INVESTIGATION INTO SUZUKI BIARYL BOND FORMATION

A Thesis Presented by

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Abstract

This thesis describes a systematic investigation into the palladium catalysed cross-coupling reaction of arylboronic acids with arylhalides (Suzuki coupling reaction) in the order of the suggested catalytic cycle and contains six chapters. Chapters two, three and four introduce and present results from the research project.

Chapter one provides a brief summary of commonly used classic and modern biaryl coupling methodologies, a discussion of the factors controlling atropisomer selection and a brief outline of the project.

Chapter two describes an investigation into the effects the components, palladium complex, solvent and base have in the suggested catalytic cyclic with a discussion of results. It was found that the use of TIOH as base in Dimethylacetamide (DMA) enabled these reactions to be carried out at room temperature. Limitations to the degree of ortho substituents were encountered.

Chapter three describes an investigation of the effects the electrophilic partner can have in the oxidative addition step, in the suggested catalytic cycle, with a discussion of results. Chapter four describes an investigation of the effects the nucleophilic partner can have in the transmetallation step, in the suggested catalytic cycle, with a discussion of results. All attempts to either accelerate the rate of the reaction or control the stereoselection of the process through affecting either the oxidative addition or transmetallation steps failed.

Chapter five briefly reviews cis-trans isomerisation in palladium complexes. Atropisomerisation in biaryl compound is also briefly reviewed.

Chapter six details the experimental procedures for the preparation of compounds coupling reaction conditions and gives spectroscopic data for the compounds that were prepared.
Acknowledgements

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<tr>
<td>(aq)</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>AsPh₃</td>
<td>triphenylarsine</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>Bu₃P</td>
<td>tri-n-butylphosphine</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>c.</td>
<td>concentration</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalytic amount</td>
</tr>
<tr>
<td>Comp</td>
<td>Complex</td>
</tr>
<tr>
<td>d.e.</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo(5.4.0)undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-Dimethylacetamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DME</td>
<td>Ethylene glycol dimethyl ether</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
<tr>
<td>dppe</td>
<td>Diphenylphosphinoethane</td>
</tr>
<tr>
<td>dppf</td>
<td>Bis-(diphenylphosphino)ferocene</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Ether</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HMPA</td>
<td>Hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>i</td>
<td><em>iso-</em></td>
</tr>
<tr>
<td>iPr</td>
<td><em>iso</em>-Propyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infra red</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Mes</td>
<td>2,4,6-Trimethylphenyl</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>Ms</td>
<td>Methanesulfonyl</td>
</tr>
<tr>
<td>nBu</td>
<td>n-Butyl</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidine</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>OTf</td>
<td>Trifluorosulphonyl</td>
</tr>
<tr>
<td>P(PhO)₃</td>
<td>triphenylphosphite,</td>
</tr>
<tr>
<td>P(MeO)₃</td>
<td>trimethylphosphite,</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PPh₃</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyldimethylsily</td>
</tr>
<tr>
<td>tBu</td>
<td>Tert-Butyl</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TFP</td>
<td>tri-2-furylphosphine</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>tht</td>
<td>Tetrahydrothiophene</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>Tolyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-Toluenesulfonyl</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-Toluenesulfonic acid.</td>
</tr>
<tr>
<td>TTFA</td>
<td>Thallium(III)trifluoroacetic acid</td>
</tr>
</tbody>
</table>
1

Introduction
1 Introduction

Highly functionalized, unsymmetrical biaryls are widespread in nature\(^1\) and are an important constituent of many pharmacologically active natural products.\(^2\) The preparation and utilisation of specific biaryl systems, particularly those which exhibit hindered rotation, is a demanding goal not only in the synthesis of natural products and pharmaceuticals, but also, for example, in the discovery of new reagents for asymmetric synthesis. Introducing a bond between two aromatic rings, either intra- or intermolecularly, is a problem familiar to many organic chemists. The most important step for biaryl coupling reactions is almost always the coupling of two aromatic partners of the molecule. For the homo coupling reactions there is a wide variety of procedures of which dimerizations of aryl halides is the oldest known method to form symmetric biaryls.

