ITERATIVE, CHEMOSELECTIVE, ENANTIOSPECIFIC, PROTECTING GROUP FREE CROSS-COUPLING OF POLYBORONATES

by

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Abstract

The Suzuki-Miyaura cross-coupling reaction is broadly defined as a palladium or nickel catalyzed C-C bond forming reaction occurring between a halide or pseudo-halide electrophile and an organoboron nucleophile. The extreme importance and power of the Suzuki-Miyaura cross-coupling reaction was recognized in 2010 when its discoverer and prolific developer, Professor Akira Suzuki, was awarded one-third of the Nobel Prize 'for palladium-catalyzed cross-couplings in organic synthesis'. This decision was widely applauded by the scientific community, both in industry and academia, which had long recognized the value and impact of this discovery.

Despite its discovery in 1979 the Suzuki-Miyaura reaction has, until recently, remained confined to the realm of assembling 'flat' molecules. It is extremely efficient and reliable in its construction of C^{sp2}- C^{sp2} bonds namely in the synthesis of stereodefined polyenes, vinylarenes, and biaryl motifs, but much less so when a C^{sp3} partner is involved. The poor performance of C^{sp3} coupling partners is particularly acute in secondary aliphatic compounds; these are the compounds required to engage in cross-coupling to synthesize stereodefined C-C bonds.

However, since the turn of the century, solutions have begun to emerge to this persistent problem. The Crudden group contributed significantly to leading this charge when, in 2009, the first report of an enantiospecific cross-coupling of secondary benzylic pinacol boronates was published. This helped to ignite a renewed interest in developing an asymmetric variant for this Nobel Prize winning reaction.

Described herein is the application of this innovative achievement to the successful development of an intriguing methodology. We have successfully exploited the difference in reactivity of B-C^{sp2} and B-C^{sp3} bonds towards an iterative cross-coupling strategy that is devoid of protecting groups. Furthermore, where stereodefined B-C bonds are subjected to the reaction, the stereochemical outcome of the reaction is good to excellent. The applicability of this methodology to a known active pharmaceutical ingredient was also achieved.

Acknowledgements

There are many people I need to thank for their various contributions to my life during the past 2 years. In no particular order I need to thank, Brian Bestvater, Jason Rygus, Sam Voth, and Eric Keske for their contributions to my growth as a chemist and success in the lab. In particular I need to thank Jason, Phillip Unsworth and Masakazu Nambo of ITBM for their considerable contributions to this project. Without their work our recent submission (and eventual publication) would have certainly taken much longer.

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It would be impossible to conclude all of this without mentioning my incredible girlfriend, Tia. I wish everyone could experience the kind of love and support you have continuously shown me in our years together. I am very proud of you, and I am excited to see what great things the future has in store for you.

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List of Schemes

List of Abbreviations

9-BBN = 9-borabicyclo[3.3.1] nonane

Ac = acyl

acac = acetylacetone

B:L = branched:linear

BINAP = 2,2'-bis(diphenylphosphino-1,1'binaphthyl

Bu = butyl

Cat. = catalyst

COD = 1,5-cyclooctadiene

CPME = cyclopentyl methyl ether

Dan = 1,8-diaminonaphthalene

Dba = dibenzylideneacetone

DIPPF = diisopropylphosphinoferrocene

DME = 1,2-dimethoxyethane

DMF = N,N-dimethylformamide

dpe = 1,2-bis(diphenylphosphino)ethane

dppb = 1,4-bis(diphenylphosphino)butane

dppf = 1,1'-bis(diphenylphosphino)ferrocene

EDG = electron donating group

ee = enantiomeric enrichment

er = enantiomer ratio

es = enantiospecificity

ESI = electronspray ionization

EWG = electron withdrawing group

GC-MS = gas chromatography mass spectrometry

GmbH = Gesellschaft mit beschränkter Haftung

GP = general procedure

GPC = preparative recycling HPLC

HPLC = high-performance liquid chromatography

HRMS = high resolution mass spectrometry

IR = infrared

MIDA = N-methyliminodiacetic acid

mp = melting point

NMR = nuclear magnetic resonance

PhMe = toluene

pin = pinacol

ppm = parts per million

PTLC = preparative thin layer chromatography

(*S*)-quinap = (*S*)-(−)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline

SFC = supercritical fluid chromatography

TADDOL = α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol

THF = tetrahydrofuran

TLC = thin layer chromatography

TMS = tetramethylsilane

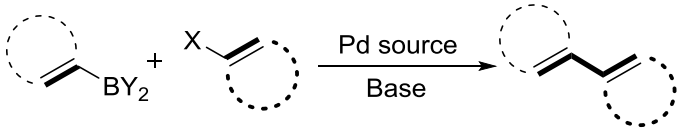
UV = ultraviolet

Chapter 1

Introduction

1.1 Introduction

Since it was first reported in 1979, the Suzuki-Miyaura cross-coupling reaction has reshaped the landscape of synthetic organic chemistry.[1] Its importance and utility were underscored when Akira Suzuki shared one third of the Nobel Prize 'for palladium-catalyzed cross-couplings in organic synthesis' alongside Richard Heck and Ei-ichi Negishi. The reaction itself is the cross-coupling of an organoboron partner, a nucleophile, with an organohalide partner, an electrophile, typically under palladium catalysis in the presence of a base.[2] The nature of the coupling partners is predominantly sp^2, but ever greater numbers of sp^3-tolerant conditions are being reported.[3,4] Additionally, nickel catalyzed variants are also known and discussed where relevant.[5]



Scheme 1-1 Generic Suzuki-Miyaura cross-coupling

The seminal Suzuki-Miyaura cross-coupling reaction report described the synthesis of polyenes; however, three and a half decades and considerable research efforts have broadened the scope of this reaction significantly. Some of these improvements have been devoted to the synthesis of increasingly complex or sterically hindered biaryls, as well as stereo-defined polyene compounds with ever lower catalyst loadings under milder conditions. The mildness of the modern reaction conditions, namely the use of weak bases and non-elevated temperatures, renders the reaction tolerant to a plethora of functional groups in both the organoboron and halide coupling

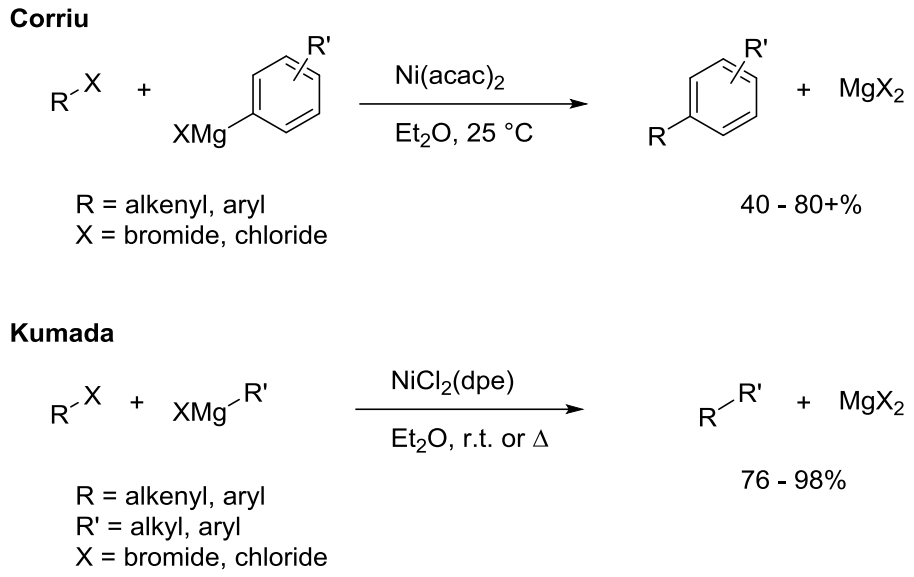
partners.[2,4] Moreover, developments have been made which render previously recalcitrant sp^3 hybridized partners competent for the cross-coupling reaction.[4] Arguably then, the final frontier for this powerful reaction, and thus the thrust of the work to be discussed herein, is to develop protocols whereby stereodefined C-C bonds are accessible by Suzuki-Miyaura cross-coupling.

1.2 Transition Metal Catalysis Employing Organometallic Reagents

1.2.1 Emergence of Modern Cross-Coupling and Palladium

Although reactions involving transition metals had been investigated as early as the 19th century it was not until the 1950s that Wacker Chemie GmbH would discover and refine the palladium catalyzed oxidation of alkenes.[6] This Wacker oxidation work made palladium more than simply a curiosity, and would inspire Richard Heck to begin investigating the reactivity of organomercury compounds with alkenes in the presence of catalytic amounts of palladium.[7] The eventual result of that work was the nearly simultaneous discovery of the coupling of alkenes with aryl, benzyl, and styryl halides, first by Mizoroki[8], and shortly thereafter by Heck[9], now known as the Mizoroki-Heck reaction.

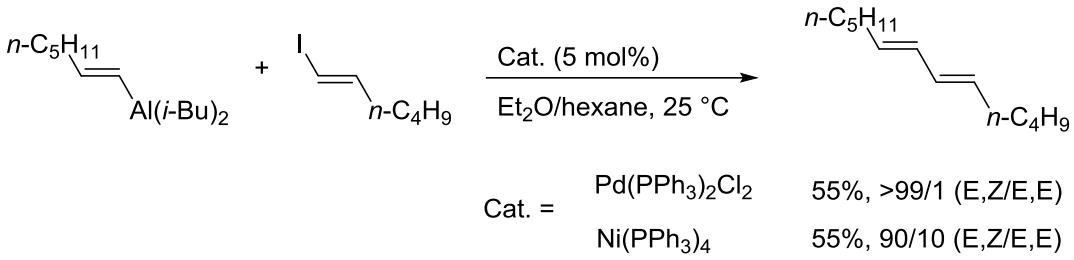
In 1972, the same year as Heck's ground-breaking report, came nearly simultaneous reports from Corriu[10] and Kumada[11] detailing the nickel catalyzed cross-coupling of aryl and vinyl halides with aryl and alkyl Grignard reagents (Scheme 1-2). These reports are widely regarded as the point from which the modern cross-coupling era began, and before the decade was out, Suzuki and Miyaura would have already made their historic discovery.[1]



Scheme 1-2 Nickel catalyzed cross-coupling of Grignard reagents with alkenyl and aryl halides

An aspect of Kumada's report, the importance of which only became obvious in retrospect, was the introduction of a phosphine ligand to modulate the reactivity of the transition metal catalyst. Furthermore, Kumada astutely hypothesized that the enhanced reactivity imparted by the tested bidentate phosphines was due to the formation of the more favourable *cis*-diorganonickel complex.[11] This consideration remains important in modern ligand design.

It was only four years later, that the first report of a non-Grignard reagent cross-coupling reaction, involving alkenyl-alanes and halides under nickel or palladium catalysis, would emerge (Scheme 1-3).[12] In this report by Negishi, some advantages of palladium over nickel were recognized for the first time, namely, the high degree of stereospecificity (≥ 97% retention of starting material's stereochemical information in the product) and lack of an appreciable amount of undesired homocoupled products.[12]



Scheme 1-3 Stereospecific cross-coupling of alkenyl alanates under palladium or nickel catalysis

1.2.2 Exploring Organometallic Cross-Coupling Reaction Partners

The above extremely influential reports, in addition to the discovery of the Sonogashira cross-coupling in 1975[13] which further propelled palladium to the fore, would be followed by another wave of development. This wave would focus largely on exploring the nature of organometallic species used as the coupling partner in the reaction, rather than the catalyst itself. A clear drawback of cross-couplings which employ highly reactive nucleophilic partners such as organomagnesium or organolithium reagents is limited functional group tolerance in addition to problematic side reactions. Showing tremendous foresight, Negishi conducted a variety of experiments contrasting both palladium and nickel based catalytic systems as well as screening different organometallics.[14] The push towards the use of milder organometallics has resulted in the discovery of organo-aluminum, boron, silicon, tin, zinc and zirconium reagent cross-coupling reaction conditions; however, Negishi's systematic screening pointed towards boron, tin, and zinc as being particularly promising.[14]

1.3 Suzuki-Miyaura Cross-Coupling Mechanism

1.3.1 General Mechanistic Overview

In his Nobel lecture, Suzuki explained the origins of the idea that organoboron compounds, previously believed to be too stable to be effective cross-coupling partners, could indeed undergo

the reaction. In 1973, Gropen and Haaland[15] reported that the methyl group of tetramethylborate was calculated to be five times more electronegative than those in trimethylborane (Figure 1-1). This of course has an influence on the nucleophilicity of the compound as a whole, as well as, the substituents ligating boron. This led Suzuki to the hypothesis that boranes could be rendered reactive in their borate form, a hypothesis supported by the requirement for stoichiometric amounts of base in most Suzuki-Miyaura cross-couplings.

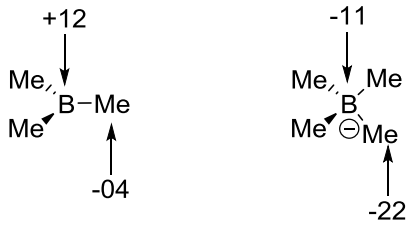
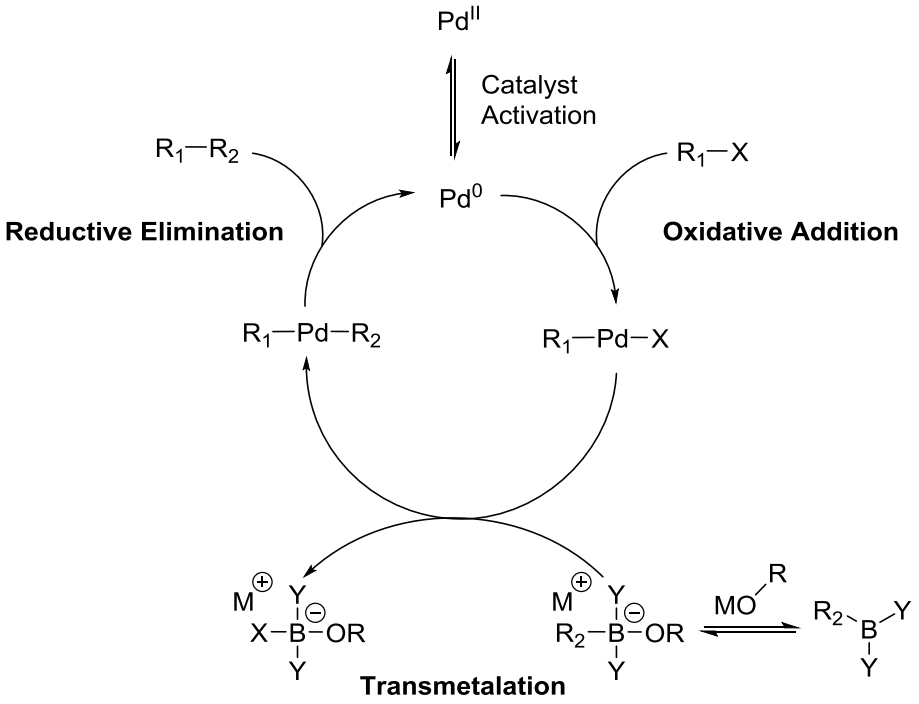


Figure 1-1 Calculated atomic charges, in 0.01 electron units, of trimethyl borane and corresponding ate complex

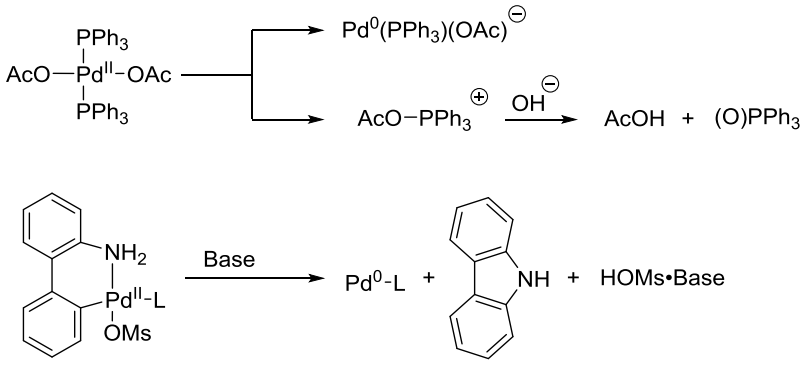
Today the generally accepted mechanism (Scheme 1-4) for a plethora of transition metal catalyzed cross-couplings, including the Suzuki reaction, is composed of at least three elementary steps. The first is an oxidative addition of an electrophile, typically an organohalide, to an electron rich metal catalyst, often palladium(0). This is followed by a transmetalation of an organometallic nucleophile to the aforementioned catalyst furnishing a diorganometallic intermediate. Lastly, reductive elimination results in the loss of both organic ligands from the catalyst, thus generating the coupled product and regenerating palladium(0).[2]



Scheme 1-4 Generally accepted simplified mechanism of the Suzuki-Miyaura cross-coupling. Off cycle base activation of organoboron shown.

1.3.2 Precatalyst Activation

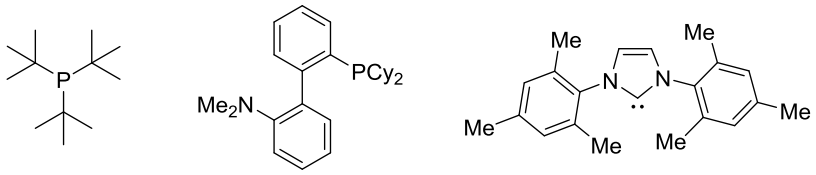
Prior to oxidative addition, and prior to any catalytic process, in cases where the palladium source added to the reaction is a palladium(II) compound, it must first be reduced to palladium(0). This activation typically occurs by oxidation of a phosphine ligand, present in excess in the reaction, through the action of the base (Scheme 1-5). This is known to occur by an inner-sphere mechanism, with retention of configuration at phosphorous.[16,17] Monoligated palladium(0), likely the active species in oxidative addition[18], may also be cleanly generated from different preformed palladacycles[19], often referred to as precatalysts (Scheme 1-5). Under the reaction conditions, these precatalysts readily undergo reductive elimination forming 1 equivalent each of the active catalyst and a byproduct.



Scheme 1-5 Palladium(II) reduction by phosphine oxidation (top) or reductive elimination from a preformed palladacycle (bottom)

1.3.3 Oxidative Addition

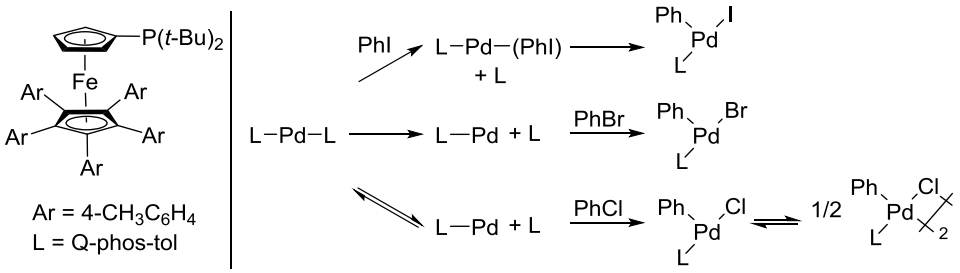
Depending on the nature of the electrophile being employed, oxidative addition can be rate limiting.[20,21] The general trend in reactivity is as follows: I > OTf > Br >> Cl.[2,20] Aryl and alkenyl chlorides can be rendered more reactive if they are activated by the proximity of an EWG rather than EDG or in selected heterocyclic examples.[22] This is an unfortunate problem as arylchlorides are more readily available and more stable towards other manipulations in comparison with other halides; in many ways this could make them the ideal cross-coupling partner. Researchers have taken note of this and their efforts to find a general solution to this challenge has been found in addressing the reactivity of the palladium catalyst. To this end specialized bulky phosphine ligands, which are rendered electron rich by virtue of bearing two or three alkyl substituents, can oxidatively add to arylchlorides thereby making them competent coupling partners.[23] Carbenes, another vast field of research, have found some use here as well.[24]



Fu 1998 **Buchwald 1998** **Nolan 1999**

Figure 1-2 Ligands developed to increase palladium's reactivity towards oxidative addition

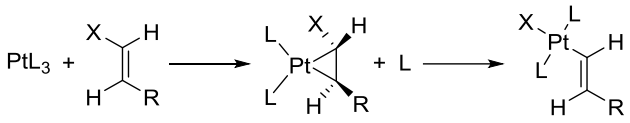
The actual mechanism by which oxidative addition proceeds has proven somewhat elusive, in that there appears to be multiple operative mechanisms.[25] In his 1977 report, Stille suggests that the operative mechanism in any particular case may be dictated by the catalyst system, the nature of the coupling partners, as well as aryl halide employed.[25]



Scheme 1-6 Different mechanisms for the oxidative addition of iodoarenes (top), bromoarenes (middle), and chloroarenes (bottom)

This suspicion was confirmed in 2005 by a report from Hartwig, which examined the oxidative addition of chloro-, bromo-, and iodoarenes to [Pd(Q-phos-tol)$_2$] (Scheme 1-6).[18] It was found that the addition of iodoarenes proceeded through an associative mechanism, where the iodoarene displaces a phosphine ligand and is then bound to palladium in an η^1 fashion through iodide or an η^2 fashion through the arene.[18] This differed for chloro- and bromoarenes, which required phosphine dissociation to generate a monoligated palladium(0) intermediate prior to oxidative addition.[18] In the case of chloroarenes, ligand dissociation was reversible and after oxidative addition, an equilibrium with a chloro-dimer was established.[18]

These processes differ substantially from alkylhalides, which undergo an invertive S_N2 type of oxidative addition with a coordinatively unsaturated palladium(0) complexes.[26] This mode of addition is again in contrast with that of vinylhalides, which usually retain their configuration.[27] Since three-membered platinocycles, which can rearrange to a σ-vinyl complex, have been isolated, a similar pathway for palladium oxidative addition has been proposed to account for the observed stereospecificity (Scheme 1-7).[27]

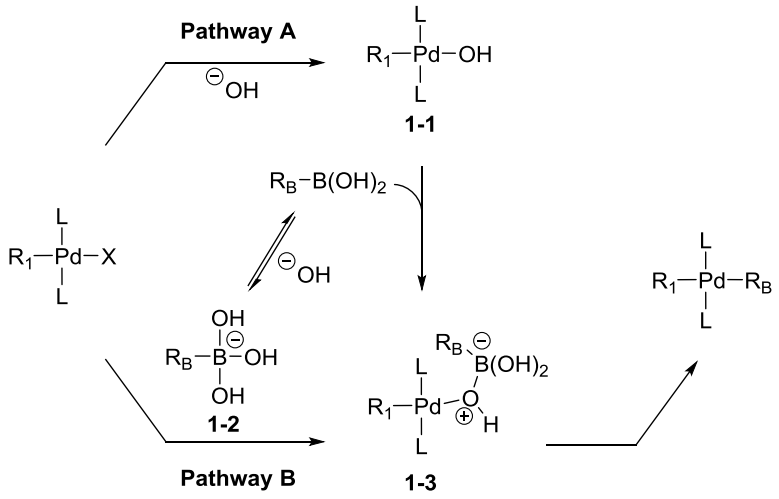


Scheme 1-7 Oxidative addition of coordinatively unsaturated Pt(0) complex to vinyl halide

1.3.4 Transmetalation from Boron to Palladium

Although each step of the catalytic cycle has been carefully studied, none is more scrutinized, contentious or as widely debated as the path by which transmetalation of the organic component of the boron organometallic to palladium occurs. Typical mechanisms proposed for the transmetalation reaction (Scheme 1-8) are shown below (Pathways A (oxopalladium) and B (borate)). Although each mechanism is proposed to share a common intermediate, **1-3**, the nature of the proceeding reactive compounds has received considerable attention.

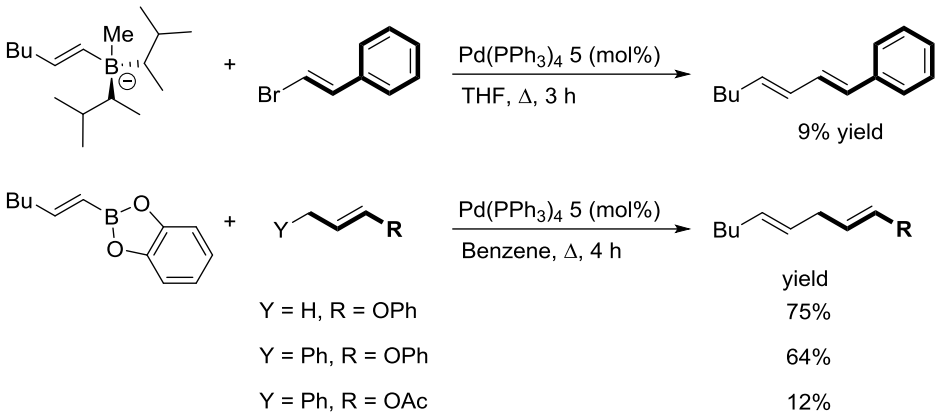
There is significant evidence that a fleeting intermediate oxopalladium species, **1-1**, undergoes reaction with a boronic acid via Pathway A (Scheme 1-8**)**. Assuming A is operative, transmetalation releases the corresponding boronate and leads to the formation of the diorganopalladium species which continues through the catalytic cycle.



Scheme 1-8 Possible mechanisms for transmetalation

Additionally, pathway A has been supported by numerous reports from Amatore and Jutand[28] as well as Hartwig,[29] whereby the proposed oxopalladium species is generated by addition of OH^- to palladium halide complexes.

In a series of ^{31}P NMR experiments directed towards measuring the rate of transmetalation in each case, Hartwig[29] demonstrated a significantly higher rate of reaction for a hydroxopalladium complex when compared with the corresponding halide complex. Calculations indicated that the reaction of the hydroxopalladium complex with a boronic acid (pathway A) had a rate constant four orders of magnitude larger than did the halide complex with trihydroxyborate (pathway B).[29]

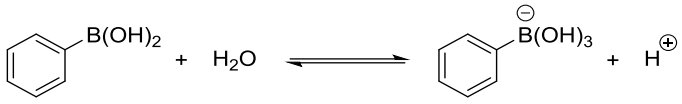


Scheme 1-9 Experiments demonstrating the potential for an oxopalladium(II) intermediate to perform transmetalation

Suzuki, Miyaura *et al*. reported in 1985 that after subjecting lithium (1-hexenylmethyl)disiamylborate to cross-coupling conditions with β-bromostyrene (*vide supra*) only a 9% yield of the product was obtained (Scheme 1-9).[30] This led the authors to explore the possibility of an alternate pathway involving an alkoxopalladium species in their catalytic cycle. When alkenylboronates were exposed to cross-coupling conditions with allylic phenoxides or acetates in the absence of base the reaction was found to occur (Scheme 1-9). This suggested the intermediacy of a (π-allylphenoxo)- or (π-allylacetoxo)palladium(II) complex, as the more reactive intermediate in the transmetalation step rather than a borate. This hypothesis is supported by the results of Hartwig, Amatore, and Jutand (*vide supra*), each of which favour pathway A.

Despite this evidence for the involvement of an oxopalladium intermediate in the transmetalation, the inability of *in situ* monitoring techniques to detect any such species remains an issue.[31,32] Thus, an alternate explanation to invoking an oxopalladium species involves the equilibrium formation of a borate (Scheme 1-10), such as **1-2** in pathway B (Scheme 1-8), by adding an anionic ligand, RO^- (R = H, alkyl, acyl, etc.), via coordination through the vacant p-orbital on boron.[33,34] Moreover, a mechanism invoking a borate might be rationalized by boron's high oxophilicity.[33] As noted previously, expanding the coordination number enhances the

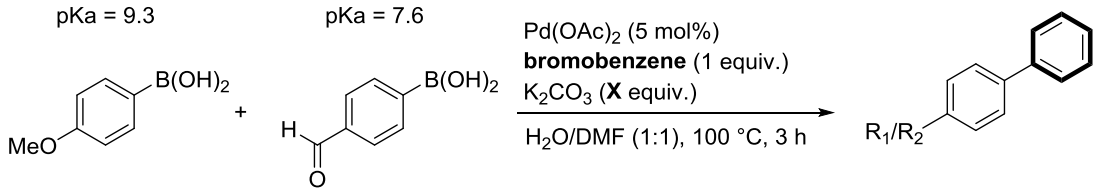
nucleophilicity of the organic ligand(s) of boron, thus promoting transmetalation. In contrast to Brønsted acids, the pKa of boronic acids refer to an equilibrium involving their corresponding tetravalent anionic form rather than a deprotonated anionic form, or conjugate base (Scheme 1-10).[33]



Scheme 1-10 Equilibrium formation of a borate from phenylboronic acid

Studies supporting pathway B, proceeding through a borate intermediate, typically employ aqueous reaction conditions, where it is known that the equilibrium formation of $[Pd(Ar)(L)_2(OR)]$ from $[Pd(Ar)(L)_2X]$ (X = I, Br, Cl) is disfavoured.[29] The difference in reaction conditions begins to appear as a possible culprit for the divergence in experimental observations.

Table 1-1 Competition experiments highlighting the effect of pKa on relative rates of boronic acid cross-coupling



Entry			X	R_1 = OMe : R_2 = CHO
1	1 equiv.	1 equiv.	1	35 : 65
2	1 equiv.	1 equiv.	2.5	68 : 32
3	1 equiv.	1 equiv.	4.6	81 : 19
4	2 equiv.	1 equiv.	1	48 : 52
5	1 equiv.	2 equiv.	1	17 : 83

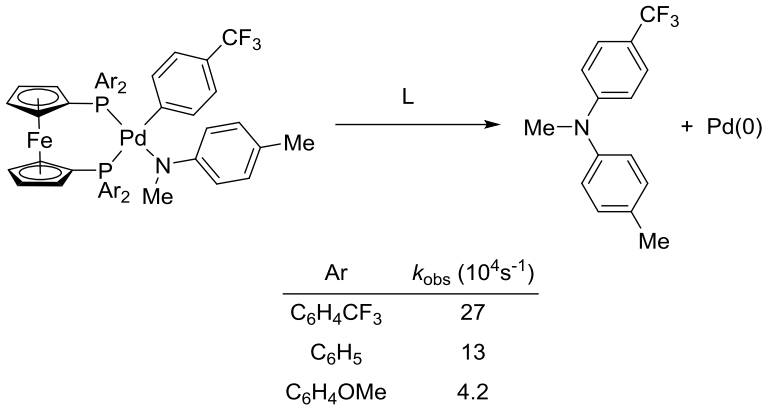
In any case, under aqueous reaction conditions, competition experiments by Santos *et al*. have also demonstrated that arylboronic acids with lower pKa values are more reactive towards

transmetalation than boronic acids of higher pKa (Table 1-1, entry 1); however, these reactions were run to completion, which does not give an accurate assessment of relative reactivity.[34] The pKa, and thus Lewis acidity of the arylboronic acids, was determined by recording the UV absorption changes that occur as pH is varied and the position of the boronate-borate equilibrium changes (Scheme 1-10).[35,36] These results indicate that boronic acids which exist preferentially as the boronate under the reaction conditions undergo coupling more rapidly. The selectivity for the more Lewis acidic boronic acid was particularly acute when only 0.5 equivalents of base were used relative to the boronic acids (Table 1-1, entries 4 and 5).[34] Only as increasing equivalents of either base or boronic acid with greater pKa were added did the cross-coupling selectivity begin to favour the innately better nucleophile, that is the boronic acid bearing an EDG (-OMe) rather than an EWG (-CHO) (Table 1-1, entries 2 and 3).[34]

1.3.5 Reductive Elimination

Reductive elimination is the final step in the catalytic cycle, in which a C-C bond is formed and palladium(II) is reduced back to palladium(0), enabling it to re-enter the catalytic cycle. Researchers have investigated this step by examining both the electronic[37] and steric[38] effects of the ancillary ligands and the reductively eliminating groups themselves.

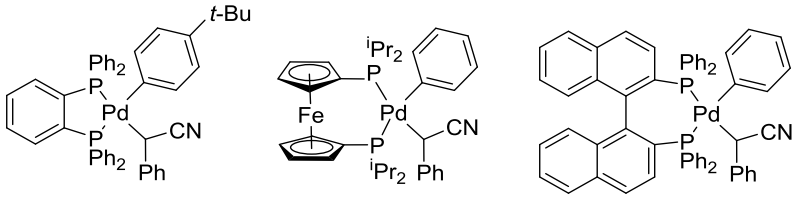
With regards to ancillary ligand electronic effects, a general trend has been observed. Reductive elimination is typically slower from palladium(II) complexes when electron rich ligands are present in comparison with electron-poor examples (Scheme 1-11).[37,42] This is rationalized by the stabilizing effect an electron rich ligand would have on the otherwise reactive palladium(II) complex, and the lack of a driving force to give electrons back to the Pd(II) centre.



Ar	k_{obs} ($10^4 s^{-1}$)
$C_6H_4CF_3$	27
C_6H_5	13
C_6H_4OMe	4.2

Scheme 1-11 Effect of various ancillary ligand electronic properties on rates of reductive elimination

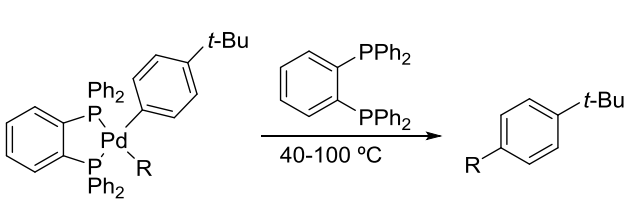
With respect to the steric effects on reductive elimination, it has been found that increasing steric demand of ancillary ligands increases the rate of reductive elimination.[38,39,40] This is rationalized by postulating that reductive elimination lowers the coordination number of the metal center, thus relieving steric congestion.[37] In the case of P(*t*-Bu)$_3$ as an ancillary ligand, Hartwig reported that the driving force to relieve steric strain meant that arylhalides were formed from arylpalladium(II) halide complexes by reductive elimination of "Ar" and "Cl" groups.[39] This is quite remarkable as one would expect an electron-rich trialkyl phosphine to actually stabilize a palladium(II) species. Additionally, bidentate ligands with increasing bite angles, which force the other substituents to closer proximity, have been demonstrated to accelerate reduction (Figure 1-3).[38]



bite angle	86°	104°	92.7°
k_{rel}	1	60	60

Figure 1-3 Effect of bite angle on relative rates of reductive elimination.

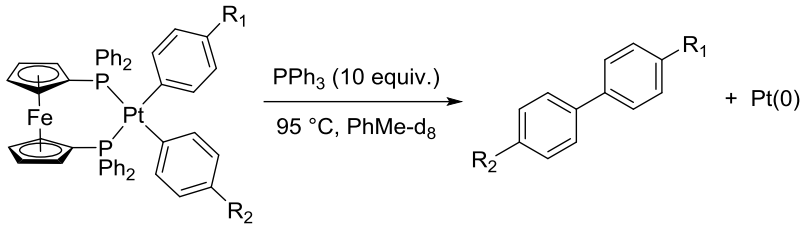
In regards to reactive ligands electron-rich reactive ligands undergo more rapid reductive elimination than electron-poor reactive ligands (Scheme 1-12).[37,42] A specific example of this is the single report of reductive elimination forming a C-CF_3 bond from a palladium trifluoromethyl complex[41], whereas many eliminations from palladium methyl complexes forming C-CH_3 bonds are known.



R =	σ*	k_{rel}
Me	0	>600
CH_2Ph	0.22	>250
$CH_2C(O)Ph$	0.60	31
CH_2CF_3	0.92	1.7
CH_2CN	1.30	1
CF_3	2.60	n.r.

Scheme 1-12 Relative rates of reductive elimination for substituted palladium methyl complexes

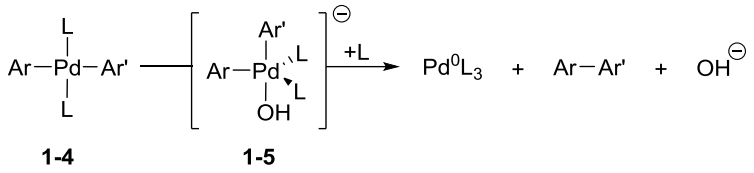
Another curious observation made by Hartwig is the electronic effect of reactive ligands relative to each other. It was found that the greater the difference in electronic properties of the two species undergoing reductive elimination, the faster the reductive elimination proceeds.[37] This observation was made while studying reductive elimination from biarylplatinum complexes (Scheme 1-13).



R_1	R_2	k_{obs} (s^{-1})
CF_3	CF_3	1
NMe_2	NMe_2	23
NMe_2	CF_3	114

Scheme 1-13 Rates of reductive elimination from electronically biased biarylplatinum complexes

In addition to the aforementioned steric and electronic factors, Amatore and Jutand propose, among the other roles of hydroxide bases in Suzuki cross-coupling, that reductive elimination can be accelerated by the formation of **1-5**, a 5 coordinate anionic palladium(II) intermediate (Scheme 1-14).[28]



Scheme 1-14 Role of hydroxide in reductive elimination as proposed by Amatore and Jutand

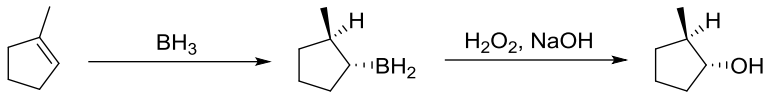
This proposal came from the surprising observation that the *trans*-biarylpalladium(II) intermediate (**1-4**) could be characterized by both ^{1}H and ^{31}P NMR (Scheme 1-14). It was only after the addition of 5 equiv. of OH^- that the intermediate disappears and the formation of biaryl product as well as $[Pd^0(PPh_3)_3]$ could be detected.[28]

Contrary to the proposal by Amatore and Jutand, kinetic data collected by Hartwig *et al*. indicated that reductive elimination takes place directly from a three-coordinate T-shaped arylpalladium amido complex.[42] Moreover, a three-coordinate arylpalladium amido complex bearing a single $P(t\text{-}Bu)_3$ ligand was found to undergo reductive elimination faster than an analogous four-coordinate complex bearing dppf, a bidentate ligand.[42]

1.4 Suzuki-Miyaura Cross-Coupling Reaction of sp^3 Boronates

1.4.1 Forming B-C Bonds

Arguably the most well-known B-C bond forming reaction is the hydroboration reaction of alkenes and alkynes, first reported in 1956 by H. C. Brown (Scheme 1-15).[43] Indeed it was this reaction that initially sparked Professor Suzuki's interested in organoboron compounds.

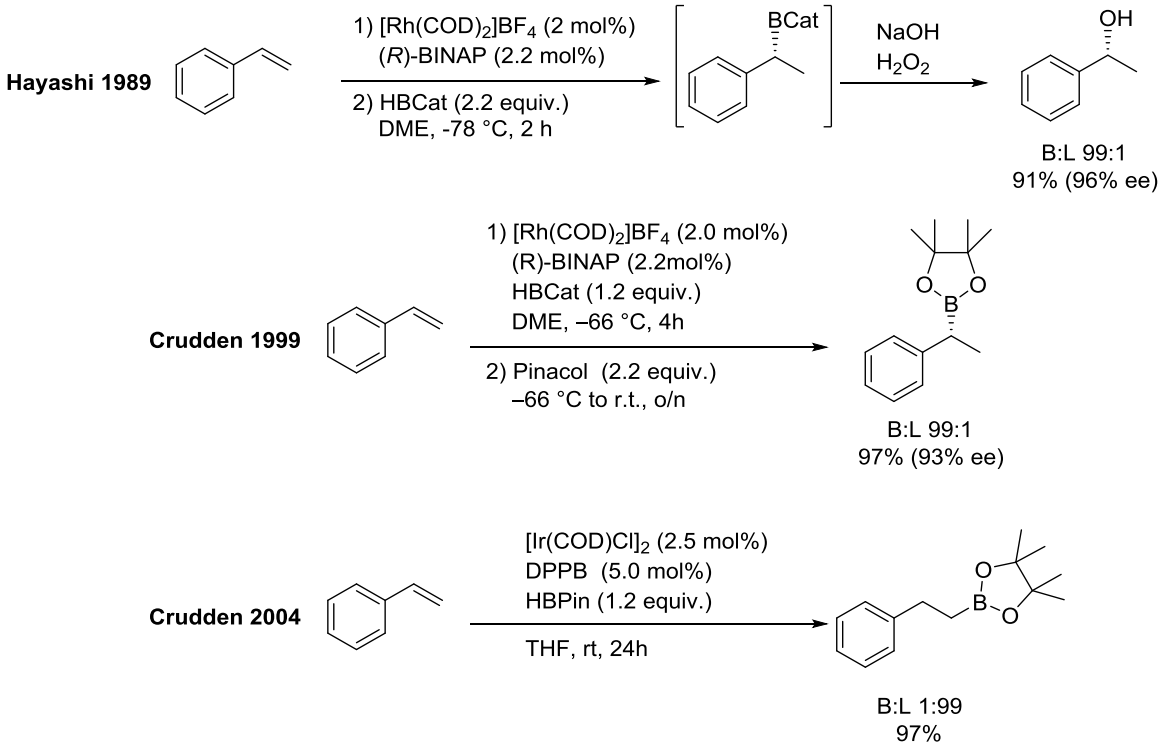


Scheme 1-15 1-Methylcyclopentene hydroboration-oxidation sequence clearly depicting reaction diastereoselectivity of the Brown hydroboration

Hydroboration itself involves the concerted anti-Markovnikov addition of a hydrogen atom and BR_2 across a π-bond in a *syn* fashion.[44] This reaction was employed by Suzuki in order to synthesize both E and Z alkenylboron compounds for the stereoselective synthesis of alkadienes.[30] Unfortunately, alkylboron compounds initially proved to be recalcitrant towards cross-coupling.[45]

However, if one is interested in forming stereodefined C-C bonds using the Suzuki-Miyaura cross-coupling, the ability to construct stereodefined B-C bonds will be of great importance. This is certainly the case, as Soderquist has elegantly demonstrated that the transmetalation of primary alkylboranes to palladium is a stereospecific process.[46] If this holds true for secondary alkylboron compounds, then the goal of forming stereodefined C-C bonds by cross-coupling may be attainable.

Since the pioneering work of Brown,[43] the methods of B-C bond construction have expanded to include asymmetric transition metal catalyzed hydroboration[47,48] and diboration[49] reactions. In regards to asymmetric hydroboration reactions, we were particular interested in the rhodium catalyzed hydroboration of styrene derivatives first demonstrated by Hayashi in 1989[47] and then further developed in the Crudden lab in 1999[48]. This reaction represented a major advance in B-C bond formation for several reasons: firstly, high regioselectivity (branched:linear, B:L) was observed in an opposite sense compared with the uncatalyzed reaction, secondly, high levels of enantioselectivity were observed and finally, low catalyst/chiral ligand loadings were needed, in contrast to previous stoichiometric approaches. Interestingly, in 2004, Crudden reported that exchanging the rhodium catalyst for iridium led to the complete reversal in regioselectivity and afforded almost exclusively the linear hydroboration isomer (Scheme 1-16).[50]

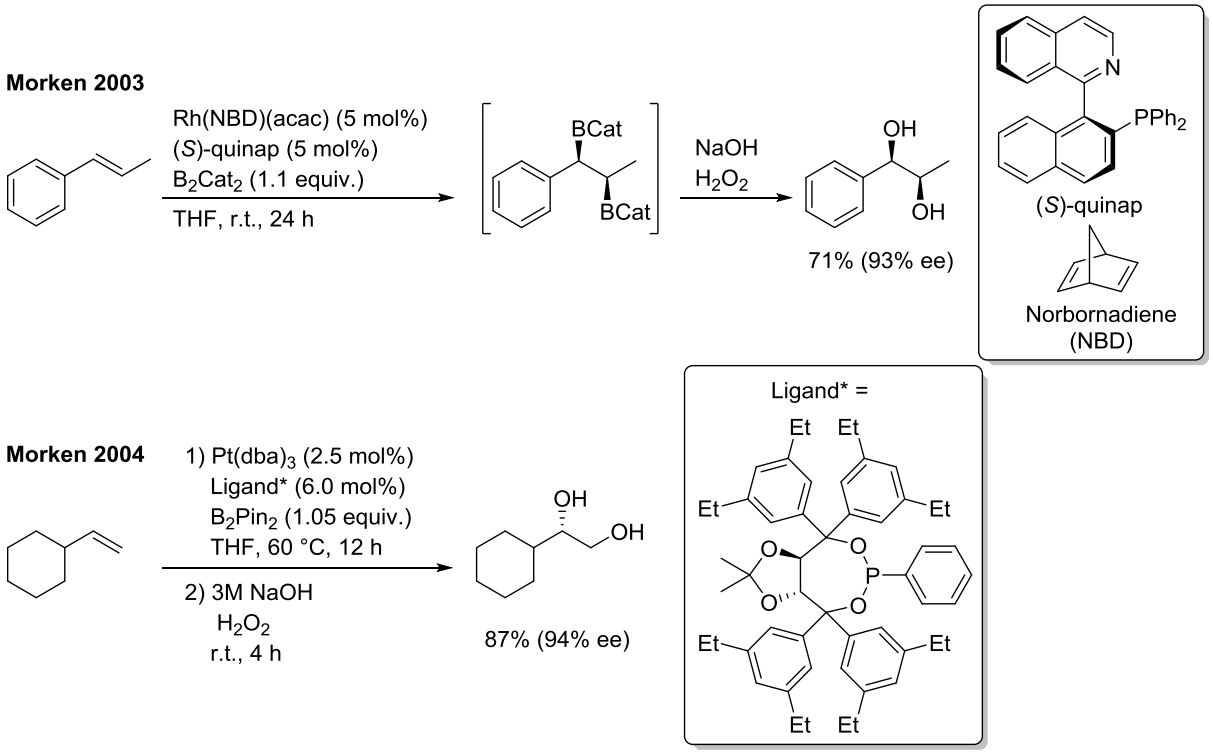


Scheme 1-16 Rhodium catalyzed enantioselective hydroboration of styrene demonstrated by Hayashi and Crudden as well as regiochemistry selectivity reversal under iridium catalysis

In Crudden's 1999 report, it was shown that the hydroboration product could be transesterified via a pinacol quench, (rather than methanol followed by an oxidative workup) and the resulting benzylic pinacol boronate could be successfully isolated in excellent yield and enantioselectivity.[97] This advance would prove crucial to the discovery of novel Suzuki-Miyaura cross-coupling reactions in the future (*vide infra*).

