ENANTIOSPECIFIC, REGIOSELECTIVE SUZUKI-MIYAURA CROSS-COUPLINGS OF SECONDARY, ALLYLIC BORONIC ESTERS

by

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Abstract

The stereochemical course of the Pd–catalyzed Suzuki-Miyaura cross-coupling of α-substituted, enantioenriched allylic boronic esters with phenyl iodide has been examined. The secondary boronic esters were prepared in both racemic and enantioenriched forms *via* borylation of a lithiated carbenoid with a geometrically defined vinyl boronic ester. The geometric purities were determined to be >99% and the enantiomeric excesses of stereodefined secondary boronic esters were found to exceed 98:2. In total, 8 allylic boronic esters were successfully cross-coupled, providing arylated products with high regioselectivities (>90:10) and complete enantiospecificities (>99%). The cross-coupling of a sterically and electronically unbiased, deuterated substrate confirmed that fully equilibrated π-allylic intermediates are not involved. Additionally, correlating the absolute configurations of the allylic boronic ester and the cross-coupling product allowed us to confirm that the transmetalation step of the reaction proceeded through a closed transition state *via* a *syn*-S_E' mechanism, which further suggests the importance of the distinct Pd-O-B bond linkage.

Further, the cross-coupling of vinyl iodides to secondary boronic esters was investigated.

Co-Authorship

I hereby declare that this thesis incorporates material from collaborations undertaken with post-doctoral research fellows: Dr. Kazem Ghozati (Department of Chemistry, Queen's University; Kingston, Ontario, Canada); collaborations have been appropriately cited. All spectra and characterization data herein were recorded and analyzed by the author.

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To my friends whom I have met during my time in Kingston, you've seen me on the best of days when we probably had a good laugh together or played a game of soccer together and (little did you know) you carried me through the darker ones. Queen's University is truly a place where the world meets and right from day one in Leonard Hall, I enjoyed meeting so many new people from so many interesting places. We have met here in Kingston, but I know that many of us will stay in touch no matter where we travel for our careers and respective life journeys.

To my parents, who have taught their children the meaning of love, acceptance and perseverance. Your spirited support has meant everything to me and I owe all of my success to you. To my sister, who is my closest ally; we beat Beethoven, Addy! To my grandparents, thank-you for your mentorship, zest for life and close friendship throughout many years. To my late brother Alex, growing up with you taught me about some of the biggest lessons life has to offer. We love you and miss you very much and we have faith that you are watching over us, safe in our Father's arms at last. To my extended family consisting of many aunts, uncles and cousins: you are all so much fun to be around and you make family reunions a boisterous time of

telling stories, sharing laughs and keeping us inspired to be our best. Thank-you for being the generous and warm company that you are.

List of Abbreviations

$\Delta H^{\neq}$	enthalpy of activation
ΔG	Gibbs Free Energy
9-BBN	9-borabicyclo[3.3.1]nonane
alk	alkyl
amphos	di-*tert*-butyl(4-dimethylaminophenyl)phosphine
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
B:L	branched to linear
Bn	benzyl
COOEt	carbethoxy
Cyp	cyclopropyl
dba	dibenzylidene acetone
DKR	dynamic kinetic resolution
DME	dimethoxyethane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
D*o*M	directed ortho metalation
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	di-*tert*-butyl(4-dimethylaminophenyl)phosphine
dppp	1,3-bis(diphenylphosphino)propane
DTR	dynamic thermodynamic resolution
dr	diastereomeric ratio
e^-	electron
ee	enantiomeric excess
er	enantiomeric ratio
es	enantiospecificity
Et	ethyl
exp	experimental

GC-MS	gas chromatography – mass spectrometry
HBcat	catecholborane
HBpin	pinacolborane
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
*i*Bu	isobutyl
*i*Pr	isopropyl
L	ligand
LUMO	lowest unoccupied molecular orbital
M	metal
Me	methyl
n-Bu	*n*-butyl
neop	neopentyl glycol = 2,2-dimethyl-1,3-propanediol
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
OAc	acetyl
Cb	*N,N*-diisopropylcarbamoyl
OTf	triflate
Ph	phenyl
PhCO	benzoyl
pin	pinacol = 2,3-dimethyl-2,3-butanediol
R	proton/ variable organic group
RNA	ribonucleic acid
S	solvent
s-Bu	sec-butyl
T	temperature
TASF	tris(dimethylamino)sulfonium difluorotrimethyl silicate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran

TIB	2,4,6-triisopropylbenzoyl
TMEDA	*N, N, N',N'*-tetramethylethylene diamine
X	halogen
XRD	X-Ray Diffraction
ε_s	solvent polarity

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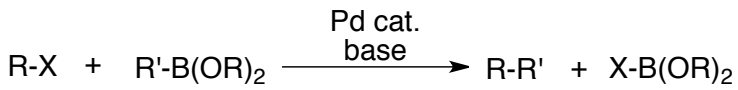
To Alex

Chapter 1: Suzuki-Miyaura Cross-Coupling

1.0 Introduction to Suzuki-Miyaura Cross-Coupling

Suzuki-Miyaura cross-coupling of an organohalide and an organoborane under Pd or Ni catalysis is one of the most significant C-C bond forming reactions in organic chemistry.[1] Suzuki-Miyaura cross-coupling has afforded methodologies to synthesize C-C bonds that have changed the way the modern chemist conceptualizes and constructs organic molecules. Furthermore, asymmetric variants of Suzuki-Miyaura cross-coupling have added to the ever-expanding toolbox of the synthetic chemist.[2] In a Suzuki-Miyaura cross-coupling, an organic halide (R-X) reacts with an organoborane (R'-$B(OR)_2$) via a metal catalyst, for example Pd, to afford the cross-coupling product (R-R') (Equation 1). Suzuki-Miyaura cross-coupling has been pivotal in the synthesis of fine chemicals, pharmaceutical targets, agrochemicals, materials and critical to convergent syntheses of natural products.[3] In 2010, Akira Suzuki was included in a portion of the Nobel Prize in Chemistry as recognition of his contribution to this reaction.[4]



Equation 1. General Suzuki-Miyaura cross-coupling reaction.

Initially, this reaction was used to form bonds between sp^2 hybridized carbon atoms[5]; products were either dienes or biaryl compounds, which is a significant limitation to this otherwise important reaction. Now, the reaction enjoys a broader range of scope owing, in large part, to the work done in the past ten years from Fu[6], Gevorgyan[7], Molander[8] and van den Hoogenband[9] among others to include cross-couplings at secondary positions. The advancement to include coupling at chiral, secondary sp^3 hybridized carbon centers drew much attention from the

synthetic community, since there are a plethora of ways to synthesize organoboron compounds enantioselectively.[10, 11, 12, 13, 14]

The aim of our research has been to employ enantiomerically enriched boronic esters in coupling reactions with transfer of chirality[15] and secondary organoboranes with high levels of regio-control in the coupling reaction[16]. The results section of this thesis will discuss recent advancements in the Suzuki-Miyaura cross-coupling of secondary, allylic boronic esters to aryl iodides with complete stereospecificity and high regioselectivity. The importance of enantioselective synthesis is obvious as chiral biomolecules are found throughout nature.

Chirality is ubiquitous in nature. Supramolecular biopolymers, such as DNA, RNA, enzymes, proteins and receptors are all examples of chiral biomolecules. In the words of Louis Pasteur, "L'universe est dissymmétrique" such that the interaction of enantiomers, compounds that are not identical, but are non-superimposable mirror images of each other, with various biomolecules, can elicit different responses *in vivo*. Nature's inherent chirality results in an extraordinary chiral recognition system. A classic, yet tragic example of chiral molecule interaction *in vivo* is the drug 'thalidomide'. In the 1950's, before the effects of chirality in biochemical systems were understood, Thalidomide was given to pregnant women as a mixture of enantiomers. Tragically, one of the two enantiomers caused significant birth defects, as it restricted the development of blood vessels in rapidly dividing tissue, while its mirror image had the desired sedative properties. The molecule limonene constitutes another example of chiral molecule interaction *in vivo* (Figure 1), with the S enantiomer of limonene having the smell of an orange and the R enantiomer having the smell of a lemon. To illustrate further, the R enantiomer of carvone smells of caraway seeds, where the S enantiomer smells of spearmint.

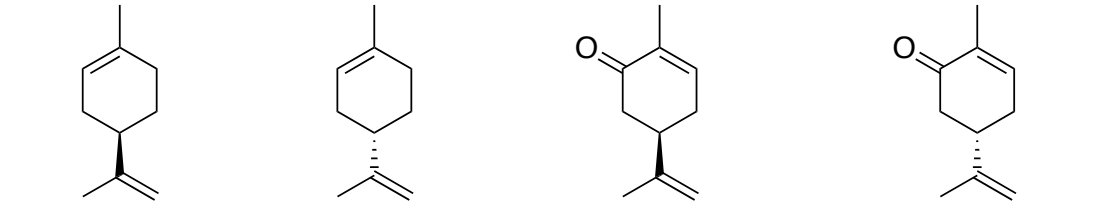


Figure 1. Chiral compounds in nature.

Indeed, chirality is of vital importance to fragrance and drug manufacturers, although for the latter it could be a matter of life and death. In fact, the S enantiomer of 3,4-dihydroxyphenylalanine ((*S*)-dopa) is used to treat Parkinson's disease to restore nerve function; its enantiomer, (*R*)-dopa is not only ineffective as a treatment to Parkinson's disease, but is actually quite toxic (Figure 2).

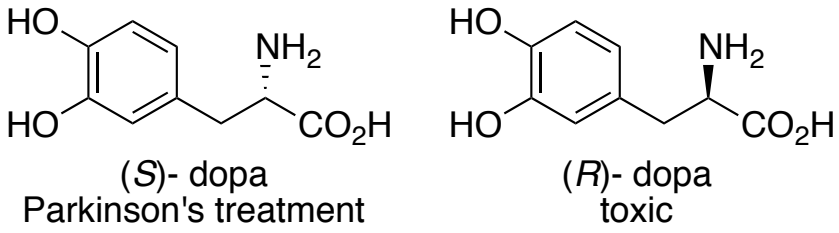


Figure 2. Enantiomers of dopa, 3,4-dihydroxyphenylalanine.

A plethora of examples exist in which enantiomers, or in the case of many natural products, diastereomers, produce different biological outcomes one which may be desirable while the other outcome may be detrimental to human health. Hence, it is important that asymmetric reactions are developed that are highly stereospecific leading to the production of one enantiomer exclusively over the other.

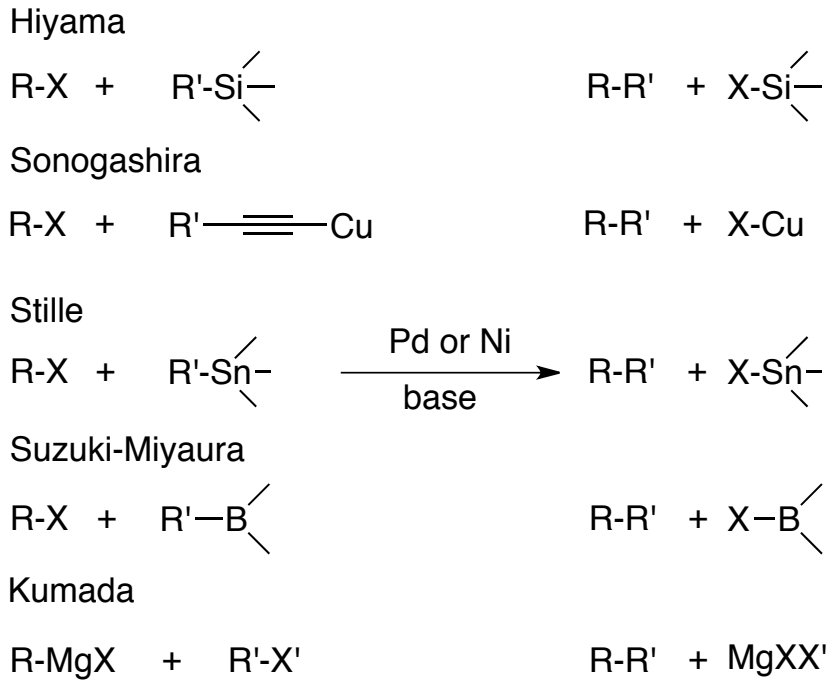
1.1 Suzuki-Miyaura Cross-Coupling - A Historical Perspective

Historically, cross-coupling methods in which C-C bonds are formed include the Kumada, Hiyama, Negishi, and Stille reactions in addition to the Suzuki-Miyaura coupling. The Grignard reaction, dating back to the turn of the 20th century[17] employs an organobromide (R-Br) and an electrophilic partner, which is typically a carbonyl-containing compound. The ultimate shortcoming of the Grignard reaction is due to the high reactivity and oxygen sensitivity of the *in situ* generated nucleophile (R-MgBr), and hence the Grignard reaction is troubled by a lack of chemoselectivity and low functional group tolerance.

In the early 1970's, Kumada[18] and Corriu[19] independently discovered the first examples of Ni catalyzed cross-coupling reactions of organomagnesium compounds with aryl and alkenyl halides. The Negishi cross-coupling reaction, also discovered in the 1970's, employs an organobromide (R-Br) and an organozinc reagent with catalytic amounts of Pd or Ni.[20] Due to the ease of preparation of organozinc compounds, and wide spread use of this Pd catalyzed cross-coupling reaction, Ei-ichi Negishi was co-awarded the Nobel Prize in Chemistry in 2010, along with Akiro Suzuki and Richard Heck.[21]

In 1979, the Suzuki-Miyaura cross-coupling reaction was first reported, in which an alkenyl organoborane was cross-coupled to various 1-alkenyl halides and produced conjugated (E)-dienes intended for the Diels-Alder reaction.[22] The reaction employed catalytic amounts of $Pd(PPh_3)_4$ and stoichiometric amounts of base, producing (E)-dienes with high regio- and stereospecificity in good yields.[22] In 1981, Suzuki reported a similar coupling leading to biaryls, in which an aryl boronic acid was coupled to an aryl halide.[23] The report describes the use of catalytic amounts of a Pd complex and stoichiometric amounts of an alkoxide base as reaction conditions.[23] The Suzuki-Miyaura publication was followed by other significant C-C bond

forming reactions reported by Hiyama,[24] Sonogashira,[25] Kumada,[18] and Stille[26] all of which are catalyzed by Pd but differ in nucleophilic coupling partner with Si, Cu, Mg, and Sn compounds employed, respectively (Scheme 1).



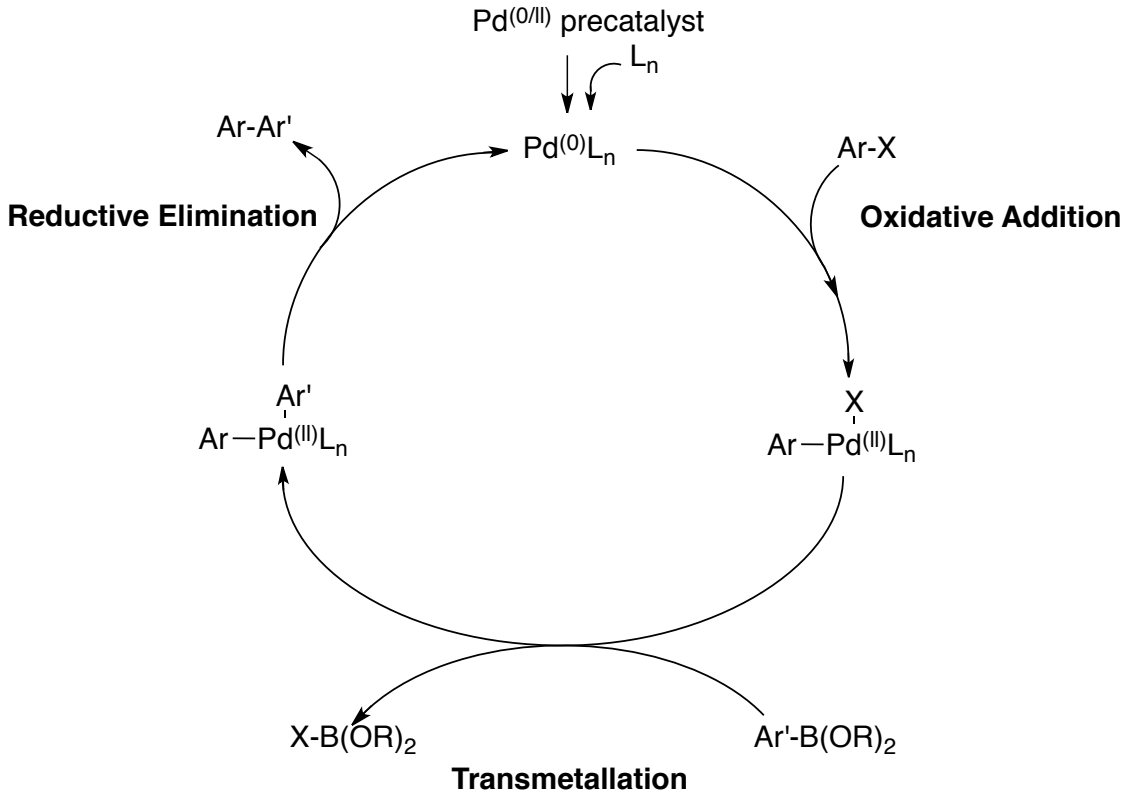
Scheme 1. Representative Cross-Coupling reactions.

The Suzuki-Miyaura reaction, in comparison to other Pd-catalyzed cross-coupling methods, offers many advantages that makes it one of the most employed C-C bond forming reactions in pharmaceutical syntheses.[27] The starting materials for the Suzuki-Miyaura reaction are air and moisture stable organoboranes and organohalides, as opposed to the highly moisture sensitive organolithium or Grignard reagents. Also, commercially available, air-stable, 18 e^- Pd pre-catalysts, such as $Pd(PPh_3)_4$, are often employed to effect the cross-coupling reaction. Benign organoboranes are employed as the nucleophilic cross-coupling partners instead of toxic organotin compounds found in Stille couplings. Furthermore, factors that make the Suzuki-

Miyaura cross-coupling reaction favorable include: generally mild reaction conditions, water stability, and tolerance to a variety of functional groups. In addition, these reactions generally proceed with good regio- and stereocontrol, require low catalyst loadings, are often applied in one-pot syntheses and require relative ease of separation of products from inorganic borate by-products.[28]

1.2 Mechanism of Suzuki-Miyaura Cross-Coupling

The generally accepted catalytic cycle of the Suzuki-Miyaura reaction involves four steps (Scheme 2); the first is formation of the coordinately unsaturated active catalyst from the saturated 18 e^- precatalyst.[26] (For the sake of simplicity, palladium will be discussed as the metal catalyst in the mechanistic section in this thesis, despite the fact that other metals, such as Ni and Cu[29] are known to facilitate Suzuki-Miyaura cross-couplings.) The second step, oxidative addition, involves the addition of the carbon halide bond across the Pd catalyst. Base facilitates the third step, transmetalation of the boronic ester to the Pd catalytic center.[49, 50] In the fourth and final step, reductive elimination, facilitated by sterically bulky ligands, releases the cross-coupling product (R-R') and regenerates the catalyst.[30]



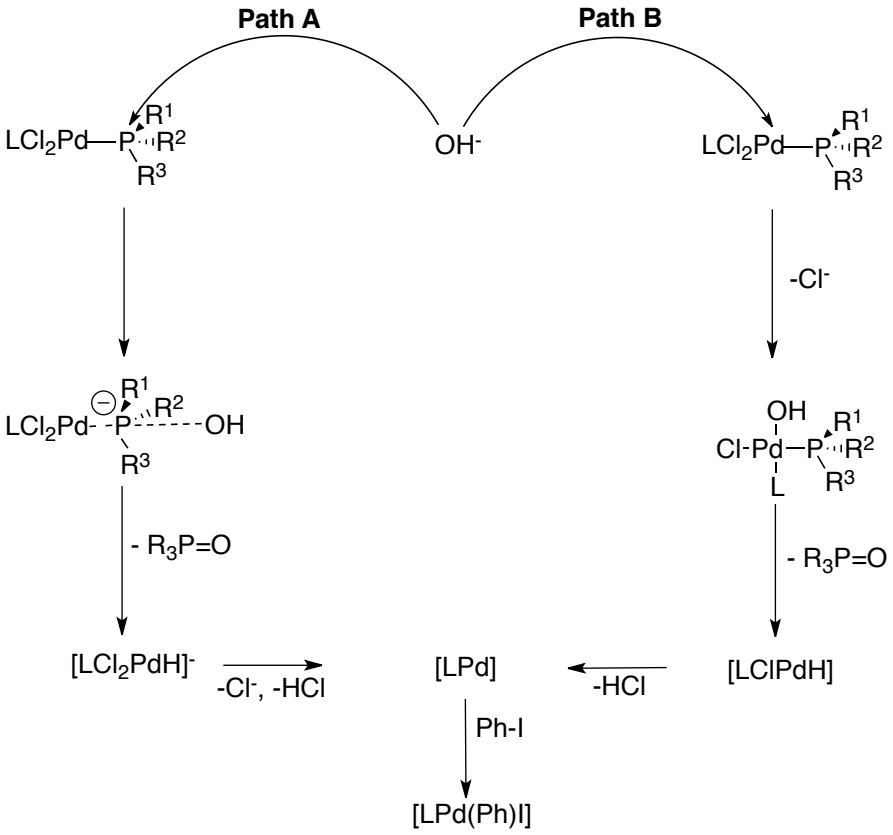
Scheme 2. Generally accepted mechanism of Suzuki-Miyaura Cross-Coupling reaction.

Metal precatalysts that are often employed in the Suzuki-Miyaura cross-coupling reaction are of the Pd(II) oxidation state and must be reduced to the Pd(0) oxidation state in order to be susceptible to oxidative addition. In 1993, Grushin and Alper of the University of Ottawa proposed a mechanism for the reduction of Pd(II) precatalysts to Pd(0) species.[31] The mechanism of disproportionation of L_2PdCl_2 species produces Pd(0) and triphenylphosphine oxide.[31]

Two plausible mechanisms, depicted in Scheme 3, involve the reaction between $[L_2PdCl_2]$ (L= tertiary phosphine) and OH^-. In path A, the hydroxide anion can attack the electron deficient phosphorous center and directly reduce palladium in this S_N2 reaction that evolves a tertiary phosphine oxide and anionic $[LPd(H)Cl_2]^-$.[31] Path B involves attack of

hydroxide on the palladium center directly, expunging chloride. Upon release of tertiary phosphine oxide, followed by reductive elimination of HCl, a monoligated, highly unstable, reduced, 12 e^- LPd is produced, which is active to oxidative addition.

When employing a chiral, tertiary phosphine, retention of configuration at the phosphine, (*R*)-benzylmethylphosphine was observed and therefore path B was held as the most plausible mechanism of Pd(II) disproportionation, since path A would result in inversion of configuration.[31]



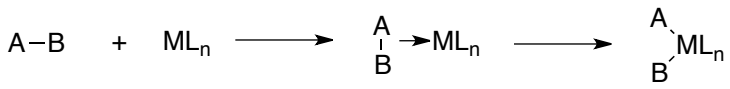
Scheme 3. Alkaline disproportionation of $L_2Pd(II)Cl_2$ to palladium(0) species.[31]

1.2.1 Oxidative Addition

Oxidative addition (OA) in the Suzuki-Miyaura cross-coupling reaction is believed to proceed through the widely applied mechanistic framework that is associated with many other metal

catalyzed cross-couplings.[32] Many literature reports suggest that the active catalyst for oxidative addition is either a mono- or bis- ligated Pd center having one ligand (PdL) or two (PdL_2) donor ligands. In the case of the $Pd(PPh_3)_4$ precatalyst, the Pd complex loses two phosphine ligands to generate the coordinatively unsaturated 14 e^- complex $Pd(PPh_3)_2$ leaving two vacant sites for catalysis on the Pd (0) center. In 1990, Amatore et al. studied the oxidative addition of variously substituted Ar-I to $Pd(PPh_3)_4$ and reported that the aryliodide oxidatively added to the bis-ligated $Pd(PPh_3)_2$ complex despite an equilibrium heavily favoring the tris-ligated $Pd(PPh_3)_3$.[33, 49]

The pathway of OA is dependent on the halide and the Pd catalyst. Different mechanisms of oxidative addition have been proposed, most invoking a concerted, three center, two-electron transformation (Scheme 4).[37] The concerted pathway involves the initial formation of the associative complex between the metal the carbon-halide bond (represented A-B in the diagram below).[37] The sigma bond of A-B is cleaved by the π -back bonding of the metal into the σ^* orbital of the carbon – halide sigma bond to form the oxidatively added A-$M^{(II)}BL_n$ complex.



Scheme 4. Three center, two-electron oxidative addition.

The oxidatively added Pd catalyst rapidly isomerizes from the *cis* to the *trans* isomer once the A-B bond is broken.[33] Another observable consistent with a three center, two-electron, cis addition, results in retention of configuration for secondary alkyl halides and vinyl halides and OA proceeds with inversion of stereochemistry for allylic and benzylic halides.[34]

Oxidative addition is facilitated by electron rich, strong σ-donor ligands on the metal catalyst, which also provide stability to the Pd(II) center. The speed of oxidative addition is also

affected by the carbon-halide or carbon-pseudohalide bond strength. The rate of addition precedes in the following order I > Br > OTf > Cl >> F with the weakest bonds such as C-I proceeding through oxidative addition with ease and the strongest bonds C-F proceeding through oxidative addition slowly or not at all. [35]

Studies from Amatore[36, 37, 38], Hartwig[39, 40, 41], and Fu[26, 28, 35] have aimed to examine the effect of ligand sterics, dependence of rate with the strength of the C-X bond and identification of the active catalytic species.

Amatore in 1997 published findings directed towards determining the active catalytic species in bidentate systems using $Pd(dba)_2$ as the catalyst precursor and phenyliodide as the electrophile.[37] They demonstrated that, in the presence of triphenylphosphine, the 18 e^- precursor $Pd(dba)_2$ was converted to the catalytically competent 14 e^- bisligated $Pd(PPh_3)_2$ complex to oxidatively add Ph-I. It was noted that 8 equivalents of PPh_3 were required to deligate the second dba ligand, hence it was established that dba was not as labile as generally accepted.[36] The sterically hindered, 18 e^- $Pd(dba)(PPh_3)_2$ was shown to not be the active catalytic species for oxidative addition into Ph-I. Amatore et al. demonstrated that contrary to the usual belief at the time, dba plays a crucial antagonistic role in consuming Pd metal, forming the more stable and correspondingly less reactive $Pd(dba)L_2$ or Pd(dba)(L-L) species, that subsequently diminishes the concentration of Pd in the active catalytic form ($Pd(PPh_3)_2$).[36]

The mechanism and rates of oxidative addition of Ph-I to tetrakis(triphenyl phosphine)palladium(0) were also studied by the same group.[37] The experimentally determined rate law for the oxidative addition is shown in [1].

$$\boldsymbol{v = -\frac{d[Pd^0]}{dt} = k_0{}^{exp}[ArI][Pd^0]/[PPh_3]} \qquad \mathbf{[1]}$$

The study measured dissociation constants of the dissociation of PPh_3 from the $Pd(PPh_3)_4$ catalyst precursor. The equilibrium constants associated with the dissociation of the first and second PPh_3, K_1 and K_2, respectively were determined (Scheme 5).

$$Pd^0(PPh_3)_4 \rightleftharpoons Pd^0(PPh_3)_3 + PPh_3 \quad K_1$$

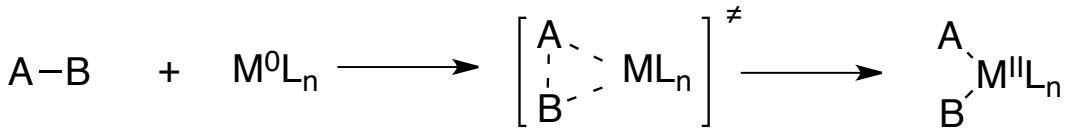
$$Pd^0(PPh_3)_3 \rightleftharpoons Pd^0(PPh_3)_2 + PPh_3 \quad K_2$$

$$Pd^0(PPh_3)_2 + ArI \rightleftharpoons Ar\text{-}Pd^{II}I(PPh_3)_2 \quad k^{exp}$$

Scheme 5. Dissociative equilibria in $Pd(PPh_3)_4$ and subsequent oxidative addition of ArI.

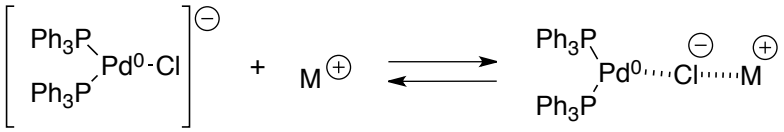
The equilibrium constant, K_1 was determined to be $>> 10^{-3}$ M and $K_2 < 10^{-4}$M; this second equilibrium forms a fleeting, highly reactive 14 e^- species, bisligated $Pd(PPh_3)_2$ that is formed in an endergonic ligand dissociation which acts as a pre-equilibrium to oxidative addition.[37]

Additionally, several key thermodynamic parameters were derived; nearly identical ρ values were obtained in THF and toluene (2.0 and 2.3 ± 0.2, respectively). Enthalpies of activation were found to be: $\Delta H^{\neq}$ (exp)= 75 kJ mol^{-1} in toluene and $\Delta H^{\neq}$ (exp)= 77 kJ mol^{-1} in THF, respectively.[37] Since the solvents vary greatly in polarities (ε_s= 7.58 for THF and ε_s= 2.38 for toluene), the near identical magnitude of $\Delta H^{\neq}$(exp) and ρ values indicated that no charge is built up in the transition state of oxidative addition. From their studies, the authors proposed a three-center, two-electron transition state of oxidative addition consistent with their observations involving a minimum build up of charge (Scheme 6).[37]



Scheme 6. Three-center, two electron transition state of oxidative addition proposed by Amatore et al. in 1997.[37]

In 2000, Amatore published findings pertaining to identification of the active catalyst in cross-coupling reactions when employing Pd^{II} pre-catalysts such as $PdCl_2L_2$ and $Pd(OAc)_2$.[38] Contrary to their previous studies that established PdL_2 as the active catalyst for oxidative addition when Pd^0 precursors are used[37], they found that anionic zero valent species such as $Pd^0(X)(L)_2^-$ undergo facile oxidative addition to aryl halides when Pd^{II} precursors are used.[38] The rate of oxidative addition is strongly dependent on the anion coordinated to the palladium(0). The rate of oxidative addition in these active $Pd^0(X)(L)_2^-$ anionic complexes is accelerated by cations which are believed to interact with palladium halide, affording a more "naked" palladium species, destabilizing the anionic palladium complex by ion-pairing and forming a complex closer to $Pd(0)(PPh_3)_2$ which is active to oxidative addition (Equation 2).[38]

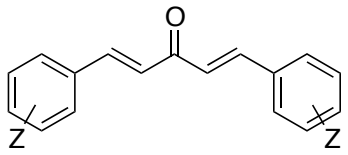


Equation 2. Ion pairing of an anionic $Pd(0)(X)L_2^-$ complex with a metal counteraction.

This study also demonstrated that the previously postulated oxidative addition complex, *trans*-$ArPdI(PPh_3)_2$ was not produced as a main intermediate but alternatively, penta-coordinated anionic complexes $ArPd(X)(PPh_3)_2^-$ (where X= Cl^- or OAc^-) were formed upon oxidative addition. The formation of these penta-coordinate complexes ruled out most textbook

mechanisms at the time, providing a more detailed picture of the catalytic cycle of cross-coupling reactions employing Pd^{II} precursors.[38]

Ian Fairlamb and coworkers have extensively studied the electronic effects of ligands on the rate of catalysis.[42] Specifically, they studied the effect of various electronic substitution on the dba ligand (Figure 3) and measured the rate constants when cross-coupling para-chlorotoluene with phenylboronic acid. The greatest reaction rate was found when electron rich dba derivatives were employed as ligands.[42]

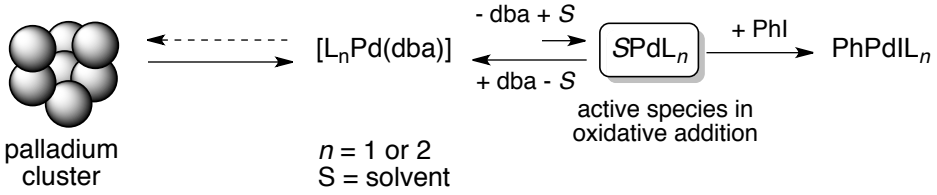


Z = H (dba), 4,4'-OMe, 4,4'-tBu, 3,5,3',5'-OMe
3,3'-NO2, 4,4'-CF3, 4,4'-F, 4,4'-Cl, 4,4'-Br

Figure 3. Various electronic substitution on dba in $Pd(dba)_n$ precatalysts used in Suzuki-Miyaura cross-coupling.

Fairlamb and coworkers went on to correlate electronic effects to reaction rate, with the stability of the $L_nPd^0 - \eta^2 - dba$ complex, which is stabilized by strong π-back bonding from the Pd dπ HOMO electrons to the dba π^* LUMO. The authors reasoned that electron donating dba ligands destabilize the π-back bonding ($d\pi - \pi^*$) interaction and therefore, increase the amount of active Pd catalyst available for oxidative addition (Scheme 7).[42] As shown in Scheme 7, electron rich groups on dba push the equilibria forward resulting in the generation of highly unsaturated Pd catalysts such as the solvent ligated *S*PdL_n species, which is capable of reacting via oxidative addition.

Indeed, if the ligand, L, in the $L_nPd(dba)$ complex is very electron rich, such as trialkylphosphines or N-heterocyclic carbenes, the $L_nPd(dba)$ complex will be more stable since π-acidic dba will accept electron density from the electron-rich, *trans* ligand and, as a consequence, the equilibrium will shift to the more stable, and unreactive $L_nPd(dba)$ species, locking Pd in a form inactive to catalysis, thus decreasing the overall reaction rate.[42] Strong σ-donors trans to the (non π-acidic) leaving group enhance the rate of oxidative addition by increasing the electron density on the Pd center, yet, it should be mentioned that σ strong donors are antagonistic to reductive elimination, decreasing the rate of the latter, also important reaction.[42] Therefore, the degree of σ donor strength of employed ligands must be carefully optimized.



Scheme 7. Equilibria of [$L_nPd(dba)$] pre-catalyst.

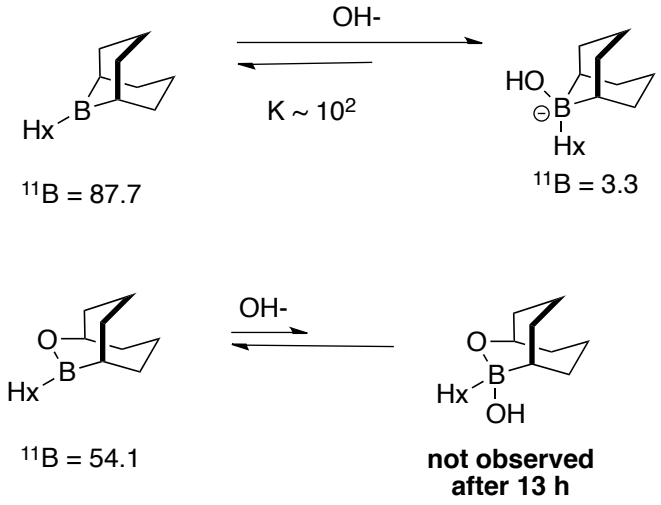
Additionally, Fairlamb and coworkers have discussed an important topic in catalysis: the ligand amount must be carefully optimized as the ligand employed in this thesis, dba, is required to prevent Pd agglomeration, which produces clusters and colloids. Ligation to the Pd center increases catalyst longevity, however, too much ligand will push the equilibrium to a highly ligated Pd complex, which will block coordination sites required for catalysis.[42] Therefore, the ligand concentration and rate of oxidative addition are intimately dependent, as this delicate balance exists between these two variables. The effect of ligand amount on the Pd catalyst and

pre-catalyst stability is more pronounced when OA becomes rate limiting, as is the case for aryl chlorides.[42]

1.2.2b) Transmetalation and Role of Base

Transmetalation (TM) in the Suzuki-Miyaura reaction involves transfer of the organic group from boron to palladium. The transmetalation step requires addition of base to facilitate the transfer.[43] In fact, when Baba and Negishi tried to cross-couple organoboron reagents prior to Suzuki, the omission of base to the Pd catalyzed reaction led to cross-coupling product with only a 2% yield.[44] Upon Suzuki and Miyaura's 1979 discovery, the same reaction was repeated to generate the cross-coupling product with a 59% yield, demonstrating the importance of exogeneous base.[43]

Mechanistically, there is much debate in the literature concerning the role of the base with most arguments predicated on the reactivity of the cross-coupling reagent, predominantly the Lewis acidity of the organoborane. Trialkylboranes such as R-B-9-BBN are stronger Lewis acids than boronic acids or esters, since in the latter case, oxygen atoms adjacent to trivalent B donate electron density into the empty p orbital resulting in a decrease in the Lewis acidity.[50] The difference in Lewis acidity of alkyl-B-9-BBN and alkyl-B-OBBN derivatives is illustrated in Scheme 8.



Scheme 8. Variance in Lewis acidities of organoboranes.[50]

Hence, bases such as OH^- interact more strongly with trialkyl boranes by virtue of their increased Lewis acidity and, on the contrary, boronic acids and esters have a weaker interaction with exogeneous base, resulting in a more favorable activation of the base with the palladium center.

Matos and Soderquist further demonstrated the difference in reactivity of 9-BBN and OBBN derivatives by running a competition reaction, in which the authors reported a more facile cross-coupling of alkyl-B-9-BBN derivatives (Figure 4).[50]

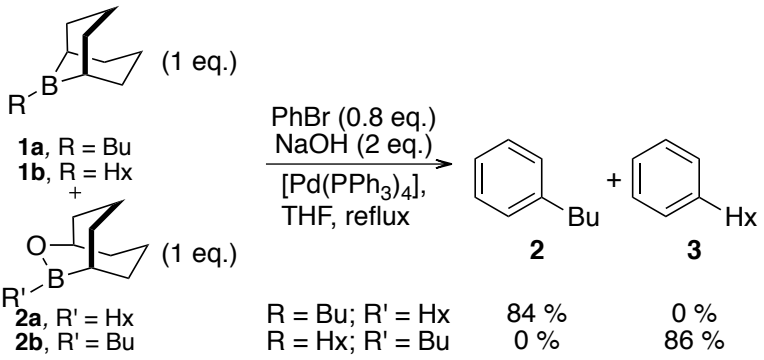
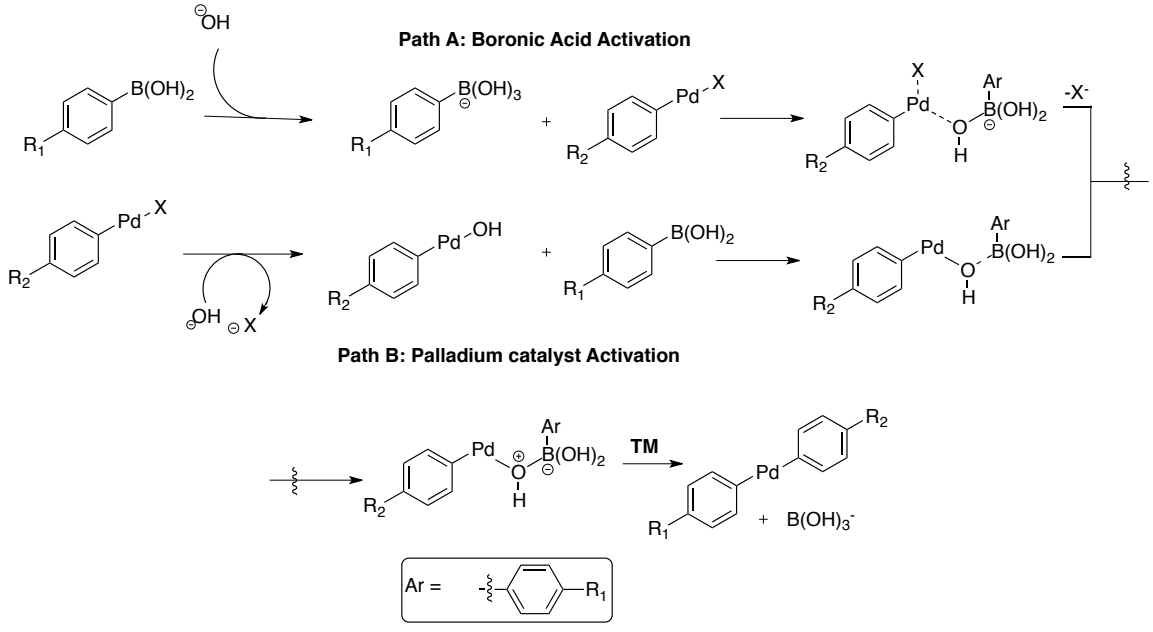


Figure 4. Variance in reactivity of R-OBBN and R-9-BBN substituted nucleophiles.

Braga et al.[45] employed B3LYP level DFT calculations to determine an energy profile diagram corresponding to the reaction of the vinyl Pd complex $Pd(CH{=}CH_2)(PPh_3)_2Br$ and $CH_2{=}CHB(OH)_2$ as the boronic acid and OH^- as base. Additional calculations were performed for the reaction of $Pd(CH{=}CH_2)(PPh_3)_2(OH)$ as the initially formed Pd complex and $CH{=}CHB(OH)_2$ as the organoboron coupling partner. The report summarizes two major mechanisms of transmetalation as: path A) where the base binds to the trivalent organoboron to form an organoboronate salt, which then transmetalates; or path B) where base displaces the halide in the coordination sphere of the palladium complex forming a hydroxo Pd species which undergoes transmetalation with the trivalent boronic acid (Scheme 9). Path A and B provide a dichotomy of transmetalation possibilities that are more fully discussed in a recently published review by Professor Lloyd-Jones and Lennox.[46] He notes that Path A and B, at first glance, appear to be a debate of strictly academic interest, but upon further examination, distinguishing

between these two pathways may assist in the intelligent design of catalytic systems that increase turnover and minimize protodeboronation, β-hydride elimination and homocoupling products.[46] The calculations indicated that reaction of R-Pd-X(PPh_3)$_2$ with the tetravalent organoborate salt proceeds with a more favorable energy profile (Path A).[45] DFT gas-phase calculations predict that the complex formed in Path A prior to transmetalation ($PhPdL_n$----Br coordinated to $PhB(OH)_3^-$) is lower in energy by 2.5 kcal mol^{-1} than the complex formed in Path B prior to transmetalation ($PhPdL_nOH$ coordinated to $PhB(OH)_2$) and therefore, suggests that path A (formation of the 'ate' complex proceeded by 'Pd-Br' coordination) is the predominate mode of transmetalation.[45] The energies of the complexes formed during the two pathways converge at $PhL_nPd\text{-}(OH)^+\text{-}B^-(OH)_2Ph$ complex formation. The transfer of the Ph^B compound to the Ph^XPdL_n complex is the rate-determining step with an activation barrier of 22.2 kcal mol^{-1}.[45]



Scheme 9. Role of base in transmetalation.

However, studies that are more recent predict the involvement of the Pd-hydroxo species ArL_2Pd^{II}-OH (Path B) as the preferred pathway for transmetalation. Recent studies from Amatore and Jutland[47, 48] employed electrochemical techniques to confirm what has now been widely accepted, that OH^- is crucial in promoting the transmetalation step. The study claims that OH^- serves three roles in the Suzuki-Miyaura reaction: 1) to form the hydroxo *trans*-$[ArPdOH(PPh_3)_2]$ catalyst 2) to accelerate the rate of reductive elimination and an antagonistic effect 3) as the concentration of OH^- increases, the rate of the overall reaction rate decrease. Therefore, optimization of the stoichiometry of base is crucial to maximizing the rate of Suzuki-Miyaura cross-couplings. The latter concept is rationalized as follows: the overall reactivity is controlled by the concentration of OH^- and passes through a maximum as hydroxide concentration increases. The authors reason that increasing the concentration of OH^- beyond the point that corresponds to a maximum overall cross-coupling rate, results in increased formation of the unreactive tetravalent Ar'-$B(OH)_3^-$ species and would trap the boron reagent in a non-reactive state and thus lower the overall rate of reaction.[47] The preceding statement is only reasonable if Path B is operative where the palladium-hydroxo and boronic acids are reactive to transmetalation.

