Modifications to the Suzuki Reaction and Mechanistic Insights on the NBS Mediated Cleavage of Benzylidene Acetals

By

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A thesis submitted to the Department of Chemistry in partial fulfillment for the requirements of the degree Master of Science

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September 2003
Brock University
St. Catharines, Ontario
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Acknowledgements

First and foremost, I would like to thank my supervisor, Professor James McNulty for the guidance, encouragement, and knowledge he provided me over the last four years. The experiences and work ethic gained under his supervision will be a great asset in my future chemistry career.

I would like to also thank my committee members, Professors Capretta and Atkinson, who gave valuable insight into (and took the time to read) my thesis over the two years.

I am also appreciative of all the faculty and staff for making the six years I spent getting my BSc and MSc at Brock an enjoyable and rewarding time. A special thanks to Dr. Hartman for the help whenever I needed it. Tim Jones for the mass spectral data, and Olga, Chris, and Veronika for keeping me in line.

To my colleagues in lab H204; Jeff Dyck, Dr. Vladimir Laritchev, Justin Mao, and Amanda Rochon, I would like to show my utmost appreciation for all the assistance throughout the last couple of years. Everyone there made coming to the lab to work an enjoyable time. To Jen, thanks for everything you have done for me over the last two years, which pretty much covers everything at one time or another. To my classmates and friends, especially, Grant, Dr. Tim, Phil, and even Hamilton, if it weren’t for you the last two years would definitely not been as fun and exciting as they were.

Last, but not least, I would like to give a big thanks to my family who has shown an incredible amount of patience and support over the last six years because I would not have been able to get through this if it were not for them
ABSTRACT

One of the most challenging tasks for a synthetic organic chemist today, is the development of chemo, regio, and stereoselective methodologies toward the total synthesis of macromolecules.

The objective of my thesis was to develop methodologies towards this end. The first part of my project was to develop highly functionalized chirons from D-glucose, a cheap, chiral starting material, to be utilized in this capacity. The second part of the project dealt with modifying the carbon-carbon bond forming Suzuki reaction, which is utilized quite often as a means of combining molecular sub units in total synthesis applications.

As previously stated the first area of the project was to develop high value chirons from D-glucose, but the mechanism of their formation was also investigated. The free radical initiated oxidative fragmentation of benzylidene acetals was investigated through the use of several test-case substrates in order to unravel the possible mechanistic pathways. This was performed by reacting the different acetals with N-bromosuccinimide and benzoyl peroxide in chlorobenzene at 70°C in all cases. Of the three mechanistic pathways discussed in the literature, it was determined, from the various reaction products obtained, that the fragmentation of the initial benzylic radical does not occur spontaneously but rather, oxidation proceeds to give the benzyl bromide, which then fragments via a polar pathway. It was also discovered that the regioselectivity of the fragmentation step could be altered through incorporation of an allylic system into the benzylidene acetal. This allows for the acquisition of a new set of densely functionalized,
chiral, valuable synthetic intermediates in only a few steps and in high yields from α-D-glucose.

The second part of the project was the utilization of the phosphonium salt room temperature ionic liquid tetradecyltrihexylphosphonium chloride (THPC) as an efficient reusable medium for the palladium catalyzed Suzuki cross-coupling reaction of aryl halides, including aryl chlorides, under mild conditions. The cross-coupling reactions were found to proceed in THPC containing small amounts of water and toluene using potassium phosphate and 1% Pd$_2$(dba)$_3$. Various substituted iodobenzenes, including electron rich derivatives, reacted efficiently in THPC with a variety of arylboronic acids and afforded complete conversion within 1 hour at 50 °C. The corresponding aryl bromides also reacted under these conditions with the addition of a catalytic amount of triphenylphosphine that allowed for complete conversion and high isolated yields. The reactions involving aryl chlorides were considerably slower, although the addition of triphenylphosphine and heating at 70 °C allowed high conversion of electron deficient derivatives. Addition of water and hexane to the reaction products results in a triphasic system in which the top hexane phase contained the biaryl products, the palladium catalyst remained fully dissolved in the central THPC layer, while the inorganic salts were extracted into the lower aqueous phase. The catalyst was then recycled by removing the top and bottom layers and adding the reagents to the ionic liquid which was heated again at 50 °C; resulting in complete turnover of iodobenzene. Repetition of this procedure gave the biphenyl product in 82-97% yield (repeated five times) for both the initial and recycled reaction sequences.
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List of Abbreviations

Ac                  acetyl
Ac$_2$O             acetic anhydride
Bn                  benzyl
BPO                 benzoyl peroxide
BINOL               (+ or -)-2,2’-dihydroxy-1,1’-dinaphthyl
DABCO               diazabicyclo[2,2,2]octane
dba                 dibenzylideneacetone
DCM                 dichloromethane
DMF                 N,N-Dimethylformamide
Et                  ethyl
EtOH                ethanol
iPr                 isopropyl
Me                  methyl
NBS                 N-bromosuccinimide
Ph                  phenyl
PhCl                chlorobenzene
PhMe or tol         toluene
PTSA                p-tolusulphonic acid
Py                  pyridine
THF                 tetrahydrofuran
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Chapter I

Introduction

1.1 MOLECULAR CHIRALITY, ENANTIOMERS, AND THEIR IMPORTANCE

The discovery with the largest impact for present day synthetic organic chemistry quite possible occurred in 1849 when Louis Pasteur began his work on crystalline salts of tartaric acid. He found that upon crystallization two different crystals had formed that were mirror images of each other. With this simple observation came the discovery of molecular chirality and the relationship of molecular configuration to optical rotation. This idea was far ahead of its time as it wasn’t for 25 years until van't Hoff and Le Bel confirmed his ideas of the asymmetric carbon atom.

Enantiomers or optical isomers exhibit identical functionality in the same configurational arrangement, but differ in three-dimensional arrangement about a given stereogenic center. Thus they are non-superimposable mirror images of each other. Enantiomers of a given molecule have identical physical and chemical properties, such as melting point, dipole moment, reactivity towards achiral molecules, as well as spectroscopic properties. They do, however, differ from each other by their ability to rotate plane-polarized light in equal and opposite directions. An enantiomerically pure compound is said to be optically pure when rotating the plane-polarized light a maximum value to the right or left. If the light is rotated to the left it is said to be levorotatory designated by (l) or (-), to the right is dextrorotatory (d) or (+). Since they rotate the light in by the same amount in opposite directions, if an equimolar amount of each enantiomer
is present, the net rotation is zero, and the mixture is called a racemic mixture or racemate\(^2\). Either an R or S designates the various stereogenic centers of a given molecule according to the Cahn-Ingold-Prelog Rules. An example of an enantiomeric pair is given below:

\[
\begin{align*}
(\text{S})\text{-chlorobutane} & \quad H_3C\quad CH_2CH_3 \quad Cl \\
(\text{R})\text{-chlorobutane} & \quad H_3C\quad CH_2CH_3 \quad Cl 
\end{align*}
\]

Figure 1. The structures of (S)- and (R)-chlorobutane

An area where this was an extremely important find, was in the pharmaceutical design field. Although enantiomers have similar chemical natures, they can behave considerably different when involved in interactions with other chiral materials such as biological receptors and as a result may exhibit dramatically different activities. This is best described by the ‘lock and key’ analogy that is adopted by biochemical researchers, on how only one of the 3-D spatially arranged molecules will fit into the proper biological (also chiral) receptor\(^4\). This phenomena is shown in the figure 2 below:

Figure 2. Effect of enantiomers in biological activity
As seen enantiomer (a) easily fits into the biological receptor site to exert its biological effect, but the other enantiomer (b) can’t fit into the same receptor the same way.

Until the 1960’s little was known about the effects that enantiomerically impure drugs could have on the body. As seen above different enantiomers do not bind in the same manner to the various sites and can mediate drastically different responses. This is best illustrated in the case of thalidomide, which was given to pregnant mothers in the 60’s in a racemic form as a sedative. Within a few years there were many reports of fetal death and deformities of children of women who used the drug in the first few months of their pregnancies. As it turns out, the R enantiomer had no sedative properties at all but, on the other hand, was a powerful teratogen. Had the drug been administered in the enantiomerically pure S form, which contains the desired sedative properties, this tragedy would have been averted.

![Thalidomide structures](image)

Figure 3 Structures and biological properties of the thalidomide enantiomers

Another example of this phenomenon, although not as drastic, is the commonly used drug ibuprofen, which also contains one stereogenic center. This widely marketed substance named Advil, Motrin, and Nuprin is sold in its racemic form. The S enantiomer is an analgesic / anti-inflammatory agent useful in treating rheumatism and is the active component in the drug. Even though the R enantiomer of ibuprofen has no
biological effect on the body at all, it's presence in the racemic form is known to substantially affect the rate at which the S enantiomer takes effect in a negative manner. This practice is not only chemically wasteful, but misleading to the consumers of this common over the counter drug.

(S)-ibuprofen an analgesic (R)-ibuprofen inhibits the effects of (S)

Figure 4 Structures and biological properties of the ibuprofen enantiomers

With the aforementioned cases in mind it is easy to see the necessity for obtaining molecules that have high optical purity. Thus the challenge of developing methods for asymmetric syntheses has now emerged as one of the most important fields for synthetic organic and medicinal chemists. Little was known before the 60’s about the importance of enantiomerically pure compounds, but the establishment of asymmetric syntheses is of great importance in the development of potent, selective drugs to combat cancer, viruses such as HIV and any number of other illnesses.

1.2 ASYMMETRIC SYNTHESIS

By definition asymmetric synthesis is the synthesis of a compound that selectively generates an excess of one enantiomer over the other. Although this is most often the goal the efficiency of the synthesis is not perfect and leads to the production of a single enantiomer in excess. Thus, the reaction can be characterized in terms of enantiomeric
excess (e.e.). The e.e. is calculated by the following: e.e. = \% enantiomer A - \% enantiomer B. Thus an e.e. value of 80\% is a representation of the two enantiomers in a 9:1 ratio. Similarly, if the reaction yielded products with an e.e. of 0\%, that given reaction produces a racemic mixture of products and is in no way enantioselective. The e.e. can be determined by obtaining an optical rotation of the product and comparing to a known value of the enantiomerically pure compound or via GCMS, or HPLC analysis on a chiral stationary phase.

With the frequent discovery of new compounds isolated from various marine or terrestrial sources with varying degrees of biological activities and significance, methods of total synthesis of such natural products, or analogues thereof are of utmost importance. New methodologies are being developed in order to synthesize chiral compounds more efficiently in an enantiomerically pure manner as they are usually complex molecules with multiple chiral centers. In order for a pharmaceutical to gain FDA approval in the U.S. it must exist in an enantiomerically pure state, an e.e. of 99.5\% or above, unless it is rigorously justified as the racemate\(^7\).

![Plakoridine A](image1)

![Amphodinilide A](image2)

Figure 5 Structures of biological active chiral anticancer agents

A stereoselective reaction is one where the molecule reacts via a preferred stereochemical pathway for kinetic or thermodynamic reasons. A graphical
representation of this fact is seen in the free energy diagram below. Whereas stereospecific reaction applies to a reaction whose outcome is determined by its mechanism to yield a specific stereoisomer as product.

