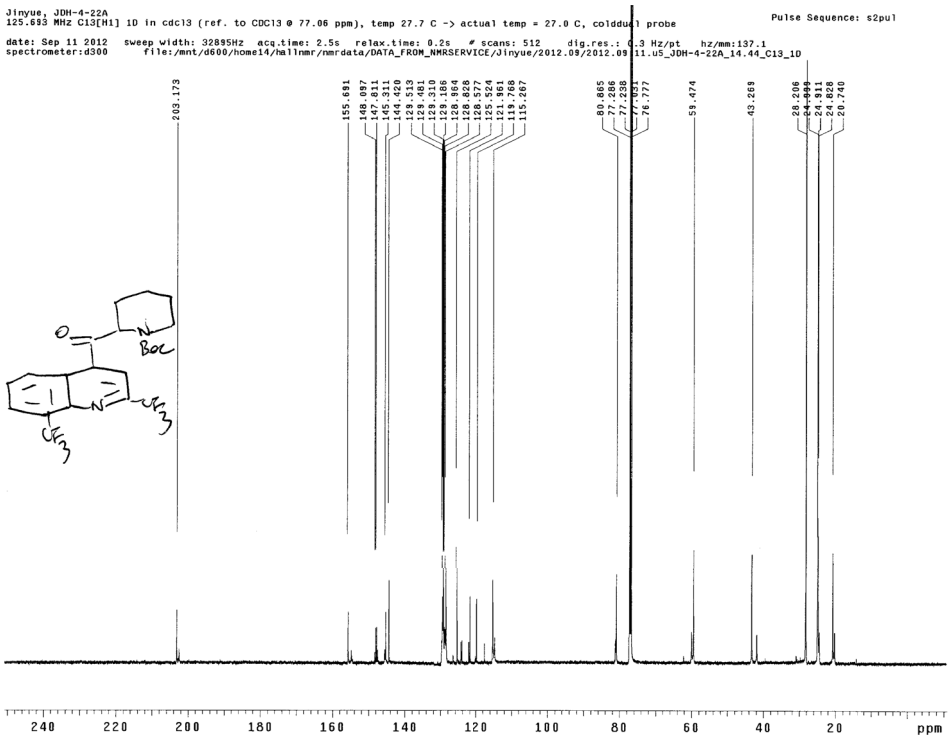
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 4-32 in $CDCl_3$ at 25 ^{o}C



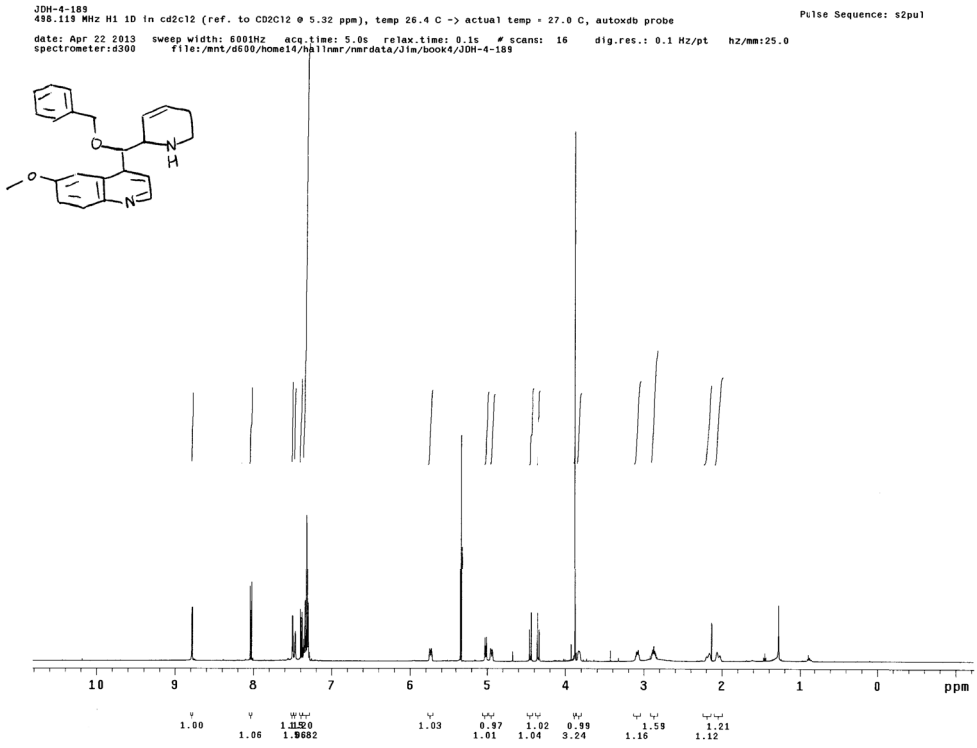


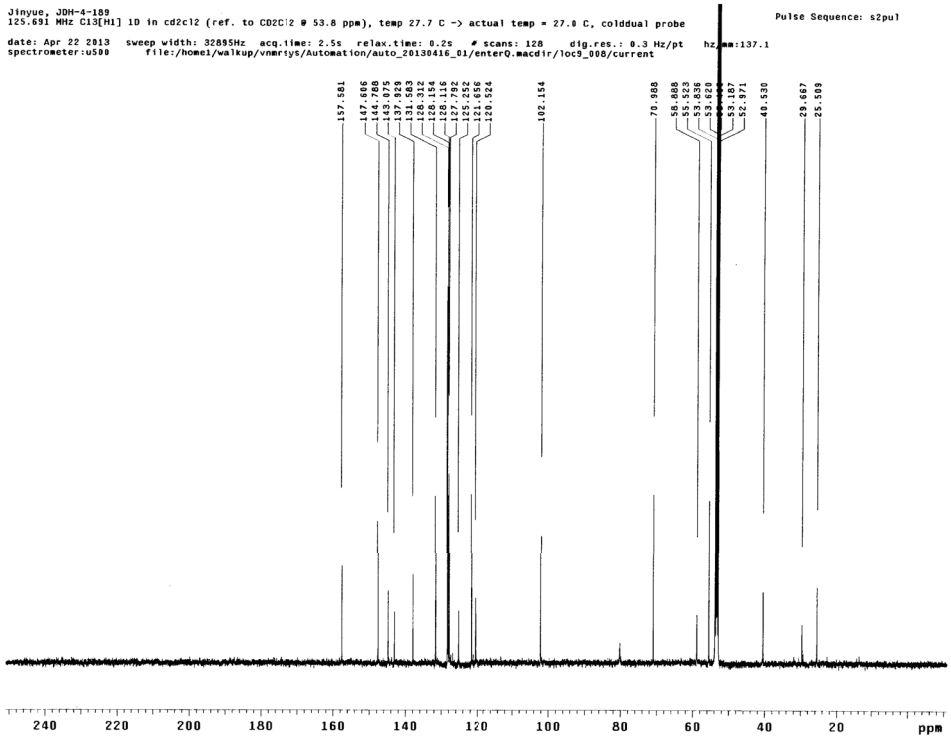
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 4-37 in $CDCl_3$ at 25 ^{o}C



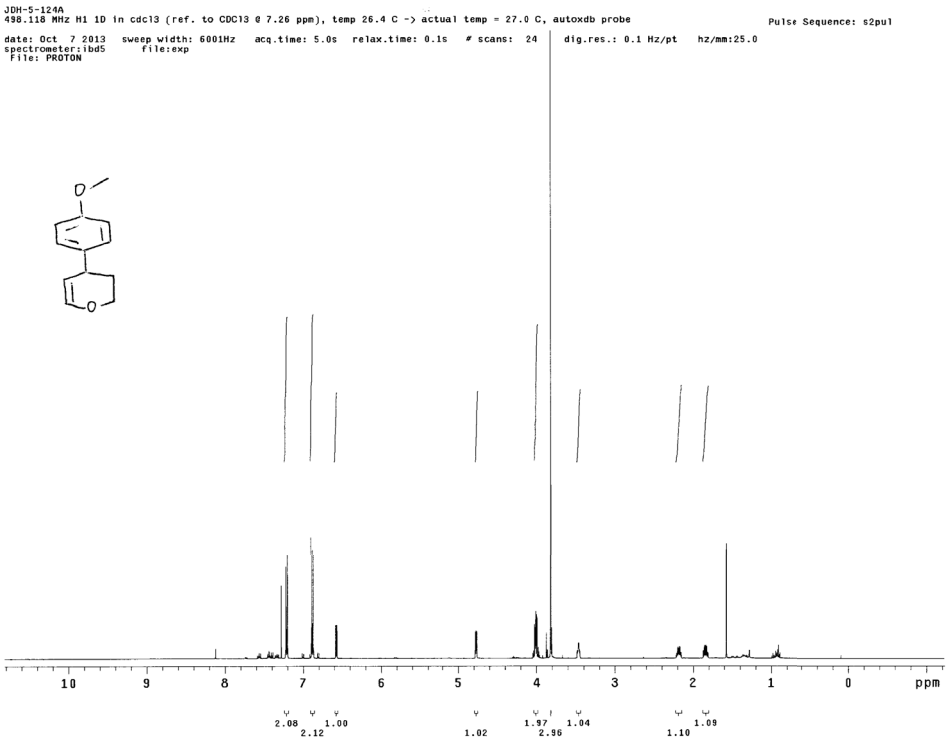


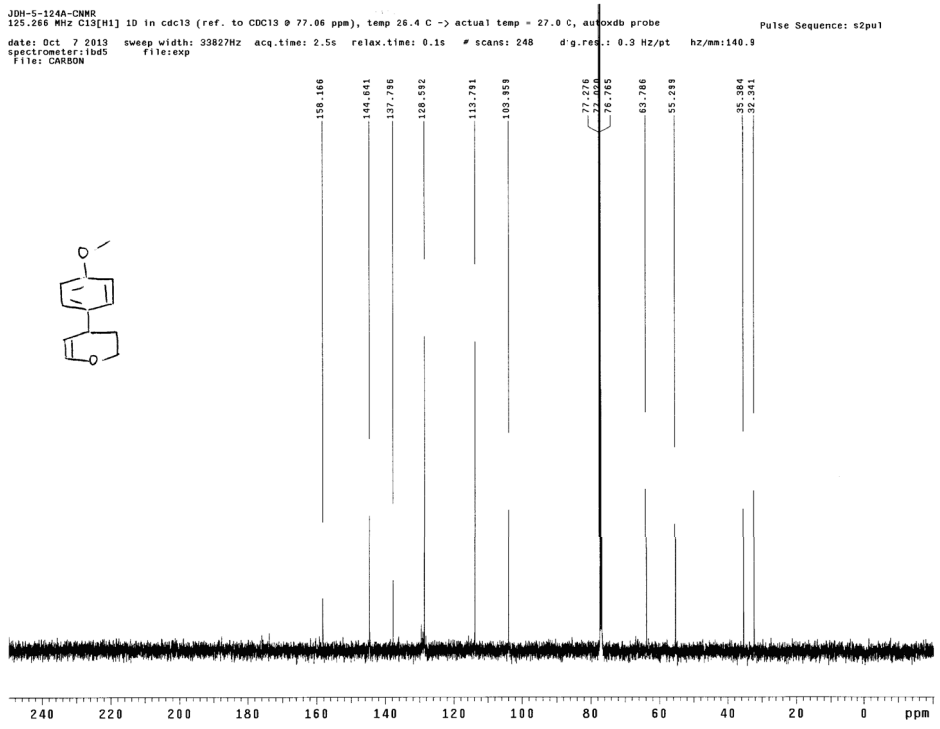
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 4-44 in $CDCl_3$ at 25 ^{o}C



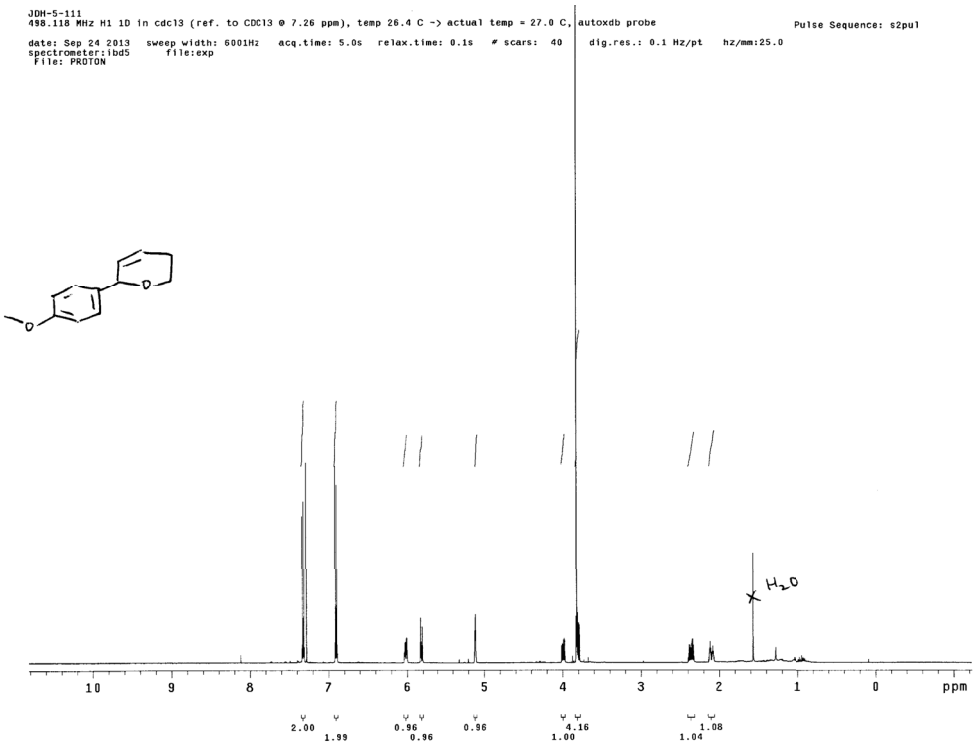


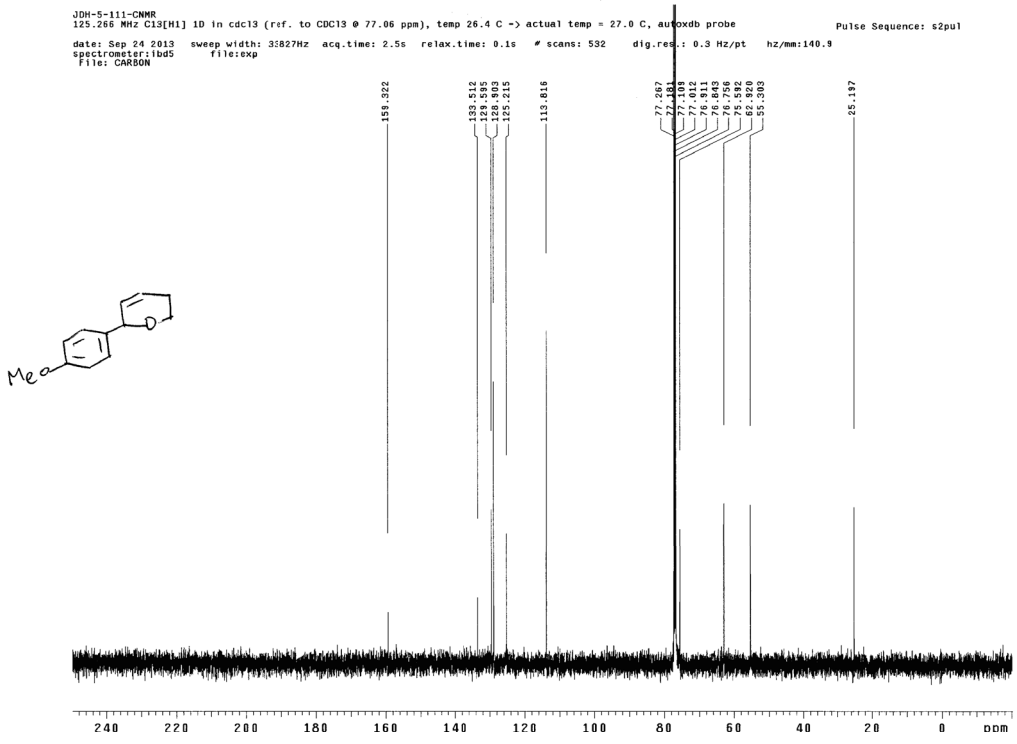
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-21 in $CDCl_3$ at 25 ^{o}C



