AN ABSTRACT OF THE DISSERTATION OF

Christopher R Emerson for the degree of Doctor of Philosophy in Chemistry presented on November 10, 2011.

Title: Stereoselective Synthesis and Application of Enantioenriched Main Group α-Haloalkyl Organometal Reagents.

Abstract approved:

Paul R. Blakemore

Sulfoxide-ligand exchange (SLE) and asymmetric halogen-metal exchange (AHME) processes were separately examined for the enantioselective synthesis of functionalized alpha-haloalkylmetal (carbenoid) reagents. Carbenoids derived from SLE were used to effect stereospecific reagent-controlled homologation (StReCH) of boronic esters and those generated via AHME were engaged in Darzens-type chemistry with aldehydes.

Abstract for Part 1. Scalemic syn alpha-chloroalkylsulfoxides p-TolS(O)CHClR [R = allyl, (1,3-dioxolan-2-yl)methyl, properygyl, and 2-(benzyloxy)ethyl] were prepared from the corresponding thioethers by Jackson-Ellman-Bolm catalytic enantioselective sulfoxidation [cat. $VO(acac)_2$, tert-leucinol derived chiral Schiff base ligand, aq. H_2O_2, $CHCl_3$; 76-80% yield, >98% ee] followed by non-racemizing chlorination mediated by N-chlorosuccinimide in the presence of potassium carbonate (84-86% yield, syn:anti ≥ 20:1). The corresponding anti diastereoisomers were accessed from their syn epimers by sodium hexamethyldisilazide mediated deprotonation (THF, –78 °C) followed by treatment with either CH_3OH or CD_3OD to yield alpha-[^{1}H] or alpha-[^{2}H] isotopomers, respectively (88% yield, anti:syn ≥ 17:1). Allyl and (1,3-dioxan-2-yl)methyl substituted chlorosulfoxides reacted with R'Li (t-BuLi or PhLi, THF, –78 °C) to give the expected products of SLE [p-TolS(O)R' and LiCHClR or LiCDClR]; however, neither the benzylether nor propargyl substituted substrates gave

wholly satisfactory results under the same reaction conditions. The functionalized carbenoid reagents so obtained, 1-chloro-3-butenyllithium and 1-chloro-2-(1,3-dioxolan-2-yl)ethyllithium, were applied to the StReCH of B-(2-chloropyrid-5-yl) pinacol boronate but only the latter gave acceptable yields of chain extended products. The anti alpha-[^{2}H]-chlorosulfoxide dioxolanyl bearing carbenoid precursor gave superior results to the analogous syn or anti alpha-[^{1}H]-chlorosulfoxides for StReCH of the B-pyridyl boronate [79% conversion, ≥ 89% ee (99% stereofidelity), vs. ≤ 68% conversion for non-deuterated chlorosulfoxides]. The origin of this isotope effect was traced to a deleterious proton transfer pathway between the alpha-chloroalkyllithium reagent and its chlorosulfoxide precursor. Sequential double iterative StReCH of B-(2-chloropyrid-5-yl) pinacol boronate with two separate portions of (*S*)-1-[^{2}H]-1-chloro-2-(1,3-dioxolan-2-yl)ethyllithium (generated via SLE with phenyllithium) followed by oxidative work-up (with KOOH) gave (1*R*,2*R*)-1,2-[^{2}H]$_2$-2-(2-chloropyrid-5-yl)-1,2-bis[(1,3-dioxolan-2-yl)methyl]ethanol (40% yield, ≥ 98% ee, dr = 85:15). Substitution of the (*R*)-configured carbenoid for its antipode in the second StReCH stage above gave the *unlike* (1*S*,2*R*)-isomer of the same pyridylethanol derivative (49% yield, ≥ 98% ee, dr = 79:21). The *unlike* diastereoisomer was advanced to the trifluoroacetamide of (1*R*,2*R*)-1,2-[^{2}H]$_2$-1-amino-2-(2-chloropyrid-5-yl)cyclohex-4-ene (6 steps, 5% overall yield); the non-deuterated isotopomer of this compound was previously advanced to the analgesic alkaloid (–)-epibatidine by Corey and co-workers.

Abstract for Part 2. Scalemic planar chiral N,N-dialkyl 2-iodoferrocene carboxamides envisioned as recyclable precursors to ferrocenyl metal reagents for AHME, were prepared from ferrocene carboxylic acid by a three step sequence of: acid chloride formation [$(COCl)_2$ and cat. DMF)], aminolysis (with R_2NH, R = Me, Et, *i*-Pr; 65-80% yield over 2 steps), and *sec*-butyllithium/(–)-sparteine mediated enantioselective directed ortho-metallation (DoM) followed by iodinolysis (87% yield, ≥ 96% ee). Attempts to access more elaborate 5-substituted 2-iodoferrocene carboxamides via DoM/iodinolysis of ortho-substituted ferrocene carboxamides (Me, Ph, or $SiMe_3$ substituents) mostly failed; however, analogous trisubstituted ferrocene oxazolines could be synthesized. Treatment of *N*,*N*-diisopropyl 2-iodoferrocene carboxamide

(**298**, ≥ 96% ee) with *n*-BuLi (THF, –78 °C) resulted in complete conversion to the corresponding lithioferrocene (**327**) via I/Li interchange; subsequent iodinolysis initiated reverse Li/I exchange and returned iodoferrocene **298** without diminished enantiomeric excess, establishing configurational stability for the lithiated ferrocene intermediate. Prochiral ($RCHI_2$) and racemic (RCHICl) geminal dihalide substrates for AHME studies were prepared by electrophilic quench of dihalomethylsodiums with either $Ph(CH_2)_3I$ or Me_3SiCl (50-78% yield). Of the four dihalides so produced, only prochiral substrate Me_3SiCHI_2 engaged in I/Li exchange with scalemic lithioferrocene **327** resulting in regeneration of its precursor iodoferrocene **298** and the formation of a putative chiral carbenoid $Me_3SiCHLiI$. Trapping of the carbenoid with aldehydes RCHO (R = Ph, 4-$MeOC_6H_4$, $Ph(CH_2)_2$, c-C_6H_{11}) in the presence of Me_2AlCl gave the expected epoxysilane products (35-40% yield, cis:trans ≥ 2:1) but without discernable enantiomeric excess. Hypotheses to account for the apparent lack of stereoinduction in this AHME cycle are presented. Comparable experiments using analogous magnesiated ferrocenes failed to produce putative carbenoid species from the same set of geminal dihalide substrates.

Stereoselective Synthesis and Application of Enantioenriched Main Group α-Haloalkyl Organometal Reagents

by

Christopher R. Emerson

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APPROVED:

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Major Professor, representing Chemistry

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Chair of the Department of Chemistry

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Christopher R. Emerson, Author

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Stereoselective Synthesis & Application of Enantioenriched Main Group α-Haloalkyl Organometal Reagents

Chapter 1 *– Introduction to Carbenoids*

1.1 *– Background*

The term 'carbenoid' has evolved during the last several decades to include a wide range of highly reactive carbon centered species that possess both electrophilic and nucleophilic character. Presently, the term is used ubiquitously throughout synthetic and organometallic chemistry when discussing main group organometallic, hetero-atom substituted or transition metal centered species that exhibit similar reactivity to carbenes without specifically being a free divalent carbon species.

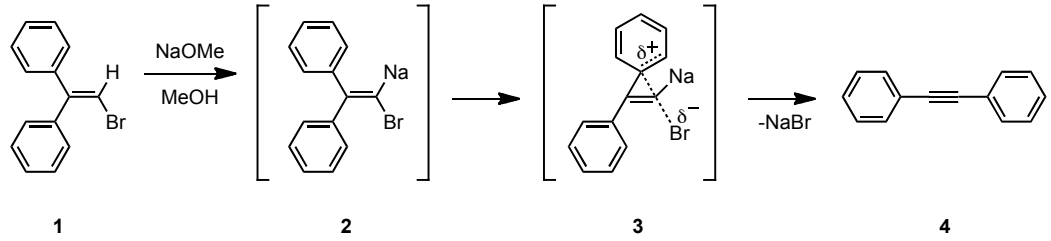
Genesis of carbenoid terminology began with the original definition that implied the formation of a carbene species through base catalyzed decomposition of tosylhydrazones in aprotic solvents.[1] Some years later, the term was used to describe a ligand exchange process where a bivalent carbon atom is substituted for another element.[2] Finally, in 1964 Closs and Moss introduced the term 'carbenoid' as a means to describe a species of reagent that exhibits the electrophilic behavior associated with carbenes without actually being a divalent species and this is where the term stands in today's lexicon.[3]

The following introduction will discuss the salient features of carbenoids as related to their structure and reactivity. This introduction is not intended to be comprehensive as several excellent reviews currently exist in the literature,[4,5,6,7] but it is intended to bring the reader's attention to the unique bifunctional character of these highly transient species as it relates to the work presented in this thesis.

1.2 *- Overview of Reactivity*

In 1894 the first synthetic transformation involving a carbenoid was recorded. The Fritsch-Buttenberg-Wiechell rearrangement describes the conversion of β-aryl substituted vinylic halides to alkynes.[8] As shown in Scheme 1, α-metallation of vinyl bromide **1** produces the transient vinylic α-bromovinyl sodium carbenoid **2** which undergoes transformation to alkyne **4** through the bridging arenium ion **3**. Following initial discovery, more than 60 years passed before experimental evidence supporting the existence of the implicated carbenoid intermediates was provided.[9,10,11]

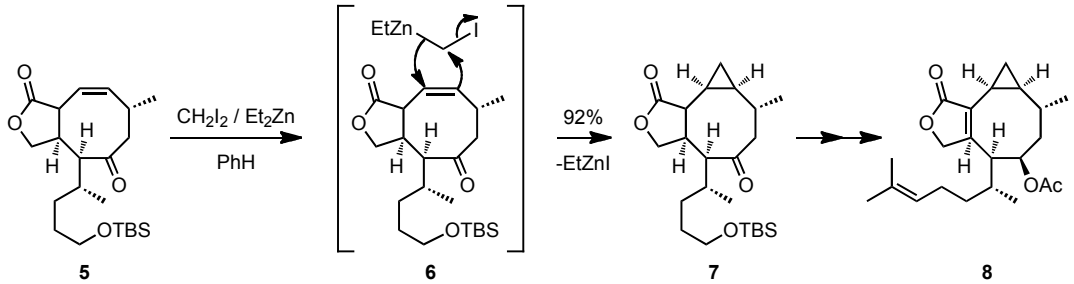
Scheme 1. Fritsch-Buttenberg-Wiechell Rearrangement of β-Aryl Vinylic Halides



The bifunctional character of carbenoids has led to their application in solving long-standing synthetic problems in chemistry. The Simmons-Smith cyclopropanation is a prime example, where zinc carbenoids are employed to stereospecifically convert unfunctionalized alkenes into cyclopropanes. Original conditions employed diiodomethane and a zinc-copper couple to generate *in-situ* zinc carbenoid species which react stereospecifically with unfunctionalized alkenes to produce stereodefined cyclopropanes.[12]

Advancements in this methodology have led to readily reproducible carbenoid formation through the Yamakawa modification (Et_2Zn, CH_2I_2) and several enantioselective variants have been developed including Charette's modification employed for allylic alcohol substrates.[13,14] The impact of this reaction in synthetic chemistry should not be understated as it continues to be used as a primary method of cyclopropane formation and has been applied in numerous total syntheses to date, including that of (+)-acetoxycrenulide where the Z-olefin **5** is converted to *cis*-cyclopropane **8**, Scheme 2.[15]

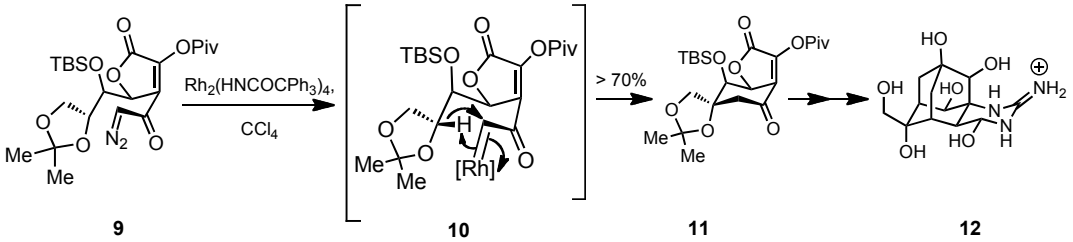
Scheme 2. Simmons-Smith Cyclopropanation in Synthesis of (+) - Acetoxycrenulide



Carbenoid reactivity however, is not limited to 1,2-shifts or additions across carbon-carbon double bonds as they are used in reaction with carbon-heteroatom double bonds[16] and to access other reactive intermediates such as formation of carbonyl ylides.[17] Carbenoids are also employed when inserting between carbon-hydrogen σ-bonds during C-H insertion processes and are implicated during the conversion of aldehydes to alkynes through halovinylidene intermediates, *vide infra*.[18]

Carbenoids may also be formed catalytically in the presence of transition metals where the resulting metallo-centered carbenoids undergo a myriad of useful transformations, most of which are employed for C-H insertion or cyclization processes. Although several different transition metals may be used for this process, Rh and more recently Au are perhaps the most widely employed. Au-carbenoids are typically used in cyclization processes involving both carbo- and heterocycles as well as during enyne isomerizations.[19] Rh-bound carbenoids are the cornerstone of powerful methodologies that exploit the latent oxidation potential of C-H σ-bonds, converting these previously unreactive bonds into functional groups.[20,21] Successful completion of several challenging total syntheses have relied heavily upon these C-H insertion methodologies of transition metal carbenoids.[22]

Scheme 3. Rh-Carbenoid Cyclization During Synthesis of (–)-Tetrodotoxin

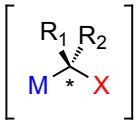


For example, the Du Bois group employed a Rh-carbenoid insertion into the densely functionalized ethereal C-H position of acetonide **9** when closing the cyclohexanone ring **10**, Scheme 3. Butenolide **11** was then successfully converted over several steps to the densely functionalized highly polar puffer fish toxin (–)- tetrodotoxin **12**.[23]

As highlighted above, carbenoids comprise a wide range of reactive species that possess bifunctional electronic character which may be exploited to carry out various fundamental synthetic transformations.

The following body of work will focus on the stereoselective synthesis and application of a specific class of carbenoids, namely - α-haloalkylmetal carbenoids. As depicted in Figure 1, these carbenoids are defined by a stereogenic sp^3-hybridized carbon center (*) bonded directly to an electropositive main group element (e.g., M = Li, MgCl, etc.) and an electronegative halogen atom (X = Cl, Br, I). These α-haloalkylmetal carbenoids display the same nucleophilic and electrophilic reactivity as described above and will be given a more thorough treatment in the following sections.

Figure 1. General Representation of an α-Haloalkylmetal Carbenoid



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M = Li, MgCl, etc
X = Cl, Br, I

Carbenoid formation occurs through four main pathways - transition metal-catalyzed diazo decomposition, α-metallation, sulfoxide-ligand exchange (SLE) and halogen-metal exchange. The latter two processes are employed exclusively in the following work and will be discussed in the following chapters starting with the SLE reaction in Part I for Stereospecific Reagent Controlled Homologation (StReCH) chemistry and halogen-metal exchange in Part II for Asymmetric Halogen Metal Exchange (AHME).

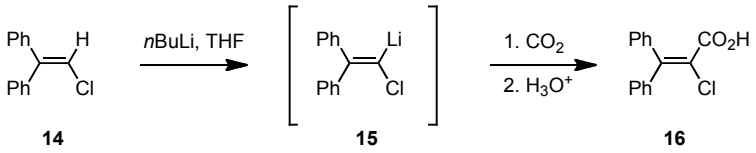
1.3 – Structure and Reactivity of α-Haloalkylmetal Carbenoids

The unique structure and reactivity profile of α-haloalkylmetal carbenoids has contributed significantly to the difficulty associated with carbenoid characterization and their controlled use during synthesis. Wittig originally postulated these carbenoids as reactive intermediates as early as 1941.[24,25] Circumstantial and indirect

evidence regarding carbenoid formation persisted over the next two decades until seminal investigations by Köbrich and co-workers provided unequivocal direct evidence for the existence of α-haloalkylmetal reagents.[26,27]

The example shown in Scheme 4 was used to verify the postulated nucleophilic character of α-haloalkylmetal reagents. α-Metallation of alkenylchloride **14** was used to generate lithium carbenoid **15** which was trapped with CO_2 leading to α-chlorocarboxylic acid **16**. Since these reports, the progression of experimental techniques and advances in instrumentation has permitted the characterization of α-haloalkylmetal reagents through ongoing structural elucidation using NMR spectroscopy,[28] X-ray diffraction,[29] and computational efforts.[30]

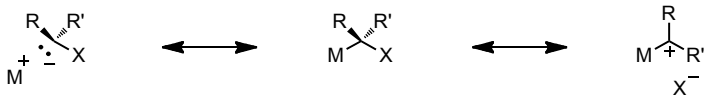
Scheme 4. Evidence for Nucleophilic Character of α-Haloalkylmetal Reagents



14 **15** **16**

α-Haloalkyl carbenoids exhibit both electrophilic and nucleophilic character at the same carbon center. In this regard, it is useful to view carbenoid reactivity by identifying the two extremes of the reactivity spectrum as defined by the resonance structures shown in Scheme 5. As originally postulated by Köbrich, the fully dissociated metal cation **17** leaves an anionic species that accounts for the observed nucleophilic behavior. At the other end of the spectrum (**19**), is a fully dissociated nucleofuge and an electrofuge with a positively charged carbon center which accounts for the electrophilic behavior.

Scheme 5. Resonance Depiction of Carbenoid Reactivity



17 **18** **19**

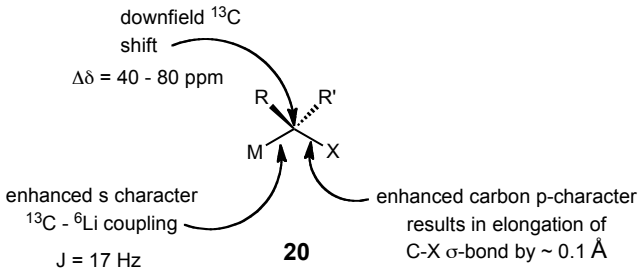
Original investigation into this class of reagent primarily focused on vinylidene carbenoids possessing a halogen atom and metal atom bonded directly to an sp^2 hybridized carbon (e.g. **15**). It was proposed that bonding between the carbon center and halogen atom was significantly different than that of the carbon center and metal atom. Köbrich postulated that the nucleophilic C-M σ-bond would have greater s-character on the carbon atom, while the C-X σ-bond would exhibit pronounced p-character on the carbon atom which would result in bond elongation between the carbon atom and the halogen atom.[31] Köbrich's postulated bonding scheme accounts for the observed dual reactivity and was eventually corroborated by theoretical studies, NMR spectroscopy and X-ray crystallographic analysis.[25,26]

Although no treatment will be given here toward theoretical investigation of carbenoid structure and reactivity, there has been extensive inquiry using computational methods that started with Schleyer's investigation into the structure and stability of $LiCH_2F$ carbenoids.[32] The groups of Houk[33] and Bernardi[34] have also examined the stabilities and geometries of α-heteroatom substituted carbenoids.

Extensive spectroscopic work by Seebach and co-workers provided experimental evidence that significant downfield shifts occur within the ^{13}C signal of the α-heteroatom substituted carbenoids. These downfield shifts were measured between $\Delta\delta \approx 40$ to 80 ppm, depending on the the carbenoid structure and the heteroatom present. The strong deshielding promoted by the elongated C-X σ-bond leads to partial localization of the cationic charge on the carbon nucleus and this polarization is responsible for the significant observed downfield shift and the pronounced p character on the carbon atom of the carbenoid carbon-halogen σ-bond.[25,35] Several years later, evidence supporting the proposed enhanced s character of the carbon atom within the carbon-lithium σ-bond was reported. As before, low temperature NMR spectroscopy techniques were utilized to probe the coupling between ^{13}C and ^{6}Li. The large and persistent 17 Hz coupling constant observed for the ^{13}C-^{6}Li coupling was determined to be a direct artifact of the reduced sp^3 hybridization of carbon-atom bonded to lithium.[36,37] This J-value is considerably larger than the 8 to 10 Hz J-value typically seen for organolithium ^{13}C-^{6}Li coupling constants. The findings of these

spectroscopic studies in conjunction with reported experimental data may be summarized with the carbenoid representation **20**, Figure 2.[26]

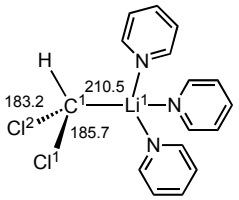
Figure 2. – Carbenoid NMR Structural Elucidation



20

Reported bonding tendencies associated with elongated C-X σ-bonds and the increased s character of the carbon atom hybridization in the C-M bond has also been verified through solid state structures. Although to date there have been a small handful of vinylidene carbenoids isolated and characterized by low temperature X-ray diffraction, there is only a single example of an sp^3-hybridized α-haloalkylmetal reagent which has been characterized in the solid state. Boche and co-workers were able to isolate and characterize by low temperature diffraction the $LiCHCl_2 \cdot 3pyr$ carbenoid **21**, Figure 3.[26,31,32,38]

Figure 3. Isolation and Characterization of the Tetrahedral Carbenoid $LiCHCl_2 \cdot 3pyr$



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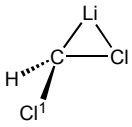

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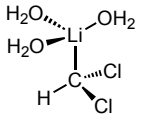

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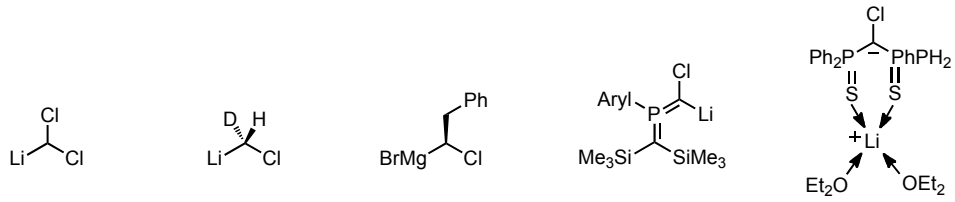
The crystal structure of **21** revealed that both C^1-Cl^1 and C^1-Cl^2 bond lengths were ~ 0.1 Å longer than the observed 1.746 Å bond length for CH_2Cl_2, while considerable tightening of the bond angle from the standard 328° for tetrahedral carbons to a more acute angle sum of 308°.[39] This data verified that the carbenoid carbon atom possessed enhanced p-character, but this finding was not in agreement with the originally proposed low energy structure **22** which invoked a bridging Li species.

Revised calculations centered on the species where three H_2O molecules solvated a Li atom (**23**) resulting in near perfect agreement with the tetrahedral carbon of crystal structure **21**.

1.4 *– Configurational Stability*

The desire to utilize stereodefined α-haloalkylmetal reagents in the context of stereocontrolled synthesis has been a long pursued goal. Although stereocontrolled synthesis has been realized utilizing vinylidene carbenoids,[40] the ability to target newly formed stereogenic centers through scalemic sp^3-hybridized carbenoids has taken a significantly longer period of time to develop. This is a consequence of the chemical and configurational lability of the α-haloalkylmetal reagent, which is directly related to the timescale involved for carbenoid generation and deployment.[41] In order to fully exploit the potential of stereodefined carbenoids in asymmetric synthesis, an understanding of their chemical and configurational stability is paramount.

Scheme 6. Comparison of Thermal Stability for α-Haloalkylmetal Reagents



24 — chemically stable -100°C [42]

25 — config. & chemically stable < -80°C [43]

26 — config. stable < -60°C [44]

27 — chemically stable < -10°C [45]

28 — chemically stable 25°C [46]

A picture describing the thermal lability of α-haloalkylmetal reagents is shown in Scheme 6, where carbenoid stability trends with respect to the electropositivity associated with bonded metal atom such that Li < Mg < Zn.[42,43,44,45,46] Lithium carbenoids are typically the least chemically stable of any α-haloalkylmetal reagent and the actual limits of configurational stability are assumed to be at least that of the carbenoids thermal stability as these species essentially decompose at temperatures > –78°C.[47] Moving to a less electropositive metal leads to carbenoids with greater chemical stability, where examples are known of magnesium carbenoids exhibiting

configurational stability for up to 3 hours at temperatures < –60°C.[38] This trend of α-haloalkylmetal reagent stability tracking with decreasing metal atom electropositivity continues for Zn carbenoids. Thus, while lithium carbenoids do not typically persist longer than 15 minutes at temperatures > –100°C, Mg-carbenoids may be generated over several hours prior to use at –78°C and Zn carbenoids may be formed up to 0°C.[48,49] Taking Zn-carbenoids used for Simmons-Smith cyclopropanations aside, lithium and magnesium carbenoids are the most synthetically relevant main group organometallic metals used in formation of sp^3 hybridized carbenoids.

1.5 *– Solvent and Aggregation Effects*

Solvent and aggregation effects play a significant role in the structure-reactivity relationship of α-haloalkylmetals. Organolithium and organomagnesium species typically do not as exist as discrete monomeric species in solution although for clarity they are often depicted as such.[50] Extensive spectroscopic and theoretical investigation of synthetically relevant simple alkyllithiums has shown that the order of aggregation of these species directly effects their structure and reactivity. By correlation, it may be assumed that similar solvent effects and aggregation have similar impact upon α-haloalkylmetal carbenoids.

In solutions devoid of Lewis base, most alkyllithiums tend to form tetrameric and hexameric aggregates which are governed by electrostatic interactions, the lithium atom's coordination sphere and steric effects resulting from the substituents on the lithium atom.[51,52,53] Aggregation states are also at play with α-haloalkylmetal reagents adding more complexity to the overall structure / reactivity picture. Reducing the overall aggregation state typically leads to an increase of reactivity, hence the propensity for carbenoid chemistry to be carried out in ethereal solvents (e.g. 1,2-dimethoxyethane, THF) or in the presence of nitrogenous ligands (TMEDA, (–)-sparteine). Polar ethereal solvents may lead to further increased polarization of C-Li σ-bond, significantly enhancing the carbon atom increased s character.[54]

Stabilizing the polarized C-Li σ-bond with Lewis basic solvents or additives may help to decrease the decomposition rate of α-haloalkylmetal reagents.

It has been shown, however, that competition between Lewis basic solvents and α-heteroatom substituted carbenoids for lithium coordination sites can lead to distortion of the C-Li bond angles resulting in distortion of optimal aggregation geometry. These perturbations may lead to destabilizing energies, which in turn affect the activation barriers associated with α-halo alkylmetal reagent reactivity, possibly leading to alternative reaction pathways.[55]

1.6 *- Reactivity of α-Haloalkylmetal Reagents*

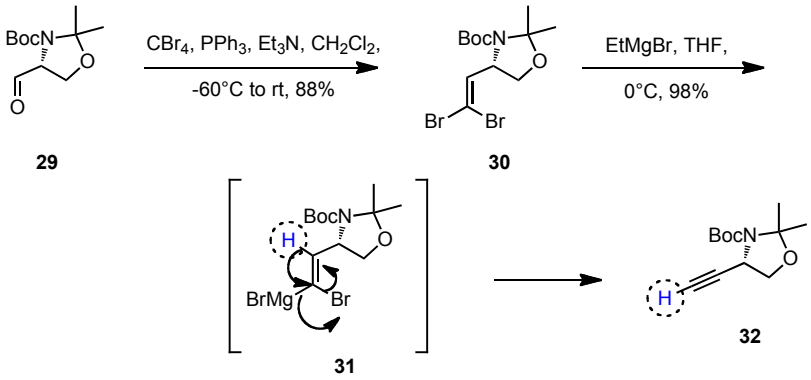
Due to the presence of a C-M σ-bond, α-haloalkylmetal reagents tend to be viewed as primarily nucleophilic species; however, this is not entirely the case and as detailed above, electrophilic behavior accounts for a significant portion of carbenoid reactivity. On the other hand, the nucleophilic/basic character exhibited by carbenoids must also be kept in mind, as they are known to metalate acidic C-H bonds and initiate equilibrium processes through halogen-metal exchange with *gem*-dihalo substrates. Examples of carbenoid reactions that have relevance to the work presented in subsequent chapters are highlighted below.

1.6.1 *- 1,2-Shift (Aryl, Hydride)*

Carbenoid vinyl halides may undergo a migration of a trans β-aryl group during the Fritsch-Buttenberg-Wiechell reaction as discussed above. Although β-alkyl groups do not participate in this rearrangement, β-hydrogens may undergo an analogous 1,2-hydride shift which occurs concomitantly with metal assisted ionization (MAI)[56] of the vinylidene halide. The Corey-Fuchs alkyne synthesis exploits this behavior.[16] For example, as shown in Scheme 7, Fukuyama and co-workers converted Garner's aldehyde **29** to 1,1-dibromoalkene **30** before treatment with two equivalents of EtMgBr to initiate carbenoid **31** formation. A resulting 1,2-hydride shift then generates alkyne **32** which was then converted to both of the tryptostatins A and B.[57,58] β-Hydride migration is not solely relegated to vinylidene carbenoid rearrangement, it may also be a significant decomposition pathway for sp^3-hybridized

α-haloalkylmetal carbenoids such as Figure 1. In a similar vein to the MAI β-hydride migration, carbenoid dimerization also occurs readily.

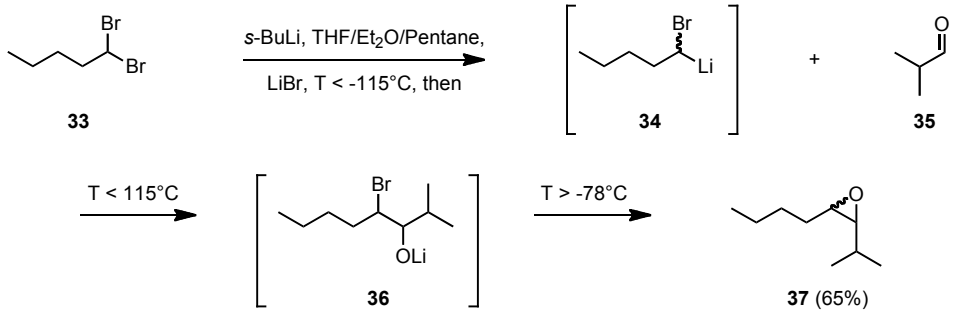
Scheme 7. 1,2-Hydride Shift Utilized in the Total Synthesis of Tryptostatin A and B



1.6.2 - *Carbonyl Addition*

α-Haloalkylmetal reagent addition to carbonyl groups is also well documented and has been used in epoxide formation. For example as shown in Scheme 8, generation of putative lithium carbenoid **34** from *gem*–dibromide **33** with *sec*-BuLi is followed by trapping with isobutyraldehyde **35** which transiently generates bromo-lithium alkoxide **36**. The lithium alkoxide immediately collapses and nucleophilic displacement of bromide by intramolecular attack by the lithium alkoxide forms epoxide **37**, Scheme 8.[59]

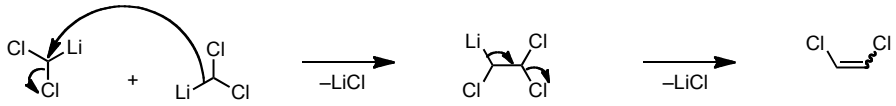
Scheme 8. Epoxide Formation Through Lithium Carbenoid Addition to Carbonyl



1.6.3 *- Decomposition*

The final degradative pathway commonly observed for α-haloalklmetal reagents is the carbenoid dimerizing α-elimination. The umpolung reactivity of lithium carbenoids is fully displayed as proposed in Scheme 9, where one carbenoid (**24**) assumes the role of the nucleophile and the other functions as an electrophile. S_N2 addition and loss of LiCl forms trichlorocarbenoid **38** which then undergoes β-elimination of LiCl to form 1,2-dichloroethene **38a**. Köbrich and co-workers discuss this type of pathway as a Wurtz-Fittig reaction due to the half-life of dichloromethyllithium.[60]

Scheme 9. Alkene Formation Through Carbenoid Decomposition



1.7 *– Summary*

Since the discovery of the first putative α-haloalkylmetal reagent in 1894, the importance of this class of organometallic reagents in synthetic chemistry has been well established. The ability to harness the inherent reactivity of carbenoids has steadily progressed in concert with a more thorough understanding of their structure and electronic properties. The potential for carbenoid reagents to have a significant impact in synthetic chemistry has already been effectively demonstrated by their development and application in both the Simmons-Smith cyclopropanation reaction[11] and in the conversion of aldehydes to alkynes.[16] It could be argued, that application of α-haloalkylmetal reagents in asymmetric transformations could have a similar impact.

Logically, utilizing carbenoids in stereocontrolled synthesis is the next progression. Stereodefined sp^3-hybridized α-haloalkylmetal reagents may be viewed as fundamental building blocks that contain the requisite inherent chiral information within their structure to facilitate asymmetric carbon-carbon and carbon-heteroatom

bond construction. This thesis focuses on new methods for using enantioenriched α-haloalkylmetal reagents (StReCH – Part I) and investigation into alternative modes for generating such species (AHME - Part II).

Part I

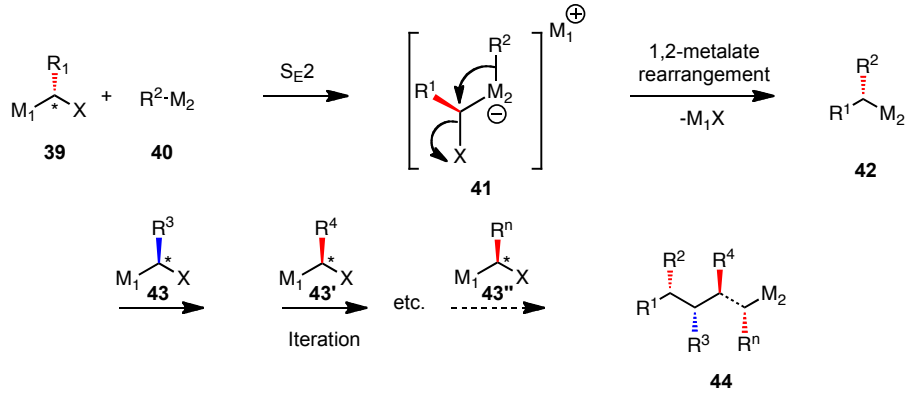
A Programmable Approach to Contiguous Stereogenic Formation via Stereospecific Reagent Controlled Homologation: Formal Synthesis of (–)-Epibatidine

Chapter 2: Stereospecific Reagent-Controlled Homologation (StReCH)

2.1 – StReCH Concept

Stereoselective synthesis has evolved significantly over the last 58 years since Woodward used conformationally restricted cyclic systems to install requisite stereocenters during the seminal synthesis of strychnine.[61] Progression in stereoinduction based asymmetric synthesis led to processes of significantly better stereocontrol through substrate directed approaches,[62] chiral auxilliaries[63] and/or double asymmetric synthesis.[64] An orthogonal stereocontrol model to a stereoinduction approach, relies on the stereospecific reactivity of a chiral reagent during the formation of stereogenic centers. In this manner the reagent itself may be viewed as a stereodefined fundamental building block that facilitates the construction of asymmetric bonds. Repetition of this process would result in the targeting of arbitrary stereocenters and represents a conceptually simplistic and powerful method for asymmetric synthesis. A burgeoning concept for this type of unified asymmetric synthesis is the StReCH manifold, Scheme 10.

Scheme 10. Iterative Stereosepecific Reagent Controlled Homologation (StReCH) Enables Programmable Stereospecific Synthesis



A scalemic α-haloalkyl organometallic reagent **39** adds as a nucleophile into the vacant bonding orbital (M=B, Si, Cu) of a metalloid leading to an intermediate "ate-complex" **41**. A stereospecific 1,2-metalate rearrangement of **41** leads to enantioenriched chain extended product **42**. This cycle may be iterated as many times as necessary in order to access the desired target (**44**). Newly formed stereocenters

reflect the stereochemistry inherent to the α-haloorganometallic reagent building blocks (**39** and **43)**, eventually generating a polysubstituted target **44** of any stereochemical configuration desired. Compound **44** also possesses significant molecular complexity, the result of a completely modular approach to asymmetric carbon-carbon bond formation through a sequence of conceptually and operationally simple steps.

There are three underlying precepts that must be satisfied for the successful realization of the StReCH concept.

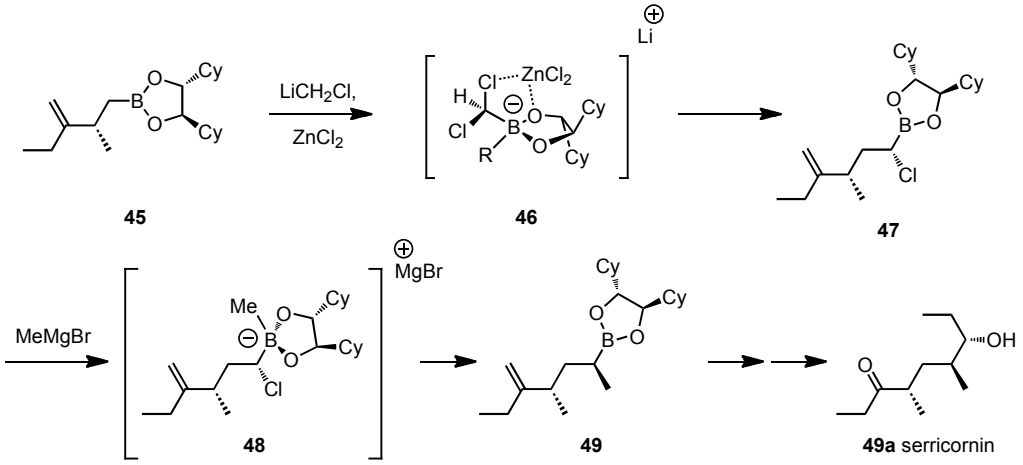
1) α-haloorganometal carbenoid **39** must be chemically and configurationally stable on the time scale of formation of ate-complex **41**;
2) ate-complex formation and ate-complex breakdown **41** (1,2-metalate rearrangement) must proceed in a completely stereospecific fashion;
3) excess α-halocarbenoid **39** must be completely consumed or self-immolated before 1,2-metalate rearrangement proceeds in order to prevent oligomerization - an artifact arising from multiple insertions of carbenoid **39**

To date three StReCH variants that satisfy the above requirements have been reported and are detailed below.

2.2 *- The Hoffmann-Matteson StReCH Manifold*

In 1963, Matteson and Mah demonstrated that α-haloboronic esters underwent facile substitution by Grignard reagents.[65] The observed net S_N2 reaction was found to proceeded via intermediate metalate-complexes such as that depicted in **48**. Dichloromethyllithium carbenoids were also found to be effective promoters of ate-complex formation and were used to facilitate continued chain extension by forming subsequent α-chloroboronic esters following initial homologation.[66] A stereocontrolled variant was first introduced using pinanediol as a chiral director, but this was eventually replaced by the superior C_2 symmetric dicyclohexyl ethanediol (DICHED) chiral director.[67,68] An illustrative example of Matteson's substrate controlled asymmetric chain extension method as applied in the synthesis of insect pheromone serricornin is shown in Scheme 11.

Scheme 11. Matteson's Asymmetric Chain Extension in Synthesis of Serricornin

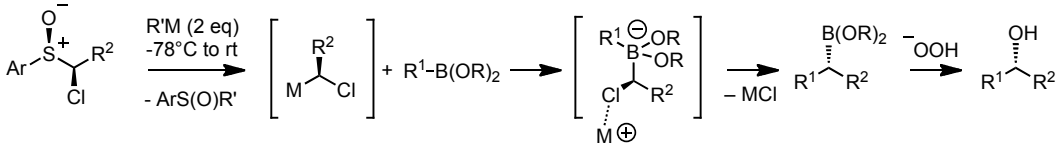


Dioxaborolane **45** was homologated with dichloromethyl lithium[69] and rearrangement of the resulting diastereomeric ate-complex (**46**) was facilitated by the addition of Lewis acidic $ZnCl_2$, which also functions to suppress epimerization of the α-chloroboronic ester **47** by sequestering the chloride anion nucleofuge.[70] Addition of MeMgBr to boronate **47** followed by 1,2-metalate rearrangement of ate-complex **48** installed the α-methyl stereocenter of boronate **49** which was subsequently converted to the natural product. Although excellent diastereoselectivity is observed when utilizing this methodology, the reliance on substrate control does not permit the programmable installation of arbitrary stereogenic centers without the exchange of the chiral directing groups at some point during iteration.[71]

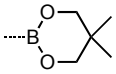
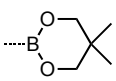
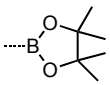
Ate-complex intermediates such as **48** could also be generated by using an orthogonally functionalized set of reagents such that the chiral information is introduced through a stereodefined α-chloroalkyl metal reagent into an achiral boronate. This would constitute a change of the stereocontrol model moving from a substrate approach to reagent control process. This is in turn, would by-pass the limitation inherent to substrate control with regard to chiral directing groups when targeting an arbitrary array of stereogenic centers. However, in order to realize this perspective shift, a reliable method for generating enantioenriched α-haloalkylmetal reagents is necessary.

Hoffmann and co-workers developed a method to access scalemic α-haloalkylmetal reagents through sulfoxide ligand exchange (SLE) of stereodefined α-chlorosulfoxides.[44,72] Exploiting SLE to generate scalemic carbenoids, the Blakemore group successfully demonstrated proof-of-concept for StReCH using these highly reactive organometallic reagents. The initial study utilized both Grignard and alkyllithium reagents to form α-chloro carbenoids through SLE of enantioenriched α-chlorosulfoxides **50**. The putative scalemic carbenoids generated were used to homologate boronic esters **52** which led to enantioenriched homologated boronic esters **54** following 1,2-metalate rearrangement and were subsequently oxidized to 2° alcohols **54a** to assay the selectivity of the reaction, Table 1 (selected examples).[73,74] Initially, α-chloromagensium carbenoids, entries 1 and 2, were examined in non-coordinating, non-polar PhMe as solvent. The homologated 2° alcohol was generated in moderate yield of 48% and enantioselectivity (82% ee), entry 1.

Table 1. StReCH Proof-of-Concept: Formation of Scalemic Alcohols via Chain Extension of Boronic Esters



50 (2 eq) **51** **52** **53** **54** **54a**

entry	boronic ester[a]		sulfoxide[b]	reaction cond.			isolated 2° alcohol	
	R^1	--$B(OR)_2$	R^2	RM	solvent	T	% yield	%ee
Magnesium carbenoid investigation[72]								
1	$BnCH_2$		Bn	EtMgCl	PhMe	Δ	48	82
2	c-C_6H_{11}		Bn	EtMgCl	PhMe	Δ	9	60
Lithium carbenoid investigation[73]								
3	$BnCH_2$		Bn	n-BuLi	THF	0°C	70	96
4	c-C_6H_{11}		Bn	n-BuLi	THF	0°C	86	87
5	$BnCH_2$		Bn	t-BuLi	PhMe	rt	76	92
6	c-C_6H_{11}		Bn	t-BuLi	PhMe	rt	67	82

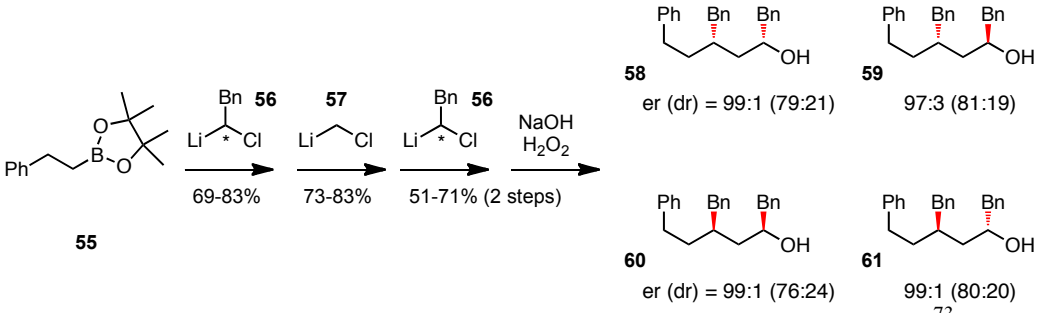
[b] %ee ≥ 98%, Ar = p-Tol or p-ClC_6H_4

The putative magnesium carbenoid **51** (M = MgX) required the less sterically encumbered neopentylglycol boronic ester or the greater Lewis acidic catechol boronate (not shown) for successful nucleophilic addition, while 1,2-metalate rearrangement (**53**) was sluggish and required heating for completion. When the sterically encumbered cyclohexyl substituted boronic ester, entry 2, was used a significant decrease in yield (9%) and enantioselectivity (60%) was observed. It was postulated that the attenuated nucleophilicity of the Mg carbenoids in concert with a demanding steric environment, complicated ate-complex formation allowing for possible α-chloromagnesium carbenoid **51** (M = Mg) racemization and potential decomposition.

Considering the ample precedent for boronic ester homologation with α-haloalkyllithium reagents,[6,75,76] Blakemore and co-workers investigated the efficacy of lithium carbenoids generated through SLE for stereocontrolled homologation, entries 3-6. Bearing in mind that lithium carbenoids have much greater thermal lability than the analogous Grignard species, initial StReCH conditions consisting of *n*-BuLi/ THF/neopentyl glycol boronates were eventually optimized to *t*-BuLi/PhMe/ pinacol boronate.[77] As seen from entries 3 and 4, a considerable boost in yield and enantioselectivity was observed when switching to the system of *n*-BuLi/ THF/ neopentyl glycol boronates. This is attributed to the greater nucleophilicity of lithium carbenoids compared to magnesium carbenoids although their lower stability meant that lithium carbenoids must be generated in the presence of boronates under Barbier type conditions and cannot be pre-generated before addition of the boronic ester. Enhanced carbenoid reactivity also provides the added advantage of being able utilize a more robust, less Lewis acidic boronic ester. Application of pinacol boronates led to significant practical enhancements such as increased stability during handling, column chromatography and reduced susceptibly to unwanted aerial oxidation, all of which facilitate easier compound purification and handling. Taken together the additive effects have a positive direct impact the application of StReCH in synthesis.

Expanding the scope of StReCH with α-halolithium carbenoids, the Blakemore lab demonstrated the ability to install multiple stereocenters of an arbitrary stereodiad

Scheme 12. Programmed Synthesis of Multiple Stereogenic Centers Using Iterative StReCH

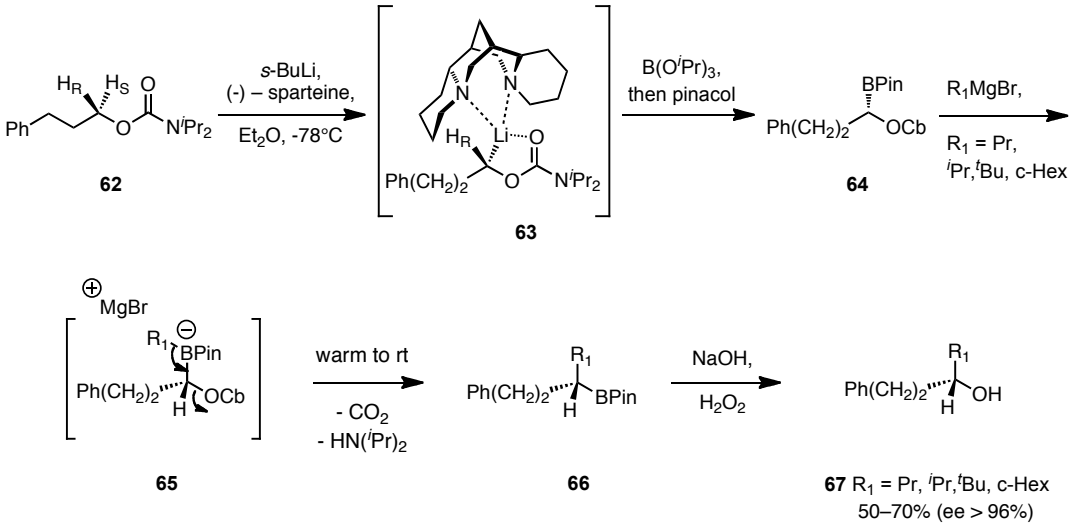


system, Scheme 12, ultimately targeting all four possible stereoisomers.[73] The putative benzyl bearing carbenoid **56**, a benchmark α-chloroalkyllithium reagent, and phenethyl boronate **55** were employed for the initial stereospecific homologation. Chain extension through methylene insertion of chloromethyllithium (**57**) preceded a second stereospecific homologation with a second portion of benzyl bearing carbenoid **56**.[74] This subsequent StReCH iteration installed the second stereocenter and following oxidation generated 2° alcohols (**58**-**61**) which were isolated in very good yield, modest diastereoselectivity and excellent enantioenrichment. The synthesis of all four stereoisomers of carbinol **58** via iterative StReCH hinted at some of the power of this technique; however, a more convincing demonstration would be the controlled elaboration of multiple contiguous stereocenters.

2.3 - The Hoppe-Matteson StReCH Manifold

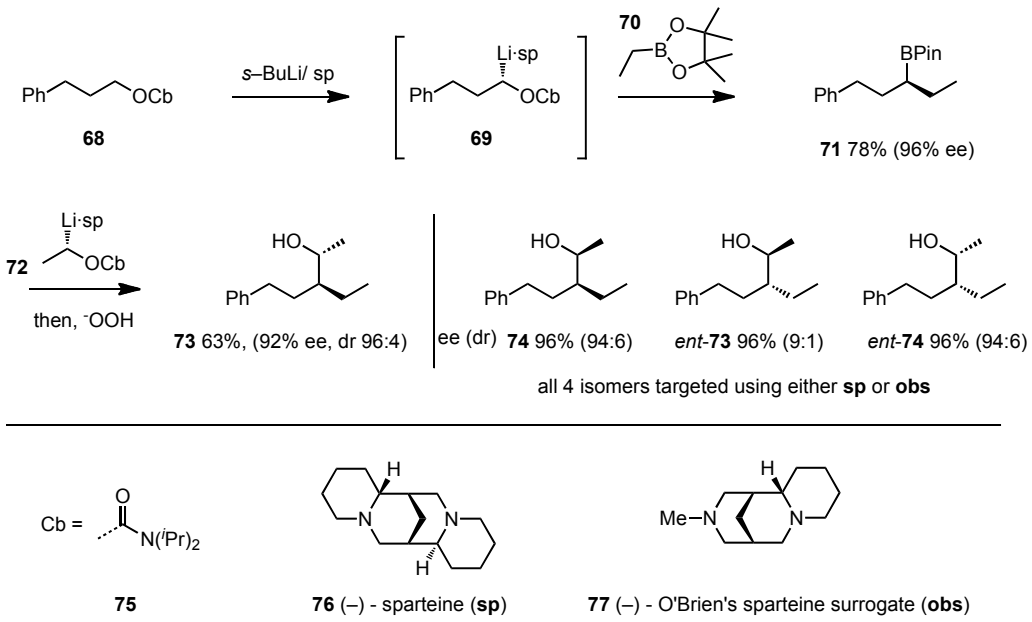
An alternative method for generating enantioenriched α-heteroatom lithium carbenoids has been developed and optimized by Hoppe, Scheme 13. The chiral reagent pair of *sec*-BuLi/(–)-sparteine was shown to discriminate between the enantiotopic α-protons of *N*,*N*-diisopropyl alkyl carbamates **62**, resulting in net enantioselective lithiation, selectively forming lithium carbenoid **63**. This lithium carbenoid was quenched with triisopropyl borate and then transesterified generating pinacol boronate **64**. Addition of Grignard reagent (R_1MgBr) to boronate **64** formed ate-complexes **65**, which underwent stereospecific breakdown through a 1,2-metalate rearrangement leading to homologated boronic esters **66** which were oxidized to yield the 2° alcohols **67** in good yield (50%-70%) and excellent enantioselectivity (> 96%ee).[78]

Scheme 13. Enantioselective Deprotonation of Alkyl Carbamates Using *s*-BuLi/(–)-Sparteine



Aggarwal and co-workers extended this lithium carbenoid methodology by reacting enantioenriched lithiated alkyl carbamates directly with boronic esters, offering an alternative route into the StReCH manifold, Scheme 14.[79] After initially demonstrating efficient homologation through formation of enantioenriched 2° alcohols in good yield and excellent selectivity, a series of four stereoisomers of a stereodiad scaffold were targeted. The resulting doubly homologated 2° alcohols were generated in good overall yield and high selectivity. Starting from carbamate **68** enantioselective α-metalation with *s*-BuLi/(–)-sparteine generated lithium carbenoid **69** which reacted directly with ethyl pinacol boronate **70** leading to chain extended boronate **71** following ate-compelx formation and 1,2-metalate rearrangement. A second iteration with lithium carbenoid **72** and after oxidation led to 2° alcohol **73** in excellent enantioenrichment (92%) and very good diastereoselectivity (96:4). The other three stereoisomers, **74** and *ent*-**73**/**74**, were similarly targeted using either (–)-sparteine **76** or O'Brien's (+) - sparteine surrogate **77** resulting in nearly equal yields and stereoselectivities as before.[80]

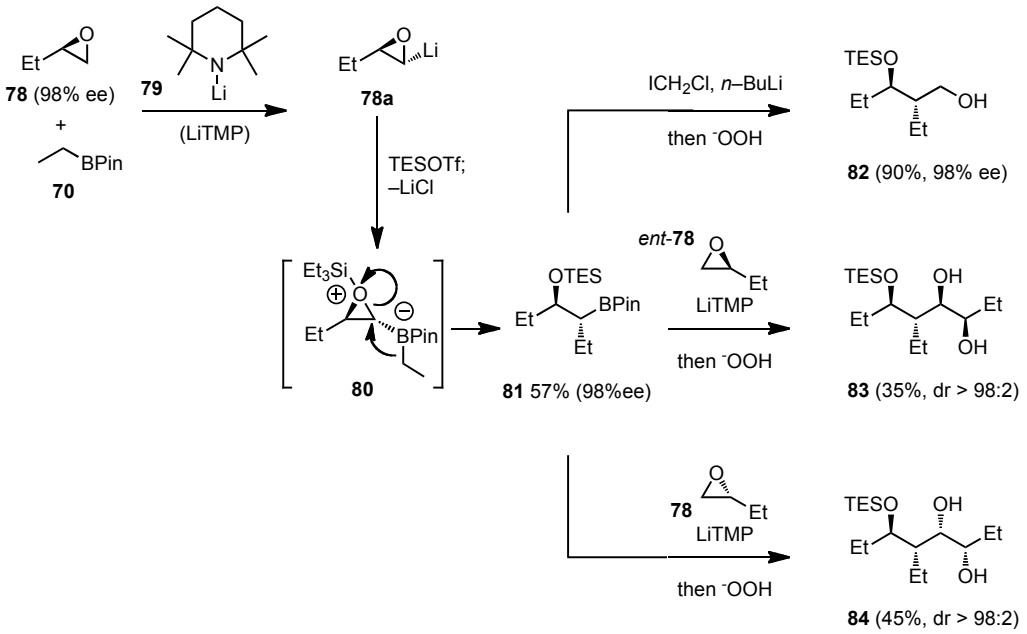
Scheme 14. Aggarwal's Demonstration of the Matteson-Hoppe StReCH Manifold



2.4 *- StReCH with Metallated Oxiranes and Aziridines*

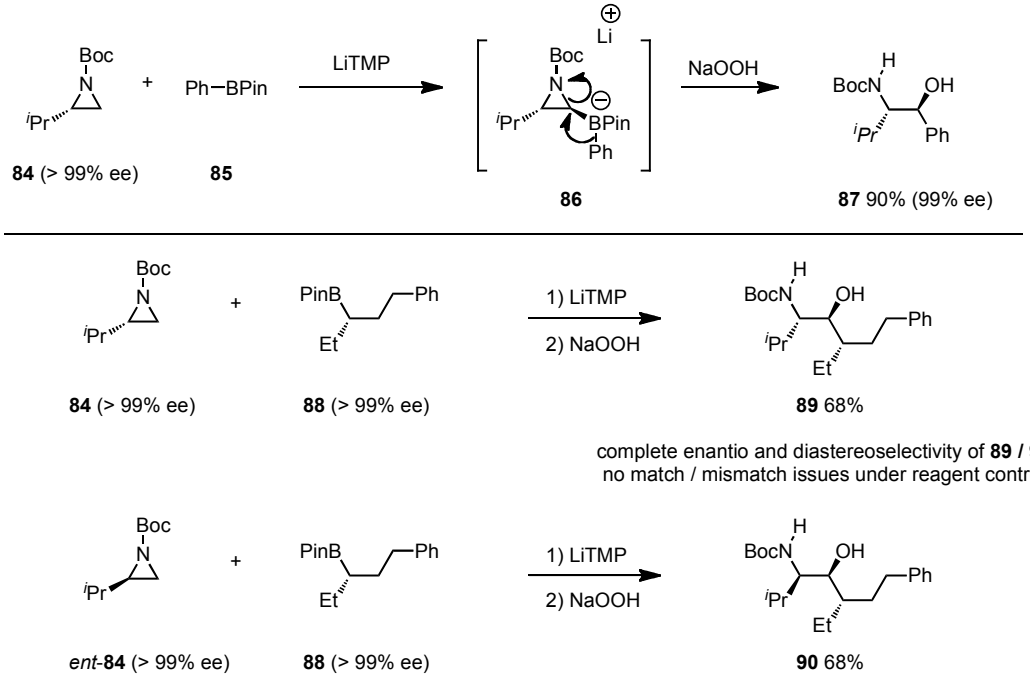
A recent report detailed the use of StReCH to synthesize 1,2-*syn* diols by homologating boronic esters with enantioenriched lithiated terminal epoxides, Scheme 15.[81] It was shown that enantioenriched terminal propyleneoxide **78** can be selectively lithiated trans to the oxiranyl ethyl group with LiTMP **78** in the presence of ethyl pinacol boronate **70** to form intermediate ate-complex **80** which participates in stereospecific 1,2-metalate rearrangement following activation with TESOTf.[82] The resulting homologated boronic ester **81** was isolated in good yield and excellent enantioenrichment and provided a common intermediate which was then converted into 1,3-diol **82** following a methylene insertion/oxidation sequence and into 1,2-*syn* diols **83** and **84** following a second StReCH iteration of α-lithiooxirane **78a**.

Scheme 15. Stereospecific Synthesis of Enantioenriched 1,2-*syn* Diols via Hoppe-Matteson StReCH Manifold



StReCH was also implemented to access β-amino alcohols by using analogous stereodefined lithiated aziridines for boronic ester homologation, Scheme 16.[83] Stereoselective lithiation of enantiopure Boc-protected aziridine **84** with LiTMP in the presence of phenyl pinacol boronate (**85**) led to enantiopure amino alcohol **87** after stereospecific ate-complex **86** formation, 1,2-metallate rearrangement and oxidation. The synthesis of amino alcohols **89**/**90** demonstrated the process is under absolute reagent control as there is no observable diminution of enantio- or diastereocontrol when starting from either antipode of Boc-protected aziridine **84**/*ent*-**84**.

Scheme 16. Stereoselective Synthesis of β-Amino Alcohols via StReCH with Lithiated Aziridines



Considering the pioneering and extensive work by Matteson in developing boronic ester homologation over the last several decades and the recent introduction of StReCH chemistry, the above introduction defines the current state of this art. In the following sections, studies to advance the Hoffmann-Matteson StReCH manifold will be presented in detail.

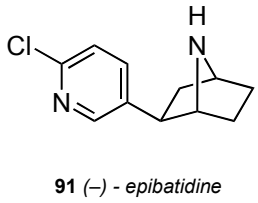
Chapter 3 *– Aim of Part I*

To date, nearly all reports of StReCH reactions involve the construction of acyclic compounds including a total synthesis of (+)-faranal which demonstrated StReCH chemistry in the context of natural product synthesis.[84] The lack of cyclic structures targeted *via* StReCH provided the impetus to clearly delineate the following aims for this thesis: 1) to demonstrate the utility of the Hoffmann-Matteson StReCH protocol to install contiguous stereocenters in a modular programmable fashion; 2) to explore the application of α-chloroalkylmetal reagents bearing functionalized side chains in StReCH; 3) and to elaborate the newly installed side chains of the chain extended product into a cyclic target of interest which possess relevant biological activity. In order to demonstrate this principle, the analgesic small molecule (–)-epibatidine was targeted.

3.1 *- Epibatidine - Isolation and Structural Elucidation*

Most traditional analgesic agents for the relief of severe acute and chronic pain elicit their mode of action against the broad class of opioid receptors.[85,86] Analgesics working at these receptors such as morphine, display high potency and effectiveness, typically mitigating pain within minutes. These naturally occurring alkaloids are isolated from opium extracted from the prolific and abundant *Papaver somniferum* poppy. The potent analgesic properties of the central nervous system (CNS) acting opiate alkaloids are not without the potential for adverse side-effects, such as significant respiratory depression and the high potential for addiction. In order to circumvent the negative drawbacks of opioid agonists while retaining the desired analgesic effects, there is a continual effort to discover other viable and effective pain attenuating agents. One such agent that has captivated the attention of the scientific community for more than 20 years is the azabicycloheptyl alkaloid (–)-epibatidine **91**, Figure 4 .

Figure 4. (–)-Epibatidine from *Epipidobates tricolor*



91 *(–) - epibatidine*

Epibatidine **91** is a uniquely structured 7-azabicyclo[2.2.1]heptane small molecule natural product possessing an *exo*-2-chloropyridyl unit. Originally isolated from the skin excretions of the Ecuadorian tree frog *Epipedobates tricolor* in 1976 by Daly and co-workers, the structural elucidation was not completed until 16 years later. At that time, NMR spectroscopic technology had advanced enough that instrument sensitivity and power were sufficient for structural elucidation of an irreplaceable 1 mg sample of epibatidine.[87]

Epibatidine's biological activity was initially discovered when trace alkaloids isolated from the methanolic skin extract of *Epipidobates tricolor* were applied to mice in the Straub-tail reaction, an assay that serves to identify opioid receptor agonists.[88] This alkaloid (**91**) displayed highly potent analgesic properties at roughly 200 times that of morphine. Interestingly, introduction of the opioid antagonist naloxone had no effect on epibatidine's high potency in either the Straub-tail test or a hot-plate based pain test, indicating that this unique alkaloid was not an opioid receptor agonist, but rather, its action was effected at some as yet unknown pain mediating receptor.[89] Biological and pharmacological evalutation of epibatidine identified that its mechanism of action was against several archetypal nAChR CNS subtypes, including $\alpha 4\beta 2$ and $\alpha 7$, categorizing it as a potent nicotinic agonist. Activity was also observed at ganglionic and neuronal subtypes, validating that the agonist activity against central nicotinic receptors was the key to epibatidine's analgetic properties.[4a-c] Unfortunately, epibatidine (**91**) was found to be toxic within the tolerances of effective analgesic doses and did not possess the necessary selectivity between the various nAChR subtypes, thereby leading to its termination in further clinical development.[90d]

In regard to the possible biogenesis of epibatidine, it has been determined that the poisonous alkaloids excreted by these amphibians are not the result of an intrinsic biosynthetic pathway. Rather, the alkaloid results from either a developed or overexpressed inherent biological system that assimilates the toxins from dietary arthropod sources. Toxins are accumulated and then excreted through the frog's granular poison glands as a subsumed component of its natural chemical defense system.[91]

The initial isolation of epibatidine in 1976 required the collection of 750 frogs to yield a single milligram of adequately pure material, which became invaluable a few years later when the dendrobatid amphibians were placed onto a 1984 endangered species list, precluding any further isolation of this alkaloid.[92] The unique biology of epibatidine and the dearth of available material provided the impetus for an intensive push by both academia and the private sector to develop synthetic strategies and routes to access the quantities necessary for further biological testing and pharmacological evaluation. Although epibatidine was ultimately determined too toxic for further development, its high affinity for nAChR subtypes has transformed it into a lead discovery candidate for other nAChR receptor drugs for nearly two decades.[93]

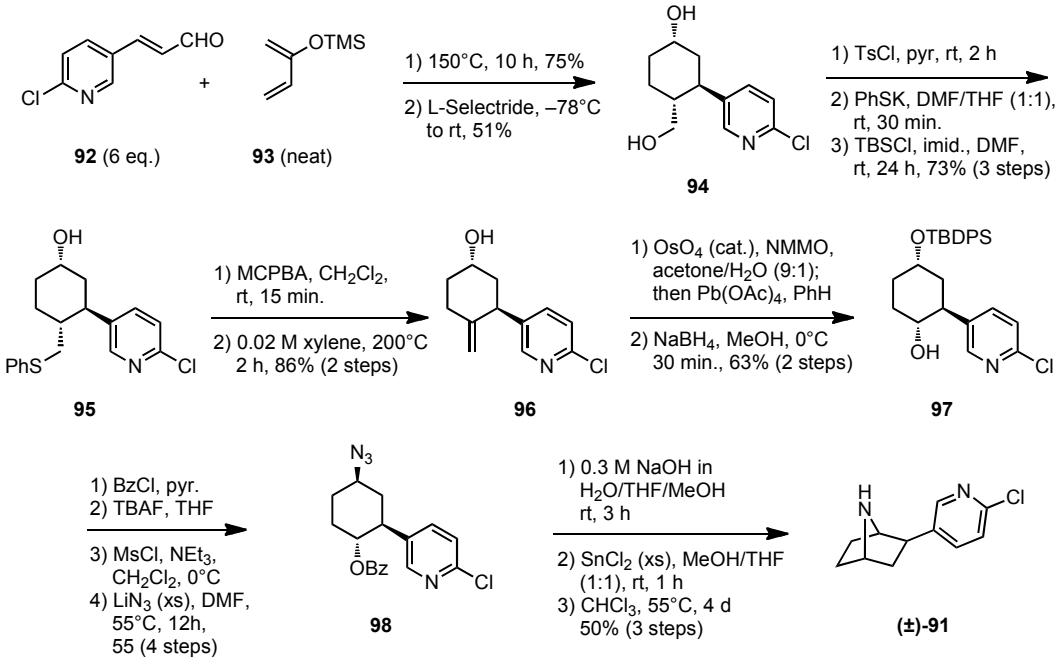
***3.2** - Selected Previous Total Syntheses of Epibatidine (**91**)*

In light of epibatidine's interesting molecular scaffold and uniquely potent biological activity,[94] there have been in excess of 25 reports towards epibatidine synthesis[95] and several reviews[96,97] have been written over the past two decades concerning this topic, therefore only a few selected syntheses will be highlighted herein.

The first total synthesis of epibatidine **91** was reported by Broka[95a] in 1993 and utilized a Diels-Alder cycloaddition to access the core 7-azabicyclo[2.2.1]heptane scaffold from which the synthesis was completed, Scheme 17. Diels-Alder cycloaddition between 2-chloropyridyl enal **92** and 2-(trimethylsilyloxy)-1,3-butadiene (**93**) was followed by acid hydrolysis and carbonyl reduction with L-

Selectride to yield diol **94**. The primary alcohol of **94** was converted into the phenylsulfoxide followed by a [2,3]-sulfoxide elimination generating the *exo*-methylene **96** which was subsequently converted into secondary alcohol **97** through a sequence of $OsO_4/Pb(OAc)_4$ oxidation, followed by $NaBH_4$ reduction. The alcohol was converted to the requisite amine through desilylation, mesylation and azide displacement to form the 7-azabicycle **98**. Benzyloxy removal and conversion to the mesylate enabled intramolecular S_N2 displacement by the reduced azide to complete the synthesis of epibatidine **91** in 17 steps with an overall yield of 4.1%.