![Free Energy Diagram](image)

Figure 6 Free energy diagram showing the reason for asymmetric reactions

The figure above shows how it is possible to differentiate between the two enantiomers. The formation of a diastereomeric transition state, which causes a difference in activation energy, or energy needed to overcome in order to form products. If the energy differential is great enough the reaction will form one enantiomer more than the other causing an enantiomeric excess, and if the difference is large enough an enantiomerically pure product. There are two basic approaches to obtaining an enantiomerically pure product. The first is to obtain the product in a racemic mixture, followed by resolution, for example, via the conversion to two diastereomeric salts, which will have different chemical and physical properties. This is typically followed by crystallization, yielding the salt of one diastereomer and the other still in solution is simply filtered off. This method can be is employed in the resolution of DL-alanine in the manner observed in scheme 1. In most cases the determination of a crystallization
protocol is non-trivial and quite time consuming. This can be solved when there are sufficient chemical differences between the two enantiomers in order to separate them via chiral column chromatography or HPLC. Even with this, the method still involves a couple of extra chemical steps as well as only generating a maximal yield of 50 % under the best circumstances.

Scheme 1 Resolution of racemic alanine via diastereomeric salts

The second manner is the aforementioned asymmetric synthesis of the molecule via three different methodologies, the chiral pool approach, chiral auxiliaries, and catalytic asymmetric synthesis.

The chiral pool approach uses enantiomerically pure starting materials derived from a pool of naturally occurring chiral compounds. Chiral pool materials include carbohydrates, amino acids, and terpenes such as menthone. In this process the stereochemistry of the final product is derived entirely from that of the starting material, as in the synthesis of azimine or carpaine, two molecules that exhibit a wide range of
biological activities from the chiral pool starting material L-alanine\textsuperscript{39}.

Scheme 2 The chiral pool method using the chiral pool starting material L-alanine

The main problem with this methodology is the dependence on the chiral starting material. There may not be available a natural source with the proper functionality for the desired product as well as the fact that in nature the molecule is more than likely found in only one enantiomer, either the R or S configuration which limits the product to only one possible enantiomer.

The second form of asymmetric synthesis to be discussed employs the attachment of a chiral auxiliary to an achiral substrate in order to promote the formation of a stereogenic center in a stereoselective manner, followed by the removal of the auxiliary to yield, ideally, a single enantiomer of the desired product. There is still the drawback of the extra steps necessary to add and remove the chiral auxiliary, which may bring about a lower overall yield of product. One of the most well known and successful chiral auxiliaries in use is the Oppolzer sultam, which is employed in a variety of reactions ranging from Diels-Alder\textsuperscript{10}, anti-aldol, and Baylis-Hillman reactions\textsuperscript{12}. The other major chiral auxiliary used is Evan’s oxazolidinone\textsuperscript{13}, which has also been shown to be extremely effective in a number of different types of reactions.
Figure 7 Structures of chiral auxiliaries: Oppolzer’s sultam and Evans’ oxazolidinone

An excellent example of the effectiveness of the chiral auxiliary form of reaction is seen in the DABCO catalyzed Baylis-Hillman reaction using the Oppolzer camphor sultam chiral auxillary\(^\text{14}\). The reaction had an overall yield ranging from 33 - 98 % depending on the R group used in the starting material and in all cases the e.e. obtained was greater than 99%.

![Scheme 3 Asymmetric synthesis of Baylis-Hillman products using a chiral auxiliary](image)

Although the chiral auxiliary methods can yield an enantiomerically pure product with fairly good yields they still utilize two extra steps in the reaction and require one equivalent of the chiral material to facilitate the reaction in the desired manner.

The final type of methodology, asymmetric catalysis, is the most recent and most aggressively studied today and is now in the forefront of organic chemistry. This method solves the problems of the other approaches to asymmetric synthesis, there are no extra
steps necessary to install and remove chirality to prochiral starting materials, and more importantly, only catalytic amounts of chiral material is needed to promote the reaction stereoselectively. In this type of reaction mechanism the achiral substrate first encounters some degree of interaction with the chiral catalyst through metal chelation, hydrogen bonding, pi-stacking or steric effects in order to get a large enough ΔΔG value (see Fig. 6) in transition state energies in order to stereoselectively facilitate the formation of a single enantiomer. This is followed by a dissociation of the product and the catalyst so that the catalyst may now enter its next catalytic cycle.

There are many examples of asymmetric catalysis that can now be found in the literature covering a wide range of reaction types. The early examples of work in this field came in the form of asymmetric transfer of atoms like hydrogen, oxygen, and nitrogen to organic substrates in such reactions as, hydrogenations and epoxidations. These reactions are now routinely used in organic synthesis providing products in high yields in an asymmetric fashion (e.e. > 99%) using very small amounts of the catalyst. This is of great benefit for chemistry that is done at the macro or industrial level. One of the classic examples is the Takesago synthesis of (-)-menthol.

Scheme 4 The Takesago synthesis of (-)-menthol
In the synthesis of (-)-menthol from β-pinene, Takasago uses Rh-(S)-BINAP as the catalyst to asymmetrically isomerize the allylamine\textsuperscript{16}. This synthesis replaced the old method of obtaining the (-)-menthol via isolation from oil of wintergreen because it can be obtained from cheaper starting materials in an extremely good yield and with an optical purity greater than that isolated in nature.

The main advantages of the catalytic asymmetric synthesis approach are not just due to the elimination of reaction steps, but by the generality in which they may be used. In principal, any chiral molecule can be generated by carefully modifying the structure of the catalyst\textsuperscript{17}. It is for these reasons that this methodology has quickly overshadowed the classical methods of achieving chirality.

1.3 Carbohydrate Chemistry

The field of carbohydrate chemistry has been studied for over a hundred years, and is still one of the most published areas in chemistry. It is their abundance in nature as well as the diversity of roles they play in nature that make them attractive targets of study in both biological and chemical research. As parts of natural products, they play important roles in conferring certain physical, chemical, and biological properties to their carrier molecules. Furthermore, they have been implicated in many cellular processes, including cell-cell recognition, cellular transport, and adhesion; they appear in all cells in some form or another, for example; as peptido- and proteoglycans, glycoproteins, nucleic acids, lipopolysaccharides, or glycolipids\textsuperscript{18}. As a result, carbohydrates have been extensively studied as synthetic building blocks, synthetic targets, and potential drug
candidates. One of the first reactions published in this area, over a century ago, was a glycosidation by Koenigs and Knorr\textsuperscript{19}. There are a great number of variations of this reaction such as the TOPCAT method developed by Hanessian\textsuperscript{20} and numerous enzymatic processes\textsuperscript{21} to control the resulting stereochemistry of the reaction.

Scheme 5. The Koenigs-Knorr, TOPCAT, and enzymatic glycosidation methods

There are hundreds of different reactions done on carbohydrates all with the goal of manipulating them in such a manner to make them synthetically useful for a given synthetic problem.

Carbohydrates are rich in functionality and stereochemistry and it is for this reason they are appealing as starting materials in total synthesis applications. This is an example of the chiral pool methodology of total synthesis. There are many advantages to using carbohydrates as starting materials, which include their known absolute stereochemistry, the renewable nature of their source, and the often low cost. The diverse nature of their functionality makes them simply manipulalable by chemists to offer a
multitude of easily obtained, highly functionalized chirons. The basic scheme below shows a few basic methods that simple sugars are transformed into useful building blocks or to the synthetic target itself\textsuperscript{22}.

![Diagram](image)

**Figure 8.** New synthetic technologies in carbohydrate chemistry

### 1.4 Cleavage of Cyclic Benzylidene Acetals

The method of manipulation that was used in this research project was the formation, and subsequent regioselective cleavage of benzylidene acetals. There are a number of different methods in the literature used to achieve the cleavage of benzylidene acetals. It is one the most useful and widely utilized methods for differentiating the C-4 hydroxyl group of sugars. The reaction has been done reductively, oxidatively, through radical processes, and with Lewis acids. The cleavage of benzylidene acetals has been known for over fifty years. One of the first published studies of the reaction was by
Huyser and Garcia in 1962\textsuperscript{23}, who performed peroxide-induced conversions of cyclic acetals of benzaldehyde to benzoate esters.

\[
\begin{array}{c}
\text{Scheme 6: Peroxide induced acetal cleavage} \\
\text{The reaction is done under quite harsh conditions and they only used C}_2\text{-symmetrical substrates so no regioselectivity of the reaction was discussed. Failla also performed this reaction using the brominating agent N-bromosuccinimide (NBS) in concert with the radical initiator benzoyl peroxide (BPO) in refluxing benzene in 1966}\textsuperscript{27}. It wasn’t until 1968 that Hanessian used NBS to cleave the \textit{o}-benzylidene acetals of sugars that the utility of the reaction was truly realized\textsuperscript{24,25,26}. He published that the reaction is completely regioselective and the product is the primary bromide, secondary benzylidene moiety. This is true for all the substrates used regardless of what R group is attached or if it is a 5 or 6-membered ring sugar. The reaction also can be performed under slightly less harsh conditions by refluxing the substrate in carbon tetrachloride with NBS.
\end{array}
\]

\[
\begin{array}{c}
\text{Scheme 7: NBS mediated cleavage of an \textit{o}-benzylidene sugar} \\
\text{There have been many other novel oxidative methods reported in the literature since the reaction was discovered. Ten years after Hanessian’s report}\textsuperscript{24}, Jeppesen and coworkers\textsuperscript{34} utilized a method similar to Huyser and Garcia on benzylidene derivatives of glucopyranoses and observed the same stereoselective reaction product (a hydrogen atom}
\end{array}
\]
replacing the bromine being the only difference as they do not use a brominating agent as the chain propagating agent in the reaction). The reaction conditions are still harsh 140°C for up to 24 hours and the yields are only up to 60%, and thus a lot of room for improvement still exists. As an improvement of this method in 2001 Roberts and Smits have published that using a thiol, tert-dodecanethiol or tri-tert-butoxysilanethiol, as the chain propagating agent and 2,2-di-tert-butylperoxybutane as the radical initiator increases the yields to near quantitative with no apparent loss of selectivity. The more complex or highly substituted substrates have much higher selectivity with the sugar substrates only showing one product being formed.

Another oxidative method, this time using ozone, to obtain hydroxyester products was first published in 1974 for which only C₂-symmetrical substrates were investigated and the products differed to previous methods as an oxygen atom from the ozone was inserted into the carbon-hydrogen bond of the acetal. The reaction is quantitative after only 10 minutes for benzylidene acetal.

