University of Alberta

Preparation and Synthetic Applications of Chiral Alkyl Boronates and Unsaturated Alkenyl Boronates

by

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Abstract

As Organic Chemistry evolves into the 21st Century, the goal of this discipline has altered dramatically from merely accessing target molecules to efficiently synthesizing these compounds with minimization of non-strategic functional group manipulations and interconversions. Organoboron reagents represent one of the potential solutions towards reaching this goal. These versatile compounds can either be used to construct the desired carbon−carbon bond through various cross-coupling reactions, or be converted directly to the desired functionality through different chemical reactions. Direct transformations make interconversions between different functional groups unnecessary, thus making the overall process step-economical. In this thesis, several synthetic methods were developed to synthesize chiral alkyl boronates or alkenyl boronates through metal-catalyzed chemical transformations. These methodologies are based on early introduction strategy which applies well-established synthetic protocols to substrates with a pre-installed boronyl moiety. The subsequent applications of these compounds were also investigated, leading to a variety of synthetically valuable adducts.

In order to access novel chiral secondary alkyl boronates, catalytic asymmetric conjugate addition reactions of 3-boronyl α,β-unsaturated esters with Grignard reagents were developed. Chapter 2 describes the details of optimization of this methodology and the applications of the chiral alkyl boronate products.

Aiming to explore the intrinsic reactivity of enantioenriched 1,1-diboron compounds, their synthesis was accomplished for the first time by performing

asymmetric conjugate borylation on 3-boronyl enoates. The resulting optically enriched 1,1-diboron compounds were found to be excellent cross-coupling partners in Suzuki-Miyaura cross-couplings, leading to chiral alkyl boronates with excellent enantioselectivity. The details of these studies are presented in Chapter 3.

In order to conduct a thorough examination of substrate scope in asymmetric conjugate reductions of 3-boronyl-3-aryl α,β-unsaturated esters, a diastereoselective protocol for the preparation of these alkenyl boronates through Heck coupling was developed. In Chapter 4, the optimization of the coupling process, the substrate scope, and the subsequent application of these alkenyl boronates are discussed.

Due to the synthetic potential of cyclic alkenyl boronates, new methods for their efficient synthesis are desirable. In Chapter 5, the preparation of novel cyclic alkenyl boronates through gold-catalyzed enyne cycloisomerizations is presented.

Acknowledgements

Although this thesis bears only my name, the work presented here is certainly a collective effort. I am deeply indebted to a vast group of people without whom this thesis would not have been possible.

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Last but not least, I would like to thank my parents and brothers. They constantly stay close to me, giving me support throughout my graduate studies. No matter how difficult the situation gets, they are always there for me. Here I would like to express my deepest gratitude to all of them.

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List of Schemes

List of Abbreviations

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

DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
de	Diastereomeric excess
DFT	Density functional theory
DIPPF	Diisopropylphosphinoferrocene
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DOS	Diversity oriented synthesis
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dq	Doublet of quartets
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact
eq	Equation
equiv	Equivalents
ESI	Electrospray ionization
Et	Ethyl
Et_2O	Diethyl ether

EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hour
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
LTMP	Lithium 2,2,6,6-tetramethylpiperazide
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MIDA	*N*-Methyliminodiacetic acid
MS	Molecular sieves
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
Nu	Nucleophile
ORTEP	Oak ridge thermal ellipsoid plot
Ph	Phenyl

pin	Pinacolato
PMB	*p*-methoxybenzyl
PMHS	Polymethylhydrosiloxane
i-Pr	Isopropyl
q	Quartet
qd	Quartet of doublets
qq	Quartet of quartets
qt	Quartet of triplets
quint	Quintet
rt	Room temperature
SET	Single electron transfer
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
td	Triplet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
tol	Tolyl
Ts	*para*-Toluenesulfonyl

tt	Triplet of triplets
tq	Triplet of quartets

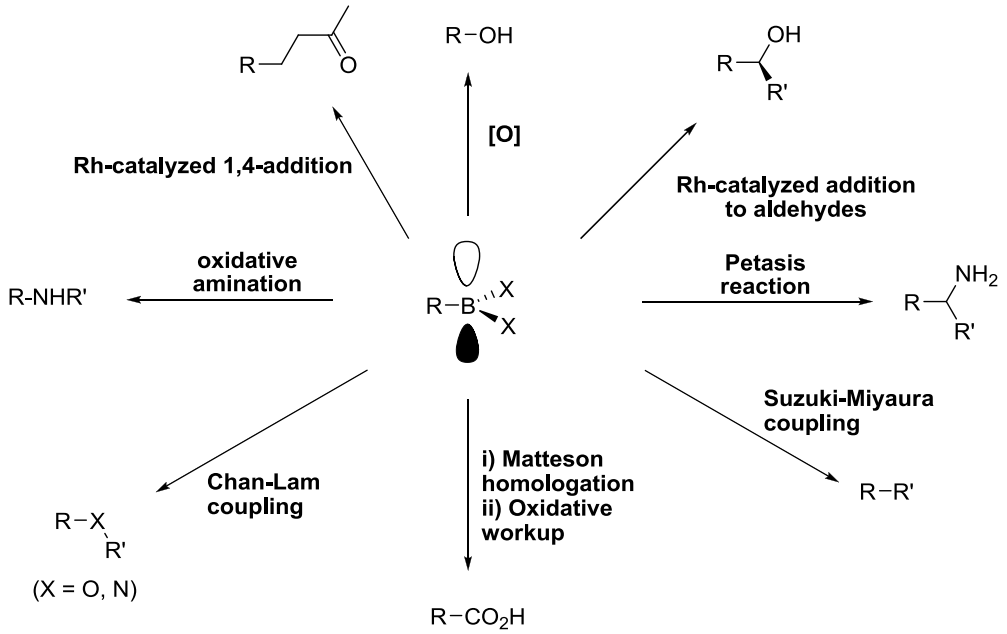
Chapter 1

Introduction: Preparative Methods and Synthetic Utility of Chiral Alkyl Boronic Acid Derivatives

1.1 The importance of boronic acids

As organic chemistry evolves into the 21st century, the goal of this discipline has altered dramatically from merely accessing target molecules to efficiently synthesizing these compounds with minimization of non-strategic functional group manipulations and interconversions, as well as reducing the use of protecting groups.[1] Organoboron reagents represent one of the potential solutions towards reaching this goal, since these versatile compounds can either be used to construct the desired carbon−carbon bond through various cross-coupling reactions, or be converted directly to the desired functionality through various chemical transformations.[2] This direct transformation makes interconversion between different functional groups unnecessary, thus shortening the synthetic sequences. In addition to their synthetic versatility, organoboron reagents hold several other merits: (1) They are known to be environmentally benign because all boronic acids ultimately can be oxidized in air to boric acid. (2) Most of the classes of organoboronates, as long as they are properly protected, are fairly stable and can be easily isolated. Due to these reasons, the preparation and application of these compounds has experienced a tremendous leap in recent years, resulting in many synthetically useful methods. Not only can these boron compounds be oxidized to oxygen or nitrogen derivatives, but they can also be used for various carbon−carbon bond connections through reactions such as carbonyl and imine allylborations, Petasis reaction, rhodium-catalyzed 1,2- or 1,4-additions, Suzuki-Miyaura cross-coupling reaction, to name only a few (Scheme 1).[2] Moreover, under copper-catalyzed conditions, boronic acids are also known to cross-couple efficiently with various nucleophilic alcohols or amines to form carbon−heteroatom bonds. The unique synthetic utility of boronic acid derivatives enables them to be one of the focal points in the synthetic community for organic chemists. Due to these highly efficient chemical transformations, organoboron

compounds have been utilized prevalently in the pharmaceutical industries.



Scheme 1-1: Selective chemical transformations involving organoboronates.

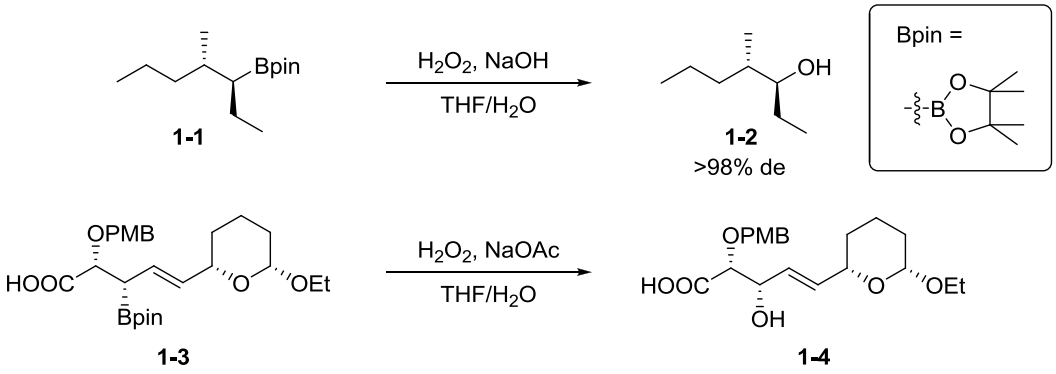
1.2 Chiral boronic acid derivatives

Since the beginning of the 20th century, it is well understood that a single optically pure enantiomer often exhibits a higher biological activity in comparison with its non-superimposible mirror image.[3] As a result, in the pharmaceutical industry it is often important to prepare target molecules in an enantioselective manner.[4] Due to the wide range of synthetic transformations available to boronic acid derivatives, direct transformations from chiral boronates to various chiral functionalities would be highly desired. In addition to the well-established oxidations of boronic acids to alcohols, which proceed with retention of stereochemistry, several other transformations of chiral boronic acid occur with an overall preservation of stereochemical integrity. In the following sections a brief summary of these reactions will be presented.

1.2.1 Oxidation of organoboronates to alcohols

The origin of methodology for oxidizing organoboronates with hydrogen peroxide and aqueous bases can be dated back to 1930 when various aryl boronic acids and

esters were oxidized to phenols.[5] This protocol has since been used prevalently, especially in a one-pot protocol with alkene hydroboration.[6] When chiral aliphatic boronates are used as starting materials, the oxidized products can be acquired with a very high degree of retention of stereochemistry. As depicted in Scheme 1-2, oxidation of α-substituted pinacol boronate **1-1** occurred with retention of stereochemistry, leading to the resulting secondary alcohol **1-2** with a high degree of diastereoselectivity.[7] In a more recent example, the Hall Group utilized this protocol for the diastereoselective synthesis of chiral secondary alcohol **1-4** en route to the synthesis of palmerolide A.[8]

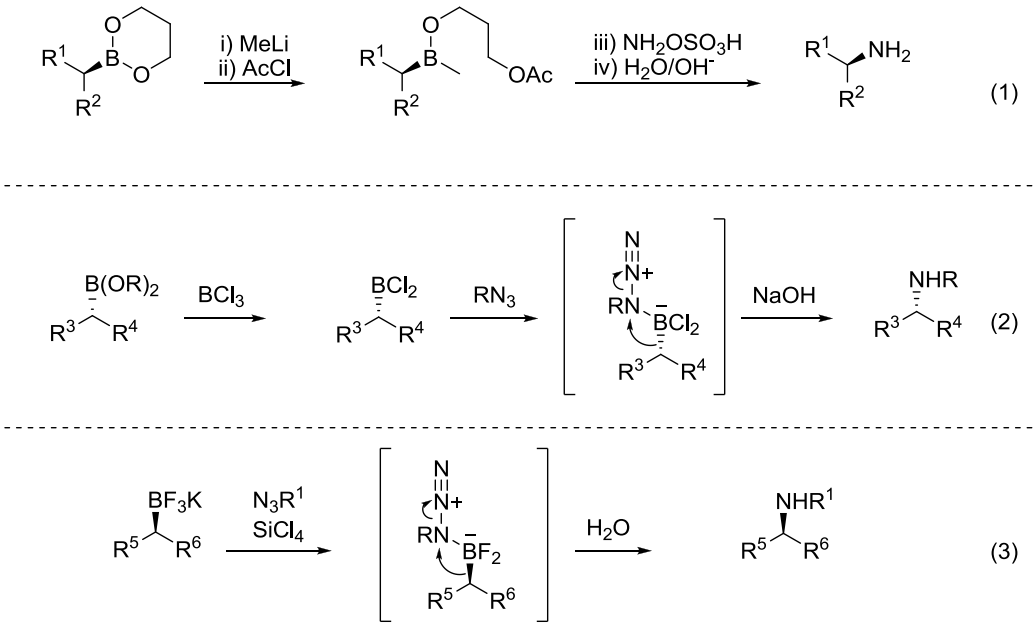


Scheme 1-2: Representative examples for the oxidation of chiral alkyl boronates into alcohols.

1.2.2 Conversion of boronic acid derivatives to amines

In comparison with oxidation to alcohols, oxidative aminations of aliphatic boronic acid derivatives are known to be more difficult. Under most conditions with organoazides as the reagents, boronic acid derivatives are not electrophilic enough to afford the corresponding products. The Brown group discovered that the Lewis acidity of the boron group can be enhanced by transforming boronic esters to the corresponding borinic esters.[9] The highly electrophilic borinic esters can then react with hydroxylamine-*O*-sulfonic acids to yield the desired amination products (Equation 1, Scheme 1-3). Alternatively, boronic esters can also be transmetalated to more Lewis acidic dichloroboranes prior to a successful oxidation with organoazides.[10] 1,2-Migration followed by hydrolysis with base will then provide the desired chiral amines (Equation 2, Scheme 1-3). In 2001,

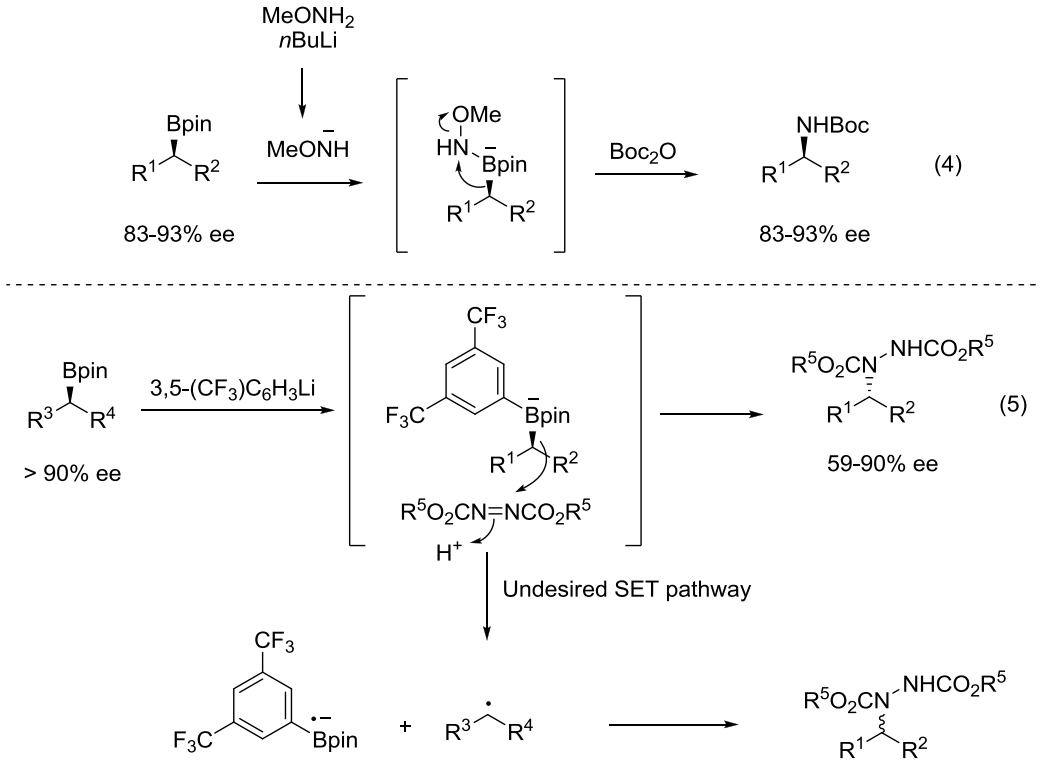
Matteson and coworkers reported stereoselective amination of highly stable trifluoroborate salts. Under Lewis acid mediated conditions, highly reactive difluoroboranes can be generated *in-situ*, allowing its coordination with organoazides. The same subsequent steps, 1,2-migration followed by hydrolysis can occur to afford the desired products (Equation 3, Scheme 1-3).[11] All of the methods described above occur with a high degree of retention of stereochemistry, allowing synthetically valuable chiral amines to be synthesized in a stereoselective manner.



Scheme 1-3: Oxidation of boronic acid derivatives with organoazides to amines.

Unlike the above approaches where the Lewis acidity of the boron atom has to be modified to form the key ate-complex, the Morken group recently discovered that the key ate-complex could also be generated between a strongly nucleophilic amide anion and a boron pinacolate.[12] The strongly nucleophilic amide anion, made *in-situ* by deprotonating methoxyamine with *n*-butyllithium, could coordinate with the bulky boron pinacolate to form the ate-complex. 1,2-Rearrangement followed by Boc protection then afforded the protected chiral amines with retention of stereochemistry (Equation 4, Scheme 1-4). Aggarwal and coworkers recently developed a conceptually distinct approach where

organoboronates can be used as nucleophiles.[13] Once the boron atom is activated by a strong base, the organoboron species can then act as nucleophiles to react with different electrophiles, affording products with inversion of stereochemistry in an S_N2 like mechanism (Equation 5, Scheme 1-4). Depending on the nature of the activating group (aryl lithium), undesired SET pathway may predominate to afford products with greatly diminished enantiomeric purity. After screening through bases with different electronic properties, the Aggarwal Group eventually found that the electron-deficient species 3,5-$(CF_3)C_6H_3Li$ was the optimal activating reagent as it was able to significantly depress the undesired SET pathway to yield the desired products with good stereoselectivity.

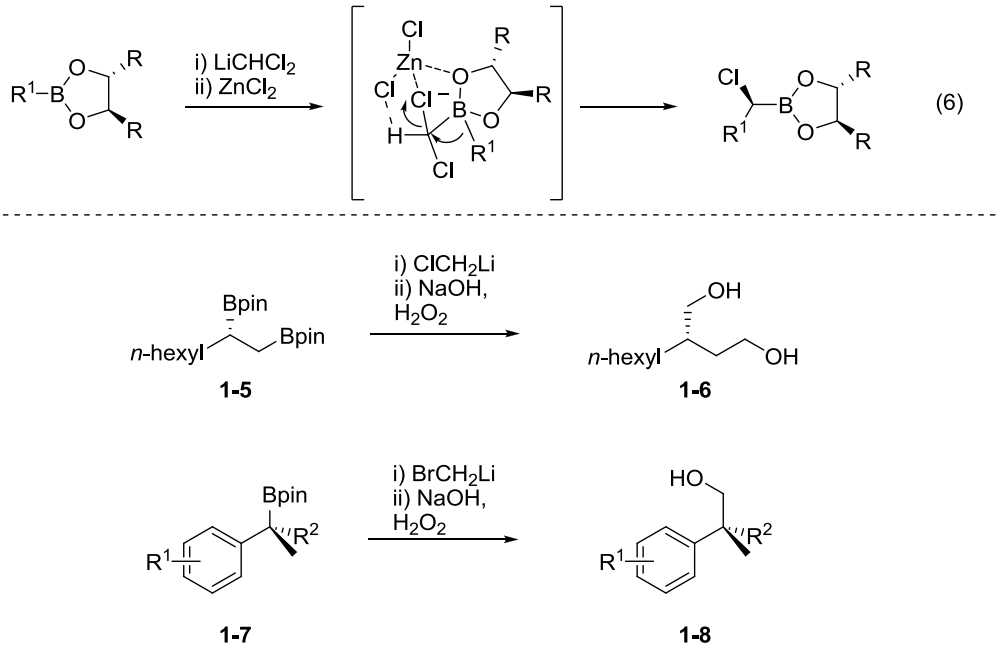


Scheme 1-4: Recent advances in aminations of boronic acid derivatives.

1.2.3 Matteson asymmetric homologation

In addition to oxidation reactions, organoboron reagents are also capable of undergoing a rearrangement process called the Matteson homologation, in which a carbon atom is inserted into the carbon−boron bond.[14] The first step of the

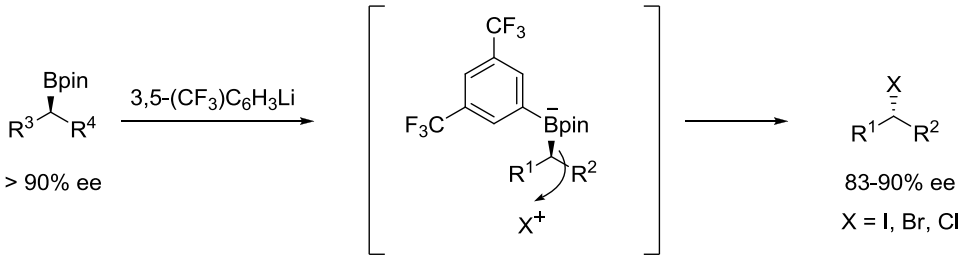
reaction involves the activation of a chiral boronate by a nucleophile such as (dihalomethyl)lithium in the presence of $ZnCl_2$. The activated ate-complex then undergoes a 1,2-rearrangement to give the homologated product in an diastereoselective manner due to the chiral masking group on the boron atom (Equation 6, Scheme 1-5). Recently, this approach has been applied to boronates bearing stereogenic carbons. Morken and coworkers demonstrated that secondary chiral diboronate **1-5** can be homologated and oxidized to diol **1-6**.[15] Similarly, the same approach can be used for tertiary chiral boronate **1-7**. The Aggarwal group found, however, that the leaving group of the lithiating reagent greatly influences the 1,2-migration process.[16] When chloride was used as the leaving group, *O*-migration was observed as a significant side reaction. On the other hand, when bromide was used as the bulkier and less electronegative leaving group, *C*-migration predominates and afforded the desired products with quaternary carbon centres. Due to the geometrical restriction during the 1,2-migration step, Matteson homologation occurs with retention of stereochemistry.



Scheme 1-5: Matteson asymmetric homologation of chiral alkyl boronates.

1.2.4 Halogenation, alkenylation, and protodeboronation

As discussed previously in Section 1.2.2, organoboronates can be activated to react with azodicarboxylates to form various aminated products. The Aggarwal Group found that by changing the electrophiles from azodicarboxylates to various halogen sources, halogenation of chiral boronates can occur with good efficiency and enantioselectivity.[11] By using the same optimized base, 3,5-$(CF_3)C_6H_3Li$, the activated borate complex can react with various halogen sources to afford chiral halogens with inversion of stereochemistry (Scheme 1-6).

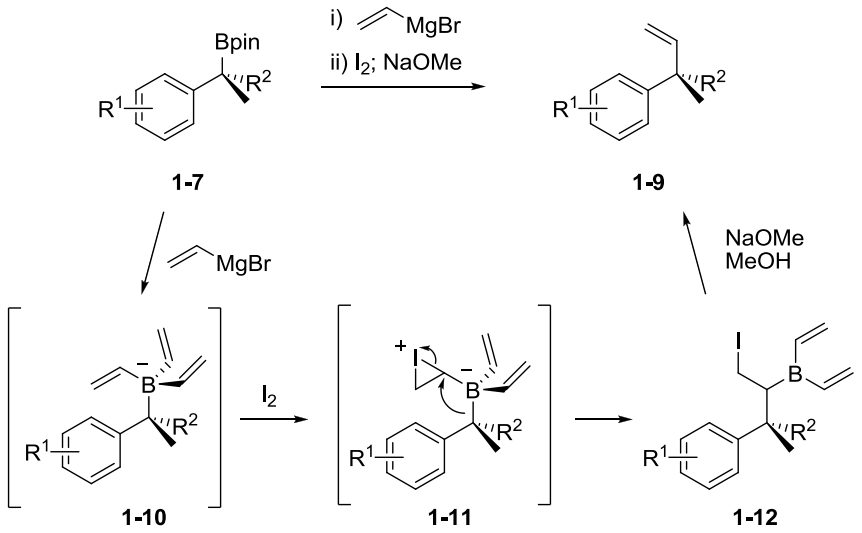


Scheme 1-6: Halogenation of chiral alkyl boronates.

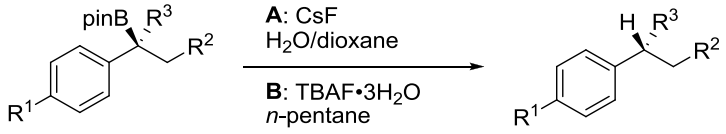
Pioneered by Zweifel and coworkers back in the 1960s, alkenylation of an organoboronate is also a viable option to provide an alkenylated product.[17] The Aggarwal Group recently applied this protocol to various tertiary chiral boronates, giving the desired products with retention of stereochemistry (Scheme 1-7).[14] The proposed mechanism is outlined in Scheme 1-7, where vinyl magnesium bromide first reacts with chiral tertiary boronate **1-7** to give the borate complex **1-10**. The ate-complex **1-10**, which was confirmed by ^{11}B NMR analysis, then reacts with iodine to form the iodonium species **1-11**. At this point, 1,2-migration of the tertiary alkyl group can occur, giving chiral borane **1-12**. Under basic conditions with NaOMe and MeOH, the boron and iodine atoms can be eliminated to give the observed alkenylation product **1-9**.

Recently, the same group found that protodeboronations of chiral boronates can similarly be performed stereoselectively to afford products with tertiary stereogenic centres with retention of stereochemistry.[18] In this seminal report, fluoride was used as the base to mildly activate the boron atoms for

protodeboronations to occur stereoselectively (Scheme 1-8).



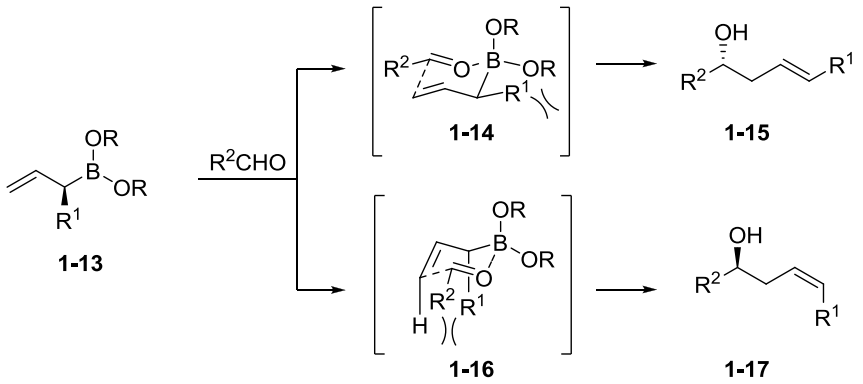
Scheme 1-7: Alkenylation of chiral boronates.



Scheme 1-8: Stereoretentive protodeboronation of chiral boronates.

1.2.5 Carbonyl allylboration

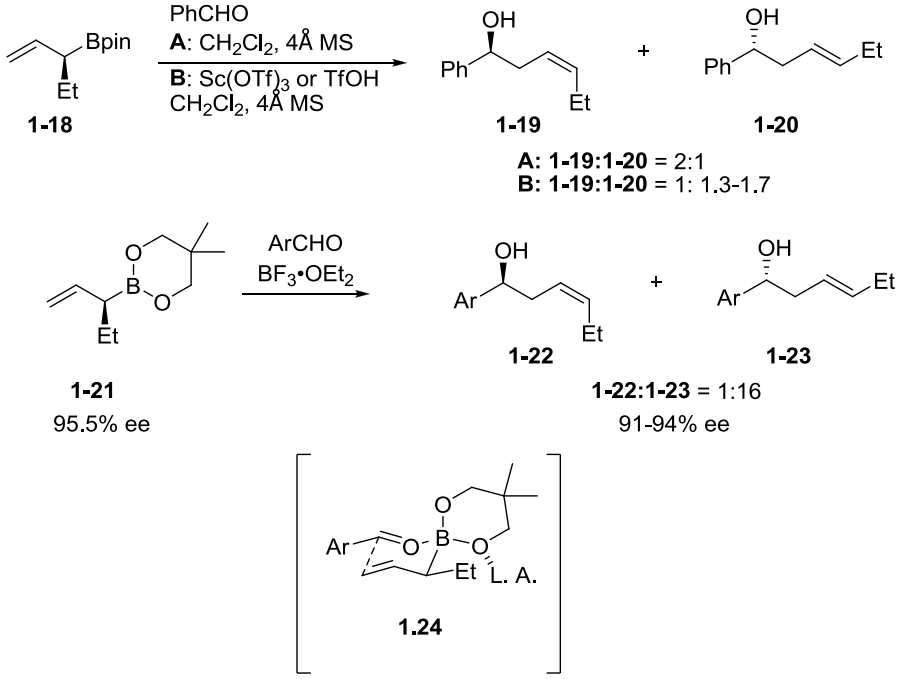
Carbonyl allylation chemistry has become a ubiquitous tool in the field of natural product synthesis over the past few decades for the stereocontrolled formation of carbon−carbon bonds. [19] Allylation with organoboron reagents is especially prevalent due to the excellent stereocontrol resulting from the Zimmerman-Traxler chair-like transition state.[20] Most of the allylborations performed in the past were done with allylboranes due to the high reactivity and selectivity associated with these allylation reactions. These compounds, however, often suffer from poor stability and as a result are difficult to prepare in certain cases. Allylboronates, on the other hand, are stable alternatives that suffer from poor reactivity. This issue was independently solved in 2002 by the groups of Hall and Miyaura where the use of a catalytic amount of Lewis acid was found to significantly accelerate the reaction rate and enhance the stereoselectivity.[21]



Scheme 1-9: Proposed transition states for carbonyl allylboration of α-substituted allylic boronates.

In comparison with *B*-chiral allylboronates, *C*-chiral allylboronates have received relatively less attention due to the tedious preparation in synthesizing these compounds. The Hoffmann Group conducted a comprehensive study on the effect of the R^1 α-substituent and the boronate group (**1-13)** on the stereoselectivity of allylboration reactions with aldehydes (Scheme 1-9).[22] They found that two diastereomers, **1-15** and **1-17**, were formed with different ratios through transition states **1-14** and **1-16**. The ratios observed can be explained by the steric and dipolar nature of the R^1 substituent and the boronate groups. More recently, the Hall Group found that the addition of a catalytic amount of Lewis acid could reverse the selectivity observed from thermal reactions.[23] As shown in Scheme 1-10, while a ratio of 2:1 was observed between the *Z*-configured product **1-19** and the *E*-configured product **1-20** under thermal conditions, a ratio of 1:1.3 to 1:1.7 was observed when the reaction was catalyzed by TfOH or $Sc(OTf)_3$. The authors rationalized this observation by suggesting that due to the coordination of the Lewis acid to the oxygen atom of boron pinacolates (similar to **1-24**), a more advanced transition state will be generated, leading to a longer B−C bond and a shorter B−O(aldehyde) bond. This effect relieves the steric interaction between the R^1 substituent and the boronate, favouring the formation of *E*-configured products. The same group later discovered that the difference in ratios can be further improved by replacing the bulky pinacolate protecting group with less sterically demanding neopentyl glycol boronate (**1-21)**.[24] Due to the reduced steric

interaction between the ethyl group and the smaller boronate (**1-24**), the *E*-configured product **1-23** is significantly favoured over the *Z*-configured product **1-22**.[25] It is important to note here that the stereochemical integrity of the starting material is preserved, affording products with high levels of enantioselectivity.



Scheme 1-10: Carbonyl allylboration of chiral α-substituted allylic boronates.

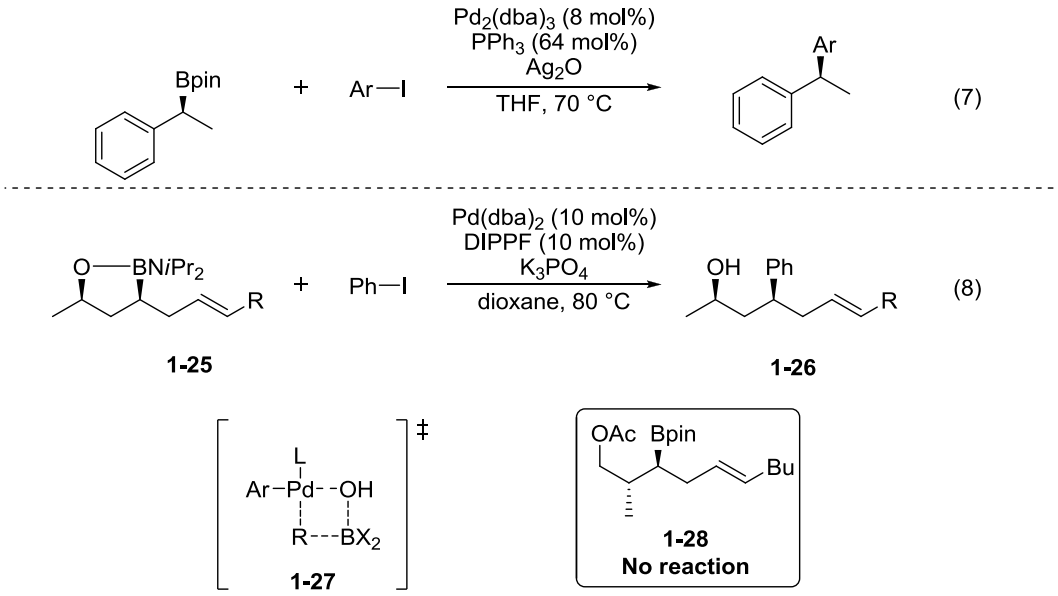
1.2.6 Suzuki-Miyaura cross-couplings of chiral boronates

The construction of carbon−carbon bonds through metal-catalyzed cross-coupling reactions has become a ubiquitous method for synthesizing organic molecules. In addition to traditional organic synthesis, the realm of cross-coupling reactions has expanded to various interdisciplinary research areas such as medicinal chemistry, chemical biology, materials and nanotechnology.[26] The significance of this class of reactions has been recognized in the attribution of the 2010 Nobel Prize in Chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki for their contributions in developing Pd-catalyzed cross–coupling reactions. Among these cross-coupling reactions, the Suzuki-Miyaura cross-coupling reaction, which employs organoboron reagents and organohalides as cross-coupling partners, has been embraced universally in both academic and industrial laboratories.[26] Boronic

acids, which are the most prevalent organoboron reagents used in Suzuki-Miyaura cross-coupling reactions, possess several distinctive advantages over other organometallic reagents: thousands of boronic acid derivatives are commercially available, and most classes exhibit air, moisture and heat stability. Due to the robust nature of these reagents, Suzuki-Miyaura cross-coupling reactions in general employ mild conditions, tolerate various functional groups, and generate non-toxic boron by-products such as boric acid.[27]

While the development of Suzuki-Miyaura cross-coupling reactions of sp^2 carbon centers has made remarkable progress over the past few decades, cross-coupling reactions of saturated carbon centers represent a more difficult task. Cross-coupling reactions of sp^3 (alkyl) boranes or boronates are often difficult because the transmetallation step involving these boron species is usually very slow.[23] Under these circumstances, protodeboronation becomes a problematic side reaction and often an excess of organoboron reagent is necessary to promote the reaction. Once transmetallated, reductive elimination involving sp^3-sp^3 or sp^3-sp^2 carbon centers is problematic since a slow reductive elimination step is usually accompanied by significant amounts of β-hydride elimination as an irreversible side reaction. In spite of all these challenges, in 2009 Crudden and coworkers developed stereoselective Pd-catalyzed Suzuki-Miyaura cross-coupling reactions of benzyl boronates with retention of stereochemistry (Equation 7, Scheme 1-11).[28] The key to the successful cross-coupling is the utilization of silver oxide as the base. Pioneered by Kishi and coworkers, silver oxide is known to enhance the rate of transmetallation, which has long been the bottleneck of alkyl Suzuki-Miyaura cross-couplings. [29] The observed retention of stereochemistry was likely achieved through the four-membered cyclic transition state (such as **1-27,** Scheme 1-11) for transmetallation that was originally proposed by Soderquist and coworkers.[30] Since reductive elimination is known to proceed with retention of stereochemistry, the overall cross-coupling proceeds also with retention of stereochemistry.[26] In 2011, the Suginome Group discovered that Suzuki-Miyaura cross-coupling reactions of cyclic boronate derivatives **1-25** also proceed with

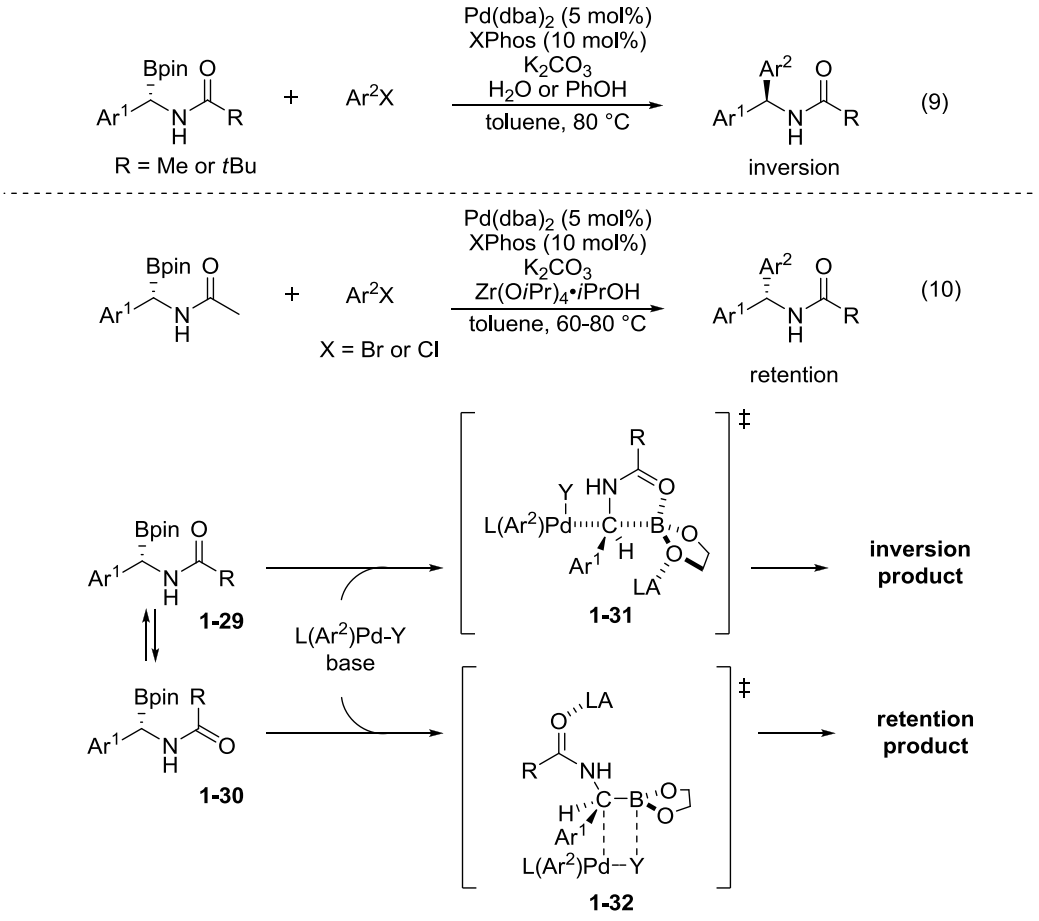
retention of stereochemistry (Equation 8, Scheme 1-11).[31] Interestingly, when the cyclic boronate was converted to a Bpin subunit (**1-28**), none of the desired cross-coupled products could be obtained, demonstrating the need for the intramolecular bond between the oxygen and the boron atoms in the substrate. The authors suggested that the enhanced reactivity might be due to the cyclic nature of organoboronates **1-25**, a feature that is similar to triolborates studied by the Miyaura group.[32]



Scheme 1-11: Stereoselective Suzuki-Miyaura cross-coupling reactions of secondary alkyl boronates.

While these two reports have similar stereochemical outcomes as the previously published observations, Suginome and coworkers in 2010 found that cross-coupling reactions of enantioenriched α-acyl(amino)benzyl boronic esters proceed with inversion of stereochemistry (Equation 9, Scheme 1-12).[33] Due to the intramolecular interaction between the amide oxygen and the boron atom, the authors suggested that the 4-membered cyclic transition state **1-32** cannot be reached. Based on previous studies on different types of cross-coupling reactions,[34] Suginome and coworkers proposed that the coordinated organoboronate could transmetallate via an open transition state possibly through

a S_E2 mechanism (**1-31**). By employing $Pd(dba)_2$ and XPhos as the catalyst and the ligand, respectively, K_2CO_3 as the base and water as the additive, cross-coupling reactions of this class of compounds were achieved with various aryl bromides and chlorides in excellent yields and stereoselectivity. Recently, the same group reported that phenol as an additive was more effective in promoting the cross-coupling reactions, allowing the R substituent to be expanded from *tert*-butyl to a more convenient methyl group (Equation 9, Scheme 1-12).[35] Interestingly, when the additives were switched from Brønsted acids to metal oxides, the authors observed cross-coupled products with retention of stereochemistry (Equation 10, Scheme 1-12). Optimization of various metal oxides eventually led to the use of $Zr(OiPr)_4 \cdot iPrOH$ as the optimal Lewis acid



Scheme 1-12: Stereoselective cross-coupling reactions of α-aminobenzylic boronates.

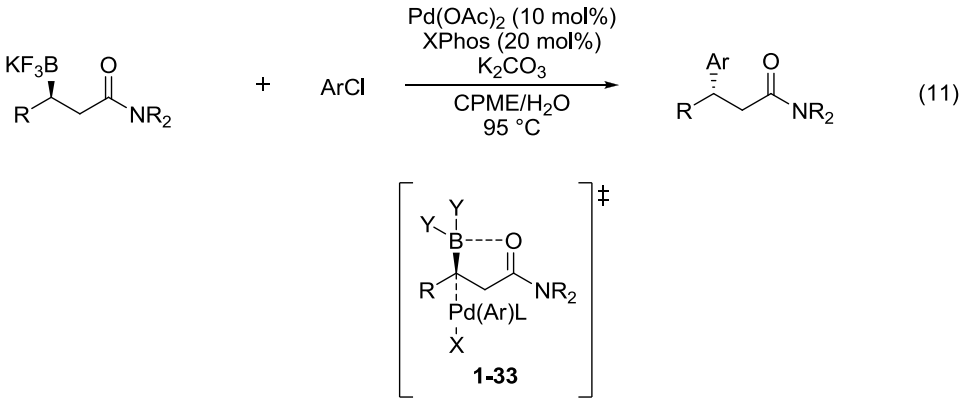
additive that could promote the reaction with good stereoselectivity and retention of stereochemistry. These two contrasting acid additives were proposed to promote different modes of activation. The mild Brønsted acids such as water or phenol were proposed to bind selectively to the oxygen atom of the boronic esters to enhance the intramolecular coordination, thus accelerating the transmetallation step (**1-31**). On the other hand, metal oxides are suspected to compete with boron and bind selectively to the amide carbonyl oxygen, thus disfavouring the intramolecular coordination and facilitating the normal four-membered cyclic transition state **1-32** that leads to retention of stereochemistry.

All of the above examples of stereoselective cross-coupling reactions, however, are restricted to either benzylic or intramolecularly coordinated cyclic boronates. In 2010, the Molander Group successfully expanded the concept of stereoselective cross-coupling reactions to optically enriched trifluoroborates with strongly coordinating β-amide groups (Equation 11, Scheme 1-13).[36] Various aryl chlorides could be cross-coupled with these trifluoroborate salts with inversion of stereochemistry, high stereoselectivity and excellent yields. Common side reactions such as protodeboronation and β-hydride elimination products were not observed during the reaction. The authors proposed that amide coordination to boron could, similar to the effect proposed by Suginome and coworkers, accelerate the transmetallation step (**1-33**). Moreover, the competing β-hydride elimination was suppressed likely due to two main reasons: 1) the intramolecular coordination from the amide oxygen to the palladium species might prevent the organopalladium from adopting the *syn*-coplanar arrangement that is necessary for β-hydride elimination, and 2) the coordination might also inhibit interactions between the palladium species with the α-hydrogen, which is the prerequisite for β-hydride elimination.

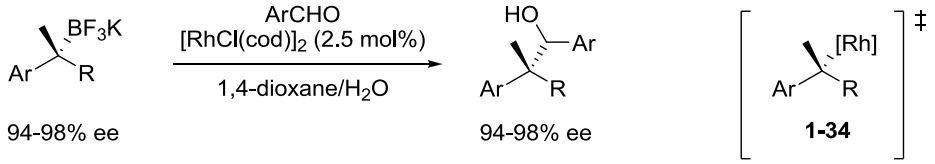
1.2.7 Rh-catalyzed 1,2-additions to aldehydes

In addition to Pd-catalyzed Suzuki-Miyaura cross-couplings, Rh-catalyzed 1,2-additions of chiral boronates have also been conducted to construct carbon−carbon bonds (Scheme 1-14).[37] The Aggarwal Group found that the

addition of various chiral trifluoroborate salts to electron-deficient aldehydes is stereoretentive. The authors suggested that the organorhodium intermediate, **1-34**, is likely configurationally stable, leading to products with retention of stereochemistry.



Scheme 1-13: Stereoselective Suzuki-Miyaura cross-coupling reactions of β-boronyl amides.



Scheme 1-14: Rh-catalyzed 1,2-addition of chiral trifluoroborate salts.

1.3 Strategies towards the synthesis of chiral boronates

As discussed in the previous section, chiral boronates are synthetically valuable intermediates that can be converted to different functionalities with preservation of stereochemistry. Strategies for synthesizing chiral alkyl boronates can be classified into two main categories: (1) late introduction of the boron right before the desired transformation, and (2) early introduction of the boron atom, where the boron functionality is installed several steps prior to the desired reaction (Figure 1-1). While the approach of late installation avoids losing the boron functionality during different reaction conditions, it limits the synthesis of chiral boronates to known enantioselective borylation protocols. On the other hand,

early introduction of the boron functionality complements the late introduction strategy by allowing various well-established asymmetric chemical transformations to be performed on these substrates.[38] The drawback of this approach lies in the risk of losing the boron functionality through incompatible reaction conditions encountered in the required sequence. In the following section, a brief summary of chiral boronate synthesis through both strategies will be presented.

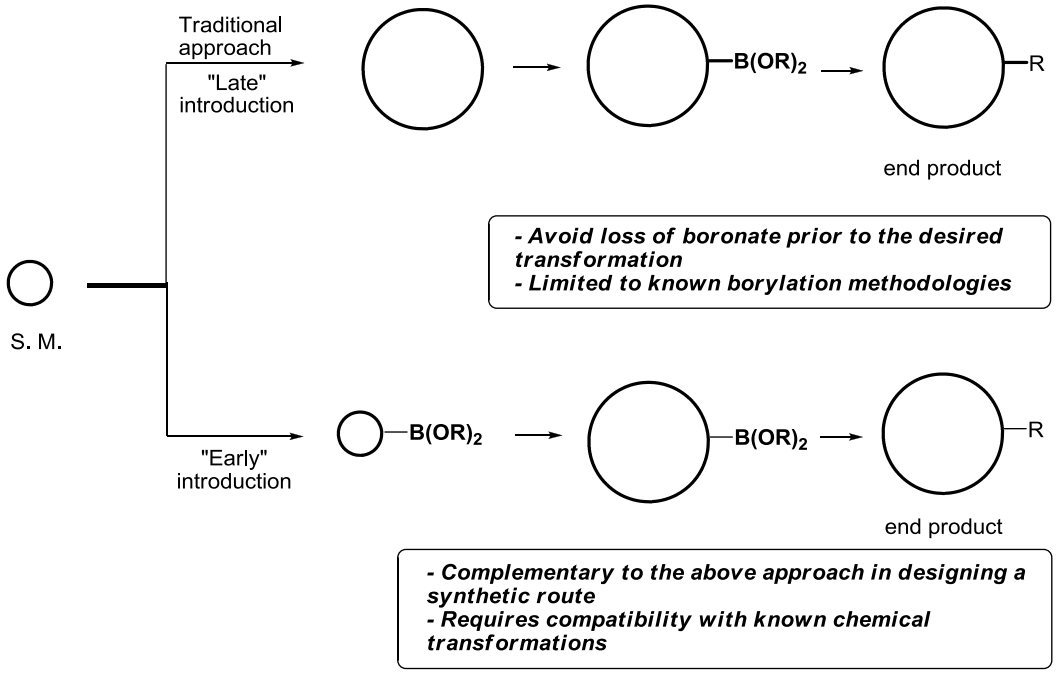
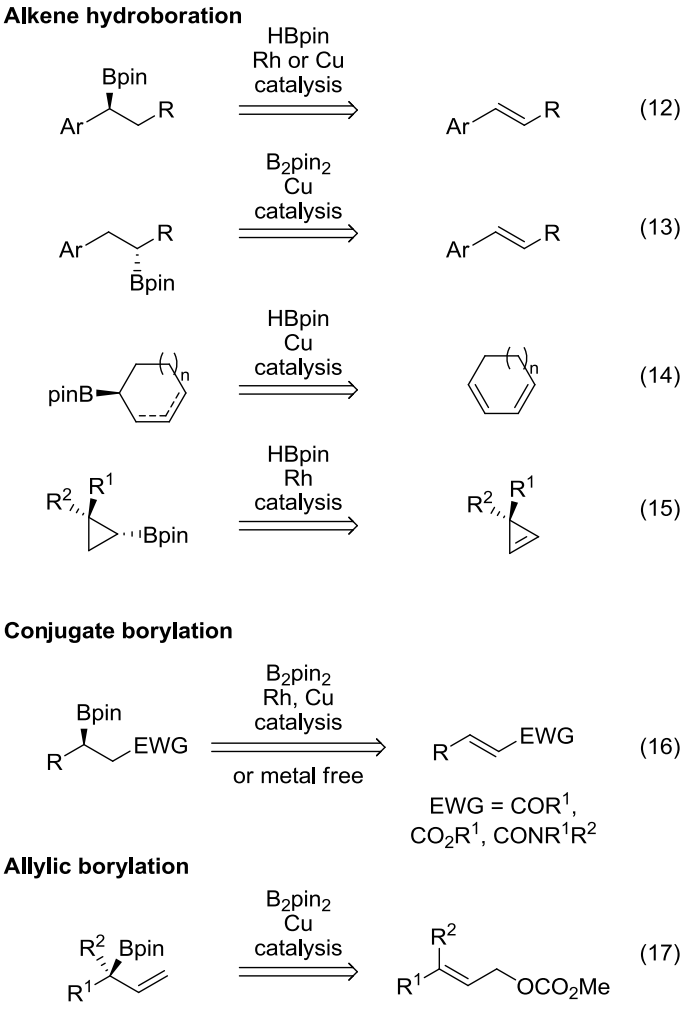


Figure 1-1: Different synthetic strategies towards the synthesis of chiral alkyl boronates.

1.3.1 Late introduction of the boron functionality for the synthesis of chiral alkyl boronates

Hydroboration of alkenes followed by oxidation to alcohols is a prevalent synthetic protocol for the installation of primary alcohols in an anti-Markovnikov fashion. Through metal-catalysis, hydroboration of styrenes can be performed in both Markovnikov or anti-Markovnikov fashions depending on the reaction conditions, yielding chiral alkyl boronates regio- and enantioselectively (Equations 12 and 13, Scheme 1-15).[39] Cyclic alkenyl or dienyl substrates have

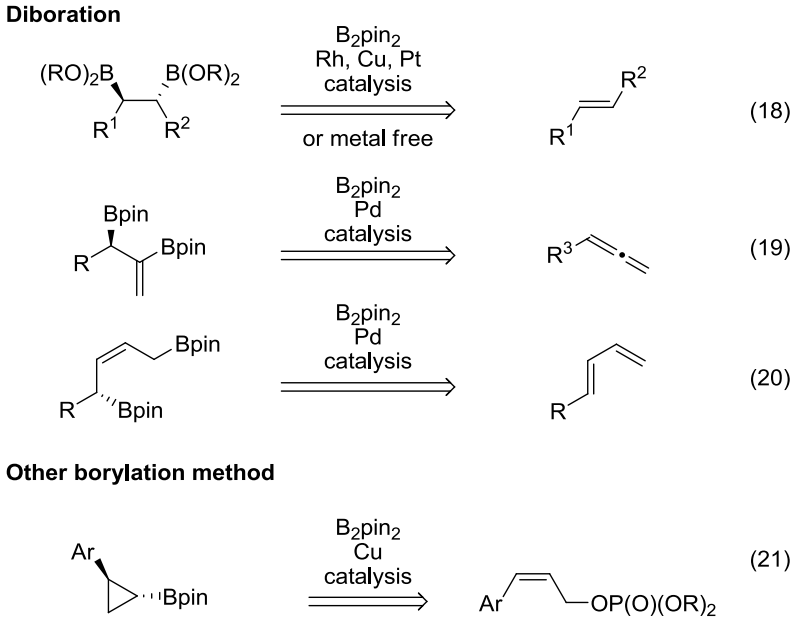
also been demonstrated to undergo enantioselective hydroborations to afford cyclic chiral boronates with good efficiency and excellent enantioselectivity (Equations 14 and 15, Scheme 1-15).[40] An alternative method for synthesizing chiral boronates is the asymmetric conjugate borylation of traditional Michael acceptors. Since the discovery by Yun and coworkers that MeOH can be used as an effective additive to dramatically enhance the rate of the reaction, various enantioselective conjugate borylation protocols have been developed for addition to α,β-unsaturated ketones, esters and amides (Equation 16, Scheme 1-15).[41] Metal-free variants were recently developed by the groups of Fernandez and



Scheme 1-15: Catalytic enantioselective methods for synthesizing chiral alkyl boronates.

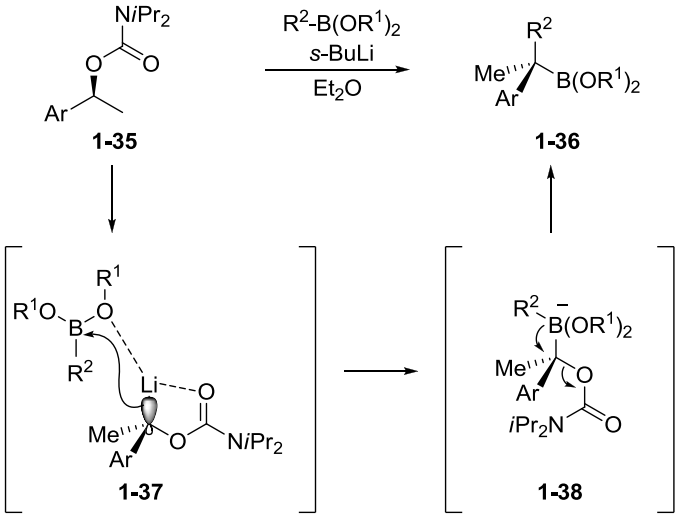
Hoveyda, allowing chiral boronates to be synthesized in a "greener" fashion.[42] A similar late-borylation approach can also be applied to allylic carbonates, where the carbonates are displaced by boronates in an S_N2' fashion enantioselectively. The resulting allylboronates can be either oxidized to allylic alcohols, or undergo carbonyl allylboration reactions to afford chiral homoallylic alcohols (Equation 17, Scheme 1-15).[43]

Under metal-catalyzed borylation conditions with diboronyl compounds $B_2(OR)_2$ as the borylating reagents, diborations of alkenes,[44] allenes,[45] or dienes[46] can all be conducted, leading to chiral diboronates with excellent enantioselectivity (Equations 18, 19, and 20, Scheme 1-16). Recently, Sawamura and coworkers discovered that when allylic phosphonates are substituted with aryl groups, the desired asymmetric allylic borylation reactions did not occur (as shown previously in Equation 17, Scheme 1-14). [47] Instead, enantioenriched cyclopropanyl boronates were synthesized with excellent yields, presumably due to the preferred attack of the copper nucleophiles to the central carbon atom rather than one of the terminal carbon atoms (Equation 21, Scheme 1-15).



Scheme 1-16: Catalytic enantioselective methods for synthesizing chiral boronates.

In addition to transition metal-catalyzed borylation protocols, Aggarwal and coworkers have recently reported syntheses of various tertiary chiral alkyl boronates starting from chiral carbamates **1-35** (Scheme 1-17).[48] In close similarity to the work of Hoppe[49] and Matteson,[14] the first step of the process involves a deprotonation of the carbamate with *s*-BuLi, resulting in the formation of configurationally stable alkyl lithium **1-37**. Through coordination with the incoming boronate electrophile, the ate-complex formation occurs with retention of stereochemistry to afford borate **1-38**. At this point, 1,2-migration can occur, giving the desired tertiary chiral alkyl boronates **1-36** with excellent yields and enantioselectivity (Scheme 1-17).

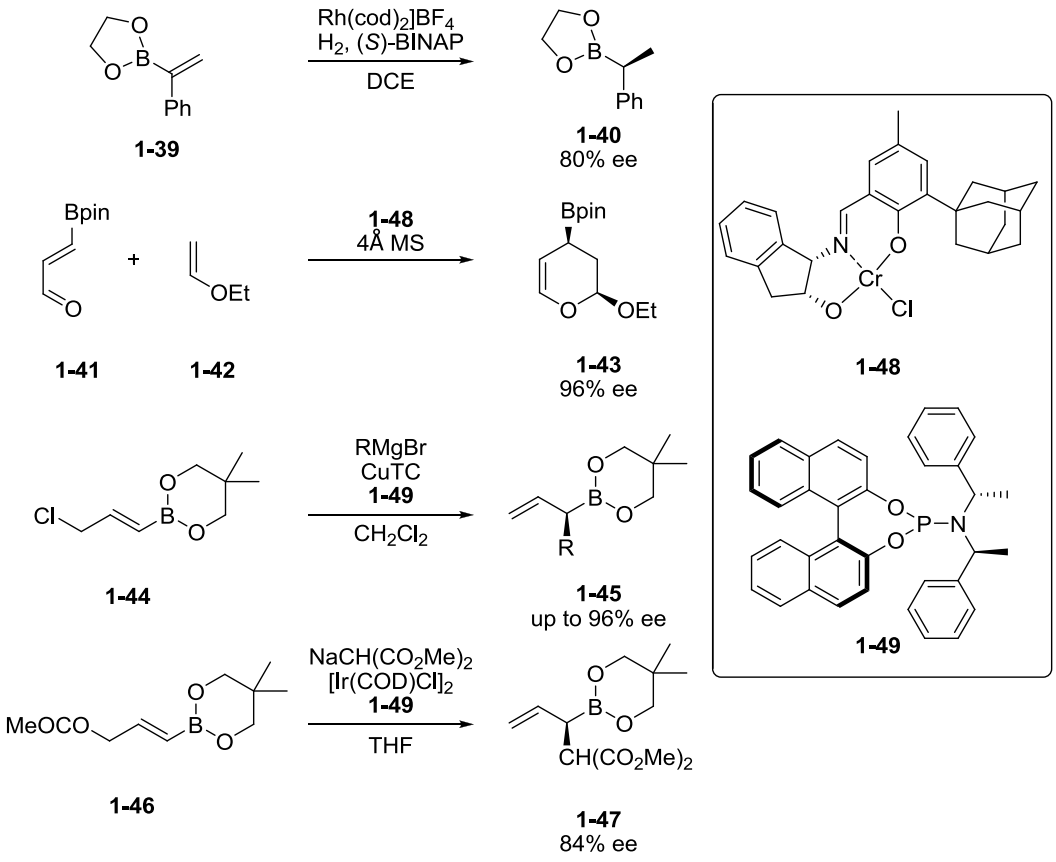


Scheme 1-17: Synthesis of chiral alkyl boronates from chiral carbamates.

1.3.2 Early introduction of the boron functionality for the synthesis of chiral alkyl boronates

In contrast to the approach featuring late introduction of the boronyl unit to form the desired chiral compounds, the early introduction approach has been relatively sparse. Miyaura and coworkers reported a reduction protocol to hydrogenate 1-phenylethenylboronic acid **1-39** to afford chiral boronate **1-40** with a good enantioselectivity (Scheme 1-18).[50] The main challenge associated with this reaction lies in the possibility for undesired B−C bond insertion from the catalyst, leading to various side products. More recently, the Hall Group[51a] reported an

asymmetric inverse-electron-demand-Diels-Alder cycloaddition between 3-boronoacrolein **1-41** and ethyl vinyl ether **1-42** by using the chromium (III) catalyst that was originally developed by Jacobsen and coworkers.[51 b] The enantioselectivity of the cycloadduct **1-43** is heavily dependent on the purity of 3-boronoacrolein **1-41**. The authors noticed that when distilled 3-boronoacrolein **1-41** was used as the diene, a low catalytic loading could be used and an excellent enantiomeric excess could be observed. The resulting cycloadduct **1-43** was found to be an excellent reagent for allylboration of aldehydes, and had been used to synthesize natural products such as thiomarinol and palmerolide A.[6, 52] In addition to this cycloaddition method, the same group has also applied Cu-catalyzed asymmetric allylic substitutions of 3-chloropropenylboronate **1-44** with Grignard reagents to give chiral α-



Scheme 1-18: Selected examples of chiral alkyl boronate synthesis using early introduction strategy.

substituted allylboronates **1-45** with excellent enantioselectivity.[22] A transition metal catalyzed variant of asymmetric allylic alkylation of 3-hydroxypropenyl boronates **1-46**, on the other hand, was more problematic as it tends to suffer from undesired B−C bond insertion.[53] This issue was partially solved by using the iridium complex as the catalyst instead of the palladium complex. Under optimized conditions, moderate to good enantioselectivity could be obtained when stabilized nucleophiles were used during the reaction.

1.4 Thesis objectives

As discussed in previous sections of this chapter, chiral alkyl boronates are synthetically prized compounds that can act as chiral surrogates for different functionalities. It has been demonstrated that chemical transformations of chiral boronates often result in preservation of stereochemical integrity, allowing these compounds to be used as useful synthetic intermediates for the synthesis of different target molecules. In spite of their synthetic value, the classes of chiral boronates that are currently available to organic chemists are still relatively limited. The goal of this thesis is to develop more efficient synthetic methods toward the preparation of these compounds through the early introduction strategy (Section 1.3). The resulting novel chiral boronates will allow new synthetic transformations to be investigated.

In light of recent advances in asymmetric conjugate additions with various unstabilized organometallics, my studies were initiated by testing out different known conjugate addition conditions on 3-boronyl α,β-unsaturated esters. The Lewis acidity of the boron atom was found to be problematic, and an optimal boron protecting group had to be used for asymmetric conjugate additions to occur smoothly.[54] The problems encountered with various organometallic reagents, and the solutions that were found in the end will be discussed in detail in Chapter 2.

Being inspired by recent methodologies involving 1,1-organodiboron compounds, I set out to explore the possibility of synthesizing the hitherto, unknown

enantioenriched 1,1-organodiboron compounds. By either varying the Lewis acidity of the boron atom or the Lewis basicity of the carbonyl group, these compounds were found to be excellent cross-coupling partners in Suzuki-Miyaura cross-couplings to give chiral boronates with excellent enantioselectivity.[55] The optimization of these processes and their applications will be presented in Chapter 3.

In order to conduct a thorough examination of substrate scope in asymmetric conjugate additions and reductions of 3-boronyl-3-substituted α,β-unsaturated esters, it is important to prepare the required trisubstituted enoates efficiently with high diastereoselectivity. In this regard, Chapter 4 presents the optimization of Heck couplings to form the desired trisubstituted enoates.[56] A brief summary of the subsequent asymmetric conjugate reductions, which were performed by my colleague Jinyue Ding, will also be included.

In addition to chiral alkyl boronates, geometrically defined novel alkenyl boronates are also highly valuable due to the broad scope of chemical transformations that can be performed with these substrates. In Chapter 5, the preparation of different unsaturated organoboronates through gold-catalyzed enyne cycloisomerizations will be presented.[57] Moreover, the preparation of the starting materials, optimization of the reaction conditions, and the applications of the resulting alkenyl boronates will also be discussed.

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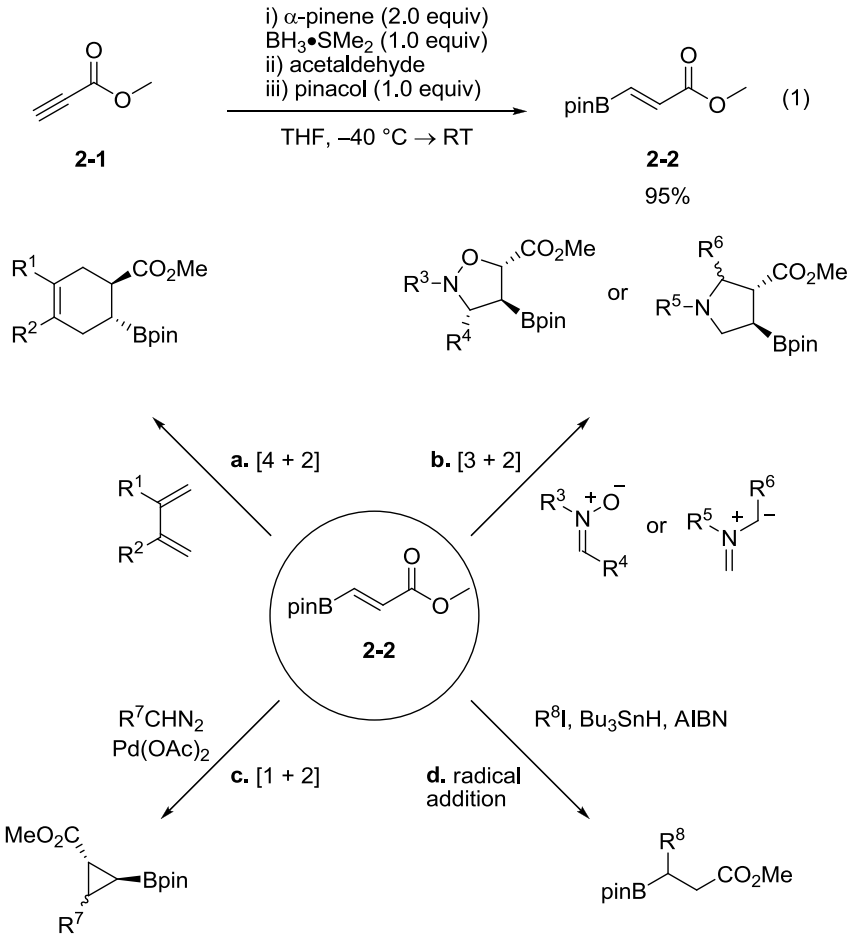
Chapter 2

Chiral Alkyl Boronate Derivatives via Cu-Catalyzed Enantioselective Conjugate Addition Reactions

2.1 Introduction

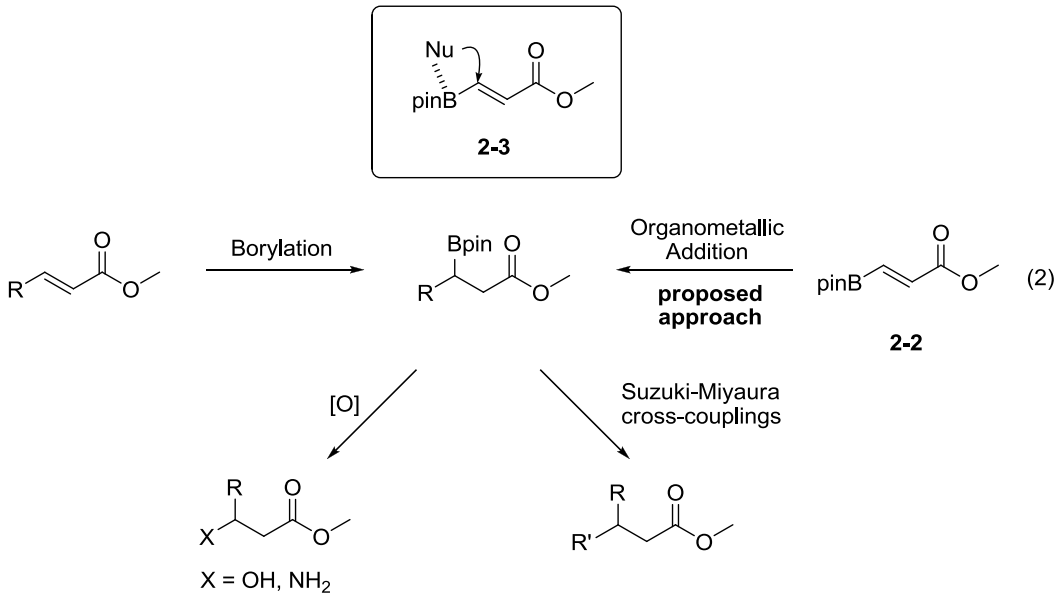
As discussed in Chapter 1, chiral alkyl boronates are valuable synthetic building blocks due to the broad scope of chemical transformations that can be achieved with this class of compounds. Our group focuses on the early introduction strategy for preparing chiral alkyl boronates where chemical transformations are performed on substrates with a pre-installed boronyl unit (Section 1.3). As a result, it is important to identify an organoboronate precursor that can be readily functionalized with different chemical reactions. The synthesis of 3-boronoenoate **2-2** was reported 20 years ago by Vaultier and coworkers through hydroboration of methyl propiolate **2-1** (Equation 1, Scheme 2-1).[1] Since its reported preparation, 3-boronoenoate **2-2** has been utilized as a cycloaddition partner in [4 + 2] cycloadditions (**a**, Scheme 2-1),[2] [3 + 2] cycloadditions (**b**, Scheme 2-1),[3] and [1 + 2] cycloadditions (**c**, Scheme 2-1)[4] to afford various synthetically important adducts. In addition to these reactions, compound **2-2** also acts as an excellent acceptor for radical addition reactions, giving β-boronyl esters with good efficiency (**d**, Scheme 2-1).[5] None of the methods mentioned above, however, is enantioselective. Aiming to access chiral alkyl boronates, it was envisioned that these compounds can potentially be synthesized through catalytic asymmetric conjugate additions onto 3-boronoenoates with different nucleophiles.

Most of the catalytic asymmetric conjugate addition methodologies reported to date, however, are associated with more reactive enones rather than α,β-unsaturated esters.[6] Through the incorporation of a boronyl unit at the β-position of the enoate, it was envisioned that the incoming nucleophile might interact with boron's empty *p*-orbital, leading to an enhanced reactivity (**2-3**, Scheme 2-2). This new approach to the preparation of enantioenriched β-boronyl esters is complementary to the traditional method where the boronyl subunit is introduced



Scheme 2-1: Preparation and synthetic utility of 3-boronoenoate **2-2**.

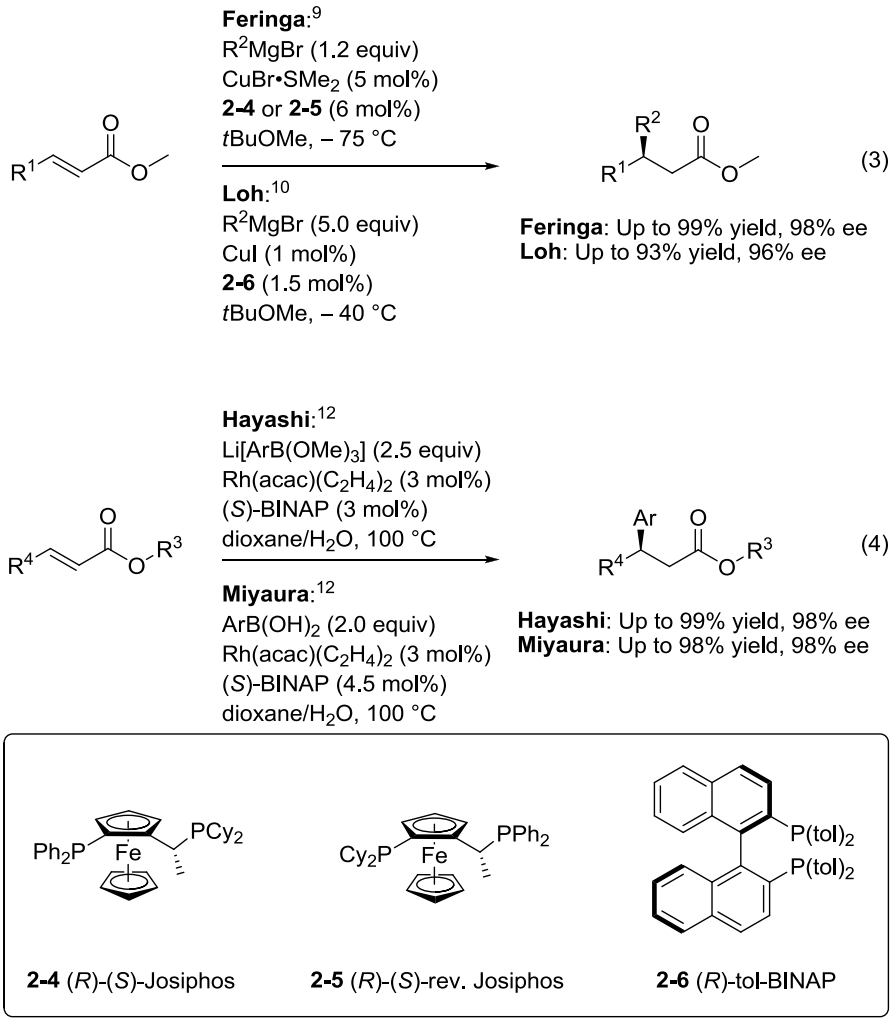
onto various β-substituted enoates through conjugate borylation reactions with $B_2(pin)_2$ or pinacolborane as the boron sources (Equation 2, Scheme 2-2).[7,8] In addition to the previously discussed merits of modifying substrates with pre-installed boronates (Section 1.3), this proposed approach avoids the preparation of various 3-substituted enoates for every different 3-boronyl ester product. The desired chiral secondary alkyl boronates, upon oxidation and hydrolysis, can be transformed into β-hydroxy or β-amino acids which constitute important building blocks for the synthesis of natural products or pharmaceuticals. Furthermore, through a Suzuki-Miyaura cross-coupling, a new carbon−carbon bond may be synthesized to generate an enantioenriched tertiary carbon centre which is also of great synthetic value.



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

Among all of the catalytic asymmetric methodologies reported for non-borylated substrates, metal-catalyzed asymmetric conjugate addition protocols with unstabilized organometallic reagents are especially attractive. Through catalysis, synthetically valuable enantiomer can be selectively produced from relatively less expensive prochiral starting materials. These reactions are also atom-economical, generating less waste throughout the reactions. Due to these attributes, the 2001 Nobel Prize in chemistry was awarded to W. S. Knowles, R. Noyori, and K. B. Sharpless for their contribution in the area of enantioselective catalysis. Recently, several synthetic methods have been reported for asymmetric catalytic conjugate additions of α,β-unsaturated esters.[6] In 2005, Feringa and coworkers discovered that copper (I) salts and bisphosphine ligands such as Josiphos **2-4** and **2-5** can be used to catalyze the addition of Grignard reagents to enoates, resulting in products with excellent yields and enantioselectivity.[9] The Grignard reagents, however, are limited to primary alkyl ones due to both steric and electronic factors. Shortly thereafter in 2007, the Loh Group found that copper iodide and tol-BINAP **2-6** can be used as an efficient catalytic system to expand the scope of substrates, allowing secondary alkyl Grignard reagents to be incorporated to afford products

with high yields and enantioselectivity.[10] One alternative approach to copper-catalyzed conjugate additions of Grignard reagents to enoates is the conjugate addition of aryl borates or boronic acids through rhodium catalysis (Equation 4, Scheme 2-3).[11] By employing (*S*)-BINAP as the ligand, both the Hayashi Group and the Miyaura Group have shown that the conjugate addition adducts can be obtained efficiently.[12] One potential problem associated with applying such systems to 3-boronoenoates is unselective B−C bond insertion of rhodium catalysts into both the starting β-boronyl enoate and the aryl boronic acid derivatives.

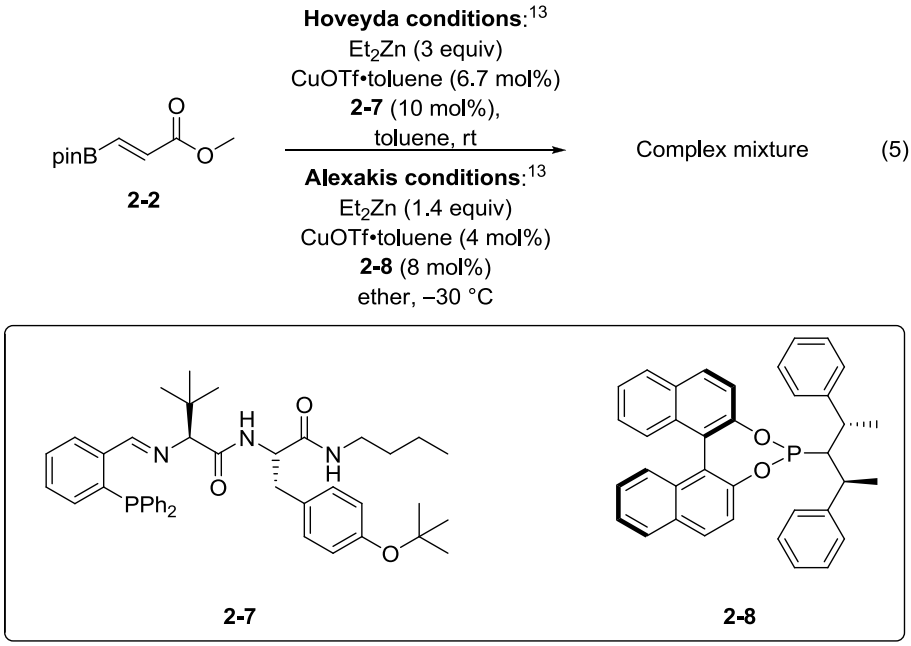


Scheme 2-3: Known methods for asymmetric conjugate additions on acyclic enoates.

2.2 Screening of various conjugate addition conditions on enoate 2-2

2.2.1 Asymmetric conjugate addition with diorganozinc as nucleophiles

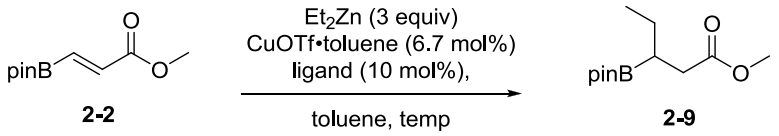
Even though organozinc reagents are relatively milder nucleophiles that have never been reported in asymmetric conjugate additions on enoates,[6] it was surmised that due to the activation of the boron atom, a successful conjugate addition could be performed to obtain the desired products. Two standard protocols, reported independently by the Hoveyda and the Alexakis groups for asymmetric conjugate addition of diorganozincs to enones, were examined (Equation 5, Scheme 2-4).[13] Unfortunately, under the standard conditions, complex mixtures were observed and none of the desired products could be isolated. In an attempt to reduce the amount of impurities that were formed from the reactions, lower reaction temperatures and different ligands were inspected in comparison with the standard Hoveyda conditions (Table 2-1).



Scheme 2-4: Asymmetric conjugate addition with standard conditions developed by Hoveyda and Alexakis groups.

When the reaction was performed at −10 ºC, a 10% yield of the desired product was isolated for the first time (Entry 1, Table 2-1). A quick screening of various

ligands revealed that (*R*)-tol-BINAP **2-6** was more efficient than peptidic ligand **2-7** (Entry 3, Table 2-1). Although phosphoramidite **2-8** was found to be almost as effective as bisphosphine **2-6**, the product isolated contained a small amount of impurity (Entry 2, Table 2-1). Possibly due to the suppression of undesired side reactions, a higher yield of the desired product **2-14** can be isolated at lower temperatures (Entries 4-6, Table 2-1). Similar bisphosphine ligands such as (*S*)-BINAP gave the product with lower yield (Entry 7, Table 2-1).



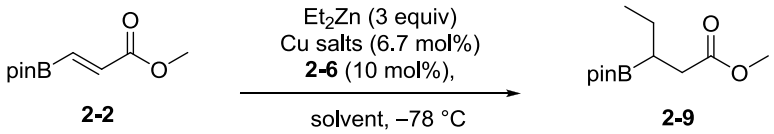
Entry	Ligand	Temp (°C)	Yield[a]
1	**2-7**	–10	10%
2	**2-8**	–10	30%
3	**2-6**	–10	30%
4	**2-7**	–30	28%
5	**2-6**	–30	46%
6	**2-6**	–78	61%
7	**(*S*)-BINAP**	–78	51%

[a] Isolated yields of products after flash column chromatography.

Table 2-1: Optimization of ligand and reaction temperature.

The next sets of parameters that were investigated were different copper salts and solvents. With toluene as the solvent, various copper (I) salts such as CuI, CuBr•SMe_2, CuCl, and CuTC were tested. CuCl was found to be a superior catalyst in comparison to the other Cu(I) salts, giving the desired product with a better yield (Entries 1-5, Table 2-2). Surprisingly, a Cu(II) salt such as $Cu(OAc)_2$ was found to be as efficient as CuCl, giving a comparable yield at −78 ºC (Entry 6, Table 2-2). It has been proposed that Cu(II) salts can be used in asymmetric conjugate additions because they are reduced *in-situ* to Cu(I) salts by the organometallic reagents.[13b] Other typical solvents such as *t*BuOMe and diethyl

ether led to diminished yields, while THF afforded a complex mixture (Entries 7-10, Table 2-2). Possibly due to the enhanced solubility for the copper salts, dichloromethane is an excellent solvent for conjugate additions with organozinc reagents (Entry 11, Table 2-2). Other Cu(II) salts and ligands were also tested and were found to be inferior to $Cu(OAc)_2$ and bisphosphine **2-6** (Entries 12-15, Table 2-2).



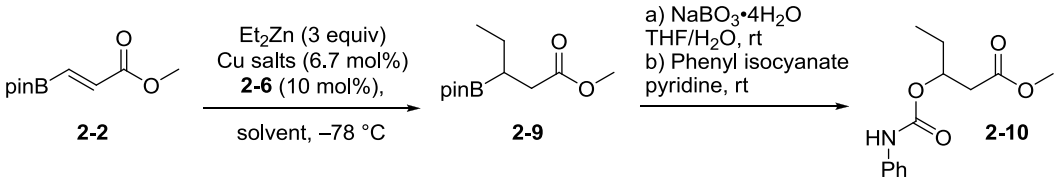
Entry	Cu salt	Solvent	Yield[a]
1	CuOTf•toluene	toluene	61%
2	CuI	toluene	63%
3	$CuBr•SMe_2$	toluene	68%
4	CuCl	toluene	70%
5	CuTC	toluene	48%
6	$Cu(OAc)_2$	toluene	72%
7	CuI	*t*BuOMe	59%
8	$CuBr•SMe_2$	*t*BuOMe	60%
9	$Cu(OAc)_2$	ether	58%
10	$Cu(OAc)_2$	THF	-[b]
11	**$Cu(OAc)_2$**	**CH_2Cl_2**	**77%**
12	$Cu(OAc)_2$	CH_2Cl_2	72%[c]
13	$Cu(OTf)_2$	CH_2Cl_2	61%
14	$Cu(acac)_2$	CH_2Cl_2	28%
15	CuCl	CH_2Cl_2	73%

[a] Isolated yields of products after flash column chromatography. [b] Complex mixture. [c] **2-5** was used as the ligand.

Table 2-2: Optimization of Cu salt and solvent.

With the optimized reaction conditions in hand, the enantioselectivity of the conjugate addition adduct **2-9** was then analyzed. Due to the lack of chromophore in product **2-9**, the boronate functionality had to be transformed to an aryl

carbamate through oxidation with sodium perborate and condensation with phenyl isocyanate. This type of chromophore installation is similar to the one previously conducted in the Hall Group by Dr. Lisa Carosi.[14] The enantiomeric excess of the synthesized carbamate **2-10** could then be measured by chiral HPLC. Unfortunately, under all of the conditions that led to good yields of the desired product **2-9**, no enantiomeric excess was observed for the carbamate products **2-10** (Entries 1-5, Table 2-3). Different ligands were also tested, but none of them led to enantioenriched products.



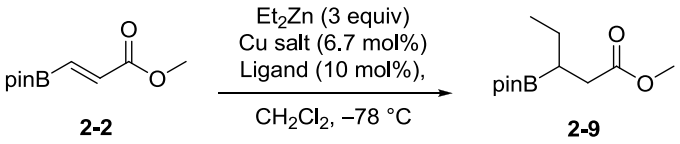
Entry	Cu salts	Solvent	Yield (**2-9**)[a]	ee (**2-10**)[b]
1	CuOTf•toluene	toluene	61%	0
2	$Cu(OAc)_2$	toluene	72%	0
3	$Cu(OAc)_2$	*t*BuOMe	59%	0
4	$Cu(OAc)_2$	ether	58%	0
5	$Cu(OAc)_2$	CH_2Cl_2	77%	0

[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 2-3: Determination of enantiomeric excess of the product **2-10**.