Scheme 17. Broka's First Total Synthesis of (±)-Epibatidine **91**

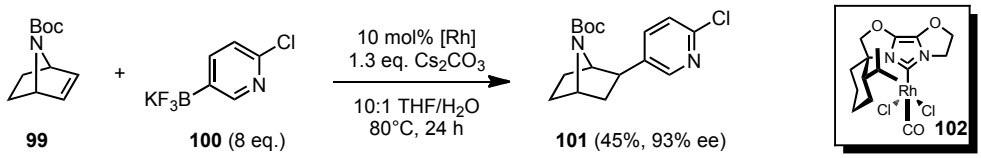


[4+2] Cycloaddition routes have been a primary method for formation of epibatidine's cyclohexane moiety, but there have also been numerous alternative methods investigated that include a [3+2] dipolar cycloaddition,[98] solid polymer support[993], radical cyclizations[100,101] and even an *aza*-Prins-pinacol route.[102]

Recently, Bexrud and Lautens reported on the concise enantioselective synthesis, Scheme 18, of *N*-Boc-epibatidine (**101**) utilizing their newly developed *N*-heterocyclic carbene ligand (IBiox[(-)menthyl]) for rhodium catalyzed hydroarylation.[103] This transformation involves transmetallation between the

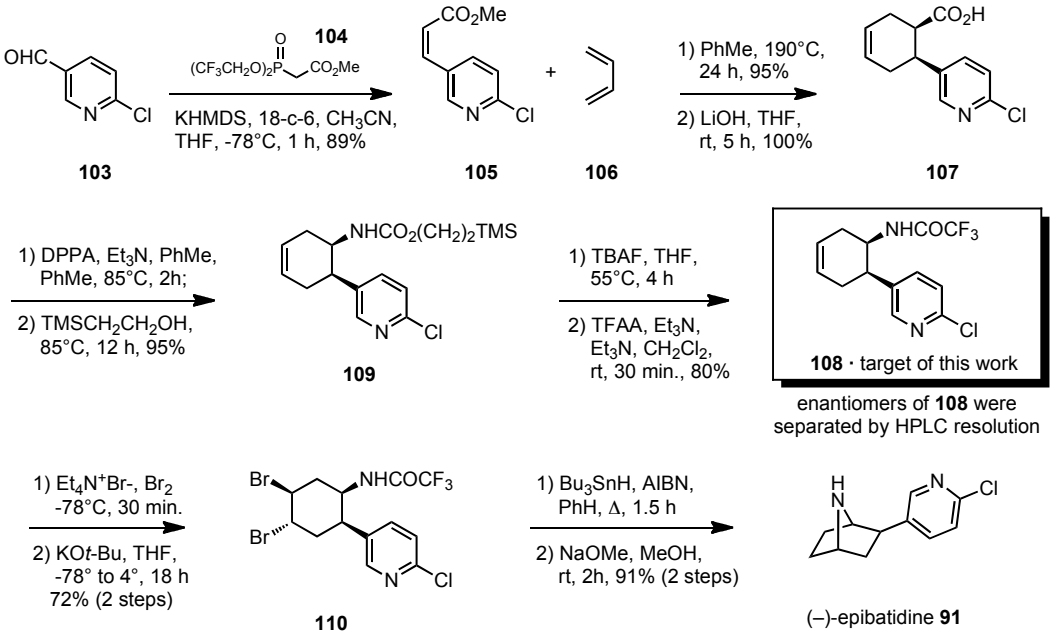
rhodium catalyst **102** and potassium(2-chloropyrid-5-yl)trifluoroborate (**100**) followed by regioselective carborhodination of the *N*-Boc-7-azanorbornene (**99**) double bond leading to formation of the observed product **101** in 45% yield and 93% enantioselectivity.

Scheme 18. Lautens Synthesis of *N*-Boc Protected Epibatidine **101**



Following the structural elucidation of epibatidine, several groups published synthesis of this alkaloid within the span of a few months.[86] The Corey group published a total synthesis of epibatidine that relied on a [4+2] cycloaddition to set the two contiguous stereocenters which then facilitated a substrate stereocontrolled approach to complete the synthesis.

Scheme 19. Corey's Synthesis of (–)-Epibatidine (**91**) Relying on HPLC Based Enantiomer Resolution



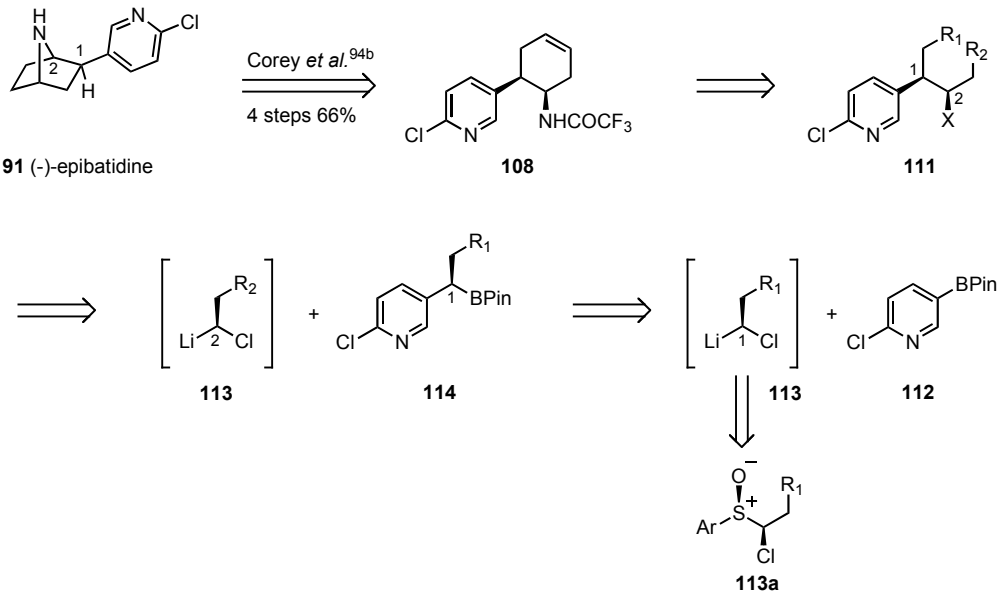
The starting aldehyde **103** was arrived at through a reduction/oxidation sequence of 6-chloropyridine-3-carboxylic acid before subjection to the Still-Gennari modified Horner-Wadsworth-Emmons olefination that selectively gave the (*Z*)-α,ß-unsaturated

ester **105**.[104] Conversion of the ester to the *cis*-disubstituted cyclohexene carboxylic acid **107** occurred under thermal [4+2] cycloaddition conditions with 1,3-butadiene (**106**) followed by saponification with LiOH. A four-step sequence involving acyl azide formation followed by Curtius rearrangement gave carbamate (**109**) which was acylated with trifluoroacetic anhydride giving trifluoroacetamide **108** in 76% yield over 4 steps. Regioselective bromination led to a vicinal dibromide which facilitated intramolecular nucleophilic substitution by the trifluoroacetamide nitrogen to form the 7-azabicyclo[2.2.1]heptane scaffold **110**. The final two steps involved tin mediated bromide reduction and alkaline hydrolysis of the trifluoroacyl group to give epibatidine **91** in a total of 11 steps and 42% overall yield. Enantiomeric resolution of cyclohexene **108** (Corey's intermediate) by preparative HPLC enabled the remaining steps to be conducted in each enantiomeric series. The *cis*-disubstituted cyclohexene **108** was the target to be converged upon using functionalized enantioenriched α-chloroalkylmetal reagents *via* StReCH chemistry in this work.

*3.3 - Retrosynthetic Analysis Converging on the Disubstituted Cyclohexene Intermediate **108***

It was proposed that a sequence of consecutive StReCH reactions could set the vicinal stereodiad contained within the *cis*-disubstituted cyclohexene (**108**) and is

Scheme 20. Proposed StReCH Route to Disubstituted Cyclohexene **108**



highlighted in Scheme 20. Cyclohexene **108** is arrived at through the acyclic pyridine precursor **111** through ring closing metathesis (RCM) or some other type of annulation chemistry. The functionalized precursor **111** is the product following two consecutive StReCH reactions that would proceed through homologated boronic ester **114**. The initial StReCH reaction would occur between putative enantioenriched lithium carbenoid **113** and pyridylboronate **112**. The vicinal nature of the stereodiad provides an excellent platform on which to demonstrate the power of StReCH to target any array of contiguous stereogenic centers.

Chapter 4: *Results and Discussion*

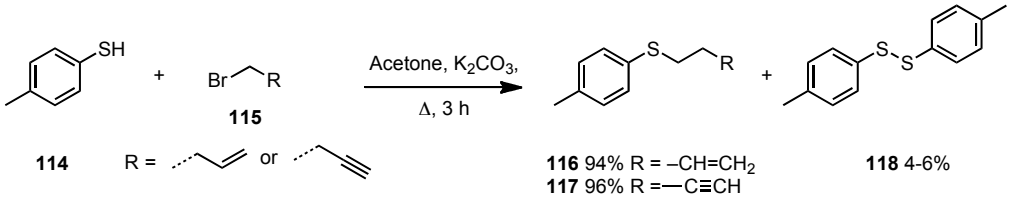
4.1 - Stereoselective Synthesis of α-Chlorosulfoxides

As stated in section **2.1.1**, successful execution of the Hoffmann-Matteson StReCH manifold requires reliable access to scalemic α-chloroalkyl sulfoxides. These carbenoid precursors must be prepared through a minimum number of robust and scalable steps to deliver the target α-chlorosulfoxides in high stereochemical purity (i.e., high er and dr). An equally important requirement these α-chlorosulfoxides must satisfy is near perfect stereochemical fidelity during stereospecific sulfoxide ligand exchange (SLE) reaction during the formation of the targeted enantioenriched α-chloroalkylmetal reagents. Currently, stereoselective α-chlorosulfoxide synthesis relies on an enantioselective sulfoxidation protocol developed by Jackson, Ellman and Bolm[105,106,107] followed by a diastereoselective Yamakawa chlorination.[108] This sequence is used exclusively in the following studies. Earlier StReCH studies have focused on α-chlorosulfoxides bearing various alkyl side chains (ethyl, benzyl, ^{i}Pr, etc.),[73,74] a keystone of this thesis, however, is the exploration of functionalized α-chlorosulfoxides as potential carbenoid precursors.

4.2 - Synthesis of Racemic α-Chlorosulfoxides

The synthesis of racemic α-chlorosulfoxides follows a three-step protocol beginning with alkylation of *p*-thiocresol **115**, Scheme 21. Standard alkylating conditions were employed to generate sulfides possessing unsaturated four carbon side chains, e.g. **116** and **117**.

Scheme 21. Synthesis of Functionalized *p*-Tolyl Sulfides

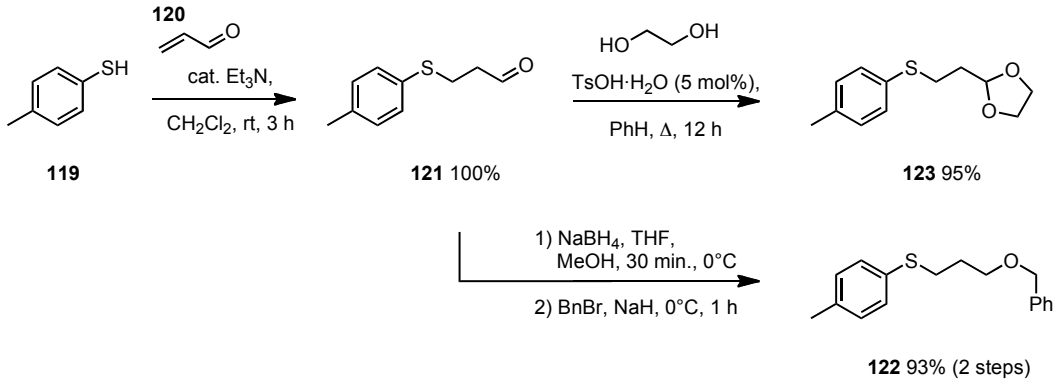


Heteroatom bearing sulfides **123** and **122** were synthesized following conjugate addition of *p*-thiocresol (**119**) to acrolein (**120**) generating intermediate aldehyde **121**. This aldehyde was then diverted into either dioxolanyl acetal **123** under dehydrative

conditions or benzyl ether **122** following reduction and benzylation, both products were formed in excellent yield, Scheme 22.

Formation of aldehyde **121** was initially attempted using *in-situ* generated NaOEt as base, but yields were highly variable.[109] Switching to sub-stoichiometric equivalents of Et_3N as initiating base led to consistent aldehyde (**121**) formation in quantitative yield.[110]

Scheme 22. Synthesis of Heteroatom Functionalized pTolyl Sulfides



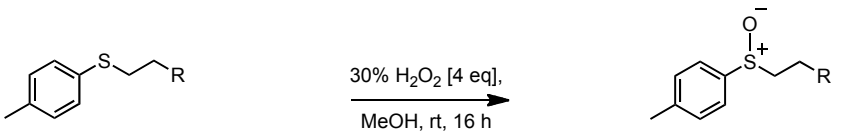
119 **121** 100% **123** 95%

122 93% (2 steps)

Following alkylation, thioether oxidation was originally performed using the molybdate catalyst $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (5 mol%) in the presence of aq. 30% H_2O_2 as oxidant.[111] This transformation consistently led to low sulfoxide yield due to over-oxidation resulting in significant sulfone formation. Other procedures were examined as well, but found to be inadequate due to consistent over-oxidation.[112]

Over-oxidation was suppressed by using conditions shown in Scheme 23, where sulfides **116, 117, 122** and **123** were oxidized with 30% H_2O_2 (4 eq) in the presence of MeOH at room temperature generating racemic sulfoxides **129-132** in nearly quantitative yield with no detectable formation of sulfone by ^1H NMR analysis.[113] This procedure has now been fully adopted for racemic aryl alkyl sulfoxide synthesis by the entire Blakemore research group and has exhibited chemoselective sulfinyl generation for all substrates tested.

Scheme 23. Racemic Sulfoxide Formation

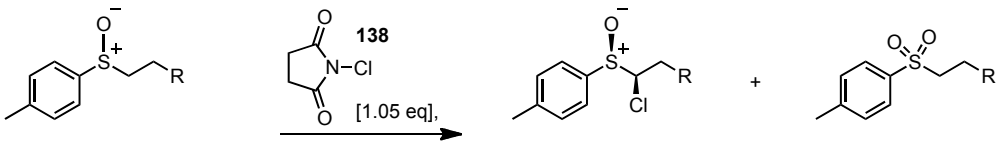


116 R = –CH=CH_2
117 R = –CH≡CH
122 R = –CH_2OBn
123 R = –CH(O(CH_2)$_2$O)

129 98% R = –CH=CH_2, > 99%
130 96% R = –CH≡CH, > 99%
131 98% R = –CH_2OBn, > 99%
132 95% R = –CH(O(CH_2)$_2$O), > 99%

Following sulfoxide formation, racemic α-chlorosulfoxides (**133-136)** were generated through a diastereoselective electrophilic chlorination of the sulfoxide α-position, Scheme 24. The moderate isolated yields are a consequence of over-oxidation to the dichlorinated and/or sulfone **137** by-products. Chlorination predominantly favors formation of the *syn* diastereoisomer (major isomer shown **133-136**) over the *anti* diastereomer, typically in the range between 4 - 6.2 : 1 (*syn:anti*). Interestingly, formation of alkynyl α-chlorosulfoxide **134** was much more *syn* selective (dr=15.8:1). A mechanistic hypothesis that accounts for the observed *syn* diastereoselectivity and stereochemical inversion on sulfur, *vide infra*, is provided in Scheme 28.

Scheme 24. Synthesis of Racemic Diastereoselective α-Chlorosulfoxides



129 R = –CH=CH_2
130 R = – C≡CH
131 R = –CH_2OBn
132 R = –CH(O(CH_2)$_2$O)

133 55%, dr 5.2 : 1
R = –CH=CH_2
134 86%, dr = 15.8 : 1
R = – C≡CH
135 63%, dr = 4.8 : 1
R = –CH_2OBn
136 58%, dr = 6 : 1
R = –CH(O(CH_2)$_2$O)

137 14–45%
For all R groups

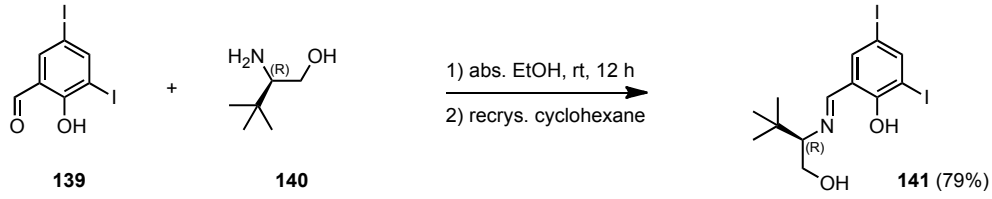
4.3 *- Synthesis of Scalemic α-Chlorosulfoxides **133** and **136***

Only two (**133** and **136**) of the four racemic α-chlorosulfoxides (**133-136**), were found to be viable StReCH reagent precursors (*vide infra*) necessitating their enantioselective synthesis as highlighted below.

The stereochemistry at sulfur, initially set during sulfoxide formation, determines the stereochemical outcome of the electrophilic α-chlorination and is ultimately

responsible for the configuration of the α-chloroalkyllithium carbenoid following SLE. Initial induction of stereochemistry at sulfur is accomplished through an enantioselective sulfoxidation protocol based on earlier work by Jackson, Ellman and Bolm that employs the *tert*-leucine derived salicylaldehyde ligand **141** which is easily prepared in one step, Scheme 25.

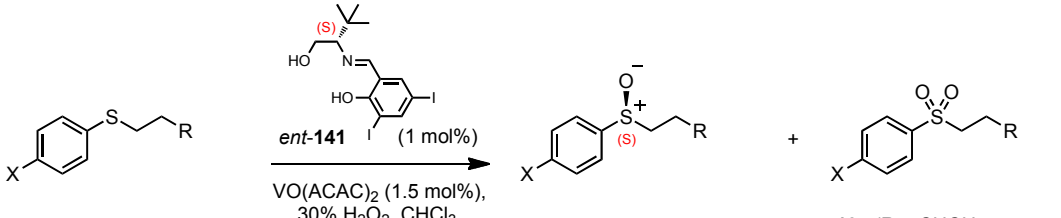
Scheme 25. Synthesis of Ligand for Enantioselective Jackson-Ellman-Bolm Oxidation



139 **140** **141** (79%)

Sulfides **125** and **128**, Scheme 26, were converted to sulfoxides **129** and **132** in very good yield (76-88%) with high levels of enantioenrichment (94-98% ee) using this protocol. A simultaneous background reaction that progresses at a much slower rate is the over-oxidation of sulfoxides **125**/**128** to sulfones **129**/**132**. During oxidation, any untargeted enantiomeric sulfoxide that is initially formed is preferentially converted to sulfone via kinetic resolution. If the reaction progresses long enough, over-oxidation of the targeted sulfoxide to sulfone is observed and the ensuing kinetic resolution leads to near perfect enantioenrichment of the targeted sulfoxide **129**/**132**, albeit, at the expense of overall sulfoxide yield.

Scheme 26. Enantioselective Synthesis of Functionalized Sulfoxides



116 (X = Me; R = –CH=CH_2)
123 (X = Me; R = –CH(O(CH_2)$_2$O)
142 (X = Cl; R = –CH=CH_2)

129 76% (> 98% ee)
(X = Me; R = –CH=CH_2)
132 80% (> 98% ee)
(R = –CH(O(CH_2)$_2$O)
143 88% (94% ee)
(X = Cl; R = –CH=CH_2)

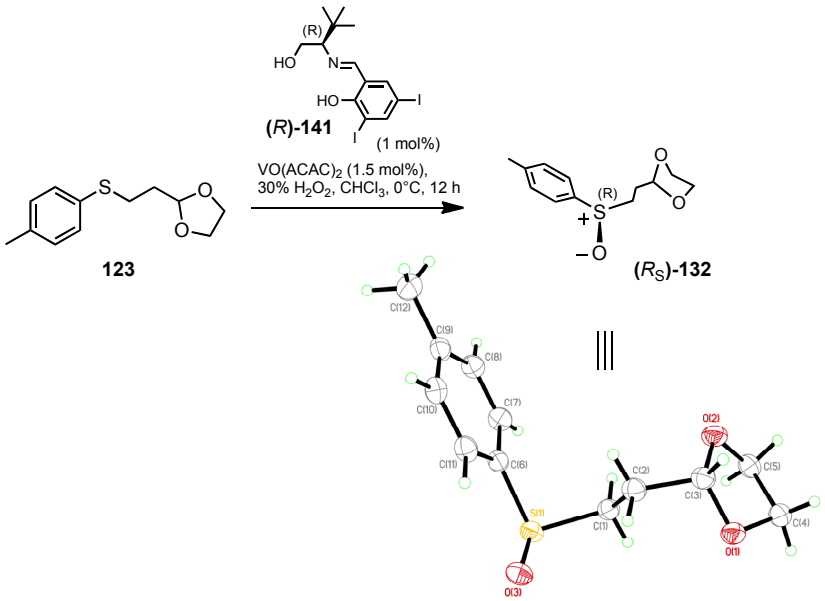
137 (R = $CHCH_2$,
X = Me), 24%
137 (R = CH(O(CH_2)$_2$O),
X = Me), 20%
137 R = $CHCH_2$,
X = Cl), 12%

The literature precedent for *p*-tolyl methyl sulfide oxidation, reports that 48 hours is required for the full conversion of sulfide to sulfoxide and with an enantioenrichment of > 98% ee.[106] It was discovered, however, that the nature of the R group has a

direct influence on sulfide **125**/**128** oxidation rate, requiring the optimization of reaction times and temperatures in order to maximize the balance between sulfoxide yield and enantioenrichment. Maximizing enantioenrichment of sulfoxide **129**/**132** is not completely critical at this stage as a partial loss (~10%ee) in sulfoxide stereochemical fidelity occurs during the subsequent electrophilic chlorination.

Optimized conditions are shown in Scheme 26, where ligand *ent*-**141** is first pre-complexed with $VO(acac)_2$ before addition of sulfide **125**/**128** which is followed by oxidation at 0°C using aq. 30% H_2O_2 as the terminal oxidant. It was found that only 4 hours were needed for the allyl bearing sulfide (**129**) to reach the optimal conversion point between maximum yield and enantioenrichment. Acetal bearing sulfoxide **132** requires a slightly longer reaction time of 12 hours for comparable results. The highly crystalline nature of acetal sulfoxide **132** permitted the determination of its absolute configuration through anomalous dispersion X-ray diffraction analysis, Figure 5.

Figure 5. Absolute Configuration of Acetal Sulfoxide by Anamolous Dispersion X-ray Diffraction Analysis

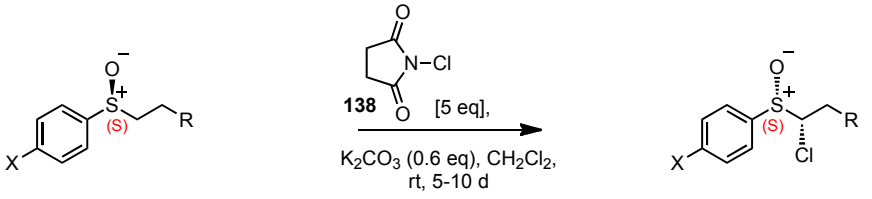


Partial racemization of the starting sulfoxide **129**/**132** during electrophilic chlorination leads to a small loss of enantiopurity of α-chlorosulfoxide **133**/**136**; however, this does not preclude access to enantiopure α-chlorosulfoxides, as

successive recrystallizations allow for isolation of essentially enantiopure (> 98% ee) and highly diastereoenriched α-chlorosulfoxides **133**/**136** (*syn:anti* = 95:5).

As shown in Scheme 27, sulfoxides **129**/**132** are converted into α-chlorosulfoxides **133**/**136** in the presence of a solution of *N*-chlorosuccinimide (NCS) [5 eq] **138** and K_2CO_3 [0.6 eq] in CH_2Cl_2 at room temperature over a period of 5-10 days.

Scheme 27. Diastereoselective Electrophilic α-Chlorination



129 (X = Me; R = –CH=CH_2)
132 (X = Me; R = –CH(O$(CH_2)_2$O)
143 (X = Cl; R = –CH=CH_2)

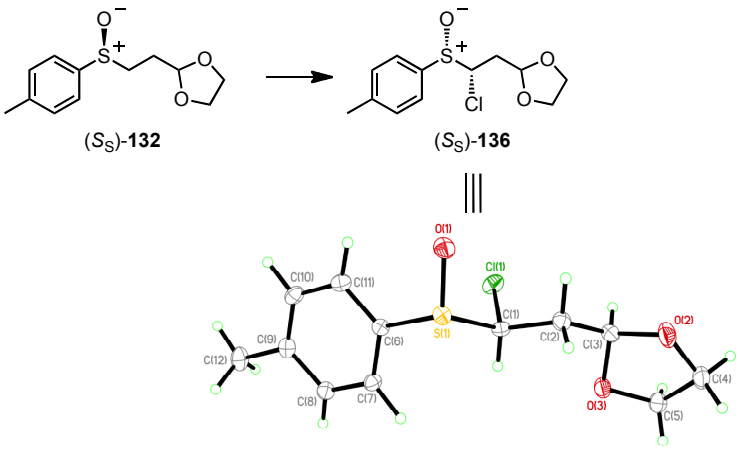
133 84% (X = Me; R = –CH=CH_2)
dr 7.5:1; 2x recrys dr ≥ 30:1
136 86% (X = Me; R = –CH(O$(CH_2)_2$O)
dr 5.6:1; dr 95:5 2x recrys
144 88% (X = Cl; R = –CH=CH_2)
dr 6.1:1

Variations in reaction conditions, such as altering equivalents of NCS or increased reaction temperature does not result in shortened reaction times, in fact, these changes typically lead to racemization of the sulfoxide center even when starting with highly enantioenriched material.

It should be noted that due to the difficulty of isolating **133** in diastereomerically pure form, synthesis of the *p*-chlorosubstituted chlorosulfoxide **144** was also investigated. The tolyl group is in essence a spectator group during SLE and it has been previously demonstrated that changing the *p*-methyl group to a chlorine atom may afford the chlorosulfoxide increased crystallinity, thereby facilitating its purification by recyrstallization. A significant detractor to this approach is the excessive time required during the α-chlorination step (≥ 16 days), coupling this with the fact that **144** did not lead to superior quality material nor perform better during SLE studies influenced the decision to continue studies with the p-tolyl α-chlorosulfoxide **133**. Fortunately, conditions were discovered that facilitated the precipitation and recyrstallization of chlorosulfoxide **133** generating highly enantio- and diastereoenriched material, (≥ 98% ee, dr > 30:1).

The crystalline nature of the acetal α-chlorosulfoxide **136** permitted the growth of a single crystal quality material that was analyzed by X-ray diffraction to determine both relative and absolute configuration. The presence of heavy atoms, such as sulfur in sulfoxide **132** and chlorine in **136**, makes these substrates amenable to resonance scattering in X-ray analysis, which is used to determine absolute stereochemistry.[114] In total, these studies have provided independent verification regarding the absolute configuration following the enantioselective oxidation and both the relative and absolute configuration of the α-chlorosulfoxide resulting from non-racemizing chlorination (including the observed inversion of sulfur).

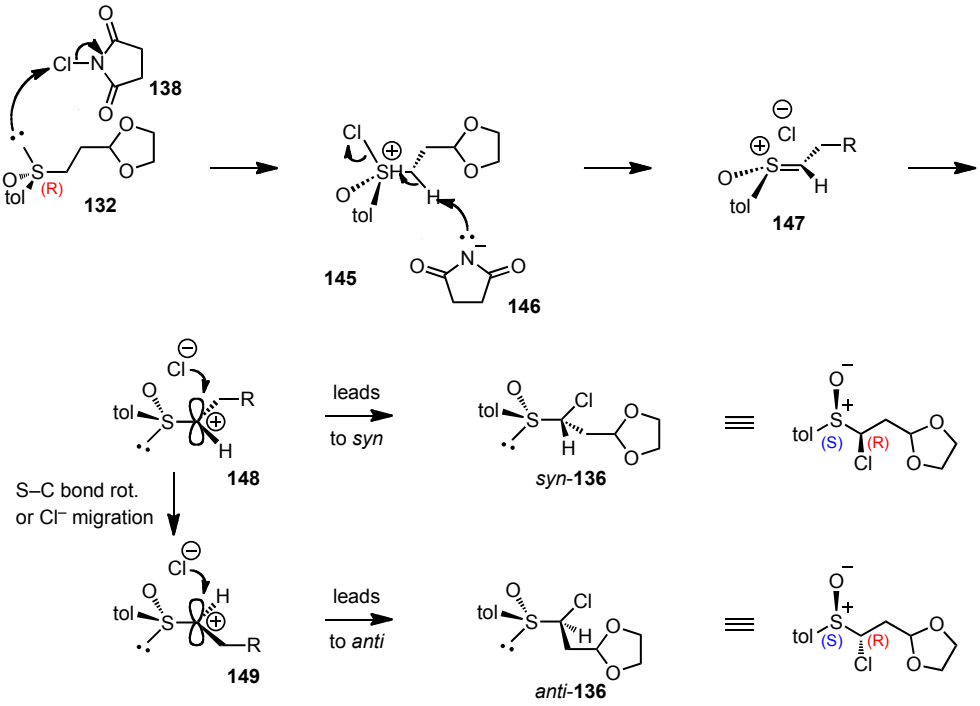
Figure 6. Relative and Absolute Configuration of Acetal α-Chlorosulfoxide by X-ray Diffraction



It has been proposed that electrophilic sulfoxide halogenation occurs as either a doubly retentive ($S_{ret}C_{ret}$) or doubly invertive ($S_{inv}C_{inv}$) stereochemical process.[115] The sulfoxides studied here, however, contain prochiral α-carbons and α-chlorination has been observed to occur with exclusive inversion of stereochemistry at sulfur. A mechanism involving deprotonation with concomitant halogen migration has been suggested to occur in concerted fashion, this however, would not account for the results observed in the present case.[116] To account for the exclusive inversion of stereochemistry at sulfur and the formation of *syn* diastereomers, the following mechanism is proposed, Scheme 28. Nucleophilic attack at the electrophilic chlorine atom of NCS by the lone pair of (*R*) - acetal bearing sulfoxide **128** generates chlorosuloxonium ion **145** which eliminates HCl in *anti*-periplanar fashion forming

thiocarbenium ion **147**. Electrostatic repulsion between the chloride ion and the electronegative oxygen atom (**147**) create a destabilizing Coulombic repulsion that is minimized through the inversion of sulfur by forming contact ion pair **148**. Nucleophilic addition of the chloride ion into the carbocation empty p-orbital occurs *anti* to the sulfur lone pair leading to formation of the major diastereomer *syn*-**136**. The selectivity for the minor diastereomer (*anti*-**136**) formation, occurs after inversion at sulfur and possibly arises from a S-C bond rotation or migration of chloride ion in **148** to form **149** following attack of the empty p-orbital by the chloride ion.

Scheme 28. Proposed Mechanism for α-Chlorination of Sulfoxide



With viable α-chloroalkyl lithium carbenoid precursors (**133**/**136**) in hand, the investigation of these stereodefined homologating reagents to function as chiral building blocks *via* StReCH in the synthesis of (–)-epibatidine was undertaken.

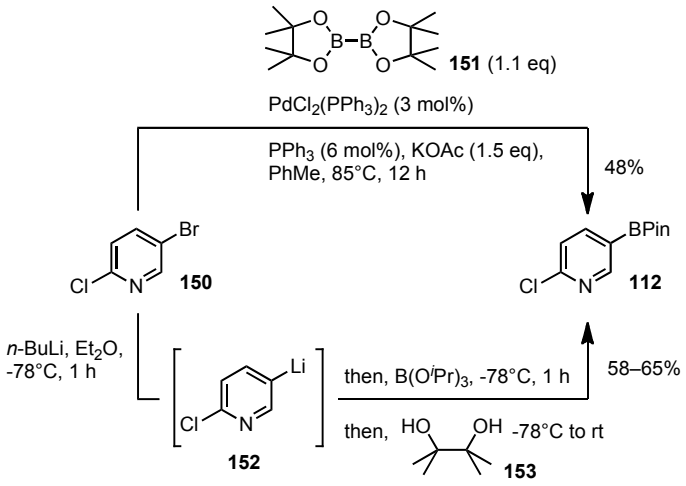
4.4 *- Investigation of Allyl Bearing Carbenoids, 1-Chlorobuten-3-yllithium and 1-(Carbamoyloxy)buten-3-yllithium, in StReCH Based Approach to (–)-Epibatidine*

As detailed in the synthetic plan, section **3.3**, the shortest route to the disubstituted cyclohexene epibatidine precursor **108** requires the allyl bearing lithium carbenoid **131**. Realization of this approach would constitute the first demonstration of a modular stereospecific approach to vicinal stereogenic center construction using the Hoffmann-Matteson StReCH manifold. This undertaking would initially be pursued via a series of sequential single chain extensions, with the intent to ultimately perform both steps in a single reaction vessel.

4.5 *- Synthesis of 2-Chloropyridyl Boronic Ester **112***

Two routes were investigated during the preparation of 2-chloropyridyl boronic ester **112** starting from 2-chloro-5-bromopyridine (**150**), Scheme 29. The first proceeded via palladium catalyzed Miyaura borylation of bromopyridine **145** with bis(pinacolato)diboron (**151**) and gave the target boronic ester **112** in 48% yield.[117]

Scheme 29. Synthesis of Pyridylboronate **112**

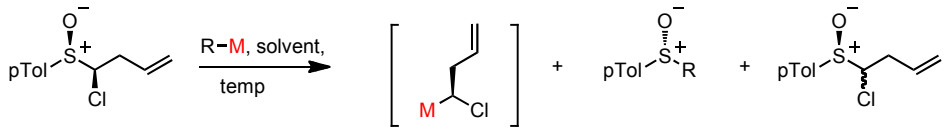


A second route consisting of three operations began with bromine-lithium exchange to form lithiated pyridine **152** followed by electrophilic quench with triisopropyl borate and then transesterification to pinacolboronate **112**. This sequence was found to give overall better yields and was subsequently applied during these studies.

4.6** - SLE and Initial Homologation Studies with Allyl Bearing Carbenoid **131

SLE studies of allyl bearing α-chlorosulfoxide **133** verified that this compound successfully formed putative α-chloroalkylmetal reagent (**153**/**154**) upon reaction with main group organometals, Scheme 30. A range of reaction conditions were examined starting with previously optimized conditions (*t*-BuLi/PhMe/–78°C), entry 1. The 67% yield of SLE by-product **155** was in the expected range and the observed *syn*:*anti* diastereomeric ratio (1:1) of recovered epimerized α-chlorosulfoxide (*epi*-**133**) was not without precedent.[77,74] The impetus to examine other SLE initiation conditions arises from the fact that α-chlorosulfoxides each exhibit unique behavior during SLE. For example, another previously employed SLE protocol (*n*-BuLi/THF/–78°C), entry 2, led to an intractable mixture of crude material and therefore was not investigated further. By contrast, magnesium carbenoid **154** was easily generated as indicated by the substantially higher yield of isolated SLE sulfoxide by-product (**155**) following addition of EtMgCl to a solution of **133** in PhMe (85% - yield of SLE sulfoxide by-product sets an upper bound for the amount of carbenoid formed). The lessened reactivity of magnesium carbenoids compared to lithium carbenoids in StReCH should be considered when evaluating the potential usefulness of Grignard initiated SLE reactions.

Scheme 30. SLE Studies of Allyl Bearing Carbenoid



133 | **153** (M = Li), **154** (M = MgCl) | **155** | *epi*-**133**

Entry	**133** dr (*syn*:*anti*)	R–M	Solvent	Temp (°C)	**155** SLE yield (%)	*epi*-**133** Recovered (%)	*epi*-**133** dr (*syn*:*anti*)
1	7 : 1	*t*–BuLi	PhMe	-78°C	67	33	1-1.6:1
2	9.6 : 1	*n*–BuLi	THF	-78°C	N / D	N / D	N / D
3	9.6 : 1	EtMgCl	PhMe	-78°C	85	15	9.6 : 1
4	33 : 1	PhLi	THF	-78°C	74	26	2.6:1

Following SLE studies, the viability of putative enantioenriched lithium carbenoid **153** in StReCH reactions was thoroughly examined and the most salient data

collected during these protracted studies are shown in Table 2. The formation of SLE by-product (**155**) typically ranged between 67-77% yield in almost all cases involving the lithium carbenoid reagent **153** under standard reaction conditions, entry 1. In all cases, the efficiency of StReCH was determined by isolation of the alcohol (**157**) derived from oxidative work-up.

Magnesium carbenoid **154** generated using EtMgCl as the SLE initiator, entry 2, failed to homologate pinacol boronate **112**. In an attempt to promote ate-complex rearrangement, the temperature was raised to 85°C for 3.5 hours following low temperature lithium carbenoid formation, entry 3. Cooling to –100°C for lithium carbenoid formation resulted in a more efficient SLE, but the boost in available carbenoid did not lead to an increase in product yield, in fact, a lower isolated yield of alcohol **157** was observed, entry 4.

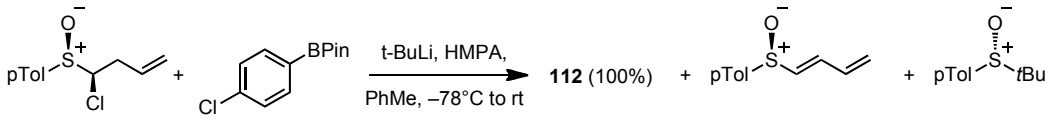
Immediately following StReCH initiation with *t*-BuLi/PhMe (which at the time constituted optimized SLE conditions) an orange globule of insoluble material would form and slowly re-dissolve over time as the reaction warmed from –78°C to rt. It was postulated that this material might be the desired ate-complex and an attempt was made to promote faster 1,2-metallate rearrangement by removing the reaction from the cold bath immediately following SLE initiation, entry 5. This course of action did not, however, lead to a different outcome. In a subsequent attempt to determine if the composition of the globular mass was different than that remaining in solution following SLE initiation, a solvent change was affected by syringing out the original PhMe solvent and replacing it with fresh PhMe solvent, entry 6. Upon workup it was found that the removed solvent and the remaining material in the original reaction exhibited roughly the same product distribution.

Equimolar quantities of *t*-BuLi and α-chlorosulfoxide **133** with pyridyl boronate **112** led to comparable results obtained under standard StReCH conditions, entry 1. Superstoichiometric ratios of *t*-BuLi and α-chlorosulfoxide **133**, however, led to less overall isolated product yield (< 5%) while carbenoid formation was relatively the same, entry 8. This last result led to speculation that α-metallated α-chlorosulfoxide,

the result of an undesired α-deprotonation instead of SLE, was possibly associating with the empty p-orbital of boronate **112** thereby removing it from a productive StReCH pathway. Ultimately, the discovery of an internal proton transfer, *vide infra*, between α-chlorosulfoxides and the putative lithium carbenoids provided a more likely explanation for the attenuation in product yield under superstoichiometric conditions.

HMPA and LiCl are known to influence the aggregation states of organometallic reagents, thereby possibly affecting accessibility and reactivity of the carbenoid.[118] Inclusion of these additives during homologation did not lead to an observable increase in product yield, entries 9-11. Curiously, the formation of diene **359** through a presumptive elimination pathway, Scheme 32, appears to only operate in the presence of HMPA. This may be similar in nature to the observed elimination of HCl from propargylic α-chlorosulfoxide **134** (section **4.6**).

Scheme 32. Observed Diene Formation Through an Elimination Pathway in the Presence of HMPA

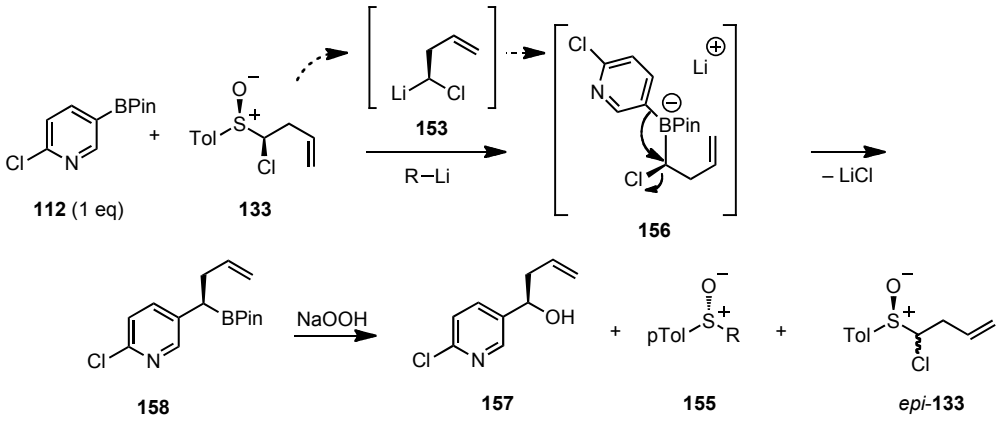


133 **112** **359** (31%) **155** (69%)

Inspired by earlier work on Matteson homologations, use of Lewis acidic $ZnCl_2$ as a reaction additive was also investigated. Matteson had demonstrated that $ZnCl_2$ promoted rearrangement of boron ate-complexes that were capable of 1,2-metallate rearrangements.[119] In the present case, dosing $ZnCl_2$ 30 minutes after the SLE/ate-complex formation event gave no enhancement in the overall StReCH yield, but for some as yet unexplained reason this activation mode consumed all traces of boronate **112**.

Finally, newly optimized StReCH conditions, entry 12, led to comparable results as those in entry 1. The PhLi based protocol was also explored in the presence of

Table 2. Homologation with Allyl Bearing Carbenoid **153** and Chloropyridine Boronate **112**.



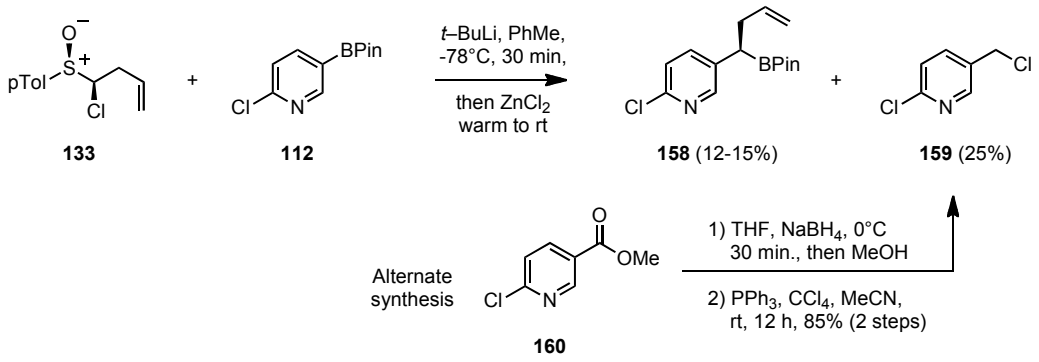
Entry	R–M	Solvent	Stoichiometry (eq) **133**	R–M	Additive	Temp	**157** yield (%)	**155** yield (%)	Recovered *epi*-**133** (%, dr *syn*:*anti*)
Original StReCH cond.									
1	*t*–BuLi	PhMe	2	2	–	-78°C to rt	12	67	33, 1:1
2	EtMgCl	PhMe	2	2	–	-78°C to rt	0	88	12, > 95:5
Temperature Variation									
3	*t*–BuLi	PhMe	2	1	–	-78°C to 85°C	13	67	33, 1.4:1
4	*t*–BuLi	PhMe	2	2	–	-100°C to rt	< 2	82	18, 1:1
Time / Solvent Exchange									
5[a]	*t*–BuLi	PhMe	2	2	–	-78°C to rt	11	64	36, 1.2:1
6[b]	*t*–BuLi	PhMe	2	2	–	-78°C to rt	12	63	37, 1.1:1
Stoichiometry Variation									
7	*t*–BuLi	PhMe	1	1	–	-78°C to rt	10	66	34, 1.2:1
8	*t*–BuLi	PhMe	3	3	–	-78°C to rt	< 5	64	36, 1.1:1
Additive Effects									
9	*t*-BuLi	PhMe	2	2	HMPA	-78°C to rt	0	69	0
10	*t*-BuLi	PhMe	2	2	LiCl	-78°C to rt	10	64	36
11	*t*–BuLi	PhMe	2	2	$ZnCl_2$ (1.6 eq)	-78°C to rt	16	65	35, 1.2:1
2nd Generation SLE/StReCH Conditions with Additive Effects									
12	PhLi	THF	1.2	1.2	–	-78°C to rt	11	75	25, 2.2:1
13	PhLi	THF	1.2	1.2	LiCl	-78°C to rt	12	73	27, 2.1:1
14	PhLi	THF	1.2	1.2	TMEDA	-78°C to rt	11	72	28, 2.4:1

a) reaction removed from cold bath immediately following addition of *t*-BuLi; b) solvent exchanged after formation of insoluble orange material following *t*-BuLi SLE initiation (see text)

both LiCl and TMEDA, entries 13 & 14, but neither of these variations led to an increase in product yield, even though the new StReCH conditions did result in a greater yield of SLE sulfoxide by-product **155**. This finding provided a means to isolate the targeted homologated boronic ester **158** as a single component, which was difficult to do in the presence of unreacted starting boronate **112**.

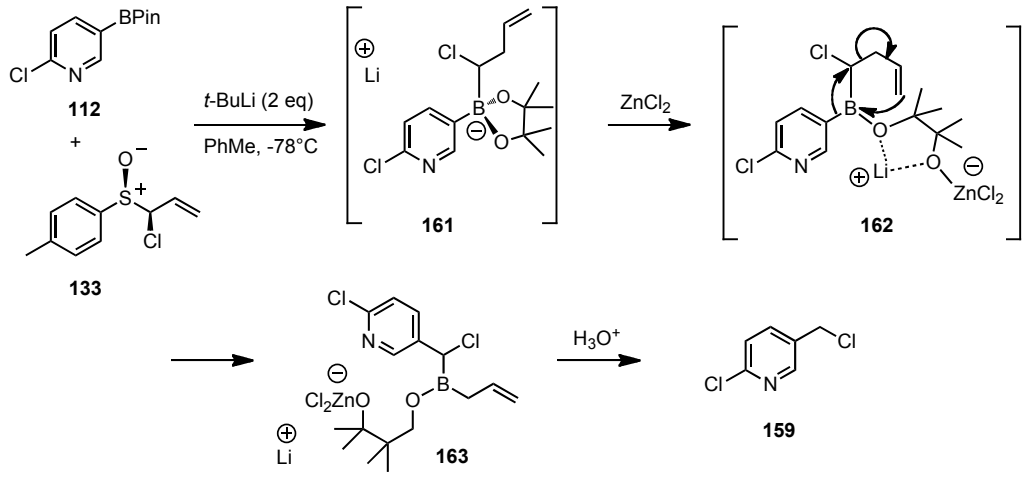
The addition of $ZnCl_2$ was found to not only remove all traces of starting boronic ester **112**, but also resulted in formation of 2-chloro-5-(chloromethyl) pyridine (**159**) in 25% yield, Scheme 33. The identity of this unexpected reaction by-product was confirmed by independent synthesis. Chloropyridyl ester **160** was converted to chloromethyl pyrdine **159** following reduction and phosphine activated chlorination. Chloropyridine **159** generated in this unambiguous manner was identical in all respects to that obtained from the StReCH experiment with $ZnCl_2$ additive.

Scheme 33. Formation and Synthesis of Chloromethyl 2-Chloropyridine **159**



Control experiments demonstrated that all the reagents used in the StReCH reaction were necessary for chloromethyl pyridine (**159**) formation as this transformation was not observed under any other conditions. A proposed mechanism for chloromethylpyridine **159** formation is shown in Scheme 34 and involves diversion of the ate-complex required for StReCH (**161**) along a different pathway. Before 1,2-metallate rearrangement occurs, $ZnCl_2$ promotes migration of the pyridine with loss of an allyl group instead of chloride (**162**). Benzylic boronate **163** is then activated for proto-deborylation leading to chloromethyl pyridine **159**. Ample precedent exists for related proto-deborylation reactions from benzylic positions.[121,122]

Scheme 34. Proposed Mechanism Leading to 2-Chloro-5-(Chloromethyl)pyridine

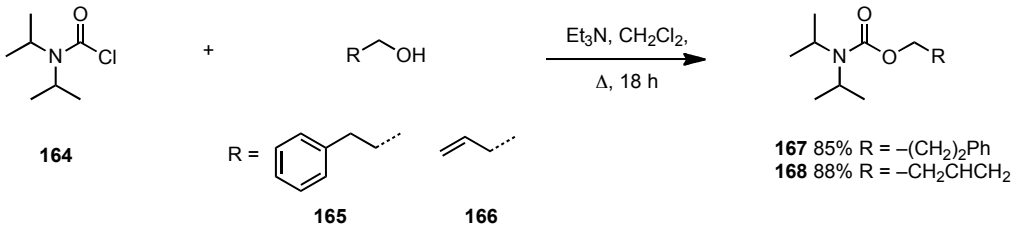


Clearly the SLE of α-chlorosulfoxide **133** was occurring with typical efficiency, but consistently poor isolated yields of the desired homologated product (**157**) indicated that the stability and/or reactivity of the resulting putative lithium carbenoid **154** was poorly understood. Part of the difficulty in elucidating the predominant decomposition pathways occuring is tied to the volatile nature exhibited by any of the quenched lithium carbenoid by-products.

4.7 - Hoppe-Matteson Homologation with an Allyl Bearing Carbenoid

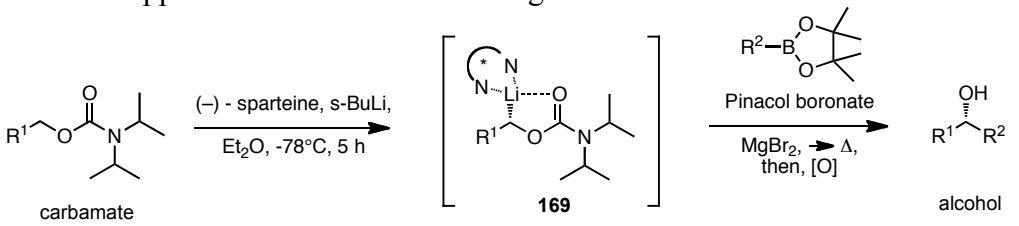
In light of the fact that pyridyl boronate **112** was not homologated efficiently with putative 1-chloro-3-butenyllithium (**153**) generated from a α-chlorosulfoxide carbenoid precursor, an investigation using the Hoppe-Matteson StReCH protocol was undertaken to accomplish the same aim. Synthesis of the necessary carbamate carbenoid precursor occurred by condensing carbamoyl chloride **164** with homoallyl alcohol **166** under refluxing conditions in CH_2Cl_2 leading to very good product yields, Scheme 35. A model carbamate **167** was also prepared for comparative purposes.

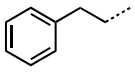
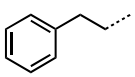
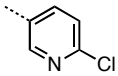
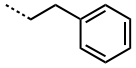
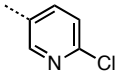
Scheme 35. Synthesis of Hoppe Carbamates



Carbenoid precursor **167** was targeted in order to validate the reported literature precedent for the Hoppe-Matteson homologation. After control experiments verifying formation of lithium carbenoid **169** (R^1=$(CH_2)_2$Ph) and considerable effort optimizing this complex reaction, the product alcohol **172** was isolated in 63% yield, entry 1.[79] Next, the carbenoid precursor was held constant while the boronic ester was changed from ethylboronate (**170**) to 2-chloropyrdine (**112**) leading to alcohol **173** in low yield, entry 2. This result suggests that boronic ester **112** is a less reactive substrate for StReCH than ethyl boronate **170**, more evidence to support this hypothesis is provided later, *vide infra*.

Table 3. Hoppe-Matteson StReCH Investigation



entry[a]	carbamate	R^1	pinacol boronate	R^2	alcohol	yield (%)
1	**167**		**170**	Et	**172**	63 (90%)[b]
2	**167**		**112**		**173**	9 -15
3	**168**		**171**		**174**	≤ 20
4	**165**		**112**		**157**	0

a) all reactions carried out in a minimum of duplicate runs; b) yield reported in literature

Switching to the allyl bearing carbenoid carbamate precursor (**168**) and boronic ester **171**, which has been previously used extensively for StReCH, gave alcohol **174** in an isolated yield ≤ 20%, entry 3. This result is in close agreement, albeit in overall less yield, with the comparable reaction conducted using the Hoffmann-Matteson homologation protocol (see Scheme 36).

Finally, homologation of pyridyl boronate **112** with the allyl bearing carbenoid **169** (R^1=CH_2CHCH_2) was examined, entry 4. It was revealed through several unsuccesful attempts that no chain extended product was isolated nor even observed by ^{1}H NMR. Chloropyridyl boronate **112** was fully recovered from the reaction, while only 7% of the alkenyl carbenoid precursor **168** was recovered, suggesting that the lithiated carbamate **169** (R^1=CH_2CHCH_2) was successfully formed, but that it was unable to trap (or rearrange) with boronic ester **112** under these conditions. In a control experiment, formation of lithiated carbamate **169** (R^1=CH_2CHCH_2) was verified through the deprotonation of carbenoid precursor **168** with *s*-BuLi/(–)-sparteine followed by deuterolysis with D_4-MeOH (90% yield, 83% D incorporation). This same carbamate **168** has been investigated by Aggarwal as well and shown to be difficult reagent for homologating boronic esters. It is proposed that a Li-π interaction between the lithium cation which is coordinated with the Lewis basic oxygens and the pendent alkene prevents the ate-complex from the proper anti-periplanar orientation required for 1,2-metallate rearrangement.[120]

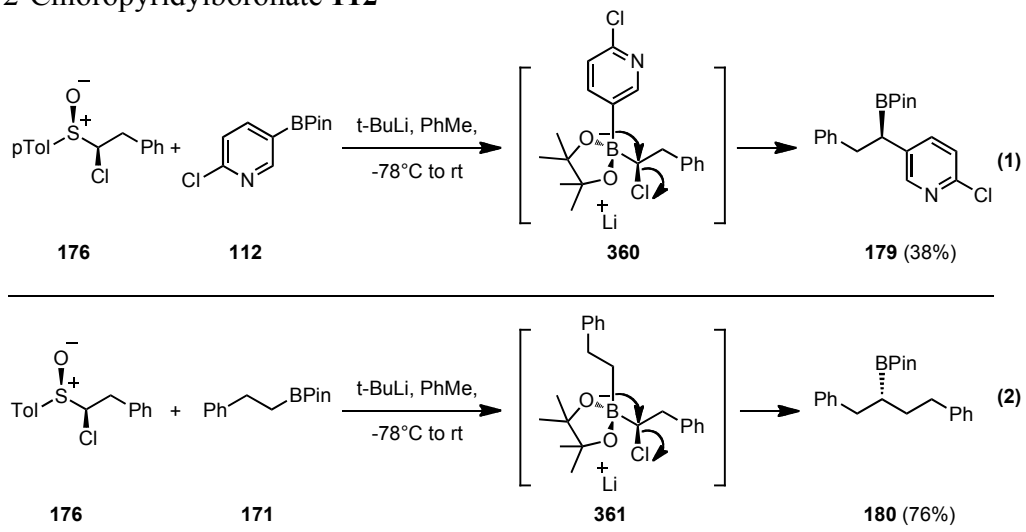
*StReCH Reactivity of 2-Chloropyridyl Pinacol Boronate **112***

The heteroaromatic boronic ester **112** displays significantly different steric and electronic properties than any previously examined boronate substrate used for StReCH. Migratory aptitude plays a major role during 1,2-metallate rearrangement where both the electronic and steric character of this B-chloropyridyl moiety may be influencing the propensity of the ate-complex (**161**) to rearrange.[121]

Control experiments conducted with the benzyl bearing lithium carbenoid precursor **176** also contributed to the empirical evidence that chloropyridyl boronate **112** is less reactive, Scheme 36. It has been demonstrated that the benzyl bearing carbenoid

derived from α-chlorosulfoxide **176** can be very efficient in StReCH chemistry, e.g., equation 2, but it only homologated pyridylboronate **112** in a very modest yield of 38%, equation 1.[73,74] As discussed in section **4.5**, very good yields were eventually obtained with this boronic ester, but it required a carbenoid with presumed greater nucleophilic character and chemical stability.

Scheme 36. StReCH Chemistry Using A Benzyl Bearing Lithium Carbenoid and 2-Chloropyridylboronate **112**

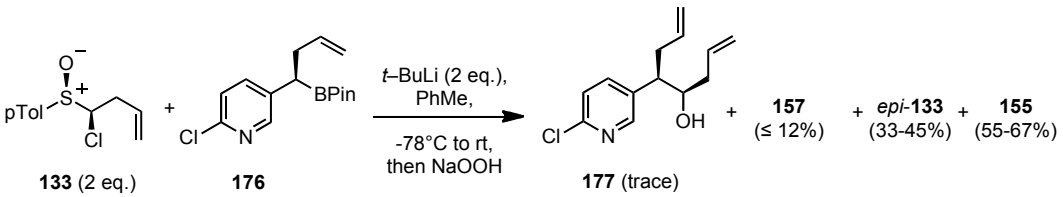


176 **112** **360** **179** (38%)

176 **171** **361** **180** (76%)

Although homologation of boronate **112** was less than optimal with lithium carbenoid **153**, continued chain extension of the homologated product (**176**) from this reaction was briefly entertained. Scheme 37 shows the conditions employed for the second homologation, but no doubly homologated product (**177**) was ever isolated or characterized from these attempts. At best, only trace amounts of product were observed by ^{1}H NMR, even when employing the newly optimized reaction conditions of PhLi / THF.

Scheme 37. Attempted Double StReCH with Allyl Bearing Carbenoid **153**



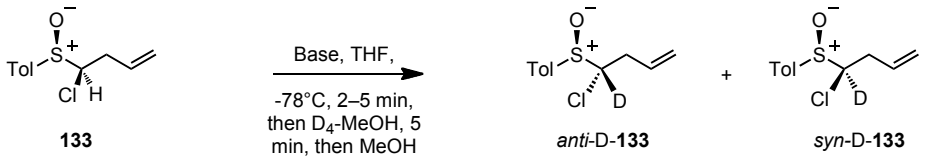
133 (2 eq.) **176** **177** (trace)

4.8 *- Revisiting the Allyl Bearing Carbenoid as the α-Deuterated Analogue*

Following discovery that isotopomeric α-deuterated-α-chlorosulfoxide carbenoid precursors perform better in StReCH reactions, *vide infra*, a final investigation into the use of an allyl bearing lithium carbenoid for the epibatidine synthesis was pursued.

Epimerization conditions to convert the *syn* α-protio-chlorosulfoxide **133** to *anti* α-deuteride **133** were found and optimized, Table 4. As detailed, a series of mostly hexamethyldisilazide metal amide bases were examined and it was discovered that the nature of the counter-ion had a significant impact on the relative stereochemistry of the recovered *anti* α-deutero-α-chlorosulfoxide (**133**). Two points need to be addressed concerning the epimerization reaction, the first is that 100% deuterium incorporation has not been observed for this substrate during any trials. Second, this transformation does not work well when attempting to convert more than 3 mmols of the α-protio-α-chlorosulfoxide (**133**). This practical scalability issue with *syn* to *anti*epimerization of chlorosulfoxide **133** has only been observed for this particular case.

Table 4. Optimization of the Synthesis of *anti* α-Deutero-α-Chlorosulfoxide **133**



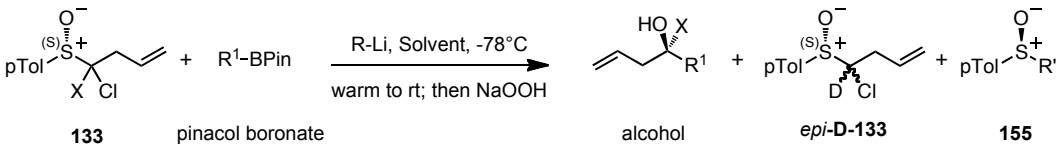
133 *anti*-D-**133** *syn*-D-**133**

Entry	Base	eq.	dr (*anti* : *syn*)	D% incorporation	yield %
1	KHMDS	1.3	1 : 1	90%	90%
2	NaHMDS	1.3	4 : 1	80%	80%
3	NaHMDS	3.0	4.5 : 1	82%	82%
4	LiHMDS	1.3	3 : 1	88%	88%
5	LDA	1.3	7-10 : 1	88%	88%

Substitution of deuterium for the α-proton in the α-chlorosulfoxide carbenoid precursors has been shown to have a positive impact on the yield of StReCH reactions. This effect is further exemplified by the data shown in Table 5. Thus,

when α-protio-α-chlorosulfoxide **133** (X = *syn*-H) was applied to the StReCH reaction with phenethyl boronate **171**, followed by oxidative work-up, the expected alcohol **178** (X = H) was obtained in up to a 32% yield and 82% ee, entries 1 and 2. In contrast, a two-fold improvement in yield (62%) was recorded for an otherwise identical StReCH reaction that employed α-deutero-α-chlorosulfoxide **133** (X = *anti*-D) as the carbenoid precursor, entry 3. An even more pronounced deuterium effect was observed for StReCH of pyridyl boronate **112** with the same carbenoid, entries 4 and 5. The nature and origin of the effect is discussed in detail in section **4.3**.

Table 5. Observed Deuterium Affect for First Homologation



133 pinacol boronate alcohol ***epi*-D-133** **155**

entry	X (dr)	R^1	pinacol boronate	R–Li (eq.)	solvent	alcohol	(%)$^{(\%ee)}$	**D-133** (%)$^{(syn:anti)}$	**155** (%)
1	*syn*-H (> 25:1)		**171**	*t*-BuLi (2)	PhMe	**178**	20$^{(85)}$	31$^{(1.8:1)}$	67
2	*syn*-H (> 25:1)	Ph	**171**	PhLi (1.2)	THF	**178**	32$^{(82)}$	28$^{(2.2:1)}$	70
3	*anti*-D (~5.3:1)		**171**	PhLi (1.2)	THF	**178**	62$^{(61)a}$	30$^{(2.3:1)}$	70
4	*syn*-H (> 25:1)	Cl N	**112**	PhLi (1.2)	THF	**157**	~10-12$^{(0)}$	32$^{(2.4:1)}$	67
5	*anti*-D (~7:1)		**112**	PhLi (1.2)	THF	**157**	33$^{(0)}$	25$^{(2.5:1)}$	74

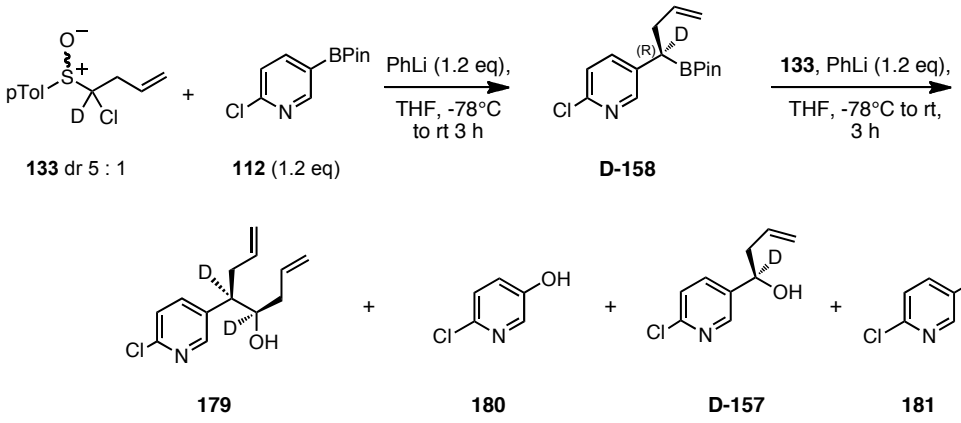
a) 61%ee represents an overall stereofidelity of this reaction of 91% based on the diastereomeric ratio of staring α-chlorosulfoxide carbenoid precursor (~5.3:1)

Some issues concerning the different levels of stereocontrol exhibited during these reactions warrant comment. First, the lower enantiomeric excess obtained for StReCH adduct **178** (X = D, entry 3) as compared to its protio isotopomer is an artifact of the different stereoisomeric purity of the relevant α-chlorosulfoxide carbenoid precursors involved in each case [i.e., carbenoid er cannot exceed the dr of its α-chlorosulfoxide precursors, therefore, maximal %ee for the allyl bearing carbenoid involved in entries 1 and 2 was > 92%, but no greater than 68% for the case in entry 3]. Second, alcohols derived through StReCH of pyridyl boronate **112** by allyl bearing carbenoids from any α-chlorosulfoxide source (**133**), were racemic.

This observation is likely a consequence of non-stereospecific B-O conversion during NaOOH mediated oxidation.

As mentioned earlier, double homologation of chloropyridyl boronate **112** was not realized using the α-protiochlorosulfoxide **133** in StReCH, however, some success was had by employing the deuterium effect, Scheme 38. Various reaction conditions were investigated starting with sequential single iterative steps involving the isolation of intermediate boronate **D-158** before performing the second homologation reaction. This procedure failed to produce more than trace quantities, detectable by crude ^{1}H NMR analysis, of the doubly homologated product **179**. The benzylic nature of **D-158** has consequences regarding its stability both during purification and during the second homologating event, *vide infra*.

Scheme 38. Alkene Double Homologation with *anti*-Deuteride **133**



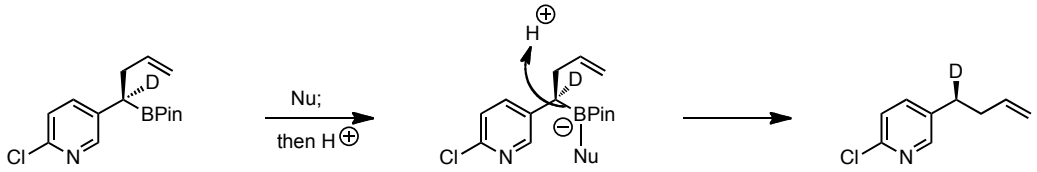
entry	**133** configuration		**D-158** (%)	*epi*-**133** (%)	**179** (%)	**180** (%)	**D-157** (%)	dr	**181** (%)
Two pot									
1	(R_s)-*anti*		28-33	30	< 5	10-20	25-30	2:1	45-60
Single pot									
	1st iteration	2nd iteration							
2	(S_s)-*anti*	(S_s)-*anti*	n / a	n / a	15	20	20-25	2.1:1[a]	40

a) the maximal dr possible for this doubly homologated compound is 2.5 : 1, this calculation is shown in **2.5.3**

Due to the instability of intermediate **D-158**, consideration was given to by-passing its isolation and carrying out both homologations in a single pot to overcome the

difficulty of generating the targeted diene **179**, entry 2. The doubly homologated alcohol (**179**) was eventually isolated in 15-18% yield, though this was much lower than necesssary in order to carry the material forward to the disubstituted cyclohexene **108**. The other products isolated from the reaction indicate that there was substantial unreacted chloropyridyl boronate **112** remaining from the first homologation event. The significant quantity of proto-deborylated material **181** (40%) suggests that loss of boron from **112** is facile and may be occurring between the first and second step. Many attempts were made to optimize this reaction but the results were nearly always consistent with formation of **181** as the predominant pathway. Finally, isolation of the oxidized 2-chloropyridine **180** indicates that a major portion of the boronic ester **112** is not reacting with any of the generated lithium carbenoid during either of the homologations.