![Scheme 8 Acetal cleavage using ozone](image)

Many other oxidative methods of obtaining hydroxyesters have been published since using a variety of reagents, such as Ph₃CBF₄, t-butyl hydroperoxide, NBS/H₂O, and NaBrO₃/Na₂S₂O₄ to name a few. The reactions occur with varying degrees of regioselectivity, or suffer from use of toxic materials or harsh reaction conditions. One of the latest examples published uses molecular oxygen catalyzed by N-hydroxythalimide/cobalt (II) acetate. It is not a very regioselective reaction with the
best results only obtaining a 2:1 selectivity. The product is different from the Hanessian product as the primary benzoate and secondary alcohol is preferred albeit only slightly.

![Scheme 9](image)

**Scheme 9** New method for oxidative cleavage using a thalidomide catalyst

Since then there have been many other methods of cleaving benzylidene acetals developed, most of which are done reductively. The reaction was first done reductively in 1981 by Gelas\textsuperscript{28} using LiAlH\textsubscript{4}-AlCl\textsubscript{3}, which selectively cleaved to give the primary benzoate and secondary alcohol, the opposite product from the Hanessian type reaction. The reductive cleavage has also been performed using NaCNBH\textsubscript{3}-HCl\textsuperscript{29}, DIBAL\textsuperscript{30}, and a TES/TFA system\textsuperscript{31} to name a few. The resulting reaction product is totally dependent on the method of reduction that is used; two examples of this phenomenon can be seen in scheme 10 below.

![Scheme 10](image)

**Scheme 10** Reductive cleavage of benzylidene acetals

The differing products and these reactions selectivity for non-sugar substrates, which are far less selective, can be explained mechanistically as reported by D.R. Gaultier\textsuperscript{32}. Lewis acid complex A\textsuperscript{1} is higher in energy than B\textsuperscript{1} when an electron withdrawing aryl group
(Ar) is incorporated into the substrate. DIBAL also associates with the less hindered oxygen in complex B¹ as well, thus complex B¹ should be favoured both kinetically and thermodynamically in this case. This however does not seem to be the case, the product determining factor appears to be the stabilization of the oxocarbenium ions A² or B². An electron withdrawing aryl group will destabilize the ion B² and not affect the A² ion as significantly.

Figure 9 Mechanism of Reductive cleavage of benzylidene acetal

This methodology is taken one step further by Harada et al. in 2001 when they use a chiral boron reagent to selectively desymmetrize meso 1,3-diols. Though the reaction is not completely enantioselective, the results are better than previously reported for non-sugar substrates and the reaction conditions are much milder than other methods reported. In most cases the enantioselectivity is about 5:1, but selectivity of 10:1 can be achieved, making this a fairly good method of differentiating meso 1,3-diols.

There are many good methods for the cleaving of benzylidene acetals, yet there are still many areas to be improved upon. The selectivity for these reactions to non-sugar substrates is not very good, reaction conditions for the majority are fairly harsh, and the ability to obtain different regioisomers remains to be studied in this area. There is also a controversy in the literature with regards to the mechanism for these reactions and this will be discussed in detail in the results and discussion section.
1.6 Ionic Liquids in Organic Synthesis

An ionic liquid is defined as a liquid consisting of only ions, which melt at temperatures less than 100 °C and possess a moderate viscosity. There has been a dramatic increase in the attention paid to this area of study in recent years due to the drive to instill more environmentally friendly technologies into practice, especially ones involving damaging and volatile organic solvents. Ionic liquids are considered “environmentally friendly” alternatives based on their low vapour pressure, thermal and chemical stability, non-flammable nature, and high ionic conductivity. Probably the most important attribute that ionic liquids are known for is their ability to act as catalysts for certain reactions.

The first reported ionic liquid was an alkylpyridinium based chloroaluminate first made in 1951 by Hurley, but it wasn’t until the discovery of the 1,3-dialkylimidazolium-based chloroaluminate ionic liquids by Wilkes and co-workers in 1982, and after subsequent work in the early 90’s that an increased interest into the study of this area was noticable. They have been used for many purposes such as: bioprocessing operations, as electrolytes, in liquid-liquid extractions, heat transfer liquids, but most importantly as “green” solvents or catalysts for organic synthesis.

There are many ionic liquids that have been developed; the four major types of cation used are shown in figure 10 below.
As many types of cations that are utilized there are even more anions that are used in conjunction with them. Some of the most commonly used are tabled below:\(^{43}\).

<table>
<thead>
<tr>
<th>Anion</th>
<th>Cation</th>
<th>Anion</th>
<th>Cation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF(_4^-)</td>
<td>PF(_6^-)</td>
<td>SbF(_6^-)</td>
<td>CH(_3)CO(_2^-)</td>
</tr>
<tr>
<td>NO(_3^-)</td>
<td>NO(_2^-)</td>
<td>OTs(^-)</td>
<td>AlCl(_4^-)</td>
</tr>
</tbody>
</table>

Table 1 Commonly used ionic liquid anions

The pairing of different anions with a given cation can dramatically change the physical properties of the resultant salt. For example, varying the anion paired with 1-ethyl-3-methylimidizolium can change the melting point within a range of \(-14\) to \(87^\circ\text{C}\) \(^{51}\). Ionic liquids can now be obtained with melting points as low as \(-96^\circ\text{C}\) opening up many more possibilities for their application.

One of the biggest areas in which the ionic liquids have been utilized in organic synthesis is in transition-metal-mediated catalysis. Ionic liquids have been used in this respect in numerous types of reactions; for example, hydrogenations\(^{52}\), oxidations\(^{53}\), Heck reactions\(^{54}\), Trost-Tsuji coupling\(^{55}\), and Suzuki cross coupling\(^{56}\) to name a few. In these types of reactions there were a multitude of advantages realized by the incorporation of ionic liquids as the solvent. In many cases unprecedented reactivities are observed in addition to the easy isolation of the product and catalyst recovery\(^{56}\). One other major advantage to using ionic liquids is that enhanced selectivity is achieved for many of the
reactions. Recently even biocatalysis using phosphatase\textsuperscript{57}, lipases\textsuperscript{58}, and acylases\textsuperscript{59} have been reported to work extremely well when an ionic liquid was used as the solvent in conjunction with water to greatly increase selectivity. With all the aforementioned advantages, the range of reactions that ionic liquids can be used for and the push for “green” chemistry it seems that there will be much more work done using ionic liquids in the future.

1.7 The Suzuki Cross Coupling Reaction

The Suzuki reaction is a palladium-catalyzed cross coupling reaction between an organoboron compound and an organic halide or triflate providing a general methodology for the formation of carbon-carbon bonds\textsuperscript{60}. The reaction was first published in 1979\textsuperscript{61}, and has become one of the most important cross coupling reactions, totalling about a quarter of all palladium catalyzed cross coupling reactions\textsuperscript{62}. It is because of the availability of reagents as well as the mild reaction conditions employed that make this a very versatile reaction. It is separated further from other metal mediated coupling reactions based on the fact that it is unaffected by the presence of water, is tolerant of many functional groups, and the by-product of the reaction is non-toxic and easily removed from the reaction making the Suzuki coupling reaction suitable for both lab and industrial processes\textsuperscript{60}.

\[
\begin{array}{c}
\text{R} \quad \text{X} \quad + \quad \text{R} \quad \text{B(OH)}_2 \quad \xrightarrow{\text{Pd cat., solvent, base, heat}} \quad \text{R} \\
\end{array}
\]

Scheme 11 A general Suzuki cross coupling reaction scheme
Aliprantis and Canary,\textsuperscript{63} using electrospray ionization mass spectrometry, have studied the mechanism for the Suzuki reaction in detail. They were able to analyze the reaction mixture of a Suzuki reaction. The experiment yielded data that corresponded to the two major intermediates I and II, as seen in Figure 11 below.

Figure 11 The Pd catalytic Cycle during a Suzuki cross coupling reaction

A general catalytic cycle for the cross coupling of most organometallics have the same catalytic cycle as above, which involves oxidative addition, transmetalation, and reductive elimination.

Oxidative addition is often the rate-determining step in the catalytic cycle. The relative rates of substrate reactivity for this step can be summarized by the following: \( I > OTf > Br >> Cl \). The reagent can also be activated by having electron withdrawing functionality and consequently deactivated by electron donating groups. A wide range of palladium catalysts are employed in this reaction such as: \( \text{Pd(PPh}_3)_4 \), \( \text{PdCl}_2(\text{PPh}_3)_2 \), \( \text{Pd}_2(\text{dba})_3 \), and \( \text{Pd(OAc)}_2 \) plus other phosphine ligands. Palladium catalysts that contain fewer than four phosphine ligands or bulky phosphine ligands have been found to be
highly reactive in the oxidative addition stage as they readily coordinate to form unsaturated palladium species\(^6\).

The reductive elimination step of the catalytic cycle liberates the newly formed coupled molecule and regenerates the palladium (0) complex. The reaction occurs directly from the *cis* isomer of reaction intermediate II seen in Figure 11 and the *trans* isomer only after isomerization to its *cis* counterpart.

![Scheme 12. Cis-trans isomerization and subsequent reductive elimination](image)

The order of reactivity for the complexes formed is as follows: diaryl > alkyl-aryl > dialkyl. This suggests that there is participation of the \(\pi\)-bond of the aryl orbital of the aryl group during bond formation\(^5\).

Although the mechanisms of oxidative addition and reductive elimination are reasonably well understood, far less is understood about the process of transmetalation. It is highly dependant on the organometallic used and reaction conditions making it more difficult to study\(^6\). In fact, in the case of organoboron reagents, they are quite unlikely to participate in transmetalation since they have been shown to be inert to organopalladium (II) halides\(^7\). Thus it is apparent that proper choices of ligands and bases in the transition metal complexes are essential. The cross coupling reaction involving organoboron compounds with organic halides can only selectively react in the presence of a negatively charged base, sodium or potassium carbonate, phosphate, or hydroxide\(^8\). It is because of
the low nucleophilicity of the boron atom that transmetalation does not occur readily. However, the nucleophilicity of the organoboron reagent can be enhanced by quaternization at the boron atom with the negatively charged base giving the corresponding “ate” species\textsuperscript{69}. Thus, during the transmetalation phase of the catalytic cycle for Suzuki couplings a base is necessary.

There are many different substrates that can be employed for this reaction, which is why the reaction is such a powerful coupling method. The boron substrate can be alkenyl, aryl, or even alkyl and in turn can be coupled to either alkenyl halides, triflates, vinylic sulfides, aryl halides, and most recently iodoalkanes making the reaction that much more useful in synthesis. In the scope of this research project aryl-aryl couplings were examined, thus I will focus on aryl coupling reactions. The first published method of aryl coupling using a palladium catalyst occurred in 1987\textsuperscript{70}, which reacted phenyl boronic acid with various aryl iodides and Pd(PPh\textsubscript{3})\textsubscript{4} with Na\textsubscript{2}CO\textsubscript{3} as the base. Since then there have been numerous modifications to the reaction conditions to get either specific reactions to work or make them more general. There have been many different palladium catalysts employed together with many different types of phosphine ligands and a number of different bases\textsuperscript{71-75}. Chlorobenzene derivatives are fairly inert towards oxidative addition, except for some \pi-deficient aryl chlorides that do form coupling products in good yields. The reaction proceeds much better as a homogeneous reaction solution, but is also largely unaffected by the presence of water and reasonable yields are obtained using heterogeneous mixtures. Another major feature of this type of Suzuki coupling is the fact that steric hindrance of the aryl halide is not a factor in the formation of highly substituted biaryls.
Ar-X: 2-methoxyiodobenzene (80%), 2-chloriodobenzene (94%)
2-bromonaphthalene (86%).