From these results, the necessity for chiral ligands in these conjugate addition reactions became suspect. In order to confirm this hypothesis, several control experiments were conducted to understand the roles of each reagent during these reactions. Surprisingly, it was found that both copper salts and chiral ligands were unnecessary. Although the addition of copper salts and chiral ligands led to products with higher yields, diethylzinc alone was enough to react with 3-boronoenoates with a moderate yield (Entries 1-4, Table 2-4). Thus, it is safe to assume that both copper salts and chiral ligands do not directly participate in the conjugate addition reaction under the conditions of Table 2-3. This phenomenon was very surprising since diethylzinc is normally not reactive enough to interact with α,β-unsaturated esters. From these observations, it is reasonable to propose

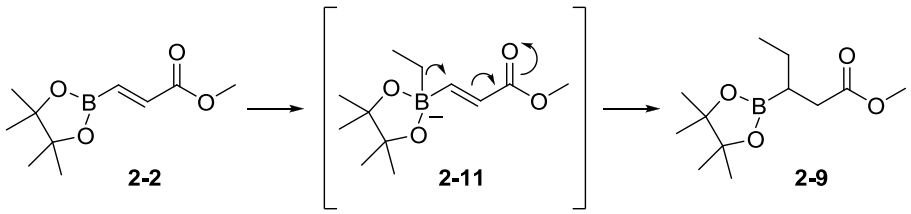
that diethylzinc, instead of reacting directly with the β-carbon of the enoate, coordinates first with the boron atom through its interaction with boron's empty orbital (**2-11**, Scheme 2-5). The ethyl group then migrates to the β-carbon through an intramolecular anionic 1,2-rearrangement similarly to the mechanism commonly seen in a Matteson homologation.[15] Due to these unsuccessful results, the attention was then turned to other types of unstabilized organometallic reagents that had been reported in asymmetric conjugate additions.



Entry	Cu Salt	Ligand	Yield[a]
1	CuCl	**2-6**	73%
2	CuCl	-	32%
3	-	**2-6**	58%
4	-	-	38%

[a] Isolated yields of products after flash column chromatography.

Table 2-4: Control experiments to assess the role of Cu salts and ligands.

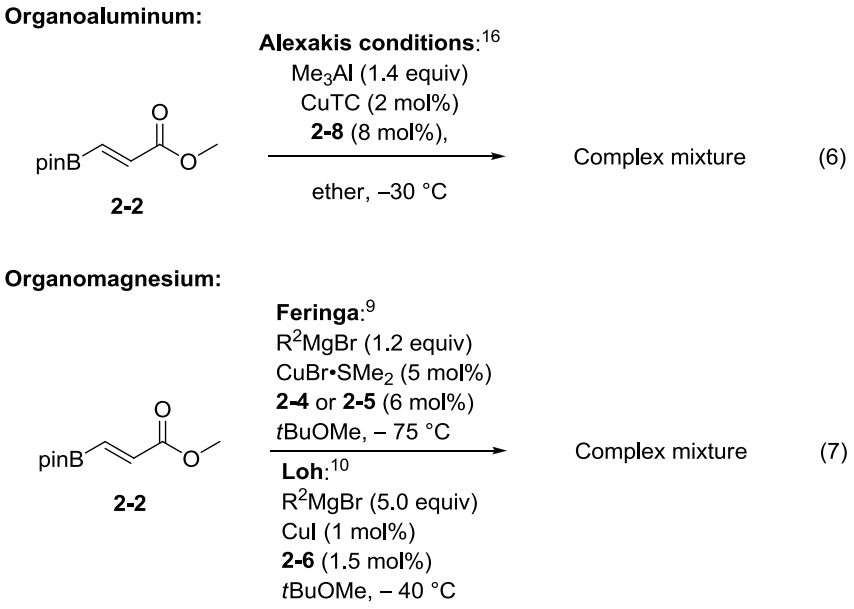


Scheme 2-5: Proposed mechanistic pathway for the formation of conjugate addition adducts as a racemic mixture when diethylzinc was used as the nucleophile.

2.2.2 Asymmetric conjugate addition with organoaluminum, organomagnesium, or organoboron reagents as nucleophiles

In addition to diorganozinc reagents, organoaluminum reagents have also been reported as promising nucleophiles for conjugate additions to cyclic or acyclic

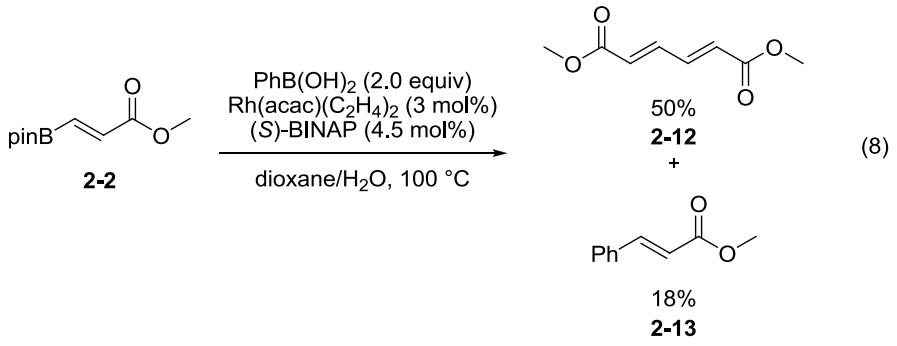
enones.[6, 16] Unfortunately, these reagents were not suitable nucleophiles for substrate **2-2**, resulting in a complex mixture (Equation 6, Scheme 2-6). Modification of different reaction parameters did not lead to any improvements in the reaction outcome. Knowing that organoaluminum reagents probably are not reactive enough towards conjugate addition with enoates, the attention was then turned towards organomagnesium reagents. As discussed previously, Grignard reagents are the only unstabilized nucleophiles to date that have been reported for the asymmetric conjugate addition on α,β-unsaturated esters.[9,10] Under the standard conditions developed by both the Feringa and Loh groups, however, only complex mixtures can be acquired when β-boronylenoate **2-2** was used as the Michael acceptor (Equation 7, Scheme 2-6).

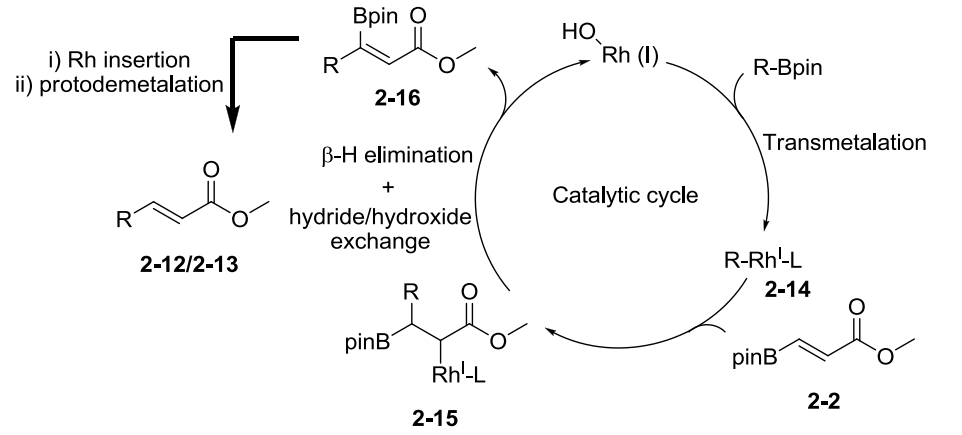


Scheme 2-6: Attempted asymmetric conjugate additions with organoaluminum and organomagnesium reagents.

One other option for asymmetric conjugate addition on enoates is the rhodium-catalyzed addition of aryl boronic acids (Equation 4, Scheme 2-3). In spite of potential chemoselective issues associated with the transmetallation step – rhodium can potentially insert into either the aryl boronic acid or boronate ester **2-2** –it was hypothesized that since aryl boronic acids are both electronically and

sterically more favourable for this process, the desired conjugate addition could be favoured to access the desired products. Unfortunately, when the reaction was performed with typical rhodium-catalyzed conditions,[12] only either homo-coupling products **2-12** or the deboronylated adducts **2-13** were isolated (Equation 8, Scheme 2-7). The predominant formation of the homo-coupling products implies that the insertion of rhodium catalyst to substrate **2-2** is favoured, affording the undesired side products. In a similar way to most rhodium-catalyzed conjugate additions, it was proposed that the rhodium catalyst first transmetalates with either the boronic acid or boronate **2-2** to give intermediate **2-14** (Scheme 2-7). This rhodium (I) species then inserts into the conjugate double bond of substrate **2-2** to afford rhodium enolate **2-15**. Instead of protodemetalation, which is popular in most asymmetric conjugate additions with organoboron reagents at this stage, β-H elimination probably occurred to yield β-boronylenoate **2-16**.





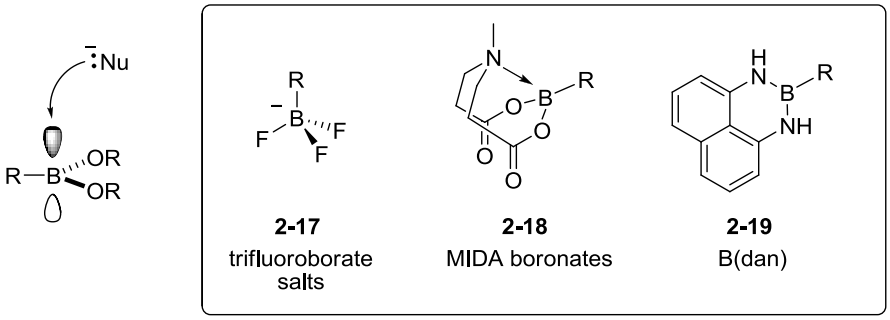
Scheme 2-7: Attempted asymmetric conjugate additions with organoboron reagents and the proposed mechanism for the observed products.

Boronate **2-16** is then prone to undergo further insertion by the rhodium catalyst and protodemetalation to yield the observed unsaturated products **2-12** and **2-13**.

2.3 Examination of different masking groups for boronic acids in asymmetric conjugate addition additions

2.3.1 Preparation of protected boronates and their subsequent asymmetric conjugate addition reactions

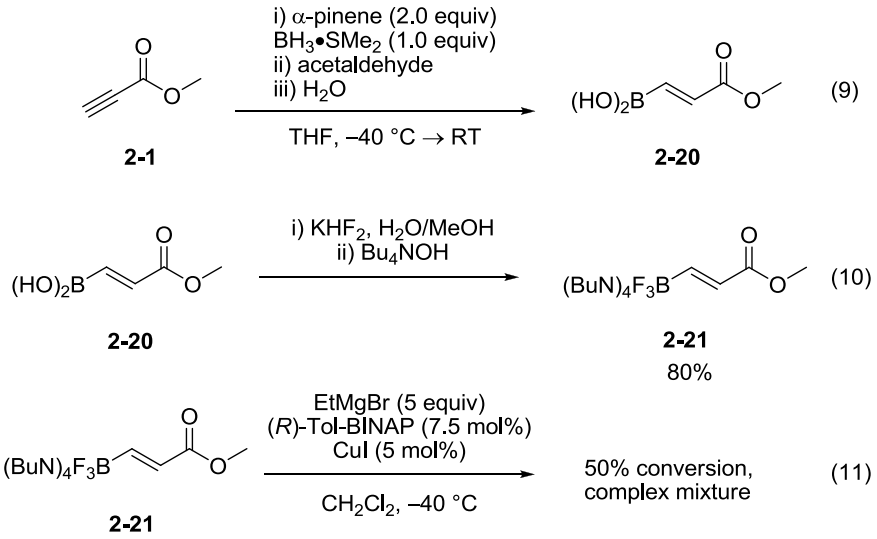
One hypothesis of unsuccessful conjugate additions at this stage is that most of the unstabilized organometallic nucleophiles likely interact with the empty *p*-orbital of the pinacol boronates, leading to undesired side reactions. In order to avoid the interaction between the nucleophiles or the catalyst with boron's empty *p*-orbital, various protecting groups that have been developed in recent years to suppress the Lewis acidity of boronic acid derivatives were examined (Scheme 2-8). The goal at this point was to address whether the Lewis acidity of boronate **2-2** was indeed associated with unsuccessful conjugate addition reactions.



Scheme 2-8: Problems with most boronic acids/esters and known boronic acids/esters masking groups.

The first class of protected boronate explored in this study was trifluoroborate salts.[17] Due to the occupation of the empty *p*-orbital of the boron atom by fluoride, trifluoroborates are tetrahedral complexes that are generally inert in the presence of various nucleophiles (**2-17**, Scheme 2-8). Trifluoroborate salts were originally discovered by Chambers and coworkers back in 1960,[18] and were made prevalent by the Vedejs Group through the development of an efficient synthetic methodology.[19] As a result of their low Lewis acidity, these trifluoroborate salts

have demonstrated a robust nature by displaying an ability to remain intact during various chemical transformations such as epoxidation and catalytic hydrogenation conditions. To test if a trifluoroborate salt is a proper protecting group for asymmetric conjugate addition reactions, the corresponding boronic acid **2-20** was first prepared. Similar to the preparation of substrate **2-2**, boronic acids **2-20** was synthesized by hydroboration of methyl propiolate, followed by hydrolysis (Equation 9, Scheme 2-9). The isolation of alkenyl boronic acids was previously optimized by a former Hall group member, Dr. Michel Gravel.[20] In this procedure, pure boronic acids can be prepared through simple extraction and trituration techniques. With boronic acid **2-20** in hand, the corresponding potassium trifluoroborate salt was synthesized using the standard protocol developed by the Vedejs Group.[19] In order to enhance the solubility of the trifluoroborate salt in most common solvents used for asymmetric conjugate addition reactions, a cation exchange reaction was performed where tetrabutylammonium cation was used in place of potassium to form borate salt **2-21** (Equation 10, Scheme 2-9).[21] At this point, the substrate was then treated under standard asymmetric conjugate addition conditions with ethyl magnesium bromide (Equation 11, Scheme 2-9).

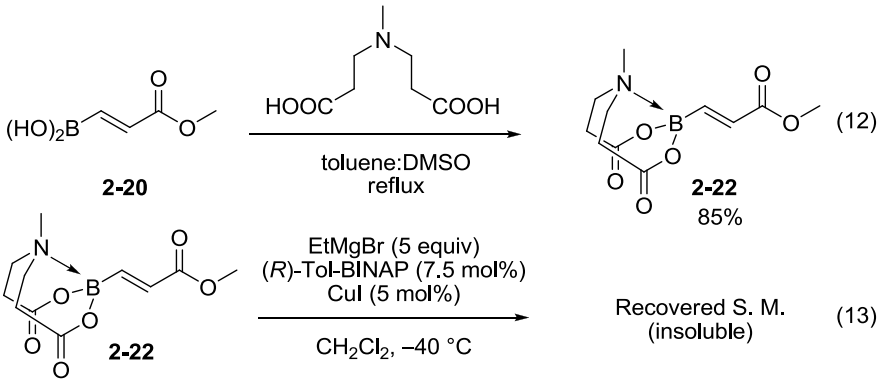


Scheme 2-9: Preparation of trifluoroborate salt **2-21** and its subsequent use in asymmetric conjugate addition reactions.

Disappointingly, only 50% conversion of the starting material was observed, and

the converted materials were complex mixtures that could not be deciphered. Varying the reaction conditions and nucleophiles did not change the outcome.

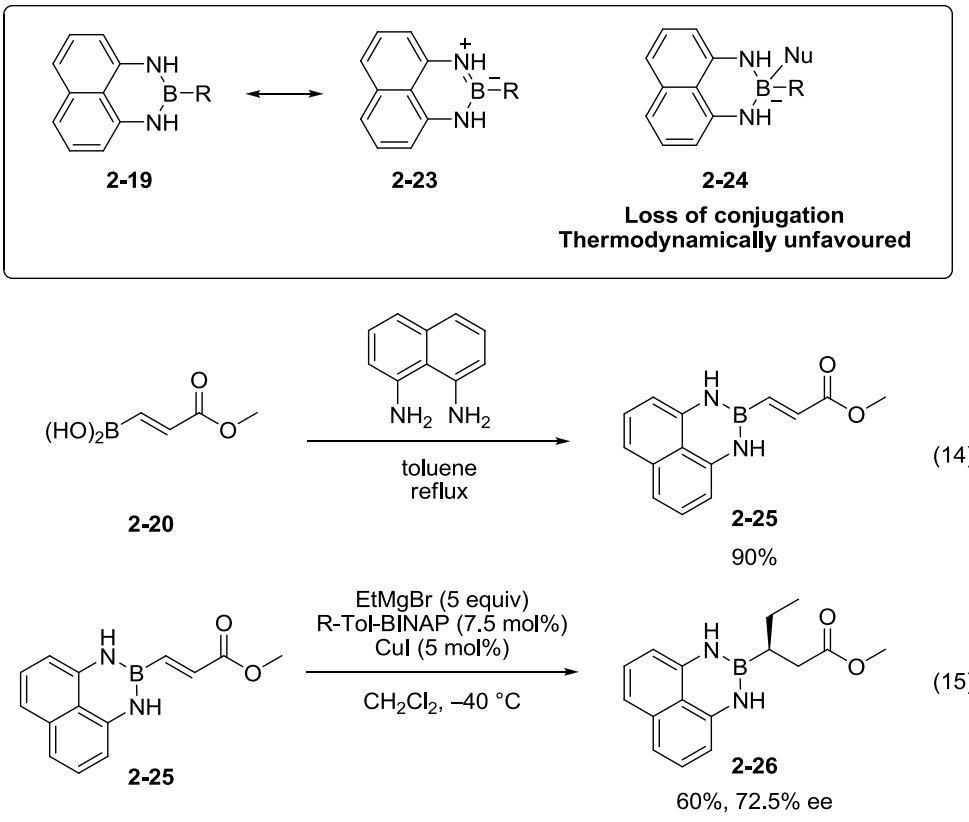
With this failure, the attention was turned towards MIDA boronates **2-18**, which were recently developed by the Burke group in 2007.[22] Due to the intramolecular coordination between the pendant nitrogen and boron's empty *p*-orbital, the protected MIDA boronates demonstrate remarkable stability towards various harsh reaction conditions such as Jones oxidation, reduction and other chemical transformations such as aldol reactions, Wittig olefinations, and Suzuki-Miyaura cross-coupling reactions. Encouraged by these promising precedents, the free boronic acid **2-20** was protected with methyl N-iminodicarboxylic acids to form MIDA boronate **2-22** in an excellent yield (Equation 12, Scheme 2-10). The resulting MIDA boronate **2-22** exhibited a low solubility in most of the common solvents for asymmetric conjugate addition, resulting in the recovery of starting material in most cases (Equation 13, Scheme 2-10). A small amount of deprotected boronic acids **2-20** was isolated as a side product, indicating that organomagnesium reagents could be used to deprotect MIDA boronates, similar to the general observation that these protecting groups can be deprotected under strongly basic conditions.



Scheme 2-10: Preparation of MIDA boronate **2-22** and its subsequent use in asymmetric conjugate addition reactions.

Due to these unsuccessful attempts, an alternative boron protecting group that could tolerate strongly basic conditions was sought. 1,8-Diaminonaphthalene, a

robust protecting group originally developed by Suginome and coworkers in 2007, was shown to be stable under various basic conditions and can only be deprotected under acidic conditions.[23] Unlike trifluoroborate salts and MIDA boronates, 1,8-diaminonaphthalene masks the boron atom not by shielding the empty *p*-orbital, but by providing a planar and conjugated backbone with the partially conjugated B−N bond (**2-19** and **2-23**, Scheme 2-11). This partial conjugation makes coordination of Lewis bases to the boron atom thermodynamically unfavourable since a tetrahedral boron atom cannot be involved in ring conjugation (**2-24**, Scheme 2-11). The synthesis of the protected boronic acid was relatively straightforward, leading to the formation of B(dan) boronate **2-25** in an excellent yield by using a Dean-Stark apparatus to azeotropically remove water. With this compound in hand, asymmetric conjugate

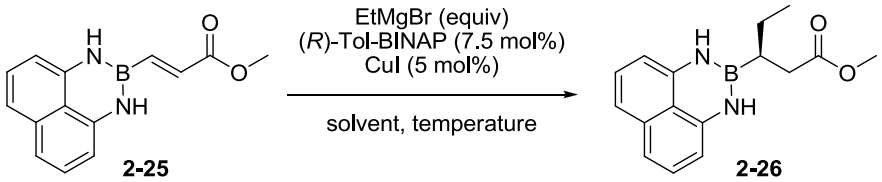


Scheme 2-11: Preparation of B(dan) **2-26** and its subsequent use in asymmetric conjugate addition reactions.

additions of this substrate were performed with ethyl magnesium bromide. Gratifyingly, for the first time the desired product **2-26** with a significant enantiomeric excess could be isolated when the reaction was maintained at −40 ºC (Equation 15, Scheme 2-11).

2.3.2 Optimization of reaction conditions

At this point, the main task at hand was to optimize the yield and enantiomeric excess through varying the reaction parameters. As shown in Table 2-5, 2-methyl THF was not a suitable solvent in this reaction even though it has been reported as having distinctive advantages over other solvents in asymmetric conjugate additions (Entry 2, Table 2-5).[24] *t*BuOMe was also found to be ineffective, mainly due to the low solubility of substrate **2-25** in this solvent. Diethyl ether, on the other hand, was an excellent solvent for the reaction, affording the desired product with a good yield and excellent enantiomeric excess (Entry 4, Table 2-5). By



2-25 **2-26**

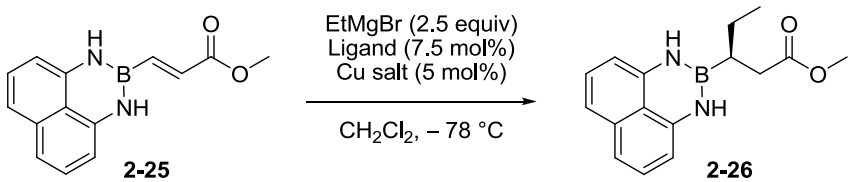
Entry	Temperature	Solvent	EtMgBr (equiv)	Yield[a]	ee[b]
1	– 40 °C	CH_2Cl_2	5	60%	72.5%
2	– 78 °C	2-methyl-THF	5	<5%	ND[c]
3	– 78 °C	*t*BuOMe	1.2	<5%	ND[c]
4	– 78 °C	ether	5	62%	93.4%
5	– 78 °C	ether	0.9	58%	98%
6	– 78 °C	ether	1.2	64%	97%
7	– 78 °C	ether	2.5	75%	97%
8	**– 78 °C**	**CH_2Cl_2**	**2.5**	**92%**	**95.5%**

[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] ND = not determined

Table 2-5: Optimization of reaction conditions.

lowering the equivalents of Grignard reagent used, higher yields were observed possibly due to the decrease of side products (Entries 5-7, Table 2-5). Eventually it was found that dichloromethane could act as a suitable solvent for this reaction at – 78 ºC, affording the desired product not only in an excellent yield, but also in outstanding enantiomeric excess (Entry 8, Table 2-5).

In addition to the Loh system, the Feringa conditions were also tried, leading to lower yield and enantioselectivity (Entry 1, Table 2-6).[10] Phosphoramidite in this case was not an effective ligand, yielding none of the desired product (Entry 2, Table 2-6). Copper halides were found to be essential, as CuCl afforded products with good yield and enantioselectivities, while CuOTf•toluene was not effective in catalyzing the asymmetric conjugate addition reaction (Entries 3-4, Table 2-6).



2-25 **2-26**

Entry	Ligand	Cu salt	Yield[a]	ee[b]
1	**2-5**	$CuBr•SMe_2$	39%	80%
2	**2-8**	CuI	<5%	ND[c]
3	**2-6**	CuCl	63%	96.5%
4	**2-6**	CuOTf•toluene	<5%	ND[c]

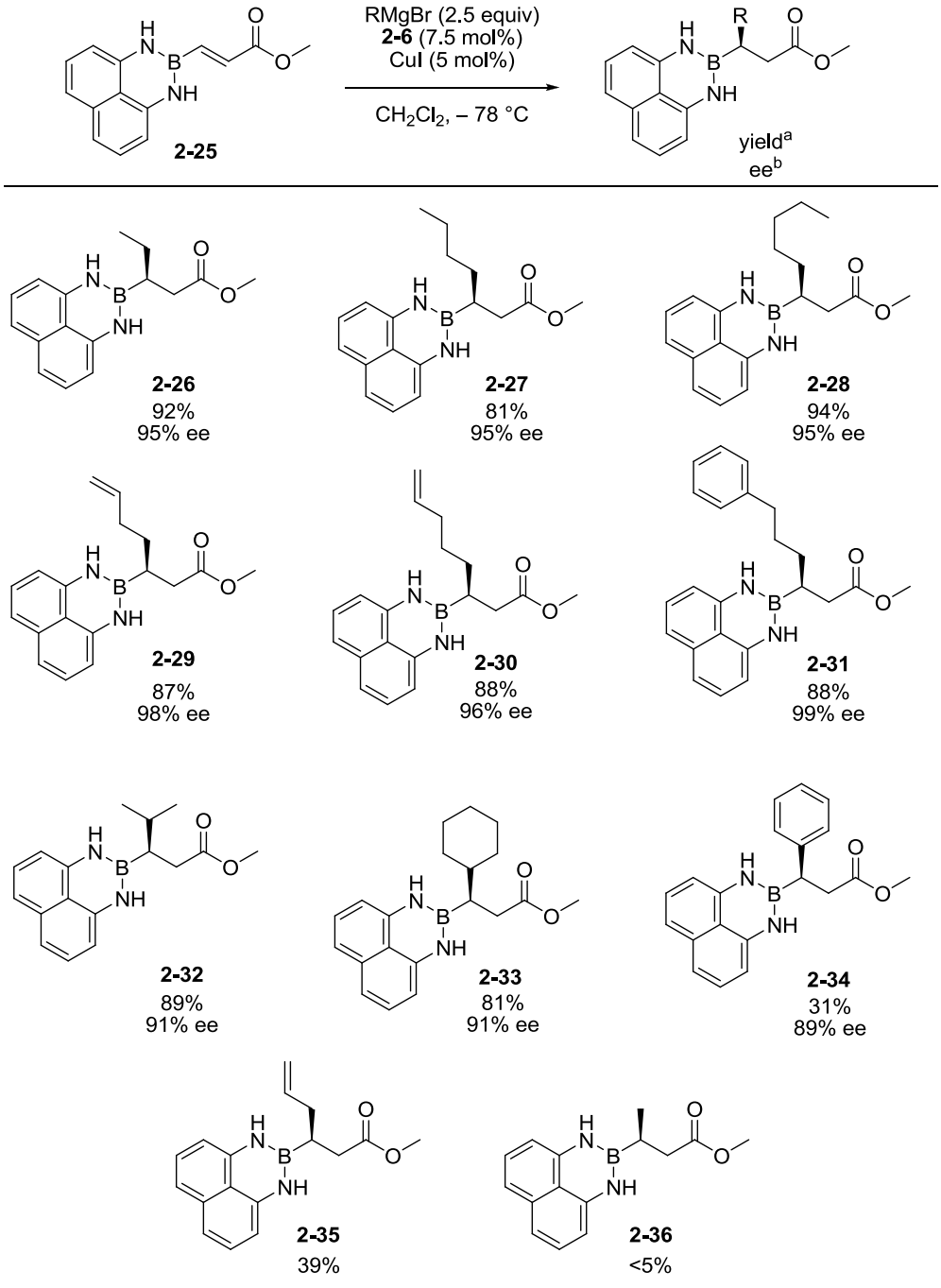
[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] ND = not determined

Table 2-6: Screening of different ligands and copper salts.

2.3.3 Substrate scope of different Grignard reagents

With the optimized conditions in hand (Entry 8, Table 2-5), the scope of different organomagnesium reagents for this asymmetric conjugate addition was examined. Primary alkyl Grignard reagents were found to be excellent nucleophiles in these conjugate addition reactions, affording the desired products with good yields and enantioselectivities (**2-26** to **2-28**, Table 2-7). Grignard reagents bearing

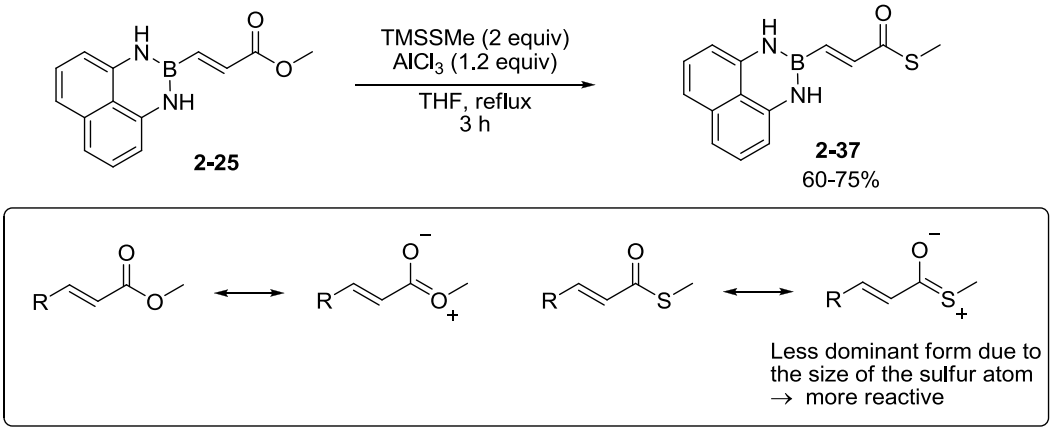
functionalities such as alkene and phenyl groups were also tolerated, allowing the possibility for further elaboration of the products into useful synthetic intermediates (**2-29**-**2-31**, Table 2-7). In addition to primary Grignard reagents,



[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 2-7: Substrate scope of asymmetric conjugate addition on substrate **2-25**.

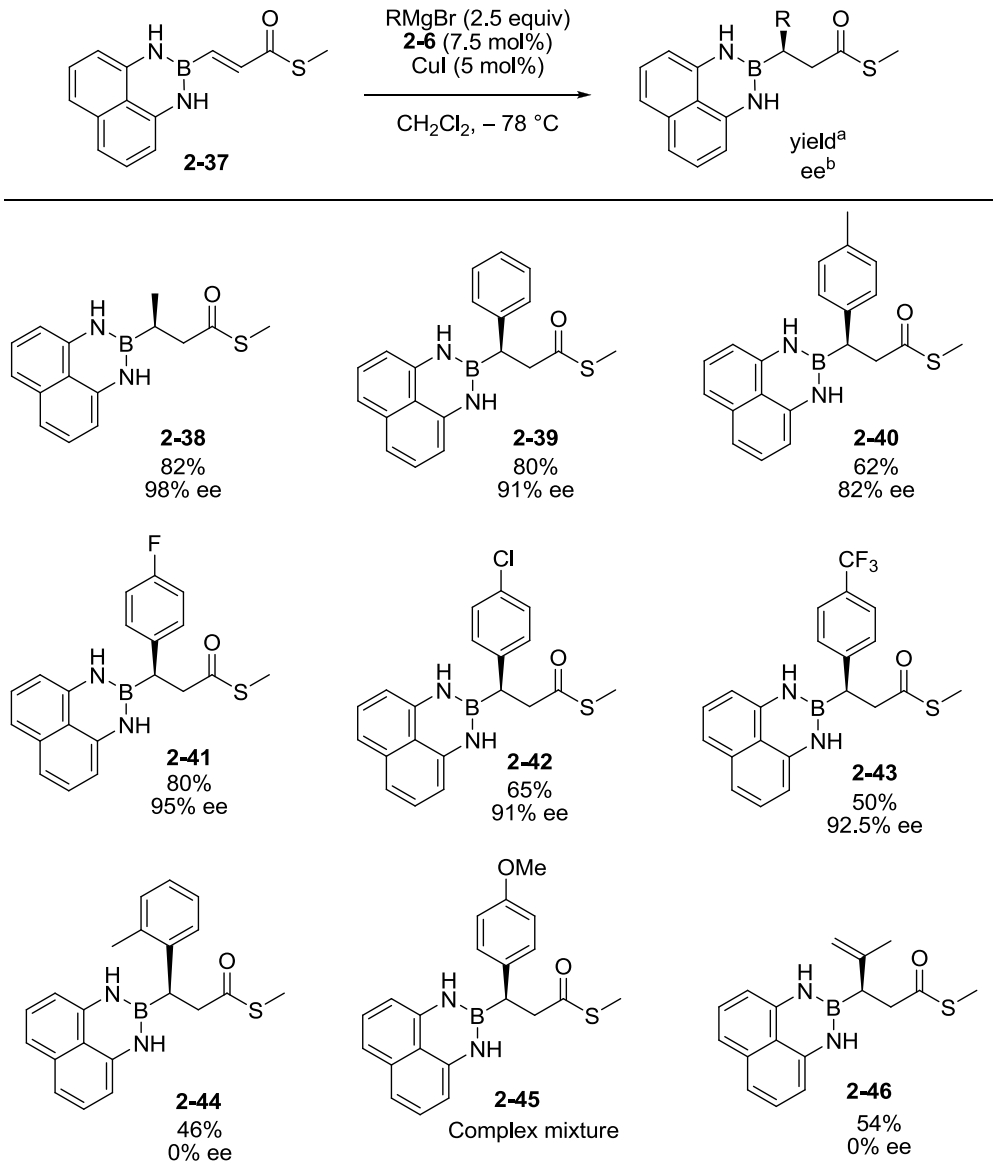
several branched nucleophiles were also found to be effective in asymmetric conjugate additions with enoate **2-25** to afford products with slightly lower enantioselectivity (**2-32** and **2-33**, Table 2-7). Less reactive Grignard reagents, such as phenyl, allyl and methyl magnesium bromides, reacted much more slowly with enoate **2-25,** which resulted in lower conversion and yields of the desired products. Thus, in order to further expand the substrate scope of the conjugate addition reaction, it was important to modify enoate **2-25** in order to enhance its reactivity. Feringa and coworkers recently explored α,β-unsaturated thioesters as Michael acceptors in conjugate addition reactions and successfully expanded the substrate scope to include methylmagnesium bromide.[25] Due to the lower degree of delocalization of electrons from the lone pair of the sulfur atom, the intrinsic reactivity of α,β-unsaturated thioesters is higher than α,β-unsaturated oxoesters (Scheme 2-12). As a result, the corresponding α, β-unsaturated thioester **2-37** was prepared from enoate **2-25** by the use of $AlCl_3$ as a Lewis acid and the protected form of methyl thioether as the sulfur source (Scheme 2-12).



Scheme 2-12: Synthesis of the corresponding α,β-unsaturated thioester **2-37**.

By using α,β-unsaturated thioester **2-37** as the Michael acceptor, various Grignard reagents of moderate reactivity could be used for the asymmetric conjugate addition reactions to form the desired chiral alkyl boronates. MeMgBr, which did not react with the corresponding oxoester, reacted smoothly with substrate **2-37** to yield the desired product **2-38** with an excellent yield and enantioselectivity

(Table 2-8). Due to the importance of polypropionate units in biologically important natural products, chiral boronate **2-38** represents a valuable synthetic building block for the construction of pharmaceutically important molecules. In addition to methyl Grignard reagents, less reactive aryl Grignard reagents also exhibit excellent reactivity with enoate **2-37** to yield the desired products in



[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 2-8: Substrate scope for the asymmetric conjugate additions on substrate **2-37**.

excellent yields and high enantioselectivity. It is noteworthy to mention that similar conditions for the addition of phenylmagnesium bromide to non-boron substituted α,β-unsaturated thioesters led to a racemic mixture of the desired products.[24c] The results listed here indicate that the B(dan) boronate plays an important role in enhancing the enantioselectivity, instead of just behaving like a carbon substituent. Various functional groups such as methyl, fluoro, chloro, and trifluoromethyl groups on the arylmagnesium reagents were all tolerated, leading to a variety of products with excellent yields and high enantiomeric excesses (**2-39**−**2-43**, Table 2-8). The reaction time of these reactions correlated well with the reactivity of these Grignard reagents, where more reactive Grignard reagents often afforded the products within 30 minutes, while less reactive electron deficient Grignard reagents often required more than 10 hours for the reactions to be complete. The substituents on the arylmagnesium bromides, however, were limited to *para*-substitution. *Ortho*-substituted Grignard reagents could be used to give the product with a decent yield, but the enantioselectivity suffered as a result (**2-44**, Table 2-8). Alkenyl Grignard reagents were also examined, and it was found that these nucleophiles afforded the desired product as racemic mixtures (**2-46**, Table 2-8).

In addition to the Grignard reagents mentioned above, various other functionalized organic halides were reacted with magnesium in diethyl ether (Figure 2-1). The resulting Grignard reagents, however, were not soluble in diethyl ether, and precipitation was observed upon the addition of organic halides

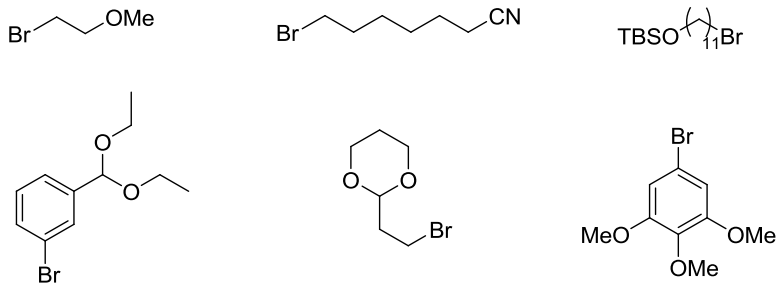
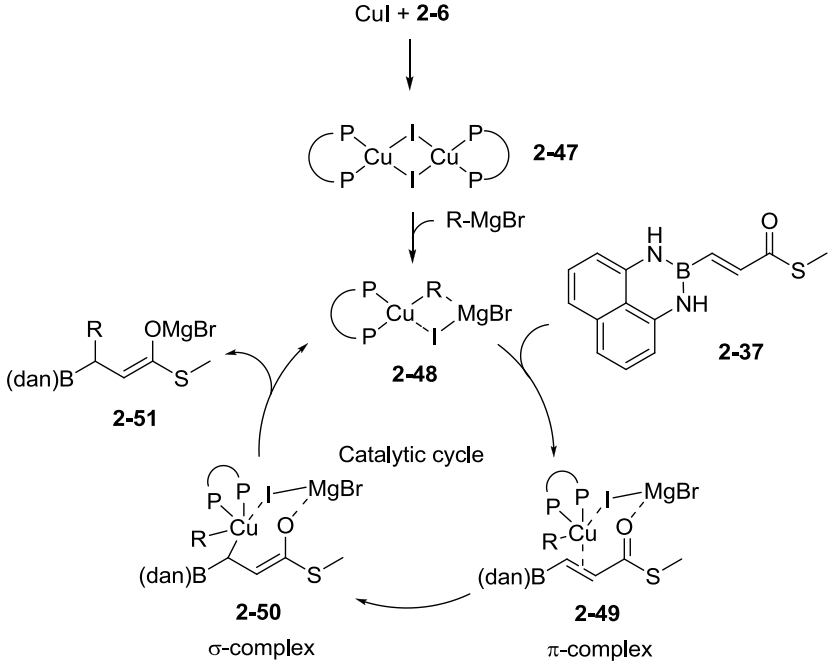


Figure 2-1: List of organic halides that failed to be converted to Grignard reagents in diethyl ether.

to magnesium. While these Grignard reagents can be prepared in THF, this solvent was found to be detrimental to the conjugate addition reaction, giving products with low conversion. As a result, due to the low solubility of these Grignard reagents in diethyl ether, these compounds could not be used in the desired conjugate addition reactions.

2.4 Proposed mechanistic cycle

The mechanistic cycle of copper-catalyzed asymmetric conjugate additions with Grignard reagents has been properly studied by the Feringa Group.[26] It was found that a dimeric complex **2-47** is formed the moment CuI is mixed with bisphosphine **2-6** (Scheme 2-13). Upon the addition of the Grignard reagent, the active catalyst, **2-48**, was formed and characterized by NMR. The nucleophilic species **2-48** then reacts with enoate **2-37** to form the π-complex **2-49**, before undergoing oxidative addition to give the σ-complex **2-50**. At this point, reductive elimination would yield the desired product **2-51** as a magnesium enolate and regenerate the catalyst. (Scheme 2-13)

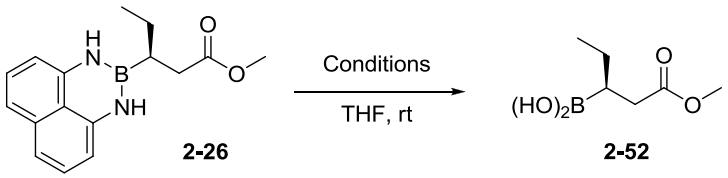


Scheme 2-13: Proposed catalytic cycle for Cu-catalyzed asymmetric conjugate additions with Grignard reagents.[25]

2.5 Examination of the synthetic utility of chiral boronates and the confirmation of the absolute stereochemistry of the products synthesized

2.5.1 Protecting group exchange of B(dan) boronates to pinacol boronates

In order to demonstrate the synthetic utility of the chiral alkyl boronates synthesized, it is very important to develop a method for the conversion of the chemically unreactive B(dan) boronates to other more versatile functionalities such as the free boronic acids or pinacol boronates. According to the Suginome group, deprotection of the B(dan) boronates to boronic acids can be performed under acidic conditions with either 2M H_2SO_4 or 5M HCl.[22] However, upon treatment of model substrates **2-26** with these acidic reagents, only the formation of complex mixtures was observed. Lowering the stoichiometry of acid did not improve the results, again giving unidentifiable products (Entries 1-6, Table 2-9).



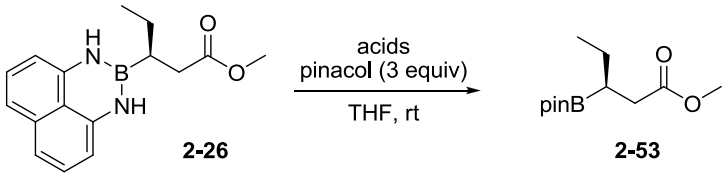
2-26 **2-52**

Entry	Conditions	Results
1	2M H_2SO_4 (4 equiv)	complex mixture
2	2M H_2SO_4 (2 equiv)	complex mixture
3	2M H_2SO_4 (1 equiv)	complex mixture
4	5M HCl (4 equiv)	complex mixture
5	5M HCl (2 equiv)	complex mixture
6	5M HCl (1 equiv)	complex mixture

Table 2-9: Various conditions tried to deprotect the B(dan) boronate.

It was anticipated that the deprotected alkylboronic acid **2-52** could be unstable since alkylboronic acids are known to readily undergo side reactions such as protodeboronation and oxidation reactions. As a result, it was attempted to trap the *in-situ* generated boronic acid **2-52** directly with pinacol to afford pinacol boronate **2-53**. Since the *in-situ* formed boronic acid **2-52** is likely an unstable

compound, the deprotection of B(dan) boronate **2-26** is preferably slow, so that the boronic acid **2-52** formed could be immediately trapped by pinacol. By using hydrochloric acid as the acidic source, a moderate yield of the desired product was obtained (Entry 1, Table 2-10). Increasing the stoichiometry of the acids led to decomposition of the product, confirming the hypothesis that deprotection had to be performed slowly. After switching the acid source to sulfuric acid, it was found that the desired pinacol boronate **2-53** could be isolated with excellent yields (Entries 3-4, Table 2-10). With this compound in hand, the stage was now set to explore various applications of the chiral secondary alkyl boronates synthesized since pinacol boronates are known to undergo numerous organic transformations to different functionalities.



2-26 **2-53**

Entry	acids	Yield[a]
1	5M HCl (4 equiv)	60%
2	5M HCl (20 equiv)	complex mixture
3	2M H_2SO_4 (4 equiv)	85%
4	2M H_2SO_4 (2 equiv)	90%

[a] Isolated yields of products after flash column chromatography.

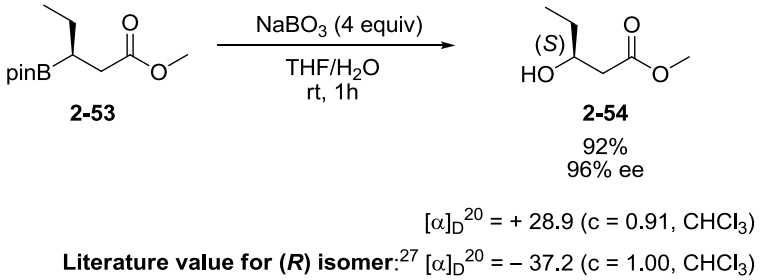
Table 2-10: Various conditions tried to trans-esterificy B(dan) boronates **2-26** to Bpin boronates **2-53**.

2.5.2 Oxidation reactions and the determination of the absolute stereochemistry of the conjugate addition reactions

Oxidation of boranes or boronates to alcohols is one of the most well-known organic transformations in organic chemistry. In this regard, chiral boronate **2-53** was oxidized with sodium perborate, a reagent which slowly releases hydrogen peroxide under the reaction conditions (Scheme 2-14). The oxidation occurred

smoothly to afford the desired chiral alcohol **2-54** with an excellent yield. This approach for the synthesis of chiral alcohols complements asymmetric aldol reactions or Reformatsky reactions where a different bond disconnection can be envisioned.[27]

It is well known that oxidation of boronates to alcohols occurs with retention of stereochemistry. In order to determine the absolute configuration of the conjugate addition products, the oxidized product **2-54** was directly compared with optically pure literature samples. The synthetic sample exhibits opposite stereochemistry to the known (*R*)-chiral alcohol based on $[\alpha]_D^{20}$ values, thus indicating that the chiral alcohol **2-54** possesses the (*S*)-stereochemistry.[28]



Scheme 2-14: Oxidation to yield chiral alcohols and the determination of absolute configuration of **2-54** through $[\alpha]_D^{20}$ comparison with a known compound.

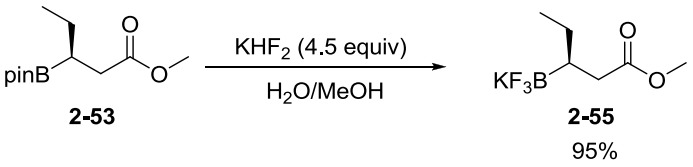
2.5.3 Other attempts at expanding the applications of chiral alkyl boronates

2.5.3.1 Preparation of trifluoroborate salts

In addition to their usages as protecting groups for boronic acids, trifluoroborate salts have been used extensively in Suzuki-Miyaura cross-couplings due to their enhanced stability under cross-coupling conditions (vide infra).[17] As a result, it would be highly beneficial to prepare the corresponding enantioenriched trifluoroborate salts from pinacol boronates. Following the standard protocol developed by the Vedejs Group, the synthesis of trifluoroborate salt **2-55** was accomplished, giving the desired product with a 95% yield (Scheme 2-15).

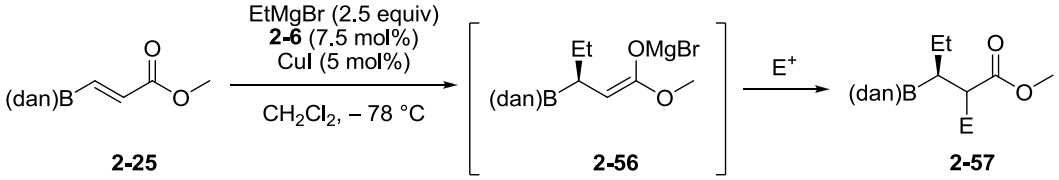
2.5.3.2 Attempted three-component reactions with various electrophiles

As shown previously in the catalytic cycle (Section 2.4), the products of conjugate



Scheme 2-15: Formation of enantioenriched trifluoroborate salt **2-55** from pinacol boronate **2-53**.

addition reactions are magnesium enolates prior to hydrolysis. Thus, it may be possible to trap this intermediate with different electrophiles to complete a three-component coupling process. The Feringa Group in 2006 showed that various aldehydes can be trapped through a conjugate addition/aldol reaction sequence to acquire products with two contiguous stereogenic centres.[29] Unfortunately, when the trapping of the magnesium enolate **2-56** was attempted with various electrophiles, only complex mixtures or conjugate addition products could be isolated (Entries 1-4, Table 2-11). Based on the observation that there is a new product formed upon the addition of benzaldehyde, the aldol reaction had likely occurred, but all attempts at isolating the desired products failed.



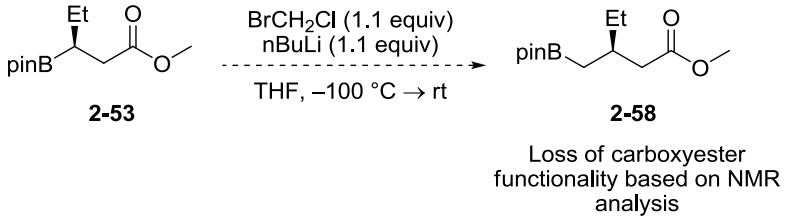
Entry	E^+ (3 equiv)	Result
1	benzaldehyde	complex mixture
2	formaldehyde	complex mixture
3	allyl bromide	**2-26**
4	allyl iodide	**2-26**

Table 2-11: Attempted three-component couplings with various electrophiles.

2.5.3.3 Matteson homologation

In addition to three-component coupling reactions, homologation of the chiral

alkyl boronates with Matteson's protocol was also attempted. Unfortunately, under the typical reaction conditions, the organolithium generated *in-situ* preferentially reacted with the carboxyester instead of the boronic esters, leading to decomposition of the starting material (Scheme 2-17). Different reaction parameters were tested, but they were met with limited success as the organolithium generated always preferentially reacted with the carboxyester moiety.



Scheme 2-16: Attempted Matteson homologation of boronate **2-53**.

2.6 Summary[30]

In this section, β-boronyl α,β-unsaturated esters and thioesters were found to be suitable Michael acceptors for asymmetric conjugate addition reactions to form chiral secondary alkyl boronates. The key to this reaction is the utilization of a suitable masking group on the boronyl unit to suppress the reactivity from boron's empty *p*-orbital. In order to expand the reagent scope to less reactive Grignard reagents, more reactive α,β-unsaturated thioesters were synthesized and used as the Michael acceptors. The scope of suitable reagents can thus be expanded to aryl Grignard reagents, which have previously been shown to be ineffective nucleophiles in similar conjugate addition reactions. The chiral alkyl boronates synthesized from this approach complements the late introduction strategy where the boronyl functionality can be introduced through asymmetric conjugate borylation. The resulting chiral B(dan) alkyl boronates can be efficiently trans-esterified to pinacol boronates and oxidized without any loss of stereochemical integrity. Although the synthetic utility of these chiral alkyl boronates at this stage is somewhat limited, these compounds offer opportunities for subsequent methodology development in the near future.

2.7 Experimental

2.7.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Toluene and dichloromethane were distilled from CaH_2. THF, 2-methyl THF and Et_2O were distilled from sodium with benzophenone as an indicator. Acetone was distilled from 4 Å molecular sieves. Anhydrous *t*BuOMe was used as received from Alfa Aesar. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR spectroscopic data are presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; sxt, sextet; spt, septet, dd, doublet of doublets; tt, triplet of triplets, m, multiplet. The error of coupling constants from ^1H NMR analysis is ±0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumber. Grignard reagents were either purchased from Aldrich (MeMgBr, EtMgBr, PhMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in Et_2O following standard procedures. Grignard reagents were titrated using the method developed by Krasovskiy and Knochel.[31] Racemic 1,4-addition products were obtained by reaction of the enoates with the corresponding RMgX reagents (–20 ^oC, Et_2O) and CuI (100 mol%) or using *rac*-BINAP by following the catalytic conjugate addition method detailed below. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD or Chiralpak-AS columns with UV detection (in comparison to racemic products prepared as discussed

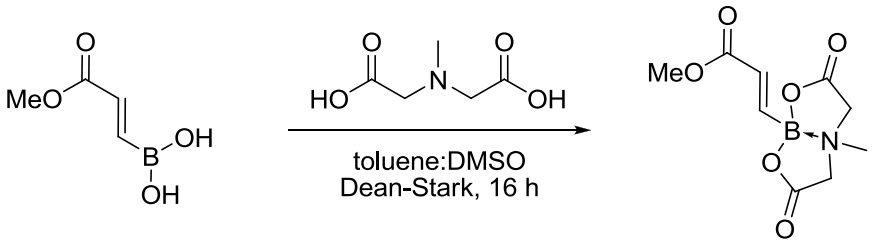
above). The starting materials were synthesized according to the literature procedures:

(*E*)-3-methoxy-3-oxoprop-1-enylboronic acid (**2-20**)[20] and

(*E*)-methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (**2-2**).[1]

2.7.2 Preparation of protected 3-boronyl unsaturated esters or thioesters

2.7.2.1 (*E*)-Methyl 3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)acrylate (2-22)



2-20 **2-22**

To a stirred solution of boronic acid **2-20** (1.00 g, 7.70 mmol) in toluene (8.0 mL) and DMSO (3.0 mL) was added *N*-methyliminodiacetic acid (1.30 g, 8.50 mmol). The reaction was then heated under reflux for 16 h with azeotropic removal of water. Once the reaction was done, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (CH_3CN/EtOAc = 1:1) to give **2-22** (1.59 g, 85%) as a white solid.

^{1}H NMR (400 MHz, CD_3CN) δ 6.91 (d, *J* = 18.0 Hz, 1H), 6.28 (d, *J* = 17.8 Hz, 1H), 4.00 (d, *J* = 17.0 Hz, 2H), 3.85 (d, *J* = 17.0 Hz, 2H), 3.70 (s, 3H), 2.80 (s, 3H).

^{13}C NMR (100 MHz, CD_3CN) δ 169.1, 167.3, 133.7, 62.8, 52.2, 47.9, 38.1.

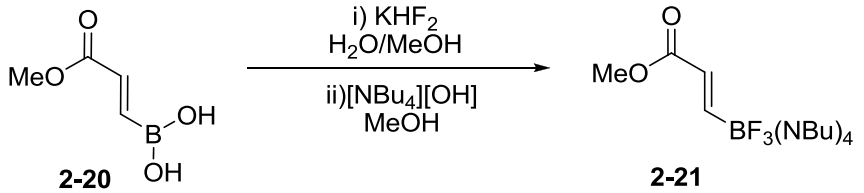
^{11}B NMR (160 MHz, CD_3CN) δ 10.0.

IR (Microscope, cm^{-1}) 3049, 3021, 2998, 2962, 1755, 1738, 1725, 1714.

HRMS (ESI) for $C_9H_{12}BNO_6$: calcd. 241.0758; found 241.0766.

M. P. 177 – 179 °C.

2.7.2.2 Tetrabutylammonium (*E*)-trifluoro(3-methoxy-3-oxoprop-1-enyl)borate (2-21)



To a stirred solution of **2-20** (500 mg, 3.85 mmol) in methanol (7.5 mL) was added a solution of KHF_2 (1.50 g, 19.0 mmol) in H_2O (4.0 mL). The mixture was stirred for 1 hour at room temperature. The reaction mixture was then concentrated *in vacuo* and washed with hot acetone (3 × 20 mL). The acetone fractions were then filtered and concentrated *in vacuo* to provide the crude product. The solid was further washed with hexanes and diethyl ether to give the potassium trifluoroborate salt.

The trifluoroborate salt was dissolved in a mixture of dichloromethane (5.0 mL) and H_2O (5.0 mL). The solution was cooled to 0 °C, at which point a solution of tetrabutylammonium hydroxide (2.4 mL, 3.7 mmol) was added to the solution slowly. The solution was then warmed to room temperature and stirred for another hour. Once the reaction was complete, the reaction mixture was diluted with dichloromethane (20 mL) and the layers were separated. The aqueous layer was further extracted with dichloromethane (3 × 20 mL) and the combined organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford **2-21** as a yellow solid (1.22 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 18.1 Hz, 1H), 6.11 (d, J = 18.0 Hz, 1H), 3.62 (s, 3H), 3.13 (m, 8H), 1.55 (m, 8H), 1.37 (sxt, J = 7.3 Hz, 8H), 0.95, (t, J = 7.1 Hz, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 125.4, 58.5, 50.8, 23.8, 19.6, 13.6. (The boron-bound carbon was not detected due to quadrupolar relaxation)

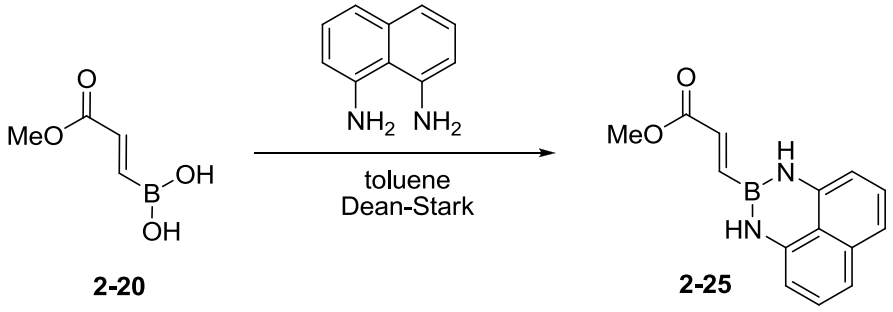
^{11}B NMR (160 MHz, $CDCl_3$) δ 2.1.

IR (Microscope, cm^{-1}) 2964, 2878, 1708, 1615.

HRMS (ESI) for $C_{20}H_{41}BF_3NO_2$: calcd. 153.0341; found 153.0340.

M. P. 63 – 64 °C.

2.7.2.3 Naphthalene-1,8-diamido (dan) derivative (2-25)



2-20 **2-25**

A stirred mixture of boronic acid **2-20** (500 mg, 3.85 mmol), 1,8-diaminonaphthalene (615 mg, 3.89 mmol) in toluene (40 mL) was heated for 2 h under reflux with azeotropic removal of water. The reaction mixture was then concentrated *in vacuo* and recrystallized (EtOAc) to give **2-25** (873 mg, 90%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.02 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.00, (d, *J* = 18.5 Hz, 1H), 6.43 (d, *J* = 18.4 Hz, 1H), 6.33 (dd, *J* = 7.1, 1.1 Hz, 2H), 5.80 (br s, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.5, 136.4, 132.9, 127.6, 120.3, 118.3, 106.2, 51.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

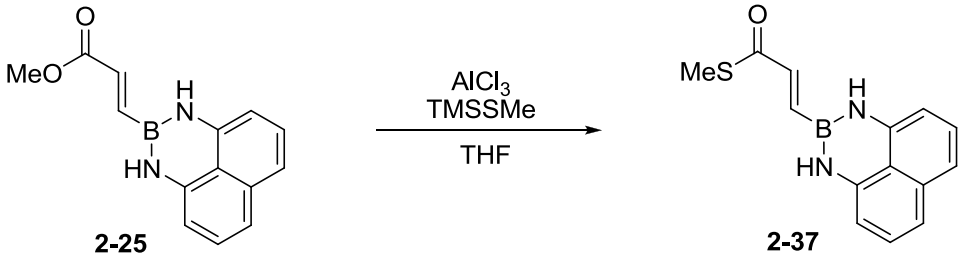
^{11}B NMR (160 MHz, $CDCl_3$) δ 27.9.

IR (Microscope, cm^{-1}) 3404, 3387, 3374, 3055, 3014, 2946, 1711, 1653, 1626, 1598, 1513.

HRMS (ESI) for $C_{14}H_{13}BN_2O_3$: calcd. 253.1145; found 253.1145.

M. P. 160 – 165 ˚C (decomposed).

2.7.2.4 Naphthalene-1,8-diamido (dan) derivative (2-37)



2-25 **2-37**

To a stirred solution of **2-25** (889 mg, 3.53 mmol) in THF was added $AlCl_3$ (564 mg, 4.22 mmol) and TMSSMe (848 mg, 7.05 mmol) sequentially. The solution was then stirred under reflux for 3 h before being quenched by the addition of aq.

phosphate buffer solution (pH = 7) at room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layer was then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 19:1) to give **2-37** (766 mg, 81%) as a red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.02 (dd, *J* = 8.4 Hz, 1.1 Hz, 2H), 6.87 (d, *J* = 18.1 Hz, 1H), 6.67 (d, *J* = 18.1 Hz, 1H), 6.33 (dd, *J* = 7.3, 1.1 Hz, 2H), 5.81 (br s, 2H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 140.5, 136.4, 132.9, 127.6, 120.3, 118.3, 106.2, 51.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 27.5.

IR (Microscope, cm^{-1}) 3404, 3387, 3374, 3055, 3014, 2946, 1711, 1653, 1626, 1598, 1513.

HRMS (ESI) for $C_{14}H_{13}BN_2OS$: calcd. 268.0842; found 268.0842.

M. P. 173 – 176 °C (decomposed).

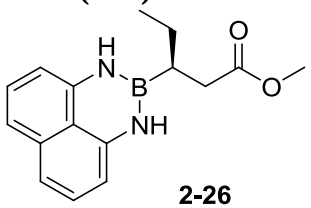
2.7.3 Catalytic asymmetric conjugate addition

2.7.3.1 General procedure

(*R*)-Tol-BINAP (25.5 mg, 0.0375 mmol) and CuI (4.8 mg, 0.025 mmol) were dissolved in dichloromethane (1.0 mL) and stirred at room temperature for 30 minutes until the solution turned yellow. Substrate **2-25** (126 mg, 0.500 mmol) or **2-37** (134 mg, 0.500 mmol) and dichloromethane (7.0 mL) were then sequentially added into the reaction mixture, which was stirred for 5 minutes before being cooled to –78 °C. Then, the Grignard reagent (1.25 mmol) was added into the reaction mixture dropwise over a span of 2 minutes. After stirring for 12 hours, the reaction mixture was quenched with MeOH (1.0 mL) and 1 M NH_4Cl (4.0 mL) and was allowed to warm to room temperature. The layers were separated, and the aqueous layer was further extracted with diethyl ether (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated *in*

vacuo. The crude product was then purified by flash column chromatography to give the pure product.

2.7.3.2 Naphthalene-1,8-diamido (dan) derivative 2-26



2-26

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-26** (92% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.00 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.30 (dd, J = 7.3, 1.0 Hz, 2H), 5.77 (br s, 2H), 3.66 (s, 3H), 2.44 (m, 2H), 1.49 (m, 2H), 1.36 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.0, 136.3, 127.5, 119.7, 117.5, 105.7, 51.7, 36.1, 24.6, 13.4. (The boron-bound carbon was not detected due to quadrupolar relaxation)

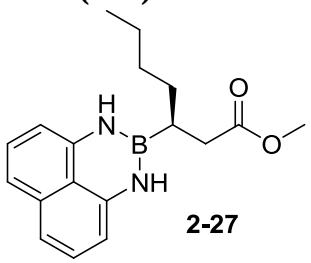
IR (Microscope, cm^{-1}) 3394, 3053, 2955, 2929, 2872, 1722, 1629, 1601, 1510.

HRMS (ESI) for $C_{16}H_{19}BN_2O_2$: calcd. 283.1615; found 283.1617.

$[\alpha]_D^{20}$: –5.3 (c = 1.62, chloroform) for 95% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 53.7 min, T_{minor} = 38.0 min, ee = 95%.

2.7.3.3 Naphthalene-1,8-diamido (dan) derivative 2-27



2-27

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-27** (94% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.4, 7.3 Hz, 2H), 6.99 (dd, *J* = 8.3,

0.9 Hz, 2H), 6.30 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.74 (br s, 2H), 3.65 (s, 3H), 2.42, (m, 2H), 1.42 (m, 3H), 1.31 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.0, 136.3, 127.5, 119.7, 117.5, 105.7, 51.6, 36.4, 31.5, 31.1, 22.9, 14.0. (The boron-bound carbon was not detected due to quadrupolar relaxation)

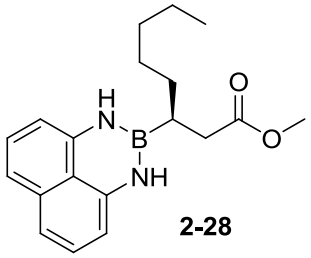
IR (Microscope, cm^{-1}) 3395, 3054, 2954, 2925, 2870, 2856, 1723, 1629, 1602, 1511.

HRMS (ESI) for $C_{18}H_{23}BN_2O_2$: calcd. 310.1853; found 310.1858.

$[\alpha]_D^{20}$: +5.0 (c = 4.01, chloroform) for 95% ee

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 32.0 min, T_{minor} = 21.8 min, ee = 95%.

2.7.3.4 Naphthalene-1,8-diamido (dan) derivative 2-28



2-28

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-28** (81% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.2, 7.4 Hz, 2H), 7.00 (dd, *J* = 8.4, 1.0 Hz, 2H), 6.31 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.76 (br s, 2H), 3.66 (s, 3H), 2.43 (m, 2H), 1.27-1.43 (m, 9H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.1, 136.3, 127.5, 119.7, 117.5, 105.7, 51.6, 36.4, 32.1, 31.8, 28.6, 22.5, 14.1. (The boron-bound carbon was not detected due to quadrupolar relaxation)

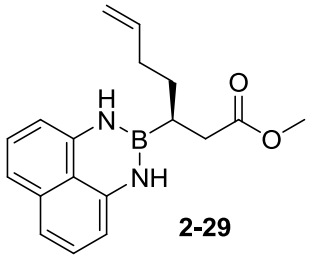
IR (Microscope, cm^{-1}) 3395, 3054, 2953, 2924, 2854, 1724, 1629, 1602, 1510.

HRMS (ESI) for $C_{19}H_{25}BN_2O_2$: calcd. 325.2085; found 325.2085.

$[\alpha]_D^{20}$: +5.9 (c = 1.50, chloroform) for 95% ee

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 30.6 min, T_{minor} = 21.3 min, ee = 95%.

2.7.3.5 Naphthalene-1,8-diamido (dan) derivative 2-29



2-29

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-29** (87% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.00 (dd, *J* = 8.4, 0.9 Hz, 2H), 6.30 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.83-5.74 (m, 3H), 5.06-4.94 (m, 2H), 3.66 (s, 3H), 2.44 (m, 2H), 2.12 (m, 2H), 1.41-1.62 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.0, 138.3, 136.3, 127.5, 119.7, 117.6, 115.0, 105.7, 51.7, 36.3, 33.0, 30.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

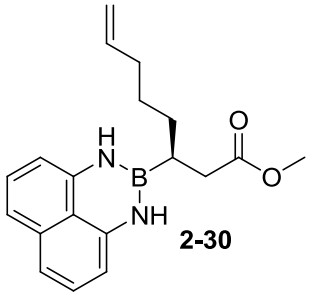
IR (Microscope, cm^{-1}) 3394, 3055, 2950, 2918, 2850, 1723, 1629, 1602, 1510.

HRMS (ESI) for $C_{18}H_{21}BN_2O_2$: calcd. 309.1772; found 309.1765.

$[\alpha]_D^{20}$: +1.6 (c = 2.44, chloroform) for 98% ee

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minutes, λ = 250 nm, T_{major} = 37.1 min, T_{minor} = 23.1 min, ee = 98%.

2.7.3.6 Naphthalene-1,8-diamido (dan) derivative 2-30



2-30

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-30** (88% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.2, 7.3 Hz, 2H), 6.99 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.29 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.80-5.72 (m, 3H), 5.02-4.92 (m, 2H),

3.65 (s, 3H), 2.42 (m, 2H), 2.05 (m, 2H), 1.44 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 141.0, 138.5, 136.3, 127.5, 119.7, 117.5, 114.8, 105.7, 51.7, 36.4, 33.9, 31.2, 28.2. (The boron-bound carbon was not detected due to quadrupolar relaxation)

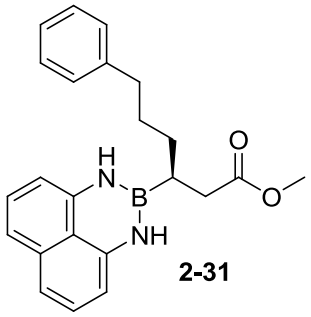
IR (Microscope, cm^{-1}) 3394, 3055, 2975, 2924, 2853, 1723, 1629, 1602, 1501.

HRMS (ESI) for $C_{19}H_{23}BN_2O_2$: calcd. 322.1853; found 322.1856.

$[\alpha]_D^{20}$: +4.2 (c = 3.71, chloroform) for 96% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 30.8 min, T_{minor} = 23.3 min, ee = 96%.

2.7.3.7 Naphthalene-1,8-diamido (dan) derivative 2-31



2-31

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-31** (88% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.22-7.16 (m, 2H), 7.10 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.02 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.29 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.70 (br s, 2H), 3.67 (s, 3H), 2.64(m, 2H), 2.44 (m, 2H), 1.71 (m, 2H), 1.48 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 142.2, 140.9, 136.3, 128.4, 128.3, 127.5, 125.8, 119.7, 117.5, 105.8, 51.7, 36.4, 36.0, 31.1, 30.6. (The boron-bound carbon was not detected due to quadrupolar relaxation)

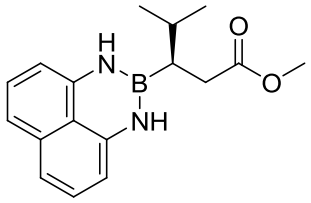
IR (Microscope, cm^{-1}) 3399, 3056, 3026, 2927, 2855, 1723, 1629, 1602, 1510.

HRMS (ESI) for $C_{23}H_{25}BN_2O_2$: calcd. 372.2009; found 372.2004.

$[\alpha]_D^{20}$: +3.3 (c = 3.57, chloroform) for 98.5% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 46.7 min, T_{minor} = 30.1 min, ee = 98.5%.

2.7.3.8 Naphthalene-1,8-diamido (dan) derivative 2-32



2-32

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-32** (89% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.2, 7.3 Hz, 2H), 6.99 (dd, *J* = 8.4, 0.9 Hz, 2H), 6.29 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.74 (s, 2H), 3.64 (s, 3H), 2.52 (dd, *J* = 16.0, 5.4 Hz, 1H), 2.39 (dd, *J* = 16.0, 9.9 Hz, 1H), 1.78 (spt, *J* = 7.3 Hz, 1H), 1.22 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.96 (d, J = 4.6 Hz.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 141.0, 136.3, 127.5, 119.7, 117.5, 105.7, 51.7, 33.9, 29.6, 22.3, 21.8.

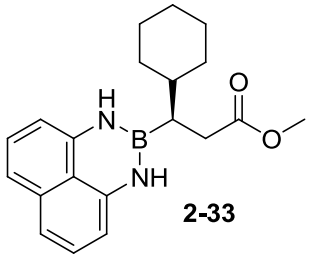
IR (Microscope, cm^{-1}) 3396, 3054, 2955, 2869, 1723, 1629, 1601, 1509.

HRMS (ESI) for $C_{17}H_{21}BN_2O_2$: calcd. 297.1772; found 297.1774.

$[\alpha]_D^{20}$: +5.8 (c = 1.58, chloroform) for 91% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 33.1 min, T_{minor} = 20.0 min, ee = 91%.

2.7.3.9 Naphthalene-1,8-diamido (dan) derivative 2-33



2-33

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-33** (81% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.1, 7.2 Hz, 2H), 6.99 (dd, *J* = 8.2, 0.7 Hz, 2H), 6.29 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.73 (br s, 2H), 3.64 (s, 3H), 2.53 (dd, *J* = 16.1, 5.3 Hz, 1H), 2.40 (dd, *J* = 16.1, 9.7 Hz, 1H), 1.58-1.83 (m, 6H), 1.32-

1.44 (m, 1H), 0.82-1.30 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 141.0, 136.3, 127.5, 119.7, 117.4, 105.7, 51.7, 39.6, 33.6, 32.9, 32.4, 26.6. (The boron-bound carbon was not detected due to quadrupolar relaxation)

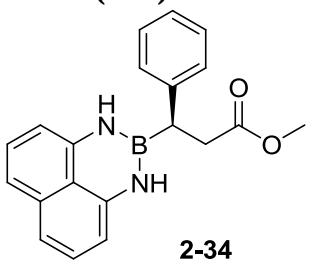
IR (Microscope, cm^{-1}) 3394, 3053, 2923, 2850, 1723, 1629, 1601, 1510.

HRMS (ESI) for $C_{20}H_{25}BN_2O_2$: calcd. 336.2009; found 336.2011.

$[\alpha]_D^{20}$: -1.8 (c = 1.98, chloroform) for 91% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 34.0 min, T_{minor} = 20.0 min, ee = 91%.

2.7.3.10 Naphthalene-1,8-diamido (dan) derivative 2-34



2-34

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 9:1) yielded **2-34** (31% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 2H), 7.27-7.17 (m, 3H), 7.08 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.00 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.25 (dd, *J* = 7.2, 1.1 Hz, 2H), 5.68 (br s, 2H), 3.68 (s, 3H), 3.00-2.74 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 142.7, 140.8, 136.3, 129.0, 127.9, 127.5, 125.7, 119.6, 117.8, 106.0, 51.9, 36.7. (The boron-bound carbon was not detected due to quadrupolar relaxation)

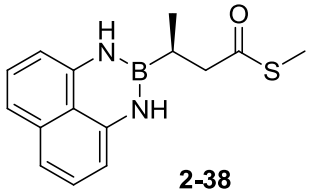
IR (Microscope, cm^{-1}) 3395, 3056, 2950, 1725, 1628, 1601, 1559, 1507.

HRMS (ESI) for $C_{20}H_{19}BN_2O_2$: calcd. 330.1536; found 330.1545.

$[\alpha]_D^{20}$: +0.7 (c = 1.35, chloroform) for 89% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 51.2 min, T_{minor} = 58.7 min, ee = 89%.

2.7.3.11 Naphthalene-1,8-diamido (dan) derivative 2-38



2-38

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-38** (82% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 8.3, 7.3 Hz, 2H), 6.99 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.30 (dd, *J* = 7.2, 1.0 Hz, 2H), 5.70 (br s, 2H), 2.71 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.61 (dd, *J* = 15.4, 7.1 Hz, 1H), 2.30 (s, 3H), 1.61 (sxt, *J* = 7.5 Hz, 1H), 1.08 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 141.0, 136.3, 127.6, 119.7, 117.6, 105.8, 47.8, 16.2, 11.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

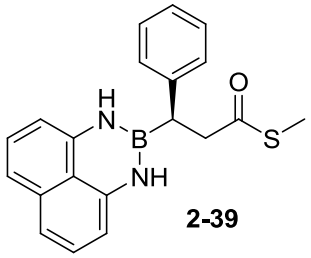
IR (Microscope, cm^{-1}) 3398, 3053, 2952, 2927, 2872, 1676, 1629, 1602, 1509.

HRMS (ESI) for $C_{15}H_{17}BN_2OS$: calcd. 284.1155; found 284.1160.

$[\alpha]_D^{20}$: +19.7 (c = 0.37, chloroform) for 98% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 39.7 min, T_{minor} = 36.8 min, ee = 98%.

2.7.3.12 Naphthalene-1,8-diamido (dan) derivative 2-39



2-39

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-39** (80% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 7.27-7.18 (m, 3H), 7.07 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.4, 1.0 Hz, 2H), 6.25 (dd, *J* = 7.1, 1.1 Hz, 2H), 5.64 (br s, 2H), 3.15-3.00 (m, 3H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 142.3, 140.8, 136.3, 129.0, 127.9, 127.5, 126.1, 119.6, 117.8, 106.0, 46.2, 11.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

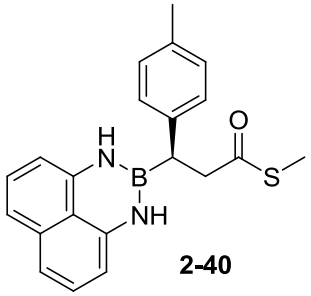
IR (Microscope, cm^{-1}) 3404, 3054, 3027, 2978, 2928, 1678, 1629, 1601, 1508.

HRMS (ESI) for $C_{20}H_{19}BN_2OS$: calcd. 346.1311; found 346.1314.

$[\alpha]_D^{20}$: –16.3 (c = 0.92, chloroform) for 91% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 23.5 min, T_{minor} = 27.1 min, ee = 91%.

2.7.3.13 Naphthalene-1,8-diamido (dan) derivative 2-40



2-40

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-40** (62% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.05 (m, 6H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.25 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.65 (br s, 2H), 3.12-2.95 (m, 3H), 2.35 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 140.8, 139.1, 136.3, 135.6, 129.7, 127.8, 127.5, 119.6, 117.7, 106.0, 46.3, 21.0, 11.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2.

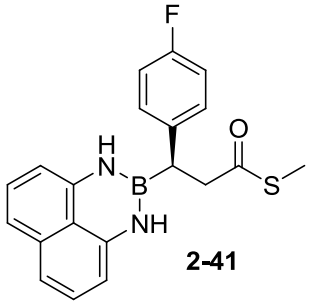
IR (Microscope, cm^{-1}) 3403, 3052, 2926, 1678, 1628, 1600, 1506.

HRMS (ESI) for $C_{20}H_{19}BN_2OS$: calcd. 360.1468; found 360.1470.

$[\alpha]_D^{20}$: –12.7 (c = 2.25, chloroform) for 82% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 20.5 min, T_{minor} = 23.3 min, ee = 81%.

2.7.3.14 Naphthalene-1,8-diamido (dan) derivative 2-41



2-41

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-41** (80% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.00 (m, 8H), 6.26 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.60 (br s, 2H), 3.14-2.95 (m, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 161.3 (d, *J* = 245.0 Hz), 140.6, 137.8 (d, *J* = 3.3 Hz), 136.3, 129.4 (d, *J* = 7.9 Hz), 127.5, 119.6, 118.0, 115.8 (d, *J* = 21.2 Hz), 106.1, 46.3, 11.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –117.3.

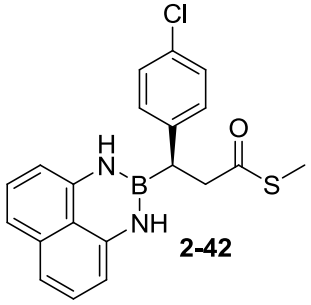
IR (Microscope, cm^{-1}) 3419, 3399, 3054, 2929, 1679, 1629, 1602, 1507.

HRMS (ESI) for $C_{20}H_{19}BN_2OS$: calcd. 364.1217; found 364.1227.

$[\alpha]_D^{20}$: –16.2 (c = 2.62, chloroform) for 95% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 25.4 min, T_{minor} = 30.3 min, ee = 95%.

2.7.3.15 Naphthalene-1,8-diamido (dan) derivative 2-42



2-42

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc =

19:1) yielded **2-42** (65% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 2H), 7.21 (m, 2H), 7.07 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.00 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.26 (dd, *J* = 7.2, 0.9 Hz, 2H), 5.58 (br s, 2H), 3.12-2.90 (m, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 140.7, 140.6, 136.2, 131.9, 129.3, 129.1, 127.5, 119.6, 118.0, 106.1, 46.0, 11.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2.

IR (Microscope, cm^{-1}) 3417, 3055, 2928, 1678, 1629, 1602, 1511.

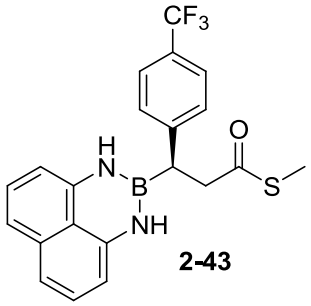
HRMS (ESI) for $C_{20}H_{19}BN_2OS$: calcd. 380.0921; found 380.0929.

$[\alpha]_D^{20}$: –1.8 (c = 1.42, chloroform) for 91% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 366 nm, T_{major} = 27.7 min, T_{minor} = 34.7 min, ee = 91%.*

* The racemic sample prepared from *rac*-BINAP did not react completely and the product synthesized could not be separated from the starting material since they show up on the same TLC spot. Thus, a starting material peak was observed in the HPLC spectrum for the racemic sample.

2.7.3.16 Naphthalene-1,8-diamido (dan) derivative 2-43



2-43

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-43** (50% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.08 (m, 2H), 7.03 (m, 2H), 6.27 (d, *J* = 7.2, 2H), 5.59 (br s, 2H), 3.20-3.08 (m, 3H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 146.5, 140.4, 136.2, 128.2, 127.5, 125.9 (q,

J = 3.7 Hz), 124.2 (q, *J* = 272 Hz), 119.6, 118.1, 106.2, 45.6, 11.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.7.

IR (Microscope, cm^{-1}) 3398, 3054, 2929, 1677, 1629, 1602, 1508.

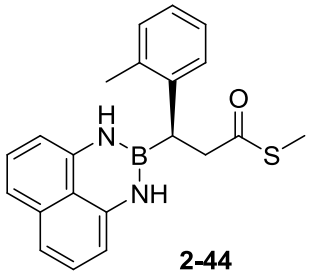
HRMS (ESI) for $C_{20}H_{19}BN_2OS$: calcd. 414.1185; found 414.1186.

$[\alpha]_D^{20}$: –1.9 (c = 1.37, chloroform) for 92.5% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 28.1 min, T_{minor} = 37.7 min, ee = 92.5%.*

* The racemic sample prepared from *rac*-BINAP did not react completely and the product synthesized could not be separated from the starting material since they show up on the same TLC spot. Thus, a starting material peak was observed in the HPLC spectrum for the racemic sample.

2.7.3.17 Naphthalene-1,8-diamido (dan) derivative 2-44



2-44

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-44** (46% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.10 (m, 4H), 7.07 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 2H), 6.23 (dd, *J* = 7.2, 1.2 Hz, 2H), 5.61 (br s, 2H), 3.24-3.05 (m, 3H), 2.34 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 140.8, 140.7, 136.2, 135.9, 127.5, 126.7, 126.6, 126.0, 119.6, 117.8, 106.0, 45.7, 20.3, 11.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

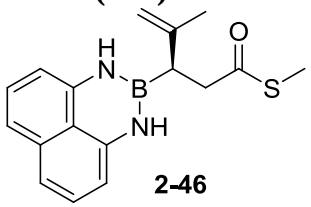
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3.

IR (Microscope, cm^{-1}) 3412, 3054, 2928, 1679, 1629, 1600, 1504.

HRMS (ESI) for $C_{20}H_{19}BN_2OS$: calcd. 360.1468; found 360.1474.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T = 17.5 min and 21.9 min, ee = 0%.

2.7.3.18 Naphthalene-1,8-diamido (dan) derivative 2-46



2-46

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate addition. Flash column chromatography (hexanes/EtOAc = 19:1) yielded **2-46** (54% yield) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 8.2, 7.3 Hz, 2H), 7.00 (dd, *J* = 8.2, 0.9 Hz, 2H), 6.29 (dd, *J* = 7.2, 1.0 Hz, 2H), 5.75 (s, 2H), 4.89 (m, 1H), 4.72 (s, 1H), 2.91 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.81 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.40 (t, J = 7.7 Hz, 1H), 2.30 (s, 3H), 1.79 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 146.6, 140.9, 136.3, 127.6, 117.8, 109.7, 106.0, 44.3, 23.7, 11.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

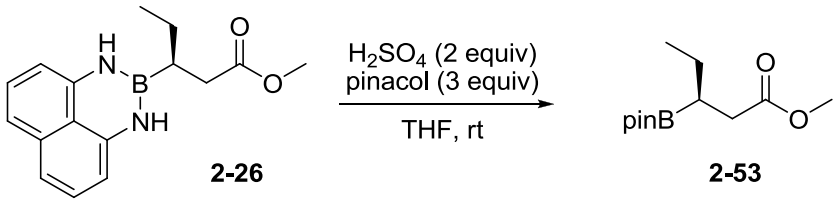
IR (Microscope, cm^{-1}) 3401, 3054, 2969, 2929, 1681, 1629, 1602, 1505.

HRMS (ESI) for $C_{17}H_{19}BN_2OS$: calcd. 310.1311; found 310.1315.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T = 70.4 and 76.3 min, ee = 0%.

2.7.4 Transformations to other protected boronates

2.7.4.1 Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (2-53)



2-26 **2-53**

To a stirred mixture of **2-26** (127 mg, 0.500 mmol) in THF was added 2 M H_2SO_4 (1.0 mL, 2.0 mmol) and pinacol (177 mg, 1.50 mmol) sequentially. The reaction was stirred for 24 h at room temperature before being diluted with the addition of water (10 mL). The mixture was then extracted by diethyl ether (3 x 10 mL), dried

over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (hexane/EtOAc = 19:1) to give pure **2-53** (98.0 mg, 90%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 2.39 (d, *J* = 6.2 Hz, 1H), 2.37 (d, *J* = 4.2 Hz, 1H), 1.23-1.55 (m, 3H), 1.22 (s, 6 H), 1.20 (s, 6H), 0.89 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 83.1, 51.4, 35.3, 24.8, 23.6, 13.2. (The boron-bound carbon was not detected due to quadrupolar relaxation)

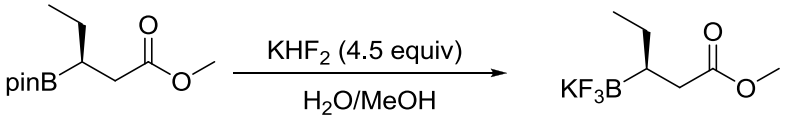
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8.

IR (Microscope, cm^{-1}) 2978, 2961, 2934, 2876, 1739.

HRMS (ESI) for $C_{12}H_{23}BO_4$: calcd. 242.1690; found 242.1697.

$[\alpha]_D^{20}$: +14.1 (c = 1.63, chloroform).