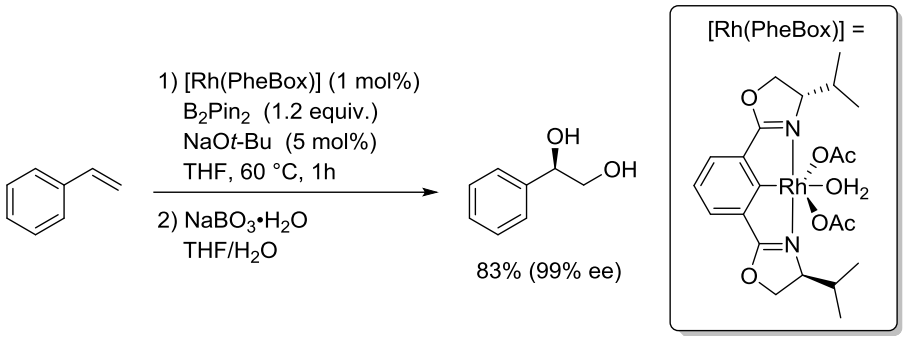
An enantioselective diboration reaction was first report by Morken and colleagues in 2003; however, the diboronates were typically directly oxidized before isolation (Scheme 1-17).[49] A report in the following year by Morken outlined a one-pot diboration/Suzuki cross-coupling/oxidation procedure to access chiral homo-benzylic alcohols.[51] This demonstrated that the new boron substituents could be used for reactions other than for oxidation. The Morken group

has followed up these reports with the development of a platinum catalyst system, which is most successful with aliphatic terminal alkenes. With respect to styrene derivatives, a complimentary approach with a chiral rhodacycle has been reported by Nishiyama as shown below (Scheme 1-18).[52]



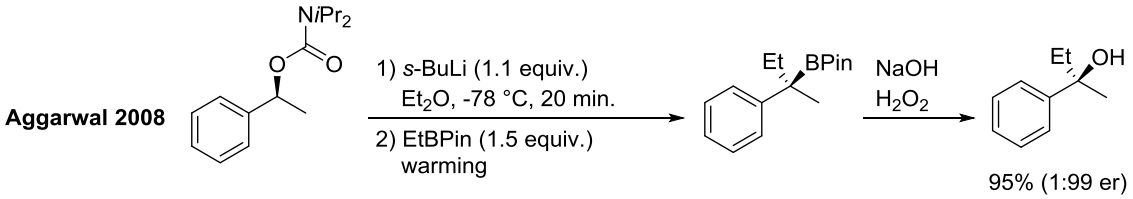
Scheme 1-17 First report of enantioselective alkene diboration (above) and enantioselective diboration of terminal alkenes (below) under platinum catalysis

Nishiyama's method employs a valine-derived *bis*-oxazoline ligand to effect asymmetric conjugate reductions of α,β-unsaturated ketones and esters.[53] It was subsequently reported that this catalyst was also suitable for enantioselective β-borylations of α,β-unsaturated carbonyl compounds[54] and enantioselective diborations of styrene derivatives[52]. The diboration reactions with a 1 mol% catalyst loading proceeded in high yield and enantioselectivity in only 1 hour.



Scheme 1-18 Enantioselective [Rh(PheBox)] catalyzed diboration of styrene

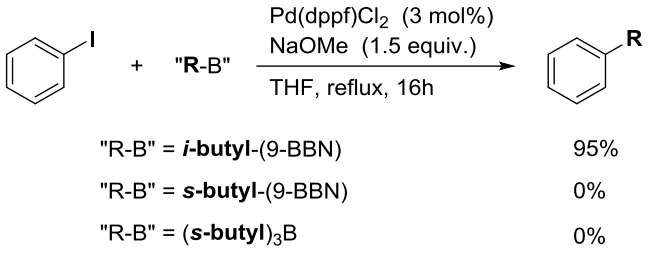
In addition to hydroboration and diboration, B-C bonds can also be constructed by other methods including Miyaura borylation[55], C-H activation[56], and the rearrangements of borates[57] to name a few. In another important example, Aggarwal has demonstrated that chiral carbamates can be used to access chiral boronic esters through 1,2-rearrangements[57] (Scheme 1-19).



Scheme 1-19 Accessing chiral boronic esters through the rearrangement of borates

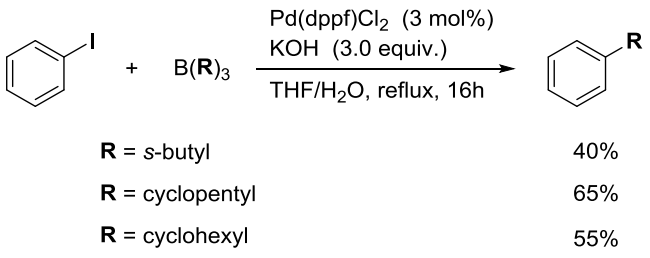
1.4.2 Cross-Coupling of Primary sp^3 Boronates

The main challenge with cross-coupling primary alkyl organoboron compounds: is that they tend to have very sluggish rates of transmetalation. In 1986, Suzuki reported that slow rates of transmetalation could be resolved in the case of B-octyl-9-borabicyclo[3.3.1]nonanes (B-octyl-9-BBN) when Pd(dppf)Cl_2 was used as the catalyst.[45,60] These studies clearly revealed that the aptitude towards transmetalation of the primary alkyl moiety on boron was higher than that of the secondary alkyl group. When both types of alkyl substituents are present on boron, none of the product arising from secondary alkyl transmetalation was observed. Moreover, entirely secondary trialkylboranes were engaged in cross-coupling, but to no avail (Scheme 1-20).[60]



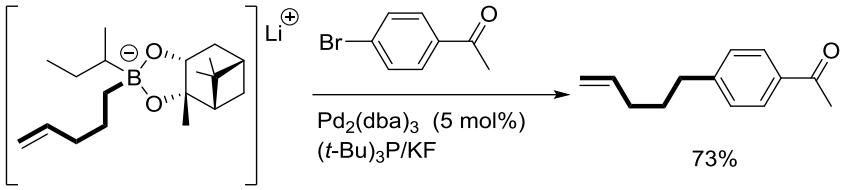
Scheme 1-20 Failed cross-coupling of secondary alkylboranes with iodobenzene under conditions for successful primary alkylboranes.

Three years later, some success was realized with secondary trialkylboranes (Scheme 1-21).[58] Interestingly, the reaction conditions were similar to those that had previously failed, but the use of potassium hydroxide in water as the base was observed to be a key requirement (Scheme 1-21). Suzuki also made two other observations in these reactions: firstly, yields were lower when compared to primary alkylboranes; secondly, between 10% and 30% of the biphenyl product was formed from arylhalide homocoupling.[58] These observations led him to propose that sluggish transmetalation may be to blame for the reduced yield, less so than β-hydride elimination, as less than 1% of *n*-butylbenzene was formed in the reaction with B(*s*-butyl)$_3$.[58]



Scheme 1-21 Cross-coupling of secondary trialkylboranes with iodobenzene promoted by aqueous KOH

Another report by Falck *et al*., highlights the inherent differences in the cross-coupling of primary vs secondary sp^3 substituents on boron by placing them on the same boron atom (Scheme 1-22).[59]



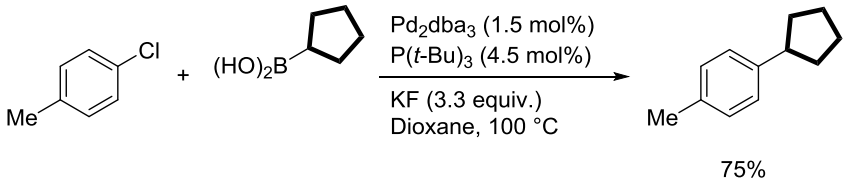
Scheme 1-22 Activation of primary alkylboronates as borates with s-BuLi

However valuable polyene and biaryl targets may be, the inability of the Suzuki-Miyaura cross-coupling to tolerate secondary sp^3 organoboron nucleophiles has precluded it from being used to assemble more complex structures including, of course, stereodefined C-C bonds. This detracts from the overall utility of the reaction itself. Given the variety of ways in which the requisite enantioenriched secondary alkylboronates are accessible, it would be a true break through if conditions could be found, whereby these compounds are competent cross-coupling partners.

1.4.3 Cross-Coupling Secondary sp^3 Boronates

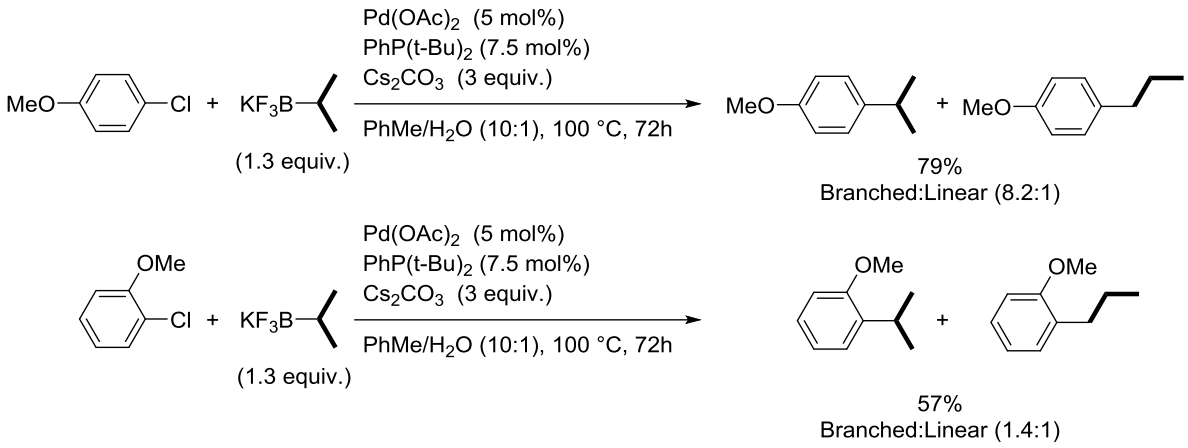
As detailed above, the cross-coupling of alkyl boronates is challenging due to slow rates of transmetalation, however, with secondary alkyl boronates the presence of β-hydrogens introduces the additional problem of β-hydride elimination. β-hydride elimination can result in the loss of stereochemical and positional information upon reinsertion of the newly formed palladiumhydride to the olefin intermediate (*vide infra*).[45,60] Within approximately the last ten years, interest in solving this challenging problem, and reports to that end, have begun to appear. In 1996, Deng reported the cross-coupling of *trans*-2-butylcyclopropylboronic acid and bromoarenes with complete retention of configuration and in some cases with near quantitative conversion.[61] However, this report does not represent a generally applicable solution as it derives its success from the innate characteristics of cyclopropanes, specifically the high degree of sp^2 character of the carbon being transmetalated and the formation of cyclopropenes by β-hydride elimination is extremely unfavourable due to ring strain.

A considerable amount of work in the area of sp^3–hybridized coupling partners as both nucleophiles and electrophiles has been contributed by Fu and colleagues.[62] In 2001, using a $Pd_2dba_3/P(t\text{-}Bu)_3$ catalyst system Fu described the coupling of a secondary alkylboron partner, cyclopentylboronic acid, within a paper otherwise dedicated entirely to the coupling of primary boronic acids.[63] This particular substrate is somewhat specialized in that the symmetry of the boronic acid makes any potential β-hydride elimination-reinsertion events undetectable. Thus the utility of this work with non-symmetrical systems is unclear; however, at least the transmetalation of these difficult substrates was described.



Scheme 1-23 Cross-coupling of cyclopentyl boronic acid

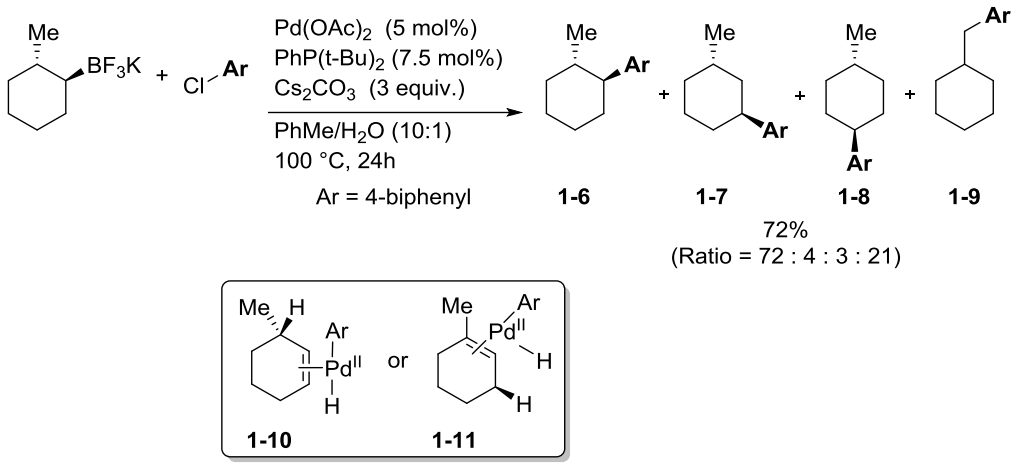
More recent advances showing efficient transmetalation while minimizing β-hydride elimination have come from Molander *et al*. wherein 2-propyl potassium trifluoroborates were employed as coupling partners for chloroarenes.[64] In these cases, even though the borate being employed is symmetrical, the β-hydride elimination-reinsertion pathway will be indirectly observable as regioisomers of the coupling product. β-Hydride elimination events should favour formation of the least sterically hindered alkylpalladium(II) organometallic intermediate which, following reductive elimination, will lead to the formation of the undesired regioisomer.



Scheme 1-24 Effect of sterics on the regiochemistry of 2-propyl potassium trifluoroborate with arylchlorides

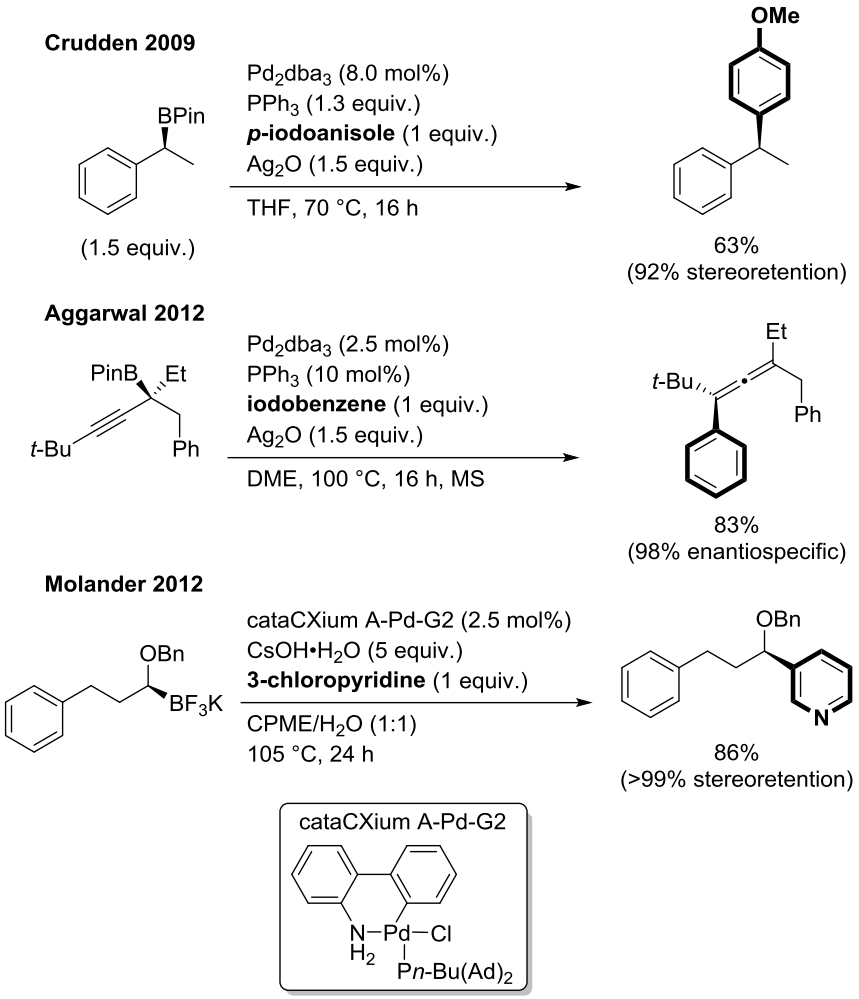
Indeed, Molander was reported that under the optimized conditions, a synthetically useful ratio of the product with the desired regiochemistry was attainable with 4-chloroanisole, however, when 2-chloroanisole, a more sterically demanding substrate, was employed this selectively was greatly eroded (Scheme 1-24).[64]

Molander subjected *trans*-2-methyl-cyclohexyltrifluoroborate to the same conditions and, again, found that the β-hydride elimination-reinsertion pathway resulted in the formation of at least three undesired regioisomers.[64] Interestingly, products **1-6**, **1-7**, and **1-8** (Scheme 1-25) were formed as single diastereomers.[64] This implies that during the β-hydride elimination-reinsertion pathway, the palladium hydride stays bound to one face of the alkene intermediate. However, since the species travels though the symmetrical intermediate, **1-10** or **1-11**, any chiral information is lost.



Scheme 1-25 Products of the cross-coupling of a diastereomerically enriched potassium trifluoroborate with an arylchloride. Presumptive intermediates are also shown.

Following this report, several discoveries have been made in the area of enantiospecific cross-couplings. These discoveries generally fall into one of two categories. The first is π-directed couplings (Scheme 1-26) which includes reports from Crudden,[65,66] Aggarwal,[67] Crudden and Aggarwal in collaboration,[68] and Molander,[69] the second is heteroatom-directed couplings (Scheme 1-28) which includes reports from Suginome,[70,71,72] Molander,[73] and most recently Morken[74].

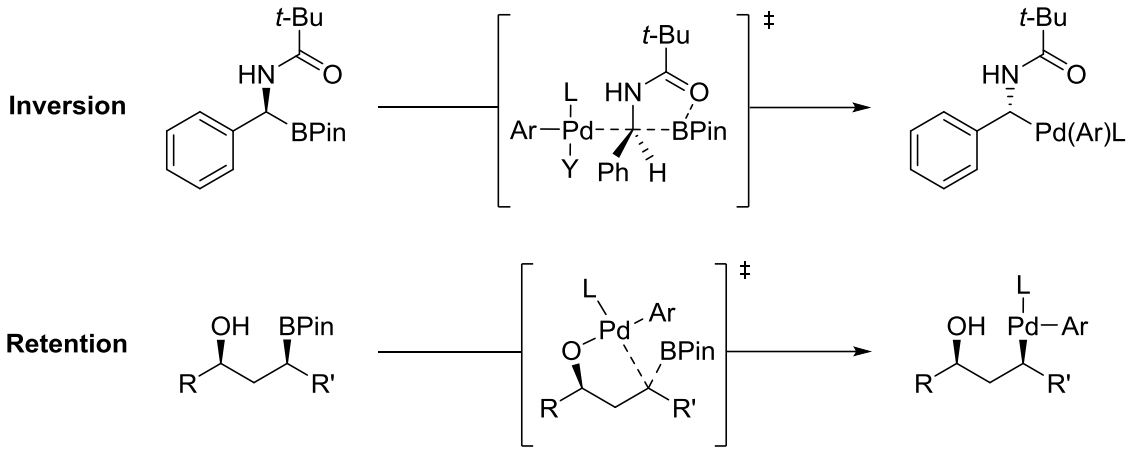


Scheme 1-26 Enantiospecific cross-couplings of secondary alkyl boronates with adjacent π-systems

In the case of π-directed stereoretentive couplings, one of the key components is a requirement for Ag_2O. Although the precise role(s) of Ag_2O remain unknown, the requirement that these pinacol boronates be benzylic, allylic, or propargylic could mean that the π-acidity of silver is a factor. A fascinating observation noted in the 2009 report by Crudden, is the remarkable chemoselectivity of the conditions for benzylic boronates.[65] Counterintuitively, primary alkyl boronates were found to be completely unreactive under these conditions.[65]

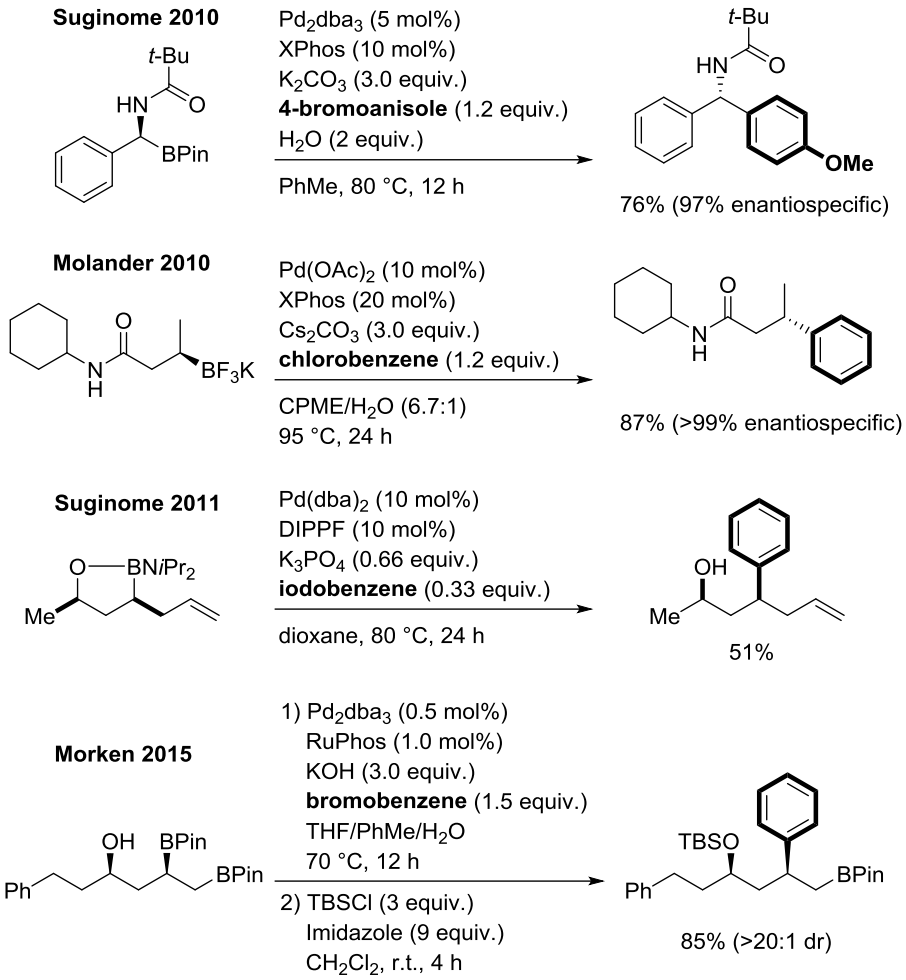
In the case of the heteroatom–directed examples (Scheme 1-28), the cross-coupling reaction typically proceeds with inversion of stereochemistry[70,73] with the exception of two

examples from Suginome and the recent report by Morken[74]. The observation of net inversion is proposed to occur in the transmetalation step (Scheme 1-27, Inversion), which is promoted by intramolecular coordination of an adjacent oxygen lone pair to the boronate.



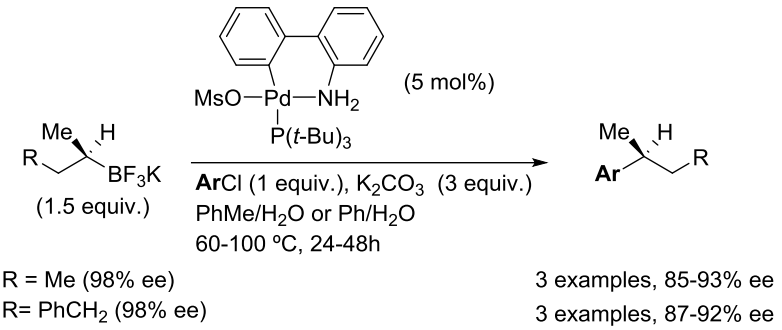
Scheme 1-27 Transition state proposed by Morken for divergent stereochemical observations in hydroxyl-directed cross-couplings

The departure from inversion under Morken's conditions suggests a difference in mechanism. The proposed explanation is an inner-sphere stereoretentive transmetalation which occurs through an alkoxopalladium(II) intermediate (Scheme 1-27, Retention).[74] This also accounts for the selective coupling of the secondary alkyl boronate in the presence of a more reactive primary boronate.[74] Furthermore, the methodology itself is also interesting in that a single cross-coupling of a polyboronate is achieved without the use of exotic protecting group chemistry (*vide infra*). This work builds on a 2011 report from Suginome illustrating the increased reactivity of a secondary boronate when bound to a nearby heteroatom.[72]



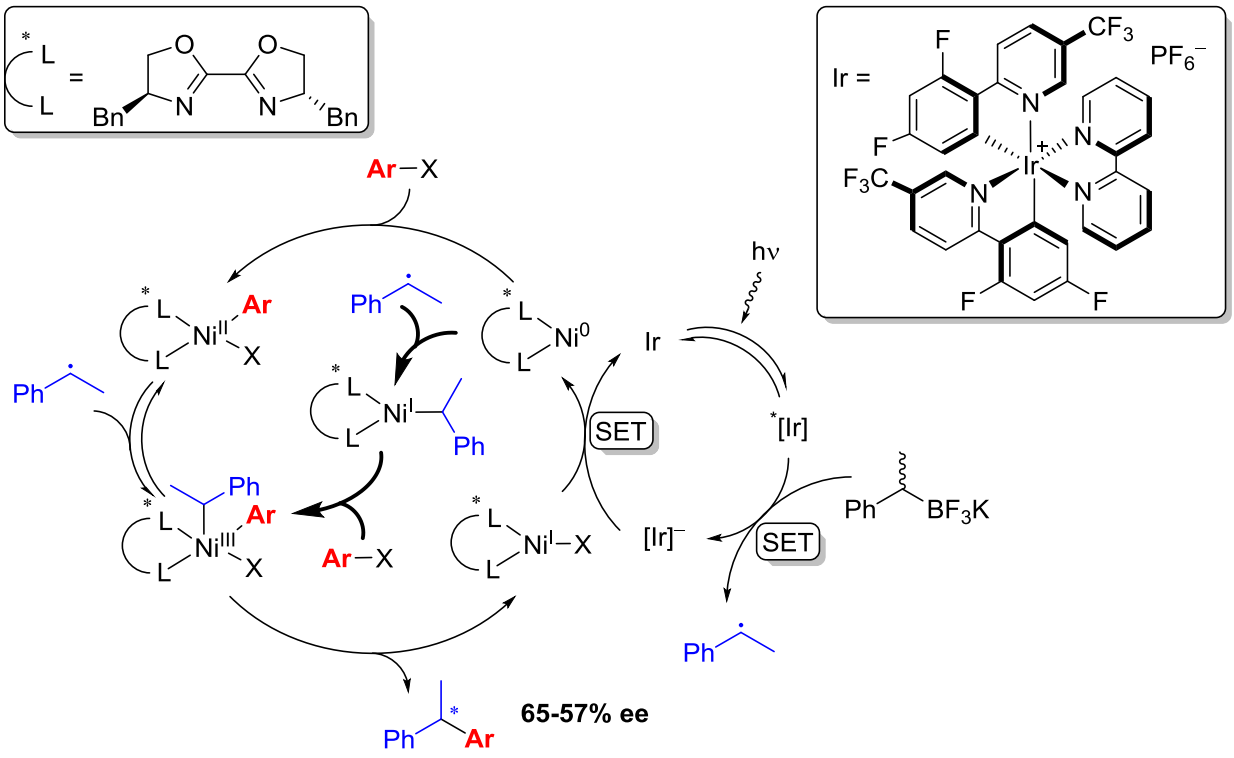
Scheme 1-28 Examples of Suzuki-Miyauara cross-couplings promoted by adjacent heteroatoms

In addition to these mechanistically distinct heteroatom directed reactions, a recent report has come out from the Biscoe group, wherein secondary alkyl potassium trifluoroborates and boronic acids were cross-coupled with chloroarenes.[75] The reaction was found to proceed with excellent regioselectivity (200:1, branched:linear).[75] Intriguingly, when enantioenriched alkyltrifluoroborates are employed, the products are obtained with inversion of stereochemistry despite the absence of an ancillary heteroatom (Scheme 1-29).[75]



Scheme 1-29 Cross-coupling of unactivated alkyltrifluoroborates with net inversion

However, more recently Molander has reported results that may represent a great leap towards a more general solution to this persistent problem. In order to achieve the treacherous transmetalation, without using forcing conditions which may promote β-hydride elimination or protodeboronation among other unwanted competing processes, a radical or 'barrier-less transmetalation' was accomplished (Scheme 1-30).[76] Using an iridium photocatalyst, an sp^3 centered radical is generated from an alkyl potassium trifluoroborate, which can then undergo 'transmetalation' under relatively very mild conditions. Given that the mechanism is radical in nature, a nickel catalyst is used in place of palladium. The precise sequence of events in the mechanism of the reaction is still to be definitively determined. The latest calculations suggest that a pathway where transmetalation to a nickel(0) complex, forming a nickel(I) intermediate, precedes oxidative addition (Scheme 1-30, bolded) leading to a diorganonickel(III) intermediate, is most energetically favourable.[77] The reversal of the ubiquitous transmetalation and oxidative addition steps is not uncommon for nickel catalyzed processes. Encouragingly, when a chiral ligand is employed enantioenriched products were accessible, although in low enantioselectivity at present. Calculations also suggest that stereoinduction is achieved in the reductive elimination step and is aided by a dynamic kinetic resolution of the proposed nickel(III) intermediate.[77] The value of this departure from conventional approaches to cross-coupling will probably only be born out through further pushing its limits and remains to be seen.

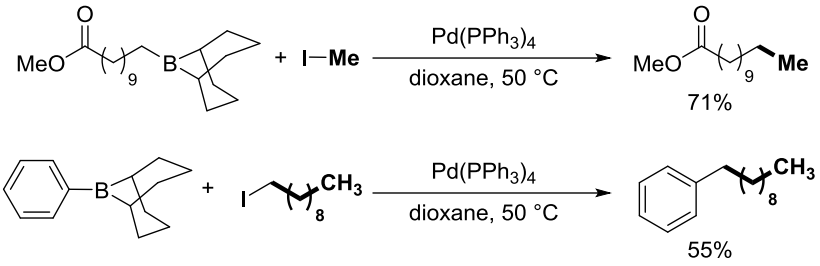


Scheme 1-30 Nickel/iridium dual catalyzed stereoconvergent cross-coupling of alkyl potassium trifluoroborates and arylhalides

1.5 Suzuki-Miyaura Cross-Coupling of sp^3 Electrophiles

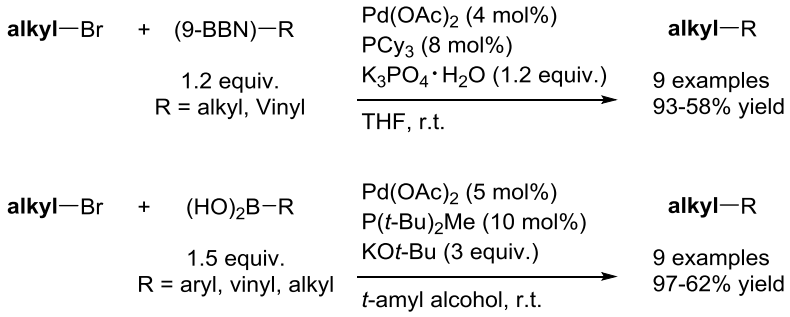
1.5.1 Primary sp^3 Hybridized Electrophiles

The cross-coupling reaction of alkylhalides encounters many of the same pitfalls as that seen for alkylboron compounds. In 1995 Suzuki remarked that the cross-coupling of alkyl electrophiles might not be possible because when β-hydrogens are present oxidative addition is slow and β-hydride elimination from the resultant organopalladium(II) species is fast.[2] Of course this issue does not arise with alkylhalides devoid of β-hydrogens, such as benzylhalides or iodomethane, and these are typically be coupled with good success (Scheme 1-31).[78]



Scheme 1-31 Cross-coupling of primary alkyliodides with trialyklboranes

This issue has again garnered the attention of many research groups, including the Fu group who have prior experience developing catalytic systems which will efficiently undergo oxidative addition to very challenging electrophiles. Indeed, two separate reports from the Fu group, disclosed the cross-coupling of primary alkyl bromides bearing β-hydrogens, with 9-BBN[62] and boronic acid[79] coupling partners, respectively (Scheme 1-32). Each of these systems made use of an electron-rich trialkylphosphine ligand to overcome lethargic oxidative addition and were later modified to accommodate tosylates[80] and chlorides[81].

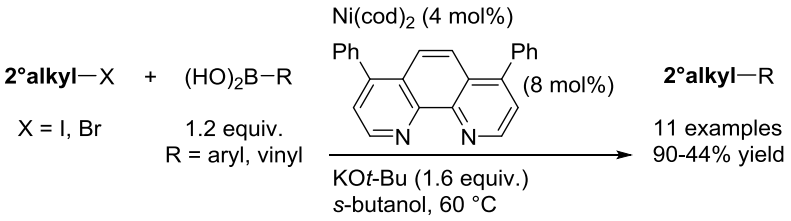


Scheme 1-32 Palladium catalyzed cross-coupling of primary alkylhalides promoted by electron-rich phosphine ligands

1.5.2 Secondary and Tertiary sp^3 Hybridized Electrophiles

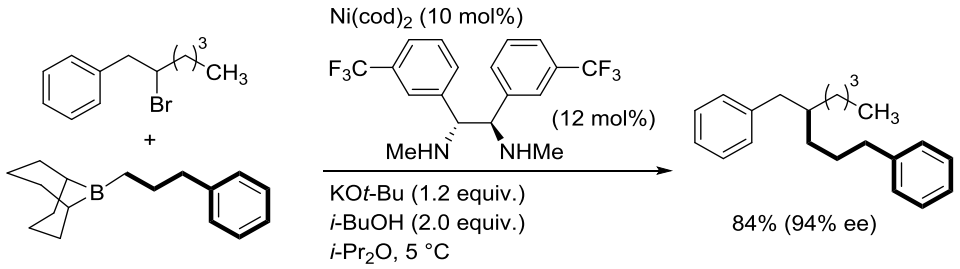
In 2004, the Fu group expanded their contributions in the area of alkylhalide coupling partners to include secondary alkylhalides.[82] It was found that a nickel catalytic system, instead of

a palladium system, could affect the cross-coupling of vinyl and aryl boronic acids with both primary and secondary alkyl bromides and iodides (Scheme 1-33).[82]



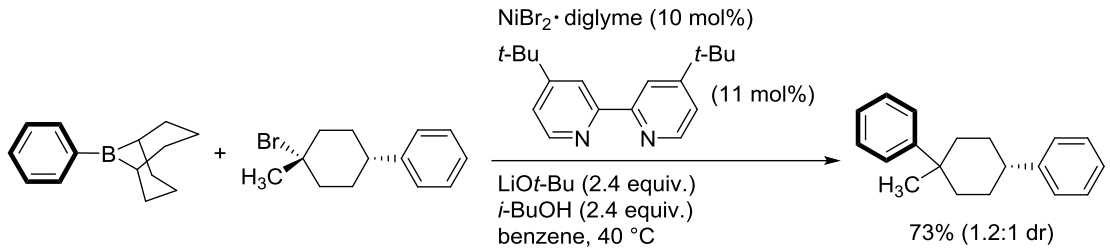
Scheme 1-33 Nickel catalyzed cross-coupling of secondary alkylhalides with boronic acids

Following their success with nickel catalysis the Fu group developed an asymmetric variant to the system in 2008 to achieve a stereoconvergent cross-coupling of secondary homobenzylic alkylbromides with primary alkyl-(9-BBN) derivatives (Scheme 1-34).[83] Under these conditions, ee's as high as 94% were attainable.[83]



Scheme 1-34 Stereoconvergent nickel catalyzed cross-coupling of secondary homobenzylic alyklbromides

The power of nickel to add to very challenging unactivated alkyl halides has been taken to the limit again by the Fu group when, in 2013, the first cross-coupling of a tertiary alkylhalide was reported (Scheme 1-35).[84] In this case, the catalytic system employed a 2,2'-bipyridyl ligand but was unfortunately demonstrated to proceed with very low diastereoselectivity when a single alkylhalide diastereomer was tested.[84] It is interesting that the cross-coupling of unactivated alkyl electrophiles is seemingly dominated by nickel catalysis.

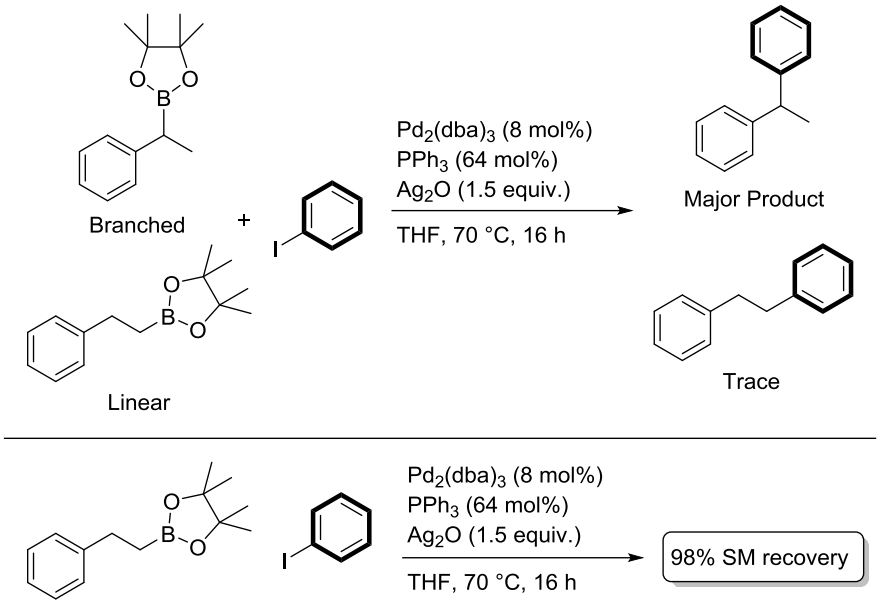


Scheme 1-35 Nickel catalyzed cross-coupling of tertiary alkylbromide with low diastereoselectivity

1.6 Research Outlook

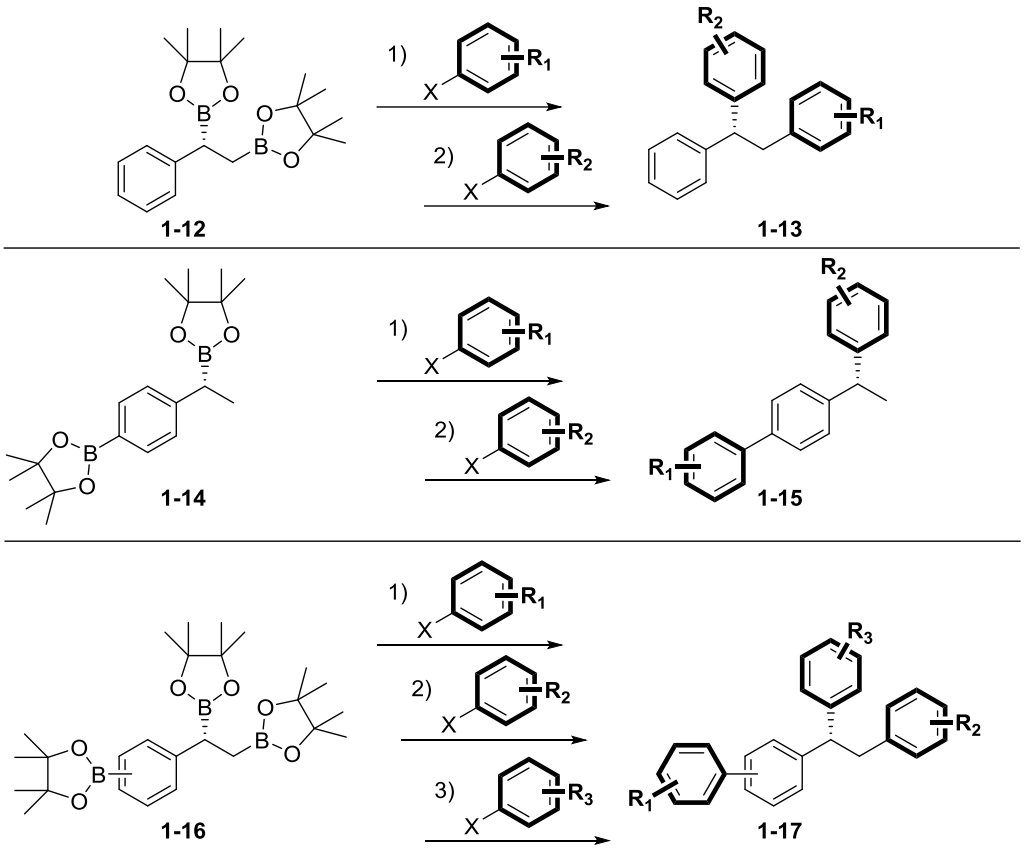
From the literature discussed above, it is clear that in order for the Suzuki-Miyaura cross-coupling reaction to be modernized the development of manifolds for stereogenic Csp^3- Csp^2 and Csp^3- Csp^3 bond formation is of great importance. The construction of compounds with increasing degrees of saturation is also demonstrably useful for the modern medicinal chemist. A report from Lovering and colleagues in 2009 highlighted the over representation of more saturated compounds in successful drug targets than all other phases of clinical trials.[85] The authors hypothesize that increasing saturation generally leads to an increasing degree of complexity within a molecule in terms of the number of isomers, as well as introducing possible stereocenters.[85]

With this knowledge in mind, and drawing on some surprising observations in the 2009 report[65] from our lab (*vide infra*), we set out to develop a unique cross-coupling methodology.



Scheme 1-36 Competition experiment highlighting the chemoselectivity of Ag_2O promoted conditions

The motivations for the idea illustrated below (Scheme 1-37) were competition experiments described above, which starkly demonstrated the high degree of chemoselectivity inherent in the Ag_2O promoted benzylic boronate cross-coupling conditions (Scheme 1-36).[65] These conditions showed incredible selectivity for what one would expect to be the more difficult cross-coupling partner, all the while leaving the primary boronate almost completely intact. In this thesis it is hypothesized that if a substrate bears more than one boron substituent suitable for cross-coupling, that these substituents can be iteratively cross-coupled using the high degree of chemoselectively inherent in the substrate and in different cross-coupling conditions.



Scheme 1-37 Proposed iterative cross-coupling methodology

This approach would capitalize on the previous successes in our lab with coupling protocols for benzylic pinacol boronates[65] and apply these to substrates containing a more reactive aryl or primary alkyl boronate. The next logical step for this idea is to combine all three different boronates on a single substrate to find the limits of this new methodology (Scheme 1-37). If successful, we would also be circumventing the use of any protecting groups, and thus the installation and removal of such groups, to achieve iterative cross-couplings. The use of protecting groups in the Suzuki-Miyaura reaction is a large area of research onto itself and it is discussed below in detail.