Scheme 39. Observed Proto-deborylation with Benzyl Substituted Boronic Esters



D-158 **182** **181**

The benzylic nature of the activated pinacol boronate **182** primes the ate-complex for proto-deborylation in the presence of both strong and weak nucleophiles, Scheme 39. This proto-deborylation was also observed when investigating the analogous acetal boronate **190,** *vide infra*, although in the acetal case it was found that a single pot double homologation sequence could overcome this limitation. Similar benzylic proto-deborylation has also recently been reported and even exploited to succesfully install tertiary stereogenic centers on comparable substrates.[122,123]

Following the extensive investigations into α-chlorosulfoxide allyl bearing carbenoid precursor **133** and the unequivocal determination of its inherently poor reactivity when applied to StReCH chemistry, especially during the installation of contiguous asymmetric stereocenters, this reagent was not studied any further.

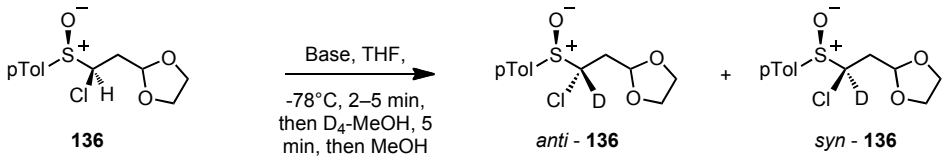
***4.9** - Generation of A Contiguous Stereodiad Using an Acetal Bearing α-Chloroalkyllithium Regeant: Synthesis of Cyclic Targets Related (–)-Epibatidine via StReCH*

This section of thesis was performed in collaboration with Prof. Paul R. Blakemore and was recently disclosed as a communication.[124]

Reactivity and application of the acetal bearing lithium carbenoid **184** is discussed in this section and synthesis of its relevant α-chlorosulfoxide carbenoid precursor (**136**) was addressed in section **4.2**. Acetal bearing lithium carbenoid **184** was instrumental in the discovery of several key StReCH processes involving α-chlorosulfoxide carbenoid precursors and carbenoid formation *via* SLE. It has also been shown to be an effective stereodefined reagent for successful StReCH homologation leading to vicinal stereogenic centers.

During preliminary SLE investigation of acetal α-chlorosulfoxide **136**, it was found that recovered α-chlorosulfoxide *epi*-**136** was epimerized with an *anti*:*syn* ratio of 4:1, exceeding the typical (≤ 3 :1) *anti*:*syn* epimerization ratio of α-chlorosulfoxides.[77] Coupling this observation with the knowledge that highly crystalline α-chlorosulfoxides are readily isomerically enriched through successive recrystallizations provided the impetus to investigate *anti* α-chlorosulfoxide **136** formation, Table 6. Optimized conditions provided a route for reliable access to *anti*

Table 6. Base Promoted Epimerization of *syn* α-Chlorosulfoxide **136**



136 *anti* - **136** *syn* - **136**

Entry	Base	eq.	**136** dr (*anti* : *syn*)	D% incorporation	yield	ee (%) before	ee (%) after
1[a]	LDA	1.3	18 : 1	83%	87%	89	74
2	LDA	1.5	18 : 1	90%	82%	87	72
3	LiHMDS	1.5	14 : 1	84%	83%	89	77
4	KHMDS	1.3	2 : 1	84%	82%	87	85
5	NaHMDS	1.3	7 : *1*	87%	88%	88	85
6	NaHMDS	2.2	13 : 3	88%	88%	88	86

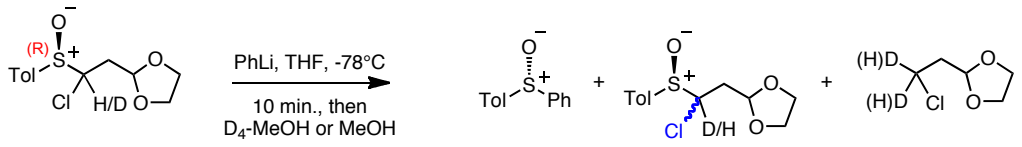
a) 30 min allowed for deprotonation

α-chlorosulfoxide **133** in excellent yield (88%) and with a high level of deuterium incorporation (>88%), entry 6. It is interesting that a change in counter-ion during epimerization has such a dramatic effect on deuterolysis diastereoselectivity and the potential for racemization. Ready availability of both *syn* and *anti* α-chlorosulfoxides **136** provided an opportunity to explore their effectiveness during SLE formation of acetal bearing lithium carbenoids. As discussed in section **4.3.2**, formation of predominantly *syn* α-chlorosulfoxide is a consequence of the diastereoselectivity of the chlorination reaction. In light of this, there were unanswered questions concerning possible differences in reactivity between *syn* and *anti* α-chlorosulofoxide carbenoid precursors and a thorough investigation was now possible.

*4.10 - SLE Studies Involving syn and anti Acetal Bearing α-Chlorosulfoxide **136***

Three different variants of α-chlorosulfoxide **136**, all (*R*)-configured at sulfur, were studied in the SLE reaction with PhLi and the results are provided in Table 7. *Syn* α-chlorosulfoxide, entry 1, with a > 95 : 5 (*syn*:*anti*) ratio gave SLE by-product sulfoxide **155** in 47% yield, along with highly deuterated, epimerized adduct **136** in

Table 7. Acetal SLE Studies of *syn* and *anti* α-Chlorosulfoxide **136**



136 **155** **136** **183**

entry	Configuration	*anti*$^{\%D}$: *syn*$^{\%D}$	quench	**155**	recovered **136** (*anti*$^{\%D}$: *syn*$^{\%D}$)	**183** % (HH : HD : DD)
1	R_S–*syn*–H	$< 5^{0} : > 95^{0}$	D_4–MeOH	47%	20% ($78^{\geq 99} : 22^{\geq 99}$)	28% (> 95 : < 5 : 0)
2	R_S–*anti*–H	$93^{0} : 7^{0}$	D_4–MeOH	51%	20% ($80^{\geq 99} : 20^{\geq 99}$)	33% (> 95 : < 5 : 0)
3	R_S–*anti*–D	$92^{87} : 8^{\geq 80}$	MeOH	58%	16% ($77^{< 2} : 23^{< 2}$)	35% (22 : 50 : 28)
4	R_S–*anti*–D	$92^{87} : 8^{\geq 80}$	D_4–MeOH	63%	16% ($73^{96} : 27^{89}$)	26% (14 : 59 : 27)

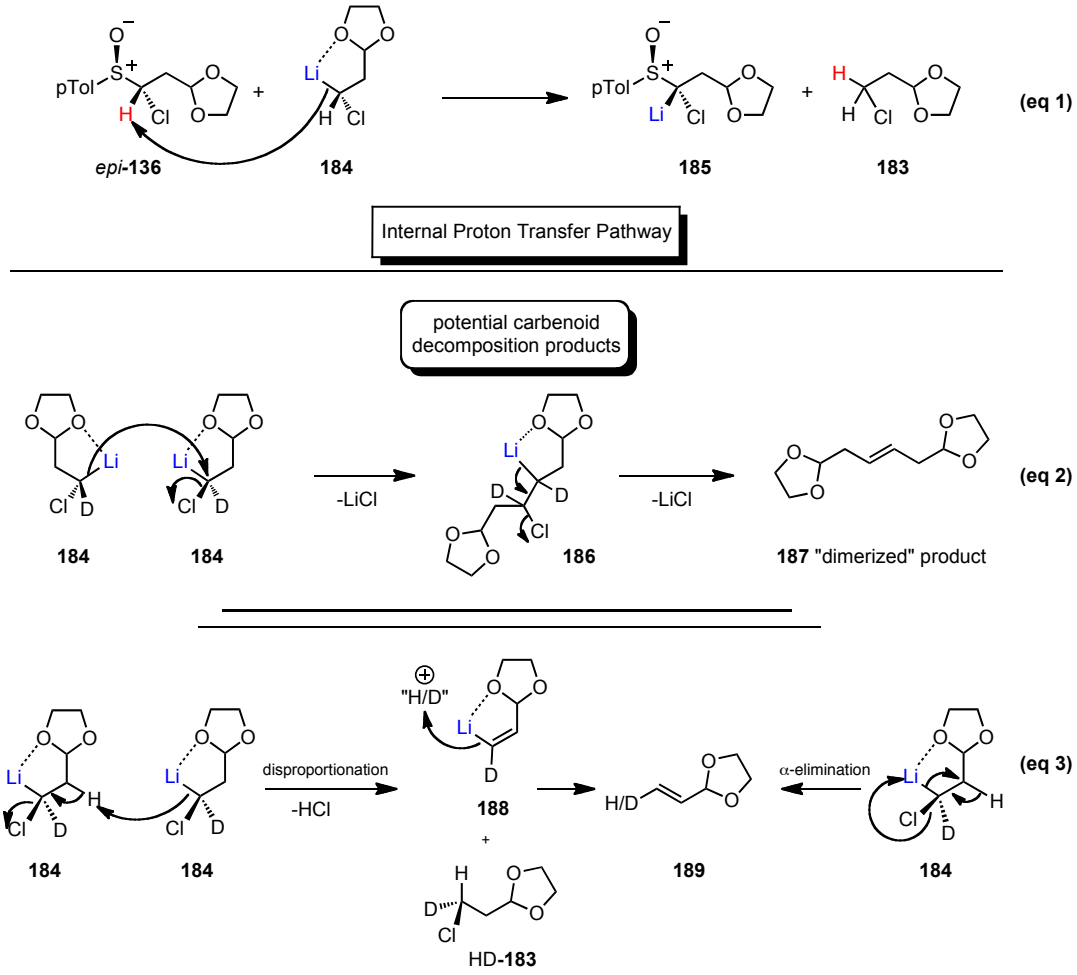
20% yield (*anti*:*syn* = 78 : 22) following treatment with PhLi followed by deuterolysis. Significantly, alkyl chloride **183** was also isolated (28%), but with a minimum deuterium level < 5%. Alkyl chloride **183** is the product from a proton transfer to the putative α-chloroalkyllithium reagent (**184**) and its formation

suggested that an *in-situ* proton source is quenching the carbenoid during the 10 minute reaction time. Comparable results were observed when this experiment was repeated with **136**$_{anti\text{-H}}$, entry 2. Partially epimerized *epi*-**136**$_{D}$ was isolated and fully deuterated at the α-position indicating that α-lithiation is a competing pathway with SLE. Recovery of **183** with similarly low deuterium incorporation (< 5%) corroborated the hypothesis that an internal proton transfer to the carbenoid is occuring. The observed results suggest that lithium carbenoid **184** exhibits significant chemical stability, *vide infra*, considering it persists long enough to engage in a bimolecular quench pathway with the acidic α-proton of α-chlorosulfoxide *epi*-**136**. To advance this hypothesis, a deuterium labeling study was undertaken, entry 3, where *anti* deutero-α-chlorosulfoxide (**136**) is treated with PhLi and then quenched after 10 minutes with a proton source. A slight increase in SLE sulfoxide by-product (**155**) yield was observed, while recovered epimerized chlorosulfoxide **136** exhibited complete protonation at the α-position by ^{1}H NMR spectroscopic analysis. Alkyl chloride **183**, however, did display significant levels of double deuteration even when quenched with a proton source. When repeated with a deuterium quench, entry 4, a comparable level of doubly deuterated DD-**183** was observed providing direct evidence for internal lithium carbenoid quench. Formation of all three isotopomers of **183** (HH:HD:DD) is most likely a consequence of starting with less than 100% α-deuterated chlorosulfoxide **136** and the faster kinetic deprotonation of residual α-protio-chlorosulfoxide **136** in the presence of the α-deutero-chlorosulfoxide **136**.

A mechanism to account for the internal proton quench was posited and is shown in Scheme 40, where lithium carbenoid **184** deprotonates the acidic α-position of α-chlorosulfoxide **136**. In the absence of a boronic ester, lithium carbenoid **184** generated *via* SLE of α-chlorosulfoxide **136** should decompose through the pathways discussed in the carbenoid introduction section **1.6**. For example, a carbenoid "dimerization" pathway involving two lithium carbenoids, eq. 1, leads to lithiated bisacetal **186** that then loses a second equivalent of lithium chloride to give the bisacetal **187** (which has been typically isolated in < 5% yield). The other likely

carbenoid decomposition pathway is α-elimination with concomitant 1,2-hydride shift, which would result in vinyl acetal **189** formation, eq. 2.

Scheme 40. Proposed Internal Proton Transfer to Lithium Acetal Carbenoid **183** and Alternative Carbenoid Decomposition Pathways



The vinyl acetal product **189** is most likely too volatile for isolation, but lack of its detection/isolation does not refute the possibility of its formation. β-Elimination of carbenoid **184** by a second molecule of lithium carbenoid **184**, may also contribute to higher levels of HD-**183**, eq. 3.

Formation of DD-**183**, entry 3, is only possible through deprotonation of α-deuterated chlorosulfoxide **136**$_{anti\text{-D}}$, providing indisputable evidence that an internal quenching pathway is in fact operable during generation of lithium carbenoids, such

as **184**, from α-chlorosulfoxide precursors *via* SLE. Discovery of this internal proton transfer pathway has significant implications as this competing background reaction removes both lithium carbenoid (**184**) and the carbenoid precursor (**136**) from a productive StReCH pathway. Accordingly, this may account in part for the wide variability in yield typically observed for SLE based StReCH reactions.

*4.11 - StReCH with Acetal Bearing Lithium Carbenoid **184***

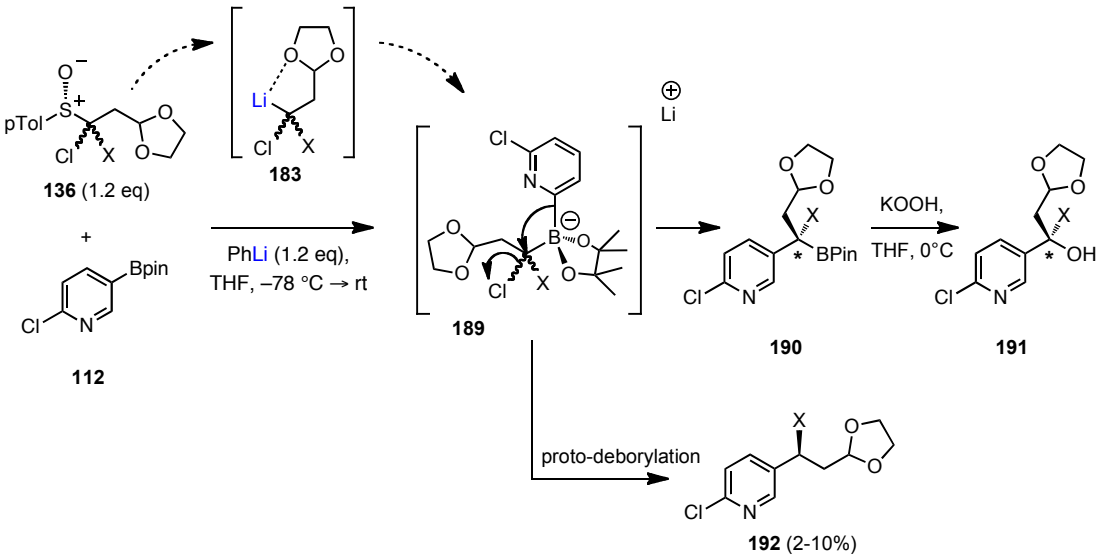
Homologation studies were conducted using the α-chlorosulfoxide carbenoid precursor **136** and pyridylboronic ester **112**, Scheme 41. Newly optimized SLE conditions with *syn*-protio chlorosulfoxide **136**$_{syn\text{-H}}$, entry 1, led to the formation of putative lithium carbenoid **183**, represented here with internal chelation between the Lewis basic acetal oxygen and carbenoid lithium atom. This type of chelation and stabilizing effect is well precedented and was incorporated into the design of this lithium carbenoid reagent in an effort to exploit this interaction.[125,126,127,128,129,130]

Ate-complex formation followed by stereospecific breakdown generated benzylic boronate **190** which was then oxidized to the benzyl substituted alcohol **191** in 68% conversion. The *anti*-protio chlorosulfoxide **136**$_{anti\text{-H}}$, entry 2, and the *anti*-deutero chlorosulfoxide **136**$_{anti\text{-D}}$, entry 3, were also examined under these conditions. Comparable results were obtained for both α-protio versions while enhanced SLE and increased yield of carbinol **191** were observed for the α-deuteride case, entry 3. This result may be accounted for considering carbenoid self-quench would be kinetically slower with the α-deuteride **136**$_{anti\text{-D}}$, leading to a more efficient SLE and greater lithium carbenoid availability for StReCH.

Stereochemical fidelity during this StReCH reaction was found to be excellent, entries 1 and 3. Diastereomeric α-chlorosulfoxides possessing the same configuration at sulfur, lead to opposite enantiomeric lithium carbenoids upon SLE, therefore the 90% level of enantioenrichment determined for benzylic alcohol **191** in entry 3, is at its maximal level as the starting material had an *anti*:*syn* diastereomeric ratio of 95:5. This indicates that lithium carbenoid **183** does not significantly racemize on the time scale of the reaction and that 1,2-metallate rearrangement of the ensuing ate-complex

is stereospecific. Isolation of boronic ester **190** is accompanied by minor amounts of proto-deborylated by-product **192** (2-10%) observed for all three cases. By-product **192** is the result of a proposed facile proto-deborylation, as discussed previously in section **4.7**.[123,124]

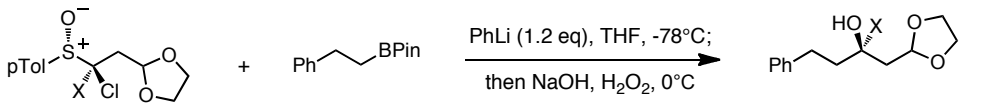
Scheme 41. First Homologation with Acetal Carbenoid



Entry	**136** Configuration	*anti : syn*	targeted boronate **190**	Conversion to **191**	**191** ee (%)
1	(R_s)–*syn*–H	< 5 : > 95	* = (R); X = H	68%	93
2	(R_s)–*anti*–H	93 : 7	* = (S); X = D	62%	nd
3	(S_s)–*syn*–D	95 : 5	* = (R); X = D	79%	89

A model study conducted to verify the deuterium effect is shown in Scheme 42. α-Chlorosulfoxide $\mathbf{133}_{anti\text{-D}}$ gave higher yield (85%) in the StReCH reaction with boronate **171**, than the analogous reaction employing $\mathbf{133}_{anti\text{-H}}$ (76%). The stereoselectivity of both of the reactions is in the range observed for this homologating reagent (~91% of maximum).

Scheme 42. Observed Deuterium Effect for Acetal α-Chlorosulfoxide **133** in StReCH



133 X = H, dr = 18:1
133 X = D, dr = 17:1

171

193 76%, R = H, 80%ee
194 85%, R = D, 81%ee

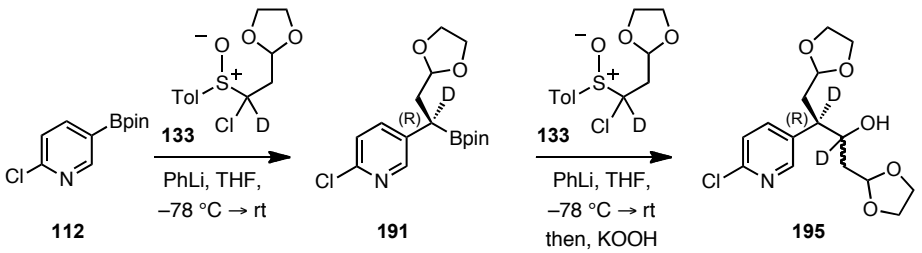
Considering the better performance of $\mathbf{136}_{anti\text{-}D}$ over the analogous *syn*-protio-α-chlorosulfoxide $\mathbf{136}_{syn\text{-}H}$, the remaining synthetic studies were conducted exclusively with the deuterated congener.

4.12 - Double StReCH with Acetal Bearing α-Chloroalkyllithium Reagent to Install Vicinal Stereogenic Centers

Validating the modular assembly of vicinal stereogenic centers *via* iterative StReCH, a key aim of this thesis, is detailed in this section. Initially, the experimental procedure for the double homologation sequence involved isolation of the intermediate chain extended boronate **191**, Table 8, which was then subjected to a second StReCH reaction, entry 1. Targeting the "like" series (same configured starting chlorosulfoxide for both homologations) resulted in doubly homologated *bis*-acetal **195** being isolated in fair yield (23%) and good diastereoselectivity (89:11). The "unlike" series, entry 2, led to very similar results in both yield (22%) and diastereoselectivity (90:10). Unfortunately, double homologations separated by isolation of boronate **191** led to significant proto-deborylation (51-60%) during the second homologation event.

To overcome this limitation, the double homologation sequence was carried out in a single pot, entry 3, generating the "like" series 2° alcohol **195** in comparable diastereoselectivity (85:15) to the step-wise homologation sequence, but with an improved overall yield of 40%. The "unlike" series, entry 4, was targeted as well and constitutes the best example to date for the double StReCH with an overall yield of 49%.

Table 8. Synthesis of Contiguous Stereodiad via StReCH

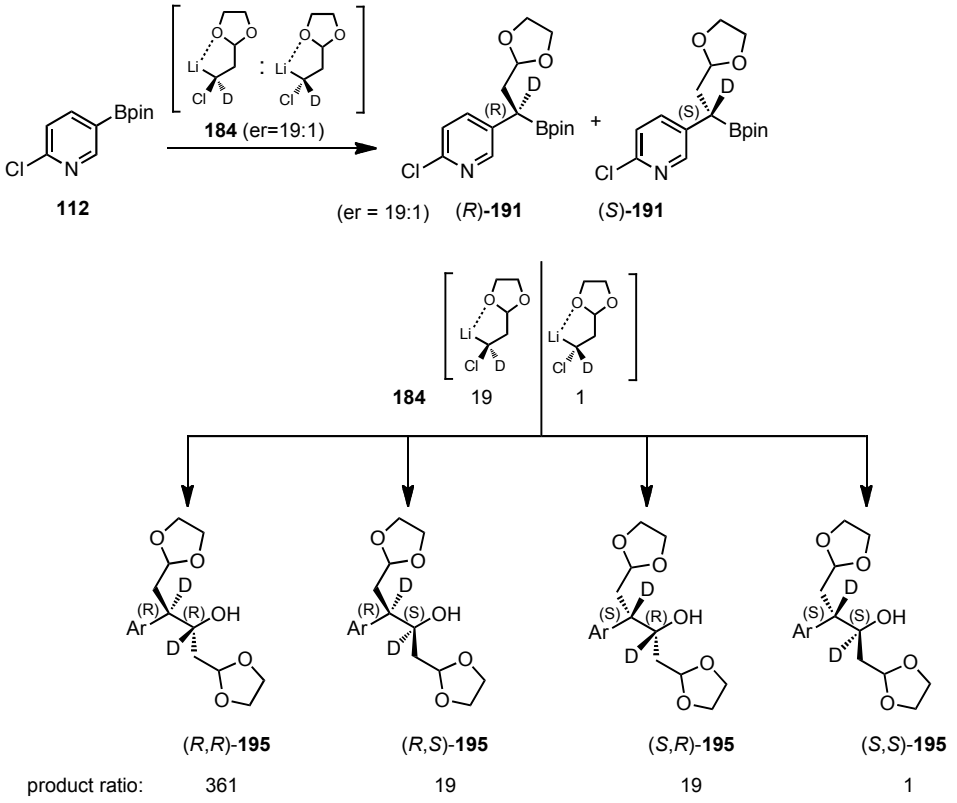


Entry	**133** Configuration		*anti : syn*	targeted isomer of alcohol **195**	yield (%)	dr$^{(\%ee)}$
Two Pot : **191** → **195** only						
1	(R_S)–*anti*-D		96 : 4	(R,R) "like"	23	$89^{(\geq 98)}$:$11^{(< 24)}$
2	(S_S)–*anti*-D		93 : 7	(R,S) "unlike"	22	$90^{(\geq 98)}$:$10^{(\sim 28)}$
Single Pot : **112** → [**191**] → **195**						
	1st iteration	2nd iteration				
3	(S_S)–*anti*-D	(S_S)–*anti*-D	95 : 5	(R,R) "like"	40	$85^{(\geq 98)}$:$15^{(<10)}$
4	(S_S)–*anti*-D	(R_S)–*anti*-D	(S) 95:5 / (R) 93:7	(R,S) "unlike"	49	$79^{(\geq 97)}$:$21^{(\sim 1)}$

Slightly diminished selectivity (79:21) was observed for the "unlike" series, but this erosion in diastereoselectivity may be accounted for by considering that unreacted (S_S)-configured starting α-chlorosulfoxide (**133)** from the first homologation still remains in solution and will compete against (R_S)-configured α-chlorosulfoxide (**133**) during the second StReCH reaction. The targeted "unlike" series was ultimately carried forward in the synthesis of isotopically labeled disubstituted cyclohexene **108** toward (–)-epibatidine.

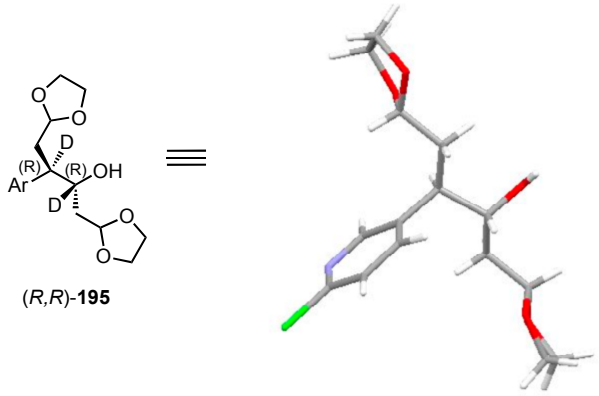
The near perfect enantioenrichment observed in the targeted major diastereomers of both the like and unlike series, entries 1-4, results from enantiomeric amplification arising from the so-called Horeau or statistical enantiomeric amplification effect.[131] In an ideal stereospecific reaction combining two scalemic materials of er = x:1 and er = y:1 the result will be a new molecule of dr = (xy+1):(x+y) where the major diastereomer has er = xy:1 and the minor diastereomer er = x:y, Scheme 43.

Scheme 43. Statistical Enantiomeric Amplification



This effect may be explained as follows: StReCH of boronate **112** with lithium carbenoid **184** (er = 19:1) leads to homologated boronate **191** which reflects the same enantiomeric ratio of 19:1 (90% ee), assuming all components react stereospecifically. Enantioenriched boronate **191** is reacted with a second equivalent of lithium carbenoid **184** also exhibiting an er of 19:1 leading to formation of major diastereoisomer (*R*,*R*)-**195** with er = 361:1. The minor diastereomer (*R*,*S*)/(*S*,*R*)-**195** will have an er = 19:19, from this relationship the maximal diastereoselectivity for the major product may be predicted, dr = (xy+1):(x+y) = (19^2+1):(19+19) = 362 : 38 = 90.5 : 9.5. As seen in Table 8, double homologated products (**195**), entry 3 and 4, are in the expected range of predicted maximal diastereoselectivity. Figure 10 shows the solved X-ray structure for the double chain extended bis-acetal (*R*,*R*)-**195**.

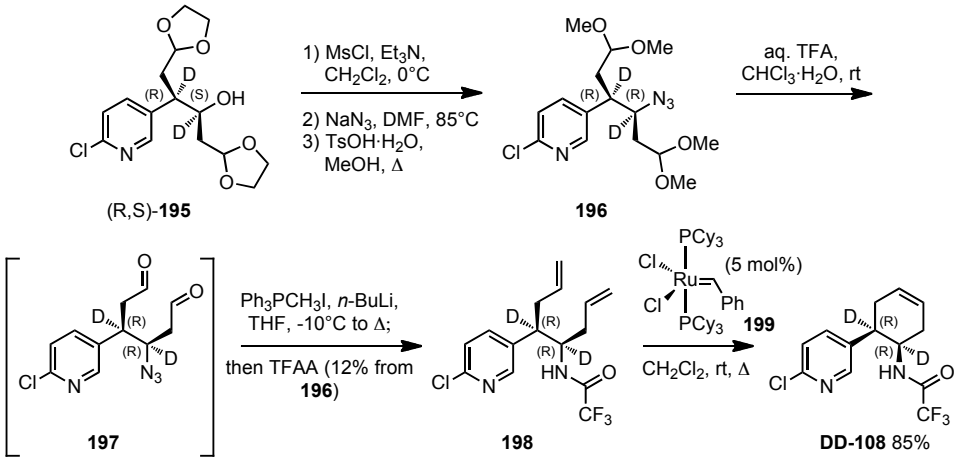
Figure 10. Relative and Absolute Configuration of (*R,R*)-**195**



4.13 *- Formal Synthesis of (–)-Epibatidine Through Corey's Intermediate*
The following work was completed by Prof. Paul R. Blakemore

Conversion of bisacetal (R,S)-**195** to the doubly deuterated isotopomer of Corey's intermediate (**DD-108**) is shown in Scheme 44. Mesylation of alcohol **195** followed by azidation with NaN_3 and transacetalization gave bis-dimethyl acetal **196**. Acidic hydrolysis gave the fragile azidodialdehyde **197** which was immediately subjected to a double Wittig/Staudinger process to give diene **197** in low overall yield. Finally, ring closing metathesis of the bisalkene generated a dideutero isotopomer of Corey's epibatidine precursor (**DD-108**).

Scheme 44. Conversion of (R,S)-**195** To The Cyclic Isotopomeric Intermediate en Route Toward (–)-Epibatidine **91**



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4.14 - Miscellaneous α-Chloroalkylmetal Reagents Bearing Functionalized Sidechains

In addition to the previously described work on allyl bearing carbenoids, section **4.4**-**4.8**, and acetal bearing carbenoids, section **4.9**-**4.13**, side-chain functionalized carbenoids bearing benzyl ethers and alkynyl moieties were also investigated. Alcohol (generated through benzyl deprotection) and alkyne functional groups would provide versatile synthetic handles that are easily manipulated following StReCH homologations.

4.15 - α-Chloroalkylmetal Reagent with Ether Functionalization

The synthesis of the α-chlorosulfinyl benzyl ether **135** was detailed in section **4.2**. SLE studies, Table 9, commenced using previously optimized conditions (*t*-BuLi/PhMe), entry 1. The SLE by-product sulfoxide **155** (R=*t*-Bu) was isolated in 30% yield, which is substantially lower than typically observed with this kind of system (~60-72%). Employing *n*-BuLi for SLE, entry 2, led to increased lithium carbenoid formation as determined by SLE sulfoxide **155** (R=*n*-Bu) formation, but this yield was still less than optimal. Curious as to whether the observed epimerization for recovered α-chlorosulfoxide *epi*-**135**, entries 1 and 2, could be exploited as a method to access *anti* α-chlorosulfoxides, LDA deprotonation was examined, entry 3. The epimeric ratio observed from LDA deprotonation did not, however, lead to the same diastereoselectivity.* Lastly, magnesium carbenoid generation was examined, entry 4. Commensurate with previous magnesium carbenoid results,[73] SLE efficiency is significantly improved when using Grignard initiating reagents in relation to alkyllithium initiators as determined by isolation of sulfoxide by-product **155** (R=Et) in 80% yield.

Magnesium carbenoids from Grignard reagent initiated SLE display greater thermal and configurational stability than lithium carbenoids, while having less nucleophilic/basic character.[44,74,132] For example, no deuterium incorporation is

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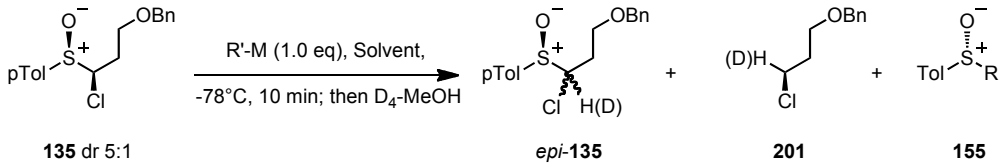
* The *anti* α-chlorosulfoxide was not pursued for this substrate due to the lack of its crystallinity. Separation of *syn*:*anti* diastereoisomers is not adequate through chromatographic techniques, necessitating the need to use recrystallization to reach the necessary levels of diastereomeric purity.

observed at the α-position of recovered α-chlorosulfoxide *epi*-**135** when the SLE reaction is quenched with deuterium, entry 4.

Table 9. – SLE Studies with Ethereal Functionalized Carbenoid Precursor **135**



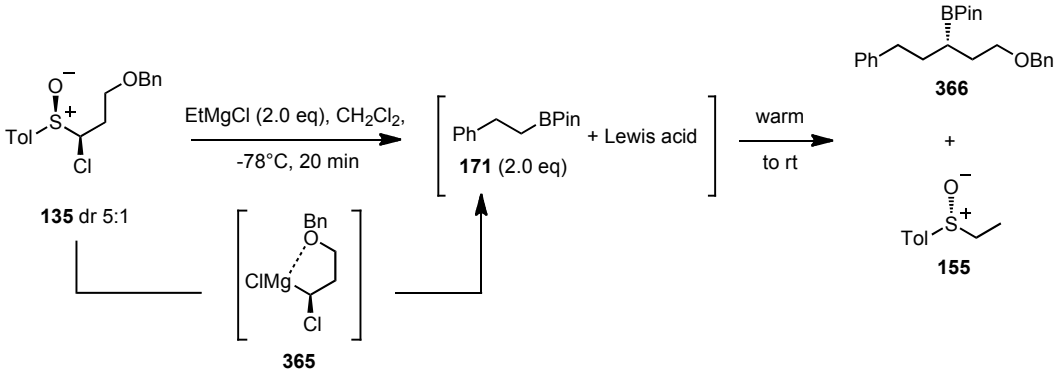
135 dr 5:1 | *epi*-**135** | **201** | **155**

Entry	R'-M	Solvent	*epi*-**135** yield (%)	*epi*-**135** $syn^{(D\%)}$:$anti^{(D\%)}$	**201** yield (%)$^{(D)}$	**155** yield (%)
1	*t*-BuLi	PhMe	70	$1.87^{(29)}$:$1^{(66)}$	n / a	30, R = *t*-Bu
2	*n*-BuLi	THF	48	$1^{(91)}$: $6.1^{(87)}$	n / a	45, R = *n*-Bu
3	LDA[a]	THF	98	$1^{(72)}$: $3.4^{(84)}$	n / a	n / a
4	EtMgCl	THF	20	$4.75^{(0)}$: $1^{(0)}$	$80^{(87)}$	80, R = Et

Magnesium possesses a larger atomic radius than lithium and this size has a bearing on the reactivity of corresponding carbenoids. Steric interactions between magnesium carbenoids and the methyl groups of pinacol boronates make homologation with these two reagents difficult at best. Switching to neo-pentylglycol boronates relieves steric interactions with the magnesium carbenoids, but these boronates do not share the same stability during purification and storage as pinacolboronates.[2,74] In light of this, a series of homologations using Mg carbenoid **202** were attempted which examined the possibility of pre-activating pinacol boronates with Lewis acids, Table 10.

Magnesium carbenoids were pre-generated at –78°C for 20 minutes in non-coordinating CH_2Cl_2 before combining with pre-mixed phenethyl boronate **171** and the Lewis acids in entries 1-3. As seen from the results Lewis acids do not promote the desired reaction of magnesium carbenoids with pinacol boronates in StReCH. Succesful application of magnesium carbenoids in StReCH would open up previously unaccessible transformations and this very limited study should not be interpreted as definitve on the use of additives for enhanced activation.

Table 10. Attempted Pinacol Boronate Lewis Acid Pre-Activation



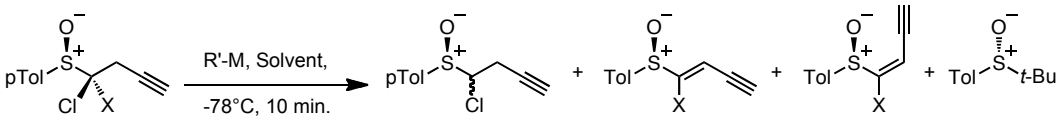
Entry	Lewis acid (1.0 eq)	**366** yield (%)	**155** yield (%)
1	N / A	0	79
2	$BF_3{\cdot}OEt_2$	0	77
3	Me_2AlCl	0	77
4	$MgBr_2$	0	78

4.16 - α-Chloroalkynyllithium Reagent

A fourth and final functionalized α-chlorocarbenoid precursor **134** bearing a propargyl side-chain was prepared as discussed in section **4.2**. Generation of the corresponding α-chloroalkynyllithium reagent was attempted *via* SLE of alkynyl α-chlorosulfoxide **134**, Table 11.

Initial SLE studies of α-chlorosulfinyl alkyne **134** produced an unanticipated result in the formation of enynes (*E*/*Z*)-**204** that appear to be the product of a previously unobserved elimination pathway. Attempted SLE with racemic **134**, entry 1, resulted in quantitative conversion of all starting α-chlorosulfoxide to sulfinyl enynes *E*-**204** / *Z*-**204** and SLE by-product **206** formation was observed. As observed with the benzyl ether, *vide supra*, the SLE by-product (**206**) formation was substantially lower than typically observed, but the remaining isolated products accounted for the mass balance. This result suggests that the typically diffusion controlled SLE process is in competition with a very facile elimination pathway.[133]

Table 11. SLE Study of Propargyl α-Chlorosulfoxide **134**



134 *epi*-**134** *E*-**204** *Z*-**204** **206**

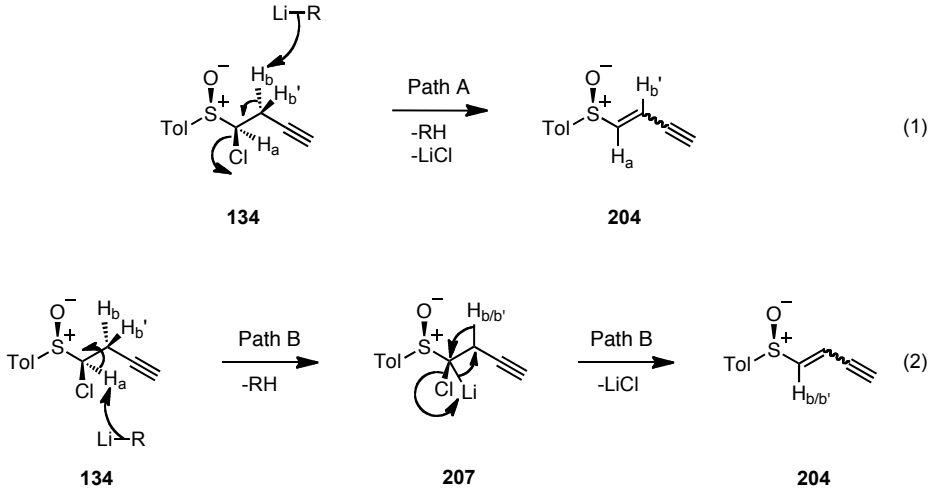
Entry	X	Base	Solvent	*epi*-**134** (%)	*E*-**204** (%)$^{(\alpha\text{-D\%})}$	*Z*-**204** (%)$^{(\alpha\text{-D\%})}$	**206** (%)	Path A / B
1[a]	H	*t*-BuLi	PhMe	0	68	3	29	n / d
2	H	PhLi	THF	4	37	13	50	n / d
3	H	LDA	THF	0	99	1	0	n / d
4	D	*t*-BuLi	PhMe	0	40$^{(32)}$	27$^{(58)}$	33	(65% / 35%)
5	D	PhLi	THF	0	25$^{(37)}$	20$^{(60)}$	55	(55% / 45%)

a) addition of HMPA during identical reaction conditions does not suppress elimination

Satoh recently reported on an unintended rearrangement pathway that converted α-chloro-α-lithiocyclopropyl carbenoids to allenes. This non-productive pathway was suppressed by the addition of HMPA which was proposed to stabilize the lithium carbenoid, thereby preventing rearrangement.[134] Repeating the SLE experiment, entry 1, in the presence of HMPA did not, however, lead to a different outcome. Recently optimized SLE conditions (PhLi/THF), entry 2, did result in more efficient SLE, but enyne formation was still a dominant pathway, while treatment with LDA, entry 3, led to almost exclusive formation of the *E*-enyne (**204**). Two possible pathways, E2 elimination or a 1,2-hydride shift, accounting for the observed enyne formation are shown in Scheme 46. E2 elimination of homo-propargyl halide **134** under basic conditions, eq. (1), would lead to formation of enyne **204**. Although this would appear to be a facile process for substrates of this type, this behavior is not observed under standard SLE conditions with allyl bearing carbenoid precursor **133**, *vide supra*.[135] α-Metallation followed metal assisted ionization (MAI) with concomitant 1,2-hydride shift may would also lead to enyne formation, eq. (2), and this type of pathway has been reported with alkylidene carbenoids, section **1.6**. 1,2-Hydride shift has been reported for chloroalkyl carbenoids and was observed during the AHME investigation in part II of this thesis. Yajima and co-workers recently

reported on a rearrangement of cyclopropylidenes to allenes which is the basis for the Doering-LaFlamme allene synthesis[136] and this has also been reported for cyclopropylidenes generated from *gem*-dihalocyclopropanes with both alkylithiums and Grignard reagents.[137]

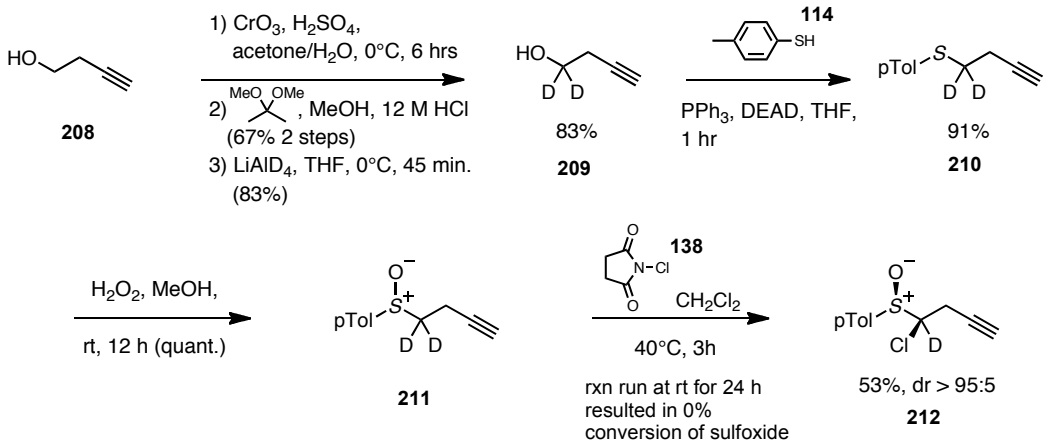
Scheme 46. Possible Elimination Pathways Leading to Enyne **204**



An isotopic labeling study was conducted to determine the nature of the elimination pathway and this investigation required the synthesis of α-deutero-α-chloropropargyl sulfoxide, Scheme 47. A three step sequence leading to sulfoxide **212** began with a Jones oxidation of homopropargyl alcohol **208** followed by a Fischer esterification and finally ester reduction with $LiAlD_4$ to provide the doubly deuterated 1° alcohol **209**. Mitsunobu conditions[138] were employed to form thioether **210**, which was then converted to α-deutero-α-chlorosulfoxide **212** through the oxidation and chlorination steps described in section **4.2**. Interestingly, the diastereoselective chlorination step with the doubly deuterated analogue **211** did not proceed at the same rate as the protio analogue (**130**) as standard chlorinating conditions at room temperature failed to produce any detectable α-chlorosulfoxide even after 24 hours (this is in sharp contrast to the protio analogue **130** which is fully converted in 1 hour at room temperature). A significant isotope effect is observed during this reaction as indicated by the requirement heat the reaction to 40°C for three hours in order to generate the targeted α-chlorosulfoxide **212**. This would provide support for the proposed mechanism,

Scheme 28, that α-deprotonation is occurring and would appear to be the rate-determining step.

Scheme 47. Synthesis of Doubly Deuterated Propargyl Carbenoid Precursor **212**

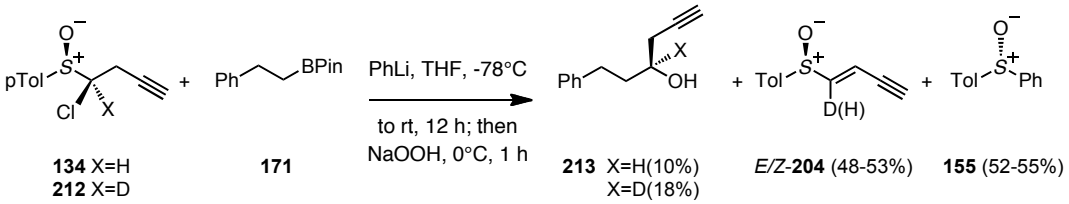


α-Deuterated alkynylchlorosulfoxide **212** was then subjected to SLE conditions, Table 11, in order to elucidate the predominant pathway for enyne formation. *t*-BuLi initiated SLE conditions, entry 4, led to an observed increase in SLE sulfoxide (**206**) formation in comparison to the α-protio analogue, but failed to suppress the elimination pathway. PhLi initiated SLE conditions were also examined, entry 5. The observation of complete deuterium incorporation in the product enyne **204** would strongly suggest that an E2 β-elimination pathway (eq. 1) was exclusively followed. No deuterium incorporation into enyne **204** would indicate α-metallation followed by 1,2-hydride shift was the exclusive pathway (eq. 2). The results however, indicate the following: *E*-enyne (*E*-**204**) formation is predominantly occurring through α-elimination pathway (pathway B), while *Z*-enyne (*Z*-**204**) formation is predominantly occurring through an E_2 elimination pathway.

The SLE generated propargyl-group bearing lithium carbenoid does participate in the basic StReCH, Scheme 48, however, the propensity for reagent **134**/**212** to undergo facile elimination / rearrangement to enyne (*E*/*Z*)-**204** results in significant diminution of the homologated product yield. Missing mass balance between SLE

by-product (**155**) formation and homologated product is most likely accounted for in lithium carbenoid decomposition - the products of which are not isolable.

Scheme 48. – Deuterated vs Non-Deuterated Propargyl Bearing Carbenoid Precursor **134** In StReCH



134 X=H
212 X=D

171

213 X=H(10%)
X=D(18%)

E/Z-**204** (48-53%)

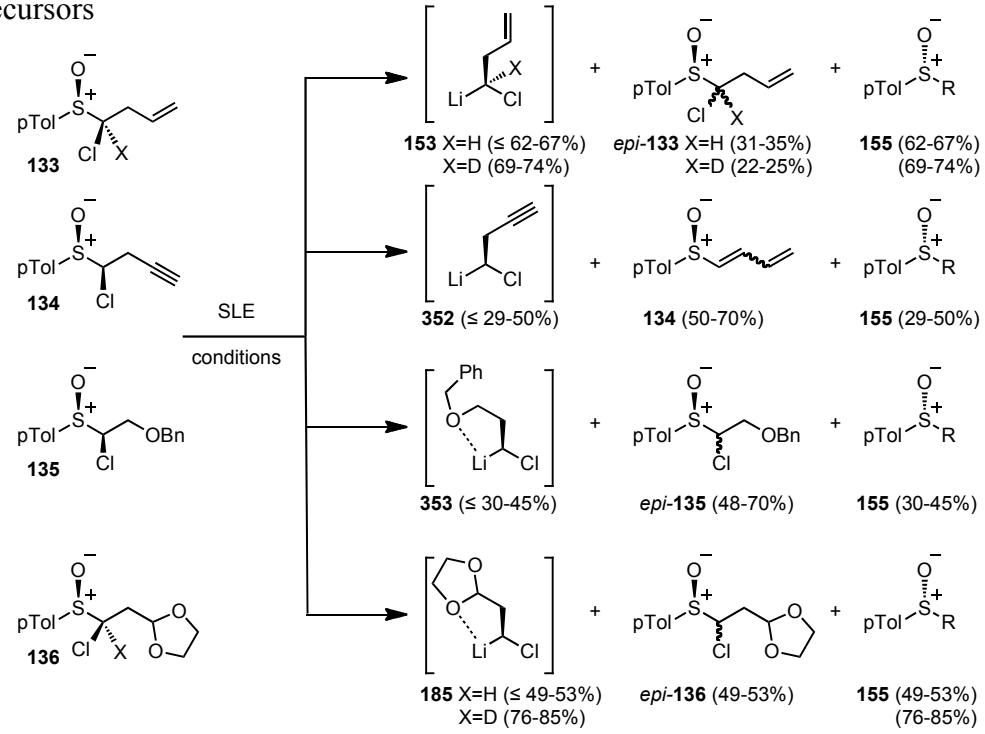
155 (52-55%)

Chapter 5 – *Conclusion*

In conclusion, the work in part I of this thesis has demonstrated that the iterative StReCH reaction is a powerful method for constructing contiguous stereogenic centers substituted with functionalized side chains. The putative functionalized enantioenriched α-chloroalkylmetal reagents employed during StReCH are accessed *via* the sulfoxide ligand exchange (SLE) reaction of stereodefined α-chlorosulfoxide carbenoid precursors. The linear structural motifs arising from StReCH reactions exhibit significant molecular complexity which was built up in a short sequence of steps and were successfully converted into cyclic structures related to (–)-epibatidine.

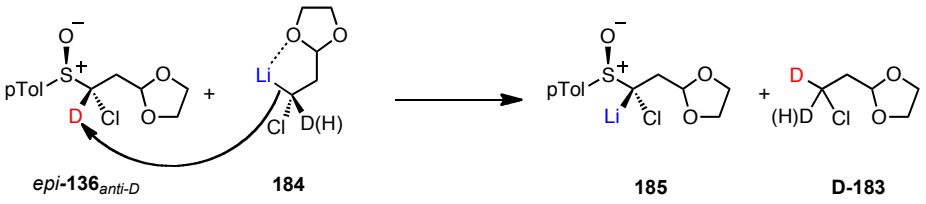
Functionalized α-chlorosulfoxides may be synthesized through a previously established route that involves an enantioselective sulfoxidation protocol and an electrophilic diastereoselective α-chlorination. These functionalized carbenoid precursors were shown to exhibit distinctly unique reactivity when applied to the SLE reaction during formation of the targeted carbenoids, Scheme 49.

Scheme 49. SLE of Variously Functionalized α-Chlorosulfoxide Carbenoid Precursors



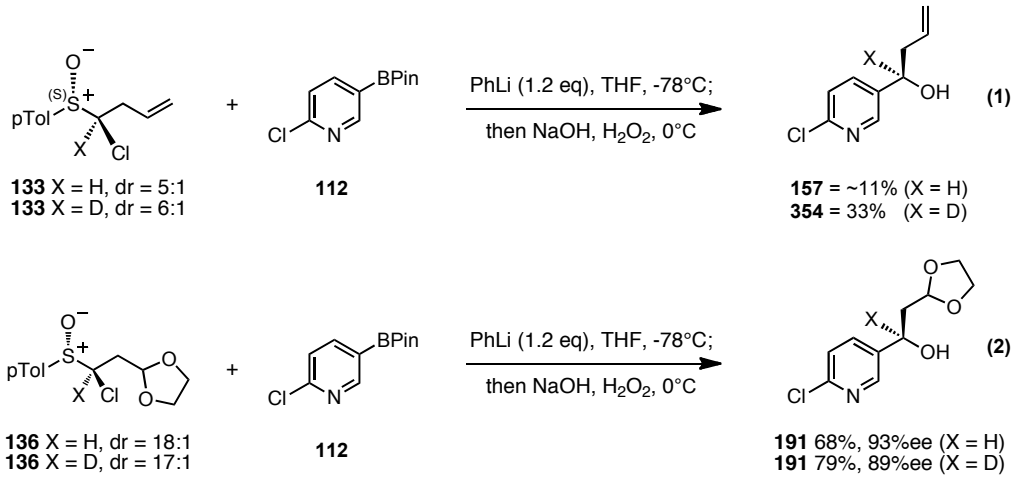
SLE investigation of the functionalized α-chlorocarbenoid precursors (**133-136**) led to the discovery that an internal proton transfer between the acidic α-proton of the α-chlorocarbenoid precursor and the carbenoid was leading to premature carbenoid immolation and subsequent removal of the carbenoid precursor through an unproductive α-deprotonation event, Scheme 50.

Scheme 50. Discovery of Internal Proton Transfer / Lithium Carbenoid Quench Pathway



Suppression of this deleterious pathway was accomplished in part by exploiting a kinetic isotope effect through the substitution of the α-chlorosulfoxide proton by deuterium. This event also enabled an investigation that concluded that there is no apparent enhancement in observed carbenoid formation, StReCH product yield or StReCH stereoselectivity whether starting from the *syn* or *anti* α-chlorosulfoxide carbenoid precursors. Enhancement is observed, however, in StReCH product yield when using deuterated α-chlorosulfoxide carbenoid precursors to generate carbenoids *via* SLE in the presence of boronic esters, Scheme 51. The magnitude of this deuterium effect varies depending on the nature of the α-chlorosulfoxide carbenoid precursor and the resulting carbenoid.

Scheme 51. Enhanced StReCH Product Formation Through the Deuterium Effect



133 X = H, dr = 5:1
133 X = D, dr = 6:1

112

157 = ~11% (X = H)
354 = 33% (X = D)

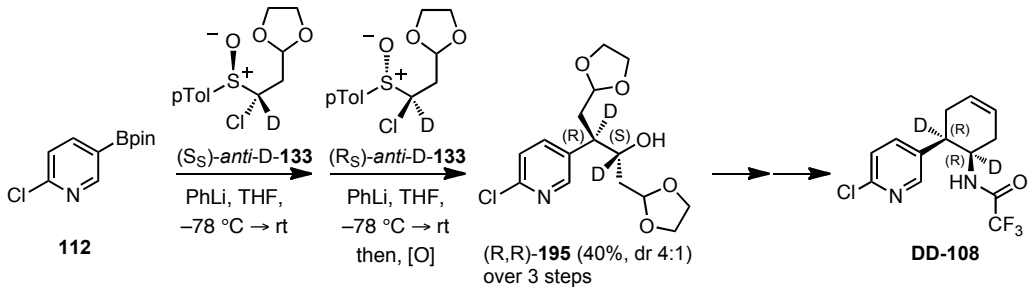
136 X = H, dr = 18:1
136 X = D, dr = 17:1

112

191 68%, 93%ee (X = H)
191 79%, 89%ee (X = D)

The acetal bearing α-chlorosulfoxide carbenoid precursor (**136**) was found to outperform all other functionalized α-chlorosulfoxides in regard to both carbenoid formation via SLE and in the StReCH product formation. This may be a reflection of a proposed internal chelation that stabilizing the putative carbenoid. The acetal bearing lithium carbenoid (**184**) was used in the StReCH of 2-chloropyridyl boronate **112** to target a cyclic intermediate en route to (–)-epibatidine (**91**). Although the original proposal was that a route to cyclohexene **108** using StReCH chemistry would ultimately result in a more concise approach than that reported by Corey, this was not the end result. The length of the synthesis was not a consequence of StReCH itself, but was an artifact of difficulties associated with the StReCH reagents involved. Due to the failure of the alkene α-chlorosulfoxide **133** to satisfactorily perform in StReCH through SLE necessitated the use of acetal chlorosulfoxide **136**. The performance of this reagent was far superior, but the nature of functionalization required several circuitous steps in order to generate cyclohexene **108**, thereby adding several overall steps to the route. On the other hand, unlike Corey's synthesis which required enantiomeric resolution, the StReCH route did provide direct access to **DD-108** through stereospecific transformations.

Scheme 52. Highly Stereoselective Continguous Asymmetric Stereocenter Programmability via StReCH



In closing, StReCH shows considerable promise as a methodology for facile construction of asymmetric carbon-carbon bonds. Generating fundamental chiral building blocks containing heteroatoms (e.g., OR, NR_2) for stereoselective introduction into carbon frameworks through StReCH may be the next major advance to come. An immediate limitation that has been identified is the propensity for lithium carbenoid self-immolation when in the presence of the α-chlorosulfoxide carbenoid precursor. If conditions can be identified that facilitate boronic ester homologation with magnesium carbenoids, then this limitation may be overcome and SLE may still be a relevant mode for accessing α-haloalkylmetal reagents in StReCH. Addressing these challenges will significantly broaden the scope and applicability of StReCH.

Part II

Asymmetric Halogen-Metal Exchange Between Enantioenriched Planar Chiral Ferrocenylmetal Reagents and Geminal Dihalides

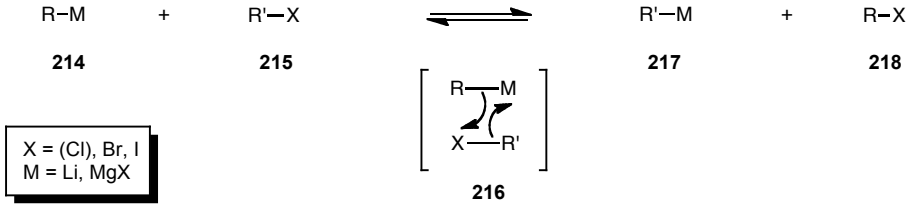
Chapter 6: *Halogen-Metal Exchange and Asymmetric Variants*

6.1- Introduction to Halogen-Metal Exchange

Halogen-metal exchange is a process used to generate nucleophilic organometallic carbon intermediates from organohalide substrates. As such, halogen-metal exchange is a reaction of significant importance and synthetic utility within organic chemistry, yet it is poorly understood mechanistically.[139,140]

Formally a metathesis reaction, halogen-metal exchange generates a carbanionic nucleophile **217** from an initiating organometallic reagent **214** and organohalide **215**, Scheme 53. The four-centered transition state **216** has been proposed as a possible mechanistic pathway, but it is depicted here for illustrative purposes only.[141] Following exchange, the newly formed organometallic species **217** is typically deployed in the presence of electrophilic carbon atoms leading to carbon-carbon bond formation. Halogen-metal exchange also occurs with other main group metals (Zn & Sn), but the intent of this thesis is to focus solely on main group metals Li and Mg.[142,143]

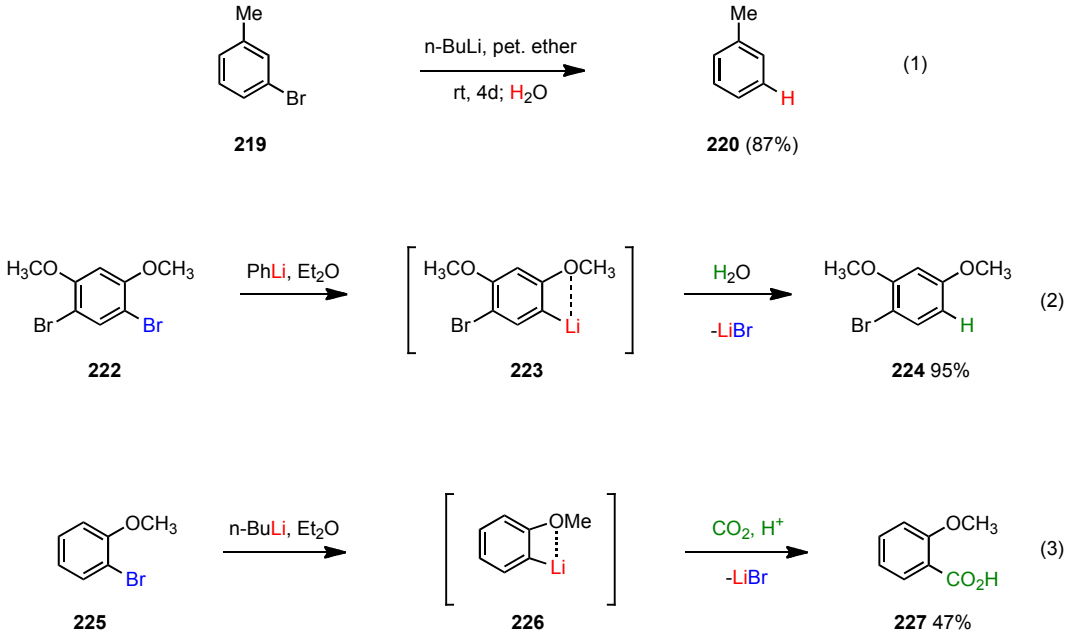
Scheme 53. Representation of the Halogen-Metal Exchange Reaction



Halogen-metal exchange was initially observed in 1927 by Marvel after stirring *m*-bromotoluene **219** with *n*-BuLi for four days in petroleum ether yielded toluene **220** in 87% yield, eq. 1, Scheme 54.[144] The significance of this observed result was not fully realized until a decade later when Wittig began investigating the same transformation. Bromine-lithium exchange between PhLi and 4,6-dibromo-1,3-dimethoxy-benzene (**222**), led to a transient aryl lithium **226**, which formed aryl mono-bromide **224** in 95% yield following hydrolysis, eq. 2.[145] Gilman's investigation of halogen-metal exchange was described in a pioneering report

concerning the conversion of *o*-bromoanisole (**225**) to *o*-methoxybenzoic acid (**227**), eq. 3.[146] Bromine-lithium exchange initiated with *n*-BuLi led to aryllithium intermediate **226** which was subsequently trapped with CO_2 and generating carboxylic acid **227** (47%) upon acidic work up.

Scheme 54. Seminal Investigations of the Halogen-Metal Exchange Reaction

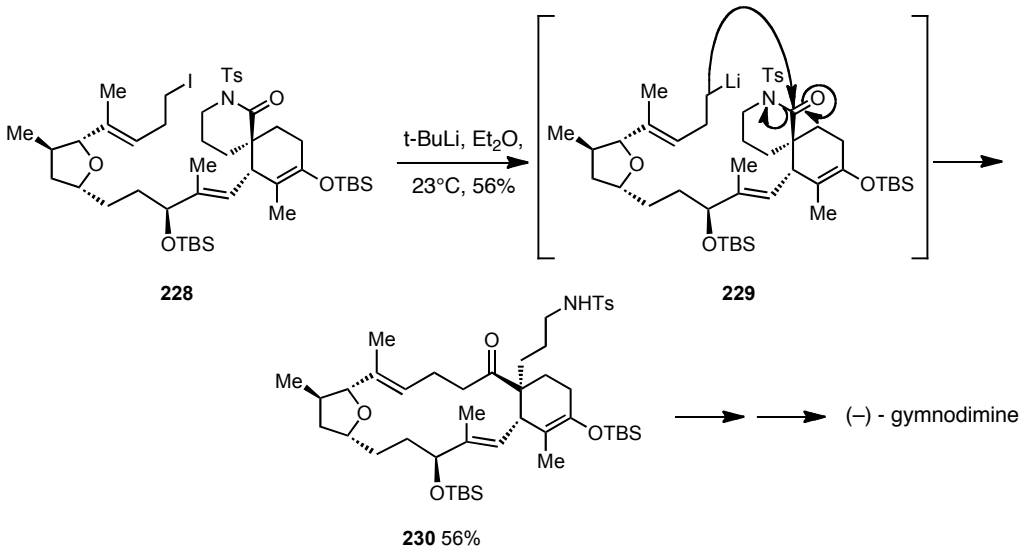


Following these early reports and Gilman's extensive follow-up investigations, details gained from the empirical observations established the following guidelines concerning halogen-metal exchange that are still useful today: 1) aryl fluorides and aryl chlorides do not generally exchange;[147] 2) halide exchange rates follow the trend I > Br >> Cl;[148] 3) exchange is a thermodynamic process, equilibrating to the more stable organometallic reagent.[149]

During the 70 years following the seminal reports of both Wittig and Gilman, previously inaccessible main group organometallic (Li and Mg) reagents have been prepared primarily by utilizing halogen-metal exchange. This important topic has been the subject of several reviews.[140,150,151,152] Recently halogen-metal exchange has been used to access transient organometallic reagents to be used directly in the

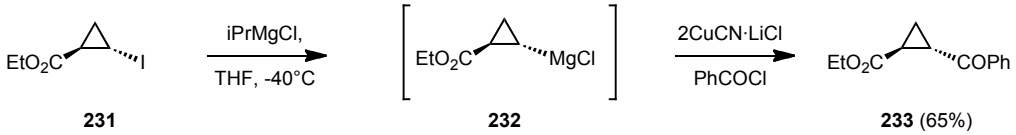
synthesis of complex natural products. For example, in the synthesis of (–)-gymnodimine primary alkyl iodide **228** was converted into the reactive intermediate alkyllithium **229** through iodine-lithium exchange before nucleophilic addition into the tosyl protected spiro-lactam, resulting in macrocyclization to form ketone **230** in 56% yield, Scheme 55.[153]

Scheme 55. Iodine-Lithium Exchange Mediated Macrocyclization Toward the Synthesis (–) - Gymnodimine



Over the past decade halogen-metal exchange has developed as a powerful new method for accessing highly functionalized Grignard reagents that cannot be generated through traditional methods.[154] For example, ethyl ester substituted *trans*-iodocyclopropane **231** undergoes iodine-magnesium exchange forming cyclopropyl Grignard reagent **232**. This transient intermediate is converted to a higher order cuprate and quenched with electrophilic benzoyl chloride leading to benzoyl cyclopropane **233** in good yield and with complete stereoselectivity, Scheme 56.[155]

Scheme 56. Accessing Functionalized Grignard Reagents Through Halogen-Metal Exchange



Despite wide-spread implementation of halogen-metal exchange reactions within synthetic and organometallic chemistry, mechanistic elucidation of the entire process is still poorly understood and even contested.[156]

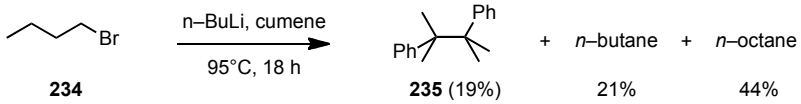
6.2 *- Possible Mechanisms for the Halogen-Metal Exchange Reaction*

Experimental and theoretical evidence has been obtained to support proposed mechanisms involving a radical and a nucleophilic pathway.

6.3 *- Halogen-Metal Exchange Through A Radical Mechanism*

The presence of radicals during halogen-metal exchange was initially proposed by Bryce-Smith as a result of isolating the homodimerized by-product 2,3-dimethyl-2,3-diphenylbutane (**235**) from the reaction between *n*-BuLi and *n*-butyl bromide (**234**) in cumene, Scheme 57.[157] Although this product (**235**) may result from recombination of two cumyl radicals in a Wurtz-type coupling, there was no explicit attempt to address the actual role of radicals during halogen-metal exchange.

