Breaking New Ground with the Suzuki-Miyaura Reaction: Stereoselective Cross-Couplings of 1,1-Diboronyl Alkanes

by

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Abstract

Synthetic organic chemistry is an area that has seen incredible growth through the years. The level of molecular complexity that can be achieved through available synthetic methods today is remarkable. Still, as the field continues to progress, increasing focus is being placed upon the strategic development of methods that are both efficient and selective in order to allow for the rapid assembly of molecular complexity. In this regard, organoboron reagents represent a class of compounds that have demonstrated great synthetic diversity. These compounds have been applied, through a range of methods, in the efficient construction of C–heteroatom and C–C bonds. Arguably among some of the most frequently used processes is the Suzuki-Miyaura cross-coupling. Since its conception, this reaction has been widely applied in a broad range of fields including, but not limited to, the pharmaceutical and materials industries. To date, the application of the Suzuki-Miyaura cross-coupling to the construction of sp^2–sp^2 bond connections has been extensively studied and many groups are now directing efforts towards employing this method for the construction of stereogenic centres. To this end, this thesis details studies in developing catalytic stereoselective Suzuki-Miyaura reactions for the cross-coupling of sp^3-hybridized organoboronates for the efficient construction of stereogenic carbon centres.

In order to demonstrate the versatility of optically enriched diboronyl compounds, Chapter 2 describes the development of an iterative cross-coupling process to transform 3,3-diboronylamides into the corresponding diarylmethanes – a motif that is commonly found in pharmaceutically relevant compounds. In addition, studies were made to determine the stereochemical outcome of the cross-coupling reaction.

As a progression from the cross-coupling of optically enriched secondary boronates, Chapter 3 describes the development of an asymmetric Suzuki-Miyaura cross-coupling reaction for the desymmetrization of prochiral 1,1-diboronylalkanes. Ligand optimization in combination with mechanistic studies on the role of the base led to reaction conditions that produced optically enriched secondary organoboronates in good yields and enantioselectively. The details of the reaction scope and scalability will also be discussed.

Due to the synthetic value demonstrated by 1,1-diboronyl compounds, an extension of these cross-coupling methods to 1,1,1-triboronylated compounds is desirable, as this would represent a unique way to construct complex stereogenic centres. In Chapter 4, initial studies on the synthesis of 1,1,1-triboronyl alkanes will be described. Given their similar potential as a synthetic handle for the construction of stereogenic centres, the development of a method that produces 3,3-diboronyl-3-silyl ketones as the products will also be discussed.

Preface

Chapter 1 of this thesis has been published as Sun, H.-Y.; Hall, D. G. "At the Forefront of the Suzuki-Miyaura Reaction: Advances in Stereoselective Cross-Couplings", book chapter in "Topics in Organometallic Chemistry: Synthesis and Application of Organoboron Compounds" (Eds. Fernandez, E. & Whiting, A), Springer, Heidelberg, **2014**. I compiled the necessary references and wrote the book chapter with assistance from Hall, D. G. The supervisory author was Hall, D. G., who was involved with the initiation of this writing project.

Chapter 2 of this thesis has been published as Lee, J. C. H.; Sun, H.-Y.; Hall, D. G. "Optimization of Reaction and Substrate Activation in the Stereoselective Cross-Coupling of Chiral 3,3-Diboronyl Amides" *J. Org. Chem.* **2015**, *in press*. (DOI: 10.1021/acs.joc.5b00991). I was responsible for gaining experimental evidence which provided insight on the stereochemical outcome of the reaction (*i.e.* inversion *vs.* retention). I was also responsible for performing the iterative cross-coupling sequence to give the diarylmethane product and took part in data collection and analysis of the compounds synthesized. I assisted in the writing of the manuscript in collaboration with Lee, J. C. H. and Hall, D. G. Hall D. G. was the supervisory author and was involved with the project conception and initiation.

Chapter 3 of this thesis has been published as Sun, H.-Y.; Kubota, K.; Hall, D. G. "Optimization of Ligand, Scalability, and Mechanistic Insights on the Catalytic Enantioselective Desymmetrization of 1,1-Diboronylalkanes *via* Suzuki-Miyaura Cross-Coupling" *Chem. Eur. J.* **2015**, *in press.* (DOI: 10.1002/chem.201406680). I was responsible for the reaction conditions optimization, catalyst optimization, study of substrate scope, study of reaction scalability and data collection and analysis of the compounds synthesized. Kubota, K. assisted in the catalyst optimization process. I wrote the manuscript with assistance from Hall, D. G. Hall, D. G. was the supervisory author and was involved with the project conception and initiation.

Acknowledgements

Over these past five years, I have worked with many incredible individuals who have helped make my time here at the University of Alberta exciting and enjoyable. I am most indebted to my supervisor and mentor Prof. Dennis Hall who has guided and supported me throughout my studies. He has continuously challenged me and helped me grow and cultivate my skills as a researcher, for which I am extremely grateful. I am also thankful for all the opportunities he has presented to me over the years, sending me to various conferences and symposia. I feel that I have learned so much from these experiences and I feel extremely lucky to have had these opportunities. Most of all, however, he has shown great faith in my knowledge and ability, even when I felt traces of doubt, and for that, thank you simply isn't enough.

My appreciation and thanks are also extended to both the excellent administrative and research services at the University of Alberta. I am particularly indebted to Lynne Lechelt and Anita Weiler for all their administrative assistance as well as all of the staff from the NMR, Mass Spectrometry, and Analytical labs, the machine shop, the storeroom, and the glass shop. I am also extremely grateful to Ed Fu for all his help with the HPLC. I feel extremely fortunate to have had all the help these individuals have provided.

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Of course, I cannot forget my wonderful lab mates, past and present, with whom I have had the pleasure to work. They are all extremely talented individuals and I have learned a lot just from working alongside them. I am most thankful to Jack Lee, Xiaobin Mo, Samantha Kwok and Joshua Yakiwchuk for their friendship and the amazing memories I have had the chance to create with them. In addition, I would particularly like to thank Dr. Hayley Wan for her unwavering friendship, her patience, and for always being there for me.

Last, but certainly not least, I am so grateful to my family for their continuous love and support. To Mom, Dad, Man-Yee, and Hughanna, thank you for encouraging me through difficult times and giving me the courage and perseverance I needed to pursue my Ph. D. For all that you have done for me, I will be forever grateful.

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List of Schemes

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List of Abbreviations

Ac	Acetyl
acac	Acetylacetonate
ACS	American Chemical Society
t-Am	*tert*-Amyl
Ar	Aryl
BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
Bn	Benzyl
br	Broad
i-Bu	*Iso*-Butyl
n-Bu	Normal butyl
t-Bu	Tertiary butyl
calcd	Calculated
cm^{-1}	Wavenumbers
COD	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
dan	1,8-Diaminonaphthyl
dba	Dibenzylideneacetone
DCE	Dichloroethane

DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DFT	Density functional theory
DIPPF	Diisopropylphosphinoferrocene
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBM	Di-*tert*-butyl methoxy
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	Diethylether
EtOAc	Ethyl acetate
EtOH	Ethanol
gem	Geminal

h	Hour
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
MIDA	*N*-Methyliminodiacetic acid
mol	Mole
Ms	Mesyl
neop	Neopentyl glycol
NMR	Nuclear magnetic resonance
Nu	Nucleophile
PEPPSI	Pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	Phenyl
pin	Pinacolato
i-Pr	Isopropyl
q	Quartet
quint	Quintet
rt	Room temperature
sep	Septet

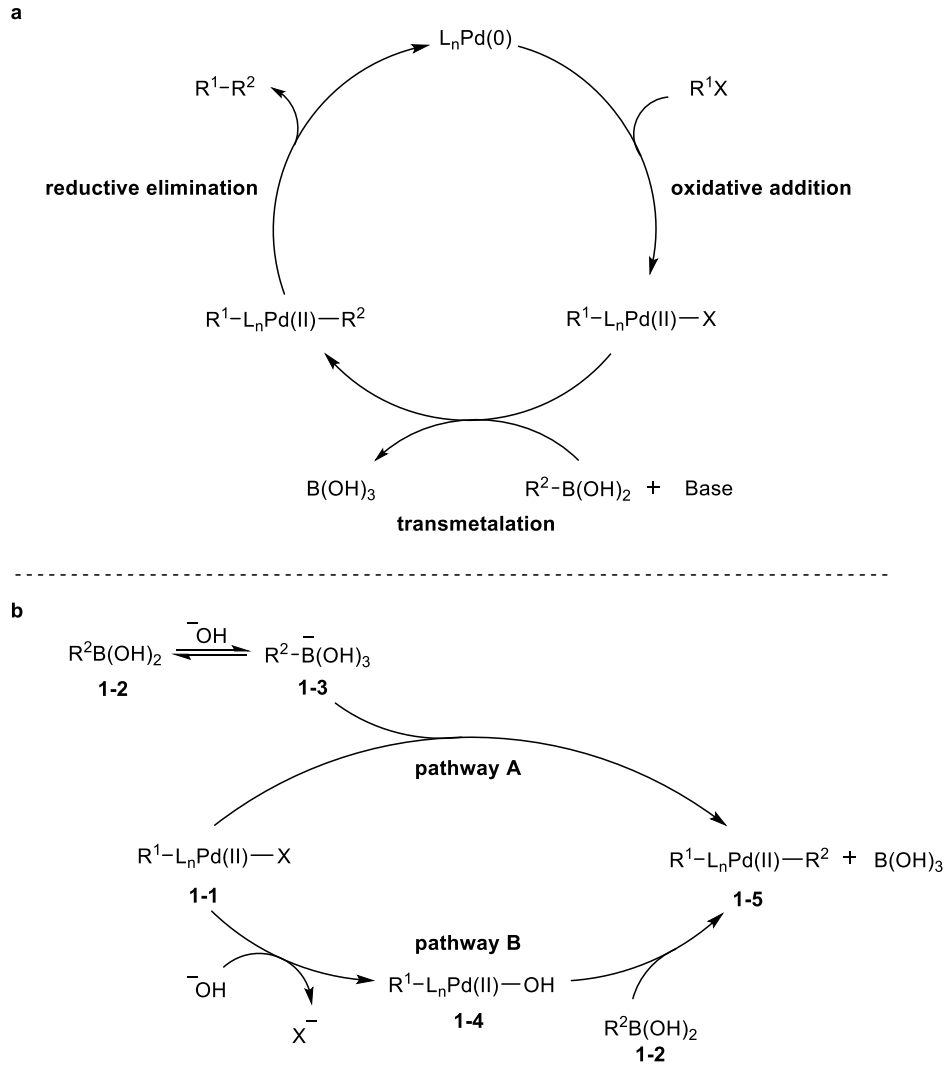
sex	Sextet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Tf	Triflyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
tol	Tolyl
o-tol	*ortho*-Tolyl
Ts	*para*-Toluenesulfonyl
t	Triplet
UV	Ultraviolet

Chapter 1
Advances in the Asymmetric Suzuki-Miyaura Cross-Coupling Reaction

Since carbon-carbon bonds make up the framework of most organic molecules, the construction of these bonds lies at the heart of organic synthesis. For over a century, chemists have been in pursuit of various means to construct carbon-carbon bonds which has led to landmark discoveries including the aldol condensation, Wittig olefination, and Friedel-Crafts alkylations, to name only a few. In current times, the formation of carbon-carbon bonds through transition-metal catalyzed cross-coupling reactions has become ubiquitous in organic synthesis, having found use in a broad selection of research areas including medicinal chemistry, materials and nanotechnology, and agrochemistry. The value of this class of reactions is evidenced by the awarding of the 2010 Nobel Prize in Chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki for their contributions to developing Pd-catalyzed cross-coupling reactions. Among these processes, the Suzuki-Miyaura reaction, which involves the coupling of an organoboron reagent with an organohalide partner, has become a fundamental synthetic tool in both academic and industrial settings.[1] Its success may be attributed to several factors: the general ease of accessibility of organoboron reagents, the robustness of these reagents, allowing for mild reaction conditions and good functional group tolerance, and the generation of non-toxic by-products such as boric acid. Over the years, the use of the Suzuki-Miyaura reaction for the construction of sp^2-sp^2 bonds in "flat" compounds has been thoroughly studied, and this process has now been globally adopted for creating this type of bond connection. In contrast, there are far fewer examples of applying the Suzuki-Miyaura cross-coupling towards the generation of axial chirality or stereogenic carbon centres due to various mechanistic challenges associated with these processes.

In order to assess the challenges of stereoselective Suzuki-Miyaura cross-couplings, an understanding of the reaction mechanism is required. The generally accepted mechanism of the Suzuki-Miyaura cross-coupling involves three key steps: oxidative addition, transmetalation, and

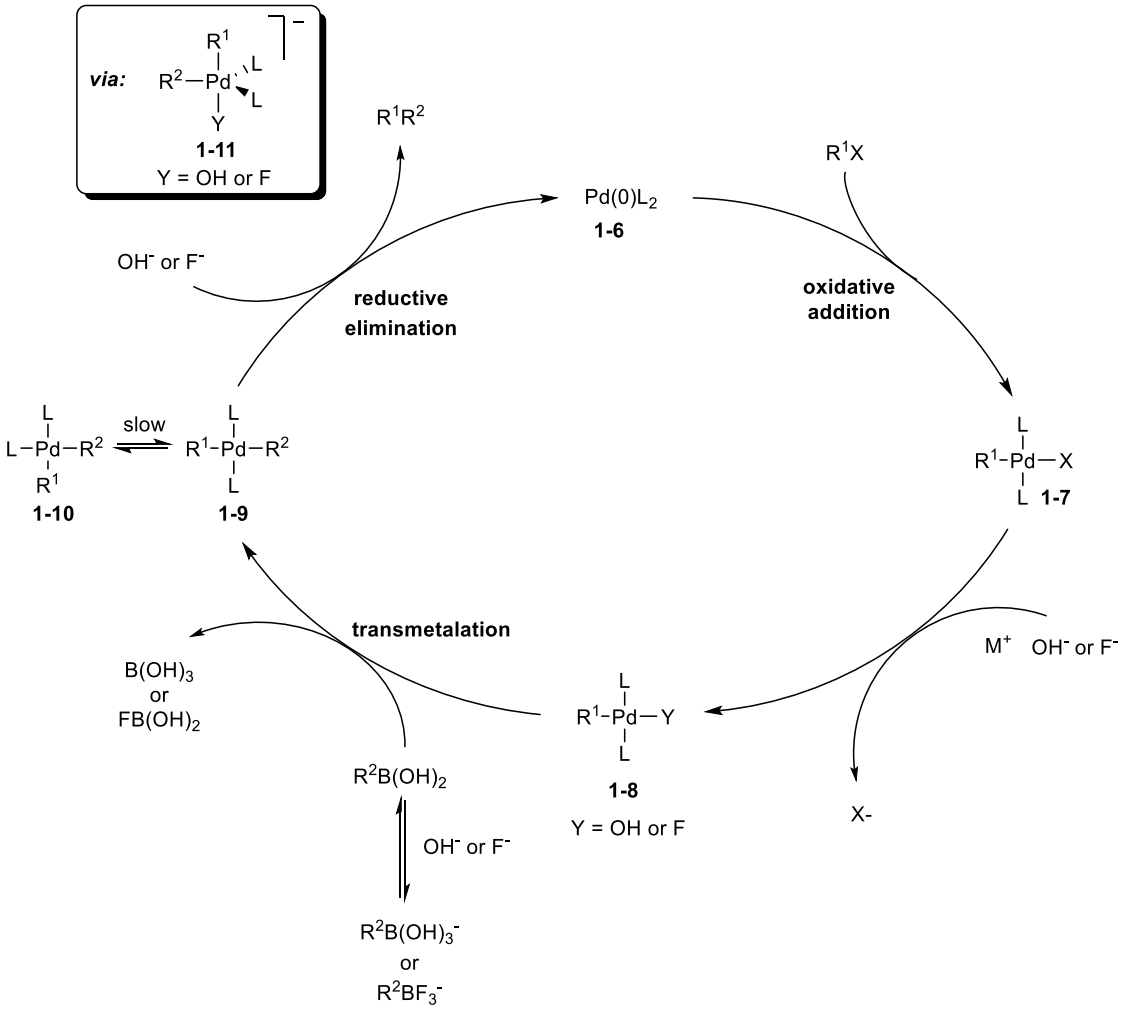
reductive elimination (Scheme 1-1a). While the oxidative addition and reductive elimination processes are considered to be well-understood,[1] transmetalation, in contrast, has been significantly less studied. To date, there have been two main proposed pathways for the transmetalation step of the Suzuki-Miyaura reaction (Scheme 1-1b), both of which have been corroborated by computational studies.[2] The first involves the coordination of a pre-formed borate **1-3** to ArPdX **1-1** to eventually give the transmetallated Pd intermediate **1-5**. The second pathway proposes that transmetalation occurs between the palladium hydroxo complex **1-4** and the neutral boronic acid **1-2**.



Scheme 1-1. (a) General mechanism for a Suzuki-Miyaura cross-coupling reaction. (b) Proposed pathways for transmetalation.

Recently, independent efforts have been made by the Amatore[3] and Hartwig[4] groups towards a more thorough understanding of the transmetalation process leading to the formation of key complex **1-5**. The Hartwig group provided a quantitative assessment of the rates of pathways A and B by isolating key catalytic intermediates and using these intermediates in various stoichiometric and catalytic studies. The chosen reaction conditions used common ligands such as PPh_3 and PCy_3, and mild base like K_2CO_3 in aqueous THF, which is representative of some of the most common reaction conditions for Suzuki-Miyaura reactions. These studies showed that the rate of reaction of hydroxo complex **1-4** with neutral boronic acid is several orders of magnitude faster than the reaction of halide complex **1-1** with borate **1-3**, suggesting pathway B as the dominant pathway for transmetalation. These conclusions, however, do not rule out pathway A for systems employing other metal/ligand systems or systems which employ stronger bases and would thus have higher concentrations of borate.

In line with Hartwig's findings, the Amatore group used electrochemical techniques to obtain kinetic data that also indicated that reaction of **1-4** with boronic acid was much more rapid than the reaction of the halide complex **1-1** with the borate species.[3a] In addition to forming the palladium hydroxo species, the Amatore group also identified a secondary role for hydroxide ion in the acceleration of the reductive elimination step through promoting the formation of pentacoordinate complex **1-11** (Scheme 1-2). In the absence of base, the product of transmetalation was found to be the *trans*-complex **1-9,** which needs to isomerize to the corresponding *cis*-complex **1-10** prior to reductive elimination. Previous work from this group[5] has shown that **1-9** is energetically more stable than **1-10**, thus this isomerization is often slow and can potentially reduce the overall reaction rate. This problem is avoided when base is used, as hydroxide will coordinate to palladium to give pentacoordinated palladium complex **1-11** which can then undergo facile reductive elimination to give the cross-coupled product and regenerated Pd(0) catalyst. In a more recent report, the Amatore group reported that fluoride may behave similarly to hydroxide in the catalytic cycle.[3b]



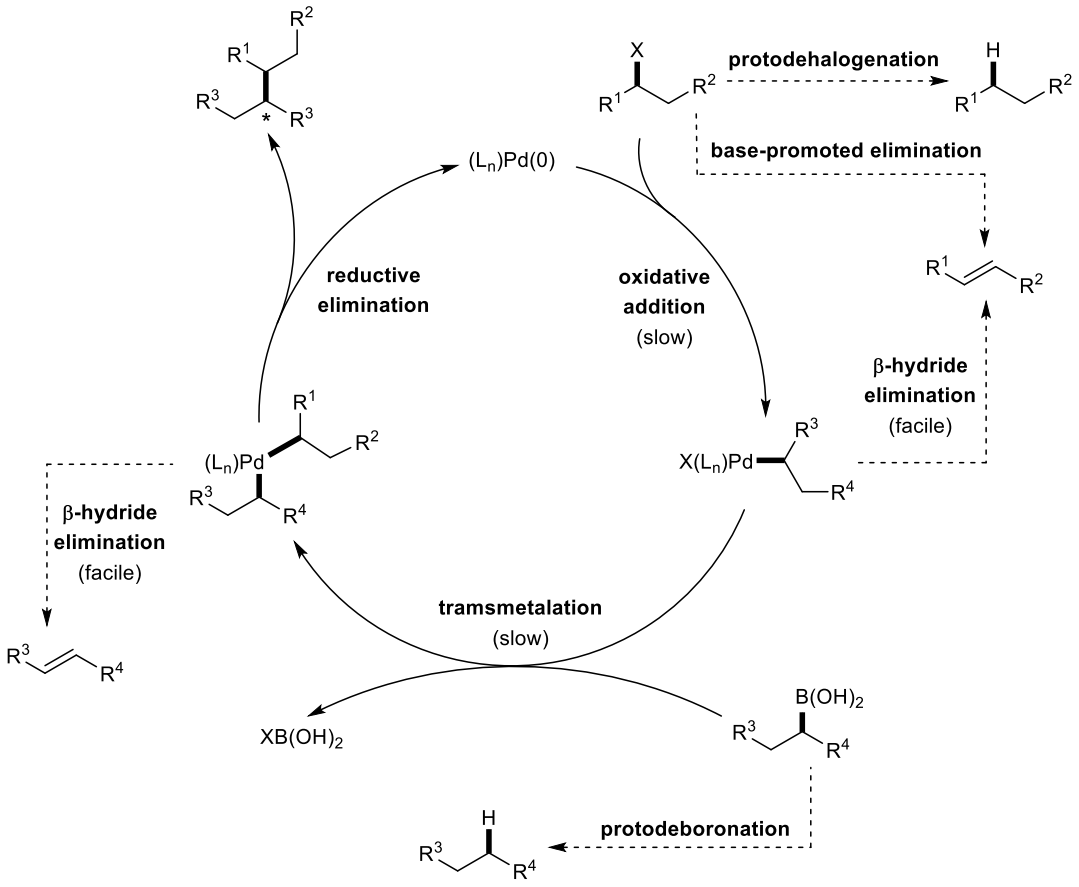
Scheme 1-2. Detailed catalytic cycle as proposed by the Amatore Group.

1.1 Important mechanistic considerations in the cross-coupling of sp^3 centres

1.1.1 Challenges of cross-coupling of saturated carbon centres

In contrast to $C(sp^2)$–$C(sp^2)$ coupling, the coupling of sp^3 centres using the Suzuki-Miyaura cross-coupling has been slow in its development. The challenge of these couplings lies in mechanistic pitfalls at various stages in the catalytic cycle (Scheme 1-3). The oxidative addition of the metal catalyst into the C–X bond of an alkyl halide has been observed to be slower than the

aryl/alkenyl counterpart.[6] Aryl and alkenyl groups also have the added advantage of π-stabilizing interactions with the empty *d*-orbitals of the transition metal. The absence of this interaction in alkyl couplings results in a less stable C–M complex, which will be prone to undergo various side reactions such as protodehalogenation or β-hydride elimination.[6]



Scheme 1-3. Mechanistic challenges in sp^3 Suzuki-Miyaura cross-coupling reactions.

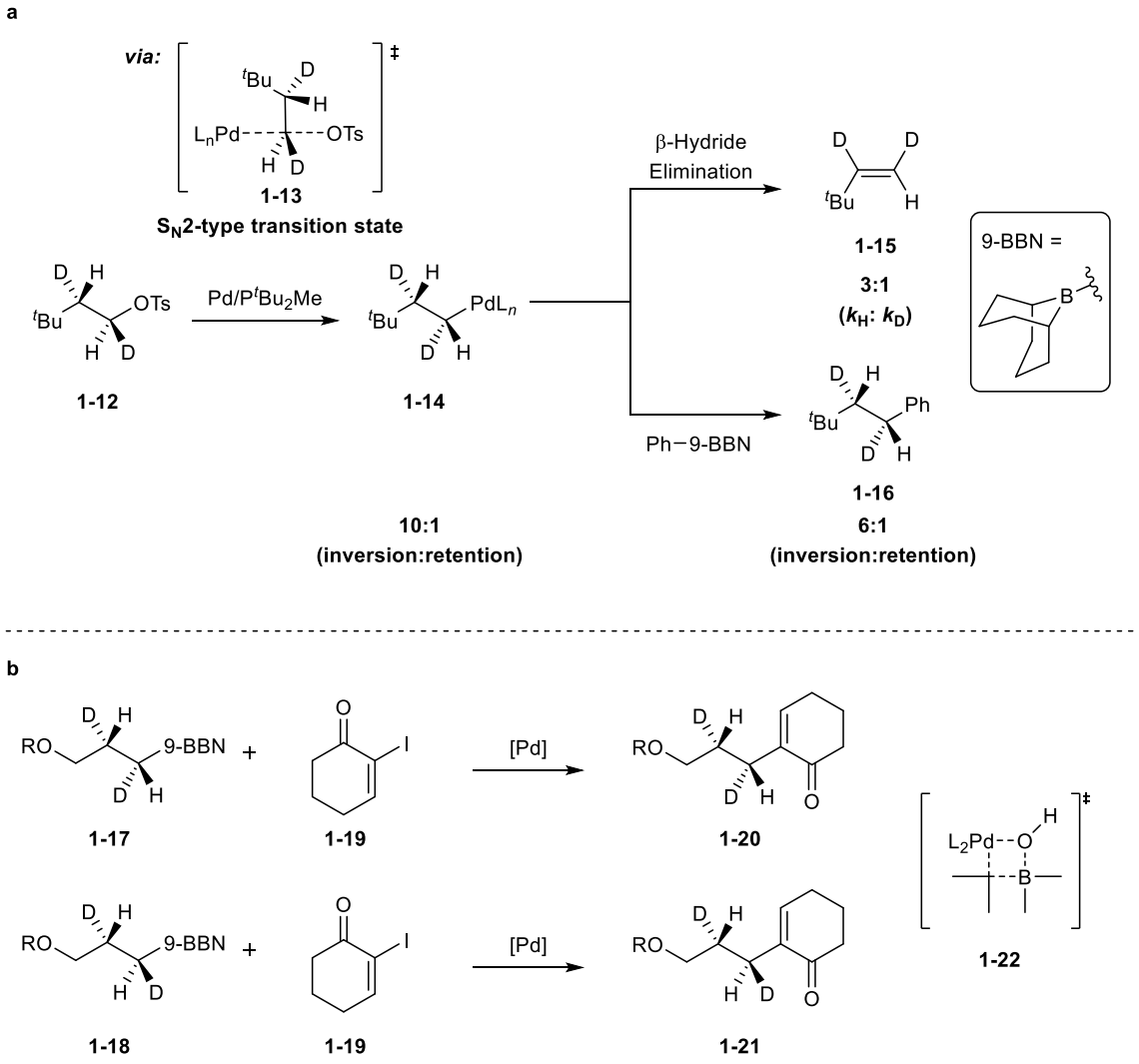
Similarly, when performing a cross-coupling reaction of a sp^3 alkyl borane or boronate, the transmetalation step can be slow due to steric hindrance, especially in the case of secondary alkyl boranes and boronates.[1b,d] In this case, protodeborylation becomes a competing side reaction, resulting in the frequent need for the use of excess organoboron reagent. In addition to protodeborylation, the transmetalated organometallic intermediate is also at risk of undergoing undesired β-hydride elimination if the reductive elimination step is too slow. Most of the previous reports on the coupling of secondary alkyl boronates have been limited to cyclopropyl boronic acids.[8j] The unique hybridization of these substrates imparts significant s-character to the exocyclic

C–B bond thus making the cross-coupling of these compounds more similar to the relatively easier coupling of sp^2 boronates.

Despite these challenges, advances have been made in the area of sp^3 couplings. The first catalytic cross-coupling of an alkylborane with aryl or alkenyl halides was first reported by Suzuki and Miyaura in 1986,[7] and since then, numerous other alkyl Suzuki-Miyaura reactions have been developed and studied.[8] It is only recently, however, that significant advances have been made in the area of stereoselective sp^3 cross-couplings.

1.1.2 Stereochemistry of various steps of the catalytic cycle

When designing a stereoselective cross-coupling reaction, the stereochemical consequence of each individual step of the catalytic cycle must be considered since every stage could have a potential impact on the overall outcome of the reaction. Studies have shown that the oxidative addition of palladium into an alkyl halide C–X bond occurs via an S_N2-type mechanism (Scheme 1-4a).[9] The stereochemical outcome of the oxidative addition step was studied by Fu and co-workers in 2002 through a deuterium labelling study (Scheme 1-4a). Diastereomerically pure tosylate **1-12** was treated with Pd/P^{t}Bu$_2$Me in the absence of the organoborane coupling partner and base, and the olefins resulting from oxidative addition followed by β-hydride elimination were then examined. Based on NMR analysis of the products, it was found that oxidative addition occurred primarily with overall inversion of configuration. Since β-hydride elimination is known to proceed with the hydride and palladium in a syn conformation, the stereochemistry of the oxidative addition step may be inferred by the stereochemistry of the olefin products, which can be determined by NMR. The authors then went on to explore the stereochemical course of the coupling of **1-14** with an organoborane. It was found that the coupled product occurs primarily with inversion of configuration. Since oxidative addition was found to occur with inversion of stereochemistry and reductive elimination is well-known to occur in a stereoretentive manner,[10] these results indicate that the stereochemistry set during oxidative addition is preserved during transmetalation.



Scheme 1-4. (a) Stereochemical studies showing evidence of an invertive oxidative addition step. (b) Stereochemical studies showing evidence of a retentive transmetalation step.

The stereochemistry of the transmetalation step in the Suzuki-Miyaura coupling of aryl and alkenyl halides with sp^3 organoboranes was independently studied by Woerpel,[11] Soderquist,[12] and more recently Jarvo.[13] Deuterium-labelled substrates **1-17** and **1-18** were subjected to the coupling conditions and revealed a stereoretentive transmetalation step, leading to products **1-20** and **1-21**, respectively (Scheme 1-4b). This observation was attributed to a 4-membered transition state **1-22**, which was first proposed by Soderquist in 1998.[12]

1.2 Stereoselective C(sp^3)–C(sp^2) Suzuki-Miyaura cross-coupling reactions

1.2.1 Stereoselective couplings of alkyl boronates with aryl or alkenyl halides

Due in part to their versatility as synthetic intermediates towards the synthesis of enantioenriched alcohols and amines *via* C–B bond oxidation, significant efforts, in recent years, have been placed into the synthesis of optically enriched organoboron compounds. With improved access to these substrates,[14] optically enriched organoboronates have emerged as useful substrates in stereoselective Suzuki-Miyaura cross-coupling reactions.

In 2009, Crudden and co-workers reported the seminal example of a cross-coupling between chiral secondary benzyl boronates with aryl iodides which proceeded with good stereochemical integrity (equation 2, Figure 1-1).[15] Benzylic boronates **1-23** were synthesized with high levels of regio- and enantiocontrol using a rhodium-catalyzed asymmetric hydroboration previously developed by Hayashi and Ito.[16] While modification of the phosphine ligand did little to improve the yield of the process in the initial stages of the study, using silver oxide as the base dramatically improved the yield of the reaction. The authors proposed that the silver oxide played a role in accelerating a slow transmetalation step. It was found that this process proceeded with good stereoretention, presumably *via* 4-membered transition state **1-26** (see Section 1.1.2).[11,12] Furthermore, upon subjection of a benzylic boronate **1-27** and homobenzylic boronate **1-28** to the reaction conditions in a competition reaction, it was observed that there was a complete selectivity for the benzylic boronate over the homobenzylic boronate, an indication that there is an important role imparted upon the benzylic nature of the boronate functionality (equation 3, Figure 1-1).

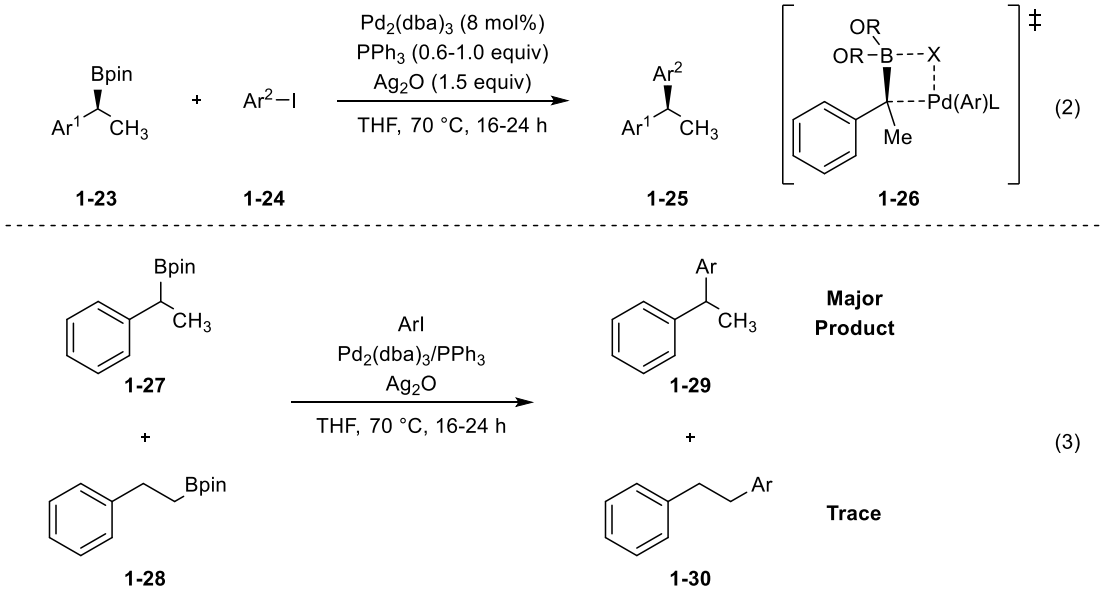
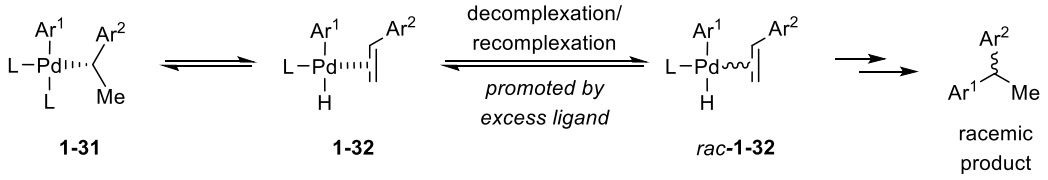
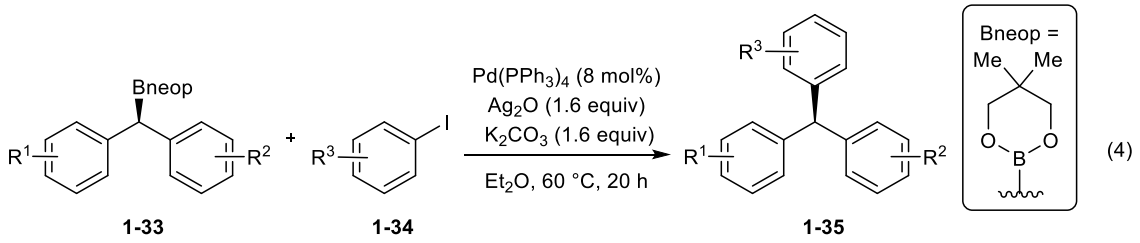


Figure 1-1. Stereoretentive Suzuki-Miyaura coupling of benzylic boronates.

In a later report,[17] it was found that the amount of triphenylphosphine had a direct impact on both the yield and stereochemical outcome of the reaction. At high loadings of phosphine ligand (8-12 equiv with respect to Pd), a higher yield was obtained but at the cost of lower enantioselectivity. This phenomenon was eventually attributed to a racemization pathway involving hydride elimination of the post-transmetalation intermediate **1-31** followed by racemization via decomplexation of the resulting olefin, which is promoted by excess phosphine (Scheme 1-5). With their newly optimized conditions in hand, the Crudden Group was able to apply their method to the construction of enantiomerically enriched triarylmethanes **1-35** (equation 4), motifs which are known to have various biological activities as well as important materials properties.[18]

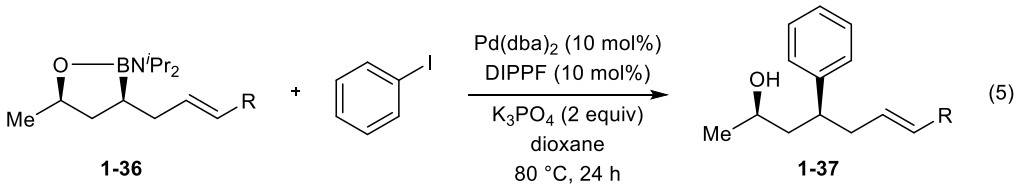


Scheme 1-5. Potential pathway for product racemization by the presence of excess ligand.



1-33 **1-34** **1-35**

In 2011, Suginome and co-workers reported a Pd-catalyzed stereoselective cyclizative alkenylboration of olefins to give products of type **1-36**. In this report, the authors showed that **1-36** could undergo stereospecific Suzuki-Miyaura cross-coupling with aryl iodides, giving the cross-coupled product **1-37** with complete retention of configuration at the stereogenic carbon atom (equation 5).[19] As an extension of this finding, the Suginome Group also developed a highly stereoselective Suzuki-Miyaura reaction involving the coupling of enantioenriched α-(acylamino)benzylboronic esters with aryl bromides and chlorides.[20] In contrast to the Crudden system, it was found that this process occurred with inversion of stereochemistry. In a later report,[21] the Suginome group described a remarkable ability to direct the stereochemical course of their system simply by modifying their choice of acidic additives (Figure 1-2). While using phenol as an additive promoted enantiospecific invertive C–C bond formation, the use of Zr(O*i*-Pr)$_4$•*i*-PrOH conversely resulted in an enantiospecific, retentive C–C bond formation. Based on these observations, the authors proposed that the intramolecular coordination of the amide oxygen atom to the boron centre of the boronate results in the approach of the oxidatively inserted palladium(II) species only from the opposite side of the boronate, thus leading to **1-39**, which results in an invertive transmetalation step. It is believed that phenol enhances this intramolecular interaction by protonating the pinacolate ligand thus leading to enhanced enantioselectivity in the invertive coupling reaction. In the case of Zr(O*i*-Pr)$_4$•*i*-PrOH, it was proposed that competitive coordination of the Lewis acid to the carbonyl oxygen of the amide prevents the intramolecular coordination between the carbonyl and the boronate. As a result, the process is thought to proceed through **1-41** which, as in Crudden's cross-coupling, leads to overall retention of configuration.



1-36 **1-37**

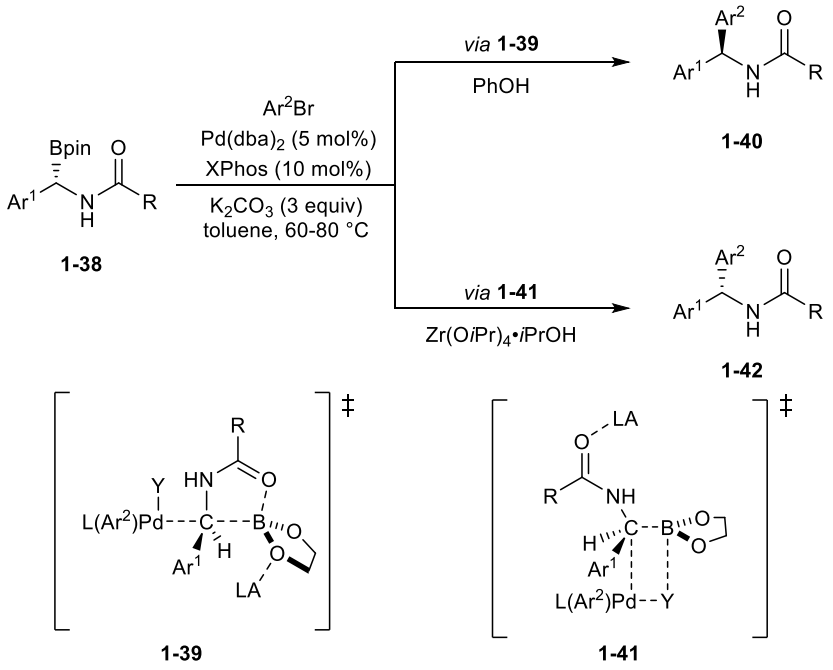


Figure 1-2. Control of stereoselectivity in the coupling of α-(acylamino)benzylboronic esters.

In 2010, Molander and co-workers reported a successful stereospecific cross-coupling of enantioenriched non-benzylic secondary alkyl trifluoroborates (Figure 1-3a).[22] As in Suginome's system, Molander's chosen substrates, acyclic secondary β-trifluoroboratoamides **1-43**, benefit from intramolecular coordination from the amide carbonyl to the boronyl group, thus similarly resulting in a transmetalation occurring with inversion of stereochemistry to give products **1-45**.

Notably, these β-trifluoroboratoamides are substrates that have the potential to undergo β-hydride elimination, yet with their optimized conditions, the authors observed less than 2% of products resulting from this competitive side pathway. It was proposed that the lack of competing β-hydride elimination was attributed to the complexation of the amide carbonyl to the boron atom of the intermediate diorganopalladium complex as seen in **1-44**. This coordination may restrict the reaction intermediate from adopting the necessary syn-coplanar arrangement of the palladium and β-hydrogens in order for elimination to occur.

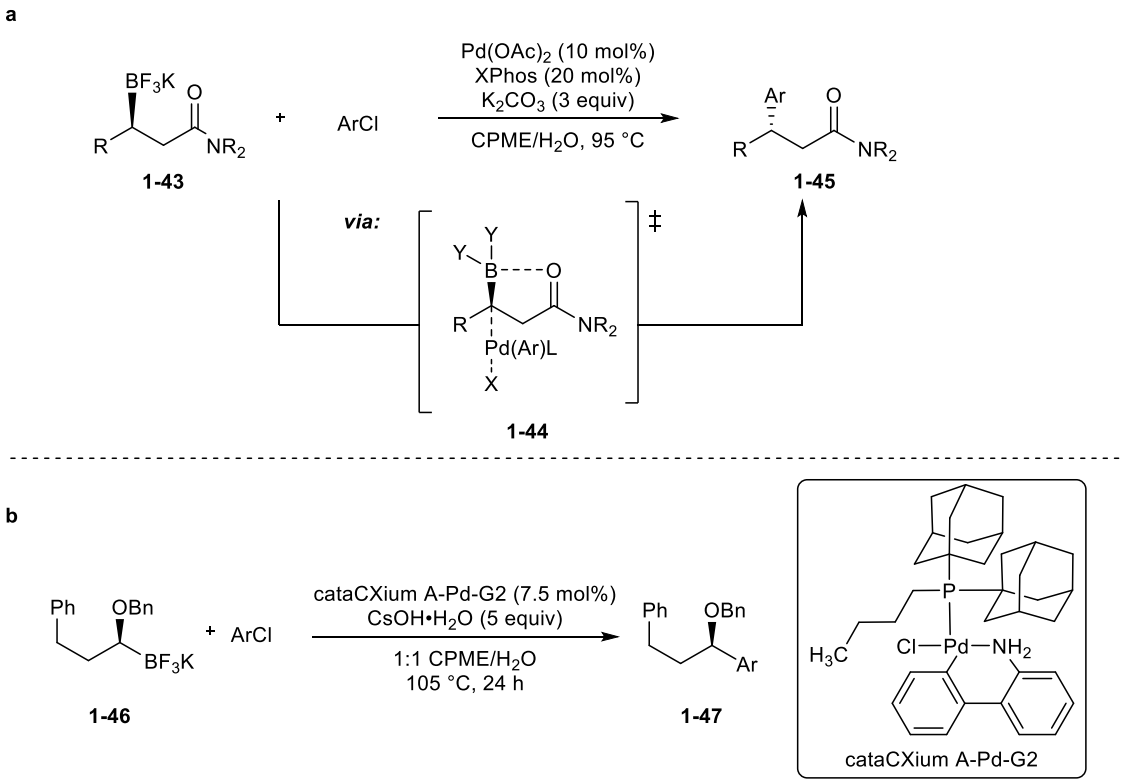


Figure 1-3. (a) Invertive cross-coupling of β-trifluoroboratoamides. (b) Retentive cross-coupling of α-benzyloxytrifluoroborates.

Following this initial report, Molander and co-workers have also reported the successful stereospecific cross-coupling of secondary organotrifluoroborates containing an α-benzyloxy group **1-46**. The benzyloxy group is thought to prevent competing β-hydride elimination by acting as a hemilabile ligand.[23] Prior research has demonstrated that these types of ligands can serve several roles in the prevention of β-hydride elimination. One important advantage is their ability to reduce the necessary agostic interactions between the metal and the neighbouring β-hydrogens[24] in two ways: 1) by acting as an inductively electron withdrawing group, thus reducing the electron density of the β-hydrogens and 2) by coordinating to the metal centre, which reduces the electron deficiency of the metal. Coordination to the metal centre also has the added benefit of potentially inhibiting *syn*-β-hydride elimination by restricting the conformation of the organometallic intermediate. Due to the lack of a coordinating group to boron, however, this coupling proceeds with the usual retention of configuration (Figure 1-3b).

In 2011, the Hall Group developed a chemoselective and stereospecific cross-coupling of optically enriched 3,3-diboronyl carboxyesters **1-50** (Figure 1-4b).[25] It was previously shown by Shibata and co-workers that achiral 1,1-diboronyl compounds[26] are capable of undergoing chemoselective cross-coupling resulting only in mono-coupled products.[27] It has been suggested that one boronyl unit serves as an activator for the cross-coupling of the second boronyl unit via stabilization of the transient α-B-Pd(II) intermediate. In this regard, Hall and co-workers proposed that optically pure 3,3-diboronyl carboxyesters could be cross-coupled in a chemoselective and stereospecific fashion. Their efforts led to the first report of the synthesis of optically enriched diboronyl compounds **1-49**, prepared by a Cu-catalyzed conjugate addition process using the chiral ligand (*R*)-(*R*)-Walphos(CF_3) (Figure 1-4a).[25]

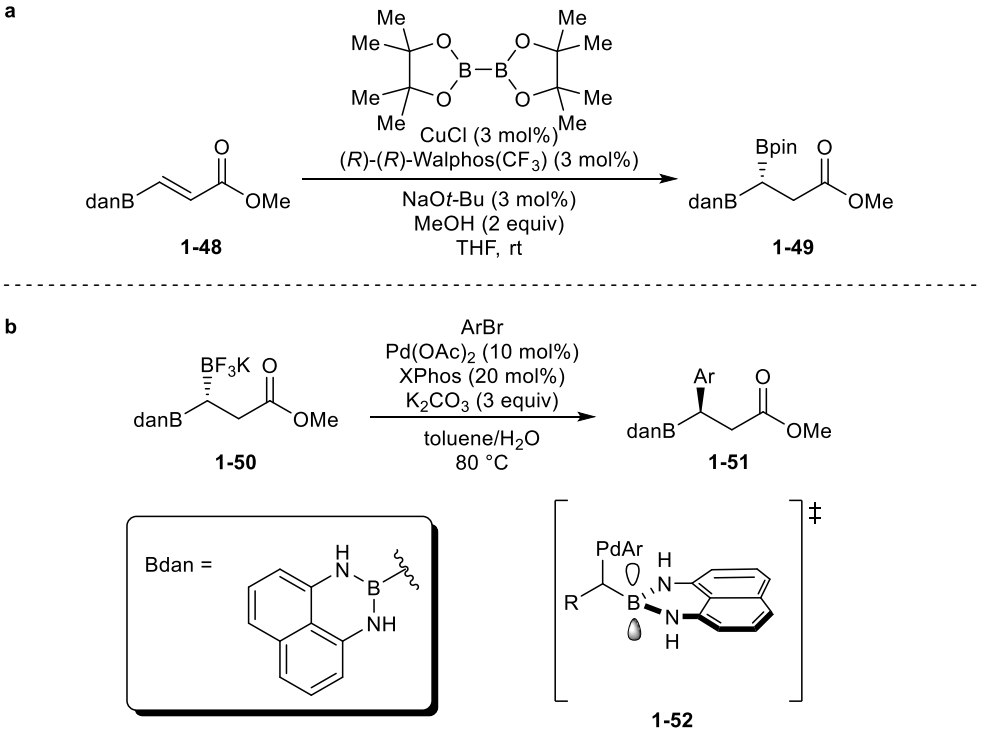
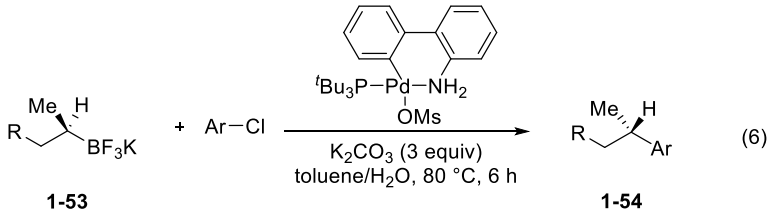


Figure 1-4. (a) Copper-catalyzed synthesis of optically enriched 3,3-diboronyl carboxyesters. (b) Chemo- and stereoselective cross-coupling of 3,3-diboronyl carboxyesters.

These enantioenriched 3,3-diboronyl carboxyesters were then cross-coupled chemoselectively with various aryl and alkenylbromides with high stereoselectivity by first transforming the boron pinacolate **1-49** to the corresponding trifluoroborate **1-50** (Figure 1-4b). The cross-coupling process benefits from two modes of stabilization: (1) coordination of the carbonyl oxygen to the

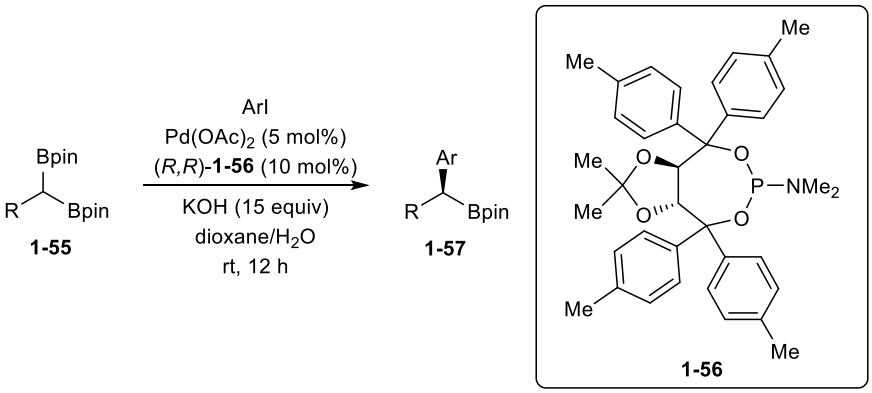
boron atom and (2) stabilization of the α-B-Pd(II) intermediate by the second boronyl unit **1-52**, both of which are thought to assist in the transmetalation process. Predictably, as in the Suginome and Molander studies, the cross-coupling occurs with overall inversion of stereochemistry due to the coordination of the carbonyl oxygen to the boron atom.

More recently, Biscoe and co-workers reported the successful stereoinvertive cross-coupling of secondary alkyltrifluoroborate salts. Remarkably, this system required neither a coordinating group nor a benzylic boronate for a successful coupling to occur (equation 6).[28]



(6)

In 2014, the Morken Group reported the successful cross-coupling of 1,1-diboryl compounds of type **1-55** to give optically enriched organoboronates by using a chiral catalyst (equation 7).[29] In this catalytic, enantioselective desymmetrization process, the optimal ligand was found to be TADDOL-derived phosphoramidite **1-56**. The cross-coupled products were obtained in moderate to good yields and *ee*. Using isotopic boron labelling experiments, the authors determined that transmetalation is stereospecific and likely the stereodetermining step in the reaction mechanism.

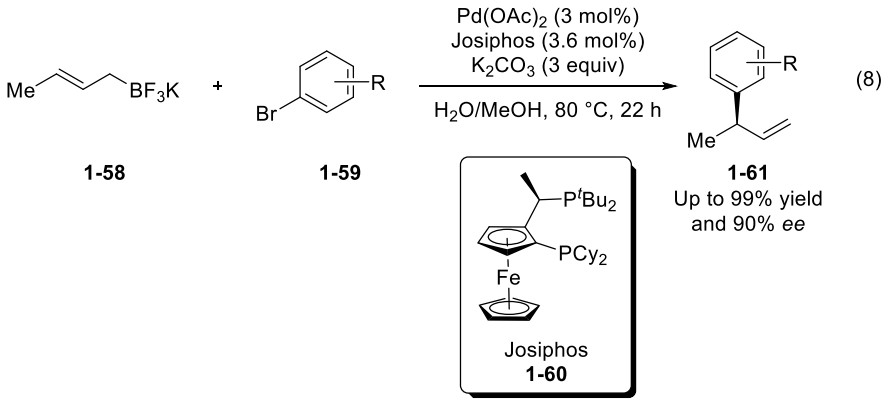


(7)

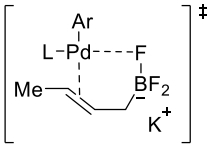
1.2.2 Stereoselective couplings of allylic boronates with aryl or alkenyl halides

The cross-coupling of allylic boronates has, in addition to stereoselectivity, the added challenge of regioselectivity leading to two possible regioisomers. Regioselectivity is often controlled by the

steric and electronic properties of the allylic substrate and attempts to invert the intrinsic preference of the substrate can be extremely challenging. Nevertheless, progress has been made in the cross-coupling of allyl boronic acids and their derivatives. The first report of an asymmetric cross-coupling of an allylic boronate came from Miyaura and co-workers in 2006, where allylic trifluoroborate **1-58** was reacted with aryl bromide **1-59** in the presence of $Pd(OAc)_2$ and (R,S)-Josiphos **1-60** to selectively give the branched product **1-61** in up to 99% yield and 90% *ee* (equation 8).[30] Mechanistic studies[31] revealed transmetalation as the likely enantiodetermining step. Thus, during the S_E2' transmetalation of the allylic boronate, the chiral catalyst preferentially selects one of the prochiral faces of the boronate. In order to account for the high degree of selectivity observed for the branched product, the authors propose that the reaction proceeds through transition state **1-62**, resulting from the coordination of the double bond in **1-58** to the oxidatively inserted palladium intermediate (Figure 1-5).



Proposed transition state for observed γ-selectivity:

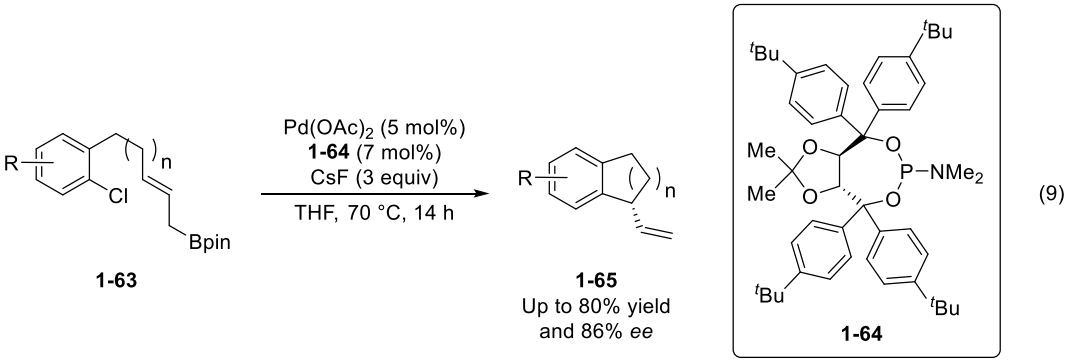


1-62

Figure 1-5. Regio- and stereoselective intermolecular cross-coupling of allylic trifluoroborates with aryl bromides

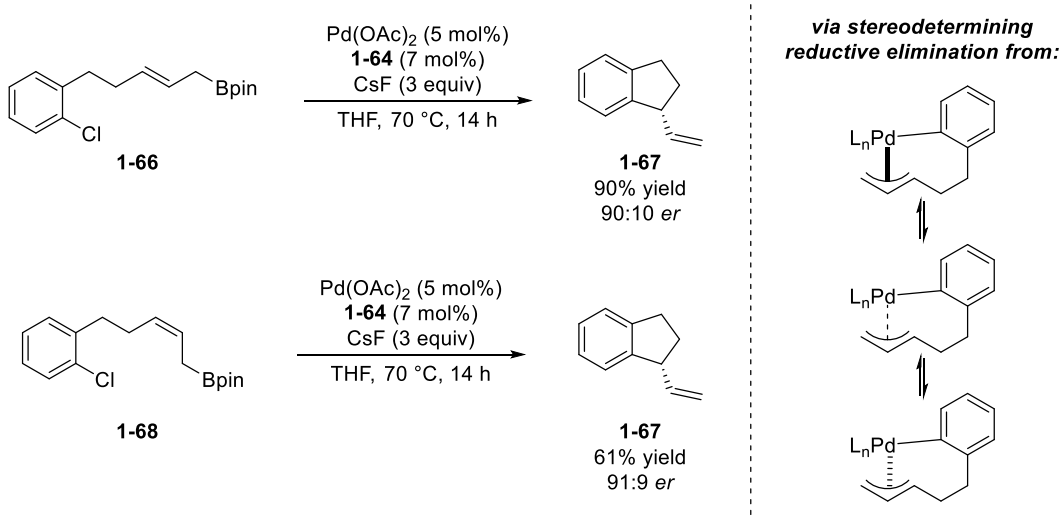
In the same vein, Morken and co-workers reported an intramolecular variant of asymmetric allylic boronate coupling.[32] The enantioselective carbocyclization of **1-63** was accomplished by employing $Pd(OAc)_2$ and phosphoramidite **1-64** as the chiral ligand, furnishing products of type

1-65 in up to 80% yield and 86% *ee* (equation 9). The length of the tether between the aryl electrophile and the allyl boronate could also be increased to form the corresponding 6- and 7-membered carbocycles in modest yields and selectivities.



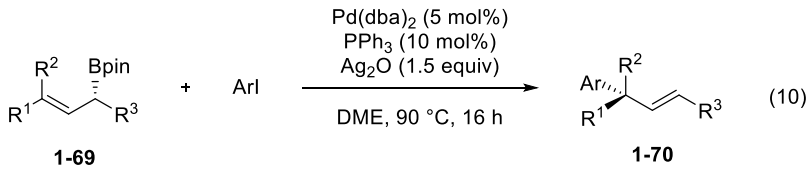
(9)

In an attempt to identify the origin of stereoinduction, both the *E*- and *Z*-allyl boronates, **1-66** and **1-68** respectively, were subjected to the reaction conditions. It was found that in both cases, the product was formed with similar levels of selectivity (Scheme 1-6). Moreover, when the polarities of the coupling partners were inversed, the selectivities achieved were again similar. These results suggest that the process proceeds stereoconvergently through a common palladacycle intermediate, likely via allyl equilibration of the transmetalation product, followed by stereodetermining reductive elimination to give the optically enriched cyclization product.



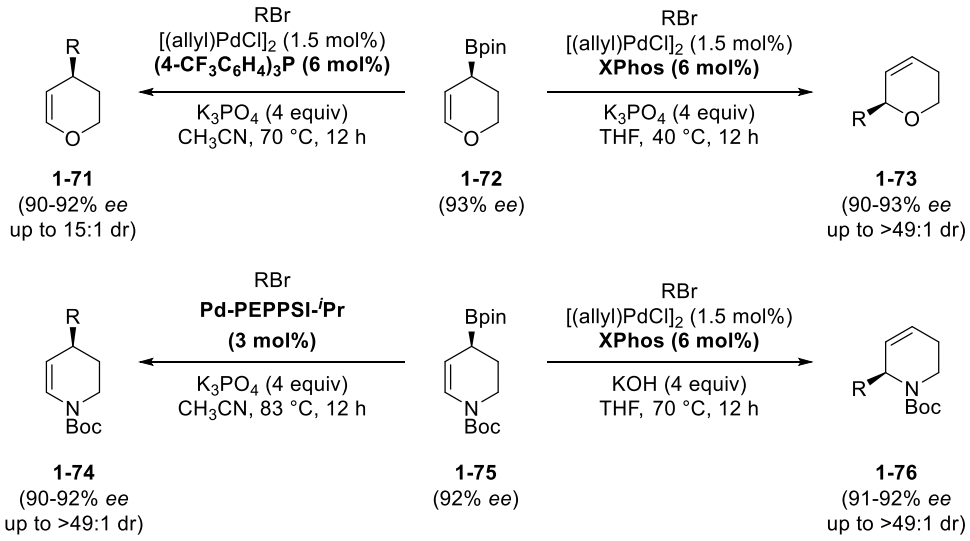
Scheme 1-6. Evidence for a stereoconvergent pathway in the asymmetric intramolecular cross-coupling of allylic boronates.

Recently, efforts have been directed towards the stereoselective cross-coupling of optically enriched allylic boronates. In 2013, Crudden and Aggarwal reported the enantio- and regioselective Suzuki-Miyaura cross-coupling of secondary allylic boronates to give the corresponding branched product in excellent yield and *ee* (equation 10).[33] Mechanistic studies showed that the regio- and stereoselectivity of the process is likely due to a *syn*-S_E' intramolecular transmetalation step.



(10)

In 2014, Hall and co-workers described a regio- and stereospecific Suzuki-Miyaura cross-coupling of heterocyclic allylic boronates.[34,35] Given the prevalence of heterocycles in pharmaceuticals, this selective coupling represents a conceptually novel way of synthesizing structural scaffolds relevant to drug discovery with an unprecedented level of regio- and stereocontrol. It was found that by changing the palladium catalyst system, independent access to both regioisomers of the cross-coupled product could be obtained. A wide scope of aryl and alkenyl halides were successfully reacted with dehydropyranyl boronate **1-72** and dehydropiperidyl boronate **1-75** to give the corresponding products, with either α- or γ-selectivity, in excellent yields, enantiomeric excess, and regioselectivities (Scheme 1-7).



Scheme 1-7. Stereodivergent enantioselective Suzuki-Miyaura cross-couplings of heterocyclic allylic boronates.

This method was successfully applied towards the concise syntheses of two pharmaceutical agents: (+)-anabasine (a nicotinic acetylcholine receptor agonist) and (+)-paroxetine (an anti-depressant) (Figure 1-6).

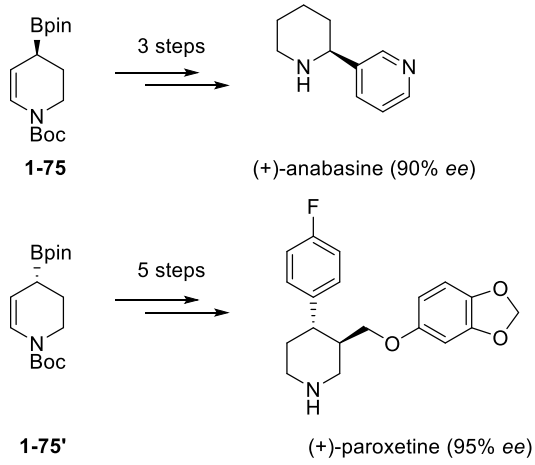


Figure 1-6. Heterocyclic allylic boronates as synthetic precursors to pharmaceutical agents.

1.2.3 Stereoselective couplings of alkyl halides and pseudohalides with aryl or alkenyl boronates

Stereoselective Suzuki-Miyaura cross-coupling reactions of stereodefined sp^3 alkyl halides is a new and valuable synthetic strategy with great potential in the formation of saturated C−C bonds. In order to explore the feasibility of stereoselective Suzuki-Miyaura cross-coupling reactions, Asensio and co-workers first examined diastereoselective variants using configurationally defined α-bromosulfoxides **1-77** as substrates (equation 11, Figure 1-7).[36] Using this method, either enantioenriched or racemic *syn*-α-bromosulfoxides **1-77** could be cross-coupled with arylboronic acids, to furnish α-arylsulfoxide **1-78** with inversion of stereochemistry at the stereogenic α-carbon center. Cross-coupling reactions of this class of compounds afforded products with only moderate yields due to side reactions such as protodehalogenation and β-hydride elimination. The inversion of stereochemistry observed at the α-carbon can be explained based on the expected mechanistic course of the cross-coupling process. While oxidative addition of sp^3 alkyl bromides proceeds with inversion of stereochemistry (see Section 1.1.2), transmetalation and reductive elimination both feature retention of stereochemistry, leading to the observed products with an overall inversion of stereochemistry. Interestingly, in contrast to *syn*-α-bromosulfoxide **1-77**, *anti*-α-bromosulfoxide **1-79** failed to cross-couple with aryl boronic acids, implying the important influence of a stereogenic center at the sulfur atom (equation 12, Figure 1-7). The authors rationalized this result by assuming that *syn*-α-bromosulfoxides **1-77** would preferentially adopt a preferred conformation **1-80**. In this conformation, the lone electron pair lies *anti* to the bromide, thus allowing the Pd-catalyst to approach the substrate from a S_N2-like trajectory during the oxidative addition step. With this model, the *anti*-α-bromosulfoxide **1-79** would have difficulty adopting this specific orientation due to the gauche interaction between the methyl and the phenyl groups in conformation **1-81**.