2.7.4.2 Potassium trifluoro(1-methoxy-1-oxopentan-3-yl)borate (2-55)



2-53 **2-55**

To a stirred solution of **2-53** (1.00 g, 4.10 mmol) in methanol (8.0 mL) was added a solution of KHF_2 (1.60 g, 20.5 mmol) in H_2O (5.0 mL). The mixture was stirred for 1 hour at room temperature. The reaction mixture was then concentrated *in vacuo*, and washed with hot acetone (3 × 20 mL). The acetone fractions were then filtered and concentrated *in vacuo* to give the crude product. The solid was further washed with hexane and diethyl ether to give trifluoroborate salt **2-55** (871 mg, 95%) as a white solid.

^{1}H NMR (400 MHz, acetone-d_6) δ 4.90 (s, 3H), 3.57 (dd, *J* = 14.0, 6.9 Hz, 1H), 3.40 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.76 (m, 1H), 2.51 (m, 1H), 2.20 (t, *J* = 7.3 Hz, 3H), 2.04 (m, 1H).

^{13}C NMR (100 MHz, acetone-d_6) δ 177.7, 50.9, 36.8, 24.7, 13.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, acetone-d_6) δ 5.3.

IR (Microscope, cm^{-1}) 2955, 2937, 2917, 2856, 1727.

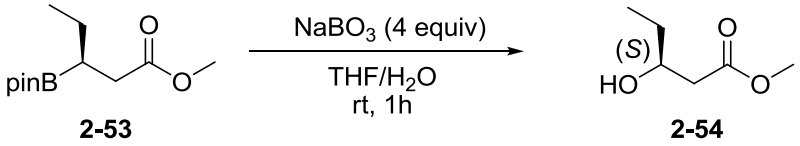
HRMS (ESI) for $C_6H_{11}BF_3KO_2$: calcd. 183.0811; found 183.0808.

$[\alpha]_D^{20}$: –7.2 (c = 0.47, chloroform).

M. P. 113 – 115 °C.

2.7.5 Determination of absolute stereochemistry

2.7.5.1 (*S*)-Methyl 3-hydroxypentanoate (2-54)



2-53 **2-54**

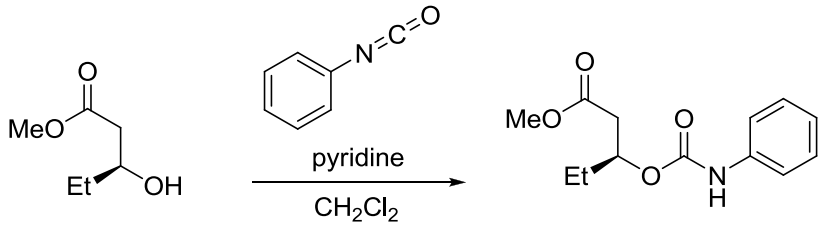
The title alcohol was prepared independently using the reported procedure (92%).[32]

The characterization data for this compound matched that of a previous report.[27]

The $[\alpha]_D^{20}$ of this compound was measured to be +28.9 (c = 0.91, chloroform), opposite to the reported for the (R)-isomer (–37.2, c = 1.00, chloroform). Thus, this proves that the compounds synthesized using our procedure from (*R*)-Tol-BINAP as the ligand have the *S*-configuration on the stereogenic carbon.

2.7.6 Enantiomeric Excess Measurement of the Oxidized Product

2.7.6.1 (*S*)-Methyl 3-(phenylcarbamoyloxy)pentanoate (2-10)



2-54 **2-10**

To a stirred solution of alcohol **2-54** (40 mg, 0.36 mmol) in dichloromethane (1.0 mL) at 0 ºC was added pyridine (40 µL, 0.54 mmol) followed by phenylisocyanate (57 µL, 0.71 mmol). The mixture was stirred overnight while being allowed to reach room temperature. It was diluted with water and the water layer was extracted with dichloromethane (3 × 5.0 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography to yield **2-10** (28 mg, 37%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 2H), 7.35-7.25 (m, 2H), 7.06 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.24 (br s, 1H), 5.16 (m, 1H), 3.69 (s, 3H), 2.64 (m, 2H), 1.72 (m, 2H), 0.97 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 152.9, 137.8, 129.0, 123.2, 118.6, 51.8, 38.8, 27.2, 22.1, 9.4.

IR (Microscope, cm^{-1}) 3324, 3060, 2978, 2935, 2881, 1733, 1599, 1542, 1501

HRMS (ESI) for $C_{13}H_{17}NO_4$: calcd. 251.1158; found 251.1157.

$[\alpha]_D^{20}$: – 0.9 (c = 1.16, chloroform) for 96% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 17.2 min, T_{minor} = 22.3 min, ee = 96%.

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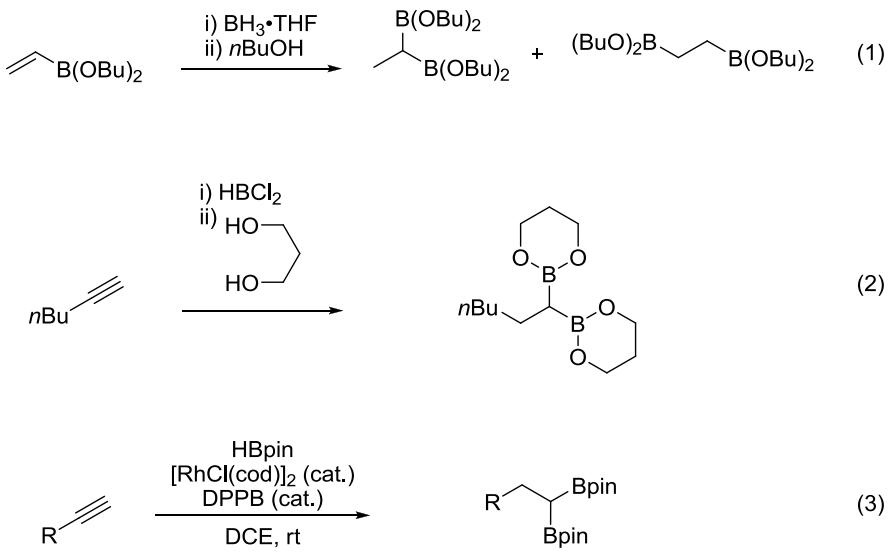
Chapter 3

Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds

3.1 Introduction

3.1.1 Preparation of *gem*-polyboron compounds

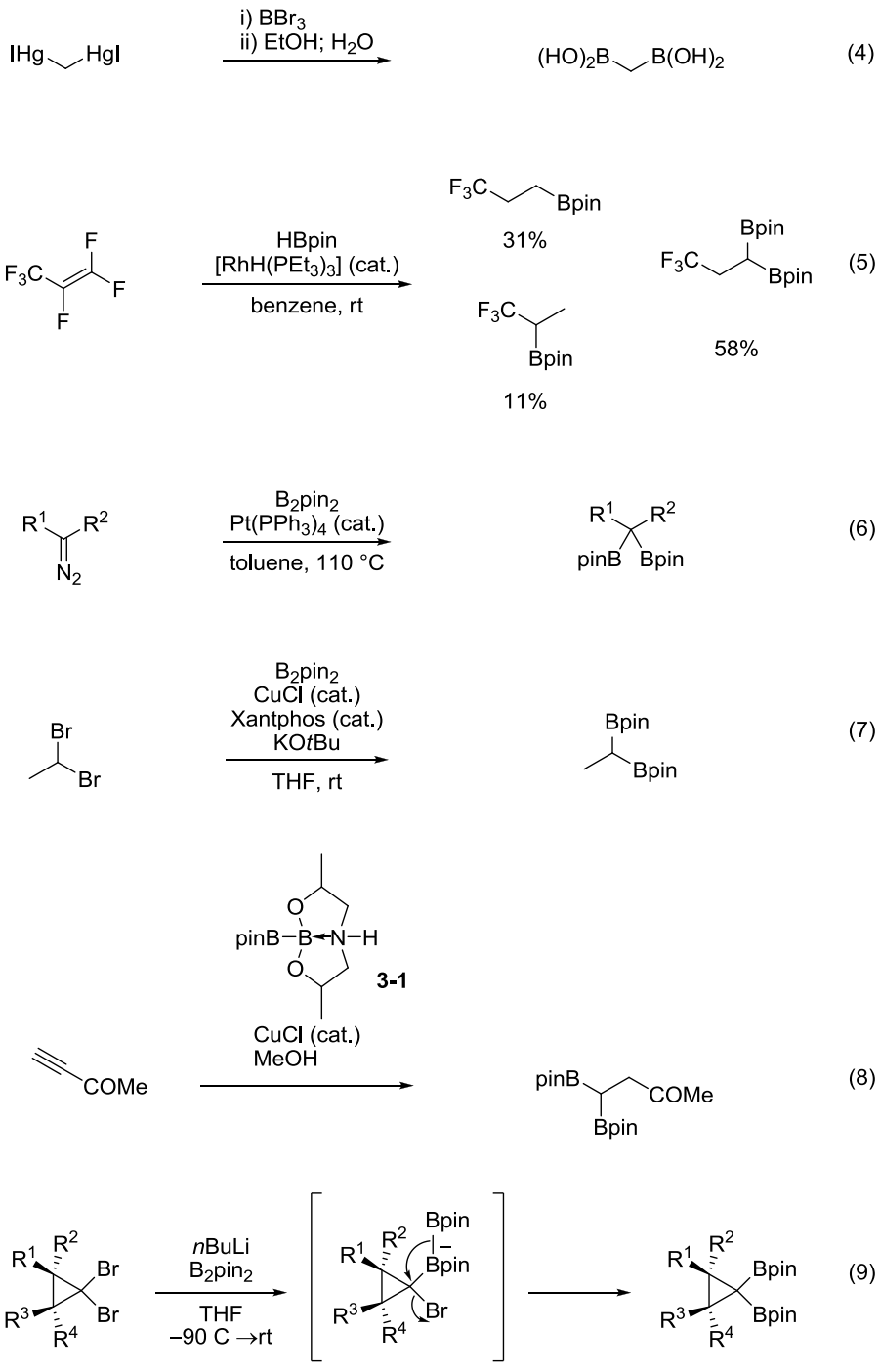
Due to the unique reactivity associated with 1,1-organodimetallics, there is significant interest in synthesizing these compounds.[1] *gem*-Polyboronates are especially attractive among this class of compounds because of the broad scope of chemical transformations that can be achieved with the boronyl functionality. The presence of extra boronyl groups on the same carbon can serve to alter the reactivity of the first boronate, allowing for a different reactivity to be observed in comparison with normal organoboronates. Once the first boron group is transformed to a different functionality, the remaining boronates can undergo various chemical transformations, as discussed in Chapter 1, to a variety of different synthetically valuable compounds. As a result, these compounds can also be viewed as attractive synthetic templates for diversity oriented synthesis (DOS). In 1961, a 1,1-diboron compound was first synthesized *in-situ* by the Brown Group through hydroboration of acetylenes.[2] The 1,1-diborane, due to its instability, was directly oxidized to aldehydes. The first isolation of this type of compounds was accomplished by Matteson and coworkers, where a mixture of 1,1-diboronyl and 1,2-diboronyl compounds could be synthesized and characterized (Equation 1, Scheme 3-1).[3] In another example, regioselective hydroboration of alkynes could be performed with dichloroborane, a reactive hydroboration reagent generated *in-situ* from silane and trichloroborane, to afford a 1,1-diboronate as a single regioisomer (Equation 2, Scheme 3-1).[4] Recently, Shibata and coworkers developed a modern rhodium-catalyzed hydroboration protocol to successively add two boronyl units to alkynes regioselectively (Equation 3, Scheme 3-1).[5] The reaction is quite general, tolerating different functional groups to afford the desired 1,1-diboron products with moderate to good yields.



Scheme 3-1: Preparation of 1,1-diboron compounds through hydroboration.

In addition to hydroboration, other methods have also been developed to synthesize 1,1-diboron compounds. Matteson and coworkers made 1,1-diboronic acids through nucleophilic displacement of boron tribromide with dimercuric iodides followed by hydrolysis (Equation 4, Scheme 3-2).[6] Braun and coworkers discovered that borylation of hexafluoropropene through C−F activation is also feasible, although a significant amount of undesired regioisomers was also observed (Equation 5, Scheme 3-2). [7] Another alternative approach for synthesizing 1,1-diboron compounds was to employ a carbenoid insertion into the B−B bond, as demonstrated by Srebnik and coworkers.[8] The platinum catalyst first undergoes oxidative addition into the diboron reagent, before insertion and reductive elimination can occur to afford the desired 1,1-diboron product (Equation 6, Scheme 3-2). A similar approach is also applicable to tosylhydrazones, as illustrated by the Wang Group. [9] Recently, a direct displacement of *gem*-dibromides to *gem*-diboronates was performed by the Ito Group.[10] Under copper-catalyzed conditions with Xantphos as the ligand and KO*t*Bu as the base, the 1,1-diboron adduct could be synthesized with a good yield (Equation 7, Scheme 3-2). In this coupling reaction, the base is used to activate the diboron reagent, bis(pinacolato) diboron, which then transmetalates with CuCl to give the active nucleophilic CuBpin catalyst. A similar Cu-catalyzed borylation

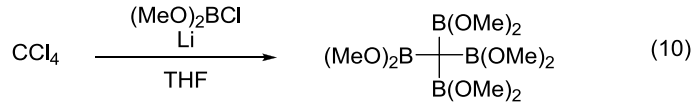
approach was employed by the Santos Group for the addition of boronyl groups to 3-butyne-2-one (Equation 8, Scheme 3-2).[11] They discovered that when sp^3-sp^2 hybridized diboron **3-1** was used as the borylating reagent, the usual pre-

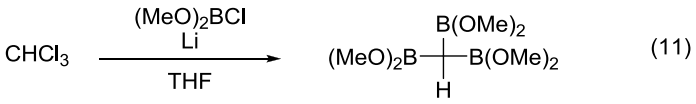


Scheme 3-2: Other approaches for synthesizing 1,1-diboron compounds.

activation from base was unnecessary and the reaction could be performed without any base or ligand to give the desired product with a good yield (Equation 8, Scheme 3-2). In addition to acyclic 1,1-diboron compounds, the Shimizu Group has also shown that diborylations can be applied to *gem*-dibromo cyclopropanes to give 1,1-diborylated products (Equation 9, Scheme 3-2).[12] Halogen-lithium exchange followed by nucleophilic attack of the diboron reagent affords the ate-complex. 1,2-Rearrangement of the boryl group then affords the observed 1,1-diborylated cyclopropane product.

Higher order *gem*-polyboronates are also known, and were prepared by the Matteson group back in the 1960s. Treatment of carbon tetrachloride or chloroform with lithium *in-situ* generated nucleophilic organolithium species that could be trapped by boron electrophiles. Sequential borylation through this pathway then yielded 1,1,1,1-tetraboronyl methane or 1,1,1-triboronyl methane (Equations 10 and 11, Scheme 3-3).[13]



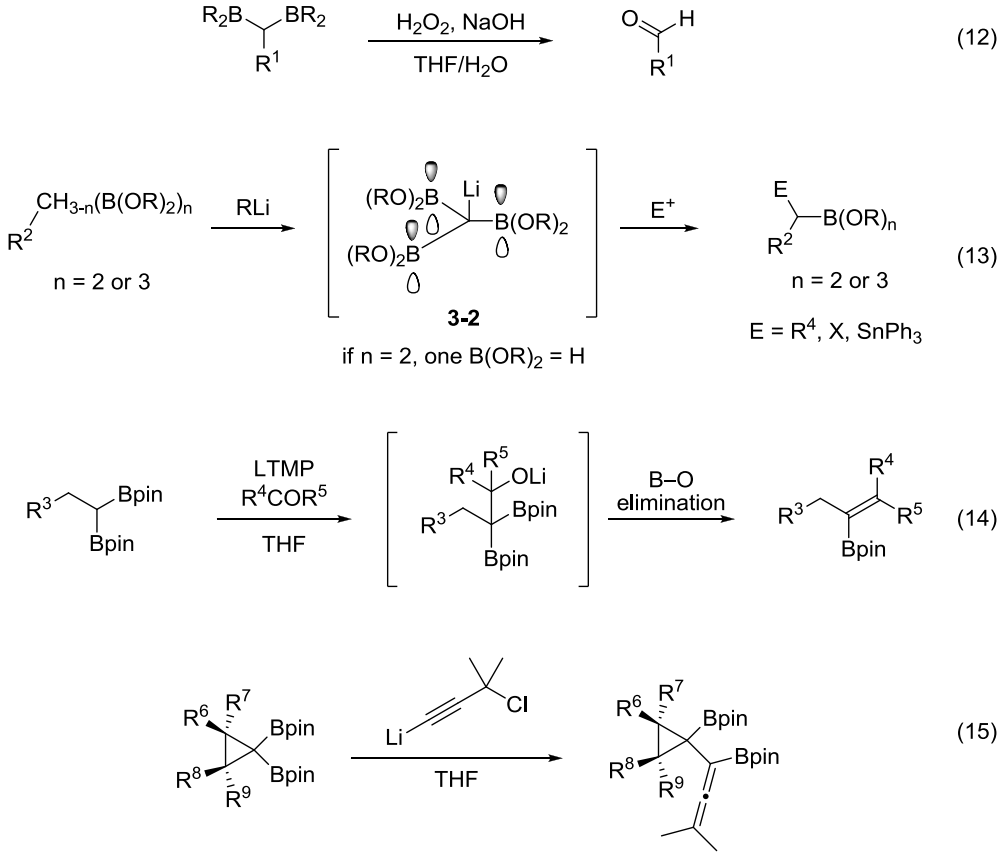


Scheme 3-3: Syntheses of 1,1,1-triboronyl or 1,1,1,1-tetraboronyl methane.

3.1.2 Applications of *gem*-polyboronated compounds

In spite of their low availability, *gem*-polyboronated compounds have been demonstrated to have intriguing properties through different chemical transformations. Standard oxidation of 1,1-diboranes affords aldehydes as products (Equation 12, Scheme 3-4). This oxidation protocol was used often in the early days to confirm the presence of 1,1-diboron compounds.[2] Due to the empty *p*-orbitals of boron atoms on the same carbon, the proton on the carbon becomes relatively acidic. Matteson and coworkers demonstrated that with various

organolithium bases, these α-protons are readily deprotonated to give highly stable organolithium intermediates **3-2**. Trapping of organolithium species **3-2** with different electrophiles then afforded various adducts.[14] Alkyl halides, halogens, and organotin electrophiles can all react effectively with **3-2** (Equation 13, Scheme 3-5). When the electrophile is an aldehyde or a ketone, however, the alkoxide intermediate does not get protonated to afford the anticipated alcohol product. Instead, B−O elimination can occur stereoselectively to give the tri- or tetra-substituted alkenes in a stereospecific manner (Equation 14, Scheme 3-4). This type of addition/elimination sequence was first discovered by the Matteson Group,[15] and generalized recently by the Shibata Group.[16] In addition to deprotonation reactions, these 1,1-diboron compounds are also susceptible to Matteson homologation with a propargyl chloride.[12] As shown in Equation 15 (Scheme 3-4), allenyl adducts could be synthesized with efficacy

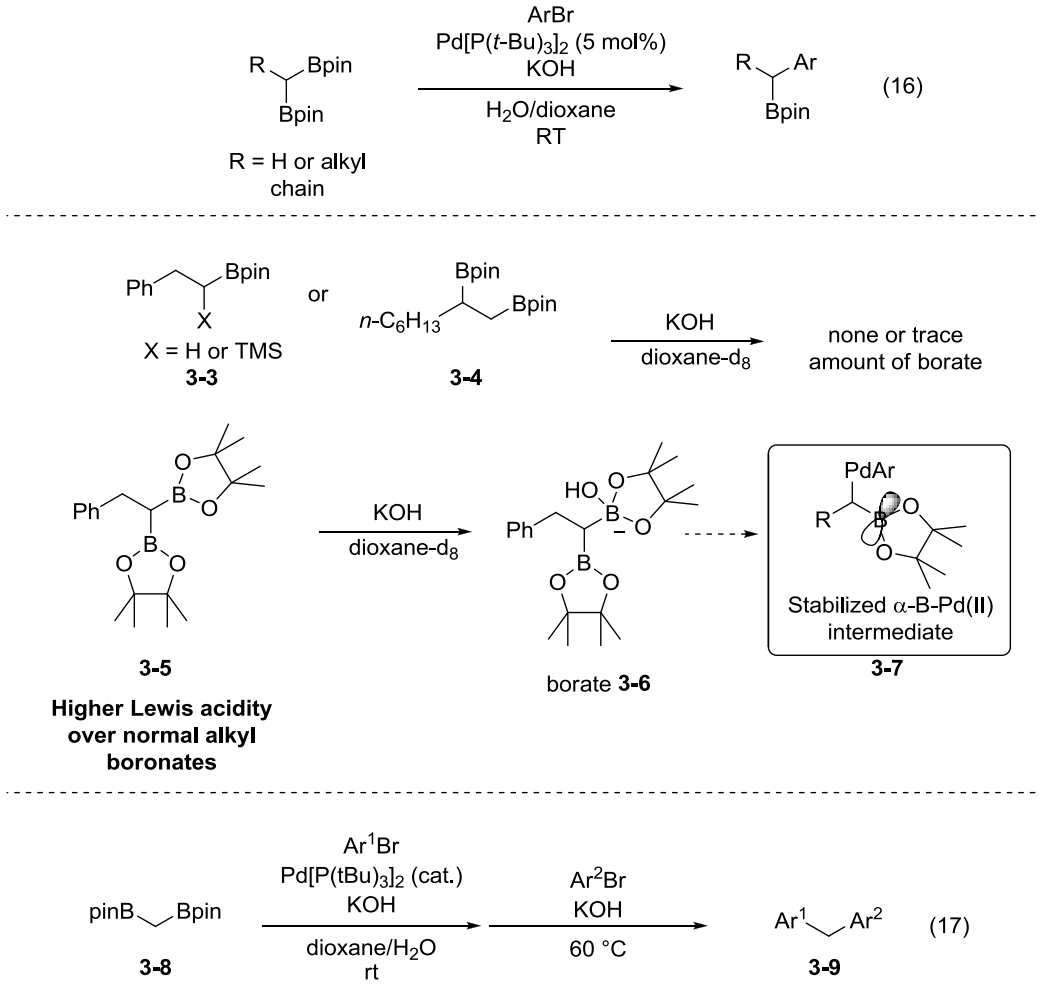


Scheme 3-4: Applications of *gem*-polyboronated compounds.

from 1,1-diboronyl cyclopropanes.

As discussed in Chapter 1, the Suzuki-Miyaura cross-coupling reaction is a powerful synthetic tool in constructing C−C bonds. Due to fast protodeboronation and slow transmetallation, however, direct cross-coupling reactions of secondary alkyl boronic acids are notoriously difficult. In order to enhance the stability of these boronic acids, various diols can be used to react with boronic acids to form more stable boronic esters. Unfortunately, the Lewis acidity dramatically decreases in this case mainly due to the increased steric bulk surrounding the boron atom, making the transmetalation more difficult. In this regard, in 2010 Shibata and coworkers examined a system where one of the carbon substituents is another boron pinacolate (Equation 16, Scheme 3-5).[17] Since boron atoms are known to stabilize α-carbanions due to the empty *p*-orbitals on boron, the installation of an extra boron pinacolate unit on the same carbon atom significantly enhances the Lewis acidity for one of the boron atoms. To confirm that the additional boron pinacolate unit is indeed responsible for the spontaneous borate formation, the Shibata Group performed NMR experiments of various substrates with KOH. The authors discovered that when the second boronate is replaced with either hydrogen or trimethylsilane (**3-3**), no borate formation was observed. Furthermore, when one of the two boron atoms is shifted to the β-position (**3-4**), only a trace amount of borate was formed, showing the importance of having a second boronyl unit on the same carbon atom. Not only was the second boronyl group responsible for enhancing the Lewis acidity of the first boron atom, but according to DFT calculations, it also stabilizes the α-B-Pd(II) intermediate **3-7** to dramatically improve the rate of transmetallation.[17] Indeed, when these 1,1-diboronylalkanes were reacted with various aryl bromides in Pd-catalyzed Suzuki-Miyaura cross-coupling reactions, a variety of cross-coupled products were obtained in excellent yields under very mild conditions (Scheme 3-5). Recently, the same group expanded their methodology to cross-couple 1,1-diboronyl methane sequentially to form pharmaceutically important unsymmetrical diarylmethane core structures (Equation 17, Scheme 3-5).[18] Due to

the activation from the second boronate, the first cross-coupling could be performed at room temperature. The second cross-coupling, on the other hand, was more difficult. The authors found that by increasing the reaction temperature to 60 ℃, the second cross-couplings between the boronate and aryl bromides can be conducted efficiently to afford various unsymmetrical diarylmethanes with excellent efficiency.

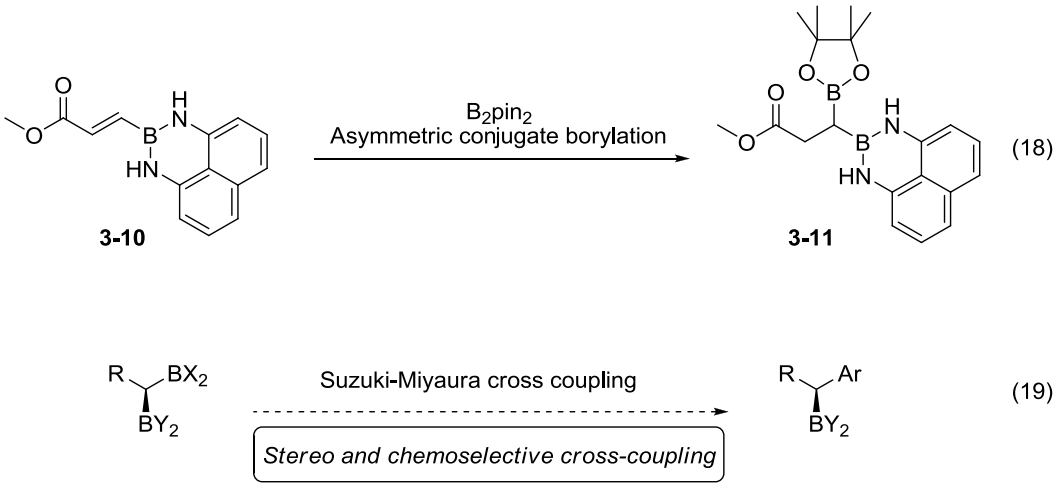


Scheme 3-5: Suzuki-Miyaura cross-couplings of 1,1-diboron compounds.

3.1.3 Objectives

In spite of their interesting properties in various chemical transformations, 1,1-diboron compounds, at the time when I started this project, were limited to achiral substrates. Aiming to explore the physical properties and synthetic utility of chiral

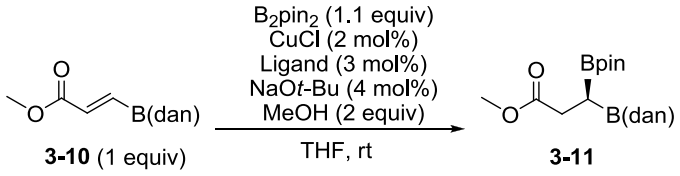
1,1-diboron compounds, the first goal of the project involved the synthesis of a 1,1-diboron compound with a stereogenic carbon bearing two different boronyl units (i.e. two different protected boronates). This goal can be accomplished potentially through asymmetric borylation reactions of substrates bearing boronate functionality (Early introduction strategy, Chapter 1).[19] One compound that could be applicable to this approach is the 3-boronyl enoate **3-8**, which was shown to be a robust substrate in asymmetric conjugate additions with organomagnesium nucleophiles (Chapter 2). Instead of conjugate addition with organometallic reagents, asymmetric conjugate borylations (Chapter 1) of enoate **3-10** could afford the desired 1,1-diboron product **3-11** enantioselectively (Equation 18, Scheme 3-6). The second half of the project would involve synthetic applications of the optically enriched 1,1-diboron compound. One main application that is especially attractive, as discussed in Chapter 1, is the chemo- and stereoselective Suzuki-Miyaura cross-coupling of these chiral 1,1-diboron compounds (Equation 19, Scheme 3-6). The enantioenriched chiral boronates synthesized through this approach would constitute another valuable route towards synthetically important chiral secondary alkyl boronates.



Scheme 3-6: Proposal for synthesizing optically enriched 1,1-diboron compounds and their subsequent applications.

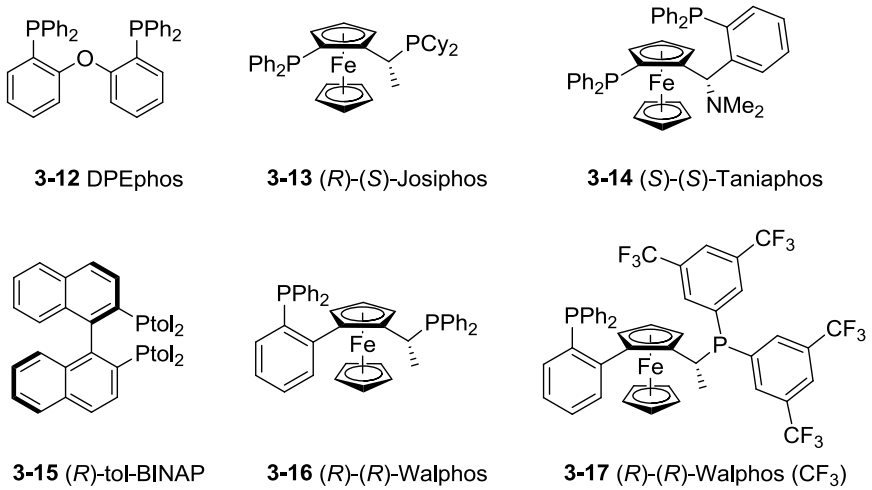
3.2 Syntheses of optically enriched 1,1-diboron compounds

Based on the previous report describing the preparation of optically enriched boronic esters via copper-catalyzed conjugate additions of organomagnesium reagents to 1,8-diaminonaphthalenyl (dan) 3-boronyl enoate **3-10** (Chapter 2),[20] I envisioned that an asymmetric conjugate borylation of **3-10** with B_2pin_2 could deliver the desired, chiral 1,1-diboronyl ester **3-11** with high enantioselectivity (Table 3-1). Upon screening known reaction conditions, the protocol developed by



Entry	Ligand	Yield (%)[a]	ee (%)[b]
1	**3-12**	90%	0%
2	**3-13**	86%	-13%
3	**3-14**	88%	0%
4	**3-15**	91%	-79%
5	**3-16**	74%	82%
6	**3-17**	88%	99%

[a] Isolated yield after column chromatography [b] Measured by chiral HPLC.



3-12 DPEphos **3-13** (*R*)-(*S*)-Josiphos **3-14** (*S*)-(*S*)-Taniaphos

3-15 (*R*)-tol-BINAP **3-16** (*R*)-(*R*)-Walphos **3-17** (*R*)-(*R*)-Walphos (CF_3)

Table 3-1: Optimization of reaction conditions for the preparation of chiral 1,1-diboron compound **3-11**.

Yun and coworkers quickly allowed access to the desired 1,1-diboron **3-11** with a good yield (Entry 1, Table 3-1), albeit with a low enantioselectivity when (*R*)-(*S*)-Josiphos **3-13** was employed as the ligand (Entry 2, Table 3-1).[19a] In order to further improve the enantioselectivity of the reaction, a more thorough evaluation of various chiral diphosphine ligands was conducted. Taniaphos **3-14** was found to be ineffective, whereas (*R*)-tol-BINAP **3-15** afforded a much improved enantiomeric excess at 79% (Entries 3-4, Table 3-1). The enantioselectivity could be improved to 82% using Walphos **3-16** (Entry 5, Table 3-1). Gratifyingly, it was found that the trifluoromethyl substituted Walphos ligand **3-17** provided the desired enantioenriched 1,1-diboron product **3-11** with 99% ee (Entry 6, Table 3-1). The mechanistic details of how the steric and electronic effects of the ligand affect the stereoselectivity are at the present time unclear. This enantioenriched compound is stable to silica column chromatography purification and could be recrystallized from hot methanol to give X-ray quality crystals. The X-ray analysis was completed by Dr. Robert McDonald from the department of chemistry at the University of Alberta.

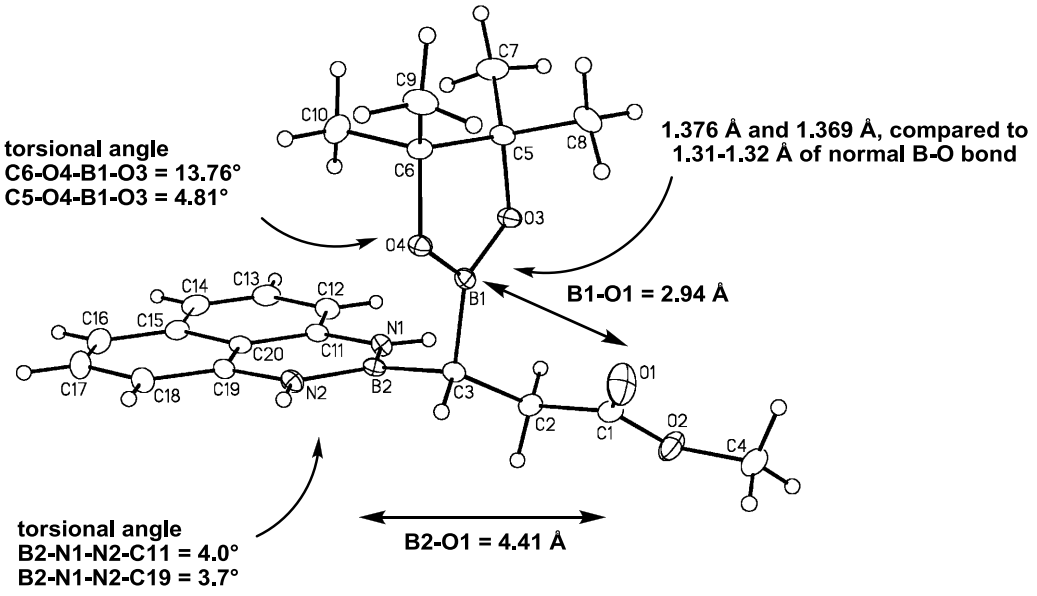
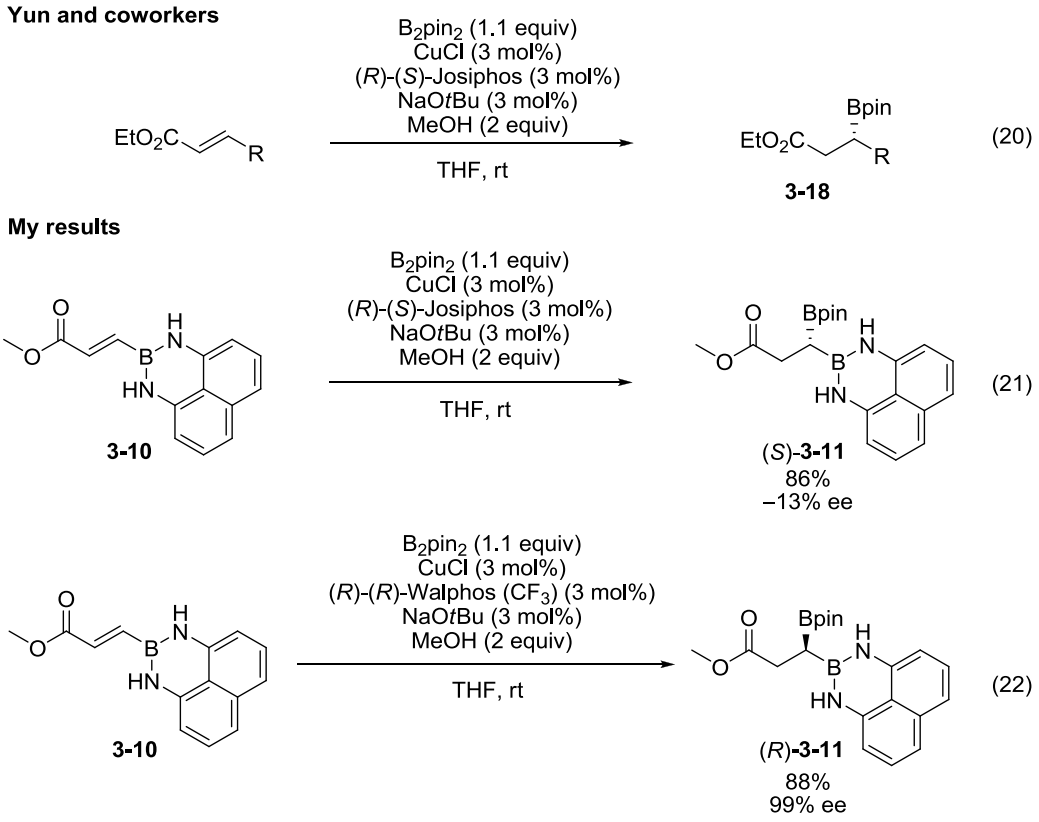


Figure 3-1: ORTEP representation of X-ray crystallographic structure of chiral 1,1-diboron **3-11**.

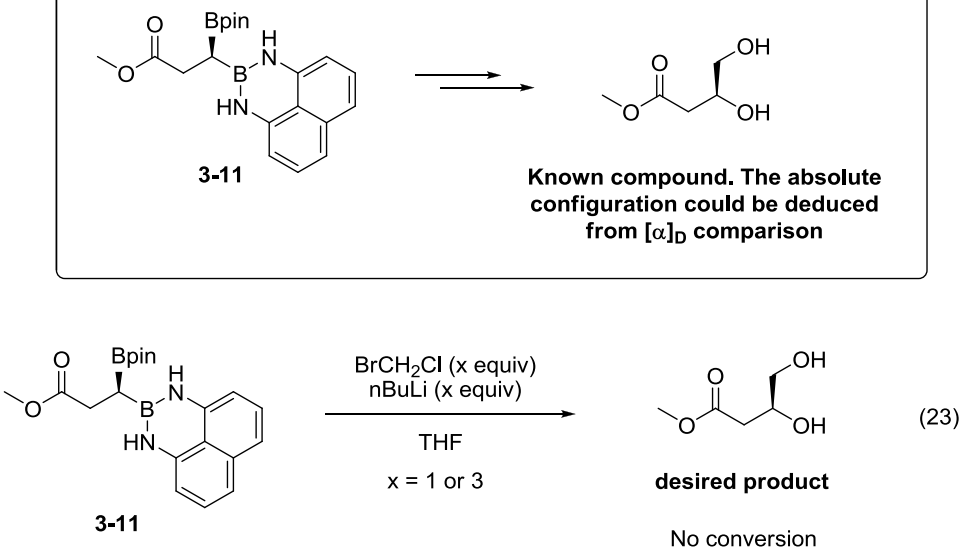
The X-ray crystallographic structure of **3-11** reveals that the carbonyl oxygen of the methyl ester is much closer to the boron atom of the pinacolate unit, with a distance of 2.94 Å, than to the boron atom of the Bdan unit with a distance of 4.41 Å (Figure 3-1). This data suggests that the boron pinacolate is coordinated with the ester, therefore is more acidic and could be the active unit participating in the subsequent Suzuki-Miyaura cross-coupling reaction. Moreover, the longer B–O bond lengths (1.376 Å and 1.369 Å) compared to standard B–O bond lengths of tricoordinate pinacol esters (usually around 1.31–1.32 Å) is indicative of a weaker π-overlap between the oxygens of the boronic ester and the boron atom in **3-11**.[21] This comparison further supports the possibility for coordination between the carbonyl oxygen of the methyl ester and the boron atom. In addition, the torsional angles of the boron pinacolate unit between C6–O4–B1–O3 and C6–O4–B1–O3 are 13.75° and 4.81°, respectively. This data suggests that the boron pinacolate is slightly distorted from planarity possibly due to the coordination of the carbonyl oxygen. On the other hand, the torsional angles for the Bdan unit, B2–N1–N2–C11 and B2–N1–N2–C19, are 4.0° and 3.7°, respectively, indicating that the Bdan unit is nearly trigonal planar. These observations and the reported inertness of the Bdan unit in cross–coupling reactions are strongly suggestive that the pinacol boronate could be cross-coupled chemoselectively.[22]

3.2.1 Determination of the absolute stereochemistry of the 1,1-diboron compound 3-11

In order to determine the stereochemical outcome of the subsequent chemical transformations of 1,1-diboron **3-11**, it is important to identify the absolute configuration of this compound. One way to determine the absolute stereochemistry of 1,1-diboron **3-11** is by analogy with previous literature studies. Based on the report published by Yun and coworkers, the borylated products were isolated with absolute configurations shown as in boronates **3-18** when **3-13** was used as the ligand (Equation 20, Scheme 3-7).[19a] As a result, if B(dan) is to be treated the same as any R group, the absolute stereochemistry of diboron **3-11** can be assigned (*S*) when ligand **3-13** was used (Equation 21, Scheme 3-7). Since the



Scheme 3-7: Determination of stereochemistry based on analogy with previous studies.



Scheme 3-8: Determination of the absolute configuration through comparison with known literature compounds.

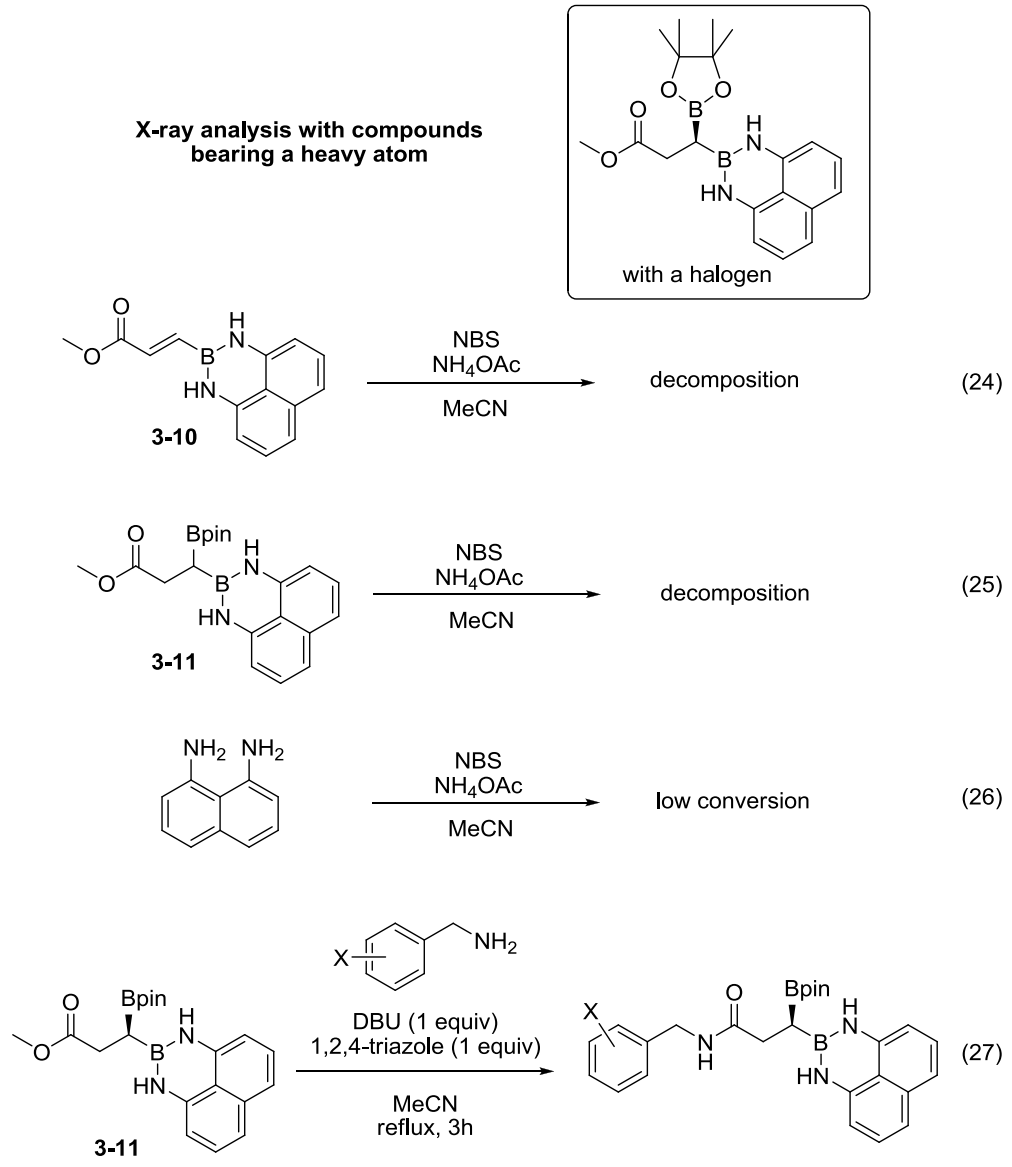
opposite enantiomer was found to be dominant through HPLC analysis when ligand **3-17** was used as the ligand, the absolute stereochemistry of 1,1-diboron **3-11** was assigned (*R*) through this analogy study (Equation 22, Scheme 3-7).

This absolute configuration assignment, however, is not convincing enough mainly due to the low enantiomeric excess observed when **3-13** was used as the ligand (Equation 21, Scheme 3-7). An alternative way of determining the absolute stereochemistry is to convert 1,1-diboron compound **3-11** to a known literature compound through chemical transformations that retain its stereochemical integrity. As discussed previously in Chapter 1, the Matteson homologation inserts methy groups into a C−B bond stereospecifically, affording products with retention of stereochemistry. Therefore, 1,1-diboron **3-11** was treated with a mixture of bromochloromethane and *n*-butyl lithium. Unfortunately, no conversion to desired product was observed, leading to the recovery of starting material **3-11** (Scheme 3-8).

A direct method to confirm the absolute configuration of 1,1-diboron **3-11** is through X-ray crystallographic analysis with incorporation of a heavy atom such as bromine or iodine into the molecule.[23] Through analysis of the structure of 1,1-diboron compound **3-11**, it ensues that a halogen can either be installed onto the aromatic naphthyl ring, or onto the ester moiety through trans-esterification or trans-amidation reactions. Since the 1,8-diaminonaphthalene moiety is electron rich, electrophilic aromatic brominations of the aromatic system were performed. Unfortunately, regardless of the compounds utilized, only complex mixtures or a low conversion of starting material were obtained (Equations 24-26, Scheme 3-9). At this point, an alternative approach where the transformation of the ester functionality to a halogenated benzyl amide was employed (Equation 27, Scheme 3-9). Preparation of these amides was straightforward;[24] however the resulting products are unstable amorphous solids that are difficult to recrystallize.

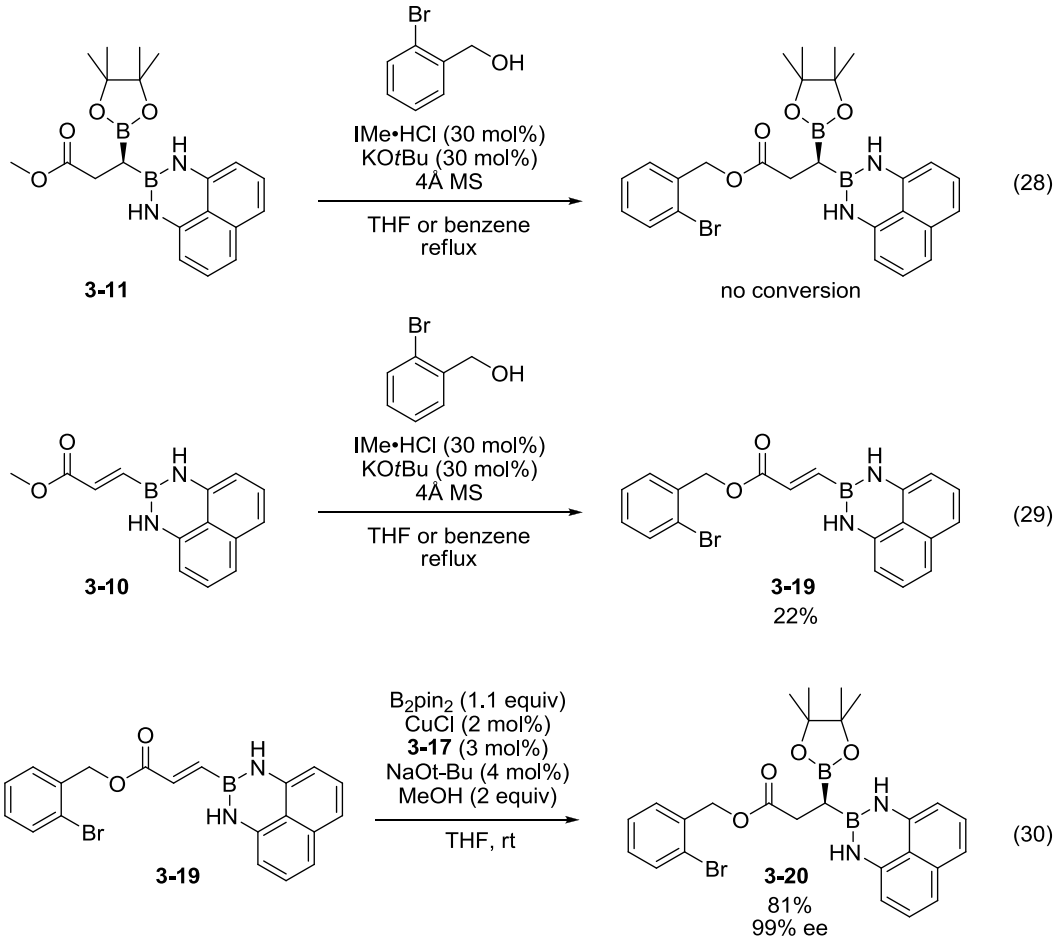
Having successfully recrystallized 1,1-diboron **3-11** from hot methanol to produce X-ray quality crystals, it was realized that the ester moiety is important for

maintaining crytallinity. Direct trans-esterification of a methyl ester, however, is notoriously difficult due both to the harsh conditions required for such a process and the reversibility of the reaction.[25] In spite of these difficulties, several NHC-catalyzed transesterification protocols have been developed and were applied to compounds **3-10** and **3-11**. By employing the method developed by Nolan and coworkers,[25] transesterification of 1,1-diboron **3-11** was unsuccessful, while the



Scheme 3-9: Synthesis of halogenated derivatives of **3-11** for X-ray crystallographic analysis.

transesterification of 3-boronyl enoate **3-10** with 2-bromobenzyl alcohol gave the desired product **3-19** with a 22% yield (Equations 28 and 29, Scheme 3-10). With this compound in hand, standard asymmetric conjugate borylation using ligand **3-17** could be conducted to afford 1,1-diboron **3-20** with a good yield and excellent enantioselectivity. Possibly due to the ester functionality, this compound could be recrystallized readily in hot methanol to give X-ray quality crystals. The absolute stereochemistry of 1,1-diboron **3-20** was assigned to be (*R*) based on X-ray crystallography (Figure 3-2). Compound **3-20** crystallized in the chiral space group *P*1. The high quality of the diffraction data and the presence of a bromine atom in the molecule allowed absolute configuration to be reliably determined via anomalous dispersion methods; the final value of the Flack absolute structure



Scheme 3-10: Synthesis of 1,1-diboron compound **3-20** for absolute configuration analysis.

parameter was 0.016(6).[23]

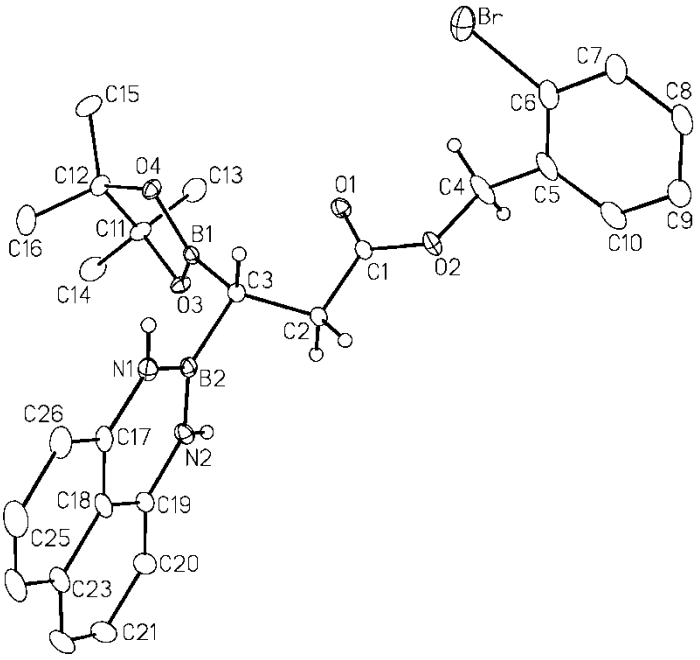


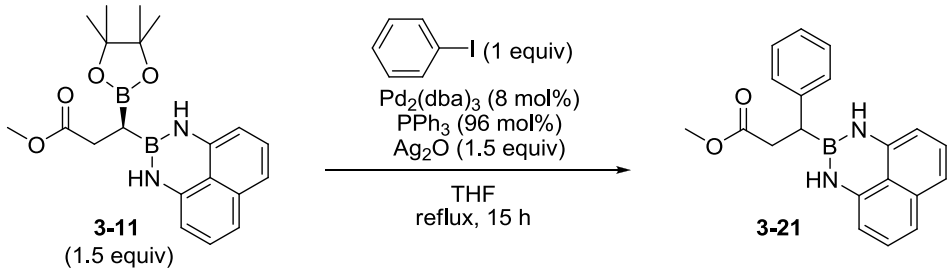
Figure 3-2: ORTEP representation of X-ray crystallographic structure of chiral 1,1-diboron **3-20**.

3.3 Suzuki-Miyaura cross-couplings of 1,1-diboron compounds

3.3.1 Initial attempts at cross-coupling 1,1-diboron 3-11

3.3.1.1 Variation of Crudden's cross-coupling conditions

As discussed previously in Chapter 1, direct, stereoselective cross-coupling of alkyl boronates is a formidable challenge in organic synthesis. Crudden and coworkers were the first group to accomplish this feat, performing cross-coupling

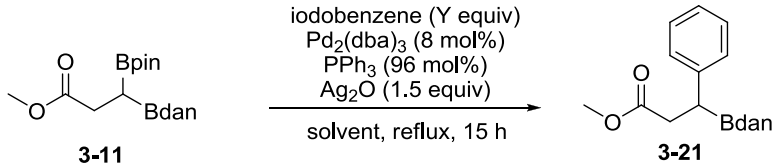


Scheme 3-11: Suzuki-Miyaura cross-coupling reaction of 1,1-diboron **3-11** under standard Crudden conditions[26].

reactions of enantioenriched secondary benzylic organoboronates with various aryl iodides to give the products with retention of stereochemistry.[26] Due to this success, the Crudden conditions were chosen as the standard cross-coupling conditions for 1,1-diboron **3-11** with iodobenzene. Under identical conditions as Crudden's protocol, the desired cross-coupled product **3-21** could be isolated with a 30% yield (Scheme 3-11). Optimization of different reaction parameters was then conducted to improve the yield of the reaction.

3.3.1.1.1 Effect of solvent and stoichiometry of starting materials

In order to improve the yield of this cross-coupling reaction, the stoichiometry of the starting materials was adjusted. In Suzuki-Miyaura cross-coupling reactions, an excess amount of the organoboronate is usually necessary due to side reactions such as protodeboronation. Indeed, when 1,1-diboron **3-11** was employed as the limiting reagent for the cross-coupling reaction, a lower yield was observed (Entry 2, Table 3-2). The effect of solvent was also examined at this stage. While toluene was found to be ineffective for this cross-coupling reaction (Entry 3, Table



Entry	X/Y	Solvent	Yield[a]
1	1.5/1	THF	30%
2	1/2	THF	10%
3	1/2	toluene	trace
4	1/2	dioxane	15%
5	1.5/1	dioxane	46%
6	1.1/1	dioxane	39%

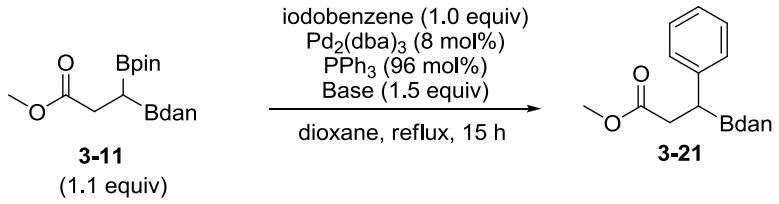
[a] Isolated yields of products after flash column chromatography.

Table 3-2: Optimization of cross-coupling conditions by changing the solvent and the stoichiometry of starting materials.

3-2), dioxane was found to be a better solvent, giving the desired product with a higher yield (Entry 4, Table 3-2). After further modifying the ratio of 1,1-diboron **3-11** versus iodobenzene, it was found that only a slight excess of 1,1-diboron compound was necessary in order to afford the desired product with a moderate yield (Entries 5-6, Table 3-2).

3.3.1.1.2 Effect of base and reaction concentration

Aiming to further enhance the yield of the cross-coupling reaction, other reaction parameters such as base and concentration were studied. Among all bases tested, only Ag_2O was effective in promoting the reaction. Other bases gave minimal product formation unless they were used in combination with Ag_2O (Entries 2-7,



Entry	Base	[ ] (PhI)	Yield[a]
1	Ag_2O	0.1 M	39%
2	Cs_2CO_3	0.1 M	No conversion
3	NaO*t*Bu	0.1 M	No conversion
4	KOH	0.1 M	No conversion
5	Et_3N	0.1 M	No Conversion
6	CsF (2 equiv) Ag_2O (1.5 equiv)	0.1 M	32%
7	K_2CO_3 (2 equiv) Ag_2O (1.5 equiv)	0.1 M	36%
8	Ag_2O	0.2 M	26%
9	Ag_2O	0.05 M	38%

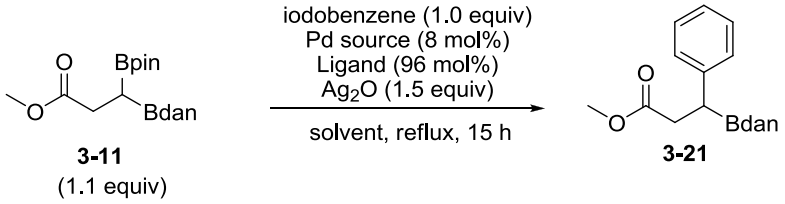
[a] Isolated yields of products after flash column chromatography.

Table 3-3: Optimization of cross-coupling conditions by varying bases and concentration.

Table 3-3). These results suggest that transmetalation is indeed the rate determining step and silver oxide is necessary to accelerate this key step to give the cross-coupled product.[27] Different reaction concentrations were also screened, and it was found that a higher concentration led to lower product yields possibly due to the lower solubility of silver oxide in the reaction medium (Entry 8, Table 3-3). A much lower concentration of 0.05 M, on the other hand, gave the product with a 38% yield, similar to what is observed in standard concentration (Entry 9, Table 3-3).

3.3.1.1.3 Effect of source of Pd and nature of ligands

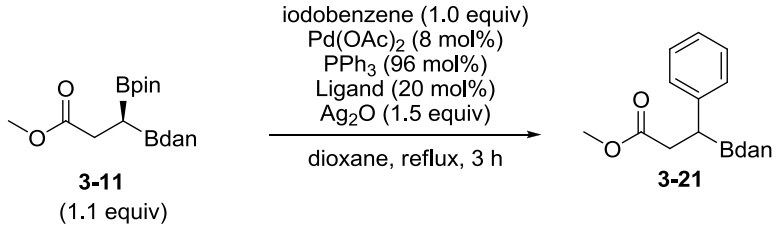
The development of more potent supporting ligands for Suzuki-Miyaura cross-couplings has been one of the focal points in improving the conditions and expanding the scope of substrates of this popular reaction. Various phosphine[28] and NHC ligands [29] have been developed over the past two decades to dramatically enhance the rate of cross-coupling. In general, electron-rich σ-donor ligands are favoured to enhance the rate of oxidative addition, while sterically



Entry	Pd source	Ligand	Yield[a]
1	$Pd(PPh_3)_4$	-	Low conversion
2	$Pd(PtBu_3)_2$	-	Low conversion
3	$Pd_2(dba)_3$	$PtBu_3$	Low conversion
4	$Pd(OAc)_2$	PPh_3	33%
5	$Pd(OAc)_2$	PPh_3	68%[b]
6	$PdCl_2(PPh_3)_2$	PPh_3	61%[b]

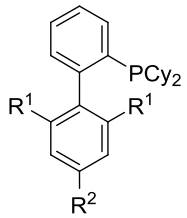
[a] Isolated yields of products after flash column chromatography. [b] The reaction was run over 30 hrs

Table 3-4: Optimization of cross-coupling conditions by testing different sources of Pd and ligands.

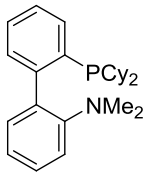


Entry	Ligand	Yield[a]	ee[b]
1	RuPhos	79%	0%
2	PCy_3	77%	0%
3	SPhos	ND	0%
4	Davephos	ND	0%
5	QPhos	ND	0%
6	XPhos	ND	0%
7	RuPhos	ND	0%[c]
8	RuPhos	ND	0%[d]
9	RuPhos	no conversion	0%[e]

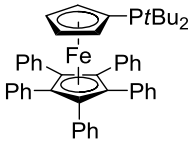
[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] In THF instead of in dioxane. [d] The reaction was performed at 50 °C. [e] PPh_3 was not added. ND = not determined



RuPhos
R^1 = O*i*Pr, R^2 = H
SPhos
R^1 = OMe, R^2 = H
XPhos
R^1 = R^2 = *i*Pr



Davephos



QPhos

Table 3-5: Ligand optimization and determination of enantiomeric excess of product **3-21**.

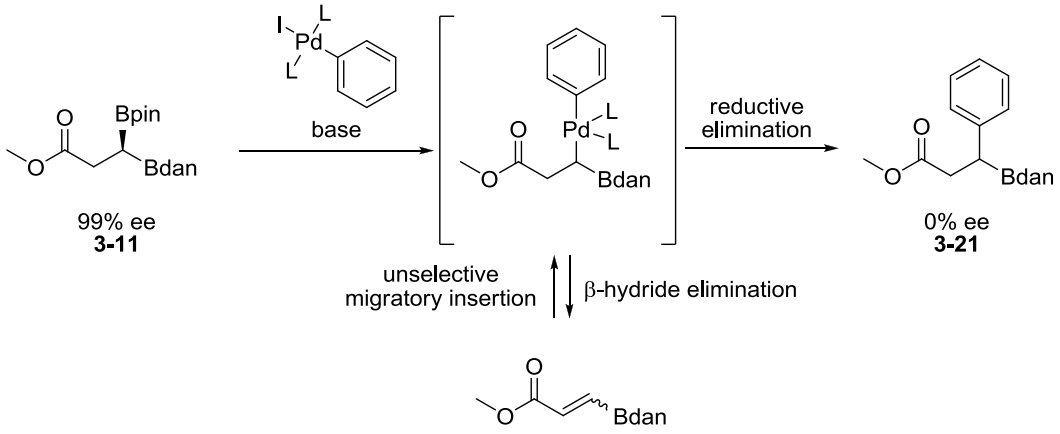
hindered ligands are necessary to improve the rate of reductive elimination and to release the cross-coupled products. In order to further enhance the rate of the cross-coupling reaction with diboron **3-11**, different Pd sources and ligands were tested. When Pd(0) sources such as $Pd(PPh_3)_4$ or $Pd(P\textit{t}Bu_3)_2$ were used, low

conversions were obtained, indicating that an excess amount of external phosphine ligands are probably necessary (Entries 1-2, Table 3-4). As observed by Crudden and coworkers, electron-rich tri-*tert*-butylphosphine was found to be inferior to triphenylphosphine. While $Pd_2(dba)_3$ or $Pd(dba)_2$ have been consistently used as the Pd(0) sources for Suzuki-Miyaura cross-coupling reactions, dba can coordinate to metal centres and attenuate the reactivity of these catalysts.[30] As a result, different Pd(II) sources that can be reduced readily *in-situ* to Pd(0) are sometimes the preferred catalyst precursors for cross-coupling reactions. When $Pd(OAc)_2$ was used as the palladium source, a low yield of the desired product was isolated under standard reaction time of 15 hours. However, by prolonging the reaction time from 15 hours to 30 hours, a much improved yield was obtained (Entries 4-5, Table 3-4). Other Pd(II) source such as $PdCl_2(PPh_3)_2$ was found to be inferior in comparison to $Pd(OAc)_2$ (Entry 6, Table 3-4).

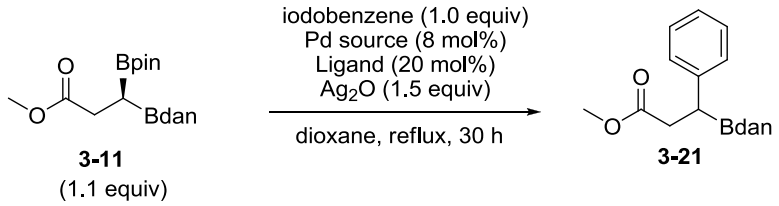
In light of a recent report from the Buchwald Group that a mixture of ligands could be used in a single cross-coupling reaction due to rapid ligand exchange, additional sources of ligands were added to triphenylphosphine (Table 3-5).[31] By adding additional electron-rich phosphine ligands such as RuPhos or tricyclohexylphosphine, the rate of the reaction increases dramatically, allowing these cross-coupling reactions to reach completion within 3 hours (Entries 1-2, Table 3-5). Unfortunately, the coupling product isolated from these runs was found to be racemic even though enantiomerically enriched 1,1-diboron compound **3-11** was used as the starting material. Other electron-rich phosphine ligands were also tested, but all of them led to racemate **3-21** (Entries 3-6, Table 3-5). Changing the solvent from dioxane to THF or lowering the reaction temperature to 50 ºC also did not improve the enantioselectivity (Entries 7-8, Table 3-5). A control reaction where triphenylphosphine was absent was also conducted. Unfortunately, in this case no conversion of the starting material was observed (Entry 9, Table 3-5).

In order to rationalize the formation of racemic product from optically enriched substrate **3-11**, it is safe to assume that one of the cross-coupling steps racemizes

the stereogenic centre. However, both transmetalation and reductive elimination are known to be stereospecific to give products with retention of stereochemistry.[32] As a result, the racemization is surmised to come from an



Scheme 3-12: Proposed mechanistic rational for observed racemization of optically enriched 1,1-diboron **3-11**.



Entry	Pd source	Ligand	Yield[a]
1	$PdCl_2dppf_2$	-	No conversion
2	$PdCl_2dppf_2$	dppf	No conversion
3	$Pd(OAc)_2$	dppf	No conversion
4	$Pd(OAc)_2$	*rac*-BINAP	No conversion
5	$Pd(OAc)_2$	dppf	No conversion[b]
6	$Pd(OAc)_2$	dppf	No conversion[c]

[a] Isolated yields of products after flash column chromatography. [b] The reaction was performed in THF. [c] The reaction was performed in toluene.

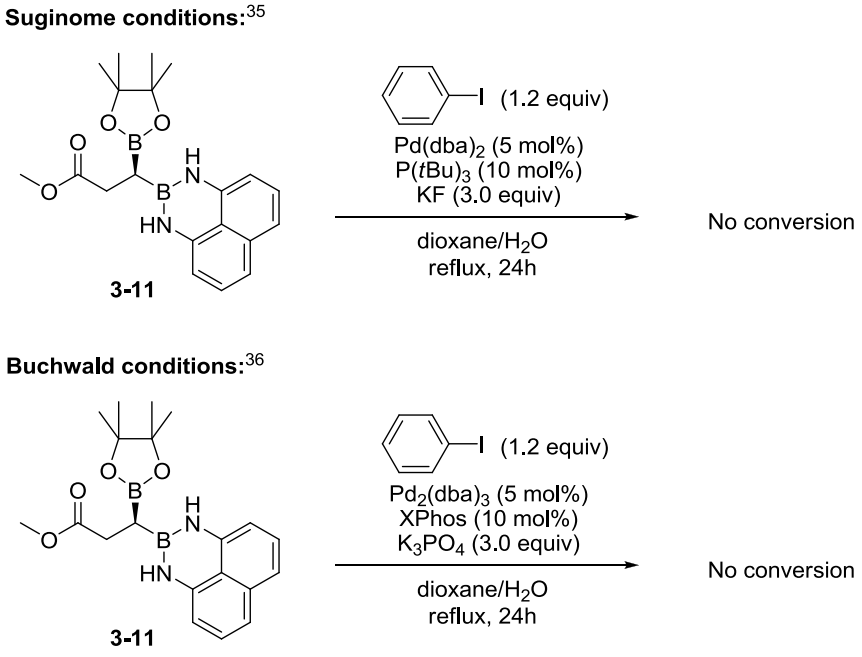
Table 3-6: Optimization of cross-coupling conditions by using biphosphine ligands.

alternative pathway such as β-hydride elimination. Even though β-boronyl enoate was not observed as a side product during the reaction, this compound can undergo facially non-selective migratory insertion to give racemized intermediate (Scheme 3-12).[33] As long as the rate of β-hydride elimination is faster than reductive elimination, racemized product **3-21** will be obtained.

One approach that has been reported to effectively suppress β-hydride elimination and accelerate reductive elimination in cross-coupling reactions is to employ biphosphine ligands for cross-coupling reactions.[34] Unfortunately, when biphosphine ligands such as dppf and *rac*-BINAP were employed instead of triphenylphosphine, no conversion of the starting material **3-11** was observed (Entries 1-4, Table 3-6). Performing the reaction in different solvents proved to be ineffective, again leading to unconverted starting materials (Entries 5-6, Table 3-6).

3.3.1.2 Cross-couplings of diboron 3-11 with other standard conditions

In addition to the Crudden procedure, other standard conditions for cross-coupling

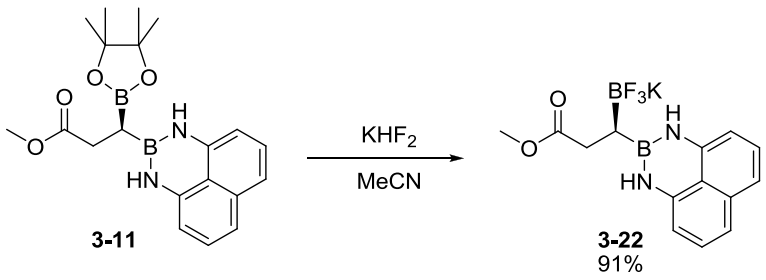


Scheme 3-13: Other conditions attempted for cross-coupling of 1,1-diboron **3-11**.

of alkylboronates were also attempted. Suginome and coworkers reported cross-coupling of benzylic boronates and various aryl halides with high efficiency,[35] while the Buchwald Group reported the usage of XPhos as a superior ligand to dramatically improve the reaction rate of Suzuki-Miyaura cross-coupling reactions. [36] As illustrated in Scheme 3-13, however, standard conditions developed from both the Suginome and the Buchwald groups unfortunately gave none of the desired product.

3.3.2 Suzuki-Miyaura cross-couplings with trifluoroborate salts

At this point, due largely to unsuccessful cross-coupling attempts with 1,1-diboron **3-11**, the attention was turned to trifluoroborate salts. The impact and popularity of organotrifluoroborates has escalated drastically over the past decade due mainly to their performance in metal-catalyzed cross-coupling reactions. Trifluoroborate salts hold several advantages over boronic acids: (1) they are shelf-stable compounds usually in the form of powders or crystalline solids. (2) In comparison with boronic acids, trifluoroborate salts usually exhibit higher stability and undergo less side reactions such as protodeboronation during cross-coupling reactions. (3) These reagents are tolerant to various reaction conditions, thus allowing them to be pre-installed several steps prior to the desired Suzuki-Miyaura cross-coupling reaction. [37] Due to these promising aspects of trifluoroborate salts and a recent report by the Molander Group highlighting one example of involving a non-benzylic trifluoroborate salt (Chapter 1), [38] the transformation of pinacol boronates **3-11** to trifluoroborate salt **3-22** was conducted. Although methanol was normally used as the solvent for



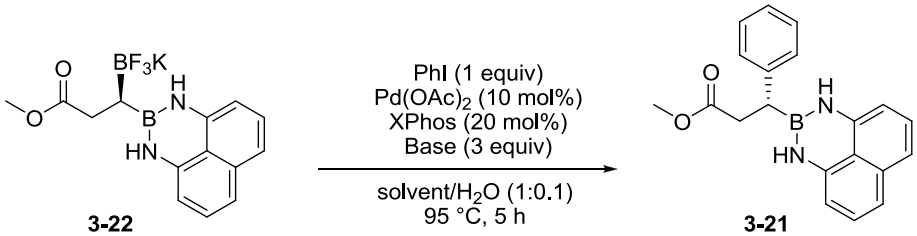
Scheme 3-14: Synthesis of trifluoroborate salt **3-22** from 1,1-diboron **3-11**.

trifluoroborate salt formation, the low solubility of 1,1-diboron **3-11** prevents the conversion of the starting material. On the other hand, when acetonitrile was used as the solvent, trifluoroborate salt **3-22** could be isolated smoothly with a 91% yield (Scheme 3-14).

3.3.2.1 Optimization of cross-couplings between trifluoroborate salt 3-22 and aryl halides

3.3.2.1.1 Effect of solvent and base in cross-coupling reactions

Under standard Molander conditions, a low yield of the desired product could be isolated (Entry 1, Table 3-7). Unlike 1,1-diboron **3-11**, however, the reaction was stereospecific and the product could be obtained with 99% ee. The absolute configuration of **3-22** was confirmed to be (*R*) through comparison with the reported optical rotation of the corresponding alcohol.[39] Combining this result with the (*R*) stereochemistry of 1,1-diboron **3-11** (vide supra), it ensues that the



3-22 (1.1 equiv)

3-21

Entry	Base	Solvent	Yield[a]	ee[b]
1	K_2CO_3	CPME	23%	99%
2	Cs_2CO_3	CPME	20%	ND
3	KF	CPME	16%	ND
4	K_2CO_3	dioxane	No conversion	ND
5	K_2CO_3	toluene	39%	99%
6	K_2CO_3	toluene	53%[c]	ND

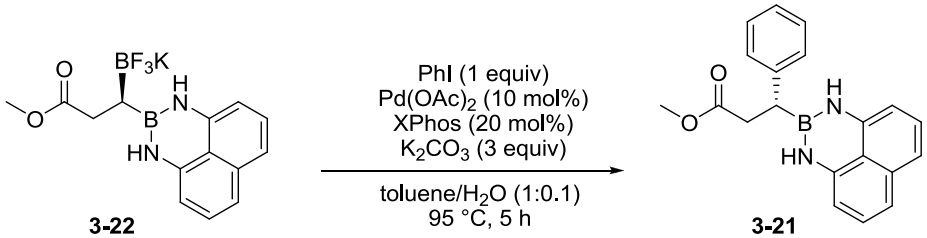
[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] The reaction was performed at 80 °C. CPME = cyclopentyl methyl ether. ND = not determined

Table 3-7: Optimization of cross-coupling reaction between trifluoroborate salt **3-22** and iodobenzene.

observed cross-coupling product **3-21** underwent a complete inversion of stereochemistry similar to that observed in the Suginome and Molander examples (Chapter 1).[36,40] Different inorganic bases were also screened, but none was found to be superior to K_2CO_3 (Entries 2-3, Table 3-7). When dioxane was used as the solvent, no conversion was observed (Entry 4, Table 3-7). On the other hand, toluene was found to be more effective than cylopentylmethyl ether, giving the desired product with a 39% yield (Entry 5, Table 3-7). When the reaction temperature was lowered to 80 ºC, a slightly improved yield of the cross-coupled product **3-21** could be obtained (Entry 6, Table 3-7).

3.3.2.1.2 Effect of ligand

Different phosphine ligands were also screened in order to further improve the efficiency of the cross-coupling reaction. All of the electron-rich phosphine



Entry	Ligand	Yield[a]	ee[b]
1	XPhos	39%	99%
2	SPhos	24%	ND
3	DavePhos	No conversion	ND
4	QPhos	No conversion	ND
5	PCy_3	No conversion	ND
6	RuPhos	13%	ND
7	P*t*Bu$_3$	38%	82%

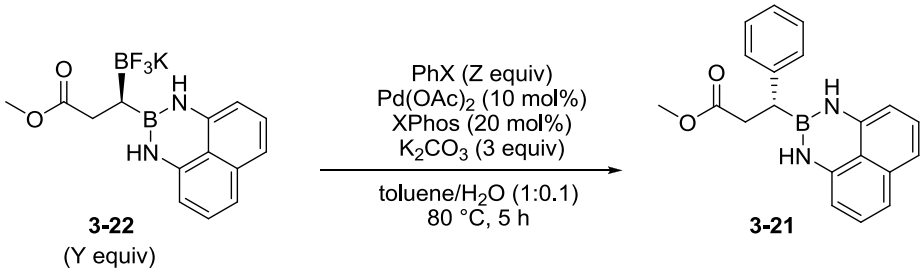
[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. ND = not determined

Table 3-8: Optimization of ligand in model cross-coupling reaction of 1,1-diboron **3-22**.

ligands, however, were found to be less effective than XPhos (Entries 2-6, Table 3-8). Tri-*tert*-butylphosphine was the only ligand that was comparable to XPhos in terms of yield, however in this case the enantioselectivity suffered, giving the product with only 82% ee (Entry 7, Table 3-8).

3.3.2.1.3 Effect of halide and stoichiometry of starting materials

Since protodeboronation is the main side reaction observed in these cross-coupling reactions, an increase in the equivalents of 1,1-diboron compound **3-22** could serve to enhance the yield of the reaction. Indeed, when 1.5 equivalent of 1,1-diboron **3-22** was used, a 78% yield of the desired product was isolated (Entry 2, Table 3-9). Surprisingly, when the halide source was changed from iodobenzene to bromobenzene, a higher yield of the desired product was obtained (Entry 3, Table 3-9). Due to higher activation energy of aryl bromides relative to aryl iodides during the oxidative addition step,[41] lower efficiency is normally



3-22
(Y equiv)

3-21

Entry	Y/Z	X	Yield[a]	ee[b]
1	1.1/1	I	53%	ND
2	1.5/1	I	78%	ND
3	1.5/1	Br	92%	ND
4	1.5/1	Cl	Low conversion	ND
5	1.2/1	Br	89%	99%
6	1/2	Br	81%	ND

[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. ND = not determined

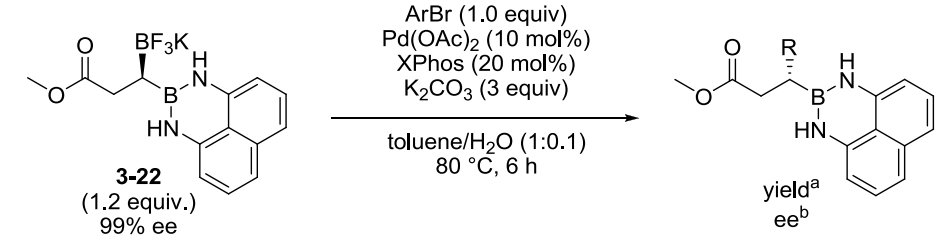
Table 3-9: Optimization of stoichiometry and halide source in cross-coupling reaction of 1,1-diboron **3-22**.

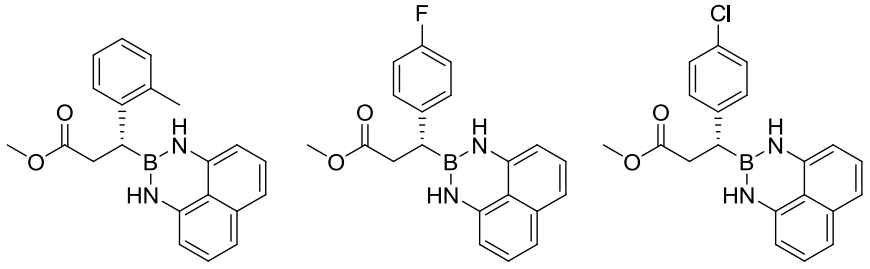
observed when aryl bromides are the coupling partners. However, there is precedent that aryl bromides or chlorides can perform better than aryl iodides in cross-coupling reactions. The reasoning is unclear, but the intermediate ArPdI might be more prone to undergo side reaction such as protodehalogenation relative to ArPdBr. Chlorobenzene, however, is not reactive in this cross-coupling reaction, giving unconverted starting material (Entry 4, Table 3-9). When bromobenzene was used as the coupling partner, only a slight excess of 1,1-diboron **3-22** was necessary, allowing the cross-coupling reaction to be conducted efficiently (Entry 5, Table 3-9). When 1,1-diboron **3-22** was used as the limiting reagent, a lower yield was isolated (Entry 6, Table 3-9). The main by-product observed in these cross-coupling reactions is the protodeboronated product, therefore a slight excess of the diboron reagent is necessary in order to ensure a high yield of the desired coupling process. This remarkable result (Entry 5, Table 3-9) constitutes another advance in the Suzuki-Miyaura cross-coupling of alkyl boronates. Indeed, in their previous communication, Molander and coworkers mentioned that the direct cross-coupling reaction with a β-boronyl carboxy ester was not possible, and a stronger coordinating amide was necessary.[36] Consequently, the successful coupling of 1,1-diboron **3-22** demonstrates that a strong cooperative effect is at play, which facilitates the transmetallation step through both the coordination of the methyl ester to the boron atom and the stabilization of the α-borylated, Pd(II) intermediate (vide infra).