Scheme 57. Initially Proposed Radical Character of Halogen-Lithium Exchange

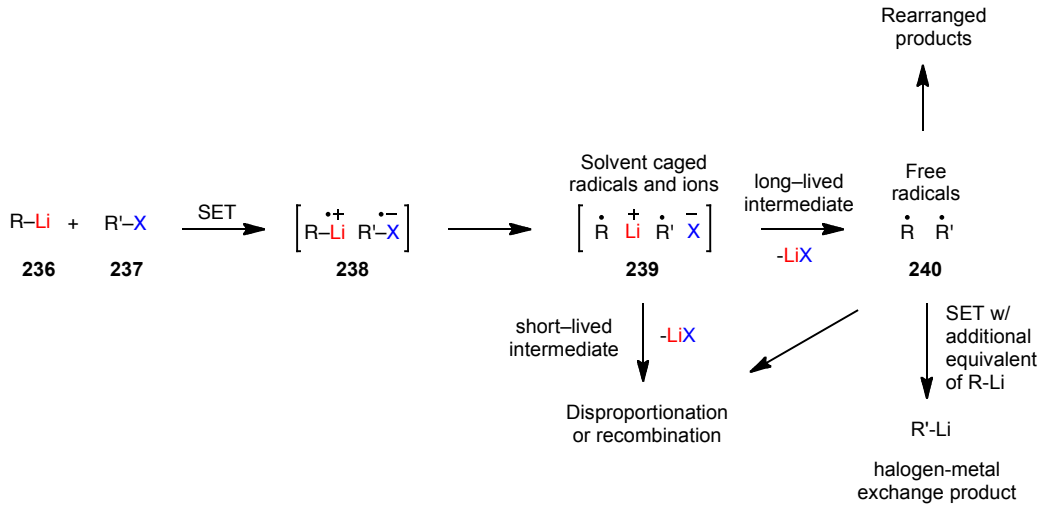


The presence of radicals during halogen-metal exchange reactions has been detected by both electron-spin resonance (ESR) and chemically induced dynamic nuclear polarization (CIDNP).[158,159] ESR studies determined that radicals are not observed when 1° alkyllithiums or phenyllithium initiate halogen-metal exchange. However, radicals have been observed when 2° or 3° alkyllithiums are used to initiate exchange or when stoichiometric Lewis basic additives, Et_2O and TMEDA, are present during exchange of alkyl bromides and iodides with *n*-BuLi or *sec*-BuLi.[16]

Halogen-metal exchange reactions probed by CIDNP have led to observed polarization of the following proton NMR signals: 1) for dimeric Wurtz-type coupling products,[160,161] 2) in the alkyl halide reactant and product,[18,19,162] and 3) during the formation of alkenes through elimination pathways.[163,164] The overall understanding these investigations provide is that detected radicals are not explicitly

implicated during the halogen-exchange process, but are most likely involved in secondary pathways which result from an initial single electron transfer (SET) mechanism, Figure 7.[1]

Figure 7. Proposed Single Electron Transfer Mediated Radical Pathway



An initial SET from organolithium **236** to organohalide **237** generates a radical-cation and a radical-anion within a solvent cage (**238**), which then evolve to discrete species of radicals and ions within the solvent cage (**239**). Two alternative reaction pathways are available depending on the lifetime of species involved. Short-lived species follow a disproportionation/recombination pathway following the loss of lithium salt, thereby removing the targeted R group from a productive pathway. Longer lifetime intermediates may become "free" radicals (**240**) after loss of lithium salt and diffusion out of the solvent cage. The resulting carbon centered radicals can disproportionate/recombine, transform into rearranged products depending on the molecular scaffold or undergo a second SET with alkyllithium **236** to generate the targeted halogen-metal exchange product.[10]

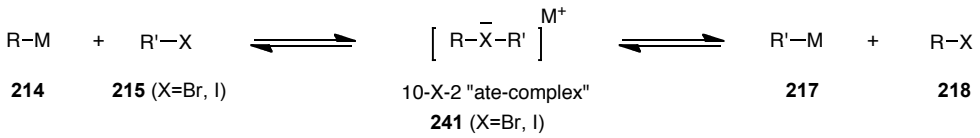
Radical probes capable of skeletal rearrangement have been used for mechanistic elucidation of halogen-metal exchange, but pursuit of this method must be carried out in conjunction with control experiments that determine if the corresponding carbanionic species undergo identical isomerizations.[165,166,167] This experimental

rigor is a necessity considering some organometallic reagents have a propensity to mimic radical behavior during certain topological rearrangements.[168,169]

6.4 - *Nucleophilic Halogen-Metal Exchange Mechanism*

During initial halogen-metal exchange investigations, Wittig and Schöllkopf first postulated that halogen-metal exchange proceeds through an "ate-complex", Figure 8.[170,171] This involves nucleophilic attack of the organohalide with the organometallic reagent forming a hyper-valent halogen (X = Br, I) species (**241**) that then breaks down into the exchanged products.

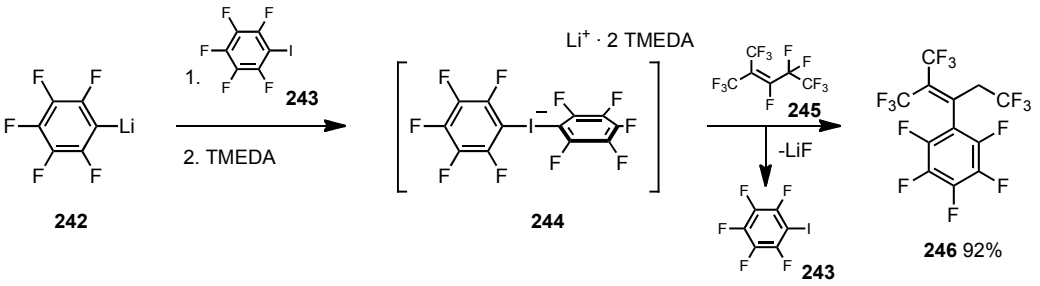
Figure 8. Formation of Ate-Complex During Halogen-Metal Exchange



The intermediacy of the ate-complex has been probed extensively using halogen-metal exchange systems such as PhLi and variously substituted bromobenzenes,[172,173] in the reaction of *n*-BuLi with perfluoro-*n*-heptyl iodide,[174] and in kinetic studies during exchange of *n*-BuLi and variously substituted bromobenzenes.[175] Theoretical studies concerning the nature of the ate-complex have also been conducted.[176,177]

Evidence supporting the intermediacy of ate-complex formation was provided by Reich and co-workers during investigation of the exchange kinetics between iodobenzene and PhLi.[178] Shortly thereafter, Farnham and Calabrese reported the first isolable iodinane ate-complex **244**, a *bis*-pentafluoroaryl hypervalent (10-I-2) iodine compound, Figure 9. Isolation of this iodine ate-complex enabled the full structural characterization of this type of postulated ate-complex intermediate. Nucleophilic character associated with the iodine ate-complex **244** was demonstrated by its reaction with electrophilic perfluoro-2-methyl-2-pentene **245**, resulting in release of a full equivalent of pentafluoroiodobenzene **243** and delivery of the C_6F_5 group forming perfluoro compound **246** in 92% yield.[179]

Figure 9. Isolated and Characterized Hypervalent (10-I-2) Ate-Complex



Considering the data collected and the ample evidence supporting both of the proposed mechanisms for halogen-metal exchange, it is generally agreed upon that the substrate class and reaction conditions strongly influence the mechanism involved. The following guidelines have been distilled from all the relevant data relating to the mechanism of halogen-metal exchange:

1) radical pathways predominate during exchange of alkyl bromides and compete when 2° alkyl iodides are used
2) nucleophilic pathways prevail for 1° alkyl iodides involving polar intermediates, while
3) aryl bromides/iodides proceed through ate-complex formation

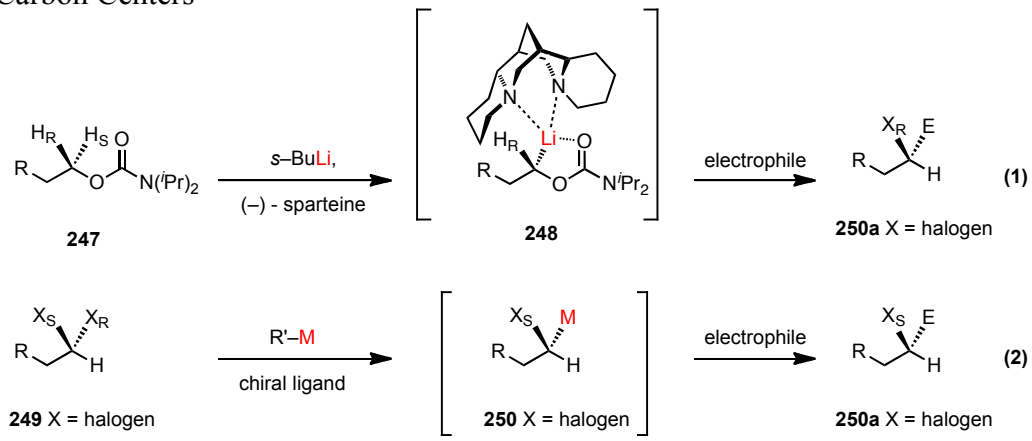
6.5 - *Asymmetric Halogen Metal Exchange*

Stereoinduction typically relies on the discrimination between the two faces of a planar sp^2-hybridized center. During this process, sp^2-to-sp^3 rehybridization results in the formation of diastereomeric intermediates. These transient intermediates have different barriers to activation which leads to kinetically controlled product formation as one diastereomeric complex reacts preferentially over the other. A stereoselective transformation is the end result. By contrast, enantioselective transformations at prochiral sp^3 hybridized atom centers have been less commonly explored.

In the best known example, discrimination between enantiotopic groups of sp^3-hybridized centers, eq. 1, Scheme 58, has been demonstrated during the enantioselective deprotonation of enantiotopic hydrogens of alkyl carbamates such as **248** by the chiral complex of *s*-BuLi/(–)-sparteine.[77] Considering this, it should be possible to apply this same concept when discriminating between other types of

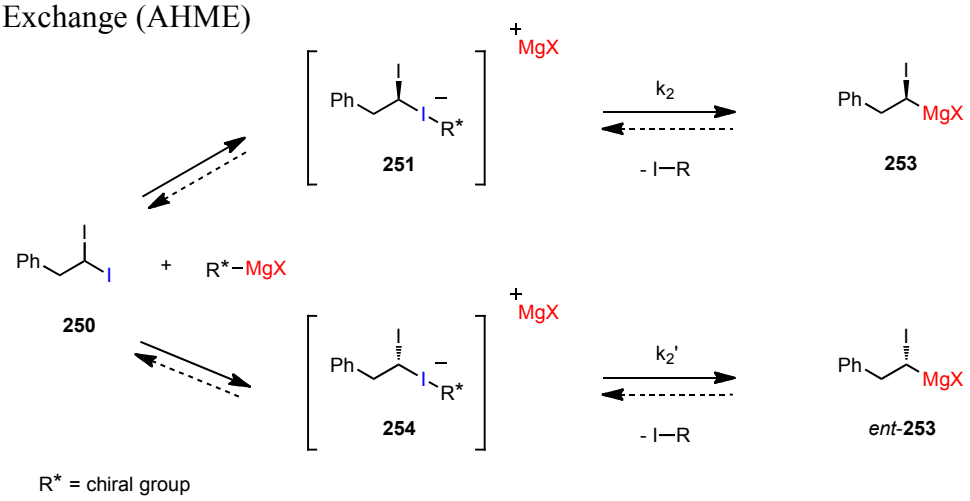
enantiotopic groups residing on sp^3-hybridized carbons. Of interest to this thesis, eq. 2, the enantiotopic groups are halogen atoms that lead to a chiral carbenoid through an asymmetric halogen-metal exchange.

Scheme 58. Discrimination of Enantiotopic Groups on sp^3-hybridized Carbon Centers



As the nucleophilic mechanism for iodine-metal exchange is presumed to proceed through two-steps, ate-complex formation and ate-complex breakdown; both steps must be examined to determine which step is stereodifferentiating during formation of stereogenic centers.[140] Seminal work by Hoffmann investigating asymmetric halogen-metal exchange at sp^3-hybridized carbon centers has illuminated important facets of this process.[180]

Scheme 59. Formation of Chiral Grignard Through Asymmetric Halogen-Metal Exchange (AHME)

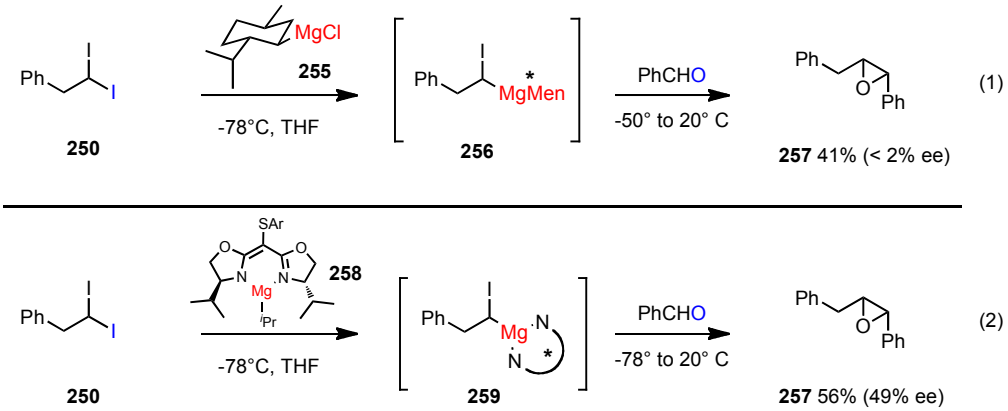


During exchange, if reaction between pro-chiral diiodide **250** and the chiral Grignard reagent is irreversible, then formation of iodine ate-complexes **251**/**254** is under kinetic control, therefore should be the stereoinduction step, Scheme 59. However, if formation of ate-complex **251**/**254** is reversible, then ate-complex breakdown (k_2/k_2') may be responsible for stereoinduction leading to enantioenriched magnesium carbenoids **253**/*ent*-**253**.[18,143,152]

Hoffmann's initial investigation began with putative α-iodomagnesium carbenoid **256** formed by iodine-magnesium exchange between 1,1-diodoalkane **250** and menthyl Grignard **255**, eq. 1, Scheme 60. Trapping magnesium carbenoid **256** with benzaldehyde led to formation of the predominantly *cis* (> 97%) epoxide **257** in 41% yield, but the level of enantioenrichment was negligible (≤ 2%). It was postulated that if the first step was under kinetic control, then menthyl Grignard **255** should have discriminated between enantiotopic iodine atoms with greater efficiency leading to more significant enantioenrichment in the product (**257**). Hoffmann postulated that this result implies that the second step during exchange controls stereoinduction, in which case, ate-complex breakdown required greater attention and more influence from the chiral Mg cation.

In testing this hypothesis, the C_2-symmetric bis-oxazoline Grignard reagent **258**, Scheme 60, was employed for iodine-magnesium exchange with 1,1-diodoalkane **250** generating putative enantioenriched magnesium carbenoid **259**. Trapping with benzaldehyde led to *cis* (97%) epoxide **257** in 56% yield and with significantly improved enantioenrichment (49%). In this case (**259**), the chiral magnesium cation is held in close proximity to the intermediate chiral anionic 10-I-2 ate-complex through Coulombic interaction which tightly binds the chiral information during ate-complex breakdown. Stereochemical influence resulting from this proximity effect is most likely responsible for the enhanced selectivity observed during the reaction.

Scheme 60. Chiral Grignard Initiated Asymmetric Halogen-Metal Exchange

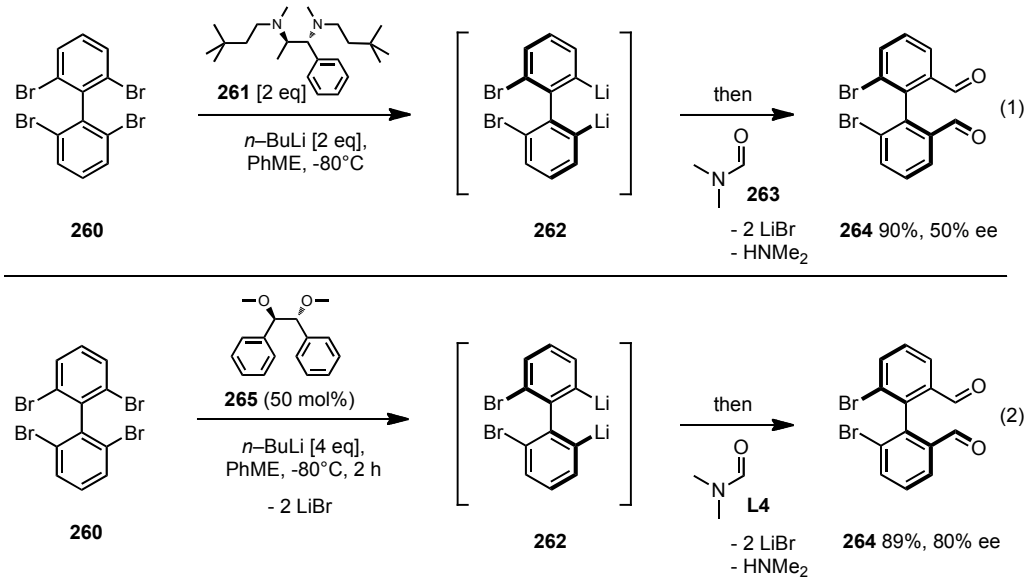


To date, Hoffmann's work remains the sole report on asymmetric halogen-metal exchange at sp^3 hybridized carbon centers. Recently, Alexakis and co-workers reported the asymmetric lithium-bromine exchange of prochiral biaryl molecules leading to desymmetrized chiral biaryl compounds. Although this exchange focuses on discrimination between enantiotopic bromine atoms at sp^2-hybridized carbon atoms, stereoinduction occurs via desymmetrization so only the salient features of this transformation will be highlighted.[181,182]

Newly developed enantioenriched chiral diamine ligand, **261**, eq. 2 Scheme 61, was targeted as a chiral director for asymmetric lithium-bromine exchange in axial prochiral biaryl compounds. Lithium-bromine exchange initiated with *s*-BuLi/**261** leads to dilithiated species **262** which is subsequently trapped with *N*,*N*-dimethylformamide **263** generating desymmeterized biaryl **264** in 90% yield and modest enantioselectivity, 50% ee. It was shown that use of (–)-sparteine (**76**) as the enantioenriched ligand gave comparable results.

Further development of a chiral ligand for asymmetric lithium-bromine exchange led to C_2 symmetric bis-ether **265**, which under catalytic loading (50 mol%) effected the same formylation reaction but with a marked improvement in yield (89%) and a significant increase in enantioselectivity (80% ee) for biaryl **264**, eq. 2.

Scheme 61. Asymmetric Lithium-Bromine Exchange of Enantiotopic Bromides in the Desymmetrization of Prochiral Biaryls.



Chapter 7: *Project Aim*

It was the aim of part II of this thesis to improve upon the nascent asymmetric halogen-metal exchange process through the implementation of two key concepts. First, generation of the crucial chiral organometallic reagent will occur through an iodine-metal exchange, in this way, the sequential events leading to formation of the targeted enantioenriched carbenoid will regenerate the iodide precursor of the chiral organometallic reagent. Providing stereochemical fidelity during the exchange process, it may be possible to re-use the organometallic reagent, or even establish a catalytic cycle. Second, to ensure optimal stereoselectivity during exchange, the inherent stereochemical information of the chiral organometallic reagent must be effectively transferred during ate-complex formation and breakdown. Reagent substructure will direct and complex the M^+ ion in a predefined asymmetric space, that will influence both addition and electrophilic substitution, leading to the generation of scalemic carbenoids which may be deployed in reactions of interest - Darzens-type condensation in this work. Isolating the addition adducts and analyzing them for enantioenrichment will provide an indirect method for measuring the stereoselectivity of the halogen-metal exchange process. Realization of the entire proposed AHME cycle may offer a complementary route to sulfoxide ligand exchange for the generation of α-haloalkylmetal reagents for StReCH chemistry.

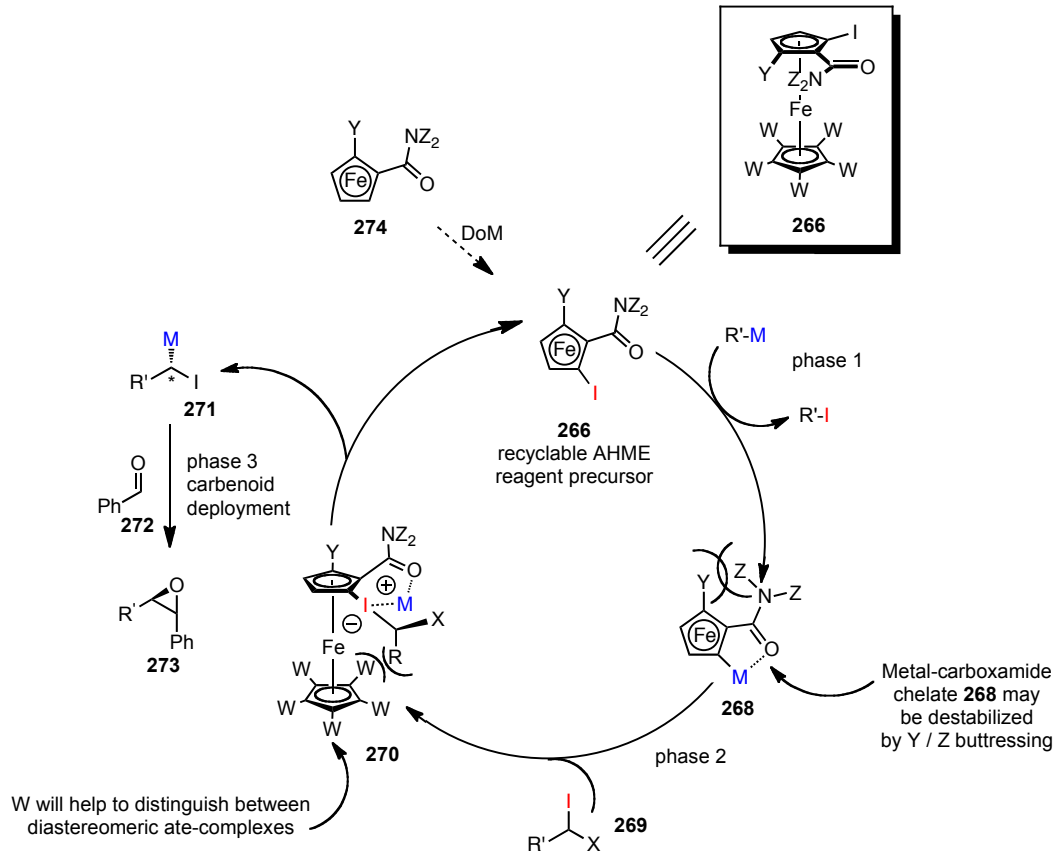
7.1 *- Design of Planar Chiral Iodoferrocene Organometallic Reagent Precursor*

Design of a planar chiral organometallic reagent (**268**)/reagent precursor (**266**) for AHME, Scheme 62, is guided by the consideration that, iodine-metal exchange is a two-step process that occurs through ate-complex formation and breakdown. To maximize enantioselectivity in AHME of *gem*-dihalides, stereochemical influence must be exerted during both steps of the exchange process, as previously described.

Application of ferrocene derivatives in asymmetric synthesis is rapidly expanding due to their chemical stability and the ease of desymmetrizing this common metallocene.[183,184,185] Three key design elements are incorporated into the AHME reagent precursor **266**: 1) an iodine atom for facile metallated ferrocene formation through iodine-metal exchange; 2) a carboxamide functional group to facilitate

desymmetrization leading to planar chirality and to further influence the

Scheme 62. Proposed Reagent for AHME and Reaction Cycle



stereoinducing event; 3) a buttress group Y, where Y≠ H, to help drive the thermodynamic metal-iodine exchange process toward product formation and prevent possible racemization of the planar chiral metallated ferrocene, Scheme 62. A final component of the reagent design is the ability to fine tune the electronic nature and steric environment during iodine-metal exchange by varying the substitution of the lower Cp ring, by setting W ≠ H. This may be necessary if the observed metal-iodine exchange and/or stereocontrol is not optimal for the organometallic reagent where W = H.

7.2 - Proposed AHME Cycle

Applying the trisubstituted organometallic reagent precursor **266** to the proposed AHME cycle is shown in Scheme 62, where three distinct, sequential *in-situ* phases must be satisfied in order to successfully realize the entire process. An initial iodine-

metal exchange involving iodoferrocene **266** with an achiral organometallic reagent ($R^{'}$-M = *n*-BuLi, *t*-BuLi, EtMgCl, etc) leads exclusively to formation of metallated ferrocene **268**, as lower Cp ring metallation or β-elimination of I^- will not occur under halogen-metal exchange conditions.[186,187] A second metal-iodine exchange occurs between the newly formed metallated ferrocene **268** and a subsequently introduced prochiral (X = I) or racemic (X = Cl) gem-dihalo substrate **269** leading to formation of the crucial iodine ate-complex **270**. This proposed intermediate embodies the focal point of the AHME cycle and reagent design, where the pervasive chiral environment created by diastereomeric iodine ate-complex **270**, influences both steps of the iodine-metal exchange process.

The carboxamide directing group plays a critical role during this process by chelating the M^+ cation during ate-complex formation and breakdown. During breakdown, which is formally an S_E2 reaction, Coulombic interaction is proposed to hold the cation in close proximity and in stereodefined space with the ate-complex (**270**) facilitating stereoselective electrophilic substitution at the *gem*-dihalo carbon center leading to the enantioenriched carbenoid reagent **271**. As discussed in section **3.1.1**, halogen-metal exchange between metallated aromatics and iodine is a thermodynamic process, therefore, if iodine-metal exchange is sluggish, tuning the Z groups of the carboxamide may provide a destabilizing steric interaction with the buttressing Y group and drive exchange with the sp^3-hybridized *gem*-dihalo substrate to form the scalemic carbenoid **271**.

Trapping the putative enantioenriched carbenoid **271** with an electrophile, for example benzaldehyde (**272**) as shown, constitutes the AHME cycles third and final phase. Herein, epoxide **273** formation will provide a platform for assessing the level of stereoselectivity arising from the overall process (%ee of addition adduct **273** will provide a lower bound for the enantioenrichment of carbenoid **271**). Regeneration of starting iodoferrocene **274** is concomitant with carbenoid formation, fulfilling the recyclability of the organometallic precursor **274**. Protonolysis of any unreacted metallated ferrocene **269** during work-up leads to planar chiral ferrocene **274**, that

may also be recycled to iodoferrocene **267** through ortho-metallation and electrophilic iodine quench.

Chapter 8: *Results and Discussion*

8.1 *- Synthesis of gem-Dihalo Carbenoid Precursors and Planar Chiral Iodoferrocenyl AHME Reagent Precursor*

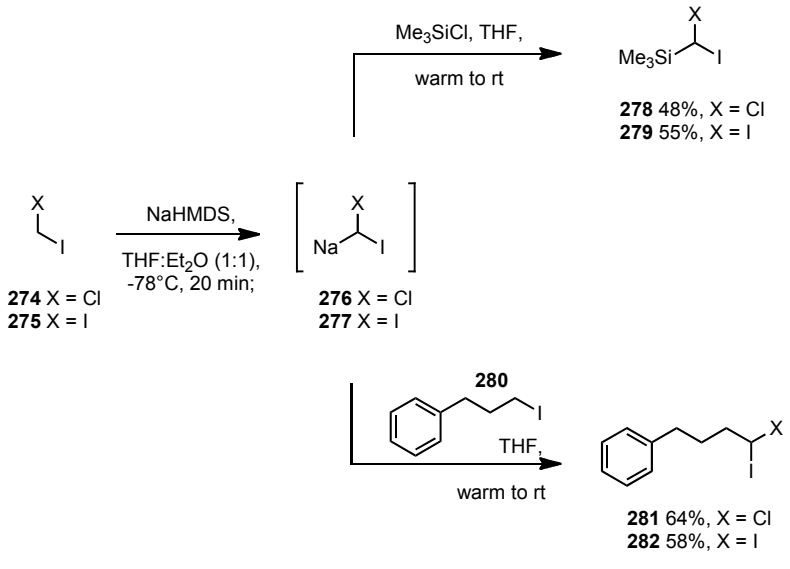
Investigation of asymmetric halogen metal exchange began with the synthesis of the requisite substrates and reagents followed by an initial investigation of the viability for halogen-metal exchange with metallated ferrocene reagents.

8.2 *- Synthesis of gem-Dihalo Reagents*

Two sets of closely related *gem*-dihalo reagents were synthesized and then tested as α-haloalkylmetal reagents in the AHME cycle. Possible reactivity differences relating to carbenoid stability and nucleophilicity as a function of the variously substituted α-position halogen atoms, were to be addressed by the use of both *gem*-chloroiodo and *gem*-diiodido reagents. In conjunction, the effects resulting from from stabilizing substituents (e.g. $SiMe_3$) and non-stabilizing substitutents (e.g. alkyl) was to be examined.[188]

Synthesis of the *gem*-dihalide carbenoid precursors, Scheme 63, was achieved by modification of procedures originally reported by Julia and Charette.[189,190] Deprotonation of either chloroiodomethane **274** or diiodomethane **275** with NaHMDS generates α-metallated intermediates **276**/**277** which were then converted to either

Scheme 63. Synthesis of *gem*-Dihalo Reagents

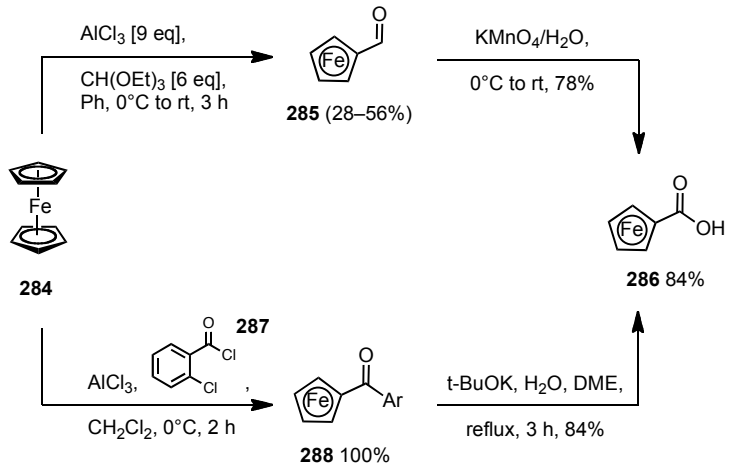


gem-dihalosilanes **278-279** or *gem*-dihaloalkanes **281-282**, in moderate yields. Purification of these compounds presented some challenges as separation of the starting materials and by-products from the targeted *gem*-dihalo reagents was complicated by similarities in both polarity and boiling points. This necessitated the use of both column chromatography and distillation to arrive at the pure compound.

8.3 *- Synthesis of Planar Chiral Ferrocene Reagents*

A series of routes were explored to access ferrocene carboxylic acid **286**, only the two approaches giving reproducible results are shown in Scheme 64. Friedel-Crafts acylation of ferrocene **284**, in the presence of excess $AlCl_3$ and $CH(OEt)_3$, produced

Scheme 64. Synthesis of Ferrocene Carboxylic Acid

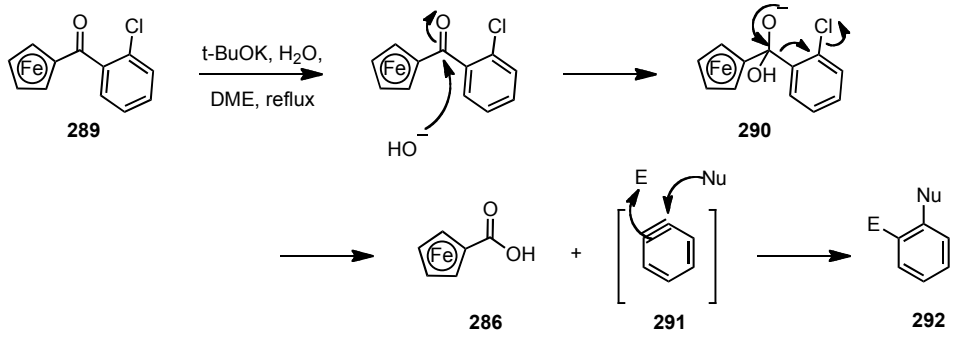


ferrocene carboxaldehyde **285** in variable yield (28-56%), which was considerably lower than that reported in the literature.[191] $KMnO_4$ oxidation to the carboxylic acid **286** was straightforward, but consistently low yields of carboxaldehyde **285** necessitated the exploration of an alternative route. In the second approach, Friedel-Crafts acylation with 2-chlorobenzoyl chloride led to ferrocenyl ketone **288** in quantitative yield and after hydrolysis led to carboxylic acid **286** in good yield.[192]

The hydrolysis reaction is a point-of-interest as it most likely leads to transient benzyne formation, Scheme 64. Potassium *tert*-butoxide mediated deprotonation of H_2O generates nucleophilic hydroxide ion which adds to ferrocenylphenone **289**, breakdown of the resulting tetrahedral intermediate **290** and loss of the proposed benzyne intermediate **291** leads to formation of the targeted carboxylic acid **286**.

Benzyne intermediate **291** is trapped by some nucleophile present in solution leading to the formation of a substituted benzene derivative **292**.

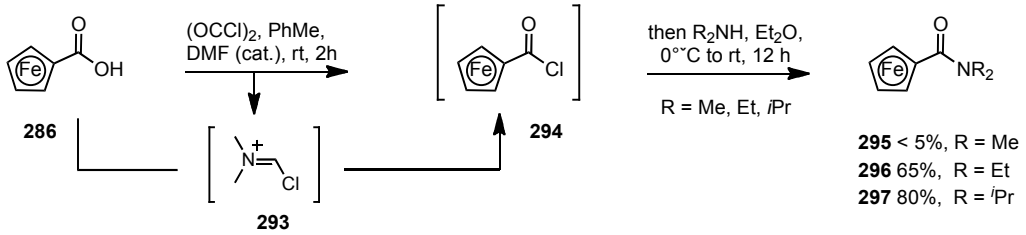
Scheme 64. Proposed Mechanism for Ferrocenylphenone Hydrolysis



Conversion of ferrocene carboxylic acid (**286**) to ferrocene carboxamides **295**-**297**, Scheme 65, was accomplished via reaction with Vilsmeier-Hack reagent **293**, which gave acid chloride **294**. Trapping by nucleophilic secondary amines, $HNEt_2$ and $HNiPr_2$, leads to ferrocene carboxamides **296**/**297** in fair to moderate yield. Most likely, the difficulty in synthesizing *N*,*N*-dimethyl carboxamide **295** is related the facile hydrolysis of this amide.[193]

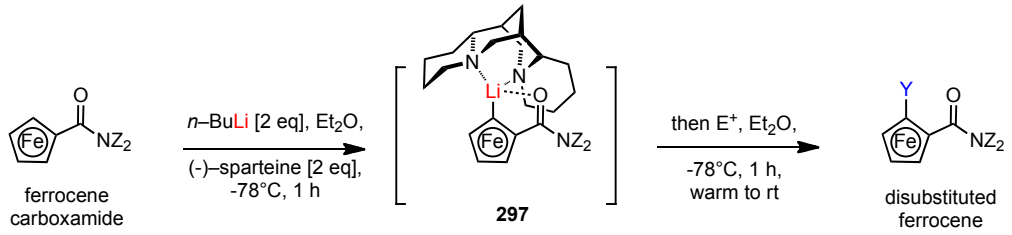
With carboxamides **296-297** in hand, installation of the buttressing Y group was undertaken. Using Snieckus' protocol, enantioenriched 1,2-disubstituted ferrocene carboxamides were targeted, Table 12.[194] Overall high yields and excellent enantioselectivities were observed for the diisopropyl amide, entries 1-3, while moderately lower yields and comparable enantioenrichment were seen for the diethyl amide, entries 4-6.

Scheme 65. Synthesis of Ferrocene Carboxamides



Iodoferrocene's **298**/**301** entries 1 and 4, were generated as cross-coupling precursors in very good yield. Methyl substituted carboxamides **299**/**302**, entries 3

Table 12. Synthesis of Disubstituted Carboxamides

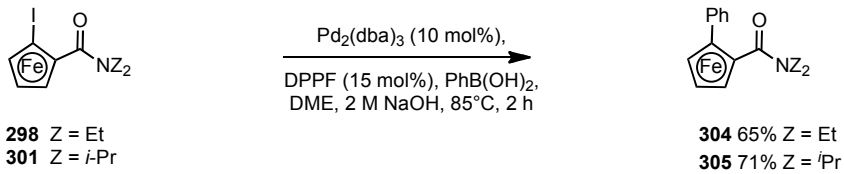


entry	Z	E^+	Y	disubstituted ferrocene	yield (%)	% ee
1	^{i}Pr	$I(CH_2)_2I$	I	**298**	87	96
2	^{i}Pr	MeI	Me	**299**	88	95
3	^{i}Pr	TMSCl	$SiMe_3$	**300**	85	96
4	Et	$I(CH_2)_2I$	I	**301**	89	96
5	Et	MeI	Me	**302**	88	95
6	Et	TMSCl	$SiMe_3$	**303**	65	96

and 5, and trimethyl silyl substituted carboxamides **300**/**303**, entries 3 and 6, were synthesized with the intent of investigating whether the interatomic distance of carbon sp^3-sp^2 bonds (~1.507 Å) and the carbon sp^2-Si sp^3 bond distance (1.750 Å) would lead to any reactivity differences during exchange that may arise by relieving potential torsional strain.[195]

Iodoferrocenes **298**/**301** were subjected to palladium catalyzed Suzuki-Miyaura cross-coupling conditions to install the ortho phenyl substituent in moderate to good yield, Scheme 66.[196]

Scheme 66. Synthesis of Phenyl Substituted Carboxamides **304**/**305**

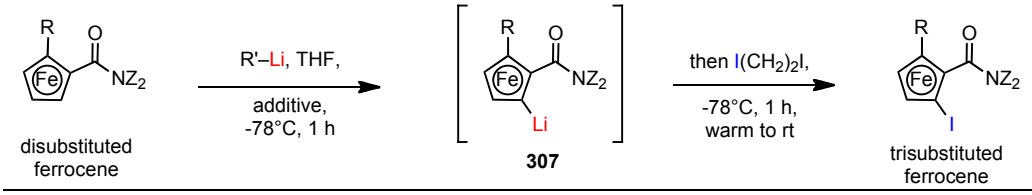


298 Z = Et
301 Z = *i*-Pr

304 65% Z = Et
305 71% Z = ^{i}Pr

Extensive exploration into conditions that would lead to the targeted trisubstituted iodoferrocenes was not met with success. A few examples representing different attempts are shown in Table 13, where variation in α-metallation reagent, temperature, and time, were examined. Ultimately it was discovered that ortho

Table 13. Attempted Synthesis of Trisubstituted Iodoferrocenes



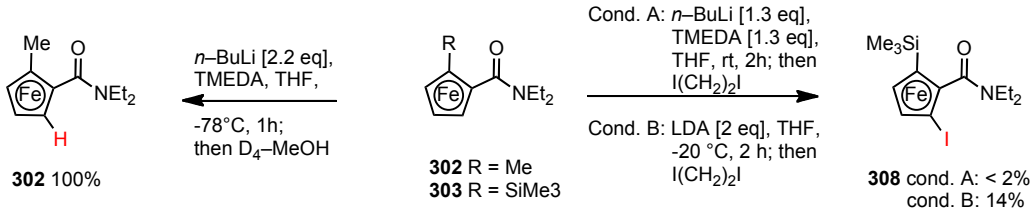
entry	ferrocene	Z	R	R'–Li	temp (°C)	time (h)	yield trisub. ferrocene(%)	recovered starting material (%)
1	**305**	^{i}Pr	Ph	*n*-BuLi	-78	1	0	100
2	**299**	^{i}Pr	Me	*t*-BuLi	-78	1	0	100
3	**299**	^{i}Pr	Me	*n*-BuLi	rt	2	0	100[a]
4	**299**	^{i}Pr	Me	*n*-BuLi	56	2	0	90[b]
5	**300**	^{i}Pr	$SiMe_3$	*n*-BuLi	rt	2	0	100
6	**304**	Et	Ph	*n*-BuLi	rt	2	0	65

a) an analogous reaction that replaced the quenching reagent from diiodoethane to D_4-MeOH did not result in any incorporation of deuterium into starting ferrocene carboxamide. b) 10% loss accounted for by crude ^{1}H NMR analysis indicating possible formation of *n*-butyl ferrocenone

substituted ferrocene carboxamides **306** (Z=*i*-Pr) do not undergo ortho-metallation at the α'-position, thereby preventing synthesis of the targeted trisubstituted iodoferrocene (Z = ^{i}Pr). *N,N*-Diethyl ferrocene carboxamides **302**-**303** were also examined under the same ortho-metallating conditions when attempting to synthesize iodoferrocene **304** (Z = Et), entry 6, but was not successful for the phenyl substituent.

A single 1,2-disubstituted ferrocene *N,N*-diethyl carboxamide was eventually converted into a 1,2,3-trisubstituted iodoferrocene **308**, Scheme 67. Attempts to convert ferrocene *N,N*-diethyl ferrocene carboxamide **302** were unsuccessful, but similar conditions did lead to ortho-functionalization of **303**, albeit in trace quantity, conditions A. Reaction conditions eventually found to give reproducible results are shown in condition B. Unfortunately, the yield obtained for iodoferrocene **308** never

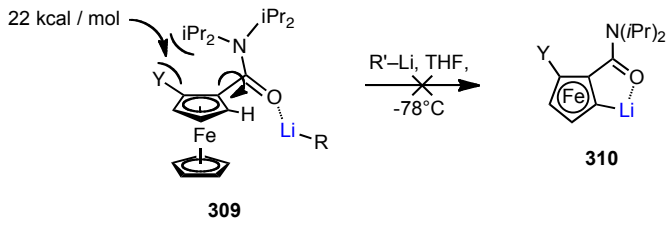
Scheme 67. Synthesis of Tri-substituted Ferrocene Diethyl Carboxamide



exceeded 14% and this limitation prevented further examination of this reagent within the proposed AHME cycle.

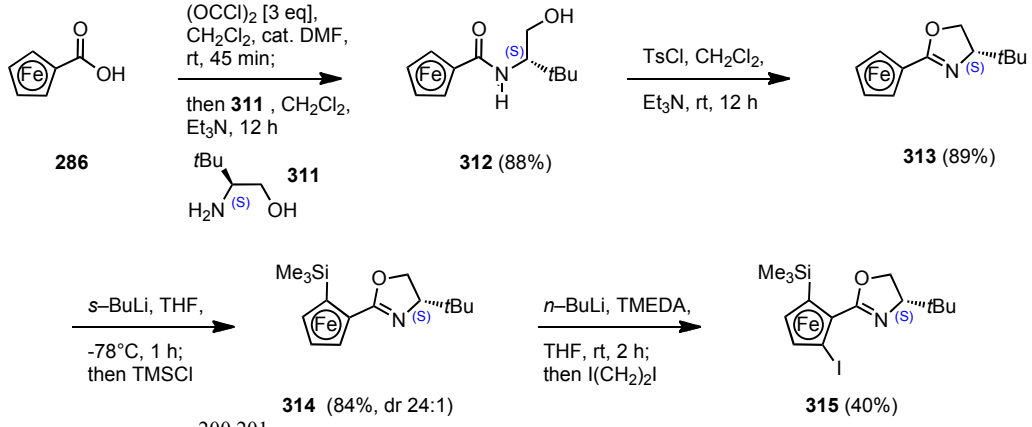
In all probability, the hypothesis that the buttress group Y will destabilize a given α-metallated ferrocene, such as **309**, in order to facilitate iodine-metal exchange, is actually preventing the required second ortho-metallation, Scheme 68. Directed ortho-metallating (DoM) related processes require a co-planar geometry between the directing group and the carbon-hydrogen bond that is to be broken. Deprotonation/lithiation results in formation of a five member chelate (see **268**, Scheme 62) which is trapped with an electrophile to form the 1,2-disubstituted ferrocene.[197,198] A second DoM event should follow the same pathway, but the steric interaction between the ortho-substituent and the amide substituents of the directing group prevents optimal co-planar geometry. Destabilization of the co-planar 5-member chelate **310** is relatively facile considering the barrier to torsional rotation which results in out-of-plane twisting by the amide **309** of 22 kcal/mol.[199] A second ortho-metallation event is therefore prevented and installation of the iodine atom is precluded. Synthesis of trisubstituted ferrocene carboxamide **308** may be the result of the lengthened C-Si bond length permitting enough steric relief from the buttressing effect to allow partial formation of lithiated ferrocene **310** (Y = $SiMe_3$).

Scheme 68. Proposed Explanation Accounting for Difficulty in Generating 1,2,3-Trisubstituted Ferrocene



The original proposal of the AHME reagent design incorporating a buttressing Y group at the α-position was pursued further by switching focus from carboxamide directing groups to other potential ortho-metallation directing groups. Examination of the literature for trisubstituted ferrocenes revealed several known compounds, some of which displayed excellent reactivity during highly stereoselective

Scheme 69. Synthesis of Tri-substituted Oxazoline Ferrocence



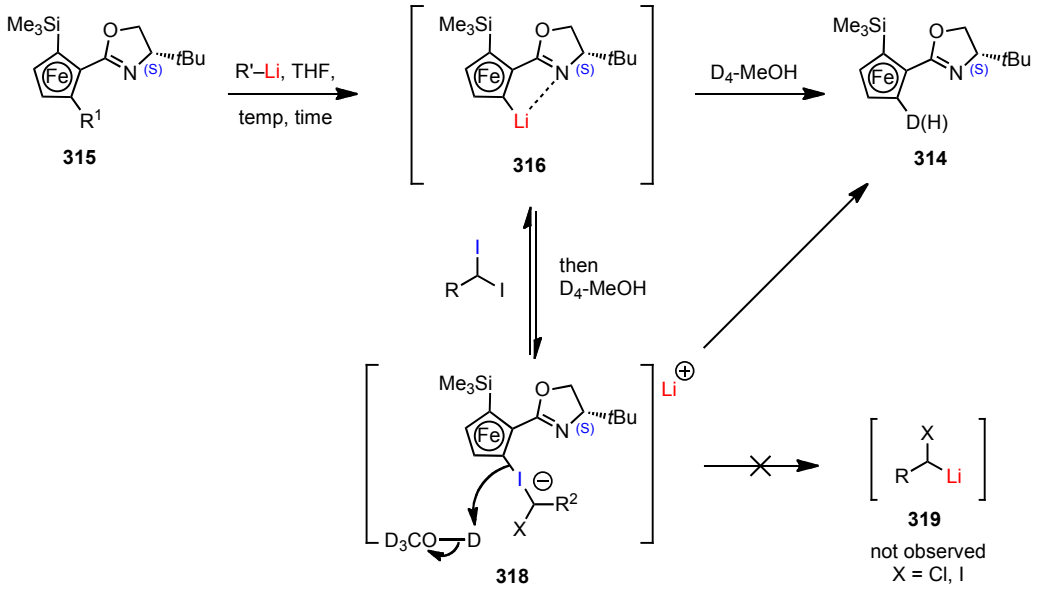
transformations.[200,201] One such compound was identified and targeted based on the earlier result with trisubstituted ferrocene **308**, Scheme 69. Ferrocene carboxylic acid **286** was converted into enantioenriched 2° amide **312** following acid chloride formation and subsequent trapping with (S)-*tert*-leucinol **311**. Tosylation of alcohol **312** followed by intramolecular trapping with the amide carbonyl group and subsequent isomerization led to ferrocenyl oxazoline **313** in excellent yield.[202] *sec*-BuLi promoted α-metallation followed by Me_3SiCl quench generated 1,2-disubstituted oxazolinyl ferrocene **314** in high yield (84%) and with excellent diastereoselectivity (24 : 1). A second ortho-metallation (which required optimization of the literature procedure) converted the disubstituted ferroceone **314** to the targeted trisubstituted iodoferrocene **315** in fair yield (40%).[203]

*8.4 - Halogen-Metal Exchange with Trisubstituted Iodoferrocene **315***

With trisubstituted iodoferrocene oxazoline **315** in hand, the viability of the ferrocenylithium derived from this reagent (**316**) to effect halogen-metal exchange from dihalide substrates was investigated. Iodine-lithium exchange from **315** (R = I), Table 14, was shown to occur with both *n*-BuLi, entry 1, and with *t*-BuLi, entry 2,

with full conversion of the starting iodide to a mixture of deuterated/protonated ferrocene **D(H)-314** following D_4-MeOH quench of putative lithiated ferrocene **316**.

Table 14. Iodine-Lithium Exchange from Lithiated Ferrocenyl Oxazoline



entry	R	R'–M	additive	temp (°C)	time (min)	quench	yield **314** (%) (D%)
1	I	*t*–BuLi [2 eq]	none	-78	12	D_4–MeOH	$100^{(68)}$
2	I	*n*–BuLi	none	-78	12	D_4–MeOH	$100^{(\leq 70)}$
3	H	*n*–BuLi [1.3 eq]	TMEDA [1.3 eq]	rt	120	D_4–MeOH	$100^{(\leq 40)}$
4	H	*t*–BuLi [0.9 eq]	none	0	15	D_4–MeOH	$100^{(\leq 38)}$
5	I	*t*–BuLi [2 eq]	none	-78	12	**281**	$100^{(68)}$
6	I	*t*–BuLi [2 eq]	none	-78	12	**282**	$100^{(70)}$
7	I	*t*–BuLi [2 eq]	none	-78	12	**279**	$100^{(70)}$

It is curious that 100% deuterium incorporation was not observed as all starting material is consumed and an excess of the deuterium source was used. A partial internal quench most likely accounts for the less than complete deuterium incorporation.

Proof-of-principal that an exchange cycle is possible for **315** was investigated starting with *t*-BuLi followed by addition of *gem*-diiodo alkane, entry 5, but regeneration of **315** was not observed. To validate if this occurred for other substrates as well, both alkyl *gem*-chloroiodide, entry 6, and *gem*-diiodosilane, entry 7, were

investigated, but similar results were obtained with recovery of **314** (Y=D) and no regeneration of **315** (R = I). The *gem*-dihalide reagents were fully recovered in all cases. These results suggest that either: 1) lithiated ferrocene **316** is the more stable organometallic reagent and does not enter into Li/I exchange with iodides **317** or 2) the ate-complex **318** is persistent and electrophilic quench occurs from either lithiated ferrocene **316** or from ate-complex **318**. If quench occurs from **318** then the ferrocene-hypervalent iodine bond appears to be the more nucleophilic bond as no iodine incorporation was observed for any case, even when using the silyl substituted *gem*-diiodide which has been shown to be the most effective AHME *gem* dihalide reagent, *vide infra*.

8.5 *- Simplification of AHME Reagent Design By Negating Buttressing Group*

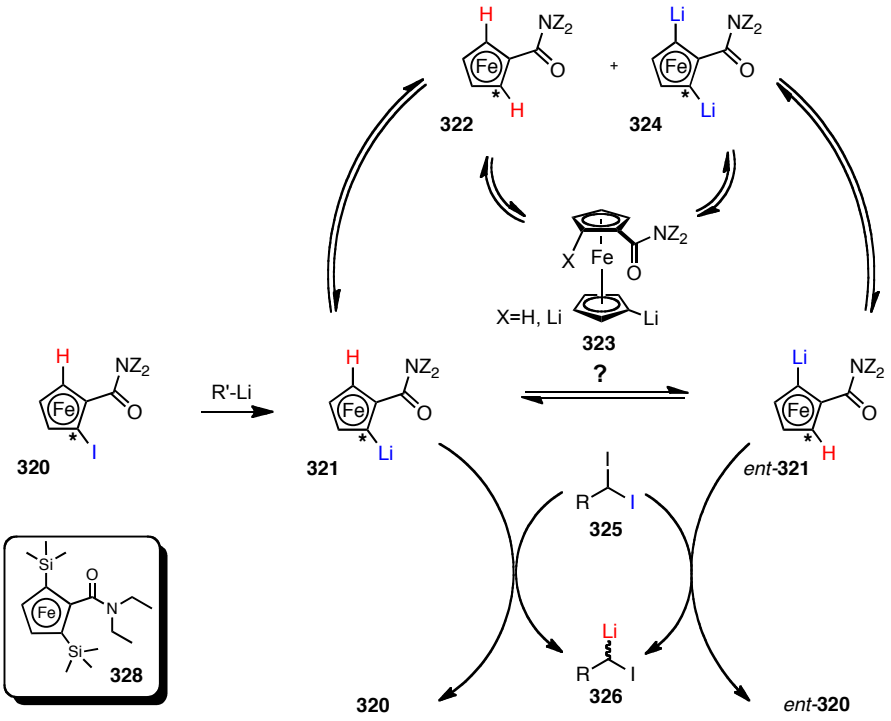
In light of the difficulty encountered in preparing trisubstituted iodoferrocenes and given the failure of attempted AHME cycles employing the handful of similar reagents that could be synthesized, a change in course was warranted for this project. Two course corrections were deemed most logical in order to further pursue this project: either simplify or re-design the organometallic AHME precursor reagent altogether. Simplification was determined to be the most advantageous course, therefore the necessity of the buttressing Y group had to be reconsidered. The principal reason to include the group Y≠H was to prevent the possible racemization of enantioenriched lithioferrocene reagents such as **321** via a 'ping-pong' type mechanism. However, the reality of such a racemization pathway had yet to be established.

8.6 *- Evaluation of 1,2-Substituted Planar Chiral Iodoferrocenes in AHME Cycles*

As shown in Scheme 70, two possible racemization pathways are potentially available to enantioenriched lithioferrocene reagent **321** leading to formation of *ent*-**321**. The first involves either protonolysis or lithiation of **321** leading to achiral **322** or **324**, both of which may develop further into a mixture of **321**/*ent*-**321**. Another possible route or intermediate involved during racemization is detailed as **323** (X = H,

Li) which arises from a lower Cp ring lithiation.[204] This species could also be involved during a hypothetical interconversion of **321** and *ent*-**321**.

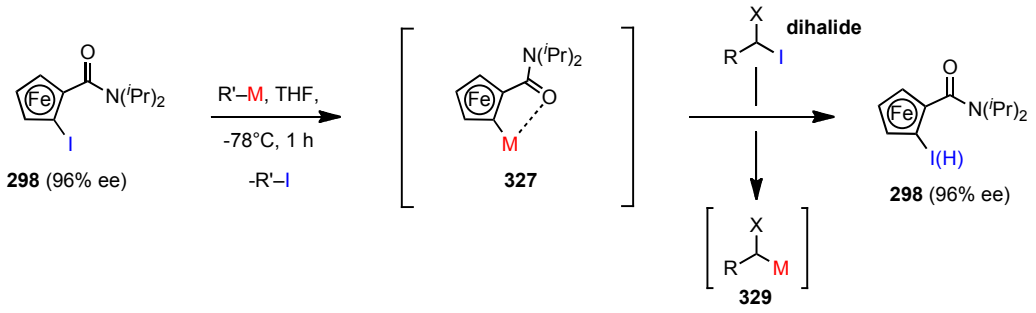
Scheme 70. Proposed Racemization Pathway



Addition of a pro-chiral *gem*-diiodide (**325**) followed by iodine-lithium exchange with **321**/*ent*-**321** leads to formation of both enantiomers of lithium carbenoid **326** and formation of both iodoferrocene **321** and *ent*-**321**. Assay of the recovered iodoferrocene **320** for ee would therefore indicate whether or not racemization occurs.

It is important to note that trepidation concerning possible racemization was not completely without merit. During early investigations into substituted ferrocene carboxamide synthesis doubly silylated ferrocene diethyl carboxamide **328** was often isolated in substantial yield (~30%). This provided direct evidence that lithiation of ferrocene carboxamide was possible at both ortho-positions. Control experiment results are shown in Table 15, entries 1 & 2, where halogen-metal exchange of iodoferrocene **298** conducted at –78°C and regeneration of iodoferrocene **298** through subsequent halogen-metal exchange of silylsubstituted *gem*-diiodide **328** (X=I, R=Me_3Si) did not lead to any racemization as judged by chiral stationary phase

Table 15. Iodine-Metal Exchange Involving 1,2-Disubstituted Carboxamide Iodoferrocene **298**



entry	R'–M	Temp (°C)	dihalide	R	X	M	yield **298** Iodide (%)[c]
1	*n*–BuLi [1 eq]	-78	**279**	Me_3Si	I	Li	72 (96% ee)
2[a]	*n*–BuLi [1 eq]	-78 to rt	**279**	Me_3Si	I	Li	73 (80% ee)
3	*n*–BuLi [1 eq]	-78	**356**	H	I	Li	73
4	*n*–BuLi [1 eq]	-78	**355**	H	Cl	Li	58
5	*n*–BuLi [1 eq]	-78	**278**	Me_3Si	Cl	Li	44
6	*n*–BuLi [1 eq]	-78	**282**	$Ph(CH_2)_3$	I	Li	52
7	*n*–BuLi [1 eq]	-78	**281**	$Ph(CH_2)_3$	Cl	Li	30
exchange with Mg							
11[b]	*n*–BuLi [1 eq]	-78	**279**	Me_3Si	I	Mg	12%

a) reaction warmed to rt for 2 hours before exchange with *gem*-diiodide, assay of regenerated **298** %ee indicated ~15% erosion of enantioenrichment; b) then transmetallation with $MgBr_2$ following 1 h; c) the mass balance of yield was the recovered **298**(H).

HPLC analysis. When lithiated ferrocene **327** was warmed to room temperature for 2 hours before iodine-lithium exchange, some erosion (~15%) of stereochemical fidelity was observed as ascertained by chiral HPLC analysis. This key result indicated that a simplification of the planar chiral ferrocene reagent could be implemented and the AHME study could go forward without a potential redesign of the reagent. Next, halogen-metal exchange between lithiated ferrocene **327** and *gem*-dihalo substrates was investigated starting with diiodomethane and chloroiodomethane, entries 3 and 4. The resulting lithium carbenoids from this particular exchange are achiral, but these *gem*-dihalides were tested nonetheless to validate the exchange process. It was assumed that these *gem*-dihalomethanes would exhibit exchange efficiency somewhere between the silyl substituted and the alkyl substrates, but as seen from the results, they displayed equal propensity for exchange

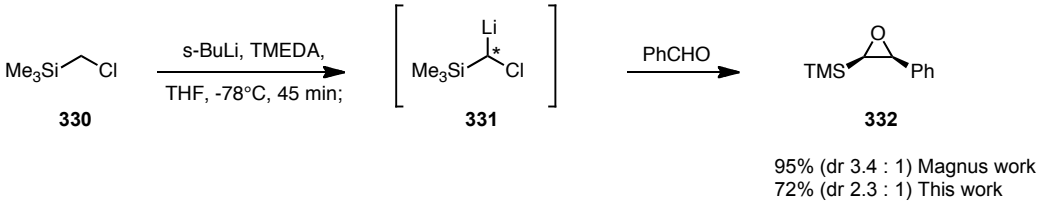
as *gem*-diiodomethyl silane **279**, entry 1, and slightly better exchange than *gem*-chloroiodosilane **278**, entry 5. The trend observed for all substrates, including the alkyl *gem*-dihalides, entries 6 and 7, is the increased exchange efficiency between lithiated ferrocene **327** for *gem*-diiodo substrates in comparison to the *gem*-chloroiodo substrates. This pattern might suggest that ate-complex formation and breakdown with *gem*-diiodides is thermodynamically more favorable than the corresponding *gem*-chloroiodide reagents.

Iodine-metal exchange initiated with magnesium organometallic reagents did not occur as readily for iodoferrocene **298**. In fact, under standard exchange conditions (THF, –78°C, 45 min.), there was no observable iodine-magnesium exchange. Iodoferrocene **298** was recovered quantitatively, even when isolated following electrophilic deuterium quench, entry 8. Increasing the temperature during exchange and using a more reactive magnesium reagent (*i*PrMgCl·LiCl) did not lead to any observable exchange either, entries 9 and 10.[205] Eventually iodine-magnesium exchange was initiated by increasing the reaction time to two hours at room temperature, but these conditions only resulted in a 50% exchange.[206] Exchange between **327** (M=MgCl) with **279** (R=Me_3Si, X=I) was effected by transmetallating lithium ferrocene **327** (M=Li) with $MgBr_2$, followed by addition of the geminal dihalide. Unfortunately, iodine-magnesium exchange from magnesiated ferrocene **327** (M=MgCl) was very inefficient as only 12% of iodoferrocene **298** was isolated, entry 11.

8.7 - α-Haloalkyl Metal Reagent Formation and Deployment

Following validation that exchange between iodoferrocene **298** and the *gem*-dihalo substrates is thermodynamically feasible and that the Y blocking group was not required, investigation into trapping the generated α-haloalkyl metal reagent **329** (X=Cl, I; R=Me_3Si, alkyl) with aldehydes was pursued, as a means of generating epoxides.

Scheme 71. The Magnus Reaction



330 **331** **332**

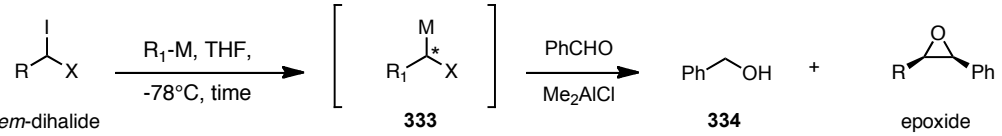
95% (dr 3.4 : 1) Magnus work
72% (dr 2.3 : 1) This work

Of particular interest were α-β-epoxy silanes which are synthetically relevant reagents that have garnered limited exposure due to the dearth of methodology available for their generation. Typically formation of α,β-epoxysilanes is accomplished through the epoxidation of vinyl silanes, but Magnus developed methodology to synthesize these masked carbonyl groups through carbon-carbon bond formation.[207] α-Metallation of α-chloromethyltrimethylsilane **330** with a TMEDA / *s*-BuLi complex, leads to α-silylated lithium carbenoid **331** which is trapped with benzaldehyde to form α,β-epoxysilane **332** in excellent yield (95%) and fair diastereoselectivity (*cis:trans* 3.4:1), Scheme 71. This alternative pathway for α,β-epoxysilane formation was chosen as a test piece to showcase the AHME cycle. After repeating the experimental conditions reported for α,β-epoxysilane formation, it was found that in essence, the literature results could be repeated, but isolated yields were lower (~20%) and the same diastereoselectivity was not observed (2:1 vs 3.4:1).

Next, carbenoid reagents ostensibly identical to those prepared by Magnus *via* deprotonation were targeted instead *via* halogen-metal exchange from *gem*-dihalide substrates, Table 16. This was necessary in order to validate that carbenoids generated through halogen-metal exchange would participate in the Magnus reaction. Initial success was observed for halogen-metal exchange initiated Magnus reaction when α,β-epoxysilane **332** was generated in 32% yield, from diiodomethyl silane **279**, entry 1. This seemingly straightforward result, turned out to be quite misleading. Subsequent attempts failed to reproduce the initial results; instead complete consumption of the starting *gem*-dihalide substrates was consistently observed along with isolation of benzyl alcohol and trace amounts of epoxide **332**.

This was interspersed with infrequent (1 in 7 attempts) isolation of α,β-epoxysilane **332** in approximately 10-15% yield.

Table 16. Halogen-Metal Exchange Initiated Magnus Reaction with *gem*-Dihalide Substrates



gem-dihalide **333** **334** epoxide

entry	*gem*-dihalide	R	X	R_1–M	M	Me_2AlCl (eq)	**334** (%)	epoxide	yield (%)	dr (*cis:trans*)
1	**279**	Me_3Si	I	*n*–BuLi	Li	0	> 95	**332**	< 5	N / A
2	**279**	Me_3Si	I	*t*–BuLi [2 eq]	Li	0	> 95	**332**	< 5	N / A
3	**279**	Me_3Si	I	*i*PrMgCl	MgCl	0	> 95	**332**	< 5	N / A
4	**278**	Me_3Si	Cl	*i*PrMgCl	MgCl	0	< 5	**332**	< 5	6 : 1
5	**279**	Me_3Si	I	*n*–BuLi	Li	1.1	< 5	**332**	59	2.3 : 1
6	**282**	$Ph(CH_2)_3$	I	*n*–BuLi	Li	1.1	< 5	**335**	51	2.2 : 1
7	**282**	$Ph(CH_2)_3$	I	*i*PrMgCl	MgCl	0	15	**335**	54	3.5 : 1
8	**281**	$Ph(CH_2)_3$	Cl	*n*–BuLi	Li	1.1	< 5	**335**	52	2.3 : 1
9	**281**	$Ph(CH_2)_3$	Cl	*i*PrMgCl	MgCl	1.1	15	**335**	54	3.3 : 1

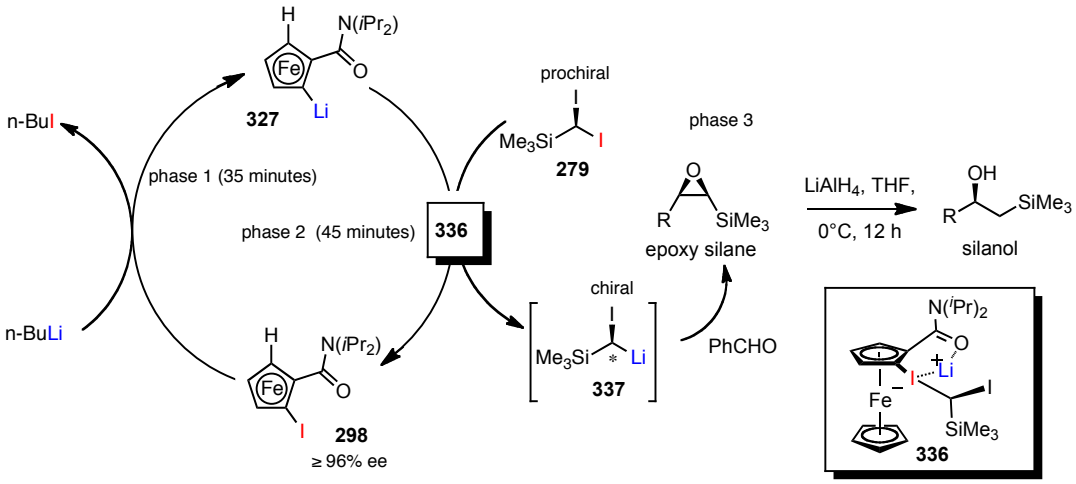
It was postulated that a SET initiation might be occurring during iodine-metal exchange resulting in an electron transfer process that was reducing the aromatic aldehyde. Iodinayl radicals generated during iodine-metal exchange have previously been reported and shown to be competent reducing agents of carbonyl groups.[167] To prevent SET processes occuring, attempts were made to remove all traces of oxygen from the reaction mixture, including use of THF distilled from Na^0/benzophenone followed by successive freeze-thaw cycles of the reagents under inert atmosphere before initiating halogen-metal exchange. Even under these precautionary conditions, reproducibility of the reaction only increased to a 60% success rate, but epoxide formation was still inefficient with yields of only 10-14% isolated. Reduction of the carbonyl group during this process was not confined to aromatic aldehydes as this process was also observed for dihydrocinnamaldehyde (not shown). Eventually, it was discovered that reduction could be suppressed by pre-complexing benzaldehyde and Me_2AlCl before addition to the pre-generated carbenoid (**333**), which led to

wholesale reproducibility, entries 5, 8 and 9, where all *gem*-dihalide substrates were shown to form epoxide **332**/**335**.

8.8 - *Investigation of Entire AHME Cycle*

Following successful validation of each of the three phases of AHME separately, the entire cycle was examined as a continuous process in a single reaction vessel. Considering that the carbenoid **337** derived from the *gem*-diiodomethyl silane **279** consistently produced the best exchange results with lithiated ferrocene **327** and is a competent reactant for the Magnus reaction, this reagent was employed during validation of the entire AHME process, Table 17.

Table 17. Asymmetric Halogen-Metal Exchange Cycle



entry	R	Temp (°C)	**298** recovery (%)[b]	epoxy silane	yield (%)	silanol	yield (%)	ee (%)
1[a]	Ph	-78	55	**332**	40 / (0)[a]	**339**	80	0
2	4–$MeOC_6H_4$	-78	53	**337**	37	**340**	82	0
3	$Ph(CH_2)_2$	-78	55	**335**	35	**341**	75	0
4	Cy	-78	55	**338**	36	**342**	85	0

a) reaction run under identical conditions with the addition of LiCl. b) HPLC analysis of recovered iodoferrocene **298** indicated ≥ 96% ee in all cases

Starting from enantioenriched iodoferrocene **298**, an initial iodine-lithium exchange with *n*-BuLi at –78°C in THF, occured over 35 minutes resulting in formation of lithiated ferrocene **327**, completing phase 1 of the AHME cycle.