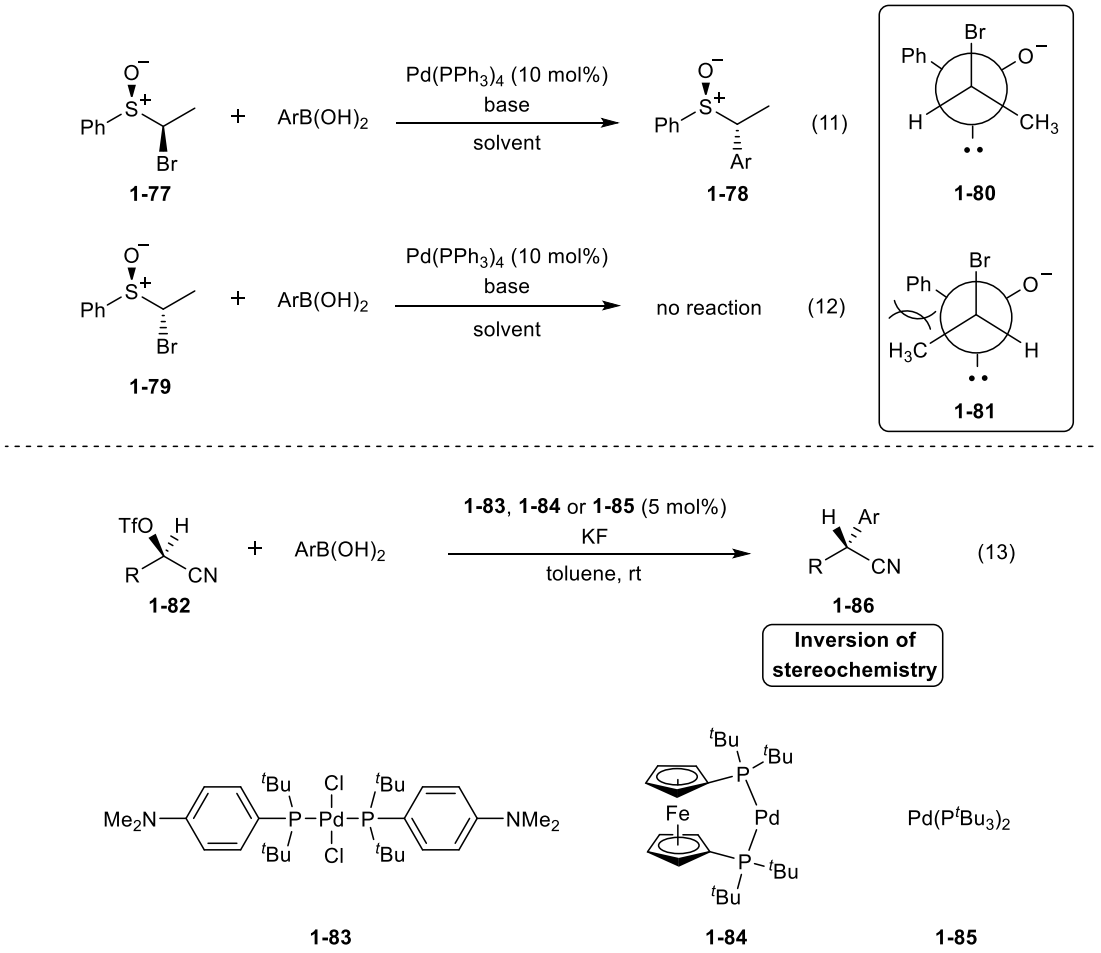


Figure 1-7. Stereoselective Suzuki-Miyaura cross-couplings of stereodefined alkyl halides.

In 2010, Falck and co-workers conducted stereospecific Suzuki-Miyaura cross-coupling reactions with enantioenriched α-cyanohydrin triflates **1-82** (equation 13, Figure 1-7).[37] This substrate class was chosen because nitriles are a versatile functional group, which can also act as electron-withdrawing groups to facilitate the key oxidative addition step. By employing enantiomerically enriched α-cyanohydrin triflates **1-82** under the optimized conditions, the authors found that various α-aryl nitriles **1-86** could be produced with inversion of stereochemistry. The stereochemical outcome can be explained as outlined in Section 1.1.2.

Because of the limited availability and potential instability of chiral secondary alkyl halides and triflates, there has been interest in the identification of alternative electrophiles for use in stereoselective cross-coupling reactions of organoboron derivatives. Based on the precedent of using arylammonium salts as cross-coupling partners in nickel-catalyzed sp^2–sp^2 Suzuki-Miyaura

cross-couplings,[38] Watson and co-workers developed a mild and effective variant involving benzylic trimethyl ammonium salts **1-87**.[39] Careful optimization of reaction conditions led to a stereospecific preparation of diarylethane compounds **1-88** from optically enriched secondary benzylic amines as stable precursors (equation 14, Figure 1-8). The nature of the ligand was found to bear a significant influence on the chirality transfer, with tri-*o*-tolylphosphine and *t*-butyl-XantPhos providing the highest level of enantioselectivity. While various benzylic ammonium substrates can be employed, naphthyl ammonium salts provide higher yields of products. The reaction was found to be general with respect to the boronic acid and tolerates various common functional groups such as aryl ethers, esters, nitrile, amides, sulfones, and fluoride. Alkenylboronic acids are suitable substrates that provide coupling products with high enantiomeric purities, however in lower yields compared to arylboronic acids. Likewise, one example of heteroaromatic boronic acid, quinolineboronic acid, only afforded a low product yield.

Based on limited mechanistic studies, a catalytic cycle was proposed whereby the electron-rich Ni(0) catalyst undergoes oxidative addition into the ammonium benzylic C–N bond with inversion of stereochemistry to provide a configurationally stable η^3 benzylic Ni(II) complex. This step is followed by a stereochemically retentive transmetalation with the boronic acid, then reductive elimination, a mechanistic step well-precedented to occur with retention of stereochemistry. The resulting diarylethane products **1-88** are formed by overall inversion of configuration and are isolated in up to 99% enantiomeric excess. Recently, Watson and co-workers reported an improved procedure with a phosphine-free catalyst that provides an expanded reaction scope including heteroaromatic boronic acids.[40]

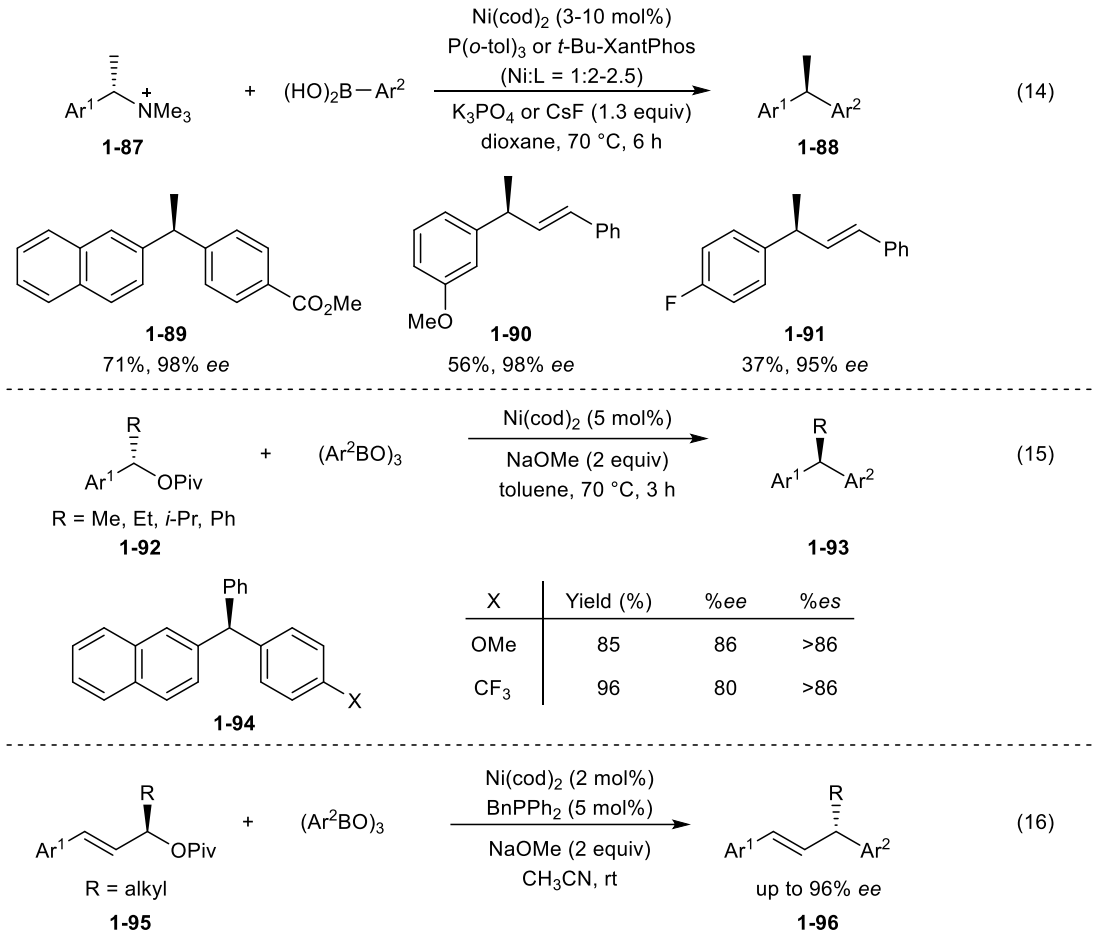


Figure 1-8. Nickel-catalyzed stereospecific coupling of benzylic and allylic electrophiles.

The same group reported the use of chiral secondary benzylic pivalates **1-92** in stereoselective Suzuki-Miyaura cross-couplings with arylboroxines (equation 15, Figure 1-8).[41] By making use of sodium methoxide as the optimal base and phosphine-free conditions, the nickel-catalyzed couplings afforded the corresponding diarylalkane and triarylmethane products **1-93** with modest to high retention of optical purity. Like the ammonium salts described above, overall inversion of stereochemistry is also observed with these trimethylacetic esters. Interestingly, arylboroxines were found to afford higher yields of products with superior enantiospecificity compared to the use of the corresponding arylboronic acids. As demonstrated with control experiments, the presence of water is detrimental to the reaction, thus explaining the advantage provided by the use of boronic anhydrides as a dry form of boronic acids. Although the reaction is limited to 2-naphthyl substituted secondary alkylpivalates (a single example of a benzylic pivalate led to a lower yield of 33%), it displays a wide scope of suitable arylboroxines in the formation of diarylalkane

products. Triarylmethane compounds can be obtained in high yield from coupling of the corresponding diaryl methanol esters, however with significant erosion of optical purity. Using similar conditions, allylic pivalates **1-95** can also be used as substrates to produce the cross-coupled products **1-96** with high regioselectivity and stereochemical fidelity (equation 16, Figure 1-8).[42] The observed selectivities could potentially be due to a two-electron, S_N2-like oxidative addition step between the nickel catalyst and the electrophilic coupling partner.

1.3 Stereoselective C(sp^3)–C(sp^3) Suzuki-Miyaura cross-coupling reactions

Since the seminal report by Suzuki and Miyaura in 1992 on the successful cross-coupling of primary alkyl iodides with alkyl boranes,[43] very little progress was made in the following years in the area of alkyl-alkyl couplings[44] due to the numerous challenges associated with these processes (see Section 1.1.1). In recent years, Fu and co-workers have been the key players in the development of C(sp^3)–C(sp^3) couplings. By using a nickel catalyst in conjunction with a chiral amine ligand, Suzuki-Miyaura cross-couplings of racemic alkyl halides with alkyl boranes may be achieved with high enantioselectivities. The key feature leading to the success of this reaction lays in the use of nickel as the catalyst in place of palladium. First-row transition metals such as nickel are more prone to undergo oxidative additions by one-electron mechanisms, whereas lower elements like palladium tend to proceed through two-electron processes. The factors leading to reaction *via* a radical or two-electron process is dependent not only on the metal, but also the substrate. Unlike Watson's cross-couplings of alkyl ammonium salts and pivalates (Section 1.2.3), Fu made use of alkyl bromides and chlorides as their choice electrophiles. In this case, the electrochemical potential between the nickel catalyst and the electrophile is high enough for a radical process to occur. As a result, the racemic alkyl halides are converted to prochiral alkyl radicals from which enantiomerically enriched products may be obtained through chiral information provided by the chiral catalyst. Through this strategy, the Fu group has developed a range of successful alkyl-alkyl Suzuki-Miyaura cross-couplings.

1.3.1 Stereoselective couplings of alkyl boranes with alkyl halides

The first enantioselective cross-coupling of unactivated racemic secondary alkyl bromides with organoborane reagents was first reported by Fu and co-workers in 2008.[45] Until this breakthrough, stereoselective cross-couplings of this type were limited to substrates bearing activated electrophiles, such as allylic and benzylic halides or α-halocarbonyl compounds. In the presence of $Ni(cod)_2$ and chiral diamine **1-98**, the cross-coupled products were obtained with good enantioselectivity (equation 17, Figure 1-9). The selectivity of the reaction was found to be dependent on the presence and proper placement of the aromatic group on the electrophile (equation 18, Figure 1-9). It was proposed that this phenomenon was due to coordination of the aromatic group to the Ni catalyst during the enantiodetermining step. This coordination allows for successful stereoinduction from the metal-bound chiral ligand.

During these studies, it was noted that lower enantioselectivities were achieved with ether containing substrates. Fu and co-workers speculated that these observations could be due to coordination of the ether oxygen to the Ni catalyst and that this result could be exploited to develop a method for the cross-coupling of oxygenated unactivated electrophiles **1-102** (equation 19, Figure 1-9).[46] Over the years, the same group has developed a number of methods for the coupling of unactivated electrophiles employing a variety of coordinating groups, including nitrogen,[47] amides,[48] and carbamates.[49] The scope of these processes have also been expanded to include secondary alkyl chlorides as well as aryl boranes, aryl boronates, and secondary alkyl boranes. In all cases, the coordinating ability of the heteroatom on the electrophile is essential to the stereochemical outcome of the reaction.

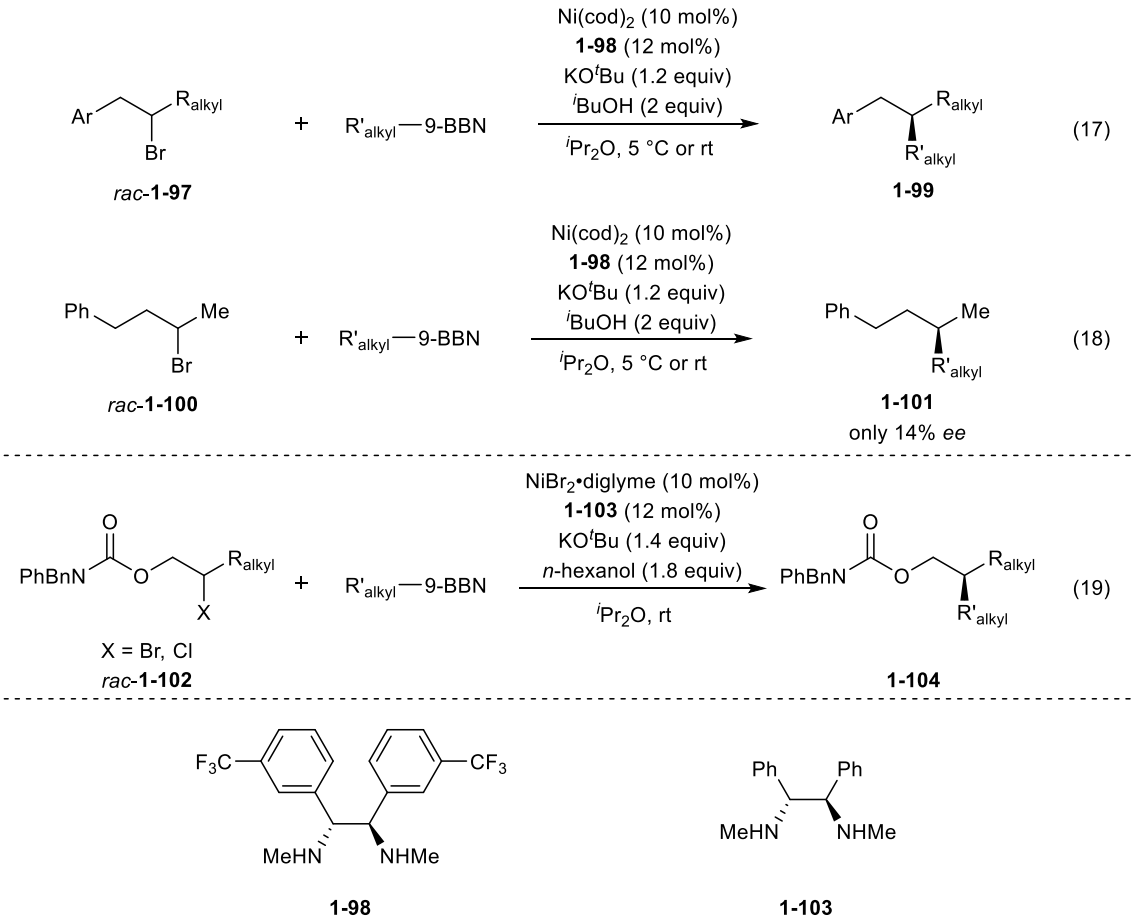
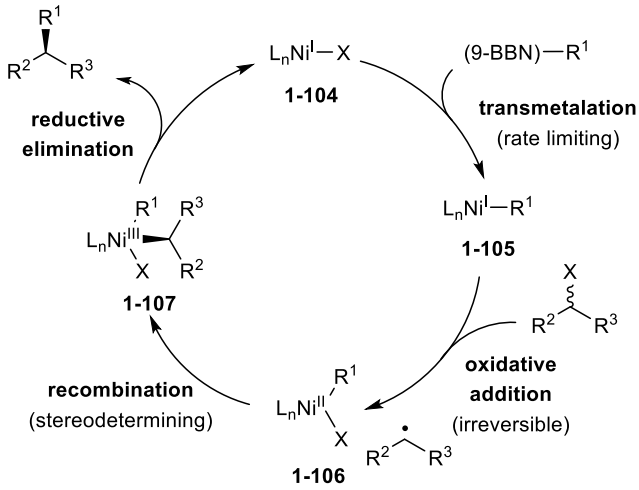


Figure 1-9. Stereoconvergent Suzuki-Miyaura cross-coupling reactions of alkyl halides with alkyl boranes.

The stereoselectivity of these reactions stems from a stereoconvergent mechanism in which the oxidative addition step proceeds through a radical process. As a result, the initial stereogenic centre of the racemic electrophilic coupling partner is lost at the oxidative addition step and the stereochemical outcome of the reaction is determined solely by the chiral catalyst during the recombination step. Kinetic studies showed that the rate law is first order in the catalyst and the organoborane, but zeroth order in the electrophile, which is consistent with a turnover-limiting transmetalation step.[47] Monitoring the reaction of optically pure alkyl halide showed no erosion of *ee* of the electrophile over time, suggesting an irreversible oxidative addition step.[48] Based on these findings, the following catalytic cycle may be proposed (Scheme 1-8): first, rate-limiting transmetalation of the organoborane with the Ni(I) catalyst occurs to give **1-105**, which may then undergo an irreversible oxidative addition into the alkyl halide to give catalytic intermediate **1-106**

and an alkyl radical. The alkyl radical and **1-106** may then undergo recombination to give Ni(III) species **1-107**. This recombination process occurs with stereoselectivity by virtue of the asymmetric environment provided by the chiral ligand "L". Subsequent reductive elimination with retention of stereochemistry gives the cross-coupled product and regenerates the Ni(I) catalyst.



Scheme 1-8. Proposed catalytic cycle of Ni-catalyzed stereoconvergent Suzuki-Miyaura cross-coupling reactions.

1.4 Thesis objectives

Since its original discovery in 1979, the Suzuki-Miyaura cross-coupling has continued to receive significant interest from both academic and industrial chemists due to its tremendous potential in $C(sp^2)$–$C(sp^2)$ bond formation. With the recent advances made in stereoselective cross-coupling reactions for the formation of stereogenic centers, the value of this synthetic method has increased even further.

Nevertheless, there is still much to be explored in this area of cross-coupling. Recent breakthroughs notwithstanding, the Suzuki-Miyaura reaction is still by no means a fully matured method. Cross-coupling of aliphatic substrates, in spite of recent developments, is still in its infancy in terms of its applications to organic synthesis. The main objective of this thesis is to

develop stereoselective cross-coupling methods of alkylboronates for the generation of new stereogenic centres.

In light of recent advances in the area of stereospecific cross-coupling of optically enriched secondary organoboronates, Chapter 2 presents the stereospecific cross-coupling of optically enriched 1,1-diboryl Weinreb amides and the derivatization of the cross-coupling products. Attempts at performing an iterative cross-coupling sequence also shed light on the roles of the coordinating group of the Weinreb amide and the second boryl unit in the first coupling event.

As a progression from the cross-coupling of optically enriched organoboronates, an asymmetric cross-coupling of prochiral *gem*-diboronylalkanes was also investigated. Chapter 3 will present a detailed study on ligand optimization and observations of the effect of ligand structure on the selectivity of the reaction. Mechanistic studies addressing the role of the base and water in the reaction will also be discussed. With this combined knowledge on the cross-coupling process, a reliably scalable process (up to 1 gram of diboryl substrate) was developed.

From the development of an asymmetric cross-coupling of prochiral 1,1-diboryl compounds, it was envisioned that a logical progression would be to study 1,1,1-trifunctionalized substrates and their potential use in the generation of complex stereogenic centres. To this end, Chapter 4 presents the attempts made towards the synthesis of 1,1,1-triboryl and 1,1,1-diborylsilyl compounds. Initial attempts in the chemoselective functionalization of the 1,1,1-diborylsilyl compounds will also be discussed.

1.5 References

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Chapter 2
Enantio- and Chemoselective Cross-Coupling of Optically Enriched 1,1-Diboron Compounds[†]

2.1 Introduction

The challenges associated with the coupling of alkyl boronic acids includes a variety of undesirable side reactions, including β-hydride elimination and protodeborylation (Chapter 1). One strategy to circumvent this problem has been to enhance the stability of the boronic acid by transforming it into the corresponding boronic ester. While this approach improves the robustness of the boron reagent, it also causes a significant decrease in the Lewis acidity of the boron center, due in large part to increased steric hindrance. The result is a lower rate of transmetalation.

In 2010, Shibata and co-workers reported a study on the cross-coupling of 1,1-diboronylalkanes (Figure 2-1a).[1] Since boron is known to help stabilize α-anions through its empty p-orbital, it was believed that the presence of the second boronate in this class of compounds greatly enhances the Lewis acidity of the first boronate, thus allowing for facilitated transmetalation. Support for this proposal was gained through NMR studies of various organoboronates under basic aqueous conditions (i.e. in the presence of KOH) (Figure 2-1b). When diboronylalkane **2-1** was subjected to KOH, ^{11}B NMR analysis showed significant borate formation. In contrast, when one boronic ester was replaced by either a hydrogen (**2-3**) or a trimethylsilyl group (**2-4**), no borate formation was observed. Furthermore, when one of the boron groups was shifted to the β-position (**2-5**), only trace amounts of borate was formed. These observations support the hypothesis that the second boronate imparts higher Lewis acidity upon the first. In addition to this experimental evidence, the authors also reported DFT evidence that indicates stabilization of organometallic intermediate **2-6** (the product of transmetalation of a 1,1-diboronylalkane with oxidatively inserted Pd(II)) by the empty p-orbital of the boronate (Figure 2-1c). These characteristics of 1,1-diboronylalkanes led to

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the development of a chemoselective Suzuki-Miyaura mono-cross-coupling reaction. This method was later modified and applied successfully towards the synthesis of various unsymmetrical diarylmethanes **2-8** (Figure 2-1d).

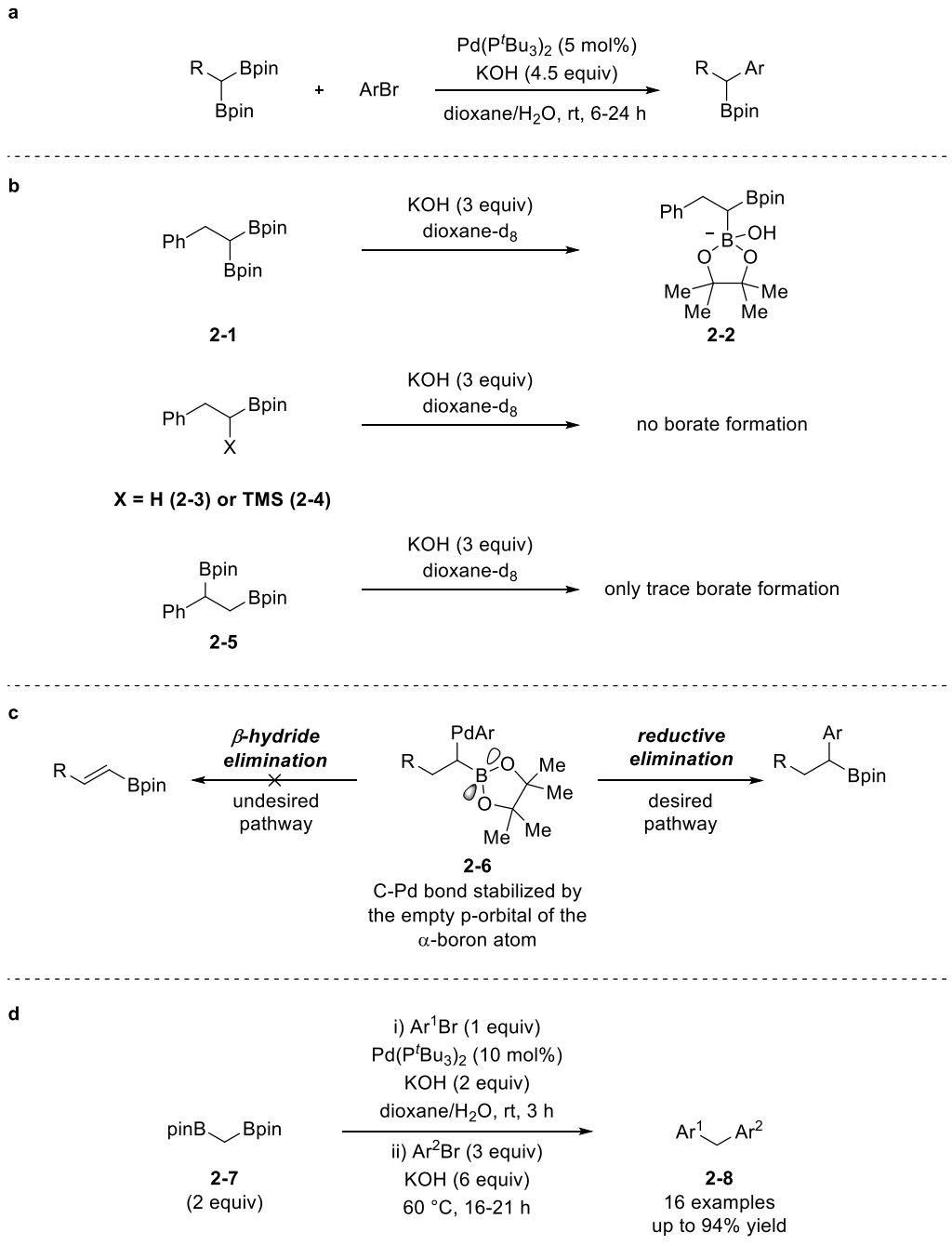
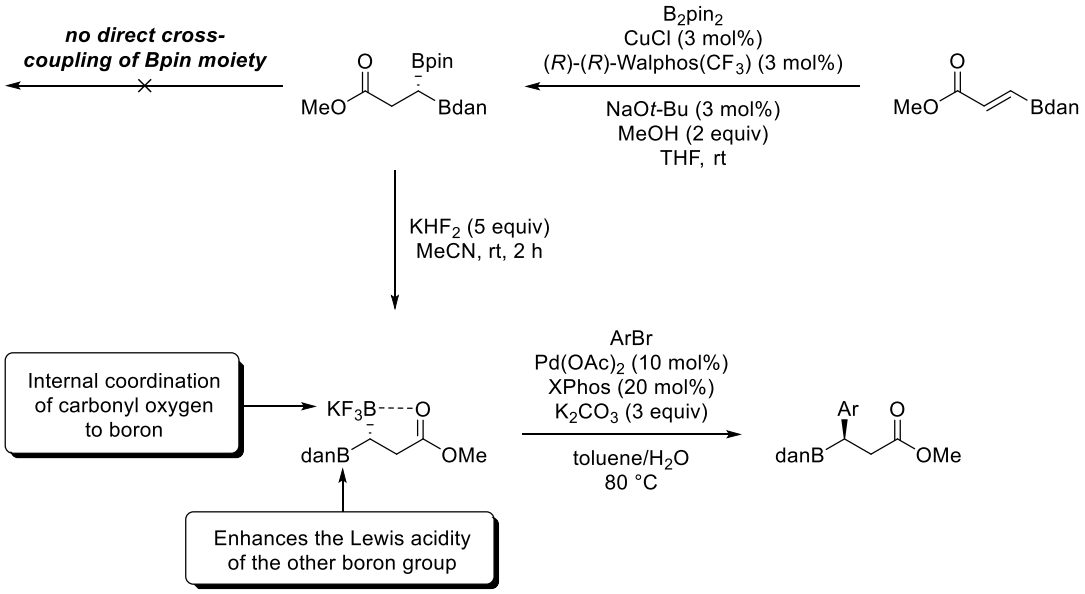


Figure 2-1. (a) Shibata's cross-coupling of 1,1-diboronylalkanes. (b) Studies on borate formation and the Lewis acidity of various organoboronates. (c) Stabilization of a cross-coupling

intermediate by an α-boronyl group. (d) Sequential Suzuki-Miyaura cross-coupling of 1,1-diboronylalkanes for the synthesis of unsymmetrical diarylmethanes.

Drawing inspiration from Shibata's work, the Hall group reported a chemo- and stereoselective Suzuki-Miyaura cross-coupling of chiral 3,3-diboronyl carboxyesters (Section 1.2.1).[2] This cross-coupling was made possible by facilitating transmetalation through two modes of activation: 1) using a second boron group to increase the Lewis acidity of the first, and 2) internal coordination of the carbonyl oxygen to the boronate (Scheme 2-1).



Scheme 2-1. Stereoselective cross-coupling of optically enriched 3,3-diboronyl carboxyesters.

One drawback of this method, however, is that cross-coupling requires prior conversion of a pinacol boronate to the corresponding trifluoroborate salt. Trifluoroborate salts are often used as a form of "masked" boronic acid, which may be released upon exposure to hydrolytic conditions.[3] As a result, the organometallic coupling partner, now the boronic acid, becomes more reactive towards transmetalation than the original, more hindered pinacol boronate. This requirement for the synthesis of a trifluoroborate salt causes the overall cross-coupling process to be less step economical. A more ideal scenario would involve the direct coupling of the pinacol boronate itself. It was believed that by increasing the Lewis basicity of the coordinating group in the substrate, stronger activation of the pinacol boronate through coordination effects could allow for its direct coupling. Thus, the coordinating group was modified from a carboxyester to various amides in

order to increase the strength of the O–B coordination, and it was found that, with slight modification to the reaction conditions, Weinreb amide **2-9** satisfactorily gave the cross-coupled product in both excellent yield and enantioselectivity. The reaction was found to tolerate a variety of functional groups on the aryl bromide coupling partner (Figure 2-2), including methyl, fluoro, chloro and methoxy groups (**2-10b-e**). Different substitution positions were also well tolerated (**2-10g-i**). Unfortunately, alkenyl halides were incompatible coupling partners and did not yield any of the desired secondary allylboronate under the optimized reaction conditions (**2-10j**).*

* Work performed by Jack Lee.

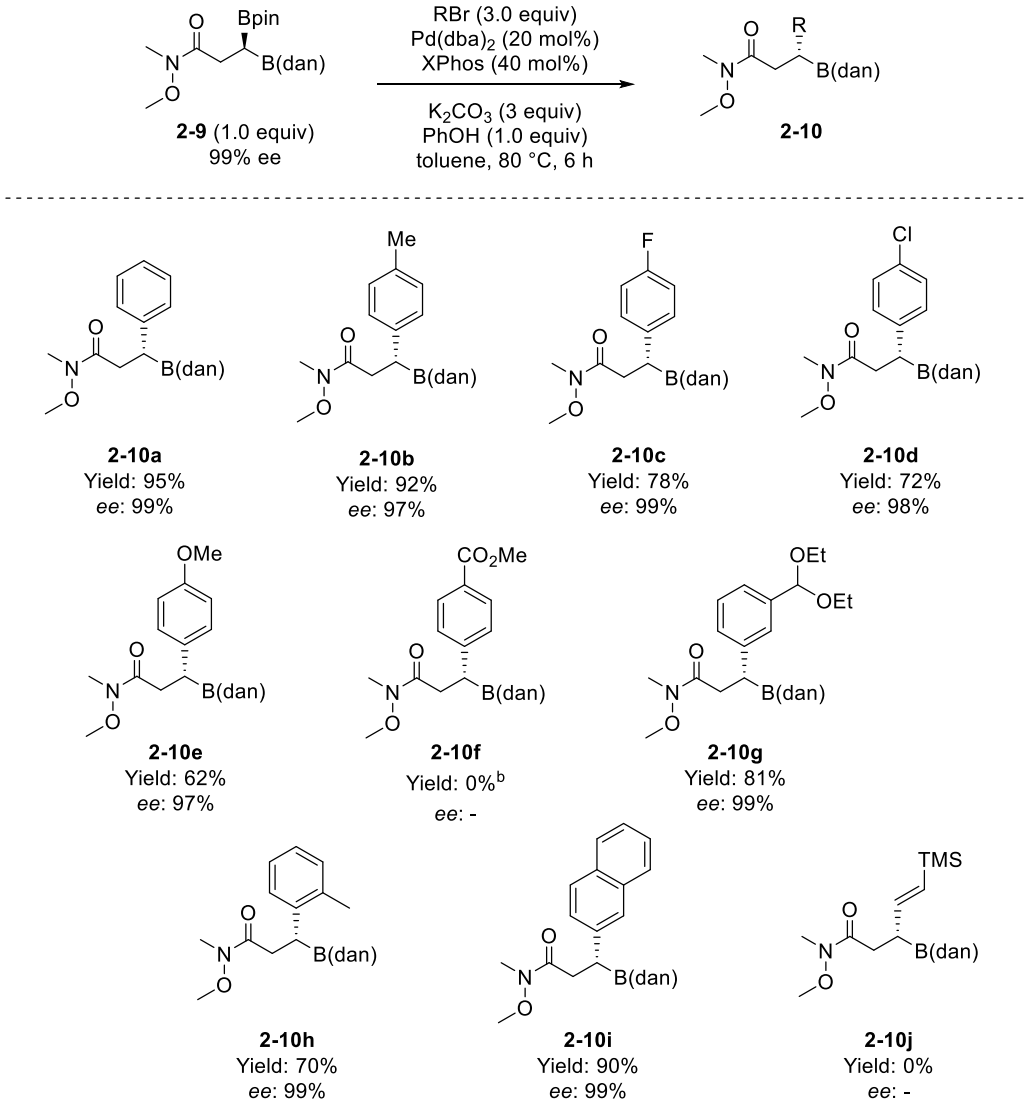
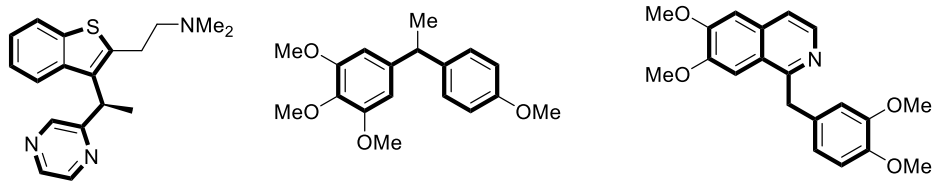


Figure 2-2. Scope of aryl bromides in the cross-coupling of optically enriched diboronyl compounds.

2.2 Objectives

Diarylmethanes have emerged as important motifs in many classes of pharmaceutically relevant compounds (Figure 2-3).[4] Given the successful development of reaction conditions for the direct coupling of pinacolboronate **2-9** by past Hall group member Jack Lee, reagent **2-9** may be seen as a precursor to this class of compounds and thus, in this chapter, methods allowing for the derivatization of this substrate, including a possible iterative cross-coupling of both boronyl units,

will be explored. The challenge in the coupling of the second boronate will lie in the diminished Lewis acidity of that boronate given there is no longer the presence of a second boronyl group at the α-position. Efforts will also be made in derivatizing the Weinreb amide moiety of the substrate as a demonstration of the synthetic versatility of this class of compounds. Since previous reports on the cross-coupling of similar substrates have been stereoinvertive, the stereochemical outcome of this process is also expected to be invertive. Without experimental evidence, however, one cannot exclude the possibility of a stereoretentive process. Thus, experimental verification of the stereochemical nature of this reaction will also be studied.

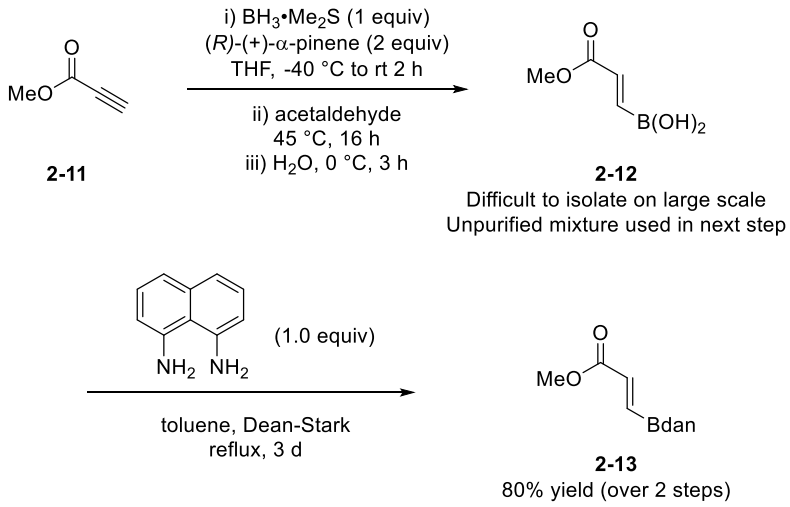


antihistamine activity | **antiviral activity** | **papaverine** (potential therapeutic use against psychosis & schizophrenia)

Figure 2-3. Pharmaceutically relevant compounds bearing diarylmethane backbones.

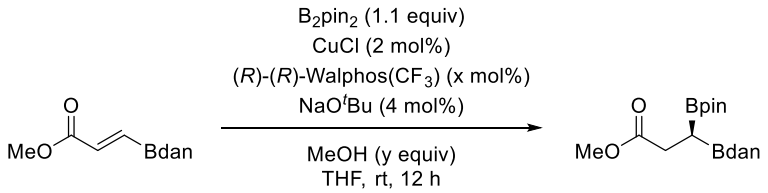
2.3 Synthesis of the required starting materials

Efforts began with the synthesis of the required optically enriched 3,3-diboronylamide **2-9**. Methyl propiolate was transformed into the desired (*E*)-1-alkenylboronic acid **2-12** through selective hydroboration using diisopinocamphenylborane (Scheme 2-2).[5] At large scale (10.0 grams of methyl propiolate), the boronic acid product proved difficult to isolate and was thus used as a crude mixture following oxidative workup with acetaldehyde in the subsequent esterification step. Following refluxing using a Dean-Stark apparatus in the presence of 1,8-diaminonaphthalene, the desired dan-protected boronate **2-13** was obtained in 80% yield.



Scheme 2-2. Synthesis of conjugate boronylation precursor **2-13**.

With boronate **2-13** in hand, the next step was to synthesize the optically enriched diboronyl compound via an asymmetric copper-catalyzed conjugate boronylation. When the reaction was performed under the originally published conditions,[2] the conjugate boronylation product was obtained in both decreased yield and *ee* when compared to the original published results (Table 2-1, entry 1). The cause for decreased efficiency of the reaction was thought to originate from the increased scale of the reaction (from 0.1 g of **2-13** to 1.0 g), leading to increased frequency of the competing background non-selective boronylation. Consequently, the ligand:Cu ratio was increased from 3:2 to 5:2 to promote the enantioselective process. With increased amount of ligand, the boronylated product was achieved in excellent *ee* (99%), however the yield was still found to be low (Table 2-1, entry 2). Modification of the stoichiometry of MeOH was thus explored. Methanol is known to be a crucial additive for rate enhancement of these types of conjugate boronylation. In their report of a copper-catalyzed addition of bis(pinacolato)diboron (B_2pin_2) to various α,β-unsaturated carbonyl compounds,[6] Yun and co-workers showed that even with no ligand present the reaction can proceed with high conversion in the presence of methanol. As a result, the influence of MeOH could have a detrimental effect on the selectivity of the reaction by promoting the non-selective background reaction. With this knowledge, portion-wise addition of excess MeOH was explored. After 12 hours reaction time, two more equivalents of MeOH was added followed by another 12 hours of stirring at room temperature. With this adjustment, the yield of the reaction could be improved to 86% while maintaining the *ee* at 99% (Table 2-1, entry 3).



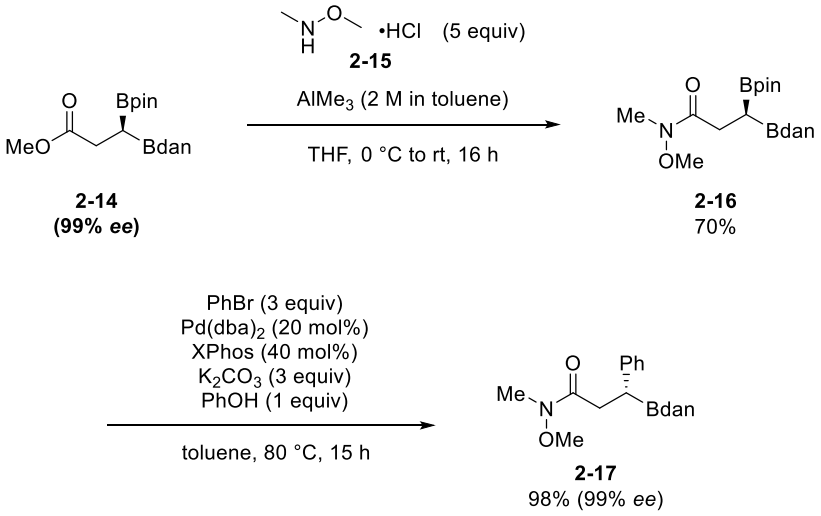
2-13 **2-14**

Entry	(*R*)-(*R*)-Walphos(CF_3) (x mol%)	MeOH (y equiv)	Yield (%)[a]	*ee* (%)[b]
1	3	2	45	40
2	5	2	45	99
3	5	4[c]	86	99

[a]Isolated yields. [b]Measured by chiral HPLC. [c]An initial 2 equiv of MeOH was added. After 12 hours, another 2 equiv of MeOH was added (for a total of 4 equivalents used) and the reaction was stirred for an additional 12 h.

Table 2-1. Optimization of the conjugate boronylation reaction for large scale preparation of optically enriched 3,3-diboronylesters.

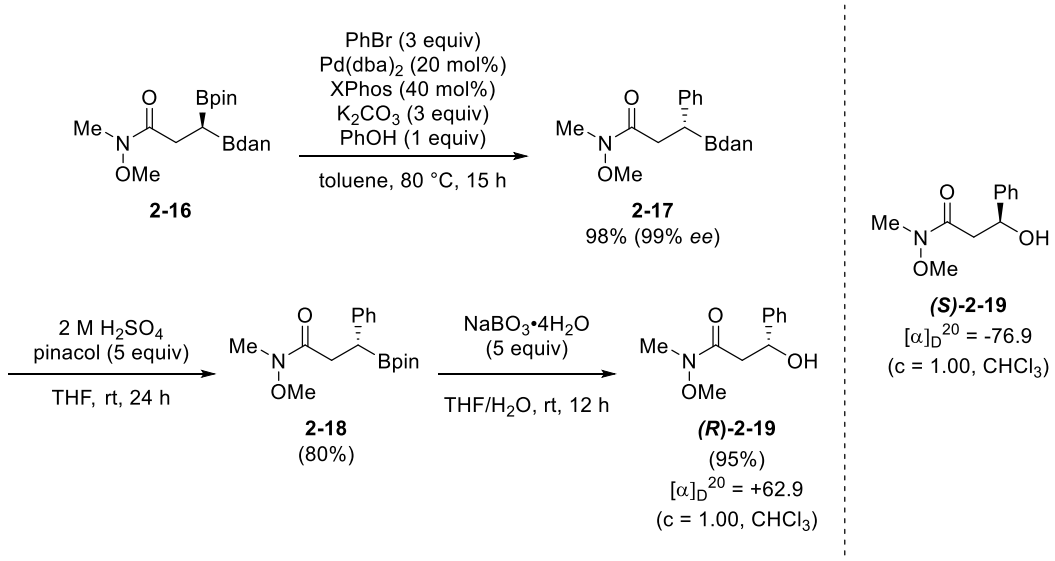
The next step was to convert the ester into the corresponding Weinreb amide, which was accomplished by treating ester **2-14** with $AlMe_3$ and **2-15** to give the desired product **2-16** in 70% yield. Finally, the direct cross-coupling of the pinacol boronate unit of **2-16** was performed on gram scale to produce the cross-coupled product **2-17** in 98% yield and 99% *ee* (Scheme 2-3).



Scheme 2-3. Synthesis of the Weinreb amide and subsequent direct coupling of the pinacol boronate.

2.4 Verification of the stereochemical course of the cross-coupling process

In order to demonstrate the stereochemical outcome of this reaction, efforts were made to derivatize compound **2-17** into a stereoisomer of known alcohol ***(S)*-2-19** (either the same stereoisomer, or the opposite isomer). It was envisioned that **2-17** could be transformed into the corresponding pinacol boronate **2-18**, which could then undergo oxidation to give the alcohol (Scheme 2-4). If cross-coupling of **2-16** is stereoretentive, then the alcohol product obtained should have the same stereochemistry as the known compound ***(S)*-2-19**.[7] If the process is stereoinvertive, then the opposite stereoisomer should be obtained. When the synthetic sequence was performed, the alcohol product was found to have an $[\alpha]_D^{20} = +62.9$ (c = 1.00, $CHCl_3$) for 99% *ee*, compared to ***(S)*-2-19**, which has an $[\alpha]_D^{20} = -76.9$ (c = 1.00, $CHCl_3$). Since the optical rotation values for the two compounds are of opposite signs, it was determined that the cross coupling of **2-16** proceeds in a stereoinvertive fashion.



Scheme 2-4. Experimental evidence for a stereoinvertive cross-coupling process.

2.5 Attempts at developing an iterative cross-coupling process

To access the desired diarylmethane scaffold, efforts were placed into performing a cross-coupling of the second boronyl unit. Since dan-protected boronates are known to be relatively inert under most cross-coupling conditions, the diaminonaphthyl group was exchanged with pinacol under acidic conditions to give the corresponding pinacol boronate (see Section 2.4). Direct coupling of the pinacol boronate was attempted under various conditions reported in the literature for stereospecific cross-coupling of optically enriched secondary organoboronates. Stereoretentive cross-coupling conditions for benzylic boronates reported by the Crudden group[8] was first applied, however it was found that very little conversion of starting material was achieved (Figure 2-4, equation 2). The NMR analysis of the crude product showed β-hydride elimination as a predominant pathway. When the conditions used in the initial cross-coupling of the first boronate was used, no conversion of the product was obtained (Figure 2-4, equation 3). Furthermore, using Suginome's conditions employing Zr(^{i}OPr)$_4$•^{i}PrOH as a Lewis acid activator[9] did not yield any of the desired cross-coupled product **2-20** (Figure 2-4, equation 4). The difficulty of this second cross-coupling emphasizes the importance of the Lewis acidity of the second boronyl group in the success of these Suzuki-Miyaura reactions.

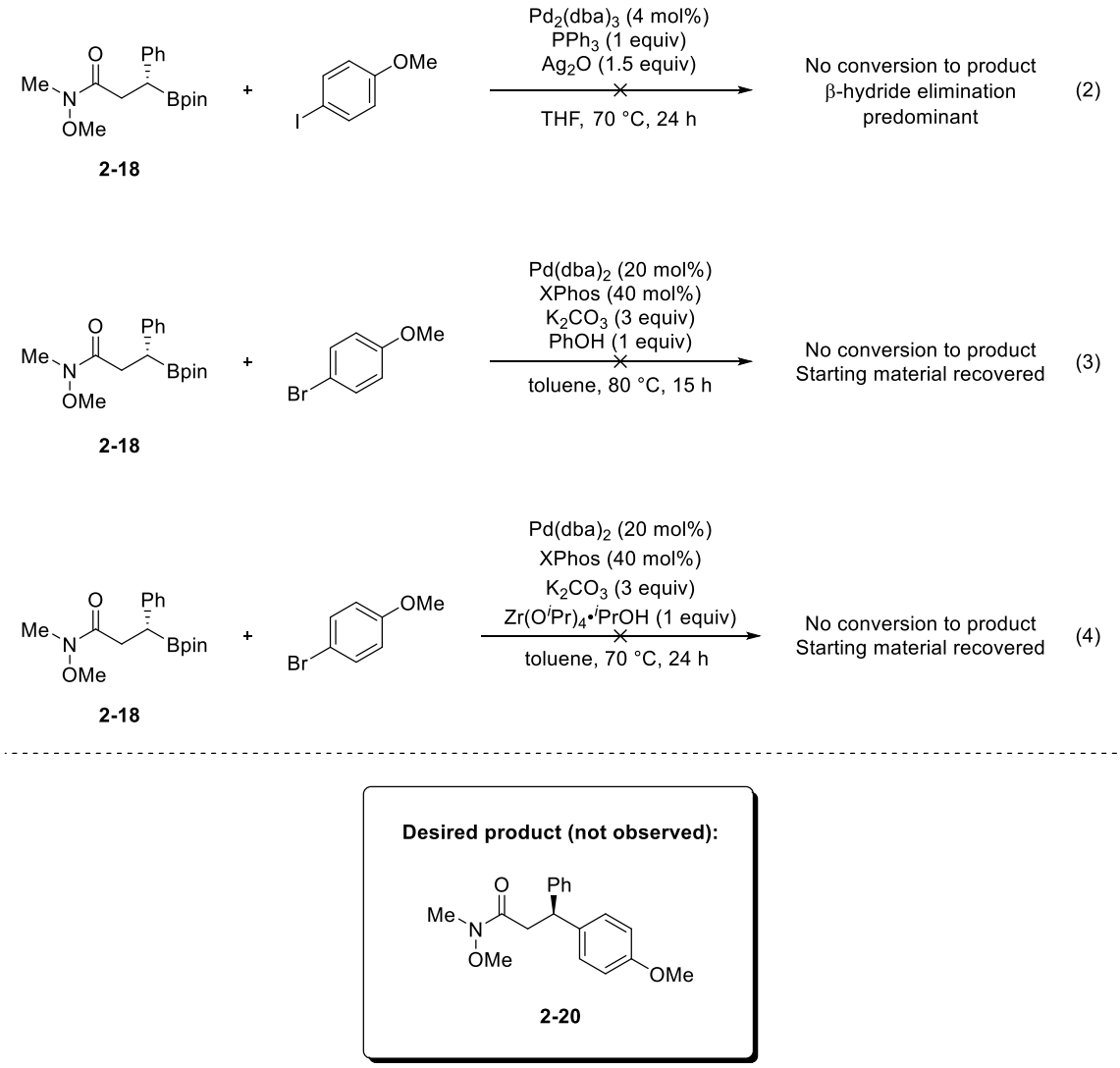
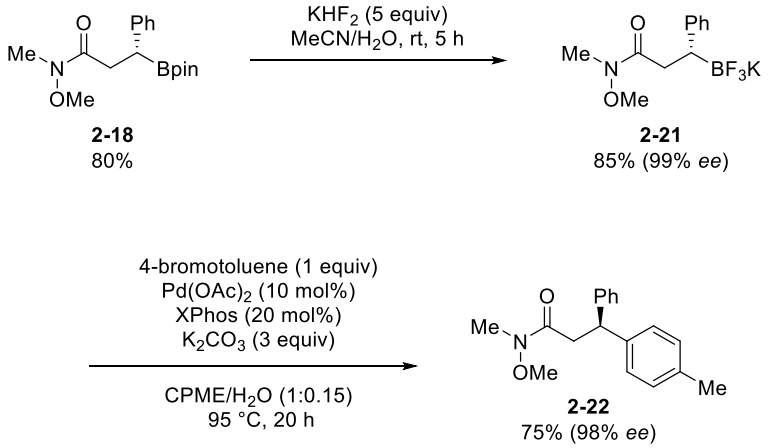


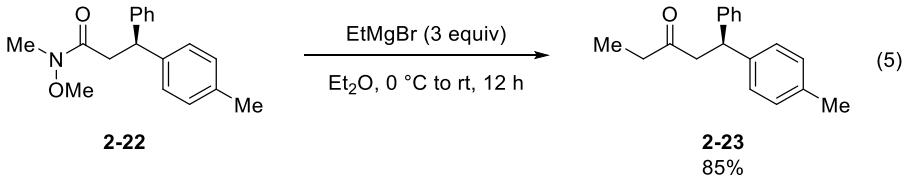
Figure 2-4. Attempts made at direct cross-coupling of the boron pinacolate group.

In an attempt to facilitate the second cross-coupling, the pinacol boronate was transformed into the corresponding trifluoroborate salt **2-21** (Scheme 2-5). The cross-coupling of **2-21** under a modified version of conditions reported by Molander and coworkers for the cross-coupling of α-trifluoroboratoamides[10] proceeded smoothly to provide diarylmethane **2-22** in 75% yield and 98% *ee*. Based on previous reports of similar cross-coupling processes,[2,10] the transmetalation presumably proceeded with inversion of stereochemistry due to the presence of the Weinreb amide coordinating group, however without experimental evidence, one could not completely rule out a stereoretentive process.



Scheme 2-5. Synthesis of diarylmethane compound **2-22**.

In addition to possible direct coupling of pinacol boronates, another advantage offered by Weinreb amide substrate **2-16** is the possibility of simple post-coupling modifications. As an example, following the second cross-coupling, Weinreb amide **2-22** was successfully transformed into the ethyl ketone **2-23** in 85% yield *via* addition of ethylmagnesium bromide (equation 5).



2.6 Summary

In summary, this chapter reports the successful derivatization of the cross-coupling product **2-18** into a diarylmethane compound – a relevant motif in various pharmaceutical compounds. Effort was also placed into the brief re-optimization of the asymmetric conjugate boronylation reaction to effectively give the desired cross-coupling substrate, optically enriched 3,3-diboronylester **2-14**, in good yield and excellent *ee* at a higher scale than the original report from our group.[2] Ligand:Cu ratio was found to be the essential factor in achieving good enantioselectivity, while the amount of MeOH used was found to play an integral part in the yield of the reaction. The presence of the Weinreb amide moiety on the substrate allows post-coupling modifications to be

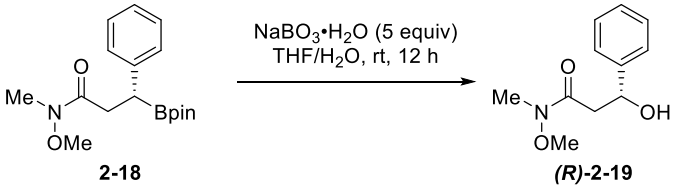
easily made. These applications highlight the versatility of chiral secondary alkylboronates and demonstrate the numerous synthetic possibilities associated with enantioenriched 1,1-diboronyl compounds.

2.7 Experimental

2.7.1 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 a solvent system prior to use. Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 plates. Visualization was accomplished by irradiation with a UV light and $KMnO_4$ stain. Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz or 500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal references. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet. The error of coupling constants from ^1H NMR analysis is estimated at ± 0.3 Hz. High-resolution mass spectra were recorded on a oaTOF analyzer. Infrared (IR) spectra were obtained using cast-film technique with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumbers. Methyl (E)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylate was synthesized according to the literature procedure.[11] The enantiomeric excesses for chiral compounds were determined using high-performance liquid chromatography (HPLC) with Chiralcel-OD, Chiralpak-AS, or Chiralpak-IC columns with UV detection.

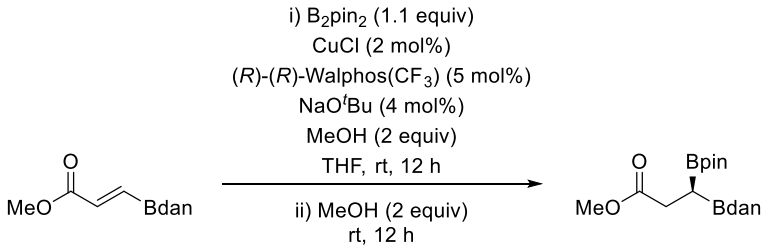
2.7.2 Experimental evidence for an invertive cross-coupling process



2-18 ***(R)*-2-19**

Pinacol boronate **2-18** was oxidized to alcohol ***(R)*-2-19** using a previously reported procedure. The resulting alcohol has found to have an $[\alpha]_D^{20}$ = +62.9 (c = 1.00, $CHCl_3$) for 99% ee. The enantiomer ***(S)*-2-19** has been reported to have an $[\alpha]_D^{25}$ = –76.7 (c = 1.00, $CHCl_3$).[1] All other spectroscopic data of ***(R)*-2-19** matches that of the reported enantiomer.

2.7.3 Preparation of diboron compound 2-14



2-13 **2-14**

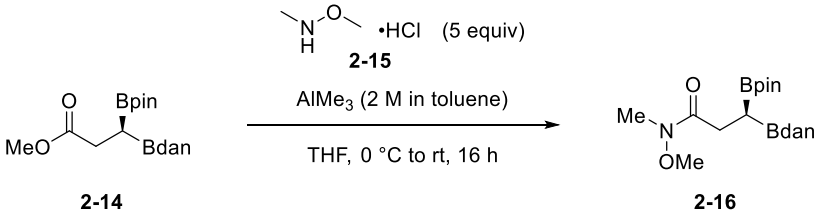
***(S)*-Methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2-14)**

CuCl (7.8 mg, 79 μmol), *(R)-(R)*-Walphos(CF_3) (0.18 g, 0.20 mmol), and NaO^{t}Bu (15.2 mg, 0.16 mmol) were dissolved in THF (3.5 mL) and stirred at room temperature for 30 minutes before the addition of pinacolato diboron (1.11 g, 4.36 mmol) in THF (2.5 mL). The reaction was further stirred for 10 minutes and methyl (E)-3-(1H-naphtho[1,8-de][1,3,2]diazaborinin-2(3H)-yl)acrylate **2-13** (1.0 g, 3.97 mmol) was then added along with THF (2.5 mL) and dropwise addition of MeOH (0.32 mL, 7.93 mmol). After 12 hours of stirring, a second portion of MeOH was added dropwise (0.32 mL, 7.93 mmol) and the reaction was allowed to stir for a further 12 h. The reaction mixture was evaporated in vacuo and directly purified by flash silica column chromatography

[1] Roche, C.; Labeeuw, O.; Haddad, M.; Ayad, T.; Genet, J.-P.; Ratovelomanana-Vidal, V.; Phansavath, P. *Eur. J. Org. Chem.* **2015,** 3977–3986.

(EtOAc/Hexanes = 1:4) to give **2-14** (1.30 g, 86%) as a colourless solid. The characterization data matched that of a previous report.[2]

2.7.4 Procedure for the synthesis of Weinreb Amide 2-16



***(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 (2-16)**

Compound **2-16** was synthesized according to a modified protocol reported by Evans et al.[12] 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, 2 M in toluene, 32 mmol). The solution was stirred at room temperature for 30 minutes, cooled to 0 ºC, before the addition diboronylalkane **2-14** (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 1 M HCl, it was extracted by dichloromethane (3 × 100 mL), dried with anhydrous $MgSO_4$, and filtered. This crude solution was then concentrated and purified with flash silica column chromatography (hexanes/EtOAc = 1:1) to afford the pure product as a white solid (1.8 g, 65%).

^{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).

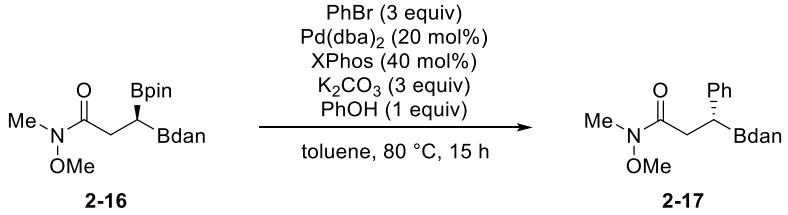
^{11}B NMR (160 MHz, $CDCl_3$) δ 31.0.

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

HRMS (EI) for $C_{21}H_{29}B_2N_3O_4$ (m/z): Calcd. 409.2344, Found 409.2353; $[\alpha]_D^{20}$: –44 (c = 0.09, $CHCl_3$).

Melting point: 165-167 °C.

2.7.5 Procedure for the stereoselective cross-coupling of 1,1-diboron compound 2-16



***(R)*-*N*-Methoxy-*N*-methyl-3-(1*H*-naphtho[1,8-*de*][1,3,2]diazaborinin-2(3*H*)-yl)-3-phenylpropanamide (2-17)**

$Pd(dba)_2$ (28 mg, 48 μmol), XPhos (47 mg, 98 μmol), K_2CO_3 (1.01 g, 7.34 mmol), aryl bromide (7.34 mmol), phenol (0.23 g, 2.44 mmol) and 1,1-diboron **2-16** (0.51 g, 2.44 mmol) were stirred in toluene (24.4 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 (hexanes/EtOAc = 60:40) to afford the title product **2-17** (0.86 g, 98% 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).

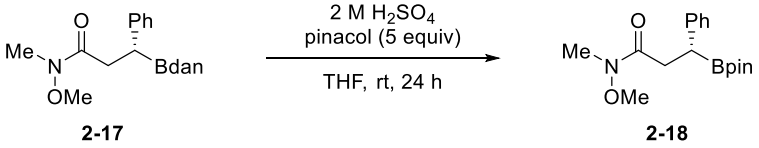
^{11}B NMR (160 MHz, $CDCl_3$) δ 32.0; IR (Microscope, cm^{-1}) 3417, 3348, 3054, 3023, 2962, 2935, 1642, 1630, 1600, 1512.

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

[α]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%.

2.7.6 Synthesis of pinacol boronate 2-18



2-17 **2-18**

***(R)*-*N*-Methoxy-*N*-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanamide (2-18)**

To a stirred solution of **2-17** (718 mg, 2.00 mmol) in THF (20 mL) was added 2 M H_2SO_4 (3.0 mL, 6.0 mmol) and pinacol (1.18 g, 10.00 mmol) sequentially. The reaction was stirred for 24 h at room temperature before being quenched by the addition of water (20 mL). The mixture was then extracted by diethyl ether (20 mL x 3), 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 **2-18** (510 mg, 80%) 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).

