CHEMOSELECTIVE SUZUKI-MIYAURA CROSS-COUPLING OF DI AND TRI BORONIC ESTER SUBSTRATES

by

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A thesis submitted to the Department of Chemistry
In conformity with the requirements for
the degree of Master of Science

Queen's University
Kingston, Ontario, Canada
(March, 2015)

Abstract

In industry and academia, the palladium catalyzed Suzuki-Miyaura cross coupling reaction is one of the most often used methods for the synthesis of new C-C bonds. Recent advancements in this area have expanded the scope of this reaction to include nucleophiles with defined stereochemistry, resulting in enantioenriched, non-racemic products. Prior to this work, the Suzuki-Miyaura cross-coupling reaction was only applicable to processes which formed bonds between sp^2 and primary sp^3 hybridized carbons.

The first successful example of the cross-coupling of enantioenriched secondary boronic esters was published by our group in 2009. The key components in this reaction were the incorporation of silver oxide and excess triphenylphosphine. Not only did these conditions prove effective for the coupling of these substrates, they also showed selectivity for branched benzylic species in the presence of linear alkyl boronic esters.

In order to further probe this selectivity, *bis* and *tris* substrates were prepared that incorporated aryl, secondary benzylic and linear boronic esters. Interestingly, cross-coupling at the secondary benzylic and linear boronic ester requires specialized conditions for the reaction to proceed. This allows introduction of two different substituents in place of the boron groups, based solely off reaction conditions, eliminating the need of protecting groups. In further expansion of the scope, we have prepared the respective enantioenriched substrates and examined their stereoretention. Herein, we discuss the successful iterative Suzuki-Miyaura cross-coupling of both racemic and enantioenriched substrates that contain an aryl sp^2 and secondary benzylic sp^3 boronic (diboronic ester) or, an aryl sp^2, secondary benzylic sp^3, and alkyl linear boronic ester (tris boronic ester) with high retention of stereochemistry.

Acknowledgements

First and foremost, I would like to thank my supervisor Dr. Cathleen Crudden. Over the course of my masters degree, she has been a guiding light through rough times and not only has helped me become a better person, but also a better chemist. I could not thank her enough for all the opportunities to present in front of visiting professors, but also the valuable advice given when considering future endeavors. Being a part of the Crudden group has given me the opportunity to work with very talented individuals on a daily basis. I would like to thank Brian Bestvater, Eric Keske and Chris Ziebenhaus for the endless quotes, support and advice. Particularly, I would like to thank Chris for helping complete this project. For giving my family a roof over our heads in the final months, I would like to thank Patrick Eisenberger and Ayca Toprak.

Over the past two years I have had the pleasure of calling Kingston home, and have the opportunity to make some wonderful friends. I would like to take the opportunity to thank those who made life in Kingston enjoyable, with particular mention to Marie Barnes, Majd Abdelqader and Jeremy Durelle. To Suzie, Kevin and Steve, thank you for the support, love, late night phone calls, and making the trek out to Kingston to sleep on the floor and explore the area with me. I would like to thank my parents for their continual support regardless of what crazy idea I dreamt up next, for listening to me banter on about chemistry, and for always being there.

These past two years has been nothing short of an adventure, and I would like to finally acknowledge my wonderful husband Mitchell for all of his advice and support. My time in Kingston would not have been the same without you.

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List of Schemes

List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
acac	acetylacetone
Alk	alkyl
Ar	aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
B:L	branched to linear ratio
COD	1,5-cyclooctadiene
Cp	cyclopentyldienyl
Cp^*	pentamethylcyclopentadienyl
Cy	cyclohexyl
dan	1,8-diaminonaphthalene
dba	dibenzylideneacetone
DFT	density functional theory
DME	dimethoxyethane
DoM	directed ortho metallation
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,2-bis(diphenylphosphino)ferrocene
dtby	4,4’-di-*tert*-butyl-2-2’bipyridyl
EDG	electron donating group
e.e.	enantiomeric excess
e.r.	enantiomeric ratio
e.s.	enantioselectivity

ESI-MS	electrospray ionization mass spectroscopy
EWG	electron withdrawing group
FTIR	fourier transform infrared spectroscopy
GCMS	gas chromatography mass spectrometry
h	hours
HBCat	catecholborane
HBpin	pinacolborane
HRMS	high resolution mass spectroscopy
IR	infrared
L	ligand
MIDA	*N*-methyliminodiacetic acid
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
OA	oxidative addition
OMs	mesylate
ONIOM	our own n-layered integrated molecular orbital and molecular mechanics
OTf	triflate
OTs	tosylate
PCy_3	tricyclohexylphosphine
PTLC	preparatory thin layer chromatography
rbf	round bottom flask
rt	room temperature
RE	reductive elimination
R, X, Y, Z	proton or variable organic group

SFC	supercritical fluid chromatography
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SPS	solvent purification system
THF	tetrahydrofuran
TM	transmetalation
Tol	toluene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Chapter 1

The Suzuki-Miyaura Cross Coupling Reaction

1.1 Introduction

The synthesis of complex synthetic natural products and drugs utilizing affordable and available reagents under mild conditions is important in all industrial pharmaceutical processes. Control over regioselectivity, chemoselectivity, and/or stereoselectivity requires the use of various techniques. Unfortunately, this can muddle the pathway to target compounds, destroying both purity and yield of the desired product. At the start of the 1970's, the first metal catalyzed cross-coupling reactions emerged using Grignard reagents with nickel and iron catalysts.[1] However metal catalyzed cross-coupling reactions using sp^3 organometallics suffered from serious problems such as: decomposition of alkyl-organometallics due to proto-demetalation, air sensitivity of reagents, slow transmetalation requiring extra additives, and cost of using stoichiometric amounts of regents to achieve moderate conversion.[1] While advancements have been made, and successful cross-couplings of alkyl electrophiles and primary alkyl boronic acid derivatives are now common place, the development of a general protocol for cross-coupling of *secondary* boronic acid derivatives is still in its infancy.[2]

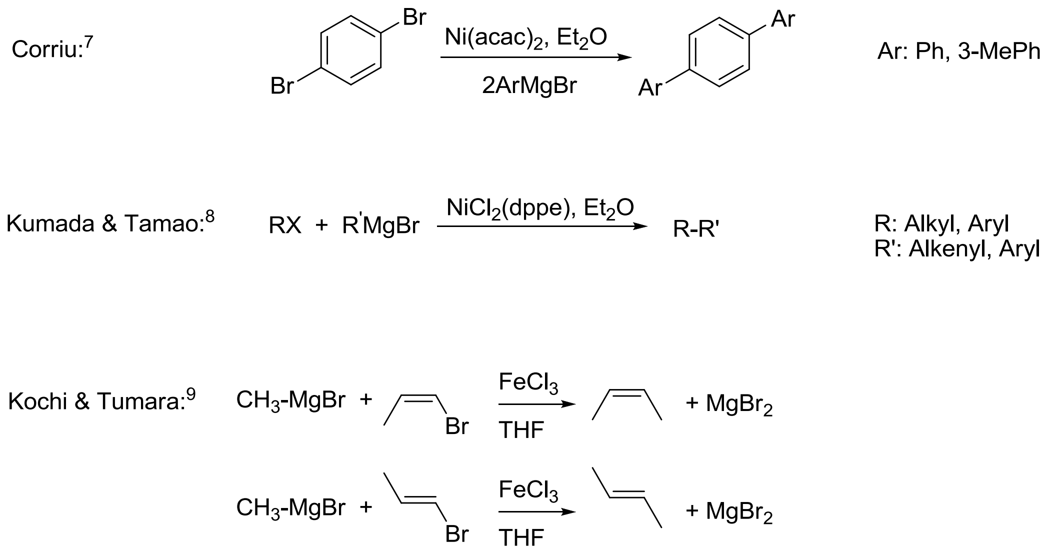
Since 1972, new methods to form carbon-carbon bonds have been explored extensively using a variety of transition metal coupling techniques.[3] First published in 1979, the Pd-catalyzed Suzuki-Miyaura cross-coupling has proven to be one of the most important synthetic methods to form new carbon-carbon bonds.[4] The simple yet robust nature of this reaction stands out among all others for its low environmental impact and mildness.[5] This reaction can even be performed in the presence of air, water, and with low loadings of Pd catalyst.[4b] For the majority of its lifetime, the reaction has been limited to the formation of sp^2-sp^2 bonds resulting in biaryls (Scheme 1-1), with some extensions to the coupling of primary sp^3 hybridized organoboron substrates.[6] Over time however, new emerging techniques would demonstrate just how versatile this reaction is.

Scheme 1-1: Generalized Suzuki-Miyaura Cross Coupling Reaction

1.2 Transition-Metal Catalysis: Utilizing Organometallic Reagents

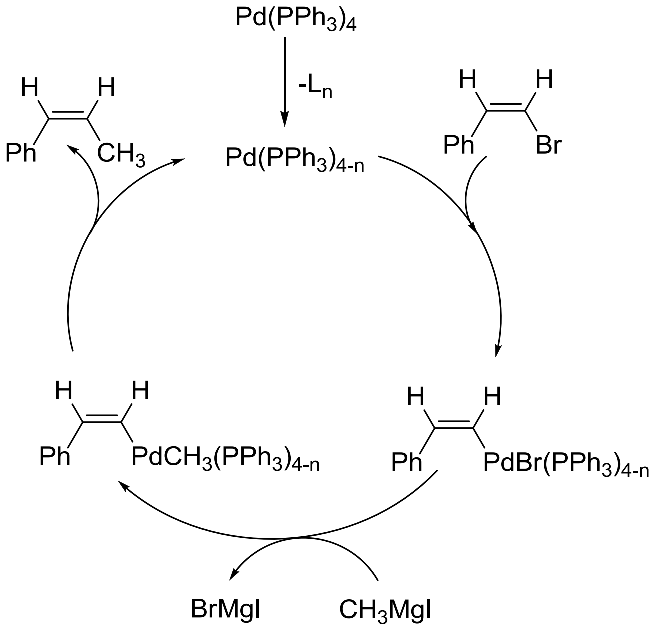
1.2.1 Cross-Coupling with Organomagnesium Reagents

Organomagnesium and lithium species have been extensively utilized for over a century as strong nucleophilic reagents.[7] In 1972, Corriu,[8] as well as Kumada and Tamao,[9] independently reported Ni catalyzed organomagnesium cross-coupling reactions of alkenyl or aryl halides. Kochi and Tamura[10] also reported similar reactions in the presence of an Fe (III) catalyst (Scheme 1-2). Although these reactions could be successfully used for the synthesis of biaryl and alkenyl species, several limitations were present. These included: undesired side reactions resulting from the use of highly reactive magnesium species,[11] limited functional group tolerance,[11] and the presence of homocoupled biaryls as major side products via metal halogen exchange.[11] Stereochemical scrambling of both starting materials and organometallic species eliminated the possible application of these methods in stereoretentive coupling.[11]



Scheme 1-2: Early Cross Coupling Reactions Using Organomagnesium and Lithium Reagents

In 1975, Murahashi reported the first palladium catalyzed reaction of σ-arylpalladium complexes with Grignard reagents to form vinyl palladium complexes for the selective synthesis of aryl olefins (Scheme 1-3).[12] In the event, *(Z)*-bromostyrene was treated with iodide and methyl magnesium iodide in benzene, giving *(Z)*-propenyl-benzene in a reported 3400% yield based on palladium employed.[12] Recovery of the desired olefinic product, with retention of stereochemistry, indicates that the addition of Pd(PPh$_3$)$_{4-n}$ to vinyl halides proceeds through retention of configuration. This establishes that no free radicals are involved in the proposed catalytic cycle.[12] The system was unreactive in the presence of methyllithium, and elimination of vinyl halide to form unwanted phenylacetylene was observed.[12] The less reactive Grignard reagents were well tolerated, allowing for the recycling of the palladium catalyst and a decrease in unfavorable byproducts.[12]



Scheme 1-3: Murahashi's Envisioned Mechanism Palladium Catalyzed Grignard Reaction of α-Bromostyrene[12]

1.2.2 Nickel and Palladium Catalyzed Cross Coupling Reactions

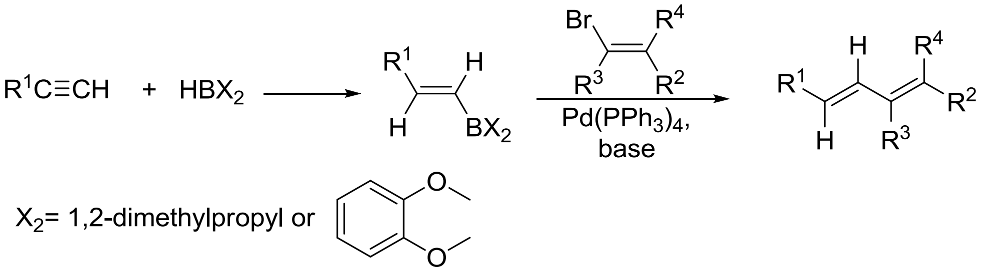
Following Murahashi's publication, Negishi demonstrated that milder organometallics, such as: organoaluminium,[13] zinc,[14] and zirconium species,[15] could be coupled utilizing nickel and palladium catalysts (Scheme 1-4). The efforts of this work provided a mild and synthetically viable route to unsymmetrical biaryls, diarylmethanes, and arylated alkenes in high chemoselectivity and, with minimal amounts of homocoupling (<5%).[14]

$$\mathrm{RZnX} + \mathrm{R^1X^1} \xrightarrow{\text{cat. Ni or Pd}} \mathrm{R\text{-}R^1}$$

R= Alkenyl, aryl, allyl, or alkyl
R^1=Alkenyl, aryl, allyl, alkynyl or propargyl
X= Br, Cl or I
X^1=Br, Cl, or I

Scheme 1-4: General Scheme for Cross Coupling under Negishi Conditions

Following Negishi's work in 1979, the Suzuki and Miyaura group went on to demonstrate the ability of *sp*^{2} boryl species to participate in cross-coupling reactions.[4a] This report detailed the palladium-catalyzed stereoselective cross-coupling of *(E)*-alkenyldisiamylboranes and *(E)*-1-alkenyl-1,3,2-benzodioxaboroles with 1-alkenyl or 1-alkynyl halides to produce the corresponding *(E)*-dienes or *(E)*-enynes in high-yield including high regio and stereospecificity. The key to their discovery was the use of exogenous bases such as NaOH, NaOMe, NaOEt, and NaOAc, which were thought to aid in transmetalation (Scheme 1-5).[4a]



Scheme 1-5: Suzuki-Miyaura Cross Coupling of 1-alkenylboranes with 1-alkenyl Halides

Following the publication of the Suzuki-Miyaura cross-coupling reaction,[4a] a wide variety of other organometallic species, such as organosilicon reagents, have also been proven to be competent reagents.[3] Building on the work of Mizoroki,[16] Heck[17] showed that similar palladium catalyzed conditions could also provide a viable synthetic handle for formation of substituted alkenes. However, this was achieved through a different mechanism, leading to the Mizoroki-Heck reaction. The importance and vast utility of the Suzuki-Miyaura cross-coupling reaction in both pharmaceutical and academic labs did not go unnoticed and in 2010 Suzuki, Negishi, and Heck went on to receive the Nobel Prize in Chemistry.[4c]

1.2.3 Organoboron Reagents and Hydroboration

Structurally, boronic acids are trivalent boron-containing organic compounds with 6 valence electrons and a vacant *p*-orbital on the *sp*^{2}-hybridized boron atom that is partially filled by overlap with adjacent oxygen atoms.[18] Boronic acids and their derivatives have unique features, such as mild Lewis acidity,[18] low toxicity,[18] and are often considerably more environmentally friendly when compared to other organometallic species such as organomercury reagents.[18] In addition, due to their relative stability, these reagents tend to be user friendly and easily handled.[19,18] As a consequence of these characteristics, and their wide availability (Figure 1-1), organoboron compounds have become tremendously important in organic synthesis.[18] Primary sources of boron can be derived through the acidification of borax ($Na_2B_4O_7{\cdot}10H_2O$) with carbon dioxide to form boric acid which can be further dehydrated with pinacol to form boronic esters with relative ease (Figure 1-1).[18]

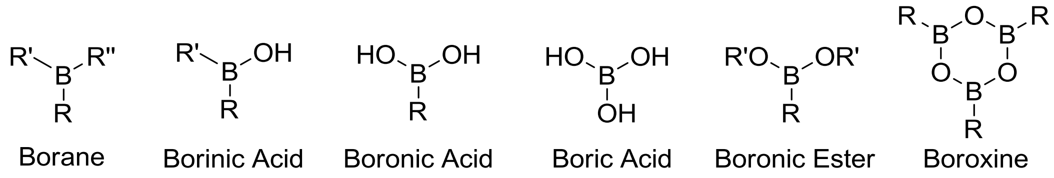
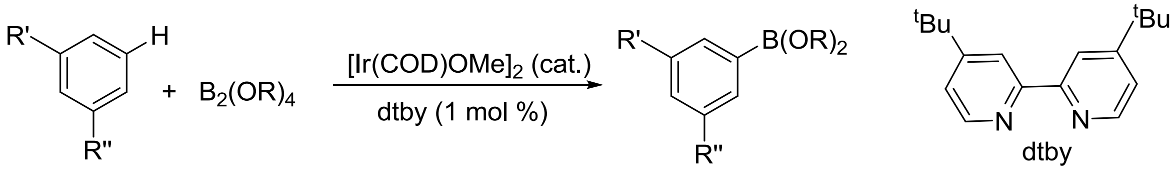


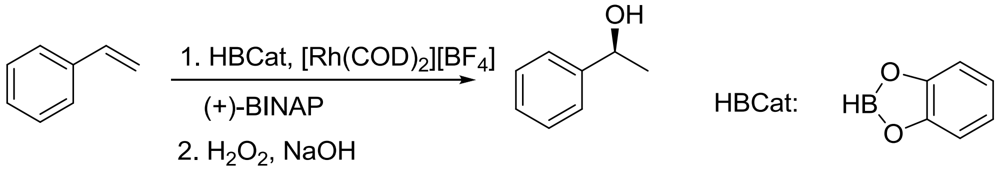
Figure 1-1: Common Oxygenated Organoboron Reagents

Traditionally, the synthesis of aromatic organoboron reagents has been performed by reacting an electrophilic boron compound with organometallic species, such as aryl Grignard reagents or aryllithium reagents.[20] More recently, the metal-catalyzed C-H borylation of arenes has become a powerful method in the synthesis of aryl boronate esters directly from C-H bonds without the need for prefunctionalized aryl halides (Scheme 1-6).[20]



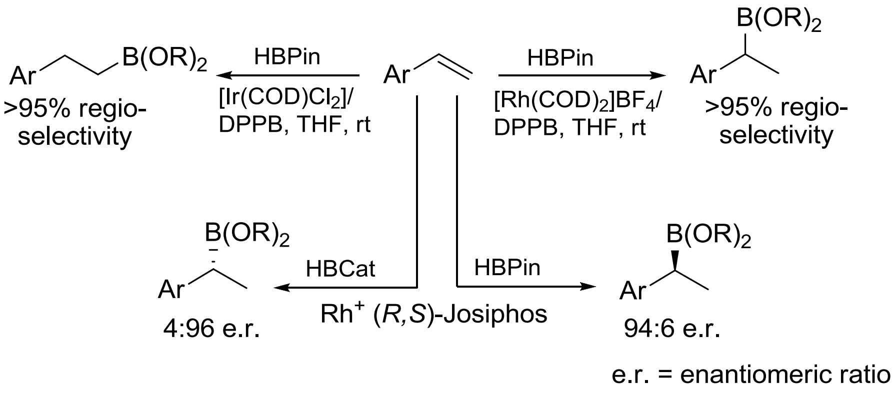
Scheme 1-6: Ir Catalyzed C-H Borylation for the Synthesis of Aryl Boronate Esters

In 1989, Hayashi and Ito demonstrated the synthesis of chiral, enantiomerically enriched benzylic boranes by reacting styrene derivatives with catechol borane (HBCat) using a cationic rhodium catalyst (Scheme 1-7).[21] The authors reported optical activity of up to 96% enantiomeric excess (e.e) and regioselective formation of benzyl boranes in the hydroboration of *(E)*-1-phenylpropene and 2-phenylpropene in a 99:1 and 70:30 ratio respectively. The resulting alkyl BCat containing species are typically unstable and can be difficult to isolate by traditional purification methods. For this reason, they are typically oxidized to their corresponding alcohols.[22]



Scheme 1-7: Asymmetric Hydroboration and Oxidation of the Boronic Ester Products

In 2004, the Crudden group went on to demonstrate effective regio- and enantiocontrol for the hydroboration of vinyl arenes at room temperature with pinacol borane (HBPin) that gave 95% selectivity for either branched or linear products, depending on choice of catalyst (Rh or Ir respectively) (Scheme 1-8).[23] The use of HBPin in place of HBCat meant a dramatically enhanced stability over catechol derivatives, specifically to column chromatography. The added ease of purification led to new cross-coupling conditions established by the group in 2009.[23]



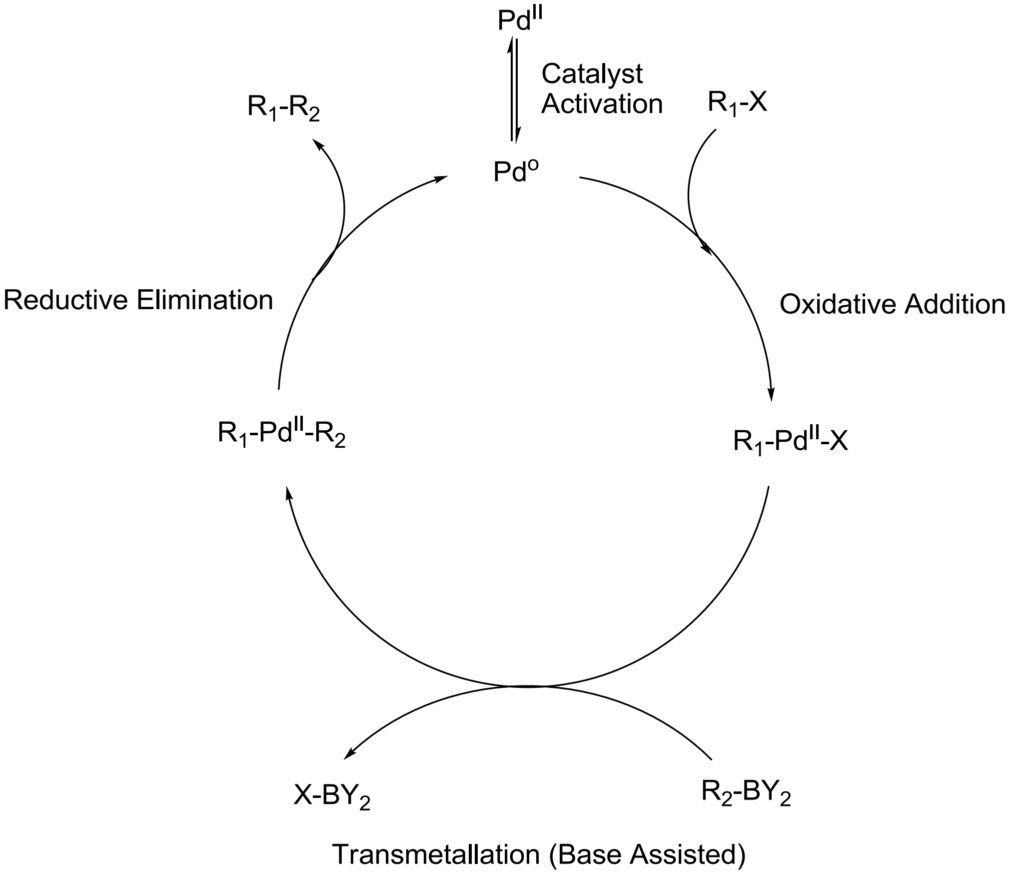
Scheme 1-8: Enantio and Regiocontrol of the Hydroboration of Styrenes from the Crudden Group[23]

Subsequently, this provided a simple and efficient method to enantiomerically enriched boronic esters. However, it was evident that there was no existing method to couple such substrates.

1.3 Mechanistic Details of the Suzuki-Miyaura Cross Coupling Reaction

1.3.1 The General Catalytic Cycle

The generally accepted catalytic cycle for the Suzuki-Miyaura reaction (Scheme 1-9) requires either the use of a Pd^0 active catalyst or its generation from a Pd^{II} pre-catalyst.[24] The electron rich Pd^0 undergoes oxidative addition (OA) to an aryl halide or pseudohalide to give a Pd^{II} intermediate, followed by transmetalation (TM) of an arylboron species and finally, reductive elimination (RE) to give a new carbon-carbon bond and the regeneration of the Pd^0 catalyst.[24] A great deal of mechanistic detail about this reaction has been reported.[25] Some of the intricate events, such as the role of the base and generation of active Pd catalyst, are still under investigation. Thus specific details about the catalytic cycle, as well as its major steps, will be covered in more detail in the following subchapters where appropriate.



Scheme 1-9: Suzuki-Miyaura Catalytic Cycle

1.3.2 The Generation of an Active Pd Catalyst

Commonly, Pd^0 or divalent Pd^{II} pre-catalysts are used in the Suzuki-Miyaura cross-coupling reaction, Pd^{II} complexes having the added benefit of being oxidatively stable. The *in-*

situ generated Pd^0 complex is believed to have either 14 or 12 valence electrons since an 18 electron species would be coordinatively saturated and unable to proceed through the catalytic cycle.[26] The *in situ* reduction of Pd^{II} to Pd^0 was first examined in 1993 by Alper in a Pd-catalyzed carbonylation of haloarenes.[27] To explore the mechanism, $[L^*Cl_2Pd]$ was used where L^* represents an enantioenriched phosphine.[27] When the *(S)*-benzylmethylphenyl phosphorus ligated Pd complex was exposed to OH^-, no change in stereochemistry was observed and *(S)*-benzylmethylphenyl phosphorus oxide was successfully isolated in >99.1% optical purity. Therefore following the mechanistic pathway, a chloro ligand is exchanged with OH^- in the $L_nCl_2Pd\text{-}PPh_3$ species, followed by reductive elimination to regenerate the catalytically active Pd^0 species.[27] Their work was further validated in 1995 when Amator and Jutand used kinetic data to show the reductive elimination of an acetate and phosphine ligands in $Pd(OAc)_2(PPh_3)_2$ to give to corresponding Pd^0 complex.[26]

1.3.3 Oxidative Addition

Pd^0 enters the catalytic cycle through an oxidative addition of an aryl, alkenyl or even alkyl halide to generate a Pd^{II} complex. The observed reactivity typically follows a trend of I > OTf > Br >> Cl as Pd insertion of an organohalide is favored when the carbon halide bond is weak.[4b] Since this step in the catalytic cycle is often the rate limiting step, there has been considerable effort in investigating this step in hopes to understand and optimize it.[25a] For example, the Buchwald group has developed catalysts to favor the oxidative addition process by providing an intramolecular π-system which both stabilizes the catalyst and ensures a vacant coordination site (Figure 1-2).[28]

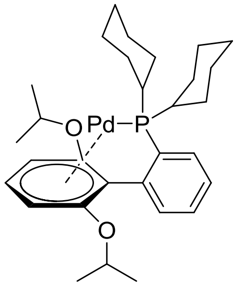
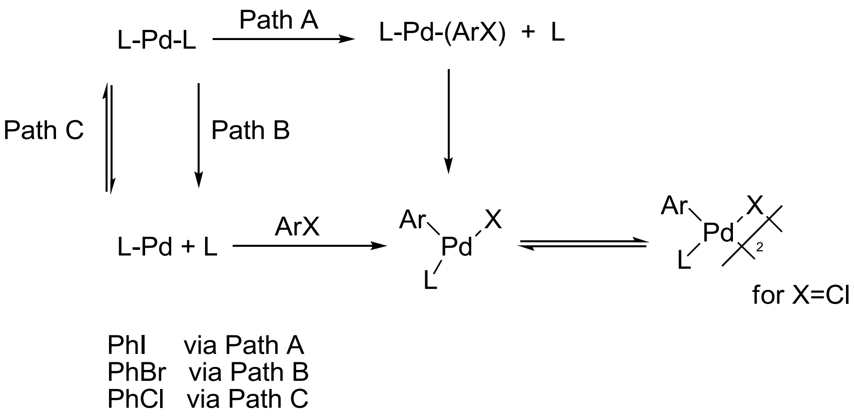


Figure 1-2: Buchwald's RuPhos Mono-ligated to Pd^{0} [28]

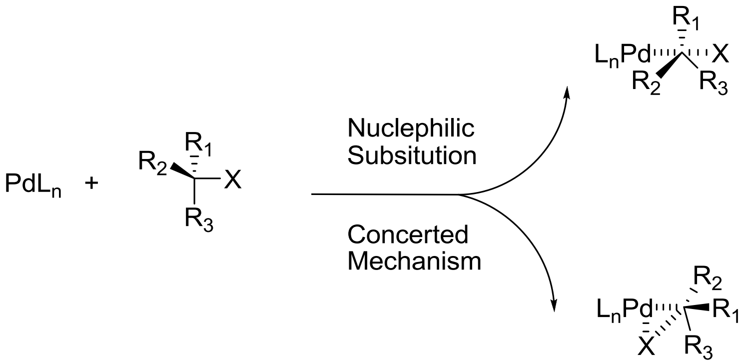
While the scientific community agrees that the oxidative addition proceeds through either a monoligated (PdL) or bisligated (PdL_2) active species, the mechanism of the actual step remains complicated.[29] In 1990, Amatore et al. reported that the oxidative addition of PhI through $Pd(PPh_3)_4$ proceeded through $Pd(PPh_3)_2$.[30] Barrios-Landeros and Hartwig in 2004 further performed a full mechanistic comparison of aryl iodides, bromides, and chlorides with [Pd(Q-phos-tol)$_2$].[31] Interestingly, each aryl halide proceeded through oxidative addition following a different mechanism (Scheme 1-10). Aromatic iodides proceeded through a mechanism with associative displacement of a phosphine ligand; thus forming a bisphosphine complex due to the soft nature of the halide.[29, 32] For aryl chlorides, the rate limiting oxidative addition is due to the reversible phosphine dissociation[29, 32] thus forming a mono-phosphine complex since a more reactive intermediate was needed to cleave the weak carbon chloride bond.[29, 32] Aryl bromides were uniquely different in mechanistic pathways for Pd catalysts with L= 1-AdP(^{t}Bu)$_2$ and L = CyP(^{t}Bu)$_2$. Two competitive pathways between B and C were proposed due to the rate determining step where bisphosphine complexes gave rise to monophosphine intermediates.[33]



Scheme 1-10: Oxidative Addition Mechanism Pathways for ArI, ArBr and ArCl

In 2010, Harvey et al. described the steric and electronic effect of phosphine ligands PMe_3, $P(CF_3)_3$, PPh_3 and $P(^tBu)_3$ on oxidative addition.[34] The rate of the oxidative addition step was determined to depend upon the electronic nature of the ligand, which confirms that electron rich donor ligands make the process more facile by decreasing activation barriers.[34]

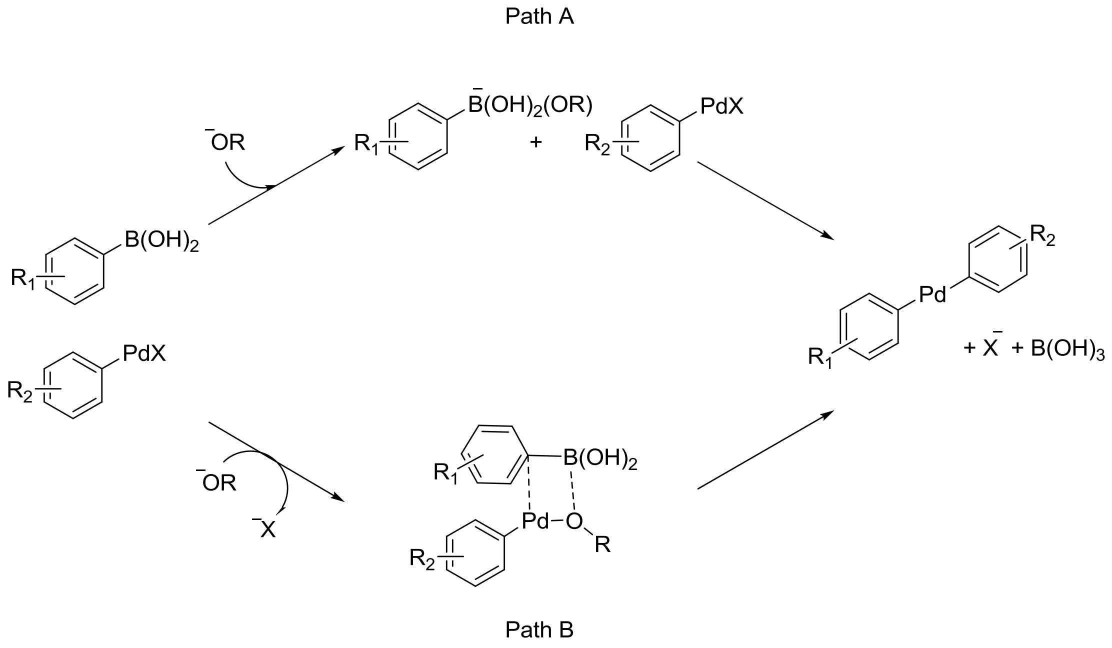
While concerted processes have only been discussed, “nucleophilic attack” on the carbon electrophile by Pd^0 species has also been proposed by Stille (Scheme 1-11).[35] An S_N2 process similar to that commonly found in organic reaction mechanisms was postulated.[29, 36]

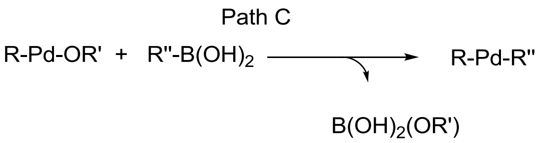


Scheme 1-11: Nucleophilic and Concerted Mechanism for Oxidative Addition

1.3.4. Transmetalation

While the mechanism for oxidative addition has become moderately well understood in transition metal catalyzed reactions, the transmetalation step still remains under investigation.[37] While the Suzuki-Miyaura cross-coupling reaction requires the addition of base, the precise reason for this is still under debate.[37] In 2002, Miyaura suggested three probable processes for transmetalation (Scheme 1-12) but was unsure which process was dominant.[38] When coupling organoboron compounds in an alkaline solution each pathway was highly dependent on the particular reagent and their functionality.[38] The treatment of *trans*-Pd(Ph)(Br)(PPh_3)$_2$ with KOAc formed *trans*-Pd(Ph)(OAc)(PPh_3)$_2$ which was further coupled at room temperature with bis(pinacolato)diboron to yield phenylboronic ester,[38] leading to their assumption of Path B for the cross-coupling reaction.[38] Path C proceeded under neutral conditions with allyl acetates since oxidative addition yielded π-allylpalladium acetate,[38] whereas Path A was dominant in the reaction of 9-alkyl-9-BBN with KOH and iodobenzene.[38-39]



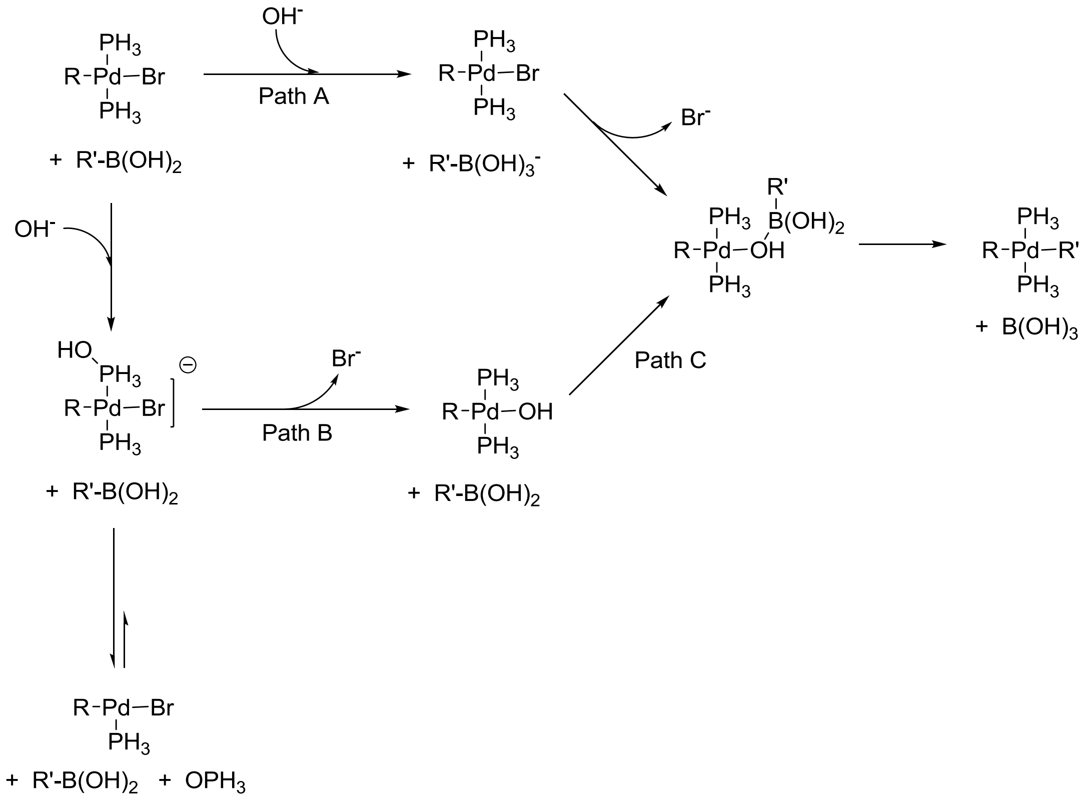


Scheme 1-12: Potential Roles of Base in Transmetalation[38]

In 2005, Maseras and coworkers analyzed the process by theoretical evaluations, such as density functional theory (DFT) and "our own n-layered integrated molecular orbital and molecular mechanics" (ONIOM), and summarized most available data on transmetalation.[37] Their analysis showed an elevated energy barrier without the addition of base, which confirmed the requirement of base during this step.[37] Similar to Miyaura, Masers postulated two plausible mechanistic pathways (A and B) (Scheme 1-13). The initiation of Path A begins with boronate species formation via reaction of the base and boronic acid followed by transmetalation of the aryl group to palladium center.[37] Alternatively, in Path B, the halide is substituted via base in the coordination sphere of Pd. Unfortunately generation of phosphine oxides in large quantities lead to destruction of the catalyst leaving Path B as an unfavorable possibility.[37]

In 2011, both Schmidt as well as Carrow and Hartwig reported kinetic data that supported a preference for path B.[40] Schmidt showed transmetalation occurring through a neutral phenyl boronic acid in the presence of an anionic base and palladium complex.[40a] Carrow and Hartwig showed that rate of transmetalation between the *trans*-ArPd(OH)L_2 and aryl boronic acid was several orders of magnitude higher than that of the analogous trihydroxyborate species.[40b]

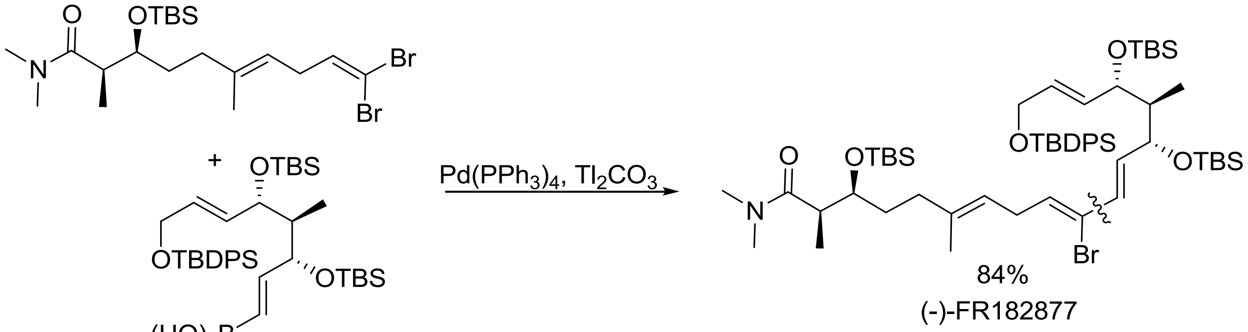
Following this, through kinetic studies, Amatore et al. proposed three important roles of the base in the catalytic cycle.[41] Reductive elimination from the *trans*-$Ar^1PdAr(PPh_3)_2$ complex was accelerated when *trans*-$ArPd(OH)(PPh_3)_2$ reacted with aryl boronic acid.[41] Consequently, generation of the aryl borate anion ($Ar^1B(OH)_3^-$) is proposed to be detrimental as it is believed to be unreactive with $ArPdX(PPh_3)_2$, therefore decreasing the concentration of the active Pd species.[41] Amatore et al. further examined the effect of countercations of anionic bases in transmetalation and observed a decrease in reaction rate.[42]



Scheme 1-13: Transmetalation Pathways by Maseras and co-workers[37]

This followed a decrease in the reactivity order: *n*Bu_4NOH> KOH> CsOH> NaOH due to complexation of hydroxo ligands in the reactive $ArPd(OH)(PPh_3)_2$ by the metal cation.[42] Acetate bases were determined to not be efficient, even though they form the reactive *trans*-$ArPd(OAc)(PPh_3)_2$ complex as it does not transmetalate with $Ar^1B(OH)_2$ while carbonates (from Cs_2CO_3 in water) lead to slower reactions than *n*Bu_4NOH at similar concentrations due to the slow release of hydroxyl anions.[42] If oxidative addition is fast in the Suzuki-Miyaura cross-coupling reaction, the rate of transmetalation needs to be increased, requiring the most efficient base: OH^- > CO_3^{2-} >> AcO^- to optimize the $[OH^-]/[Ar^1B(OH)_2]$ ratio and the best counter ions of the anionic base: Tl^+ or Ag^+ > $n\mathrm{Bu}_4N^+$ > K^+ > Cs^+ > Na^+.[42]

When applied to cross-coupling reactions, these counter ions can have a dramatic impact. In the synthesis of (-)-FR182877 (Scheme 1-14), it was reported that use of a Tl^+ counterion resulted in enormous time economy and the reaction could be completed almost instantaneously even at 0°C with minimal byproduct formation.[43,44]



Scheme 1-14: Synthesis of (-)-FR182877 using Tl_2CO_3[43]

1.3.5 Reductive Elimination

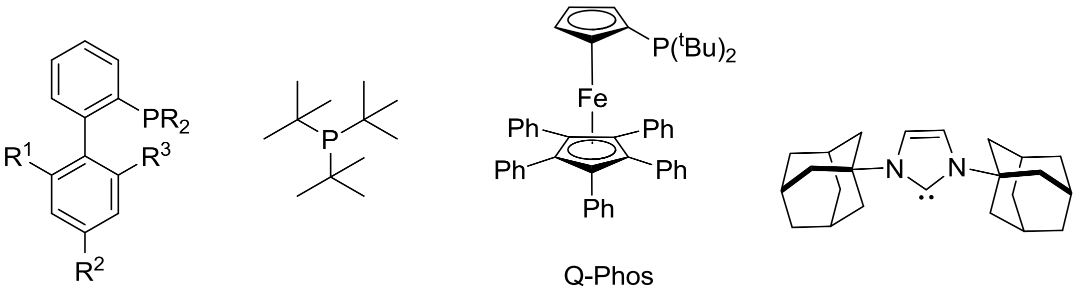
Completing the catalytic cycle and regenerating the active Pd^0 complex, reductive elimination forms the new carbon-carbon bond in the product. Similar to oxidative addition, the reductive elimination process is thought to proceed most easily from a monoligated [PdL] complex as proposed by Stille, who also noted the requirement that organic groups must be *cis*.[45] Bidentate ligands with large bite angles, such as Xantphos and DPPF, proceed through a bisligated Pd complex which increases the rate of reductive elimination by decreasing the distance between organic groups.[46]

Electronic factors have a significant effect on the rate of reductive elimination, such that the reaction is favored by electron deficient metal centers. Thus systems that utilize π acidic ligands, such as dibenzylideneacetone (dba), facilitate reductive elimination by pulling electron density from the Pd^{2+} metal center into the π- system. [47]

1.3.6 Ligand Development

Introduced in 1998, monodentate, bulky electron rich phosphines have been used as supporting ligands in palladium catalyzed cross-coupling reactions.[28] The relationship between the ratio of ligands and palladium can play a large role in the performance of the catalyst.[28] Monodentate ligands have a variety of attractive features such as: commercial availability, straightforward one pot synthesis, and air and thermal stability.[28] Recently, N-heterocyclic carbenes (NHCs) have also emerged as new and exciting alternatives for phosphine ligands in a variety of cross-coupling reactions.[48]

Dialkylbiarylphosphines and ferrocenyl dialkylphosphines developed by Buchwald, Fu, and Hartwig (Figure 1-3) have tunable steric and electronic properties, making them valuable commodities in organic synthetic chemistry.[28] Such bulky electron rich ligands provide access to highly ligated activated palladium complexes that are able to cross-couple even non-active arylchlorides at room temperature. These coordinatively unsaturated 14 or 12 electron species are thought to be extremely reactive, reacting immediately with ligands or aryl halides and proceeding through to the next step of the catalytic cycle.[49]



Q-Phos

Buchwald Fu Hartwig Herrmann

Figure 1-3: Examples of Electron Rich Phosphine Ligands and a Pd^0 NHC[28]

Phosphine ligands contribute to catalytic activity through a combination of electronic and steric effects.[28] Several key species of the catalytic cycle are expected to be a monoligated, therefore L_1Pd intermediates stabilized by bulky electron rich ligands will be an asset to the reaction.[28]

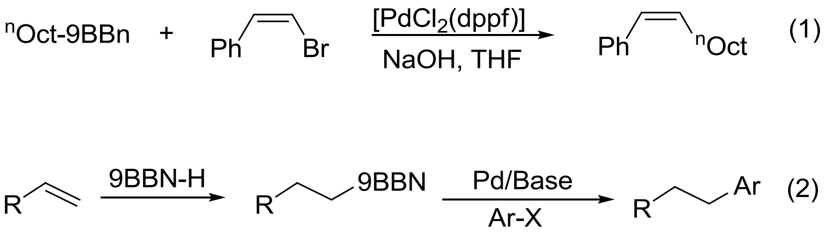
1.4 Developments in Cross-Coupling Partners for the Suzuki-Miyaura Cross-Coupling Reaction

1.4.1 Introduction and Brief Overview of Coupling Partners for the Suzuki-Miyaura Reaction

The initial form of the Suzuki-Miyaura cross-coupling reaction had several important limitations, which are beginning to be addressed. While there are many achiral sp^3 coupling systems that work, early examples of chiral sp^3 organoboron species were limited to cyclopropyl boronic acids, displaying significant sp^2 character.[50] These systems were not hindered with common problems such as, β-hydride elimination/reinsertion, and Pd chain walking in larger systems such as observed in unsymmetrical cyclohexyl-BF_3K compounds.[51] The following subchapters will describe recent advancements in Suzuki-Miyaura cross-coupling reaction that are pertinent to this thesis.