1.1 Classic methods

1.1.1 Ullmann reaction

The coupling of aryl halides with copper is called the Ullmann reaction (Eq. 1.1), and is one of the oldest methods for biaryl formation. The Ullmann reaction, using copper bronze as a reducing reagent, gives the highest yields with electron-poor aryl iodides. Nitro and methoxycarbonyl groups are strongly activating, especially if in the ortho position.\(^3\) R and OR groups activate in all positions. Whereas the functional groups, OH, NH\(2\), and NHCOR inhibit, and COOH,
SO\textsubscript{2}NH\textsubscript{2}, and similar reactive groups shut down the coupling reactions. The reaction mechanism is not known exactly. However, this classical method, even today, is still the chemists choice for simple, nonsterically hindered, symmetric biaryls.

\begin{equation}
\text{MeO} \begin{array}{c}
\text{Br} \\
\text{COOMe}
\end{array} \xrightarrow{\text{Cu}} \begin{array}{c}
\text{MeO} \\
\text{COOMe}
\end{array}
\end{equation}

\textbf{Equation 1.1}

The synthesis of unsymmetrically substituted arenes have been examined using the Ullmann reaction. It is common practise to react an activated aryl halide with another which is relatively inert. Thus the slow addition of excess 2-chloropyridine (3) to a suspension of copper powder in dimethylformamide containing 3-iodopyridine (4) affords 2,3’-bipyridyl (5) in 42% yield.\textsuperscript{4} (Eq. 1.2)

\begin{equation}
\begin{array}{c}
\text{Cl} \\
\text{N}
\end{array} + \begin{array}{c}
\text{I} \\
\text{N}
\end{array} \xrightarrow{\text{Cu}} \begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\end{equation}

\textbf{Equation 1.2}
Although these kind of reactions generally require high reaction temperatures, milder methods are known. Semmelhack's work has show that by using stoichiometric amounts of homogeneous Ni(0) complexes high yields of biaryls are obtained at reaction temperatures of 40-50 °C. More modern methods, which until now have been applied merely to simple substrates, use only catalytic amounts of nickel reagents. The reactive low-valent nickel species can be regenerated either electrochemically or by co-reductants such as zinc or sodium hydride. These methods make it possible to use harder halides (aryl chlorides react most rapidly) and more convenient solvents such as THF.

1.1.2 Oxidative methods

The commonly used oxidising agents are vanadium compounds such as vanadium (IV) chloride, vanadium (V) oxychloride, and vanadium (V) oxyfluoride. These are powerful reagents for intra and intermolecular biaryl coupling, especially for hydroxy or alkoxy substituted aryls. One successful coupling with vanadium (V) oxyfluoride is shown below (Eq. 1.3).
Chapter One

Introduction

Equation 1.3

No mechanism has yet been formulated for coupling reactions employing the vanadium reagent. Reactions proceed at room temperature and give reasonable yields of coupled products. An increase of the yield of methyl-6,7-dimethoxyphenanthrene-9-carboxylate (7) from 44% to 81% observed by switching from trifluoroacetic acid to boron trifluoride diethyl etherate as the lewis acid component.\textsuperscript{9}

Thallium (III) trifluoroacetate (TTFA) is another oxidative coupling reagent. This in particular makes possible dehydrdimerization of electron rich aromatic compounds. (Eq. 1.4)

\[
\begin{align*}
\text{TTFA/TFA} &\quad 46\% \\
\end{align*}
\]

\(8\) \(9\)

Equation 1.4

It is believed the mechanism of the coupling, is via radical cation intermediates (10)\textsuperscript{10} (Eq.1.5).
The main problem of this method for the construction of biaryl axes are the side reactions. Sometimes reactions give arylthallium di(trifluoroacetates) exclusively. For example, in the mesityl case, bimesitylene (13) formed in 10 % yield while mesitylthallium di(trifluoroacetates) was formed in 44 % yield (Eq. 1.6).
1.1.3 Radical methods

1.1.3.1 Gomberg-Bachmann reaction

Normally, if an acidic solution of a diazonium salt is made basic, the aryl part of the diazonium salt can couple with another aromatic ring in solution. This reaction is known as the Gomberg Bachmann reaction.\(^\text{11}\) The yields of the reaction, because of side reactions of diazonium salts, are not high, usually under 40%. The mechanism of the Gomberg-Bachmann reactions involves free radicals.
(Scheme 1.1). The diazonium salt (17) is in equilibrium with the diazohydroxide (18) in basic solution. Aryl diazohydroxide then reacts with another diazonium salt to give the bis-(diazenyl) ether (19) (Scheme 1.1).