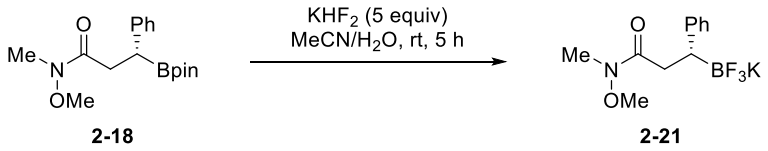
^{11}B NMR (160 MHz, $CDCl_3$) δ 32.3.

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

HRMS (EI) for $C_{17}H_{26}BNO_4$ (m/z): Calcd. 319.1955, Found 319.1959.

[α]D[20]: –20 (c = 0.60, $CHCl_3$).

2.7.7 Synthesis of trifluoroborate salt 2-21



2-18 **2-21**

Potassium trifluoro(3-(methoxy(methyl)amino)-3-oxo-1-phenylpropyl)borate (2-21)

Pinacol boronate **2-18** (500 mg, 1.6 mmol) was dissolved in MeCN (17.4 mL) before the addition of sat. aq. KHF_2 (4.50 M, 1.4 mL, 6.3 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 (10 mL × 3), filtered, and concentrated in vacuo. To the resulting oil was added Et_2O (20 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 desired product as a waxy grey solid (399 mg, 85%).

^{1}H NMR (400 MHz, acetone-d_6) δ 7.16 (d, J = 7.3 Hz, 2H), 7.02 (dd, J = 7.5, 7.5 Hz, 2H), 6.86 (ddd, J = 7.3, 7.3, 1.3 Hz, 1H), 3.58 (s, 3H), 2.98 (s, 3H), 2.74 (dd, J = 15.2, 6.0 Hz, 1H), 2.63 (dd, J = 15.2, 6.0 Hz, 1H), 2.28-2.21 (m, 1H).

^{13}C NMR (125 MHz, acetone-d_6) δ 150.8, 129.3, 127.8, 123.6, 66.1, 61.3, 35.7 (The boron-bound carbon was not detected due to quadrupolar relaxation of boron).

^{11}B NMR (128 MHz, acetone-d_6) δ 4.5.

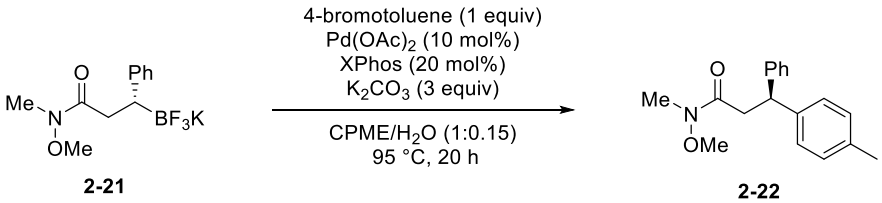
^{19}F NMR (376 MHz, acetone-d_6) δ –145.2.

IR (Microscope, cm^{-1}) 3392, 3057, 3023, 2938, 1711, 1642, 1450, 1071, 998.

HRMS (EI) for $C_{11}H_{14}BF_3NO_2$ [M–K]: Calcd. 260.1077, Found 260.1075.

$[\alpha]_D^{20}$: –2 (c = 0.23, acetone).

2.7.8 Synthesis of diarylmethane 2-22



***(S)*-*N*-Methoxy-*N*-methyl-3-phenyl-3-(*p*-tolyl)propanamide (2-22)**

$Pd(OAc)_2$ (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 **2-21** (75 mg, 0.25 mmol) 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 = 80:20) to afford the purified product **2-22** (53 mg, 75%) as a colourless waxy solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.26 (m, 4H), 7.19-7.15 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.66 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.57 (s, 3H), 3.17 (d, *J* = 7.7 Hz, 2H), 3.12 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 144.5, 141.2, 135.8, 129.2, 128.5, 127.8, 127.7, 126.3, 61.3, 53.4, 46.0, 38.0, 32.2, 21.0.

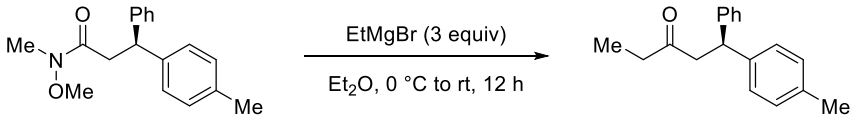
IR (Microscope, cm^{-1}) 3026, 3002, 2936, 1663, 1513, 1417, 1384, 1178, 995.

HRMS (EI) for $C_{18}H_{22}NO_2$ $[M+H]^+$: Calcd. 284.1645, Found 284.1645.

$[\alpha]_D^{20}$: 14 (c = 0.15, $CHCl_3$) for 98% *ee*.

HPLC (Chiralpak IC): 5:95 *i*-PrOH/Hexanes, 0.5 mL/minute, λ = 230 nm, T_{major} = 37.0 min, T_{minor} = 39.3 min, *ee* = 98%.

2.7.9 Transformation of Weinreb amide 2-22 into ketone 2-23



2-22 **2-23**

***(S)*-1-Phenyl-1-(*p*-tolyl)pentan-3-one (2-23)**

Weinreb amide **2-22** (19 mg, 0.07 mmol) was dissolved in Et_2O (1.3 mL) and cooled to 0 °C. Ethyl magnesium bromide (0.20 mmol, 3 M solution in Et_2O, 67 µL) was added *via* syringe. The resulting solution was allowed to warm to room temperature and was stirred overnight. The reaction was cooled to 0 °C and quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (5 mL x 3) and the combined ethereal layers were washed with brine, dried with anhydrous $MgSO_4$, filtered then concentrated in vacuo to give pure **2-23** (15 mg, 85%) as a white waxy solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.24-7.23 (m, 2H), 7.20-7.17 (m, 1H), 7.14-7.09 (m, 4H), 4.61 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.16 (d, *J* = 7.6 Hz, 2H), 2.36 (q, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 144.2, 141.0, 135.9, 129.2, 128.5, 127.7, 127.6, 126.3, 48.6, 45.7, 36.8, 21.0, 7.6.

IR (Microscope, cm^{-1}) 3026, 2976, 2922, 1715, 1494, 1111, 821, 699.

HRMS (EI) for $C_{18}H_{20}O$ (m/z): Calcd. 252.1514, Found 252.1515.

$[\alpha]_D^{20}$: 3.2 (c = 0.32, $CHCl_3$) for 98% *ee*.

2.8 References

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Chapter 3
Desymmetrization of Prochiral 1,1-Diboronylalkanes *via* an Asymmetric Suzuki-Miyaura Cross-Couping Reaction[†]

3.1 Introduction

As discussed in Chapter 1, the highly popular Nobel prize-winning class of palladium-catalyzed cross-coupling reactions achieves carbon-carbon bond-formation between sp^2-hybridized carbon groups with a wide substrate generality.[1] The Suzuki-Miyaura cross-coupling of aryl and alkenyl halides with organoboron reagents,[2] in particular, has found wide application in both academic and industrial settings due in part to its mild reaction conditions as well as the environmentally benign reaction by-products. In the past decade, numerous new and effective methods have been developed for the preparation of chiral secondary and tertiary alkyl- and allylboronates for use as intermediates mainly toward formation of optically enriched alcohols (B–C bond oxidation), and carbonyl allylboration, respectively.[3] The ability to achieve stereoselective Suzuki-Miyaura cross-coupling between these chiral boronates to establish sp^2-sp^3 and sp^3-sp^3 C–C bonds would greatly expand their utility and thus, provide a new strategic approach to assemble chiral units of more complex molecules like natural products and pharmaceutical drugs. Coupling of alkylboronates, however, is notoriously challenging. It is rendered difficult by a slower transmetalation and possible side-reactions such as β-hydride elimination and protodeboronation.[4] When using chiral secondary alkylboron intermediates, these challenges are amplified by the issue of stereocontrol. Despite these hurdles, significant advances have been reported in recent years (Figure 3-1).[5] Stereospecific cross-coupling of optically enriched secondary alkylboronates was first demonstrated by Crudden and co-workers (equation 1, Figure 3-1).[5a] These stereoretentive coupling conditions, however, were restricted to the use of benzylic boronates as substrates. In

[†] A version of this chapter has been published. Sun, H.; Kubota, K.; Hall, D. G. *Chem. Eur. J.* **2015**, *21*, in press. DOI: 10.1002/chem.201406680.

2010, Suginome and co-workers reported stereoinvertive cross-couplings of α-(acylamino)benzylboronic esters (equation 2, Figure 3-1).[5b-c]

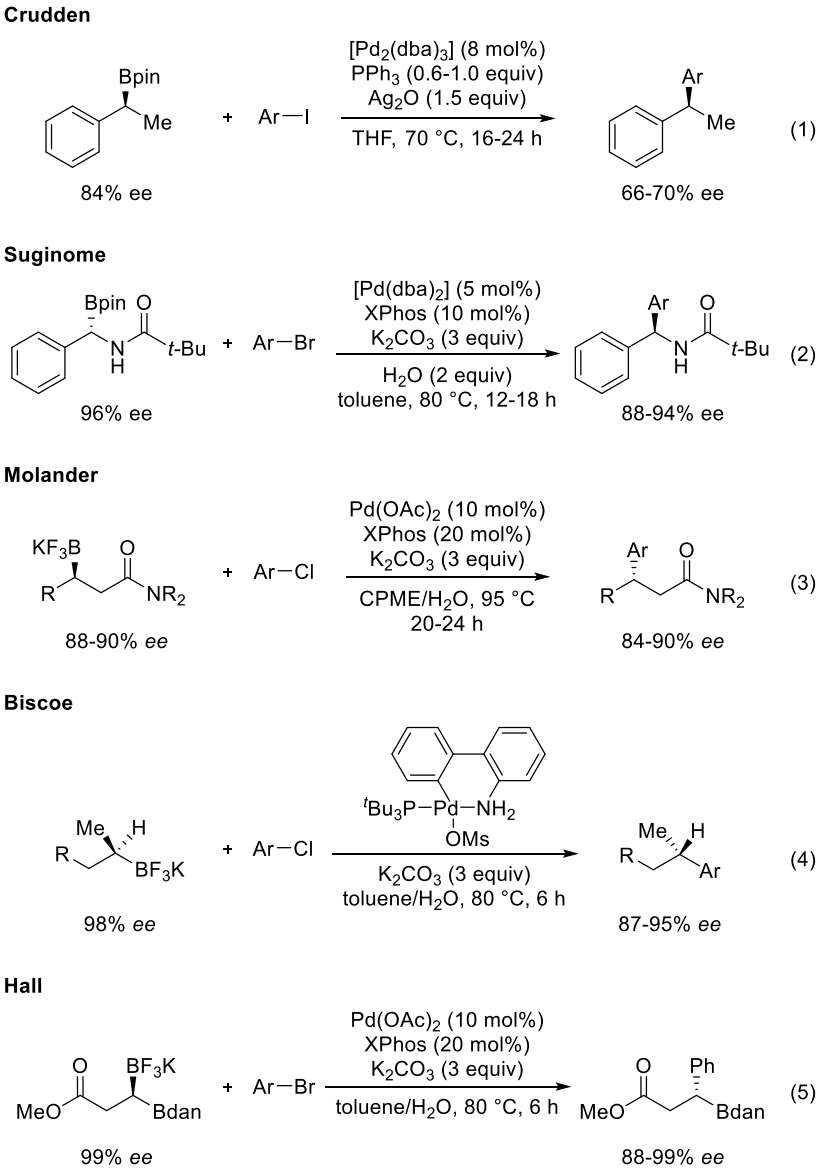


Figure 3-1. Stereospecific Suzuki-Miyaura cross-coupling of optically enriched secondary organoboronates.

Subsequently, Molander and co-workers provided the first example of stereospecific cross-coupling of a non-benzylic, secondary alkyltrifluoroborate derivative (equation 3, Figure 3-1).[5d]

More recently, a stereoinvertive cross-coupling of chiral secondary alkyl trifluoroborates was reported by Biscoe and co-workers (equation 4, Figure 3-1).[5f] Remarkably, this cross-coupling occurs without the need for any boron-coordinating group.

Inspired by Shibata's discovery that 1,1-diboronylalkanes can be subjected to a single, chemoselective cross-coupling with aryl halides,[6a] our laboratory reported the first synthesis and stereospecific cross-coupling of an optically enriched 1,1-diboronyl compound that was made chiral by virtue of differentially protected boronyl units (equation 5, Figure 3-1).[5e]

While these methods represent significant advances made to this area of study, they do suffer from a few drawbacks. Most of these methods require some form of boronate activation through a coordinating group on the substrate, which imparts a limitation on the scope of these cross-coupling reactions (equations 2, 3 & 5, Figure 3-1). In others, the reaction is limited to specific types of organoboronates, such as benzylic boronates (equation 1, Figure 3-1). In all cases, there is also the requirement for optically enriched organoboronates, thus these methods depend heavily on the ease of access to such starting materials.

3.2 Objectives

An alternate strategy to asymmetric cross-coupling would consist in achieving enantioselective desymmetrization by mono-cross-coupling of prochiral 1,1-diboryl alkanes such as bis-pinacolates. This method would represent an efficient approach towards the construction of chiral diarylalkanes, which are prominently featured motifs in important pharmaceutical compounds (Figure 3-2).[7] This chapter will discuss efforts placed towards the development of an asymmetric Suzuki-Miyaura cross-coupling of 1,1-diboronylalkanes, leading to optically enriched secondary organoboronates. This objective may be achieved through methodical optimization of ligand structure and reaction conditions. Mechanistic studies may also shed light on the finer details of the desymmetrization process, which could aid in the successful optimization of the cross-coupling reaction.

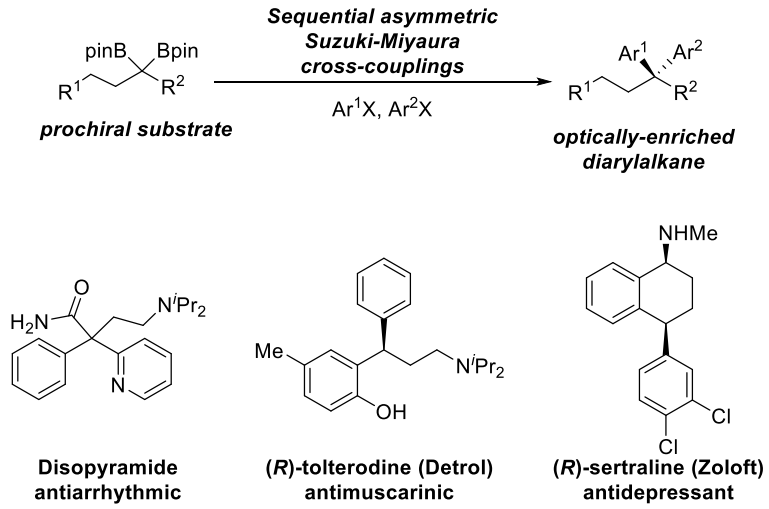
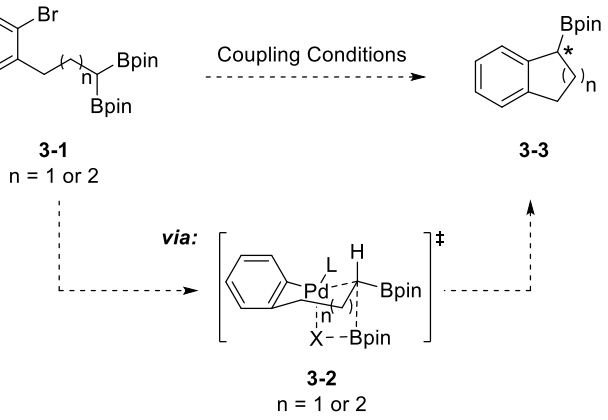


Figure 3-2. Application of the desymmetrization of 1,1-diboron compounds towards the synthesis of diarylalkanes.

3.3 Developing an intramolecular asymmetric cross-coupling reaction

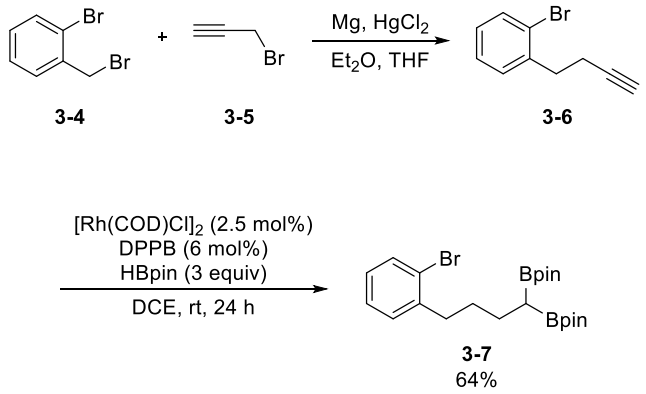
Initial attempts at developing an asymmetric Suzuki-Miyaura cross-coupling were directed towards an intramolecular variant of the reaction. It was postulated that an intramolecular cross-coupling of substrate type **3-1** would potentially proceed through an ordered 6- or 7-membered cyclic transition state and allow for better enantioselectivities (Scheme 3-1).



Scheme 3-1. Strategy for an asymmetric intramolecular cross-coupling of 1,1-diboronylalkanes.

3.3.1 Developing suitable reaction conditions for an intramolecular Suzuki-Miyaura cross-coupling reaction

Efforts were first placed into finding suitable conditions for the racemic cross-coupling. The cross-coupling substrate was synthesized according to the sequence shown in Scheme 3-2. Propargyl bromide **3-5** was transformed into the corresponding Grignard reagent and was then treated with benzylbromide **3-4**. The resulting alkyne **3-6** was then subjected to a Rh-catalyzed diboration using $[Rh(COD)Cl]_2$/DPPB and pinacolborane.[6b]



Scheme 3-2. Synthesis of diboronylalkane substrate for the intramolecular Suzuki-Miyaura cross-coupling reaction.

Various conditions reported for the successful cross-coupling of secondary boronates were then tested. When $Pd(P^tBu_3)_2$ was used as the catalyst with excess aqueous KOH as the base,[6] only a trace amount of the desired cyclized product **3-8** was obtained with protodeboronation as the dominating reaction pathway (equation 6, Figure 3-3). When $Pd_2(dba)_3/PPh_3$ was used as the catalyst with Ag_2O as the base,[5] protodeboronation product was again found to be dominant (equation 7, Figure 3-3).

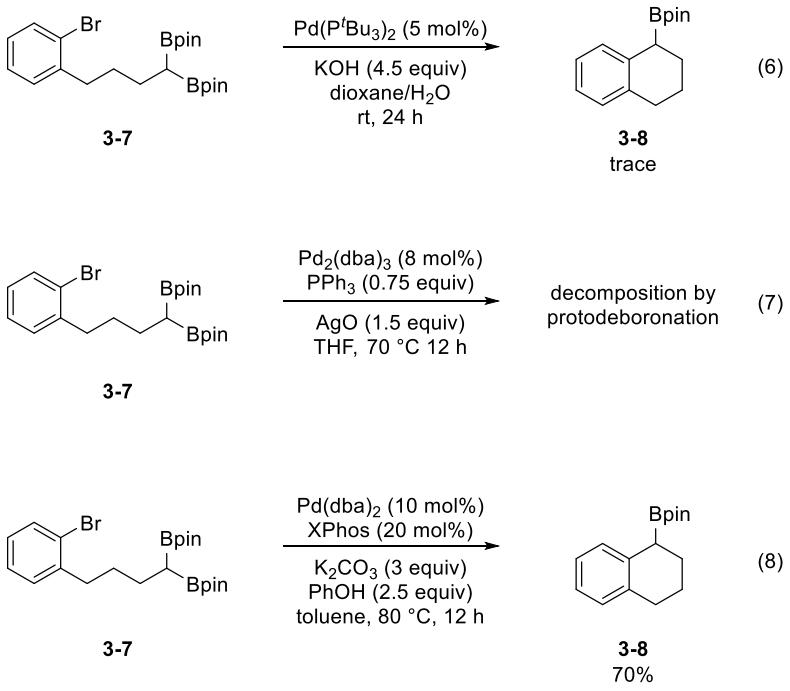


Figure 3-3. Screening of reaction conditions for the intramolecular cross-coupling of 1,1-diboronylalkanes.

Gratifyingly, successful cyclization was achieved when a weaker base was used (K_2CO_3) in the presence of water (equation 8, Figure 3-3). In this case, $Pd(dba)_2$ was used with XPhos as a ligand, which is known to exhibit high reactivity in cross-coupling reactions due to several design features.[8] The electron-rich dicyclohexylphosphine moiety helps to accelerate oxidative addition, while the bulky nature of the biaryl backbone assists in the acceleration of reductive elimination (Figure 3-4). Phenol was also used as an additive as it is known to help promote cross-coupling, presumably through hydrogen bonding with the oxygen lone pairs in the pinacol boronate, thus increasing the Lewis acidity of the boron centre.[5c]

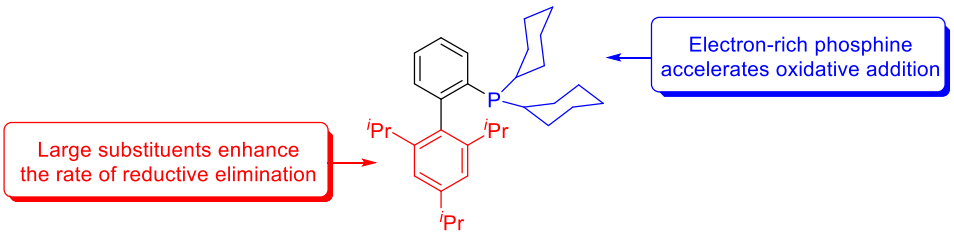


Figure 3-4. Design elements of XPhos that contribute to enhanced reactivity in Suzuki-Miyaura cross-coupling reactions.

3.3.2 Evaluating chiral ligands for the enantioselective intramolecular desymmetrization of 1,1-diboronylalkanes

With suitable racemic coupling conditions in hand, efforts were then made to examine various chiral ligands for the development of an asymmetric system. A range of chiral ligands known to be active in other transition metal-catalyzed reactions were screened for enantioinduction (Figure 3-5), including phosphoramidite **L1**, BINAP-derived ligands **L2** and **L3**, as well as ferrocenyl bidentate ligands like **L4**, **L5** and **L6**. Unfortunately, all ligands led to either no product formation or to only trace conversion to product.

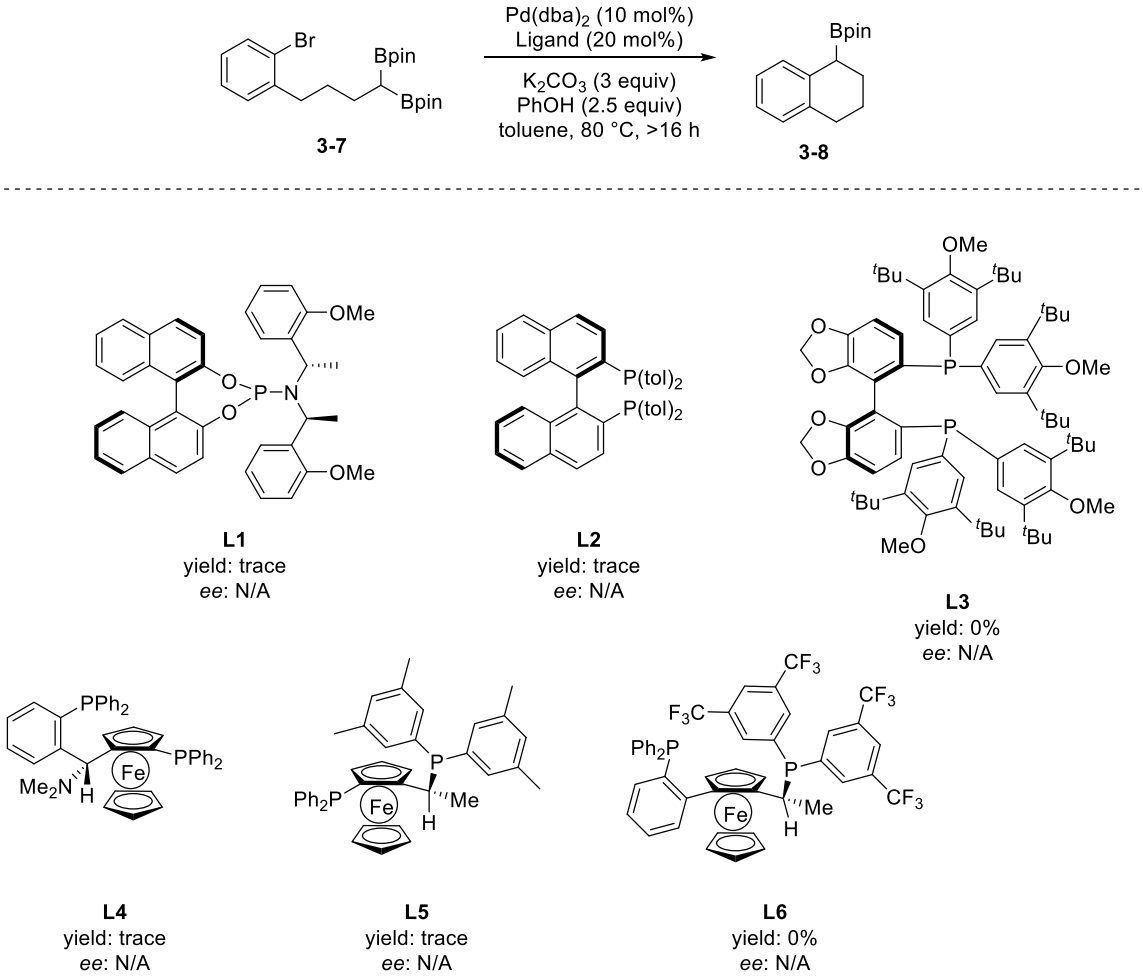
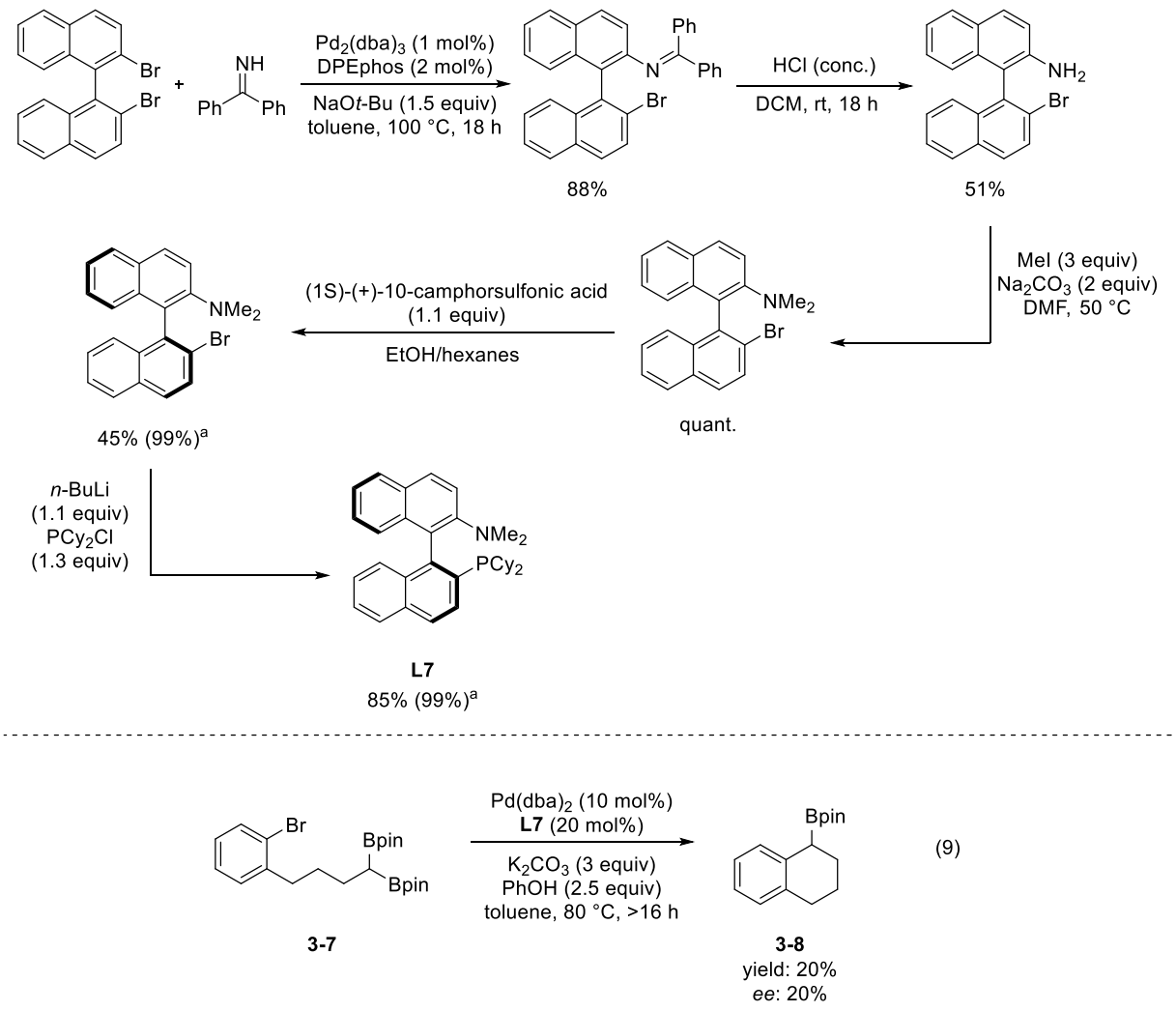


Figure 3-5. Screening of chiral ligands for the development of an asymmetric intramolecular Suzuki-Miyaura reaction.

Efforts were then placed into the synthesis of Kenphos **L7**, which is a ligand that was originally applied to the synthesis of chiral biaryl compounds (Scheme 3-3).[9] It was rationalized that Kenphos could lead to a more successful coupling than the other chiral ligands screened given the similarities in electronic properties between the phosphorous centres of Kenphos and XPhos. Unfortunately, the cross-coupling using Kenphos as the chiral ligand led only to 20% yield and 20% *ee* (measured by chiral HPLC) (equation 9, Scheme 3-3). Given the lengthy synthesis required for the synthesis of these types of chiral monophosphine ligands, and the relatively small number of reported variants in the literature, efforts at further developing the asymmetric intramolecular Suzuki-Miyaura cross-coupling reaction was discontinued.



Scheme 3-3. Synthesis of Kenphos and its performance in the asymmetric intramolecular Suzuki-Miyaura cross-coupling reaction of 1,1-diboronylalkanes. [a]Values in brackets denote the *ee* of the compound.

3.4 Development of an intermolecular desymmetrization of 1,1-diboronylalkanes

3.4.1 Initial screening of ligands

Studies on the intermolecular asymmetric cross-coupling began with an examination of various chiral phosphine ligands (Figure 3-6). Shibata's reported conditions for the racemic coupling[6a]

were chosen as a starting point, however the palladium source was changed from $Pd(P^tBu_3)_2$ to $Pd(OAc)_2$ in order to eliminate potential competition between P^tBu_3 and the chiral ligand being examined. Diboronyl compound **3-15** and aryl halide **3-16** were chosen as the coupling partners as they were reported to undergo the racemic cross-coupling in good yield.[6] Chiral bidentate ligands including Chiraphos (**L8**), BINAP (**L9**), Tunephos (**L10**) and DTBM-Segphos (**L3**) were all low-yielding and gave poor selectivity (Figure 3-6). Ferrocenyl-based bidentate ligands like Mandyphos (**L11**), Josiphos (**L12**) and Walphos (**L6**) were also unsuccessful, giving a low yield with little to no enantioselectivity. Taniaphos (**L13**) gave 22% *ee*, however attempts at increasing the enantioselectivity by examining Taniaphos derivatives were unfruitful (**L4**).

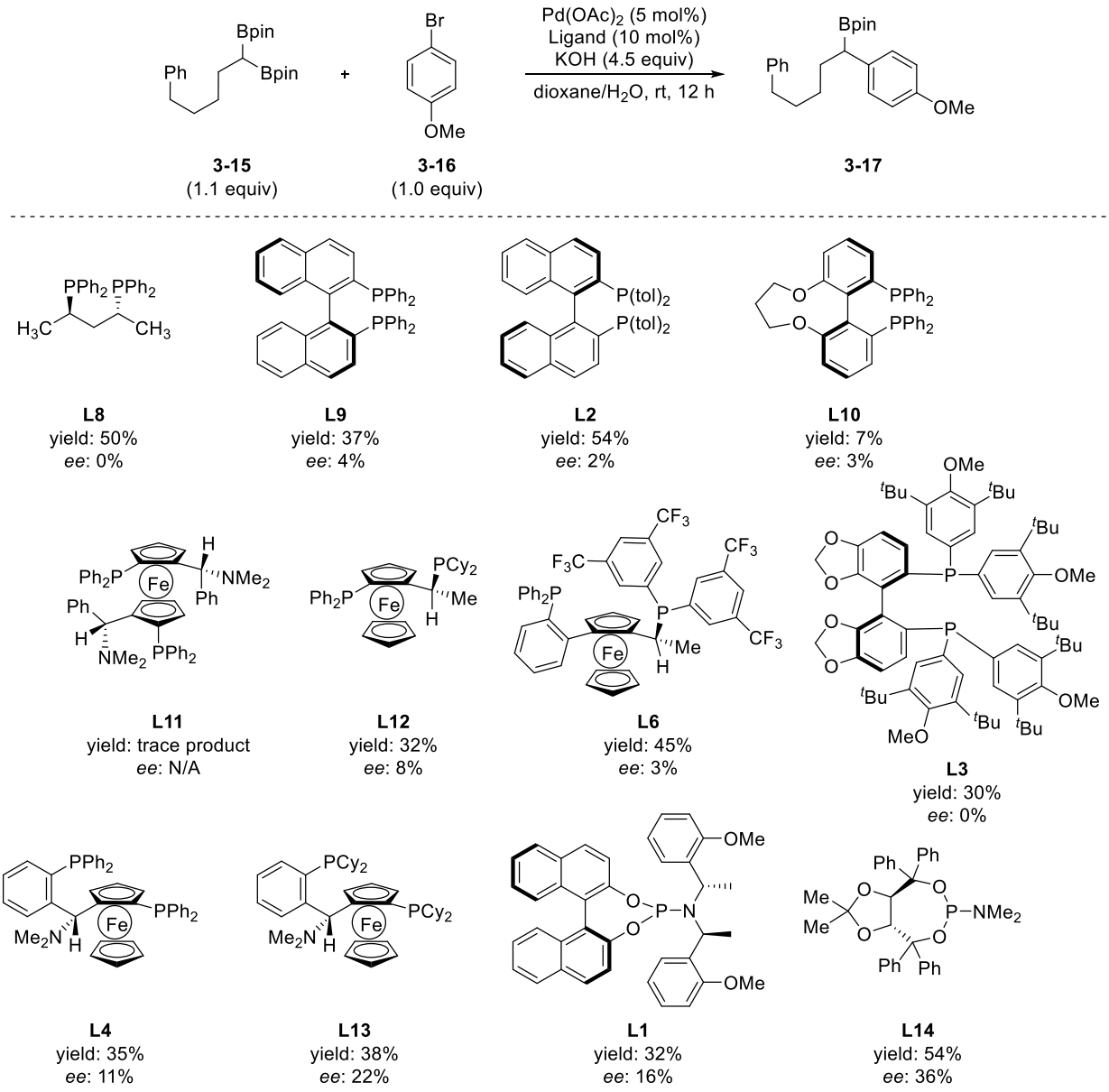
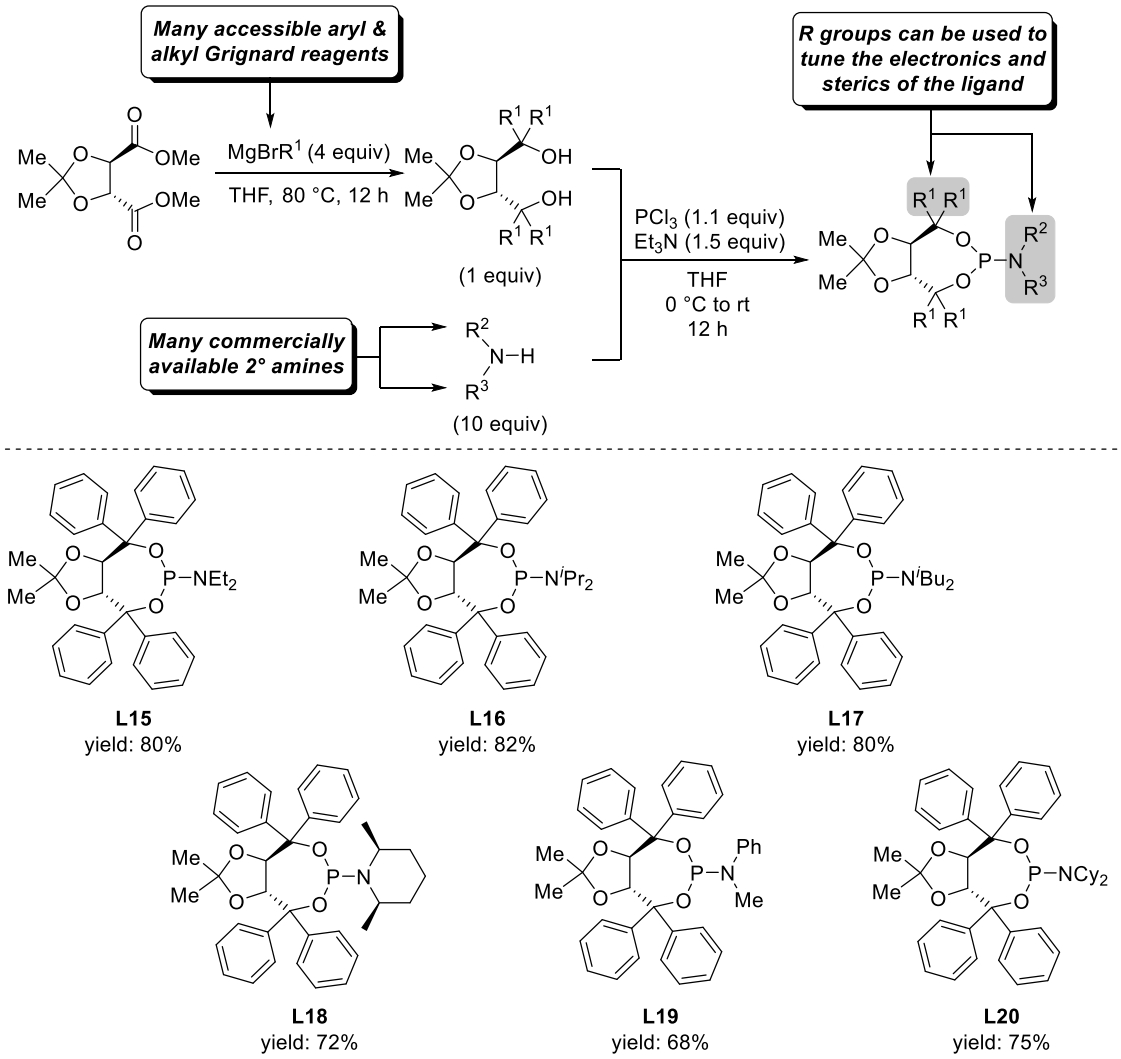


Figure 3-6. Initial screen of chiral phosphorous-based ligands. The reaction was run at a scale of 0.1 mmol of aryl bromide.

When BINOL-derived phosphoramidite **L1** was used, the product was formed in 16% *ee*. While the enantioselectivity was not high, it was believed that a comprehensive investigation of various phosphoramidites should be pursued given the relative ease of access to this class of ligands. To our satisfaction, it was encouraging to find that TADDOL-derived ligand **L14** gave the desired cross-coupled product in 36% *ee*. Phosphoramidites bearing the TADDOL core were a particularly attractive class of ligands to examine due to the modularity of their synthesis (Scheme 3-4),[10]

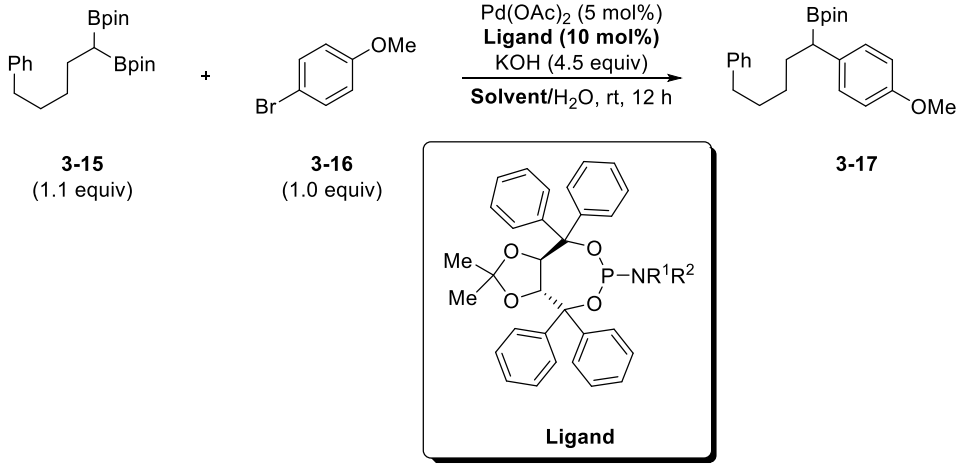
which makes steric and electronic tuning of the ligand possible and relatively straightforward. The aryl groups on the TADDOL backbone may be modified with a variety of substituted arenes, introduced simply through Grignard additions to the tartrate precursor. Ligands bearing varying amino groups were also accessible due to the commercial availability of a large number of secondary amines. Thus a variety of phosphoramidites bearing varying amino moieties were synthesized in yields ranging from 68-82% (Scheme 3-4).



Scheme 3-4. Synthesis of TADDOL-derived chiral phosphoramidites.

Screening of the synthesized TADDOL-derived ligands (Table 3-1) revealed that increasing the size of the amine substituents had a positive effect on the outcome of the reaction (Table 3-1, entries 1-5). More specifically, superior selectivities were observed when diisopropylamino (**L16**)

and 2,6-dimethylpiperidyl (**L18**) groups were used. Attempts at increasing the size of the amino group (e.g. to di-*tert*-butylamino or 2,2,6,6-tetramethylpiperidyl groups) were unsuccessful as the synthesis of the desired ligands proved to be problematic with the significant increase in size of the amine being used. The use of the more electronically deficient *N*-methylaniline was found to decrease the activity of the catalyst and led to both poor yield and selectivity (Table 3-1, entry 6). Due to the simpler purification of **L16** in comparison to **L18**, **L16** was chosen as the optimal catalyst. A screen of different solvents revealed that ethereal solvents like dioxane and THF were the most compatible with the reaction conditions (Table 3-1, entries 3 & 8). Other solvents like dichloromethane, toluene and acetonitrile simply resulted in decreased reactivity and enantioselectivity (Table 3-1, entries 9-13).



Entry	Ligand	NR^1R^2	Solvent	Yield[a] (%)	*ee*[b] (%)
1	**L14**	NMe_2	dioxane	54	36
2	**L15**	NEt_2	dioxane	60	54
3	**L16**	N^iPr_2	dioxane	41	55
4	**L17**	N^iBu_2	dioxane	45	53
5	**L18**	2,6-dimethylpiperidyl	dioxane	63	59
6	**L19**	NPhMe	dioxane	30	2
7	**L20**	NCy_2	dioxane	50	6
8	**L16**	N^iPr_2	THF	56	59
9	**L16**	N^iPr_2	toluene	trace	-
10	**L16**	N^iPr_2	MeCN	28	25

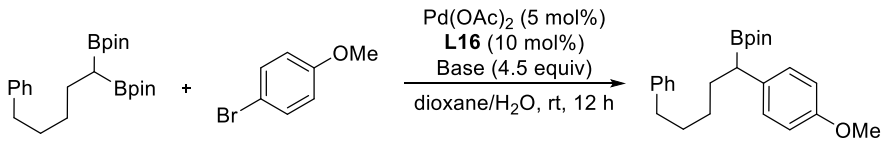
11	**L16**	N^iPr_2	^{t}BuMeO	trace	-
12	**L16**	N^iPr_2	2-MeTHF	trace	-
13	**L16**	N^iPr_2	DMF	trace	-

Reactions were performed at a scale of 0.1 mmol of aryl bromide. [a]Isolated yield. [b] The *ee* of the corresponding alcohol, synthesized through oxidation of the boronate (see experimental section for details), was measured by chiral HPLC.

Table 3-1. Optimization of TADDOL-derived phosphoramidite ligand and reaction solvent.

3.4.2 Optimization of the base

Attempts at improving the selectivity of the desymmetrization process were also made by examining the base and its effect on the reaction outcome. Interestingly, the base was found to have a profound influence on the cross-coupling process. The reaction would only proceed in the presence of strong bases like metal hydroxides, which was in agreement with previously documented observations.[6a]



3-15 (1.1 equiv) **3-16** (1.0 equiv) **3-17**

Entry	Base	Concentration (in H_2O)	Equiv	Yield[a] (%)	*ee*[b] (%)
1	K_2CO_3	8 M	4.5	0	-
2	K_3PO_4	8 M	4.5	0	-
3	KOH	8 M	4.5	41	55
4	LiOH	8 M	4.5	59	64
5	CsOH	8 M	4.5	46	60
6	NaOH	8 M	4.5	18	75

7[c]	NaOH	8 M	4.5	59	75
8[c]	None	-	-	0	-
9	$Ba(OH)_2$	4 M	2.2	trace	-
10	$NaBu_4OH$	40% w/w	4.5	trace	-

Reactions were performed at a scale of 0.1 mmol of aryl bromide. [a]Isolated yield. [b]Measured by chiral HPLC. [c]KHF_2 (1.5 equiv) was added as an additive.

Table 3-2. Optimization of the base

The use of weaker bases like carbonates and phosphonates did not yield any product (Table 3-2, entries 1 & 2). What was surprising, however, was that the counter ion of the hydroxide base being used had a profound impact on the selectivity of the reaction. While KOH, LiOH and CsOH led to moderate selectivities and yields (Table 3-2, entries 3-5), no conversion was achieved with $Ba(OH)_2$ (a 4 M solution, and 2.2 equivalents were used in order to have a total 8 M concentration and 4.4 equivalents of hydroxide ion) (Table 3-2, entry 9). NBu_4OH also yielded no product (Table 3-2, entry 10). The use of NaOH was found to give a significantly higher *ee* than the rest of the bases screened, however the yield of the cross-coupled product was quite low (Table 3-2, entry 6). The influence of the counter ion in these inorganic bases, while not entirely clear, may be linked to the strength with which they may coordinate to ligands present on the palladium catalyst, thus affecting the catalyst's activity.[11]

In an attempt to improve the yield, KHF_2 was added as an additive, since fluoride has been known to help increase the rate of Suzuki-Miyaura cross-couplings.[11] It was found that the combination of NaOH with KHF_2 was successful in increasing the yield without affecting the selectivity (Table 3-2, entry 7). The cross-coupling did not occur when KHF_2 was used on its own (Table 3-2, entry 8), indicating that NaOH plays an integral role in this process.

3.5 Mechanistic studies on the asymmetric cross-coupling process

3.5.1 Studies on the role of the base

The observed influence of the base on the reaction outcome garnered interested in further investigating the roles of NaOH and KHF_2 in this cross-coupling process. Studies have shown that hydroxide plays an essential role in the transmetalation step of a Suzuki-Miyaura cross-coupling.[12] To date, there have been two main proposals, both of which have been corroborated by various computational studies[13]: 1) the hydroxide forms an anionic borate **3-19**, which then undergoes transmetalation with oxidatively inserted palladium(II) **3-20** or 2) the hydroxide is involved in the formation of a palladium-hydroxo species **3-21** which may then undergo transmetalation with neutral organoboronate **3-18** (Figure 3-7).

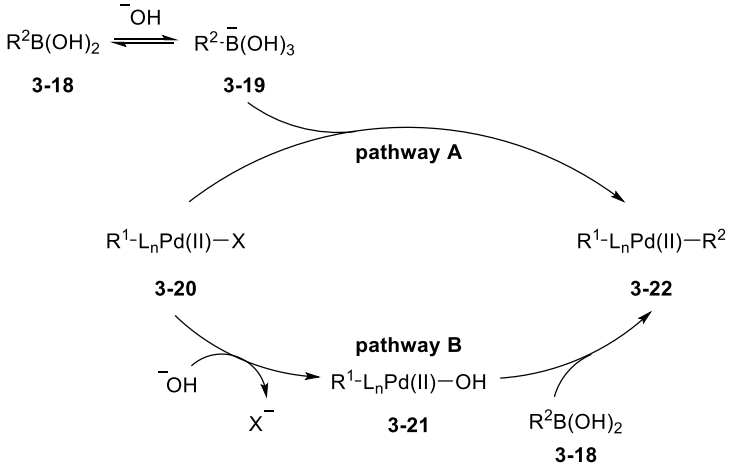


Figure 3-7. Proposed mechanisms of base-assisted transmetalation in Suzuki-Miyaura reactions.

It was believed, however, that these requirements for transmetalation alone could not completely account for the need of this system for an additive like KHF_2 in addition to a large excess of NaOH when it is known that Suzuki-Miyaura couplings are capable of proceeding with the use of weaker bases like K_2CO_3 in the presence of water.[12b] For this reason, we surmised that the base was in fact playing the additional role of hydrolyzing the pinacol boronate prior to the cross-coupling event. Indeed, when diboronyl compound **3-15** was subjected to NaOH and KHF_2 in a dioxane/H_2O mixture in the absence of palladium, ligand and aryl halide, followed by the addition of pinanediol, the corresponding transesterified product **3-23** was isolated in 75% yield (equation 13, Figure 3-8).

This product was likely formed *via* the intermediacy of free boronic acids. In the absence of NaOH and KHF_2, no transesterified product was obtained (equation 14, Figure 3-8). These results suggest that hydrolysis of the pinacol boronate groups is possible under the conditions of the cross-coupling reaction. Unfortunately, attempts at observing the evolution of free pinacol *via* NMR analysis were unsuccessful due to too many overlapping signals in the region of interest, thus we sought further support of this proposal through more experimental evidence.

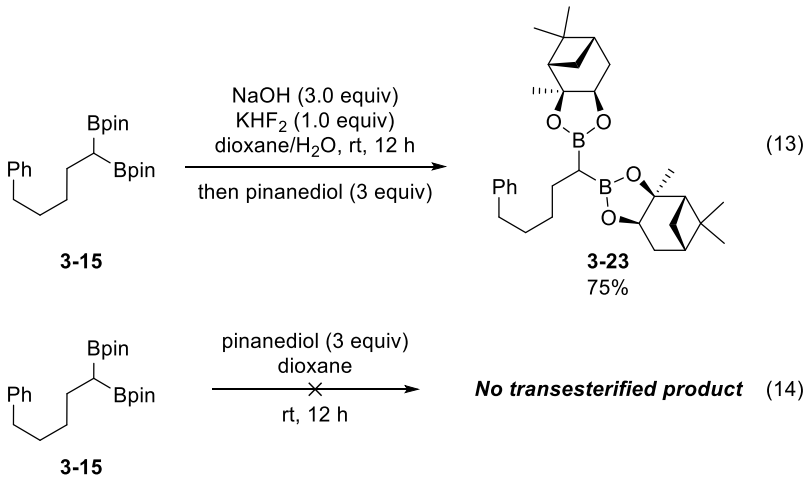
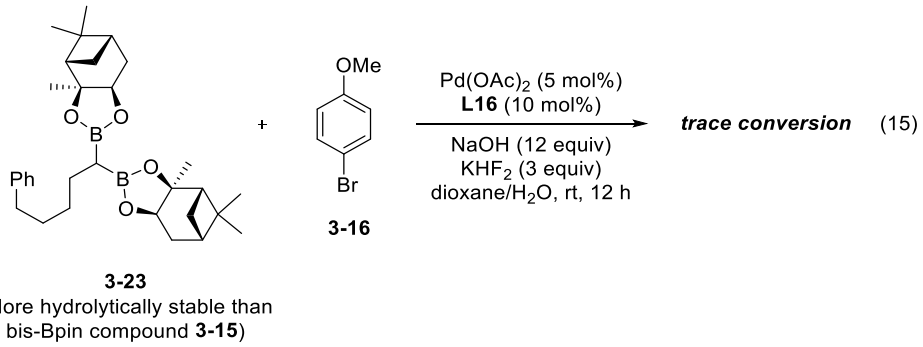


Figure 3-8. Hydrolysis of the diboronyl coupling partner.

Since sterically hindered boronates like the corresponding pinanediol derivative **3-23** are known to be quite hydrolytically stable, it was predicted that the cross-coupling of diboron compound **3-23** would proceed more slowly than bis-pinacolate **3-15**. In the event where **3-23** was used as the substrate, only trace conversion to product was observed (equation 15), which supports the hypothesis that pre-hydrolysis of the boronic ester to the boronic acid as a pre-requisite to cross-coupling.



If hydrolysis of the boronic ester is truly occurring, however, one must consider the possibility of forming a racemic monohydrolyzed product (Figure 3-9). The coupling of this racemic compound could have a negative impact on the enantioselectivity of the reaction. It was speculated that if hydrolysis of the pinacol boronate was in fact a pre-requisite to cross-coupling, then the equivalents of base used should have an effect not only on the yield, but also the selectivity of the reaction. If a substoichiometric amount of base was used with respect to the equivalents of pinacol boronate groups present in the reaction mixture, a low enantiomeric excess may be expected since this would likely result in incomplete hydrolysis of the diboronyl substrate. In contrast, we reasoned that a large excess of base would promote the hydrolysis of both pinacol boronates to the diboronic acid, thus resulting in increased enantiomeric excess.

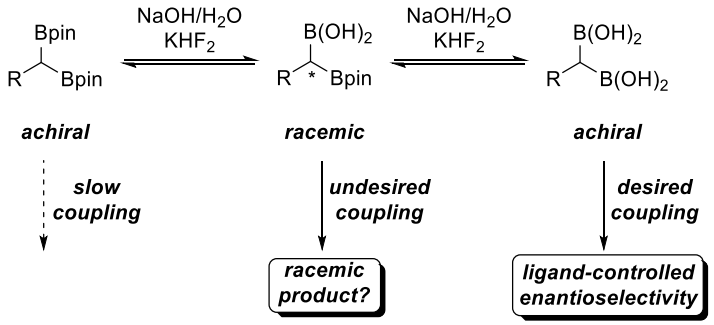
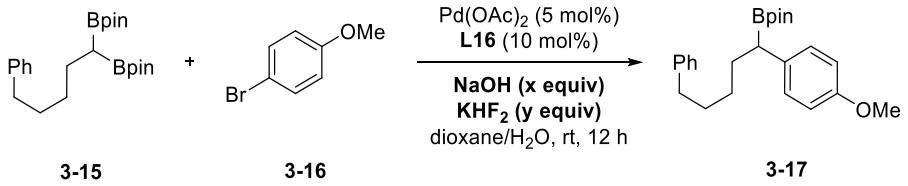


Figure 3-9. Potential reaction pathways for the cross-coupling of diboronylalkanes under hydrolytic conditions.

Accordingly, we found that when only 1.5 equivalents of NaOH and 0.5 equivalents of KHF_2 were used in the presence of 3.0 equivalents of pinacol boronate moieties (i.e. 1.5 equivalents of diboronyl compound **3-15**), the cross-coupled product was obtained in only 13% yield and 40% ee (Table 3-3, entry 1). When 12.0 equivalents of NaOH and 3.0 equivalents of KHF_2 were used, the product was obtained in 78% yield and 75% ee (Table 3-3, entry 3). Both the increased yield and *ee* when a large excess of base is used support hydrolysis of the pinacol boronates to the corresponding diboronic acid as a prerequisite to the cross-coupling event.



3-15 **3-16** **3-17**

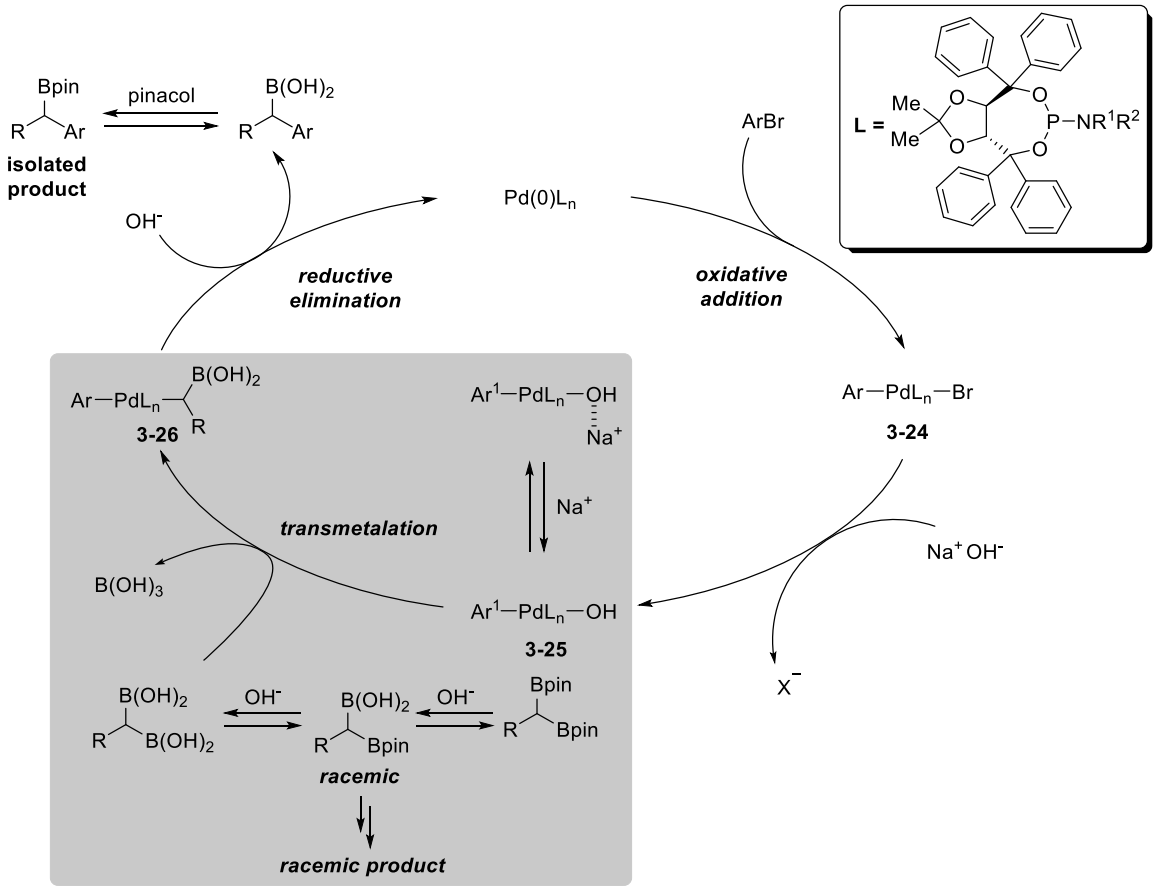
Entry	NaOH (equiv)	KHF_2 (equiv)	Yield[a] (%)	*ee*[b] (%)
1	1.5	0.5	13	40
2	4.5	1.5	59	75
3	12.0	3.0	78	75

[a]Isolated yield. [b]Measured by chiral HPLC.

Table 3-3. Modification of base stoichiometry.

3.5.2 Proposed catalytic cycle

From these findings, the following mechanism is proposed (Scheme 3-5): oxidative addition of ligand-bound palladium(0) into the C–Br bond of the aryl bromide gives palladium(II) complex **3-24**. Ligand exchange with sodium hydroxide then gives the palladium hydroxo species **3-25**. The bispinacolate undergoes hydrolysis under the reaction conditions to give the diboronic acid, which may then undergo an enantiodetermining transmetalation with **3-25** to give intermediate **3-26**. Intermediate **3-26** may then undergo hydroxide-assisted reductive elimination[12c] to give the chiral secondary alkylboronic acid. Since the isolated product of this reaction is in fact the secondary pinacol boronate and boronate formation is known to be reversible,[14] it is believed that the pinacol initially released during the hydrolysis step may condense onto the boronic acid product to give the isolable pinacolate product.

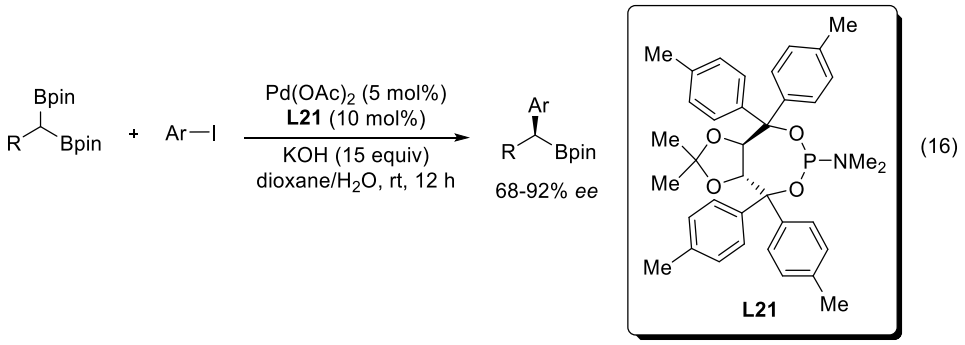


Scheme 3-5. Proposed mechanism for the desymmetrization of 1,1-diboronylalkanes.

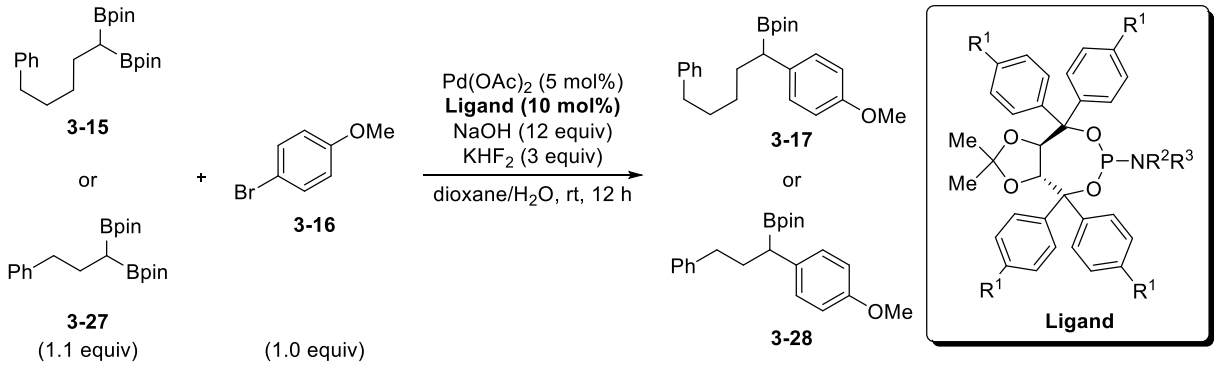
3.6 Further ligand optimization

Halfway through these studies, similar conditions were reported by Morken and co-workers using **L21** – a TADDOL-derived phosphoramidite bearing four tolyl groups (equation 16).[15] While this study included a brief examination of the arene substitution, the effect of the amino moiety was left unexplored. Since our initial ligand optimization showed a significant effect of the amino group on selectivity, we decided that a logical progression would be an examination of the combined effects of both the aryl substituent and the amine moiety. Furthermore, the report from Morken and co-workers implemented the use of KOH as the base (the same as the originally reported conditions for the racemic coupling conditions developed by the Shibata Group). As shown, in Sections 3.4.2 and 3.5.1, however, KOH is not the optimal base of this cross-coupling

system. Thus, the objective then became to optimize the yield and selectivity of this desymmetrization process by: 1) re-optimize the ligand by determining the degree of cooperation between the aryl and amino groups on the TADDOL-derived phosphoramidite and the effect of these groups on selectivity, and 2) to combine the newly optimized ligand with the optimized base and additives to develop a cross-coupling reaction with improved generality.