Introduction of pro-chiral *gem*-diiodide **279** began phase 2, where ate-complex formation and breakdown **336** ostensibly occured over a 45-minute period. Putative enantioenriched lithium carbenoid **337** was then trapped during phase 3 following addition of a pre-complexed Me_2AlCl-PhCHO adduct leading to formation of α,β-epoxysilane **332**. Isolation of **332** (40%) was followed by regiospecific epoxide opening in the presence of $LiAlH_4$ generating silanol **339** (82%) which was assayed for enantioenrichment with chiral stationary phase HPLC analysis, Table 17, entry 1. This cycle was repeated for an electron donating aromatic aldehyde, entry 2, and also aliphatic aldehydes, entries 3 and 4. In all cases examined, the isolated reduced Magnus reaction products (**339**-**342**) were racemic.

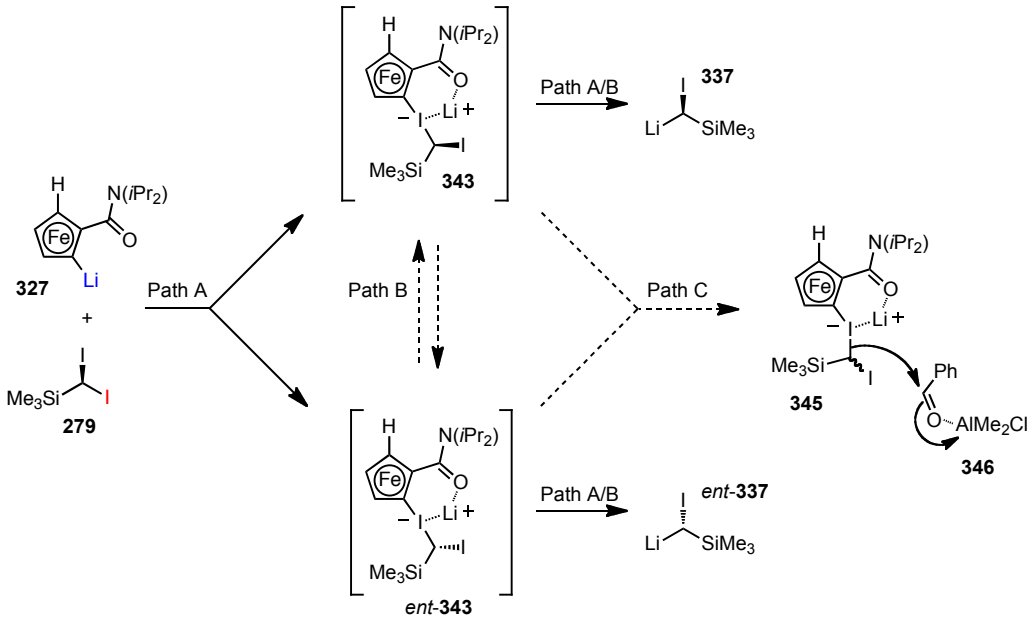
These results validated that the proposed AHME cycle was in fact viable, but certain issues need to be addressed concerning the overall lack of any observable stereoselectivity. At the present time, no direct evidence exists to illuminate which step(s) in the AHME cycle that is compromising stereoselectivity. It may occur during the initial stereoinduction step, be eroding at some later point of the process, or possibly a mixture of both. Although several possibilities exist that may account for the results observed in this study the most prominent are detailed below and shown in Scheme 72:

(a) If ate-complex formation during iodine-lithium exchange is irreverisible, Path A, the spatial influence of the chiral organometallic reagent may not be sufficient to facilitate discrimination between the enantiotopic iodine atoms and both diastereomeric ate-complexes are formed **343**/**344** in equal ratio. Ensuing ate-complex breakdown leads to generation of both lithium carbenoid enantiomers **337**/*ent*-**337** ultimately leading to racemic product following aldehyde quench.

(b) Assuming the first step is reversible, then Curtin-Hammet type kinetics possibly operate during the interconversion of diastereomeric ate-complexes **343**/**344**, Path B. A situation then

arises where the energy barrier between the two diastereomeric ate-complex formation and breakdown does not adequately influence product distribution, leading to a mixture of both lithium carbenoid enantiomer **337**/*ent*-**337** formation.

Scheme 72. Proposed Pathways Accounting for Lack of AHME Stereoselectivity

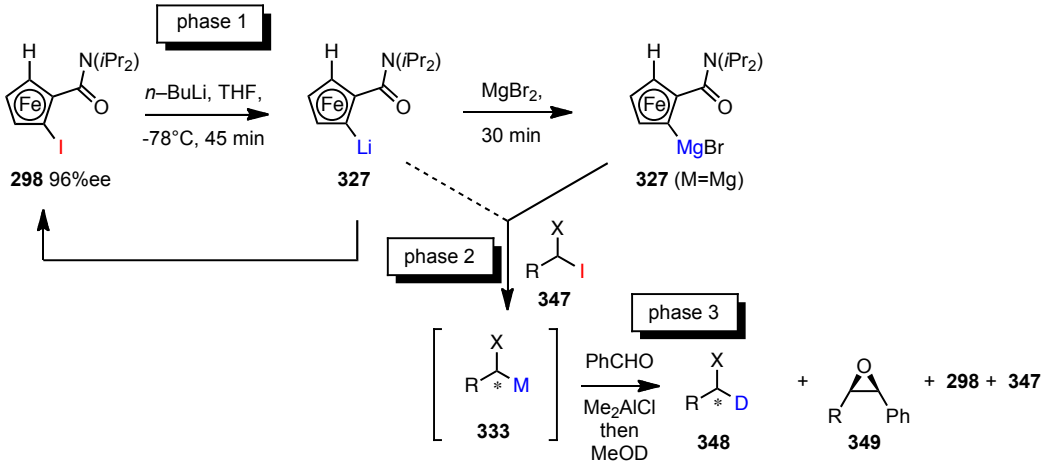


(c) The possibility that lithium carbenoid **337** is not a discrete species and nucleophilic addition occurs from the ate-complex itself, is represented by path C.[190] This path would arise if the lithiated ferrocene **327** or ate-complex **343** is more stable than the resulting lithium carbenoid (**337**). The nucleophilic character of the ate-complex hypervalent iodine bond is such that reaction with aldehyde complex **346** is possible. This would be the opposite case than that presented in section **8.4** where the nucleophilic character of the ate-complex is exhibited between the ferrocene-iodine bond.

(d) A related possibility exists where a discrete lithium carbenoid species **337** is formed, but on the time scale of the reaction,

racemization occurs before electrophilic trapping, a scenario that has been observed for carbamate substituted silylcarbenoids.[208,209,210]

Table 18. Attempted AHME Cycle with the Three Remaining *gem*-Dihalo Substrates



entry	R	X	$MgBr_2$ (eq.)	**348** yield (%)	**349** yield (%)	**298** yield (%)	**347** recovered (%)
1	$SiMe_3$	Cl	0	N/A	0	30	70
2	$SiMe_3$	I	1.1	N/A	0	12	88
3	$SiMe_3$	Cl	1.1	0	0	0	100
4	$Ph(CH_2)_3$	I	0	50	0	50	50
5	$Ph(CH_2)_3$	I	1.1	0	0	0	100
6	$Ph(CH_2)_3$	Cl	0	30	0	30	70
7	$Ph(CH_2)_3$	Cl	1.1	0	0	0	100

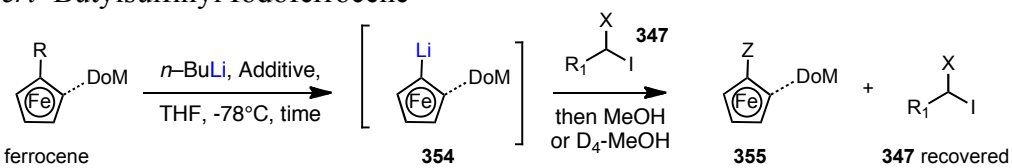
Finally, the remaining three *gem*-dihalo substrates were examined under AHME conditions, Table 18. Each substrate was investigated for potential reactivity as both the lithium carbenoid and the magnesium carbenoid analogue followed by reaction with benzaldehyde. The silyl substituted *gem*-chloroiodo reagent **347** (R=Me_3Si, X=Cl) did show partial exchange with lithiated ferrocene **327** as iodoferrocene **298** was recovered in 30%, but no epoxide **349** formation was observed, entry 1. This experiment was repeated for both *gem*-dihalosilanes, entry 2 and 3, following conversion of lithium ferrocene **327** to putative magnesiated ferrocene **327** (M=MgCl) following transmetallation with $MgBr_2$. Iodine-magnesium exchange was only observed for the *gem*-diiodo substrate **347** (R=Me_3Si, X=I), but exchange was

very inefficient with only 12% of regenerated **298** isolated. The *gem*-chloroiodosilane **347** (R=Me_3Si, X=Cl) did not exchange, but deuterated **298** was recovered along with the starting dihalide **347** (R=Me_3Si, X=Cl). Iodine-magnesium exchange was not observed for the two remaining alkyl *gem*-dihalo substrates **347** (R=$Ph(CH_2)_3$, X=Cl, I), entries 5 and 7. Lithium carbenoid formation (**333**) for these substrates did not occur either, as no epoxide formation was observed, entry 4 and 6, but mass balance recovery of protonated/deuterated starting alkyl halides **347** (R=$Ph(CH_2)_3$, X=Cl, I) suggests that iodine ate-complexes such as **345** are possibly nucleophilic enough to protonate/deuterate between the hypervalent iodine-sp^3 bond, but does not exhibit enough nucleophilic character to attack the Lewis acid activated benzaldehyde.

8.9 *- Miscellaneous Studies*

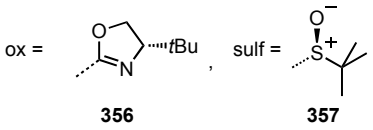
A survey into the viability of other 1,2-disubstituted planar chiral organometallic ferrocenes to function as AHME reagents was carried out with material on hand from previous reagent syntheses, Table 19. Iodine-lithium exchange occurred smoothly, entry 1, for oxazoline substituted iodoferrocene **350** leading to nearly quantitative recovery of protonated **353**. Attempted iodine-lithium exchange from lithiated **352** and *gem*-diiodosilane **347** (R=Me_3Si, X=I), did not lead to exchange and both starting diiodide and protio-**353** were fully recovered, entry 2, but lithiated ferrocene **352** generated from iodine-lithium exchange, entry 3, did incorporate iodine from the electrophilic iodine source $I(CH_2)_2I$, in substantial yield (75%). α-Metallating conditions in the presence of TMEDA, entries 4 and 5, did not promote iodine-lithium exchange between lithiated ferrocene **352** and *gem*-diiodosilane **347** (R=Me_3Si, X=I). Comparable results were observed using the *t*-butyl sulfoxide directing group , where iodine-lithium exchange, entries 6 and 7, and α-metallation, entry 8, lead to lithiated ferrocene **352**, however, no exchange occurs with *gem*-diiodo **347** (R=Me_3Si, X=Cl, I) substrates.

Table 19. Investigation of Iodine-Lithium Exchange Between Oxazolinyl/ *tert*–Butylsulfinyl Iodoferrocene



ferrocene **354** **355** **347** recovered

entry	ferrocene	DoM	R	additive	R_1	X	**355** Z =	yield (%)	**347** recovered(%)
1	**350**	ox	I	N/A	N/A	N/A	H	> 95	> 95
2	**350**	ox	I	N/A	Me_3Si	I	H	> 95	> 95
3	**350**	ox	I	N/A	ICH_2	H	I	75	n / a
4	**351**	ox	H	TMEDA	Me_3Si	I	H	> 95	> 95
5	**351**	ox	H	TMEDA	$Ph(CH_2)_3$	I	H	> 95	> 95
6	**352**	sulf	I	N/A	Me_3Si	Cl	H	> 95	> 95
7	**352**	sulf	I	N/A	Me_3Si	I	H	> 95	> 95
8	**353**	sulf	H	TMEDA	Me_3Si	I	D	72	> 95



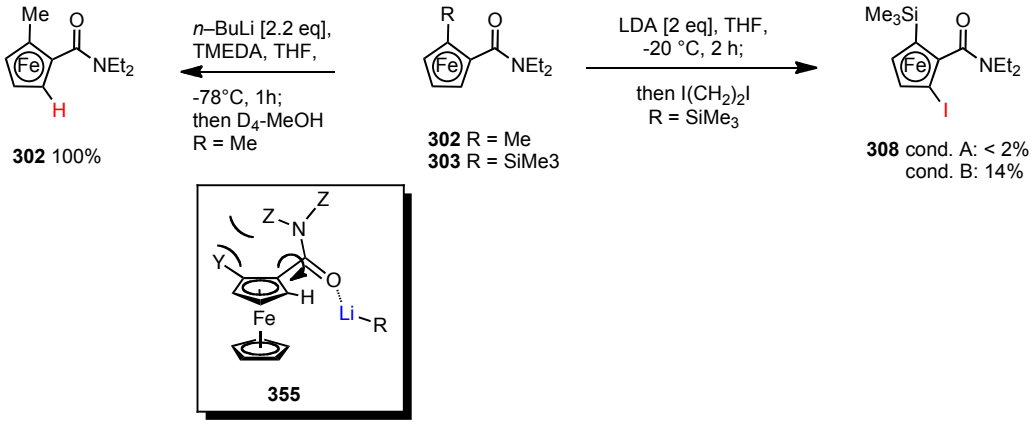
356 **357**

Chapter 9 *- Conclusion*

In conclusion, it has been demonstrated that a planar chiral recyclable organometallic reagent may be used with prochiral *gem*-diiodo substrates for halogen-metal exchange that proceeds through iodine ate-complex formation and breakdown. The entire AHME cycle was validated with *gem*-diiodosilane **279**, unfortunately the isolated addition adducts did not display any enantioenrichment indicating that a breakdown in stereoselectivity is occurred at some stage.

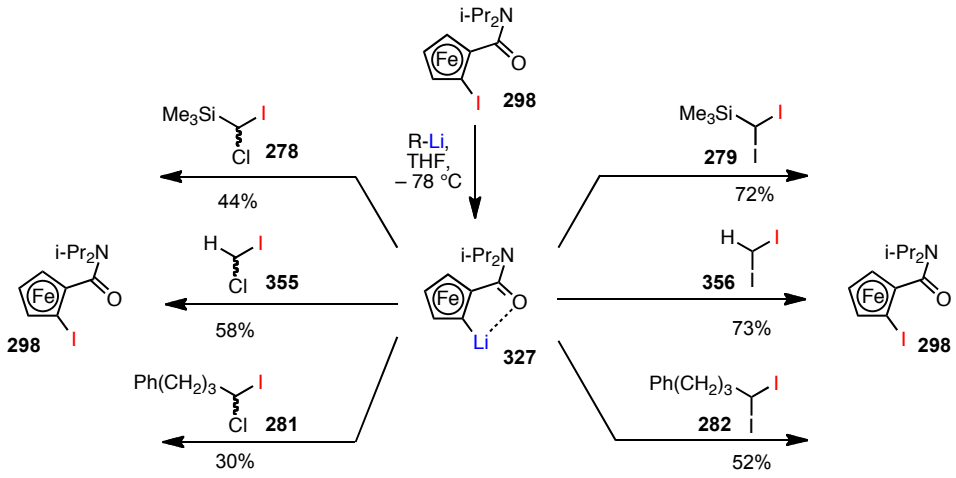
The buttressing group design element was originally proposed as a means of maintaining organometallic reagent stereochemical fidelity and to help drive the thermodynamic iodine-metal exchange process toward carbenoid formation, but this substituent was found to prevent the synthesis of the targeted class of reagent, Scheme 73.

Scheme 73. Buttressing Group (Y) Prevents Synthesis of Trisubstituted Ferrocene Carboxamides



Removing the Y buttressing group led to a simplified organometallic reagent precursor that was investigated for thermodynamic viability to exchange with *gem*-dihalide substrates. It was found that exchange would occur with from the lithiated reagent **327**, while the magnesiated analogue **327** (M=MgCl) exhibited minimal exchange with only a single *gem*-dihalide substrate (**279**) in poor efficiency, Scheme 74.

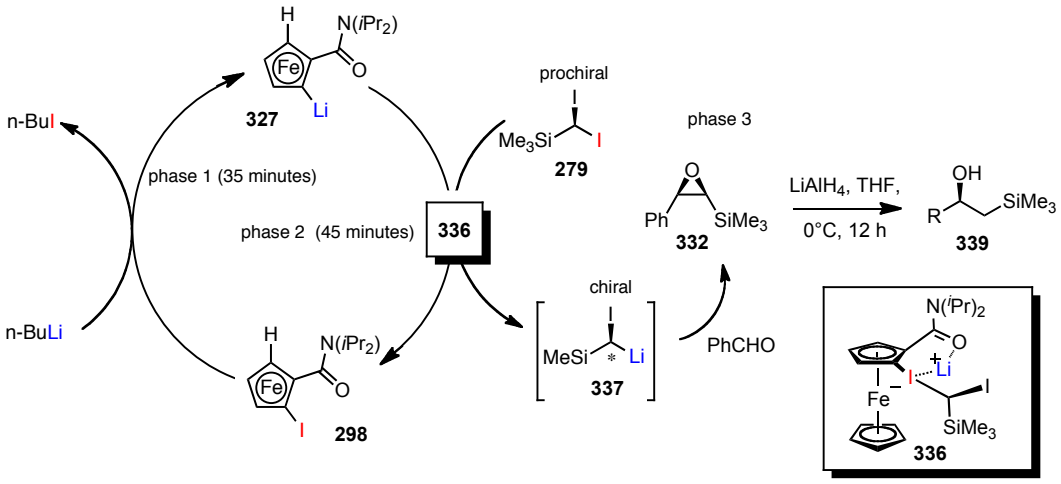
Scheme 74. Iodine-Metal Exchange with 1,2-Disubstituted Ferrocene Carboxamide **298**



Formation of α,β-epoxysilanes through a halogen-metal exchange variant of the Magnus reaction was developed to serve as a means for assaying the level of stereoinduction during the AHME cycle. Iodine-lithium and iodine-magnesium exchange were both shown to be effective methods of forming α,β-epoxysilanes using all *gem*-dihalide substrates.

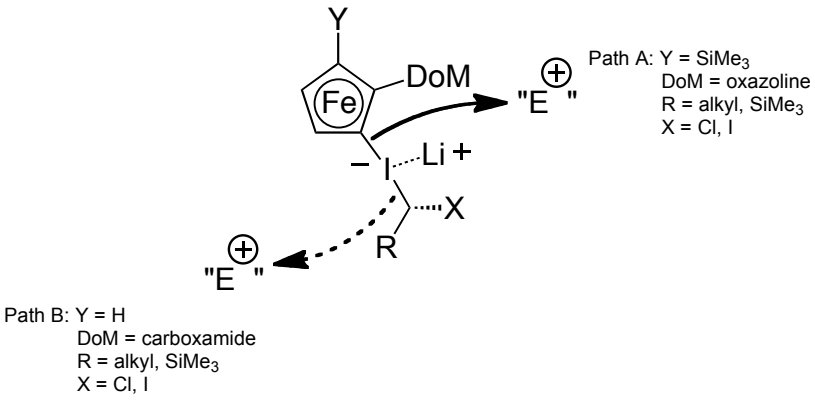
The AHME cycle was validated in part through the use of *gem*-diiodomethyl silane **279**, 1,2-disubstituted ferrocenyl organometallic reagent precursor **298** and a series of aldehydes. AHME reagent recyclability was found to be fairly efficient, while addition adducts were isolated in fair yield following the double exchange process. No detectable level of enantioenrichment was found for any of the addition adducts, indicating that there was either a lack of stereoinduction during exchange or racemization was occurring with the α-haloalkylmetal reagent before trapping with an electrophile, Scheme 75.

Scheme 75. Example of Completed AHME Cycle



Obviously, the nature of all components involved during the AHME cycle has a direct impact on the process of iodine ate-complex formation and breakdown. The evidence provided from this work suggests that the electronic character of these various ate-complexes is strikingly different depending on the nature of the Y buttressing group, Directing ortho metallating (DoM) group, *gem*-dihalide substrate and electrophile involved, Scheme 76.

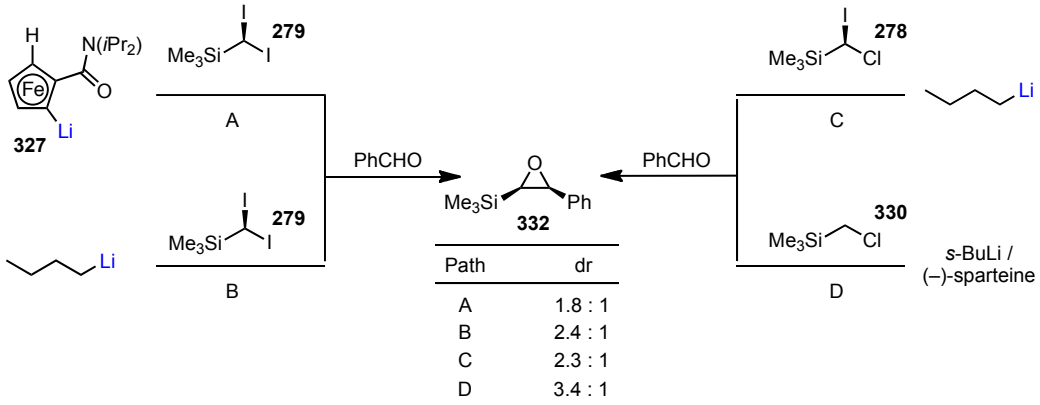
Scheme 76. Nature of the Iodine Ate-Complex



Another point of interest is the observation that the nature of the putative carbenoid varies depending on the mode of access. This is highlighted by the fact that when *gem*-diiodomethyl silane **279** is used in generation of α,β-epoxysilane **332** variation

in the diastereoselectivity is observed depending on putative carbenoid generation. A similar trend is observed with the putative α-chlorocarbenoid formed from either *gem*-chloroiodomethyl silane **278** or chloromethyl trimethylsilane **330**. This suggests a different carbenoid species formed under each condition.

Scheme 77. Nature of the Putative Carbenoid Depends on Mode of Access



Following these studies, it is logical to propose that AHME reagent **327** will not discriminate between enantiotopic groups bonded to sp^3-hybridized centers of *gem*-dihalide substrates similar to those investigated. The possibility does exist, however, that this reagent may discriminate between enantiotopic groups of larger systems that may provide a more defined spatial interaction between the enantiotopic groups and the organometal reagent. A proposed example would be application toward prochiral biaryl complexes similar to those described in section **6.5**.

In closing, the concept of AHME is sound, but the method for developing a suitable reagent for discrimination of enantiotopic halogen atoms needs attention. A delicate balance is required between reactivity, configurational stability, and the favorable thermodynamic driving force necessary for successful exchange. Rational design of a recyclable reagent may still be possible, but any subsequent investigation would benefit most from the identification of a reagent system which exchanges directly from an sp^3 hybridized organometallic reagent. Finally, the substrates involved need to be examined more thoroughly to determine if they are configurationally stable during carbenoid formation and trapping.

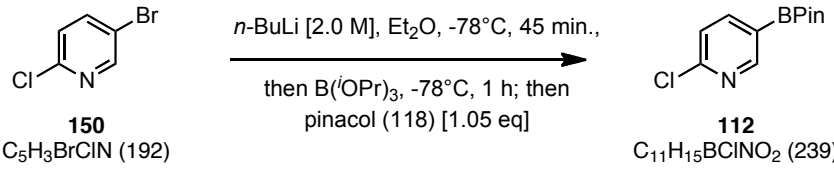
Chapter 10: Experimental Section for Parts I & II

General techniques: All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of Ar. THF and Et_2O were freshly distilled from sodium benzophenone ketyl prior or taken from a SPS using activated Al_2O_3 drying columns, dispensed under Ar.[211] CH_2Cl_2 and PhMe were taken from a SPS using activated Al_2O_3 drying columns, dispensed under Ar. Anhydrous DMF was taken from a SPS fitted zeolite based (4Å MS) drying column. Preparative chromatographic separations were performed on Silicycle silica gel 60 (35-75 μm) and reactions followed by TLC analysis using Sigma-Aldrich silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized with UV, phosphomolybdic, I_2/SiO_2 or *p*-anisaldehyde. All commercially available reagents were purchased from Aldrich, VWR Scientific or Acros and were used as received unless otherwise noted.

Melting points were recorded using open capillary tubes on a Griffin melting point apparatus and are uncorrected. Optical rotations were measured at ambient temperature (22 °C) from $CHCl_3$ solutions on an a Perkin-Elmer 343 polarimeter using a 1 mL cell with 0.2 dm path length. Infra-red spectra were recorded on a Nicolet Nexus 470 FT-IR spectrometer using a thin film supported between NaCl plates or KBr discs where stated. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified on Bruker Avance 700, 400 and 300 MHz FT-NMR spectrometers. Spectra were obtained from the specified deuterated solvents in 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows: **$CDCl_3$** δ_H ($CHCl_3$) = 7.26 ppm, δ_C = 77.2 ppm; **$(CD_3)_2SO$** δ_H (CD_3SOCHD_2) = 2.50 ppm, δ_C = 39.5 ppm; **C_6D_6** δ_H (C_6HD_5) = 7.16 ppm, δ_C = 128.0 ppm; **CD_3OD** δ_H (CHD_2OD) = 3.31 ppm, δ_C = 49.0 ppm; **$(CD_3)_2CO$** δ_H (CD_3COCHD_2) = 2.05 ppm, δ_C = 29.8 ppm. Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in Hz. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Low (MS) and high resolution

(HRMS) mass spectra were obtained using either electron impact (EI), chemical ionization or electrospray (ES) ionization techniques. Ion mass/charge (*m/z*) ratios are reported as values in atomic mass units.

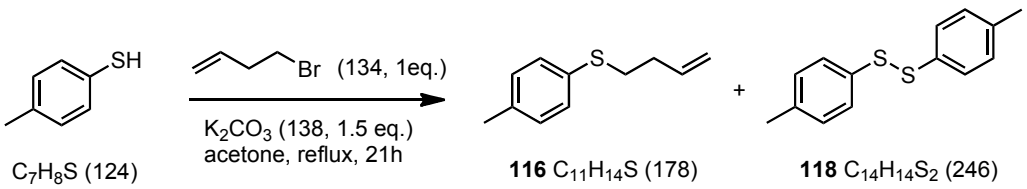
Part 1 – StReCH Experimental



150
C_5H_3BrClN (192)

112
$C_{11}H_{15}BClNO_2$ (239)

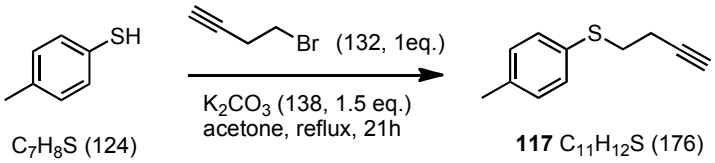
Pyridylboronate -112: A slurry of *n*-BuLi (8.5 mL, 17.0 mmol, 2.0 M in hexanes) and Et_2O (6 mL) was cooled to –78° C and stirred for 1.5 h, followed by addition of 2-chloro-5-bromo pyridine (2.50 g, 13.0 mmol) in Et_2O (8 mL) directly into reaction over 25 minutes. The brown reaction was stirred at –78° C for an additional 65 minutes before addition of triisopropyl borate (3.89 mL, d = 0.82, 3.19 g, 17.0 mmol) in Et_2O (4 mL) over 2 minutes down side of flask. Reaction allowed to warm to rt overnight, then pinacol (1.53 g, 13.0 mmol) in Et_2O (4 mL) was added to the red-orange reaction over 30 s and then taken to reflux for 1 h, followed by a 40 min period of stirring with aq. 5% H_2SO_4 (25 mL). The layers were separated and the aqueous was washed with Et_2O (2 x 25 mL), organics combined, washed with H_2O (2 x 20 mL), washed with brine (40 mL), dried (Na_2SO_4 and concentrated *in vacuo* to yield and soft orange solid (2.18 g) that was purified by recrystallization (1x) in TBME/hexanes to yield the title pyridine as a crystalline orange solid (1.71 g, 7.16 mmol, 55%). mp 84.5-85.5° C (MTBE/hexanes); IR (neat) ν 2980, 2929, 1579, 1552, 1537, 1135, 1104, 1014, 855, 734, cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, dd, *J* = 1.93, 0.8 Hz), 7.95 (1H, dd, *J* = 8.0, 2.0 Hz), 7.26 (1H, dd, *J* = 7.9, 0.86 Hz), 1.29 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (1), 154.2 (0), 144.8 (1), 123.8 (1), 84.5 (0), 24.8 (3) ppm. ^1H NMR data in agreement with that reported by Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R. *Tetrahedron* **2002**, *58*, 2885.



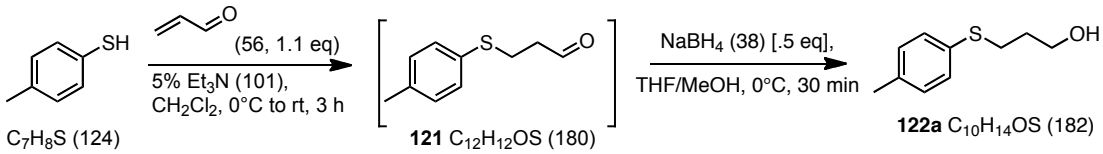
Sulfide -116: A mixture of *p*-thiocresol (3.64 g, 45.5 mmol), homoallyl bromide (1.78 mL, d = 1.46, 2.59 g, 19.4 mmol) and K_2CO_3 (9.41 g, 68.2 mmol) in acetone was stirred at reflux for 21 h. The resultant reaction mixture was filtered under vacuum through a pad of celite®, the pale yellow filtrate concentrated under reduced pressure, then dissolved in EtOAc (60 mL). The organic phase was washed with aq. NaOH (2 x 30 mL, 1.1 M), then H_2O (45 mL) followed by brine (45 mL) and the organic layer dried (Na_2SO_4) then concentrated *in vacuo* to yield the crude product which was purified by column chromatography (SiO_2 eluting with 10%EtOAc in hexanes) to afford the following compounds in order of elution:

Sulfide -116: (yellow oil 3.27 g, 18.3 mmol, 95%); IR (neat) ν 2922, 1641, 1490, 1091, 988, 917, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.3 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 5.85 (1H, ddt, J = 17.1, 10.3, 6.7 Hz), 5.07 (1H, dq, *J* = 17.1, 1.6 Hz), 5.05 (1H, dq, *J* = 10.1, 1.3 Hz), 2.95 (2H, t), 2.39 (2H, m), 2.32 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (0), 136.7 (1), 136.3 (0), 132.7 (1), 130.4 (0), 129.8 (0), 116.3 (2), 33.9 (2), 33.6 (2), 21.2 (3) ppm. ^1H NMR data in agreement with that reported by Wardell, J.; Wigzell, J. M. *J. Chem. Soc. Dalton Trans.: Inorg. Chem.* **1982**, *12*, 2321.

Disulfide -118: (240 mg, 0.98 mmol, 5%), IR (neat) ν 2921, 1632, 1600, 1467, 1392; ^1H NMR (700 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.3 Hz), 7.14 (2H, d, *J* = 7.9 Hz), 2.35 (6H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.6 (0), 134.0 (0), 129.9 (1), 128.6 (1), 21.3 (3) ppm. ^1H NMR data in agreement with that reported by Nair, V.; Augustine, A. *Org. Lett.* **2003**, *5*, 543.

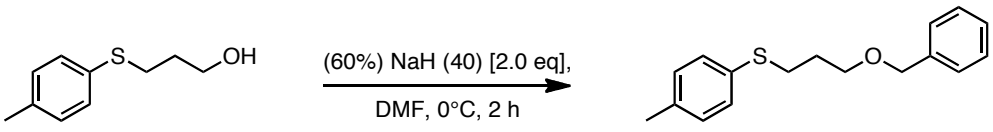


Alkyne -117: A mixture of *p*-thiocresol (833 mg, 6.72 mmol), 4-bromo-1-butyne (0.64 mL, d = 1.41, 904 mg, 6.80 mmol) and K_2CO_3 (1.35 g, 10.1 mmol) in acetone was stirred at reflux for 6 h. The resultant reaction mixture was filtered under vacuum through a pad of celite, the pale yellow filtrate concentrated under reduced pressure, then dissolved in EtOAc (35 mL). The organic phase was washed with aq. NaOH (2 x 15 mL, 1.1 M), then H_2O (25 mL) followed by brine (25 mL) and the organic layer was dried (Na_2SO_4) then concentrated *in vacuo* to afford the title thioether as a yellow oil (1.09 g, 92%, 6.18 mmol) that was recovered and required no further purification. IR (neat) ν 3310, 2935, 2145, 1490, 1091, 917, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.3 Hz), 7.34 (2H, d, *J* = 8.0 Hz), 3.07 (2H, t, J = 7.5 Hz), 2.49 (2H, dt, *J* = 7.5, 2.3 Hz), 2.39 (3H, s), 2.05 (1H, t, *J* = 2.3 Hz) ppm. ^1H NMR data in agreement with that reported by Capella, L; Montevecchi, P. C.; Nanni, D. *J. Org. Chem.* **1994**, *59*, 3368.



Alcohol -122a: A flask was charged w/ CH_2Cl_2 (80 mL) followed by acrolein (2.2 g, d = 0.84, 2.7 mL, 40 mmol) and Et_3N (0.47 g, d = 0.73, 0.65 mL, 4.7 mmol) stirred to homogeneity and then cooled to 0°C. After 15 min addition of *p*-thiocresol (6.0 g, 48.0 mmol) followed by warming to rt over 3 h during which time the reaction color progressed from colorless to pale yellow. After all starting material was consumed as judged by TLC (15% EtOAc/hexanes), Na_2SO_4 (~15 g) was added and the heterogeneous mixture stirred for 15 min before vacuum filtration and conc. *in vacuo* to yield a pale yellow oil (7.30 g). The crude oil was taken up in THF (45 mL) and MeOH (5 mL) and cooled to 0°C before slow addition of $NaBH_4$ (912 mg) over 15 min, during which time evolution of H_2 was observed. Following 30 min, the

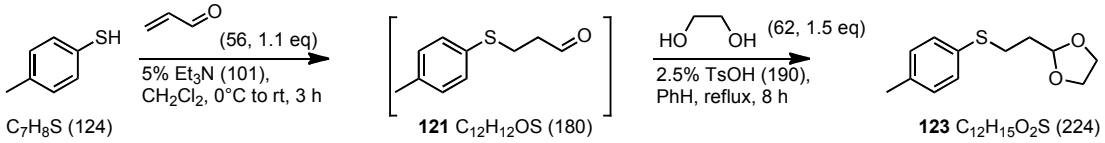
reaction was checked by TLC (20% EtOAc/hexanes) and all starting material was consumed. Slow addition of 1.1 M HCl (8 mL) before partitioning in EtOAc and conc. *in vacuo* led to the crude alcohol (7.2 g) which was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title alcohol **122a** as a colorless oil: (6.92 g, 38.0 mmol, 95%); IR (neat) ν 3338, 3023, 2941, 2867, 1497, 1434, 1260, 1092, 1038, 913, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.1 Hz), 7.10 (2H, d, *J* = 7.9 Hz), 3.74 (2H, t, *J* = 6.1 Hz), 2.98 (2H, t, *J* = 7.1 Hz), 2.32 (3H, s), 1.94 (1H, OH, s), 1.86 (2H, tt, *J* = 6.8, 6.4) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4 (0), 132.5 (0), 130.2 (1), 129.8 (1), 61.5 (2), 31.9 (2), 31.1 (2), 21.1 (3) ppm. ^1H NMR data in agreement with that reported by Tanner, D.; He, H. M. *Tetrahedron* **1985**, *45*, 4309.



122a $C_{10}H_{14}OS$ (182) **122** $C_{17}H_{20}OS$ (272)

Benzyl ether -122: A flask was charged with NaH (1.32 g of a 60% oil dispersion, 32.9 mmol) and washed with hexanes (2 x 6 mL), a color change from grey to off-white was observed, before addition of DMF (18 mL, 0.92 M). This heterogeneous mixture was cooled to 0°C and equilibrated for 15 min before dropwise addition of *p*-tolyl-3-hydroxypropyl sulfide (3.0 g, 16.5 mmol) in DMF (10 mL) over 5 min. Evolution of gas ensued and continued for 30 min at 0°C and the mixture stirred for an additional 30 min before benzyl bromide (2.35 mL, 3.39 g, 19.8 mmol) was added dropwise over 5 min. The reaction was allowed to warm to rt and stir for 2 h, during which time it had progressed from a colorless opaque to a light orange/pink opaque, before quenching with sat. NH_4Cl (5 mL) then diluted with H_2O (20 mL) and Et_2O (20 mL), the layers were shaken and separated and the aq. layer extracted with Et_2O (3 x 20 mL), the organic layers combined, washed with H_2O (2 x 20 mL), then brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a crude golden oil that was purified by column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to

yield the title benzyl ether **122** (, 15.2 mmol, ^{1}H NMR data in agreement with that reported by Linn, J. A.; Kelley, J. L. *Nucleosides and Nucleotides* **1993**, *12*, 199.

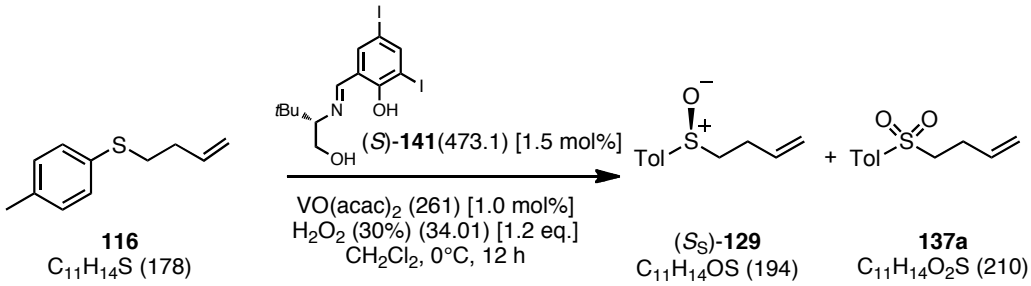


C_7H_8S (124) **121** $C_{12}H_{12}OS$ (180) **123** $C_{12}H_{15}O_2S$ (224)

Acetal -123: A flask was charged w/ CH_2Cl_2 (80 mL) followed by acrolein (5.8 g, d = 0.84, 6.9 mL, 103 mmol) and Et_3N (0.47 g, d = 0.73, 0.65 mL, 4.7 mmol) stirred to homogeneity and then cooled to 0°C. After 15 min addition of *p*-thiocresol (12.0 g, 94 mmol) followed by warming to rt over 3 h during which time the reaction color progressed from colorless to pale yellow. After all starting material was consumed as determined by TLC (15% EtOAc/hexanes), Na_2SO_4 (~15 g) was added and the heterogeneous mixture stirred for 15 min before vacuum filtration and conc. *in vacuo* to yield a pale yellow oil. This residue was taken up in PhH (80 mL) followed by addition of ethylene glycol (8.7 g, d = 1.1, 7.9 mL, 141 mmol) and *p*-TsOH (0.45 g, 2.4 mmol) and then the mixture was fitted with a Dean-Stark trap and heated to reflux for 8.5 h. After all the intermediate aldehyde was consumed, the yellow reaction was cooled to rt, diluted with EtOAc (35 mL) , shaken w/ sat. $NaHCO_3$ (50 mL), H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), conc. *in vacuo* to yield the title acetal as a light orange oil (21.0 g, 100%, 94.0 mmol). The product was used without further purification. **Aldehyde -121:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, s), 7.27 (2H, m), 7.12 (1H, d, *J* = 8.0 Hz), 3.14 (2H, t *J* = 2.6 Hz), 2.74 (1H, t, *J* = 7.1 Hz), 2.32 (3 H, s), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (0), 137.0 (0), 131.2 (0), 131.0 (1), 129.9 (1), 43.4 (2), 27.2 (2), 21.0 (3) ppm. ^{1}H NMR data in agreement with that reported by Ranu, B. C.; Dey, S. S. *Tetrahedron* **2004**, *60*, 4183.

Acetal -123: IR (neat) ν 3074, 3022, 2948, 2883, 2670, 1894, 1495, 1440, 1394, 1138, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.3), 7.10 (2H, d, *J* = 7.9), 4.98 (1H, t), 3.96 (2H, dd, *J* = 7.3, 6.0), 3.85 (2H, dd, *J* = 7.3, 6.0), 2.98 (2 H, dd, ABC, *J* =), 2.32 (3H, s), 1.97 (2H, dt, *J* = 7.8, 4.5 ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (0), 132.5 (0), 130.2 (1), 129.8 (1), 128.5 (0), 103.3 (1), 65.1 (2), 33.8

(2), 28.7 (2), 21.1 (3) ppm. MS (EI) *m/z* 224 $(M+H)^+$; HRMS (ES) *m/z* 224.0877 (calcd. for $C_{12}H_{16}O_3S$; 224.08710).



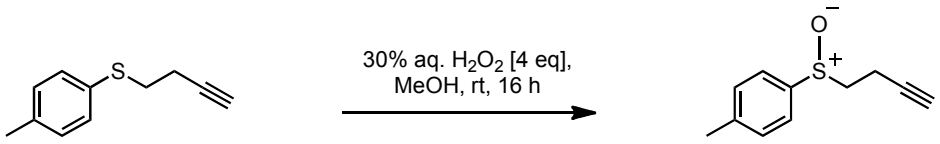
Sulfoxide -129: A mixture of ligand (S)-(**141**) (473 mg, 1.00 mmol) and $VO(acac)_2$ (178 mg, 0.67 mmol) in $CHCl_3$ (35 mL) was pre-aged at rt for 2 h. Next was added *p*-tolyl homoallyl sulfide (12.1 g, 67.9 mmol) in $CHCl_3$ (33 mL) to stir for an additional 30 min, after which time the reaction was cooled to 0° C followed by addition of aq. 30% H_2O_2 (2.73 g, d = 1.11, 8.2 mL, 80.3 mmol). After 2 h at 0°C the reaction was quenched with aq. 10% $Na_2S_2O_3$ (200 mL) and the layers separated. The aqueous phase was washed with $CHCl_3$ (3 x 100 mL), organic phases dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown crude oil (19.6 g) which was purified by column chromatography (eluting with 10-50% EtOAc in hexanes) to afford the products in the order of elution.

Sulfone -137: (3.42 g, 16.3 mmol, 24%) yellow oil, crystallized upon standing IR (neat) ν 2922, 1641, 1490, 1091, 988, 917, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.3 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 5.85 (1H, ddt, J = 17.1, 10.3, 6.7 Hz), 5.07 (1H, dq, *J* = 17.1, 1.6 Hz), 5.05 (1H, dq, *J* = 10.1, 1.3 Hz), 2.95 (2H, t), 2.39 (2H, m), 2.32 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (0), 136.7 (1), 136.3 (0), 132.7 (1), 130.4 (0), 129.8 (0), 116.3 (2), 33.9 (2), 33.6 (2), 21.2 (3) ppm. ^1H NMR data in agreement with that reported by Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc.* **1991**, *64*, 2321.

Sulfoxide -129: (9.64 g, 49.6 mmol, 76%) bright yellow oil $[\alpha]_D$ = + 25.3 (c = 1.00, CHCl3); IR (neat) ν 2920, 1638, 1492, 1393, 1088, 649, 615, 610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.2 Hz), 7.32 (2H, d, *J* = 7.9 Hz), 5.79 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz), 5.11 (1H, dq, *J* = 17.1, 1.6 Hz), 5.06 (1H, dq, *J* = 10.1, 1.34 Hz),

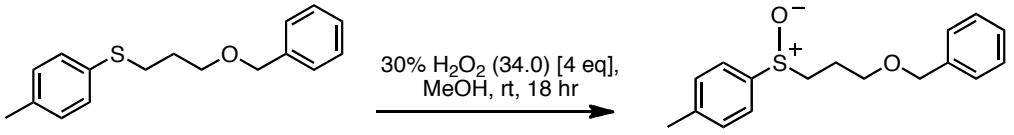
2.71 (2H, t), 2.60-2.25 (2H, m), 2.41 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7 (0), 140.6 (0), 131.1 (2), 130.2 (2), 124.2 (2), 117.1 (2), 56.3 (2), 26.4 (2), 21.6 (3) ppm. ^{1}H NMR data in agreement with that reported by Arnone, A.; Bravo, P.; Cavicchio, G.; Frigerio, M. Viani, F. *Tetrahedron* **1992**, *48*, 8523.

Chiral HPLC analysis of (±)-**129** by [O] of **116** with 30% aq. H_2O_2 in MeOH, performed with a Daicel Chiralcel® OD column, eluting with 10% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(–)-(R_R)-**129**) = 14.4 min. t_{ret} [(+)-(R_S)-**129**) = 17.1 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of > 98% ee in favor of the (*S*)-enantiomer.



117 $C_{11}H_{12}S$ (176) **130** $C_{11}H_{12}SO$ (192)

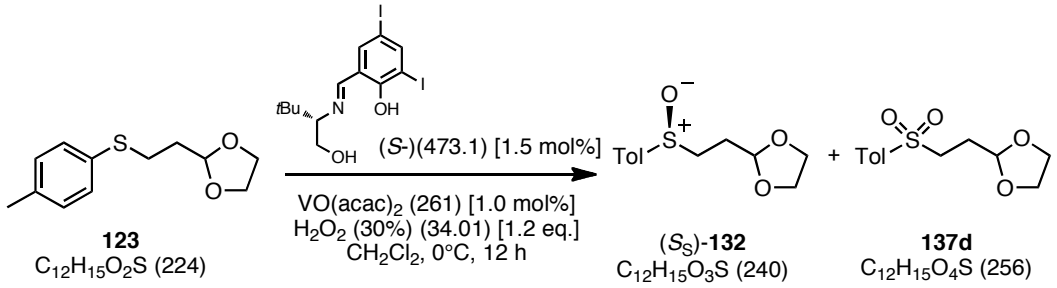
Alkyne -130: A solution of but-1-yne *p*-tolyl-sulfide (1.4 g, 7.8 mmol) in MeOH (20 mL) was treated with 30% aq. H_2O_2 (4.2 mL, d=1.11, 1.4 g, 39.0 mmol) and stirred for 16 h at rt. The resulting pale yellow mixture was partitioned between brine (20 mL) and the layers separated. The aqueous phase was extracted with $CHCl_3$ (3 x 6 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to yield a crude golden oil which was purified by column chromatography (SiO_2 eluting with a gradient of 5-30% EtOAc in hexanes) to afford the title sulfoxide **130** as a yellow oil (1.5 g, 7.8 mmol, 98%). IR (neat) ν 3030, 2921, 2867, 2360, 1723, 1494, 1451, 1086, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.1 Hz), 7.30 (7H, m), 4.46 (2H, s), 3.55 (2H, m), 2.89 (2H, m), 2.40 (3H, s), 2.04 (1H, m), 1.89 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (0), 140.7 (0), 138.2 (0), 130.0 (1), 128.6 (1), 127.8 (1), 124.3 (1), 73.1 (2), 68.6 (2), 54.5 (2), 22.7 (2), 21.5 (3) ppm.



122 $C_{17}H_{20}OS$ (272)

131 $C_{17}H_{20}O_2S$ (288)

Sulfoxide -131: A solution of *p*-tolyl-3-benzylpropyl ether sulfide **122** (1.0 g, 3.7 mmol) in MeOH (6 mL) was treated with 30% aq. H_2O_2 (1.5 mL, d = 1.11, 0.49 g, 14.7 mmol) and stirred for 18 h at rt. The resulting pale yellow mixture was partitioned between brine (20 mL) and the layers separated. The aqueous phase was extracted with $CHCl_3$ (3 x 6 mL) and the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo* to yield a golden yellow oil which was purified by column chromatography (SiO_2 eluting with 40% EtOAc in hexanes) to afford the title sulfoxide **131** as a yellow oil (0.690 g, 2.39 mmol, 65%). IR (neat) ν 3030, 2921, 2867, 2360, 1723, 1494, 1451, 1086, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.1 Hz), 7.30 (7H, m), 4.46 (2H, s), 3.55 (2H, m), 2.89 (2H, m), 2.40 (3H, s), 2.04 (1H, m), 1.89 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (0), 140.7 (0), 138.2 (0), 130.0 (1), 128.6 (1), 127.8 (1), 124.3 (1), 73.1 (2), 68.6 (2), 54.5 (2), 22.7 (2), 21.5 (3) ppm. ^1H NMR data in agreement with that reported by Linn, J. A.; Kelley, J. L. *Nucleosides and Nucleotides* **1993**, *12*, 199.



123
$C_{12}H_{15}O_2S$ (224)

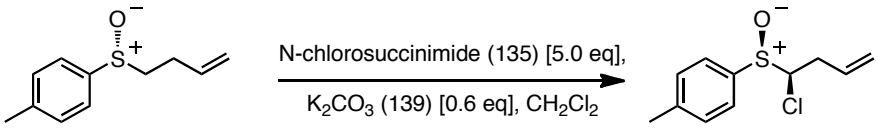
(S_S)-**132**
$C_{12}H_{15}O_3S$ (240)

137d
$C_{12}H_{15}O_4S$ (256)

Sulfoxide -132: A flask was charged w/ the (*S*)-**141** catalyst (158 mg, 0.33 mmol), $VO(acac)_2$ (59.0 mg, 0.22 mmol) followed by CH_2Cl_2 (20 mL). Catalyst complexation occurred while stirring at rt for 2 h as the emerald green solution turned to a caramel brown, after this time sulfide **123** (5.0 g, 22.0 mmol) dissolved in CH_2Cl_2 (15 mL) was added at once and stirred at rt for 30 min. The reaction was then cooled to 2°C (refrigerator) and equilibrated for 30 min before addition of 30% H_2O_2 (d = 1.11, 2.7 mL, 27.0 mmol) at once, then stirred at this temp. until TLC (35%

EtOAc/hexanes) indicated all starting material was consumed, 19.5 h. The dark orange reaction was quenched with 10% $Na_2S_2O_3$ (20 mL), layers shaken and separated, aq. extracted with CH_2Cl_2 (2 x 20 mL), organics combined, brine wash, dried (Na_2SO_4) and conc. *in vacuo* to yield a brown/orange oil (6.4 g) that was purified by column chromatography (SiO_2 eluting with 35% to 75% EtOAc in hexanes) to yield the title sulfoxide (S_S)-**132** (4.3 g, 85%, 17.9 mmol) as a colorless oil: $[\alpha]_D$ = –97.3 (c 1.0, $CHCl_3$); IR (neat) ν 2951, 2880, 1491, 1401, 1135, 1083, 1047, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 8.2), 7.32 (2H, d, *J* = 8.0), 4.96 (1H, t), 3.93 (2H, m), 3.84 (2H, m), 2.90 (2H, m), 2.41 (3H, s), 2.09 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6 (0), 140.6 (0), 130.1 (1), 124.4 (1), 102.9 (1), 65.3 (2), 51.2 (2), 26.4 (2), 21.6 (3) ppm. MS (EI) *m/z* 240 $(M+H)^+$, 242 $(M+H)^+$; HRMS (ES) *m/z* 240.0816 (calcd. for $C_{12}H_{16}O_3S$ 240.08202).

Chiral HPLC analysis of (±)-**132** by [O] of **123** with 30% aq. H_2O_2 in MeOH, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes at 0.5 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(R_S)-**132**) = 25.6 min. t_{ret} [(–)-(S_S)-**132**) = 29.0 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of > 99% ee in favor of the (*S*)-enantiomer.



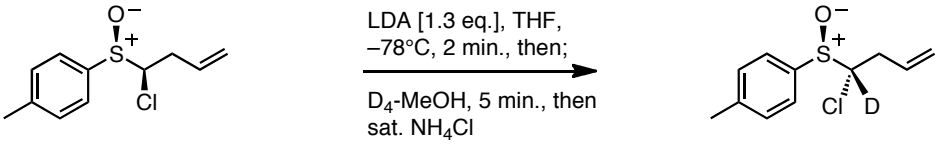
(R_S)-**129**
$C_{12}H_{13}OS$ (194)

(R_S)-**133**
$C_{12}H_{13}OS$ (229)

Chlorosulfoxide -133: A mixture of *p*-tolyl homoallyl sulfoxide (R_S)-**129** (3.26 g, 16.8 mmol, 86.5% ee), K_2CO_3 (1.40 g, 10.1 mmol) and CH_2Cl_2 (22.0 mL, 0.75 M) was stirred vigorously while *N*-chlorosuccinimide (11.3 g, 83.7 mmol) was added in three portions over 45 min. The yellow heterogeneous reaction stirred at rt for 5 days at which time the starting sulfoxide was consumed as determined by TLC (eluting with 25% EtOAc in hexanes). The reaction was diluted with Et_2O (50 mL) and quenched with 4% aq. NaI (100 mL) followed by 10% aq. $Na_2S_2O_3$ (100 mL), layers were separated and aqueous layer washed with $CHCl_3$ (3 x 45 mL), organic layers

combined, washed with brine (55 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange oil (4.27 g) which was purified by column chromatography (eluting with 25% EtOAc in hexanes) to yield the title sulfoxide (R_S)-**133** (1.86 g, 8.16 mmol, 49%, ee 99%); $[\alpha]_D$ –131.2 (c 1.0, $CHCl_3$); IR (neat) ν 3084, 2978, 2930, 2356, 2327, 2235, 1908, 1643, 1596, 1489, 1302, 1180, 1088, 919 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.2), 7.36 (2H, d, *J* = 7.9 Hz), 5.86 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz), 5.23 (2H, dq, *J* = 17.1, 1.6 Hz), 4.55 (1H, dd, *J* = 9.5, 5.3 Hz), 3.04 (1H, m), 2.45 (3H, s), 2.28 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (0), 135.8 (0), 131.7 (1), 129.8 (1), 125.8 (1), 120.1 (2), 75.2 (1), 35.4 (2), 21.7 (3) ppm. HRMS (EI) *m/z* 228.03767 (calcd. for $C_{11}H_{13}{}^{35}ClOS$: 228.03757).

Chiral HPLC analysis of (±)-**133**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 7% *i*-PrOH in hexanes at 0.5 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(S)-**133**] = 10.8 min. t_{ret} [(–)-(R)-**133**] = 12.5 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of 98% ee in favor of (R)-enantiomer.



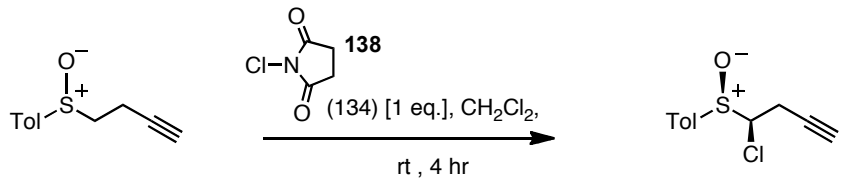
syn-(R_S)-**133**
$C_{12}H_{13}ClOS$ (229)

anti-(R_S)-**133**
$C_{12}H_{12}ClDOS$ (230)

Chlorosulfoxide -133*anti*-D**:** A flask was charged w/ a solution of *syn* chlorosulfoxide (660 mg, 2.9 mmol) followed by THF (0.5 mL) and cooled to –78°C [CO_2/acetone] then equilibrated for 15 min, before addition of LDA [1.2 eq.] down the side of flask over 10 s. Immediately the reaction turned from pale yellow to dark red/orange, after stirring for 2 min, D_4-MeOH (573 mg, 0.65 mL, d = 0.88, 15.8 mmol) was added at once down the side of flask and stirred for an additional 5 min before addition of sat. NH_4Cl (3 mL). The reaction was then removed from the cold bath and warmed to rt over 30 min, then partitioned between EtOAc (4 mL), layers shaken and separated, aq. extracted with EtOAc (3 x 4 mL), organic layers combined, washed with brine, dried (Na_2SO_4) and conc. *in vacuo* to yield an orange oil (529 mg, dr = 8:1, %D = 87) that was further purified by column chromatography (SiO_2 eluting

with a gradient of 7% to 10% EtOAc in hexanes) to yield the title *anti* deuterated chlorosulfoxide (288 mg, 1.3 mmol, 44%, dr = 11:1, %D = 87). The diastereo-enrichment is an artifact resulting from selective fraction isolation during purification. The diastereomers are barely separable and the recorded mass of product is only for the highest enriched fractions that were isolated from semi-prep HPLC OD Daicel column. A mass balance (212 mg, 0.93 mmol, 32%) of *anti*/*syn* chlorosulfoxide mixture was also collected. This sample was combined with other samples of similar quality for later use. $(R_S) = [\alpha]_D$ –95.79 (c 0.95, $CHCl_3$) IR (NEAT) ν 2987, 200, 1915, 1641, 1596, 1492, 1308, 1089, 1058, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* = 8.1), 7.35 (2H, d, *J* = 8.0), 5.87 (1H, dddd, *J* = 16.0, 10.0, 7.6, 6.0), 5.27 (2H, m), 4.4 (1H/D (87%), dd, *J* = 8.9, 3.3), 2.76 (1H, dd, *J* = 14.9, 6.5), 2.75 (1H, dd, *J* = 14.9, 7.1), 2.44 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (0), 137.7 (0), 131.0 (1), 128.6 (1), 129.8 (1), 125.9 (1), 120.2 (2), 35.6 (3), 21.6 (3) ppm. MS (EI) *m*/*z* 231 $(M+H)^+$; HRMS (EI) *m*/*z* 229.0438 (calcd. for $C_{11}H_{12}DClOS$: 229.0490).

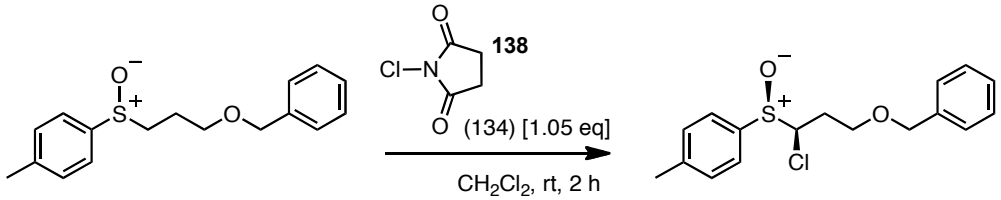
Chiral HPLC analysis of (±)-**133**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 7% *i*-PrOH in hexanes at 0.5 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(S)-$\mathbf{133}_{anti\text{-}D}$] = 10.3 min. t_{ret} [(–)-(R)-$\mathbf{133}_{anti\text{-}D}$] = 12.4 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of 80% ee in favor of (R)-enantiomer.



130 $C_{11}H_{12}OS$ (192) **134** $C_{11}H_{11}ClOS$ (226)

Chlorosulfoxide -134: A flask was charged with a solution of butynyl sulfoxide **130** (350 mg, 1.82 mmol) in CH_2Cl_2 (4 mL) and stirred at rt for 4 h until all starting sulfoxide was consumed as determined by TLC (30% EtOAc in hexanes). The reaction was diluted with H_2O (5 mL) and partitioned in EtOAc (5 mL), the layers shaken and separated, organic layers combined, washed with brine, dried (Na_2SO_4)

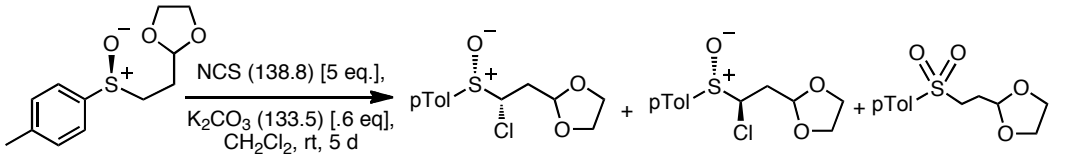
and concentrated *in vacuo* to yield the crude product as an orange oil (430 mg). The crude product was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to afford the title alkyne **134** as a colorless oil (380 mg, 1.7 mmol, 88%); IR (neat) ν 3290, 3223, 1600, 1495, 1421, 1310, 1179, 1310, 1179, 1061, 1013, 927 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.56 (2 H, d, J = 8.1 Hz), 7.35 (2 H, d, J = 8.5 Hz), 4.61 (1 H, dd, J = 8.0, 5.8 Hz), 3.16 (1 H, ddd, J = 8.5, 5.8, 2.6 Hz), 2.52 (1 H, ddd, J = 10.7, 7.9, 2.7 Hz), 2.43 (3 H, s), 2.18 (1 H, t, J = 2.6 Hz) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.0 (0), 135.5 (0), 129.9 (1), 125.6 (1), 77.7 (1), 73.9 (0), 72.6 (1), 22.6 (1), 21.7 (2) ppm. MS (EI) *m/z* 226.0 $(M)^+$, 139.2 (100%), 92.2 (100%), 77.2 (100%); HRMS (EI) *m/z* 226.02221 (calcd. for $C_{11}H_{11}ClOS$: 226.02192).



131 $C_{17}H_{20}O_2S$ (288) *syn*-**135** $C_{17}H_{19}ClO_2S$ (323)

Chlorosulfoxide -*syn*-(**135**)**:** A flask was charged with a solution of sulfoxide (950 mg, 3.29 mmol) in CH_2Cl_2 (5 mL, 0.67 M) and stirred at rt for 2 h until all starting sulfoxide was consumed as determined TLC (25% EtOAc in hexanes). The reaction was diluted with Et_2O (10 mL) and quenched with aq. 4% NaI (10 mL) followed by 10% $Na_2S_2O_3$ (10 mL), layers were shaken and sep., aq. extracted with EtOAc (3 x 5 mL), organic layers combined and washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude product as a yellow-green oil (1.22 g). The crude product was purified by column chromatography (SiO_2 eluting with 25% EtOAc in hexanes) to afford the title α-chlorosulfoxide **135** as a colorless oil (670 mg, 2.1 mmol, 64%) in a *syn*:*anti* diastereomeric ratio (4.4 : 1). NMR data recorded for major *syn* diastereomer. IR (neat) ν 3330, 3063, 3029, 2925, 2860, 2317, 1715, 1602, 1493, 1461, 1361, 1276, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (2 H, d, J = 8.2), 7.32 (2 H, m), 4.80 (1 H, dd, J = 10.1, 3.8), 4.51 (2 H, s), 3.69 (2 H, m), 2.58 (2 H, m), 2.43(3 H, s), 1.88 (1 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6

(0), 129.9 (1), 129.8 (0), 128.7 (1), 128.0 (1), 127.8 (1), 125.7 (0), 74.2 (1), 73.4 (2), 65.8 (2), 32.2 (2), 21.7 (3) ppm. MS (CI) *m/z* 323.0 / 325.0 $(M)^+$, 230.0 (10%), 197 (10%), 140 (15%); HRMS (CI) *m/z* 323.0866 (calcd. for $C_{11}H_{11}{}^{35}ClOS$: 323.0873).



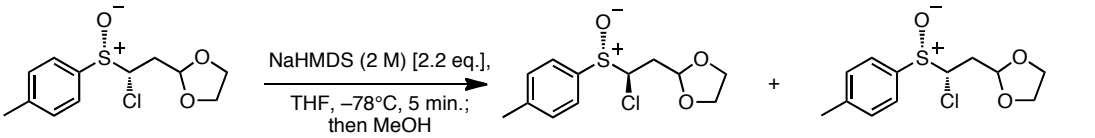
132 (S_S)-$C_{12}H_{15}O_3S$ (240) | *syn*-**136** (S_S)-$C_{12}H_{15}ClO_3S$ (275) | *anti*-**136** (S_S)-$C_{12}H_{15}ClO_3S$ (275) | **137d** $C_{12}H_{15}O_4S$ (256)

dr 5.6 : 1

Acetal -136: A flask was charged w/ a pale yellow solution of the starting enantioenriched sulfoxide (1.7 g, 6.9 mmol) in CH_2Cl_2 (20 mL), stirred to homogeneity for 10 min., before addition of K_2CO_3 (554 mg, 4.1 mmol) followed by *N*-chlorosuccinimide (4.8 g, 35 mmol) and the resulting heterogenous reaction stirred vigorously at rt for 6 d until all starting material was consumed as adjudged by TLC (35% EtOAc in hexanes). The yellow, heterogeneous reaction was quenched with aq. 4% NaI (30 mL), followed by aq. 10% $Na_2S_2O_3$ (40 mL) and the organic layer drawn off. The aq. layer was extracted with CH_2Cl_2 (2 x 25 mL), organic portions combined, brine wash, dried (Na_2SO_4) and conc. *in vacuo* to yield a colorless fluffy solid. The residue was purified by column chromatography (SiO_2 eluting with 60% EtOAc in hexanes) to afford the desired sulfoxide ^{1}H NMR analysis indicated that this material was This solid was comprised of the *syn*:*anti* α-chlorosulfoxide in a 5.6:1 ratio, respectively. A small sample (300 mg) of the crude was recrystallized from MTBE to yield long colorless spars of pure *syn* α-chlorosulfoxide *syn*-(S_S)-**136** (220 mg, 74%, 0.81 mmol); mp 126-128°C (MTBE); $[\alpha]_D$ +108.6 (c 1.15, $CHCl_3$); IR (neat) ν 2957, 2918, 2883, 1595, 1491, 1397, 1144, 1083, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.2), 7.34 (2H, d, *J* = 8.3), 5.14 (1H, dd, *J* = 6.6, 3.3, acetal), 4.78 (1H, dd, *J* = 4.8, 3.4, α-cl), 3.97 (2H, m), 3.89 (2H, m), 2.47 (1H, ddd, *J* = 14.3, 6.6, 6.5), 2.43 (3H, s), 1.91 (1H, ddd, *J* = 3.5, 3.3, 3.3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8 (0), 135.5 (0), 129.8 (1), 126.0 (1), 101.5 (1), 71.4 (1),

65.3 (2), 65.1 (2), 35.4 (2), 21.7 (3) ppm; MS (EI) *m/z* 276 $(M+H)^+$, 274 $(M+H)^+$; HRMS (EI) *m/z* 274.0430 (calcd. for $C_{12}H_{15}O_3ClS$).

Chiral HPLC analysis of (±)-*syn*-**136** generated with NCS (1.0 eq), CH_2Cl_2 at rt for 1 h, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 3% *i*-PrOH in hexanes at 1.1 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(R_S)-**136**) = 29.0 min. t_{ret} [(–)-(S_S)-**136**) = 31.6 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of > 98% ee in favor of the (R)-enantiomer.



