INVESTIGATIONS INTO CROSS-COUPLING OF SECONDARY ORGANOBORONIC ESTERS

by

Amy Marie Holland

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Abstract

Until recently, secondary organoboronic esters were not viable substrates in the Suzuki-Miyaura cross-coupling reaction; however under recently reported conditions from the Crudden group[1], which includes the addition of silver oxide to a palladium/phosphine catalyst system, this coupling can now be achieved.

This thesis centres on optimizing the reaction conditions and expanding the substrate scope of this difficult but important secondary coupling. Optimal coupling conditions, for the example reaction of 4-iodoacetophenone and (R)-pinacol(1-phenylethyl)boronate, were found to be 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, 1.5 eq. Ag_2O and 1.5 eq. K_2CO_3 in DME at 85 °C for 24 h. This gave the desired coupling product in 64 % yield with 99.5 % retention of stereochemistry. Using this set of conditions, an array of aryl iodides were screened. The reaction conditions could not be extended to triflate or diazonium electrophiles.

Amide functionality is important in many natural products and pharmaceuticals. The extension of reaction conditions to amides possessing boronic ester functionality at the β-position was attempted; however, no conditions could be determined to generate the cross-coupling product. An α-substitution pattern would better exemplify the benzylic positioning found to work for the original substrates. Attempts to synthesize the α-substituted amide were made without success.

The optimal reaction conditions gave hope for differentiation between an aryl and a secondary aliphatic boronic ester. Using an aryl triflate to couple the aryl position and an aryl iodide to couple the aliphatic position, conditions for selective coupling were determined and applied to a one-pot procedure.

Acknowledgements

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List of Abbreviations

°C	degrees Celsius
9-BBD	9-borabicyclo[3.3.2]decane
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
ACN	acetonitrile
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
B:L	branched to linear ratio
BOC	*tert*-butyloxycarbonyl
Bu	butyl
cod	cyclooctadiene
cy	cyclohexyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DPPB	1,4-bis(diphenylphosphino)butane
dppf	(diphenylphosphino)ferrocene
EDCI	N-(3-demithylaminopropyl)-N'-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
e.r	enantiomeric ratio
eq.	equivalence
Et	ethyl
ether	diethylether
Fer	ferrocenyl
GC	Gas Chromatography
GC/MS	Gas Chromatography/Mass Spectrometry

Glyme	1,2-dimethoxyethane
h	hours
HBcat	catechol borane
HBpin	pinacol borane
^{i}Bu	*iso*-butyl
^{i}Pr	*iso*-propyl
L	ligand
M	metal centre
m	organometallic metal centre
Me	methyl
min	minutes
nbd	2,5-norbornadiene
NMR	nuclear magnetic resonance
o/n	over-night
OMe	methoxy
OTf	triflate
Pent	pentane
Ph	phenyl
PPh_3	triphenylphosphine
py	pyridine
QUINAP	1-(2-diphenylphosphino-1-napthyl)isoquinoline
Rbf	round-bottom flask
R or R’	alkyl, aryl, alkenyl
R.T.	room temperature
RuPhos	2-dicyclohexylphosphino-2’,6’-diisopropoxybiphenyl
s	seconds
^{s}Bu	*sec*-butyl
SPhos	2-dicyclohexylphosphino-2’,6’-dimethylbiphenyl
^{t}Bu	*tert*-butyl
THF	tetrahydrofuran
Tol	toluene
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Chapter 1: Introduction

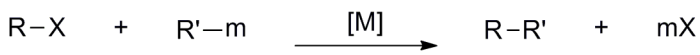
Many of the challenges faced in organic synthesis today are no longer centred on finding a route to the desired compound but on accomplishing it asymmetrically. Asymmetric or enantiomeric synthesis is the method of selectively generating one enantiomer of a chiral centre over that of the other. Employing this method of synthesis for the generation of chiral molecules is of great value to all of us; one example being its application in the pharmaceutical industry, where the two enantiomers of a drug can have significantly different properties. One of the most convenient methods for generating new carbon-carbon bonds enantiomerically is through the use of asymmetric transition metal-catalyzed cross-coupling reactions. Within this document, asymmetric cross-coupling methods and reagents will be discussed in detail, with particular attention paid to the preparation of 1,1-diarylethanes using this methodology.

1.1 Cross-Coupling Reactions

Carbon-carbon bonds have proven to be some of the most difficult, and important bonds to generate. Unlike functional group transformations, the generation of carbon-carbon bonds is important for assembling the backbone of the molecule and is critical in convergent syntheses. The importance of this reaction is reflected in the fact that, on average, over 110 publications have been published on this topic every year for the past decade.[2] Metal catalyzed cross-coupling reactions have become a mainstay of organic synthesis.[3] In general, cross-coupling reactions employ catalytic amounts of a metal complex, [M], to combine an organometallic reagent (R'-m, where R' = aryl group) with alkenyl or aryl halides and related compounds (R-X) to give a new coupled product (R-R'), as seen in Scheme 1.[4] Since the new bond is made at an sp^2-carbon centre, the generation of chiral products cannot be accomplished

and most research is now focused on expanding this system to sp^3-hybridized substrates to generate new enantiomerically enriched molecules.

Scheme 1: General Cross-Coupling Reaction[4]



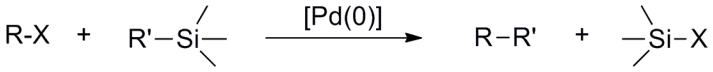
M = Ni or Pd
m = Mg, Li, Zn, Al, Zr, Sn, B, Si, Cu, In, Bi, Ti, etc.
R' = aryl or alkenyl
X = Cl, Br, I, OSO_2CF_3, $OPO(OR)_2$, etc.

As indicated in Scheme 1, there is a wealth of variability in R, R', m, X and [M], where the choice of these variables is based on the desired product, availability of starting materials and desired conditions. The availability of substrates (R-X and R'-m) has become increasingly larger over time as this area of research continues to grow and conquer new problems.

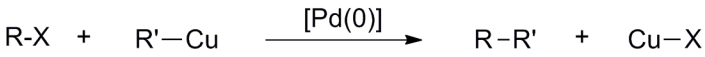
The field of cross-coupling is relatively young in comparison to traditional organic chemistry and much of the work originates in the early 1970s.[3] In 1972 Kumada[5] and Corriu[6] independently found that nickel could catalyze the reaction of organomagnesium compounds with alkenyl and aryl halides. Shortly after this, Murahashi reported the palladium catalyzed reaction of Grignard reagents;[7] however, it was Negishi who described the use of organoaluminum, zinc and zirconium in cross-coupling reactions.[8] The Suzuki-Miyaura reaction, which is the focus of this thesis, was described in 1979, and followed by other key coupling reactions, including the Hiyama, Sonogashira, and Stille cross-couplings (Scheme 2).[4] All of these reactions are all similar to each other in that the transmetallation of a variety of organometallic nucleophiles is the key step.

Scheme 2: Representative cross-coupling reactions[4]

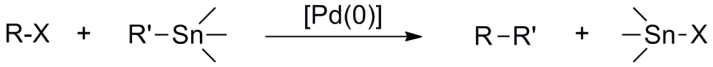
Hiyama



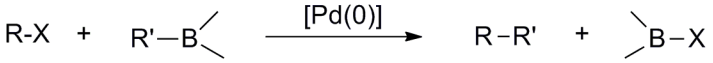
Sonogashira



Stille

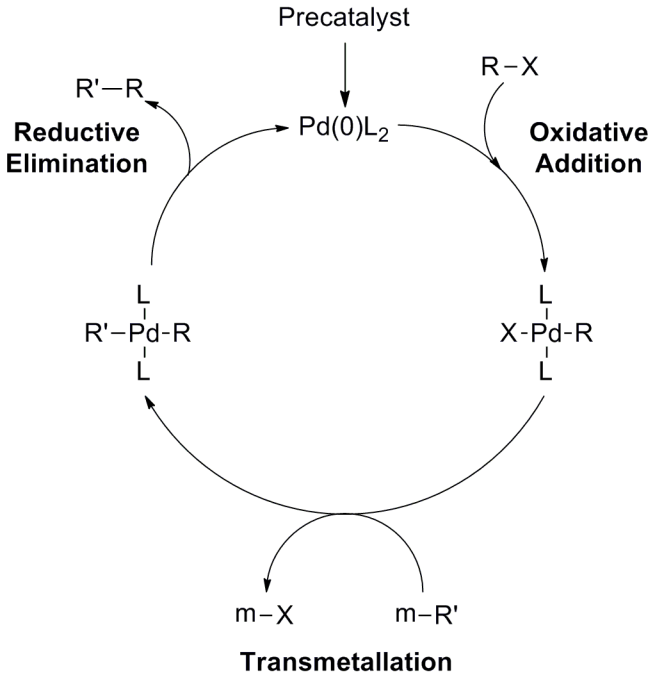


Suzuki-Miyaura



The cross-coupling reaction is composed of three key steps: oxidative addition, transmetallation and reductive elimination, as represented in Scheme 3.[4] Initially there is the formation of the active catalyst, which is either $Pd(0)L_2$ or Pd(0)L (where L = ligand) catalyst from a more stable $Pd(0)L_4$ or Pd(II) species, *via* the dissociation of the excess ligands or reduction of Pd by the ligands.[9] The organic halide (R-X) then undergoes oxidative addition to this Pd(0) species yielding R-Pd(II)-X. Following this, the key transmetallation step occurs, in which the R' moiety from R'-m is transferred to the Pd(II) species with loss of an equivalent of m-X. Finally, reductive elimination from R-Pd(II)-R' proceeds to give the desired product R-R' and regenerate the active Pd(0) catalyst species. Each of these processes will be discussed below for the palladium catalyzed Suzuki-Miyaura cross-coupling reaction, along with several side reactions that can occur over the course of such a reaction.

Scheme 3: Mechanism for a general Pd-catalyzed cross-coupling reaction[4]



1.2 Suzuki-Miyaura Cross-Coupling

One of the most influential cross-couplings to date is the Suzuki-Miyaura coupling. It is the number one reaction employed for generating carbon-carbon bonds in pharmaceutical synthesis,[10] largely due to the many advantages the Suzuki-Miyaura reaction offers over other cross-coupling reactions, such as: the commercial availability of substrates, mild reaction conditions, water stability, toleration of a wide range of functional groups, good regio- and stereoselectivity, insignificant effects of steric hindrance, low catalyst loading, application to one-pot synthesis, reduced toxicity compared to other cross-coupling reactions and the easy separation of resulting inorganic boron compounds.[11]

Typically in this cross-coupling reaction an alkenyl or aryl halide is combined with an alkenyl or aryl boronic acid or its ester, although 9-BBN derivatives can also be employed. In

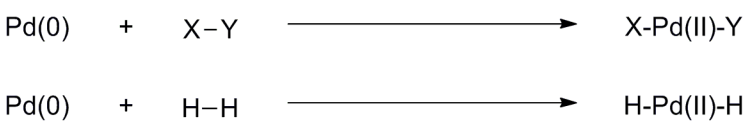
1979, Suzuki first reported the use of palladium to catalyze the coupling of alkenyl boranes and alkenyl halides to generate dienes for use in Diels-Alder reactions.[12] This procedure employed a catalytic amount of $Pd(PPh_3)_4$, with stoichiometric amounts of sodium alkoxide bases to afford the desired products with high regio- and stereoselectivity and yields. It was not long after this that the method was extended to the synthesis of biaryls, which is still the method of choice for the synthesis of these important molecules. In 1981, it was reported that phenyl boronic acid could be coupled to aryl halides using catalytic amounts of $Pd(PPh_3)_4$ and aqueous Na_2CO_3.[13] This reaction offered great advantages over the previous methods of forming sp^2-sp^2 carbon-carbon bonds due to the use of more benign boron species and the relatively simple reaction conditions. Since this first report, much research has been devoted to determining the precise details of the catalytic cycle, as well as extending the conditions to coupling other boron species and varying types of organic halides and pseudohalides.

1.2.1 Oxidative Addition

In the field of organometallic chemistry the term oxidative addition is defined differently than an organic chemist may refer to as an “oxidation”. During a cross-coupling catalytic cycle, oxidative addition is the addition of a molecule (X-Y) to Pd(0) with the cleavage of the X-Y covalent bond, forming two new bonds with the Pd metal center.[14] This process causes the palladium to formally increase its oxidation state by two, effectively going from Pd(0) to Pd(II); the palladium is thus “oxidized”. This process is similar to that of Grignard reagent preparation, where Mg(0) is oxidized to Mg(II) by the addition of an alkyl halide.[14] A key example that demonstrates the difference between an “oxidation” in organic chemistry and an “oxidative addition” in organometallic chemistry is the addition of H_2 to a metal centre to form a metal

hydride (Scheme 4). Although H_2 is considered a reducing agent, when it reacts with a metal as shown below, it leads to oxidation of the metal centre.[14]

Scheme 4: General oxidative addition to a Pd(0) metal centre[14]



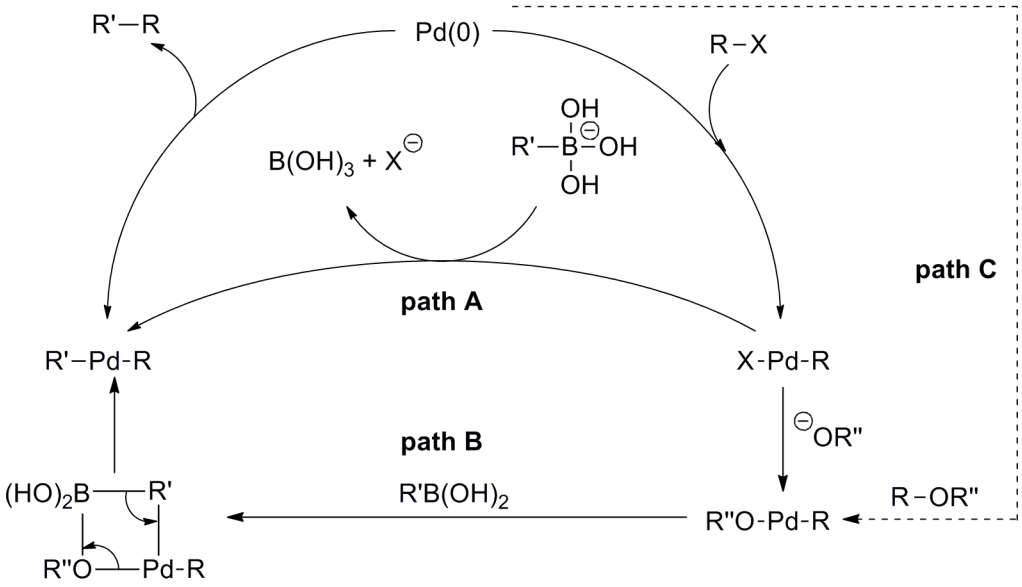
One requirement for oxidative addition to occur is that the palladium metal center must be coordinatively unsaturated.[15] As an example, in the Suzuki-Miyaura coupling, this means that the commonly used $Pd(PPh_3)_4$ must undergo a dissociation of at least two phosphine ligands to give the unstable $Pd(PPh_3)_2$ species that can then participate in oxidative addition. When an R-X moiety is oxidatively added to a metal centre, the isolable product is the *trans*-species; however, in order to undergo reductive elimination the *cis*-complex must be present.[15]

Oxidative addition is favoured by σ-donor ligands, such as electron-rich phosphines. These donate electron density to the metal center, increasing the reactivity of the Pd(0) species and stabilizing the Pd(II) species that results from oxidative addition.[14] In contrast, π-acceptor ligands, such CO, would reduce the electron density at the metal center, in turn destabilizing the Pd(II) species. In terms of substrates that can undergo oxidative addition, many nonpolar and polar substances can take part. Most common are species that possess a C-X bond, where X is a halogen or pseudohalogen, such as a triflate species, and the carbon center is sp^2 hybridized. When dealing with aryl halides/pseudohalides the rate of addition generally decreases in the following order; C-I > C-OTf > C-Br >>> C-Cl >>> C-F.[14] Due to the relative cost and availability of aryl chloride species, there is a common goal to find cross-coupling routes involving these species.

1.2.2 Transmetallation

Transmetallation is undoubtedly the least understood step of the catalytic cycle. The process involves the transfer of the organic moiety of the borane species with concurrent elimination of the halogen or pseudohalogen. In order for transmetallation to occur there must be a base present that can facilitate the transfer. While the base is necessary, its participation is not clearly understood; one theory is that the base works by coordinating to the boron atom, forming a more reactive borate complex (see Scheme 5, path A).[3] This quaternerization of the boron atom increases the nucleophilicity of the organic group on the boron, enhancing the rate of alkylation of the R-Pd-X species.[16]

Scheme 5: Proposed pathways of transmetallation[16]



Another theory behind the role of the base during transmetallation is that it may be involved in generating a Pd-oxo species that would be more reactive than the Pd-X species (Scheme 5, path B or C).[16] The very reactive nature of the Pd-OR'' species can be attributed to both the high basicity of Pd-oxo complexes and the high oxophilicity of the boron centre. Path C

illustrates that under neutral conditions and the use of an organic electrophile, the desired Pd-oxo intermediate can be obtained directly and that may undergo transmetallation with the boron species.[3] The most commonly followed pathways are that of A and B, where a base is added to facilitate the transmetallation.[17]

Matos and Soderquist have presented a detailed study on the transmetallation of alkylboranes.[18] The goals of their research were to determine the stereochemistry of the alkyl group transfer, the effect of the alkyl versus alkoxy boron ligation on the rate of coupling, the actual role of the base during coupling and the rate-limiting step of the catalytic cycle. Importantly, they show that the transmetallation step proceeds with retention of configuration at the C-B bond; meaning that enantiomerically enhanced substrates would react while maintaining the level of enrichment. From detailed kinetic studies, they were able to show that the rate of reaction is dependent on the formation of a borate complex.[18]

In summary, the key to successful transmetallation is to increase the ability of the boron reagent to form a borate complex. This insures that the organic fragment will be transferred to the palladium metal centre.

1.2.3 Reductive Elimination

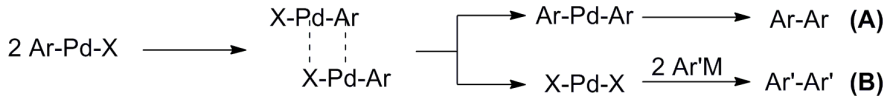
The last step in the catalytic process is the reductive elimination of the two organic fragments from the Pd metal centre to give the desired product. Like oxidative addition, reductive elimination has a different definition for organometallic chemists than for organic chemists. 'Reductive elimination' by organometallic definitions is the concept of removing two organic groups from the metal centre in order to reduce the metal centre from a Pd(II) to a Pd(0) species.[14] In order for the two R-groups to concurrently eliminate, they must be orientated

in a *cis*-conformation about the Pd-centre, which requires the isomerization from the *trans*-species after transmetallation has occurred.[14] Reductive elimination can be favoured by the removal of electron density from the metal centre; hence, the use of π-acceptor and/or bulky electron-withdrawing ligands will enhance the rate of elimination. The use of bidentate, bulkier phosphine ligands also increases the rate of reductive elimination since they 'push' the two R-groups closer together on the Pd-metal centre; however, the bite angle has a large influence on this reaction, which is controlled by the chelate ring size, such that certain chelates accelerate this reaction while others slow it.[14] Bulky ligands work for this process because they dissociate from the metal centre to make a low coordinate metal, which can then readily undergo reductive elimination.

1.2.4 Side Reactions of Suzuki-Miyaura Cross-Coupling

There exist three main competing processes that have an influence on Suzuki-Miyaura cross-coupling reactions. The first side reaction is the generation of homocoupled products from both the organic halides and organoboron species. One possible route to homocoupled products is shown in Scheme 6. When the transmetallation process is slow, homocoupled products can form from the organic halides (Route A). Also, in the presence of base the homocoupling of arylboronic acids will happen readily when exposed to oxygen (Route B).[17]

Scheme 6: Proposed route to homocoupled by-products[17]



Another common side reaction is protodeboronation. Under aqueous conditions the hydrolytic cleavage of the B-C bond can occur, causing $RB(OR')_2$ to be converted into RH. This

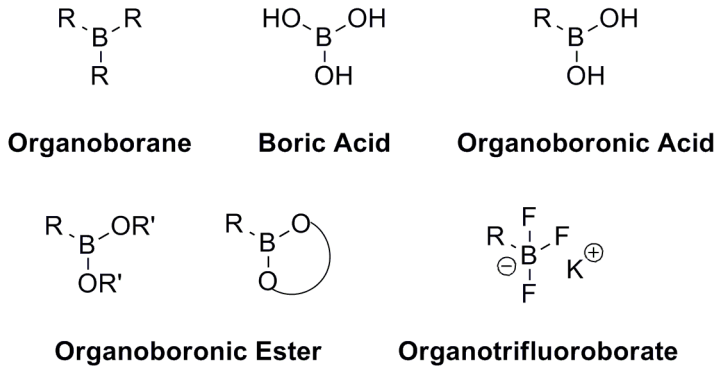
pathway is accelerated by the presence of base, adjacent heteroatoms, and the presence of ortho-substituents.[3] By scrupulously drying solvents this pathway can be minimized.

The last important side reaction is considered to be one of the most problematic for cross-coupling sp^3-hybridized species. When alkyl reagents possessing β-hydrogens are subjected to coupling conditions the chance of β-hydride elimination/re-addition can occur. This process is competitive with reductive elimination and ruins any enantiomeric excess that may be installed within substrates.[14] This reversible process will be discussed in section 1.4.2.2 with relevance to the cross-coupling of secondary sp^3-hybridized organoboron species.

1.3 Boron Reagents

There are four main classifications of boron reagents used in Suzuki cross-coupling reactions: organoboranes, organoboronic acids, organoboronic esters and organotrifluoroborates (see Scheme 7). The choice of species is dependent upon the reaction conditions, the stability of the boron species under such conditions and the method of synthesis of the organoboron species.

Scheme 7: Relevant boron containing compounds



1.3.1 Organoboranes

Organoboranes are compounds that have three organic groups attached to a single boron centre. These compounds are extremely easy to synthesize; however, they are generally unstable in the presence of air and are not commerically available.[19] Therefore, they must be generated prior to use in cross-coupling reactions. Most organoborane species are synthesized by hydroboration, which is discussed in section 1.3.4.

1.3.2 Organoboronic Acids

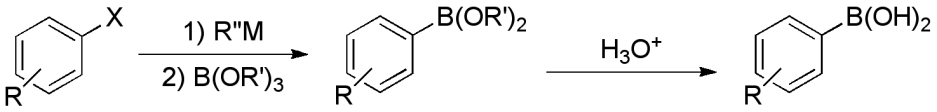
Organoboronic acids are species that contain a trivalent boron centre possessing one organic substituent and two hydroxyl substituents. They exist in an sp^2-trigonal planar geometry that allows the vacant p-orbital on the boron centre to be orthogonal to the three substituents. These species do not exist in nature and therefore must be made from simple boron precursors such as boric acid derivatives.[19] The reactivity and properties of the boronic acid are highly dependent on the organic R-group attached to the boron centre. The combination of being mild Lewis acids, relatively air and water stable, and easy to handle make organoboronic acids an attractive group of reagents. Also, due to their low toxicity and the fact that they degrade to boric acid they are considered to be "green" reagents.[19]

The vacant p-orbital on the boron centre gives boronic acids the ability to act as Lewis acids.[18] This allows for the coordination of Lewis basic molecules that will result in a tetra-coordinate species, with a pseudo-tetrahedral geometry. This tetra-valent species is believed to be the active molecule in the transmetallation step of the catalytic cycle due to the increase in nucleophilicity of the organic group attached to the boron, which would increase the rate of transmetallation.[19]

There are many ways to synthesize organoboronic acids, of which a select three are displayed in Scheme 8. Most methods require trapping nucleophilic intermediates with electrophilic boron reagents, such as $B(OMe)_3$, followed by acidic work-up to produce the desired boronic acid. This method is effective for generating boronic esters as well, if the trapping agent used is a stable alkoxy boron species. Boronic acids can be easily made; however, many are now commercially available, which reduces the need for synthesis to only when exotic organic frameworks are desired.