Scheme 13 Suzuki reactions with sterically hindered reagents

Due to this phenomena and the ready availability of ortho-functionalized boronic acids by directed ortho-metalation-boronation sequence providing a convenient synthetic cross coupling protocol, as illustrated by Snieckus\textsuperscript{76}, this reaction shows its synthetic utility. The usefulness of this protocol has been shown with the industrial scale synthesis of a non-peptide angiotensin II receptor antagonist\textsuperscript{77}.

Scheme 14 Synthesis of a non-peptide angiotensin II receptor antagonist

This type of reaction has been used during the synthesis of many different types of natural and unnatural products and pharmaceuticals, such as: ferrocene derivatives\textsuperscript{78}, vancomycin\textsuperscript{79}, helically chiral ligands\textsuperscript{80}, michellamine\textsuperscript{81}, and rigid-rod polymers\textsuperscript{82} used as high-performance engineering materials.
Chapter II
Results and Discussion

2.1 NBS-Mediated Cleavage of benzylidene Acetals

Marvell first published the oxidative fragmentation of benzylidene acetals mediated with N-bromosuccinimide (NBS) over 50 years ago\(^3\). The overall reaction (Scheme 15) was investigated later by several groups\(^4\) and was applied to carbohydrate derivatives by Failla\(^5\) and Hanessian\(^6\). Simple benzylidene acetals such as the optically active propanediol derivative 1 and the \(\alpha\)-methyl-D-gluconopyrano-4, 6-benzylidene derivative 3 provide fragments 2 and 4 having the bromine atom on the least hindered position, usually with very high or complete regiocontrol, as seen in Scheme 15.

![Scheme 15 Examples of NBS-mediated benzylidene acetal cleavages](image)

This result is surprising as it appears radical fragmentation may have occurred via a contra-thermodynamic pathway. The reaction proceeds thermally with the use of NBS alone or, often more efficiently, through the addition of an initiator such as benzoyl
peroxide (BPO) or azoisobutyronitrile (AIBN). The reaction is initiated by H-atom abstraction from the benzyllidene position giving the radical 5, seen in Scheme 16. 

Scheme 16 Possible mechanistic pathways for the NBS-mediated fragmentation of benzyllidene acetals

Three different mechanistic pathways, outlined in Scheme 16, have been envisioned for the fate of radical 5 to account for the products observed. In the original mechanistic proposal, shown as Path A, fragmentation can give two possible radical intermediates 6 and 7 for further propagation with NBS leading to the isomeric bromides 8 and 9.

Alternatively, the radical could be opened with a bromine atom through an overall free
radical process (Path B), or the third path, brominated at the benzylic position first via a propagation step followed by an ionic fragmentation pathway (Path C). Path A\textsuperscript{84} was initially discounted\textsuperscript{84b}, since the products observed from the reaction are usually brominated at the least hindered position implying radical fragmentation via a contra-thermodynamic pathway. Support in favour of an ionic termination (Path C) route was obtained by Hanessian\textsuperscript{86c}, who was able to trap carbocation intermediates with neighbouring hydroxyl groups, and also by King and Albutt\textsuperscript{87} who trapped dioxolenium ions with the hexafluoroantimonate anion.

![Figure 12 Trapped dioxolenium anion by King and Albutt](image)

Despite this, recent evidence from the free radical mediated reduction of benzylidene acetalts in the presence of thiols is consistent with the direct fragmentation of the initial radical\textsuperscript{88}. Due to the usefulness of the functionalized products available from this reaction\textsuperscript{89}, as well as an appreciation of the large number of radical mediated reactions which have proven to be of value over the last 20 years or so\textsuperscript{90}, aspects of the mechanism of this reaction needed to be clarified to illuminate its overall scope\textsuperscript{91}.

We chose to develop test cases for the reaction employing substrates derived from the 2,4-benzilidene derivative of D-erythrose, themselves readily available from D-glucose. These truncated variants are analogs of the reaction 3 to 4 (Scheme 15) in which positions C4 and C6 are more open for potential radical or nucleophilic attack.
Scheme 17 Synthesis of glucose derived substrates

The conversion of α-D-glucose to 4, 6-dibenzylidene-D-glucose did not yield as much product as was stated by Paquette\textsuperscript{92}, instead of 78\% yield, only a yield of 30\% could be obtained after crystallization. After obtaining the dibenzylidene acetal, a diol cleavage was performed using sodium periodate to obtain the glucose-derived aldehyde (25). The aldehyde was not stable for long periods of time and thus was reacted directly with the appropriate nucleophile to obtain either 27 or 28 in yields exceeding 80\% over the two steps.

It was first determined that the regioselectivity of the fragmentation could be completely altered by simply attaching an olefin allylic to the more hindered position on the acetal (Scheme 18). Treatment of 12 under standard conditions (NBS, BPO\textsubscript{(cat)}, PhCl,
70 °C, 3h) gave the allylic bromide 13 as the single (Z)-isomer. Careful work up and purification gave 13 in 64.2% isolated yield along with 21.5% recovered 12 allowing for 85.7% overall mass balance. No other products were observed; the balance of the material is likely lost to polymerization of starting material and/or product, which is not unexpected. To my knowledge, this is the first time that the regiochemistry of the fragmentation has been altered in this fashion. The reversal of regioselectivity in the opening step mediated by the olefin is likely due to a lowering of the energy of the now allylic σ* orbital of the O3-C4 bond on the intermediate radical or cation. Product 13 appears to be the result of a concerted bromine radical or bromine anion addition at C2' on the intermediate benzylic radical or cation respectively in a SN2'-like fashion. The fact that a single olefin is obtained is evidence against an open chain allylic radical (Path A) through which both allylic isomers as well as possible E and Z configurational isomers would be expected. This result does not discriminate between the other two substitution pathways outlined in Scheme 16.

More definitive evidence against path A was obtained through the second experiment (14 to 15) shown in Scheme 18. The acryloyl substitutited olefin 14 was prepared and subjected to our standard fragmentation protocol. If fragmentation of the initial benzylic radical to give an open chain radical precedes propagation with NBS (or Br2), the intermediate radical would be expected to cyclize onto the tethered radicalophile in 6-endo-trig or even 8-endo-trig fashion.

Molecular modeling studies on the fragmented acyclic radical intermediate provide no reason why such a cyclization should not occur as either of the radical centers are in close proximity to the β–position of the acrylate. On the other hand, if radical
fragmentation does not occur prior to bromine atom or anion attack on the respective intermediate benzylic radical or cation (paths B and C), acyclic substitution products are to be expected. The reaction of substrate 14 proceeded without incident to give a single product readily identified as the allylic bromide 15 (55.2%, 25.3% recovered 14, 80.5% mass balance). No evidence for any cyclized product was obtained; the only trace impurities observed were polar allylic alcohols likely produced through slow hydrolysis of 15. This result provides strong evidence that under these conditions the initial benzylic radical does not immediately fragment or at least fragmentation is much slower than the actual opening. The major reaction pathway therefore proceeds through nucleophilic bromine atom or anion opening of the cyclic radical or cation (paths B or C).

Scheme 18 Evidence against open chain radical pathway
Reaction pathways B and C are mechanistically very similar and difficult to unravel, the major difference being whether a bromine atom or bromide anion attacks the activated intermediate. An experiment was devised to illuminate the subtle difference in reactivity expected in this process for a neutral radical or a polar anion attack on the intermediate. The results provide evidence that in fact path C is operative under these conditions. It is well known that radicals add preferentially to the β-position of enones, however since they are not subjected to the same electronic constraints as the nucleophilic addition of an anion, they may also add to the α-position of an enone in certain cases when this is mechanistically possible. Test substrate 18 was prepared as shown above, and subjected to the standard reaction (Scheme 19). Given that radical 19 is a reactive intermediate and the propensity for SN2'-like opening has already been demonstrated, epimeric bromides 21 would be expected if the reaction proceeds through path B. In contrast, if benzylic bromination occurs first following Path C and fragmentation proceeds through the purely ionic path from 20 then a direct SN2 displacement of bromide at C4 would be expected giving 22. In other words, the natural polarity of the unsaturated ester can be used to impede bromide anion attack at the C2'-position.
During the reaction, benzylidene 18 underwent fragmentation under the standard conditions to give bromide 22 (61%, 15.5% recovered 18, 76.5% mass balance) as a single isomer. The stereochemistry of the molecule is determined through direct comparisons with reported literature compounds\textsuperscript{104,105}, both syn- and anti- diastereomers, and the proton coupling observed in the product agreed with that of other syn- products. Compound 22 is fully consistent with a direct S\textsubscript{N}2-like displacement proceeding with inversion at C4 through bromide anion attack on the cyclic cation.

Taken together with the earlier results of Hannessian\textsuperscript{86}, the evidence suggests that the NBS-mediated fragmentation process proceeds through path C outlined above through a rapid ion-pair recombination involving a formal antarafacial 1,3-bromide shift. The S\textsubscript{N}2-like opening is also in accord with earlier studies reported by King\textsuperscript{87} in the trapping of similar cations. It was concluded that in the presence of NBS, the rate of chain transfer from radical 19 to the benzyl bromide 20 is faster than direct
fragmentation, whereas in the absence of NBS, the direct radical fragmentation pathway is operative allowing trapping of open-chain radicals. This is seen in the work done by Roberts and Smits using a peroxide radical initiator and a thiol chain propagator to facilitate the reaction. Lastly, the regiospecific and stereoselective fragmentations described through incorporation of an allylic alcohol into the benzylidene allows for the preparation of densely functionalized chirons such as 13, 15 and 22 in a few steps from D-glucose. Opening up a large number of easily obtained chirons with the sought after 1,2-syn functionality from an inexpensive starting material.
2.2 Suzuki Couplings in Ionic Liquids

The Suzuki cross-coupling reaction\(^6\) has become a standard method for palladium catalyzed carbon–carbon bond formation between an sp\(^2\) or non-\(\beta\)-hydride containing electrophile and a boronic acid derivative. The recent application of the reaction to aliphatic electrophiles\(^9\) has expanded its scope considerably, making it applicable to a whole new realm of substrates. Much recent effort has gone into devising new ligands for this palladium mediated process and various electron rich alkyl phosphines\(^4\) and mixed aryl/alkyl phosphine ligands\(^5\) have been described. Reaction conditions and catalysts that allow for couplings of aryl chlorides are especially sought after due to the lower cost and ready availability of these substrates. A number of catalysts have recently been developed which promote the Suzuki coupling of these chlorides with boronic acid nucleophiles\(^6, 7\).