Recently, Hartwig and Carrow published a study that examined pathways for transmetalation in the Suzuki-Miyaura reaction.[49] The kinetics of the coupling reaction were studied between stoichiometric amounts of Pd hydroxo complex reacted with aryl boronic acid and Pd halide complexes were reacted with aryltrihydroxyborate acids, respectively. The authors report that Suzuki-Miyaura cross-coupling reactions under aqueous solvent mixtures, conducted with weak base (such as the salts of phosphates and carbonates) proceed through a transmetalation involving the reaction of a palladium hydroxo complex with a trivalent boronic

acid (Path B of Scheme 9). Hence, the reaction most likely does not proceed through Path A of Scheme 9.[49] Hartwig reasons that the relative contribution of Path A and Path B to transmetalation depends on the relative concentrations of Pd-X to Pd-OH, and the relative concentrations of boronic acid to trihydroxyborate.[49] Suzuki–Miyaura reactions conducted in aqueous solvent mixtures result in slightly greater populations of Pd halide than Pd hydroxo by less than an order of magnitude.[49]

Populations of boronic acid and trihydroxyborate are similar to each other in the presence of water and base and their relative concentrations are highly dependent on the strength of base. Presence of stronger bases would shift the equilibrium to favor higher concentrations of the less reactive tetravalent boronate salt. The reaction of *trans*-[ArPdOH(PPh_3)$_2$] and *p*-tolylboronic acid both at 0.15 M concentrations in the presence of PPh_3 (0.15 M) was monitored at -40 ^oC and occurred with an observed rate constant of 2.4 x 10^{-3} s^{-1}. On the contrary, the reaction of the Pd halide complex, *trans*-[ArPdBr(PPh_3)$_2$] with *p*-tolyltrihydroxyborate at a temperature of -40 ^oC occurred with an observed rate constant of 1.7 x 10^{-7} s^{-1}. The combination of these factors then leads to the conclusion that under the reported conditions, the more facile transmetalation is the reaction between the hydroxo palladium complex with the boronic acid and the reaction between that Pd-X and trihydroxyborate salt proceeds more slowly.[49]

Boronic esters were also reacted at -40 ^oC, as in the above examples, and based on the assumption that boronic esters do not react faster than trihydroxyborates, then the pathway of transmetalation for boronic esters would also occur by reaction of a neutral boron with a palladium hydroxide complex (Path B).[49] Pinacol esters were noted to react more sluggishly than the neopentyl glycol and catechol esters (Figure 5), however pinacol esters were noted to be more stable than the latter.[48]

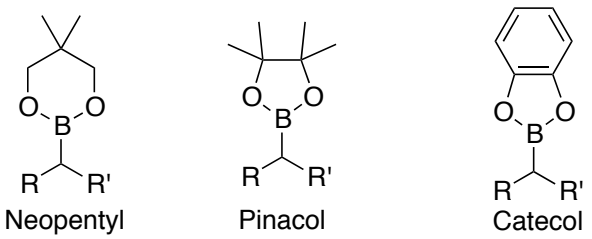
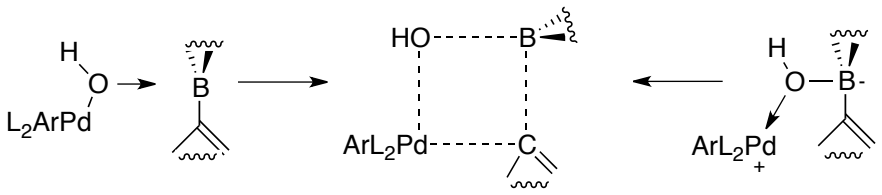


Figure 5. Neopentyl, pinacol and catechol boronic esters.

A detailed study by Matos and Soderquist[50] provided further insight to the role of base. Five possible roles of base in Suzuki-Miyaura cross-coupling reactions were proposed: the formation of $[HO(R)\text{-}9\text{-}BBN]^{-1}$, the hydrolysis of $Ph(Ph_3P)_2PdBr$ to generate the $Ph(Ph_3P)_2PdOH$ monomer, the hydrolysis of $X\text{-}B(OR)_2$ which competes with the alkyl borane for base (hence the frequent use of excess base), accelerated rates for R-OBBD cross-couplings, and base may also assist in catalyst regeneration.[50] The interaction of alkyl-9-BBN with base is much greater than the interaction of R-OBBD with base, in this case hydroxide (Scheme 8). As previously noted, the degree of boronate formation was found to be dependent on the respective Lewis acidities of the organoborane under study and hence R-OBBD and alkyl-9-BBN compounds display much different reactivities with hydroxide. The coupling reactions of alkyl-9-BBN derivatives exhibit first-order dependence on the phenyl bromide concentration, which is indicative of oxidative addition being the rate-determining step.[50] In contrast, the coupling reaction of R-OBBD exhibits a first-order dependence on hydroxide concentration, $[OH^-]$ which is indicative that Pd hydrolysis (Scheme 9, Path B) is the rate-limiting step.[50]

The authors also proposed a four-membered transition state with the oxygen of exogeneous base, Pd, and the C-B bond, coordinated to facilitate the transfer of the organic

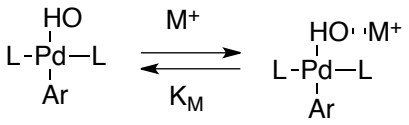
group from the organoborane to the Pd catalyst (Scheme 10). It was proposed that transmetalation proceeds via a hydroxo μ_2–bridged intermediate that facilitates the alkyl fragment transfer from B to Pd which proceeded with retention of configuration.[50]



Scheme 10. Four membered transition state of transmetalation.

The product of transmetalation, $PhPdR(PPh_3)_2$ rapidly reductively eliminates to give the cross-coupling product, R-Ph and regenerates the catalytically active 14 e^- $Pd(PPh_3)_2$. The boron byproduct, $X\text{-}B(OR)_2$ can be hydrolyzed by OH^- and then competes with R-9-BBN for base. Correspondingly, the optimal R-9-BBN/OH^{-1} stoichiometry is 1:2, to ensure that sufficient amounts of $(R\text{-}9\text{-}BBN(OH))^{-1}$ are present to continue the cycle once the oxidative addition product has been generated.[50] A minor pathway involves the hydrolysis of $PhPdBr(PPh_3)_2$ to generate $PhPdOH(PPh_3)_2$ which then reacts with R-9-BBN through the four-membered transition state to contribute to the transmetalation process. The authors noted that the less Lewis acidic B-OBBN organoboranes predominately transmetalate through the hydrolyzed $PhPdOH(PPh_3)_2$ pathway, in which case the hydrolysis of $PhPdBr(PPh_3)_2$ is rate limiting.[50]

Interestingly, a strong cation effect on the rate of transmetalation has been observed.[51] Cations such as Na^+ strongly decrease the rate of transmetalation (Equation 3).[51] The effect from strongest decelerator to weakest decelerator of transmetalation for the alkali metals proceeds the following order: $Na^+ > Cs^+ > K^+$.[51]



Equation 3. Effect of alkali metal cation, M^+ on palladium hydroxo species.

1.2.2.b) Role of Fluoride

Many functional groups are sensitive to Brønsted-Lowry bases and accordingly, various protocols have been developed employing fluoride ions as transmetalation promoters in place of hydroxide generating bases. Fluoride has replaced base in many Suzuki-Miyaura cross-coupling reactions and its success as a powerful transmetalation promoter has been attributed to its poor basicity and nucleophilicity, weak F-Pd bond strength and to the high fluorophilicity of boron (Equation 4).[52]

A 1994 study published by Wright et al. detailed the fluoride-mediated cross-coupling of phenyl boronic acids to various aryl bromides and triflates, respectively with excellent yields in most cases.[52] A screen of various fluoride sources was reported, including alkylammonium fluoride, cesium fluoride, sodium fluoride and potassium fluoride salts in various polar protic and aprotic solvents. The best fluoride source for this transformation was selected based on the cost per mole, reaction time, reaction yield, solvent choice and ease of drying. The best source of fluoride in a broad screen of sources was cesium fluoride, which left sensitive functionalities intact including: aliphatic acid methyl esters, aliphatic nitriles, trifluoroacetimide and β-phenethyl acetates.[52]

Lloyd-Jones and coworkers compared the reactivity of *p*-F-C_6H_4-BF_3K salts to

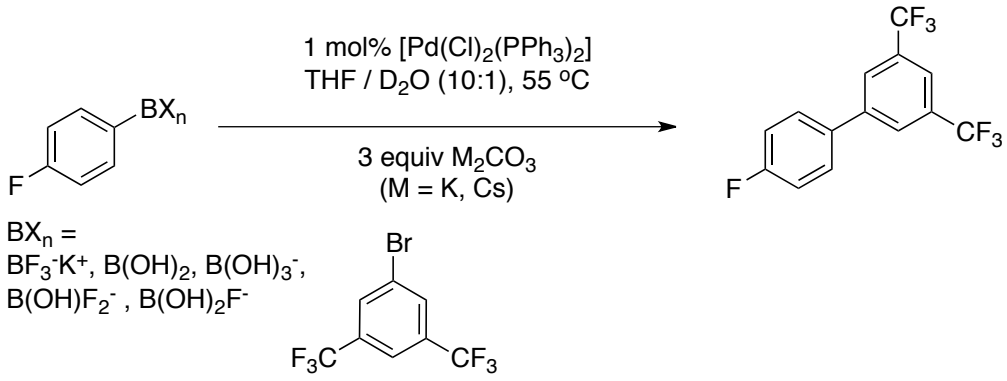
p-F-C_6H_4-$B(OH)_2$ in the cross-coupling reaction with MesBr using $PdCl_2(PPh_3)_2$ as a pre-catalyst.[53] In the cross-coupling of *p*-F-C_6H_4-$B(OH)_2$ with MesBr it was established that the boronic acid reacted in low yield (<32%) and the major product was the protodeboration product, fluorobenzene in 55 % yield. In contrast, the trifluoroborate salt reacted with MesBr to give the biarylated product in yields greater than 95% in anhydrous THF.[53] The study found that upon addition of base, *p*-F-C_6H_4-BF_3K salts were converted quantitatively to the corresponding boronate *p*-F-C_6H_4-$B(OH)_3K$. Bases $CsCO_3$, K_2CO_3, KOH all worked equally well with 3 equivalents of the carbonate and 6 equivalents of KOH required to effect the quantitative conversion. The question was posed: why is the reaction between R-BF_3K salts more efficient than the reaction starting with R-$B(OH)_2$, since it appears that the former is converted to the latter in the presence of base?

The authors reasoned that in the presence of aqueous base, R-BF_3K is converted to R-$B(OH)_2$ to some extent, however the concentration of R-$B(OH)_2$ is highly dependent on the concentration of water in the polar organic solvent.[53] The authors measured the conversion of R-BF_3K to R-$B(OH_3)K$ passing through a R-$B(OH)_2$ on the stepwise hydrolysis of the trifluroroborate in 100 % D_2O (55 M) and found the equilibrium lies heavily to the boronate (> 98%). In 100 % THF, the equilibrium favored the boronic acid (> 98%) thereby resulting in complete suppression of protodeboration byproducts.[53] A solvent composition of 10:1 toluene to water, resulted in a base concentration-independent mole fraction of boronate (with respect to boronic acid) of <10% in which case protodeboration is negligible, as in less than <0.1% of fluorobenzene was generated in 12 days, as opposed to 46% in 47 M D_2O.

Hence, the generation of large quantities of R-$B(OH)_3K$ appears to favor undesirable protodeboration byproducts. The formation of byproducts other than protodeborated

compounds, such as homocoupled products and formation of phenols was also observed to decrease with use of the trifluoroborate salts in comparison to the analogous boronic acid.[53] This point is of considerable interest since the R-$B(OH)_2$ is the dominant transmetalating species.

The above factors combined point to a fine balance that is reached in efficient cross-coupling reactions where the hydrolysis of the trifluoroborate salt to produce a low concentration of boronic acid is rate limiting, with respect to the rate of catalytic turnover. The above-described process allows for a decrease in homocoupling and protodeboration side products that are observed upon formation of high mole fractions of trihydroxyboronate salts.[53] At a 10:1 ratio of THF to water, the mole fraction of boronate to boronic acid of 0.1 was measured, which was found to be optimal for cross-coupling (Equation 4), thereby minimizing protodeboration and homocoupling byproducts (<0.1-2%).

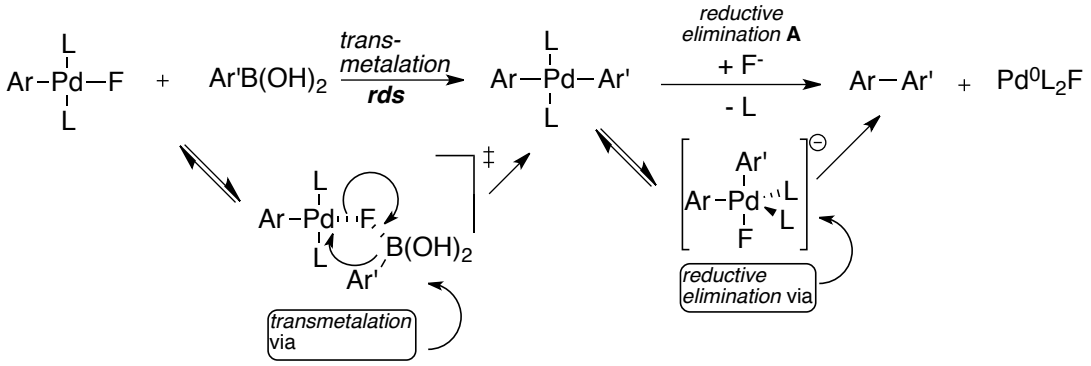


Equation 4. Cross-Coupling of various organoborane species to mesitylbromide under aqueous conditions.

Jutland and Amatore published results recently[54] discussing the successive hydrolysis of Ar'-BF_3K salts into partially hydrolyzed organoboronate salts (Ar'-$B(OH)_{3-n}F_n$). They stated that

this process is entirely reversible, such that in the presence of large amounts of fluroride anions boronic acids, R-B(OH)$_2$ are converted to trifluoroboronate salts, R-BF$_3$M.

The authors proposed the reaction pathway involves a L$_n$Pd-OH complex reacting with R-B(OH)$_2$ in the transmetalation step; however various sources of fluoride were substituted for hydroxide bases and this resulted in clean cross-coupling reactions. If R-BF$_3$K is unreactive to cross-coupling in the absence of base then the question becomes what is the role of fluoride in these cross-coupling reactions? Jutland and Amatore established that [ArPdFL$_2$] undergoes transmetalation with Ar'-B(OH)$_2$ as a consequence of the fluorophilicity of boron. The fluoride anion (much like OH$^-$) further enhances reductive elimination by forming a proposed pentacoordinate anionic Pd complex that undergoes rapid reductive elimination, as opposed to the slow trans to cis isomerization that must occur via the "cis/trans" pathway indicated (Scheme 11).



Scheme 11. Transmetalation of an aryl boronic acid to a Pd-F catalyst proceeded by cis/trans isomerization and fluoride assisted reductive elimination.

Reminiscent of OH$^-$, fluoride has an antagonistic effect at high concentrations, in which fluoride forms the non-reactive boronates, Ar'-B(OH)$_{3-n}$F$_n$. As a consequence of these effects,

the overall rate passes through a maximium as F^- concentration increases. The dependence of cross-coupling reaction rate on fluoride concentration is depicted in [2] below.

$$Cross\ Coupling\ Reaction\ Rate\ \alpha \frac{[F^-]}{[ArB(OH)_2]} \qquad [2]$$

The roles of OH^- and F^- are compared and contrasted: the roles of the F^- ion are much more complicated than the OH^- since a variety of R-$B(OH)_{3-n}F_n$ may be generated in the former case. The roles of F^- and OH^- are very similar with respect to the overall effect they have on cross-coupling reactions, since both speed up reductive elimination, facilitate transmetalation, and both can have an antagonistic effect at high concentrations to form non-reactive tetravalent boronates. It is noted however, that the oxophilicity of B is much greater than its fluorophilicity and therefore, at higher $[OH^-]$ the reaction is inhibited by formation of non-reactive boronate.[54] Amatore and Jutland[54] highlighted the difference in reactivity by stating the overall rate of reactions that employ base are governed by the $[OH^-]/[Ar'B(OH)_2]$ ratio which must be lower than 1 to minimize boronate formation. The overall cross-coupling reaction rate is much more tolerant to high F^- concentrations and directly correlates to the $[F^-]/[Ar'B(OH)_2]$ ratio which may be greater than 1 to effect efficient cross-coupling reactions.

Silver and thallium bases have been explored to effect difficult transmetalations with the rationale that silver and thallium cations may act as halide scavengers.[55] Silver and thalium cations can harvest halides from such complexes as: $XPdAr(PPh_3)_2$) generating AgX and TlX, respectively. The cationic Pd center is left to react with base to generate the more reactive palladium-hydroxo species $[Pd(OH)Ar(PPh_3)_2]$ or the palladium catalyst may interact with the tetravalent boronate (Scheme 9).

In order to optimize cross-coupling rates involving quick oxidative additions, as is the case for aryliodides, the following parameters must be optimized: find the best $[OH^-]$/

[$ArB(OH)_2$] ratio and select the best counter cation to scavenge halides: Tl^+ / Ag^+ > $n$$Bu_4N^+$, K^+, Cs^+, Na^+ and select the best base: OH^-, CO_3^{2-} >> AcO^- (ranking is based on the reactivity of arylbromides and iodides, where oxidative addition is not the rate determining step in the cross-coupling of aryl boronic acids).[51]

1.2.3 Reductive Elimination

Reductive elimination (RE) is essentially the reverse of oxidative addition, whereby two distinct organic groups become coupled through the critical C-C bond-forming step and the active catalyst is regenerated. For the reductive elimination of two distinct organic groups from a metal catalyst to occur, a requirement is that both organic moieties must be bonded in a *cis* manner with respect to each other in the active catalytic metal complex.[56]

Bidentate phosphine ligands favor this *cis* bonding of organic groups on the palladium catalyst. In the process of generating the cross-coupling product, often symbolized R-R', the catalyst is reduced, and in the case of palladium, changes oxidation state from Pd(II) to Pd(0). Various research groups have studied properties of the ligand, orbital symmetry, degree of substitution on the reducing Pd center and solvent, extensively and how they relate to the reductive elimination step.[57]

Electron poor metal centers undergo facile reductive elimination, therefore this step is favored by π-acidic ligands or ligands with electron withdrawing groups. Thus π- acidic ligands, such as dba (Figure 1) are used to speed up reductive elimination since electron density that is built up during this step can be dispersed through the π^* (LUMO) orbital of the π acidic ligand. It should also be noted that ligands that are π acids are also used to reduce rates of β-hydride elimination.[58] Electron withdrawing groups on the dba ligand can favor reductive elimination by

increasing the $d\pi - \pi^*$ orbital interaction.[42] Employing Negishi variants, Knochel has studied the effects of γ unsaturated halides as coupling partners for dialkylzinc compounds. Initially, Knochel had assumed that only unsaturated halides could cross-couple under the optimized conditions, which posed a significant substrate scope limitation to the reaction.[57] However, 10 years after the initial reaction discovery, Knochel et al. discovered that the addition of 0.1 – 1 equivalents of an electron deficient olefin as a promoter (*meta*-trifluoromethylstyrene was the best) allowed for the same cross-coupling conditions to be applied to cross-couple a variety of primary alkyl iodides in good to moderate yield.[56] The authors reasoned that the olefin promoter formed a bond to the Ni catalyst and was able to pull electron density away from the metal center (reminiscent of dba) to facilitate what is known to be a difficult, alkyl-alkyl or sp^3-sp^3 C-C bond forming reductive elimination of the product.[56]

Stille proposed that a highly unsaturated complex may permit the active palladium catalyst to reductively eliminate.[59] The energies and entropies of activation for the 1,1-reductive elimination of ethane from *cis*-bis(diphenyl-methylphosphine) dimethylpalladium(II) were determined in polar solvents and non-polar solvents. The rates of elimination in polar solvents, such as acetone, DMSO, acetonitrile were slower than rates in non-polar solvents, such as benzene.[59] This difference in rate implies that polar solvents may coordinate the Pd(II) catalyst, and act as ligands that inhibit reductive elimination.

Electronic properties can also have a significant impact on the outcome of reductive elimination. 1,1-Reductive eliminations from L_2PdR_2 complexes will occur more readily in complexes where there is strong σ-donation of the leaving group and weak σ-donation trans to the leaving group.[42,58] Because of this fine electronic balance of ligand and eliminating group, there is yet again a need to fine-tune the strength of σ- donation from the ligand, especially in the

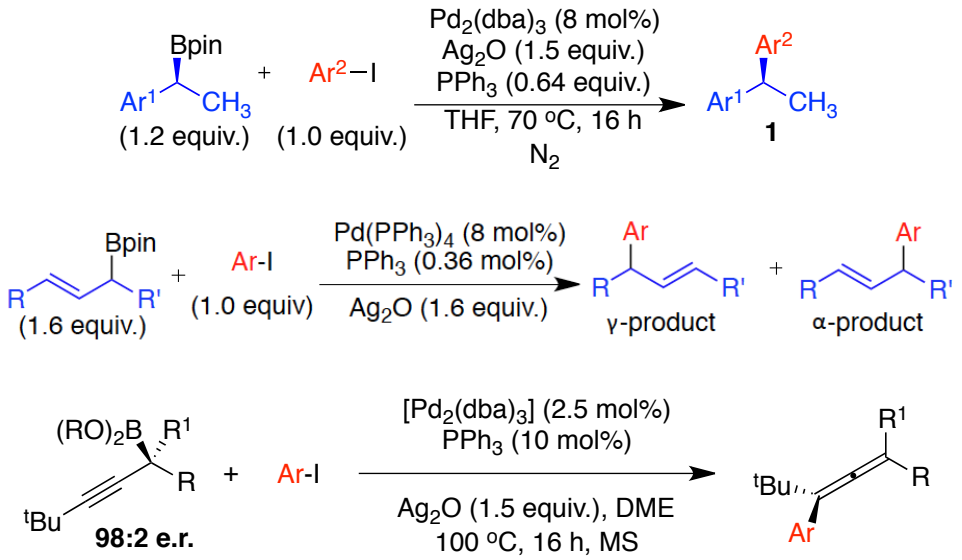
cases of ligands that are well known to be strong σ-donors such as NHCs and trialkylphosphines[60] in order to observe optimal reaction output.

The Suzuki-Miyaura cross-coupling reaction proceeds through an intricate set of steps that have been extensively examined in the literature. A more thorough understanding of the role of base, ligand, metal catalyst, additives, solvent and stoichiometry of reagents has allowed for further developments and an increase of scope to be brought to this important C-C bond forming reaction. Advancements that have expanded the use of the Suzuki-Miyaura cross-coupling reaction will be discussed in the subsequent chapters of this thesis.

Chapter 2: Synthesis of Chiral Boronic Esters

2.0 Introduction to Boronic Ester Synthesis

As noted in the introductory chapter, the use of stereochemistry-bearing boronic esters was unprecedented before our 2009 publication.[61] The main purpose of our groups' research in the field of cross-coupling chemistry has been to employ boronic esters bearing stereochemistry at the C-B bond to expand the scope of the Suzuki-Miyaura cross-coupling to include reactions that generate chiral compounds. We disclosed new developments in 2009[61] and 2012[62] describing the cross-coupling of enantioenriched, secondary, benzylic boronic esters and the cross-coupling of racemic, secondary, allylic boronic esters, respectively (Equation 5). Thus, we have successfully expanded our cross-coupling to include these classes of secondary boronic esters. In addition, the Aggarwal group reported the coupling of enantioenriched, secondary, propargylic boronic esters,[63] expanding the list of useful nucleophiles that are compatible under our original, Ag_2O-mediated cross-coupling conditions reported in 2009.[61]



Equation 5. Suzuki-Miyaura cross-coupling of secondary boronic esters.

The next goal, and the topic of this thesis, was to investigate the coupling of additional classes of secondary, allylic boronic esters and study the coupling of *enantioenriched* allylic boronic esters to more completely understand the mechanism of this cross-coupling reaction. In order to synthesize the desired allylic boronic esters, both racemically and enantioselectively, we would have to select other methods than the hydroboration method routinely used to access benzylic boronic esters.[61] To this end, much of the work of this thesis has been directed towards the enantioselective synthesis of several novel boronic esters prior to submitting them to the Suzuki-Miyaura cross-coupling reaction (Chapter 3), to not only demonstrate their utility, but also, to gain a more evolved mechanistic insight.

2.1 Metal-Catalyzed Syntheses of Organoboranes

For the Suzuki-Miyaura cross-coupling reaction to be of widespread use in organic synthesis, a variety of protocols to synthesize boronic acids, organoboranes and boronic esters are

necessary.[64] The following chapter will discuss the many ways in which these useful chemicals can be synthesized both racemically and asymmetrically, from readily accessible starting materials. Additionally, once boronic esters are synthesized they can be readily oxidized to the corresponding alcohol or alternately, converted to the amine.[67] From the corresponding boronic esters, alcohols are synthesized through oxidation with $NaOH/H_2O_2$[67] and amines can be prepared by reacting trifluoroborate salts with tetrachlorosilane and an organic azide,[65] or by treatment of trialkylboranes with hydroxylamine-*O*-sulfonic acid, H_2NOSO_3H.[66] Therefore, the synthesis of organoboranes is a practical pathway used to access these prevalent functional groups.[67]

Rhodium-catalyzed asymmetric, hydroboration of olefins has been of widespread use in the past three decades, stemming from the pioneering work of Ito and Hayashi.[68, 69, 70] In the late 1990s, our group reported an efficient Markovnikov hydroboration of styrene that proceeded with high yields and excellent stereoselectivities (Figure 6).[71]

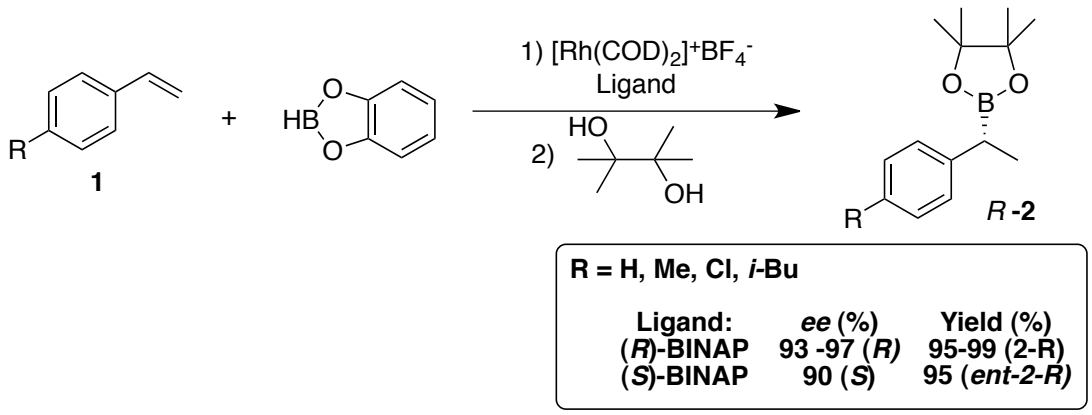
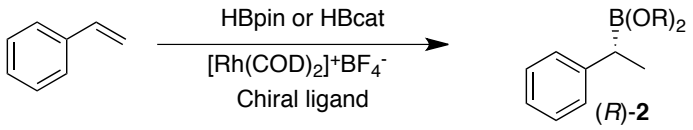


Figure 6. Markovnikov Hydroboration of *para* substituted styrene with catechol borane.[71]

In 2004, we additionally reported a room temperature hydroboration of styrene that proceeded with excellent regio- and stereocontrol.[72] Markovnikov (branched) or anti-

Markovnikov (linear) selectivity was controlled using Rh^+ or Ir as a catalyst, respectively. Enrichment in the *R* or *S* enantiomer of Markovnikov products was obtained by using HBpin or HBcat as the hydroborating reagent, respectively (Figure 7).



Ligand	Reagent	Temperature (°C)	B:L	e.r. *R*:*S*	yield (%)
(R)-BINAP	HBCat	-65	99:1	96:4	99
(R)-BINAP	HBCat	25	99:1	79:21	90
(R)-BINAP	HBPin	25	56:44	30:70	30
(R, S)-Josiphos	HBCat	-70	99:1	96:4	65
(R, S)-Josiphos	HBCat	25	N.A.	80:20	N.A.
(R, S)-Josiphos	HBPin	25	72:28	8:92	53
(S)-QUINAP	HBCat	25	97:3	6:94	69
(S)-QUINAP	HBPin	25	65:35	9:91	30

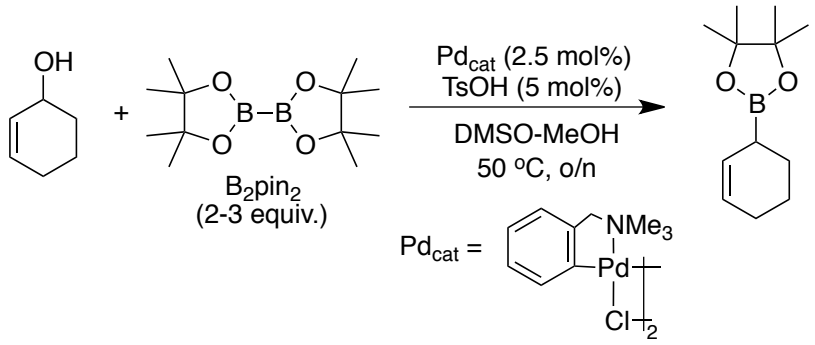
Figure 7. Asymmetric Hydroboration of Styrene with HBpin or HBcat.[72]

In addition to hydroboration, lithiation followed by trapping with a borylating agent such as $B(OMe)_3$ or *i*PrOBpin has become a standard way to generate organoboronates, a strategy particularly used in conjunction with D*o*M chemistry.[73]

Metal catalyzed C-H borylations have found increased interest recently.[74] Direction functionalization of C-H bonds can completely change the way a chemist plans a total synthesis, with C-H functionalization often resulting in direct routes to target compounds. A recent review by Hartwig et al.[75] extensively covers such processes catalyzed by rhodium, ruthenium, iridium and copper catalysts for the conversion of C-H bonds into C-B bonds.

For allylboranes, in particular, other methods are available. One such method described by Szabo converts C-O bonds into C-B bonds by reacting allylic alcohols with catalytic amounts of a *para*-toluenesulfonic acid and a palladium pincer complex with superstoichiometric amounts

of bis(pinacolato)diboron (B_2pin_2) (Equation 6).[76] The boration reaction is run at elevated temperatures overnight and allylic boronic esters are isolated in good to moderate yields (56-96 %). This method is very interesting because of the availability of allylic alcohols, but one significant drawback is that the reaction is limited in scope to the conversion of primary and cyclic allylic alcohols to allylic boronic esters (Equation 6). Thus, it would not be applicable to the synthesis of chiral organoboronic esters.



Equation 6. Palladium-Catalyzed Boronation of Allylic Alcohols.[76]

Sawamura, Ito et al.,[77] developed a method that is applicable to the synthesis of chiral organoboronic esters. In their approach, allylic carbonates are reacted with a Cu catalyst and bis(pinacolato)diboron. Mixtures of α and γ regioisomers are obtained, with the highest γ regioselectivity observed when L = Xantphos, dppe, dppp, or dppf ligands (Figure 8) bound to the Cu(O-R')L pre-catalyst.

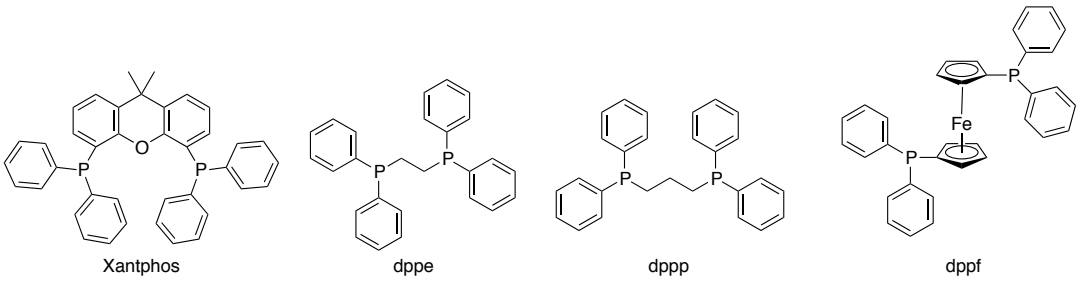
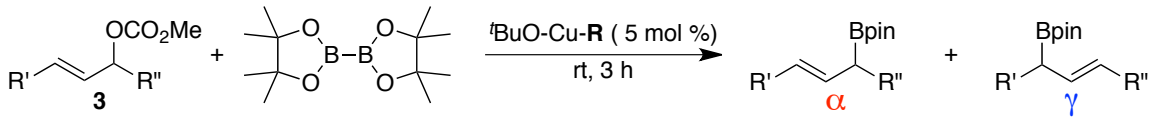


Figure 8. Chemical structures of L= Xantphos, dppe, dppp, and dppf bidentate phosphine ligands.[77]

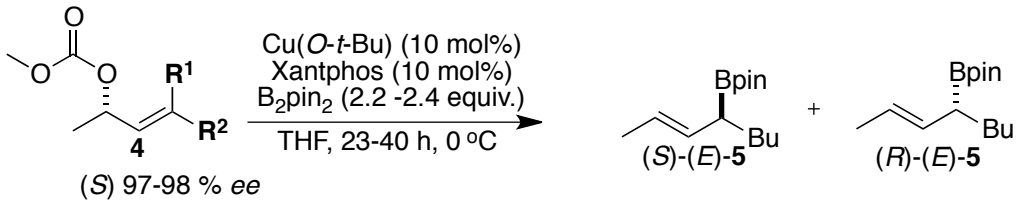
In fact, the optimal reaction conditions that offered the highest regioselectivity and yield used Cu(O-*t*-Bu)Xantphos as a pre-catalyst to yield allyl boronate products with an α : γ selectivity of 99 : 1, E/Z ratio of 97 : 3 and a yield of 100% (Figure 9).[77]



R	GC Yield (%)	Selectivity α:γ	Selectivity E/Z
Xantphos	100	99:1	97:3
Dppe	11	>99:1	62:38
Dppp	44	>99:1	97:3
Dppf	37	>99:1	96:4

Figure 9. Ligand Screen in the Borylation of Allylic Carbonates.[77]

The reaction is also applicable to enantioenriched carbamates and results in chiral, enantiomerically enriched allyl boronates.[77] Chirality transfer of the starting material is explained by an *anti*-attack of the borylcopper to the allyl carbonate in a conformation that avoids 1,3-allylic strain and target allylic boronates are obtained with *ee*'s greater than 96% (Figure 10).[77]



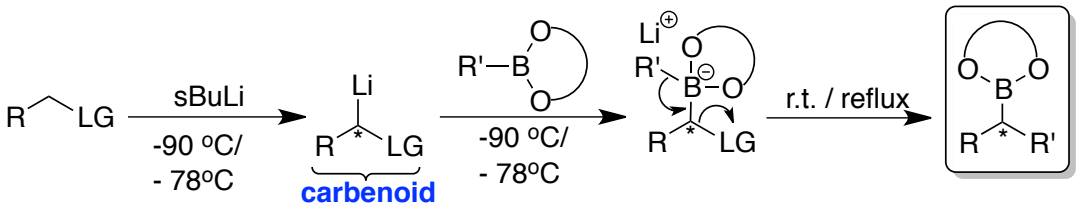
Starting Material	Product	α:γ	yield (%)	*E*:*Z*	*ee* (%)
R^1=H, R^2= Bu (*E*)	(*S*)-(*E*)-**5**	98:2	95	98:2	96
R^1=Bu, R^2= H (*Z*)	(*R*)-(*E*)-**5**	>99:1	88	>99:1	97

Figure 10. Enantiomerically-enriched, stereodivergent boronation.[77]

2.2 Homologation Reactions

In addition to metal-catalyzed methods for the enantioselective synthesis of allyl boronic esters, 1,2-metallate rearrangements of boronate-complexes can also be employed in the production of chiral organoboranes.[78, 79, 85, 88] Reactions such as these that extend the carbon count in a saturated molecule are classified as 'homologation reactions'.[80] Similarly, vinylic, linear boronic esters can be used in homologation reactions to synthesize the next higher analog, allylic boronic esters.[81]

In these 1,2-metallate rearrangements, (Scheme 12) a carbenoid (an organometallic reagent containing a suitable leaving group on the α carbon[82]) reacts with a primary boronic ester that is electrophilic at the trivalent boron atom. Following the 1,2-metallate rearrangement of the formed 'ate' complex, the carbon chain of the boronic ester is extended and secondary boronic esters are produced, often with high levels of stereocontrol under the use of an appropriate chiral auxiliary.



Scheme 12. General Homologation of Boronic Esters.

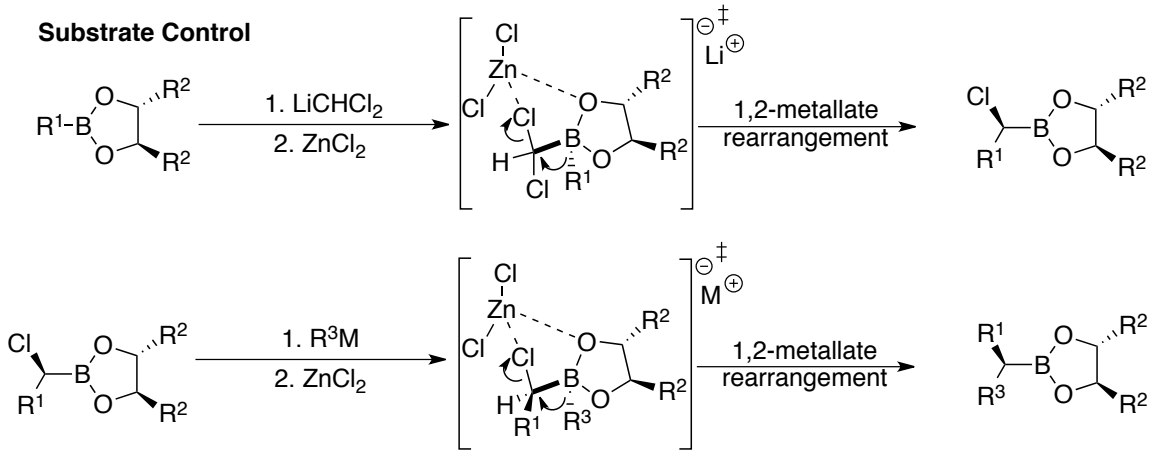
Stereocontrol in the above reaction can be highly successful by using chiral auxiliaries, as mentioned above. Chiral auxiliaries are employed either in the form of a chiral diamine ligand[82] or by use of a chiral boronic ester and Lewis acid.[85] Chiral diamine ligands assist in the enantioselective removal of either pro-*R* or pro-*S* protons in a thermodynamic or kinetic equilibrium, which has been investigated extensively by Beak[90] and Hoppe[94, 97, 98, 83, 84] and offer high utility in asymmetric homologation chemistry. Hoppe and Beak's chiral organolithium compounds have been extensively employed by the Aggarwal group over the past 7 years to produce chiral products with high levels of stereocontrol.[79,93] Alternatively, C_2-symmetric boronic esters may be employed, along with a coordinating achiral Lewis acid, to assist in a diastereoselective 1,2-metalate rearrangement that results in homologated products with high levels of stereocontrol (Matteson chemistry).[85] These two methods are key to the work in this thesis, and thus will be discussed in more detail below.

2.2.1 Homologations under Substrate Control- Matteson Chemistry

Enantioinduction in Matteson chemistry operates under substrate control arising from the use of stoichiometric amounts of enantiopure diol in the backbone of the boronic ester starting material. A zinc chloride-mediated homologation generates boronic esters with stereocenters at the carbon of the C-B bond (Scheme 13).[85]

The Matteson homologation reaction is a multi-step process that first involves the deprotonation of dicholoromethane, which then forms a complex with the boron electrophile, and is followed by a 1,2-metallate rearrangement to generate enantioenriched α-chloroboronic esters. In the next step, these stereodefined α-chloroboronic esters are reacted with a strong nucleophile such as an organolithium or a Grignard reagent. The carbon chain of the boronic ester is extended (Scheme 13) following a second, stereoinvertive, 1,2-metallate rearrangement in which the chloride is displaced.[85] Matteson chemistry produces secondary boronic esters with superb diastereomeric ratios (*dr*'s) generally exceeding 100:1.[85]

The stereoselectivity of the reaction is highly dependent on use of stoichiometric amounts of zinc chloride ($ZnCl_2$) acting as a Lewis acid. The Lewis acid plays a vital role in enantioinduction by assisting in the removal of one of two diastereotopic chlorine atoms of the $Cl_2HC\text{-}B(OR)_2$ functional group (Scheme 13) and scavenges LiCl which can racemize the product.[85] In contrast to a majority of asymmetric syntheses, the mechanism of Matteson chemistry does not involve enantioface selection. Rather, the proposed mechanism of Matteson chain extensions incorporates selective displacement of one of two diastereotopic halides (enantiotopic group selection). The stereochemistry of the iterative process is set at the first migration, since the stereocenter of the α-chloroboronic ester is inverted in the second 1,2-migration. The stereoselectivity of the reaction is orchestrated by placing the metal of the Lewis acid, Zn, in coordination to the least hindered oxygen that is located *trans* to the R^2 group of the ester in the dioxaborolane ring (Scheme 13). After binding to one of the two enantiotopic oxygen atoms, zinc chloride binds to one of the two diasterotopic chlorides and promotes cleavage of this C–Cl bond along with migration of R^1 (Scheme 13).[85]



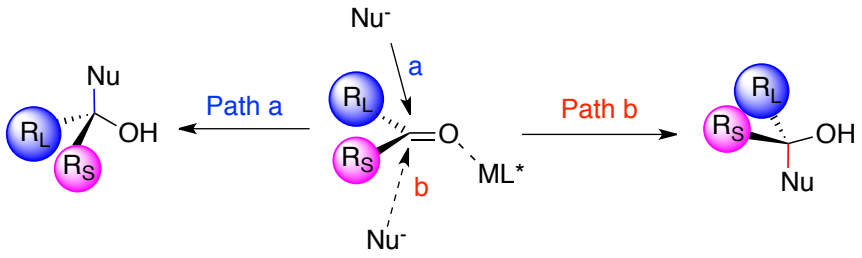
Scheme 13. Zinc chloride mediated Matteson homologations involve an iterative 1,2-metallate rearrangement to obtain enantioenriched boronic esters.

Although Matteson chemistry offers many advantages in that it has both a wide substrate scope and offers highly enantioenriched products, this homologation unfortunately suffers from some minor deficiencies. For instance, in some cases, inefficient migrations lead to *O*-migrations happening at the dioxaborolane ring instead of the expected *C*-migration.[78] As a result, a corresponding borinic ester is formed rather than the desired boronic ester. Matteson chemistry also reaches its limitation with respect to the synthesis of tertiary alcohols, where the levels of selectivity were far from reliable and the sense of enantio-induction was unforeseeable.[78] Additionally, a major disadvantage of Matteson chemistry that rendered the reaction an impediment to our studies, was the lack of geometric control with respect to the olefin (the E:Z ratio was low). Although, the reaction was expected to offer high *dr*'s in the homologated products, (>100:1) we did not pursue this method as a means to synthesize geometrically defined substrates due to the aforementioned rationale and we therefore sought another method to prepare both *stereo* and *regio* defined allylic boronic esters.

2.3 Lithiated Carbamates

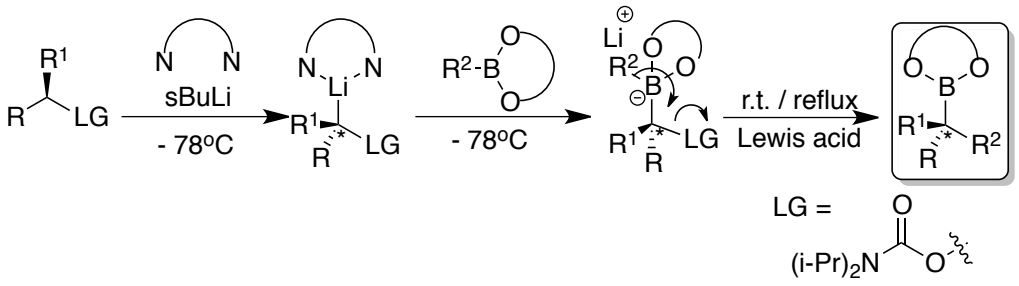
As opposed to substrate control used in Matteson chemistry, Aggarwal homologations operate under reagent control to synthesize enantioenriched products. Reagent control is powerful in asymmetric synthesis since enantioinduction is dependent on a chiral auxiliary.

Asymmetric Aggarwal homologations may employ either racemic or enantiopure carbamates as starting materials. To generate the formally sp^3-hybridized chiral carbenoid, a diamine base is used to deaggregate *s*-BuLi oligomers, making *s*-BuLi more reactive[86] and to deprotonate pro-chiral H_S or H_R protons. Similarly, enantiopure carbamates can be synthesized from the corresponding enantioenriched alcohols that are accessed *via* Noyori reduction of ketones or enzymatic resolution of racemic alcohols (Scheme 14).[87]



Scheme 14. Resolution of a Pro-chiral Ketone.[88]

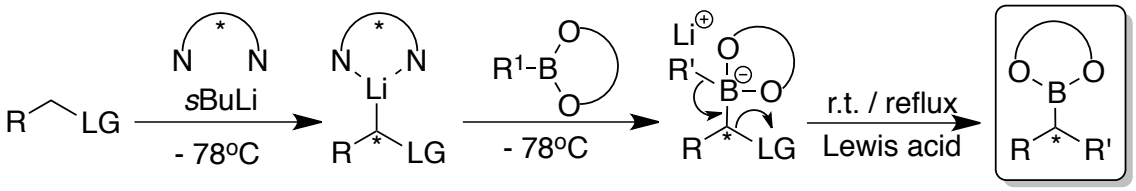
Once obtained, the enantiopure alcohol reacts with a carbomoyl chloride (usually *N,N*-diisopropyl carbamoyl chloride or *N,N*-diethyl carbamoyl chloride) to generate the enantiopure carbamate (Scheme 15). The enantiopure carbamate is subjected to the Aggarwal homologation product and a chiral diamine base is used to induce chirality in the product.