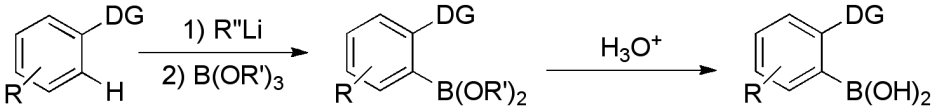
Scheme 8: Select methods for synthesizing organoboronic acids[19]

Electrophilic borate trapping of aryl-metal intermediates from aryl halides



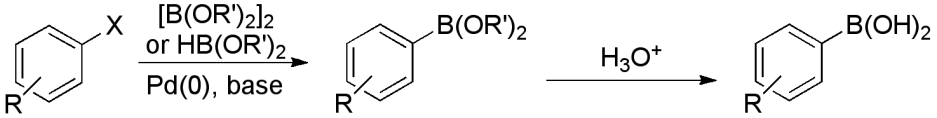
X = Br, I

Electrophilic borate trapping of aryl-metal intermediates from directed ortho-metallation



DG = Directing Group

Transition metal catalyzed coupling between aryl halides/triflates and diboryl reagents



X = Br, I, OTf

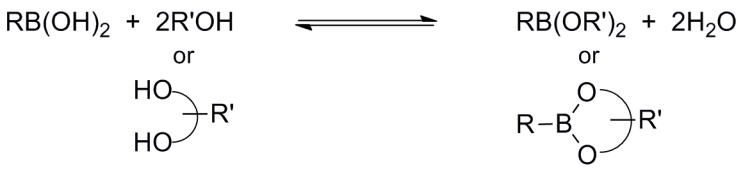
1.3.3 Organoboronic Esters

Organoboronic esters are species that possess alkoxyl substituents instead of hydroxyl groups found in organoboronic acids. Typically, organoboronic esters are less polar and easier to handle than the acid derivatives due to the loss of hydrogen bonding interactions. This hydrogen bonding causes the acids to form dimers and trimers that are more difficult to purify and characterize, which is a feature that the esters prevent. The R-groups also work as protecting groups and lower the reactivity of the species, relative to the acid analogue.[19]

Two of the most common organoboronic ester frameworks are the catechol and pinacol derivatives. Due to the opposing conjugation between the phenolic oxygen and the benzene ring the catechol derivatives are more Lewis acidic and very sensitive to hydrolysis. In contrast, the pinacol derivatives are stable towards air and moisture, making their isolation by chromatography simple.[19] As a result, the ease of handling pinacol aryl boronic esters has made them the favoured cross-coupling partners in modern synthesis over the catechol species.[19]

There are two main methods for synthesizing organoboronic esters. The first method is the condensation of a commerically available boronic acid with an alcohol or diol that would generate the desired ester linkage (Scheme 9). Often, a desiccant such as $MgSO_4$ is added to the reaction mixture to drive the equilibrium towards the products. The second method of forming boronic esters is through the hydroboration of alkenes (see Scheme 10), as discussed in the following section.

Scheme 9: General conversion of a boronic acid to a boronic ester[19]



1.3.4 Synthesis of Boron Reagents *via* Hydroboration

One of the more common ways of synthesizing alkyl boranes and organoboronic esters is through the hydroboration of alkenes, which can be achieved through both uncatalyzed or transition metal catalyzed variations. Hydroboration can also be accomplished asymmetrically, resulting in optically active boron containing compounds.

In the early days of hydroboration, uncatalyzed syntheses were accomplished asymmetrically by installing chiral auxiliary ligands, such as isopinene, onto the boron centre.[20] This method is cumbersome and costly due to the fact that the chiral auxiliary must be removed prior to the cross-coupling reaction. A more cost effective chiral auxiliary that does not interfere in subsequent coupling reactions are 9-borabicyclo[3.3.2]decane (9-BBD) derivatives.[21]

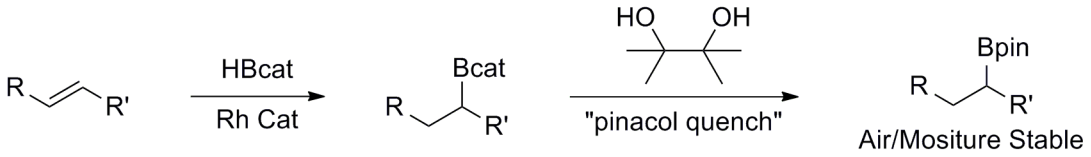
A more commonly employed method for asymmetric hydroboration of an alkene is to use chiral auxiliary ligands on a metal centre to induce chirality *via* a metal-catalyzed process. The initial report of enantioselective hydroboration came from the Hayashi group,[22,23] who reported that catechol borane, in conjunction with a cationic rhodium catalyst modified with the chiral phosphine ligand 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) produces substituted styrene substrates with high enrichment in enantiomeric excess (ee). In many cases, they were able to obtain enantiomeric excesses over 90% and regioselectivities of roughly 99:1.[22,23] Building on this work, the Brown group has demonstrated that switching from BINAP to

1-(2-diphenylphosphino-1-napthyl)isoquinoline (QUINAP) allows for milder reaction conditions while giving comparable enantio- and regioselectivities. Thus, QUINAP eliminates the need for cryogenic reaction temperatures that are necessary when using BINAP.[24,25] QUINAP is also less sensitive towards sterically encumbered substrates, allowing even internal olefins to be used.

As previously discussed, one of the most commonly used species for catalytic hydroboration is catechol borane (HBcat). Despite the popularity of HBcat, several complications can arise when using it. For instance, while the catechol backbone does work to lower the Lewis acidity of the molecule and makes it unreactive in the uncatalyzed hydroboration at ambient temperatures, it is still reactive enough to undergo severe degradation. It has been shown that HBcat will degrade to B_2cat_3 and BH_3.[26] The undesired side reaction is accelerated in the presence of nucleophilic molecules, such phosphine ligands, like PPh_3 that are common in transition-metal catalysts.[26] In the presence of unreactive substrates, such decomposition can occur at a competitive rate and the full equivalent of BH_3 can then go on to promote the uncatalyzed background reaction, making it necessary to use an excess of HBcat to ensure full conversion of the starting material.

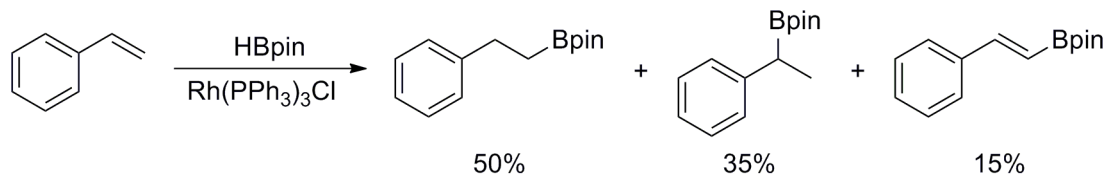
Perhaps more importantly, boronic esters resulting from hydroborations with HBcat are unstable to air and moisture, making isolation and purification of such species extremely difficult. In general, the resulting HBcat products are oxidized, *in situ*, to the corresponding alcohol or converted to a more stable ester; the most common conversion being to the pinacol ester through a trans-esterification with pinacol (Scheme 10).[27] The pinacol esters are stable enough to be isolated on the bench-top and purified by column chromatography. This is important if the product of the hydroboration is to be used in a reaction other than oxidation to the corresponding alcohol.

Scheme 10: Pinacol quench

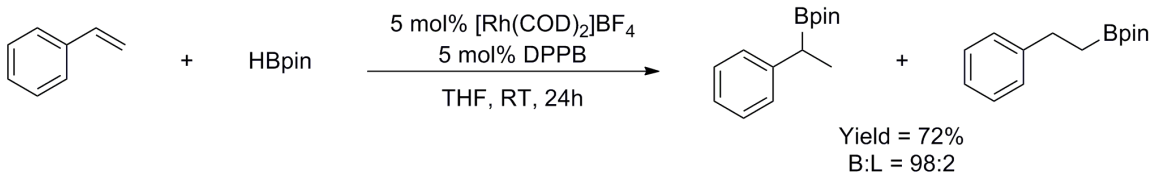


The more stable pinacol borane has recently gained in popularity as the most commonly used hydroborating reagent.[28] It was first used in thermal hydroboration of alkynes by Knochel[29]; however, application to catalyzed hydroboration reactions proved difficult. The first transition-metal catalyzed hydroboration with pinacol borane was done using zirconium, and later rhodium by the Srebnik group.[30,31,32] Unfortunately, pinacol borane cannot be combined with a neutral rhodium catalyst in the hydroboration of vinyl arenes (Scheme 11). The desired branched product is only obtained in 35 % yield; whereas when the more reactive catechol borane is employed, almost exclusive formation of the branched isomer is observed.[31] In order to make using pinacol borane feasible, employing cationic Rh-catalysts, such as $[Rh(cod)_2]BF_4$, became necessary. It was found that by using 5 mol% of $[Rh(cod)_2]BF_4$ and 5 mol% of DPPB (an achiral bisphosphine) the hydroboration of styrene could be achieved in high yields and with good selectivity for the branched isomer (Scheme 12).[33] Combining the use of cationic rhodium and chiral auxiliary phosphine ligands, the Crudden group has been able to achieve the high enantio- and regioselectivities previously observed by Hayashi with neutral catalysts.[33] This now opens up a direct, one pot synthesis to enantiomerically enriched, air and moisture stable boronic esters that can be easily handled for future transformations.

Scheme 11: Hydroboration of styrene using Wilkinson's catalyst[31]



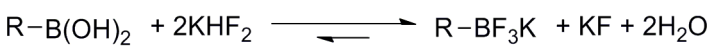
Scheme 12: Hydroboration of styrene using a cationic Rh-catalyst[33]



1.3.5 Organotrifluoroborate Salts

In recent years, the use of organotrifluoroborate salts has become popular. These reagents are particularly useful due to their stability; being both air and moisture stable crystalline salts at room temperature.[34] Until recently, the RBF_3K salts were synthesized according to a method developed by Vedejs *et al.;*[35] where the corresponding boronic acid or ester are transformed using inexpensive potassium hydrogen difluoride (KHF_2) as a fluoride ion source (see Scheme 13). They showed that KHF_2 could activate a relatively unactivated boron species under essential weakly acidic conditions; in contrast the use of KF instead of KHF_2 showed no conversion to the desired RBF_3K salt.[35]

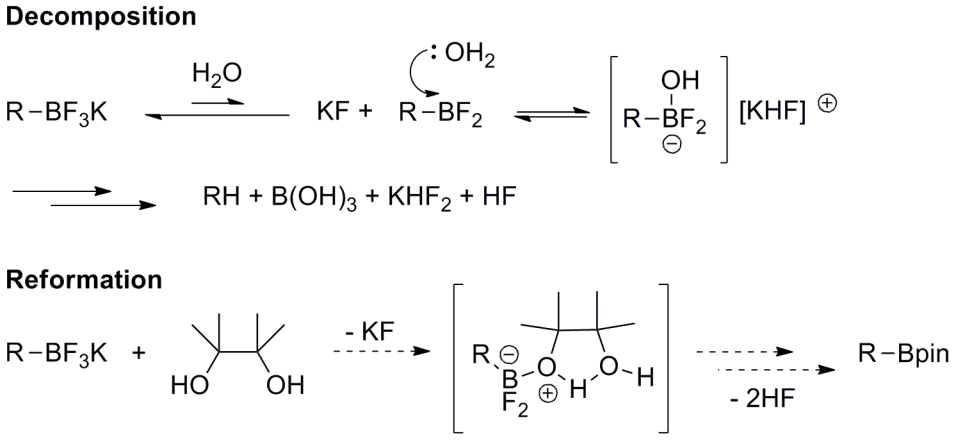
Scheme 13: Classic Vedejs's synthesis of RBF_3K salts[35]



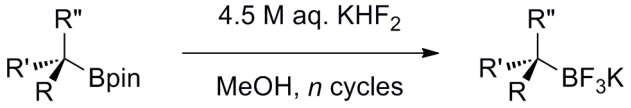
The method displayed in Scheme 13 appears to be relatively simple and in most cases produces the desired salt; however, this method could not be applied to α-branched pinacolboronic esters. It was seen that a simple recrystallization would not always afford the

desired product, and depending on the solvent employed, resulted in partial decomposition of the salt *via* a hydrolytic cleavage of the carbon-boron bond as well as increased amounts of the starting boronic ester.[34] Aggarwal and co-workers propose that the formation of pinacol may actually impede the formation of a crystalline product and cause the reformation of the starting boronic ester, through the pathway shown in Scheme 14; hence, a more effective method of removing the pinacol by-product had to be found. Through simple experimentation Aggarwal has shown that pinacol actually forms an azeotrope with water and can be easily removed through a series of dissolution-evaporation cycles (Scheme 14), where the number of cycles is dependent on the physical nature of the product.[34] This simple procedure should allow for easier application of RBF_3K salts in synthetic procedures.

Scheme 14: Decomposition of RBF_3K salt and reformation of pinacol ester[34]



Scheme 15: Aggarwal synthesis of RBF_3K salts[34]



1.4 Suzuki Cross-Coupling of sp^3-Hybridized Partners

Over the years since the initial report by Suzuki and Miyaura[12] concerning coupling alkenyl boranes with alkenyl or alkynyl halides, a great deal of effort has been placed on expanding the scope of the coupling conditions to include more challenging substrates. While coupling conditions have been improved to reduce the stoichiometry of boron reagents and access to more aggressive conditions has allowed the use of aryl chlorides under mild conditions, coupling between sp^3-hybridized partners remains relatively uncharted territory. The cross-coupling of these species proves to be significantly more difficult than sp^2-species due to the difficulty of the oxidative addition of alkyl halides to the palladium centre, the greater tendency of β-hydride elimination and the greater difficulty of transmetallation of alkyl boron compounds to transition metal complexes.[27] Ideally coupling sp^3-hybridized species would generate new stereocenters. If this could be accomplished asymmetrically, they could lead to interesting motifs potentially found in natural and unnatural products.

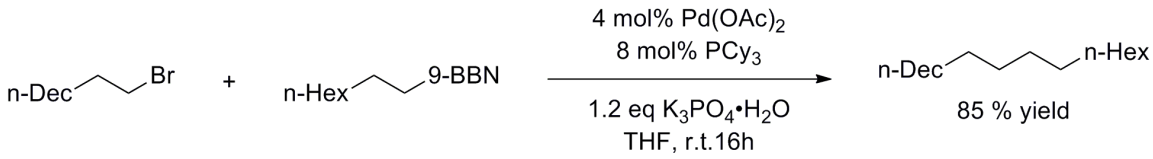
1.4.1 Suzuki Cross-Coupling of sp^3-Hybridized Electrophiles

The ultimate goal of current research in Suzuki coupling is alkyl-alkyl cross-coupling; hence, the reactivity of alkyl halides and triflates has been extensively studied. One of the earliest examples comes from Suzuki in 1992, where the synthesis of n-tetradecane was accomplished in 64 % yield through the coupling of 1-iodohexane and n-octyl-9-BBN (in the presence of catalytic $Pd(PPh_3)_4$ and stoichiometric K_3PO_4).[36] After this early report, the field of

sp^3-couplings has been dominated primarily by the work of the Fu group.[37, 38] They have shown that by careful matching of reaction conditions to the halide substrate the coupling can be achieved in high yields and with moderate stereo-selectivities.

Building on the work of Suzuki, Fu was able to conduct alkyl-alkyl coupling under very mild conditions (Scheme 16).[37] The use of a bulky phosphine ligand was essential to the success of this method. Fu has also shown that the oxidative addition of an alkyl electrophile to a palladium-trialkylphosphine complex is considered to be a S_N2-type mechanism.[38] The concept is that the PdL_2 system exhibits a nucleophilic attack on the RX substrate.[38] It was found that the rate at which the nucleophilic attack occurs with respect to the leaving group X follows the order of I >> Br > Cl, where I is the most reactive. Alkyl fluorides cannot be used.[38] Since the reaction follows a S_N2 like mechanism, the use of strongly electron donating and sterically bulky ligands is critical. The application of these systems to secondary alkyl halides is harder due to the decrease in S_N2 reactivity, the increase of sterics around the metal centre and the greater propensity for β-hydride elimination.

Scheme 16: Alkyl-alkyl coupling demonstrated by Fu (2001)[37]

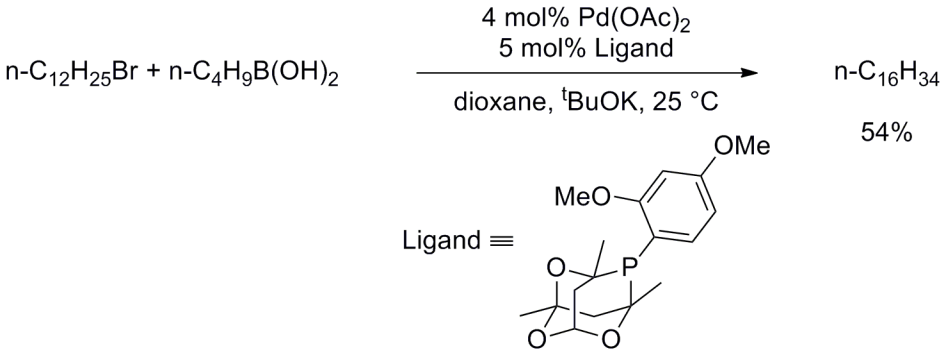


In order for Suzuki-Miyaura coupling to be applicable to secondary alkyl substrates it has been shown that Ni-catalysts (versus Pd) can be used.[39] Initially Fu reported the use of $Ni(cod)_2$ in combination with bathophenanthroline. These conditions were effective in coupling unactivated alkyl bromides and iodides in high yields. Interestingly the reaction was selective for sp^3-carbon centred bromides over aryl chlorides and when a palladium catalyst was used the

coupling did not occur.[39] This suggested that the oxidative addition was going through a one-electron radical process that is typical of nickel species.[39]

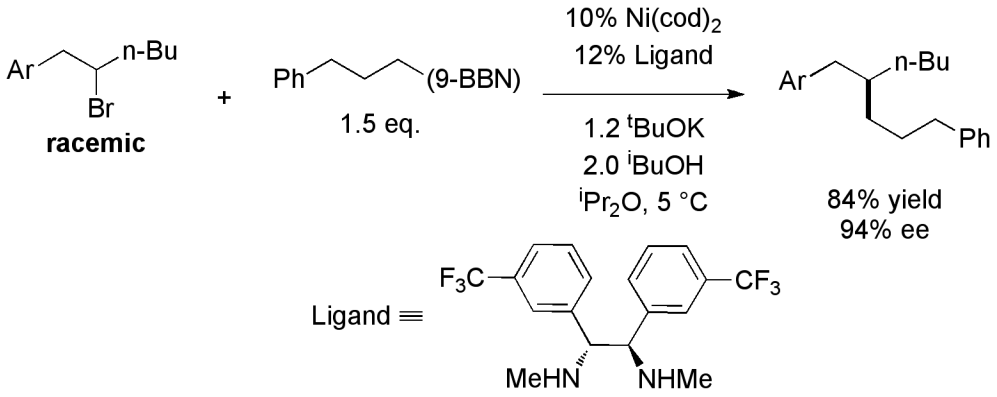
Around this same time, Fu accomplished the successful coupling of unactivated alkyl halides and tosylates possessing β-hydrogens, with either aryl or alkenyl boronic acids and alkyl boranes, using a palladium-phosphaadamatane system (Scheme 17).[40] Under this system the products were obtained in slightly lower yield; however, the method allowed for fast screening of catalyst/ligand systems in order to determine the optimal conditions.[40]

Scheme 17: Suzuki cross-coupling using phosphaadamantane ligands[40]



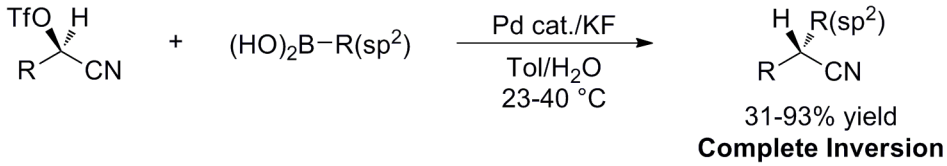
Fu was also able to extend the conditions mentioned above to the coupling of unactivated secondary alkyl chlorides, through using a NiI_2-aminoalcohol system.[41] Following this, the group also showed the coupling of secondary alkyl bromides and iodides to primary alkyl boranes.[42] This method employed a $NiCl_2$-glyme catalyst and diamine ligands to generate new sp^3-sp^3 carbon-carbon bonds. Most recently, Fu has accomplished the asymmetric coupling of unactivated homobenzylic halides with alkyl boranes.[43] This method now uses a nickel catalyst and chiral diamine ligands to couple the unactivated halides in high yields and stereoselectivities (Scheme 18). Interestingly it was noted that a secondary interaction due to the homobenzylic spacing of the halide was necessary for this reaction to achieve high ee's.

Scheme 18: Asymmetric Ni-catalyzed Suzuki coupling of unactivated homobenzylic halides[43]



Earlier this year, the coupling of secondary triflates with aryl and alkenyl boronic acids was accomplished, with complete inversion of stereochemistry, by the Falck group (Scheme 19).[44] These conditions offer advantages over others due to the use of readily available α-cyanohydrins and the fact that they can be easily transformed to other functionalities without the loss of chirality. The cyano group also facilitates the oxidative addition of the triflate to the metal centre, even at room temperature.[44] The effect of the cyano group together with the palladium catalyst bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II), which possesses a bulky electron rich phosphines, allowed for the suppression of β-hydride elimination to give the desired coupled product.[44]

Scheme 19: Cross-coupling of alkyl α-cyanohydrin triflates[44]



As seen from the examples highlighted above, the area of coupling unactivated alkyl electrophiles has been dominated by the Fu group. They have been able to advance the utility of coupling alkyl electrophiles with aryl and alkyl boron species very effectively.

1.4.2 Suzuki Cross-Coupling of sp^3-Hybridized Organoborane Species

Even though the scope of coupling sp^3-hybridized electrophiles has flourished over the years, the coupling of sp^3-hybridized organoborane species remains limited. Even so there have been significant advances in both the coupling of primary and secondary sp^3-hybridized organoboron species, as discussed below.