One of the major drawbacks of these types of palladium mediated processes is the catalyst cost in conjunction with its non-recyclability. One recently published solution involves the application of ionic liquids as solvent. Ionic liquids based on alkylimidazolium and other quaternary ammonium/pyridinium salts have emerged as valuable, alternative "green" solvents for catalytic processes over the last few years\(^8\). Given the recent push towards more environmentally friendly chemical processes over the last while, being able to carry out these types of reactions without the use of low boiling solvents is an attractive alternative. Also, using ionic liquids it is often possible to recycle the active palladium catalyst subsequent to extraction of the organic product and inorganic salts from the ionic liquid, which forms a tri-phasic system with water and
a non-polar organic solvent. This process has been applied efficiently to the palladium mediated Heck coupling reaction in quaternary nitrogen ionic liquids\textsuperscript{99} and can be conducted at room temperature with the application of ultrasound\textsuperscript{100}. The Suzuki reaction has also been carried out successfully in imidazolium ionic liquids both thermally\textsuperscript{101} and with sonication\textsuperscript{102}. Quaternary phosphonium salts are another class of readily available ionic liquids, which have received scant attention in the literature. In one case, hexadecyltributylphosphonium bromide was used to effect Heck coupling of aryl halides with acrylic esters\textsuperscript{103}. The work done herein on the use of the room temperature ionic liquid tetradecyltrihexylphosphonium chloride (THPC) containing small amounts of water and toluene (single phase) as an efficient reusable medium for the palladium catalyzed Suzuki cross-coupling reaction.

\[
\begin{array}{c}
\text{C}_6\text{H}_{13} \\
\text{H}_{13}\text{C}_6^+ \text{P} \text{C}_14\text{H}_{29}^- \text{Cl} \\
\text{C}_6\text{H}_{13}
\end{array}
\]

Figure 13 Structure of the room temperature ionic liquid tetradecyltrihexylphosphonium chloride

During the search for an optimal set of conditions many different bases were tried with varying degrees of success. The bases KF, NEt\textsubscript{3}, NEt(iPr)\textsubscript{2}, and K\textsubscript{3}PO\textsubscript{4} were used and obtained yields of 0\%, 32\%, 25\%, and 100\% were obtained respectively when used in concert with the other conditions. The addition of water to the reaction (added for salt solubility) was also found to be necessity for the reaction to proceed at an accelerated rate. In order to maintain complete solubility of both the boronic acid and aryl halide in the ionic liquid, a small amount of toluene (10-20\%) was added also. Two other aspects
of the reaction were also tested which were catalyst and catalyst loading. Two different palladium catalysts were also tested, Pd(PPh₃)₂Cl₂ and Pd₂(dba)₃ CHCl₃, and it was found that the later of the two was substantially more effective than the other. All of the reactions reported in Table 2 were therefore performed with identical reaction conditions (THPC, aryl iodide, aryl boronic acid, Pd₂(dba)₃ (1%), K₃PO₄, H₂O, toluene).

![Scheme 20](image)

Scheme 20  The general Suzuki reaction conditions employed for coupling with aryl iodides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Isolated yield (%)</th>
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<td>H</td>
<td>H</td>
<td>50</td>
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<td>90</td>
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</tbody>
</table>

Table 2  Suzuki reactions of aryl iodides with aryl boronic acids

As seen in Table 2 the cross-coupling reaction of various substituted iodobenzenes including electron rich derivatives (Table 2, entry 7) with a variety of arylboronic acids proceeded efficiently in THPC and were all complete within 1 h at 50
°C without the aid of a co-catalyst. The reaction was chemoselective in the case of the mixed halide 4-chloroiodobenzene (Table 2, entry 9). These mild conditions are promising, as the next stage of the project is to look at the aryl bromides and chlorides, which are increasing difficult to react in these types of reactions.

The corresponding aryl bromides also reacted under these conditions but proved to be somewhat more sluggish. After five plus hours the reaction yields were only moderate at best and the idea of the project was to keep the reaction conditions as mild as possible. Thus the addition of a co-catalyst was to be included, for which many were tested; PPh3, PBU3, PA-Ph, PA-o-tolyl (PA=phospho adamantine). It was found that all worked very well except PBU3 and since triphenylphosphine is less expensive and readily available it was chosen as the co-catalyst.

Scheme 21 The general Suzuki reaction conditions employed for coupling with aryl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Ligand</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Isolated yield (%)</th>
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<tbody>
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<td>PPh3</td>
<td>50</td>
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<td>95</td>
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</tbody>
</table>

Table 3 Suzuki reactions of aryl bromides with aryl boronic acids

Table 3 shows how the addition of the triphenylphosphine allows for the reaction conditions to stay mild and keep the reaction time down, while obtaining very high yields
even for the electron rich substrates such as 4-methoxybromobenzene (Table 3, entries 3 and 4).

As expected, reactions involving aryl chlorides were considerably more difficult, however addition of triphenylphosphine and heating at 70 °C allowed for high conversions when the electron deficient 4-chloroacetophenone was used as a substrate (Table 4, entries 1 and 2). The electron rich 4-methoxochlorobenzene was still slow to react under these conditions (Table 4, entry 3).

Scheme 22 The general Suzuki reaction conditions employed for coupling with aryl chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Ligand</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Isolated yield (%)</th>
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<td>30</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 4 Suzuki reactions of aryl chlorides with aryl boronic acids

The last area of the procedure that required optimization before catalyst recyclability could be tested, was work up. Previously, for results in Tables 2-4 after only one run, the ionic liquid crude reaction mixture was filtered through a silica gel plug, washed with hexane/ethyl acetate followed by silica gel chromatography of the filtrate. Running the entire crude mixture through silica gel would make re-use of the catalyst difficult. Thus a
previously reported protocol was to be adopted, which was used for the ionic liquid imidazolium salts\textsuperscript{99}. Addition of water and hexane to the reaction products in the phosphonium salt ionic liquid results in the formation of a triphasic system that differs from that reported for the imidazolium salts. In the case of imidazolium salts, the ionic liquid is more dense than water and forms the bottom phase with an aqueous central phase and organic layer on top. In the case of THPC, the palladium catalyst remains fully dissolved in the central phosphonium salt layer while the product biaryls are extracted into the top hexane phase and inorganic salts (phosphates/borates) into the lower aqueous phase. To obtain the pure biaryl product, silica gel chromatography must still be performed, as the ionic liquid THPC is slightly soluble in hexane.

The reaction of phenylboronic acid with iodobenzene was investigated extensively with the previously mentioned conditions in THPC. The yield obtained from hexane extraction and silica-gel chromatography of the hexane solubles ranged from 82–97\% over several runs. On the other hand, direct filtration of the ionic liquid through a short silica-gel column gave slightly higher isolated yields, 95–97\%, as indicated in Table 2. These results indicate that residual biaryls are still slightly soluble in THPC. This is not a major problem as the residuals can be recovered in subsequent extractions. Thus, when further quantities of iodobenzene, phenylboronic acid and K\textsubscript{3}PO\textsubscript{4}, but no further catalyst, were added to the isolated central ionic liquid, heating again at 50 °C resulted in complete turnover of iodobenzene. Repetition of the same work-up gave biphenyl in 82–97\% yield (repeated five times) for both the initial and recycled reaction sequences. Thus it is clear that a competent palladium catalyst remains fully dissolved in the phosphonium salt allowing its efficient re-use.
The Suzuki cross-coupling reaction done in THPC is a superior method in comparison to the method recently reported in imidazolium based ionic liquids, which requires ultrasonic irradiation to proceed at 30 °C\textsuperscript{102}. In addition, inactive Pd black is deposited during the reaction resulting in lower conversions (82–92%) with aryl iodides and bromides and particularly so in the case of electron deficient aryl chlorides (42–65%). The thermal Suzuki coupling reaction in these imidazolium based ionic liquids does not proceed with aryl chlorides, even at 110 °C\textsuperscript{101}. In contrast to these results, complete conversion of aryl iodides and bromides and high conversions with electron deficient chlorides can be achieved in the THPC ionic liquid without the use of a preformed catalyst at 50–70 °C. The rapid coupling of aryl iodides and bromides and high conversions obtained with the aryl chlorides indicate that a very active catalyst is produced in the THPC system. In addition, the higher conversions and recyclability of this Pd THPC–catalyst system indicate the relatively high stability of the active Pd catalyst involved in the Suzuki coupling. Lastly, no homo-coupled products have been observed using the THPC catalyst system reported here, a problem reported in many other systems.

The phosphonium salt ionic liquid THPC holds a great deal of potential as an economical, recyclable medium for metal promoted reactions and process chemistry in general and, as we have shown here, the Suzuki cross-coupling reaction in particular. Further analysis of the active Pd-catalytic species formed by dissolution of Pd\textsubscript{2}(dba)\textsubscript{3} in the phosphonium salt ionic liquid and applications of the process to other coupling partners are currently under investigation in our laboratories.
Chapter III

Experimental

3.1.1 General Procedures and Physical Data

Unless otherwise specified all reagents used as starting materials were obtained commercial suppliers and used without further purification unless noted. All glassware used in the various experiments were first, flame dried under a stream of argon and all reactions were preformed under an argon atmosphere and agitated with a magnetic stirring bar. Air-sensitive reagents were transferred via canula under a positive pressure of argon. Reactions that required lowered temperatures were done under the following conditions: for -78 °C in an acetone / dry ice bath, for -41 °C acetonitrile / dry ice, for -40 °C to 0 °C were obtained using the cryostat in an isopropyl alcohol bath, and 0 °C water / ice. On the reverse, any reaction that required heating were immersed in a Cat M26-controlled mineral oil bath.

All solvents used in extractions work up procedures and purifications, via column or recrystallization were reagent grade without further purification. Distilled water was used in all aqueous extractions. Organic solvents used in reactions were distilled and pre-dried according to published methods: pyridine, cyclohexane, and dichloromethane were dried with calcium hydride; toluene with sodium / benzophenone; THF with lithium aluminum hydride, then sodium / benzophenone; and finally ethanol and methanol with magnesium. Concentrated in vacuo means to remove volitile solvents from the reaction flask via a Buchi rotary evaporator equipped with a water aspirator, followed by evaporation with vacuum to a constant weight.
All column chromatography was done using gravity, unless otherwise mentioned, under the designated solvent system on 70 - 300 mesh silica gel. All thin layer chromatography (TLC) was performed on Polygram Sil G/ UV254 precoated plastic plates. Visualization was done using a UV lamp or via dyeing the plate with: vanillin, DNP, anisaldehyde, or sulfuric acid in ethanol, followed by heating. The gas chromatographic separations that were completed were performed on a Hewlet Packard HP6890 GC system equipped with a chiral column.

Melting point determinations were obtained using an electrothermal apparatus. IR spectra were reported on a Mattson Research Series FT-IR spectrometer and were completed in chloroform on KBr plates or as a solid film in solid solution with KBr and reported in wave numbers. The abbreviations used for the reported IR spectra results are as follows: strong (s), medium (m), weak (w), and broad (br).