Our efforts led to the observation that both the steric size on the aryl substituent and the amine had a profound effect of the activity of the catalyst. Ligand **L21** gave poor yield and selectivity under our reaction conditions (Table 3-4, entry 1). Selectivity was generally observed to increase with increasing size of the alkyl substituent, although anomalies were observed in this trend when comparing ethyl substitution to *n*-propyl substitution (Table 3-4, entries 7-10). This observation hints that the aryl and amino sites of the ligand are not independent of one another. The use of *isopropyl* groups resulted in the highest *ee*. Further increasing the size of the alkyl substituent to a *tert*-butyl group had little effect on the selectivity of the reaction. It was also found that larger amine size led to higher selectivity. Thus, the phosphoramidite bearing *isopropyl* groups in combination with a 2,6-dimethylpiperidyl group (**L32**) was determined to be the optimal ligand to be employed in the study of reaction scope (Table 3-4, entry 12). It should be noted that these studies were originally performed using **3-15** as the substrate (Table 3-4, entries 1, 2, and 4), however, it was decided that the rest of the optimization should be completed using substrate **3-27** in order to have a direct comparison between these results and those of Morken and co-workers.



Entry	Ligand #	Diboronyl	R^1	NR^2R^3	Yield[a] (%)	*ee*[b] (%)
1	**L21**	**3-15**	Me	NMe_2	46	44
2	**L22**	**3-15**	Me	NEt_2	30	54
3	**L23**	**3-27**	Me	N^iPr_2	83	81
4	**L24**	**3-15**	Et	NMe_2	63	51
5	**L25**	**3-27**	Et	NEt_2	50	78
6	**L26**	**3-27**	Et	N^iPr_2	77	87
7	**L27**	**3-27**	^{n}Pr	NMe_2	20	70
8	**L28**	**3-27**	^{n}Pr	NEt_2	21	66
9	**L29**	**3-27**	^{n}Pr	N^iPr_2	35	80
10	**L30**	**3-27**	^{n}Pr	N^iBu_2	60	80
11	**L31**	**3-27**	^{n}Pr	2,6-dimethylpiperidyl	80	88
12	**L32**	**3-27**	^{i}Pr	2,6-dimethylpiperidyl	82	89
13	**L33**	**3-27**	^{t}Bu	2,6-dimethylpiperidyl	70	87

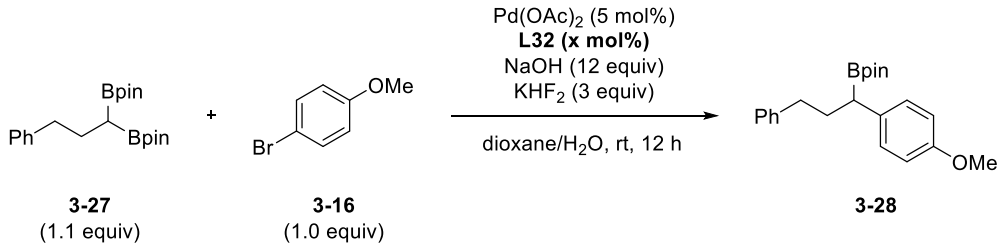
All reactions were run at a scale of 0.1 mmol of aryl bromide. [a]Isolated yield. [b]Enantiomeric excesses of the corresponding alcohols were measured by chiral HPLC.

Table 3-4. Second-round optimization of the ligand.

3.6.1 Modification of the ligand stoichiometry and its effect on selectivity

With the hope of further improving the yield and selectivity, the effect of ligand stoichiometry on the outcome of the reaction was studied by varying the amount of chiral ligand used with respect

to the amount of palladium acetate pre-catalyst (Table 3-5). It was found that a 1:2 Pd:**L32** ratio was optimal for the reaction in terms of both yield and selectivity. Lowering the amount of ligand used to 5 mol% (amounting to a Pd:**L32** ratio of 1:1) resulted in a significant decrease in yield as well as a drop in *ee* (from 89% to 77%). Increasing the amount of ligand to 15 mol% (Pd:**L32** ratio of 1:3) also resulted in a decrease in yield and selectivity. These results seem to indicate an inhibitory effect of excess ligand, however the exact number of ligands bound on the palladium centre at the stereodetermining step cannot be concretely determined by these findings alone.



3-27 (1.1 equiv) + **3-16** (1.0 equiv) → **3-28**

Entry	L32 (mol%)	Pd:L##	Yield[a] (%)	*ee*[b] (%)
1	5	1:1	32	77
2	10	1:2	82	89
3	15	1:3	36	80

[a]Isolated yield. [b]Measured by chiral HPLC.

Table 3-5. Modification of ligand stoichiometry and its effect on the yield and enantioselectivity of the cross-coupling reaction.

Attempts to improve the selectivity of the reaction were also made by applying systems of mixed ligands. A concept pioneered by Reetz and co-workers,[16] this methodology becomes relevant whenever there is a possibility that at least two monodentate ligands are coordinated to the metal centre at the transition state of a reaction. A simple case, depicted in Figure 3-10, involves two ligands L^a and L^b, and a metal centre, leading to three possible catalyst combinations that exist in equilibrium with one another (two homocombinations and one heterocombination).

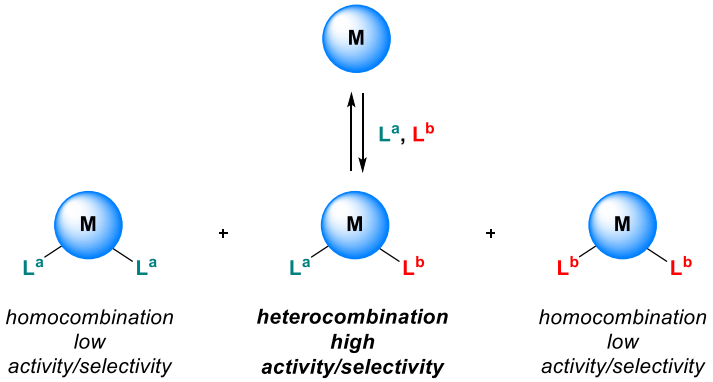


Figure 3-10. The concept of using mixtures of monodentate ligands in a transition metal-catalyzed reaction.

In asymmetric catalysis, the combinations of ligands used have involved both mixtures of two chiral ligands as well as mixtures of chiral and achiral ligands. One example where the use of a mixed chiral/achiral ligand system led to enhanced enantioselectivity is the iridium-catalyzed ketamine reduction to give chiral amines.[17] In this reaction, it was found that a combination of chiral phosphorous acid diester **L34** with triphenylphosphine gave the best result (Figure 3-11).

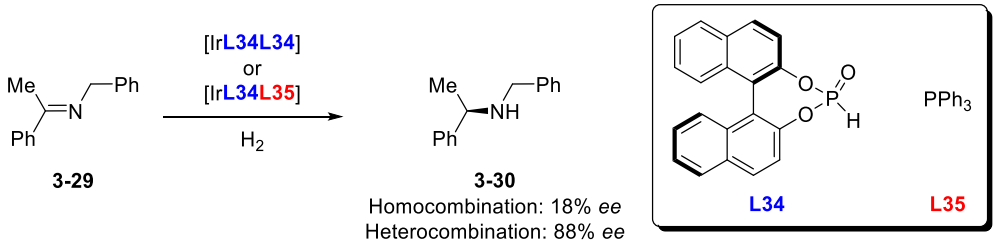
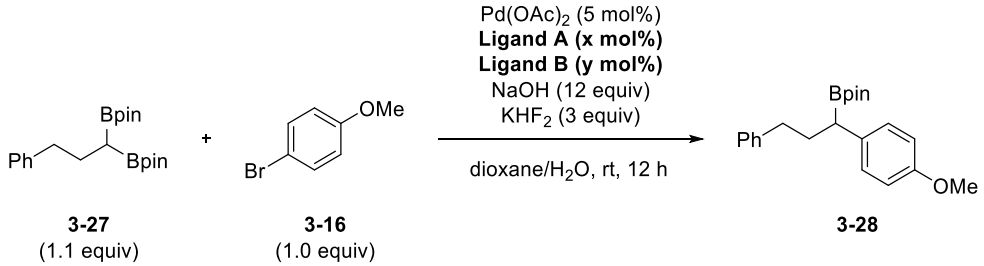


Figure 3-11. Iridium-catalyzed asymmetric reduction of ketamines to chiral amines using a chiral/achiral ligand mixture.

A few different mixtures were examined for the asymmetric cross-coupling of 1,1-diboronylalkanes (Table 3-6). When optimized phosphoramidite **L32** (10 mol%) was used in conjunction with PPh_3 (10 mol%) in the presence of $Pd(OAc)_2$ (5 mol%), a significant decrease in selectivity was observed (entry 2, Table 3-6). The same mixture was attempted again with reduced loading of the two ligands (5 mol% of each ligand) in an attempt to mimic more accurately the optimized Pd:ligand ratio (entry 3, Table 3-6). This combination, however, led to an even greater decrease in the observed selectivity of the reaction. Finally, a mixture of two chiral ligands differing in steric size was examined. When **L32** was used in combination with **L21**, it was found

that both the yield and selectivity of the reaction was decreased (entry 4, Table 3-6). Since the combination of ligands in this catalytic system seemed unfruitful, further studies were conducted using only the optimal ligand **L32**.



Entry	Ligand A (mol%)	Ligand B (mol%)	Yield[a] (%)	*ee*[b] (%)
1	**L32** (10)	N/A	82	89
2	**L32** (10)	PPh_3 (10)	50	71
3	**L32** (5)	PPh_3 (5)	70	66
4	**L32** (5)	L21 (5)	30	60

[a]Isolated yield. [b]Measured by chiral HPLC.

Table 3-6. Examination of mixtures of ligands for the asymmetric Suzuki-Miyaura cross-coupling of 1,1-diboronylalkanes.

3.7 Reaction scope and scalability

Through the screening of catalysts and mechanistic findings, the optimal conditions for this asymmetric cross-coupling of diboronylalkanes were obtained (Figure 3-12, Equation 17), which allowed for subsequent examination of the scope of substrates (Figure 3-12). Most aryl halides were found to cross-couple effectively giving the desired products in good yields and high enantiomeric excesses. An electron deficient aryl halide bearing a fluoride substituent gave the product **3-32** in a lower yield and *ee*, which could potentially be attributed to the electron deficient nature of the arene promoting protodeborylation of the benzylic boronate in the product.[5e,18] Gratifyingly, it was found that under these conditions, sterically hindered electrophiles like 2-bromotoluene and 2-bromoanisole were able to efficiently give the corresponding cross-coupled

products **3-34** and **3-36** respectively, with high selectivity. Unfortunately, alkenyl bromides could not be successfully cross-coupled to give the corresponding chiral allylboronates (not shown). Cross-coupling using bispinacolate **3-15** bearing a longer alkyl chain was also attempted and it was found to also give the cross-coupled product **3-17** with good stereoselectivity. It is notable that when Morken's ligand **L21** was used as the ligand (Table 3-4, entry 1), the selectivity was significantly lower (44% *ee* compared to 90% *ee*). When compared to the existing literature,[15] only one cross-coupling was achieved in lower selectivity (Figure 3-12, product **3-34**), while all other examples were achieved in equal or higher selectivities, showing our conditions to be complementary to those that were previously reported. The successful stereospecific cross-coupling of these chiral secondary boronate products has been previously reported,[5h,15] thus this method is a direct and efficient route towards the synthesis of optically enriched diarylalkanes.

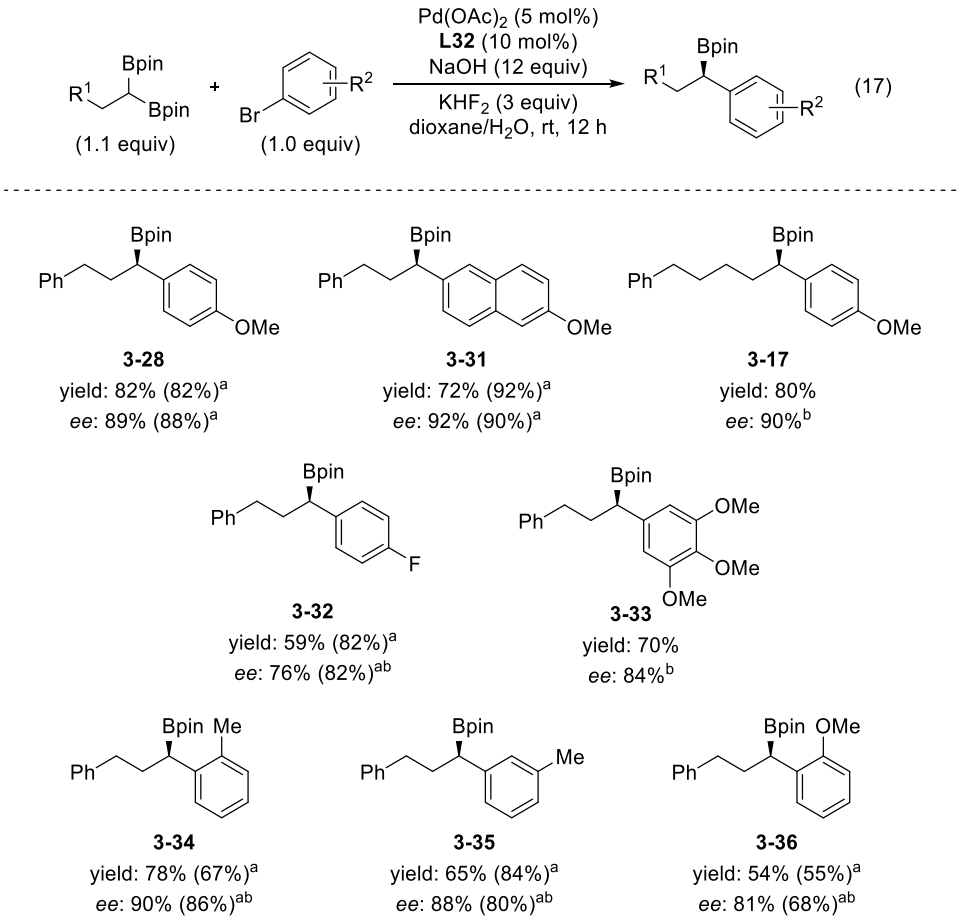
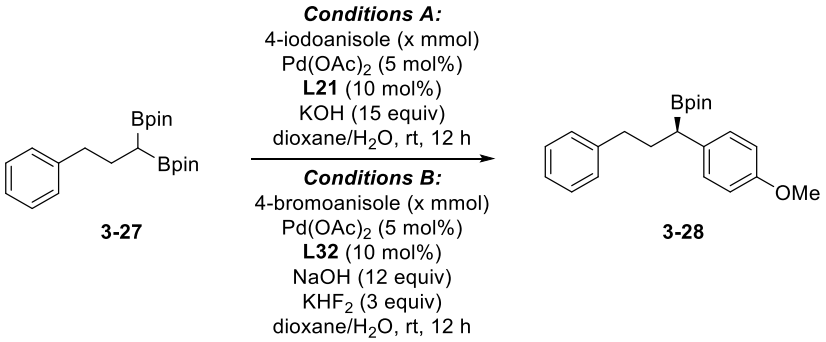


Figure 3-12. Reaction scope of the asymmetric Suzuki-Miyaura cross-coupling of 1,1-diboron compounds. Enantiomeric excesses of the corresponding alcohol were measured by chiral

HPLC. [a]Yields and selectivities in brackets are those reported by Morken and co-workers using **L21** in reference 15. [b]Yield over two steps (cross-coupling then oxidation). The crude cross-coupled product was directly oxidized to the corresponding alcohol for *ee* measurement.

During the course of our studies, we found that the cross-coupling under the original literature conditions[15] could not be reliably performed at scale larger than that reported (0.1 mmol of aryl halide). In organic chemistry, problems in the scaling up of batch reactions have been known to arise from various issues including inefficient mixing and heat transfer.[19] When the scale of the cross-coupling under literature conditions[15] was doubled to 0.2 mmol, it was found that the yield decreased from 82% to 58% and the selectivity also decreased significantly from 88% to 78% *ee* (Table 3-7, entry 2). Further increasing the scale to 0.4 mmol resulted in further diminished yield (39%) and enantiomeric excess (52%) (Table 3-7, entry 3). Of note, when the stirring of the reaction was extremely vigorous, the yield and *ee* of the reaction could be restored slightly (Table 3-7, entry 4), but not to the same level as when the reaction was performed on only a 0.1 mmol scale. This result seems to indicate that the conditions developed by Morken and co-workers are susceptible to irreproducibility due to the heterogenicity of the reaction mixture, thus vigorous mixing is required to maintain yield and *ee* at higher reaction scales. In contrast, when the cross-coupling was performed using our optimized conditions, it was found that the scale of the reaction had little effect on the outcome of the process. We were pleased to find that doubling the reaction scale from 0.1 mmol to 0.2 mmol had no detrimental effect on neither the yield nor the enantioselectivity, while cross-coupling at 0.4 mmol scale resulted only in a small decrease in yield (~10% decrease) and selectivity (3% decrease in *ee*). It is noteworthy that the cross-coupling was found to maintain its effectiveness even at over 20 times the original scale of the reaction (Table 3-7, entry 8). At a reaction scale requiring 1 g of diboronylalkane **3-27**, the desired cross-coupled product was obtained in lower yield (66%), but the selectivity of the reaction was maintained (88% *ee*).



Entry	Conditions	ArX (mmol)	Yield[a] (%)	*ee*[b] (%)
1	A	0.1	82	88
2	A	0.2	58	78
3	A	0.4	39	52
4	A	1.0[c]	57	78
5	B	0.1	80	89
6	B	0.2	82	89
7	B	0.4	71	86
8	B	2.4	66	88

[a]Isolated yield. [b]Enantiomeric excesses of the corresponding alcohols were measured by chiral HPLC. [c]The stirring plate was set to 1200 rpm.

Table 3-7. Examination of the scalability of the cross-coupling reaction.

3.8 Summary

In summary, this Chapter reports an in depth study on the optimization of ligand structure for the desymmetrization of prochiral 1,1-diboronylalkanes through a Pd-catalyzed asymmetric Suzuki-Miyaura reaction. While exploration of the intramolecular cross-coupling system proved to be unfruitful, an intramolecular variant of the asymmetric coupling was successfully developed. A thorough ligand optimization has demonstrated that both the size of the aryl groups and the amine groups on the phosphoramidite ligand exhibit significant effect on catalyst activity. Mechanistic studies have also shown that NaOH and KHF_2 likely serve to hydrolyze the pinacolboronates to

the corresponding diboronic acids, and this hydrolysis event could be a prerequisite to cross-coupling. According to the results of our studies, improved conditions were developed, which allows the reaction procedure to be scaled more reliably than the previously reported conditions.[15] Given the numerous known methods of derivatizing chiral boronates[14] the chiral secondary boronates produced through this desymmetrization process may be used as useful and versatile precursors in the synthesis of even more complex molecules.

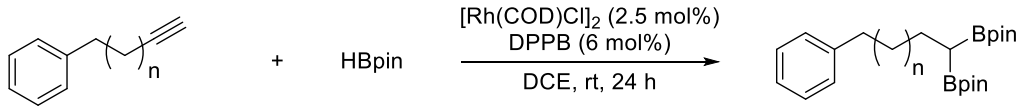
3.9 Experimental

3.9.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. THF, toluene, dichloromethane, and methanol, and DMF were treated by Fisher Scientific MBraun MB SPS* solvent system prior to use. Thin layer chromatography (TLC) was performed on Silicycle SiliaPlate™ TLC plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian Mercury-400, DDR MR-400, or VNMRS-500 MHz intruments. The residual solvent protons (^1H) and solvent carbons (^{13}C) were used as internal standards. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; sex, sextet; sep, septet, m, multiplet. 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-IF with frequencies expressed in cm^{-1}. Optical rotations were obtained on a Perkin Elmer 241 Polarimeter.

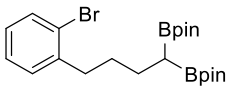
3.9.2 Synthesis of diboronylalkanes

General procedure for the preparation of 1,1-diboronylalkanes 3-7 and 3-15



The *gem*-diboronylalkanes **3-7** and **3-8** were synthesized according to the literature procedure[6] with some minor modifications. To a 25 mL round-bottomed flask equipped with a magnetic stir bar was added $[Rh(COD)Cl]_2$ (43 mg, 0.09 mmol) and DPPB (89 mg, 0.21 mmol). The reaction vessel was capped with a rubber septum and was evacuated and refilled with nitrogen gas. DCE (3.5 mL) was added via syringe, followed by the alkyne (3.47 mmol). Pinacol borane (1.5 mL, 10.41 mmol) was then added dropwise via syringe. The resulting solution was allowed to stir at room temperature for 24 hours. The reaction was then diluted with Et_2O and was then filtered through a pad of silica. The filtrate was concentrated in vacuo and purified by flash silica column chromatography (EtOAc/Hexanes, 5:95) to give the desired product as an oil.

2,2'-(4-(2-Bromophenyl)butane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3-7)



3-7

The title compound was synthesized according to the general procedure to afford a yellow oil (1.03 g, 64%).

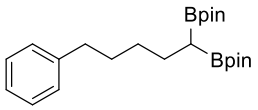
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.28 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.8, 7.5, 1.8 Hz, 1H), 2.60 (t, *J* = 7.6, 2H), 1.54-1.60 (m, 2H), 1.28-1.35 (m, 2H) 1.21 (s, 12H), 1.20 (s, 12H), 0.72 (t, *J* = 7.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 132.5, 131.2, 128.9, 127.6, 125.2, 88.9, 45.2, 35.3, 32.8, 25.2, 18.2.

IR (Microscope, cm^{-1}) 3000, 2987, 2878, 1370, 1316, 1145, 980, 865, 550.

HRMS (EI) for $C_{22}H_{35}B_2BrO_4$ (m/z): calcd: 464.1905; found: 464.1908.

2,2'-(5-Phenylpentane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3-15)

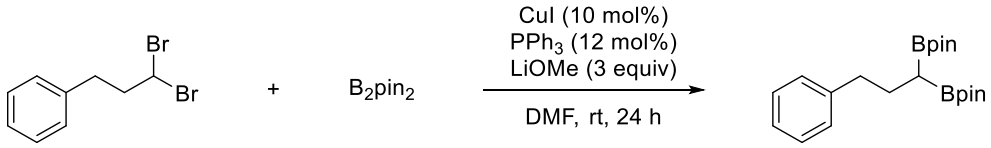


3-15

The title compound was synthesized according to the general procedure to afford a yellow oil (1.00 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.19 (m, 2H), 7.14-7.10 (m, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.52-1.61 (m, 4H), 1.26-1.34 (m, 2H), 1.21 (s, 12H), 1.20 (s, 12H), 0.72 (t, *J* = 7.9 Hz, 1H). Full characterization data is available in Ref 6b.

Synthesis of diboronylalkane 3-27



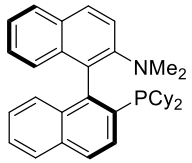
3-27

2,2'-(3-Phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (3-27)

The title compound was prepared according to the literature procedure[15] with slight modifications. To a 25 mL round-bottomed flask equipped with a magnetic stir bar was added CuI (19.2 mg, 0.10 mmol), B_2pin_2 (508 mg, 2.00 mmol), PPh_3 (34.4 mg, 0.13 mmol) and LiOMe (114 mg, 3 mmol). The reaction vessel was capped with a rubber septum and was evacuated and refilled with nitrogen gas. A solution of (3,3-dibromopropyl)benzene (prepared according to literature procedure[20] (278 mg, 1.00 mmol) in DMF was added via syringe. The resulting solution was allowed to stir at room temperature for 24 hours. The reaction was then diluted with Et_2O (6 mL) and filtered through a plug of Celite. The filtrate was washed with water (3 x 10 mL) and dried over $MgSO_4$(s), then concentrated in vacuo. The crude mixture was purified flash silica column chromatography (1-5% EtOAc/Hexanes) to give the desired product as a white solid (75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.19 (m, 2H), 7.15-7.08 (m, 3H), 2.56 (t, *J* = 7.9 Hz, 2H), 1.82 (q, *J* = 7.9 Hz, 2H), 1.20 (s, 12H), 1.20 (s, 12H), 0.78 (t, *J* = 7.9 Hz, 1H). Full characterization data is available in Ref 15.

3.9.3 Synthesis of Kenphos (L7)

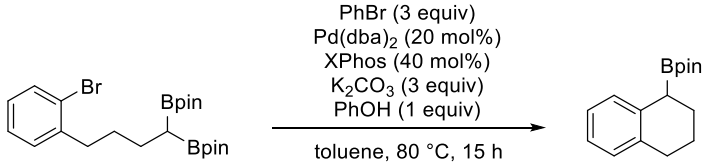


L7

The synthesis of Kenphos was performed according to literature procedures.[9] All spectroscopic data match that of the published literature. Proton NMR data for the final ligand has been included for proof of purity.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-7.90 (m, 3H), 7.82 (d, *J* = 5.3 Hz, 2H), 7.48 (d, *J* = 5.4 Hz, 2H), 7.46 (d, *J* = 5.3 Hz, 1H), 7.37 (d, *J* = 4.8 Hz, 1H), 7.25 (dd, *J* = 4.6, 4.6 Hz, 1H), 7.23 (dd, *J* = 4.6, 4.6 Hz, 1H), 7.05 (dd, *J* = 4.5, 0.9 Hz, 1H), 6.83 (d, *J* = 5.1 Hz, 1H), 2.53 (s, 6H), 2.55-0.69 (m, 22H). Full characterization data is available in Ref 9b.

3.9.4 Racemic intramolecular Suzuki-Miyaura cross-coupling



3-7 **3-8**

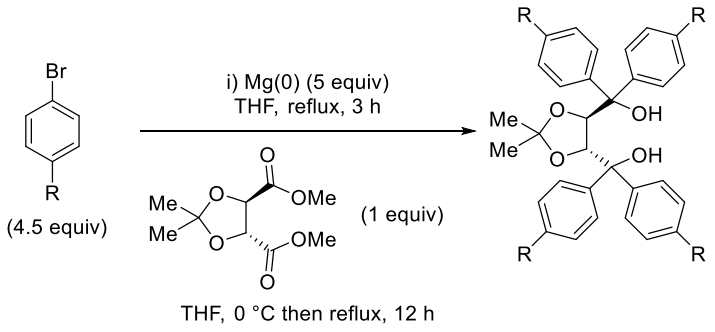
4,4,5,5-Tetramethyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)-1,3,2-dioxaborolane (3-8)

$Pd(dba)_2$ (2.8 mg, 4.8 μmol), XPhos (4.7 mg, 9.8 μmol), K_2CO_3 (101 mg, 0.73 mmol), phenol (23 mg, 0.24 mmol) and 1,1-diboron **3-7** (51 mg, 0.24 mmol) were stirred in toluene (2.4 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 (hexanes/EtOAc = 95:5) to afford the title product **3-8** (0.43 mg, 70% yield) as a yellow oil. All spectroscopic data match that of the published literature.[21] Proton NMR data has been included for proof of purity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.02 (m, 4H), 2.78-2.75 (m, 2H), 2.58 (t, *J* = 5.8 Hz, 1H), 1.91-1.84 (m, 3H), 1.78-1.68 (m, 1H), 1.22 (s, 6H), 1.23 (s, 6H). Full characterization data is available in Ref 21.

3.9.5 Synthesis of TADDOL-derived phosphoramidite ligands

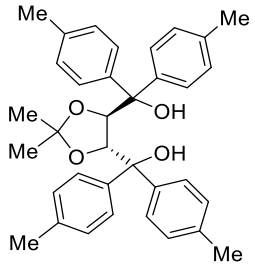
General Procedure for the synthesis of TADDOLS



All TADDOLs were prepared according to the literature procedure[10a] with slight modification. To a 100 mL round-bottomed flask equipped with a magnetic stir bar was added freshly ground magnesium turnings (0.28 g, 11.45 mmol). A single crystal of iodine was added and the flask was then fitted with a reflux condenser which was capped with a rubber septum. The reaction vessel was then evacuated and refilled with nitrogen gas. THF (18 mL) was added via syringe, followed by a slow addition of the aryl halide (10.30 mmol) as a solution in THF (7.6 mL). The reaction was then refluxed at 85 °C was 3 hours, after which it was cooled to 0 °C and a solution of 2,2-

dimethyl-1,3-dioxolane-4,5-dicarboxylate (0.50 g, 2.62 mmol) in THF (2.5 mL) was added slowly *via* syringe. The reaction was then refluxed at 85 °C for 12 h. It was then cooled to 0 °C and quenched with saturate NH_4Cl(aq) (75 mL). The mixture was then extracted with ethyl acetate (3 x 35 mL) and the combined organic layers were dried over $MgSO_4$(s), filtered and concentrated in vacuo. The crude material was then purified via flash silica column chromatography (3-10% EtOAc/Hexanes) to give the product as a white solid.

(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(di-*p*-tolylmethanol) (S1)

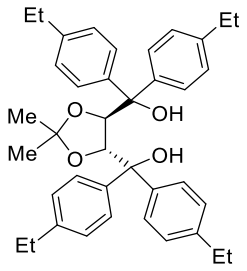


S1

The title compound was synthesized according to the general procedure to afford a white solid (1.07 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 4H), 7.25 (d, *J* = 8.2 Hz, 4H), 7.15 (d, *J* = 8.0 Hz, 4H), 7.08 (d, *J* = 8.0 Hz, 4H), 4.60 (s, 2H), 3.82 (s, 2H), 2.39 (s, 6H), 2.32 (s, 6H), 1.09 (s, 6H). Full characterization data is available in Ref 15.

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(bis(4-ethylphenyl)methanol) (S2)



S2

The title compound was synthesized according to the general procedure to afford a white solid (1.30 g, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.3 Hz, 4H), 7.26 (d, *J* = 8.4 Hz, 4H), 7.14 (d, *J* = 8.4 Hz, 4H), 7.09 (d, *J* = 8.4 Hz, 4H), 4.57 (s, 2H), 3.83 (s, 2H), 2.66 (q, *J* = 7.6 Hz, 4H), 2.60 (q, *J* = 7.6 Hz, 4H), 1.25 (t, *J* = 7.6 Hz, 6H), 1.20 (t, *J* = 7.6 Hz, 6H), 1.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 143.3, 142.9, 140.1, 128.4, 127.5, 127.5, 126.7, 109.3, 81.1, 77.9, 28.4, 28.4, 27.2, 15.4, 15.3

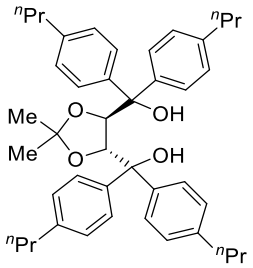
IR (Microscope, cm^{-1}) 3300, 3026, 2964, 2932, 2873, 1511, 1455, 1370, 1242, 1085, 828, 794

HRMS (ESI) for $C_{39}H_{46}O_4Na$ $[M+Na]^+$: calculated: 601.3288; found: 601.3299

$[\alpha]_D^{20}$ -58.07 (c = 0.70, $CHCl_3$)

Melting point: 72-75 °C

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(bis(4-propylphenyl)methanol) (S3)



S3

The title compound was synthesized according to the general procedure to afford a white solid (1.33 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 4H), 7.25 (d, *J* = 8.6 Hz, 4H), 7.12 (d, *J* = 8.3 Hz, 4H), 7.06 (d, *J* = 8.3 Hz, 4H), 4.57 (s, 2H), 3.81 (s, 2H), 2.60 (t, *J* = 6.8 Hz, 4H), 2.53 (d, *J* = 7.5 Hz, 4H), 1.66 (sex, *J* = 7.4 Hz, 4H), 1.60 (sex, *J* = 7.7 Hz, 4H), 1.01 (s, 6H), 0.94 (t, *J* = 7.3 Hz, 4H), 0.92 (t, *J* = 7.4 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 141.8, 141.4, 140.1, 128.4, 128.1, 127.4, 127.3, 109.4, 81.0, 77.9, 37.6, 27.1, 24.4, 24.3, 13.9, 13.8

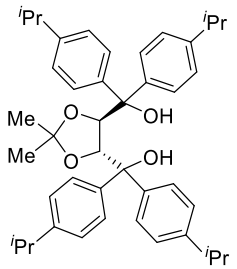
IR (Microscope, cm^{-1}) 3303, 2958, 2930, 2871, 1510, 1242, 1070, 843, 801

HRMS (ESI) for $C_{43}H_{54}O_4Na$ $[M+Na]^+$: calculated: 657.3914; found: 657.3925

$[\alpha]_D^{20}$ -60.46 (c = 0.68, $CHCl_3$)

Melting point: 58-60 °C

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(bis(4-isopropylphenyl)methanol) (S4)



S4

The title compound was synthesized according to the general procedure to afford a white solid (1.36 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 4H), 7.28 (d, *J* = 8.4 Hz, 4H), 7.17 (d, *J* = 8.2 Hz, 4H), 7.12 (d, *J* = 8.3 Hz, 4H), 4.57 (s, 2H), 3.90 (s, 2H), 2.92 (sep, *J* = 6.9 Hz, 2H), 2.86 (sep, *J* = 6.9 Hz, 2H), 1.27 (d, *J* = 6.9 Hz, 12H), 1.21 (dd, *J* = 6.9, 1.3 Hz, 12H), 1.02 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 147.5, 143.7, 140.1, 128.4, 128.5, 126.0, 125.2, 109.2, 81.1, 77.8, 33.6, 27.0, 24.0, 24.0, 23.9, 23.8.

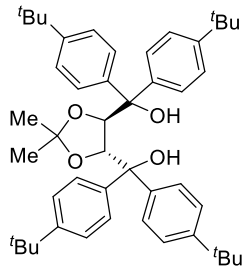
IR (Microscope, cm^{-1}) 3290, 2960, 2931, 2895, 1511, 1242, 1084, 828, 783

HRMS (ESI) for $C_{43}H_{54}O_4Na$ $[M+Na]^+$: calculated: 657.3914; found: 657.3906

$[\alpha]_D^{20}$ -59.94 (c = 0.89, $CHCl_3$)

Melting point: 93-96 °C

((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(bis(4-(*tert*-butyl)phenyl)methanol) (S5)

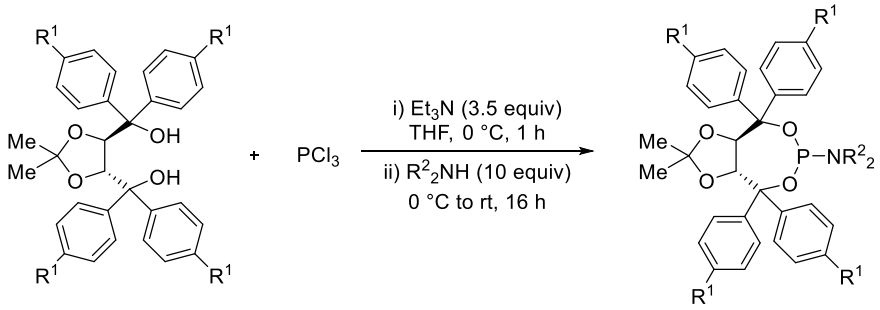


S5

The title compound was synthesized according to the general procedure to afford a white solid (1.23 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.6 Hz, 4H), 7.32 (d, *J* = 8.6 Hz, 4H), 7.29 (s, 8H), 4.57 (s, 2H), 3.91 (s, 2H), 1.33 (s, 18H), 1.23 (s, 18H), 1.01 (s, 6H). Full characterization data is available in Ref 10a.

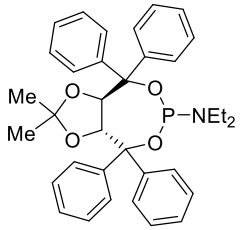
General Procedure for the synthesis of TADDOL-derived phosphoramidites



All phosphoramidites were synthesized according to literature procedure[10b] with slight modification. To a 25 mL round-bottomed flask equipped with a magnetic stir bar was added the diol (0.60 mmol). THF (3 mL) followed by Et_3N (0.29 mL, 0.95 mmol) were added via syringe, and the resulting solution was cooled to 0 °C before the dropwise addition of phosphorous trichloride (58 μL, 0.66 mmol). The reaction mixture was stirred for 1 hour and the amine (2.70 mmol) was then slowly added at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction was then diluted with Et_2O (15 mL) and filtered through a pad of Celite.

The filtrate was concentrated in vacuo and the resulting crude mixture was purified by flash silica column chromatography (0-2%EtOAc/1% Et_3N/Hexanes).

(3*aR*,8*aR*)-*N*,*N*-Diethyl-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L15)



L15

The title compound was synthesized according to the general procedure to afford a white solid (0.22 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.1 Hz, 2H), 7.60 (d, *J* = 7.1 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.42 (d, *J* = 7.1 Hz, 2H), 7.32-7.16 (m, 12H), 5.17 (dd, *J* = 8.6, 3.6 Hz, 1H), 4.74 (d, *J* = 8.5 Hz, 2H), 3.24 (m, 4H), 1.32 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 6H), 0.27 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 146.7, 142.5, 141.9, 129.1, 128.8, 128.8, 128.0, 127.6, 127.4, 127.3, 127.2, 127.2, 127.1, 127.1, 127.0, 126.9, 111.4, 82.6, 82.6, 82.4, 82.2, 81.5, 81.2, 81.2, 39.0, 38.8, 27.6, 25.3, 15.3, 15.2

^{31}P NMR (162 MHz, $CDCl_3$) δ 141.4

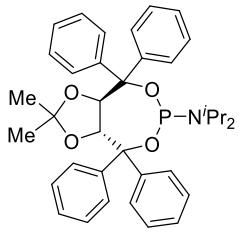
IR (Microscope, cm^{-1}) 3089, 3040, 2970, 2932, 2869, 1447, 1381, 1215, 1028, 917, 823, 758

HRMS (ESI) for $C_{35}H_{39}NO_4P$ $[M+H]^+$: calculated: 568.2611; found: 568.2604

$[\alpha]_D^{20}$ -132.77 (c = 0.35, $CHCl_3$)

Melting point: 149-151 °C

(3*aR*,8*aR*)-*N*,*N*-Diisopropyl-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L16)



L16

The title compound was synthesized according to the general procedure to afford a white solid (0.21 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.31-7.14 (m, 12 H), 5.19 (dd, *J* = 8.6, 3.8 Hz, 1H), 4.62 (d, *J* = 8.6 Hz, 1H), 3.98 (sep, *J* = 6.2 Hz, 2H), 1.42 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 0.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 147.0, 142.9, 142.1, 129.1, 128.7, 128.7, 127.8, 127.4, 127.3, 127.1, 127.1, 127.1, 126.9, 126.8, 111.0, 83.1, 83.1, 82.6, 82.4, 81.1, 81.1, 80.7, 80.7, 44.3, 44.2, 27.8, 25.0, 24.4, 24.3, 24.2, 24.1.

^{31}P NMR (162 MHz, $CDCl_3$) δ 140.4

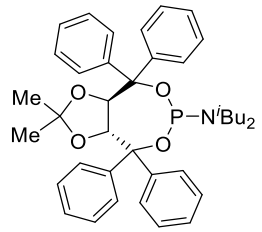
IR (Microscope, cm^{-1}) 3089, 3025, 2967, 2933, 2903, 1395, 1216, 1183, 1003, 981, 878, 736

HRMS (ESI) for $C_{37}H_{43}NO_4P$ $[M+H]^+$: calculated: 596.2924; found: 596.2924

$[\alpha]_D^{20}$ -96.64 (c = 0.82, $CHCl_3$)

Melting point: 135-138 °C

(3*aR*,8*aR*)-*N*,*N*-Diisobutyl-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L17)



L17

The title compound was synthesized according to the general procedure to afford a white solid (0.26 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 6.9 Hz, 2H), 7.56 (d, *J* = 7.1 Hz, 2H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.27-7.13 (m, 12 H), 5.18 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.69 (d, *J* = 8.6 Hz, 1H), 2.99-2.84 (m, 4H), 1.90 (sep, *J* = 6.8 Hz, 2H), 1.33 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 6H), 0.22 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 146.8, 142.6, 142.0, 129.3, 128.9, 128.8, 127.9, 127.5, 127.4, 127.3, 127.2, 127.2, 127.0, 127.0, 126.8, 52.8, 52.7, 27.7, 26.2, 26.2, 25.2, 20.5, 20.4

^{31}P NMR (162 MHz, $CDCl_3$) δ 141.8

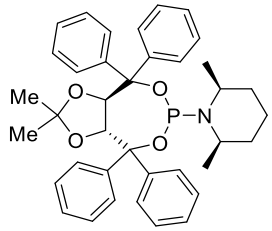
IR (Microscope, cm^{-1}) 3089, 3060, 2956, 2904, 2869, 1466, 1447, 1216, 1051, 1009, 879, 758

HRMS (ESI) for $C_{39}H_{47}NO_4P$ $[M+H]^+$: calculated: 624.3237; found: 624.3232

$[\alpha]_D^{20}$ -101.72 (c = 0.84, $CHCl_3$)

Melting point: 75-78 °C

(2*R*,6*S*)-1-((3*aR*,8*aR*)-2,2-Dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl)-2,6-dimethylpiperidine (L18)



L18

The title compound was synthesized according to the general procedure to afford a white solid (0.25 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 7.1 Hz, 2H), 7.49 (d, *J* = 7.1 Hz, 2H), 7.43 (d, *J* = 7.1 Hz, 2H), 7.32-7.15 (m, 12H), 5.15 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.68 (d, *J* = 8.6 Hz, 1H), 4.06-4.02 (m, 2H), 1.94-1.84 (m, 1H), 1.78-1.51 (m, 5H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.29 (d, 7.2 Hz, 3H), 0.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 147.0, 142.8, 142.0, 129.1, 128.8, 128.8, 128.0, 127.5, 127.1, 127.3, 127.2, 127.2, 127.1, 127.0, 126.8, 111.2, 82.8, 82.8, 82.6, 82.4, 81.2, 81.1, 81.0, 46.5, 46.3, 46.0, 45.8, 31.6, 31.3, 27.7, 25.2, 23.9, 23.8, 14.8

^{31}P NMR (162 MHz, $CDCl_3$) δ 139.9

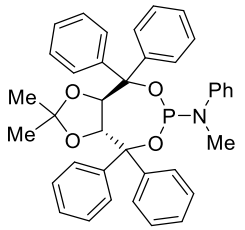
IR (Microscope, cm^{-1}) 3060, 3025, 2933, 2867, 1493, 1382, 1217, 1083, 1003, 876, 784, 700

HRMS (ESI) for $C_{38}H_{43}NO_4P$ $[M+H]^+$: calculated: 608.2924; found: 608.2914

$[\alpha]_D^{20}$ -111.91 (c = 0.85, $CHCl_3$)

Melting point: 99-102 °C

(3*aR*,8*aR*)-*N*,2,2-Trimethyl-*N*,4,4,8,8-pentaphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L19)



L19

The title compound was synthesized according to the general procedure to afford a white solid (0.17 g, 48%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 6.7 Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.30-7.16 (m, 14H), 7.04 (ddd, *J* = 8.6, 2.0, 2.0 Hz, 2H), 6.91 (dd, *J* = 7.2 Hz, 1H), 5.23 (dd, *J* = 8.5 Hz, 3.2 Hz, 1H), 4.85 (d, *J* = 8.5 Hz, 1H), 3.28 (d, *J* = 3.4 Hz, 3H), 1.29 (s, 3H), 0.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 146.9, 146.7, 146.2, 141.9, 141.4, 129.0, 128.9, 128.7, 128.7, 128.2, 127.8, 127.6, 127.5, 127.2, 127.2, 121.5, 119.3, 119.1, 111.9, 82.6, 82.6, 82.6, 82.5, 82.4, 82.0, 81.9, 31.6, 27.6, 25.3,

^{31}P NMR (162 MHz, $CDCl_3$) δ 136.7

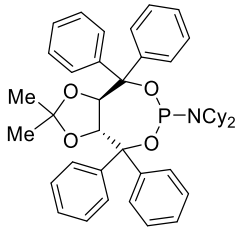
IR (Microscope, cm^{-1}) 3090, 3060, 2992, 2936, 1598, 1493, 1216, 1035, 1018, 917, 876, 739

HRMS (ESI) for $C_{38}H_{37}NO_4P$ $[M+H]^+$: calculated: 602.2455; found: 602.2441

$[\alpha]_D^{20}$ -137.02 (c = 0.82, $CHCl_3$)

Melting point: 80-83 °C

(3*aR*,8*aR*)-*N*,*N*-Dicyclohexyl-2,2-dimethyl-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L20)

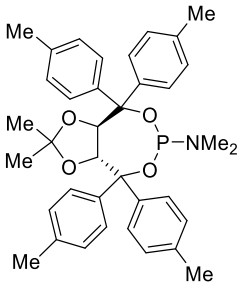


L20

The title compound was synthesized according to the general procedure to afford a white solid (0.20 g, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.42 (dd, *J* = 7.2, 2.1 Hz, 4H), 7.29-7.12 (m, 12 H), 5.12 (dd, *J* = 8.6, 3.4 Hz, 1H), 4.60 (d, *J* = 8.6 Hz, 1H), 3.45 (s, 2H), 1.85-1.74 (m, 8H), 1.59-1.28 (m, 15H), 1.02 (d, *J* = 13.1 Hz, 2H), 0.20 (s, 3H). Full characterization data is available in Ref 10b.

(3*aR*,8*aR*)-*N*,*N*,2,2-Tetramethyl-4,4,8,8-tetra-*p*-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L21)



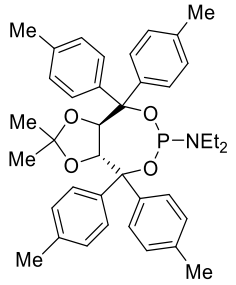
L21

The title compound was synthesized according to the general procedure to afford a white solid (0.29 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.62 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.12-7.07 (m, 6H), 7.04 (d, *J* = 8.0 Hz, 2H), 5.12 (dd, *J* = 8.4,

3.2 Hz, 1H), 4.77 (d, *J* = 8.5 Hz, 1H), 2.74 (s, 3H), 2.71 (s, 3H), 2.31 (s, 3H), 2.30 (s, 6H), 2.27 (s, 3H), 1.30 (s, 3H), 0.31 (s, 3H). Full characterization data is available in Ref 15.

(3*aR*,8*aR*)-*N*,*N*-Diethyl-2,2-dimethyl-4,4,8,8-tetra-*p*-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L22)



L22

The title compound was synthesized according to the general procedure to afford a white solid (0.27 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.1 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 6H), 7.03 (d, *J* = 8.2 Hz, 2H), 5.11 (dd, *J* = 8.9, 3.3 Hz, 1H), 4.70 (d, *J* = 8.5 Hz, 1H), 3.30-3.14 (m, 4H), 2.30 (s, 6H), 2.30 (s, 3H), 2.27 (s, 3H), 1.34 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 6H), 0.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 144.2, 139.6, 139.3, 136.7, 136.6, 136.4, 136.3, 129.0, 128.7, 128.6, 128.3, 128.2, 127.8, 127.1, 127.0, 111.2, 82.9, 82.9 , 82.6, 82.4, 81.2, 81.1, 81.0, 39.0, 38.8, 27.7, 25.3, 21.1, 21.1, 21.1, 21.0, 15.3, 15.3.

^{31}P NMR (162 MHz, $CDCl_3$) δ 141.2

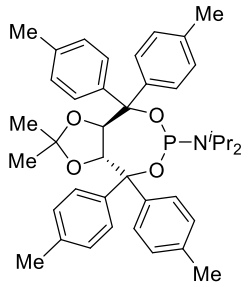
IR (Microscope, cm^{-1}) 3027, 2971, 2923, 2869, 1510, 1380, 1184, 1040, 1024, 922, 788, 754

HRMS (ESI) for $C_{39}H_{47}NO_4P$ $[M+H]^+$: calculated: 624.3237; found: 624.3244

$[\alpha]_D^{20}$ -108.38 (c = 0.40, $CHCl_3$)

Melting point: 105-108 °C

(3*aR*,8*aR*)-*N*,*N*-Diisopropyl-2,2-dimethyl-4,4,8,8-tetra-*p*-tolyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L23)



L23

The title compound was synthesized according to the general procedure to afford a white solid (0.27 g, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.06-7.00 (m, 8H), 5.11 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.54 (d, *J* = 8.6 Hz, 1H), 3.96 (sep, *J* = 6.4 Hz, 2H), 2.28 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 1.42 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.17 (d, *J* = 6.8 Hz, 6H), 0.22 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 144.4, 144.4, 140.0, 139.5, 136.5, 136.4, 136.3, 136.1, 128.9, 128.5, 128.4, 128.4, 128.2, 128.2, 127.7, 127.1, 127.0, 110.7, 83.4, 82.8, 82.7, 81.0, 80.9, 80.4, 80.4, 44.2, 44.1, 27.8, 25.1, 24.4, 24.3, 24.2, 24.1, 21.1, 21.0, 21.0

^{31}P NMR (162 MHz, $CDCl_3$) δ 139.7

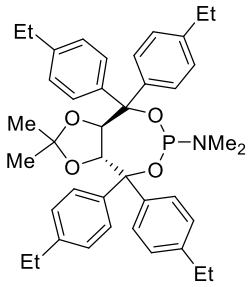
IR (Microscope, cm^{-1}) 3026, 2967, 2924, 2870, 1510, 1395, 1202, 1057, 1006, 980, 787, 753

HRMS (ESI) for $C_{41}H_{51}NO_4P$ $[M+H]^+$: calculated: 652.3550; found: 652.3550

$[\alpha]_D^{20}$ -77.54 (c = 0.89, $CHCl_3$)

Melting point: 116-118 °C

(3*aR*,8*aR*)-4,4,8,8-Tetrakis(4-ethylphenyl)-*N*,*N*,2,2-tetramethyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L24)



L24

The title compound was synthesized according to the general procedure to afford a white solid (0.29 g, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.10-7.07 (m, 6H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.12 (dd, *J* = 8.5, 3.2, 1H), 4.73 (d, *J* = 8.5 Hz, 1H), 2.72 (s, 3H), 2.70 (s, 3H), 2.62-2.55 (m, 8H), 1.29 (s, 3H), 1.21-1.16 (m, 12H), 0.23 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 144.1, 143.0, 142.8, 142.6, 139.5, 139.4, 128.9, 128.5, 128.5, 127.5, 127.1, 127.0, 126.9, 126.5, 111.4, 82.9, 82.9, 82.6, 82.5, 81.3, 81.1, 81.0, 35.4, 35.3, 28.4, 27.6, 25.2.

^{31}P NMR (162 MHz, $CDCl_3$) δ 139.4

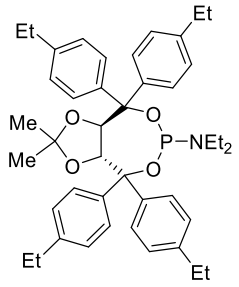
IR (Microscope, cm^{-1}) 3026, 2965, 2932, 2874, 1510, 1215, 1062, 975, 923, 842, 786, 756

HRMS (ESI) for $C_{38}H_{37}NO_4P$ $[M+H]^+$: calculated: 652.3550; found: 652.3548

$[\alpha]_D^{20}$ -109.50 (c = 0.59, $CHCl_3$)

Melting point: 87-90 °C

(3*aR*,8*aR*)-*N*,*N*-Diethyl-4,4,8,8-tetrakis(4-ethylphenyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L25)



L25

The title compound was synthesized according to the general procedure to afford a white solid (0.29 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.12-7.09 (m, 6H), 7.05 (d, *J* = 8.4 Hz, 2H), 5.14 (dd, *J* = 8.5, 3.5 Hz, 1H), 4.69 (d, *J* = 8.6 Hz, 1H), 3.32-3.17 (m, 4H), 2.65-2.59 (m, 8H), 1.36 (s, 3H), 1.24-1.13 (m, 18H), 0.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 144.4, 142.9, 142.7, 142.4, 139.9, 139.6, 129.0, 128.6, 128.6, 127.4, 127.1, 127.0, 127.0, 127.0, 126.5, 111.1, 83.1, 83.1, 82.7, 82.5, 81.2, 81.1, 81.0, 39.0, 38.9, 28.4, 27.7, 25.2, 15.7, 15.4, 15.2, 15.1

^{31}P NMR (162 MHz, $CDCl_3$) δ 141.0

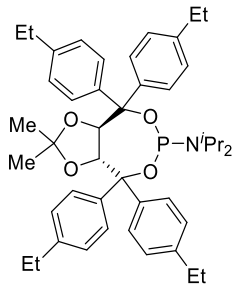
IR (Microscope, cm^{-1}) 3058, 2985, 2871, 1510, 1206, 1041, 1009, 921, 840, 785

HRMS (ESI) for $C_{43}H_{55}NO_4P$ $[M+H]^+$: calculated: 680.3863; found: 680.3865

$[\alpha]_D^{20}$ -90.44 (c = 0.39, $CHCl_3$)

Melting point: 76-79 °C

(3*aR*,8*aR*)-4,4,8,8-Tetrakis(4-ethylphenyl)-*N*,*N*-diisopropyl-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L26)



L26

The title compound was synthesized according to the general procedure to afford a white solid (0.29 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.11-7.07 (m, 6H), 7.04 (d, *J* = 8.4 Hz, 2H), 5.14 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.56 (d, *J* = 8.6 Hz, 1H), 3.99 (sep, *J* = 7.0 Hz, 2H), 2.65-2.53 (m, 8H), 1.44 (s, 3H), 1.26-1.13 (m, 24H), 0.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 144.6, 142.7, 142.7, 142.6, 142.2, 140.2, 139.7, 129.0, 128.4, 128.4, 127.2, 127.1, 127.0, 126.9, 126.8, 126.5, 110.7, 83.4, 83.4, 82.8, 82.7, 81.0, 81.0, 80.3, 44.2, 44.1, 28.4, 28.3, 28.3, 27.8, 25.0, 24.4, 24.4, 24.2, 24.1, 15.6, 15.3, 15.2, 15.0

^{31}P NMR (162 MHz, $CDCl_3$) δ 139.6

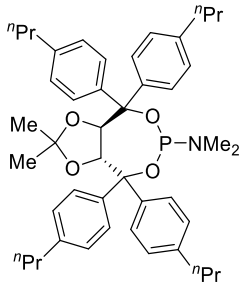
IR (Microscope, cm^{-1}) 3026, 2965, 2932, 2873, 1506, 1394, 1203, 1062, 981, 813, 782, 758

HRMS (ESI) for $C_{45}H_{59}NO_4P$ $[M+H]^+$: calculated: 708.4176; found: 708.4172

$[\alpha]_D^{20}$ -72.86 (c = 0.48, $CHCl_3$)

Melting point: 99-101 °C

(3*aR*,8*aR*)-*N*,*N*,2,2-Tetramethyl-4,4,8,8-tetrakis(4-propylphenyl)tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L27)



L27

The title compound was synthesized according to the general procedure to afford a white solid (0.31 g, 72%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.12-7.07 (m, 6H), 7.04 (d, *J* = 8.4 Hz, 2H), 5.14 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.79 (d, *J* = 8.5 Hz, 1H), 2.73 (s, 3H), 2.70 (s, 3H), 2.58-2.49 (m, 8H), 1.68-1.54 (m, 8H), 1.27 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 6H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 144.1, 141.6, 141.4, 141.3, 141.1, 139.5, 139.5, 139.5, 128.8, 128.5, 128.5, 128.0, 127.7, 127.5, 127.2, 126.9, 126.9, 111.5, 82.8, 82.7, 82.5, 82.4, 81.7, 81.2, 81.1, 37.8, 37.7, 37.6, 37.5, 35.4, 35.327.5, 25.3, 24.5, 24.3, 24.3, 24.2, 14.0, 14.0, 14.0, 13.6

^{31}P NMR (162 MHz, $CDCl_3$) δ 138.8

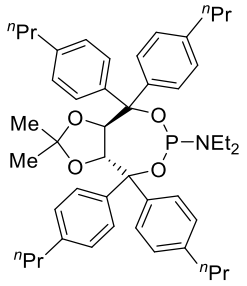
IR (Microscope, cm^{-1}) 3-59, 2958, 2930, 2871, 1510, 1308, 1215, 1022, 1000, 975, 882, 845, 764

HRMS (ESI) for $C_{45}H_{59}NO_4P$ $[M+H]^+$: calculated: 708.4176; found: 708.4181

$[\alpha]_D^{20}$ -120.55 (c = 0.70, $CHCl_3$)

Melting point: 65-69 °C

(3*aR*,8*aR*)-*N*,*N*-Diethyl-2,2-dimethyl-4,4,8,8-tetrakis(4-propylphenyl)tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L28)



L28

The title compound was synthesized according to the general procedure to afford a white solid (0.29 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3Hz, 2H), 7.10-7.07 (m, 6H), 7.03 (d, *J* = 8.4 Hz, 2H), 5.13 (dd, *J* = 8.5, 3.4 Hz, 1H), 4.71 (d, *J* = 8.5 Hz, 1H), 3.32-3.13 (m, 4H), 2.57-2.49 (m, 8H), 1.68-1.52 (m, 8H), 1.32 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 6H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.25 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 144.4, 141.4, 141.3, 141.2, 141.0, 139.9, 139.6, 128.9, 128.6, 128.5, 127.9, 127.5, 127.5, 127.1, 127.0, 127.0, 111.1, 82.9, 82.9, 82.5, 82.4, 81.2, 81.2, 81.1, 39.0, 38.8, 37.8, 37.7, 37.7, 37.5, 27.6, 25.2, 24.4, 24.3, 24.2, 15.3, 15.3, 14.0, 13.6

^{31}P NMR (162 MHz, $CDCl_3$) δ 140.9

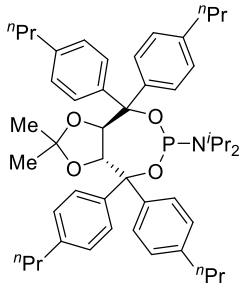
IR (Microscope, cm^{-1}) 3026, 2961, 2931, 2870, 1510, 1379, 1207, 1023, 1010, 881, 844, 772

HRMS (ESI) for $C_{47}H_{63}NO_4P$ $[M+H]^+$: calculated: 736.4489; found: 736.4498

$[\alpha]_D^{20}$ -96.35 (c = 0.60, $CHCl_3$)

Melting point: 62-68 °C

(3*aR*,8*aR*)-*N*,*N*-Diisopropyl-2,2-dimethyl-4,4,8,8-tetrakis(4-propylphenyl)tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L29)



L29

The title compound was synthesized according to the general procedure to afford a white solid (0.32 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.08-7.05 (m, 6H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.14 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.57 (d, *J* = 8.6 Hz, 1H), 3.97 (sep, *J* = 6.8 Hz, 2H), 2.57-2.48 (m, 8H), 1.69-1.55 (m, 8H), 1.42 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 6H), 1.19 (d, *J* = 6.8 Hz, 6H), 0.96-0.89 (m, 9H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.22 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 144.6, 141.2, 141.2, 141.1, 140.8, 140.2, 139.8, 128.9, 128.4, 128.4, 127.7, 127.5, 127.4, 127.2, 126.9, 110.7, 83.3, 82.7, 82.6, 81.0, 81.0, 80.5, 80.5, 44.2, 44.1, 37.7, 37.5, 27.8, 25.1, 24.4, 24.4, 24.3, 24.3, 24.2, 24.2, 24.1, 14.0, 13.9, 13.6.

^{31}P NMR (162 MHz, $CDCl_3$) δ 139.8

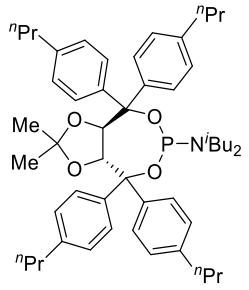
IR (Microscope, cm^{-1}) 3025, 2963, 2931, 2871, 1509, 1395, 1203, 1022, 1002, 881, 762

HRMS (ESI) for $C_{49}H_{67}NO_4P$ $[M+H]^+$: calculated: 764.4802; found: 764.4794

$[\alpha]_D^{20}$ -78.41(c = 0.84, $CHCl_3$)

Melting point: 75-78 °C

(3*aR*,8*aR*)-*N*,*N*-Diisobutyl-2,2-dimethyl-4,4,8,8-tetrakis(4-propylphenyl)tetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-amine (L30)



L30

The title compound was synthesized according to the general procedure to afford a white solid (0.29 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.04 (d, *J* = 8.3 Hz, 6H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.14 (dd, *J* = 8.6, 3.6 Hz, 1H), 4.64 (d, *J* = 8.5 Hz, 1H), 2.98-2.82 (m, 4H), 2.53-2.46 (m, 8H), 1.89 (sep, *J* = 7.2 Hz, 2H), 1.65-1.49 (m, 8H), 1.33 (s, 3H), 0.93-0.87 (m, 15H), 0.84-0.80 (m, 9H), 0.19 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 144.4, 141.4, 141.2, 141.2, 140.9, 140.0, 139.6, 129.1, 128.6, 128.6, 127.9, 127.4, 127.4, 127.2, 127.1, 127.0, 111.0, 82.7, 82.7, 82.3, 82.2, 81.3, 81.2, 81.0, 52.9, 52.8, 37.7, 37.7, 37.5, 27.7, 26.3, 26.3, 25.2, 24.4, 24.3, 24.2, 20.6, 20.5, 14.0, 14.0, 13.6.

^{31}P NMR (162 MHz, $CDCl_3$) δ 141.3

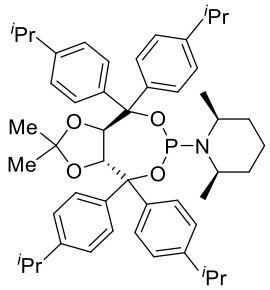
IR (Microscope, cm^{-1}) 3026, 2958, 2930, 2870, 1510, 1381, 1215, 1042, 1008, 881, 765

HRMS (ESI) for $C_{51}H_{71}NO_4P$ $[M+H]^+$: calculated: 792.5115; found: 792.5105

$[\alpha]_D^{20}$ -74.31 (c = 0.82, $CHCl_3$)

Melting point: 64-66 °C

(2*R*,6*S*)-2,6-Dimethyl-1-((3*aR*,8*aR*)-4,4,8,8-tetrakis(4-isopropylphenyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepin-6-yl)piperidine (L32)



L32

The title compound was synthesized according to the general procedure to afford a white solid (0.25 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.14-7.10 (m, 6H), 7.07 (d, *J* = 8.3 Hz, 2H), 5.12 (dd, *J* = 8.6, 3.6 Hz, 1H), 4.60 (d, *J* = 8.5 Hz, 1H), 4.11-4.03 (m, 2H), 2.91-2.79 (m, 4H), 1.98-1.84 (m, 1H), 1.79-1.64 (m, 2H), 1.61-1.49 (m, 3H), 1.39 (s, 3H), 1.38 (d, *J* = 7.9 Hz, 3H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.24-1.21 (m, 21H), 1.17 (dd, *J* = 6.9, 2.0 Hz, 9H), 0.19 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 147.3, 147.1, 146.8, 145.0, 144.5, 140.2, 139.6, 129.0, 128.4, 127.0, 126.9, 125.9, 125.6, 125.4, 125.0, 110.9, 83.2, 83.2, 82.8, 82.6, 81.0, 80.9, 80.6, 46.4, 46.2, 45.9, 45.7, 33.6, 33.6, 33.5, 33.5, 31.6, 31.4, 27.7, 24.9, 24.0, 23.9, 23.9, 23.8, 14.8

^{31}P NMR (162 MHz, $CDCl_3$) δ 139.1

IR (Microscope, cm^{-1}) 2961, 2931, 2870, 1510, 1215, 1020, 1002, 842, 812, 781, 758

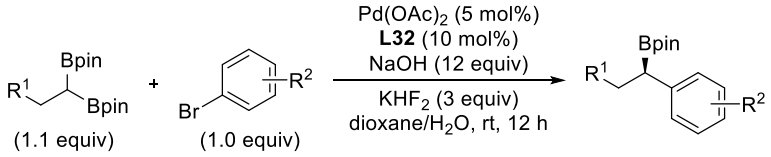
HRMS (ESI) for $C_{50}H_{67}NO_4P$ $[M+H]^+$: calculated: 776.4802; found: 776.4789

$[\alpha]_D^{20}$ -92.71 (c = 0.41, $CHCl_3$)

Melting point: 116-120 °C

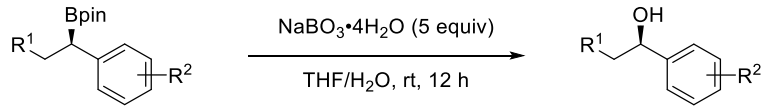
3.10 Representative procedures for the desymmetrization of 1,1-diboronylalkanes

General Procedure for the Asymmetric Suzuki-Miyaura Cross-Coupling of 1,1-Diboronyl Alkanes



To a 5 mL round-bottomed flask equipped with a magnetic stir bar was added, 1,1-diboronylalkane (0.11 mmol), aryl bromide (0.10 mmol), **L31** (8 mg, 0.01 mmol), and KHF_2 (23 mg, 0.30 mmol). The flask was capped with a rubber septum then evacuated and refilled with nitrogen. A stock solution of $Pd(OAc)_2$ in THF (0.025 M) was made and 0.2 mL of the solution was added to the reaction vessel *via* syringe. NaOH was then added as an 8 N aqueous solution (0.15 mL) via syringe, and the resulting mixture was allowed to stir at room temperature for 12 h. The reaction was then diluted with Et_2O (5 mL) and filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the crude mixture was then purified by flash silica column chromatography (1-5%EtOAc/Hexanes).