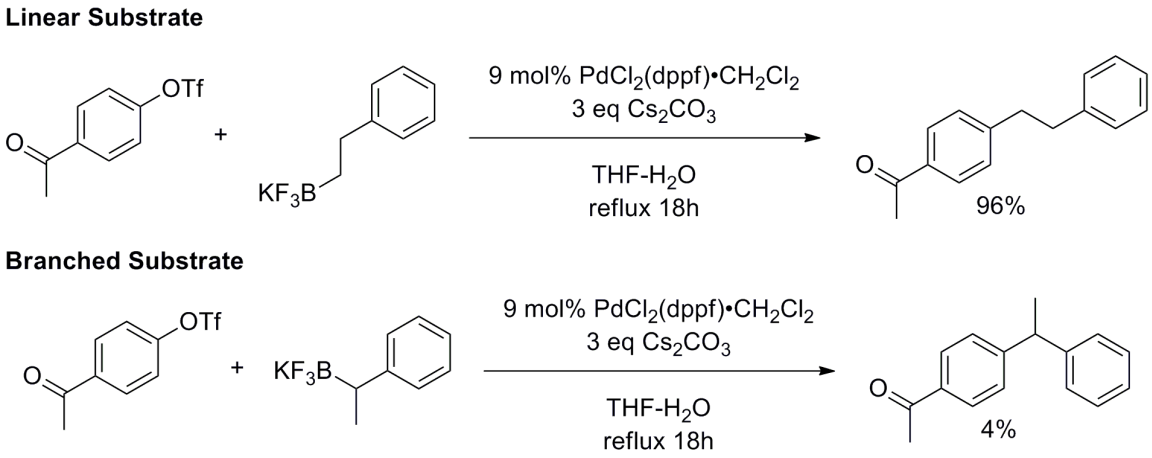
1.4.2.1 Cross-Coupling of Primary sp^3-Hybridized Organoboron Compounds

One challenge limiting the coupling of primary sp^3-hybridized organoboron species also is that transmetallation to the metal centre is quite difficult. One exception is coupling primary alkyl 9-borabicyclo[3.3.1]nonane (9-BBN) species: In 1986, Suzuki accomplished the palladium catalyzed coupling of aryl iodides with alkyl derivatives of primary 9-BBN species using strong bases, such as NaOMe.[45] In this initial report it was observed that there was no reaction when secondary *sec*-butyl boranes were employed. In subsequent investigations by Kishi,[46] and later Suzuki,[47] it was found that the use of thallium salts increased the rate of the transmetallation step in the catalytic cycle; however, due to the toxicity of thallium salts, these options were abandoned for stronger sodium and/or potassium bases.[47]

The coupling of primary sp^3-hybridized organoboranes has followed along side with the coupling of sp^3-hybridized electrophiles. As shown in Scheme 16 and Scheme 17, alkyl-(9-BBN) and alkyl boronic acid derivatives can be successfully coupled under various conditions, when a primary boron species is used. Highly stable organotrifluoroborate salts are one alternate class of reagents that have been used successfully in coupling sp^3 organoboranes.[48,49] Molander and co-workers have been able to successfully couple a variety of triflate electrophiles with these organoborane species, by using the palladium catalyst $PdCl_2(dppf)\cdot CH_2Cl_2$, in conjunction with

Cs_2CO_3 as a base, to effectively produce the desired products in high yields (Scheme 20). Interestingly this method did not effectively transfer to the coupling of secondary organotrifluoroborates, giving only 4 % of the desired product, with styrene (produced *via* β-hydride elimination) observed in the reaction mixture.[48,49]

Scheme 20: Cross-coupling of sp^3-hybridized potassium organotrifluoroborate salts[48]



Complimentary to the work above, there have been several examples using silver salts to increase the rate of transmetallation of the boron species, which will be discussed in following sections. These methods, however, were largely unsuccessful; in fact, until the 2009 report by the Crudden group, no method had been reported to affect this important transformation.[1]

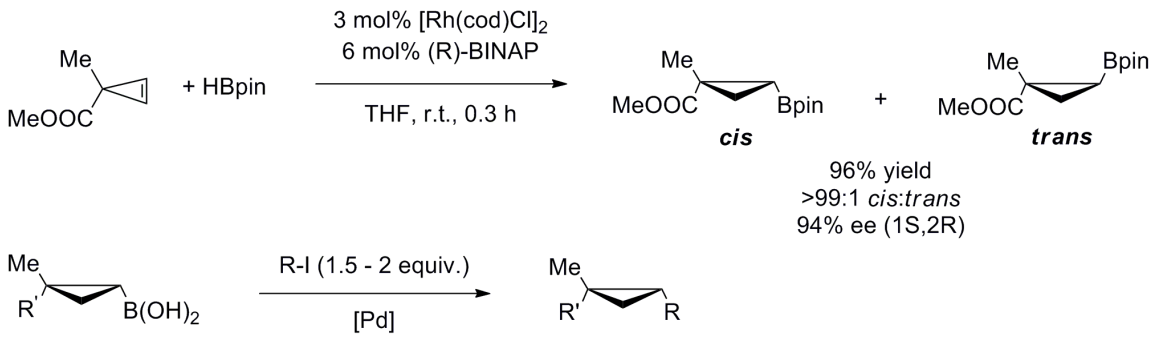
1.4.2.2 Cross-Coupling of Secondary sp^3-Hybridized Organoboron Compounds

As shown in section 1.4.1 the coupling of unsymmetrical organic halides can be accomplished using a nickel catalyst supported by multi-dentate nitrogen ligands. This catalytic system enhances the rate of reductive elimination relative to the rate of β-hydride elimination/re-addition.[50] The application of Suzuki coupling to secondary organoboron species

is far rarer than that of the organic halides and most examples reported to date are effective only for cyclic ring structures.[51]

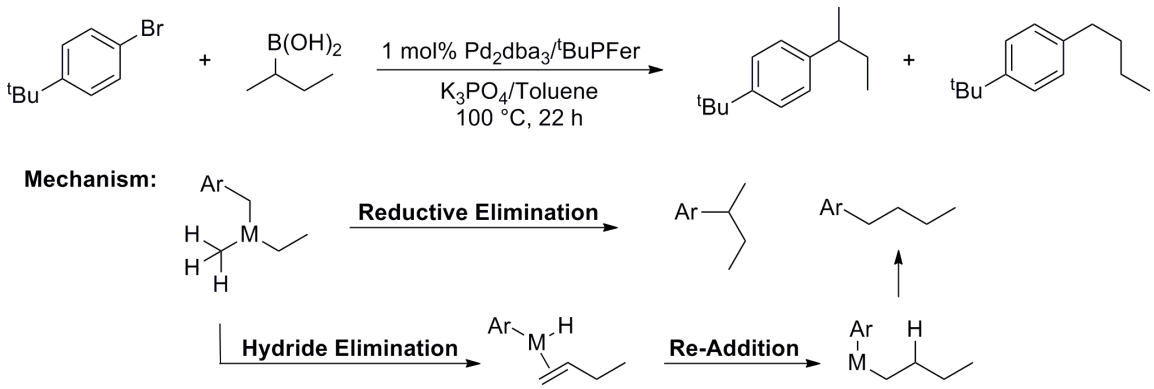
Many of the early examples of coupling secondary organoboranes employ cyclopropyl boronic esters. The cyclopropyl species are privileged systems to investigate for coupling due to their sp^2 like character and their predisposition against β-hydride elimination. The properties of these substrates allow for easy incorporation in Suzuki-Miyaura cross-coupling. Gevorgyan and co-workers have shown that if the boron fragment is incorporated asymmetrically it can be coupled with retention of stereochemistry.[52] It is important to note that almost all syntheses of optically active cyclopropyl boron compounds employ stoichiometric quantities of chiral auxiliary moieties at the boron centre. Unfortunately, these cyclopropyl reagents are limited to the preparation of 1,2-disubstituted cyclopropyl rings. Also, Gevorgyan has shown the facile diastereoselective hydroboration of cyclopropyl rings using catalytic amounts of rhodium catalyst in conjunction with the chiral bidentate ligand (*R*)-BINAP (Scheme 21).[52] It was seen that the pinacol esters would not succumb to coupling; however after the mild conversion to the corresponding boronic acid (with retention of stereochemistry) they were able to achieve coupling, using the conditions outlined by the Fu group,[53] in high yields and selectivities (Scheme 21).

Scheme 21: Stereoselective coupling of cyclopropyl boronic acids



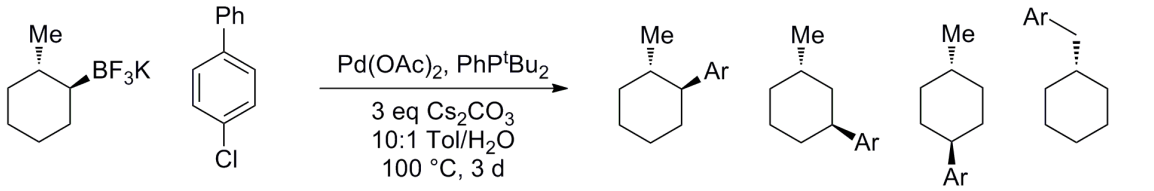
It has also been shown that unsubstituted cyclopropyl and cyclobutyl trifluoroborates are effective coupling partners; generally, higher yields were obtained with the cyclopropyl species compared to the cyclobutyl substrates.[54] Extending the scope to include larger ring systems is effective only in symmetrical systems, where the facile β-hydride elimination can go unnoticed due to all products being the same.[55] A key example of the effects that β-hydride elimination can have is a study by Hartwig in 2002.[56] He noticed that during the coupling of *sec*-butyl boronic acid the desired product was obtained, along with a great deal of the corresponding n-butyl product. This undesired product is generated through the process displayed in Scheme 22: the sec-butyl palladium species (resulting from transmetallation of the boron species to the palladium centre) undergoes β-hydride elimination and re-addition before reductive elimination can occur. Once the primary n-butyl-palladium species is formed the reductive elimination becomes more competitive and the n-butyl product is formed. This plagues many systems with adjacent hydrogens and must be minimized in order to deem the reaction a viable coupling.

Scheme 22: Alkyl scrambling in secondary boron coupling[56]



Larger ring systems that have the potential to be plagued by β-hydride elimination/re-addition have been successfully coupled as organotrifluoroborate salts. Independently, the groups of Molander[55] and van den Hoogenband[57] were able to couple the cyclopentyl and cyclohexyl trifluoroborate salts with aryl chlorides and bromides, respectively. These systems were still overwhelmed by the β-hydride elimination/re-addition mentioned above; however, under optimized conditions this undesirable pathway could be mostly suppressed. This optimized process allowed for the successful coupling of unsymmetrical systems in a moderate yield, minimizing isomerization products (Scheme 23). Even though the coupling was accomplished, the reversibility of the β-hydride elimination/re-addition would destroy any enantiomeric excess at the coupling position.[55]

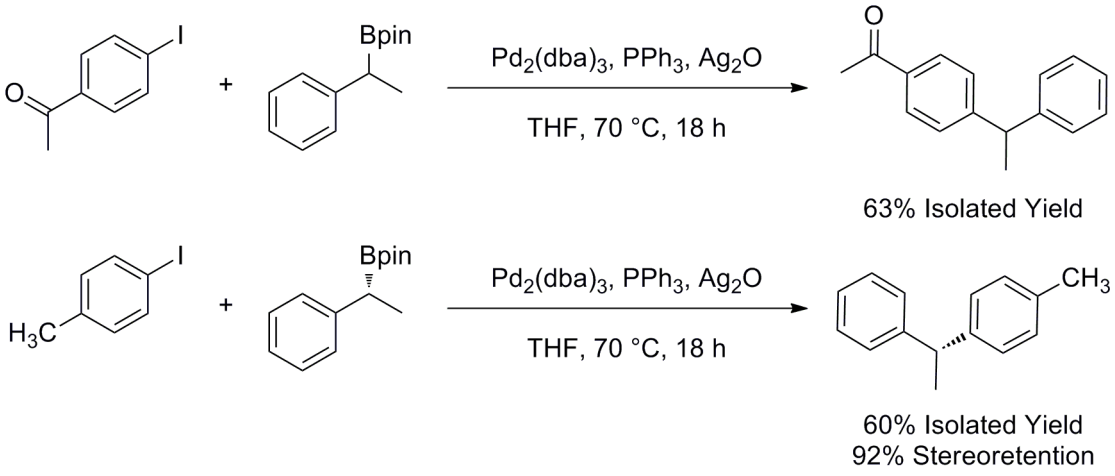
Scheme 23: Coupling of enantiomerically enriched cyclohexyl trifluoroborates[55]



72% yield as a mixture of isomers (27.7:1.6:1.0:8.1)

The first successful example of coupling an enantiomerically enriched secondary boronic esters came from the Crudden group in early 2009 (Scheme 24).[1] This was the first example of coupling secondary organoborates with retention of stereochemistry and essentially complete immunity to β-hydride elimination. Through the asymmetric rhodium catalyzed hydroboration of styrene, our group was able to generate the corresponding boronic ester in high yields and high retention of enantiomeric excess (Scheme 10). Thus any enantiomeric enrichment achieved during the hydroboration reaction could be effectively retained after cross-coupling.[1] The unique aspect of this reaction is the use of silver oxide as the base and a relatively high ratio of palladium and phosphine (1:8) to facilitate the coupling and hinder the β-hydride elimination. When common Suzuki bases were used, such as K_2CO_3 or Cs_2CO_3, in place of silver oxide no coupling product was observed.[1]

Scheme 24: Cross-coupling of secondary organoboronic esters with retention of configuration[1]

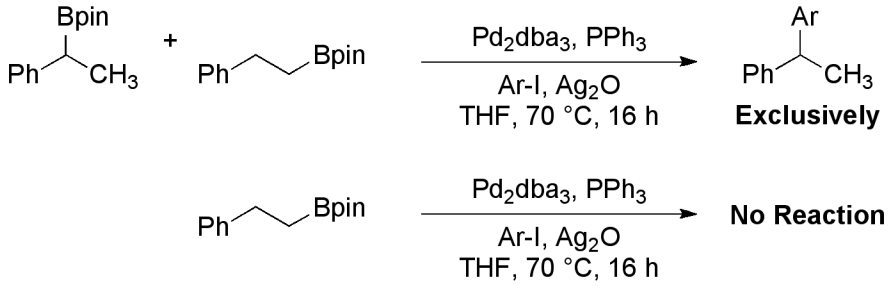


The reaction conditions were applicable to a wide range of substituents, resulting in moderate yields and high retentions of configuration. One limitation is sterically-hindered aryl iodides react with lower yields: for instance, the *p*-iodotoluene product was observed in 86% yield, whereas the *o*-iodotoluene product was found in 48% yield. It was also found that

functionality could be installed both on the aryl iodide and the boronic ester without a large decrease in yield or retention.

Lastly, it was found that the reaction was selective for branched sp^3-hybridized boronic esters in the presence of linear boronic esters (Scheme 25). Thus when a mixture of branched and linear boronic esters was subjected to the reaction conditions, the exclusive formation of the branched coupling product was observed. When a solution of only the linear boronic ester was exposed to the reaction conditions no cross-coupling was observed at all.[1] This interesting result shows that the Crudden method is complementary to that of Molander for cross-coupling primary organotrifluoroborate salts (see Scheme 20). Also, this selectivity allows for the prospective application of the coupling in selective syntheses, which is currently being pursued in our laboratory.

Scheme 25: Branched vs linear selectivity of secondary organoboronic ester cross-coupling[1]

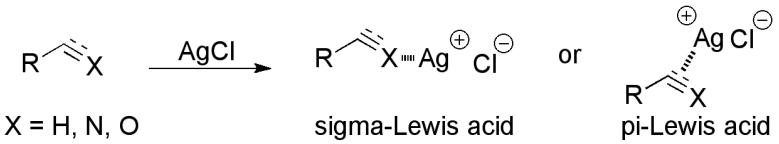


1.5 Silver Mediated Reactions

Silver, like most transition metals, displays a Lewis acid character and this property has driven its use in organic synthesis.[58] Silver offers another advantage due to the high lattice energy when silver-halogen salts are formed, they tend to be insoluble. This "halogenphilicity" has thus been exploited as a driving force in many reactions. From a bonding perspective, silver can act as a σ-Lewis acid and a π-Lewis acid, depending on the substrate for the reaction (see

Scheme 26). Taking advantage of the π-association and the alkynophilicity of silver, one can observe nucleophilic attack of a π-system.[58] In the literature surrounding this subject, "mediated" and "catalyzed" are sometimes used interchangeably; however, in the following sections mediated will refer to the addition of stoichiometric amounts of a silver species to the reaction, which results in the acceleration of the reaction.

Scheme 26: Coordination of silver to an alkyne[58]



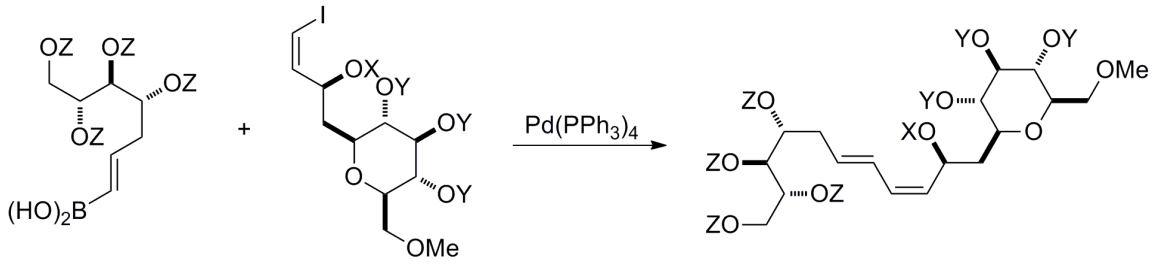
1.5.1 Silver-Mediated Cross-Coupling Reactions

There are two main drives to employ silver in cross-coupling reactions. First, due to its high affinity for halogens, silver works remarkably well at abstracting halide ions from a metal centre. This process results in a more electropositive metal centre and creates a vacant coordination site, allowing for substrate coordination or promoting reductive elimination. When halide abstraction is not the goal of silver in a reaction, it is generally added to a reaction mixture to produce an organo-silver species that can undergo an easier transmetallation to the catalytic metal centre.[58]

One of the first examples using silver to promote a reaction is found in Kishi's synthesis of Palytoxin (Scheme 27).[46] Silver oxide, as well as thallium hydroxide and potassium hydroxide, induced a dramatic rate enhancement for the coupling of vinyl boronic acids and vinyl iodides.[46] It was reasoned that using a base that would produce a water-insoluble salt (after halogen abstraction) could accelerate the rate of the coupling reaction. As seen in Table 1, TlOH proved

to be the most effective at enhancing the rate of reaction; however, due to the toxicity of Tl-compounds, their use is undesirable in synthesis and silver oxide is a more practical alternative.

Scheme 27: Example of cross-coupling in Palytoxin synthesis[46]



X = Ac; Y = Z = $Si(Me)_2(t\text{-}Bu)$

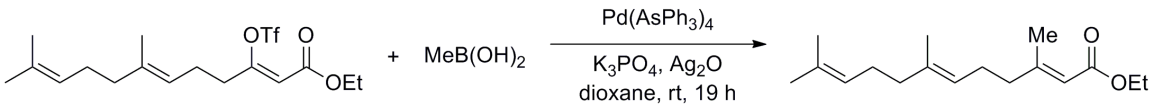
Table 1: Representative results from Palytoxin synthesis[46]

Base	mol% Pd	Temp (°C)	time	yield (%)
KOH	25	R.T	2 h	86
TlOH	25	R.T.	<< 30 s	92
Ag_2O	25	R.T.	5 min	92

Silver oxide has been used by several other groups to facilitate the cross-coupling of substrates. The Gibbs group has used a combined system of Ag_2O and K_3PO_4 to synthesize all-*trans*-geranylgeraniols (Scheme 28), from the corresponding isoprenoid triflate and organoboronic acid.[59] This coupling can be accomplished using tin reagents in conjunction with a Pd/Cu co-catalyst system; however, this system is hindered by the limited availability of the organotin starting material, the inability to transfer a variety of alkyl groups and the overall toxic nature of the organotin compounds. Hence, a more benign system was desired and it was proposed that Suzuki coupling could be an alternative. The optimal conditions of K_3PO_4/Ag_2O yields 79% of the desired product after 19 hours at room temperature. It should be noted that

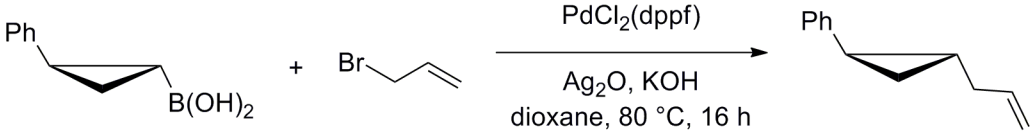
separately Ag_2O does not facilitate the coupling and K_3PO_4 results in a very sluggish process. This implies that the silver does not only participate in the formation of the borate complex but also in the halogen abstraction. This process was accomplished stereoselectively and is the second example of methylation and the first example of using an alkylboronic acid in Suzuki coupling.[59]

Scheme 28: Silver oxide utilization in all-*trans*-geranylgeraniol synthesis[59]



In 2000 it was shown that silver oxide could be used to facilitate the coupling of cyclopropylboronic acids with allylic bromides (Scheme 29).[60] As noted previously, the cyclopropyl system is privileged since it possesses sp^2-character; however, in this case the classical sp^2-coupling conditions did not result in the desired product. It took the addition of thallium and/or silver compounds before any product was observed. It was thought that the failure to react was due to the slow transmetallation between the boronic acid and the π-allyl palladium complex, formed after oxidative addition of the allyl bromide. The best conditions found were a mixed base system of Ag_2O and KOH in dioxane.[60] This system represents one of the first couplings of a cyclopropylboronic acid species and, most importantly, the reaction proceeds with complete retention of stereochemistry.[60]

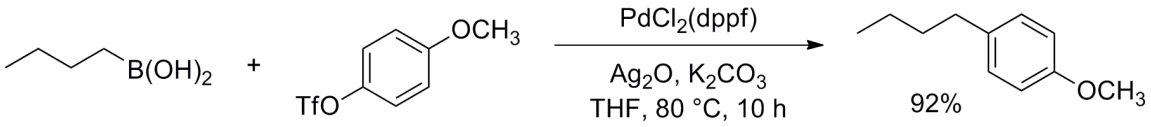
Scheme 29: Silver mediated cross-coupling of cyclopropylboronic acid and allyl bromide[60]



Finally, the last example of silver mediated Suzuki coupling is the reaction of *n*-alkylboronic acids with aryl and alkenyl halides or triflates (Scheme 30). Generally, aryl and

alkenyl boronic acids can be coupled to result in relatively high yields of the desired product; however, alkylboronic acids require harsher conditions or alterations to increase their reactivity. The Falck group has been able to take the unactivated *n*-butyl boronic acid and couple it with a variety of aryl and alkenyl halides/triflates by simply using a Ag_2O/K_2CO_3 base system.[61] This simple modification has generated a practical method of Suzuki coupling to produce high yields of the desired products, under mild conditions and without pre-activation of the boronic acid species.[61]

Scheme 30: Silver promoted cross-coupling of *n*-alklboronic acids[61]



1.6 Research Objectives

As mentioned, in 2009 the Crudden group published the use of silver oxide to facilitate the cross-coupling of secondary organoboronic esters with aryl halides (Scheme 24).[1] This was the first example of using the Suzuki-Miyaura cross-coupling reaction to produce these unique 1,1-diarylethanes with high retention of the stereochemistry. The objective of this thesis is to probe the reaction mechanism of the reported silver-mediated Suzuki cross-coupling, in order to improve the reaction conditions previously reported in terms of yield and retention of stereochemistry. By varying reaction conditions it is hoped that a greater understanding of the mechanism can be gained. The extension of reaction conditions to the coupling of more interesting compounds will be investigated, such as larger aryl systems and amides, along with the use of improved conditions for selective coupling of various boron substituents in the same molecule.

Chapter 2: Optimization and Mechanistic Investigation

2.1 Introduction

The cross-coupling of a secondary aliphatic organoboronic esters is an important addition to the Suzuki-Miyaura reaction in that it results in the creation of a carbon-carbon bond with chirality. Through the use of silver oxide, the Crudden group has been able to effectively generate 1,1-diarylethane products in high yields, with essentially complete retention of stereochemistry.[1] These diaryl species are difficult to synthesize through other methods and open up a unique class of molecules to be explored.

Prior to the result of the Crudden group there were many examples of coupling at a primary position (refer to section 1.4.2.1); however, the secondary coupling proved to be considerably more difficult. As an example, the Molander group was able to successfully couple 4-acetylphenyl trifluoromethanesulfonate with the primary 2-phenylethyltrifluoroborate salt in high yield, using a palladium-based catalyst system. When these conditions were applied to the coupling of the secondary organotrifluoroborate analogue the desired product was observed in 4 % yield (see Scheme 20).[48] The use of silver oxide made this reaction feasible, resulting in coupling yields of >80 %. At the time of publication, the specific role of the silver oxide was not fully understood but it was proposed that it facilitated the transmetallation process.

The purpose of the following section of this thesis is to further optimize the reaction conditions to improve yield and stereoselectivity, while increasing the range of substrates

available to participate in the coupling. Further elucidation of the role of silver oxide in the reaction pathway was another goal of this study.