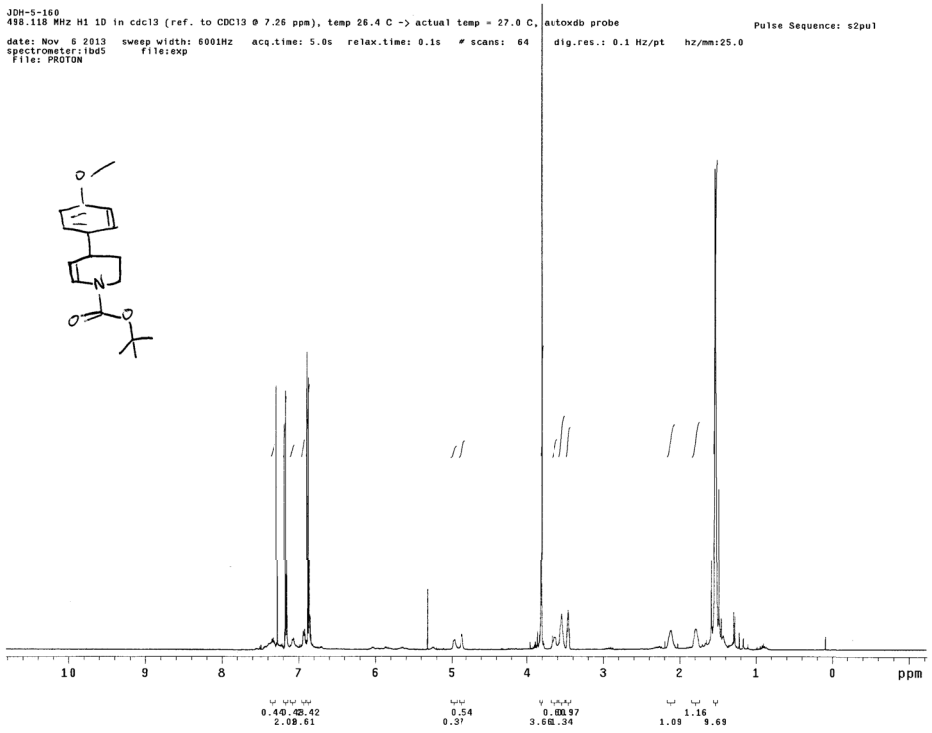


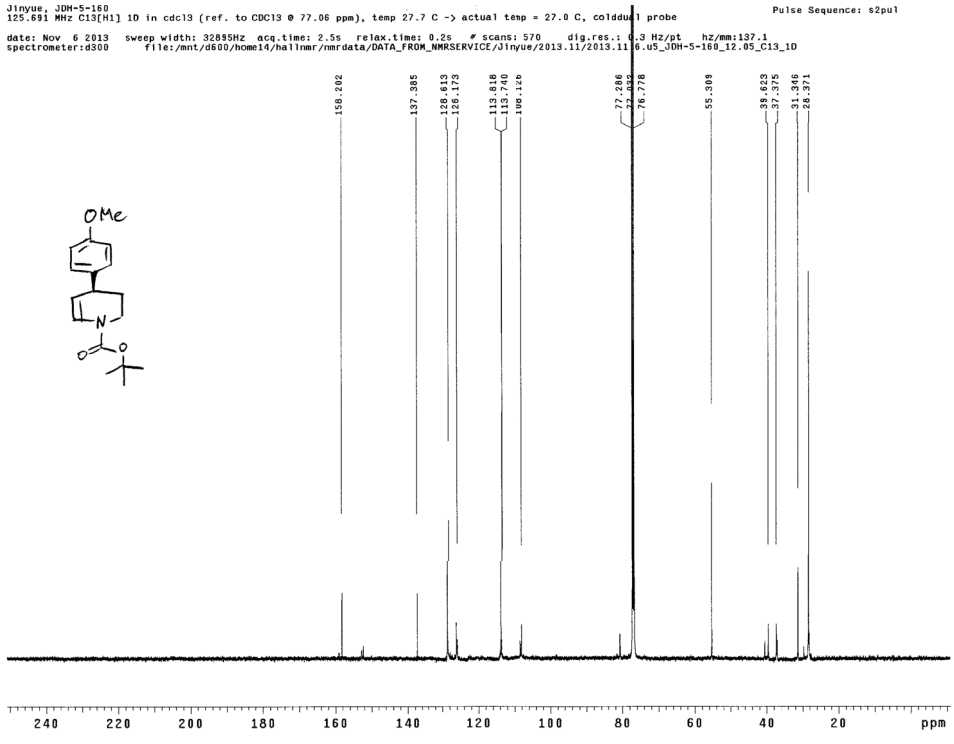
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-22 in $CDCl_3$ at 25 ^{o}C



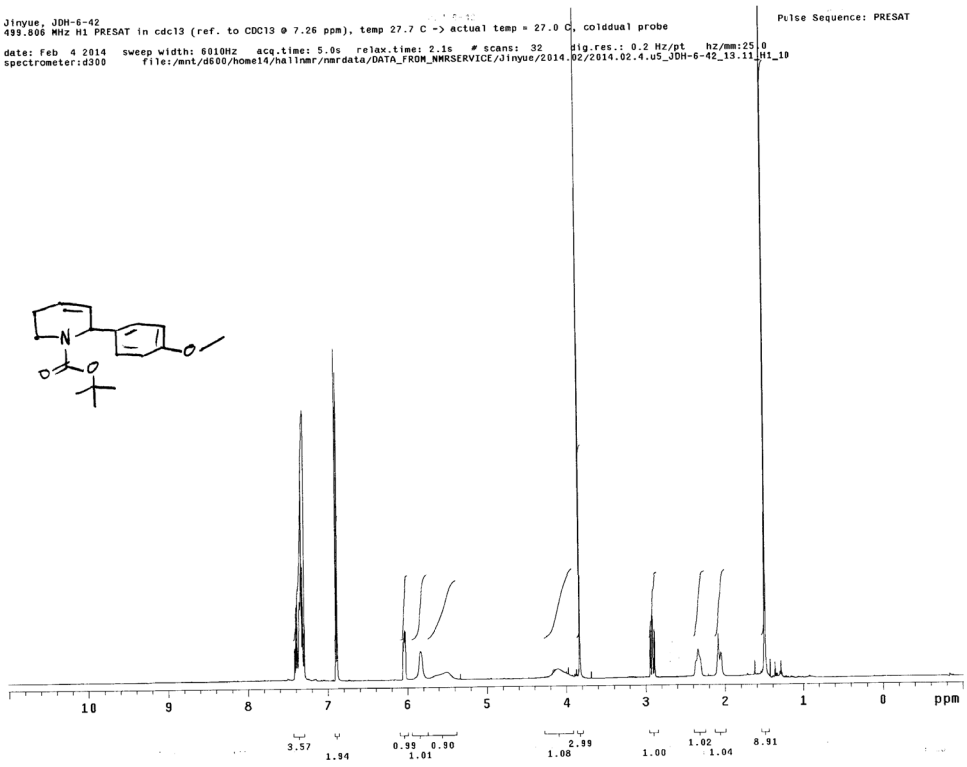


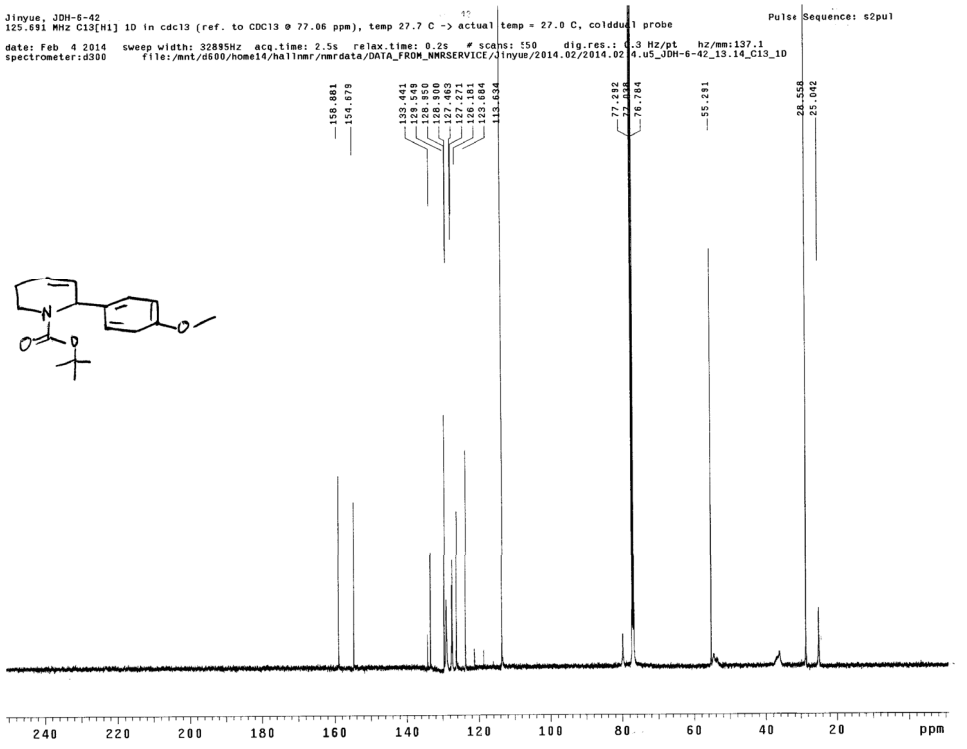
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-23 in $CDCl_3$ at 25 ^{o}C



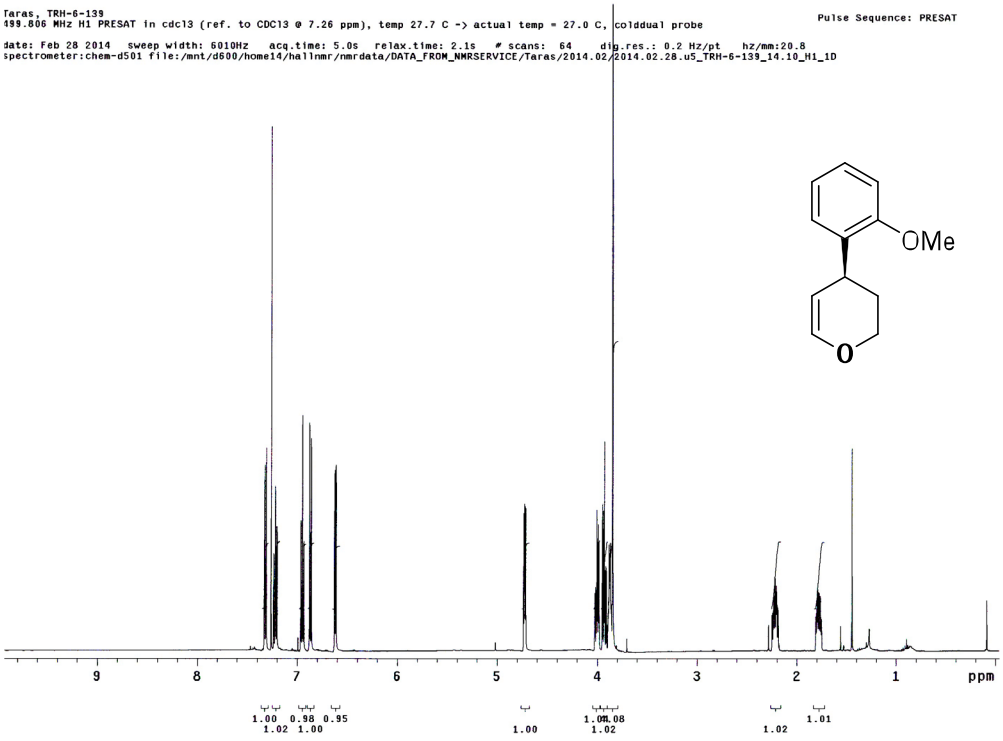


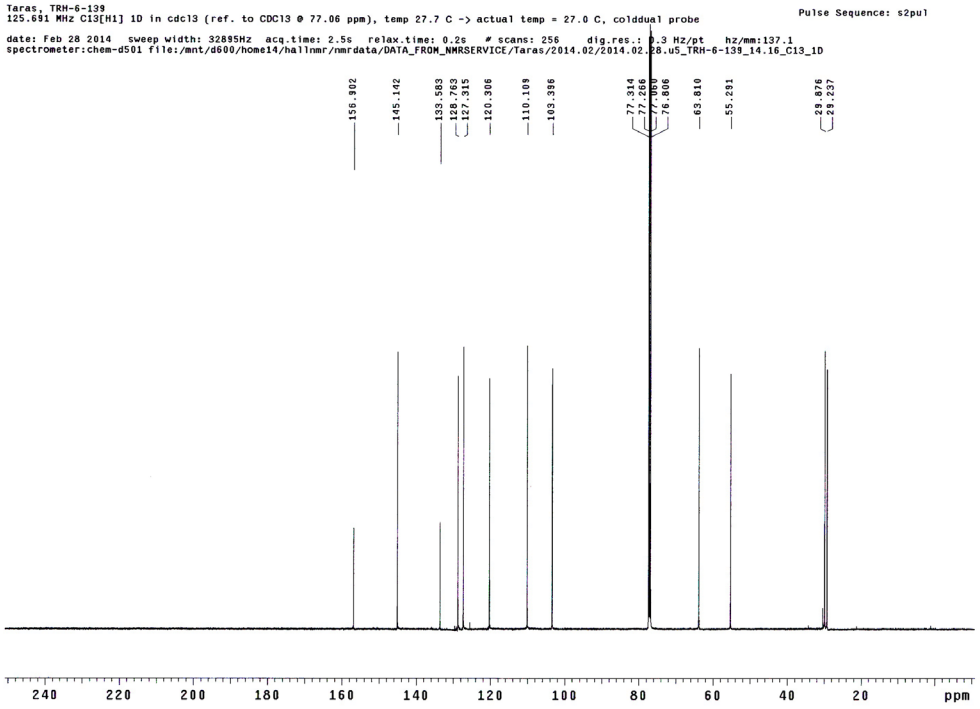
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-24 in $CDCl_3$ at 25 ^{o}C