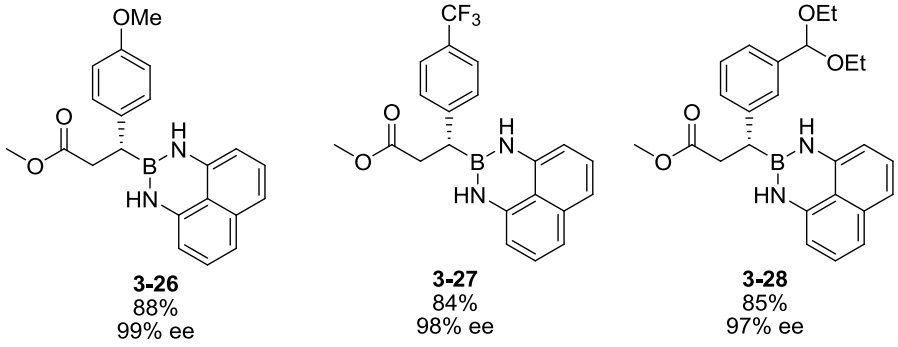
3.3.2.2 Scope of aryl bromides

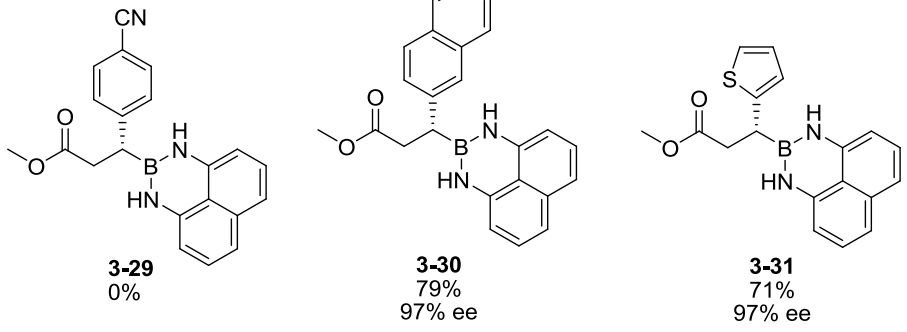
With this optimized procedure in hand, the scope of substrates for cross-coupling reactions with the 1,1-diboron **3-22** was examined. Most of the coupling reactions with aryl electrophiles proceeded efficiently, leading to high yield and almost complete enantiomeric inversion while tolerating various functional groups (**3-23**-**3-28**, Table 3-10). Unfortunately, a nitrile substituted electrophile did not fare well and afforded a mixture of protodeboronated side products (Entry **3-29**, Table 3-10). It is interesting to note here that when the aromatic ring system bears a nitrile group such as in **3-29**, the Bdan unit is no longer stable and

protodeboronation product was observed. The reaction tolerates various ortho- or meta- substituted electrophiles, demonstrating that sterics is not a major factor in





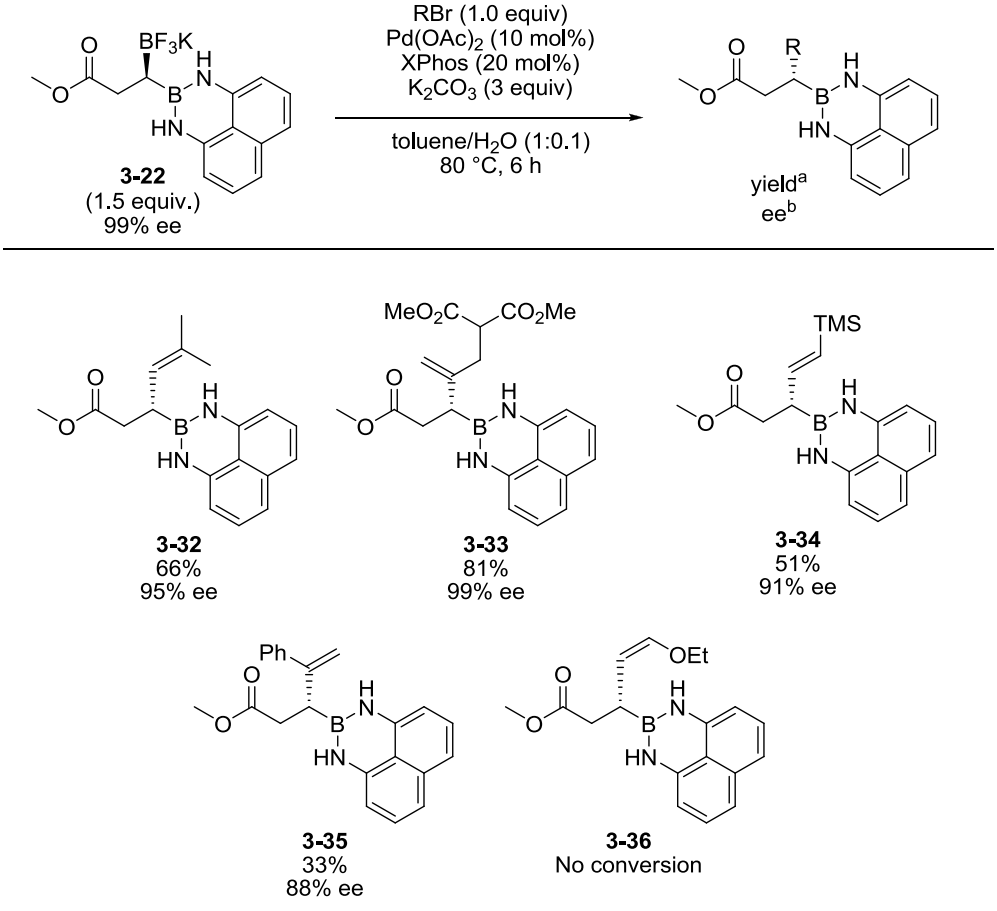




[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 3-10: Scope of aryl bromides in cross-coupling reactions of 1,1-diboron **3-22**.

these cross-coupling reactions (**3-23** and **3-28**, Table 3-10). Furthermore, naphthalene derivatives or heteroaromatics such as thiophene can also undergo the desired reactions to give the corresponding products **3-30** and **3-31** in good yields (Table 3-10). To our satisfaction, not only aryl electrophiles, but also alkenyl electrophiles could be cross-coupled with the 1,1-diboronyl reagent (Table 3-11). This approach constitutes a new way of preparing enantioenriched allylic boronates,[42] which can undergo carbonyl allylation reactions to form carbon−carbon bonds stereoselectively (**3-32**-**3-36**, Table 3-11).[43] Coupling of **3-22** with alkenyl electrophiles, however, is slower than cross-coupling reactions with aryl electrophiles. The reaction requires 1.5 equivalent of the diboron reagent



[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 3-11: Scope of alkenyl bromides in cross-coupling reactions of 1,1-diboron **3-22**.

and tends to provide lower product yields (**3-32**-**3-35**, Table 3-11). A particularly interesting example is the cross-coupling reaction of diboron reagent **3-22** with 2-trimethylsilyl-bromoethene (**3-34**, Table 3-11). The resulting product represents a Type I double allylation reagent that is capable of undergoing sequential allylation or oxidation reactions leading to different functionalities.[44]

3.3.2.3 Mechanistic proposal of the cross-coupling reaction of 1,1-diboron 3-22

3.3.2.3.1 Role of trifluoroborate salt

The main side-reactions associated with organoboron compounds in cross-coupling chemistry include protodeboronation,[45] homocoupling[46] and oxidation reactions. While most boronic acids are stable to air and moisture, electron-deficient aromatic, heteroaromatic, and alkyl ones are prone to undergo protodeboronation under basic conditions. As a result, a large excess of boronic acid derivatives is usually necessary, causing a loss in atom economy and a rise in the waste generated during the reaction. Protodeboronation may be suppressed when anhydrous solvent and weak bases are utilized. However, this is not applicable to all substrates and this limitation significantly restricts the types of conditions that can be employed in the reaction. Recently, several groups have

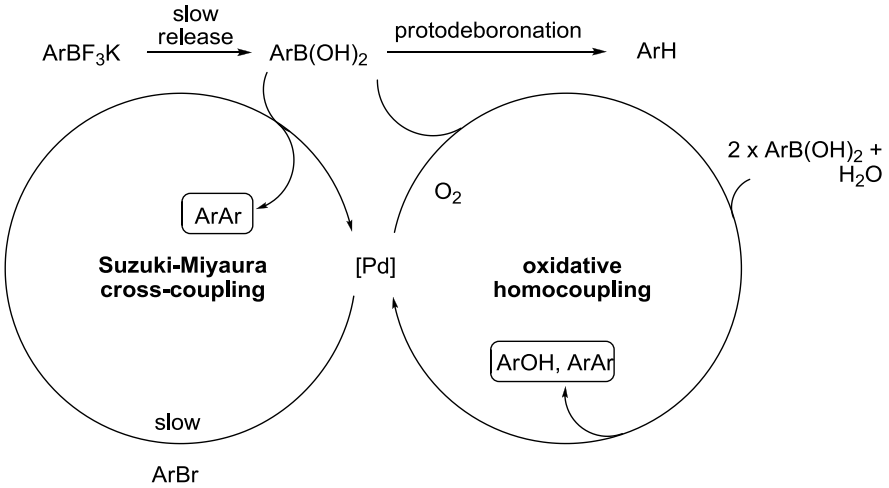


Figure 3-3: Side reactions encountered in Suzuki-Miyaura cross-coupling reactions.

found that these troublesome side-reactions can be dramatically suppressed when organotrifluoroborate salts are employed as coupling partners.[35, 43a] While these protected boronates themselves are not reactive towards cross-coupling reactions, they slowly release the reactive boronic acid form into the reaction mixture.[47] This effect results in a low concentration of boronic acid relative to the active palladium catalyst, causing the desired cross-coupling process to readily occur without going through undesired side reactions (Figure 3-3). Over the past decade, numerous research groups have successfully applied organotrifluoroborates as cross-coupling partners and discovered that only a stoichiometric amount of trifluoroborates is necessary in order to achieve good yields of the desired product.[35] Recently, Lloyd-Jones and coworkers conducted a comprehensive study on the mode of action of trifluoroborates.[47] The authors discovered that both trifluoroborates and the mixed intermediates $R\text{-}BF_{3-n}(OH)_nK$ are inactive towards the desired cross-coupling reactions, and have surmised that boronic acids instead are most likely the reactive species. In comparison with trifluoroborate salts, pinacol boronates are usually quite robust to hydrolysis, and as a result are thought not to hydrolyze in-situ to boronic acids under most Suzuki-Miyaura cross-coupling conditions.

3.3.2.3.2 Catalytic cycle

The mechanism of these stereospecific cross-coupling reactions probably follows a pathway similar to that suggested previously by Suginome, Molander and Shibata.[17,36,38] Subsequent to the oxidative addition of Pd(0) into the C–X bond, the resulting intermediate is surmised to readily transmetallate by inversion of configuration with the borate to provide the σ–alkyl–Pd(II)Ar intermediate **3-37** (Figure 3-4). This key transmetallation step is known to be notoriously difficult for alkyl boronates due to potential β–H elimination and protodeboronation side reactions. Despite this apprehension, the desired cross-coupled products were obtained in high yields. Thus, it is believe that the second boronyl unit, B(dan), stabilizes the α–B–Pd(II) intermediate **3-37** in a manner similar to Shibata's work with bis-pinacolates even though the 1,8-diaminonaphthalene protecting group

partially suppresses the Lewis acidity of the boron atom. In addition, the facile transmetallation step is also likely facilitated by the internal coordination between the carbonyl oxygen and the boron atom. This internal coordination becomes much more evident in trifluoroborate salt **3-22** than pinacolate **3-11** likely due to the formation of the boronic acid intermediate reported to be the active species in cross-coupling reactions of trifluoroborate salts.[45] The dual effect greatly facilitates the transmetallation step for the 1,1-diboronic ester. The resulting σ–alkyl–Pd(II)Ar **3-37** could then undergo reductive elimination to afford products while regenerating the Pd(0) catalyst.

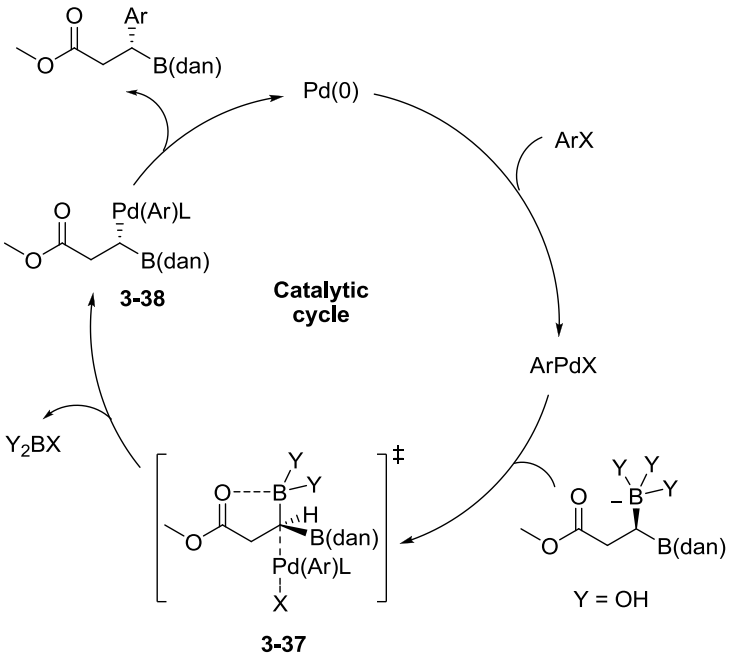


Figure 3-4: Mechanistic proposal for the cross-coupling reaction of 1,1-diboron **3-22**.

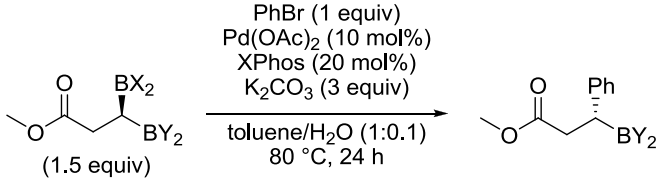
3.3.3 Suzuki-Miyaura cross-coupling reactions of 1,1-diboron compounds bearing pinacol boronate

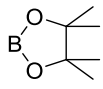
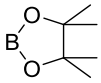
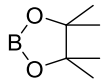
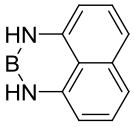
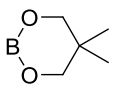
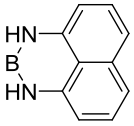
Based on the results as summarized above and those observed in other groups, cross-coupling efficiencies depend greatly upon the intramolecular coordination between the carbonyl oxygen atom and the Lewis acidic boron atom. As a result, it is hypothesized that a proper evaluation of the Lewis acidity of the boron atom

and the Lewis basicity of the carbonyl group could serve to further expand the cross-coupling toolbox to different 1,1-diboron cross-coupling partners.

3.3.3.1 Variation of boronates in 1,1-diboron compounds for cross-coupling reactions

Recent papers from the Shibata Group demonstrated that Lewis acidity of the boron atom can be enhanced by installing another boron atom at the geminal position.[17] Due to the empty *p* orbital of the second boron atom, the formal borate anion generated from the base could be greatly stabilized, thus facilitating borate formation and the subsequent cross-coupling reactions. By conducting a comprehensive study on the effect of Lewis acidity of boron atoms, weaker coordinating carbonyl groups could be used to expand the cross-coupling toolbox. Based on this premise, different 1,1-diboron compounds were prepared and tested



entry	BX_2	BY_2	Yield
1			no conversion
	3-39		
2	 (Bpin)	 (Bdan)	no conversion
	3-11		
3			protodeboronation side product obtained
	3-40		

[a] No conversion. [b] Protodeboronation product was isolated.

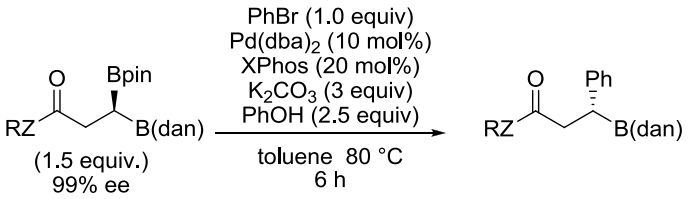
Table 3-12: Suzuki-Miyaura cross-coupling reactions of 1,1-diboron compounds bearing different boronates.

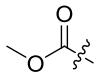
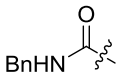
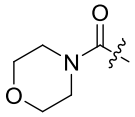
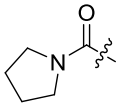
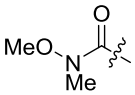
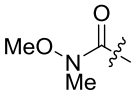
in cross-coupling reactions. In spite of the enhanced Lewis acidity, 1,1-diboron bis(pinacolate) **3-39** failed to convert, giving back the starting material. Turning one of the pinacol boronates to a 1,8-diaminonaphthalene protected boronate (Bdan) allow for the possibility of stereoselective cross-coupling, but unfortunately the compound failed to undergo cross-coupling reaction as well (Entry 2, Table 3-12). Neopentyl glycol is known to be a readily hydrolysable protecting group, and therefore the boron atom should possess higher Lewis acidity than the boron atom of pinacol boronates. The corresponding neopentyl glycol boronate **3-40**, however, was found to be prone to undergo protodeboronation, as listed in Table 3-12 (Entry 3).

3.3.3.2 Variation of the carbonyl group of 1,1-diboron compound

In spite of the successful cross-coupling reactions developed as described above (Section 3.3.2), the synthesis of trifluoroborate salts requires an additional synthetic step, thus lowering their synthetic appeal. Based on this premise, one important goal is to cross-couple pinacol boronates stereoselectively in order to enhance the overall efficiency of the cross-coupling sequence. However, due to their bulkiness, pinacol boronates in general have a much lower Lewis acidity in comparison to boronic acids, and therefore are more difficult substrates in cross-coupling chemistry. In order to address this problem, a systematic examination of various carbonyl groups that possess different nucleophilicity is necessary in order to optimize the interaction between the carbonyl oxygen and the boron atom. As described previously (Section 3.3.3.1), when the carbonyl group is a weakly coordinating ester, no conversion was obtained, indicating that a stronger nucleophilic carbonyl group is necessary (Entry 1, Table 3-13). Substituting the ester group with an *N*-benzyl amide did not solve the problem, affording decomposed products (Entry 2, Table 3-13). In order to further enhance the nucleophilicity of the carbonyl group, tertiary amides such as morpholine and pyrrolidine amides (**3-43** and **3-45**) were prepared and tested. Both of these compounds can be cross-coupled to give the desired products with good yields and more importantly, with high retention of stereochemical integrity (Entries 3-4, Entry 3-13). The retention of enantiomeric purity, however, is not complete and

there is a slight erosion of the enantiomeric excess after the reaction. Based on the trend observed up to this point, it is hypothesized that the slight erosion of ee is possibly due to incomplete coordination between the carbonyl oxygen and the boron atom. One way to increase this interaction between these two different



entry	RZ	Yield[a]	ee[b]
1	 **3-11**	No conversion	ND
2	 **3-41**	Trace **3-42**	ND
3	 **3-43**	75% **3-44**	90%
4	 **3-45**	86% **3-46**	90%
5	 **3-47**	82% **3-48**	99%
6	 **3-49**	96% **3-50**	-[c]

[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] Bpin instead of B(dan), the reaction was performed at 60 °C. ND = not determined

Table 3-13: Suzuki-Miyaura cross-coupling reactions of carbonyl groups having different Lewis basicity.

functional groups is to exploit the α-effect into the amide *N*-substituent.[48] As a result, the Weinreb amide **3-47** was synthesized and tested for the subsequent cross-coupling reaction. Satisfactorily, potentially due to the increased nucleophilicity of the Weinreb amide, cross-coupling products can be synthesized with a good yield and an excellent enantiomeric excess (Entry 5, Table 3-13). This series of results demonstrates the importance of nucleophilicity of the carbonyl group when the boron atom is not very Lewis acidic. To illustrate that the second boron atom is indeed influential on the efficacy of cross-coupling reactions, the B(dan) subunit of 1,1-diboron **3-47** is replaced by a pinacol boronate. Theoretically, through substitution of the weakly Lewis acidic B(dan) unit to a more Lewis acidic Bpin unit, the Lewis acidity of the first boronate should be enhanced, thus allowing the cross-coupling reaction to be performed under milder conditions (Figure 3-5). Indeed, 1,1-diboron **3-49** was found to be highly reactive in cross-coupling reactions, allowing a lower temperature (60 ℃) to be employed to afford cross-coupled product **3-50** with an excellent yield (Entry 6, Table 3-13). This result again shows the importance of the second boron atom during cross-coupling reactions.

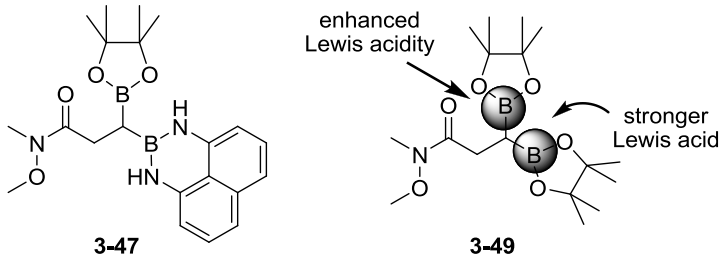
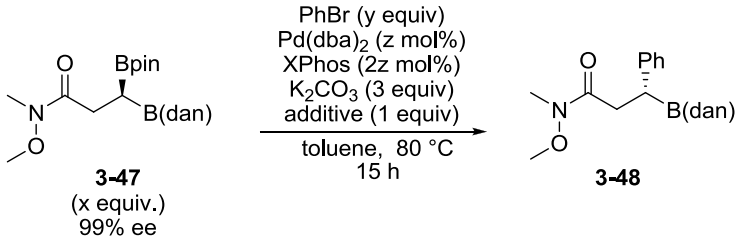


Figure 3-5: Comparison of Lewis acidity between compounds **3-47** and **3-49**.

3.3.3.3 Optimization of reaction conditions

After successfully identifying that a Weinreb amide is an effective coordinating group to directly cross-couple pinacol boronate **3-47**, an optimization of cross-coupling conditions was conducted. Other palladium sources and ligands were found to be inferior than $Pd(dba)_2$ and XPhos, giving the desired products with lower conversion and yields (Entries 2-4, Table 3-14). The Brønsted acidic

additive, PhOH, was found to be necessary to achieve a complete retention of stereochemical integrity (Entry 5, Table 3-14).[49] One dramatic difference between this new 1,1-diboron compound **3-47** in comparison with the previously reported trifluoroborate salt **3-22** is that the 1,1-diboron **3-47** is more stable under the reactions. Thus, the synthetically valuable 1,1-diboron compound **3-47** can be used as the limiting reagent in this reaction without any observation of protodeboronation product (Entries 6-7, Table 3-14). When water was used as an



Entry	Diboron/halide (x equiv/y equiv)	Additive	Yield[a]	ee[b]
1	1.5/1	PhOH	82%	99%
2	1.5/1	PhOH	trace[c]	ND
3	1.5/1	PhOH	35%[d]	ND
4	1.5/1	PhOH	22%[e]	ND
5	1.5/1	-	52%	91%
6	1/3	H_2O	70%	ND

[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] $Pd(PtBu_3)_2$ was used as the Pd source. [d] Pd-XPhos precatalyst was used as the Pd source. [e] $Pd(OAc)_2$ was used as the Pd source. ND = not determined.

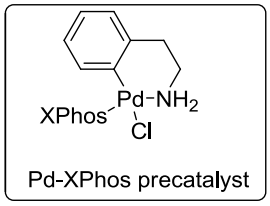
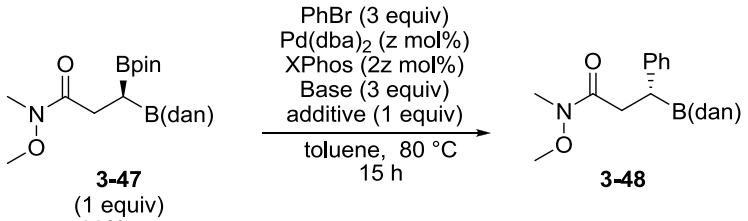


Table 3-14: Optimization of Pd source and stoichiometry of starting materials.

additive, good yields of cross-coupling products could also be obtained especially when a higher catalytic loading was employed (Entries 1-5, Table 3-15). However, the enantiomeric excess acquired is similar to the reactions without any additive (Entry 5, Table 3-14 and entry 5, Table 3-15). Other bases such as KF and Cs_2CO_3 led to either lower yield or faster decomposition rate, respectively (Entries 3-4, Table 3-15). Ultimately, the optimized condition was found with phenol as the additive, 20 mol% of the catalysts to afford the cross-coupling products with an excellent yield and retention of stereochemical integrity (Entry 7, Table 3-15). Lower temperature led to incomplete conversion of the desired



Entry	Pd (mol%)	Additive	Base	Yield[a]	ee[b]
1	20	H_2O	K_2CO_3	80%	ND
2	20	H_2O	Cs_2CO_3	78%	ND
3	20	H_2O	KF	38%	ND
4	20	H_2O	NaO*t*Bu	-	ND
5	30	H_2O	K_2CO_3	94%	91%
6	10	PhOH	K_2CO_3	75%	ND
7	**20**	**PhOH**	**K_2CO_3**	**95%**	**99%**
8	20	PhOH	K_2CO_3	-[c]	-

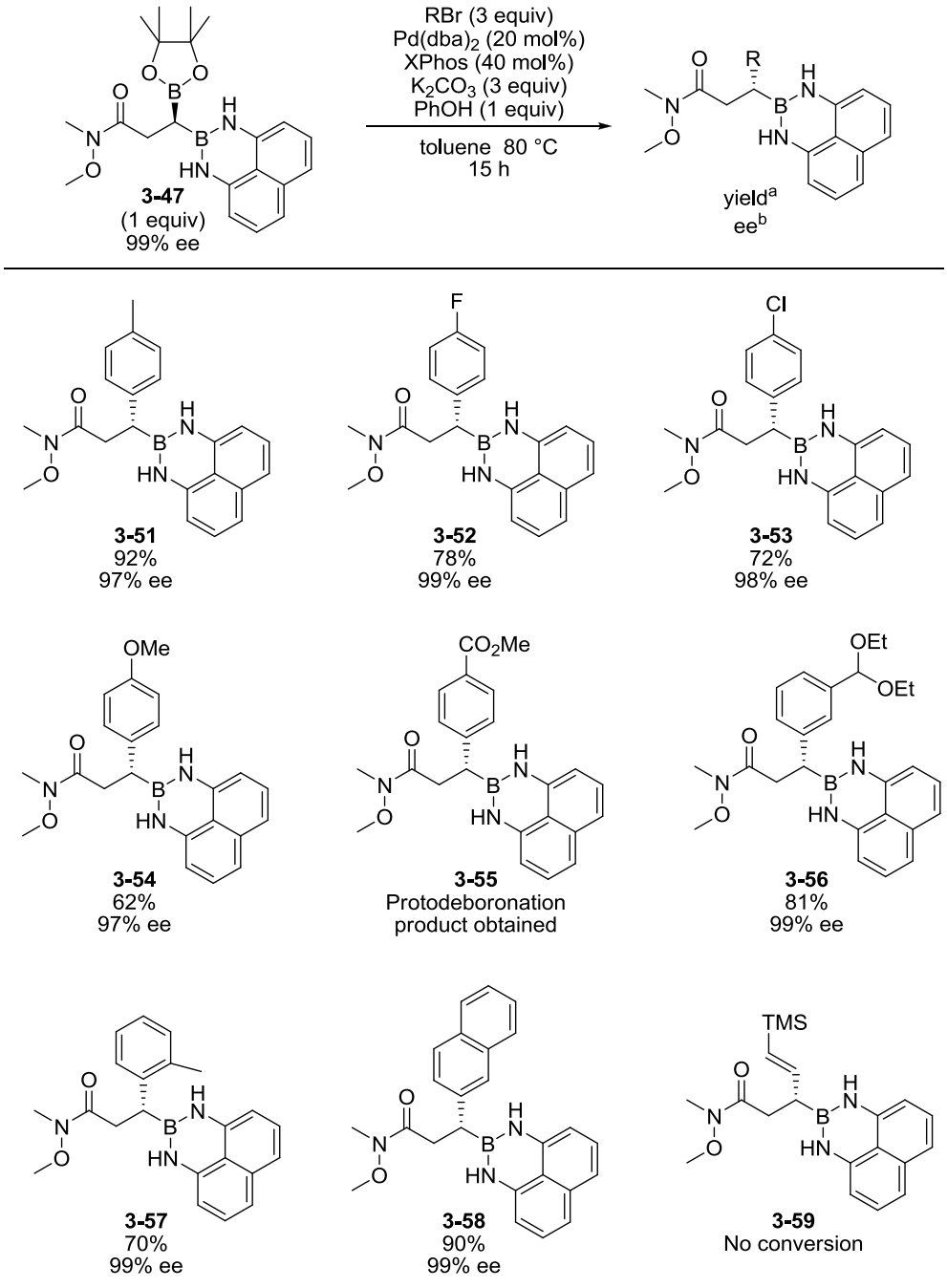
[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC. [c] The reaction was performed at 50 °C. ND = not determined.

Table 3-15: Optimization of catalyst loading, base and additive for the cross-coupling between 1,1-diboron **3-47** and bromobenzene.

product (Entry 8, Table 3-15).

3.3.3.4 Scope of aryl bromides for the cross-coupling of 1,1-diboron 3-47.

With the optimized conditions in hand, the scope of substrates was then examined.



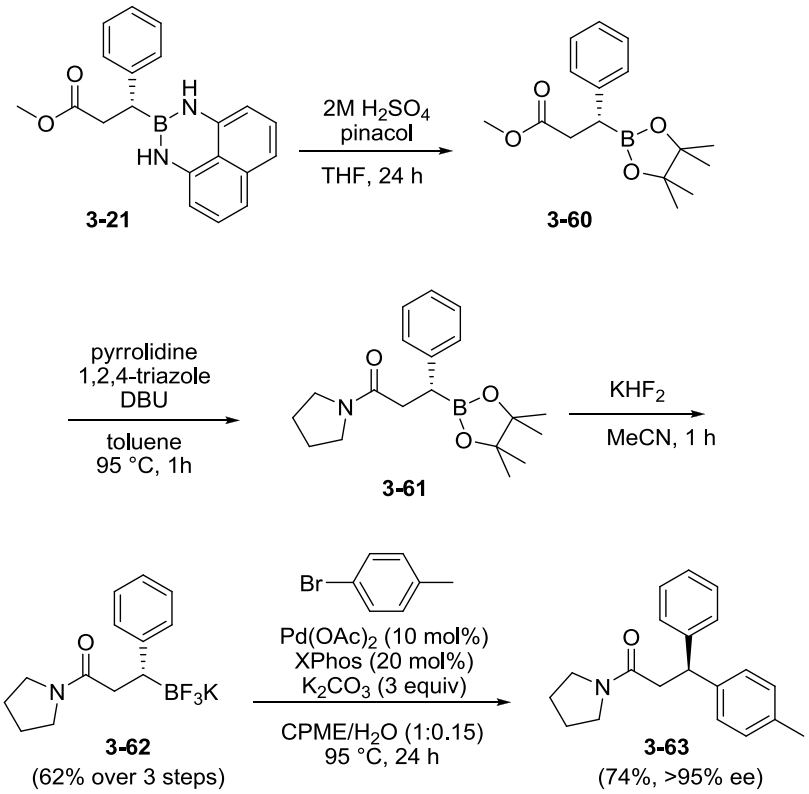
[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 3-16: Scope of aryl bromides for the cross-coupling of 1,1-diboron **3-47**.

Various functional groups on aryl bromides such as methyl, fluoro, chloro, and methoxy groups are all tolerated, affording products with good yields and excellent enantiomeric purity with inversion of stereochemistry (**3-51**-**3-54**, Table 3-16). Unfortunately, when methyl 4-bromobenzoate was used as the cross-coupling partner, protodeboronation product was isolated similar to the result obtained when diboron **3-22** was used as the cross-coupling partner. Different substitution positions such as meta- or ortho-substituted groups are also tolerated, although longer reaction times are generally necessary to obtain the products with complete conversions (**3-56** and **3-57**, Table 3-16). Moreover, polyaryl halide such as 2-bromonaphthalene is also a suitable cross-coupling partner (**3-58**, Table 3-16), allowing the cross-coupled product to be isolated with an excellent efficiency. Unfortunately, alkenyl halide was found to be unable to cross-couple with 1,1-diboron **3-47** (**3-59**, Table 3-16).

3.4 Synthetic applications of chiral secondary alkyl boronates

To demonstrate the versatility of the products obtained in these stereospecific cross-couplings, the iterative second cross-coupling with the chiral boronate **3-21** acquired from the first coupling was examined. However, it was not possible to cross-couple the boronate **3-21** directly even after transforming the 1,8-diaminonaphthalene protecting group to the corresponding trifluoroborate salt. It was found necessary to transform the carboxyester to the amide **3-62** in order to effect the desired reaction. As shown in Scheme 3-15, following the conversion of the Bdan unit to the pinacol boronate **3-60**, a triazole-catalyzed trans-amidation protocol was conducted to form the corresponding amide **3-61**.[24] Trifluoroborate salt formation afforded **3-62**, and this compound could be cross–coupled successfully with *p*-bromotoluene to afford the enantioenriched diarylmethine **3-63**. The enantioenriched diarylmethane core structure represents an important pharmacophore, and 1,1-diboryls could serve as a universal template for their synthesis.[50] Our method represents a new way to prepare these synthetic intermediates where both of the aryl groups can be assembled through simple cross-coupling reactions with readily available aryl bromides.

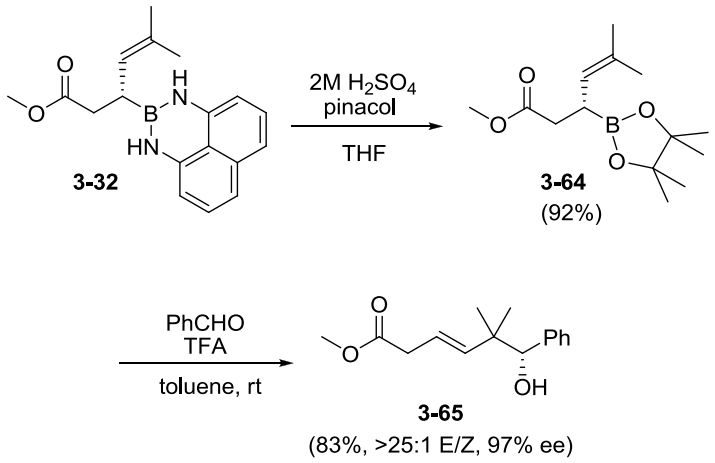


Scheme 3-15: Iterative cross-coupling of the second boronyl unit.

Another synthetically valuable application of the mono cross-coupled products of alkenyl halides is the carbonyl allylboration reaction. Once the Bdan group was removed to provide access to allyl boronic acid pinacol ester **3-64**, a Brønsted acid catalyzed allylboration reaction could be achieved to afford the homoallylic alcohol **3-65** (Scheme 3-16).[51] The enantiomeric excess, as measured by chiral HPLC analysis, was found to be fully retained in the alcohol product **3-65** (Scheme 3-16). Based on the excellent retention of optical purity and the *E*/*Z* ratio, the reaction most likely proceeded through the expected chair-like transition state.[41,52] All these preliminary applications demonstrate the potential value of enantioenriched 1,1-diboron compounds as intermediates in organic synthesis.

3.5 Summary[53]

In summary, the first synthesis of enantiomerically pure 1,1-diboron compounds was achieved through asymmetric conjugate borylation of β-boronyl enoates. The intriguing physical property and absolute stereochemistry were revealed from X-



Scheme 3-16: Carbonyl allylboration reaction to synthesize enantioenriched homoallylic alcohol **3-65**.

ray crystallographic analysis. Through enhancing the Lewis acidity of the 1,1-diboron compound by transforming the pinacol boronate to trifluoroborate salt, these compounds can be cross-coupled chemo- and stereoselectively with various organic electrophiles under palladium catalysis. Both the coordination of the carbonyl oxygen to the boron atom and the stabilization provided by the second boronyl unit in the α–B–Pd(II) intermediate are thought to assist the transmetallation process, thus facilitating this notoriously difficult mechanistic step in cross–coupling reactions of alkyl boronates. On the other hand, by enhancing the Lewis basicity of the carbonyl group from an ester to a Weinreb amide, cross-coupling of the boron pinacolate unit becomes possible, allowing cross-coupling reactions to be performed with these relatively less acidic, but more commonly used boronates. The cross-coupling reactions reported in this chapter represent rare examples of successful use of non–benzylic secondary alkylboronates, and they occur with preservation of stereochemical integrity. The resulting enantioenriched benzylic or allylic boronates can undergo different reactions including a second iterative cross-coupling, carbonyl allylation and oxidation reactions. These applications highlight the versatility of chiral secondary alkyl boronates and demonstrate the numerous synthetic possibilities associated with enantioenriched 1,1-diboron compounds.

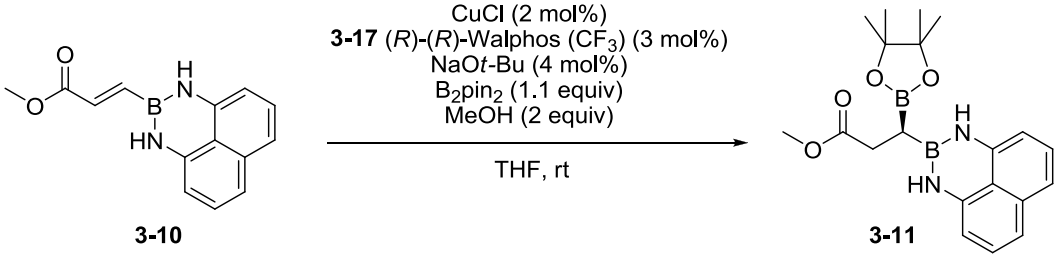
3.6 Experimental details and compound characterization data

3.6.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were treated by Fisher Scientific-MBraun MB SPS* solvent system prior to use. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. The error of coupling constants from ^1H NMR analysis is ±0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumber. X-ray diffraction data were collected by the University of Alberta X-Ray Crystallography Laboratory. Compound **3-10** was synthesized according to the literature procedure.[20] The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD or Chiralpak-AS columns with UV detection.

3.6.2 Preparation of 1,1-diboron compounds 3-11 and 3-20

3.6.2.1 (*S*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3-11)



CuCl (1.0 mg, 10 μmol), ligand **3-17** (10 mg, 15 μmol), and NaO*t*Bu (1.9 mg, 20 μmol) were dissolved in THF (0.4 mL) and stirred at room temperature for 30 minutes before the addition of pinacolato diboron (140 mg, 0.55 mmol) in THF (0.3 mL). The reaction was further stirred for 10 minutes and boronate **3-10** (126 mg, 0.500 mmol) was then added along with THF (0.3 mL) and dropwise addition of MeOH (41 μL, 1.00 mmol). After 12 hours of stirring, the reaction mixture was evaporated *in vacuo* and directly purified by flash silica column chromatography (EtOAc/Hexanes = 1:4) to give **3-11** (167 mg, 88%) as a colourless solid. The product could be recrystallized from hot MeOH to give X-ray quality crystals (72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.2, 7.4 Hz, 2H), 7.00 (dd, *J* = 8.2, 0.9 Hz, 2H), 6.30 (dd, *J* = 7.2, 0.9 Hz, 2H), 5.87 (br s, 2H), 3.69 (s, 3H), 2.64 (dd, *J* = 16.8, 9.7 Hz, 1H), 2.54 (dd, *J* = 16.8, 6.1 Hz, 1H), 1.26 (s, 6H), 1.24 (s, 6H), 1.11 (dd, *J* = 9.8, 6.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 141.0, 136.2, 127.5, 119.5, 117.4, 105.6, 83.5, 51.7, 30.7, 24.9, 24.5. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.8, 31.0.

IR (Microscope, cm^{-1}) 3371, 3011, 2989, 2981, 2954, 1728, 1628, 1606, 1520.

HRMS (EI) for $C_{20}H_{26}B_2N_2O_4$: calcd. 380.20786; found 380.20856.

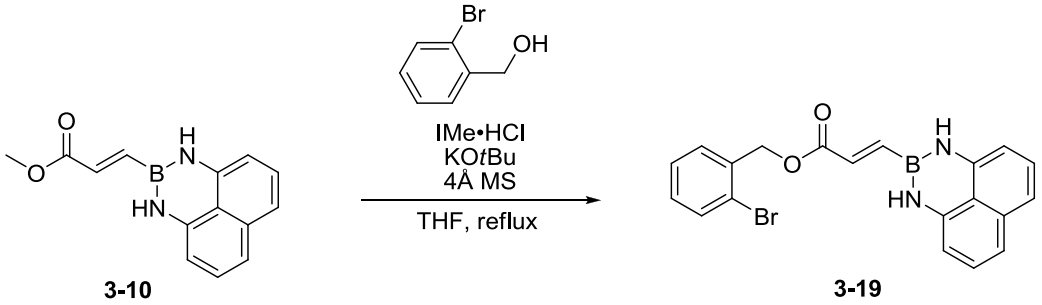
$[\alpha]_D^{20}$: –16 (c = 0.22, CH_2Cl_2).

M. P. 169–171 °C.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250

nm,T_{major} = 15.9 min, T_{minor} = 13.1 min, ee = 99% (prior to recrystallization).

3.6.2.2 (*E*)-2-bromobenzyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)acrylate (3-19)



3-10 3-19

Compound **3-19** was synthesized according to a modified protocol reported by Grasa et al.[25] To a solution of IMe•HCl (34 mg, 0.10 mmol) in THF (0.5 mL) was added KO*t*Bu (11 mg, 0.10 mmol). The solution was stirred at room temperature for 15 minutes before the sequential addition of 2-Bromobenzyl alcohol (935 mg, 5.00 mmol), 4Å molecular sieves (500 mg) and boronate **3-10** (252 mg, 1.00 mmol). The reaction mixture was then heated at reflux for 12 hours before being filtered, concentrated and purified with flash silica column chromatography to afford the pure product. The product was further recrystallized from hot chloroform to give the adduct **3-19** (90 mg, 22%) as a red solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.46 (ddd, *J* = 7.6, 2.0, 0.4 Hz, 1H), 7.35 (td, *J* = 7.6, 1.6 Hz, 1H), 7.22 (td, *J* = 8.0, 1.6 Hz, 1H), 7.12 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.09 (d, *J* = 18.4 Hz, 1H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 6.53 (d, *J* = 18.4 Hz, 1H), 6.35 (dd, *J* = 8.0, 1.2 Hz, 2H), 5.83 (br s, 2H), 5.34 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 140.0, 135.9, 134.7, 132.5, 132.4, 129.6, 129.5, 127.2, 127.1, 123.2, 119.8, 117.9, 105.8, 65.8. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

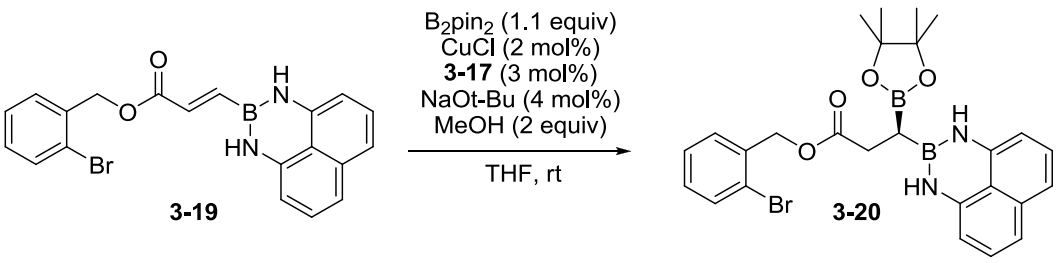
^{11}B NMR (160 MHz, $CDCl_3$) δ 27.6.

IR (Microscope, cm^{-1}) 3404, 3388, 3061, 1727, 1717, 1630, 1610, 1512.

HRMS (EI) for $C_{20}H_{16}BBrN_2O_4$: calcd. 408. 0468; found 408.0477.

M. P. 184–185°C.

3.6.2.3 (*R*)-2-bromobenzyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3-20)



CuCl (0.4 mg, 4.4 μmol), ligand **3-17** (6.2 mg, 6.6 μmol), and NaO*t*Bu (0.9 mg, 8.8 μmol) were dissolved in THF (0.2 mL) and stirred at room temperature for 30 minutes before the addition of pinacolato diboron (62 mg, 0.24 mmol) in THF (0.15 mL). The reaction was further stirred for 10 minutes and boronate **3-19** (90 mg, 0.22 mmol) was then added along with THF (0.15 mL) and dropwise addition of MeOH (18 μL, 0.44 mmol). After 12 hours of stirring, the reaction mixture was evaporated *in vacuo* and directly purified by flash silica column chromatography (EtOAc/Hexanes = 1:4) to give **3-20** (95 mg, 81%) as a yellow solid. The product could be recrystallized from hot MeOH to give X-ray quality crystals (clear colourless).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.26 (td, *J* = 7.6, 1.2 Hz, 1H), 7.16 (td, *J* = 8.0, 2.0 Hz, 1H), 7.10 (dd, *J* = 8.0, 7.2 Hz, 2H), 7.00 (dd, *J* = 8.4, 0.8 Hz, 2H), 6.35 (dd, *J* = 7.2, 1.2 Hz, 2H), 5.89 (br s, 2H), 5.24 (d, *J* = 13.1 Hz, 1H), 5.22 (d, *J* = 13.1 Hz, 1H), 2.75 (dd, *J* = 16.8, 9.2 Hz, 1H), 2.65 (dd, *J* = 17.2, 6.8 Hz, 1H), 1.25 (s, 6H), 1.23 (s, 6H), 1.18 (dd, *J* = 9.2, 6.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 140.6, 135.9, 135.0, 132.4, 129.5, 129.2, 127.1, 127.0, 123.0, 119.1, 117.1, 105.3, 83.2, 65.5, 30.5, 24.6, 24.1. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 30.1.

IR (Microscope, cm^{-1}) 3371, 3062, 2978, 2927, 1721, 1710, 1626, 1517.

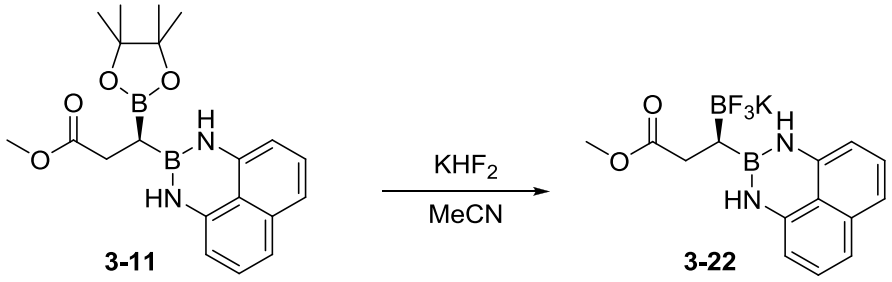
HRMS (EI) for $C_{26}H_{29}B_2BrN_2O_4$: calcd. 536.1488; found 536.1476.

$[\alpha]_D^{20}$: –4.5 (c = 0.13, CH_2Cl_2).

M. P. 151°C (decomposed).

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm,T_{major} = 37.5 min, T_{minor} = 22.7 min, ee = 99% (prior to recrystallization).

3.6.2.4 (*S*)-Potassium trifluoroborate salt (3-22)



3-11 3-22

The 1,1-diboron **3-11** (2.69 g, 7.00 mmol) was dissolved in MeCN (80 mL) before the addition of sat. aq. KHF_2 (4.50 M, 6.30 mL, 28.0 mmol) was taken place. The resulting solution was stirred at room temperature for 5 hours, concentrated and evaporated in vacuo. After drying in high vacuum overnight, the crude mixture was dissolved in hot MeCN (50 mL × 3), filtered, and concentrated *in vacuo*. To the resulting oil was added Et_2O (50 mL), followed by sonication for 30 minutes to afford a suspension of colourless powders in the solution. The pure product was then filtered and dried *in vacuo* to provide the title compound **3-22** as a white powder (2.30 g, 91%).

^{1}H NMR (300 MHz, acetone-d_6) δ 6.96 (dd, J = 8.3, 7.4 Hz, 2H), 6.79 (dd, J = 8.4, 1.0 Hz, 2H), 6.42 (br s, 2H), 6.28 (dd, J = 7.4, 1.0 Hz, 2H), 3.52 (s, 3H), 2.46 (dd, J = 15.2, 5.2 Hz, 1H), 2.32 (dd, J = 15.2, 10.5 Hz, 1H), 0.40 (m, 1H).

^{13}C NMR (100 MHz, acetone-d_6) δ 178.3, 144.1, 137.6, 128.3, 120.4, 116.2, 105.5, 51.1, 33.3. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (128 MHz, acetone-d_6) δ 32.8, 5.0.

^{19}F NMR (376 MHz, acetone-d_6) δ –140.4.

IR (Microscope, cm^{-1}) 3407, 3052, 2922, 2852, 1710, 1628, 1601, 1511.

HRMS (EI) for $C_{14}H_{14}B_2F_2N_2O_2$ (M–FK): calcd. 302.1209; found 302.1213.

$[\alpha]_D^{20}$: –66 (c = 0.07, acetone).

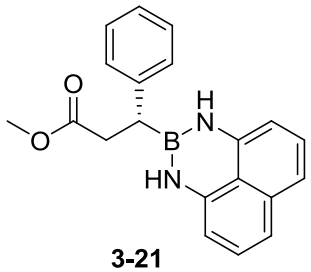
M. P. 160°C (decomposed).

3.6.3 Stereoselective cross-coupling reactions with 1,1-diboron 3-22

3.6.3.1 General procedure (Table 3-10 and 3-11)

$Pd(OAc)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.30 mmol), aromatic or alkenyl bromide (0.10 mmol), and 1,1-diboron **3-22** (0.12 or 0.15 mmol) were stirred in toluene (1.0 mL) and H_2O (0.10 mL) at 80°C for 6 hours. The reaction mixture was then cooled down and evaporated *in vacuo*. The crude reaction mixture was purified with flash silica column chromatography to afford the title product.

3.6.3.2 Naphthalene-1,8-diamido (dan) derivative 3-21

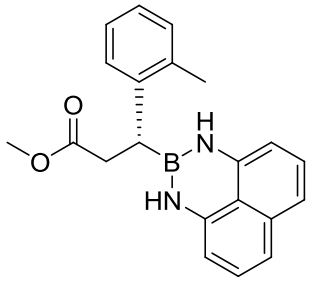


3-21

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-21** (29 mg, 0.09 mmol, 89% yield) as a yellow oil.

The characterization data for this compound matched that of a previous report.[20]

3.6.3.3 Naphthalene-1,8-diamido (dan) derivative 3-23



3-23

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-23** (29 mg, 0.08 mmol, 83% yield) as a

yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.11 (m, 4H), 7.07 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 2H), 6.23 (dd, *J* = 7.1, 1.2 Hz, 2H), 5.65 (br s, 2H), 3.70 (s, 3H), 3.14 (dd, *J* = 8.9, 6.6 Hz, 1H), 2.93 (dd, *J* = 16.2, 9.0 Hz, 1H), 2.83 (dd, *J* = 16.2, 6.5 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 141.0, 140.8, 136.3, 136.0, 130.7, 127.5, 126.6, 126.5, 125.9, 119.7, 117.7, 105.9, 51.9, 36.2, 20.2. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.8.

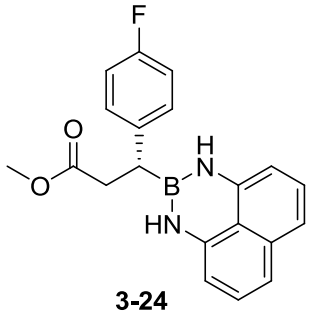
IR (Microscope, cm^{-1}) 3413, 3053, 3015, 2950, 1727, 1629, 1601, 1505.

HRMS (EI) for $C_{21}H_{21}BN_2O_2$: calcd. 344.1696; found 344.1698.

$[\alpha]_D^{20}$: 18 (c = 0.48, CH_2Cl_2) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 36.3 min, T_{minor} = 38.0 min, ee = 99%.

3.6.3.4 Naphthalene-1,8-diamido (dan) derivative 3-24



3-24

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-24** (30 mg, 0.09 mmol, 86% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–6.90 (m, 8H), 6.26 (dd, *J* = 7.0, 1.0 Hz, 2H), 5.64 (br s, 2H), 3.67 (s, 3H), 2.93 (apparent t, *J* = 7.6 Hz, 1H), 2.88 (dd, *J* = 15.8, 7.9 Hz, 1H), 2.76 (dd, *J* = 15.6, 7.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 161.2 (d, *J* = 244 Hz), 140.2, 137.8, 135.8, 128.9 (d, *J* = 7.7 Hz), 127.1, 119.2, 117.5, 115.5 (d, *J* = 21 Hz), 105.6, 51.5, 36.5.

(The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ –117.1.

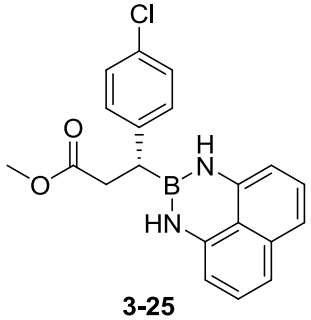
IR (Microscope, cm^{-1}) 3394, 3053, 2952, 1728, 1628, 1602, 1523, 1507.

HRMS (EI) for $C_{20}H_{18}BFN_2O_2$: calcd. 348.1445; found 348.1448.

$[\alpha]_D^{20}$: –18 (c = 0.62, CH_2Cl_2) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 37.2 min, T_{minor} = 40.2 min, ee = 99%.

3.6.3.5 Naphthalene-1,8-diamido (dan) derivative 3-25



3-25

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-25** (31 mg, 0.09 mmol, 85% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5, 2H), 7.13 (d, *J* = 8.5, 2H), 7.08 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 2H), 6.26 (dd, *J* = 7.1, 1.2 Hz, 2H), 5.63 (br s, 2H), 3.68 (s, 3H), 2.93 (apparent t, *J* = 7.5 Hz, 1H), 2.86 (dd, *J* = 15.7, 7.8 Hz, 1H), 2.77 (dd, *J* = 15.7, 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 140.7, 140.2, 135.8, 131.4, 128.8, 127.1, 119.2, 117.5, 105.6, 51.6, 36.2. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5.

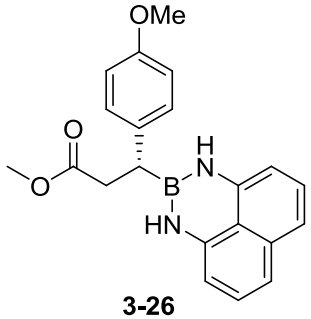
IR (Microscope, cm^{-1}) 3418, 3393, 3054, 2951, 1726, 1629, 1602, 1508.

HRMS (EI) for $C_{20}H_{18}BN_2O_2Cl$: calcd. 364.1150; found 364.1150.

$[\alpha]_D^{20}$: –21 (c = 1.62, CH_2Cl_2) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 40.9 min, T_{minor} = 44.7 min, ee = 99%.

3.6.3.6 Naphthalene-1,8-diamido (dan) derivative 3-26



3-26

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-26** (32 mg, 0.09 mmol, 88% yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5, 2H), 7.13 (d, *J* = 8.5, 2H), 7.08 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 1.2 Hz, 2H), 6.26 (dd, *J* = 7.1, 1.2 Hz, 2H), 5.63 (br s, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 2.93 (apparent t, *J* = 7.5 Hz, 1H), 2.86 (dd, *J* = 15.7, 7.8 Hz, 1H), 2.77 (dd, *J* = 15.7, 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 157.4, 140.4, 135.8, 134.6, 128.4, 127.1, 119.2, 117.3, 114.0, 105.5, 54.9, 51.5, 36.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.9.

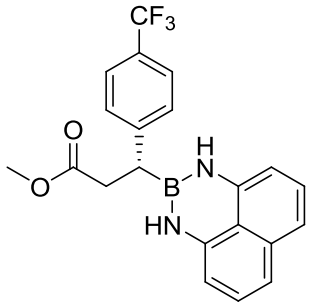
IR (Microscope, cm^{-1}) 3391, 3053, 3002, 2951, 2836, 1726, 1628, 1602, 1509.

HRMS (EI) for $C_{21}H_{21}BN_2O_3$: calcd. 360.1645; found 360.1650.

$[\alpha]_D^{20}$: –22 (c = 0.32, CH_2Cl_2) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 36.6 min, T_{minor} = 39.7 min, ee = 99%.

3.6.3.7 Naphthalene-1,8-diamido (dan) derivative 3-27



3-27

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-27** (33 mg, 0.08 mmol, 84% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0, 2H), 7.32 (d, *J* = 8.0, 2H), 7.08 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.02 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.27 (dd, *J* = 7.3, 1.1 Hz, 2H), 5.61 (br s, 2H), 3.68 (s, 3H), 3.05 (apparent t, *J* = 7.8 Hz, 1H), 2.91 (dd, *J* = 16.2, 8.1 Hz, 1H), 2.83 (dd, *J* = 16.2, 7.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ173.1, 146.5, 140.0, 135.8, 127.7, 127.1, 125.5, 125.5, 119.2, 117.6, 105.7, 51.6, 35.9. (One of the peaks is overlapped with the other carbon peaks. The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.3.

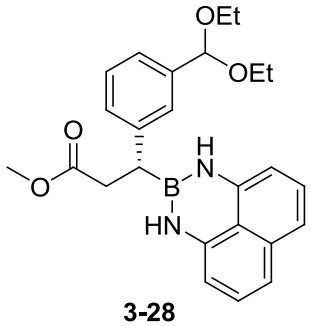
IR (Microscope, cm^{-1}) 3394, 3055, 2953, 1726, 1629, 1602, 1508.

HRMS (EI) for $C_{21}H_{18}BF_3N_2O_2$: calcd. 398.1414; found 398.1418.

$[\alpha]_D^{20}$: –15 (c = 0.31, CH_2Cl_2) for 98% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 43.5 min, T_{minor} = 49.9 min, ee = 98%.

3.6.3.8 Naphthalene-1,8-diamido (dan) derivative 3-28



3-28

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-28** (37 mg, 0.09 mmol, 85% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 3H), 7.15 (m, 1H), 7.09 (dd, *J* = 8.3, 7.2 Hz, 2H), 7.02 (dd, *J* = 8.2, 0.6 Hz, 2H), 6.25 (dd, *J* = 7.3, 0.8 Hz, 2H), 5.70 (br s, 2H), 5.52 (s, 1H), 3.70 (s, 3H), 3.65 (q, *J* = 7.1 Hz, 1H), 3.64 (q, *J* = 7.0 Hz, 1H), 3.58 (dq, *J* = 7.1 Hz, 1H), 3.57 (q, *J* = 7.0 Hz, 1H), 3.00 (dd, *J* = 8.8, 6.8 Hz, 1H), 2.92 (dd, *J* = 15.9, 8.8 Hz, 1H), 2.84 (dd, *J* = 16.0, 6.7 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 142.6, 140.8, 139.8, 136.2, 128.8, 127.8, 127.5, 126.0, 124.4, 119.6, 117.7, 105.9, 101.6, 61.2, 51.9, 36.7, 15.2. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.1.

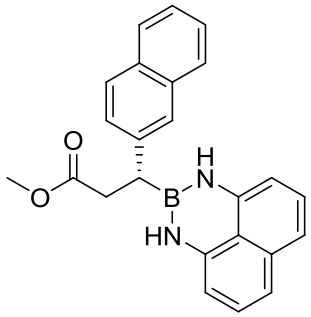
IR (Microscope, cm^{-1}) 3390, 3053, 2974, 2928, 1726, 1629, 1601, 1559, 1511.

HRMS (EI) for $C_{25}H_{29}BN_2O_4$: calcd. 432.2221; found 432.2223.

$[\alpha]_D^{20}$: –6.7 (c = 0.63, CH_2Cl_2) for 97% ee.

HPLC (Chiralcel OD): 5:95 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 74.3 min, T_{minor} = 64.7.0 min, ee = 97%.

3.6.3.9 Naphthalene-1,8-diamido (dan) derivative 3-30



3-30

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-30** (30 mg, 0.08 mmol, 79% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (m, 3H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.48 (m, 2H), 7.32 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.06 (dd, *J* = 8.3, 7.3 Hz, 2H), 7.00 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.22 (dd, *J* = 7.2, 1.0 Hz, 2H), 5.70 (br s, 2H), 3.68 (s, 3H), 3.15 (apparent t, *J* = 7.8 Hz, 1H), 2.99 (dd, *J* = 16.0, 8.3 Hz, 1H), 2.93 (dd, *J* = 16.0, 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 140.3, 139.8, 135.8, 133.4, 131.6, 128.2, 127.3, 127.1, 126.5, 125.9, 125.2, 125.1, 119.2, 117.4, 105.6, 51.5, 36.2. (One of the peaks is overlapped with the other carbon peaks. The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.8.

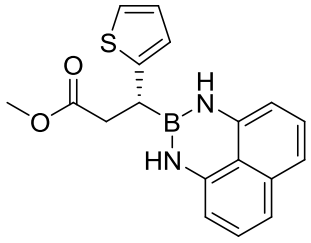
IR (Microscope, cm^{-1}) 3414, 3053, 2951, 1726, 1629, 1602, 1506.

HRMS (EI) for $C_{24}H_{21}BN_2O_2$: calcd. 380.1696; found 380.1697.

$[\alpha]_D^{20}$: 2.2 (c = 1.3, CH_2Cl_2) for 97% ee.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 250 nm, T_{major} = 76.2 min, T_{minor} = 88.1 min, ee = 97%.

3.6.3.10 Naphthalene-1,8-diamido (dan) derivative 3-31



3-31

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-31** (24 mg, 0.07 mmol, 71% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.07 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.97 (dd, *J* = 5.2, 3.5 Hz, 2H), 6.83 (dt, *J* = 3.5, 0.9 Hz, 2H), 6.28 (dd, *J* = 7.2, 1.0 Hz, 2H), 5.76 (br s, 2H), 3.70 (s, 3H), 3.25 (apparent t, *J* = 7.8 Hz, 1H), 2.86 (d, *J* = 7.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 145.1, 140.3, 135.8, 127.1, 126.8, 123.5, 122.8, 119.3, 117.5, 105.7, 51.6, 37.4. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.1.

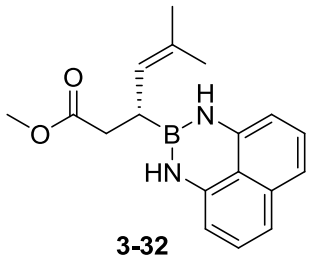
IR (Microscope, cm^{-1}) 3400, 3053, 2950, 1726, 1629, 1602, 1509.

HRMS (EI) for $C_{18}H_{17}BN_2O_2S$: calcd. 336.1104; found 336.1092.

$[\alpha]_D^{20}$: 0.53 (c = 1.0, CH_2Cl_2) for 97% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 41.3 min, T_{minor} = 36.9 min, ee = 97%.

3.6.3.12 Naphthalene-1,8-diamido (dan) derivative 3-32



3-32

The title compound was prepared using the general procedure for the

stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 85:15) yielded **3-32** (20 mg, 0.07 mmol, 66% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.2, 7.4 Hz, 2H), 7.03 (dd, *J* = 8.3, 0.7 Hz, 2H), 6.33 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.79 (br s, 2H), 5.13 (dt, *J* = 9.3, 1.3 Hz, 1H), 3.71 (s, 3H), 2.60–2.40 (m, 3H), 1.80 (d, *J* = 1.0 Hz, 3H), 1.69 (d, *J* = 1.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.0, 136.3, 132.6, 127.5, 124.3, 119.7, 117.6, 105.8, 51.7, 36.5, 25.9, 18.2. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (128 MHz, $CDCl_3$) δ 28.8.

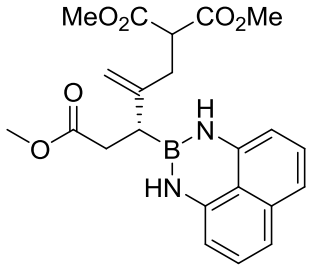
IR (Microscope, cm^{-1}) 3394, 3053, 2951, 1726, 1628, 1602, 1508.

HRMS (EI) for $C_{18}H_{21}BN_2O_2$: calcd. 308.1696; found 308.1698.

$[\alpha]_D^{20}$: –33 (c = 2.7, CH_2Cl_2) for 95% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 23.1 min, T_{minor} = 21.8 min, ee = 95%.

3.6.3.13 Naphthalene-1,8-diamido (dan) derivative 3-33



3-33

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 80:20) yielded **3-33** (34 mg, 0.08 mmol, 81% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.01 (dd, *J* = 8.3, 0.9 Hz, 2H), 6.34 (dd, *J* = 7.3, 1.0 Hz, 2H), 6.00 (br s, 2H), 4.89 (s, 1H), 4.83 (s, 1H), 3.80–3.70 (1H overlapped in the peaks), 3.74 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 2.80–2.60 (m, 4H), 2.36 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.4, 147.6, 140.9, 136.2, 127.5, 119.8, 117.7, 109.5, 106.0, 52.7, 51.8, 50.0, 35.8, 35.2. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.3.

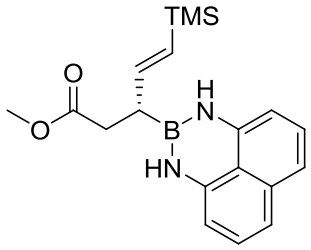
IR (Microscope, cm^{-1}) 3394, 3053, 3003, 2953, 1732, 1630, 1601, 1511.

HRMS (EI) for $C_{22}H_{25}BN_2O_6$: calcd. 424.1806; found 424.1809.

$[\alpha]_D^{20}$: 4.8 (c = 0.24, CH_2Cl_2) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 34.7 min, T_{minor} = 38.7 min, ee = 99%.

3.6.3.14 Naphthalene-1,8-diamido (dan) derivative 3-34



3-34

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 90:10) yielded **3-34** (18 mg, 0.05 mmol, 51% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.4, 7.4 Hz, 2H), 7.01 (dd, *J* = 8.4, 1.0 Hz, 2H), 6.30 (dd, *J* = 7.3, 1.0 Hz, 2H), 6.11 (dd, *J* = 18.7, 7.3 Hz, 1H), 5.75 (br s, 2H), 5.68 (dd, *J* = 18.7, 1.4, 1H), 3.69 (s, 3H), 2.60 (d, *J* = 7.3, 3.3 Hz, 2H), 2.41 (m, 1H), 0.09 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 146.5, 140.8, 136.3, 129.8, 127.5, 119.7, 117.7, 105.9, 51.7, 34.8, –1.1. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.7.

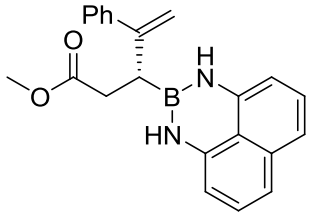
IR (Microscope, cm^{-1}) 3399, 3054, 2953, 1727, 1628, 1602, 1514.

HRMS (EI) for $C_{19}H_{25}BN_2O_2Si$: calcd. 352.1778; found 352.1784.

$[\alpha]_D^{20}$: 1.3 (c = 0.45, CH_2Cl_2) for 91% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm,T_{major} = 24.0 min, T_{minor} = 16.1 min, ee = 91%.

3.6.3.15 Naphthalene-1,8-diamido (dan) derivative 3-35



3-35

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 80:20) yielded **3-35** (12 mg, 0.03 mmol, 33% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2H), 7.34–7.27 (m, 3H), 7.08 (dd, *J* = 8.2, 7.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 1.0 Hz, 2H), 6.28 (dd, *J* = 7.3, 1.0 Hz, 2H), 5.87 (br s, 2H), 5.44 (d, *J* = 0.7 Hz, 1H), 5.06 (s, 1H), 3.70 (s, 3H), 2.90 (dd, *J* = 8.2, 7.5 Hz, 1H), 2.75 (dd, *J* = 16.3 Hz, 6.8 Hz, 1H), 2.73 (dd, *J* = 16.1 Hz, 8.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 150.7, 141.9, 140.8, 136.2, 128.5, 127.8, 127.5, 126.4, 119.8, 117.8, 111.3, 106.0, 51.9, 35.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4.

IR (Microscope, cm^{-1}) 3404, 3054, 2950, 1726, 1629, 1601, 1506.

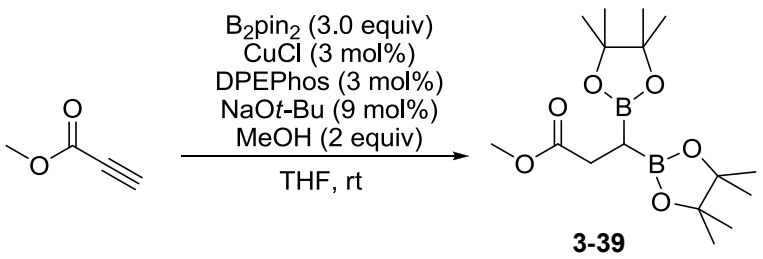
HRMS (EI) for $C_{22}H_{21}BN_2O_2$: calcd. 356.1696; found 356.1696.

$[\alpha]_D^{20}$: 67 (c = 0.15, chloroform) for 88% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 27.4 min, T_{minor} = 31.0 min, ee = 88%.

3.6.4 Preparation of other diboron compounds

3.6.4.1 Methyl 3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate



3-39

CuCl (30 mg, 0.30 mmol), DPEPhos (162 mg, 0.30 mmol), and NaO*t*Bu (86 mg, 0.90 mmol) were dissolved in THF (8.0 mL) and stirred at room temperature for 30 minutes before the addition of pinacolato diboron (7.6 g, 30 mmol) in THF (6.0 mL). The reaction was further stirred for 10 minutes and methyl propiolate (841 mg, 890 µl, 10 mmol) was then added along with THF (6 mL) and dropwise addition of MeOH (1.3 g, 1.7 mL, 40 mmol). After 12 hours of stirring, the reaction mixture was evaporated *in vacuo* and directly purified by flash silica column chromatography (EtOAc/Hexanes = 1:19) to give **3-39** (1.9 g, 56%) as colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.56 (d, J = 8.3 Hz, 2H), 1.24 (s, 12 H), 1.22 (s, 12H), 1.07 (t, J = 7.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 82.8, 51.0, 29.9, 24.3, 24.0. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.6.

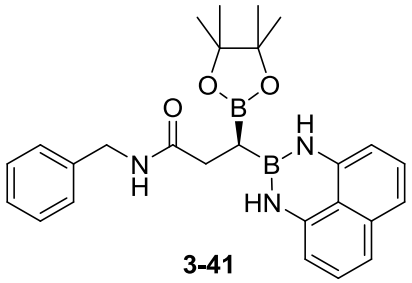
IR (Microscope, cm^{-1}) 2979, 2951, 1739.

HRMS (EI) for $C_{15}H_{27}B_2O_6$ $(M - CH_3)^+$: calcd. 325.1994; found 325.1977.

3.6.4.2 General procedure for the synthesis of 1,1-diboron 3-41, 3-43, 3-45

To a stirred solution of **3-11** (1.0 mmol) in toluene (2.0 mL) was added pyrrolidine (3.0 mmol), 1,2,4-triazole (69 mg, 1.0 mmol), and DBU (152 mg, 150 µL, 1.0 mmol), sequentially. The reaction was stirred for 2 h at 95 °C before being concentrated *in vacuo*. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 1:1) to give amides in pure form.

3.6.4.2.1 *N*-Benzyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide



3-41

The title compound was prepared using the general procedure **3.6.4.2** for the amide formation (racemic form). Flash silica column chromatography (hexanes/EtOAc = 20:80) yielded **3-41** (155 mg, 0.34 mmol. 34 % yield) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 7.14-7.12 (m, 2H), 7.03 (dd, *J* = 8.3, 0.6 Hz, 2H), 6.33 (dd, *J* = 7.3, 0.7 Hz, 2H), 6.16 (br s, 2H), 4.46 (d, *J* = 4.0 Hz, 1H), 4.45 (d, *J* = 4.0 Hz, 1H), 2.58 (dd, *J* = 14.8, 8.6 Hz, 1H), 2.51 (dd, *J* = 14.8, 5.9 Hz, 1H), 1.30-1.20 (m, 12H), 1.17 (dd, *J* = 8.5, 6.0 Hz, 1H).

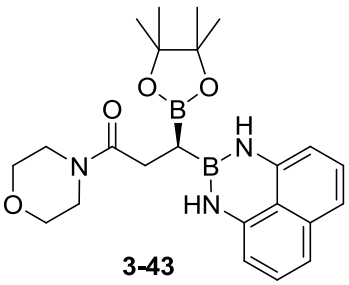
^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 141.3, 138.4, 136.3, 128.7, 127.8, 127.6, 127.5, 119.6, 117.3, 105.7, 83.7, 43.8, 33.2, 24.9, 24.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.5.

IR (Microscope, cm^{-1}) 3405, 3324, 3055, 2976, 2924, 1630, 1600, 1628, 1602, 1514.

HRMS (EI) for $C_{26}H_{31}B_2N_3O_3$: calcd. 455.2552; found 455.2573.

3.6.4.2.2 *N*-Benzyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide



3-43

The title compound was prepared using the general procedure **3.6.4.2** for the

amide formation. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **3-43** (200 mg, 0.50 mmol, 46 % yield) as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.09 (m, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.32 (d, *J* = 7.2 Hz, 2H), 6.08 (br s, 2H), 3.76-3.58 (m, 6H), 3.54-3.40 (m, 2H), 2.66-2.58 (m, 2H), 2.51 (dd, *J* = 14.8, 5.9 Hz, 1H), 1.30, (s, 6H), 1.27 (s, 6H), 1.04 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 141.3, 136.3, 127.6, 119.6, 117.3, 105.5, 83.1, 66.9, 66.6, 45.9, 42.6, 30.8, 25.0, 24.7. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

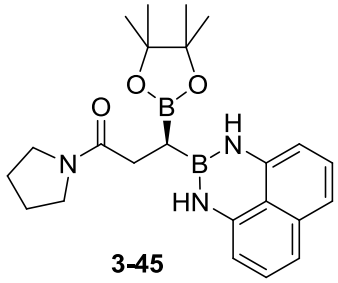
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6.

IR (Microscope, cm^{-1}) 3362, 3052, 2976, 2898, 1625, 1600, 1521.

HRMS (EI) for $C_{23}H_{31}B_2N_3O_4$: calcd. 435.2501; found 435.2515.

$[\alpha]_D^{20}$: –13 (c = 0.70, $CHCl_3$).

3.6.4.2.3 (*R*)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-1-(pyrrolidin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one



3-45

The title compound was prepared using the general procedure **3.6.4.2** for the amide formation (racemic form). Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **3-45** (192 mg, 0.46 mmol, 46 % yield) as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.08 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.31 (d, *J* = 8.0 Hz, 2H), 6.12 (br s, 2H), 3.60-3.40 (m, 4H), 2.61-2.56 (m, 2H), 2.02-1.85 (m, 4H), 2.51 (dd, *J* = 14.8, 5.9 Hz, 1H), 1.29, (s, 6H), 1.28 (s, 6H), 1.02 (t, *J* = 8.2 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 141.5, 136.3, 127.5, 119.6, 117.2, 105.4, 82.7, 46.6, 46.2, 32.6, 26.0, 25.0, 24.8, 24.4. (The boron-bound carbon was not

detected due to quadrupolar relaxation of boron)

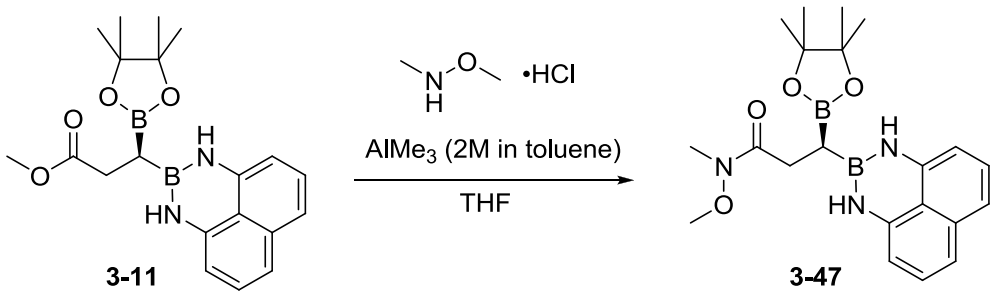
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.7.

IR (Microscope, cm^{-1}) 3403, 3324, 3051, 2974, 2928, 1628, 1600, 1514.

HRMS (EI) for $C_{23}H_{31}B_2N_3O_3$: calcd. 419.2552; found 419.2552.

$[\alpha]_D^{20}$: –15 (c = 0.10, $CHCl_3$).

3.6.4.3 (*R*)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide



3-11 **3-47**

Compound **3-47** was synthesized according to a modified protocol reported by Evans et al.[54] To a mixture of *N*-methoxy-*N*-methylamine hydrochloride (3.1 g, 32 mmol) in THF (32 mL) at 0 ºC was added trimethylaluminum (15.6 mL, 2M in toluene, 32 mmol). The solution was stirred at room temperature for 30 minutes, cooled to 0 ºC, before the addition of **3-11** (2.4 g, 6.3 mmol) in THF (10 mL). The reaction mixture was then stirred at 0 ºC for 2 hours, and at room temperature overnight. After the solution was quenched by the addition of 1M HCl, it was extracted by dichloromethane (3 × 100 mL), dried with $MgSO_4$, and filtered. This crude solution was then concentrated and purified with flash silica column chromatography (hexanes/EtOAc = 1:1) to afford the pure product **3-47** (1.7 g, 4.1 mmol, 65%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14-7.10 (m, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.33 (d, *J* = 7.2 Hz, 2H), 6.02 (br s, 2H), 3.76 (s, 3H), 3.23 (s, 3H), 2.75 (d, *J* = 7.7 Hz, 2H), 1.30, (s, 6H), 1.28 (s, 6H), 1.12 (t, *J* = 7.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 141.3, 136.3, 127.5, 119.6, 117.3, 105.5, 83.3, 61.3, 32.6, 29.0, 25.0, 24.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

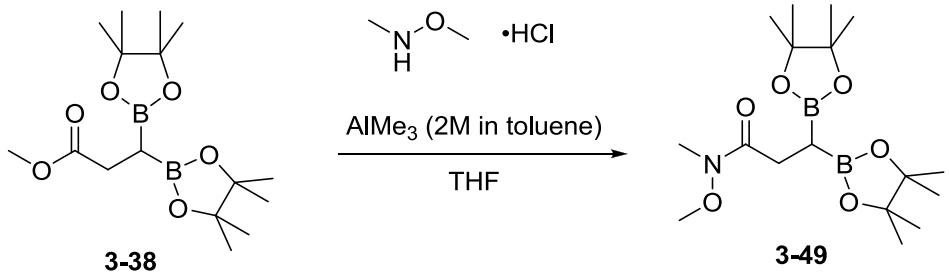
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.0.

IR (Microscope, cm^{-1}) 3367, 3053, 2975, 1652, 1601, 1513.

HRMS (EI) for $C_{21}H_{29}B_2N_3O_4$: calcd. 409.2344; found 409.2353.

$[\alpha]_D^{20}$: –44 (c = 0.09, $CHCl_3$).

3.6.4.4 *N*-methoxy-*N*-methyl-3,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (3-49)



3-38 **3-49**

3-49 was synthesized according to a modified protocol reported by Evans et al.[53] To a mixture of *N*-methoxy-*N*-methylamine hydrochloride (975 mg, 10 mmol) in THF (10 mL) at 0 ºC was added trimethylaluminum (5.0 mL, 2M in toluene, 10 mmol). The solution was stirred at room temperature for 30 minutes, cooled to 0 ºC, before the addition of **3-38** (680 mg, 2.0 mmol) in THF (10 mL). The reaction mixture was then stirred at 0 ºC for 2 hours, and at room temperature overnight. After the solution was quenched by the addition of 1M HCl, it was extracted by dichloromethane (3 × 100 mL), dried with $MgSO_4$, and filtered. This crude solution was then concentrated and purified with flash silica column chromatography (hexanes/EtOAc = 1:1) to afford the pure product **3-49** (368 mg, 1.0 mmol, 52%) as a light pink solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.18 (s, 3H), 2.72 (d, *J* = 7.7 Hz, 2H), 1.27 (s, 12H), 1.25 (s, 12H), 1.05 (t, *J* = 8.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 83.0, 61.1, 32.6, 28.8, 24.8, 24.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.6.

IR (Microscope, cm^{-1}) 2977, 2935, 1666.

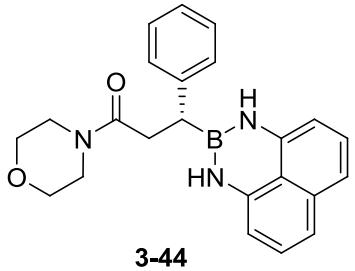
HRMS (EI) for $C_{16}H_{30}B_2NO_6$ $(M - CH_3)^+$: calcd. 354.2259; found 354.2274.

3.6.5 Stereoselective cross-coupling reactions with 1,1-diboron compounds 3-43 and 3-45, and 3-49

3.6.5.1 General procedure (Table 3-12)

$Pd(dba)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.30 mmol), bromobenzene (0.10 mmol), phenol (0.25 mmol) and 1,1-diboron **3-43** or **3-45** (0.15 mmol) were stirred in toluene (1.0 mL) at 80°C for 15 hours. The reaction mixture was then cooled down, filtered through celite and evaporated *in vacuo*. The crude product was then purified with flash silica column chromatography to afford the title product.

3.6.5.2 (*R*)-1-morpholino-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenylpropan-1-one (3-44)



3-44

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **3-44** (29 mg, 0.08 mmol, 75% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (m, 2H), 7.30-7.20 (m, 3H), 7.10-7.07 (m, 2H), 7.01 (d, *J* = 8.1, 2H), 6.27 (d, *J* = 7.3 Hz, 2H), 6.03 (br s, 2H), 3.75-3.50 (m, 6H), 3.45-3.40 (m, 2H), 3.02 (dd, *J* = 9.8, 4.3 Hz, 1H), 2.94 (dd, *J* = 15.2, 9.9 Hz, 1H), 2.80 (dd, *J* = 15.1, 4.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 143.6, 141.1, 136.3, 129.0, 128.2, 127.5, 126.1, 119.7, 117.5, 105.9, 66.8, 66.4, 46.2, 42.2, 36.1, 24.9. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.3.

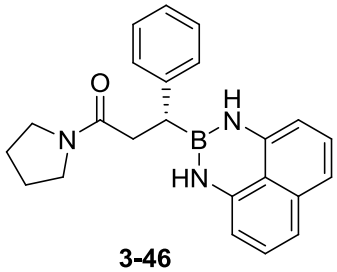
IR (Microscope, cm^{-1}) 3419, 3341, 3356, 3006, 2969, 2922, 2857, 1628, 1599, 1513.

HRMS (EI) for $C_{23}H_{24}BN_3O_2$: calcd. 385.1962; found 385.1875.

$[\alpha]_D^{20}$: 1.6 (c = 0.22, $CHCl_3$) for 90% ee.

HPLC (Chiralcel OD): 50:50 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm,T_{major} = 42.5 min, T_{minor} = 49.5 min, ee = 90%.

3.6.5.3 (*R*)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (3-46)



3-46

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 30:70) yielded **3-46** (32 mg, 0.09 mmol, 86% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 2H), 7.31-7.22 (m, 3H), 7.08 (dd, *J* = 8.2, 7.5 Hz, 2H), 6.99 (dd, *J* = 8.3, 0.8 Hz, 2H), 6.27 (dd, *J* = 7.3 Hz, 0.9 Hz, 2H), 6.15 (br s, 2H), 3.57-3.50 (m, 2H), 3.40-3.35 (m, 2H), 3.09 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.92 (dd, *J* = 15.6, 10.6 Hz, 1H), 2.74 (dd, *J* = 15.6, 3.9 Hz, 1H), 1.96-1.84 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 144.0, 141.3, 136.3, 128.9, 128.1, 127.5, 125.8, 119.7, 117.3, 105.8, 46.8, 46.0, 38.0, 26.1, 24.9, 24.4. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.7.

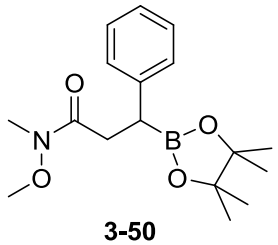
IR (Microscope, cm^{-1}) 3418, 3316, 3053, 2972, 2874, 1627, 1597, 1513, 1504.

HRMS (EI) for $C_{23}H_{24}BN_3O$: calcd. 369.2012; found 369.2014.

$[\alpha]_D^{20}$: 16 (c = 0.78, $CHCl_3$) for 89% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm,T_{major} = 26.9 min, T_{minor} = 31.9 min, ee = 89%.

3.6.5.4 *N*-methoxy-*N*-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide



3-50

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-50** (31 mg, 0.1 mmol, 96% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 7.20-7.14 (m, 1H), 3.66 (s, 3H), 3.19 (s, 3H), 3.05-2.93 (m, 1H), 2.90-2.85 (m, 1H), 2.74 (dd, *J* = 11.0, 5.7 Hz, 1H), 1.25 (s, 6H), 1.20 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 142.1, 128.5, 128.4, 125.5, 83.3, 61.2, 35.9, 32.3, 24.6, 24.5. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.3.

IR (Microscope, cm^{-1}) 3059, 3026, 2976, 2934, 1660, 1602.

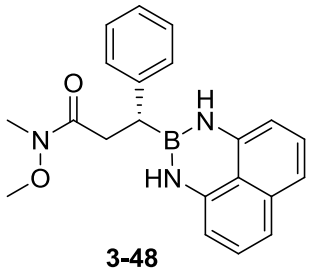
HRMS (EI) for $C_{17}H_{26}BNO_4$: calcd. 319.1955; found 319.1959.

3.6.6 Stereoselective cross-coupling reactions with 1,1-diboron 3-47

3.6.6.1 General procedure (Table 3-14)

$Pd(dba)_2$ (20 μmol), XPhos (40 μmol), K_2CO_3 (0.30 mmol), bromobenzene (0.30 mmol), phenol (0.10 mmol) and 1,1-diboron **3-47** (0.10 mmol) were stirred in toluene (1.0 mL) at 80°C for 15 hours. The reaction mixture was then cooled down, filtered through celite and evaporated *in vacuo*. The crude product was then purified with flash silica column chromatography to afford the title product.

3.6.6.2 (*R*)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenylpropanamide (3-48)



3-48

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-48** (34 mg, 0.1 mmol, 95% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 2H), 7.29-7.24 (m, 3H), 7.11-7.08 (m, 2H), 7.00 (dd, *J* = 8.3, 0.7 Hz, 2H), 6.26 (dd, *J* = 7.3 Hz, 0.9 Hz, 2H), 5.92 (br s, 2H), 3.69 (s, 3H), 3.25 (s, 3H), 3.10-2.90 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.7, 141.1, 136.3, 128.9, 128.0, 127.5, 125.9, 119.7, 117.5, 105.9, 61.4, 34.7, 32.4. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.0.

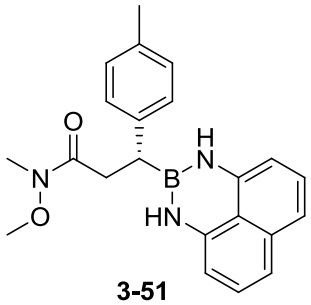
IR (Microscope, cm^{-1}) 3417, 3348, 3054, 3023, 2962, 2935, 1642, 1630, 1600, 1512.

HRMS (EI) for $C_{21}H_{22}BN_3O_2$: calcd. 359.1805; found 359.1812.

$[\alpha]_D^{20}$: 6.5 (c = 0.90, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 18.5 min, T_{minor} = 21.5 min, ee = 99%.

3.6.6.3 (*R*)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-*p*-tolylpropanamide (3-51)



3-51

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-51** (34 mg, 0.09 mmol, 92% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.10-7.05 (m, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.26 (d, *J* = 7.3 Hz, 2H), 5.92 (br s, 2H), 3.69 (s, 3H), 3.24 (s, 3H), 3.05-2.98 (m, 2H), 2.95-2.87 (m, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.2, 140.6, 136.3, 135.3, 129.5, 127.9, 127.5, 119.7, 117.3, 105.8, 61.4, 34.9, 32.4, 21.0. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.1.

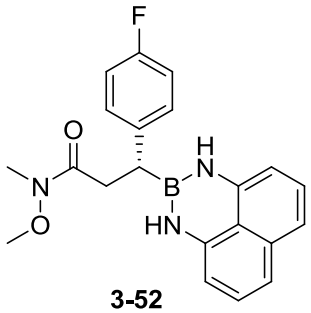
IR (Microscope, cm^{-1}) 3416, 3344, 3052, 3008, 2934, 1642, 1630, 1600, 1511.

HRMS (EI) for $C_{22}H_{24}BN_3O_2$: calcd. 373.1962; found 373.1964.