1.7 Thesis Objectives

The objectives of the research detailed in this thesis are fourfold:

1. To achieve the syntheses of the requisite diboronates (**1-12** and **1-14**) with high ee
2. Find conditions under which the more reactive primary alkylboronate of **1-12** and arylboronate of **1-14** may be chemoselectively cross-coupled leaving the benzylic boronate intact in each case
3. Find conditions whereby the resultant benzylic boronates can be cross-coupled with high enantiospecificity
4. Apply what has been learned from each diboronate substrate to a triboronate (**1-16**)

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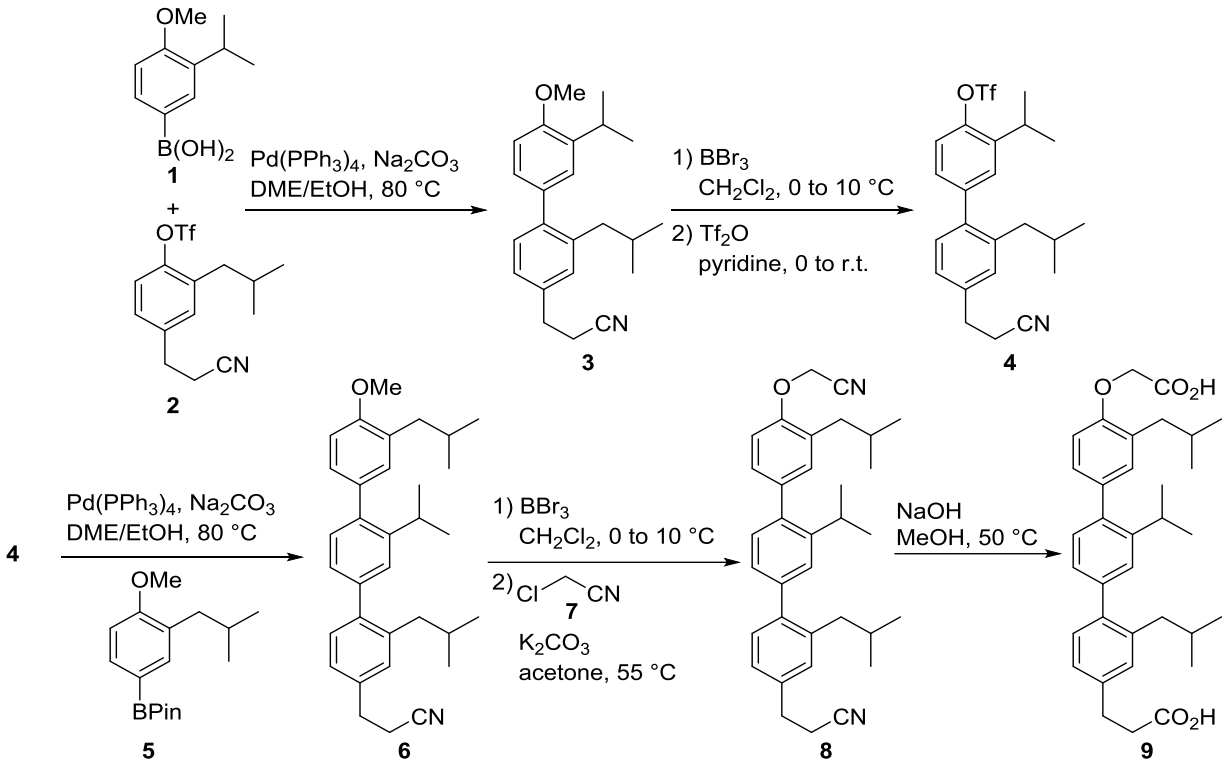
Chapter 2

Iterative, Chemoselective, Stereospecific, Protecting Group Free Cross-Coupling of Polyboronates

2.1 Introduction

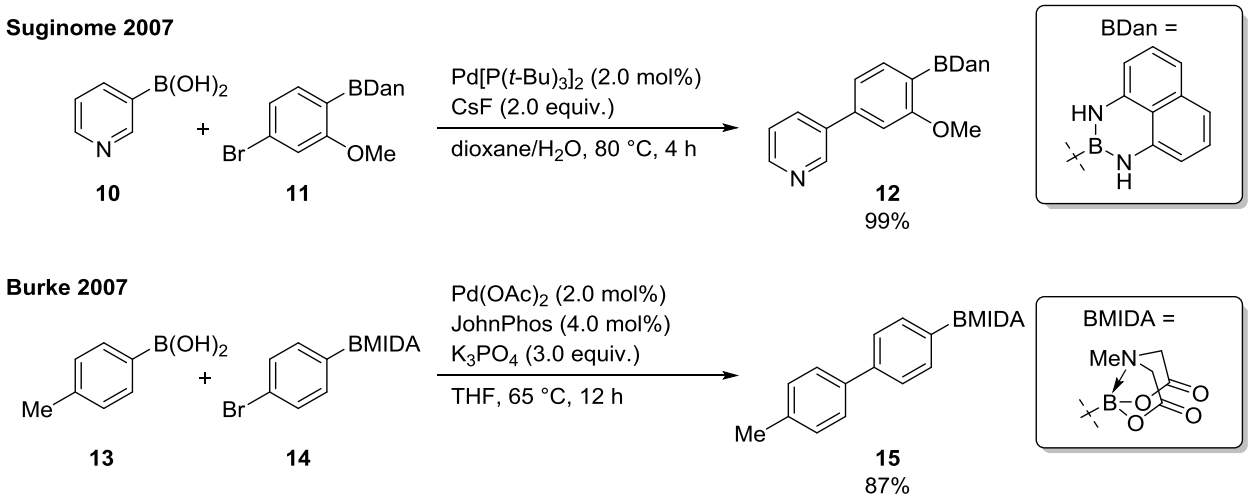
2.1.1 Iterative Cross-Coupling Using Protecting Group Chemistry

The first report of iterative coupling involving boronic esters appeared in 2002 by Hamilton *et al*.[86] and involved the coupling of anisole derived boronic acids, subsequent arylether cleavage, and triflation of the hydroxyl group to furnish **4** (Scheme 2-1). The newly formed triflate could then be cross-coupled with another anisole derived boronic acid. Exploiting the nascent bimodal reactivity inherent to the boronate, eventually granted them access to their target triphenyl compound, **9**. This process was improved upon in a 2006 report by Manabe using hydroxylphenylboronic acids thus eliminating the arylether cleavage step.[87]



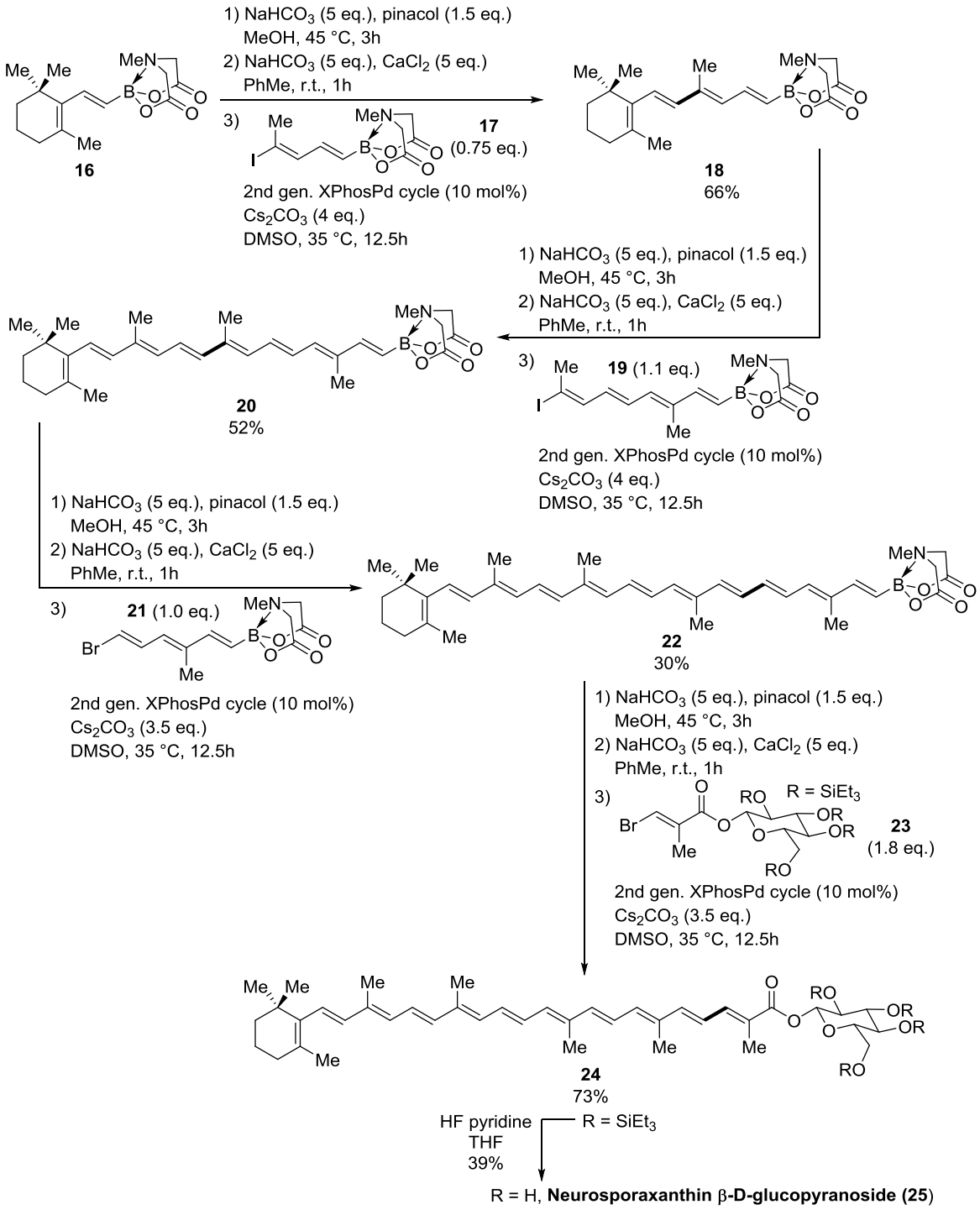
Scheme 2-1 First reported iterative cross-coupling strategy

In 2007, a new strategy in iterative coupling emerged. Suginome and colleagues introduced naphthalene-1,8-diaminato (Dan)[88] and shortly thereafter Burke and colleagues introduced N-methyiminodiacetic acid (MIDA)[89] as ligands for boron (Scheme 2-2). These new 'masking' or protecting groups for boron completely remove boron's ability to participate in transmetalation.[88,89] This report created an opportunity for a completely different strategy compared to the previously described approach of cross-coupling followed by hydroxyl triflation to set up a possible cross-coupling reaction. The effect of these masking groups is that a single compound has the ability to act as first an electrophile then, after deprotection, as a nucleophile.



Scheme 2-2 Deactivation of boron substituents towards transmetallation with deactivating protecting groups

Burke has proposed that this strategy can be used to access the polyene motifs of as many as 75% of known polyene natural products from a minimal number of halo MIDA boronates.[90] The potential of this approach is exemplified by the rapid synthesis of three such natural products, including neuroporaxanthin β-D-glucopyranose (Scheme 2-3), for which no total synthesis had been previously reported.[90] Furthermore, MIDA boronates are also demonstrably stable towards the harsh reaction conditions of other functional group interconversions.[91] These reports have garnered such attention for their potential impact and generated such research interest that many MIDA and halo MIDA boronates are now commercially available.[92]

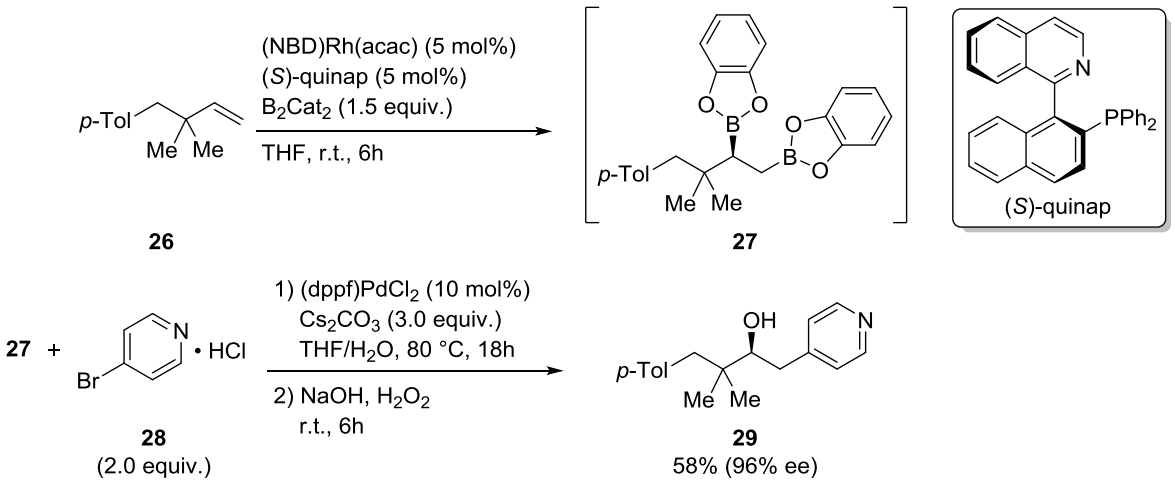


Scheme 2-3 Total synthesis of Neurosporaxathing β-D-glucopyranoside using an iterative deprotection and cross-coupling strategy

2.1.2 Selective Cross-Coupling Reactions without Deactivating Protecting Groups

The obvious drawbacks when using any protecting group approach are the additional manipulations required to install and later to remove said protecting group(s). With respect to cross-couplings of polyboronates, where a Dan, MIDA, or similarly deactivating ligand is not used to prevent a transmetalation, relatively little progress has been made.

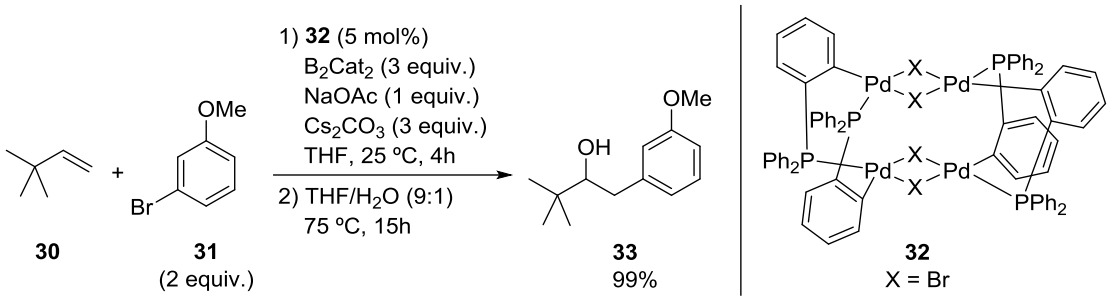
The first report of an iterative and chemoselective diboronate transformation came from the Morken lab in 2004 (Scheme 2-4).[93] Diboration of alkene **26** resulted in diboronate **27**. The more reactive primary alkyl boronate of **27** could then undergo a cross-coupling reaction after which the secondary alkyl boronate was oxidized, affording homobenzylic alcohol **29**. Importantly, this demonstrated that the new boron substituents in **27** could be used for reactions other than oxidation and that under the appropriate conditions, they could be chemoselectively transformed.



Scheme 2-4 Chemoselective iterative Suzuki-Miyaura-oxidation sequence following a diboration

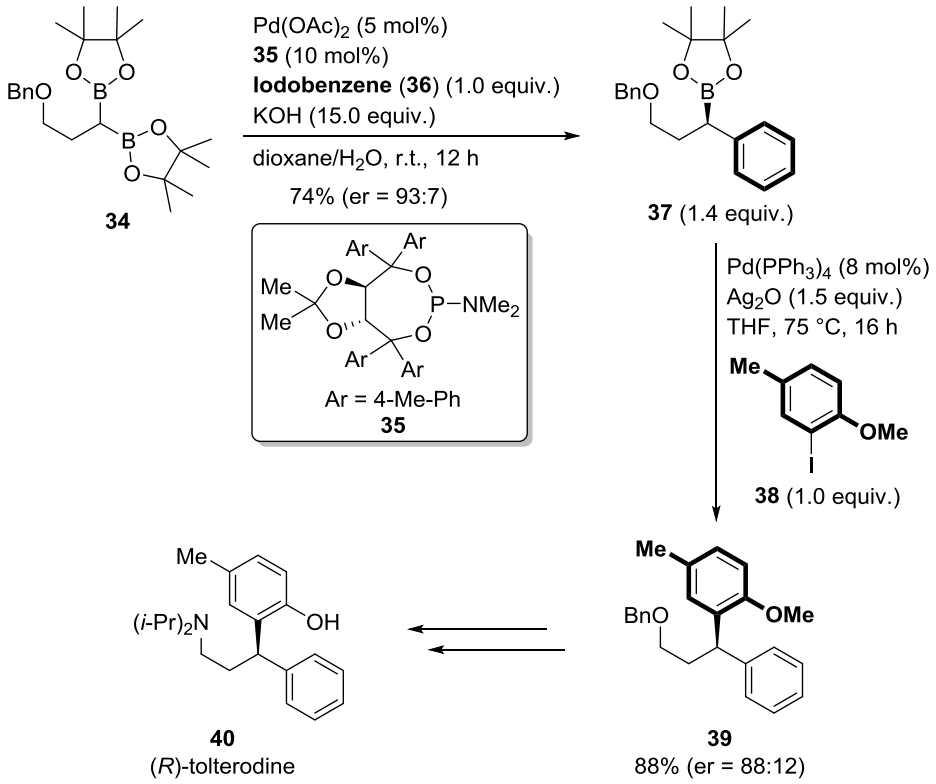
In 2008, Fernandez described a similar approach with a highly efficient Pd complex (**32**).[94] It was her desire to find a novel catalytic system which, with equal efficiency, could catalyze both the diboration and Suzuki-Miyaura cross-coupling processes.[94] Interestingly, this report demonstrated that Pd complex **32** could quantitatively perform both catalytic transformations, thus

terminal alkenes were smoothly converted into monoarylated homobenzylic alcohols, such as **33**, in a tandem diboration-Suzuki cross-coupling sequence (Scheme 2-5).[94]



Scheme 2-5 Palladium catalyzed diboration and Suzuki-Miyaura cross-coupling, followed by oxidation, sequence to access homobenzylic alcohols

It was the Morken group again in 2014 that reported the first instance of an iterative diboronate transformation where both reactions were Suzuki-Miyaura cross-coupling reactions. They first demonstrated an enantiotopic-group-selective Suzuki-Miyaura reaction of 1,1-diboronates, such as **34**, to afford a benzylic boronate (Scheme 2-6).[95] In this stereoconvergent process, cross-coupling of the second pinacol boronate is abated by virtue of it becoming a benzylic boronate after the introduction of an aryl moiety, and by the fact that the coupling of the geminal diboronate is accelerated. This observation was actually first reported in a racemic system by Shibata in 2010.[96] The benzylic boronate, such as **37**, can be isolated and then subjected to Ag_2O promoted coupling conditions to afford a diarylated product, such as **39** (Scheme 2-6).[95] Morken followed this development with the aforementioned report of a stereospecific hydroxyl directed cross-coupling.[74] What makes this report standout is that cross-coupling takes place selectively at the secondary pinacol boronate, in the presence of the more reactive primary boronate. Although it was not actually demonstrated, these substrates may be amenable to sequential chemoselective cross-couplings as the primary pinacol boronate remains intact in the isolated product. This sequence was used to prepare tolterodine, an active pharmaceutical ingredient.



Scheme 2-6 Formal total synthesis of (R)-tolterodine (**40**) by way of an enantiotopic-group-selective and iterative cross-coupling approach

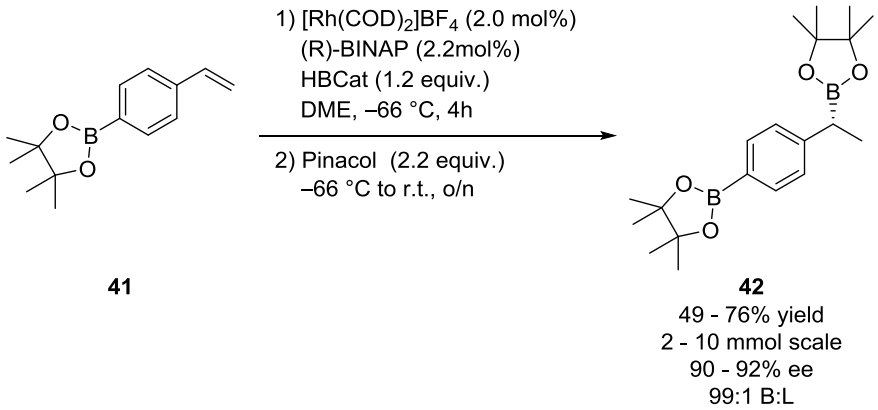
The precedents described above underscore and lend perspective to the complimentary nature of work detailed herein (vide infra).

2.2 Synthesis of Requisite Starting Materials

2.2.1 Enantioselective Hydroboration of Alkenes

As detailed above, since the pioneering discovery by H. C. Brown in 1956[43], B-C bond construction has been greatly advanced by the introduction of transition metal catalyzed routes.[47,48,50] Specifically we sought to exploit one of the earliest and most successful of these reports from Hayashi in 1989,[47] later elaborated upon by the Crudden lab.[97]

In Crudden's 1999 report, it was shown that the hydroboration product could be transesterified and successfully isolated in excellent yield and with high enantioselectivity.[97] The work detailed below began with the discovery that these conditions, without any optimization, can be successfully applied to 4-vinylphenyl boronic acid pinacol ester (**41**), to reproducibly access one of the requisite diboronates (**42**) to begin our studies (Scheme 1-37). The yield was found to be good to moderate, with similarly high enantioselectivity and excellent regioselectivity (Scheme 2-7).

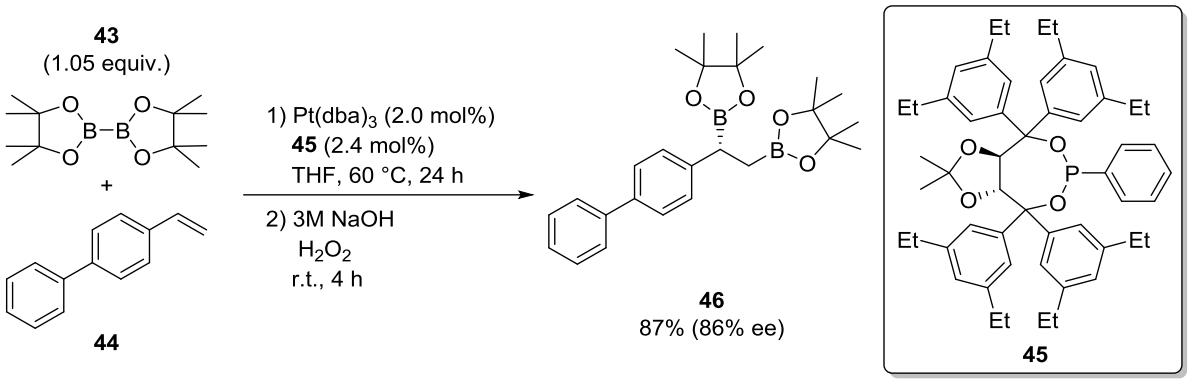


Scheme 2-7 Rhodium catalyzed enantioselective selective hydroboration of **41**

2.2.2 Enantioselective Diboration of Alkenes

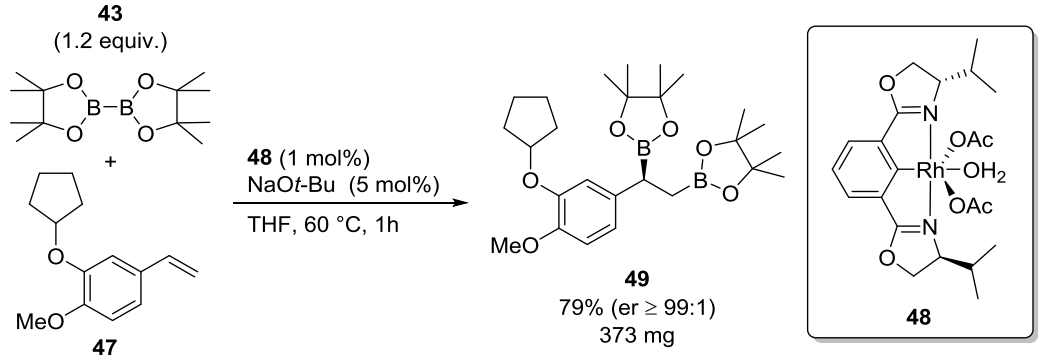
For the achievement of a protecting group-free iterative coupling concept, access to enantiomerically enriched 1,2-diboronates will also be critical. As outlined above, enantioselective diboration has been known since 2003[49] and the products of this transformation were first utilized in 2004 (Scheme 2-4).[49] However, the Morken lab has followed these reports using rhodium catalysts, with the development of a more active platinum catalyst system over the past decade. Additionally, a different system using a chiral rhodacycle (**48**) was reported by Nishiyama as recently as 2013. [98] Prior to this work, in 2006, Nishiyama and colleagues reported a rhodium system which employed a valine-derived *bis*-oxazoline derived ligand to effect asymmetric conjugate reductions of α,β-unsaturated ketones and esters.[53] It was subsequently reported that this catalyst was also suitable for asymmetric β-borylations of α,β-unsaturated carbonyl compounds[99] and diborations of styrene derivatives[98]. The diboration reactions with a 1 mol% catalyst loading proceeded in high yield and enantioselectivity within only 1 hour reaction time.

For the synthesis of enantiomerically enriched diboronates, we first explored the applicability of Morken's platinum/phosphonite (**45**) system, typically used in the asymmetric diboration of terminal alkenes, to styrene derivative. Unfortunately, this was not particularly successful. The reaction proved to be very sluggish and required a doubling of the typical catalyst loading in addition to 24 hour reaction times to achieve useful conversion levels to diboronate **46**. Furthermore, the product was obtained with only 86% ee. Product isolation was also made very challenging by virtue of the residual B_2Pin_2 (**43**) which was not consumed during the course of the reaction. As a result of this limited success, in addition to a troubling ligand synthesis, we turned our attention towards Nishiyama's rhodium based system.[98]



Scheme 2-8 Enantioselective diboration of styrene **44** under platinum catalysis

In terms of styrene derivatives, this rhodium catalyzed system proved to be, in our hands, far superior (Scheme 2-9) to Morken's platinum catalyzed system (Scheme 2-8). In particular, an intriguing isovanillin derived diboronate, **49**, was accessible in high yield and excellent enantiomer ratio using this catalyst system.



Scheme 2-9 Enantioselective rhodium catalyzed diboration of styrene derivative

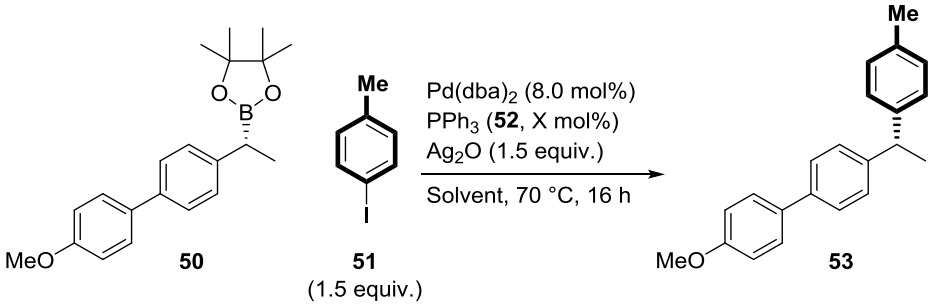
2.3 Optimization of Previously Reported Stereodefined Secondary Benzylic Pinacol Boronate Cross-Coupling Conditions

Prior to proceeding to study the iterative cross-coupling, we re-optimized the enantiospecific benzylic cross-coupling conditions reported by the Crudden lab[65], particularly with regard to the effect of H_2O as well as the equivalents of PPh_3 on both the yield and stereochemical

outcome of the reaction. This was particularly important in light of possible one pot sequential coupling processes, where amounts of these two components might be variable.

This work began by studying the effects of water on the cross-coupling reaction between benzylic boronate **50** with aryliodide **51**. The reaction was conducted where either 350 ppm of H_2O was added or anhydrous conditions were employed. The results were very clear. The yield for each reaction was determined to be 82% of the desired product; however, when H_2O was present, the er of the product dropped from 91:9 to 85:15 (Table 2-1, entries 1 and 2). The effect of H_2O on the reaction was unequivocally negative.

Table 2-1 Investigating the effect of PPh_3 loading and H_2O on yield and stereochemical outcome of benzylic cross-coupling



	PPh_3 (mol%)	Solvent	Yield[a]	e.r.
1	64 mol%	DME/H_2O (350 ppm)	82%	85:15
2	64 mol%	DME	82%	91:9
3	48 mol%	DME	90%	92:8
4	32 mol%	DME	69%	93:7

[a] Determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard

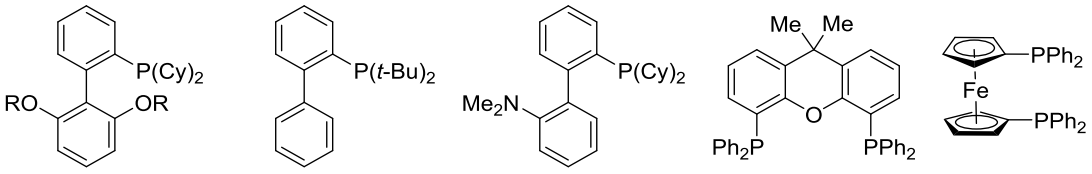
We then turned out attention to the effect of PPh_3 loading on the reaction. Since previous work had used either eight equivalents to palladium or higher, we were interested in any possible benefits to reducing the ligand loading. Interestingly, when either six or four equivalents to palladium were tested, the er in both cases was approximately 92.5:7.5, however, the yield decreased sharply, from 90% to 69% (Table 2-1, entries 3 and 4). We noted that this work is

consistent with prior results from the Crudden lab.[100] From these experiments we derived a new set of optimized conditions, which would use no H_2O and six: one ratio of PPh_3 to palladium rather than eight: one.

2.4 Chemoselective Cross-Coupling of Compounds Containing Primary Alkyl and Stereodefined Secondary Benzylic Pinacol Boronates

2.4.1 Cross-Coupling of Primary Alkyl Boronate in Stereodefined 1,2-Diborated Styrene Derivatives

This research began by examining the cross-coupling of diboronate **46**, the synthesis of which was previously discussed (Scheme 2-8). We were particularly interested in investigating **46** as we had never previously investigated a biaryl diboronate and suspected this might have implications in our development of a chemoselective triboronate cross-coupling manifold (Scheme 2-17, Scheme 2-18). Given that it is known that alkyl boronates are challenging substrates to engage in cross-coupling, stemming from sluggish transmetalation and, in some cases, a propensity towards β-hydrogen elimination, we sought to tap into the considerable research reported towards solving these problems. Additionally, previous research from both Veronique Laberge and Samantha Voth in the Crudden lab would prove to be a useful starting point.[101,102] In particular they had demonstrated that Buchwald type ligands, such as SPhos (**54**) and RuPhos (**55**), efficiently promoted the desired cross-coupling.

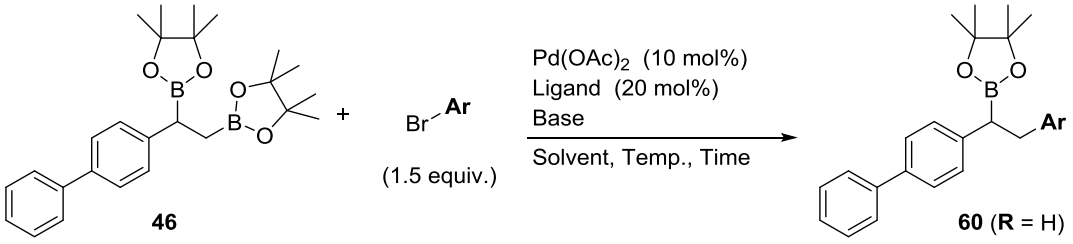


54 (SPhos) R = Me
55 (RuPhos) R = *i*-Pr
56 (JohnPhos)
57 (DavePhos)
58 (XantPhos)
59 (dppf)

Figure 2-1 Ligands tested in diboronate cross-coupling optimization

Our reinvestigation of the reaction (Table 2-2) was consistent with these results. The poor performance of similar ligands, namely, JohnPhos (**56**) and DavePhos (**57**), was also confirmed along with the poor performance of arylphosphines, specifically XantPhos (**58**) and dppf (**59**, Scheme 2-4) (Table 2-2, entries 8 and 10 respectively). Unfortunately, the optimized conditions (Table 2-2, entry 5) failed when 4-bromopyridine hydrochloride salt (**28**) was tested (Table 2-2, entry 9). Compound **59** was also tested in a reaction with **28** but to no avail (Table 2-2, entry 10).

Table 2-2 Optimization of chemoselective diboronate cross-coupling

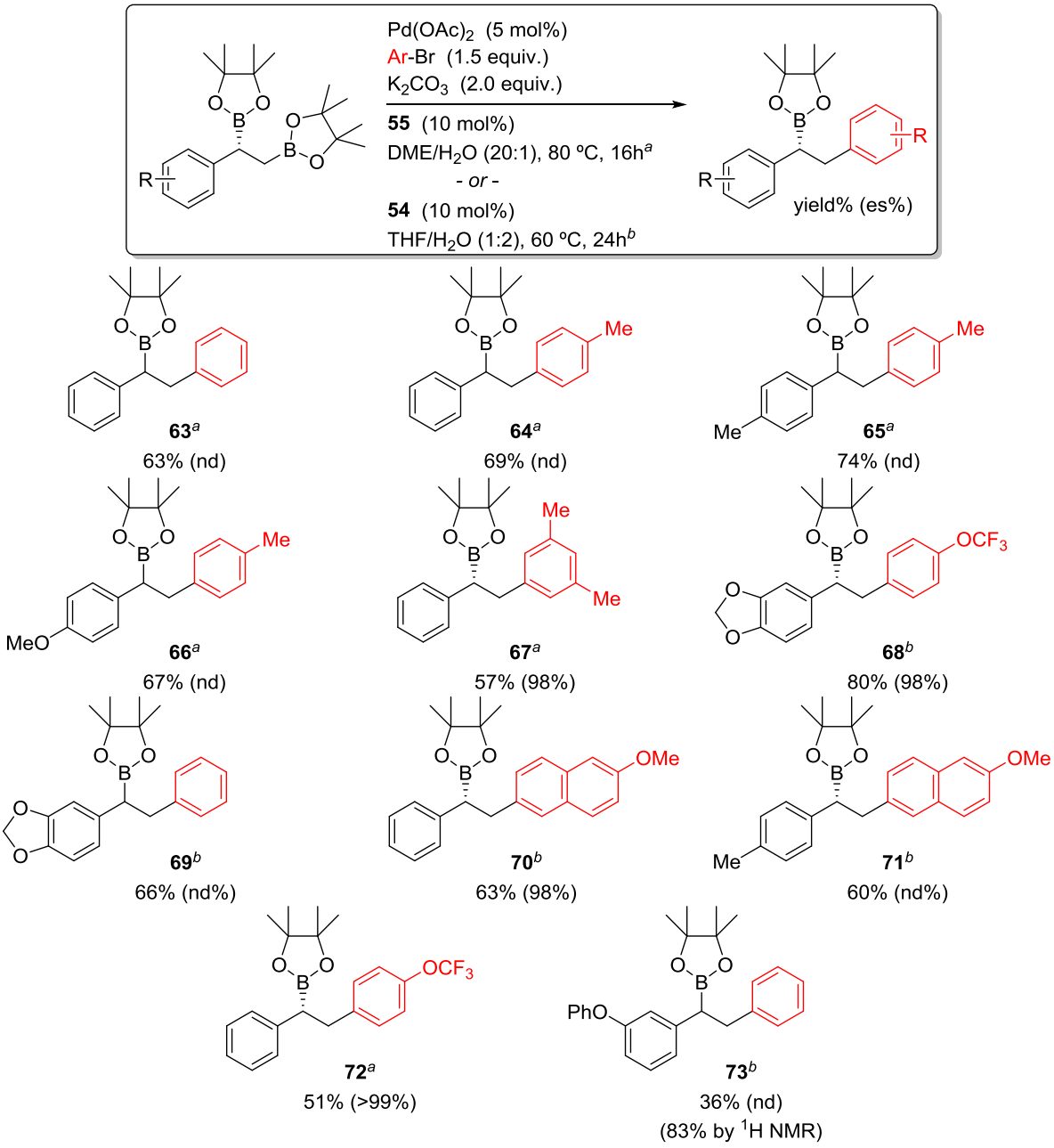


	Ar	Ligand	Base (equiv.)	Solvent	temp. (°C)	time (hours)	% conv.[a]
1	*m*-xylene (**61**)	RuPhos[b]	K_2CO_3 (1.9)	DME/H_2O (20:1)	80	16	100%[c]
2	**61**	RuPhos[d]	KOH (3.0)	THF/H_2O (10:1)	70	1	100%[c]
3	**61**	RuPhos[d]	KOH (3.0)	THF/H_2O (10:1)	45	1	100%[c]
4	phenyl (**62**)	RuPhos	K_2CO_3 (2.0)	THF/H_2O (1:2)	60	24	65% (52)[e]
5	**62**	SPhos	K_2CO_3 (2.0)	THF/H_2O (1:2)	60	24	86% (83)[e]
6	**62**	JohnPhos	K_2CO_3 (2.0)	THF/H_2O (1:2)	60	24	17%
7	**62**	DavePhos	K_2CO_3 (2.0)	THF/H_2O (1:2)	60	24	nd[f]
8	**62**	XantPhos	K_2CO_3 (2.0)	THF/H_2O (1:2)	60	24	38%
9	**28**[g]	SPhos	K_2CO_3 (3.5)	THF/H_2O (1:2)	60	24	nd[c]
10	**28**[g]	dppf	K_2CO_3 (3.5)	THF/H_2O (1:2)	60	24	100%[c]

[a] based on **46.** [b] 25 mol% [c] no desired product observed. [d] 2.5 mol% $Pd(OAc)_2$ and RuPhos. [e] isolated yield. [f] complex mixture. [g] HCl salt

Where full consumption of starting material was observed, in particular when none of the desired product was formed, the product distribution included deborylation of **60**, benzylic deborylation of **46**, and small amounts (2-5%) of styrene **44**.

In addition to reinvestigating the effect of the ligand on the reaction, we also examined other solvent systems in an effort to suppress β-hydrogen elimination and protodeboronation side reactions (Table 2-2). Surprisingly, we found that diboronate **46** benefitted from the presence of an unusually high proportion of water in the mixed solvent system (Table 2-2, entries 4 and 5). Interestingly, other diboronates also underwent cross-coupling efficiently under these atypical reaction conditions (Scheme 2-10). This could possibly be due to a change in the pH of the reaction mixture, as it is demonstrably influential on the rate of both cross-coupling[34] and protodeboronation[103] reactions. Pleasingly, in probing the substrate scope, we found that both electron rich and electron poor arylbromides were equally well tolerated (Scheme 2-10). Unfortunately, heterocyclic halides such as 3-bromopyridine, 3-bromoquinoline, and 2-bromothiophene were unsuccessful. In some cases we believed the yield of isolated product misrepresented the true yield of the reaction. To test this, graduate student Jason Rygus examined the yield of compound **73** by ^{1}H NMR of the crude reaction mixture and compared this to the yield of the isolated, purified compound. Indeed the yield of isolated compound was found to be more than 50% lower. This supports the hypothesis of the cross-coupled products **63-73**, being sensitive towards the purification procedure, specifically the silica gel chromatography.

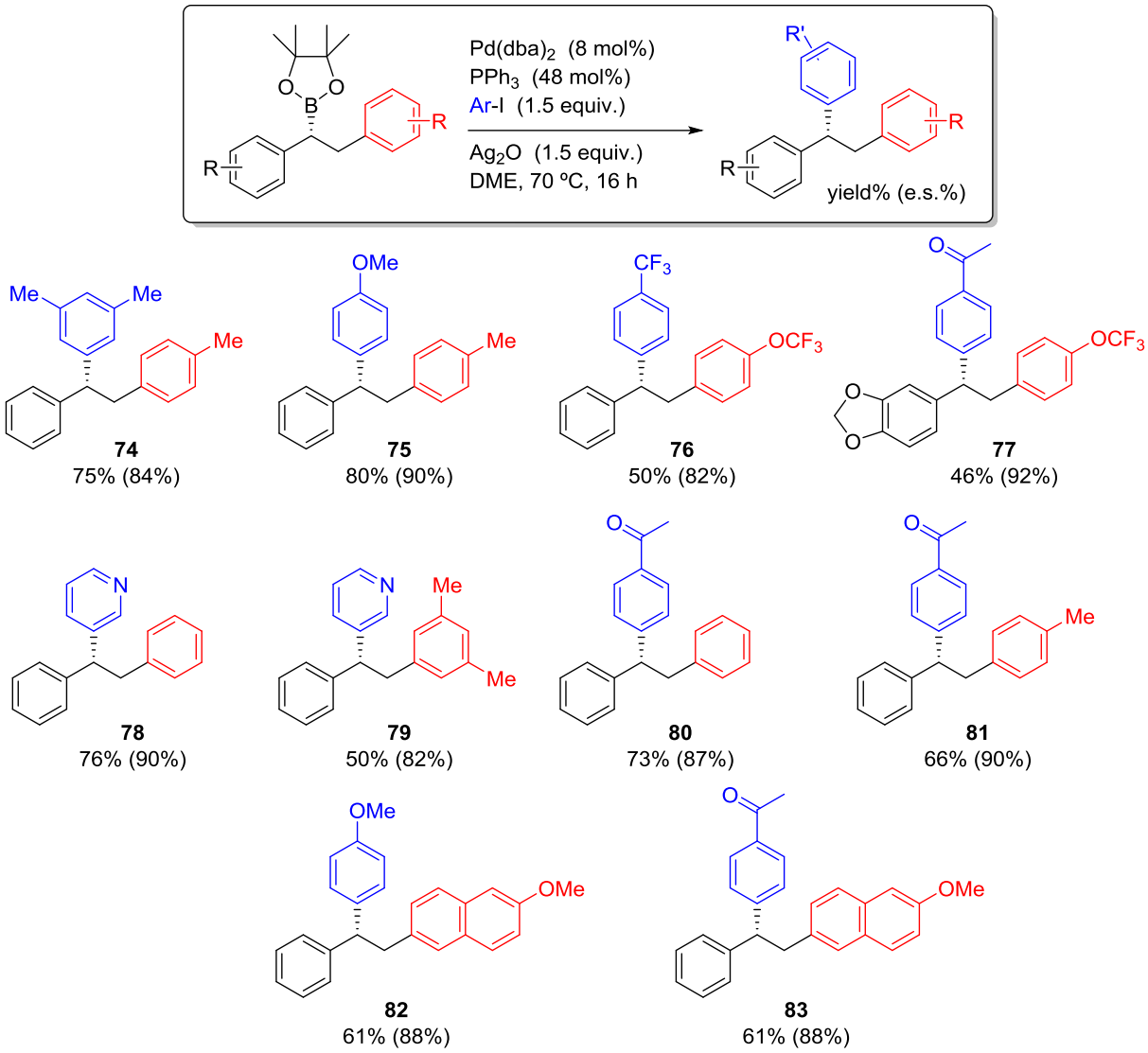


Scheme 2-10 Investigation of scope of cross-coupling in linear position of 1,2-diboronates

2.4.2 Cross-Coupling of Chiral 1,2-Diarylethanes Bearing a Secondary Benzylic Boronate

With a variety of chiral 1,2-diarylethane pinacol boronates in hand, as well as optimized conditions for the benzylic cross-coupling, student Jason Rygus and postdoctoral fellow Phillip Unsworth investigated the scope of the penultimate Suzuki-Miyaura reaction. Gratifyingly, they

found the reaction proceeded smoothly with a wide range of coupling partners. Both electron rich (**75** and **82**) and electron poor (**76**, **77**, **80**, **81**, and **83**) aryliodides, as well as N-heterocycles (**78** and **79**) and fluorinated substrates (**76** and **77**), were tolerated (Scheme 2-11). Yields of isolated products ranged from 80 to 46% and the enantiospecificities observed were between 82 and 92%. Enantiospecificity (es) is defined as the ee of the product divided by that of the starting material, and is a measure of how much stereochemical information is transmitted in the reaction. Interestingly, the best result was obtained with a high electron rich benzylic boronate **68**, which underwent coupling in 46% yield and 92% enantiospecificities respectively to furnish **77**.



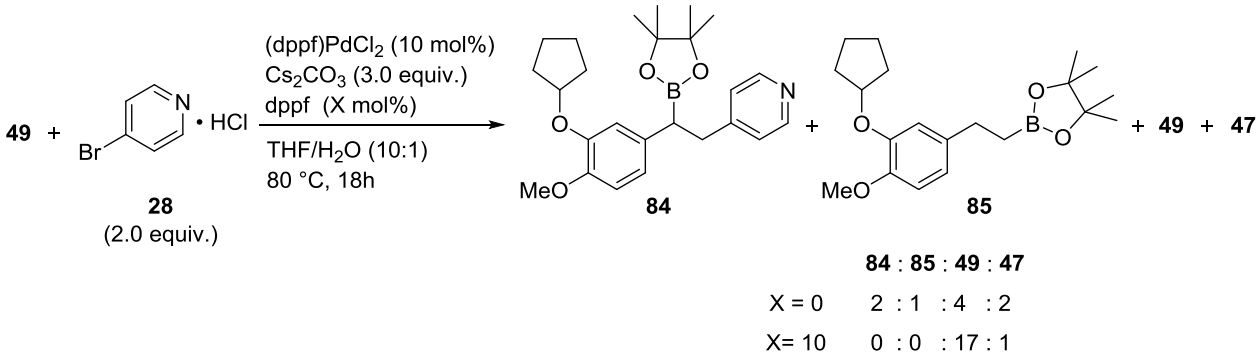
Scheme 2-11 Scope of stereospecific benzylic cross-coupling reaction using $Pd(dba)_2$ (8 mol%), PPh_3 (48 mol%), aryliodide (1.5 equiv.), and Ag_2O (1.5 equiv.) in DME at 70 °C for 16 hours

2.4.3 Synthesis of CDP840 – a Bioactive Chiral 1,1,2-Triarylethane

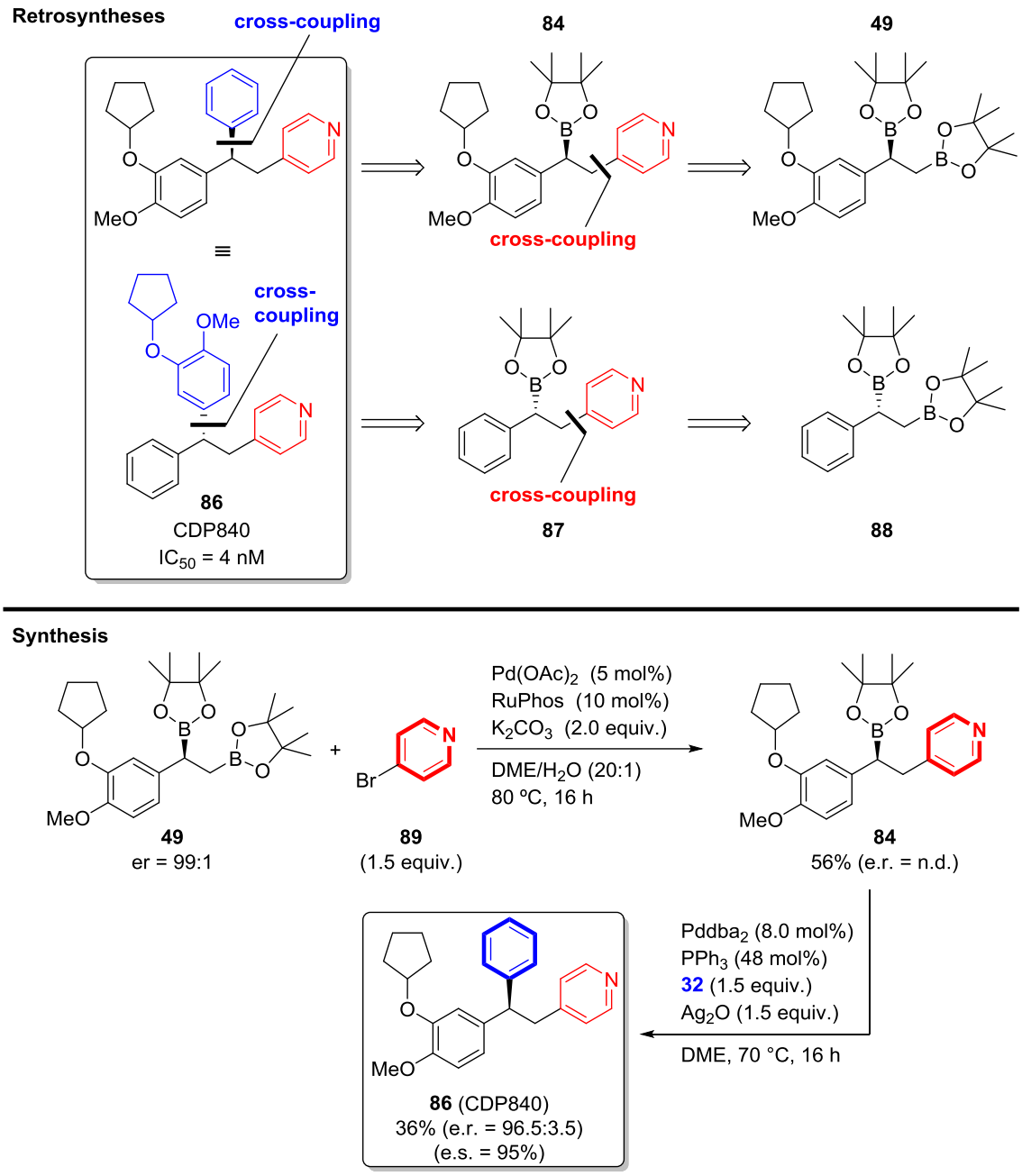
With the scope of iterative cross-couplings of 1,2-diboronates having been investigated, we endeavoured to highlight this methodology with a target-oriented synthesis. CDP840 (**86**), an orally active anti-inflammatory phosphodiesterase 4 inhibitor with an IC_{50} value = 4 nM, a chiral 1,1,2-triarylethane, was selected as the target.[104] The retrosynthetic disconnections (Scheme 2-13),

although straightforward, were problematic. In our investigations of the reaction scope, we had not had great success in enticing heteroarylbromides to undergo cross-coupling with the primary alkylboronate (Table 2-2). This was going to be an essential task if we were to reach the target molecule. Ultimately, our approach took into consideration two observations: firstly, the possible positive effect EDGs had on the benzylic coupling of 1,2-diboronates (Scheme 2-11) and secondly, the clear positive effect of EDGs on the stereospecific cross-coupling of biaryl benzylic boronates (Scheme 2-16).

Previously, 4-bromopyridine hydrochloride (**28**), had been successfully employed in a cross-coupling reaction with an aliphatic 1,2-diboronate (Scheme 2-4).[93] For this, Morken used what could be considered typically primary alkylboronate cross-coupling conditions, being the use of (dppf)$PdCl_2$ and Cs_2CO_3 in a THF/H_2O solvent system with **28**, to introduce a 4-pyridyl moiety.[93] While these conditions were fairly successful for aliphatic diboronate **26**, when diboronate **49** was subjected to the same conditions the result was only trace product formation (Scheme 2-12). The addition of another equivalent of ligand to palladium actually seemed to hinder the reaction further (Scheme 2-12).