\[
\text{(17)} \quad \text{ArNNO}^+ \quad \text{H}_2\text{O} \quad \text{(18)} \quad \text{N} = \text{N} + \text{OH}
\]

\[
\text{(17)} \quad \text{ArNNO}^+ \quad \text{(18)} \quad \text{N} = \text{N} + \text{OH}
\]

\[
\text{Ar}^+ + \text{O} - \text{N} = \text{N} - \text{Ar} \quad \text{ArNNO}^+ \quad \text{OH}
\]

\[
\text{Ar}^+ + \text{O} - \text{N} = \text{N} - \text{Ar} \quad \text{ArNNO}^+ \quad \text{OH}
\]

**Scheme 1.1** Mechanistic representation for Gomberg Bachmann reaction.

The resulting radical (Ar•) can react with another aryl ring in solution. Proton abstraction by diazohydroxide radical or •OH gives the biaryl (Eq.1.8).

\[
\text{Ar}^+ + \text{Ar} \quad \text{Ar} \quad \text{Ar} \quad \text{Ar}
\]

\[
\text{Ar}^+ + \text{Ar} \quad \text{Ar} \quad \text{Ar}
\]

**Equation 1.8**
As this aromatic substitution involves radicals, when using this method to prepare unsymmetrical biaryls, it is best to start with any substituents on the diazonium ring and to keep the ring to be added as simple as possible. For example, using phenyldiazonium salt and toluene yielded (20) 66% of ortho-, 19% of meta-, and 14% of para-substituted biaryls. The Gomberg Bachmann coupling reactions mentioned above are low yielding and normally do not give good regioselectivity.

Since the discovery that reactions of aryl Grignard compounds with organic halides (the Kharasch reaction) can be accelerated by nickel or palladium derivatives, other catalytic transition metal have been employed for this C-C bond formation. In order to tolerate reactive functional groups, such as aldehyde, less aggressive organo-zinc, aluminium, tin, boron, etc. analogues of Grignard reagents with catalytic quantities of transition metals have become popular, for cross-coupling reactions. Organo zinc derivatives can be readily obtained by transmetallation of the corresponding lithium or magnesium compounds. Larson and Raphael published a regioselective synthesis of steganone (23) using aryl zinc compounds in a good yield (Eq. 1.9).
For this biaryl formation there are no steric problems as there are two ortho substituents on the same ring. When there are ortho substituents on different rings, yields fall dramatically to the extent that no coupling products are obtained with three ortho substituents. Arylzinc reagents in organic syntheses have been extensively investigated especially with regard to C-C formation.\(^{14}\)

Sensitive functional groups, like aldehydes, gave by-products with reactive organometallics. These disadvantages can be avoided by using less electropositive metals (Modern methods) such as silicon, tin (Stille) or boron (Suzuki) with a transition metal catalyst.

**1.2 Modern biaryl coupling methodologies**

**1.2.1 Meyers biaryl coupling methodology**
The oxazoline moiety readily promotes displacement of ortho-alkoxy and -fluoro groups on aromatic substrates by strong nucleophiles (Eq. 1.10). This characteristic of oxazolines has allowed Meyers to use them in the synthesis of certain hindered biaryls.\textsuperscript{15-16}

\[
\begin{align*}
\text{Nu}^- & \quad \text{X} = \text{F or OR} \\
\text{X} & \quad \text{Nu}
\end{align*}
\]

Equation 1.10

In 1975 Meyers published nucleophilic displacement of o-methoxy groups by several organometallics\textsuperscript{15} and suggested that the reaction was most probably occurring by an addition-elimination sequence (Scheme 1.2) and not by a free-radical mechanism.

\[
\begin{align*}
\text{M} & \quad \text{Me} \\
\text{Me} & \quad \text{R}
\end{align*}
\]

Scheme 1.2 Mechanistic representation for Meyers reaction.
Depending on the nucleophile this reaction can work at sub ambient temperatures. It is easy and usual to use Grignard reagents as the organometallic nucleophile. The Grignard reagents can be introduced at room temperature or if necessary, with heating without any addition to the oxazoline moiety (Eq. 1.11).