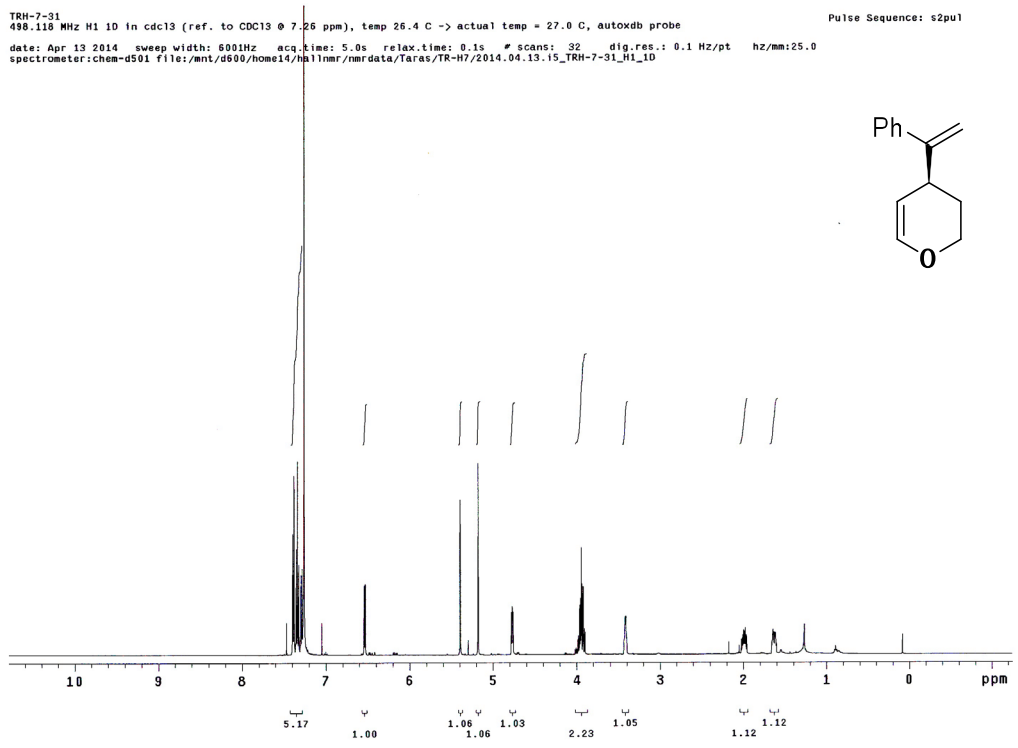


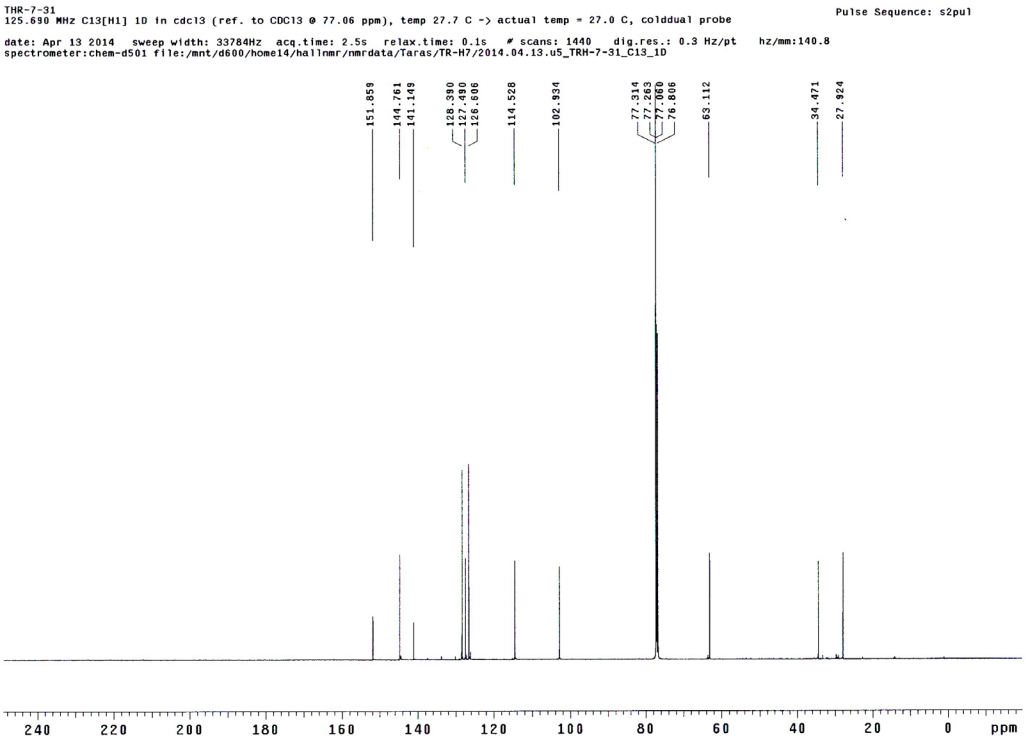
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-25 in $CDCl_3$ at 25 ^{o}C



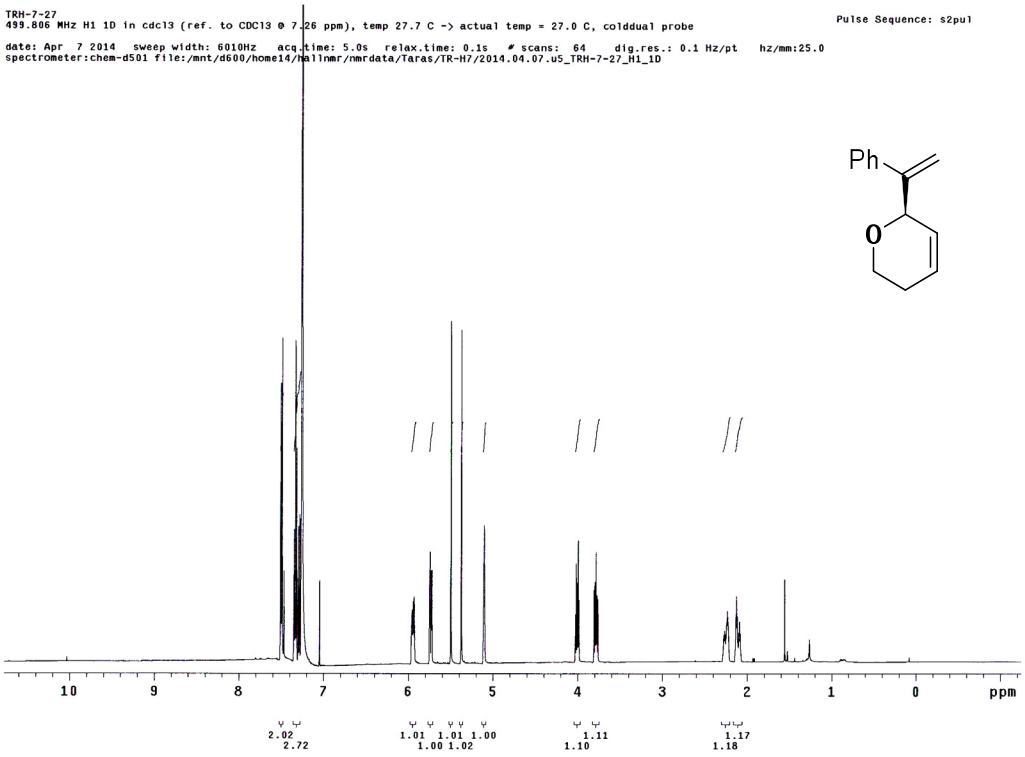


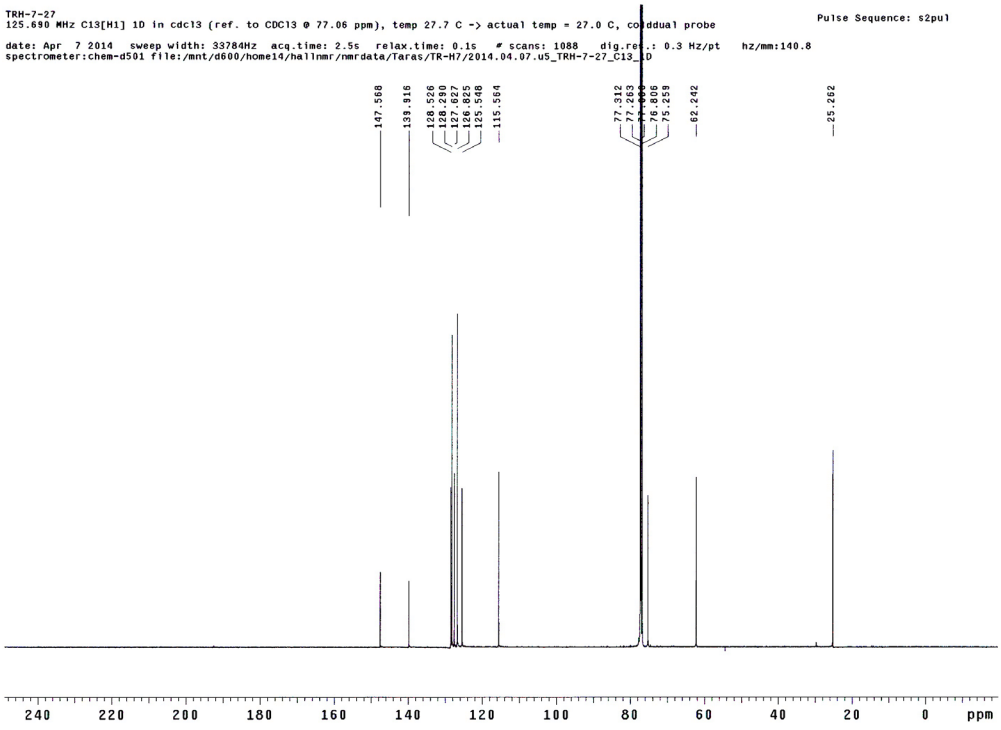
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-30 in $CDCl_3$ at 25 ^{o}C



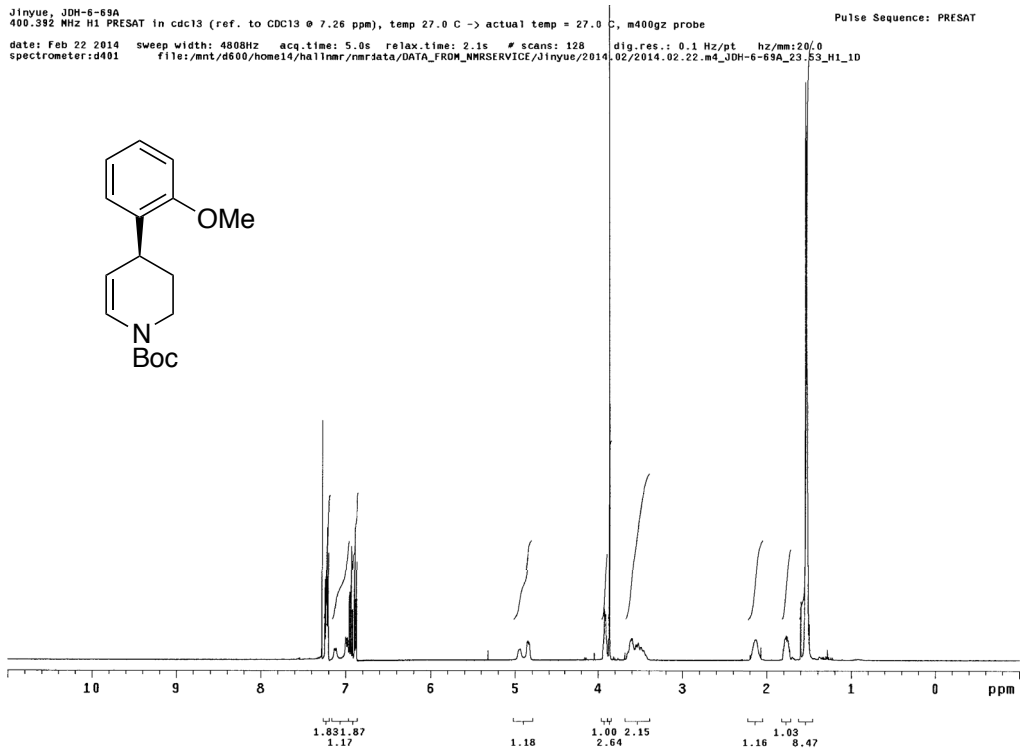


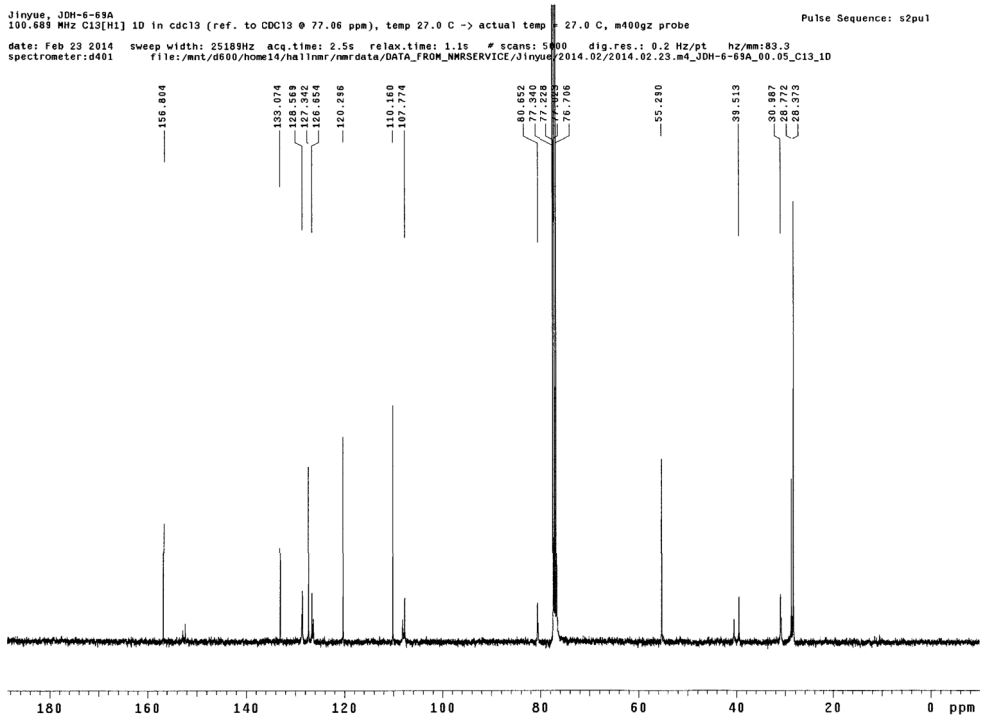
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-37 in $CDCl_3$ at 25 ^{o}C



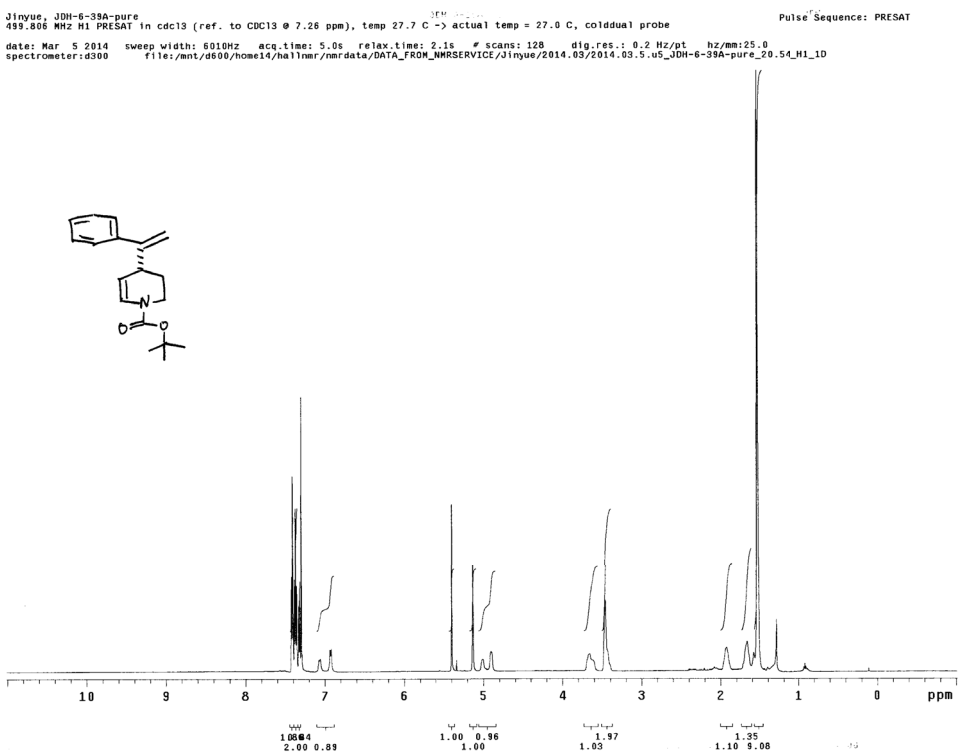


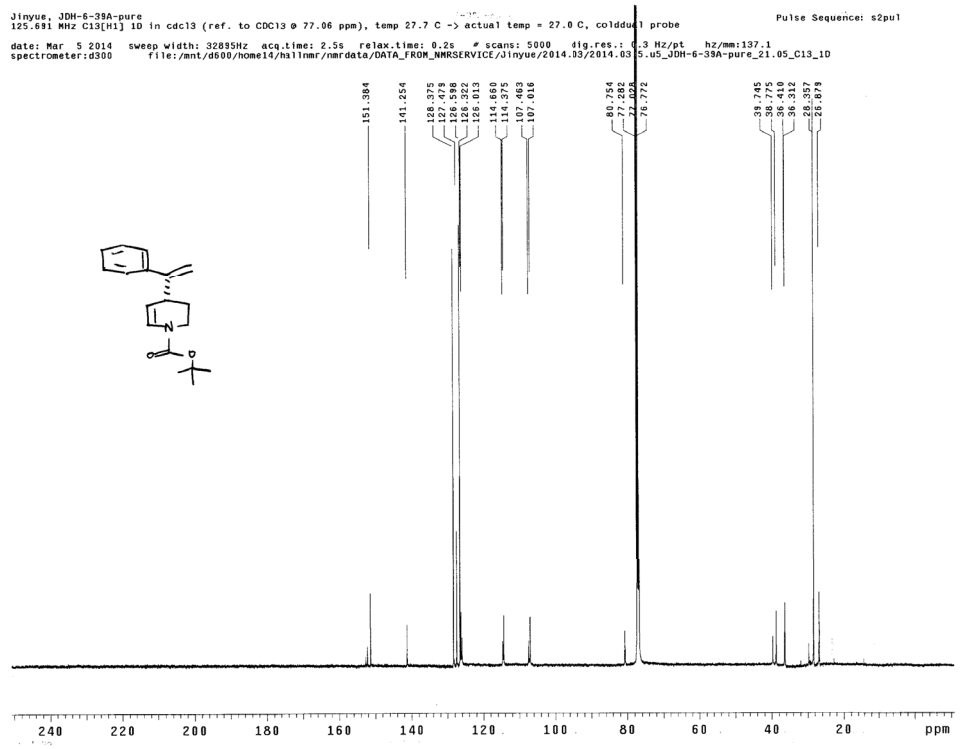
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-39 in $CDCl_3$ at 25 ^{o}C