Scheme 2-12 Cross-coupling of diboronate **49** under Morken's conditions[93]



Scheme 2-13 Retrosyntheses and synthesis of CDP840, a bioactive 1,1,2-triarylethane

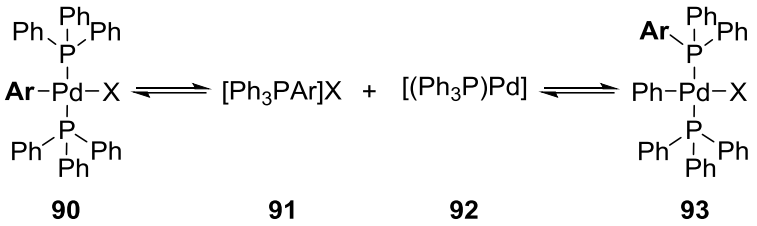
In the case of diboronate **49**, Phillip Unsworth found that our previously optimized $Pd(OAc)_2$/RuPhos system afforded a 56% yield of benzylic boronate **84** when the free base of 4-bromopyridine hydrochloride, **89**, was used. Initially, the reaction was performed with the

hydrochloride salt, **28**, as carried out by Morken (Scheme 2-4), but the sensitivity of the product to column chromatography conditions and a complex reaction mixture made isolation problematic. After successfully installing the 4-pyridyl ring, the phenyl moiety was successfully introduced to achieve the synthesis of CDP840 (Scheme 2-13, **86**). Although the yield of **86** was unfortunately only 36%, the product was obtained with a very high enantiomer ratio and excellent enantiospecificity. The favourable stereochemical outcome is consistent with the previous observation that EDGs have a positive effect on the reaction. It also serves to validate our choice of retrosynthetic approach.

2.5 Chemoselective Cross-Coupling of Compounds Containing Aryl and Secondary Benzylic Pinacol Boronates

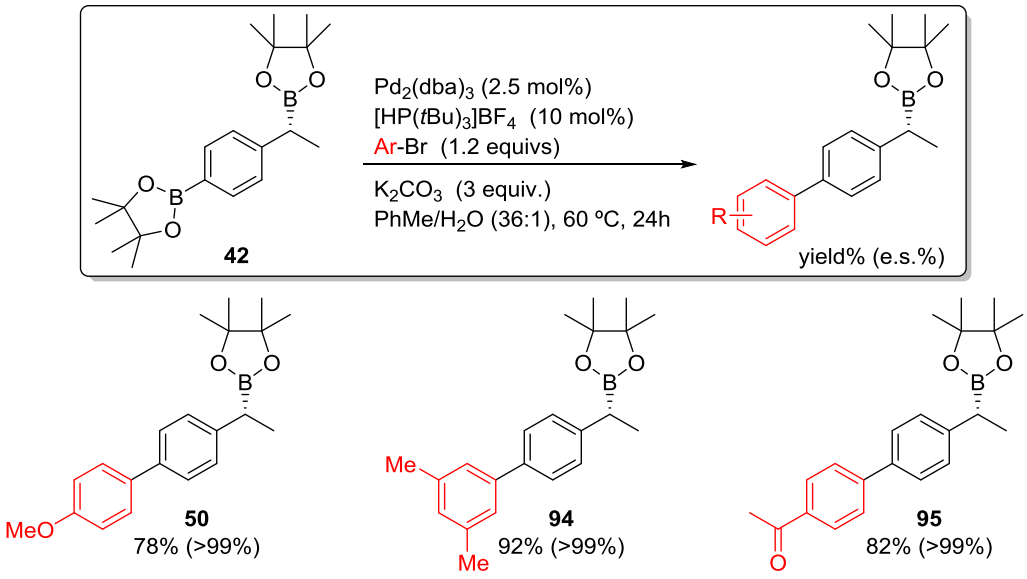
2.5.1 Cross-Coupling of an Aryl Boronate in the Presence of a Benzylic Boronate

With the chemoselective and iterative cross-coupling of 1,2-diboronates successfully achieved, we turned our attention to a different class of polyboronate. We have demonstrated that a primary boronate will undergo transmetalation much more readily than a secondary alkyl boronate (*vide supra*). Now we endeavoured to prove that the same feat could be accomplished when the substrate contained both a secondary benzylic B-C^{sp3} and an aryl B-C^{sp2} bond. Indeed this chemoselectivity had been previously demonstrated in our lab[102,105], and it was found that under conditions employing tetrakis(triphenylphosphine)palladium(0) as the catalyst, the desired sp^2 arylated product, with the benzylic boronate intact, was formed in high yield. Disappointingly, an undesired sp^2 phenylated side product was also observed by both Marieke Hutchinson[105] and Samantha Anderson[102]. This product is known to arise from scrambling of the aryl moiety on palladium after oxidative insertion with a phenyl group from the phosphine ligand.[106]



Scheme 2-14 Mechanism of ayrl/phenyl scrambling when PPh_3 is a ligand

The rate and occurrence of the scrambling process is dependent on the temperature, solvent, and nature of the halide, X, but generally proceeds via reductive elimination of a tetraarylphosphonium salt (**91**) from an arylpalladium(II) halide, such as **90**. Palladium(0) intermediate **92** can then undergo oxidative addition to a C-P bond of **91**.[106] This C-P activation results in the formation of the phenylpalladium(II) intermediate **93** which can then re-enter the catalytic cycle, forming the undesired phenylated product. Subsequent investigations by Marieke Hutchinson of conditions previously developed by the Fu group[23] using an electron rich sterically hindered trialkyl phosphine, P(*t*-Bu)$_3$, and a palladium(0) source, $Pd_2(dba)_3$, found that the product could be furnished in high yield, whilst avoiding the formation of the phenylated side product.[105]



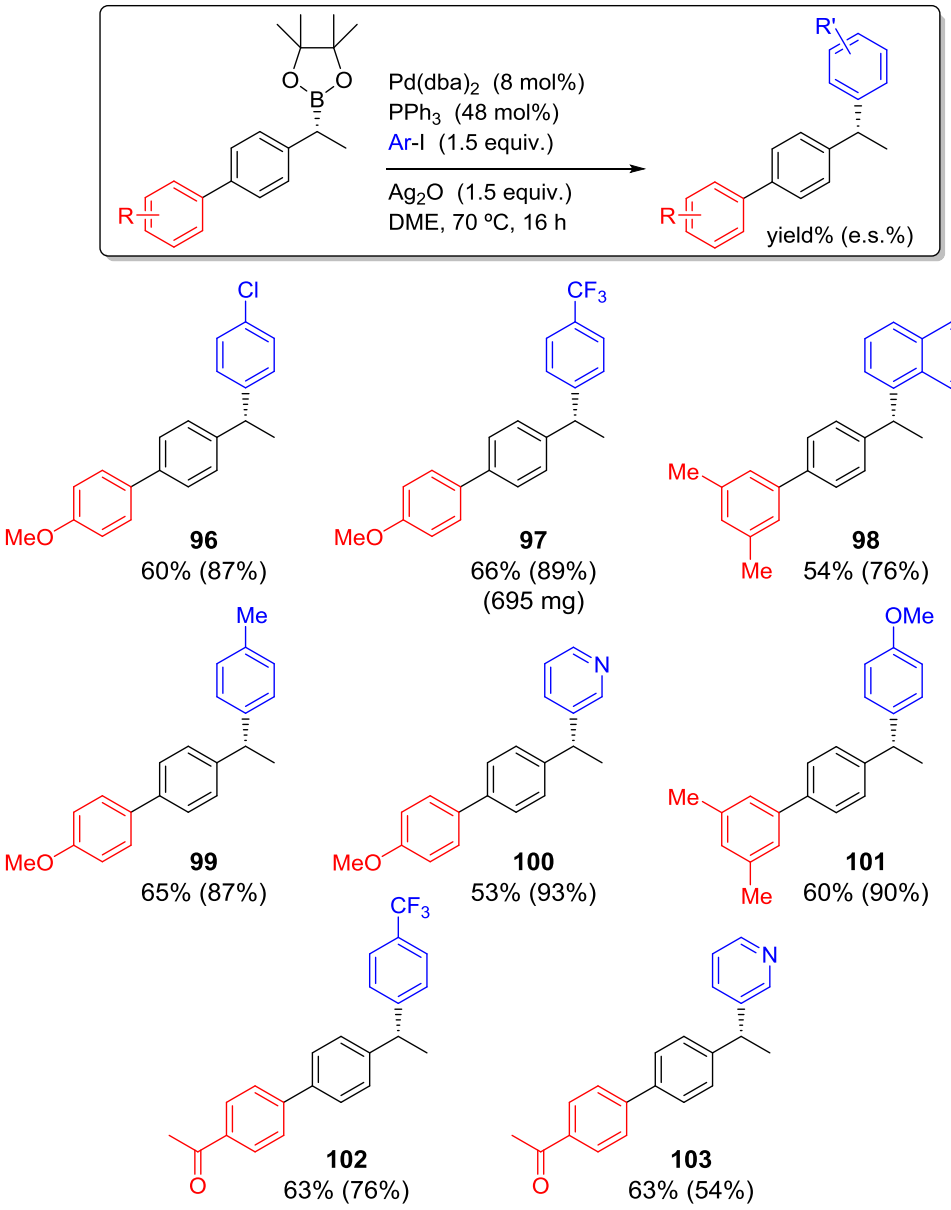
Scheme 2-15 Synthesis of biaryl benzylic boronates

In this work we found that these conditions could be used to reproducibly synthesize three biaryl secondary benzylic boronates on multi-gram scale with no detectable loss of previously installed stereochemistry (Scheme 2-15). Altering the electronic effects of substituents in these products was possible and desirable as it would provide useful insight into the effect this had on the subsequent stereospecific cross-coupling.

2.5.2 Cross-Coupling of Stereodefined Secondary Benzylic Boronate in Biphenyl Derivatives

In the study of electronically biased substrates under to the Ag_2O promoted cross-coupling conditions, a clear trend emerged (Scheme 2-16). When the electron poor benzylic boronate **95** was subjected to the reaction conditions, there was a significant deterioration of stereochemistry (**102** and **103**). As the precise mechanism by which this reaction proceeds is unknown the cause of this deleterious effect remains illusory.

In order to determine if the poor es observed in **102** and **103** was indeed a result of the electronic properties of **95** the same aryliodides were cross-coupled with boronate **50**. In each product (**97** and **100**), a high level of enantiospecificity was observed. This observation is consistent with what was previously observed in the synthesis of 1,1,2-triarylethanes, where electron rich benzylic boronates were shown to undergo cross-coupling with consistently high enantiospecificity (Scheme 2-11). Gratifyingly, both electron rich (**50**) and neutral (**94**) compounds gave good results regardless of the electronic properties of the aryliodide. Furthermore we found the reaction would tolerate N-heterocycles (**100** and **103**) with excellent enantiospecificity as well as π-extended electrophiles albeit with a decreased amount retained stereochemical information. This disappointing result with 1-iodonaphthalene (**98**) could, however, be the result of a sensitivity to steric effects.



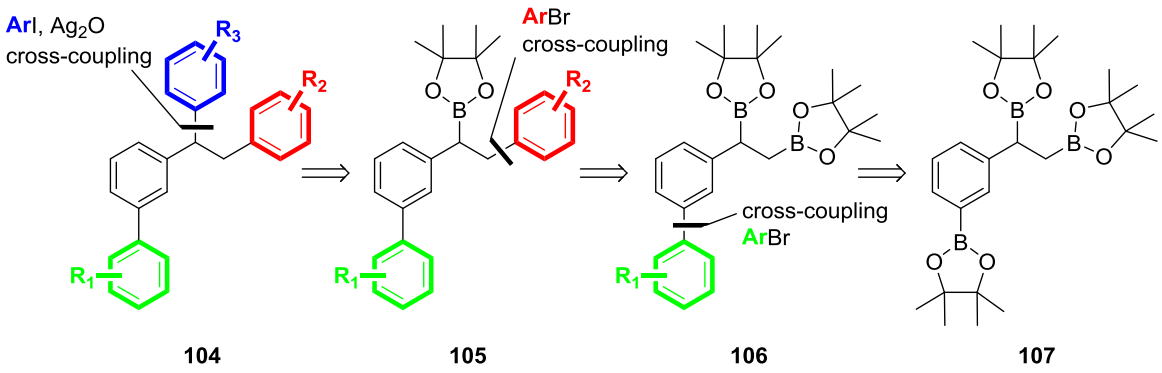
Scheme 2-16 Scope of enantiospecific cross-coupling reaction of biaryl benzylic boronates using $Pd(dba)_2$ (8 mol%), PPh_3 (48 mol%), aryliodide (1.5 equiv.), and Ag_2O (1.5 equiv.) in DME at 70 °C for 16 hours

With the scope of the reaction having been explored we turned our attention to another concern, namely the solubility, or lack thereof, of Ag_2O in DME. As the geometry of the reaction vessel for Suzuki-Miyaura cross-couplings has been shown to be a factor in determining the outcome of the reaction, we wanted to investigate the suitability of these conditions for larger scale reactions.[107] Pleasingly, we found that this was not an issue. When 1 gram of benzylic boronate

50 was subjected to the reaction conditions with 4-iodobenzotrifluoride we observed high enantiospecificity (89%) and obtained a higher yield (66%, 695 mg) of **97** than for any other substrates (Scheme 2-16).

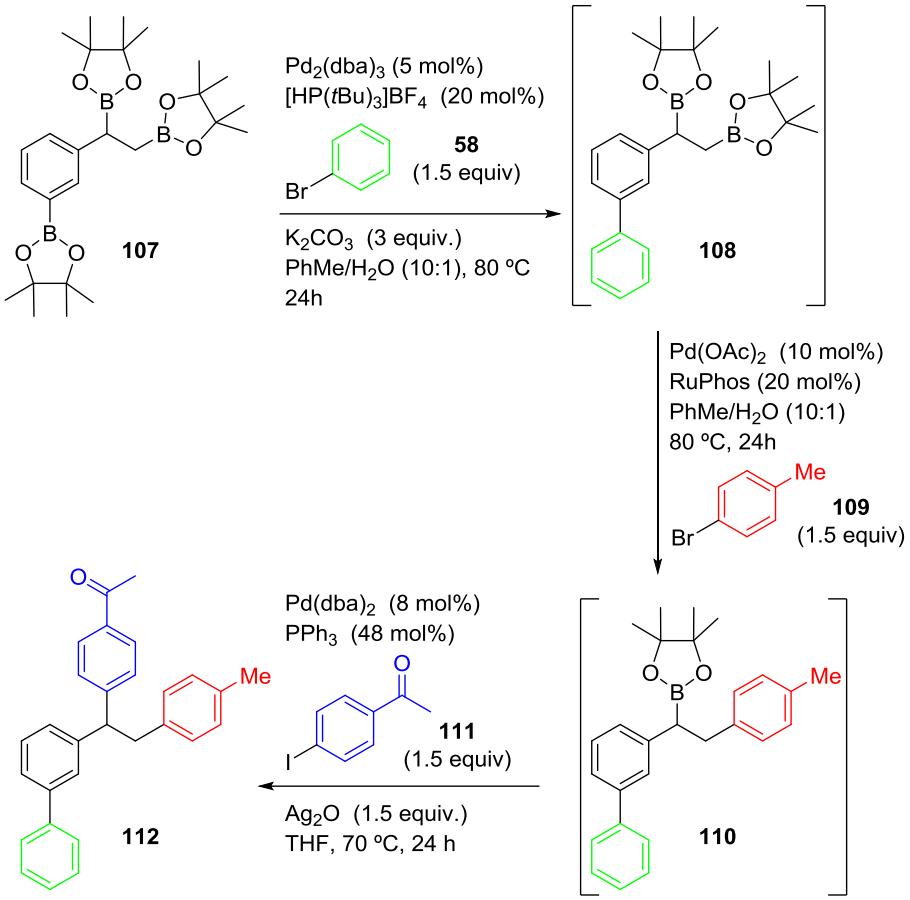
2.6 Chemoselective Cross-Coupling of 107 Containing Aryl, Primary Alkyl, and Secondary Benzylic Pinacol Boronates

Having established conditions for the cross-coupling of both an aryl and a primary alkyl pinacol boronate in the presence of a secondary benzylic boronate (*vide supra*), we were eager to test the suitability of a triboronate to these conditions. As the trend in boronate transmetallation reactivity favours aryl over both primary and secondary alkyl boronate, we anticipated an sp^2 arylation being well suited to precede two subsequent sp^3 cross-couplings (Scheme 2-17). This worked was performed by Masakazu Nambo at the Institute for Transformative Biomolecules.



Scheme 2-17 Retrosynthetic sequence of three iterative arylations

Pleasingly, he found that our conditions previously employed for chemoselective sp^2 cross-couplings (Scheme 2-15) were similarly selective in the case of triboronate **107**. Rather than isolating diboronate **108**, Nambo found it was amenable to cross-coupling at the linear position in one-pot, after adding fresh reagents, affording **110**.



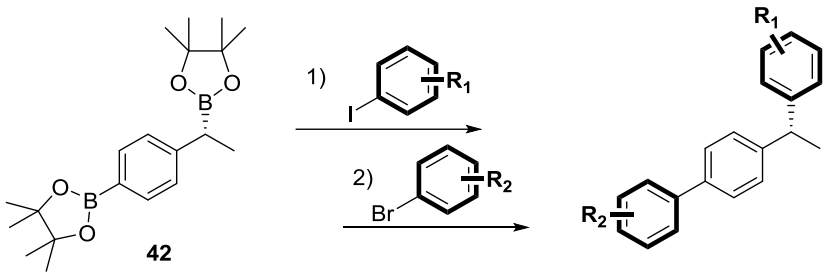
Scheme 2-18 Iterative, sp^2, primary sp^3, and secondary sp^3 cross-coupling sequence

After filtering through silica, removing inorganic by products, the Ag_2O promoted cross-coupling proceed as expected, furnishing the iteratively triarylated product **112** in 32% yield (Scheme 2-18). This demonstrates the highly chemoselective nature of each unique set of reaction conditions.

2.7 Investigations Towards Cross-Coupling Order Reversal and One-Pot Sequential Reactions

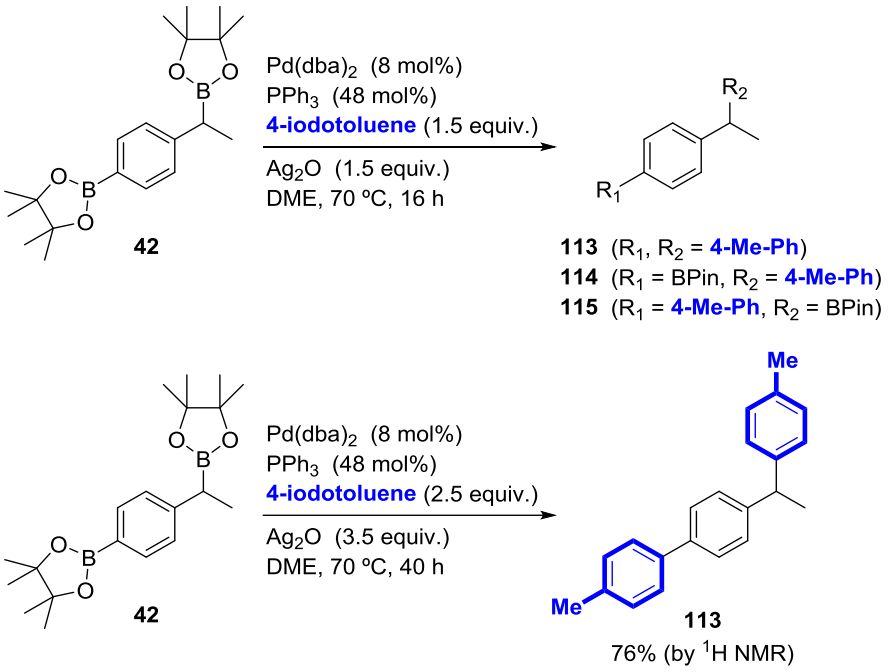
2.7.1 Towards Cross-Coupling Reactivity Reversal

Having broadly demonstrated that the relative reactivity of chemically unequivalent pinacol boronates can be harnessed towards an iterative methodology, circumventing the need for protecting group chemistry, we began investigating if this trend might be reversed. That is to say, could we chemoselectively effect cross-coupling of a secondary benzylic pinacol boronate in the presence of primary or aryl boronate (Scheme 2-19).



Scheme 2-19 Proposal to achieve benzylic boronate cross-coupling before sp^2 coupling

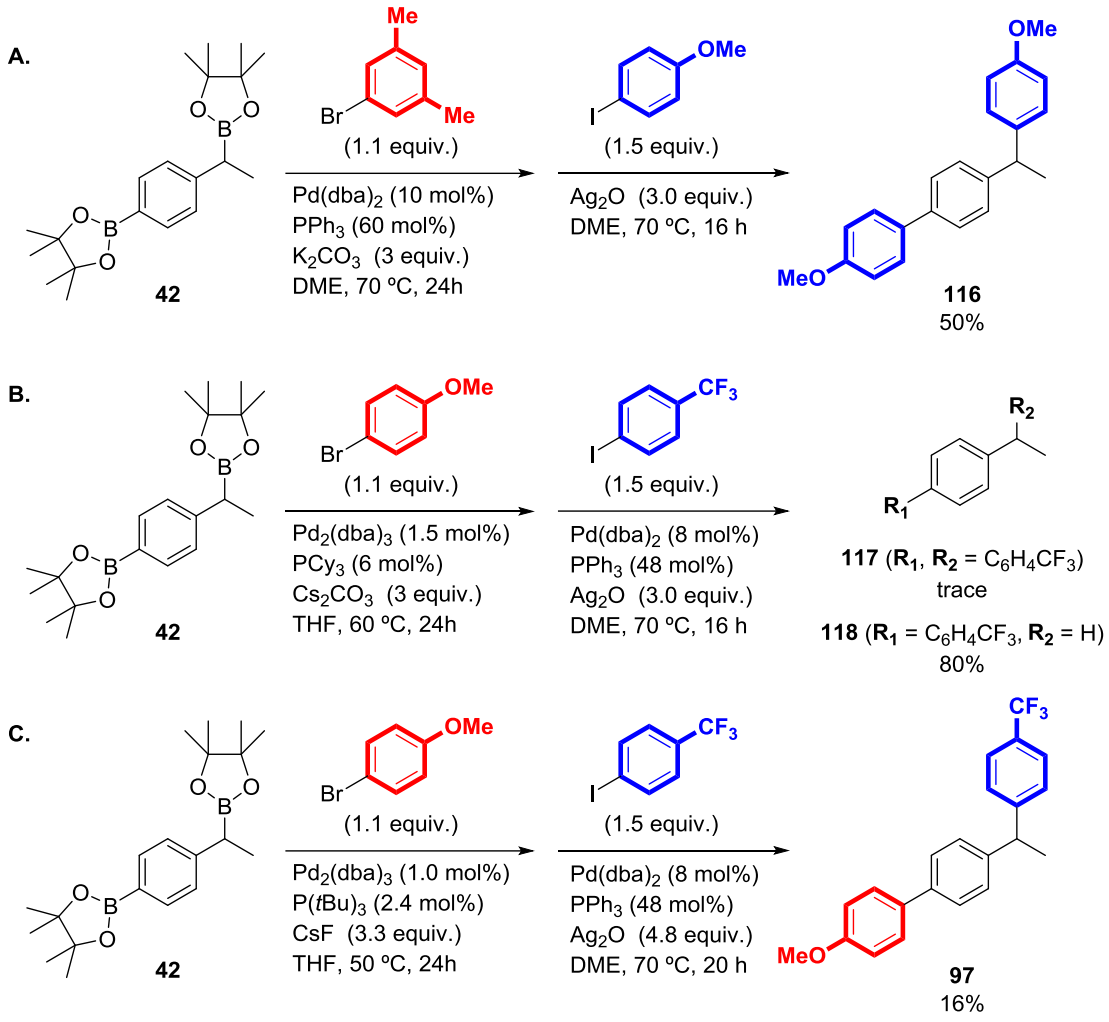
We first chose to investigate diboronate **42** and subjected it to our Ag_2O promoted conditions with an aryliodide. Unfortunately, the level of selectivity seen in previous competition experiments (Scheme 1-37) was not observed and a mixture of arylated products was observed (Scheme 2-20). As consolation however, we did fine that it was possible to affect both cross-couplings simultaneously if excess aryliodide and silver oxide was present (Scheme 2-20).



Scheme 2-20 Unselective cross-coupling of diboronate **42** and an aryliodide under Ag_2O promoted conditions. Yield determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

2.7.2 Towards One-Pot Sequential Reactions

Since the first attempts at affecting a reverse–order chemoselective cross-coupling revealed that it would likely be extremely challenging, we chose instead to direct our focus elsewhere, namely, we envisaged an iterative one-pot sequence of aryl boronate followed by benzylic boronate cross-coupling. Given that water has proven to have a detrimental effect on the stereochemical outcome of the benzylic cross-coupling and our optimized aryl boronate cross-coupling conditions use an aqueous solvent system, we could not simply apply these conditions in sequence if we desired to access enantioenriched products. The first hurdle then, was in finding alternate conditions where the sp^2 arylation could be performed selectively and under anhydrous conditions. An additional challenge in this endeavor was the restriction to either THF or DME as solvents for the benzylic cross-coupling. This limitation was revealed by early solvent screening in the development of this reaction.



Scheme 2-21 Attempted one-pot sequential sp^2 and sp^3 cross-couplings. Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard

With this in mind, for the first attempt, DME was the solvent of choice with amounts of the palladium and ligand needed for both cross-couplings added at the beginning of the reaction along with only an arylbromide (**57**). After heating the reaction mixture for 24 hours, it was cooled and returned to the glovebox where an aryliodide and an excess of silver oxide was added. Disappointingly, it appeared that the aryl boronate of **42** is inert under these conditions until silver oxide is added (Scheme 2-21, A). Interestingly, we observed that although some arylbromide was

present in the crude reaction mixture it was not incorporated in any position and **116** was formed in 50% yield. This implies, not surprisingly, that the aryliodide participated more readily in each cross-coupling than the arylbromide. We believe that this could lead to an exciting new area of research (*vide infra*).

Following this attempt, we turned back to the work of Fu to find anhydrous conditions.[108] The conditions were modified from those reported[108] to avoid the use of KF as a base. The report notes that the reaction is much faster with both CsF and KF as opposed to a carbonate base. However, we foresaw that fluoride might interfere or undergo reaction undesirably with the silver oxide to be added later. Similar to the previously successful sp^2 arylations, this second attempt used $Pd_2(dba)_3$ as the palladium source and a trialkylphosphine ligand, PCy_3, but with THF as the solvent and Cs_2CO_3 as the base. After 24 hours, this was followed by the addition of fresh palladium, PPh_3, aryliodide, silver oxide, and our ideal solvent, DME.

Unfortunately, the conditions employed for B-C^{sp2} cross-coupling seem to have failed as again, only incorporation of the aryliodide was observed in either position to give **117** (Scheme 2-21, B). Curiously, we observed that biaryl **118** was the major product of this reaction indicating that rapid deborylation of the benzylic position also took place. As the modified literature conditions[108] tested were optimized with aryl boronic acids, rather than boronic esters, it is possible that the lack of reactivity and unwanted side reactions are due to inappropriate and/or unproductive speciation of boron.[109] With this result in hand, we decided to investigate if indeed fluoride as a base could promote the first coupling and be tolerated by the subsequent Ag_2O promoted conditions. Returning to the procedure from Fu and colleagues which used P(*t*Bu)$_3$ as a ligand instead of PCy_3 alongside a fluoride source were chosen.[108] Gratifyingly, we did observe formation of the desired product (**97**) arising from 4-bromoanisole coupling in the aryl boronate and 4-

iodobenzotrifluoride with the benzylic boronate of **42**, albeit in a low 16% yield (Scheme 2-21, C). Although not an ideal result, this represents an encouraging starting point for any future work.

2.8 References

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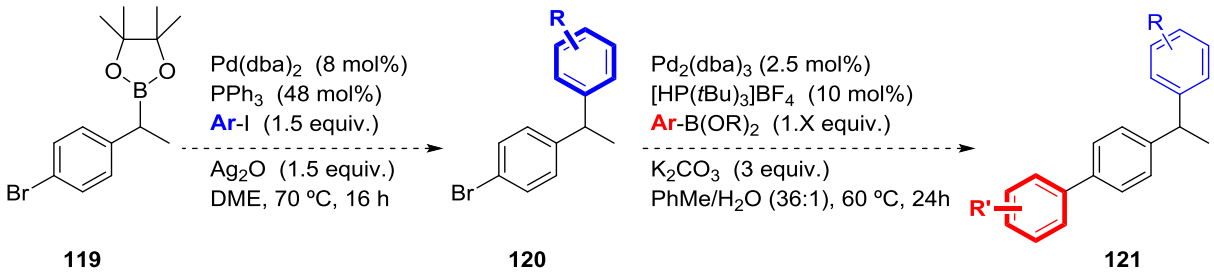
Chapter 3

Proposed Future Work and Conclusion

3.1 Proposed Future Work

With the serendipitous observation that, aryliodides undergo cross-coupling with secondary benzylic pinacol boronates preferentially to arylbromides (Scheme 2-21, **A** and **B**), a complementary idea came in to focus. When viewed with the knowledge that rates of oxidative addition are typically greater for iodides when compared to bromides this result is somewhat expected. Given that it seems unlikely that a successful chemoselective reversal in the cross-coupling order of diboronate **42** is forthcoming (Scheme 2-20), promise could lie in brominated benzylic boronate **119** (Scheme 3-1).



Scheme 3-1 Proposed haloboronate cross-coupling sequence to reverse aryl group installation and circumvent protecting group chemistry.

Presumably, since oxidative insertion by palladium(0) to the C-I bond should be much faster than to the C-Br bond, the cross-coupling with the pinacol boronate is expected to occur with the aryliodide rather than the bromide. This may mean that the differentiation between a nucleophilic and electrophilic site within the same substrate is possible without the use of a masking group such as Dan or MIDA to arrest the boronate's reactivity. If successful, this would represent a novel addition to the field of haloboronate cross-coupling chemistry as it relies solely on the

innate chemoselectivity imparted by the Ag_2O promoted conditions rather than on any protecting group chemistry.

3.2 Conclusion

We began this research with the overarching goal of developing a chemoselective and protecting group free methodology, whereby different polyboronates could be iteratively and stereospecifically cross-coupled.

Indeed we succeeded in synthesizing the requisite diboronates, such as **42** (Scheme 2-7) and **49** (Scheme 2-9), as well as triboronate **107** (Scheme 2-18). Conditions were found whereby the primary alkylboronate of a 1,2-diboronate, and the aryl boronate of **42** could be cross-coupled furnishing products where the stereodefined benzylic boronates remained intact. The resultant benzylic boronates were then successfully cross-coupled, under the reoptimized conditions reported herein, with high levels of enantiospecificity.

We found that this chemistry could also be successfully applied towards the synthesis of an active pharmaceutical ingredient, specifically CDP840 (**86**), with excellent enantiospecificity and high e.r. Moreover, this methodology was also successfully applied to triboronate **107**, affording a product which had been iteratively arylated with three unique arylhalides.

The successful completion of our main objective represents an exciting new entry into the burgeoning field of polyboronate cross-coupling. It is our hope that this can be the start of a new approach to compliment the work with protecting groups already reported in this area.[88-92]

Chapter 4

Experimental

4.1 General Experimental Considerations

Unless otherwise specified, all manipulations were carried out under at atmosphere of dry argon in oven-dried glassware or under a nitrogen atmosphere in an M. Braun glovebox with oxygen and water levels <2 ppm. Toluene, THF, and 1,2-dimethoxyethane (DME) were either distilled from either calcium hydride (CaH_2) or sodium metal (Na), deoxygenated with a minimum of three freeze-pump-thaw cycles and stored under N_2 or Ar over molecular sieves (4Å) prior to use. Anhydrous methanol (MeOH) was purchased from Avantor Performance Materials and used without further purification. Catechol borane was purified by distillation under reduced pressure and stored at -20 °C under nitrogen.

Silver (I) oxide was synthesized according to a literature procedure.[110] Triphenylphosphine and 1,4-bis(diphenylphosphino)butane were recrystallized from hot ethanol and stored under N_2. $Pd(dba)_2$, $Pd_2(dba)_3$, and $[Rh(COD)_2][BF_4]$ were stored and used in a M Braun glovebox as purchased from either Aldrich or Johnson Matthey**.** Distilled water was deoxygenated by sparging with argon for a minimum of 30 minutes prior to use. B_2pin_2 was purchased from Oakwood Products Inc. and used without further purification. Methyltriphenylphosphonium bromide and $(t\text{Bu})_3\text{PH}]BF_4$ were purchased from Sigma-Aldrich and used without further purification. Iodobenzene, 4-iodobenzotrifluoride, 1-iodonaphthalene, 1-bromo-3,5-dimethylbenzene, 4-bromoanisole, and HBCat were purified by distillation from calcium hydride under reduced pressure, followed by three freeze-pump-thaw cycles, and stored under N_2. 3-iodopyridine and pinacol were recrystallized from hot ethanol. 1-chloro-4-iodobenzene, 4-iodoanisole, 4-iodotoluene, and 4-iodoacetophenone were purified by sublimation and stored under N_2.

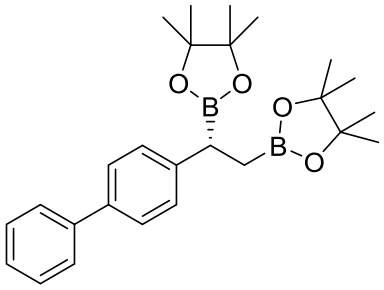
IR spectra were collected on a Bruker ALPHA Platinum ATR as neat solids and absorption bands ($\tilde{\nu}$, s = strong, m = medium, w = weak) are given in cm^{-1}. Melting points were recorded on an Electrothermal MEL-TEMP apparatus connected to a Fluke 51 II Thermometer. Compounds were not recrystallized. Temperatures are given in degree Celsius (°C) and are uncorrected. Thin layer chromatography (TLC) was performed on aluminum-backed silica plates and visualized by UV (254, 365 nm). The indicators utilized to stain were phosphomolybdic acid or potassium permanganate. Column chromatography was performed 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 30m by 250 μm by 0.25μm nominal, 250 inlet, splitless detector.

NMR spectra were recorded on Bruker Avance 300 (^{1}H: 300.13 ^{13}C: 75.47), Bruker Avance 400 (^{1}H: 400.13, ^{11}B: 128.38, ^{13}C: 100.62), Bruker Avance 500 (^{1}H: 500.19, ^{11}B: 160.27, ^{13}C: 125.62) or JEOL ECS-400 and JEOL AL-400 (^{1}H: 400.13, ^{11}B: 128.38, ^{13}C: 100.62) instruments operating at the denoted spectrometer frequency given in Mega Hertz (MHz) for the specified nucleus. All NMR samples were prepared using $CDCl_3$. To specify the signal multiplicity, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet; br. indicates a broad resonance; app = apparent. Shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an external standard for ^{1}H- and ^{13}C NMR spectra and calibrated against the solvent residual peak or in case of protio-solvents against known solvent resonances.[111] SFC (supercritical fluid chromatography) traces for the assessment of enantiopurity were obtained from a JASCO Instruments SFC HPLC equipped with HPLC columns (CHIRALPAK IA, IB, IC, ID, IE, IF: length 250 mm, 4.6 mm, particle size 5 μm), operating at the stated flow-rate and pressure of supercritical CO_2 with the indicated amount of admixed modifier solvent. Retention times (t_R) are given in minutes (min). Optical rotations $[\alpha]^{22}_{D}$ were measured on a Perkin-Elmer

241MC polarimeter as solutions in dichloromethane at concentration of 0.01 g mL^{-1} at 22 °C at 589 nm in a 0.5 dm cell, and given as specific rotations (° cm^2 g^{-1}).

4.2 Synthesis of 46

(R)-2,2'-(1-([1,1'-biphenyl]-4-yl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) - 46



Prepared according to the procedure by Morken and co-workers.[112] To a flame-dried, round bottom flask with magnetic stir bar in a nitrogen filled glove box was added $Pt(dba)_3$ (13.5 mg, 0.015 mmol), (*R,R*)-3,5-diethylphenyl-TADDOLPPh (14.0 mg, 0.018 mmol), B_2pin_2 (328 mg, 1.3 mmol) and tetrahydrofuran (2.5 mL). The flask was sealed with a septum, removed from the glove box, and heated to 80 °C in an oil bath for 30 min. The flask was cooled to room temperature, returned to the glove box and a solution of 4-vinyl-1,1'-biphenyl (133 mg, 0.74 mmol) in THF (2.0 mL) was added. The flask was sealed, removed from the glove box, and stirred at 60 °C for 3h. The reaction mixture was cooled and subjected to filtration through a plug of silica, eluted with EtOAc and concentrated *in vacuo*. Purification by column chromatography (hexane/EtOAc (96.5:3.5)) afforded **46** as an ocher solid (275 mg, 86% yield); e.r. 93:7.

^{1}H NMR (400MHz, $CDCl_3$): 7.58 (d, *J* = 7.3 Hz, 2H, Ar**H**), 7.48 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.41 (t, *J* = 7.7 Hz, 2H, Ar**H**), 7.32-7.27 (m, 3H, Ar**H**), 2.57 (dd, *J* = 10.9 Hz, 5.7 Hz, 1H, C**H**BCBHH'), 1.41 (dd, *J* = 15.9 Hz, 10.9 Hz, 1H, CHBC**H**H'), 1.21 (s, 12H, C(C**H**$_3$)(C**H**$_3$)'C(C**H**$_3$)(CH$_3$)'), 1.20 (s, 6H, C(CH$_3$)(CH$_3$)'C(CH$_3$)(C**H**$_3$)') 1.15 (dd, *J* = 16.0 Hz, 5.7 Hz, 2H, CHBCH**H'**) **^{13}C NMR (100 MHz, $CDCl_3$)**: 144.8 (**C**), 141.5 (**C**), 137.8 (**C**), 128.8 (**C**H), 128.5 (**C**H), 127.0 (**C**H), 126.9 (**C**H), 83.4 (**C**-OB), 83.2 (**C**-OB), 25.1 (**C**H$_3$), 24.87 (**C**H$_3$), 24.82 (**C**H$_3$), 24.7 (**C**H$_3$), peaks not

observed for **C**'s bound to B's; **^{11}B NMR (128 MHz, $CDCl_3$)**: 32.8; **IR (film) cm^{-1}**: 3028w, 2990s, 1484w, 1314s, 1140s, 845m, 703m,; **HRMS (ESI^+)**: $C_{26}H_{36}B_2O_4$ ($M+H^+$) requires 434.2800; found 434.2809.

In order to determine the e.r. by SFC analysis, the diboronate was oxidized to the diol by a modified literature procedure[112] (general procedure, **GP1**): To a solution of diboronate (0.05 mmol) in THF (0.5 mL) was added a 2:1 mixture of 2 M aq. NaOH/30% aq. H_2O_2 (1 mL) at 0 °C. The mixture was warmed to RT and stirred for 4 hours. Saturated ammonium chloride (2 mL) and Et_2O (5 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 5 mL). The combined organics were washed with brine (5 mL), dried ($MgSO_4$), subjected to filtration and concentrated *in vacuo*.

IB, 2mL/min, 100 bar, 50 °C, 1% → 35% MeOH over 10 min then 35% MeOH for 5 min; t_R 10.59 (minor), 10.79 (major).

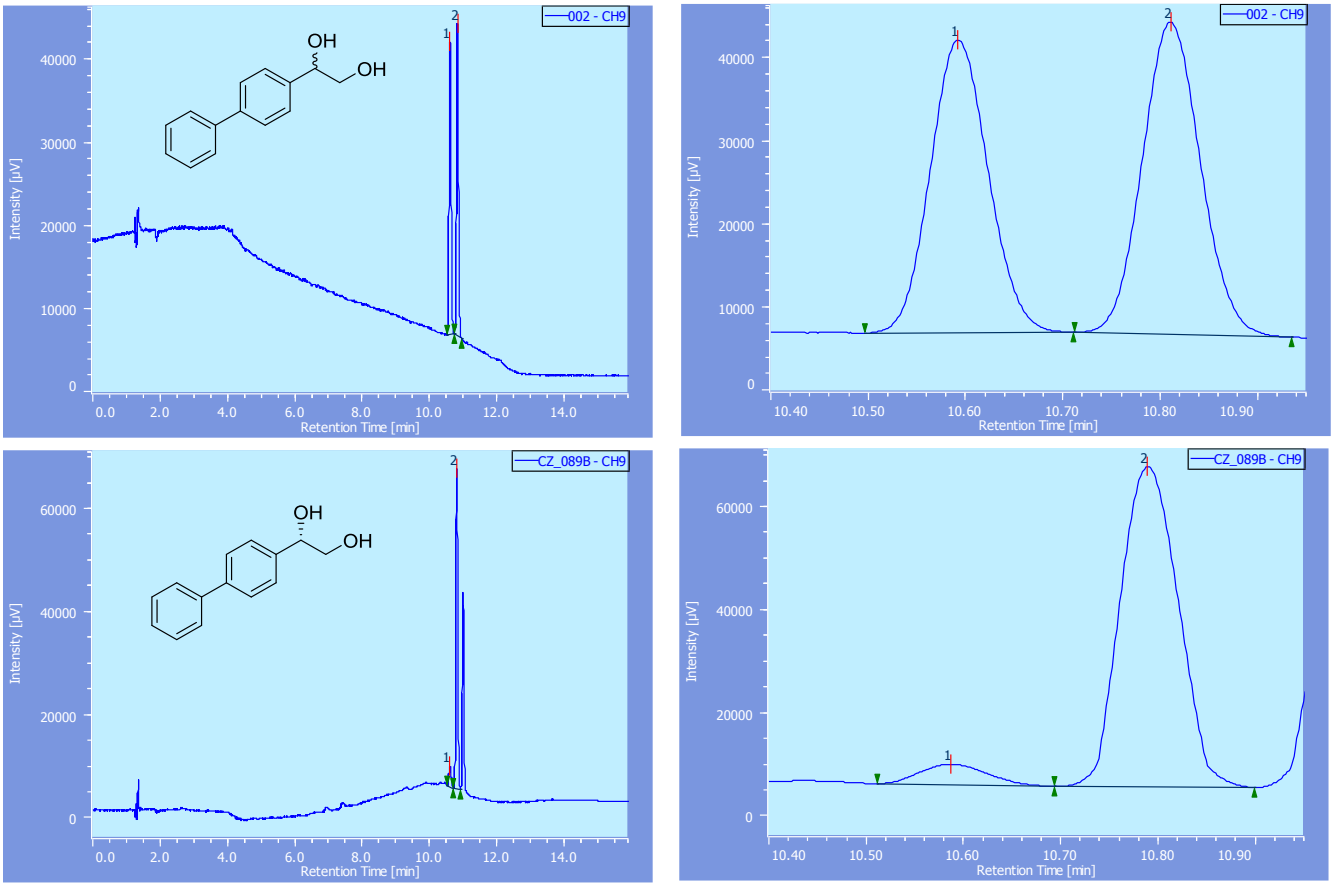
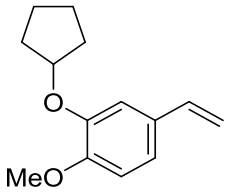


Figure 4-1 Chiral SFC spectra for oxidized **46**, racemate (above) and scalemic (below).

4.3 Synthesis of CDP840 – a Bioactive Chiral 1,1,2-Triarylethane

2-(Cyclopentyloxy)-1-methoxy-4-vinylbenzene - 47

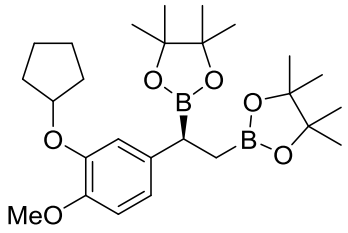


The title compound (**47**) was synthesized according to a modified literature procedure.[113] To a suspension of methyltriphenylphosphonium bromide (9.61 g, 26.9 mmol, 1.3 equiv.) in THF (54 mL) at 0 °C was added a solution of potassium *tert*-butoxide (3.02 g, 26.89 mmol, 1.3 equiv.) in THF (26 mL) dropwise. The flask was rinsed with 2 x 1 mL of THF to ensure complete transfer. After stirring at room temperature for 10 minutes, the solution was cooled to 0 °C and a solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (4.56 g, 20.7 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise. The flask was rinsed with 3 x 2 mL of THF to ensure complete transfer. The resultant mixture was stirred at room temperature for 16 hours. After concentration *in vacuo*, the crude material was purified by column chromatography (10% ethyl acetate/hexanes) to afford **47** (4.48 g, 20.5 mmol, 99%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 6.97 (d, *J* = 2.0 Hz, 1H, Ar**H**), 6.93 (dd, *J* = 8.2 Hz, 1.9 Hz, 1H, Ar**H**), 6.82 (d, *J* = 8.2 Hz, 1H, Ar**H**), 6.64 (dd, *J* = 17.5 Hz, 10.8 Hz, 1H, C**H**=CH_2), 5.59 (dd, *J* = 17.5 Hz, 0.8 Hz 1H, CH=C**H**$_2$-(Z)), 5.13 (dd, *J* = 10.8 Hz, 0.8 Hz 1H, CH=C**H**$_2$-(E)), 4.85-4.75 (m, 1H, OC**H**-$(CH_2)_2$), 3.96 (s, 3H, OC**H**$_3$), 1.88 (m, 6H, Cp CH**H**/C**H**$_2$), 1.62 (m, *2*H, Cp CH**H**/C**H**$_2$); **^{13}C NMR (100 MHz, $CDCl_3$)**: 150.2 (**C**), 147.8 (**C**), 136.7 (**C**H), 130.8 (**C**), 119.4 (**C**H), 112.7 (**C**H), 111.9 (**C**H), 111.7 (**C**H_2), 80.6 (**C**H),

56.1 (**C**CH_3), 32.9 (**C**H_2), 24.1 (**C**H_2); **IR (film) cm^{-1}:** 2956w, 1628w, 1508w, 1134w, 987w; **HRMS (EI)**: $C_{14}H_{18}O_2$ requires 218.1307; found 218.1301.

