Harnessing the Synthetic Potential of Bis-1,1-Allyldiboron Reagents for α-Alkylations, γ-Alkylations, α-Conjugate Additions, and γ-Conjugate Additions

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DEDICATION

Over a year ago, nearly every semblance of normalcy was stripped away from the world as SARS-CoV-2 began to emerge as a fatal virus. To this day, the pandemic has left more than 1.6 million individuals dead and many more in financial, physical, and social disarray.

During these devastating times, we have realigned several of our priorities and have relied on numerous individuals who have and are continually sacrificing their own well-being for others. Whether it has been social distancing and self-quarantining or it has been working on the frontlines as an essential worker, emerging from this global crisis has already required and will continue to require a collective effort. This thesis is dedicated to these individuals.

Beyond the individuals aforementioned, I would also like to dedicate this work to my parents and siblings who have financially and emotionally supported me throughout my undergraduate career. By allowing me to freely pursue all of my passions, they have fostered an environment that has encouraged me to expose myself to a range of experiences that inform my worldview and that have catalyzed my passion and commitment for a lifetime in service of others. I am forever grateful.

Lastly, I dedicate this work to my mentors and friends who have pushed me to become my best self. To Chris Faison, thank you for providing me the opportunity to participate in the first cohort of *Start Strong* and for being a consistent mentor and friend throughout my time at Carolina. To Dr. Ronald Strauss, thank you for believing in me when I did not believe in myself— I am now committed, more than ever, to pursue my dreams. And, finally, to Kaaren Haldeman, Pamela Best, Paris Miller, and Rep. Marcia Morey, thank you for teaching me how to be an advocate for others. It has been through our conversations and collective efforts where I have learned the intersectionality and intentionality that a lifetime of public service requires.

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In addition, I would like to thank those members of the lab group that I have yet to mention for always making me feel welcome and for being there to guide me as I developed my lab skills. Justin Marcum, thank you for watching over me as I worked with pyrophoric chemicals and for helping me to become a more confident lab scientist. Tia Ceravich, thank you for helping me understand how to perform successful extractions and for providing advice as I navigated Synthetic Lab. Emilie Wheatley, thank you for always bringing positive energy to the lab and for answering my countless questions. Hawa Keita, thank you for watching over my reactions when Michael was

not around. To Nick McDonald, Joe Zanghi, Miles Mason, and Brock Swartz, thank you for always making me feel welcome in lab and for being there to learn alongside me.

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ABSTRACT

With increasing amounts of therapeutic and diagnostic drugs containing boron being synthesized by industry, the ability to efficiently generate them poses many obstacles, including environmental impact and monetary cost.[1] Harnessing the power of Bis-1,1-allyldiboron reagents to perform α-alkylations, γ-alkylations, α-conjugate additions, and γ-conjugate additions with electrophilic species allows for the creation of new stereocenters and for the installation of a boronate ester which can participate in multiple types of downstream and value-added transformations, including oxidations, homologations, halogenations, aminations, and cross-couplings. Although the research is ongoing, this work begins to outline the developing theory and methodology that allows for the production of a diverse array of bioactive, boronate ester-containing molecular scaffolds that demonstrate promise for industry and organoboron literature due to their ability to operate within a simple Lewis Base, phase-transfer catalyst (PTC), crown ether system, under nonpolar solvent and low to ambient temperature conditions. Notably, the PTC system has already exhibited the ability increase site-selectivity (i.e., selection for α-product versus γ-product) for α-alkylations with secondary chlorides and α-conjugate additions as well as increasing product yield for γ-conjugate additions, demonstrating promise for directing regioselectivity and stereochemistry.

INTRODUCTION AND RELEVANT BACKGROUND

Increasing medical applications of organoboron compounds for therapeutic and diagnostic medicine have warranted the development of efficient, broadly applicable, and selective synthetic routes for their formation. Regarding diagnostic potential, organoboron compounds have proven useful in optical and nuclear imaging to detect illness, such as cardiovascular disorders and

neurodegenerative diseases (e.g. Alzheimer's). Therapeutically, organoboron compounds have been synthesized to target and destroy cancer, viruses, unwanted bacteria, and fungi. Two notable examples of recently developed drugs that incorporate boron are *Tavaborole* (**Figure 1**), an anti-fungal medication to treat onychomycosis, and *Bortezomib* (**Figure 2**), a proteasome inhibitor for the treatment of multiple myeloma and non-Hodgkin's lymphoma.[1,2] With significant medical and financial promise, it is evident why organoboron chemistry has become an increasingly coveted field of research.

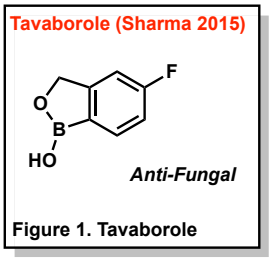


Figure 1. Tavaborole

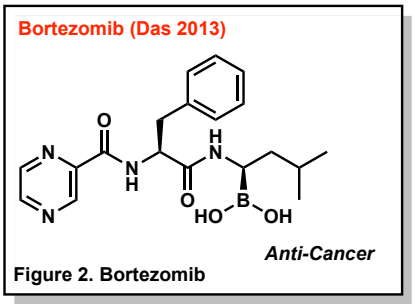


Figure 2. Bortezomib

While there are many applications of organoboron chemistry, the ability to perform enantioselective, catalytic reactions via polarized bonds poses fascinating theoretical and experimental questions. Specifically, the introduction of electron density to an empty boron p-orbital within a trivalent boronate ester (**Figure 3**) sufficiently polarizes Boron-Carbon (B-C) bonds for nucleophilic attack via a borate intermediate, converting to an Sp^3 tetrahedral geometry from an Sp^2 trigonal planar geometry (**Figures 4** and **5**).[2]

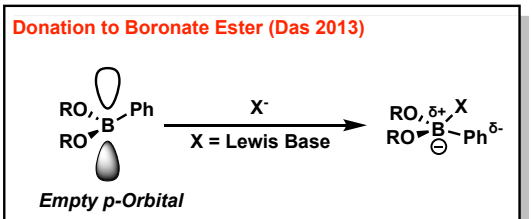


Figure 3. Activation of Boronate Ester

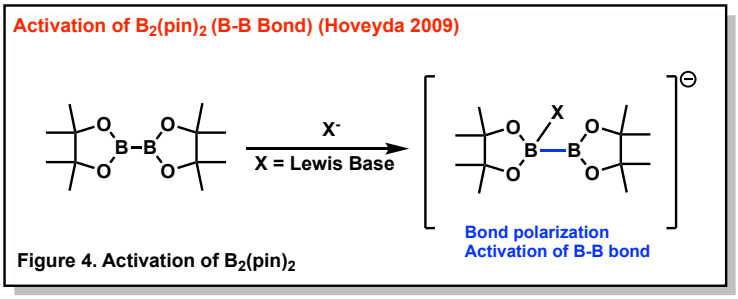


Figure 4. Activation of $B_2(pin)_2$

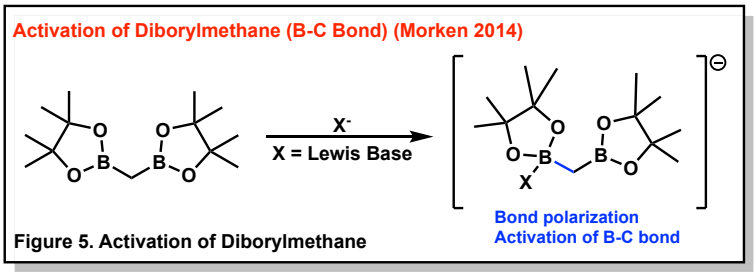
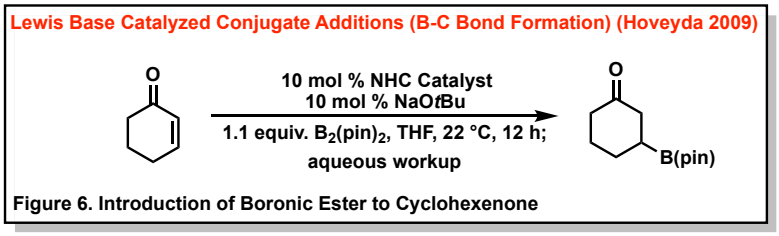
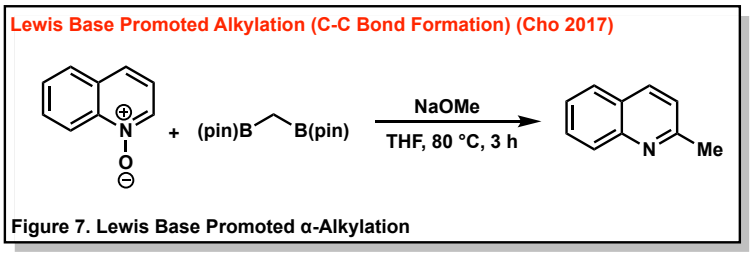


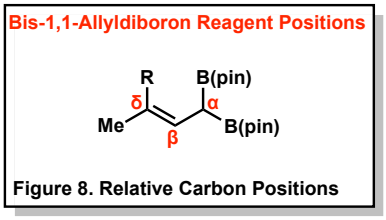
Figure 5. Activation of Diborylmethane



Relatively new research on the activation of diboron and bis-1,1-allyldiboron reagents by Lewis Bases via electron donation to generate polarized Boron-Boron (B-B) and B-C bonds demonstrating that it is possible to introduce a borate nucleophile to the electrophilic substrate, without utilizing transition metals (**Figure 6**).[3,4] Synthesizing boronic ester-containing compounds via catalytic methods has necessitated study due to their scalability for important industrial applications and due to the ability of boronic esters to participate in a multitude of downstream and value-added transformations, when activated, including oxidation, amination, cross coupling, homologation, and halogenation.[5]



In addition to the transformational abilities of the boronic ester, it should also be noted that this research was explored due to the ability of B-B and B-C activation to generate complex quaternary stereocenters. While our work looked to previous literature implement methods of transformation for stereocenters that are generated via donation from the B-αC bond under mildly polar conditions (**Figure 7**), the utilization of bis-1,1-allyldiboron reagents have also demonstrated the possibility of harnessing addition and alkylation power to attack via the γ-carbon of a borate intermediate, when acting as a carbanion within a delocalizable pi-system (**Figure 8**).[6]



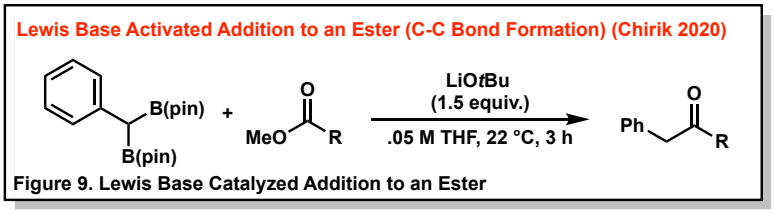


Figure 9. Lewis Base Catalyzed Addition to an Ester

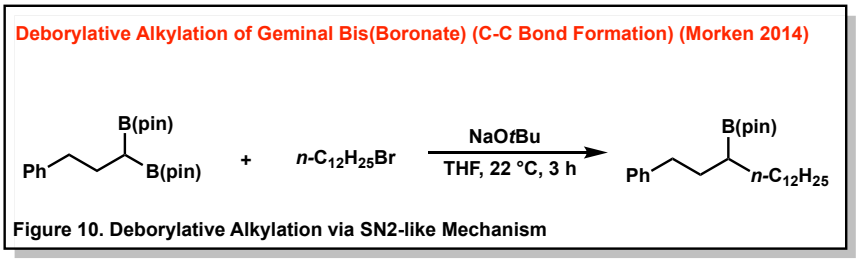


Figure 10. Deborylative Alkylation via SN2-like Mechanism

It should be noted that the research described throughout this thesis has further basis from the literature. **Figure 9** depicts a Lewis Base activated addition to an ester promoted by LiO*t*-Bu. This reaction is novel in that the polarized B-C bond in the borate species allows for nucleophilic addition into the electrophilic ester's pi-system.[7] The ability for the 1,1-allyldiboron to contribute into a pi-system provides further compelling evidence that 1,1-allyldiboron reagents promoted by a Lewis Base could participate in nucleophilic reactions with the γ-carbon. This phenomenon was further explored in the research outlined by this paper. Another example of note within the literature highlights the versatility and merits of this research's approach. Specifically, the generation of a polarized B-C borate bond via Lewis Bases, such as NaO*t*-Bu, can be harnessed for alkylations as well. Alkylations continue to illustrate the versatility of 1,1-organodiboron reactions promoted by Lewis Bases because they present addition into non-delocalizable, sigma-systems, with potential for establishing a quaternary stereocenter. Furthermore, the reaction introduces a boronic ester into the quaternary stereocenter-containing final product, which could be altered through the various transformations highlighted. **Figure 10** depicts the alkylation to proceed via an S_N2-like reaction, which suggests that deborylative alkylations could provide viable means for generating a large scaffold of diverse molecules with potential for stereospecificity.[4]

When coupled with a 1,1-allyldiboron reagent, it is possible to generate multiple adjacent quaternary stereocenters via α- and γ-additions.

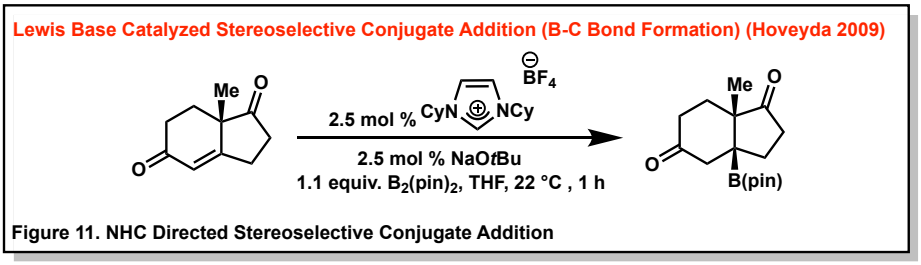


Figure 11. NHC Directed Stereoselective Conjugate Addition

Throughout this project, various catalytic, optimization, and reaction screening methods have been implemented to explore the feasibility of several Lewis Bases and conditions that promote the desired reactions. Recently, phase-transfer catalysts (PTCs) have come to the fore as a potentially viable means for promoting site-selective and stereoselective conjugate addition and alkylation reactions. Specifically, the coupling of a solid ionic salt (e.g., NaOMe) that can be brought into solution as counterions to generate a Lewis Base activator with a crown ether and a quaternary ammonium or pyrazolium species in a nonpolar aprotic solvent (e.g., Benzene) has been explored in such reactions with electrophiles containing a good leaving group.

In part, this unique combination and implementation of phase-transfer catalysts stems from similar work that explored the use of N-heterocyclic carbenes (NHCs) as potential catalysts for conjugate addition reactions.[3,8] Notably, Hoveyda's earlier work substantiates the pairing of catalyst species and Lewis Bases with certain electrophilic substrates because it demonstrates the ability to harness the activation power of the two in order to direct the reactivity and stereoselectivity of an organoboron reaction (**Figure 11**).