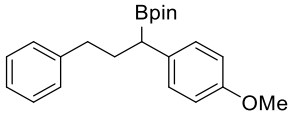
General Procedure for the Oxidation of Cross-Coupling Products



To a 10 mL round-bottomed flask equipped with a magnetic stir bar was added the cross-coupling product (0.1 mmol), THF (0.5 mL) and H_2O (0.5 mL). Sodium perborate tetrahydrate (78 mg, 0.5 mmol) was then added and the reaction vessel was capped with a rubber septum and the mixture was stirred at room temperature for 12 h. The reaction was then diluted with H_2O (10 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The organic extracts were combined and washed with water (10 mL) then brine (10 mL). The organic layer was then dried over $MgSO_4$ and

concentrate in vacuo. The resulting crude material was analyzed for enantiomeric excess without further purification.

2-(1-(4-Methoxyphenyl)-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3-28)

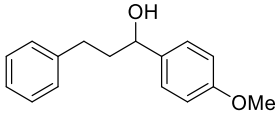


3-28

The title compound was prepared using the general procedure. Flash column chromatography (1-5% EtOAc/Hexanes) yielded the product as a colourless oil (30 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H), 7.17-7.12 (m, 5H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 8.0 Hz, 2H), 2.29 (t, *J* = 8.0 Hz, 1H), 2.16-2.07 (m, 1H), 1.98-1.88 (m, 1H), 1.21 (s, 6H), 1.19 (s, 6H). Full characterization data is available in Ref 15.

1-(4-Methoxyphenyl)-3-phenylpropan-1-ol (S3-28)



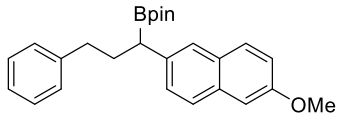
S3-28

The title compound was prepared using the general procedure. The product was obtained as a white waxy solid (20 mg, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 4H), 7.20-7.16 (m, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.64 (dd, *J* = 7.6, 5.7 Hz, 1H), 3.82 (s, 3H), 2.77-2.61 (m, 2H), 2.19-2.10 (m, 1H), 2.06-2.00 (m, 1H). Full characterization data is available in Ref 15.

HPLC (Chiralcel OD) 5:95 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 62.2 min, T_{minor} = 53.3 min, *ee* = 88%

2-(1-(6-Methoxynaphthalen-2-yl)-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3-31)

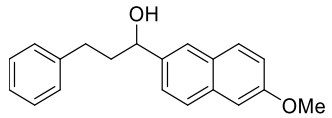


3-31

The title compound was prepared using the general procedure. Flash column chromatography (1-5% EtOAc/Hexanes) yielded the product as a pale yellow oil (29 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 9.6, 4.3 Hz, 2H), 7.58 (d, *J* = 1.4 Hz, 1H), 7.36 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.28-7.24 (m, 2H), 7.18-7.14 (m, 3H), 7.12-7.10 (m, 2H), 3.91 (s, 3H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.49 (t, *J* = 8.0 Hz, 1H), 2.28-2.19 (m, 1H), 2.12-2.02 (m, 1H), 1.21 (s, 6H), 1.19 (s, 6H). Full characterization data is available in Ref 15.

1-(6-Methoxynaphthalen-2-yl)-3-phenylpropan-1-ol (S3-31)



S3-31

The title compound was prepared using the general procedure. The product was obtained as a white waxy solid (21 mg, quant.)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.74 (m, 3H), 7.48 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.32-7.28 (m, 2H), 7.24-7.21 (m, 3H), 7.20-7.17 (m, 2H), 4.86 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.95 (s, 3H), 2.83-2.77 (m, 1H), 2.75-2.69 (m, 1H), 2.29-2.22 (m, 1H), 2.20-2.11 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 141.8, 139.6, 134.2, 129.4, 128.7, 128.5, 128.4, 127.2, 125.9, 124.6, 124.6, 119.0, 105.7, 74.0, 55.3, 40.3, 32.1.

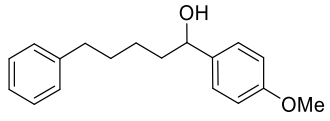
IR (Microscope, cm^{-1}) 3236, 3022, 2944, 2924, 2875, 2859, 1453, 1213, 1030, 857, 741, 698

HRMS (EI) for $C_{20}H_{20}O_2$ (m/z): calculated: 292.1463; found: 292.1467

$[\alpha]_D^{20}$ 4.80 (c = 0.45, $CHCl_3$)

HPLC (Chiralcel OD) 5:95 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 103.6 min, T_{minor} = 68.3 min, *ee* = 92%

1-(4-Methoxyphenyl)-5-phenylpentan-1-ol (S3-17)



S3-17

The title compound was prepared using the general procedure. The product was obtained as a pale yellow waxy solid (22 mg, 80%) over two steps starting from the corresponding 1,1-diboronylalkane (cross-coupling then oxidation).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 4H), 7.19-7.14 (m, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.61 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.81 (s, 3H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.88-1.79 (m, 1H), 1.76-1.60 (m, 4H), 1.51-1.41 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 142.6, 137.0, 128.4, 128.2, 127.1, 125.6, 113.8, 74.2, 55.3, 38.8, 35.9, 31.4, 29.7, 25.6

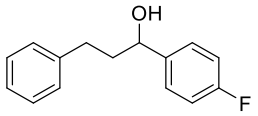
IR (Microscope, cm^{-1}) 3386, 3026, 3001, 2929, 2855, 1611, 1512, 1463, 1247, 1175, 1035, 832, 700

HRMS (EI) for $C_{18}H_{22}O_2$ (m/z): calculated: 270.1620; found: 270.1618

$[\alpha]_D^{20}$ 10.40 (c = 0.30, $CHCl_3$)

HPLC (Chiralcel OD) 5:95 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 47.4 min, T_{minor} = 52.0 min, *ee* = 90%

1-(4-Fluorophenyl)-3-phenylpropan-1-ol (S3-32)



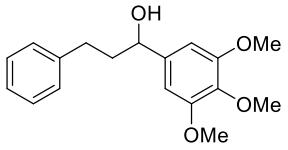
S3-32

The title compound was prepared using the general procedure. The product was obtained in as a white waxy solid (14 mg, 59%) over two steps starting from the corresponding 1,1-diboronylalkane (cross-coupling then oxidation).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.23-7.20 (m, 3H), 7.06 (dd, *J* = 8.7, 8.7, 2H), 4.72-4.70 (m, 1H), 2.79-2.73 (m, 1H), 2.72-2.66 (m, 1H), 2.20-2.11 (m, 1H), 2.06-1.99 (m, 1H), 1.82 (d, *J* = 2.2 Hz, 1H). Full characterization data is available in Ref 15.

HPLC (Chiralcel OD) 5:95 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 210 nm, T_{major} = 49.4 min, T_{minor} = 38.2 min, *ee* = 92%

3-Phenyl-1-(3,4,5-trimethoxyphenyl)propan-1-ol (S3-33)



S3-33

The title compound was prepared using the general procedure. The product was obtained as a white waxy solid (21 mg, 70%) over two steps starting from the corresponding 1,1-diboronylalkane (cross-coupling then oxidation).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.14 (m, 3H), 6.54 (s, 2H), 4.61-4.58 (m, 1H), 3.83 (s, 6H), 3.81 (s, 3H), 2.78-2.62 (m, 2H), 2.15-2.06 (m, 1H), 2.02-1.94 (m, 1H), 1.82 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 141.7, 140.4, 137.3, 128.4, 128.4, 125.9, 102.8, 74.1, 60.8, 56.1, 40.4, 32.2

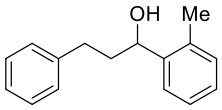
IR (Microscope, cm^{-1}) 3446, 3024, 2999, 2937, 2838, 1592, 1456, 1327, 1125, 1008, 750, 700

HRMS (EI) for $C_{18}H_{22}O_4$ (m/z): calculated: 302.1518; found: 302.1512

$[\alpha]_D^{20}$ 11.33 (c = 0.51, $CHCl_3$)

HPLC (Chiralcel OD) 10:90 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 61.8 min, T_{minor} = 39.0 min, *ee* = 92%

3-Phenyl-1-(*o*-tolyl)propan-1-ol (S3-34)



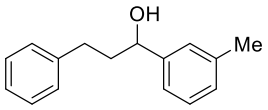
S3-34

The title compound was prepared using the general procedure. The product was obtained as a white waxy solid (18 mg, 78%) over two steps starting from the corresponding 1,1-diboronylalkane (cross-coupling then oxidation).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.24 (m, 3H), 7.18-7.10 (m, 5H), 7.06-2.02 (m, 1H), 4.68 (dd, *J* = 7.8, 5.4 Hz, 1H), 2.79-2.73 (m, 1H), 2.70-2.64 (m, 1H), 2.36 (s, 3H), 2.17-2.10 (m, 1H), 2.06-1.99 (m, 1H), 1.79 (br s, 1H). Full characterization data is available in Ref 15.

HPLC (Chiralcel OD) 2:98 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 64.3 min, T_{minor} = 60.7 min, *ee* = 90%

3-Phenyl-1-(*m*-tolyl)propan-1-ol (S3-35)



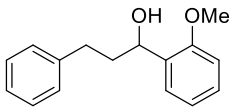
S3-35

The title compound was prepared using the general procedure. The product was obtained as a white waxy solid (15 mg, 65%) over two steps starting from the corresponding 1,1-diboronylalkane (cross-coupling then oxidation).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.23 (m, 3H), 7.21-7.09 (m, 6H), 4.66 (dd, *J* = 7.8, 5.3 Hz, 1H), 2.79-2.73 (m, 1H), 2.70-2.64 (m, 1H), 2.36 (s, 3H), 2.17-2.10 (m, 1H), 2.06-1.99 (m, 1H), 1.79 (br s, 1H). Full characterization data is available in Ref 15.

HPLC (Chiralcel OD) 5:95 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 43.0 min, T_{minor} = 32.6 min, *ee* = 88%

1-(2-Methoxyphenyl)-3-phenylpropan-1-ol (S3-36)



S3-36

The title compound was prepared using the general procedure. The product was obtained as a waxy white solid (13 mg, 54%) over two steps starting from the corresponding 1,1-diboronylalkane (cross-coupling then oxidation).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.16 (m, 6H), 6.98-6.94 (m, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 4.89 (d, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 2.86-2.81 (m, 1H), 2.72-2.66 (m, 1H), 2.58 (d, 1H), 2.19-2.06 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 142.2, 132.3, 128.5, 128.4, 128.3, 127.0, 125.7, 120.8, 110.6, 70.8, 55.2, 38.7, 32.4

IR (Microscope, cm^{-1}) 3406, 3026, 2925, 2849, 2837, 1602, 1492, 1464, 1241, 1050, 1030, 754, 700

HRMS (EI) for $C_{16}H_{18}O_2$ (m/z): calculated: 242.3180; found: 242.1305

$[\alpha]_D^{20}$ 21.00 (c = 0.10, $CHCl_3$)

HPLC (Chiralcel OD) 5:95 *i*-PrOH/Hexanes, 0.5 mL/min, λ = 230 nm, T_{major} = 52.5 min, T_{minor} = 34.4 min, *ee* = 81%

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Chapter 4
Efforts Towards the Synthesis of 1,1,1-Triboronyl- and 3,3,3-Diboronyl-Silylalkanes

4.1 Introduction

4.1.1 Synthesis of *gem*-polyboronated compounds

Owing to their unique reactivity, *gem*-organodimetallics have become increasingly studied in organic and organometallic chemistry.[1] Since boron functionalities are known to undergo a broad spectrum of transformations, *gem*-polyboronated compounds have become a particularly attractive class of compounds in synthesis. Due to the presence of a second boron group on the same carbon atom, the reactivity of the first may be altered, leading to enhanced propensity to undergo unique and otherwise challenging transformations.

The first synthesis of a 1,1-diboron compound was accomplished by Brown in 1961 through the hydroboration of various acetylenes.[2] Due to the apparent instability of the diboronyl compound, the product was directly oxidized to the corresponding aldehyde. The first successful isolation of a 1,1-diboronylalkane was reported by Matteson and co-workers (equation 1, Figure 4-1).[3] The hydroboration of vinyl boronates led to a mixture of 1,1- and 1,2-diboronylalkanes, both of which were isolated and characterized. In a later report, the same group was able to perform a regioselective hydroboration of alkynes using dichloroborane (a reactive hydroboration reagent formed *in situ* from silane and trichloroborane) to give the 1,1-diboronylalkane as a single regioisomer (equation 2, Figure 4-1).[4] More recently, Shibata and co-workers reported a rhodium-catalyzed hydroboration of alkynes to selectively give the corresponding 1,1-diboronylalkane.[5] The mild nature of this reaction allowed for a broad functional group tolerance (equation 3, Figure 4-1).

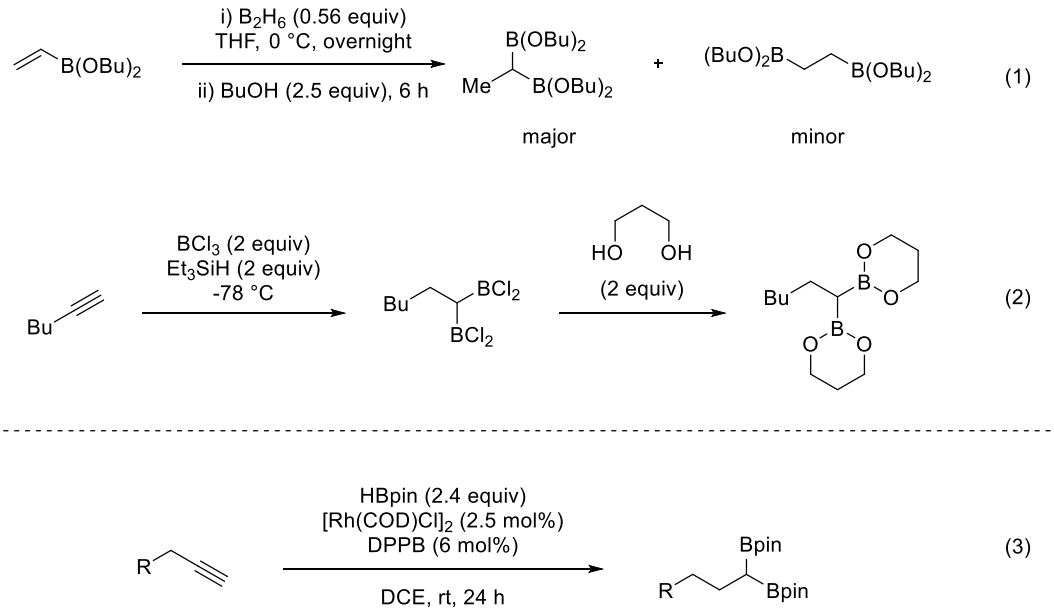


Figure 4-1. Synthesis of diboronylalkanes through hydroboration reactions.

Methods other than hydroboration have also been applied to the synthesis of diboronylalkanes. Matteson and co-workers synthesized a series of diboronic acids *via* nucleophilic displacement of boron tribromide using dimercuric iodides, followed by hydrolysis (equation 4, Figure 4-2).[6] Carbenoid insertion has also been adopted for the generation of this class of compounds. In 2001, Srebnik reported the platinum-catalyzed synthesis of diboronylalkanes.[7] This process occurs first with oxidative addition of $Pt(PPh_3)_4$ into B_2pin_2 followed by insertion of the carbene then reduction elimination (equation 5, Figure 4-2). A similar approach was taken by the Wang group using tosylhydrazones as the substrate, which when subjected to sodium hydride, may undergo a formal carbon insertion into the B–B bond of B_2pin_2 (equation 6, Figure 4-2).[8]

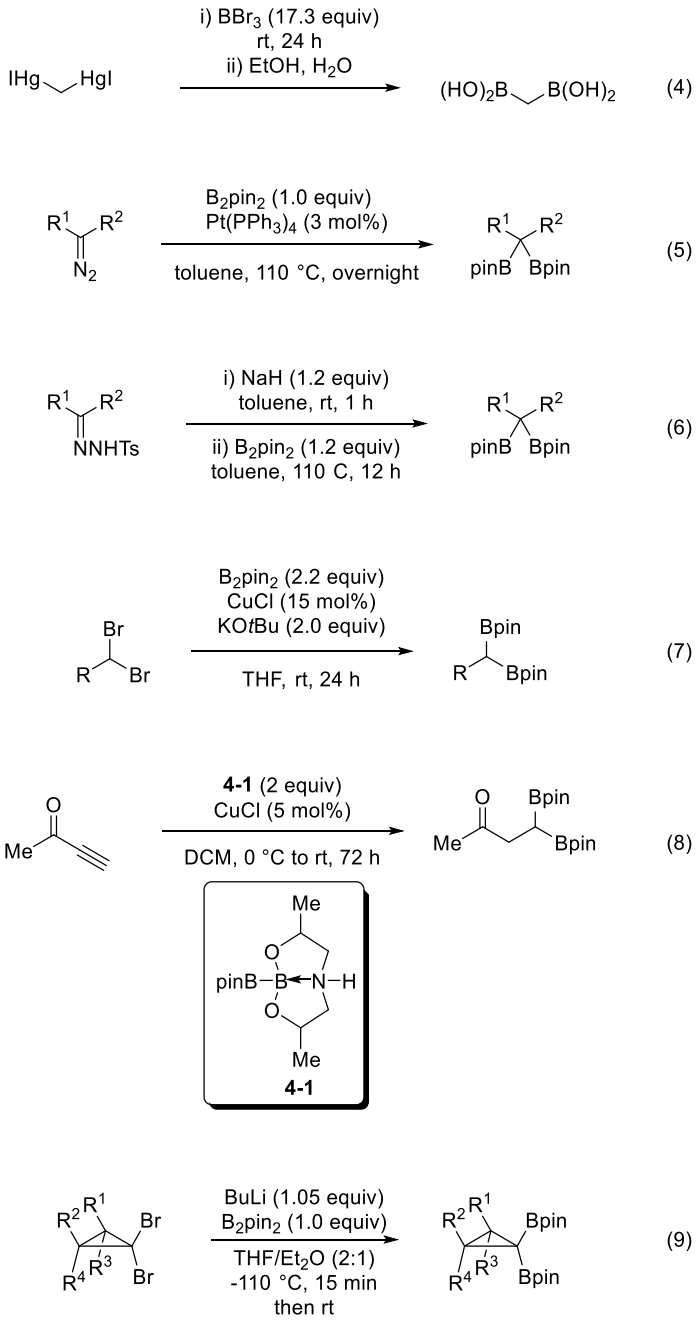


Figure 4-2. Other approaches to synthesizing *gem*-diboronylalkanes.

1,1-Diboronylalkanes may also be accessed through copper-catalyzed boronylations of the corresponding *gem*-dibromides (equation 7, Figure 4-2).[9] This reaction relies on the use of KO^{t}Bu in order to activate the boronylating agent (B_2pin_2) towards transmetalation with copper. The Santos group developed another copper-catalyzed di-boronylation that uses diboron reagent **4-1** in place of B_2pin_2 (equation 8, Figure 4-2).[10] This reagent has a built in coordinating group which

allows for base-free preactivation of the boron moiety. In addition to linear 1,1-dibromoalkanes, *gem*-dibromocyclopropanes have also been shown to be effective substrates in boronylation reactions. The Shimizu group has demonstrated that substrate of type *gem*-dibromocyclopropanes may be successfully converted to the 1,1-diboronylated products through halogen-lithium exchange, followed by nucleophilic addition onto the diboron reagent to give the ate-complex (equation 9, Figure 4-2).[11] Subsequent 1,2-rearrangement of the boronyl group then affords the 1,1-diboronyl cyclopropane product. In 2011, the Hall group reported the successful synthesis of chiral 3,3-diboronylesters via copper catalyzed-conjugate boronylation (Chapter 1). The boronylated products were achieved in both excellent yield and *ee*.[12]

Higher order *gem*-polyboronates, containing three or even four boron groups on a single carbon, have also been successfully synthesized. The first reported example was from Matteson and co-workers in 1975, where chloroform or carbon tetrachloride were subjected to lithium metal and dimethoxyboron chloride to give tris- and tetra(dimethoxyboryl)methane, respectively (equations 10 and 11, Figure 4-3).[13] More recently, the synthesis of a triboronylalkane via iridium-catalyzed C–H activation was reported (equation 12, Figure 4-3).[14] This process requires the use of a nitrogen directing group in the form of a pyridine ring. The authors showed that the electronic nature of the pyridine ring had a significant effect on the yield of triboration. Electron donating groups on the pyridine ring led to high yields of the desired product, while the use of electron withdrawing groups led to less than 10% conversion to product. Substitution ortho to the nitrogen atom also led to attenuated reactivity, likely due to decreased coordination of the nitrogen atom to the metal center as a result of increased steric bulk.

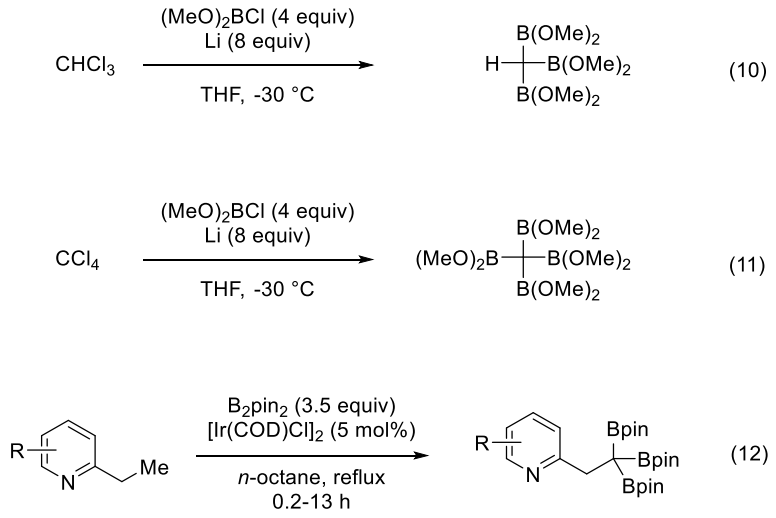


Figure 4-3. Synthesis of higher order *gem*-polyboronates.

4.1.2 Applications of *gem*-polyboronated compounds

Despite relatively limited access to this class of compounds, *gem*-polyboronated compounds have been shown to undergo different chemical transformations, including simple oxidation, which leads to the corresponding aldehyde, and stereoselective Suzuki-Miyaura cross-coupling reactions (Chapter 2 and Chapter 3). The Morken group has demonstrated that 1,1-diboronates **4-2** may be efficiently converted into an α-boronyl carbanion nucleophile **4-3** through deboronylation with an alkoxide base (equation 13, Figure 4-4).[15] Recently, Meek and co-workers reported a copper-catalyzed enantio- and diastereoselective addition of 1,1-diboronylalkanes to aldehydes to give a 1,2-hydroxyboronate **4-7** as the product (equation 14, Figure 4-4).[16] Polyboronylated compounds have also been functionalized through the use of strong organolithium bases. Due to the adjacent empty p-orbitals present on each boron atom, the proton on the carbon bearing the boron groups becomes quite acidic. As a result, one approach to functionalizing compounds like **4-8** has been to generate a reactive but stabilized carbanion **4-9**, which may then undergo trapping of various electrophiles including alkyl halides, halogens and organotin reagents to give products of type **4-10** (equation 15, Figure 4-4).[17]

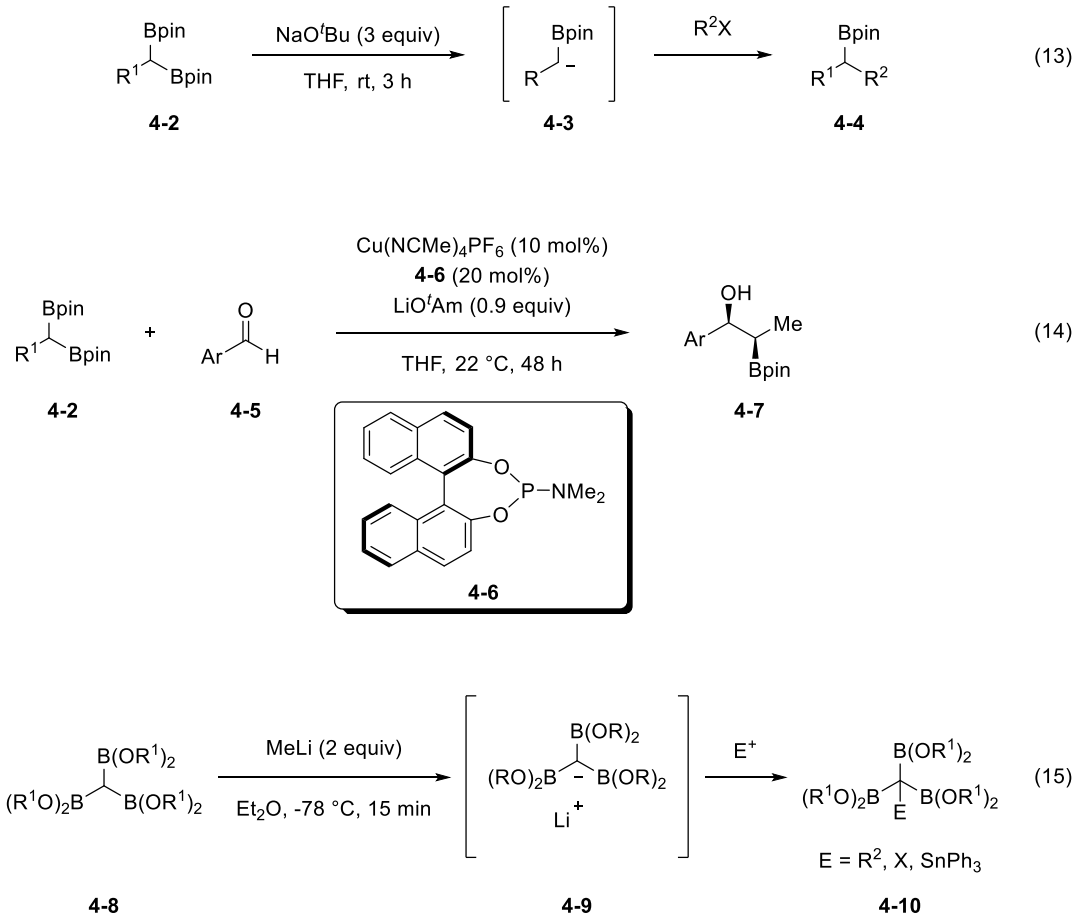


Figure 4-4. Some applications of *gem*-polyboronylated compounds.

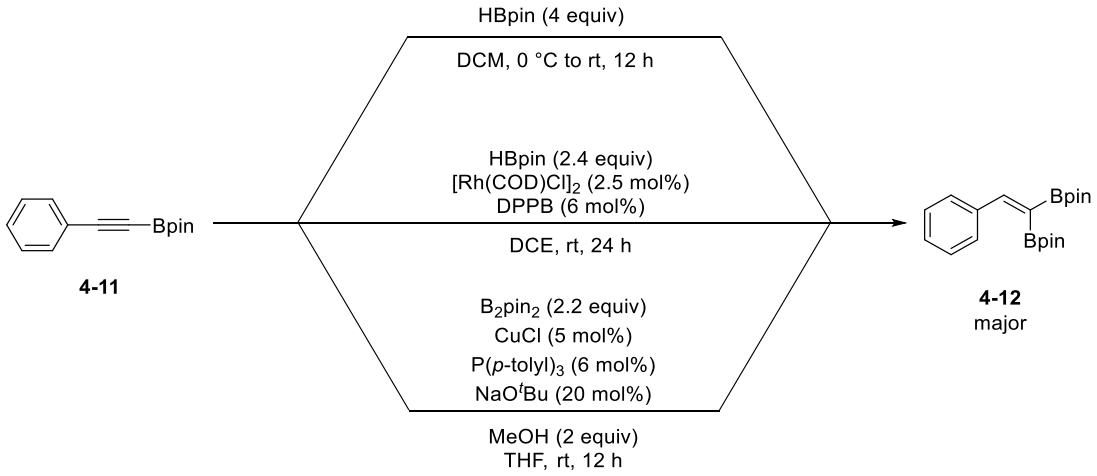
4.1.3 Objectives

Given the potential for unique reactivity displayed by *gem*-polyboronated compounds, the development of more methods for the synthesis of these compounds should be pursued. While there are several ways of accessing 1,1-diboronyl compounds, the synthesis of 1,1,1-triboronylalkanes has remained relatively unexplored. A general method for access to this class of compounds would allow for an expanded study of their properties and reactivity. This chapter will discuss some approaches taken in a preliminary effort to develop a more general method for the synthesis of 1,1,1-triboronylalkanes.

4.2 Efforts toward the synthesis of 1,1,1-triboronylalkanes

4.2.1 Thermal and metal-catalyzed hydroborations

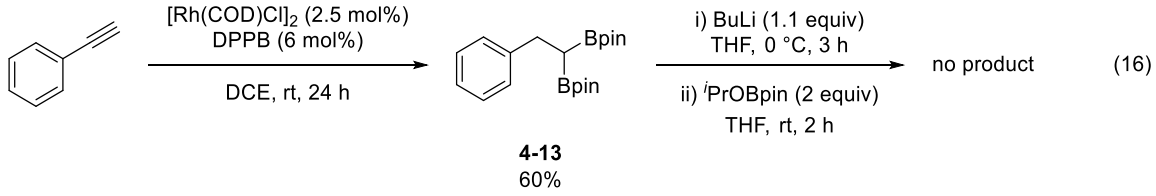
Hydroboration of alkenes and alkynes is a well-established method of creating carbon-boron bonds. As such, a thermal hydroboration was performed on alkyne **4-11** in an attempt to access the triboronylated product. It was found, however, that the hydroboration only occurred once to give the alkenyl *gem*-diboronyl compound (Scheme 4-1). The difficulty of the second hydroboration likely stems from the steric hindrance developing on the carbon bearing the two boronate groups, making the addition of the third boronate extremely challenging.



Scheme 4-1. Approaches applying thermal and metal-catalyzed hydroboration reactions.

Metal-catalyzed hydroboration reactions were subsequently attempted for the synthesis of 1,1,1-triboronylalkanes (Scheme 4-1). A rhodium-catalyzed process reported by Shibata and co-workers allows for the synthesis of 1,1-diboronylalkanes from terminal alkynes.[5] This method was thus applied towards the diboronylation of alkyne **4-11** in order to access the corresponding 1,1,1-triboronylalkane. Unfortunately, the hydroboration only occurred once to give diboronyl **4-12**, likely due to the increased steric size of the substituent on the alkyne (pinacol boronate versus a hydrogen). Conditions for a copper-catalyzed borononyl addition to alkynes developed by the Yun group[18] was also attempted, however this method also led to undesired **4-12** as the major product observed by crude NMR.

Efforts were also spent on installing the third boronyl unit *via* electrophilic trapping of an α-boronyl carbanion with *i*-PrOBpin. To this end, hydroboration of phenylacetylene was performed using the reported procedure by Shibata and coworkers[5] to afford the corresponding diboronylalkane in 80% yield. Product **4-13** was then treated with NaO*t*-Bu, however, no product was formed following addition of the boron electrophile, potentially due to significant steric interactions between the carbanion and the incoming electrophile.



4.2.2 Conjugate boronylation as a strategy to access to polyboronylated compounds

An alternative approach to the installation of multiple boron units on a single carbon would be conjugate boronylation. This strategy has been documented to successfully add one or more boron groups to the β-position of α,β-unsaturated carbonyl compounds, including ketones and esters.[19] In order to access 3,3,3-triboronyl carbonyl compounds like **4-15**, one could imagine applying conjugate diboronylation to a substrate of type **4-14**.

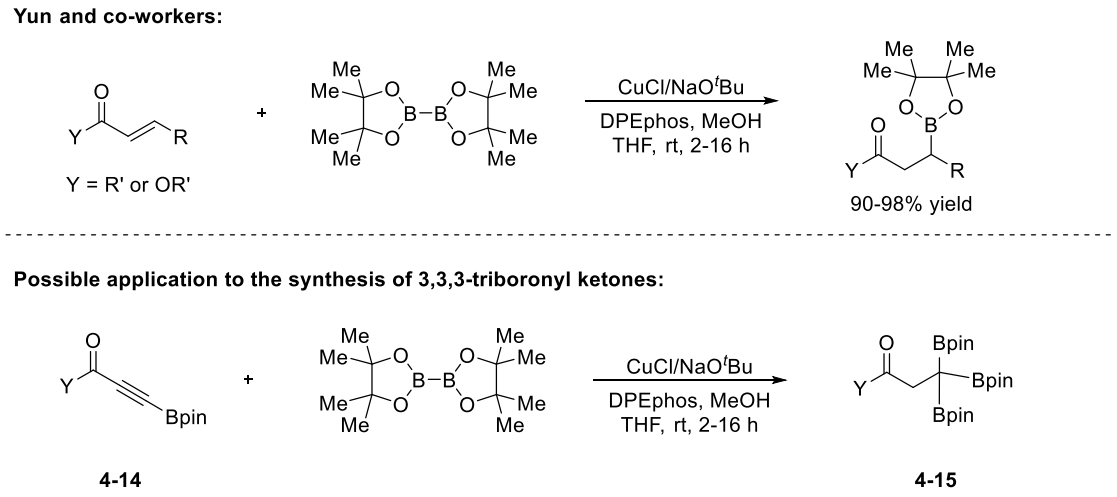
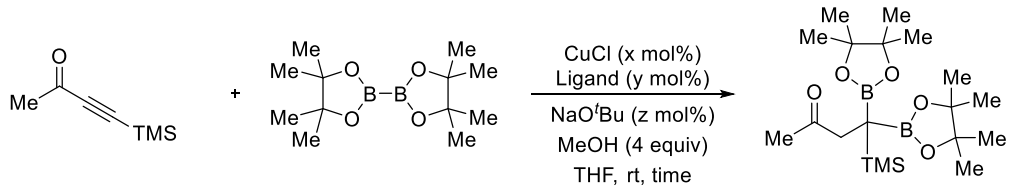


Figure 4-5. Application of conjugated boronylation towards the synthesis of *gem*-triboronylated compounds.

Since most of the reported conjugate diborations have been performed on terminal alkynes, one concern is the steric size of the Bpin moiety. Since substrate **4-16** bearing a TMS group at the β-position is readily available from commercial sources, it was chosen as a substrate to test the viability of performing conjugate boronylation of more hindered substrates. Moreover, the TMS group also has the potential for chemoselective functionalization since it possesses certain reactivities that are distinct from boron (*e.g.* anion-relay chemistry, halogenation).[20] Thus, using conditions from the Yun group as a starting point, alkyne **4-16** was treated with CuCl/DPEphos as the catalyst with NaO*t*-Bu and MeOH as additives. The desired diboronylated product **4-17** was obtained with 13% yield. Increasing the catalyst loading from 3 mol% to 5 mol% led to an increase in yield to 41%. It was found that changing the ligand from DPEphos to dppBz could yield the product in a similar 42% yield, but in this case, the required catalyst loading was lower. Increasing the stoichiometry of B_2pin_2 was found to have an insignificant effect on the reaction outcome.



4-16 (1 equiv) (xx equiv) **4-17**

Entry	B_2pin_2 (equiv)	CuCl (mol%)	Ligand (mol%)	NaO^{t}Bu (mol%)	Time (h)	Yield (%)
1	2.2	3	DPEphos (3)	9	16	13
2	2.2	5	DPEphos (5)	9	16	41
3	2.2	3	dppBz (3)	9	16	42
4	4.0	3	dppBz (3)	9	16	38

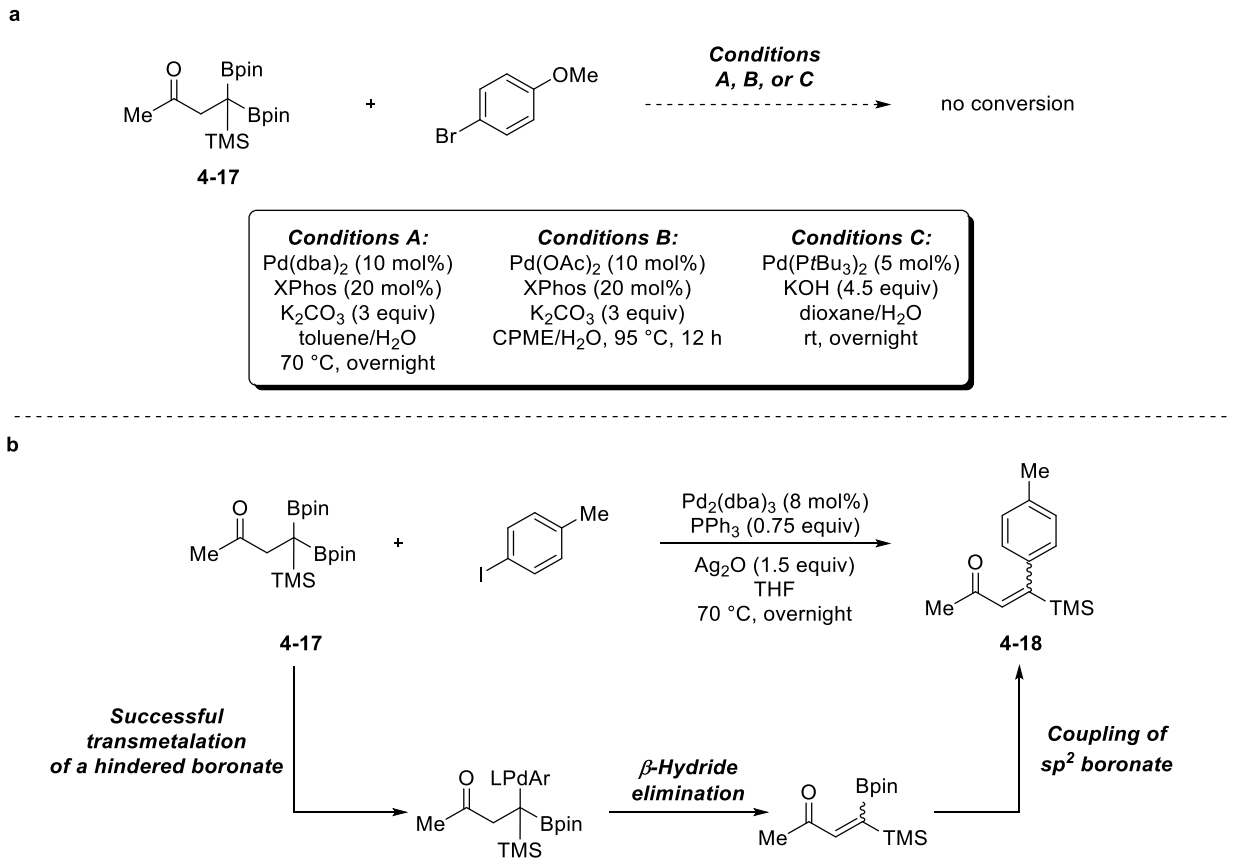
Table 4-1. Initial optimization of reaction conditions for diboronylation *via* copper-catalyzed conjugate addition.

4.3 Initial attempts at cross-coupling of 3,3-diboronyl-3-silylketones

Compound **4-17** was regarded as a good synthetic handle for the modular construction of complex stereogenic centers through chemoselective functionalization of the boronyl and silyl units. Efforts were first placed into the mono-arylation of one pinacolboronate moiety. The most obvious challenge foreseen in this process was the congested nature of the functionalizable carbon. Cross-coupling of quaternary organoboronates is notoriously difficult due to a slow transmetalation step, and existing examples in the literature are sparse. Various conditions for the cross-coupling of alkyl boronates were tested. Conditions from the Hall Group[12] (Conditions A, Scheme 4-2a) and the Molander Group[21] (Conditions B, Scheme 4-2a) were tested since the substrates from these previous reports all bear a carbonyl coordinating group β to the cross-coupling site. These conditions, however, led to no conversion of the starting material to the product. The Lewis basicity of the coordinating group has been identified as a critical feature of these types of cross-couplings, thus it may be seen that in previous reports, the coordinating carbonyl was often electron-rich esters and amides. Given these previous observations, a possible

reason for the inactivity of these substrates under these conditions (in addition to steric congestion) could be the weaker coordinating power of the ketone group. Shibata's cross-coupling conditions for the mono-coupling of 1,1-diboronylalkanes were applied next (Conditions C, Scheme 4-2a),[22] however, these conditions also led to no conversion of the starting material.

Finally, Ag_2O-assisted coupling conditions developed by Crudden and co-workers were attempted.[23] While these conditions did not lead to the desired product, the formation of alkene **4-18** was observed by NMR analysis of the crude product. The likely pathway for the formation of this product is shown in Scheme 4-2: oxidatively inserted LPd(II)Ar undergoes successful transmetalation with the hindered boronate followed by undesired β-hydride elimination. The cross-coupling of the second boronate then becomes a relatively facile sp^2 coupling.



Scheme 4-2. (a) Attempts at the Suzuki-Miyaura cross-coupling of 3,3-diboronyl-3-silyl ketone **4-17**. (b) Potential pathway leading to the formation of alkene **4-18**.

4.4 Summary

This chapter reports initial studies in the development of a method for the synthesis of 1,1,1-triboronylalkanes. While the synthesis of triboronyl compounds was not realized, the successful synthesis of 3,3-diboronyl-3-silyl ketones was achieved. Initial studies on the cross-coupling of these compounds have demonstrated that transmetalation of a boronate is difficult, likely due to the steric congestion around the carbon centre bearing the boronyl and silyl groups. A potentially successful transmetalation of the hindered sp^3 boronate was achieved, however, under conditions promoted by a Ag_2O additive. Cross-coupling could be performed if the subsequent undesired β-hydride elimination can be suppressed. Efforts should thus be placed into examining different ligands which can help accelerate the desired reductive elimination pathway. If selective functionalization of these compounds may be achieved, these compounds could become a useful scaffold in the generation of complex quaternary stereogenic centres and in strategies like diversity oriented synthesis.

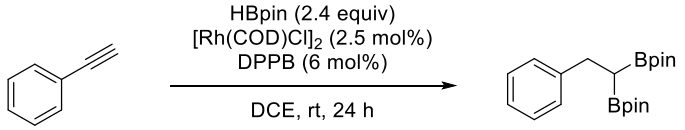
4.5 Experimental

4.5.1 General information

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere using flame-dried glassware. Acetonitrile was distilled from CaH_2. THF, toluene, dichloromethane, and methanol were treated by a solvent system prior to use. Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 plates. Visualization was accomplished by irradiation with a UV light and $KMnO_4$ stain. Nuclear magnetic resonance (NMR) spectra were recorded on 400 MHz or 500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal references. Boron NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data is presented as follows: chemical shift in ppm (δ) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. The error of coupling constants from ^1H NMR analysis is estimated at ± 0.3 Hz. High-resolution

mass spectra were recorded on a oaTOF analyzer. Infrared (IR) spectra were obtained using cast-film technique with frequencies expressed in cm^{-1}. The resolution of the IR instrument is 4 wavenumbers.

4.5.2 Synthesis of *gem*-diboronyl compound 4-13



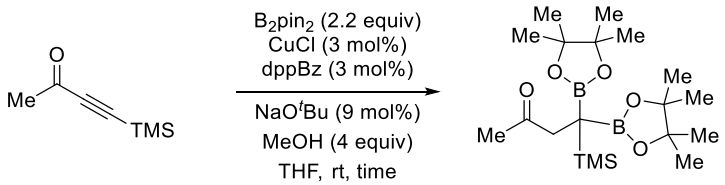
4-13

2,2'-(2-Phenylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (4-13)

The *gem*-diboronylalkanes **4-13** was synthesized according to the literature procedure[5] with some minor modifications. To a 25 mL round-bottomed flask equipped with a magnetic stir bar was added $[Rh(COD)Cl]_2$ (43 mg, 0.09 mmol) and DPPB (89 mg, 0.21 mmol). The reaction vessel was capped with a rubber septum and was evacuated and refilled with nitrogen gas. DCE (3.5 mL) was added via syringe, followed by phenylacetylene (0.38 mL, 3.47 mmol). Pinacol borane (1.5 mL, 10.41 mmol) was then added dropwise via syringe. The resulting solution was allowed to stir at room temperature for 24 hours. The reaction was then diluted with Et_2O and was then filtered through a pad of silica. The filtrate was concentrated in vacuo and purified by flash silica column chromatography (EtOAc/Hexanes, 5:95) to give the desired product (0.22 g, 60%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6) δ 7.32 (m, 2H), 7.15 (m, 2H), 7.03 (m, 1H), 3.24 (d, J = 8.2 Hz, 2H), 1.50 (t, J = 8.3 Hz, 1H), 1.04 (s, 24H). Full characterization data is available in Ref 5.

4.5.3 Preparation of 3,3-diboronyl-3-silylalkanes



To a 25 mL round-bottomed flask equipped with a magnetic stir bar was added CuCl (15 mg, 0.15 mmol), dppbz (67 mg, 0.15 mmol), and NaO*t*Bu (43 mg, 0.45 mmol). THF (4.0 mL) was then added to the reaction vessel and the resulting mixture was stirred at room temperature for 30 minutes before the addition of pinacolato diboron (2.80 g, 11.0 mmol) in THF (3.0 mL). The reaction was further stirred for 10 minutes and **4-16** (0.82 mL, 5.0 mmol) was then added, followed by THF (3.0 mL). MeOH (0.85 mL, 20.0 mmol) was then added in a dropwise fashion. After 12 h of stirring at room temperature, the reaction mixture was evaporated in vacuo and directly purified by flash silica column chromatography (EtOAc/Hexanes, 5:95) to give **4-17** (0.83 g, 42%) as a soft waxy white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (s, 2H), 2.10 (s, 3H), 1.19 (s, 12H), 1.16 (s, 12H), 0.08 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 82.5, 43.4, 29.0, 24.8, 24.5, -1.6.

IR (Microscope, cm^{-1}) 2972, 2930, 1709, 1363, 1331, 1147, 842.

HRMS (EI) for $C_{18}H_{22}O_4$ (m/z): calcd: 396.2675; found: 396.2677.

4.6 References

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Chapter 5
Conclusions and Future Perspectives

In recent years, increasing importance has been placed upon the tri-dimensionality of pharmaceutically relevant compounds and its link to the clinical success of these compounds. As a result, effective methods for the construction of stereogenic carbon centres, especially in a catalytic fashion, have become increasingly sought after. To this end, this thesis has described the synthetic utility of polyboronylated compounds as a means to access complex stereogenic centres, with a particular focus on stereoselective Suzuki-Miyaura cross-coupling reactions as the key vector. The Suzuki-Miyaura represents a quick and efficient catalytic method for the construction of stereogenic carbon centres (Chapter 1), and when applied to polyboronylated compounds, the resulting benzylic boronates are in themselves versatile synthetic building blocks as they are capable of undergoing a variety of transformations.

In Chapter 2, the successful transformation of optically enriched 3,3-diboronylamides into a diarylmethane product was described. Since this method represents an efficient route to pharmaceutically relevant diarylmethanes, efforts should be made to further streamline this process. The overall efficiency of this process may be improved in several ways (Figure 5-1). One way is to develop reactions conditions that would allow for the direct cross-coupling of the second boronyl unit without the need to first transform it into the trifluoroborate salt (Figure 5-1a). Alternatively, the asymmetric conjugate boronylation step may also be investigated, and efforts could be made to expand the scope of this reaction to include amides so that the cross-coupling precursor may be directly formed (as opposed to first generating the 3,3-diboronyl ester followed by an amidation reaction) (Figure 5-1b). Finally, another direction associated with this project could involve the development of more general reaction conditions that can expand the scope to include the cross-coupling of alkenyl bromides (Figure 5-1c). If this coupling can be achieved, the resulting allylboronates would represent a versatile synthetic building block that could access different classes of compounds than those accessed by benzylic boronates.

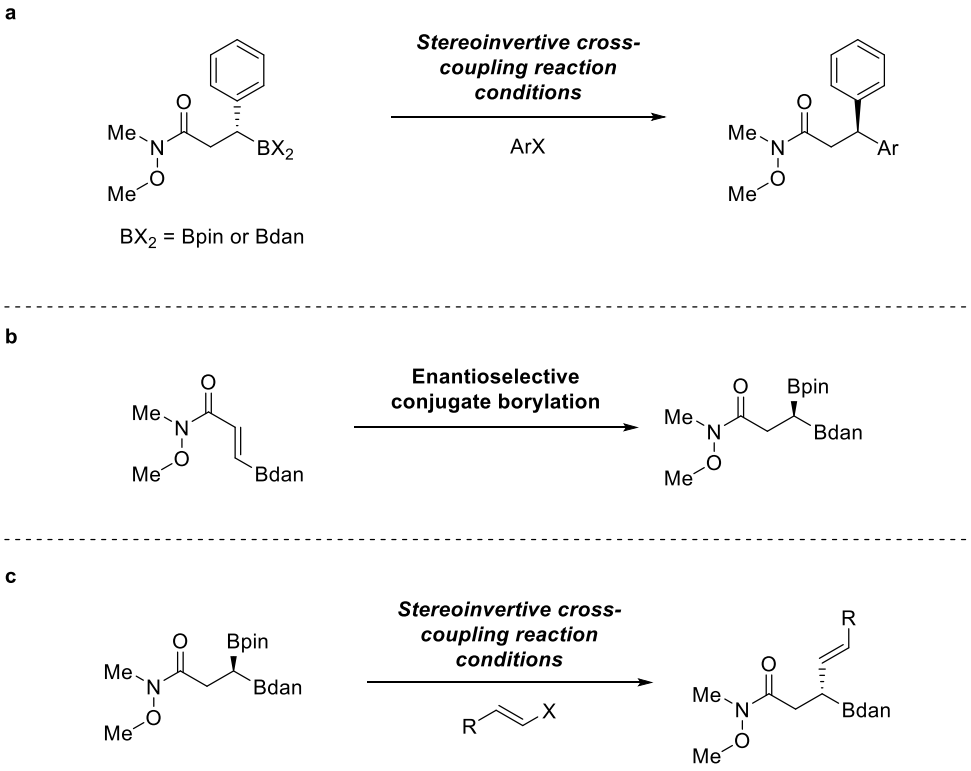
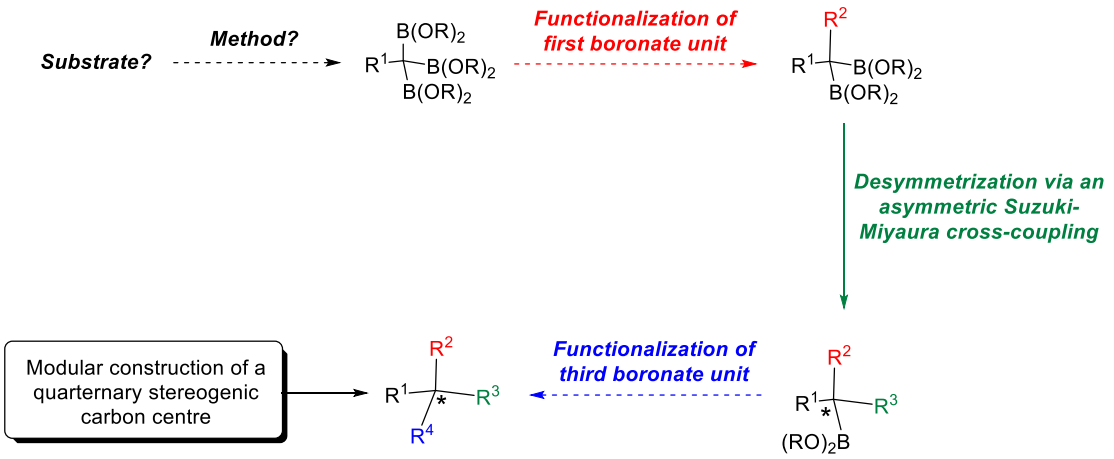


Figure 5-1. (a) Direct cross-coupling of a Bpin and/or Bdan moiety. (b) Direct conjugate borylation of a Weinreb amide substrate. (c) Stereoselective cross-coupling of an alkenyl bromide.

Chapter 3 described the development of an asymmetric Suzuki-Miyaura cross-coupling reaction applied in the desymmetrization of prochiral 1,1-diboronyl alkanes. This method provides access to optically enriched products without the need for optically enriched chiral 1,1-diboronyl starting materials. One desirable extension of this study would be to apply this strategy to the cross-coupling of 1,1,1-triboronyl and 1,1,1,1-tetraboronyl precursors (Scheme 5-1). The synthetic sequence to be developed would need to be both chemoselective (only one boronate should be coupled at a time) and stereoselective. Of course, with each subsequent cross-coupling, there would also be the added challenge of steric congestion. This strategy would represent a modular way to construct stereogenic carbon centers. Of course, an efficient means to access 1,1,1-triboronyl and 1,1,1,1-tetraboronyl compounds would be required. While initial studies were described in Chapter 4, efforts should continue to be made in developing a general method for the synthesis of this class of compounds.

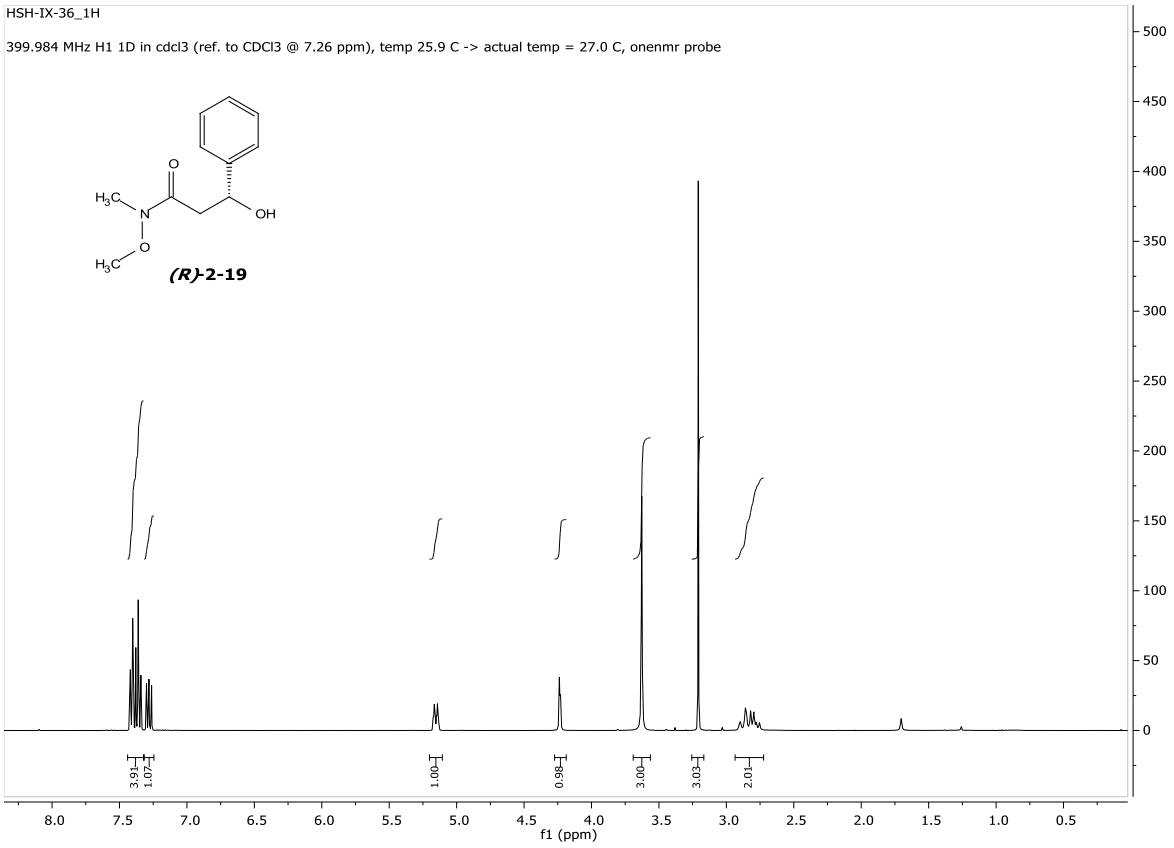


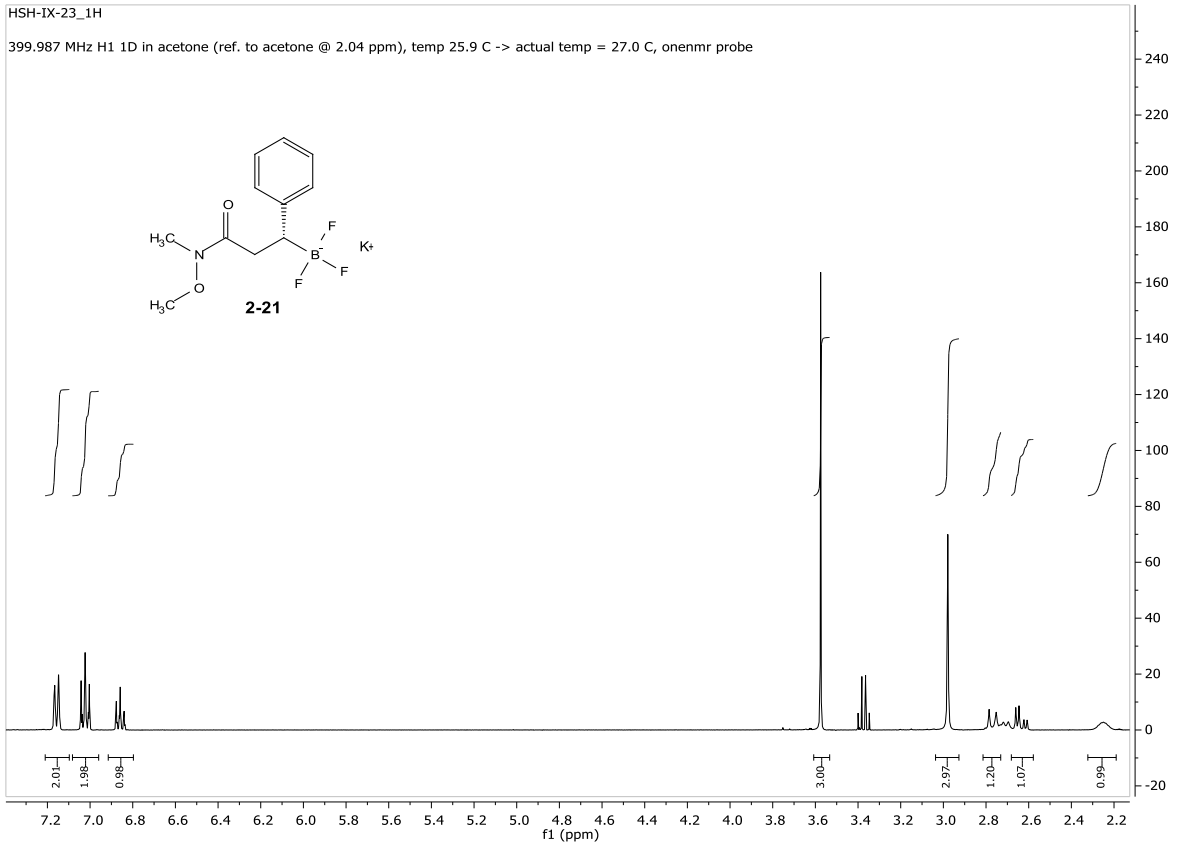
Scheme 5-1. Strategy for the application of *gem*-polyboronylated compounds to the construction of quaternary stereogenic carbon centres.

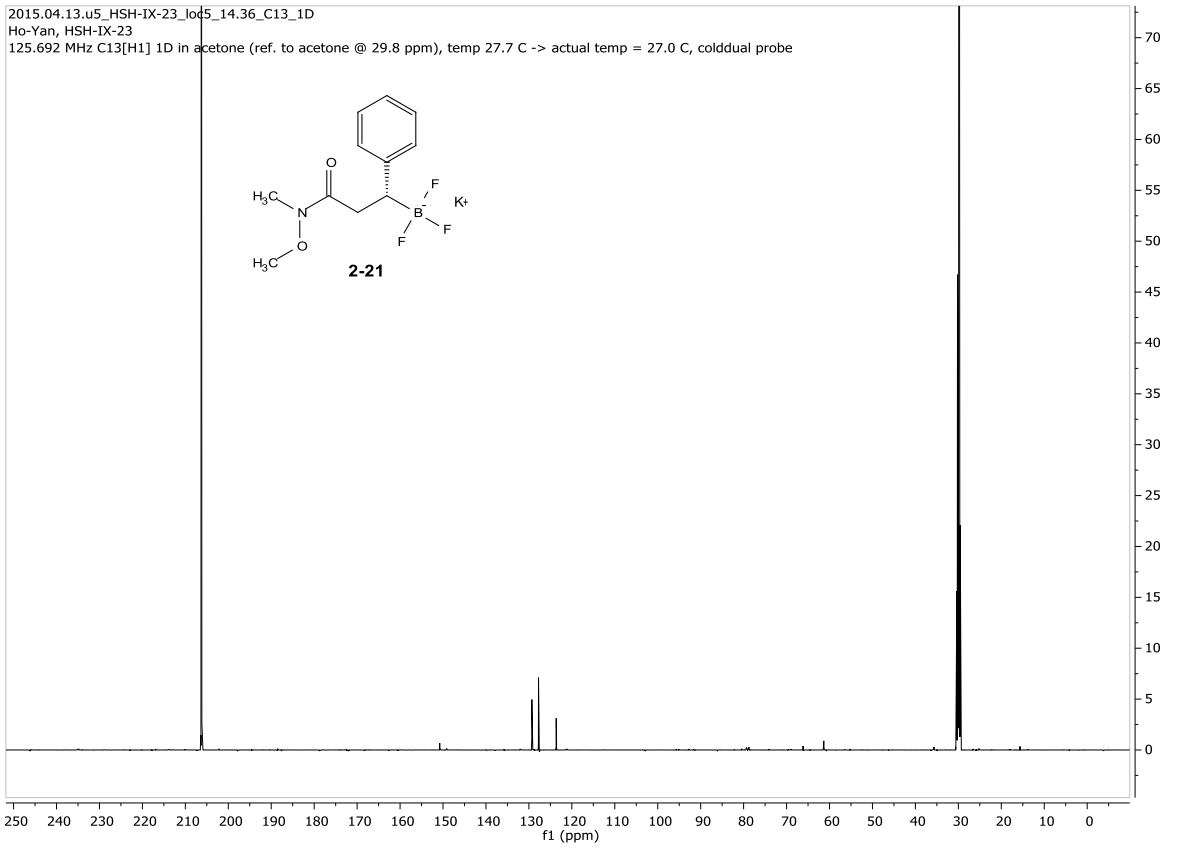
The extensions of the studies presented in this thesis mentioned above constitute only a small extent of the potential offered by this research. Continued endeavours into this area of study will surely expose even more avenues through which more synthetic methods and strategies can be developed to the benefit of both academic and industrial-based research.