Scheme 15. Aggarwal lithiation-borylation of enantioenriched carbamates.

Deprotonation of the carbamate occurs through a two-step process that first involves the formation of a pre-lithiation complex that brings the reactive groups into proximity and is followed by a directed deprotonation.[89] This process has been termed the complex-induced proximity effect (CIPE).[89] The CIPE has been supported by kinetic studies in the deprotonation of C-H bonds neighboring amides, carbamates and ureas.[90]

Building on Hoppe[94, 97, 98, 91, 84], Beak[90] and Sneickus[92] contributions, the Aggarwal homologation employs a carbamate-directed CIPE.[92] Aggarwal homologations involve a three-step process with first the lithiation of a carbamate, borylation, followed by a Lewis acid-assisted 1,2-metallate rearrangement (Scheme 16).[79] The asymmetric deprotonation is directed by the presence of a chiral diamine base, such as (-)-sparteine and the subsequent borylations proceed by a 1,2-metalate rearrangement that leads to highly enantiomerically enriched products (*ee* >96%).[82]



Scheme 16. General Aggarwal homologation reaction involving lithiation of a prochiral substrate, borylative substitution, and a 1,2 Lewis acid assisted migration.

The enantioselectivity of the lithiation depends mainly on two factors: the configurational stability of the resulting lithium/carbanion pair and the stereodifferentiation in the abstraction of pro-(*R*) or pro-(*S*) protons.

Many factors contribute to the configurational stability of the asymmetric organolithium compound and include: solvent, temperature, the nature of the coordinating heteroatom (both inter and intramolecular coordination) and whether the anion generated is in conjugation with an extended π-system.[93]

Two types of resolutions are possible for the organolithium complexes generated by CIPE. In one resolution pathway, the lithiated diastereomeric complexes are configurationally stable, such as TMEDA-ligated, secondary, benzylic organolithium complexes[98] or TMEDA-ligated, alkyl organolithium complexes[98] at cold temperatures (-78 ^{o}C) and there is a large barrier to epimerization with respect to their reaction rates with electrophiles.[90] In this case, the enantioselectivity of the substitution reaction is directly proportional to the ratio of diastereomeric complexes that is established prior to the substitution step.[90] Thus, the enantiomeric ratio of substituted products is directly proportional to the ΔG between diastereomeric lithiated complexes.[90] This process of enantio-differentiation is termed *dynamic thermodynamic resolution* (DTR).[90] Processes operating under DTR benefit from a warm-cool protocol in which lithiation generally occurs at -78 ^{o}C, the reaction is then "warmed" to -25 ^{o}C to

allow a sampling of the free energy profile and to establish a thermodynamic equilibrium.[90] Warming of the reaction mixture is required to cause epimerization of the lithiated complexes.[84] The ratio of diastereomeric complexes attained in the "warm" cycle is preserved, as the reaction is cooled to temperatures suitable for electrophilic quench (-78 ^{o}C).[90]

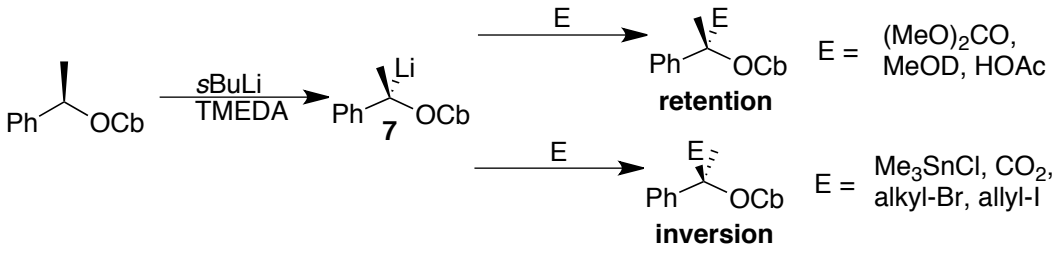
The second pathway for the generation of lithiated diastereomeric complexes involves configurationally labile organolithium reagents.[90] In this case, the diastereomeric complexes interconvert more quickly than the rate of reaction with the electrophile.[90] However, one epimer reacts more quickly with the electrophile, leading to an enantiomeric enrichment in the product. This described process of enantio-differentiation is termed a *dynamic kinetic resolution* (DKR).[90] The enantiomeric product ratio of a DKR is determined by the difference in diastereomeric transition-state energies for the reaction with the electrophiles ($\Delta G^{\neq}$).[90] Unlike DTR, enantioinduction in DKR processes do not experience enantioenrichment from a warm-cool sequence, instead maintenance of temperatures below -70 ^{o}C usually lead to increased *ee's*.

Enantiomeric excesses of products are dependent on reaction temperatures of substitution reactions. Optimization of *ee* in the product benefits from discernment of whether DKR *or* DTR is operative; as enantioenrichment in DTR processes usually improve from a warm-cool sequence.

2.3.1 Stereochemistry of Carbenoid Substitution

The stereochemistry of organolithium complex substitution is electrophile dependent and may occur with either retention or inversion. An experiment by Hoppe et al. conducted in the early 1990s, took enantioenriched, secondary, benzylic lithiated carbamates and quenched these reagents with a variety of electrophiles.[94] The stereochemical outcome of these experiments

varied depending on the electrophile used in the quenching step. An *N,N*-diisopropylcarbamate (synthesized from (*R*)-1-phenylethanol (97% ee)) was deprotonated with *sec*-butyllithium/TMEDA in hexane and was trapped with chlorotrimethylsilane.[94] The stereocenter of the lithiated (*R*)-1-phenylethyl *N,N*-diisopropylcarbamate was maintained with high integrity as the silane obtained from the quenching experiment was 96% enantioenriched, which indicated that at most 1% racemization occured.[94] Quenches of the (*R*)-benzylic lithiated carbamate with dimethylcarbonate, *n*-propylbromide, and chlorotrimethylstannane all gave products with retention of the stereocenter.[94] A carbon dioxide quench surprisingly occurred with inversion of the stereocenter, despite CO_2 normally adding with retention in most cases.[95] Protonation of the enantioenriched lithiated carbamate with methanol gives back the starting material with the (*R*) stereocenter intact; while interestingly, protonation with acetic acid proceeds with inversion of configuration (Scheme 17).[94]



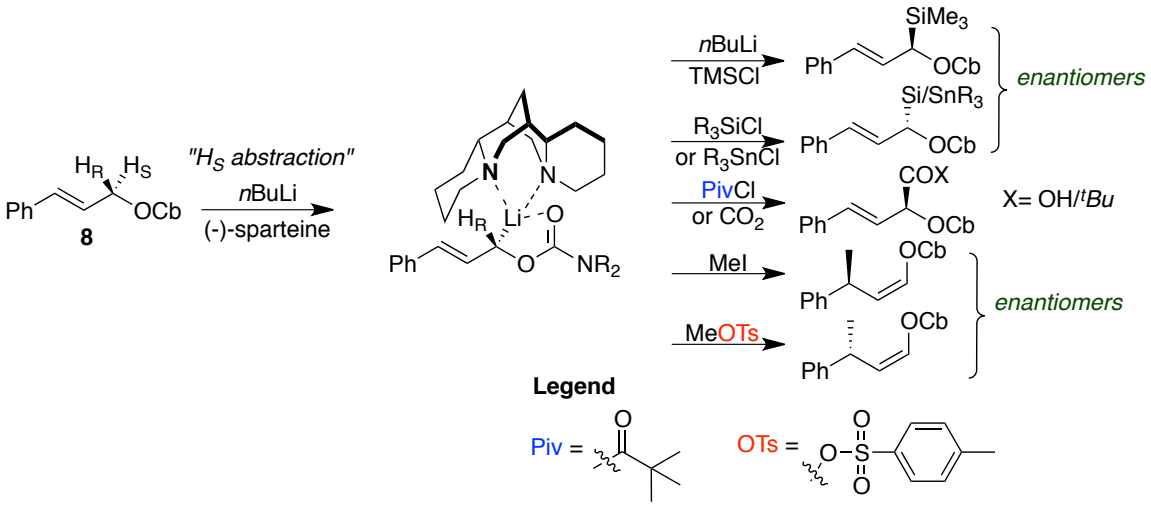
Scheme 17. Stereodivergent electrophilic substitution of configurationally stable, lithiated benzylic carbamate, 7.[96]

These results demonstrated that deprotonation of enantiopure benzylic carbamates with *s*-BuLi/TMEDA occurs with retention of stereochemistry.[97] Hoppe and co-workers have further demonstrated that both secondary, allylic and secondary, benzylic enantioenriched lithiated carbamates are configurationally stable at low temperatures (<-70^{o}C) when ligated with suitable

diamine bases such as TMEDA or (-)-sparteine.[97] The enantiospecific, electrophilic substitution of the aforementioned lithium complexes would operate under DTR and enantiomeric excesses of these substitutions are expected to increase when subjected to a warm-cool cycle (*vide supra*). On the contrary, primary benzyllithium complexes are configurationally labile and are subject to DKR at cryogenic temperatures (<-78 ^{o}C).[84] Enantiomeric excesses of DKR substitution products would be expected to be optimal at temperatures no greater than -70 ^{o}C (*vide supra*).

Hoppe has concluded that the carbanion of benzylic lithium complexes is not completely planar and thus has a considerable electron density at the rear face of the electron-lone pair that occupies the sp^3 orbital.[98] The approaching electrophile can attack antarafacially or suprafacially, however chelation of a bulky diamine base hinders the latter approach.[98] Electrophiles that prefer inversion (acyl chlorides, cyanides and stannyl chlorides) have energetically low-lying LUMOs, but do not possess groups able to chelate the lithium cation.[98] However, if the electrophile has a relatively higher LUMO and strong electron-donating ability, then retentive or suprafacial attack is generally preferred (as is the case for esters, alcohols, aliphatic aldehydes, ketone, boronic esters or alkyl halides).[98]

Similar to the benzylic systems described above, cinnamyl lithiated carbamates undergo electrophile dependent invertive or retentive substitution. For example, *s*-BuLi/(-)-sparteine is known to have a strong tendency to deprotonate the H_S proton of the prochiral crotyl carbamate (compound **8** in Scheme 18) which slowly epimerizes to the *R* complex, unless TMSCl is present. Silylation is thus said to occur with inversion of configuration, as does substitution with pivaloyl chloride and CO_2.[93] The site of regioselective substitution was also dependent on the electrophile. Reaction of the crotyl carbenoid with methyl tosylate proceeded retentively *via* an *syn*-S_E' mechanism and methyl iodide reacts invertively *via* an *anti*-S_E' mechanism (Scheme 18).



Scheme 18. Regio- and Stereo- Divergent Lithiation and Substitution of 8.[93]

The Hoffman test was conducted on the Li^+/(-)-sparteine ligated cinnamyl carbenoid and revealed that the compound was configurationally stable in non-polar solvents at low temperatures and a DTR was operative.[93] Thirty minutes were required to establish a thermodynamic equilibrium at -78 °C.[93] In a modified Hoffmann test, methyl iodide was employed as the electrophile and revealed that the minor diastereomer reacted more quickly.[93]

It should be noted that the above discussion provides a framework to rationalize observed configurations that have been experimentally characterized and by no means serves as a discrete guideline. Individual lithiation and substitution steps are subject to many factors; a wide variation of these factors is to be expected from one experiment to the next.

These observations from Hoppe and Beak among many others concerning chiral carbenoids, formed a fundamental foundation from which Aggarwal and co-workers would build their homologation chemistry program.

2.4 Aggarwal Homologation Reactions – From Theory to Utility

Aggarwal et al. have studied the stereochemistry of the electrophilic quench of secondary benzylic, lithiated carbamates.[88] As expected, enantiopure benzylic carbamates were deprotonated with retention of stereochemistry.[88] Interestingly, during the electrophilic quench, *retention* of stereochemistry was observed when boronic esters proceeded through a 1,2-metallate rearrangement.[88] In contrast, chiral, benzylic, organolithium reagents underwent *inversion* when 9-BBN boranes were employed.[88] The stereochemistry of the benzylic substitution reaction is explained by a chelation argument (Figure 11).

The stereocenter is retained during electrophilic substitution of chiral carbenoids by coordination of the oxygen atoms of the attacking boronic ester to the Li^+ cation on the suprafacial face of the substrate (Figure 11).[88] Alternately, the stereocenter is inverted when boranes are used as electrophiles, as there are no heteroatoms present to coordinate to the Li^+ cation. Additionally, the chiral diamine base (usually (-)-sparteine in the case of Aggarwal homologations) is proposed to block the suprafacial lobe of the formally sp^3 hybridized orbital, leaving antarafacial attack to be the predominant mode of stereoinvertive substitution.[88]

Contrary to the benzylic case, secondary, enantiopure, *alkyl* carbamates underwent retention of configuration when boranes and boronic esters were reacted during the borylation and 1,2-migration step, respectively (Figure 11).[88]

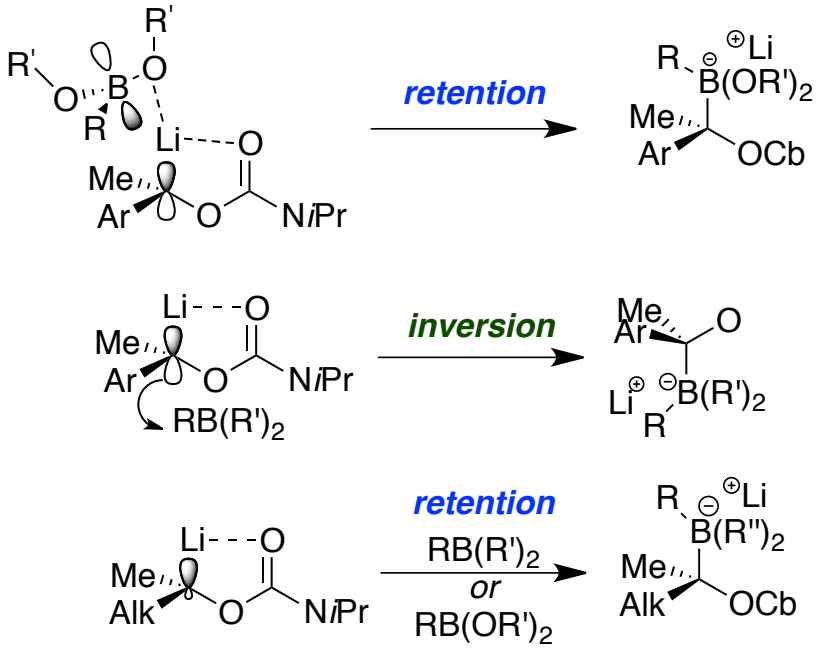


Figure 11. Explanation of stereoretentive/invertive borylation of benzylic lithiated carbamates for boronic esters ($RB(OR')_2$) and boranes ($RB(R')_2$), respectively. Borylation of lithiated alkyl carbamates occurs with retention for both boranes and boronic esters.[88]
Me = methyl, *i*Pr = isopropyl, Cb = *N,N*-diisopropylcarbamoyl, and Alk = Alkyl.

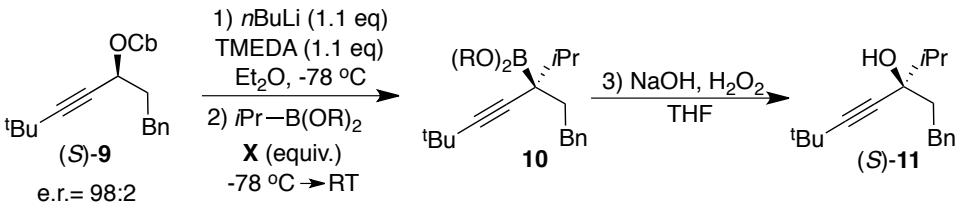
The degree of pyramidalization of the C_1 carbanion has a major influence on the stereochemical outcome of the reaction.[93] Alkyl carbamates that are sp^3–hybridized react with retention of stereochemistry, whereas slightly pyramidalized allyl carbanions interact with electrophiles antarafacially. If (-)-sparteine is exchanged for the less sterically demanding TMEDA, then electrophiles may coordinate the Lewis acidic Li^+ ion, in which case suprafacial attack is preferred.[93]

A direct challenge that faces the Aggarwal reaction involves the last step: the 1,2-metallate rearrangement, which often requires addition of super-stoichiometric amounts of Lewis acid ($MgBr_2 \cdot OEt_2$), refluxing temperatures and extended reaction times to realize homologated products. In a recent publication, Aggarwal et al. investigated benzoate esters as leaving groups in place of carbamates to increase the rate of the 1,2-migration.[82] Although this strategy proved

useful in Aggarwal's reports, it was not attempted in our case since the rate of 1,2-migration was not problematic.

In a recent publication, the Aggarwal lithiation-borylation strategy was extended to include sterically encumbered propargylic carbamates.[99] An enzymatic resolution provided access to enantiopure propargylic alcohols that were submitted to carbamoylation with *N,N*-diisopropylcarbamoyl chloride. The enantiopure carbmate was lithiated at -78 ^{o}C using *n*-BuLi as base and TMEDA as ligand (Figure 12). The lithiated carbamate was substituted with *i*PrBpin/*i*PrBneop/*i*PrBglycol esters, respectively to provide tertiary propargylic boronic esters upon 1,2-metalate rearrangement.[99] The enantiospecificity of the homologation reaction varied amongst pinacol, neopentyl glycol and ethylene glycol boronic esters and gave enantiomeric ratios of 50:50, 89:11 and 98:2.[99] These results indicate that the enantiospecificity (*es*) of the reaction was found to be highly dependent on the boronic ester diol, as the least sterically encumbered ethylene glycol diol offered the greatest stereofidelities in the homologation sequence when compared to other diols.[99]

One additional equivalent of neopentyl and ethylene glycol boronic esters were found to increase the enantiospecificity of the reaction (Figure 12). The additional equivalent of boronic ester is believed to drive the forward reaction of the 'ate' complex converted to 1,2-metallate-rearrangement product over the reverse reaction that involved the 'ate' complex converting back to the organolithium.[99] The reverse reaction is believed to contribute to the racemization of homologated product.[99] As observed, the least sterically encumbered boronic ester *i*PrBglycol carried the stereochemical information through the 1,2-metallate rearrangement most effectively, which lead the authors to investigate the homologation rates of forward and reverse reactions further using the "two electrophile test".



Diol[$(OR)_2$]	**X** (equiv.)	Product	yield (%)	e.r.	e.s. (%)
pinacol	2	10	55	51:49	2
pinacol	3	10	55	52:48	4
neopentyl	2	(*S*)-11	51	68:32	38
neopentyl	3	10	80	89:11	81
ethylene glycol	2	(*S*)-11	48	98:2	100

Figure 12. Effect of boronic ester diol on the lithiation-borylation sequence of propargyllic carbamates.[99]

The "two electrophile test" involves a 20-minute lithiation of the enantioenriched carbamate at -78 °C and is followed by an isothermal 1 h borylation.[99] The first electrophile, allyl bromide, was introduced at this time to determine if borylation was complete.[99] After 10 minutes the second electrophile, deuterated methanol (CD_3OD), was introduced to determine the rate of reversibility of the 'ate' complex reacting back to the lithiated species, with respect to the rate of the reaction of the 'ate' species to proceed forward through the 1,2-metallate rearrangement (Figure 12).[99]

After conducting the "two electrophile test", the authors observed no allylation product, which indicated that borylation was complete after 1 h. Instead, the authors observed deuterated allene product, indicating that the rate of the reverse reaction of 'ate' complex converting back to lithiated complex is faster than the rate of the 1,2-metallate rearrangement for the test substrate.[99]

The reaction tolerated a variety of carbamates and R' migrating functional groups with moderate yields and good enantiospecificities (Figure 13) making the Aggarwal reaction a suitable route for our own secondary boronic ester syntheses.

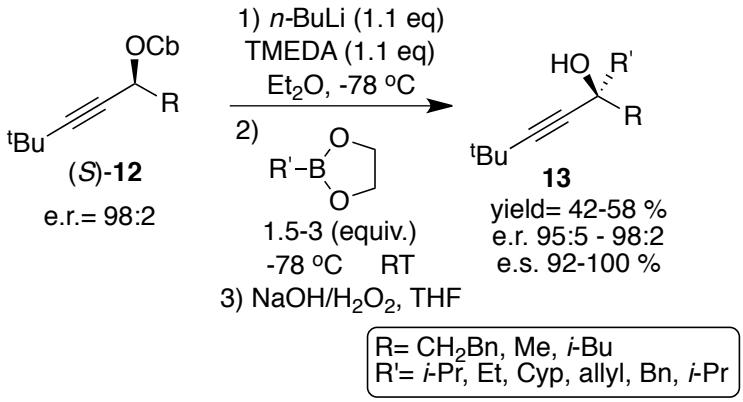


Figure 13. Substrate scope of lithiation–borylation of various substituted carbamates and ethylene glycol boronic esters.[99] Bn = benzyl, Cyp = cyclopropyl

The synthesized tertiary, stereodefined boronic esters were submitted to the cross-coupling conditions reported by our group in 2009.[100] Aggarwal et al. found that these boronic esters did indeed cross-couple with high γ selectivity, yielding quaternary allene products with high enantiospecificities (94-100 %).[99] In only a few instances was protodeboration observed as a side reaction in the Suzuki-Miyaura cross-coupling. The reaction proceeded with moderate to good yields in all examples reported (65-83%).[99] A one-pot synthesis starting from the stereodefined carbamate was used to synthesize stereodefined tertiary allenes. The TBAF-mediated protodeboration of tertiary propargyl boronic esters was developed in which pinacolate boronic esters were eliminated *via* a *syn*-S_E' mechanism to yield tri-substituted allenes with complete transfer of stereochemistry.[99]

An advantage of Aggarwal homologation chemistry is that enantioinduction occurs under reagent control. Despite the fact that no source or synthetic route for the enantiomer for (-)-sparteine is known, a molecule close to the geometry of "(+)-sparteine" (Figure 14) has been used to effect stereochemistry of the opposite handedness in these lithation-borylation reactions.[101]

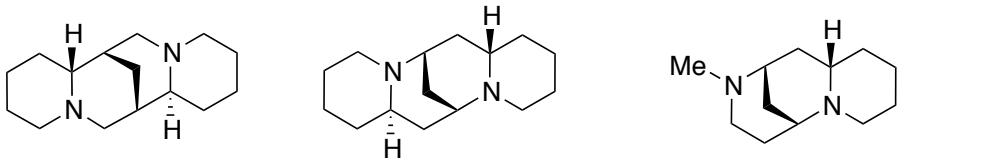


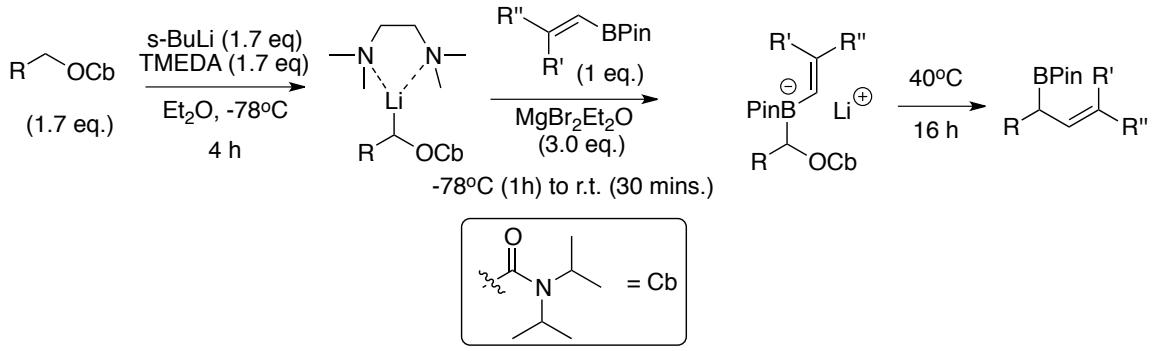
Figure 14. (-)-Sparteine and (+)-antipodes: (+)-sparteine and O'Brien's surrogate.

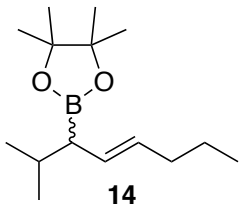
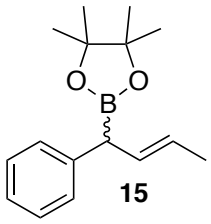
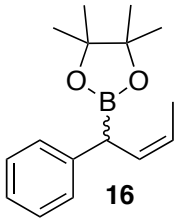
Although the preparation of O'Brien's (+)-sparteine surrogate involves a lengthy synthesis from (-)-cytisine precursor originating in *Laburnum anagyroides cytisus* seeds.[102] In a three-step process, 5.25 grams of (-)-cytisine is converted to 2.65 grams of pure O'Brien's (+)-sparteine surrogate, constituting an overall 61% yield.[103] The (+)-sparteine substitute can be accessed (through an indirect synthesis) and effects opposite stereochemistries to (-)-sparteine with slight erosions in *ee* observed.[101]

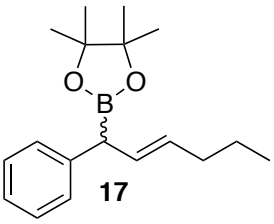
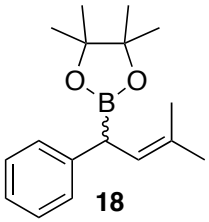
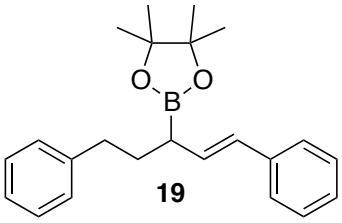
2.5 Results and Discussion of Allylic Boronate Synthesis

Aggarwal homologations were employed to make six racemic, allylic boronic esters (Table 1); asymmetric variants were applied to the synthesis of enantioenriched allylic boronic esters (Table 2). Sawamura chemistry was employed in the synthesis of a deuterated allylic boronic ester substrate (*vide infra*). The yields of the racemic, allylic boronic ester syntheses are detailed in the table below.

Table 1. Summary of Allylic Boronic Ester Synthesis.



Entry	Allylic Boronic Esters[a]	Isolated Yield (%)	E:Z[b]	Reaction Scale[c] (mmol)
1	 **14**	75	99:1	2.55
2	 **15**	35	99:1	1.19
3	 **16**	15	1:99	2.97

4	 **17**	81	99:1	2.04
5	 **18**	46	N/A	0.857
6	 **19**	82	86:14	2.17

*[a]Entry **1** synthesized by author (spectral characterizations included); entries **2-6** synthesized by co-author Dr. Kazem Ghozati. [b]E:Z ratios determined by GC-MS integrations of corresponding peaks in chromatogram. [c]Scale based on 1 equivalent of vinyl boronic ester used in the homologation.*

Our first attempt to synthesize compound **15** using Ito chemistry[70] resulted in decomposition of the boronic ester target. At the time, powdered K*t*-OBu was available and was used as base, resulting in decomposition of product. This result is contrasted to the synthesis used in the Ito publication that we were following[77] that used K*t*-OBu in THF.

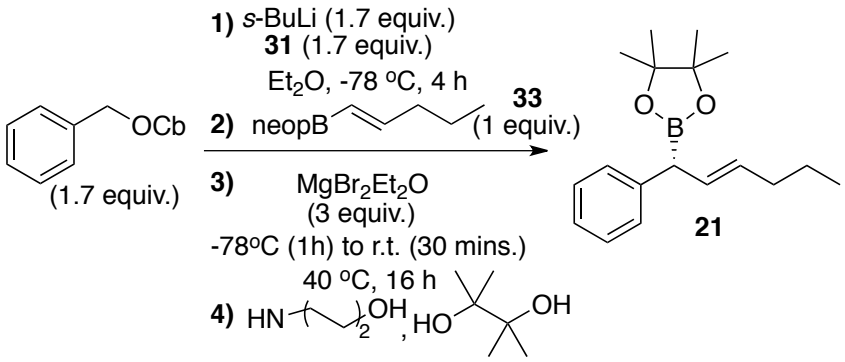
Allylic boronic esters were synthesized by Aggarwal homologation. We chose to synthesize allylic substrates *via* the Aggarwal homologation based on the broad range of scope, consistently high enantiomeric excesses and access to the allylic targets with definition of the olefin geometry, which ultimately could not be afforded *via* Matteson homologations. The homologation of vinyl boronic esters was not without challenges, as several key problems arose throughout the syntheses.

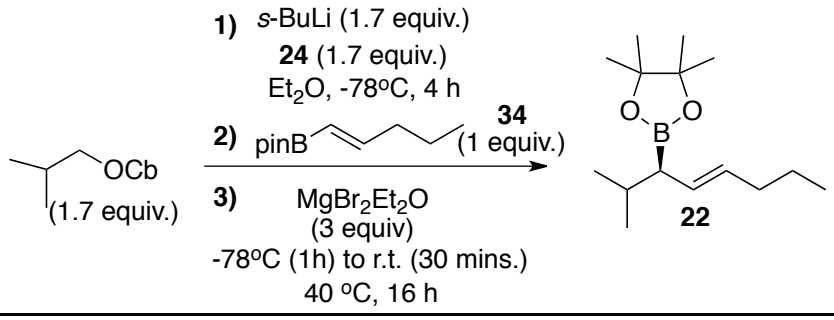
Of note, the vinyl boronic ester starting materials, were chromatographically inseparable from the allylic products and therefore, the reaction conditions had to be adjusted to consume all of the vinyl boronic ester. Initially, the reaction stoichiometry used in the homologation employed: 1.0 equivalent of carbamate, 1.2 equivalents of TMEDA, 1.2 equivalents of *s*-BuLi and 1.1 equivalent of vinyl boronic ester. The aforementioned conditions are those that had been initially optimized in the Aggarwal group and were recommended as a starting point for our allylic boronic ester synthesis. We employed these conditions for the synthesis of compound **14** in table **1** and it was discovered that incomplete consumption of vinyl boronic ester continuously plagued our column chromatography purification attempts. In order to deal with these difficulties, we increased the amounts of TMEDA, *s*-BuLi, and carbamate to 1.7 equivalents with respect to the 1.0 equivalent of boronic ester employed. Fortunately, this alteration in the homologation conditions resulted in complete consumption of the vinyl boronic ester and permitted efficient chromatographic purification of allylic, homologated boronic ester product without co-elution of the vinyl boronic ester. Upon further optimization, it was discovered that the combination of pentane (instead of hexanes) in a 9:1 ratio with ethyl acetate would effect separation of allyl boronic esters and its homologue chromatographically (when ≈1-20% vinyl boronic ester contaminated the sample). The slight polarity difference in pentane and hexanes arises from less London dispersion forces for the C5 hydrocarbon, resulting in a modestly lower polarity of pentane with respect to the polarity of hexanes. This minute polarity difference was enough to effect separation of target allylic, boronic esters from trace contaminating vinyl boronic ester starting materials. However, this alteration to the purification method was discovered subsequent to the synthesis of a majority of the allylic targets and was not employed for most compound isolations.

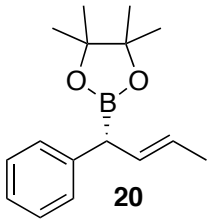
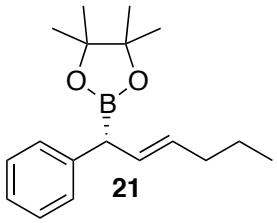
Racemic homologation reactions were run on 0.9-2.6 mmol reaction scale with respect to the vinyl boronic ester. Yields varied drastically from 15-82%. Migrating *trans* and *cis* propenyl groups of compounds **15** and **16** proved to offer significant challenges as entries **2** and **3** from table **1** were synthesized in low yields: 35% and 15%, respectively. Compounds **17**, **18**, and **19** were isolated in yields of 81, 46 and 82%, respectively. All boronic esters synthesized in high E:Z ratios exceeding 99:1 (Table 1).

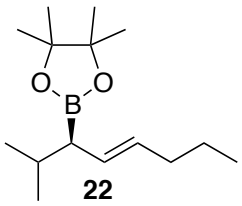
In addition, enantioenriched boronic esters were synthesized using a similar procedure, with one variation. A chiral diamine base, either (-)-sparteine (**24)** or a C_2-symmetric bisoxazoline ligand (**28)** was used for chiral induction purposes in place of TMEDA (Table 2).

Table 2. Asymmetric Allylic Boronic Ester Synthesis.



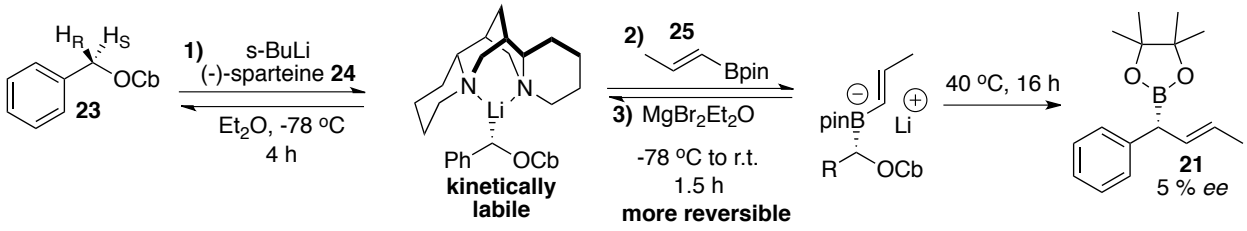


Entry	Allylic Boronic Esters	Yield (%)[a]	E:Z[b]	Diamine Base	Enantiomeric Excess (%)[c]
1	 **20**	35	99:1	**24**	5
2	 **21**	95	99:1	**31**	96

3	 **22**	57	99:1	**24**	92

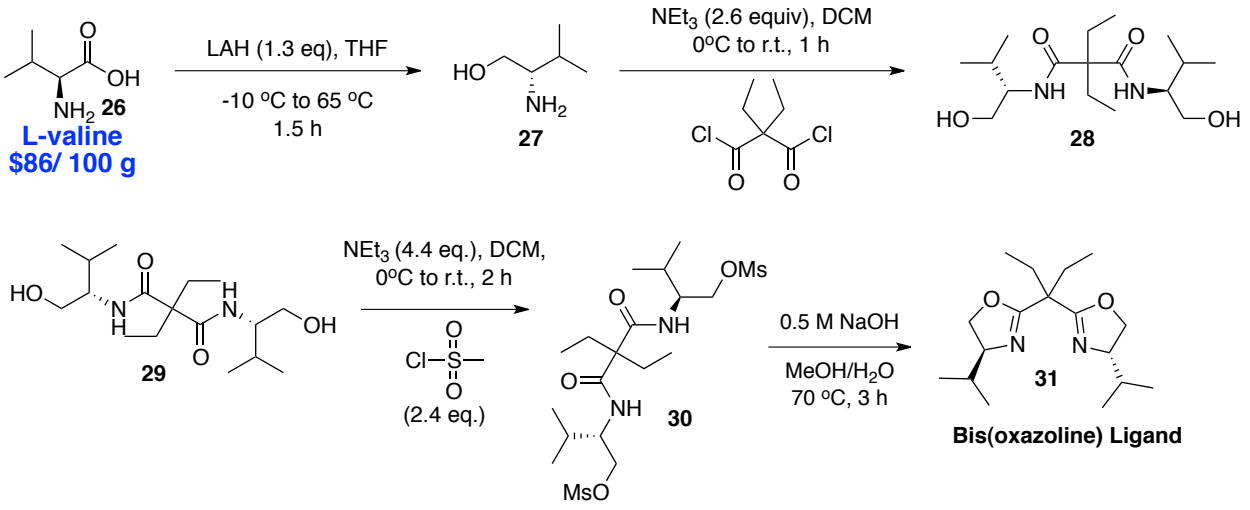
[a]Isolated yield. Based on 1 equivalent of vinyl boronic ester used in homologation reaction. [b]Determined by GC-MS integration. [c]Determined by chiral SFC/ HPLC chromatography.[104]

For the synthesis of compound **20** in entry **1** of table 2, we again employed Aggarwal homologation conditions, using (-)-sparteine as the diamine and the corresponding vinyl, pinacolate boronic ester as starting material.[99] The homologation reaction was run on a 2.38 mmol scale and provided the product in a 25% yield. The secondary allylic boronic ester was oxidized and the enantiomeric excess of the corresponding alcohol was measured to be only 5%, which was of little use in our asymmetric cross-coupling enantiospecificity measurements. The fact that the rest of the mass balance was observed as unreacted starting material suggested that the reverse reaction of the 'ate' complex back to the primary organolithium was favored and possibly may have contributed to the erosion of *ee* observed in the product (Scheme 19). We, therefore, expanded our search for a base suitable to induce high enantiomeric excesses in the homologated product.



Scheme 19. (-)-Sparteine ligand-facilitated, enantioselective synthesis of 21 in 5% *enantiomeric excess*.

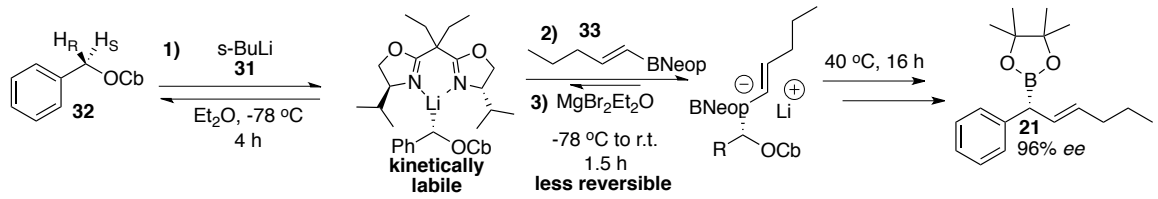
Literature on the use of bisoxazolines in asymmetric lithiation chemistry offered insight into exploring the possibility of these ligands as diamine bases.[105, 106] Bisoxazoline ligands have been employed in a variety of metal-catalyzed, asymmetric reactions.[105] The bisoxazoline ligand (**31**) we used was synthesized *via* a multi-step procedure (Scheme 20) and afforded the desired ligand in good yield.



Scheme 20. Bisoxazoline ligand synthesis.

The synthesis of **31** began with the reduction of L-valine, followed by condensation with a diethyl malonyl dichloride. The resulting dihydroxy diamide was activated with mesyl chloride and then cyclized by treatment with base to afford the C_2-symmetric bisoxazoline ligand (**31**).[105]

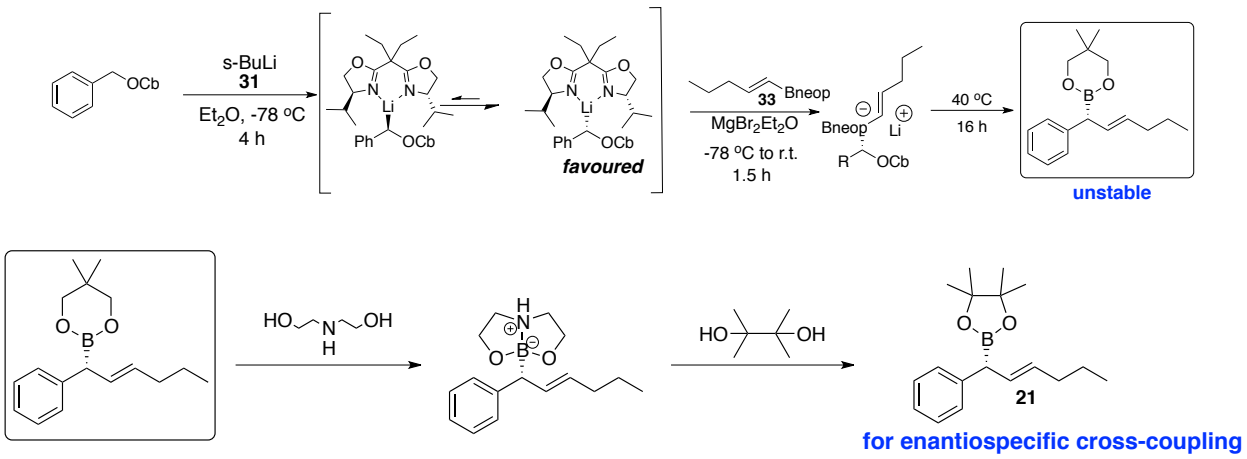
The bisoxazoline ligand was used in the homologation to generate compound **21**, entry **2** of table 2 replacing (-)-sparteine. Additionally, vinyl neopentylate boronic esters were also used in place of pinacol and this resulted in a much-improved 98:2 *er* (Scheme 21).



Scheme 21. Bisoxazoline ligand-facilitated, enantioselective synthesis of 21 with 96% *ee*.

A comparison of the results from compound **20** and **21** of table 2 reveals that three major reaction conditions were altered. First, (-)-sparteine (**24**) was exchanged for the bisoxazoline diamine base (**31**). Also, the pinacolate ester, **25** (Bpin is bound to a *trans*-pentenyl hydrocarbon) was exchanged for the neopentylate boronic ester, **33** (Bpin is bound to a *trans*-propenyl hydrocarbon). As shown in Scheme 19 low selectivity with pinacol boronate **25** was attributed to reversibility in the formation of the 'ate' complex upon borylation of a (-)-sparteine-bound, lithiated, benzylic carbamate with sterically demanding pinacolate boronic esters. In order to alleviate steric bulk at the borate complex and favor the 1,2-rearrangement, neopentylate ester **33** and the bisoxazoline ligand **31** were employed. As shown in Scheme 21, this strategy was successful and the resulting allylic boronic ester (**21**) was prepared in high enantioselectivity (98:2). Our observation saw that a decrease of sterics in the vinyl, boronic ester resulted in increases in enantioinduction in allylic boronic ester product. This was in accord with the enantiospecificities measured during Aggarwal, propargylic boronic ester synthesis, whereby increased enantioenrichment in homologated product was observed when reacting less sterically hindered boronic esters (*vide supra*).[99] Additionally, use of **31** in place of **24** is also attributed to playing a major role in altering the high enantioinduction that was observed for compound **21**, as use of the less sterically hindered bisoxazoline resulted in a less reversible 'ate' complex

formation and an increase in enantioinduction. Use of **24** resulted in a more reversible 'ate' complex formation and a decrease in *ee*. The obtained neopentylate boronic esters were prone to oxidative degradation and had to be transesterified to pinacolate boronic ester **21** in order to isolate this chiral compound with the ester intact (Scheme 22).



Scheme 22. Synthesis of enantioenriched (*R*)-21.

Treatment of the neopentylate crude with 1.58 equivalents of diethanolamine resulted in the precipitation of a salt. The salt was filtered and treated with 10 equivalents of 1M HCl generating the boronic acid *insitu*, which was then reacted with 5 equivalents of pinacol. The pinacol boronic ester (compound **21,** entry **2,** table 2) was isolated in 22 % yield from the neopentylate crude reaction mixture.

We hypothesize that the enantio-inducing process of compound **21** is a result of a DKR with abstraction of the pro-chiral benzylic proton favoring H_S substitution, followed by subsequent stereoretentive, suprafacial attack of the vinyl boronic ester; this observation is supported by the current literature.[88] DKR is postulated to be operative, since primary, benzyllithium, diamine-ligated carbamates are configurationally labile.[84] Also, the *ee* of the

product was presumed to erode (in theory) with an increase of temperature greater than -70 ^{o}C. The (*R*) stereochemistry of the product (obtained by abstract of the pro-(*S*) proton) is also supported by observations from both Hoppe and Aggarwal. Abstraction of H_S proton (Scheme 21) is generally favored in chiral auxiliary-assisted CIPE lithiation of benzylic carbamates;[84] and attack of boronic esters to benzyllithium carbamates generally precedes suprafacially.[88] In concert, these two propositions explain the observed (*R*) stereochemistry of homologated product of compound **21**.

Primary, benzylic organolithium complexes are configurationally labile and epimers are expected to where rapidly interconvert; a DKR is expected to be operational in this case. The stability of organolithium complexes (or lack thereof) is contrasted between primary benzylic organolithiums and alkyl organolithium complexes. (-)-Sparteine-ligated, *alkyl* organolithiums are configurationally labile and a DKR is expected to be operational.

The enantiospecific synthesis of compound **22** of table 2 involved the synthesis of the configurationally stable alkyl lithium complexes. Since the organolithium complex is configurationally stable, (does not rapidly epimerize with respect to its rate of reaction with the electrophile) the borylation step is expected to proceed under DTR. Compound **22** was isolated in 57% yield, with a 92% *ee*, and an *E:Z* ratio of 99:1.

In conclusion, novel, secondary, allylic boronic esters have been made by way of Aggarwal homologation[65,67,78,79,88,99,101] in varying yield. These compounds were submitted to the Suzuki-Miyaura cross-coupling reaction to study their regioselectivity and stereospecificity (Chapter 3). Their synthesis was not without challenge as purification of allylic boronates from their vinyl homologues required optimization. Additionally, asymmetric lithiation-borylation reactions of benzylic carbamates proved a difficult task that was well suited for bisoxazoline

asymmetric induction. Reversible 'ate' complex conversion back to the labile, primary, benzylic organolithium was assumed to contribute to the racemization of asymmetric borylation-lithiation reactions. The forward reaction of 'ate' complex to undergo 1,2-migration to product was successfully promoted by using a less sterically hindered neopentylate boronic ester in place of the more bulky pinacolate ester. Additionally, switch of the diamine base from (-)-sparteine to the L-valine derived-bisoxazoline ligand also contributed to the forward reaction to 1,2-migration product affording enantioenriched, benzylic-allylic boronic ester **21** in 96% *ee*. Neopentylate boronic esters had to be converted to pinacolate esters *via* the diethanolamine zwitterionic salt, since the former are unstable and are prone to oxidation to the alcohol. The conversion of the neopentylate boronic ester to the corresponding pinacolate, proceeded through a multi-step process (Scheme 22).