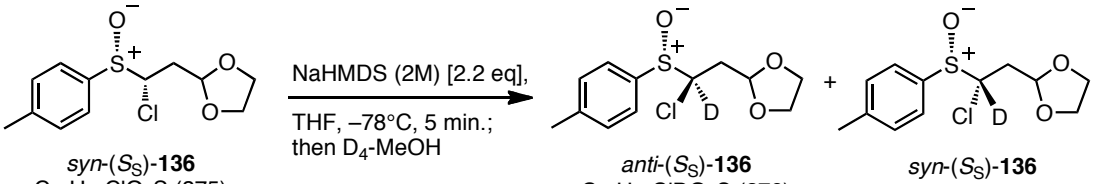
136 (S_S)-$C_{12}H_{15}ClO_3S$ (275) dr 5.6 : 1

136*anti*-H (S_S)-$C_{12}H_{15}ClO_3S$ (275) dr 12.2 : 1

136*anti*-H (S_S)$C_{12}H_{15}ClO_3S$ (275)

anti-**Chlorosulfoxide -136***anti*-H**:** A flask was charged with a sample of *syn*-α-chlorosulfoxide (1.0 g, 3.7 mmol) in THF (12 mL), cooled to –78°C (CO_2/acetone) and equilibrated for 15 min before the addition of NaHMDS (1.8 M in THF, 4.0 mL, 8.0 mmol) down the side of the flask over 30 s. The pale yellow reaction became dark orange and stirred at -78°C for 5 min, before being quenched with MeOH (1 mL) and stirring for additional 2 min., before addition of sat. NH_4Cl (6 mL) followed by removal from the cold bath and warm to rt over 30 min. The dark orange reaction was partitioned between EtOAc, shaken, separated and aq. layer extracted with EtOAc (3 x 6 mL), organics combined, brine wash, dried (Na_2SO_4) and conc. *in vacuo* to yield a colorless solid (1.1 g) that was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title *anti* α-chlorosulfoxide **136**$_{anti\text{-H}}$ (0.88 g, 88%, 3.2 mmol) of *anti:syni* (12.2 : 1). *anti:syni* diastereomers do not separate using this purification technique. A small sample was recyrstallized in MTBE and a single crystal grown. *anti:syn* (17 : 1) mp 86-91°C (MTBE); $[\alpha]_D$ +80.6 (c 1.0, $CHCl_3$); IR (KBR) ν 2964, 2886, 1397, 1135, 1089, 1050, 940, 817 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* = 8.2), 7.34 (2H, d, *J* = 7.9), 5.18 (1H, dd, *J* = 6.4, 3.2, acetal), 4.67 (1H, dd, *J* = 10.1, 3.5, α-cl), 3.92 (2H, m), 2.43 (3H, s), 2.39

(ddd, J = 14.4, 6.4, 6.4), 2.25 (1H, ddd, J = 3.5, 3.3, 3.3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (0), 137.4 (0), 130.0 (1), 126.1 (1), 101.4 (1), 65.3 (2), 65.1 (2), 36.0 (2), 21.7 (3) ppm; MS (EI) *m/z* 276 $(M+H)^+$, 274 $(M+H)^+$; HRMS (EI) *m/z* 274.0430 (calcd. for $C_{12}H_{15}O_3{}^{35}ClS$: 274.0430).



syn-(S_S)-**136**
$C_{12}H_{14}ClO_3S$ (275)

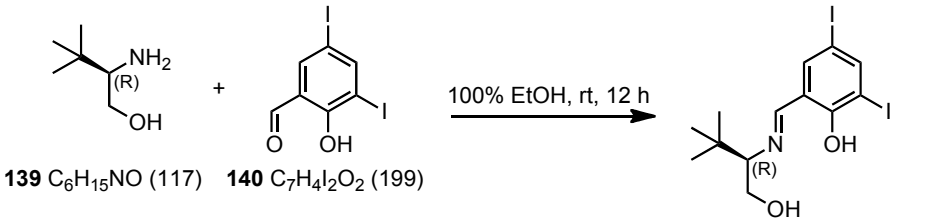
anti-(S_S)-**136**
$C_{12}H_{14}ClDO_3S$ (276)

syn-(S_S)-**136**
$C_{12}H_{14}ClDO_3S$ (276)

dr 12.2 : 1

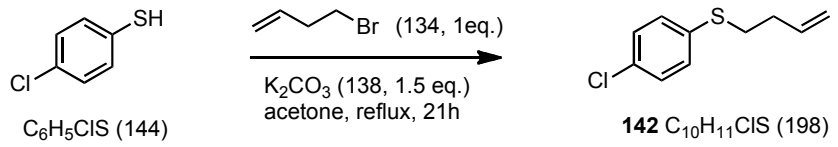
anti-**Chlorosulfoxide -136**$_{anti\text{-}D}$**:** The above sample *syn*-(S_S)-**136** (1.0 g, 3.7 mmol) was taken up in THF (12 mL), cooled to –78°C (CO_2/Acetone) and equilibrated for 15 min before the addition of NaHMDS (1.8 M in THF, 4.0 mL, 8.0 mmol) down the side of the flask over 30 s. The pale yellow reaction became dark orange and stirred at –78°C for 5 min, before being quenched with D_4-MeOH (1 mL) and stirring for additional 2 min, before addition of sat. NH_4Cl (6 mL) followed by removal from the cold bath and warm to rt over 30 min. The dark orange reaction was partitioned between EtOAc, shaken, separated and aq. layer extracted with EtOAc (3 x 6 mL), organics combined, brine wash, dried (Na_2SO_4) and conc. *in vacuo* to yield a colorless solid (1.1 g) that was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title *anti* α-chlorosulfoxide **136**$_{anti\text{-}D}$ (0.88 g, 88%, 3.2 mmol) of *anti:syni* (12.2 : 1). *anti:syni* diastereomers do not separate using this purification technique. A small sample was recyrstallized in MTBE and a single crystal grown (880 mg, 88%, 3.2 mmol): mp 86-87°C (MTBE); $[\alpha]_D^{23}$ = +133.1 (c = 0.96) IR (KBR) n 2961, 2866, 2218, 1595, 1495, 1401, 1138, 1066, 1044, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, d, J = 8.2), 7.34 (2H, d, J = 7.9), 5.17 (1H, dd, J = 6.4, 3.3, acetal), 4.66 (1H, dd, J = 10, 3.5, a-cl), 3.93 (2H, m), 2.43 (3H, s), 2.37 (1H, dd, J = 14.4, 6.4), 2.25 (1H, dd, J = 14.4, 2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (0), 147.3 (0), 129.8 (1), 126.1 (1), 101.4 (1), 65.3 (2), 65.1 (2), 35.8 (2), 21.7 (3) ppm. HRMS (ES) *m/z* 300.0353 (calcd. for $C_{12}H_{14}DO_3Na^{37}ClS$: 300.0361), 298.0377 (calcd. for $C_{12}H_{14}DO_3Na^{35}ClS$: 298.0391).

Chiral HPLC analysis of (±)-*syn*-**136** generated through base mediated epimerization detailed above, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 3% *i*-PrOH in hexanes at 1.1 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(S_S)-**136**$_{anti\text{-}D}$) = 34.3 min. t_{ret} [(–)-(R_S)-**136**$_{anti\text{-}D}$) = 38.9 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of > 97% ee in favor of the (S)-enantiomer.



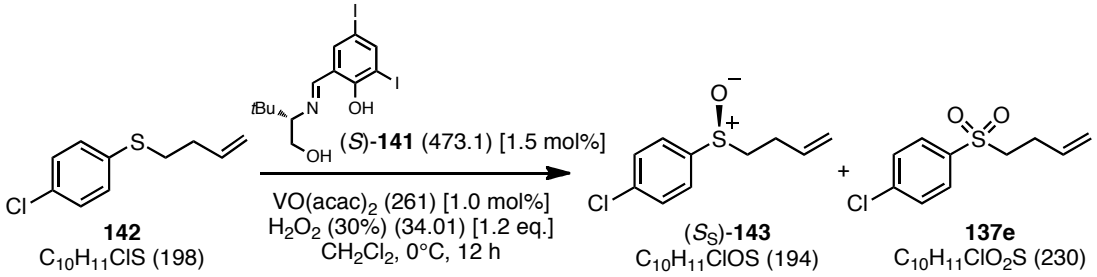
139 $C_6H_{15}NO$ (117) **140** $C_7H_4I_2O_2$ (199) **141** $C_{13}H_{17}I_2NO_2$ (473)

Alcohol -141: The hydrochloride salt of *tert*-leucinol was washed with aq. 10% NaOH (30 mL) and partitioned between EtOAc to obtain the free base. A mixture of the *tert*-leucinol (122 mg, 1.04 mmol), 3,5-diiodosalicylaldehyde (408 mg, 1.09 mmol) and EtOH (5 mL, 0.2 M) was stirred while was added over 2 min. The reaction was then stirred at room temperature for 12 h and the resulting yellow precipitate was collected by vacuum filtration after which time the solvent was removed under reduced pressure from the yellow, heterogeneous reaction and reaction filtered. The yellow solid was recrystallized from cyclohexane, yielding a yellow solid that was filtered and washed with $CHCl_3$ (10 mL) and then the solvent removed to yield the title imine **141** as a yellow solid (402 mg, 0.85 mmol, 82%); m.p. 163-164° C (9:1 hexanes/benzene); $[\alpha]_D^{23}$= –16.6 (c = 0.98, acetone) IR (neat) ν 3338, 2967, 2871, 2356, 2334, 1636, 1448, 1364, 1221, 1136, 1055, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (1H, s), 7.9 (1H, d, *J* = 2.1 Hz), 7.50 (1H, d, *J* = 2.14 Hz), 4.00 (1H, d, *J* = 9.4 Hz), 3.69 (1H, t), 3.09 (1H, dd, *J* = 9.48, 6.85), 0.999 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (0), 164.5 (1), 149.6 (1), 140.8 (1), 118.3 (0), 79.2 (1), 62.2 (2), 33.2 (0), 27.1 (3) ppm. ^{1}H NMR data in agreement with that reported by Legros, J.; Bolm, C.; *Chem. Eur. J.* **2005**, *11*, 1086.



C_6H_5ClS (144) **142** $C_{10}H_{11}ClS$ (198)

Sulfide -142: A mixture of *p*-chlorothio phenol (4.03 g, 27.9 mmol), homoallyl bromide (2.03 mL, d = 1.46, 2.97 g, 22.0 mmol) and K_2CO_3 (4.55 g, 32.9 mmol) in acetone was stirred at reflux for 24 h. The resultant reaction mixture was filtered under vacuum through a pad of celite, the pale yellow filtrate concentrated under reduced pressure, then dissolved in EtOAc (30 mL). The organic phase was washed with aq. NaOH (2 x 25 mL, 4.0 M), then H_2O (40 mL) followed by brine (40 mL) and the organic layer dried (Na_2SO_4) then concentrated *in vacuo* to afford a crude yellow oil (4.91 g) that was purified by column chromatography (eluting with 2% EtOAc in pentane) to afford the title thioether **142** as a yellow oil (3.72 g, 18.7 mmol, 84%). IR (neat) ν 3077, 2972, 2921, 2361, 2334, 1641, 1474, 1388, 1096, 1007, 917, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 8.6 Hz), 7.31 (3H, d, *J* = 10.9 Hz), 5.87 (1H, ddt, J = 17.1, 10.3, 6.7 Hz), 5.12 (1H, dq, *J* = 17.1, 1.6 Hz), 2.99 (2H, t,), 2.41 (2H, q), ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3 (0), 130.7 (1), 129.5 (0), 129.1 (1), 116.6 (2), 33.4 (2), 33.4 (2) ppm. ^1H NMR data in agreement with that reported by Landini, D.; Montanari, F.; Rolla, F. *J. Org. Chem.* **1983**, *48*, 604.



142 $C_{10}H_{11}ClS$ (198) (S_S)-**143** $C_{10}H_{11}ClOS$ (194) **137e** $C_{10}H_{11}ClO_2S$ (230)

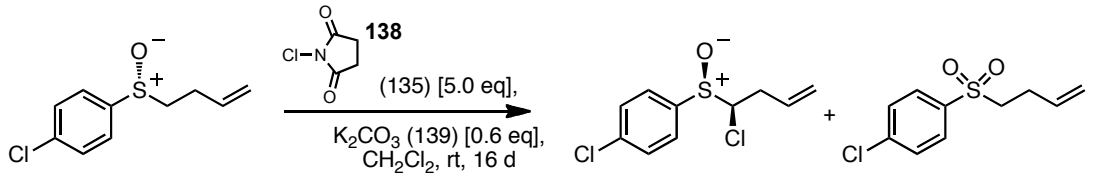
Sulfoxide –(S_S)-(**143**)**:** A mixture of ligand (*S*)-**141** (107 mg, 0.23 mmol) and $VO(acac)_2$ (40.0 mg, 0.150 mmol) in $CHCl_3$ (7 mL) was pre-aged at rt for 2 h. Next was added *p*-chlorophenyl homoallyl sulfide **142** (2.97 g, 15.0 mmol) in $CHCl_3$ (7 mL) to stir for an additional 30 min, after which time the reaction was cooled to 0° C followed by addition of aq. 30% H_2O_2 (612 mg, d = 1.11, 1.84 mL, 17.9 mmol). After 2 h at 0° C the reaction was quenched with aq. 10% $Na_2S_2O_3$ (40 mL) and the layers separated. The aqueous phase was washed with $CHCl_3$ (3 x 20 mL), organic

phase dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown crude oil which was purified by column chromatography (eluting with 5-50% EtOAc in hexanes) to afford the products in order of elution:

Sulfone -137e: (401 mg, 1.74 mmol, 12%) as a bright yellow oil. IR (neat) ν 3084, 2978, 2915, 2364, 2331, 1640, 1577, 1478, 1393, 1313, 1276, 1144, 1085 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 6.7 Hz), 7.56 (2H, d, *J* = 8.2 Hz), 5.72 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz) 5.07 (1H, dq, *J* = 17.1, 1.6 Hz), 3.16 (2H, m), 2.46 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (0), 137.6 (0), 133.6 (1), 129.8 (1), 129.8 (1), 117.5 (2), 55.5 (2), 27.0 (2) ppm. ^1H NMR data in agreement with that reported by Arnone, A.; Bravo, P.; Cavicchio, B.; Frigerio, M.; Viani, F. *Tetrahedron* **1993**, *49*, 6873.

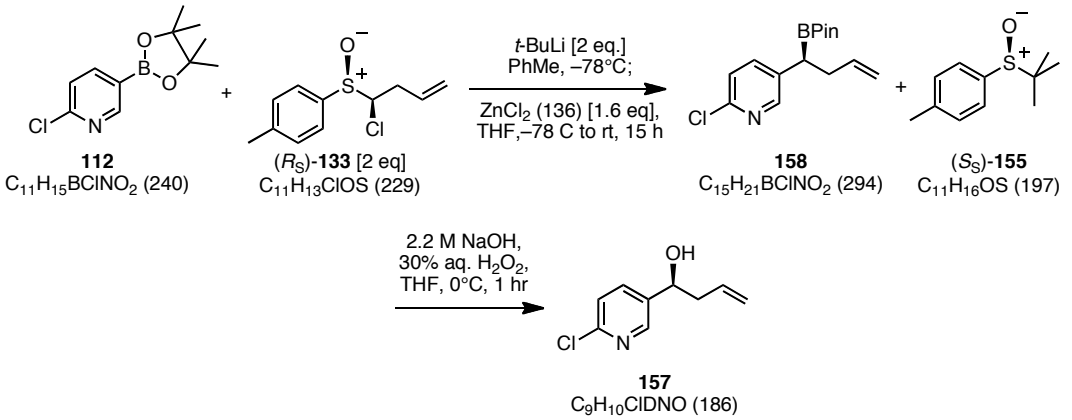
Sulfoxide -(S_S)-**143:** (3.06 g, 14.3 mmol, 88%, 94% ee) bright yellow oil. $[\alpha]_D$ = +118.5 (c = 1.0, $CHCl_3$) IR (neat) ν 3077, 2978, 2912, 2356, 2331, 1640, 1570, 1478, 1386, 1096, 1077, 1044, 1008, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (4H, ddt, *J* = 18.7, 8.8, 2.0 Hz), 5.79 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz), 5.11 (1H, dq, *J* = 17.1, 1.6 Hz), 2.84 (2H, m), 2.52 (1H, m), 2.33 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4 (0), 137.4 (0), 134.8 (1), 129.7 (1), 125.7 (1), 117.5 (2), 56.4 (2), 26.3 (2) ppm.

Chiral HPLC analysis of (±)-**143** by [O] of **142** with 30% aq. H_2O_2 in MeOH, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.0.5 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(R_S)-**143**) = 15.8 min. t_{ret} [(–)-(S_S)-**143**) = 17.4 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of > 95% ee in favor of the (R)-enantiomer.



(R_S)-**143** $C_{10}H_{11}ClOS$ (214) (R_S)-**144** $C_{10}H_{10}Cl_2OS$ (248) **137e** $C_{10}H_{10}ClO_2S$ (229)

Alkene -144: A mixture of *p*-chlorophenyl homoallyl sulfoxide (R_S)-**143** (2.40 g, 11.0 mmol, ee 94%), K_2CO_3 (0.910 g, 6.6 mmol) and CH_2Cl_2 (22.0 mL, 0.75 M) was stirred vigorously while *N*-chlorosuccinimide (7.4 g, 55.0 mmol) was added in two portions over 30 min. The yellow heterogeneous reaction stirred at rt for 9 days at which time the starting sulfoxide was consumed as determined by TLC (eluting with 25% EtOAc in hexanes). The reaction was diluted with Et_2O (50 mL) and quenched with 4% aq. NaI (65 mL) followed by 10% aq. $Na_2S_2O_3$ (65 mL), layers were separated and aqueous layer washed with CH_2Cl_2 (3 x 35 mL), organic layers combined, washed with brine (55 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange oil (2.57 g) which was purified by column chromatography (eluting with 25% EtOAc in hexanes) to yield the title chlorosulfoxide **144**: (1.99 g, 8.02 mmol, 75%, ee > 96%); $[\alpha]_D$ –9.56 (c 0.975, $CHCl_3$); IR (neat) ν 3374, 3082, 2916, 1747, 1649, 1574, 1477, 1392, 1101, 1048, 1016, 919 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.49 (4H, m), 5.79 (1H, ddt, *J* = 16.8, 10.6, 7.2 Hz), 5.18 (1H, dd, *J* = Hz), 5.09 (1H, ddd, *J* = Hz), 4.54 (1H, dd, *J* = 9.4, 4.3 Hz), 2.5 (1H, m), 2.31 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7 (0), 135.8 (0), 131.7 (1), 129.8 (1), 125.8 (1), 120.1 (2), 75.2 (1), 35.4 (2), 21.7 (3) ppm. MS (CI) *m/z* 323.0 / 325.0 $(M)^+$, 233 (40%), 198 (20%), 159 (22%); HRMS (CI) *m/z* 247.8786 (calcd. for $C_{10}H_{10}{}^{35}Cl_2OS$: 247.9830).



112
$C_{11}H_{15}BClNO_2$ (240)

(R_S)-**133** [2 eq]
$C_{11}H_{13}ClOS$ (229)

158
$C_{15}H_{21}BClNO_2$ (294)

(S_S)-**155**
$C_{11}H_{16}OS$ (197)

157
$C_9H_{10}ClDNO$ (186)

Alcohol -158: A flask was charged with homoallyl α-chlorosulfoxide *syn*-(R_S)-**133** (228 mg, 1 mmol), boronic ester **112** (120 mg, 0.5 mmol) and PhMe (1.5 mL), then cooled to –78°C with stirring to equilibrate for 30 min before addition of *t*-BuLi (1.2 mL, 0.8 M in pentane, 1 mmol) down side of flask over 15 s. The reaction became red and slushy and stirred for 30 min at –78°C, after which time a solution of anhydrous $ZnCl_2$ (108 mg, 0.8 mmol) in anhydrous THF (1.5 mL) was added over 10 s and the reaction warmed to rt over 22 h. The dark orange reaction was quenched with sat. NH_4Cl (2 mL), the layers shaken and separated, then the aq. layer extracted with EtOAc (3 x 5 mL), organics combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield an orange oil (275 mg). The residue was purified by column chromatography (SiO_2 eluting with a gradient from 10%-35% EtOAc in hexanes) to yield in order of elution:

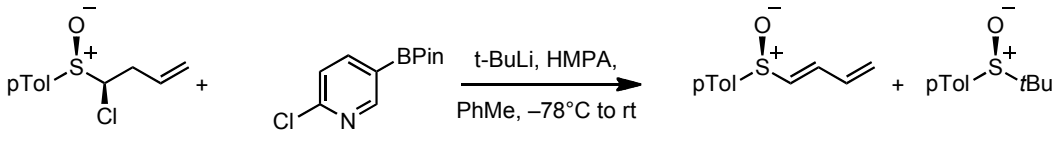
Boronate -158: (12 mg, 0.05 mmol, 10%) $[\alpha]_D$ –9.75 (c 0.40, CH_2Cl_2); IR (neat) ν 3074, 2976, 2921, 2850, 1636, 1587, 1554, 1456, 1353, 1140, 1097, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 2.3 Hz), 7.51 (1H, dd, *J* = 8.2, 2.5 Hz), 7.21 (1H, dd, *J* = 8.2, 0.3 Hz), 5.74 (1H, ddt, *J* = 17.1, 10.3, 3.3 Hz), 4.98 (2H, dq, *J* = 16.4, 2.1 Hz), 3.87 (1H, m), 2.38 (2H, m), 1.20 (12H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (1), 148.7 (0), 139.0 (1), 137.0 (1), 129.5 (0), 123.9 (1), 116.4 (2), 84.1 (0), 36.5 (2), 24.9 (3), 24.8 (3) ppm; MS (EI+) *m/z* 293 $(M+H)^+$; HRMS (EI) *m/z* 293.1358 (calcd. For $C_{15}H_{21}BClNO_2$: 293.1353)

Sulfoxide -155: IR (neat) ν 3019, 2976, 2925, 2863, 2361, 2326, 1590, 1497, 1450, 1361, 1046 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.3 Hz), 7.27 (2H,

d, J = 8.1 Hz), 2.39 (3H, s), 1.15 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6 (0), 136.7 (0), 129.1 (1), 126.3 (1), 55.7 (0), 24.9 (3), 22.8 (3) ppm. ^{1}H NMR data in agreement with that reported by Bohe, L.; Lusinchi, M.; Lusinchi, X. *Tetrahedron* **1999**, *55*, 155.

A small sample of chain extended boronate (6 mg, 0.02 mmol) was taken up in THF (1.5 mL) and cooled to 0°C before addition of 2.2 M NaOH (0.2 mL) followed by 30% aq. H_2O_2 (0.1 mL) and stirred for 1.5 h. The reaction was diluted with 10% aq. $Na_2S_2O_3$ (2 mL) and partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (2 x 5 mL), washed with brined (10 mL), dried Na_2SO_4, conc. *in vacuo* to yield a coloress oil (6 mg) that was purified by column chromatography (SiO_2 eluting with 10% EtOAc in hexanes) to yield the alcohol **157** as a colorless oil: (3 mg, 0.18 mmol, 90%) IR (neat) ν 3074, 2976, 2921, 2850, 1636, 1587, 1554, 1456, 1353, 1140, 1097, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (1H, d, J = 2.3), 7.67 (1H, dd, J = 8.2, 2.4 Hz), 7.32 (1H, d, J = 8.2), 5.78 (ddt, J = 18.7, 8.8, 2.0 Hz), 5.19 (dq, J = 17.1, 1.6 Hz), 4.79 (apparent t, J = 6, 6 Hz), 2.50 (2H, m), 2.15 (1H, b, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9 (1), 148.7 (0), 139.0 (0), 137.0 (1), 129.5 (0), 123.9 (1), 116.4 (2), 84.1 (0), 36.5 (2), 24.9 (3), 24.8 (3) ppm. ^{1}H NMR data in agreement with that reported by Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *57*, 7381.

Chiral HPLC analysis of (±)-**157**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 7.5% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} **157** = 11.7 min., t_{ret} *ent*-**157** = 14.3 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of 0% ee.



(*R*$_S$)-*syn*-**133** $C_{11}H_{11}ClOS$ (228)

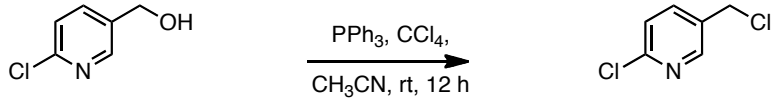
112 $C_{11}H_{15}ClBNO_2$ (239)

359 $C_{11}H_{12}OS$ (192)

(*S*$_S$)-**155** $C_{13}H_{12}OS$ (216)

Diene -359: A flask was charged with a solution of α-chlorosulfoxide *syn*-(R_S)-**133** (73 mg, 0.32 mmol), 2-chloropyridyl boronate **112** (75 mg, 0.32 mmol) in PhMe (1 mL) followed by HMPA (0.37 mL, d = 1.0, 376 mg, 2.1 mmol) this was cooled to –78°C and equilibrated for 15 min before addition of *t*-BuLi (0.86 M in pentane, 0.37 mL, 0.315 mmol) immediately generated a dark red/orange color that persisted for 45 min as the reaction warmed to rt over 12 h. After this time the black reaction was diluted with H_2O (3 mL) and partitioned in Et_2O (5 mL) aq layer extracted with Et_2O (3 x 6 mL), organics washed with brine (15 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield the crude product (54 mg) as a viscous dark orange oil. This was purified by column chromatography (SiO_2 eluting with 10% EtOAc in hexanes) to yield the title diene **204** as a colorless oil as a mixture of Z/E isomers (0.099 mmol, 19 mg, 31%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 8.1 Hz), 7.28 (2H, d, *J* = 8.26 Hz), 6.98 (1H, dd, *J* = 15.3, 10.2 Hz), 6.41 (dt, *J* = 16.0, 10.6 Hz), 6.42(d, *J* = 15.4 Hz), 5.54 (d, *J* = 17.0 Hz), 5.40 (1H, d, *J* = 10.8 Hz), 2.39 (3H, s) ppm ^{1}H NMR data in agreement with that reported by Mikolajczyk, M.; Perlikowska, W.; Omelanczuk, J.; Cristau, H.-J.; Perraud-Darcy, A. *J. Org. Chem.* **1998**, *63*, 9716.

Sulfoxide (S_S)-**155:** (0.22 mmol, 43 mg, 69%).

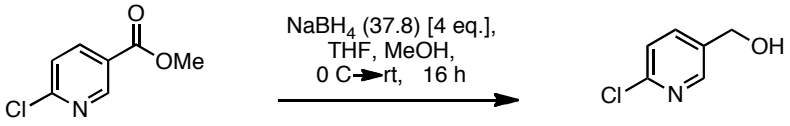


160b
C_6H_6ClNO (142)

159
$C_6H_5Cl_2N$ (162)

Methylchloride -159: A flask was charged with 2-chloro-5-methylcarbinol pyridine **160b** (260 mg, 1.8 mmol), PPh_3 (910 mg, 3.5 mmol) in CH_3CN (5 mL) stirred for 5 min then addition of CCl_4 (2 mL) over 1 min. The reaction was stirred at rt for 15 h and then partitioned in Et_2O (15 mL), washed with H_2O (20 mL), then brine (20 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield a colorless solid (1.2 g) which was purified by column chromatography (SiO_2 eluting with 10% EtOAc in hexanes) to afford the title chloride **159** as a colorless solid (310 mg, 1.75 mmol, 95%) m.p. 40° C. IR (neat) ν 2960, 2933, 2844, 1458, 1380, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, d, *J* = 2.3 Hz), 7.71 (1H, dd, *J* = 8.2, 2.5 Hz), 7.34 (1H, d, *J* = 8.2), 4.56 (2H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (0), 149.5 (1), 139.2 (1), 132.1 (0),

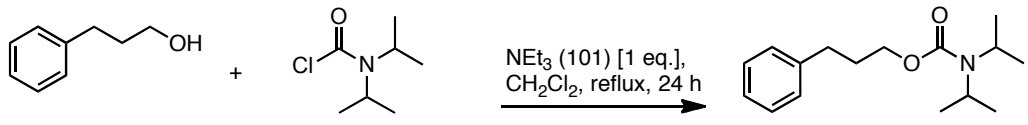
124.6 (0), 42.3 (2) ppm. ^{1}H NMR data in agreement with that reported by Cananal-Duvillard, I.; Berrien, J.-F. *Heterocyclic Communications* **1999**, *5*, 257.



160
$C_7H_6ClNO_2$ (172)

160b
C_6H_6ClNO (142)

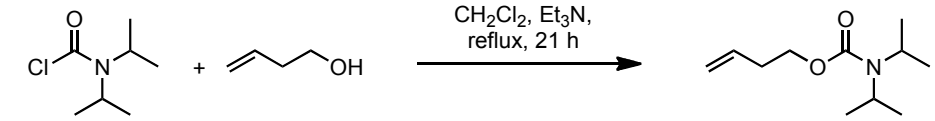
Pyridyl alcohol -160b: A flask was charged with 6-chloro-3-carbomethoxy pyridine (0.5 g, 2.91 mmol) and anhydrous THF (7 mL) and cooled to –5° C with stirring for 30 min, after which time sodium borohydride (0.44g, 11.6 mmol) was added at once, the reaction changing from colorless to pale yellow. This mixture was stirred for 30 min before dropwise addition of MeOH (2.5 mL, d = 0.79, 1.98 g, 61.6 mmol) resulting in a color change to vibrant yellow-lime green. The reaction warmed to rt over 20 h, after which time it was quenched with HCl (4 mL, 1M) in 1 mL increments where noticeable color changes to cranberry, bright yellow and finally to pale yellow occurred after each subsequent addition. The mixture was filtered through Celite, the filtrate concentrated, then the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL), yellow organic layers combined, washed with brine (20 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield a yellow residue (0.37g) which was purified by column chromatography (SiO_2 eluting with 12% EtOAc in hexanes) to afford the title alcohol as a yellow crystalline oil (0.30 g, 2.1 mmol, 78%) IR (neat) ν 3382, 1642, 1565, 1458, 1380, 1280, 1105, 1028, 820 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, dd, *J* = 2.5, .54 Hz), 7.68 (1H, dd, *J* = 8.2, 2.4 Hz), 7.31 (1H, d, *J* = 8.2), 4.71 (2H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (0), 148.3 (1), 137.9 (1), 135.5 (0), 124.4 (1), 61.9 (2) ppm. ^{1}H NMR data in agreement with that reported by Lee, C.-L.. K.; Loh, T.-P. *Org. Lett.* **2007**, *7*, 2965.



$C_9H_{12}O$ (136) $C_7H_{14}ClNO$(164) [1.05 eq]

167
$C_{16}H_{25}NO_2$ (263)

Phenyl carbamate -167: A flask was charged with carbamoyl chloride (2.0 g, 12.2 mmol), 3-phenyl propanol (1.63 mL, d = 1.00, 1.63 g, 11.9 mmol) followed by CH_2Cl_2 (18 mL, 0.57 M), stirred for 5 min at rt then addition of NEt_3 (1.71 mL, d = 0.72, 1.23 g, 12.2 mmol) at once. The reaction mixture was heated and held at reflux for 24 h. The pale rose colored reaction was quenched with H_2O (25 mL), layers separated, aqueous layer extracted with CH_2Cl_2 (3x20 mL), organic layers combined, washed with brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield a rose colored oil (3.22 g) that was purified by column chromatography (SiO_2 eluting with 10% EtOAc in hexanes) to afford the title carbamate as a colorless oil with a pleasant odor (2.72 g, 10.3 mmol, 85%); IR (neat) ν 3029, 2967, 2356, 2334, 1691, 1438, 1316, 1294, 1217, 1132, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (5H, m), 4.12 (2H, t, *J* = 6.5 Hz), 2.72 (2H, t, *J* = 7.8), 1.98 (2H, m), 1.23 (12H, d, *J* = 6.8) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0 (0), 141.7 (1), 128.6 (1), 128.5 (1), 126.1 (1), 64.2 (2), 46.1 (1), 32.7 (2), 31.1 (2), 21.2 (1) ppm. ^1H NMR data in agreement with that reported by Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *47*, 2791.

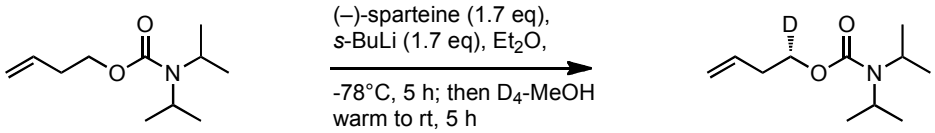


$C_7H_{14}ClNO$ (163) C_4H_8O (72)

168
$C_{11}H_{21}NO_2$ (199)

Alkenyl carbamate -168: A mixture of diisopropyl carbamoylchloride (2.49 g, 15.3 mmol), Et_3N (2.17 mL, d = 0.72, 1.57 g, 15.5 mmol) and $CHCl_2$ (26.0 mL, 0.59 M) were vigorously stirred to homogeneity at which time 4-buten-1-ol (1.34 mL, d = 0.83, 1.11 g, 15.5 mmol) was added at once. Reaction was taken to reflux and maintained at that temperature for 21 h until the carbamate was consumed as judged by TLC (eluting 10% EtOAc in hexanes). Reaction was partitioned with H_2O (45 mL) and the layers separated. Aqueous layer washed with CH_2Cl_2 (3 x 40 mL), organic layers combined and washed with brine (50 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield a colorless oil (3.12 g) which was purified by column chromatography (eluting with 10% EtOAc in hexanes) to yield the title carbamate

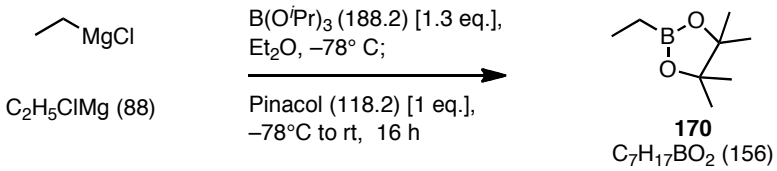
(2.33 g, 11.7 mmol, 77%). IR (neat) ν 3077, 2968, 2357, 2338, 1696, 1641, 1439, 1310, 1287, 1131, 1069, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz), 5.09 (1H, dq, *J* = 17.1, 1.6 Hz), 5.07 (1H, dq, *J* = 10.1, 1.34 Hz), 4.14 (2H, t, *J* = 6.6), 4.05-3.65 (2H, m, br), 2.40 (2H, tq, *J* = 6.6, 1.3 Hz), 1.19 (12H, d, *J* = 6.84) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (0), 135.0 (1), 117.0 (2), 63.9 (2), 45.7 (1), 33.8 (2), 21.2 (3) ppm. ^1H NMR data in agreement with that reported by Hoppe, D.; Hanko, R.; Borenneke, A.; Lichtenberg, F. *Angew. Chem. Int. Ed.* **1981**, *93*, 1106.



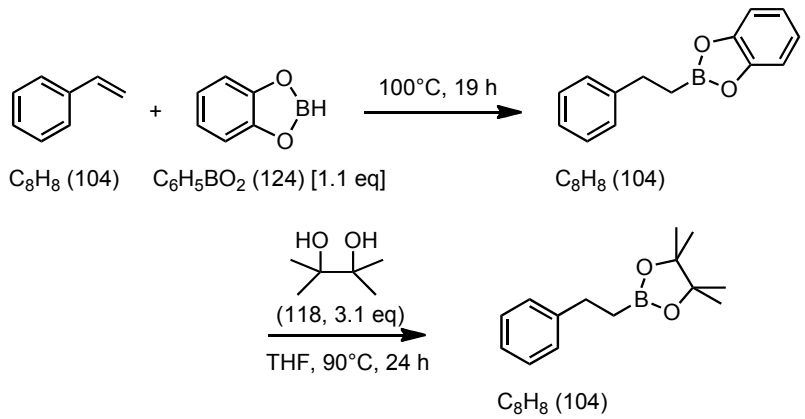
168
$C_{11}H_{21}NO_2$ (199)

D-168
$C_{11}H_{21}DNO_2$ (200)

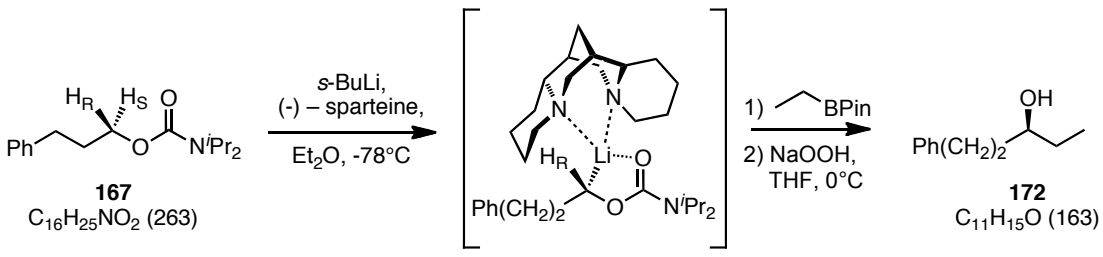
Deuterated carbamate -D-168: A flask was flame dried under Ar and charged with a solution of freshly distilled (–)-sparteine (399 mg, d= 1.02, 0.39 mL, 1.7 mmol) in Et_2O (3 mL) followed before cooling -78°C to equilibrate for 10 min before addition of *s*-BuLi (0.48 M in cyclohexane, 3.5 mL, 1.7 mmol) downside of flask over 2 min. Following a period of 20 min a solution of alkene **168** (199 mg, 1.0 mmol) in Et_2O (1 mL) was added downside of flask over 1 min and stirred at –78°C for 5 h. After this time an entire D_4-MeOH ampule (0.75 mL) was added downside of flask and the reaction allowed to warm to rt over 2 h. The reaction progressed to a beige color and was quenched with sat. NH_4Cl (5 mL) and partitioned in EtOAc (10 mL), brine wash and drying (Na_2SO_4), crude conc. *in vacuo* to yield a the crude product as a pale yellow oil (120 mg) that was isolated and required no further purification. Deuterium level was determined through ^1H NMR analysis of the 4.14 ppm signal. IR (neat) ν 3077, 2968, 2357, 2338, 1696, 1641, 1439, 1310, 1287, 1131, 1069, 913 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz), 5.09 (1H, dq, *J* = 17.1, 1.6 Hz), 5.07 (1H, dq, *J* = 10.1, 1.34 Hz), 4.14 (1.1H, 1D, m), 4.05-3.65 (2H, m, br), 2.39 (2H, q), 1.19 (12H, d, *J* = 6.84) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (0), 135.0 (1), 117.0 (2), 63.9 (2), 45.7 (1), 33.8 (2), 21.2 (3) ppm.



Boronate -170: A flask was charged with EtMgCl (7.5 mL, 1.63 M in THF, 1.1 g, 12.2 mmol) and anhydrous Et_2O (24 mL) and cooled to –78° C with stirring for 90 min. To this dark grey solution was added triisopropyl borate (neat, 4.2 mL, d = 0.82, 3.44 g, 18.3 mmol) down the side of the flask over 5 min, then stirred for an additional 1 h at –78°C at which time the grey opaque reaction was allowed to warm to rt over 90 min. Next, a solution of pinacol (1.51 g, 12.8 mmol) in Et_2O (6 mL, 2.1 M) was added dropwise resulting in the reaction color changing from grey to colorless, this reaction stirred at rt for 12 h. The reaction was quenched with 5% H_2SO_4 (50 mL) resulting in a biphasic system, the layers separated and the aqueous layer was extracted with Et_2O (3 x 20 mL), organic layers combined, washed with brine (25 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield 1.9 g of a pale yellow oil that was purified by column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to afford the title boronic ester as a colorless oil with a pungent odor (1.4 g, 8.97 mmol, 72%) IR (neat) ν 2960, 2933, 2844, 1458, 1380, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (12H, s), 0.94 (3H, t, J = 7.7 Hz), 0.75 (2H, q, J = 7.2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.0 (0), 25.0 (3), 7.8 (3), 4.5 (2, br) ppm. ^1H NMR data in agreement with that reported by Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *47*, 2791.

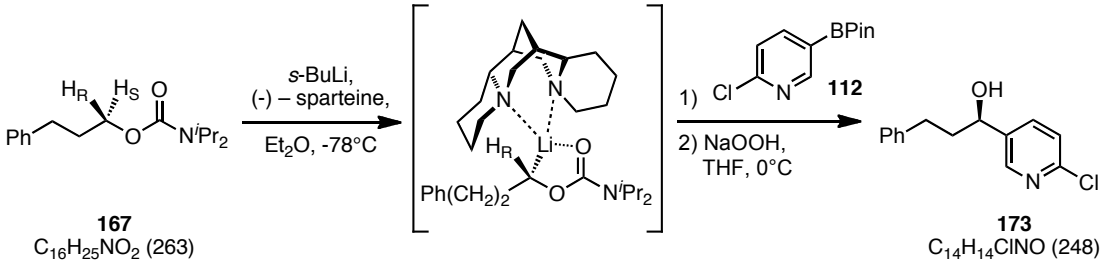


Boronate -171: A 100 mL RB flask was flame dried under Ar then charged with catechol borane (7.2 mL, d=1.13, 8.1 g, 68 mmol) followed by styrene (7.0 mL, d=0.91, 6.4 g, 61 mmol) and heated to 95°C. The resulting pale yellow mixture stirred for 19 h at 95°C during which time the color changed to brown and the reaction cooled to rt, diluted with dry THF (40 mL) and then transferred by cannula to a second flask charged with a solution of pinacol (22 g, 192 mmol) in THF (10 mL) and set to reflux for 24 h. The reaction was cooled to rt and was concentrated *in vacuo* to yield a colorless oil that was partitioned in EtOAc (100 mL) and washed with H_2O (5x50 mL), then brine (75 mL), dried Na_2SO_4 and concentrated *in vacuo*. The crude residue (25.2 g) was purified by column chromatography (SiO_2 eluting with 20% EtOAc in Hexanes) to afford a clear colorless residue (10.2 g, 44 mmol, 72%) IR (neat) ν 3008, 2924, 1592, 1299, 1147, 625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.4 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 3.12 (3H, s), 2.45 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (0), 137.9 (0), 130.1 (3), 127.6 (3), 44.8 (1), 21.4 (1) ppm. ^1H NMR data in agreement with that reported by Blakemore, P. R.; Burge, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3068.



Alcohol -172: A flask was flame dried under Ar and charged with a solution of freshly distilled (–)-sparteine (183 mg, d= 1.02, 0.191 mL, 0.783 mmol) in Et_2O (1.5

mL) followed before cooling –78°C to equilibrate for 10 minutes before addition of *s*-BuLi (0.48 M in cyclohexane, 1.63 mL, 0.783 mmol) downside of flask over 2 min. Following a period of 20 min a solution of carbamate **167** (265 mg, 0.783 mmol) in Et_2O (1 mL) was added downside of flask over 1 min and stirred at –78°C for 5 h. After this time, a solution of 2-chloropyridine-5-pinacolboronate (110 mg, 0.46 mmol) in Et_2O (1 mL) was added downside of flask and stirred at –78°C for 30 min before addition of freshly prepared $MgBr_2$ in Et_2O (2 mL), warmed to rt then refluxed over 12 h. The reaction was then cooled to 0°C followed by addition of 2M NaOH (2.5 mL) and 30% aq. H_2O_2 stirred for 1 hour then quenched with 10% $Na_2S_2O_3$ (5 mL) partitioned in EtOAc (10 mL), then brine wash (15 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield pale yellow oil (203 mg) that was purified by column chromatography (SiO_2) eluting with 25% EtOAc in hexanes to yield the product as a colorless solid (17 mg, 0.068 mmol, 15%) m.p. 34-35°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, m), 7.20 (3H, m), 3.56 (1H, tt, *J* = 8.0, 4.4 Hz), 2.79 (1H, ddd, *J* = 13.3, 9.6, 5.6 Hz), 2.67 (1H, ddd, *J* = 13.4, 9.8, 6.9 Hz), 1.80 (1H, m), 1.75 (1H, m), 1.55 (1H, m), 1.48 (1H, m), 0.95 (3H, t, *J* = 7 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2 (0), 128.8 (1), 128.6 (1), 125.9 (1), 72.3 (1), 38.8 (2), 32.2 (1), 30.5 (1), 9.9 (3) ppm. ^{1}H NMR data in agreement with that reported by Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *47*, 2791.

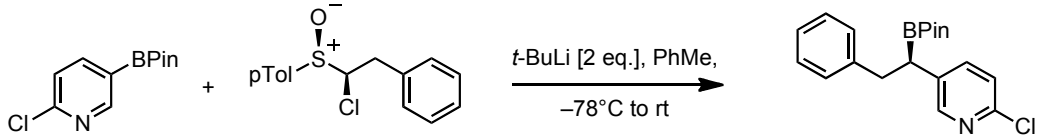


167
$C_{16}H_{25}NO_2$ (263)

173
$C_{14}H_{14}ClNO$ (248)

Pyridyl alcohol -173: A flask was flame dried under Ar and charged with a solution of freshly distilled (–)-sparteine (183 mg, d= 1.02, 0.18 mL, 0.78 mmol) in Et_2O (3 mL) followed before cooling –78°C to equilibrate for 10 min before addition of *s*-BuLi (0.48 M in cyclohexane, 1.63 mL, 0.78 mmol) downside of flask over 2 min. Following a period of 20 min a solution of carbamate **167** (206 mg, 0.78 mmol) in

Et_2O (2.5 mL) was added downside of flask over 1 min and stirred at –78°C for 5 h. After this time a solution of 2-chloropyridyl pinacol boronate **112** (110 mg, 0.46 mmol) in Et_2O (1 mL) was added downside of flask and stirred at –78°C for 30 min before addition of freshly prepared $MgBr_2$ in Et_2O (3 mL), warmed to rt then refluxed over 12 h. The reaction was then cooled to 0°C followed by addition of 2M NaOH (2 mL) and 30% aq. H_2O_2 stirred for 1 hour then quenched with 10% $Na_2S_2O_3$ (5 mL) partitioned in EtOAc (10 mL), then brine wash (15 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield pale yellow oil (203 mg) that was purified by column chromatography (SiO_2) eluting with 25% EtOAc in hexanes to yield the product as a colorless solid **173** (17 mg, 0.61 mmol, 15%); m.p. 35-36°C; $[\alpha]_D^{23}$= +24.2 (c = 0.95, CH_2Cl_2); IR (neat) ν 3077, 2968, 2357, 2338, 1696, 1641, 1439, 1310, 1287, 1131, 1069, 913 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ .32 (1H, d, *J* = 2.3 Hz), 7.67 (1H, dd, *J* = 8.2, 2.4 Hz), 7.29 (4H, m), 7.19 (4H, m), 4.74 (1H, dd, *J* = 7.9, 5.1), 2.73 (2H, m), 2.12 (1H, m), 2.01 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7 (0), 147.8 (1), 141.1 (0), 139.0 (0), 136.8 (1), 128.7 (1), 128.6 (1), 126.3 (1), 124.4 (1), 70.9 (1), 40.6 (2), 31.9 (2) ppm.



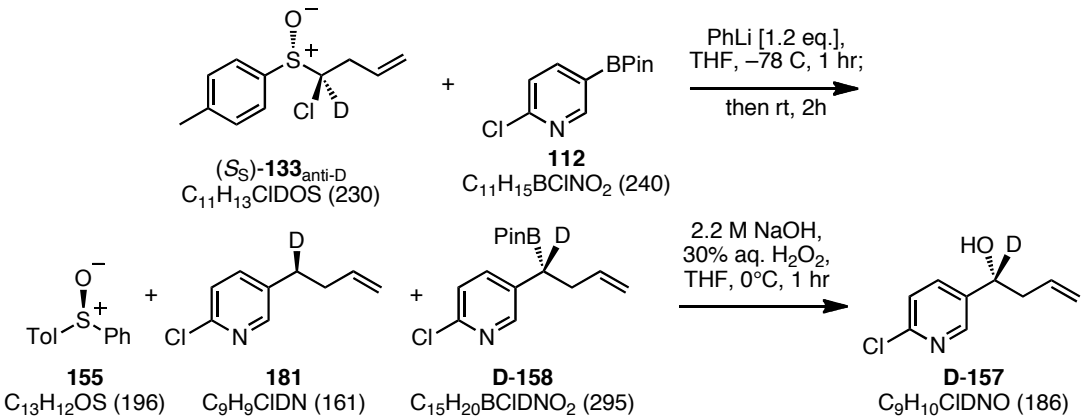
112
$C_{11}H_{15}BClO_2$ (239)

(R_S)-**176**
$C_{15}H_{15}ClOS$ (279)

179
$C_{17}H_{24}BClNO_2$ (321)

Pyridyl boronate -179: A flask was charged with a solution of 2-chloropyridyl boronate **112** (100 mg, 0.33 mmol), α-chlorosulfoxide (R_S)-**176** (173 mg, 0.66 mmol) in PhMe (3 mL, 0.11 M in boronate) and cooled to –78°C and equilibrated for 20 min before addition of *t*-BuLi (1.27 M in pentane, 0.52 mL, 0.66 mmol) that resulted in the reaction turning to a light orange color and formation of a globular insoluble mass that slowly dissolved as the reaction warmed to rt overnight. The orange reaction was diluted with sat. NH_4Cl (5 mL), partitioned in EtOAc (5 mL), the aq. layer extracted with EtOAc (3 x 5 mL), washed with brine (20 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield the crude product as an orange/brown oil (335 mg) that was purified by column chromatography (SiO_2 eluting with 10% EtOAc in hexanes) to yield the

title boronate **179** as a colorless oil (36 mg, 0.11 mmol, 34%) IR (neat) ν 3077, 2968, 2357, 2338, 1696, 1641, 1439, 1310, 1287, 1131, 1069, 913 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, d, *J* = 3.0 Hz), 7.52 (1H, dd, *J* = 7.5, 3.2 Hz), 7.41-7.12 (6H, m), 3.19 (1H, dd, *J* = 13.8, 9.6 Hz), 2.98 (1H, dd, *J* = Hz), 2.71 (1H, apparent t), 1.21 (12H, d, *J* = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4 (0), 128.8 (1), 128.6 (1), 125.9 (0), 72.9 (1), 38.9 (2), 32.3 (2), 30.5 (2), 9.9 (3) ppm.



Alkene -D-158: A flask was charged with homoallyl α-chlorosulfoxide (S_S)-**133**$_{anti\text{-}D}$ (165 mg, 0.72 mmol), followed by 2-chloro-5-pinacol boronic ester **112** (143 mg, 0.59 mmol), then THF (4 mL). This solution was stirred and cooled to –78°C [CO_2/acetone] and equilibrated for 15 min before addition of PhLi (1.58 M in *n*-Bu_2O, 0.46 mL, 0.72 mmol). PhLi added dropwise over 10 seconds and the reaction stirred at –78°C for 1 h, during which time the reaction progressed to a pale orange color. Following one hour, the reaction was removed from the cold bath and warmed to rt over 2 h. After approximately 20 min the reaction became dark orange/red and remained this color for the duration of reaction. The reaction as then quenched with sat. NH_4Cl (3 mL) then partitioned immediately in EtOAc (4 mL), layers were shaken and separated and the aq. layer was extracted with EtOAc (3 x 5 mL), organic layers combined, washed with brine (15 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a crude dark orange oil (500 mg). The crude sample was further purified by column chromatography (SiO_2 eluting with a gradient of 5% to 10% EtOAc in hexanes) to afford the following compounds in order of elution:

Alkene -181: colorless oil, 20 mg, 0.12 mmol, 25%. $[\alpha]_D$ + 0.00 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 2.2), 7.46 (1H, dd, *J* = 8.2, 2.5 Hz), 7.24 (1H, d, *J* = 8.2), 5.79 (1H, dddd, *J* = 16.0, 10.0, 7.6, 6.0), 5.02 (2H, m), 2.67 (1H, dd, *J* = 15.1, 7.3), 2.35 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (1), 149.3 (0), 139.0 (1), 136.9 (1), 136.0 (0), 124.0 (1), 116.3 (1), 35.1 (2), 31.6 (2) ppm; MS (EI) *m/z* 169 $(M+H)^+$; HRMS (EI) *m/z* 168.0565 (calcd. for C_9H_9DClNO: 168.0564).

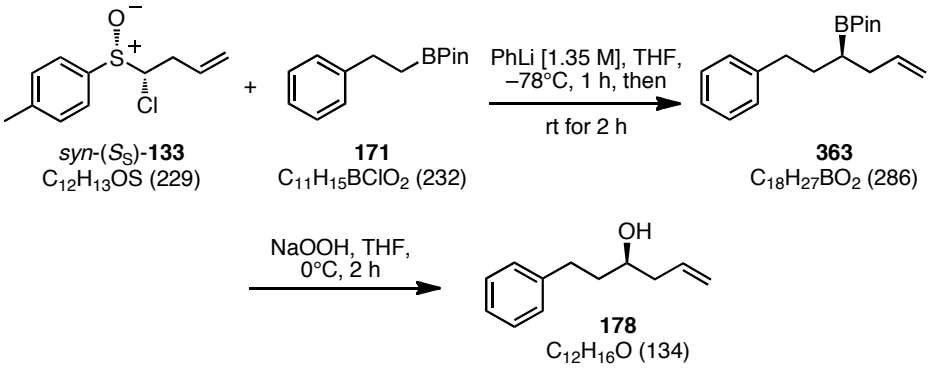
Boronate -D-158: colorless oil, 50 mg, 0.17 mmol, 29%. $[\alpha]_D$ + 9.20 (c 0.500, CH_2Cl_2); IR (neat) ν 3074, 2976, 2921, 2850, 1636, 1587, 1554, 1456, 1353, 1140, 1097, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* = 2.2), 7.51 (1H, dd, *J* = 8.2, 2.5 Hz), 5.75 (1H, ddd, *J* = 16.0, 10.0, 6.0 Hz), 4.98 (2H, m), 2.56 (1H, dd, *J* = 14.2, 6.8), 2.36 (1H, dd, *J* = 13.7, 6.3 Hz), 1.20 (12H, d, *J* = 3.3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (1), 148.5 (0), 138.8 (1), 136.9 (0), 136.8 (1), 123.8 (1), 116.2 (2), 83.9 (0), 36.3 (2), 24.7 (3) ppm.

Sulfoxide -155: (104 mg, 67%, 0.48 mmol); IR (NEAT) ν 3051, 2915, 1595, 1488, 1443, 1093, 1041, 804, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.25 (9 H, m), 2.36 (3 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0 (0), 142.7 (0), 141.8 (0), 131.2 (0), 130.2 (1), 129.4 (1), 125.2 (1), 125.0 (1), 124.9 (1), 21.6 (3) ppm. ^1H NMR data in agreement with that reported by Zhengxu, H.; Dhileepkumar, K.; Grover, P.; Wilkinson, S.; Fang, K.; Xiping, S.; Zhi-Hui, L.; Magiera, D.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 2032.

A small sample of homologated boronate (5 mg, 0.017 mmol) was taken up in THF (1 mL) and cooled to 0°C before addition of 2.2 M NaOH (0.2 mL) followed by 30% aq. H_2O_2 (0.1 mL) stirred and warmed to rt over 1.5 hours. The reaction was quenched with 10% $Na_2S_2O_3$ (1 mL), partitioned in EtOAc (3 mL), aq. layer extracted with EtOAc (2 x 5 mL), washed with brine (15 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield a crude product (6 mg) that was purified by column chromatography (SiO_2 eluting with 15% EtOAc in hexanes) to yield the title alcohol **D-157**: (3 mg, 0.015 mmol, 88%) as a colorless oil: $[\alpha]_D$ = + 0.00 (c 0.30, $CHCl_3$); IR (neat) ν 3360, 2856, 2932, 2730, 1623, 1534, 1554, 1410, 1290, 1180, 1015, 789 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 2.2), 7.79 (1H, dd, *J* = 8.2, 2.5 Hz), 7.20 (1H, d, *J* = 8.2 Hz), 5.79 (2H, ddd, *J* = *J* = 15.9, 10.4, 6.3 Hz), 5.17 (2H, dd, *J* = 15.9, 10.2 Hz), 4.70 (1H, m (H/D) 14.5%), 2.53 (1H, dd, *J* =), 2.48 (1H, dd, *J* =), 2.15 (1H, d, *J* = Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8 (1), 138.1 (0), 136.6 (1), 133.3 (1), 124.3 (1), 120.0 (2), 70.4 (2), 44.0 (2), 36.5 (2) ppm.

Chiral HPLC analysis of (±)-**157**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 5% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} **157**] = 11.7 min., t_{ret} *ent*-**157**] = 14.3 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of 0% ee.



syn-(S_S)-**133**
$C_{12}H_{13}OS$ (229)

171
$C_{11}H_{15}BClO_2$ (232)

363
$C_{18}H_{27}BO_2$ (286)

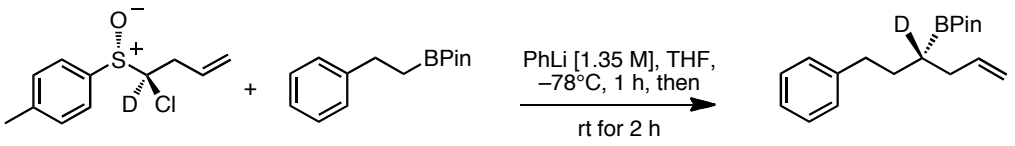
178
$C_{12}H_{16}O$ (134)

Alcohol -178: A flask was charged w/ a solution of *syn*-(R_S)-**133** (120 mg, 0.525 mmol) in THF (2.5 mL) followed by phenethyl pinacolboronate **171** (101 mg, 0.44 mmol) and then cooled to –78°C [CO_2/acetone] allowing thermal equilibration for 15 min before addition of PhLi (0.39 mmol, 1.35 M in *n*-Bu_2O) which was added dropwise over 10 s when a noticeable orange color appeared. The reaction stirred at this temperature for 30 min before being removed to warm to rt over 2.5 h. After approximately 25 min at rt, the reaction became dark red/orange and maintained this color throughout the rest of the reaction. After the allotted time the reaction was quenched with sat. NH_4Cl (3 mL), the layers were shaken and separated and the aq. was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine and dried over (Na_2SO_4) and conc. *in vacuo* to yield a dark orange oil (231 mg) that was purified by column chromatography (SiO_2 eluting with a gradient of 2% to 5% EtOAc in hexanes) to yield the title boronate **363** as a colorless oil (42 mg,

0.15 mmol, 34%) $[\alpha]_D$ = +6.42 (c = 0.8, $CHCl_3$); IR (NEAT) ν 3061, 3025, 2980, 2918, 2857, 1644, 1602, 1498, 1449, 1371, 1310, 1141, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, m), 7.16 (3H, m), 5.81 (1H, dddd, *J* = 16.0, 10.0, 7.6, 6.0), 4.99 (2H, ddd, *J* = 12.8, 7.3, 0.9), 2.61 (2H, m), 2.20 (2H, m), 1.80-1.62 (2H, m), 1.26 (3H, s), 1.15 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2 (0), 134.8 (1), 128.6 (1), 128.6 (1), 126.0 (1), 118.5 (2), 70.1 (1), 42.3 (2), 38.6 (2), 32.2 (2), 25.1 (3), 25.0 (3), 25.0 (3), 25.0 (3) ppm. MS (EI) *m/z* 169 $(M+H)^+$; HRMS (EI) *m/z* 286.2117 (calcd. for $C_{18}H_{27}BO_2$: 286.2104).

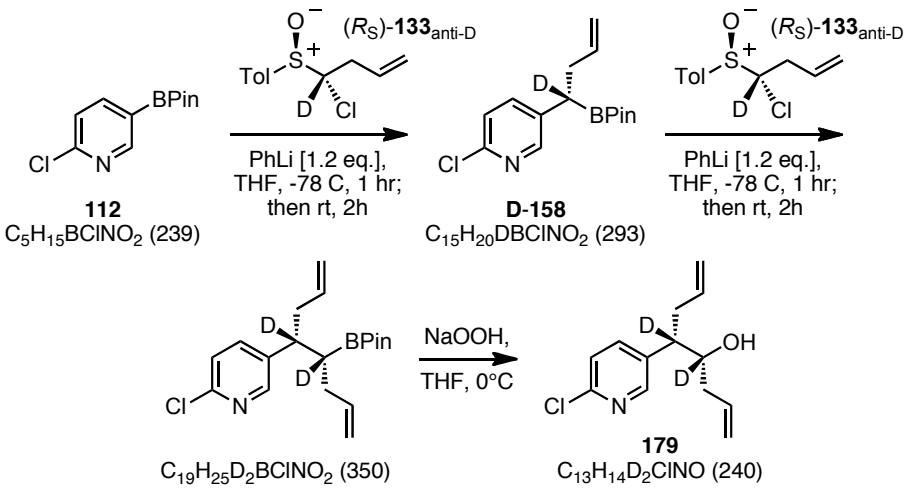
A small sample (8 mg, 0.28 mmol) was taken up in THF (1 mL) and cooled to 0°C, equilibrated for 10 min before addition of 2.2 M NaOH (0.3 mL) followed by 30% H_2O_2 (0.2 mL) and stirred for 1.5 h at reaction warmed to rt. Reaction was quenched with 10% $Na_2S_2O_3$ (3 mL), then partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 4 mL), brine wash (10 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield the crude product (10 mg) that was purified by column chromatography (SiO_2 eluting with 12% EtOAc in hexanes) to yield the title alcohol **178** as a colorless oil:$[\alpha_D]$ = +24.9 (c 0.95, $CHCl_3$); IR (NEAT) ν 3734, 3381, 2928, 1648, 1561, 1492, 1053, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, m), 7.31 (3H, m), 5.83 (1H, dddd, *J* = 16.0, 10.0, 7.6, 6.0), 5.15 (2H, ddd, *J* = 16.2, 12.8, 0.9), 3.68 (1H, m), 2.82 (1H, ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2 (0), 134.8 (1), 128.6 (1), 128.6 (1), 126.0 (1), 118.5 (2), 70.1 (1), 42.3 (2), 38.6 (2), 32.2 (2) ppm. ^1H NMR data in agreement with that reported by Denmark, S.; Nguyen, S. T. *Org. Lett.* **2009**, *11*, 781.

Chiral HPLC analysis of (±)-**178**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 10% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} [(+)-(R)-**178**] = 9.14 min. t_{ret} [(–)-(S)-**178**] = 13.7 min. Analysis of the enantioenriched material prepared as described above revealed an enantiomeric excess of 82% ee in favor of (R)-enantiomer.



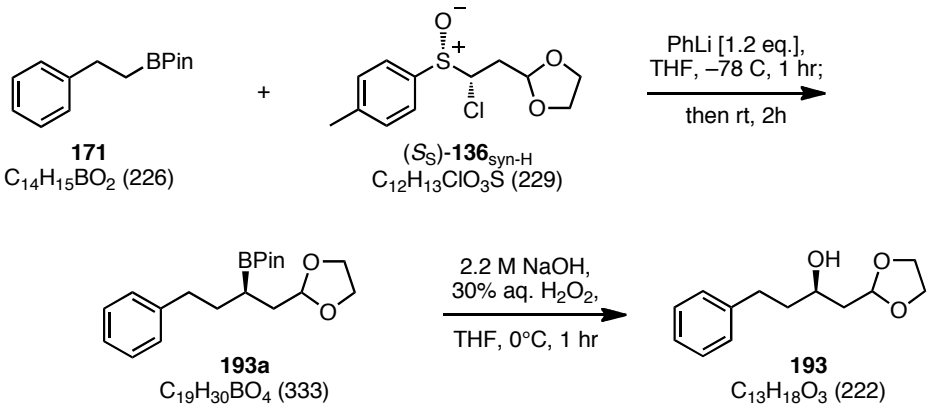
(S_S)-**133**$_{anti\text{-}D}$ $C_{12}H_{12}DOS$ (230) | **171** $C_{11}H_{15}BClO_2$ (232) | **D-178** $C_{18}H_{26}BDO_2$ (287)

Alkene - D-178: A flask was charged w/ a solution of (S_S)-**133**$_{anti\text{-}D}$ (60 mg, 0.26 mmol) in THF (1.5 mL) followed by phenethyl pinacolboronate **171** (52 mg, 0.22 mmol) and then cooled to –78°C [CO_2/acetone] allowing thermal equilibration for 15 min. followed by addition of PhLi (0.26 mmol, 1.35 M in *n*-Bu_2O) dropwise over 10 s as a noticeable orange color occurred in the reaction. The reaction stirred at this temperature for 30 min before being removed to warm to rt over 2.5 h. After approximately 25 min at rt, the reaction became dark red/orange and maintained this color throughout the rest of the reaction. After the allotted time the reaction was quenched with sat. NH_4Cl (4 mL), the layers were shaken and separated and the aq. was extracted with EtOAc (3 x 4 mL). The organic layers were combined, washed with brine and dried over (Na_2SO_4) and conc. *in vacuo* to yield a dark orange oil (129 mg) that was purified by column chromatography (SiO_2 eluting with a gradient of 2% to 5% EtOAc in hexanes) to yield the title pinacol boronate **D-178** as a colorless oil (42 mg, 0.15 mmol, 21%) $[\alpha]_D$ = + 6.48 (c = 0.7, $CHCl_3$); IR (neat) ν 3061, 3025, 2980, 2918, 2857, 1644, 1602, 1498, 1449, 1371, 1310, 1141, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, m), 7.16 (3H, m), 5.81 (1H, dddd, *J* = 16.0, 10.0, 7.6, 6.0), 4.99 (2H, ddd, *J* = 12.8, 6.5, 0.9), 2.61 (2H, m), 2.20 (2H, m), 1.80-1.62 (2H, m), 1.26 (3H, s), 1.15 (1H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2 (0), 134.8 (1), 128.6 (1), 128.6 (1), 126.0 (1), 118.5 (2), 70.1 (1), 42.3 (2), 38.6 (2), 32.2 (2), 25.1 (3), 25.0 (3), 25.0 (3), 25.0 (3) ppm. HRMS (EI) *m/z* 287.2103 (calcd. for $C_{18}H_{26}BDO_2$: 287.2093).



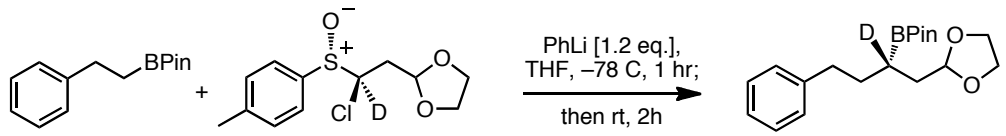
Bis-alkene - 179: A stirred solution of 2-chloropyridyl boronate **112** (85 mg, 0.36 mmol) and α-chlorosulfoxide (R_S)-**133**$_{anti\text{-}D}$ (98 mg, 0.43 mmol, dr ~8:1) in anhydrous THF (2.0 mL, 0.18 M in boronate) at –78 °C under Ar, was treated dropwise with PhLi (0.26 mL, 1.74 M in *n*-Bu_2O, 0.43 mmol) during 20 s. The resulting light yellow mixture was allowed to stir for 1 h at –78 °C, then warmed to rt and stirred for 2 h during which time the color darkened. The reaction mixture was then re-cooled to –78 °C and (R_S)-**133**$_{anti\text{-}D}$ (98 mg, 0.26 mmol, dr ~ 8:1) in dry THF (1.0 mL) added. After a period of 10 min to ensure that the flask contents had returned to ca. –78 °C, the reaction mixture was treated with a second portion of PhLi (0.26 mL, 1.74 M in *n*-Bu_2O, 0.43 mmol) during 20 s. The reaction was again initially stirred for 45 minutes at –78 °C and then warmed to rt and stirred for a further 2 h. The contents of the flask, which were by now very darkly colored (resembling a solution of I_2), were then cooled to 0 °C and treated with 2M aq. NaOOH (0.5 mL) followed by 30 wt.% aq. H_2O_2 (0.30 mL) and the biphasic mixture stirred vigorously for 1.5 h. The mixture was then partitioned between EtOAc (10 mL) and H_2O (10 mL) and the layers separated. The aq. phase was extracted with EtOAc (10 mL) and combined organic phases were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, eluting with 20% EtOAc in hexanes) to afford the targeted alcohol (*R*,*R*)-DD-**179** (13 mg, 0.053 mmol, 15%) as a colorless oil. Crude ^{1}H NMR analysis indicated dr = 2.4 : 1; $[\alpha]_D^{23}$ = – 3.53 (c. = 0.65, $CHCl_3$), ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.24 (1H, (b) d, *J* =), 7.65 (1H, d, *J* =

7.3), 5.76 (1H, ddd, *J* = 14.1, 10.3, 7.2), 5.63 (1H, ddd, *J* = 14.2, 10.1, 7.8), 2.60 (1H, dd, *J* = 14.1, 7.21), 2.48 (1H, dd, *J* = 14.2, 6.8), 2.16 (1H, dd, *J* = 13.8, 6.2), 1.91 (1H, dd, *J* = 13.9, 7.8), 1.59 (2H,) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.8 (0), 139.7 (0), 135.7 (1), 134.2 (1), 117.5 (2), 117.4 (2), 40.3 (1), 36.9 (1), 34.1 (0), 34.0 (2), 25.1 (3) ppm. MS (CI+) *m/z* 233 $(M+H)^+$; HRMS (CI+) *m/z* 240.1134 (calcd. for $C_{13}H_{15}ClD_2NO$: 240.1124).