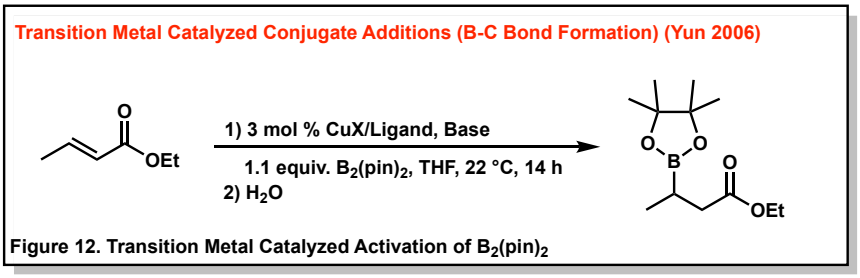


Figure 12. Transition Metal Catalyzed Activation of $B_2(pin)_2$

Undoubtedly, as new medicinal uses for specific organoboron compounds continues to increase, efficiently synthesizing them will become of increasing importance for industry. Further, generating these complex molecules will require unique 1,1-organodiboron reagents that can also participate in alkylations, extending beyond the synthetic potential of $B_2(pin)_2$ and diborylmethane. It is also plausible that continued use of transition metals for these reactions, although effective in generating desired product (**Figure 12**), will not prove to be as robust (e.g. extra step of transmetalation, conditions), tunable, operationally simple, and cost-effective as the potential use of Lewis Bases optimized for the same syntheses— especially, if able to confer similar or higher levels of stereoselectivity.[9]

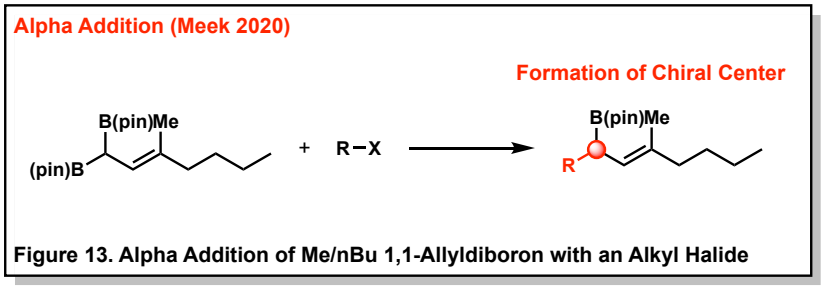


Figure 13. Alpha Addition of Me/nBu 1,1-Allyldiboron with an Alkyl Halide

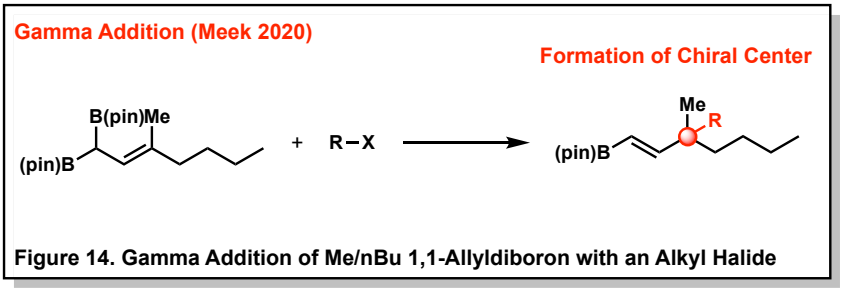


Figure 14. Gamma Addition of Me/nBu 1,1-Allyldiboron with an Alkyl Halide

Throughout this thesis, current and past research coupled with theoretical explanations of the types of catalytic reactions aforementioned will be analyzed; furthermore, implications of the research and subsequent steps will be proposed. We believe the synthetic merits of the

organoboron chemistry outlined in this thesis are multi-fold and are of special note due to their ability to promote C-C bond formation, all carbon quaternary centers at the γ-carbon, and chiral centers at the α-carbon,while simultaneously installing a boronic ester that could be harnessed for downstream, value-added transformations (**Figure 13** and **Figure 14**).

EXPERIMENTAL

A. Research Approach and Catalysts Utilized

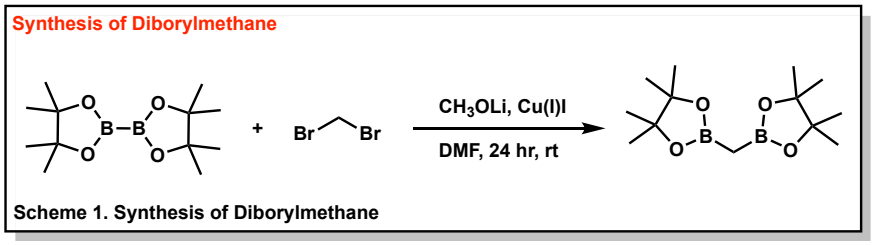
Given the fairly unprecedented nature of this research project as it relates to the literature surrounding organoboron chemistry, it was necessary to synthesize various reagents from less complex precursors (e.g., 1,1-organodiborons synthesized from diborylmethane and lithiated diborylmethane). Specifically, this project required the synthesis of 1,1-organodiborons, which would serve as nucleophilic species in the reaction; various tosylate, mesylate, and electron withdrawing species (e.g., primary and secondary chlorides), which would serve as electrophiles (**Figure 15)**; activators, which included various ionic salts that would serve as Lewis Bases; and catalysts, including pyrazolium phase transfer catalysts, quaternary ammonium phase transfer catalysts, and crown ethers (**Figure 16**).

Aside from the need to synthesize starting materials for the reactions, it was necessary to develop strategies that optimized the reactions for product yield via tuning conditions, such as temperature, activator equivalents, catalyst equivalents, and solvent.

From testing various combinations of starting materials with a series of temperatures and solvents, it was possible to begin gauging which conditions and reagents proved to be most robust and efficient for promoting syntheses high in product yield and with promise for high enantiomeric excess.

B. Methods for Reagent Synthesis

Synthesis of Diborylmethane



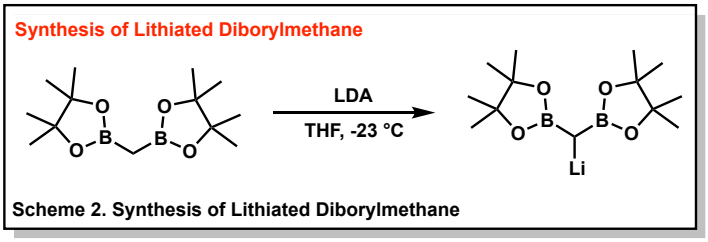
Scheme 1. Synthesis of Diborylmethane

Following the literature, $B_2(pin)_2$ (118.14 mmol, 2 equiv) was dried outside of the glovebox overnight. Inside the glovebox, Copper (I) Iodide (2.9535 mmol, .05 equiv) and Lithium methoxide (177.21 mmol, 3 equiv) were added to a round-bottom equipped with a stir bar and rubber septum.[10]

The round-bottom was subsequently removed from the glovebox and both flasks were placed under N_2, while DMF (.82 mL/mmol $B_2(Pin)_2$)) was added to the round-bottom containing $B_2(Pin)_2$ and one-part DMF (.41 mL/mmol $B_2(Pin)_2$)) was added to the round-bottom from within the glovebox. The solution was allowed to stir for ten minutes, prior to the $B_2(Pin)_2$ solution being cannula transferred to the round-bottom from the glovebox. The solution was allowed to stir for an additional ten minutes, prior to the addition of dibromomethane via syringe at room temperature (59.069 mmol, 1 equiv) (dens. = 2.5 g/mL). The solution was allowed to stir for 12 hours.

After stirring, Et_2O (1.64 mL/mmol $B_2(Pin)_2$) was added and filtered through a silica plug, prior to being rinsed with additional ether. Then, hexanes (2.46 mL/mmol $B_2(Pin)_2$) were added, and the solution was washed with water ((.61 mL/mmol $B_2(Pin)_2$) x 4), before being dried over sodium sulfate and placed under vacuum. The resulting compound appears as a soft, white crystalline structure. ^{1}H NMR (400 MHz, CDCl3) δ 1.26 (s, 24H), 0.38 (s, 2H).

Synthesis of Lithiated Diborylmethane

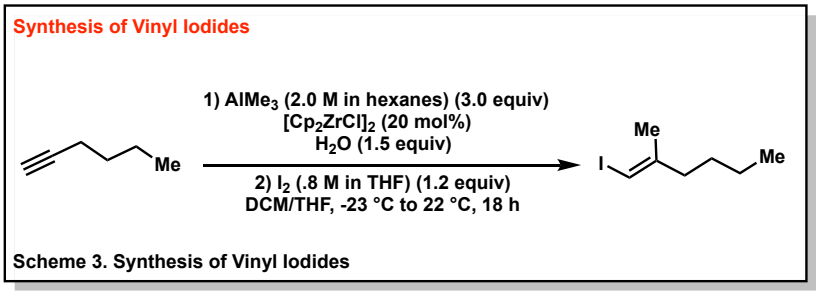


Scheme 2. Synthesis of Lithiated Diborylmethane

Following the literature, to generate lithiated diborylmethane, LDA was first prepared by the addition of nBuLi (1.1 equiv) to Di-isopropylamine (1.1 equiv) in THF. The resulting mixture was cooled in a 9:1 solution of Ethylene Glycol:Ethanol with dry ice to reach a temperature of -23 °C. The mixture was allowed to stir for 30 minutes.[11]

Upon preparation of LDA, the strong base, which deprotonates diborylmethane, was slowly added to an actively stirring 0 °C solution of diborylmethane and Hexanes. The resulting mixture was additionally allowed to stir in a -23 °C bath, prior to being transferred into the glovebox. The product was isolated utilizing a Buchner Funnel and was thereafter washed with cold hexanes. The purified lithiated diborylmethane product was placed in a small vial and was stored in a freezer.

General Procedure A: Synthesis of Vinyl Iodides



Scheme 3. Synthesis of Vinyl Iodides

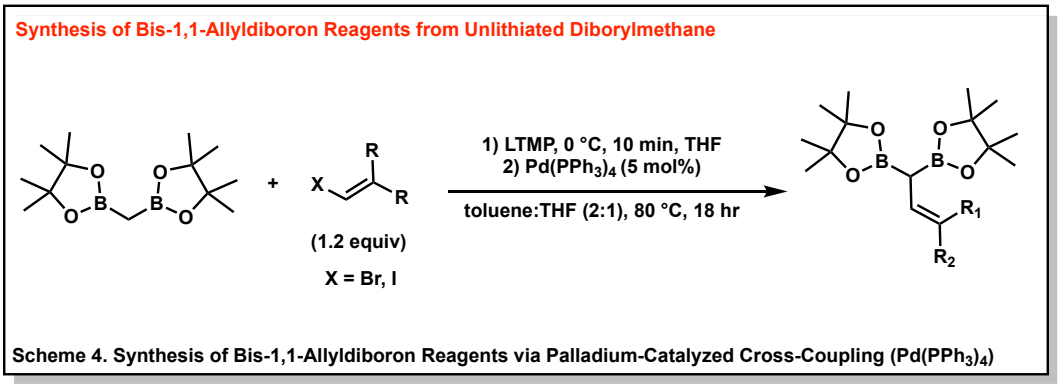
Following the literature, in a glovebox under nitrogen atmosphere, zirconocene dichloride (20 mol%) was introduced to a round-bottom flask charged with a stir bar. The flask was sealed with a septum cap and taped, prior to being removed from the glovebox and placed under positive pressure of N_2 gas.[12]

After, dry DCM (17 mL/mmol $ZrCp_2Cl_2$) was added to the flask, followed by a 2.0 M solution of trimethylaluminum in hexanes (3 equiv). Upon addition of trimethylaluminum, the yellow solution was cooled to -23 °C via ethylene glycol/ethanol/dry ice bath (90:10 ethylene glycol:ethanol) and was allowed to stir for ten minutes.

Following cooling of the solution, water (1.5 equiv, sparged with N_2) was slowly added to the stirring solution (Note: the addition of water evolves large amounts of gas so ensure that vent needles are added prior to addition). Once water was added, the solution was allowed to stir at -23 °C. After stirring for ten additional minutes, a solution of 1-hexyne (1.0 equiv, 0.65 M in DCM) was transferred to the stirring mixture via cannula, and the resulting solution was allowed to stir for an additional 10 minutes at -23 °C. After, a 0.8 M solution of I_2 (1.2 equiv) in THF was added dropwise to the stirring solution. The reaction remained yellow and was allowed to slowly warm to room temperature overnight with stirring.

Subsequently, the reaction was cooled back to 0 °C, prior to being quenched with saturated K_2CO_3 aqueous solution (100 µL/1 mmol $AlMe_3$, evolves large amount of methane). After ten minutes of stirring, solid magnesium sulfate was added to the white suspension. The solids were filtered and washed with diethyl ether. The filtrate was purified via silica plug (100% pentane) and utilized without further purification. Vinyl iodides turned pink upon standing and thus required quick use in cross-coupling reactions to generate bis-1,1-diborylallyl reagents. ^{1}H NMR (400 MHz, CDCl3) δ 5.88 (h, J = 1.2 Hz, 1H), 2.22 (td, J = 7.5, 1.2 Hz, 2H), 1.85 (d, J = 1.1 Hz, 3H), 1.50 – 1.38 (m, 2H), 1.38 – 1.24 (m, 3H), 0.92 (t, J = 7.2 Hz, 4H).

General Procedure B: Synthesis of Bis-1,1-Diborylallyl Reagents via Palladium-Catalyzed Cross-Coupling (non-lithiated diborylmethane)



Scheme 4. Synthesis of Bis-1,1-Allyldiboron Reagents via Palladium-Catalyzed Cross-Coupling ($Pd(PPh_3)_4$)

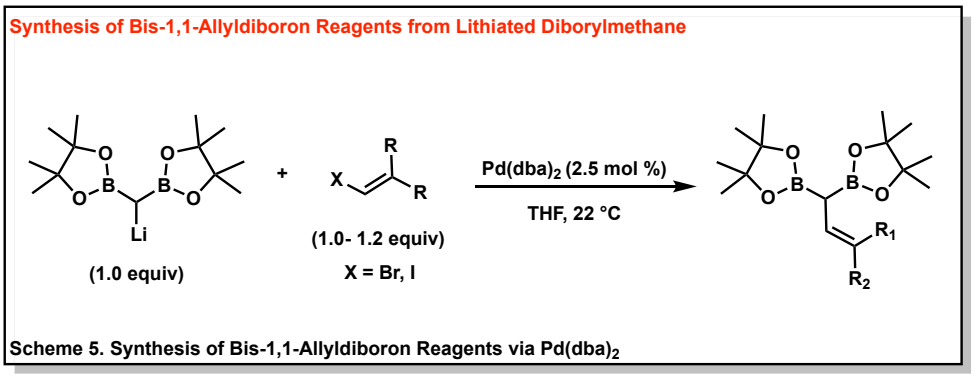
Following the literature, in a glovebox under nitrogen atmosphere, Tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (5 mol%) was added to a round-bottom flask, and in two additional round-bottom flasks diborylmethane (non-lithiated) (1.0 equiv) and Lithium 2,2,6,6-tetramethylpiperidide (LTMP) (1.05 equiv) were added, respectively.[12] All three flasks were charged with magnetic stir bars and sealed with septum caps and tape, prior to being removed from the glovebox.

Upon evacuation from the glovebox, each flask was placed under positive pressure of inert nitrogen gas, then dry THF was added to the flasks containing diborylmethane (generating a 1.00 M solution) and LTMP (generating a 0.78 M solution), respectively. Once this was completed, dry toluene was added to the $Pd(PPh_3)_4$-containing flask (generating a 12.2 mM solution). The flasks containing diborylmethane and LTMP were cooled to 0 °C in ice baths for ten minutes.

After warming to room temperature, the amber-colored LTMP solution was cannula transferred to the diborymethane solution and allowed to stir for ten additional minutes at 0 °C. The resulting deprotonated diborylmethane solution was cannula transferred to the room temperature flask containing $Pd(PPh_3)_4$. Immediately upon transfer, vinyl halide (1-bromo-2-methylprop-1-ene) (1.2 equiv) was added via syringe. An oven-dried condenser under inert nitrogen atmosphere was then placed on the flask and heated to 80 °C for 18 hours with stirring.

The resulting solution was allowed to cool to room temperature, prior to the addition of saturated aqueous ammonium chloride. The aqueous layer of the biphasic mixture was extracted with diethyl ether (3x). All organic (aqueous) layers were combined, dried over magnesium sulfate and filtered via Buchner Funnel, prior to concentration under rotary evaporation to obtain crude bis-allyl-1,1-organodiboron reagent as an amber-colored oil. Purified product was obtained via flash silica gel chromatography. This process varied slightly for each product. ^{1}H NMR (600 MHz, CDCl3) δ 5.40 (dp, J = 9.1, 1.5 Hz, 1H), 1.86 (d, J = 9.1 Hz, 1H), 1.75 – 1.68 (m, 3H), 1.61 – 1.56 (m, 3H), 1.29 – 1.19 (m, 24H) (Me/Me Allyl Diboron Reagent).