$[\alpha]_D^{20}$: 0.0 (c = 0.54, $CHCl_3$) for 97% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 16.9 min, T_{minor} = 19.0 min, ee = 97%.

3.6.6.4 (*R*)-3-(4-fluorophenyl)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanamide (3-52)



3-52

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-52** (29 mg, 0.08 mmol, 78% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 2H), 7.11-7.04 (m, 4H), 7.01 (dd, *J* = 8.3, 0.8 Hz, 2H), 6.27 (dd, *J* = 7.3, 0.7 Hz, 2H), 5.87 (br s, 2H), 3.70 (s, 3H), 3.24 (s, 3H), 3.10-2.80 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 161.1 (d, *J* = 244 Hz), 141.0, 139.3, 136.3, 129.4 (d, *J* = 7.7 Hz), 127.5, 119.6, 117.6, 115.7 (d, *J* = 21.1 Hz), 105.9, 61.4, 34.9, 32.4. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

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

^{19}F NMR (469 MHz, $CDCl_3$) δ −117.4.

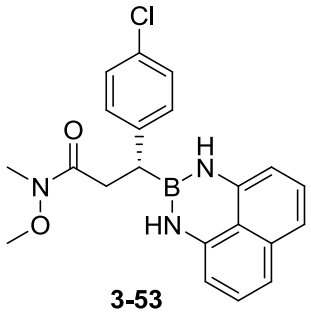
IR (Microscope, cm^{-1}) 3422, 3348, 3054, 3007, 2967, 2937, 1642, 1601, 1506.

HRMS (EI) for $C_{21}H_{21}BN_3O_2F$: calcd. 377.1711; found 377.1717.

$[\alpha]_D^{20}$: 0.70 (c = 0.92, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 21.0 min, T_{minor} = 25.2 min, ee = 99%.

3.6.6.5 (*R*)-3-(4-chlorophenyl)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanamide (3-53)



3-53

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-53** (28 mg, 0.07 mmol, 72% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.12-7.08 (m, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.28 (dd, *J* = 7.3, 0.7 Hz, 2H), 5.86 (br s, 2H), 3.70 (s, 3H), 3.24 (s, 3H), 3.10-2.84 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 142.2, 140.9, 136.3, 131.6, 129.4, 129.0, 127.5, 119.7, 117.7, 106.0, 61.4, 34.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

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

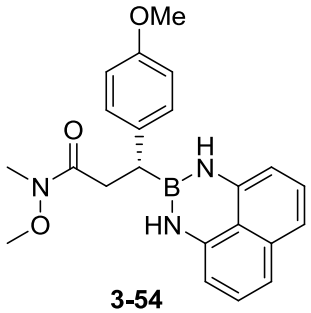
IR (Microscope, cm^{-1}) 3420, 3350, 3053, 3008, 2964, 2936, 1645, 1601, 1513.

HRMS (EI) for $C_{21}H_{21}BN_3O_2Cl$: calcd. 393.1415; found 393.1413.

$[\alpha]_D^{20}$: 4.7 (c = 0.11, $CHCl_3$) for 98% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 22.0 min, T_{minor} = 28.6 min, ee = 98%.

3.6.6.6 (*R*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanamide (3-54)



3-54

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-54** (24 mg, 0.06 mmol, 62% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.7 Hz, 2H), 7.08 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.01 (dd, *J* = 8.3, 0.8 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.27 (dd, *J* = 7.3, 0.9 Hz, 2H), 5.92 (br s, 2H), 3.85 (s, 3H), 3.69 (s, 3H), 3.24 (s, 3H), 3.05-2.85 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 157.7, 141.1, 136.3, 135.6, 129.0, 127.5, 119.7, 117.4, 114.3, 105.7, 61.4, 55.3, 35.0, 24.9. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.7.

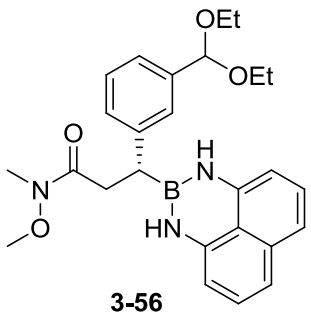
IR (Microscope, cm^{-1}) 3416, 3349, 3053, 3004, 2960, 2935, 1640, 1628, 1600, 1509.

HRMS (EI) for $C_{22}H_{24}BN_3O_3$: calcd. 389.1911; found 389.1917.

$[\alpha]_D^{20}$: −5.6 (c = 0.99, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 24.2 min, T_{minor} = 28.1 min, ee = 99%.

3.6.6.7 (*R*)-3-(3-(diethoxymethyl)phenyl)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanamide (3-56)



3-56

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-56** (37 mg, 0.08 mmol, 81% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (m, 3H), 7.24-7.18 (m, 1H), 7.10-7.05 (m, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.25 (d, *J* = 7.3 Hz, 2H), 5.92 (br s, 2H), 5.54 (s, 1H), 3.80-3.55 (m, 7H), 3.24 (s, 3H), 3.05-2.85 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 141.1, 139.7, 136.3, 128.8, 128.1, 127.5, 126.2, 124.3, 119.7, 117.4, 105.8, 101.8, 61.3, 58.5, 34.7, 32.4, 18.5, 15.3 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.2.

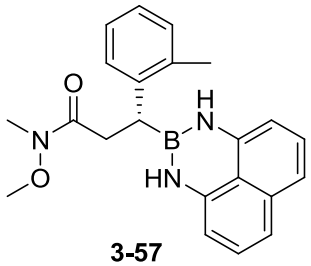
IR (Microscope, cm^{-1}) 3417, 3352, 3053, 3006, 2973, 2933, 1649, 1590, 1528.

HRMS (EI) for $C_{26}H_{32}BN_3O_4$: calcd. 461.2486; found 461.2492.

$[\alpha]_D^{20}$: −10 (c = 0.22, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 15.0 min, T_{minor} = 16.9 min, ee = 99%.

3.6.6.8 (*R*)-*N*-methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-*o*-tolylpropanamide (3-57)



3-57

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 50:50) yielded **3-57** (26 mg, 0.07 mmol, 70% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.15 (m, 4H), 7.11-7.06 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 2H), 6.25 (d, *J* = 7.3 Hz, 2H), 5.90 (br s, 2H), 3.72 (s, 3H), 3.30-3.20 (m, 4H), 3.15-3.05 (m, 1H), 3.00-2.90 (m, 1H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 142.1, 141.2, 136.3, 136.1, 130.7, 127.5, 126.8, 126.5, 125.7, 119.7, 117.4, 105.8, 61.4, 34.2, 32.4, 20.7. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

^{11}B NMR (160 MHz, $CDCl_3$) δ 31.8.

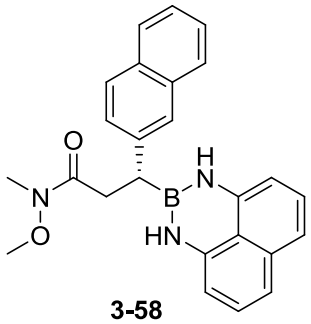
IR (Microscope, cm^{-1}) 3419, 3346, 3053, 3009, 2958, 2932, 2856, 1650, 1629, 1600, 1512, 1504.

HRMS (EI) for $C_{22}H_{24}BN_3O_2$: calcd. 373.1962; found 373.1957.

$[\alpha]_D^{20}$: 9.4 (c = 0.11, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 2.5:97.5 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 60.1 min, T_{minor} = 54.7 min, ee = 99%.

3.6.6.9 (*R*)-*N*-methoxy-*N*-methyl-3-(naphthalen-2-yl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanamide (3-58)



3-58

The title compound was prepared using the general procedure for the stereoselective cross coupling reactions. Flash silica column chromatography (hexanes/EtOAc = 60:40) yielded **3-58** (37 mg, 0.09 mmol, 90% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.84 (m, 3H), 7.70 (s, 1H), 7.56-7.45 (m, 2H), 7.40 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.11-7.06 (m, 2H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.25 (d, *J* = 7.2 Hz, 2H), 5.96 (br s, 2H), 3.72 (s, 3H), 3.30-3.00 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 141.4, 141.1, 136.3, 133.9, 132.0, 128.6, 128.1, 127.7, 127.5, 127.2, 126.3, 125.7, 125.4, 119.7, 117.5, 105.9, 61.4, 34.7, 30.9. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

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

IR (Microscope, cm^{-1}) 3417, 3346, 3052, 3010, 2967, 2935, 1642, 1630, 1600, 1506.

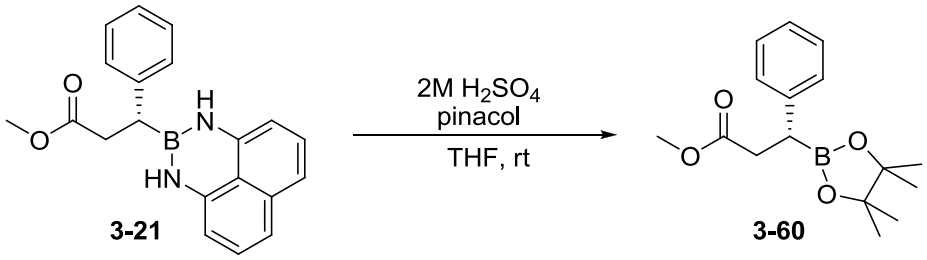
HRMS (EI) for $C_{25}H_{24}BN_3O_2$: calcd. 409.1962; found 409.1969.

$[\alpha]_D^{20}$: 23 (c = 0.16, $CHCl_3$) for 99% ee.

HPLC (Chiralcel OD): 5:95 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 76.2 min, T_{minor} = 80.8 min, ee = 99%.

3.6.7 Iterative cross-coupling sequence

3.6.7.1 (*S*)-Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (3-60)



To a stirred solution of **3-21** (330 mg, 1.00 mmol) in THF (10 mL) was added 2 M H_2SO_4 (1.5 mL, 3.0 mmol) and pinacol (591 mg, 5.00 mmol) sequentially. The reaction was stirred for 24 h at room temperature before quenched by the addition of water (10 mL). The mixture was then extracted by diethyl ether (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 9:1) to give pure **3-66** (260 mg, 90%) as a yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 4H), 7.20–7.15 (m, 1H), 3.67 (s, 3H), 2.92 (dd, *J* = 16.2, 10.0 Hz, 1H), 2.77 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.69 (dd, *J* = 15.9, 6.0Hz, 1H), 1.24 (s, 6H), 1.20 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 141.3, 128.5, 128.2, 125.7, 83.6, 51.5, 37.1, 24.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

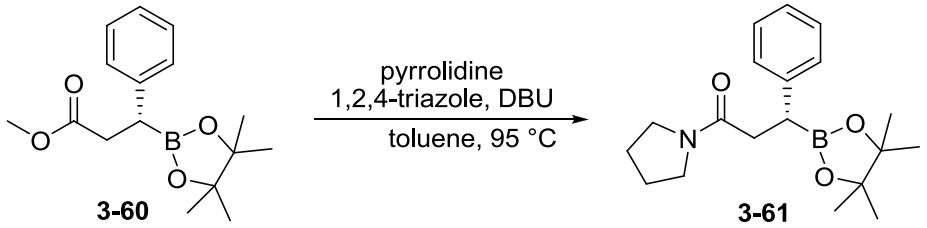
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.2.

IR (Microscope, cm^{-1}) 3085, 3027, 2979, 2952, 1738, 1495.

HRMS (EI) for $C_{16}H_{23}BO_4$: calcd. 290.1690; found 290.1690.

$[\alpha]_D^{20}$: –13 (c = 0.62, CH_2Cl_2).

3.6.7.2 (*S*)-3-Phenyl-1-(pyrrolidin-1-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (3-61)



To a stirred solution of **3-60** (250 mg, 0.860 mmol) in toluene (2.0 mL) was added pyrrolidine (184 mg, 214 μL, 2.58 mmol), 1,2,4-triazole (23.8 mg, 0.345 mmol), and DBU (52.0 mg, 51.5 μL, 0.345 mmol), sequentially. The reaction was stirred for 2 h at 95 °C before being concentrated *in vacuo*. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 1:1) to give **3-61** (220 mg, 77%) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.18 (m, 4H), 7.12–7.07 (m, 1H), 3.47 (t, *J* = 7.0 Hz, 2H), 3.45–3.25 (m, 2H), 2.80 (dd, *J* = 16.6, 10.8 Hz, 1H), 2.72 (dd, *J* = 16.5, 6.6 Hz, 1H), 2.61 (dd, *J* = 10.8, 6.5 Hz, 1H), 1.96–1.76 (m, 4H), 1.12 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 142.8, 127.9, 127.7, 124.6, 81.7, 46.2, 45.7, 38.7, 25.4, 24.3, 24.0. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

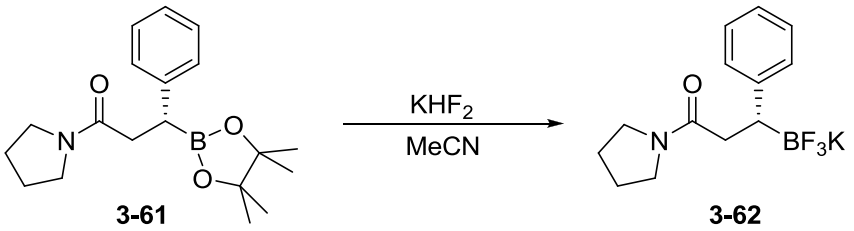
^{11}B NMR (128 MHz, $CDCl_3$) δ 28.0.

IR (Microscope, cm^{-1}) 3083, 3024, 2974, 2931, 2876, 1637, 1602, 1495.

HRMS (EI) for $C_{19}H_{28}BNO_4$: calcd. 329.2162; found 329.2165.

$[\alpha]_D^{20}$: –15 (c = 0.18, CH_2Cl_2).

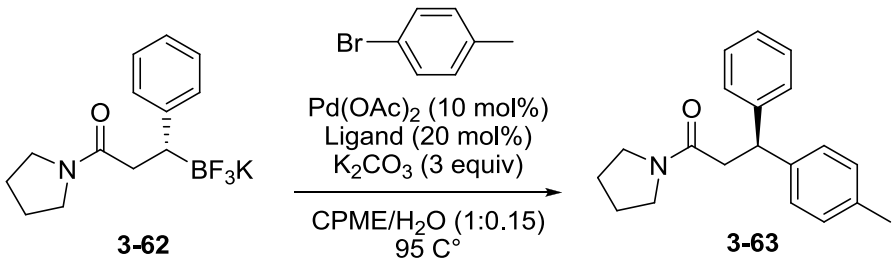
3.6.7.3 (*S*)- Potassium 3-phenyl-1-(pyrrolidin-1-yl)-3-(trifluoroborato)propan-1-one (3-62)



3-61 **3-62**

The title compound was prepared according to the reported procedure.[38] The characterization data for this compound matched that of a previous report.

3.6.7.4 (*R*)-3-Phenyl-1-(pyrrolidin-1-yl)-3-p-tolylpropan-1-one (3-63)



$Pd(OAc)_2$ (5.6 mg, 25 μmol), XPhos (24 mg, 50 μmol), K_2CO_3 (104 mg, 0.750 mmol), 4-bromotoluene (43 mg, 0.25 mmol), and trifluoroborate salt **3-62** (77 mg, 0.25 μmol) was added into a sealed tube (10 mL Biotage microwave vial). The tube was then sealed and purged with N_2 (3 times) before the addition of CPME (1.0 mL) and H_2O (0.15 mL). The reaction mixture was stirred at 95 °C for 20 hours in an oil bath, after which the reaction mixture was cooled down and evaporated *in vacuo*. The crude reaction mixture was purified with flash silica column chromatography (hexane/EtOAc = 1:1) to afford the purified product **3-63** (54 mg, 74%) as a colourless solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.22 (m, 4H), 7.20–7.04 (m, 5H), 4.68 (t, *J* = 7.5 Hz, 1H), 3.38 (t, *J* = 6.5 Hz, 2H), 3.26–3.16 (m, 2H), 2.96 (d, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.84–1.66 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 144.5, 141.3, 135.7, 129.1, 128.4, 127.9, 127.8, 126.2, 46.6, 45.6, 41.1, 26.0, 24.3, 20.9.

IR (Microscope, cm^{-1}) 3049, 3032, 3022, 3001, 2975, 2871, 1635, 1515, 1468.

HRMS (EI) for $C_{20}H_{23}NO$: calcd. 293. 1780; found 293. 1781.

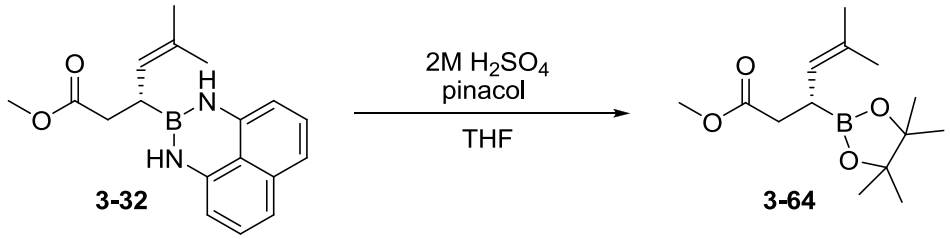
$[\alpha]_D^{20}$: 7.1 (c = 0.60, CH_2Cl_2) for >95% ee.

M.P. 134–135°C.

HPLC (Chiralcel OD): 10:90 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm,T_{major} = 20.8 min, T_{minor} = 22.3 min, ee = >95%.

3.6.8 Cross Coupling/allylboration reactions

3.6.8.1 (*S*)-Methyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-enoate (3-64)



To a stirred solution of **3-32** (308 mg, 1.00 mmol) in THF (10 mL) was added 2 M H_2SO_4 (1.5 mL, 3.0 mmol) and pinacol (591 mg, 5.00 mmol) sequentially. The reaction was stirred for 24 h at room temperature before quenched by the addition of water (10 mL). The mixture was then extracted by diethyl ether (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 9:1) to give pure **3-64** (247 mg, 92%) as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.00 (dsep, *J* = 9.5, 1.3 Hz, 1H), 3.62 (s, 3H), 2.50 (dd, *J* = 16.2, 9.0 Hz, 1H), 2.38 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.27 (ddd, *J* = 9.3, 9.3, 6.3 Hz, 1H), 1.66 (d, *J* = 1.1 Hz, 3H), 1.61 (d, *J* = 1.2 Hz, 3H), 1.22 (s, 6H), 1.19 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 131.9, 122.4, 82.7, 51.0, 35.7, 25.4, 24.2, 24.0, 17.6. (The boron-bound carbon was not detected due to quadrupolar relaxation of boron)

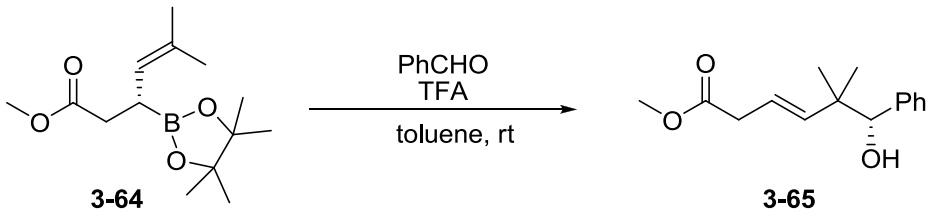
^{11}B NMR (128 MHz, $CDCl_3$) δ 32.6.

IR (Microscope, cm^{-1}) 2978, 2929, 1739, 1603.

HRMS (EI) for $C_{14}H_{25}BO_4$: calcd. 268.1846; found 268.1847.

$[\alpha]_D^{20}$: –21 (c = 0.80, CH_2Cl_2).

3.6.8.2 (*R*,*E*)-Methyl 6-hydroxy-5,5-dimethyl-6-phenylhex-3-enoate (3-65)



To a stirred solution of **3-64** (144 mg, 0.537 mmol) and benzaldehyde (114 mg,

109 μL, 1.07 mmol) in toluene (1 mL) was added trifluoroacetic acid (6.1 mg, 4.0 μL, 54 μmol). The reaction was stirred for 12 h at room temperature before concentrated *in vacuo*. The crude product was then purified by flash silica column chromatography (hexanes/EtOAc = 4:1) to give pure **3-65** (206 mg, 83%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 5.68 (dt, *J* = 15.8, 1.2 Hz, 1H), 5.57 (dt, *J* = 15.8, 6.8 Hz, 1H), 4.43 (s, 1H), 3.72 (s, 3H), 3.11 (dd, *J* = 6.8, 1.2 Hz, 1H), 2.20 (br s, 1H), 1.05 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 141.2, 140.8, 127.8, 127.5, 127.4, 121.3, 80.9, 51.9, 41.7, 38.0, 24.7, 21.7.

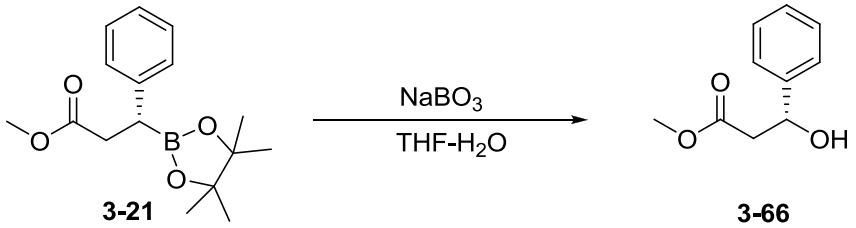
IR (Microscope, cm^{-1}) 3504, 3086, 3061, 3030, 2962, 2909, 2873, 1739, 1493.

HRMS (ESI) for $C_{15}H_{20}NaO_3$ $(M+Na)^+$: calcd. 271.1305; found 271.1302.

$[\alpha]_D^{20}$: –45 (c = 0.57, CH_2Cl_2).

3.6.9 Determination of absolute stereochemistry

3.6.9.1 (*S*)-Methyl 3-hydroxy-3-phenylpropanoate (3-66)



3-21 **3-66**

The title alcohol was prepared independently using the reported procedure (92%).[19a]

The characterization data for this compound matched that of a previous report.[39]

The $[\alpha]_D^{20}$ of this compound was measured to be 29 (c = 0.39, chloroform), the same as the reported for the (*R*)-isomer ($[\alpha]_D^{20}$ = 47, c = 1.2, chloroform). Thus, this proves that the compounds synthesized using (*R*)-(*R*)-CF_3-Walphos **3-17** as the ligand have a (*R*)-configuration at the stereogenic centre.

3.7 References

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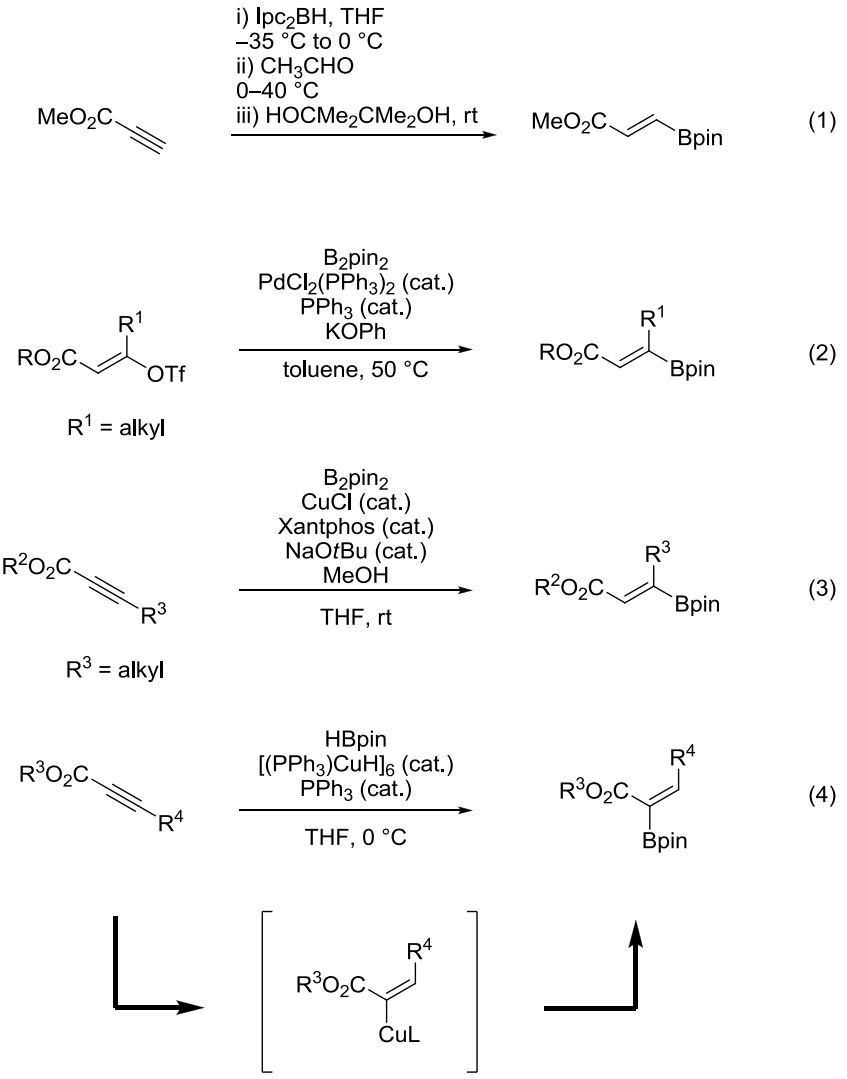
Chapter 4

Stereoselective Preparation of and Synthetic Applications of β-Aryl-β-Boronyl Enoates

4.1 Introduction

In addition to chiral alkyl boronates, alkenyl or alkynyl boronates are also synthetically versatile compounds that can be transformed into various valuable functionalities through different chemical reactions (Chapter 1). Among these substrates, α,β-unsaturated esters substituted with boronyl groups are especially synthetically attractive since these compounds have various reactive sites that can be functionalized regio- and stereoselectively. To date, a few different synthetic methodologies have been developed for the preparation of this class of compounds. Vaultier and coworkers developed a hydroboration approach for the installation of boronates to methyl propiolate (Equation 1, Scheme 4-1).[1] The corresponding boronic acid analogue can also be prepared similarly, as demonstrated by the Hall Group.[2] This approach, however, is limited to hydroboration of terminal alkynes, and therefore only disubstituted β-boronyl esters can be accessed through this reaction. In 2003, the Miyaura Group demonstrated that borylation of triflates can be readily accomplished with palladium catalysis to afford trisubstituted β-boronyl enoates stereoselectively (Equation 2, Scheme 4-1).[3] Similar adducts can also be prepared through conjugate borylation of various substituted ynoates, as illustrated in Scheme 4-1 (Equation 3, Scheme 4-1).[4] These two approaches, however, are limited to precursors bearing alkyl substituents, and the synthesis of aryl variants to date is still an unsolved problem due possibly to the difficult preparation of starting materials. In addition to these synthetic methods for the installation of boronyl groups to the β-position of enoates, the Lipshutz Group has recently reported a conjugate reduction/transmetallation sequence for the incorporation of boronyl groups to the α-position (Equation 4, Scheme 4-1).[5] By employing CuH as the nucleophile, the reagent adds to the alkyne in a *syn* fashion, affording the resulting α-cuprio enoate stereoselectively. Subsequent stereoretentive transmetallation

with pinacolborane then yields the desired α-boronyl enoate.

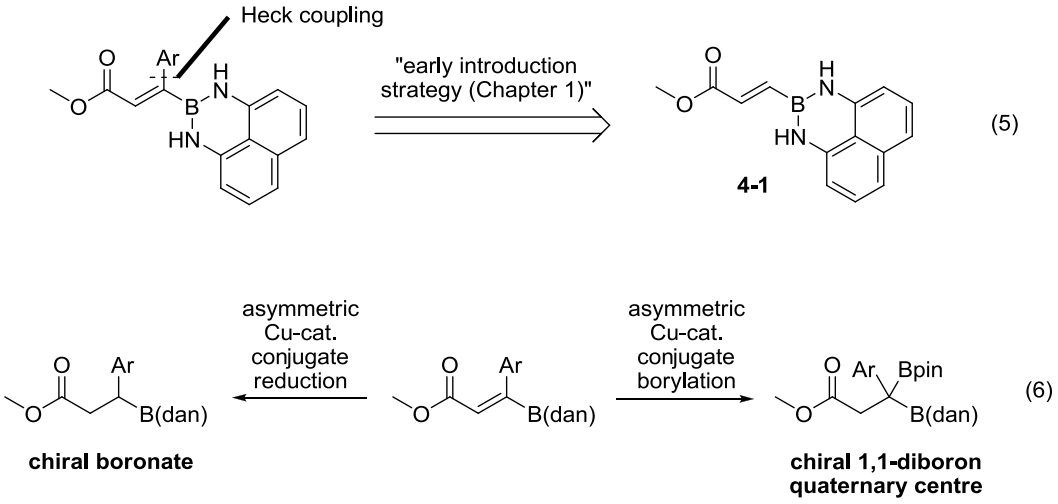


Scheme 4-1: Known methods for the preparation of boronyl enoates.

4.2 Objectives

As mentioned in the above section, the known literature approaches for synthesizing trisubstituted 3-boronyl enoates are restricted to aliphatic side chains at the β-position. Due to the synthetic value of aryl-substituted β-boronyl enoates, a new route for the formation of these compounds is necessary. Knowing that compound **4-1** is robust and can undergo various synthetic transformations (Chapter 2 and 3), it was envisioned that the synthesis of these trisubstituted

alkenes could arise from β-boronyl enoate **4-1** through a Heck reaction (Equation 5, Scheme 4-2). Couplings using the Heck Reaction have become a ubiquitous tool in organic synthesis for the formation of C−C bonds.[6] Owing to its importance in organic synthesis, material and pharmaceutical industries, Richard Heck was awarded the 2010 Nobel Prize along with Akira Suzuki and Ei-ichi Negishi for their contribution in Pd-catalyzed cross-coupling reactions. The difficulty of the proposed approach of Scheme 4-2 would again reside on the possibility for metals to insert into the C−B bond of substrate **4-1**. As demonstrated in the previous chapters and by the Suginome group,[7] however, the C−B bond of compound **4-1** should be stable to allow the desired cross-coupling reaction to be performed. In addition to the synthetic utility presented in Chapter 2 that includes cycloadditions and radical additions, other synthetic transformations will be attempted in order to prepare novel organoboronates that are synthetically valuable. As illustrated in Scheme 4-2 (Equation 6), asymmetric conjugate borylation reactions on these trisubstituted enoates would afford chiral 1,1-diboron compound with quaternary centres, which to date have never been prepared in the literature.[8] On the other hand, these compounds can also undergo asymmetric conjugate reductions to give chiral alkyl boronates with great

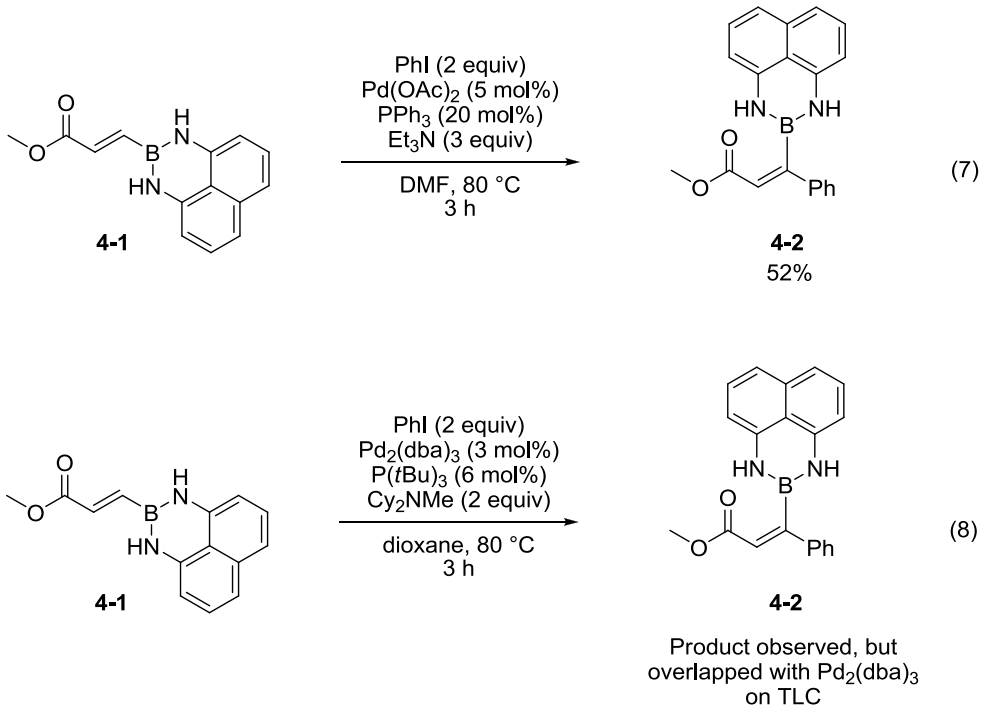


Scheme 4-2: Proposed approach for the synthesis of trisubstituted β-aryl-β-boronyl enoate and their subsequent applications.

synthetic value, as discussed in Chapter 2.[9]

4.3 Reaction optimization

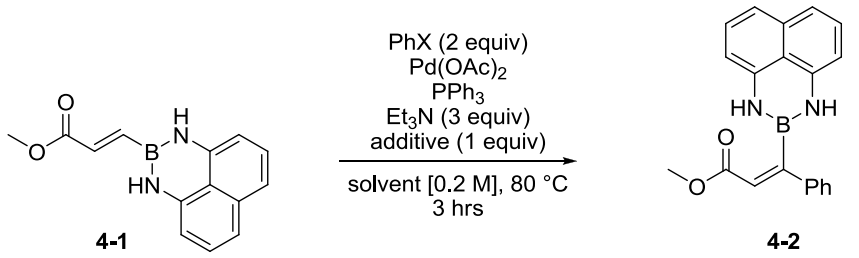
In order to test whether the proposed Heck coupling can be used to synthesize the desired trisubstituted β-aryl-β-boronyl enoates, a standard Heck protocol with $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand, and triethylamine as the base was used. Impressively, the desired model product **4-2** could be isolated with a 52% yield (Equation 7, Scheme 4-3) stereoselectively with a (*E*)-geometry (vide infra). In addition to this standard conditions, another protocol which was developed by the Fu Group was also attempted to access the desired compound.[10] As shown in Scheme 4-3, when $P(tBu)_3$ was used as the ligand, the desired adduct **4-2** could be synthesized with a decent yield based on NMR spectroscopy analysis. Unfortunately, in this instance the product showed up at the same Rf value as $Pd_2(dba)_3$, making the isolation process problematic. Due both to this difficulty and the sensitive nature of $P(tBu)_3$, an optimization process based on the



Scheme 4-3: Initial attempts for the synthesis of trisubstituted 3-boronyl enoate **4-2**.

$Pd(OAc)_2/PPh_3$ system was performed to improve the efficiency of the coupling reaction.

Since organoboron reagents are prone to undergo side reactions during cross-couplings (Chapter 3), a slight excess of the boron compound **4-1** was used in comparison with iodobenzene. Substrate **4-1**, however, is fairly stable under the reaction conditions, and only a low yield of the desired transformation could be accomplished (Entry 2, Table 4-1). An excess amount of phosphine was unnecessary, and as such it was found that only a small amount of phosphine ligand was required to achieve a good yield of the coupling process (Entry 3, Table 4-1). Since the molar ratio of the ligand is lower than the palladium catalyst, it was proposed that triphenylphosphine in this reaction is mainly used to



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

[a] Isolated yields of product after flash column chromatography, *E/Z* > 98% by ^{1}H-NMR. [b] PhI (1 equiv), and **4-1** (1.5 equiv). [c] 1M instead of 0.2 M.

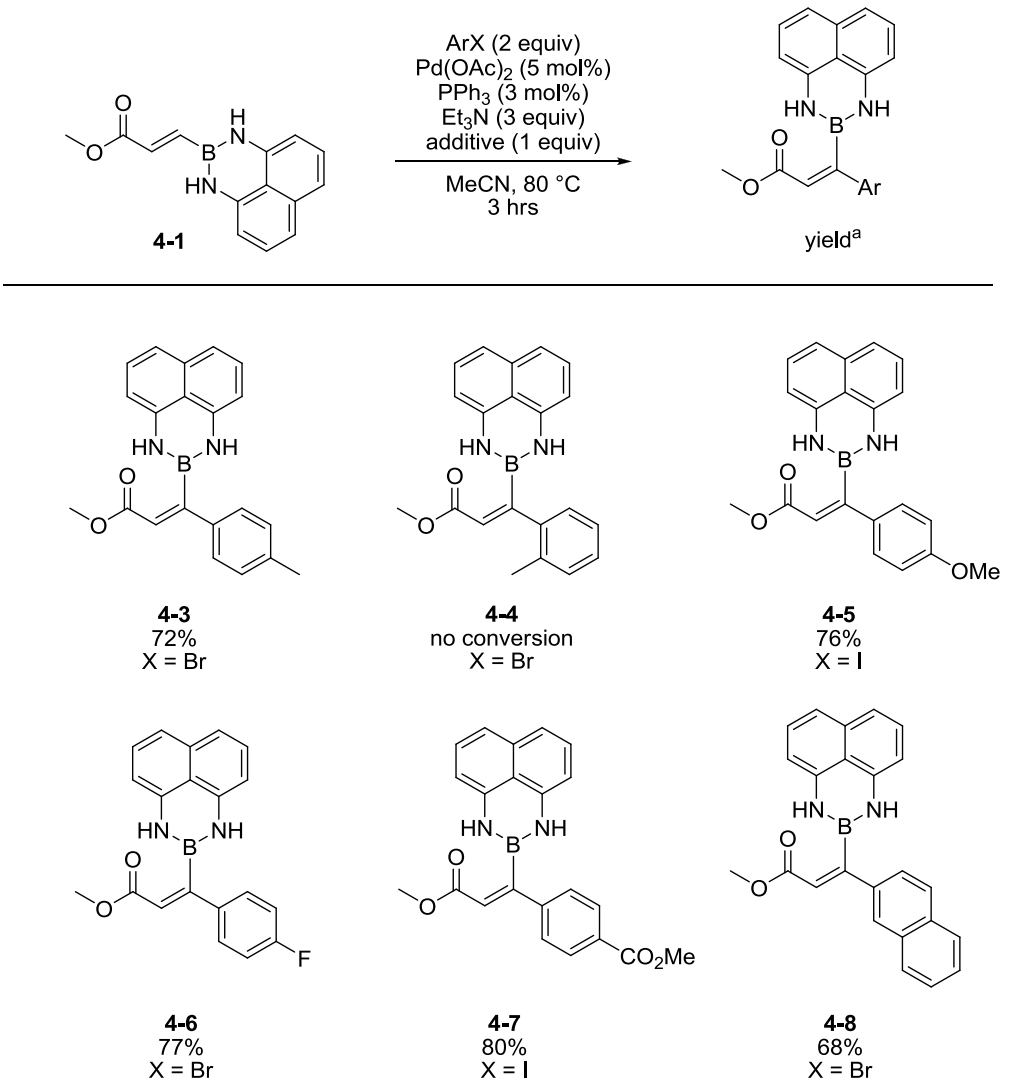
Table 4-1: Optimization of reaction conditions for the synthesis of substrate **4-3**.

reduce Pd(II) to the active Pd(0) *in-situ*. To further improve the reaction efficiency, Bu_4NHSO_4 was added as an additive (Entries 4, 6 and 7, Table 4-1). The reaction yield remained relatively similar when iodobenzene was used as the coupling partner, but a dramatic increase in yield can be observed when bromobenzene was used. There are several roles that this additive might play during the reaction: (1) the anions can serve to activate the palladium centre to accelerate the oxidative addition step. (2) They can stabilize the palladium complex and increase the lifetime of the catalyst.[6a] By coordinating to the palladium centre, the catalyst becomes a more stable neutral or anionic complex due to Coulombic interactions, thus avoiding cluster formation and decomposition. After some experimentation, it was found that only 5 mol% of the palladium catalyst was necessary to achieve a good yield of the desired coupling product (Entry 8, Table 4-1). In terms of the reaction solvent, DMF and acetonitrile were found to be optimal, while other solvents such as toluene afforded a lower yield (Entries 9-11, Table 4-1). Overall, the reaction conditions shown in Entry 11 were chosen as the optimal procedure for the syntheses of various β-aryl-β-boronyl enoates due to the lower boiling point associated with acetonitrile.

4.4 Scope of aryl halides in Heck Reaction

The scope of aryl halides towards the preparation of β-aryl-β-boronyl α,β-unsaturated esters was examined under the optimal reaction conditions. As shown in Table 4-2, while bromobenzene and 4-bromotoluene can be used as coupling partners to afford the desired coupling products **4-2** and **4-3** with good yields, coupling of 2-bromotoluene failed to occur (Table 4-2). The steric hindrance from the *ortho*-substituent is probably problematic for oxidative addition to take place. In terms of electronic factors, both electron rich and electron deficient aryl halides are tolerated, affording the desired β-aryl-β-boronyl α,β-unsaturated esters as single stereoisomers with good yields (**4-5**-**4-7**, Table 4-2). Oligoaryl bromide such as naphthalenyl bromide can also be used, giving the desired enoate **4-8** with a good efficiency (Table 4-2). In some of these cases, aryl iodides have to be

utilized presumably to enhance the rate of oxidative addition (**4-5** and **4-7**, Table 4-2).



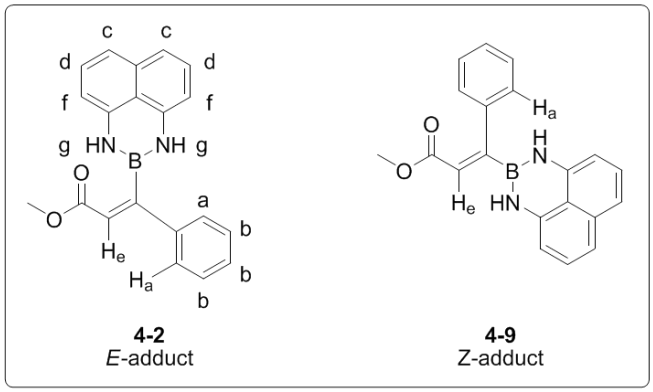
[a] Isolated yields of products after flash column chromatography.

Table 4-2: Scope of aryl halides in Heck Reaction of boronyl compound **4-1**.

4.5 Determination of the absolute stereochemistry of the coupling product

In order to determine the absolute stereochemistry of the double bond formed from the coupling process, a nOe experiment of the cross-coupled product **4-2** was conducted. As illustrated in Figure 4-1, the alkene hydrogen, H_e, couples strongly with the *ortho*-hydrogens of the aromatic ring, H_a. This through-space

coupling interaction is only possible in the (*E*)-isomer since the two hydrogen atoms are within 5Å distance. On the other hand, this coupling interaction cannot be present in the (*Z*)-adduct **4-9**, confirming the double bond geometry.



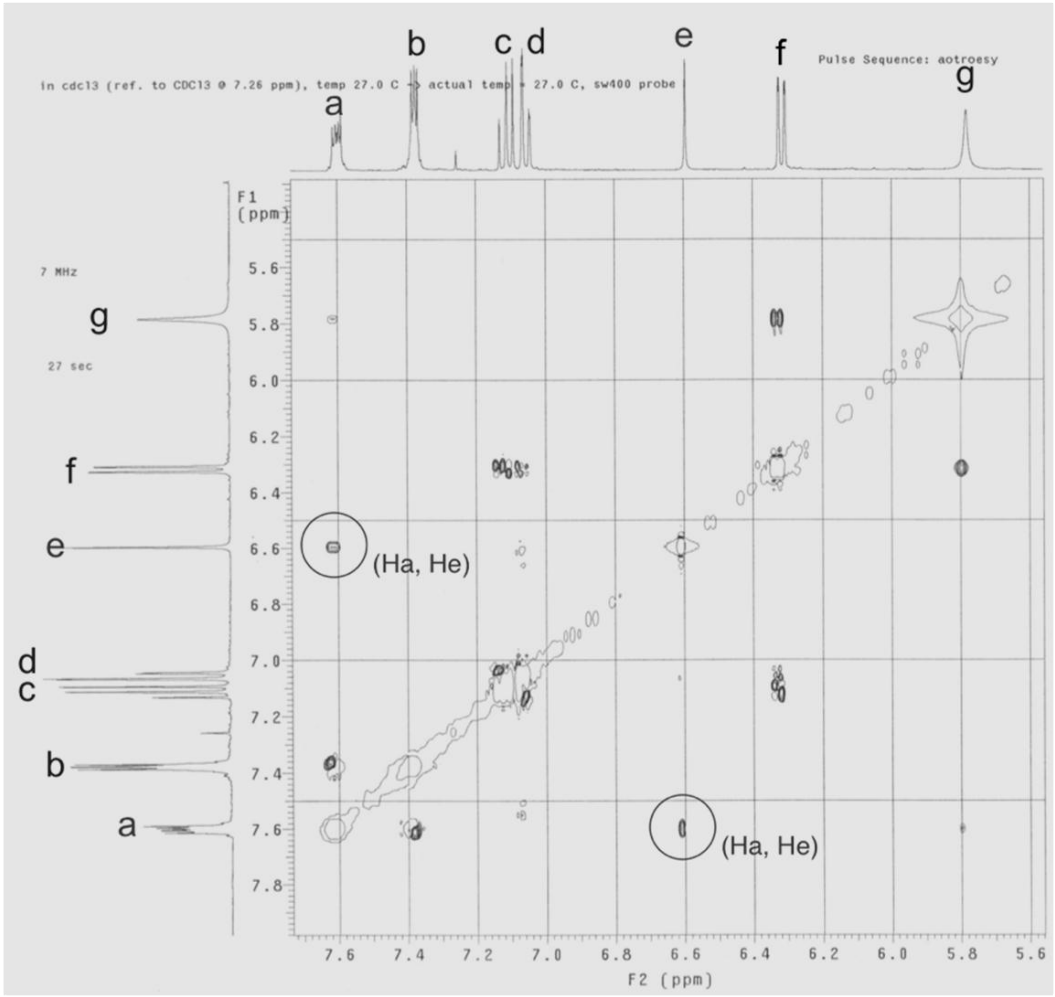


Figure 4-1: NOESY experiment to determine the *E/Z* stereochemistry of Heck coupling product **4-2**.

4.5.1 The proposed rationale behind the observed selectivity

Since it is known that the migratory insertion has to occur in a *syn*-fashion, only one diastereomer, **4-10**, could be formed from the insertion step.[6] The subsequent β-hydride elimination between the palladium centre and the hydrogen atom also has to occur in a *syn*-fashion as shown below,[6] and as a result only the (*E*)-product **4-2** could be formed selectively under the reaction conditions (Figure 4-2). The other diastereomer **4-11** results from migratory insertion of ArPdX species to (*Z*)-**4-1**, and thus is not observed as a by-product of this cross-coupling reaction.

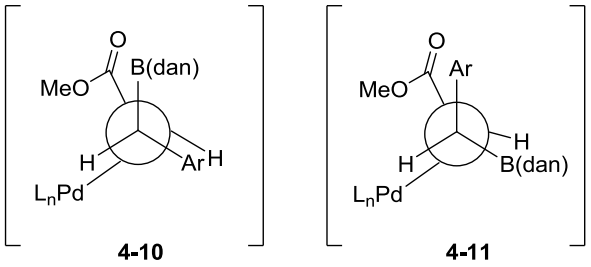
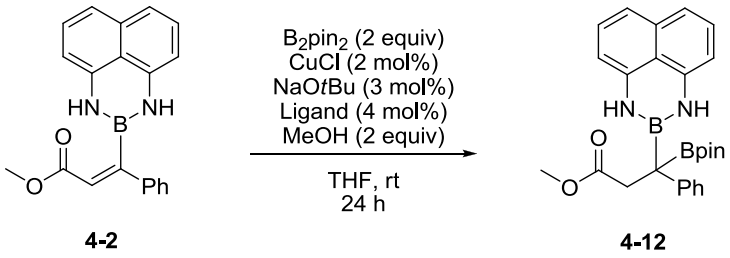


Figure 4-2: Stereochemical rationale for the observed double bond geometry of products **4-2** to **4-8**.

4.6 Synthetic applications of trisubstituted β-boronyl enoates

4.6.1 Asymmetric conjugate borylation

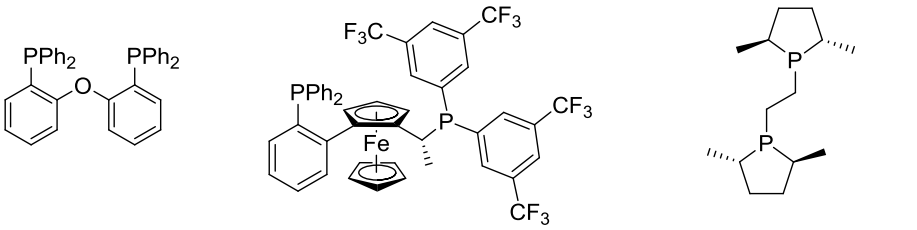
To test whether conjugate borylation can be conducted with trisubstituted β-aryl-β-boronyl enoate, model substrate **4-2** was subjected to typical conjugate borylation condition with DPEphos as the ligand (Entry 1, Table 4-3). Unfortunately, no conversion of the starting material was observed both at room temperature and at elevated temperature (Entries 1-2, Table 4-3). Other ligands such as CF_3-Walphos **4-13** and Me-Duphos **4-14** were also found to be ineffective to promote the desired transformation (Entries 3 and 5, Table 4-3).[8] In light of a recent report claiming that the rate of conjugate borylation can be dramatically enhanced by using a higher molar ratio of base, one equivalent of NaO*t*Bu was used instead of a catalytic amount.[11] In this case, however, a complex intractable mixture was produced (Entry 4, Table 4-3).



4-2 **4-12**

Entry	Ligand	Yield[a]
1	**4-12**	No conversion
2	**4-12**	No conversion[b]
3	**4-13**	No conversion
4	**4-13**	Complex mixture[c]
5	**4-14**	No conversion

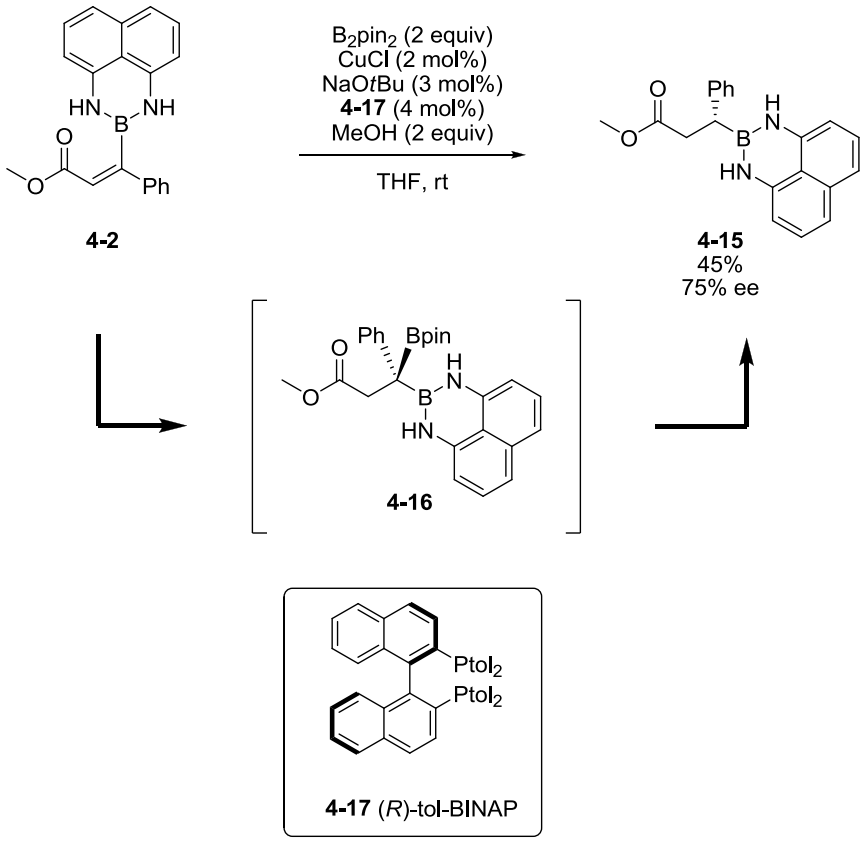
[a] Isolated yields of product after flash column chromatography. [b] The reaction was conducted under reflux temperature. [c] NaO*t*Bu (1 equiv).



4-12 DPEphos **4-13** (*R*)-(*R*)-Walphos (CF_3) **4-14** (*S*)-(*S*)-Me-Duphos

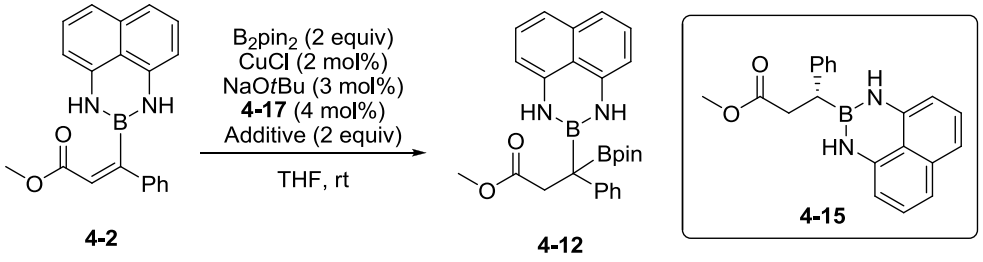
Table 4-3: Screening of ligands in an attempt to perform conjugate borylation on trisubstituted β-aryl-β-boronyl enoate **4-2**.

Surprisingly, when tol-BINAP **4-17** was used as the ligand, chiral boronate **4-15** could be isolated with a modest yield and good enantioselectivity (Scheme 4-4). It is proposed that chiral boronate **4-15** likely arises from the desired 1,1-diboron **4-16** through stereoretentive protodeboronation. This undesired side reaction, as discussed in Chapter 1, would occur with partial retention of stereochemistry to give the isolated chiral alkyl boronate **4-15** enantioselectively. This overall process affords a formal asymmetric conjugate reduction to give chiral alkyl boronate **4-15** stereoselectively from β-boronyl enoate **4-2**.



Scheme 4-4: Attempted asymmetric conjugate borylation of compound **4-2** with **4-17** as the ligand.

In an attempt to avoid the undesired protodeboronation, different additives were used to trap the copper enolate in order to turn over the catalyst. A protic source such as *t*BuOH was ineffective, giving the protodeboronation product similar to when MeOH was used (Entry 1, Table 4-4). When benzaldehyde was used as the electrophile, no conversion was observed and only the starting material could be recovered. In conjugate borylation reactions, protic addtives are necessary to turn over the active catalyst. Since these additives are thought to be the source of protodeboronation, one equivalent of the active catalyst was used to avoid this potential side reaction (Entry 4, Table 4-4). Unfortunately, again the protodeboronated product **4-15** was isolated, showing that the proton source in the protodeboronation is likely from the substrate itself (such as the amine hydrogen atoms on the B(dan) unit).



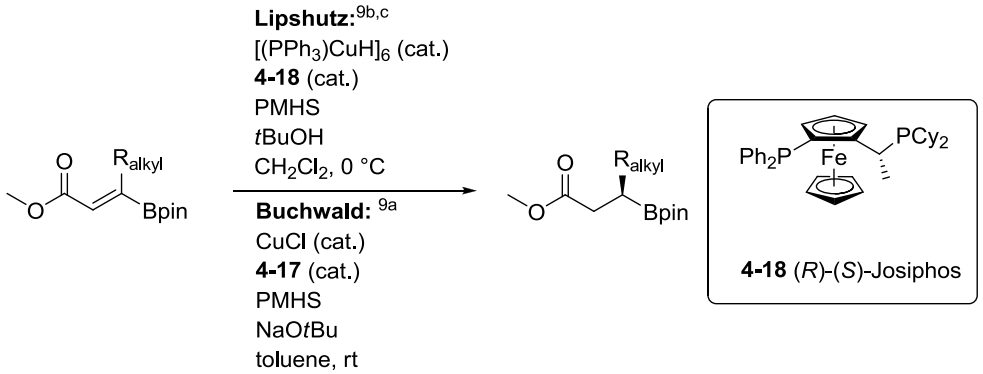
Entry	Additive	Result
1	*t*BuOH	Protodeboronation product
2	Benzaldehyde	No conversion
3	MeOH[a]	Protodeboronation product
4	-[b]	Protodeboronation product

[a] 1 equiv. [b] CuCl (1 equiv), NaO*t*Bu (1 equiv), and **4-17** (1 equiv).

Table 4-4: Optimization of additives in order to avoid undesired protodeboronation.

4.6.2 Asymmetric conjugate reduction

The Buchwald[9a] and Lipshutz[9b,c] groups have independently developed efficient copper-catalyzed enantioselective methods for conjugate reduction of α,β-unsaturated compounds with polymethylhydrosiloxane (PMHS) as a mild hydride source. Recently, the Hall group applied these methodologies to β-alkyl-β-boronyl α,β-unsaturated esters to access the corresponding chiral secondary



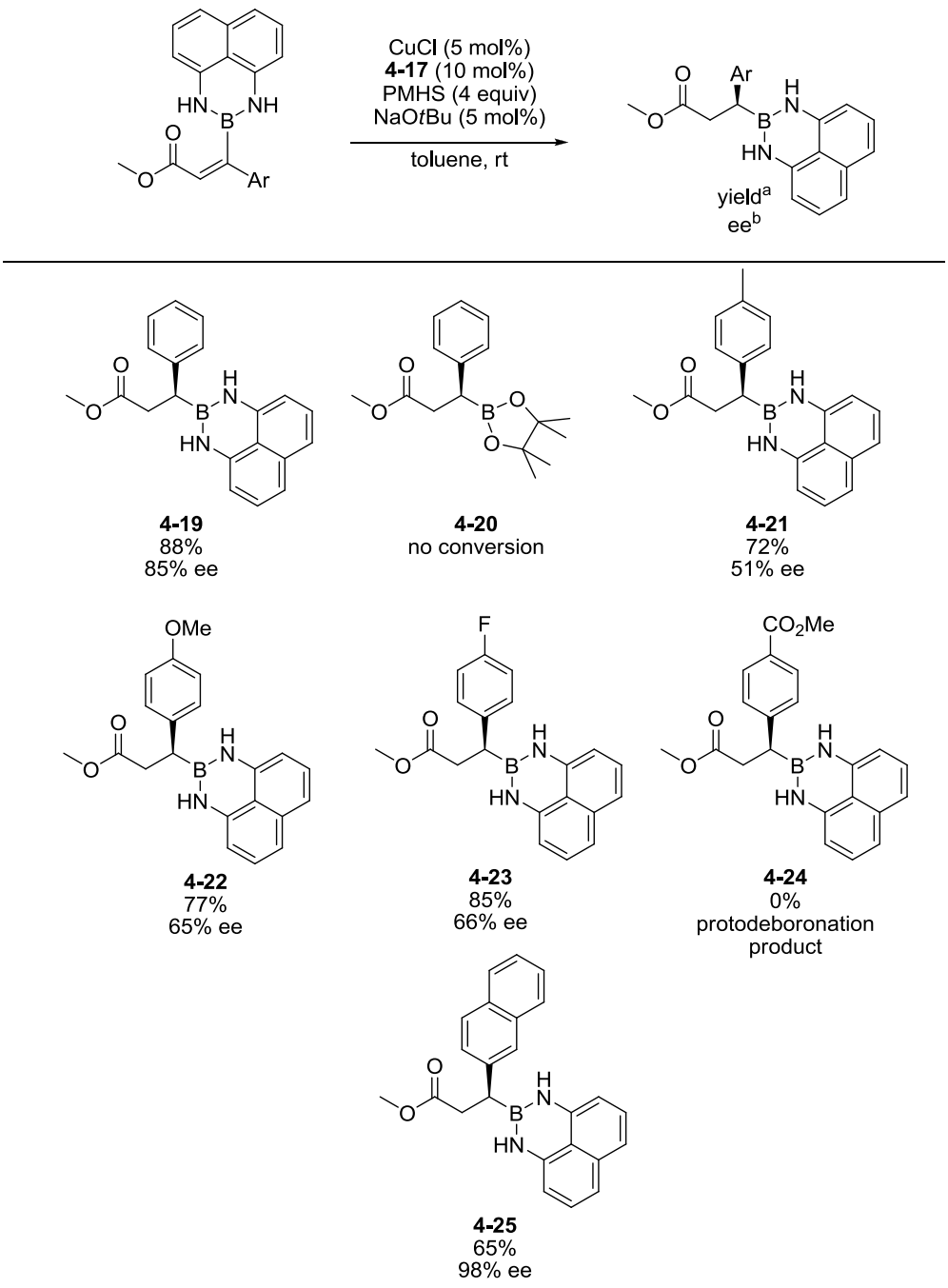
Scheme 4-5: Asymmetric conjugate reduction of β-boronyl-β-alkyl enoates.

alkylboronates in excellent yields and good to high levels of enantioselectivity (Scheme 4-5).[12] In order to further expand this methodology, the scope of asymmetric conjugate reduction of β-aryl-β-boronyl enoates was explored. This part of the work was conducted by my colleague, Jinyue Ding.

As shown in Table 4-6, both electron rich and electron poor substrates afforded the desired products with moderate to high yields. Diminished enantiomeric excesses, however, were observed for substituted aryl groups (**4-21**-**4-23**, Table 4-5). When carbomethoxy-substituted enoate **4-7** was used, the corresponding protodeboronation product was isolated. Impressively, naphthyl substituted substrate **4-25** could be synthesized with excellent enantioselectivity. This high selectively likely arises from its large, conjugate planar structure (of **4-8**), resulting in enhanced interactions with the catalyst. In order to study the influence of boron protecting groups on enantioselectivity, the 1,8-diaminonaphthalene (dan) protecting group was compared with the pinacol (pin) protecting group (**4-19** and **4-20**, Table 4-5).[12] An enhanced reactivity for the B(dan) substrate was observed for asymmetric conjugate reduction. The key for the improved reactivity is proposed to arise from the usage of a planar 1,8-diaminonaphthalene masking group over a bulky pinacol protecting group, allowing the catalysts to approach more effectively to lead to the product with a better yield.

4.7 Summary[13]

In summary, a new and efficient approach to access synthetically valuable β-boronyl β-aryl enoates through Heck coupling between b-boronyl enoate **4-1** and aryl halides was developed. Subsequent copper(I)-catalyzed enantioselective conjugate reduction of these enoates could be performed to produce various chiral secondary alkyl boronate derivatives. This method constitutes the first general approach for the syntheses of β-boronyl β-aryl enoates in high *E/Z* selectivity. In comparison with the previous report where pinacol boronates were used,[12] the substrates presented here are found to be better reaction partners for asymmetric conjugate reductions, affording the desired optically enriched alkyl secondary boronates with substantially improved reactivity and selectivity. These



[a] Isolated yields of products after flash column chromatography. [b] Measured by chiral HPLC.

Table 4-5: Asymmetric conjugate reduction of β-boronyl-β-aryl enoates (conducted by Jinyue Ding from the Hall Group).

improvements are attributed to the utilization of the planar 1,8-diaminonaphthalene as a superior boron masking group over the bulky pinacolate.

With chiral boronic acid derivatives emerging as important and versatile functional groups in organic synthesis, the synthetic methods reported herein are valuable tools to access a variety of important organic intermediates.

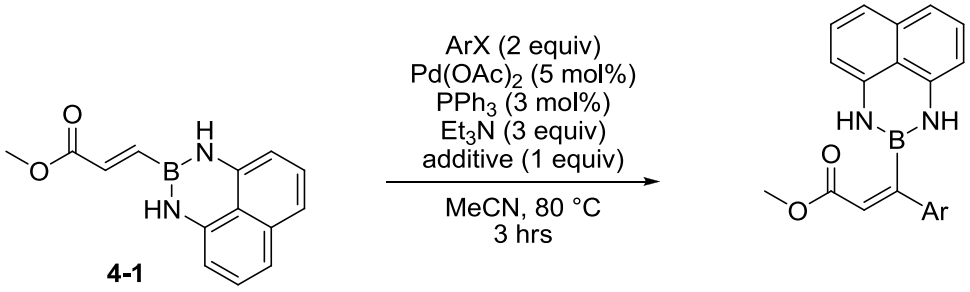
4.8 Experimental

4.8.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were obtained from a MBraun MB SPS* solvent system prior to use. $(Ph_3P)CuH$ was purchased form Acros Organics, +97%; chiral ligands **3-9** were generously provided by Solvias AG. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets; dse, double of septets; m, multiplet. The error of coupling constants from ^1H NMR analysis is ±0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumber. The enantiomeric excesses for chiral compounds were determined using a HPLC Agilent instrument with Chiralcel-OD or Chiralpak-AS columns with UV detection. Compound **4-1**[14] was synthesized according to the literature procedure.

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

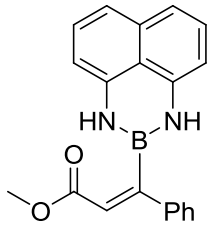
4.8.2.1 General procedure for preparation of β-boronyl-β-aryl α, β-unsaturated esters (Table 4-2)



4-1

To a mixture of enoate **4-1** (1.0 mmol), aryl halide (2.0 mmol), $Pd(OAc)_2$ (0.050 mmol), PPh_3 (0.030 mmol), and Et_3N (3.0 mmol) was added acetonitrile (1 mL). The solution was stirred for 10 hours at 80 °C before it was allowed to cool down to room temperature. The reaction mixture was then concentrated *in vacuo*, and the crude product was purified with flash silica column chromatography to afford the pure product.

4.8.2.2 (*E*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenyl acrylate 4-2



4-2

The title compound was prepared using the general procedure for Heck couplings between **4-1** and phenyl bromide. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **4-2** (76% yield) as an orange solid.

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

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 140.4, 138.7, 136.0, 129.2, 128.5, 127.3,

127.1, 124.3, 119.3, 117.4, 105.7, 51.5. (The boron-bound carbon was not detected due to quadrupolar relaxation)

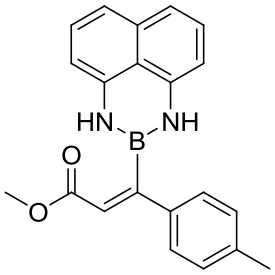
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0.

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

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

M.P.: 152-153 °C.

4.8.2.3 (*E*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(*p*-tolyl) acrylate 4-3



4-3

The title compound was prepared using the general procedure for Heck couplings between **4-1** and 4-bromotoluene. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **4-3** (72% yield) as a brown solid.

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

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

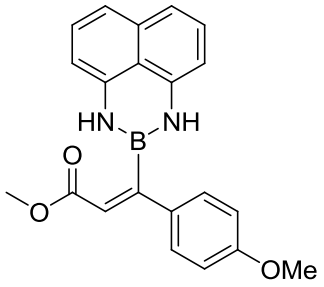
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7.

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

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

M.P.: 177 -180 °C.

4.8.2.4 (*E*)-Methyl 3-(4-methoxyphenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)acrylate 4-4



4-5

The title compound was prepared using the general procedure for Heck couplings between **4-1** and 1-iodo-4-methoxybenzene. Flash silica column chromatography (hexanes/EtOAc = 8:2) yielded **4-5** (76% yield) as a yellow solid.

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

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

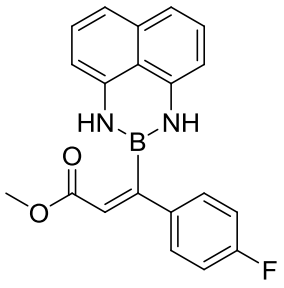
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.7.

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

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

M.P.: 75-76 °C (dec.).

4.8.2.5 (*E*)-Methyl 3-(4-fluorophenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl) acrylate 4-6



4-6

The title compound was prepared using the general procedure for Heck couplings

between **4-1** and 1-bromo-4-fluorobenzene. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **4-6** (77% yield) as a yellow solid.

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

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

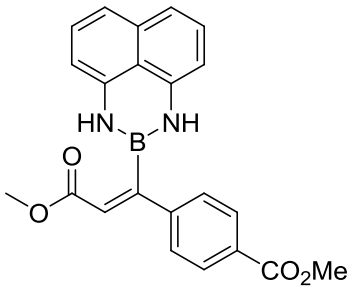
^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0.

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

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

M.P.: 104 °C.

4.8.2.6 (*E*)-Methyl 4-(3-methoxy-1-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-oxoprop-1-en-1-yl)benzoate 4-7



4-7

The title compound was prepared using the general procedure for Heck couplings between **4-1** and methyl 4-iodobenzoate. Flash silica column chromatography (hexanes/EtOAc = 8:2) yielded **4-7** (80% yield) as a yellow solid.

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

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

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

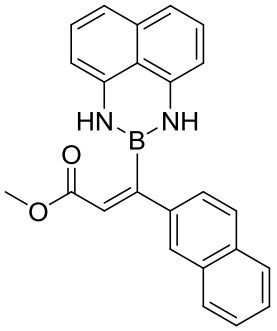
IR (Microscope, cm^{-1}) 3427, 3400, 3054, 3006, 2951, 2845, 1726, 1716, 1626,

1603, 1509.

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

M.P.: 167 °C (dec.).

4.8.2.7 (*E*)-Methyl 3-(naphthalen-2-yl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)acrylate 4-8



4-8

The title compound was prepared using the general procedure for Heck couplings between **4-1** and 2-bromonaphthalene. Flash silica column chromatography (hexanes/EtOAc = 8.5:1.5) yielded **4-8** (68% yield) as a yellow solid.

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

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

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

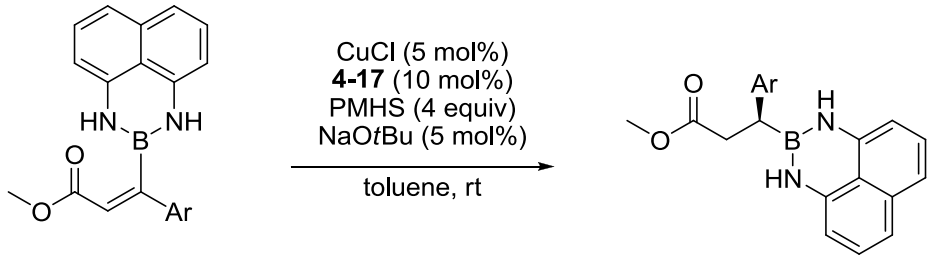
IR (Microscope, cm^{-1}) 3409, 3054, 2948, 1706, 1625, 1601, 1504.

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

M.P.: 180 -181 °C.

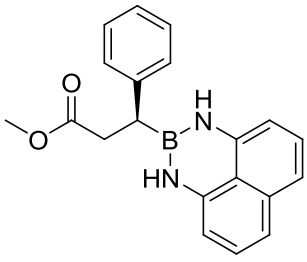
4.8.3 Preparation of chiral β-boronyl carboxyesters (By Jinyue Ding from the Hall Group, included for the comprehensiveness of this Chapter)

4.8.3.1 General procedure for the asymmetric conjugate reduction of enoates (Table 4-6)



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

4.8.3.2 (*S*)-Methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenyl propanoate 4-19



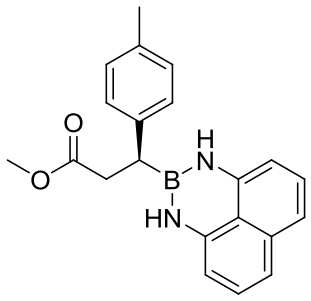
4-19

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **4-19** as a yellow oil. The characterization data for this compound matched that of a previous report. [13]

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

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

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



4-21

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **4-21** as a yellow oil.

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

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

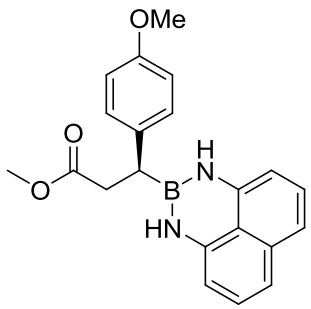
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.6.

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

HRMS (EI) for $C_{21}H_{21}BN_2O_2$: calcd. 344.16962; found 344.16941.

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

4.8.3.4 (*S*)-Methyl 3-(4-methoxyphenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanoate



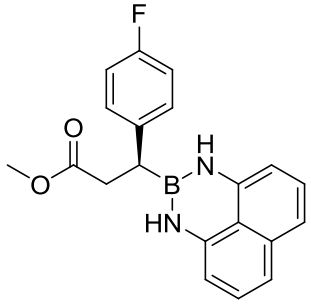
4-22

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **4-22** as a yellow oil. The characterization data for this compound matched that of a previous report.[15]

$[\alpha]_D^{20}$: 13 (c = 0.59, $CHCl_3$) for 65% ee.

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

4.8.3.5 (*S*)-Methyl 3-(4-fluorophenyl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanoate 4-23



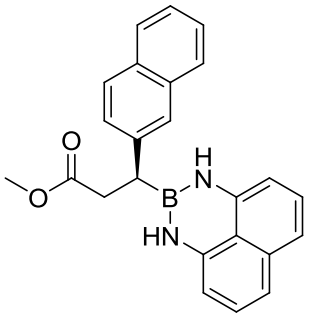
4-23

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **4-23** as a yellow oil. The characterization data for this compound matched that of a previous report.[14]

$[\alpha]_D^{20}$: 7.6 (c = 0.56, $CHCl_3$) for 66% ee.

HPLC (Chiralcel OD): 20:80 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 210 nm, T_{major} = 35.3 min, T_{minor} = 42.2 min, ee = 66%.

4.8.3.6 (*S*)-Methyl 3-(naphthalen-2-yl)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)propanoate 4-25



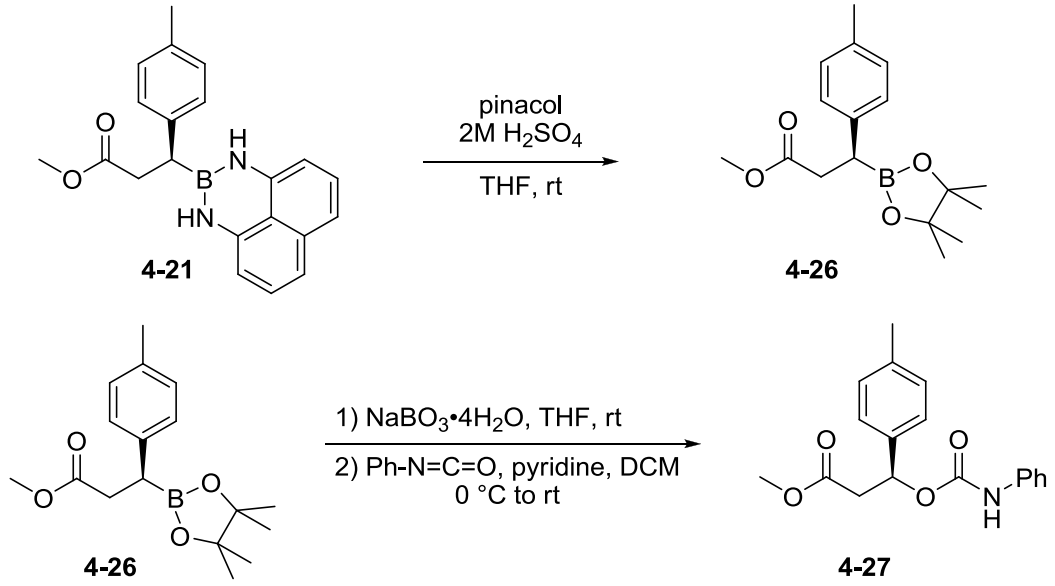
4-25

The title compound was prepared using the general procedure for the catalytic asymmetric conjugate reduction to yield **4-25** as a yellow oil. The characterization data for this compound matched that of a previous report.[14]

$[\alpha]_D^{20}$: −8.7 (c = 0.56, $CHCl_3$) for 98% ee.

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

4.8.4 Enantiomeric excess measurement of the oxidized product (By Jinyue Ding from the Hall Group, included for the comprehensiveness of this Chapter)

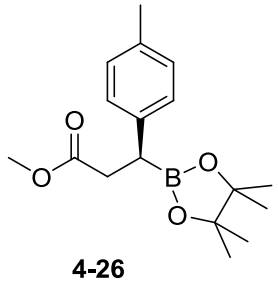


4-21 **4-26** **4-26** **4-27**

In order to measure the enantiomeric excess of **4-21**, the oxidized derivative **4-27**

was prepared using the reported procedures[13] with 33% overall yield over three steps.

4.8.4.1 (*S*)-Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*p*-tolyl) propanoate 4-26



4-26

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.06 (m, 4H), 3.65 (s, 3H), 2.87 (dd, *J* = 15.6, 9.4 Hz, 1H), 2.69 (dd, *J* = 15.6, 15.6 Hz, 1H), 2.64 (dd, *J* = 16.0, 9.6 Hz, 1H), 2.30 (s, 3H), 1.21 (s, *6*H), 1.19 (s, 6H).

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

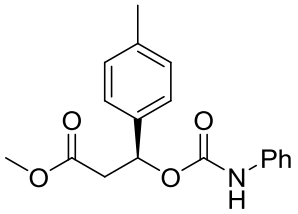
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.1.

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

HRMS (ESI) for $C_{17}H_{25}BO_4$: calcd. 304.18460; found 304.18423.

$[\alpha]_D^{20}$: 5.9 (c = 0.58, chloroform)

4.8.4.2 (*S*)-Methyl 3-((phenylcarbamoyl)oxy)-3-(*p*-tolyl)propanoate 4-27



4-27

^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.37-7.25 (m, 5H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.07-7.01 (m, 2H), 6.70 (br s, 1H), 6.16 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.69 (s, 3H), 3.03 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.81 (dd, *J* = 15.6, 5.2 Hz, 1H), 2.34 (s, 3H).

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

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

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

$[\alpha]_D^{20}$: 30 (c = 2.3, chloroform) for 51% ee.

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

4.9 References

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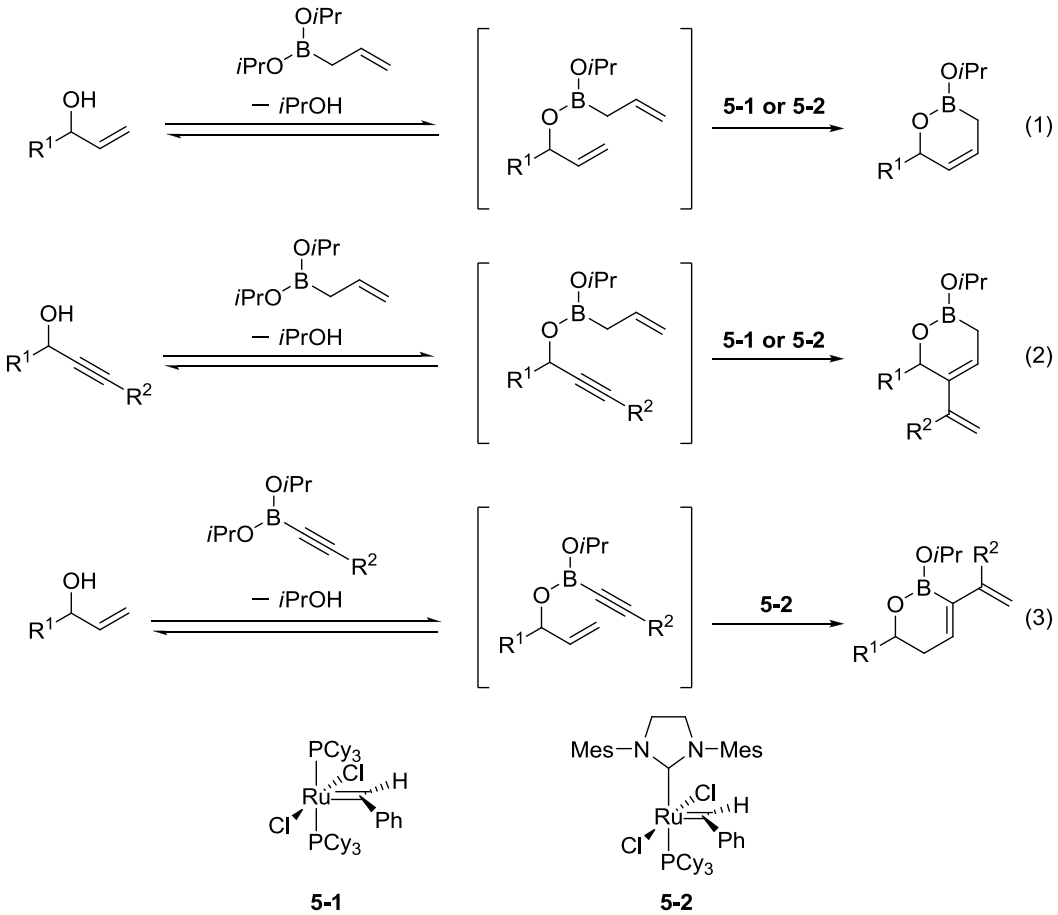
Chapter 5

Gold-Catalyzed Cycloisomerization Reactions of Boronated Enynes

5.1 Introduction

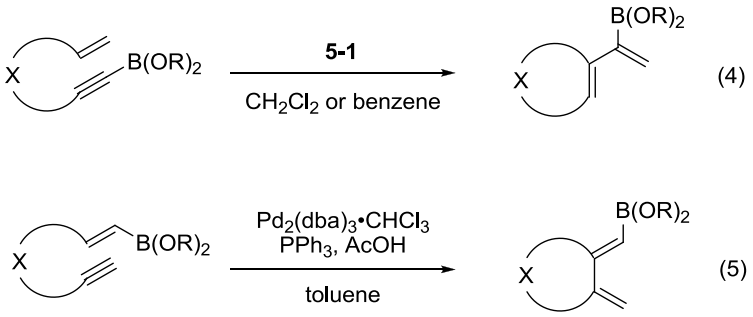
Transition metal-catalyzed cycloisomerization reactions have become increasingly important in modern day organic chemistry due to their ability to increase structural complexity in an atom economical manner.[1] The high functional group compatibility of these cycloisomerizations has extended their applications to various structural motifs, such as boronated enynes. Schreiber and coworkers have described an innovative approach for performing ring closing metathesis on



Scheme 5-1: Literature examples of ring-closing metathesis of boronated dienes or enynes through mixed organoboronate intermediates.

enynes generated *in-situ* from the corresponding boronic esters.[2] By combining either allylic or propargylic alcohols with allylic boronates, transient trans-esterified organoboronates could be formed *in-situ*, allowing ring closing metathesis to be conducted to give cyclic allylic boronates (Equations 1 and 2, Scheme 5-1). Alternatively, allylic alcohols could be mixed with alkynyl boronates, leading to cyclic alkenyl boronates after ring closing metathesis (Equation 3, Scheme 5-1). With these approaches, a variety of alcohols or boronates can be used, allowing a diverse array of different small molecules to be prepared and tested for their biological activities (diversity oriented synthesis).

In addition to using boronates intermolecularly with alcohols, Renaud and coworkers have developed methodologies to afford cyclic dienyl boronates through ring closing enyne metathesis of boronated dienes or enynes (Equation 4, Scheme 5-2).[3] More recently, Carboni and coworkers demonstrated that palladium catalyzed enyne cycloisomerization could also be performed on boronated enynes (Equation 5, Scheme 5-2),[4] giving a diene functionality which could then undergo Diels-Alder cycloaddition/allylboration sequences to afford tricyclic core structures in a one-pot fashion. In the same communication, two examples of rhodium and platinum catalyzed cycloisomerization reactions could also be conducted to give products with different structural complexity.

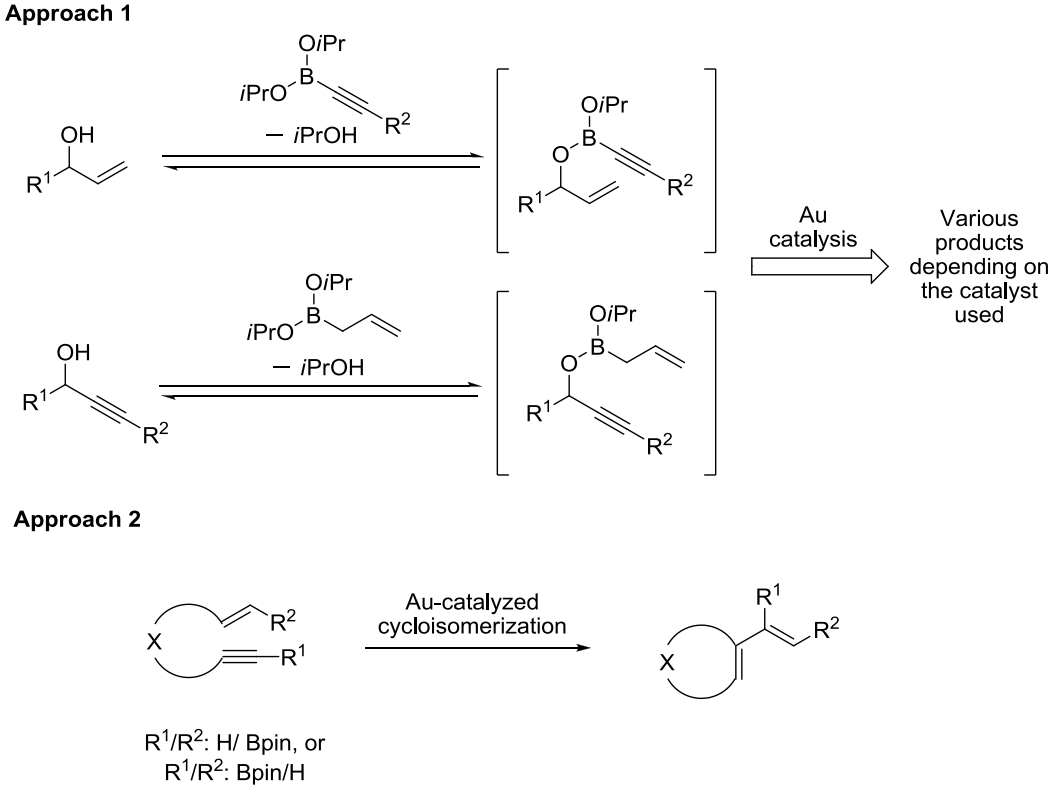


Scheme 5-2: Known cycloisomerization reactions involving boronated enynes.