1.4.2 Primary Boronic Acid Coupling Partners

In 1986, Suzuki and Miyaura demonstrated that primary *sp*^{3} organoboron derivatives were effective cross-coupling partners (Scheme 1-15 equation 1).[52] Combining back-to-back hydroboration of an alkene and coupling provides a straight forward easy method, making the reaction even more useful (Scheme 1-15 equation 2).[53]

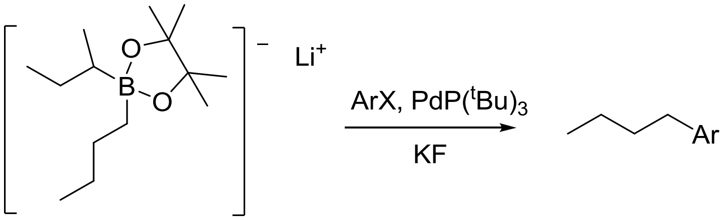


Scheme 1-15: (1) Early Primary *sp*^{3}-Hybridizd Boron Nucleophile Coupling Using 9BBN[52] (2) Back-to-Back Coupling of Primary 9BBN Derivative under Suzuki-Miyaura Conditions[53]

The development of primary *sp*^{3}-hybridizied organoboron nucleophiles as coupling partners has been extensively investigated in the Suzuki-Miyaura cross-coupling reaction for the synthesis of complex organic target molecules.[54]

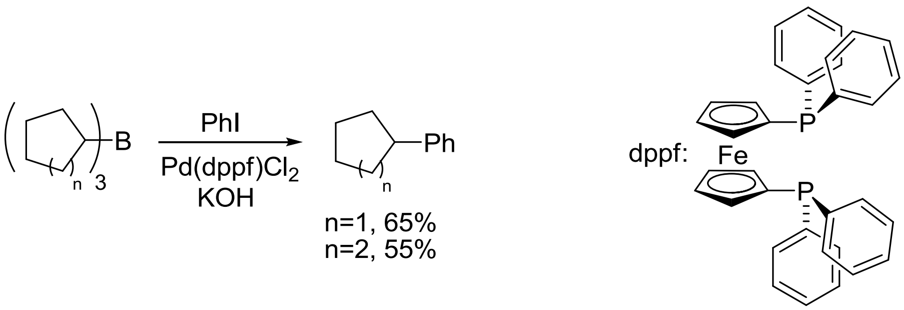
While alkylborane derivatives are interesting, *B*-alkylated-9-BBN are notoriously difficult to handle.[5, 53] Alkylboronic acids and esters are air-stable and easier to use with overall better atom economy and greater regiocontrol in hydroborations. Interestingly, alkylboronic esters did not react under typical conditions used for alkylboronic acids, as noted by Suzuki and co-workers.[53, 55] To increase their activity, the authors reported the use of thallium (I) salts to overcome the sluggish transmetalation step.[55] The extremely toxic nature of thallium was undesirable to work with and researchers sought out alternatives. In 2001, Ag_2O was demonstrated to successfully aid in the cross-coupling of various primary alkylboronic acids with aryl halides.[56] Once again, it was thought that Ag_2O was aiding in sluggish transmetalation, but its exact mode of action was unclear.[56]

While dominating cross-coupling research for almost two decades, primary *sp*^{3} organoboron coupling partners paved the way for secondary *sp*^{3} substrates. However, these compounds are difficult to activate in cross-coupling; transmetalation for branched compounds is particularly problematic due to increased steric effects at the secondary site.[5] Falck demonstrated that when coupling a lithium dialkyl pinacol boronate substrate bearing primary and secondary butyl groups, the only product coupled resulted from coupling of the primary alkyl substituent (Scheme 1-16).[56]



Scheme 1-16: Primary and Secondary Coupling Competition

This work further validated the early work of Suzuki and Miyaura, who observed similar results when cross-coupling triorganoboranes containing both primary and secondary alkyl groups: only the primary group coupled.[53] In the absence of primary alkyl groups, there are isolated examples of the coupling of secondary alkyl organoboron compounds (Scheme 1-17).[53]

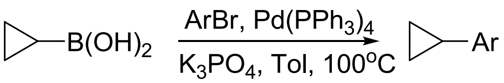


Scheme 1-17: Secondary Coupling in the Absence of Primary Alkyl Groups

1.4.3 Secondary Coupling Partners and BF_3K Derivatives

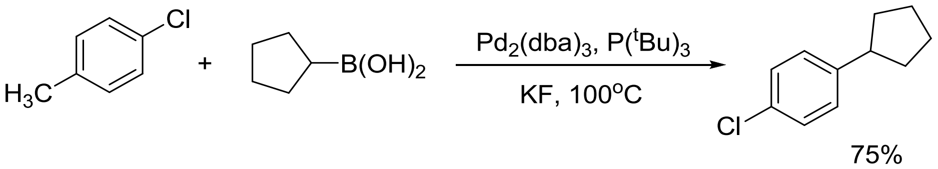
Accomplishing the successful coupling of secondary organoboron derivatives that are unsymmetrical requires overcoming the propensity to β-hydride eliminate/hydride re-add forming the undesired, linear product.[5] The cyclic symmetrical systems described thus far mask the addition/elimination sequence, which is only visible when coupling unsymmetrical or chiral enantioenriched substrates.[5] Since there are a variety of methods to prepare enantioenriched secondary boronic acid derivatives,[23] the possibility of employing these in stereoselective couplings makes this transformation extremely important.

The first reports of successful Suzuki-Miyaura cross-coupling of secondary organoboron nucleophiles described the coupling of cyclopropyl boronic acid substrates.[57] These compounds have increased *sp*^{2} character, likely facilitating transmetalation and impeding β-hydride elimination (Scheme 1-18).[57] Thereafter potassium trifluoroborate[58] and boronic ester[50, 59] analogues were developed.



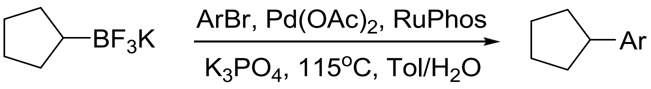
Scheme 1-18: Cyclopropyl Cross Coupling

Moving into systems with full *sp*^{3} character, Fu et al. highlighted the first example of a palladium catalyzed cross-coupling reaction of cyclopentylboronic acid with *p*-methylchlorobenzene in the presence of KF (Scheme 1-19).[60] The authors noted that to stabilize the catalyst and to decrease precipitation of palladium metal, higher temperatures and ratios of $P(^tBu)_3$: Pd (1.5:1) were required.[60] However, even under these conditions, electron-rich aryl chlorides, including 4-chloroaniline, could be coupled efficiently with both aryl- and alkyl-boronic acids.[60]



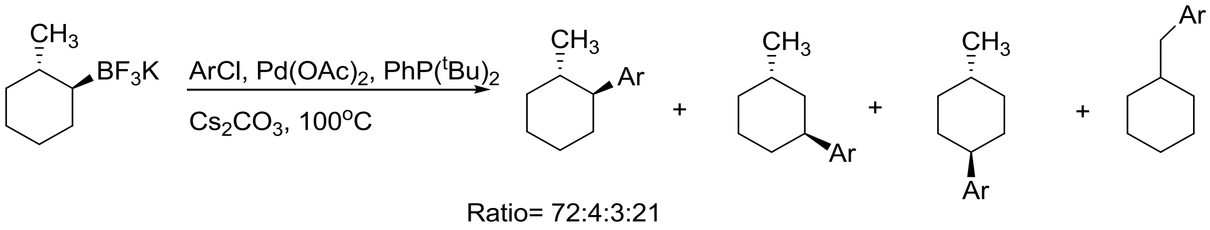
Scheme 1-19: Palladium Catalyzed Cross-Coupling of Cyclopentylboronic acid with *p*-Methylchlorobenzene[60]

Following the work of Fu et al., Van Den Hoogenband would describe the cross-coupling of cyclopentyl-BF_3K using RuPhos and $Pd(OAc)_2$ (Scheme 1-20) in good yields.[51] While these systems provided an important advancement in cross-coupling and appeared to be successful, they were all symmetrical. Thus the effects of β-hydride elimination and addition events were not visible.



Scheme 1-20: Cross Coupling Utilizing BF_3K Symmetrical Derivatives

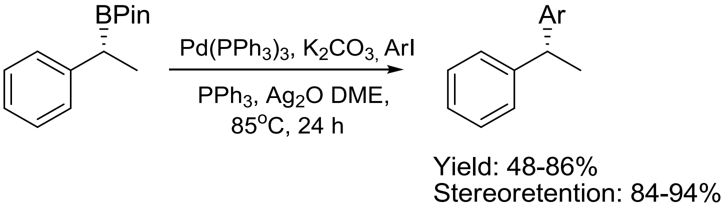
Demonstrating this concept, Molander and coworkers elegantly showed the chain walking of Pd and aryl incorporation throughout the entire structure.[61] They demonstrated that bulky electron rich phosphine ligands, such as PhP(^{t}Bu)$_{2,}$ decreased this effect, but even under optimized conditions, significant chain walking was observed (Scheme 1-21).[61]



Scheme 1-21: Chain Walking in Unsymmetrical Systems via β-Hydride Elimination/Addition

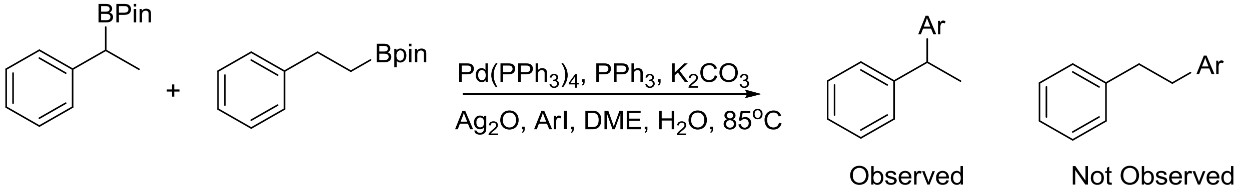
1.4.4 Secondary Boronic Esters as Coupling Partners

In 2009, the Crudden group would be the first to demonstrate successful cross-coupling of enantioenriched boronic esters that did not undergo the problematic β-hydride elimination/addition sequence (Scheme 1-22).[62] The resulting diaryl ethane products were obtained in good yield with high stereofidelity, and with high retention of stereochemistry.



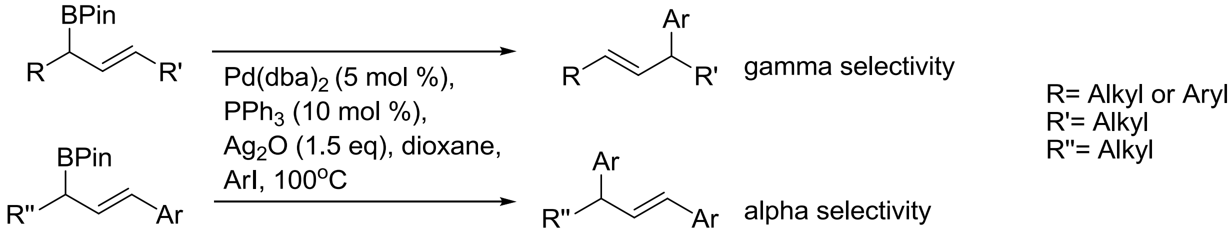
Scheme 1-22: Crudden Group Benzylic Cross-Coupling[62]

The benzylic organoboronate substrates can be synthesized by the rhodium-catalyzed regio- and enantioselective hydroboration of styrene.[11, 23] Our group determined that the use of silver oxide as an additive was critical to overcome a sluggish transmetalation of the benzylic organoboranes. Interestingly, these coupling conditions were specific enough that when competition reactions were performed between branched and linear substrates, only the branched substrate was reactive (Scheme 1-23).[11]



Scheme 1-23: Competition of Branched vs. Linear Under Crudden Coupling Conditions[2, 62]

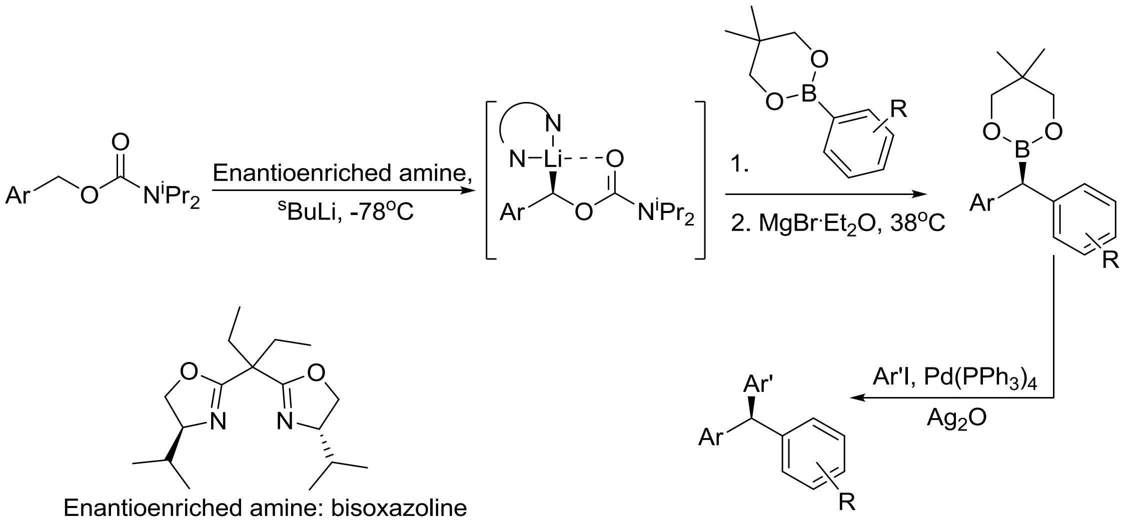
These conditions were extremely effective at cross-coupling pinacol benzyl boronic esters. However, with benzylic BF_3K salts, no cross-coupling products were formed.[5] If a site of π-unsaturation is installed allylic to the boronic ester, the resulting coupling reaction works.[5] These observations lead to the first general protocol for cross-coupling of secondary allylic boronic esters with gamma product formation typically occurring unless there is a styrenyl unit in the product, in which case the alpha coupling product is generated (Scheme 1-24).[63]



Scheme 1-24: Allylic Boronic Ester Cross Coupling Using Suzuki-Miyaura Conditions

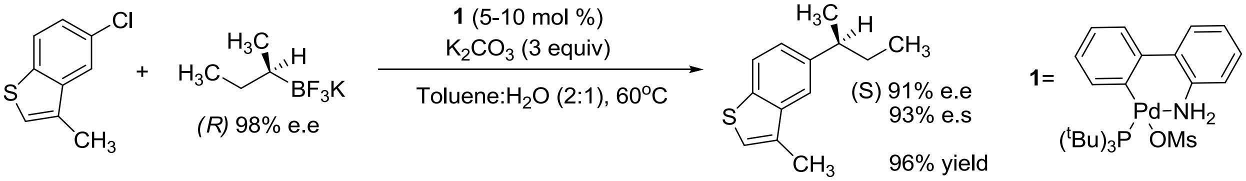
To better understand the reaction, deuterated substrates were prepared where 90% of the deuterium labeling is in a vinylic position and two identical methyl groups occupy the allylic position.[64] The expected 50:50 mixture was not observed, and instead γ-selective coupling products were seen in a ratio of 85:15.[64] These deuterium labeling studies lead to the conclusion that the mechanism proceeds through γ-transmetalation, followed by a fast reductive elimination.[64]

Similar conditions for benzylic systems have been applied to allylic, benzylic, propargylic and dibenzylic boronic esters, and in all cases, enantioenriched products can be formed.[5] Expanding the breadth of the group's already impressive cross-coupling portfolio, the Crudden group examined enantioselective triaryl methane synthesis. To prepare the starting materials, a variant of Aggarwal’s chemistry utilizing benzyl carbamates and a bis-oxazoline ligand was employed, giving reasonable enantioselectivies (80-100%) in the boronic ester products. (Scheme 1-25).[65,5] The resulting silver oxide-promoted coupling took place with good levels of stereoretention.



Scheme 1-25: Total Synthesis of Enantiomerically Enriched Triaryl Methanes

In 2014, Biscoe et al. reported the development of a stereospecific palladium catalyzed cross-coupling reaction of unactivated secondary alkylboron nucleophiles and aryl chlorides (Scheme 1-26).[66] When an optically active alkyltrifluoroborate is employed, the authors observed inversion of absolute configuration in the cross-coupled product.[66] The reaction does not occur with any significant isomerization of the alkyl nucleophile, and is also tolerant to secondary alkylboronic acids.[66] The process should expand the use of optically active alkylboron compounds as building blocks in the construction of natural and synthetic products and optically active drug libraries.[66]

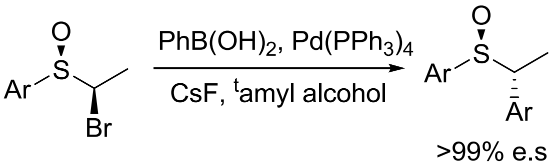


Scheme 1-26: Stereospecific Cross-Coupling Reaction of Unactivated Secondary Alkylboron Nucleophiles and Aryl Chlorides[66]

1.4.5 Cross-Coupling of Alkyl Electrophiles

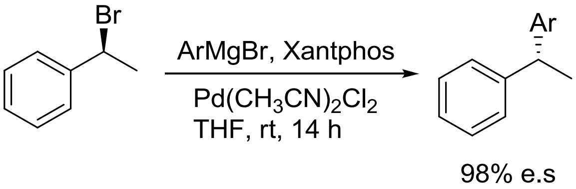
As described previously, nucleophilic coupling partners have played an important role in the development of the Suzuki-Miyaura reaction. Compared to their electrophilic counterparts, both primary and secondary electrophiles have been used successfully in the Suzuki-Miyaura cross-coupling reaction, giving an alternative route to otherwise difficult product formation.[5]

The first report of a stereospecific Suzuki-Miyaura cross-coupling reaction was in 2007, when Medio-Simon and coworkers activated a secondary bromide by placement of a sulfoxide adjacent to it (Scheme 1-27).[67] The reaction proceeds with perfect inversion of stereochemistry, which is proposed to occur during oxidative addition.[67] The authors propose that the S_N2 nature of the oxidative addition step leads to the observed inversion of stereochemistry, proposing that the rest of the catalytic cycle proceeds with retention of configuration.[67]



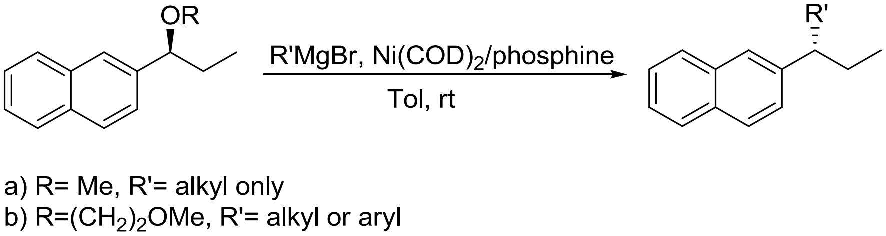
Scheme 1-27: Bromide Activation via Adjacent Sulfoxide for High Stereoinversion

By 2010, Carretero et al. demonstrated that enantiomerically enriched 2-phenylethyl bromide could be cross-coupled with almost perfect stereoinversion under Kumada-Corriu conditions using Xantphos as the ligand to inhibit β-hydride elimination (Scheme 1-28).[68] Thus, a new method for the synthesis of enantioenriched 1,1-diarylethanes was developed. Unfortunately, the methods available to make enantiopure alkyl halides is severely lacking, limiting the utility of the overall method.[5]



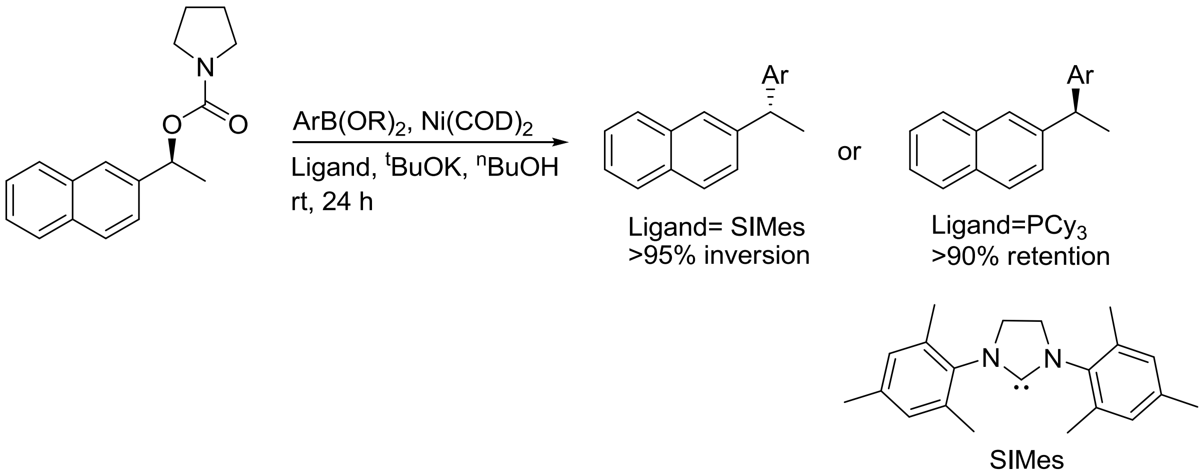
Scheme 1-28: Synthesis of 1,1-Diarylethanes with High Stereoinversion

Jarvo and coworkers further demonstrated the Ni-catalyzed Kumada-Corriu coupling of stereodefined benzylic alkyl ethers.[69] This work significantly advanced research in the area of stereospecific coupling of enantioenriched organic nucleophiles by widening the breadth of possible enantiomerically enriched species, including alcohols that could be easily prepared.[5] In following papers, the importance of the ether group was highlighted when chelating groups could be employed to expand the reactions to include aryl Grignard reagents (Scheme 1-29), making enantiomerically pure triaryl methanes with high stereoinversion.[70]



Scheme 1-29: Kumada-Corriu Coupling Expansion by Jarvo

Recently the Jarvo group demonstrated that aryl boronic esters could be used in Ni-catalyzed Suzuki-Miyaura cross-coupling reactions and by changing ligands to either 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene (SIMes) or tricyclohexylphosphine (PCy_3) the reactions will proceed with either inversion or retention, respectively (Scheme 1-30).[71]



Scheme 1-30: Control of Stereochemical Inversion or Retention via Ligand

1.5 Research Objectives

As described earlier, the Crudden group developed the initial conditions for Suzuki-Miyaura cross-coupling of enantioenriched secondary benzylic boronic esters with a wide scope of aryl iodides that afforded compounds in high yield and stereofidelity with retention of configuration.[62] The goal of this thesis is to chemo and enantioselectivity couple substrates that contain multiple boronic ester moieties (Figure 1-4).

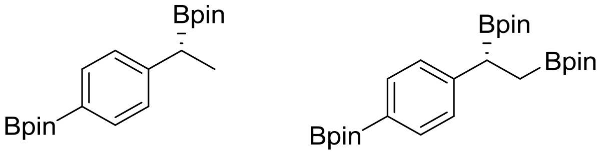


Figure 1-4: Boronic Ester Substrates for the Preparation of Multiply Arylated Compounds via Suzuki-Miyaura Cross Coupling

The following chapter will discuss and examine the nuances of each substrate and their application for the formation of difficult organic frameworks with potential for targeted drug molecule synthesis.

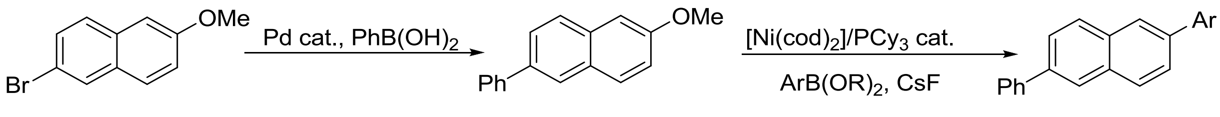
Chapter 2

Cross-Coupling Di- and Tri Boronic Ester Substrates Chemoselectivity with Retention of Stereochemistry

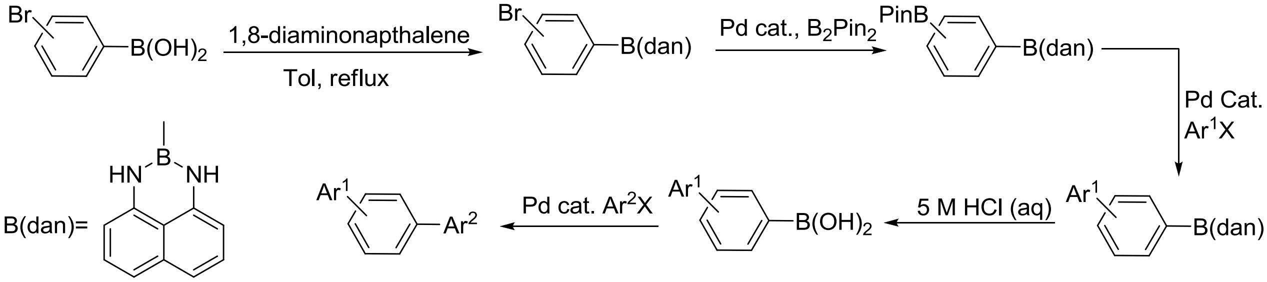
2.1 Introduction

Although the synthesis of small molecules can be a relatively inefficient and difficult process to accomplish in a systemized manner, efforts are underway to streamline and even automate this.[72,73] Ideally, the starting reagents would be commercially available with preinstalled stereochemistry of functional groups, already in their correct oxidation states.[74] These reagents could then be combined via iterative coupling procedures with high retention of stereoconfiguration.[74] The Suzuki-Miyaura cross-coupling reaction represents a powerful method for the synthesis of new carbon-carbon bonds in highly complex molecules.[11] The ability to tune the starting organohalide and boronic acid derivative allows for the development of more efficient coupling reactions.[5] Recently, there has been an increasing interest in developing synthetic strategies that would allow multiple cross-coupling processes to be completed within the same molecule at different reaction sites.[72, 75] This has been accomplished by either discriminating at the electrophilic partner (I>Br>> Cl or pseudohalides) or the boron site.[72, 76] The key in this strategy has been the modification of electron density and/or the hybridization state of the boron site (Scheme 2-1A-B).[76a]

A) Electrophilic Discrimination[76a]

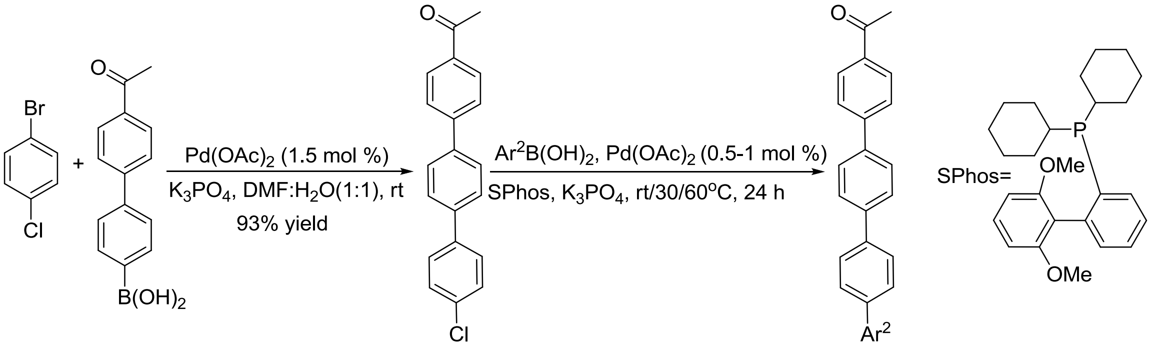


B) Boron Site Discrimination[72, 76b]



Scheme 2-1: Electrophilic (A) and Boron (B) Site Discrimination for Iterative Cross-Coupling

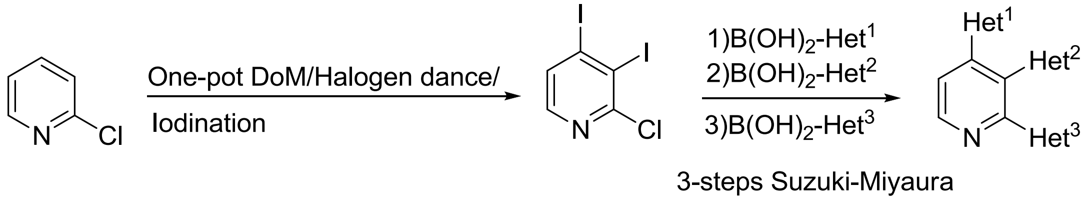
However, the most effective approach to date with regard to modulating these iterative cross-coupling reactions is to exploit the difference in reactivity between aryl (pseudo) halides (Scheme 2-1A).[76a] In 2007, Hii and coworkers developed a sequential chemoselective Suzuki-Miyaura cross-coupling of chloro-bromobenzenes with a broad range of arylboronic acids in the synthesis of *o*-, *m*- and *p*-terphenyls.[77] The first coupling reaction occurred at the more reactive bromide, under very mild conditions at room temperature using $Pd(OAc)_2$ and K_3PO_4 as a base. The second coupling was performed at the less reactive chloride site and was facilitated by the use of 2-dicyclohexylphosphino-2’-6’-dimethoxybiphenyl (SPhos) (Scheme 2-2).[77]



Scheme 2-2: Iterative Coupling by Discrimination of Electrophilic Sites[77]

Interestingly, in their synthesis of both *p*- and *m*-terphenyls, they reported no sensitivities with regards to sterics or electronic characteristics associated with cross-coupling their substrates.[77] If the second cross-coupling was in the ortho position and the aromatic ring was electron deficient or neutral, the reactions proceeded with high yields.[77] However, the presence of electron rich functional groups led to a dramatic decrease in yield. They concluded that *o*-terphenyls were cross-coupled more efficiently if sterically demanding groups were installed in the second coupling reaction via the appropriate arylboronic acid.[77]

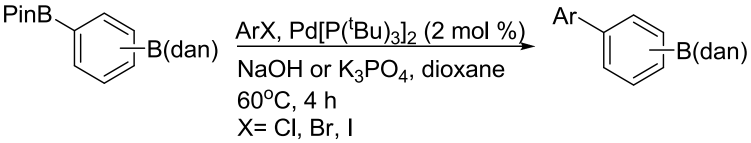
In 2010, Bryce and coworkers described a one-pot directed ortho metallation/halogen dance/ iodination sequence from 2-chloropyridines to form 2-chloro-3,4-diiodopyridines (Scheme 2-3).[78] After successfully performing a 3-step Suzuki-Miyaura cross-coupling reaction, they were able to form a variety of versatile mono-, bis-, and triheteroarylpyridine derivatives.[78] This was the first example of pyridine derivatives bearing heteroaryl units in the 2, 3 and 4 positions. The reactions were tolerant to even sterically hindered derivatives.[78]



Scheme 2-3: Bryce and Coworkers DoM/ 3-Step Suzuki-Miyaura Coupling for mono-, bis- and triheteroarylpyridine derivatives[78]

To achieve iterative cross-coupling with multiple boron moieties, it has been necessary to employ protecting or masking groups to deactivate one boron functional group relative to another.

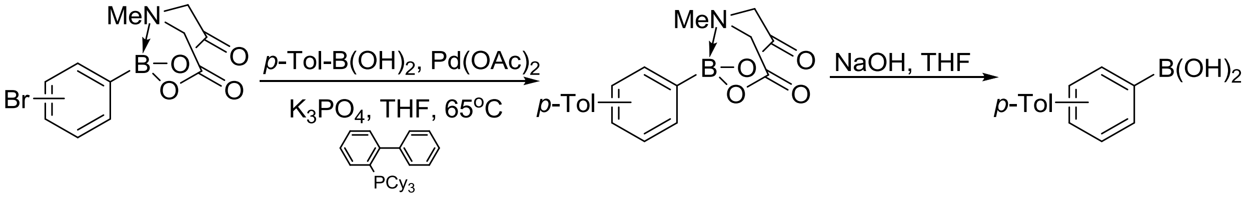
In 2007, Suginome and coworkers developed a boron masking strategy, utilizing a 1,8-diaminonaphthalene (dan) protecting group, for boron substituted oligoarenes that efficiently underwent a highly selective *sp*^{2} Suzuki-Miyaura cross-coupling reaction forming products with the protected boron left intact (Scheme 2-4).[76b] The diaminoboron substituent decreases the Lewis acidity at the boron center due to the π- electron donation from the nitrogen substituents.[76b] Therefore, the activity of the Bdan moiety is decreased and unreactive with the palladium catalyst, relative to the BPin moiety.[76b]



Scheme 2-4: Suginome B(dan) Protecting Group for Highly Selective Synthesis of Multi-aryl Rings[76b]

Removal of the protecting group, using mildly acidic conditions, exposes the boronic acid, which can then be coupled through a second Suzuki-Miyaura reaction. Using this methodology, limitless iterative coupling could be possible for the synthesis of large complex aryl structures.[76b]

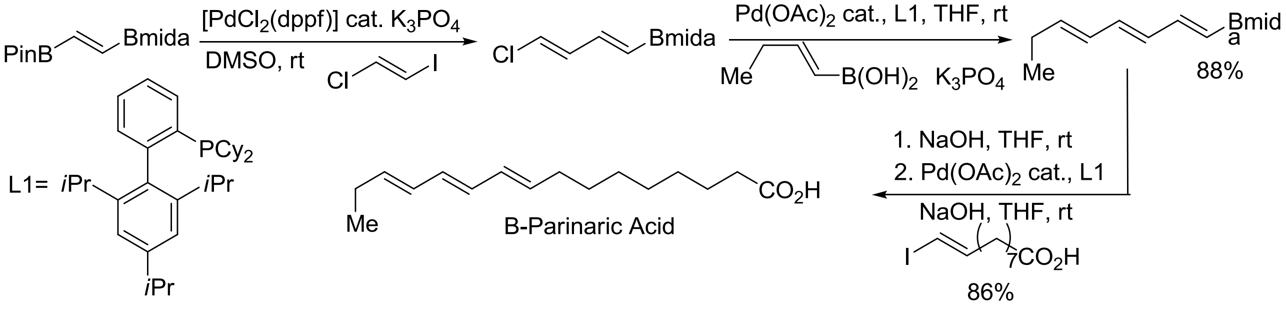
In 2007, Burke and coworkers reported the use of the MIDA (methyliminodiacetic acid) masking agent which re-hybridizes the boron center from *sp*^{2} to *sp*^{3} (Scheme 2-5).[72] When the Lewis acidity of the new *sp*^{3} boron terminus is reduced, it is unable to transmetalate readily in the presence of the boronic acid moiety giving selective coupling between the two.[72] Amazingly, these boronate esters are protected during coupling at temperatures of 80°C for 28 hours, however upon exposure to mild aqueous basic conditions (1 M NaOH/THF 10 min) deprotection can be achieved.[72] The newly exposed boronic acid can then be used in a subsequent coupling.



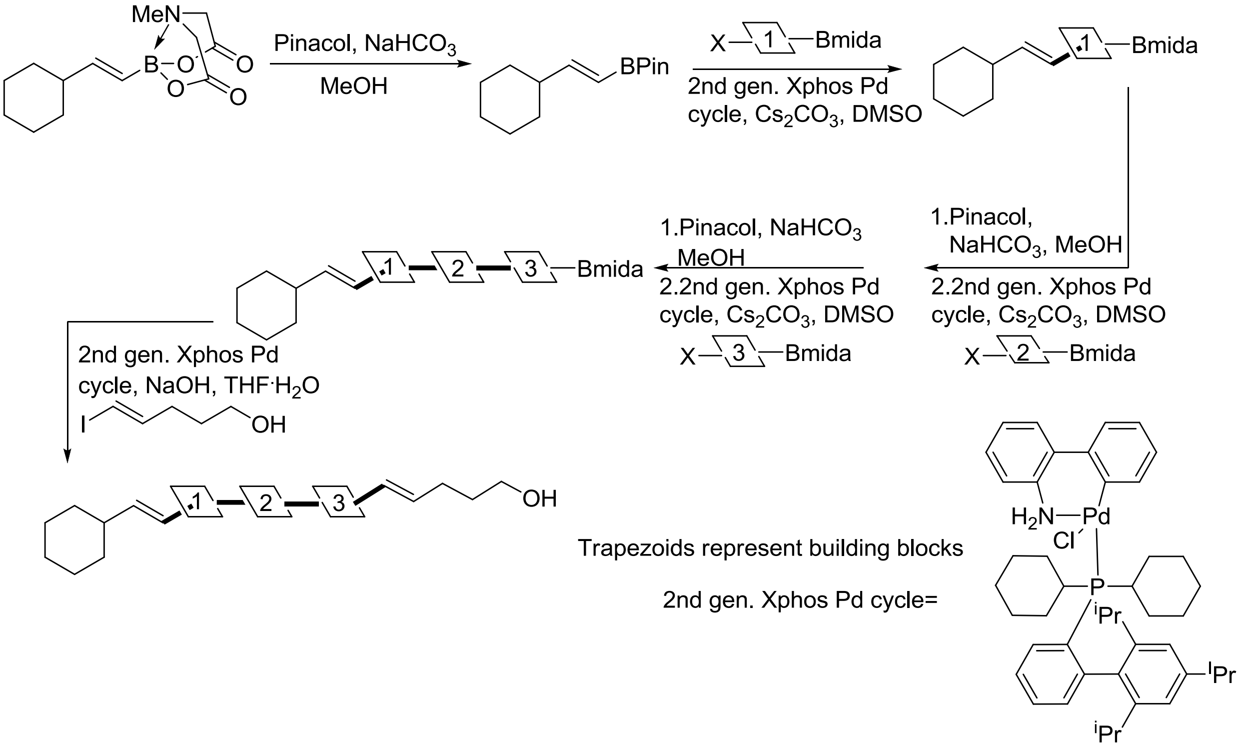
Scheme 2-5: Iterative Coupling using MIDA Masking Agent by Burke[72]

Burke and coworkers went on to demonstrate the power of this reaction in the synthesis of polyene natural products (Scheme 2-6A).[72,79] The three step synthesis utilized materials that were readily available, which allowed the authors to selectively pair the bifunctional dienylchloride and *(E)*-1-butenylboronic acid yielding a trans-trienyl boronate species which was stable to chromatography.[80] Deprotection was once again achieved under mild aqueous basic conditions, followed by cross-coupling with the final vinyl iodide.[80] In 2014, Burke and coworkers further demonstrated that only 12 building blocks and 1 cross-coupling reaction could be used to synthesize more than 75% of all polyene natural products, containing a polyene motif (Scheme 2-6B).[81] This advancement suggests a more generalized approach for the synthesis of small molecules in laboratories.[81]

A) Burke's MIDA Masking Agents and Their Application to the Synthesis of Polyene Natural Products[80]

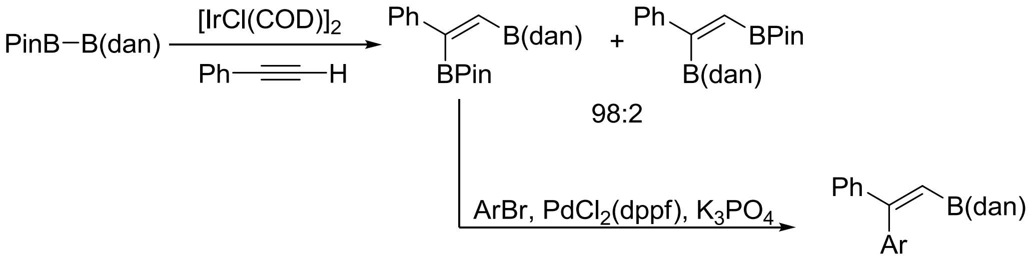


B) Synthesis of Most Polyene Natural Products using 1 Cross-Coupling and 12 Building Blocks[81]



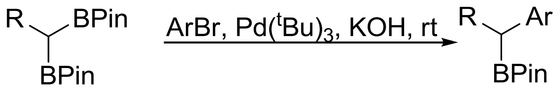
Scheme 2-6: Advancement of Iterative Cross-Coupling by Burke and Coworkers for the Synthesis of Polyene Natural Products from 2007 (A)[80] and 2014 (B)[81]

In 2010, Suginome et al. described the 1,2-diboration of phenylacetylene using an unsymmetrical diboron reagent in the presence of $[IrCl(COD)]_2$, yielding to the desired 1-alkene-1,2-diboronic acid derivative in high regioselectivites (98:2) (Scheme 2-7).[82] The diboronate ester derivative product then underwent coupling at the branched position with high chemoselectivity (98:2).[82] This is in contrast to a substrate containing $B_2(pin)_2$, in which the terminal Bpin group in the compound is selectively coupled.[82]



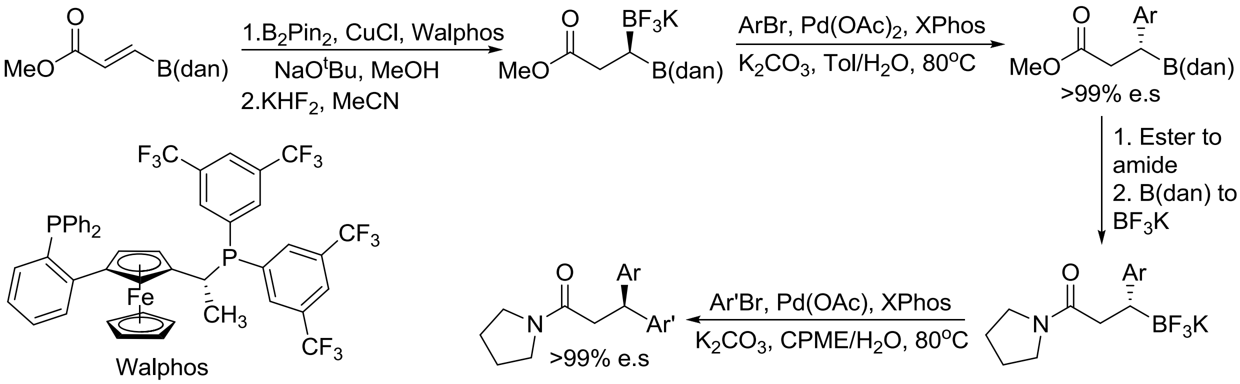
Scheme 2-7: Unsymmetrical Diboron Cross-Coupling by Suginome et al.