Mass spectra were obtained using the Kratos Concept IS mass spectrometer in either fast atom bombardment, or electron impact mode and reported with values of a mass to charge ratio (m/z).

$^1$H and $^{13}$C NMR spectra were taken on the Bruker advance DPX-300 digital FT spectrometer in deuterated chloroform and using trimethylsilane as the internal standard. The NMR data is reported in the following manner: chemical shift (multiplicity, number of corresponding protons via integration, coupling constant in Hz). The abbreviations used for explaining multiplicity are: singlet (s), doublet (d), triplet (t), quartet (q), or broad (br).
3.2 Experimental Procedures (Project A)

**Compound 1:** (4S)-4-methyl-2-phenyl-1,3-dioxolane

![Chemical Structure]

To a round bottom flask fitted with a reflux condenser was added 25 µL of (s)-(+)1,2-propanediol (1.0 eq), 51.3 µL benzaldehyde dimethyl acetal (1.0 eq), and 3mg (0.05 eq) PTSA in 1.0 ml of toluene. The reaction mixture was gently refluxed at 70°C for 24h. The reaction was then quenched using NaCO₃ (aq) followed by an aq/org workup using ethyl acetate/water. The crude product was purified using a 30 x 1 cm Si gel column with the following solvent ratios: 100 mL 80:20, 100 mL 70:30 hexanes: ethyl acetate. The reaction yielded a clear and colourless oil product in an 86.6% yield and was characterized. **¹H NMR (300MHz, CDCl₃)** \( \delta 1.41 \text{(d, 1.5H, } J=8.5 \text{ Hz)}, 1.43 \text{(d, 1.5H, } J=6.1 \text{ Hz)}, 3.61 \text{(m, 1H)}, 4.15 \text{(t, 0.5H, } J=6.9 \text{ Hz)}), 4.30 \text{(t, 0.5H, 6.1 Hz)}, 4.39 \text{(m, 1H)}, 5.85 \text{(s, 0.5H)}, 5.97 \text{(s, 0.5H)}, 7.35 \text{(m, 2H)}, 7.35 \text{(m, 3H)}; \) **¹³C NMR (300 MHz, CDCl₃)** \( \delta 138.5, 138.4, 130.3, 130.1, 128.9, 128.8, 127.1, 127.0, 126.8, 104.5, 103.6, 73.9, 72.8, 72.5, 72.8, 53.1, 19.0, 18.8; \) **LRMS (EI)** m/z 163 (100%), 105 (63%), 164 (39%), 77 (25%), 119 (9%), 133 (3%); **HRMS (EI)** m/z calcd 164.0837, found 164.0831; \([\alpha]_D^\text{+30.85 (c=0.376, MeOH).}\)
Compound 2: (1S)-2-bromo-1-methylethyl benzenecarboxylate

![Chemical Structure of Compound 2]

In a dried round bottom flask filled with Ar and fitted with a reflux condenser was added 6.5 mg (1.0 eq) of substrate 1, 7.1 mg (1.0 eq) NBS, 1.0 mg (0.05 eq) BPO, in 0.75 mL of PhCl. The reaction mixture was heated to 70°C for 2h, then was quenched with NaCO₃ (aq) followed by aq/org workup using DCM/water. The crude product was purified using flash chromatography on a 30 x 1 cm Si gel column utilizing the following solvent ratios: 98:2, 95:5, 90:10 all hexanes: ethyl acetate in 50 mL increments. The reaction yielded 7.3 mg (76.1% yield) of clear and colourless oil product 2, which was characterized. 

1H NMR (300MHz, CDCl₃) δ 1.51 (d, 3H, J=5.8 Hz), 3.60 (d, 2H, J=4.8 Hz), 5.33 (q, 1H, J=5.6 Hz), 7.47 (t, 2H, 7.1 Hz), 7.50 (t, 1H, J=8.0 Hz), 8.08 (m, 2H); 13C NMR (300 MHz, CDCl₃) δ 166.1, 134.7, 133.5, 130.2, 129.3, 70.2, 35.8, 19.1; IR (KBr film) 2978, 2922, 1794, 1643, 1547, 1466, 1388, 1096 cm⁻¹; LRMS (EI) m/z 105 (100%), 77 (45), 122 (38), 51 (21), 176 (4), 149 (3), 163 (1), 242 (>1), 206 (>1); HRMS (EI) m/z calcd 241.9942, found 241.9915; [α]D +13.33 (c=0.0195, MeOH).

Compound 12: 1-(2-phenyl-4-vinyl-1,3-dioxan-5-yl)-1-ethanone

![Chemical Structure of Compound 12]

To a round bottom flask was added 1.0 eq of 2-phenyl-4-vinyl-1,3-dioxan-5-ol
followed by 1 mL of pyridine and 1 mL of acetic anhydride. The solution was stirred at room temperature for 2h, the volatiles were removed in vacuo, and an aq/org work up was performed using DCM/NaHCO₃ (aq). The product was sufficiently pure for further use. The white crystalline solid product was obtained quantitatively. The product 12 was isolated and characterized. m.p. range of 59-65°C; ¹H NMR (300MHz, CDCl₃) δ 2.01 (s, 3H), 3.70 (t, 2H, J=10.4 Hz), 4.23 (dd, 1H, J=6.6, 9.5 Hz), 4.41 (dd, 2H, J=5.3, 10.6 Hz), 4.89 (dt, 1H, J=5.3, 9.9 Hz), 5.30 (d, 1H, J=10.5 Hz), 5.44 (d, 1H, J=17.1 Hz), 5.58 (s, 1H), 5.95-5.87 (m, 1H), 7.38 (m, 3H), 7.51 (m, 2H); ¹³C NMR (300 MHz, CDCl₃) δ 169.3, 137.7, 134.4, 129.5, 128.7, 126.6, 119.3, 101.6, 80.76, 68.55, 66.6, 21.2; IR (KBr film) 3466, 2880, 2854, 1738, 1454, 1376, 1254, 1113, 1087, 1053, 1030, 994, 764, 700 cm⁻¹; LRMS (EI) m/z 43 (100%), 149 (52), 107 (42), 91 (20), 77 (14), 51(7), 205 (4), 248 (2), 188 (2), 171 (1); HRMS (EI) m/z calcd 248.1049, found 248.1037; [α]D – 42.71 (c=0.10, MeOH).

**Compound 13:** (2S,3E)-2-(acetyloxy)-5-bromo-3-pentenyl benzenecarboxylate

\[
\text{Ph} \quad \text{OAc} \quad \text{NBS, BPO} \quad \text{C}_6\text{H}_5\text{Cl} \quad 70^\circ\text{C} \quad \text{Br} \quad \text{OBz} \quad \text{OAc}
\]

To a round bottom flask was added 1.0 eq of compound 12, 1.2 eq NBS, 0.05 eq BPO, and 1.0 mL of PhCl. The mixture was placed on an oil bath at 70°C. After 1h a furthur 0.2 eq of NBS and 0.05 BPO were added in 100 µL of PhCl. After stirring at 70°C for a further 2h the reaction was quenched with NaHCO₃ (aq), followed by an aq/org workup with DCM / H₂O. The crude product was purified using silica gel 30 x 1 cm column with the following solvent system: 400 mL 5:95 ethyl acetate: hexanes. There was an 85.7%
yield of a clear and colourless oil product based on 21.5% recovery of starting material. The product 15 was isolated and characterized. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 2.12 (s, 3H), 3.97 (d, 1H, J=7.4 Hz), 4.38 (dd, 1H, J=6.6, 11.8 Hz), 4.49 (dd, 1H, J=4.0, 11.8 Hz), 5.70 (dd, 1H, J=6.3, 10.5 Hz), 5.84 (dd, 1H, J= 6.4, 15.3 Hz), 6.10 (m, 1H), 7.38 (t, 2H, J=7.6 Hz), 7.49 (t, 1H, J=7.4 Hz), 7.95 (d, 2H, J=7.2 Hz); $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 170.3, 164.2, 133.6, 131.1, 130.1, 129.3, 128.8, 126.7, 77.0, 71.1, 31.3, 21.4; IR (KBr film) 3441, 2956, 2924, 1720, 1646, 1451, 1372, 1273, 1228, 1110, 1025, 711 cm$^{-1}$; LRMS (EI) m/z 105 (100%), 43 (38), 77 (28), 149 (14), 247 (10), 122 (9), 177 (4); HRMS (EI) m/z calcd 328.98642 ([M]+-1H), found 325.00696; [$\alpha$]$_D$ +30.8 (c=0.10, MeOH).

**Compound 14:** 2-phenyl-4-vinyl-1,3-dioxan-5-yl acrylate

![Reaction diagram]

To a dried round bottom flask was added 2-phenyl-4-vinyl-1,3-dioxan-5-ol (1.0 eq) in 1.0 mL of DCM and cooled to 0°C. This is followed by the addition of triethyl amine (1.2 eq), then acryloyl chloride (1.2 eq). The resultant solution was then stirred at 0°C. After 2.5 h, a further addition of 1.2 eq of both triethyl amine and acryloyl chloride are added and stirred for another 15h. An aq/org workup was performed at this point using NaHCO$_3$ (aq)/DCM. The crude mixture was then purified using a 30 x 1 cm Si gel column with the following solvent ratios: 85:15 100 mL, 75:25 100 mL hexanes: ethyl acetate. The reaction afforded a clear and slightly yellow oil product 14 in a 71% yield. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 3.74 (t, 1H, J=10.5 Hz), 4.29 (dd, 1H, J=6.4, 9.5
Hz), 4.46 (dd, 1H, J=5.3, 10.6 Hz), 4.96 (dt, 1H, J=5.3, 9.8 Hz), 5.30 (d, 1H, J=10.6 Hz), 5.44 (d, 1H, J=17.2 Hz), 5.91 (m, 2H), 6.12 (dd, 1H, J=10.5, 17.3 Hz), 6.45 (dd, 1H, 1.3, 17.3 Hz), 7.38 (m, 3H), 7.55 (m, 2H); $^1^3$C NMR (300 MHz, CDCl$_3$) δ 164.6, 137.7, 134.2, 132.2, 129.5, 128.7, 128.1, 126.6, 119.3, 101.62, 80.7, 68.6, 66.7; IR (KBr film) 3091, 3041, 2969, 2869, 1728, 1635, 1457, 1404, 1285, 1103, 1024, 1005, 767, 702 cm$^{-1}$; LRMS (EI) m/z 55 (100%), 161 (92), 105 (28), 91 (119), 149 (15), 77 (77), 259 (4), 204 (2), 188 (2), 260 (1); HRMS (EI) m/z calcd 260.1049, found 260.1033; [α]D $-55.2$

(c=0.002, MeOH).