Asymmetric lithiation of alkyl carbamates proved to be less difficult as these organolithium compounds are configurationally stable.[93] Both (-)-sparteine (**24**) and pinacolate boronic ester **34** were employed in the asymmetric synthesis of **22** with 92% *ee*.

Chapter 3: Secondary Suzuki-Miyaura Cross-Couplings

3.0 Introduction

The cross-coupling of enantioenriched, secondary boronic esters is a significant advance in the Suzuki-Miyaura reaction as chiral C-C bonds are created. Our interest in developing conditions to cross-couple enantioenriched boronic esters was influenced by our group's asymmetric hydroboration work (discussed in Chapter 2).[155, 156] Silver oxide mediated cross-couplings were reported by our group and have effectively generated the unique class of compounds: 1,1-diarylethane products in high yield and enantiospecificity (Equation 5 in Chapter 2).[125] Enantioenriched 1,1-diaryl substituted compounds are difficult to make by other means, and therefore this reaction constituted a significant advance. In fact, at the time of this publication, no method for cross-coupling chiral, secondary boronic esters had been established (with the exception of cyclopropyl derivatives[121]). Additionally, the Suzuki-Miyaura cross-coupling of allylic, secondary nucleophiles has provided new avenues to C-C substituted allylic targets.[135] The goal of the research presented herein, was to employ the synthesized allylic boron nucleophiles (Chapter 2) as coupling partners in the Suzuki-Miyaura reaction in both racemic and asymmetric cases. Our ultimate goal in this exercise was to not only demonstrate additional examples of allylic boronates as suitable coupling partners, but also to gain a greater perspective on mechanistic properties of this reaction. The following chapter will discuss the expanding repertoire of secondary electrophiles and nucleophiles in the Suzuki-Miyaura cross-coupling reaction; selections of asymmetric variants are also discussed.

3.1 Recent Advancements in Stereospecific Suzuki-Miyaura Cross-Couplings

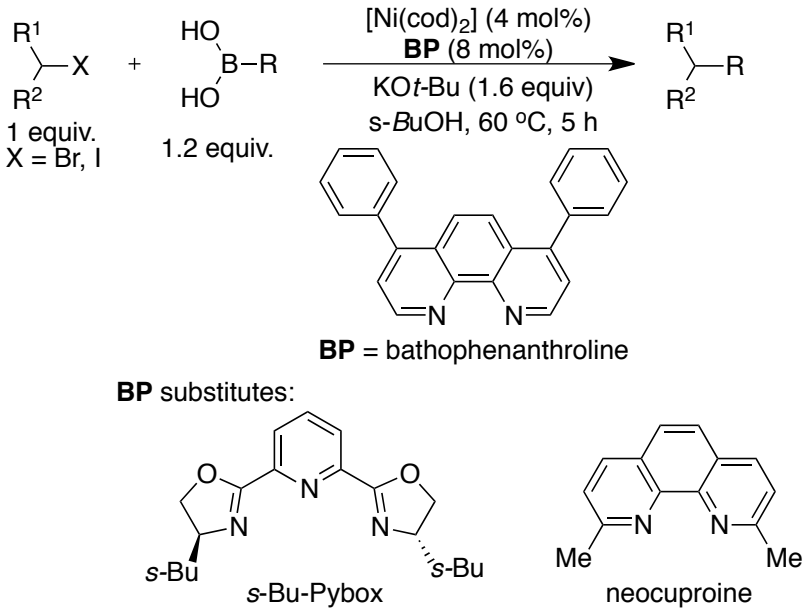
It would be an oversight not to mention the considerable contributions of Fu,[110, 111, 114, 107109] Jarvo[116], Watson[118], Molander[123, 130], Gevorgyan[121], Hall[134], Aggarwal[129], Suginome[131,133] and Crudden[125, 135] in the field of secondary Suzuki-Miyaura cross-couplings. Secondary couplings constitute a difficult class of C-C bond forming reactions since they are usually plagued by rate-determining transmetalations and β-hydride eliminations. Additives such as silver oxide are included in the reaction mixture to increase the rate of transmetalation.[125] Additionally, the increase of sterics around the metal center adds to the difficulty in cross-coupling secondary substrates.

3.1.1: Cross-Coupling Secondary and Tertiary Electrophiles- Fu Chemistry

The work of Gregory Fu et al. has addressed several key limitations to the Suzuki-Miyaura cross-coupling reaction. Accomplishments from the Fu lab include the successful coupling of both difficult classes of substrates, namely secondary and tertiary electrophiles (C-X) and secondary nucleophiles (C-B) of C-sp^3 hybridization. Key to the success of these reactions has been using optimal ligand/metal combinations to effect these difficult transformations, thereby minimizing undesirable by-products.

In 2004, Fu reported the first successful Suzuki-Miyaura cross-coupling of unactivated secondary alkyl bromides and iodides with aryl boronic acids.[107] An optimal metal-base combination of 4 mol% $Ni(cod)_2$/8 mol% bathophenanthroline provided the desired cross-coupling product at an outstanding yield of 91%.[107] At the time, the nickel/bathophenanthroline combination was the only metal/catalyst combination reported to achieve catalytic turnover to cross-coupling product.[109] Employing the correct source of metal precatalyst was found to be

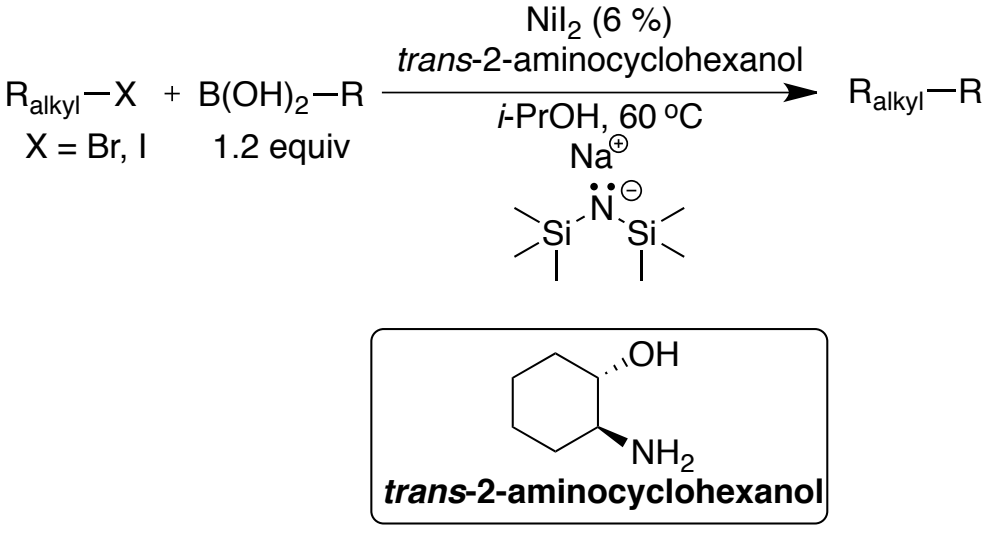
absolutely critical to the cross-coupling reaction as $Ni(acac)_2$ and $NiBr_2$ provided product in low yields (24% and <2%, respectively). Equally critical to the success of the reaction was correct choice of ligand since $P(t\text{-}Bu)_2Me$, *s*-Bu-Pybox, the 2/9-substituted phenanthroline neocuproine and even the classic PPh_3 ligand (in place of bathophenanthroline, BP) failed to provide cross-coupling product in yields greater than 3 % (Equation 7). Both aryl and primary, alkenyl boronic acids successfully cross-coupled to secondary electrophiles in good to moderate yield. One shortcoming of the developed conditions was that primary and tertiary alkyl bromides, chlorides, boronic acids and *ortho*-substituted aryl boronic acids did not react well under the reaction conditions.[108] The reaction also displayed a weak functional group tolerance.[109]



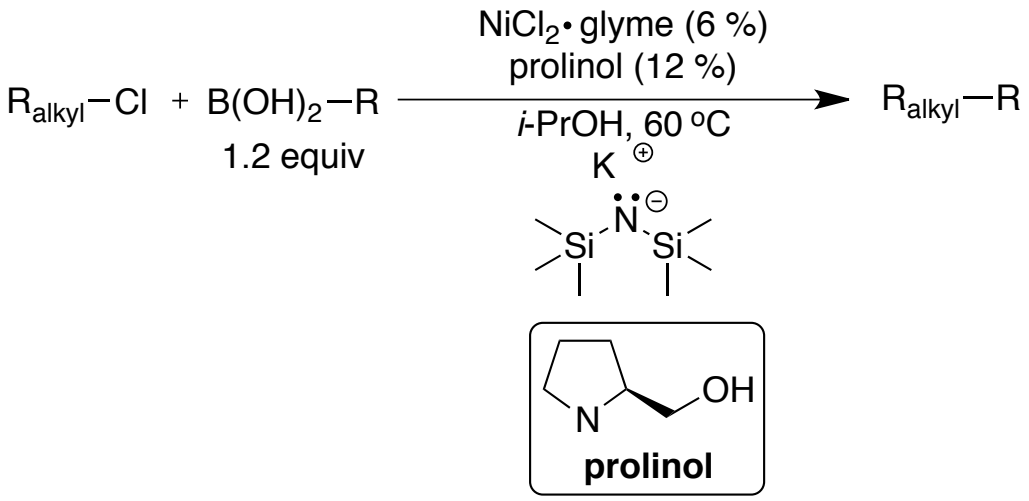
Equation 7. Fu's 2004 Suzuki-Miyaura cross-coupling of cyclic and acyclic secondary organoborates.[107] R = aryl/vinyl functional groups.

To address the shortcomings of the conditions published in 2004, González-Bobes and Fu reported conditions[109] that could cross-couple both primary and secondary unactivated alkyl bromides and chlorides in good to excellent yield. *Ortho*-substituted boronic acids also cross-

coupled with high efficiency. Readily accessible amino alcohols were used as ligands and were found to successfully facilitate the cross-coupling reaction with considerably improved scope.[109] The limitations of the 2004 publication were addressed by the newly developed conditions that successfully facilitated the cross-coupling of both secondary and primary bromides, chlorides, and iodides.[109] The reaction offers major advantages, as both ligand and Ni precatalyst are commercially available.[109] Both cyclic and acyclic alkyl chlorides and arylboronic acids functionalized with both electron-rich and electron-donating groups, are compatible cross-coupling partners.[109] *Ortho*-substituted aryl boronic acids were cross-coupled effectively, however, electron-rich aryl boronic acids underwent a competitive protodeboronation reaction; in order to minimize this challenging side-reaction, 2 equivalents of boronic ester were required.[109] These reaction conditions constituted the first example of Suzuki-Miyaura cross-coupling of unactivated secondary alkyl chlorides.[108]

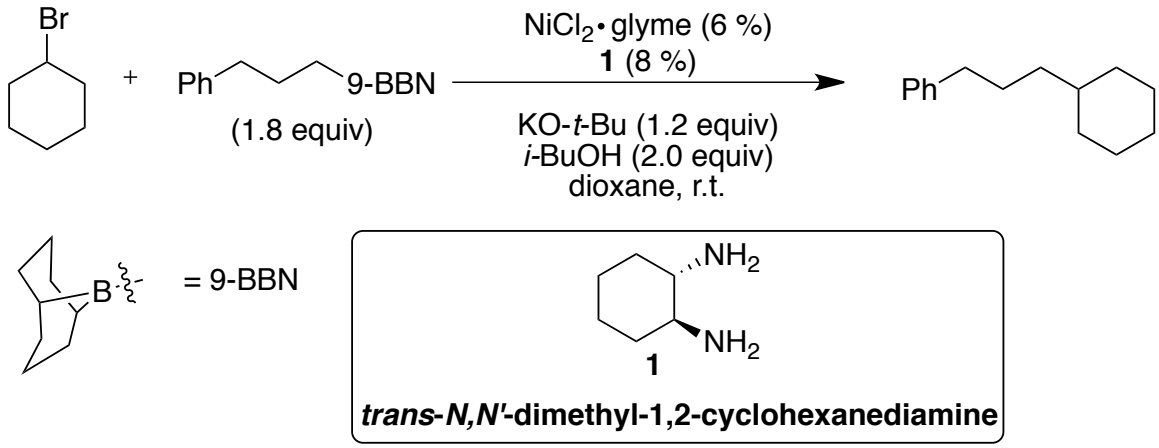


Scheme 23. González-Bobes and Fu reported conditions that cross-couple both primary and secondary, cyclic and acyclic unactivated alkyl bromides and iodides in good to excellent yield.[109] R = aryl.



Scheme 24. González-Bobes and Fu reported conditions that cross-couple cyclic and acyclic, unactivated alkyl chlorides in good to excellent yield.[109] R = aryl.

The boundaries of the Suzuki-Miyaura reaction were further expanded with a 2007 publication that described the first alkyl-alkyl cross-coupling (Equation 8).[110] Prior to this publication, conditions to cross-couple alkyl-vinyl[107] and alkyl-aryl[109] bonds were reported. Key to the success of this cross-coupling was employing the right ligand/metal catalyst combination that was also observed in the 2004 $Ni(cod)_2$/bathophenanthroline system.[107] The combination of trans-*N,N*-dimethyl-1,2-cyclohexanediamine and $NiCl_2$.glyme as catalyst furnished the alkyl-alkyl cross-coupling product in good yield (>80% in most reported cases).[110] Additionally, mild reaction conditions have been reported for this cross-coupling as bromocyclohexane and alkyl-9-BBN boranes coupled in good yield at *room temperature*.[110] A wide range of alkyl-alkyl bonds are accessed through the reported coupling conditions with cyclic, bicyclic as well as acyclic alkyl bromides coupling effectively with primary alkyl-9-BBN boranes.[110] The alkoxide forming, KO*t*-Bu/*i*-BuOH combination was found to activate the organoborane reagent to form the corresponding 'ate' complex quantitatively, which was confirmed by ^{11}B NMR.[110]



Equation 8. Saito and Fu's 2007 cross-coupling of unactivated secondary, cyclic and acyclic secondary alkyl bromides.[110]

With further advancements made in the coupling of molecules at sp^3 hybridized carbon centers, the Fu group was able to complement this work by reporting conditions to generate asymmetric centers.

In 2008, the first, asymmetric, alkyl-alkyl Suzuki-Miyaura cross-coupling of unactivated, secondary alkyl bromides to primary alkyl-9-BBN compounds was reported.[111] A major factor leading to the success of this cross-coupling was the optimization of reaction conditions. Altering the ligand and nickel source from the "standard" conditions (Equation 8) impacted both the enantiomeric excess and the yield. The optimal combination in this respect was found to be 10 mol% $Ni(cod)_2$ and 12 mol% (*R,R)*-1with the reaction proceeding in diisopropylether (*i*-Pr_2O) at 5 ^oC.[111] A base alcohol combination of 1.2 equivalents of KO*t*-Bu and 2.0 equivalents of *i*-BuOH was used to form the corresponding alkoxide-bound alkyl-9-BBN 'ate' complex, and thereby promoting the boron reagent to transmetalate.[111] The Suzuki-Miyaura cross-couplings reported constituted the first example of unactivated electrophiles that react below room

temperature.[111] In all cases, variously substituted homobenzylic bromides and alkyl-9-BBN are cross-coupled in a range of yields (68-86%) and enantiomeric excesses (70-94%) (Figure 15).[111]

The requirement of the electrophile to be homobenzylic is of major significance to the enantiomeric excess of the reaction. It was reasoned that the chiral Ni/(*R,R*-**1**) complex differentiates between $PhCH_2$ and alkyl groups in the key stereodefining step; to obtain good *ee*, it is necessary to have the aromatic ring in the correct, homobenzylic position with respect the bromide (site of oxidative addition).[111]

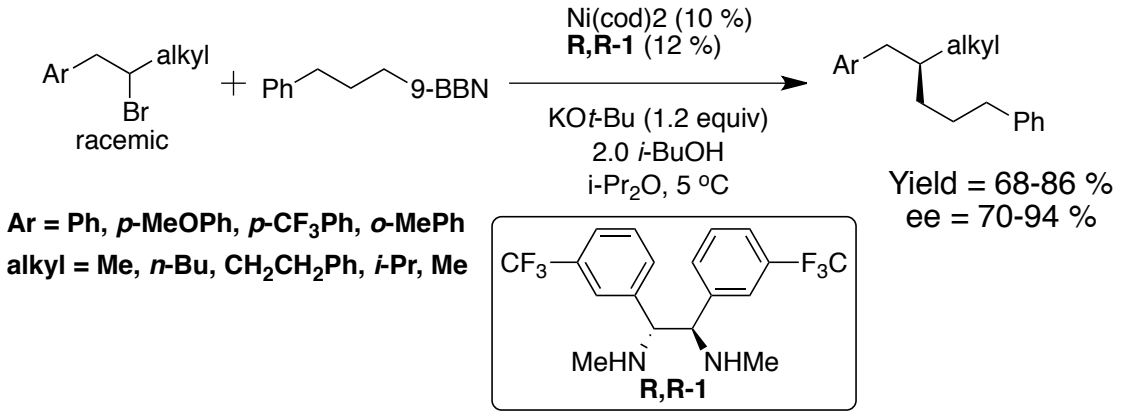


Figure 15. Saito and Fu conditions to cross-couple racemic secondary alkyl bromides to primary alkyl-9-BBN stereoconvergently.[111]

This 2008 report was followed up by several others describing the enantioselective γ and δ alkylation of carbonyl containing compounds (Figure 16).[112]

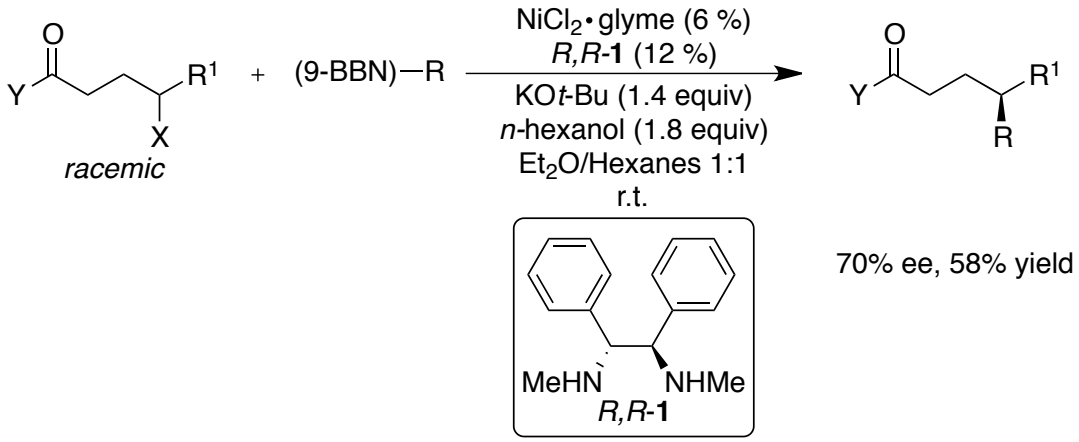
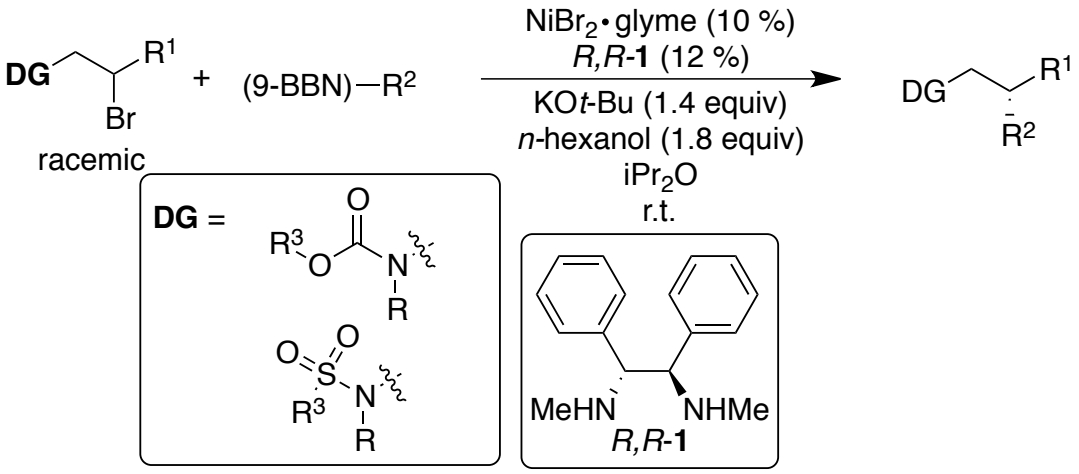


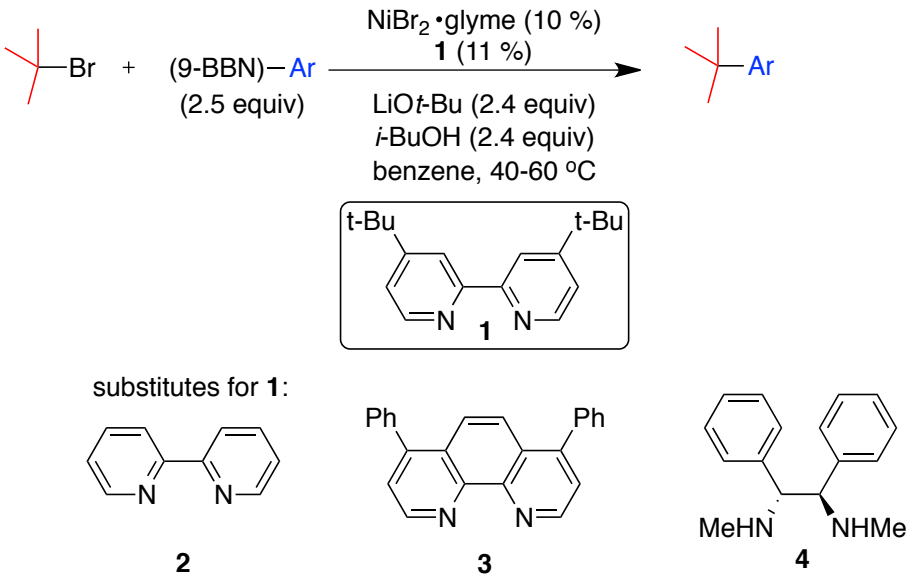
Figure 16. Stereoconvergent Suzuki-Miyaura cross-coupling of functionalized secondary alkyl bromides.[112]

Fu has also described the use of directing groups[113] to increase the enantioselectivity of cross-coupling unactivated, secondary, alkyl bromides from the 70% enantiomeric excess achieved without the use of directing groups (Figure 16).[111] Two forms of protected amines: carbamates and sulfonamides served as directing groups (DG). These directing groups increase the *ee* of the product by ligating the substrate to the Ni catalyst through a two-point interaction, thereby decreasing the conformational degrees of freedom of the substrate (Equation 9).[113]



Equation 9. Stereoconvergent Suzuki-Miyaura cross-coupling of β functionalized, racemic secondary alkyl bromides.[113]

Most recently (at the time of publication of this thesis) Fu has disclosed perhaps his most impressive advancement to Suzuki-Miyaura cross-coupling to date: the coupling of tertiary electrophiles with aryl-9-BBN nucleophiles to generate all carbon quaternary centers.[114] Analogous to the conditions reported for cross-coupling primary and secondary electrophiles, the conditions to cross-couple tertiary electrophiles are very specific. Key to the success of the cross-coupling conditions were employing the correct combination of metal, ligand, base, solvent et cetera (Equation 10).[114]



Equation 10. Suzuki-Miyaura cross-coupling of Tertiary Electrophile with Aryl Organoboranes.[114]

The choice of diamine is critical as use of diamines **2** and **3** in place of **1** lead to decreased yields of 72% and 63%; the reaction has a yield of 88% when coupling 1-methyl-1-bromocyclohexane with Ph-9-BBN and employing **1** as the ligand.[114] Even more critical is the role of the Li^+ counterion, as replacement with K^+ or Na^+ is completely deleterious to the yield offering yields less than 2% in both cases.[114] A limitation to the reaction conditions is that *para* and *ortho* substituents are not tolerated in the aryl-(9-BBN) nucleophile. Substitution in the *meta* position of the aryl-9-BBN coupling partner is important, however, since *meta* functionalization cannot be accessed through use of Friedel-Crafts alkylation.[114]

The future prospects for Suzuki-Miyaura reaction of challenging electrophiles lies in the coupling of tertiary alkyl halides to secondary and tertiary alkyl boranes, as methods to accomplish this racemically and asymmetrically have eluded the cross-coupling community up until this point in time.

3.1.2 Stereospecific Cross-Coupling of Enantioenriched Electrophiles

Based on the seminal work of Kuwano[115 a,b,c], Jarvo et al. have recently reported the enantiospecific, Ni-catalyzed cross-coupling of benzylic pivalates and carbamates to aryl and heteroaryl boronic esters.[116] The use of carbamates as leaving groups boded well for the stereochemical outcome of this cross-coupling reaction, offering enantiospecificities greater than 97% in most reported cases.[116] The reaction proceeded with either inversion or retention depending on the ligand. When SIMes was employed as a ligand, *inversion* of stereochemistry was observed, while use of PCy_3 led to *retention* of configuration.[116]

The reaction benefits from addition of three equivalents of *n*-BuOH as the yields of the cross-coupling reactions were maximized at 88% and enantiospecificities greater than 99% were observed (Figure 17).[116] The cross-coupling is moisture sensitive as addition of 3 equivalents of water to the reaction conditions led to decreases in enantiospecificities (10 %).[116]

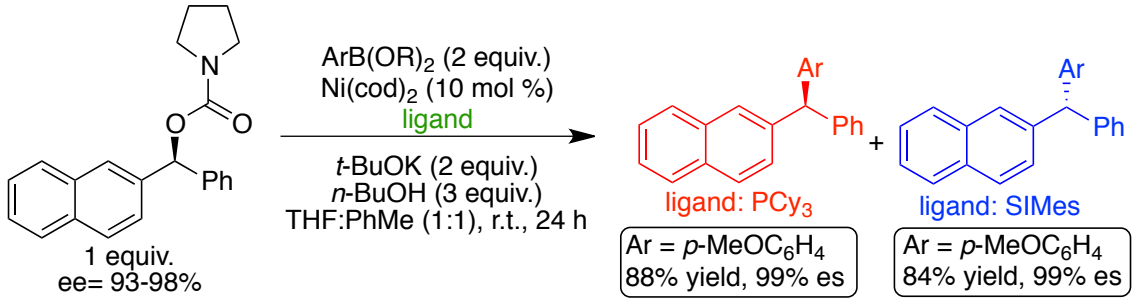


Figure 17. Stereospecific Suzuki-Miyaura cross-coupling of stereodefined electrophiles with retention or inversion.[116]

The Jarvo conditions offer a route to access the triarylmethanes, which are common pharmacophores that are difficult to prepare enantioselectively.[116] Another advantage to these reaction conditions is that either enantiomer of the cross-coupling product can be readily attained

from a single enantiomer of starting material by use of either phosphine or *N*-heterocyclic carbene as ligand.[116]

Jarvo et al. recently incorporated methyl groups in Negishi couplings with high levels of stereocontrol to generate tertiary, benzylic centers, which are common motifs found in medicinal compounds (Figure 18).[117] Traceless directing groups (DGs that leave during the course of the reaction) were employed to promote the cross-couplings of otherwise unreactive substrates. As such, thioether ligands were found to be the most effective at activating stereodefined electrophiles to maximize both the yield (up to 98%) and *es* (>99%) of the cross-coupling reaction.[117] This methodology was efficiently applied in the total synthesis of a fatty acid hydrolase inhibitor-FAAH (87% yield, 92% *ee*, 97% *es*) and a retinoic acid receptor agonist (92% yield, 90% *ee* and 97% *es*).[117]

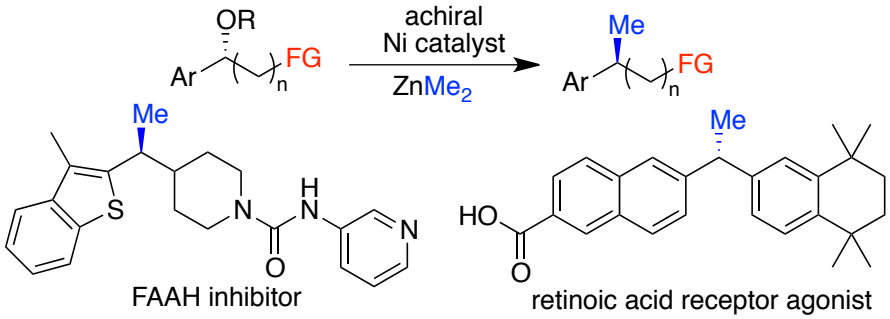


Figure 18. Nickel-catalyzed, enantioselective cross-coupling to construct tertiary, methyl-bearing benzylic stereocenters.[117]

In an extremely similar coupling, Watson reported the stereospecific, high yielding cross-coupling of benzylic pivalates with arylboroxines in the presence of a simple Ni(0) precatalyst.[118] Products of the cross-couplings are the pharmaceutically relevant enantioenriched triarylmethanes and diarylalkylmethanes, respectively.[116] The solubility of base was crucial to

both yield and enantiospecificity of the reaction. NaOMe was uniquely effective facilitating both a high yield (98%) and a high degree of stereofidelity (97%, *S*) (Figure 19). The identity of the cation was critical to the reaction as LiOMe led to 0 % yield (the authors reasoned that this base was not soluble in the reaction mixture and could not effect the coupling) and KOMe gave only moderate yields (74 %) and *ee*'s (69 *S* %) in the coupling product.

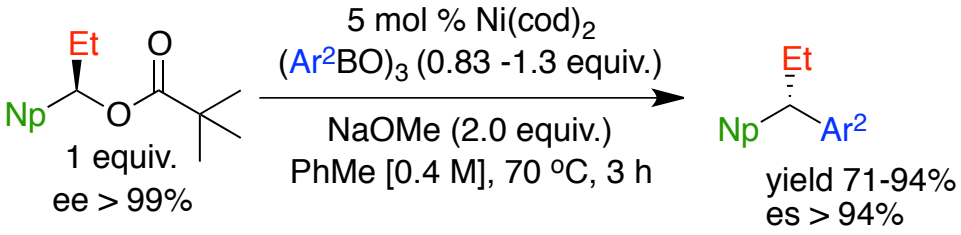


Figure 19. Enantiospecific Suzuki-Miyaura Cross-Coupling of Enantioenriched Pivalates.[116]

Boroxines cross-coupled more effectively than boronic acids, offering optimal increases in both yield and chirality transfer. In the best-reported case, boronic acids coupled at 100 °C with 99% yield and 93% *ee* (*S*), whereas boroxines required lower temperatures (70 °C) to cross-couple in 98% yield, offering an improvement in enantiospecificity with a 97% *ee* (*S*). Similar to Jarvo's couplings, Watson had proposed that since boroxines coupled more effectively than boronic acids, that water could be detrimental to the reaction. Sure enough, addition of 1 equivalent of water confirmed this suspicion, as this the yield decreased from 98% to 59% although, addition of 1 equivalent of water only slightly eroded the enantiomeric excess from 97% (*S*) to 94% (*S*).[116]

Watson et al. have recently reported highly efficient, Ni-catalyzed methods to make both diarylmethanes in a broad substrate scope and diarylethanes with excellent chirality transfer (Figure 20).[119] Chiral, benzylic ammonium salts are cross-coupled to aryl boronic acids a net *inversion* of configuration.[119] Inversion of the stereocenter is postulated to arise from an invertive oxidative addition proceeded by retentive transmetalation and reductive elimination steps.[119]

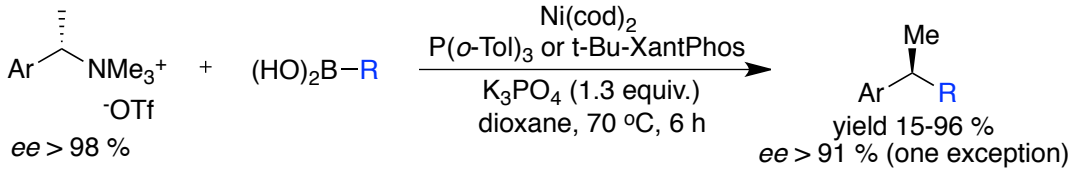
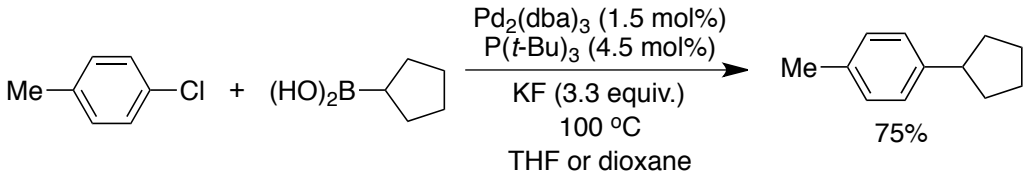


Figure 20. Nickel-catalyzed cross-coupling of chiral benzylic ammonium salts.[119]

3.1.3: Cross-Coupling Secondary and Tertiary Nucleophiles

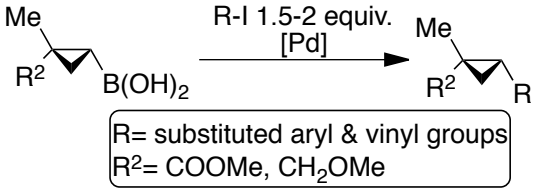
Conditions to attain Suzuki-Miyaura cross-coupling of secondary boronic esters have been developed by the Fu[120], Gevorgyan[121], Molander[123], van den Hoogdenband[124], Aggarwal[129], Suginome[131, 133] and Crudden[125, 135] research groups.

In 2000, Fu reported the sp^2-sp^3 cross-coupling of aryl chlorides with alkyl boronic acids, and in this publication, one example of the coupling of cyclopentyl boronic acid was reported (facilitated by a Pd catalyst, P(*t*-Bu)$_3$ and KF).[120] The reaction required elevated temperatures (100 ^{o}C) to effect the coupling of the secondary organometallic; in juxtaposition: *aryl* boronic acids couple to aryl bromides at room temperature under $Pd_2(dba)_3$/P(*t*-Bu)$_3$ catalysis.[120] Any *β*-hydride elimination event is rendered invisible in as the cyclopentyl ring of the boronic acids is symmetrical and thus, an addition/elimination sequence was unobservable (Equation 11).



Equation 11. Suzuki-Miyaura Cross-Couplings of Unactivated Aryl Chlorides.[120]

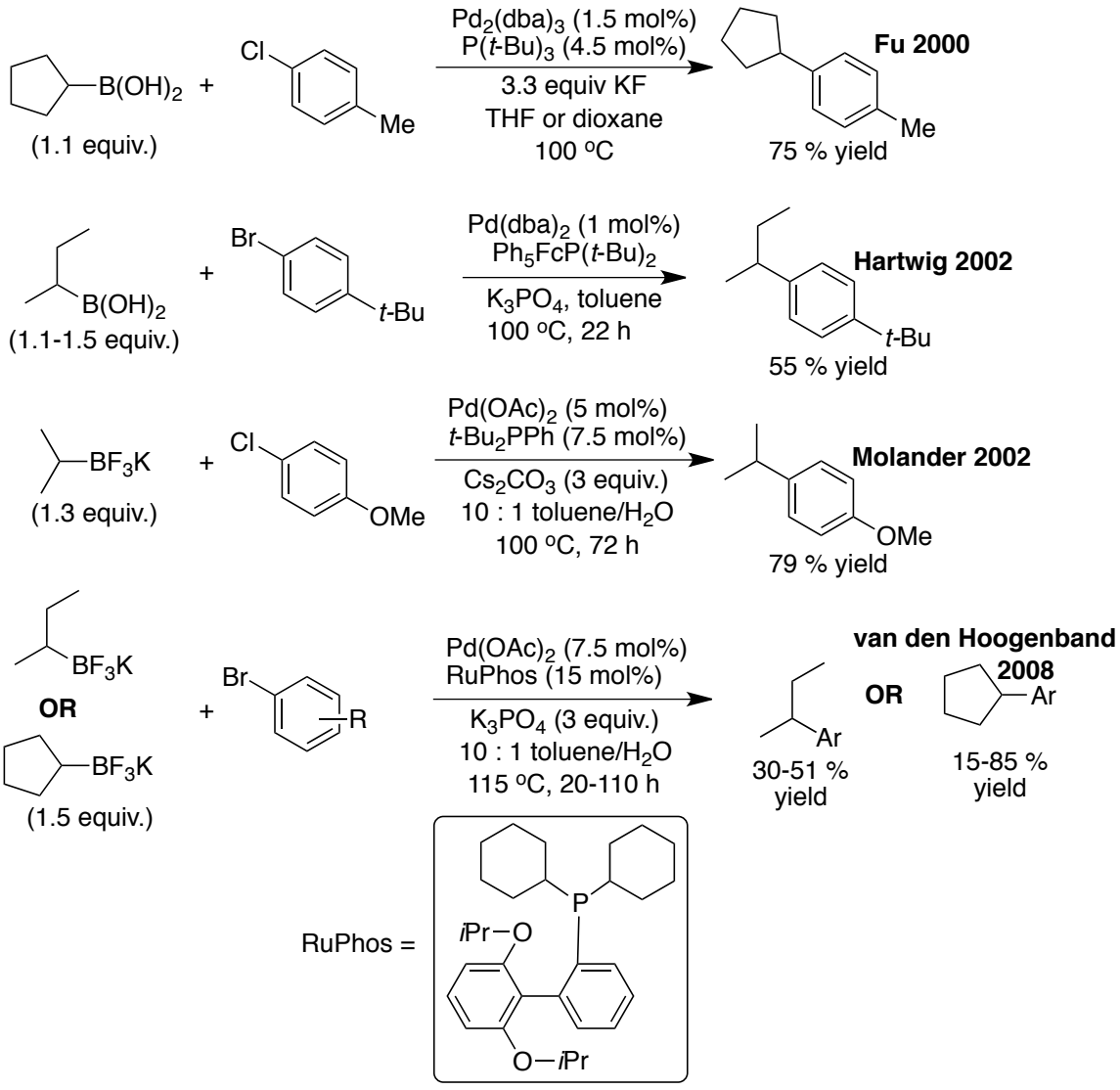
Gevorgyan et al. contributed to the pool of asymmetric Suzuki-Miyaura cross-coupling by demonstrating the utility of stereodefined cyclopropyl boronic acids as coupling partners.[121] He reacted stereodefined cyclopropylboronic acids with vinyl and aryl iodides effectively to produce optically active tri-substituted cyclopropanes (Equation 12).[121] Cyclopropyl species are privileged systems to investigate in cross-coupling since the carbon framework of the cycle imparts a sp^2-hybridization on the exocyclic C-B bond. Furthermore, β-hydride elimination is highly disfavoured due to the limited degrees of conformational freedom associated with the cyclopropyl ring and due to the high amount of ring strain of a cyclopropenyl moiety. Enantiospecific cross-coupling of stereodefined cyclopropyl boronic acids showed that stereochemical information in the C-B bond was carried through the C-C bond forming event.[121]



Equation 12. Suzuki-Miyaura Cross-Coupling of optically active, trisubstituted cyclopropyl boronic acids.[121]

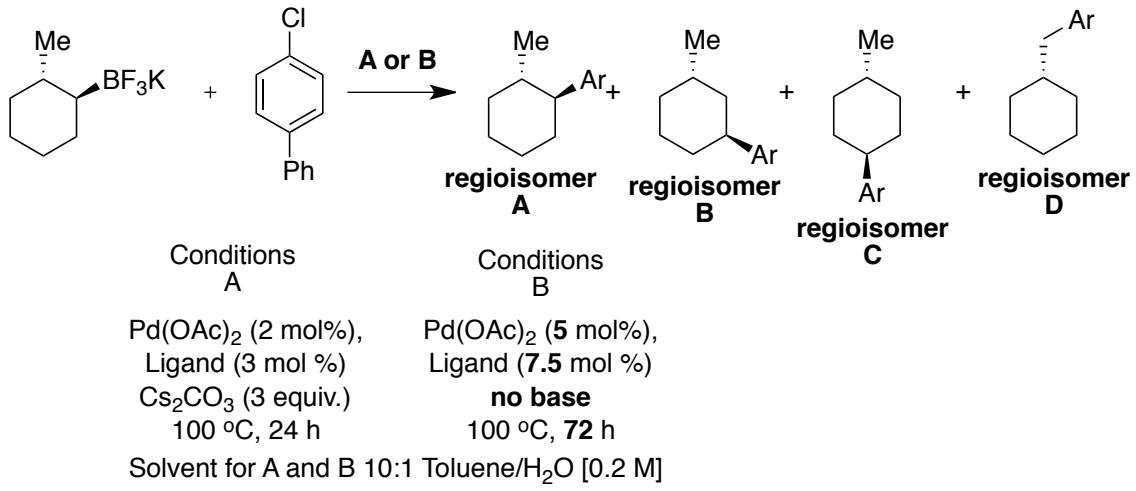
A major advance in the cross-coupling of secondary organoboranes came in 2008 with Molander's conditions to cross-couple secondary boronic acids and trifluoroborates.[123] The

coupling of secondary organometallics constitutes a significant feat in cross-coupling as this class of nucleophile is prone to both β-hydride elimination and protodeboronation, as mentioned above.[123] Trifluoroborates were employed successfully as coupling partners as this class of compound has been demonstrated to undergo transmetalation with limited protodeboronation side reactions (Scheme 25).[123]



Scheme 25. Suzuki-Miyaura cross-coupling of secondary boronic acids. Fu,[120] Hartwig,[122] Molander,[123] and van den Hoogenband[124]

Microscale parallel experimentation was used to discover catalyst systems capable of coupling electronically demanding aryl chlorides.[123] Substantial amounts of β-hydride shifts were observed in unsymmetrical, cyclohexyl trifluoroborate couplings.[123] The β-hydride elimination/addition sequence added and eliminated on the same face of the enantioenriched organoboron and generated ligand-dependent distributions of 4 isomeric products (Figure 21).[123]



		Regioisomer				
Ligand	Conditions	A	B	C	D	% isolated yield
n-BuPAd$_2$	A	4.4	1.0	2.0	1.4	80
t-Bu$_3$P	B	16.0	1.0	1.0	6.0	48
PhP*t*-Bu$_2$	B	27.7	1.6	1.0	8.1	72

Figure 21. Cross-Coupling of Potassium *trans*-2-Methylcyclohexyltrifluoroborate with 2-Chlorobiphenyl.[123]

Simultaneously, van den Hoogenband et al. also affected the cross-coupling of challenging secondary substrates.[124] As is often observed in the coupling of secondary organoboronates, slow transmetalations and reductive eliminations result in the β-hydride pathway to become competitive with the desired reaction outcome. Several components of the

reaction conditions were examined: including the change of both cross-coupling solvent from MeOH to toluene/water 10:1 and change of base from K_2CO_3 to K_3PO_4, which gave the cross-coupling product in a low yield (16%). The observation of cyclopentene in the reaction crude led the authors to conclude that *β*-hydride elimination was the major pathway leading to undesirable by-products. The solvent was changed to xylene/water 10:1 and no improvement was observed. Additionally, change of base from K_3PO_4 to Cs_2CO_3 proved to be deleterious to the desired outcome.

To minimize the *β*-hydride elimination side-reaction, the van den Hoogenband group found that the more sterically bulky ligand, RuPhos instead of SPhos was more effective.[124] To demonstrate the utility of their newfound conditions, a variety of aryl and heteroaryl bromides were coupled to both potassium cyclopentyltrifluoroborate salts and *sec*-butyl potassium trifluoroborate salts in low to moderately good yields (15-85%). Drawbacks of the reported conditions included extended reaction times (20 to 110 h in some reported cases) and elevated temperatures of 115 ^{o}C. Of significant importance, isomerization of the *sec*-butyl trifluoroborate nucleophile to *n*-butyl was not observed, thereby demonstrating that the *β*-hydride elimination/addition pathway had been reduced by use of the bulky, electron-rich phosphine, RuPhos.[124]

In 2009, our group reported the first example of the coupling of benzylic, secondary boronic esters with complete retention of stereochemistry, which was the first example of acyclic, enantioenriched boronic esters cross-coupling with nearly complete stereofidelity and little sign of *β*-hydride elimination.[125] Several additives were found to be key to the success of the stereoretentive cross-coupling. Silver (I) oxide was essential for catalytic turnover to cross-coupling product, which was reasoned to assist in the difficult transmetalation[125] and to scavenge

iodide.[126] Both electron-donating and electron-withdrawing aryliodides cross-coupled with moderate to good yields from 48-86% and stereoretentions were found to be >90% in all reported cases (with the exception of one). Interestingly, the related linear boronic ester was completely unreactive under these conditions.[125] The reaction was reported to be completely immune from β-hydride elimination, however a 1:8 palladium to phosphine ratio was required to completely shutdown this side-reaction (Figure 22).