(S)-2,2'-(1-(3-(cyclopentyloxy)-4-methoxyphenyl)ethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) - 49

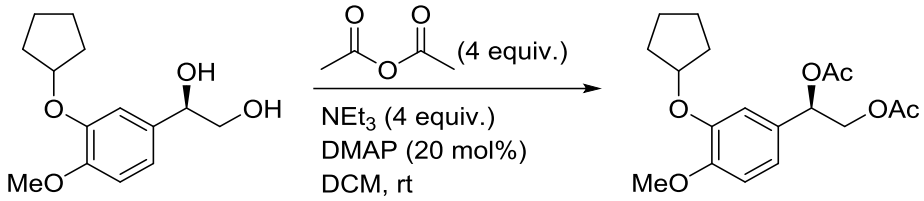


The title compound, **49**, was prepared according to Nishiyama and co-workers[52]: B_2Pin_2 (394 mg, 1.55 mmol, 1.2 eq), NaO^{t}Bu (6.2 mg, 0.065 mmol, 0.05 eq) and [Rh{(*R*,*R*)-Phebox-*i*Pr}$OAc_2(H_2O)$][53] (7.0 mg, 0.013 mmol, 0.01 eq) were placed in a dry Schlenk flask under argon. THF (1.3 mL) was added followed by a solution of **47** (282 mg, 6.10 mmol, 1 eq) in THF (1.3 mL) and the reaction mixture was immediately placed into a preheated oil bath at 60 °C and stirred for 1h. The reaction mixture was cooled and aq. sat. NH_4Cl (15 mL) and Et_2O (15 mL) were added. The layers were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organics were washed with brine (15 mL), dried ($MgSO_4$), subjected to filtration and the filtrate was concentrated *in vacuo*. Purification by column chromatography (pentane/EtOAc (10:1)) gave **49** as a colourless solid (435 mg, 71% yield); e.r. 99:1; mp 84.0-85.0 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 6.78 (s, 1H, Ar**H**), 6.73 (m, 2H, Ar**H**), 4.73 (m, 1H, Ar**H**), 4.28 (q, *J* = 6.8 Hz, 1H, OC**H**-$(CH_2)_2$), 3.78 (s, 3H, OC**H**$_3$), 2.43 (dd, *J* = 11.2 Hz, 5.4 Hz, 1H, C**H**CHH'), 1.89 (m, 4H, Cp CH**H**/C**H**$_2$). 1.81 (m, 2H, Cp CH**H**/C**H**$_2$), 1.57 (m, 2H, Cp CH**H**/C**H**$_2$), 1.33 (dd, *J* = 16.0 Hz, 11.3 Hz, 1H, CHC**H**H'), 1.20 (s, 12H, C(C**H**$_3$)$_2$C(C**H**$_3$)$_2$), 1.18 (s, 6H, C(C**H**$_3$)(CH$_3$)'C(C**H**$_3$)(CH$_3$)'), 1.17 (s, 6H,

C(CH_3)(C**H**$_3$)'C(CH_3)(C**H**$_3$)'), 1.08 (dd, *J* = 16.0 Hz, 5.4 Hz, 1H, CHCH**H'**); **^{13}C NMR (100 MHz; $CDCl_3$)**: 147.7 (**C**), 147.4 (**C**), 138.0 (**C**), 119.7 (**C**H), 115.2 (**C**H), 112.2 (**C**H), 83.3 (**C**-OB), 83.2 (**C**-OB), 80.2 (O**C**H), 56.3 (**C**H_3), 32.99 (**C**H_2), 32.97 (**C**H_2), 25.1 (**C**H_3), 24.88 (**C**H_3), 24.82 (**C**H_3), 24.7 (**C**H_3), 24.2 (**C**H_2), peaks not observed for **C**'s bound to B's; **^{11}B NMR (128 MHz; $CDCl_3$)**: 33.2; **IR (film) cm^{-1}:** 2975w, 1509w, 1315w, 1135w, 850w; **HRMS (EI)**: $C_{26}H_{42}B_2O_6$ requires 472.3168; found 472.3172; $[\alpha]_D^{20}$ = +28.6 (*c* 0.7, $CHCl_3$).

The e.r. was determined by oxidation to the diol (by **GP1**) and acylation by a procedure according to Morken and co-workers[114] followed by analysis by chiral SFC:



IC, 2mL/min, 100 bar, 50 °C, 1% → 40% MeOH over 10 min; t_R 7.39 (minor), 7.79 (major)

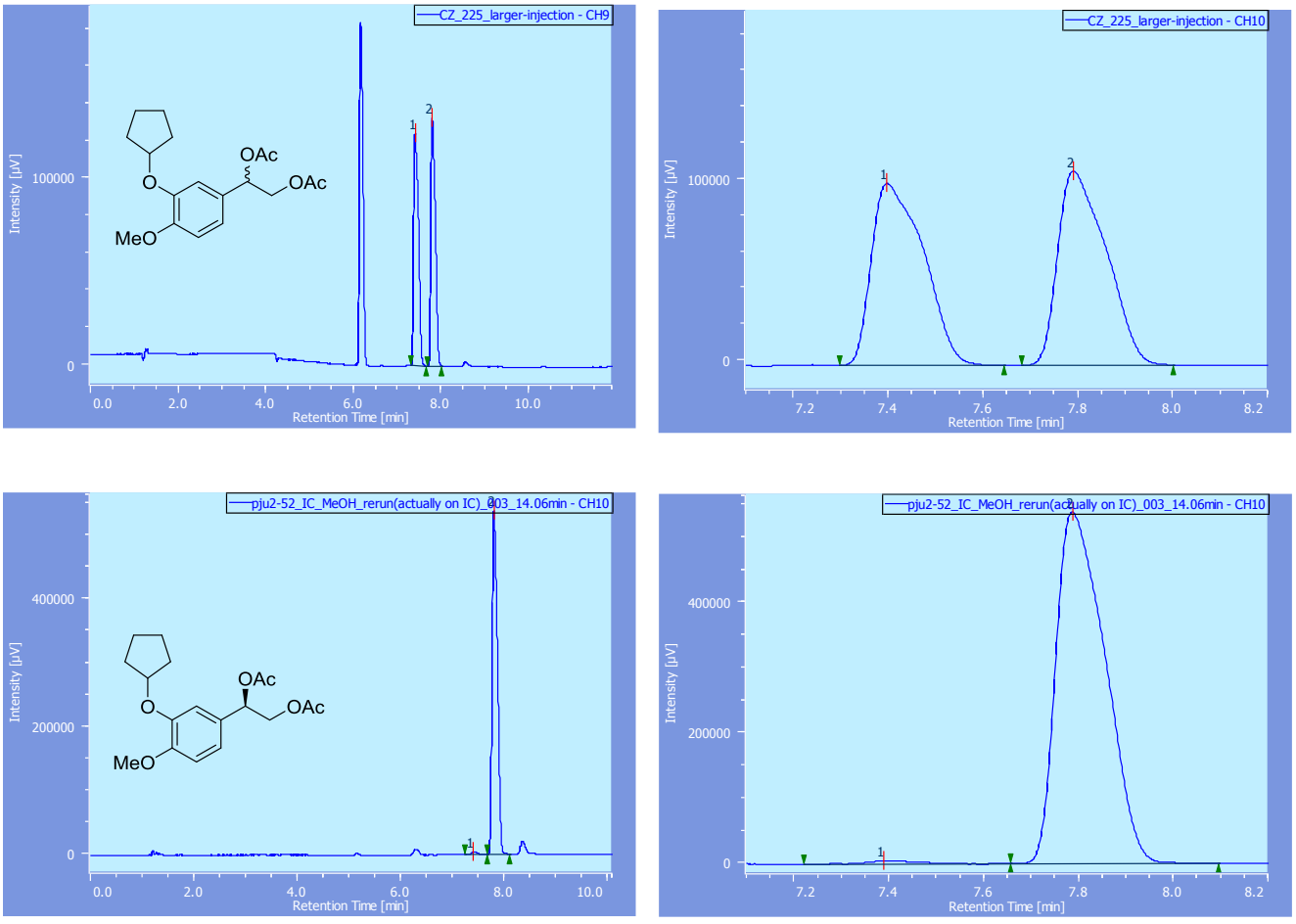
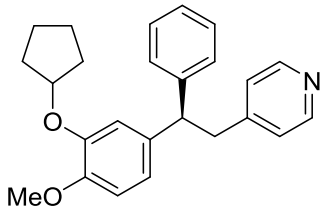


Figure 4-2 Chiral SFC spectra for oxidized & acylated **49**, racemate (above) and scalemic (below).

(R)-4-(2-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-phenylethyl)pyridine (CDP840, 86)



In a nitrogen filled glove box, benzylic boronic ester **84** (110 mg, 0.26 mmol, 1 eq, 99:1 e.r. (assumed based on e.r. of diboronate **49**)), iodobenzene (79.5 mg, 0.39 mmol, 1.5 eq), $Pd(dba)_2$ (12.0 mg, 0.021 mmol, 0.08 eq), PPh_3 (32.7 mg, 0.125 mmol, 0.48 eq) and Ag_2O (90 mg, 0.39 mmol, 1.5 eq) were weighed into a pressure tube and DME (5.2 mL) was added. The reaction vessel was sealed, removed from the glove box and heated at 70 °C for 16 h. The reaction mixture was cooled and subjected to filtration through a plug of silica, eluted with EtOAc (30 mL) and concentrated *in vacuo*. Purification by column chromatography (DCM/EtOAc (7:1)) gave **86** as a pale yellow oil (36 mg, 37%); e.r. 96.5:3.5, 95% e.s. (over 2 steps from diboronate **49**).

^{1}H NMR (400 MHz, $CDCl_3$): 8.40 (brs, 2H, Ar**H**), 7.31-7.24 (m, 2H, Ar**H**), 7.23-7.15 (m, 3H, Ar**H**), 6.94 (d, *J* = 4.9 Hz, 2H, Ar**H**), 6.76 (d, *J* = 7.2 Hz, 1H, Ar**H**), 6.70 (dd, *J* = 7.2 Hz, 1.9 Hz, 1H, Ar**H**), 6.67 (d, *J* = 1.9 Hz, 1H, Ar**H**), 4.66 (m, 1H, C**H**O), 4.16 (t, *J* = 7.9 Hz, 2H, CHPhC$\mathbf{H}_2$), 3.80 (s, 3H, OC$\mathbf{H}_3$), 3.32 (d, *J* = 7.9 Hz, 1H, C**H**Ph), 1.89-1.69 (m, 6H, Cp CH**H**/C$\mathbf{H}_2$), 1.65-1.51 (m, 2H, Cp CH**H**/C$\mathbf{H}_2$); **^{13}C NMR (100 MHz, $CDCl_3$)**: 149.6 (**C**), 149.4 (**C**H), 148.9 (**C**), 147.6 (**C**), 144.1 (**C**), 136.1 (**C**), 128.6 (**C**H), 127.8 (**C**H), 126.6 (**C**H), 124.6 (**C**), 120.1 (**C**H), 115.6 (**C**H), 112.1 (**C**H), 80.6 (**C**H), 56.1 (**C**H_3), 51.7 (**C**H), 41.8 (**C**H_2), 32.9 (**C**H_2), 32.8 (**C**H_2), 24.1 (**C**H_2); **IR (film) cm^{-1}**: 2954w,

1598w, 1508w; **HRMS (ESI$^+$)**: $C_{25}H_{28}NO_2$ (M + H^+) requires 374.2115; found 374.2105; $[\alpha]_D^{20}$ = +40.0 (*c* 1.6, MeOH) {Lit.[115] $[\alpha]_D^{20}$ = +38.6 (*c* 1.0, MeOH) for e.r. 90:10}. Data were consistent with those reported in the literature.[115]

The e.r. was determined by analysis by chiral SFC:

IB, 5mL/min, 3% MeOH, 100 bar, T = 35 °C; t_R 23.0 (minor), 25.4 (major).

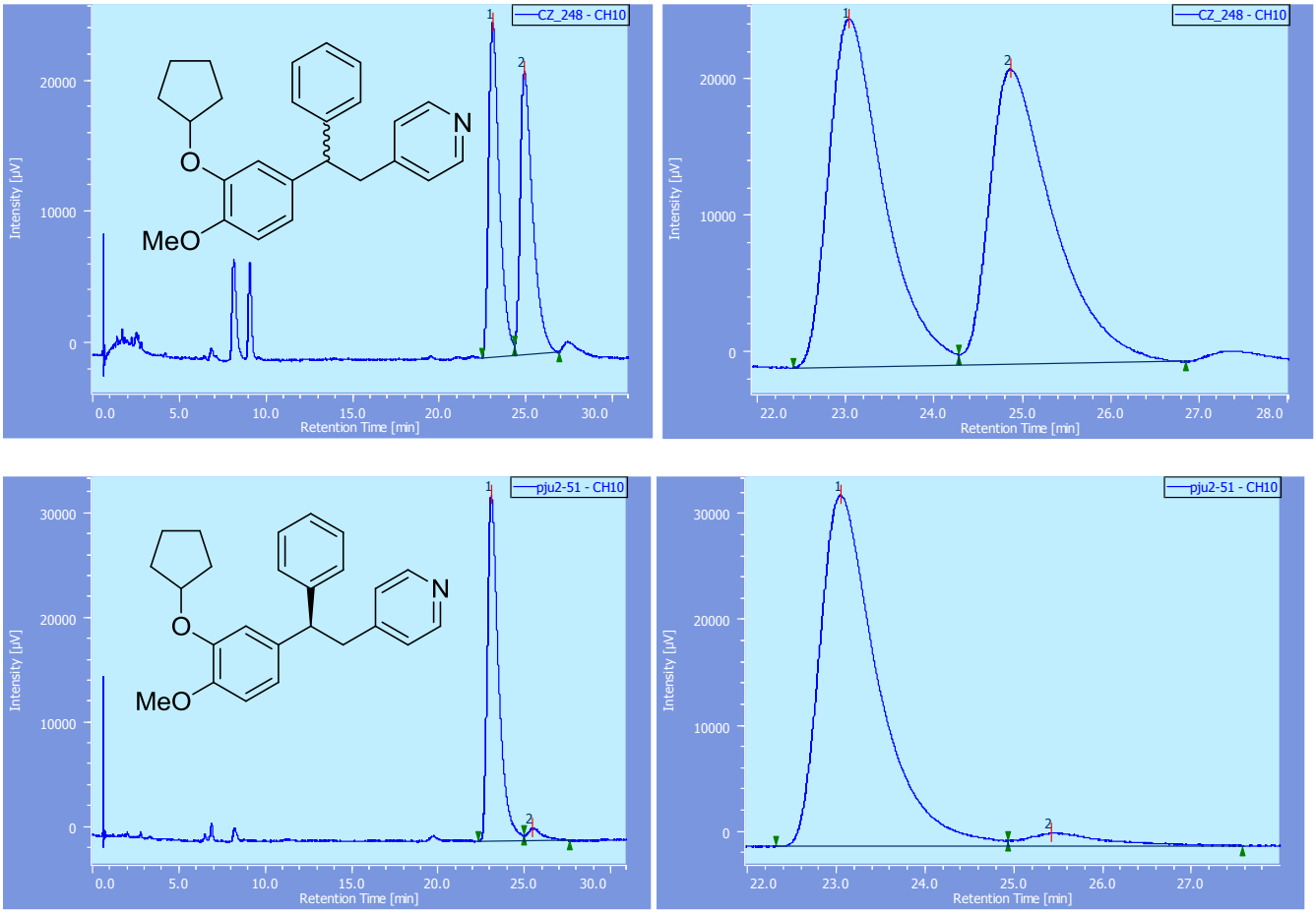
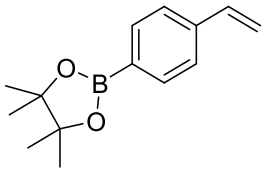


Figure 4-3 Chiral SFC spectra for **86**, racemate (above) and scalemic (below).

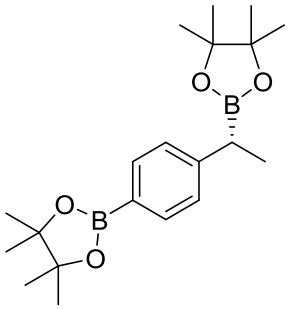
4.4 Synthesis of Diboronate 42

4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane - 41



The title compound was prepared according to a modified literature procedure.[116] In a round bottom flask with a stir bar, 4-vinylphenylboronic acid (396.9 mg, 2.50 mmol, 1 equiv.), $MgSO_4$ (60.2 mg, 0.50 mmol, 0.2 equiv.), and pinacol (301.4 mg, 2.55, 1.02 equiv.) were taken up in tetrahydrofuran (12.5 mL). The heterogeneous mixture was stirred at room temperature for 2 hours. After concentration under reduced pressure, the remaining solids were washed repeatedly with 3 x ~15 mL diethyl ether, and the combined supernatant was subjected to filtration through a plug of silica gel and a PROMAX™ 0.22 µm PTFE syringe filter. The combined washes were concentrated under reduced pressure to afford **41** (575.3 mg, 2.5 mmol, quant.) as a clear colourless oil. Spectroscopic data were in agreement with the literature.[116]

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 - 42



The title compound was prepared according to a modified literature procedure.[48] In a nitrogen filled glove box, to an oven dried schlenk tube was added $[Rh(COD)_2]BF_4$ (16.3mg, 0.04 mmol, 0.02 equiv.), (*R*)-BINAP (28.1 mg, 0.045 mmol, 0.22 equiv.), and 1,2-dimethoxyethane (1.0 mL). The resultant solution was stirred at glovebox temperature for 15 minutes after which time **41** (471.6 mg, 2.05 mmol, 1 equiv.) was added using an additional 1.5 mL of 1,2-dimethoxyethane. The resultant solution was removed from the glovebox, placed under argon, and cooled to −68 °C. A solution of catecholborane (293.3 mg, 2.45 mmol, 1.19 equiv.) in 1,2-dimethoxyethane (1 mL) was then added dropwise down the wall of the schlenk tube over 40 minutes. After an additional 4 hours at −68 °C, pinacol (613.0 mg, 5.19 mmol, 2.53 equiv.) was added in one portion and the reaction mixture was warmed to room temperature overnight. After concentration under reduced pressure, the crude material was purified by column chromatography (4% ethyl acetate/hexanes) to afford **42** (546 mg, 1.52 mmol, 74%) as a colourless solid; mp 128.6-130.0 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 7.72 (d, *J* = 7.9 Hz, 2H, Ar**H**), 7.23 (d, *J* = 8.0 Hz, 2H, Ar**H**), 2.45 (q, *J* = 7.4 Hz, 1H, C**H**-CH_3), 1.33 (m, 15H, CHC**H**$_3$ & C(C**H**$_3$)$_2$C(C**H**$_3$)$_2$), 1.20 (s, 6H, C(C**H**$_3$)(CH_3)'C(C**H**$_3$)(CH_3)')), 1.19 (s, 6H, C(CH_3)(C**H**$_3$)'C(CH_3)(C**H**$_3$)')); **^{13}C NMR (100 MHz; $CDCl_3$)**: 149.7 (**C**), 135.0 (**C**H), 127.4 (**C**H), 83.7 (**C**-OB), 83.4 (**C**-OB), 25.0 (**C**H), 24.73 (**C**H_3), 24.70 (**C**H_3), 16.9 (**C**H_3), peaks not observed for **C**'s bound to B's; **^{11}B NMR (128 MHz; $CDCl_3$)**: 32.7; **IR (film) cm^{-1}:** 2978w, 1606w, 1321, 1138w, 845w; **HRMS (EI^{+})**: $C_{20}H_{32}B_2O_4$ requires 358.2487; found 358.2491; $[\alpha]_D^{20} = -5.7$ (*c* 1.4, CH_2Cl_2).

The e.r. was determined by oxidizing a portion of the product to the diol (by **GP1**) followed by analysis by chiral SFC:

IF, 2mL/min, 100 bar, 50 °C, 1% → 40% MeOH over 10 min then 40% MeOH for 1 min; t_R 8.11 (major), 8.23 (minor).

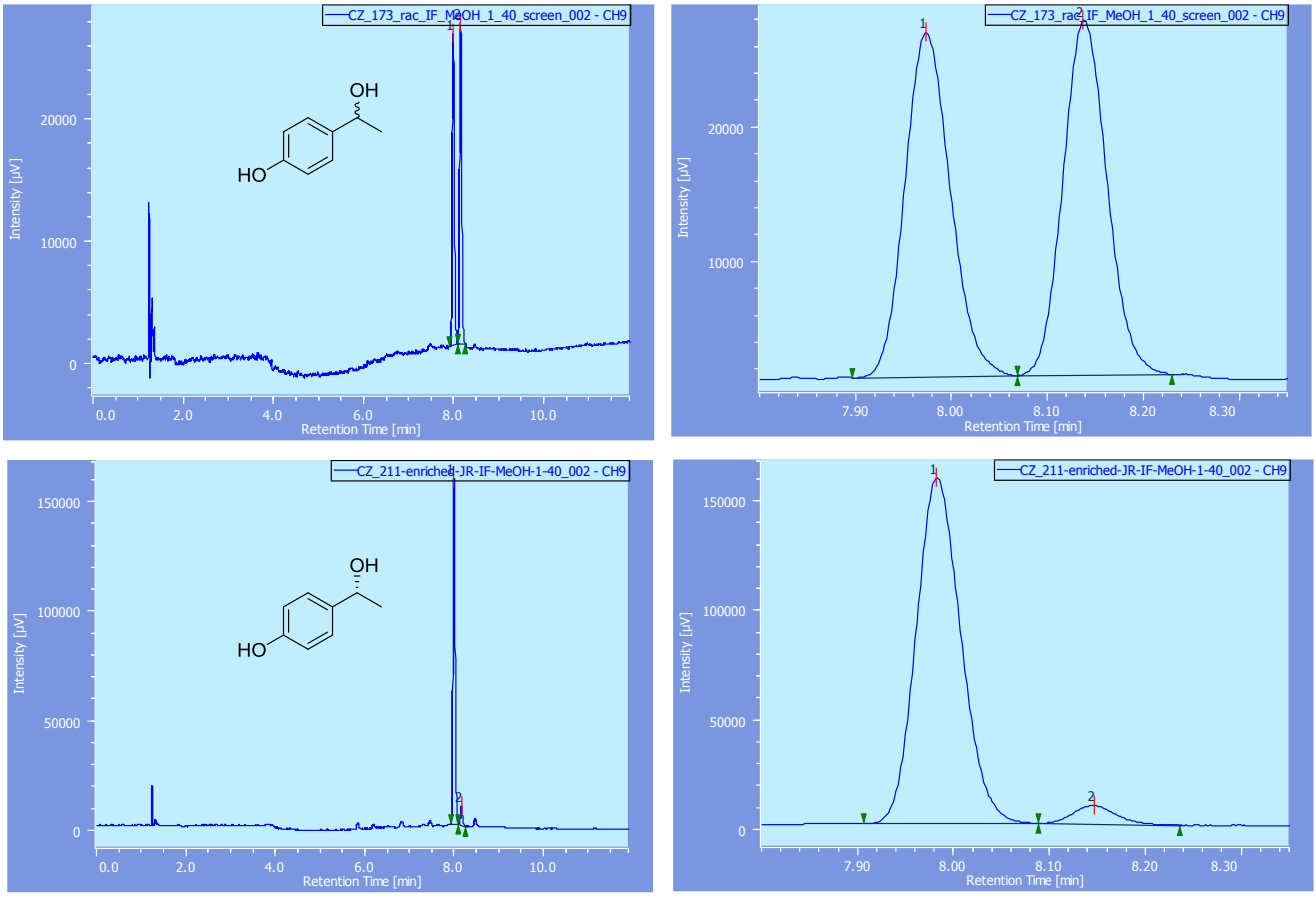
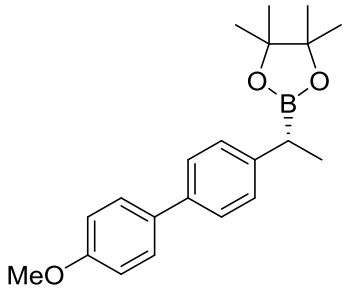


Figure 4-4 Chiral SFC spectra for oxidized **42**, racemate (above) and scalemic (below).

4.5 Procedures for the Chemoselective Cross-Coupling an Aryl Boronate in the Presence of a Secondary Benzylic Pinacol Boronate

General Procedure 2: An oven dried pressure tube with a magnetic stir bar in a glovebox was charged with diboronate **42** (615.5 mg, 1.72 mmol, 1 equiv.), $Pd_2(dba)_3$ (77.1 mg, 0.084 mmol, 0.05 equiv.), $[(t\text{Bu})_3\text{PH}]BF_4$ (98.2 mg, 0.34 mmol, 0.2 equiv.), K_2CO_3 (703.9 mg, 5.09 mmol, 2.96 equiv.), 4-bromoanisole (380.8 mg, 2.04 mmol, 1.2 equiv.), and toluene (3.4 mL). The pressure tube was sealed with a rubber septum, removed from the glovebox, and placed under argon. Water sparged with argon (95 µL) was added and the rubber septum was replaced with a lid. The reaction was heated to 60 °C for 24 hours. After cooling to room temperature, the reaction mixture was subjected to filtration through a plug of silica gel (ca. 2 mL) and a PROMAX™ 0.22 µm PTFE syringe filter using copious ethyl acetate (~30 mL).

2-(1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane - 50



The title compound was prepared according to **general procedure 2**. After filtration, the crude material was purified by column chromatography (2% to 3% ethyl acetate/hexanes) to afford **50** (451 mg, 1.33 mmol, 78%) as an ocher solid; e.r. 96:4; mp 64.5-66.3 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 7.53 (d, *J* = 8.7 Hz, 2H, Ar**H**), 7.47 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.28 (d, *J* = 8.1 Hz, 2H, Ar**H**), 6.96 (d, *J* = 8.7 Hz, 2H, Ar**H**), 3.85 (s, 3H, OC**H**$_3$), 2.48 (q, *J* = 7.4 Hz, 1H, C**H**-CH_3), 1.37 (d, *J* = 7.5 Hz, 3H, CH-C**H**$_3$), 1.24 (s, 6H, C(C**H**$_3$)(CH_3)'C(C**H**$_3$)(CH_3)')), 1.23 (s, 6H, C(CH_3)(C**H**$_3$)'C(CH_3)(C**H**$_3$)')); **^{13}C NMR (100 MHz; $CDCl_3$)**: 159.0 (**C**), 143.7 (**C**), 137.7 (**C**), 134.0 (**C**), 128.3 (**C**H), 128.1 (**C**H), 126.8 (**C**H), 114.2 (**C**H), 83.5 (**C**-OB), 55.5 (**C**H_3), 24.8 (**C**H_3), 24.75 (**C**H_3), 17.26 (**C**H_3), peak not observed for **C** bound to B; **^{11}B NMR (128 MHz; $CDCl_3$)**: 33.3; **IR (film) cm^{-1}:** 2970w, 1607w, 1494w, 1322w, 818w; **HRMS (EI)**: $C_{21}H_{27}BO_3$ requires 338.2053; found 338.2046; $[\alpha]_D^{20} = -5.0$ (*c* 2.0, CH_2Cl_2).

The e.r. was determined by oxidizing a portion of the product to the alcohol (by **GP1**) followed by analysis by chiral SFC:

IB, 2mL/min, 100 bar, 50 °C, 1% → 40% MeOH over 10 min then 40% MeOH for 1 min; t_R 9.30 (minor), 9.57 (major).

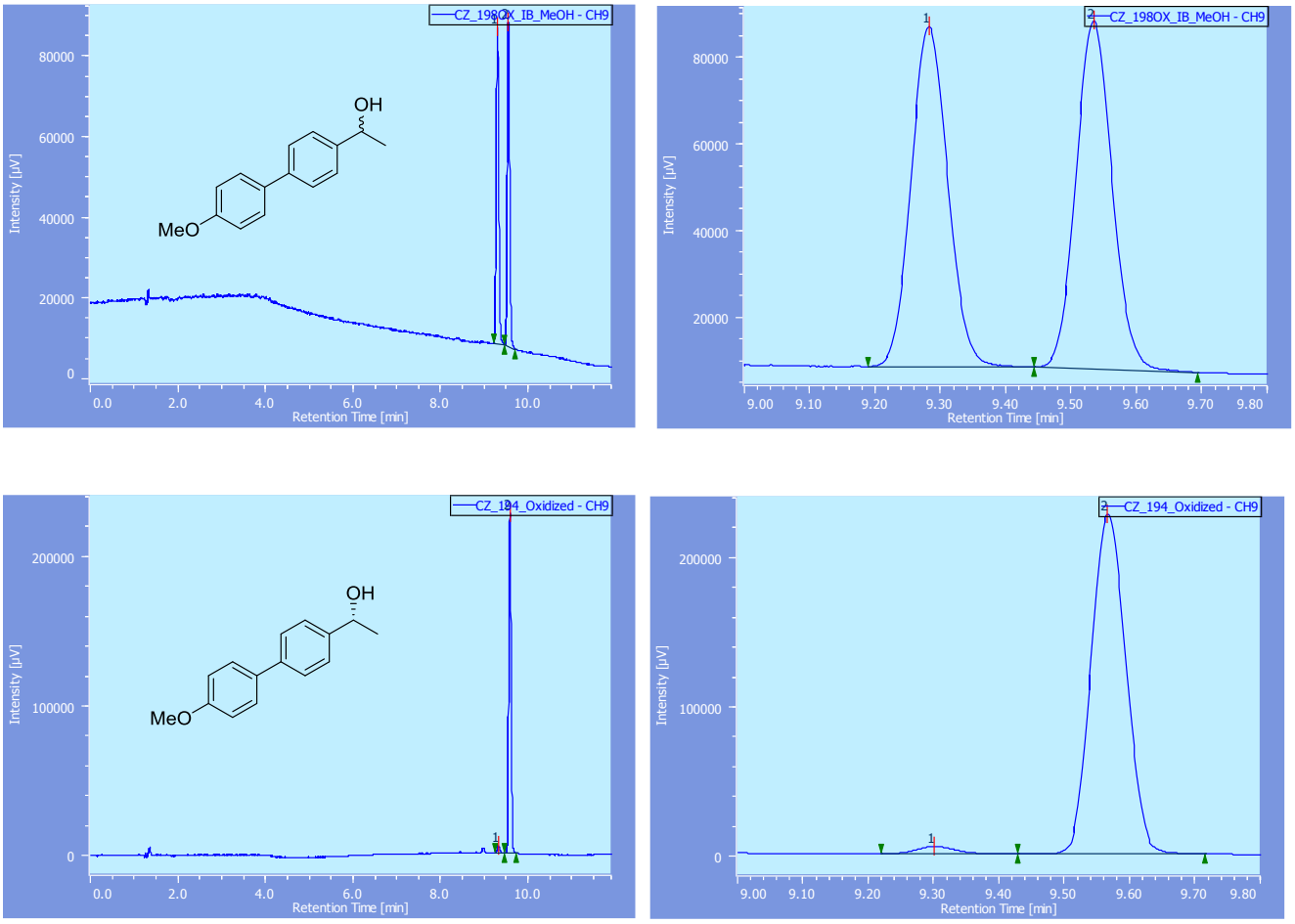
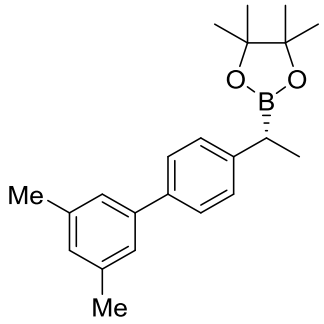


Figure 4-5 Chiral SFC spectra for oxidized **50**, racemate (above) and scalemic (below).

2-(1-(3',5'-dimethyl-[1,1'-biphenyl]-4-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane - 94



The title compound was prepared according to **general procedure 2** using diboronate **42** (609.2 mg, 1.70 mmol, 1 equiv.), $Pd_2(dba)_3$ (78.2 mg, 0.085 mmol, 0.05 equiv.), [(*t*Bu)$_3$PH]BF_4 (100.2 mg, 0.35 mmol, 0.2 equiv.), K_2CO_3 (711.6 mg, 5.15 mmol, 3.0 equiv.), and 1-bromo-3,5-dimethylbenzene (385.0 mg, 2.1 mmol, 1.2 equiv.). After filtration, the crude material was purified by column chromatography (2% to 2.5% ethyl acetate/hexanes) to afford **94** (523 mg, 1.56 mmol, 91%) as an ocher solid; e.r. 96:4; mp 65.8-67.7 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 7.46 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.25 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.18 (s, 2H, Ar**H**), 6.93 (s, 1H, Ar**H**), 2.45 (q, *J* = 7.4 Hz, 1H, C**H**-CH_3), 2.34 (s, 6H, C**H**$_3$), 1.35 (d, *J* = 7.5 Hz, 3H, CH-C**H**$_3$), 1.20 (s, 6H, C(C**H**$_3$)(CH_3)'C(C**H**$_3$)(CH_3)')), 1.19 (s, 6H, C(CH_3)(C**H**$_3$)'C(CH_3)(C**H**$_3$)')); **^{13}C NMR (100 MHz; $CDCl_3$)**: 144.1 (**C**), 141.4 (**C**), 138.3 (**C**), 138.2 (**C**H), 128.6 (**C**H), 128.2 (**C**H), 127.2 (**C**H), 125.0 (**C**H), 83.5 (**C**-OB), 24.8 (**C**H_3), 24.75 (**C**H_3), 21.6 (**C**H_3), 17.2 (**C**H_3), peak not observed for **C** bound to B; **^{11}B NMR (128 MHz; $CDCl_3$)**: 33.3; **IR (film) cm^{-1}:** 2980w, 2871w, 1601w, 1317w,

1140w, 829w; **HRMS (EI)**: $C_{22}H_{29}BO_2$ requires 336.2261; found 336.2253; $[\alpha]_D^{20} = -4.1$ (*c* 1.5, CH_2Cl_2).

The e.r. was determined by oxidizing a portion of the product to the alcohol (by **GP1**) followed by analysis by chiral SFC:

IE, 3.9mL/min, 100 bar, 50 °C, 1% → 59.5% MeOH over 15 min; t_R 10.72 (major), 11.22 (minor).

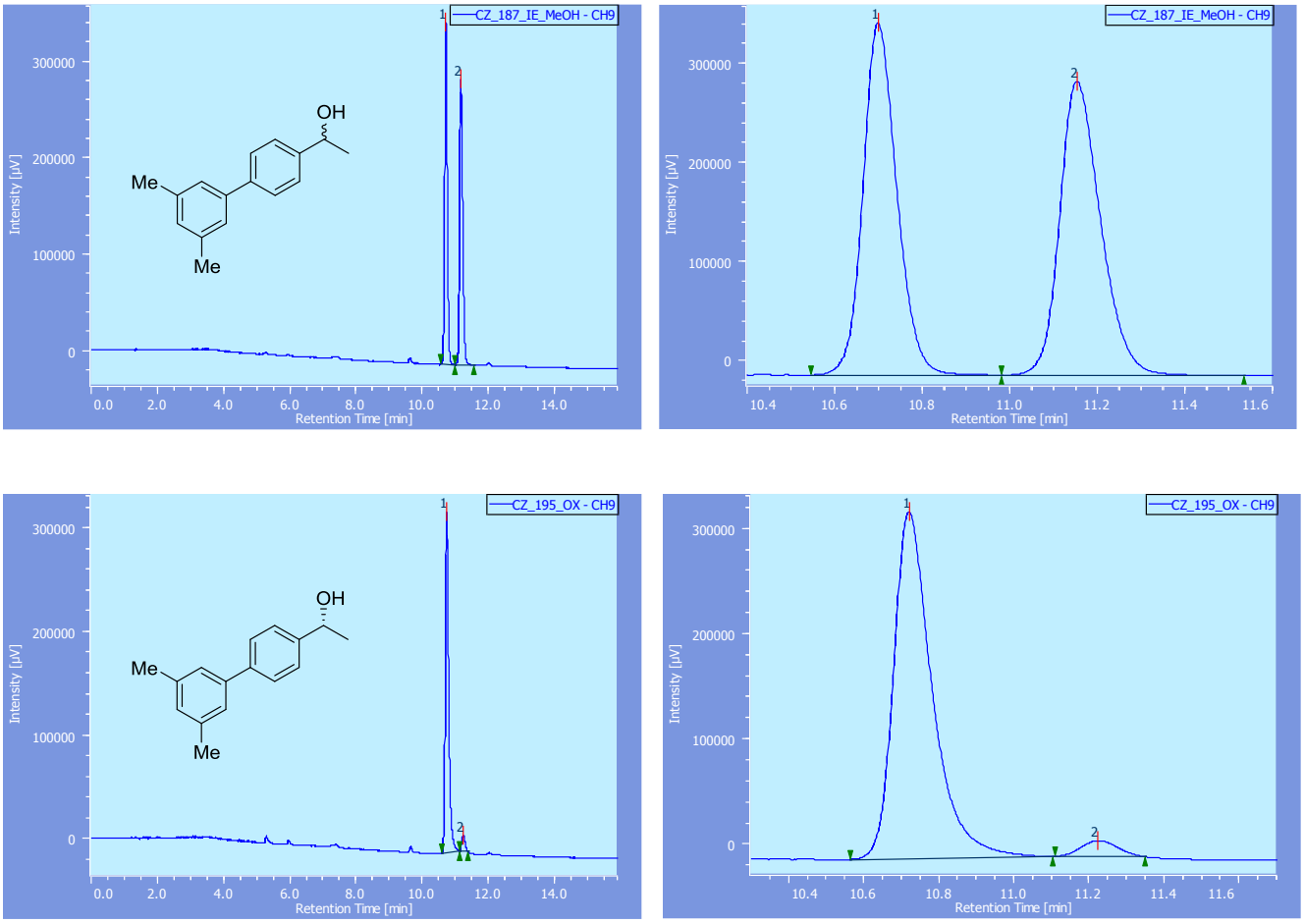
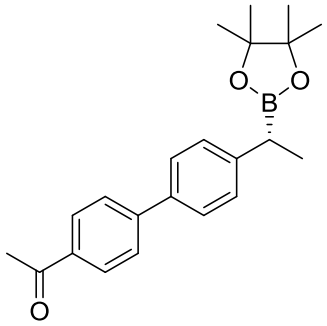


Figure 4-6 Chiral SFC spectra for oxidized **94**, racemate (above) and scalemic (below).

1-(4'-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one - 95



The title compound was prepared according to **general procedure 2** using diboronate **42** (616.6 mg, 1.72 mmol, 1 equiv.), $Pd_2(dba)_3$ (77.3 mg, 0.084 mmol, 0.05 equiv.), [(*t*-Bu)$_3$PH]BF_4 (105.6 mg, 0.36 mmol, 0.2 equiv.), K_2CO_3 (717.1 mg, 5.19 mmol, 3.0 equiv.), and 4-bromo-acetophenone (411.0 mg, 2.1 mmol, 1.2 equiv.). After filtration, the crude material was purified by column chromatography (4% ethyl acetate/hexanes) to afford **95** (497 mg, 1.42 mmol, 82%) as an ocher solid; e.r. 96:4; mp 100-101.6 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 8.01 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.68 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.55 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.33 (d, *J* = 8.2 Hz, 2H, Ar**H**), 2.62 (s, 3H, C**H**$_3$), 2.50 (q, *J* = 7.4 Hz, 1H, C**H**-CH_3), 1.38 (d, *J* = 7.5 Hz, 3H, CH-C**H**$_3$), 1.23 (s, 6H, C(C**H**$_3$)(CH_3)'C(C**H**$_3$)(CH_3)')) 1.22 (s, 6H, C(CH_3)(C**H**$_3$)'C(CH_3)(C**H**$_3$)')); **^{13}C NMR (100 MHz; $CDCl_3$)**: 197.9 (**C**=O), 146.0 (**C**), 145.6 (**C**), 136.7(**C**), 135.6 (**C**), 129.0 (**C**H), 128.5 (**C**H), 127.3 (**C**H), 127.0 (**C**H), 83.6 (**C**-OB), 26.8 (**C**H_3), 24.8 (**C**H_3), 24.75 (**C**H_3), 17.2 (**C**H_3), peak not observed for **C** bound to B; **^{11}B NMR (128 MHz; $CDCl_3$)**: 33.1; **IR (film) cm^{-1}:** 2975w, 1678w, 1600w, 1322w, 818w; **HRMS (EI)**: $C_{22}H_{27}BO_3$ requires 350.2053; found 350.2066; $[\alpha]_D^{20} = -3.7$ (*c* 1.1, CH_2Cl_2).

The e.r. was determined by oxidizing a portion of the product to the alcohol (by **GP1**) followed by analysis by chiral SFC:

IA, 2mL/min, 100 bar, 50 °C, 10% MeOH; t_R 19.28 (minor), 20.68 (major).

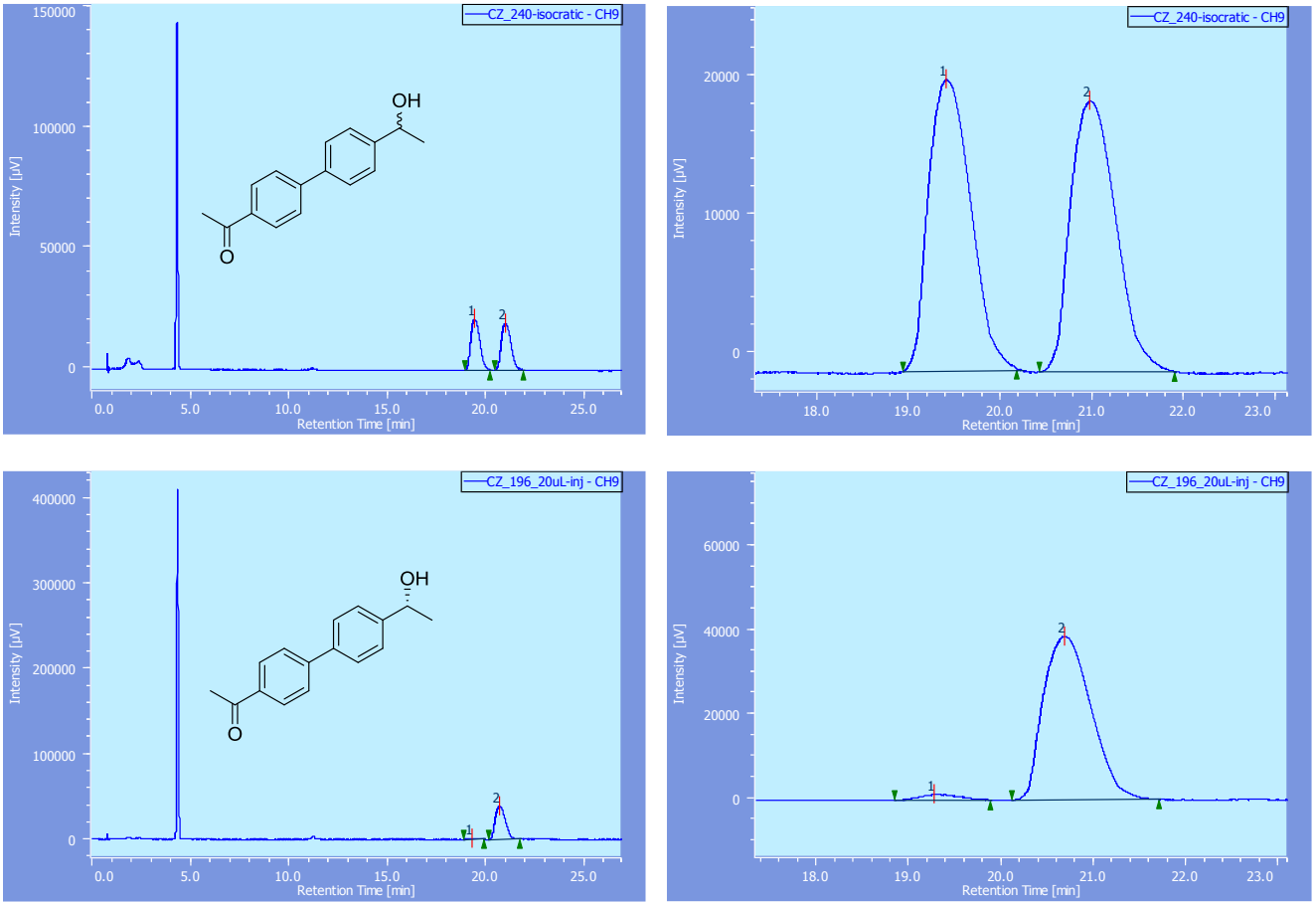
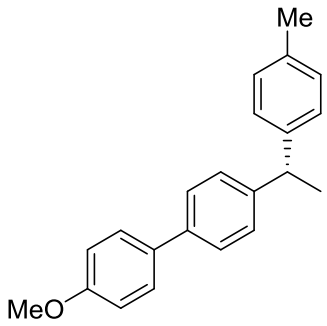


Figure 4-7 Chiral SFC spectra for oxidized **95**, racemate (above) and scalemic (below).

4.6 Cross-Coupling of Stereodefined Secondary Benzylic Boronate in Biphenyl Derivatives 50, 94, and 95

General Procedure 3: An oven dried pressure tube with a stir bar in a glovebox was charged with benzylic boronic ester **50** (174.7 mg, 0.52 mmol, 1 equiv.), $Pd(dba)_2$ (23.5 mg, 0.041 mmol, 0.08 equiv.), PPh_3 (66.2 mg, 0.25 mmol, 0.49 equiv.), Ag_2O (178.0 mg, 0.77 mmol, 1.48 equiv.), 4-iodotoluene (105.3 mg, 0.81 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). The pressure tube was sealed, removed from the glovebox, and heated to 70 °C for 16 hours. After cooling to room temperature the reaction mixture was subjected to filtration through a plug of silica gel and a PROMAX™ 0.22 μm PTFE syringe filter using ethyl acetate (~30 mL).

4-methoxy-4'-(1-(p-tolyl)ethyl)-1,1'-biphenyl - 99



The title compound was prepared according to **general procedure 3**. After filtration, the crude material was purified by column chromatography (2% ethyl acetate/hexanes) to afford **99** (101.0 mg, 0.33 mmol, 65%) as an ocher solid; e.r. 90.5:9.5, 88% e.s. (over 2 steps from 96:4 e.r. diboronate **42**); mp 131-133 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 7.54 (d, *J* = 8.7 Hz, 2H, Ar**H**), 7.50 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.30 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.19 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.15 (d, *J* = 8.0 Hz, 2H, Ar**H**), 6.99 (d, *J* = 8.7 Hz, 2H, Ar**H**), 4.19 (q, *J* = 7.2 Hz, 1H, C**H**-CH_3), 3.87 (s, 3H, OC**H**$_3$), 2.36 (s, 3H, C**H**$_3$), 1.69 (d, *J* = 7.2 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 159.1 (**C**), 145.2 (**C**), 143.5 (**C**), 138.6 (**C**), 135.6 (**C**), 133.7 (**C**), 129.2 (**C**H), 128.1 (**C**H), 128.0 (**C**H), 127.6 (**C**H), 126.8 (**C**H), 114.3 (**C**H), 55.4 (**C**H_3), 44.2 (**C**H), 22.1 (**C**H_3), 21.1 (**C**H_3); **IR (film) cm^{-1}:** 2960w, 1603w, 1493w, 1034w, 826w; **HRMS (EI)**: $C_{22}H_{22}O$ requires 302.1671; found 302.1659; $[\alpha]_D^{20}$ = +8.7 (*c* 1.4, CH_2Cl_2).

The e.r. was determined by analysis by chiral SFC:

IE, 2mL/min, 100 bar, 50 °C, 1% → 40% MeOH over 10 min then 40% MeOH for 3 min; t_R 9.25 (major), 9.68 (minor).