2.2 Results and Discussion

2.2.1 Catalyst Variations

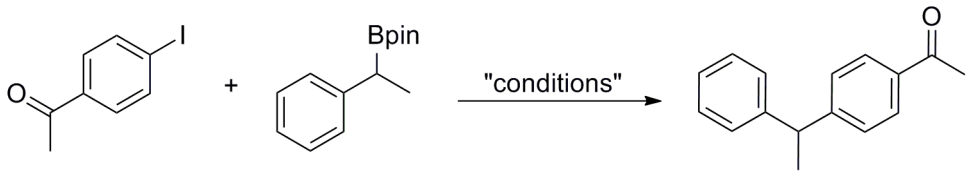
Generally, the active catalytic species in the Suzuki-Miyaura coupling reaction is thought to be a Pd(0)L or Pd(0)L_2 species. Two ways to access this species are: (1) start with a Pd(0)L_4 and affectively disassociate the appropriate number of ligands in solution; or (2) start with a Pd(II) pre-catalyst bound to phosphines and *in situ* reduce the Pd(II) to Pd(0) to generate the active catalyst. In the Crudden group, we have traditionally started from the common Pd_2dba_3 pre-catalyst. Some earlier work explored tailoring the catalyst to phosphine ratio in order to investigate the effect of different phosphines on the activity of the catalyst.[1] At the time of our initial publication,[1] it was determined that the best result could be achieved using an 8:1 ratio of PPh_3 to Pd. In this work, the goal was to determine the effect of using other Pd sources on the reaction conditions.

There are two other common Pd catalysts traditionally used in Suzuki coupling: $Pd(PPh_3)_4$ and $Pd(OAc)_2$.[14] Table 2 summarizes the experiments conducted using these other Pd sources; neither provided an increased yield of cross-coupled product. It is interesting to note that the use of $Pd(PPh_3)_4$ (entry 3) gives essentially the same yield as that of the previously reported Pd_2dba_3 (entry 1).[1] While the activity of the two Pd sources seems comparable, cost and handling should be considered as a factor in which species to use for larger scale reactions; while $Pd(PPh_3)_4$ is significantly cheaper, it requires handling under inert and dry conditions, whereas Pd_2dba_3 is much more robust. The other interesting point about $Pd(PPh_3)_4$ is that an

increase in the overall amount of phosphine ligand is needed. When only $Pd(PPh_3)_4$ is used, with no extra phosphine ligand added (entry 2), the yield actually decreases. When the extra phosphine ligand is added (entry 3) the yield is comparable to the original system (entry 1). This result emphasizes the importance of using the appropriate $Pd:PPh_3$ ratio. It is important to use enough phosphine to insure that a coordinately saturated system is achieved. This ensures that side reactions, such as β-hydride elimination, do not interfere with the coupling process.

The use of $Pd(OAc)_2$ did not afford a high yield of the desired product. This may be due to the need for more phosphine ligand in the system. The phosphine must reduce the Pd from Pd(II) to Pd(0); therefore, a greater yield may have been achieved if a higher loading of phosphine was used to compensate for reducing of the catalyst.

Table 2: Result of catalyst screening experiments



Entry*	Catalyst (mol% Pd)	Ligand (mol%)	Base (eq.)	GC Yield (%)
1	Pd_2dba_3 (8)	PPh_3 (64)	Ag_2O (1.5)	65
2	$Pd(PPh_3)_4$ (4)	----	Ag_2O (1.5)	30
3	$Pd(PPh_3)_4$ (8)	PPh_3 (64)	Ag_2O (1.5)	64
4	$Pd(OAc)_2$ (8)	PPh_3 (64)	Ag_2O (1.5)	45

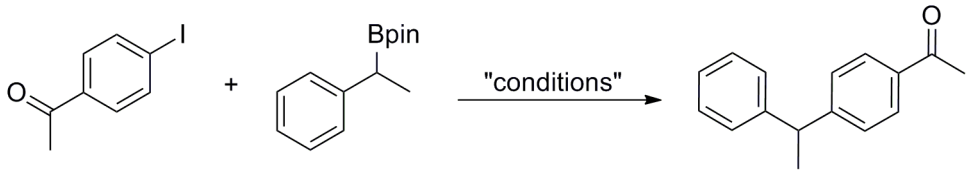
*Rxn Conditions = THF, 70 °C, 18 h

Overall, varying the catalyst did not give way to a higher yielding process. It will be seen in the following sections that tailoring other reaction conditions were more fruitful than switching palladium sources.

2.2.2 Solvent Choice

The initial conditions reported were optimized in THF;[1] however, at the time of publication other solvents had not been investigated. One of our research goals was to examine a range of solvents for the optimal cross-coupling reaction. Table 3 summarizes this study, where the best solvents identified for this cross-coupling were ethereal and moderately polar.

Table 3: Results of solvent screening experiments



Entry*	Solvent	GC Yield (%)	Entry*	Solvent	GC Yield (%)
1	THF	65	7	1,4-dioxane	63
2	Benzene	50	8	ACN	0
3	Toluene (70 °C)	52	9	DMF	19
4	Toluene (110 °C)	39	10	^{i}PrOH	0
5	Et_2O	64	11	MeOH	<1
6	DME	52			

*Rxn Conditions = 8 mol% Pd_2dba_3, 64 mol% PPh_3, 1.5 eq. Ag_2O, 70 °C, 18 h

When solvents possessing an exchangeable hydrogen were employed (such as methanol and isopropanol) the reaction ceased to produce any product. This could be that the catalyst or base underwent a side reaction with the solvent. Ultimately, the ethereal solvents proved to be the best at facilitating the reaction. THF works as a suitable solvent, but ether, DME and dioxane work as alternatives.

2.2.3 Base Screening

In order for the Suzuki reaction to proceed there has to be base present in the reaction mixture. It is commonly thought that the base works to generate a borate complex that will be more reactive in the transmetallation process (see section 1.2.2). Detailed investigations by Matos and Soderquist[18] suggest that there are actually several roles that the base plays throughout the catalytic cycle. They propose that the base not only acts to form the reactive borate complex, but also works to abstract the halide from the Pd-metal centre, complex any boron by-products that may compete with the organoboron species for coupling and assist in the regeneration of the catalyst.[18] While our group has identified that the silver oxide was essential to the reaction for coupling the secondary organoboronic esters; a complete understanding of its role mechanistically was lacking. Hence, we set out to investigate the effects of other silver salts and commonly used Suzuki bases on the original reaction conditions.

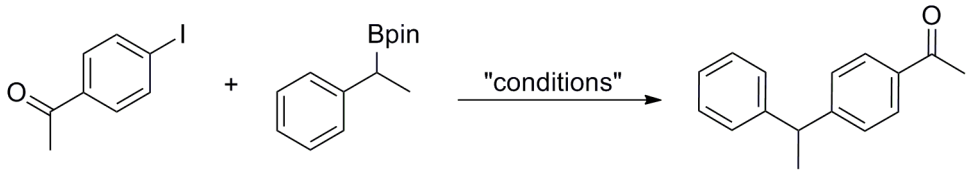
Thus, holding the catalyst and phosphine loading as constraints several different combinations of silver(I) salts and common bases were investigated. Table 4 summarizes the resulting yields for numerous combinations of bases. Unfortunately, the original silver oxide system still proved to be the best; however, our results did provide some clarity on the nature of the silver required to affect the reaction (entry 1). Silver(I) salts, such as $AgBF_4$, in combination with common bases, such as Cs_2CO_3 and K_3PO_4, were investigated with the hypothesis that the silver could be used to remove the iodide from the metal centre and the other base would work to form the more reactive borate species. When an anhydrous system was used (entries 3 and 4) it was found that no coupling product could be observed (by GC); however, when a small amount of water was added to the system (entries 8 through 12) the coupling product could be seen, albeit in lower yield than that in the silver oxide system (entry 1). However, by comparing

entries 1 and 2 it can be seen that water has a deleterious effect on the yield of the coupling product. From this it can be reasoned that in the original system the Ag_2O is soluble enough in the THF that it works to participate in both events, where as in the mixed base system the bases were not soluble in the THF until the water was added, which was deleterious to the reaction. This theory led us to examine DME, which may allow for a mixed base system to be soluble.

When switching from THF to DME, the Ag_2O/K_2CO_3 system (entry 13) now becomes comparable to that of the Ag_2O in THF. The addition of K_2CO_3 to the silver oxide system in DME actually increases the yield as compared to Table 3, entry 6. To follow up, Ag_2CO_3 was examined (entry 14) as a method of combining the silver of Ag_2O with the carbonate base, K_2CO_3. However, Ag_2CO_3 actually produced a lower yield than the combined base system (entry 13).

Lastly, to insure that the effect was indeed due to the use of silver oxide and not just any metal oxide, copper(I) oxide and a mixed system of copper(I) oxide in combination with K_2CO_3 (entries 15 and 16) were screened. The use of Cu_2O did not facilitate the cross-coupling reaction, meaning the silver is essential to the reaction. In conclusion, after screening several bases and alternative metal oxides, it appears that silver oxide plays a critical role in the reaction.

Table 4: Results of base screening experiments



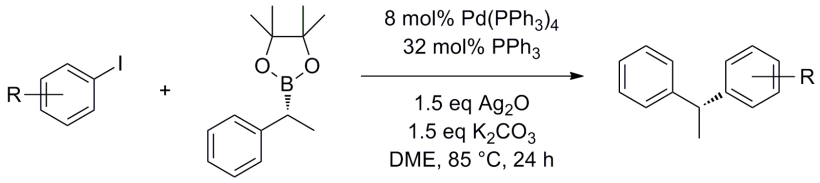
Entry*	Base (eq.)	Solvent	GC Yield (%)
1	Ag_2O (1.5)	THF	65
2	Ag_2O (1.5)	30:1 THF:H_2O	45
3	$AgBF_4$ (3)/K_3PO_4 (1.5)	THF	0
4	$AgBF_4$ (3)/Cs_2CO_3 (1.5)	THF	0
5	AgOAc (3)	THF	0
6	Ag_2O (1.5)/NaOAc (1.5)	THF	55
7	$AgBF_4$ (3)/NaOAc (1.5)	THF	0
8	$AgBF_4$ (3)/K_3PO_4 (1.5)	12:1 THF:H_2O	4
9	$AgBF_4$ (3)/Cs_2CO_3 (1.5)	12:1 THF:H_2O	10
10	$AgBF_4$ (3)/Cs_2CO_3 (1.5)	30:1 THF:H_2O	33
11	$AgBF_4$ (3)/Cs_2CO_3 (1.5)	120:1 THF:H_2O	36
12	$AgNO_3$ (1.5)/Cs_2CO_3 (1.5)	30:1 THF:H_2O	16
13	Ag_2O (1.5)/K_2CO_3 (1.5)	DME	64
14	Ag_2O (1.5)/Ag_2CO_3 (1.5)	DME	49
15	Cu_2O (1.5)	DME	0
16	Cu_2O (1.5)/K_2CO_3 (1.5)	DME	0

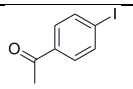
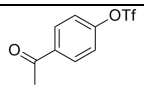
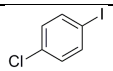
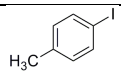
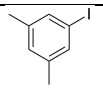
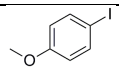
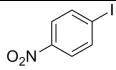
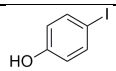
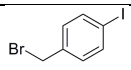
* Conditions: 8 mol% Pd_2dba_3, 64 mol% PPh_3, THF = 70 °C, DME = 85 °C, 24 h

2.2.4 Optimal Conditions and Substrate Scope

In collaboration with fellow student Martins Oderinde, it was found that the use of silver oxide and potassium carbonate in DME, with only 32 mol% PPh_3 and 8 mol% $Pd(PPh_3)_4$ (instead of 64 mol% and Pd_2dba_3) actually increased the retention of stereochemistry of product, even though the overall yield of the reaction was similar to the yield when the reaction was conducted in THF (Table 4, entry 1). This increase in retention of stereochemistry could be due to two potential factors: (1) the additional base (K_2CO_3) increases the rate of the transmetallation step and (2) the lower phosphine loading does not erode the enantiomeric excess of the boron species. Using these conditions (1.5 eq. Ag_2O, 1.5 eq. K_2CO_3, 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, DME, 85 °C, 24 h) as an optimal method, a variety of substrates were examined in this coupling. This screen included an array of electronically and sterically diverse aryl iodides to determine the effect of these parameters on the overall coupling (see Table 5).

Table 5: Summary of substrate scope for optimized cross-coupling conditions



Entry	Substrate	Previous Yield (%)[1]	Previous Retention (%)[1]	New Isolated Yield (%)	Retention of Stereochemistry (%)
1		63	92	64	99.5
2		----	----	0	----
3		62	91	75	99
4		60	92	78[b]	99
5		64	93	77[b]	97
6		48[a]	93	71	99
7		----	----	39	97
8		----	----	0	----
9		48[a]	93	64[b]	96
10		----	----	0[c]	----
11		----	----	81	93
12		----	----	96	95
13		----	----	0	----

[a] Yield determined by ^{1}H NMR. [b] Sample contains 5-10% homo-coupled product.

[c] Performed using 8 mol% Pd_2dba_3, 64 mol% PPh_3, 1.5 eq Ag_2O in THF at 70 °C

As can be seen from Table 5 the conditions are fairly general and, more importantly, proceed with essentially complete retention of stereochemistry for a variety of substrates. Overall, when comparison is made between these (columns 5 and 6) and previously reported yields and retentions[1] (columns 3 and 4), all these samples show higher results in both categories. The complete retention of configuration is essential for the application of this method to the synthesis of natural products.

It is noteworthy that the optimized conditions used for the substrates in Table 5 only apply to the coupling of aryl iodides. When an alternative to iodide, such as triflate is used, as in entry 2, the reaction does not proceed (compare to entry 1). The reaction is also selective when a choice of halogen is available. As seen in entry 3, the reaction proceeds exclusively at the iodo-position over that of the less reactive chloro-position. These observations could prove useful in the selective coupling of multi-functional substrates.

When comparing activated and deactivated aryl iodides, it appears that the reaction is not terribly sensitive to electronic substituents. One exception is the significantly lower yield found for the *para*-nitro substrate (entry 7), likely due to the extreme electron withdrawing or deactivating nature of the substituent. The failure of *para*-iodophenol (entry 8) to react is attributed to the likely deprotonation of the hydroxyl functionality in the presence of the base, which potentially could coordinate to the catalyst, causing its deactivation. Hydroxyl groups are commonly found in many natural and pharmaceutical products; therefore, the coupling of phenolic species would have been ideal. Despite this result, the reaction could still be applied to such species since many hydroxyl groups are masked as methoxy substituents and then deprotected later in a synthetic scheme.

The reaction seems to be slightly sensitive towards sterically bulky groups positioned ortho to the leaving group (compare entries 4, 9 and 10). The *ortho*-methyl group seems to cause a slight decrease in yield and retention of stereochemistry (relative to the *para*-methyl substituent, entry 4. A more drastic result is observed when the *ortho*-acetyl substrate (entry 10) is examined. The incorporation of the bulky and potentially chelating acetyl group apparently shuts down the catalytic cycle, resulting in no product formation.

Substrates 11, 12 and 13 were examined in an attempt to extend the reaction conditions to more complicated motifs, such as larger aromatic frameworks that are commonly found in many natural and pharmaceutical products. The cross coupling of 1-iodonaphthalene (entry 11) proceeded with a relatively high yield (81 %) and decent stereoselectivity (93 %). This result opens up a new set of substrates to be considered. Extending the cross-coupling to species possessing more complicated substitution around the naphthyl ring would increase the diversity of the reaction conditions and generate an interesting set of products.

Along with larger aromatic systems, aryl rings containing heteroatoms are common among natural products and pharmaceuticals. In order to probe the robustness of the reaction conditions to aryl rings possessing heteroatoms, 4-iodopyridine was considered (entry 12). The cross-coupling of this species proceeded in excellent yield and good selectivity, 96 % and 95 % respectively. This result suggests other heteroatoms may also be tolerated; the scope needs to be followed up with expansion to hetero-aromatic rings containing oxygen atoms and more substitution.

Lastly, a species containing two differently hybridized carbon atoms was probed to assess the potential of selective halide coupling. 1-(Bromomethyl)-4-iodobenzene (entry 13) offers the chance to couple at the sp^2-iodo position and the sp^3-bromo position. If the iodo

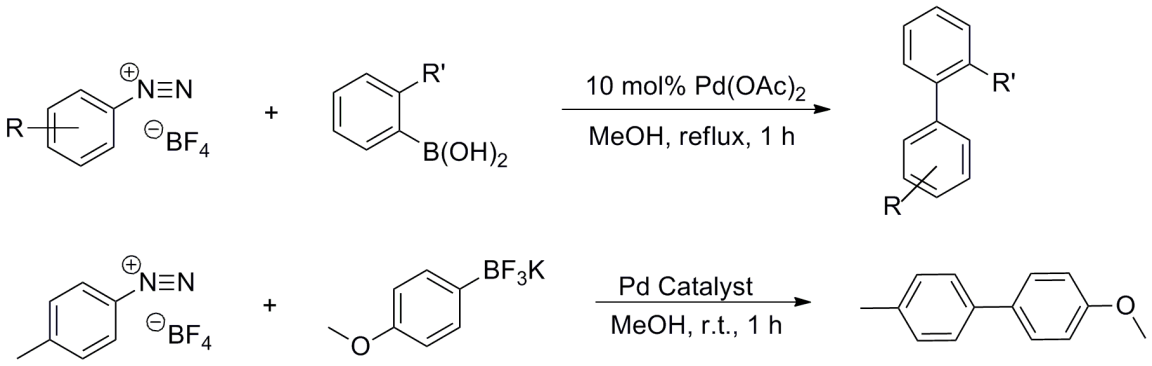
could first be coupled by our method, then the bromo could be coupled using a method developed by Fu[37] (see Scheme 16). Unfortunately, no cross-coupled product was observed under these conditions, but rather decomposition products were observed.

2.2.5 Cross-Coupling of Aryl Diazonium Salts

To enlarge the scope of the Suzuki reaction conditions described above and gain a mechanistic insight into the role of the silver oxide, we choose to investigate the coupling of aryl diazonium salts. It was thought that if the action of the silver oxide was only to remove the iodide from the metal centre, prior to the transmetallation of the boronic ester to the metal centre, then the reaction should occur without the addition of silver oxide. If silver oxide was acting to enhance the transmetallation of the boronic ester to the metal centre, then it would be required during the coupling of the aryl diazonium salts.

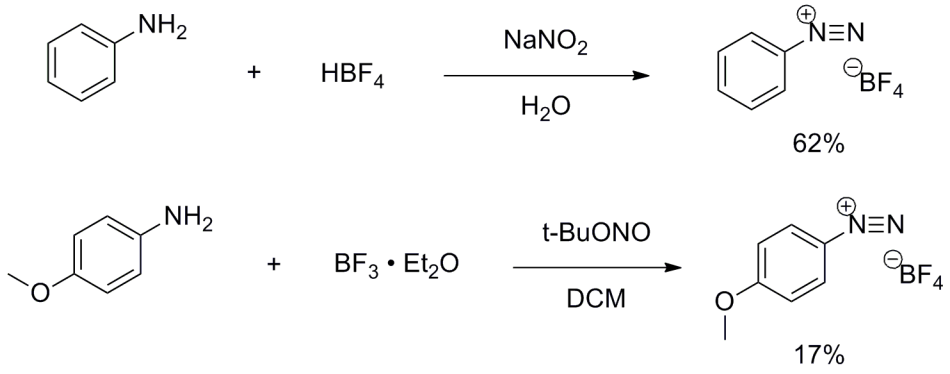
Aryl diazonium salts have been used as substrates in many transition metal catalyzed processes. In particular, diazonium salts have been used in the cross-coupling of arylboronic acids[62] and potassium aryltrifluoroborates[63], as shown in Scheme 31. Diazonium salts offer a unique substrate to study. Technically they should add to a metal centre more readily than an aryl halide since the oxidative addition of a diazonium to a metal centre will favorably release diatomic nitrogen as the leaving group. The evolution of nitrogen gas should drive the catalytic cycle forward; however, if the subsequent transmetallation and reductive elimination are not fast enough the homo-coupling of the diazonium substrate may prevail as the major pathway.

Scheme 31: Example diazonium cross-coupling reactions[62,63]



In order to synthesize the diazonium salts, the method shown in Scheme 32 was followed. The benzene diazonium tetrafluoroborate could be isolated in 62 % yield, while the *para*-methoxybenzene diazonium tetrafluoroborate was isolated in 17 %. The synthesis of *para*-acetylbenzene diazonium tetrafluoroborate was attempted several times; however, upon workup it would decompose to a red tar. This product would have been analogues to the model aryl iodide (4-iodoacetophenone) used previously. Once a family of diazonium salts was obtained attempts at cross-coupling were pursued.

Scheme 32: Synthetic method for obtaining diazonium salts

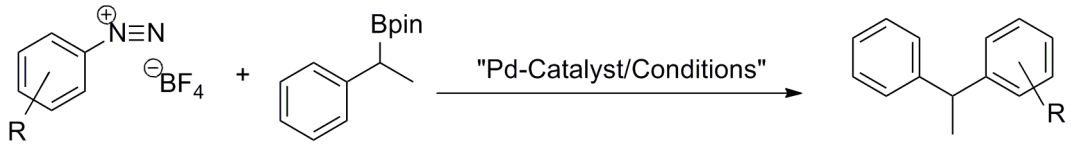


The unsubstituted and *para*-methoxy substituted diazonium salts were subjected to numerous coupling conditions, as seen in Table 6, with the effort directed towards obtaining a facile route to the desired coupling product. Unfortunately, conditions could not be obtained under which coupling was observed. It is known that PPh_3 can act as a nucleophile in the presence of diazoniums, causing the degradation of the diazonium species, which might explain the lack of reaction observed with these electrophiles.[62] Attempting the reaction in the absence of phosphine led to no reaction.

Most diazonium reactions take place in alcoholic solvents and at room temperature; however, varying either of these parameters did not give way to the synthesis of the desired product.

Overall, under none of the examined circumstances was the desired product observed by GC, but rather only the formation of homo-coupled diazonium salt was seen. This result is quite surprising, since facile coupling can be accomplished with the aryl boronic acids and potassium organotrifluoroborate salts, mentioned above. This does, however, illustrate the difficulty of transmetallation with secondary boronic esters. The generation of the homo-coupled product proceeded faster than that of the cross-coupling reaction, implying that the rate determining step was the transmetallation.

Table 6: Conditions attempted to cross-couple aryl diazonium salts



Entry	R	Catalyst (8 mol%)	Phosphine (64 mol%)	Base (eq.)	Solvent	Temp (°C)	Yield (%)
1	H	$Pd_2(dba)_3$	PPh_3	Ag_2O (1.5)	THF	70	0
2	H	$Pd_2(dba)_3$	PPh_3	----	THF	70	0
3	H	$Pd_2(dba)_3$	----	Ag_2O (1.5)	THF	70	0
4	H	$Pd_2(dba)_3$	----	Ag_2O (1.5)	THF	R.T.	0
5	H	$Pd_2(dba)_3$	----	Ag_2O (1.5)	MeOH	70	0
6	H	$Pd_2(dba)_3$	----	Ag_2O (1.5)	MeOH	R.T.	0
7	H	$Pd(OAc)_2$	----	Ag_2O (1.5)	MeOH	70	0
8	H	$Pd(OAc)_2$	----	Ag_2O (1.5)	MeOH	R.T.	0
9	H	$Pd(OAc)_2$	----	Ag_2O (1.5)	THF	70	0
10	H	$Pd(OAc)_2$	----	Ag_2O (1.5)	THF	R.T.	0
11	p-MeO	$Pd_2(dba)_3$	PPh_3	Ag_2O (1.5)	THF	R.T.	0
12	p-MeO	$Pd_2(dba)_3$	PPh_3	----	THF	70	0
13	p-MeO	$Pd_2(dba)_3$	PPh_3	----	^{i}PrOH	R.T.	0
14	p-MeO	$Pd_2(dba)_3$	PPh_3	Ag_2O (1.5)/K_2CO_3 (1.5)	DME	45	0
15	p-MeO	$Pd_2(dba)_3$	PPh_3	----	DME	45	0

2.3 Conclusions and Future Work

The application of the Suzuki-Miyaura cross-coupling reaction to secondary sp^3-hybridized boronic esters has been limited. The Crudden group has established a method using silver oxide to achieve set coupling in moderate yields, with high retention of stereochemistry.[1] We set out to improve on these conditions by varying the catalyst source, the solvent and the base. It was found that using the conditions presented in Table 5 (1.5 eq. Ag_2O, 1.5 eq. K_2CO_3, 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, DME, 85 °C, 24 h) a comparable yield but higher retention of stereochemistry could be obtained. This increase could be due to the extra base accelerating the transmetallation process and the lower phosphine loading not eroding the stereochemistry of the starting material and the product.