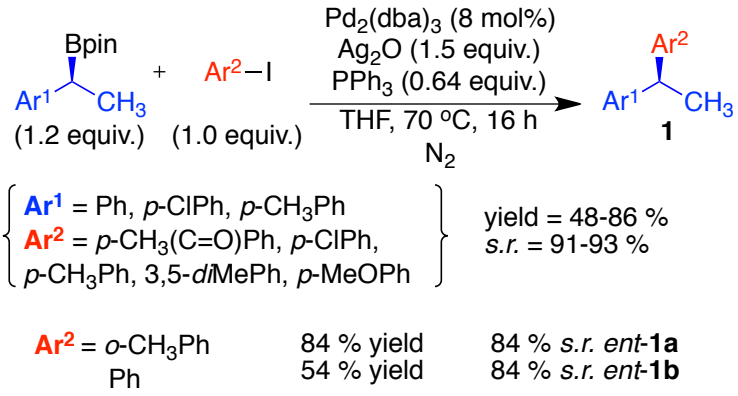


Figure 22. Stereoretentive Suzuki-Miyaura cross-coupling of secondary boronic esters.[125]

A later discovery by our group, demonstrated that addition of K_2CO_3 to the reaction conditions would increase the stereofidelity of coupling enantioenriched, secondary boronic esters, although this may have to do with scavenging water in the system.[127] Dr. Kazem Ghozati, a post-doctoral researcher in our group, has studied the impact of base on the enantiospecificity of the reaction. He found that when cross-coupling *p*-iodoacetophenone to the secondary benzylic, boronic ester, base had no significant impact on the stereofidelity of the cross-coupling (Figure 23).[128]

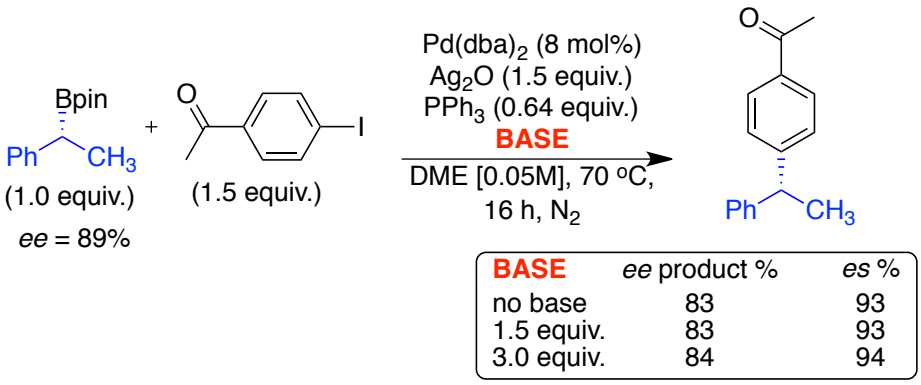


Figure 23. Impact of base on enantiospecificity of Suzuki-Miyaura cross-coupling of chiral, secondary boronic esters.[128]

The Aggarwal group successfully applied the conditions reported by our group[125] to propargylic boronic esters with high retention of stereochemistry and perfect regioselectivity (Figure 24).[129] In an unprecedented coupling, stereodefined, tertiary, propargylic boronic esters underwent cross-coupling with regioselectivity for the γ position, furnishing stereodefined tetra-substituted allenes as products.[129] Enantiospecificities for the cross-coupling reaction were essentially perfect (98%) and coupling was observed for both electron-rich and electron-poor aryliodides.

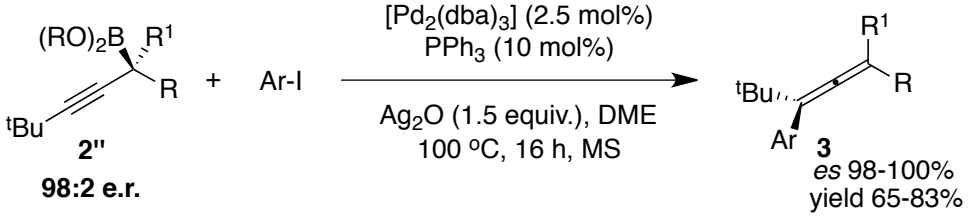
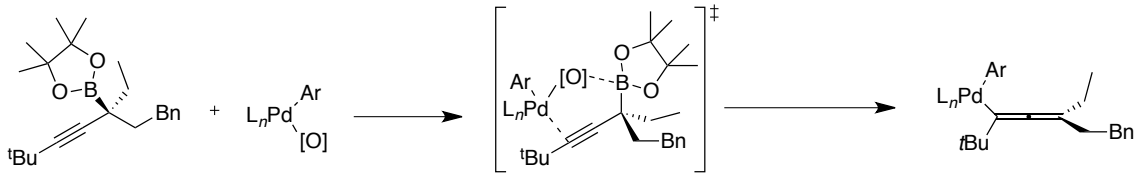


Figure 24. Scope of cross-coupling tertiary propargylic boronic esters.

The proposed mechanism accounts for the retention of configuration observed during the reaction and invokes a *syn* transmetalation of the arylated-Pd^{II} species followed by a retentive

reductive elimination (Scheme 26).[129] Crystal structures of the coupling product allowed the authors to assign the absolute stereochemistry and propose a mechanism of the coupling reaction that involves a key palladium-hydroxo species.[129]



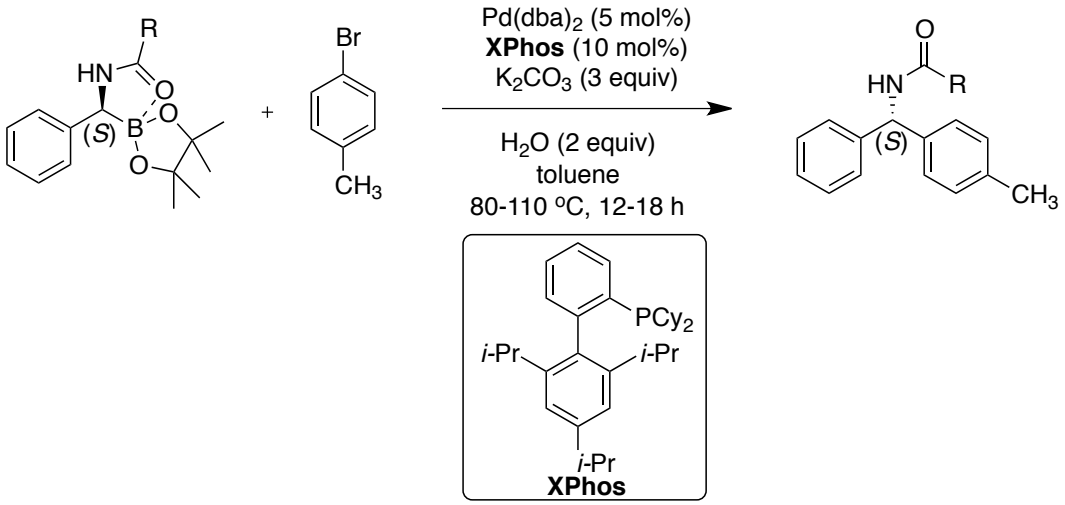
Scheme 26. Proposed mechanism of transmetalation to account for the stereochemistry of the cross-coupling.[129]

In 2012, Molander reported the stereospecific cross-coupling of enantiopure 1-(benzyloxy)alkyltrifluoroborates with aryl and heteroaryl chlorides.[130] The *β*-hydride elimination reaction pathway is minimized by a benzyl protecting group, which is postulated to coordinate Pd upon transmetalation forming a diorganopalladium intermediate (Scheme 27).[130] The reaction occurs with complete retention of stereochemistry and the authors invoke a four-member transmetalation transition state that has become marquee to retentive Suzuki-Miyaura cross-coupling reactions. Molander et al. demonstrated in over 40 coupling reactions, yields ranging from 39-95% and enantiomeric excesses greater than 97% (*es* 98-100%).[130]

The first stereo-invertive Suzuki-Miyaura cross-coupling of a new class of compounds: enantioenriched α-(acylamino)benzylboronic esters added to the expanding class of substrates able to undergo this reaction.[131] Contrary to the cross-coupling of benzylic boronic esters that proceeded with *retention* of stereochemistry observed by our group[125], Suginome's α-(acylamino)benzylboronic esters underwent C-C bond formation with *inversion* of configuration in the absence of a Lewis acid (Figure 25).[131] The amount of protodeborylation was dependent

on phosphine ligand/base combinations as P(*t*-Bu)$_3$/KF led to 78% cross-coupling product with <10% protodeborylation product observed. However, change of base to K_2CO_3 led to a 28% yield of the cross-coupling product and 38% protodeborylation.[131]

The stereochemical effect of substituent on the α-(acylamino)benzylboronic ester cross-coupling was examined by placing Me, Et, Ph and *t*-Bu on the acyl groups. Of note, all α-(acylamino)benzylboronic esters cross-coupled with *inversion* of configuration, however, some acyl functional groups proceeded to a higher enantiospecificity then other functional groups. To improve the enantiospecificity of the cross-coupling, sterically bulky groups bonded to the benzylic amine, such as pivaloic acid (Figure 25) were used. Electron-rich and electron-poor aryl chlorides also cross-coupled invertively with high enantiospecificities (>96%).[131]



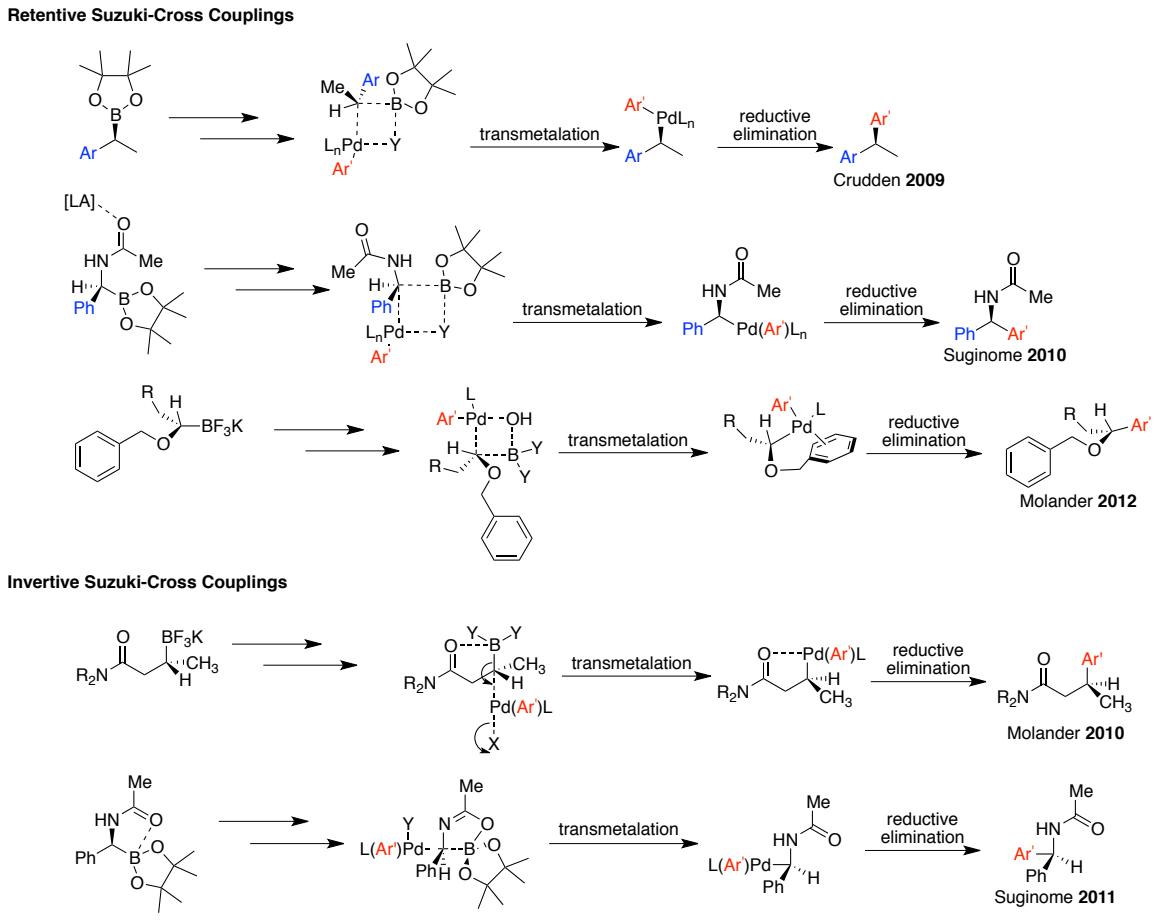
Entry	substrate (R) (% *ee*)	temperature (°C)	% yield	% *ee*	% *es*
1	Me (87%)	110	95	51	59
2	Et (95 %)	110	85	65	68
3	Ph (87 %)	110	65	77	89
4	*t*-Bu (96 %)	110	80	92.7	96.5
5	*t*-Bu (96 %)	80	84	93.4	97.3

Figure 25. Effect of acyl group on stereoinvertive Suzuki-Miyaura cross-coupling of stereodefined α-(acylamino)benzylboronic esters with an aryl bromide.[131]

The Suginome group investigated further the impact of additives on the enantiospecificity of cross-coupling α-(acylamino)benzylboronic esters. Surprisingly, the stereochemical outcome proceeded with *inversion* or *retention* depending on the whether a Lewis acid or Brønsted acid was employed. For instance, phenol was added to the original standard conditions (Scheme 27) and the authors found the reaction proceeded with increased levels of *inversion* than what was originally observed[131] (*es* >91 % when R= Me, Scheme 27). In contrast, addition of Zr(O*i*-Pr)$_4$•*i*-PrOH yielded cross-coupling product with *retention* of stereochemistry when coupled with a variety of electron-donating and withdrawing aryl bromides. Yields of the cross-coupling product were within 54-96% and *ee*'s ranged from 78-93%.[133]

From their studies, Suginome et al. proposed transition states of transmetalation that aim to explain *invertive* versus *retentive* Suzuki-Miyaura cross-coupling outcomes.[133] Invertive Suzuki-Miyaura cross-couplings of α-(acylamino)benzylboronic esters typically involve intramolecular coordination of a carbonyl group to the boronic ester leading to an S_E2 mechanism involving an open-chain transition state[133] that is favored in polar solvents.[131] Alternately, coordination of a Lewis acid to the carbonyl group of the stereodefined boronic ester compound, invokes the four-membered transition state in which Pd is bridged by either oxygen or a halide to the boronic ester resulting in a *retentive* transmetalation (Scheme 27).[133] Of interest, stereochemical *inversion* observed by Suginome et al. upon addition of phenol is explained that PhOH functions as a Brønsted acid and protonates the oxygen of the boronic ester.[133] As a result, this protonation causes the Lewis acidity of the trivalent boron to increase and results in a stronger intramolecular coordination of the carbonyl and increased *stereoretention*.[133]

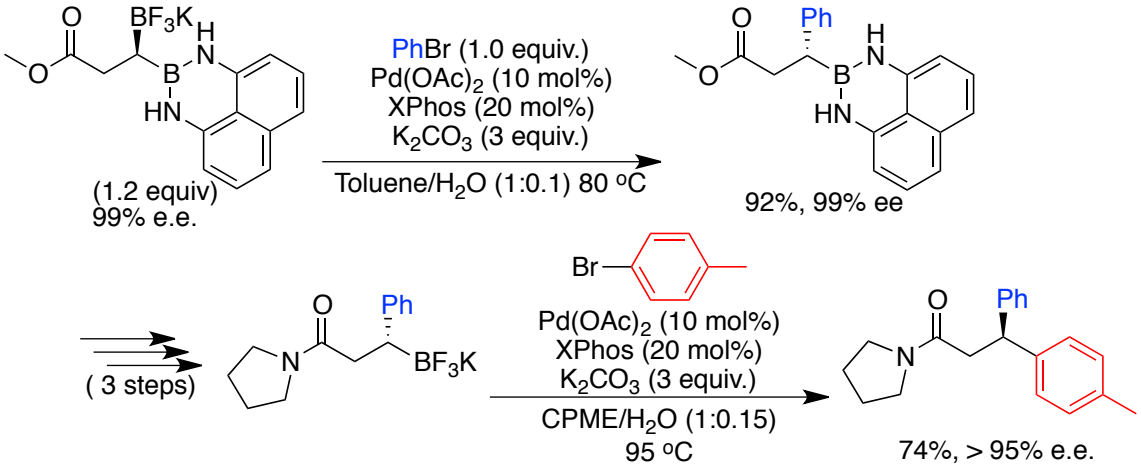
In 2010, Molander reported the cross-coupling of *non*benzylic, enantioenriched, secondary alkyl boron compounds.[132] Cross-couplings occurred with complete *inversion* of stereochemistry and presented an important extension to the previously reported couplings of secondary organometallics.[132] β–hydride elimination pathways were minimized and product formation was maximized by a postulated intramolecular coordination of a pendant carbonyl to the metal catalyst in the diorganopalladium intermediate (Scheme 27).[132]



Scheme 27. Stereospecificity of various Suzuki-Miyaura cross-coupling reactions.[130]
*References for Retentive couplings: Crudden **2009**[125], Suginome **2010**[131], **2012.**[130] References for Invertive couplings: Molander **2010**[132], Suginome **2011.**[133]*

Key contributions from Dennis Hall[134] in asymmetric coupling have added to the expanding repertoire of enantioenriched nucleophiles that under go stereodefined C-C bond formations (Scheme 28). Enantioenriched 1,1-diboron compounds were prepared with an enantiomeric excess greater than 99% and were chemoselectively cross-coupled with high retention of stereochemistry. Absolute configurations were assigned based on X-ray crystallography of a brominated derivative.[134] The first of two stereoselective cross-couplings of aryl bromides to the optically pure 1,1-biboronyl compound offer products with enantiomeric excesses greater than 97% and occur with inversion. A crystal structure of the 1,1-diboronyl compound revealed coordination of the Lewis acidic trivalent boron atom to the oxygen of the proximal carboxy ester. This coordination was reasoned to assist in the difficult transmetalation by activating the C-B bond. Additionally, upon an invertive transmetalation the σ-alkyl-Pd(II)Ar intermediate is stabilized by coordination to the proximal Lewis base (carbonyl of the nearby ester functionality).

Stereoselective cross-coupling of the second trifluoroborate salt led to enantioenriched coupling product with a 74% yield and enantiomeric excess greater than 95% constituting high levels of stereocontrol in iterative Suzuki-Miyaura cross-couplings.[134]



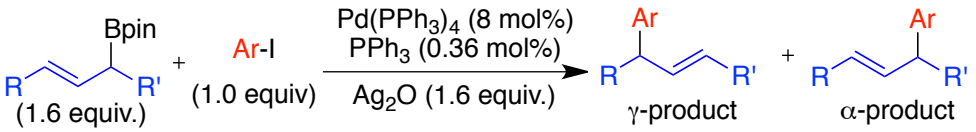
Scheme 28. Chemoselective, stereospecific Suzuki-Miyaura cross-coupling of highly optically enriched 1,1-diboron compounds.[134]

3.2 Results of Secondary, Allylic Boronic Ester Cross-Coupling

Building on the work our group disclosed in both 2009 (enantiospecific, benzylic boronic ester coupling)[125] and 2012 (racemic, allylic boronic ester coupling)[135] we extended the cross-coupling methodology to include *enantioenriched,* allylic boronic esters.

In 2012, allylic boronic esters, in addition to secondary benzylic boronic esters, were also shown by our group to be successful nucleophilic coupling partners,[135] however γ and α regioisomers were produced with an average ratio of 85:15 (Table 3). The main goal of this thesis was to determine the enantiospecificity of the cross-coupling reaction for this class of substrate. Additional goals were to improve the regioselectivity of the reaction[135] and to gain a clearer mechanistic insight of the C-C bond forming process.

Table 3. Regioselective Suzuki-Miyaura cross-coupling of secondary, allylic boronic esters.[135]



Entry	R	R'	Ar	Yield[a]	γ: α[b]
1	CH_3	C_6H_{13}	*p*-CH_3COPh	84	87:13
2	CH_3	C_6H_{13}	*p*-ClPh	83	79:21
3	CH_3	C_6H_{13}	*p*-MePh	70	86:14
4	CH_3	C_6H_{13}	3,5-*di*MePh	72	90:10
5	CH_3	Ph	*p*-CH_3COPh	81	84:16
6	CH_3	Ph	*p*-MePh	82	91:9
7	C_4H_9	Me	*p*-CH_3COPh	65	50:50
8	Ph	C_6H_{13}	*p*-CH_3COPh	53	19:81
9	Ph	C_6H_{13}	*p*-CH_3Ph	55	16:84

[a]Isolated yields after silica gel chromatography. [b]Obtained from integrations of GC-MS chromatogram.

In contrast to the successful cross-coupling of allylic systems, (Table 3), under these conditions, cyclohexyl pinacolate boronic esters, that do not contain β unsaturation were unsuitable as nucleophilic coupling partners (Figure 26).[125] This result was key in demonstrating the significant impact that the carbon-carbon double bond, β to the boronic ester has on the success (or lack thereof) of the cross-coupling reaction (Figure 26).

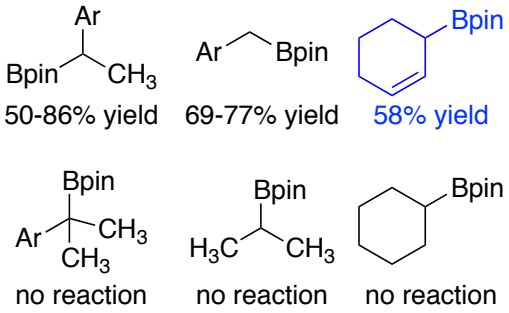


Figure 26. Suzuki-Miyaura cross-coupling yields of secondary boronic esters.[135]

Building on the accomplishments of Glasspoole et. al.[135], we next conducted a preliminary study of optimal cross-coupling conditions. Studies from Fu,[110, 111, 114, 107109] Hartwig,[122] and Buchwald[139] have demonstrated repeatedly that examination of base, solvent, metal-ligand combinations and temperature are key to obtaining cross-coupling product in prime yield. Our cross-coupling conditions were optimized by our collaborators on this project, including, namely Dr. Laëtita Chausset-Boissarie from Bristol University as she examined the impact of ligand, metal and base sources on yield and γ:α ratios.

A scan of metal catalyst sources revealed $Pd(PPh_3)_4$ and $PdCl_2$(dppf) to be equally effective in furnishing cross-coupling product in 86-87% yield with similar E:Z ratios of 91:9 and 86:14, respectively (dppf=1,1'-Bis(diphenylphosphino)ferrocene).[136] Regioselectivity of the cross-coupling reaction was equal within error, averaging a γ:α ratio of 81:19 (Figure 27). PEPPSI, $Pd\{(P^tBu)_3\}_2$, $NiCl_2(PPh_3)_2$, $NiCl_2$(dppf) were tried as metal pre-catalysts and resulted in degradation of starting materials.[136]

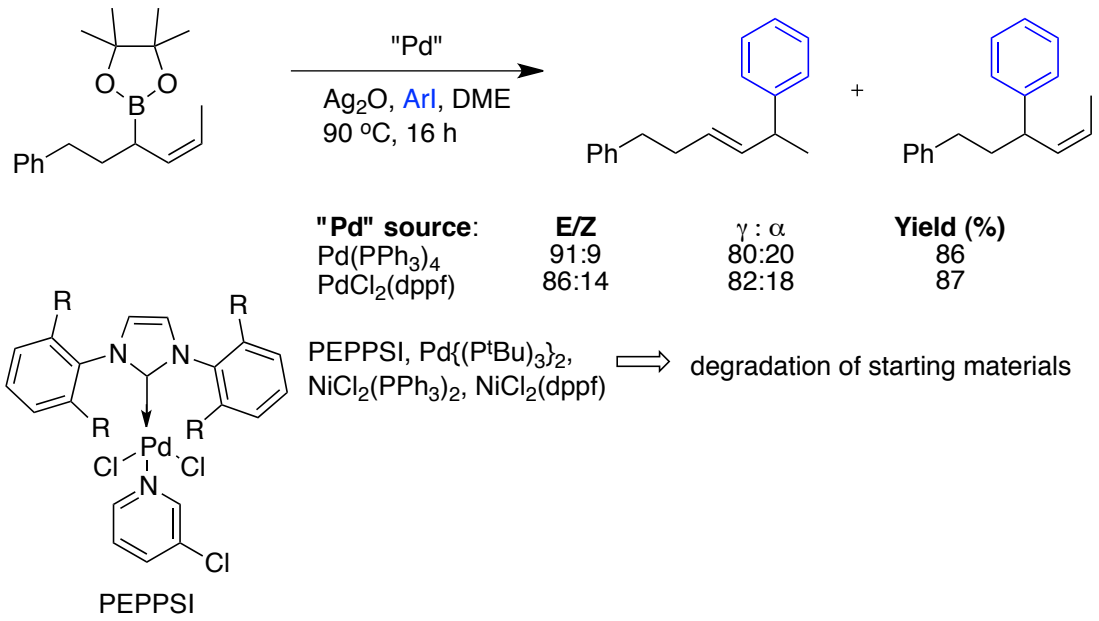
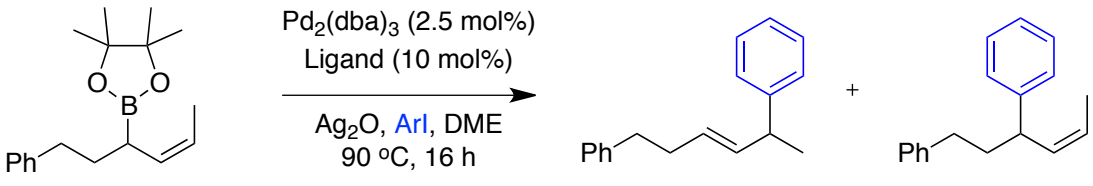


Figure 27. Metal precatalyst-screen for Suzuki-Miyaura cross-coupling of allylic boronates.[136]

$Pd_2(dba)_3$ was examined as precatalyst in combination with several different phosphine sources including mono- and bi- dentate ligands. A screen of twenty different phosphine ligands revealed PPh_3 to not only be the most cost effective, but also the ligand that facilitated cross-coupling product in relatively high yield (80 %) (Figure 28). The size of bite angle was shown to not impact the γ:α ratio to any sizeable extent.[137]



Bidentate

Ligand	E/Z	γ:α	Yield (%)
dppe	90:10	79:21	66
dppp	93:7	82:18	60
dppb	90:10	78:22	75
dppf	87:13	80:20	50
dppf^{t}Bu	81:19	81:19	47
JosiPhos	79:21	75:25	35
XantPhos	83:17	85:15	60
DifluoroPhos	94:6	82:18	63

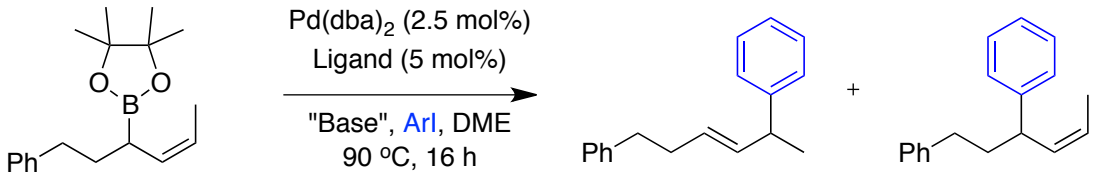
Monodentate

Ligand	E/Z	γ:α	Yield (%)
P(*p*-tolyl)$_3$	93:7	80:20	95
P(furyl)$_3$	94:6	80:20	60
P(OPh)$_3$	94:6	76:24	43
PPh$_3$	92:8	84:16	80

P(Cy)$_3$, P(*o*-tolyl)$_3$, TTMPP ⟹ degradation of starting materials

Figure 28. Phosphine screen for Suzuki-Miyaura cross-coupling of allylic boronates.[137]

A scan of silver (I) oxide, silver (I) carbonate, and potassium carbonate as base revealed that silver sources facilitated the reaction at a greater rate than K_2CO_3.



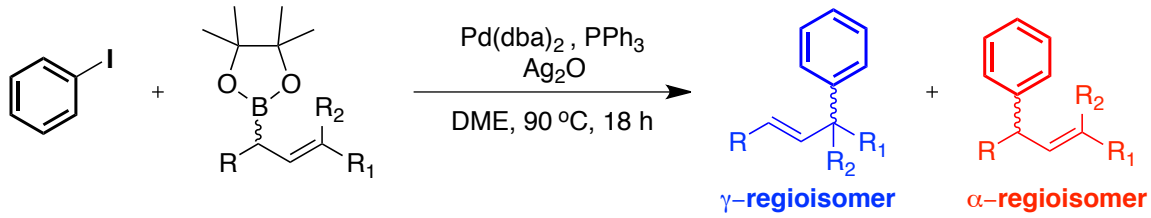
Base	E/Z	γ:α	Yield (%)
Ag_2O	92:8	85:15	96
Ag_2CO_3	95:5	84:16	75
K_2CO_3	-	-	-

Figure 29. Base screen for Suzuki-Miyaura cross-coupling of allylic boronates.[138]

Cross-coupling conditions were optimized to 1.5 equivalents of silver (I) oxide in combination with 2.5 mol% catalyst, $Pd(dba)_2$ in a 2:1 P:Pd ratio with PPh_3 as ligand, gave the highest yield (96%) (Figure 29). The aforementioned conditions gave product with high regioselectivity, high control of olefin geometry and in comparatively high yield. Remarkably, these conditions are the same as those employed in our 2009 study[125], with the one exception that only a 2:1 ratio of phosphine to Pd is needed. Accordingly, these conditions were used for the remainder of our studies.

Using these conditions, we carried out the palladium-catalyzed, cross-coupling of α-substituted boronic esters with phenyl iodide (Table 4). Beginning with racemic allylic boronic esters, in which the geometry of the olefin is defined, we examined the effect of the various alkyl and aryl substituents on the allyl boron unit in the coupling with phenyl iodide. The reaction gave cross-coupling product in a range of isolated yields from 28 to 78 % with a range of γ:α regio-isomeric ratios from 39:61 to 97:3 in the best-reported selectivity (Table 4). We report high *E:Z* ratios in most reported couplings (99:1) with the exception of one example (entry **2**).

Table 4. Suzuki-Miyaura cross-coupling of secondary, allylic boronic esters.



Entry	R	R_1	R_2	γ:α[a]	*E:Z*[b]	Yield (%)[c]
1	*i*-Pr	*n*-Pr	H	93:7	99:1	71
2	$Ph(CH_2)_2$	Ph	H	39:61	86:14	28
3	Ph	CH_3	H	97:3	99:1	65
4	Ph	H	CH_3	92:8	99:1	70
5	Ph	*n*-Pr	H	96:4	99:1	77
6	Ph	CH_3	CH_3	92:8	99:1	40

Reaction conditions: *Phenyliodide (0.245 mmol, 1.0 equivalent), α-substituted allylic boronic ester (1.2 equivalent), $Pd(dba)_2$ (2.5 mol%), PPh_3 (10 mol %), Ag_2O (1.5 equivalent) 2.45 mL of DME, 90 °C, 18 h.* [a] *α:γ ratios were obtained from GC-MS integrations of crude reactions.* [b] *E:Z ratios (of the major regioisomer) were obtained from GC-MS integrations of crude reactions.* [c] *Chromatographically isolated yield of major regioisomer.*

Entry **1** cross-couples with high levels of γ selectivity with a γ:α ratio in the coupling product of 93:7. Branched aliphatic substituents were well-tolerated in providing product in both high γ-selectivity and in good control of the olefin geometry of the product with a *trans: cis* ratio of 99:1.

The reaction proceeded with high levels of regioselectivity for all entries with the exception of entry **2**. Entry **2** shows an alternate α selectivity when compared to all other entries that are γ selective. Mechanistically, this result is of particular interest, since two pathways

leading to α and γ aryl substituted products can be proposed (*vide infra*). The conservation of a styrenyl subunit during transmetalation and reductive elimination is thought to contribute to the α selectivity of this particular substrate. As shown in Scheme 29 below, if R_1 is a phenyl ring then the π-system is in conjugation with the adjacent sp^2 hybridized carbon atoms of the C=C olefin, thus forming an electronically stable styrenyl subunit. The α–selectivity observed in this Suzuki-Miyaura cross-coupling may be explained through a four-membered transmetalation transition state, resulting in the retentive delivery of the arylated Pd(II) species to the α-carbon of the organoboron reagent. Another possibility has the initially formed σ-allyl intermediate σ–**37** of Scheme 29 undergoes σ-π-σ isomerization after transmetalation; this is another mechanism to achieve recovery of the styrene unit of entry **2**.

Entries **3** to **6** constitute a special class of cross-coupling as γ selectivity leads to the generation of a styrenyl subunit and increases the conjugation of the R = phenyl ring incidentally present in the boronic ester (Scheme 29). Hence, secondary, benzylic-allylic boronic esters (entry **3**, **4**, **5**, **6)** cross-coupled with the highest observed γ regioselectivity. We hypothesized that the main driving force for the γ regioselectivity of cross-coupling benzylic-allylic boronic esters was to *generate* a styrenyl subunit in the product, which thereby increased the conjugation of the π-system.

To examine the mechanism that arises to give the observed regioisomerism of the products in the cross-coupling of α–substituted, allylic boronic esters, a postdoctoral fellow in our group, Dr. Kazem Ghozati, prepared compounds **34** and **36** (Figure 30). Compound **36** cross-coupled under our standard conditions; coordination of the arylated Pd(II) through a proposed hydroxyl bridge, proceeded by a S_E' transmetalation yields organopalladium intermediate σ-**37**. Direct reductive elimination of σ-**37** yields compound γ-**41** (R=Ph) in which

the olefin and aromatic ring of the boronic ester starting material are in conjugation (Scheme 29). This enrichment in the γ–regioisomer is observed with branched and unbranched aliphatic system, when R, R_1 =alkyl is expected to undergo a similar Pd-O-boronic ester coordination, followed by S_E' transmetalation to offer organopalladium σ-**37** which reductively eliminates to provide γ-regiosomers (γ-**41**) in these cases as well as the R=Ar examples (Scheme 29).

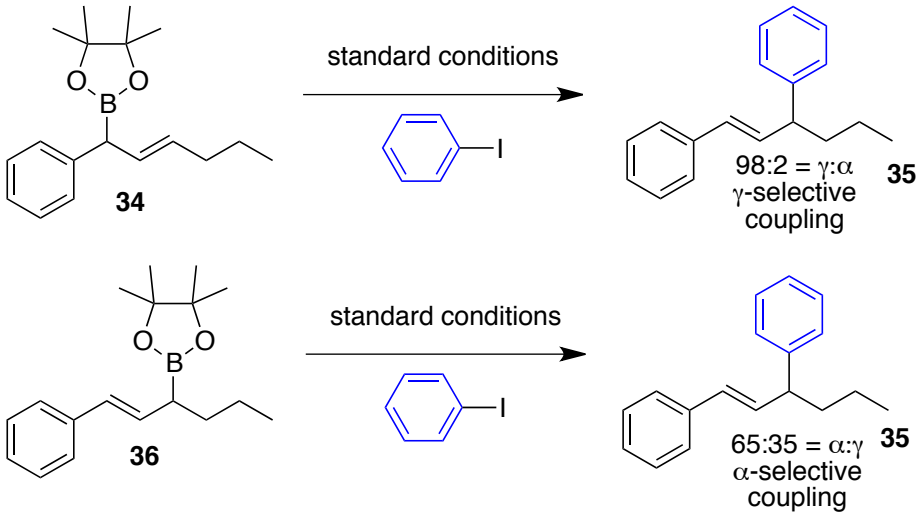
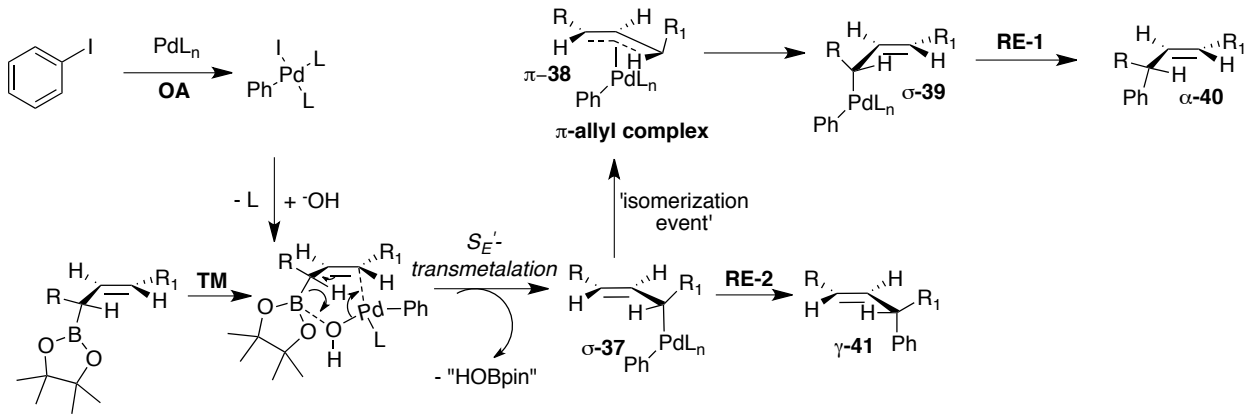


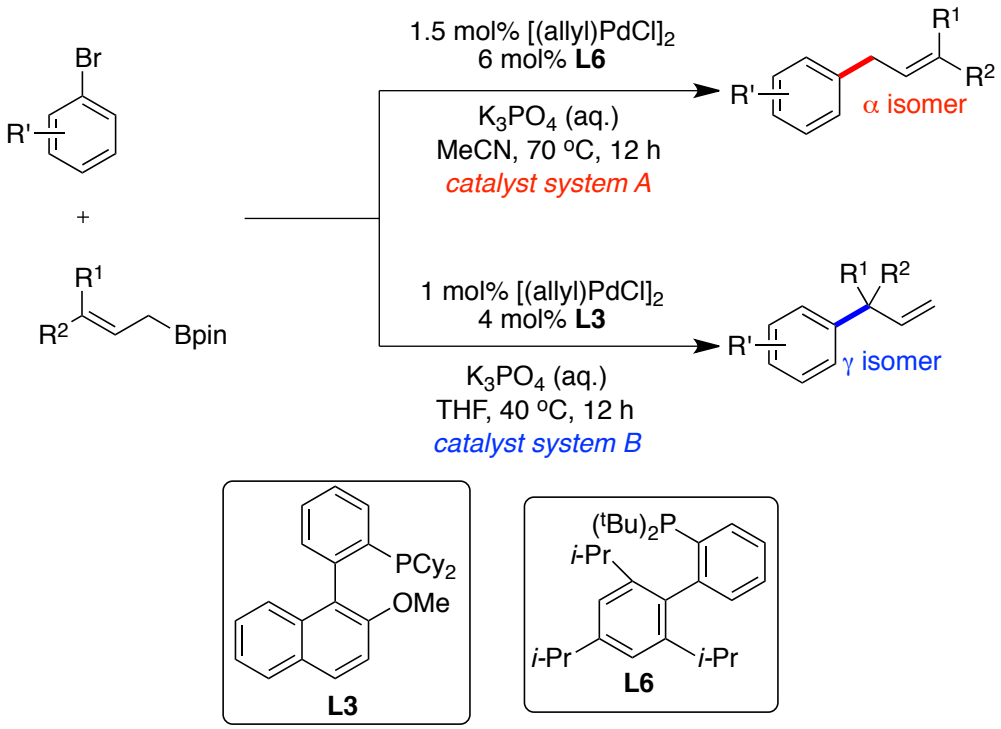
Figure 30. Cross-coupling of isomers 34 and 36 to yield 35 in varying selectivity.

For compound **36,** S_E'-transmetalation disrupts conjugation of the olefin to the aromatic ring (*vice versa*). In this case, an isomerization event to organopalladium σ-**37** may proceed through π-allyl π–**38** to σ-**39**, which restores the extended aromatic-olefin conjugation (R_1 = Ph) of the styrene unit and reductively eliminates, to give rise to α-**40**.



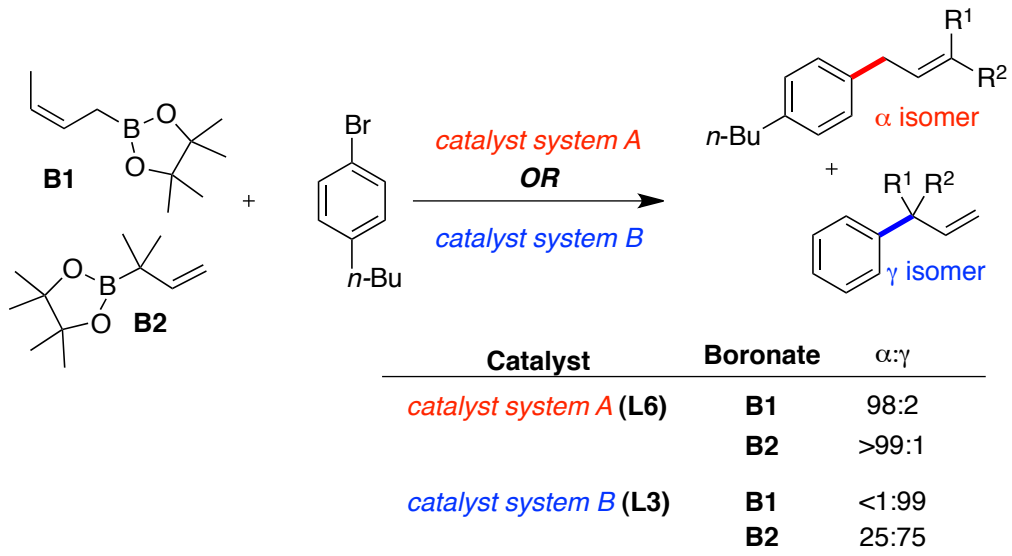
Scheme 29. Mechanisms giving rise to regioisomerism observed for the Suzuki-Miayura cross-coupling of secondary, allylic boronic esters.

This is consistent with recent results published by the Buchwald group in non-chiral systems.[139] The Buchwald group has recently published regiodivergent cross-coupling of terminal allyl boronates (Scheme 30).[139] Allylated arene architectures are afforded by operationally simple catalyst systems by which a change in ligand results in divergent regioisomeric products.[139] Choice of ligand was reasoned to impact the transmetalation mechanism, the rate of σ-π-σ interconversion, and the rate of reductive elimination and was the key component in regiocontrol.[139]



Scheme 30. Ligand-Controlled Palladium-Catalyzed Regiodivergent Suzuki-Miyaura Cross-Coupling of Allylboronates and Aryl Halides.[139]

The Buchwald group have proposed three different mechanisms that give rise to regioisomeric cross-coupling products. When coupling with the sterically bulky ligand **L6** (Scheme 30), the linear product was favored. In contrast, the less sterically bulky **L3** (Scheme 30) ligand facilitates coupling to favor the branched product. Coupling of boronic esters **B1** and **B2** using **L3** afforded coupling product in drastically varying γ:α selectivity (Figure 31).



Catalyst	Boronate	α:γ
catalyst system A **(L6)**	**B1**	98:2
	B2	>99:1
catalyst system B **(L3)**	**B1**	<1:99
	B2	25:75

Figure 31. Mechanistic insight of a ligand controlled, Palladium-catalyzed, regiodivergent cross-coupling of allylboronates with an aryl bromide.[139]

These cross-coupling results suggest that complexes σ-**37** and σ-**39** do not reach equilibrium via a π-allyl intermediate **5** before reductive elimination occurs (with reference to Scheme 29).[139] In contrast, the bulkier **L6** afforded linear product α-isomer with excellent selectivity for both boronic esters **B1** and **B2**. The transmetalation of **B1** and **B2** proceeds through two different S_E2 pathways (depicted in Scheme 32) that result in the same organopalladium complex that reductively eliminates to give the linear isomer. In this case, the rate of reductive elimination exceeds the rate of σ-π-σ interconversion. In the case where the bulky ligand **L6** reacts to the γ isomer, two different σ-organopalladium complexes are produced, σ-**37** and σ-**39**, that experience a rapid σ-π-σ interconversion prior to formation of the σ-bound organopalladium complex (σ-**6**) that slowly reductively eliminates to give the branched γ regioisomer.

To probe the transmetalation event in our system, an electronically and sterically unbiased substrates (*iso*-**42** and *iso*-**43**) were prepared by postdoctoral fellow Kazem Ghozati using Sawamura borylation chemistry (please see SI for details) and was submitted to Suzuki-

Miyaura cross-coupling. Hypothetically, if the transmetalation were to proceed through a π-allyl intermediate π **-38** we would expect a 50:50 ratio of γ:α regioisomers. Equal amounts of α-**40** and γ-**41** (Scheme 29) are expected in an electronically and sterically unbiased system that establishes equilibrium through a π-allyl complex π-**38**. The results of our deuterated substrate cross-coupling are illustrated in Figure 32 below.