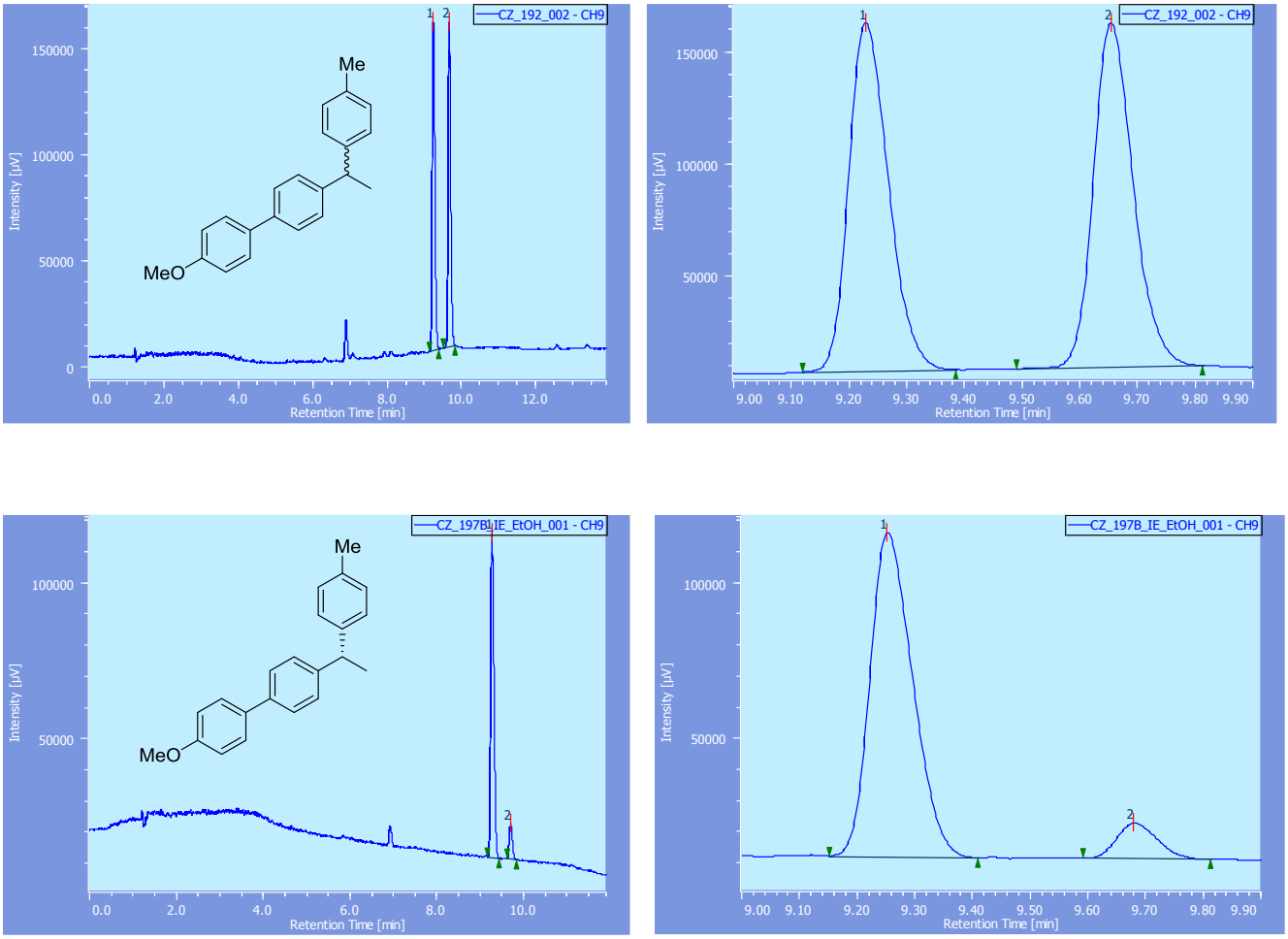
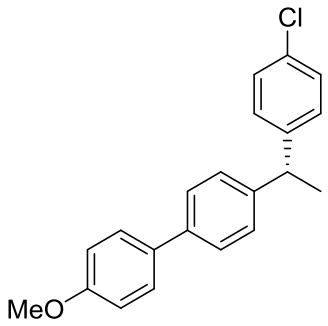


Figure 4-8 Chiral SFC spectra for **99**, racemate (above) and scalemic (below).

4-(1-(4-chlorophenyl)ethyl)-4'-methoxy-1,1'-biphenyl - 96



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **50** (174.0 mg, 0.51 mmol, 1 equiv.), $Pd(dba)_2$ (23.4 mg, 0.041 mmol, 0.08 equiv.), PPh_3 (66.2 mg, 0.25 mmol, 0.49 equiv.), Ag_2O (174.2 mg, 0.75 mmol, 1.44 equiv.), 1-chloro-4-iodobenzene (179.8 mg, 0.75 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). After filtration, the crude material was purified by column chromatography (1.5% ethyl acetate/hexanes) to afford **96** (97.0 mg, 0.30 mmol, 60%) as an ocher solid; e.r. 90:10, 87% e.s. (over 2 steps from 96:4 e.r. diboronate **42**); mp 156.2-158.2 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 7.51 (m, 4H, Ar**H**), 7.26 (m, 4H, Ar**H**), 7.19 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.97 (m, 2H, Ar**H**), 4.16 (q, *J* = 7.2 Hz, 1H, C**H**-CH_3), 3.85 (s, 3H. OC**H**$_3$), 1.65 (d, *J* = 7.2 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 159.2 (**C**), 145.0 (**C**), 144.4 (**C**), 139.0 (**C**), 133.6 (**C**), 131.9 (**C**), 129.1 (**C**H), 128.6 (**C**H), 128.2 (**C**H), 128.0 (**C**H), 126.9 (**C**H), 114.33 (**C**H), 55.47 (**C**H_3), 44.0 (**C**H), 22.0 (**C**H_3); **IR (film) cm^{-1}:** 2965w, 1603w, 1486w, 1206w, 823w; **HRMS (EI)**: $C_{22}H_{19}ClO$ requires 322.1124; found 322.1137; $[\alpha]_D^{20}$ = +6.0 (*c* 1.0, CH_2Cl_2).

The e.r. was determined by analysis by chiral SFC:

IE, 2mL/min, 100 bar, 50 °C, 1% → 40% MeOH over 10 min then 40% MeOH for 3 min; t_R 11.24 (minor), 11.71 (major).

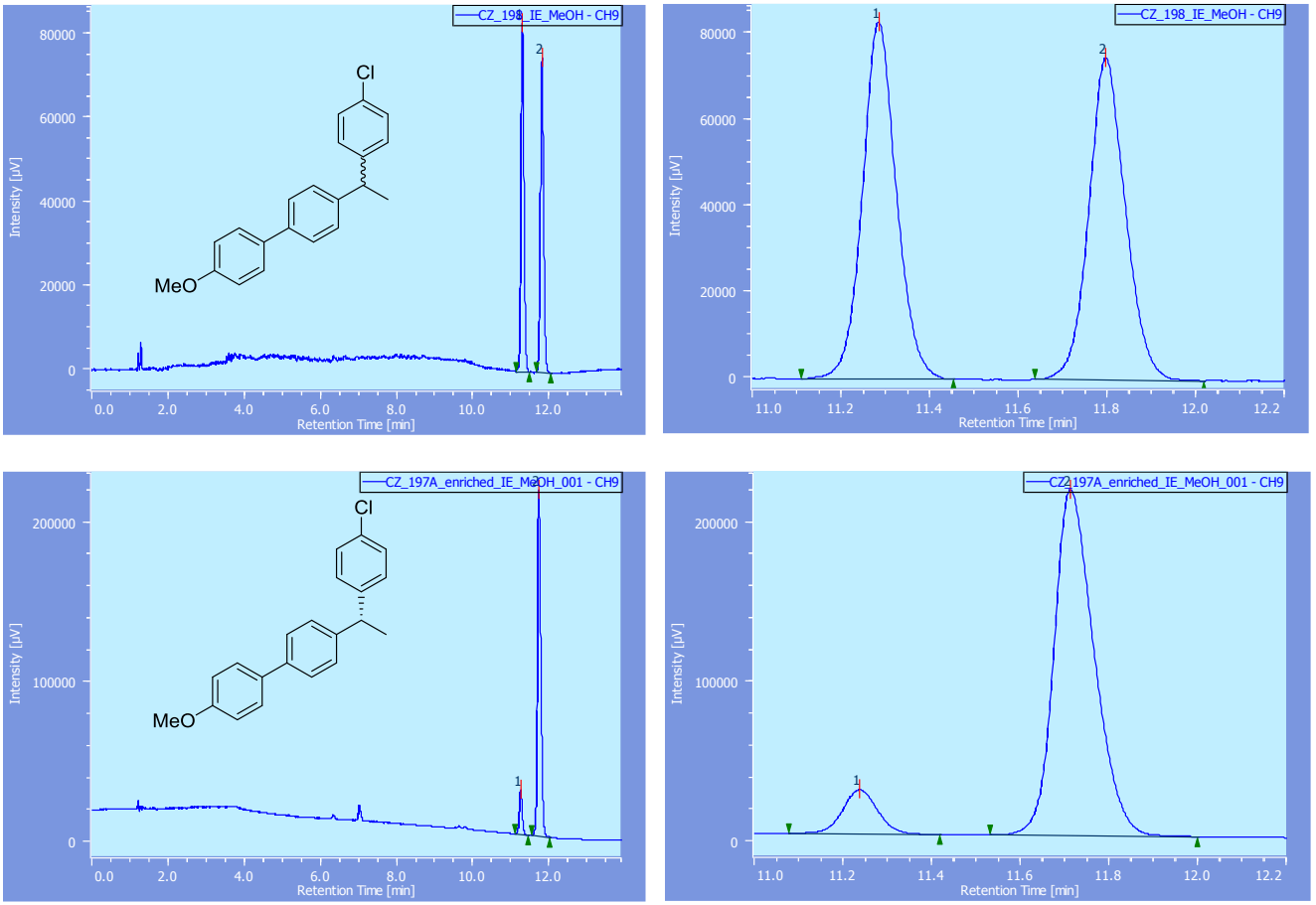
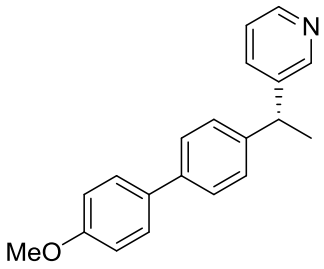


Figure 4-9 Chiral SFC spectra for **96**, racemate (above) and scalemic (below).

3-(1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)pyridine - 100



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **50** (102.4 mg, 0.30 mmol, 1 equiv.), $Pd(dba)_2$ (13.6 mg, 0.024 mmol, 0.08 equiv.), PPh_3 (37.5 mg, 0.14 mmol, 0.48 equiv.), Ag_2O (108.2 mg, 0.47 mmol, 1.56 equiv.), 3-iodopyridine (93.3 mg, 0.46 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). After filtration, the crude material was purified by column chromatography (10% ethyl acetate/hexanes + 2 v/v% NEt_3) to afford **100** (46.0 mg, 0.16 mmol, 53%) as an ocher solid; e.r. 93:7, 96% e.s. (over 2 steps from 95:5 e.r. diboronate **42**); mp 105-107.

^{1}H NMR (400 MHz; $CDCl_3$): 8.56 (brs, 1H, Ar**H**), 8.45 (brs, 1H, Ar**H**), 7.49 (m, 5H, Ar**H**), 7.22 (m, 3H, Ar**H**), 6.95 (d, *J* = 8.6 Hz, 2H, Ar**H**), 4.20 (q, *J* = 7.1 Hz, 1H, C**H**-CH_3), 3.83 (s, 3H, OC**H**$_3$), 1.68 (d, *J* = 7.2 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 159.2 (**C**), 149.5 (**C**H), 147.7 (**C**H), 143.6 (**C**), 141.7 (**C**), 139.2 (**C**), 135.1 (**C**H), 133.4 (**C**), 128.1 (**C**H), 128.0 (**C**H), 127.0 (**C**H), 123.5 (**C**H), 114.3 (**C**H), 55.5 (**C**H_3), 42.2 (**C**H), 21.7 (**C**H_3); **IR (film) cm^{-1}:** 2966w, 1604w, 1494w, 1250w, 825w; **HRMS (EI)**: $C_{20}H_{19}NO$ requires 289.1467; found 289.1461; $[\alpha]_D^{20}$ = +8.7 (*c* 0.9, CH_2Cl_2) °C.

The e.r. was determined by analysis by chiral SFC:

IE, 3.9mL/min, 100 bar, 50 °C, 1% → 59.5% MeOH over 15 min; t_R 13.87 (major), 14.85 (minor).

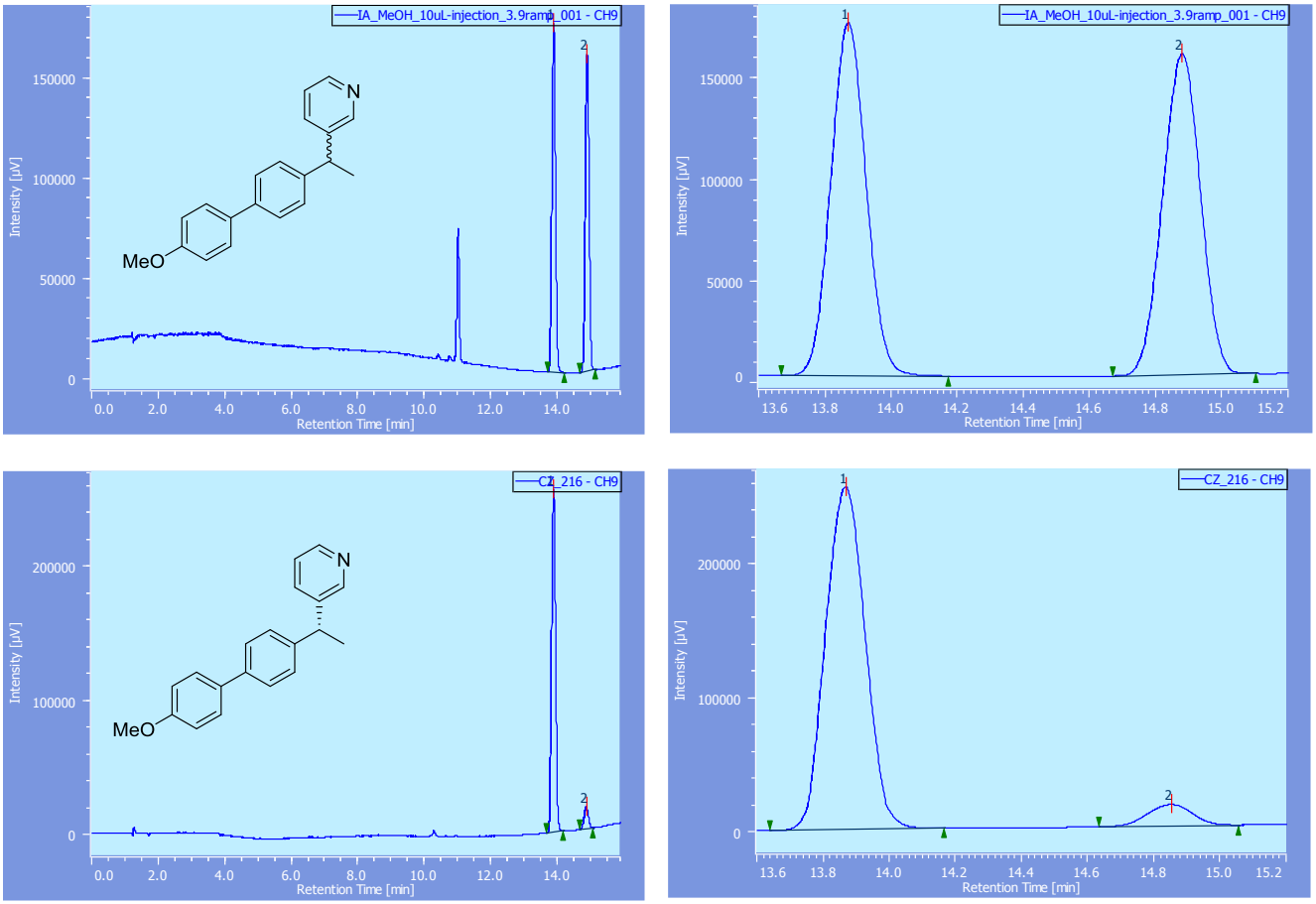
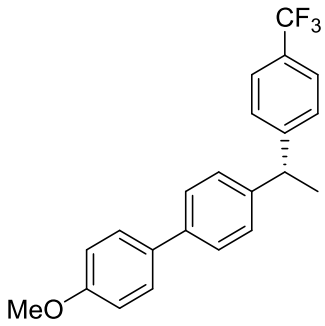


Figure 4-10 Chiral SFC spectra for **100**, racemate (above) and scalemic (below).

4-methoxy-4'-(1-(4-(trifluoromethyl)phenyl)ethyl)-1,1'-biphenyl - 97



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **50** (1.00 g, 2.96 mmol, 1 equiv.), $Pd(dba)_2$ (136.9 mg, 0.238 mmol, 0.08 equiv.), PPh_3 (377.7 mg, 1.44 mmol, 0.49 equiv.), Ag_2O (1.03 g, 4.45 mmol, 1.5 equiv.), 4-iodobenzotrifluoride (1.22 g, 4.48 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (60.0 mL). After filtration, the crude material was purified by column chromatography (2.0% ethyl acetate/hexanes) to afford **97** (695 mg, 1.95 mmol, 66%) as an ocher solid; e.r. 90:10, 89% e.s. (over 2 steps from 90:5 e.r. diboronate **42**); mp 155.8-157 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 7.55 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.50 (m, 4H, Ar**H**), 7.37 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.25 (d, *J* = 7.8 Hz, 2H, Ar**H**), 6.97 (d, *J* = 8.8 Hz, 2H, Ar**H**), 4.24 (q, *J* = 7.1 Hz, 1H, C**H**-CH_3), 3.85 (s, 3H. OC**H**$_3$), 1.69 (d, *J* = 7.2 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 159.3 (**C**), 150.6 (**C**), 143.8 (**C**), 139.8 (**C**), 133.5 (**C**), 128.5 (q, *J* = 32.4 Hz, (**C**) 128.14 (**C**H), 128.09 (**C**H), 128.08 (**C**H), 127.0 (**C**H), 125.5 (q, *J* = 3.8 Hz, (**C**H), 124.5 (q, *J* = 271.9 Hz, **C**F_3), 114.4 (**C**H), 55.4 (**C**H_3), 44.5 (**C**H), 21.8 (**C**H_3); **^{19}F NMR (377 MHz; $CDCl_3$)**: 60.51; **IR (film) cm^{-1}:** 2973w, 1604w, 1419w, 1107w, 825w; **HRMS (EI)**: $C_{22}H_{19}F_3O$ requires 356.1388; found 356.1392; $[\alpha]_D^{20}$ = +10.0 (*c* 1.0, CH_2Cl_2).

The e.r. was determined by analysis by chiral SFC:

IE, 2mL/min, 100 bar, 50 °C, 10% → 20% MeOH over 10 min; t_R 8.44 (major), 8.76 (minor).

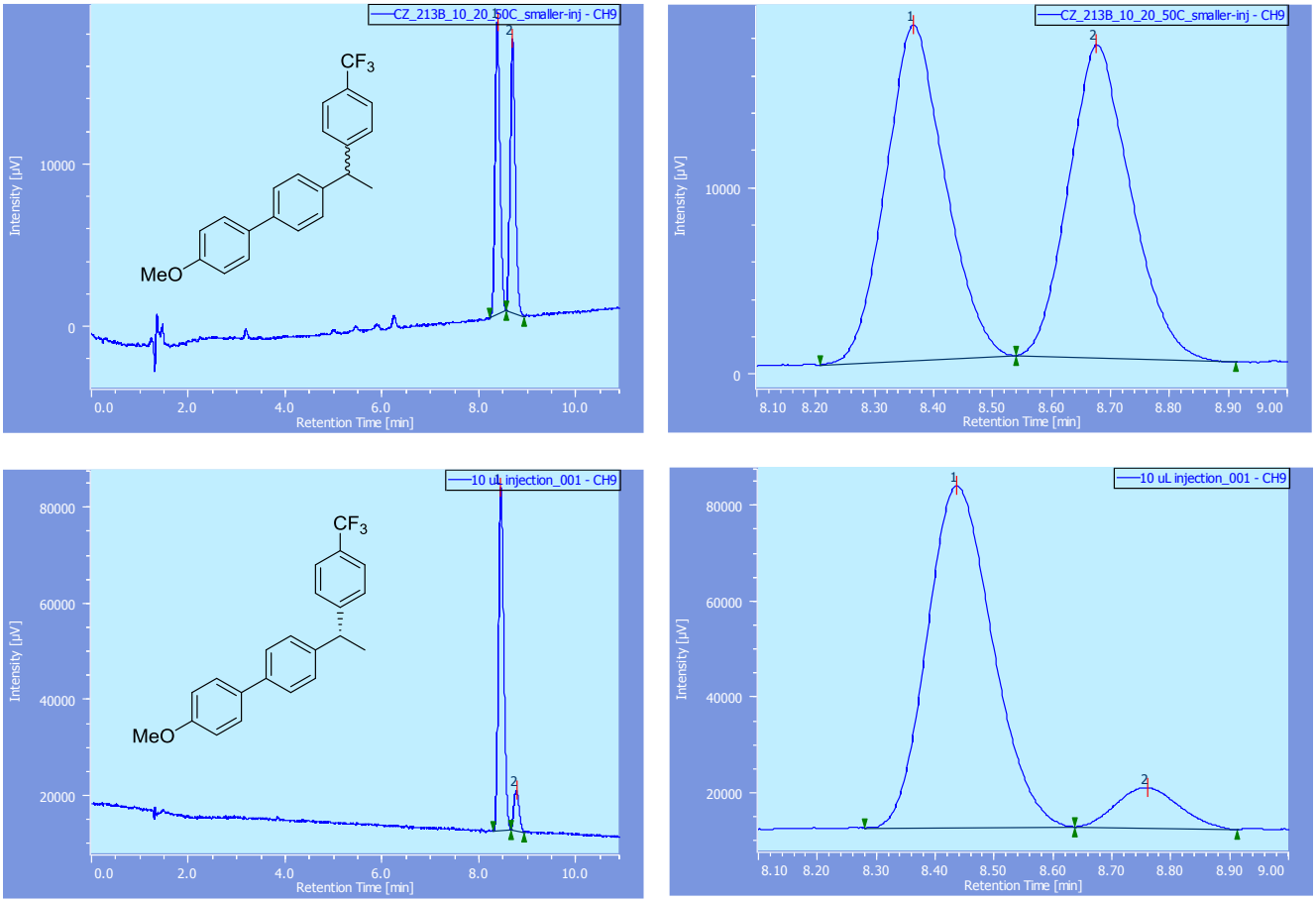
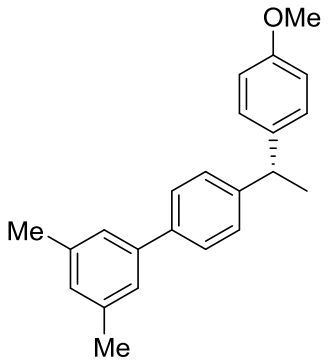


Figure 4-11 Chiral SFC spectra for **97**, racemate (above) and scalemic (below).

4'-(1-(4-methoxyphenyl)ethyl)-3,5-dimethyl-1,1'-biphenyl - 101



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **94** (100.8 mg, 0.30 mmol, 1 equiv.), $Pd(dba)_2$ (13.2 mg, 0.023 mmol, 0.08 equiv.), PPh_3 (37.8 mg, 0.14 mmol, 0.48 equiv.), Ag_2O (103.6 mg, 0.45 mmol, 1.5 equiv.), 4-iodoanisole (105.0 mg, 0.45 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). After filtration, the crude material was purified by column chromatography (0.5% ethyl acetate/hexanes) to afford **101** (57.0 mg, 0.18 mmol, 60%) as a pale oil; e.r. 91:9, 90% e.s. (over 2 steps from 96:4 e.r. diboronate **42**).

^{1}H NMR (400 MHz; $CDCl_3$): 7.45 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.22 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.14 (s, 4H, Ar**H**), 6.93 (s, 1H, Ar**H**), 6.81 (d, *J* = 8.7 Hz, 2H, Ar**H**), 4.10 (q, *J* = 7.2 Hz, 1H, C**H**-CH_3), 3.73 (s, 3H, OC**H**$_3$), 2.33 (s, 6H, C**H**$_3$), 1.61 (d, *J* = 7.2 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 158.0 (**C**), 145.8 (**C**), 141.2 (**C**), 139.2 (**C**), 138.6 (**C**), 138.3 (**C**), 128.8 (**C**H), 128.6 (**C**H), 128.0 (**C**H), 127.2 (**C**H), 125.1 (**C**H), 113.9 (**C**H), 55.3 (**C**H_3), 43.8 (**C**H), 22.2 (**C**H_3), 21.5 (**C**H_3); **IR (film) cm^{-1}:** 2961w, 1603w, 1508w, 1243w, 1033w, 826w; **HRMS (EI)**: $C_{23}H_{24}O$ requires 316.1827; found 316.13837; $[\alpha]_D^{20}$ = +3.6 (*c* 1.0, CH_2Cl_2).

The e.r. was determined by analysis by chiral SFC:

IA, 2mL/min, 100 bar, 50 °C, 1% → 40% MeCN over 10 min then 40% MeCN for 3 min; t_R 10.33 (minor), 10.75 (major).

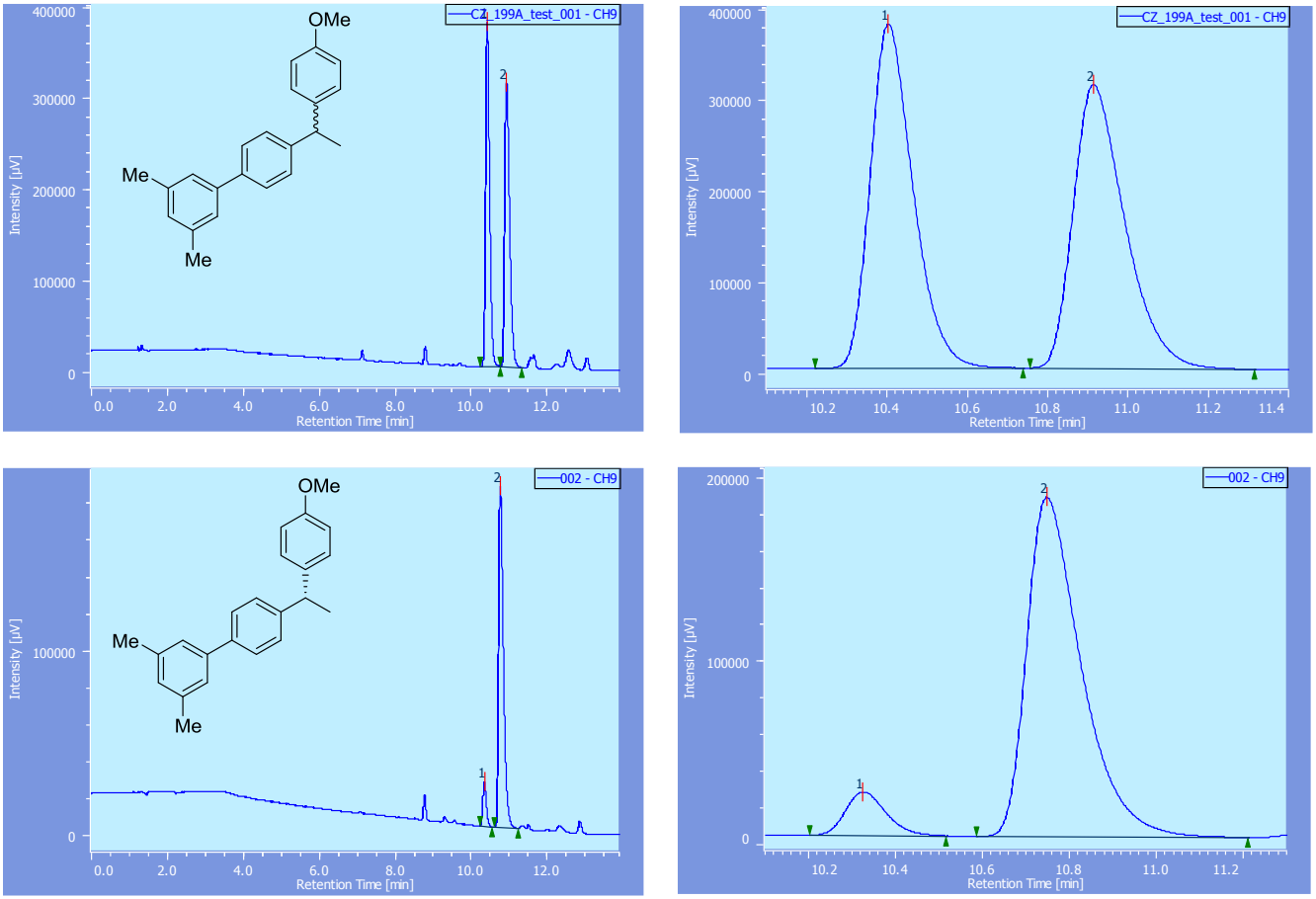
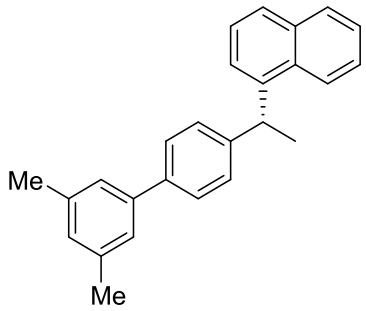


Figure 4-12 Chiral SFC spectra for **101**, racemate (above) and scalemic (below).

1-(1-(3',5'-dimethyl-[1,1'-biphenyl]-4-yl)ethyl)naphthalene - 98



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **94** (100.2 mg, 0.30 mmol, 1 equiv.), $Pd(dba)_2$ (13.3 mg, 0.023 mmol, 0.08 equiv.), PPh_3 (37.8 mg, 0.14 mmol, 0.48 equiv.), Ag_2O (107.4 mg, 0.46 mmol, 1.5 equiv.), 1-iodonaphthalene (111.5 mg, 0.43 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). After filtration, the crude material was purified by column chromatography (0.5% ethyl acetate/hexanes) to afford **98** (58.0 mg, 0.17 mmol, 57%) as an ocher solid; e.r. 85:15, 76% e.s. (over 2 steps from 96:4 e.r. diboronate **42**); mp 123-125 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 8.06 (dd, *J* = 6.2 Hz, 3.5 Hz, 1H, Ar**H**), 7.83 (dd, *J* = 6.1 Hz, 3.4 Hz, 1H, Ar**H**), 7.73 (dd, *J* = 6.8 Hz, 2.2 Hz, 1H, Ar**H**), 7.43 (m, 6H, Ar**H**), 7.25 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.14 (s, 2H, Ar**H**), 6.93 (s, 1H, Ar**H**), 4.93 (q, *J* = 7.1 Hz, 1H, C**H**-CH_3), 2.32 (s, 6H, C**H**$_3$), 1.77 (d, *J* = 7.1 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 145.7 (**C**), 141.7 (**C**), 141.1 (**C**), 139.3 (**C**), 138.3 (**C**), 134.2 (**C**), 131.9 (**C**), 128.9 (**C**H), 128.8 (**C**H), 128.0 (**C**H), 127.3 (**C**H), 127.2 (**C**H), 126.0 (**C**H), 125.6 (**C**H), 125.5 (**C**H), 125.1 (**C**H), 124.5 (**C**H), 124.1 (**C**H), 40.4 (**C**H), 22.7 (**C**H_3), 21.5 (**C**H_3); **IR (film) cm^{-1}:** 2916w, 1596w, 1454w, 828w, 780w; **HRMS (EI)**: $C_{26}H_{24}$ requires 336.1878; found 336.1872; $[\alpha]_D^{20}$ = +47.3 (*c* 1.1, CH_2Cl_2).

The e.r. was determined by analysis by chiral SFC:

IB, 2mL/min, 100 bar, 45 °C, 1% → 30% MeCN over 13 min then 30% MeCN for 1 min;

t_R 13.12 (minor), 13.29 (major).

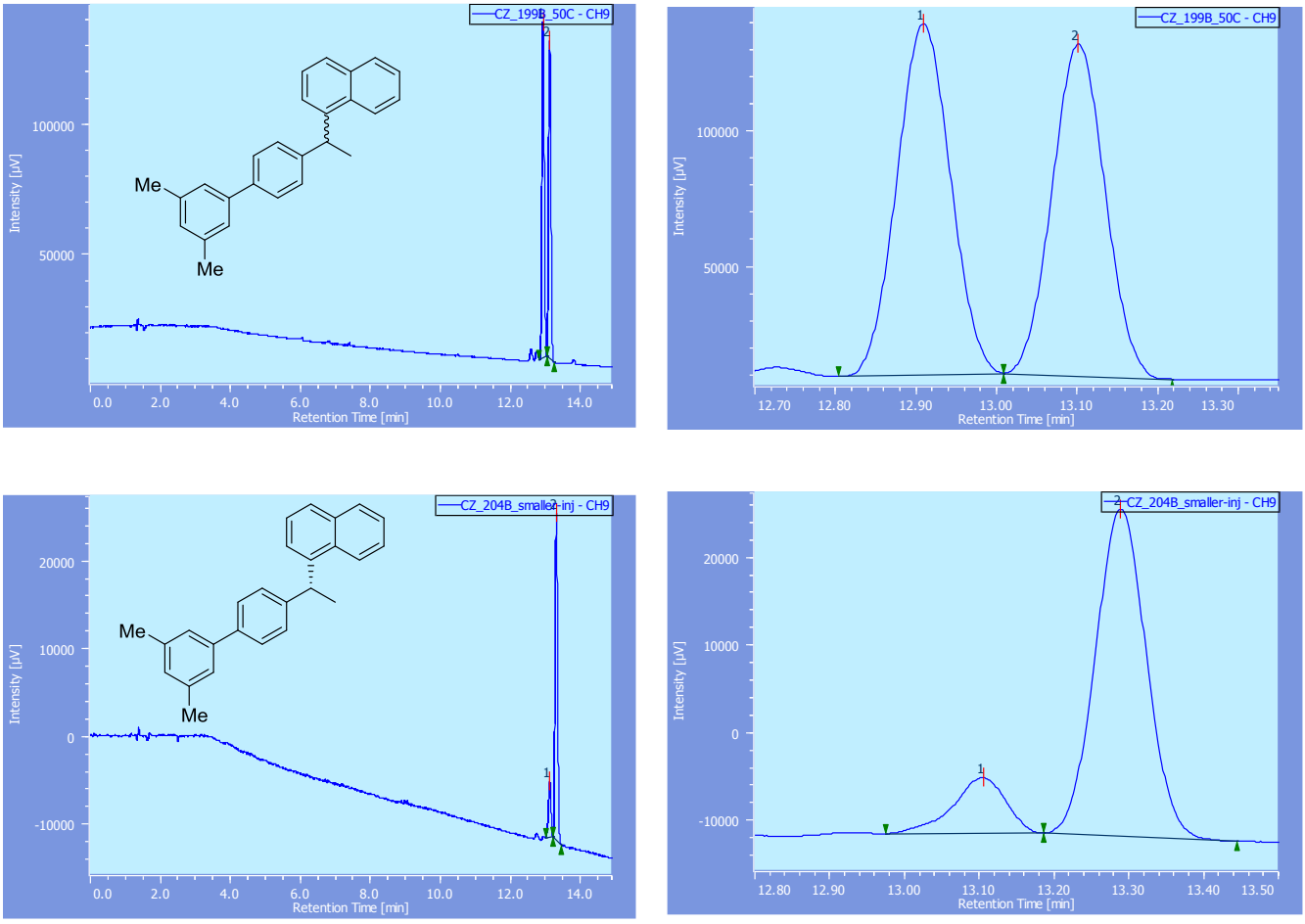
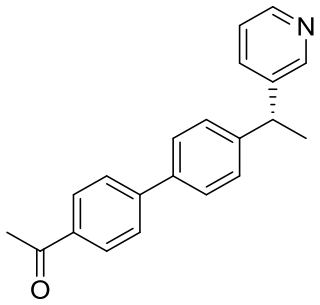


Figure 4-13 Chiral SFC spectra for **98**, racemate (above) and scalemic (below).

1-(4'-(1-(pyridin-3-yl)ethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one - 103



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **95** (104.9 mg, 0.30 mmol, 1 equiv.), $Pd(dba)_2$ (13.6 mg, 0.024 mmol, 0.08 equiv.), PPh_3 (39.6 mg, 0.15 mmol, 0.50 equiv.), Ag_2O (104.5 mg, 0.45 mmol, 1.5 equiv.), 3-iodopyridine (91.2 mg, 0.44 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). After filtration, the crude material was purified by column chromatography (30% ethyl acetate/hexanes + 2 v/v% NEt_3) to afford **103** (57.0 mg, 0.19 mmol, 63%) as an ocher solid; e.r. 75:25, 54% e.s. (over 2 steps from 96:4 e.r. diboronate **42**).

^{1}H NMR (400 MHz; $CDCl_3$): 8.55 (brs, 1H, Ar**H**), 8.45 (brs, 1H, Ar**H**), 8.00 (d, *J* = 8.3 Hz, 2H, Ar**H**), 7.64 (d, *J* = 8.2 Hz, 2H, Ar**H**), 7.55 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.52 (d, *J* = 7.9 Hz, 1H, Ar**H**), 7.30 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.21 (dd, *J* = 7.5 Hz, 4.8 Hz, 1H, Ar**H**), 4.21 (q, *J* = 7.0 Hz, 1H, C**H**-CH_3), 2.60 (s, 3H, C**H**$_3$), 1.69 (d, *J* = 7.2 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 197.7 (**C**=O), 149.4 (**C**H), 147.7 (**C**H), 145.32 (**C**), 145.30 (**C**), 141.3 (**C**), 138.1 (**C**), 135.8 (**C**), 135.0 (**C**H), 129.0 (**C**H), 128.2 (**C**H), 127.5 (**C**H), 127.1 (**C**H), 123.5 (**C**H), 42.2 (**C**H), 26.7 (**C**H_3), 21.5 (**C**H_3); **IR (film) cm^{-1}:** 2976w, 1677s, 1599w, 1265w, 813w; **HRMS (EI)**: $C_{21}H_{19}NO$ requires 301.1467; found 301.1461; $[\alpha]_D^{20}$ = +6.0 (*c* 1.0, CH_2Cl_2); mp 78.2-80 °C.

The e.r. was determined by analysis by chiral SFC:

IA, 2mL/min, 100 bar, 50 °C, 1% → 73% EtOH over 15 min; t_R 13.34 (major), 13.98 (minor).

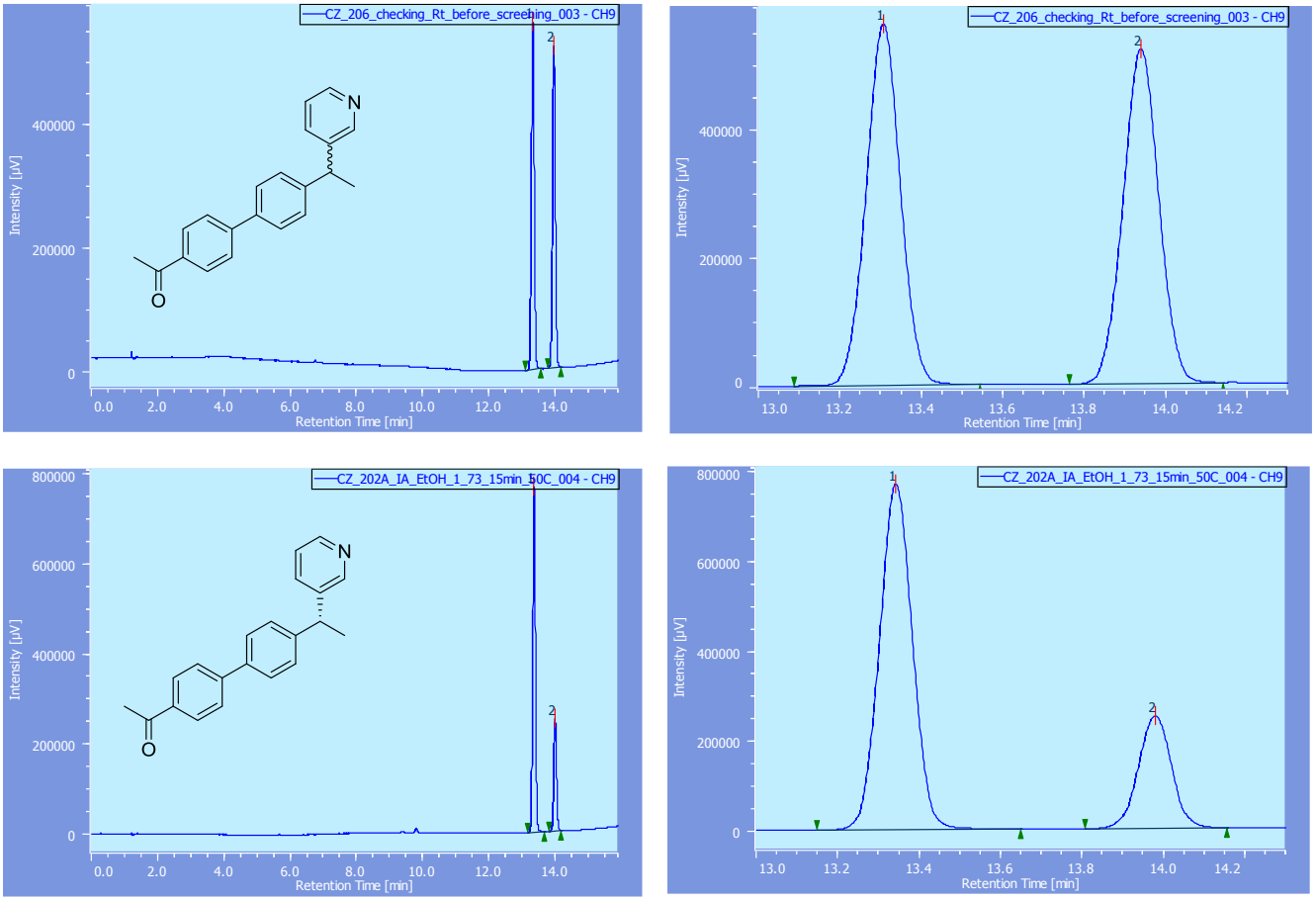
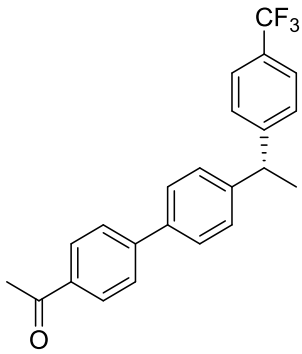


Figure 4-14 Chiral SFC spectra for **103**, racemate (above) and scalemic (below).

1-(4'-(1-(4-(trifluoromethyl)phenyl)ethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one - 102



The title compound was prepared according to **general procedure 3** using benzylic boronic ester **95** (105.8 mg, 0.30 mmol, 1 equiv.), $Pd(dba)_2$ (13.2 mg, 0.023 mmol, 0.08 equiv.), PPh_3 (37.5 mg, 0.14 mmol, 0.48 equiv.), Ag_2O (106.4 mg, 0.46 mmol, 1.5 equiv.), 4-iodobenzotrifluoride (120.2 mg, 0.44 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (6.0 mL). After filtration, the crude material was purified by column chromatography (3.0% ethyl acetate/hexanes) to afford **102** (70.0 mg, 0.17 mmol, 63%) as an ocher solid; e.r. 85:15, 76% e.s. (over 2 steps from 96:4 e.r. diboronate **42**); mp 132.5-134.1 °C.

^{1}H NMR (400 MHz; $CDCl_3$): 8.03 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.67 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.58 (m, 4H, Ar**H**), 7.38 (d, *J* = 7.8 Hz, 2H, Ar**H**), 7.33 (d, *J* = 7.9 Hz, 2H, Ar**H**), 4.28 (q, *J* = 6.8 Hz, 1H, C**H**-CH_3), 2.64 (s, 3H, C**H**$_3$), 1.71 (d, *J* = 7.1 Hz, 3H, CH-C**H**$_3$); **^{13}C NMR (100 MHz; $CDCl_3$)**: 197.7 (**C**=O), 150.2 (**C**), 145.6 (**C**), 145.4 (**C**), 138.1 (**C**), 135.9 (**C**), 129.0 (**C**H), 128.6 (**C**H), 135.0 (**C**H), 129.0 (**C**H), 128.6 (q, *J* = 32.3 Hz, (**C**), 128.3 (**C**H), 128.1 (**C**H), 127.5 (**C**H), 127.1 (**C**H), 125.5 (q, *J* = 3.8 Hz, (**C**H), 124.4 (q, *J* = 271.9 Hz, **C**F_3), 44.5 (**C**H), 26.7 (CO**C**H_3), 21.7 (CH**C**H_3); **^{19}F NMR (377 MHz; $CDCl_3$)**: 62.8; **IR (film) cm^{-1}:** 2994w, 1677s, 1599w, 1324w, 819w; **HRMS (EI)**: $C_{23}H_{19}F_3O$ requires 368.1388; found 368.1381; $[\alpha]_D^{20}$ = +8.0 (*c* 1.0, CH_2Cl_2).

The e.r. was determined by analysis by chiral SFC:

IF, 2mL/min, 100 bar, 50 °C, 1% → 40% MeCN over 10 min then 40% MeCN for 3 min;

t_R 12.58 (major), 13.12 (minor).