Cross-coupling 1,1-diborylalkanes with a variety of aryl halides at room temperature was reported in 2010 by Shibata et al. (Scheme 2-8).[83] Their results demonstrated a new method for protection-free chemoselective Suzuki-Miyaura cross-coupling on a multi-substituted *sp*^{3}-carbon.[83] The presence of two adjacent boron atoms in 1,1-diborylalkanes was determined to be one of the key factors in promoting transmetalation of this otherwise hindered substrate.[83] In addition, the authors noted that no β-hydride elimination was observed, proposing that the adjacent boron atom provided increase stabilization of key σ-alkylpalladium intermediates.[83]



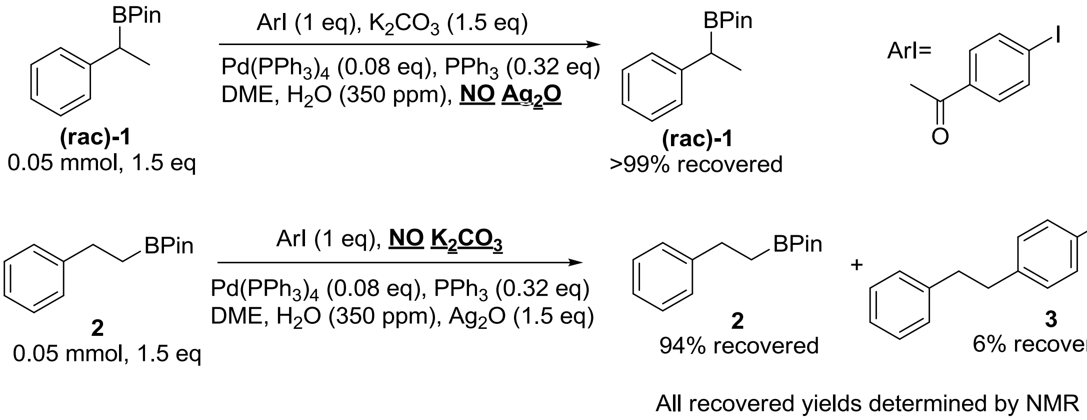
Scheme 2-8: Cross-Coupling 1,1-Diborylalkanes at Room Temperature by Shibata et al.[83]

In 2011, the Hall group demonstrated the use of Suginome's dansyl protecting group in the formation of highly optically enriched 1,1-diboron compounds.[84] The authors described a catalytic asymmetric borylation of β-boronylacrylates, forming geminal diboronate products, which were subsequently cross-coupled (Scheme 2-9).[84] Chemoselective cross-coupling of the BF_3K salt proceeded with inversion of stereochemistry.[84] Interestingly, the ester is activating in the presence of the germinal diboron moieties. However, once the first Suzuki-Miyaura cross-coupling is performed, the ester needs to be converted to an amide for the final coupling to take place.[5] Stabilization of the difficult transmetalation is believed to be achieved by the second boronyl unit as well as internal coordination of the oxygen from the carboxyester.[84]



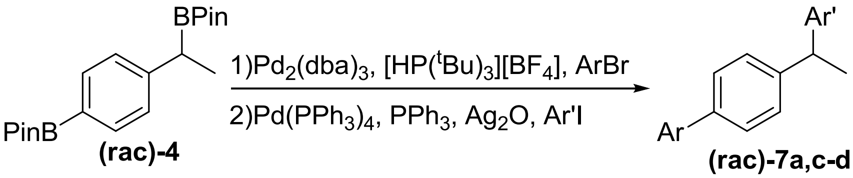
Scheme 2-9: Sequential Coupling of β-diboryl Carbonyl Compounds[84]

Prior to 2009, the use of secondary organoboron species as coupling partners was still largely an unsolved problem, with the exception of cyclopropyl or symmetrical substrates.[58a] Originally such systems were proposed as difficult substrates due to significant problems such as β-hydride elimination/addition, which would racemize pre-installed enantioenriched centers.[5] While cyclopropyl and butyl systems, developed by the Molander[58a] group, were a good alternative, this was not a general solution. In 2009, the Crudden group developed conditions for the cross-coupling of secondary benzylic boronic esters.[62] In order for the reaction to be successful, it was observed that the use of Ag_2O and excess PPh_3 were necessary.[62] Silver oxide in particular was required to overcome the difficult transmetalation, which is required to complete the catalytic cycle.[44] Interestingly in a non-competitive scenario, cross-coupling at the secondary benzylic position without silver oxide results in no product formation, however, cross-coupling at the linear position afforded 6% product formation and 94% of the starting material was recovered (Scheme 2-10).



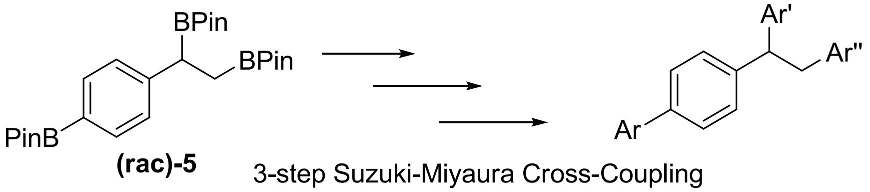
Scheme 2-10: Non-competitive Cross-Coupling Excluding and Including Silver Oxide at the Secondary Benzylic and Linear Boronic Ester Position

Previous masters student Marieke Hutchinson successfully established that a carbon-*sp*^{2} C–B bond could be coupled in the presence of a racemic secondary benzylic *sp*^{3} bond (Scheme 2-11).[85] Retention of stereochemistry was not assessed since the reaction was carried out on racemic compounds.[85] Based on these results, the same task was performed on enantiomerically enriched substrates.



Scheme 2-11: Successful Coupling of an *sp*^{2} Bond in the Presence of a Secondary Benzylic *sp*^{3} Bond[85]

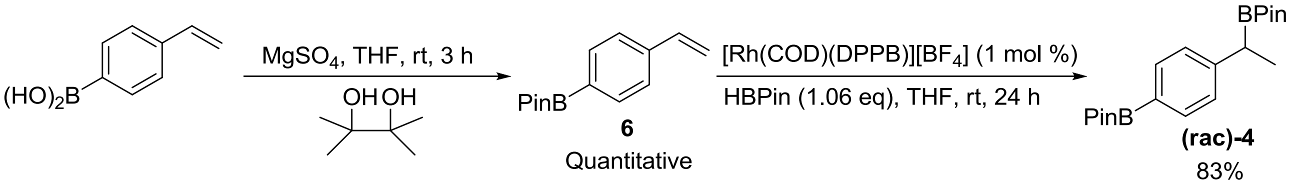
In addition, we were interested in expanding this concept to attempt the cross-coupling of *sp*^{2} and *sp*^{3} linear boronic esters in the presence of each other. If successful, then we would be successfully able to chemoselectively couple three separate positions without the need for protecting groups (Scheme 2-12).



Scheme 2-12: Proposed Three Step Suzuki-Miyaura Cross-Coupling Without the Need for Protecting Groups

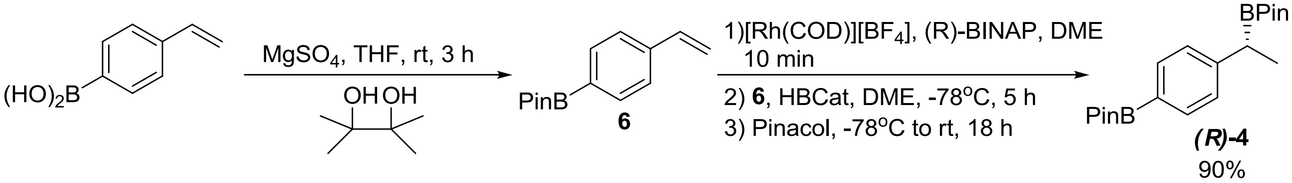
2.2 Chemoselective Coupling of a Diboronic Ester Substrate Containing Aryl and Secondary Benzylic Boronic Esters

Synthesis of the racemic diboronic ester substrate **(rac)-4** was achieved by treating 4-vinylphenyl boronic acid under esterification conditions with pinacol, resulting in a quantitative conversion to 4-vinylphenyl boronic ester **6**.[86] Subsequently, a Rh-catalyzed hydroboration reaction was performed on substrate **6** to produce the desired product in good yield (Scheme 2-13).[23]



Scheme 2-13: Synthesis of Racemic Diboronic Ester Substrate Containing Both Aryl and Secondary Benzylic Boronic Esters

A similar approach was employed for the synthesis of the enantioenriched diboronic ester ***(R)*-4,** by replacing DPPB with *(R)*-BINAP. However, small changes were required to achieve high levels of enantioselectivity. Specifically, the more reactive HBCat[23, 87] was instead utilized as a boron source, which was followed by a pinacol quench at -78°C to obtain ***(R)*-4** (Scheme 2-14). Both products **(rac)-4** and ***(R)*-4** are stable enough to be purified via flash chromatography on silica gel and were obtained in a high yield. Product **(rac)-4** in particular was also subjected to Kugelrohr distillation at 50°C and left under high vacuum for up to 48 hours without any sign of decomposition.



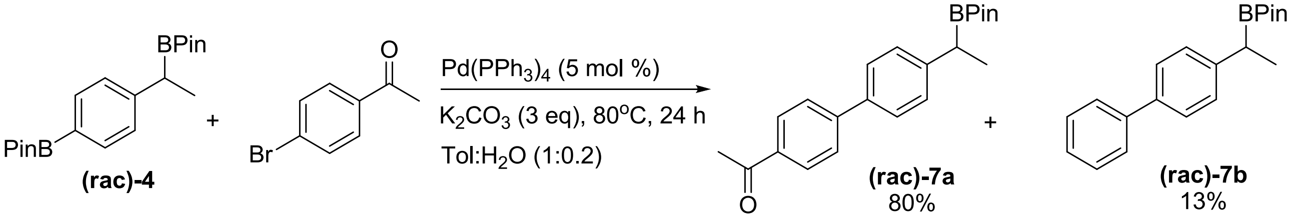
Scheme 2-14: Synthesis of Enantioenriched Diboronic Ester Substrate Containing Aryl and Secondary Benzyl Boronic Esters[21, 23]

Neither substrate **(rac)-4** nor ***(R)*-4** was able to be oxidized due to decomposition of the starting materials to 4-vinylphenyl boronic ester **6** and other unwanted oxidized products. Oxidation was attempted using standard NaOH/H_2O_2 conditions as well as using literature procedures utilizing less harsh conditions such as $NaBO_3$.[88] However, both attempts were met with failure. Since coupling takes place initially at the sp^2 position, any enantioenrichment established at the sp^3 site is hypothesized to be left intact. Unfortunately, due to time restrictions this hypothesis was unable to be fully tested. It should be noted, that the assigned absolute stereochemistry of *(R)* (for all hydroborated and cross-coupled products) is based off of previous work performed in the Crudden lab, there were no further experiments performed to confirm this for compounds presented in this thesis.[2, 23, 62]

2.2.1 Suzuki-Miyaura Cross-Coupling at the sp^2Aryl Position

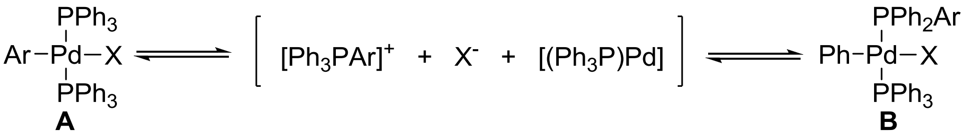
To achieve chemoselective cross-coupling with diboronic ester substrate ***(R)*-4**, the conditions required for the cross-coupling of *sp^2* aryl boronic ester had to both be orthogonal and mild enough to ensure that there would be no decomposition of the benzylic boronic ester. Since the nucleophilicity of the *sp^2* carbon-boron bond is greater than that of the benzylic *sp^3* C–B bond due to the presence of π-bonding in the latter, the transmetalation step occurs more readily.[11]

Development of optimized conditions began by subjecting phenyl boronic ester to three sets of conditions,[89] which showed efficient *sp^2* Suzuki-Miyaura cross-couplings with aryl halides. Previous lab member, Marieke Hutchinson, subjected phenyl boronic ester to literature conditions described by Wright,[89a] Keay,[89b] and Fu[89c] and found that the conditions described by Keay et al.[89b] gave the highest GC yield (71%) using the lowest palladium loading (5 mol %). Application of these conditions to substrate **(rac)-4** led to protodeboronation, but optimization gave the desired cross-coupled product in 80% isolated yield (Scheme 2-15). Based on these conditions, it was determined that water played an important role in the cross-coupling, possibly by aiding in the solubilization of the base and increasing the rate of transmetalation.



Scheme 2-15: Keay et al. Coupling Conditions (Without Ethanol) Applied to Substrate (rac)-4[89b]

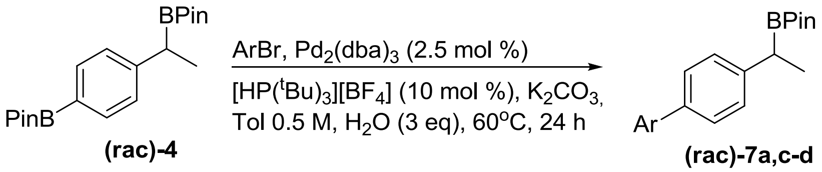
Although these results seemed promising, previous work by Marieke Hutchinson showed byproduct formation resulting from incorporation of one of the phenyl substituents of triphenylphosphine into the product (Scheme 2-15 **(rac)-7b** and Scheme 2-16).[85] Common methods to suppress this reaction including: performing the reaction in low polarity solvents, increasing palladium and ligand loadings, and increasing the amount of aryl halide, were examined, but all failed in our case.[90]

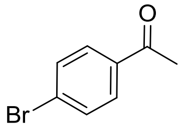
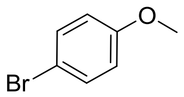
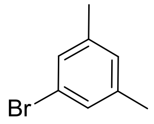


Scheme 2-16: Catalyst Scrambling by Aryl/Aryl Exchange

Alternatively, by utilizing a trialkyl phosphine, this problem can be avoided as alkyl groups are less likely to undergo this reaction. By changing our palladium/phosphine system to conditions reported by Fu, who used $Pd_2(dba)_3/P(^tBu)_3$, Marieke was able to circumvent any catalyst scrambling.[85] Final optimized conditions required the use of lower temperatures, 3 equiv. of K_2CO_3 as base, and adding 3 equiv. of H_2O to prevent protodeborylation and provide the product in good isolated yields. I applied these conditions to racemic substrate **(rac)-4** and obtained high isolated yields of the desired products (Table 2-1).

Table 2-1: Suzuki-Miyaura Cross-Coupling of an *sp*^{2}Aryl Boronic Ester [a]

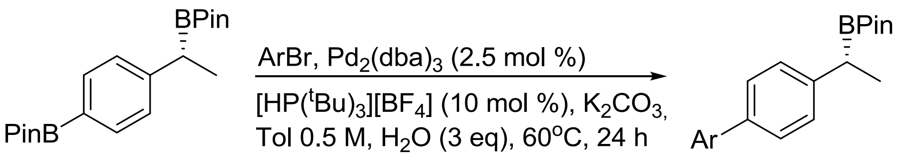


Entry	Aryl Bromide	Compound Number	Yield (%)
1		**(rac)-7a**	88
2		**(rac)-7c**	85
3		**(rac)-7d**	95

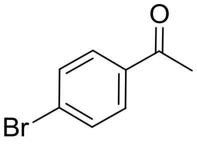
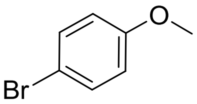
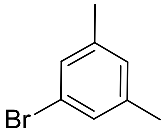
[a] Reaction conditions: Substrate (rac)-4 (1 equiv), ArBr (1.2 equiv), K$_2$CO$_3$ (3 equiv), Tol (0.5 M). Water was purged with argon for 15-30 minutes prior to its addition to the reaction. All products were isolated by flash chromatography.

To determine the retention time of the racemic substrates **(rac)-7a,c-d**, each compound was subjected to standard oxidation conditions (NaOH/H$_2$O$_2$), producing the respective alcohols. These products were then analyzed by supercritical fluid chromatography (SFC). Following assessment of the racemic substrates, the scope of the reaction was expanded by cross-coupling enantiomerically enriched substrate ***(R)*-4** to products ***(R)*-7a,c-d** in comparable yields to their racemic counterparts (Table 2-2). While the scope does not include ortho functionality, there does not seem to be deleterious effect of 3,5-dimethyl *meta* functional groups in either the racemic or enantiomerically enriched examples (**7d** vs **7a** and **7c**).

Table 2-2: Suzuki-Miyaura Cross-Coupling of Enantioenriched Substrate *(R)*-4 at the *sp*^{2} aryl Boronic Ester [a]



***(R)*-4** → ***(R)*-7a,d-c**

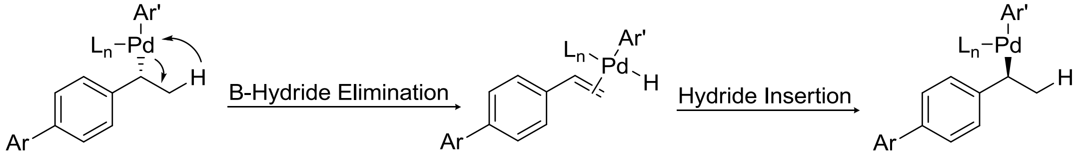
Entry	Aryl Bromide	Compound Number	Yield (%)	e.r.[b]
1		***(R)*-7a**	81	5:95
2		***(R)*-7c**	76	5:95
3		***(R)*-7d**	89	3:97

[a] Reaction conditions: Substrate *(R)*-4 (1 equiv), ArBr (1.2 equiv), K$_2$CO$_3$ (3 equiv), Tol (0.5 M). Water was purged with argon for 15-30 minutes prior to its addition into the reaction vial. Products isolated by flash chromatography. [b]Oxidation conditions: Substrates *(R)*-7a,c-d (0.06 mmol), 1 M NaOH, 30% H$_2$O$_2$, 0^{o}C 1 h. Isolated in quantitative yield, purified by Preparatory Thin Layer Chromatography (PTLC). [b] Please see supporting information for characterization and SFC data for each respective alcohol. Optical analysis by SFC, enantiomeric ratio is described in terms of S:R, based on extrapolation from previous literature precedent.[62]

Products ***(R)*-7a,c-d** were again oxidized to alcohols and assessed by SFC. As expected, enantiomeric ratios (e.rs.) fell into the range previously observed in our earlier 2009 paper (S:R of 6:94) (Table 2-2).[62]

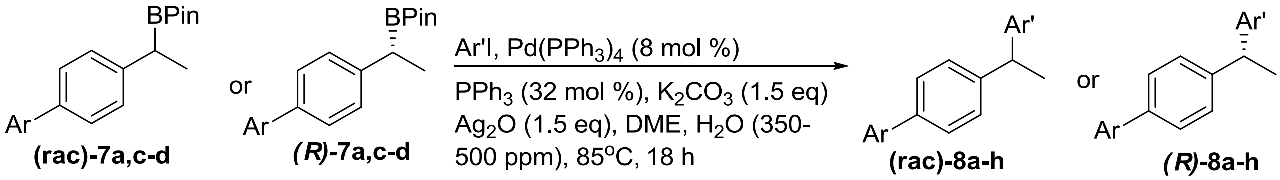
2.2.2 Suzuki-Miyaura Cross-Coupling of Secondary Benzylic Boronic Esters

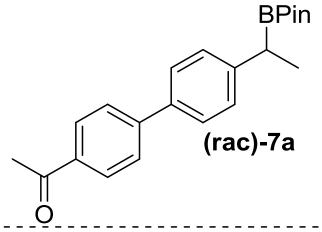
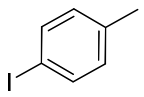
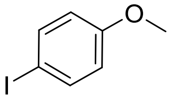
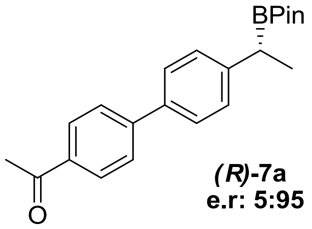
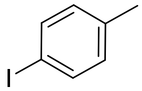
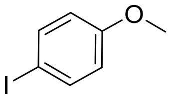
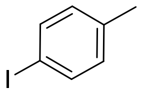
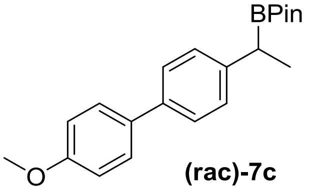
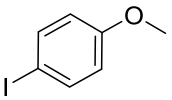
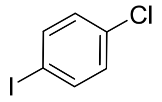
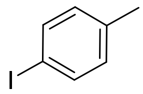
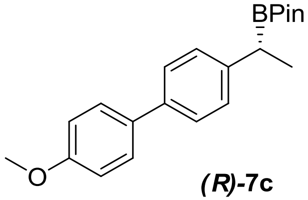
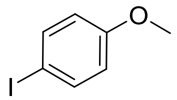
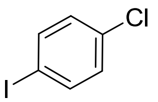
Previous conditions developed for cross-coupling at the secondary benzylic position included a large excess of PPh_3 and Ag_2O.[11, 62] Since our publication in 2009, the conditions have been slightly modified to include 1.5 equiv. of K_2CO_3, which was found to increase stereoretention in some cases.[85, 91] Water was also shown to be important as 350-500 ppm was determined to be needed to maximize yields.[63] The effect of water is still not fully understood and research continues in this area.[2] The next step in the chemoselective Suzuki-Miyaura cross-coupling reaction of bis boronic esters **(rac)-4** and ***(R)*-4,** was to apply the previously optimized conditions for coupling of the sp^3 C-B bond. Cross couplings were performed with 8 separate aryl iodides to give various multi-aryl ring systems with yields ranging from 49-70% in both racemic and enantioenriched substrates (Table 2-3). Enantiomeric ratios (e.rs.) and enantiospecificity (e.s.) of the final coupled products were lower than expected when compared to the cross-coupled *(R)*-4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane products, reported by former Crudden lab members.[2, 62] While we were unable to find β-hydride elimination products using GCMS analysis or examining the crude NMR, it is possible that the stereochemistry was scrambled by β-hydride elimination followed by reinsertion (Scheme 2-17).

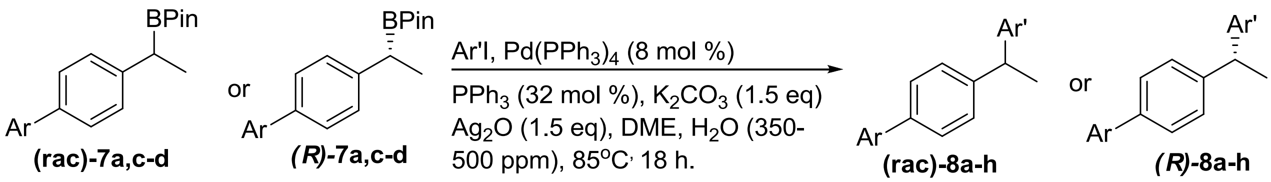


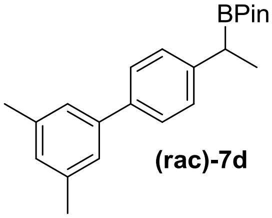
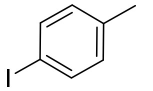
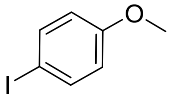
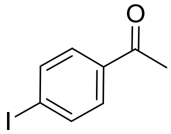
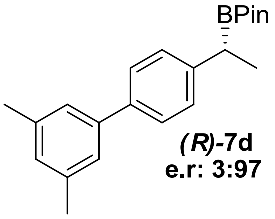
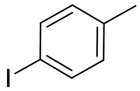
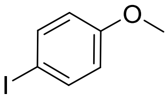
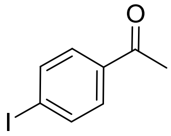
Scheme 2-17: Stereochemical Scrambling by β-Hydride Elimination and Hydride Insertion

Table 2-3: Suzuki Miyaura Cross-Coupling Reaction of Secondary Benzylic Boronic Esters[a]



Entry	Boronic Ester	Aryl Iodide	Compound Number	Yield (%)	e.r.	e.s. (%)
1	 **(rac)-7a**		**(rac)-8a**	52	n/a	n/a
2			**(rac)-8b**	63	n/a	n/a
3	 ***(R)*-7a** **e.r: 5:95**		***(S)*-8a**	64	81:19	68
4			***(R)*-8b**	50	13:87	81
5			**(rac)-8c**	50	n/a	n/a
6	 **(rac)-7c**		**(rac)-8d**	60	n/a	n/a
7			**(rac)-8e**	49	n/a	n/a
8			***(S)*-8c**	52	83:17	75
9	 ***(R)*-7c** **e.r: 5:95**		***(R)*-8d**	48	19:81	75
10			***(R)*-8e**	54	10:90	90



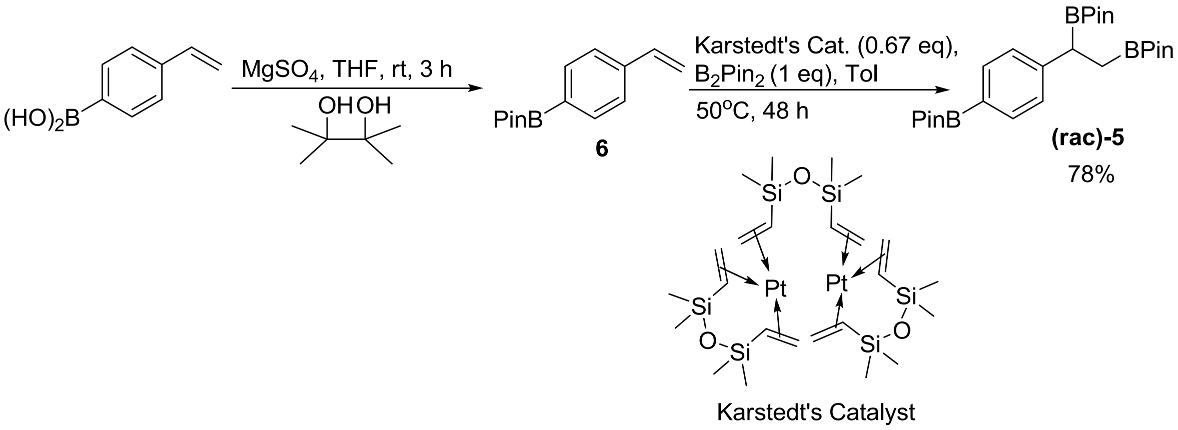
Entry	Boronic Ester	Aryl Iodide	Compound Number	Yield (%)	e.r.	e.s. (%)
11	 **(rac)-7d**		**(rac)-8f**	60	n/a	n/a
12			**(rac)-8g**	62	n/a	n/a
13			**(rac)-8h**[b]	46	n/a	n/a
14	 ***(R)*-7d** **e.r: 3:97**		***(S)*-8f**	68	90:10	85
15			***(R)*-8g**	73	11:89	80
16			***(R)*-8h**[b]	67	---	---

[a] General Conditions: ArI (1 equiv), BPin (1.5 equiv), 350-500 ppm H_2O. Water was purged with argon for 15-30 minutes prior to its addition to the reaction vial. All products isolated by column chromatography [b] Unable to be separated on SFC. Optical analysis by SFC, enantiomeric ratio (e.r.) is described in terms of S:R, with R being the major enantiomer with the exception of cross-coupled products of *p*-iodotoluene. Optical analysis by Supercritical Fluid chromatography, enantiomeric ratio is described in terms of R:S, based on extrapolation from previous literature precedent.[62]

2.3 Chemoselective Suzuki-Miyaura Cross-Coupling of Tris Boronic Ester Substrates

2.3.1 Synthesis and Cross-Coupling of Racemic Tris Boronic Ester Substrates

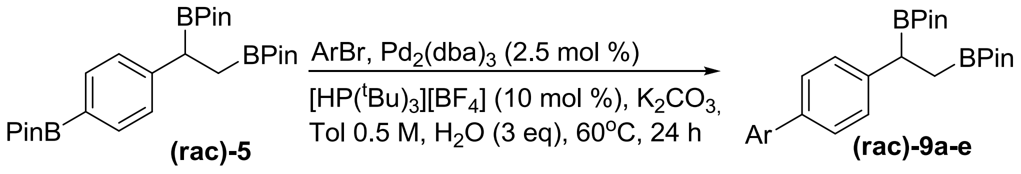
After completing the coupling of bis boronic ester substrates **(rac)-4** and ***(R)*-4**, we proceeded to the next goal of selectively cross-coupling a substrate that incorporates an aryl, secondary benzylic and linear boronic esters such as **(rac)-5** and ***(R)*-5**. The synthesis of starting material **(rac)-5** was achieved in a moderate yield using modified conditions previously published by Miyaura et al. in 1997 (Scheme 2-18).[92]

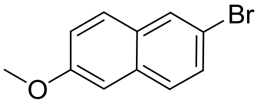
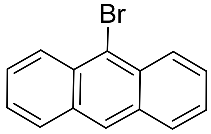
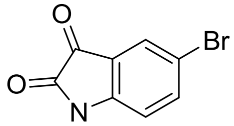
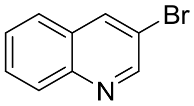
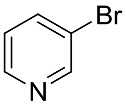


Scheme 2-18: Synthesis of Substrate (rac)-5 via Diboration using Karstedt's Catalyst[93]

Following our earlier synthetic strategy, coupling was performed at the aryl position first (Table 2-4). Bulky π-extended substrates, such as 2-bromo-6-methoxynapthylene (**(rac)-9a**) and 9-bromoanthracene (**(rac)-9b**), afforded the desired product in good yields. Attempts at cross-coupling heteroatom-containing substrates 3-bromoquinoline and 3-bromopyridine did not result in any discernible product. While pyridyl-containing substrates are an important class of coupling partners, they present an added difficulty due to their decreased nucleophilicity, sluggish transmetalation, and propensity for dimerization.[94]

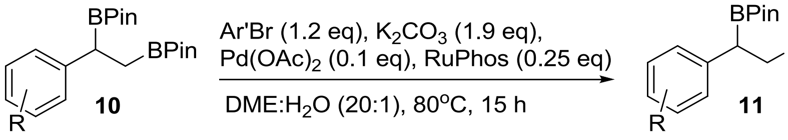
Table 2-4: Aryl Coupling of Tris Boronic Ester Substrate (rac)-5 with Extended π Systems [a]



Entry	Aryl Bromide	Compound Number	Yield (%)
1		**(rac)-9a**	81
2		**(rac)-9b**	74
3		**(rac)-9c**	NR
4		**(rac)-9d**	NR
5		**(rac)-9e**	NR

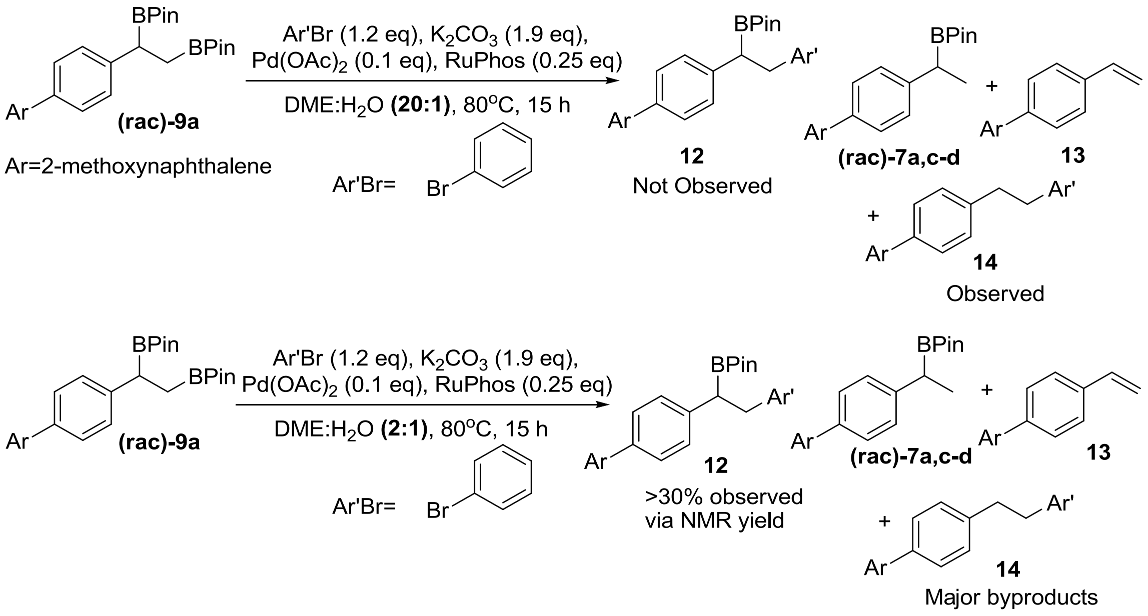
[a] Reaction conditions: Substrate (rac)-5 (1 equiv), ArBr (1.2 equiv), K_2CO_3 (3 equiv), Tol (0.5 M). Water purged prior to addition to reaction vial by argon for 15-30 minutes. All products isolated by flash column chromatography. NR: No reaction

The next step was the linear boronic ester coupling using conditions previously established by former post-doctoral fellow Kazem Ghozati and former graduate student Veronique Laberge (Scheme 2-19).[95]



Scheme 2-19: Diboronic Ester Coupling Conditions

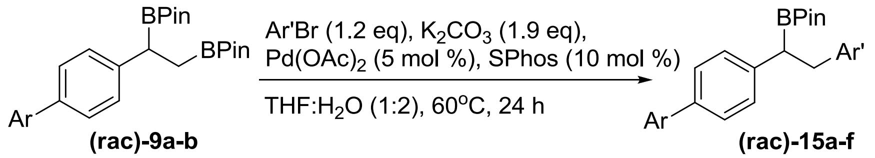
Unfortunately, with substrate **(rac)-9a**, the coupling failed and massive deborylations at both the linear and benzylic positions were observed (Scheme 2-20). Attempts at optimizing time and temperature were met with failure, however minimal product formation was observed when the solvent to water ratio was changed from 20:1 to 2:1.



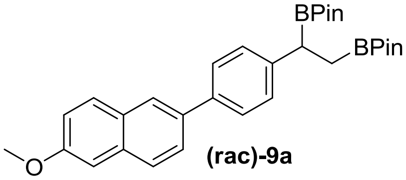
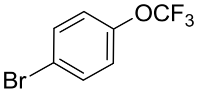
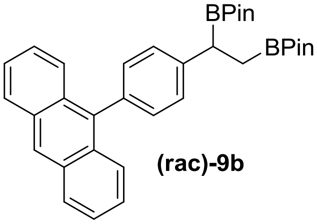
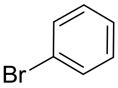
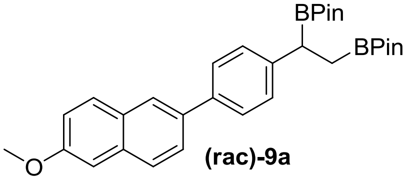
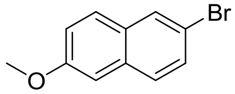
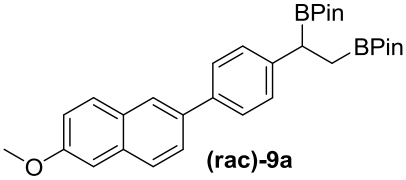
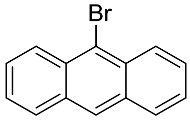
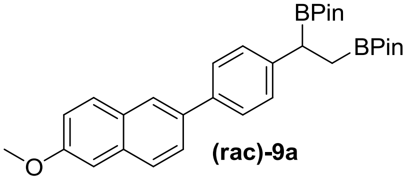
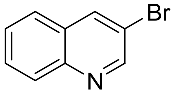
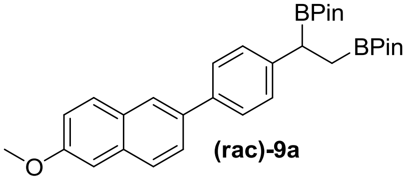
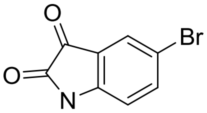
Scheme 2-20: Linear Coupling Attempts with 20:1 and 2:1 Solvent to Water

The final conditions using a surprising 1:2 ratio of solvent:water, as well as SPhos, was optimized with help from Dr. Masakazu Nambo and Dr. Daniel Canseco at ITBM in Nagoya, Japan as well as lab co-worker Chris Ziebenhaus (Table 2-5). While initial attempts yielded 40% and 42% of **(rac)-15a** and **(rac)-15b,** respectfully, these reactions were unable to be reproduced at similar yields. With the continued effort of Dr. Masakazu Nambo and Chris Ziebenhaus, yields for these reactions have now reached 70-80%. The new conditions include 5 mol % $Pd(OAc)_2$, 10 mol % SPhos, 1.5 equiv. of ArBr, 2 equiv. of K_2CO_3, a $THF:H_2O$ ratio of 1:2, and reaction temperatures of 60^{o} C for 24 hours. Prior to these new results, yields consistently dropped as low as 10-20% with no discernible explanation. Due to the weight of these materials, they were unable to be qualitatively analyzed by GCMS, so all experiments were examined by crude NMR. The most significant byproduct observed was styrene **13** (30-40%), while both starting material **(rac)-9a** (5-10%) and aryl halide (5-10%) were also recovered (Table 2-20). Based on results, with simple substrates, it appears that substrates with π-conjugation in the para position are much more sensitive to decomposition. Therefore, a possible reason for unreacted starting material could possibly be due to the high humidity found in lab during the summer months. Another explanation could be due to decomposition during purification. To remove volatile impurities (such as aryl halides and styrene derivatives), samples were heated to low temperature and high vacuum without actual distillation of the compound on a Kugelrohr distillation apparatus. It was thought this might avoid purification of racemic substrates on silica gel, however, I was unable to remove all contaminants using this method and short silica plugs were still required (as determined by crude NMR). Attempts to couple bulky substrates and substrates containing heteroatoms in the linear position failed.

Table 2-5: Attempted Linear Coupling [a]



(rac)-9a-b → **(rac)-15a-f**

Entry	Boronic Ester	Aryl Bromide	Compound Number	Yield (%)
1	 **(rac)-9a**		**(rac)-15a**	40
2	 **(rac)-9b**		**(rac)-15b**	42
3	 **(rac)-9a**		**(rac)-15c**	NR
4	 **(rac)-9a**		**(rac)-15d**	NR
5	 **(rac)-9a**		**(rac)-15e**	NR
6	 **(rac)-9a**		**(rac)-15f**	NR

[a] Reaction conditions: Substrate 9a-b (1 equiv), THF:H_2O (1:2).Water was purged with argon prior to its addition to the reaction vial. All reactions were subjected to Kugelrohr distillation to remove volatile impurities. A short silica gel plug (60 mL glass frit, 2 inches of silica gel) was used to further purify the product.

The conversion of **(rac)-9a-b** to **(rac)-15a-b** is a remarkable reaction considering the ratio of water to solvent required. In 2014, the Morken group discussed the effect of water and proposed that there may be a cooperative binding of a hydroxide by the benzylic BPin resulting in an 'ate' complex (C).[96] Alternatively, Lewis acidity enhancement of the linear BPin via coordination of the benzylic neighbor (D) may aid in activating the linear BPin (Figure 2-1).[96] Examination of the stereochemical outcome provides insight into the operative reaction mechanism as C would occur via an outer-sphere path resulting in inversion of stereochemistry, while its counterpart D would proceed through an inner-sphere pathway retaining the stereochemical configuration.[96]

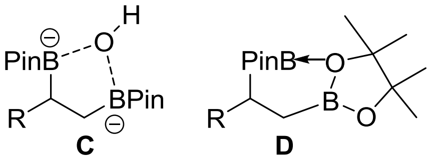
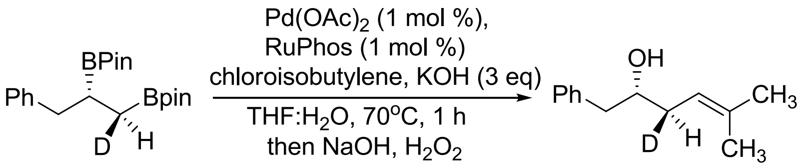


Figure 2-1: Formation of 'ate' complex (C) vs Enhanced Lewis Acidity via Coordination (D) for Activation of Linear BPin

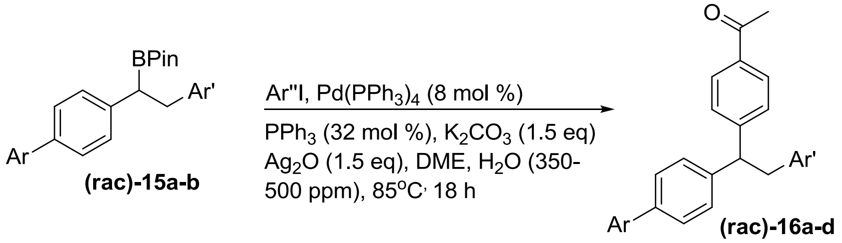
Isotopically labeled substrates were prepared and it was found that the stereochemical information was retained and an inner-sphere transmetalation may be occurring (Scheme 2-21).[96] In our case, increasing the ratio of water from 20:1 DME:H_2O to 1:2 THF:H_2O may facilitate a faster transmetalation.



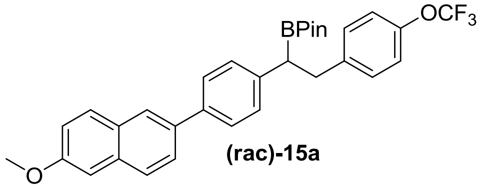
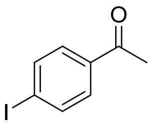
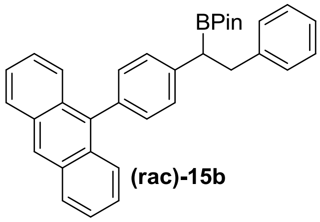
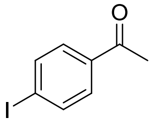
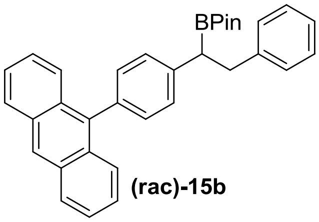
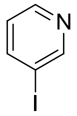
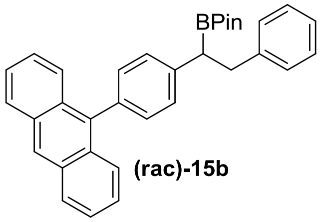
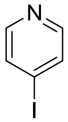
Scheme 2-21: Isotopic Studies to Determine Inner (D) or Outer-Sphere (C) Mechanism

Using conditions that had been previously developed in our lab for coupling at the benzylic position, the reactions of compounds **(rac)-15a-b** were attempted. Both compounds **(rac)-16a-b** were obtained in a low yield (Table 2-6). Once again, attempted couplings of 3-iodopyrdine and 4-iodopyridine were met with failure and no product formation was observed. A pure NMR spectrum of **(rac)-16b** was unable to be obtained due to the low amount of product isolated (0.5-2 mg). This is partially due to the low yields of at both positions.

Table 2-6: Benzylic Coupling for Synthesis of Fully Coupled Racemic Tris Boronic Ester Product [a]



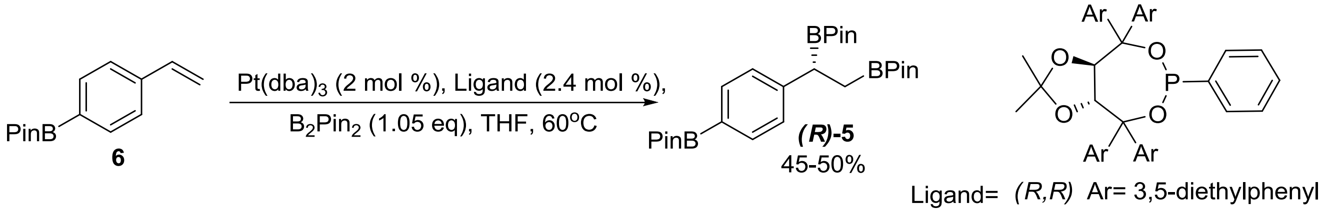
(rac)-15a-b → **(rac)-16a-d**

Entry	Starting BPin	Aryl Iodide	Compound Number	Yield (%)
1	 **(rac)-15a**		**(rac)-16a**	43
2	 **(rac)-15b**		**(rac)-16b**	49
3	 **(rac)-15b**		**(rac)-16c**	NR
4	 **(rac)-15b**		**(rac)-16d**	NR

[a] Reaction conditions: Substrate (rac)-15a-b (1.5 equiv), ArI (1 equiv). 350-500 ppm H_2O. Water was purged with argon for 15-30 minutes prior to its addition to the reaction vial. Products isolated by Preparatory Thin Layer Chromatography PTLC.

2.3.2 Synthesis and Cross Coupling of Enantioenriched Tris Boronic Ester Substrates

Synthesis of enantioenriched substrate ***(R)*-5** followed a published literature procedure that co-worker Chris Ziebenhaus further optimized (Scheme 2-22).[97] Optical purity was not assessed due to the unstable nature of the compound to be oxidized. However, since initial coupling does not take place at the enantioenriched center it was assumed that no racemization would occur.

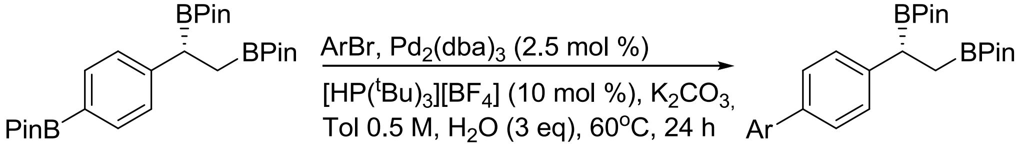


Scheme 2-22: Synthesis of Enantioenriched Tris Boronic Ester *(R)*-4

Subsequent aryl coupling afforded the desired product in good yield (Table 2-7). Unfortunately, compounds ***(R)*-9a-b** had lower enantiomeric ratios than previous reported compounds using the same enantioenriched ligand system.[96] While we are currently investigating this phenomenon, it is hypothesized that both electronic factors as well as β-hydride elimination during synthesis of substrate ***(R)*-5** could lead to decreased retention of stereochemistry.

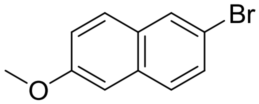
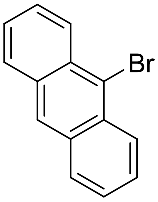
Following aryl coupling, ***(R)*-9a-b** were cross-coupled with 4-(trifluoromethoxy)benzyl bromide and bromobenzene, respectively, to form products ***(R)*-15a** (35%) and ***(R)*-15b** (28%) in low yield (Table 2-8). These compounds were not subjected to Kugelrohr distillation and instead were purified by short silica gel plugs to avoid decomposition and possible racemization. Optical purity assessment of the enantioenriched diol alcohols to the enantioenriched mono-alcohols showed no change in stereoretention from ***(R)*-9a** (87:13) and ***(R)*-9b** (89:11) to ***(R)*-15a** (13:87) and ***(R)*-15b** (11:89), respectively. These results confirm what was hypothesized previously, that reactions not taking place at the enantioenriched center do not decrease optical purity.