Equation 1.11

This method led to the stereo selective syntheses of chiral biaryls by the use of a chiral oxazoline. This work showed that substituents on the 6' position (31) have a dramatic effect on diastereoselectivity (Scheme 1.3).
Scheme 1.3 Mechanistic representation for stereoselective Meyers reaction.

The magnesium ion is chelated with the methoxymethyl group of the oxazoline effectively blocking the lower face from nucleophilic attack. The Grignard attacks predominantly from the β-face giving the azaenolate intermediate (33). The selectivity is reserved with a strongly chelating alkoxide group in the 6'-position (R=CH₂OCH₃) which competes effectively with the 2'-MeO producing the R-product (34) in 90% de but with a decreased yield.¹⁷

1.2.2 Palladium catalysed biaryl couplings (Stille, Suzuki)

1.2.2.1 Palladium complexes as a catalyst

There are several reasons to choose palladium in organic syntheses. Most importantly, palladium offers more possibilities of catalytic carbon-carbon bond formation than any other transition metal. The tolerance of palladium reagents to
many functional groups such as carbonyl and hydroxyl is the second important feature, allowing Pd-catalysed reactions to be carried out without protection of these functional groups. Certain palladium reagents and catalysts are not very sensitive to oxygen and moisture, or even acid and base. The fact that a number of industrial processes, based on Pd-catalysed reactions, have been developed, and are now operated, reflects the advantages of using Pd catalysis commercially.18

We normally use palladium in organic syntheses as Pd(0) or Pd(II) compounds. There are two Pd(0) complexes commercially available. Pd(PPh₃)₄ is light-sensitive, unstable in air and when pure appears as yellowish crystals. The complex is prepared from PdCl₂ with various reducing agents, such as hydrazine,¹⁹ in the presence of PPh₃. Sometimes Pd(PPh₃)₄ is not so reactive a catalyst because it is coordinately saturated and will not allow the coordination of reactants. Pd₂(dba)₃-CHCl₃ (dba=dibenzylideneacetone) is the second commercially available Pd(0) complex which is prepared from recrystalization of Pd(dba)₂ from CHCl₃. Crystallisation from benzene or toluene gives the corresponding Pd₂(dba)₃-benzene or Pd₂(dba)₃-toluene complexes.¹⁹ All of these Pd(dba)ₙ complexes shows similar properties in catalytic reactions. They are particularly useful as the dba ligand is easily displaced by 2 equivalents of a monodentate ligand. This leads to a range of coordinately unsaturated Pd(0) complexes that can be formed in situ.

Pd(II) compounds are commercially available and used either as stoichiometric reagents or as catalysts. They are stable compounds and can be reduced to Pd(0) easily. For instance Pd(OAc)₂ can be reduced to Pd(0) complexes in situ in the
presence of phosphine ligands, with several reducing agents such as metal hydrides or Et$_3$N.

Over the past two decades the number of palladium catalysed cross-couplings of organometallics (Mg, Li, Cu, Zn, Zr, Al, Sn and B) with organic electrophiles has increased dramatically. In cross-coupling reactions many sensitive functionalities, such as carbonyl compounds cannot tolerate organometallic coupling partners derived from Li, Mg, or Cu. Also, the most important point, is that some of these organometallics are air, moisture or light sensitive. They are sometimes very difficult to prepare, purify and store, and some of these reagents are highly toxic.

1.2.2.2 Stille biaryl coupling methodology

Stille biaryl coupling methodology$^{20}$ can be described as the palladium catalysed cross-coupling of aryltin reagents with aryl electrophiles (Eq. 1.12).

\[
\begin{align*}
\text{Ar-SnR}_3 + \text{Ar'}^\cdot X & \xrightarrow{\text{PdL}_n} \text{Ar-Ar'} + \text{XSnR'}_3 \\
X &= \text{I}, \text{Br} \text{ or } \text{OTf} \text{ and 1.5 equivalent LiCl} \\
R &= \text{Methyl or Butyl}
\end{align*}
\]

Equation 1.12

Aryltin compounds can be prepared by a number of routes such as the reaction of sodium trimethylstannane with an aryl bromide or hexa alkyl distannanes with
arylhalides. In general they are not air or moisture sensitive. Stille chemistry is compatible with many functional groups, thereby eliminating the protection / deprotection strategies which are a necessity with most other organometallic reactions. In the palladium catalysed coupling of aryl electrophiles with aryltin reagents, essentially only the aryl group on tin enters into the reaction (Scheme 1.4). An unsymmetrical organotin reagent containing three simple alkyl groups (such as methyl or butyl) will preferentially transfer its aryl group.