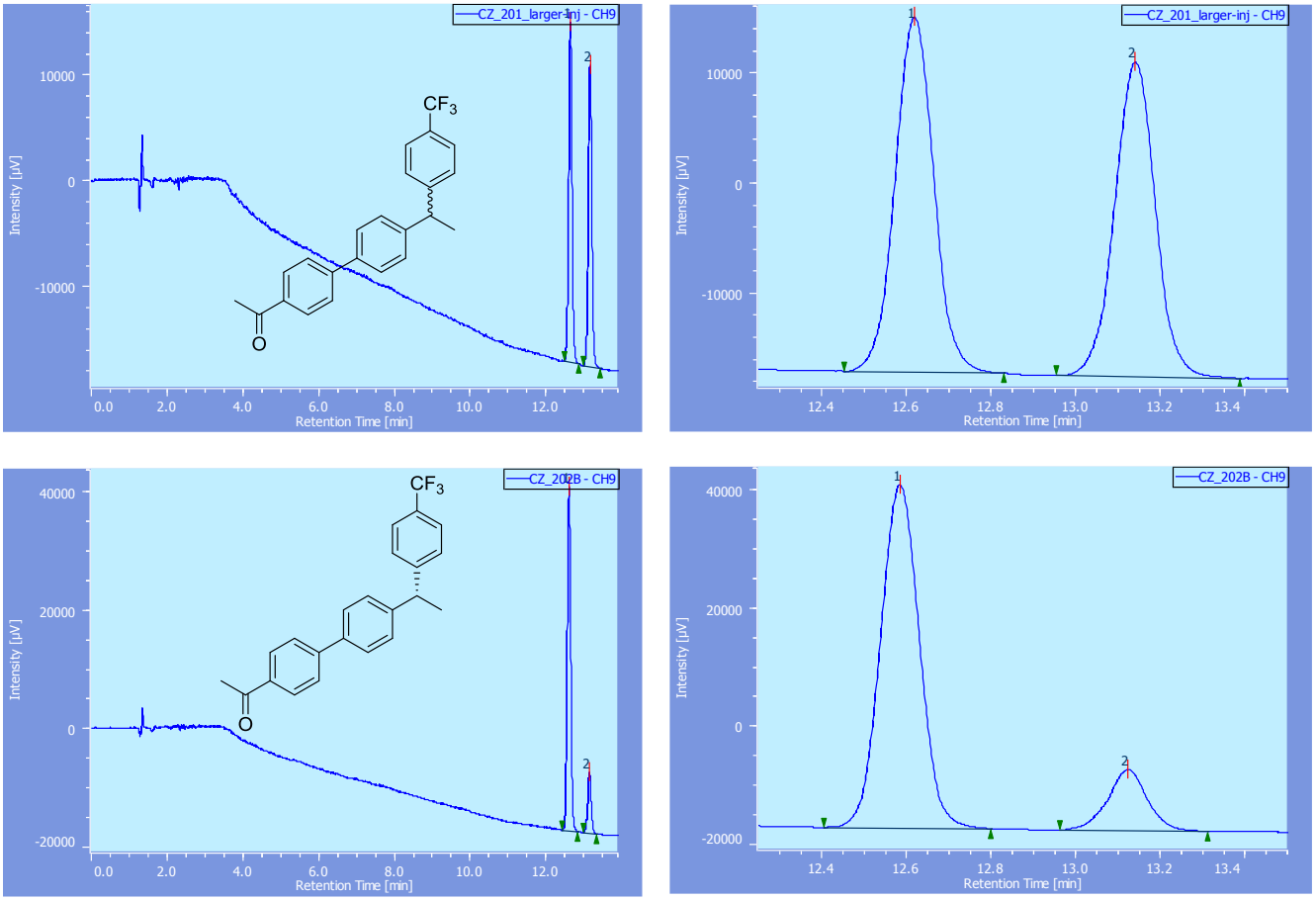
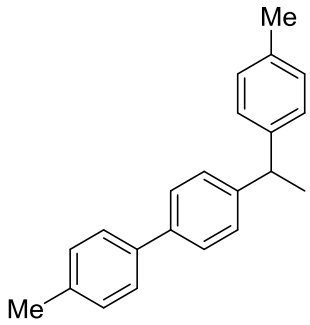


Figure 4-15 Chiral SFC spectra for **102**, racemate (above) and scalemic (below).

Di-arylation of diboronate 42 and Determination of Yield by ^{1}H NMR

4-methyl-4'-(1-(p-tolyl)ethyl)-1,1'-biphenyl



A 1 dram vial with a magnetic stir bar in a glovebox was charged with diboronate **42** (35.8 mg, 0.1 mmol, 1.0 equiv.), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 0.1 equiv.), PPh_3 (15.7 mg, 0.06 mmol, 0.6 equiv.), Ag_2O (80.8 mg, 0.35 mmol, 3.5 equiv.), 4-iodotoluene (76.3 mg, 0.35 mmol, 3.5 equiv.), and 1,2-dimethoxyethane (2.0 mL). The vial was sealed with a Teflon cap, removed from the glovebox, and heated to 70 °C for 40 hours. The reaction mixture was then cooled to room temperature and internal standard (200 µL of a solution of 18.0 mg 1,3,5-trimethoxybenzene in 1 mL $CHCl_3$) was added. An aliquot of the reaction was subjected to filtration through a pipette of silica gel with $CHCl_3$, concentrated *in vacuo* and subjected to ^{1}H NMR analysis to determine the yield of product (76%).

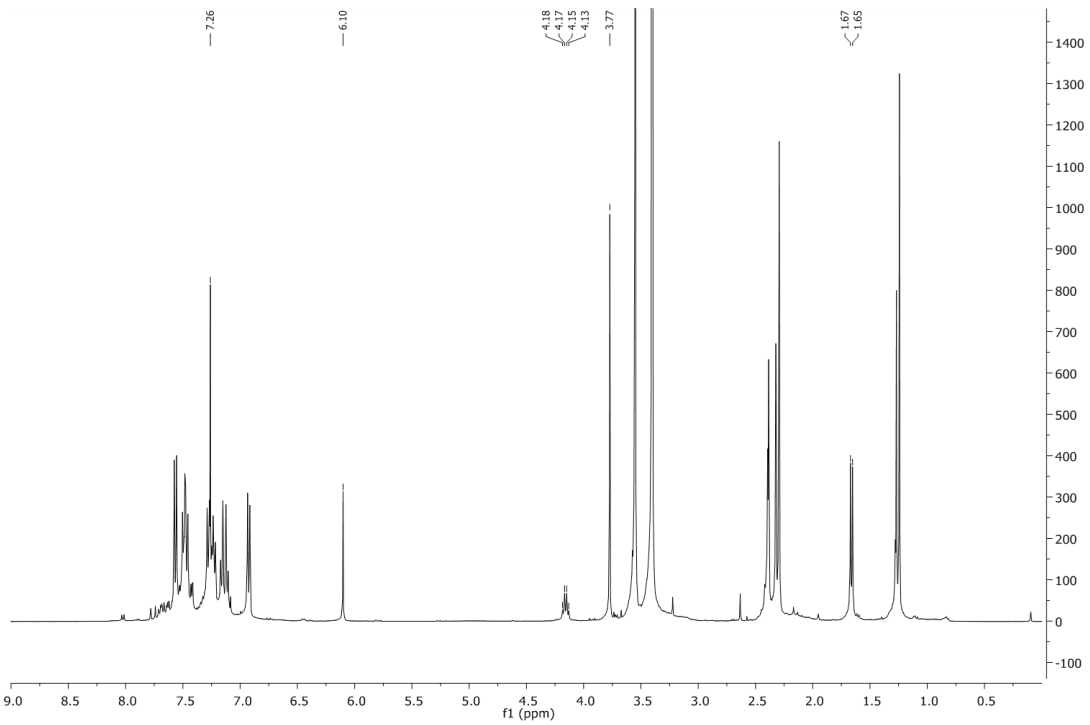


Figure 4-16 [1]H NMR of crude reaction mixture after diarylation for **42**.

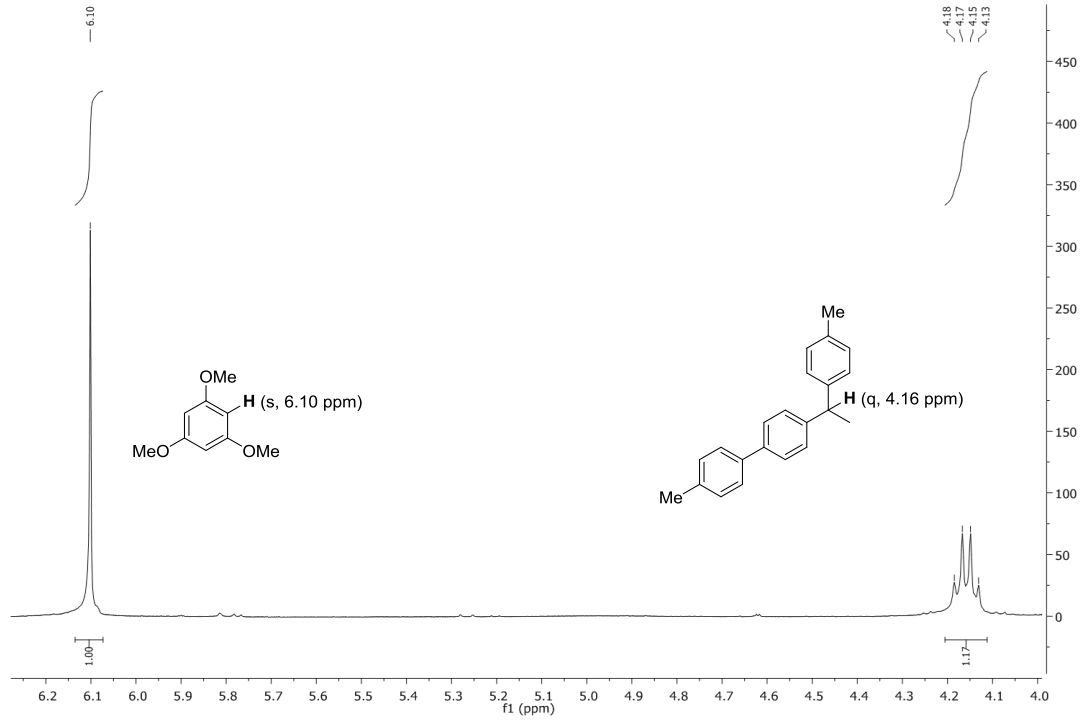
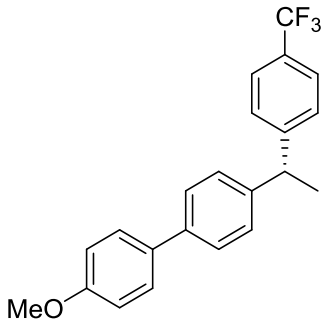


Figure 4-17 Expansion of [1]H NMR of crude reaction mixture after diarylation for **42**.

One-Pot Sequential Arylations of diboronate 42 and Determination of Yield by ^{1}H NMR

4-methoxy-4'-(1-(4-(trifluoromethyl)phenyl)ethyl)-1,1'-biphenyl



A 1 dram vial with a magnetic stir bar in a glovebox was charged with diboronate **42** (35.8 mg, 0.1 mmol, 1 equiv.), $Pd_2(dba)_3$ (0.92 mg, 0.001 mmol, 0.01 equiv.), P(*t*-Bu)$_3$ (0.5 mg, 0.0024 mmol, 0.024 equiv.), CsF (50.1 mg, 0.33 mmol, 3.3 equiv.), 4-bromoanisole (20.6 mg, 0.11 mmol, 1.1 equiv.), and THF (0.25 mL). The vial was sealed with a teflon cap, removed from the glovebox, and heated to 60 °C for 24 hours. The vial was then cooled to room temperature and returned to the glovebox. The vial was charged with $Pd(dba)_2$ (4.6 mg, 0.008 mmol, 0.08 equiv.), PPh_3 (12.5 mg, 0.05 mmol, 0.5 equiv.), Ag_2O (111.2 mg, 0.48 mmol, 4.8 equiv.), 4-iodobenzotrifluoride (40.8 mg, 0.15 mmol, 1.5 equiv.), and 1,2-dimethoxyethane (2.0 mL). The vial was sealed with a teflon cap, removed from the glovebox, and heated to 70 °C for 16 hours. The reaction mixture was then cooled to room temperature and internal standard (200 µL of a solution of 18.0 mg 1,3,5-trimethoxybenzene in 1 mL $CHCl_3$) was added. An aliquot of the reaction was subjected to filtration through a pipette of silica gel with $CHCl_3$, concentrated *in vacuo* and subjected to ^{1}H NMR analysis to determine the yield of product (16%).

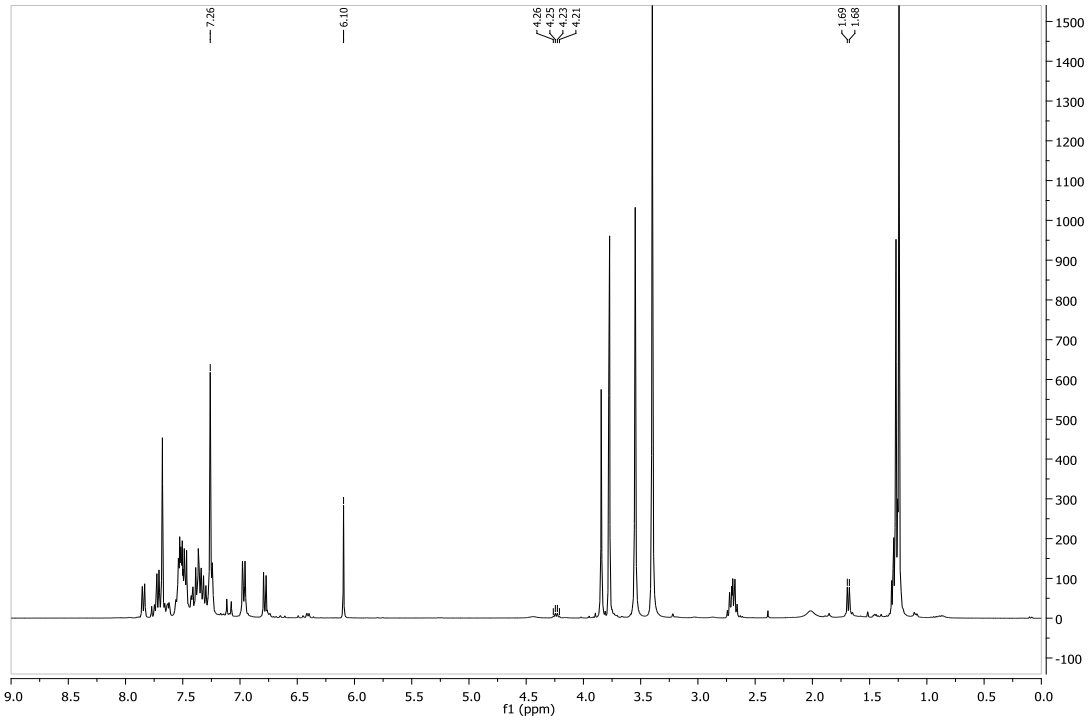


Figure 4-18 ^{1}H NMR of crude reaction mixture after diarylation for **42**.

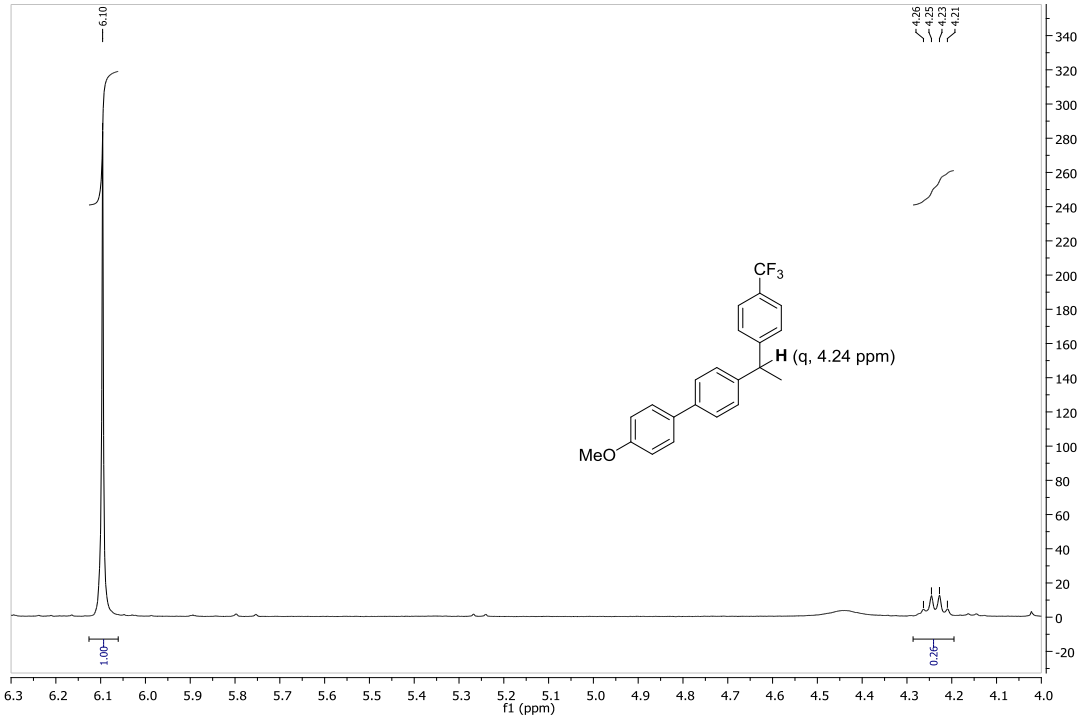


Figure 4-19 Expansion of ^{1}H NMR of crude reaction mixture after diarylation for **42**.

4.7 References

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4.8 Appendix

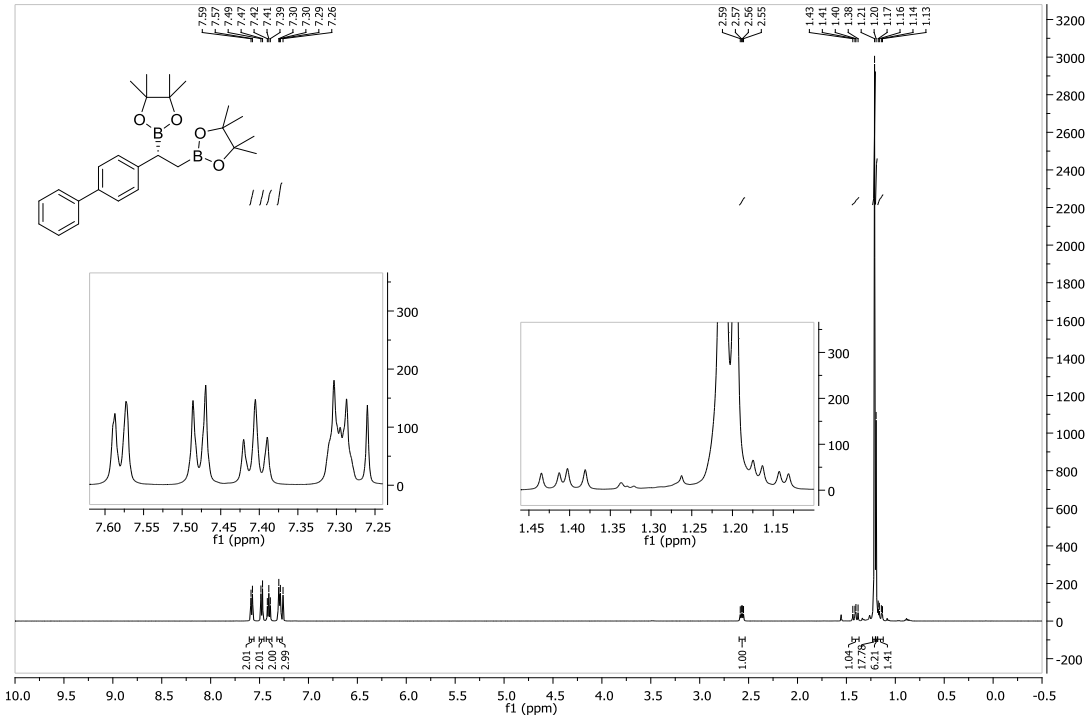

Figure 4-20 ^{1}H NMR of **46**.