5.2 Project objectives

Interest in gold-catalyzed reactions has increased tremendously in recent years mainly due to the high efficiency of gold complexes towards alkyne activation.[5]

In this way, various nucleophiles have been shown to react remarkably well with gold activated alkynes, affording a range of diverse products under mild conditions with both great efficiency and chemoselectivity. In light of these discoveries, it was envisioned that perhaps gold catalysis could be performed with unsaturated organoboronates to afford synthetically valuable adducts. In order to develop new methodologies to access novel organoboronates that are of interest to synthetic chemists, two different approaches that are similar to the ones discussed above will be examined. The first approach would consist of forming the transient mixed boronates from allylic or propargylic alcohols and allylic or alkynyl boronates. The transient boronated enyne intermediates can then undergo gold-catalyzed cycloisomerizations to afford novel boronated adducts (Approach 1, Scheme 5-3). Alternatively, gold-catalyzed cycloisomerization reactions with pre-formed boronated enynes will also be tested (Approach 2, Scheme 5-3). Both



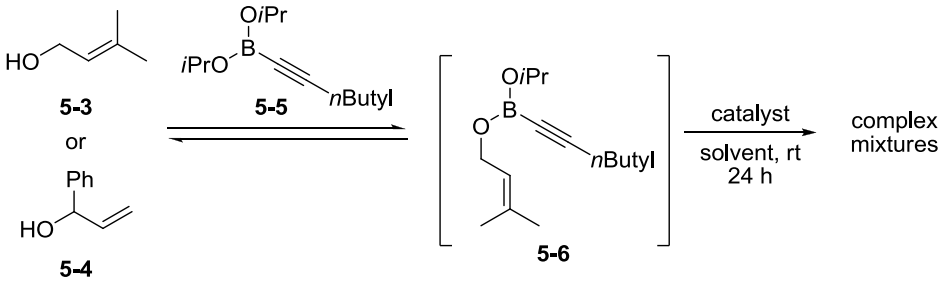
Scheme 5-3: Proposal for the synthesis of structurally complex, cyclic organoboronates through gold or platinum catalysis.

approaches belong to the early-introduction strategy advocated by our research group (Chapter 1), where boronates are introduced onto the substrates several steps prior to the desired functionalization of these structural motifs.

5.3 Synthesis of cyclic organoboronates through gold-catalyzed enyne cycloisomerization reactions

5.3.1 Attempts to synthesize cyclic boronates through Approach 1

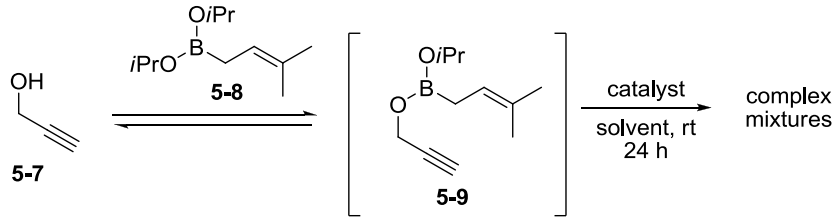
In order to test whether novel cyclic boronates could be formed intermolecularly between allylic alcohols and alkynyl boronates, efforts were first spent on isolating the mixed boronate **5-6** from alcohol **5-3** (or **5-4**) and alkyne **5-5**. Compound **5-6**, however, was difficult to be identified based ^{1}H NMR analysis and was also not detectable by mass spectroscopy. Due to this difficulty, various gold catalyzed reactions were then performed directly from *in-situ* generated mixed boronate **5-6**. Different typical gold catalysts and solvents were evaluated at room temperature, but unfortunately only complex mixtures could be obtained under all conditions attempted (Entries 1-4, Table 5-1).



Entry	catalyst (20 mol%)	solvent
1	$AuPPh_3Cl$ $AgSbF_6$	toluene
2	$AuCl_3$	toluene
3	$AuPPh_3Cl$ $AgSbF_6$	CH_2Cl_2
4	$AuCl_3$	CH_2Cl_2

Table 5-1: Attempts at forming cyclic organoboronates through gold catalysis from allylic alcohols or alkynyl boronate **5-5**.

Since the electronic properties of boronates is very important in these cycloisomerization reactions, allylic boronate **5-8** was also attempted instead of alkynyl boronate **5-5**. By combining allylic boronate **5-8** with propargylic alcohol **5-7**, the boronated enyne intermediate **5-9** could be formed *in-situ*, allowing gold catalyzed reactions to be conducted. Under all conditions tried, however, only complex mixtures were produced, similar to previous attempts with **5-5**. Knowing that the stability of products could potentially be a problem, different isolation methods such as column chromatography, precipitation, recrystallization and distillation were all tried. Unfortunately, none of them led to identifiable products. Due to these unsuccessful results, the attention was turned to Approach 2.



Entry	catalyst (20 mol%)	solvent
1	$AuPPh_3Cl$ $AgSbF_6$	toluene
2	$AuCl_3$	toluene
3	$AuPPh_3Cl$ $AgSbF_6$	CH_2Cl_2
4	$AuCl_3$	CH_2Cl_2

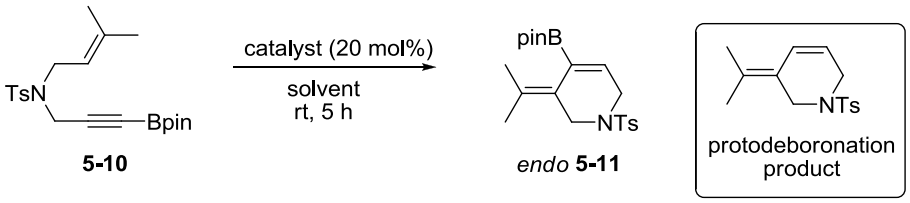
Table 5-2: Attempts at forming cyclic organoboronates through gold catalysis from propargyl alcohol **5-7** and allylic boronate **5-8**.

5.3.2 Attempts to synthesize cyclic boronates through Approach 2

5.3.2.1 Optimization of reaction conditions of enyne cycloisomerizations.

Alkynylboronates are easily accessible through Brown's methodology.[6] In order to probe the possibility of performing gold-catalyzed cycloisomerzations, the initial study was focused on alkynyl pinacol boronate **5-10**. Following the typical procedure for non-borylated enynes described by the Echavarren group,[7] the desired product **5-11** could be accessed with a 32% yield. It was found that a

significant amount of protodeboronated product was obtained as the main by-product (Entry 2, Table 5-3). Altering the silver salts or the gold source proved to be ineffective, either affording the undesired deboronated products or the unconverted starting materials (Entries 2-4, Table 5-3). Various solvents were also tested, and dichloromethane was the most effective, delivering the product with a relatively higher yield (Entries 5-8, Table 5-3). Eventually it was found that lowering the reaction time to 3 hours and the catalyst loading to 5 mol% decreases the amount of the deboronated side product and increases the yield of the desired product **5-11** to 45%. Remarkably, no *exo* product (Equation 6, Scheme 5-4) was observed and only the *endo* product was isolated in this reaction. This result is unprecedented because the original studies by the Echavarren Group suggested that only enynes with unsubstituted alkynes could generate the *endo* product.[7c] Despite this interesting observation, 25% of the deboronated product could still be isolated. To probe the possibility that product **5-11** could participate in a transmetallation/protodeauration sequence,[8] the isolated dienyl boronate **5-11** was subjected back into the reaction conditions. The result showed that **5-11** underwent less than 10% protodeauration over a period of one day, thus indicating that transmetallation/protodeauration sequence was only a minor pathway leading to the loss of the boronate moiety.



Entry	Cat.	Solvent	Yield[a] (%)
1	$AuPPh_3Cl$ $AgSbF_6$	CH_2Cl_2	32
2	$AuPPh_3Cl$ $AgBF_4$	CH_2Cl_2	20
3	$AuCl_3$	CH_2Cl_2	-[c]
4	AuCl	CH_2Cl_2	-[c]

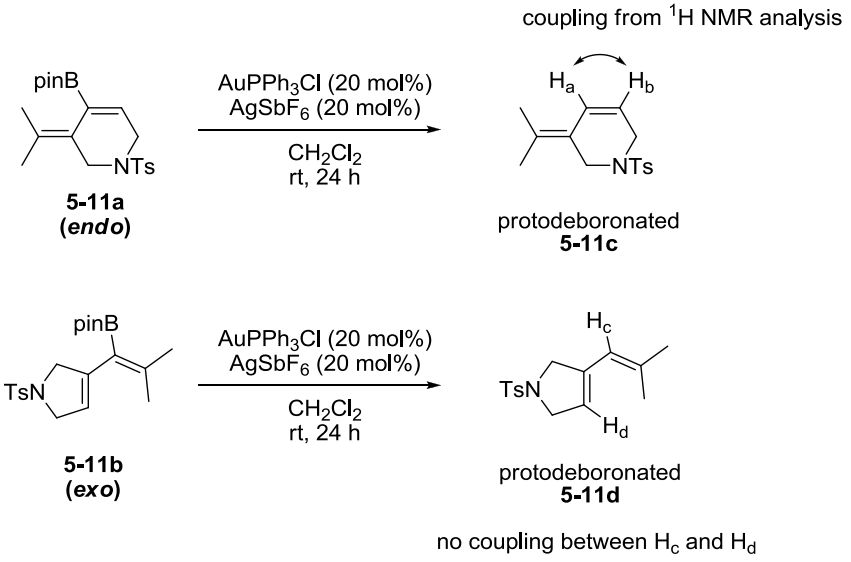
5	$AuPPh_3Cl$ $AgSbF_6$	toluene	15
6	$AuPPh_3Cl$ $AgSbF_6$	MeOH	trace
7	$AuPPh_3Cl$ $AgSbF_6$	THF	-[b]
8	$AuPPh_3Cl$ $AgSbF_6$	CH_3CN	-[c]
9	**$AuPPh_3Cl$ $AgSbF_6$**	**CH_2Cl_2**	**45[d]**

[c] Isolated yields of product after purification by flash column chromatography. [b] Deboronated product was isolated. [c] No conversion. [d] 5 mol% catalyst loading, 3 hours

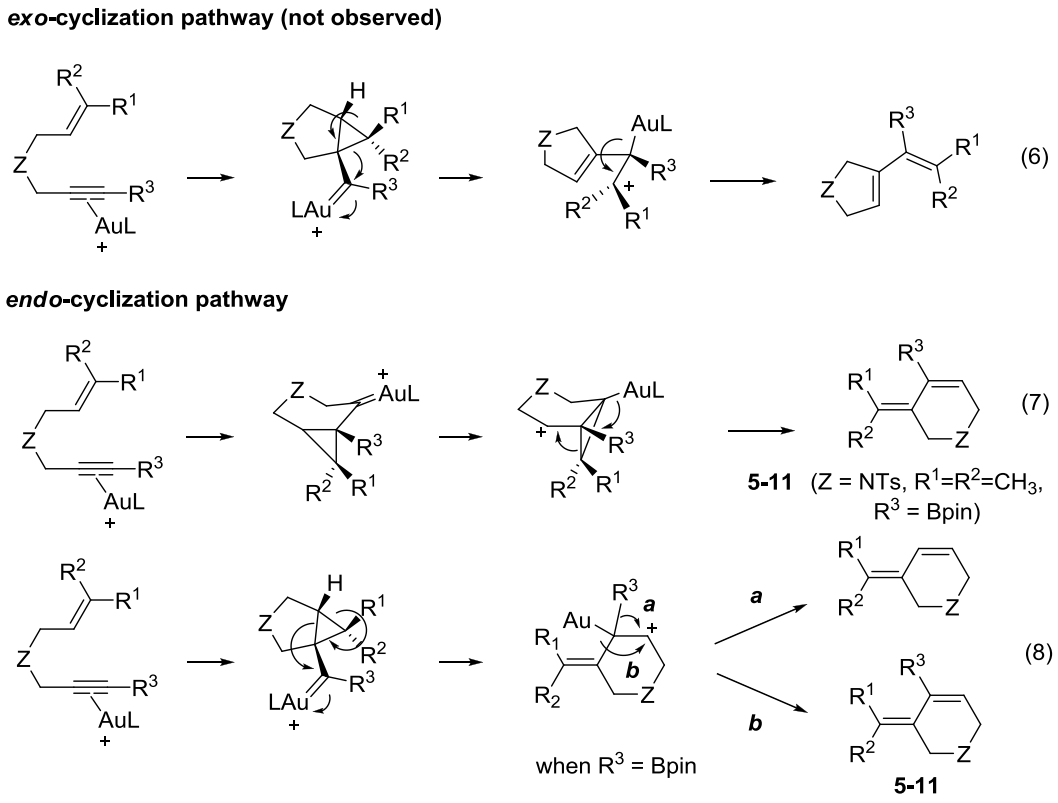
Table 5-3: Optimization of reaction conditions for the cycloisomerization reaction of boronated enyne **5-10**.

5.3.2.1.1 Confirmation of the boronate 5-11 as *endo* product rather than *exo* product

In order to determine the mode of cyclization of enyne boronate **5-10**, it is important to further functionalize the cyclized product **5-11** since *endo* and *exo* cyclized products **5-11a** and **5-11b** would possess very similar ^{1}H NMR spectra. Upon treatment of the isolated cyclic boronate **5-11** with gold-catalyzed reaction conditions under a prolonged period of reaction time, a small portion of the cyclic boronate became protodeboronated (similar to what was observed in Section 5.3.2.1). The isolated protodeboronated product, after ^{1}H NMR analysis, was confirmed to be compound **5-11c** since the two alkenyl hydrogen atoms were found to couple with one another. On the other hand, if the cyclic boronate formed was the *exo* product **5-11b**, then the protodeboronated product **5-11d** should not have couplings between H_c and H_d since these two protons are too far away. Since gold-catalyzed cycloisomerizations are known to be irreversible,[5] these results proved that *endo* **5-11a** was the product isolated from the cycloisomerization reactions.



Scheme 5-4: Determination of the mode of cyclization of boronate **5-10**.



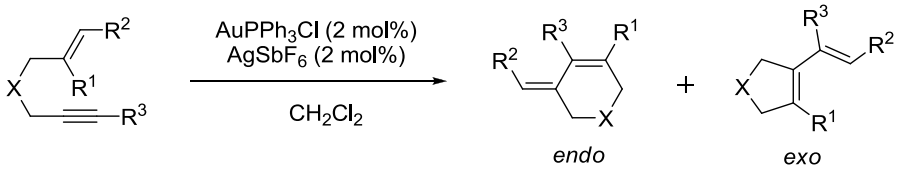
Scheme 5-5: Mechanistic proposal for the formation of *exo* and *endo* products along with deboronated side products.

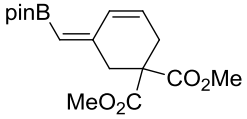
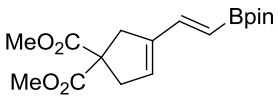
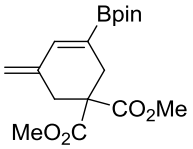
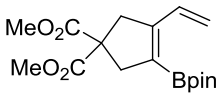
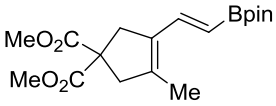
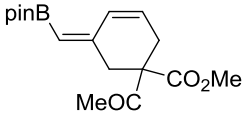
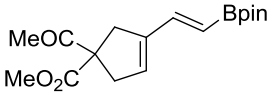
5.3.2.2 Proposed mechanistic pathways for side product formation

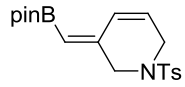
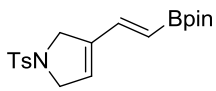
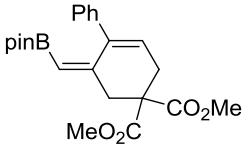
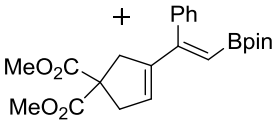
Through analyzing the potential intermediates of the proposed mechanism (Equation 7, Scheme 5-5 is the originally proposed mechanism for the *endo* product[7a-b], and Eq. 8 is another potential pathway proposed in 2007[7c]), pinacol boronate could potentially participate in a competitive elimination event with the gold species, resulting in a mixture of the desired product **5-11** with the protodeboronated by-product (path **a**, Equation 8, Scheme 5-5). Thus, unlike the normal pathway where the gold intermediate could be eliminated to afford the observed product **5-11** (path **b**, Equation 8, Scheme 5-5), boronate could participate in the elimination event, giving the observed protodeboronated product.

5.3.2.3 Substrate scope of gold-catalyzed enyne cycloisomerizations of boronated enynes

In order to circumvent the problem where boronate could participate in the elimination step, the attention of the project was turned to alkenyl pinacol boronates. According to the proposed mechanism (Equation 8, Scheme 5-5), the boronate of alkenylboronate cannot participate in the elimination event, thus avoiding protodeboronation and could favour the desired product formation. Indeed, boronated enyne **5-12** experienced little problem undergoing the desired cycloisomerization reaction to give a mixture of *endo* or *exo* products **5-13** and **5-14** in a 6:1 ratio (Entry 1, Table 5-4). Interestingly, the *endo* product, which is usually the minor product when malonate substrates were used in the original publications,[7] becomes the major product in this case. By switching the position of the boronate from the external carbon to the internal carbon of the alkene moiety, the ratio can then be reversed to favour the *exo* product **5-17** in a 5:1 ratio over the *endo* product **5-16** (Entry 2, Table 5-4). Trisubstituted alkenyl boronate **5-18** also works well, affording the *exo*- product with a 79% yield without any observation of the *endo* isomer (Entry 3, Table 5-4). Switching one of the malonate esters to a ketone was somewhat tolerated, lowering the yield to 51% (Entry 4, Table 5-4), while changing the malonate moiety to a tosylamino group completely suppressed the reactivity of the substrate (Entry 5, Table 5-4). Unfortunately, the alkyne substituent proves to be very crucial, and replacing this



Entry	Enyne	t (h)	Product	Yield [a] (%)
1	X = $C(CO_2Me)_2$ R^1 = H R^2 = Bpin R^3 = H **5-12**	0.5	 **5-13** +  **5-14**	90% (**5-13**:**5-14** = 6:1)
2	X = $C(CO_2Me)_2$ R^1 = Bpin R^2 = H R^3 = H **5-15**	0.5	 **5-16** +  **5-17**	95% (**5-16**:**5-17** = 1:5)
3	X = $C(CO_2Me)_2$ R^1 = CH_3 R^2 = Bpin R^3 = H **5-18**	0.5	 **5-19**	79%
4	X = $MeOCCCO_2Me$ R^1 = H R^2 = Bpin R^3 = H **5-20**	0.5	 **5-21** +  **5-22**	51% (**5-21**:**5-22** = 6:1)

5	X = NTs R^1 = H R^2 = Bpin R^3 = H **5-23**	12	 **5-24** +  **5-25**	_b
6	X = $C(CO_2Me)_2$ R^1 = H R^2 = Bpin R^3 = Ph **5-26**	12	 **5-27** +  **5-28**	_b

[a] Isolated yields of product after purification by flash column chromatography. *Endo* and *exo*-products and are inseparable. [b] No conversion

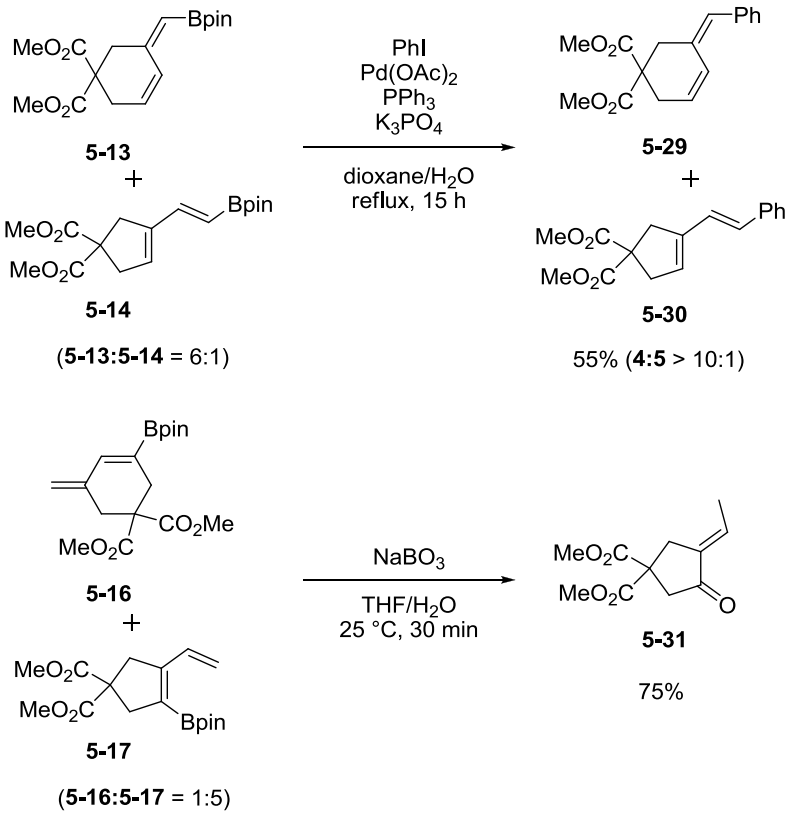
Table 5-4: Substrate scope for the cycloisomerization of alkenyl boronates.

substituent from hydrogen to a phenyl ring also depresses the reactivity of the substrate (Entry 6, Table 5-4). It is very important to note here that prolonged reaction times in some cases lead to a significant amount of protodeboronated by-products, implying that transmetallation/protodeauration sequence could play a larger role depending on the substrates.

5.3.2.4 Synthetic applications of cyclic organoboronate products

To broaden the synthetic utility of these cycloisomerization products, various transformations with the newly acquired dienyl boronates were then performed. From **5-13/5-14**, Suzuki-Miyaura cross-coupling reaction with iodobenzene afforded the desired cross-coupling products **5-29** and **5-30** with a 55% yield in larger than 10 to 1 ratio, while direct oxidation of the pinacol boronates **5-16** and **5-17** (1:5 ratio) rendered the α,β-unsaturated ketone **5-31** (Scheme 5-6), where the

remote olefin had been isomerized into the internal position under the basic conditions employed. These synthetic applications indicate the advantages of conducting cycloisomerization reactions with boronated enynes and the versatility of organoboron reagents, where different chemical transformations could be achieved to access various different functionalities.



Scheme 5-6: Suzuki-Miyaura coupling and oxidation reactions of the cycloisomerized boronated products.

5.4 Summary[9]

In summary, a protocol for gold-catalyzed cycloisomerization reactions with boronated enynes was successfully developed. Both alkynyl boronates and alkenyl boronates reacted effectively and provided the desired products in an atom economical manner with a dramatic increase in structural complexity. This gold-catalyzed cycloisomerization protocol generates diene products that differ from the previously reported enyne metathesis or palladium catalyzed

cycloisomerization reactions, thus complementing the existing synthetic tools for organic chemists. With the versatile boronate functionality installed in the products, these synthetically useful intermediates can then be either elaborated into biologically active natural products, or be used as a platform for diversity-oriented synthesis towards the development of important pharmaceuticals.

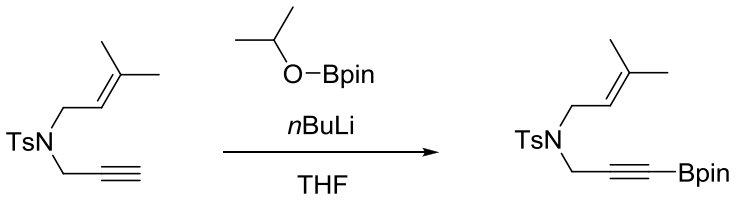
5.5 Experimental

5.5.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were treated by Fisher Scientific-MBraun MB SPS* solvent system prior to use. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; qt, quartet of triplets, dtd, doublet of triplet of doublets, m, multiplet. The error of coupling constants from ^1H NMR analysis is ±0.3 Hz. High-resolution mass spectra were recorded by the University of Alberta mass spectrometry services laboratory using either electron impact (EI) or electrospray ionization (ESI) techniques. Infrared spectra were obtained on a Nicolet Magna-IR with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumber. The following starting materials were synthesized according to the literature procedures: **5-12**[4]**, 5-23**[4]**, 5-32**[10], **5-33**[11], **5-35**[12], **5-38**[13], **5-39**[14], and **5-40**[15].

5.5.2 Preparation of boronated enyne starting materials

5.5.2.1 4-Methyl-*N*-(3-methylbut-2-enyl)-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-ynyl)benzenesulfonamide (5-10)



5-32 **5-10**

To a solution of benzenesulfonamide **5-32** (2.00 g, 7.20 mmol) in THF (20.0 mL) at –78 °C was added dropwise *n*-BuLi (2.90 mL, 2.5 M hexane solution, 7.20 mmol). The reaction mixture was stirred for 1 hour at –78 °C, before being added to a solution of 4,4,5,5-tetramethyl-2-(1-methylethoxy)-1,3,2-dioxaborolane (1.47 mL, 7.20 mmol) in THF (20.0 mL) –78 °C. After being stirred for 2 hours at –78 °C, the reaction mixture was quenched with 4.0 M HCl/dioxane (1.80 mL, 7.20 mmol), and the mixture was warmed to room temperature with additional 1 h stirring. Filtration and evaporation afforded a dark red solid. Recrystallization from diethyl ether afforded **5-10** (1.51 g, 52% yield) in pure form.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.08 (br t, *J* = 7.3 Hz, 1H), 4.08 (s, 2H), 3.79 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.69 (br s, 3H), 1.65 (br s, 3H), 1.21 (s, 12H).

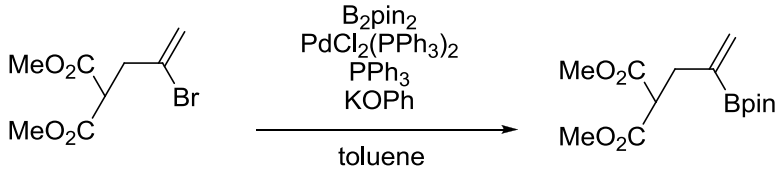
^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 139.2, 135.8, 129.4, 127.8, 117.8, 84.2, 44.1, 36.2, 25.8, 24.6, 24.5, 21.6, 17.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 23.2.

IR (Microscope, cm^{-1}) 3028, 2984, 2918, 2209, 1668, 1599.

HRMS (ESI) Only the boronic acid was visible through HRMS $C_{15}H_{20}BNNaO_4S$: $(M + Na)^+$ calcd. 344.1098; found 344.1096.

5.5.2.2 Dimethyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate (5-34)



5-33 **5-34**

$PdCl_2(PPh_3)_2$ (21.0 mg, 0.03 mmol), Ph_3P (15.7 mg, 0.06 mmol), bis(pinacolato)diboron (279 mg, 1.10 mmol), and KOPh (198 mg, 1.50 mmol) were charged with toluene (6.0 mL) and alkenyl bromide **5-33** (251 mg, 1.00 mmol). The mixture was then stirred at 50 °C for 12 hours, before being treated with water (5.0 mL) at room temperature and extracted with diethyl ether (3 × 10 mL). The combined organic solution was then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-34** (259 mg, 87%) in pure form.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 3.1 Hz, 1H), 5.66 (br s, 1H), 3.78 (t, *J* = 8.1 Hz, 1H), 3.70 (s, 6H), 2.73 (dt, *J* = 8.0, 1.0 Hz, 2H), 1.26 (s, 12H).

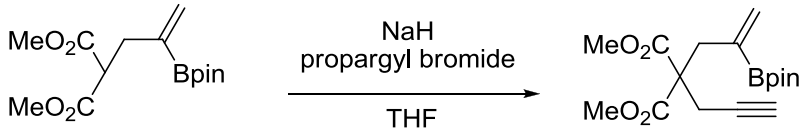
^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 132.1, 83.6, 52.3, 51.3, 34.9, 24.7. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.6.

IR (Microscope, cm^{-1}) 3063, 2980, 2955, 1755, 1740, 1653.

HRMS (EI) for $C_{14}H_{23}BO_6$: calcd. 298.1588; found 298.1583.

5.5.2.3 Dimethyl-2-(prop-2-ynyl)-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate (5-15)



5-34 **5-15**

To a suspension of NaH (67.0 mg, 1.70 mmol) in dry THF (5.0 mL) at 0 °C was added **5-34** (500 mg, 1.70 mmol) in THF (5.0 mL). After stirring for 30 min, propargyl bromide (200 mg, 1.70 mmol) was added and the reaction was stirred for an additional 15 h. After addition of a saturated ammonium chloride solution

(5.0 mL), the mixture was extracted with diethyl ether (3 × 10 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-15** (338 mg, 60%) in pure form.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, *J* = 3.5 Hz, 1H), 5.83 (d, *J* = 3.3 Hz, 1H), 3.73, (s, 6H), 2.92 (d, *J* = 0.8 Hz, 2H), 2.74 (d, *J* = 2.7 Hz, 2H), 2.00 (t, *J* = 2.7 Hz, 1H), 1.23 (s, 12H).

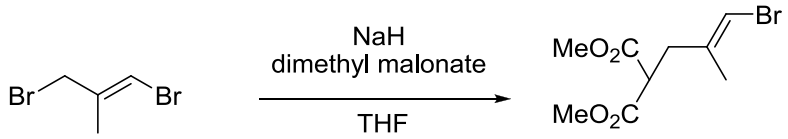
^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 135.6, 83.6, 79.5, 71.4, 57.1, 52.5, 36.4, 24.7, 22.5. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.9.

IR (Microscope, cm^{-1}) 3283, 2980, 2956, 2123, 1738.

HRMS (ESI) for $C_{17}H_{26}BO_6$ $(M + H)^+$: calcd. 337.1822; found 337.1828.

5.5.2.4 (*E*)-Dimethyl 2-(3-bromo-2-methylallyl)malonate (5-36)



5-35 **5-36**

To a suspension of NaH (1.03 g, 20.6 mmol) in dry THF (15 mL) at 0 °C was added dimethyl malonate (3.09 g, 18.7 mmol) in THF (50 mL). After stirring for 30 min, allyl bromide **5-35** (4.00 g, 18.7 mmol) was added and the reaction was stirred for an additional 15 h. After addition of a saturated ammonium chloride solution (50 mL), the mixture was extracted with diethyl ether (3 × 50 mL) and dried over $MgSO_4$. The resulting solution was then filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-36** (3.26 g, 66%) in pure form.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (br s, 1H), 5.83 (d, *J* = 3.3 Hz, 1H), 3.70, (s, 6H), 3.54 (t, *J* = 7.8 Hz, 1H), 2.68 (d, *J* = 7.7 Hz, 2H), 1.77 (s, 3H).

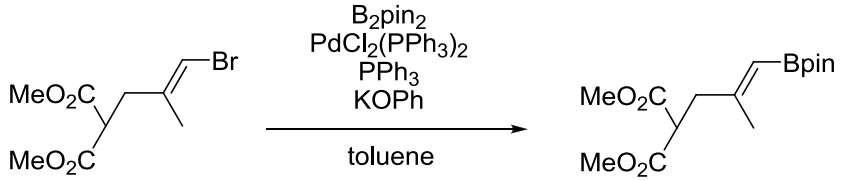
^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 137.4, 104.4, 52.7, 49.9, 37.1, 18.7

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.5

IR (Microscope, cm^{-1}) 3078, 3000, 2955, 1754, 1738, 1633

HRMS (ESI) for $C_9H_{14}BrO_4$ $(M + H)^+$: calcd. 265.0070; found 265.0068.

5.5.2.5 (*E*)-Dimethyl 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate (5-37)



5-36 **5-37**

$PdCl_2(PPh_3)_2$ (79.0 mg, 0.110 mmol), Ph_3P (59.0 mg, 0.220 mmol), bis(pinacolato)diboron (1.05 g, 4.18 mmol), and KOPh (748 mg, 5.70 mmol) were charged with toluene (25 mL) and alkenyl bromide **5-36** (1.00 g, 3.80 mmol). The mixture was then stirred at 50 °C for 12 hours, before being treated with water (25 mL) at room temperature and extracted with diethyl ether (3 × 30 mL). The combined organic solution was then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-37** (672 mg, 57%) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (d, J = 1.0 Hz, 1H), 3.65, (s, 6H), 3.58 (t, J = 7.6 Hz, 1H), 2.63 (dt, J = 7.7, 1.0 Hz, 2H), 1.93 (s, 3H), 1.18 (s, 12H).

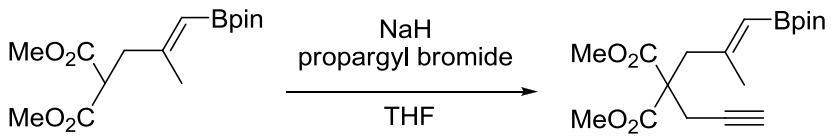
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 157.4, 82.7, 52.4, 50.0, 40.2, 24.7, 21.0. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (128 MHz, $CDCl_3$) δ 29.2.

IR (Microscope, cm^{-1}) 2979, 1755, 1740, 1641.

HRMS (ESI) for $C_{15}H_{26}BO_6$: $(M + H)^+$ calcd. 313.1822; found 313.1822.

5.5.2.6 (*E*)-Dimethyl 2-(2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)-2-(prop-2-ynyl)malonate (5-20)



5-37 **5-20**

To a suspension of NaH (86.1 mg, 2.20 mmol) in dry THF (5.0 mL) at 0 °C was added **5-37** (672 mg, 2.20 mmol) in THF (10.0 mL). After stirring for 30 min, propargyl bromide (320 mg, 2.20 mmol) was added and the reaction was stirred for an additional 15 h. After addition of a saturated ammonium chloride solution (5.0 mL), the mixture was extracted with diethyl ether (3 × 15 mL) and dried over $MgSO_4$. The solution was then filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-20** (468 mg, 62%) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (br m, 1H), 3.71, (s, 6H), 2.89 (s, 2H), 2.79 (d, J = 2.6 Hz, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.86 (br s, 3H), 1.22 (s, 12H).

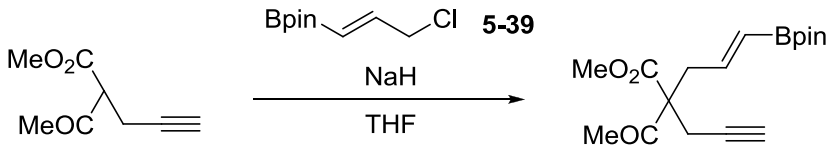
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.6, 82.8, 79.1, 71.8, 56.5, 52.7, 43.7, 24.8, 22.6, 21.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (128 MHz, $CDCl_3$) δ 29.4.

IR (Microscope, cm^{-1}) 3289, 2979, 1741, 1637.

HRMS (ESI) for $C_{18}H_{28}BO_6$: $(M + H)^+$ calcd. 351.1979; found 351.1978.

5.5.2.7 (*E*)-Methyl 2-acetyl-2-(prop-2-ynyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enoate (5-23)



5-38 **5-23**

To a suspension of NaH (80.0 mg, 2.00 mmol) in dry THF (4.0 mL) at 0 °C was added **5-38** (308 mg, 2.00 mmol) in THF (4.0 mL). After stirring for 30 min, allyl

chloride **5-39** (404 mg, 2.00 mmol) was added and the reaction was stirred for an additional 15 h. After addition of a saturated ammonium chloride solution (5.0 mL), the mixture was extracted with diethyl ether (3 × 15 mL) and dried over $MgSO_4$. The solution was then filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-23** (247 mg, 39%) in pure form.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dt, *J* = 17.7, 7.4 Hz, 1H), 5.68 (dt, *J* = 17.7, 1.4 Hz, 1H), 3.73 (s, 3H), 2.92 (ddd, *J* = 14.4, 7.1, 1.4 Hz, 1H), 2.82 (dd, *J* = 14.5, 7.5, 1.3 Hz, 1H), 2.73 (d, *J* = 2.8 Hz, 2H), 2.15 (s, 3H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.22 (s, 12H).

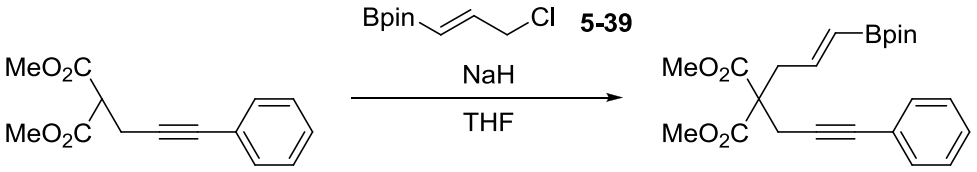
^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 170.7, 145.9, 83.3, 78.9, 71.8, 62.6, 52.8, 37.8, 26.5, 24.7, 21.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.1.

IR (Microscope, cm^{-1}) 3286, 2980, 2123, 1746, 1719, 1640.

HRMS (EI) for $C_{17}H_{25}BNO_5$: calcd. 320.1795; found 320.1780.

5.5.2.8 (*E*)-Dimethyl 2-(3-phenylprop-2-ynyl)-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate (5-26)



5-40 **5-26**

To a suspension of NaH (113 mg, 2.82 mmol) in dry THF (5.0 mL) at 0 °C was added **5-40** (694 mg, 2.82 mmol) in THF (5.0 mL). After stirring for 30 min, allyl chloride **5-39** (571 mg, 2.82 mmol) was added and the reaction was stirred for an additional 15 h. After addition of a saturated ammonium chloride solution (5.0 mL), the mixture was extracted with diethyl ether (3 × 15 mL) and dried over $MgSO_4$. The solution was then filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 17:3) to give **5-26** (744 mg, 64%) in pure form.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 - 7.30 (m, 2H), 7.28 - 7.25 (m, 3H), 6.42 (dt, *J* = 17.7, 7.2 Hz, 1H), 5.61 (dt, *J* = 17.7, 1.4 Hz, 1H), 3.75 (s, 6H), 3.02 (s, 2H), 2.97 (dd, *J* = 7.3, 1.4 Hz, 2H), 1.24 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 146.4, 131.7, 128.2, 128.0, 123.2, 84.1, 83.8, 83.2, 57.1, 52.8, 38.8, 24.8, 23.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.9.

IR (Microscope, cm^{-1}) 2979, 2954, 1739, 1640, 1599.

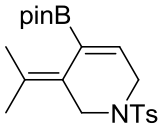
HRMS (EI) for $C_{23}H_{29}BO_6$: calcd. 412.2057; found 412.2066.

5.5.3 Gold catalyzed cycloisomerization reactions

5.5.3.1 General procedure (Table 5-4)

A solution of boronated enyne (0.3 mmol) in dichloromethane (1.5 mL) was added to a mixture of $AuPPh_3Cl$ (2.0 mol%) and $AgSbF_6$ (2.0 mol%) in dichloromethane (1.5 mL). The mixture was stirred at room temperature for 30 minutes, before being filtered through a silica gel plug. The resulting solution was then evaporated *in vacuo* to afford the crude product. The residue was purified by silica gel column chromatography to give the pure product.

5.5.3.2 3-(Propan-2-ylidene)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (5-11)



endo **5-11**

The title compound was prepared from compound **5-10** (121 mg, 0.3 mmol) using the general procedure for the gold catalyzed cycloisomerization reactions except 5.0 mol% catalysts and 3 hours reaction time were used. Flash column chromatography (hexanes/EtOAc = 8:2) yielded **5-11** (54 mg, 0.14 mmol, 45% yield) in pure form.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.15 (t, *J* = 3.3 Hz, 1H), 3.87 (d, *J* = 3.2 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 3H), 1.76

(s, 3H), 1.62 (s, 3H), 1.25 (s, 12H).

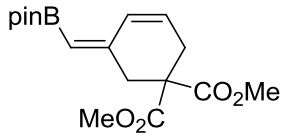
^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 134.8, 134.6, 131.6, 129.4, 127.5, 123.7, 83.7, 46.5, 45.0, 24.6, 23.2, 21.5, 20.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.6.

IR (Microscope, cm^{-1}) 2976, 2929, 1604.

HRMS (EI) for $C_{21}H_{30}BNO_4S$: calcd. 403.1989; found 403.1993.

5.5.3.3 (*Z*)-Dimethyl 5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)cyclohex-3-ene-1,1-dicarboxylate (5-13)



5-13

The title compound was prepared from compound **5-12** (101 mg, 0.3 mmol) using the general procedure for the gold catalyzed cycloisomerization reactions. Flash column chromatography (hexanes/EtOAc = 17:3) yielded **5-13** + **5-14** (91 mg, 0.27 mmol, 90% yield) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dtd, *J* = 10.1, 2.0, 0.7 Hz, 1H), 5.92 (dtd, *J* = 10.1, 4.2, 1.5 Hz, 1H), 5.20 (m, 1H), 3.70 (s, 6H), 2.93 (d, J = 1.5 Hz, 2H), 2.71 (ddd, *J* = 4.2, 2.0, 0.7 Hz, 2H), 1.25 (s, 12H).

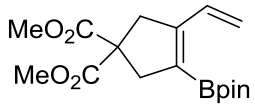
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 151.2, 128.7, 127.9, 82.5, 53.8, 52.4, 38.8, 30.8, 24.4. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.6.

IR (Microscope, cm^{-1}) 2979, 2966, 1737, 1690, 1632, 1594.

HRMS (EI) for $C_{17}H_{25}BO_6$: calcd. 336.1744; found 336.1750.

5.5.3.4 Dimethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-vinylcyclopent-3-ene-1,1-dicarboxylate (5-17)



5-17

The title compound was prepared from compound **5-15** (101 mg, 0.3 mmol) using the general procedure for the gold catalyzed cycloisomerization reactions. Flash column chromatography (hexanes/EtOAc = 17:3) yielded **5-16** + **5-17** (96 mg, 0.29 mmol, 95% yield) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.24 (d, *J* = 17.8 Hz, 1H), 5.24, (d, *J* = 10.3 Hz, 1H), 3.72 (s, 6H), 3.26 (s, 2H), 3.25 (s, 2H), 1.26 (s, 12H).

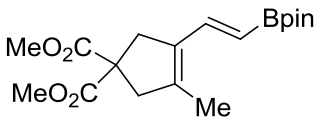
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 152.7, 133.1, 117.3, 83.2, 58.3, 52.8, 44.5, 41.9, 24.9. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (160 MHz, $CDCl_3$) δ 29.3.

IR (Microscope, cm^{-1}) 2980, 2957, 1737, 1676.

HRMS (EI) for $C_{17}H_{25}BO_6$: calcd. 336.1744; found 336.1747.

5.5.3.5 (*E*)-Dimethyl 3-methyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclopent-3-ene-1,1-dicarboxylate (5-19)



5-19

The title compound was prepared from compound **5-18** (105 mg, 0.3 mmol) using the general procedure for the gold catalyzed cycloisomerization reactions. Flash column chromatography (hexanes/EtOAc = 17:3) yielded **5-19** (83 mg, 0.24 mmol, 79% yield) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 18.2 Hz, 1H), 5.38 (d, J = 18.1 Hz, 1H), 3.72 (s, 6H), 3.15 (br s, 2H), 3.08 (br s, 2H), 1.83 (br s, 3H), 1.26 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 142.1, 139.0, 132.6, 83.1, 57.0, 52.8, 46.8,

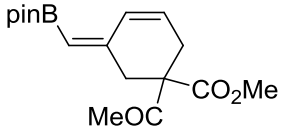
40.5, 24.7, 13.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

^{11}B NMR (128 MHz, $CDCl_3$) δ 29.9.

IR (Microscope, cm^{-1}) 2979, 2955, 1737, 1642, 1603.

HRMS (ESI) for $C_{18}H_{27}BO_6$: calcd. 350.1901; found 350.1907.

5.5.3.6 (*Z*)-Methyl 1-acetyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)cyclohex-3-enecarboxylate (5-21)



5-21

The title compound was prepared from compound **5-20** (96 mg, 0.3 mmol) using the general procedure for the gold catalyzed cycloisomerization reactions. Flash column chromatography (hexanes/EtOAc = 17:3) yielded **5-21** + **5-22** (49 mg, 0.15 mmol, 51% yield) in pure form.

^{1}H NMR (400 MHz, $CDCl_3$) δ6.97 (dtd, *J* = 10.0, 2.0, 0.4 Hz, 1H), 5.93 (dtd, *J* = 10.0, 4.2, 1.5 Hz, 1H), 5.21 (br s, 1H), 3.70 (s, 3H), 2.95 (dd, J = 15.4, 1.5 Hz, 1H), 2.88 (dd, J = 15.5, 1.4 Hz, 1H), 2.66 (dd, *J* = 4.4, 1.8 Hz, 2H), 2.17 (s, 3H), 1.25 (s, 12H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 171.8, 151.8, 129.4, 128.4, 83.0, 60.2, 52.8, 38.9, 30.4, 25.9, 24.8. (The boron-bound carbon was not detected due to quadrupolar relaxation)

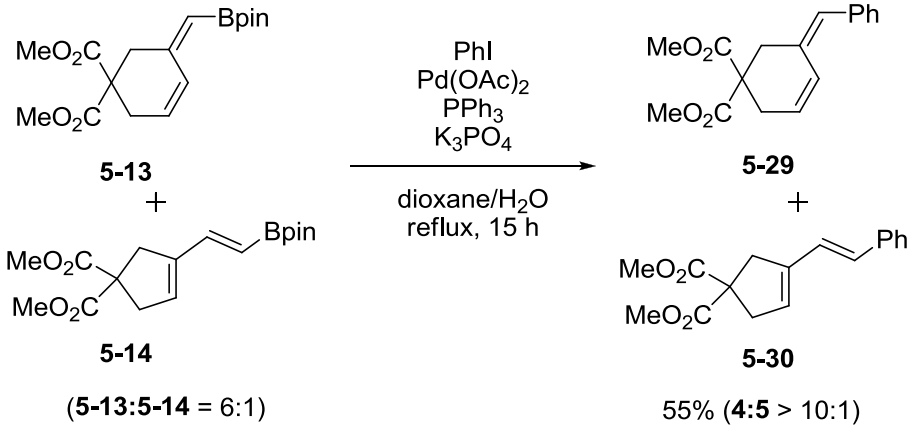
^{11}B NMR (128 MHz, $CDCl_3$) δ 29.4.

IR (Microscope, cm^{-1}) 2979, 1742, 1717, 1632, 1594.

HRMS (ESI) for $C_{17}H_{25}BNaO_5$: $(M + Na)^+$ calcd. 338.2136; found 338.2126.

5.5.4 Transformations to other functionalities

5.5.4.1 (*Z*)-Dimethyl 5-benzylidenecyclohex-3-ene-1,1-dicarboxylate (5-29)



To a mixture of alkenyl boronate **5-13** + **5-14** (168 mg, 0.50 mmol), iodobenzene (204 mg, 1.00 mmol), $Pd(OAc)_2$ (5.60 mg, 0.03 mmol), PPh_3 (15.7 mg, 0.06 mmol), and K_3PO_4 (318 g, 1.5 mmol) was added dioxane (2.5 mL) and H_2O (0.25 mL). The mixture was then heated under reflux for 15 hours. The reaction mixture was then brought to room temperature and brine (10 mL) was added. The aqueous layer was further extracted with diethyl ether (3 × 10 mL), and the combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 8:2) to give **5-29** + **5-30** (79.0 mg, 55%) in pure form.

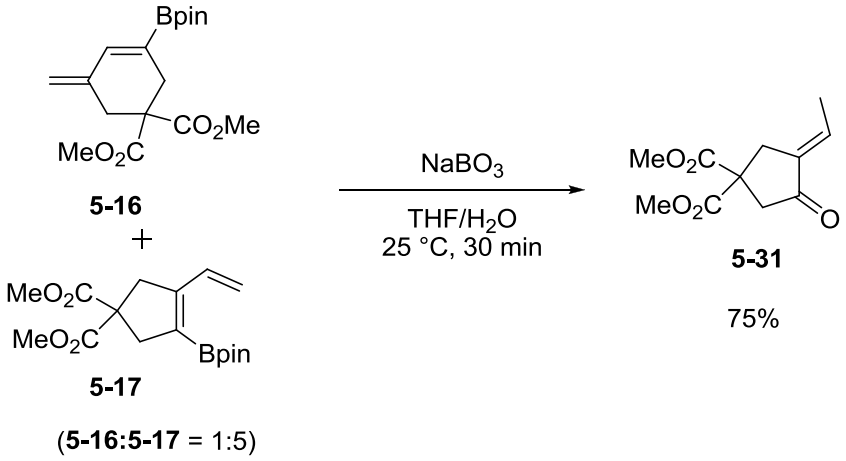
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.25 – 7.20 (m, 3H), 6.61 (dtd, *J* = 10.1, 2.0, 1.0 Hz, 1H), 6.35 (br s, 1H), 5.87 (dtd, *J* = 10.1, 4.1, 1.7 Hz, 1H), 3.73 (s, 6H), 2.97 (d, *J* = 1.6 Hz, 2H), 2.77 (ddd, *J* = 4.0, 2.1, 0.9 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 137.0, 131.5, 129.2, 128.1, 128.0, 127.6, 126.7, 125.1, 54.3, 52.8, 37.7, 31.9.

IR (Microscope, cm^{-1}) 3025, 3000, 2953, 2909, 1736, 1597.

HRMS (EI) for $C_{17}H_{18}O_4$: calcd. 286.1205; found 286.1205.

5.5.4.2 (*E*)-Dimethyl 3-ethylidene-4-oxocyclopentane-1,1-dicarboxylate (5-31)



To a solution of **5-16** + **5-17** (100 mg, 0.30 mmol) in THF (2.0 mL) and water (2.0 mL) was added sodium perborate (1.5 mmol, 229 mg). The reaction mixture was stirred vigorously for 1 hour at room temperature, before the reaction mixture was quenched with water (5.0 mL). The solution was then extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified with flash column chromatography (hexanes/EtOAc = 8:2) to give **5-31** (50.4 mg, 75%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (qt, J = 7.3, 2.8 Hz, 1H), 3.77 (s, 6H), 3.19 (dt, J = 2.8, 1.9 Hz, 2H), 2.92 (br s, 2H), 1.84 (dt, J = 7.2, 1.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 171.3, 135.2, 133.5, 54.1, 53.2, 45.4, 34.3, 15.3.

IR (Microscope, cm^{-1}) 2957, 2919, 1736, 1656.

HRMS (ESI) for $C_{11}H_{14}O_5$: calcd. 226.0841; found 226.0842.

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Chapter 6

Conclusions and Future Perspectives

In modern day organic chemistry, efficiency in synthesis has become a primary goal due to limited resources available to humans. As a result, much of the effort currently spent by chemists is associated with a more efficient generation of the desired molecules. As discussed repeatedly throughout this thesis, organoboronates are synthetically valuable adducts because various chemical transformations can be conducted with these compounds to form important C−C or C−heteroatom bonds with efficacy. These transformations are often chemo- and stereoselective, allowing the desired products to be synthesized with none or little side product. In this thesis, several different approaches were described for the synthesis of various unsaturated organoboronates and chiral alkyl boronates through the "early introduction" strategy (Chapter 1). By conducting well-established synthetic protocols on substrates with a pre-installed boronyl unit, novel organoboronates could be accessed with excellent efficiency and stereoselectivity. The robustness of the boronyl unit in these reactions can be fine-tuned through the utilization of different boron masking groups. The high efficiency of these reactions demonstrates that synthesizing organoboronates through the "early introduction" strategy, in contrast to the normally employed "late boronyl introduction" strategy, is advantageous and offers opportunities for accessing the desired compounds with different reaction pathways. In order to demonstrate the synthetic utility of the boronate products obtained, these organoboronates were transformed to other important structural motifs stereoselectively through different chemical transformations.

These studies not only illustrate the importance of these organoboronates, but also have opened doors to different avenues of organoboron chemistry. For example, the chiral alkyl boronates prepared from the synthetic methods as discussed previously in this thesis (Chapters 2 and 3) can be used to develop novel chemical transformations associated with these compounds. Although numerous chemical transformations of chiral alkyl boronates are known (Chapter 1), these reactions

often require harsh conditions such as strong bases and high temperatures. Therefore, future studies in this field will be necessary in order to expand the efficiency and the scope of these reactions. In addition to investigating the synthetic utility of chiral boronates, other synthetic methods are also needed to prepare novel optically enriched 1,1-diboron compounds. As mentioned in Chapter 3, the chiral 1,1-diboron compounds prepared in this thesis are to date the only asymmetric examples of this class of substrates. Owing to their interesting reactivity such as demonstrated in Suzuki-Miyaura cross-coupling reactions, other types of chiral 1,1-diboron compounds should be investigated to unveil the full intrinsic properties and reactivity of these compounds. One other direction associated with this project would involve the synthesis of higher order *gem*-polyboronated compounds, such as 1,1,1-triboronyl or 1,1,1,1-tetraboronyl adducts. Ultimately, these compounds can be regarded as synthetic templates to access different molecules where the boronate moiety can be functionalized iteratively to give the desired adducts. Due to the ready availability of achiral 1,1-diboron compounds (Chapter 3), however, a direct desymmetrization approach where one of the prochiral boronate functionalities could be transformed to different groups stereoselectively will also be desirable. This will allow access to chiral products without the necessity to prepare chiral optically enriched 1,1-diboron compounds. The proposed projects mentioned here only constitute a small amount of potential future directions from my thesis. I believe that by continuously investing research efforts into the preparation of organoboronates and functionalizing these moieties, more efficient synthetic methodologies can be developed to benefit other areas such as pharmaceutical or material research.

Appendices

Appendix 1: X-ray Crystallographic data for 3-11

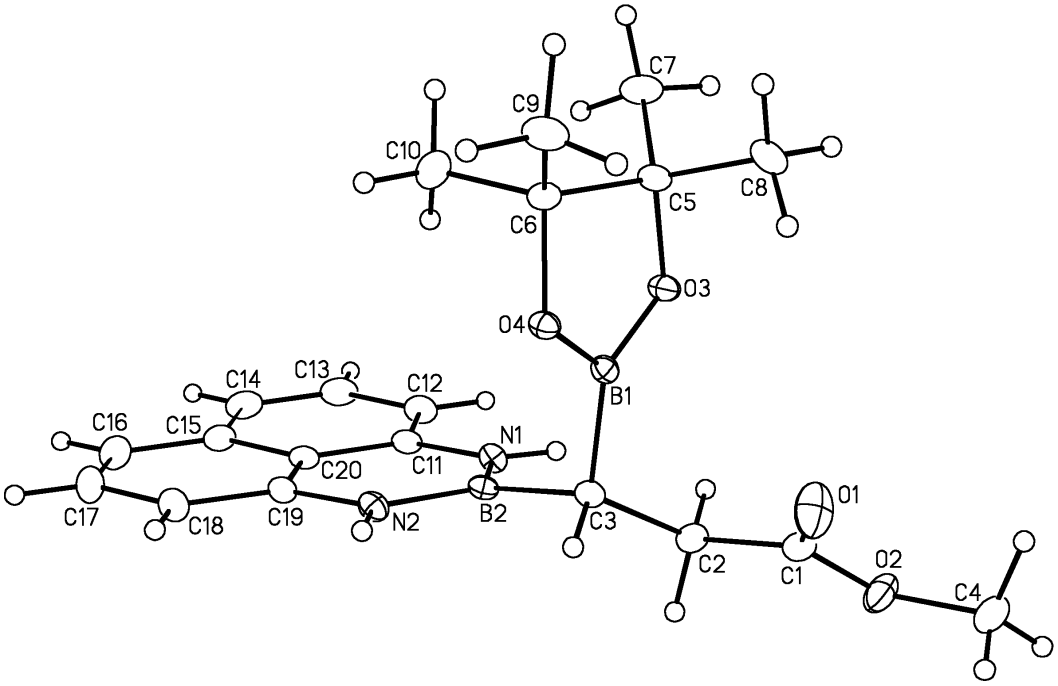
XCL Code: DGH1101 **Date:** 14 January 2011

Compound: methyl 3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate

Formula: $C_{20}H_{26}B_2N_2O_4$

Supervisor: D. G. Hall **Crystallographer:**

M. J. Ferguson



For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta:

Dr. Robert McDonald **E-Mail:** Bob.McDonald@ualberta.ca
Dr. Michael J. Ferguson **E-Mail:** Michael.Ferguson@ualberta.ca
Lab: E3-09; **Office:** E3-13 Gunning/Lemieux Chemistry Centre
Phone: +1 780 492 2485; **Fax:** +1 780 492 8231

X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta,

Edmonton, Alberta, T6G 2G2, Canada

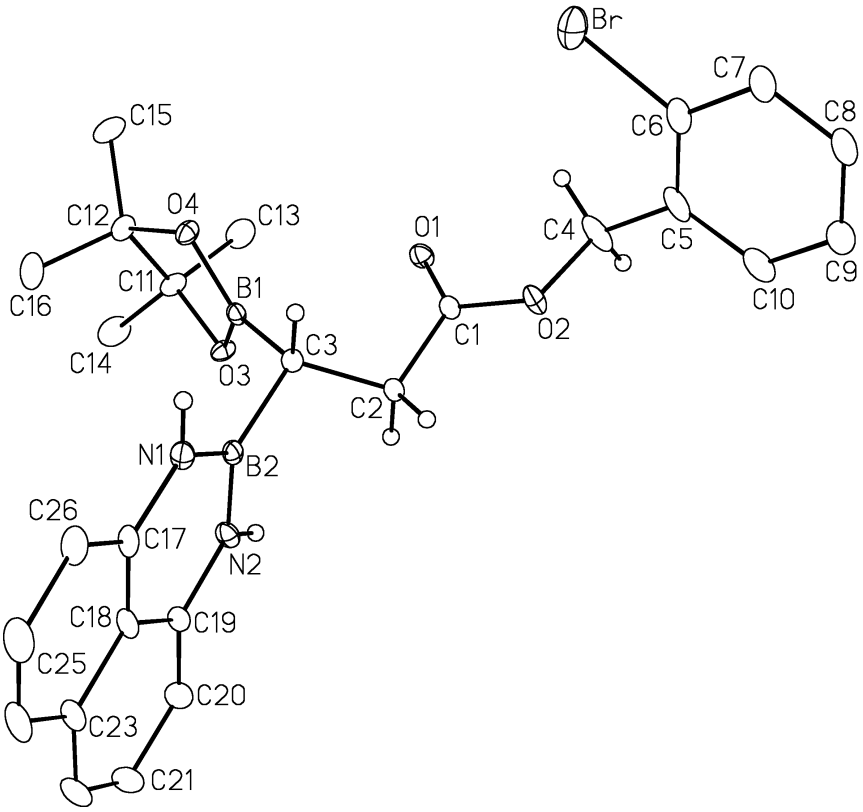
Appendix 2: X-ray Crystallographic data for 3-20

XCL Code: DGH1106 **Date:** 18 May 2011

Compound: 2-Bromobenzyl (3*R*)-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate

Formula: $C_{26}H_{29}B_2BrN_2O_4$

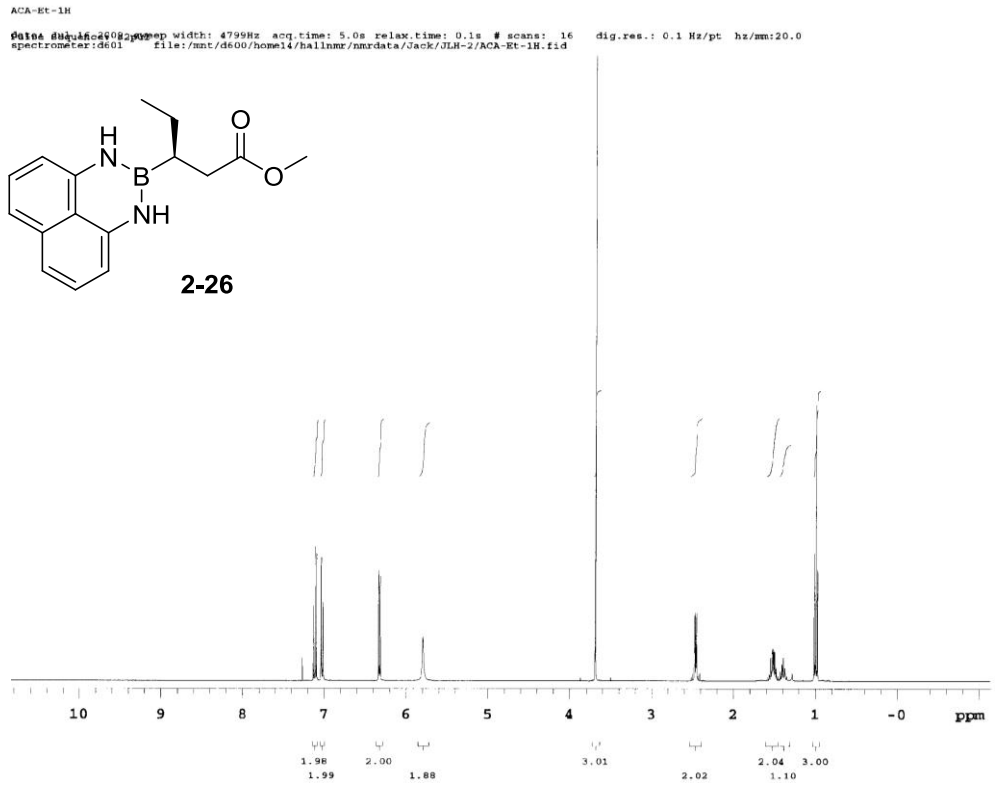
Supervisor: D. G. Hall **Crystallographer:** R. McDonald

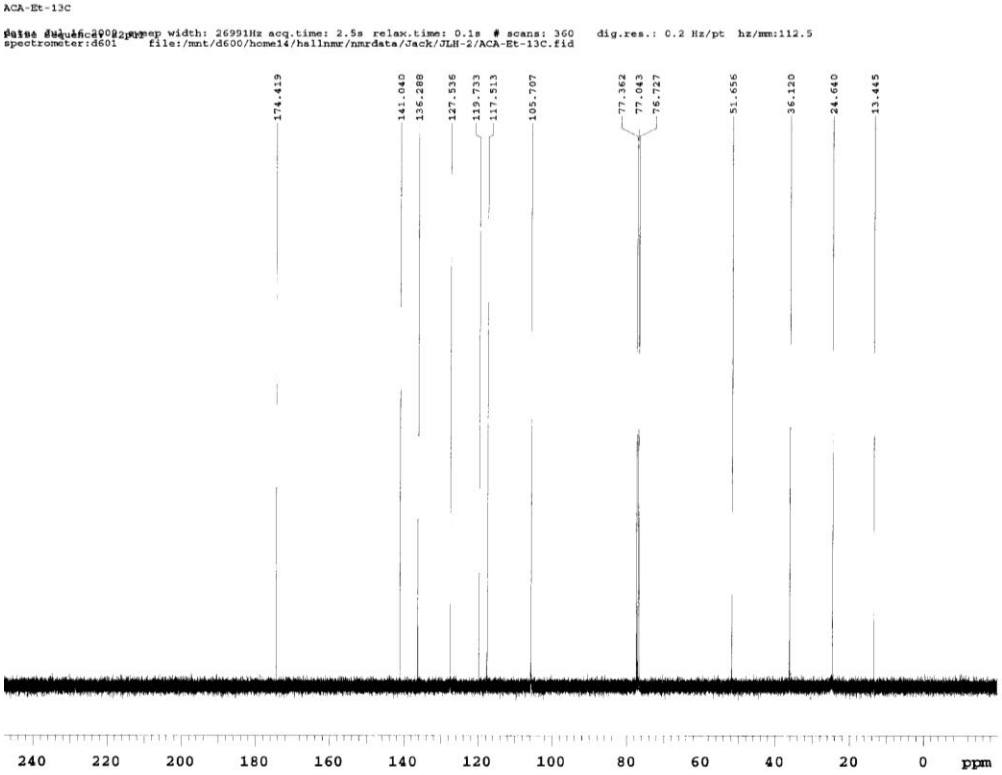


For further information regarding this X-ray, please contact the X-ray crystallography laboratory at the University of Alberta:
Dr. Robert McDonald **E-Mail:** Bob.McDonald@ualberta.ca
Dr. Michael J. Ferguson **E-Mail:** Michael.Ferguson@ualberta.ca
Lab: E3-09; **Office:** E3-13 Gunning/Lemieux Chemistry Centre
Phone: +1 780 492 2485; **Fax:** +1 780 492 8231
X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2, Canada

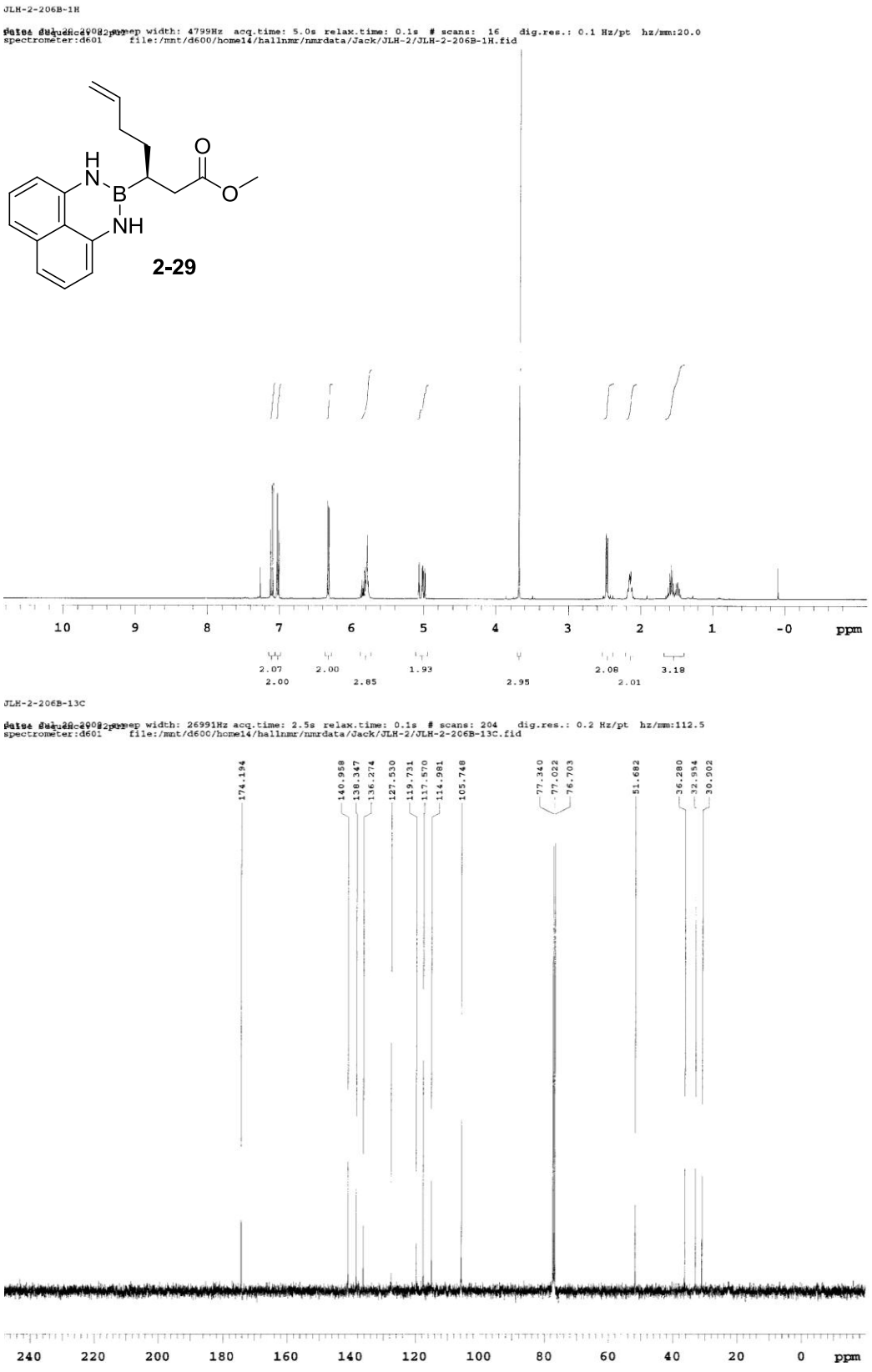
Appendix 3: Copies of NMR spectra for selected chiral alkyl boronates

^{1}H- and ^{13}C- NMR of 2-26 in $CDCl_3$ at 25 ^{o}C

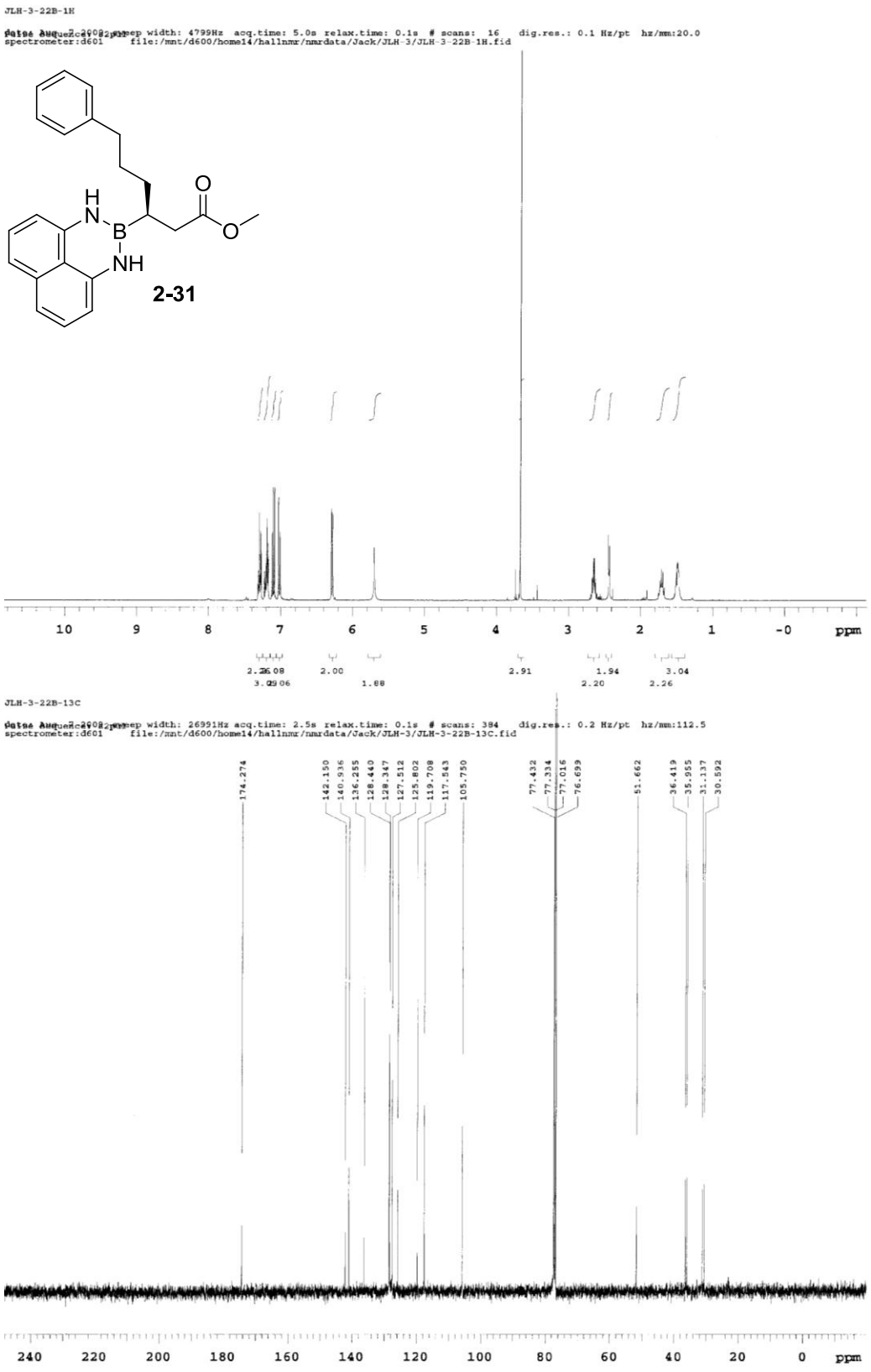




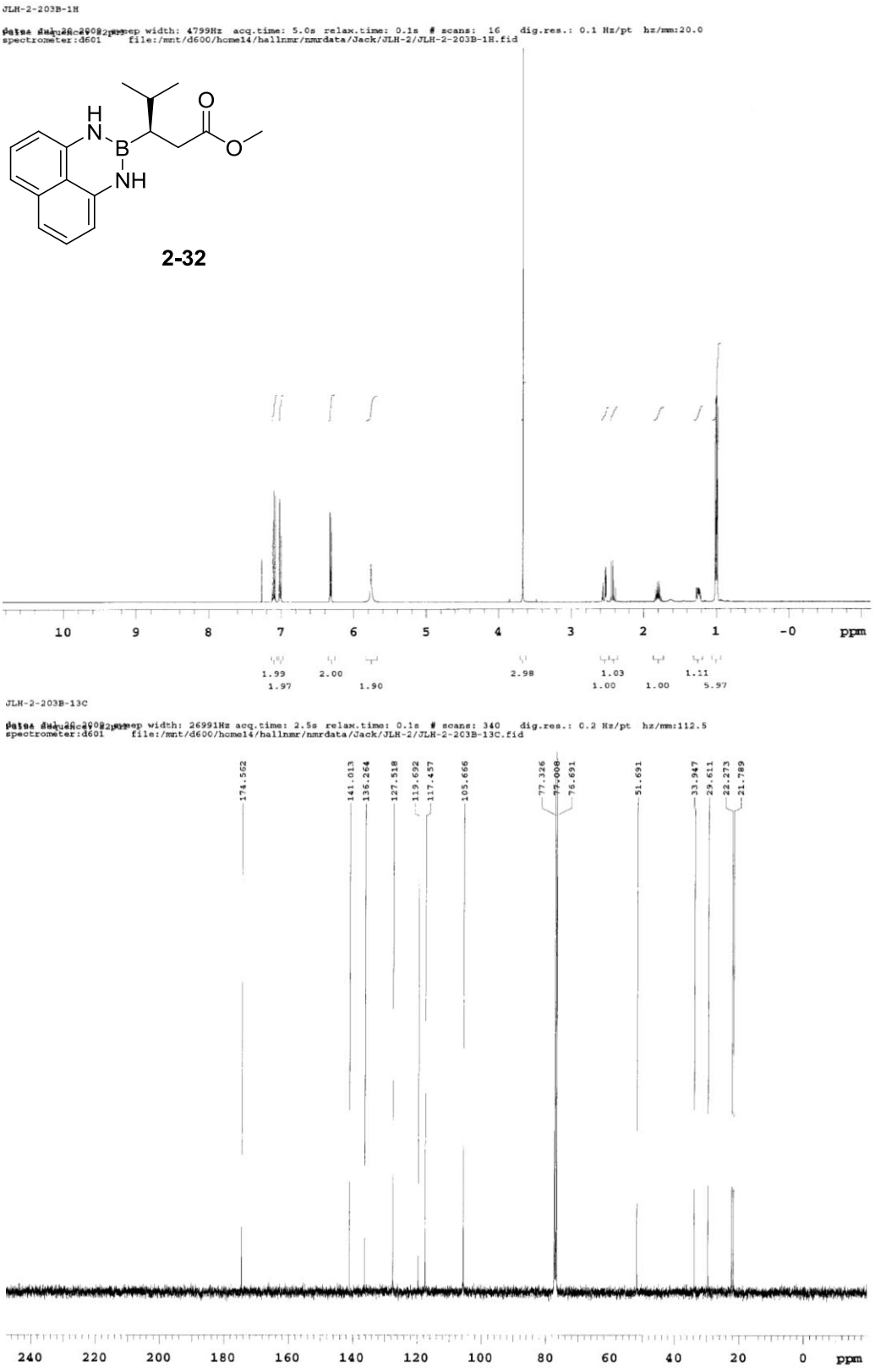
^{1}H- and ^{13}C- NMR of 2-29 in $CDCl_3$ at 25 ^{o}C



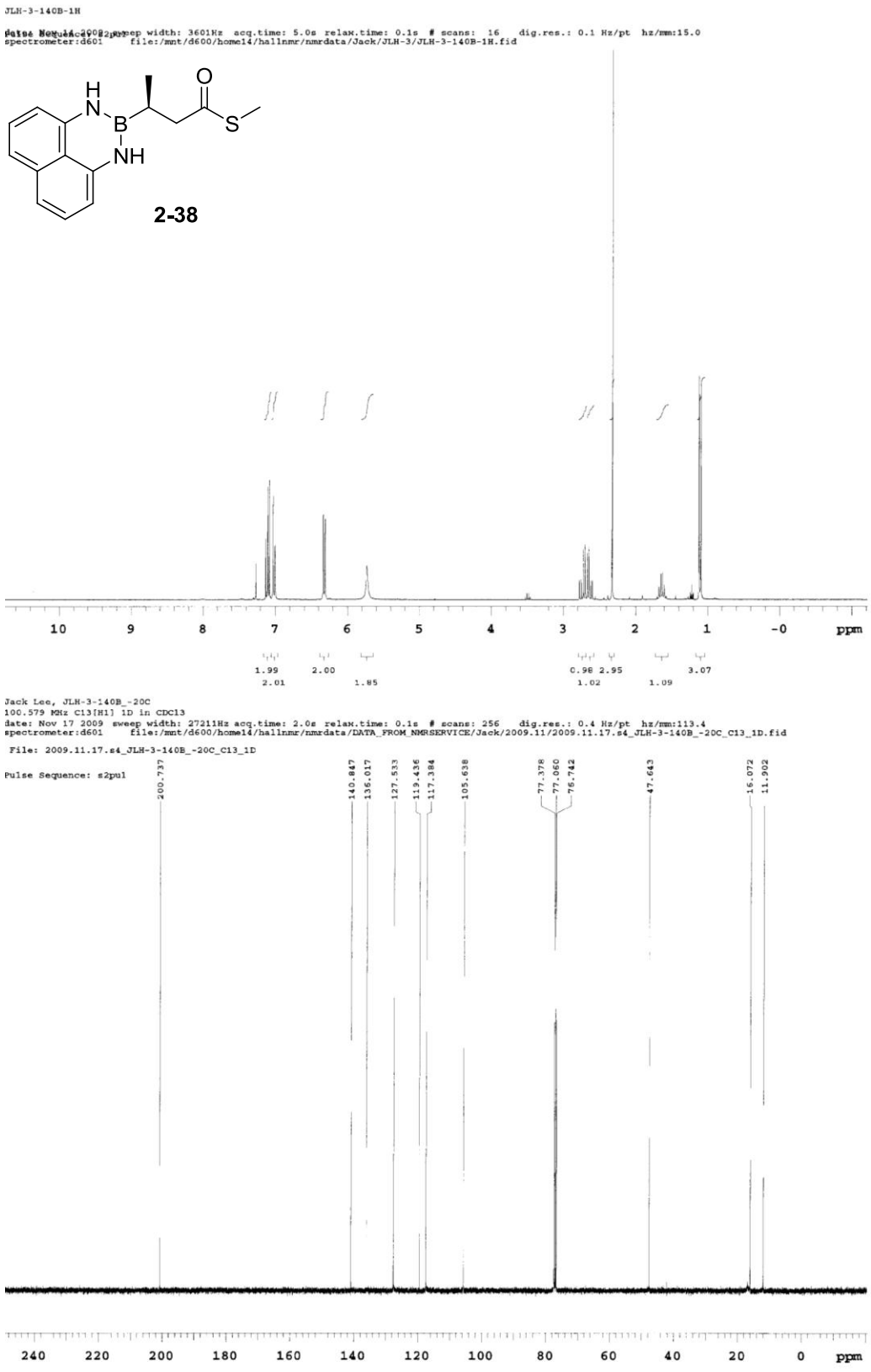
^{1}H- and ^{13}C- NMR of 2-31 in $CDCl_3$ at 25 ^{o}C



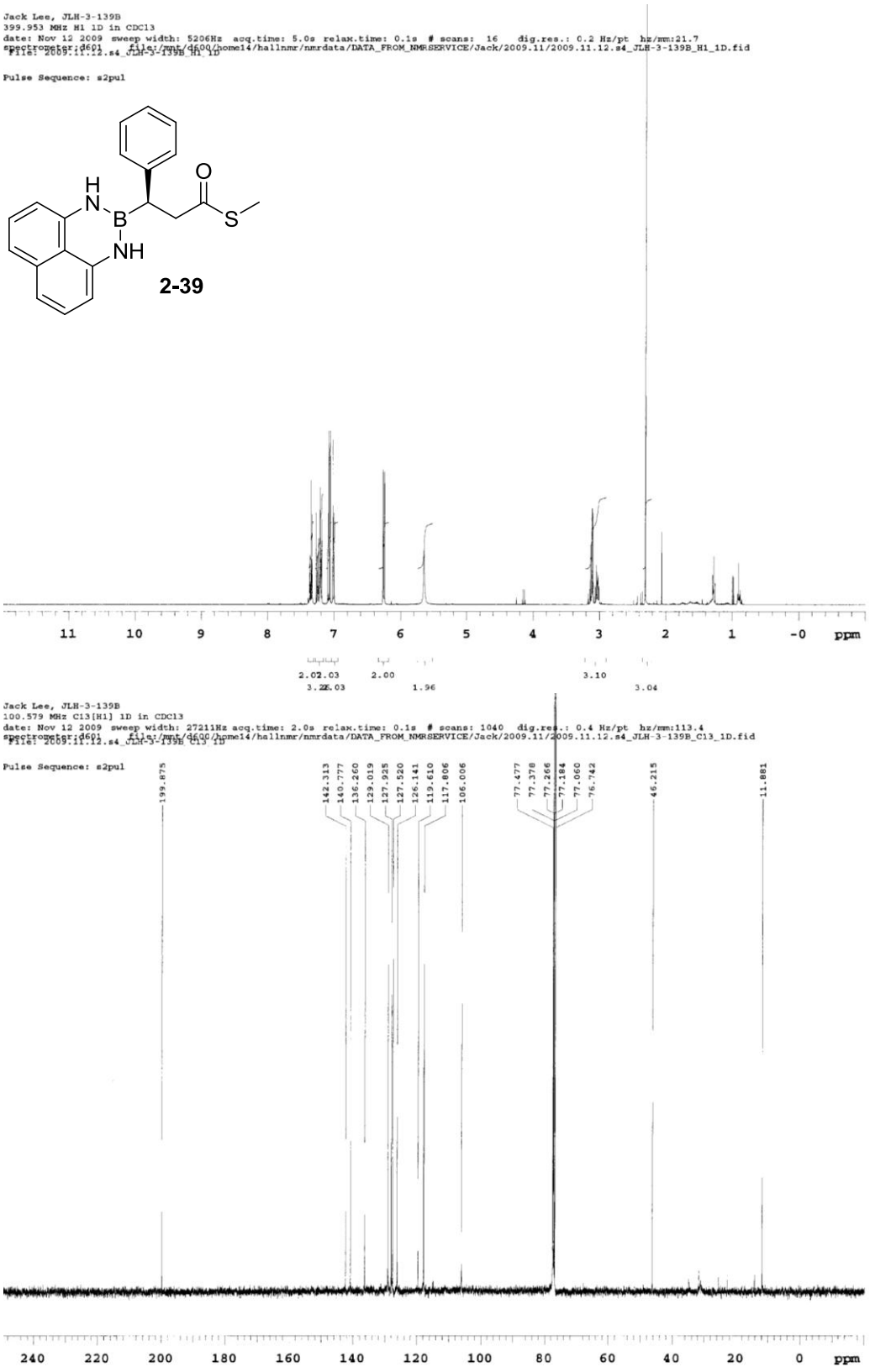
^{1}H- and ^{13}C- NMR of 2-32 in $CDCl_3$ at 25 ^{o}C