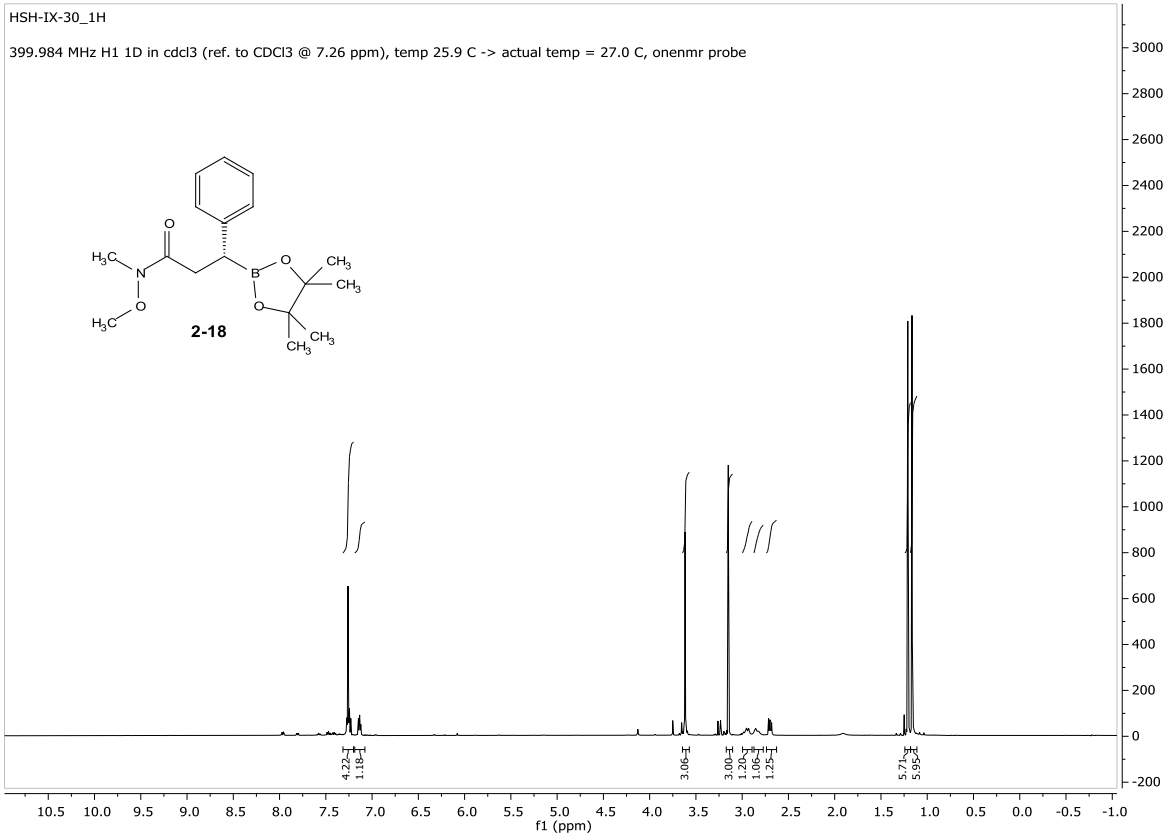
Appendices

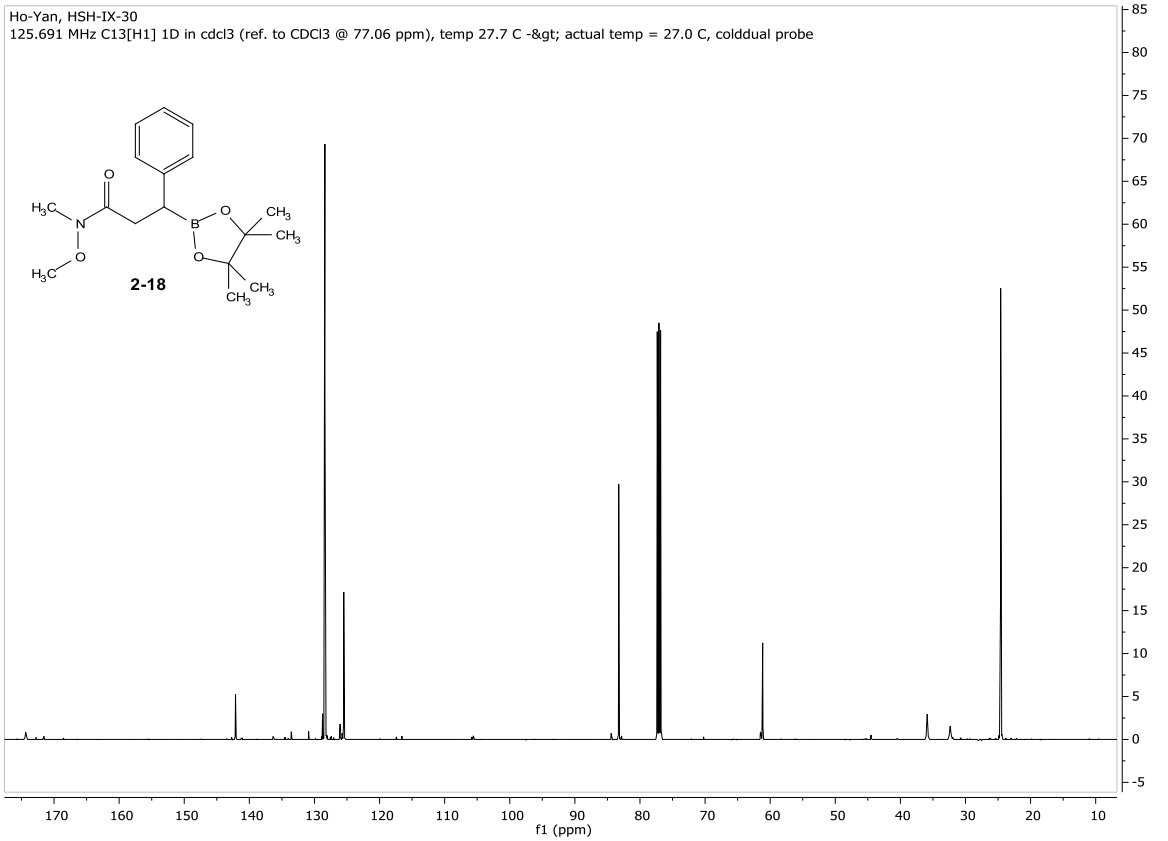
Appendix 1: Selected copies of NMR spectra

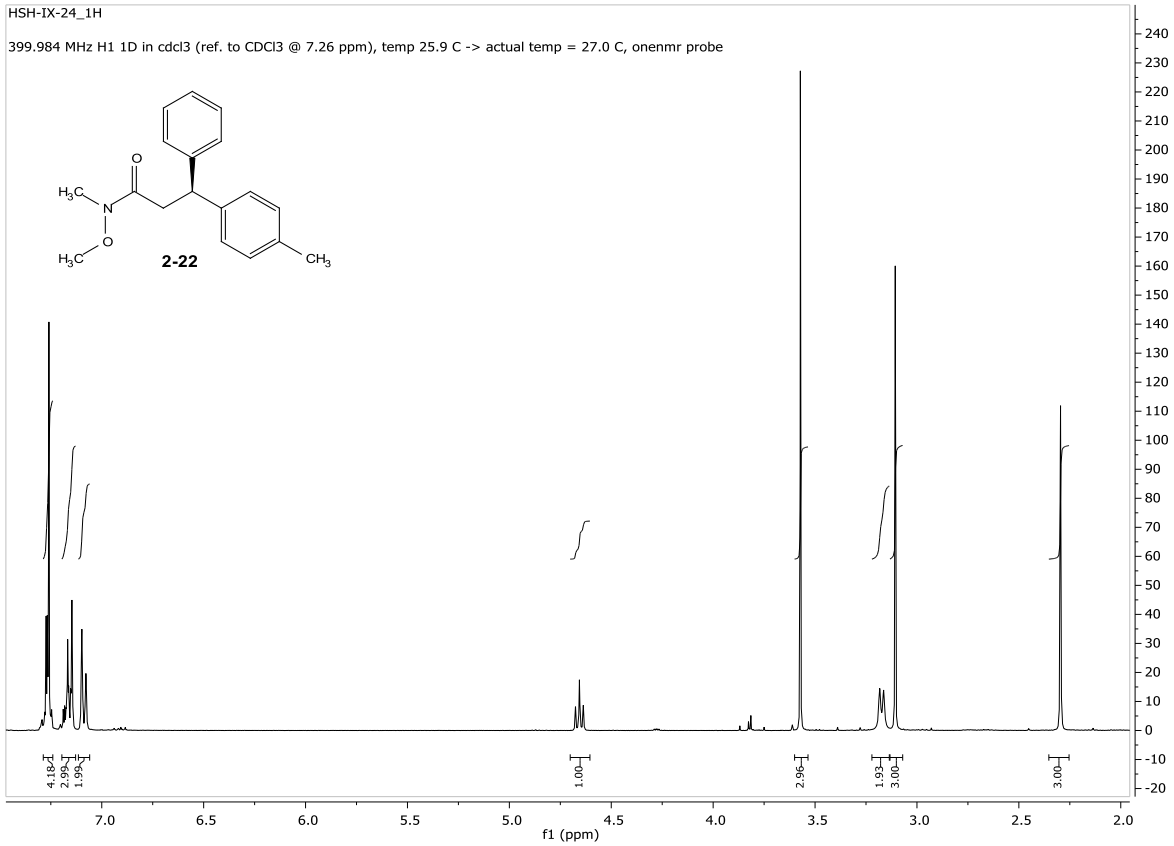


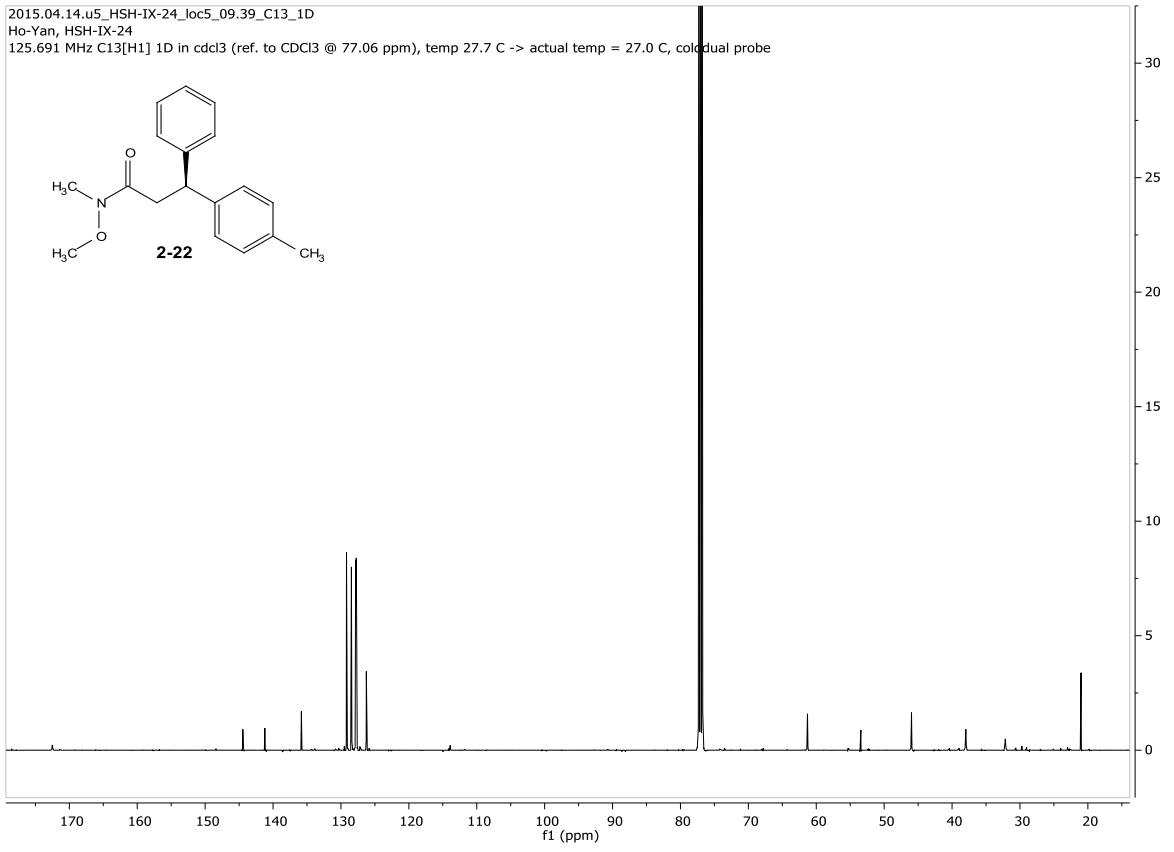

HSH-IX-23_1H
399.987 MHz H1 1D in acetone (ref. to acetone @ 2.04 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
2-21
2.01
1.98
0.98
3.00
2.97
1.20
1.07
0.99
f1 (ppm)

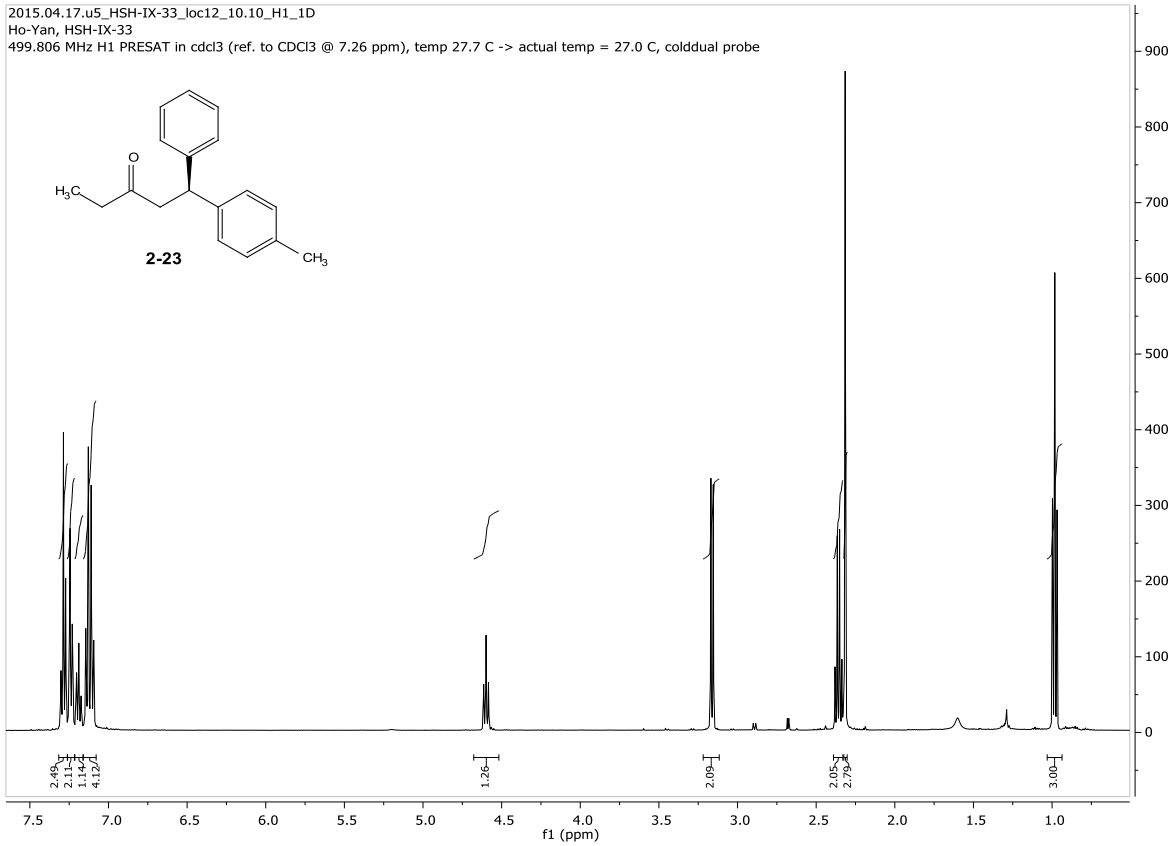

2015.04.13.u5_HSH-IX-23_lod5_14.36_C13_1D
Ho-Yan, HSH-IX-23
125.692 MHz C13[H1] 1D in acetone (ref. to acetone @ 29.8 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
2-21
f1 (ppm)

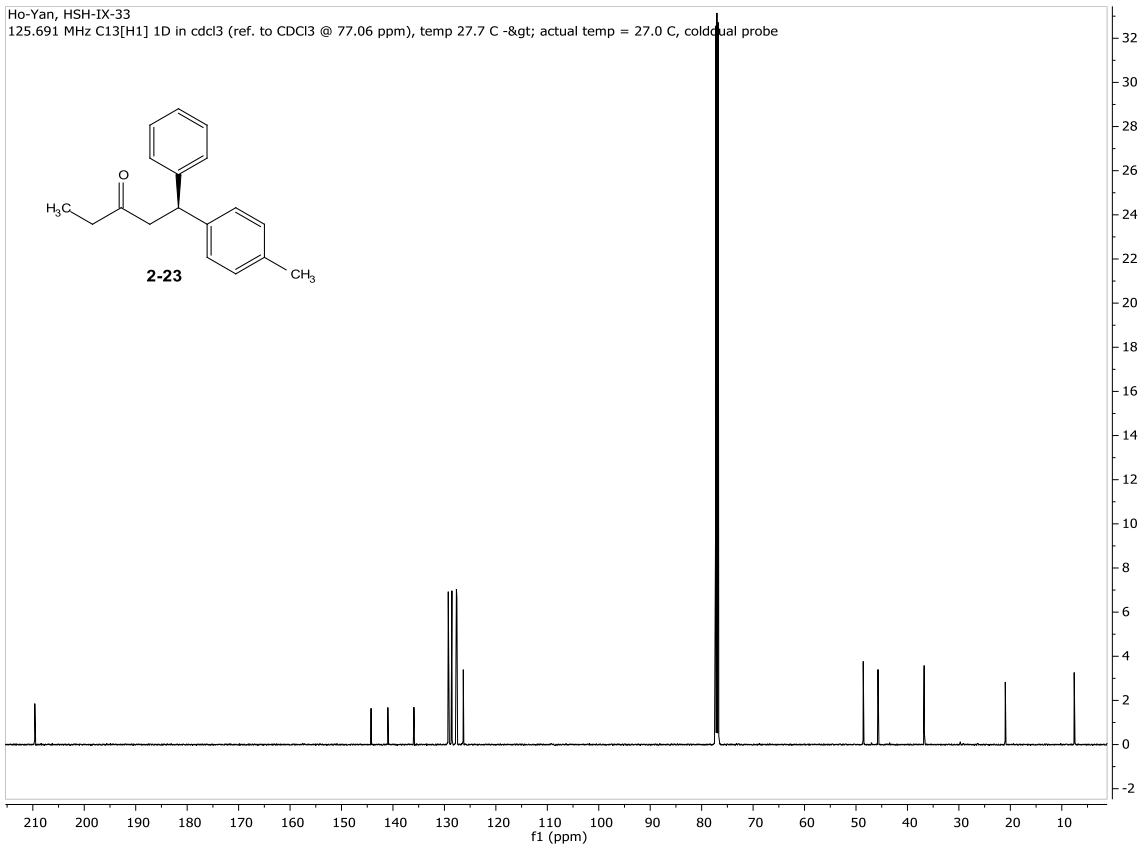

HSH-IX-30_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
2-18
4.22
1.18
3.06
3.00
1.20
1.06
1.25
5.71
5.95
f1 (ppm)

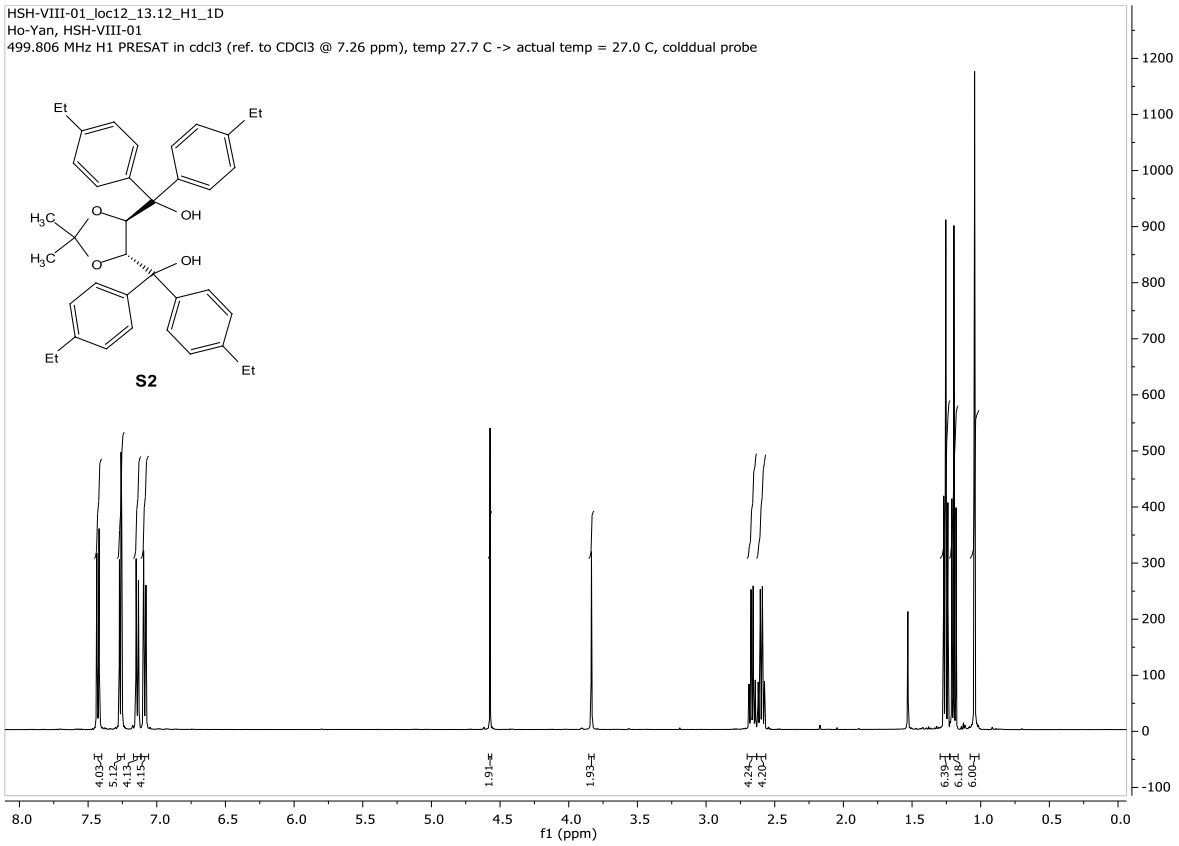

Ho-Yan, HSH-IX-30
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
2-18
f1 (ppm)

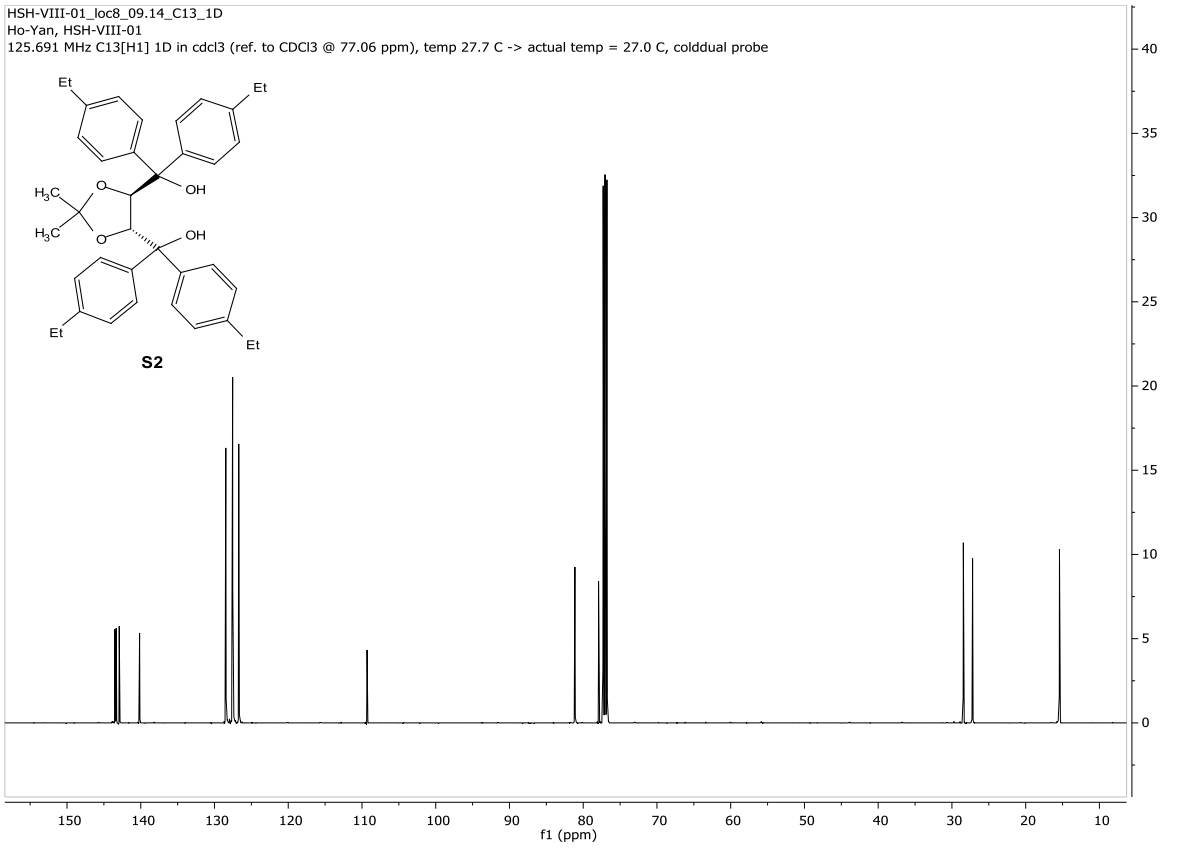

HSH-IX-24_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
2-22
4.18
2.99
1.99
1.00
2.96
1.93
3.00
3.00
f1 (ppm)

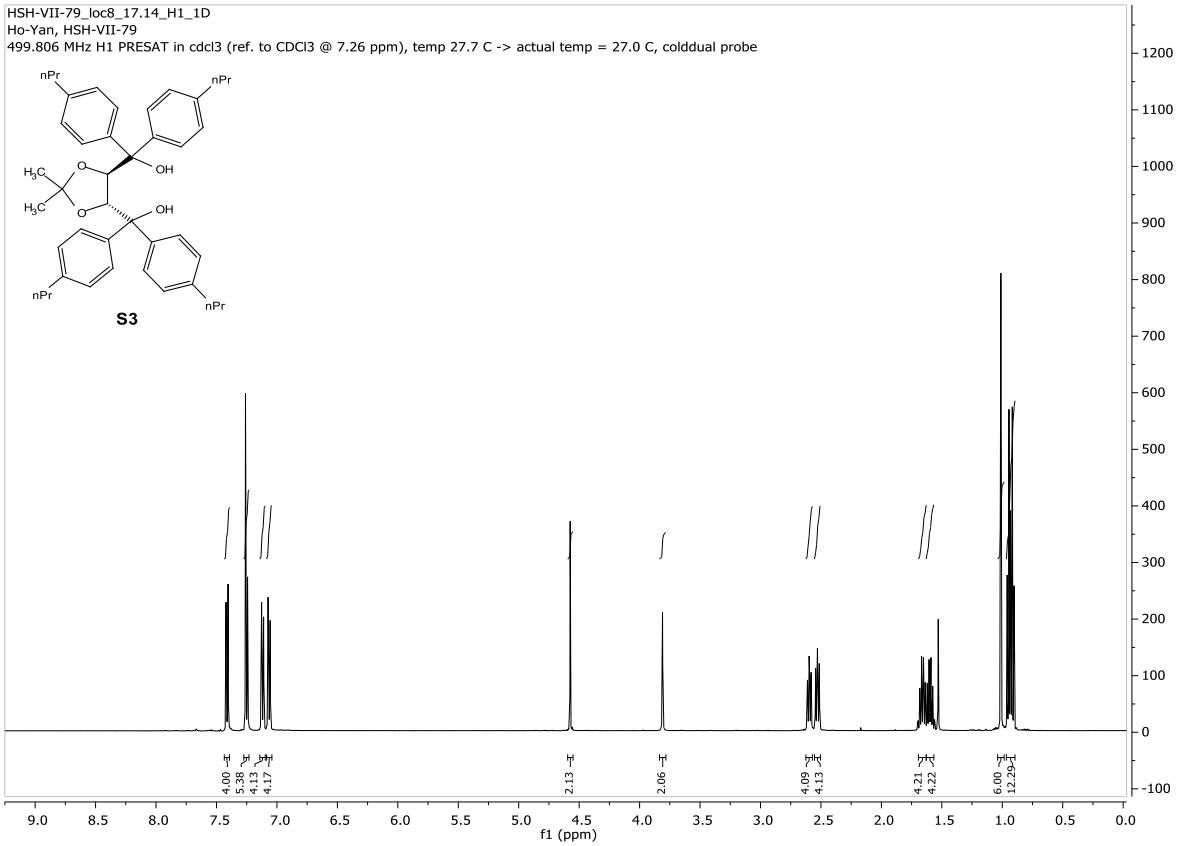

2015.04.14.u5_HSH-IX-24_loc5_09.39_C13_1D
Ho-Yan, HSH-IX-24
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
2-22
f1 (ppm)

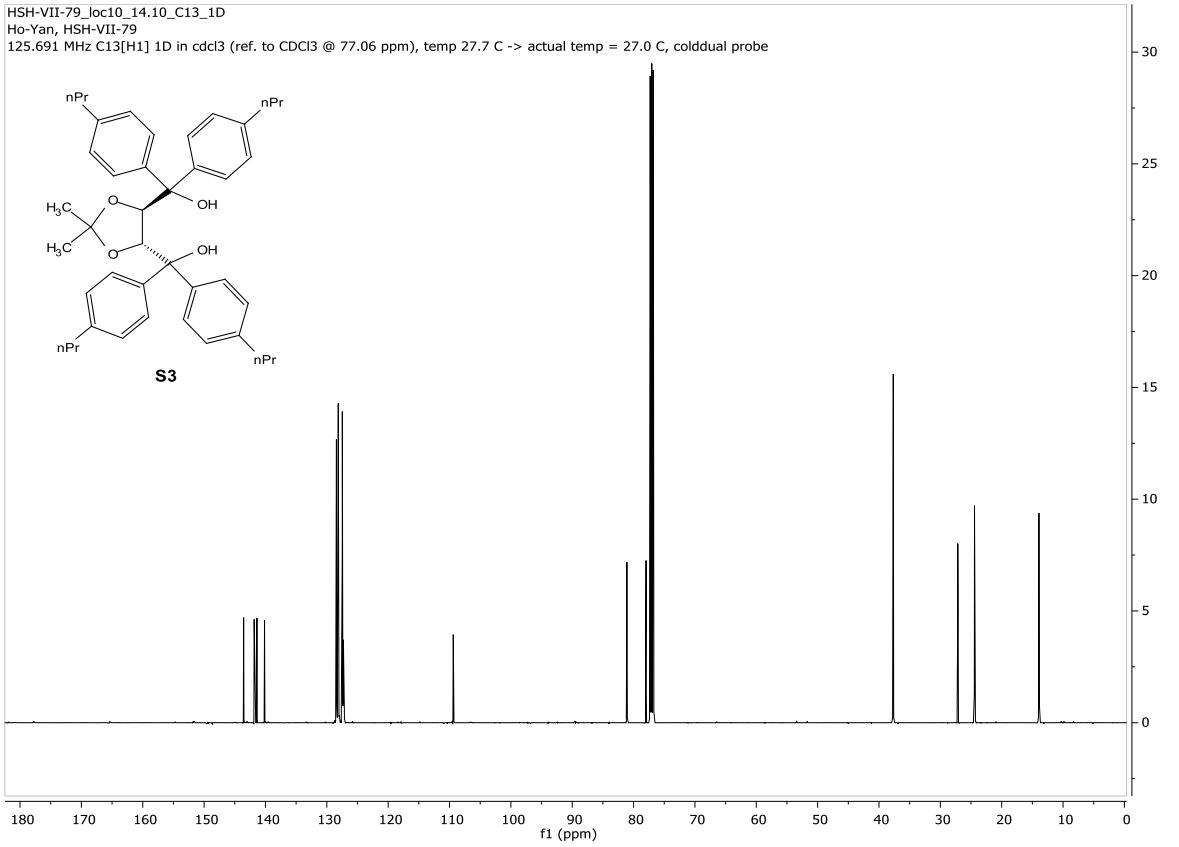

2015.04.17.u5_HSH-IX-33_loc12_10.10_H1_1D
Ho-Yan, HSH-IX-33
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
H3C
CH3
2-23
2.49
2.11
1.14
4.12
1.26
2.09
2.05
2.79
3.00
f1 (ppm)

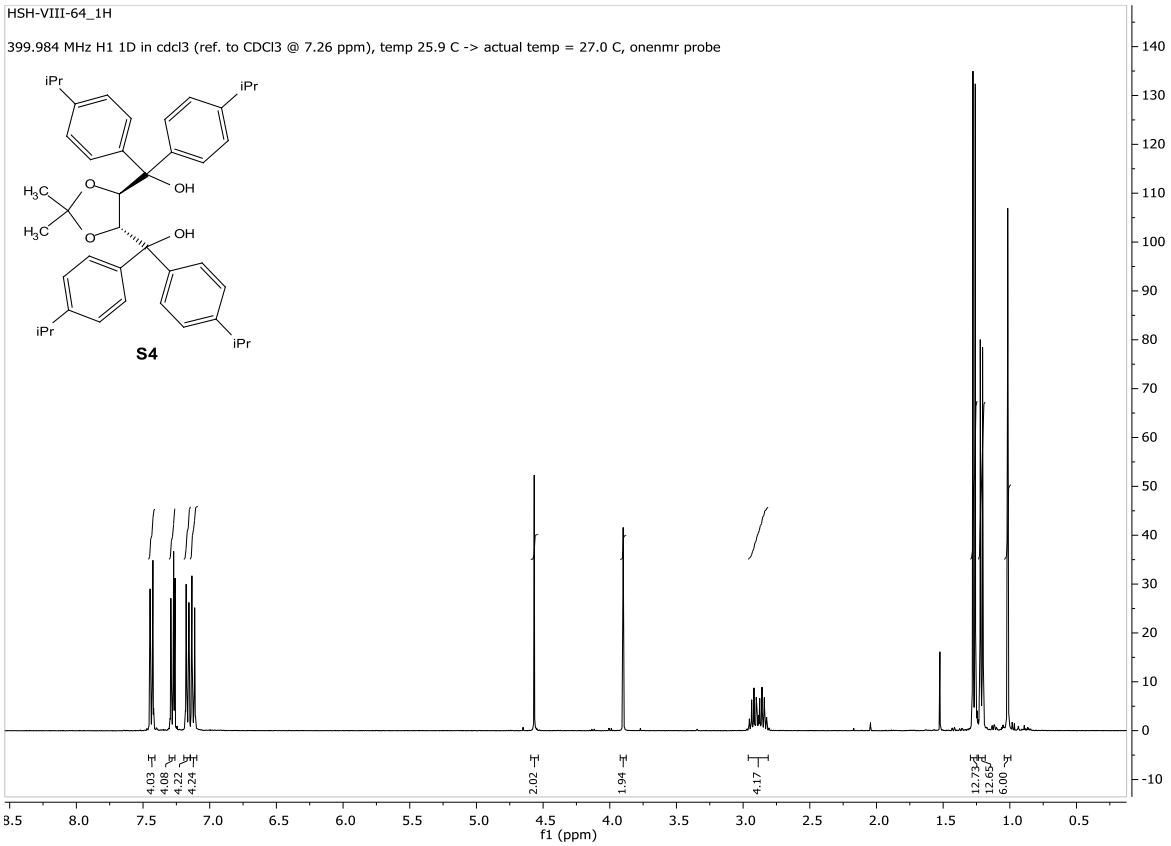

Ho-Yan, HSH-IX-33
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
O
H3C
CH3
2-23
f1 (ppm)

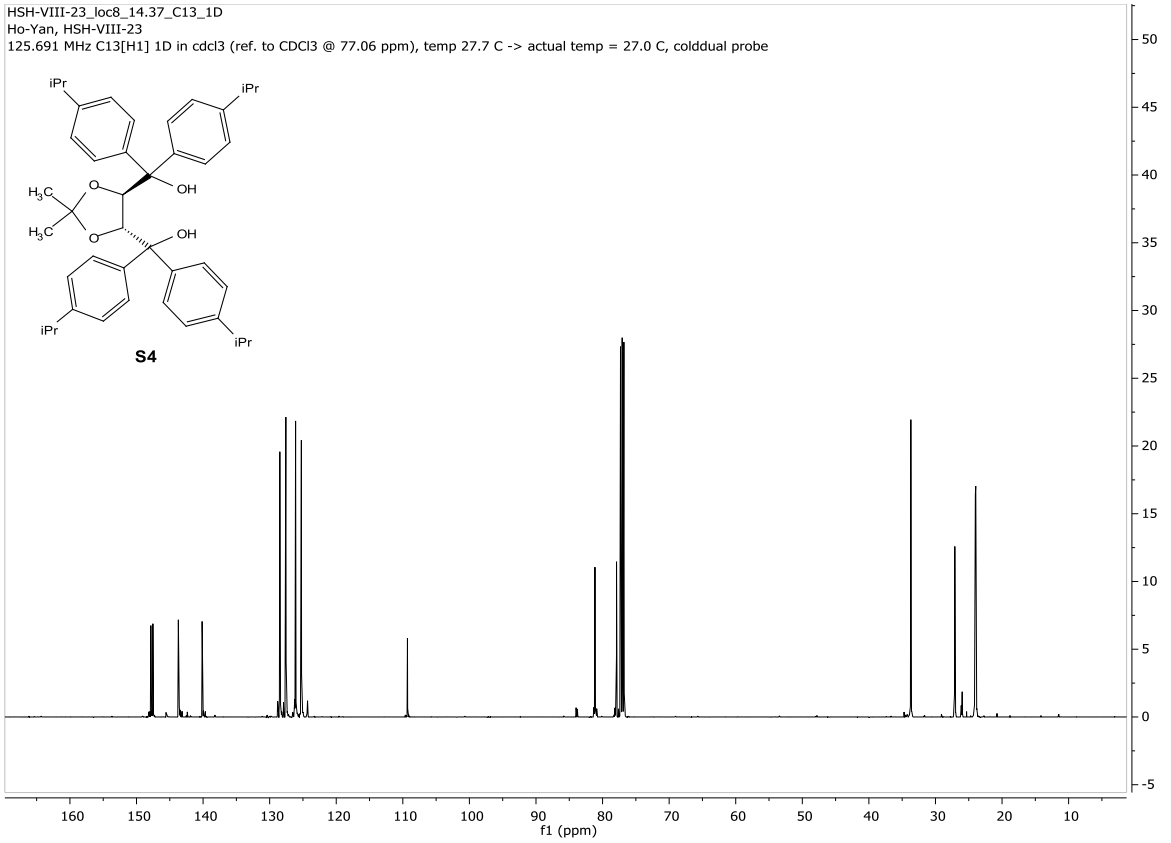

HSH-VIII-01_loc12_13.12_H1_1D
Ho-Yan, HSH-VIII-01
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
Et
Et
OH
OH
Et
Et
S2
4.03
5.12
4.13
4.15
1.91
1.93
4.24
4.20
6.39
6.18
6.00
f1 (ppm)

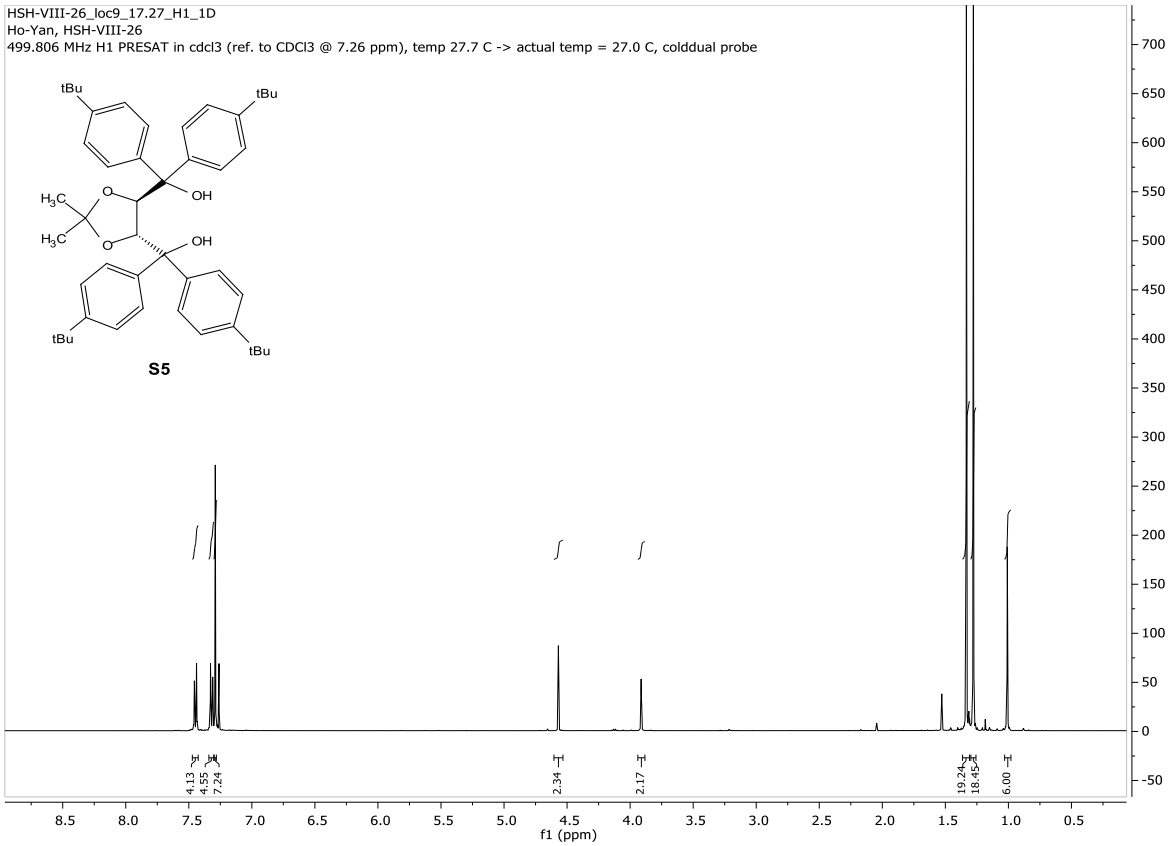

HSH-VIII-01_loc8_09.14_C13_1D
Ho-Yan, HSH-VIII-01
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
Et
Et
OH
OH
Et
Et
S2
f1 (ppm)

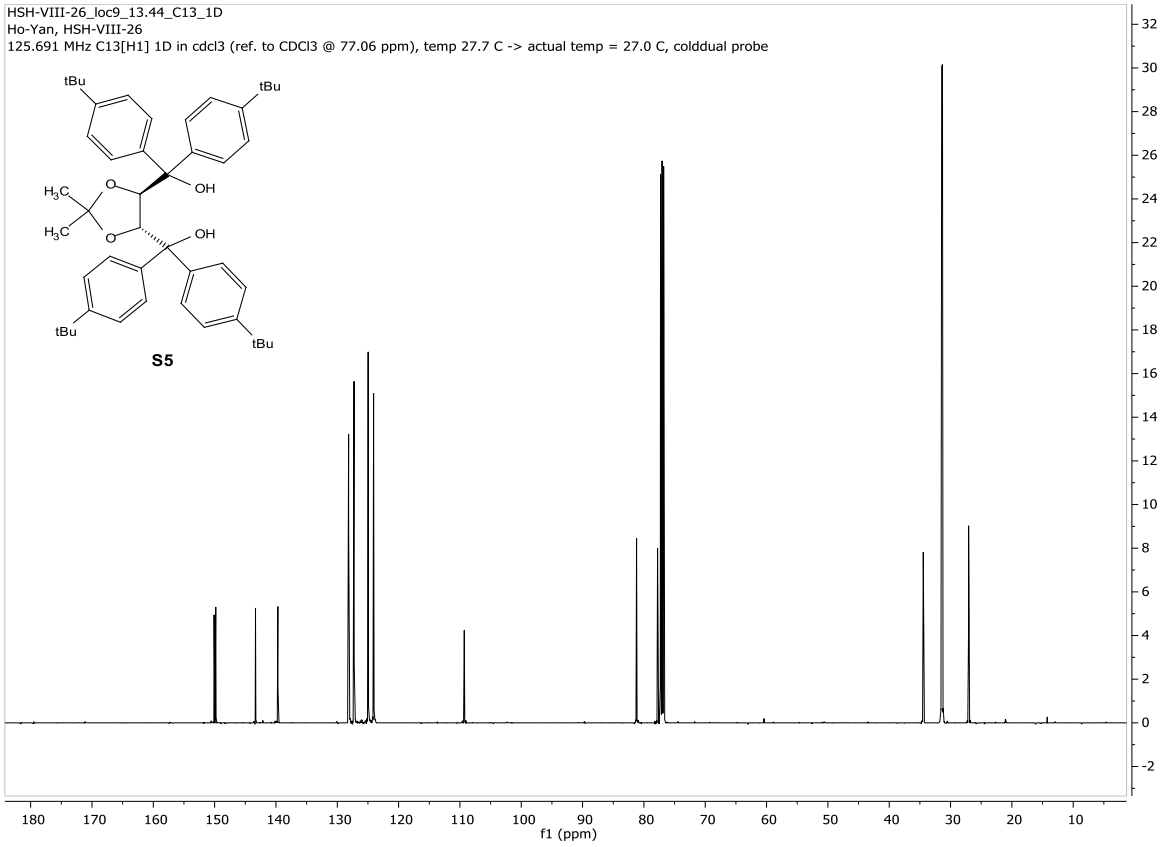

HSH-VII-79_loc8_17.14_H1_1D
Ho-Yan, HSH-VII-79
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
nPr
nPr
OH
OH
nPr
nPr
S3
4.00
5.38
4.13
4.17
2.13
2.06
4.09
4.13
4.21
4.22
6.00
12.29
f1 (ppm)

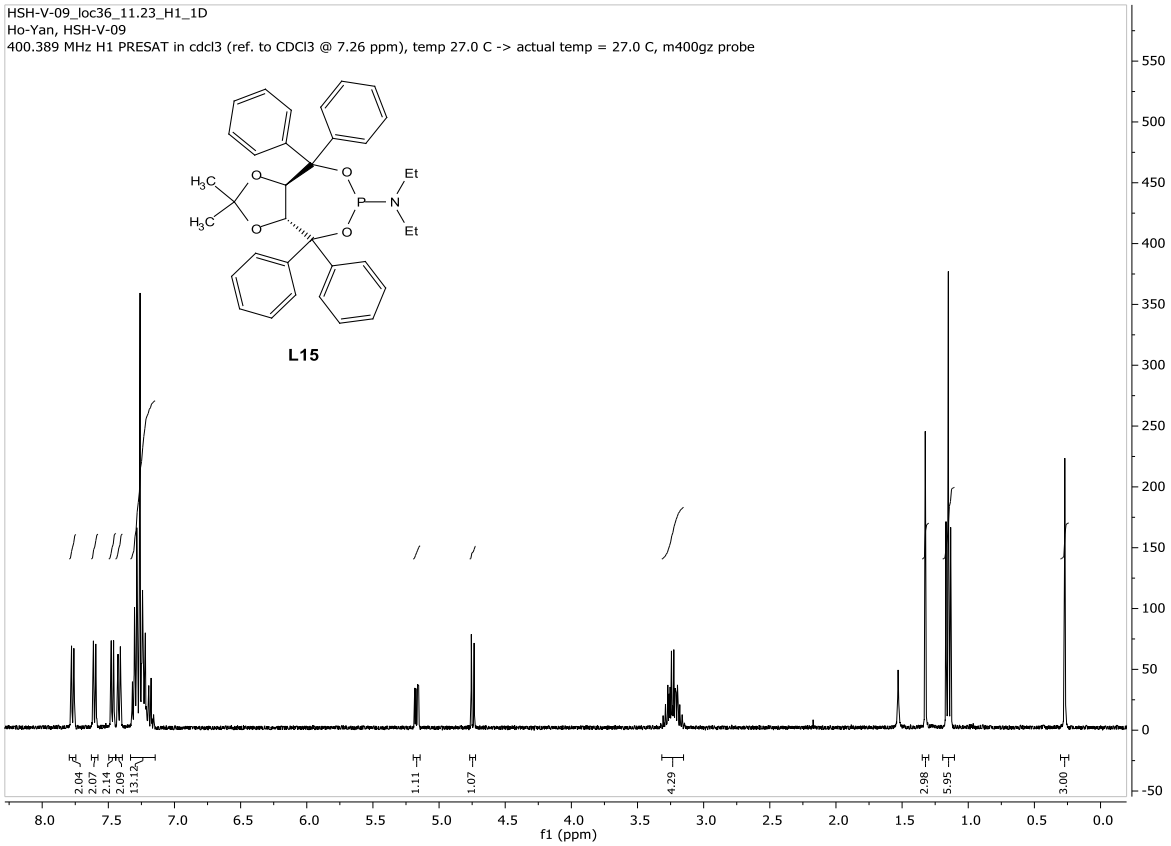

HSH-VII-79_loc10_14.10_C13_1D
Ho-Yan, HSH-VII-79
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
nPr
nPr
OH
OH
nPr
nPr
S3
f1 (ppm)

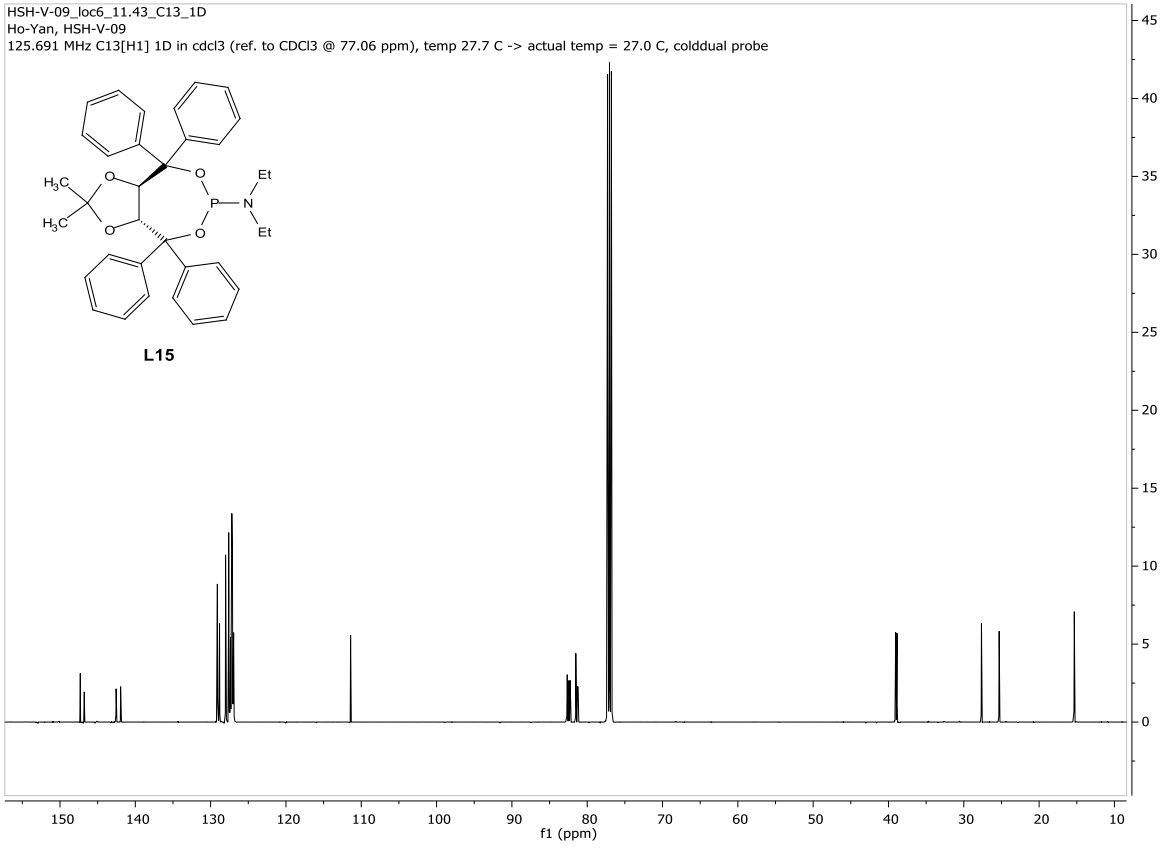

HSH-VIII-64_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
iPr
iPr
OH
H3C
O
H3C
O
OH
iPr
iPr
S4
4.03
4.08
4.22
4.24
2.02
1.94
4.17
12.73
12.65
6.00
f1 (ppm)

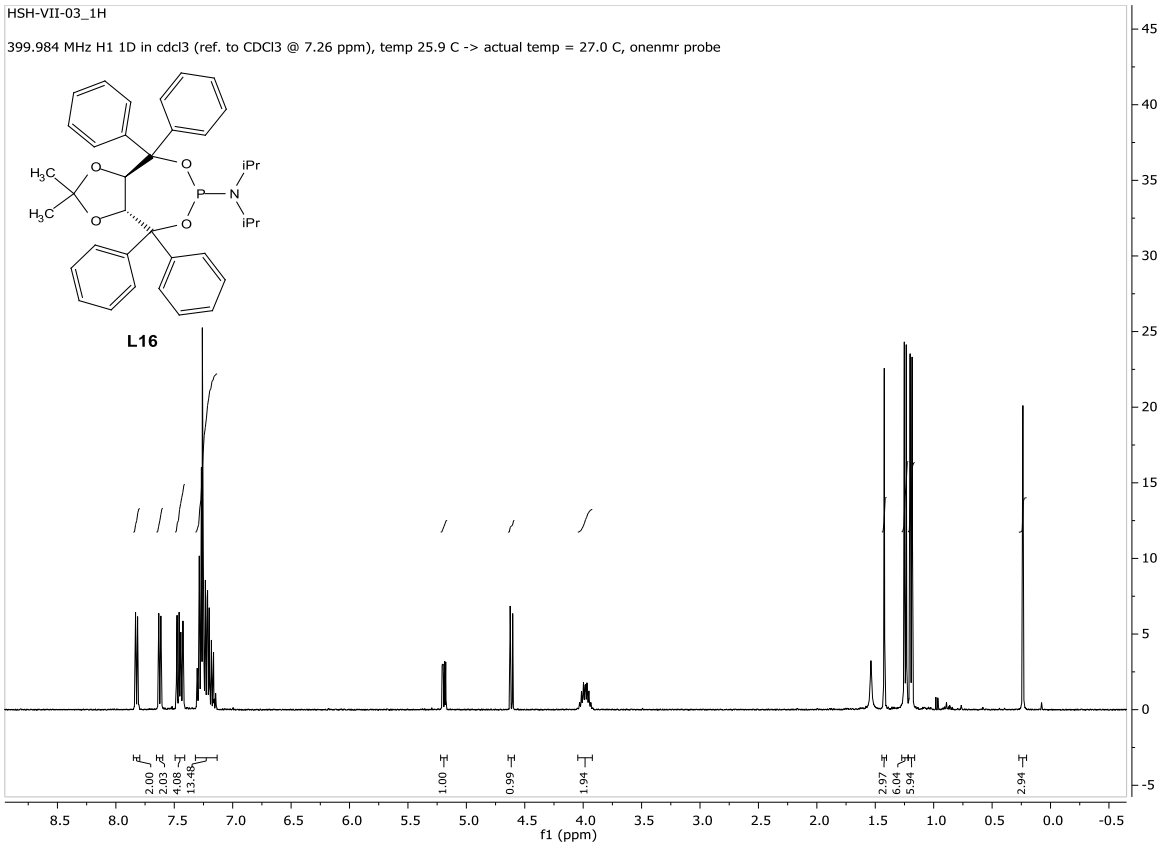

HSH-VIII-23_loc8_14.37_C13_1D
Ho-Yan, HSH-VIII-23
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
iPr
iPr
OH
H3C
O
H3C
O
OH
iPr
iPr
S4
f1 (ppm)

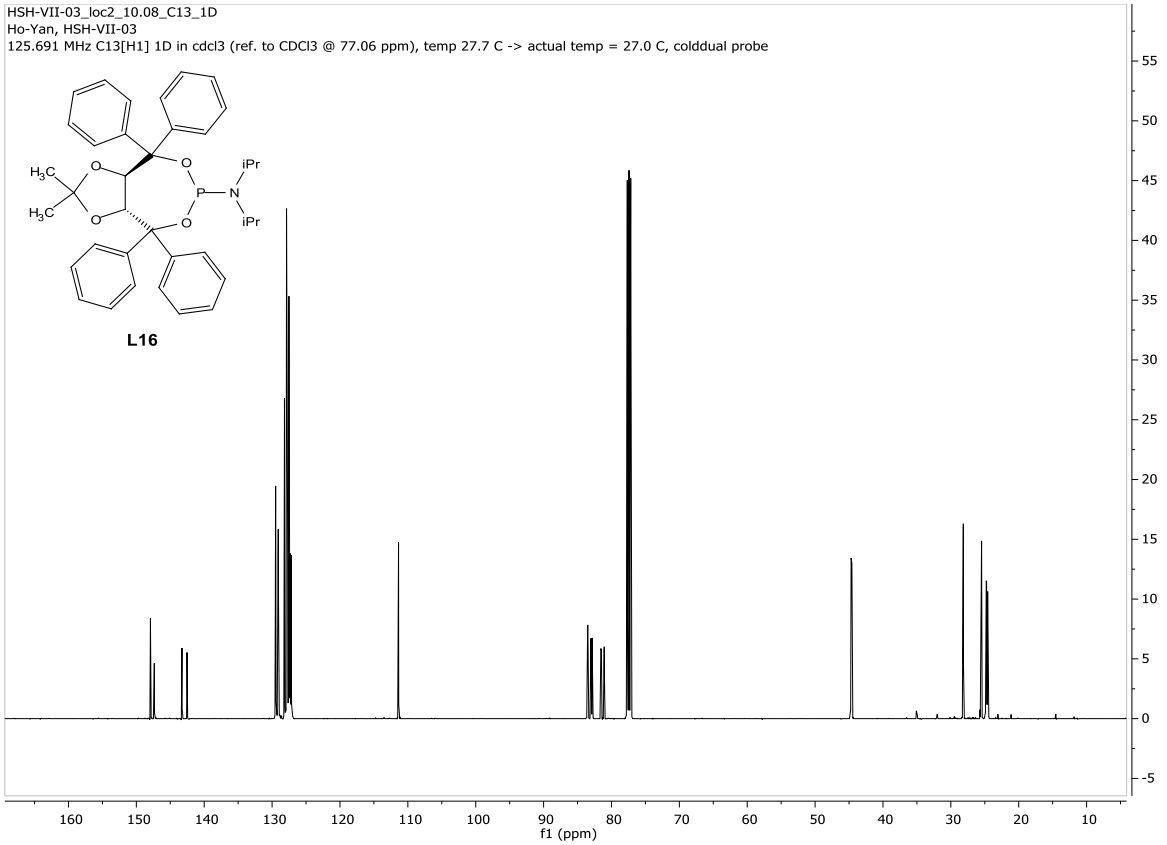

HSH-VIII-26_loc9_17.27_H1_1D
Ho-Yan, HSH-VIII-26
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
tBu
tBu
OH
OH
tBu
tBu
S5
4.13
4.55
7.24
2.34
2.17
19.24
18.45
6.00
f1 (ppm)

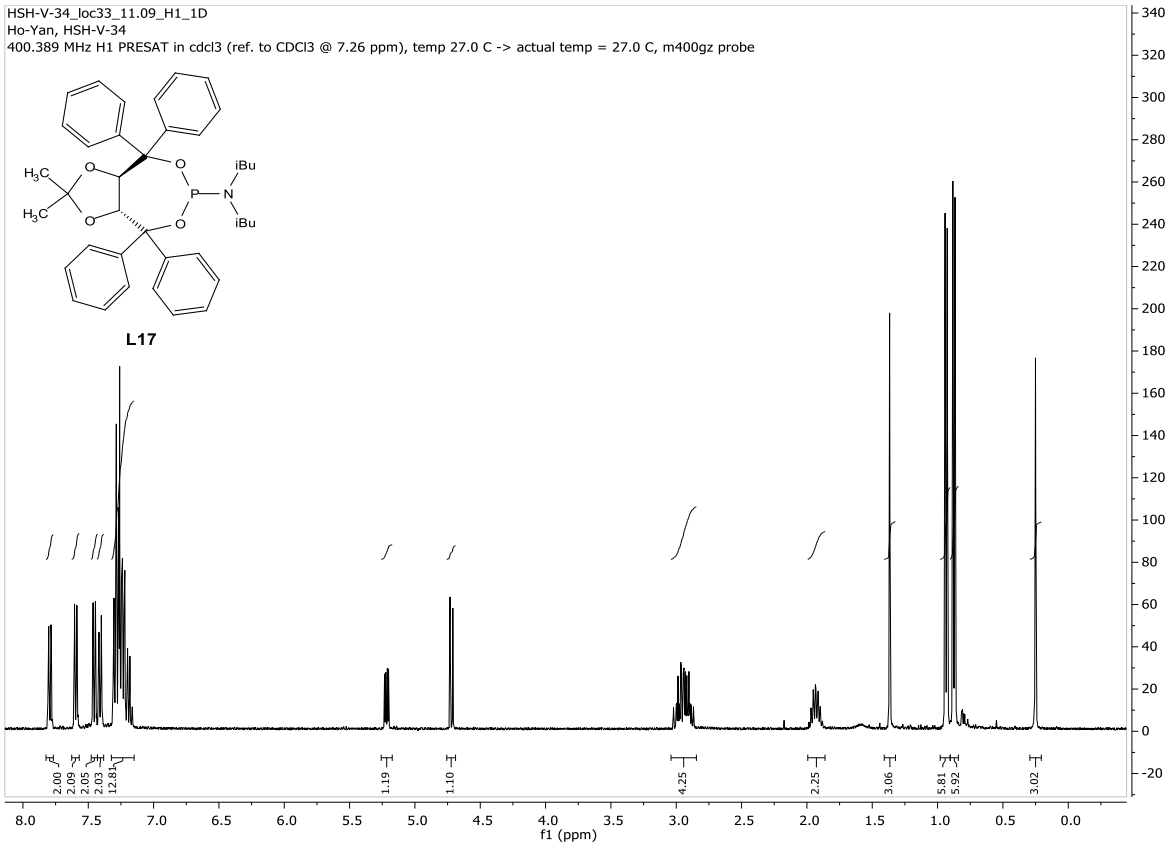

HSH-VIII-26_loc9_13.44_C13_1D
Ho-Yan, HSH-VIII-26
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
tBu
tBu
OH
OH
tBu
tBu
S5
f1 (ppm)