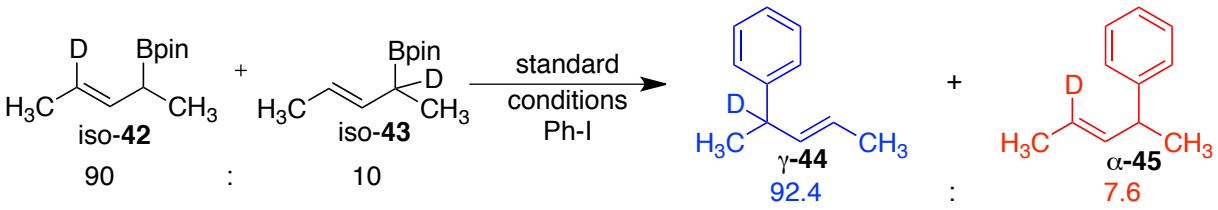


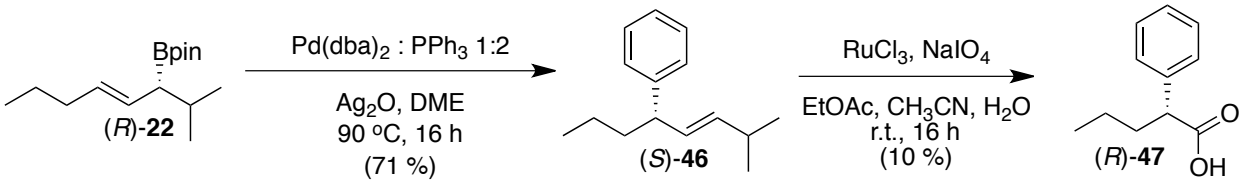
Figure 32. Suzuki-Miyaura cross-coupling of predominately isomer A (iso-42) under the "standard conditions". α isomer is shown in red and γ isomer is shown in blue.

Upon analysis of the deuterium NMR (Appendix) we observed a γ:α ratio in the cross-coupling product of 92:8 of γ-**44**:α-**45** (integration of benzylic to vinylic ^{2}H NMR signal) indicating that the transition step in the transmetalation step does not strictly proceed through a symmetrical π-allyl. This result indicates that at most, 5% or less reach a post-transmetalation equilibrium via the π-allyl complex π-**38**. These results are suggestive of a S_E2 transmetalation (S_E2 and S_E2' transmetalations are depicted in Scheme 32 below) that is preceded by a direct reductive-elimination.

The proposed, predominant pathway of transmetalation that leads to γ selectivity proceeds through a six-membered transition state *via* a *syn*-S_E' or an *anti*-S_E' mechanism. In a *syn*-S_E' mechanism the boronic ester is linked to the Pd catalyst *via* a hydroxo bridge (Scheme 29). This transient six-membered species is then proposed to collapse and provide the γ bound

organopalladium species that reductively eliminates the aryl and allylic organic components to give the γ-cross-coupling product with *retention* of the stereocenter. In juxtaposition, an *anti*-S_E' mechanism proceeds through an open-transition state where the organoborane attacks the metal electrophile that results in *inversion* of the stereocenter. These two mechanisms lead to cross-coupling products with opposite stereochemistry. In order to understand which is operative, correlation of the absolute configuration of boronic ester starting materials and cross-coupling product was required.

Thus, stereodefined allylic boronic ester (*R*)-**22** configurations cross-coupled with phenyl iodide (Table 5) to provide cross-coupling product of (*S*)-**46** configuration and *trans* geometry in the double bonds. Cross-coupling products were converted to the corresponding carboxylic acid (*R*)-**47** by oxidation with $RuCl_3$ and $NaIO_4$[140, 141] (with stereochemistry intact) for HPLC *ee* determination and optical rotation measurements (Scheme 31).

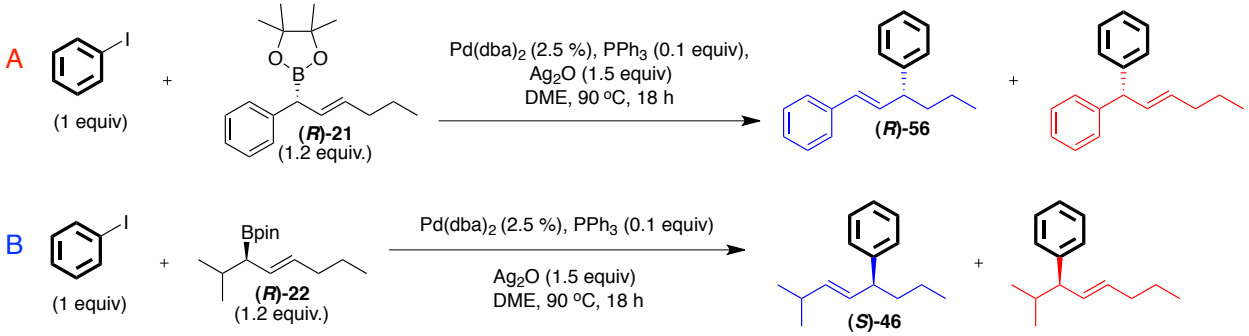


Scheme 31. Absolute configurations of starting material, cross-coupling product and phenylpropionic acid, oxidized cross-coupling product.

The experimentally determined optical rotation of (*R*)-**47** above was $\alpha_D^{23.0}$ = -28 (*c* 0.5, $CHCl_3$) and was compared to the optical rotation of it enantiomer (*S*)- α-(+)phenylpentanoic acid $\alpha_D^{23.0}$ = +54.5 (*c* 1.0, $CHCl_3$).[142] (The benzylic stereocenter is noted to be sensitive to epimerization, and may have attributed to decay in enantiomeric excess, leading to lower optical rotation than expected.) The absolute configuration of cross-coupling product was confirmed by

optical rotation and compared to literature values of known compounds (Scheme 31). From the analysis of starting material and product stereocenters, it is clear that the reaction proceeded with retention of stereochemistry, which most likely occurs via a closed, *syn*-S_E' transmetalation (Scheme 29).

Table 5. Suzuki-Miyaura Cross-Coupling of Asymmetrically Defined Allylic Boronic Esters.



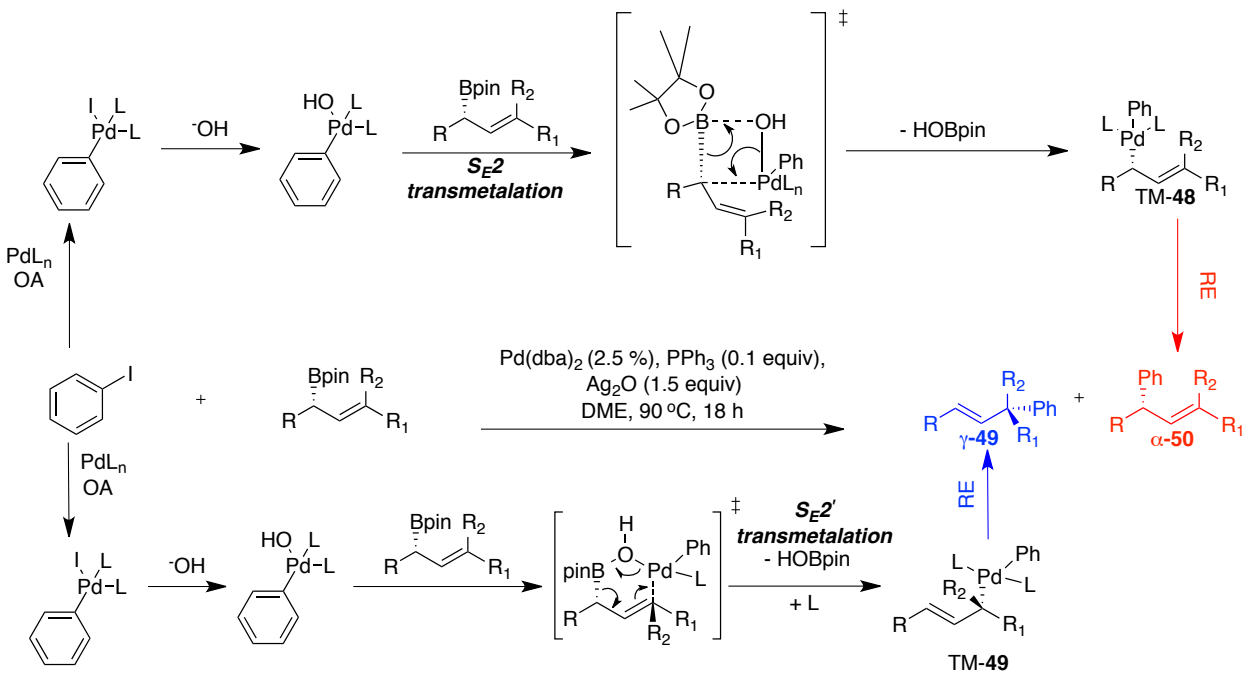
Reaction	γ : α	*E:Z*	Isolated Yield (%)[a]	*Product e.r.*[a]	*e.s.*	Inversion or Retention
A	98:2	>99:1	78	98:2	>99	Retention
B	92:8	>99:1	71	96:4	>99	Retention

[a] *Determined by HPLC analysis of corresponding $RuIO_4$/ oxidation product.*

Another proposal that gives rise to the observed regioisomerism of secondary allylic boronic ester cross-coupling is provided below. Direct and *retentive* transmetalation at the α-carbon, proceeds by direct reductive elimination would give rise to the α-regioisomeric organopalladium complex TM-**48** that reductively eliminates to give α-**50**. In this case, the rate

of reductive elimination of compound TM-**48** would be faster than the rate of σ-π-σ isomerization.

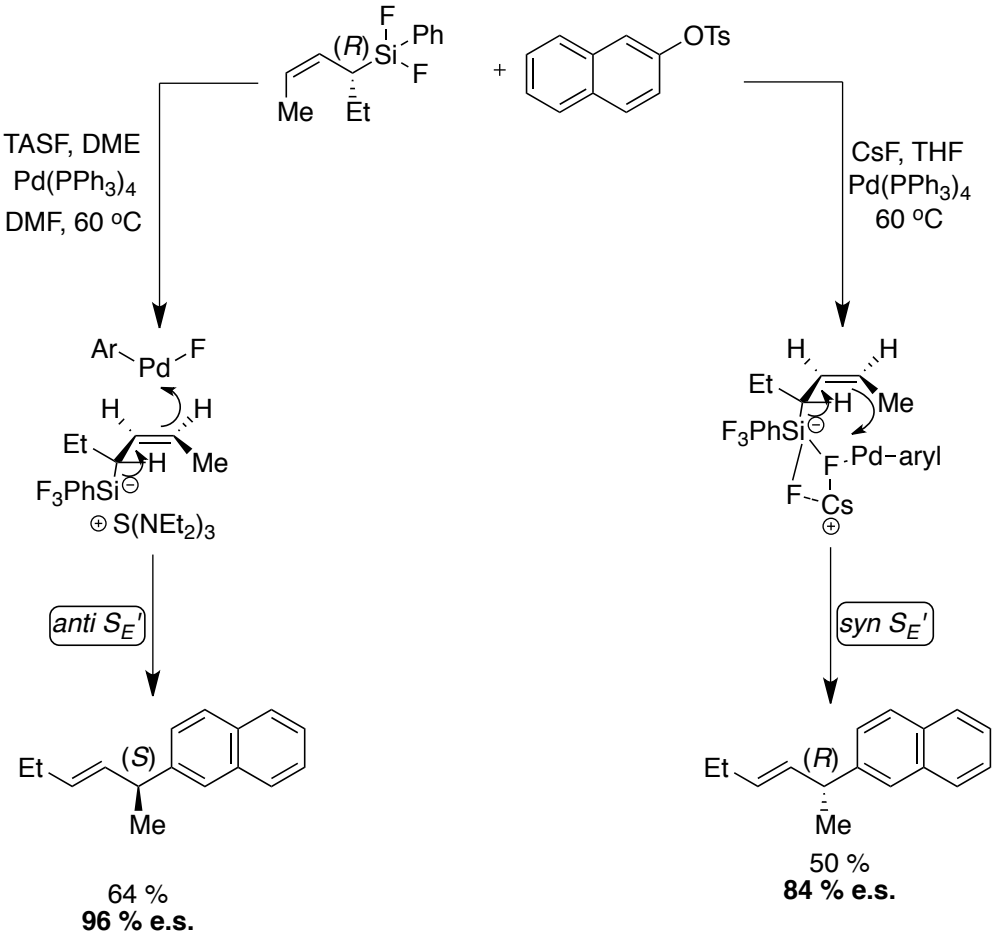
A process that would give rise to the γ–regioisomer of the cross-coupling product involves a six-membered transition state that forms a B-O-Pd linkage (commonly observed and proposed in other cross-couplings[143, 144, 145, 146]), resulting in reactions that are *stereo-retentive*, γ-selective in asymmetric cross-couplings (*vide infra*). The transmetalation described above proceeds through a *syn*-S_E' mechanism and yields TM-**49** that reductively eliminates to give γ-**49** (Scheme 32).



Scheme 32. Proposed mechanism describing the regioselectivity of allylic boronate cross-coupling. α isomer is represented in red and γ isomer is shown in blue.

The *syn*-S_E' mechanism that we observed is highly reminiscent of the *syn*-S_E' mechanism Hiyama et al. observed[147] for the stereodivergent cross-couplings of α-substituted, enantioriched allylic trifluorosilicate salts (Scheme 33). The cross-coupling of trifluorosilicate salts proceeds

through either *anti* or *syn* attack of the metal electrophile to yield enantiomers of this stereospecific cross-coupling reaction. A closed transition state is proposed when CsF is used as a fluoride source leading to products of *R* stereochemistry. Alternately, an open transition state, in which transmetalation proceeds through an *anti*-S_E' mechanism when TASF is employed as fluoride source leading to products of *S* configuration.



Scheme 33. Reagent controlled *syn*-S_E' and *anti*-S_E' mechanisms leading to cross-coupling enantiomers.[148]

The tris(dimethylamino)sulfonium cation is coulombically attracted to the trifluorosilicate anion and blocks the lower face from electrofugal attack. Transmetalation

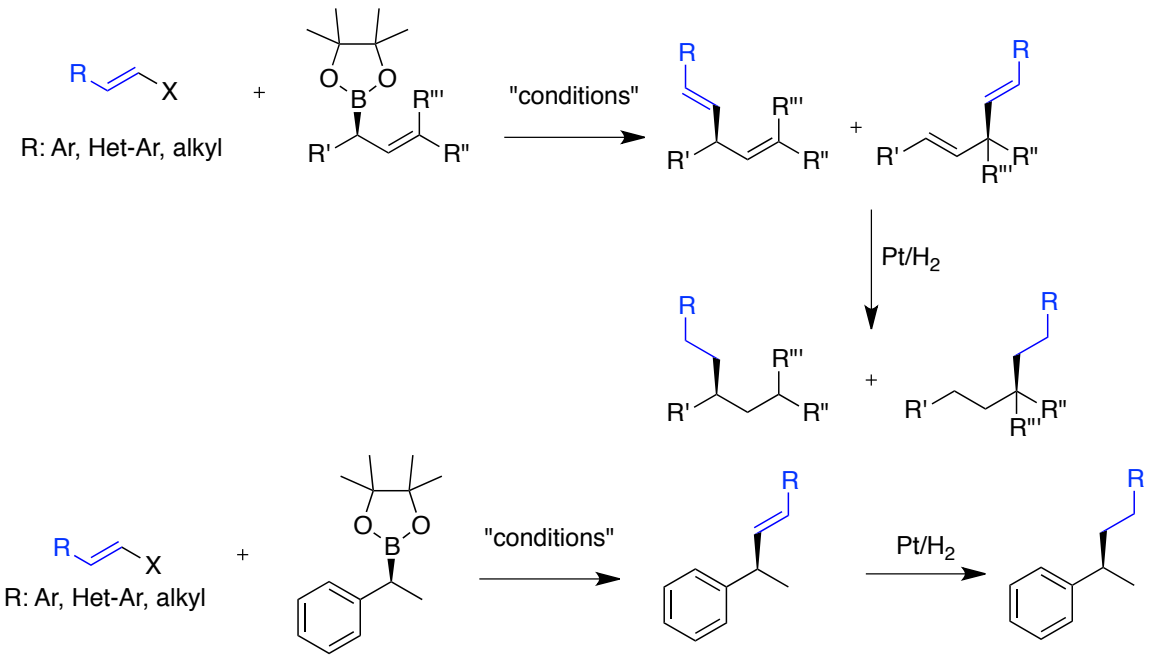
proceeds with inversion of the stereocenter *via* an open face, *anti*-S_E' mechanism. Addition of a coordinating fluoride source (CsF) provides the right conditions for a closed-transition state that leads to a *syn*-S_E' mechanism and retention of stereochemistry (Scheme 33).

In conclusion, novel, secondary, allylic boronic esters were synthesized and cross-coupled to phenyl iodide in varying yield and high γ–regioselectivity. Generation and preservation of styrenyl conjugation in the product was found to be a key driving force that contributed to high regioselectivity in some reported cases. Mechanistic studies show that the reaction proceeds through a *syn,* γ-selective transmetalation that is followed by reductive elimination. Reductive elimination is in competition with a π-allyl intermediate; our deuterium labeling experiment indicated that reductive elimination occurs at a faster rate that π-allyl formation for alkyl substituted allylic boronates. The stereochemical course of the reaction was followed and we determined that a *syn*-S_E' mechanism was operative and further demonstrates the importance of the Pd-O-B bond linkage for facile transmetalations. The reaction proceeded with virtually complete transfer of chirality from starting materials to their respective products.

Chapter 4: Attempts to Cross-Couple Vinyl Iodides

4.0 Introduction to Vinyl Iodide Cross-Coupling

In an attempt to expand the scope of electrophiles that participate in the stereospecific Suzuki-Miyaura coupling, we examined the coupling of vinyl iodides with secondary, benzylic boronic esters. The overall goal that we were striving towards involved finding the cross-coupling conditions capable of generating C-C bonds between vinyl iodides and secondary, benzylic boronic esters. Our additional goals included the application of these conditions to enantiospecific cross-coupling, proceeded by a Pt/H_2 hydrogenations of olefinic C=C double bonds, thereby generating branched alkyl chains with stereodefinition at the branching carbon (Scheme 34).



Scheme 34. Generalized, stereospecific, Suzuki-Miyaura cross-coupling of vinyl halides followed by hydrogenation of C=C double bond.

4.1 Vinyl Halide Cross-Coupling Precedents

The successful coupling of vinyl halides and pseudo-halides to *primary* organoboranes has been accomplished; their reaction conditions and factors contributing to successful couplings are described below.

The Buchwald group employed a sterically bulky monophosphine to effect coupling of vinyl tosylates in high yield (94%).[149] The reaction benefits from use of a commercially available catalyst and hydrated phosphate base. A tolerance of amide and cyano functional groups were displayed as short reaction times of only 1 hour were required to obtain product in high yield (92%) (Figure 33).[149] A shortcoming of this report is that only two examples of vinyl tosylates were included in the extensive list of compatible electrophiles that was heavily represented by aryl tosylates.

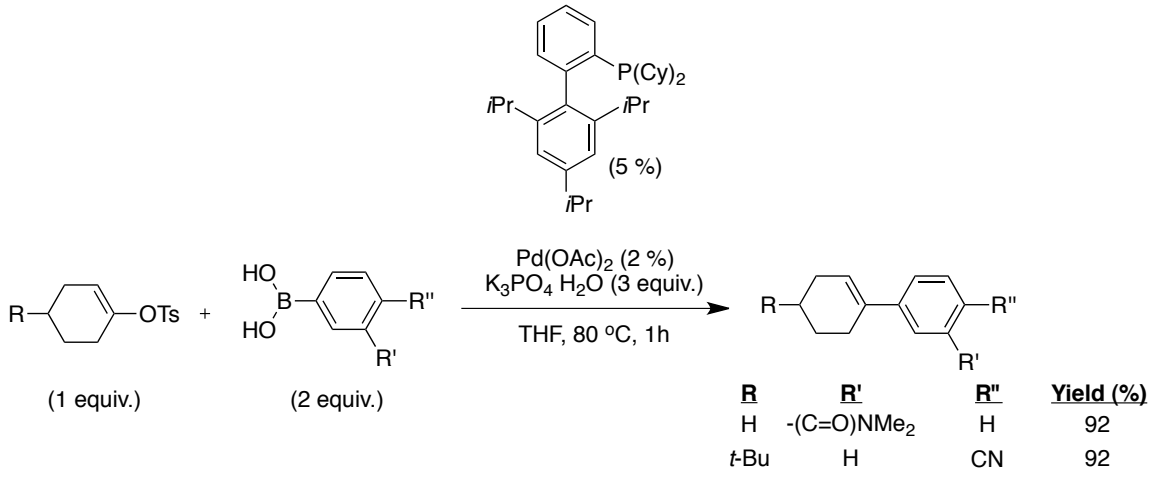
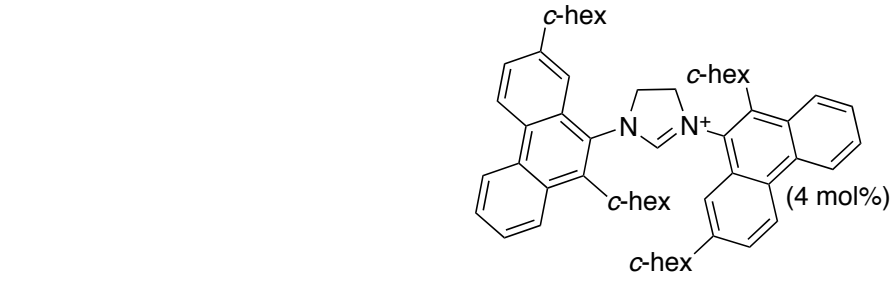


Figure 33. Suzuki-Miyaura Cross-Coupling of secondary, vinyl tosylates.[149]

NHC-palladium complexes continue to be used in catalytic reactions due to their increased stability and reactivity compared to the more commonly applied phosphine ligands.[150] The first reported conditions that use NHC ligands to cross-couple vinyl chlorides were

accomplished at refluxing temperatures and variant reaction times (Figure 34).[151] Aryl pinacolate boronic esters and phenyl boronic acid were cross-coupled in high yield, although electron-rich aryl boronic acids cross-coupled with only modest yields under the same reaction conditions.[151] A crown ether (18-crown-6) was employed in the cross-coupling reaction to increase the solubility of the KF base and, ultimately, the yield in the aqueous THF solvent. KF is also recognized as being a potent Lewis basic boronic acid activator.[151]

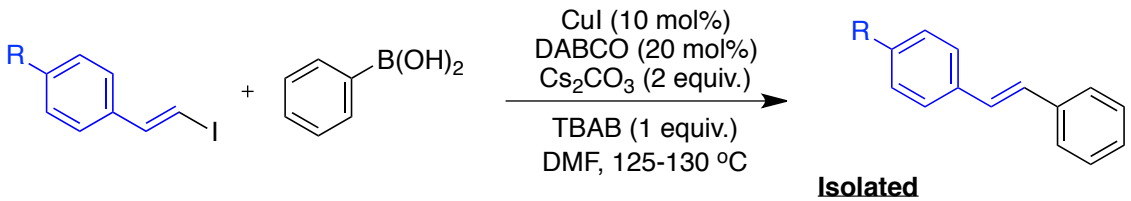


VC	BE	Reaction Time (h)	Yield (%)
1	1	16	87
	2	24	68
	3	24	81
2	1	12	92
	2	24	58
	3	16	91
3	1	16	77
	2	24	52
	3	24	83

Figure 34. *N*-heterocyclic carbene used as a ligand in Suzuki-Miyaura cross-coupling reactions of vinyl chlorides.[151]

A copper (I) iodide / DABCO system was used to cross-couple *β*-iodostyrene with phenyl boronic acid in good to moderate yields (95-58%).[152] Electronics of the iodostyrene were varied

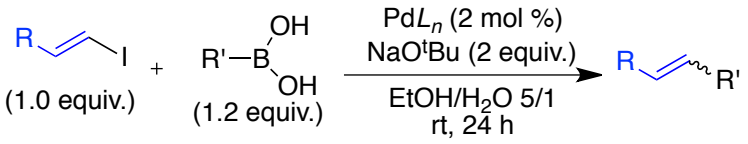
(R in Figure 35) and the yield was maximized at 95% with *para*-methoxy group making the vinyl iodide electron-rich.[152]



R	Reaction time (h)	Isolated Yield (%)	
H	20	83	
H	20	58	(without TBAB)
Cl	19	63	(without DABCO)
OMe	20	95	

Figure 35. TBAB-CuI catalyzed Suzuki-Miyaura cross-coupling of vinyl iodides and phenylboronic acid.[152]

Ligand effects of the palladium precatalyst (PdL_n) were also found to control the *cis:trans* isomerization event in the cross-coupling of vinyl iodides and bromides to aryl and primary, alkyl boronic acids (Figure 36).[153] The starting material was a *cis* vinyl halide (*Z*/*E* = 96/4) and the *Z* to *E* isomerization in the cross-coupling was minimized through use of Pd(P(*o*-Tol)$_3$)$_2$ as pre-catalyst in the reaction conditions.[153] During optimization, Lipshutz et al. found that combination of strong base (NaO-*t*-Bu) in EtOH enhances conversion to product and minimizes homocoupling of the vinyl iodide.[153]



R	R'	PdL_n	Yield (%)	Z/E
n-C_6H_{13}	Ph	Pd(P(*t*-Bu)$_3$)$_2$	61	62/38
		Pd(Amphos)$_2$Cl$_2$	70	71/29
		Pd(P(*o*-Tol)$_3$)$_2$	**89**	**99/1**
Ph		**Pd(P(*t*-Bu)$_3$)$_2$**	**87**	**95/5**
		Pd(Amphos)$_2$Cl$_2$	60	92/8
		Pd(P(*o*-Tol)$_3$)$_2$	59	96/4

Figure 36. Ligand-dependent, stereo-retentive vinyl iodide Suzuki-Miyaura cross-coupling.[153]

E:Z isomerization may involve a zwitterionic palladium carbene (Figure 37).[153] The equilibrium between E:Z forms is a function of ligand bound to the palladium catalyst (L_n) and the residue (R) of the vinyl group bound to palladium, which is delivered in the oxidative addition step.[153] Electronic resonance between zwitterion carbene forms allow for facile, single bond rotation to allow equilibrium to be established between the *Z* isomer and the *E* isomer.[153]

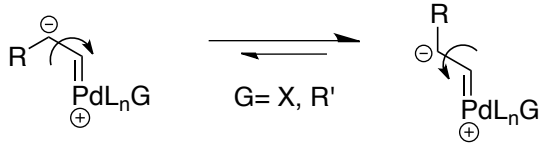
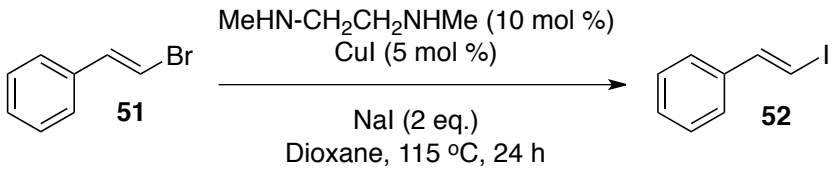


Figure 37. Mechanism of *Z*-to-*E* isomerization involving a zwitterionic palladium carbene intermediate.[153]

4.2 Synthesis of Starting Materials and Suzuki-Miyaura Cross-Coupling Attempts

The synthesis of *β*-iodostyrene involved an efficient copper iodide-catalyzed, Finkelstein of *β*-bromostyrene **51** (Equation 13).[154] Iodides are known to be more reactive in Suzuki-

Miyaura cross-coupling than their bromide counterparts on account of the C-I bond being weaker than C-Br, which causes the oxidative addition to occur at a quicker rate for iodides in the cross-coupling of benzylic boronic esters reported by our group.[125]



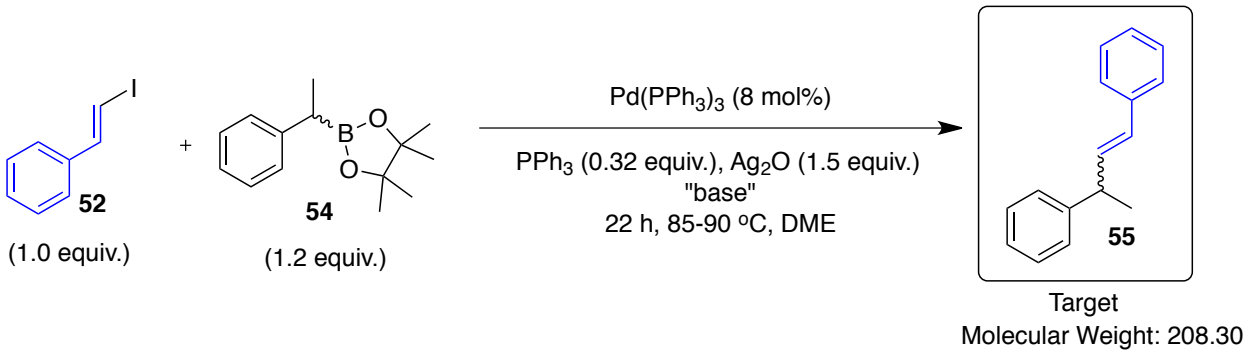
Equation 13. Synthesis of *β*-iodostyrene (52).

The nucleophilic cross-coupling partner, a secondary, benzylic boronic ester, was synthesized as described before by a rhodium-catalyzed hydroboration of styrene (*vide supra*).[155, 156]

Once both electrophilic and nucleophilic starting materials were in hand, we then attempted the Suzuki-Miyaura cross-coupling reaction (Table 6). Entry **1** of table 6 employs reaction conditions disclosed in our 2009 publication.[125] Examination of the reaction by GC-MS (extended run time) revealed that substantial amounts of boronic ester remained intact, which is potentially indicative of a difficult transmetalation. In entry **2**, reaction conditions were changed by adding 300 ppm of water to no avail of the target product. The counter-ion of the carbonate base was changed from K^+ to Cs^+ (as a substantial counter-ion effect was observed in Fu 2013 publication[114]) in entry **3** producing a similar result to the previous 2 entries. In entry **4**, the stoichiometric amounts of Ag_2O were increased from 1.5 equivalents to 3.0 equivalents, which still left the secondary boronic ester intact. In entry **5**, attempts to push the cross-coupling reaction to completion by having the aryl iodide in mass excess (5 equivalents) thereby changing the limiting reagent to be the secondary boronic ester proceeded with no avail of target product.

Unfortunately, the target material was not observed in the GC-MS to any appreciable extent. In entry **6**, the base is changed from a carbonate to a fluoride base, CsF but again coupling was not observed. Further efforts are required to find the conditions that are capable of effecting what has proven to be, a non-trivial transformation.

Table 6. Base scan in vinyl iodide cross-coupling.



Entry	Base	Base Equivalents	Temperature (°C)	Reaction Result
1	K_2CO_3	1.5	85	N.R.
2	K_2CO_3	1.5	85	N.R.[a]
3	Cs_2CO_3	1.5	90	N.R.
4	K_2CO_3	1.5	90	N.R.[b]
5	K_2CO_3	1.5	90	N.R.[c]
6	CsF	1.5	90	N.R.

*Reaction conditions: β-iodostyrene **52** (1.0 equivalent), boronic ester **54** (1.2 equivalents), $Pd(PPh_3)_4$ (8 mol%), PPh_3 (0.32 mol%), Ag_2O (1.5 equivalents), base (1.5 equivalents), temperature 85/90 °C, DME [0.1 M]. [a]0.3 uL of water added to 1 mL distilled DME reaction solvent. [b]3.0 equivalents of Ag_2O in place of 1.5. [c]5.0 equivalents of β-iodostyrene **52** instead of 1.0 equivalent.*

In conclusion, a variety of efforts have been made in the past decade to employ vinyl halides, including iodides, as electrophilic coupling partners in the Suzuki-Miyaura cross-coupling reaction. Additional work will be required to address the coupling of vinyl iodides with the difficult-to-cross-couple secondary, organoboronanes. Recommendations to leverage this result include: the use of highly active NHC-Pd complexes as catalysts, use of fluoride sources to activate boronic acid derivatives, elevated temperatures, and a metal-ligand screen. The metal screen should be expanded to Cu and Ni precatalyst as well as various Pd(0) and Pd(II) precatalysts, among the NHC-Pd complexes are recommended. Ligand effects are also expected to have a profound effect on the stereochemical outcome, namely the *Z*:*E* ratio of the cross-coupling product.[153]

Chapter 5: Conclusions and Outlook

We have demonstrated the stereospecific cross-coupling of stereodefined boronic esters that proceed through a *syn*-S_E' mechanism to yield products with high levels of regio-control. The *generation* or conversely, the *conservation* of a styrenyl sub-unit in the product was a major driving force to obtain the highest levels of γ and α regioselectivity, respectively. The assignment of absolute configuration of both starting material and product allowed for assignment of the *syn*-S_E' mechanism. As a result of the mechanistic studies that determined the *syn* transmetalation pathway, we further demonstrated the importance of a discrete Pd-O-B bond linkage in the facile transmetalation step. The presence of a π-allyl intermediate of the transmetalation transition state was probed by the cross-coupling of a deuterated substrate (Figure 32) which indicated that the transmetalation intermediate is asymmetric and most likely does not proceed through strictly a π-allyl intermediate. The involvement of σ-π-σ isomerization to generate the α-bound organopalladium species that reductively eliminates to give the minor regioisomer was determined to be the minor pathway. Further mechanistic investigations of allylic boronic esters are currently being undertaken in our research lab.

Attempts were made to cross-couple *β*-iodostyrene **52** with a secondary, benzylic pinacolate boronic ester. GC-MS traces of crude reaction mixtures revealed substantial amount of the pinacolate ester intact and are indicative of a difficult transmetalation. Further work will be required to address this challenging reaction.

Chapter 6: Experimental

6.1 Methods

Spectral analyses were all conducted at Queen's University Department of Chemistry. Crude 1-D and 2-D NMR spectra were recorded on a Varian 400 (^{1}H: 400 MHz, ^{11}B: 128 MHz, ^{13}C: 101 MHz) or Bruker Avance 400 (^{1}H: 400.13, ^{11}B: 128.38, ^{13}C: 100.62) or a Varian 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) NMR spectrometer. ^{1}H and ^{13}C NMR spectra were referenced to the residual $CHCl_3$ *via* the residual *protio* solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in ppm. Alpha to gamma ratios were determined by GC-MS using an Agilent 6890 apparatus or on a HP 6850 network GC-MS equipped with Agilent 5975C VL MSD with Triple-axis detector. GC analyses were performed on an HP 6850 network FID-GC with automatic injector. The column used was a supelco B-Dex of 60 m in length with an internal diameter of 0.25 mm. The inlet conditions were 250 °C, 20 psi and a flow rate of 1.0 ml/min using a splitless injector with helium as the carrier gas. Chiral HPLC separations were done using an Agilent 1100 or 1260 series normal phase high performance liquid chromatography units using HP Chemstation for LC or LC-MS. Daicel Chiralcel with Chiralpak IA Guard Cartridge (10 x 4 mm), with Chiralpak IB Guard Cartridge (10 x 4 mm) or Chiralpak IC Guard Cartridge (10 x 4 mm) Chiralpak IC Guard Cartridge (10 x 4 mm) columns were used. Chiral GC analysis was carried out on an Agilent Technologies 6890N Network GC system equipped with Chiral GC Top Enhanced software and a Supelco Betadex 120 fused silica capillary column (30 m × 0.25 mm × 0.30 μm) or Chiraldex β-Dimethyl cyclodextrin (β-DM, 30 m × 0.25 mm). Thin Layer Chromatography was performed on aluminum backed silica plates and visualized with a UV source (254, 365 nm) and were stained with phosphomolybdic acid followed by heating. Column chromatography was run with flash grade silica (Silicycle, 50 μm particle size

and 60 Å porosity) and using reagent grade solvents. Optical rotation measurements were measured with AP-300 Automatic Polarimeter. The polarimeter was calibrated with an Atago-made "quartz control plate" (l= 50 mm, $\boldsymbol{\alpha_D^{23.0}}$= 15.09°) and optical rotations were recorded at 589 nm. A sample of (+)-camphor (acquired from Aldrich) was run after sample measurements to verify direction of rotation.

6.2 Materials

Unless otherwise noted, all air and moisture sensitive manipulations were carried out in oven dried (160 °C) glassware, under an atmosphere of argon gas. Diethylether and dimethoxyethane were distilled from Na-benzophenone ketal directly prior to use. All other chemicals were purchased from Acros, Alfa Aesar, Fisher Scientific, Sigma Aldrich, Strem and TCI Europe and were used without further purification unless otherwise stated. Of notable mention, both (*Z*)-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane and the corresponding isomer (*E*)-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane were purchased from Aldrich. Both dinitrogen bases: *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) and (-) sparteine were dried over CaH_2 and distilled prior to use.

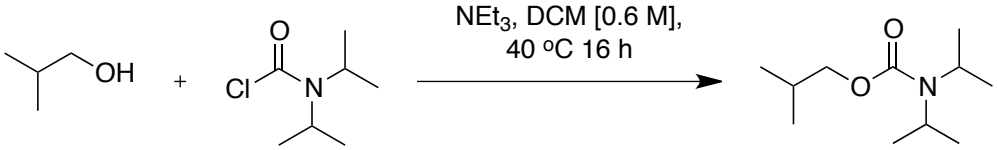
Unless otherwise noted, all cross coupling reactions were carried out in oven dried (160 °C) glassware, under an atmosphere of dinitrogen gas. Solvents were dried and deoxygenated with a minimum of three freeze-pump-thaw cycles before use and stored over molecular sieves (4 Å). Ag_2O was purified by Soxhlet extraction in water, and PPh_3 was recrystallized from ethanol. $Pd(dba)_2$ was used as received. Following standard procedures[157], iodobenzene was washed with $Na_2S_2O_3$ then water, and was then dried over $CaCl_2$, decolorized with charcoal and distilled under reduced pressure. Kugelrohr distillation was used to purify the compound further.

Coupling of aryl iodides with secondary allylic boronic esters were performed in 4 dram vials with air-tight Teflon caps under an atmosphere of nitrogen. Sealed vials were removed from the glovebox after the addition of reagents and solvent and stirred at 70 ºC for 16-24 h. Reaction solutions were cooled to room temperature, passed through a Celite plug and washed with copious amounts of diethyl ether.

6.3 Representative Synthetic Methods

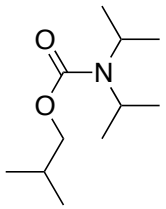
6.3.1 Representative Carbamate Synthesis

Isobutyl diisopropylcarbamate (CAS No. 959685-40-6)



A 250 mL flask containing a magnetic stir bar was charged with 2-methyl-1-propanol (6.20 mL, 5.00 g, 46.3 mmol, 1.00 equiv), *N*,*N*-diisopropylcarbamoyl chloride (7.95 g, 48.6 mmol, 1.05 equiv), triethylamine (6.97 mL, 4.92 g, 48.6 mmol, 1.05 equiv) and dichloromethane (80.6 mL, c = 0.57 M). A reflux condenser is fitted to the flask and is connected to an argon line. The reaction mixture is stirred and heated at reflux for 24 h. The reaction mixture was cooled to room temperature and transferred to a separatory funnel and washed with water (2 x 50 mL); the combined aqueous phases are extracted with dichloromethane (2 x 40 mL). The combined organic layers are washed with brine. Next, combined organic layers are dried over magnesium sulfate. After filtration of solids, the filtrate is concentrated *in* vacuo using a rotary evaporator. The carbamate is purified via silica gel chromatography with an eluent composition of hexanes: ethyl acetate = 95:5. The carbamate was visualized as a colorless spot using phosphomolybdic

acid dye. The carbamate, isobutyl diisopropylcarbamate (CAS No. 959685-40-6) was obtained as a colourless oil in 79% yield (7.32 g, 36.36 mmol).



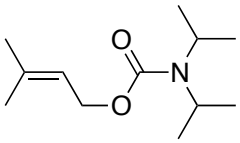
Color and state: colorless oil.

Yield: 7.32 g (79%, 36.36 mmol).

^{1}H NMR matched literature data for the compound.[158]

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (br. m, 2H, 2xNC*H*), 3.87 (d, J = 6.9 Hz, 2H, CH_3-CH-C*H*$_2$-OCb), 1.95 (m, 1H, $(CH_3)_2$-C*H*-CH_2), 1.21 (d, J = 6.9 Hz, 12H, 2x CH(C*H*$_3$)$_2$), 0.96 (d, J = 6.9 Hz, 6H, 2x (*CH*$_3$)-CH-CH_2-OCb).

3-Methylbut-2-en-1-yl diisopropylcarbamate (CAS No. 79792-72-6)

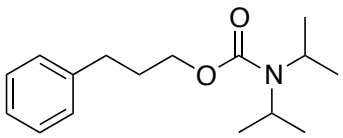


Color and state: colorless oil.

Yield: 3.75 g (86%, 17.6 mmol)

3-Methylbut-2-en-1-yl diisopropylcarbamate was synthesized via the general procedure described above via condensation of 3-methyl-2-buten-1-ol (2.7 mL, 20.4 mmol) with *N*,*N* – diisopropylcarbamoyl chloride (3.5 g, 1.05 equiv) and was isolated via column chromatography (hexanes:ethyl acetate = 9:1). (No literature data available) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.43-5.31 (m, 1H, C=C*H*), 4.57 (d, J = 7.2 Hz, 2H, C*H*$_2$OCb), 4.17-3.70 (br. s, 2H, 2 x NC*H*), 1.72 (d, J = 14.7 Hz, 6H =C(C*H*$_3$)$_2$), 1.19 (d, J = 6.9 Hz, 12H, 4 x O_2CN(CHC*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.0, 137.5, 120.0, 61.7, 46.0 (br), 25.9, 21.2, 18.2.

3-Phenylpropyl diisopropylcarbamate (CAS No. 218601-55-9)

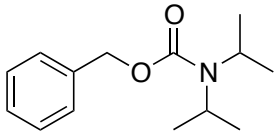


Color and state: colorless oil.

Yield: 1.97 g (79%, 7.95 mmol).

3-Phenylpropyl diisopropylcarbamate was synthesized via the general procedure via condensation of 3-phenylpropanol (1.3 mL, 10.1 mmol, 1.00 equiv) with *N,N*-diisopropylcarbamoyl chloride (1.76 g, 10.6 mmol, 1.05 equiv) and was isolated via chromatography (hexanes:ethyl acetate = 9:1). ^{1}H and ^{13}C NMR spectra matched literature.[158] ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.37-7.30 (m, 2H, Ph), 7.28-7.21 (m, 3H, Ph), 4.18 (t, J = 6.8 Hz, 2H, C$\underline{H_2}$-OCb), 3.84 (br. m, 2H, 2 x C$\underline{H}$N), 2.72 (t, J = 7.8 Hz, 2H, Ph-C$\underline{H_2}$), 1.98 (m, 2H, Ph-CH_2-C$\underline{H_2}$), 1.28 (d, J = 6.4 Hz, 12H, 4 x C$\underline{H_3}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 141.9, 128.7, 128.7, 126.2, 64.4, 45.1 (br), 32.9, 31.2, 21.4 (br).

Benzyl diisopropylcarbamate (CAS No. 26382-04-7)

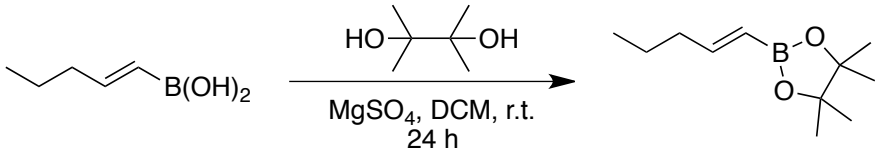


Color and state: colorless oil.

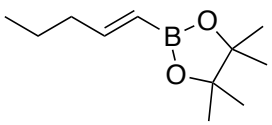
Yield: 3 g (74%, 12.8 mmol).

Benzyl diisopropylcarbamate was synthesized via the general procedure via condensation of benzyl alchohol (1.78 g, 17.6 mmol, 1.00 equiv) with *N, N*- diisopropylcarbamoyl chloride (2.96 g, 18.1 mmol, 1.05 equiv). ^{1}H and ^{13}C NMR spectra matched literature.[159] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 5 H, Ph), 5.03 (s, 2 H, Ph-C$\underline{H_2}$-OCb), 3.83 (br. m, 2 H, 2 x C$\underline{H}$N), 1.21 (d, *J* = 6.6 Hz, 12 H, 2 x CH(C$\underline{H_3}$)$_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 137.4, 128.7 (2C), 128.2 (2C), 128.0, 66.8, 46.2 (2C), 21.5 (4C).

6.3.2 Representative Boronic Ester Synthesis

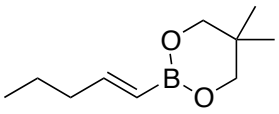


To a flask was added *trans*-1-penten-1-ylboronic acid (500 mg, 4.38 mmol, 1 equiv), 2,3-dimethyl-2,3-butanediol (517 g, 4.38 mmol, 1 equiv) and magnesium sulfate (2.64 g, 21.9 mmol, 2.5 equiv). The mixture was brought up in 22 mL of dichloromethane and allowed to react at room temperature for 24 h. The reaction mixture was then filtered, rinsed with dichloromethane and the filtrate was concentrated *in vacuo* using a rotary evaporator. *Trans*-1-penten-1-ylboronic acid pinacol ester (CASNo. 161395-96-6) was purified via silica gel chromatography (Hexanes: EtOAc = 95:5) to give 741 mg of the corresponding boronic ester in an 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (dt, *J*= 18, 6.4 Hz, 1 H, C*H*=CHBpin), 5.37 (d, *J* = 18 Hz, 1H, CH=C*H*Bpin), 2.12 (m, 2H, CH_2CH=CHBpin), 1.43 (m, 2 H, $CH_3CH_2CH_2$), 1.26 (s, 12H, BPin-(CH_3)$_4$), 0.90 (t, *J*= 7.2 Hz, 3 H, $CH_3CH_2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 83.3, 38.3, 25.1, 21.8, 14.1.