General Procedure C: Synthesis of 1,1-Diborylallyl Reagents via Diborylmethane (lithiated)



Scheme 5. Synthesis of Bis-1,1-Allyldiboron Reagents via $Pd(dba)_2$

Following a literature procedure, in a glovebox under nitrogen atmosphere, lithiated diborylmethane (500.0 mg, 1.83 mmol, 1.0 equiv) was combined with THF (3.7 mL) in a flask equipped with a stir bar and septa cap.[13] In an additional flask equipped with a stir bar and septa cap, bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) (26.2 mg, 45.6 µmol, 0.025 equiv) and toluene (7.3 mL) were combined. The flask containing Pd(dba)2 was cannula transferred to the flask containing lithiated diborylmethane, and the resulting solution was allowed to stir. After five minutes of stirring, alkenyl iodide (316.4 µL, 1.83 mmol, 1.0 equiv) was added. The reaction mixture was allowed to stir 18 hours at 23 °C, before aqueous ammonium chloride (4 mL) quenching. The product was extracted with diethyl ether (3 x 10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified via silica gel flash chromatography (40:1 hexanes:ethyl acetate) to generate the desired 1,1-diborylallyl white solid product in 43% yield (296.1 mg, 783.0 µmol). ^{1}H NMR (600 MHz, CDCl3) δ 5.40 (dp, J = 9.1, 1.5 Hz, 1H), 1.86 (d, J = 9.1 Hz, 1H), 1.75 – 1.68 (m, 3H), 1.61 – 1.56 (m, 3H), 1.29 – 1.19 (m, 24H).

Electrophile Syntheses

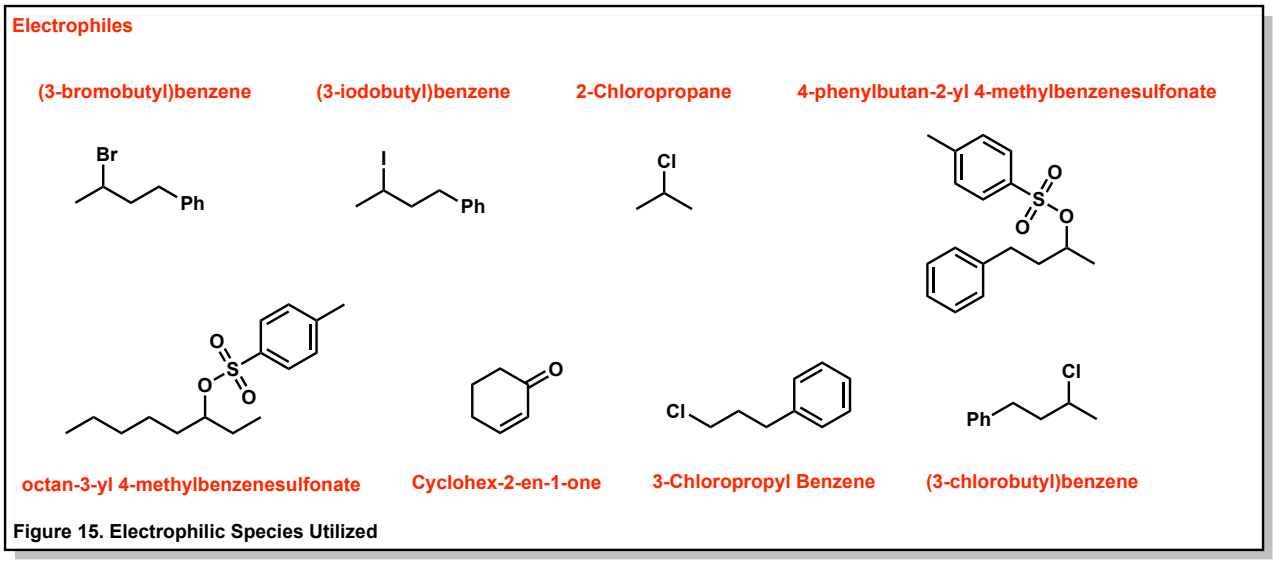


Figure 15. Electrophilic Species Utilized

Figure 15 depicts the electrophiles either purchased or synthesized following the literature.[14, 15, 16, 17, 18, 19, 20]

Catalyst Syntheses

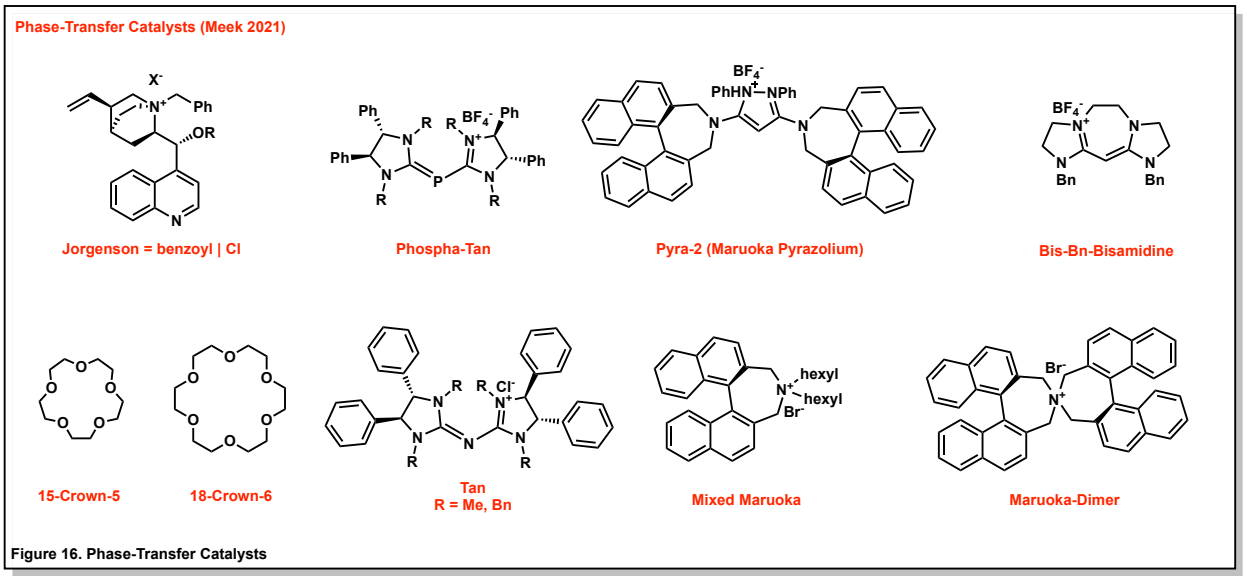
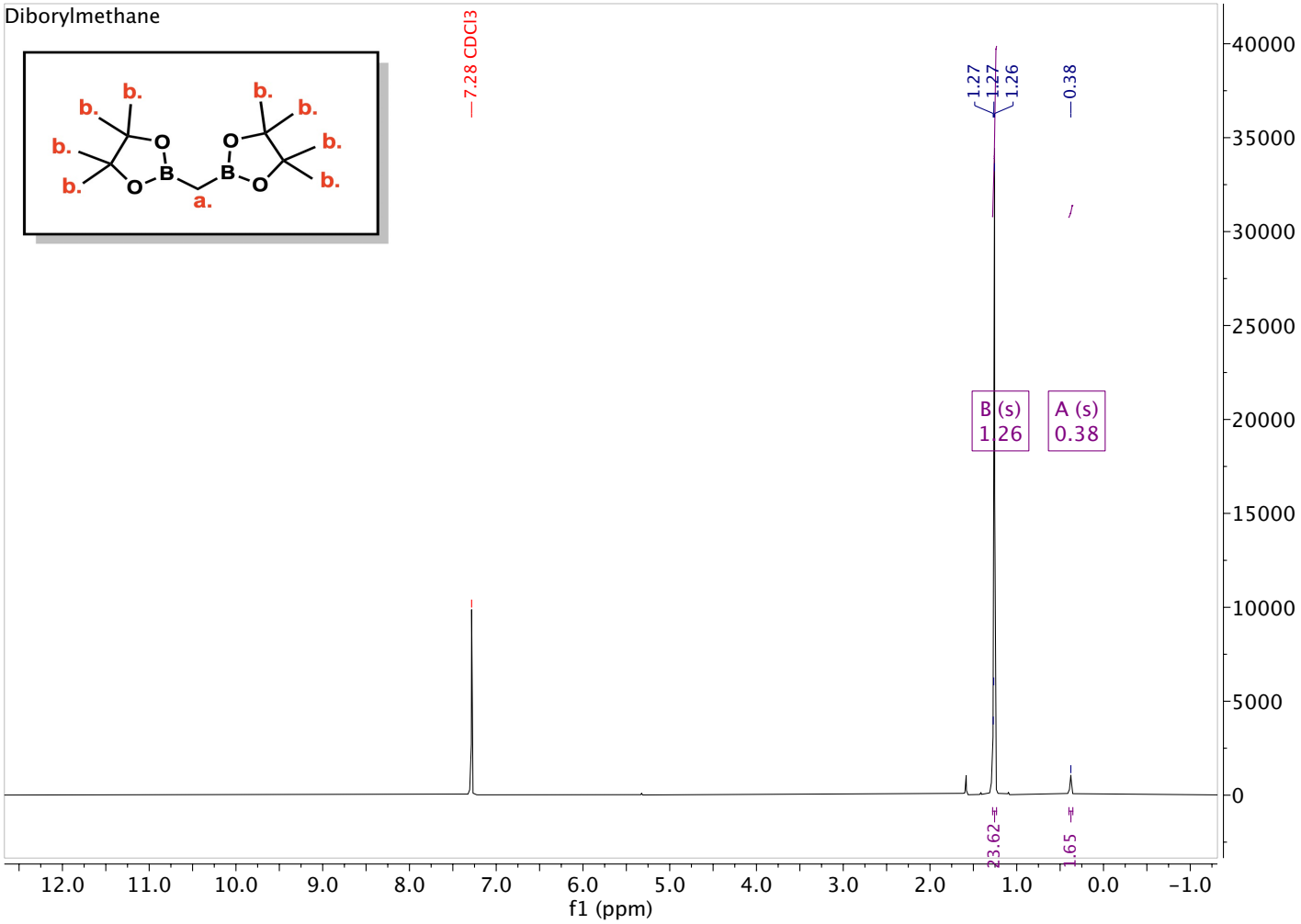


Figure 16. Phase-Transfer Catalysts

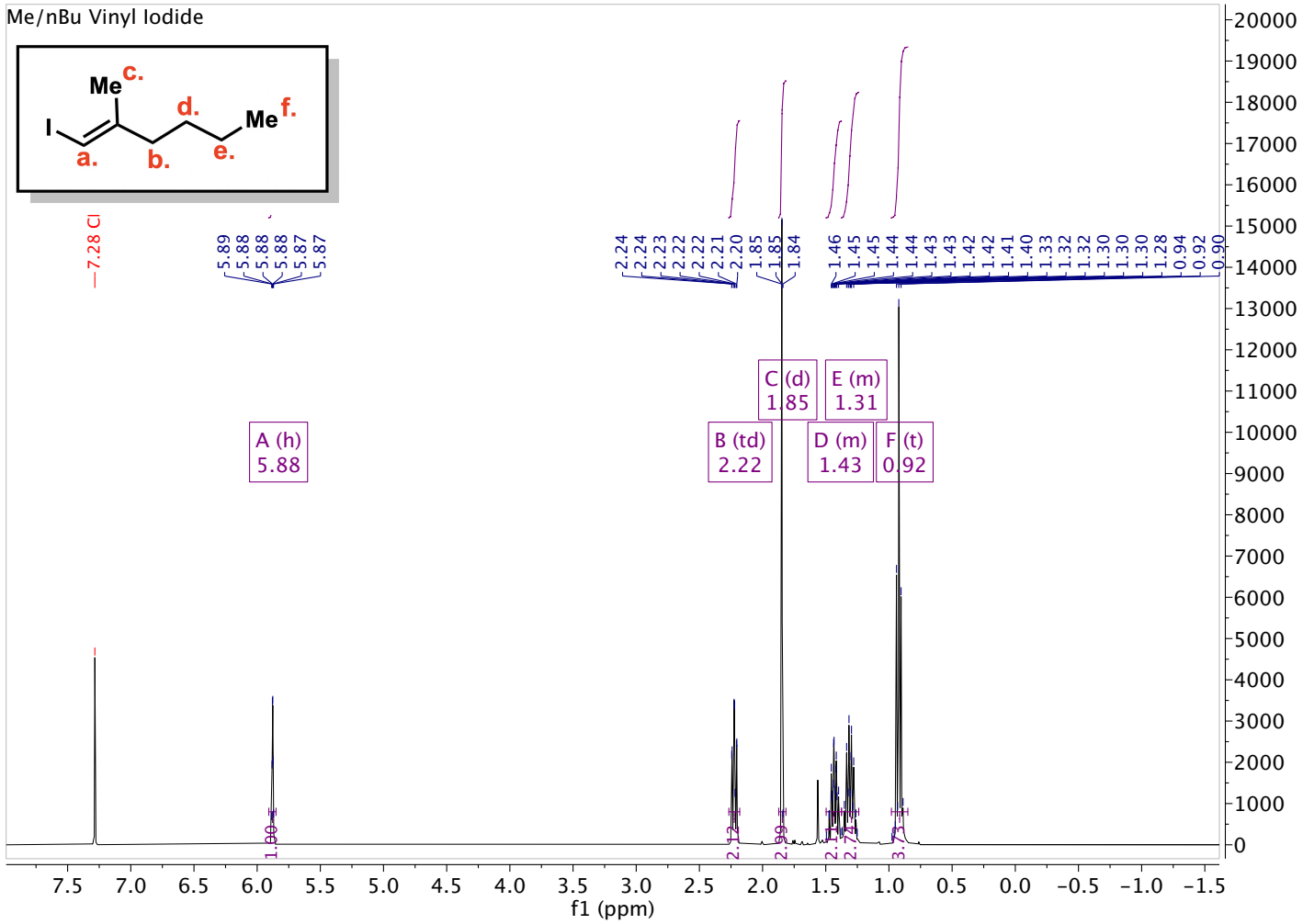
Figure 16 depicts the various pyrazolium and quaternary ammonium PTC species utilized. They were synthesized following the literature.[21, 22, 23, 24, 25]