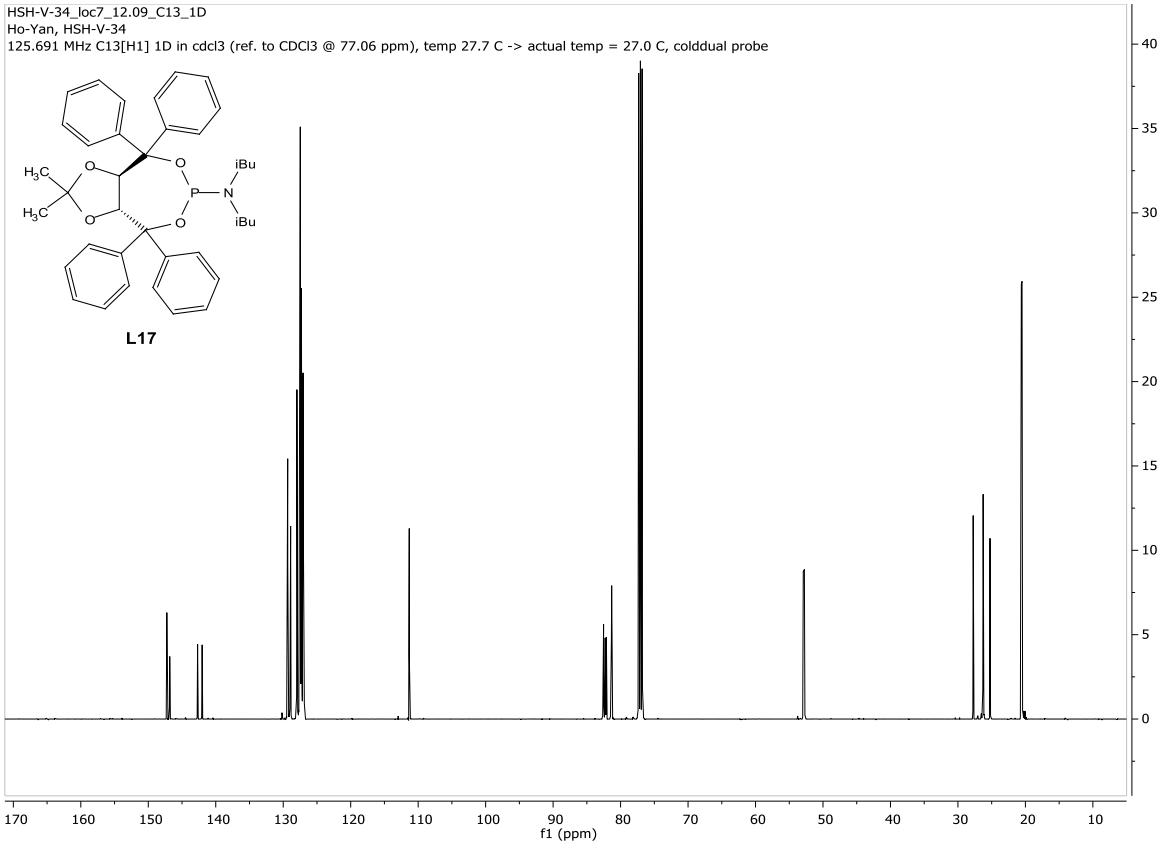

HSH-V-09_loc36_11.23_H1_1D
Ho-Yan, HSH-V-09
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
L15
2.04
2.07
2.14
2.09
13.12
1.11
1.07
4.29
2.98
5.95
3.00
f1 (ppm)

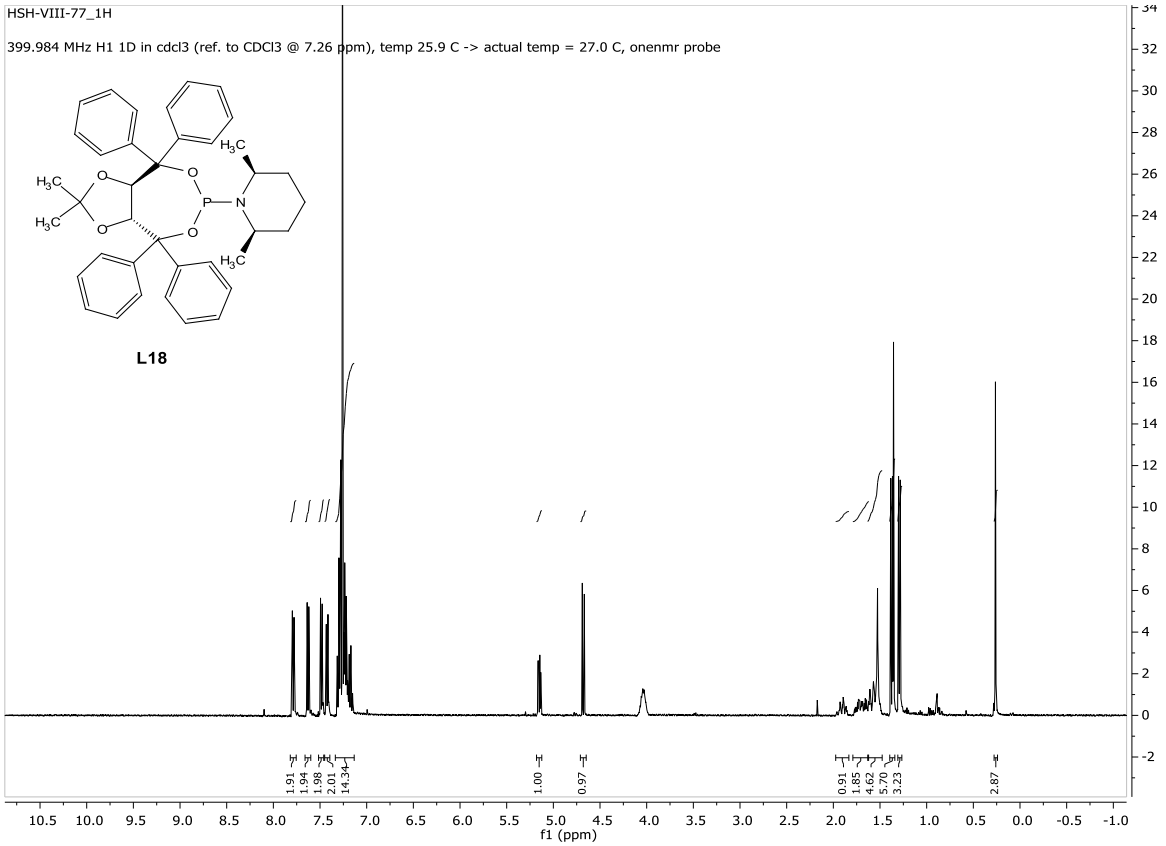

HSH-V-09_loc6_11.43_C13_1D
Ho-Yan, HSH-V-09
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L15
f1 (ppm)

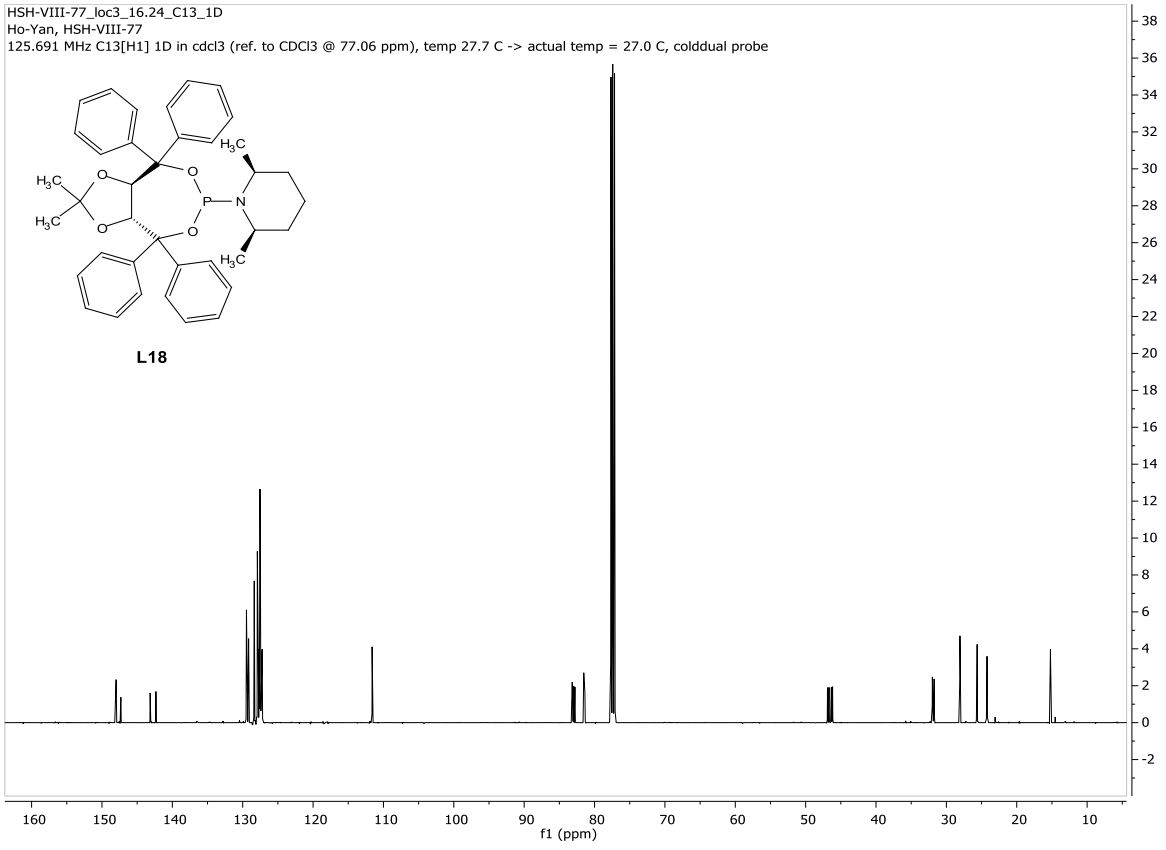

HSH-VII-03_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L16
2.00
2.03
4.08
13.48
1.00
0.99
1.94
2.97
6.04
5.94
2.94
f1 (ppm)

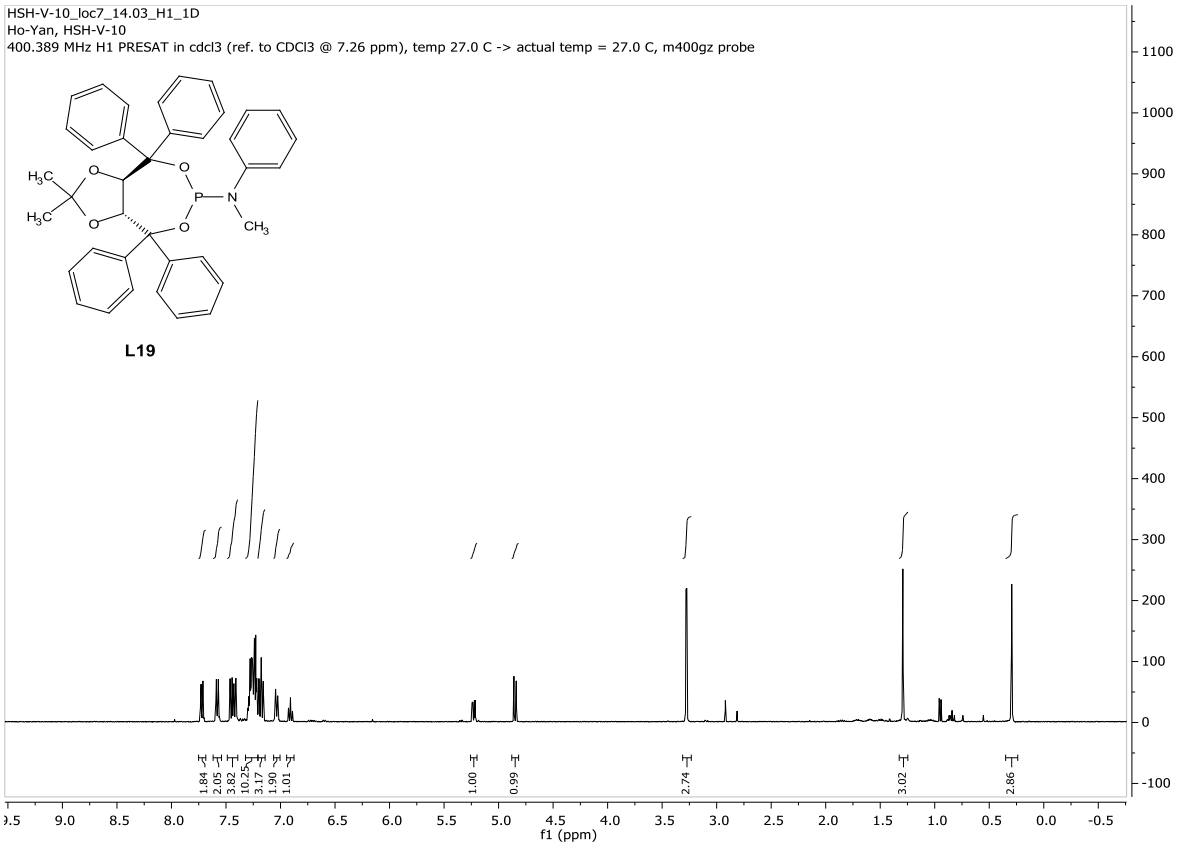

HSH-VII-03_loc2_10.08_C13_1D
Ho-Yan, HSH-VII-03
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L16
f1 (ppm)

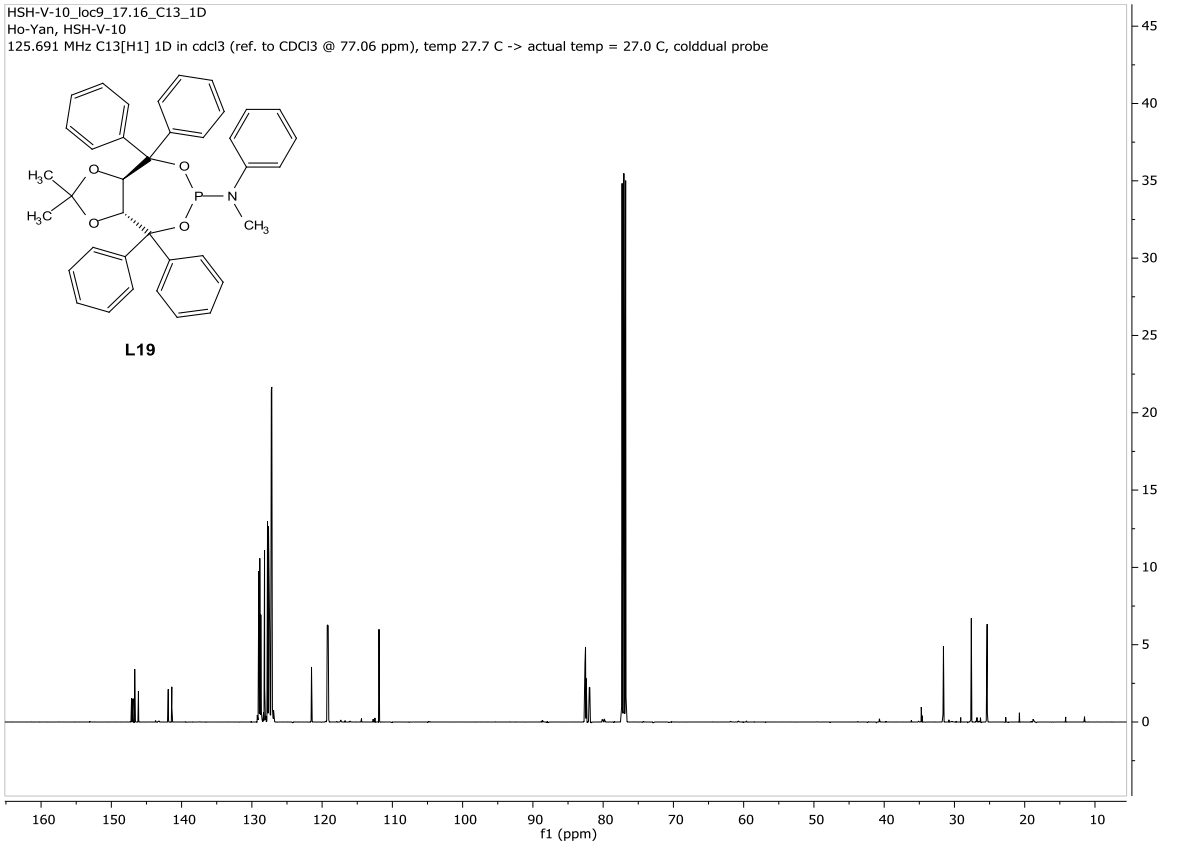

HSH-V-34_loc33_11.09_H1_1D
Ho-Yan, HSH-V-34
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
L17
2.00
2.09
2.05
2.03
12.84
1.19
1.10
4.25
2.25
3.06
5.81
5.92
3.02
f1 (ppm)

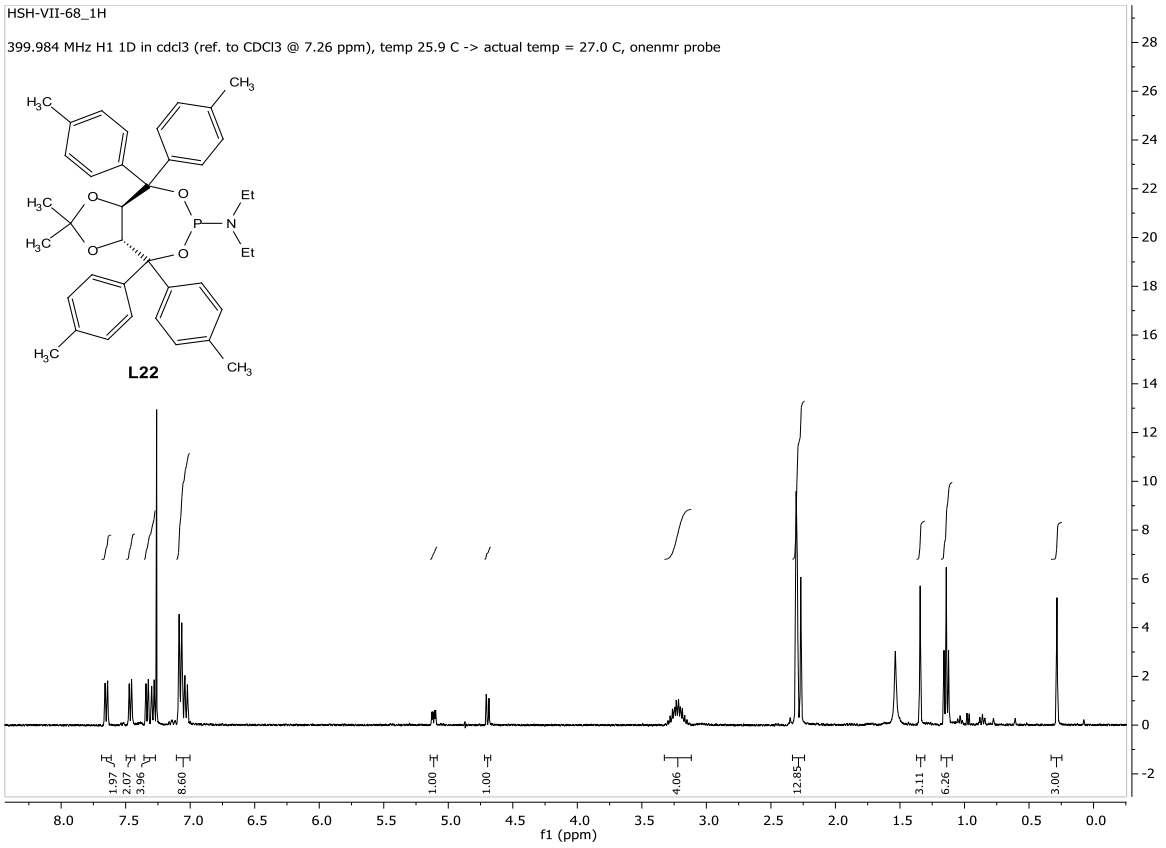

HSH-V-34_loc7_12.09_C13_1D
Ho-Yan, HSH-V-34
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L17
f1 (ppm)

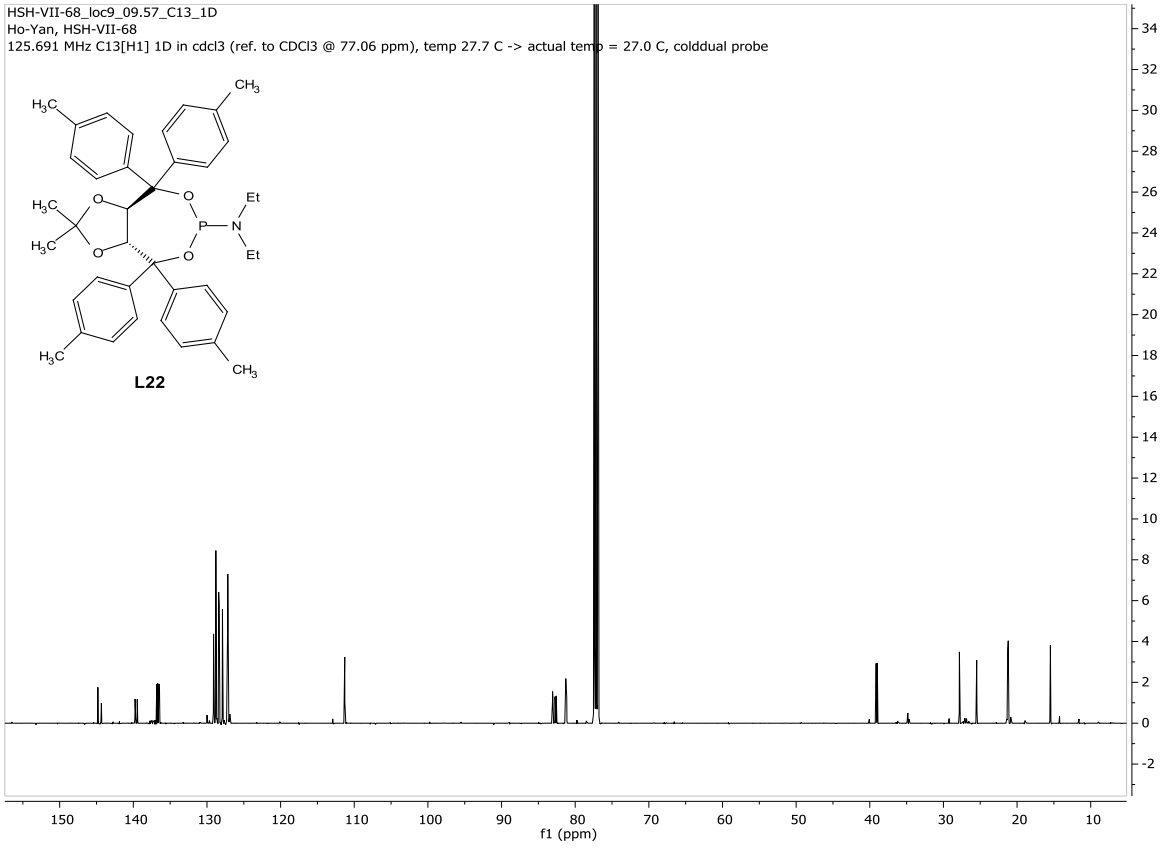

HSH-VIII-77_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L18
1.91
1.94
1.98
2.01
14.34
1.00
0.97
0.91
1.85
4.62
5.70
3.23
2.87
f1 (ppm)

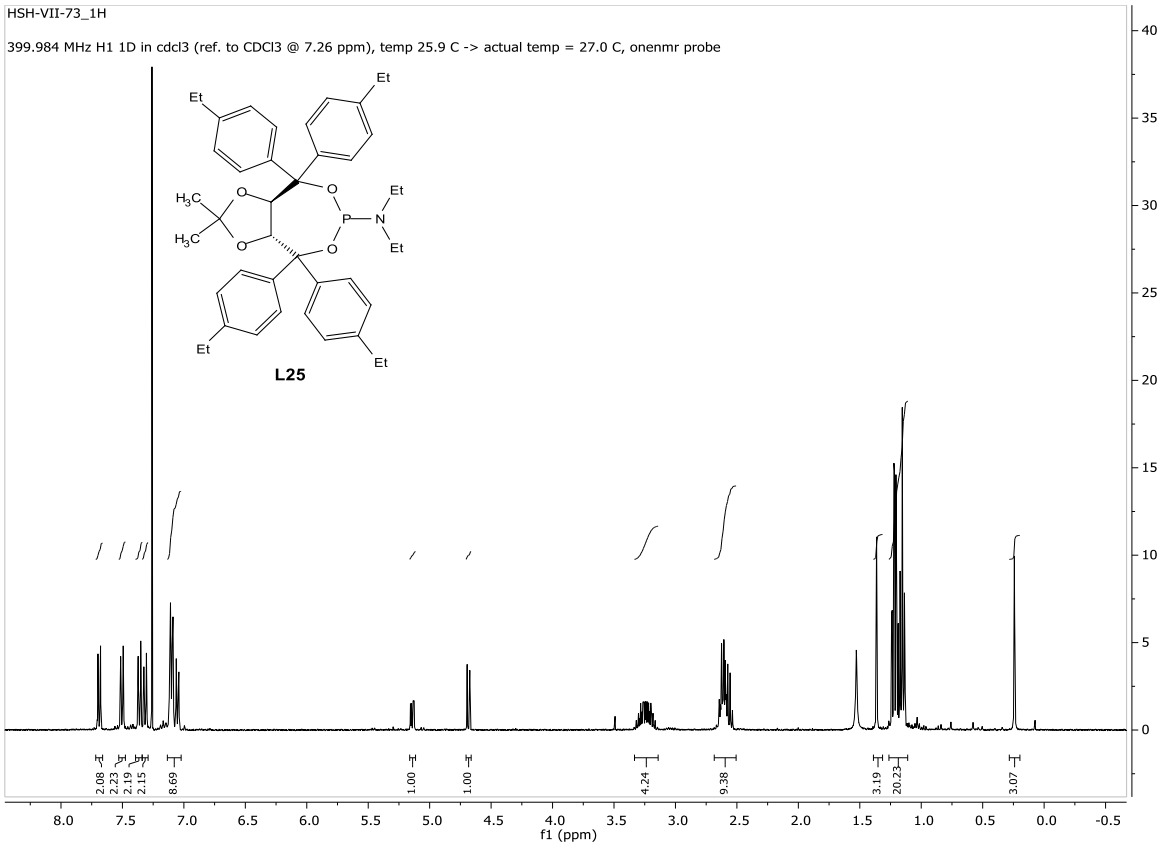

HSH-VIII-77_loc3_16.24_C13_1D
Ho-Yan, HSH-VIII-77
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L18
f1 (ppm)

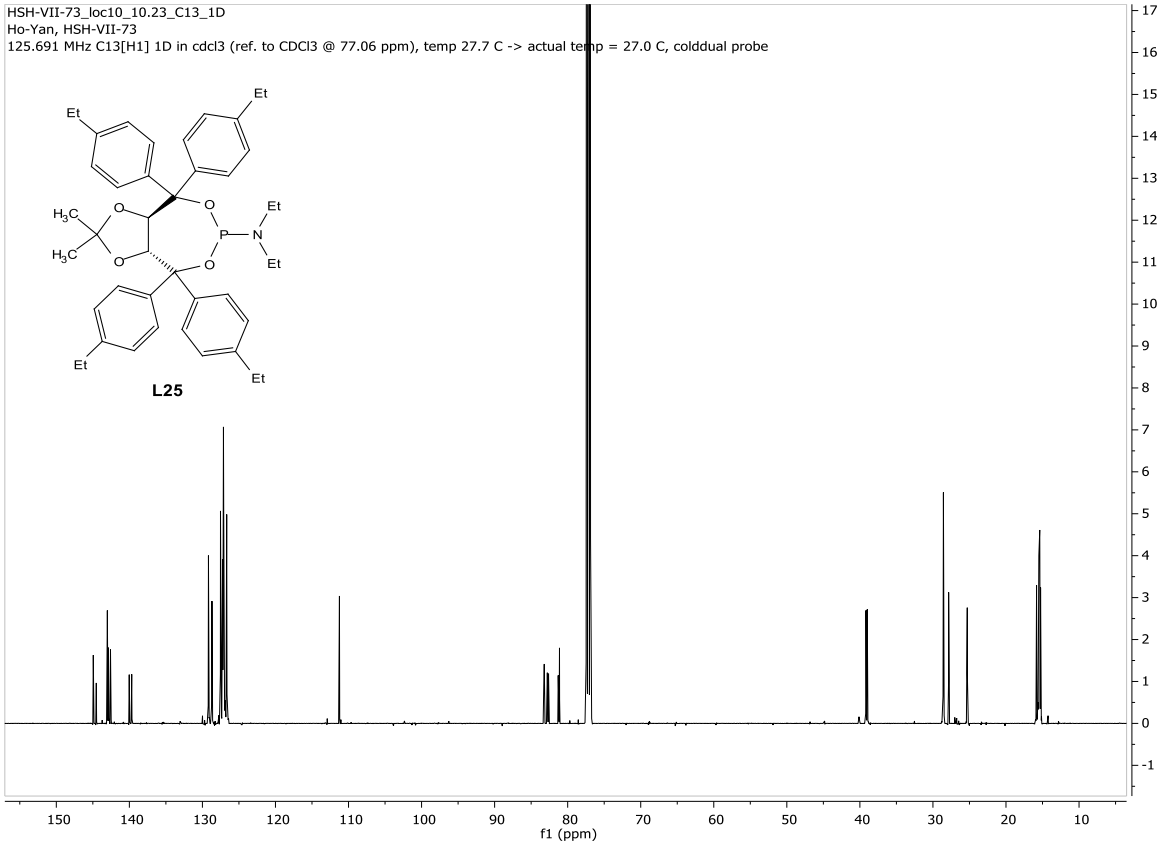

HSH-V-10_loc7_14.03_H1_1D
Ho-Yan, HSH-V-10
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
L19
1.84
2.05
3.82
10.25
3.17
1.90
1.01
1.00
0.99
2.74
3.02
2.86
f1 (ppm)

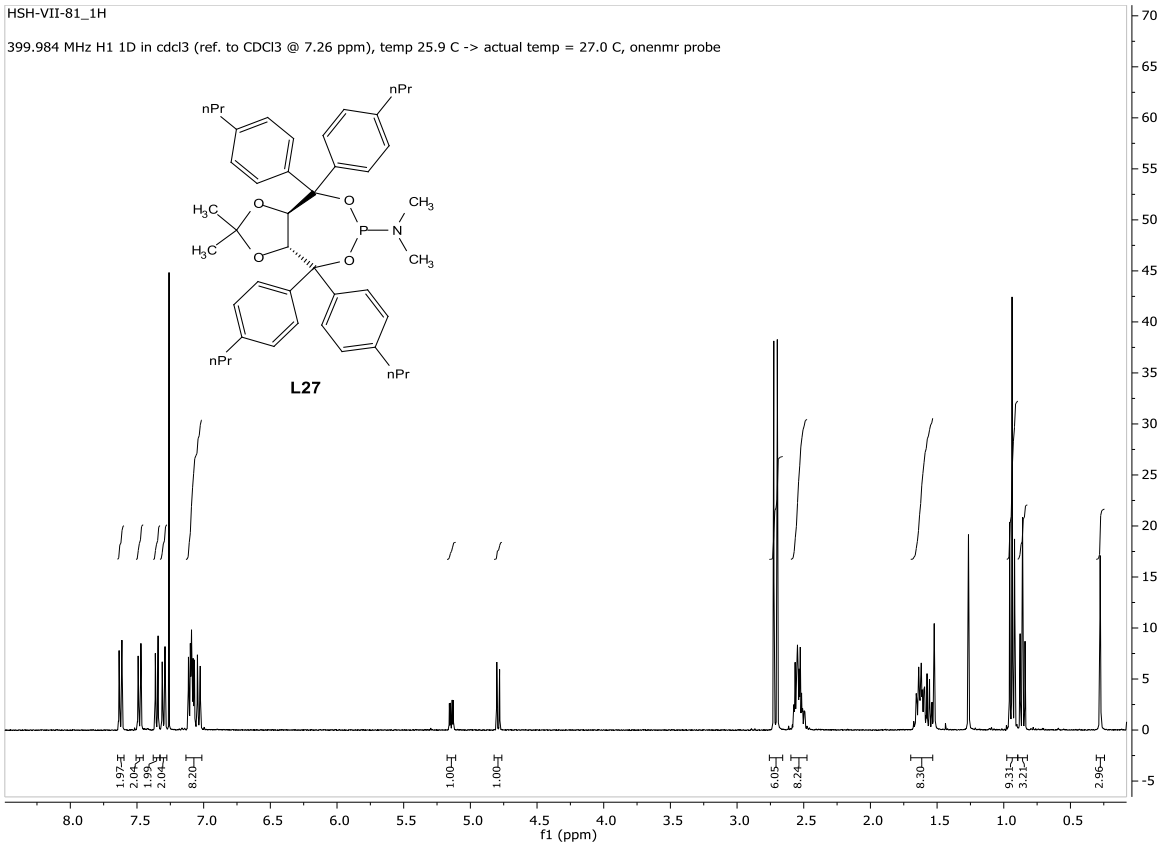

HSH-V-10_loc9_17.16_C13_1D
Ho-Yan, HSH-V-10
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L19
f1 (ppm)

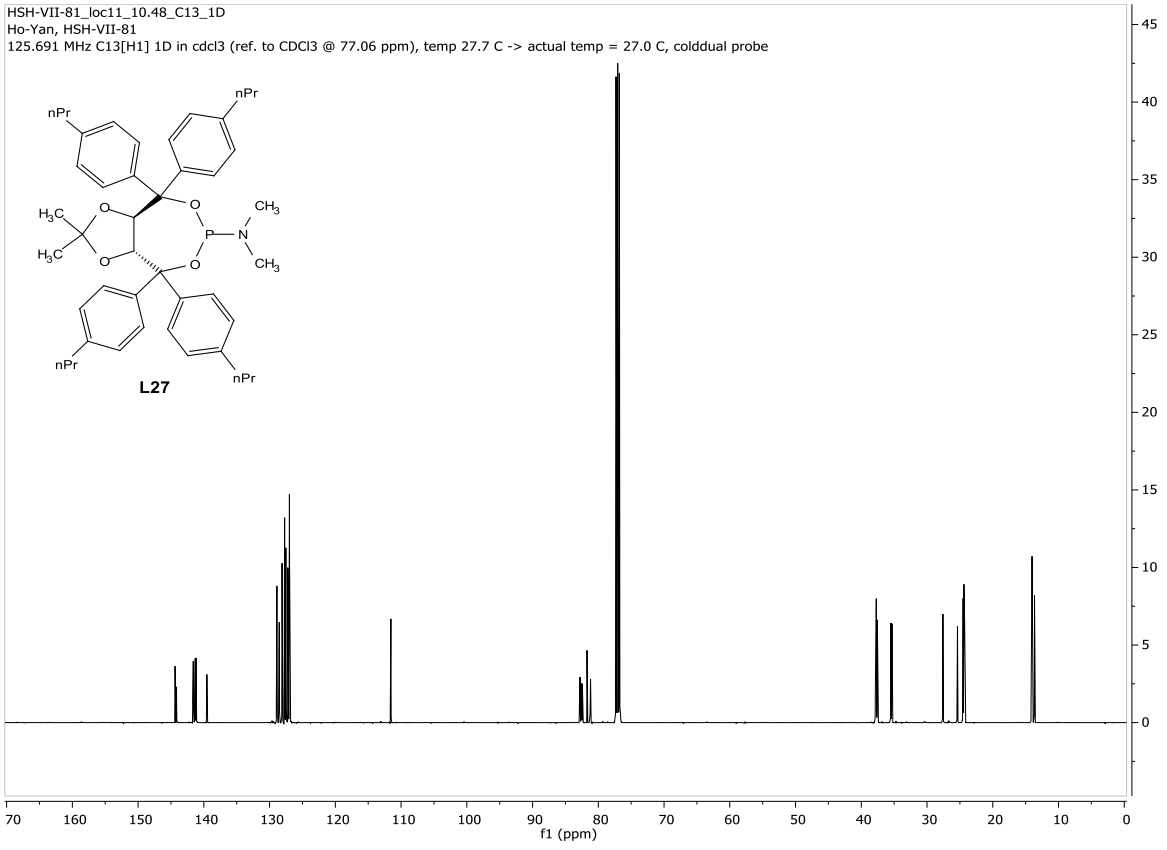

HSH-VII-68_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L22
1.97
2.07
3.96
8.60
1.00
1.00
4.06
12.85
3.11
6.26
3.00
f1 (ppm)

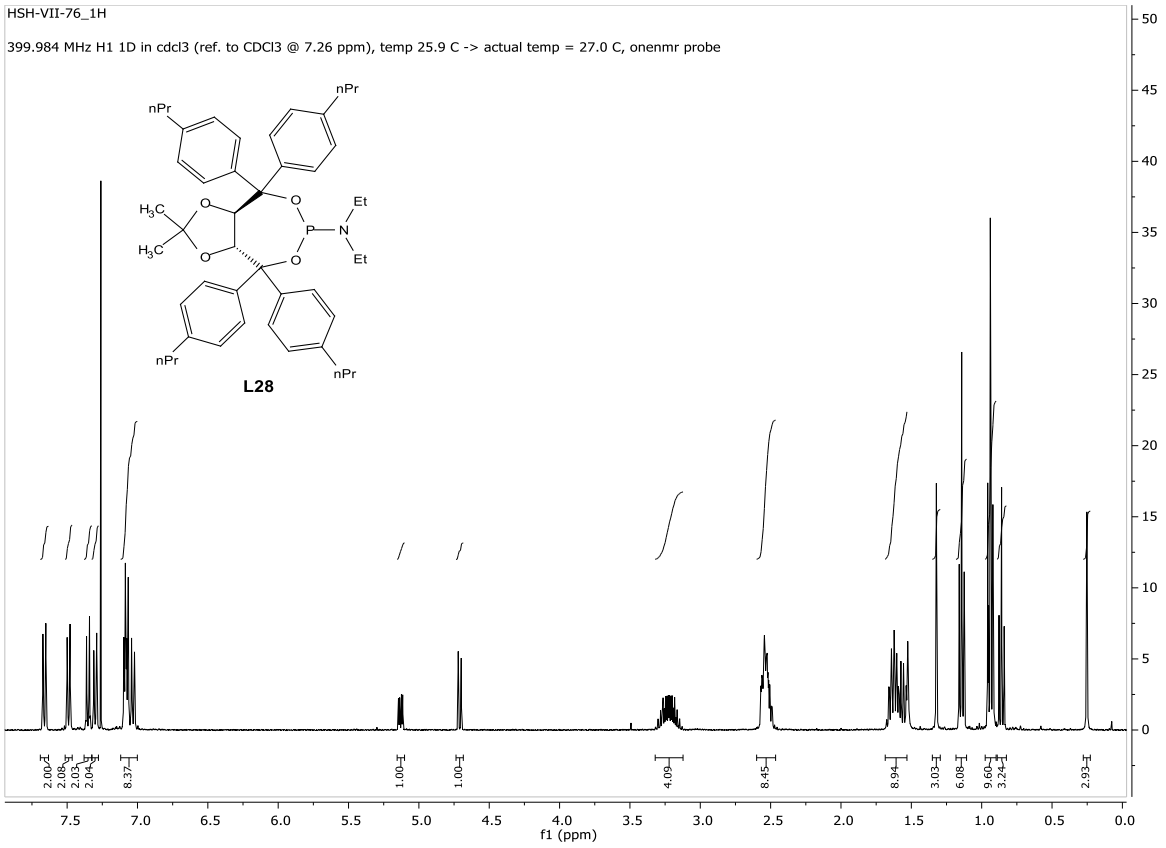

HSH-VII-68_loc9_09.57_C13_1D
Ho-Yan, HSH-VII-68
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L22
f1 (ppm)

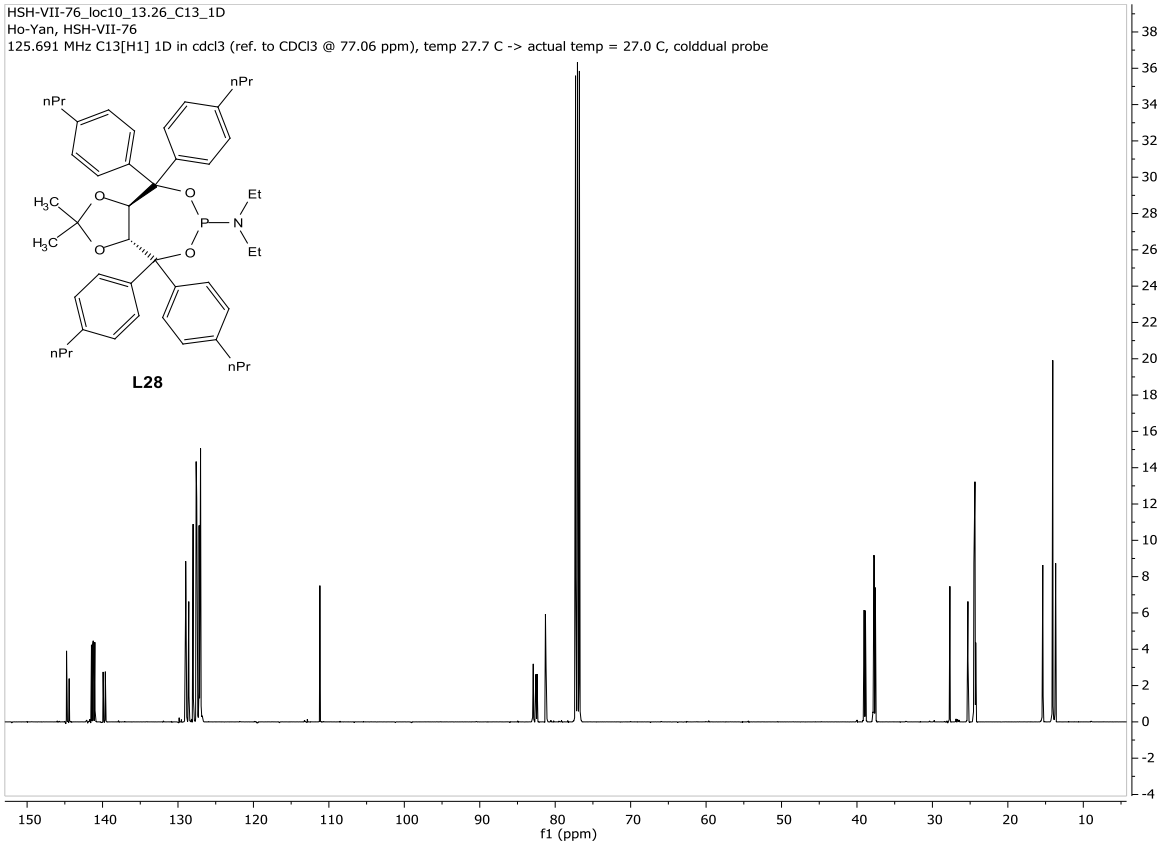

HSH-VII-73_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L25
2.08
2.23
2.19
2.15
8.69
1.00
1.00
4.24
9.38
3.19
20.23
3.07
f1 (ppm)

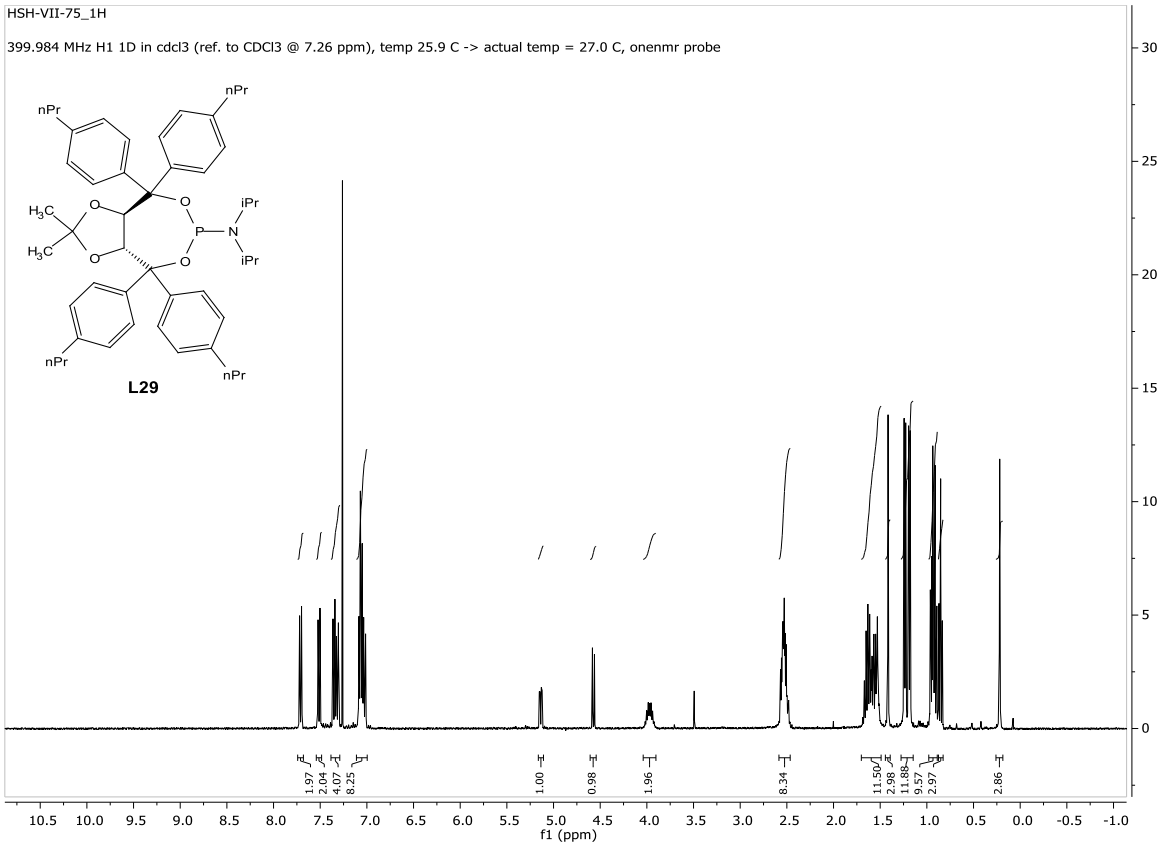

HSH-VII-73_loc10_10.23_C13_1D
Ho-Yan, HSH-VII-73
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L25
f1 (ppm)

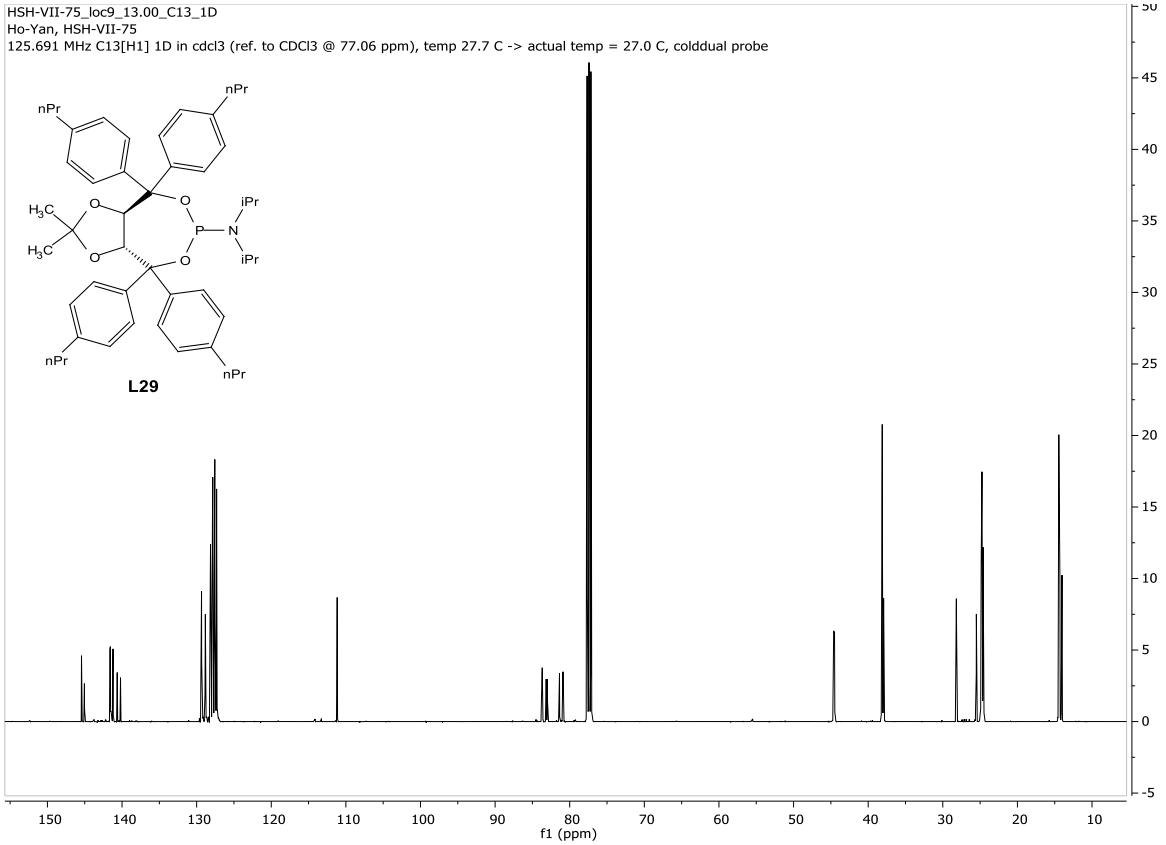

HSH-VII-81_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L27
f1 (ppm)

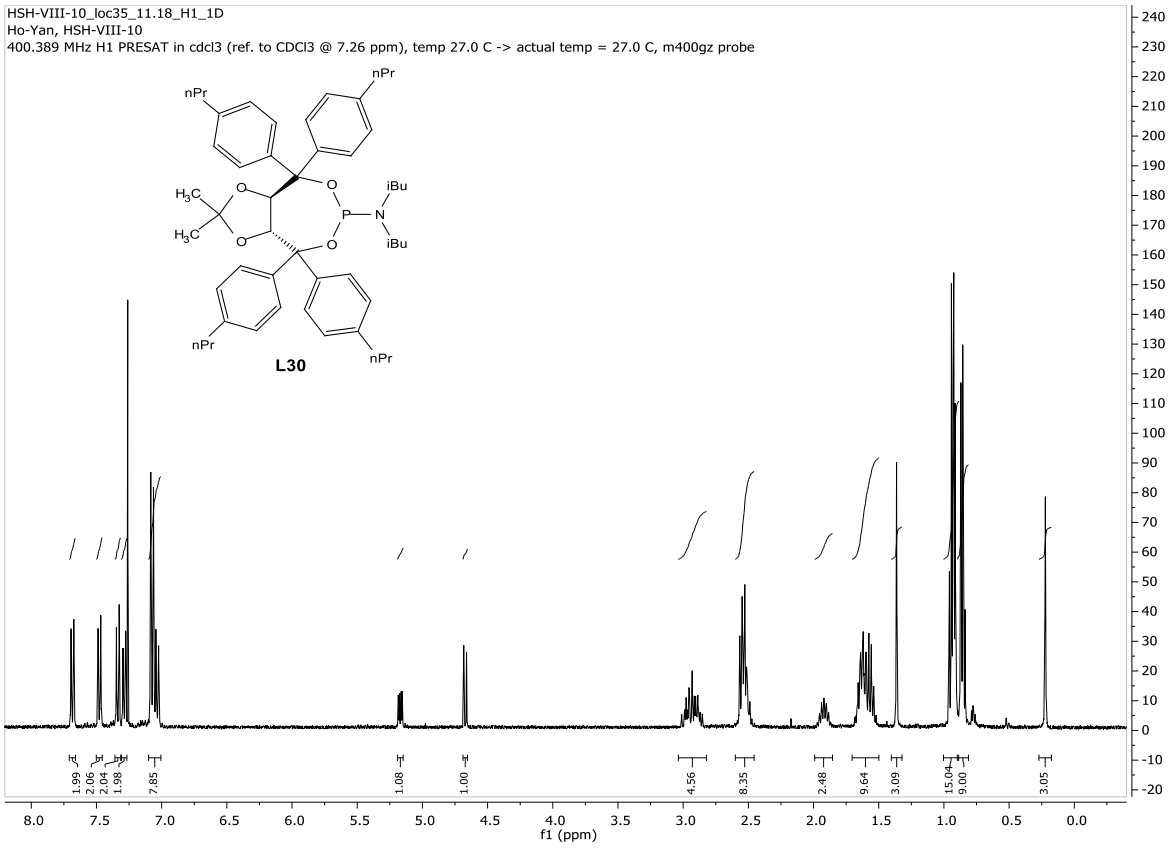

HSH-VII-81_loc11_10.48_C13_1D
Ho-Yan, HSH-VII-81
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L27
f1 (ppm)

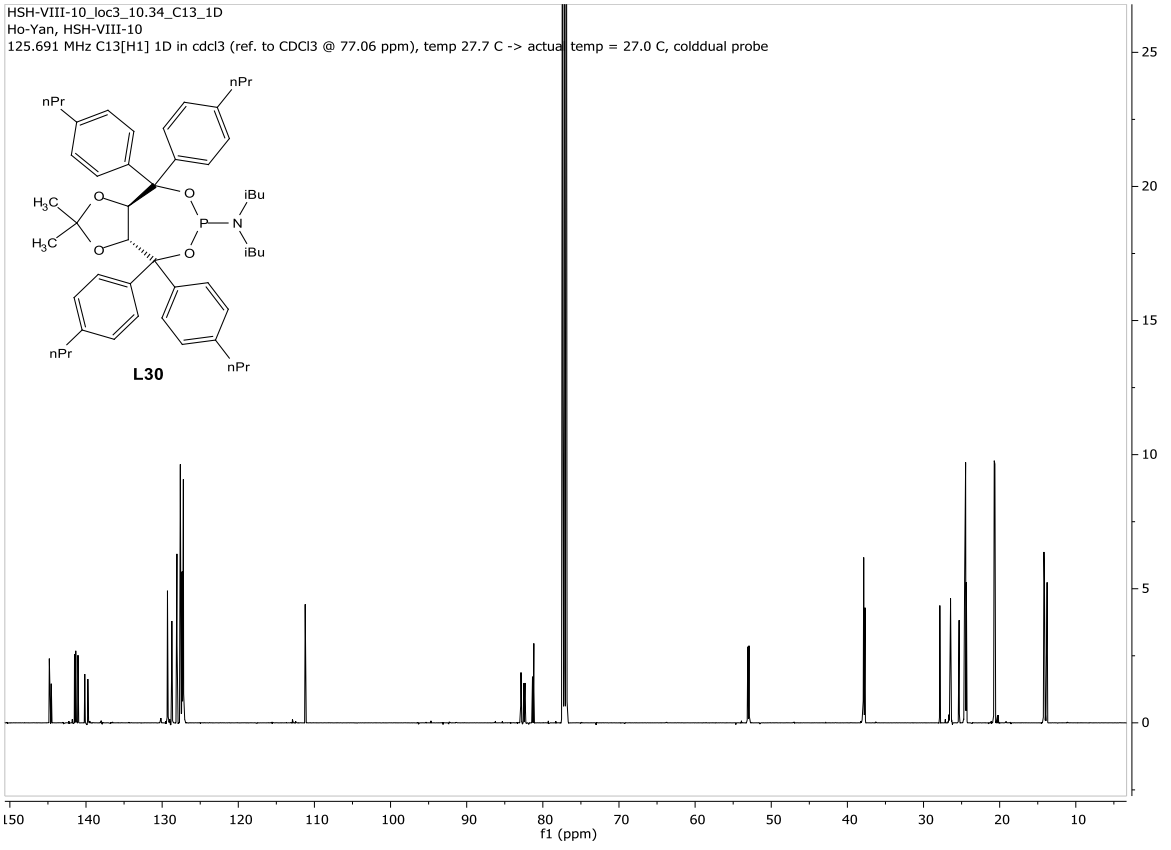

HSH-VII-76_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
nPr
nPr
H3C
H3C
O
O
O
O
P
N
Et
Et
nPr
nPr
L28
2.00
2.08
2.03
2.04
8.37
1.00
1.00
4.09
8.45
8.94
3.03
6.08
9.60
3.24
2.93
f1 (ppm)

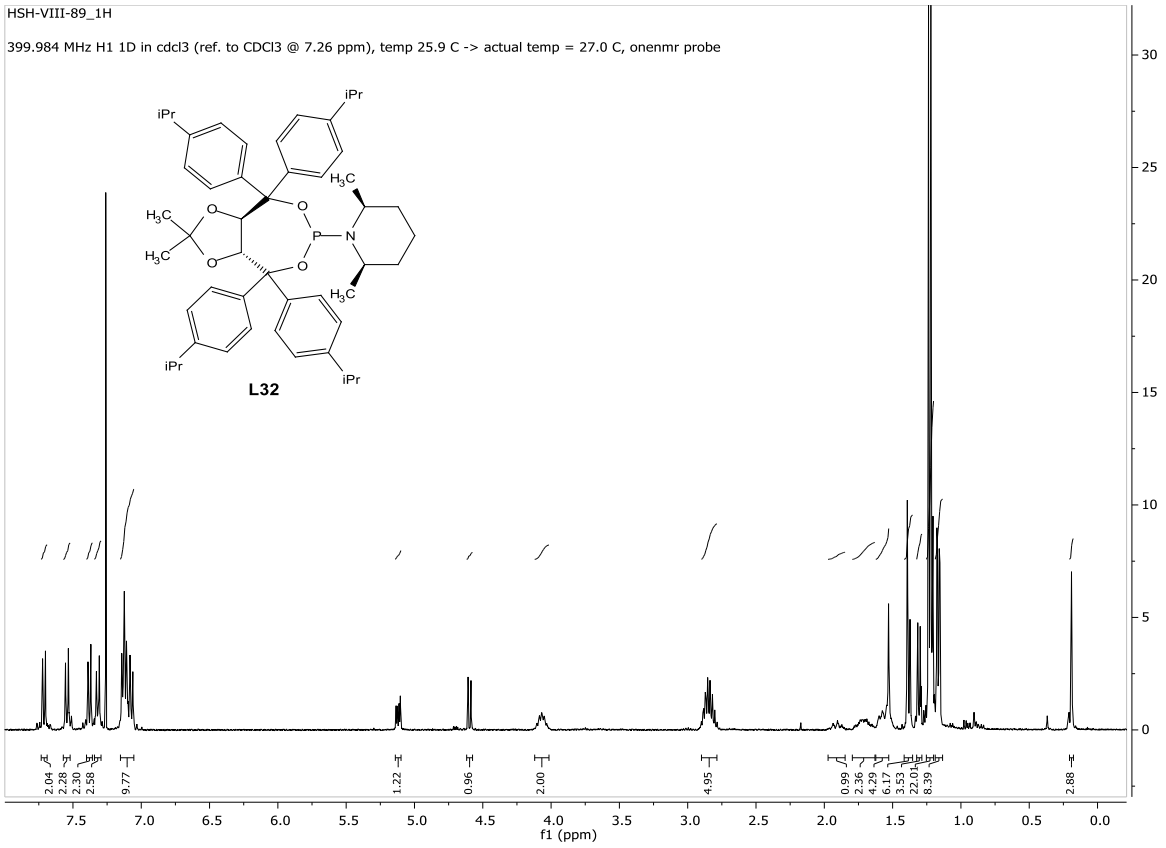

HSH-VII-76_loc10_13.26_C13_1D
Ho-Yan, HSH-VII-76
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
nPr
nPr
H3C
H3C
O
O
O
O
P
N
Et
Et
nPr
nPr
L28
f1 (ppm)

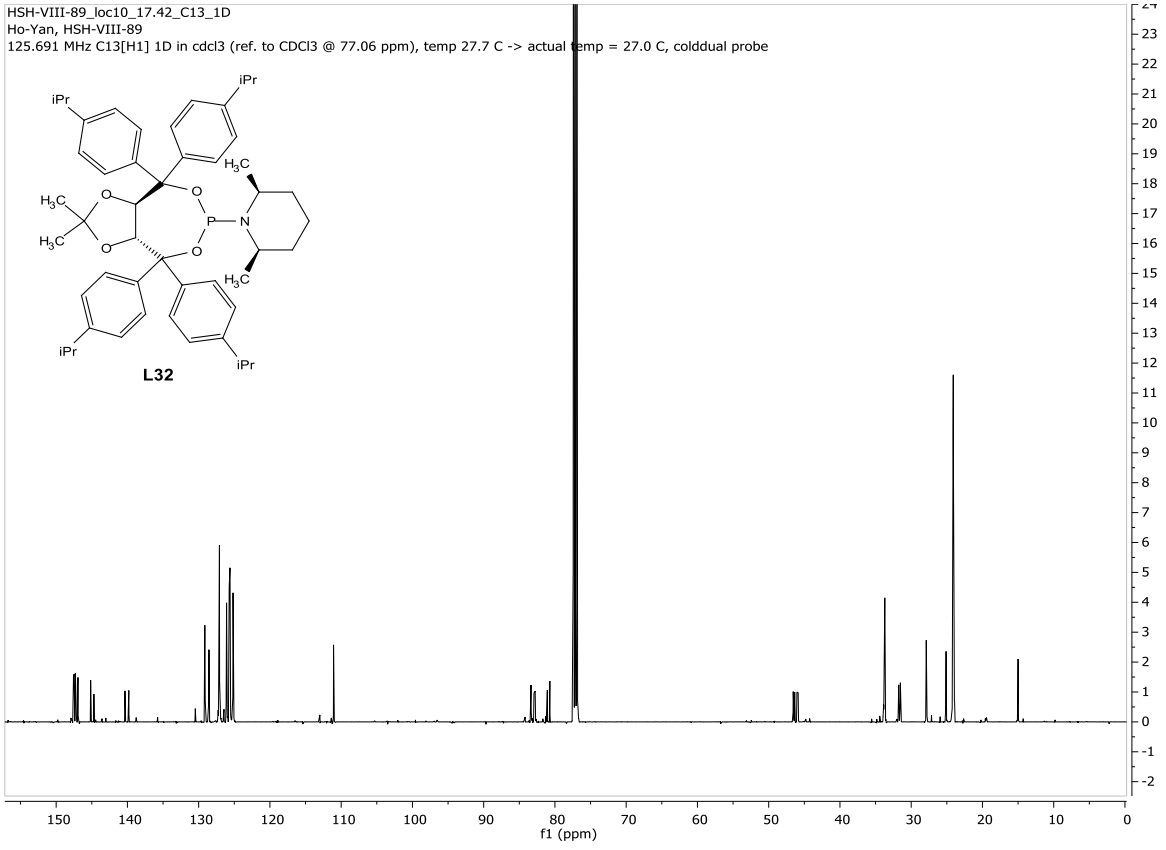

HSH-VII-75_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L29
1.97
2.04
4.07
8.25
1.00
0.98
1.96
8.34
11.50
2.98
11.88
9.57
2.97
2.86
f1 (ppm)