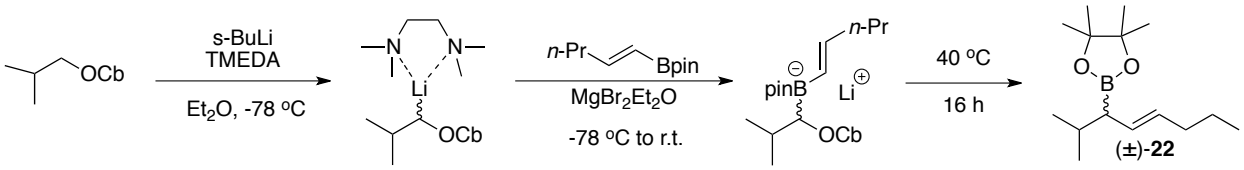
(*E*)-5,5-dimethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborinane

2,2-dimethyl-1,3-propanediol (731 mg, 7.02 mmol, 1.00 equiv) was used in place of 2,3-dimethyl-2,3-butanediol. The product (*E*)-5,5-dimethyl-2-(pent-1-en-1-yl)-1,3,2-dioxaborinane, was obtained as a colourless oil in 74% yield (946 mg, 5.20 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60-6.48 (m, 1 H, C*H*=CHBNeop), 5.37 (d, 1 H, J= 18 Hz, CH=C*H*BNeop), 3.65 (s, 4 H, (BO_2CH_2)$_2$C(CH_3)$_2$), 2.16-2.07 (m, 2 H, CH_2CH=CH), 1.50-1.38 (m, 2 H, $CH_3CH_2CH_2$), 0.99 (s, 6 H, (BO_2CH_2)$_2$C(CH_3)$_2$), 0.93 (t, *J*= 7.2 Hz, 3 H, CH_3CH_2). ^{13}C (100 MHz, $CDCl_3$) δ 151.7, 72.0, 37.6, 31.7, 21.8, 21.6, 13.7. ^{11}B NMR (128 MHz, $CDCl_3$) δ 26.0.

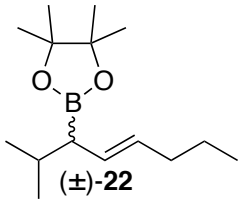


6.3.3 Representative Aggarwal Homologation Reaction

(*E*)-4,4,5,5-tetramethyl-2-(2-methyloct-4-en-3-yl)-1,3,2-dioxaborolane (±)-22

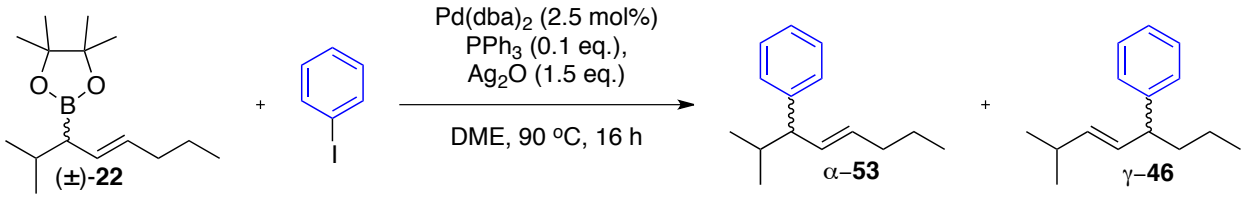


Using the procedure of Aggarwal and co-workers[79], *s*BuLi (1.6 M, 2.7 eq) was added dropwise to a -78ºC solution of carbamate (2.7 eq.) and (-)sparteine (2.7 eq) in anhydrous Et_2O (0.2 M). The mixture was stirred for 5 hours at -78ºC before a solution of vinylic boronic ester (1.0 eq) in ether (1.2 M) was added drop-wise. The mixture was stirred for 1 hour at -78 ºC when a solution of freshly prepared $MgBr_2$ in ether (0.9 M, 4.0 equiv) was added. The reaction mixture was warmed to room temperature and brought to reflux at 45 ºC for 16 hours. The reaction was cooled to room temperature and was extracted with Et_2O and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by column chromatography to give the corresponding secondary allylic boronic ester. The allylic boronic ester where *(E)*-4,4,5,5-tetramethyl-2-(2-methyloct-4-en-3-yl)-1,3,2-dioxaborolane (±)-**22** was isolated as a clear colourless oil in 75% yield:



^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41-5.26 (m, 2 H, HC=CH), 1.94 (q, 2 H, ^{3}J= 8 Hz, HC=CHCH_2), 1.75 (m, 1H, CH(CH_3)$_2$), 1.47 (t, 1 H, ^{3}J= 8 Hz, =C-CHB), 1.33 (sextet, 2 H, ^{3}J= 8 Hz, $CH_2CH_2CH_3$), 1.21 (s, 12 H, pin-(CH_3)$_4$), 0.89 (d, 3 H, ^{3}J= 8 Hz, CH_2CH_3), 0.85 (m, 6 H, (CH_3)$_2$CH). ^{13}C NMR (400 MHz): δ 130.7, 129.9, 82.9, 34.9, 29.6, 24.6, 24.7, 24.6, 22.8, 22.6, 21.9, 13.6. ^{11}B NMR (400 MHz): 35.47 ($BF_3 \bullet Et_2O$ referenced) HR-MS: calculated for $C_{15}H_{29}BO_2$ 252.2261(M^+), found 252.2270 (M^+).

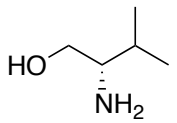
6.3.4 Representative Suzuki-Miyaura Cross-Coupling of Aryl Iodides with Benzylic Boronic Esters



In a glovebox, under a nitrogen atmosphere the boronic ester (*E*)-4,4,5,5-tetramethyl-2-(2-methyloct-4-en-3-yl)-1,3,2-dioxaborolane (±)-**22**, 35 mg, 1.39 x10^{-1} mmol], 4-iodoacetophenone (25 mg, 0.120 mol), Ag_2O (40 mg, 0.173 mmol), $Pd(dba)_2$ (3.32 mg, 5.77 x10^{-3} mmol, 5 mol% Pd), and PPh_3 (4.54 mg, 1.73 x10^{-2} mmol) were taken up in DME (1.16 mL) in a 4 dram vial. The vial was sealed with a Teflon cap and brought out of the glovebox and was stirred at 90 ºC for 24 h. The crude cross-coupling reaction mixture was passed through a Celite plug and was rinsed with copious amounts of hexanes and Et_2O. The filtrate was concentrated *in vacuo* and the cross-coupled product was isolated by column chromatography (95:5 hexanes: ethyl acetate). Isomers α–**53** and γ-**46** were separable via column chromatography. (*E*)-(7-methyloct-5-en-4-yl)benzene γ-**46** was isolated in 71% yield as a white powder. The major regioisomer was determined by COSY NMR spectroscopy of the crude cross coupling mixture (representative spectra is included). ^{1}H NMR (*E*)-(7-methyloct-5-en-4-yl)benzene γ-**46** (400 MHz, $CDCl_3$): δ 7.36 (d, 1H, ^{3}J= 6.9 Hz, *para*- Ar<u>H</u>), 7.30 (m, 4 H, *ortho*, *meta*-Ar<u>H</u>), 5.56-5.39 (m, 2H, C<u>H</u>=C<u>H</u>), 3.26-3.14 (m, 1 H, Ar-C<u>H</u>), 2.34-2.18 (m, 1H, $(CH_3)_2C\underline{H}$), 1.66 (m, 2H, =C-$C\underline{H_2}CH_2CH_3$), 1.40-1.17 (m, 2H, =C-$CH_2C\underline{H_2}CH_3$), 1.28 (s, 6 H, $(C\underline{H_3})_2CH$), 0.96 (m, 3H, ^{3}J= 8 Hz, $CH_2C\underline{H_3}$). ^{13} C NMR: δ 146.3, 137.5, 137.2, 130.9, 130.2, 128.3, 127.5, 125.8, 48.5, 38.5, 31.2, 29.8, 22.6, 20.7, 14.1. HR-MS calcd for $C_{15}H_{22}$: 202.1722, found 202.1726

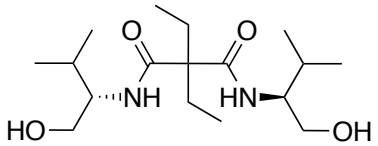
6.3.5 Total Ligand Synthesis (<u>31</u>)

L-valinol (CAS No. 2026-48-4)



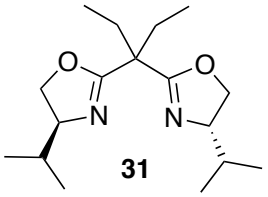
According to the literature procedure[160] $LiAlH_4$ (2.32 g, 61 mmol, 1.3 equiv) was crushed and put in a dry two neck round bottom flask that was fitted with a reflux condenser and was purged under Argon. The flask was cooled to 0 ºC and L-valine (5.5 g, 47 mmol, 1.00 equiv) was added portionwise. The reaction was heated at reflux for 1 h. After this time, the reaction mixture was cool to 0 ºC. An aqueous solution of KOH (1.28 g, 5 mL water, 4.6 M) was carefully added to the reaction mixture. The reaction mixture was again brought to reflux for 0.5 h during which the grey LAH suspension changed color to white. The reactions crude was extracted three times with dichloromethane and the combined organic layers were dried over $MgSO_4$. Upon filtration, the filtrate was concentrated *in vacuo* to give a crude yield of 4.8g (84%).

2,2-diethyl-*N*^{1},*N*^{3}-bis((*S*)-1-hydroxy-3-methylbutan-2-yl)malonamide.



4.07 g of crude L-valinol was taken up in 80 mL of dichloromethane, followed by addition of freshly distilled triethylamine and was cooled to 0 ºC. Diethylmalonyldichloride was added to the reaction mixture dropwise and was stirred for an additional 5 minutes at 0 ºC before warming to room temperature for 1 h, during which the reaction changed colour from translucent yellow to an opaque yellow suspension. The addition of dichloromethane dissolves the precipitated solid. The reaction solution was quenched with 20 mL of saturated $NH_4Cl_{(aq)}$. Aqueous layers were then washed thrice with 20 mL of dichloromethane. Combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to give a crude yield of 57% (7.36 g) of an off-white solid product.

(4*S*,4'*S*)-2,2'-(pentane-3,3-diyl)bis(4-isopropyl-4,5-dihydrooxazole)



31

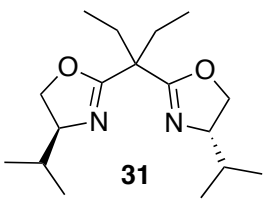
(CAS No. 160191-65-1) **31**.

Color and state: yellow oil.

7.35 g of the chiral diol (2,2-diethyl-N^1,N^3-bis((S)-1-hydroxy-3-methylbutan-2-yl)malonamide, 22.3 mmol, 1.00 equiv) was taken up in 220 mL of dichloromethane. 13.1 mL of freshly distilled NEt_3 (98 mmol, 4.4 equiv) was added to the reaction mixture and was cooled to 0 ºC. Mesylchloride was added to the solution and the reaction was stirred at 0ºC. The reaction mixture was brought to room temperature before adding NH_4Cl $_{(sat., aq.)}$ and brine. The organic layers were combined and dried over $MgSO_4$ before being filtered and concentrated *in vacuo* to yield 5.11 g of an orange oil as crude product.

3.3 g of the orange oil was taken up in 0.5 M NaOH MeOH: H_2O = 1:1 (51 mL) with a concentration of 12 mL of solvent per gram of mesylated crude. The crude was mostly soluble at room temperature. The dispersion was heated to reflux and stirred for 3h. The reaction mixture was cooled to room temperature and an additional 10 mL of MeOH was added to fully solubilize the product. The aqueous layer was extracted three times with dichloromethane and the combined organic layers were dried over $MgSO_4$. The bisoxazoline ligand, (4*S*,4'*S*)-2,2'-(pentane-3,3-diyl)bis(4-isopropyl-4,5-dihydrooxazole) **31** was isolated via column chromatography ($CHCl_3$: acetone 10:1) to give the product matching ^1H and ^{13}C NMR literature spectra.[161]

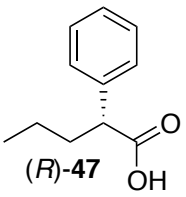
^1H NMR (500 MHz, $CDCl_3$) δ 4.22-4.14 (m, 2 H, 2 x -C*H*-N=), 4.00-3.92 (m, 4 H, 2 x -C*H*$_2$-CH-N=), 1.99 (m, 4 H, 2x -C*H*$_2$-CH_3), 1.80 (m, 2

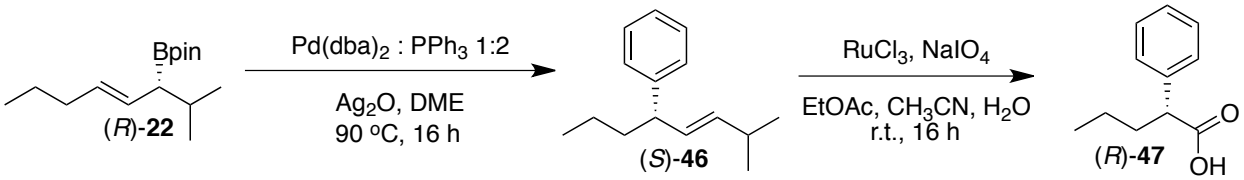


31

H, 2 x -C<u>H</u>-$(CH_3)_2$), 0.93 (d, J = 6.6 Hz, 6 H, 2x -CH_2-C<u>H_3</u>), 0.90-0.80 (m, 12 H, 2x -CH-($C\underline{H_3}$)$_2$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 72.1, 69.8, 47.0, 32.7, 25.6, 19.2, 18.1, 8.7.

6.4 Determination of the enantiomeric excess and absolute configuration of (*S*,*E*)-1-(7-methyloct-5-en-4-yl)benzene (*S*)-46: synthesis of (*R*)-2-phenylpentanoic acid (*R*)-47:





27 mg of (*S*,*E*)-1-(7-methyloct-5-en-4-yl)benzene (*S*)-**46** (0.133 mmol) was added to $NaIO_4$ (150.77 mg, 0.705 mmol, 5.3 eq) and was dissolved in a 1:1 mixture of CCl_4 and CH_3CN (1.66 mL) in a 4 dram vial. A solution of $RuCl_3.H_2O$ (1.24 mg, 0.006 mmol, 0.045 eq) in H_2O (1.25 mL) was added to the reaction mixture and the rection was stirred vigorously overnight. Three washings with 10 mL of $NaHCO_3$ was followed by three Et_2O extractions (10 mL). Concentrated $HCl_{(aq)}$ was added dropwise until the pH of the aqueous phase was 1-2. The aqueous layer was then extracted with CH_2Cl_2. The organic layers were combined and dried over $MgSO_4$. The organic solvent was filtered and dried *in vacuo*. The target compound (*R*)-2-phenylpentanoic acid (*R*)-**47** was purified by column chromatography (2% ethyl acetate in 98% hexanes). 6 mg of (*R*)-**47** was isolated in 25 % yield as a clear colourless oil. The purified carboxylic acid submitted to HPLC analysis (AD-H Column, hexane/2-propanol: 99.5/0.5, flow rate: 0.4 mL/min) t_R: 43.7 min (major), 46.7 min (minor). The enantiomeric ratio of the product was determined to be 95.9:4.1. $\boldsymbol{\alpha_D^{23.0}}$ = -28 (*c* 0.5, $CHCl_3$, optical rotation measured, average of

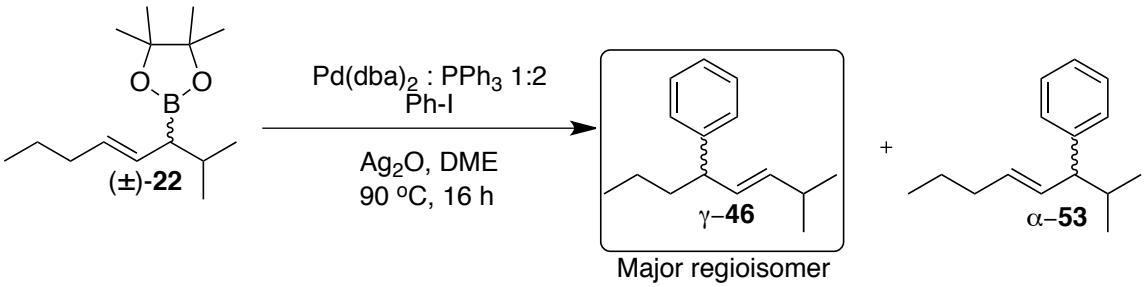
8 runs runs: -0.03 ±0.005°). Lit[162] (*S*)-(+)-2-phenylpentanoic acid $\boldsymbol{\alpha_D^{25.0}}$= +54.5 (*c* 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5 H), 3.59 (t, *J* = 7.1 Hz, 1 H), 2.13-2.01 (m, 1 H), 1.85-1.72 (m, 1 H) 1.39-1.23 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

The ^{1}H NMR was identical to that reported in the literature.[163]

6.5 Determination of Cross-Coupling Regioisomerism

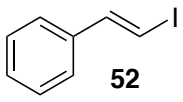
Determination of Major Regioisomer of Cross-Coupling reaction

From the 2-D COSY spectra (below) cross-peaks between olefin (5.5 ppm) and benzylic (3.2 ppm) and subsequently, benzylic (3.2 ppm) and CH_2 aliphatic (1.7 ppm) cross-peaks indicate that the γ regioisomer was present in the major amount. (We would expect aliphatic *isopropyl* CH-benzylic and benzylic olefin cross peaks for the α isomer.)



6.6 Chapter 4 – Vinyl Iodide Cross-Coupling

(*E*)-(2-iodovinyl)benzene 52

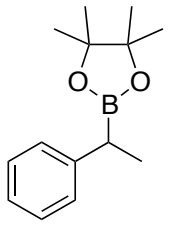


Following a literature sp^2-Finkelstein reaction[164] (*E*)-(2-bromovinyl)benzene (300 mg, 1.6 mmol, 1.0 equiv.), *N,N'*-dimethylethylene (17 μL, 0.16 mmol, 0.10 equiv.), CuI (15.2 mg, 0.08 mmol, 0.05 equiv.) and NaI (300 mg, 3.2 mmol, 2.0 equiv.) were added to a vial and purged with argon. Dioxane (0.2M) was added. The reaction was heated at 125°C for 24 hours. The crude mixture was cooled to room temperature and was passed through a Celite plug. GC-MS of reaction crude

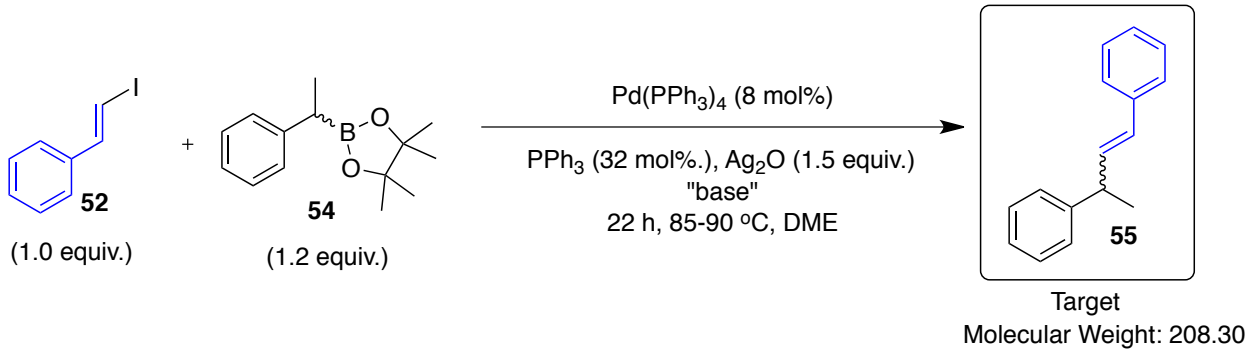
revealed complete consumption of starting material and only two peaks corresponding to the molecular weight of the product (*m/z* = 230.05). The product was purified by column chromatography, distilled twice and stored at in a freezer (-35ºC) in a glove box, away from light in a vial wrapped in aluminum. Spectra matched literature[165] ^{1}H NMR ($CDCl_3$, 400 MHz): 6.83 (1H, d, ^{3}J= 15 Hz, Ar-CH_2=C$\underline{H_2}$, *E*), 7.31 (5H, m, Ar), 7.45 (1H, d, ^{3}J= 15, Ar-C$\underline{H_2}$=CH_2, *E*).

Rhodium-Catalyzed Hydroboration of Styrene

4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane



In a N_2-filled glovebox [Rh(cod)$_2$][BF_4] (17 mg, 0.0419 mmol, 5 mol%) and *rac*-BINAP (26.06 mg, 0.0419mmol, 5 mol%) were weighed into a 4 dram vial. The solids were taken up in THF [0.022M] and were stirred for 10 minutes. The reaction mixture produced an opaque orange color and some insoluble precipitate formed. To this suspension was added styrene (96 µL, 0.8373 mmol, 1.0 equivalent) and was stirred for an additional 10 minutes. HBpin (148.2 µL, 1.0215 mmol, 1.22 equivalents) was then added. Both styrene and HBpin were measured using a micro Eppendorf pipette. The reaction was capped and was left to stir for 24 hours at glovebox temperature (~ 30 ºC). During the course of the hydroboration the reaction mixture formed an opaque orange suspension. After the reaction was complete (24 hours), the vial was removed from the glovebox and the contents were concentrated to a thick dark residue. The crude mixture was subjected to the column chromatography (95:5 hexanes: ethyl acetate). The boronic ester was collected as a clear and colourless oil (136 mg, 70%). The spectra recorded were consistent with the literature.[166] ^{1}H NMR analysis showed a branched to linear ratio of 75:25.

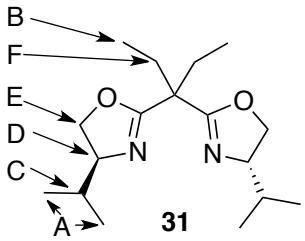


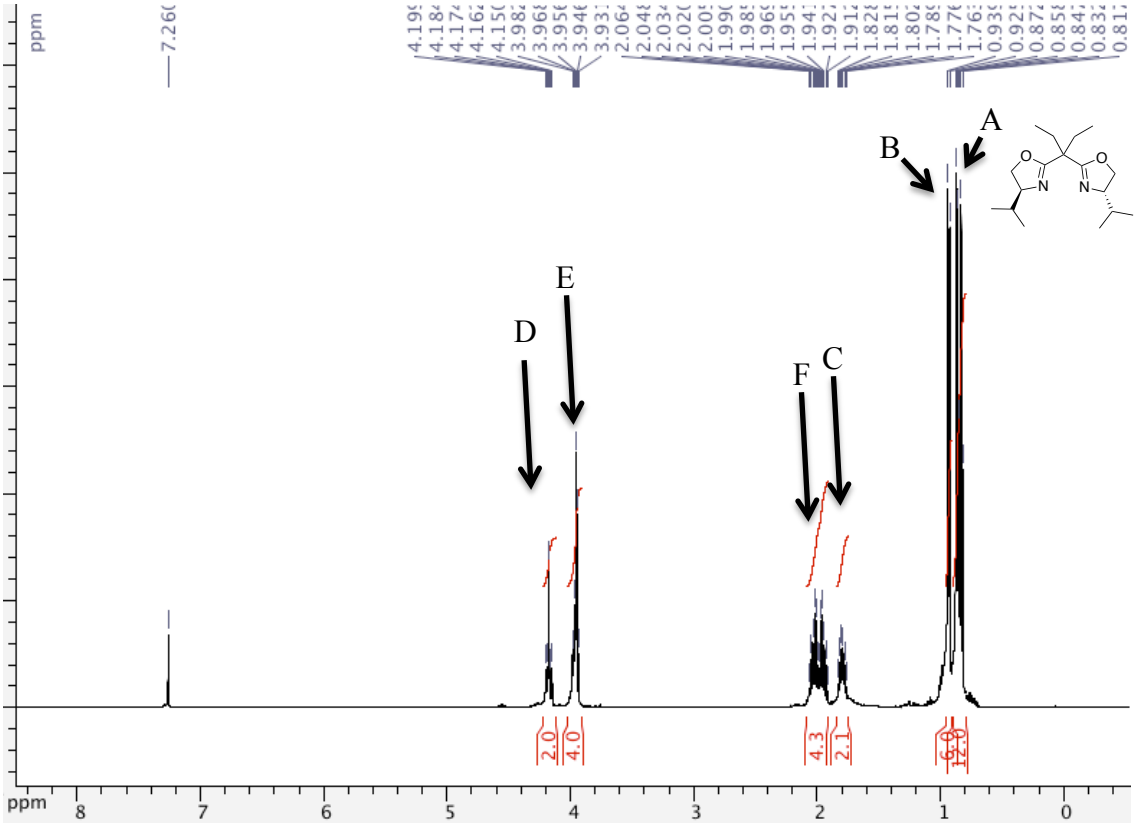
Cross-Coupling conditions: In glovebox filled with a N_2 atmosphere, β-iodostyrene **52** (11.5 mg, 0.05 mmol, 1.0 equivalent), boronic ester **54** (1.2 equivalents), $Pd(PPh_3)_4$ (8 mol%), PPh_3 (0.32 mol%), Ag_2O (1.5 equivalents), K_2CO_3 (1.5 equivalents) and DME [0.1 M] were added to a 4 dram vial and sealed with a telfon cap. The reaction vial was brought out of the glovebox and allowed to react overnight for 16 h and a temperature of 90 ^oC. After the reaction time was complete, the reaction was allowed to cool and was passed through a Celite plug with copious Et_2O washings. The crude reaction mixture was sampled for GC-MS and extended run times were used to monitor for peaks corresponding to M^+ (208.30) of the target cross-coupling product **55**. The crude reaction mixture was concentrated in vacuo and ^1H NMR spectra were recorded.

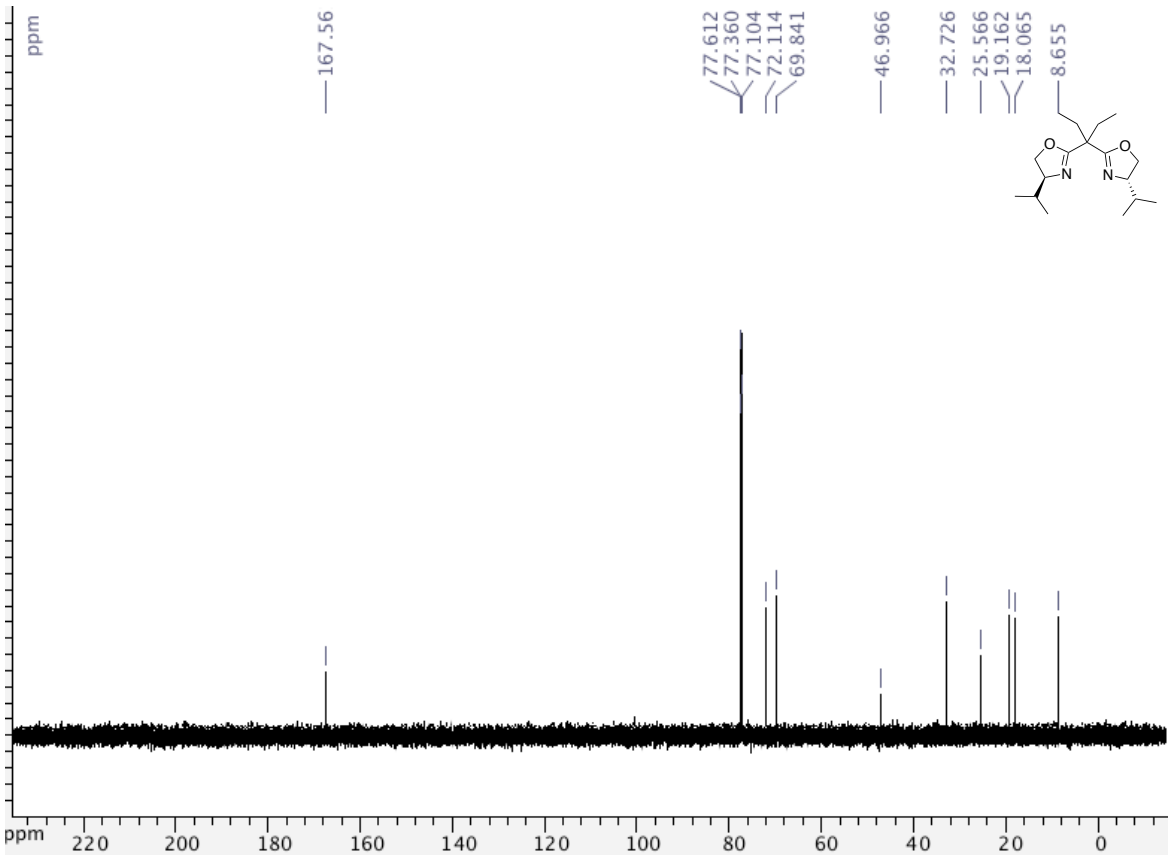
Appendix

Selected Spectra

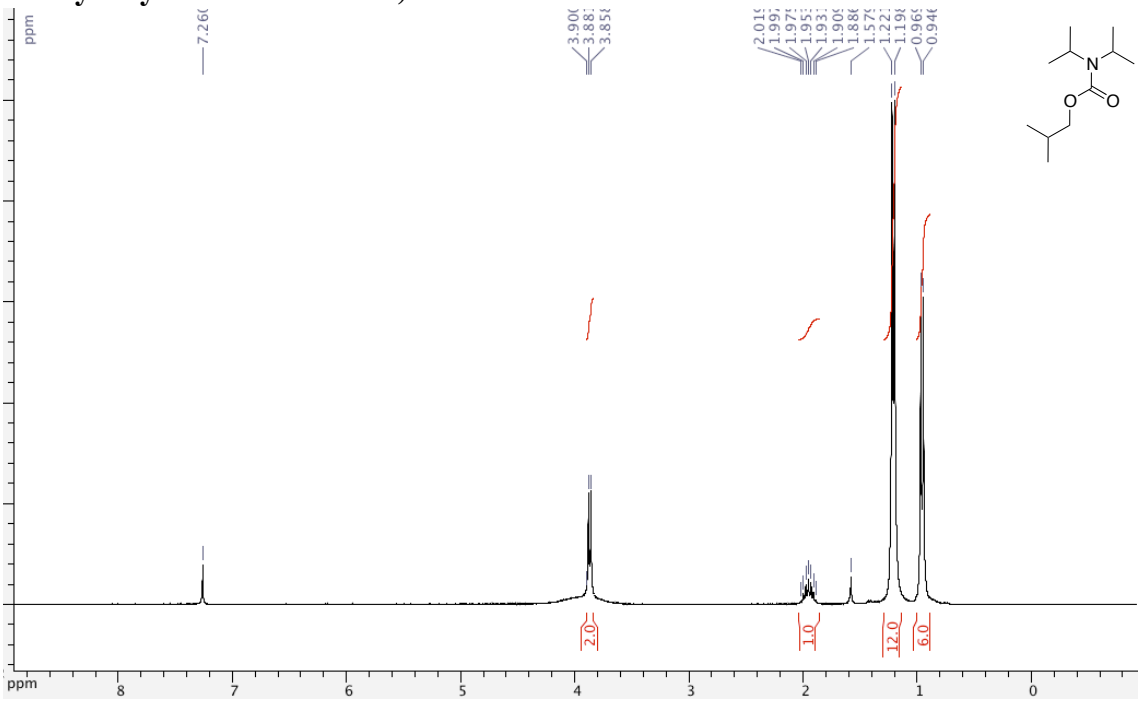
^{1}H and ^{13}C NMR Spectra of 31

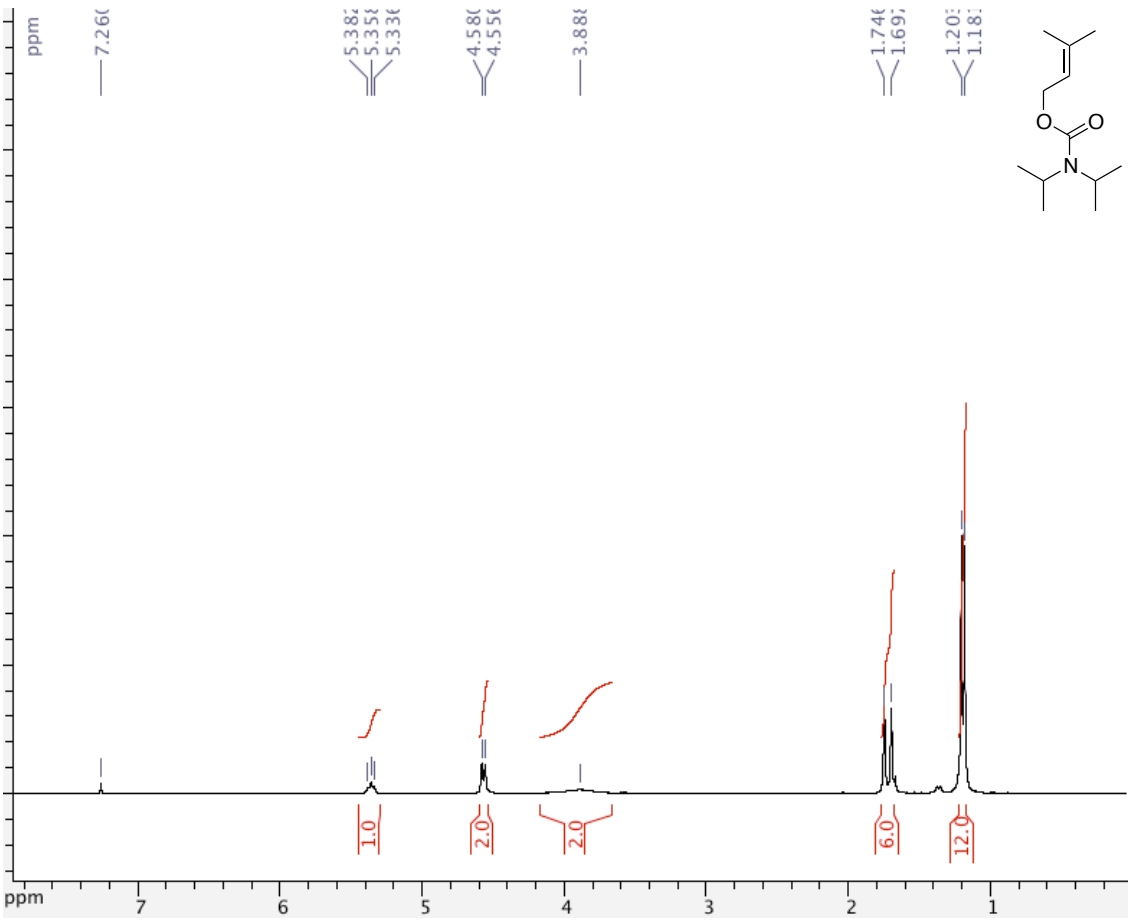


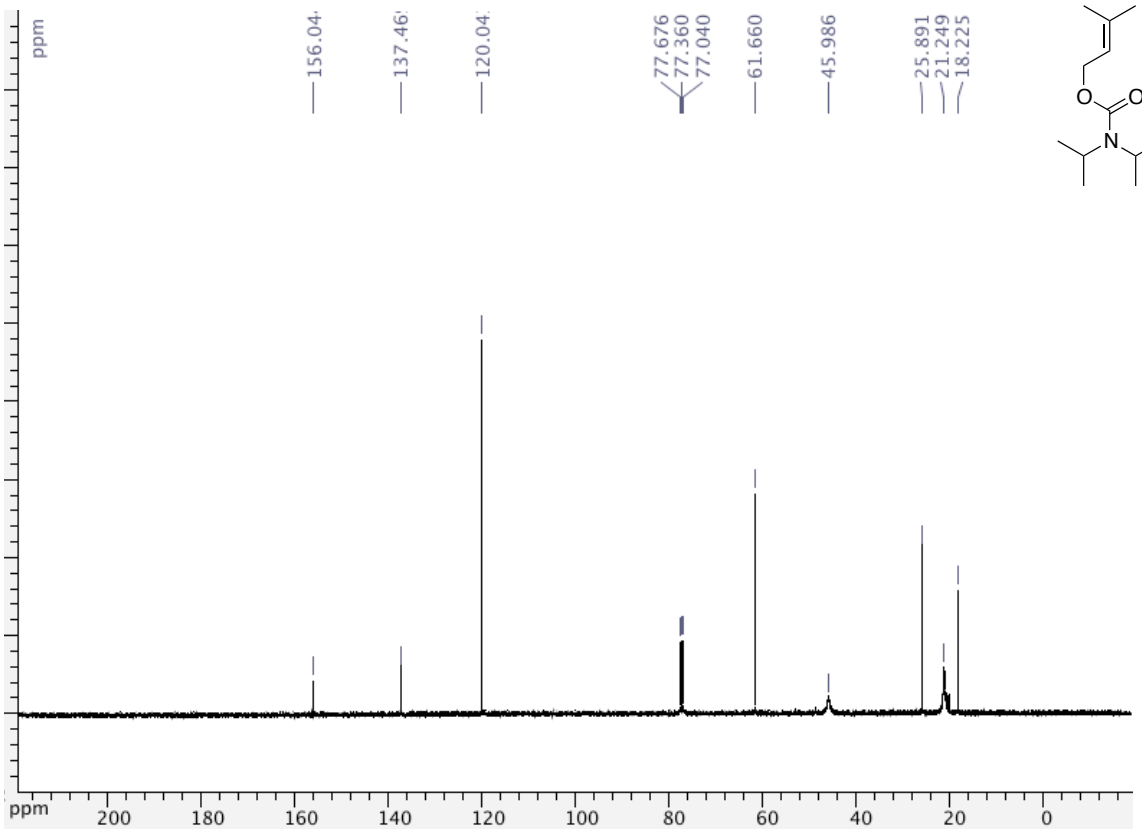


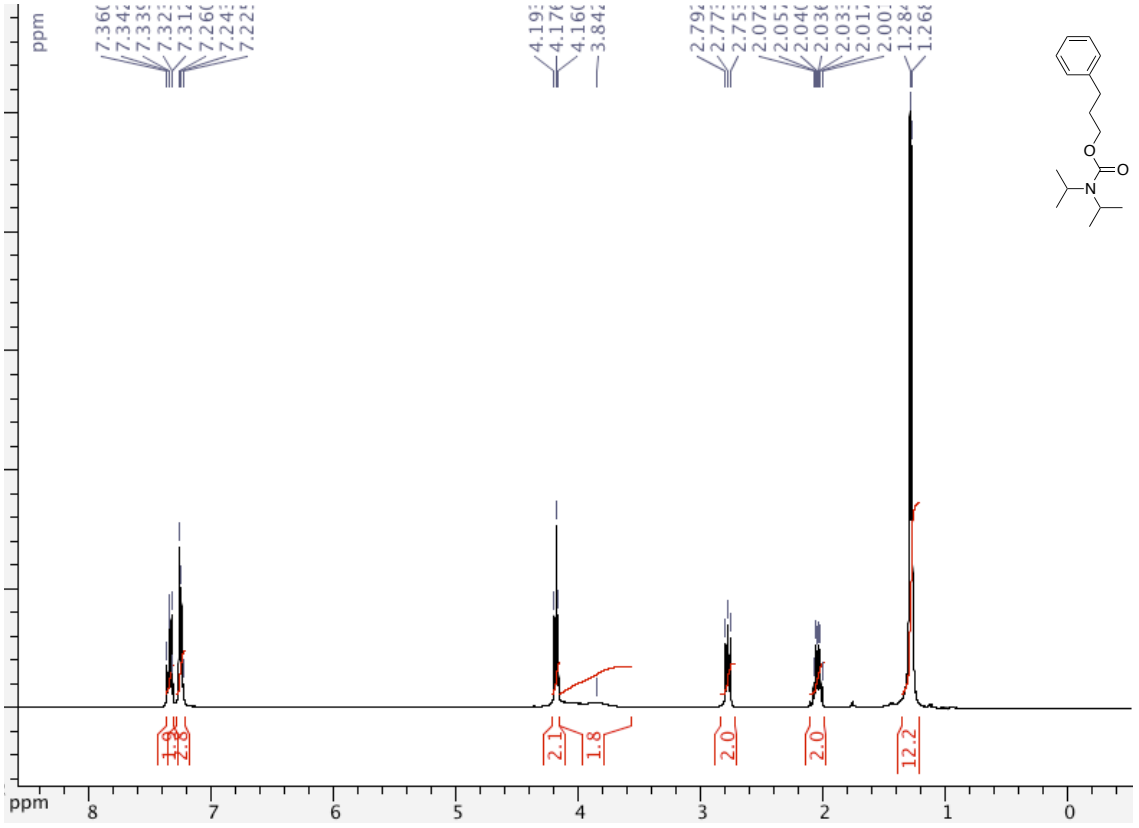


Selected Spectra (From Chapter 2 –Homologation and Chapter 3- Cross-Coupling of Secondary Allylic Boronic Esters):




ppm
7.26
5.38
5.35
5.33
4.58
4.55
3.88
1.74
1.69
1.20
1.18
1.0
2.0
2.0
6.0
12.0
ppm
7
6
5
4
3
2
1
O
O
N


ppm
156.04
137.46
120.04
77.676
77.360
77.040
61.660
45.986
25.891
21.249
18.225
O
O
N
ppm
200
180
160
140
120
100
80
60
40
20
0