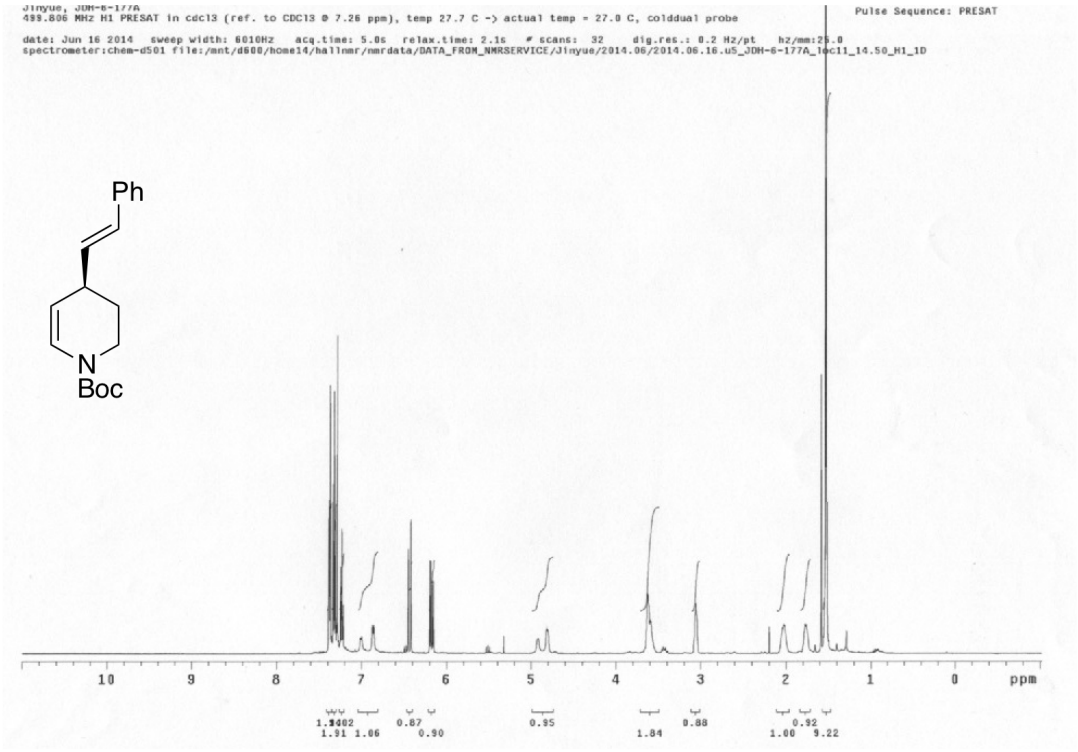


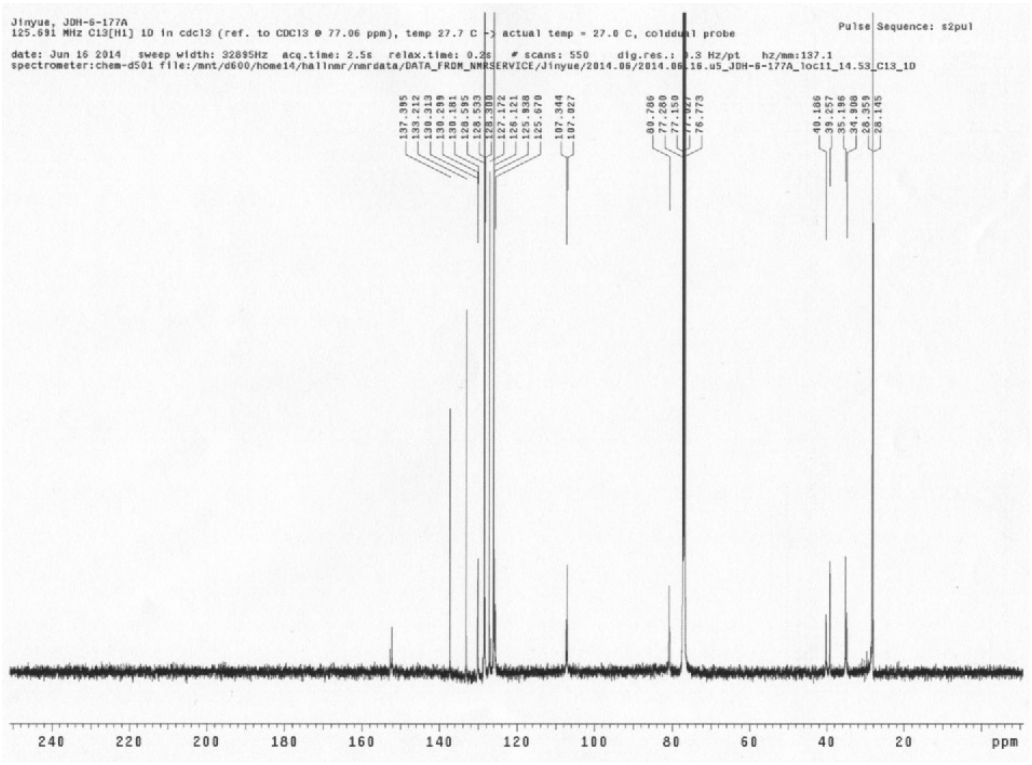
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-44 in $CDCl_3$ at 25 ^{o}C



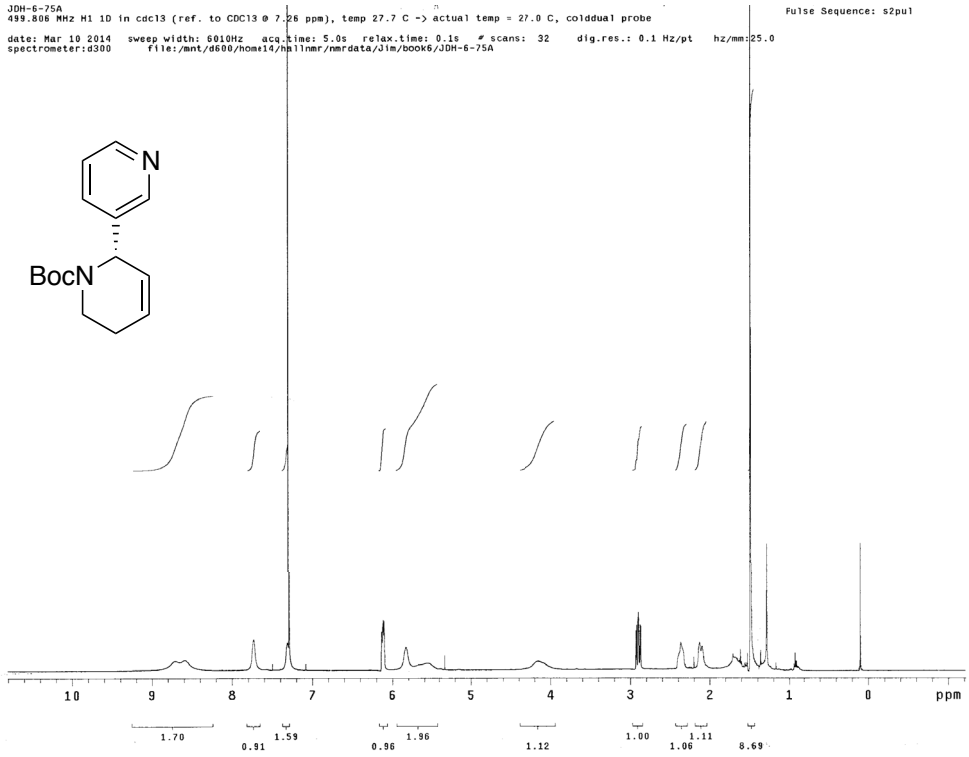


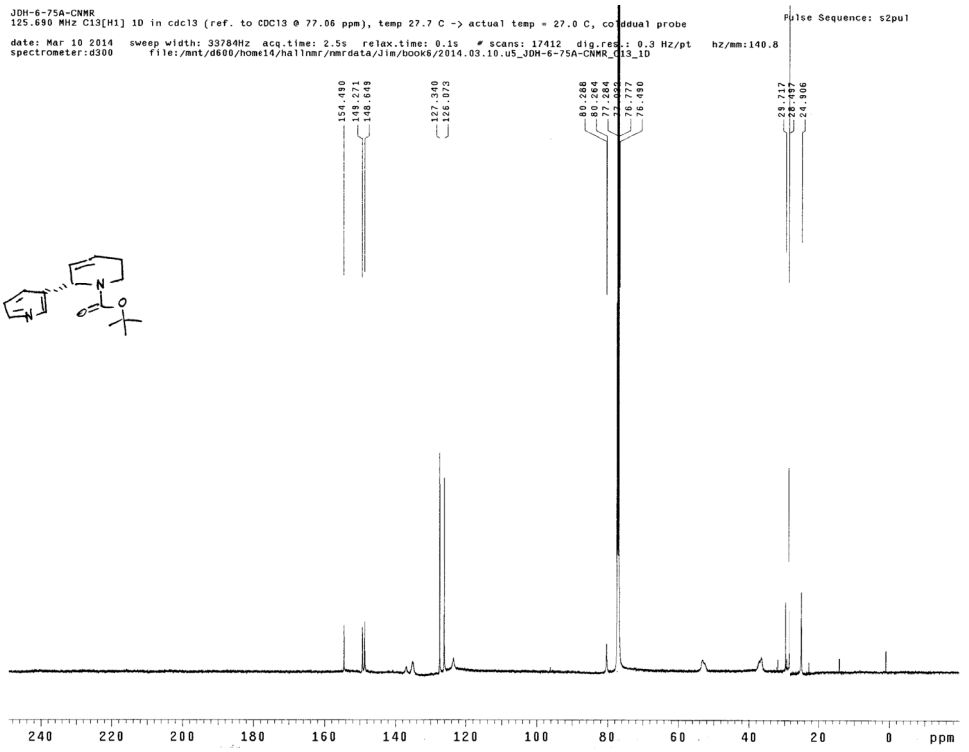
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-45 in $CDCl_3$ at 25 ^{o}C



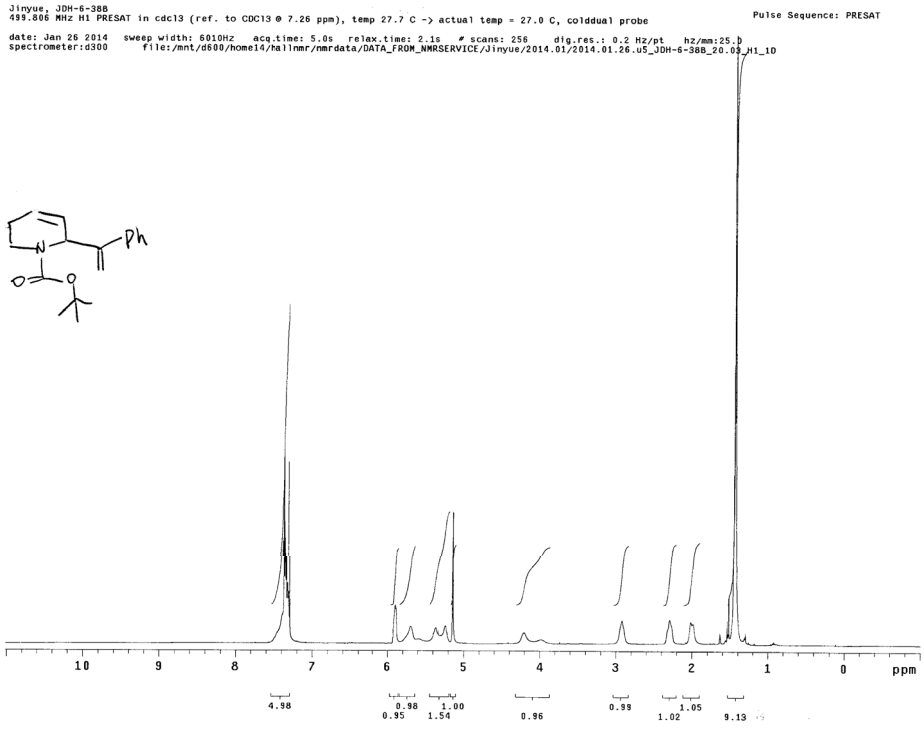


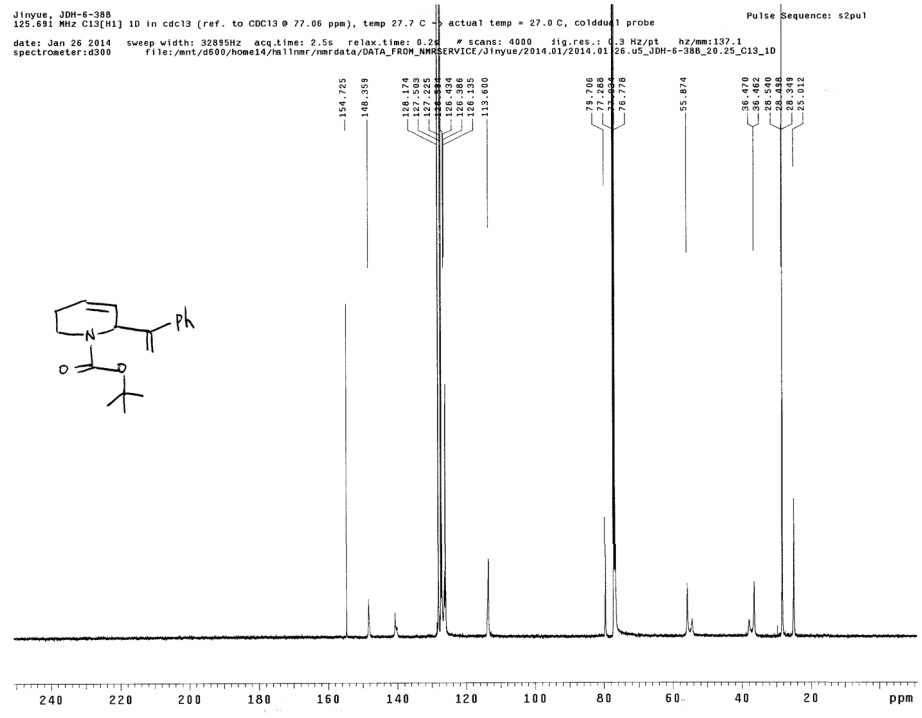
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-50 in $CDCl_3$ at 25 ^{o}C