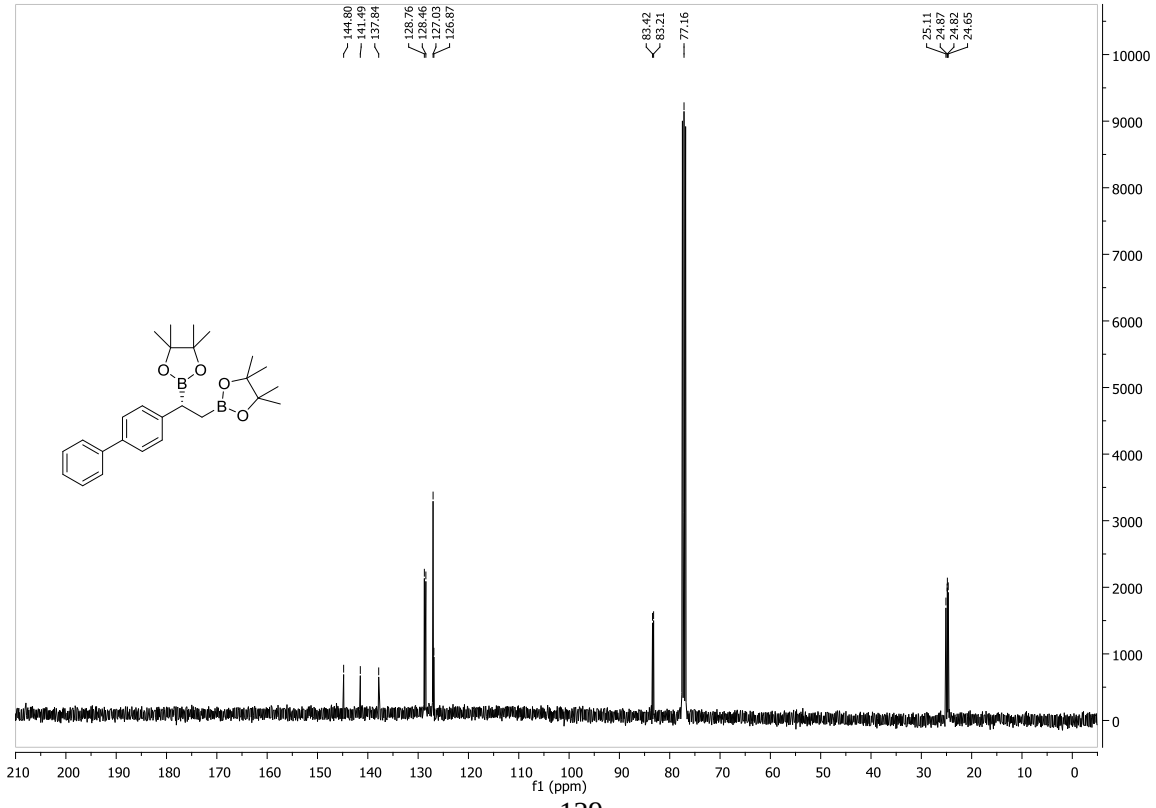

Figure 4-21 ^{13}C NMR of **46**

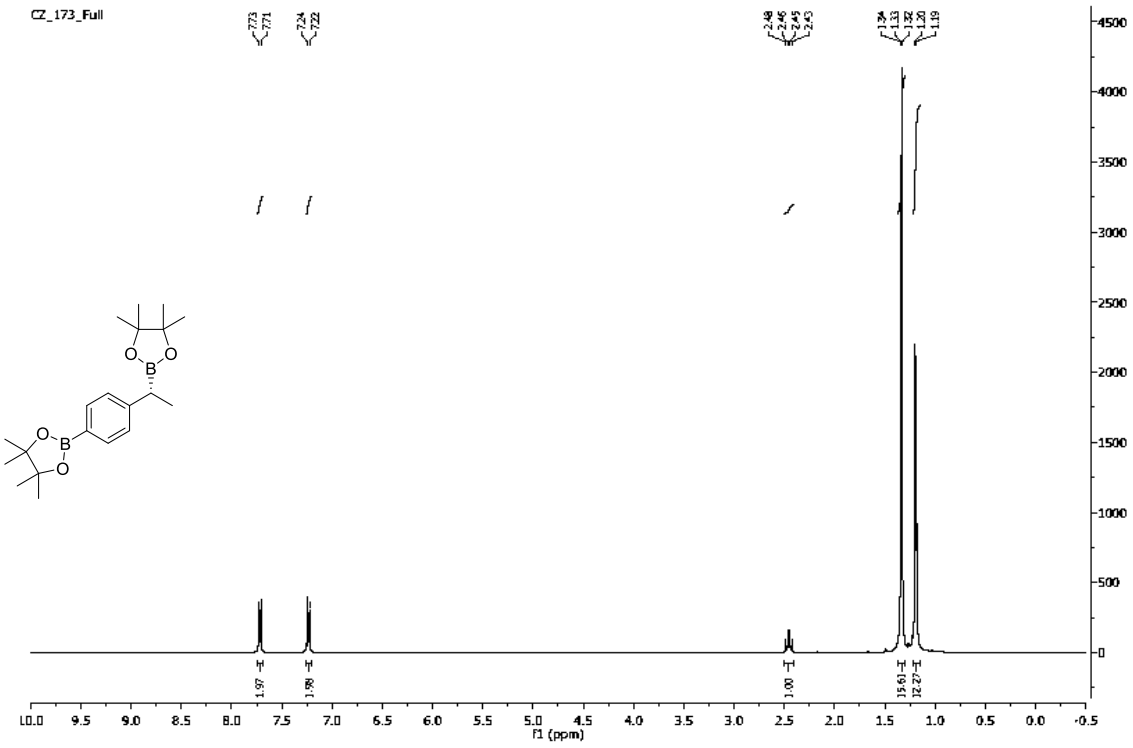

Figure 4-22 ^{1}H NMR of **42**

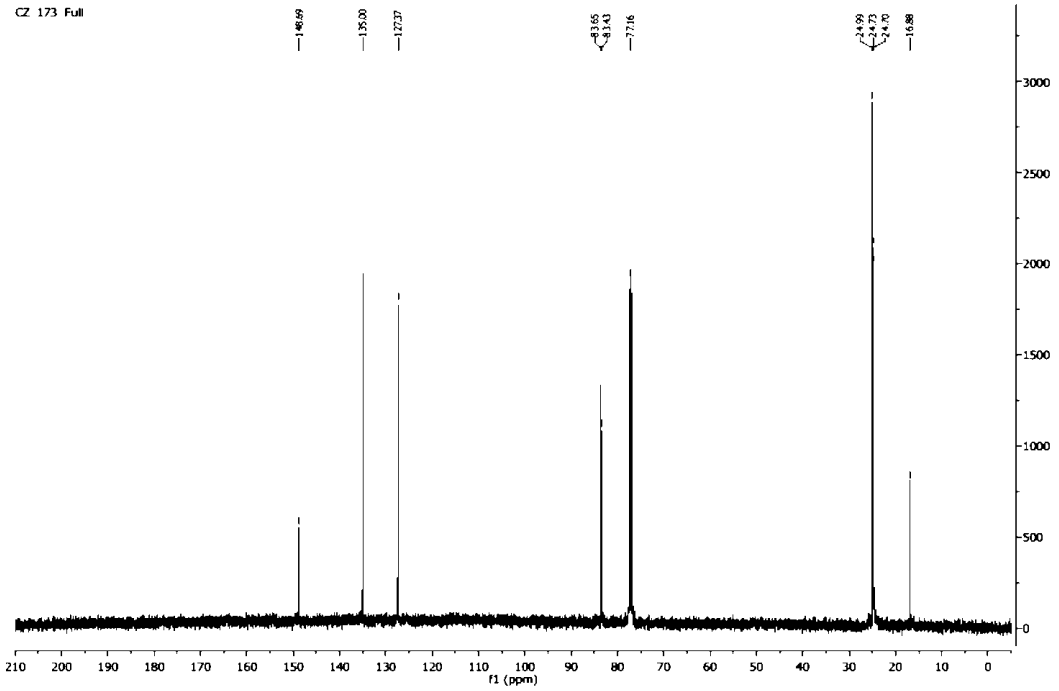

Figure 4-23 ^{13}C NMR of **42**

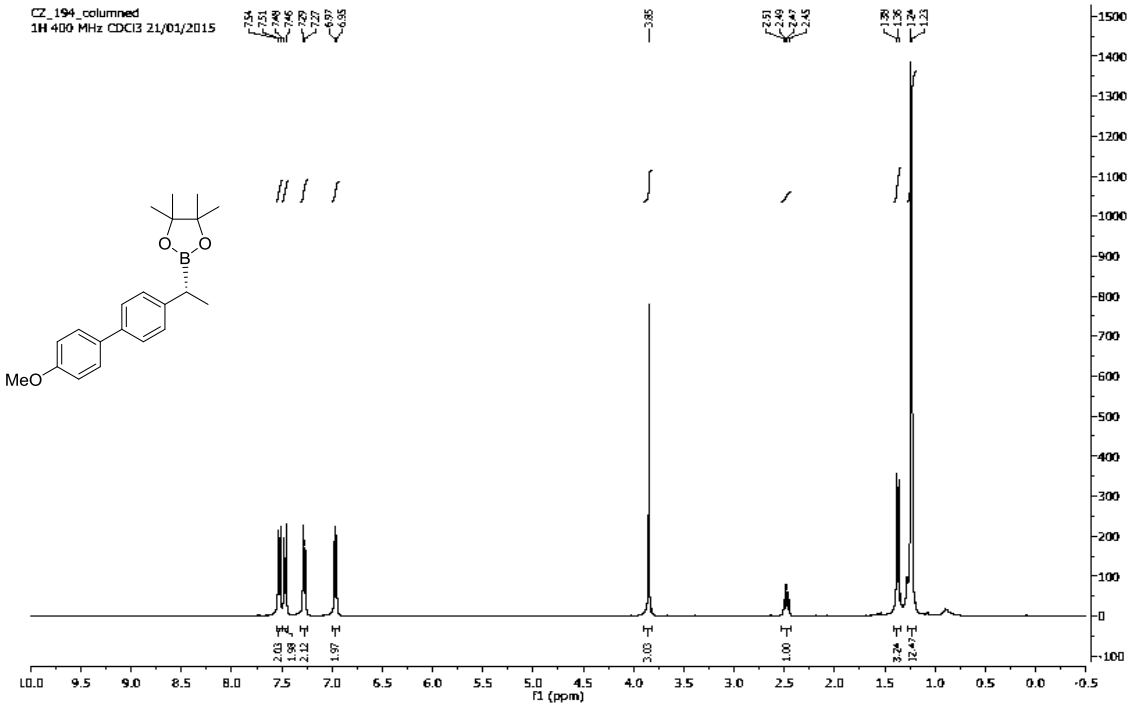

Figure 4-24 ^{1}H NMR of **50**

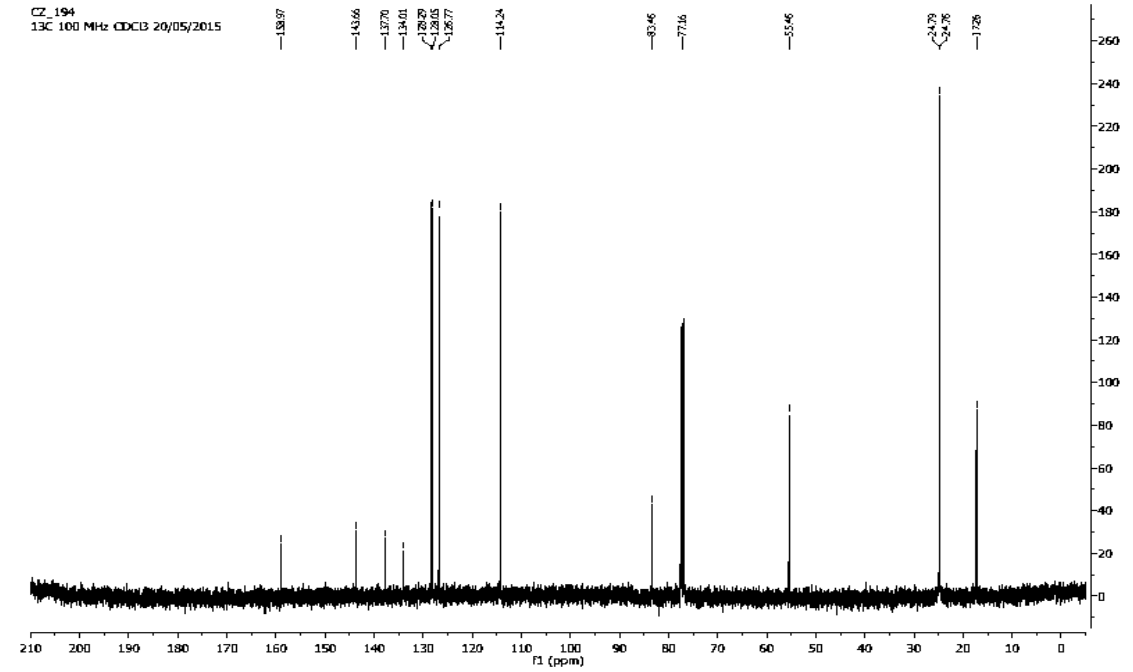

Figure 4-25 ^{13}C NMR of **50**

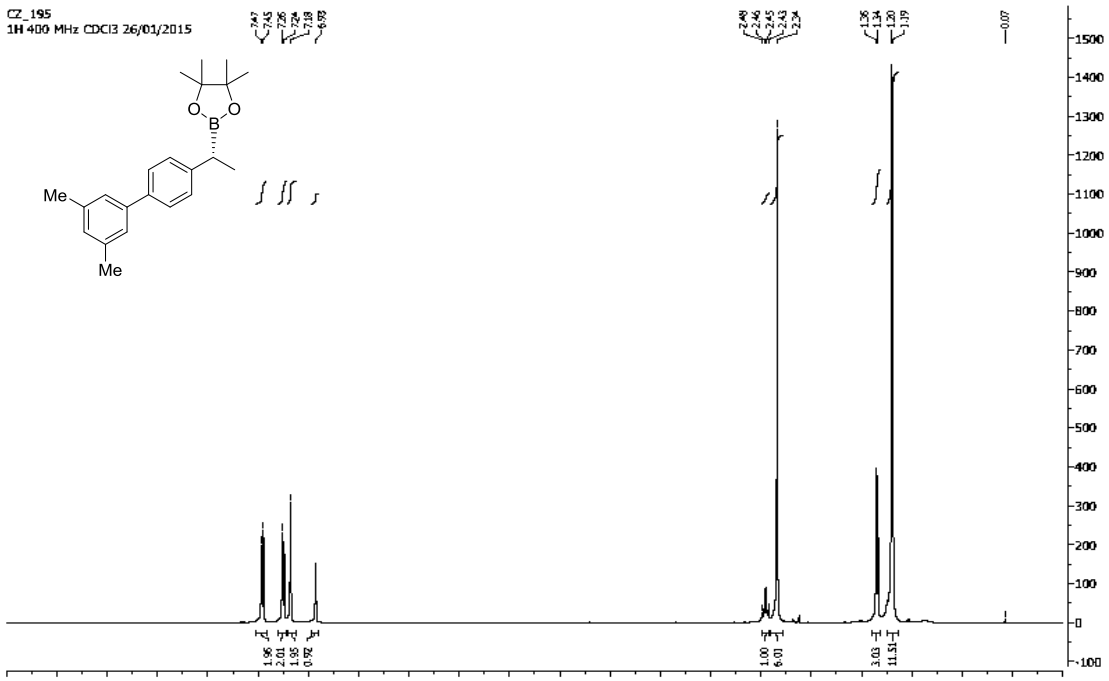

Figure 4-26 ^{1}H NMR of **94**

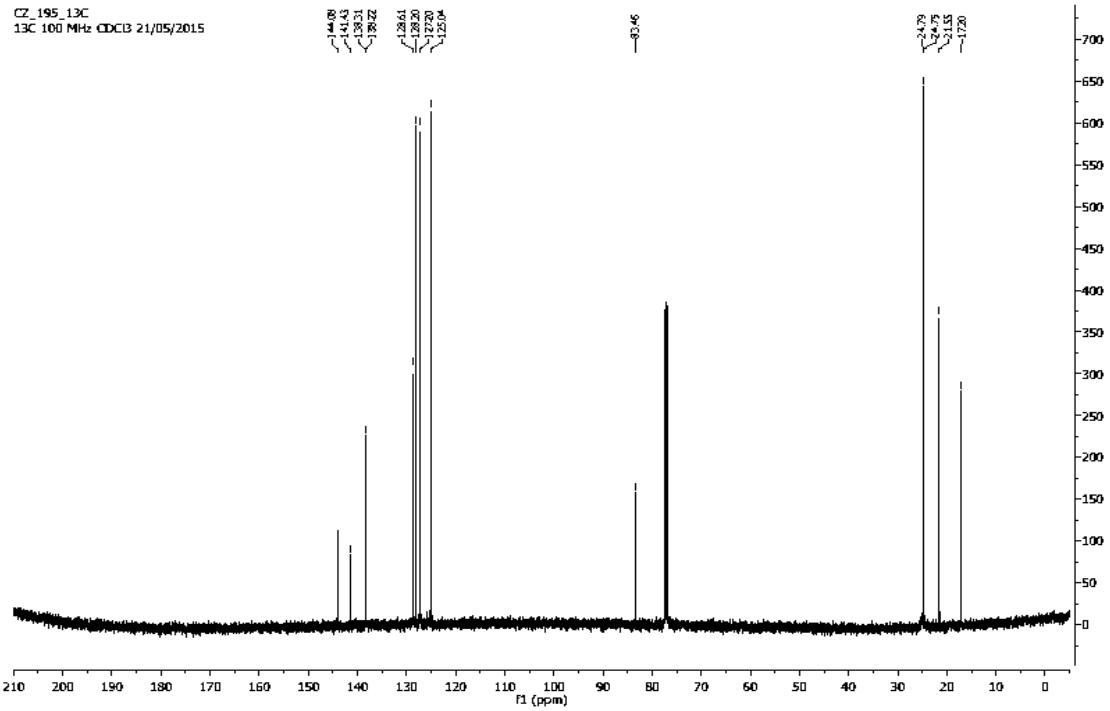

Figure 4-27 ^{13}C NMR of **94**

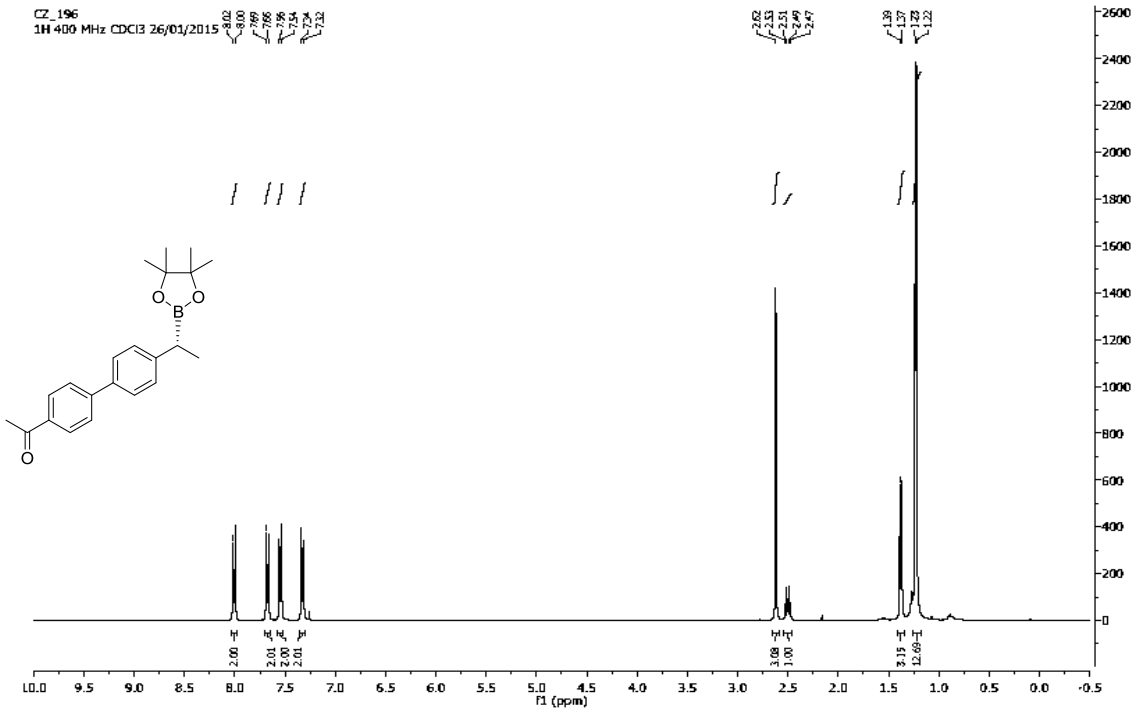

Figure 4-28 ^{1}H NMR of **95**

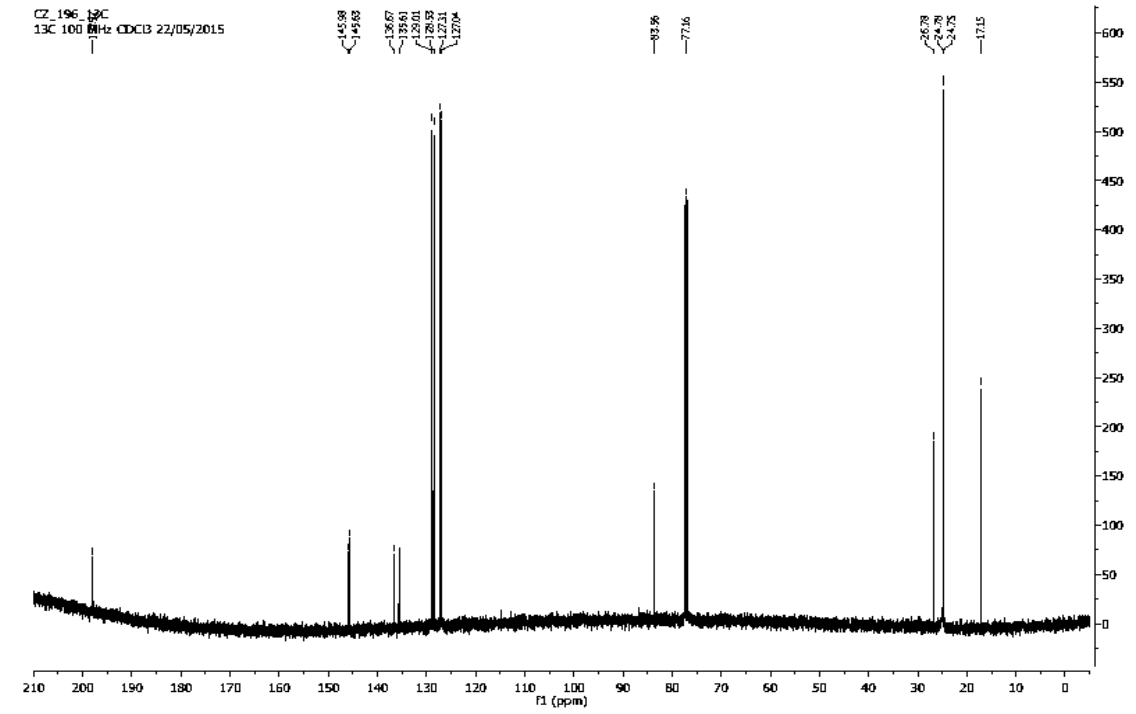

Figure 4-29 ^{13}C NMR of **95**

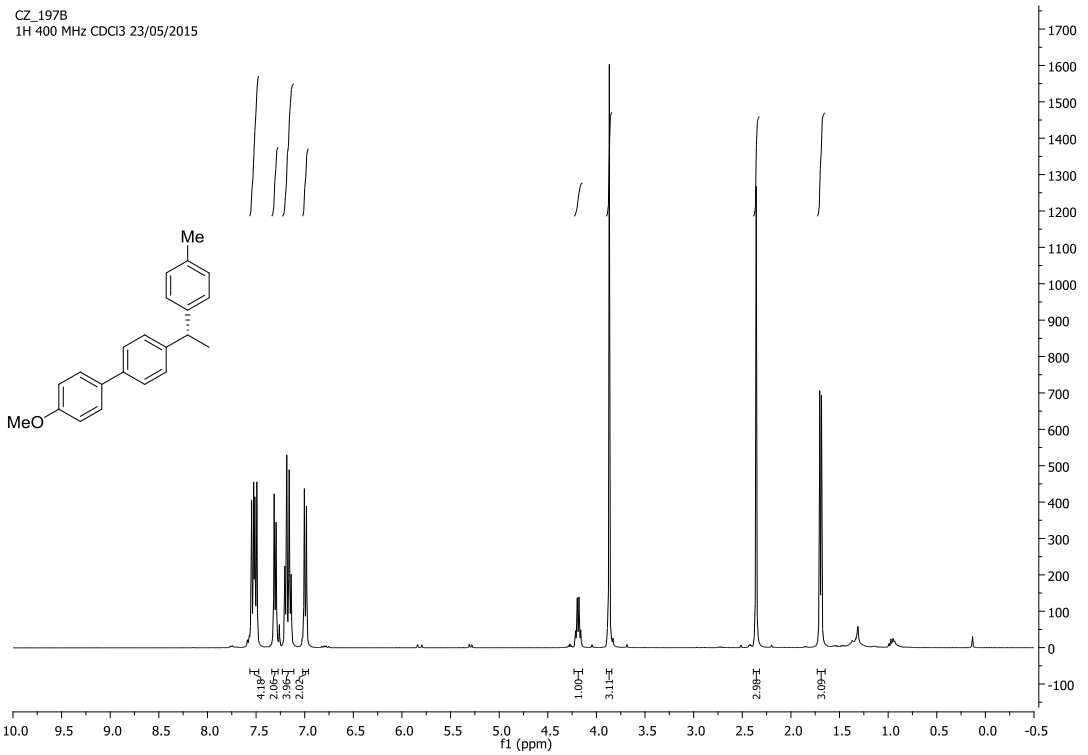

Figure 4-30 ^{1}H NMR of **99**

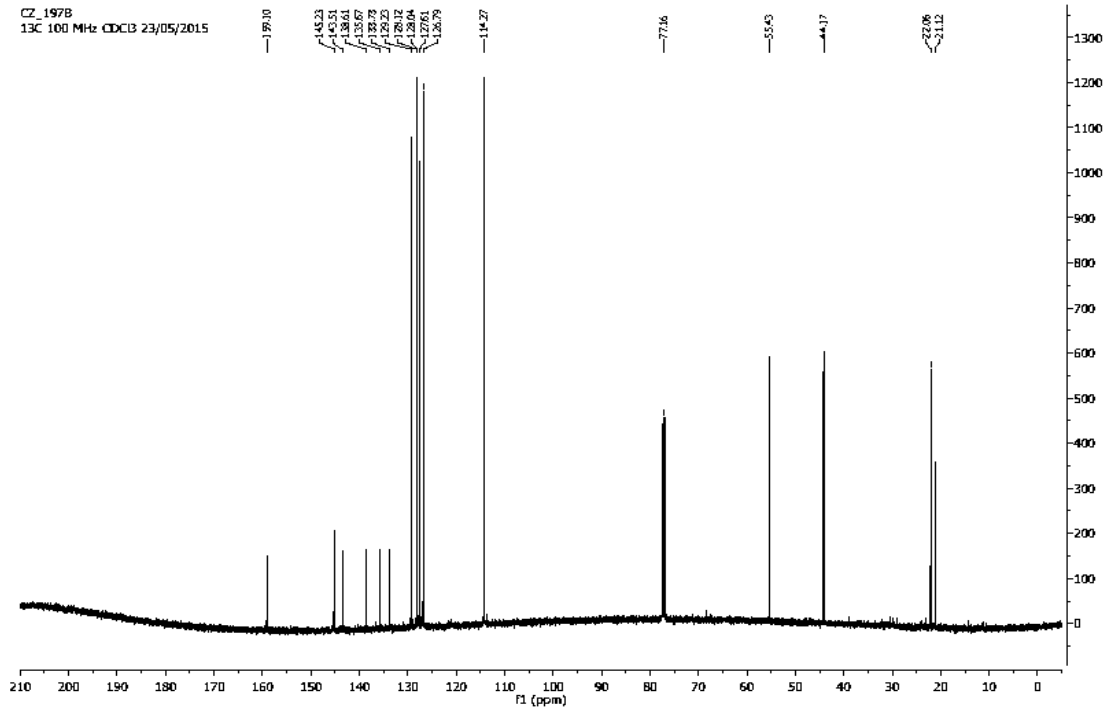

Figure 4-31 ^{13}C NMR of **99**

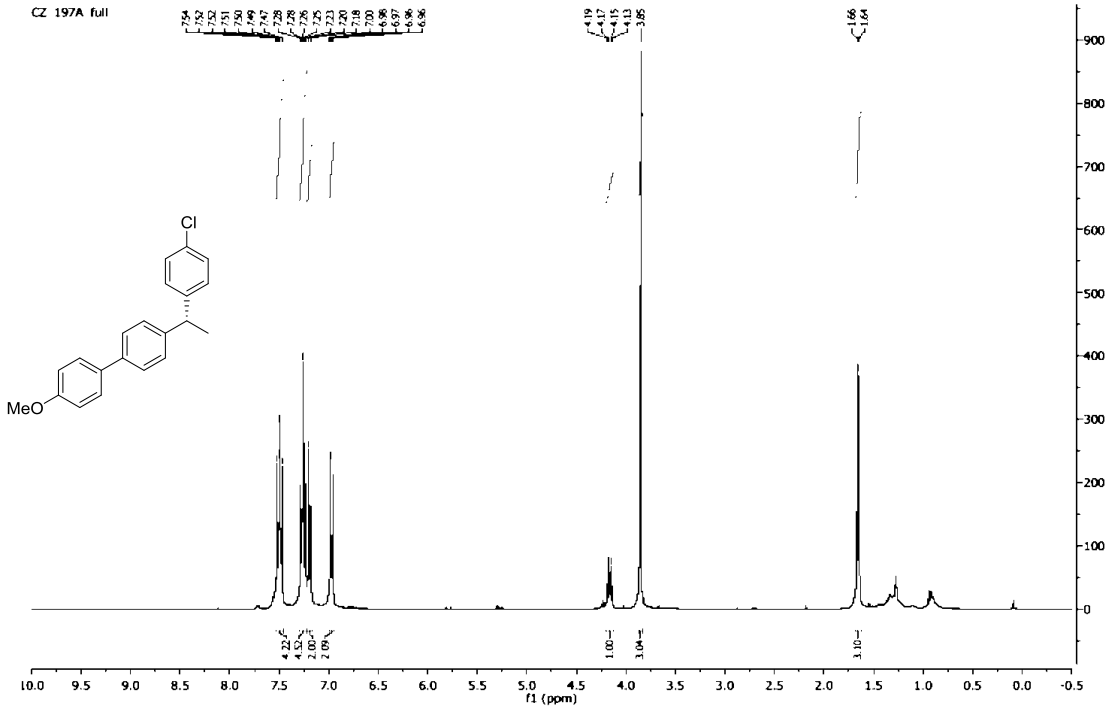

Figure 4-32 ^{1}H NMR of **96**

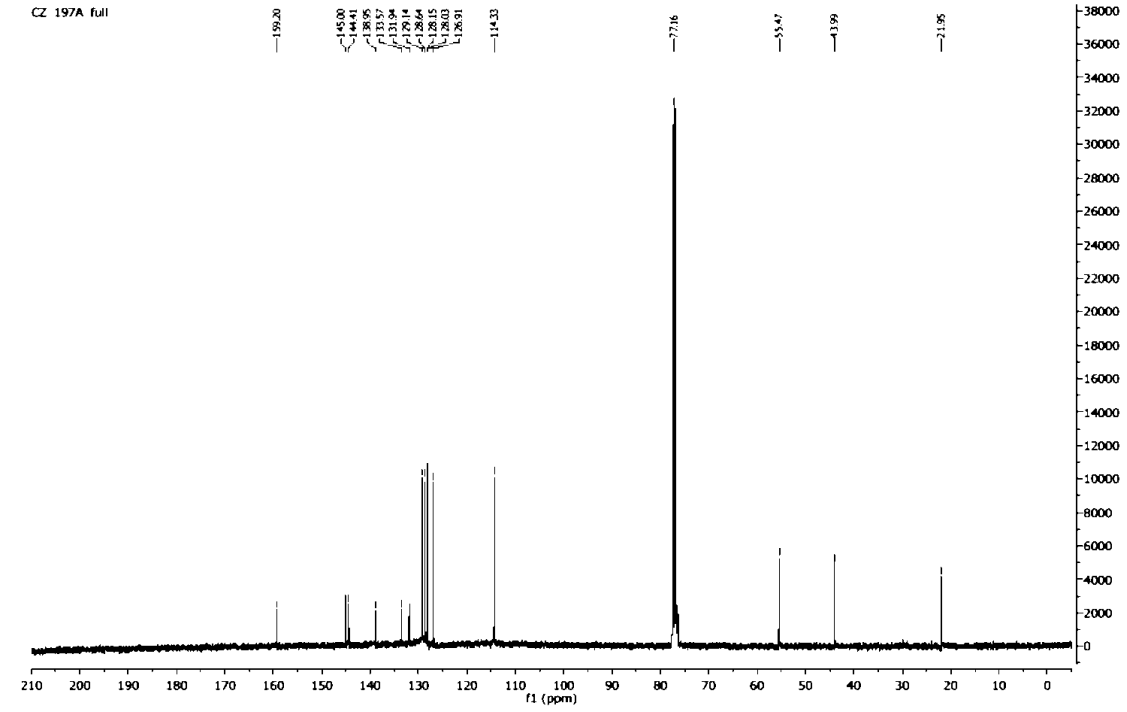

Figure 4-33 ^{13}C NMR of **96**

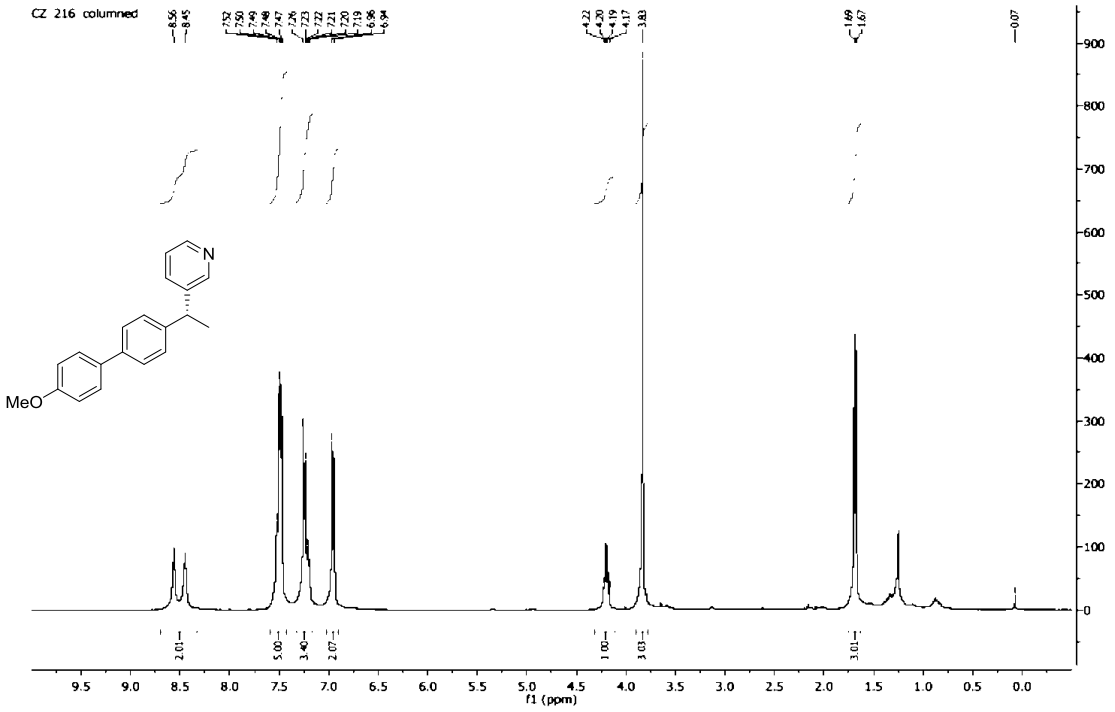

Figure 4-34 ^{1}H NMR of **100**

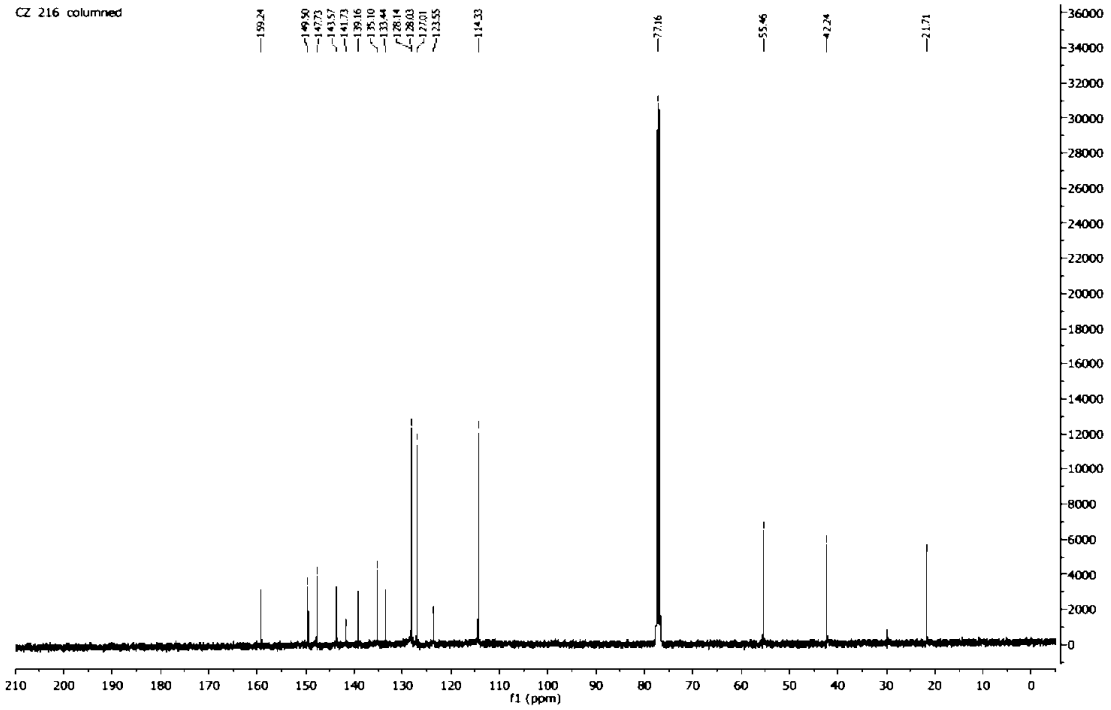

Figure 4-35 ^{13}C NMR of **100**

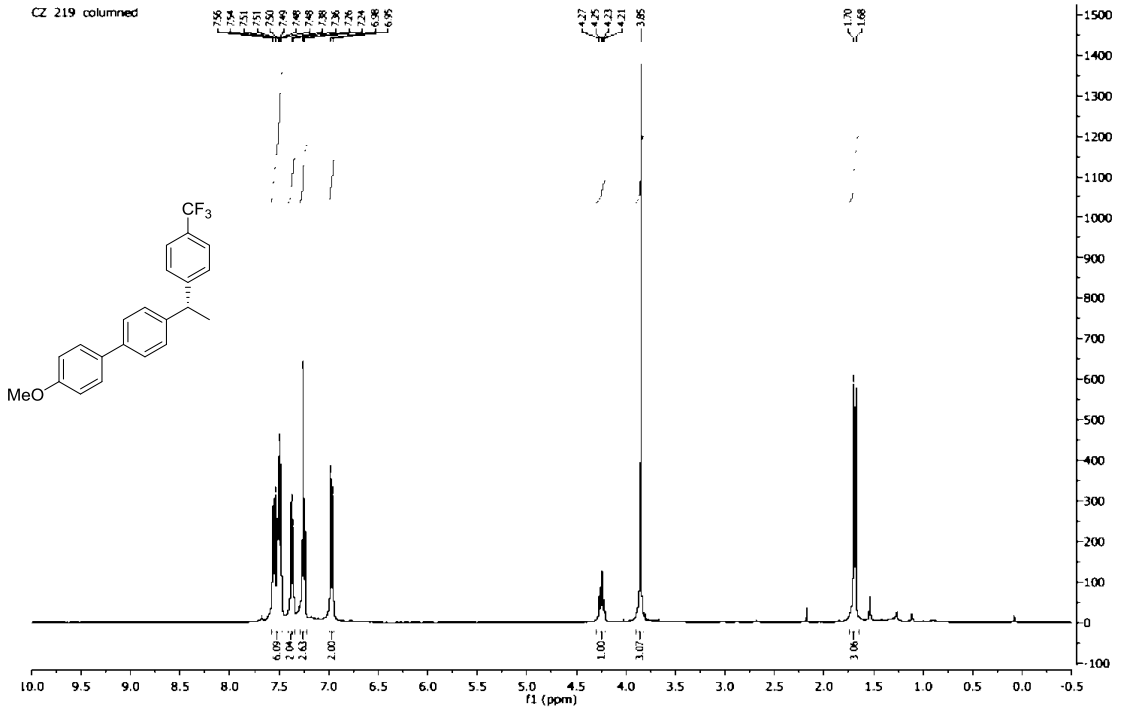

Figure 4-36 ^{1}H NMR of **97**

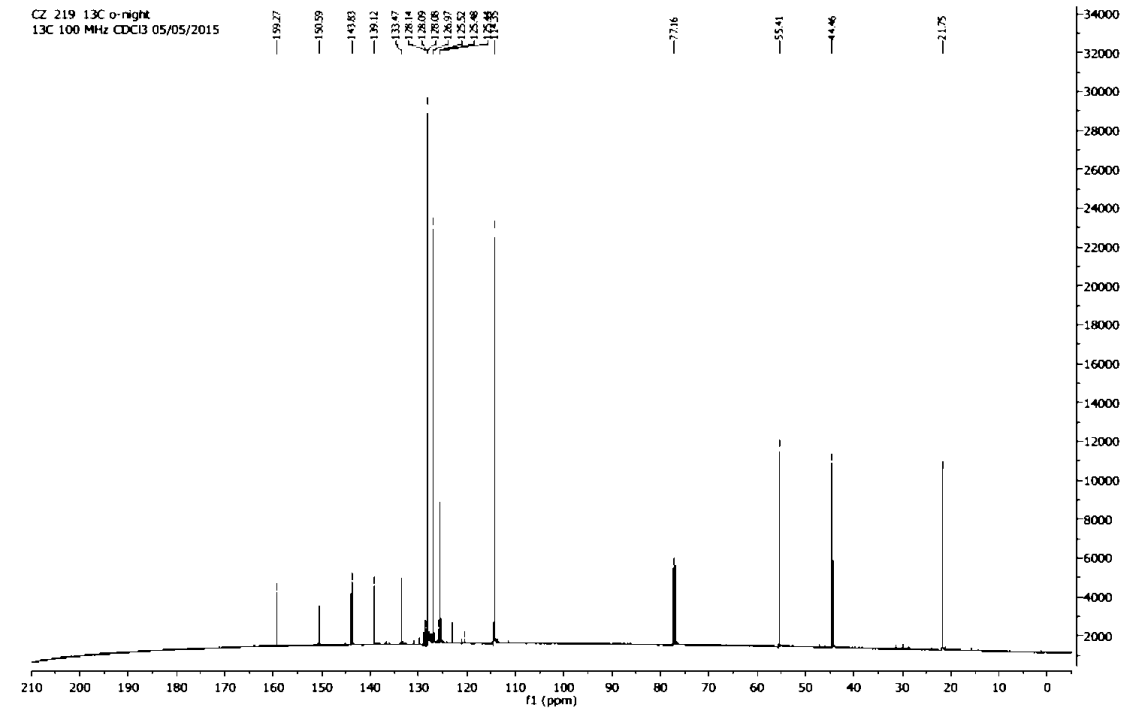

Figure 4-37 ^{13}C NMR of **97**

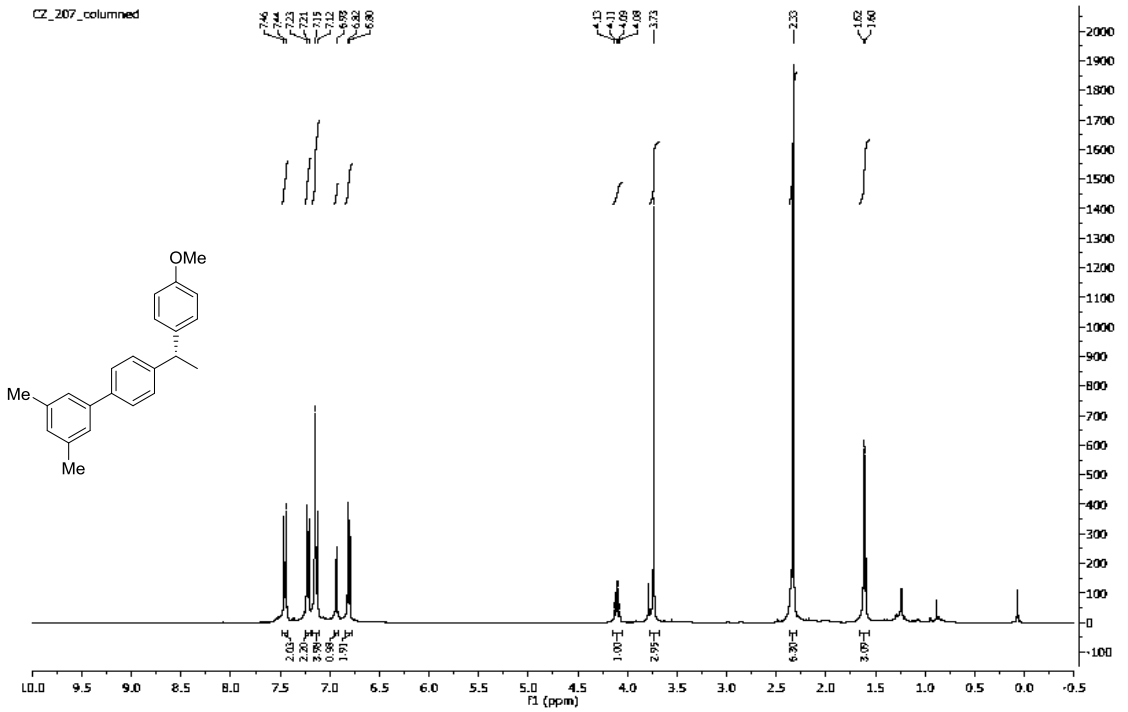

Figure 4-38 ^{1}H NMR of **101**

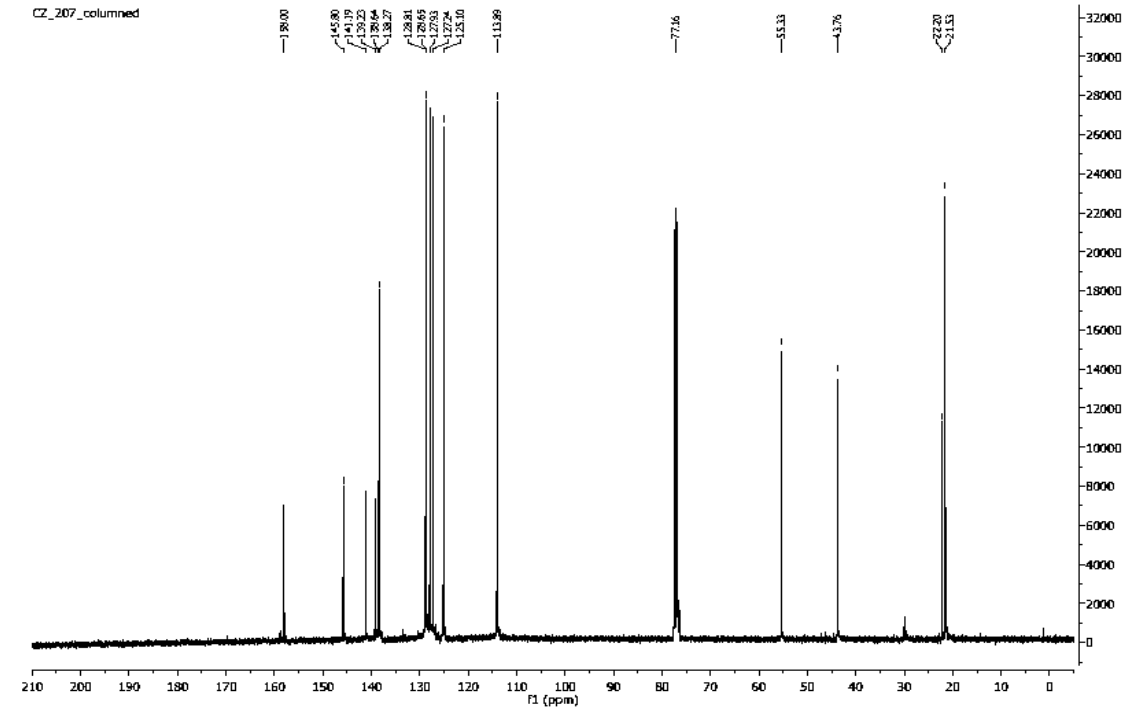

Figure 4-39 ^{13}C NMR of **101**

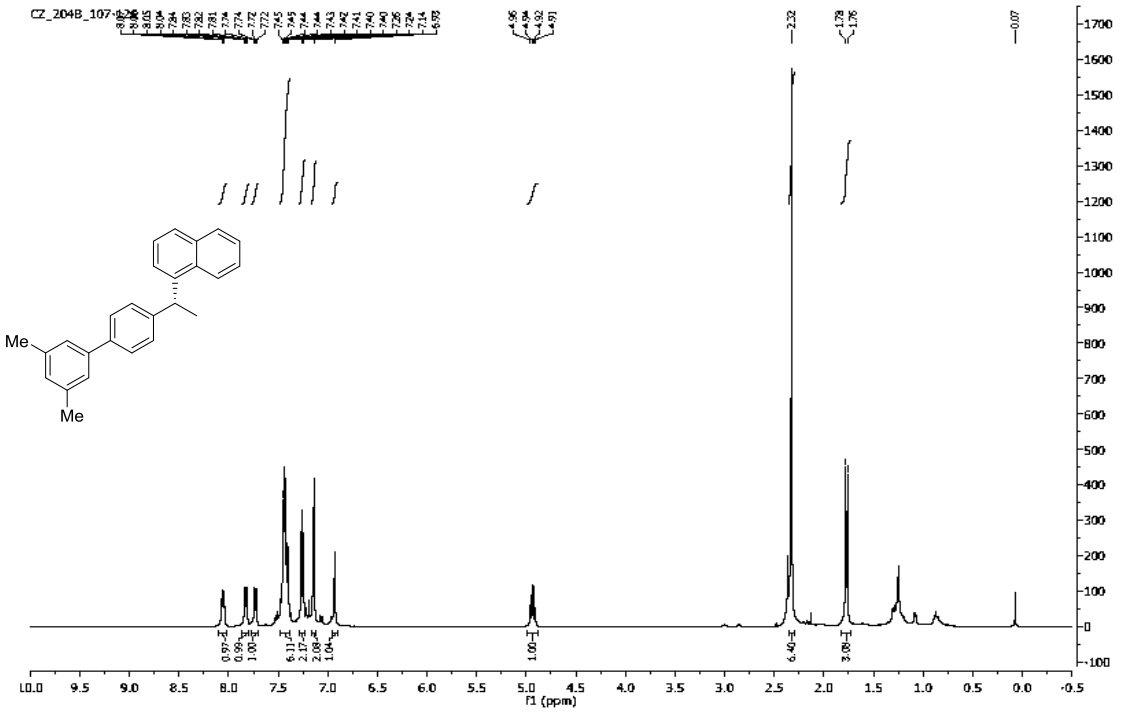

Figure 4-41 ^{1}H NMR of **98**

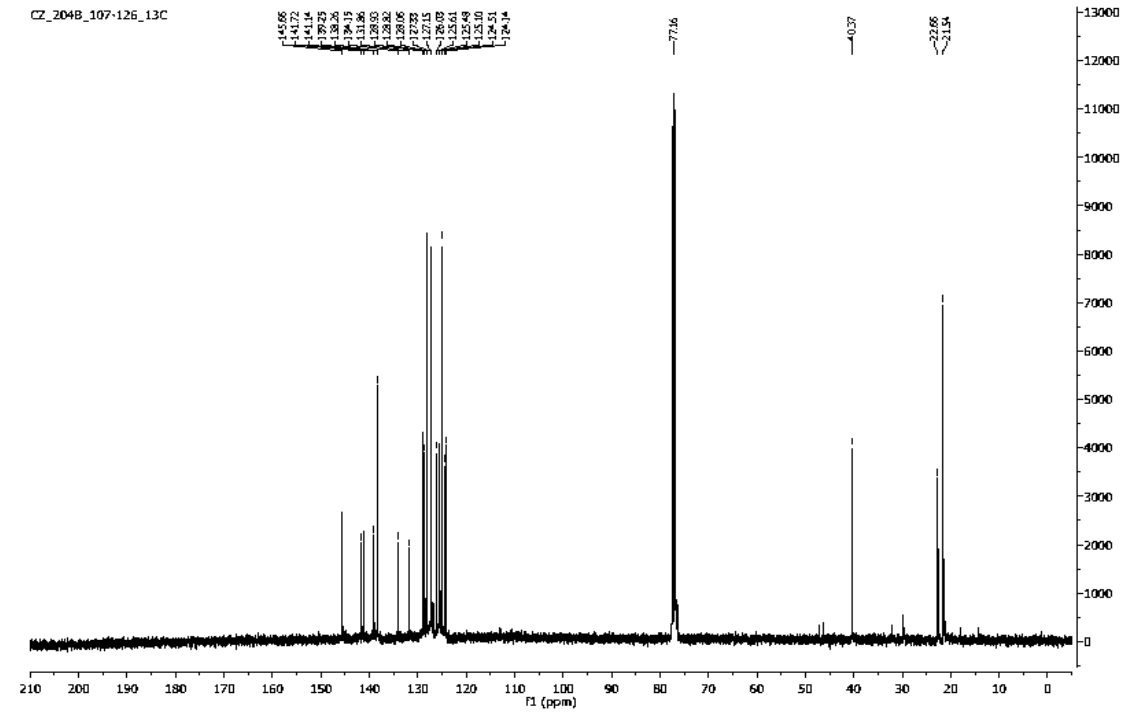

Figure 4-40 ^{13}C NMR of **98**

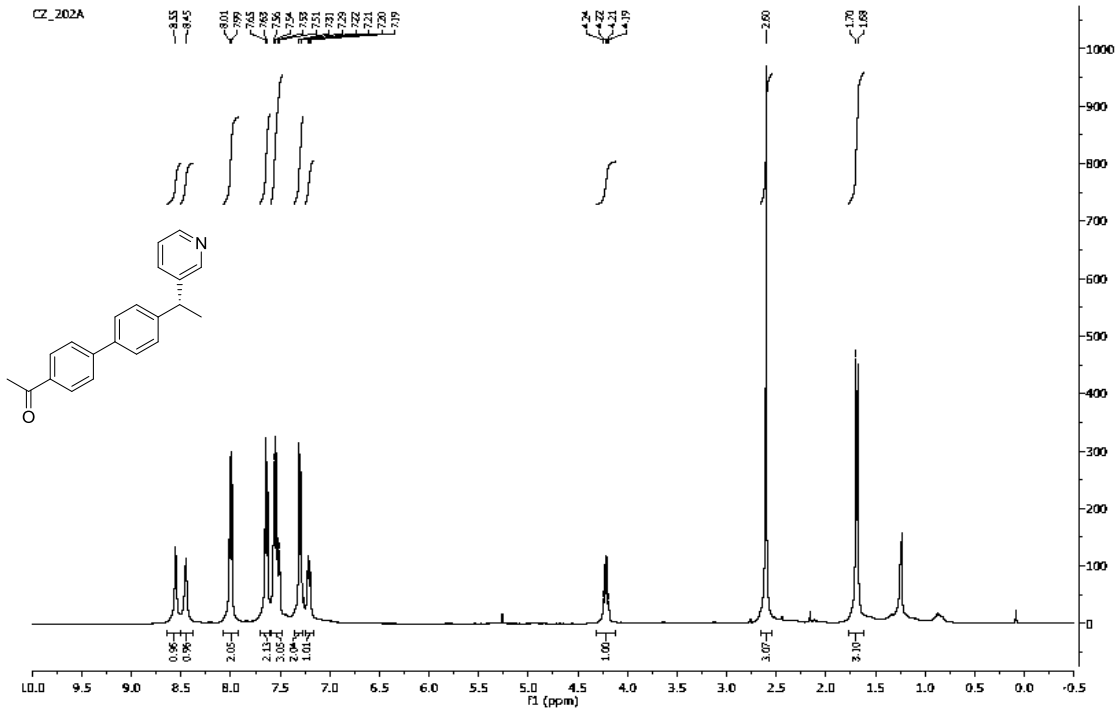

Figure 4-42 ^{1}H NMR of **103**

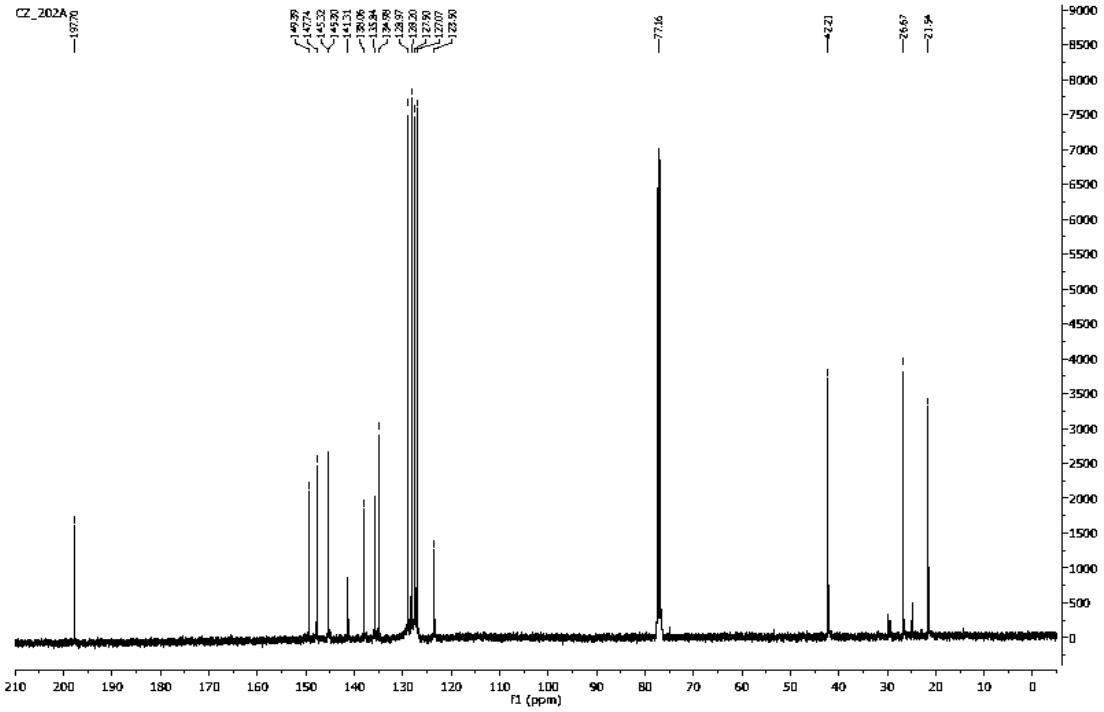

Figure 4-43 ^{13}C NMR of **103**

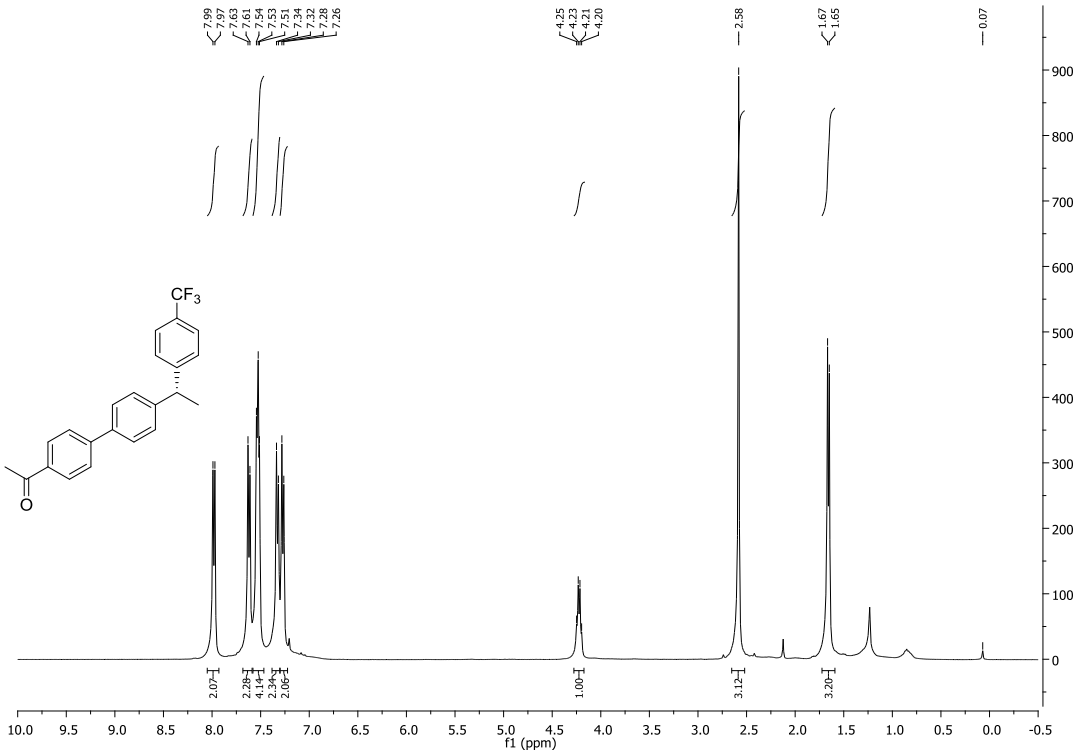

Figure 4-44 ^{1}H NMR of **102**

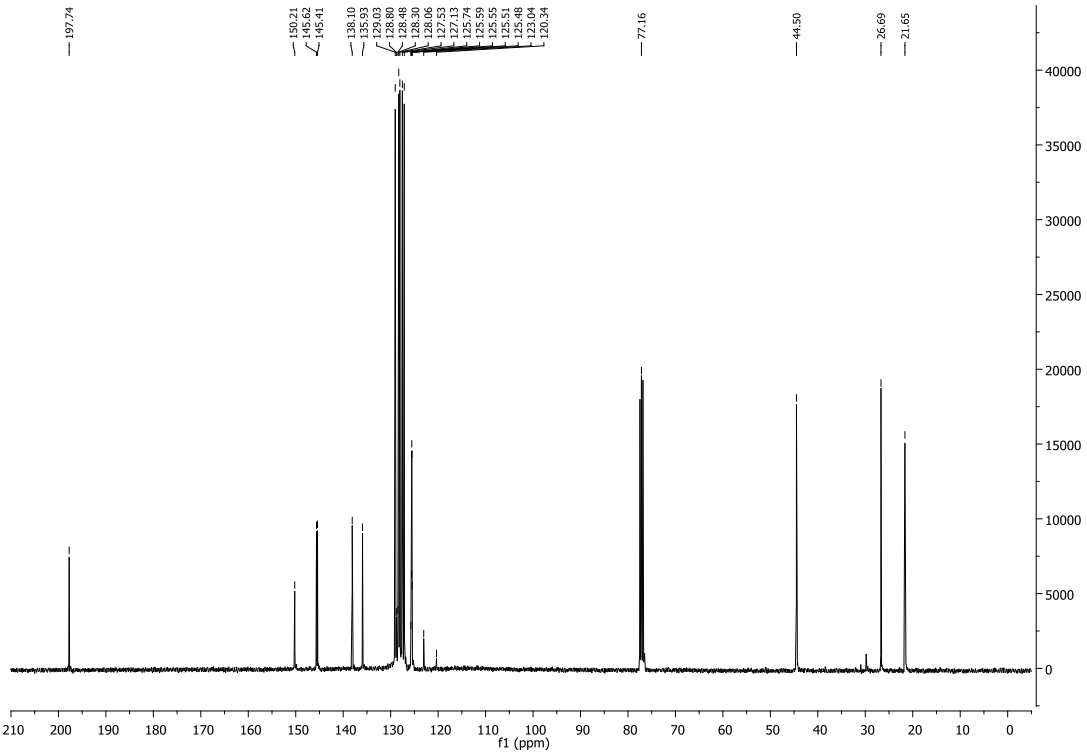

Figure 4-45 ^{13}C NMR of **102**

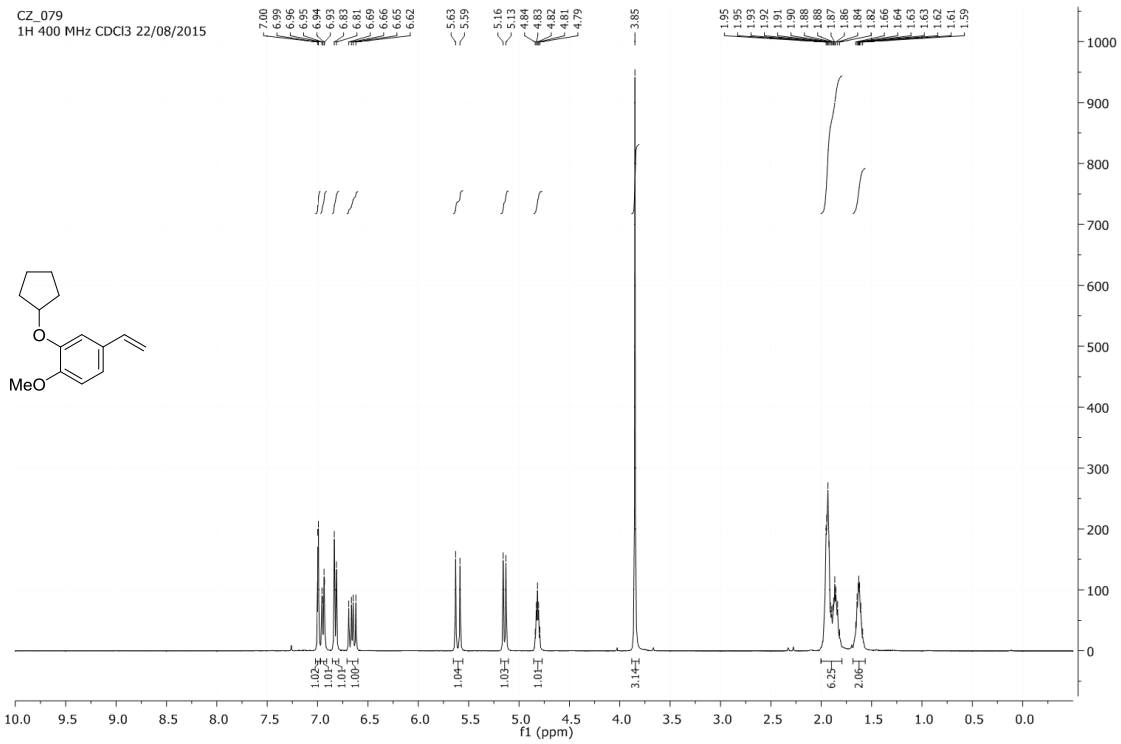

Figure 4-46 ^{1}H NMR of **47**

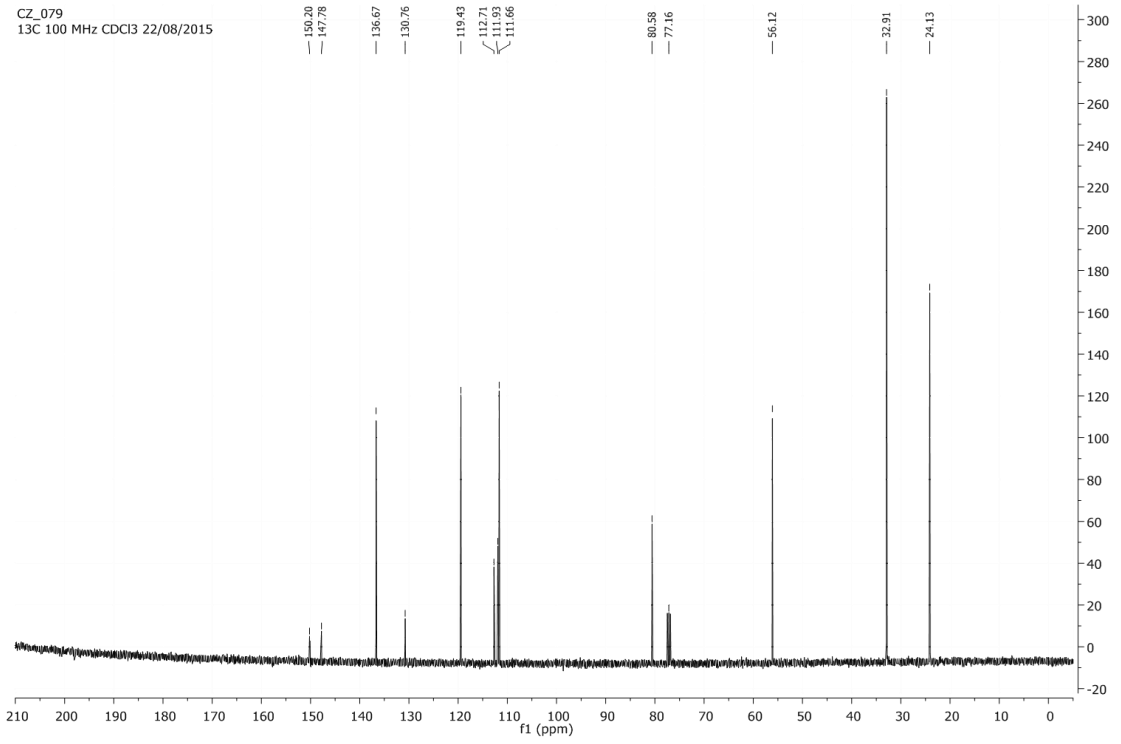

Figure 4-47 ^{13}C NMR of **47**

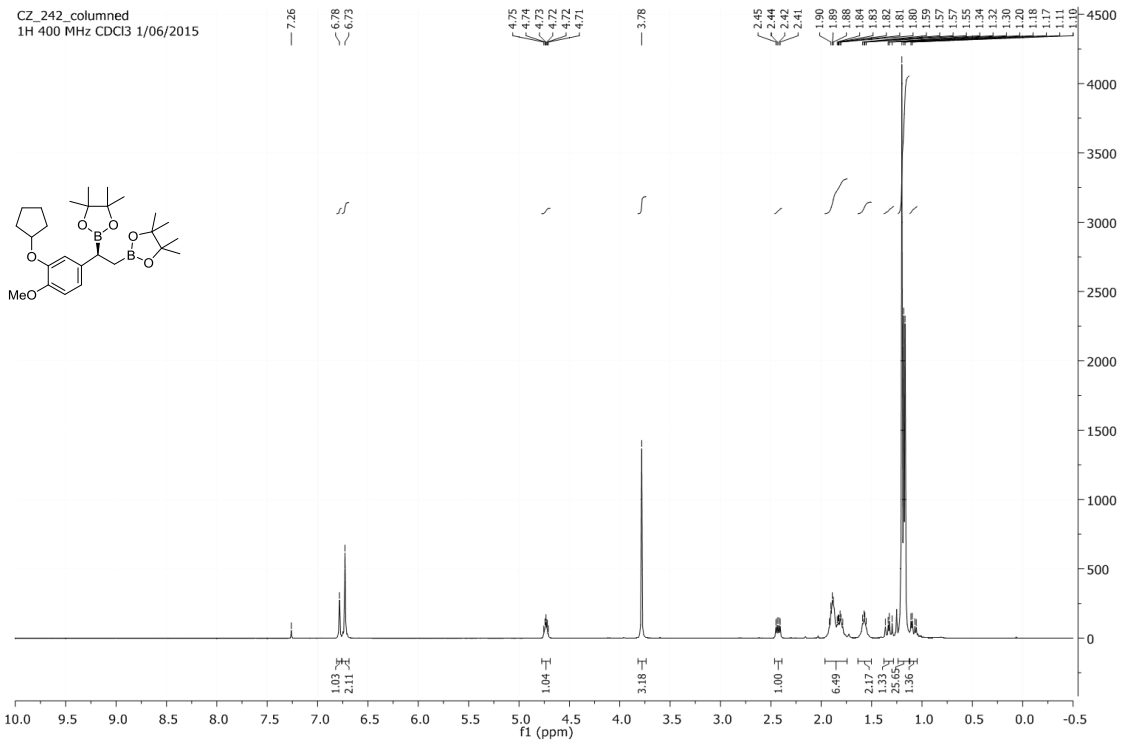

Figure 4-48 ^{1}H NMR of **49**

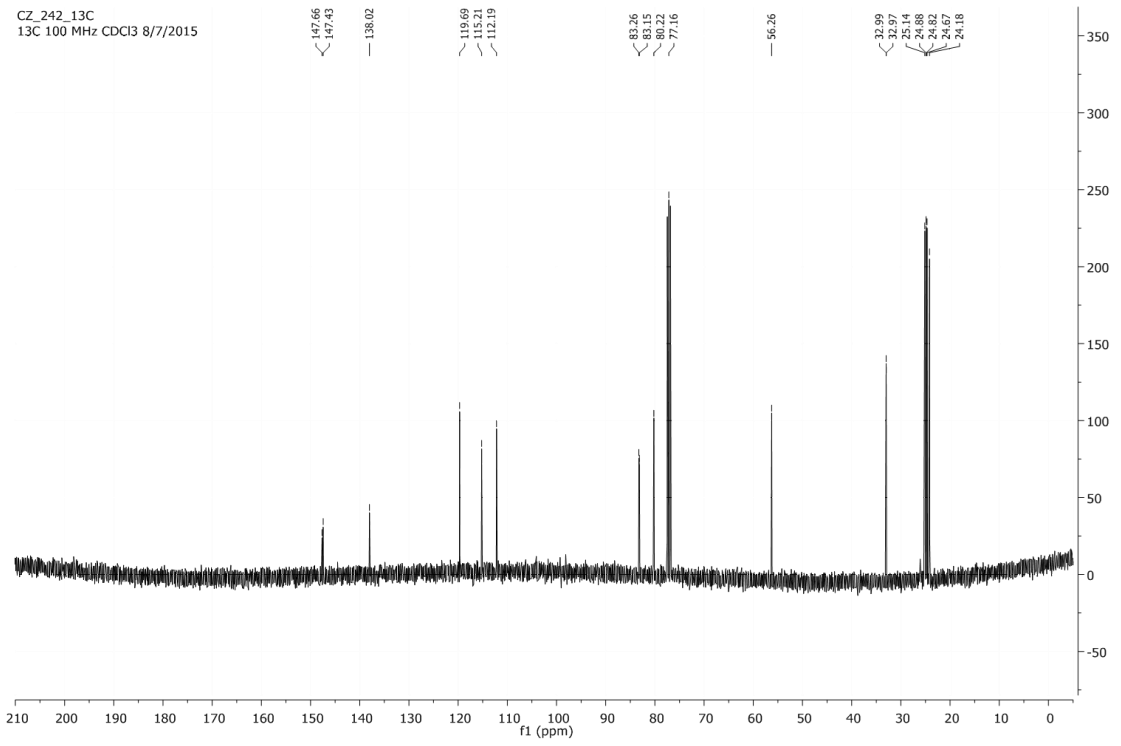

Figure 4-49 ^{13}C NMR of **49**