Table 2-7: Aryl Coupling of Enantioenriched Tris Boronic Ester Substrate to Afford Diboronic Ester Product [a]



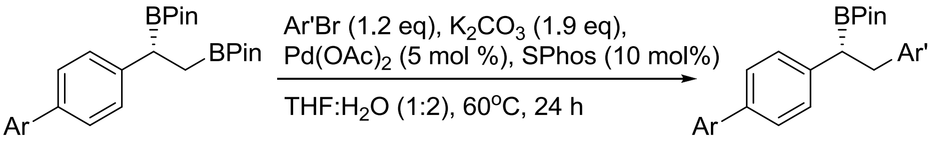
***(R)*-5**

***(R)*-9a-b**

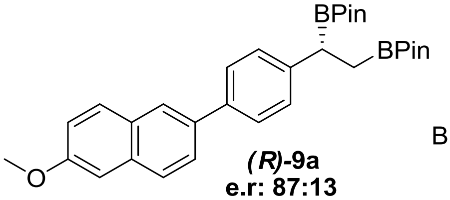
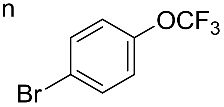
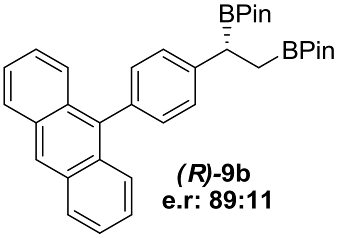
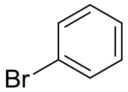
Entry	Aryl Bromide	Compound Number	Yield (%)	e.r.
1		***(R)*-9a**	79	87:13
2		***(R)*-9b**	76	89:11

[a] Reaction conditions: Substrate *(R)*-5 (1 equiv), ArBr (1.2 equiv), K_2CO_3 (3 equiv), Tol (0.5 M). Water was purged with argon for 15-30 minutes prior to its addition to the reaction vial. Products isolated by silica gel plug, see supporting information for eluent conditions. Optical analysis by Supercritical Fluid chromatography, enantiomeric ratio is described in terms of S:R, with S being the major enantiomer when oxidized to the respective alcohol. Please see supporting information for characterization and SFC data for the respective alcohols.

Table 2-8: Linear Coupling of Substrates 9a and 9b [a]



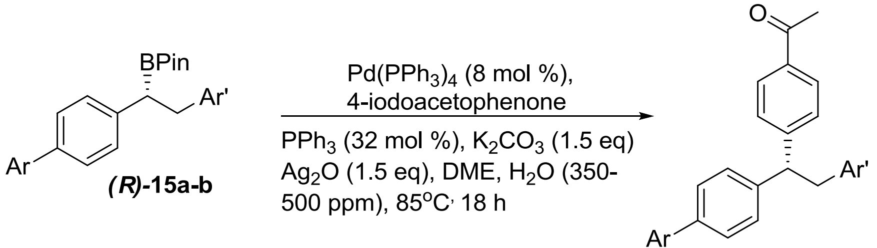
***(R)*-9a-b** → ***(R)*-15a-b**

Entry	Boronic Ester	Aryl Bromide	Compound Number	Yield (%)	e.r.	e.s. (%)
1	 ***(R)*-9a** **e.r: 87:13**		***(R)*-15a**	35	13:87	>99
2	 ***(R)*-9b** **e.r: 89:11**		***(R)*-15b**	28	11:89	>99

[a] Reaction conditions: Substrate ***(R)*-9a-b** (1 equiv), H_2O degassed for minimum 20 minutes under a medium stream of argon. All yields are isolated via silica plug. Optical analysis by Supercritical Fluid chromatography, enantiomeric ratio is described in terms of S:R, with R being the major enantiomer when oxidized to the respective alcohol. Please see supporting information for characterization and SFC data for the respective alcohols.

Finally, completing the enantioenriched tris boronic ester cross-coupling, substrates ***(R)*-15a** and ***(R)*-15b** were subjected to the same benzylic conditions utilized for their racemic counterparts to form products ***(R)*-16a** and ***(R)*-16b** in poor yields (33% and 29%, respectively). Assessment of optical purity demonstrated that both compounds were coupled with high retention of stereochemistry 87% (***(R)*-16a**) and 93% (***(R)*-16b**) (Table 2-9). These values fall into an expected range that was observed when coupling the enantioenriched bis boronic ester substrates earlier in this chapter (**(rac)** and ***(R)*-8a-h**). Therefore, we have been able to successfully cross-couple a substrate containing *sp*^{2}, linear *sp*^{3}, and secondary benzylic *sp*^{3} in the presence of each other with a minimal loss of stereoretention and without the need of protecting groups, although work needs to be done to improve yields.

Table 2-9: Final Benzylic Coupling Step with High Retention of Stereochemistry [a]

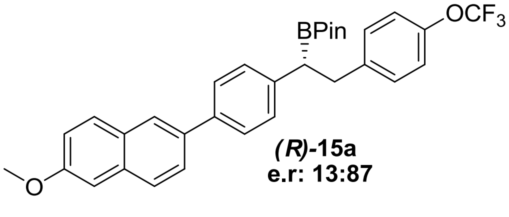
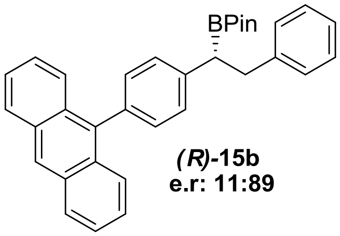


***(R)*-15a-b**

Pd(PPh$_3$)$_4$ (8 mol %), 4-iodoacetophenone

PPh$_3$ (32 mol %), K$_2$CO$_3$ (1.5 eq) Ag$_2$O (1.5 eq), DME, H$_2$O (350-500 ppm), 85^{o}C, 18 h

***(R)*-16a-b**

Entry	Boronic Ester	Compound Number	Yield (%)	e.r.	e.s. (%)
1	 ***(R)*-15a** **e.r: 13:87**	***(R)*-16a**	33	18:82	87
2	 ***(R)*-15b** **e.r: 11:89**	***(R)*-16b**	29	13:87	93

[a] Reaction conditions: ArI (1 equiv), *(R)*-15a-b (1 equiv), 350-500 ppm H$_2$O. Water was purged with argon for 15-30 minutes prior to its addition to the reaction vial. All yields isolated by PTLC. Optical analysis by Supercritical Fluid chromatography, enantiomeric ratio is described in terms of S:R, with R being the major enantiomer.

2.3.3 Synthesis and Optical Purity Assessment of Mono- and Diol Alcohols

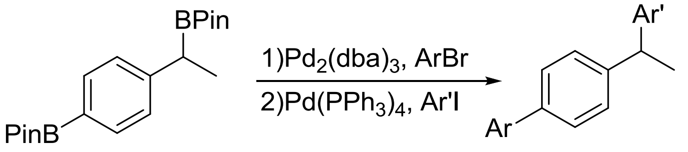
To assess optical purity, oxidations of compounds ***(R)*-9a-b and *(R)*-15a-b** were initially attempted using standard conditions that were applied to the bis boronic ester substrates. Unfortunately, the conditions were met with failure and only starting material and decomposition products were obtained. Instead, a previously reported one-pot oxidation procedure was used and, while a mixture of starting material and deborylated byproducts was observed, we were successfully able to isolate the sought after alcohols and analyze them accordingly.[97]

Compounds **(rac)-5** and ***(R)*-5** were treated under standard aryl coupling conditions, followed by additions of 3 M NaOH and 30% H_2O_2 to afford their respective racemic and enantioenriched diol alcohols. Oxidation of **(rac)** and ***(R)*-9a-b** to their respective diols proved to be extremely difficult. Crude ^{1}H NMR spectra showed major and minor byproduct of styrene as well as starting material. While these reactions were performed on a 0.1 mmol scale, and preparatory thin layer chromatography was utilized to purify the products since yields of the actual diols were extremely low (<10 mg). Due to time restrictions, oxidation procedures were not optimized.

Enantioenriched compounds ***(R)*-9a-b** and ***(R)*-15a-b** were oxidized using the same 1 pot procedure used in the synthesis of the diol and mono alcohols. All enantiomeric ratios have been reported in their respective tables (Table 2-8 and 2-7, respectively). As described previously, there was no inherent change of stereochemistry between both the diol and mono-alcohols. Synthesis and isolation of the mono-alcohols was much easier than the previous diols. However, since yields were still low (<10%), preparatory thin layer chromatography (PTLC) was once again used for purification.

2.4 Attempted One Pot Iterative Cross-Coupling of Both Bis and Tris Boronic Ester Substrates

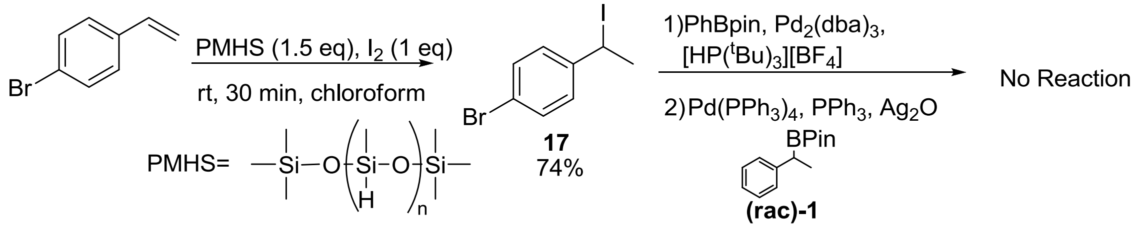
In an ideal scenario, the cross-coupling conditions that have been previously described in subchapters would be adequate for an iterative one-pot coupling of both bis and tris substrates **(rac)-4** and **(rac)-5**, respectively. However, previous attempts by former lab members had met with failure (Scheme 2-23).[85]



(rac)-4 **(rac)-8a-h**

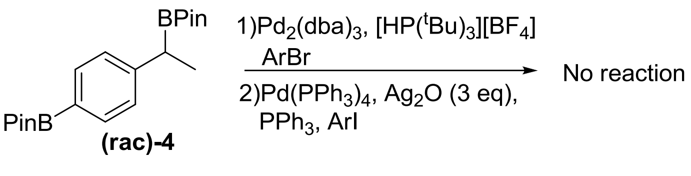
Scheme 2-23: Early Attempts at Iterative One-Pot Cross-Coupling of Bis Boronic Ester (rac)-4

Early procedures that failed involved aryl coupling followed by the standard benzylic conditions. These reactions unfortunately require the use of different palladium, ligand, aryl halide sources and water concentrations which all play a vital role in the success of each step. While it still remains unknown exactly which conditions (or mixture of conditions) are preventing product formation, we attempted to circumvent one of these problems by including two different halides (bromine and iodine) in the same starting material **17** (Scheme 2-24). It was hypothesized that when performing back-to-back couplings, any residual halide from the aryl coupling step could react with the Ag_2O to form AgBr, reducing the overall amount of Ag_2O being used to overcome the already slow transmetalation in the benzylic coupling step. Therefore, if both halides were found in the same starting material, the Ag_2O wouldn't be as likely to be converted to AgBr, reacting only at the benzylic position and not the aryl. After the allotted reaction time, a secondary benzylic boronic ester was used as a coupling partner at the secondary benzylic iodine position. While I used an unconventional boronic ester source, it was hypothesized that if this was successful, enantioenriched chirality could be installed at the secondary benzylic boronic ester. Unfortunately, there was no product observed and only starting material was recovered.



Scheme 2-24: Attempted One-Pot Iterative Coupling Using a Substrate Containing an *sp*^{2} Bromide and *sp*^{3} Iodide

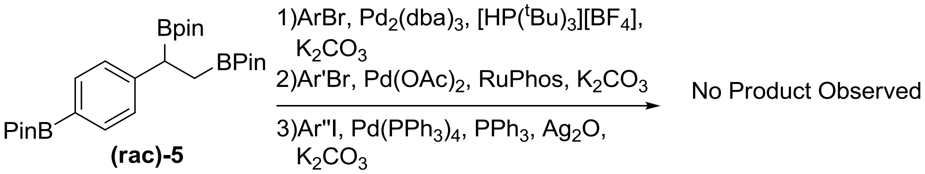
Following this, we changed the amount of silver oxide needed in the benzylic coupling to 3 equivalents assuming that residual aryl bromide from the initial step might aid in the consumption of Ag_2O to AgBr thus halting the already sluggish transmetalation. Unfortunately, no product was observed again (Scheme 2-25).



Scheme 2-25: Iterative Cross-Coupling Using 3 Equivalents of Ag_2O

Following this, we decided to examine the conditions used in previous failed one pot coupling attempts by former group members. Along with Ag_2O, both water and base play important roles in the outcome of the final coupled product. Previous attempts of adding water and base in both the aryl and benzylic cross-coupling steps could have deleterious effects. It was hypothesized that some amount of water and base could be carried over from the aryl coupling conditions, and be sufficient enough for the benzylic coupling to follow immediately after (solvent would not be removed). However, no product formation was observed. Further optimization was not performed on the bis boronic ester one pot reaction.

Iterative cross-coupling with the tris boronic ester using similar techniques to the bis boronic ester were attempted (Scheme 2-26). Two methods were attempted, one where everything was added together and the reaction was left to sit for one night at 60°C then another night at 85°C, and sequential addition. Sequential addition seemed like the most viable method, therefore modification of time, temperature, water concentration, exclusion of base and water, and increasing Ag_2O were screened through different combinations of each factor. All attempts however, were met with failure and showed no product formation.



Scheme 2-26: Iterative Cross-Coupling of a Tris Boronic Ester Substrate

Since we were not able to achieve a one-pot procedure with the bis substrate, it was not surprising that the tris also failed. Complications of achieving a successful one pot coupling with the tris can arise from the three different palladium and ligand sources, and three different aryl halides to complicate the oxidative addition and transmetalation steps. For both the bis and tris substrates to be successful, a procedure that involves using the same source of palladium and ligand is required as well as optimizing the conditions so that each aryl halide is 100% consumed to prevent cross-coupling of the wrong aryl bromide in the linear position. Furthermore, the concentration of water and base in each step would have to be fine tuned to aid in coupling at the already sensitive benzylic position.

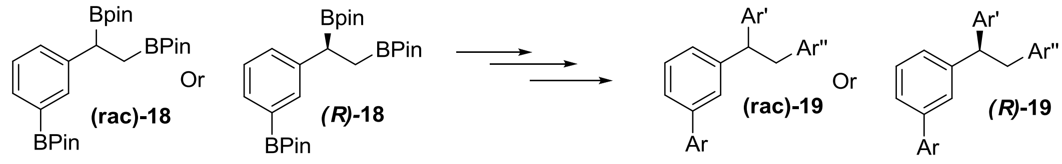
2.5 Conclusions and Future Work

We have been able to successfully cross-couple both racemic and enantioenriched bis and tris boronic ester substrates with high retention of stereochemistry using conditions that had been previously established in our group.[62] Coupling of the enantioenriched bis boronic ester substrate proceeded through conditions previously optimized by a former lab member and, while stereoretention was high, it is believed that some β-hydride elimination is occurring to give us slightly lower than expected enantioselectivity.

Coupling of the tris boronic ester substrate required re-optimization of linear coupling conditions. Coupling at the linear position on tris substrates **(rac)-9a-b** and ***(R)*-9a-b** was achieved by switching from RuPhos to SPhos and lowering both the ligand and palladium loadings while increasing the ratio of solvent:water from 20:1 to 1:2.

Oxidation of cross-coupling products from tris boronic esters **(rac)-5** and ***(R)*-5** required changing the procedure from the standard NaOH/H_2O_2 method used during oxidation of bis boronic ester substrates to a one-pot coupling followed by immediate oxidation using a 3 M NaOH/H_2O_2 method. While yields were low (as seen in the bis substrates), we were still able to isolate and examine the optical purity of both the diol and mono-alcohols.

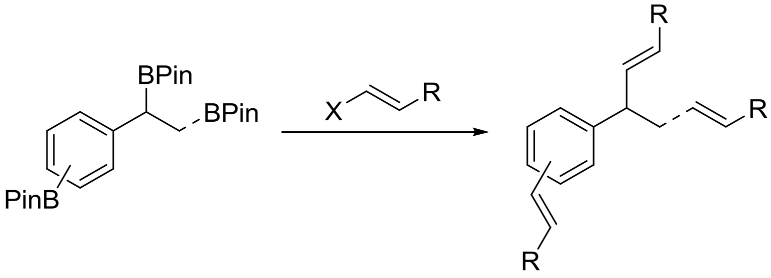
Immediate future research will include examination of meta tris boronic ester substrate and fully coupling both the racemic and enantioenriched substrates (Scheme 2-27).



Scheme 2-27: Future Cross-Coupling of Meta Tris Boronic Ester Racemic and Enantioenriched Substrates

Coupling conditions that have been previously developed can be utilized in a similar manner to that of the para tris boronic esters **(rac)-5** and ***(R)*-5.** Currently, graduate student Chris Ziebenhaus is working towards coupling such meta-substituted compounds **(rac)-19** and ***(R)*-19** to form drugs that have the same structure backbone. Interestingly, coupling of the linear position seems to be more effective using conditions similar to those developed by former post-doctoral fellow Kazem Ghozati and former masters student Veronique Laberge.

Future research into cross-coupling vinylic or allylic halides into each aryl, linear and benzylic position would be the next step (Scheme 2-28).

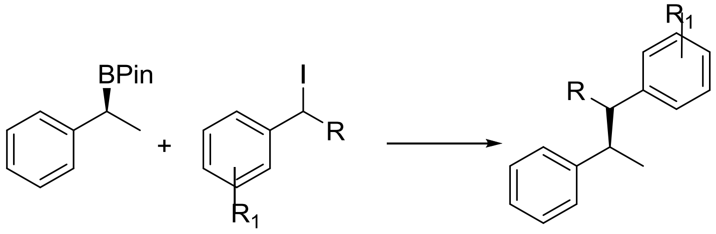


Scheme 2-28: Olefinic Coupling of a Boronic Ester

Chapter 3

Future Work

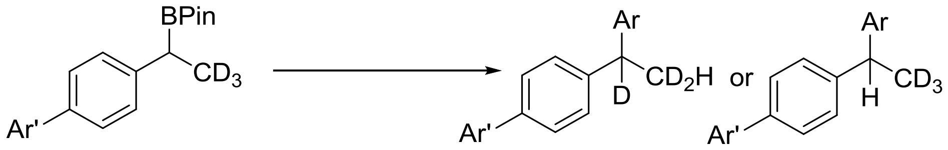
Cross-coupling at a secondary benzylic position has been hailed as difficult, especially under enantioselective conditions. Previous to the work developed by the Crudden group,[11, 62] cyclopropyl organoboron species were by far the most well studied examples, being immune to β-hydride elimination.[58a] However, expansion to larger ring systems exposed problems such as chain-walking and β-hydride elimination/addition causing racemization of enantioenriched substrates.[61] Following the development of our cross-coupling conditions,[11] a major step forward would be to expand the breadth of the reaction further to include secondary sp^3 halides and even more so, those with stereochemistry (Scheme 3-1). By expanding the scope of available partners, we could dramatically increase the amount of possible products, and find new uses for this reaction in target-oriented synthesis.



Scheme 3-1: Cross-coupling of Two Secondary Benzylic sp^3 Partners

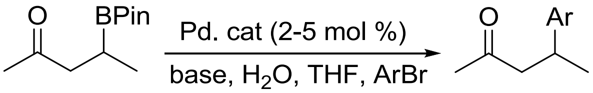
The development of such a reaction would have direct implications within the pharmaceutical industry for the total synthesis of natural products and drugs.

An additional area of the reaction that could use improvement is addressing the small loss of stereochemistry that occurs with some substrates. For example, cross-coupling of substrates ***(R)*-4** and ***(R)*-5** resulted in a notable decrease in stereoretention after coupling at the benzylic position. Investigation into the possibilities of β-hydride elimination/addition mechanism would shed light on the observed decrease in stereofidelity in the desired final product (Scheme 3-2). By using deuterium labeled starting materials, we would be able to examine the results by ^{1}H NMR using an internal standard to determine the ratio (if any) of deuterium incorporated at the benzylic versus the linear position. Any observed scrambling would confirm this mechanistic hypothesis.



Scheme 3-2: Investigation into β-Hydride Elimination/Addition

Previous work reported by former Ph.D lab member Ben Glasspoole noted that for our cross-coupling conditions to be successful, the boronic ester had to be in close proximity to a π-system, such as an aryl ring or double bond.[2] While we have since expanded this work to examine cross-coupling products in allylic systems and the effect on α : γ-selectivity,[64] we have not explored the possibilities of other π-systems such as carbonyl-containing substrates (Scheme 3-3). Previously reported systems such as α-(acylamino)benzylboronic esters,[98] and 2-chloroacetates[99] have seen success in both retention of stereochemistry and configuration and could be examined in our case to see which directing group takes precedence.



Scheme 3-3: Cross-coupling at γ Positions to π Systems

Ideally, further development of this work would not require protecting groups, proceed with high retention of stereochemistry and would not contain any other adjacent π-systems other than the already pre-installed group.

Furthermore, to complete the cross-coupling work using boronic esters developed by the Crudden group, mechanistic and kinetic studies should be undertaken to fully understand the role of Ag_2O. This could be achieved using Electron Spray Ionization Mass Spectrometry (ESI-MS) *in situ*, to monitor reactions components for cation/anions that fit theoretical data. ESI-MS has the benefit of being able to detect short lived or low concentration of intermediates and data acquisition is fast.[100] Recent studies have shown that intensities of intermediates, regents and products can be monitored over time.[100] These data would provide useful information into not only the role of Ag_2O, but also the nature of the catalyst and intermediates during transmetalation.[100]

Once the role of Ag_2O has been determined, optimization of the system as a whole can be performed. This includes the development of reactions that utilize other cost efficient additives that would potentially perform the same role as Ag_2O. Finally, tuning both the nature of the palladium catalyst and ligand could afford a more efficient system, with higher yields, lower reaction times, as well as greater stereoretention. This work would also aid in development of an efficient one-pot cross-coupling method of bis and tris boronic ester substrates previously studied in our group (racemic and enantioenriched substrates **4** and **5** respectively), which previously has been unsuccessful by other methods reported by former and current members of the Crudden group.

Chapter 4

Experimental

4.1 General Considerations and Methods

All cross coupling reactions were set up in a nitrogen-filled glovebox. All reagents used in these reactions were subjected to literature purification. Solvents were dried by refluxing them over their proper drying agents, followed by distillation into Schlenk ware. Toluene, tetrahydrofuran (THF) and 1,2-dimethoxy ethane (DME) were refluxed over sodium metal for 24 hours. Benzophenone was used as an indicator for dryness prior to distillation. Subsequently, each solvent was deoxygenated by a freeze thaw pump cycle (3 times) and stored over 4 Å molecular sieves. Boronic esters, vinyl boronic esters[86] and acids and bases were dried under high vacuum overnight before use and stored in the glove box freezer at -20°C. $Pd_2(dba)_3$, $Pd(PPh_3)_4$, $[Rh(COD)_2][BF_4]$ and Ag_2O were used in the glovebox as purchased from Aldrich, Strem, and Acros, respectively. Thin Layer Chromatography was performed on aluminum-backed silica plates and visualized by UV (254, 365 nm). The indicators utilized to stain were phosphomolybdic acid, permanganate, and 2,4-dinitrophenylhydrazine. Column chromatography was performed by using flash grade silica (Silicycle, 40-63 µm particle size, 60 Å porosity) and reagent-grade solvents. All GC-MS spectra were obtained using an Agilent Technologies 5975CVL-MSD (triple axis detector) with a capillary measuring 30 m by 250 µm by 0.25 µm nominal, 250 inlet, splitless detector. NMR spectroscopy was performed on a Bruker Advance 400 MHz spectrometer unless otherwise specified. All NMR samples were prepared using $CDCl_3$. High Resolution Mass Spectroscopy (HRMS) was performed on the Voyager DE STR MALDI TOF instrument. All infrared spectra were obtained using a Varian 640 Fourier Transform Infrared Spectrometer (FTIR). Pinacolborane (HBPin) and catecholborane (HBCat) were distilled under reduced pressure and stored in the glovebox below -20 ^{o}C. It should be noted that the assigned absolute stereochemistry of *(R)* (for all hydroborated and cross-coupled products) is based off of previous work performed in the Crudden lab, there were no further experiments performed to analyze this for all compounds presented in this thesis.[2, 23, 62]

Method A: Synthesis of Racemic Di Boronic Ester Substrates

In a nitrogen-filled glove box, $[Rh(COD)_2][BF_4]$ (5 mol %, 0.044 mmol, 89.3 mg) and DPPB (5 mol %, 0.044 mmol, 93.9 mg) were combined in a vial with 2 mL of THF and stirred for 10 minutes. 4,4,5,5-Tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **6** (0.88 mmol, 0.50 mL) was added followed by HBPin (1.03 mmol, 0.15 mL). The reaction was capped and left to sit at room temperature in the glove box for 24 hours. The reaction was filtered and impurities removed by heating under vacuum on a Kugelrohr distillation apparatus for 3 hours at 90^{o}C. Following this, purification was achieved by flash column chromatography using 5% ethyl acetate : 95% hexanes.

Note: Synthesis of $[Rh(COD)(DPPB)][BF_4]$ follows literature procedures.[101]

Method B: Synthesis of Enantioenriched Di Boronic Ester Substrates

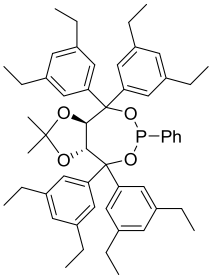
In a nitrogen-filled glove box, $[Rh(COD)_2][BF_4]$ (5.7 mol %, 24 mg) and *(R)*-BINAP (6.8 mol %, 42.3 mg) were taken up in 4 mL of DME and stirred in a Schlenk tube for 10 minutes. Subsequently, 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **6** (2.62 mmol, 1.1 eq, 603 mg) was added to yield a bright orange solution. In another oven-dried round bottom flask, HBCat (2.9 eq, 3.46 mmol, 415 mg) was taken up in 2 mL of DME. Both solutions were taken out of the glove box and cooled to -78^{o}C. HBCat was then cannula transferred to the Schlenk tube and the reaction mixture stirred for 5 hours. Under a stream of argon, pinacol (8.63 mmol, 1.02 g) was then added and the solution was left to warm to room temperature and stir overnight. The reaction mixture was loaded onto a flash column immediately after the reaction for purification using 5% ethyl acetate: 95% hexanes.

Method C: Synthesis of Racemic Tri Boronic Ester Substrates

In a oven-dried pressure tube, $Pt(dba)_3$ (2 mol %, 0.13 mmol, 120 mg) and B_2Pin_2 (1.05 eq, 6.99 mmol, 1.775 g) were combined with 3 mL of THF in the glove box. The reaction mixture was removed from the glove box and stirred at 80^oC for 30 minutes and then subsequently cooled to room temperature and brought back into the glove box. 4,4,5,5-Tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **6** (1 eq, 6.66 mmol, 1.53 g) was added to the reaction mixture. The pressure tube was sealed, brought back out of the glove box and the reaction mixture stirred at 60^oC overnight. The reaction was transferred to a round bottomed flask and concentrated *in vacuo.* Impurities were removed by heating under vacuum on a Kugelrohr distillation apparatus at 100 °C for 3 hours. Finally, the reaction was purified through a 50 mL silica plug with 10% diethyl ether: 90% hexanes.

Method D: Synthesis of Enantiomerically Enriched Tri Boronic Ester Substrates

In an oven-dried pressure tube, $Pt(dba)_3$ (2 mol %, 0.13 mmol, 120 mg), B_2Pin_2 (1.05 eq, 6.99 mmol, 1.775 g) and Ligand 1 (2.4 mol %, 127 mg) were combined in the glove box with 3 mL of THF. The pressure tube was removed from the glove box and the reaction mixture stirred at 80^oC for 30 minutes. Subsequently it was cooled and brought back into the glove box where 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **6** (1 eq, 6.66 mmol, 1.53 g) was added along with 1 mL of THF. The reaction mixture was left to stir for 3 hours at 60^oC. The reaction was then concentrated and purified via a silica plug using 100 mL (each) of 2.5% ethyl acetate: 97.5% hexanes followed by 10% ethyl acetate: 90% hexanes and finally 100% ethyl acetate.



Ligand 1: (3aR,8aR)-4,4,8,8-tetrakis(3,5-diethylphenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine

Method E: Aryl Coupling Conditions

In a nitrogen-filled glovebox, 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane **(rac)-4** (1 eq, 0.5 mmol, 179.1 mg), 1-bromo-3,5-dimethylbenzene (1.2 eq, 0.6 mmol, 132.4 mg), K_2CO_3 (3 eq, 1.5 mmol 207 mg), $Pd_2(dba)_3$ (0.025 eq, 0.0125 mmol 12 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.05 mmol, 14.5 mg) were weighed into in a 1 dram vial along with 1 mL of toluene. Around the threads of the vial, Teflon tape was wrapped and the vial was capped with a PTFE septum cap. The solution was removed from the glove box (caps wrapped in Teflon and electrical tape) and water (27 μL) (degassed with argon, 15-20 min) was added via syringe. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 60^{o}C for 24 hours. The solution was then filtered through diatomaceous earth and eluted with Et_2O. In the case of racemic compounds, impurities in the crude reaction mixture were subsequently removed by heating under vacuum on a Kugelrohr distillation apparatus at 90^{o}C for 3 hours, followed by flash chromatography. In the case of enantiomerically enriched compounds, these were only purified via flash column chromatography.

Method F: Benzylic Coupling Conditions

In a nitrogen-filled glove box, 1-4'-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)biphenyl-4-yl)ethanone **(rac)-7a** (1.5 eq, 0.15 mmol, 50.7 mg), *p*-iodotoluene (1 eq, 0.10 mmol, 23.2 mg), Ag_2O (1.5 eq, 0.15 mmol, 34.7 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20.7 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 9.2 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8.4 mg) were added to a 1 dram vial along with 2.3 mL of DME. DME (0.240 mg) was added to a separate vial. Both vials had their threads wrapped with Teflon tape before being capped with a PTFE septum cap. Both solutions were removed from the glove box and had their caps once again wrapped in Teflon and electrical tape. To the 0.240 mL of DME, degassed water (14 μL) was added (degassed via argon, 15-20 min). From the H_2O/DME solution, an aliquot (14 μL) was taken and added to the Bpin reaction mixture. The top of the cap was filled with Teflon tape and sealed with electrical tape. Subsequently, the reaction mixture was stirred vigorously at 85^{o}C for 24 hours. The solution was then filtered through a diatomaceous earth plug with Et_2O, concentrated then purified via flash column chromatography. In the case of racemic compounds, impurities were subsequently removed by heating under vacuum on a Kugelrohr distillation apparatus at 100^{o}C for 3 hours followed by flash chromatography. In the case of enantioenriched compounds, these were only purified via column/PTLC.

Method G: Linear Coupling Conditions

In the glove box, to an oven-dried Schlenk tube 2-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-15a** (1.0 eq, 0.05 mmol, 26.7 mg) was added along with $Pd(OAc)_2$ (0.1 eq, 15.7 mg), SPhos (0.1 eq, 0.005 mmol, 20 mg), K_2CO_3 (2 eq, 0.10 mmol, 14 mg) and 1-bromo-4-(trifluoromethoxy)benzene (1.5

eq, 0.075 mmol, 11.5 mg). To this mixture, 0.05 mL of THF was added and the reaction mixture was capped and removed from the glove box. Degassed (15-20 min) water (0.1 mL) was then added and the reaction mixture was subsequently stirred at 60^{o}C overnight. Following this, the reaction was filtered through a silica plug and eluted with 100% DCM into a round bottom flask and concentrated *in vacuo*. In the case of racemic compounds, impurities were subsequently removed by heating under vacuum on a Kugelrohr distillation apparatus at 90^{o}C for 3 hours followed by flash chromatography flash chromatography. In the case of enantioenriched compounds, these were only purified via column/PTLC.

Method H: Oxidation of Di Boronic Ester Substrates and SFC Sample Preparation

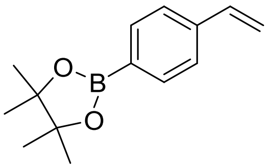
In a nitrogen-filled glove box, 2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7d** (0.061 mmol, 24 mg) was added into an oven-dried round bottomed flask and capped with a septum. The round bottomed flask was brought out of the glove box and put under a flow of argon. Diethyl ether (2 mL freshly distilled) was added. To an oven-dried 4 dram vial (caped with a septum and cooled under argon flow), 1.5 mL of both 1 M NaOH and 30% H_2O_2 was added. Both solutions were cooled in an ice bath. Subsequently 1.5 mL of the NaOH/H_2O_2 solution was added to the Bpin solution and stirred for 1 hr in the ice bath. After the allotted time, the solution was quenched with NaOH and NH_4Cl. Finally, the aqueous layer was washed 3 times with diethyl ether, dried with $MgSO_4$, filtered and then concentrated via rotary vacuum. Oxidations were quantitative as determined by GCMS. Each SFC sample was prepared utilizing 1 mg or less of crude product dissolved in HPLC grade hexanes with 1 drop of HPLC grade MeOH.

Method I: Oxidation of Tri Boronic Ester Substrates and SFC Sample Preparation

Samples were prepared using Methods E and G on a 0.10 mmol scale. After the appropriate reaction time, the vial was cooled to 0°C where 0.4 mL of 3 M NaOH was added followed by the drop wise addition of 0.2 mL of H_2O_2. A needle was left in the septum (not under argon or nitrogen purge) to allow for venting and the reaction was warmed from 0°C to room temperature for 3 hours. Following this, the reaction was quenched with NH_4Cl. In a separatory funnel, the aqueous layer was washed 3 times with ethyl acetate, separated and then dried with $MgSO_4$, filtered and then concentrated via rotary evaporation. Purification was carried out by PTLC for both racemic and enantiomerically enriched substrates. Each SFC sample was prepared utilizing 1 mg or less of crude product dissolved in HPLC grade hexanes with 1 drop of HPLC grade MeOH. Note: For all Tris alcohols (oxidized compounds of rac and *(R)*- 9a, 9b, 15a, 15b) no yields were obtained due to very low yield product formation and isolation difficulties.

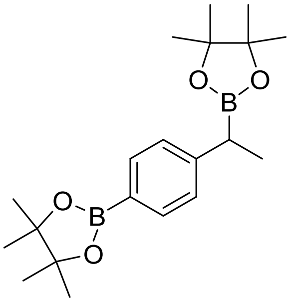
4.2: Di Boronic Ester- Aryl Coupling

Synthesis of 4,4,5,5-tetramethyl-2-(4-vinylphenyl)- 1,3,2-dioxaborolane 6:



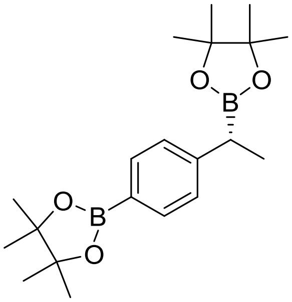
Synthesis followed literature procedures by Baltus et al.[86] 4-Vinylbenzeneboronic acid (6.76 mmol, 1.50 g), pinacol (6.80 mmol, 800 mg), $MgSO_4$ and anhydrous THF (50 mL) were left to reaction at room temperature for 3 hours. The crude reaction mixture was filtered and concentrated *in vacuo*. Purification was achieved via flash chromatography (5:1 hex:EtOAc) and the product was isolated as a colorless oil in 93% yield (1.4 g). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* =7.7 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 2H), 6.75 (dd, *J* = 10.9, 17.6 Hz, 1H), 5.85 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 10.9 Hz, 1H), 1.39 (s, 12 H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 140.2, 136.8, 135.0, 125.5, 114.8, 83.7, 24.8.

Synthesis of rac-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane (rac)-4:



Synthesis followed general procedure **method A** using [Rh(COD)(DPPB)][BF4] (0.044 mmol, 32 mg), 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2- dioxaborolane **6** (4.4 mmol, 1.0 g), HBPin (5.28 mmol,676 mg). Purification of the crude reaction mixture afforded a white powder in 83% yield (1.33 g).

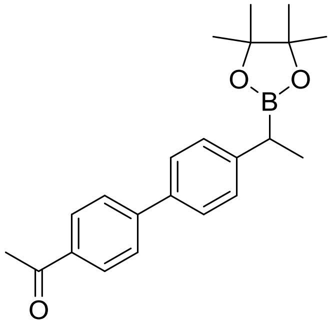
Synthesis of *(R)*-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane *(R)*-4:



Synthesis followed general **method B** using [Rh(COD)(DPPB)][BF$_4$] (0.057 mmol, 23.1 mg), *(R)*-BINAP (0.068 mmol, 42.3 mg), 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **6** (2.62 mmol, 603 mg), HBCat (2.9 eq, 3.46 mmol, 415 mg), pinacol (8.63 mmol, 1.02 g). The desired product was isolated as a white solid in a 90 % yield (1.70 g). **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 2.45 (q, *J* = 7.4 Hz, 1H), 1.33 (m, 15 H), 1.19 (m, 12 H) **^{13}C-NMR**: (CDCl$_3$, 100 MHz) δ 148.5, 134.8, 127.2, 83.5 , 83.3, 24.8, 24.6, 16.7 **^{11}B-NMR:** (CDCl$_3$, 160 MHz) δ 33. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{20}H_{32}B_2O_4$) m/z 358.2487; found 358.2491.

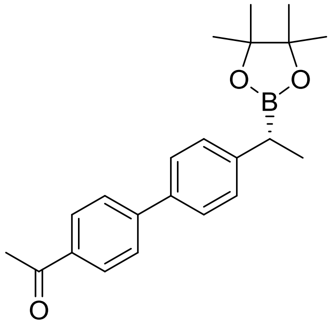
Note: Trace amounts of pinacol found in purified product

Synthesis of substrate rac-1-4'-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)biphenyl-4-yl)ethanone (rac)-7a:



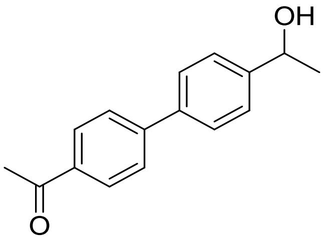
Synthesis followed general **method E** using 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane **(rac)-4** (1 eq, 1.0 mmol, 360 mg), 1-(4-bromophenyl)ethanone (1.2 eq, 1.2 mmol, 232 mg), K_2CO_3 (3 eq, 3 mmol 207 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 25 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.10 mmol, 29 mg). The desired product was isolated by flash column chromatography (30% diethyl ether: 70% hexanes) as a pale yellow solid in an 88% yield (308 mg).

Synthesis of substrate *(R)*- 1-4'-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)biphenyl-4-yl)ethanone *(R)*-7a:



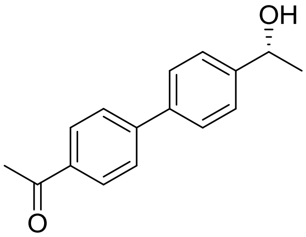
Synthesis followed general procedure **method E** using *(R)*-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl-1,3,2-dioxaborolane ***(R)*-4** (1 eq, 1.0 mmol, 356 mg), 1-(4-bromophenyl)ethanone (1.2 eq, 1.2 mmol, 230 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 31 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.10 mmol, 30 mg). The desired product was isolated by flash column chromatography (30% ether : 70% hexanes) in 81% yield (283 mg). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.64 (s, 3H), 2.51 (q, *J* = 7.4 Hz, 1H), 1.39 (d, *J* = 7.5 Hz, 3H), 1.24 (m, 15 H). **^{13}C-NMR**: (CDCl$_3$, 100 MHz) δ 197.7, 145.8, 145.5, 136.5, 135.4, 128.8, 128.4, 127.1, 126.8, 83.4, 26.6, 24.6, 17.0 **^{11}B-NMR:** (CDCl$_3$, 160 MHz) δ 33.3. **HRMS (EI-TOF):** calcd for [M]$^+$ ($C_{22}H_{27}BO_3$) m/z 350.2053; found 350.2066. **IR** (ν_{max}/cm^{-1}): 2978 (s),2249 (m),1678 (s),1269 (s). Note: Trace amounts of pinacol found in purified product

Synthesis of rac-1-(4'-(1-hydroxyethyl)biphenyl-4-yl)ethanone:



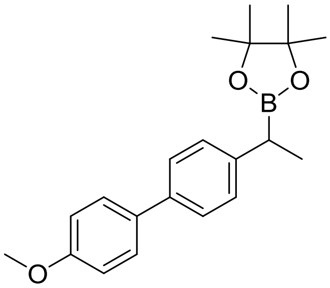
Synthesis followed general **method H** using 1-4'-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)biphenyl-4-yl)ethanone **(rac)-7a** (0.086 mmol, 30 mg) and isolated in a quantitative yield (22 mg). **SFC**: IB, 30 % MeCN, 35 MPa, 2 mL, 50°C. Retention time (min): 12.21, 12.42

Synthesis of *(R)*-1-(4'-(1-hydroxyethyl)biphenyl-4-yl)ethanone, (see Table 2-2, compound *(R)*-7a) :



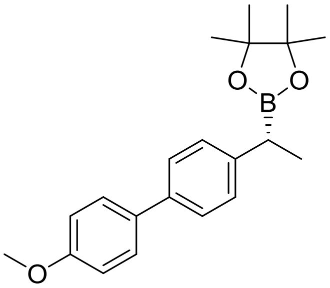
Synthesis followed general **method H** using *(R)*-1-4'-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)biphenyl-4-yl)ethanone ***(R)*-7a** (0.061 mmol, 22 mg) and isolated in a quantitative yield (14 mg) . **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 8.04 (d, *J*=8.3 Hz, 2H), 7.69 (d, *J*=8.3 Hz, 2H), 7.63 (d, *J*=8.1 Hz, 2H), 7.50 (d, *J=8.1* Hz, 2H), 4.98 (m, 1H), 2.65 (s, 3H), 1.57 (d, 3H). **^{13}C-NMR:** (CDCl$_3$, 100 MHz) δ 185.6, 128.9, 127.4, 127.1, 126.0, 70.0, 26.6, 25.2 **HRMS (EI-TOF):** calcd for [M]$^+$ $C_{16}H_{16}O_2$ calculated: 240.1150 found: 240.1159 **SFC:** IB, 30 % MeCN, 35 MPa, 2 mL, 50°C. **e.r (S:R): 5:95** Retention Time (min): 12.21, 12.43

Synthesis of rac-2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (rac)-7c:



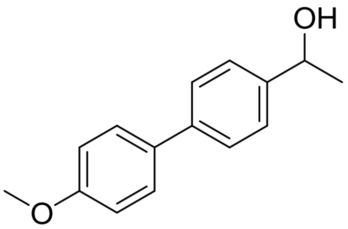
Synthesis followed general **method E** using 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane **(rac)-4** (1 eq, 1 mmol, 356 mg), 1-bromo-4- methoxybenzene (1.2 eq, 1.2 mmol, 370 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 31 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.10 mmol, 30 mg). The desired product was isolated by flash column chromatography (10% ether : 90% hexanes) as a pale yellow solid in an 85% yield (287 mg).

Synthesis of *(R)*-2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *(R)*-7c:



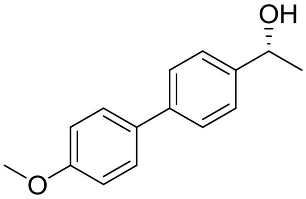
Synthesized using general **method E** using *(R)*-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)- 1,3,2-dioxaborolane ***(R)*-4** (1 eq, 1 mmol, 356 mg), 1-bromo-4- methoxybenzene (1.2 eq, 1.2 mmol, 370 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 31 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.10 mmol, 30 mg). The desired product was isolated by flash column chromatography (10% ether : 90% hexanes) as a pale yellow solid in 76% yield (256 mg). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.56 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3 H), 2.53 (q, *J* = 7.5 Hz, 1H), 1.43 (d, *J* = 7.5 Hz, 3H), 1.28 (s, 12 H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 158.8, 143.5, 137.6, 133.9, 128.1, 127.9, 126.6, 114.1, 83.3, 55.3, 24.6, 17.1 **^{11}B-NMR:** ($CDCl_3$, 160 MHz) δ 33.6. **HRMS (EI-TOF)**: calcd for $[M]^+$ ($C_{21}H_{27}BO_3$) m/z 338.2053; found 338.2046. **IR** (ν_{max}/cm^{-1}): 2971(s), 2930 (s),2251 (m),1248 (s),1143 (s).

Synthesis of rac-1-(4'-methoxybiphenyl-4-yl)ethanol:



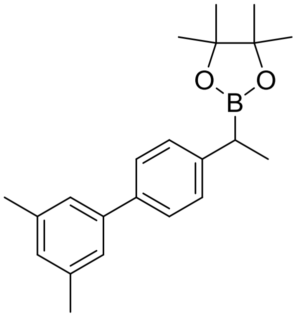
Synthesis followed general **method H** using 2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7c** (0.061 mmol, 21 mg) and isolated in a quantitative yield (13 mg) . **SFC conditions**: IB 30% EtOH 2 mL, 200bar, 35 MPa, 50^{o}C. Retention time (min): 2.87, 3.03

Synthesis of *(R)*-1-(4'-methoxybiphenyl-4-yl)ethanol (see Table 2-2, compound *(R)*-7c):



Synthesis followed general **method H** using *(R)*-2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7c** (0.061 mmol, 20 mg) and isolated in quantitative yield (12 mg) . **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 7.46 (dd, *J*= 15.9, 8.6, 4Hs), 7.36 (d, *J*= 8.3, 2H), 6.90 (d, *J*=8.6, 2H), 4.87 (m, 1H), 3.78 (s, 3H), 1.47 (d, *J*=6.6, 3H). **^{13}C-NMR:** (CDCl$_3$, 100 MHz) δ 159.1, 144.2, 140.1, 133.4, 128.1, 126.8, 125.8, 114.2, 70.2, 55.3, 25.1. **HRMS (EI-TOF):** calcd for $[M]^+$ $C_{15}H_{16}O_2$ calculated: 228.1150 found: 228.1157. **SFC conditions**: IB 30% EtOH 2 mL, 200bar, 35 MPa, 50^{o}C. **e.r (S:R): 5:95**. Retention time (min): 3.08, 3.25

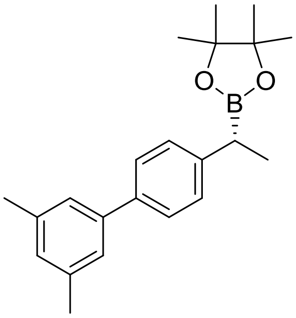
Synthesis of (rac)-2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane rac-7d:



Synthesis followed general **method E** using 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)- 1,3,2-dioxaborolane **(rac)-4** (1 eq, 1 mmol, 356 mg), 1-bromo-3,5-

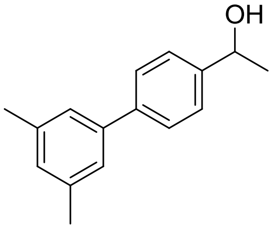
dimethylbenzene (1.2 eq, 1.2 mmol, 220 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 31 mg) and [HP(^{t}Bu)$_3$][BF$_4$] (0.10 eq, 0.10 mmol, 30 mg). The desired product was isolated by flash column chromatography (10% ether : 90% hexanes) as a pale yellow solid in a 95% yield (332 mg).