RESULTS

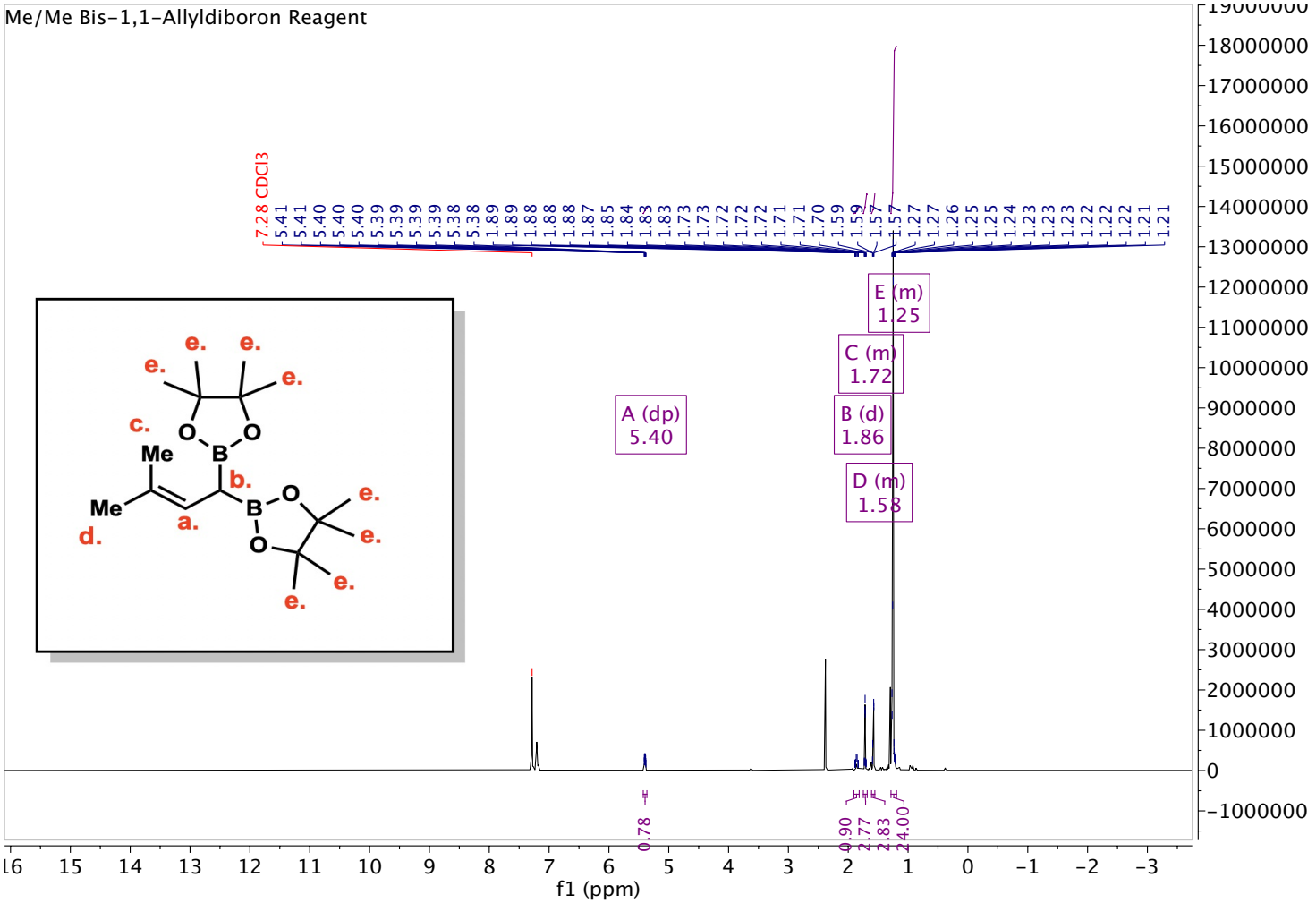
A. Spectra



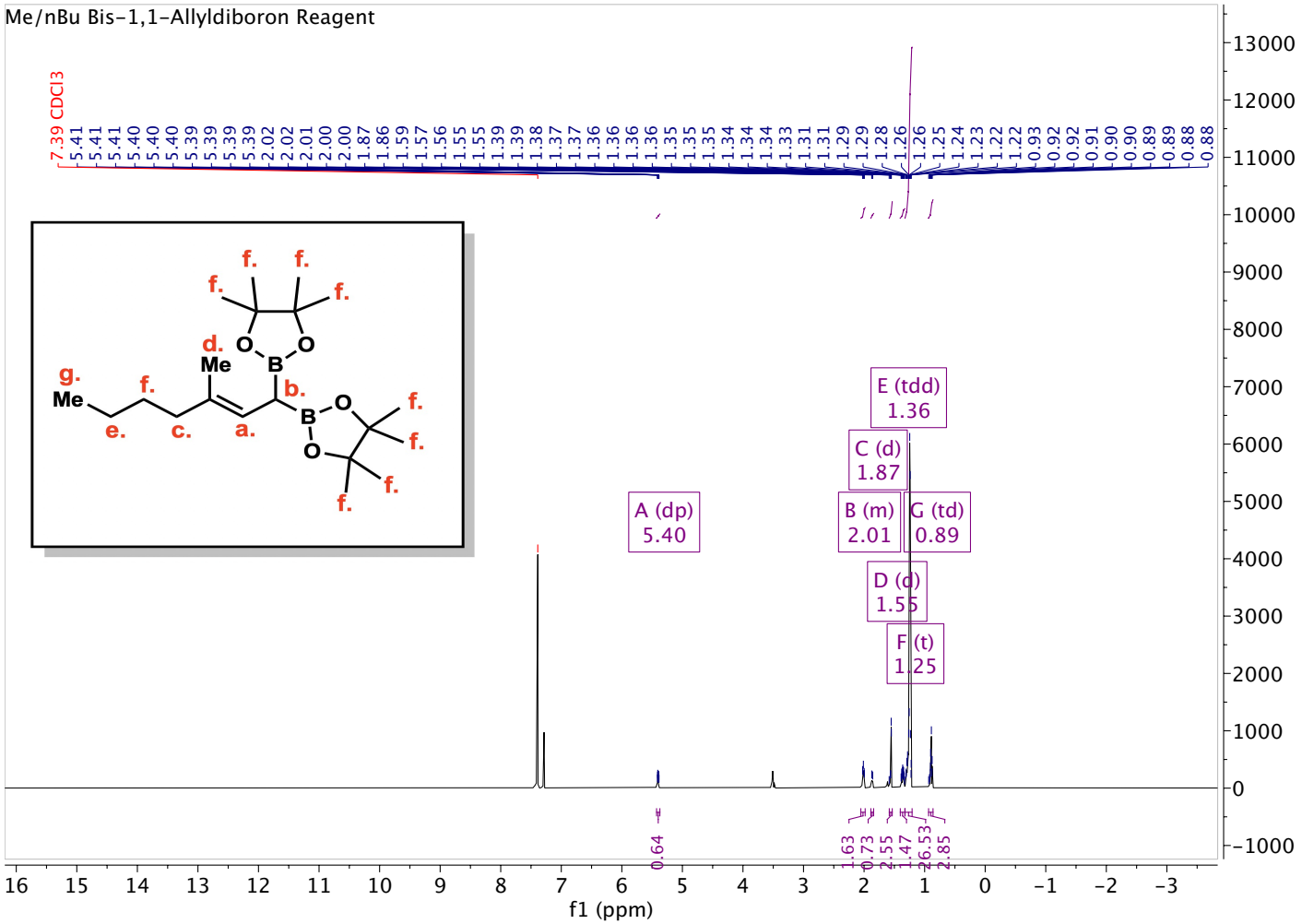
Spectra 1. ^{1}H NMR Diborylmethane



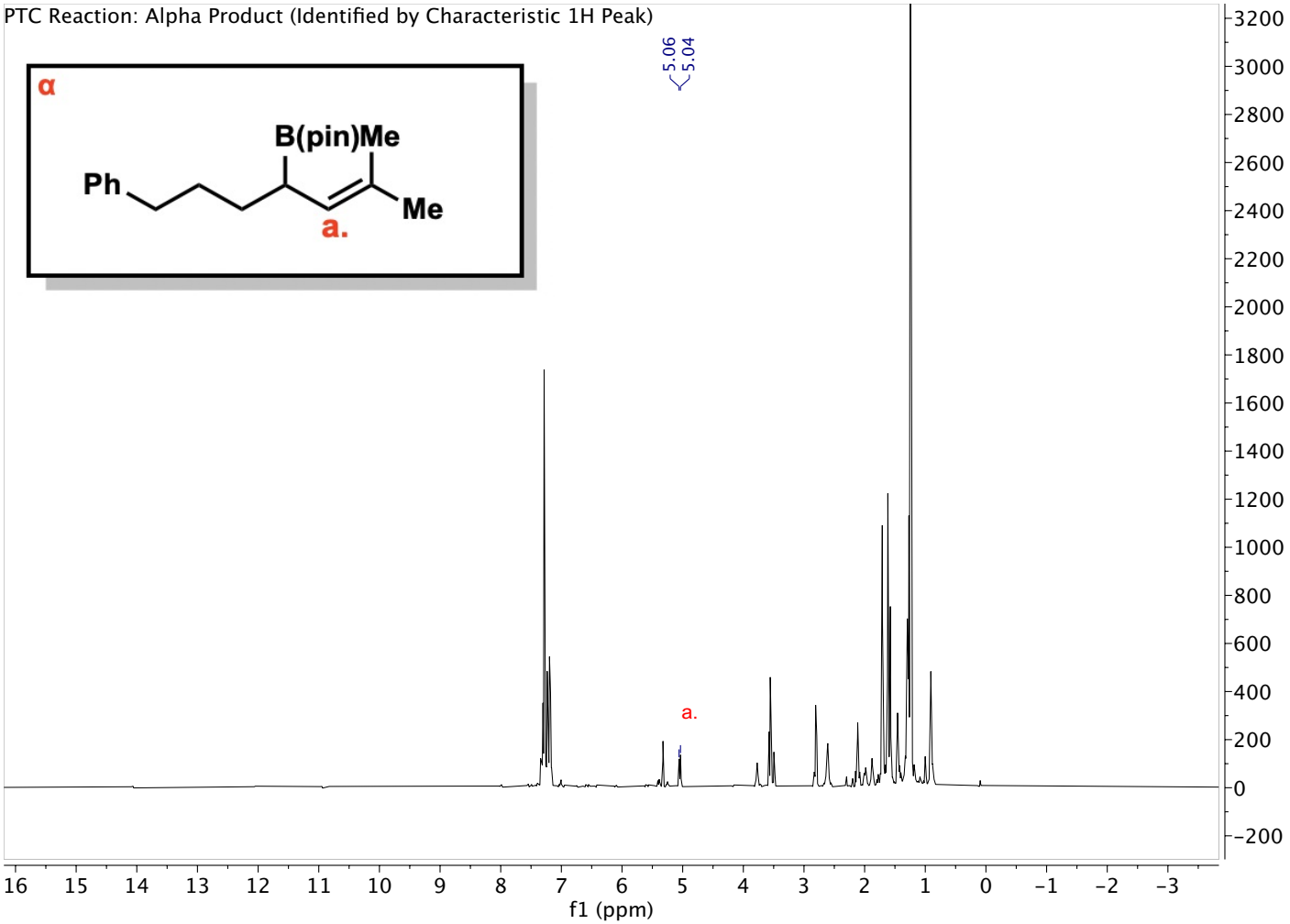
Spectra 2. ^{1}H NMR Me/nBu Vinyl Iodide



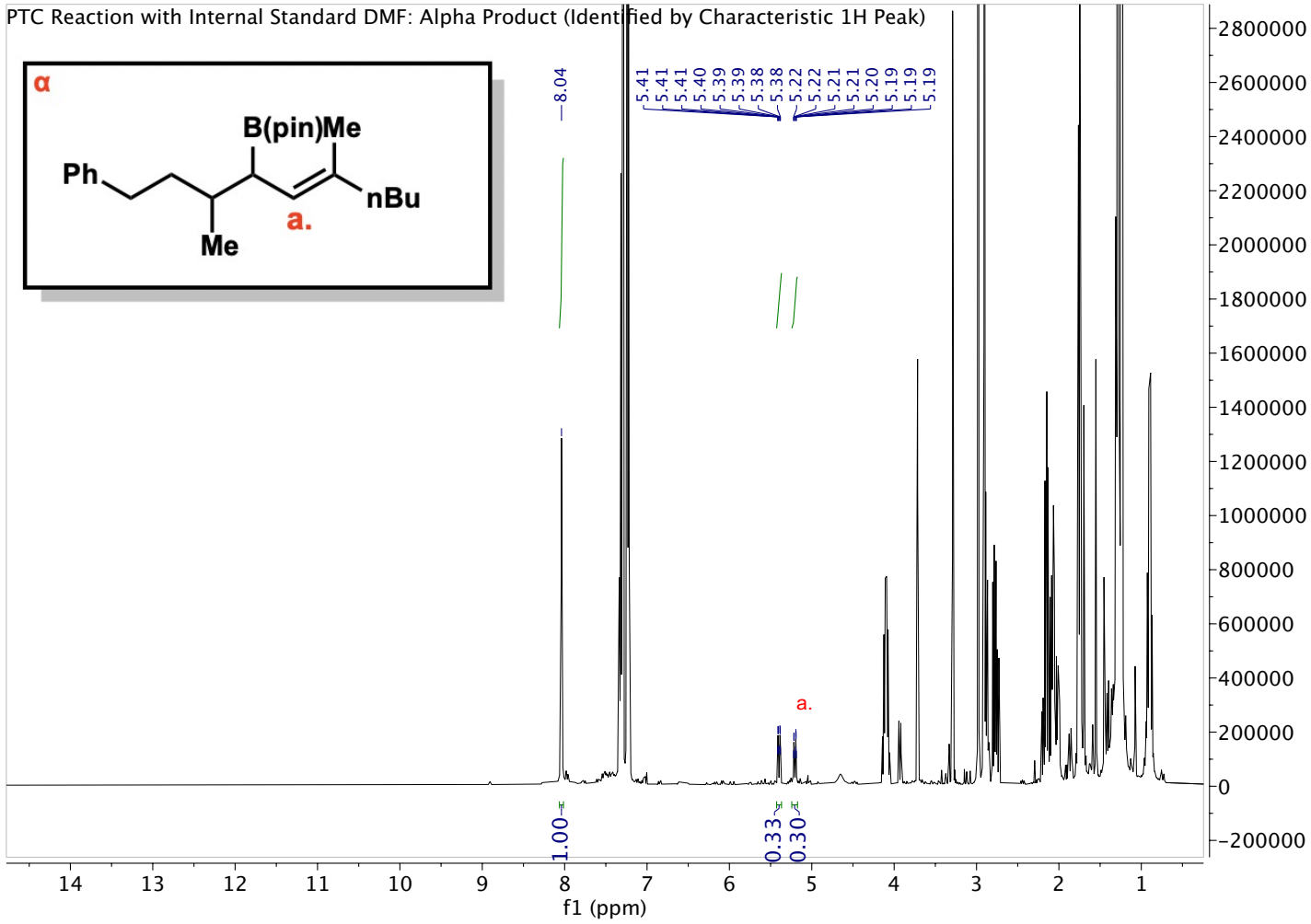
Spectra 3. ^{1}H NMR Me/Me Bis-1,1-Allyldiboron Reagent



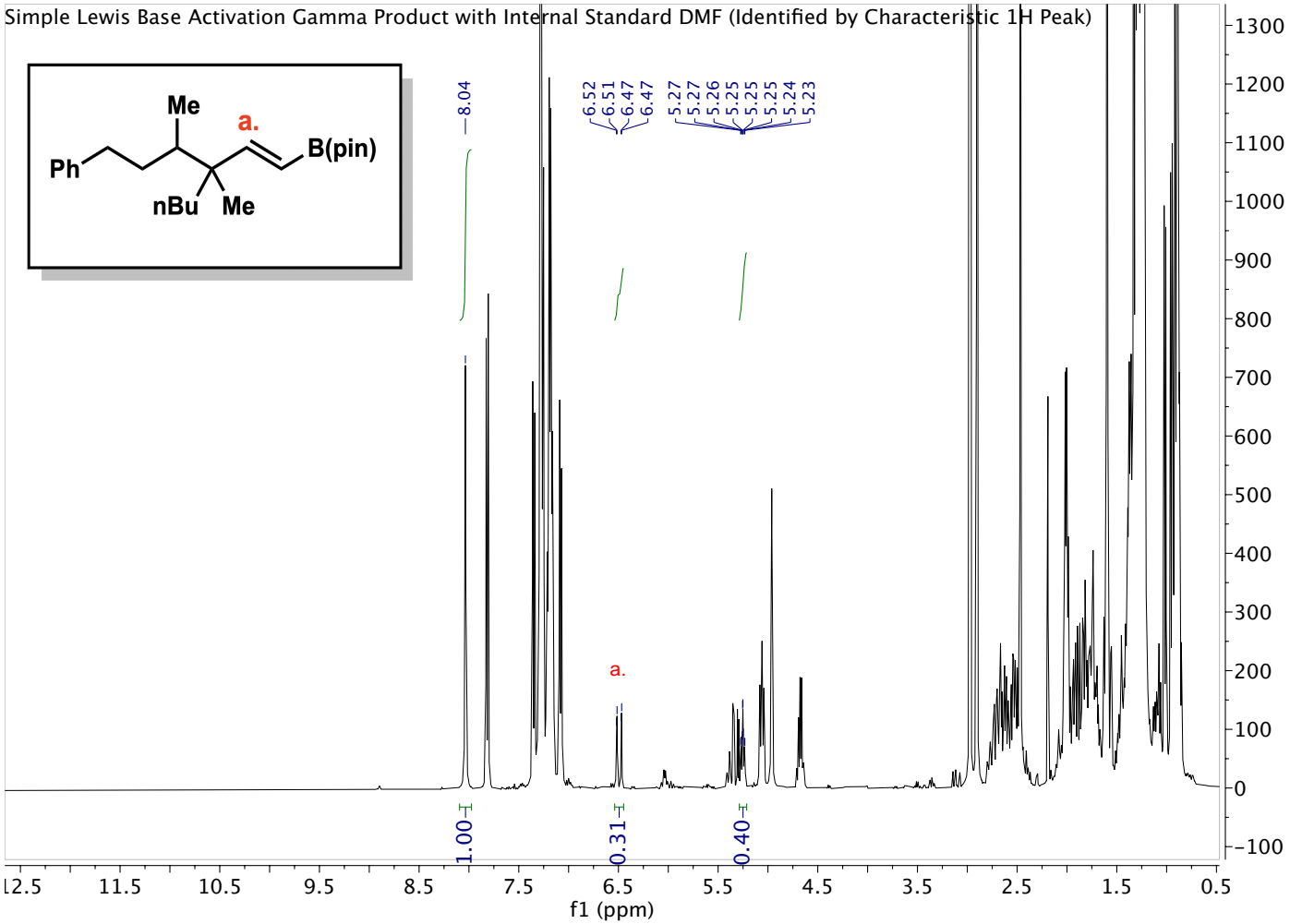
Spectra 4. ^{1}H NMR Me/nBu Bis-1,1-Allyldiboron Reagent