Using the new conditions, an expanded set of substrates were reacted and it was shown that the reaction is tolerant to a range of functionality. The reaction is slightly sensitive to electron withdrawing substituents and sterics in the ortho position to the iodide. Further work could include extending the reaction to more aromatic systems containing heteroatoms and larger ring systems.

It was thought that by using diazonium salts as electrophiles a greater mechanistic insight would be gained as to the role of silver oxide. Unfortunately, no conditions could be found to couple the diazonium salts. This result reinforces the postulate that the transmetallation is the slower step in the catalytic cycle.

Chapter 3: Investigation into Cross-Coupling Amide Substrates

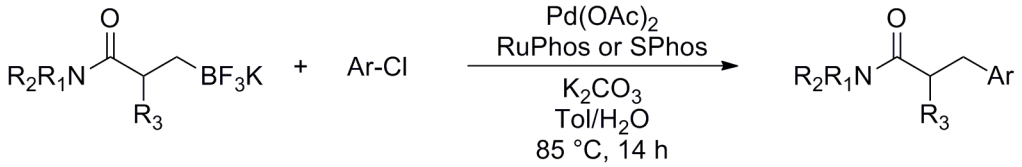
3.1 Introduction

In the hopes to expand the coupling conditions more widely, amides were investigated as potential coupling partners. Amides are important and unique substrates to consider due to their application in amino acid and peptide synthesis, their appearance in many compounds used as chiral auxiliaries (hence, they hold a great deal of importance in asymmetric synthesis) and their use in polymeric systems.

Even though amides are important moieties to consider, their presence as coupling partners in Suzuki-Miyaura cross-coupling is extremely limited. One example from the Molander group demonstrates the coupling of β-trifluoroborato amides with aryl chlorides.[64] Using the system presented in Scheme 33, they were able to couple a variety of aryl- and heteroarylchlorides with primary β-trifluoroborato amides in high yields. The use of the bulky, electron rich RuPhos provided mono-ligated organopalladium intermediates that allowed for the exclusive formation of the coupling product. This was presumably due to the effect of increasing the rate of reductive elimination relative to the β-hydride elimination. Similar to Molander's previous system that was discussed earlier (Scheme 20), this example only addresses primary organotrifluoroborates. In contrast, the Crudden silver oxide system addresses the coupling at a secondary branched boronic ester site; hence, it is reasonable to believe that it may also work for coupling secondary boronic esters possessing amide

functionality. Also, it was thought that the amide functionality may potentially accelerate the transmetallation process by forming a "metallocycle-like" complex.

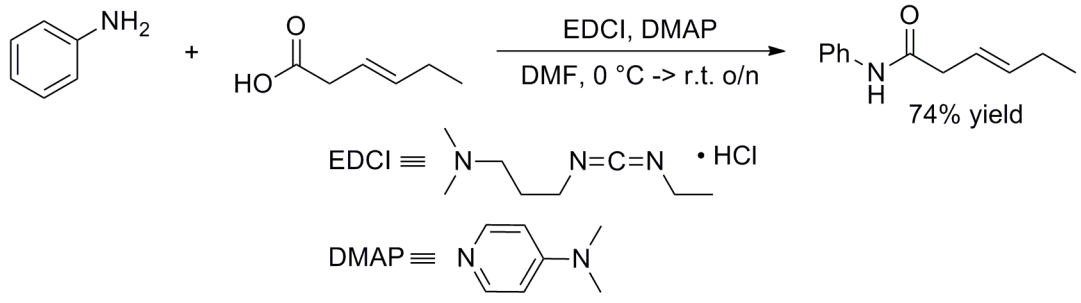
Scheme 33: Molander coupling of β-trifluoroborato amides[64]



3.2 Results and Discussion

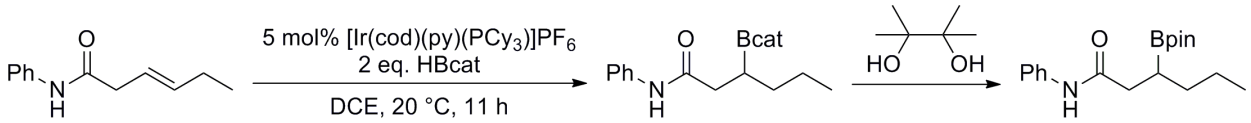
To advance these studies, we set out to synthesize secondary boronic esters at the β-position of an amide, for subsequent cross-coupling. In order to synthesize the desired amide, first the β,γ-unsaturated amide was generated followed by selective hydroboration, placing the boron substituent at the β-position. Using the coupling method displayed in Scheme 34 the desired unsaturated amide was prepared in a 74 % yield.

Scheme 34: Method used to synthesize β,γ-unsaturated amide



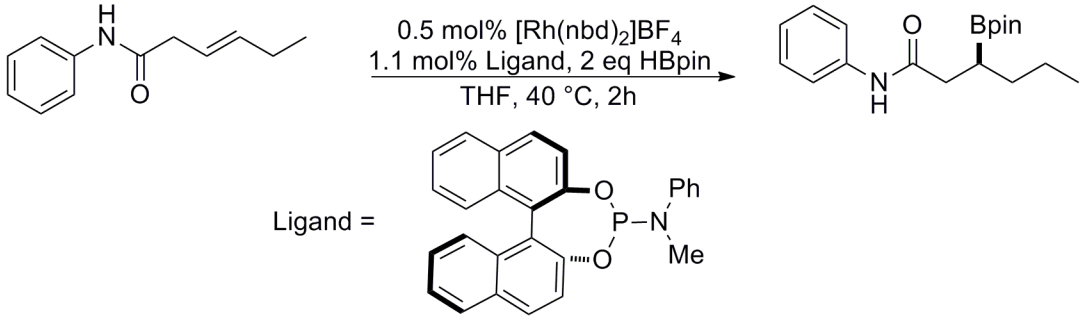
Within the literature there are only a few examples of methods that allow for the regioselective hydroboration of an β,γ-unsaturated amide: The first method uses Crabtree's catalyst, $[Ir(cod)(py)(PCy_3)]PF_6$, with HBcat in DCE (Scheme 35).[65,66] Following this method by a pinacol quench would result in the desired amide. However, after numerous attempts at performing this reaction the desired product could not be obtained. Instead small amounts of hydrogenated product were observed. This result is not totally unexpected due to the fact that Crabtree's catalyst is a very effective hydrogenation catalyst.[66]

Scheme 35: Attempted synthesis of β-substituted amide using Crabtree's catalyst



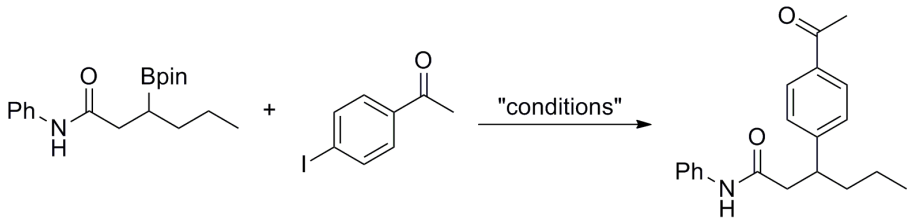
The second viable method for synthesizing the desired amide comes from the Takacs group.[67] They have developed an enantioselective hydroboration of β,γ-unsaturated amides that proceeds under mild conditions (Scheme 36), using a phosphoramidite ligand in conjunction with a cationic rhodium catalyst. When this method is employed for our unsaturated amide and using a racemic ligand, the desired boronic ester was isolated in a 73 % yield.

Scheme 36: Enantioselective amide hydroboration



With the desired substituted amide in hand, attempts at coupling immediately commenced. Under the general conditions from Table 5 (1.5 eq. Ag_2O, 1.5 eq. K_2CO_3, 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, DME, 85 °C, 24 h), the coupling of 4-iodoacetophenone and the β-substituted amide did not yield the desired product. Thus, varying the reaction conditions was attempted (refer to Table 7). By varying the catalyst, phosphine, base, solvent and temperature it was hoped to push the reaction towards the formation of the desired product. However, under a variety of conditions, we were unable to effectively couple the unactivated boronic ester. All systems attempted merely showed unreacted starting material by GC/MS. It was evident from this work that a way to activate the boronic ester was necessary.

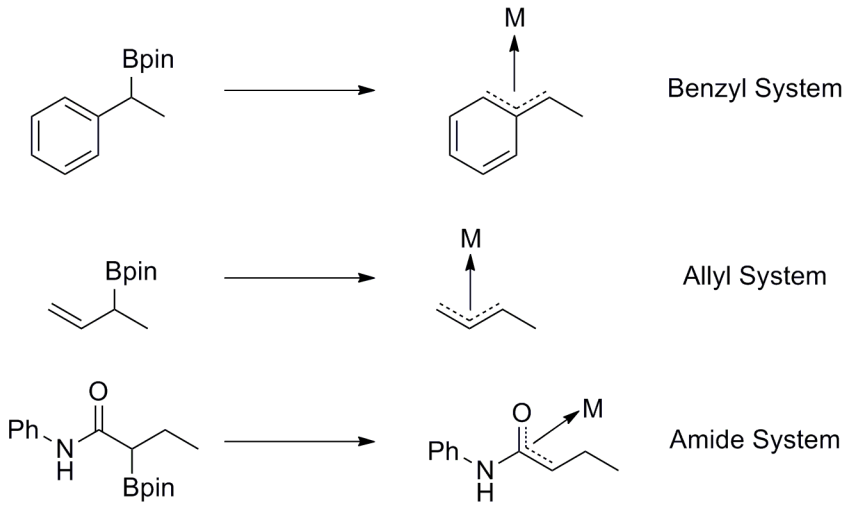
Table 7: Attempted conditions for the cross-coupling of β-substituted amides



Entry	Catalyst (mol%)	Phosphine (mol%)	Base (eq.)	Solvent	Temp. (°C)	Result (GC/MS)
1	$Pd(PPh_3)_4$ (8)	PPh_3 (32)	Ag_2O (1.5)/ K_2CO_3 (1.5)	DME	85	N.R.
2	$Pd(PPh_3)_4$ (8)	PPh_3 (32)	Ag_2O (1.5)/ K_2CO_3 (3.0)	DME	85	N.R.
3	$Pd(PPh_3)_4$ (8)	PPh_3 (32)	Ag_2O (1.5)/ Cs_2CO_3 (3.0)	DME	85	N.R.
4	$Pd(PPh_3)_4$ (8)	PPh_3 (32)	Ag_2O (1.5)/ K_3PO_4 (3.0)	DME	85	N.R.
5	$Pd(PPh_3)_4$ (8)	PPh_3 (32)	Ag_2O (1.5)/ NaOAc (3.0)	DME	85	N.R.
6	$Pd(OAc)_2$ (5)	SPhos (10)	K_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
7	$Pd(OAc)_2$ (5)	SPhos (10)	K_2CO_3 (3)	THF/H_2O (5:1)	85	N.R.
8	$Pd_2(dba)_3$ (10)	SPhos (10)	K_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
9	$Pd_2(dba)_3$ (10)	SPhos (10)	K_2CO_3 (3)	THF/H_2O (5:1)	85	N.R.
10	$Pd(OAc)_2$ (5)	XPhos (10)	K_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
11	$Pd(OAc)_2$ (5)	XPhos (10)	K_2CO_3 (3)	THF/H_2O (5:1)	85	N.R.
12	$Pd(OAc)_2$ (5)	RuPhos (10)	K_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
13	$Pd(OAc)_2$ (5)	RuPhos (10)	K_2CO_3 (3)	THF/H_2O (5:1)	85	N.R.
14	$Pd(OAc)_2$ (5)	RuPhos (10)	Ag_2O (1.5)/ K_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
15	$Pd(OAc)_2$ (5)	RuPhos (10)	Ag_2O (1.5)/ Cs_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
16	$Pd_2(dba)_3$ (5)	RuPhos (10)	Ag_2O (1.5)/ K_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
17	$Pd_2(dba)_3$ (5)	RuPhos (10)	Ag_2O (1.5)/ Cs_2CO_3 (3)	Tol/H_2O (5:1)	85	N.R.
18	$Pd_2(dba)_3$ (5)	RuPhos (10)	Ag_2O (1.5)/ Cs_2CO_3 (3)	Tol/H_2O (5:1)	120	N.R.
19	$Pd(OAc)_2$ (5)	RuPhos (10)	Ag_2O (1.5)/ Cs_2CO_3 (3)	Tol/H_2O (5:1)	120	N.R.
20	$Pd(OAc)_2$ (5)	RuPhos (10)	Cs_2CO_3 (3)	Tol/H_2O (5:1)	120	N.R.
21	$Pd(dppf)Cl_2$ (8)	----	Ag_2O (1.5)/ K_2CO_3 (1.5)	DME	85	N.R.
22	$Pd(PPh_3)_4$ (8)	PPh_3 (32)	CsF (1.5)	DME	85	N.R.
23	$Pd(PPh_3)_4$ (8)	PCy_3 (32)	Ag_2O (1.5)/ Cs_2CO_3 (1.5)	DME	85	N.R.

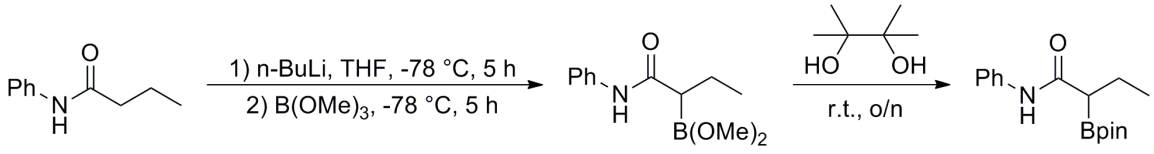
Concurrently in our lab, work was established outlining the necessity for the system to possess a boronic ester adjacent to a π-system. It was shown that 3-cyclohexenyl pinacol boronic esters would couple under our standard conditions; however, cyclohexyl pinacol boronic esters would not. This system implies that a π-electron system may be stabilizing the coordination of a metal centre during the course of the reaction (Scheme 37). The amide analogue of such system would be an α-substituted species, such as that depicted in Scheme 37.

Scheme 37: Proposed π-electron interaction



In order to generate an α-substituted system the corresponding α,β-unsaturated amide cannot be used for the subsequent hydroboration at the desired α-position. If this is attempted it would result in a 1,4-Michael addition. Therefore, the new route displayed in Scheme 38 was proposed as a method for obtaining the desired boronic ester.

Scheme 38: Proposed route to α-substituted amide



The method shown in Scheme 38 was attempted. First using 1.2 equivalents of both n-BuLi and $B(OMe)_3$ followed by 5 equivalents of pinacol, and secondly by increasing the equivalents to 5 and 10, respectively. On both occasions only a molecular ion peak representative of the staring amide could be observed by GC/MS. On the second occasion a "product" representing the mass-to-charge ratio of the starting amide was isolated; however, by NMR no amide NH peak could be observed. Over time, if left in the NMR solvent, the sample degraded back to a species possessing an amide NH peak. With this in mind, it is proposed that a nitrogen-boron adduct is formed that is unstable over time. Future work to test this theory would involve the synthesis of a representative tertiary amide and subjecting it to the reaction conditions in Scheme 38, with hopes of generating the desired α-substituted amide.

3.3 Conclusions and Future Work

The extension of coupling parameters to include substituted amides would have opened up an important class of substrates to be investigated. However, under no conditions could the desired product be obtained. This supports that idea that the benzylic positioning of the boronic ester is essential. It was thought that generating α-substituted amides would be more representative of the benzyl positioning in the aryl-secondary organoboronic acid substrates. Efforts to synthesize this substitution pattern were attempted; however the desired product could not be obtained. In the future attempts should be made with either a protecting group, such as the BOC group, attached to the nitrogen of the amide or by synthesizing a tertiary amide. This would allow for deprotonation to only occur at the α-carbon; hopefully yielding the desired product. Once obtained this substrate should be subjected to coupling conditions.

Chapter 4: Investigating Selective Cross-Coupling

4.1 Introduction

The ability to independently control the reactivity of two moieties in one molecule is critical in the design of synthetic routes that do not require protection/deprotection steps. The selective coupling of boron functionalities in the same molecule would allow for the generation of unique structures that could not be accessed through other routes.

As mentioned previously, there exist methods for the coupling of aryl and alkyl electrophiles that vary depending on the halogen atom present and the hybridization of the electrophile. The hybridization of the boron species could also be used to selectively couple one moiety over another, for example the coupling of an aryl position over an alkyl position. When the coupling of secondary organoboronic esters was initially reported by the Crudden group, the conditions showed selective coupling at the secondary position over that of a primary position.[1] This leads to the opportunity to selectively couple a secondary position over a primary position found in the same molecule.

The method reported by the Crudden group also showed selectivity for the halogen coupled in the process. When 4-chloroiodobenzene was subjected to coupling procedures there was complete reactivity at the iodo-position over the chloro-position.[1] This would allow for the selective coupling of halogen moieties in a single molecule.

Thus we set out to synthesize a molecule possessing two boron substituents on differently hybridized carbon atoms and subsequently couple each moiety while retaining the other for coupling at a later time. Once methods could be established for independently

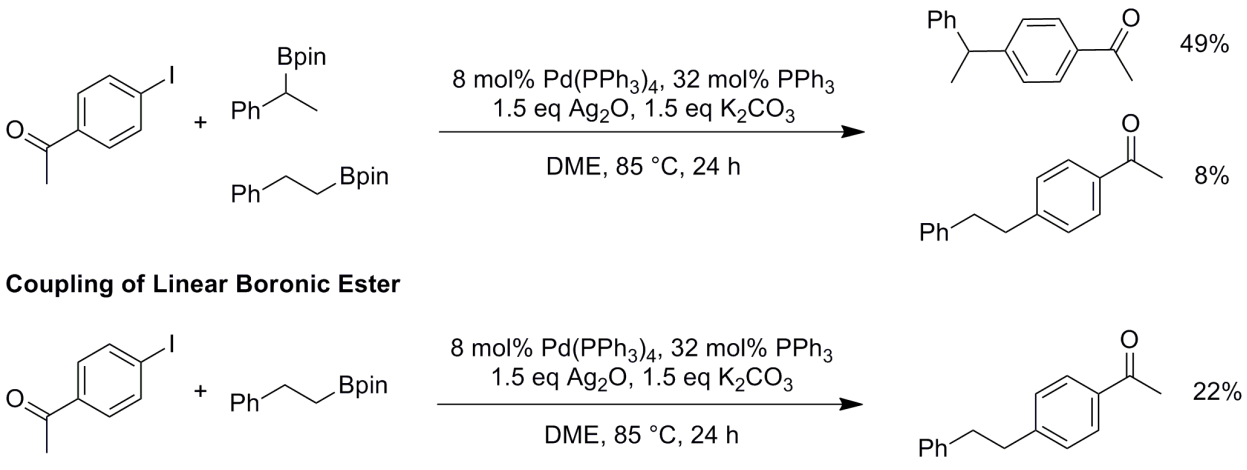
coupling one moiety over the other, the transfer of the conditions to a one-pot synthesis would be optimal.

4.2 Results and Discussion

Initial reports from the Crudden group showed that when a mixture of the branched and linear boronic esters (65:35) was subjected to the original cross-coupling conditions (8 mol% Pd_2dba_3, 64 mol% PPh_3, 1.5 eq. Ag_2O in THF at 70 °C for 18 h) the branched product was observed with only trace amounts of the linear product (Scheme 25).[1] Subsequently when a pure sample of the linear boronic ester was subjected to coupling conditions, no linear product was observed. Under the new conditions (8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, 1.5 eq. Ag_2O, 1.5 eq. K_2CO_3 in DME at 85 °C for 24 h) we postulate that the linear product would result since a traditional Suzuki base, K_2CO_3, is added to the mixture.

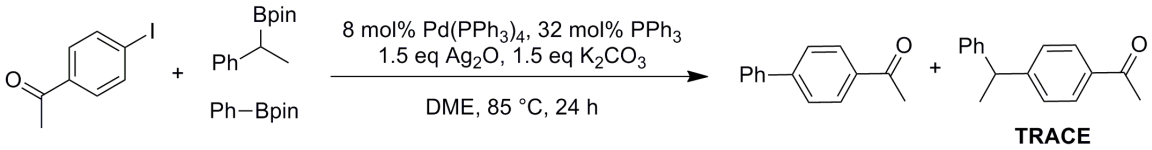
As seen from Scheme 39, when an equimolar concentration of branched and linear boronic esters is subjected to the new coupling conditions there is preference for the formation of the branched product; however, unlike previous results[1] the linear product was also observed, albeit in less than 10% yield. Under the K_2CO_3 containing conditions, when only the linear boronic ester is subjected to the new coupling conditions it couples in a 22% yield. This shows that the potassium salt is working like a traditional Suzuki base, allowing for the primary position to be coupled. These results show that in order for the selective coupling of a species containing both a branched and a linear boronic ester moiety, one would have to couple at the linear position before coupling at the branched position. This work is currently being investigated by other group members.

Scheme 39: Competitive coupling: branched versus linear



From here we chose to investigate whether the new conditions were selective for a branched boronic ester over an aryl boronic ester. In general, aryl boronic esters are easier to couple than the linear or branched species. By performing an equimolar competition study between phenyl pinacol borate and the branched pinacol(1-phenylethyl)boronate (Scheme 40) we were able to observe almost exclusive formation of the aryl coupling product, with only trace branched product by GC.