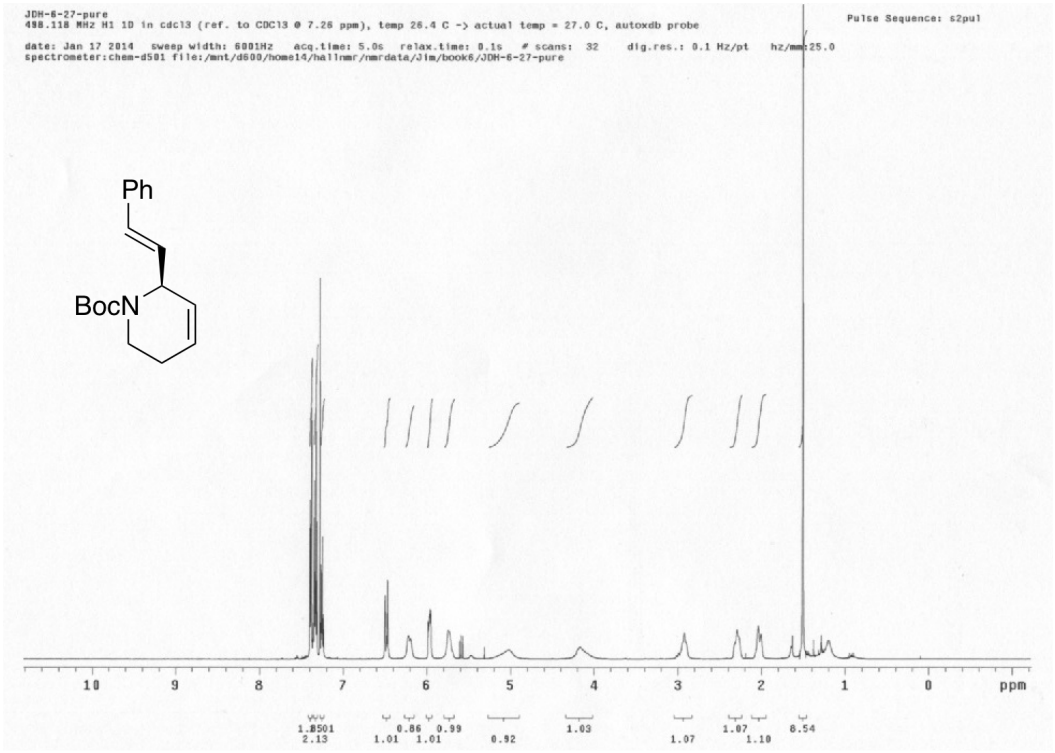


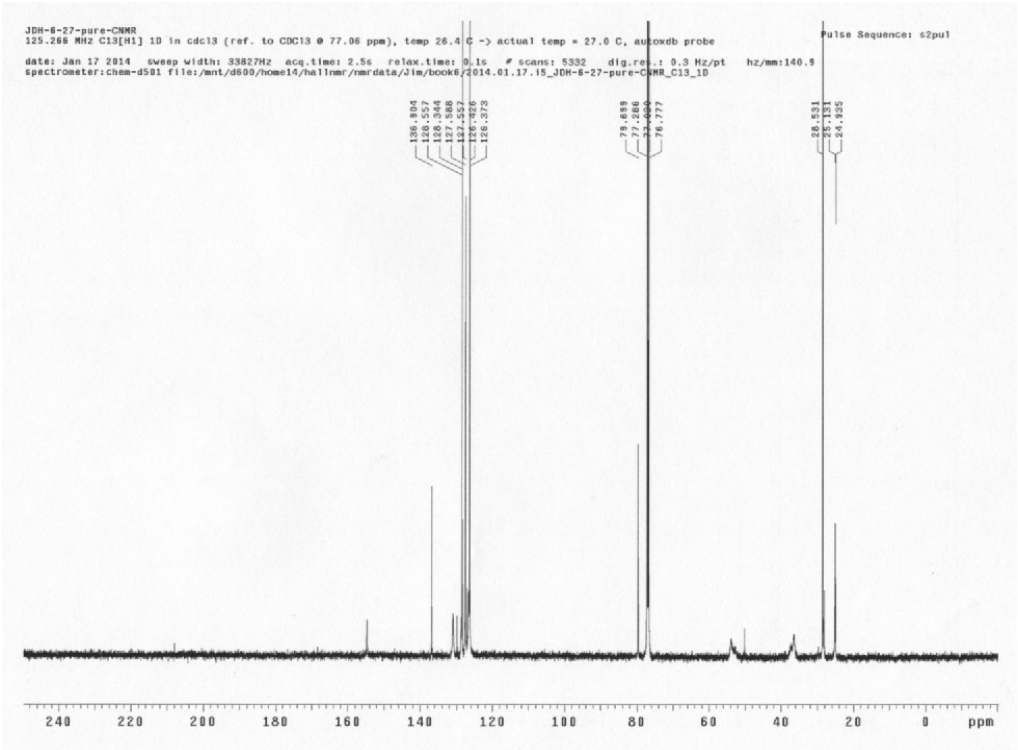
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-51 in $CDCl_3$ at 25 ^{o}C



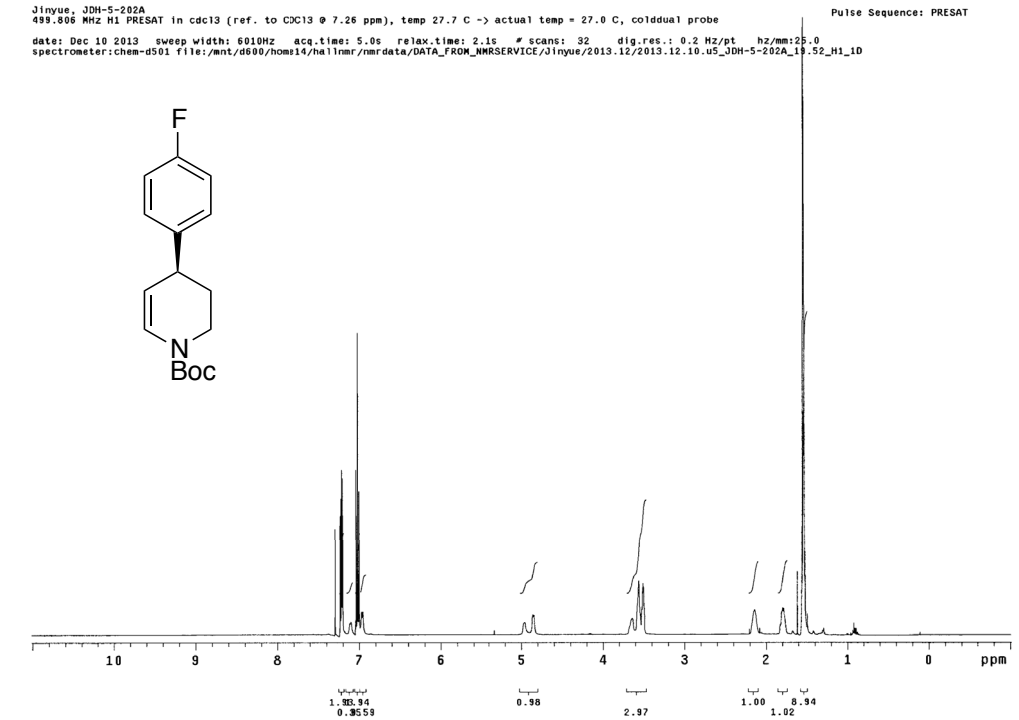


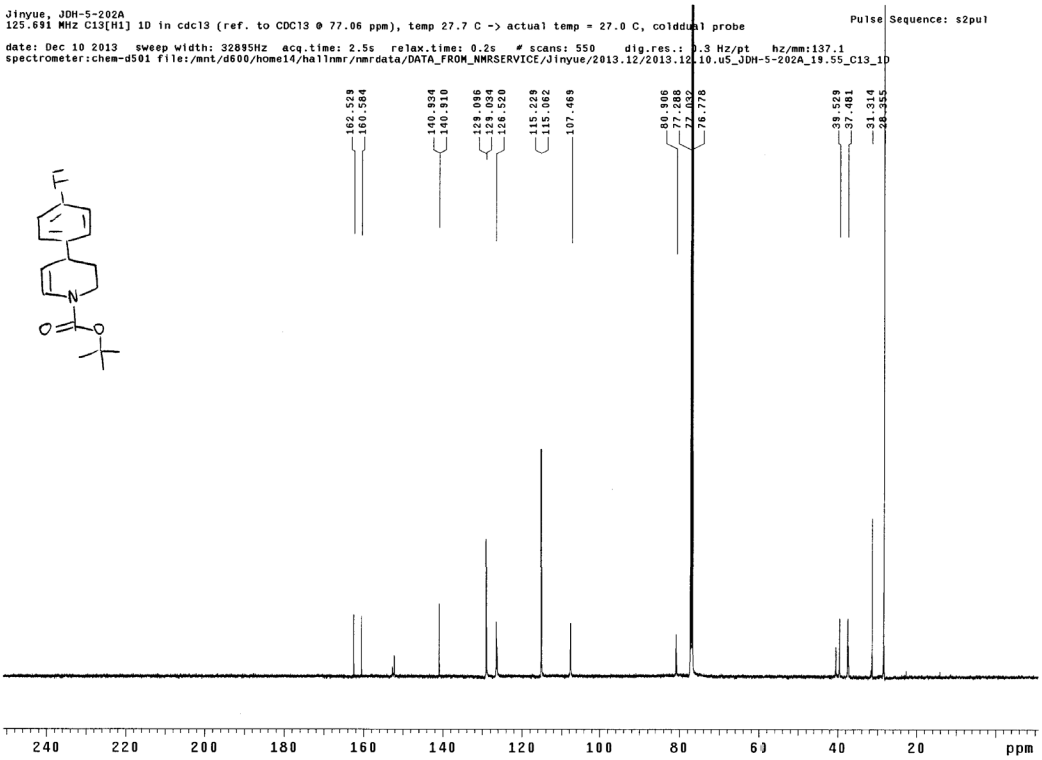
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-52 in $CDCl_3$ at 25 ^{o}C



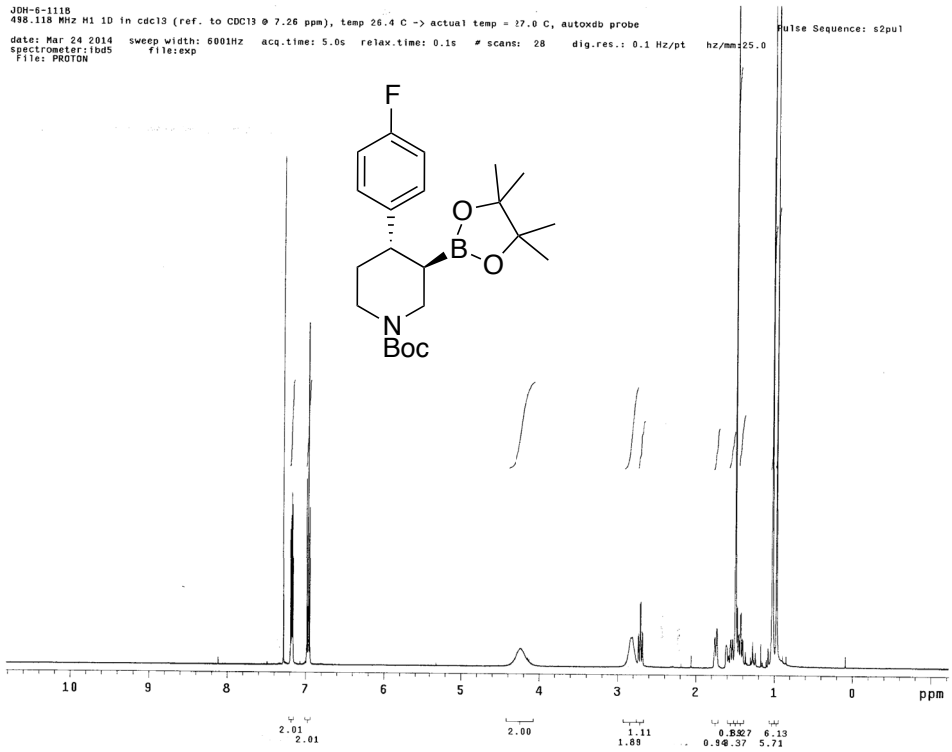


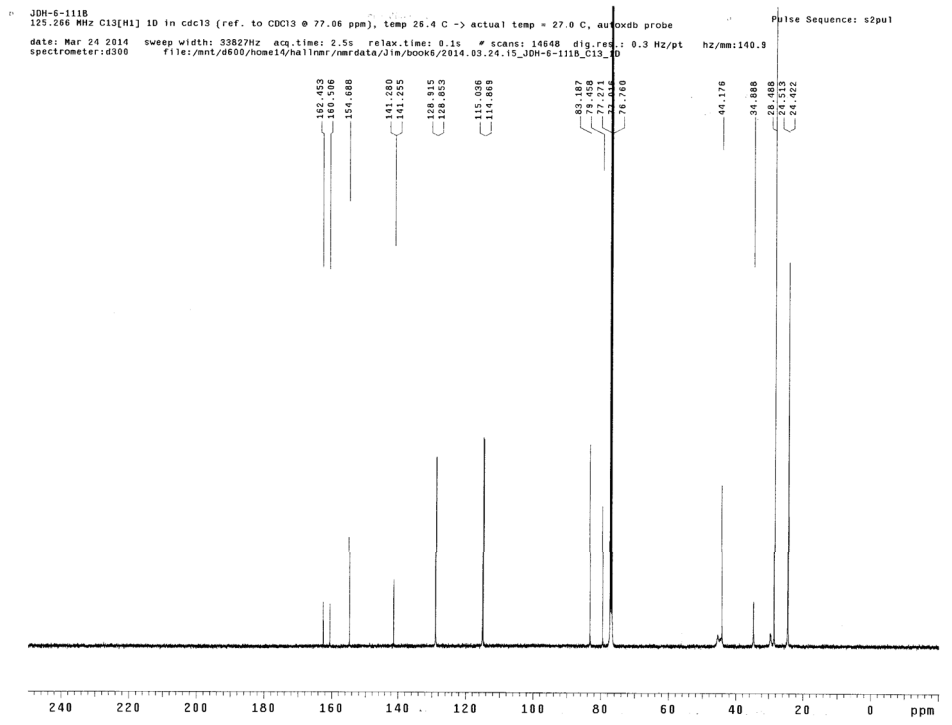
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-67 in $CDCl_3$ at 25 ^{o}C





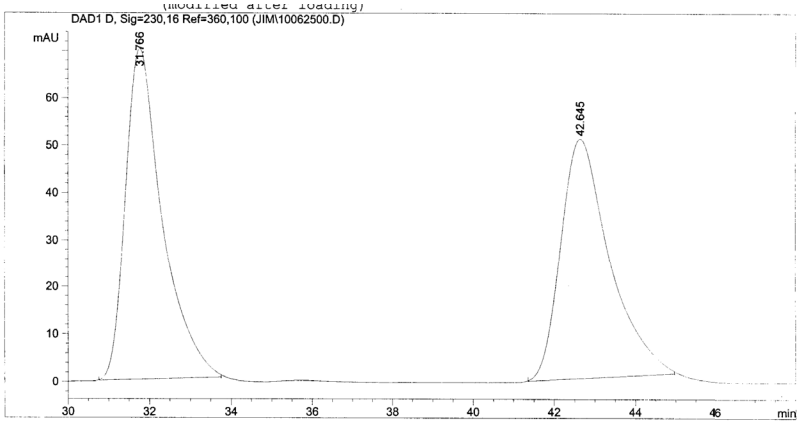
^{1}H (500 MHz) and ^{13}C (126 MHz) NMR of 5-68 in $CDCl_3$ at 25 ^{o}C