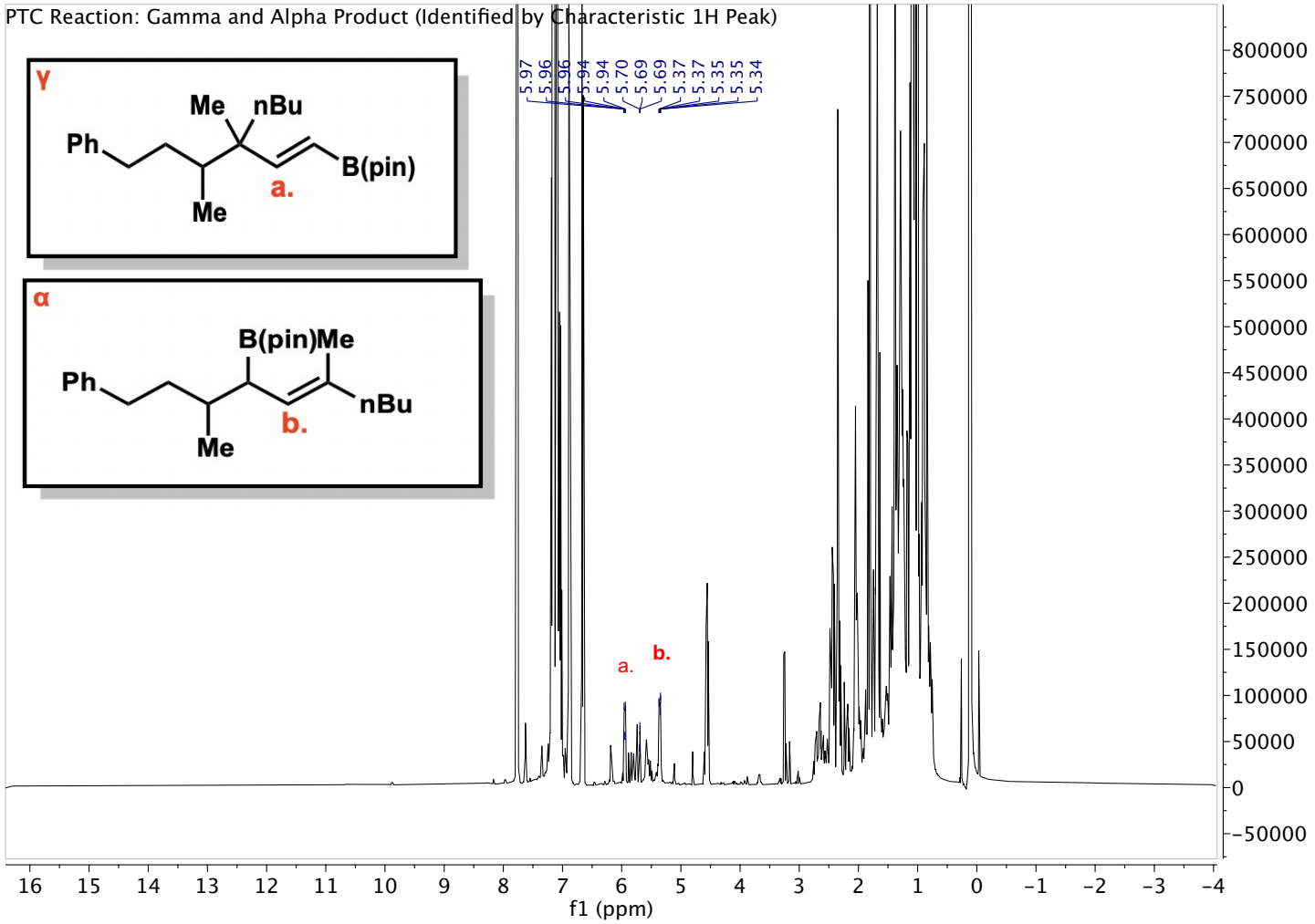
Spectra 5. ^{1}H NMR PTC Reaction Generating Me/Me Alpha Product



Spectra 6. ^{1}H NMR PTC Reaction Generating Me/nBu Alpha Product with Internal Standard DMF



Spectra 7. ^{1}H NMR Simple Lewis Base Activation Generating Me/nBu Gamma Product with Internal Standard DMF



Spectra 8. ^{1}H NMR PTC Reaction Generating Me/nBu Gamma and Alpha Product

B. Equation for Product Yield, Deborylation, Returned Electrophile, and Returned Diboron

Synopsis of Calculation

To determine the efficacy of each alkylation and conjugate addition reaction, an internal standard was added to the final product. Specifically, after each reaction workup, 2 μL (0.02594 mmol) of DMF was added to the sample being prepared for ^{1}H NMR analysis. When all expected peaks were identified in the corresponding spectra, the following equation was implemented to calculate percent conversion:

Parent Equation A: Internal Standard Equation

$$100 \times \frac{Int.\ Value\ of\ Peak\ of\ Interest}{Int.Value\ for\ Standard\ Peak\ (DMF)} \times \frac{mmol\ Standard}{mmol\ Starting\ Material\ (SM)} = \%\ Conversion$$

Parent Equation B: Converted Internal Standard Equation

$$100 \times \frac{Int.Value\ of\ Peak\ of\ Interest}{1} \times \frac{.02594\ mmol\ DMF}{mmol\ Starting\ Material\ (SM)} = \%\ Conversion$$

B. Calculations

Sample Calculation A: Bis-1,1-Allyldiboron Alpha Product (i.e., Alpha Product Yield) (**Spectra 6**)

$$100 \times \frac{.30}{1} \times \frac{.02594\ mmol\ DMF}{0.0250\ mmol\ SM} = 31\%\ Conversion$$

Sample Calculation B: Bis-1,1-Allyldiboron Gamma Product (i.e., Gamma Product Yield) (**Spectra 7**)

$$100 \times \frac{.31}{1} \times \frac{.02594\ mmol\ DMF}{0.0500\ mmol\ SM} = 16\%\ Conversion$$

Sample Calculation C: Deborylated 1,1-Allyldiboron Reagent (i.e., Deborylation) (**Spectra 7**)

$$100 \times \frac{.40}{1} \times \frac{.02594\ mmol\ DMF}{0.0500\ mmol\ SM} = 20\%\ Conversion$$

Sample Calculation D: Returned 1,1-Allyldiboron Reagent (i.e., Returned Diboron) (**Spectra 6**)

$$100 \times \frac{.33}{1} \times \frac{.02594\ mmol\ DMF}{0.0250\ mmol} = 34\%\ Returned\ Diboron$$

C. Optimization Tables

Allylboron	Substrate	Activator	Eq	Solvent	Temp (C)	Gamma (%)	Deborylation (%)	Rtn Electrophile (%)	Rtn Diboron (%)	DR
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	KOMe	1	THF	23	16	20	34	0	1:1
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	1	THF	23	14	38	24	0	20:1
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	CsF	1	DME	80	13	28	18	16	7:1
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	KOtBu	1	DME	60	13	49	53	0	20:1
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	TBAT	1	DME	80	12	31	29	51	20:1
Me/nBu	3-Iodobutyl Benzene	KOMe	1	THF	23	11	71	21	0	1:1
Me/nBu	3-Iodobutyl Benzene	NaOMe	1	THF	23	10	62	10	0	20:1
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	TBAT	1	DME	60	10	22	87	43	20:1
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	CsF	0.5	DME	80	9	41	23	0	10:1
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	KOtBu	1	DME	23	9	44	59	0	20:1
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	1	Et2O	23	9	23	34	33	-
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	TBAT	1	THF	60	8	23	21	21	1:1
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	1	Et2O	23	8	16	28	31	-

Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	0.5	THF	60	8	11	37	39	-
Me/nBu	octan-3-yl 4-methylbenzenesulfonate	KOtBu	1	THF	60	7	37	81	0	20:1

Table 1. Lewis Base Activation Optimization Table

Allylboron	Substrate	Activator	Eq	Catalyst	Catalyst (mol%)	Crown Ether (10 mol%)	Solvent	Temp (C)	Gamma (%)	Alpha (%)	Deborylation (%)	Rtn Diboron (%)
Me/Me	3-Chloropropyl Benzene	NaOMe	1	-	-	15-crown-5	PhH	23	0	10	12	78
Me/Me	3-Chloropropyl Benzene	NaOMe	1	-	-	-	PhH	23	0	0	9	85
Me/Me	3-Chloropropyl Benzene	NaOMe	1	-	-	-	THF	40	3	73	6	0
Me/Me	3-Chloropropyl Benzene	NaOMe	1	-	-	-	DCM	40	4	0	12	0
Me/Me	3-Chloropropyl Benzene	NaOMe	1	-	-	-	DME	40	3	86	8	0
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	23	3	73	8	7
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Maruoka Dimer	10	15-crown-5	PhH	23	2	72	12	21
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Jorgensen	10	15-crown-5	PhH	23	1	75	12	11
Me/Me	2-Chloropropane	NaOMe	1	-	10	15-crown-5	PhH	23	4	34	41	0

Me/Me	2-Chloropropane	NaOMe	1	-	10	15-crown-5	PhH	40	6	45	52	0
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	40	2	36	11	24
Me/nBu	3-Chlorobutyl Benzene	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	23	0	61	40	0
Me/nBu	3-Chlorobutyl Benzene	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	40	14	62	32	0
Me/Me	Cyclohex-2-en-1-one	CsF	1	Bis-NHC	10	-	THF	23	14	0	-	-
Me/Me	Cyclohex-2-en-1-one	CsF	1	Bis-NHC	10	-	PhH	23	0	0	-	-
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Benzyl-Tan	10	15-crown-5	PhH	23	3	82	14	0
Me/Me	Cyclohex-2-en-1-one	CsF	1	-	-	-	MeCN	23	18	0	10	8
Me/Me	Cyclohex-2-en-1-one	CsF	1	Maruoka Pyrazolium	10	18-crown-6	MeCN	23	22	0	9	6
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	Bis-Bn-Bisamidine	10	15-crown-5	PhH	23	47	0	23	10
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	Benzyl-Tan	10	15-crown-5	PhH	23	35	0	25	25
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Bis-Bn-Bisamidine	10	15-crown-5	PhH	23	0	30	28	24

Me/Me	3-Chloropropyl Benzene	NaOMe	1	Phospha-Tan	10	15-crown-5	PhH	23	0	47	28	18
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	Phospha-Tan	10	15-crown-5	PhH	23	74	0	4	21
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	-	-	-	PhH	23	13	0	8	80
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	-	-	15-crown-5	PhH	23	50	0	10	12
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	Maruoka Dimer	10	15-crown-5	PhH	23	30	0	10	31
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	Benzyl-Tan	10	15-crown-5	PhH	23	25	9 (2:1 dr)	8	28
Me/Me	Cyclohex-2-en-1-one	NaOMe	1	Jorgensen	10	15-crown-5	PhH	23	34	0	4	8
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	40	2	36	11	24
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Mixed Maruoka	10	-	PhH	23	0	0	0	0
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Mixed Maruoka	10	15-crown-5	PhH	23	2	46	2	0
Me/nBu	3-Chloropropyl Benzene	CsF	1	-	-	-	DME	80	0	47	30	22

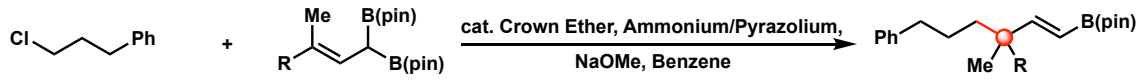
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	23	0	20	28	7
Me/Me	3-Chloropropyl Benzene	NaOMe	1	Maruoka Dimer	10	15-crown-5	PhH	23	0	36	6	0
Me/nBu	4-phenylbutan-2-yl 4-methylbenzenesulfonate	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	23	10	31	17	34
Me/nBu	3-Bromobutyl Benzene	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	23	0	0	20	76
Me/nBu	3-Iodobutyl Benzene	NaOMe	1	Maruoka Pyrazolium	10	15-crown-5	PhH	23	0	0	10	82

Table 2. Phase Transfer Catalyst Optimization Table

DISCUSSION

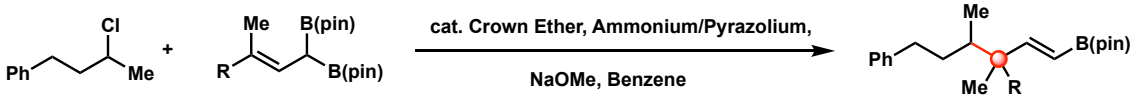
A. Theoretical Reaction Overview

Gamma Addition (Primary Chloride) (Meek 2021)



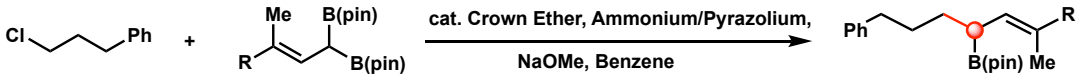
Scheme 6. Gamma Alkylation of Bis-1,1-Allyldiboron Reagent and 3-Chloropropyl Benzene

Gamma Addition (Secondary Chloride) (Meek 2021)



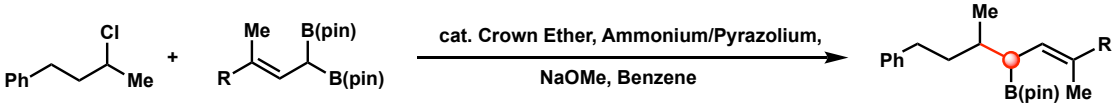
Scheme 7. Gamma Alkylation of Bis-1,1-Allyldiboron Reagent and 3-Chlorobutyl Benzene

Alpha Addition (Primary Chloride) (Meek 2021)