**Compound 15:** (2S,3E)-2-(acryloyloxy)-5-bromo-3-pentenyl benzenecarboxylate

![Chemical Structure](image)

To a round bottom flask was added 1.0 eq of compound 14, 1.2 eq NBS, 0.05 eq BPO, and 1.0 mL of PhCl. The mixture was placed on an oil bath at 70°C. After 1h a further 0.2 eq of NBS and 0.05 BPO were added in 100 µL of PhCl. After stirring at 70°C for a further 2h the reaction was quenched with NaHCO$_3$ (aq), followed by an aq/org workup with DCM / H$_2$O. The crude product was purified using silica gel 30 x 1 cm column with the following solvent system: 400 mL 60:40 DCM: hexanes. There was an 80.5% yield of a clear and colourless oil product based on 21.5% recovery of starting material. The product 15 was isolated and characterized. $^1$H NMR (300MHz, CDCl$_3$) δ 3.88 (d, 2H, J=7.3 Hz), 4.31 (dd, 1H, J=11.7, 3.9), 4.47 (dd, 1H, J=11.7, 3.9), 5.69 (m, 1H), 5.75 (m, 1H), 5.81 (d, 1H, J=9.8 Hz), 6.05 (m, 1H), 6.05 (dd, 1H, J=28.1, 10.3 Hz), 6.39 (d, 1H, J=17.3 Hz), 7.37 (t, 2H, J=7.6 Hz), 7.51 (t, 1H, J=7.3), 7.95 (d, 2H, J=7.3 Hz); $^1^3$C NMR
(300 MHz, CDCl₃) δ 166.5, 165.4, 133.6, 132.2, 131.2, 130.1, 129.9, 129.1, 128.8, 128.3, 71.3, 65.3, 31.3; IR (KBr film) 3068, 2924, 2852, 1723, 1272, 1183, 1113, 712 cm⁻¹; LRMS (EI) m/z 105 (100%), 55 (70), 259 (29), 77 (26), 124 (13), 150 (7), 260 (5), 188 (2); HRMS (EI) m/z calcd 259.09691, found 259.09703; [α]D +2.3 (c=0.009, MeOH).

**Compound Pre 18:** methyl 5-hydroxy-2-phenyl-1,3-dioxane-4-carboxylate

![Chemical structure](image)

To a round bottom flask was added 100 mg of benzylidene-D-glucose (1.0 eq) to 10 mL of distilled water and heated to ~50°C in order to dissolve the benzylidene. The reaction mixture was then cooled to room temperature where upon 20 mL of DCM, 110 mg of NaHCO₃ (3.5 eq), followed by the addition of 558.6 mg of NaIO₄ (7.0 eq). The reaction mixture was vigorously stirred, after 0.5 h an aq/org workup was performed using first DCM/water, followed by further extractions of the aqueous layer using ethyl acetate x 2. The organic layers were combined and concentrated in vacuo to yield 69.7 mg (89.8 % yield) clear and colourless oil product of sufficient purity to perform the subsequent step.

To a dried round bottom flask was added 182.9 mg of trimethyl phosphoroacetate (3.0 eq) in 3.5 mL THF and stirred at 0°C for 5 min, followed by the addition of 1.0 mL of 1.0 M LiHMDS in THF (3.0 eq) and let stir at 0°C for 15 min. This is followed by the slow drop wise addition of the pre made aldehyde (1.0 eq) in 1.5 mL THF was added via canula under Ar gas over ~2min at 0°C. After 20 min the reaction was quenched using NH₄Cl (aq) and a workup was done using water/ethyl acetate. The crude mixture was purified using a silica gel column 30 x 1 cm with the following solvent ratios: 200 mL of
80:20, 100 mL 70:30 of hexanes: ethyl acetate. 79.5 mg of a white solid product is obtained in an 80.7% yield over the two steps. The isolated major (E)-isomer was characterized. m.p. range of 122-125°C; \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) 3.70 (d, 2H, \(J=7.2\) Hz), 3.78 (s, 3H), 4.27 (m, 1H), 4.35 (d, 1H, \(J=5.8\) Hz), 5.59 (s, 1H), 6.25 (dd, 1H, \(J=1.3, 15.9\) Hz), 7.22, dd, 1H, \(J=4.5, 15.9\) Hz), 7.39 (m, 3H), 7.51 (m, 2H); \(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) 143.7, 129.5, 128.7, 126.5, 122.6, 101.2, 80.8, 71.5, 65.8, 52.2; IR (KBr film) 3439, 2950, 2864, 1709, 1660, 1453, 1319, 1204, 1080, 1021 cm\(^{-1}\); LRMS (EI) m/z 107 (100%), 149 (30), 91 (17), 79 (14), 115 (12), 221 (3), 263 (2); HRMS (EI) m/z calcld 263.10721 ([M]+ -1H), found 263.09204; \([\alpha]_D \) -43.9 (c=0.10, MeOH).

**Compound 18:** methyl 5-(acetyloxy)-2-phenyl-1,3-dioxane-4-carboxylate

![Chemical structure](image)

To a round bottom flask was added 1.0 eq Pre 18 followed by 1 mL of pyridine and 1 mL of acetic anhydride. The solution was stirred at room temperature for 2h, where upon the volatiles were removed in vacuo and an aq/org work up was done using DCM/NaHCO\(_3\) (aq). The product was sufficiently pure for further use and the white crystalline solid product was obtained quantitatively. The product 18 was isolated and characterized. m.p. range of 88-92°C; \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) 2.12 (s, 3H), 3.69 (t, 1H, \(J=10.5\) Hz), 3.77 (s, 3H), 4.47 (m, 2H), 4.80 (dt, 1H, \(J=10.0, 5.2\) Hz), 6.21 (d, 1H, \(J=15.8\) Hz), 6.99 (dd, 1H, \(J= 15.1, 4.5\) Hz), 7.40 (m, 3H), 7.51 (m, 2H); \(^{13}\)C NMR (300 MHz, CDCl\(_3\)) \(\delta\) 169.9, 166.8, 142.4, 129.7, 128.7, 126.6, 123.0, 101.6, 68.5, 66.6, 52.2, 21.2; IR (KBr
film) 3071, 2941, 1724, 1651, 1456, 1384, 1221, 1046 cm$^{-1}$; LRMS (EI) m/z 149 (100%), 43 (100), 107 (58), 169 (10), 305 (3), 264(2), 306 (1); HRMS (EI) m/z calcd 306.1103, found 306.1102; [α]$_D$ -38.5 (c=0.10, MeOH).

**Compound 22**: (2R,3R,4E)-2-(acetyloxy)-3-bromo-6-methoxy-6-oxo-4-hexenyl benzenecarboxylate

![Compound 22](image)

To a round bottom flask was added 1.0 eq of compound 18, 1.0 eq NBS, 0.05 eq BPO, and 1.0 mL of PhCl. The mixture was placed on an oil bath at 70°C. After 1h a further 0.1 eq of NBS and 0.05 BPO were added in 100 µL of PhCl. After stirring at 70°C for a further 2h the reaction was quenched with NaHCO$_3$ (aq), followed by an aq/org workup with DCM / H$_2$O. The crude product was purified using silica gel 30 x 1 cm column with the following solvent system: 100 mL 90:10, 100 mL 80:20, and 50 mL 70:30 hexanes: ethyl acetate. There was a 61.0% yield of a clear and colourless oil product. The product 22 was isolated and characterized. $^1$H NMR (300MHz, CDCl$_3$) δ 2.16 (s, 3H), 3.77 (s, 3H), 4.44 (dd, 1H, J=11.0, 5.8 Hz), 4.64 (dd, 1H, J=12.0, 4.0 Hz), 4.82 (dd, 1H, J=10.1, 6.1 Hz), 5.45 (m, 1H), 6.10 (d, 1H, J=15.1 Hz), 7.02 (dd, 1H, J=9.6, 15.3 Hz), 7.48 (t, 2H, J=7.5 Hz), 7.61, (t, 1H, J=7.5 Hz), 8.02 (d, 2H, J=7.2 Hz); $^{13}$C NMR (300 MHz, CDCl$_3$) δ 170.1, 166.2, 165.9, 141.7, 133.8, 130.1, 128.9, 125.0, 72.4, 63.7, 52.4, 48.8, 21.1; IR (KBr film) 1724, 1643, 1271, 1222, 1110, 1069, 712 cm$^{-1}$; LRMS (EI) m/z 105 (100%), 43 (31), 77 (18), 305 (13), 220 (6), 384 (1), 386 (1); HRMS (EI) m/z calcd 384.0208, found 384.02163; [α]$_D$ +22.2 (c=0.10, MeOH).
3.3 Experimental Procedures (Project B)

General procedure for Suzuki Cross Coupling Reactions

\[
\begin{align*}
R\text{-}C=\text{X} & \quad + \quad R'\text{-}C=\text{B(OH)}_2 \\
 & \xrightarrow{1\% \text{Pd}_2(\text{dba})_3\text{CHCl}_3} \\
& \text{THPC, K}_3\text{PO}_4 \\
\end{align*}
\]

All reagents were used as purchased from Aldrich without further purification, and K\textsubscript{3}PO\textsubscript{4} was ground into a fine powder before use. To a dried reaction vessel was added 1.0 mL THPC and was degassed by pumping under reduced pressure (0.5 mm Hg) for 10 min and then filled with argon. The aryl halide (0.5 mmol, 1.0 eq) and Pd\textsubscript{2}(dba)\textsubscript{3}CHCl\textsubscript{3} (0.01eq) were added and the mixture was heated briefly using a heat gun. After cooling the reaction mixture to room temperature K\textsubscript{3}PO\textsubscript{4} (3.3 eq), aryl boronic acid (1.1 eq), distilled water (0.2 mL), and toluene (0.1 mL) were added. When triphenylphosphine (0.02 eq) was used it was added as a solution with the toluene. This solution was heated at the designated temperature for the specified amount of time.

The reaction products were isolated using two different methods:

**Method A**: Addition of 5.0 mL of water and 15 mL of hexanes followed by vigorous shaking and then let settle for 0.5h. The top hexane layer of the triphasic mixture was extracted, concentrated in vacuo, and Si gel column purified. The bottom aqueous layer was discarded leaving the center ionic liquid-catalyst behind. The ionic liquid is then recharged with the aryl halide, boronic acid, base, and solvents to allow for reuse of the catalyst.

**Method B**: After only one catalytic run the in order to isolate the biaryl product, the ionic liquid crude mixture passed through a Si gel plug, washed with hexanes and EtOAc.
followed by Si gel chromatography of the filtrate using a 90:10, DCM:hexane solvent ratio.

The Aryl Iodides:

Synthesis of biphenyl

\[
\begin{align*}
\text{PhI} & + \text{PhB(OH)}_2 \\
& \xrightarrow{1\% \text{Pd}_2(\text{dba})_3\text{CHCl}_3} \text{THPC, K}_3\text{PO}_4 \\
& \text{Ph-Ph}
\end{align*}
\]

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 100%.