Synthesis of *(R)*-2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *(R)*-7d:



Synthesis followed general **method E** using *(R)*-4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane ***(R)*-4** (1 eq, 1 mmol, 356 mg), 1-bromo-3,5-dimethylbenzene (1.2 eq, 1.2 mmol, 220 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 31 mg) and [HP(^{t}Bu)$_3$][BF$_4$] (0.10 eq, 0.10 mmol, 30 mg). The compound was isolated as a pale yellow solid in 89% (295 mg) yield via flash chromatography (10% ether : 90% hexanes). **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.21 (s, 2 H), 6.96 (s, 1 H), 2.48 (q, *J* = 7.5 Hz, 1H), 2.37 (s, 6H), 1.39 (d, 3 H, *J* = 7.5 Hz), 1.23 (m, 14 H) **^{13}C-NMR**: (CDCl$_3$, 100 MHz) δ 143.9, 141.3, 138.17, 138.10, 128.4, 128.1, 127.1, 124.9 , 83.3, 24.67, 24.63, 21.4, 17.0. **^{11}B-NMR:** (CDCl$_3$, 160 MHz) δ 33. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{21}H_{27}BO_3$) m/z 336.2261; found 336.2253. **IR (ν_{max}/cm^{-1}):** 2979 (s), 2366 (m), 2253 (m), 1444 (m), 1153 (m). Note: Trace amounts of pinacol found in purified product.

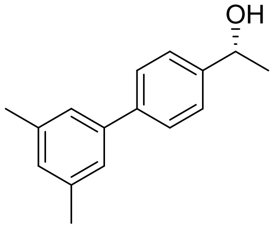
Synthesis of rac-1-(3',5'-dimethylbiphenyl-4-yl)ethanol:



Synthesis followed general **method H** using 2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane **(rac)-7d** (0.071 mmol, 24 mg) and isolated quantitatively (14 mg). **SFC** conditions: IB 5% MeOH 2 mL, 200bar, 35 MPa, 40^{o}C. Retention time (min): 8.93, 9.10

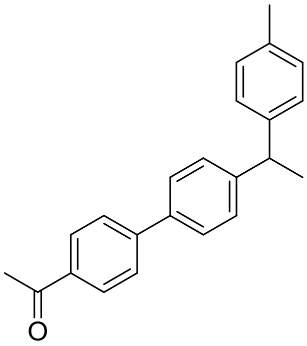
Synthesis of *(R)*-1-(3',5'-dimethylbiphenyl-4-yl)ethanol, (see Table 2-2, compound *(R)*-7d):



Synthesis followed general method H using *(R)*-2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7d** (0.071 mmol, 24 mg) and isolated in a quantitative yield (14 mg). ^{1}**H-NMR:** (CDCl$_3$, 400 MHz) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 2 H), 7.01 (s, 1 H), 4.96 (q, *J* = 6.4 Hz, 1H), 2.39 (s, 6H), 1.56 (d, *J* = 6.6 Hz, 3H) ^{13}**C-NMR**: (CDCl$_3$, 100 MHz) δ 138.2 , 128.9, 127.3, 125.7, 125.0, 70.2, 21.4 **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{16}H_{18}O$) m/z 226.1358; found 226.1365. **SFC** conditions: IB 5% MeOH 2 mL, 200bar, 35 MPa, 40^{o}C. **e.r (S:R): 3:97**. Retention time (min): 8.78, 8.90

4.3: Di Boronic Ester- Benzylic Coupling

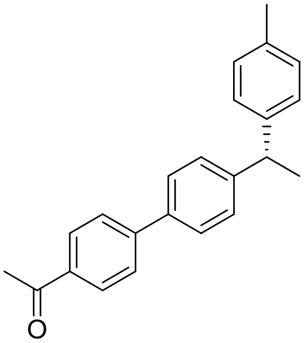
Synthesis of rac-1-(4'-(1-p-tolylethyl)biphenyl-4-yl)ethanone (rac)-8a:



Synthesis followed general method **F** using 1-(4'-(1-hydroxyethyl)biphenyl-4-yl)ethanone **(rac)-7a** (1.5 eq, 0.15 mmol, 50.7 mg), *p*-iodotoluene (1 eq, 0.10 mmol, 23 mg), Ag$_2$O (1.5 eq, 0.15 mmol, 34 mg), K$_2$CO$_3$ (1.5 eq, 0.15 mmol 20 mg), Pd(PPh$_3$)$_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh$_3$ (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (20% ether : 80%

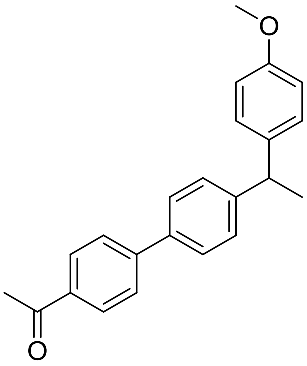
hexanes) gave a solid pale yellow powder with a yield of 62% (13 mg). **SFC conditions**: IE, 20% MeOH, 200 bar, 35 MPa, 1.5 mL, 50°C. Retention time (min): 17.09, 17.97

Synthesis of *(S)*-1-(4'-(1-p-tolylethyl)biphenyl-4-yl)ethanone *(S)*-8a:



Synthesis followed general method **E** using *(R)*-1-(4'-(1-hydroxyethyl)biphenyl-4-yl)ethanone ***(R)*-7a** and 4-iodotoluene. Flash chromatography (20% ether : 80% hexanes) gave a solid pale yellow powder with a yield of 64% (13 mg) **^{1}H-NMR:** ($CDCl_3$, 500 MHz) δ 8.00 (d, 2 H, *J* = 8.3 Hz), 7.66 (d, *J* = 8.3 Hz, 2H), 7.53 (d, 2 H, *J* = 8.0 Hz), 7.31 (d, 2 H, *J* = 8.2 Hz), 7.12 (m, 4H), 4.16 (m, 1 H), 2.62 (s, 3 H), 2.31 (s, 3 H), 1.66 (d, 3 H, *J* = 7.2 Hz). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 197.7, 146.9, 145.6, 143.0, 137.5, 135.7, 129.1, 128.8, 128.1, 127.2, 127.0, 44.1, 29.7, 26.6, 21.8, 20.98. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{23}H_{22}O$) m/z 314.1671; found 314.1660. **SFC conditions:** IE, 20% MeOH, 200 bar, 35 MPa, 1.5 mL, 50°C. **e.r (R:S): 19:81** Stereoretention: 68%, Retention time (min): 16.89, 17.76

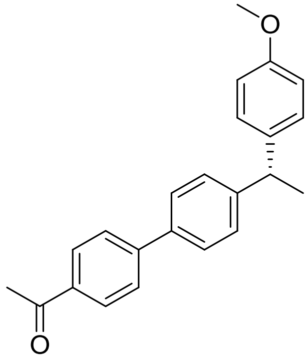
Synthesis of rac-1-(4'-(1-(4-methoxyphenyl)ethyl)biphenyl-4-yl)ethanone (rac)-8b:



Synthesis followed general method **E** using 1-(4'-(1-hydroxyethyl)biphenyl-4-yl)ethanone **(rac)-7a** (1.5 eq, 0.15 mmol, 51 mg), *p*-iodoanisole (1 eq, 0.10 mmol, 23 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol, 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography

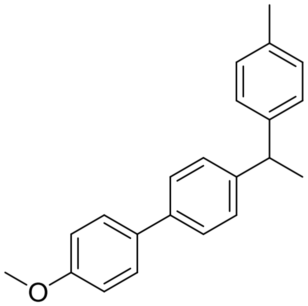
(20% ether : 80% hexanes) gave a solid pale yellow powder with a yield of 53% (12 mg) **SFC conditions:** IE, 15% MeOH, 200 bar, 1.5 mL, 50°C. Retention time (min): 24.0, 24.84

Synthesis of *(R)*-1-(4'-(1-(4-methoxyphenyl)ethyl)biphenyl-4-yl)ethanone (*R*)-8b:



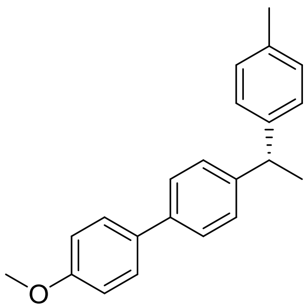
Synthesis followed general method **E** using *(R)*-1-(4'-(1-hydroxyethyl)biphenyl-4-yl)ethanone ***(R)*-7a** (1.5 eq, 0.15 mmol, 50 mg), *p*-iodoanisole (1 eq, 0.10 mmol, 23 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (20% ether : 80% hexanes) gave a solid pale yellow powder with a yield of 50% (11 mg) **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.16 (m, 1 H), 3.80 (s, 3 H), 2.63 (s, 3 H), 1.67 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 197.7, 158.0, 147.1, 145.6, 138.1, 137.5, 135.7, 128.9, 128.5, 128.1, 127.2, 127.0, 113.8, 55.2, 43.7, 26.6, 21.9. **HRMS (EI-TOF):** calcd for [M]+ ($C_{23}H_{22}O_2$) m/z 330.1620; found 330.1609. **SFC conditions:** IE, 15% MeOH, 200 bar, 1.5 mL, 50°C. **e.r (S:R): 13:87** Stereoretention 81%, Retention time (min): 23.93, 24.73

Synthesis of rac-4-methoxy-4'-(1-p-tolylethyl)biphenyl (rac)-8c:



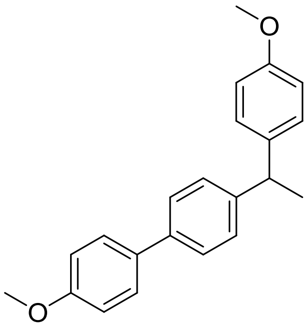
Synthesis followed general **method E** using 2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7c** (1.5 eq, 0.15 mmol, 51 mg), 1-iodo-4-methylbenzene (1 eq, 0.10 mmol, 20 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (10% ether : 90% hexanes) gave a pale yellow powder with a yield of 55% (11 mg) **SFC conditions** ID, 50% EtOH, 200 bar, 35 MPa, 2 mL, 50°C. Retention time (min): 4.03, 4.41

Synthesis of *(S)*-4-methoxy-4'-(1-p-tolylethyl)biphenyl *(S)*-8c:



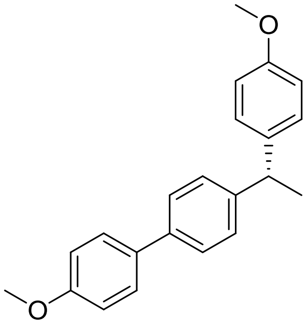
Synthesis followed general **method E** using *(R)*-2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7c** (1.5 eq, 0.15 mmol, 51 mg), 1-iodo-4-methylbenzene (1 eq, 0.10 mmol, 20 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (10% ether : 90% hexanes) gave a pale yellow powder with a yield of 52% (10 mg). **^{1}H-NMR:** ($CDCl_3$, 500 MHz) δ 7.49 (d, *J* = 7.5 Hz, 4H), 7.29 (m, 2H), 7.14 (m, 4H), 6.97 (d, *J* = 8.1 Hz, 2H), 4.16 (m, 1H), 3.85 (s, 3 H), 2.34 (s, 3 H), 1.67 (d, J = 7.2 Hz, 3H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 158.9, 145.1, 143.3, 138.4, 135.5, 133.6, 129.0, 128.0, 127.9, 127.4, 126.6, 114.1, 55.3, 44.05, 29.7, 21.9, 20.9 **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{22}O$) m/z 302.1671; found 302.1659**. SFC conditions** ID, 50% EtOH, 200 bar, 35 MPa, 2 mL, 50°C. **e.r (R:S): 17:83** Stereoretention: 75%, Retention time (min): 4.07, 4.45

Synthesis of rac-4-methoxy-4'-(1-(4-methoxyphenyl)ethyl)biphenyl (rac)-8d:



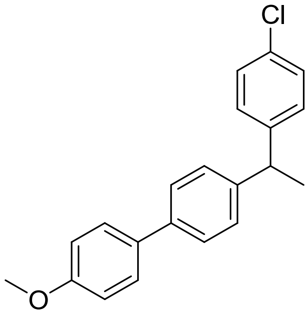
Synthesis followed general **method E** using using 2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7c** (1.5 eq, 0.15 mmol, 51 mg), 1-iodo-4-methoxybenzene (1 eq, 0.10 mmol, 24 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (10% ether : 90% hexanes) gave a very pale yellow powder with a yield of 48% (10 mg) **SFC conditions**: IF, 40% EtOH, 200 bar, 35 MPa, 2 mL, 50^{o}C. Retention time (min): 7.47, 7.83

Synthesis of *(R)*-4-methoxy-4'-(1-(4-methoxyphenyl)ethyl)biphenyl *(R)*-8d:



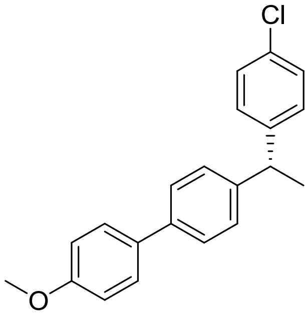
Synthesis followed general **method E** using *(R)*-2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7c** (1.5 eq, 0.15 mmol, 51 mg), 1-iodo-4-methoxybenzene (1 eq, 0.10 mmol, 24 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (10% ether : 90% hexanes) gave a very pale yellow powder with a yield of 54% (12 mg) **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.49 (d, *J* = 8.2 Hz, 4H), 7.27 (d, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 1H), 3.85 (s, 3 H), 3.80 (s, 3H), 1.66 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 158.9, 138.5, 138.4, 133.6, 128.5, 128.0, 127.8, 126.6, 114.1, 113.7, 55.3, 55.2, 43.6, 29.7, 22.07. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{22}O_2$) m/z 318.1620; found 318.1629. **SFC conditions**: IF, 40% EtOH, 200 bar, 35 MPa, 2 mL, 50^{o}C. **e.r (S:R): 19:81** Stereoretention: 75%, Retention time (min): 7.24, 7.44

Synthesis of rac-4-(1-(4-chlorophenyl)ethyl)-4'-methoxybiphenyl (rac)-8e:



Synthesis followed general **method E** using 2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7c** (1.5 eq, 0.15 mmol, 51 mg), 1-chloro-4-iodobenzene (1 eq, 0.10 mmol, 23 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (10% ether : 90% hexanes) gave a pale yellow powder with a yield of 59% (13 mg). **SFC conditions** IF, 40% EtOH, 200 bar, 35 MPa, 2 mL, 50°C. Retention time (min): 8.74, 9.32

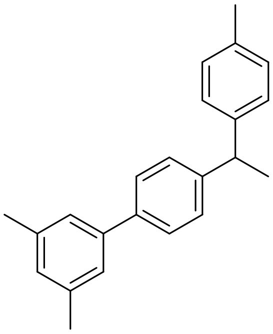
Synthesis of *(R)*-4-(1-(4-chlorophenyl)ethyl)-4'-methoxybiphenyl *(R)*-8e:



Synthesis followed general **method E** using *(R)*-2-(1-(4'-methoxybiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7c** (1.5 eq, 0.15 mmol, 51 mg), 1-chloro-4-iodobenzene (1 eq, 0.10 mmol, 23 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). Flash chromatography (10% ether : 90% hexanes) gave a pale yellow powder with a yield of 54% (11 mg). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.41 (dd, *J* = 7.3 Hz, 4H), 7.15 (m, 7H), 6.90 (d, *J* = 8.2 Hz, 2H), 4.09 (m, 1H), 3.77 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 159.0, 144.8, 144.2, 138.8, 133.4, 128.9, 128.5, 128.0, 127.8, 126.7, 114.2, 55.4, 43.86, 29.70, 21.81. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{21}H_{19}Cl$) m/z 322.1124; found 322.1137. **SFC**

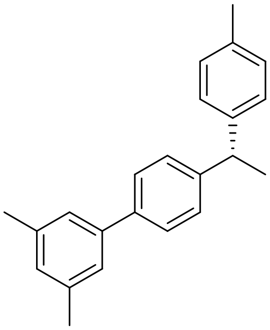
conditions IF, 40% EtOH, 200 bar, 35 MPa, 2 mL, 50^{o}C. **e.r (S:R): 10:90**. Stereoretention 90%, Retention time (min): 9.11, 9.79

Synthesis of rac-3,5-dimethyl-4'-(1-p-tolylethyl)biphenyl (rac)-8f:



Synthesis followed general **method E** 2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7d** (1.5 eq, 0.15 mmol, 50 mg), 1-iodo-4-methylbenzene (1 eq, 0.10 mmol, 22 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). PTLC (5% ether : 95% hexanes) gave a waxy pale yellow product with a yield of 74% (22 mg). **SFC conditions**: IF,30% MeOH, 35.0 MPa, 2 mL, 50C. Retention time (min): 5.68, 6.18

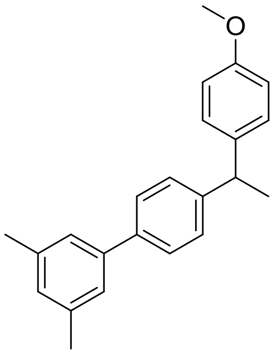
Synthesis of *(S)*-3,5-dimethyl-4'-(1-p-tolylethyl)biphenyl *(S)*-8f:



Synthesis followed general **method E** using *(R)*-2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7d** (1.5 eq, 0.15 mmol, 50 mg), 1-iodo-4-methylbenzene (1 eq, 0.10 mmol, 22 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). PTLC (5% ether : 95% hexanes) gave a waxy pale yellow product with a yield of 68% (20 mg). **^{1}H-NMR:** ($CDCl_3$, 500 MHz) δ 7.48 (d, *J* = 7.1 Hz, 2H), 7.27 (d, *J* = 7.1 Hz, 2H), 7.14 (m, 6H), 7.10 (s, 1 H) 4.16 (q, *J* = 7.2 Hz, 1H), 2.33 (s, 6 H), 2.32 (s, 3 H), 1.66 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 145.5, 143.4, 141.1, 139.1, 138.1, 135.5, 129.0, 128.6, 127.8, 127.5, 127.1, 124.9, 44.0, 21.9, 21.4, 20.9. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{23}H_{24}$) m/z 300.1878; found 300.1887 **SFC conditions**:

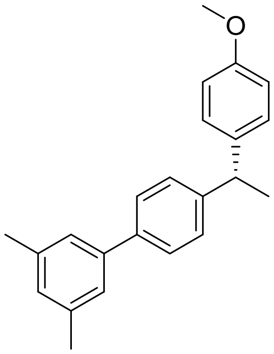
IF, 30% MeOH, 35 MPa, 2 mL, 50C. **e.r (R:S): 10:90** Stereoretention: 85% Retention time (min): 5.77, 6.11

Synthesis of rac-4'-(1-(4-methoxyphenyl)ethyl)-3,5-dimethylbiphenyl (rac)-8g:



Synthesis followed general **method E** using 2-(1-(3',5'-dimethyl biphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7d** (1.5 eq, 0.15 mmol, 50 mg), 1-iodo-4-methoxybenzene (1 eq, 0.10 mmol, 23 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg. PTLC (5% ethyl acetate : 95% hexanes) gave a waxy pale yellow product with a yield of 68% (14 mg). **SFC conditions**: IE, 40% MeOH, 35.0MPa, 2 mL, 50°C. Retention time (min): 4.62, 5.50

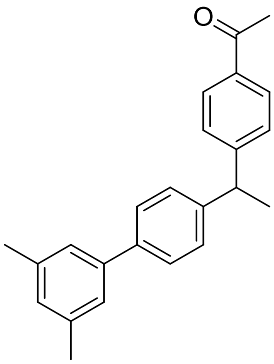
Synthesis of *(R)*-4'-(1-(4-methoxyphenyl)ethyl)-3,5-dimethylbiphenyl *(R)*-8g:



Synthesis followed general **method E** using *(R)*-2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7d** (1.5 eq, 0.15 mmol, 50 mg), 1-iodo-4-methoxybenzene (1 eq, 0.10 mmol, 23 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg. PTLC (5% ethyl acetate : 95% hexanes) gave a waxy pale yellow product with a yield of 73% (15 mg). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J*= 8.0, 2H), 7.20 (s, 4H), 6.99 (s, 1H), 6.87 (d, *J*=8.8, 2H), 4.16 (m, 1 H), 3.81 (s, 3 H), 2.32 (s, 6 H), 1.67 (d, *J* = 7.2 Hz, 3H) **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 157.8, 145.6, 141.1, 139.1, 138.5, 138.1, 128.6, 128.5, 127.8, 127.1, 124.9, 113.7, 55.2, 43.6, 22.0, 21.4. **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{23}H_{24}O$) m/z 318.1837; found

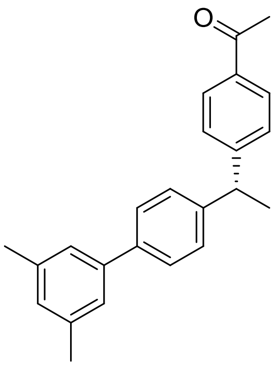
316.1827. **SFC Conditions** IE, 40% MeOH, 35.0MPa, 2 mL, 50^{o}C. **e.r (S:R): 11:89** Stereoretention 80%, Retention time (min): 4.51, 4.98

Synthesis of rac-1-(4-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)phenyl)ethanone (rac)-8h:



Synthesis followed general **method E** using 2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-7d** (1.5 eq, 0.15 mmol, 50 mg), 1-(4-iodophenyl)ethanone (1 eq, 0.10 mmol, 25 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). PTLC (5% ether: 95%hexanes) gave a waxy pale yellow product with a yield of 70% (21 mg).

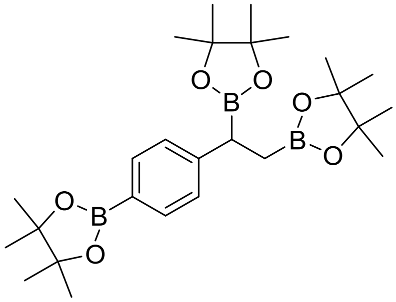
Synthesis of *(R)*-1-(4-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)phenyl)ethanone *(R)*-8h:



Synthesis followed general **method E** using *(R)*-2-(1-(3',5'-dimethylbiphenyl-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-7d** (1.5 eq, 0.15 mmol, 50 mg), 1-(4-iodophenyl)ethanone (1 eq, 0.10 mmol, 25 mg), Ag_2O (1.5 eq, 0.15 mmol, 34 mg), K_2CO_3 (1.5 eq, 0.15 mmol 20 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.008 mmol, 10 mg) and PPh_3 (0.32 eq, 0.032 mmol, 8 mg). PTLC (5% ether : 95% hexanes) gave a waxy pale yellow product with a yield of 67% (16 mg). **^{1}H-NMR:** ($CDCl_3$, 500 MHz) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J*= 8.1 Hz, 2H), 7.27 (m, 3H), 7.18 (s, 2 H), 6.99 (s, 1 H) 4.25 (q, *J* = 7.1 Hz, 1H), 2.59 (s, 3 H), 2.38 (s, 6 H), 1.70 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 145.5, 143.4, 141.1, 139.1, 138.1, 135.5, 129.0, 128.6, 127.8, 127.5, 127.1, 124.9, 44.0, 21.9, 21.4, 20.9. **SFC:** Unable to separate

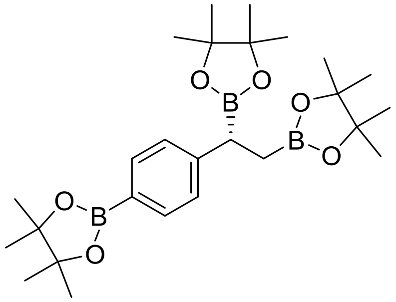
4.4: Tri Boronic Ester: Aryl Coupling

Synthesis of rac-2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (rac)-5:



Synthesis followed **method C** using 4,4,5,5-Tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (1 eq, 6.66 mmol, 1.53 g) **6**, $Pt(dba)_3$ (2 mol %, 0.13 mmol, 120 mg) and B2Pin2 (1.05 eq, 6.99 mmol, 1.775 g). The desired product was isolated by column chromatography (10:1 hex:EtOAc) in 78% yield (1.5 g).

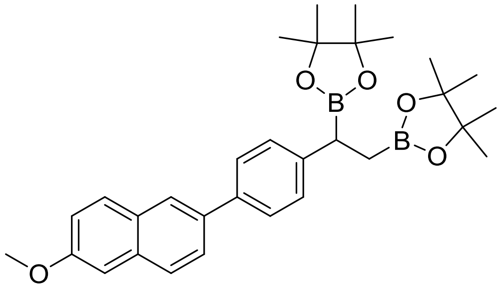
Synthesis of *(R)*-2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) *(R)*-5:



Synthesis followed **method D** using $Pt(dba)_3$ (2 mol %, 0.13 mmol, 120 mg), B_2Pin_2 (1.05 eq, 6.99 mmol, 1.775 g) , Ligand (3aR,8aR)-4,4,8,8-tetrakis(3,5-diethylphenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine (2.4 mol %, 127 mg), 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane **6** (1 eq, 6.66 mmol, 1.53 g). The desired product was isolated by column chromatography (10:1 Hex:EtOAc) in 37% (850 mg) yield. **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.68 (d, 2 H, *J* = 7.9 Hz), 7.23 (d, 2 H, *J* = 7.9 Hz), 2.54 (dd, 1 H, *J* = 11.1, 5.3 Hz), 1.24 (s, 14 H), 1.21-1.16 (m, 26 H) **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 149.0, 134.7, 127.3, 83.4, 83.2, 83.0, 24.99, 24.91, 24.8, 24.69, 24.66, 24.47 **^{11}B NMR:** ($CDCl_3$, 160 MHz) δ 34 **HRMS (EI-TOF):** calcd for $[M]^+$ ($C_{22}H_{27}BO_6$) *m/z* 484.3339; found 484.3362. **IR (ν_{max}/cm^{-1}):** 2944 (s), 2666 (m), 2253 (m). The external standard used was

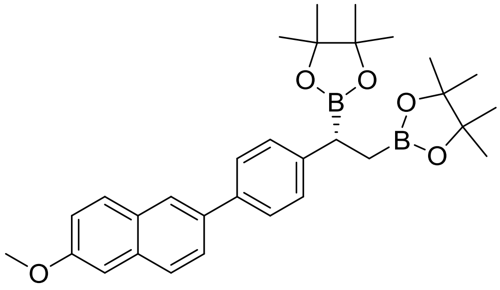
BF_3-OEt_2; appearing as a singlet at 0 ppm. Note: Trace amounts of pinacol found in purified product.

Synthesis of rac-2,2'-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (rac)-9a:



Synthesis followed **method E** using 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-5** (1 eq, 2 mmol, 900 mg), 2-bromo-6-methoxynaphthalene (1.2 eq, 2.4 mmol, 575 mg), K_2CO_3 (3 eq, 6 mmol 420 mg), $Pd_2(dba)_3$ (0.025 eq, 0.050 mmol 61 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.020 mmol, 60 mg). The desired product was isolated after impurities were removed by heating under vacuum on a Kugelrohr distillation apparatus (1 h 100°C then 2 h 125°C). The crude reaction mixture was then filtered through a 2 inch silica plug (60 mL glass frit) with 150 mL 100% pentane, 200 mL 7% ethyl acetate : 93% pentane, 200 mL of 100 % ethyl acetate. The product was isolated in an 81% yield as an off white powder (824 mg).

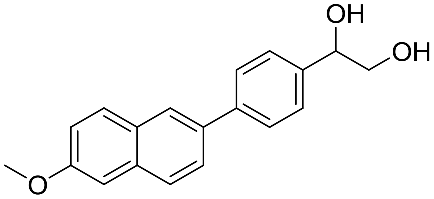
Synthesis of *(R)*-2,2'-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) *(R)*-9a:



Synthesis followed **method E** using *(R)*-2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-5** (1 eq, 1 mmol, 450 mg), 2-bromo-6-methoxynaphthalene (1.2 eq, 1.2 mmol, 290 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 30 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 30 mg).. The desired product was isolated after filtering through a 4 inch silica plug (60 mL glass frit) with 400 mL 100% pentane, 500 mL 7% ethyl acetate:

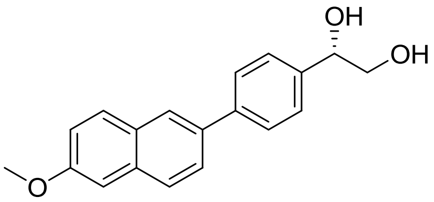
93% pentane, 400 mL of 100% ethyl acetate. The product was isolated in a 79% yield (406 mg) as a off white powder. **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.84 (s, 1 H), 7.63 (m, 3 H), 7.42 (m, 1H), 7.07 (m, 6H), 3.80 (s, 4H), 2.50 (m, 1 H), 1.10 (m, 26 H) **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 157.5, 144.5, 134.7, 129.6, 129.2, 128.4, 127.3, 127.1, 126.9, 126.0, 125.1, 118.9, 105.6, 83.5, 83.3, 83.0, 55.3, 32.1, 29.7, 25.0, 24.9, 24.8, 24.75, 24.70, 24.5, 24.4 **^{11}B NMR:** ($CDCl_3$, 160 MHz) δ 33. Note: Trace amounts of pinacol found in purified product.

Synthesis of rac-1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diol:



Synthesis followed general **method I** using 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-5** (1 eq, 0.10 mmol, 50 mg), 2-bromo-6-methoxynaphthalene (1.2 eq, 0.12 mmol, 30 mg), K_2CO_3 (3 eq, 0.30 mmol 42.0 mg), $Pd_2(dba)_3$ (0.025 eq, 0.0025 mmol 3 mg), $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 3 mg) **SFC conditions**: IE, MeCN, 1.5 mL, 1-30% gradient: Time 4 min (99% CO_2, 1% MeCN), Time 14.0min (70% CO_2, 30% MeCN), Time 14.1 min (70% CO_2, 30% MeCN), Time 54.1 min (99% CO_2, 1% MeCN), Time 52.0 (99% CO_2, 1% MeCN). Retention time (min): 24.74, 25.41

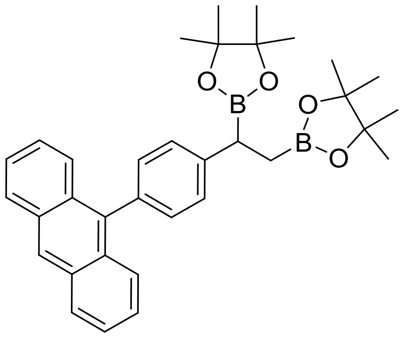
Synthesis of (*S*)-1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diol (see Table 2-7, compound *(R)*-9a):



Synthesis followed general **method I** using *(R)*- 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-5** (1 eq, 0.10 mmol, 50 mg), 2-bromo-6-methoxynaphthalene (1.2 eq, 0.12 mmol, 30 mg), K_2CO_3 (3 eq, 0.30 mmol 42.0 mg),

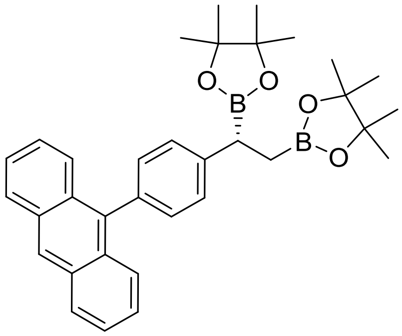
$Pd_2(dba)_3$ (0.025 eq, 0.0025 mmol 3 mg), $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 3 mg). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.65 (m, 10H), 7.42 (m, 2H), 7.07 (m, 14 H), 6.86 (m, 3 H), 6.79 (m, 3H), 4.39 (m, 1H), 3.89 (m, 7H), 3.52 (m, 3H), **SFC conditions**: IE, MeCN, 1.5 mL, 1-30% gradient: Time 4 min (99% CO_2, 1% MeCN), Time 14.0min (70% CO_2, 30% MeCN), Time 14.1 min (70% CO_2, 30% MeCN), Time 54.1 min (99% CO_2, 1% MeCN), Time 52.0 (99% CO_2, 1% MeCN). **e.r: 13:87** (R:S), Retention time (min): 23.78, 24.68

Synthesis of rac-2,2'-(1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)) (rac)-9b:



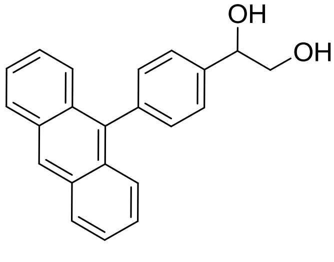
Synthesis followed **method E** using 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-5** (1 eq, 1 mmol, 450 mg), 9-bromoanthracene (1.2 eq, 1.2 mmol, 310 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 30 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 30 mg). The desired product was isolated after impurities were removed by heating under vacuum on a Kugelrohr distillation apparatus (1 h 100°C then 2 h 125°C). The crude reaction mixture was then filtered through a 2 inch silica plug (60 mL glass frit) with 15% ethyl acetate : 85% hexanes. The product was isolated in a 74% (395 mg) yield as a off orange-yellow waxy powder. **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 8.47 (s, 1 H), 8.03 (d, 2H, *J*= 8.3 Hz), 7.69 (d, 2H, *J*= 8.8 Hz), 7.45 (m, 6H), 7.32 (m, 4H), 2.71 (m, 1 H), 1.28 (m, 26H) **^{13}C-NMR**: ($CDCl_3$, 100 MHz) δ 140.4, 138.2, 131.0, 128.3, 128.2, 127.9, 127.8, 127.7, 127.5, 127.1, 127.0, 124.0, 124.9, 123.4, 88.3, 88.1, 88.0, 32.1, 29.7, 24.7, 24.6, 24.5 ^{11}**B NMR:** (CDCl$_3$, 160 MHz) δ 33. Note: Trace amounts of pinacol found in purified product.

Synthesis of *(R)*-2,2'-(1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)) *(R)*-9b:



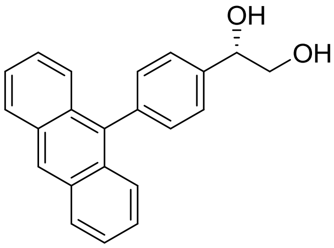
Synthesis followed **method E** using *(R)*- 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-5** (1 eq, 1 mmol, 450 mg), 9-bromoanthracene (1.2 eq, 1.2 mmol, 310 mg), K_2CO_3 (3 eq, 3 mmol 210 mg), $Pd_2(dba)_3$ (0.025 eq, 0.025 mmol 30 mg) and $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 30 mg). The desired product was isolated after impurities were removed by heating under vacuum on a Kugelrohr distillation apparatus (1 h 100°C then 2 h 125°C) then the crude mixture was filtered through a 2 inch silica plug (60 mL glass frit) with 15% ethyl acetate : 85% hexanes. The product was isolated in an 76% yield (400 mg) as a off orange-yellow powder/waxy oil . ^{1}**H-NMR:** (CDCl$_3$, 400 MHz) δ 8.47 (s, 1 H), 8.04 (d, 2H, *J*= 8.3 Hz), 7.72 (d, 2H, *J*= 8.8 Hz), 7.46-7.43 (m, 6H), 7.35-7.29 (m, 4H), 2.74 (m, 1 H), 1.34-1.22 (m, 26H) ^{13}**C-NMR**: (CDCl$_3$, 100 MHz) δ 140.5, 138.2, 131.1, 128.2, 128.2, 127.8, 127.9, 127.7, 127.5, 127.1, 127.0, 124.0, 124.9, 123.4, 88.3, 88.1, 88.0, 32.1, 29.6, 24.8, 24.7, 24.6 ^{11}**B NMR:** (CDCl$_3$, 160 MHz) δ 33. Note: Trace amounts of pinacol found in purified product.

Synthesis of rac-1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diol:



Synthesis followed general **method I** using 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-5** (1 eq, 0.10 mmol, 50 mg), 9-bromoanthracene (1.2 eq, 0.12 mmol, 31 mg), K_2CO_3 (3 eq, 0.30 mmol 42 mg), $Pd_2(dba)_3$ (0.025 eq, 0.0025 mmol 3 mg), $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 3 mg). **SFC conditions**: IA, EtOH, 1.5 mL, 1-40% gradient: Time 4 min (99% CO_2, 1% EtOH), Time 14.0 min (60% CO_2, 40% EtOH), Time 14.1 min (60% CO_2, 40% EtOH), Time 18.9 min (99% CO_2, 1% EtOH), Time 19.0 (99% CO_2, 1% EtOH). Retention time (min): 14.36, 14.58

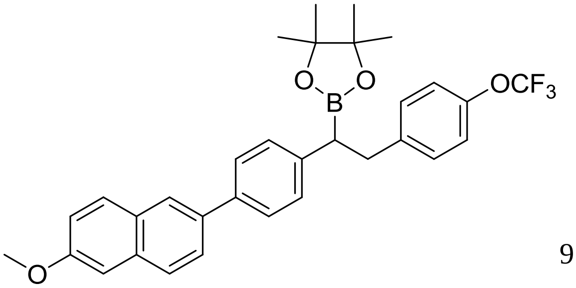
Synthesis of *(S)*-1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diol (see Table 2-7, compound *(R)*-9b):



Synthesis followed general **method I** using *(R)*- 2,2'-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-5** (1 eq, 0.10 mmol, 50 mg), 9-bromoanthracene (1.2 eq, 0.12 mmol, 31 mg), K_2CO_3 (3 eq, 0.30 mmol 42 mg), $Pd_2(dba)_3$ (0.025 eq, 0.0025 mmol 3 mg), $[HP(^tBu)_3][BF_4]$ (0.10 eq, 0.010 mmol, 3 mg). **SFC conditions:** IE, EtOH, 1.5 mL, 1-40% gradient: Time 4 min (99% CO_2, 1% EtOH), Time 14.0 min (60% CO_2, 40% EtOH), Time 14.1 min (60% CO_2, 40% EtOH), Time 18.9 min (99% CO_2, 1% EtOH), Time 19.0 (99% CO_2, 1% EtOH). **e.r: 11:89 (R:S),** Retention time (min): 14.38, 14.61

4.5: Tri Boronic Ester: Linear Coupling

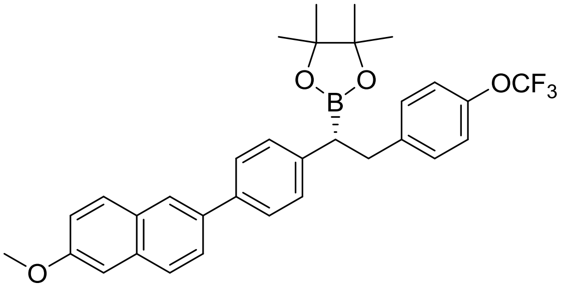
Synthesis of rac-2-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (rac)-15a:



Synthesis followed general method **G** using 2,2'-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-

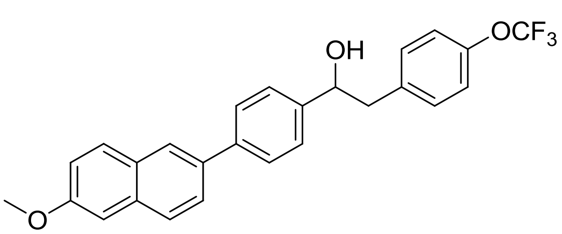
tetramethyl-1,3,2-dioxaborolane) **(rac)-9a** (1.0 eq, 0.05 mmol, 26.7 mg), Pd(OAc)$_2$ (0.1 eq, 15.7 mg), SPhos (0.1 eq, 0.005 mmol, 20 mg), K_2CO_3 (2 eq, 0.10 mmol, 14 mg) and 1-bromo-4-(trifluoromethoxy)benzene (1.5 eq, 0.075 mmol, 11.5 mg). The crude mixture was filtered through a silica plug with 100% hexanes, followed by 10% ethyl acetate : 90% hexanes and then 100% ethyl acetate. The product was isolated as a light yellow waxy solid in 40% yield (12 mg).

Synthesis of *(R)*-2-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *(R)*-15a:



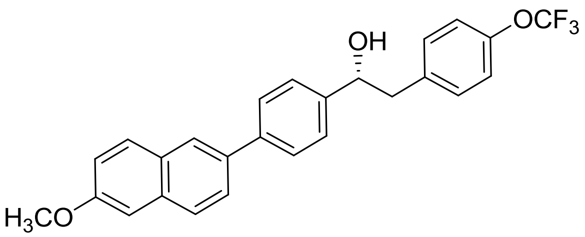
Synthesis followed general method **G** using *(R)*-2,2'-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-9a** (1.0 eq, 0.05 mmol, 26.7 mg), Pd(OAc)$_2$ (0.1 eq, 15.7 mg), SPhos (0.1 eq, 0.005 mmol, 20 mg), K_2CO_3 (2 eq, 0.10 mmol, 14 mg) and 1-bromo-4-(trifluoromethoxy)benzene (1.5 eq, 0.075 mmol, 11.5 mg). The crude mixture was filtered through a silica plug with 100% hexanes, followed by 10% ethyl acetate : 90% hexanes and then 100% ethyl acetate. The product was isolated as a yellow waxy solid in 35% yield (9 mg). **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 7.97 (s, 2H), 7.70 (m, 9H), 7.31 (m, 4 H), 7.11 (m, 5H), 3.92 (s, 4H), 3.33 (m, 1H), 3.14 (m, 1H), 2.83 (m, 1H), 1.18 (s, 12 H) **^{13}C- NMR**: (CDCl$_3$, 100 MHz) δ 155.4, 149.0, 141.6, 134.7, 130.3, 129.3, 128.4, 127.3, 127.2, 126.9, 125.4, 125.1, 119.3, 116.3, 116.2, 105.6, 83.5, 83.2, 83.0, 55.3, 46.2, 29.7, 25.00, 24.91, 24.6, 24.4 **^{11}B NMR:** (CDCl$_3$, 160 MHz) δ 33.

Synthesis of rac-1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethanol:



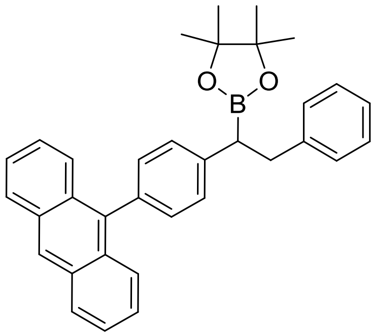
Synthesis followed general **method I** using 2,2'-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-9a** (1.0 eq, 0.10 mmol, 51 mg), Pd(OAc)$_2$ (0.1 eq, 32 mg), SPhos (0.1 eq, 0.01 mmol, 40 mg), K$_2$CO$_3$ (2 eq, 0.20 mmol, 28 mg) and 1-bromo-4-(trifluoromethoxy)benzene (1.5 eq, 0.15 mmol, 23 mg). **SFC conditions**: IE, MeCN, 1.5 mL, 1-30% gradient: Time 4 min (99% CO$_2$, 1% MeCN), Time 14.0min (70% CO$_2$, 30% MeCN), Time 14.1 min (70% CO$_2$, 30% MeCN), Time 54.1 min (99% CO$_2$, 1% MeCN), Time 52.0 (99% CO$_2$, 1% MeCN). Retention time (min): 19.63, 20.13

Synthesis of *(R)*-1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diol (see Table 2-8, compound *(R)*-15a):



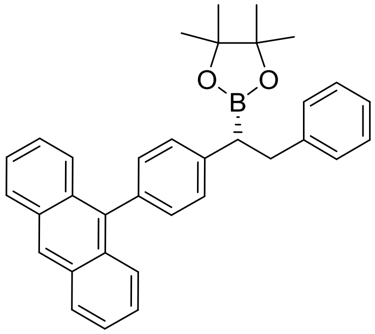
Synthesis followed general **method I** using *(R)*-2,2'-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-9a** (1.0 eq, 0.10 mmol, 51 mg), Pd(OAc)$_2$ (0.1 eq, 32 mg), SPhos (0.1 eq, 0.01 mmol, 40 mg), K$_2$CO$_3$ (2 eq, 0.20 mmol, 28 mg) and 1-bromo-4-(trifluoromethoxy)benzene (1.5 eq, 0.15 mmol, 23 mg). **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 7.99 (m, 1H), 7.81 (m, 1H), 7.71 (m, 3H),7.60 (m, 1H),7.50 (m, 2H),7.15 (m, 4H), 4.98 (m, 1H), 3.94 (m, 4H), 3.71 (m, 1H), 3.10 (m, 1H). **^{13}C-NMR:** (CDCl$_3$, 100 MHz) δ 143.3, 140.7, 136.2, 134.5, 134.0, 130.3, 130.1, 128.0, 127.3, 127.0, 125.9, 124.1, 124.0, 123.6, 102.4, 74.0, 57.4, 54.5, 46.5 **SFC conditions**: IE, MeCN, 1.5 mL, 1-30% gradient: Time 4 min (99% CO$_2$, 1% MeCN), Time 14.0min (70% CO$_2$, 30% MeCN), Time 14.1 min (70% CO_2, 30% MeCN), Time 54.1 min (99% CO_2, 1% MeCN), Time 52.0 (99% CO_2, 1% MeCN). **e.r: 13:87 (S:R),** Retention time (min): 19.82, 20.12

Synthesis of rac-2-(1-(4-(anthracen-9-yl)phenyl)-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (rac)-15b:



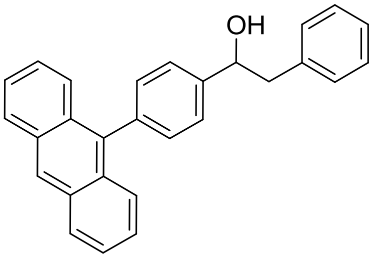
Synthesis followed general method **G** using 2,2'-(1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-9b** (1.0 eq, 0.05 mmol, 28 mg), $Pd(OAc)_2$ (0.1 eq, 15 mg), SPhos (0.1 eq, 0.005 mmol, 20 mg), K_2CO_3 (2 eq, 0.10 mmol, 14 mg) and 1-bromobenzene (1.5 eq, 0.075 mmol, 12 mg). The crude mixture was filtered through a silica plug with 100% hexanes, followed by 10% ethyl acetate : 90% hexanes and then 100% ethyl acetate. The product was isolated as a light yellow waxy solid in 40% yield (10 mg).