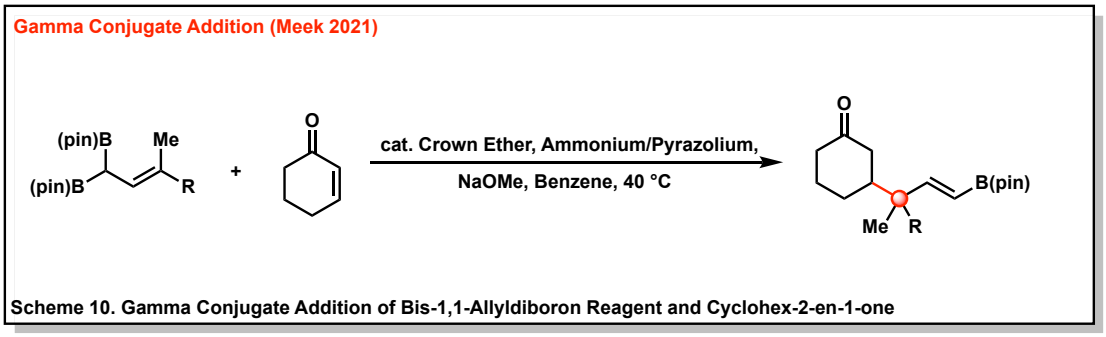


Scheme 8. Alpha Alkylation of Bis-1,1-Allyldiboron Reagent and 3-Chloropropyl Benzene

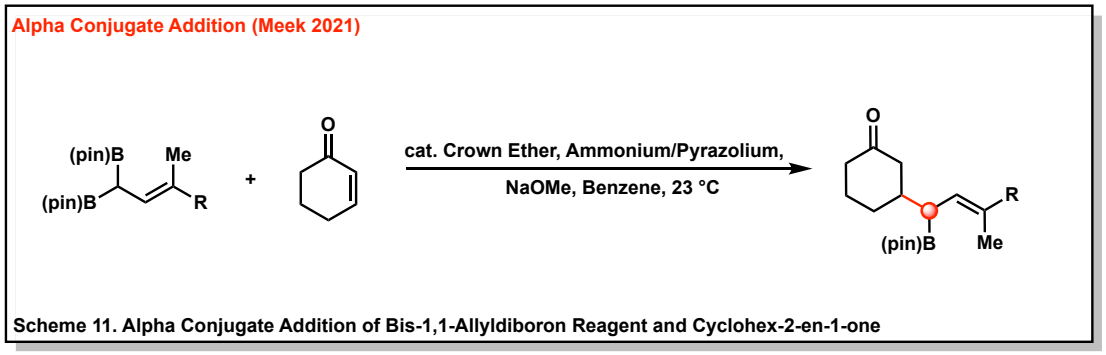
Alpha Addition (Secondary Chloride) (Meek 2021)



Scheme 9. Alpha Alkylation of Bis-1,1-Allyldiboron Reagent and 3-Chlorobutyl Benzene



Scheme 10. Gamma Conjugate Addition of Bis-1,1-Allyldiboron Reagent and Cyclohex-2-en-1-one



Scheme 11. Alpha Conjugate Addition of Bis-1,1-Allyldiboron Reagent and Cyclohex-2-en-1-one

The following schemes depict the general approach to this research. This project implemented various electrophilic species and coupled them with select catalysts under different conditions in attempt to promote regioselective and stereoselective α-additions, γ-additions, α-conjugate additions, or γ-conjugate additions with the electrophiles depicted above, while increasing yield from simple Lewis Base activation (**Figure 15**). Specifically, the types of additions were performed with primary and secondary halides (as well as tosylates) and cyclohexenone species. **Scheme 6** and **Scheme 7** highlight γ-alkylations, while **Scheme 8** and **Scheme 9** portray α-alkylations. Lastly, **Scheme 10** and **Scheme 11** illustrate the α- and γ-conjugate addition reactions tested. It should be noted that these are the general reactions believed to be possible and tested throughout this project. Since the project is ongoing, not all types of reactions have demonstrated an ability to be conferred with high rates of conversion.

Regarding product conversion, this project has seen product formation for all of the reactions depicted in the schemes previously discussed. However, not all of the reactions have demonstrated the ability to be produced with high yield— even when coupled with PTCs.

B. Overview of Experimental Approach, Optimization, and Activation Theory

For purposes of simplicity, an overview of the experimental results attained will be split into two separate phases: The first being nucleophilic activation and the second will be stabilization of the nucleophilic carbanion to increase product yield and selectivity. An extended discussion of the latter will highlight the attempted optimization of reactions from part *A* of this discussion section.

Regarding the first phase of this research, optimization of conditions that promoted generation of a nucleophilic borate intermediate species that could be utilized in alkylation and conjugate addition reactions when paired with an electrophile was required. As a result, the approach chosen was to test a series of Lewis Bases—specifically, ionic salts— that could be harnessed to donate into the vacant p-orbital of the trivalent boronate ester of the bis-1,1-allyldiboron reagent. **Table 1** highlights the use of various activators, temperatures, and solvent conditions that led to several different amounts of γ-product yield, deborylation, returned electrophile, and returned bis-1,1-allyldiboron reagent. Although the optimization conditions attempted did not promote large percentages of product conversion (e.g., only 16% product conversion with KOMe, 14% product conversion with NaOMe, 9% product conversion with CsF), the amount of deborylation provided insight into the ability to generate such nucleophilic species (i.e., borate intermediate) via Lewis Base activation. Furthermore, the diastereomeric ratio (DR) determined within each product via ^{1}H NMR analysis of the integration values between each diastereomer product provided insight into the most promising Lewis Base activators. Specifically, NaOMe was subsequently utilized due to its ability to confer 20:1 DR (**Table 1)**. Regarding Deborylation (i.e., the loss of a B(pin) from the reagent to generate a nucleophilic species), it was

observed that Lewis Bases, under optimal conditions, were donating electron density into the vacant p-orbitals. Cesium Fluoride in DME at 80 °C led to 9% product yield and 41% deborylation (**Table 1**); however, even more promising was the use of NaOMe as an activator. Specifically, one experiment determined 14% product conversion with 38% deborylation, while the other indicated 10% product conversion with 62% deborylation (**Table 1**). Logically, this observation led to an understanding that the current aspects of the reaction that were preventing regioselectivity, desired stereochemistry, and significant returns on product yield were stability of the borate intermediate species and its ability to coordinate with the electrophile for addition.

From here, the project shifted to surveying various catalysts and stabilizing species that could be introduced to the reaction mixture to not only confer higher product conversion but also demonstrate an ability to promote regioselectivity and stereoselectivity. Here, the project sought to diminish percentages of deborylation via intermediate stabilization and reactant coordination, driving product formation. **Table 2** depicts the results of several different types of optimization reactions as well as their regioselectivity. Interestingly, this work has presented many complexities; specifically, this work demonstrates how various electrophiles, catalysts, or their combination can influence regioselectivity (i.e., α-addition or γ-addition). Regarding electrophiles ability to influence selectivity within the PTC system, it was demonstrated that primary chlorides, secondary chlorides, and tosylates heavily favored α-selectivity (e.g., all reactions containing 3-Chloropropyl Benzene, 2-Chloropropane, and 4-phenylbutan-2-yl 4-methylbenzenesulfonate), while the introduction of enones tended to favor γ-selectivity (e.g., Cyclohex-2-en-1-one) (**Table 2**). Furthermore, while the introduction of catalysts did not always increase yield, it was determined that the presence of catalyst and crown ether promoted α-product formation for secondary chlorides under certain conditions (e.g., in terms of α-product yield:γ-product yield, 3-

chlorobutyl benzene led to 61%:0%), which was not the case for similar electrophilic substrates in **Table 1**. One possible reason for this trend observed in secondary chlorides could be that the α-borate intermediate, under certain conditions, was more sufficiently stabilized when coordinated with the catalyst and electrophile (in comparison to the γ-borate intermediate). Specifically, this could be due to the α-borate intermediate's ability to donate electron density into the boronate ester when coordinated with the catalyst and electrophile, stabilizing itself as a nucleophile; second, given that the α-borate intermediate does not have electron-donating alkyl groups (whereas the γ-borate intermediate does), it is likely able to best maintain stability at the α position, when coordinated with the catalyst and electrophile.

When reviewing the data based on the general reactions outlined in section *A* of this discussion. It is possible to see stark differences across the various general reactions and their ability to produce product. It should be noted that γ-alkylations with both secondary and primary halides (**Scheme 6** and **Scheme 7**) have not yet proven to be as robust as the other types of reactions (**Scheme 8, 9, 10,** and **11**). For example, the utilization of 3-chlorobutyl benzene (secondary chloride), the Maruoka pyrazolium, and 15-crown-5 under nonpolar conditions at 0 °C only yielded 14% γ-product. Additionally, γ-products generated via nucleophilic attack to a primary chloride, such as 3-chloropropyl benzene, only produced about 4% γ-product, which lowered yield upon addition of catalyst (**Table 2**).

On the other hand, strong conversion was demonstrated for the α-products. Regarding primary chlorides (**Scheme 8**), this proved to be especially interesting because two different approaches allowed for conversion upwards of 80%. One approach was the use of a primary chloride with the slightly polar aprotic solvent, DME, at 40 °C, which yielded 86% α-product; the other was achieved under PTC conditions with the benzyl-tan catalyst, 15-crown-5, and NaOMe

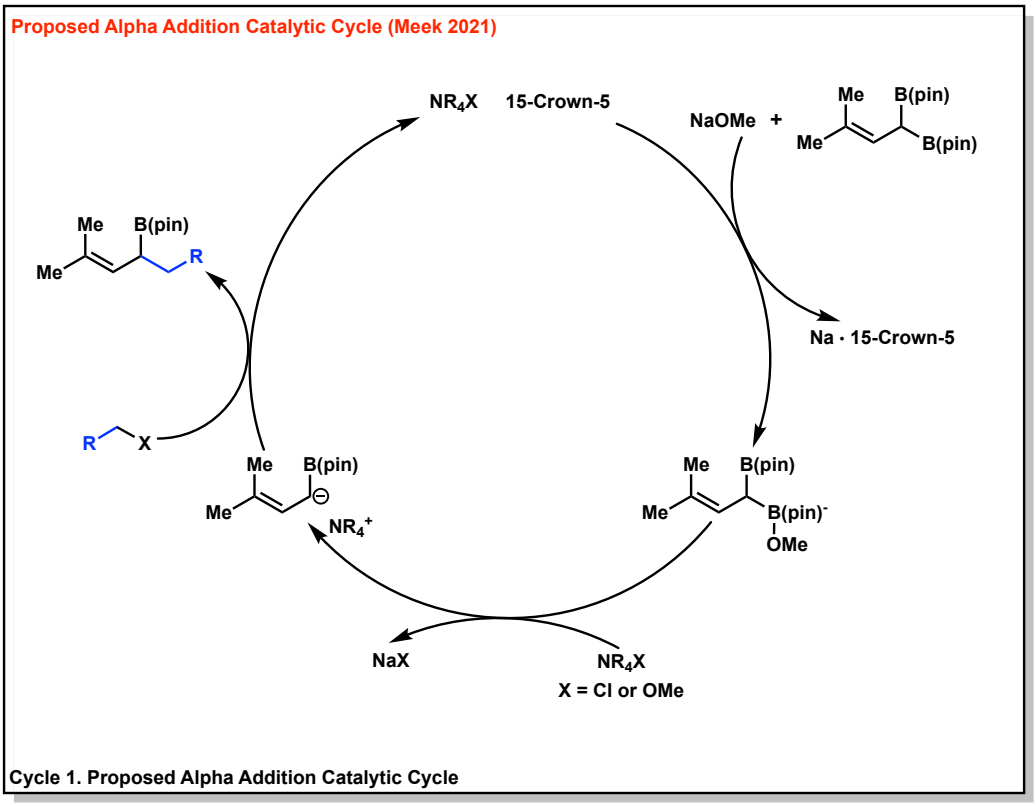
in benzene (nonpolar) at ambient temperature, which yielded 82% α-product. In the case of secondary chlorides (**Scheme 9**), such as 3-chlorobutyl benzene, as much as 62% α-product was achieved with the use of Maruoka pyrazolium, 15-crown-5, and NaOMe under nonpolar conditions at 0 °C (**Table 2**). While both of these approaches did serve to confer product with high conversion, the PTC system only demonstrated the ability to drive α-product formation in the case of secondary halides—especially when shifting from achiral to chiral catalysts.

Lastly, the implementation of PTCs and crown ethers proved to be useful for conjugate addition reactions to a cyclohex-2-en-1-one species. Although much lower in yield compared to the γ-conjugate addition counterpart, the α-conjugate addition within the PTC system did prove to be possible, yielding 9% product with a 2:1 DR (**Scheme 11**). Regarding γ-conjugate additions, it was possible to yield as much as 74% product at ambient temperature in benzene with the phospha-tan catalyst, 15-crown-5, and NaOMe. On average, the γ-conjugate additions proved to yield much more product than the α-conjugate additions (**Table 2**, **Scheme 10**).

With the possibility of generating product for all of the general reaction types outlined above, further research is warranted to increase yield, site-selectivity, and diastereomeric excess.

C. Solvent Effects and Temperature

As illustrated in **Table 1**, it was possible to generate some γ-product and α-product without the introduction of PTCs to the system; however, their usefulness in increasing yield and promoting product formation—especially α-product formation for secondary halides— was solvent (and catalyst) dependent. **Table 2** depicts nearly all reactions with significant yield—even reactions with large amounts of γ-product—utilizing benzene. It is believed that because benzene is nonpolar and likely does not interact with the substrates, the PTCs and crown ethers were able



Cycle 1. Proposed Alpha Addition Catalytic Cycle

to promote the forward reaction, diminishing unwanted reactions and allowing the catalyst species to stabilize and coordinate the nucleophilic intermediate species and the electrophile. Especially when thinking about the PTC system, solvent effects, and catalyst regeneration, it is plausible to think that the ability for crown ether to sequester multiple sodium cations and for sodium cations to react with anions from the electrophile and catalyst to regenerate the PTC system is less hindered by benzene compared to more polar solvents. It is not surprising that the reaction tended to allow higher product conversion at lower temperatures. This is plausible because, if the theory that PTCs and crown ethers play a stabilizing role within the reaction mixture, higher temperatures—corresponding to higher levels of kinetic energy—might prevent such essential coordination and intermediate stabilization. With these understandings of the PTC system and the results produced, the catalytic cycle above is proposed for α-addition reactions (**Cycle 1**).

D. Mechanistic Theory

When reviewing the data altogether and understanding the nuances between the two "phases" of this project. It is possible to begin theorizing the potential mechanistic routes attempted for each type of general reaction highlighted in part *A* of this discussion and highlighted in **Cycle 1**.

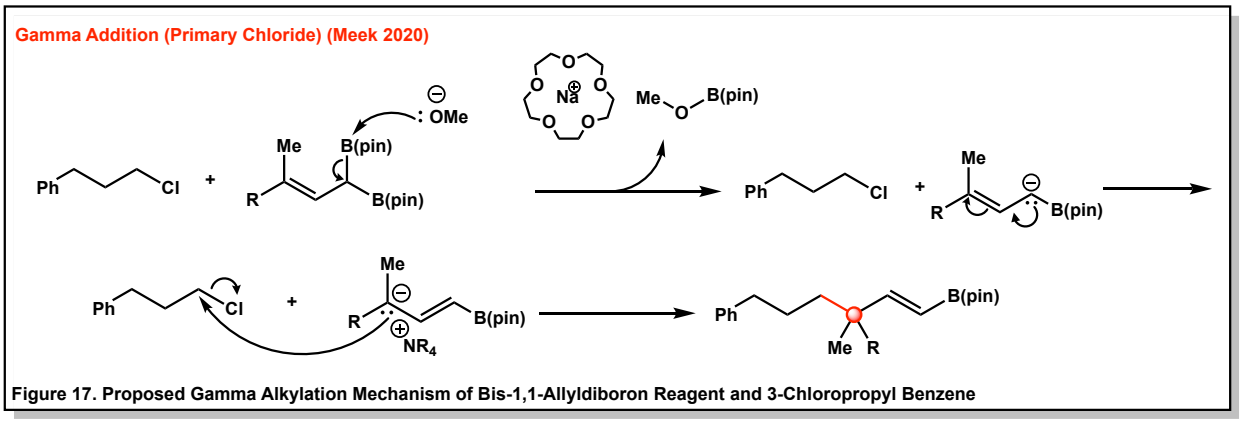


Figure 17. Proposed Gamma Alkylation Mechanism of Bis-1,1-Allyldiboron Reagent and 3-Chloropropyl Benzene

Regarding γ-alkylations of primary chlorides, though PTCs and crown ethers have not yet demonstrated the ability to promote significant product formation, **Figure 17** depicts the theoretical mechanism that substantiated their investigation in a PTC system. Given that this reaction takes place in nonpolar solvent (benzene), it should be noted that the crown ether must sequester the cationic sodium to generate the anionic methoxy Lewis Base that subsequently donates its electron density into the vacant p-orbital of the boronate ester. The carbanion intermediate subsequently resonates with the adjacent double bond to perform a 1,3-carbanion shift that generates a new nucleophilic γ-intermediate that is stabilized by the catalyst and subsequently attacks the primary chloride, generating the alkylated product, which contains an

allylic all carbon quaternary center and a Sp^2 boronate ester.