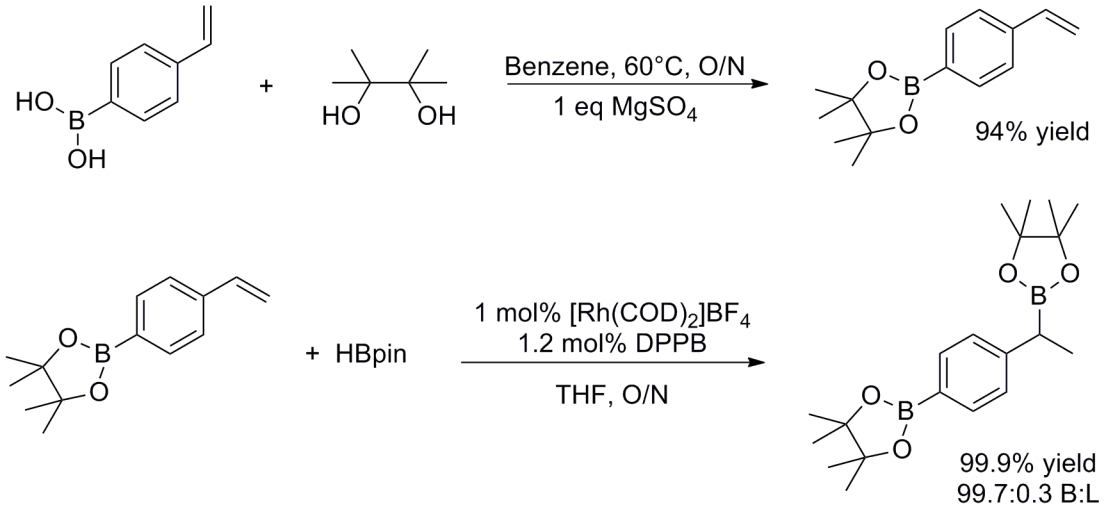
Scheme 40: Competitive aryl versus branched selectivity



This exciting result suggested that the same conditions could be used to sequentially couple both boronic ester moieties simply by the addition of a second equivalent of aryl iodide. After this we sought to examine if these conditions could be directly applied to a substrate

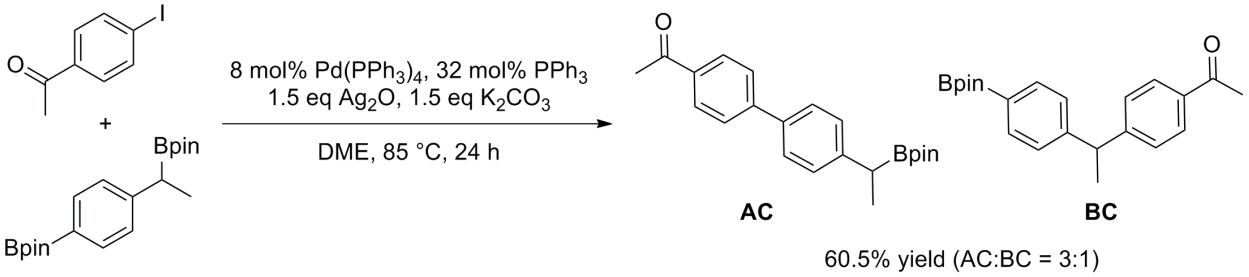
containing both an aryl and a secondary boronic ester moiety. Starting from the commercially available 4-vinylbenzeneboric acid, we were able to synthesize the desired product in two steps, in high yield and high regioselectivity (Scheme 41).

Scheme 41: Synthesis of di-boronic ester species



When the resulting di-boronic ester species was subjected to the new coupling conditions from above (1.5 eq. Ag_2O, 1.5 eq. K_2CO_3, 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, DME, 85 °C, 24 h) the results did not show the same selectivity distribution as seen during the competitive study (Scheme 40). It was found that a species with an appropriate mass-to-charge ratio of 350.26 could be isolated in 60.5 % yield; however, by NMR and GC the product was found to contain a mixture of species that were mono-coupled at the aryl position (AC) and the branched position (BC), in a ratio of 3:1 (Scheme 42). With further optimization it was proposed that the reaction could be pushed to favor the coupling at the aryl position over the branched position.

Scheme 42: Initial attempts at selective coupling in one molecule



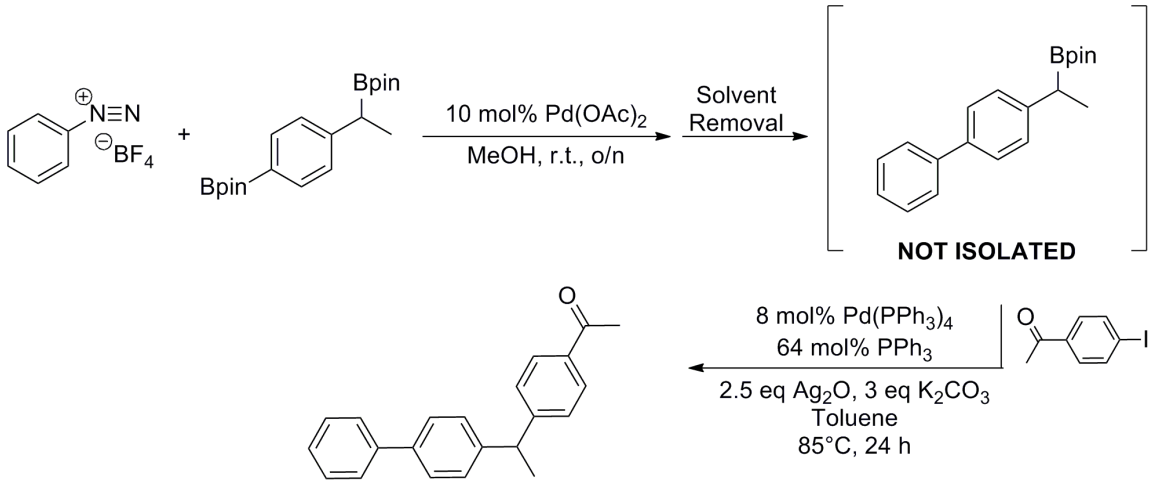
In order to optimize the reaction conditions for the cross-coupling at the aryl position (AC), over the branched position (BC), a series of various bases, catalysts, phosphine ligands and solvents were investigated (refer to Table 8 for complete conditions). Through monitoring by GC/MS conditions that would generate a single product, corresponding to the aryl-coupling product, could not be determined.

Table 8: Attempts at optimizing selective coupling

Entry	Base (eq.)	Catalyst	Ligand	Solvent	Product Distribution (by GC/MS)
1	K_2CO_3 (1.5)	$Pd(PPh_3)_4$	PPh_3	DME	Trace AC
2	K_2CO_3 (1.5)/ Ag_2O (1.5)	$Pd(PPh_3)_4$	PPh_3	DME	Trace AC & BC
3	Ag_2CO_3 (1.5)	$Pd(PPh_3)_4$	PPh_3	DME	Moderate AC & BC
4	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(PPh_3)_4$	PPh_3	DME	Trace AC
5	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(PPh_3)_4$	PPh_3	DME	Trace AC
6	Cs_2CO_3 (1.5)	$Pd(PPh_3)_4$	PPh_3	DME	Trace AC & BC
7	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(OAc)_2$	PPh_3	DME	Moderate AC
8	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(OAc)_2$	PPh_3	DME/H_2O (100:1)	Moderate AC
9	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(OAc)_2$	PPh_3	DME/H_2O (50:1)	Trace AC
10	K_2CO_3 (1.5)	$Pd(OAc)_2$	PPh_3	DME/H_2O (50:1)	Trace AC
11	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(OAc)_2$	SPhos	DME	Trace AC
12	$K_3PO_4 \cdot nH_2O$ (1.5)	$Pd(OAc)_2$	RuPhos	DME	Trace AC

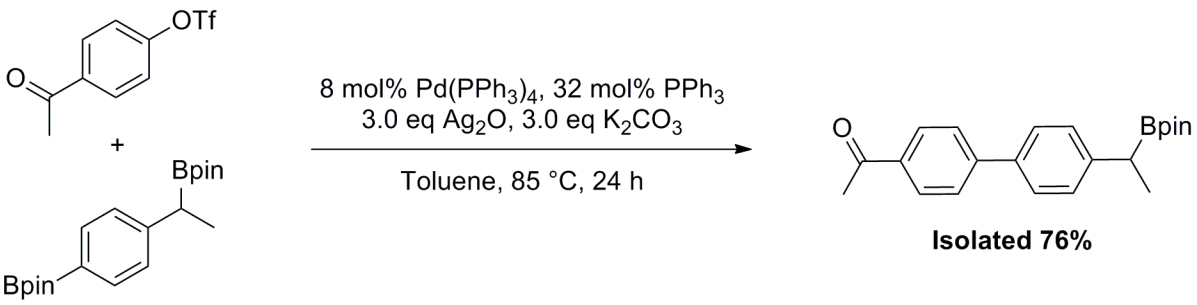
Since a set of conditions was not identified to favor the exclusive coupling of the aryl boronic ester with an aryl iodide, it was proposed that exploring alternate aryl electrophiles may be advantageous. Previously, aryl diazonium compounds were examined as potential coupling partners (refer to section 2.2.5). Since aryl diazoniums were deemed unsuitable for coupling at the branched position and there exists literature precedent for coupling at the aryl position,[68] we set out to determine if they would work as suitable selective coupling partners. Based on work by Sengupta the coupling of benzenediazonium tetrafluoroborate and pinacol phenylboronate can be accomplished using 10 mol% of $Pd(OAc)_2$ in methanol at room temperature.[62] In order to investigate the selectivity of the diazonium substrate, competition studies were done using equimolar amounts of pinacol phenylboronate and pinacol (1-phenylethyl)boronate (10 mol% of $Pd(OAc)_2$ in methanol at room temperature). The results of these studies showed complete consumption of the pinacol phenylboronate, to form biphenyl, and the non-consumption of the secondary organoboronic ester. When this reaction was applied to a one-pot procedure no sequential coupling product could be observed (Scheme 43).

Scheme 43: Attempt at selective one-pot diazonium coupling



As shown in Table 5, section 2.2.4, 4-acetylphenyl trifluoromethanesulfonate does not couple with the branched position under the standard conditions (8mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, 1.5 eq. Ag_2O, 1.5 eq. K_2CO_3 in DME at 85 °C for 24 h); hence, it seemed like a reasonable electrophile for the selective coupling. When subjected to the conditions present in Scheme 42 no cross-coupled product could be observed; however, changing the solvent from DME to THF and toluene proved important. The use of THF showed no product formation. The switch to toluene was more advantageous, as shown in Scheme 44, and the desired product could be isolated in 76 % yield as the only coupling product. We also increased the concentration of base from 1.5 equivalents of both Ag_2O and K_2CO_3 to 3.0 equivalents of each, in order to ensure the optimal yield of the desired product.

Scheme 44: Selective triflate coupling conditions

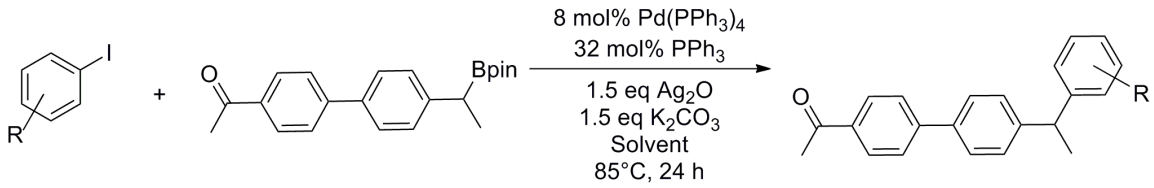


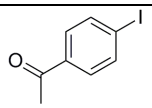
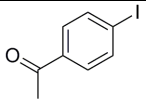
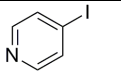
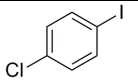
The high amount of base that was required to drive this reaction seemed wasteful and unnecessary, as K_2CO_3 alone is generally enough to couple at the aryl position. As expected when the reaction was attempted without the use of silver oxide the desired product was observed in 82 % yield (by NMR), which is comparable to the 76 % isolated yield determined when using both Ag_2O and K_2CO_3. It was also thought that the reaction may proceed at room temperature; however, this was not the case and only starting material was observed by GC/MS.

Once isolated, the mono-coupled boronic ester was subjected to the second coupling step, as shown in Table 7. It can be seen that for the 4-iodoacetophenone substrate the original optimal coupling solvent, DME, was again one of the better solvents for the second coupling step (entry 1 vs. 2). This result was not done multiple times and in fact toluene could prove to be the optimal solvent or a wider range of substrates. With this information in hand two of the best iodo-substrates, 4-chloroiodobenzene and 4-iodopyridine, from Table 5 were used to explore the second coupling step. The reaction of 4-chloroiodobenzene with the product from Scheme 44, gave the desired tri-aryl species in 55 % yield, by NMR, whereas the coupling of 4-iodopyridine gave the desired product in 32 % yield. It appears that now the extension of the ring system actually works to deactivate the coupling process, since the yields are considerably lower than when the original single boronic ester species, pinacol(1-phenylethyl)boronate, was

used. The 4-chloroiodobenzene gave 75 % yield and the 4-iodopyridine gave 96 % yield (refer to Table 5) when coupled with pinacol(1-phenylethyl)boronate). These reactions were only ran once and should be repeated in order to confirm the decrease of yields.

Table 9: Select substrates for the coupling of secondary boronic ester

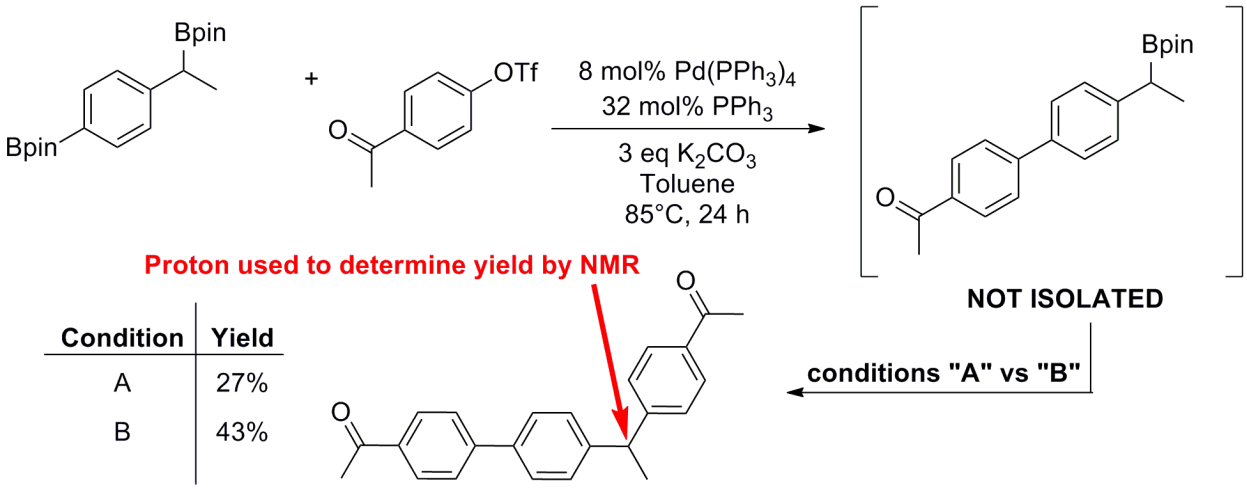


Entry	Substrate	Solvent	NMR Yield
1		DME	49%
2		Tol	43%
3		DME	32%
4		DME	55%

The ultimate goal would be to take the combined conditions for selective coupling of each boronic ester and generate a one-pot synthesis. With this goal in mind, preliminary investigations into concocting a one-pot procedure were attempted. Scheme 45 illustrates the direction with which a one-pot synthesis was attempted. It was thought that if the formation of the first coupling product could be done and then manipulated for the second coupling, the desired species could be obtained. Conditions A and B refer to steps taken after the allotted amount of time for the first coupling to occur. While both coupling steps are done under inert

atmosphere, condition A refers to the reaction mixture being exposed to air after the first coupling step was complete, then filtered through Celite and the solvent was removed by rotary evaporation. The reaction was then transferred back into the glove box and fresh $Pd(PPh_3)_4$ (8 mol%), PPh_3 (32 mol%), 1.5 eq Ag_2O, 1.5 eq K_2CO_3, DME and 1.0 eq of 4-iodoacetophenone were added. The reaction mixture was sealed, removed from the glove box and placed in an 85 °C oil bath for another 24 h. With condition B, after the first coupling step was complete, the reaction mixture was immediately taken back into the glove box and unsealed in the nitrogen atmosphere; without removing solvent, 1.0 eq of 4-iodoacetophenone and 1.5 eq. of Ag_2O were added to the solution. The reaction was resealed, removed from the glove box and placed in an 85 °C oil bath for another 24 h. By NMR, the yields from conditions A and B were found to be 27 % and 43 %, respectively. From this result it seems as though exposing the reaction mixture to air and placing it on the rotary evaporator may have actually caused the degradation of the sp^2-coupled product or generated other by-products that may work to shut down the catalytic cycle. The more interesting result is that of condition B. The same yield is obtained under this condition as that of coupling the isolated sp^2-coupled product (refer to Table 7, entry 2). This suggests that the catalyst species can be preserved during the cooling and heating procedure, as long as the reaction mixture is not exposed to air. If the second coupling step can be optimized in toluene the transfer to a one-pot procedure should proceed smoothly. This optimization will be the subject of future investigations.

Scheme 45: Attempt at one-pot selective coupling



Condition	Yield
A	27%
B	43%

4.3 Conclusion and Future Work

In the initial report by the Crudden group it was found that the coupling conditions were selective for coupling of a secondary boronic ester, over a primary one.[1] Under our new conditions of using K_2CO_3 and Ag_2O erosion of this selectivity is observed; hence, for selective coupling one would have to couple at the primary position before the secondary position.

From here we choose to investigate the selectivity at an aryl position versus the secondary boronic ester. It was found that in an intermolecular competition study that the aryl boronic ester would exclusively couple over the secondary position; however, when this was applied to a species possessing both centres the coupling occurred in a 3:1 ratio of aryl to branched products. This was unacceptable and after a series of screenings it was found that if an aryl triflate was used as the electrophile, instead of an aryl iodide, the coupling occurred only at the aryl boronic ester. The aryl-coupled product could be isolated in 76 % yield. This product was subjected to a small substrate scan of coupling at the secondary position. The yields obtained

were lower than expected based on previous coupling of the unsubstituted secondary boronic ester. Further optimization of the secondary coupling step is required.

Preliminary one-pot coupling experiments were attempted and the desired coupling products were observed in similar yields to that observed if the product of the aryl coupling was isolated and subjected to coupling at the secondary position. Once conditions are optimized for coupling at the secondary position, after aryl coupling, they should be applied to a one-pot procedure.

Chapter 5: Summary and Overall Conclusions

The application of Suzuki-Miyaura cross-coupling to secondary organobornic esters has been limited in the past. The recent advancements from the Crudden group[1], the addition of silver oxide to a palladium/phosphine catalyst system, have allowed for the coupling of this difficult substrate to be achieved. We set out to improve upon these conditions and expand the reaction to a larger number of substrates, while gaining a greater understanding of the mechanism under way. It was found that by adding K_2CO_3 (1.5 eq.) and lowering the loading of phosphine ligand (32 mol% vs. 64 mol%) a comparable yield but higher retention of stereochemistry could be obtained. This phenomenon may be due to the extra base increasing the rate of transmetallation and the lower phosphine loading not eroding the stereochemistry of the starting material and product.

The new conditions (1.5 eq. Ag_2O, 1.5 eq. K_2CO_3, 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, DME, 85 °C, 24 h) allowed for the coupling of a wide variety of substrates; however, the reaction was found to be sensitive towards strongly electron withdrawing substituents and those found in the ortho-position of the aryl iodide. The reaction could not be extended to coupling aryl-diazonium salts. This reinforces the difficulty of this reaction when concerning secondary organoboronic esters.

Attempts were made at transferring the reaction conditions to amide substrates, possessing secondary organoboronic esters in the β-position; however, under no conditions could these substrates be coupled. This work exemplifies the importance of the benzylic positioning of the boronic ester in the original substrate used for optimization. It was proposed

that an α-substituted amide would be a better analogue to the benzylic system; unfortunately attempts to synthesize such a species did not yield any of the desired product.

The initial report from the Crudden group showed selectivity of the reaction towards branched organoboronic esters over primary species.[1] It was found that this was not the case for the new conditions involving potassium carbonate. The linear boronic ester now coupled to a small degree. In terms of selectivity of the reaction, for aryl versus branched secondary boronic esters, the conditions were found to be highly selective for the aryl species, in an intermolecular competition. When the conditions (1.5 eq. Ag_2O, 1.5 eq. K_2CO_3, 8 mol% $Pd(PPh_3)_4$, 32 mol% PPh_3, DME, 85 °C, 24 h) were applied to an intramolecular competition the erosion of selectivity was observed. To overcome this dilemma the switch from aryl iodides to aryl triflates was attempted and complete selectivity at the aryl position was observed. This revelation allowed for the application of conditions to a one-pot, selective two-step coupling procedure.

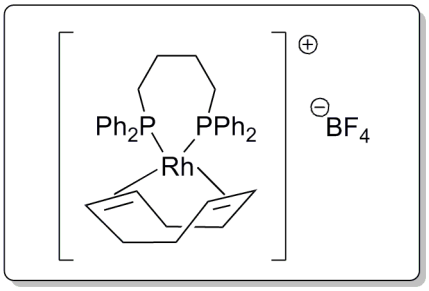
Chapter 6: Experimental

General Considerations

All reaction solvents, with the exception of water, were purified by literature procedures or taken from an alumina-dried purification system (Innovative Technologies SPS) and then degassed by a minimum of three freeze-pump-thaw cycles. When water was used in the system degassing was accomplished by rapidly bubbling inert gas (argon or nitrogen) into the stirring liquid. All dry solvents were stored over 4 Å molecular sieves. All reagents were purified by literature preparations and degassed as above when necessary. Any thin layer chromatography was performed on aluminum backed silica plates with F-254 indicator and visualized using a UV source (254, 365 nm) or by treatment with phosphomolybdic acid. Column chromatography was performed using flash grade silica (Silicycle, 50 μm particle size, 60 Å porosity) and reagent grade solvents. Unless otherwise noted all NMR spectra were obtained at 400 MHz (^{1}H), 100 MHz (^{13}C) and 161 MHz (^{31}P) in $CDCl_3$. All GC spectra were obtained using an Agilent 6850 chromatograph using an FID detector, loaded with an HP-5 column (L = 30 m; ID = 0.32 mm) and operating with splitless injection and helium as the carrier gas. All GC/MS spectra were obtained using an Agilent 6850 chromatograph coupled to a Agilent 5975C VL-MSD with triple-axis detector. All determinations of stereochemistry were done using analysis on a supercritical fluid chromatograph. Analytical Supercritical Fluid Chromatography (SFC) was performed on a Berger SFC HPLC using the specified chiral Berger Silica column and specified conditions of co-eluent, flow rate and pressure.

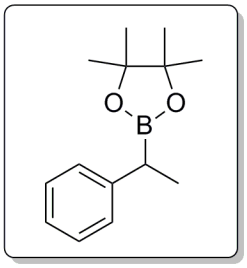
Screening of Variables for Optimal Cross-Coupling

Synthesis of Hydroboration Catalyst, [Rh(cod)(DPPB)]BF_4:



$[Rh(cod)Cl]_2$ (293.6 mg, 0.595 mmol) was weighed into an oven dried rbf and placed under vacuum for 1 h before back-filling with an N_2 atmosphere. 5 mL of distilled, deoxygenated THF was added *via* cannula to dissolve the Rh-dimer with stirring. In a nitrogen filled glove box, $AgBF_4$ (232.52 mg, 1.18 mmol) was added to a dried rbf and dissolved in 4 mL of THF. The Ag-solution was removed from the glove box and cannulated into the Rh-dimer solution, causing the immediate formation of a white precipitate. The mixture was allowed to stir for 1 h. The filtrate was transferred *via* cannula filter into a second dried Schlenk flask containing DPPB (511.86 mg, 1.20 mmol) dissolved in 10 mL of THF. The resulting red solution was allowed to stir overnight. The solution was evacuated to remove solvent and the resulting powder was washed with 2 mL of cold THF. The filtrate was removed with a cannula filter and the resulting powder dried *in vacuo* for 2 h to give the desired product in 90 % yield. ^{1}H NMR: δ 7.26-7.56 (m, 20H, PPh_2), 4.47 (br s, 4H, olefinic H of cod), 3.73 (br s, 4H, THF), 2.46 (br s, 4H, alkyl H of DPPB), 2.42-2.13 (m, 8H, alkyl H of cod), 1.66 (m, 4H, alkyl H of DPPB). $^{31}P\{^1H\}$ NMR: δ 24.06 (d, J = 143.7 Hz).