Synthesis of *(R)*-2-(1-(4-(anthracen-9-yl)phenyl)-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane *(R)*-15b:



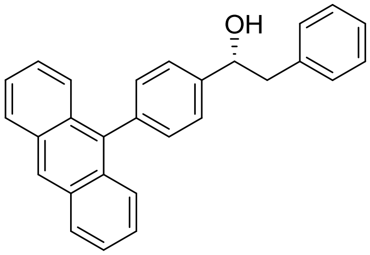
Synthesis followed general **method G** using *(R)*- 2,2'-(1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-9b** (1.0 eq, 0.05 mmol, 28 mg), $Pd(OAc)_2$ (0.1 eq, 15 mg), SPhos (0.1 eq, 0.005 mmol, 20 mg), K_2CO_3 (2 eq, 0.10 mmol, 14 mg) and 1-bromobenzene (1.5 eq, 0.075 mmol, 12 mg). The crude mixture was filtered through a silica plug with 100% hexanes, followed by 10% ethyl acetate : 90% hexanes and then 100% ethyl acetate. The product was isolated as a light yellow waxy oil in 29% yield (10 mg). **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 8.49 (m, 2H), 8.06 (m, 4H), 7.71 (m, 2 H), 7.49 (m, 11H), 7.27 (m, 12H), 3.30 (m, 1H) , 3.14 (m, 1H), 2.86 (m, 1H), 1.26 (s, 12 H) **^{13}C- NMR**: ($CDCl_3$, 100 MHz) δ 141.9, 141.7, 131.7, 131.4, 131.2, 130.3, 130.1, 129.2, 129.0, 128.7, 128.4, 128.3, 128.1, 127.9, 127.4, 127.1, 127.0, 126.2, 125.8, 125.3, 125.0, 83.6, 83.3, 67.6, 38.9, 25.0, 24.8, 24.6 **^{11}B NMR:** (CDCl$_3$, 160 MHz) δ 33.

Synthesis of rac-1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethanol:



Synthesis followed general **method I** 2,2'-(1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) **(rac)-9b** (1.0 eq, 0.1 mmol, 55 mg), Pd(OAc)$_2$ (0.1 eq, 30 mg), SPhos (0.1 eq, 0.01 mmol, 40 mg), K$_2$CO$_3$ (2 eq, 0.20 mmol, 30 mg) and 1-bromobenzene (1.5 eq, 0.15 mmol, 20 mg). **SFC conditions**: IA, EtOH, 2 mL, 1-40% gradient: Time 4min (99% CO$_2$, 1% EtOH), Time 14.0min (60% CO$_2$, 40% EtOH), Time 15.0 min (60% CO$_2$, 40% EtOH), Time 15.1 min (99% CO$_2$, 1% EtOH), Time 16.0 (99% CO$_2$, 1% EtOH). Retention time (min):12.83, 13.00

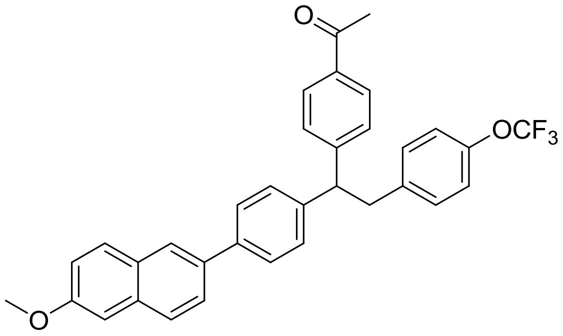
Synthesis of *(R)*-1-(4-(anthracen-9-yl)phenyl)-2-phenylethanol (see Table 2-8, compound *(R)*-15b):



Synthesis followed general **method I** using *(R)*-2,2'-(1-(4-(anthracen-9-yl)phenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) ***(R)*-9b** (1.0 eq, 0.1 mmol, 55 mg), Pd(OAc)$_2$ (0.1 eq, 30 mg), SPhos (0.1 eq, 0.01 mmol, 40 mg), K$_2$CO$_3$ (2 eq, 0.20 mmol, 30 mg) and 1-bromobenzene (1.5 eq, 0.15 mmol, 20 mg). **^{1}H-NMR:** (CDCl$_3$, 400 MHz) δ 8.51 (s, 1H), 8.06 (d, 2H, *J*= 8.3 Hz), 7.63 (m, 5H), 7.47 (m, 5H), 7.35 (m, 2H), 5.03 (m, 1H), 3.97 (m, 1H), 3.87 (m, 1H) **^{13}C- NMR**: (ppm) δ 131.5, 131.4, 128.3, 128.0, 127.9, 127.69, 127.60, 126.7, 126.1, 126.0, 125.3, 125.1, 123.5, 123.3, 74.4, 68.0, 29.7 **SFC conditions**: IA, EtOH, 2 mL, 1-40% gradient: Time 4min (99% CO_2, 1% EtOH), Time 14.0min (60% CO_2, 40% EtOH), Time 15.0 min (60% CO_2, 40% EtOH), Time 15.1 min (99% CO_2, 1% EtOH), Time 16.0 (99% CO_2, 1% EtOH). **e.r: 11:89 (S:R),** Retention time (min): 12.77, 12.88

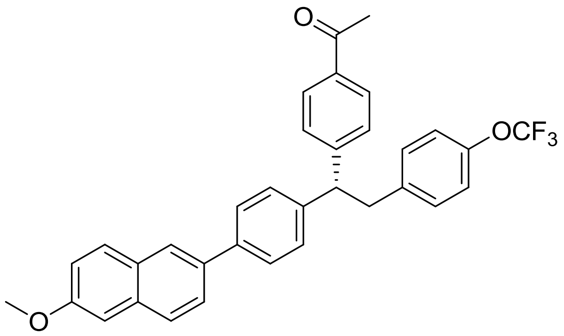
4.6: Tri Boronic Ester: Benzylic Coupling

Synthesis of rac-1-(4-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)phenyl)ethanone (rac)-16a:



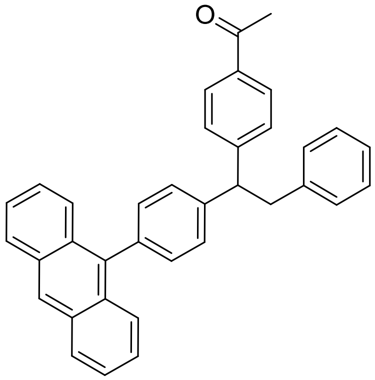
Synthesis followed general **method F** using 2-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-15a** (1.5 eq, 0.05 mmol, 45 mg), 4-iodoacetophenone (1 eq, 0.05 mmol, 13 mg), Ag_2O (1.5 eq, 0.075 mmol, 17 mg), K_2CO_3 (1.5 eq, 0.075 mmol 10 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.004 mmol, 5 mg) and PPh_3 (0.32 eq, 0.016 mmol, 4 mg). The product was isolated after PTLC (15% ethyl acetate : 85% hexanes) in a 43% yield (8 mg) as an off white powder. **SFC conditions**: IE, EtOH 1-60% gradient: Time 4 minutes : (99% CO_2, 1% EtOH), Time 14.0min (40% CO_2, 60% EtOH), Time 14.1 min (40% CO_2, 60% MeCN), Time 34.1 min (99% CO_2, 1% EtOH), Time 35.0 (99% CO_2, 1% EtOH) 1.10 mL, 50°C. Retention time (min): 29.52, 30.23

Synthesis of *(R)*-1-(4-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)phenyl)ethanone *(R)*-16a:



Synthesis followed general **method F** using *(R)*-2-(1-(4-(6-methoxynaphthalen-2-yl)phenyl)-2-(4-(trifluoromethoxy)phenyl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-15a** (1.5 eq, 0.05 mmol, 45 mg), 4-iodoacetophenone (1 eq, 0.05 mmol, 13 mg), Ag_2O (1.5 eq, 0.075 mmol, 17 mg), K_2CO_3 (1.5 eq, 0.075 mmol 10 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.004 mmol, 5 mg) and PPh_3 (0.32 eq, 0.016 mmol, 4 mg). The product was isolated after PTLC (15% ethyl acetate : 85% hexanes) in a 33% yield (6 mg) as an off white powder. **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 7.93 (s, 1H), 7.85 (d, 2H, *J*= 8.1 Hz), 7.78 (t, 2 H, *J*= 13.6 Hz), 7.64 (m, 5 H), 7.42 (s, 1H), 7.35 (m, 3H), 7.16 (m, 3 H), 7.07 (m, 1 H), 4.46 (m, 1H), 3.95 (s, 3H), 3.57 (m, 2H), 2.55 (s, 3H). **^{13}C- NMR**: ($CDCl_3$, 100 MHz) δ 150.1, 142.5, 139.4, 135.3, 134.9, 133.7, 133.0, 129.6, 129.2, 129.0, 128.4, 128.3, 128.0, 127.4, 127.37, 127.38, 127.2, 127.1, 126.6, 125.8, 125.4, 105.6, 55.3, 41.9, 31.5, 26.3 **SFC conditions**: IE, EtOH 1-60% gradient: Time 4 minutes : (99% CO_2, 1% EtOH), Time 14.0min (40% CO_2, 60% EtOH), Time 14.1 min (40% CO_2, 60% MeCN), Time 34.1 min (99% CO_2, 1% EtOH), Time 35.0 (99% CO_2, 1% EtOH) 1.10 mL, 50°C. **e.r: 18:82 (S:R),** Retention time (min): 28.27, 29.20

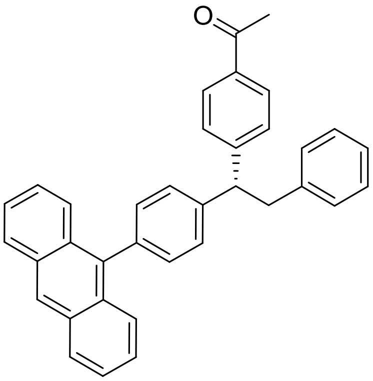
Synthesis of rac-1-(4-(1-(4-(anthracen-9-yl)phenyl)-2-phenylethyl)phenyl)ethanone (rac)-16b:



Synthesis followed general **method F** using 2-(1-(4-(anthracen-9-yl)phenyl)-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(rac)-15b** (1.5 eq, 0.05 mmol, 51 mg), 4-iodoacetophenone (1 eq, 0.05 mmol, 13 mg), Ag_2O (1.5 eq, 0.075 mmol, 17 mg), K_2CO_3 (1.5 eq, 0.075 mmol 10 mg),

$Pd(PPh_3)_4$ (0.08 eq, 0.004 mmol, 5 mg) and PPh_3 (0.32 eq, 0.016 mmol, 4 mg). The product was isolated after PTLC (15% ethyl acetate : 85% hexanes) in a 49% yield (8 mg) as an off white yellowish powder. **SFC conditions**: IE, EtOH 1-60% gradient: Time 4 minutes : (99% CO_2, 1% EtOH), Time 14.0min (40% CO_2, 60% EtOH), Time 14.1 min (40% CO_2, 60% MeCN), Time 34.1 min (99% CO_2, 1% EtOH), Time 35.0 (99% CO_2, 1% EtOH) 1.10 mL, 50°C. Retention time (min): 23.59, 24.61

Synthesis of *(R)*-1-(4-(1-(4-(anthracen-9-yl)phenyl)-2-phenylethyl)phenyl)ethanone *(R)*-16b:

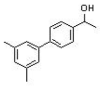


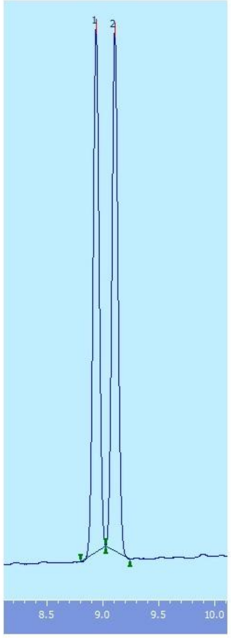
Synthesis followed general **method F** using *(R)*-2-(1-(4-(anthracen-9-yl)phenyl)-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ***(R)*-15b** (1.5 eq, 0.05 mmol, 50 mg), 4-iodoacetophenone (1 eq, 0.05 mmol, 13 mg), Ag_2O (1.5 eq, 0.075 mmol, 17 mg), K_2CO_3 (1.5 eq, 0.075 mmol 10 mg), $Pd(PPh_3)_4$ (0.08 eq, 0.004 mmol, 5 mg) and PPh_3 (0.32 eq, 0.016 mmol, 4 mg). The product was isolated after PTLC (15% ethyl acetate :85% hexanes) in a 48% yield (7 mg) as an off white yellow powder. **^{1}H-NMR:** ($CDCl_3$, 400 MHz) δ 8.34 (m, 1 H), 8.07 (d, 2H, *J*= 8.1 Hz), 7.82 (m, 1H), 7.70 (m, 18H), 7.56 (m, 8H), 7.48 (m, 16H), 4.23 (m, 1H), 3.93 (m, 2H), 2.66 (s, 3H) **SFC conditions:** IE, EtOH 1-60% gradient: Time 4 minutes : (99% CO_2, 1% EtOH), Time 14.0min (40% CO_2, 60% EtOH), Time 14.1 min (40% CO_2, 60% MeCN), Time 34.1 min (99% CO_2, 1% EtOH), Time 35.0 (99% CO_2, 1% EtOH) 1.10 mL, 50°C. e.r: **13:87 (S:R)**, Retention time (min): 24.46, 24.19

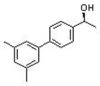
4.7: Appendix

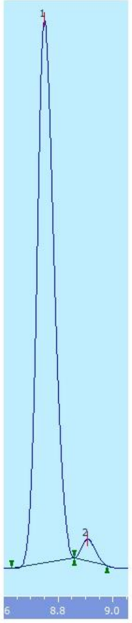
4.7.1: Supercritical Fluid Chromatographs

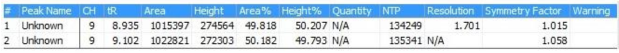
Di Boronic Esters Supercritical Fluid Chromatographs of Racemic and Enantioenriched Spectra (Side by Side)





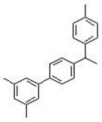


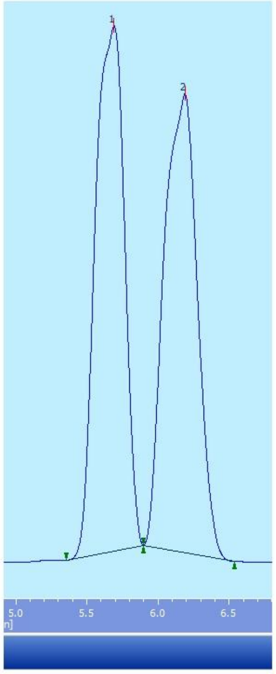


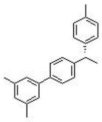


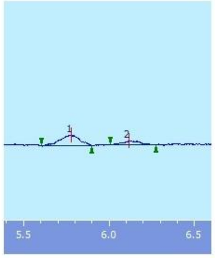
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	8.935	1015397	274564	49.818	50.207	N/A	134249	1.701	1.015	
2	Unknown	9	9.102	1022821	272303	50.182	49.793	N/A	135341	N/A	1.058	

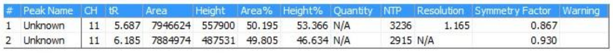
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	8.748	9409826	2164138	96.961	96.178	N/A	93041	1.499	1.181	
2	Unknown	11	8.905	294888	85996	3.039	3.822	N/A	141116	N/A	1.253	



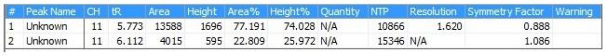




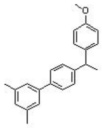


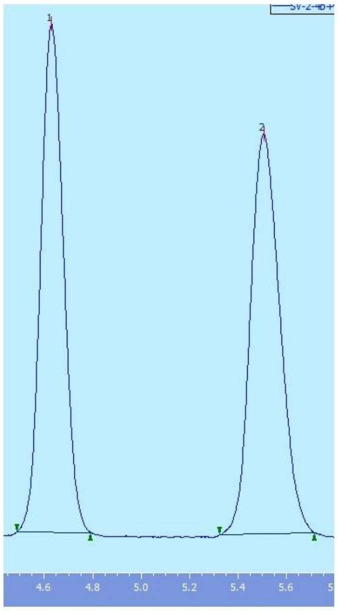


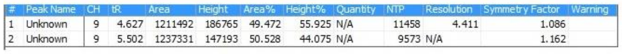
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	5.687	7946624	557900	50.195	53.366	N/A	3236	1.165	0.867	
2	Unknown	11	6.185	7884974	487531	49.805	46.634	N/A	2915	N/A	0.930	



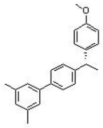
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	5.773	13588	1696	77.191	74.028	N/A	10866	1.620	0.888	
2	Unknown	11	6.112	4015	595	22.809	25.972	N/A	15346	N/A	1.086	

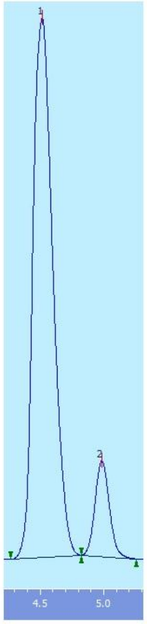


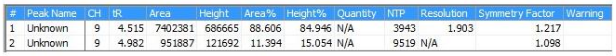




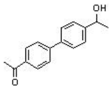
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	4.627	1211492	186765	49.472	55.925	N/A	11458	4.411	1.086	
2	Unknown	9	5.502	1237331	147193	50.528	44.075	N/A	9573	N/A	1.162	

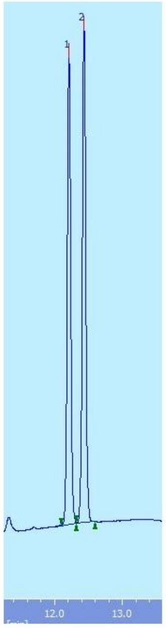


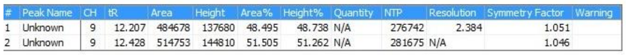




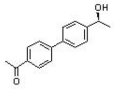
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	4.515	7402381	686665	88.606	84.946	N/A	3943	1.903	1.217	
2	Unknown	9	4.982	951887	121692	11.394	15.054	N/A	9519	N/A	1.098	

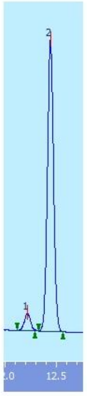


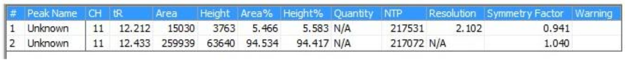




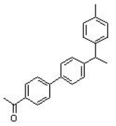
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	12.207	484678	137680	48.495	48.738	N/A	276742	2.384	1.051	
2	Unknown	9	12.428	514753	144810	51.505	51.262	N/A	281675	N/A	1.046	

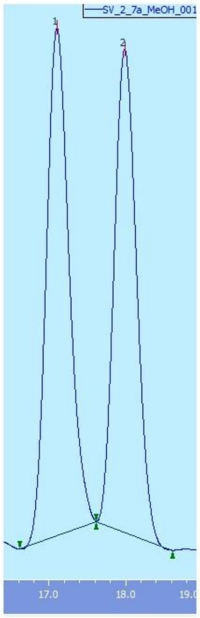


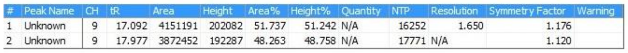




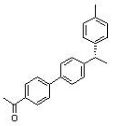
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	12.212	15030	3763	5.466	5.583	N/A	217531	2.102	0.941	
2	Unknown	11	12.433	259939	63640	94.534	94.417	N/A	217072	N/A	1.040	

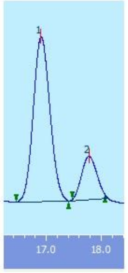


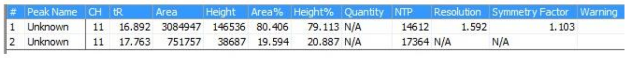




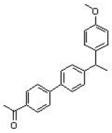
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	17.092	4151191	202082	51.737	51.242	N/A	16252	1.650	1.176	
2	Unknown	9	17.977	3872452	192287	48.263	48.758	N/A	17771	N/A	1.120	

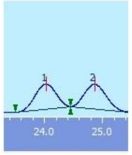


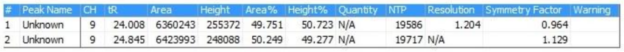




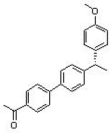
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	16.892	3084947	146536	80.406	79.113	N/A	14612	1.592	1.103	
2	Unknown	11	17.763	751757	38687	19.594	20.887	N/A	17364	N/A	N/A	

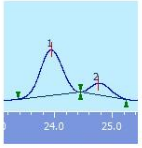


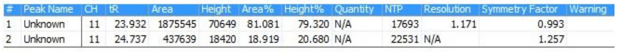




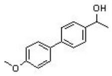
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	24.008	6360243	255372	49.751	50.723	N/A	19586	1.204	0.964	
2	Unknown	9	24.845	6423993	248088	50.249	49.277	N/A	19717	N/A	1.129	

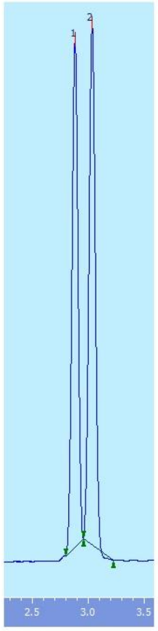




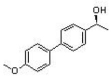


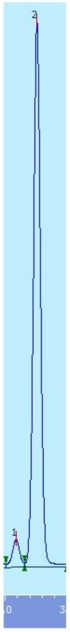
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	23.932	1875545	70649	81.081	79.320	N/A	17693	1.171	0.993	
2	Unknown	11	24.737	437639	18420	18.919	20.680	N/A	22531	N/A	1.257	

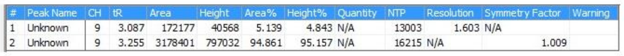




#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	2.878	918397	246586	48.114	49.339	N/A	13205	1.481	0.974	
2	Unknown	9	3.030	990380	253198	51.886	50.661	N/A	13272	N/A	1.010	







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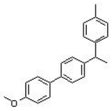
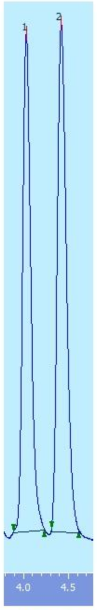
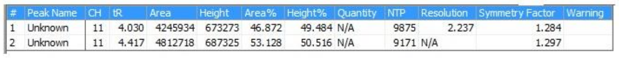
1	Unknown	9	3.087	172177	40568	5.139	4.843	N/A	13003	1.603	N/A	
2	Unknown	9	3.255	3178401	797032	94.861	95.157	N/A	16215	N/A	1.009	







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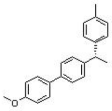
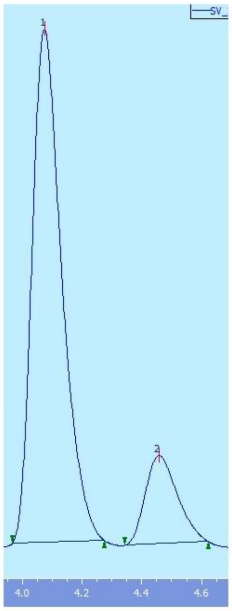
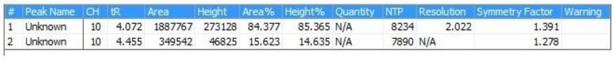
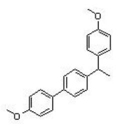
1	Unknown	11	4.030	4245934	673273	46.872	49.484	N/A	9875	2.237	1.284	
2	Unknown	11	4.417	4812718	687325	53.128	50.516	N/A	9171	N/A	1.297	

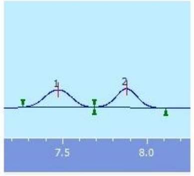


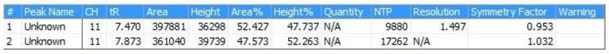




#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	10	4.072	1887767	273128	84.377	85.365	N/A	8234	2.022	1.391	
2	Unknown	10	4.455	349542	46825	15.623	14.635	N/A	7890	N/A	1.278	







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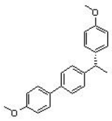
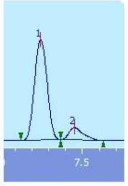
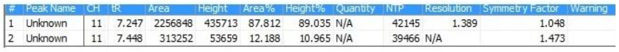
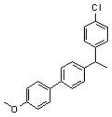
1	Unknown	11	7.470	397881	36298	52.427	47.737	N/A	9880	1.497	0.953	
2	Unknown	11	7.873	361040	39739	47.573	52.263	N/A	17262	N/A	1.032	

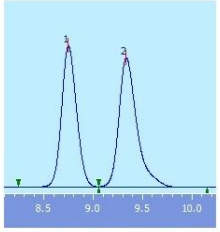


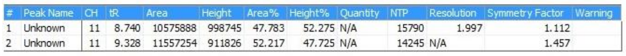




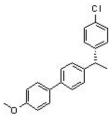
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	7.247	2256848	435713	87.812	89.035	N/A	42145	1.389	1.048	
2	Unknown	11	7.448	313252	53659	12.188	10.965	N/A	39466	N/A	1.473	

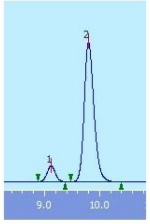


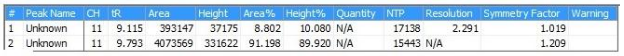




#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	8.740	10575888	998745	47.783	52.275	N/A	15790	1.997	1.112	
2	Unknown	11	9.328	11557254	911826	52.217	47.725	N/A	14245	N/A	1.457	







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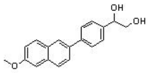
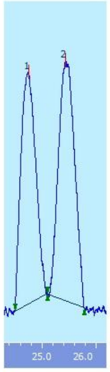
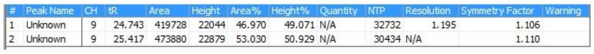
1	Unknown	11	9.115	393147	37175	8.802	10.080	N/A	17138	2.291	1.019	
2	Unknown	11	9.793	4073569	331622	91.198	89.920	N/A	15443	N/A	1.209	

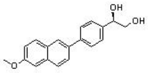
Tri Boronic Ester Supercritical Fluid Chromatographs of Racemic and Enantioenriched Spectra (Side by Side)

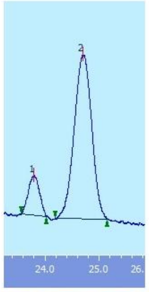


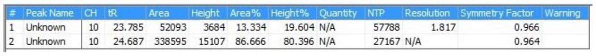




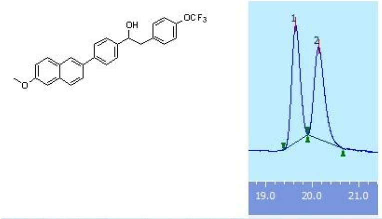
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	24.743	419728	22044	46.970	49.071	N/A	32732	1.195	1.106	
2	Unknown	9	25.417	473880	22879	53.030	50.929	N/A	30434	N/A	1.110	

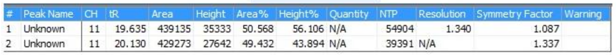




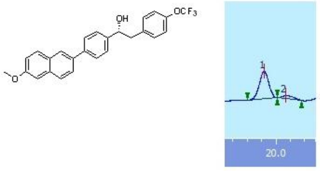


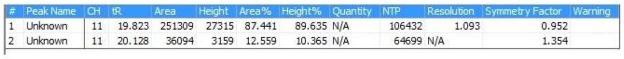
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	10	23.785	52093	3684	13.334	19.604	N/A	57788	1.817	0.966	
2	Unknown	10	24.687	338595	15107	86.666	80.396	N/A	27167	N/A	0.964	



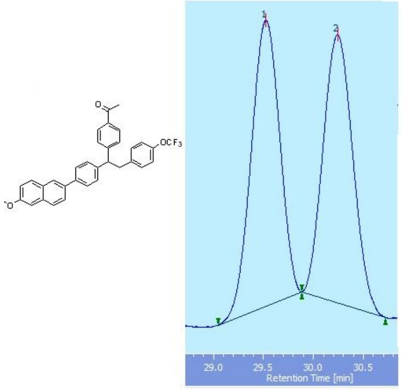


#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	19.635	439135	35333	50.568	56.106	N/A	54904	1.340	1.087	
2	Unknown	11	20.130	429273	27642	49.432	43.894	N/A	39391	N/A	1.337	

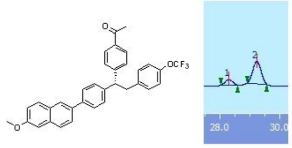




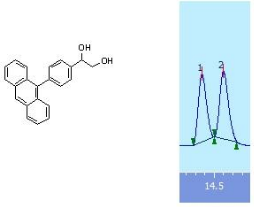
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	19.823	251309	27315	87.441	89.635	N/A	106432	1.093	0.952	
2	Unknown	11	20.128	36094	3159	12.559	10.365	N/A	64699	N/A	1.354	



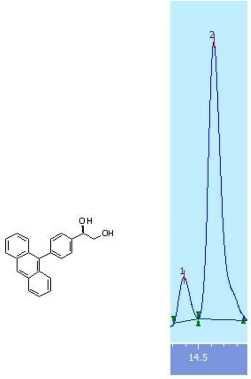
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	29.522	829118	41941	50.564	51.567	N/A	48674	1.312	0.949	
2	Unknown	9	30.237	810620	39392	49.436	48.433	N/A	47006	N/A	1.087	

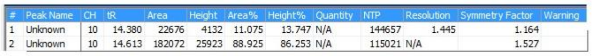


#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	12	28.270	53130	3169	18.270	20.435	N/A	57617	1.881	1.062	
2	Unknown	12	29.203	237669	12339	81.730	79.565	N/A	49675	N/A	1.045	

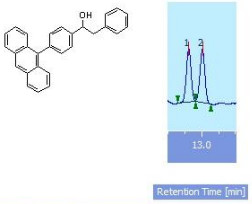


#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	14.362	1703522	285945	48.174	49.895	N/A	124630	1.361	1.168	
2	Unknown	9	14.588	1832669	287146	51.826	50.105	N/A	116113	N/A	1.263	

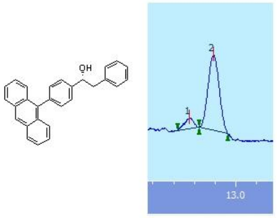


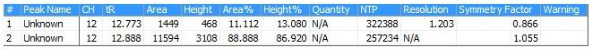


#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	10	14.380	22676	4132	11.075	13.747	N/A	144657	1.445	1.164	
2	Unknown	10	14.613	182072	25923	88.925	86.253	N/A	115021	N/A	1.527	

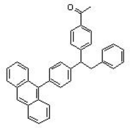


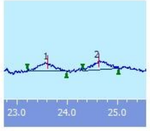
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	12.838	60915	15586	48.903	49.974	N/A	243059	1.525	0.959	
2	Unknown	11	13.000	63647	15602	51.097	50.026	N/A	230117	N/A	0.987	



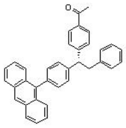


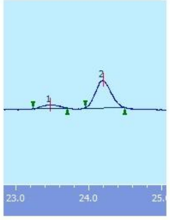
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	12	12.773	1449	468	11.112	13.080	N/A	322388	1.203	0.866	
2	Unknown	12	12.888	11594	3108	88.888	86.920	N/A	257234	N/A	1.055	





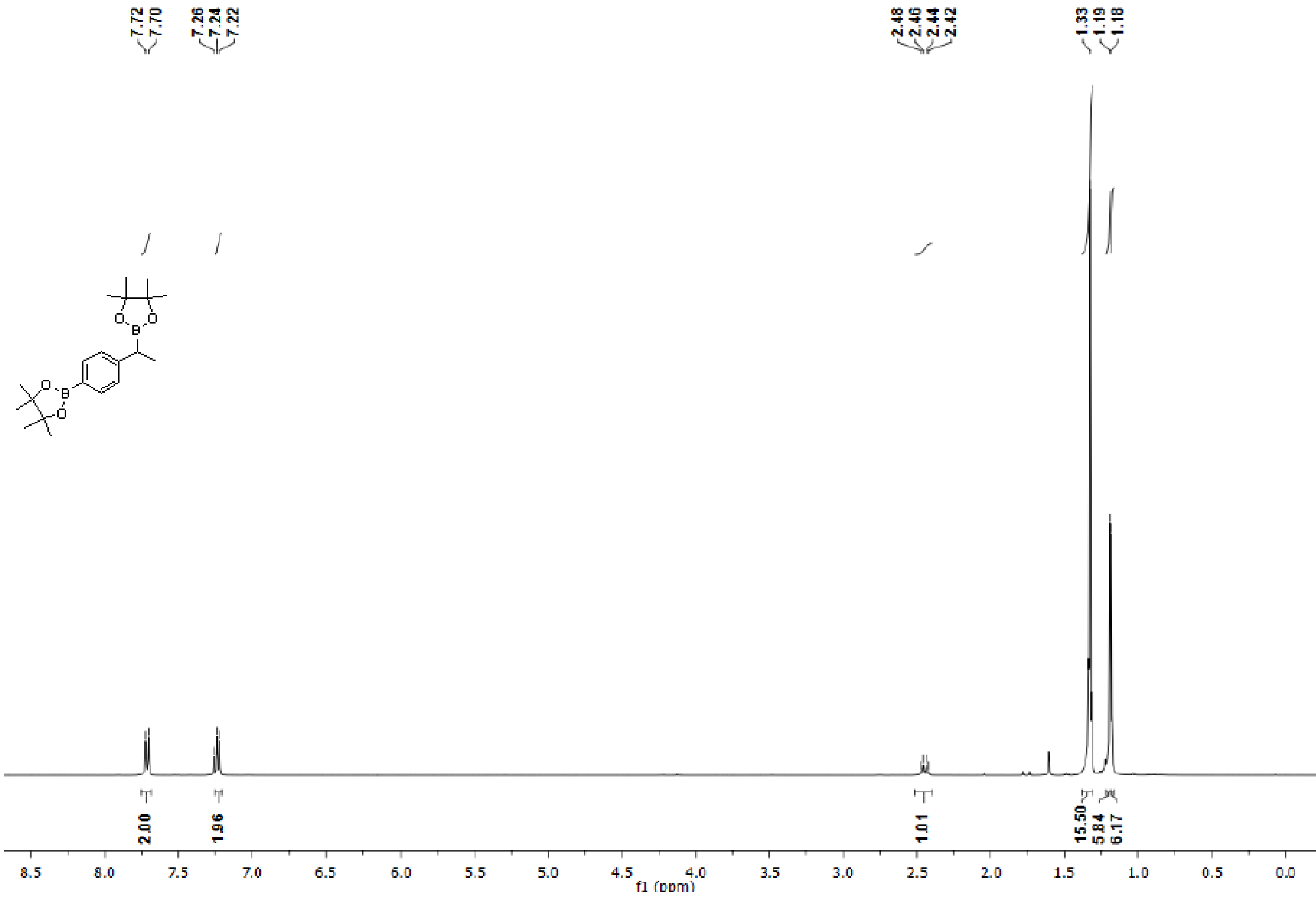
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	23.592	111980	5314	48.167	47.226	N/A	28507	1.788	0.940	
2	Unknown	11	24.618	120503	5939	51.833	52.774	N/A	27594	N/A	N/A	

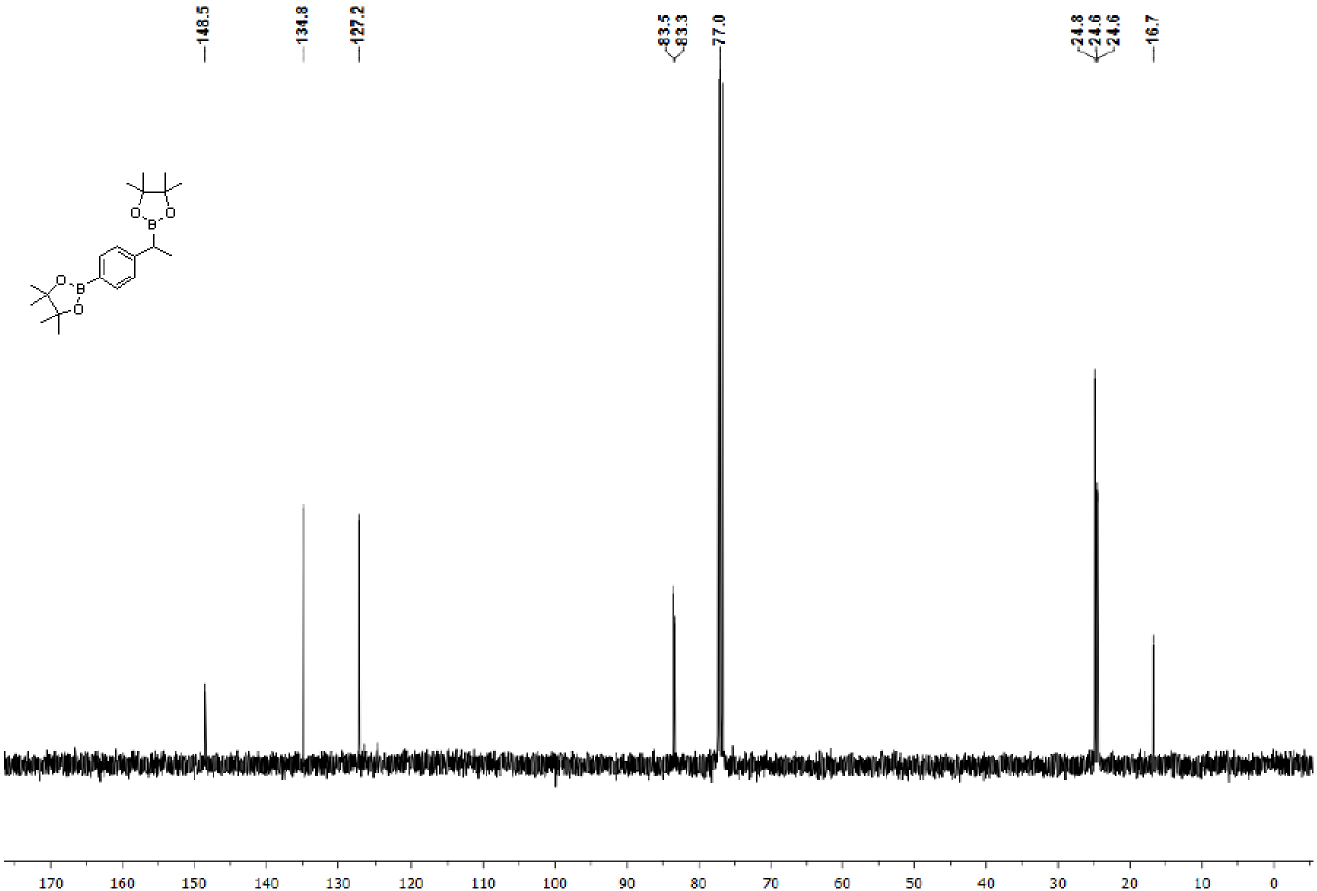


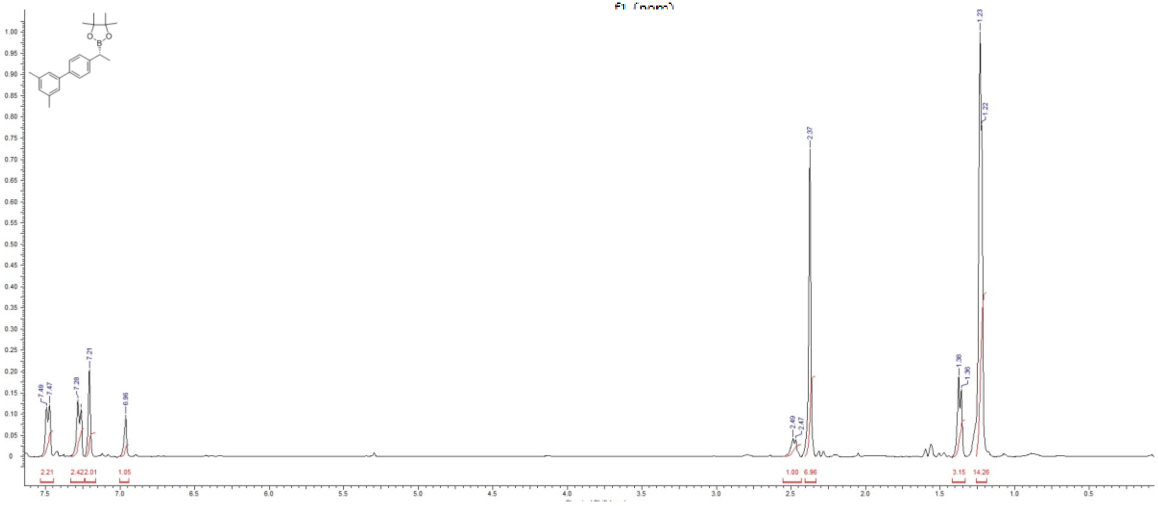


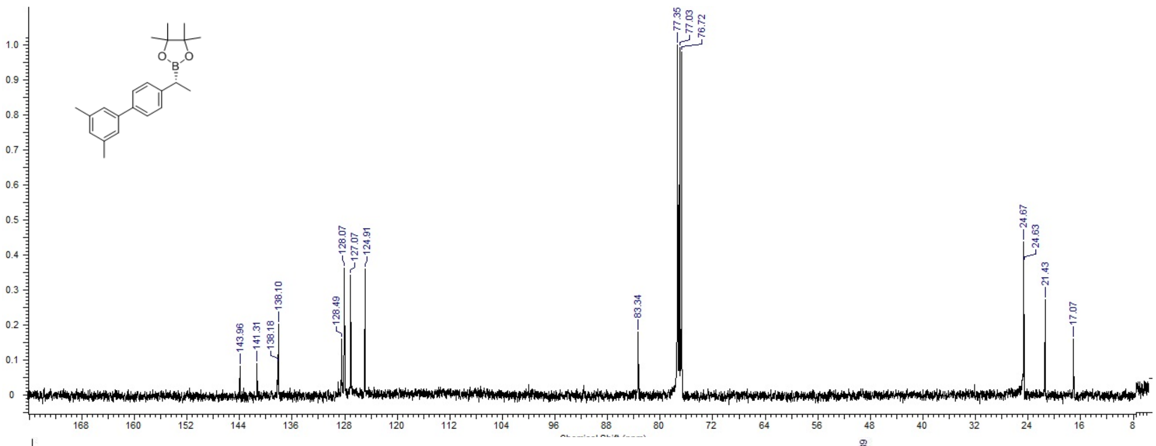
#	Peak Name	CH	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	11	23.468	114300	7199	13.233	12.480	N/A	41638	1.689	N/A	
2	Unknown	11	24.192	749476	50485	86.767	87.520	N/A	58875	N/A	1.038	