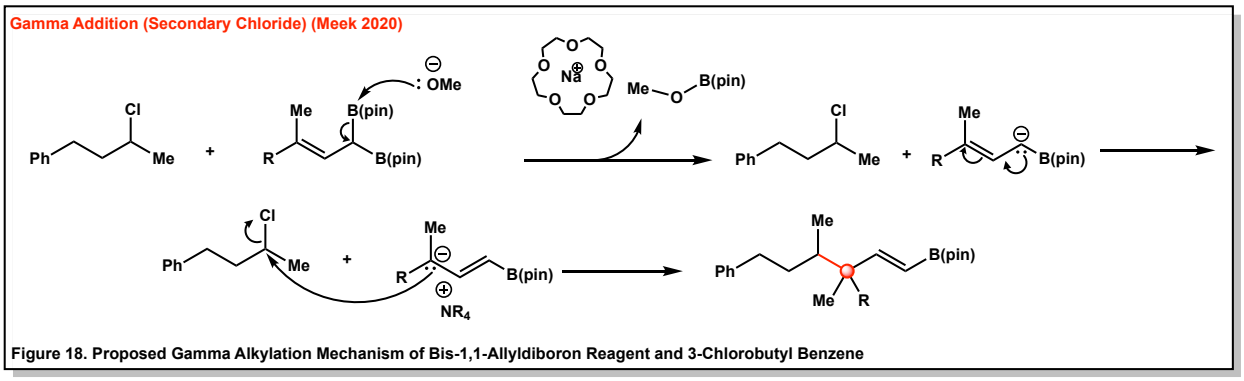


Figure 18. Proposed Gamma Alkylation Mechanism of Bis-1,1-Allyldiboron Reagent and 3-Chlorobutyl Benzene

Conversely to the γ-additions of primary chlorides, those of secondary chlorides have demonstrated the ability to promote greater product formation, though still small in yield. **Figure 18** depicts a similar theoretical mechanism. The mechanism begins with crown ether sequestering the sodium cation to generate anionic methoxy Lewis Base which contributes into the vacant p-orbital of the boronate ester, leading to the loss of the pinacol group containing the former methoxy Lewis Base and generating a carbanion intermediate. It is proposed that a methoxy pinacol by-product is released to generate a carbanion, which performs a subsequent 1,3-anionic shift to generate the γ-carbanion. At this point, it is plausible that a PTC, such as a quaternary ammonium or pyrazolium, stabilizes the anionic, nucleophilic intermediate to allow for alkylation with the secondary chloride to generate a product containing two adjacent quaternary centers with one in the allylic position and an all carbon center, simultaneously installing a Sp^2 boronate ester.

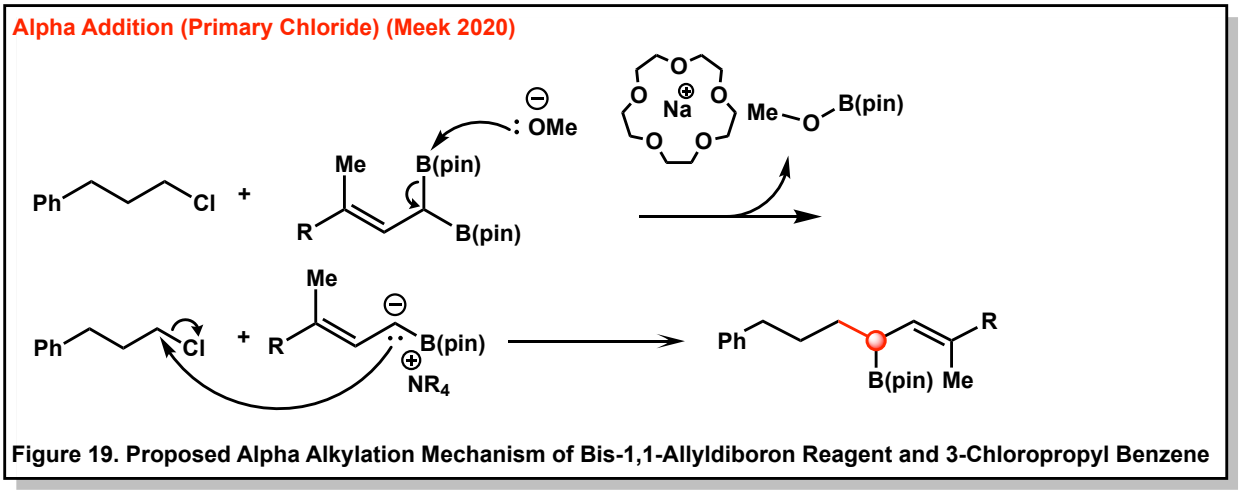


Figure 19. Proposed Alpha Alkylation Mechanism of Bis-1,1-Allyldiboron Reagent and 3-Chloropropyl Benzene

Compared to the γ-alkylations, α-alkylations have demonstrated greater promise in their ability to promote product formation upon the introduction of PTCs and crown ether. **Figure 19** depicts the proposed α-alkylation mechanism for primary chlorides, which occurs under nonpolar conditions and typically at low to ambient temperatures. Differing from the previous two mechanisms by a single intermediate step, it is theorized that the mechanism proceeds in the same manner, generating an anionic methoxy species by crown ether's sequestration of the Lewis Base's counterion. From here, the Lewis Base introduces electron density into the vacant p-orbital of the boronate ester, polarizing one of the Boron-Carbon bonds, leading to the dissociation of the pinacol group bonded to the formerly anionic Lewis Base. Subsequently, a quaternary ammonium or pyrazolium species stabilizes the alpha anionic intermediate sufficiently to promote nucleophilic attack of the primary chloride, generating α-alkylated product. This product bears a new quaternary chiral center, at which the Sp^3 boronate ester is situated; furthermore, it is formed at the allylic α position.

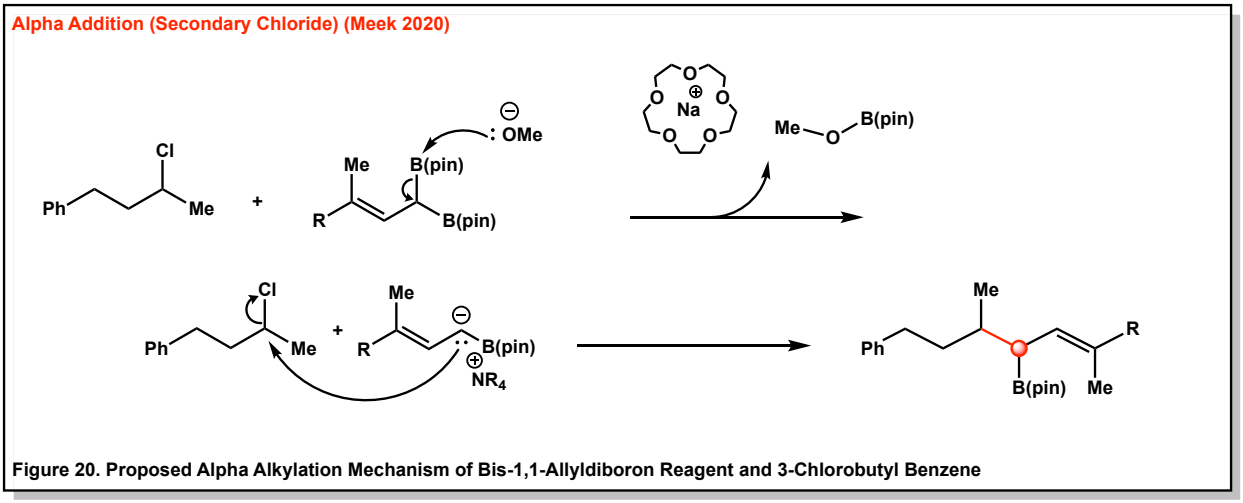


Figure 20. Proposed Alpha Alkylation Mechanism of Bis-1,1-Allyldiboron Reagent and 3-Chlorobutyl Benzene

The final α-alkylation mechanism proposed is that of secondary chlorides. It should be noted that since α-alkylation reactions with secondary chlorides showed increased site-selectivity within the PTC system, the mechanistic theory currently seems more plausible than those previously highlighted. **Figure 20** demonstrates the generation of an anionic Lewis Base species and the subsequent loss of pinacol-methoxy by-product in the exact same manner as **Figure 18** and **Figure 19**. From here, a stabilizing PTC, such as a quaternary ammonium or pyrazolium, facilitates stability of the α-anionic nucleophilic intermediate that attacks the electrophile. The result is a product similar to the previous one, containing two adjacent quaternary centers with one containing a Sp^3 boronate ester and being allylic.

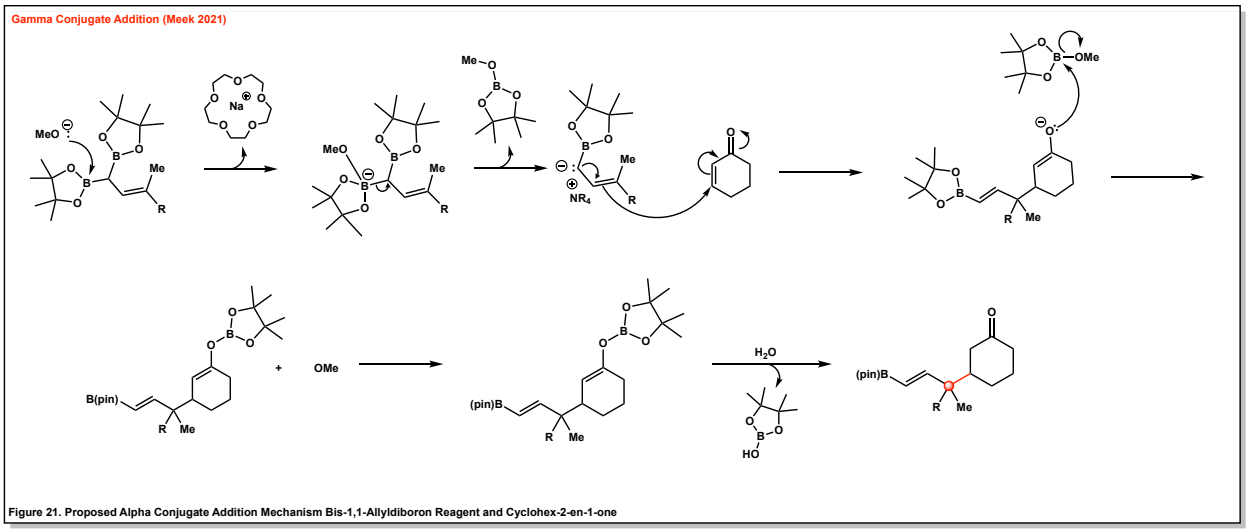


Figure 21. Proposed Alpha Conjugate Addition Mechanism Bis-1,1-Allyldiboron Reagent and Cyclohex-2-en-1-one

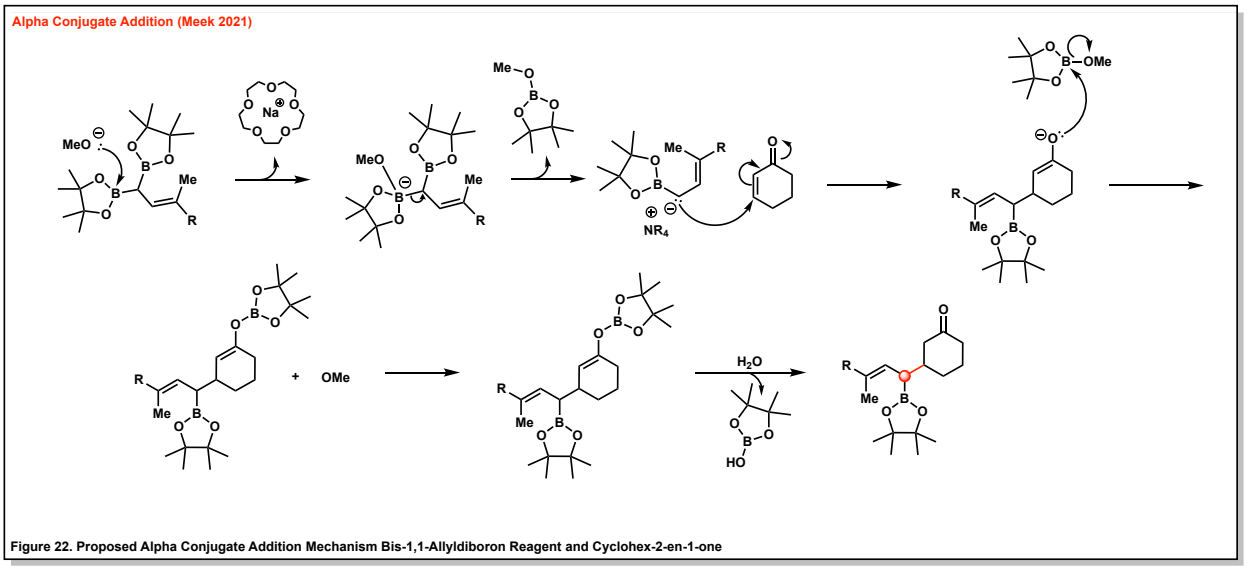


Figure 22. Proposed Alpha Conjugate Addition Mechanism Bis-1,1-Allyldiboron Reagent and Cyclohex-2-en-1-one

Although proposed to be slightly different in intermediate steps, the mechanisms for conjugate additions are highly similar to those theorized above (**Figure 21** and **Figure 22**). Regarding γ-additions, generation of the nucleophilic species is principally the same. However, the difference in the conjugate addition mechanisms is where the nucleophilic species attacks. Given that the electrophilic substrate now participates in a conjugated pi-electron system, attack by the nucleophilic intermediate occurs at the β-position of the enone because it is the most electron-deficient. As a result, the mechanism appears to be S_N2'-like for both the γ and α-conjugate additions. The difference is where the quaternary ammonium or pyrazolium stabilizes

the carbanion intermediate; based upon this, the product varies. However, the rest of the mechanism is the same. The delocalization of the double bonds in the pi-system, upon introduction of the nucleophilic intermediates electron density into the electrophilic position generates an oxyanion that attacks the pinacol-methoxy by-product. The final ketone-containing product can be achieved by aqueous workup with ammonium chloride. The γ-product contains two chiral centers with one at the allylic position, with a simultaneously-installed Sp^2 boronate ester. The α-product also contains two chiral centers with one at the allylic position; however, it differs in that the allylic center has an installed Sp^3 boronate ester.