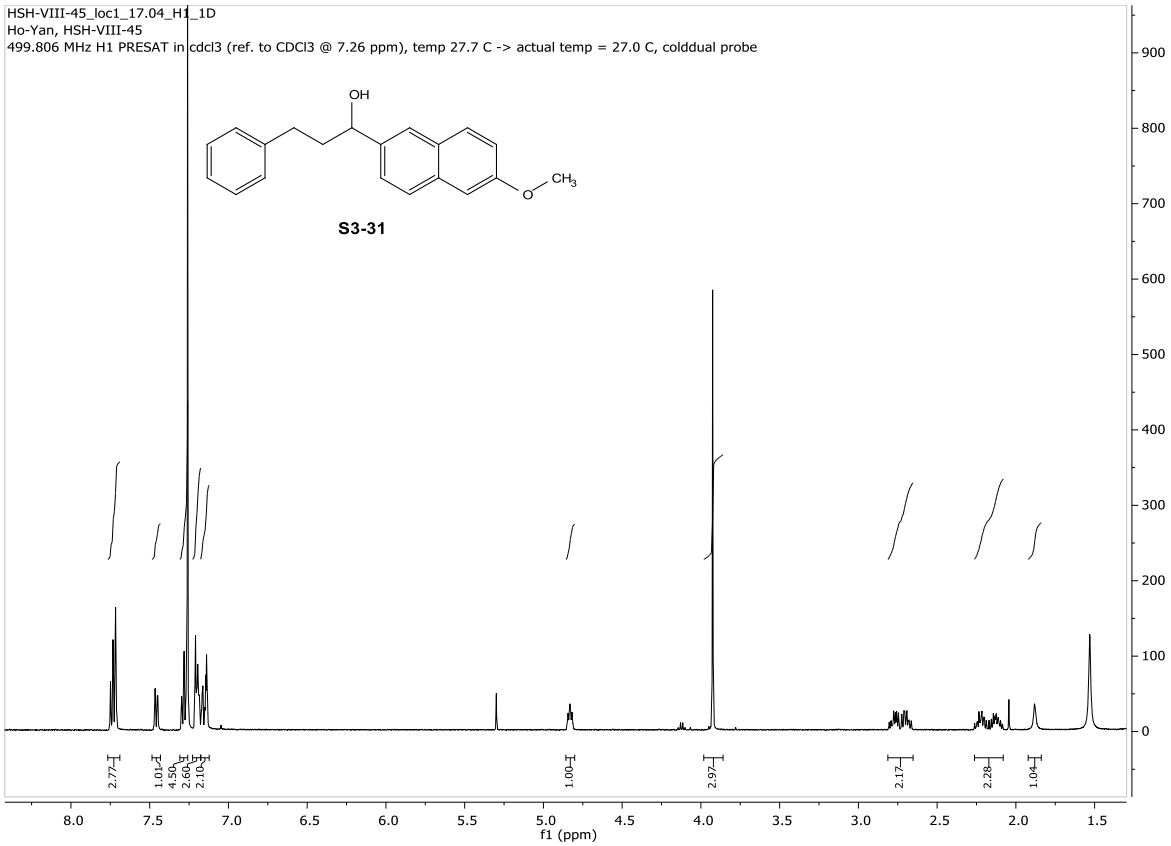

HSH-VII-75_loc9_13.00_C13_1D
Ho-Yan, HSH-VII-75
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L29
f1 (ppm)

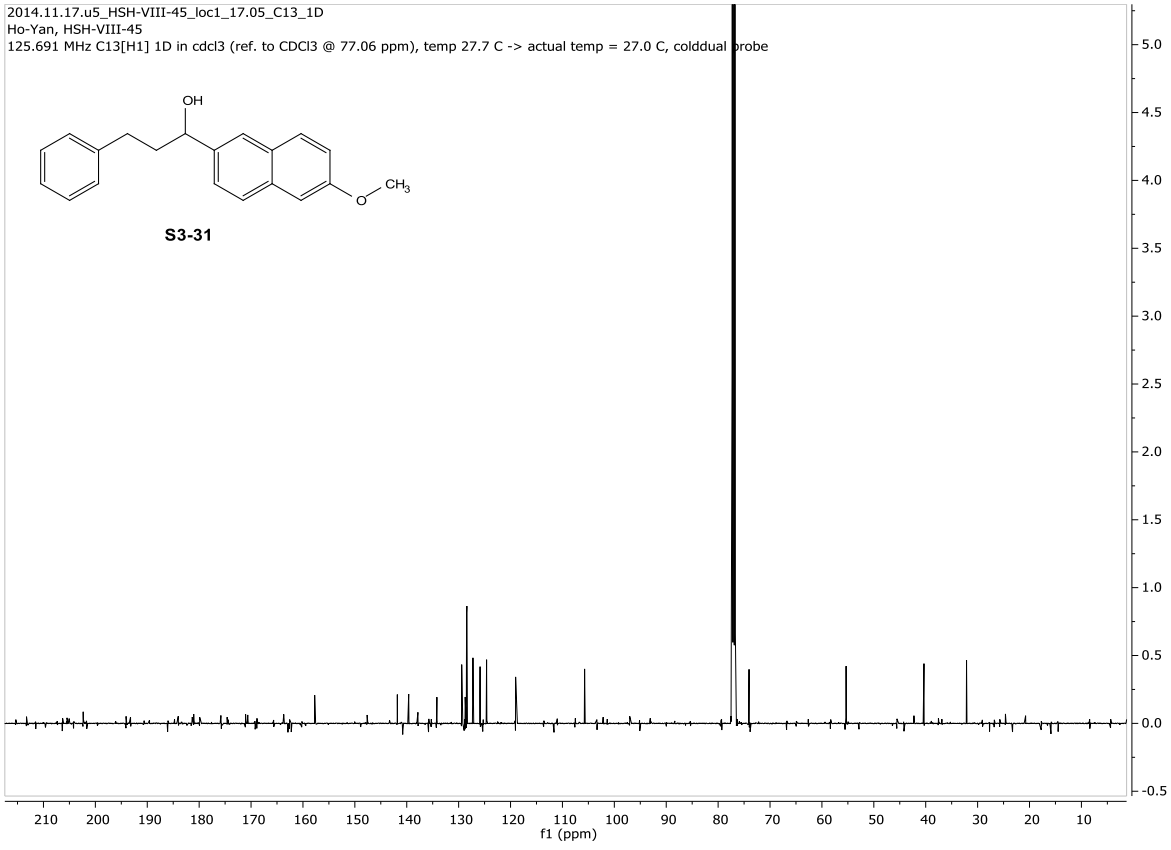

HSH-VIII-10_loc35_11.18_H1_1D
Ho-Yan, HSH-VIII-10
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
L30
1.99
2.06
2.04
1.98
7.85
1.08
1.00
4.56
8.35
2.48
9.64
3.09
15.04
9.00
3.05
f1 (ppm)

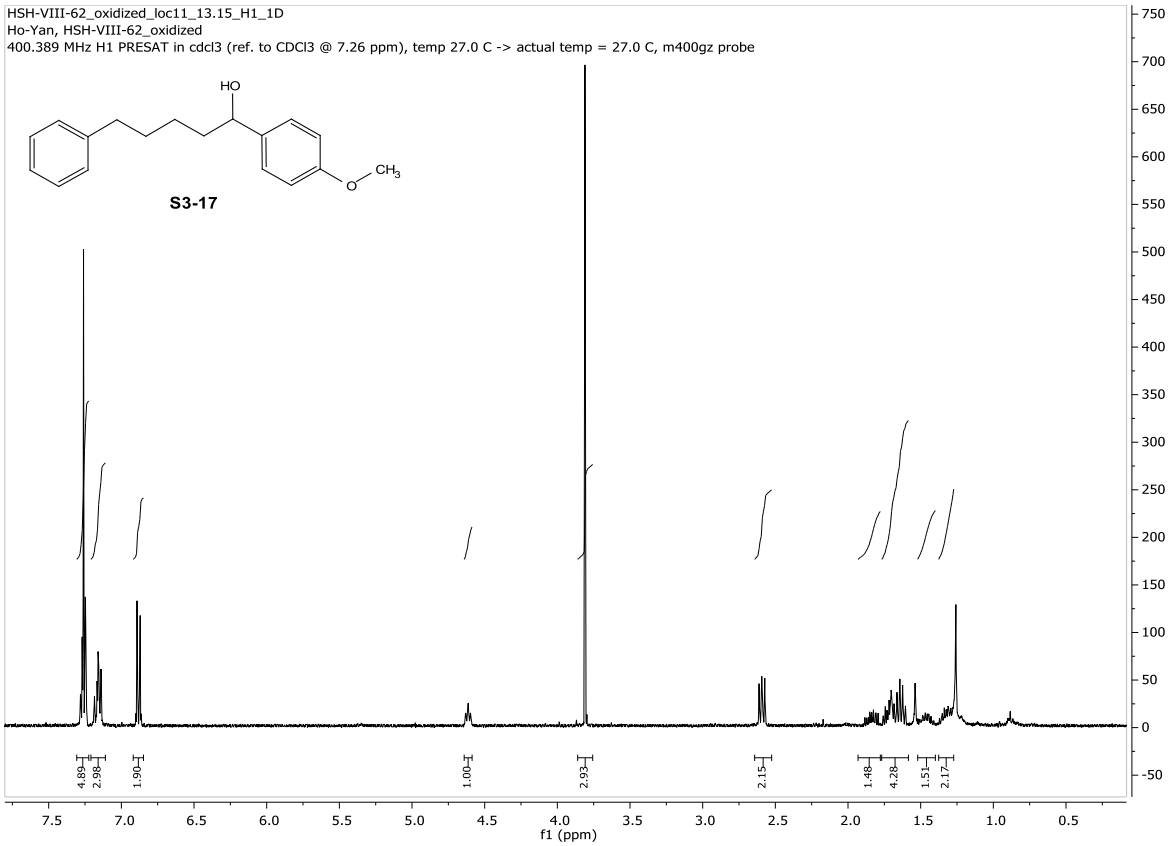

HSH-VIII-10_loc3_10.34_C13_1D
Ho-Yan, HSH-VIII-10
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L30
f1 (ppm)

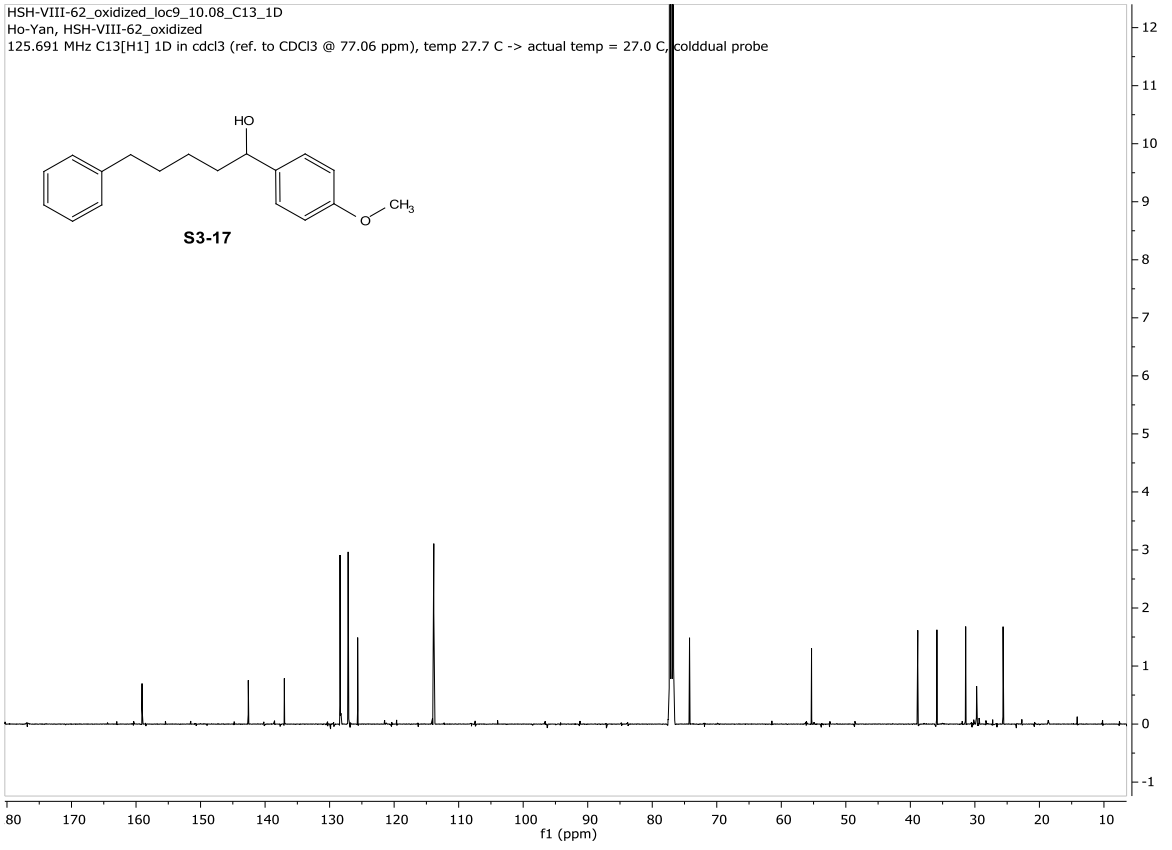

HSH-VIII-89_1H
399.984 MHz H1 1D in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 25.9 C -> actual temp = 27.0 C, onenmr probe
L32
f1 (ppm)

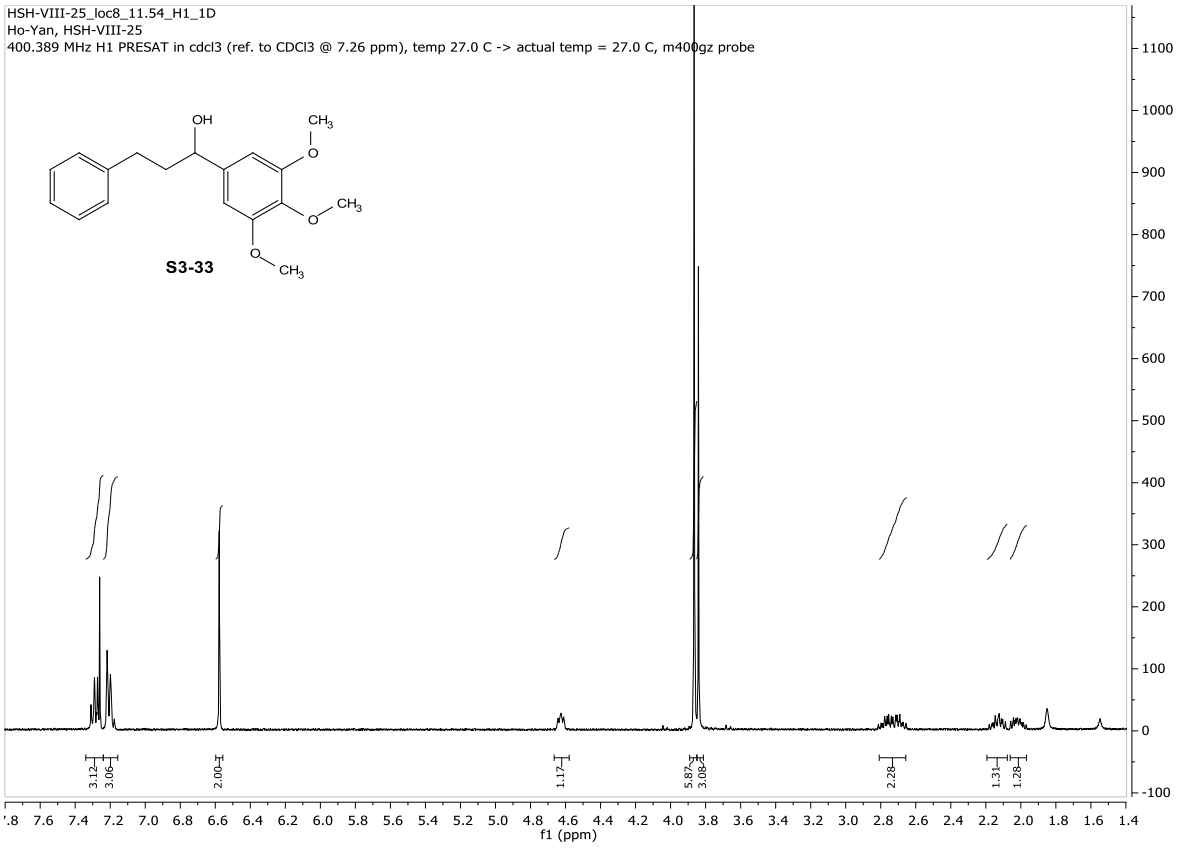

HSH-VIII-89_loc10_17.42_C13_1D
Ho-Yan, HSH-VIII-89
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
L32
f1 (ppm)

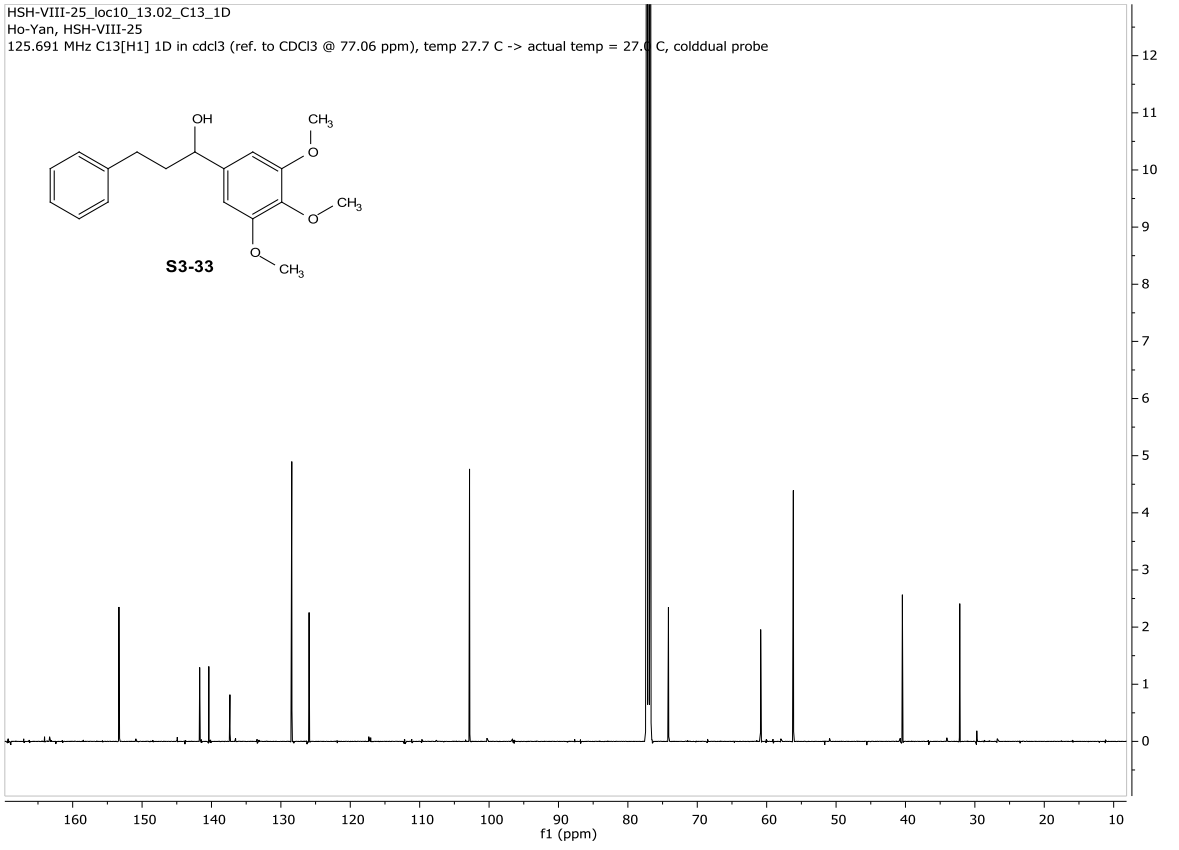

HSH-VIII-45_loc1_17.04_H1_1D
Ho-Yan, HSH-VIII-45
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
OH
O
CH3
S3-31
2.77
1.01
4.50
2.60
2.10
1.00
2.97
2.17
2.28
1.04
f1 (ppm)

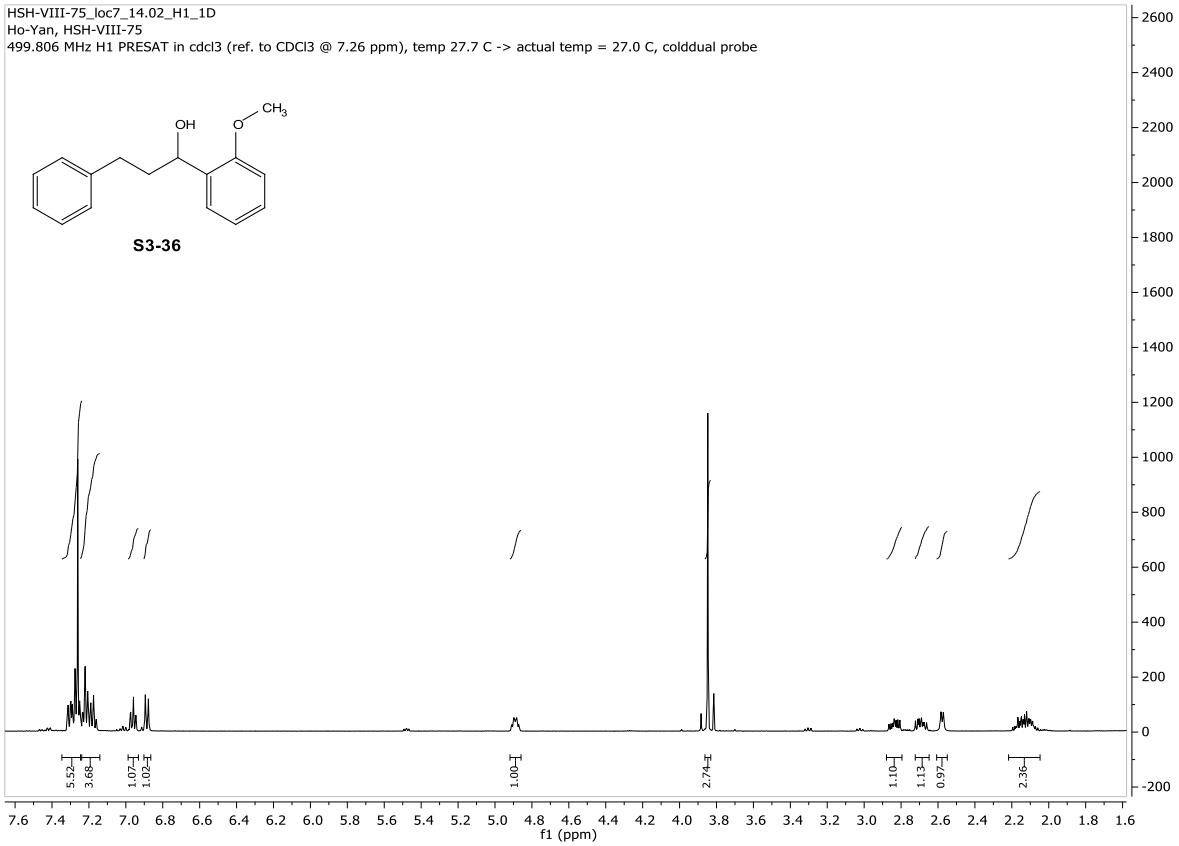

2014.11.17.u5_HSH-VIII-45_loc1_17.05_C13_1D
Ho-Yan, HSH-VIII-45
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
OH
O
CH3
S3-31
f1 (ppm)

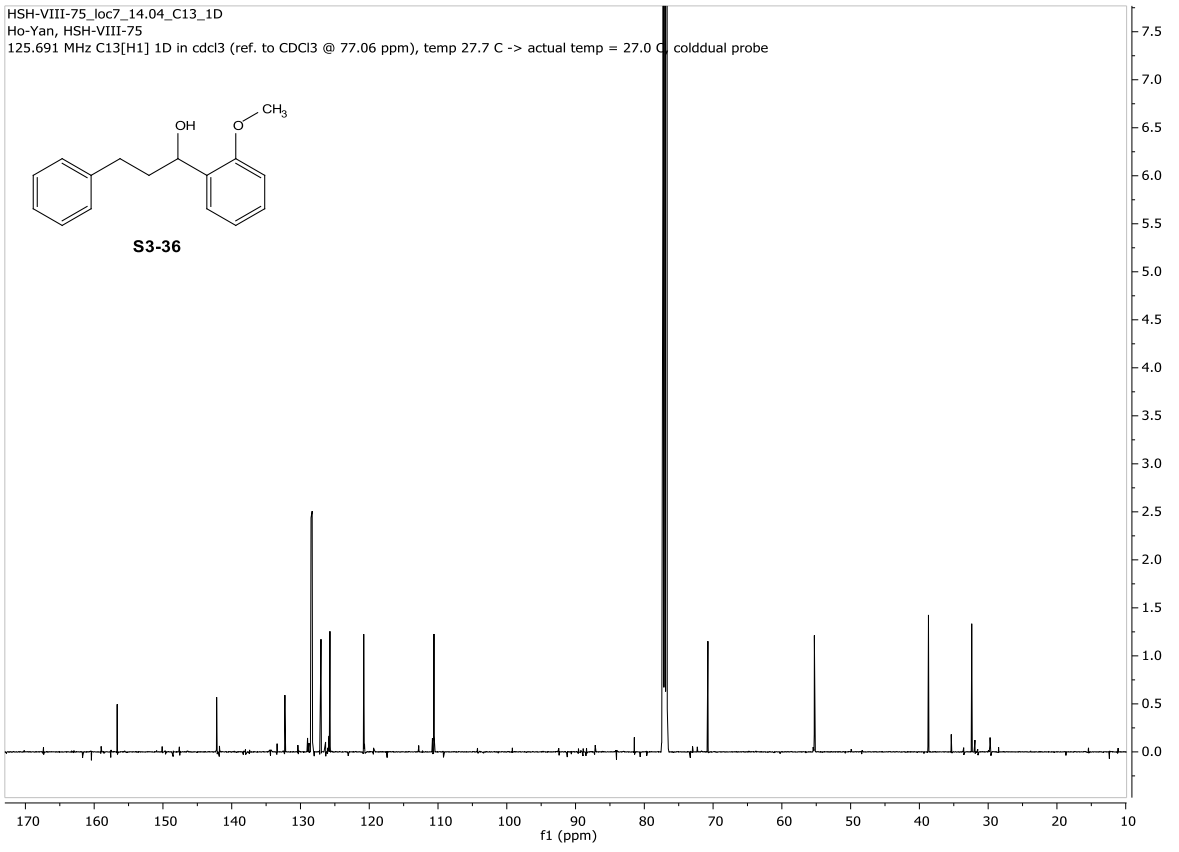

HSH-VIII-62_oxidized_loc11_13.15_H1_1D
Ho-Yan, HSH-VIII-62_oxidized
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
HO
CH3
O
S3-17
4.89
2.98
1.90
1.00
2.93
2.15
1.48
4.28
1.51
2.17
f1 (ppm)


HSH-VIII-62_oxidized_loc9_10.08_C13_1D
Ho-Yan, HSH-VIII-62_oxidized
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
HO
CH3
O
S3-17
f1 (ppm)


HSH-VIII-25_loc8_11.54_H1_1D
Ho-Yan, HSH-VIII-25
400.389 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
OH
CH3
O
CH3
O
O
CH3
S3-33
3.12
3.06
2.00
1.17
5.87
3.08
2.28
1.31
1.28
f1 (ppm)

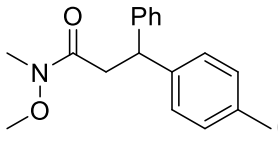

HSH-VIII-25_loc10_13.02_C13_1D
Ho-Yan, HSH-VIII-25
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
OH
CH3
O
CH3
O
O
CH3
S3-33
f1 (ppm)


HSH-VIII-75_loc7_14.02_H1_1D
Ho-Yan, HSH-VIII-75
499.806 MHz H1 PRESAT in cdcl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
OH
O
CH3
S3-36
5.52
3.68
1.07
1.02
1.00
2.74
1.10
1.13
0.97
2.36
f1 (ppm)

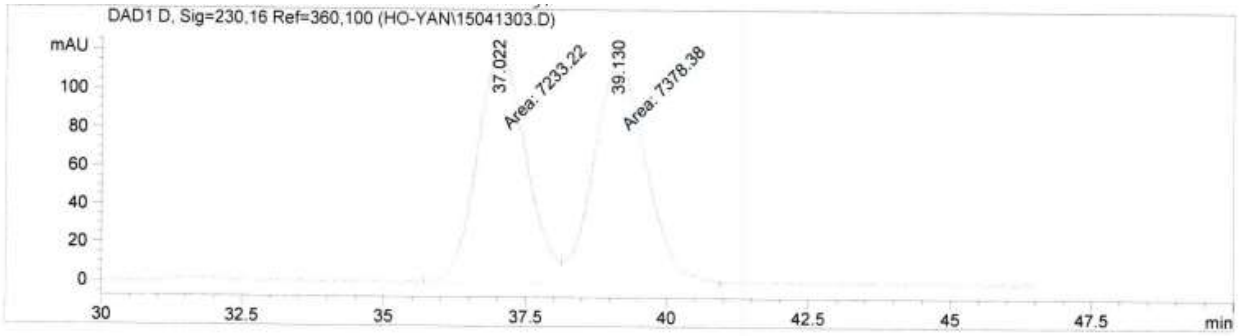

HSH-VIII-75_loc7_14.04_C13_1D
Ho-Yan, HSH-VIII-75
125.691 MHz C13[H1] 1D in cdcl3 (ref. to CDCl3 @ 77.06 ppm), temp 27.7 C -> actual temp = 27.0 C, colddual probe
OH
O
CH3
S3-36
f1 (ppm)

Appendix 2: Selected chromatograms for HPLC measurement

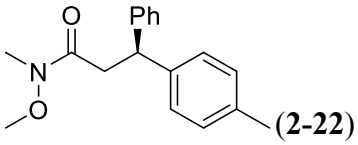
Some representative chromatograms for racemic mixtures have been included for reference.



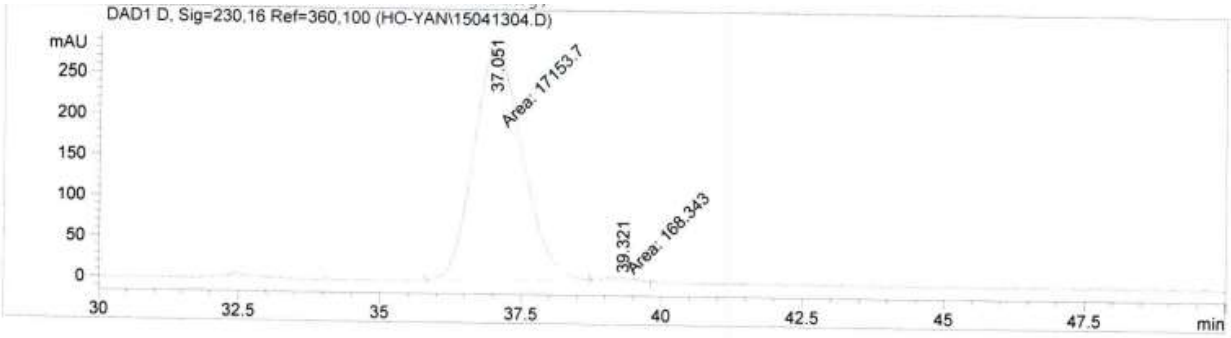
(**2-22**, racemic)




```
=====================================================================
                        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  37.022 MF    1.0040 7233.22363  120.06912  49.5033
   2  39.130 FM    1.0737 7378.37988  114.53345  50.4967

Totals :                 1.46116e4   234.60258
```



(2-22)

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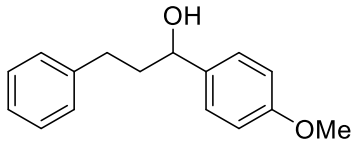
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

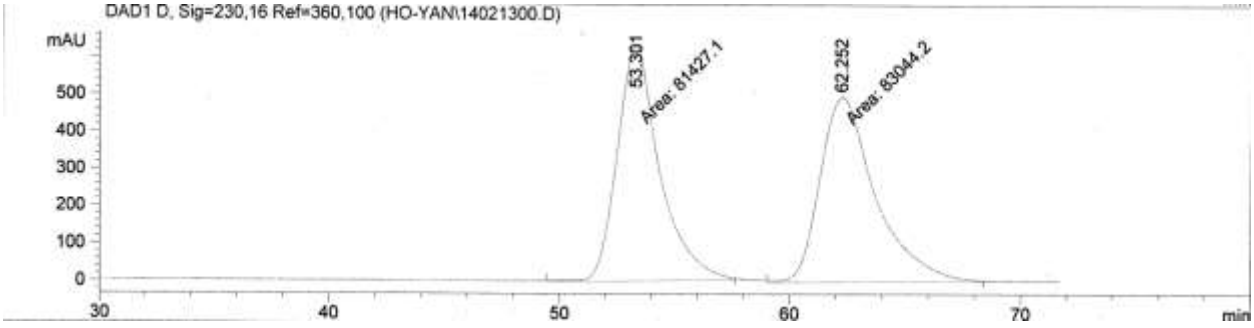

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  37.051 MM    1.0172 1.71537e4   281.04736  99.0282
   2  39.321 MM    0.6533  168.34280    4.29481   0.9718

Totals :                  1.73220e4   285.34218
```

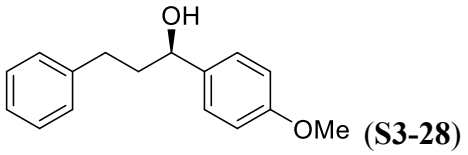


(**S3-28**, racemic)

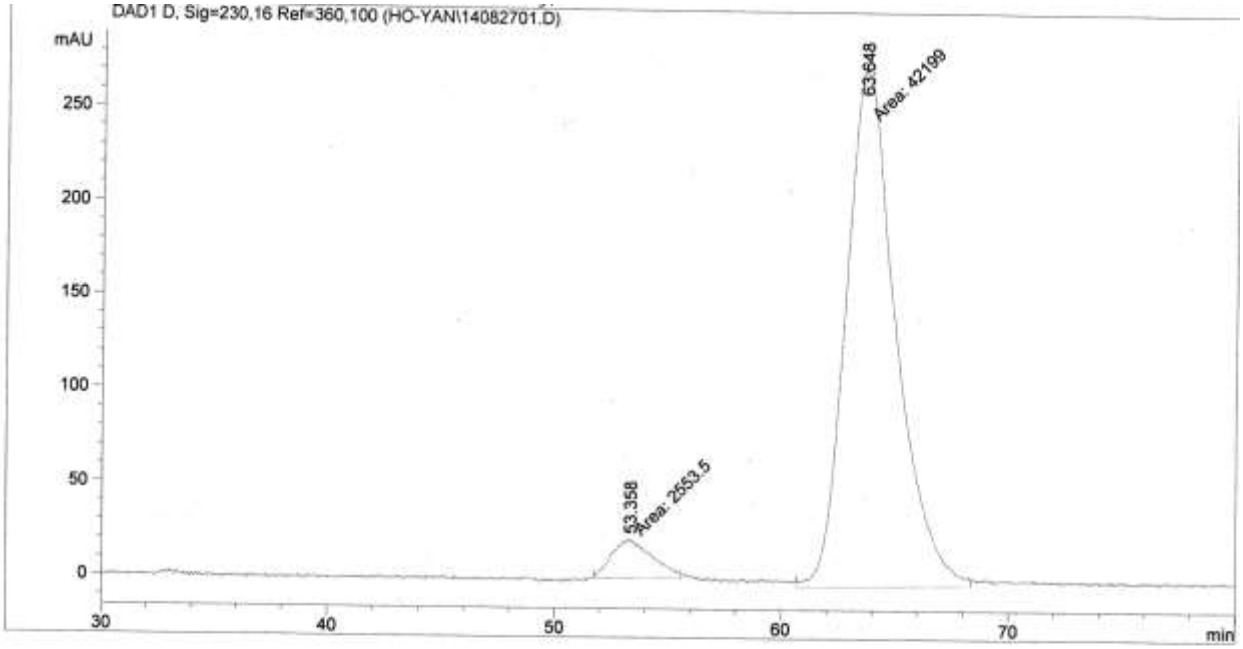


Signal 2: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.301	MM	2.1440	8.14271e4	632.97571	49.5084
2	62.252	MM	2.7744	8.30442e4	498.86737	50.4916
Totals :				1.64471e5	1131.84308	



(S3-28)

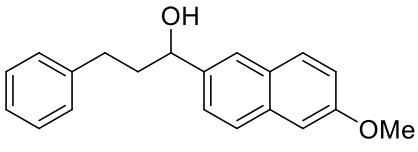


Area Percent Report

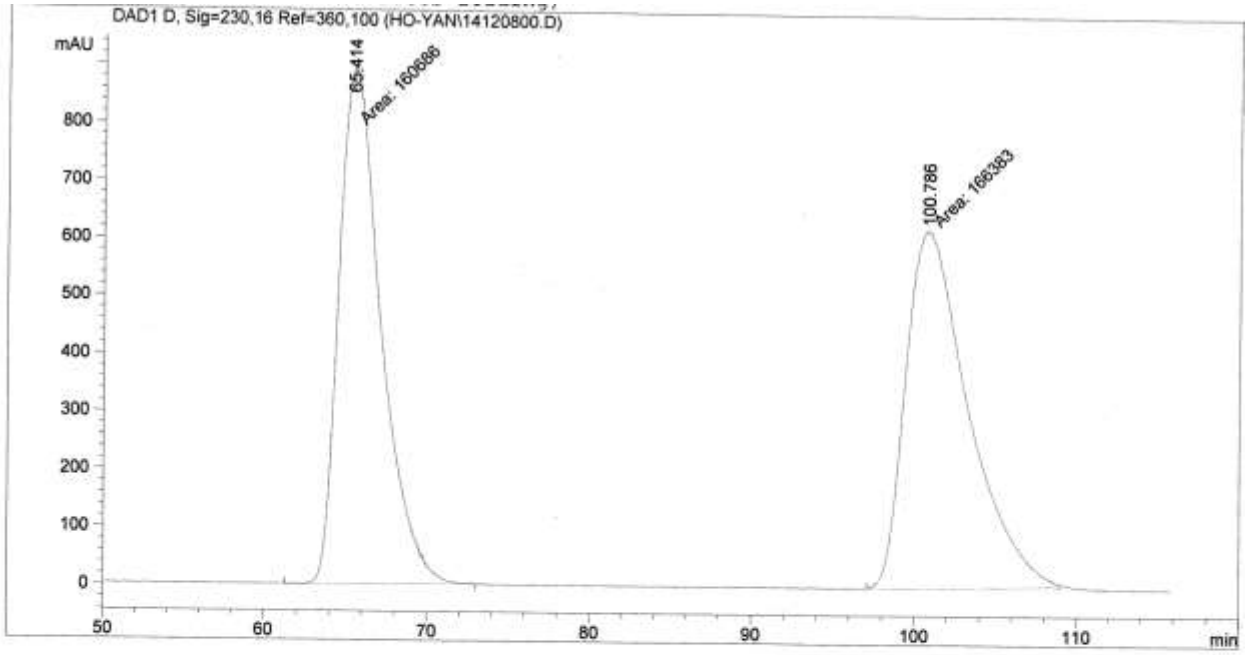
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.358	MM	2.0436	2553.49854	20.82554	5.7058
2	63.648	MM	2.5286	4.21990e4	278.14185	94.2942



(**S3-31**, racemic)

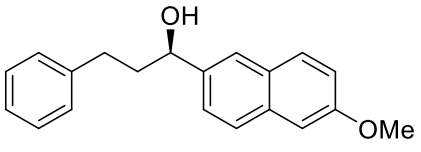


Area Percent Report

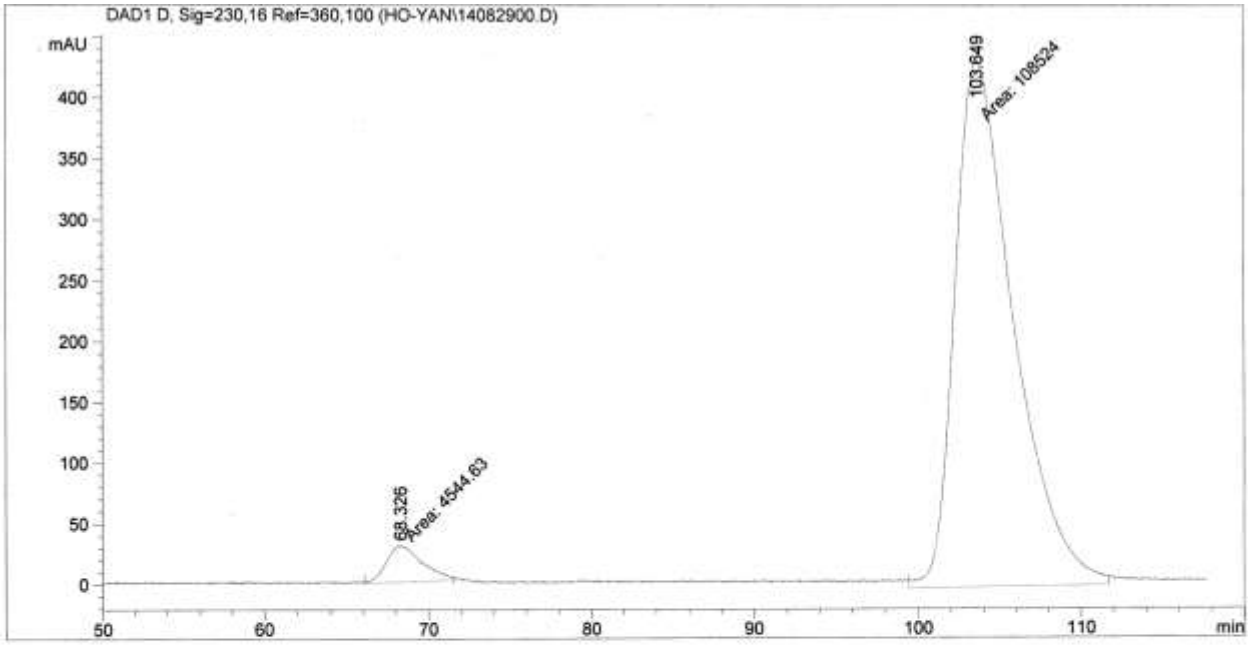
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.414	MM	2.9773	1.60686e5	899.49573	49.1291
2	100.786	MM	4.4593	1.66383e5	621.86261	50.8709
Totals :				3.27069e5	1521.35834	



(S3-31)

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=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  68.326 MM    2.4990 4544.63232   30.31001   4.0194
   2 103.649 MM    4.1673 1.08524e5   434.03299  95.9806

Totals :                  1.13069e5   464.34300
```
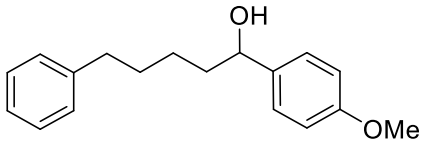
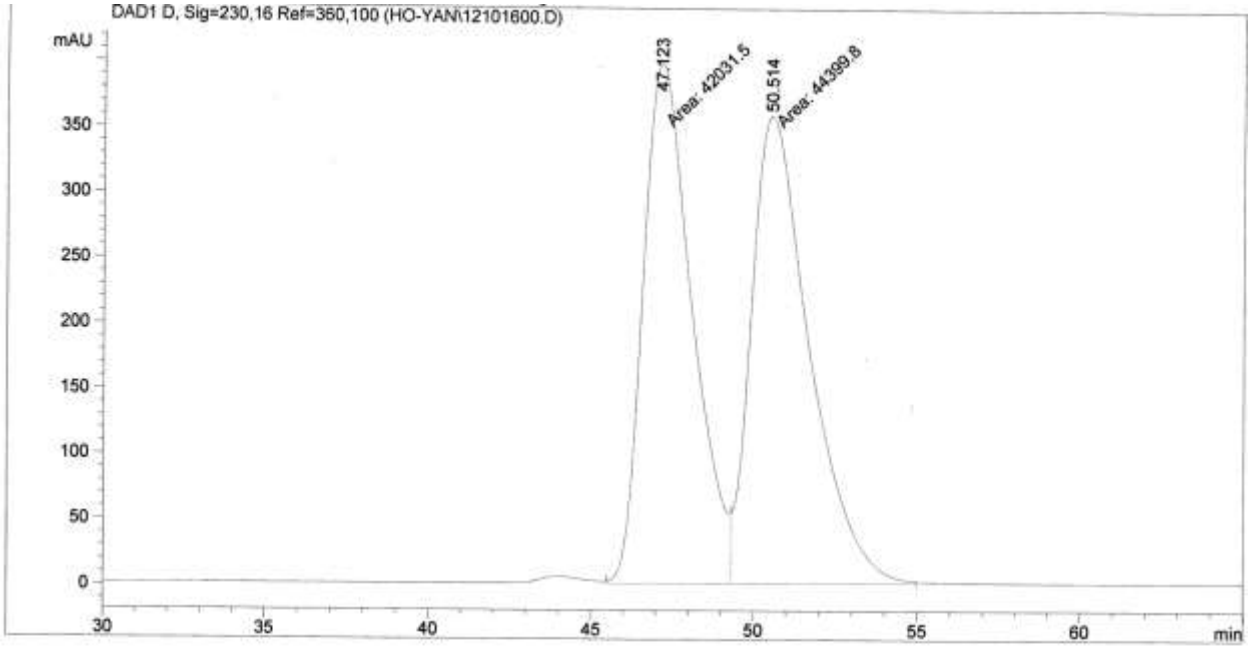
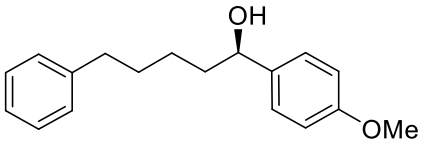



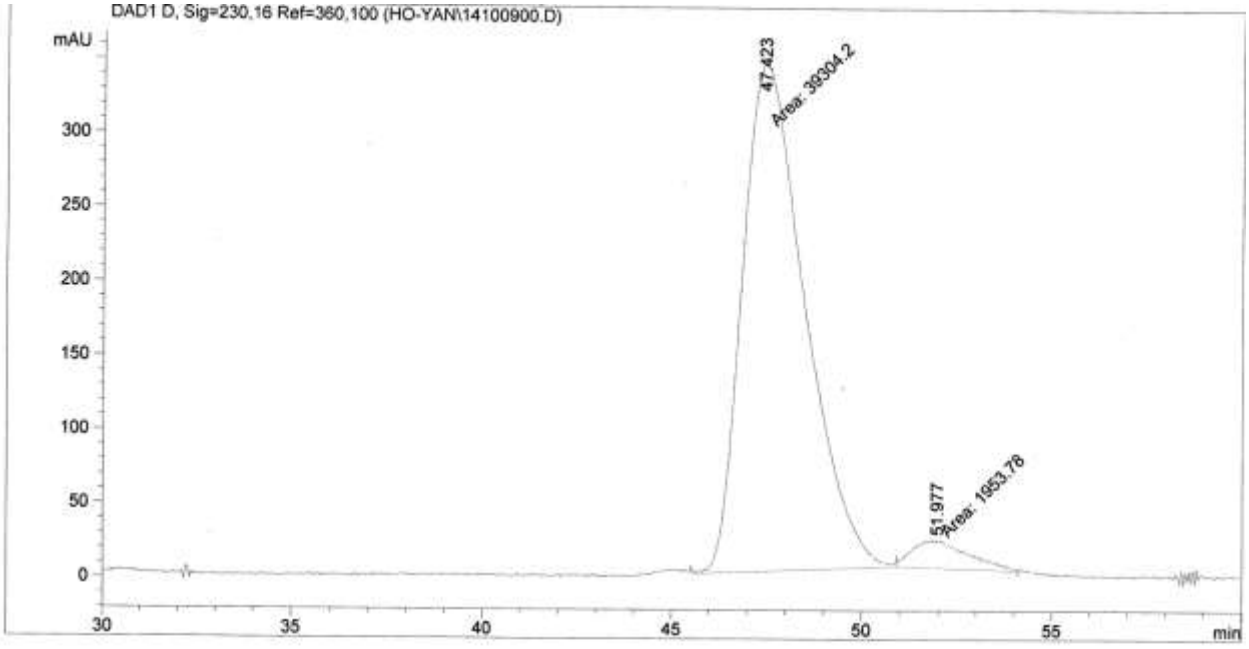
(**S3-17**, racemic)



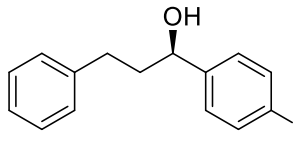

```
================================================================================
                          Area Percent Report
================================================================================

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  47.123 MF    1.7558 4.20315e4   398.97473  48.6299
   2  50.514 FM    2.0628 4.43998e4   358.73605  51.3701

Totals :                  8.64313e4   757.71078
```



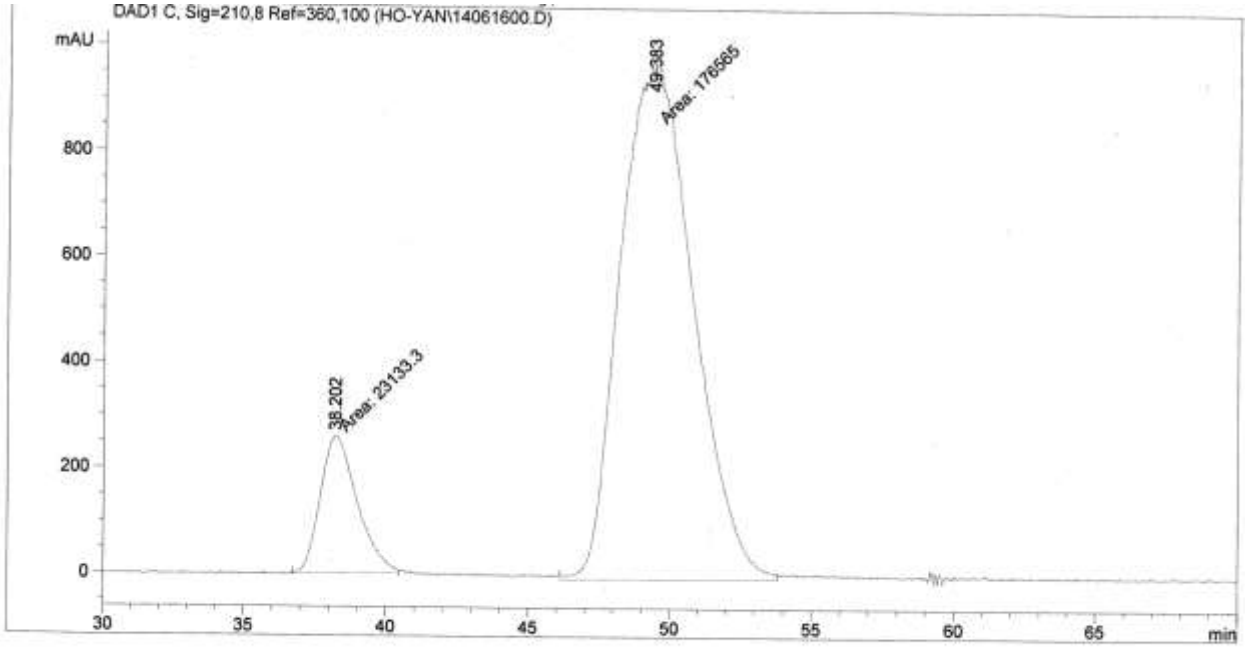
(S3-17)



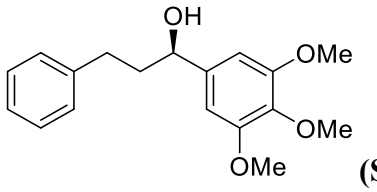

```
=====================================================================
                        Area Percent Report
=====================================================================

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  47.423 MM    1.9028 3.93042e4   344.27405  95.2645
   2  51.977 MM    1.7167 1953.78198   18.96850   4.7355

Totals :                  4.12580e4   363.24255
```



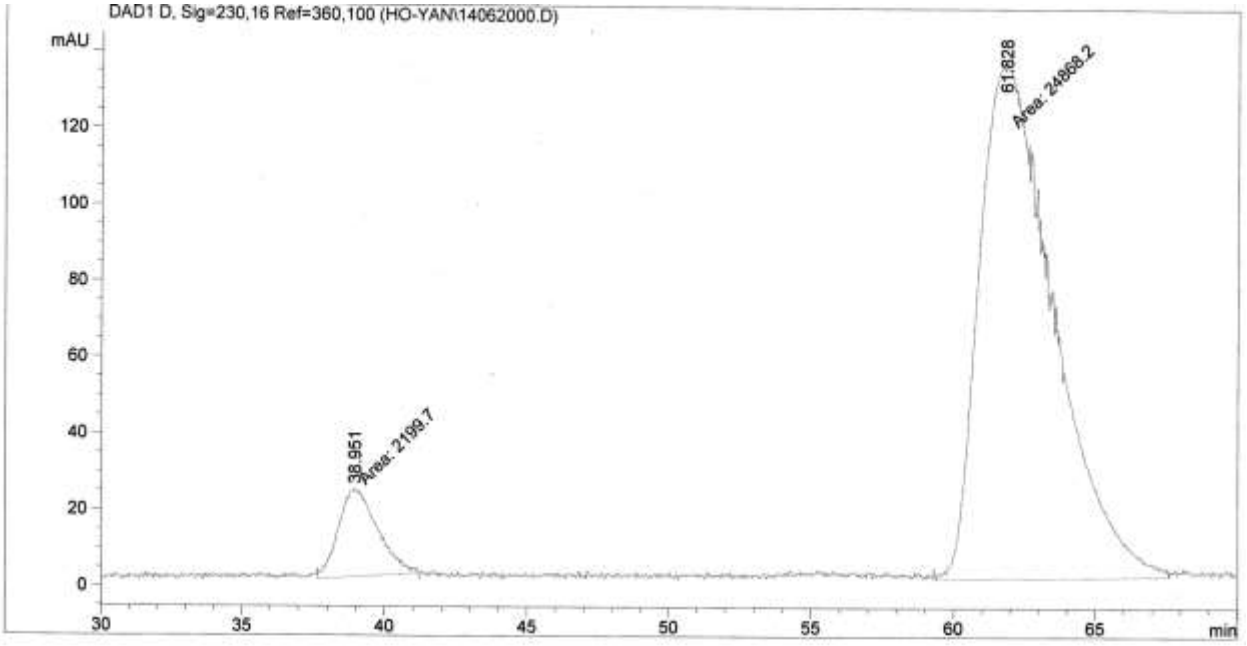
(S3-32)



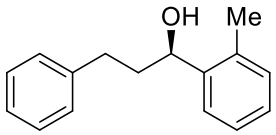

```
=====================================================================
                      Area Percent Report
=====================================================================

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  38.202 MM    1.4868 2.31333e4   259.32208  11.5841
   2  49.383 MM    3.0013 1.76565e5   980.49359  88.4159

Totals :                 1.99699e5  1239.81567
```



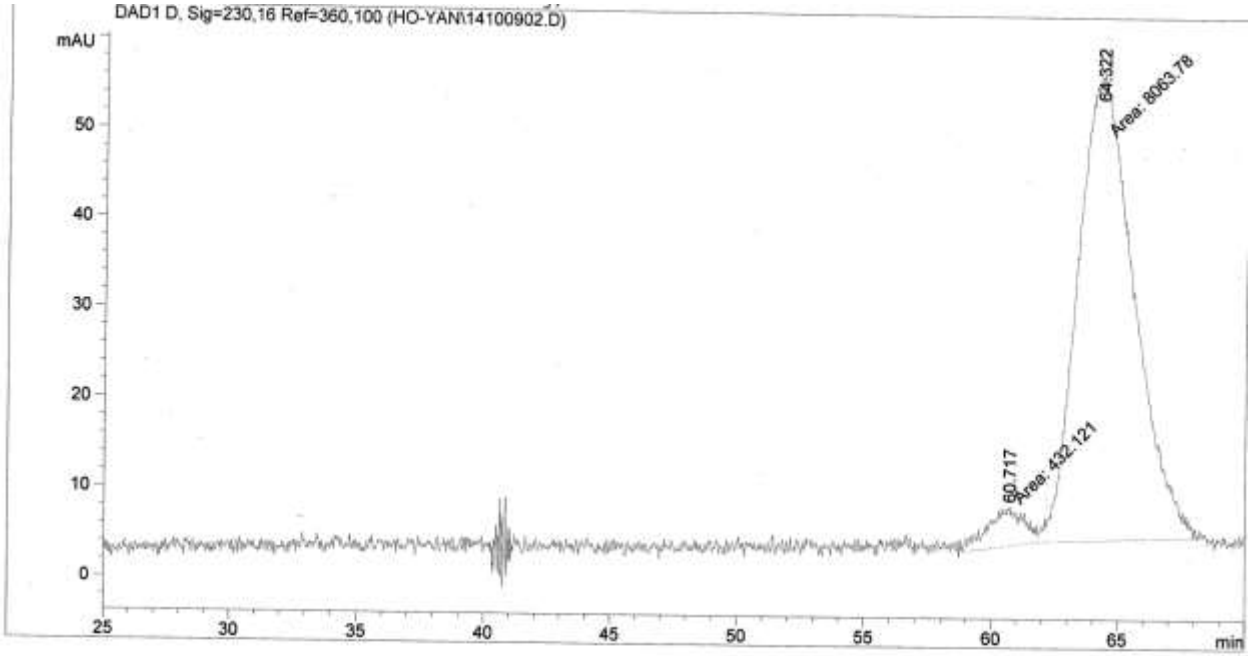
(S3-33)



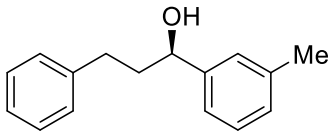

```
=====================================================================
                      Area Percent Report
=====================================================================

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  38.951 MM    1.5861 2199.69873   23.11381   8.1266
   2  61.828 MM    3.0583 2.48682e4   135.52234  91.8734

Totals :                  2.70679e4   158.63615
```



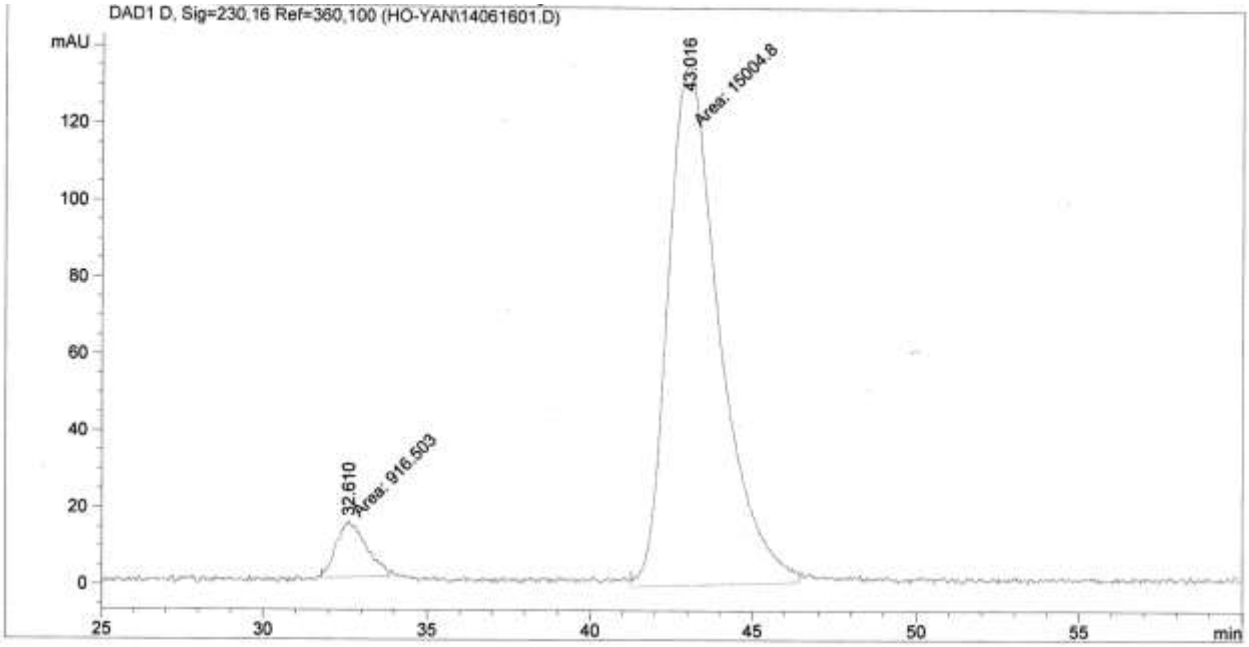
(S3-34)



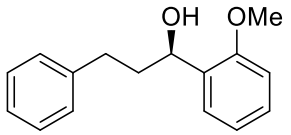

```
=====================================================================
                        Area Percent Report
=====================================================================

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  60.717 MM    1.6705  432.12051    4.31140   5.0862
   2  64.322 MM    2.5673 8063.77686   52.34939  94.9138

Totals :                  8495.89737   56.66079
```



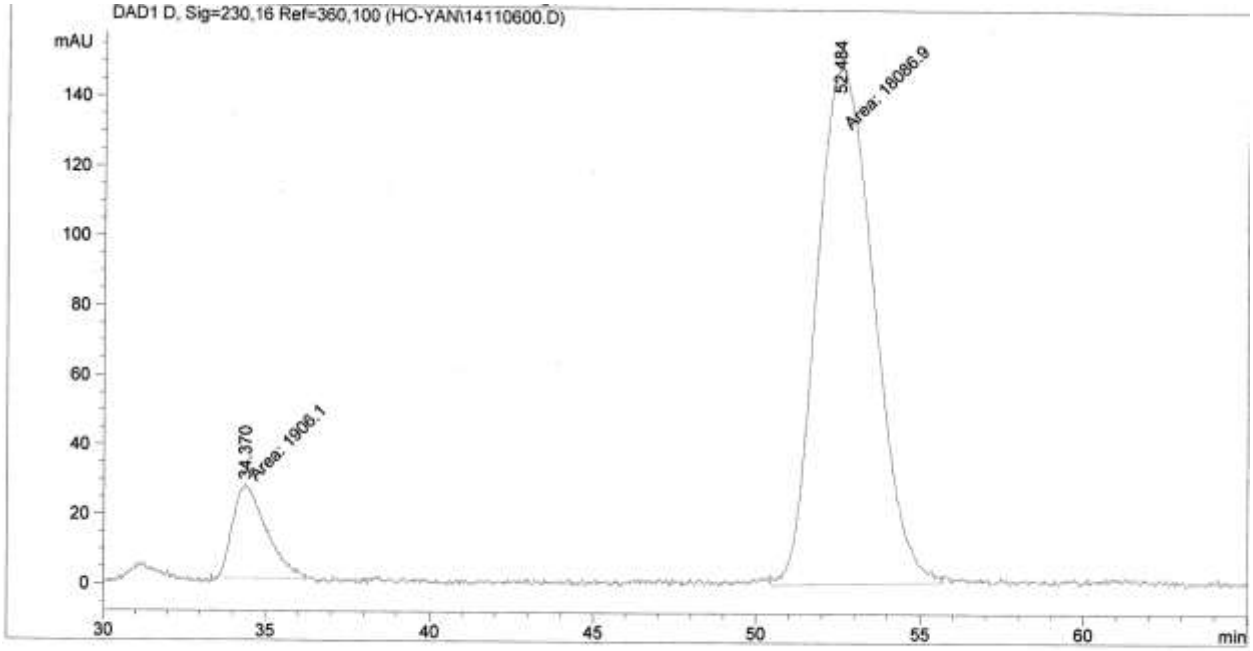
(S3-35)




```
=====================================================================
                    Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  32.610 MM    1.0433  916.50348   14.64130   5.7565
   2  43.016 MM    1.8338 1.50048e4   136.37473  94.2435

Totals :                  1.59213e4   151.01603
```



(S3-36)




```
================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  34.370 MM    1.1818 1906.09912   26.88225   9.5338
   2  52.484 MM    2.0156 1.80869e4   149.55467  90.4662

Totals :                  1.99930e4   176.43692
```

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