Boronate - 193a: A flask was charged with (*S*$_S$)-**136**$_{syn\text{-}H}$ (70 mg, 0.31 mmol), followed by phenethyl pinacol boronate **171** (98 mg, 0.37 mmol), then THF (2.5 mL). This solution was stirred and cooled to –78°C [CO_2/acetone] and equilibrated for 15 min before dropwise addition of PhLi (1.20 M in *n*-Bu_2O, 0.31 mL, 0.37 mmol) over 20 s. An immediate color change to pale orange was observed and warmed to rt over 12 h, during which time the color became dark yellow. The reaction was quenched with sat. NH_4Cl (3 mL), the layers shaken and separated and the aq. layer extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (15 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a dark yellow oil (281 mg). The crude sample was further purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to afford the title boronate **193a** as a colorless oil (71 mg, 0.21 mmol, 72%) $[\alpha]_D$ +2.58 (c 0.975, $CHCl_3$); IR (neat) ν 2970, 2921, 1735, 1653, 1602, 1559, 1499, 1456, 1367, 1317 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36 (2H, m), 7.16 (3H, m), 4.94 (1H, t), 3.96 (2H, m), 3.83 (2H, m), 2.62 (2H, t), 1.91-1.64 (4H, m), 1.27 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (0), 129.8 (1), 128.4 (1), 104.4 (1), 65.1 (2), 65.0 (2), 35.8 (2), 35.7 (2), 34.1 (0), 34.0 (2), 25.1 (3) ppm; MS (CI+) *m/z* 334 $(M+H)^+$; HRMS (CI+) *m/z* 333.2298 (calcd. for $C_{19}H_{29}BO_4$: 333.2300).

A small sample of the pinacol boronate (12 mg, 0.036 mmol) was oxidized after being taken up in THF (1.5 mL), equilibrating at 0°C (ice) for 10 min before addition of 2.2 M NaOH (0.35 mL), followed by 30% aq. H_2O_2 (0.35 mL) and stirring while warming to rt over 1.5 h. The reaction was quenched with 10% aq. $Na_2S_2O_3$ (4 mL), layers shaken and separated, aq. layer extracted with EtOAc (3 x 5 mL), organic layers combined, washed with brine (10 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a colorless oil (13 mg) that was further purified by column chromatography (SiO_2 eluting with a gradient of 10% to 15% EtOAc in hexanes) to afford the enantioenriched alcohol **193** (7.5 mg, 0.034 mmol, 94%) $[\alpha]_D$ +9.44 (c 0.90, $CHCl_3$); IR (neat) ν 3450, 3025, 2921, 28979, 1603, 1499, 1454, 1416, 1143, 1098, 1028, 949 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.28 (2H, m), 7.19 (3H, m), 5.04 (1H, dd, *J* = 5.4, 1.8), 4.02 (2H, m), 3.95 (1H, m), 3.88 (2H, m), 2.99 (1H, s, OH), 2.80 (1H, dd, *J* = 10.3, 5.5, AB), 2.69 (1H, dd, *J* = 10.1, 6.4, AB), 1.92 (1H, dd, *J* = 3.6, 2.2), 1.84 (1H, m), 1.75 (1H, m) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.2 (0), 129.4 (1), 129.3 (1), 126.7 (1), 104.4 (1), 67.8 (1), 65.5 (2), 65.3 (2), 40.6 (2), 39.5 (2), 32.2 (2) ppm. ^1H NMR data in agreement with that reported by Maier, P.; Redlich, H.; Richter, J. *Tetrahedron:Asymmetry* **2005**, *16*, 3848.



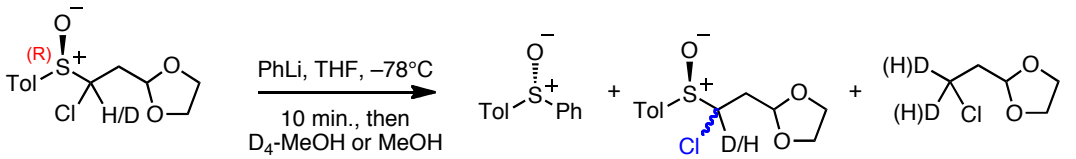
171 $C_{14}H_{15}BO_2$ (226)

(S_S)-**136**$_{anti\text{-}D}$ $C_{12}H_{12}ClDO_3S$ (230)

194 $C_{19}H_{29}BDO_4$ (334)

Alcohol -194: A flask was charged with (S_S)-**136**$_{anti\text{-}D}$ (120 mg, 0.44 mmol) followed by phenethyl pinacol boronate **171** (98 mg, 0.44 mmol), then THF (2.5 mL). This solution was stirred and cooled to –78°C [CO_2/acetone] and equilibrated for 15 min before dropwise addition of PhLi (1.33 M in *n*-Bu_2O, 0.39 mL, 0.52 mmol) over 20 s. An immediate color change to pale orange was observed and warmed to rt over 12 h, during which time the color became dark yellow. The reaction was quenched with sat. NH_4Cl (3 mL), the layers shaken and separated and the aq. layer extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (15 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a dark yellow oil (239 mg). The crude

sample was further purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to afford **boronate-194** as a colorless oil (95 mg, 0.28 mmol, 88%) $[\alpha]_D$ +2.58 (c 0.975, $CHCl_3$); IR (neat) ν 2970, 2921, 1735, 1653, 1602, 1559, 1499, 1456, 1367, 1317 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, m), 7.16 (2H, m), 4.94 (2H, t), 3.96 (2H, m), 3.83 (2H, m), 2.62 (2H, t), 1.91-1.64 (4H, m), 1.27 (12H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (0), 129.8 (1), 128.4 (1), 104.4 (1), 65.1 (2), 65.0 (2), 35.8 (2), 35.7 (2), 34.1 (0), 34.0 (2), 25.1 (3) ppm; MS (CI+) *m/z* 335 $(M+H)^+$; HRMS (CI+) *m/z* 334.2298 (calcd. for $C_{19}H_{29}BDO_4$: 334.2300).



(R_S)-**136**
$C_{12}H_{15}O_2S$ (229)

(S_S)-**155**
$C_{13}H_{12}OS$ (216)

(R_S)-**136**
$C_{12}H_{15}O_2S$ (229)

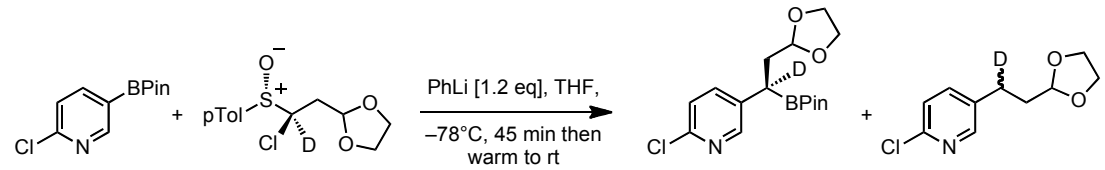
183
$C_5H_9ClO_2$ (136-138)

A representative procedure for the SLE study of α-chlorosulfoxides 136 (Table 7): A flask was charged with a solution containing the α-chlorosulfoxide (75 mg, 0.27 mmol) in THF (2 mL) and cooled to –78°C and equilibrated for 10 min before addition of PhLi (1.6 M in *n*-Bu_2O, 0.17 mL, 0.27 mmol) over 10 s. The resulting orange color reaction was stirred for 10 minutes before quench with either CH_3OH (0.30 mL) or CD_3OD (0.3 mL) as indicated in the table. The reaction was then diluted with NH_4Cl (1.5 mL) and warmed to rt before partitioning in EtOAc (5 mL) and H_2O (5 mL). The aq. layer extracted with EtOAc (3 x 5 mL) and the organics washed with brine (10 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield the crude oil which column chromatography (SiO_2 eluting with 40% EtOAc in hexanes) to yield in order of elution the SLE sulfoxide by-product and the mixture of reduced alkyl chloride (HH:HD:DD)-**183**, yield was determined from yield of SLE by-product and ratios of isotopomers determined from ^1H NMR data at the expanded range of 3.65 ppm.

^1H NMR spectral data for 2-(2-chloroethyl)-1,3-dioxolane (HH-**14**): ^1H NMR (400 MHz, $CDCl_3$) d 5.04 (1H, t, J = 4.6 Hz), 4.00-3.92 (2H, m), 3.91-3.84 (2H, m), 3.65 (2H, t, J = 7.0 Hz), 2.14 (2H, td, J = 7.0, 4.8 Hz) ppm.

^{1}H NMR spectral data for 2-(2-chloro-2-deuteroethyl)-1,3-dioxolane (HD-**14**): ^{1}H NMR (400 MHz, $CDCl_3$) d 5.04 (1H, t, *J* = 4.6 Hz), 4.00-3.92 (2H, m), 3.91-3.84 (2H, m), 3.63 (1H, t of 1:1:1, *J* = 6.9, 1.7 Hz), 2.13 (2H, dd of 1:1:1, *J* = 6.9, 4.8, 1.2 Hz) ppm.

^{1}H NMR spectral data for 2-(2-chloro-2,2-dideuteroethyl)-1,3-dioxolane (DD-**14**): ^{1}H NMR (400 MHz, $CDCl_3$) d 5.04 (1H, t, *J* = 4.6 Hz), 4.00-3.92 (2H, m), 3.91-3.84 (2H, m), 2.12 (2H, d of 1:2:3:2:1, *J* = 4.7, 1.0 Hz) ppm.



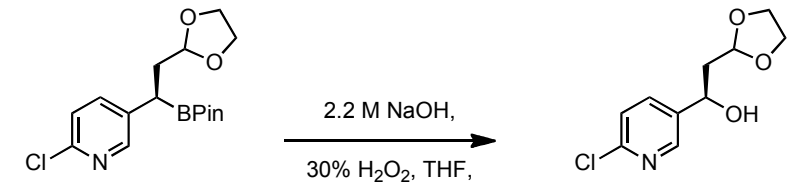
$C_{11}H_{15}BClO_2$ (239) $C_{12}H_{14}ClDO_3S$ (276) $C_{16}H_{22}BClDNO_4$ (341) $C_{10}H_{11}DClNO_2$ (215)

D-Boronate -190: A flask was charged with a solution of pinacol boronate (145 mg, 0.60 mmol) and α-chlorosulfoxide (S_S)-**136**$_{anti\text{-}D}$ (200 mg, 0.73 mmol) in anhydrous THF (3.5 mL, 0.17 M in boronate) at –78 °C under Ar, was treated dropwise with PhLi (0.55 mL, 1.33 M in *n*-Bu_2O, 0.73 mmol) during 10 s. The resulting light orange mixture was allowed to stir for 1 h at –78 °C, then warmed to rt and stirred for a further 2 h during which time the color darkened significantly. Sat. aq. NH_4Cl (2 mL) and further diluted with H_2O (5 mL) then partitioned with EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 7 mL), brine wash (20 mL), dried Na_2SO_4 and concentrated *in vacuo* to give the crude product (479 mg) as a dark orange oil. This was purified by column chromatography (SiO_2 eluting with 70% EtOAc in hexanes) to yield the title boronate as an inseparable mixture with the SLE sulfoxide by-product. (262 mg, 43 wt.% in **190**, effectively 96 mg, 0.29 mmol, 45%) as a colorless oil.

Deborylated acetal: IR (neat) n 2885, 1559, 1458, 1139, 1107, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) d 8.25 (1H, d, *J* = 2.5 Hz), 7.50 (1H, dd, *J* = 8.2, 2.6 Hz), 7.25 (1H, d, *J* = 8.2 Hz), 4.89 (1H, t, *J* = 4.5 Hz), 4.03-3.94 (2H, m), 3.92-3.83 (2H, m), 2.72 (1H, t of 1:1:1, *J* = 7.5, 1.8 Hz), 1.96 (2H, dd of 1:1:1, *J* = 7.9, 4.5, <1 Hz) ppm;

^{13}C NMR (100 MHz, $CDCl_3$) d 149.8 (1), 149.3 (0), 138.9 (1), 136.0 (0), 124.1 (1), 103.4 (1), 65.2 (2C, 2), 35.0 (2), 26.2 (CDH, 1:1:1 multiplet, $^1J_{CD}$ = 19.6 Hz) ppm; MS (EI) *m/z* 216 (16%), 214 (36), 169 (8), 141 (20), 127 (40), 101 (92), 73 (100); HRMS (CI) *m/z* 215.0694 (calcd. for $C_{10}H_{11}D^{35}ClNO_2$: 215.0698).

Acetal -D-190: ^{1}H NMR (400 MHz, $CDCl_3$) d 8.27 (1H, dd, *J* = 2.0, < 1 Hz), 7.55 (1H, dd, *J* = 8.2, 2.5 Hz), 7.21 (1H, dd, *J* = 8.2, < 1 Hz), 4.91 (1H, dd, *J* = 4.9, 3.1 Hz), 4.00-3.92 (2H, m), 3.88-3.81 (2H, m), 2.28 (1H, dd, *J* = 13.8, 4.8 Hz), 1.95 (1H, dd, *J* = 13.7, 3.0 Hz), 1.18 (6H, s), 1.16 (6H s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) d 149.6 (1), 148.6 (0), 138.7 (1), 137.6 (0), 124.0 (1), 103.3 (1), 83.9 (2C, 0), 65.3 (2), 65.1 (2), 36.1 (2), 26.6-25.7 (m, CDBpin), 24.8 (2C, 3), 24.7 (2C, 3) ppm; HRMS (ES) *m/z* 341.1523 (calcd. for $C_{16}H_{23}D_{11}B_{35}ClNO_4$: 341.1550).



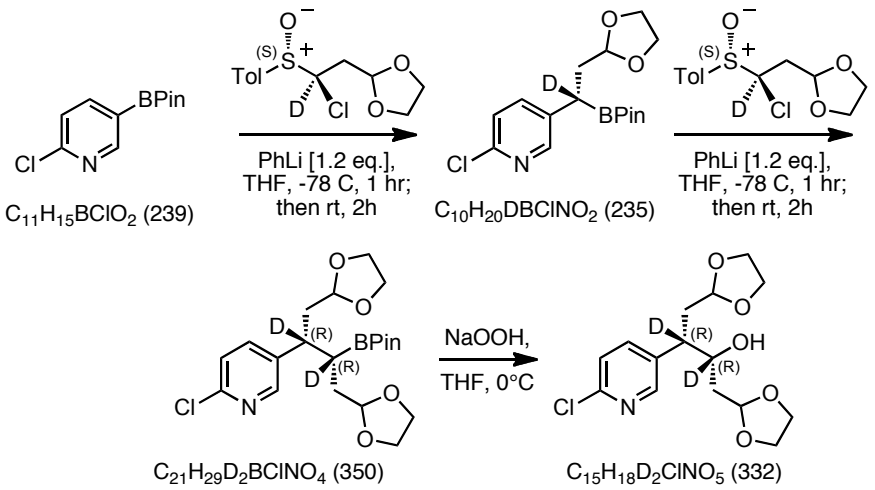
190
$C_{16}H_{22}BClDNO_4$ (341)

191
$C_{10}H_{11}ClDNO_3$ (231)

A small sample of the pinacol boronate (10 mg, 0.029 mmol) was oxidized after being taken up in THF (1.5 mL), equilibrating at 0°C (ice) for 10 min before addition of 2.2 M NaOH (0.30 mL), followed by 30% aq. H_2O_2 (0.25 mL) and stirring while warming to rt over 1.5 h. The reaction was quenched with 10% aq. $Na_2S_2O_3$ (4 mL), layers shaken and separated, aq. layer extracted with EtOAc (3 x 5 mL), organic layers combined, washed with brine (10 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a colorless oil (13 mg) that was further purified by column chromatography (SiO_2 eluting with a gradient of 10% to 15% EtOAc in hexanes) to afford the enantioenriched alcohol **H-191** (6.1, mg, 0.027 mmol, 91%) $[\alpha]_D^{23}$ = +19.8 (c = 0.95, $CHCl_3$); IR (neat) ν 3420, 2924, 1588, 1567, 1459, 1367, 1106, 1027, 944, 844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 2.5 Hz), 7.71 (1H, dd, *J* = 8.2, 2.5 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 5.07 (1H, dd, *J* = 4.4, 3.7 Hz), 4.11-4.03 (2H, m), 3.99-3.87 (2H, m), 3.62 (1H, br s), 2.15-2.04 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) d

150.6 (0), 147.7 (1), 138.3 (0), 136.6 (1), 124.2 (1), 103.1 (1), 67.3 (CDOH, 1:1:1 multiplet, $^{1}J_{CD}$ = 22.2 Hz), 65.3 (2), 65.1 (2), 42.1 (2) ppm; MS (ES) *m/z* 233 $(M+H)^+$, 231 $(M+H)^+$; HRMS (ES) *m/z* 233.0611 (calcd. for $C_{10}H_{12}D_{37}ClNO_3$: 233.0617), 231.0628 (calcd. for $C_{10}H_{12}D_{35}ClNO_3$: 231.0647).

HPLC analysis of (±)-H-**191** performed with a Daicel Chiralcel® AD column (4.6 mm ID x 250 mm), eluting with 5% *i*-PrOH in hexanes at 1.0 mL min^{-1} and monitored by UV at 210 nm, showed resolved peaks: $t_{ret.}$ [(*S*)-H-**191**] = 58.4 min, $t_{ret.}$ [(*R*)-H-**191**] = 63.5 min. Analysis of the enantioenriched deuterated material **D-191** prepared as described above revealed an enantiomeric excess of 89% in favor of the (*R*)-enantiomer.



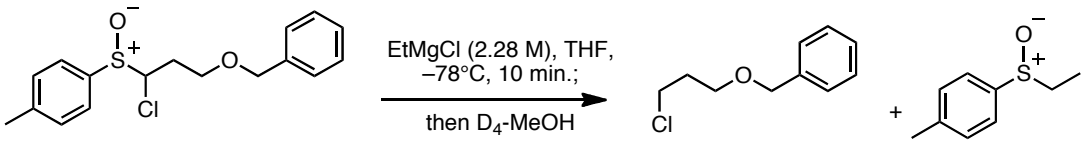
Alcohol - (R,R)-DD-195: A flask was charged with a solution of 2-chloropyridine boronate (110 mg, 0.45 mmol), (S_S)-*anti*-D-α-chlorosulfoxide (150 mg, 0.544 mmol) in THF (2.5 mL) and cooled to –78°C and equilibrated for 15 minutes before addition of PhLi (1.25 M in *n*-Bu_2O, 0.43 mL, 0.54 mmol) over 10 secs. The reaction stirred for 45 min at –78°C and was then removed from the cold bath to warm to rt over 2 h. During this time the reaction color progressed from a pale orange following SLE initiation with PhLi to a dark orange/red upon warming. After 2 h the reaction was cooled back down to –78°C and equilibrated for 10 min before addition of a second portion of (S_S)-*anti*-D-α-chlorosulfoxide (150 mg, 0.54 mmol) as a solid by quickly removing the rubber septum, this stirred for an additional 10 min before addition of a second portion of PhLi (1.25 M in *n*-Bu_2O, 0.43 mL, 0.54 mmol) over 10 s. The

reaction then stirred for 45 min at –78°C during which time the reaction became red to the point of appearing black, then removed from the cold bath and warmed to rt over 2 h before cooling to 0°C, equilibrating for several min and then adding 2.2 M NaOH (0.5 mL) followed by 30% H_2O_2 (0.4 mL) and warmed to rt with stirring over 1.5 h. The reaction was quenched with 10% $Na_2S_2O_3$ (10 mL), partitioned in EtOAc (10 mL), aq. layer extracted with EtOAc (3 x 15 mL), washed with brine (30 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield the crude product (622 mg) of dark orange/brown oil. This material was purified by column chromatography (SiO_2 eluting with 70% EtOAc in hexanes) to yield the title alcohol as colorless oil that solidified upon standing to yield colorless needles;

m.p. 113-114°C (TMBE); $[\alpha]_D^{23} = -52.9$ (c = 0.90, $CHCl_3$) (51 mg, 0.15 mmol, 34%): $[\alpha]_D^{25} = -32.3$ (c = 0.45, $CHCl_3$); IR (neat) ν 3488, 2886, 1559, 1458, 1140, 1369, 1109, 1024, 944 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* = 2.5, 0.7 Hz), 7.73 (1H, dd, *J* = 8.3, 2.5 Hz), 7.26 (1H, dd, *J* = 8.3, 0.6 Hz), 4.98 (1H, dd, *J* = 5.2, 3.4 Hz), 4.69 (1H, dd, *J* = 6.3, 3.6 Hz), 4.01-3.77 (8H, m), 3.12 (1H, s), 2.21 (1H, ddm, *J* = 14.1, 3.4 Hz), 2.12 (1H, dd, *J* = 14.1, 6.2 Hz), 1.72 (1H, dd, *J* = 14.4, 3.4 Hz), 1.39 (1H, dd, *J* = 14.6, 5.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (1), 150.1 (0), 139.8 (1), 135.6 (0), 123.9 (1), 103.6 (1), 103.0 (1), 69.4 (CDOH, 1:1:1 multiplet, $^1J_{CD} \sim 20$ Hz), 65.2 (2), 65.1 (2), 65.0 (2), 64.9 (2), 43.5 (CDR, 1:1:1 multiplet, $^1J_{CD} \sim 20$ Hz), 38.7 (2), 36.8 (2) ppm; HRMS (CI) *m/z* 332.1223 (calcd. for $C15H19D_2{}^{35}ClNO_5$: 332.1234).

The alternate "unlike" diastereomer (R,S)-DD-**195** was targeted in a similar manner as described for the "like" diastereomer by using (R_S)-**133**$_{anti\text{-}D}$ (dr = 93:7) in second StReCH step. **(R,S)-DD-195:** colorless oil; $[\alpha]_D^{23} = -35.2$ (c = 0.60, CHCl); IR (neat) n 3488, 2886, 1559, 1458, 1140, 1109, 1024, 944 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 8.26 (1H, dd, *J* = 2.5, 0.7 Hz), 7.73 (1H, dd, *J* = 8.3, 2.5 Hz), 7.26 (1H, dd, *J* = 8.3, 0.6 Hz), 4.98 (1H, dd, *J* = 5.2, 3.4 Hz), 4.69 (1H, dd, *J* = 6.3, 3.6 Hz), 4.01-3.77 (8H, m), 3.12 (1H, s), 2.21 (1H, ddm, *J* = 14.1, 3.4 Hz), 2.12 (1H, dd, *J* = 14.1, 6.2 Hz), 1.72 (1H, dd, *J* = 14.4, 3.4 Hz), 1.39 (1H, dd, *J* = 14.6, 5.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) d150.6 (1), 150.1 (0), 139.8 (1), 135.6 (0), 123.9 (1), 103.6

(1), 103.0 (1), 69.4 (CDOH, 1:1:1 multiplet, $_1J_{CD}$ ~ 20 Hz), 65.2 (2), 65.1 (2), 65.0 (2), 64.9 (2), 43.5 (CDR, 1:1:1 multiplet, $_1J_{CD}$ ~ 20 Hz), 38.7 (2), 36.8 (2) ppm; HRMS (CI) *m/z* 332.1223 (calcd. for $C_{15}H_{19}D_2{}^{35}ClNO_5$: 332.1234).



135
$C_{17}H_{19}ClO_2S$ (323)

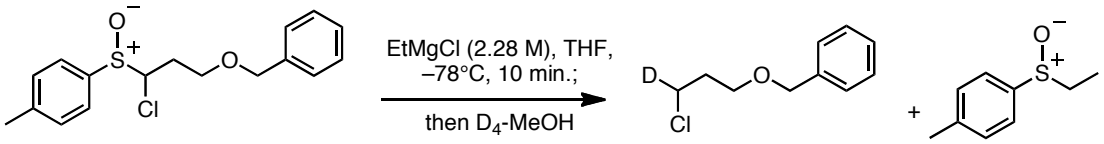
H-201
$C_{10}H_{13}ClO$ (185)

155
$C_9H_{12}OS$ (168)

Chloride - H-201: A flask was charged with a solution of sulfoxide **135** (50 mg, 0.16 mmol) in THF (1.5 mL, 0.1 M), stirred to homogeneity over several min. This was then cooled to –78°C and equilibrated for 25 min after which time dropwise addition over 10 s of EtMgCl (2.28 M in THF, 0.08 mL, 0.170 mmol) preceded stirring for 10 min when exchange occured, then the reaction was quenched with MeOH (0.15 mL, d = 0.79, 118 mg, 3.68 mmol). The reaction warmed to rt over 16 h, then diluted with sat. NH_4Cl (1 mL), layers were shaken and separated, aq. layer extracted with Et_2O (3 x 5 mL), organics were combined, washed with brine (10 mL) and dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow oil (48 mg) which was purified by column chromatography (SiO_2 eluting with 15% EtOAc in hexanes) to yield the following compounds in order of elution:

Chloride -H-201: (24mg, 0.130 mmol, 85%); IR (neat) ν 2851, 2351, 2324, 1643, 1562, 1448, 1367, 1117, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 4.52 (2H, s), 3.67 (1H, t), 3.62 (2H, t), 2.06 (2H, dt, *J* =) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 (0), 128.6 (1), 127.9 (1), 127.8 (1), 73.3 (2), 66.9 (2), 42.2 (2), 33.0 (2), 29.9 (3) ppm; MS (ES) *m/z* 180 $(M+H)^+$, 1834 $(M+H)^+$; HRMS (ES) *m/z* 183.0577.

Sulfoxide -155$_{R = Et}$: (18 mg, 0.101 mmol, 80%) IR (neat) ν 3418, 2974, 2928, 2973, 1598, 1495, 1452, 1086, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, m), 7.32 (3H, s), 2.86 (1H, apparent dt, *J* = 7.3, 5.9 Hz), 2.75 (1H, apparent dt, *J* = 7.4, 5.5 Hz), 2.41 (3H, s), 1.18 (3H, t, *J* = 7.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (0), 140.3 (0), 130.0 (1), 124.4 (1), 50.6 (2), 21.6 (3), 6.2 (3) ppm.



135
$C_{17}H_{19}ClO_2S$ (323)

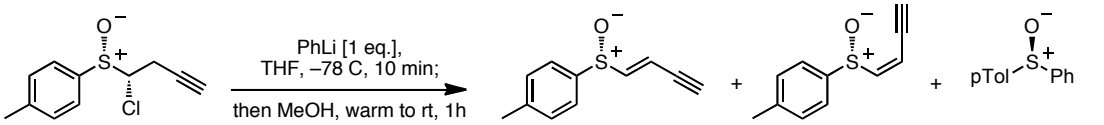
D-201
$C_{10}H_{12}ClDO$ (186)

155
$C_9H_{12}OS$ (168)

Chloride -D-201: A flask was charged with a solution of sulfoxide **135** (50 mg, 0.16 mmol) in THF (1.5 mL, 0.1 M), stirred to homogeneity over several minutes. This was then cooled to –78°C and equilibrated for 25 min after which time dropwise addition over 10 s of EtMgCl (2.28 M in THF, 0.08 mL, 0.170 mmol) preceded stirring for 10 min for the exchange to occur, then the reaction was quenched with D_4-MeOH (0.15 mL, d = 0.79, 118 mg, 3.68 mmol). The reaction warmed to rt over 15 h, then diluted with sat. NH_4Cl (1 mL), layers were shaken and separated, aq. layer extracted with Et_2O (3 x 5 mL), organics were combined, washed with brine (10 mL) and dried (Na_2SO_4) and concentrated *in vacuo* to yield a pale yellow oil (48 mg) which was purified by column chromatography (SiO_2 eluting with 25-35% EtOAc in hexanes) to yield the following compounds in order of elution:

Chloride -D-201: (21mg, 0.113 mmol, 75%); IR (neat) ν 2851, 2351, 2324, 1643, 1562, 1448, 1367, 1117, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 4.52 (2H, s), 3.67 (1H, t), 3.62 (2H, t), 2.06 (2H, dt, J = 6.2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 (0), 128.6 (1), 127.9 (1), 127.8 (1), 73.3 (2), 66.9 (2), 42.2 (2), 33.0 (2), 29.9 (3) ppm; HRMS (CI) *m/z* 186.0788 (calcd. for $C_{10}H_{13}D^{35}ClO$: 186.0796).

Sulfoxide -155: (17 mg, 0.101 mmol, 65%).



syn-**134**
$C_{11}H_{11}ClOS$ (195)

E-**204**
$C_{11}H_{10}OS$ (159)

Z-**204**
$C_{11}H_{10}OS$ (159)

155
$C_{13}H_{12}OS$ (216)

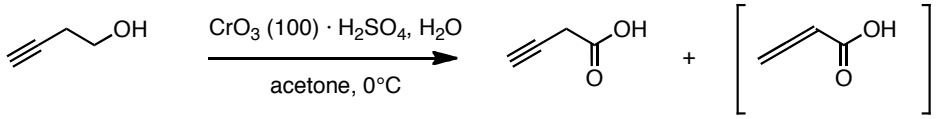
Enyne *E*/*Z*-**204:** A flask was charged with a solution of homo-propargyl chlorosulfoxide **134** (66 mg, 0.34 mmol) in THF (1.5 mL) and equilibrated at –78°C [CO_2/acetone] over 15 min. Then dropwise addition of PhLi (1.74 M in *n*-Bu_2O, 0.22 mL) over 3 s, the reaction became dark reddish-brown and stirred for 10 min before

addition of MeOH (1 mL) to quench. After warming to rt over 45 min, the reaction was diluted with H_2O (3 mL) and partitioned with EtOAC (3 mL) and the layers separated followed by extraction of the aqueous layer with EtOAc (3 x 5 mL), brine (10 mL) wash of the combined organic layers and drying with Na_2SO_4 before concentration *in vacuo* yielded an the crude product as an orange oil (92 mg). Purification by flash chromatography (SiO_2 eluting with 15% EtOAc in hexanes) to afford three separate products isolated in order of elution:

***E*-Enyne -204:** IR (neat) ν 3287, 3032, 1594, 1495, 1086, 1048, 940 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.51 (2 H, d, J = 8.2), 7.32 (2 H, d, J = 7.9), 6.82 (1 H, d, J = 16.0), 6.48 (1 H, dd, J = 15.3, 2.4), 3.25 (1 H, dd, J = 2.3, 0.4), 2.41 (3 H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.2 (1), 142.6 (0), 139.4 (0), 130.5 (1), 125.3 (1), 114.3 (1), 84.6 (0), 78.9 (1), 21.6 (3) - isolated as a colorless oil (19 mg, 0.12 mmol, 36%). ^1H NMR data in agreement with that reported by de la Pradilla, R. F.; Montero, C.; Preigo, J.; Marinez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612.

Sulfoxide -206: isolated as colorless oil (36 mg, 0.17 mmol, 50%).

***Z*-Enyne -204:** IR (neat) ν 3287, 3032, 1594, 1495, 1086, 1048, 940 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.51 (2 H, d, J = 8.2), 7.33 (2 H, d, J = 7.9), 6.66 (1 H, dd, J = 9.3, 0.77), 6.05 (1 H, dd, J = 10.0, 2.5), 3.54 (1 H, dd, J = 2.5, 0.8), 2.41 (3 H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.0 (1), 141.9 (0), 1140.8 (0), 130.3 (1), 124.1 (1), 115.9 (1), 88.4 (0), 77.6 (1), 21.6 (3) - isolated as a colorless oil (6 mg, 0.04 mmol, 12%). ^1H NMR data in agreement with that reported by de la Pradilla, R. F.; Montero, C.; Preigo, J.; Marinez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612.

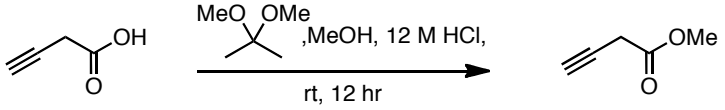


C_4H_6O (70) — **208a** $C_4H_4O_2$ (84) — **208b** $C_4H_4O_2$ (84)

Acid -208a: An erlenmeyer flask was charged with diH_2O (200 mL) followed by CrO_3 (11.4 g, 114.0 mmol) in one portion and cooled to 0°C (ice) to equilibrate. During equilibration H_2SO_4 (18 M, 76.0 mL, 1.4 mol) was added slowly over 4 min resulting in a vibrant orange color. After equilibrating for 15 min a solution of 3-

butyn-1-ol (4.3 mL, d = 0.93, 57.0 mmol) in acetone (30 mL) was added dropwise over 1 h during which time the reaction progressed to a dark brown/orange color. Stirring continued at 0°C for an additional 4.5 h and the reaction became dark ink blue in color. After this time the reaction was extracted with EtOAc (6 x 50 mL), the organic layers combined, washed with brine (100 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield the crude product as colorless oil that solidified upon standing that eminated a strong odor similar to short chain carboxylic acids(ie acetic acid) (3.8 g). The crude material was purified by dissolving in EtOAc (60 mL) and washing with 5% $KHCO_3$ (100 mL), washing the aq. layer with EtOAc (30 mL) and finally acidifying the aqueous layer with 4M HCl and extracting with EtOAc (3 x 50 mL), brine wash, dry (Na_2SO_4), and conc. *in vacuo* to yield the title carboxylic acid **208a** (3.53 g, 41 mmol, 72%) IR (neat) ν 3537, 3296, 3278, 2945, 2907, 1729, 1695, 1392, 1286, 1242, 939, 871 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 9.76 (1 H, br, OH), 3.37 (2 H, d, *J* = 2.7), 2.24 (1 H, t) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 174.3 (0), 75.1 (1), 72.6 (0), 25.8 (2) ppm. ^1H NMR data in agreement with that reported by Eglington, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3197.
If care is not taken during purification with molarity of base with K as counterion, the product will be fully converted to the allene carboxylic acid.

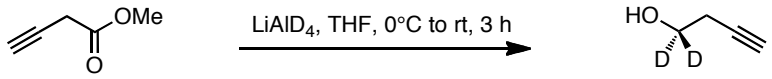
Allene -208b: IR (KBr) ν 3057, 2979, 2662, 1967, 1930, 1675, 1453, 1406, 1293, 1228, 915, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (1 H, br, COOH), 5.65 (1 H, t), 5.29 (2 H, d, *J* = 6.5) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.1 (0), 171.6 (0), 87.9 (2), 79.9 (1) ppm. ^1H NMR data in agreement with that reported by Eglington, G.; Jones, E. R. H.; Mansfield, G. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 3197.



208a $C_4H_4O_2$ (84) **208c** $C_5H_6O_2$ (98)

Methanoate -208c: An erlenmeyer flask was charged with a solution of carboxylic acid **208a** (3.5 g, 41 mmol) in MeOH (40 mL) followed by the addition of 2,2-dimethylacetal propane (5 mL, d = 0.85, 41 mmol). Next, 3 drops of 12 M HCl was

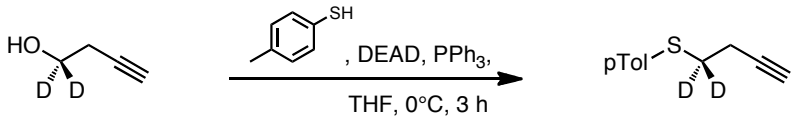
added and the reaction left to stand at rt for 18 h, after which time the reaction was diluted with H_2O (35 mL) and partitioned between EtOAc (60 mL). The layers were shaken and separated and the organic layer washed with 5% $KHCO_3$ (2 x 25 mL), followed by brine wash, dry (Na_2SO_4) and conc. *in vacuo* to yield the title methyl ester (3.7 g, 38 mmol, 93%). The ester was of sufficient purity, precluding the necessity for further purification: ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.75 (3 H, s), 3.30 (2 H, d, *J* = 2.7), 2.21 (1 H, t, *J* = 2.8) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 168.5 (0), 75.7 (1), 72.6 (0), 52.9 (3), 25.7 (2) ppm. ^{1}H NMR data in agreement with that reported by Collins, P. W.; Kramer, S. W.; Gasiecki, A. F.; Weier, R. M.; Jones, P. H.; Gullikson, G. W.; Bianchi, R. G.; Bauer, R. F. *J. Med. Chem.* **1987**, *30*, 193.



208c
$C_5H_6O_2$ (98)

209
$C_4H_4D_2O$ (72)

Alcohol - 209: A flask was charged with a solution of $LiAlD_4$ (650 mg, 16 mmol) in THF (20 mL) and cooled to –20°C and equilibrated for 15 min during which time some H_2 evolution was observed as bubbles escaping from solution. Then a solution of 3-butynmethanoate **208c** (2.6 g, 26.0 mmol) in THF (10 mL) was slowly added over 30 min dropping funnel and warmed to rt over 3 h. The reaction was checked by TLC, but spots were copolar and a small aliquot was extracted and worked up with CH_2Cl_2 and checked by ^{1}H NMR, which indicated all starting material was consumed. The reaction was cooled to –20°C and quenched with sat. NH_4Cl (3 mL) and diluted with CH_2Cl_2 (10 mL), aq. layer extracted with CH_2Cl_2 (3 x 15 mL), washed with brine (45 mL), dried Na_2SO_4 and distilled to yield the title alcohol as a colorless oil: (1.4 g, 19.5 mmol, 75%) ^{1}H NMR data in agreement with that reported by Dua, S.; Bowie, J. H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2038.

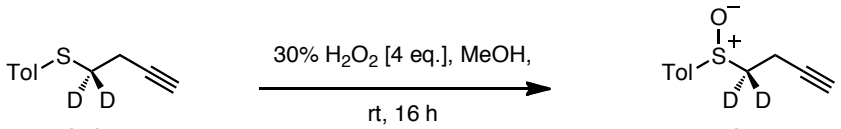


$C_4H_4D_2O$ (72)

$C_{11}H_{10}D_2S$ (178)

Sulfide - 210: A flask was charged with a solution of the doubly deuterated homopropargyl alcohol **209** (100 mg, 1.38 mmol), PPh_3 (433 mg, 1.65 mmol),

p-thiocresol (342 mg, 2.75 mmol) in THF (3.5 mL) and cooled to 0°C before dropwise addition of DEAD (312 mg, d = 1.11, 0.28 mL, 1.8 mmol) over 5 min and warmed to rt over 40 min during which time the reaction turned to a yellow color and TLC (10% EtOAc in hexanes) indicated all starting material was consumed. The reaction was quenched with sat. NH_4Cl (4 mL) and partitioned in EtOAc (6 mL), aq. layer extracted with EtOAc (3 x 8 mL), washed with 10% NaOH (10 mL), washed with brine (20 mL), dried Na_2SO_4, and concentrated *in vacuo* to yield the crude product (652 mg) of a dark orange oil. Purification by column chromatography (SiO_2 eluting with a gradient of 5 to 10% EtOAc in hexanes) gave the deuterated sulfide **210** (181 mg, 1.02 mmol, 74%) ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.28 (2 H, *J* = 8.0 Hz), 7.12 (2 H, d, *J* = 8.0 Hz), 2.44 (2 H, d, *J* = 2.0 Hz), 2.32 (3 H, s), 2.04 (1 H, t, *J* = 2.4 Hz) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.0 (0), 131.5 (1), 131.2 (1), 130.0 (1), 128.8 (1), 77.2 (0), 69.6 (1), 21.1 (1), 29.4 (2) ppm.

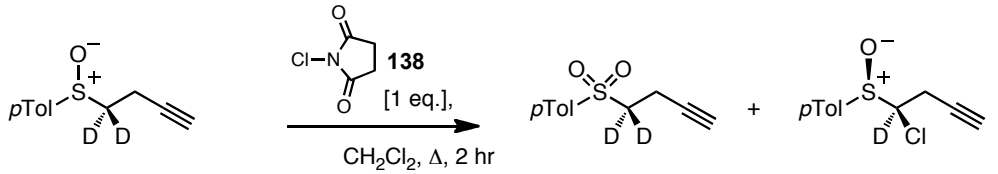


210
$C_{11}H_{10}D_2S$ (178)

211
$C_{11}H_{10}D_2OS$ (194)

Sulfoxide - 211: A flask was charged with a solution of deuterated sulfide **210** (700 mg, 3.9 mmol) in MeOH (10 mL) and stirred and rt for 5 min before addition of 30% H_2O_2 (2.1 mL, d = 1.1, 702 mg, 19.5 mmol) at once and then stirred at rt for 11 h. The pale yellow reaction was quenched by slow dropwise addition of 10% $Na_2S_2O_3$ (15 mL) with occasional cooling in an ice bath, as a slight exotherm was observed. Then the reaction was partitioned between EtOAc (25 mL) and the layers were separated. The aqueous layer was extrated with EtOAc (3 x 20 mL), organic layers combined, washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude product as a yellow oil (665 mg). Subsequent purification with column chromatography (SiO_2 eluting with a gradient of 25% to 35% EtOAc in hexanes) to yield the deuterated sulfoxide **211** as a colorless oil (544 mg, 2.8 mmol, 72%) IR (neat) ν 3291, 3227, 2918, 1598, 1498, 1303, 1086, 1044, 1021, 814 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51 (2 H, d, *J* = 8.2), 7.34 (2 H, d, *J* = 7.9), 2.69

(1 H, dd, *J* = 17.2, 1.3), 2.42 (3 H, s), 2.38 (1 H, dd, *J* = 17.2, 1.3), 2.03 (1 H, t) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.9 (0), 139.7 (0), 130.2 (1), 124.2 (1), 80.9 (1), 70.6 (0), 21.6 (2), 12.0 (3) ppm. MS (EI) *m/z* 194 $(M)^+$,165(40%),139(80%),123 (90%),91(100%),77 (88%); HRMS (EI) *m/z* 194.07323 (calcd. for $C_{11}H_{10}D_2OS$: 194.07344).



211
$C_{11}H_{10}D_2OS$ (194)

$C_{11}H_{10}D_2O_2S$ (210)

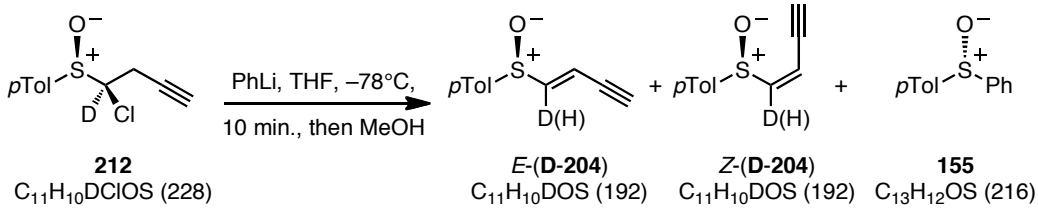
syn-**212**
$C_{11}H_{10}DClOS$ (228)

Chlorosulfoxide -*syn*-212: A flask was charged with a solution of deuterated sulfoxide **211** (100 mg, 0.58 mmol) in CH_2Cl_2 (3 mL) and heated to reflux. The reaction was followed by TLC (30% EtOAc in hexanes) for 2 h until all of the starting material was consumed. The reaction was then diluted with H_2O (5 mL), the layers shaken and separated, organic layers combined, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to yield the crude product as a yellow oil (106 mg). The product was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to afford the following compounds in order of elution:

Sulfone: (26 mg, 0.13 mmol, 22%) IR (neat) ν 3180, 3050, 1360, 1180, 870, 639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2 H, d, *J* = 8.1), 7.36 (2 H, d, *J* = 7.9), 3.49 (1 H, dd, *J* = 17.3, 2.5), 3.27 (1 H, dd, *J* = 17.3, 2.5), 2.45 (3 H, s), 2.3 (1 H, m) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.9 (0), 134.5 (0), 129.7 (1), 127.3 (1), 75.7 (0), 74.1 (1), 34.3 (2), 21.6 (3) ppm.

Chlorosulfoxide -212: α-chloro-α-deutero sulfoxide **212** as a colorless oil (89 mg, 0.39 mmol, 68%, > 96% ^{2}H incorporation) IR (neat) ν 3290, 3227, 1096, 1058, 815, 675 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.74 (2 H, d, *J* = 8.2), 7.35 (2 H, d, *J* = 8.0), 4.61 (1 H, dd, *J* = 7.9, 5.8), 3.15 (1 H, dd, *J* = 17.4, 2.6), 2.51 (1 H, dd, *J* = 17.4, 2.5), 2.43 (3 H, s), 2.17 (1 H, t) ppm ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.0 (0), 135.4 (0), 129.9 (1), 125.6 (1), 77.7 (1), 72.6 (0), 22.4 (2), 21.7 (3) ppm. MS (EI) *m/z* 227.4

$(M+H)^+$, 153.3 (12%), 140.3 (100%), 92.2 (44%), 77.2 (24%); HRMS (EI) *m/z* 227.02793 (calcd. for $C_{11}H_{10}DClOS$: 227.02819).



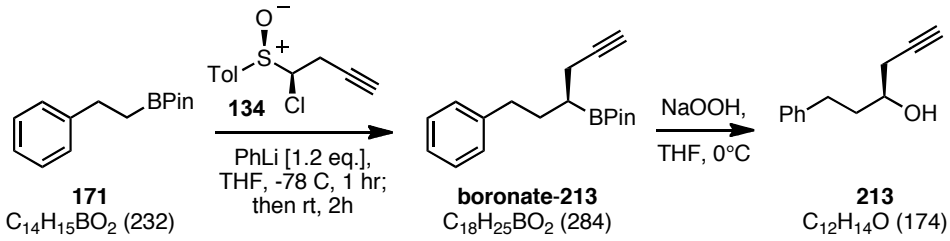
212 $C_{11}H_{10}DClOS$ (228) | *E*-(**D-204**) $C_{11}H_{10}DOS$ (192) | *Z*-(**D-204**) $C_{11}H_{10}DOS$ (192) | **155** $C_{13}H_{12}OS$ (216)

Representative example of SLE study for propargyl bearing α-chlorosulfoxide 212: A flask was charged with a solution of α-chlorosulfoxide **212** (50 mg, 0.26 mmol) in THF (1.5 mL) and cooled to –78°C and allowed to equilibrate for 15 min before addition of PhLi (1.74 M in *n*-Bu_2O, 0.15 mL, 0.26 mmol) over 5 s and allowed to stir for 10 min before quenching the reaction with MeOH (0.5 mL) and removing from the cold bath to warm to rt over 1 hour. After this time the reaction was diluted with H_2O (5 mL) and partitioned between EtOAc (5 mL), the aq. layer was washed with EtOAc (3 x 5 mL), organics washed with brine (15 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield a crude orange oil (50 mg) which was purified by column chromatography (SiO_2 eluting with 15%EtOAc in hexanes) to yield the following products in order of elution:

E-**D-204:** (IR (neat) ν 3287, 3032, 1594, 1495, 1086, 1048, 940 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.51 (2 H, d, J = 8.2), 7.32 (2 H, d, J = 7.9), 6.82 (1 H, d, J = 16.0), 6.48 (1 H, dd, J = 15.3, 2.4), 3.25 (1 H, dd, J = 2.3, 0.4), 2.41 (3 H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.2 (1), 142.6 (0), 139.4 (0), 130.5 (1), 125.3 (1), 114.3 (1), 84.6 (0), 78.9 (1), 21.6 (3) - isolated as a colorless oil (19 mg, 0.12 mmol, 36%).

Sulfoxide - 206: (isolated as colorless oil (31 mg, 0.14 mmol, 55%)

Z-**D-204:** IR (neat) ν 3287, 3032, 1594, 1495, 1086, 1048, 940 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.51 (2 H, d, J = 8.2), 7.33 (2 H, d, J = 7.9), 6.66 (1 H, dd, J = 9.3, 0.77), 6.05 (1 H, dd, J = 10.0, 2.5), 3.54 (1 H, dd, J = 2.5, 0.8), 2.41 (3 H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 150.0 (1), 141.9 (0), 130.8 (0), 130.3 (1), 124.1 (1), 115.9 (1), 88.4 (0), 77.6 (1), 21.6 (3) - isolated as a colorless oil (10 mg, 0.05 mmol, 20%).

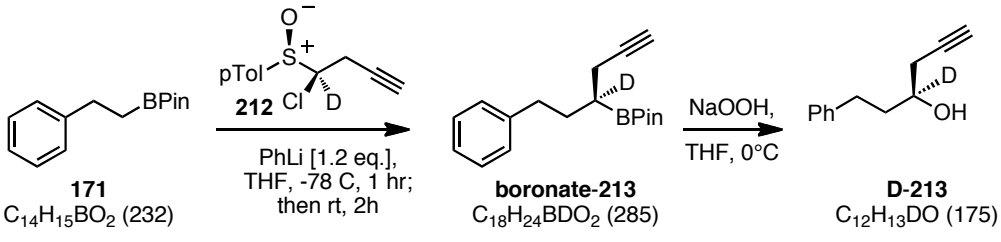


171
$C_{14}H_{15}BO_2$ (232)

boronate-213
$C_{18}H_{25}BO_2$ (284)

213
$C_{12}H_{14}O$ (174)

Alkyne - H-213: A flask was charged with a solution of α-chlorosulfoxide **134** (120 mg, 0.53 mmol), phenethylboronate **171** (102 mg, 0.44 mmol) in THF (2 mL, 0.22 M) and cooled to –78°C and equilibrated for 15 min before addition of PhLi (1.74 M in *n*-Bu_2O, 0.30 mL, 0.53 mmol) directly into the reaction. An immediate color change to orange was observed and the reaction was warmed to room temperature over 15 h, after which time the reaction color had progressed to a dark orange/brown. The reaction was quenched with sat. NH_4Cl (1 mL) followed by H_2O (3 mL) and partitioned in EtOAc (6 mL), aq. layer extracted with EtOAc (3 x 5 mL), washed with brine (15 mL), dried Na_2SO_4 and conc. *in vacuo* to yield the crude product as a brown oil (217 mg) that was with column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title alcohol (11 mg, 0.063 mmol, 13%) ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (3H, m), 7.24 (2H, m), 3.82 (1 H, unresolved), 2.85 (1H, dt, *J* = 13.8, 7.8), 2.75 (1H, dt, *J* = 13.9, 7.9), 2.49 (1H, dq, *J* = 16.7, 2.6), 2.42 (1H, dq, *J* = 16.5, 2.5), 2.11 (1H, t, *J* = 2.57), 1.99 (1H, unresolved OH), 1.91 (2H, m) ppm; ^{13}C (175 MHz, $CDCl_3$) δ 141.8 (0), 129.1 (1), 128.6 (1), 126.5 (1), 74.5 (0), 71.1 (1), 70.5 (1), 37.9 (2), 32.0 (2), 27.6 (2) ppm. ^{1}H NMR data in agreement with that reported by Kobayashi, S.; Nishio, K. *J. Chem. Am. Soc.* **1995**, *117*, 6392.



171
$C_{14}H_{15}BO_2$ (232)

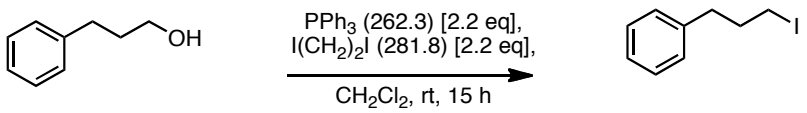
boronate-213
$C_{18}H_{24}BDO_2$ (285)

D-213
$C_{12}H_{13}DO$ (175)

Alkyne - D-213: A flask was charged with a solution of α-chlorosulfoxide *syn*-**212** (120 mg, 0.53 mmol), phenethylboronate **171** (102 mg, 0.44 mmol) in THF (2 mL, 0.22 M) and cooled to –78°C and equilibrated for 15 minutes before addition of PhLi (1.74 M in *n*-Bu_2O, 0.30 mL, 0.53 mmol) directly into the reaction. An immediate

color change to orange was observed and the reaction was warmed to room temperature over 15 h, after which time the reaction color had progressed to a dark orange/brown. The reaction was quenched with sat. NH_4Cl (1 mL) followed by H_2O (3 mL) and partitioned in EtOAc (6 mL), aq. layer extracted with EtOAc (3 x 5 mL), washed with brine (15 mL), dried Na_2SO_4 and conc. *in vacuo* to yield the crude product as a brown oil (217 mg) that was with column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title alcohol **D-213** (11 mg, 0.063 mmol, 18%) ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.32 (3H, m), 7.24 (2H, m), 3.82 (1 H, unresolved), 2.85 (1H, dt, *J* = 13.8, 7.8), 2.75 (1H, dt, *J* = 13.9, 7.9), 2.49 (1H, dq, *J* = 16.7, 2.6), 2.42 (1H, dq, *J* = 16.5, 2.5), 2.11 (1H, t, *J* = 2.57), 1.99 (1H, unresolved OH), 1.91 (2H, m) ppm; ^{13}C (175 MHz, $CDCl_3$) δ 141.8 (0), 129.1 (1), 128.6 (1), 126.5 (1), 74.5 (0), 71.1 (1), 70.5 (1), 37.9 (2), 32.0 (2), 27.6 (2) ppm.

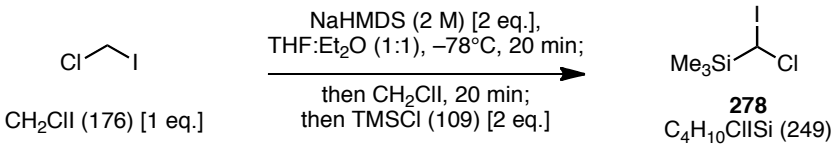
Part II - AHME



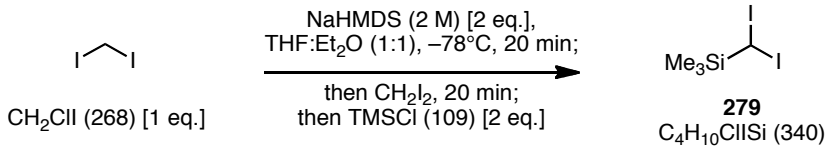
$C_9H_{12}O$ (136) $C_9H_{11}I$ (246)

3-Phenyl-1-iodopropane: A flask was charged with of PPh_3 (4.25 g, 16.2 mmol) in CH_2Cl_2 (70 mL, .11 M) stirred for 10 minutes until all of the PPh_3 had dissolved, then addition of $I(CH_2)_2I$ (4.5 g, 16.2 mmol) in CH_2Cl_2 (20 mL) resulting in an orange mixture. After 2 h most of the color had dissipated, this was followed by addition of imidazole (1.25 g, 18.4 mmol) then 3-phenyl propanol (1 mL, d=1.004, 1.0 g, 7.37 mmol) which caused immediate generation of colorless precipitation. Stirring continued for an additional 2 h, then the reaction was filtered through a pad of Celite, the volume of filtrate was reduced to ~1/2, diluted with Et_2O (20 mL) generating more precipitate that was again filtered through Celite. The filtrate was washed with 10% $Na_2S_2O_3$ (2 x 15 mL), brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a colorless solid (3.66 g) which was purified by column chromatography

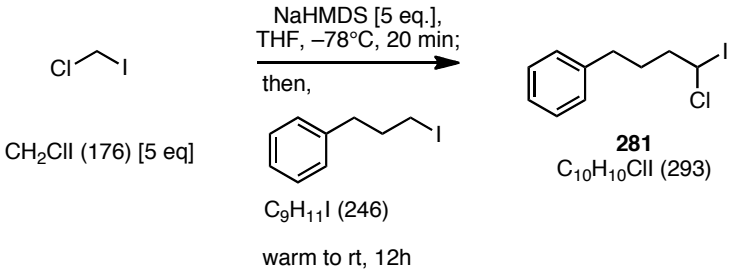
(SiO_2 eluting with 10% EtOAc in hexanes) to yield the title iodide as a colorless oil (1.57 g, 6.41 mmol, 87%) IR (neat) ν 3064, 3019, 2931, 1602, 1491, 1452, 1216 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, m), 7.21 (3H, m), 3.17 (2H, t), 2.73 (2H, t), 2.14 (2H, dt, *J* = 7.2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6 (0), 128.7 (1), 126.4 (1), 36.4 (2), 35.1 (2), 6.5 (2) ppm. ^1H NMR data in agreement with that reported by Charette, A. B.; Molinaro, C.; Brochu, C.; *J. Am Chem. Soc.* **2001**, *123*, 12160.



Chloroiodosilane - 278: A flask was charged w/ a 1:1 mixture of THF (5 mL) and Et_2O (5 mL) followed by NaHMDS (2M in THF, 4.5 mL, 9 mmol) then cooled to –78°C (CO_2/Acetone) and equilibrated for 15 min., before addition of chloroiodomethane (0.79 g, d = 2.42, 0.33 mL, 4.5 mmol). The reaction progressed to an orange color over 20 min after which time addition of chlorotrimethylsilane (0.98 g, d = 0.856, 1.1 mL, 9 mmol) at –78°C over 30 s was followed by a slow warming to rt over 17 h in the dark. The dark brown reaction had fine ppt when quenched with H_2O (10 mL) and was vacuum filtered through a small plug of Celite. Layers were shaken and separated, aq. layer extracted with CH_2Cl_2 (2 x 15 mL), organic layers combined, washed w/ brine (15 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a dark brown oil residue (1.3 g). The residue was purified by refluxing in anhydrous methanolic HCl for 4.5 h followed by column chromatography (SiO_2 eluting with hexanes) to yield the title gem-chloroiodide **278** (548 mg, 2.21 mmol, 49%) as a colorless oil $[\alpha]_D^{23}$ = +0.00 (c 1.00, $CHCl_3$); IR (neat) ν 2954, 2922, 2844, 1407, 1248, 1164, 1044, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25 (1H, s), 0.24 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (1), -2.9 (3) ppm; MS (EI+) *m/z* 219 $(M+H)^+$; HRMS (EI+) *m/z* 211.9 (Cl never observed) (calcd. for C_4H_9I(126)Si 211.95230.

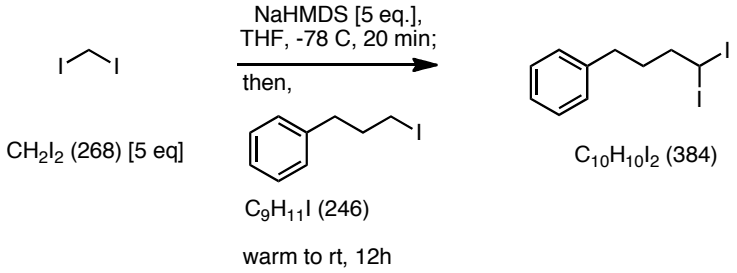


Diiodosilane - 279: A flask was charged w/ a 1:1 mixture of THF (5 mL) and Et_2O (5 mL) followed by NaHMDS (2M in THF, 5.2 mL, 10.4 mmol) then cooled to –78°C (CO_2/Acetone) and equilibrated for 15 min, before addition of diiodomethane (1.38 g, d = 3.33, 0.42 mL, 5.2 mmol). The reaction progressed to a dark purple color over 20 min. after which time addition of chlorotrimethylsilane (1.14 g, d = 0.856, 1.3 mL, 10.6 mmol) at –78°C over 30 s was followed by a slow warming to rt over 17 h in the dark. The dark brown reaction had fine ppt when quenched with H_2O (10 mL) and was vacuum filtered through a small plug of Celite. Layers were shaken and separated, aq. layer extracted with CH_2Cl_2 (2 x 30 mL), organic layers combined, washed w/ brine (25 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a dark brown oil residue (1.8 g). The residue was purified by column chromatography (SiO_2 eluting with hexanes) to yield a colorless oil (921 mg) which was then further purified by Kugelrohr distillation to yield the title diiodides as a colorless oil (843 mg, 2.48 mmol, 55%) IR (neat) ν 2967, 2902, 2814, 1397, 1212, 1164, 1021, 878 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, s), 0.25 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.95 (1), –1.91 (3). ^1H NMR data in agreement with that reported by Takai, K.; Kunisada, Y.; Tachibana, Y.; Yamaji, N.; Nakatani, E. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1581.



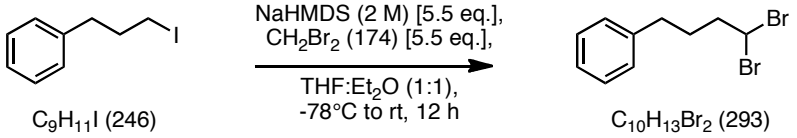
Chloroiodide - 281: A flask was charged with a colorless solution of NaHMDS (2M in THF, 11.2 mL, 22.3 mmol) in THF/Et_2O (1:1) (12 mL) and cooled to –78°C [CO_2/acetone] to equilibrate for 15 min before addition of CH_2ClI (1.6 mL, d = 2.42,

27.3 mmol) downside of flask over 1 min. An immediate generation of a vibrant orange color was observed and the reaction stirred at this temp for 20 min, during which time the color had darkened significantly. The primary iodide (1.0 g, 4.1 mmol) was added down the side of flask over 2 min and the entire flask was covered fully with aluminium foil to prevent any light exposure and the reaction warmed to room temperature over 16 h. Prior to quench the reaction was vibrant orange color, addition of H_2O followed by partitioning between EtOAc (25 mL) the layers were shaken and separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a dark red-brown viscous oil (3.2 g). Purification of the crude material was performed by first removing all lower boiling by-products (CH_2ClI, vinyl chloride and HMDS by-product) through Kugelrohr distillation leaving an orange oil residue (620 mg) which was further purified by flash chromatography (SiO_2 eluting with 1% EtOAc in hexanes) to afford the title *gem*-chloroiodide **281** as a pale yellow oil (445 mg, 1.52 mmol, 64%) IR (neat) ν 3089, 3064, 3022, 2949, 2853, 1712, 1603, 1495, 1453, 1169, 1080, 752 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.30 (2 H, m), 7.2 (2 H, m), 5.76 (1 H, t), 2.68 (2 H, t), 2.31 (2 H, dt, J = 8.7, 6.5), 1.86 (2 H, ddd, J = 7.5) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.4 (0), 128.7 (1), 128.5 (1), 126.3 (1), 46.1 (2), 34.5 (2), 30.5 (2), 30.1 (1) ppm. MS (EI+) *m/z* 294 (32%), 167 (64%), 131 (100%), 91 (78%); HRMS (EI+) *m/z* 293.9674 (calcd. for $C_{10}H_{12}ClI$: 293.96725).



Diiodide - 282: A flask was charged with a colorless solution of NaHMDS (2M in THF, 18.3 mL, 36.5 mmol) in THF/Et_2O (1:1) (12 mL) and cooled to –78°C [CO_2/acetone] to equilibrate for 15 min before addition of CH_2I_2 (0.58 mL, d = 3.32, 7.3 mmol) downside of flask over 1 min. An immediate generation of a vibrant

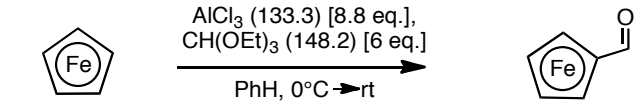
red/purple color was observed and the reaction stirred at this temp for 20 min, during which time the color had darkened significantly. The primary iodide (450 g, 1.82 mmol) was added down the side of flask over 2 min and the entire flask was covered fully with aluminium foil to prevent any light exposure and the reaction warmed to room temperature over 16 h. Prior to quench the reaction was dark orange color, addition of H_2O was followed by partitioning between EtOAc (25 mL) the layers were shaken and separated. The aqueous layer was extracted with EtOAc (3 x 25 mL), combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark red-brown viscous oil (xx mg). Purification of the crude material was performed by first removing all lower boiling by-products (CH_2I_2, vinyl iodide and HMDS derivative) through Kugelrohr distillation leaving a black oil residue (663 mg) which was further purified by flash chromatography (SiO_2 eluting with 1% EtOAc in hexanes) to afford the title *gem*-diiodide **282** as a pale yellow oil (625 mg, 1.63 mmol, 58%) IR (neat) ν 3086, 3057, 2933, 2844, 1938, 1804, 1606, 1450, 1090, 914 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.30 (2 H, m), 7.21 (2 H, m), 5.11 (1 H, t), 2.68 (2 H, t), 2.38 (2 H, dt, J = 8.7, 6.5), 1.78 (2 H, m) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.4 (0), 128.6 (1), 128.3 (1), 126.2 (1), 47.7 (2), 33.9 (2), 33.6 (2), –26.0 (1) ppm.^1H NMR data in agreement with that reported by Bull, J. A.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 8097.



$C_9H_{11}I$ (246) → $C_{10}H_{13}Br_2$ (293)

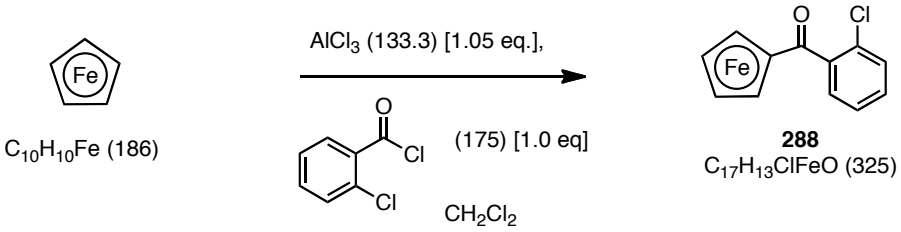
1,1-Dibromo-4-phenyl butane: A flask was charged with a mixture of THF:Et_2O (1:1) (6 mL) followed by NaHMDS (2M in THF, 11 mL, 22 mmol) and equilibrated at -78°C [CO_2/acetone] for 15 minutes before dropwise addition of CH_2Br_2 (174, d = 2.5, 1.6 mL, 22 mmol). This was followed by immediate generation of an intense red color and the reaction stirred for 20 min before addition of primary iodide (1 g, 4.1 mmol) dropwise over 2 min whereupon the color intensity attenuated and became brown. The reaction was warmed to rt in the dark over 12 h, before being quenched with H_2O (10 mL), filtered through Celite, the layers shaken and separated, aq.

extracted with Et_2O (3 x 6 mL), organic layers combined, brine washed (15 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a dark brown oil (856 mg).
The crude sample was further purified by column chromatography (SiO_2 eluting with a gradient of hexanes to 4% to 10% EtOAc in hexanes) to afford the title alkyl dibromide as a colorless oil (750 mg, 2.5 mmol, 63%) IR (neat) ν 3058, 2945, 1945, 1606, 1498, 1449, 1157, 1083, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, m), 7.20 (3H, m), 5.71 (1H, t), 2.68 (2H, t), 2.42 (2H, m), 1.89 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (0), 141.3 (1), 128.7 (1), 128.5 (1), 126.3 (1), 45.9 (1), 44.9 (2), 34.6 (2), 29.8 (2) ppm. ^1H NMR data in agreement with that reported by Chikamatsu, K.; Otsubo, T.; Ogura, F.; Yamaguchi, H. *Chem. Lett.* **1982**, 1081.