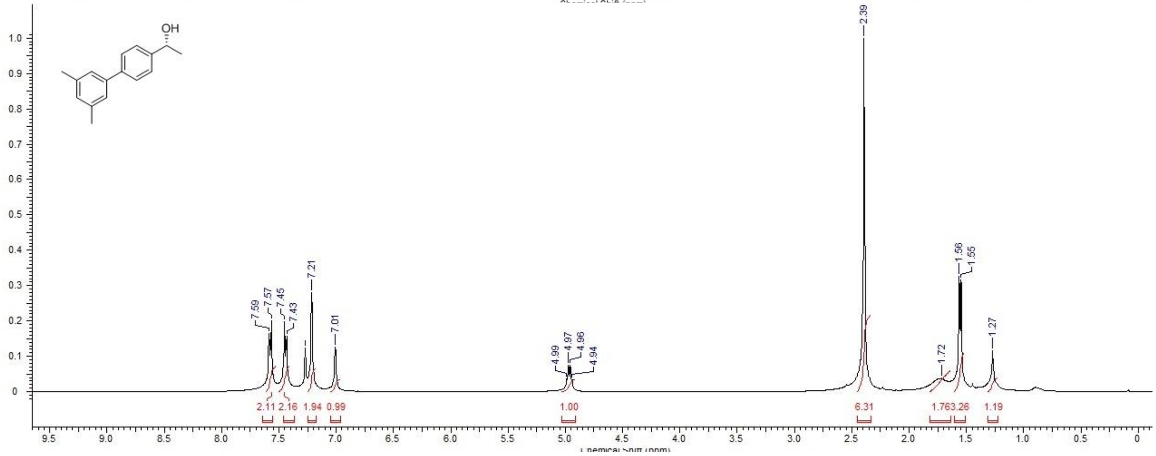
4.7.2: NMR Spectra

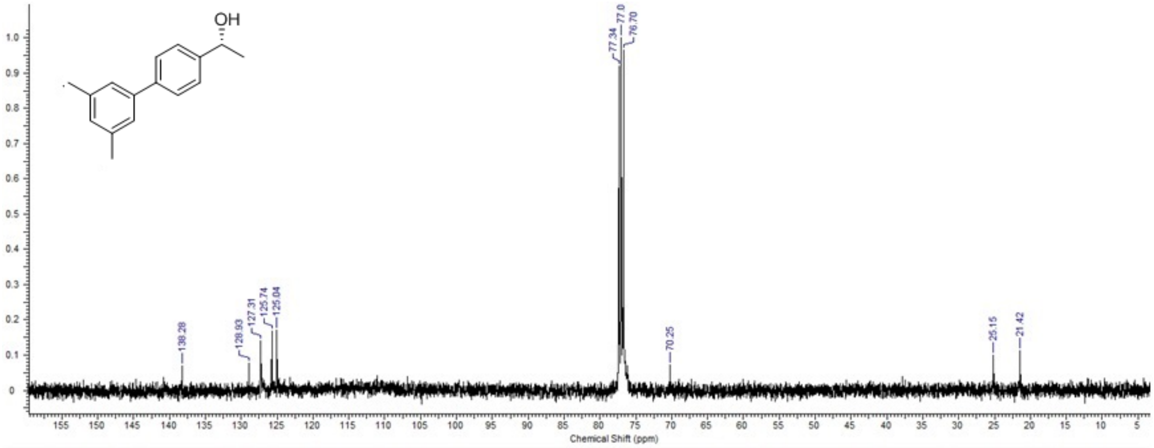

7.72
7.70
7.26
7.24
7.22
2.48
2.46
2.44
2.42
1.33
1.19
1.18
B
O
O
B
O
O
2.00
1.96
1.01
15.50
5.84
6.17
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

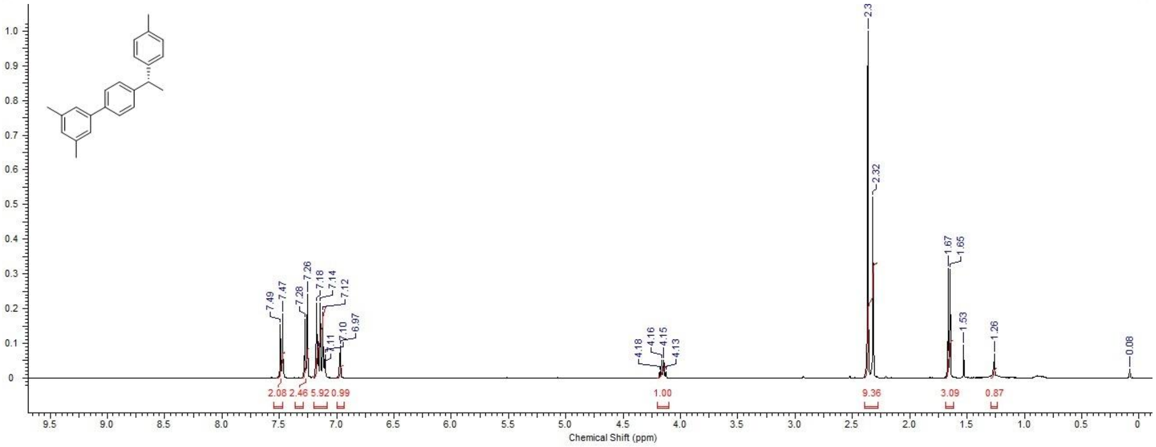

148.5
134.8
127.2
83.5
83.3
77.0
24.8
24.6
24.6
16.7
O
B
O
O
B
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

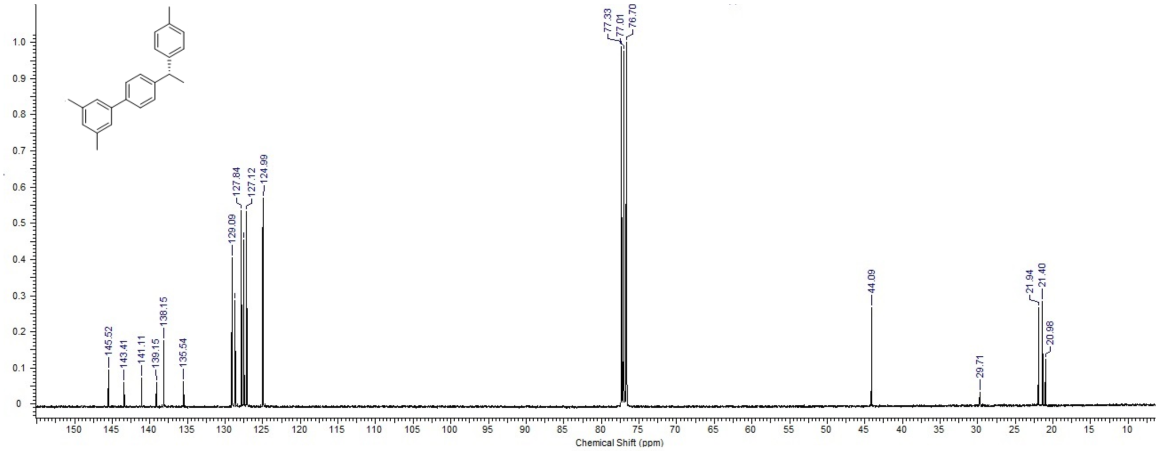

7.49
7.47
7.28
7.21
6.96
2.49
2.47
2.37
1.36
1.36
1.23
1.22
2.21
2.42
2.01
1.05
1.00
6.96
3.15
14.26
O
B
O
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

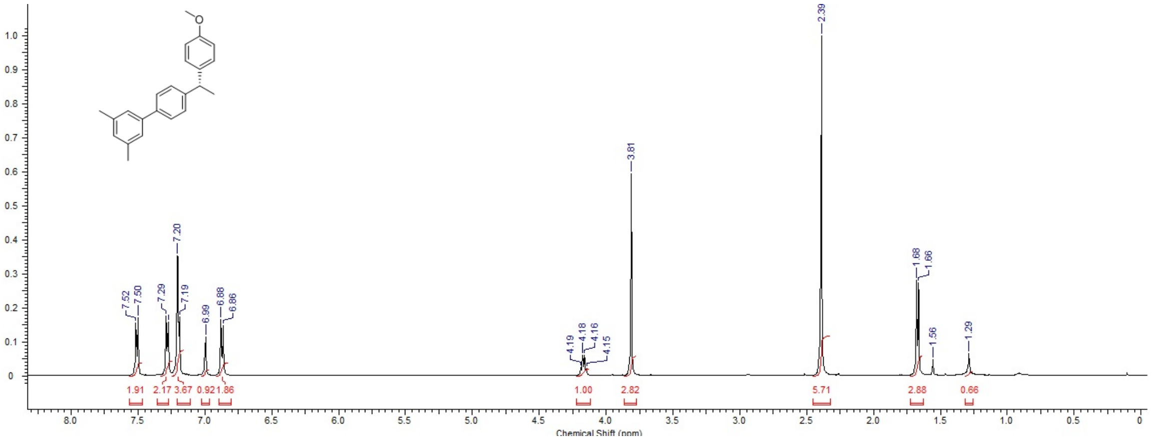

O
B
O
77.35
77.03
76.72
143.96
141.31
138.18
138.10
128.49
128.07
127.07
124.91
83.34
24.67
24.63
21.43
17.07
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8


OH
2.39
7.59
7.57
7.45
7.43
7.21
7.01
4.99
4.97
4.96
4.94
1.72
1.56
1.55
1.27
2.11
2.16
1.94
0.99
1.00
6.31
1.76
3.26
1.19
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

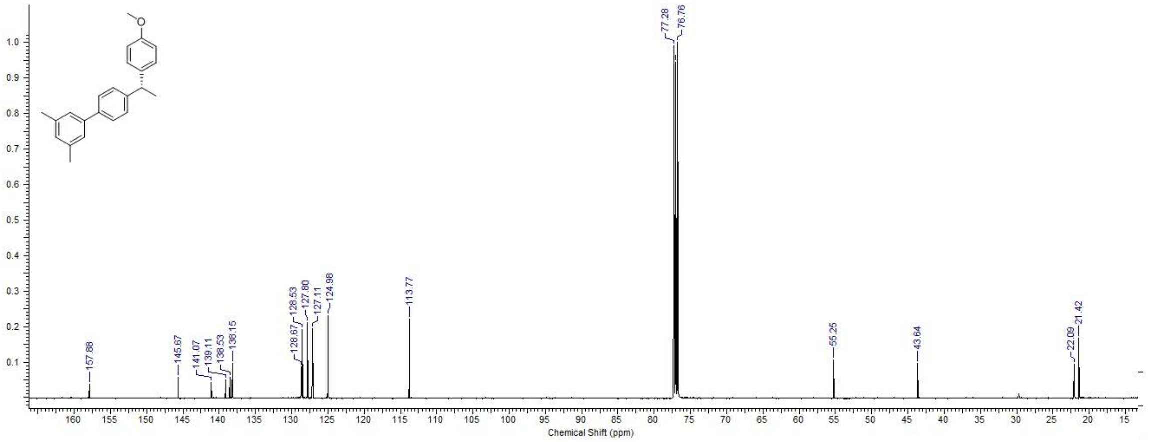

OH
77.34
77.0
76.70
138.28
128.93
127.31
125.74
125.04
70.25
25.15
21.42
Chemical Shift (ppm)


2.3
2.32
1.67
1.65
1.53
1.26
0.08
7.49
7.47
7.28
7.26
7.18
7.14
7.12
7.11
7.10
6.97
4.18
4.16
4.15
4.13
2.08
2.46
5.92
0.99
1.00
9.36
3.09
0.87
Chemical Shift (ppm)

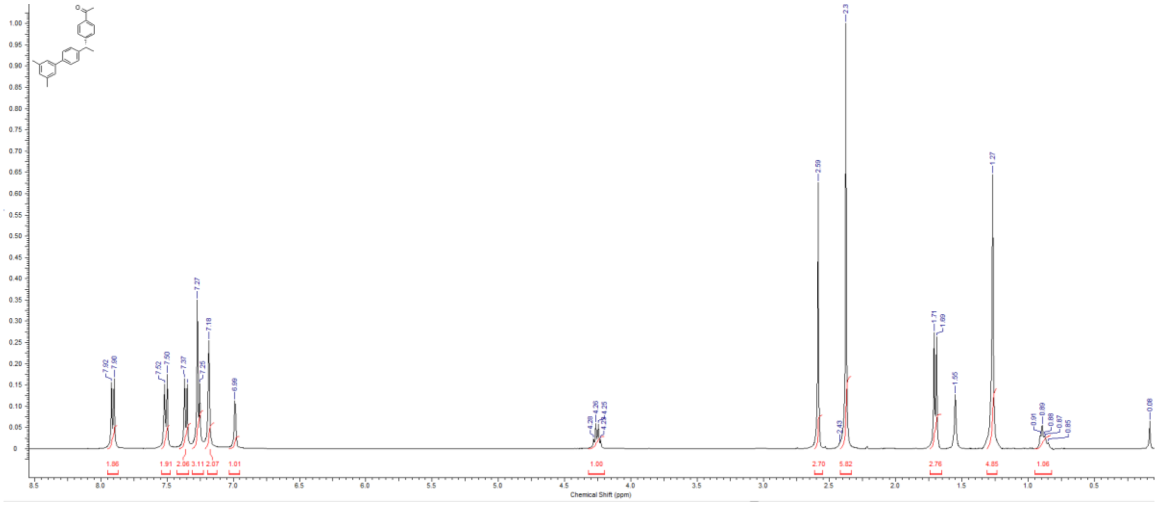

77.33
77.01
76.70
145.52
143.41
141.11
139.15
138.15
135.54
129.09
127.84
127.12
124.99
44.09
29.71
21.94
21.40
20.98
Chemical Shift (ppm)



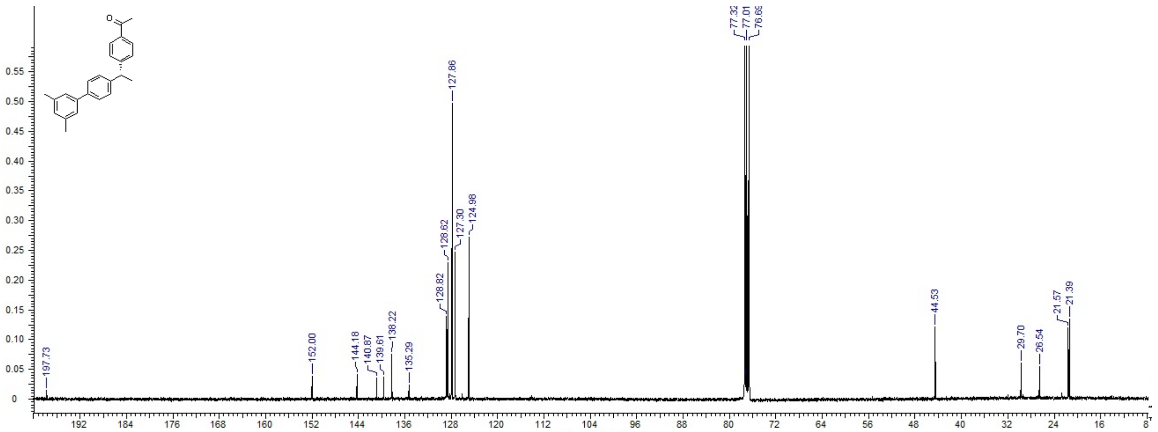
7.52
7.50
7.29
7.20
7.19
6.99
6.88
6.86
4.19
4.18
4.16
4.15
3.81
2.39
1.68
1.66
1.56
1.29
1.91
2.17
3.67
0.92
1.86
1.00
2.82
5.71
2.88
0.66
Chemical Shift (ppm)

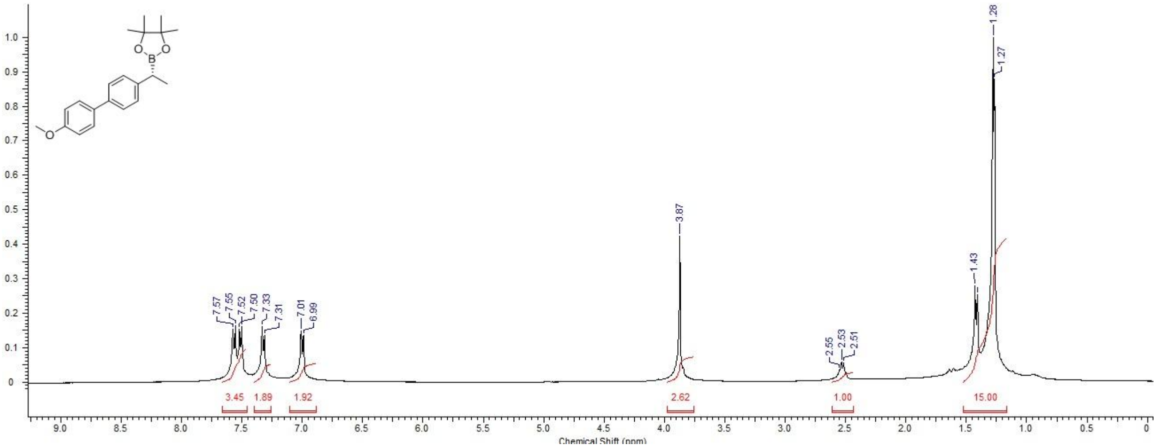


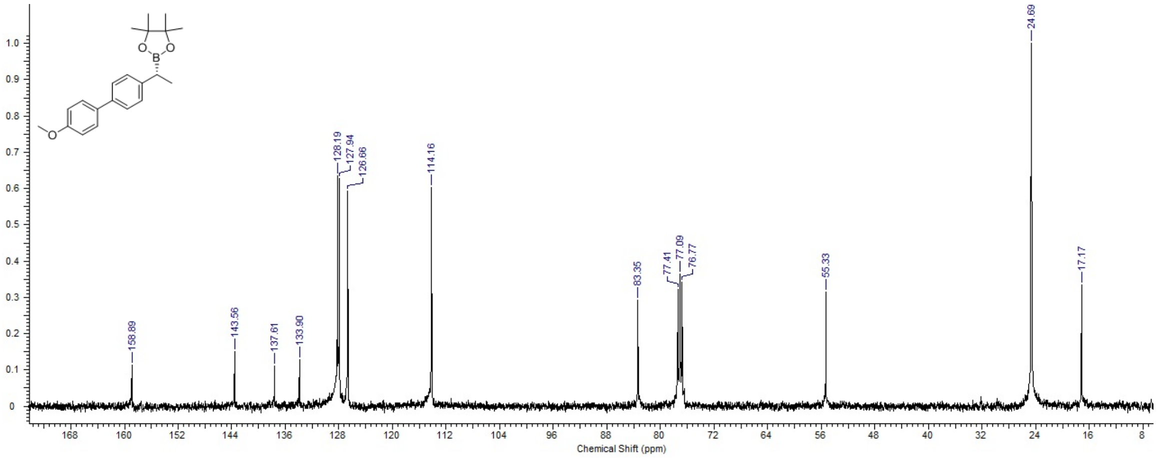
157.88
145.67
141.07
139.11
138.53
138.15
128.67
128.53
127.80
127.11
124.98
113.77
77.28
76.76
55.25
43.64
22.09
21.42
Chemical Shift (ppm)

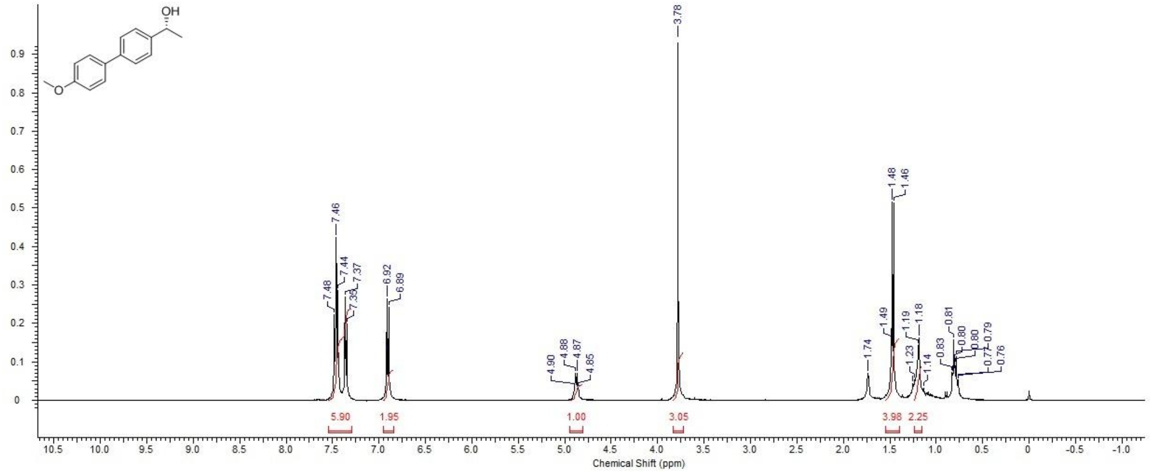


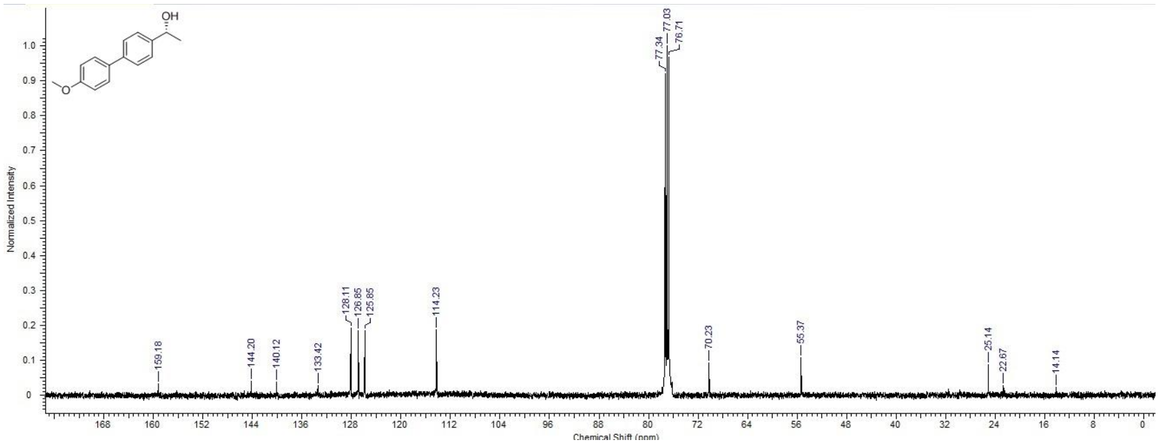
7.92
7.90
7.52
7.50
7.37
7.27
7.25
7.18
6.99
4.28
4.26
4.25
2.59
2.43
2.3
1.71
1.69
1.55
1.27
0.91
0.89
0.88
0.87
0.85
0.08
1.86
1.91
2.06
3.11
2.07
1.01
1.00
2.70
5.82
2.76
4.85
1.06
Chemical Shift (ppm)

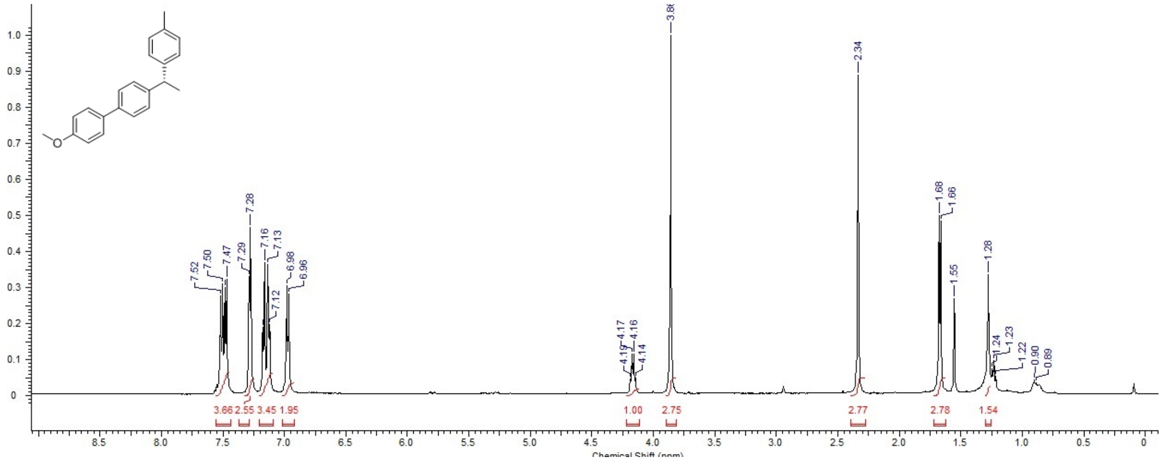

O
197.73
152.00
144.18
140.87
139.61
138.22
135.29
128.82
128.62
127.86
127.30
124.98
77.32
77.01
76.69
44.53
29.70
26.54
21.57
21.39
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

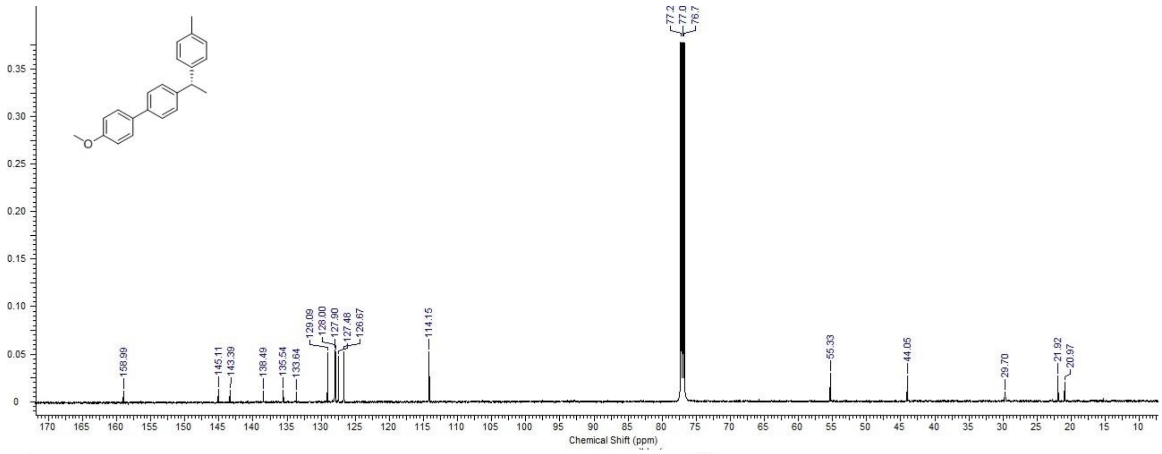

O
B
O
O
7.57
7.55
7.52
7.50
7.33
7.31
7.01
6.99
3.87
2.55
2.53
2.51
1.43
1.28
1.27
3.45
1.89
1.92
2.62
1.00
15.00
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

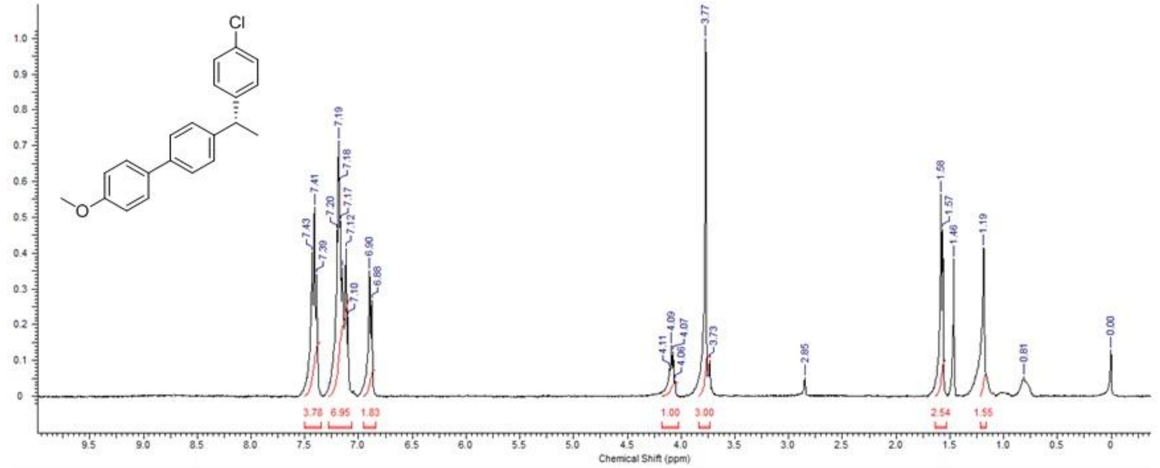

O
B
O
O
158.89
143.56
137.61
133.90
128.19
127.94
126.66
114.16
83.35
77.41
77.09
76.77
55.33
24.69
17.17
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

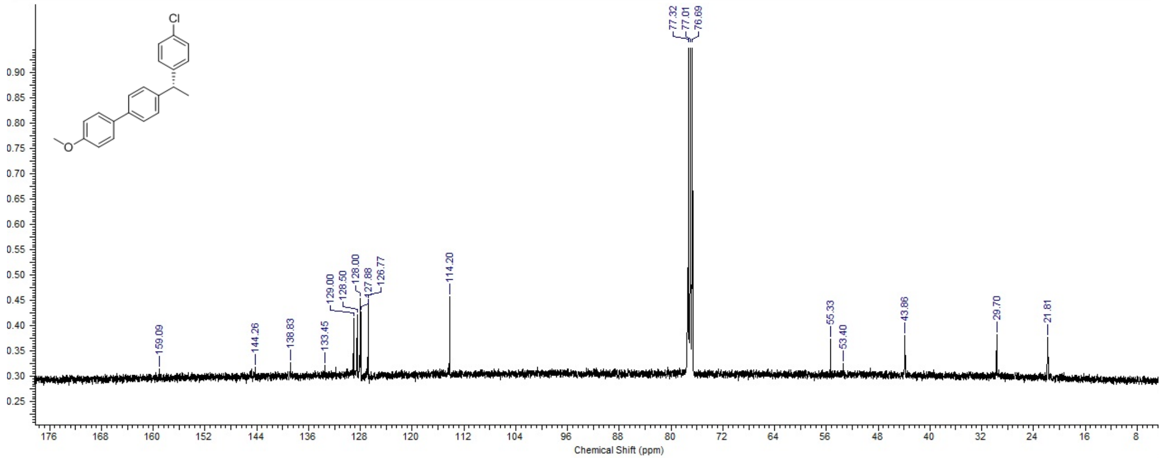

OH
O
7.48
7.46
7.44
7.39
7.37
6.92
6.89
4.90
4.88
4.87
4.85
3.78
1.74
1.49
1.48
1.46
1.23
1.19
1.18
1.14
0.83
0.81
0.80
0.80
0.79
0.77
0.76
5.90
1.95
1.00
3.05
3.98
2.25
Chemical Shift (ppm)

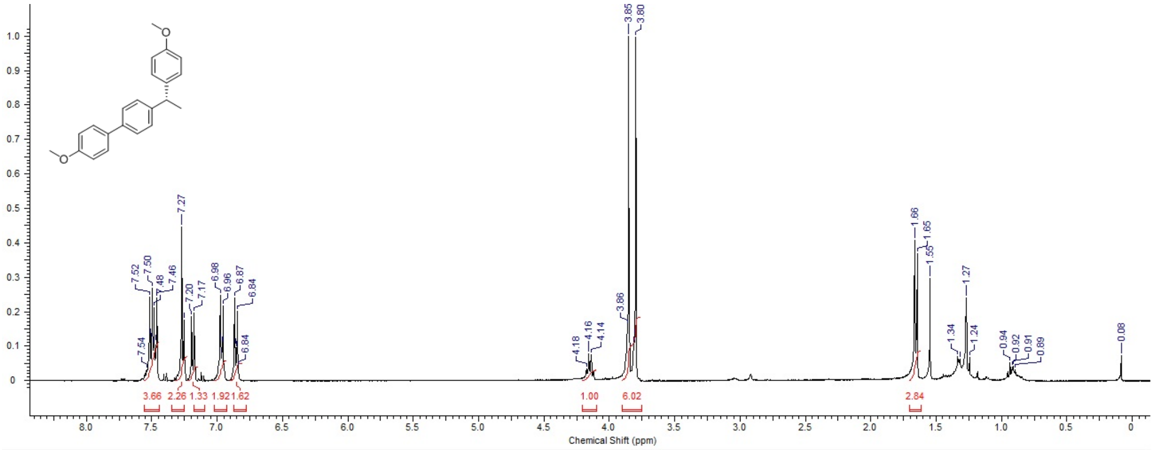

OH
O
Normalized Intensity
159.18
144.20
140.12
133.42
128.11
126.85
125.85
114.23
77.34
77.03
76.71
70.23
55.37
25.14
22.67
14.14
Chemical Shift (ppm)

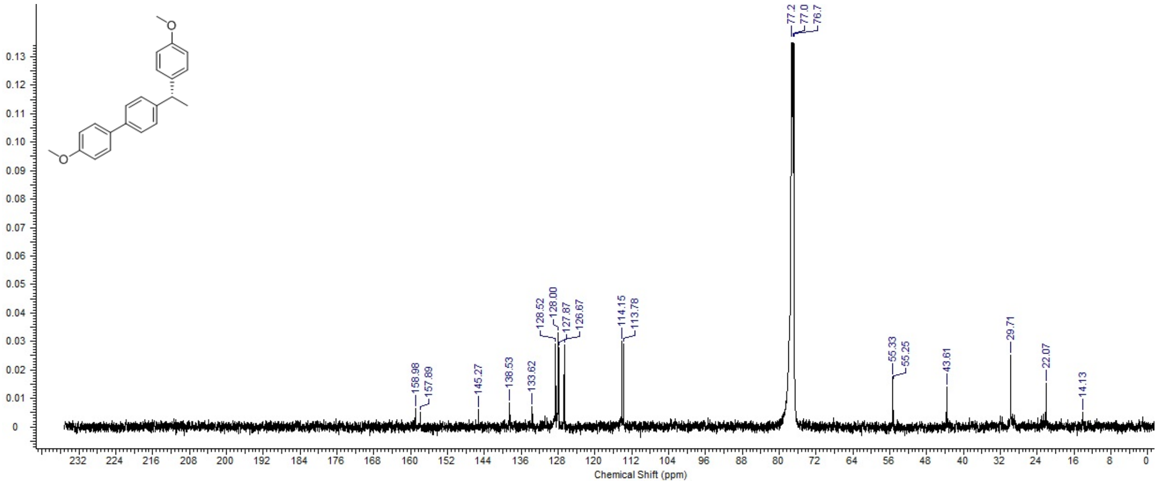

O
7.52
7.50
7.47
7.29
7.28
7.16
7.13
7.12
6.98
6.96
4.19
4.17
4.16
4.14
3.86
2.34
1.68
1.66
1.55
1.28
1.24
1.23
1.22
0.90
0.89
3.66
2.55
3.45
1.95
1.00
2.75
2.77
2.78
1.54
Chemical Shift (ppm)

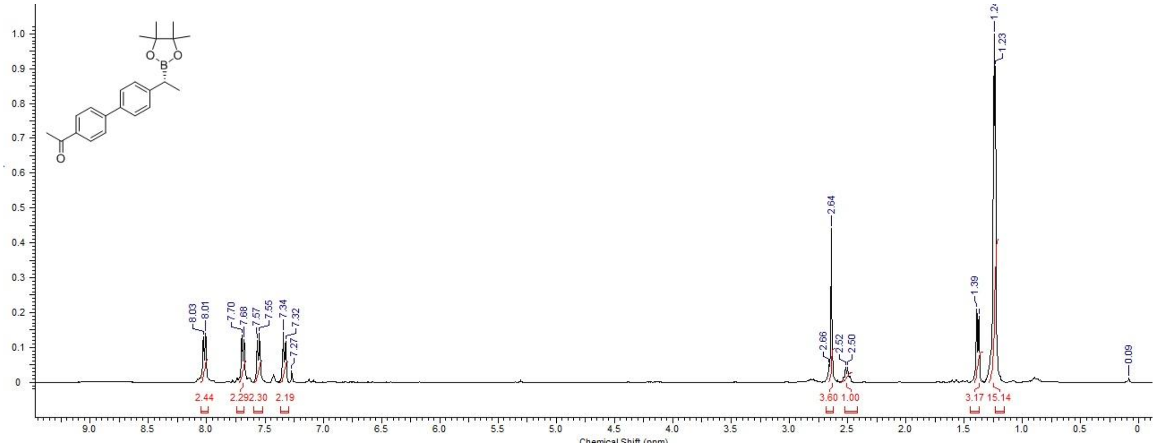

O
77.2
77.0
76.7
158.99
145.11
143.39
138.49
135.54
133.64
129.09
128.00
127.90
127.48
126.67
114.15
55.33
44.05
29.70
21.92
20.97
Chemical Shift (ppm)

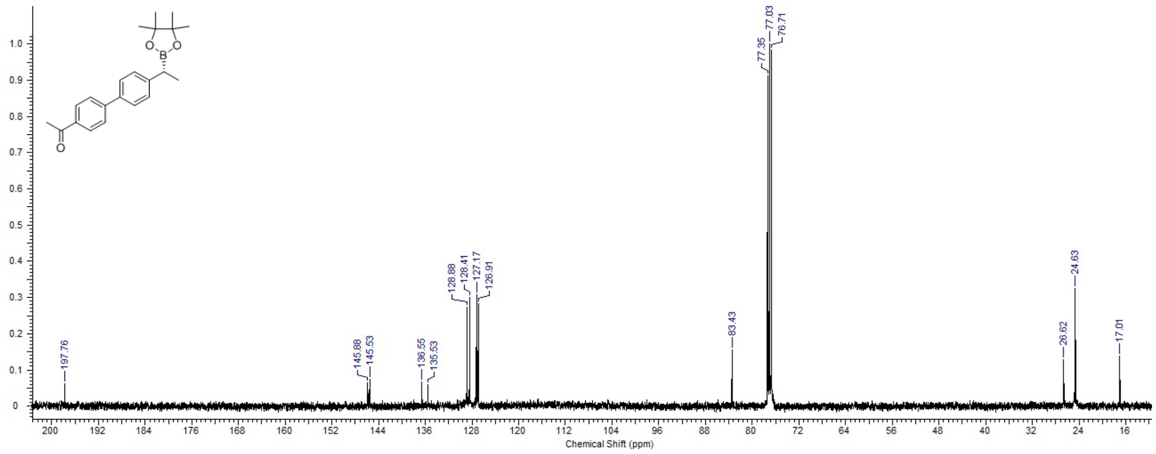

Cl
O
3.77
7.43
7.41
7.39
7.20
7.19
7.18
7.17
7.12
7.10
6.90
6.88
4.11
4.09
4.07
4.06
3.73
2.85
1.58
1.57
1.46
1.19
0.81
0.00
3.78
6.95
1.83
1.00
3.00
2.54
1.55
Chemical Shift (ppm)

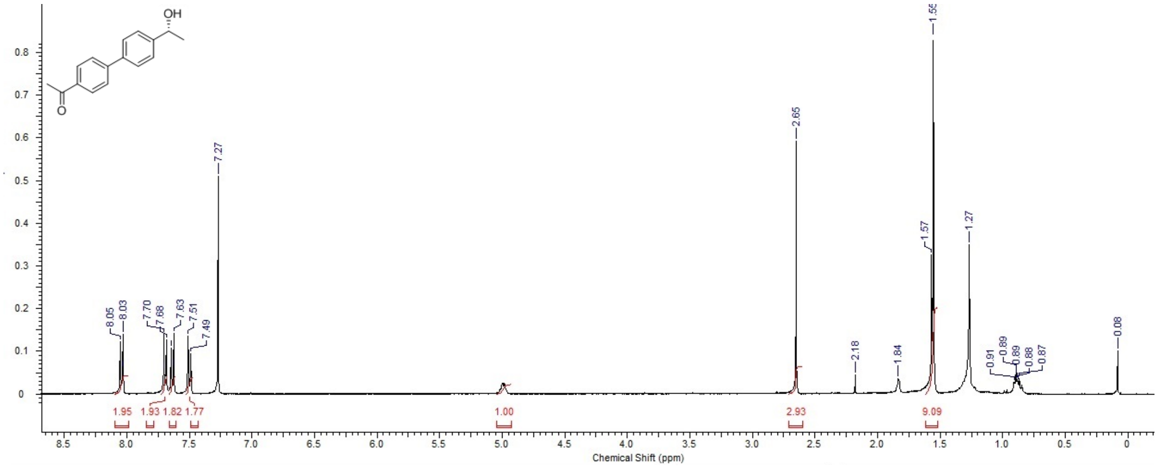

Cl
O
77.32
77.01
76.69
159.09
144.26
138.83
133.45
129.00
128.50
128.00
127.88
126.77
114.20
55.33
53.40
43.86
29.70
21.81
Chemical Shift (ppm)

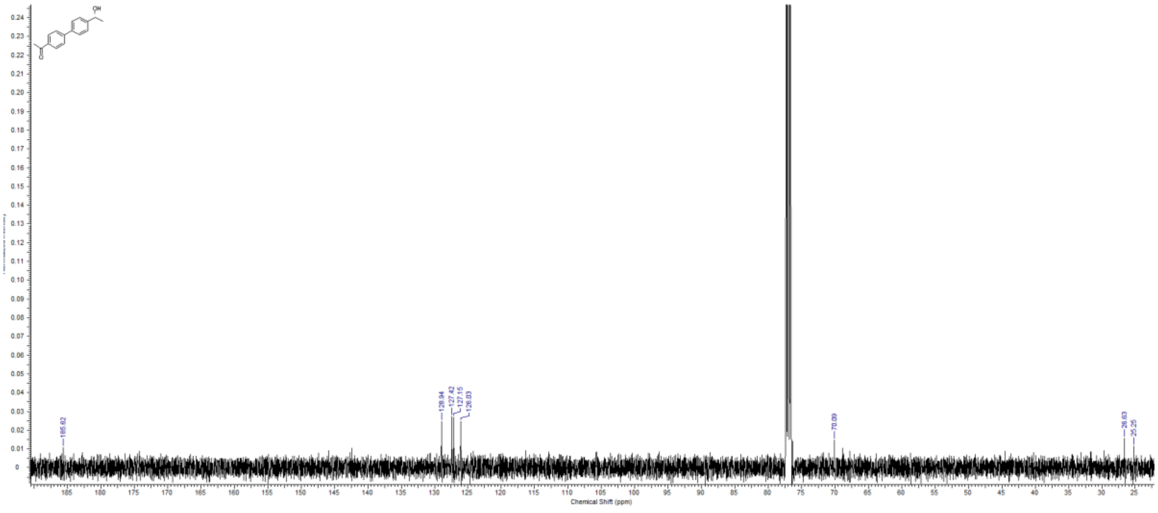

7.54
7.52
7.50
7.48
7.46
7.27
7.20
7.17
6.98
6.96
6.87
6.84
6.84
4.18
4.16
4.14
3.86
3.85
3.80
1.66
1.65
1.55
1.34
1.27
1.24
0.94
0.92
0.91
0.89
0.08
3.66
2.26
1.33
1.92
1.62
1.00
6.02
2.84
Chemical Shift (ppm)

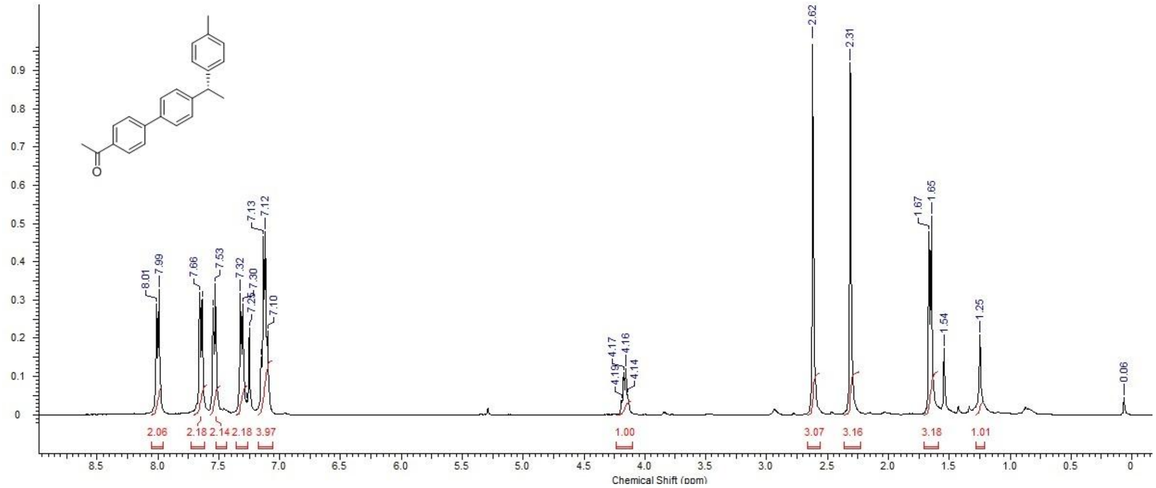

77.2
77.0
76.7
158.98
157.89
145.27
138.53
133.62
128.52
128.00
127.87
126.67
114.15
113.78
55.33
55.25
43.61
29.71
22.07
14.13
Chemical Shift (ppm)


O
B
O
O
8.03
8.01
7.70
7.68
7.57
7.55
7.34
7.32
7.27
2.66
2.64
2.52
2.50
1.39
1.2
1.23
0.09
2.44
2.29
2.30
2.19
3.60
1.00
3.17
15.14
Chemical Shift (ppm)

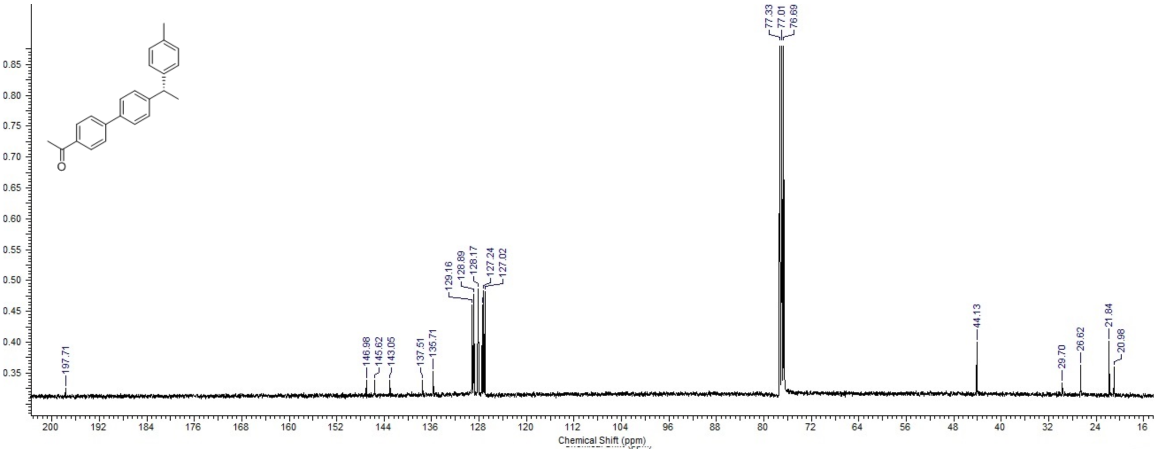

O
B
O
O
197.76
145.88
145.53
136.55
135.53
128.88
128.41
127.17
126.91
83.43
77.35
77.03
76.71
26.62
24.63
17.01
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)