Appendix 2: Chromatograms for enantiomeric excess measurement (selected)

HPLC data for the racemic (top) and optically enriched (bottom) 2-31

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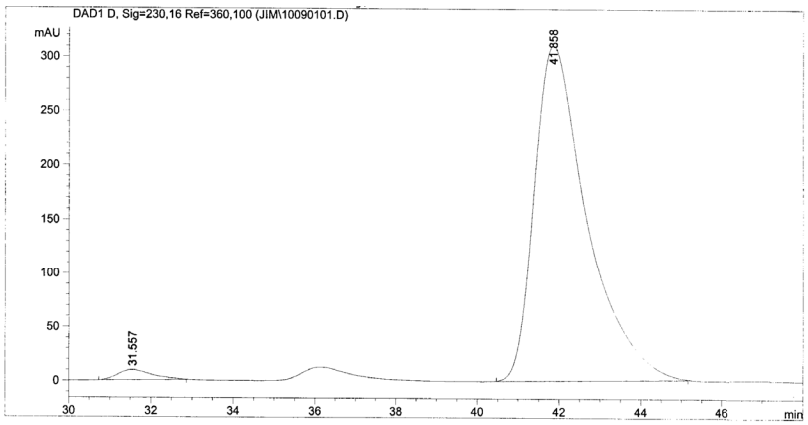
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|------|----|-------|---------|----------|--------|
   1  31.766 BB    0.9209 4395.66943   69.96925  50.9323
   2  42.645 BB    1.2046 4234.74854   50.69165  49.0677
```



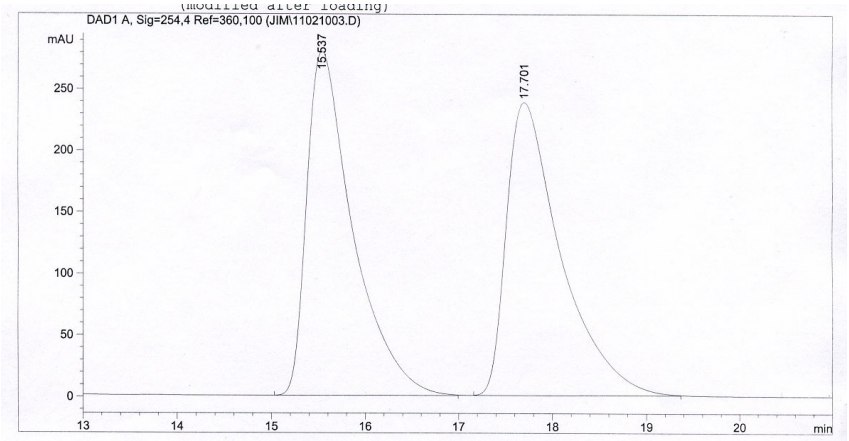

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|------|----|-------|---------|----------|--------|
   1  31.557 BB    0.7528  539.26160    9.40748   1.8987
   2  41.858 BB    1.3229 2.78624e4   310.49271  98.1013
```

HPLC data for the racemic (top) and optically enriched (bottom) 2-32

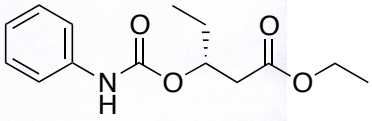


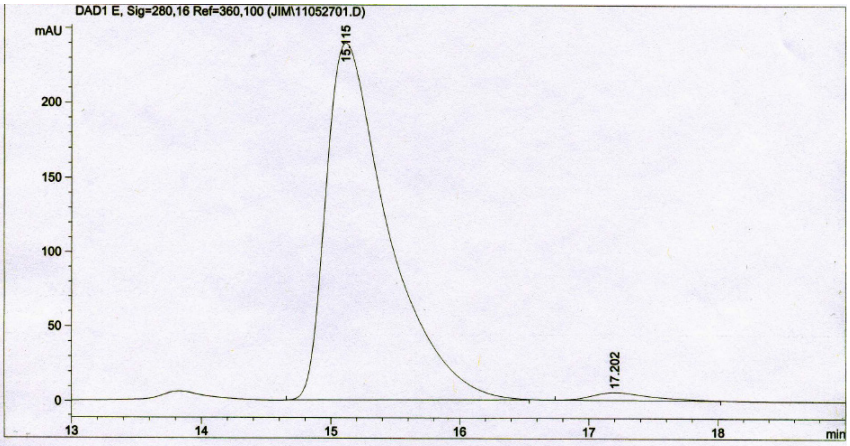
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.537	BB	0.5032	9586.62500	280.19946	49.9543
2	17.701	BB	0.5962	9604.17578	238.31078	50.0457





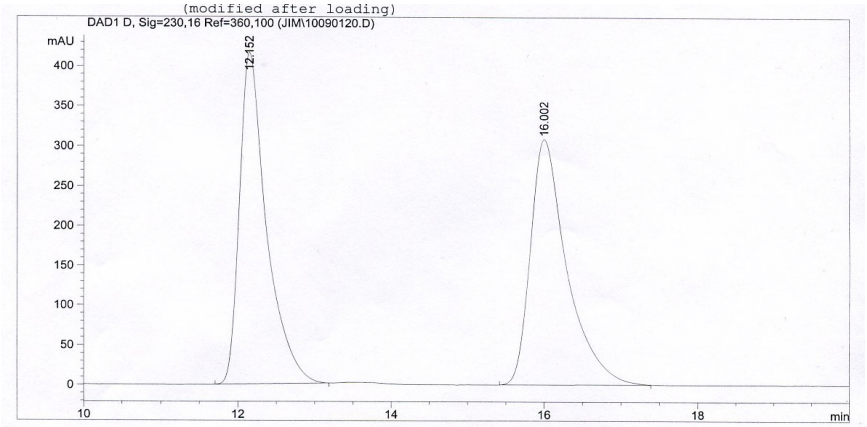
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.115	BB	0.4980	8042.00049	239.32811	97.8831
2	17.202	PB	0.4643	173.92656	5.42092	2.1169

HPLC data for the racemic (top) and optically enriched (bottom) 2-35

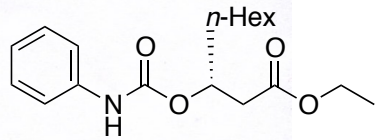


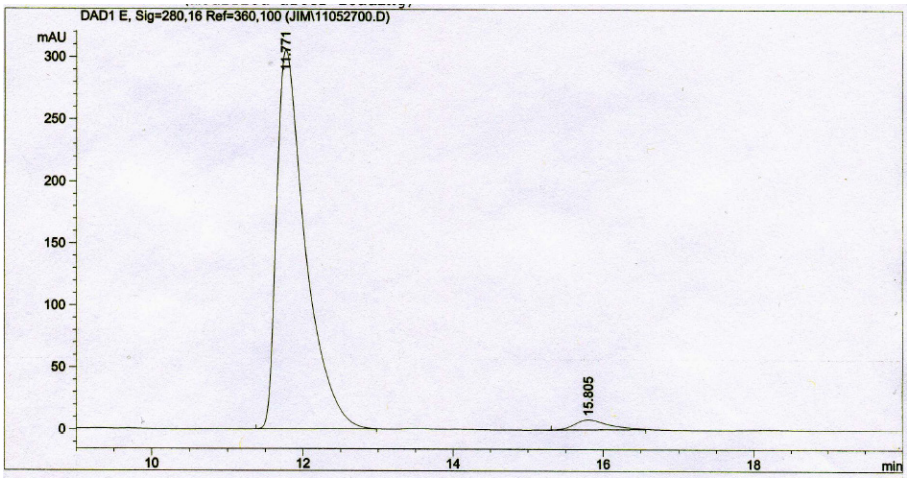

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height      Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.152 BP    0.3564 1.01505e4   416.45056  49.8334
   2  16.002 BB    0.4842 1.02184e4   308.64896  50.1666
```





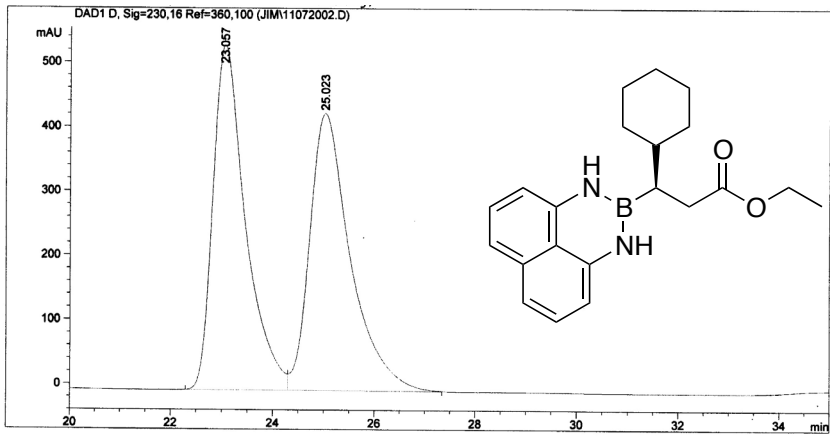

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 E, Sig=280,16 Ref=360,100

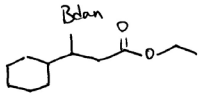
Peak RetTime Type  Width     Area      Height      Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.771 BB    0.3921 8113.77637  305.24835  96.9396
   2  15.805 BB    0.4642  256.15033    8.16021   3.0604
```

HPLC data for the racemic (top) and optically enriched (bottom) 3-23



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

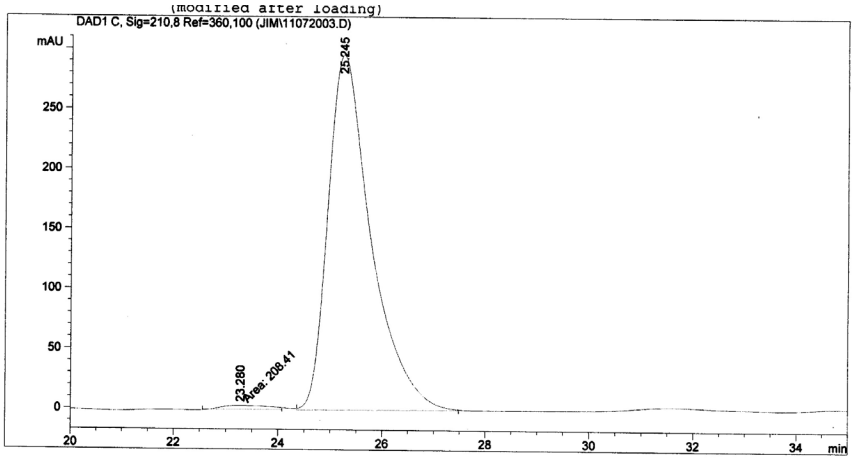


(Racemate)

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

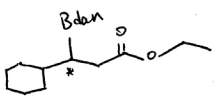
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.057	BV	0.6497	2.37224e4	536.68231	49.6203
2	25.023	VB	0.8279	2.40855e4	431.06219	50.3797

(modified after loading)



Area Percent Report

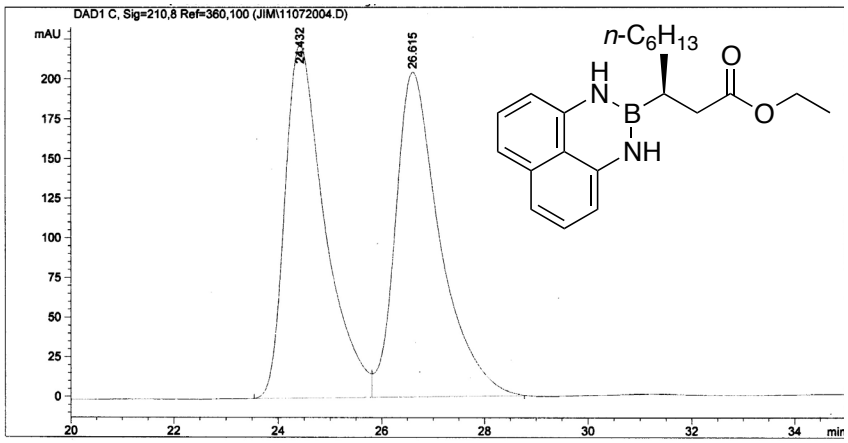
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.280	MM	1.0284	208.41026	3.37743	1.2028
2	25.245	BB	0.8425	1.71182e4	296.08917	98.7972

HPLC data for the racemic (top) and optically enriched (bottom) 3-24

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================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height      Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  24.432 BV    0.7931 1.19048e4   222.18085  49.2311
   2  26.615 VB    0.8669 1.22767e4   204.35939  50.7689
```
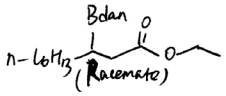
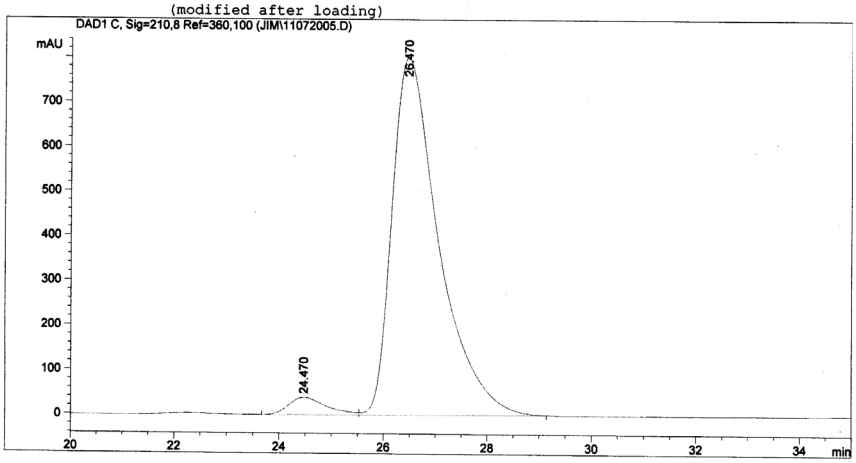
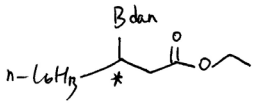



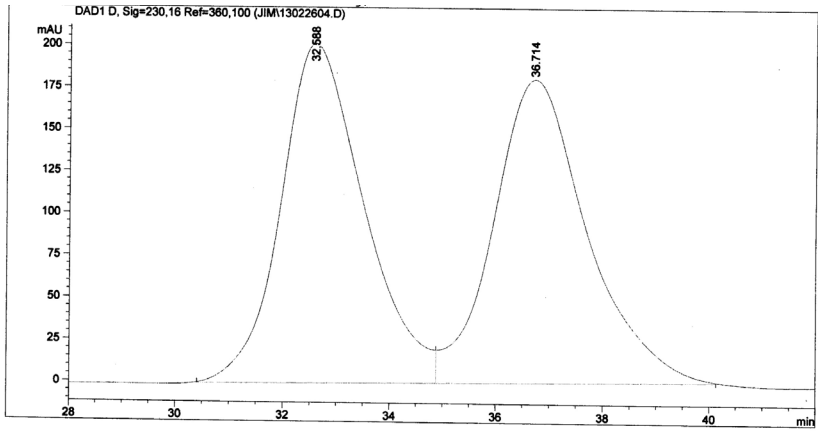
(modified after loading)