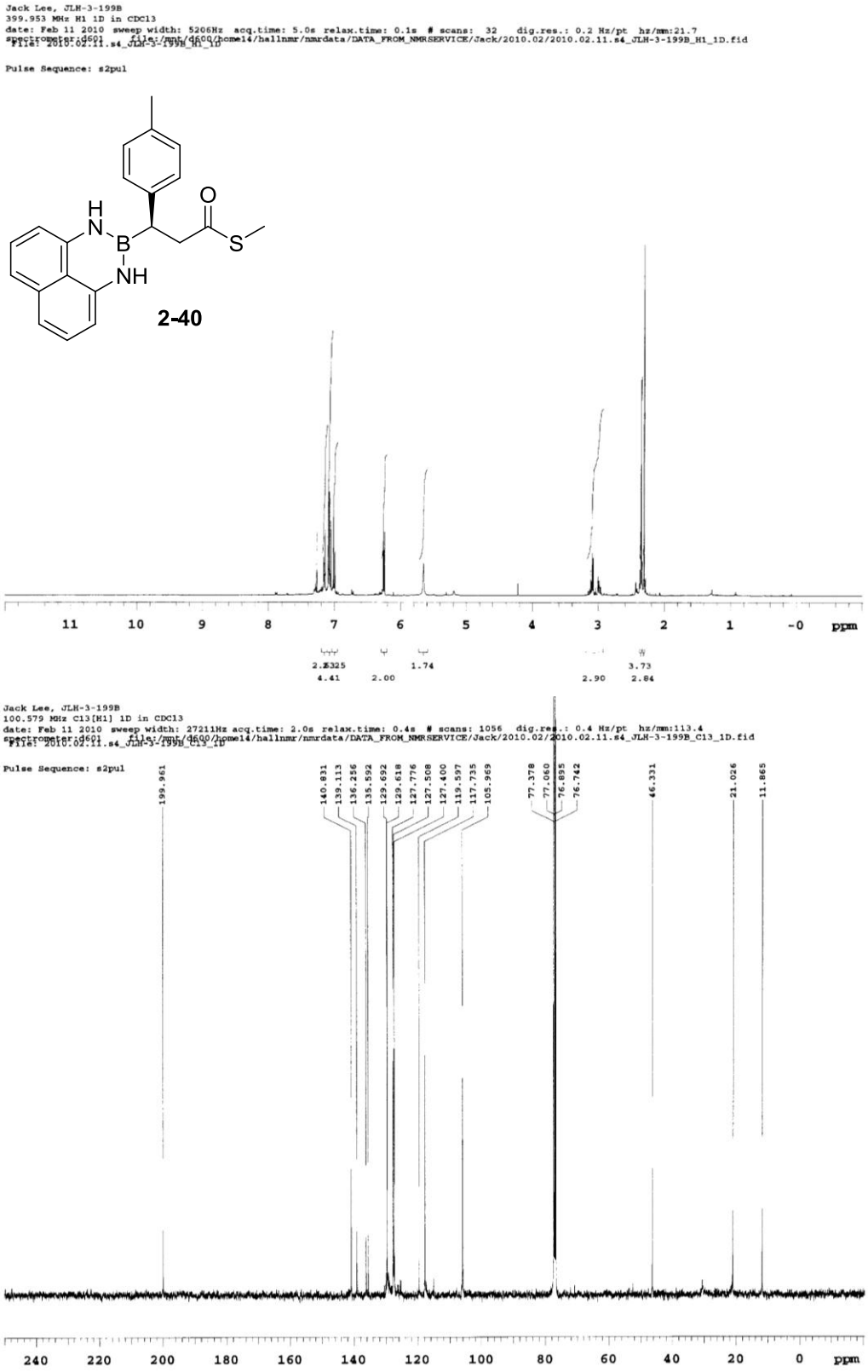
^{1}H- and ^{13}C- NMR of 2-38 in $CDCl_3$ at 25 ^{o}C



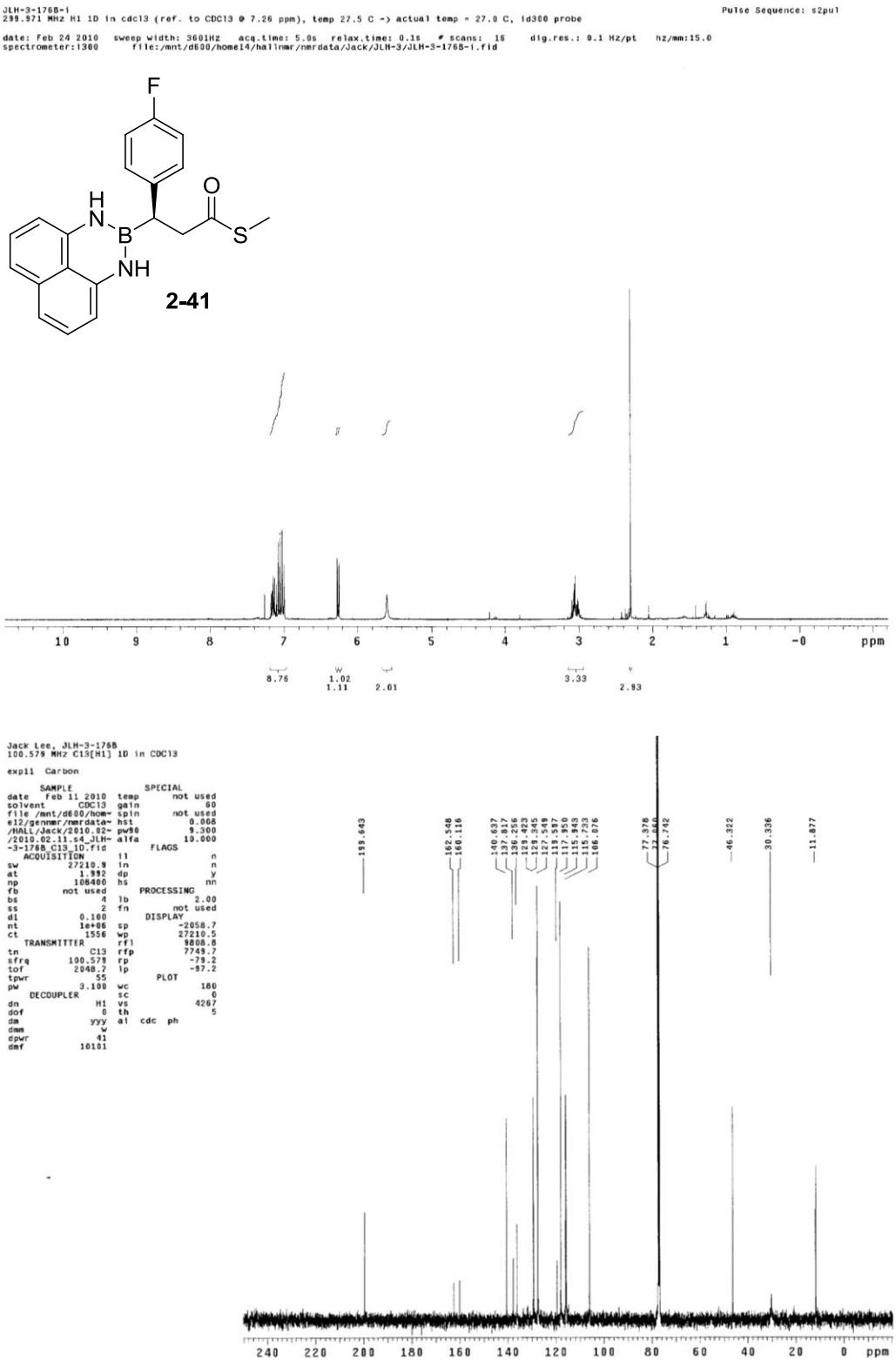
^{1}H- and ^{13}C- NMR of 2-39 in $CDCl_3$ at 25 ^{o}C



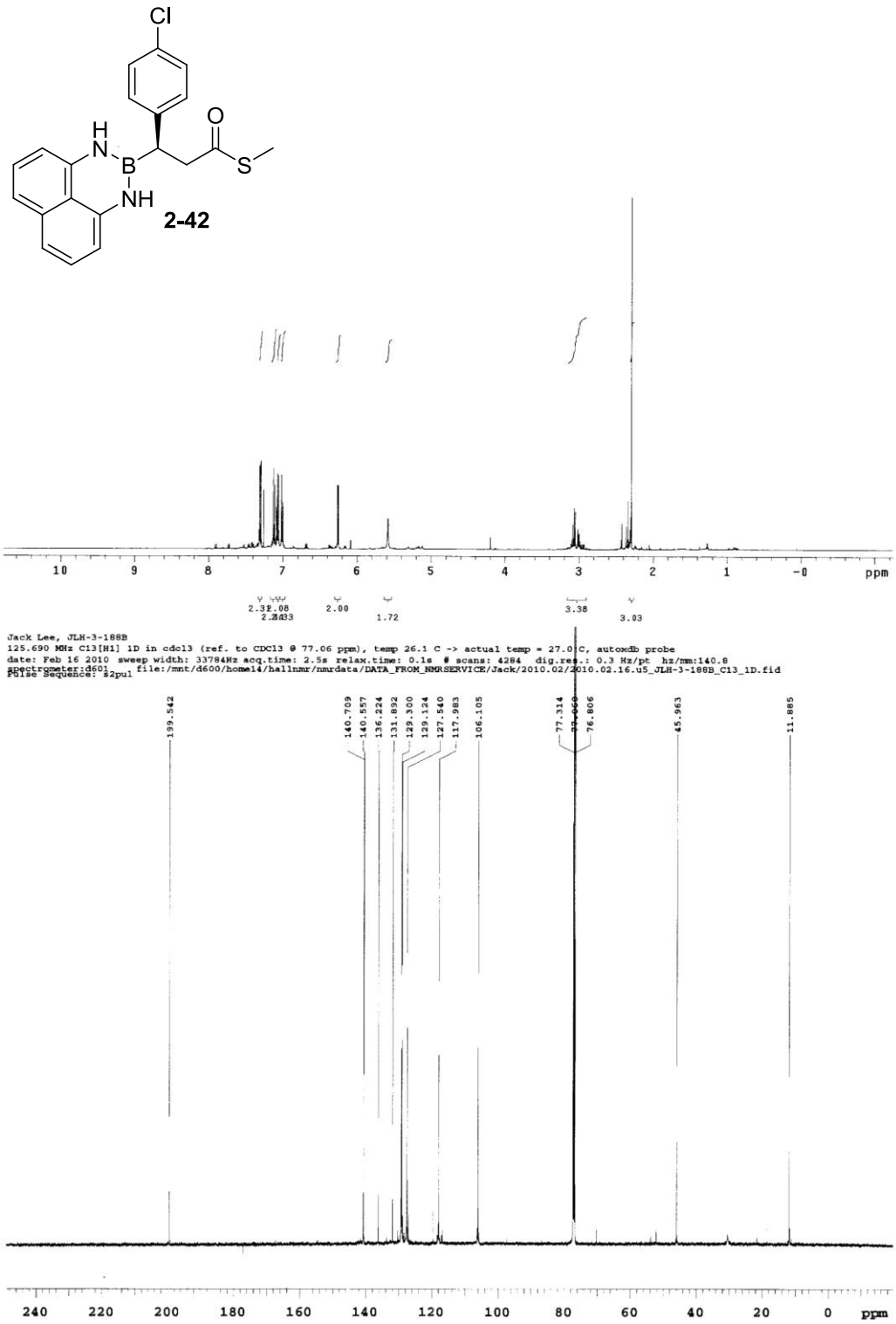
^{1}H- and ^{13}C- NMR of 2-40 in $CDCl_3$ at 25 ^{o}C



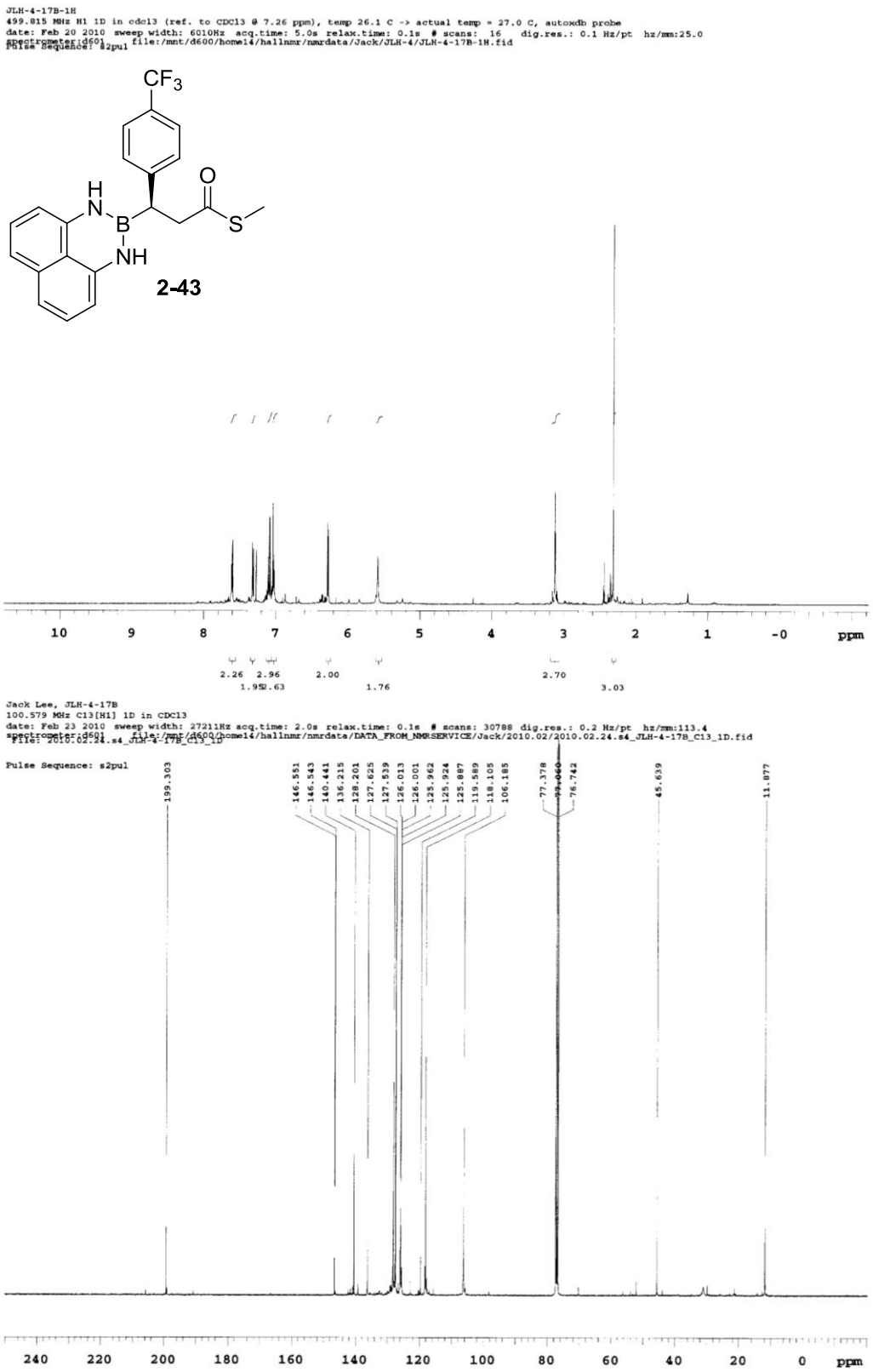
^{1}H- and ^{13}C- NMR of 2-41 in $CDCl_3$ at 25 ^{o}C



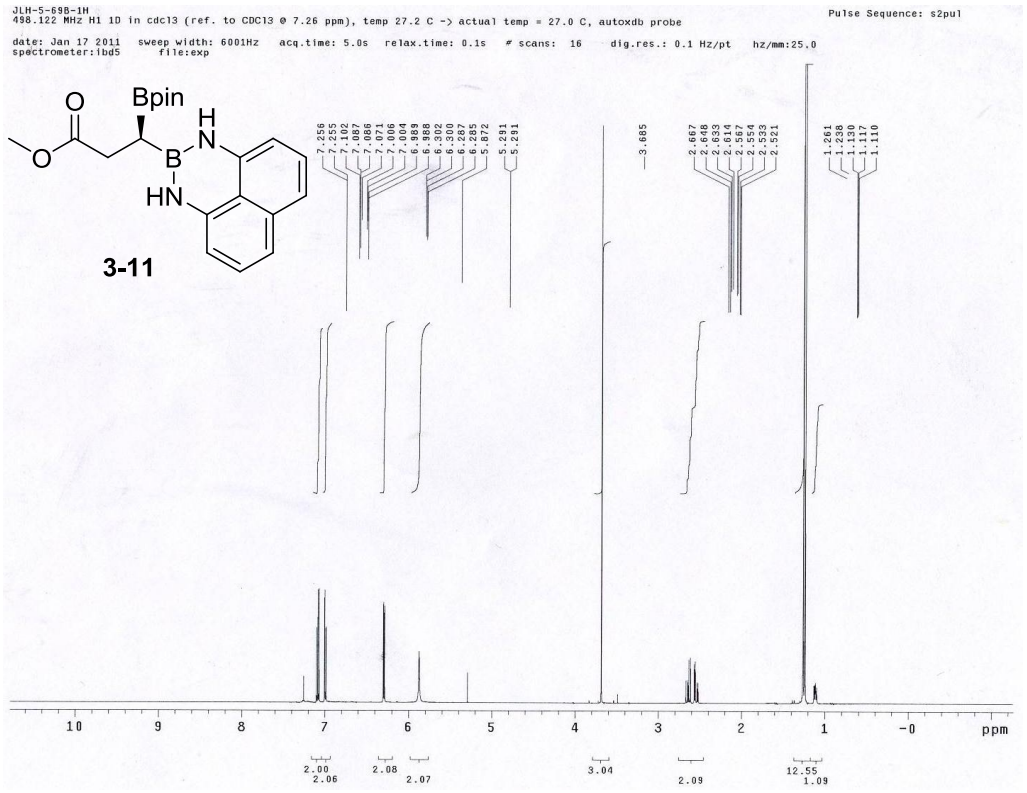
^{1}H- and ^{13}C- NMR of 2-42 in $CDCl_3$ at 25 ^{o}C

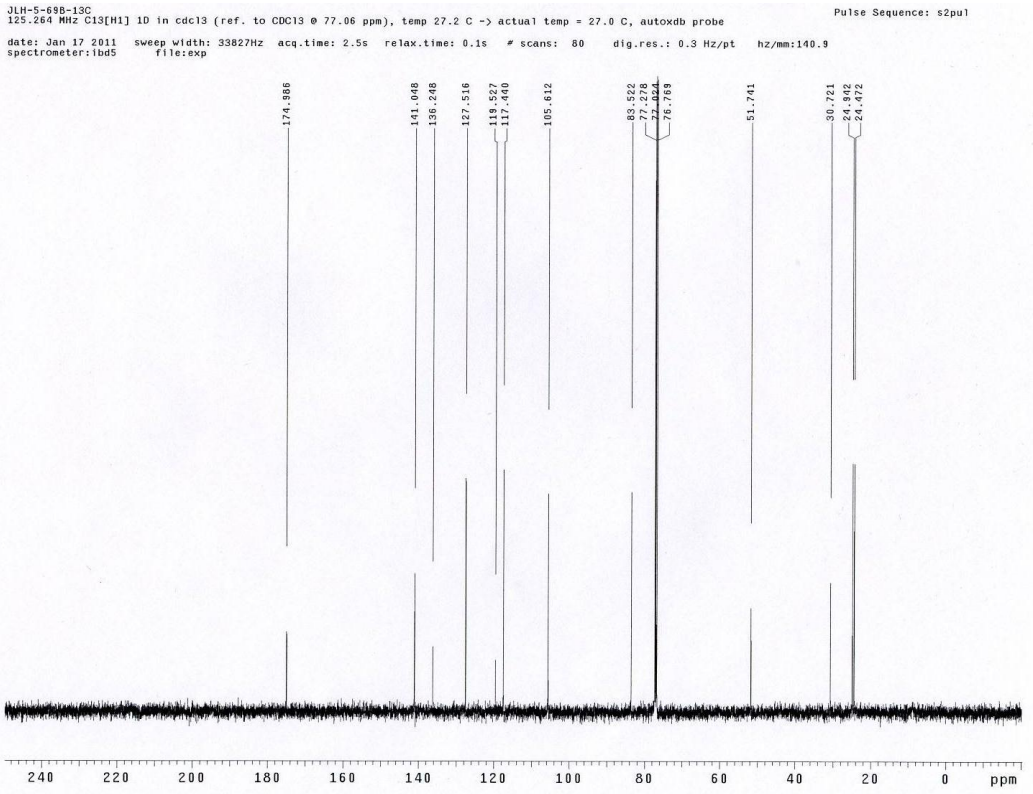


^{1}H- and ^{13}C- NMR of 2-43 in $CDCl_3$ at 25 ^{o}C

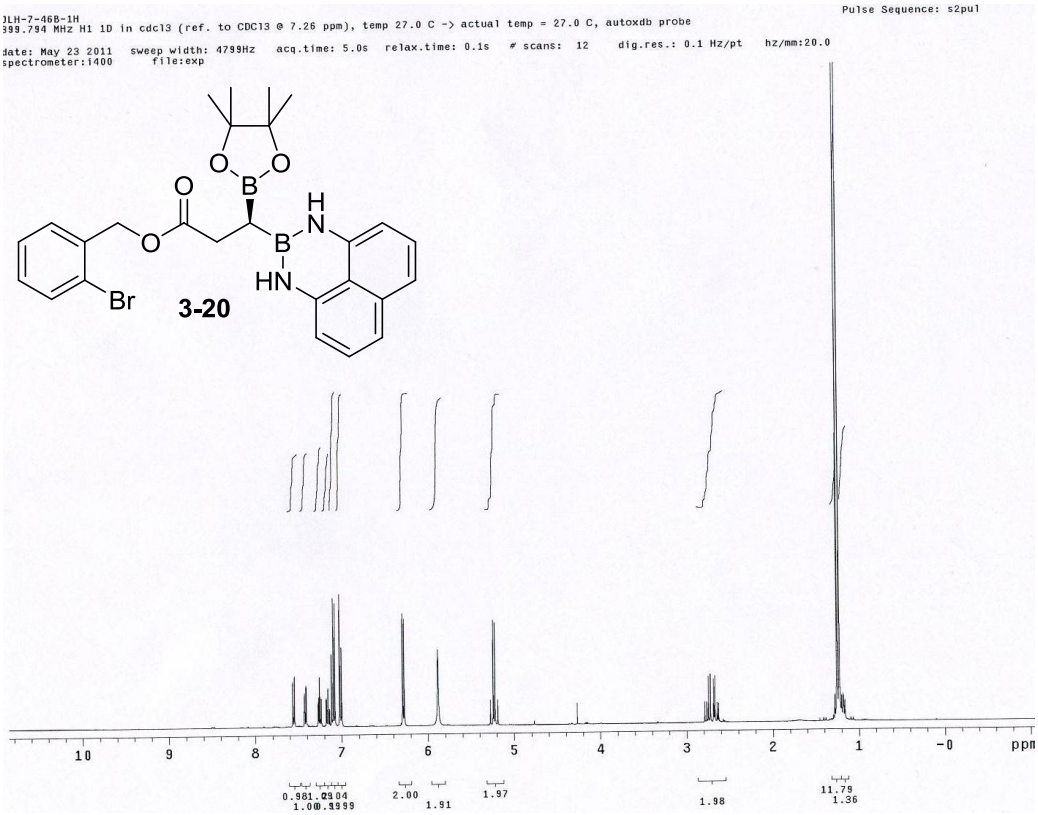


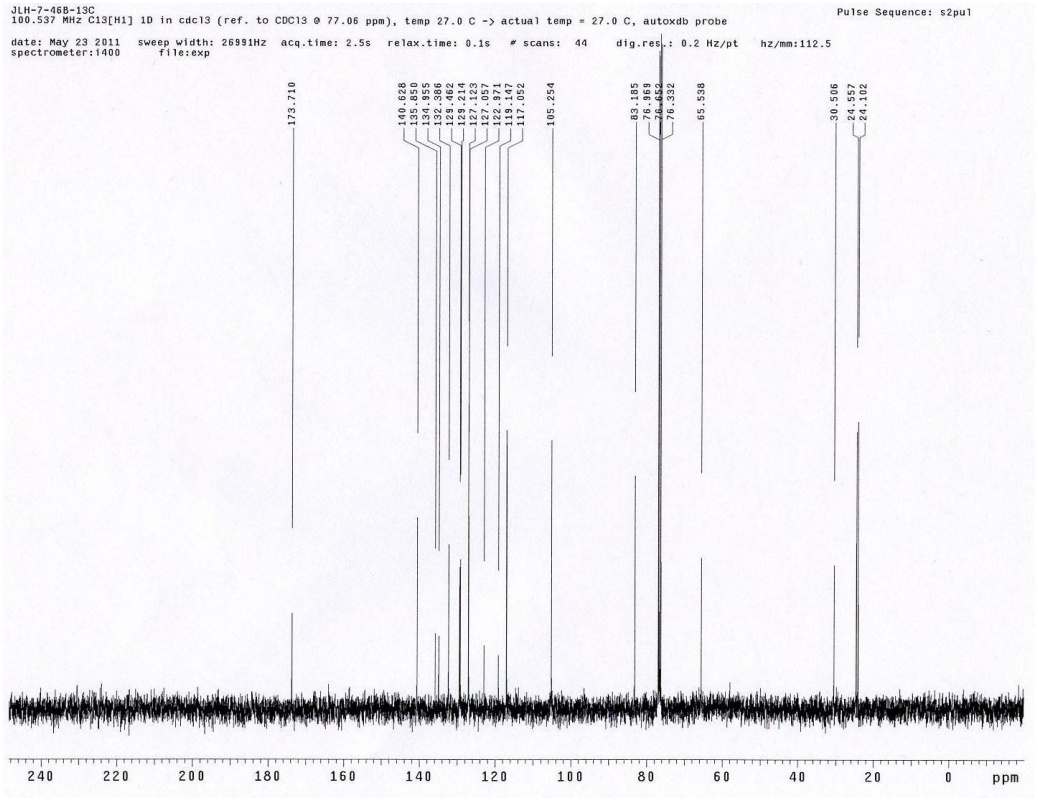
^{1}H- and ^{13}C- NMR of 3-11 in $CDCl_3$ at 25 ^{o}C



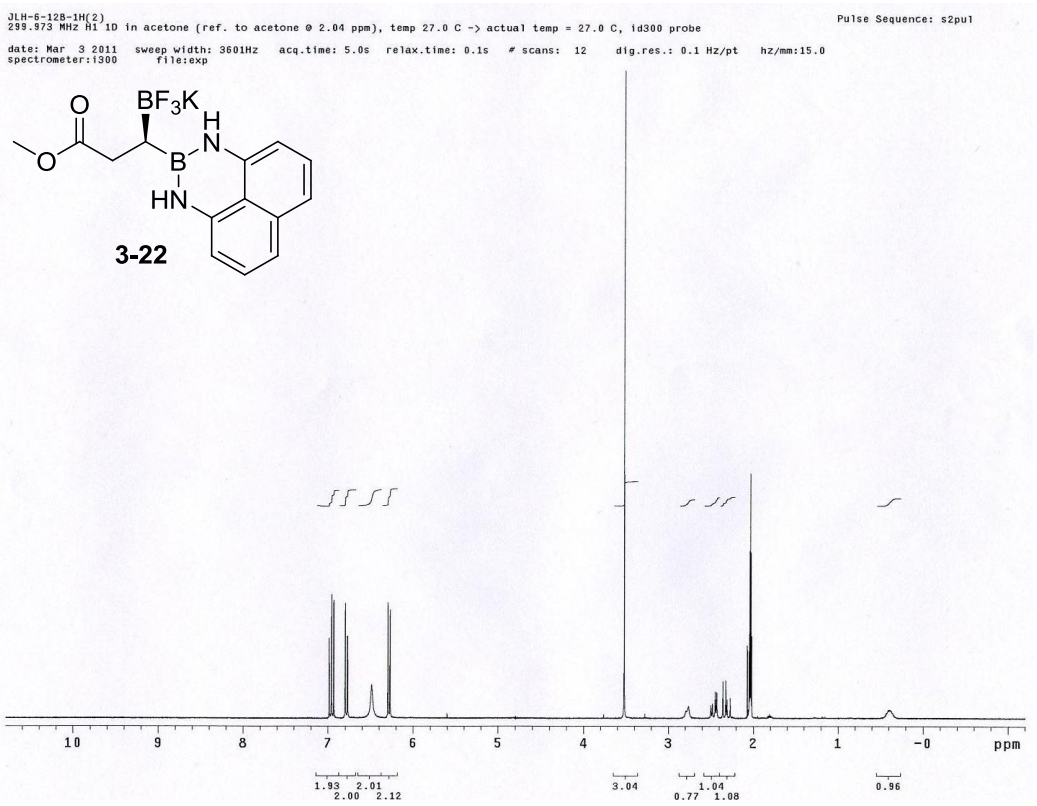


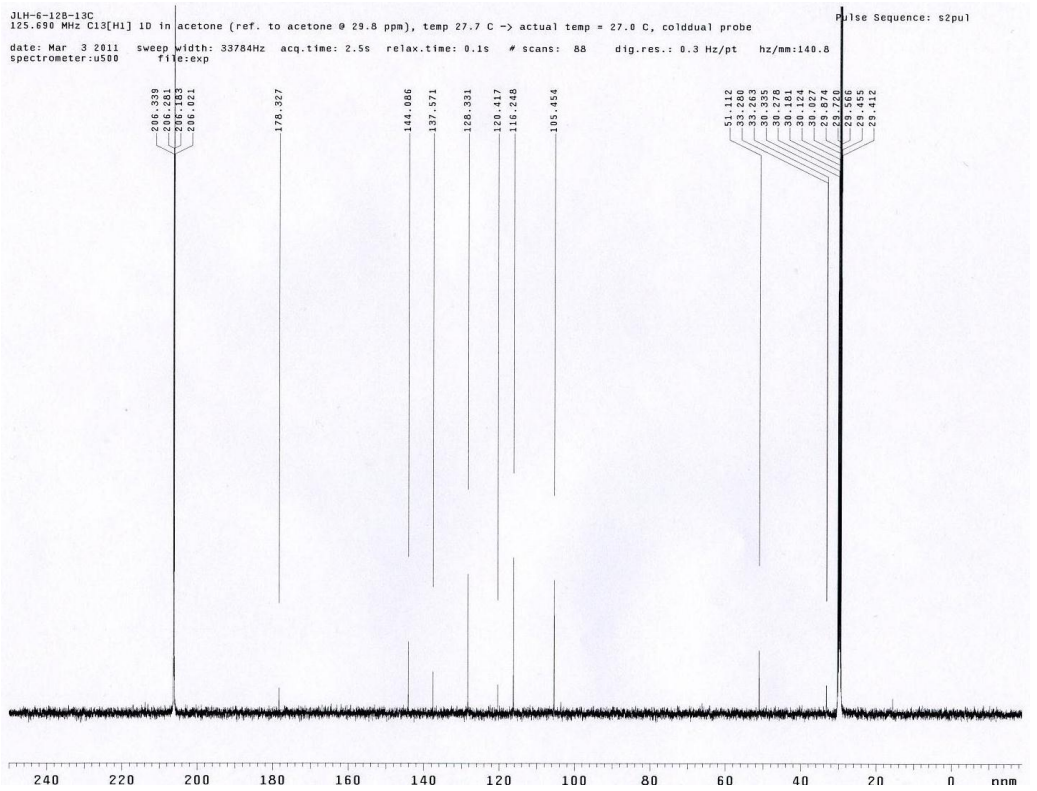
^{1}H- and ^{13}C- NMR of 3-20 in $CDCl_3$ at 25 ^{o}C



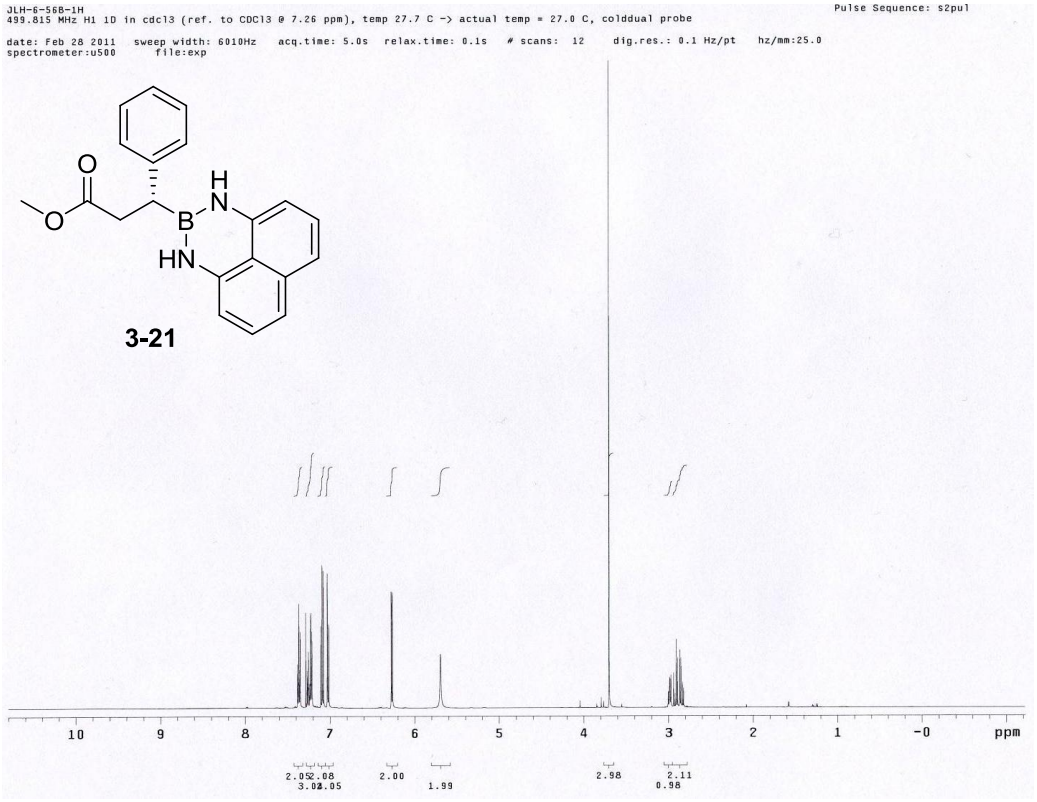


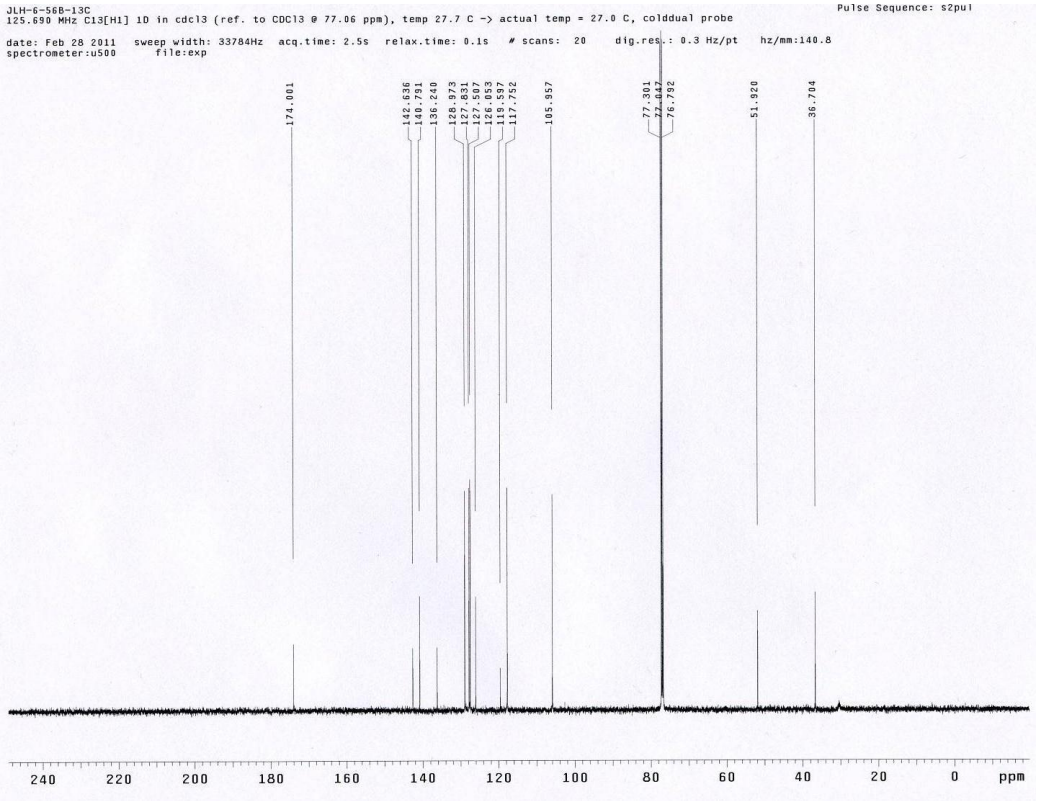
^{1}H- and ^{13}C- NMR of 3-22 in $CDCl_3$ at 25 ^{o}C



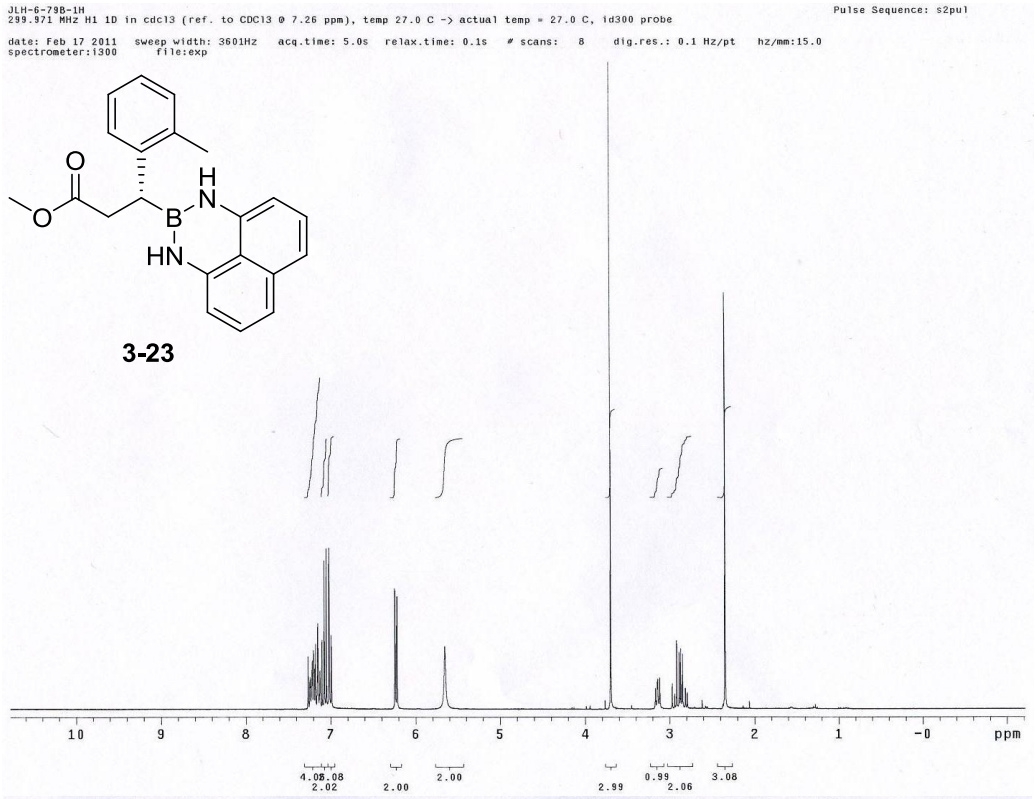


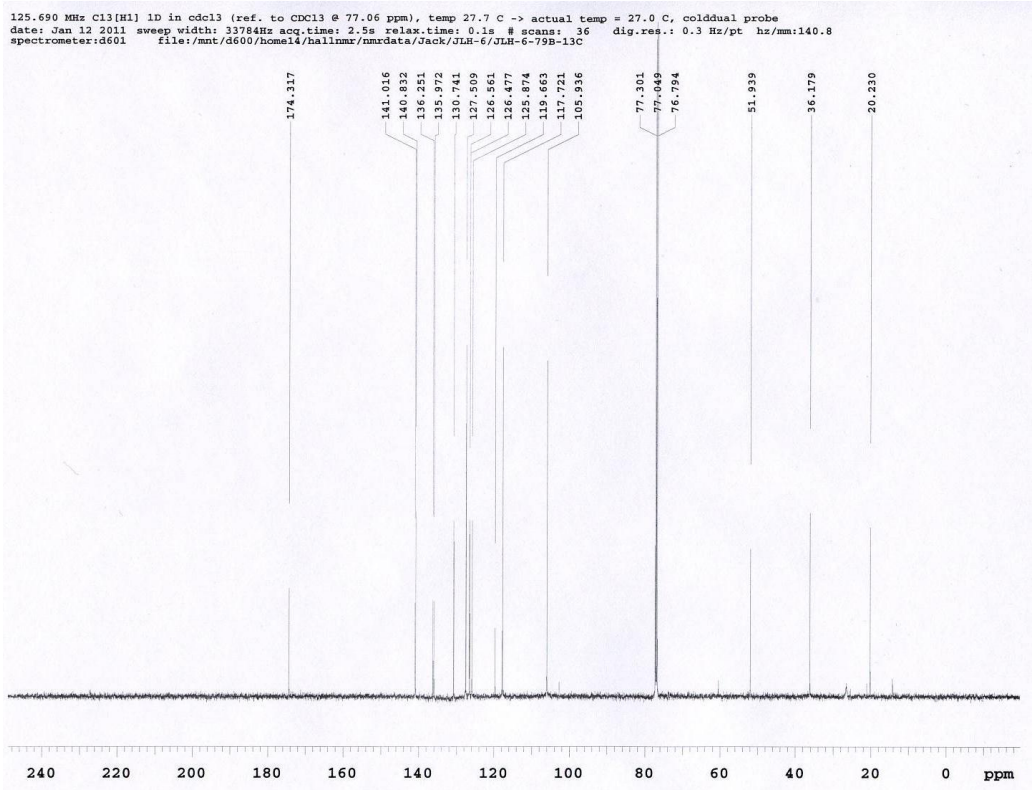
^{1}H- and ^{13}C- NMR of 3-21 in $CDCl_3$ at 25 ^{o}C



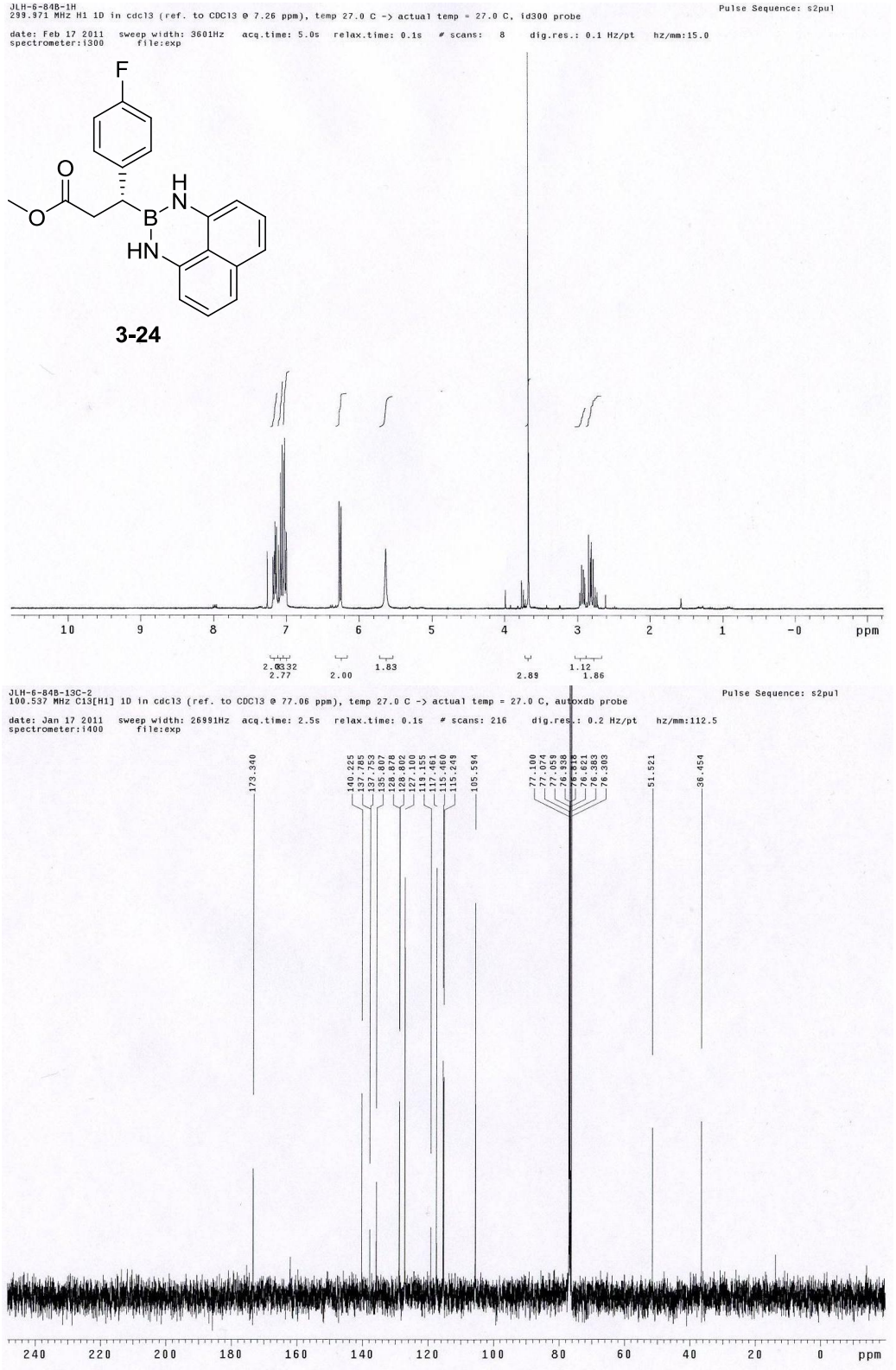


^{1}H- and ^{13}C- NMR of 3-23 in $CDCl_3$ at 25 ^{o}C

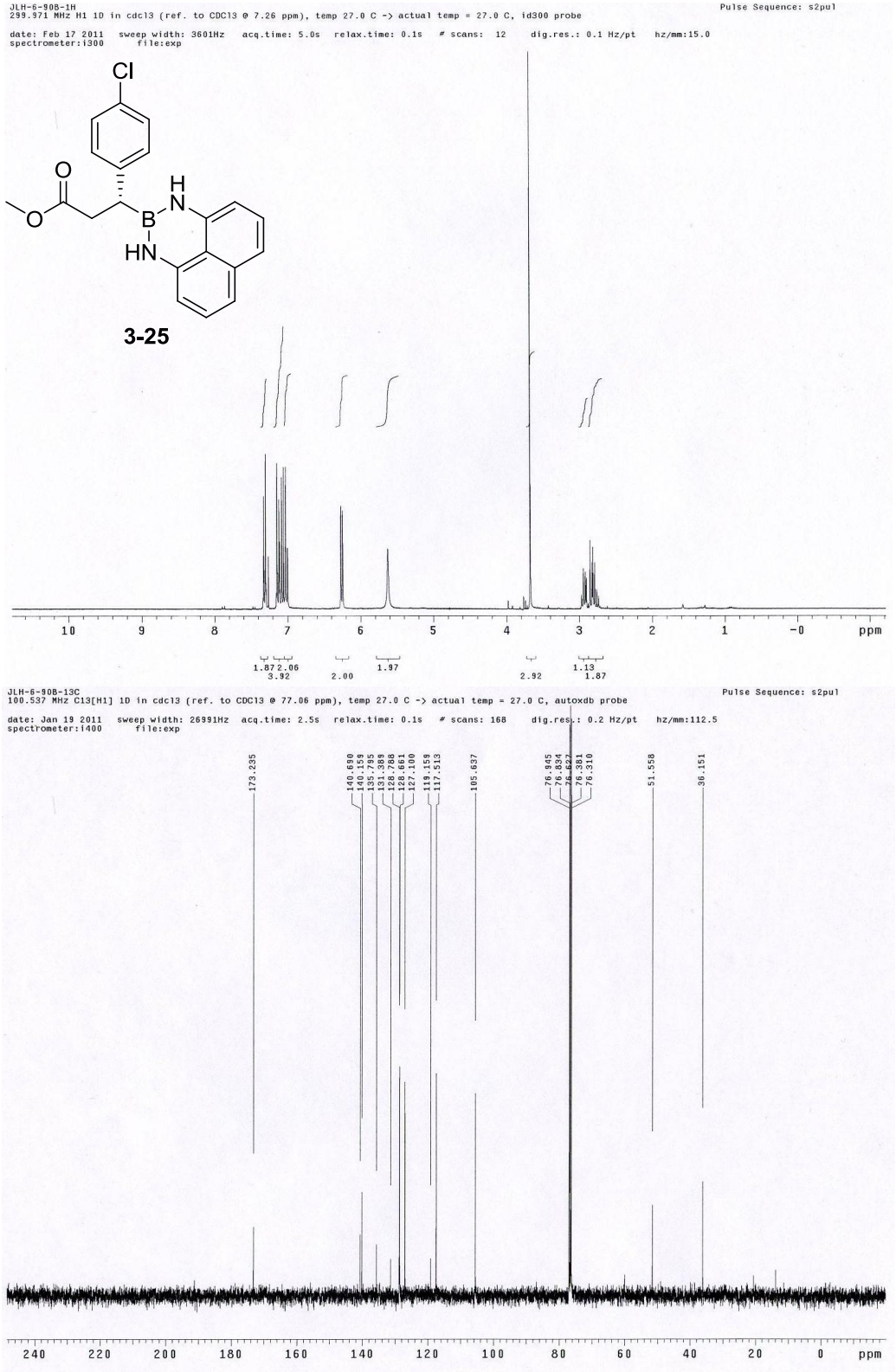




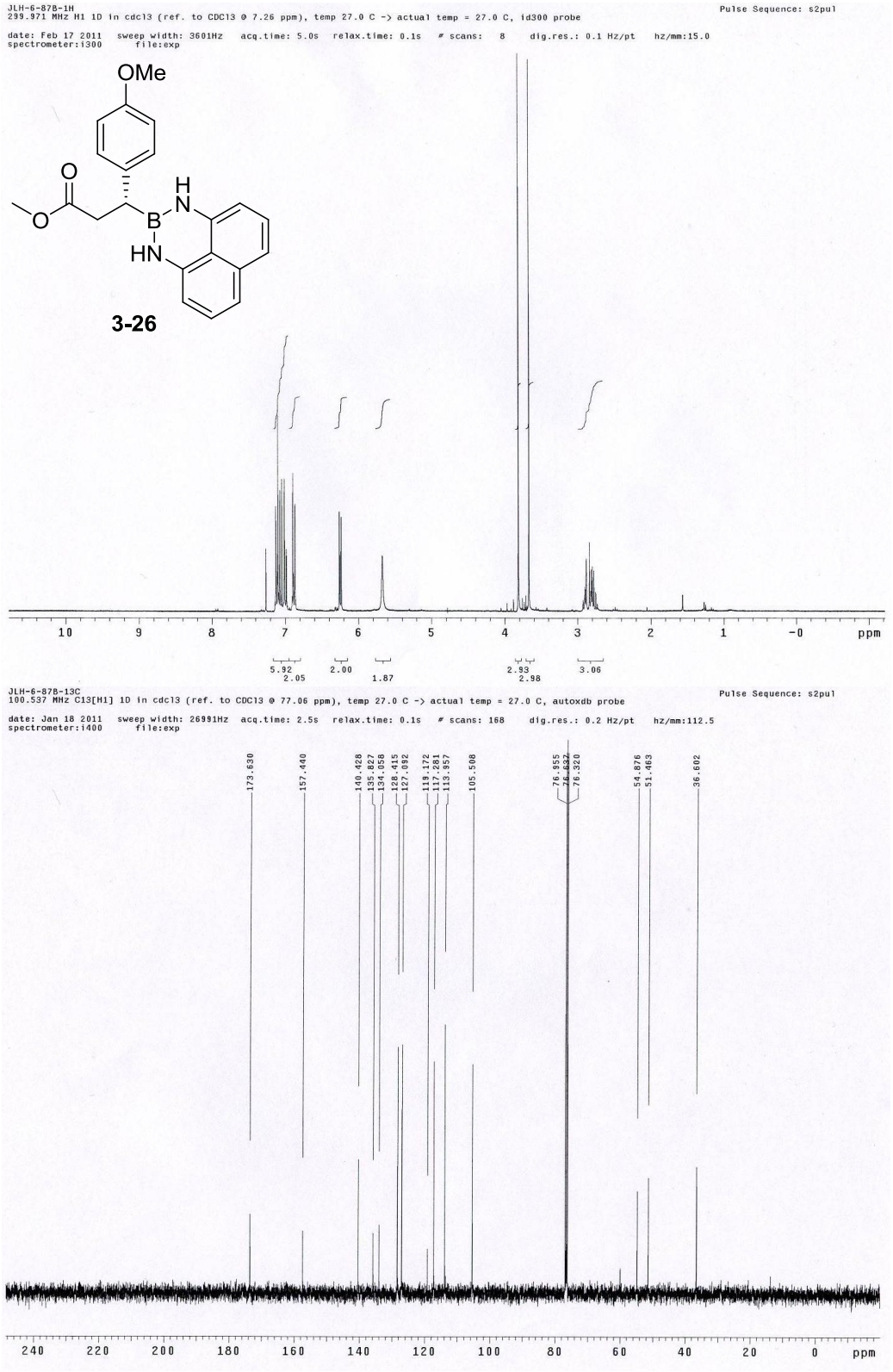
^{1}H- and ^{13}C- NMR of 3-24 in $CDCl_3$ at 25 ^{o}C



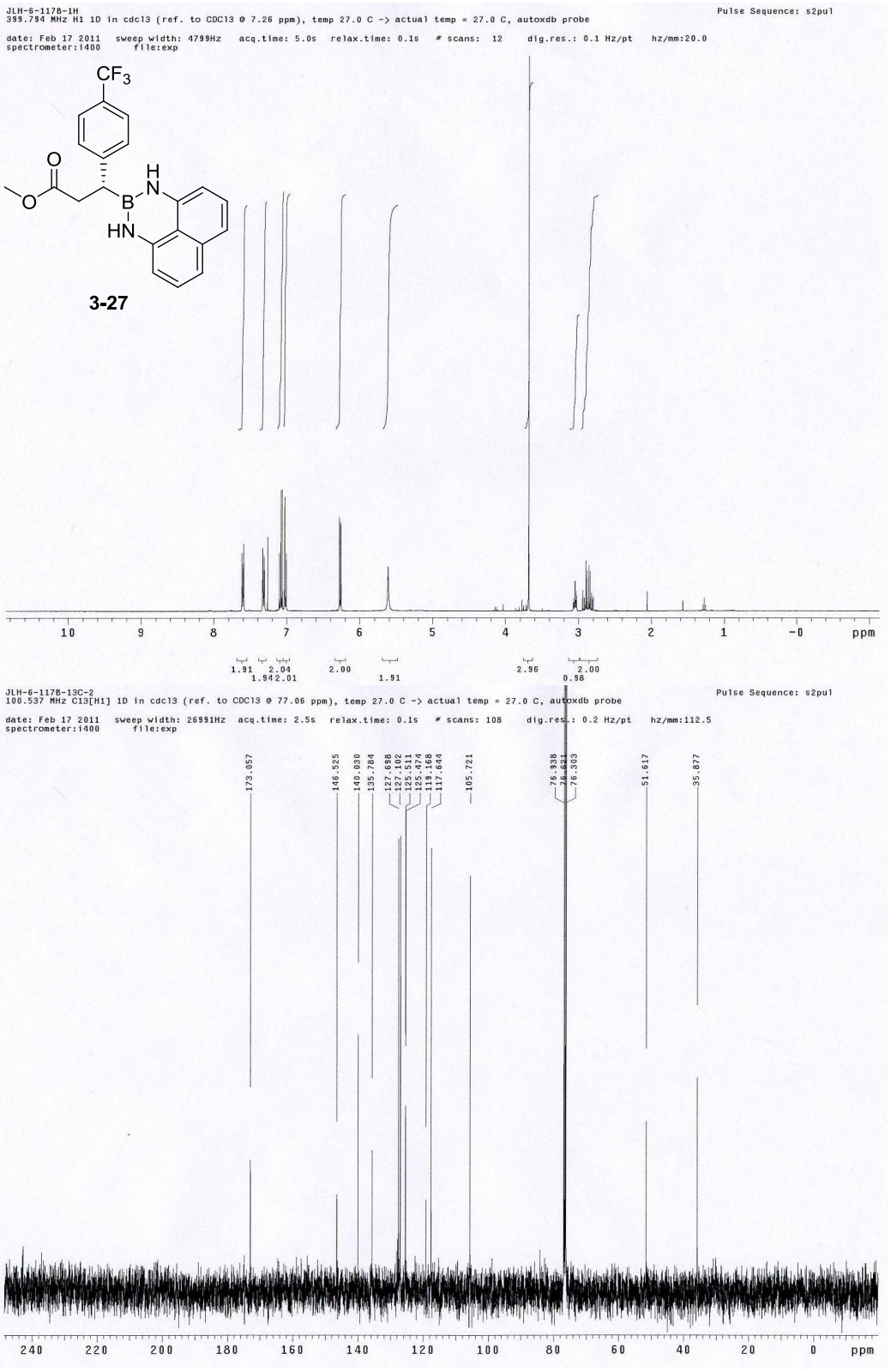
^{1}H- and ^{13}C- NMR of 3-25 in $CDCl_3$ at 25 ^{o}C



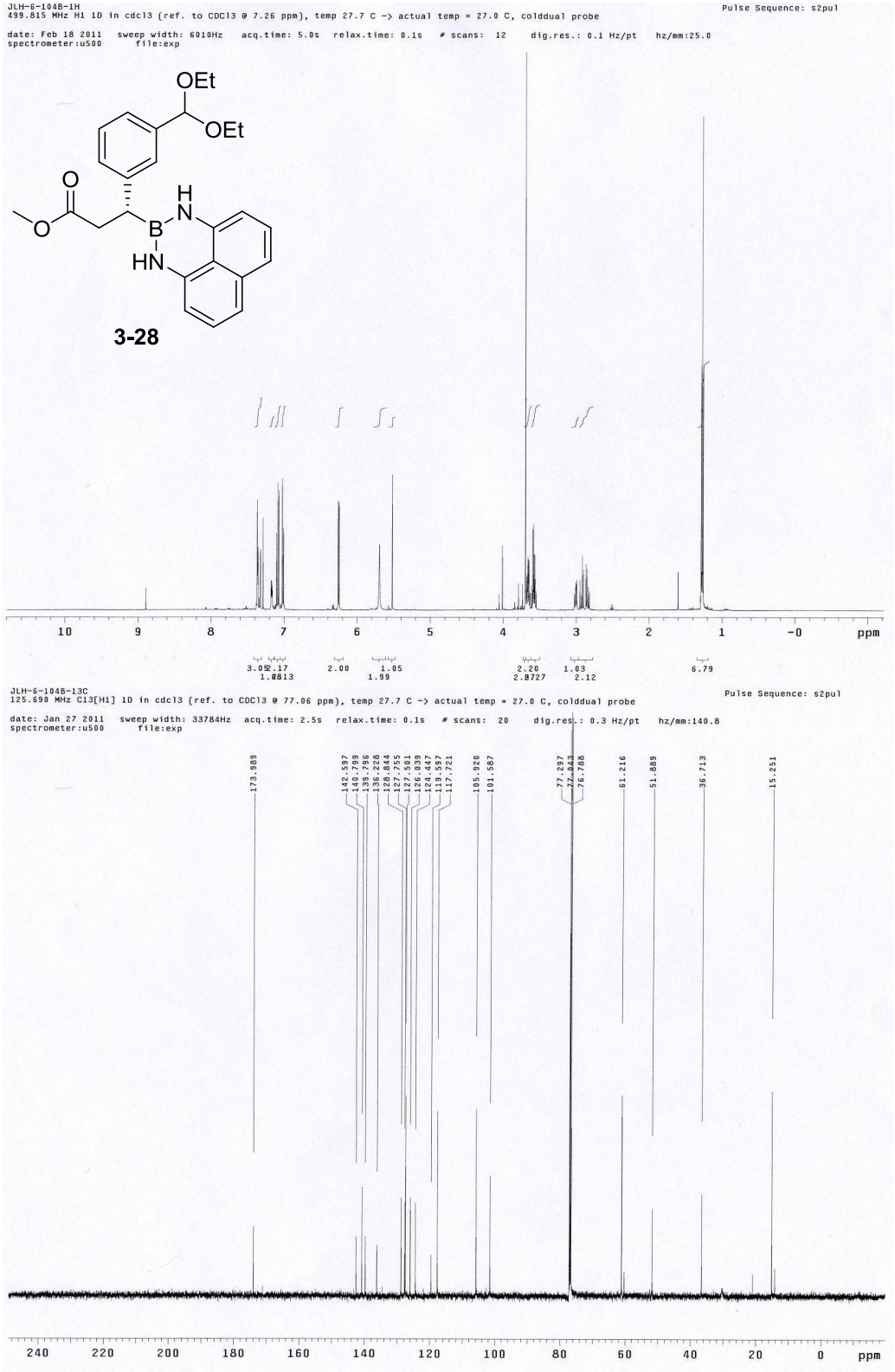
^{1}H- and ^{13}C- NMR of 3-26 in $CDCl_3$ at 25 ^{o}C



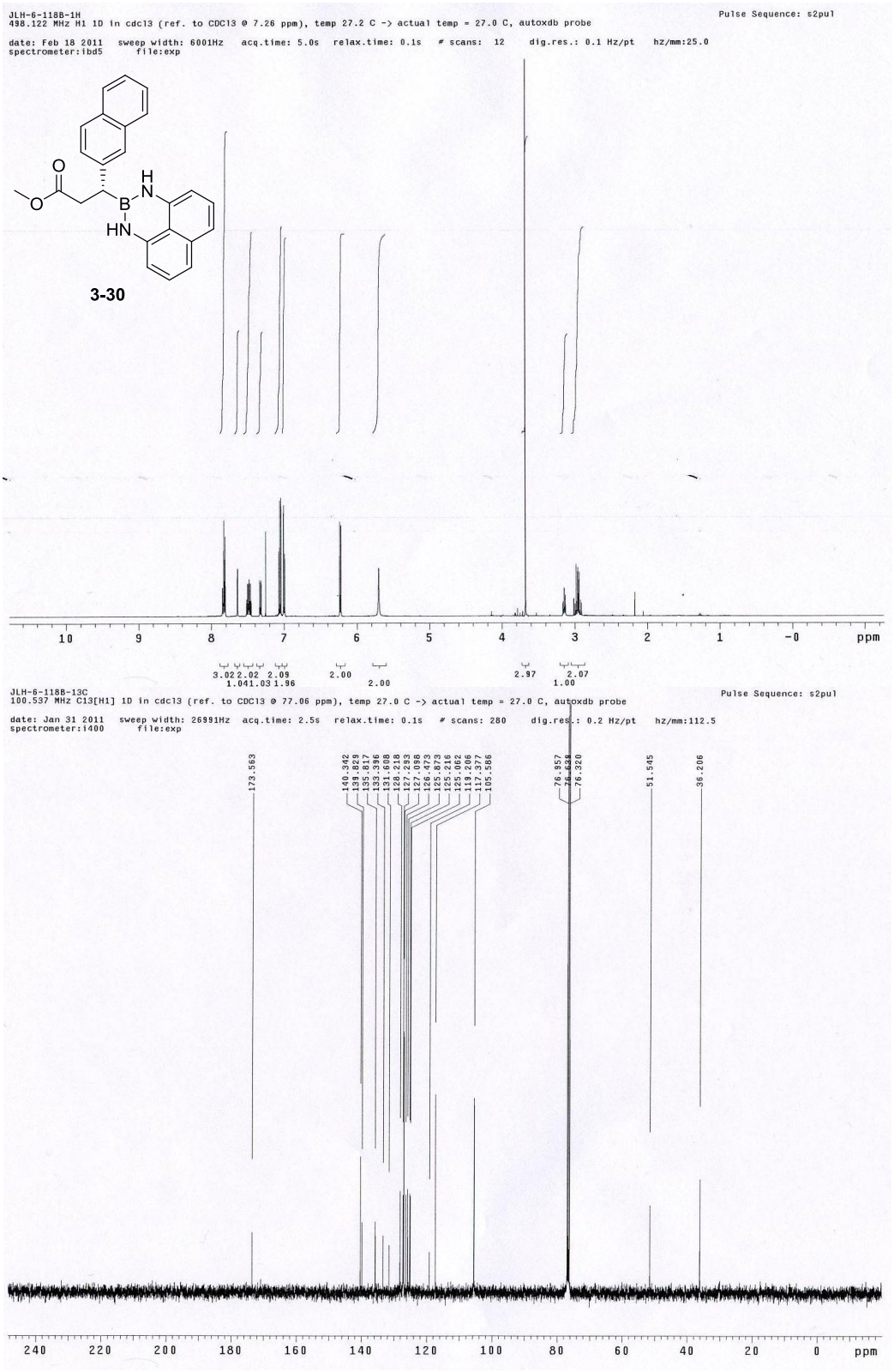
^{1}H- and ^{13}C- NMR of 3-27 in $CDCl_3$ at 25 ^{o}C



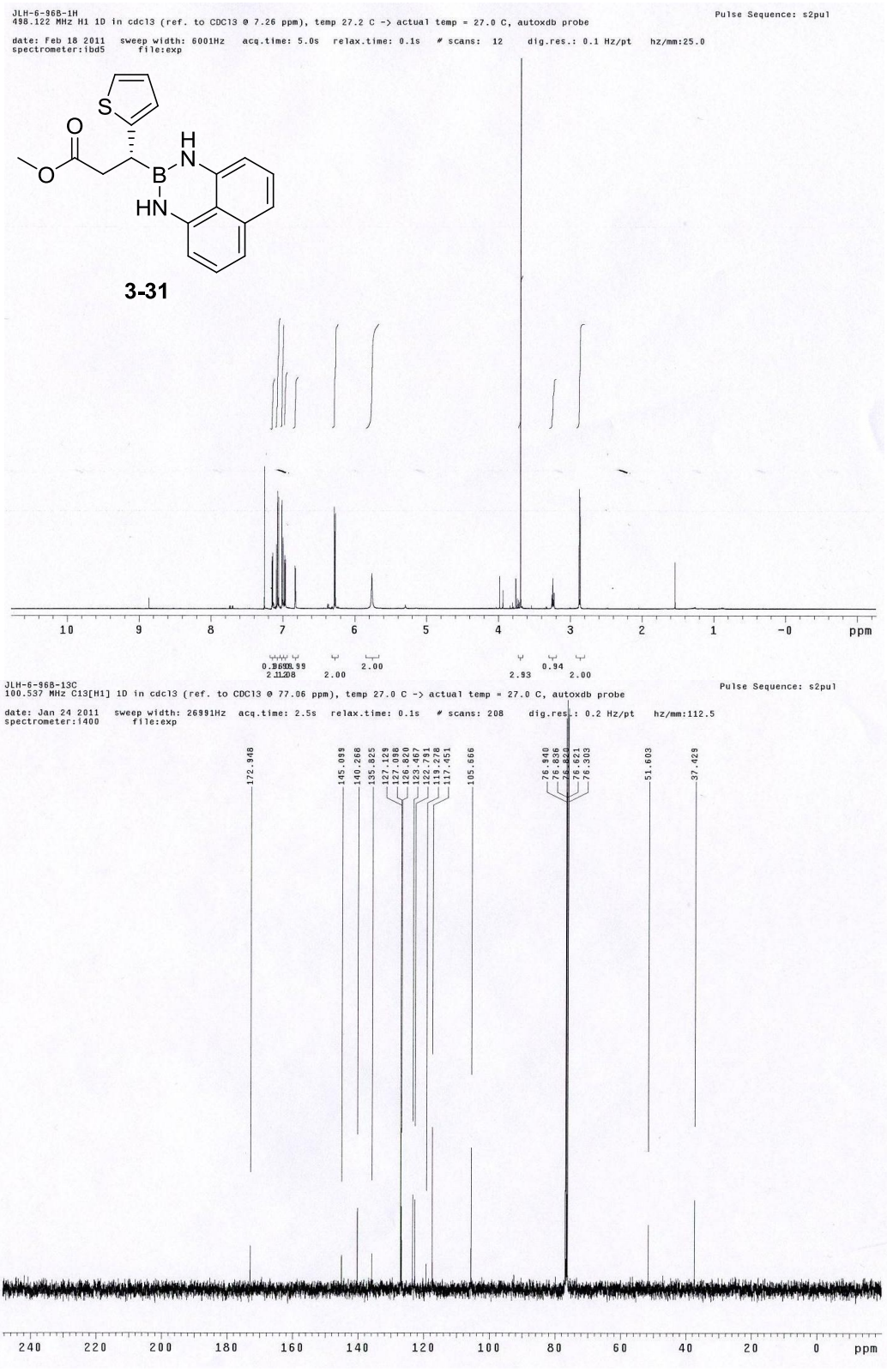
^{1}H- and ^{13}C- NMR of 3-28 in $CDCl_3$ at 25 ^{o}C



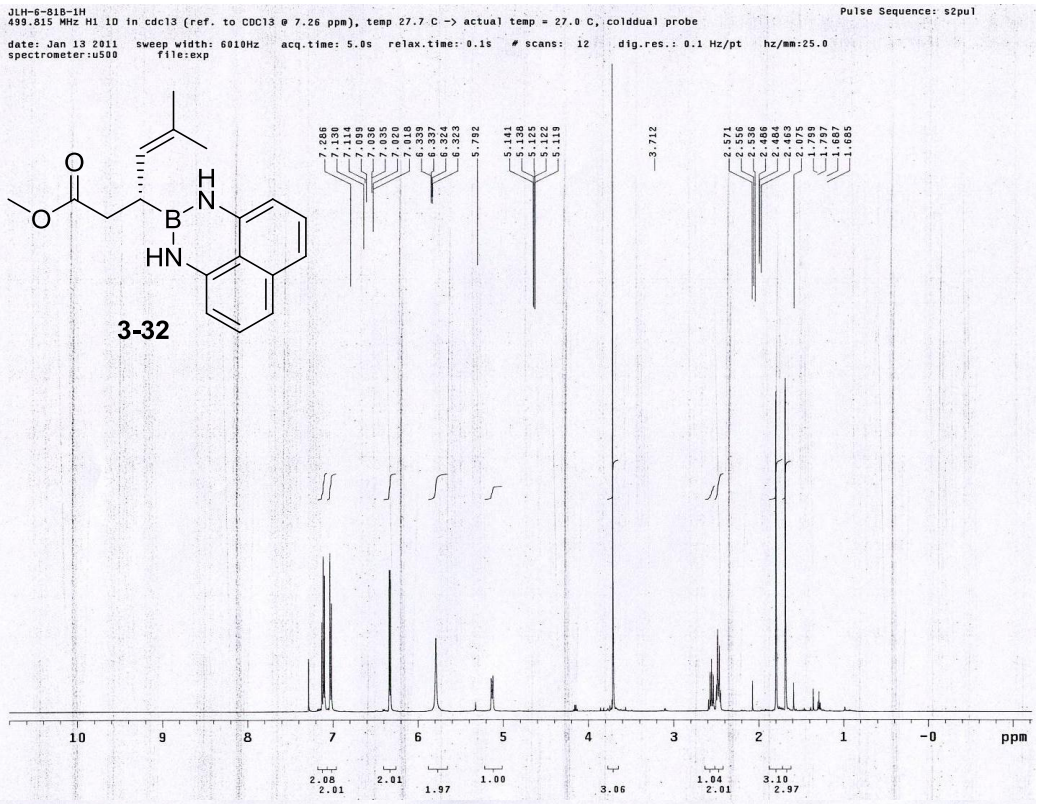
^{1}H- and ^{13}C- NMR of 3-30 in $CDCl_3$ at 25 ^{o}C

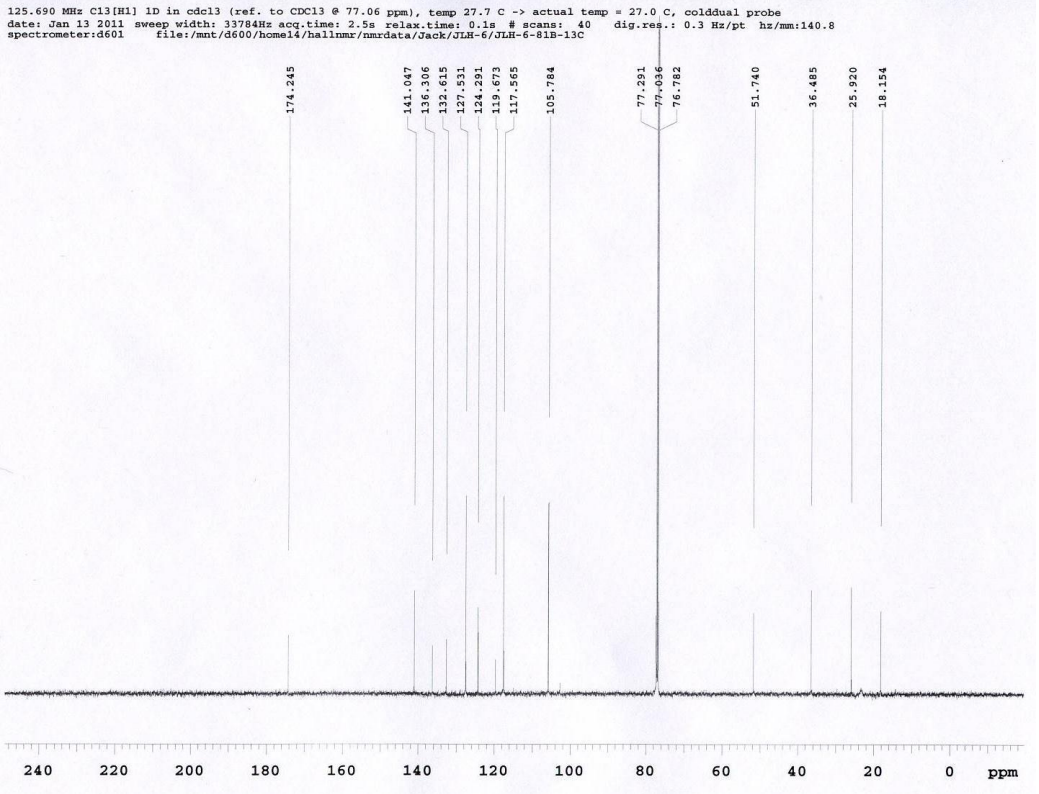


^{1}H- and ^{13}C- NMR of 3-31 in $CDCl_3$ at 25 ^{o}C

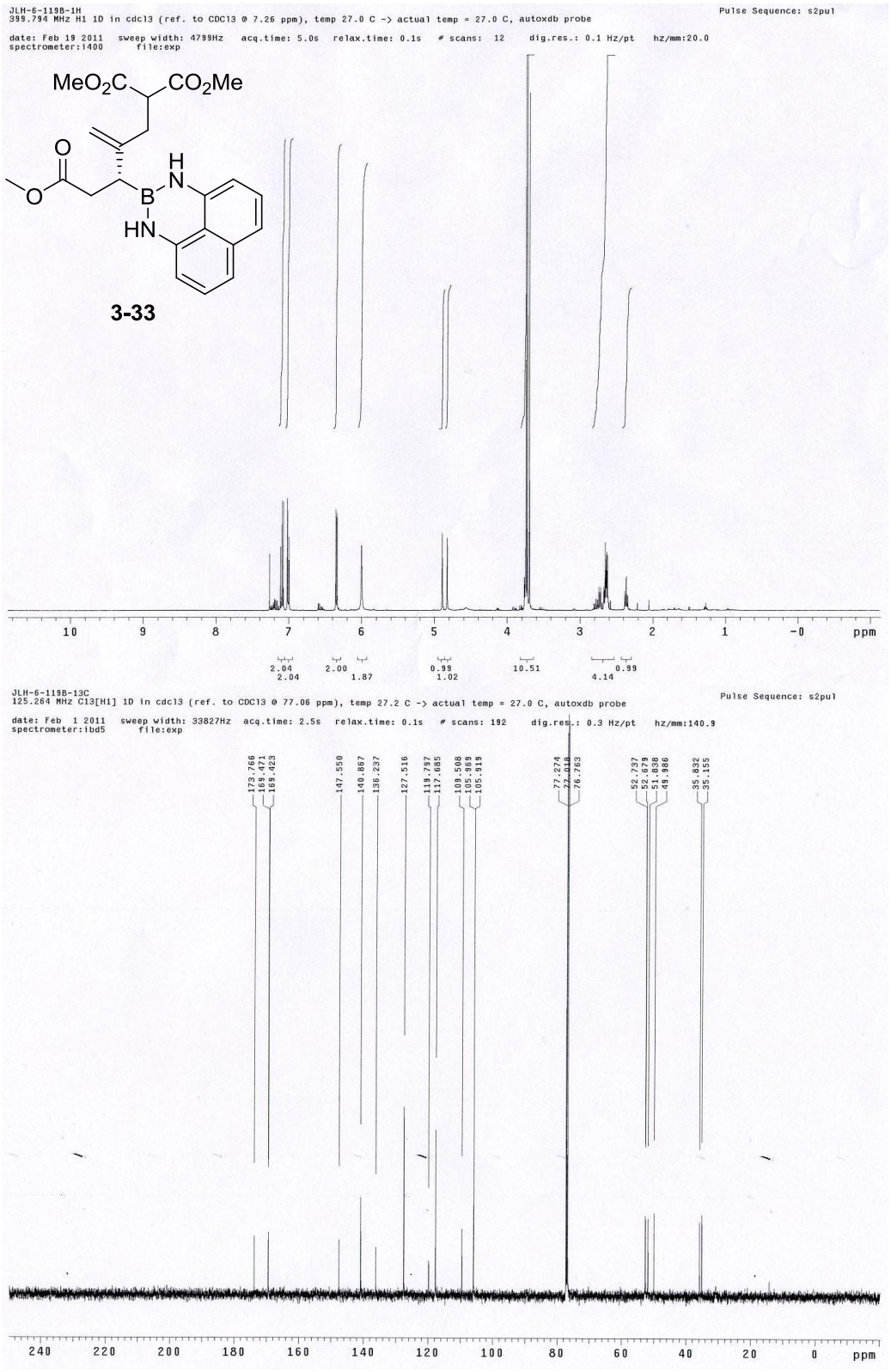


^{1}H- and ^{13}C- NMR of 3-32 in $CDCl_3$ at 25 ^{o}C

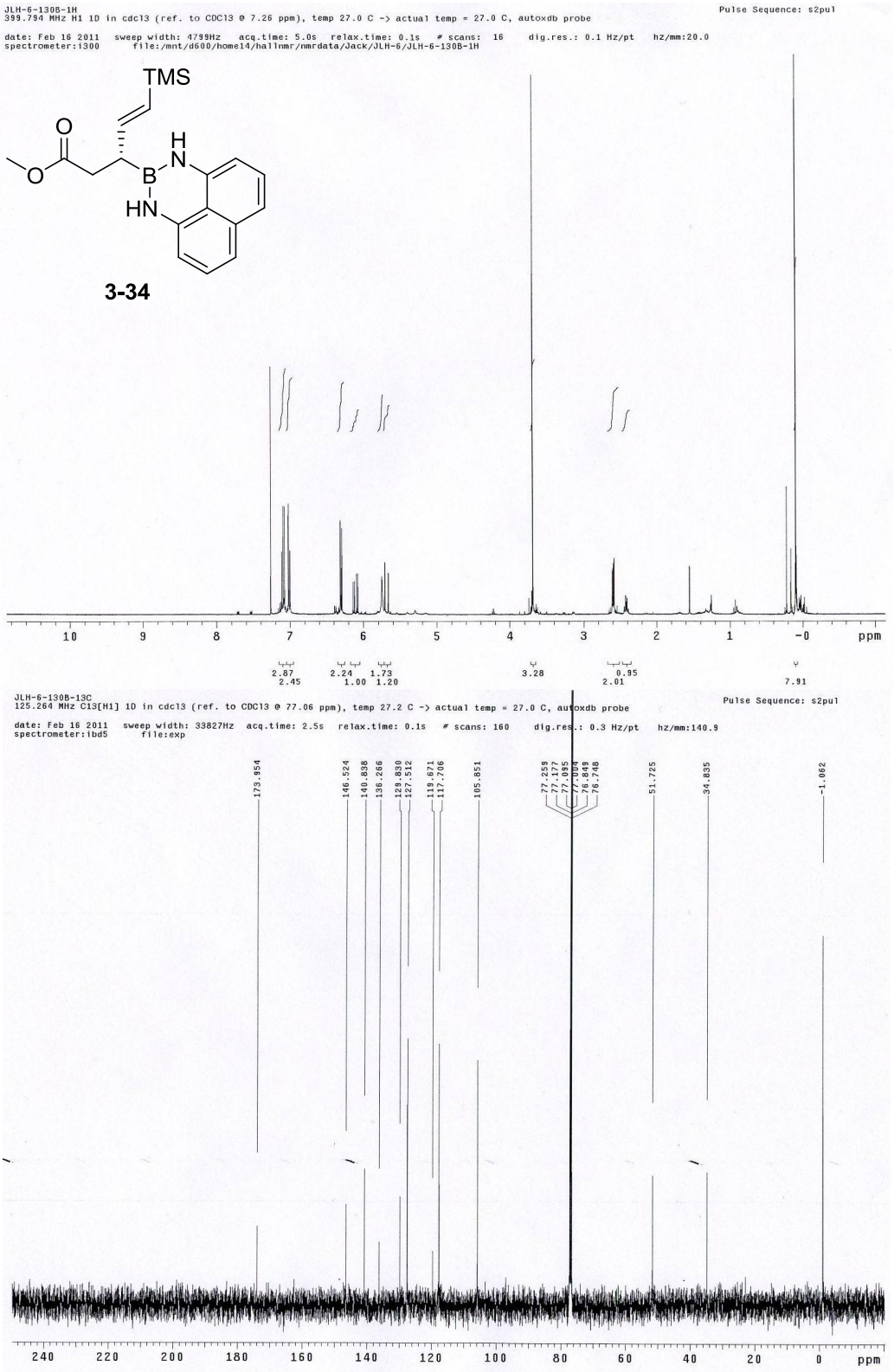




^{1}H- and ^{13}C- NMR of 3-33 in $CDCl_3$ at 25 ^{o}C

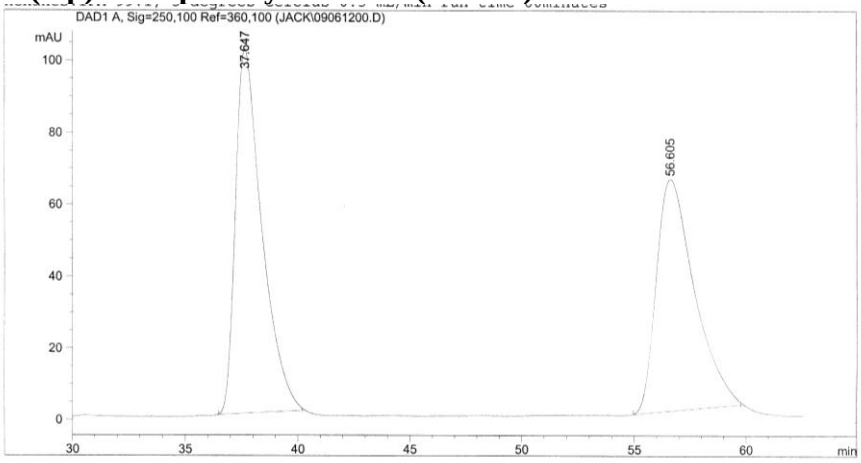


^{1}H- and ^{13}C- NMR of 3-33 in $CDCl_3$ at 25 ^{o}C



Appendix 4: Chromatograms for enantiomeric excess measurement

Racemic (top) and optically enriched (bottom) 2-26

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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   2  56.605 BB    1.4143 7642.34229   64.68838  47.9856
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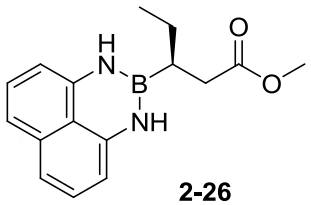
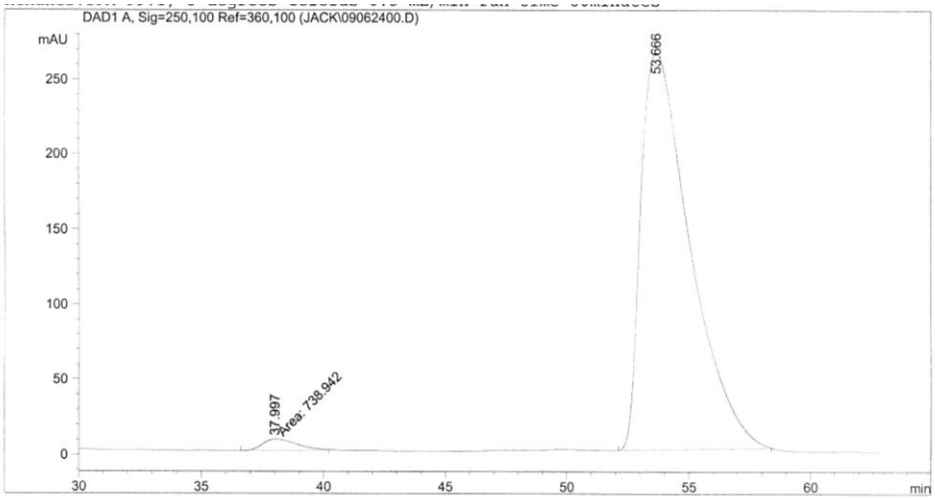