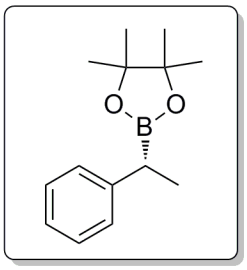
Representative Hydroboration of Styrene with Racemic Phosphine



In a nitrogen filled glove box, $[Rh(cod)_2][BF_4]$ (28.38 mg, 0.069 mmol) and DPPB (35.95 mg, 0.084 mmol) were weighed into a vial and taken up in THF (4 mL) with stirring. Separately, styrene (739.78 mg, 7.10 mmol) and HBpin (1115.95 mg, 8.72 mmol) were weighed into a vial and transferred

to the catalyst solution using 2 mL of THF. The resulting solution was capped and stirred at glove box temperature for 3 days. The resulting solution was removed from the glove box and 5 mL of water was added. The solution was extracted with 3x5 mL EtOAc. The organic layers were combined, dried with anhydrous Na_2SO_4 and passed through a plug of silica gel; washed with hexanes. The solvent was removed by rotary-evaporation, followed with placing on high-vac, and the desired product was isolated in 92% yield with a branched to linear ratio of 98:2 (by GC). ^{1}H NMR: δ 7.29-7.11 (m, 5H), 2.43 (q, J = 7.4 Hz, 1H), 1.33 (d, J = 7.4 Hz, 3H), 1.21 (s, 6H), 1.20 (s, 6H). ^{13}C NMR: δ 128.48, 128.42, 127.92, 125.20, 83.42, 24.77, 24.73, 17.19.

Representative Hydroboration of Styrene with Chiral Phosphine: (R)-Pinacol(1-phenylethyl)boronate:



In a nitrogen filled glove box, $[Rh(cod)_2][BF_4]$ (24.36 mg, 0.06 mmol) and (R)-BINAP (42.14 mg, 0.068 mmol) were weighed into a vial, taken up in 4 mL of DME and transferred to a dried Schlenk tube. After 10 min of stirring, styrene (316.06 mg, 3.03 mmol) was added to the catalyst solution. Separately HBcat (438.21 mg, 3.65 mmol) was weighed into a dried rbf and dissolved in 2 mL of DME. Both solutions were removed from the glove box and cooled to -78 °C. The HBcat solution was slowly transferred, *via* cannula, to the solution of styrene and Rh^+ catalyst. After stirring for 5 h at temperatures below -70 °C, solid pinacol (1.07 g, 9.03 mmol) was added in one addition and the system was quickly purged with argon. Reaction was allowed to warm to room temperature over night. The product was isolated by column chromatography (20:1 Hex:EtOAc) in 90% yield and NMR and GC were used to confirm the branched to linear ratio of 99:1. The product had an enantiomeric ratio of 93:7, as determined by SFC chromatography after anaerobic oxidation of the boronic ester to the corresponding alcohol using NaOH and H_2O_2

(column OD 5% MeOH, 2mL, 200 bar). ^{1}H NMR: δ 7.3-7.13 (m, 5H), 2.45 (q, J = 7.5 Hz, 1H), 1.35 (d, J = 7.5 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H). ^{13}C NMR: δ 145.11, 128.42, 127.92, 125.20, 83.41, 24.77, 24.73, 17.19.

General Procedure for Catalyst Screening (Table 2, entry 3):

In a nitrogen filled glove box, n-octadecane (internal standard, 11.06 mg), 4-iodoacteophenone (12.54 mg, 0.0510 mmol), *rac*-pinacol(1-phenylethyl)boronate (19.45 mg, 0.0838 mmol), Ag_2O (17.46 mg, 0.0753 mmol), NaOAc (6.07 mg, 0.0740 mmol), $Pd(PPh_3)_4$ (4.56 mg, 0.00395 mmol) and PPh_3 (10.95 mg, 0.0417 mmol) were weighed into a dried vial and taken up in 1 mL of THF. The reaction was sealed and stirred at 70 °C for 24 h. The reaction mixture was cooled and filtered through Celite followed by washing twice with ether. The reaction mixture was analyzed by GC to show a yield of 65%.

General Procedure for Solvent Screening (Table 3, entry3):

In a nitrogen filled glove box, n-octadecane (internal standard, 12.22 mg), 4-iodoacteophenone (12.14 mg, 0.0494 mmol), *rac*-pinacol(1-phenylethyl)boronate (17.44 mg, 0.0751 mmol), Ag_2O (17.38 mg, 0.0750 mmol), $Pd_2(dba)_3$ (1.83 mg, 0.002 mmol) and PPh_3 (8.53 mg, 0.0325 mmol) were weighed into a dried vial and taken up in 1 mL of toluene. The reaction was sealed and stirred at 70 °C for 18 h. The reaction mixture was cooled and filtered through Celite followed by washing twice with ether. The reaction mixture was analyzed by GC to show a yield of 52%.

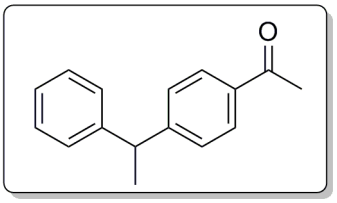
General Procedure for Base Screening (Table 4, entry 9):

In a nitrogen filled glove box, n-octadecane (internal standard, 11.25 mg), 4-iodoacteophenone (12.18 mg, 0.0495 mmol), *rac*-pinacol(1-phenylethyl)boronate (18.61 mg, 0.0802 mmol), $AgBF_4$ (29.37 mg, 0.151 mmol), Cs_2CO_3 (25.14 mg, 0.0772 mmol), Pd_2dba_3 (1.79 mg, 0.00195 mmol)

and PPh_3 (8.50 mg, 0.0324 mmol) were weighed into a dried vial and taken up in 1.20 mL of THF. The reaction was sealed with a septum and removed from the glove box. By syringe 0.1 mL of degassed H_2O was added and the septum was replaced for a Teflon cap using heavy Ar flow to avoid contaminating the atmosphere. The reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled and filtered through Celite followed by washing twice with ether. The reaction mixture was analyzed by GC.

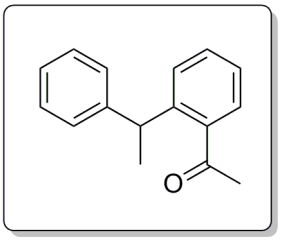
Substrate Scope Using Optimal Conditions (Table 5)

Synthesis of 1-phenyl-1-(4-acetylphenyl)ethane from 4-acetylphenyl trifluoromethanesulfonate:



In a nitrogen filled glove box, n-octadecane (internal standard, 11.16 mg), 4-acetylphenyl trifluoromethanesulfonate (11.16 mg, 0.0416 mmol), *rac*-pinacol(1-phenylethyl)boronate (16.04 mg, 0.0691 mmol), Ag_2O (17.32 mg, 0.0747 mmol), K_2CO_3 (10.30 mg, 0.0745 mmol), Pd_2dba_3 (1.69 mg, 0.00185 mmol) and PPh_3 (8.43 mg, 0.0321 mmol) were weighed into a dried vial and taken up in 1.0 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite, washed twice with ether. The reaction mixture was analyzed by GC to show no product formation.

Synthesis of 1-phenyl-1-(2-acetylphenyl)ethane:



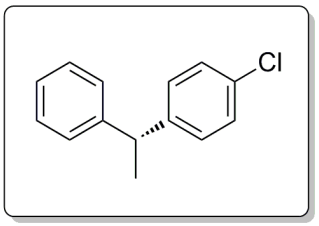
In a nitrogen filled glove box, 2-iodoacteophenone (11.64 mg, 0.0473 mmol), *rac*-pinacol(1-phenylethyl)boronate (17.27 mg, 0.0744 mmol), Ag_2O (17.30 mg, 0.0747 mmol), $Pd_2(dba)_3$ (1.91 mg, 0.00209 mmol) and PPh_3 (9.24 mg, 0.0352 mmol) were weighed into a dried vial and taken up in 1 mL of THF. The reaction was sealed and stirred at 70 °C for 18 h. The reaction

mixture was cooled and filtered through Celite followed by washing twice with ether. The reaction mixture was concentrated and 4 mg of hexamethylbenzene was added as an NMR standard. No product was observed by NMR.

Synthesis of (R)-1-phenyl-1-(4-methylphenyl)ethane:

In a nitrogen filled glove box, *p*-iodotoluene (33.09 mg, 0.152 mmol), (R)-pinacol(1-phenylethyl)boronate (53.26 mg, 0.229 mmol, e.r 94:6), Ag_2O (52.66 mg, 0.227 mmol), K_2CO_3 (32.68 mg, 0.237 mmol), $Pd(PPh_3)_4$ (14.82 mg, 0.0128 mmol) and PPh_3 (12.56 mg, 0.0479 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (pentane) in a 78% yield (containing ca. 10% homo-coupled). Enantiomeric ratio was determined by SFC (OD, 1% MeOH, 2mL, 200 bar) to be 93:7, a 99% retention of e.r. ^{1}H NMR: δ 7.29-7.07 (m, 9H), 4.11 (q, J = 7.3 Hz, 1H), 2.30 (s, 3H), 1.62 (d, J = 7.3 Hz, 3H). ^{13}C NMR: δ 148.57, 143.38, 135.46, 129.02, 128.31, 127.54, 127.46, 125.92, 44.35, 21.92, 20.99. The spectra are identical to those previously reported by the Crudden group.[1]

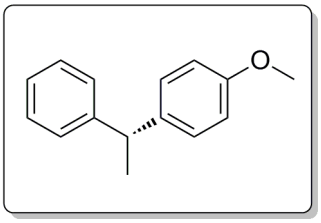
Synthesis of (R)-1-phenyl-1-(4-chlorophenyl)ethane:



In a nitrogen filled glove box, 4-chloroiodobenzene (35.96 mg, 0.151 mmol), (R)-pinacol(1-phenylethyl)boronate (51.20 mg, 0.221 mmol, e.r 94:6), Ag_2O (52.81 mg, 0.228 mmol), K_2CO_3 (32.20 mg, 0.233 mmol), $Pd(PPh_3)_4$ (13.82 mg, 0.0120 mmol) and PPh_3 (12.58 mg, 0.0480 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was

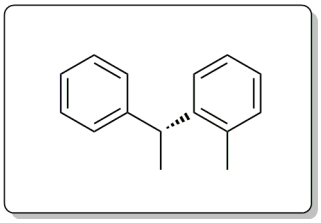
sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (pentane) in a 75% yield. Enantiomeric ratio was determined by SFC (OD, 1% MeOH, 2mL, 200 bar) to be 92.8:7.2, a 98.7% retention of e.r. ^{1}H NMR: δ 7.33-7.16 (m, 9H), 4.15 (q, J = 7.2 Hz, 1H), 1.64 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 145.94, 145.00, 131.87, 129.12, 128.60, 128.59, 127.66, 126.38, 44.32, 21.94. The spectra are identical to those previously reported by the Crudden group.[1]

Synthesis of (R)-1-phenyl-1-(4-methoxyphenyl)ethane:



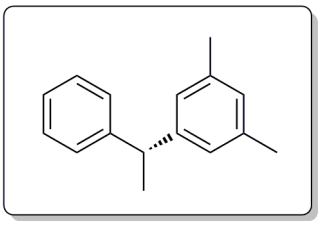
In a nitrogen filled glove box, 4-iodoanisole (35.08 mg, 0.150 mmol), (R)-pinacol(1-phenylethyl)boronate (52.67 mg, 0.227 mmol, e.r 94:6), Ag_2O (52.34 mg, 0.226 mmol), K_2CO_3 (32.12 mg, 0.232 mmol), $Pd(PPh_3)_4$ (13.55 mg, 0.0117 mmol) and PPh_3 (12.33 mg, 0.0470 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (50:1 Pent:Et_2O) in a 71% yield. Enantiomeric ratio was determined by SFC (OD, 1% MeOH, 2mL, 200 bar) to be 93.1:6.9, a 99% retention of e.r. ^{1}H NMR: δ 7.34-7.17 (m, 7H), 6.89-6.85 (m, 2H), 4.15 (q, J = 7.2 Hz, 1H), 3.82 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 157.94, 146.90, 138.68, 128.64, 128.47, 127.66, 126.06, 113.84, 55.37, 44.06, 22.20. The spectra are identical to those previously reported by the Crudden group.[1]

Synthesis of (R)-1-phenyl-1-(2-methylphenyl)ethane:



In a nitrogen filled glove box, *o*-iodotoluene (31.20 mg, 0.143 mmol), (R)-pinacol(1-phenylethyl)boronate (50.15 mg, 0.216 mmol, e.r 94:6), Ag_2O (51.21 mg, 0.221 mmol), K_2CO_3 (30.40 mg, 0.220 mmol), $Pd(PPh_3)_4$ (13.05 mg, 0.0113 mmol) and PPh_3 (12.11 mg, 0.0462 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (50:1 Pent:Et_2O) in a 64% yield (containing ca. 8% homo-coupled). Enantiomeric ratio was determined by SFC (OJ, 1.5% ^{i}PrOH, 2mL, 200 bar) to be 89.9:10.1, a 96% retention of e.r. ^{1}H NMR: δ 7.31-7.15 (m, 9H), 4.34 (q, J = 7.2 Hz, 1H), 2.26 (s, 3H), 1.63 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 146.35, 144.04, 136.23, 130.53, 128.43, 127.81, 126.80, 126.21, 126.15, 125.94, 41.13, 22.25, 19.90. The spectra are identical to those previously reported by the Crudden group.[1]

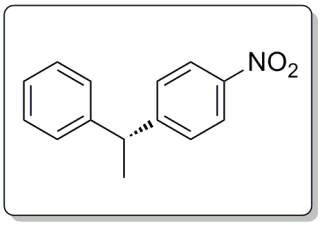
Synthesis of (R)-1-phenyl-1-(3,5-dimethylphenyl)ethane:



In a nitrogen filled glove box, 3,5-dimethyliodobenzene (32.58 mg, 0.140 mmol), (R)-pinacol(1-phenylethyl)boronate (53.47 mg, 0.230 mmol, e.r 94:6), Ag_2O (52.01 mg, 0.224 mmol), K_2CO_3 (31.11 mg, 0.225 mmol), $Pd(PPh_3)_4$ (13.15 mg, 0.0114 mmol) and PPh_3 (12.80 mg, 0.0488 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (50:1 Pent:Et_2O) in a 77% yield (containing ca. 10% homo-coupled). Enantiomeric ratio was determined by SFC (OD, 1% ^{i}PrOH, 2mL, 100 bar) to be 91.3:8.7, a 97% retention of e.r. ^{1}H NMR: δ 7.32-7.15 (m, 6H), 6.83 (m, 3H),

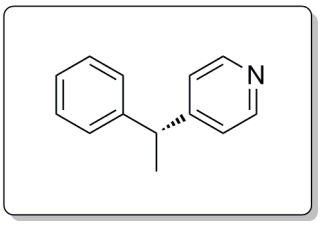
4.07 (q, J = 7.2 Hz, 1H), 2.27 (s, 6H), 1.61 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 146.71, 146.42, 137.90, 128.45, 127.91, 127.86, 127.76, 127.72, 126.04, 125.59, 44.83, 22.05, 21.52. The spectra are identical to those previously reported by the Crudden group.[1]

Synthesis of (R)-1-phenyl-1-(4-nitrophenyl)ethane:



In a nitrogen filled glove box, 1-iodo-4-nitrobenzene (37.13 mg, 0.149 mmol), (R)-pinacol(1-phenylethyl)boronate (52.92 mg, 0.228 mmol, e.r 94:6), Ag_2O (52.10 mg, 0.225 mmol), K_2CO_3 (31.15 mg, 0.225 mmol), $Pd(PPh_3)_4$ (12.92 mg, 0.0112 mmol) and PPh_3 (12.10 mg, 0.0461 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through celite. The desired product was isolated by column chromatography (10:1 Hex:EtOAc) in a 39.5% yield. Enantiomeric ratio was determined by SFC (AD, 2% MeOH, 2mL, 300 bar) to be 90.7:9.3, a 96.5% retention of e.r. ^{1}H NMR: δ 8.16-8.11 (m, 2H), 7.4-7.16 (m, 7H) 4.26 (q, J = 7.2 Hz, 1H), 1.68 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 154.18, 144.66, 128.86, 128.58, 127.69, 126.85, 123.84, 44.89, 21.65.

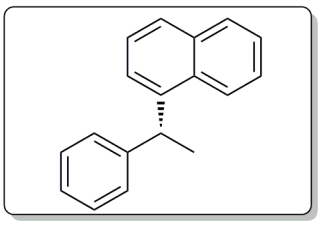
Synthesis of (R)- 4-(1-phenylethyl)pyridine:



In a nitrogen filled glove box, 4-iodopyridine (30.09 mg, 0.147 mmol), (R)-pinacol(1-phenylethyl)boronate (51.93 mg, 0.224 mmol, e.r 93.6:6.4), Ag_2O (54.46 mg, 0.235 mmol), K_2CO_3 (32.05 mg, 0.232 mmol), $Pd(PPh_3)_4$ (13.20 mg, 0.0114 mmol) and PPh_3 (12.84 mg, 0.0490 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (1:1 Hex:EtOAc) in

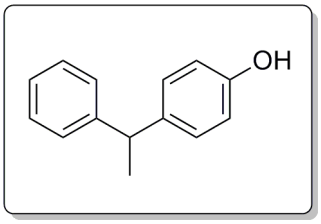
a 96% yield. Enantiomeric ratio was determined by SFC (OJ, 2% MeOH, 2mL, 200 bar) to be 89.3:10.7, a 95.4% retention of e.r. ^{1}H NMR: δ 8.55 (d, J = 4.5 Hz, 2H), 7.4-7.23 (m, 5H) 7.19 (d, J = 5.8 Hz, 2H), 4.18 (q, J = 7.2 Hz, 1H), 1.70 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 155.20, 149.93, 144.53, 128.76, 127.74, 126.77, 123.11, 44.36, 21.19.

Synthesis of (R)- 1-(1-phenylethyl)naphthalene:



In a nitrogen filled glove box, 1-iodonaphthalene (40.67 mg, 0.160 mmol), (R)-pinacol(1-phenylethyl)boronate (55.52 mg, 0.239 mmol, e.r 93.6:6.4), Ag_2O (53.78 mg, 0.232 mmol), K_2CO_3 (31.71 mg, 0.229 mmol), $Pd(PPh_3)_4$ (14.55 mg, 0.0126 mmol) and PPh_3 (13.23 mg, 0.0504 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The desired product was isolated by column chromatography (20:1 Hex:EtOAc) in a 81% yield. Enantiomeric ratio was determined by SFC (OD, 2% MeOH, 2mL, 200 bar) to be 87:13, a 93% retention of e.r. ^{1}H NMR: δ 7.86-7.78 (m, 1H), 7.64-7.59 (m, 1H), 7.54-7.50 (m, 1H), 7.28-7.16 (m, 4H), 7.06-6.90 (m, 4H), 6.96-6.90 (m, 1H), 4.70 (q, J = 7.2 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H). ^{13}C NMR: δ 146.78, 141.68, 134.12, 131.84, 128.91, 128.56, 127.76, 127.12, 126.10, 125.99, 125.57, 125.45, 124.46, 124.11, 40.70, 22.70.

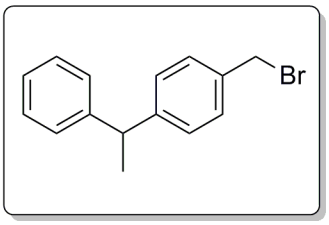
Synthesis of 4-(1-phenylethyl)phenol:



In a nitrogen filled glove box, 4-iodophenol (32.61 mg, 0.148 mmol), racemic pinacol(1-phenylethyl)boronate (55.05 mg, 0.237 mmol), Ag_2O (52.40 mg, 0.226 mmol), K_2CO_3 (31.62 mg, 0.229 mmol), $Pd(PPh_3)_4$ (13.20 mg, 0.0114 mmol) and PPh_3 (13.23 mg,

0.0504 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The resulting solution was analyzed by GC/MS and no product was observed.

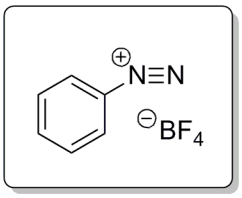
Attempted synthesis of 1-(bromomethyl)-4-(1-phenylethyl)benzene:



In a nitrogen filled glove box, 1-(bromomethyl)-4-iodobenzene (44.29 mg, 0.149 mmol), racemic pinacol(1-phenylethyl)boronate (53.19 mg, 0.229 mmol), Ag_2O (55.59 mg, 0.240 mmol), K_2CO_3 (31.00 mg, 0.224 mmol), $Pd(PPh_3)_4$ (13.50 mg, 0.0117 mmol) and PPh_3 (13.05 mg, 0.0498 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The resulting solution was analyzed by GC/MS and no product was observed.

Cross-Coupling of Diazonium Salts

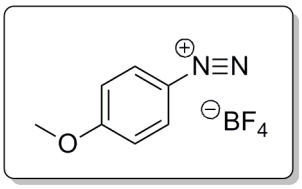
Synthesis of benzenediazonium tetrafluoroborate:



In a rbf aniline (0.8 mL, 8.78 mmol) was dissolved in the minimal amount of H_2O and the solution was cooled to below 0 °C in an ice/brine bath. Aqueous HBF_4 (5 mL of 50% wt. solution, 40.14 mmol) was slowly added to the cooled solution *via* syringe. In a separate rbf $NaNO_2$ (1.2099 g, 17.54 mmol) was dissolved in the minimal amount of H_2O and added dropwise to the acidic solution, which resulted in immediate formation of yellow precipitate. The mixture was allowed to stir for 0.5 h and then filtered. The resulting solid was dissolved in acetonitrile and reprecipitated with ether to give the desired product in 62% yield. The product can be stored in the freezer at -20 °C for several

months. NMR analysis was done in CD_3CN. ^1H NMR: δ 8.50-8.45 (m, 2H), 8.30-8.25 (m, 1H), 7.97-7.90 (m, 2H). ^{13}C NMR: δ 143.00, 133.31, 132.80.

Synthesis of 4-methoxybenzendiazonium tetrafluoroborate:



In an oven dried/argon filled, two necked rbf, $BF_3{\cdot}Et_2O$ (0.9 mL, 7.29 mmol) was cooled to below -10 °C. In a separate rbf *p*-anisidine (0.6133 g, 4.98 mmol) was weighed and the flask was purged with argon to replace the atmosphere. The amine was dissolved in the minimal amount of DCM and added dropwise to the cooled $BF_3{\cdot}Et_2O$ solution. In a separate, argon filled rbf, tert-butyl nitrite (0.7 mL, 5.89 mmol) was dissolved in the minimal amount of DCM and transferred to the amine solution *via* cannula. The resulting solution was stirred at -10 °C for 10 min and then the temperature was raised to 5 °C. The reaction was quenched with 40 mL of pentane and the resulting solid was filtered off. The solid was dissolved in acetonitrile and reprecipitated with ether to give the desired product in 17% yield. The product can be stored in a freezer at -20 °C for several months. NMR analysis was done in CD_3CN. ^1H NMR: δ 8.42-8.35 (m, 2H), 7.38-7.30 (m, 2H), 4.06 (s, 3H).

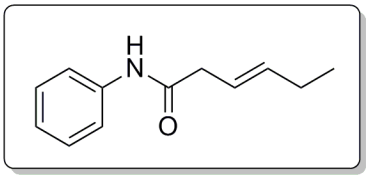
Representative Attempt at Cross Coupling Aryldiazonium Salt with Organoboronic Ester (Table 6, entry 1):

In a nitrogen filled glove box, benzenediazonium tetrafluoroborate (9.82 mg, 0.0512 mmol), racemic pinacol(1-phenylethyl)boronate (23.67 mg, 0.102 mmol), Ag_2O (18.83 mg, 0.0813 mmol), Pd_2dba_3 (2.07 mg, 0.00261 mmol) and PPh_3 (9.12 mg, 0.0348 mmol) were weighed into a dried vial and taken up in 1 mL of THF. The reaction was sealed and stirred at 70 °C for 24 h. The

reaction mixture was cooled and filtered through Celite. The resulting solution was analyzed by GC and NMR spectroscopy and no product was observed.