```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height      Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  24.470 BV    0.7277 1961.33325   39.20221   3.7650
   2  26.470 VB    0.9188 5.01330e4    800.38391  96.2350
```



HPLC data for racemic compound 4-27

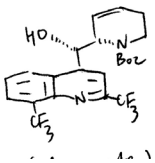


Area Percent Report

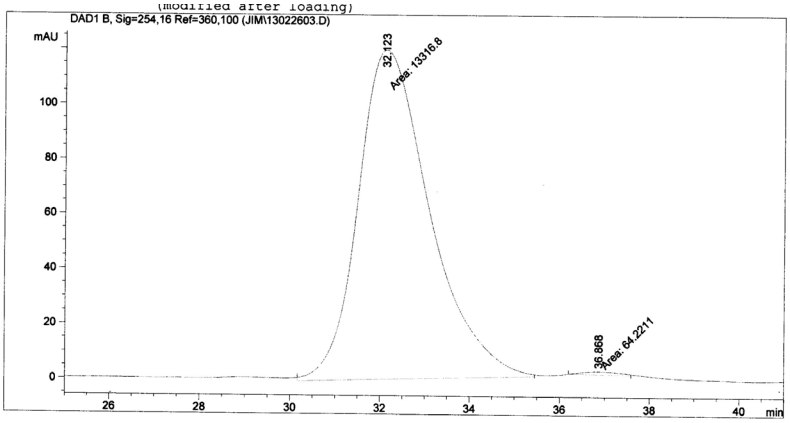
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.588	BV	1.5309	2.18326e4	201.69777	49.8975
2	36.714	VB	1.7641	2.19224e4	180.09702	50.1025



HPLC data for the optically enriched compound (+)-4-27

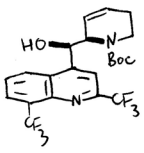


Area Percent Report

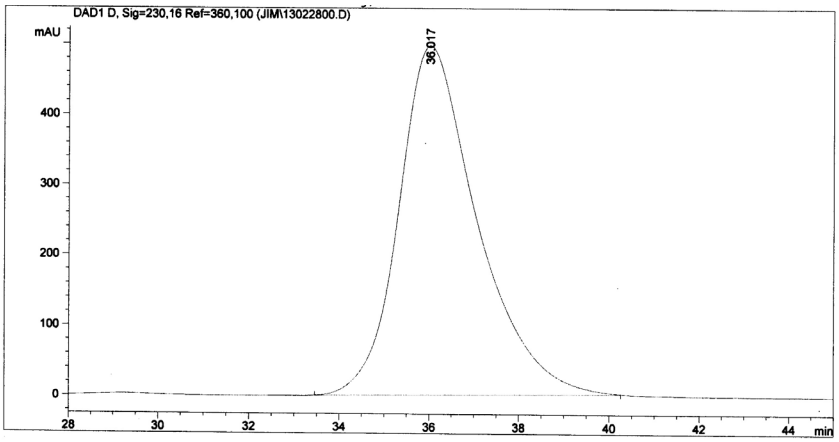
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,16 Ref=360,100

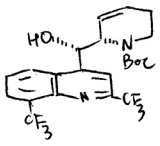
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.123	MM	1.8533	1.33168e4	119.75673	99.5201
2	36.868	MM	0.9628	64.22108	1.11176	0.4799



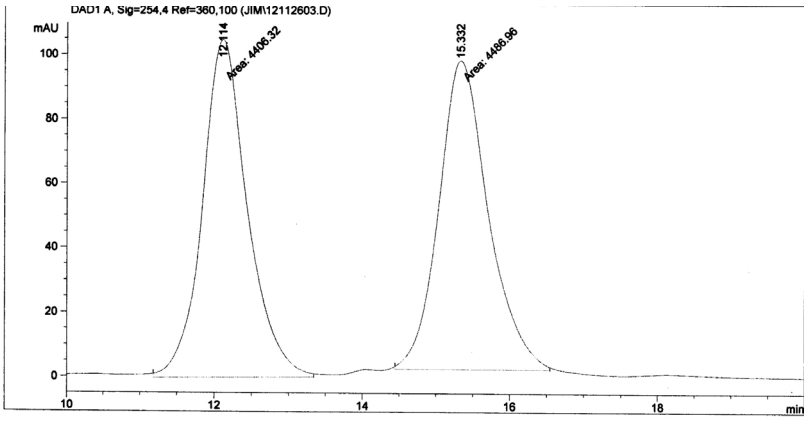
HPLC data for the optically enriched compound (−)-4-27



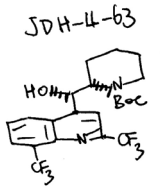

```
================================================================================
                                Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  36.017 BB    1.7549 6.05953e4   496.83051 100.0000
```



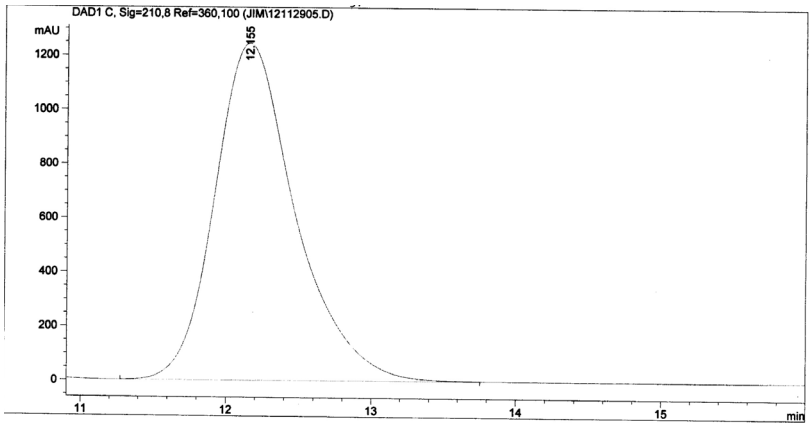
HPLC data for the Racemic compound 4-32




```
================================================================================
                                Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  12.114 MM    0.7006 4406.32227  104.82155  49.5466
   2  15.332 MM    0.7805 4486.96289   95.81474  50.4534
```



HPLC data for the optically enriched compound (+)-4-32

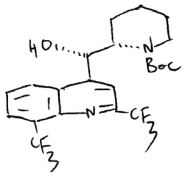


Area Percent Report

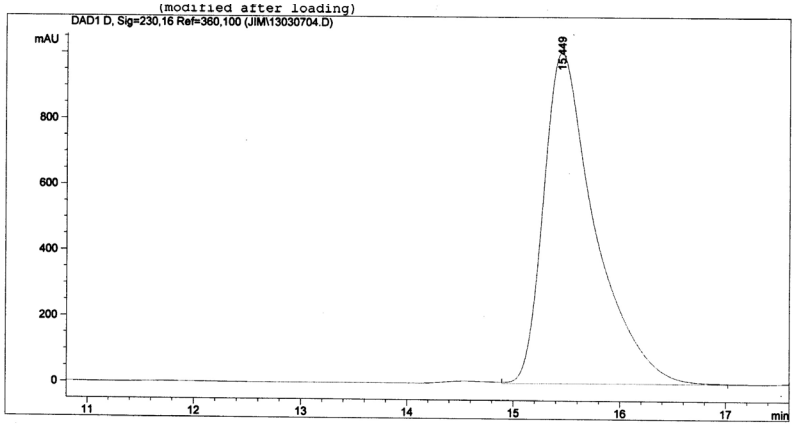
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.155	BB	0.5789	4.79114e4	1245.18994	100.0000
Totals :				4.79114e4	1245.18994	



HPLC data for the optically enriched compound (−)-4-32

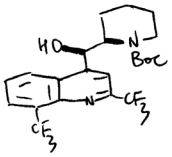


Area Percent Report

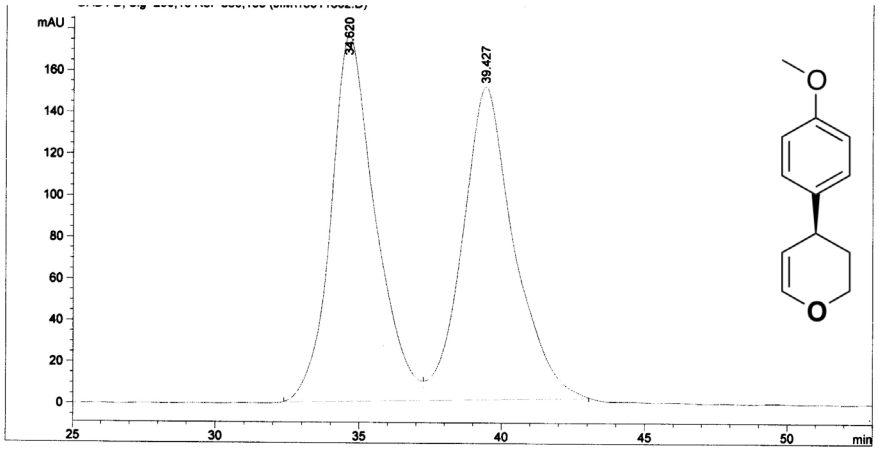
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.449	VB	0.4892	3.36427e4	1003.34625	100.0000



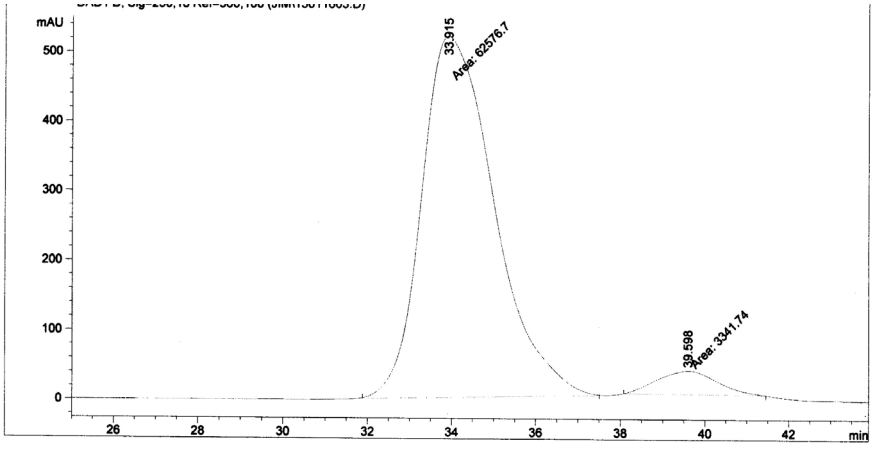
HPLC data for the racemic (top) and optically enriched (bottom) 5-21

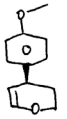


Rac.

97:3 . OD, 20°C . 0.5ml/min.

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  34.620 BV    1.5262 1.90261e4   175.86255  50.0516
   2  39.427 VB    1.7366 1.89869e4   150.42580  49.9484
```



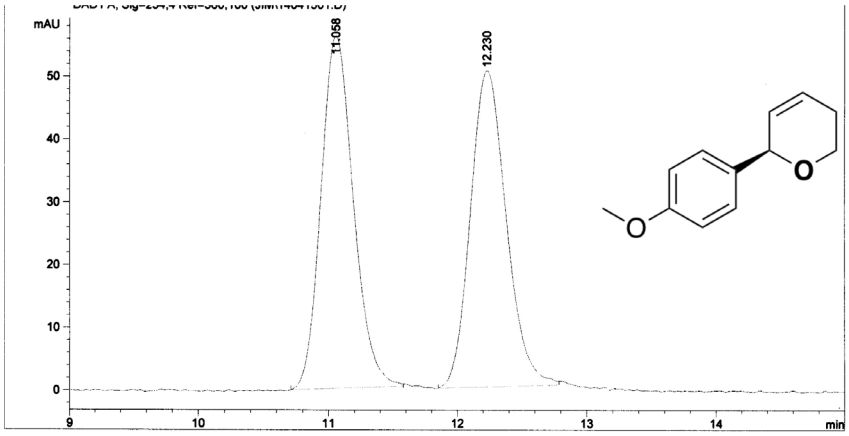


Chiral . 90% ee

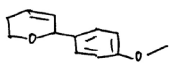
97/3, OD, 20°C . 0.5ml/min.

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  33.915 MM    2.0063 6.25767e4   519.84344  94.9305
   2  39.598 MM    1.6573 3341.74463   33.60572   5.0695
```

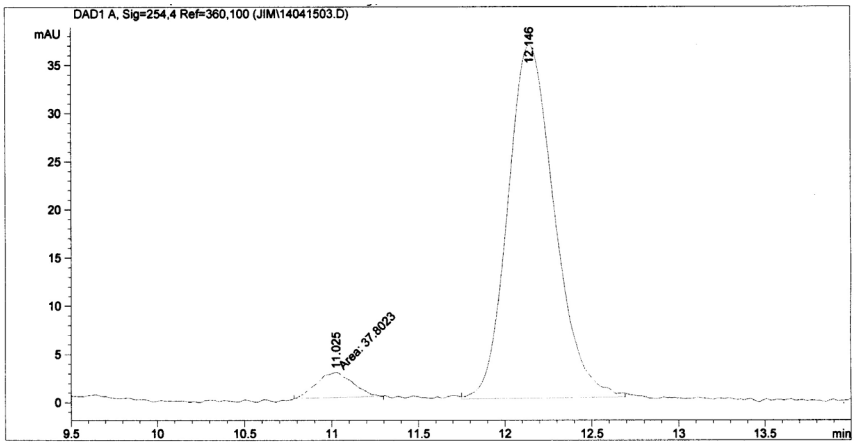
HPLC data for the racemic (top) and optically enriched (bottom) 5-22




```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  11.058 BB    0.2716  979.70471   56.14901  50.1483
   2  12.230 PB    0.2998  973.90930   50.32586  49.8517
```



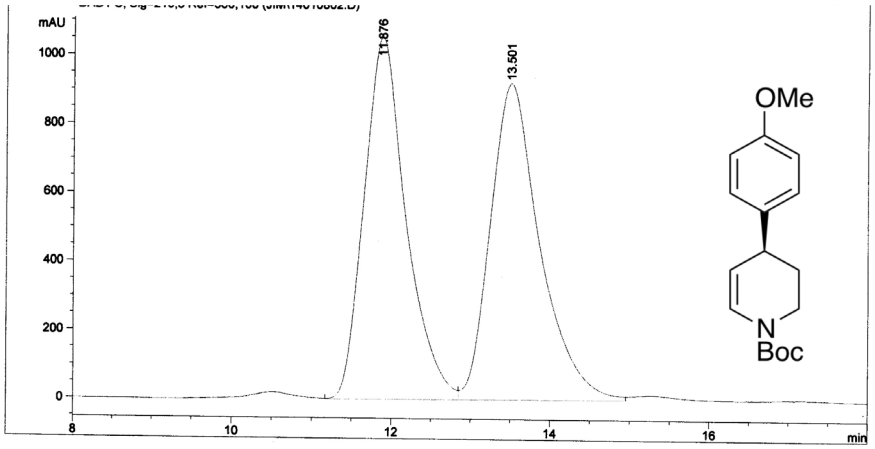
90/10, IC, 20°C, 0.5ml/min