ppm
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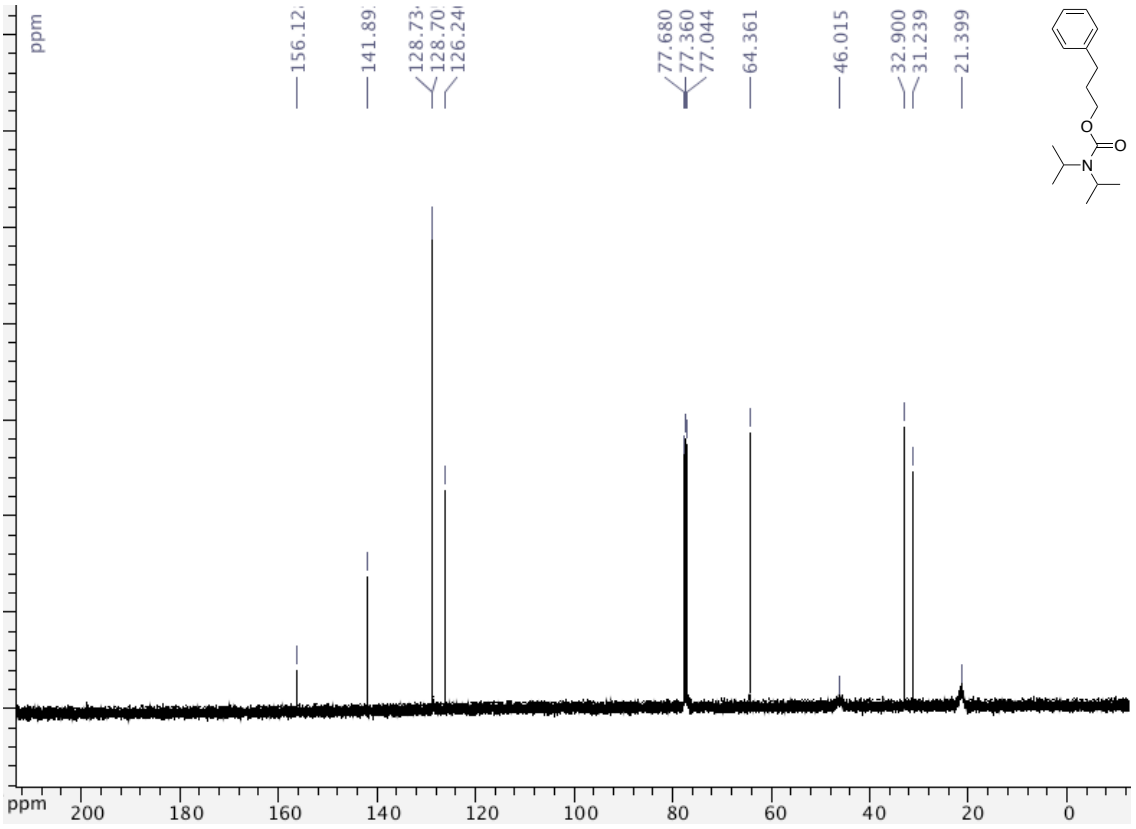
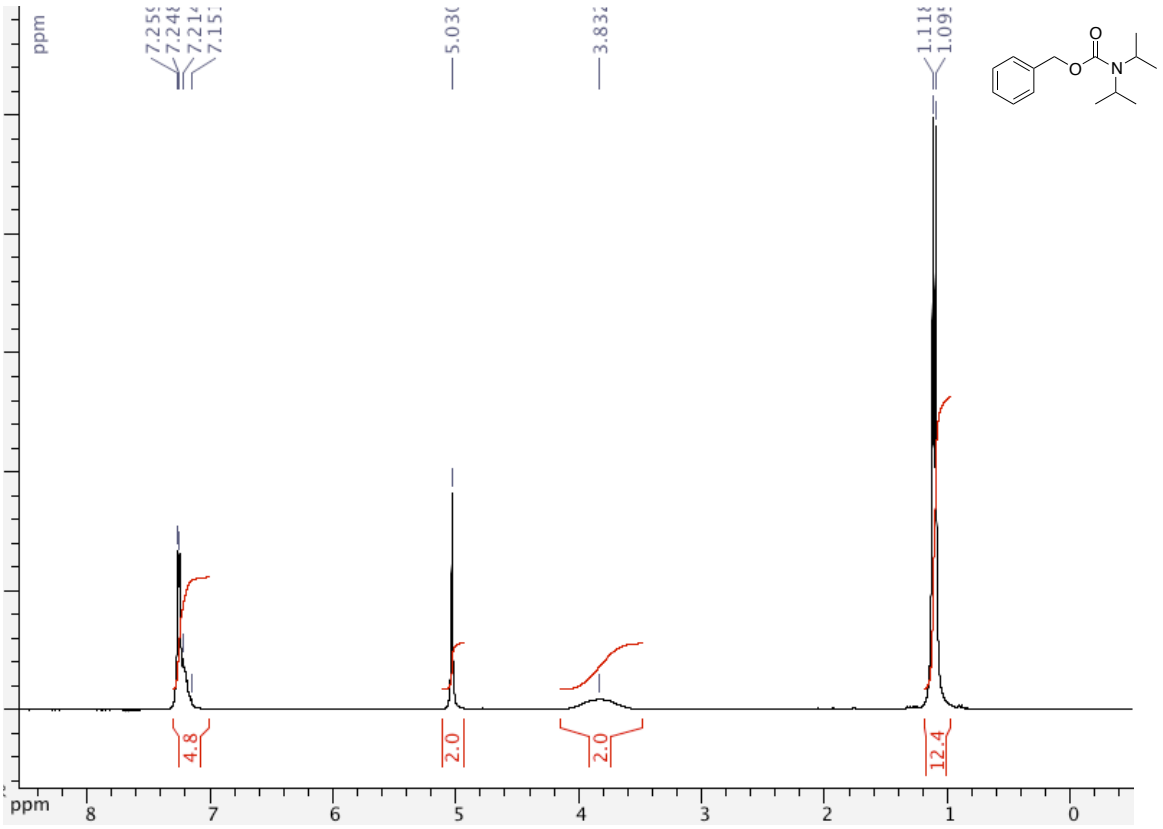
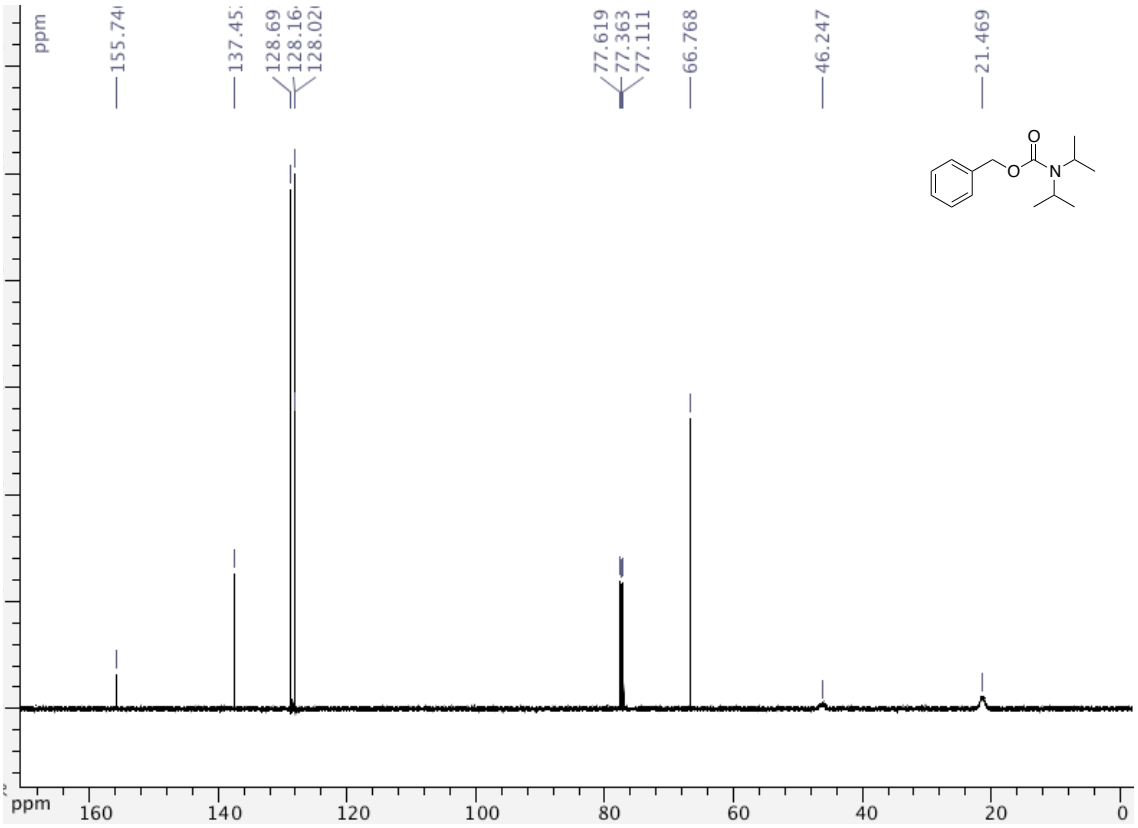
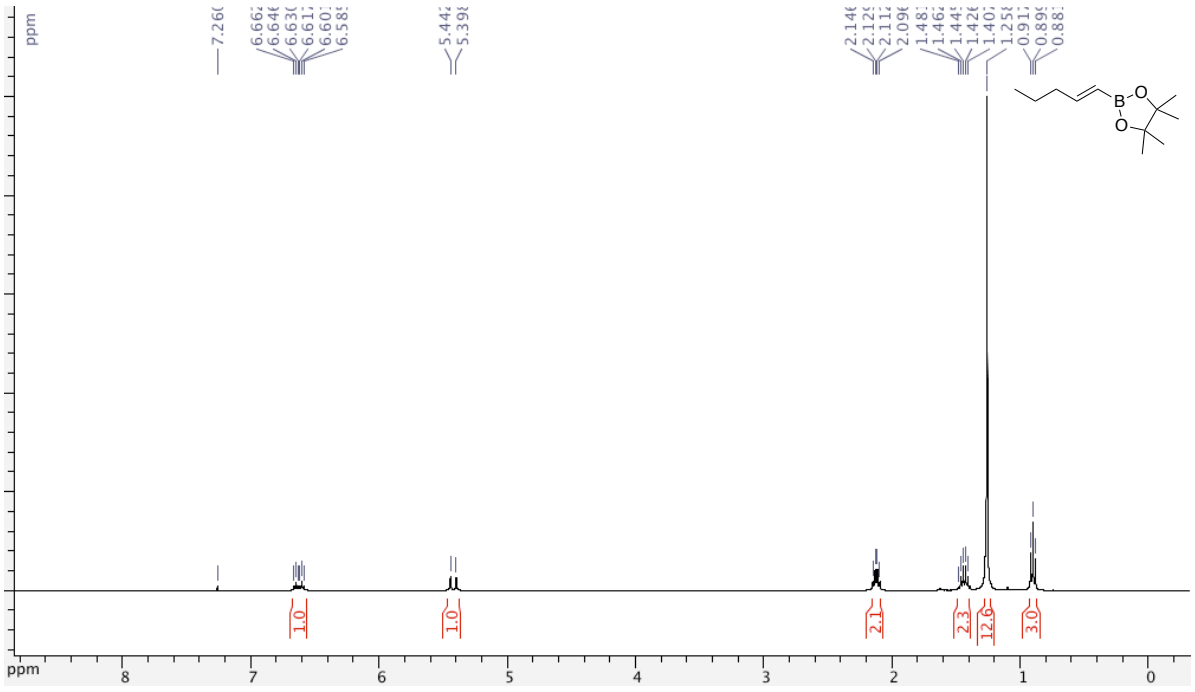
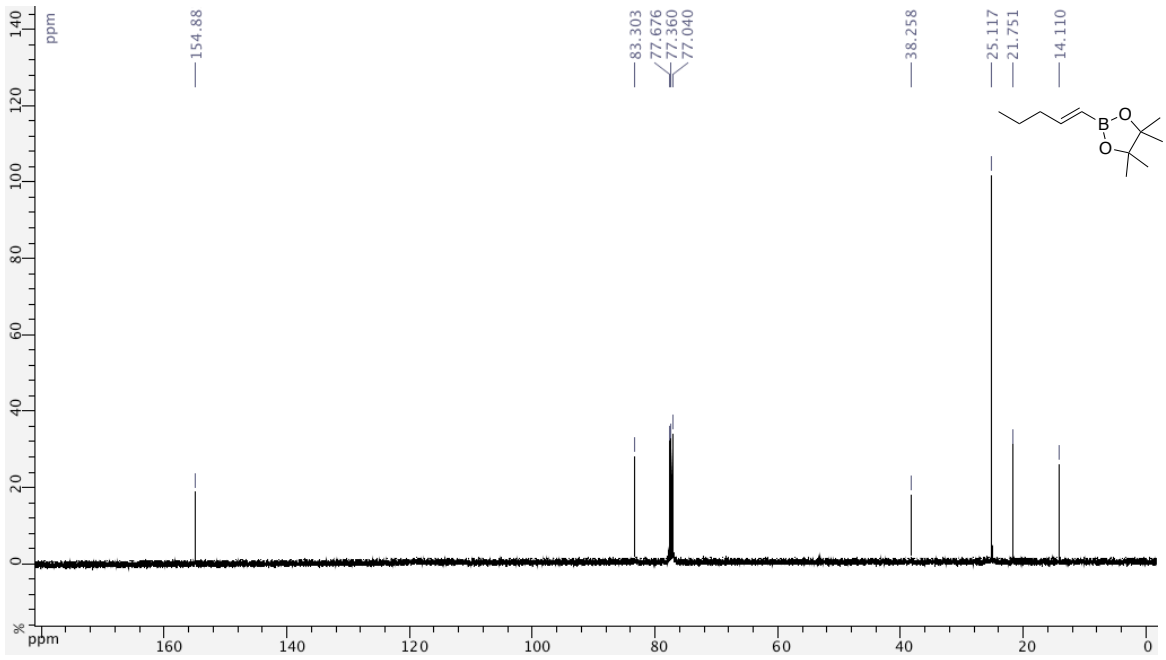
7.342
7.335
7.323
7.312
7.260
7.243
7.225
4.193
4.176
4.160
3.842
2.792
2.773
2.755
2.072
2.057
2.040
2.038
2.033
2.011
2.001
1.284
1.268
O
O
N
1.9
2.8
2.1
1.8
2.0
2.0
12.2
ppm
8
7
6
5
4
3
2
1
0

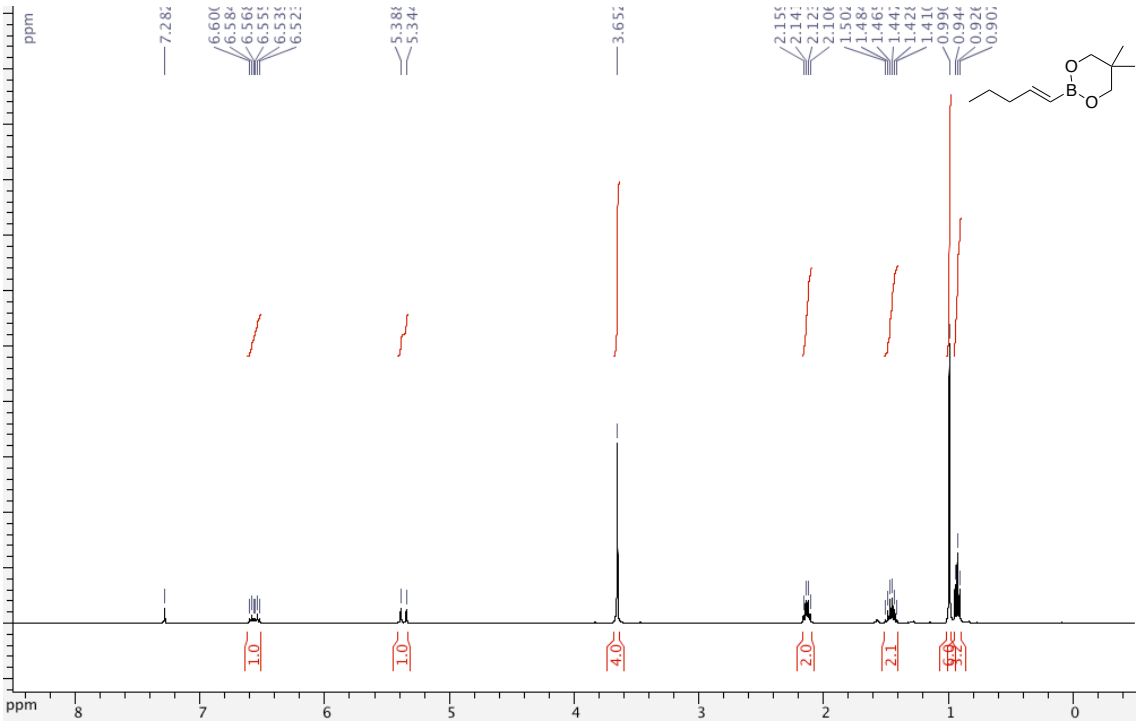

ppm
156.12
141.89
128.73
128.70
126.24
77.680
77.360
77.044
64.361
46.015
32.900
31.239
21.399
O
O
N
ppm
200
180
160
140
120
100
80
60
40
20
0


ppm
7.255
7.248
7.214
7.151
5.030
3.832
1.118
1.095
4.8
2.0
2.0
12.4
ppm
8
7
6
5
4
3
2
1
0


ppm
155.748
137.455
128.690
128.161
128.021
77.619
77.363
77.111
66.768
46.247
21.469
ppm
160
140
120
100
80
60
40
20
0

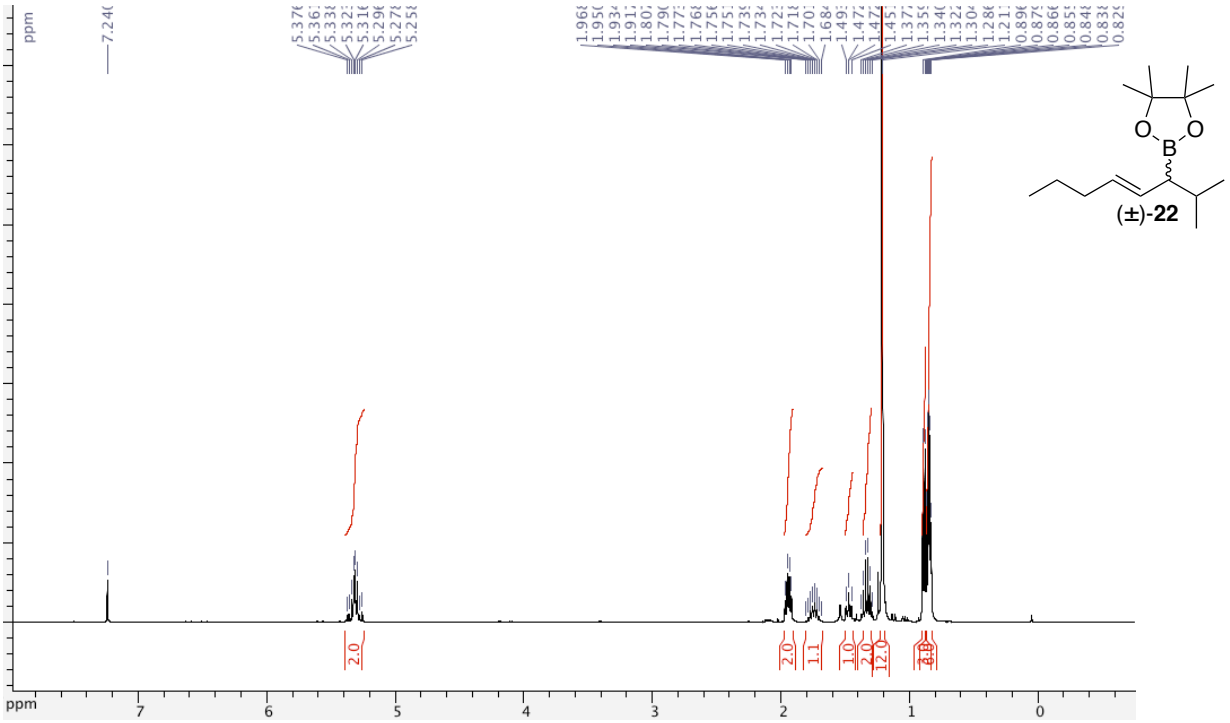

ppm
1.0
1.0
2.1
2.3
12.6
3.0

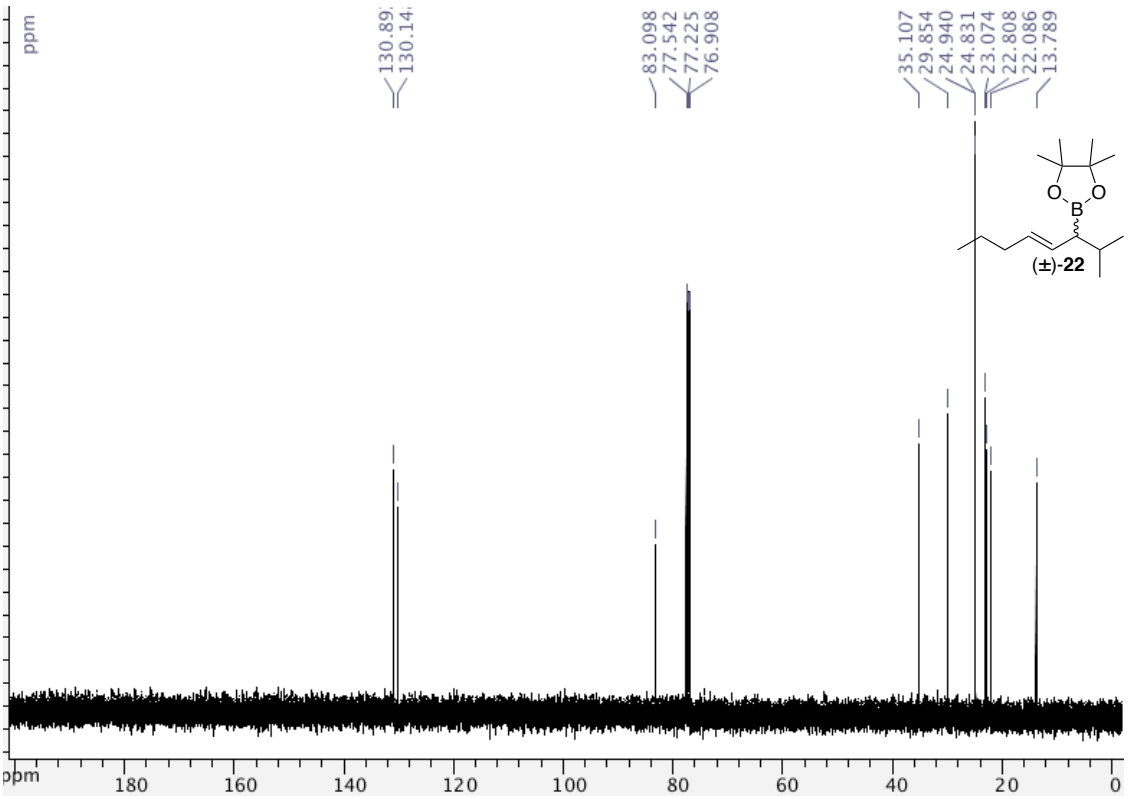

ppm
154.88
83.303
77.676
77.360
77.040
38.258
25.117
21.751
14.110



Chapter 2

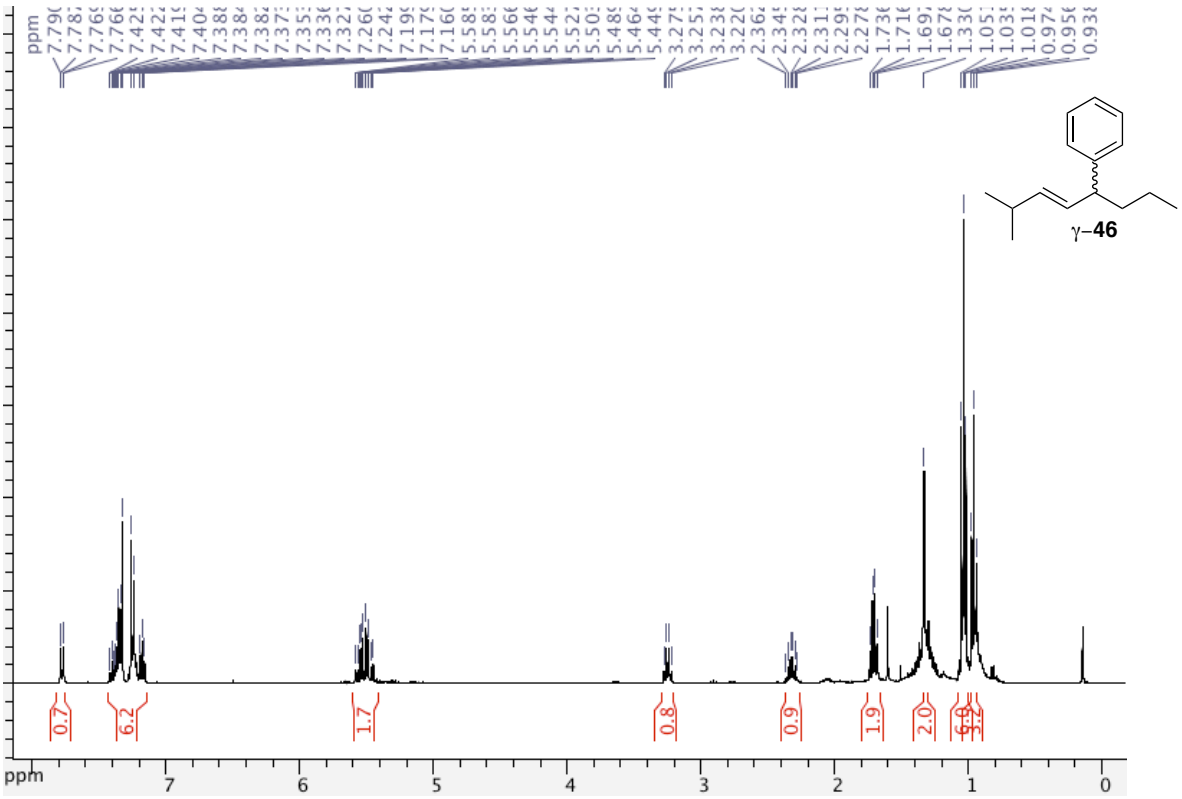
Representative Homologation Product Spectra

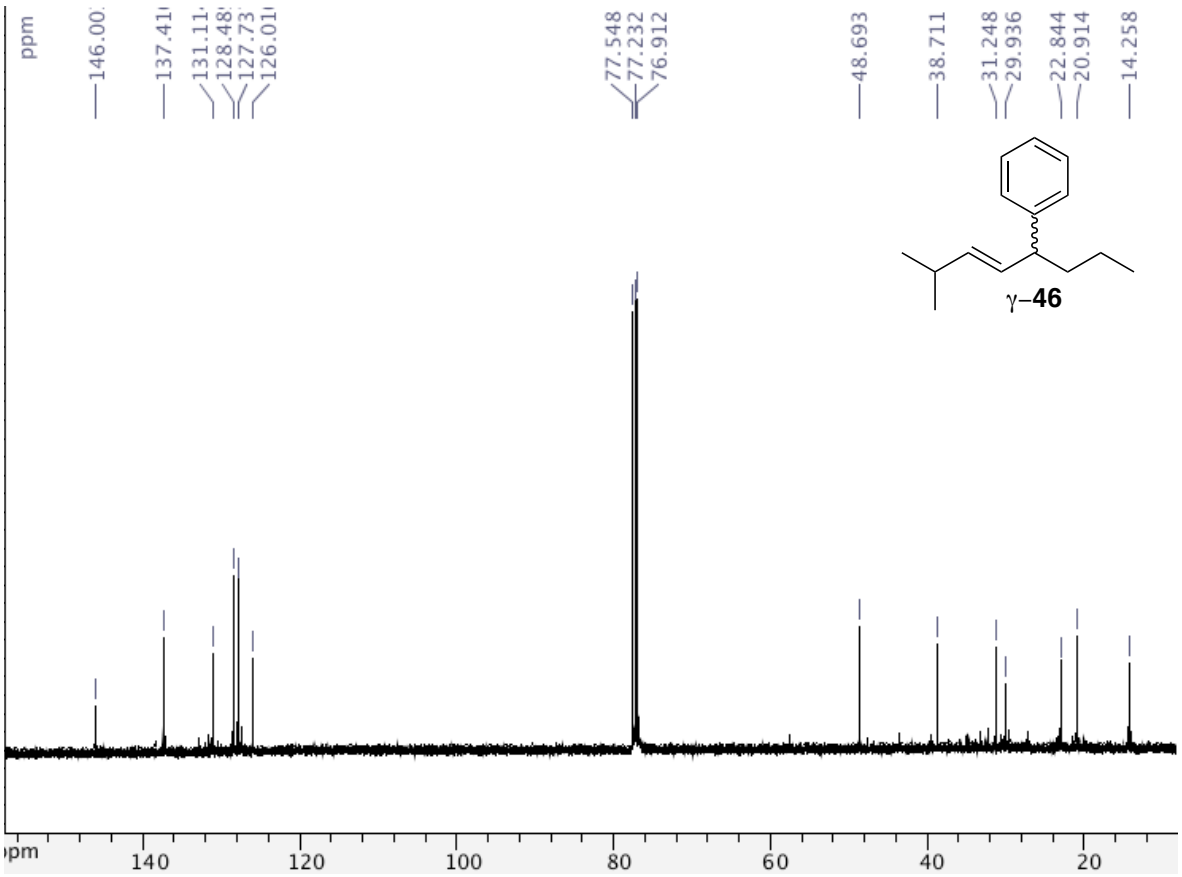




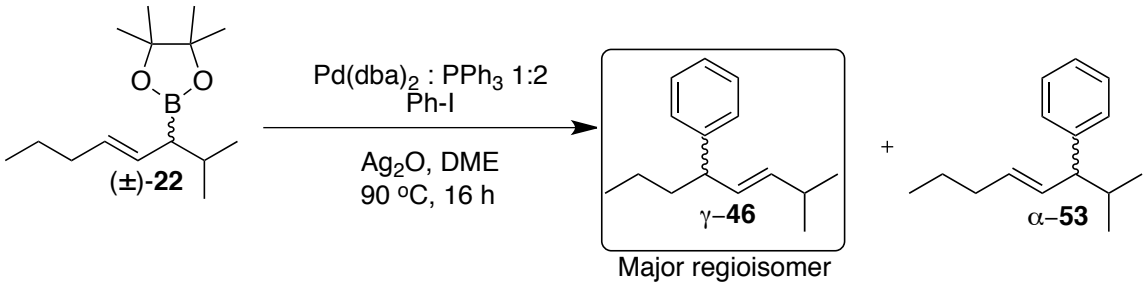
Chapter 3

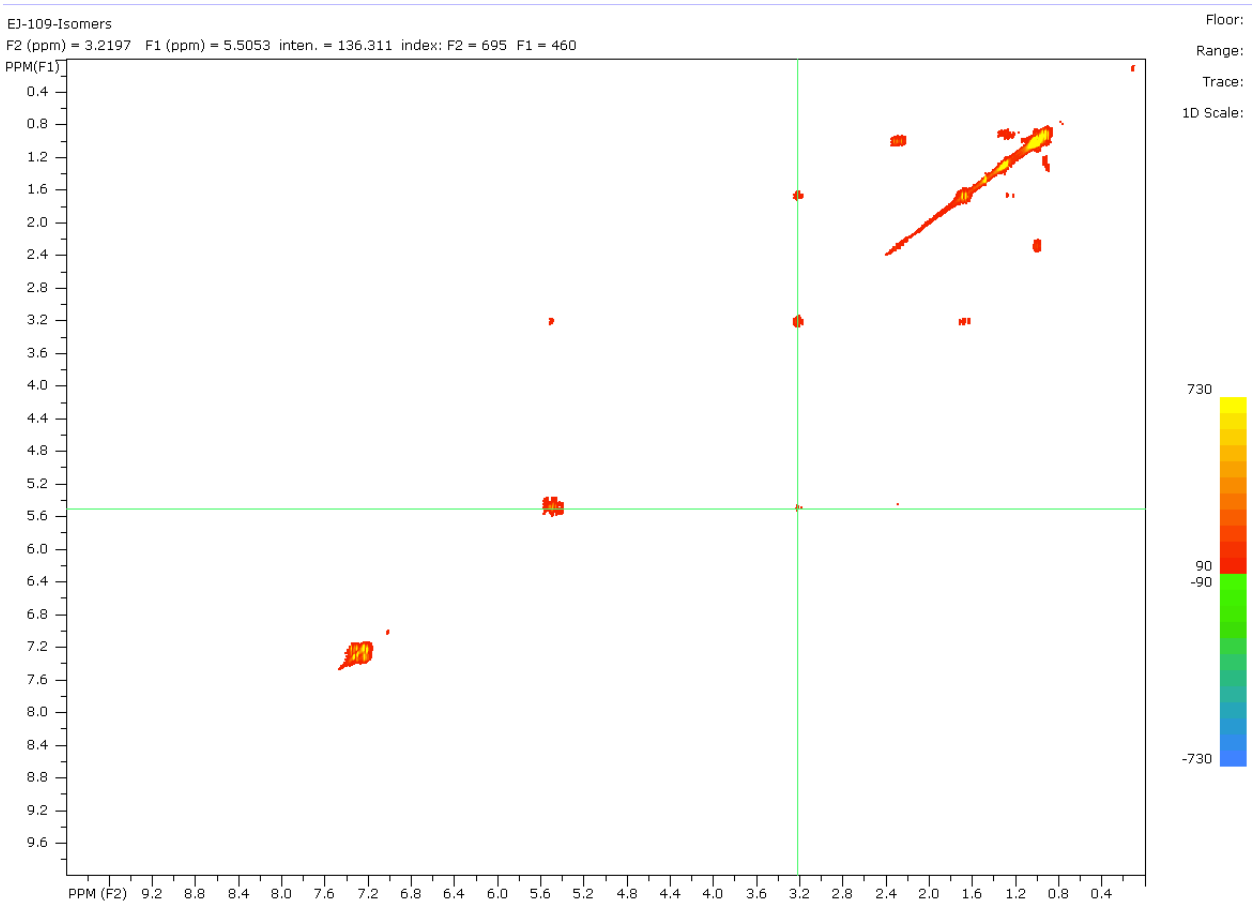
Representative Cross-Coupling Spectra

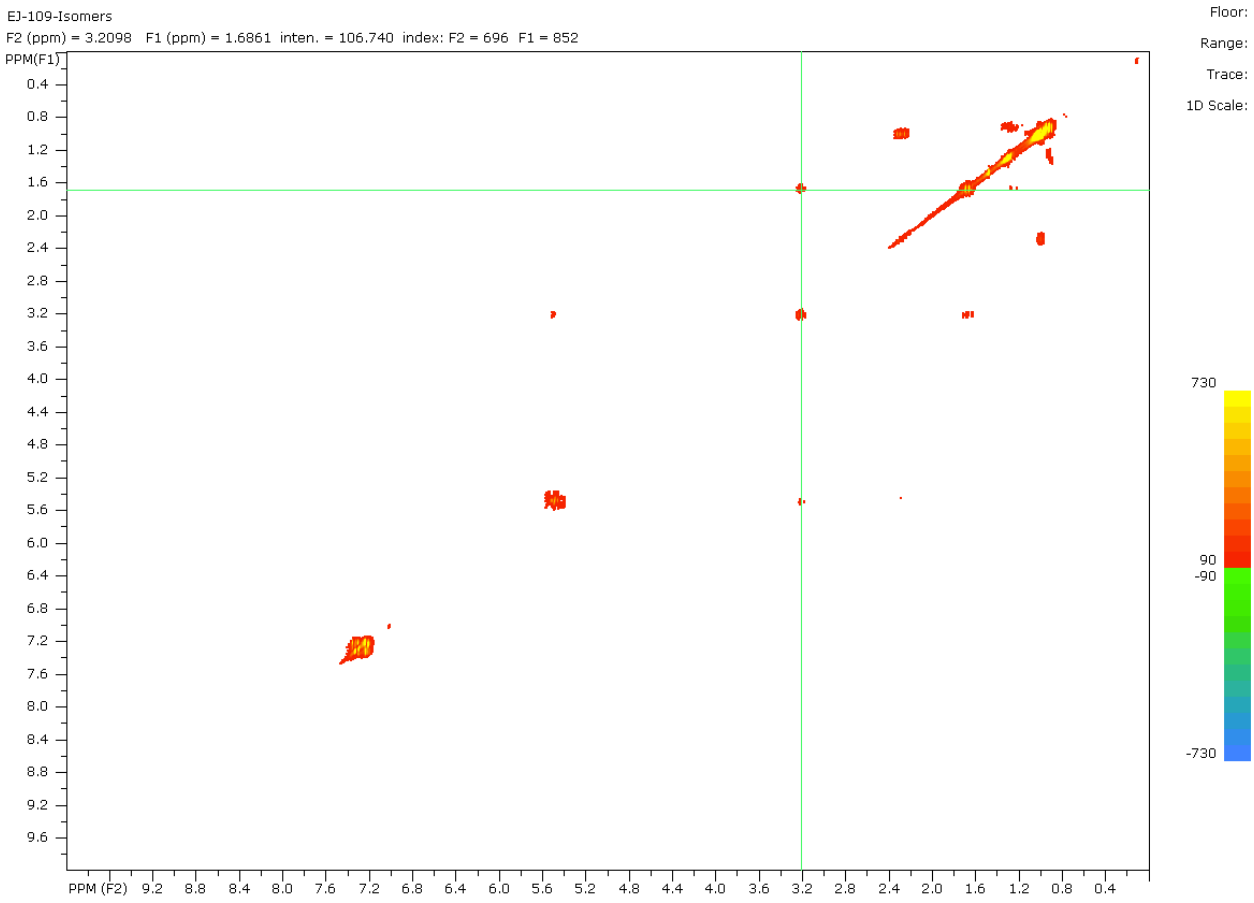

γ–46
ppm
0.7
6.2
1.7
0.8
0.9
1.9
2.0
6.0
3.2
7
6
5
4
3
2
1
0



COSY spectra of (*E*)-(7-methyloct-5-en-4-yl)benzene γ-46 (MAJOR) compound with (*E*)-(2-methyloct-4-en-3-yl)benzene α-53 (MINOR) (COSY was recorded of crude reaction mixture, post Celite plug)

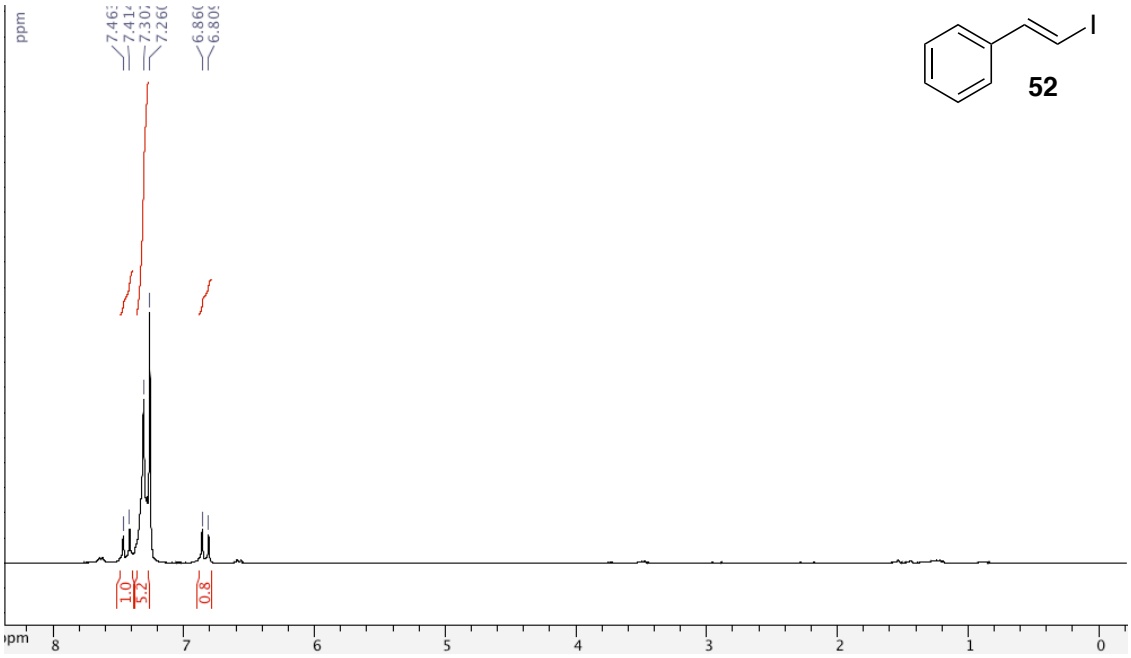



EJ-109-Isomers
F2 (ppm) = 3.2197 F1 (ppm) = 5.5053 inten. = 136.311 index: F2 = 695 F1 = 460
Floor:
Range:
Trace:
1D Scale:
PPM(F1)
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
8.0
8.4
8.8
9.2
9.6
PPM (F2) 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4
730
90
-90
-730

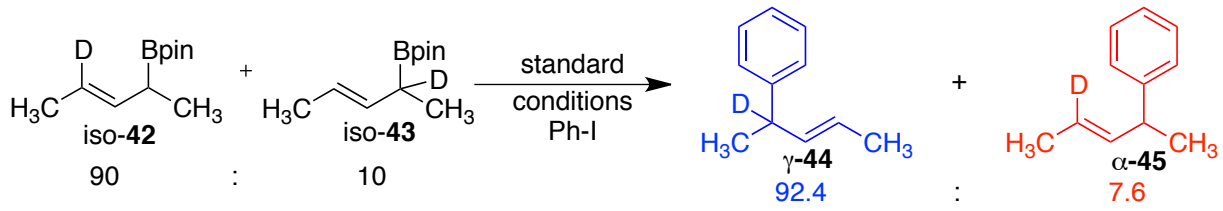

EJ-109-Isomers
F2 (ppm) = 3.2098 F1 (ppm) = 1.6861 inten. = 106.740 index: F2 = 696 F1 = 852
PPM(F1)
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
8.0
8.4
8.8
9.2
9.6
PPM (F2) 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4
Floor:
Range:
Trace:
1D Scale:
730
90
-90
-730

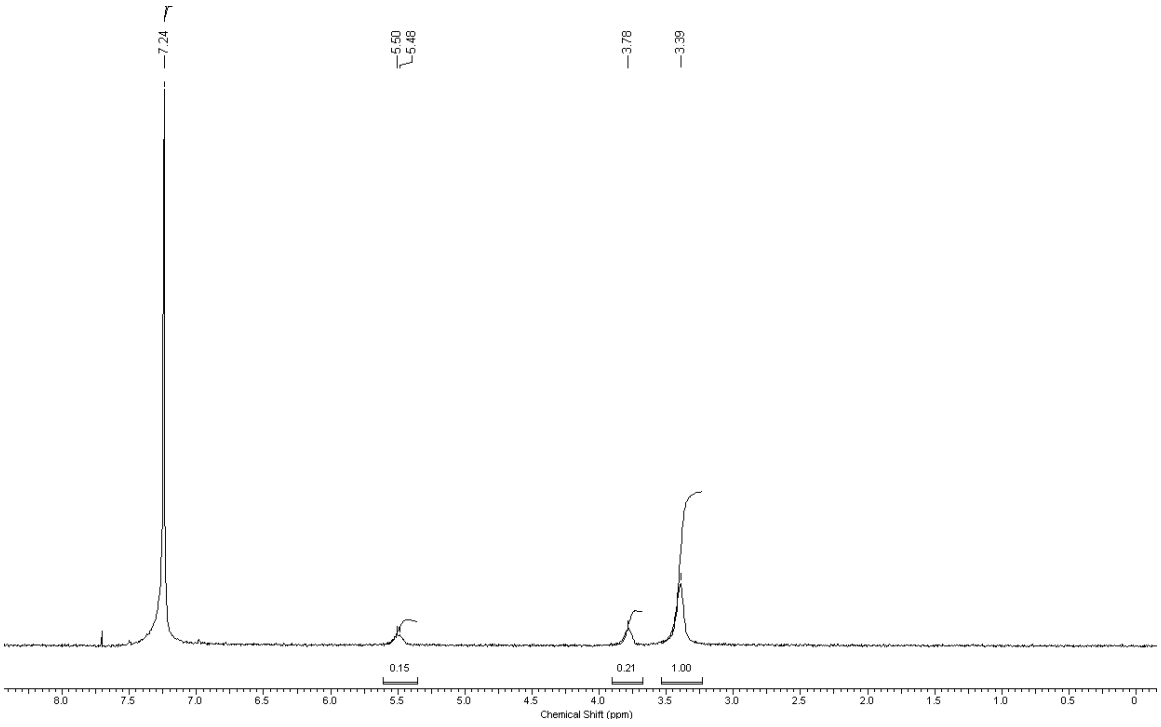
Chapter 4- Vinyl Iodide Cross-Coupling (Attempts)

^{1}H NMR Spectrum of *β*-iodostyrene 52

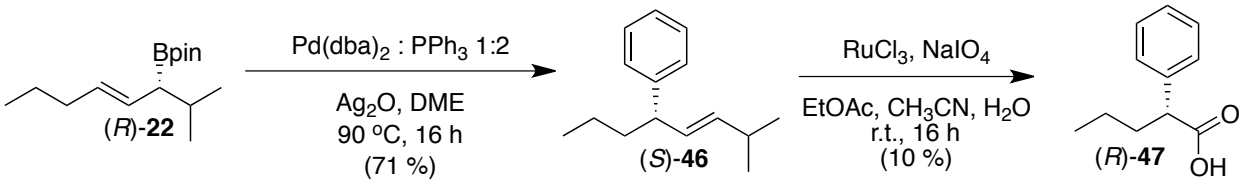


^{2}H NMR of Suzuki-Miayura Cross-Coupling of sterically and electronically unbiased deuterated, allylic boronic ester (Figure 32):





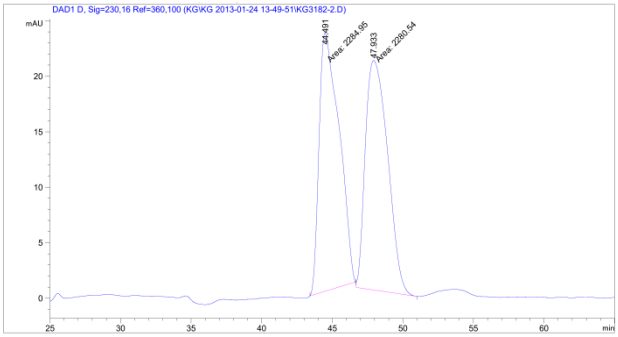
Determination of *ee* of (*R*)-21, (*R*)-22 and (*R*)-47:[104]

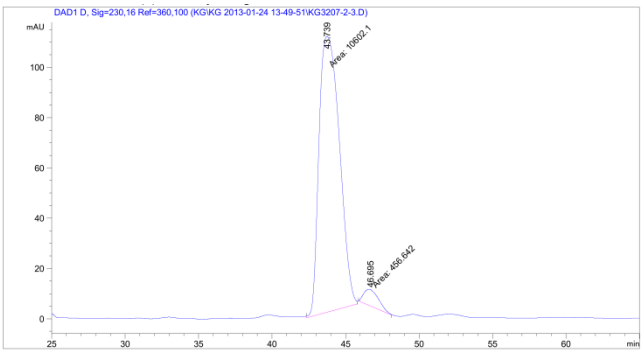


Chiral SFC/HPLC Conditions to separate the H_2O_2/NaOH oxidation product of (*R*)-22 and (*R*)-21, respectively: The *ee* of the corresponding alcohol of (*R*)-**22** was determined by SFC (OD column, 2 % MeOH, 2 mL/min., 200 bar) t_r minor: 7.5 min., t_r major: 9.8 min., e.r.= 92:2.

The *ee* of the corresponding alcohol of corresponding alcohol of compound **(*R*)-21** was determined by chiral HPLC (AD-H column, hexane : 2-propanol = 98:2, flow rate: 0.4 mL/min) t_r major: 16.9 min., t_r minor: 17.8 min, e.r. = 96:4.

Chiral HPLC Conditions to separate the RuCl3 $NaIO_4$ oxidation product (*R*)-47: AD-H column, hexanes: 2-propanol = 99.5: 0.5, flow rate: 0.4 mL/min. Retention times of major and minor isomers- t_r (minor): 43.7 min., t_r (major) 46.7 min. e.r. 95.9:4:1.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.491	MM	1.6325	2284.94653	23.32761	50.0483
2	47.933	MM	1.8388	2280.53931	20.67059	49.9517
Totals :				4565.48584	43.99820	

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.739	MM	1.6096	1.06021e4	109.77773	95.8708
2	46.695	MM	1.1794	456.64169	6.45304	4.1292
Totals :				1.10587e4	116.23078	

Chiral HPLC Conditions to seperater $RuCl_3$ and $NaIO_4$ oxidation product of compound (*R*)-56: HPLC AD-H column, hexanes: 2-propanol = 98:2, flow rate= 0.4 mL/min. t_r: 29.4 min (major) and 32.6 min (minor). e.r. 98.3:1.7.

References

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