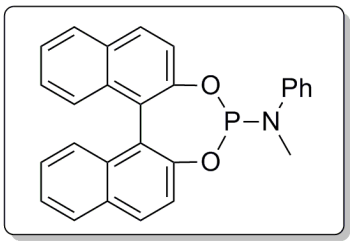
Cross-Coupling of Amide Species

Synthesis of (E)-N-phenylhex-3-enamide:



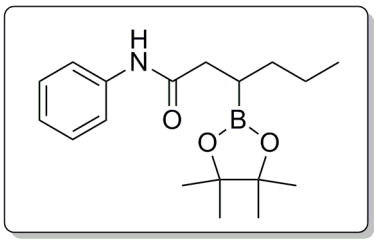
In an oven-dried 2-neck rbf, trans-3-hexenoic acid (0.6 mL, 5.06 mmol) was dissolved in 10 mL of dry DMF and degassed for 1 h. Under nitrogen atmosphere the soln was cooled to below 0 °C and aniline (0.46 mL, 5.05 mmol) was slowly added *via* syringe. The resulting mixture was stirred for 30 mins. In one addition 4-(dimethylamino)pyridine (0.6225 g, 5.10 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.9555 g, 4.98 mmol) were added, followed by quickly purging the system with nitrogen. The reaction mixture was stirred and the temperature was allowed to raise to room temperature over night. The reaction was quenched with 25 mL of saturated $NaHCO_3$ and extracted with 3x25 mL of ether. Combined ether layers were dried with anhydrous Na_2SO_4. The solution was filtered and solvent was removed to give a yellow oil. The product was isolated by column chromatography (EtOAc) followed by recrystallization from 10:1 hexanes:ethylacetate to give a white solid in 73.7% yield. ^{1}H NMR: δ 7.50 (d, J = 7.9 Hz, 2H), 7.36 (br. s, 1H), 7.32 (t, J = 7.9 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 5.84-5.57 (m, 2H), 3.11 (d, J = 7.0 Hz, 2H), 2.13 (m, 2H), 1.05 (t, J = 7.5 Hz, 3H). ^{13}C NMR: δ 169.56, 139.19, 137.90, 129.13, 124.45, 121.48, 119.81, 41.76, 25.81, 13.71. The spectra are identical to those previously reported by the Takacs group.[67]

Synthesis of racemic (BINOL)PN(Me)Ph [Ligand for amide hydroboration]:



In a 2-neck dried rbf, N-methylaniline (0.22 mL, 2.03 mmol) was dissolved in dry THF and cooled to 0°C. PCl_3 (0.18 mL, 2.06 mmol) was added dropwise to the solution *via* syringe. The resulting mixture was stirred at room temperature for 1 h and then cooled to -78°C and triethylamine (0.28 mL, 2.01 mmol) was added dropwise. After stirring at -78 °C for 0.5 h a solution of racemic 1,1'-bi-2-naphthol (0.5735 g, 2.00 mmol) and triethylamine (0.62 mL, 4.45 mmol) in dry THF (~ 2mL) was slowly added. The temperature of the resulting milky white solution was increased to room temperature overnight and then taken into the glove box and filtered through Celite under a nitrogen atmosphere. The Celite was washed with dry THF and volatiles were removed on vacuum to give a yellow oil. The desired product was isolated, as a white solid, in 41% yield, by recrystallization using 3:1 hexanes:DCM. . ^{1}H NMR: δ 8.00 (d, J = 8.8 Hz, 1H), 7.95-7.91 (m, 3H), 7.55 (d, J = 8.8 Hz, 1H), 7.46-7.40 (m, 4H), 7.38-7.27 (m, 7H), 7.11 (t, J = 7.1 Hz, 1H), 2.65 (d, J = 2.4 Hz, 3H). ^{13}C NMR: δ 132.98, 131.03, 130.62, 130.38, 129.31, 128.52, 128.47, 127.16, 127.06, 126.36, 125.12, 124.92, 123.38, 123.36, 121.96, 121.40, 121.25, 33.65. ^{31}P NMR: δ 143.77. The spectra are identical to those previously reported by the Takacs group.[67]

Synthesis of N-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide:



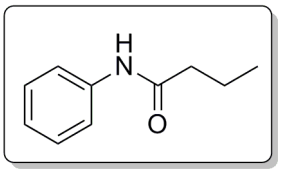
In a nitrogen filled glove box 1 g of a stock solution of $[Rh(nbd)_2]BF_4$ (2.49 mmolal) and (BINOL)PN(Me)Ph (5.58 mmolal) was diluted with 1 g of THF. To the resulting solution {$[Rh(nbd)_2]BF_4$ (0.93 mg, 0.00249 mmol) and (BINOL)PN(Me)Ph (2.35 mg, 0.00558 mmol)} (*E*)-N-phenylhex-3-enamide (94.50 mg, 0.4993

mmol) was added in 2 mL of THF. In a separate vial HBpin (125.52 mg, 0.981 mmol) was weighed and dissolved in 1 mL of THF. Both vials were removed from the glove box and cooled to 0 °C. The HBpin solution was slowly transferred, *via* cannula, into the catalyst vial and the resulting solution was stirred at 0 °C for 0.5 h. The ice bath was removed and the reaction mixture was heated to 40 °C for 2 h. The reaction was cooled to room temperature and 10 mL of H_2O was added. The solution was extracted with 3x15 mL of DCM. The combined organic layers were dried with Na_2SO_4 and filtered. The solvent was removed and the desired product was isolated by column chromatography (3:1 Hexanes:EtOAc) in 73% yield. ^{1}H NMR: δ 7.59 (br s, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.06 (t, J = 7.8 Hz, 1H), 2.52-2.32 (m, 2H), 1.53-1.33 (m, 5H), 1.26 (s, 6H), 1.25 (s, 6H), 0.90 (t, J = 7 Hz, 3H). ^{13}C NMR: δ 171.68, 138.41, 129.05, 123.92, 119.60, 83.526, 39.41, 33.16, 24.99, 24.90, 22.05, 14.42. The spectra are identical to those previously reported by the Takacs group.[67]

General Procedure for Attempting to Cross-Couple Amide Substrate (Table 8, entry1):

In a nitrogen filled glove box, 4-iodoacteophenone (12.60 mg, 0.0512 mmol), N-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexanamide (23.34 mg, 0.0736 mmol), Ag_2O (20.73 mg, 0.0895 mmol), K_2CO_3 (11.05 mg, 0.0800 mmol), $Pd(PPh_3)_4$ (5.08 mg, 0.00440 mmol) and PPh_3 (4.98 mg, 0.0190 mmol) were weighed into a dried vial and taken up in 1 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite followed by washing twice with ether. The reaction mixture was analyzed by GC/MS and NMR; however, no product was detected.

Synthesis of N-Phenylbutanamide:



In an oven-dried 2-neck rbf, butyric acid (0.46 mL, 5.00 mmol) was dissolved in 10 mL of dry DMF and degassed for 1 h. Under nitrogen atmosphere the soln was cooled to below 0 °C and aniline (0.46 mL, 5.05 mmol) was slowly *via* syringe. The resulting mixture was stirred for 30 mins. In one addition 4-(dimethylamino)pyridine (0.6108 g, 5.0 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.9611 g, 5.01 mmol) were added, followed by quickly purging the system with nitrogen. The reaction mixture was stirred and the temperature was raised to room temperature over night. The reaction was quenched with 25 mL of saturated $NaHCO_3$ and extracted with 3x25 mL of ether. The combined ether layers were dried with anhydrous Na_2SO_4. The solution was filtered and the solvent was removed to give a yellow oil. The product was isolated by column chromatography (3:1 Hex:EtOAc), to give a white crystalline solid in 72% yield. ^{1}H NMR: δ 7.52 (d, J = 7.9 Hz, 2H), 7.34 (br. s, 1H), 7.31 (t, J = 7.9 Hz, 2H), 7.10 (t, J = 7.9 Hz, 1H), 2.33 (t, J = 7.5 Hz, 2H), 1.75 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H). ^{13}C NMR: δ 171.46, 138.11, 129.09, 124.29, 119.95, 115.22, 39.81, 19.21, 13.88.

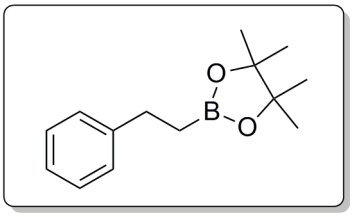
Attempted Synthesis of N-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanamide:

In an oven-dried, N_2 filled round bottom Schlenk, N-phenylbutanamide (163.67 mg, 1.00 mmol) was dissolved in 10 mL of dry THF. The solution was cooled to -78 °C and nBuLi (0.82 mL, 1.47M) was slowly added *via* syringe. The mixture was stirred for 5 h. At -78 °C trimethylborate (0.14 mL, 1.26 mmol) was added *via* syringe and let stir for 2 h. In one addition pinacol (596.3 mg, 5.05 mmol) was added and the system was quickly purged with N_2. The temperature was allowed to raise to room temperature over night. The reaction was quenched with 15 mL of H_2O and extracted with 3x15 mL of DCM. The combined DCM layers were dried over Na_2SO_4, filtered

and the solvent was removed. The crude mixture did not show the desired product by GC/MS or NMR.

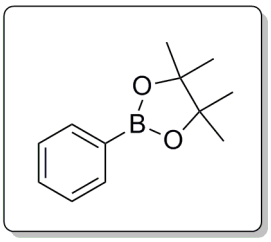
Experimental for Selective Cross-Coupling

Synthesis of Linear Boronate (Pinacol(3-phenylethyl)borate):



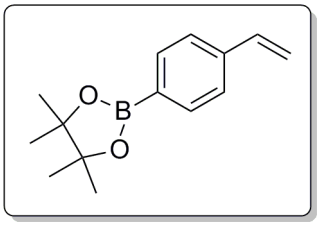
In a nitrogen filled glove box, $[Ir(cod)Cl]_2$ (33.61 mg, 0.050 mmol)and DPPB (43.31 mg, 0.102 mmol) were weighed into a dried vial and dissolved in 4.2 mL of THF. After ten min of stirring, styrene (211.94 mg, 2.03 mmol) was added to the vial, followed by HBpin (311.18 mg, 2.43 mmol). The reaction was capped and let stir for 24 h, at glove box temperature. The desired product was isolated in 84 % yield by column chromatography (10:1 Hex:EtOAc). ^{1}H NMR: δ 7.31-7.17 (m, 5H), 2.78 (t, J = 8 Hz, 2H), 1.25 (s, 12H), 1.18 (t, J = 8 Hz, 2H). ^{13}C NMR: δ 144.54, 128.13, 128.13, 125.62, 83.22, 30.09, 24.95.

Synthesis of Phenyl Pinacolborate:



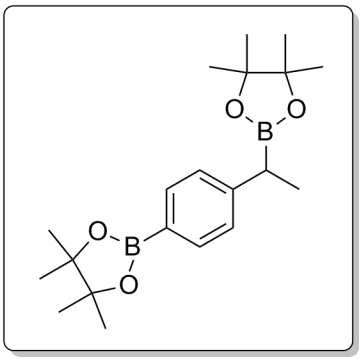
In a dried rbf phenylboronic acid (0.6096 g, 5.00 mmol) was dissolved in 42 mL of benzene. Pinacol (0.7211 g, 6.10 mmol) was added and the mixture was heated to 60 °C for 2 h. The reaction was cooled and the solvent was removed by rotary evaporation. The resulting oil was passed through a silica plug with 9:1 hexanes:EtOAc and the solvent was removed, to give the desired product in 97.2% yield. ^{1}H NMR: δ 7.85-7.81 (m, 2H), 7.50-7.44 (m, 1H), 7.41-7.35 (m, 2H), 1.36 (s, 12H). ^{13}C NMR: δ 134.87, 131.37, 127.83, 83.89, 25.01.

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



In a dried rbf 4-vinylbenzeneboric acid (1.4473 g, 9.78 mmol) was dissolved in 60 mL of benzene. Pinacol (1.4334 g, 12.13 mmol) and $MgSO_4$ (1.2036 g, 9.999 mmol) were added and the resulting mixture was heated to 60 °C for 24 h. The resulting solution was filtered and the solvent was removed by rotary evaporation. The resulting oil was passed through a silica plug with 5:1 hexanes:EtOAc. The solvent was removed, to give the desired product in 93.9% yield. ^{1}H NMR: δ 7.79 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 6.74 (dd, J = 10.9 Hz and 17.6 Hz, 1H), 5.82 (d, J = 17.6 Hz, 1H), 5.30 (d, J = 10.9 Hz, 1H), 1.40 (s, 12H). ^{13}C NMR: δ 140.33, 137.00, 135.14, 125.63, 114.97, 83.88, 24.99.

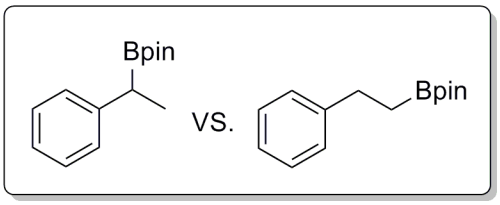
Synthesis of racemic 4,4,5,5-tetramethyl-2-(4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)phenyl)-1,3,2-dioxaborolane:



In a nitrogen filled glove box, $[Rh(cod)_2][BF_4]$ (12.40 mg, 0.0305 mmol) and DPPB (15.45 mg, 0.0362 mmol) were weighed into a vial and taken up in THF (2 mL) with stirring. Separately, 4,4,5,5-tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (691.95 mg, 3.01 mmol) and HBpin (468.70 mg, 3.66 mmol) were weighed into a vial and transferred to the catalyst solution using 2 mL of THF. The resulting solution was capped and stirred at glove box temperature for 24 h. The resulting solution was removed from the glove box and passed through a silica plug with EtOAc. The solvent was removed by rotary-evaporation; followed with placing on high-vac. The desired product was isolated, as a white solid, in 99% yield and 99.7:0.3 branched to linear ratio (by GC). ^{1}H NMR: δ 7.71 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 2.45

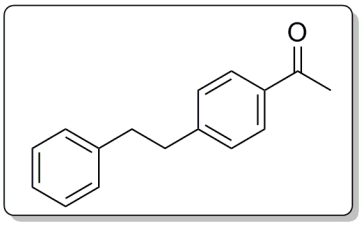
(q, J = 7.4 Hz, 1H), 1.32 (br s, 15H), 1.19 (s, 6H), 1.18 (s, 6H). ^{13}C NMR: δ 148.71, 135.01, 127.39, 100.14, 83.68, 83.46, 25.02, 24.76, 24.72, 16.90.

Branched vs Linear Competition Experiment:



In a nitrogen filled glove box, n-octadecane (internal standard, 16.30 mg), *p*-iodoacetophenone (12.43 mg, 0.0505 mmol), pinacol(1-phenylethyl)boronate (16.37 mg, 0.0705 mmol), pinacol(3-phenylethyl)borate (18.93 mg, 0.0815 mmol), Ag_2O (17.67 mg, 0.0762 mmol), K_2CO_3 (10.19 mg, 0.0737 mmol), $Pd(PPh_3)_4$ (4.41 mg, 0.00382 mmol) and PPh_3 (8.40 mg, 0.0320 mmol) were weighed into a dried vial and taken up in 1 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. A sample for GC analysis was prepared in hexanes. The resulting GC chromatogram showed 49% of branched product formed and approximately 8% of the linear product formed.

Synthesis of Linear Coupling Product Under Optimized Branched Conditions:



In a nitrogen filled glove box, n-octadecane (internal standard, 9.66 mg), *p*-iodoacetophenone (12.09 mg, 0.0492 mmol), pinacol(3-phenylethyl)borate (17.41 mg, 0.075 mmol), Ag_2O (17.66 mg, 0.0762 mmol), K_2CO_3 (10.57 mg, 0.0765 mmol), $Pd(PPh_3)_4$ (4.43 mg, 0.00383 mmol) and PPh_3 (8.84 mg, 0.0337 mmol) were weighed into a dried vial and taken up in 1 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. A sample for GC analysis was prepared

in hexanes. The resulting GC chromatogram showed approximately 22% of the linear product formed.

Branched vs Aryl Intermolecular Competition Study:

In a nitrogen filled glove box, n-octadecane (internal standard, 20.31 mg), phenyl pinacolborate (17.23 mg, 0.08 mmol), *rac*-pinacol(1-phenylethyl)boronate (18.46 mg, 0.08 mmol), *p*-iodoacetophenone (12.96 mg, 0.05 mmol) Ag_2O (19.02 mg, 0.082 mmol), K_2CO_3 (12.54 mg, 0.09 mmol), $Pd(PPh_3)_4$ (5.18 mg, 0.0045 mmol) and PPh_3 (6.88 mg, 0.026 mmol) were weighed into a dried vial and taken up in 1 mL of DME. The reaction was capped and removed from the glove box. The mixture was sealed and placed in an 85 °C oil bath and stirred for 24 h. The reaction mixture was cooled and filtered through Celite, washed twice with ether. The crude reaction mixture was analyzed by GC and showed a ratio of 800:1 of aryl coupling product to branched coupled product.

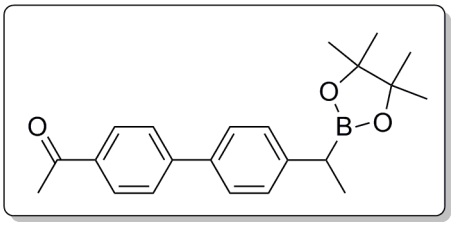
Branched vs Aryl Intramolecular Competition Study:

In a nitrogen filled glove box, *p*-iodoacetophenone (37.82 mg, 0.154 mmol), 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 (82.55 mg, 0.231 mmol), Ag_2O (55.91 mg, 0.241 mmol), K_2CO_3 (34.70 mg, 0.251 mmol), $Pd(PPh_3)_4$ (13.77 mg, 0.0119 mmol) and PPh_3 (16.06 mg, 0.0612 mmol) were weighed into a dried vial and taken up in 3 mL of DME. The mxture was capped and removed from the glove box. The reaction was sealed with Teflon and electrical tape and placed in an 85°C oil bath for 24 h. The resulting mixture was cooled to room temperature and compounds possessing the desired mass-to-charge ratio by GC/MS, were isolated by column chromatography (5:1 Hex:EtOAc) in 62 % yield. By GC it was found that the product was a 3:1 mixture of aryl product to branched product.

Diazonium Competition Study:

In a nitrogen filled glove box, n-octadecane (internal standard, 12.88 mg), phenyl pinacolborate (20.41 mg, 0.100 mmol), *rac*-pinacol(1-phenylethyl)boronate (25.31 mg, 0.109 mmol), benzene diazonium tetrafluoroborate (18.79 mg, 0.115 mmol) and $[Pd(OAc)_2]_3$ (2.36 mg, 0.0035 mmol) were weighed into a dried vial, which was capped with a septum and removed from the glove box. The mixture was taken up in 2 mL of freshly distilled methanol and stirred at 27 °C for 2 h. The reaction mixture was cooled and filtered through Celite, washed twice with ether. The crude reaction mixture was analyzed by GC and showed 71 % yield of biphenyl and no consumption of the secondary organoboronic ester.

Selective Coupling of Aryl Position using 4-acetylphenyl trifluoromethanesulfonate:



In a nitrogen filled glove box, 4-acetylphenyl trifluoromethanesulfonate (40.08 mg, 0.149 mmol), 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 (52.96 mg, 0.148 mmol), Ag_2O (106.67 mg, 0.460 mmol), K_2CO_3 (63.47 mg, 0.459 mmol), $Pd(PPh_3)_4$ (13.01 mg, 0.0113 mmol) and PPh_3 (12.73 mg, 0.0485 mmol) were weighed into a dried vial and taken up in 3.0 mL of toluene. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite, washed twice with ether and concentrated *in vacuo*. The desired product was isolated by column chromatography (3:1 Hex:EtOAc) as a white solid, in 76% yield. ^{1}H NMR: δ 8.00 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 2.62 (s, 3H), 2.50 (q, J = 7.5 Hz, 1H), 1.37 (d, J = 7.5 Hz, 3H), 1.23 (s, 6H), 1.22 (s, 6H). ^{13}C NMR: δ 197.81, 145.94, 145.60, 136.63, 135.59, 128.29, 127.26, 126.98, 83.52, 26.71, 24.75, 24.72, 17.11.

Example Coupling of Secondary Position of Coupled Aryl-Product (Table 7, Entry 1):

In a nitrogen filled glove box, 4-iodoacetophenone (10.42 mg, 0.0424 mmol), the aryl-coupled product (15.41 mg, 0.0434 mmol), Ag_2O (15.83 mg, 0.0683 mmol), K_2CO_3 (9.21 mg, 0.0666 mmol), $Pd(PPh_3)_4$ (4.28 mg, 0.0037 mmol) and PPh_3 (3.72 mg, 0.0142 mmol) were weighed into a dried vial and taken up in 1 mL of DME. The reaction was sealed and stirred at 85 °C for 24 h. The reaction mixture was cooled and filtered through Celite. The mixture was concentrated *in vacuo* and 9.26 mg of 1,4-dimethoxybenzene was added as an NMR standard. The crude mixture was taken up in $CDCl_3$ and analyzed by NMR. The yield of the desired product was determined to be 49 % by comparison to the standard.

Selective One-Pot Coupling (Condition A):

In a nitrogen filled glove box, 4-acetylphenyl trifluoromethanesulfonate (13.36 mg, 0.0498 mmol), 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 (17.99 mg, 0.0502 mmol), K_2CO_3 (20.69 mg, 0.150 mmol), $Pd(PPh_3)_4$ (5.09 mg, 0.0044 mmol) and PPh_3 (5.82 mg, 0.0222 mmol) were weighed into a dried vial and taken up in 1.0 mL of toluene. The reaction was sealed and stirred at 85 °C for 24 h. After reaction for 24 h, the solution was cooled and filtered through Celite, washed with ether and the solvent was removed by rotavap to give a black oil. The vial was taken into the glove box and fresh Ag_2O (19.89 mg, 0.0858 mmol), K_2CO_3 (10.77 mg, 0.0779 mmol), $Pd(PPh_3)_4$ (6.50 mg, 0.00562 mmol) and PPh_3 (4.82 mg, 0.0184 mmol), along with 1mL of DME and 1.0 eq of 4-iodoacetophenone (12.46 mg, 0.0507 mmol) was added. The reaction was sealed and removed from the glove box, placed in an 85 °C oil bath and heated for an additional 24 h. The reaction mixture was cooled and filtered through Celite. The mixture was concentrated *in vacuo* and 9.26 mg of 1,4-dimethoxybenzene was added as an NMR standard. The crude mixture was taken up in $CDCl_3$

and analyzed by NMR. The yield of the desired product was determined to be 27 % by comparison to the standard.

Selective One-Pot Coupling (Condition B):

In a nitrogen filled glove box, 4-acetylphenyl trifluoromethanesulfonate (14.30 mg, 0.0533 mmol), 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 (17.45 mg, 0.0487 mmol), K_2CO_3 (20.00 mg, 0.145 mmol), $Pd(PPh_3)_4$ (4.67 mg, 0.00404 mmol) and PPh_3 (4.79 mg, 0.0183 mmol) were weighed into a dried vial and taken up in 1.0 mL of toluene. The reaction was sealed and stirred at 85 °C for 24 h. After reaction for 24 h the solution was cooled to give a light yellow solution. The mixture was taken into the glovebox and unsealed. 1.0 eq of 4-iodoacetophenone (12.18 mg, 0.0495 mmol) and 1.5 eq of Ag_2O (21.68 mg, 0.0936 mmol) was added to the solution and after slightly stirring the formation of a grey lining on the vial was observed. The reaction was sealed and removed from the glove box, place in an 85 °C oil bath and heated for 24 h. The reaction mixture was cooled and filtered through Celite. The mixture was concentrated *in vacuo* and 9.26 mg of 1,4-dimethoxybenzene was added as an NMR standard. The crude mixture was taken up in $CDCl_3$ and analyzed by NMR. The yield of the desired product was determined to be 43 % by comparison to the standard.

Chapter 7: References

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