This reaction was also done using the general procedure as mentioned above then isolating the product via method A. The second catalytic run is performed and then the product is isolated using workup method B. The isolated yields for the first run range from 82-97% and the second run range is slightly higher at 95-97%. ¹HNMR (CDCl₃): δ 7.42-7.37 (m, 1H), 7.47-7.52 (m, 2H), 7.65 (d, 2H, J=7.1 Hz); ¹³CNMR (CDCl₃): δ 127.6, 127.7, 129.2, 141.6; MS: m/z (% rel.) 155 (14.8), 154 (100), 153 (30.6), 152 (29.2), 151 (7.8), 77 (10.4), 76 (18.8), 51 (6.7); HREIMS: calc’d. for C₁₂H₁₀ 154.07825; found 154.07762.
Synthesis of 4-phenylacetophenone

\[
\text{Ac-} \begin{array}{c}
\text{I} \\
\text{B(OH)}_2
\end{array}
\xrightarrow{1\% \text{Pd}_2(\text{dba})_3\text{CHCl}_3, \text{THPC, } \text{K}_3\text{PO}_4}
\text{Ac-} \begin{array}{c}
\text{I} \\
\end{array}
\]

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 100%. \(^1\)HNMR (CDCl₃): δ 2.67 (s, 3H), 7.43-7.52 (m, 3H), 7.65 (d, 2H, J=7.3 Hz), 7.71 (d, 2H, J=8.3 Hz), 8.06 (d, 2H, J=8.3 Hz); \(^1^3\)CNMR (CDCl₃): δ 27.1, 127.6, 127.7, 128.6, 129.3, 129.4, 136.2, 140.3, 146.2, 198.2; MS: m/z (% rel.) 196 (53.1), 182 (17.0), 181 (100), 153 (21.1), 152 (44.0), 151 (17.1), 76 (24.2), 43 (14.0); \textbf{HREIMS}: calc'd. for C₁₄H₁₂O 196.08882; found 196.08879.
Synthesis of 4-acetyl-2'-methylbiphenyl

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 97%. $^1$HNMR (CDCl₃): δ 2.31 (s, 3H), 2.68 (s, 3H), 7.25-7.33 (m, 4H), 7.46 (d, 2H, J=8.2 Hz), 8.05 (d, 2H, J=8.2 Hz); $^{13}$CNMR (CDCl₃): δ 20.8, 27.1, 126.4, 128.3, 128.6, 129.88, 129.91, 131.0, 135.6, 136.0, 141.1, 147.4, 198.3; MS: m/z (% rel.) 210 (54.7), 196 (15.6), 195 (100), 165 (27.8), 152 (19.1), 97 (18.2), 82 (10.8), 43 (15.9); HREIMS: calc’d. for C₁₅H₁₄O 210.10447; found 210.10485.
Synthesis of 1-[4-(1-naphthyl)phenyl]-1-ethanone

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 97%. $^1$HNMR (CDCl$_3$): $\delta$ 2.71 (s, 3H), 7.44-7.65 (m, 6H), 7.86-7.96 (m, 3H), 8.12 (d, 2H, J=8.2 Hz); $^{13}$CNMR (CDCl$_3$): $\delta$ 27.1, 125.7, 125.9, 126.4, 126.8, 127.3, 128.77, 128.82, 130.7, 131.6, 134.2, 136.4, 139.4, 146.2, 198.3; MS: m/z (% rel.) 247 (22.2), 246 (100), 231 (81.4), 203 (27.5), 202 (81.5),
115 (26.3), 101 (57.1), 100 (22.8); HREIMS: calc’d. for C_{15}H_{14}O 246.10447; found 246.10417.

Synthesis of 4-acetyl-2'-methoxybiphenyl

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 100%. $^1$HNMR (CDCl$_3$): δ 2.66 (s, 3H), 3.85 (s, 3H), 7.02-7.10 (m, 2H), 7.35-7.42 (m, 2H), 7.66 (d, 2H, J=8.3 Hz), 8.03 (d, 2H, J=8.3 Hz); $^{13}$CNMR (CDCl$_3$): δ 27.1, 56.0, 111.7, 121.4, 128.5, 129.8, 129.9, 130.1, 131.1, 135.9, 144.0, 156.8, 198.3; MS: m/z (% rel.) 227 (11.8), 226 (65.3), 212 (15.3), 211 (100), 168 (35.7), 139 (16.3), 105 (18.7), 43 (28.3); HREIMS: calc’d. for C_{15}H_{14}O$_2$ 226.09938; found 226.09943.
Synthesis of 4-acetyl-4'-methoxybiphenyl

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 99%. ¹HNMR (CDCl₃): δ 2.65 (s, 3H), 3.89 (s, 3H), 7.02 (d, 2H, J=8.6 Hz), 7.60 (d, 2H, J=8.8 Hz), 7.67 (d, 2H, J=8.3 Hz), 8.03 (d, 2H, J=8.3 Hz); ¹³CNMR (CDCl₃): δ 27.1, 55.8, 114.8, 127.0, 128.8, 129.3, 132.6, 135.7, 145.8, 160.3, 198.2; MS: m/z (% rel.) 226 (85.8), 212 (17.0), 211 (100), 168 (22.1), 140 (25.1), 139 (31.8), 105 (23.8), 43 (19.2); HREIMS: calc’d. for C₁₅H₁₄O₂ 226.09938; found 226.09918.
Synthesis of 4,4'-dimethoxybiphenyl

\[
\text{MeO—} - I + \text{MeO—} - \text{B(OH)}_2 \xrightarrow{1\% \text{Pd}_2(dba)_3\text{CHCl}_3} \text{THPC, K}_3\text{PO}_4 \rightarrow \text{MeO—} - \text{MeO—} - \text{OMe}
\]

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 86%. \(^1\text{HNMR} (\text{CDCl}_3): \delta 3.87 \text{ (s, 6H), 6.98 \text{ (d, 4H, J=8.7 Hz), 7.50 \text{ (d, 4H, J=8.6 Hz)}, 13\text{CNMR} (\text{CDCl}_3): \delta 55.7, 114.5, 128.1, 133.9, 159.1; MS: m/z (% rel.) 215 (15.5), 214 (100), 200 (9.1), 199 (52.7), 171 (14.3), 139 (7.2), 128 (13.3), 107 (15.0); HREIMS: calc’d. for C\text{Me}_4\text{H}_8\text{O}_2 214.09938; found 214.09917.
Synthesis of 4-methoxy-2’-methylbiphenyl

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 92%. $^1$HNMR (CDCl$_3$): $\delta$ 2.31 (s, 3H), 3.78 (s, 3H), 6.90 (d, 2H, J=8.6 Hz), 7.16 (d, 2H, J=8.0 Hz), 7.38 (d, 2H, J=8.0 Hz), 7.44 (d, 2H, J=8.7 Hz); $^{13}$CNMR (CDCl$_3$): $\delta$ 21.5, 55.7, 114.6, 127.0, 128.3, 129.8, 134.1, 136.7, 138.3, 159.3; MS: m/z (% rel.) 199 (15.5), 198 (100), 183 (30.0), 169 (6.0), 155 (15.1), 153 (6.0), 152 (8.0), 99 (9.2); HREIMS: calc’d. for C$_{14}$H$_{14}$O 198.10447; found 198.10385.
Synthesis of 4-methoxy-4'-chlorobiphenyl

Using the general procedure at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield of the reaction was 90%. \( ^1\text{HNMR} (\text{CDCl}_3) \): \( \delta \) 3.87 (s, 3H), 7.00 (d, 2H, J=8.7 Hz), 7.40 (d, 2H, J=8.7 Hz), 7.48-7.52 (m, 4H); \( ^{13}\text{CNMR} (\text{CDCl}_3) \): \( \delta \) 55.8, 114.7, 128.3, 129.2, 132.9, 133.1, 139.7, 159.7; \textbf{MS}: m/z (% rel.) 220 (32.1), 219 (14.9), 218 (100), 203 (25.7), 175 (21.0), 139 (17.8), 109 (9.1), 76 (8.7); \textbf{HREIMS}: calc’d. for C\(_{13}\)H\(_{11}\)ClO 218.04984; found 218.05028.
The Aryl Bromides:

Synthesis of 4-phenylacetophenone

\[
\text{Ac} - \text{Br} + \text{B(OH)}_2 \xrightarrow{1\% \text{Pd}_2(\text{dba})_3\text{CHCl}_3, \text{THPC, } \text{K}_3\text{PO}_4} \text{Ac} - \text{Ac}
\]

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield was 99%. Spectra can be found above.
Synthesis of 4-acetyl-4′-methoxybiphenyl

\[
\begin{array}{c}
\text{Ac} \quad \text{Br} + \text{MeO} \quad \text{B(OH)}_2 \\
\xrightarrow{1\% \text{Pd}_2(\text{dba})_3\text{CHCl}_3} \\
\text{THPC, K}_3\text{PO}_4 \\
\end{array}
\]

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 50°C for 1h and using work up method B. The isolated yield was 98%. Spectra can be found above.

Synthesis of 4-phenylanisole

\[
\begin{array}{c}
\text{MeO} \quad \text{Br} + \text{B(OH)}_2 \\
\xrightarrow{1\% \text{Pd}_2(\text{dba})_3\text{CHCl}_3} \\
\text{THPC, K}_3\text{PO}_4 \\
\end{array}
\]

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 50°C for 3h and using work up method B. The isolated yield was 99%. \(^1\text{HNMR (CDCl}_3)\): \(\delta\) 3.88 (s, 3H), 7.00-7.03 (m, 2H), 7.28-7.36 (m, 1H), 7.42-7.47 (m, 2H), 7.54-7.60 (m, 4H); \(^1\text{CNMR (CDCl}_3)\): \(\delta\) 55.7, 114.6, 127.06, 127.14, 127.6, 128.6, 129.1, 134.2, 141.2, 159.5; \text{MS: m/z (\% rel.) 185 (15.6), 184 (100), 169 (25.9), 141 (25.1), 139 (8.6), 115 (21.1), 92 (7.7), 76 (8.9); HREIMS: calc’d. for C}_{13}\text{H}_{12}\text{O} 184.08882; found 184.08967.\)
Synthesis of 4,4'-dimethoxybiphenyl

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 50°C for 3h and using work up method B. The isolated yield was 95%. Spectra can be found above.
The Aryl Chlorides:

**Synthesis of 4-phenylacetophenone**

\[
\text{Ac-Cl} + \text{B(OH)}_2 \rightarrow \text{Ac-} + \text{Cl} \\
\text{THPC, } \text{K}_3\text{PO}_4
\]

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 70°C for 30h and using work up method B. The isolated yield was 84%. Spectra can be found above.

**Synthesis of 4-acetyl-4′-methoxybiphenyl**

\[
\text{Ac-Cl} + \text{MeO-} + \text{B(OH)}_2 \rightarrow \text{Ac-} + \text{OMe}
\]

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 70°C for 30h and using work up method B. The isolated yield was 84%. Spectra can be found above.

**Synthesis of 4,4′-dimethoxybiphenyl**

\[
\text{MeO-} + \text{MeO-} + \text{B(OH)}_2 \rightarrow \text{MeO-} + \text{OMe}
\]

Using the general procedure with the added PPh₃ ligand at a reaction temperature of 70°C for 30h and using work up method B. The isolated yield was 17%. Spectra can be found above.

Chapter IV
References


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