2-26

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Use Multiplier & Dilution Factor with ISTDs


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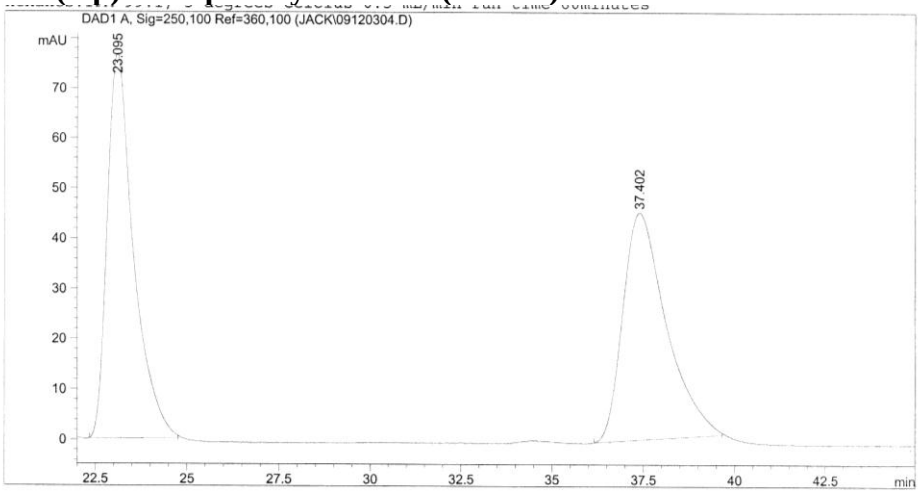
Racemic (top) and optically enriched (bottom) 2-29

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,100 Ref=360,100

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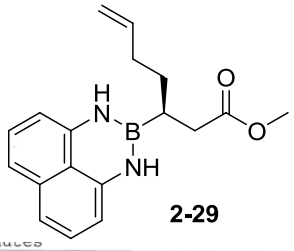
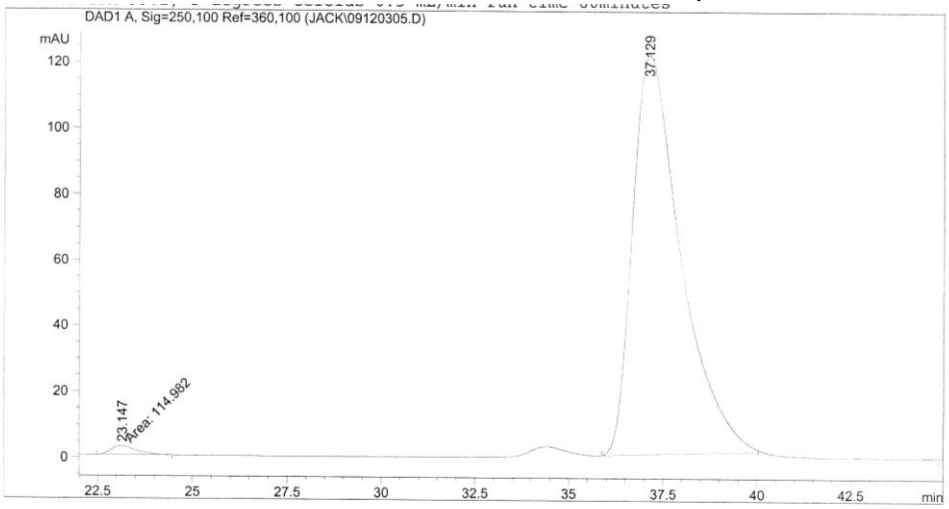


2-29

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Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,100 Ref=360,100

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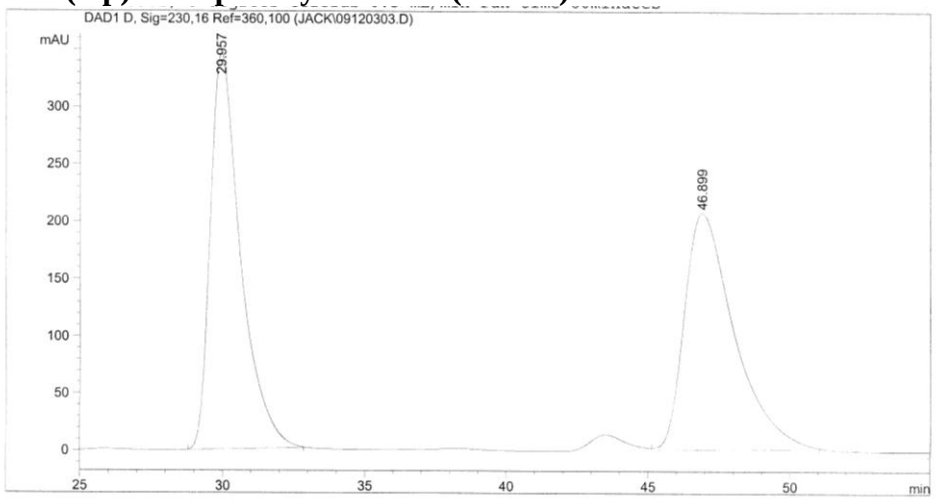
Racemic (top) and optically enriched (bottom) 2-31

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Use Multiplier & Dilution Factor with ISTDs


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   2  46.899 VB     1.7893 2.53358e4   207.08858  49.7019
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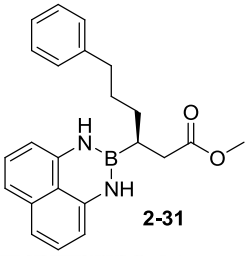

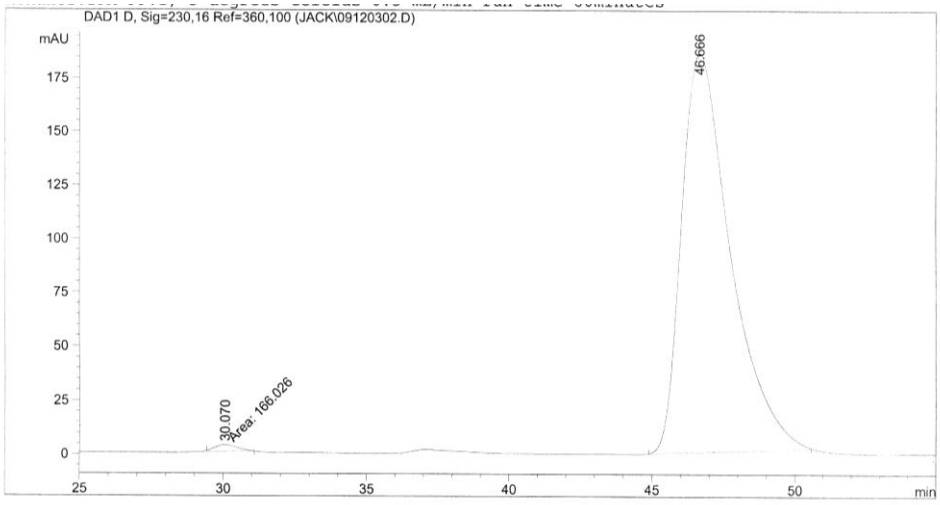


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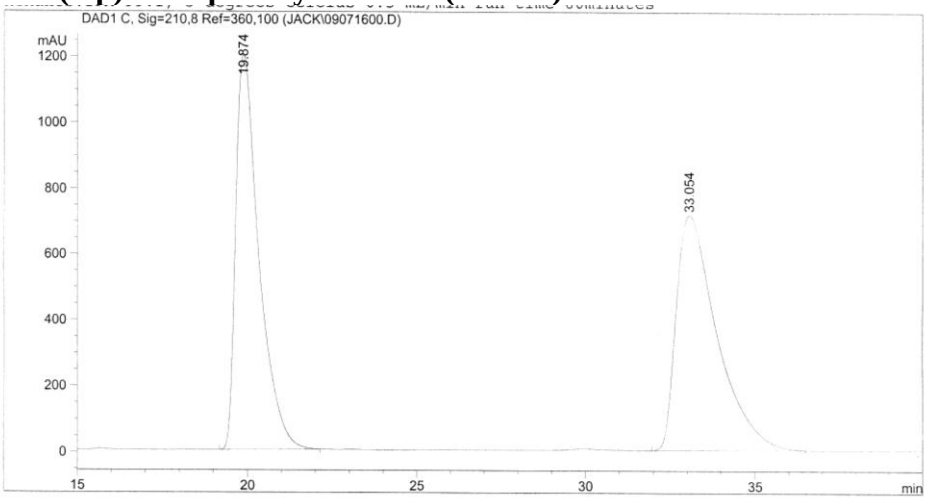
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  30.070 MM     0.6421  166.02592    3.10270   0.7437
   2  46.666 BB     1.6920 2.21577e4   185.98195  99.2563
```

Racemic (top) and optically enriched (bottom) 2-32

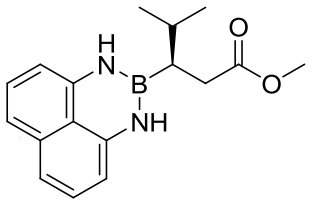



```
================================================================================
                              Area Percent Report
================================================================================

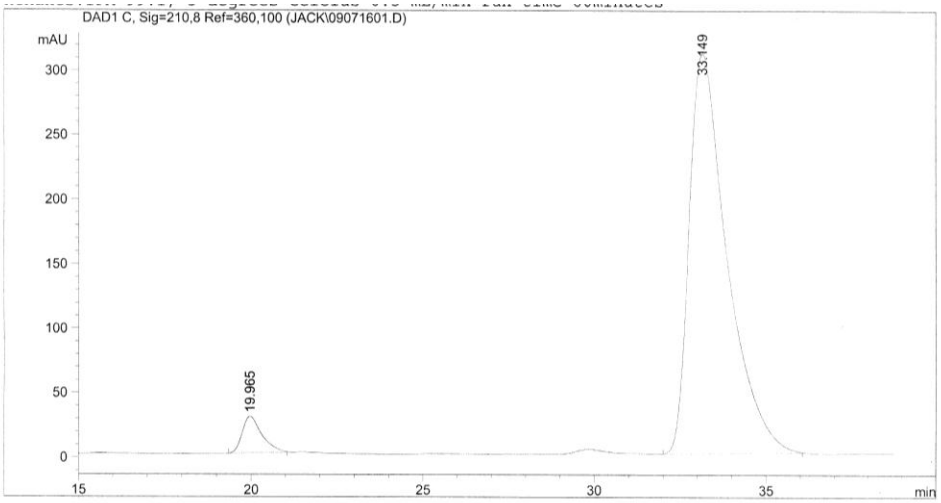
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.874 BB    0.7025 5.66745e4  1201.02454  48.8554
   2  33.054 BB    1.1739 5.93300e4   712.16003  51.1446
```



2-32



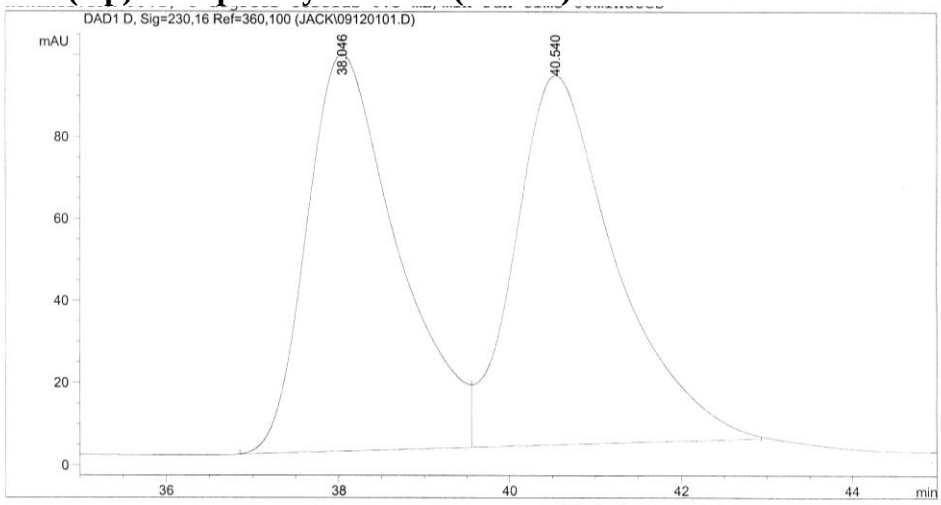

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.965 BB    0.5699 1123.88794   28.51271   4.5149
   2  33.149 BB    1.1135 2.37691e4   310.35181  95.4851
```

Racemic (top) and optically enriched (bottom) 2-38

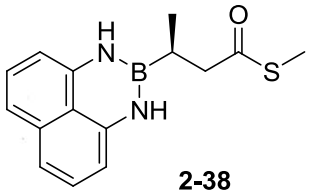



```
=====================================================================
                       Area Percent Report
=====================================================================

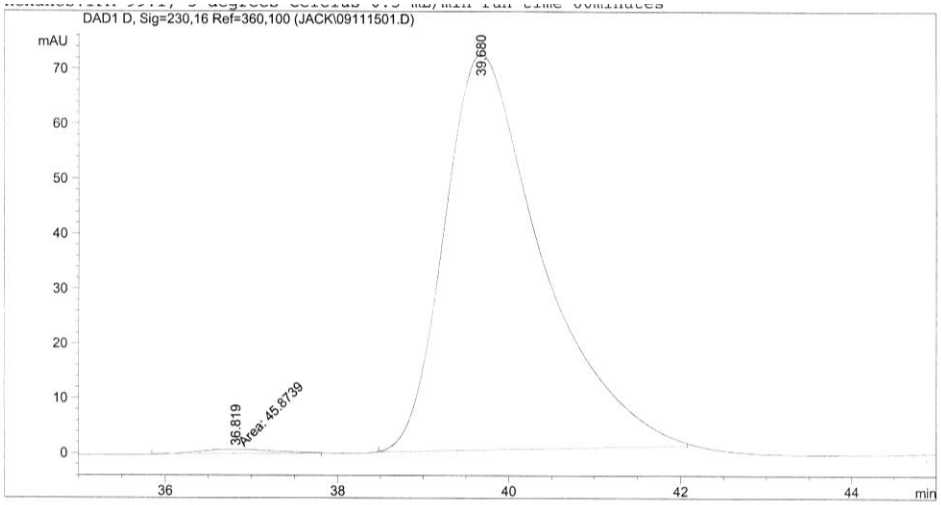
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  38.046 BV    1.0781 7100.67334   96.76659  49.0303
   2  40.540 VB    1.1959 7381.54834   90.09537  50.9697
```



2-38



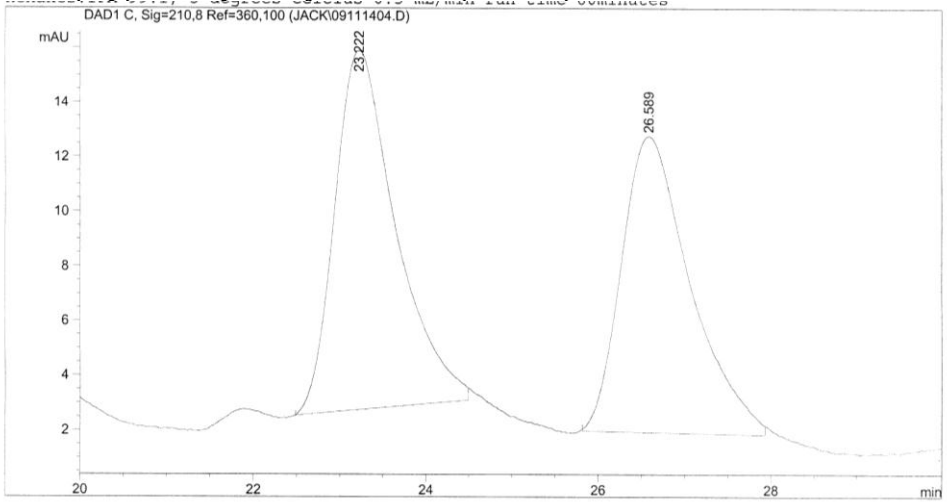

```
=====================================================================
                       Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.819 MM    0.9888   45.87392 7.73260e-1   0.7971
   2  39.680 BB    1.1646 5709.34766   72.03846  99.2029
```

Racemic (top) and optically enriched (bottom) 2-39

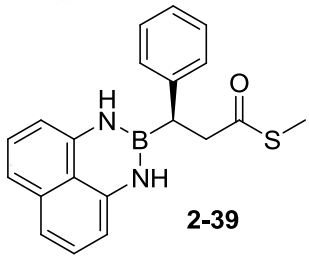



```
=====================================================================
                      Area Percent Report
=====================================================================

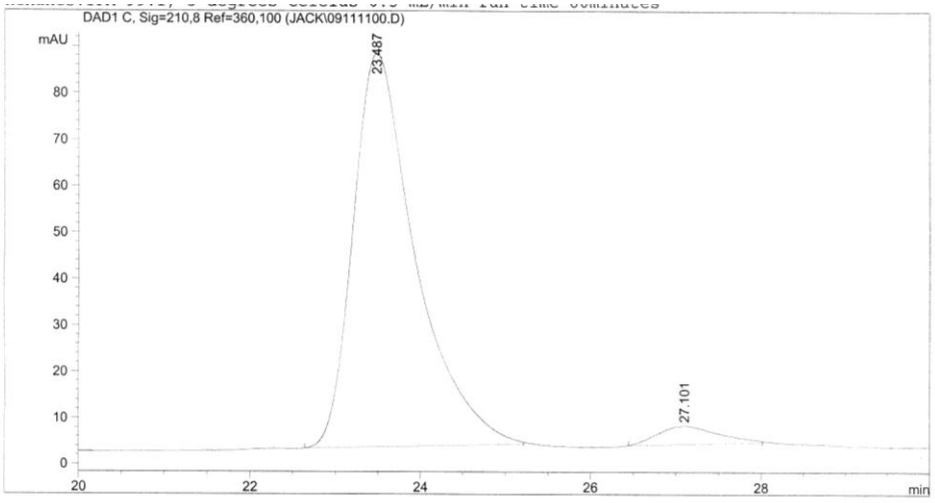
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.222 PB    0.6850  648.40863   13.15651  52.0059
   2  26.589 BB    0.7473  598.39075   10.85199  47.9941
```



2-39




```
=====================================================================
                      Area Percent Report
=====================================================================

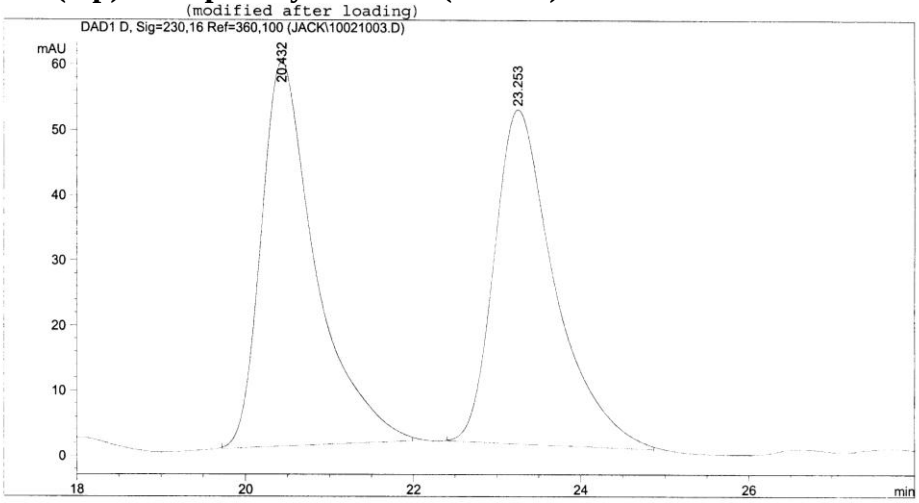
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.487 BB    0.7562 4337.98389   84.88074  95.6607
   2  27.101 BB    0.5896  196.77542    3.93347   4.3393
```

Racemic (top) and optically enriched (bottom) 2-40

(modified after loading)

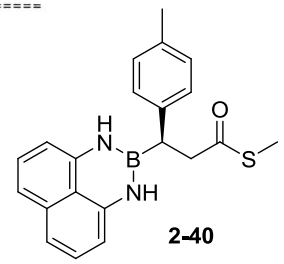



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

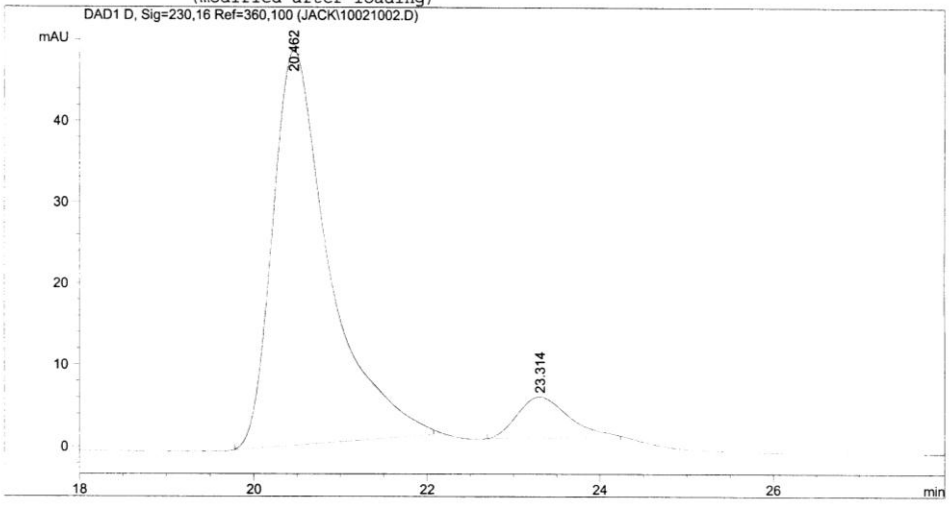

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.432 BB    0.6676 2656.01514   58.95552  50.6887
   2  23.253 BB    0.7475 2583.83838   51.31194  49.3113
```



2-40

(modified after loading)



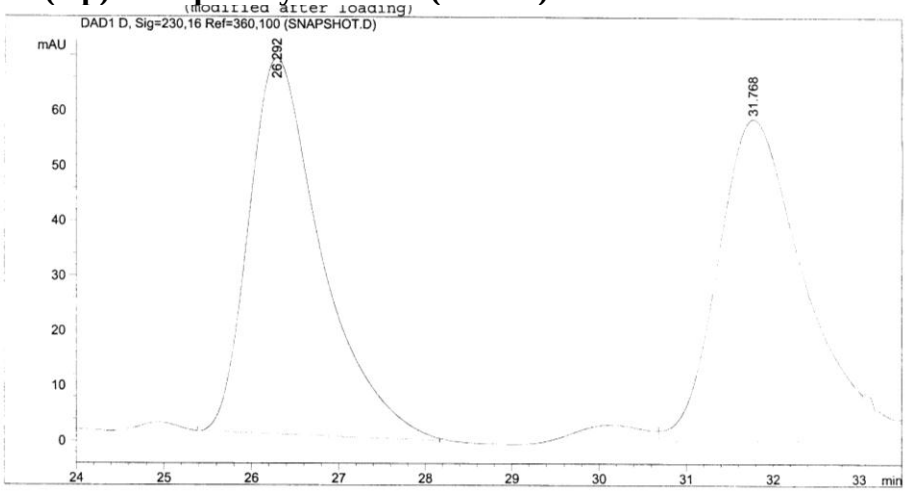

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.462 BB    0.6563 2200.04907   48.58555  90.9437
   2  23.314 BB    0.5748  219.08279    5.10378   9.0563
```

Racemic (top) and optically enriched (bottom) 2-41

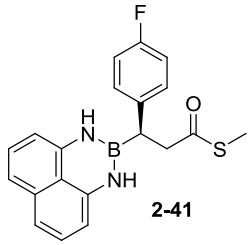


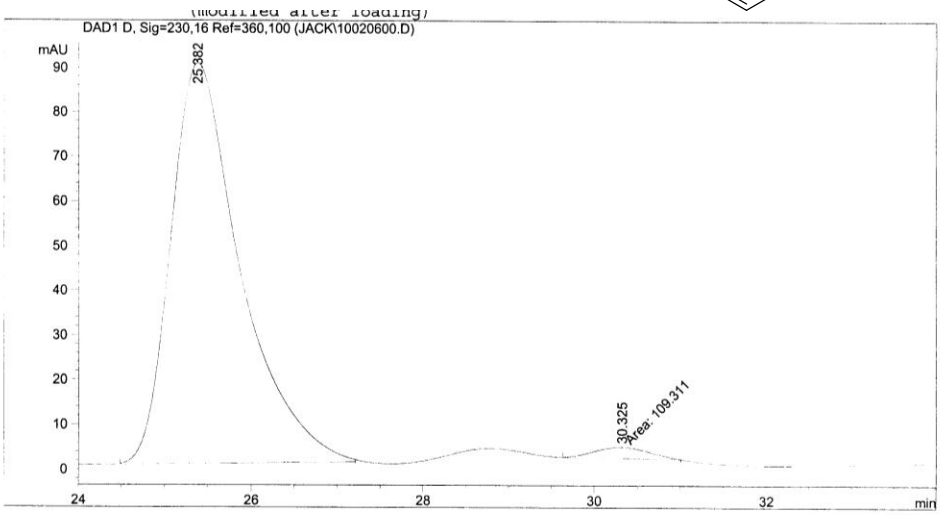

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  26.292 PB    0.8565 3949.23560   68.30573  49.8803
   2  31.768 BV    1.0005 3968.19629   58.56582  50.1197
```





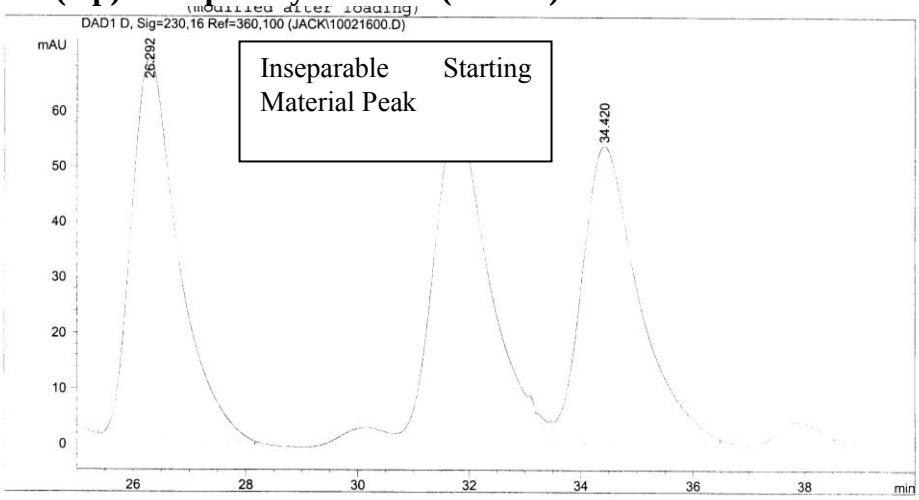

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  25.382 BB    0.8295 5012.73633   89.77046  97.8659
   2  30.325 MM    0.7299  109.31055    2.49607   2.1341
```

Racemic (top) and optically enriched (bottom) 2-42

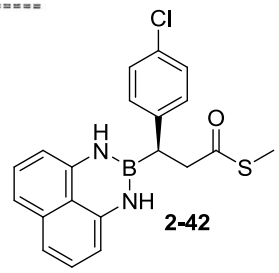


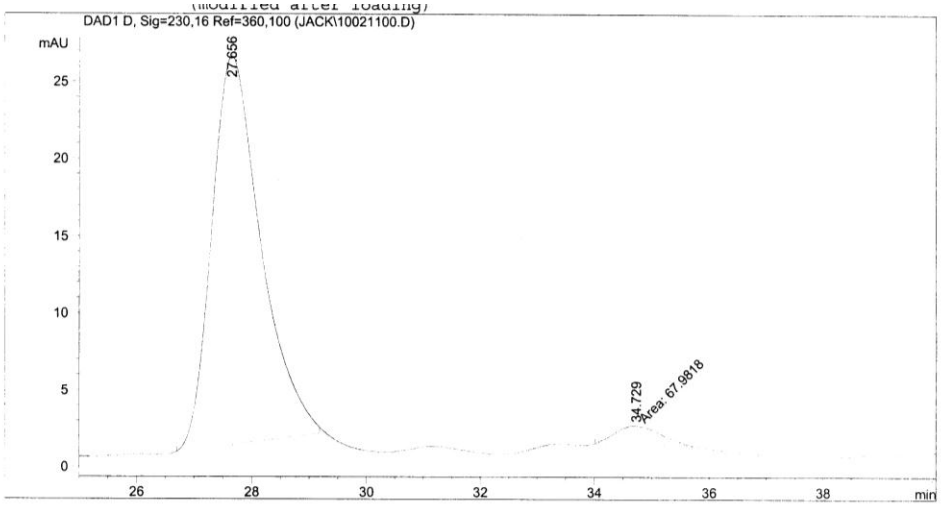

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  26.292 PB    0.8565 3949.23560   68.30573  51.0339
   2  34.420 VB    1.0311 3789.22339   53.58016  48.9661
```





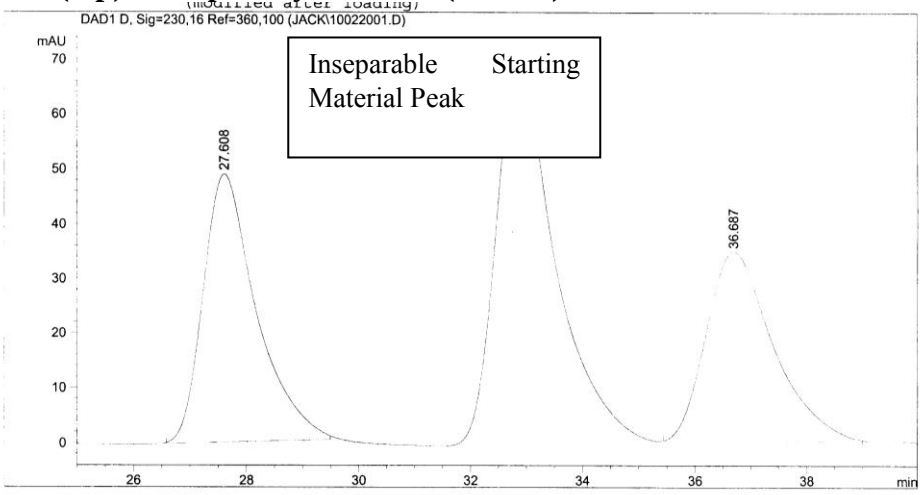

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.656 BB    0.8642 1500.22412   25.21399  95.6650
   2  34.729 MM    0.9086   67.98183    1.24695   4.3350
```

Racemic (top) and optically enriched (bottom) 2-43

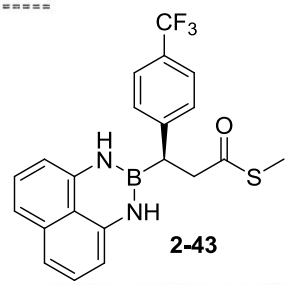



```
================================================================================
                            Area Percent Report
================================================================================

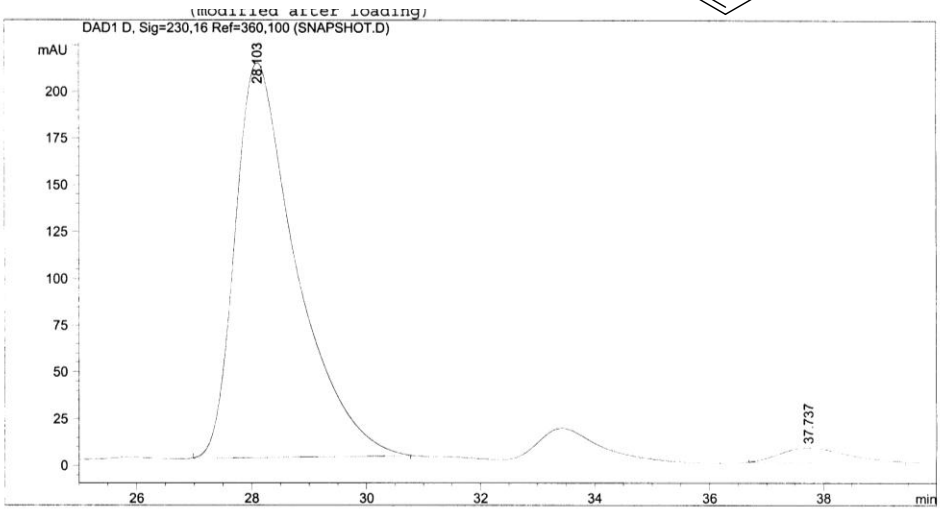
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  27.608 BB     0.9609 3190.98853   48.92805  52.6285
   2  36.687 PB     1.2198 2872.24609   34.55402  47.3715
```



2-43



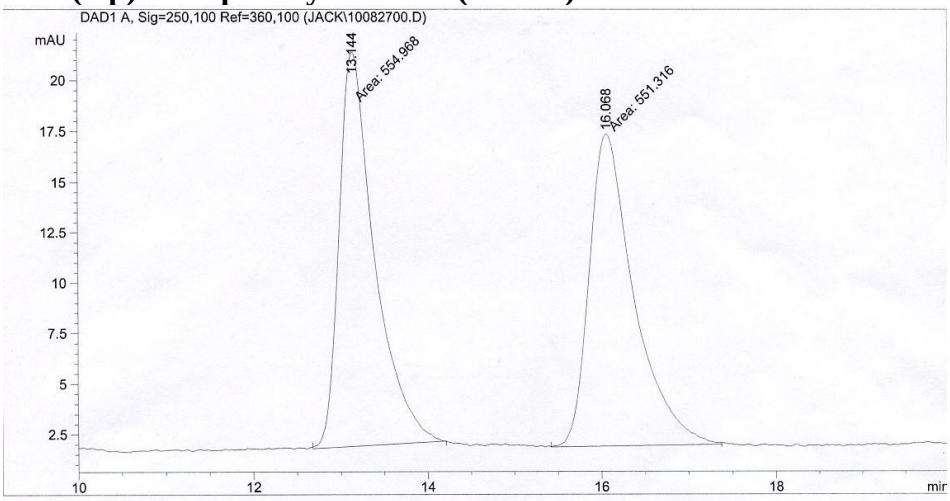

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]    [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  28.103 BB     1.0685 1.56750e4   211.54683  96.2063
   2  37.737 BB     0.9458  618.11810    7.82331   3.7937
```

Racemic (top) and optically enriched (bottom) 3-11

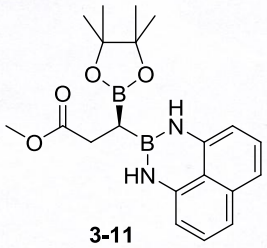



```
================================================================================
                            Area Percent Report
================================================================================

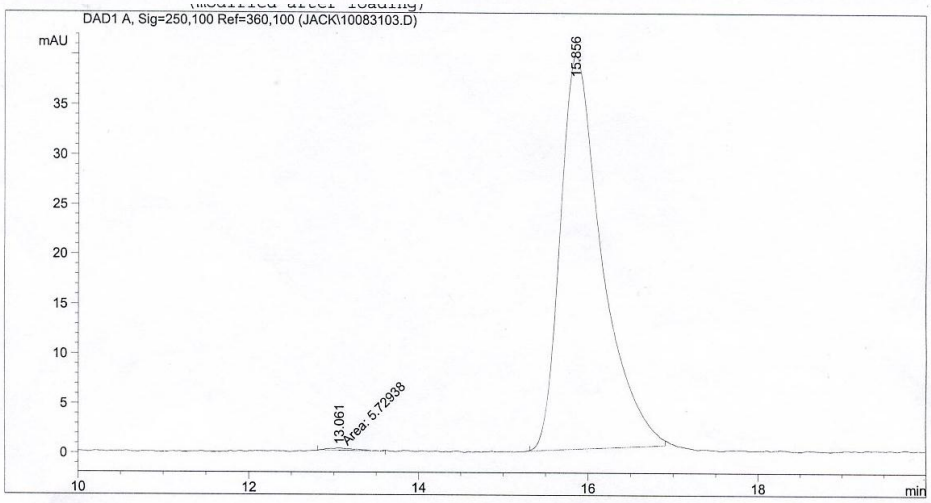
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,100 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.144 MM    0.4742  554.96771   19.50557  50.1650
   2  16.068 MM    0.5940  551.31622   15.46910  49.8350
```



3-11



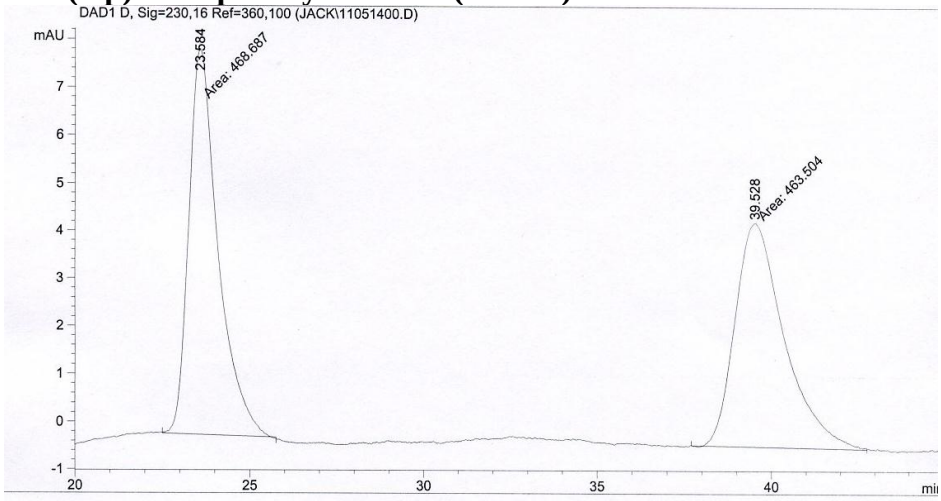

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=250,100 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  13.061 MM    0.4281    5.72938 2.23030e-1   0.4212
   2  15.856 BB    0.5037 1354.48364   39.53666  99.5788
```

Racemic (top) and optically enriched (bottom) 3-20

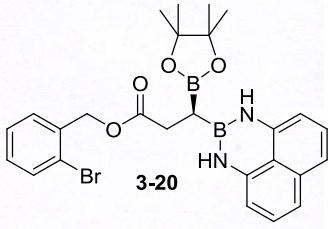


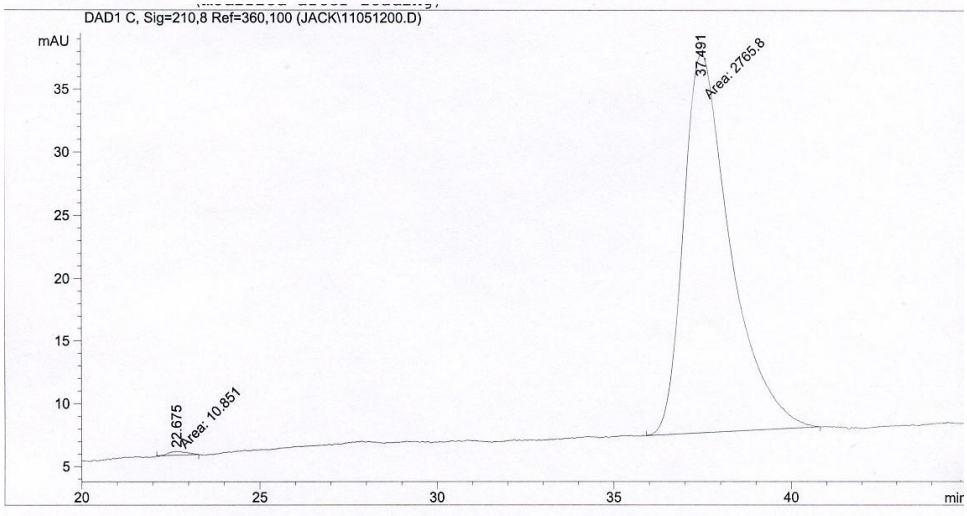

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  23.584 MM    0.9678  468.68701    8.07167  50.2780
   2  39.528 MM    1.6460  463.50378    4.69334  49.7220
```





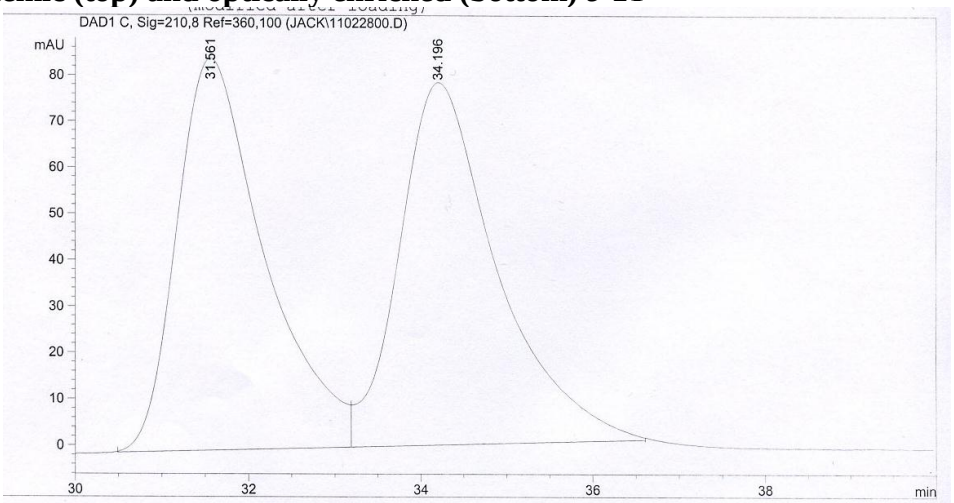

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  22.675 MM    0.5872   10.85096 3.07973e-1   0.3908
   2  37.491 MM    1.5288 2765.79956   30.15261  99.6092
```

Racemic (top) and optically enriched (bottom) 3-21

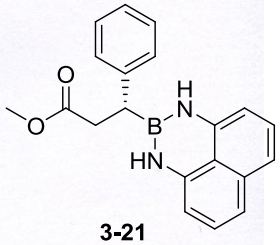



```
================================================================================
                            Area Percent Report
================================================================================

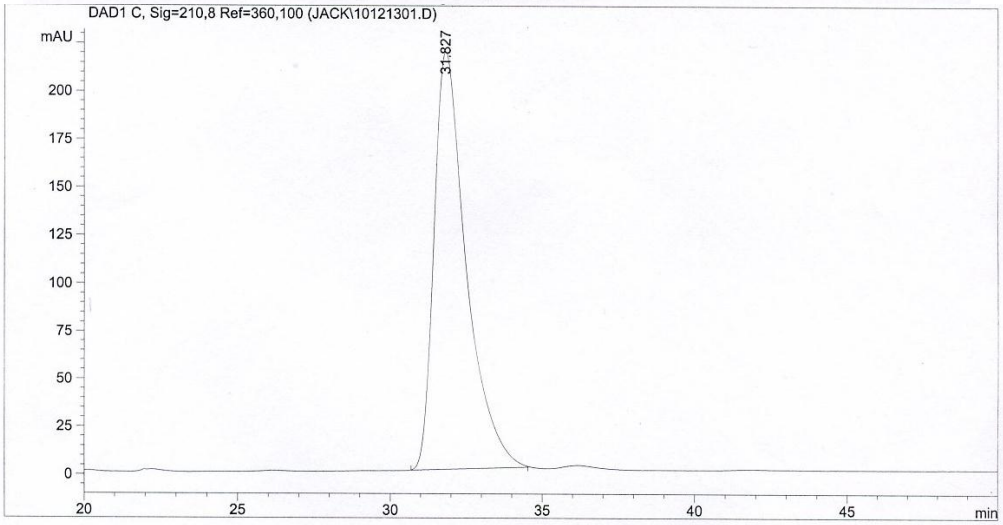
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.561 BV    1.0068 5952.28174   84.81136  49.0089
   2  34.196 VB    1.0957 6193.03174   78.38962  50.9911
```



3-21



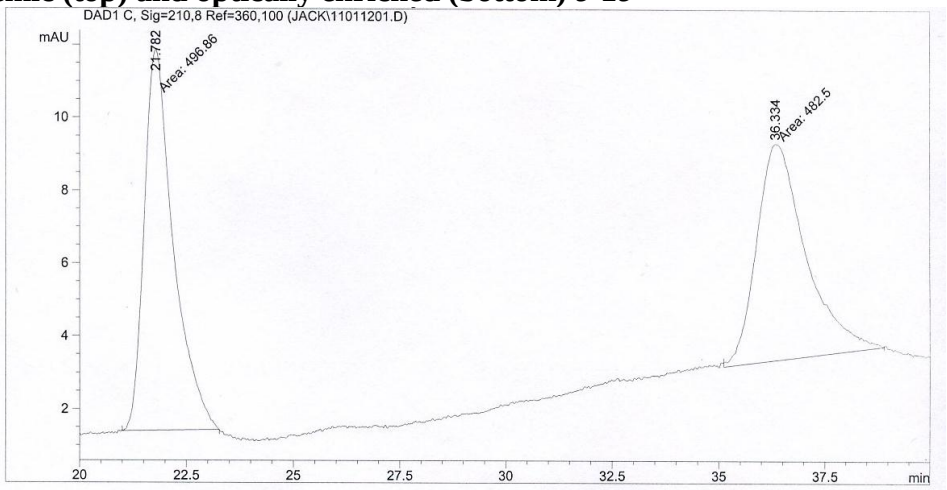

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  31.827 BB    1.0599 1.60912e4   218.30923 100.0000
```

Racemic (top) and optically enriched (bottom) 3-23

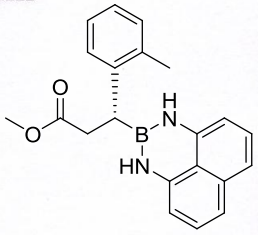



```
=====================================================================
                        Area Percent Report
=====================================================================

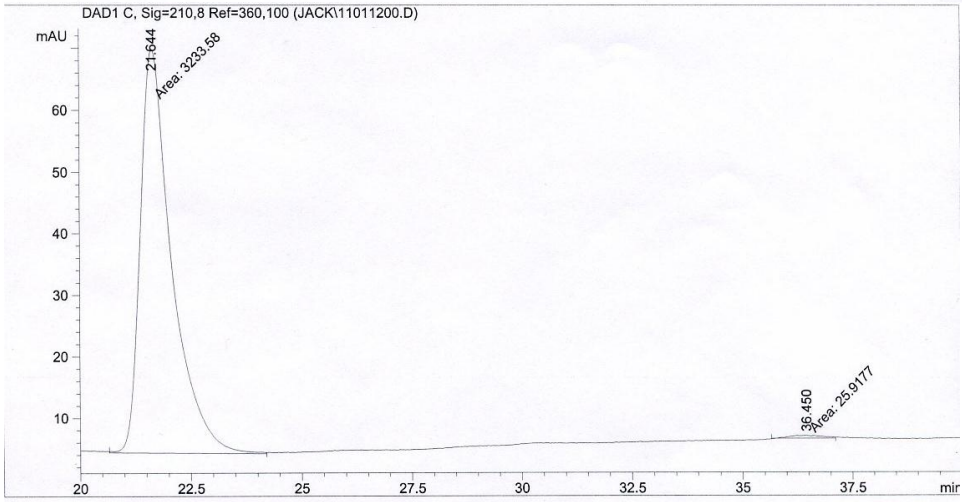
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.782 MM    0.7918  496.86014   10.45877  50.7332
   2  36.334 MM    1.3453  482.49966    5.97758  49.2668
```



3-23




```
=====================================================================
                        Area Percent Report
=====================================================================

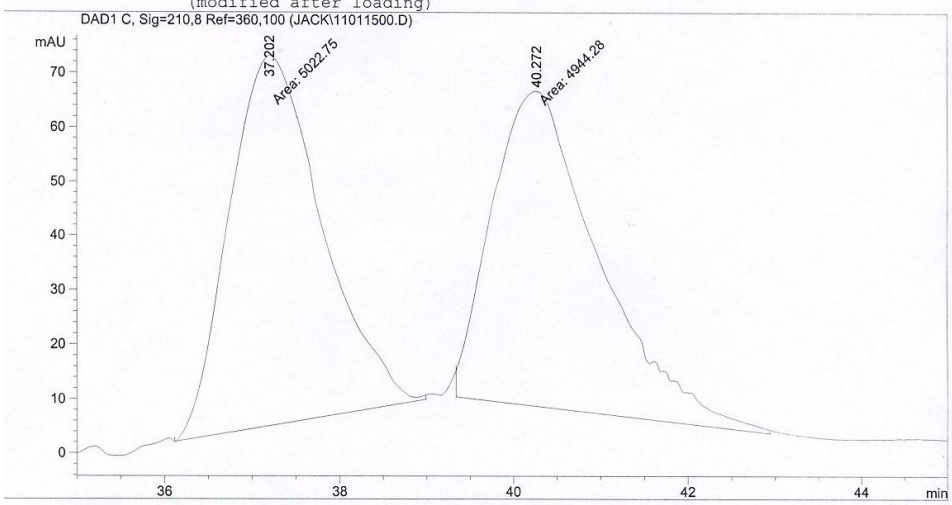
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.644 MM    0.8216 3233.58325   65.59236  99.2049
   2  36.450 MM    0.9091   25.91772 4.75176e-1   0.7951
```

Racemic (top) and optically enriched (bottom) 3-24

(modified after loading)

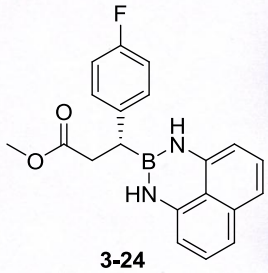



```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

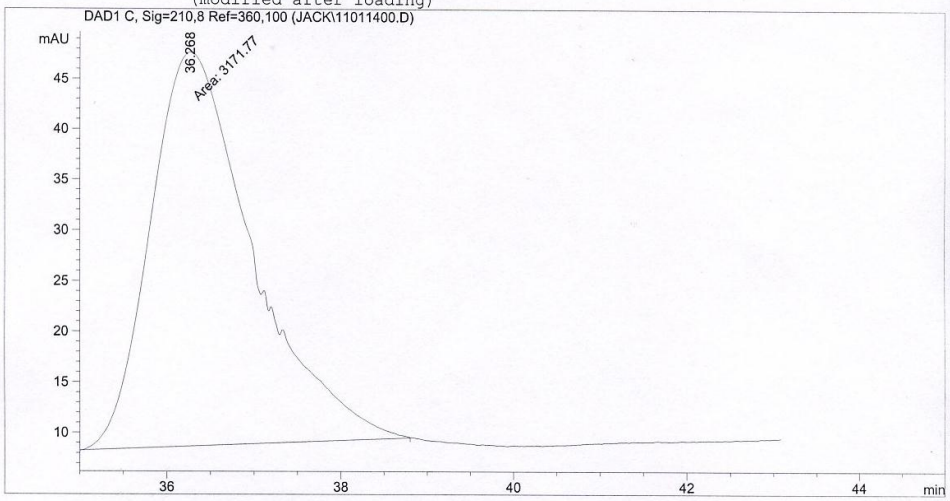

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  37.202 MM    1.2280 5022.75049   68.16708  50.3937
   2  40.272 MM    1.4211 4944.27588   57.98665  49.6063
```



3-24

(modified after loading)



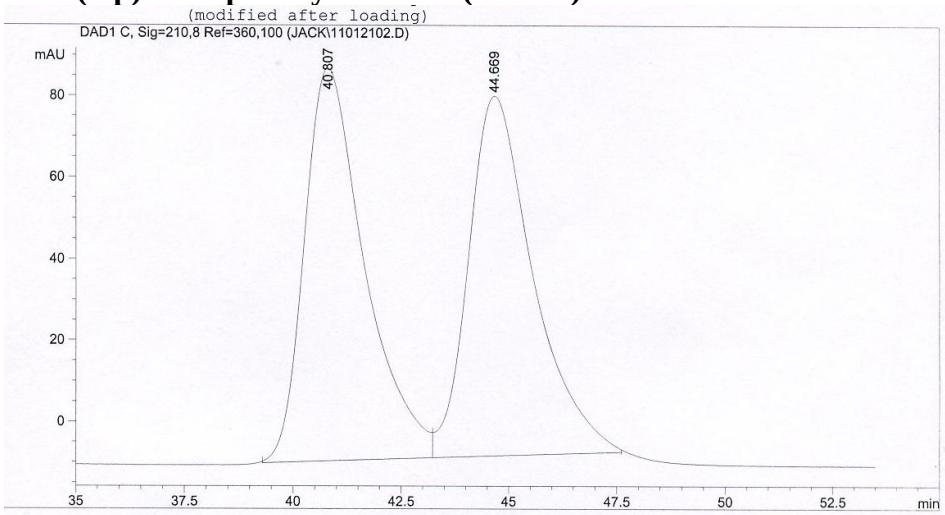

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.268 MM    1.3551 3171.76782   39.00949 100.0000
```

Racemic (top) and optically enriched (bottom) 3-25

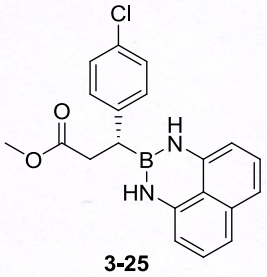



```
================================================================================
                              Area Percent Report
================================================================================

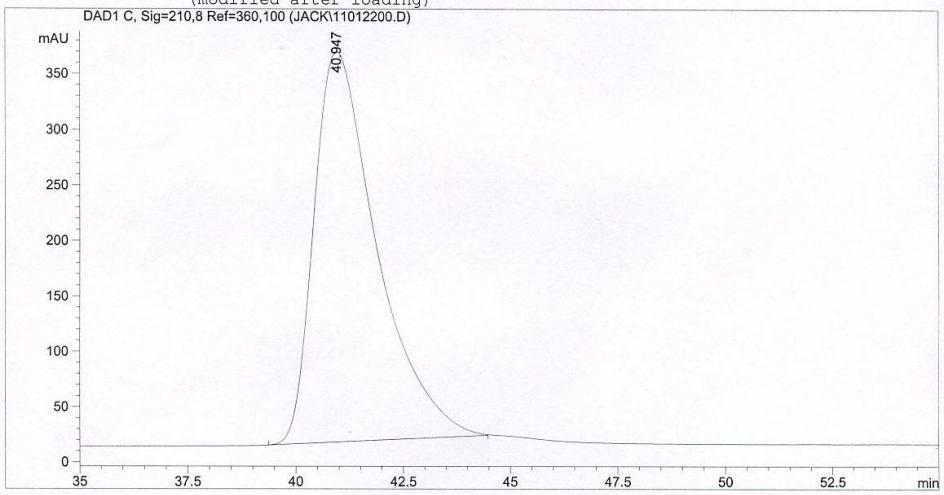
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  40.807 BB    1.3392 9351.85059   96.62184  50.2281
   2  44.669 BB    1.4498 9266.91895   88.49011  49.7719
```



3-25




```
================================================================================
                              Area Percent Report
================================================================================

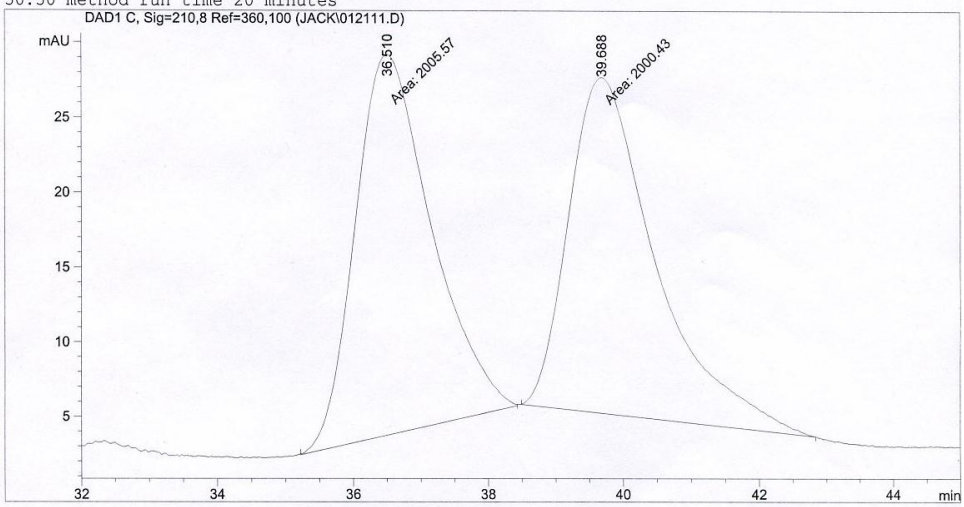
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  40.947 PB    1.4744 3.59495e4   352.32825 100.0000
```

Racemic (top) and optically enriched (bottom) 3-26

50:50 method run time 20 minutes

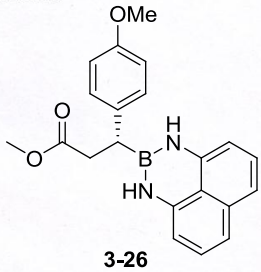



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

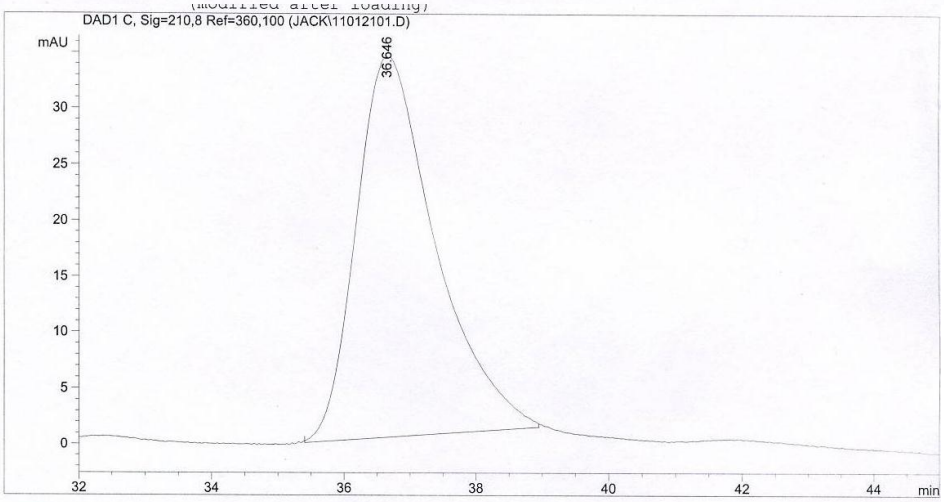

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.510 MM    0.9619 2005.57312   25.48043  50.0642
   2  39.688 MM    1.4821 2000.43188   22.49595  49.9358
```



3-26

(Modified after loading)




```
=====================================================================
                      Area Percent Report
=====================================================================

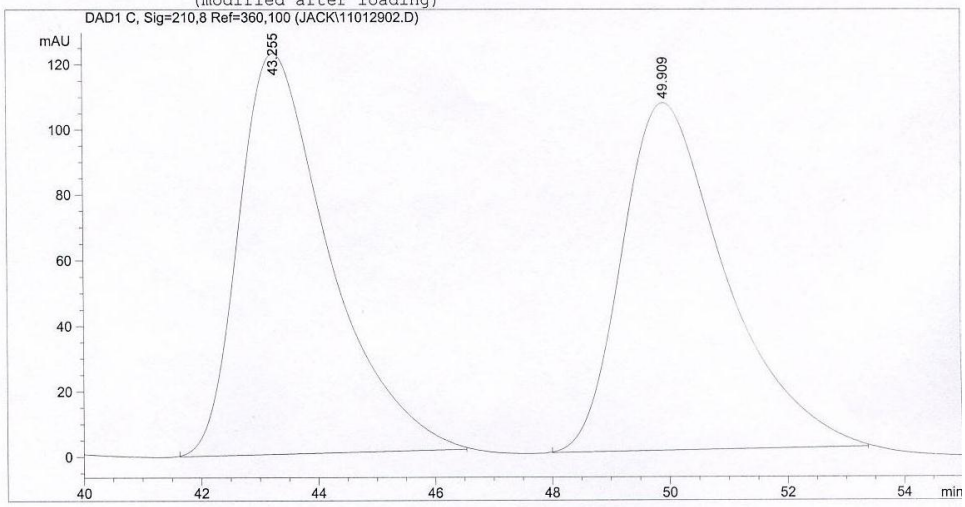
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.646 BB    0.9920 2847.66260   34.10940 100.0000
```

Racemic (top) and optically enriched (bottom) 3-27

(modified after loading)



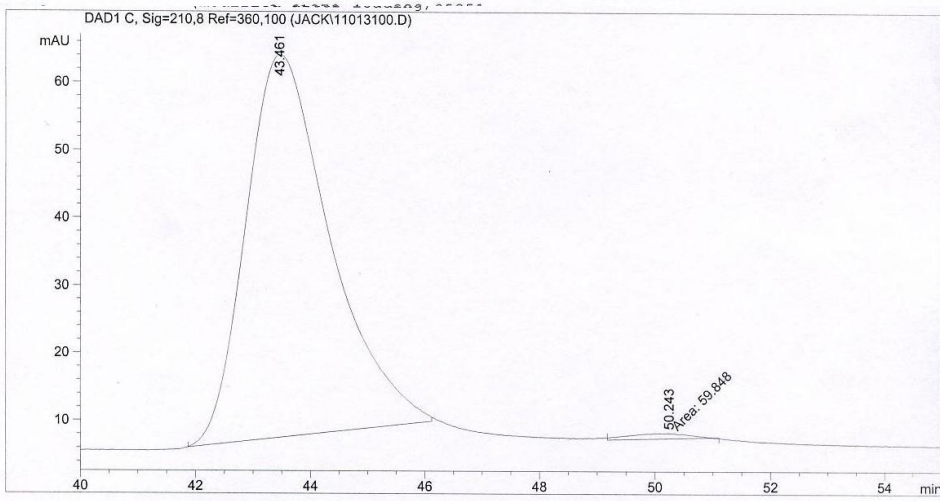

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  43.255 BB    1.4763 1.32090e4   122.66436  50.4397
   2  49.909 BB    1.5132 1.29787e4   106.39415  49.5603
```

3-27



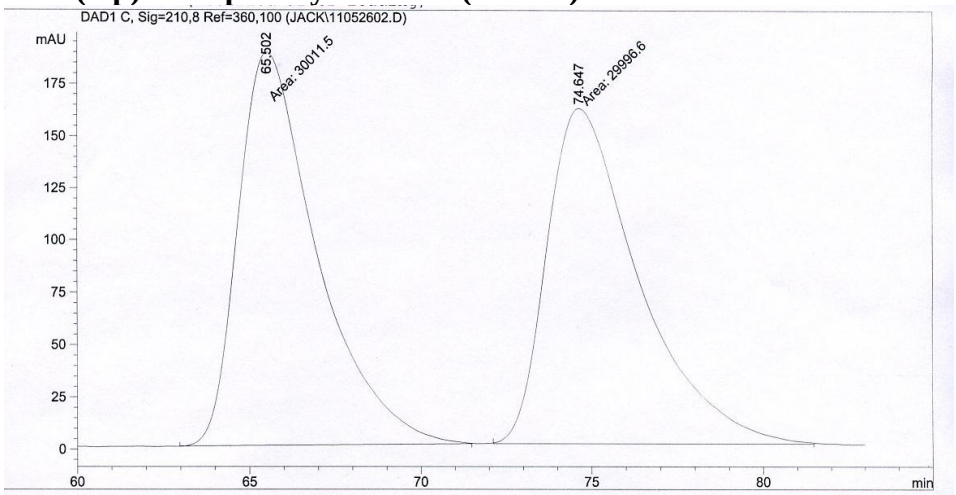

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  43.461 BB    1.2803 5771.23730   56.66130  98.9736
   2  50.243 MM    1.2705   59.84802 7.85106e-1   1.0264
```

Racemic (top) and optically enriched (bottom) 3-28

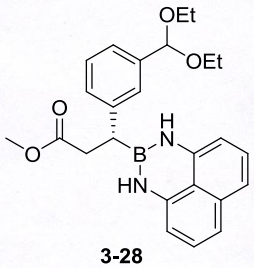



```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

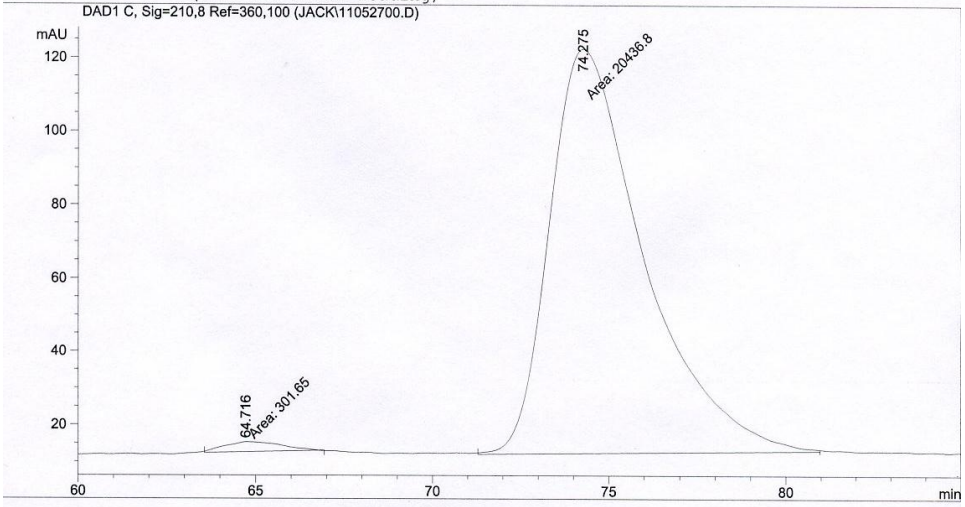

Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  65.502 MM    2.6590 3.00115e4   188.11574  50.0124
   2  74.647 MM    3.1092 2.99966e4   160.79652  49.9876
```



3-28

(modified after loading)



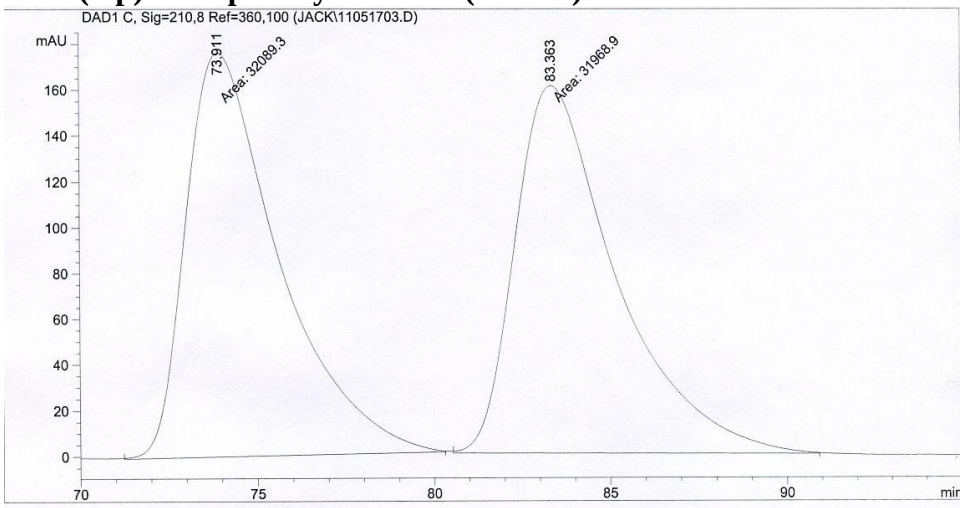

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  64.716 MM    1.8396  301.64963    2.73291   1.4545
   2  74.275 MM    3.0902 2.04368e4   110.22366  98.5455
```

Racemic (top) and optically enriched (bottom) 3-30

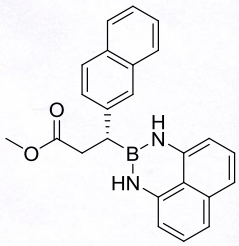



```
=====================================================================
                    Area Percent Report
=====================================================================

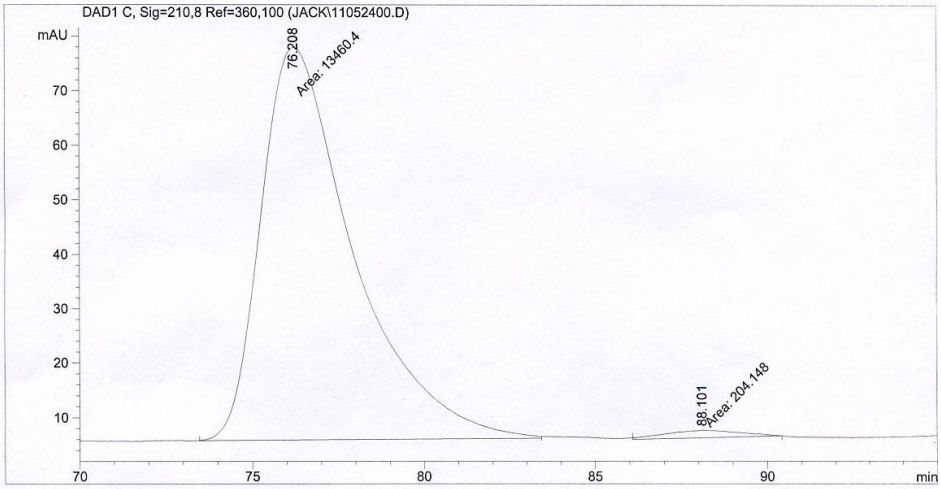
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  73.911 MM    3.0338 3.20893e4   176.29033  50.0939
   2  83.363 MM    3.3197 3.19689e4   160.50111  49.9061
```



3-30



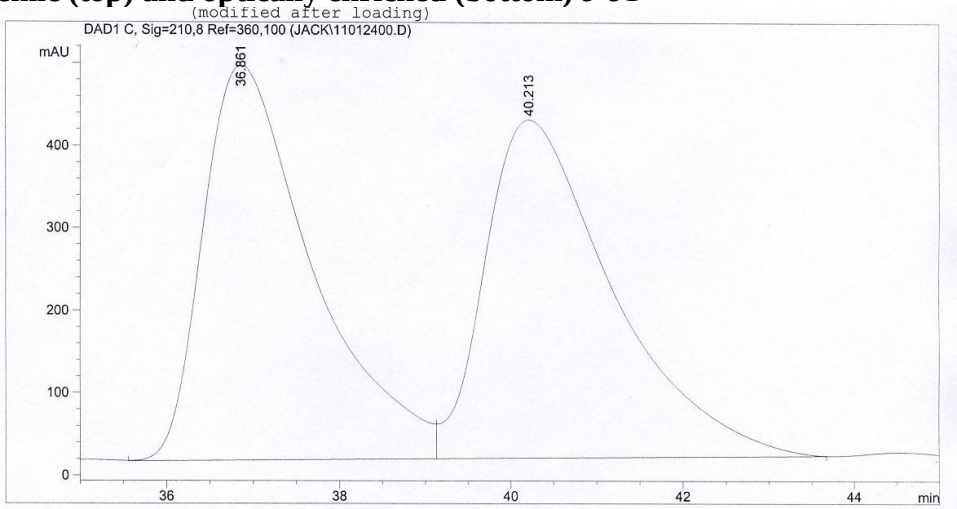

```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  76.208 MM    3.1139 1.34604e4    72.04481  98.5060
   2  88.101 MM    2.4299  204.14789    1.40024   1.4940
```

Racemic (top) and optically enriched (bottom) 3-31

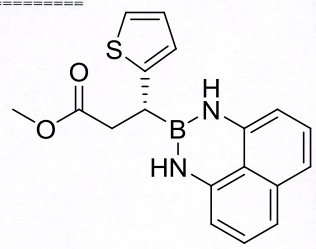



```
================================================================================
                            Area Percent Report
================================================================================

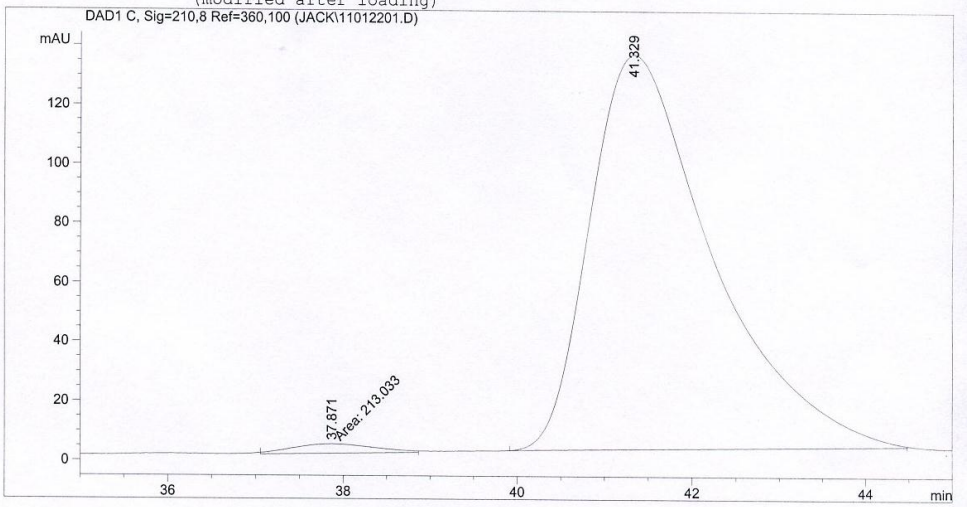
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  36.861 VV    1.2973 4.22074e4   479.31226  49.9301
   2  40.213 VB    1.4263 4.23256e4   410.69589  50.0699
```



3-31



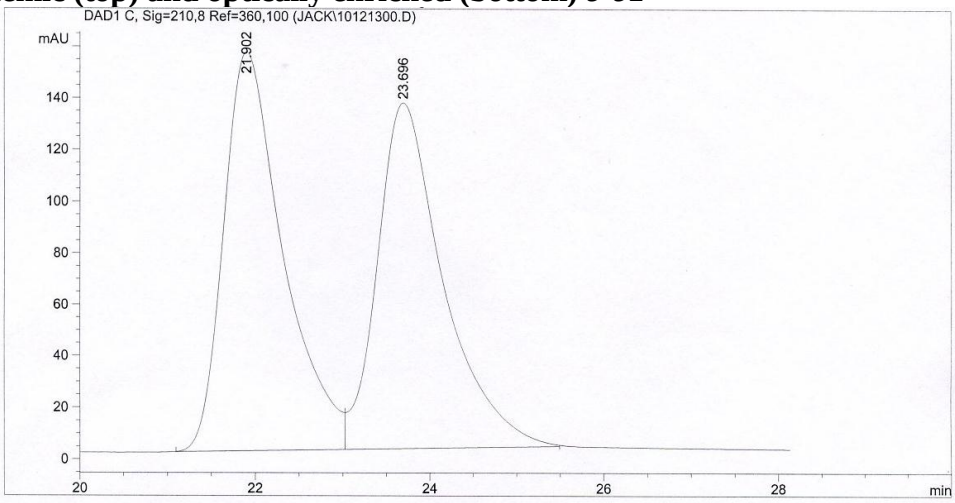

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  37.871 MM    1.0979  213.03325    3.23388   1.6144
   2  41.329 BB    1.3606 1.29824e4   133.25424  98.3856
```

Racemic (top) and optically enriched (bottom) 3-32

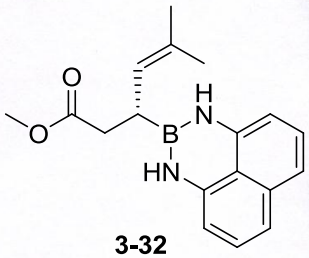



```
================================================================================
                              Area Percent Report
================================================================================

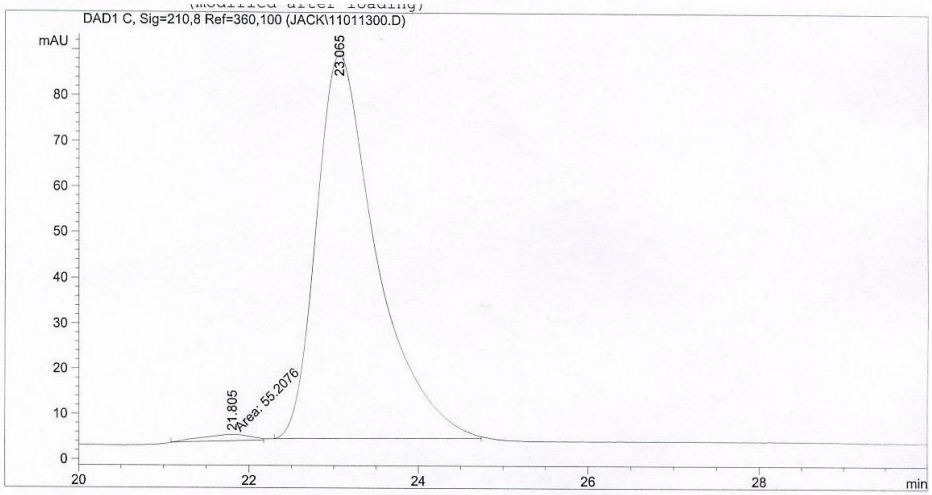
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.902 BV    0.6945 7278.30713  154.80623  50.7509
   2  23.696 VB    0.7707 7062.93359  134.05479  49.2491
```



3-32



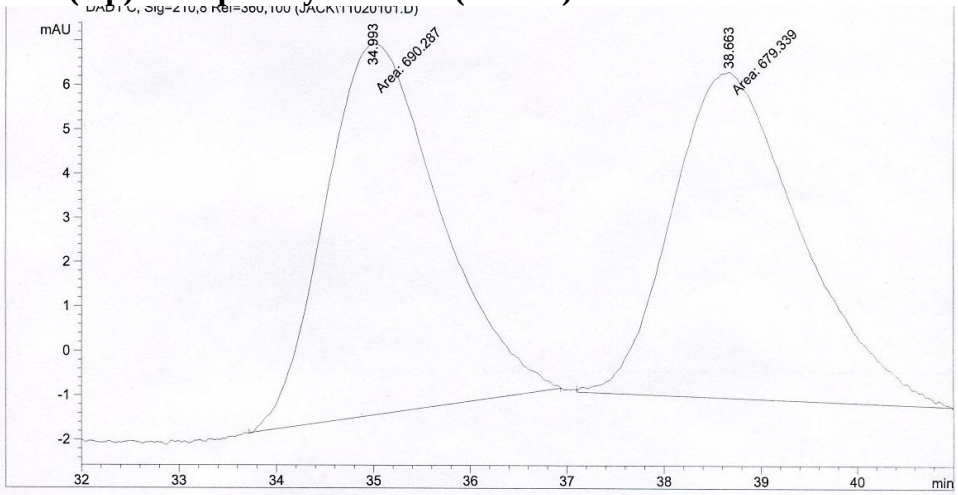

```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  21.805 MM    0.6567   55.20760   1.40113   1.3050
   2  23.065 PB    0.7271 4175.37793  84.41305  98.6950
```

Racemic (top) and optically enriched (bottom) 3-33

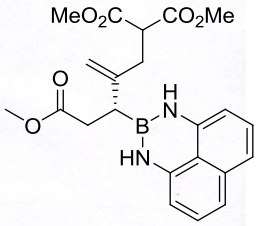



```
================================================================================
                            Area Percent Report
================================================================================

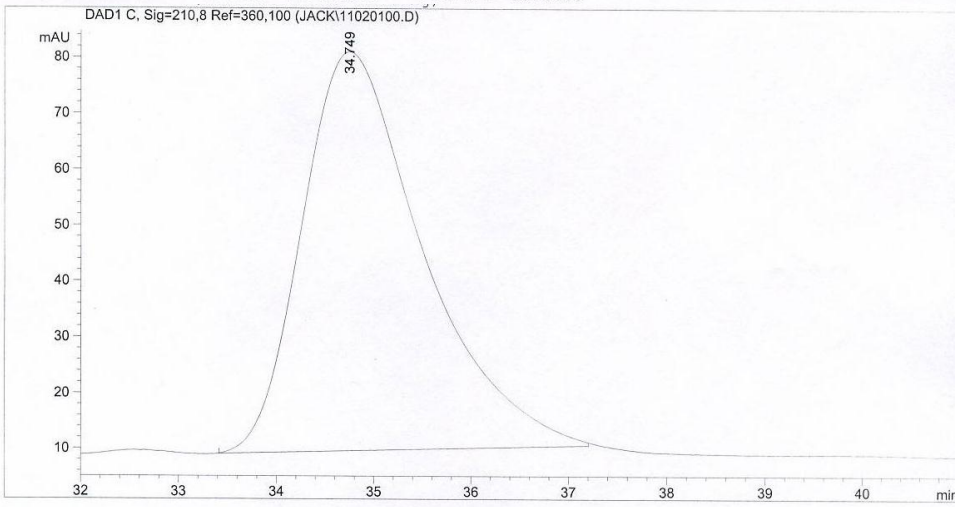
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  34.993 MM    1.3702  690.28723    8.39667  50.3997
   2  38.663 MM    1.5353  679.33868    7.37476  49.6003
```



3-33



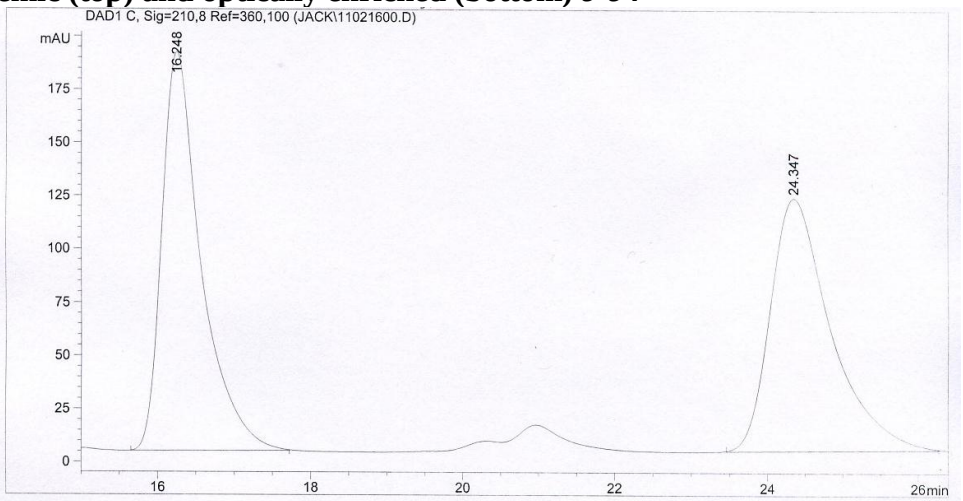

```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  34.749 BB    1.1259 6165.42139   71.50572 100.0000
```

Racemic (top) and optically enriched (bottom) 3-34

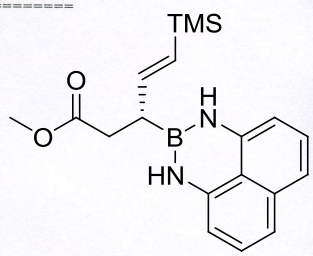


Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

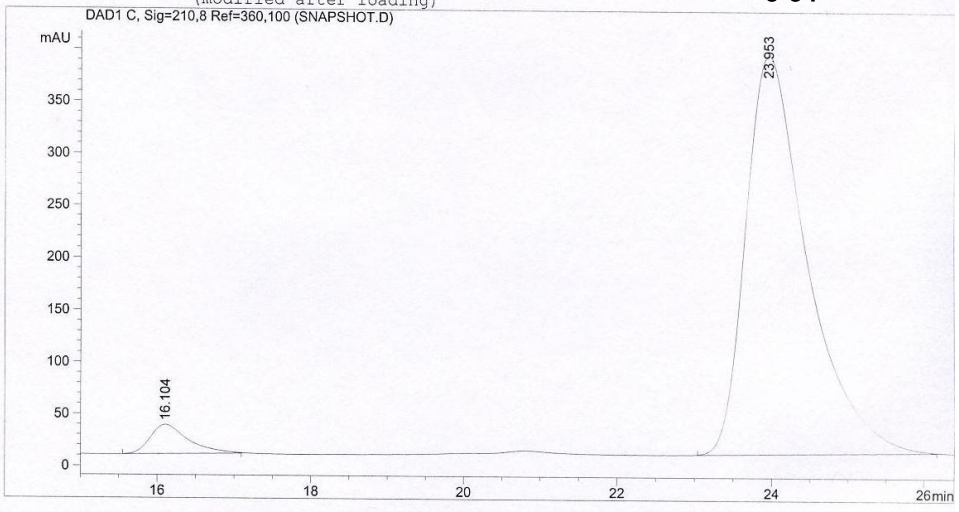
Signal 1: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.248	BB	0.5250	6669.06836	187.46428	50.1928
2	24.347	BB	0.8108	6617.83008	119.01017	49.8072



3-34

(modified after loading)



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.104	BB	0.5022	957.72827	28.19884	4.2723
2	23.953	BB	0.8233	2.14592e4	383.22028	95.7277