E. Synthetic Potential

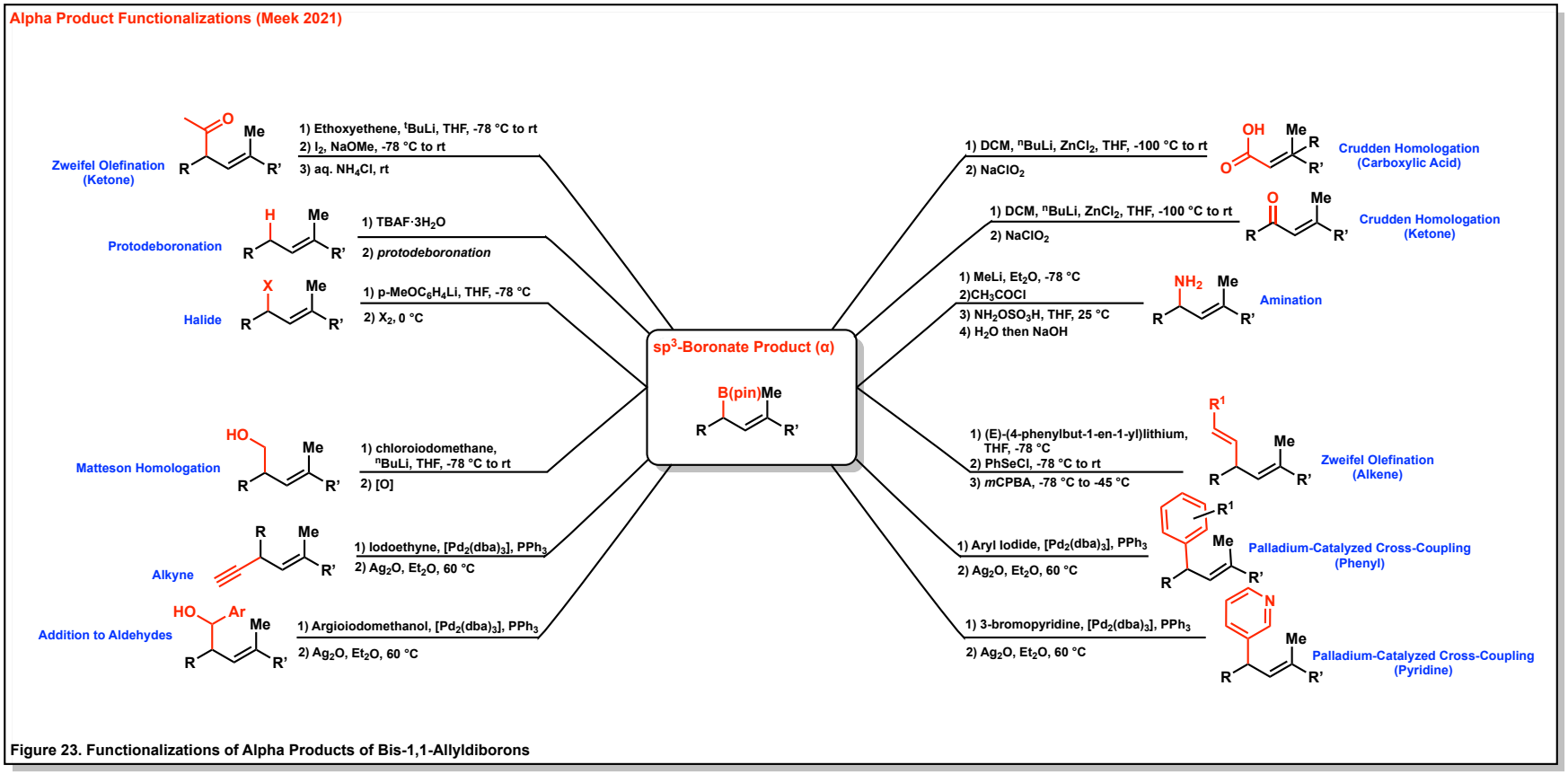


Figure 23. Functionalizations of Alpha Products of Bis-1,1-Allyldiborons

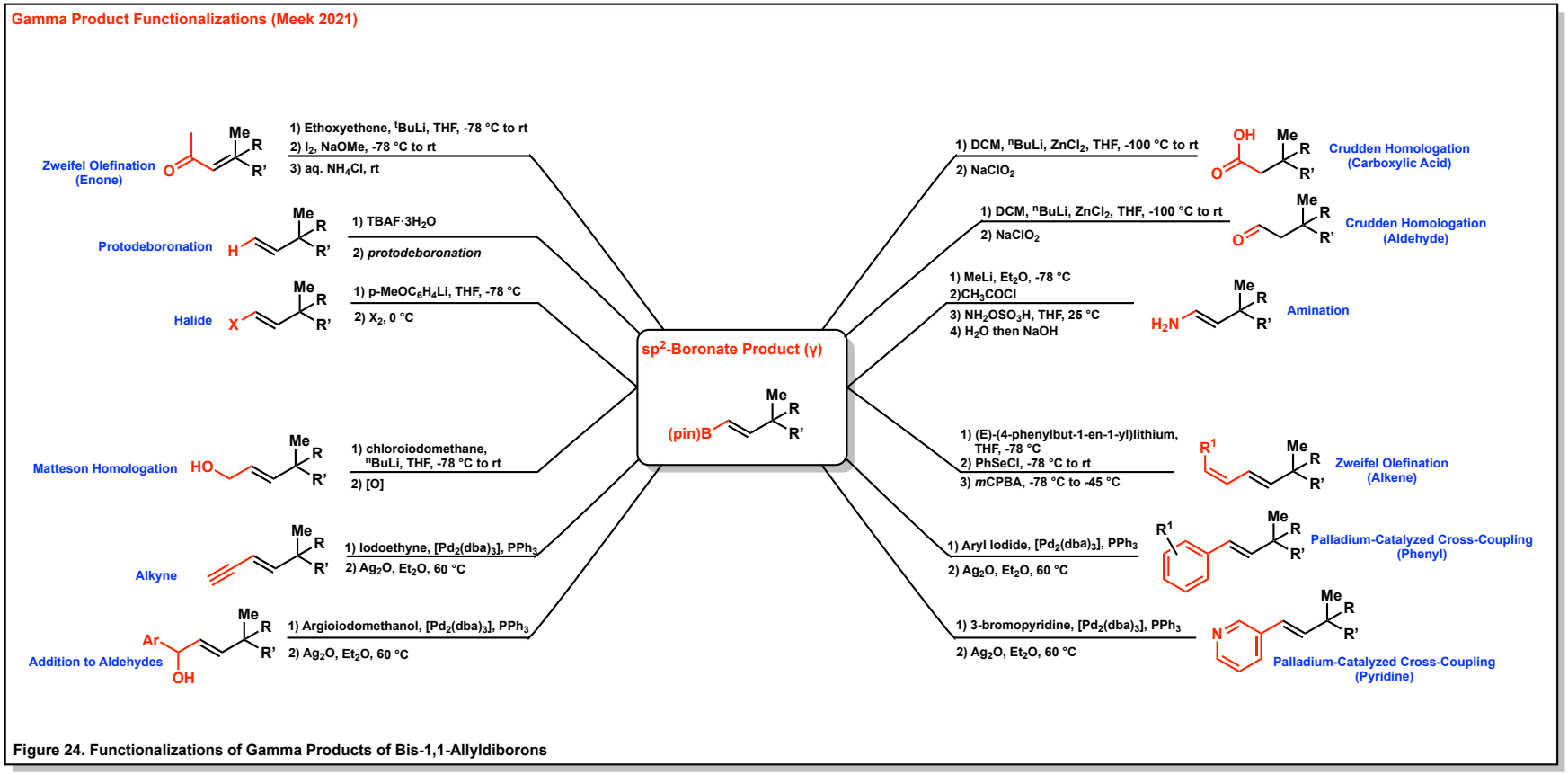


Figure 24. Functionalizations of Gamma Products of Bis-1,1-Allyldiborons

With the ability to generate both α-selective and γ-selective products containing a sp^3 or sp^2-carbon containing a boronate ester, the possibility for downfield transformations are significant and promising. The α-product has the ability to generate a quaternary center at the allylic position, while the γ-product generates a boronate ester at the vinylic position. As a result, further transformations and functionalization have the ability to lead to varied products. **Figures 23 and 24** depict the synthetic potential of both types of products.[26] Cross-coupling reactions could be harnessed to add conjugated pi-systems via phenyl-halides, heteroaryl-halides, alkynal-halides, and other aromatic halides, even containing substituent alcohols. Furthermore, functionalization that add simple alkyl alcohols, halides, and amines can be implemented. Lastly, of the downstream reactions depicted in each figure, it is possible to activate the boronic ester product to add ketones and carboxylic acids as functional groups. It should be noted that the downstream reactions depicted in the functionalization figures do *not* provide an exhaustive list of the transformational capabilities of both the α and γ products that could be synthesized by the nor do they indicate the types of reactions that could be harnessed after such functionalization. The breadth of synthetic creativity afforded by downstream transformation of such products not only provides fascinating implications for building vast pi-electron systems but also more practically highlight its potentiality for use by industry and within medicine to generate useful bioactive compounds that address the needs of society (**Figures 23, 24,** and **25**).

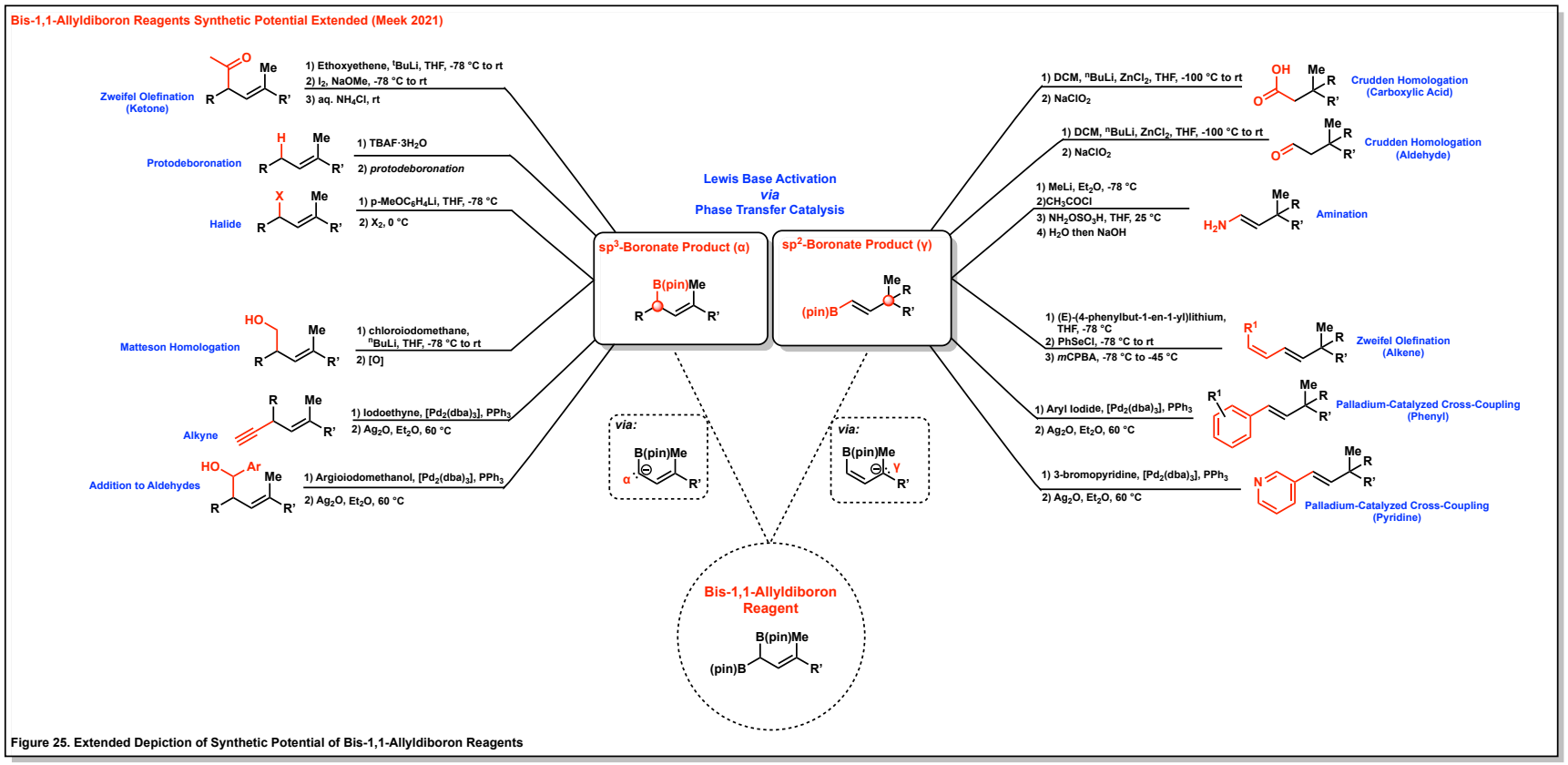


Figure 25. Extended Depiction of Synthetic Potential of Bis-1,1-Allyldiboron Reagents

F. Sources of Error

While the data outlined above do provide compelling reasons to suggest that the introduction of quaternary ammonium species as PTCs and crown ethers can participate in both α and γ-selective reactions under certain solvent and temperature conditions, it should be noted that there are a few potential sources of error in this research. Specifically, systematic error could have stemmed from possible calibration errors in instruments, such as the NMR instrumentation as well as any electronic lab scales utilized throughout the project. With regard to random error, it is possible that both observational factors, such as the reading of measurements when measuring reagents and the measuring of internal standard for conversion could have been slightly inexact. One last possible source of error is the possibility of impurities in the product NMRs that might contain overlapping peaks with the product. However, it is highly unlikely that any of these errors diminish the novelty, impact, or overall results of this research thus far.

G. Current Status of Work and Future Direction

Although product conversion has started to show promise for many of the reaction types discussed, there are three main components of organodiboron chemistry this work seeks to understand and address. First, the reactions discussed throughout this paper show potential for greater yield on some, if not all, of the reaction types. It is plausible that through continued optimization and experimentation with various conditions that higher product conversion can be achieved.

In addition to increased product yield, this work seeks to understand how chiral catalysts and chiral substrates can be utilized to promote desired stereochemistry within products. Currently, the PTC products being synthesized tend not to be produced in optical excess. Given the necessity

for many compounds with practical applications— especially within medicine— requiring specific stereochemistry, it is fundamentally important for this work to understand how such products could be synthesized.

With much of the data encapsulated throughout this paper demonstrating the ability for combinations of catalysts and electrophilic substrates to play a role in the regioselectivity of product formed, it is essential to more precisely and accurately understand the theorized mechanisms and how they can be universally harnessed to generate desired products in optical excess.

As a result of these understandings, it is recommended that further research continue to review the literature and experiment with various chiral catalysts as well as implement different chiral substrates to increase product yield for each reaction type and to determine how substrate chirality translates to regioselectivity and optical excess of product; furthermore, to further understand the mechanistic theory, systems, and universality of the reactions, it would be helpful pursue computational studies, competition experiments, and intermediate isolation experiments. Once these fundamental questions to the research are further understood, it is likely that this will present profound implications for industry and organoboron literature.

CONCLUSION

Overall, this work outlines the ability for Bis-1,1-allyldiboron reagents to participate in α-alkylations, γ-alkylations, α-conjugate additions, and γ-conjugate additions with a range of electrophilic species, under certain solvent, temperature, and catalyst conditions. Of special note is the ability of the PTC system to promote greater selectivity for α-alkylations with secondary chlorides and greater yield for γ-conjugate additions and α-conjugate additions. Although this work is not yet complete, this thesis establishes a framework and highlights the potential for this research to have an impactful contribution to the literature. With that, the data above warrant further research to increase product yield, regioselectivity (i.e., α or γ), stereochemistry, and to further understand the system and its mechanistic theory. In addition to installing a boronate ester within all products, this research illustrates the potential for alkenyl product generated via α-alkylation and γ-alkylation to contain multiple adjacent stereocenters. Regarding conjugate addition products, the ability to generate new stereocenters, install a boronic ester, and generate a ketone product also speaks to the merits of this work. With the possibility for downstream, value-added transformations, the products of these reactions can be harnessed to generate various molecular scaffolds. Especially given the monetary and environmental costs incurred by industry for its use of transition-metal catalysts coupled with increasing amount of therapeutic and diagnostic drugs incorporating the molecule boron, it is essential that this chemistry be further pursued—expanding the understanding of organoboron chemistry within the literature while promoting efficiency for practical industrial applications.

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