```
================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  11.025 MM    0.2407   37.80232    2.61704   5.2353
   2  12.146 VB    0.2900  684.25873   36.62334  94.7647
```

90/10, IC, 20°C, 0.5ml/min.

HPLC data for the racemic (top) and optically enriched (bottom) 5-23



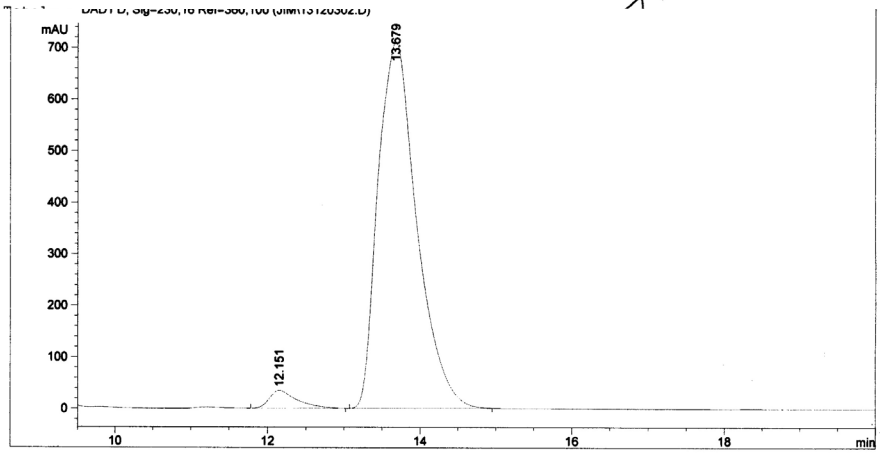
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.876	VV	0.5356	3.88013e4	1053.68823	49.3029
2	13.501	VB	0.6426	3.98986e4	918.87378	50.6971

Rac.
OD. IPA/Hex = 2/98
0°C. 210nm



Area Percent Report

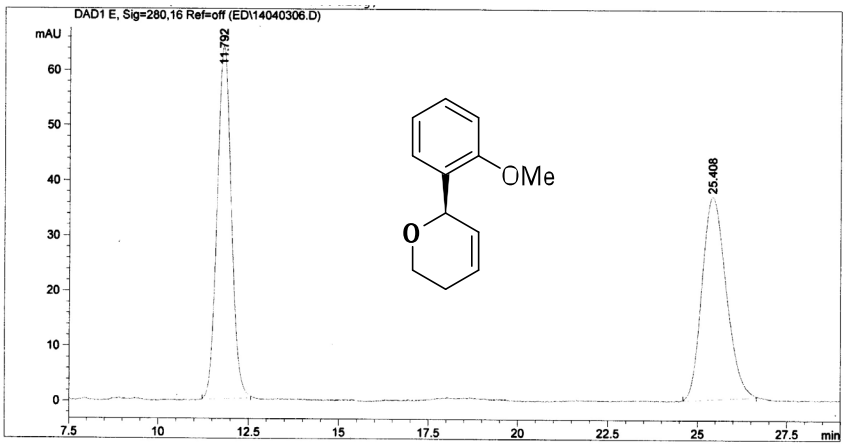
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

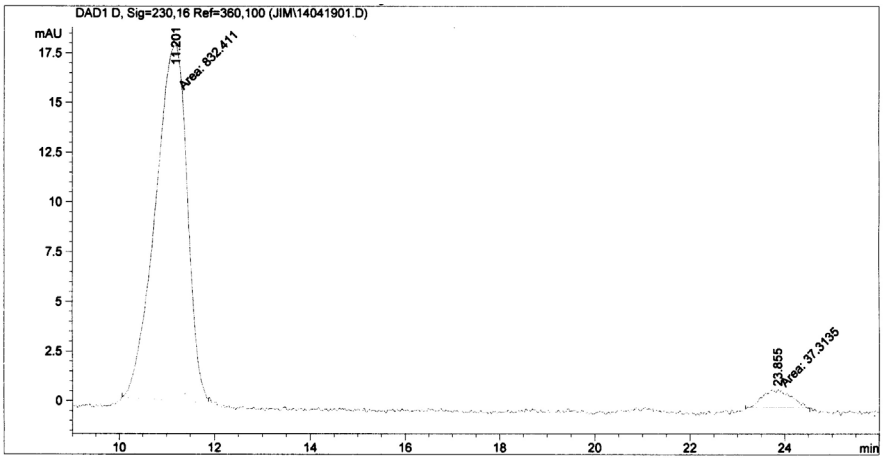
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.151	BB	0.3635	870.20691	34.82746	3.3320
2	13.679	BB	0.5565	2.52463e4	710.57703	96.6680

OD, 2/98, 0°C, 0.5 ml/min

HPLC data for racemic (top) and optically enriched (bottom) 5-32

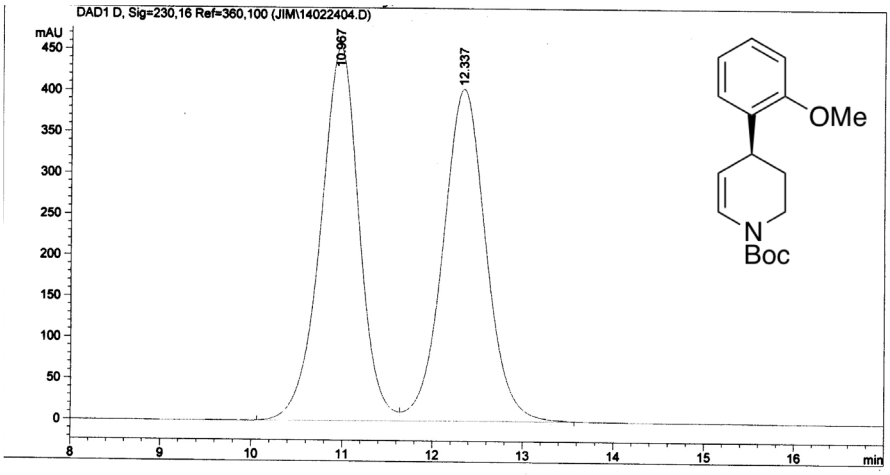



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.792 BB    0.4214 1739.64209   63.94012  49.9601
   2  25.408 BB    0.6496 1742.42163   36.71989  50.0399
```

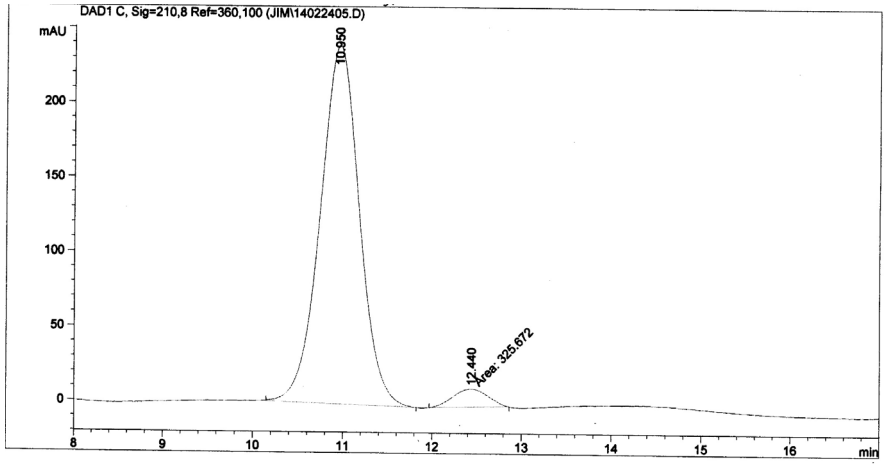



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  11.201 MM    0.7758  832.41101   17.88277  95.7097
   2  23.855 MM    0.6747   37.31351 9.21666e-1   4.2903
```

HPLC data for the racemic (top) and optically enriched (bottom) 5-39

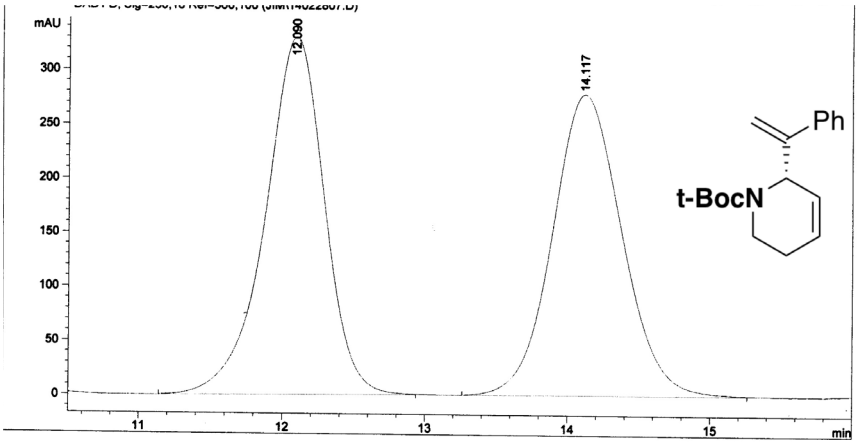



```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.967 BV    0.4487 1.33901e4   453.16089  49.9874
   2  12.337 VB    0.5077 1.33968e4   403.12704  50.0126
```




```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.950 BP    0.4645 7295.18555  240.07933  95.7266
   2  12.440 MM    0.4478  325.67194   12.12045   4.2734
```

HPLC data for the racemic (top) and optically enriched (bottom) 5-51

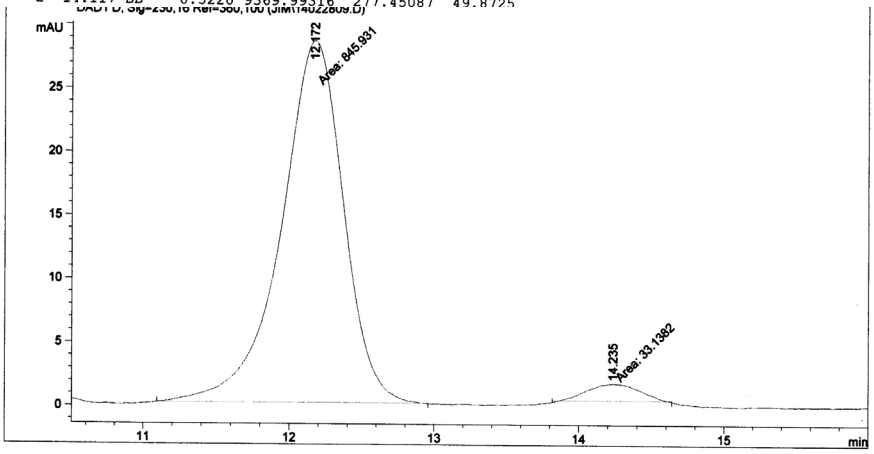


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.090	BB	0.4374	9417.89648	329.60977	50.1275
2	14.117	BB	0.5220	9369.99316	277.45087	49.8725



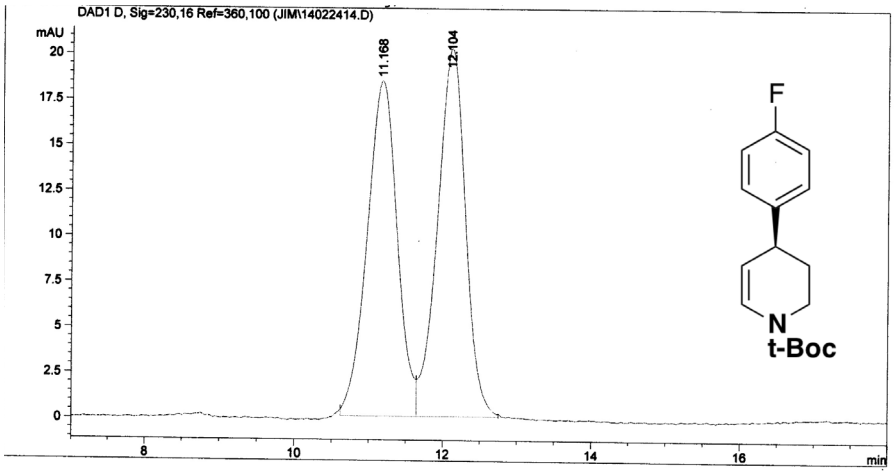
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.172	MM	0.4955	845.93140	28.45545	96.2303
2	14.235	MM	0.4156	33.13821	1.32880	3.7697

HPLC data for the racemic (top) and optically enriched (bottom) 5-67

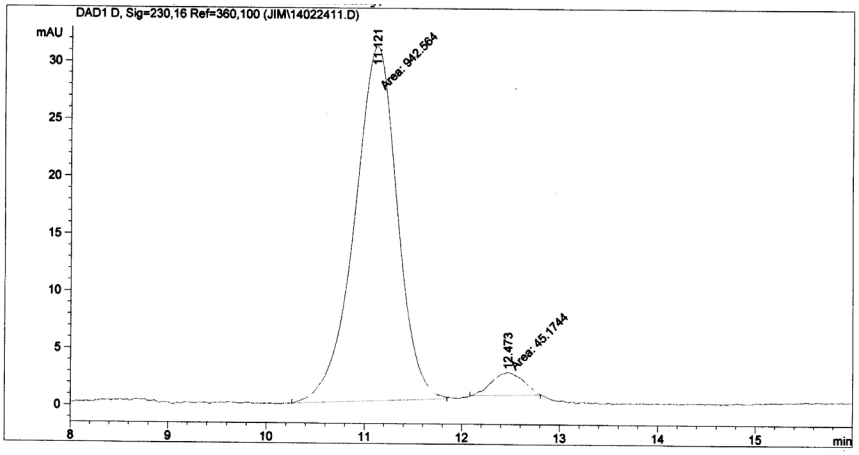


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.168	BV	0.4231	519.31079	18.41002	49.3220
2	12.104	VB	0.4021	533.58862	20.20745	50.6780



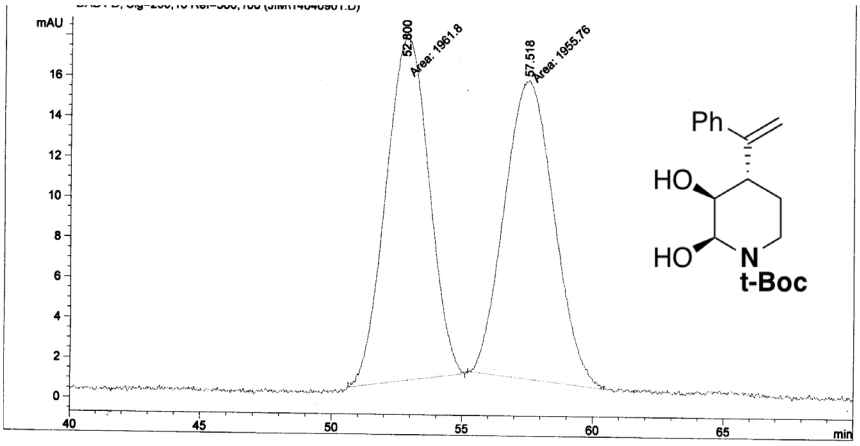
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.121	MM	0.5084	942.56372	30.90111	95.4265
2	12.473	MM	0.3771	45.17437	1.99678	4.5735

HPLC data for the racemic (top) and optically enriched (bottom) 5-44a

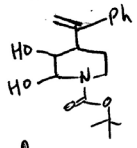


Area Percent Report

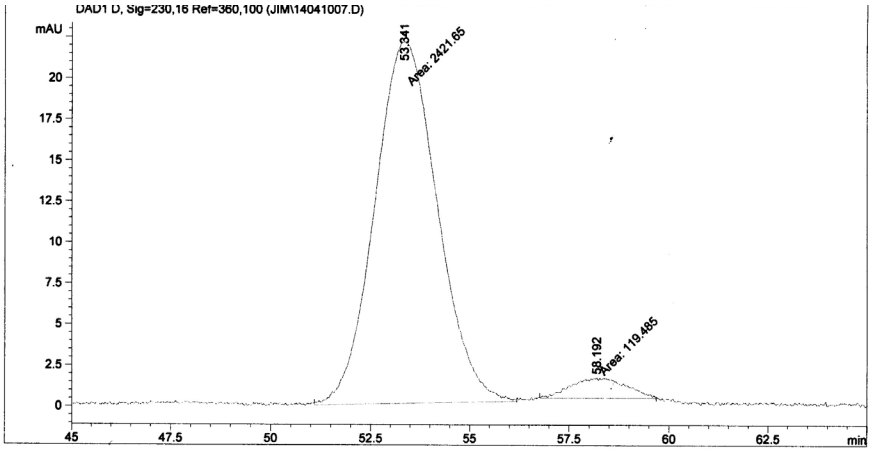
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.800	MM	1.9231	1961.80322	17.00240	50.0771
2	57.518	MM	2.2004	1955.76343	14.81387	49.9229



Rac.

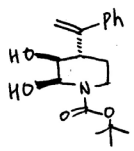


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.341	MM	1.8311	2421.65405	22.04234	95.2980
2	58.192	MM	1.6099	119.48466	1.23698	4.7020



91% ee . IC . 95/5.

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