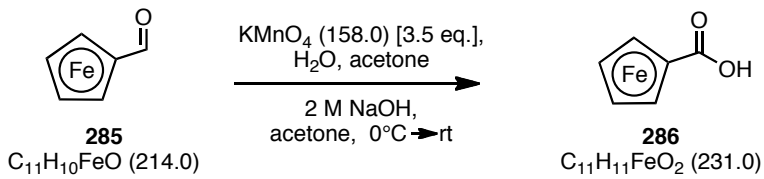


$C_{10}H_{10}Fe$ (186) $C_{11}H_{10}FeO$ (214)

Ferrocene carboxaldehyde - 285: A 2-neck flask was charged with a PhH (33 mL) followed by ferrocene (1.86 g, 10 mmol) and ethyl orthoformate (9.49 mL, 8.89 g, 60 mmol). This orange solution was cooled to 0° C and equilibrated for 30 min before addition of $AlCl_3$ (11.73 g, 88 mmol) over 4 min. The resulting deep blue mixture stirred at 0° C for 30 min more before removal from the ice bath and then stirred at rt for 1.5 h. After this time the reaction was poured into an ice-cold 25% aq. soln of Rochelle's salt. Immediate generation of a suspension of fine ppt followed and filtering twice through Celite was required to remove the ppt. The resulting dark orange/purple filtrate was extracted w/ Et_2O (3 x 50 mL), organic layers combined, washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange/purple solid (1.621 g) that was purified by column chromatography (eluting with 10% EtOAc in hexanes) to afford the title aldehyde as a purplish solid (1.197 g, 5.59 mmol, 56%) IR (neat) ν 1679, 1658, 1454, 1247, 1107, 1031, 997, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (1H, s), 4.79 (2H, s), 4.61 (2H, s), 4.28 (5H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (0), 79.6 (0), 73.4 (1), 69.8 (1) ppm. ^1H NMR data in agreement with that reported by Tang, J.; Xiao-Feng, L.; Ling-Yue, Z.; Xiu-Ling, X.; Deng-Rong, Z. *Syn. Comm.* **2000**, *37*, 1657.

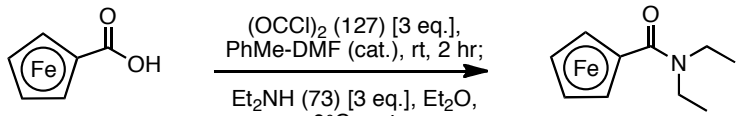


Ferrocenyl phenone - 288: A 2-neck flask was charged w/ an orange solution of ferrocene (9.30 g, 50 mmol) in CH_2Cl_2 (100 mL, 0.5 M) followed 2-chloro benzoylchloride (6.35 mL, d = 1.379, 8.75 g, 50 mmol). This mixture was cooled to –4°C (ice/salt) and equilibrated for 30 min then addition of $AlCl_3$ (6.99 g, 52.5 mmol) through an addition funnel over 25 min. At the end of the addition the reaction was a vibrant dark blue/purple and stirred for an additional 30 min at 0°C, after this time the reaction was warmed to rt and stirred for an additional 2 h. After this time the deep blue reaction cooled to 0°C (ice) then quenched with H_2O (100 mL) added over 5 min, stirred for 30 min at this temperature then the layers were separated. The aq. layer was extracted w/ CH_2Cl_2 (2 x 35 mL), the dark candle apple red layers were combined then washed with H_2O (40 mL), aq. 10% NaOH (2 x 35 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a candy apple red viscous oil (17.2 g, ~100%) that solidified upon standing. This was used in the subsequent reaction with no further purification. A small sample was recrystallized from heptane to yield dark red crystals mp 99-100°C (heptane); IR (neat) ν 2357, 1653, 1446, 1295, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (4H, m), 4.74 (2H, s), 4.59 (2H, s), 4.27 (5H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.5 (0), 73.1 (1), 71.3 (1), 70.3 (1) ppm. ^1H NMR data in agreement with that reported by Reeves, P. C. *Organic Synthesis* **1996**, *6*, 625.



Ferrocene carboxylic acid - 286: A flask was charged with a solution of ferrocene carboxaldehyde (1.9 g, 8.92 mmol) in acetone (90 mL, 0.1 M) and cooled to 0° C where it equilibrated over 20 min. Then a purple solution of $KMnO_4$ (4.93 g, 31.2

mmol) in H_2O (25 mL) was added over 3 min and the reaction warmed to rt with stirring, during this time the reaction progressed from a dark purple to a mud brown. After 2.5 h a solution of 25% NaOH (m/v) (11 mL) was added at once and stirred at rt for an additional 30 min. The reaction was filtered through a pad of Celite and washed with aq. NaOH (10% m/v) (25 mL), the filtrate was washed with Et_2O (3 x 15 mL) before being acidified to pH 4 with an aq. solution of HCl (4 M). The acidified layer was then extracted with Et_2O (4 x 20 mL), the combined organics were washed with brine (40 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield an orange crystalline solid (1.54 g, 6.67 mmol, 72%). A small sample of the material was recrystallized from $CHCl_3$ to afford small fine orange needles; mp 122-124 °C ($CHCl_3$); IR (neat) ν 2883, 2622, 1663, 1478, 1287, 1157, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (2H, t (*unresolved*)), 4.47 (2H, t (*unresolved*)), 4.26 (5H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (0), 69.9 (0), 72.2 (1), 70.8 (1), 70.3 (1) ppm. ^1H NMR data in agreement with that reported by Batsanov, A. S.; Herault, D.; Howard, J. A. K.; Patrick, L. G. F.; Probert, M. R.; Whiting, A. *Organometallics* **2007**, *26*, 2414.

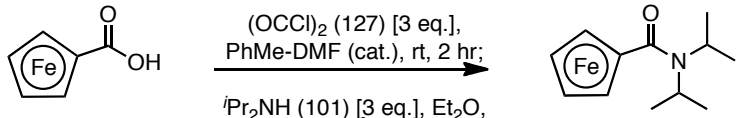


286
$C_{11}H_{10}FeO_2$ (230)

296
$C_{15}H_{19}FeO$ (285)

***N,N*-Diethyl ferrocene carboxamide - 296:** A flask was charged with an orange suspension of ferrocene carboxylic acid **286** (0.35 g, 1.52 mmol) in PhMe (2 mL, 0.7 M) and a catalytic amount of DMF (0.056 g, 0.1 mL, 0.76 mmol), stirred at rt for 5 min before addition of oxalyl chloride (0.58 g, 0.40 mL, 0.76 mmol). The resulting deep red homogenous mixture stirred at rt for 114 min, then concentrated *in vacuo* to yield a very dark red oil (0.622 g) that was taken up in Et_2O (4 mL) and cooled to 0° C and allowed to equilibrate for 20 min. Et_2NH (0.33 g, 0.47 mL, 4.6 mmol) was added over 30 s at which time the red mixture became orange in color, the reaction warmed to rt over 18 h. The reaction was quenched with sat. NH_4Cl (2 mL) and diluted with H_2O (2 mL) at which time the inorganic ppt was filtered through Celite, the filtrate was separated, aq. layer extracted with (3 x 5 mL), the dark orange organics combined, wash w/ brine (10 mL), dried (Na_2SO_4), concentrated *in vacuo* to

yield a dark orange oil (.30 g) that was purified by column chromatography (SiO_2 eluting with 40% EtOAc in hexanes) to yield the title ferrocene carboxamide **296** as a dark orange oil (0.282 g, 0.98 mmol, 65%) IR (neat) ν 3090, 2970, 2927, 2360, 1614, 1489, 1456, 1413, 1282, 1102, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (2H, t, *J* = 1.8 Hz), 4.27 (2H, t, *J* = 1.7 Hz), 4.19 (5H, s), 3.48 (4H, broad s,), 1.19 (6H, t, *J* = 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (0), 79.0 (0), 70.4 (1), 69.9 (1), 66.0 (1), 42.6 (2), 41.0 (2), 14.9 (3), 13.0 (3) ppm. ^1H NMR data in agreement with that reported by Szarka, Z.; Skoda-Folda, R.; Kuik, A.; Berente, Z.; Kollar, L. *Synthesis* **2003**, 545.

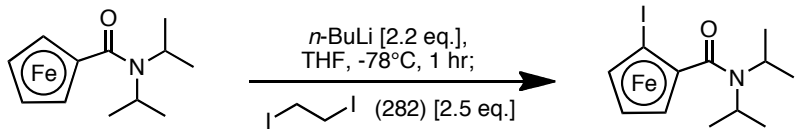


286
$C_{11}H_{10}FeO_2$ (230)

297
$C_{17}H_{23}FeO$ (313)

***N,N*-Diisopropyl ferrocene carboxamide - 297:** A flask was charged with an orange suspension of ferrocene carboxylic acid (4.0 g, 17.4 mmol) in PhMe (25 mL, 0.7 M) and a catalytic amount of DMF (635 mg, 0.67 mL, 8.7 mmol), stirred at rt for 5 min before addition of oxalyl chloride (6.62 g, 4.5 mL, 52.2 mmol) which resulted in immediate vigorous evolution of gas. This deep red homogenous mixture stirred at rt for 2 h, then was concentrated *in vacuo* to yield a very dark red oil (5.2 g) that was taken up in Et_2O (50 mL) and cooled to 0° C and allowed to equilibrate for 15 min before ^{i}PrNH (5.28 g, 7.3 mL, 52.2 mmol) was added over 30 s at which time the red mixture became orange in color and the reaction warmed to rt over 18 h. The reaction was quenched with sat. NH_4Cl (6 mL) and diluted with H_2O (4 mL) at which time the inorganic ppt was filtered through Celite, the filtrate was separated, aq. layer extracted with (3 x 35 mL), dark orange organics combined, wash w/ brine (30 mL), dried (Na_2SO_4), concentrated *in vacuo* to yield a granular dark orange solid (5.06 g, 16.1 mmol, 93%). A small sample was recrystallized from hexane to afford large dark orange prisms: mp 89-91°C (hexanes); IR (neat) ν 2965, 2927, 1636, 1462, 1369, 1314, 1097, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (2H, t, *J* = 1.8 Hz), 4.27 (2H, t, *J* = 1.7 Hz), 4.19 (5H, s), 3.48 (4H, broad s,), 1.19 (6H, t, *J* = 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (0), 81.4 (0), 70.1 (1), 69.8 (1), 69.0 (1),

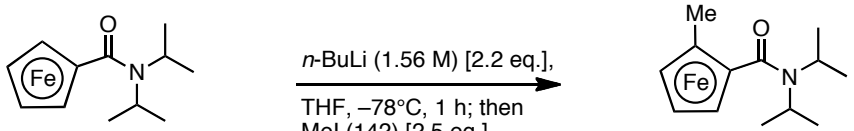
49.7 (1), 46.4 (1), 21.3 (3) ppm. ^{1}H NMR data in agreement with that reported by Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am Chem. Soc.* **1996**, *118*, 685.



297
$C_{17}H_{23}FeO$ (313)

298
$C_{17}H_{22}FeIO$ (327)

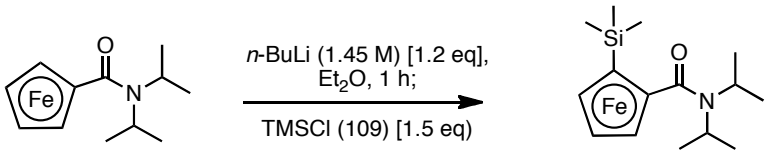
Iodoferrocene - 298: A flask was charged with ferrocene carboxamide **297** (0.50 g, 1.6 mmol) and THF (9 mL) and stirred at rt to homogeneity. This orange solution was then cooled to –78°C and allowed to equilibrate for 20 min before addition of *n*-BuLi (1.4 M in hexanes, 2.5 mL, 3.51 mmol) down the side of flask over 10 s. A noticeable color change to deep red occurred and the reaction stirred for 60 min at –78°C, after which time a solution of diiodoethane (1.1 g, 3.98 mmol) in THF (7 mL) was added down the side of the flask over 15 s. The deep red color attenuated and an orange color ensued, this warmed to rt over 17 h after which time the now dark purple reaction was quenched with 10% $Na_2S_2O_3$ (4 mL), layers separated, aq. extracted with Et_2O (3 x 15 mL), organics combined, wash w/ brine (20 mL) and conc. *in vacuo* to yield a dark brown oil (0.856 g) that was purified by column chromatography (SiO_2 eluting with 20% Et_2O in hexanes) to yield the title iodoferrocene **298** as a granular crystalline light orange solid (0.63 g, 1.43 mmol, 87%). A small sample was recrystallized from hexanes to afford fine orange needles m.p. 97-99° C (hexanes); $[\alpha]_D^{25}$ = +89.8 (c = 1.00, $CHCl_3$); IR (neat) ν 2965, 2927, 2371, 2327, 1636, 1462, 1369, 1320, 1200, 813 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (1H, dd, *J* = 2.3,1.3 Hz), 4.34 (5H, s), 4.28 (1H, dd, *J* = 2.4, 1.2), 4.16 (1H, t, *J* = 2.4), 3.61 (1H, t, *J* = 5.8 Hz), 3.40 (1H, d, *J* = 6.0 Hz), 1.09 (6H, d, *J* = 5.7), 0.98 (6H, d, *J* = 5.7 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (0), 92.8 (0), 73.8 (1), 72.9 (1), 67.8 (1), 67.0 (1), 50.9 (1), 46.1 (1), 40.6 (0), 21.1 (3), 21.0 (3), 20.8 (3) ppm. ^{1}H NMR data in agreement with that reported by Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am Chem. Soc.* **1996**, *118*, 685.



297
$C_{17}H_{23}FeNO$ (313)

299
$C_{18}H_{25}FeNO$ (327)

Methylferrocene - 299: A flask was charged with an orange solution of ferrocenecarboxamide **299** (100 mg, 0.32 mmol) in THF (2.5 mL) cooled to –78°C and equilibrated for 20 min, before addition of *n*-BuLi (0.45 mL, 1.56 M in hexanes, 0.72 mmol) over 15 s, resulting in a vibrant orange/red color, this was for stirred for 1 h at –78°C. After this time the reaction was quenched with MeI (0.1 mL, d = 2.3, 136 mg, 0.96 mmol) by addition downside of flask and then warmed to rt over 12 h. The brown-orange reaction was diluted with sat. NH_4Cl (4 mL) and H_2O (3 mL) before the layers were shaken and separated, followed by Et_2O (3 x 5 mL) extraction of aq. layer, dark orange organics combined, wash with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange-brown oil (260 mg) that was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title ferrocene **299** as an orange solid (92 mg, 0.28 mmol, 88%); Mp = 79-80°C; $[\alpha]_D^{25}$ = +23.2 (c = 1.0, $CHCl_3$); IR (neat) ν 3087, 2964, 2892, 2357, 1667, 1641, 1456, 1242, 1118, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (5H, s), 4.16 (1H, dd, *J* = 2.4, 1.6), 4.10 (1H, dd, *J* = 2.4, 1.6), 4.00 (1H, dd, unresolved), 4.00-3.90 (1H, b, isopropyl methine), 3.40-3.25 (1H, b, isopropyl methine), 2.05 (3H, s), 1.52-1.41 (3H, b), 1.1-1.0 (3H, b) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (0), 87.4 (0), 84.4 (0), 70.5 (1), 68.8 (1), 66.6 (1), 65.5 (1), 50.4 (1), 46.0 (1), 21.2 (3), 13.6 (3) ppm. ^1H NMR data in agreement with that reported by Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am Chem. Soc*. **1996**, *118*, 685.

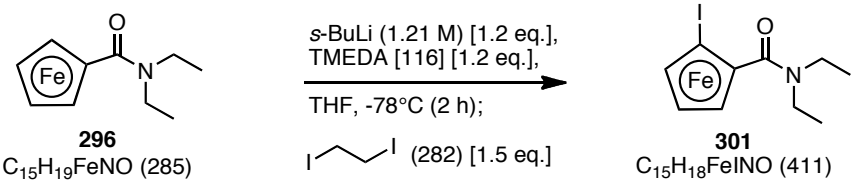


297
$C_{17}H_{25}FeNO$ (313)

300
$C_{20}H_{33}FeNOSi$ (387)

Silylferrocene - 300: A flask was charged an orange solution of ferrocene **297** (150 mg, 0.479 mmol) in Et_2O (5 mL, 0.09 M) and cooled to –78°C then equilibrate for 10

min before addition of *n*-BuLi (1.45 M in hexanes, 0.396 mL, 0.575 mmol) over 15 s and stir at –78°C for 1 h. The reaction was quenched with TMSCl (108.6, 0.12 mL, 0.72 mmol) dropwise over 30 s and the reaction stirred at –78°C for 50 min before removal from the cold bath and warmed to rt over 30 min after which time the orange reaction was diluted with sat. NH_4Cl (4 mL), layers were shaken and separated, aq. layer extracted with Et_2O (2x6 mL), orange organics combined, washed with brine (6 mL), dried (Na_2SO_4), conc. *in vacuo* to yield an orange oil that crystallized upon standing for 4 h (176 mg, 0.95 mmol, 65%). No further purification required. A small sample was recrystallized from EtOAc/Hexanes mp: 102-104°C; IR (neat) ν 3093, 2956, 2359, 1629, 1610, 1447, 1326, 1243, 1148, 1035, 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (1H, dd, *J* = 2.3, 1.2), 4.29 (2H, s), 4.27 (5H, s), 4.13 (1H, dd, *J* = 2.3, 1.2), 1.5 (6H, br), 1.11 (6H, br), 0.27 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (0), 73.8 (0), 73.6 (1), 70.0 (1), 69.5 (1), 20.9 (0), 0.7 (3) ppm. ^1H NMR data in agreement with that reported by Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am Chem. Soc.* **1996**, *118*, 685.

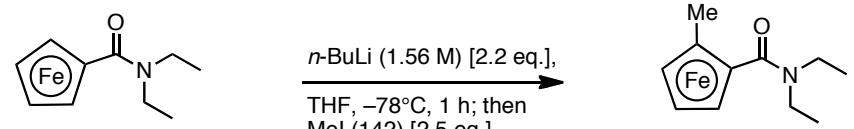


296
$C_{15}H_{19}FeNO$ (285)

301
$C_{15}H_{18}FeINO$ (411)

Iodoferrocene - 301: A flask was charged with an orange solution of ferrocene carboxamide **296** (366 mg, 1.28 mmol) in THF (7.5 mL) and cooled to –78°C and equilibrated for 25 min followed by addition of *n*-BuLi (1.6 M in hexanes, 1.76 mL, 2.82 mmol) down the side of flask over 30 s. This reaction was stirred at –78°C for an additional 55 min during which time the color progressed from an orange to deep red color, then a solution of diiodoethane (901 mg, 3.2 mmol) in THF (6 mL) was added over 40 s, no color change was observed, and warmed to rt over 16 h. The dark brown reaction was quenched with 10% $Na_2S_2O_3$ (6 mL), layers were shaken and separated, aq. extracted with Et_2O (3 x 15 mL), brown/orange organics combined, washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a

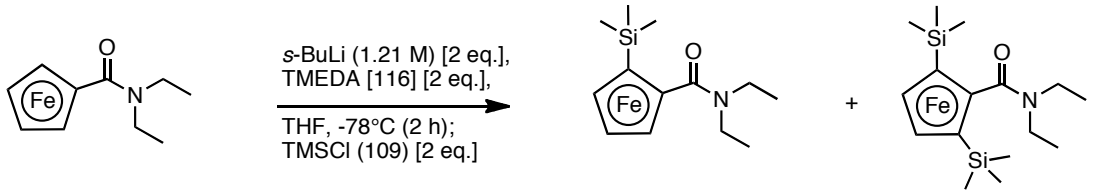
brown viscous oil (621 mg). This was purified by column chromatography (SiO_2 eluting with 18% EtOAc in hexanes) to yield the title iodide as a dark orange oil (468 mg, 1.14 mmol, 89%) IR (neat) ν 3087, 2967, 2928, 1637, 1482, 1446, 1378, 1274, 1125, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.45 (1H, dd, *J* = 2.2, 1.3), 4.36 (1H, dd, *J* = 2.5, 1.3), 4.34 (5H, s), 4.20 (1H, t), 3.72 (2H, br), 3.24 (2H, br), 1.21 (3H, br), 0.98 (3H, br) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2 (0), 89.9 (0), 74.2 (1), 73.1 (1), 68.2 (1), 67.9 (1), 41.1 (1) ppm. ^1H NMR data in agreement with that reported by Metallinos, C.; Szillat, H.; Taylor, N. J.; Snieckus, V. *Adv. Synth. Catal.* **2003**, *345*, 370.



296
$C_{15}H_{19}FeNO$ (285)

302
$C_{16}H_{21}FeINO$ (299)

Methylferrocene - 302: A flask was charged with an orange solution of ferrocene carboxamide **296** (200 mg, 0.70 mmol) in THF (4 mL) cooled to –78°C and equilibrated for 20 min, before addition of *n*-BuLi (1.1 mL, 1.40 M in hexanes, 1.54 mmol) over 30 s, resulting in a dark red color, this was for 1 h at –78°C. After this time the reaction was quenched with MeI (0.13 mL, d = 2.3, 298 mg, 2.1 mmol) by addition downside of flask and then warmed to rt over 12 h. The brown-orange reaction was diluted with sat. NH_4Cl (4 mL) and H_2O (3 mL) before the layers were shaken and separated, followed by Et_2O (3 x 5 mL) extraction of aq. layer, dark orange organics combined, wash with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange-brown oil (260 mg) that was purified by column chromatography (SiO_2 eluting with 20% EtOAc in hexanes) to yield the title ferrocene **302** as an orange solid: (192 mg, 0.64 mmol, 91%) IR (neat) ν 3087, 2964, 2892, 2357, 1667, 1641, 1456, 1242, 1118, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (6H, s, H-Cp overlap), 4.14 (1H, m), 4.00 (1H, m), 3.52 (1H, b), 3.30 (4H, b, C$\underline{H}_2$-N), 2.05 (3H, s), 1.10-1.01 (6H, 6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (0), 99.2 (0), 70.2 (1), 69.1 (1), 67.8 (1), 64.1 (1), 13.9 (3) ppm.



296 $C_{15}H_{19}FeNO$ (285)

303 $C_{18}H_{27}FeNOSi$ (347)

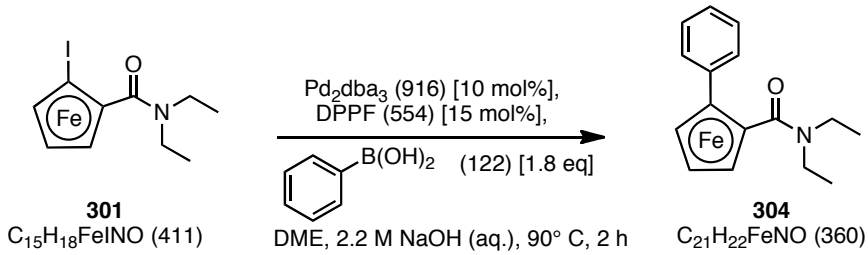
328 $C_{21}H_{35}FeNOSi_2$ (414)

Silylferrocene - 303: A flask was charged Et_2O (4 mL) followed by TMEDA (0.435 mL, d = 0.775, 334 mg, 2.88 mmol), *s*-BuLi (2.38 mL, 1.21 M in cyclohexane, 2.88 mmol) then cooled to –78°C and equilibrated for 20 min, before addition of an orange solution of ferrocene carboxamide **296** (410 mg, 1.44 mmol) in Et_2O (2.5 mL) over 30 s, then stirred for 2 h at –78°C. After this time the reaction had progressed to a dark brown color and was quenched with TMSCl (0.365 mL, d = 0.856, 312 mg, 2.88 mmol) by dropwise addition over 30 s and warmed to rt over 16 h. The brown-orange reaction was diluted with sat. NH_4Cl (4 mL) and H_2O (3 mL) before the layers were shaken and separated, followed by Et_2O (2 x 5 mL) extraction of aq. layer, dark orange organics combined, wash with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange-brown oil (534 mg) that was purified by column chromatography (SiO_2 eluting with 4% EtOAc in hexanes) to yield the following products as orange oils in order of elution:

bis-Silylatedferrocene - 328: (214mg, 0.517 mmol, 36%) $[\alpha]_D^{25}$ = +18.4 (c = 1.0, CH_2Cl_2) IR (neat) ν 3087, 2964, 2892, 2357, 1667, 1641, 1456, 1242, 1118, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (5H, s), 4.21 (2H, s), 3.42 (2H, q), 3.03 (1H, q), 1.19 (3H, t), 0.993 (3H, t), 0.251 (18H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (0), 99.2 (0), 75.2 (1), 74.0 (0), 70.4 (1), 69.7 (1), 43.6 (2), 39.1 (2), 14.1 (3), 13.2 (3), 0.7 (3) ppm. MS (CI) *m/z* 428 $(M+H)^+$; HRMS (ES) *m/z* 429.1620 (calcd. for $C_{21}H_{35}NOFeSi_2$: 429.1607).

Silylferrocene - 303: (264 mg, 0.76 mmol, 53%) IR (neat) ν 3100, 2976, 2361, 2334, 1633, 1618, 1454, 1267, 863, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, dd, *J* = 2.3, 1.1), 4.33 (1H, t), 4.27 (5H, s), 4.14 (1H, dd, 2.4, 1.2), 3.26 (4H, br), 1.11 (6H, br), 0.256 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (0), 90.1 (0),

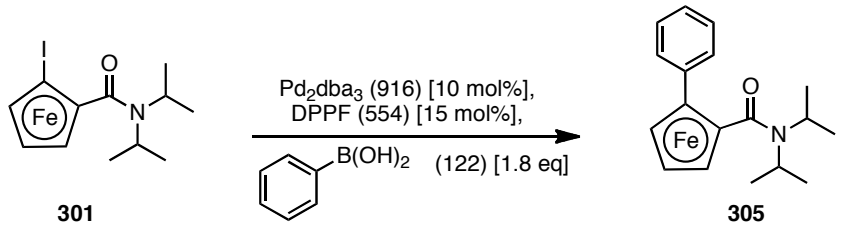
73.8 (1), 73.2 (0), 70.9 (1), 69.9(1), 42.9 (2), 39.8 (2), 14.3 (3), 13.0 (3), 0.5 (3) ppm; HRMS (EI$^+$) *m/z* 357.12110 (calcd. for $C_{18}H_{27}FeNOSi$: 357.12114).



301
$C_{15}H_{18}FeINO$ (411)

304
$C_{21}H_{22}FeNO$ (360)

Phenylferrocene - 304: A flask was charged with a black suspension of Pd_2dba_3 (14.0 mg, 0.0146 mmol) and DPPF (12.0 mg, 0.0219 mmol) in DME (1 mL, 0.0219 M), stirred at rt for while sparging with Ar for 15 min. Then addition of iodoferrocene **301** (60 mg, 0.146 mmol) in DME (0.50 mL, 0.29 mmol) followed by addition of 2.2 M NaOH (0.166 mL, 0.365 mmol) then stirred for 15 min at rt before heating to 90°C and maintaining for 2 h. After this time the black reaction was quenched with H_2O (10 mL) and diluted with EtOAc (5 mL) before layers were shaken and separated. The aq. layer was extracted with EtOAc (3 x 4 mL), organics combined, washed w/ brine (5 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a dark orange/brown oil (58 mg) that was purified with column chromatography (SiO_2 eluting with 18% EtOAc in hexanes) to yield the title substituted phenylferrocene **304** (34 mg, 0.094 mmol, 65%) as an orange solid m.p. 107-109°C (hexanes); IR (neat) ν 3089, 2966, 2935, 2328, 1623, 1464, 1268, 1109, 821, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, m), 7.23 (3H, m), 4.52 (1H, dd, *J* = 2.1, 2.0), 4.49 (1H, dd, *J* = 2.3, 1.9), 4.29 (1H, t, *J* = 2.33 Hz), 4.25 (5H, s), 3.69 (1H, dq, *J* = 13.6, 6.9), 3.15 (1H, dq, *J* = 13.6, 6.9), 2.90 (1H, dq, *J* = 13.6, 6.9), 2.73 (1H, dq, *J* = 14.0, 7.0), 1.09 (3H, t, *J* = 7.1), 0.64 (3H, t, *J* = 7.1) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (0), 138.2 (0), 128.3 (1), 127.9 (1), 126.7 (1), 87.3 (0), 73.0 (1), 71.5 (1), 70.4 (1), 67.2 (1), 65.5 (1), 42.8 (2), 39.5 (2), 13.6 (3), 12.7 (3) ppm.

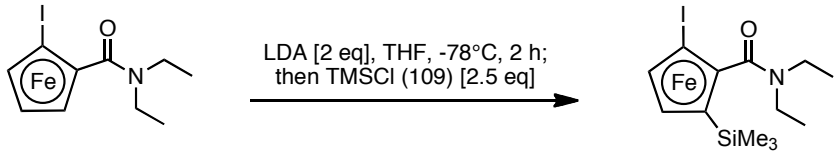


301
$C_{17}H_{22}FeINO$ (439)

DME, 2.2 M NaOH (aq.), 90° C, 2 h

305
$C_{23}H_{27}FeNO$ (377)

Phenylferrocene - 305: A flask was charged with a black suspension of Pd_2dba_3 (17.0 mg, 0.023 mmol) and DPPF (20.0 mg, 0.034 mmol) in DME (1.5 mL), stirred at rt for while sparging with Ar for 15 min. Then addition of iodoferrocene **301** (100 mg, 0.23 mmol) in DME (0.50 mL) followed by addition of 2.2 M NaOH (0.26 mL, 0.57 mmol) then stirred for 15 min at rt before heating to 90°C and maintaining for 2 h. After this time the black reaction was quenched with H_2O (10 mL) and diluted with EtOAc (5 mL) before layers were shaken and separated. The aq. layer was extracted with EtOAc (3 x 4 mL), organics combined, washed w/ brine (5 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a dark orange/brown oil (89 mg) that was purified with column chromatography (SiO_2 eluting with 15% EtOAc in hexanes) to yield the title substituted phenylferrocene (61 mg, 0.16 mmol, 61%) as an orange solid as a mixture with unreacted iodoferrocene **298**. m.p. 107-109°C (hexanes); IR (neat) ν 3089, 2966, 2935, 2328, 1623, 1464, 1268, 1109, 821, 708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.23 (5H, m), 4.49 (1H, dd, J = 2.3, 1.9), 4.29 (1H, t, J = 2.33 Hz), 4.49 (1H, dd, unresolved), 4.41 (1H, dd, unresolved), 4.28 (5H, s), 3.50 (1H, qq, J = 13.6, 6.9), 3.21 (1H, qq, J = 14.0, 7.0), 1.50 (1H, d, J = 6.9), 1.39 (1H, d, J = 7.0), 0.81 (3H, d, J = 7.1), 0.21 (3H, d, J = 6.9) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (0), 138.2 (0), 128.3 (1), 127.9 (1), 126.7 (1), 87.3 (0), 73.0 (1), 71.5 (1), 70.4 (1), 67.2 (1), 65.5 (1), 42.8 (2), 39.5 (2), 13.6 (3), 12.7 (3) ppm.

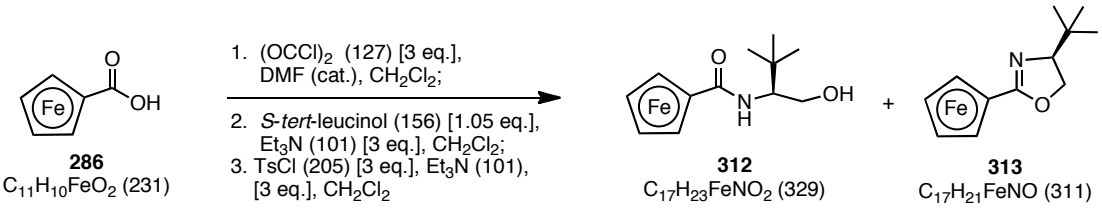


301
$C_{15}H_{18}FeINO$ (411)

308
$C_{18}H_{26}FeINOSi$ (483)

Iodoferrocene - 308: A flask was charged with an orange solution of ferrocenecarboxamide **301** (100.0 mg, 0.24 mmol) in THF (1.5 mL) and cooled to –

78°C to equilibrate for 15 min before addition of a freshly prepared solution of LDA (0.50 mmol) in THF (1 mmol) downside of flask. Reaction stirred at –78°C for 2 h before quench with TMSCl (0.15 mL, 1.22 mmol) and warming to room temperature over 9 h, before diluting with NH_4Cl (5 mL) and partitioning in EtOAc (5 mL). The aq. layer was extracted with EtOAc (3 x 4 mL), organics combined, washed w/ brine (10 mL), dried (Na_2SO_4) and conc. *in vacuo* to yield a dark orange/brown oil (112 mg) that was purified by column chromatography (SiO_2 eluting with a gradient of 5-20% EtOAc in hexanes) to yield the title iodoferrocene **308** (16 mg, 0.033 mmol, 14%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (1H, d, unresolved), 4.38 (5H, s), 4.32, (1H, d, unresolved), 3.55 (1H, dq, *J* = 14.1, 7.0), 3.35 (1H, dq, *J* = 13.6, 6.9), 3.08 (1H, dq, *J* = 13.6, 6.9), 2.90 (1H, dq, *J* = 13.6, 6.9), 1.21 (3H, t, *J* = 6.9, 7.0), 1.01 (3H, t, *J* = 7.1), 0.35 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (0), 138.2 (0), 128.3 (1), 127.9 (1), 126.7 (1), 87.3 (0), 73.0 (1), 71.5 (1), 70.4 (1), 67.2 (1), 65.5 (1), 42.8 (2), 39.5 (2), 13.6 (3), 12.7 (3) ppm. MS (ES) *m/z* 485 ($M+H^+$) *m/z* HRMS (ES) *m/z* 484.0264 (calcd. for $C_{18}H_{26}FeINOSi$: 484.0256).



286 $C_{11}H_{10}FeO_2$ (231)

312 $C_{17}H_{23}FeNO_2$ (329)

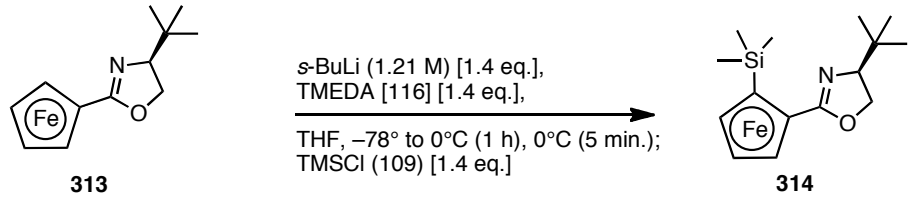
313 $C_{17}H_{21}FeNO$ (311)

Oxazolylferrocene - 313: A flask was charged an orange suspension of ferrocene carboxylic acid **286** (1.12 g, 4.85 mmol) in CH_2Cl_2 (25 mL) followed by a catalytic amount of DMF (0.05 mL, d = 0.944, 0.65 mmol) then dropwise addition of oxalyl chloride (0.68 mL, d = 1.45, 984 mg, 7.76 mmol) over 4 min, that was accompanied by vigorous evolution of gas. The reaction stirred at rt for 1 h, during which time it became a deep red homogenous mixture. After concentrating the reaction *in vacuo*, the resulting deep red oil was taken up in CH_2Cl_2 (10 mL) and added dropwise to a 0°C chilled solution of s-*tert*-leucinol (785 mg, 5.02 mmol) and Et_3N (2.12 mL, d = 0.73, 1.54 g, 15.2 mmol) in CH_2Cl_2 (25 mL), then warmed to rt over 1 h 15 min. The red reaction was diluted with Et_2O (30 mL) becoming an opaque brown color, the

layers were shaken and separated and the organic layer was washed with 1.1 M NaOH (40 mL) at which time the organic layer became clear and was dried (Na_2SO_4) then concentrated *in vacuo* to yield a brown solid (1.2 g). The crude material was dissolved in CH_2Cl_2 (40 mL) stirred at rt for 5 min before addition of tosylchloride (1.54g, 7.5 mmol) at once followed by Et_3N (2.12 mL, d = 0.725, 1.54 g, 15.2 mmol) and stirred at rt for 19 h. The dark brown reaction was quenched with sat. NH_4Cl (30 mL), the layers shaken and separated, organic layers combined and washed with brine (25 mL), then dried (Na_2SO_4) and concentrated *in vacuo* to yield a brown-orange solid (1.4 g) which was purified by column chromatography (SiO_2 eluting with 12% EtOAc in hexanes) to yield the following products as a red oil and an orange solid in order of elution:

Amide - 312: (28 mg, 0.085 mmol, 1.5%); IR (neat) ν 3356, 2964, 2928, 1718, 1641, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, d, *J* = 8.0), 4.68 (1H, d, *J* = 14.5), 4.37 (2H, q), 4.23 (5H, s), 3.95 (2H, dd, unresolved), 3.63 (1H, t), 2.06 (1H, br, OH), 1.04 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (0), 76.1 (0), 70.8 (1), 70.0 (1), 68.6 (1), 68.0 (1), 64.0 (2), 33.6 (0), 27.3 (3) ppm. ^1H NMR data in agreement with that reported by Sammakia, T.; Latham, H. A.; Schaad, D. R.; *J. Org. Chem.* **1995**, *60*, 867.

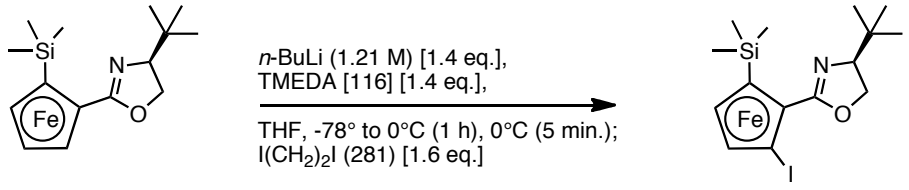
Oxazolylferrocene - 313: (800 mg, 2.6 mmol, 53%); IR (neat) ν 2950, 2365, 2079, 1662, 1494, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.77 (1H, dd, *J* = 2.2, 1.1), 4.70 (1H, dd, *J* = 2.2, 1.2), 4.32 (2H, d, *J* = 3.7, 1.6), 4.19 (2H, m), 4.19 (5H, s), 3.89 (1H, dd, *J* = 10.0, 7.5), 0.95 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (0), 76.9 (1), 70.3 (0), 70.2 (1), 69.7 (1), 69.2 (1), 69.1 (1), 68.5 (2), 33.8 (0), 26.1 (3) ppm. ^1H NMR data in agreement with that reported by Sammakia, T.; Latham, H. A.; Schaad, D. R.; *J. Org. Chem.* **1995**, *60*, 867.



313
$C_{17}H_{21}FeNO$ (311)

314
$C_{20}H_{29}FeNOSi$ (383)
d.r.= 24:1

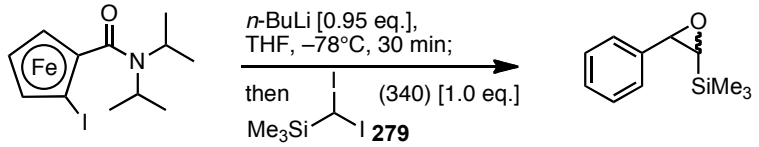
Silylferrocene - 314: A flask was charged w/ an orange solution of oxazoline **313** (800 mg, 2.57 mmol) in CH_2Cl_2 (13 mL, 0.18 M) followed by TMEDA (0.54 mL, d = 0.78, 417 mg, 3.59 mmol) then cooled to –78°C and equilibrated for 5 min. before dropwise addition of *s*-BuLi (2.97 mL, 1.21 M in cyclohexane, 3.59 mmol) over 3 min. A deep red color developed as the reaction stirred at –78°C for 2 h, then submerged in an ice bath for 5 min before quenching with TMSCl (0.47 mL, d = 0.86, 402 mg, 3.71 mmol), the reaction then warmed to rt and stirred for an additional 22 h. After this time the dark cranberry red reaction was diluted with sat. $NaHCO_3$ (25 mL) the layers were shaken and separated, then the aq. layer was extracted with Et_2O (2 x 10 mL), the dark orange organics were combined, washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange-red viscous oil (1.2 g) that was purified by column chromatography (SiO_2 eluting with 15% EtOAc in hexanes) to yield the title ferrocene **314** as a dark orange oil (885 mg, 2.31 mmol, 89%) in a diastereomeric ratio of 24:1. IR (neat) ν 3104, 2953, 2898, 2863, 2353, 2334, 1657, 1474, 1369, 1240, 1147, 987 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (1H, dd, *J* = 2.28, 1.38), 4.42 (1H, t, *J* = 2.4), 4.27 (1H, dd, *J* = 1.4, .98), 4.21 (1H, dd, *J* = 8.4, 1.6), 4.18 (5H, s), 4.08 (1H, t, *J* = 8.2), 3.88 (1H, dd, *J* = 8.1, 2.0), 0.96 (9H, s), 0.32 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (0), 77.1 (1), 76.9 (1), 73.5 (1), 71.7 (1), 69.6 (1), 68.1 (2), 33.8 (0), 26.2 (3), 0.7 (3) ppm. ^1H NMR data in agreement with that reported by Sammakia, T.; Latham, H. A.; Schaad, D. R.; *J. Org. Chem.* **1995**, *60*, 867.



314
$C_{20}H_{29}FeNOSi$ (383)

315
$C_{20}H_{28}FeINOSi$ (509)

Iodoferrocene - 315: A flask was charged w/ an orange solution of oxazoline **314** (1.32 g, 3.45 mmol) in THF (30 mL) followed by TMEDA (0.72 mL, d = 0.78, 520 mg, 4.48 mmol) then cooled 0°C and equilibrated for 5 min. before dropwise addition of *n*-BuLi (2.95 mL, 1.52 M in hexanes, 4.48 mmol) over 3 min. A deep red color developed as the reaction stirred at 0°C and warmed to rt over 2 h, after which time a solution containing $I(CH_2)_2I$ (1.26 g, 4.50 mmol) in THF (10 mL) was added and stirred for an additional 2 h before being diluted 10% Na_2SO_4 (50 mL) and then partitioned in Et_2O (3 x 25 mL), organics combined and washed with brine (45 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a dark orange-red viscous oil (1.9 g) that was purified by column chromatography (SiO_2 eluting with 2% EtOAc in hexanes) to yield the title iodoferrocene **315** as an orange solid (702 mg, 1.38 mmol, 40%) in a diastereomeric ratio of > 24:1 m.p. 78-80°C (MeOH); $[\alpha]_D^{23}$ = +64.2 (c = 0.15, $CHCl_3$); IR (neat) ν 2951, 2900, 2866, 1653, 1424, 1245, 1157, 985, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, d, *J* = 2.4), 4.26 (1H, d, *J* = 2.3), 4.24 (1H, dd, *J* = 1.4, .98), 4.21 (7H, m), 4.12 (1H, apparent t), 3.98 (1H, dd, *J* = 10.0, 8.0), 0.98 (9H, s), 0.38 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 (0), 79.4 (0), 78.9 (1), 77.3 (1), 76.7 (1), 72.8 (1), 68.0 (2), 33.8 (0), 26.1 (3), 0.3 (3) ppm. HRMS (EI^+) *m/z* 507.01588 (calcd. for $C_{20}H_{26}NOSiFeI$: 507.01781).

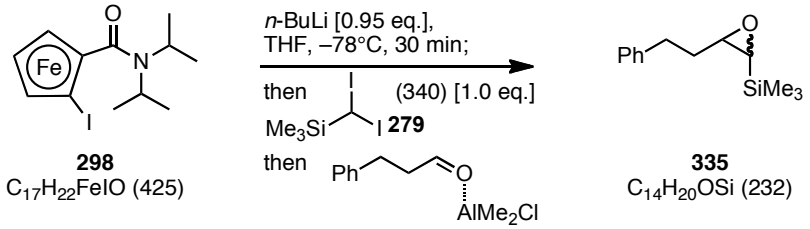


298
$C_{17}H_{22}FeIO$ (425)

332
$C_{11}H_{17}OSi$ (193)

Oxirane - 332: A flask was charged with an organge solution of iodoferrocene **298** (193 mg, 0.44 mmol) in THF (1 mL) cooled to –78°C and equilibrated for 10 min before addition of *n*-BuLi (1.98 M in hexanes, 0.22 mL, 0.42 mmol) over 10 s which

resulted in a dark organge color. After 35 min a solution of diiodosilane **279** (150 mg, 0.44 mmol) in THF (0.5 mL) was added downside of flask and stirred for 45 min before addition of a Me_2AlCl-PhCHO complex (50 mg, 0.46 mmol) in THF (0.5 mL) was added and the reaction warmed to room temperature over 9 h. The reaction was diluted with NH_4Cl (4 mL) and partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 5 mL), brine wash (20 mL), dried Na_2SO_4 and conc. *in vacuo* to yield the crude product as an orange oil (290 mg) which was purified with column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to yield the title **epoxide 332** as a colorless oil (33 mg, 0.17 mmol, 40%) IR (neat) ν 1605, 1595, 1248, 842, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (5H, m), 4.40 (1H, d, *J* = 5.1), 3.86 (1H, d, *J* = 3.1 Hz), 2.68 (1H, d, *J* = 5.2), 2.48 (1H, d, *J* = 3.3 Hz), 0.30 (9H, s) ppm. ^1H NMR data in agreement with that reported by Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1982**, 867.

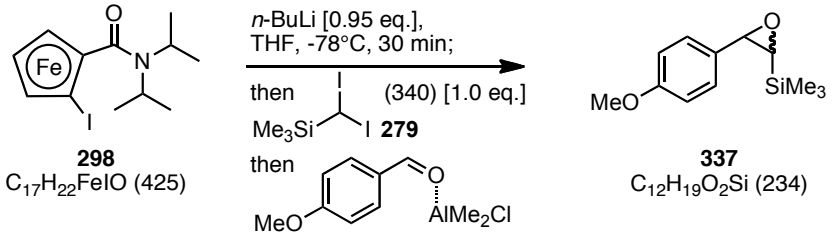


298
$C_{17}H_{22}FeIO$ (425)

335
$C_{14}H_{20}OSi$ (232)

Oxirane - 335: A flask was charged with an organge solution of iodoferrocene **298** (175 mg, 0.44 mmol) in THF (1 mL), cooled to –78°C and equilibrated for 10 min before addition of *n*-BuLi (1.98 M in hexanes, 0.22 mL, 0.42 mmol) over 10 s which resulted in a dark orange color. After 35 min a solution of diiodosilane (150 mg, 0.44 mmol) in THF (0.5 mL) was added downside of flask and stirred for 45 min before addition of a Me_2AlCl-PhCHO complex (50 mg, 0.46 mmol) in THF (0.5 mL) was added and the reaction warmed to room temperature over 9 h. The reaction was diluted with NH_4Cl (4 mL) and partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 5 mL), brine wash (20 mL), dried Na_2SO_4 and conc. *in vacuo* to yield the crude product as an orange oil (290 mg) which was purified with column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to yield the title epoxide as a colorless oil (35 mg, 0.15 mmol, 35%) IR (neat) ν 3067, 3029, 2957, 2853, 1609, 1499, 1417, 1251, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (2 H, m), 7.21 (2 H,

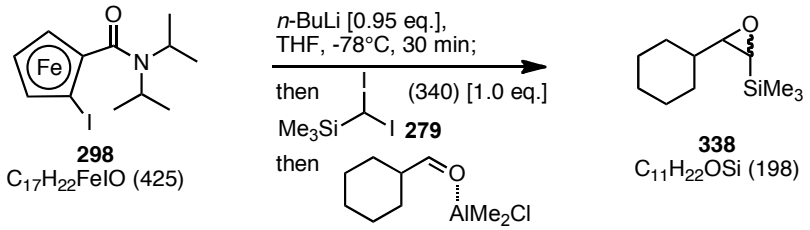
m), 3.15 (1 H, dt, *J* = 7.5, 5.0), 2.78 (2 H, m, diastereotopic benzylic protons [integration off slightly due to incorporation of *trans* isomer peaks in signal as well]), 2.23 (1 H, d, *J* = 5.1), 1.91 (1 H, m), 1.76 (1 H, m), 0.14 (9 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6 (0), 128.7 (1), 128.6 (1), 126.2 (0), 57.2 (1), 51.1 (1), 33.7 (2), 33.5 (2), –1.5 (3) ppm. MS (EI+) *m/z* 129 (58%), 91 (42%), 73 (100%); HRMS (EI+) *m/z* 232.12804 (calcd. for $C_{14}H_{20}OSi$: 232.12835).



298
$C_{17}H_{22}FeIO$ (425)

337
$C_{12}H_{19}O_2Si$ (234)

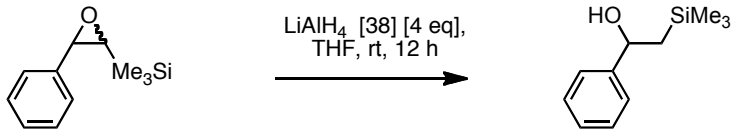
Oxirane - 337: A flask was charged with an orange solution of iodoferrocene **298** (175 mg, 0.44 mmol) in THF (1 mL), cooled to –78°C and equilibrated for 10 min before addition of *n*-BuLi (1.98 M in hexanes, 0.22 mL, 0.42 mmol) over 10 s which resulted in a dark orange color. After 35 min a solution of diiodosilane **279** (150 mg, 0.44 mmol) in THF (0.5 mL) was added downside of flask and stirred for 45 min before addition of a Me_2AlCl-anisaldehyde complex (105 mg, 0.45 mmol) in THF (0.5 mL) was added and the reaction warmed to room temperature over 9 h. The reaction was diluted with NH_4Cl (4 mL) and partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 5 mL), brine wash (20 mL), dried Na_2SO_4 and conc. *in vacuo* to yield the crude product as an orange oil (290 mg) which was purified with column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to yield the title epoxide **337** as a colorless oil (38 mg, 0.16 mmol, 37%) IR (neat) ν 2957, 2835, 1728, 1690, 1615, 1518, 1248, 1176, 1035, 844 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2 H, d, *J* = 8.0), 6.86 (1 H, d, *J* = 7.9), 4.20 (3 H, d, *J* = 5.2), 3.81 (3 H, s), 2.48 (1 H, d, *J* = 5.2), -0.16 (9 H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 159.1 (0), 130.3 (0), 127.4 (1), 113.6 (1), 57.0 (1), 55.4 (1), 53.7 (1), –2.0 (3) ppm. ^{1}H NMR data in agreement with that reported by Kang, K.-T.; Park, C. Y.; Kim, J. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 48.



298
$C_{17}H_{22}FeIO$ (425)

338
$C_{11}H_{22}OSi$ (198)

Oxirane - 338: A flask was charged with an organge solution of iodoferrocene **298** (175 mg, 0.44 mmol) in THF (1 mL), cooled to –78°C and equilibrated for 10 min before addition of *n*-BuLi (1.98 M in hexanes, 0.22 mL, 0.42 mmol) over 10 s which resulted in a dark orange color. After 35 min a solution of diiodosilane **279** (150 mg, 0.44 mmol) in THF (0.5 mL) was added downside of flask and stirred for 45 min before addition of a cyclohexanecaboxaldehyde (PhCHO (50 mg, 0.46 mmol) pre-complexed with Me_2AlCl_2 (1M in hexanes, 0.46 mL, 0.46 mmol) in THF (0.5 mL) was added downside of flask and the reaction warmed to room temperature over 9 h. The reaction was diluted with NH_4Cl (4 mL) and partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 5 mL), brine wash (20 mL), dried Na_2SO_4 and conc. *in vacuo* to yield the crude product as an orange oil (290 mg) which was purified with column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to yield the title epoxide **338** as a colorless oil (31 mg, 0.16 mmol, 36%) IR (neat) ν 2920, 1450, 1250, 890, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.12 (1 H, d, J = 5.1 Hz), 1.80-0.92 (12 H, br), 0.12 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (0), 130.3 (0), 127.4 (1), 113.6 (1), 57.0 (1), 55.4 (1), 53.7 (1), –2.0 (3) ppm. ^1H NMR data in agreement with that reported by Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1982**, 867.



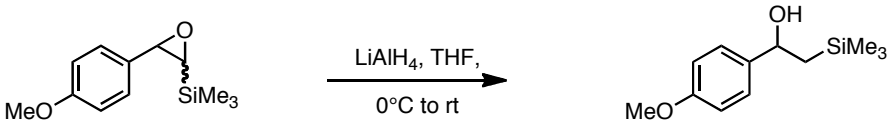
332
$C_{11}H_{16}OSi$ (192)

339
$C_{11}H_{18}OSi$ (194)

Alcohol - 339: A flask was charged with a solution of α,β-epoxy silane **332** (110 mg, 0.57 mmol) in THF (2 mL) and equilibrated at 0°C [ice] over 10 min. Addition of $LiAlH_4$ (86 mg, 2.2 mmol) was followed by immediate evolution of gas and the

heterogenous grey reaction stirred at rt for 12 h. After this time the reaction was quenched with sat. NH_4Cl (4 mL), partitioned in CH_2Cl_2 (4 mL) before the layers were shaken and separated. Aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL), organic layers combined, brined washed (10 mL), dried over Na_2SO_4 and conc. *in vacuo* to yield a yellow oil (142 mg). The crude product was purified by column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to afford the title alcohol **339** as a colorless oil (88 mg, 0.45 mmol, 80%) IR (neat) ν 3358 (br, OH), 3032, 2960, 2885, 1499, 1458, 1251, 1179, 1022, 869 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.31 (5H, m), 4.85 (1H, ddd, *J* = 11.4, 7.4, 3.4), 1.72 (1H, d, OH), 1.28 (1H, dd, *J* = 14.3, 7.5), 1.18 (1H, dd, *J* = 14.3, 7.5), -0.073 (9H, s) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 146.7 (0), 128.7 (1), 127.8 (1), 126.0 (1), 73.1 (1), 28.6 (2), –0.92 (3) ppm. ^1H NMR data in agreement with that reported by Barluenga, J.; Fananas, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798.

Chiral HPLC analysis of (±)-**339**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 1.0% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} **339** = 7.18 min. t_{ret} *ent*-**339** = 8.05 min. Analysis of the material prepared as described above revealed an enantiomeric excess of 0% ee.



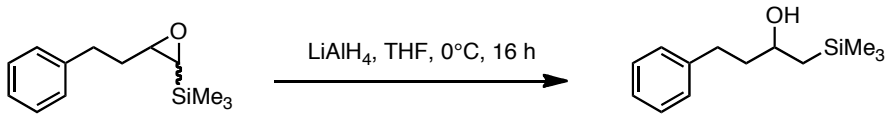
337
$C_{13}H_{18}O_2Si$ (234)

340
$C_{13}H_{20}O_2Si$ (236)

Alcohol - 340: A flask was charged with a solution of epoxy silane **337** (mg, 0.19 mmol) in THF (4 mL) and equilibrated at 0°C [ice] over 10 min. Addition of $LiAlH_4$ (30 mg, 0.75 mmol) was followed by immediate evolution of gas and the heterogenous grey reaction stirred at rt for 16 h. The reaction was cooled to 0°C before quenching with H_2O (3 mL) and partitioning between EtOAc (5 mL). Extraction of the aqueous layer with EtOAc (3 x 6 mL), organic layers combined, brine wash, dry (Na_2SO_4) and concentrate *in vacuo* to yield the crude alcohol as a dark orange oil (48 mg). The crude product was purified by column chromatography

(SiO_2 eluting with 10% Et_2O in hexanes) to afford the title alcohol **340** as a colorless oil (35 mg, 0.15 mmol, 82%) IR (neat) ν 3421, 2954, 2897, 2835, 1612, 1515, 1308, 1254, 1041, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (2 H, d, *J* = 8.6), 6.87 (1 H, d, *J* = 8.7), 4.81 (1 H, t), 3.88 (3 H, s), 1.27 (1 H, dd, *J* = 14.2, 7.2), 1.18 (1 H, dd, *J* = 14.2, 8.0), -0.089 (9 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (0), 138.8 (0), 127.3 (1), 114.0 (1), 72.7 (1), 55.5 (1), 28.5 (2), –0.90 (3) ppm. MS (CI) *m/z* 237.2 $(M+H)^+$.

Chiral HPLC analysis of (±)-**340**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 2.5% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} **340** = 7.10 min. t_{ret} *ent*-**340** = 10.6 min. Analysis of the material prepared as described above revealed an enantiomeric excess of 0% ee.



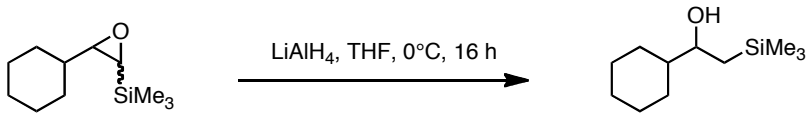
336
$C_{14}H_{20}OSi$ (232)

341
$C_{14}H_{22}OSi$ (234)

Alcohol - 341: A flask was charged with a solution of epoxy silane **336** (60 mg, 0.26 mmol) in THF (2 mL) and equilibrated at 0°C [ice] over 10 min. Addition of $LiAlH_4$ (35 mg, 0.91 mmol) was followed by immediate evolution of gas and the heterogenous grey reaction stirred at rt for 14 h. The reaction was cooled to 0°C before quenching with H_2O (3 mL) and partitioning between EtOAc (5 mL). Extraction of the aqueous layer with EtOAc (3 x 6 mL), organic layers combined, brine wash, dry (Na_2SO_4) and concentrate *in vacuo* to yield the crude alcohol as a colorless oil (67 mg). The crude product was purified by column chromatography (SiO_2 eluting with 10% Et_2O in hexanes) to afford the title alcohol **341** as a colorless oil (45 mg, 0.19 mmol, 75%) IR (neat) ν 3341, 3029, 2952, 1605, 1491, 1454, 1246, 864, 841, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (2 H, m), 7.18 (2 H, m), 3.83 (1 H, m), 2.78 (1 H, ddd, *J* = 13.7, 9.7, 5.9), 2.67 (1 H, ddd, *J* = 13.6, 9.8, 5.9), 1.79 (2 H, m), 1.22 (1 H, br s, OH), 0.90 (2 H, dd, *J* = 6.5, 2.4), 0.040 (9 H, s) ppm; ^{13}C

NMR (100 MHz, $CDCl_3$) δ 142.4 (0), 128.6 (1), 126.0 (1), 69.9 (1), 42.6 (2), 32.4 (2), 2.70 (2), –0.50 (3) ppm. MS (CI) *m/z* 235.3 $(M+H)^+$.

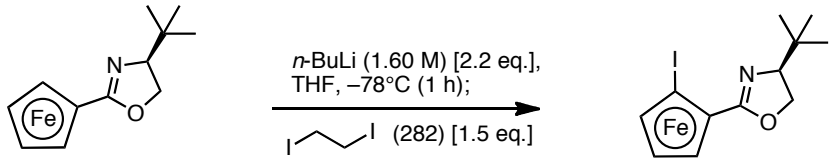
Chiral HPLC analysis of (±)-**341**, performed with a Daicel Chiralcel® OD column (4.6 mm ID x 250 mm), eluting with 2.5% *i*-PrOH in hexanes at 1.0 mL/min, monitored at 210 nm showed resolved peaks: t_{ret} **341** = 9.91 min. t_{ret} *ent*-**341** = 12.7 min. Analysis of the material prepared as described above revealed an enantiomeric excess of 0% ee.



338
$C_{11}H_{22}OSi$ (198)

342
$C_{11}H_{24}OSi$ (200)

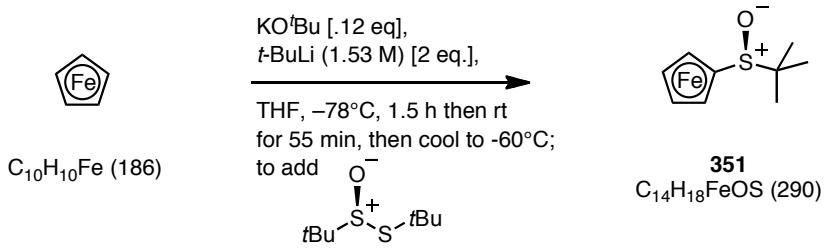
Cyclohexyl alcohol - 342: A flask was charged with a solution of epoxy silane **338** (55 mg, 0.28 mmol) in THF (4 mL) and equilibrated at 0°C [ice] over 10 min. Addition of $LiAlH_4$ (30 mg, 0.75 mmol) was followed by immediate evolution of gas and the heterogenous grey reaction stirred at rt for 16 h. The reaction was cooled to 0°C before quenching with H_2O (3 mL) and partitioning between EtOAc (5 mL). Extraction of the aqueous layer with EtOAc (3 x 6 mL), organic layers combined, brine wash, dry (Na_2SO_4) and concentrate *in vacuo* to yield the crude alcohol as a colorless oil (43 mg). The crude product was purified by column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to afford the title cyclohexyl alcohol **342** as a colorless oil (47 mg, 0.24 mmol, 85%) IR (neat) ν 3408, 2924, 2850, 1452, 1251, 1037, 985, 933 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (1 H, heptet), 1.73 (6 H, m), 1.10 (8 H, m), 0.84 (1 H, dd, *J* = 14.6, 4.4), 0.74 (1 H, dd, *J* = 14.7, 9.6) 0.046 (9 H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (0), 138.8 (0), 127.3 (1), 114.0 (1), 72.7 (1), 55.5 (1), 28.5 (2), –0.90 (3) ppm. ^1H NMR data in agreement with that reported by Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Lawrence, N. J.; Selim, M. R. J. *J. Chem. Soc. Perk. Trans. 1* **1991**, 1893.



351
$C_{17}H_{21}FeNO$ (311)

350
$C_{17}H_{20}FeINO$ (437)

Iodide - 350: A flask was charged with an orange solution of the starting oxazoline (62 mg, 0.199 mmol) in THF (1.5 mL, 0.13 M) then cooled to –78°C and equilibrated for 30 min before dropwise addition of *n*-BuLi (1.6 M in hexanes, 0.27 mL, 0.44 mmol) over 30 s and stirred for an additional 40 min at –78°C. After this time the reaction was quenched with $I(CH_2)I$ (140 mg, 0.49 mmol) in THF (1.5 mL) then warmed to rt over 4 h; then diluted with 10%$Na_2S_2O_3$ (4 mL), layers shaken and separated, aq. layer extracted w/ Et_2O (3x5 mL), organics combined, washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to yield a brown viscous oil that was purified by column chromatography (SiO_2 eluting with 5% EtOAc in hexanes) to yield the title iodide **350** as a dark orange oil (76 mg, 0.18 mmol, 88%) IR (neat) ν 3094, 2954, 2896, 2870, 2364, 2335, 1660, 1478, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, dd, *J* = 2.4, 1.4), 4.62 (1H, dd, *J* = 2.2, 1.5), 4.36 (1H, t), 4.19 (5H, s), 3.97 (2H, dt, *J* = 9.7, 7.3), 1.02 (9H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (0), 78.5 (1), 76.6 (1), 72.8 (0), 71.1 (1), 69.7 (0), 68.6 (1), 68.2 (2), 34.0 (1) 31.1 (0), 26.1 (3) ppm. ^1H NMR data in agreement with that reported by Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648.

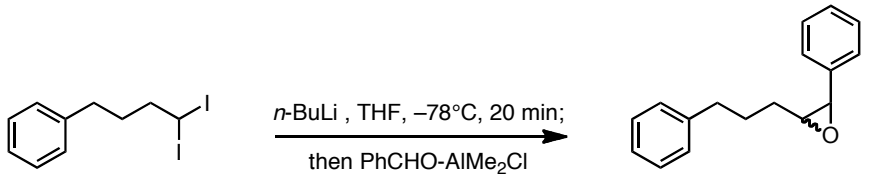


$C_{10}H_{10}Fe$ (186)

351
$C_{14}H_{18}FeOS$ (290)

***tert*-Butyl sulfoxide - 351:** A flask was charged w/ an orange solution of ferrocene (100 mg, 0.54 mmol) in anhydrous THF (3 mL), then addition of KO*t*Bu (7 mg, 0.64 mmol) then cooled to -78°C and equilibrated for 10 min., before addition of *t*-BuLi

(1.53 M, 0.70 mL, 1.07 mmol) downside of flask over 5 minutes and stirred for 1.5 hours before addition of a solution of di-*tert*-butyl sulfoxide (69 mg, 0.36 mmol) in THF (1.5 mL) was added downside of flask and the reaction warmed to room temperature over 1.5 hours. Yellow reaction was diluted with H_2O (5 mL) partitioned in EtOAc (5 mL) aq. layer extracted with EtOAc (3 x 6 mL), organic portions combined, brine wash, dried (Na_2SO_4) and conc. *in vacuo* to yield an orange granular solid (143 mg). This residue was purified by column chromatography (SiO_2 eluting with 20% to 50% EtOAc in hexanes) to yield the title sulfoxide **351** (43 mg, 40%, 0.15 mmol) as an orange solid. $[\alpha]_D$ = +334 (c 0.8, $CHCl_3$); mp 156-157°C (EtOAc/hexanes); IR (KBR) ν 2952, 2899, 1407, 1253, 1057, 916, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (1 H, dd, *J* = 1.2, 1.0), 4.40 (2 H, m), 4.37 (5 H, s), 4.35 (1 H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.6 (0), 70.3 (1), 70.1 (1), 69.9 (1), 69.6 (1), 65.6 (1), 55.1 (0), 23.0 (3) ppm. ^1H NMR data in agreement with that reported by Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1993**, *32*, 568.



282
$C_{10}H_{12}I_2$ (386)

364
$C_{17}H_{18}O$ (238)

Oxirane - 364: A flask was charged with a solution of diiodide **282** (50 mg, 0.13 mmol) in THF (3 mL) and cooled to –78°C and equilibrated for 15 min before addition of *n*-BuLi (2.03M in hexanes, 0.07 mL, 0.13 mmol) over 10 s that produced a yellow color in the reaction. This was allowed to stir for 20 min before a solution containing benzaldehyde (14 mg, d = 1.05, 0.013 mL, 0.13 mmol) pre-complexed with Me_2AlCl (1 M in hexanes, 0.13 mL, 0.13 mmol) was added down the side of the flask over 5 s, as the electrophile was added the color attenuated to pale yellow and the reaction was allowed to warm to rt over several hours after which time the reaction was quenched with sat. NH_4Cl (3 mL), diluted with H_2O (3 mL) and partitioned in EtOAc (5 mL), aq. layer extracted with EtOAc (3 x 5 mL), organics

washed with brine (15 mL), dried Na_2SO_4 and concentrated *in vacuo* to yield the crude product as an oil ( ). This was purified by column chromatography (SiO_2 eluting with 5%EtOAc in hexanes) to yield the title oxirane **364** as a colorless oil ^{1}H NMR (700 MHz, $CDCl_3$) δ (major) *cis diastereomer* 7.38-7.19 (10H, m), 4.08 (1H, d, *J* = 4.2), 3.24 (1H, ddd, *J* = ,6.3, 4.1), 2.54 (1H, t), 1.90-1.28 (4H, m) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 142.1 (0), 135.7 (0), 128.9 (1), 128.6 (1), 128.4 (1), 128.2 (1), 127.7 (1), 126.1 (1), 59.2 (1), 57.6 (1), 36.6 (2), 27.9 (2), 26.5 (2) ppm. HRMS (CI+) *m/z* 239.1443 (calcd. for $C_{17}H_{19}O$: 239.1436).

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