OH
O
8.05
8.03
7.70
7.68
7.63
7.51
7.49
7.27
2.65
2.18
1.84
1.57
1.55
1.27
0.91
0.89
0.89
0.88
0.87
0.08
1.95
1.93
1.82
1.77
1.00
2.93
9.09
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

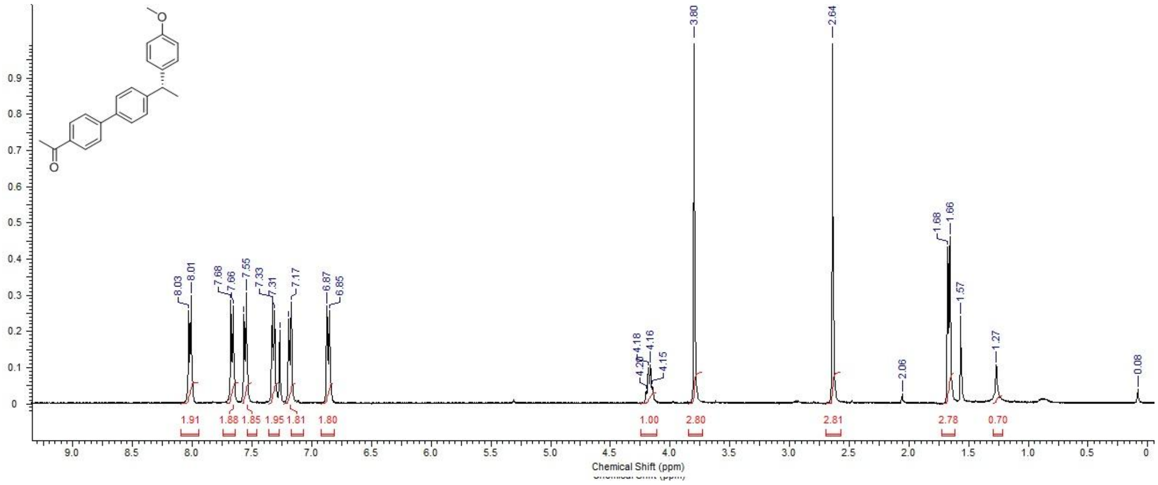

OH
O
185.62
128.94
127.42
127.15
126.03
70.09
26.63
25.25
0.24
0.23
0.22
0.21
0.20
0.19
0.18
0.17
0.16
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
Chemical Shift (ppm)



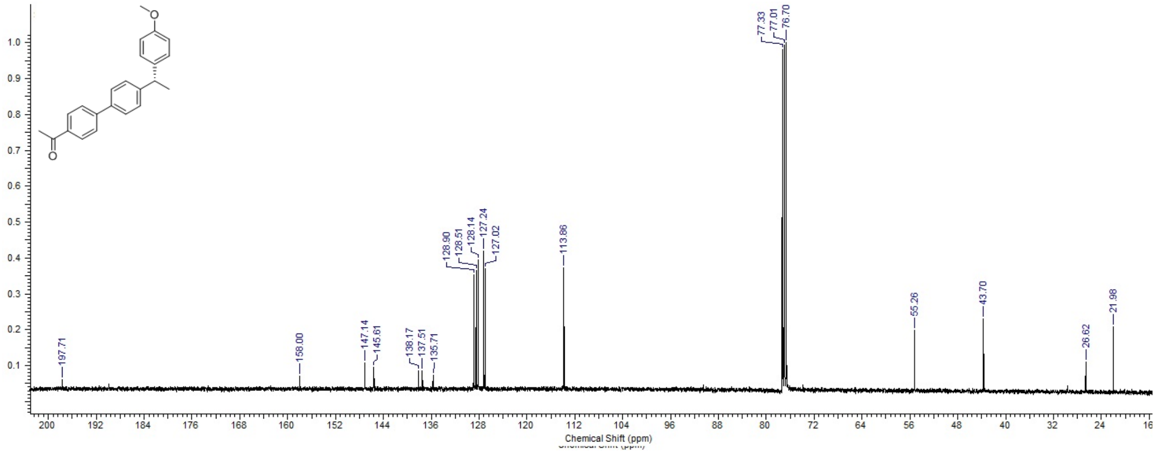
O
8.01
7.99
7.66
7.53
7.32
7.30
7.26
7.13
7.12
7.10
4.19
4.17
4.16
4.14
2.62
2.31
1.67
1.65
1.54
1.25
0.06
2.06
2.18
2.14
2.18
3.97
1.00
3.07
3.16
3.18
1.01
Chemical Shift (ppm)



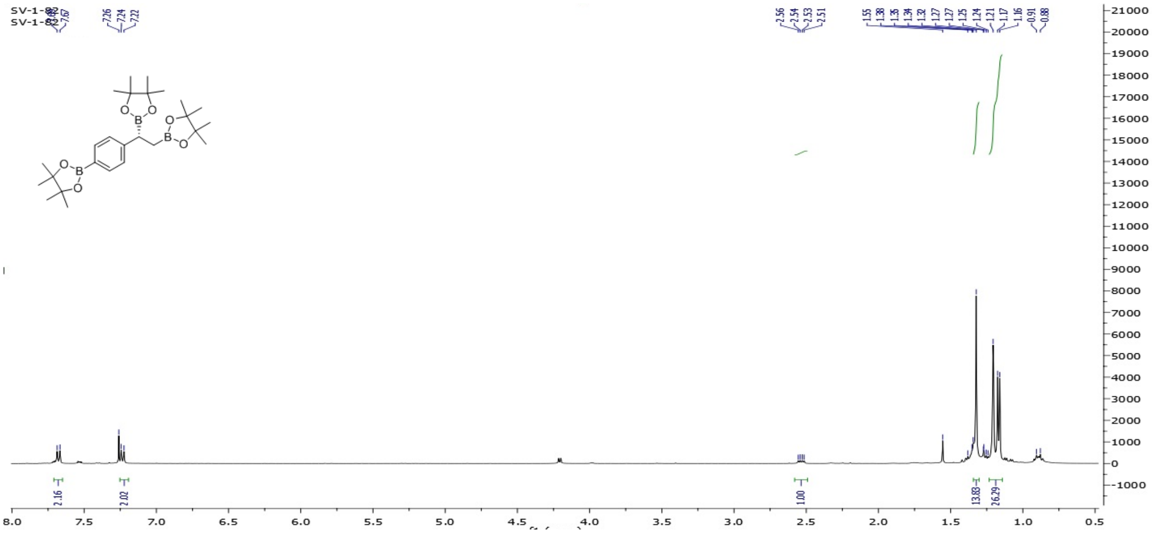
O
197.71
146.98
145.62
143.05
137.51
135.71
129.16
128.89
128.17
127.24
127.02
77.33
77.01
76.69
44.13
29.70
26.62
21.84
20.98
Chemical Shift (ppm)



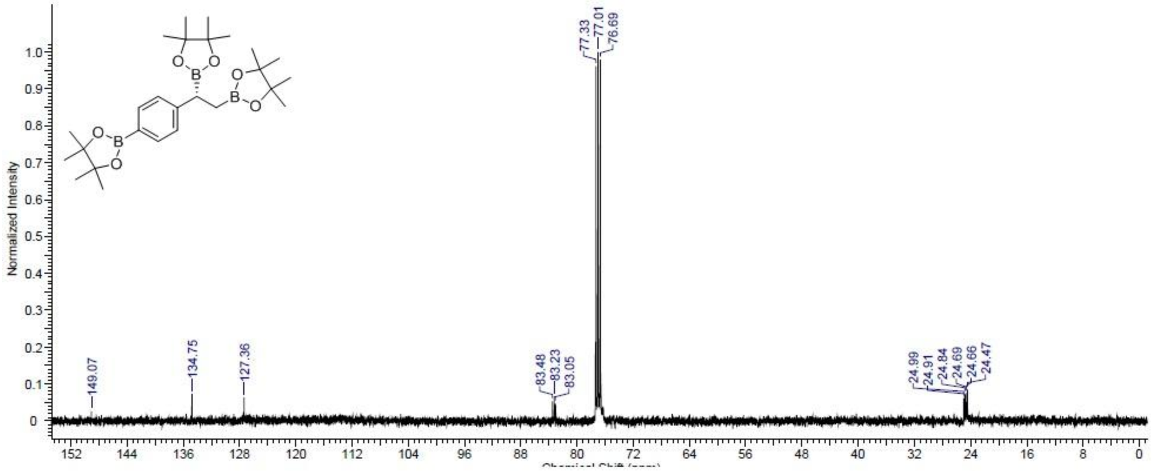
O
O
8.03
8.01
7.68
7.66
7.55
7.33
7.31
7.17
6.87
6.85
4.20
4.18
4.16
4.15
3.80
2.64
2.06
1.68
1.66
1.57
1.27
0.08
1.91
1.88
1.85
1.95
1.81
1.80
1.00
2.80
2.81
2.78
0.70
Chemical Shift (ppm)



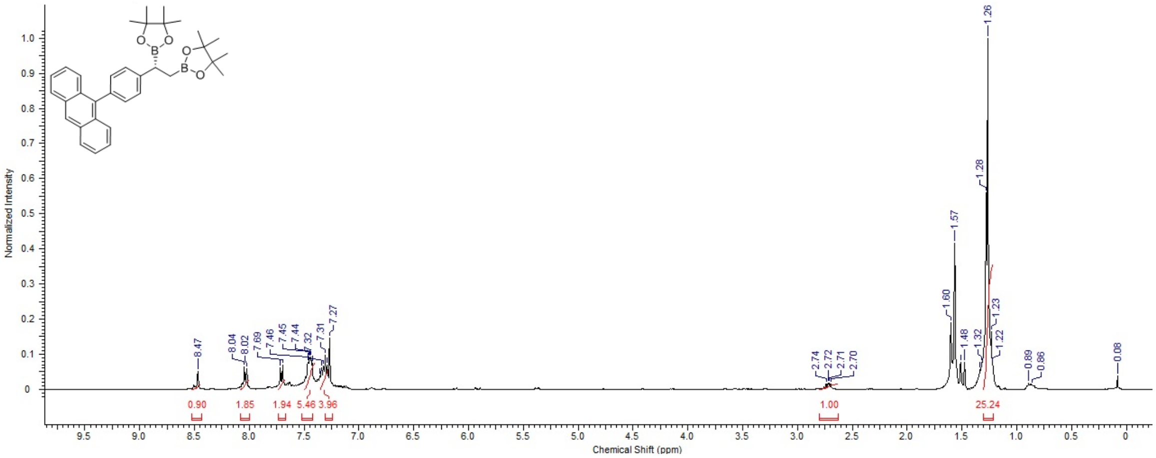
197.71
158.00
147.14
145.61
138.17
137.51
135.71
128.90
128.51
128.14
127.24
127.02
113.86
77.33
77.01
76.70
55.26
43.70
26.62
21.98
Chemical Shift (ppm)

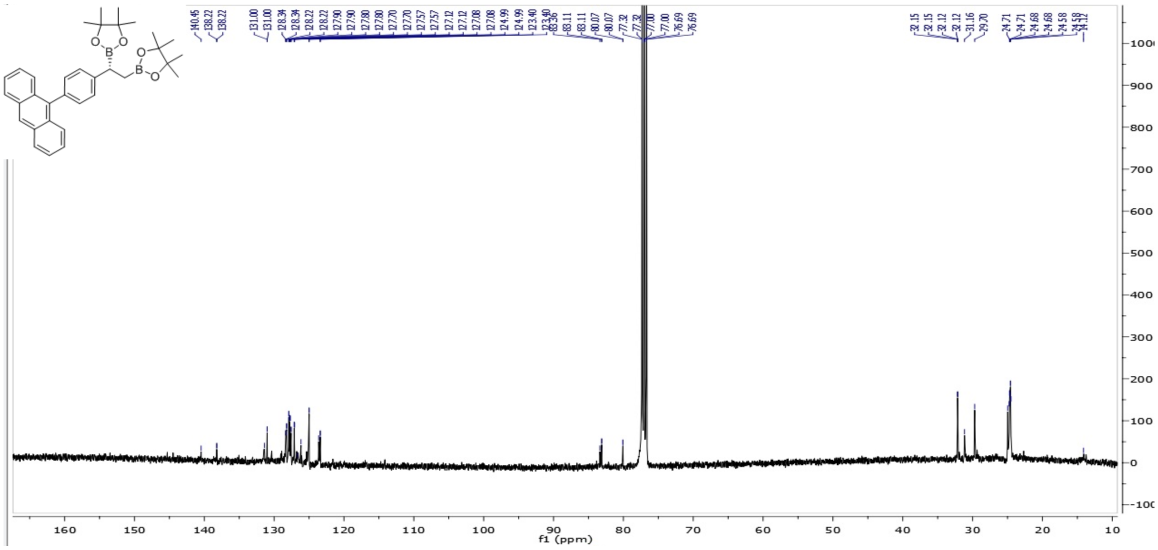


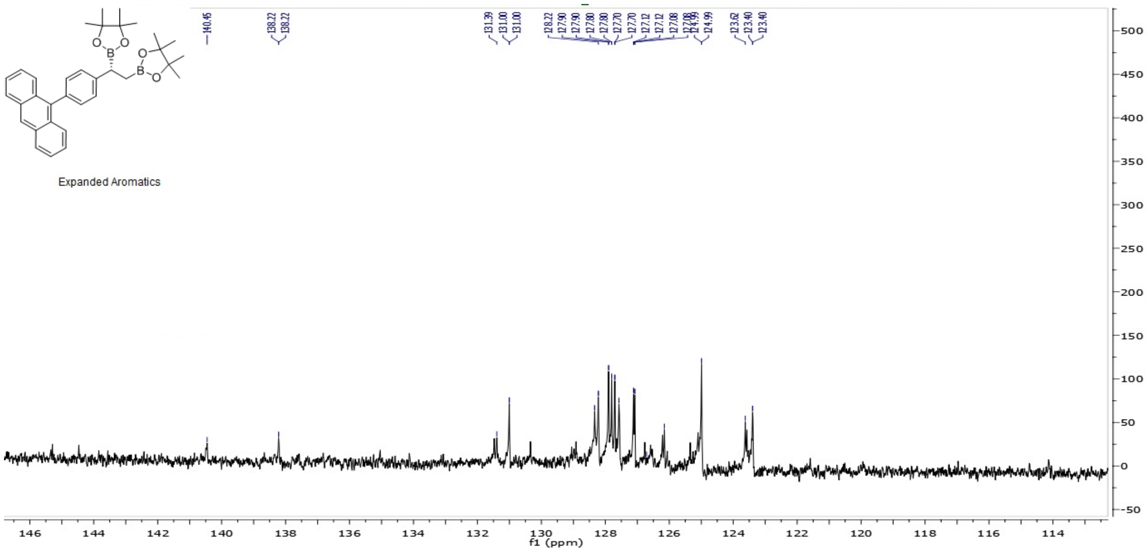
SV-1-8
7.67
7.26
7.24
7.22
2.56
2.54
2.53
2.51
1.55
1.38
1.36
1.34
1.32
1.27
1.27
1.25
1.24
1.21
1.17
1.16
0.91
0.88
2.16
2.02
1.00
13.83
26.29

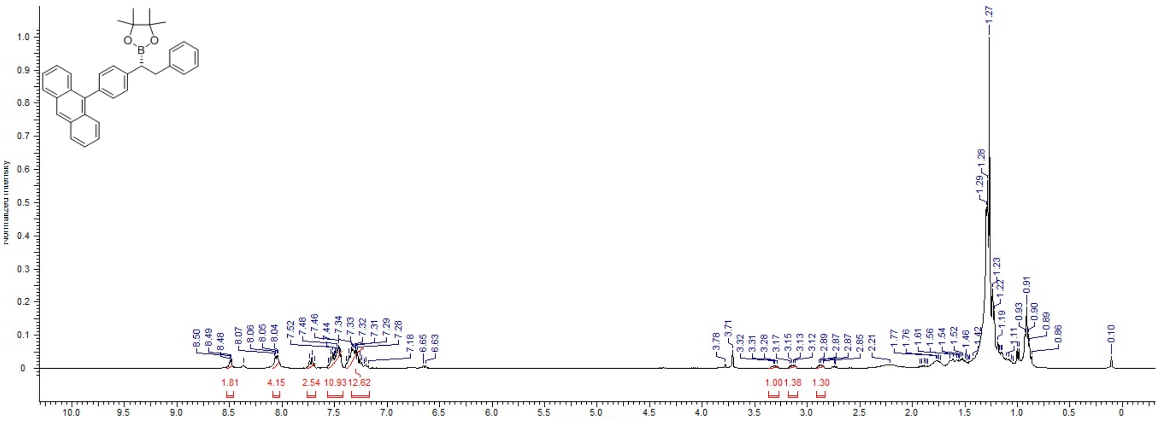


Normalized Intensity
149.07
134.75
127.36
83.48
83.23
83.05
77.33
77.01
76.69
24.99
24.91
24.84
24.69
24.66
24.47
Chemical Shift (ppm)

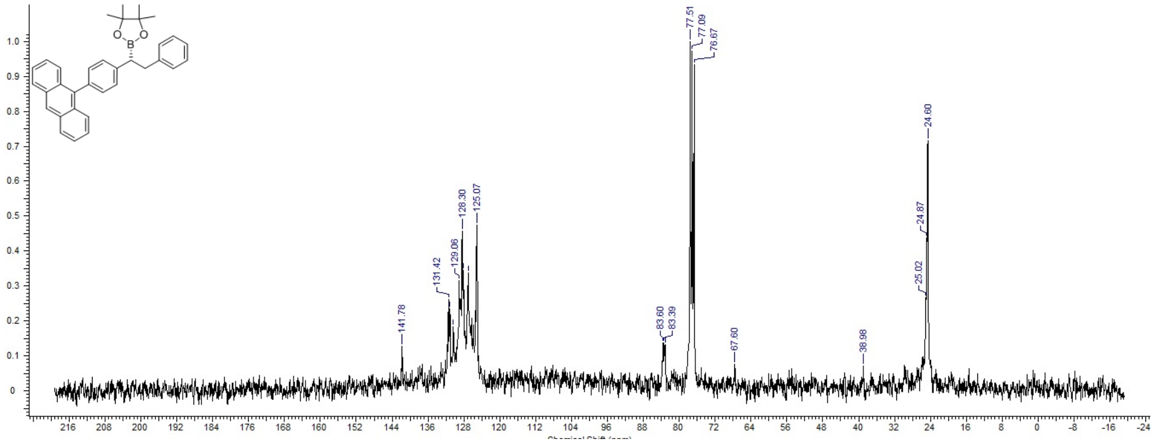

Normalized Intensity
Chemical Shift (ppm)
8.47
8.04
8.02
7.69
7.46
7.45
7.44
7.32
7.31
7.27
2.74
2.72
2.71
2.70
1.60
1.57
1.48
1.32
1.28
1.26
1.23
1.22
0.89
0.86
0.08
0.90
1.85
1.94
5.46
3.96
1.00
25.24


f1 (ppm)
140.45
138.22
131.00
128.34
128.22
127.90
127.80
127.70
127.57
127.12
127.08
124.99
123.40
83.11
80.07
77.32
77.00
76.69
32.15
32.12
31.16
29.70
24.71
24.68
24.58
14.12

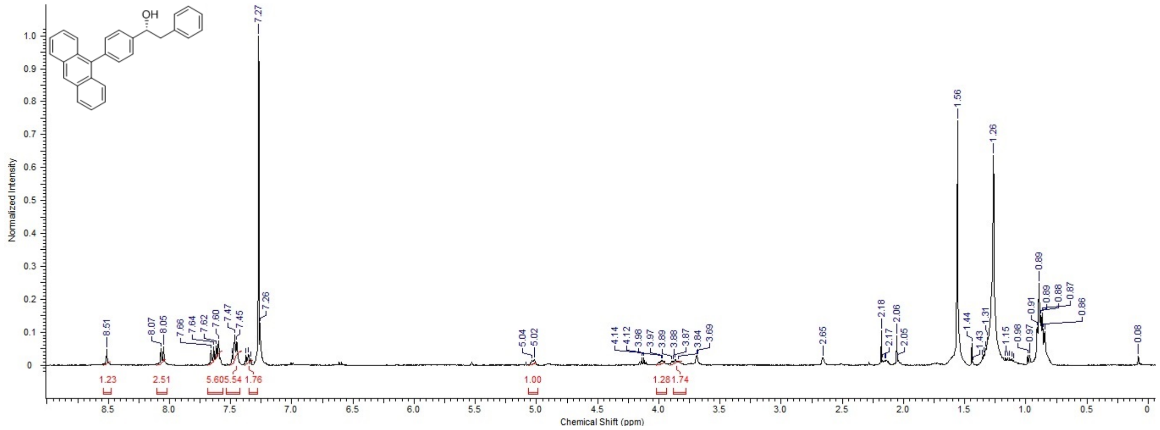

Expanded Aromatics
f1 (ppm)
140.45
138.22
131.39
131.00
128.22
127.90
127.80
127.70
127.12
127.08
124.99
123.62
123.40



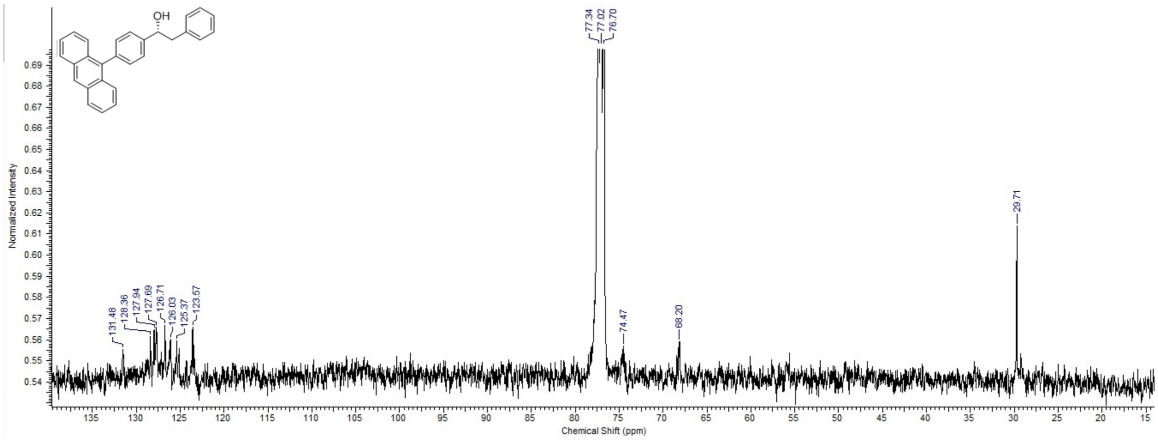
O
B
O
Normalized Intensity
1.27
1.28
1.29
1.23
1.22
1.19
1.11
0.93
0.91
0.90
0.89
0.86
0.10
8.50
8.49
8.48
8.07
8.06
8.05
8.04
7.52
7.48
7.46
7.44
7.34
7.33
7.32
7.31
7.29
7.28
7.18
6.65
6.63
3.78
3.71
3.32
3.31
3.28
3.17
3.15
3.13
3.12
2.89
2.87
2.87
2.85
2.21
1.77
1.76
1.61
1.56
1.54
1.52
1.46
1.42
1.81
4.15
2.54
10.93
12.62
1.00
1.38
1.30

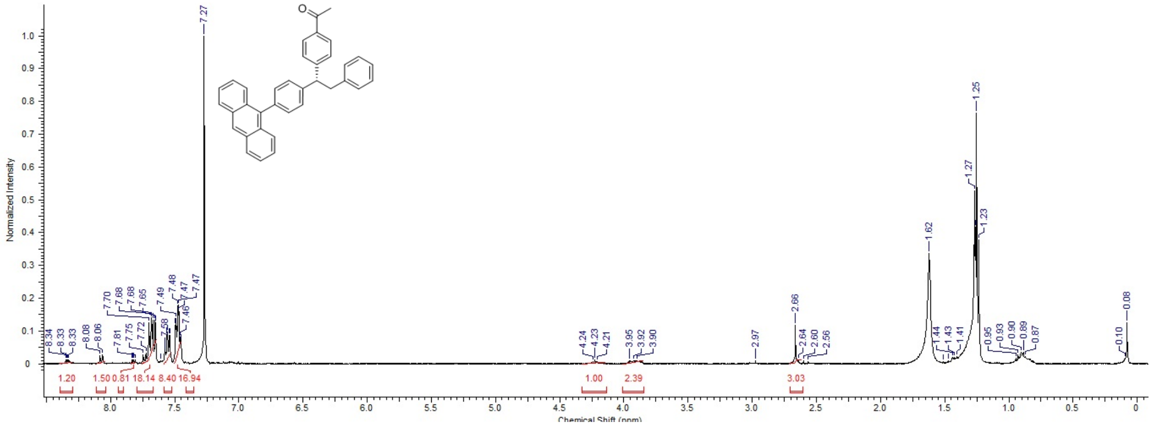


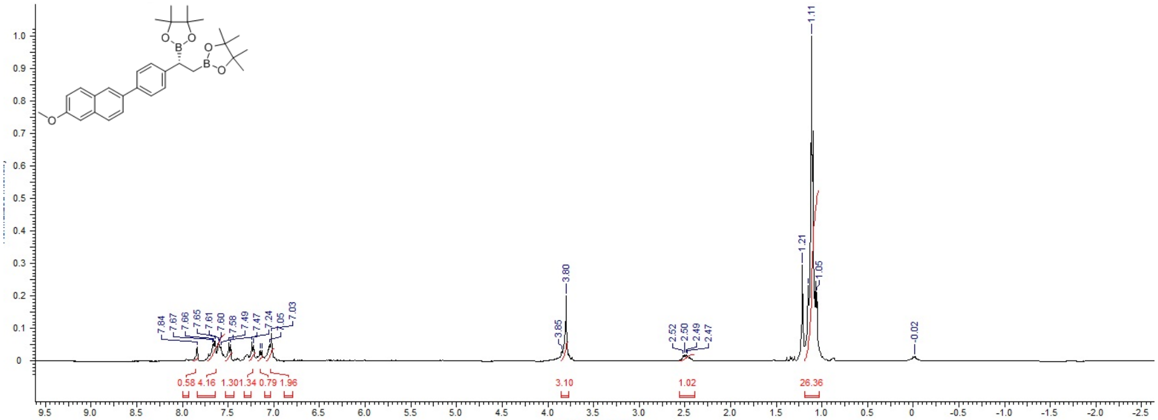
O
B
O
77.51
77.09
76.67
24.60
24.87
25.02
128.30
125.07
129.06
131.42
141.78
83.60
83.39
67.60
38.98
Chemical Shift (ppm)

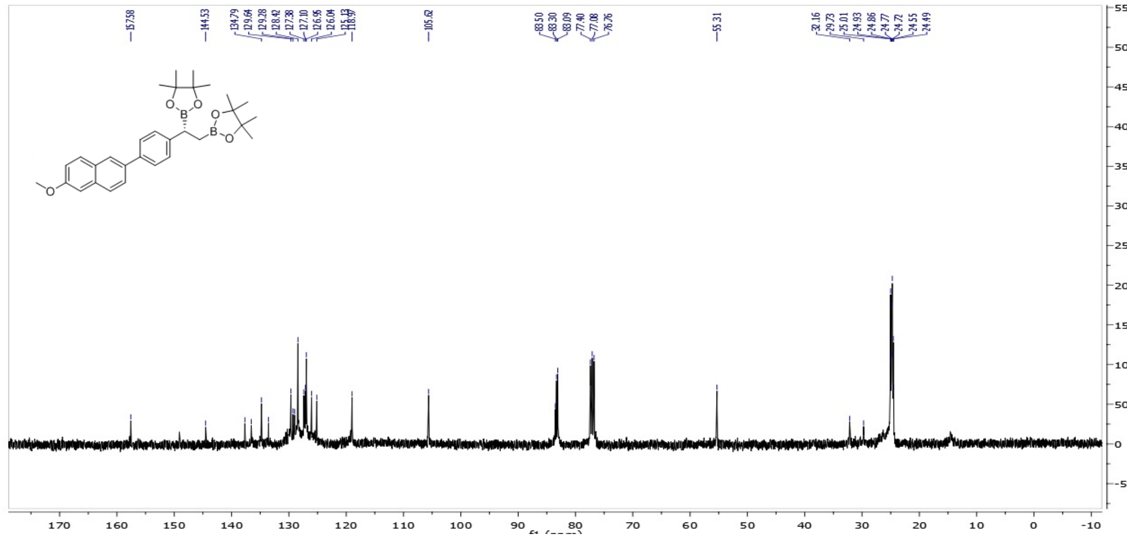


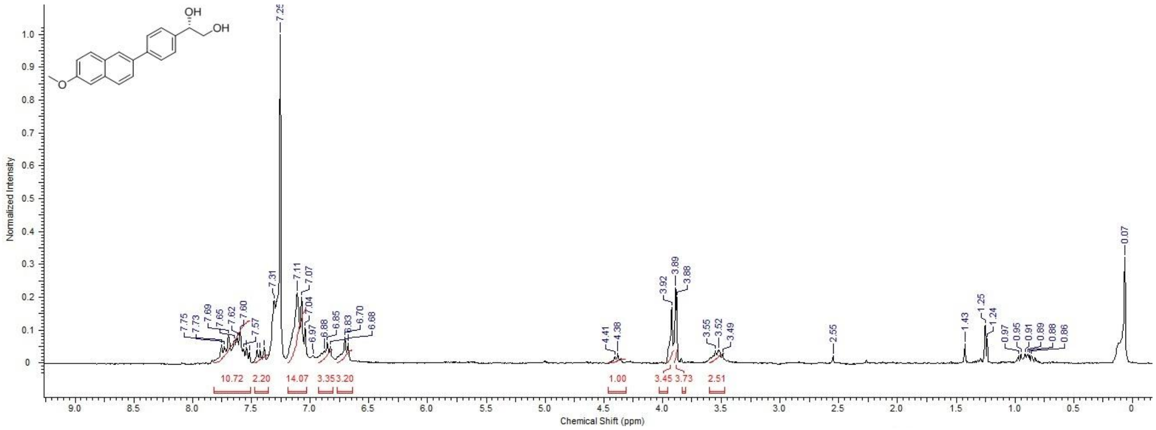
OH
Normalized Intensity
7.27
7.26
1.56
1.26
8.51
8.07
8.05
7.66
7.64
7.62
7.60
7.47
7.45
5.04
5.02
4.14
4.12
3.98
3.97
3.89
3.88
3.87
3.84
3.69
2.65
2.18
2.17
2.06
2.05
1.44
1.43
1.31
1.15
0.98
0.97
0.91
0.89
0.89
0.88
0.87
0.86
0.08
1.23
2.51
5.60
5.54
1.76
1.00
1.28
1.74
Chemical Shift (ppm)

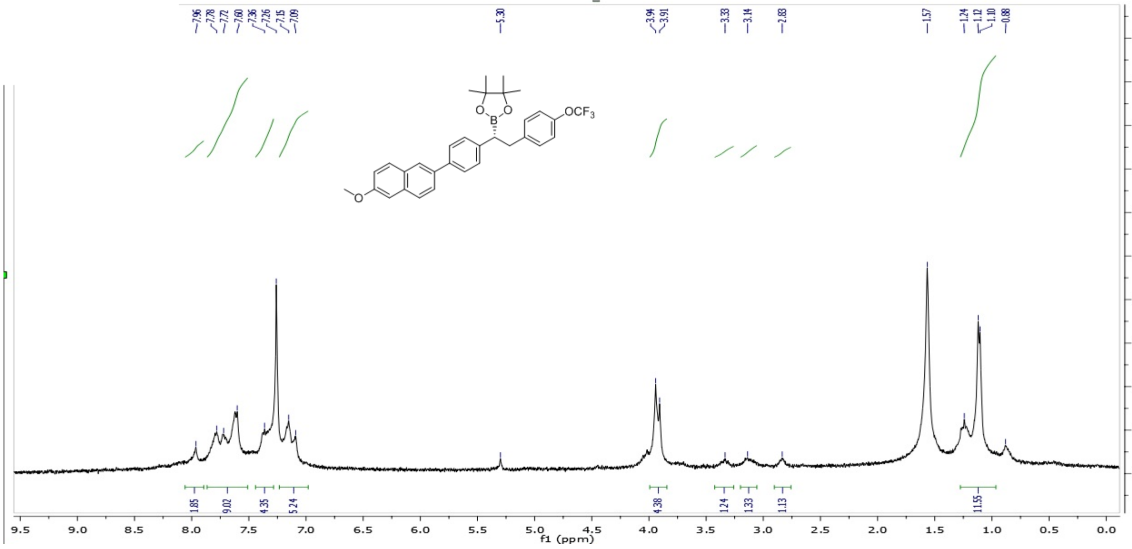

OH
Normalized Intensity
Chemical Shift (ppm)
77.34
77.02
76.70
131.48
128.36
127.94
127.69
126.71
126.03
125.37
123.57
74.47
68.20
29.71

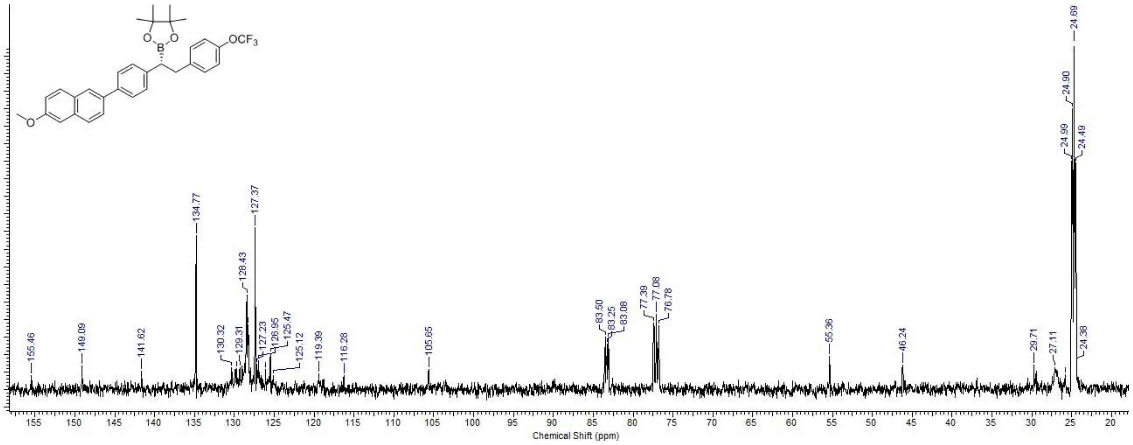

O
Normalized Intensity
Chemical Shift (ppm)
7.27
8.34
8.33
8.33
8.08
8.06
7.81
7.75
7.72
7.70
7.68
7.68
7.65
7.49
7.48
7.47
7.47
7.46
4.24
4.23
4.21
3.95
3.92
3.90
2.97
2.66
2.64
2.60
2.56
1.62
1.44
1.43
1.41
1.27
1.25
1.23
0.95
0.93
0.90
0.89
0.87
0.10
0.08
1.20
1.50
0.81
18.14
8.40
16.94
1.00
2.39
3.03

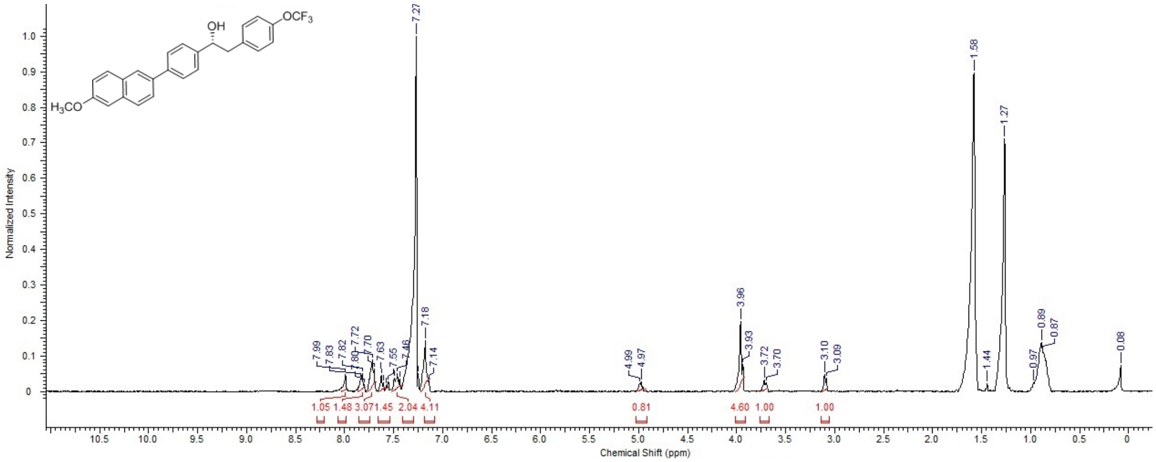

O
B
O
O
B
O
O
7.84
7.67
7.66
7.65
7.61
7.60
7.58
7.49
7.47
7.24
7.05
7.03
3.85
3.80
2.52
2.50
2.49
2.47
1.21
1.11
1.05
-0.02
0.58
4.16
1.30
1.34
0.79
1.96
3.10
1.02
26.36

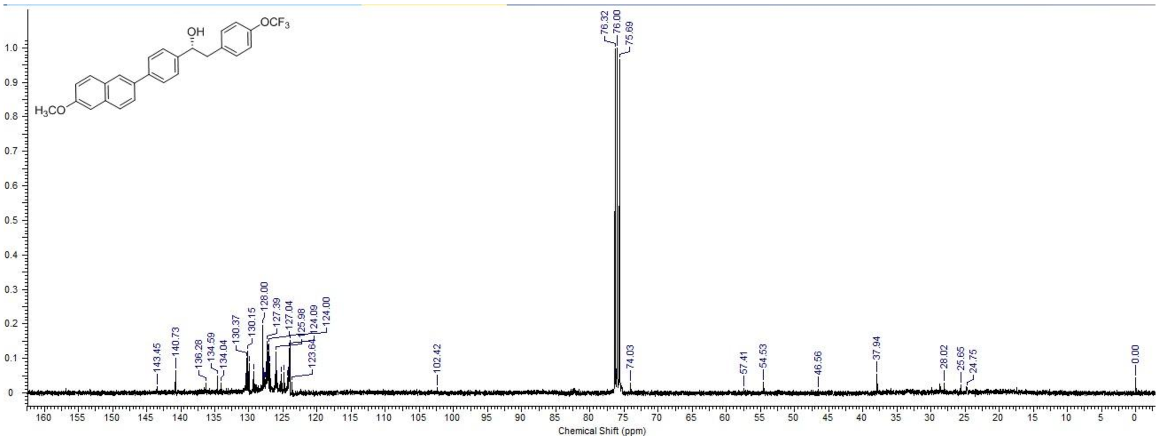

157.58
144.53
134.79
129.64
129.28
128.42
127.38
127.10
126.95
126.04
125.13
118.97
105.62
83.50
83.30
83.09
77.40
77.08
76.76
55.31
32.16
29.73
25.01
24.93
24.86
24.77
24.72
24.55
24.49
O
B
O
O
B
O
O
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

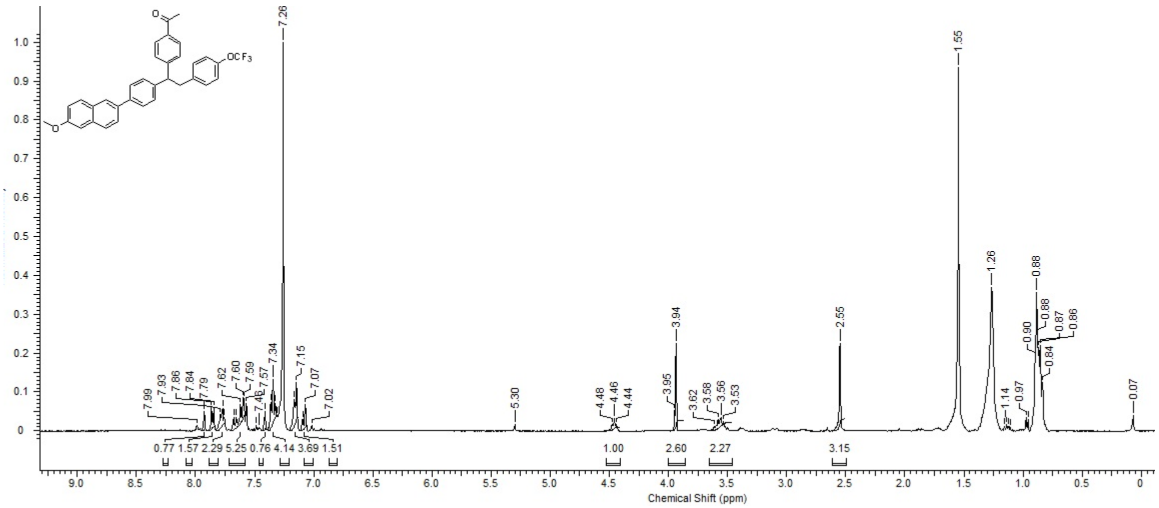

OH
OH
O
7.25
7.31
7.11
7.07
7.04
6.97
6.88
6.85
6.83
6.70
6.68
7.75
7.73
7.69
7.65
7.62
7.60
7.57
4.41
4.38
3.92
3.89
3.88
3.55
3.52
3.49
2.55
1.43
1.25
1.24
0.97
0.95
0.91
0.89
0.88
0.86
0.07
Normalized Intensity
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0
10.72 2.20 14.07 3.35 3.20 1.00 3.45 3.73 2.51
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


7.96
7.78
7.72
7.60
7.36
7.26
7.15
7.09
5.30
3.94
3.91
3.33
3.14
2.83
1.57
1.24
1.12
1.10
0.88
O
B
O
OCF3
O
100
90
80
70
60
50
40
30
20
10
0
1.85
9.02
4.35
5.24
4.38
1.24
1.33
1.13
11.55
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

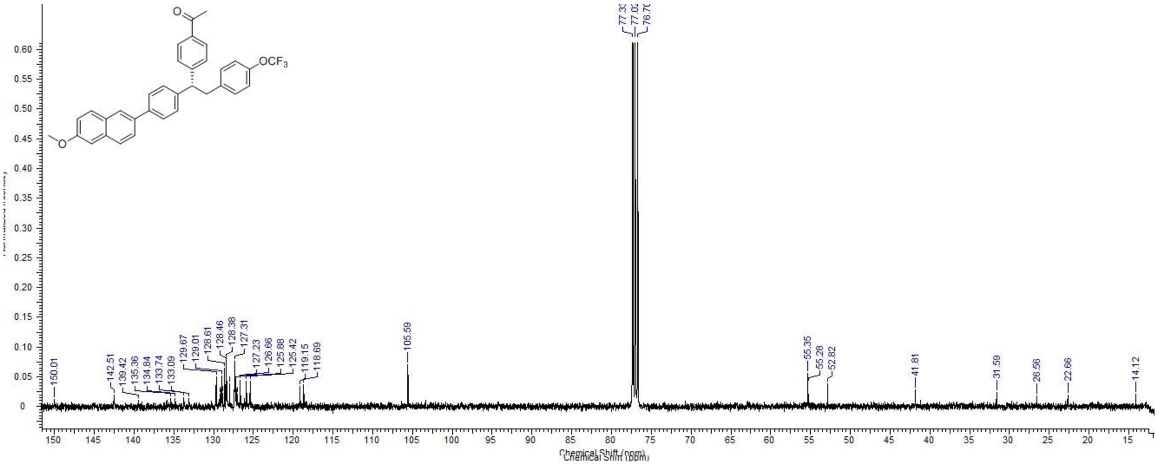

OCF3
O
B
O
155.46
149.09
141.62
134.77
130.32
129.31
128.43
127.37
127.23
126.95
125.47
125.12
119.39
116.28
105.65
83.50
83.25
83.08
77.39
77.08
76.78
55.36
46.24
29.71
27.11
24.99
24.90
24.69
24.49
24.38
Chemical Shift (ppm)


OH
OCF3
H3CO
Normalized Intensity
7.27
7.99
7.83
7.82
7.80
7.72
7.70
7.63
7.55
7.46
7.18
7.14
4.99
4.97
3.96
3.93
3.72
3.70
3.10
3.09
1.58
1.44
1.27
0.97
0.89
0.87
0.08
1.05
1.48
3.07
1.45
2.04
4.11
0.81
4.60
1.00
1.00
Chemical Shift (ppm)


OH
OCF3
H3CO
143.45
140.73
136.28
134.59
134.04
130.37
130.15
128.00
127.39
127.04
125.98
124.09
124.00
123.64
102.42
76.32
76.00
75.69
74.03
57.41
54.53
46.56
37.94
28.02
25.65
24.75
0.00
Chemical Shift (ppm)



O
OCF3
O
7.26
1.55
1.26
0.88
0.88
0.87
0.86
0.90
0.84
3.94
2.55
7.99
7.93
7.86
7.84
7.79
7.62
7.60
7.59
7.57
7.46
7.34
7.15
7.07
7.02
5.30
4.48
4.46
4.44
3.95
3.62
3.58
3.56
3.53
1.14
0.97
0.07
0.77
1.57
2.29
5.25
0.76
4.14
3.69
1.51
1.00
2.60
2.27
3.15
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)



O
OCF3
O
77.33
77.02
76.70
150.01
142.51
139.42
135.36
134.84
133.74
133.09
129.67
129.01
128.61
128.46
128.38
127.31
127.23
126.66
125.88
125.42
119.15
118.69
105.59
55.35
55.28
52.82
41.81
31.59
26.56
22.66
14.12
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
Chemical Shift (ppm)

4.8. References

1. Jana, R.; Pathak, T. P.; Sigman, M. S., Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. *Chem. Rev.* **2011,** *111*, 1417-1492.
2. Glasspoole, B. The Chemoselective, Enantiospecific Cross-Coupling of Secondary Boronic Esters and the Stability of Mesoporous Silica Supports for Pd Catalysis. Queen's University, 2011.
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