Scheme 1.4 Catalytic cycle for Stille coupling reaction

A more widely used palladium catalysed biaryl coupling is the Suzuki reaction, which has some advantages over the Stille biaryl coupling methodology. Arylboronic acids or esters are less toxic than aryltin compounds. Easy and cheap preparations of arylboronic acids are known and the reaction conditions allow the use of aqueous base and/ or water.

1.2.2.3 Suzuki biaryl coupling methodology
Suzuki biaryl coupling methodology can be described as the palladium catalysed coupling reaction of arylboronic acids, or esters, with aryl electrophiles, such as arylhalides or triflates, in the presence of base.$^{22}$

The mechanistic pathway of Suzuki's coupling is suggested as a catalytic cycle involving a palladium complex (Scheme 1.5), similar to the Stille coupling and containing 3 main steps.

1- Oxidative addition

2-Transmetallation.

3-Reductive elimination.

Scheme 1.5 Catalytic cycle for Suzuki coupling reaction
Chapter One

Introduction

The suggested catalytic cycle (Scheme 1.6) of Suzuki biaryl coupling starts with the oxidative addition of aryl halide to the coordinatively unsaturated zerovalent palladium species. The oxidative addition product, organopalladium (II) intermediate (35), can be isolated as a trans substituted complex.21,23 Although oxidative addition of aryl iodide is the most facile in comparison to arylbromides or triflates, in some cases arylbromides give better yields of the coupled product (Table 2.6 Entry 6 and 7). Normally aryl bromides are the preferred aryl halide in Suzuki biaryl coupling reaction. Arylboronic acids are not reactive enough to give diaryl palladium species (37) by means of transmetallation.

Therefore base is necessary to form the reactive boronic acid (36). In the literature there are very few examples of Suzuki coupling in which no base is employed.24 This base is also implicated in forming organopalladium hydroxide which is more reactive than organopalladium halide.25 Transmetallation gives trans- substituted diaryl palladium complex (37). This complex must isomerise to the related cis- complex (38) and then reductively eliminate to give the desired biaryl and regenerate the reactive PdL₂ species (Scheme 1.6).26 Some supportive observations for this plausible mechanism concerning the detection of catalytic intermediates with electrospray ionisations mass spectrometry (ESI-MS) has been reported.27
Although transmetallation is accepted as the rate determining step for many catalytic biaryl couplings,\textsuperscript{28} some recent work by Smith\textsuperscript{29} showed that the rate determining step in the Suzuki coupling reaction can change to oxidative addition depending on the halide used.

At the outset of this project we undertook a systematic study of the catalytic cycle of the Suzuki reaction in an attempt to develop an atropisomer selective process.

\textbf{Scheme 1.6} Mechanistic representation for Suzuki coupling reaction.
The restricted rotation around the biaryl axis caused by bulky substituents leads to the existence of atropisomers (see chapter 5). Depending upon the degree of steric hindrance from the \textit{ortho} substituents, four or three\textsuperscript{32b} substituents are needed to produce a sufficient barrier to rotation at room temperature. This particular form of axial chirality is not generally resistant to heat.\textsuperscript{32c} Acceptable yields of hindered biaryls under Suzuki or Stille conditions require high temperatures (60-110 °C) with multihour reaction times.\textsuperscript{32d} In atropisomer selective reactions these conditions would be deleterious to the discrimination between diastereomeric transition states and could racemise the biaryls formed. As a consequence we initially set out to look at ways of carrying out the Suzuki and Stille reactions at ambient temperature. This process then coupled with chiral ligands could produce an atropisomer selective process.
2

Base, solvent and Pd-complex effects
2 Base, solvent and Pd-complex effects on the Suzuki biaryl coupling reaction

2.1 Base effect in Suzuki biaryl coupling reaction

Base is the most investigated component in Suzuki biaryl coupling. Suzuki demonstrated\textsuperscript{30} that the yield of biaryl coupling reactions could be affected by changing the base and/or solvent (Tabk 2.1)\textsuperscript{30} For example, the reaction between mesityl boronic acid (39) and iodobenzene (40) at 80 °C, gave coupled product (41) in 25 % yield with sodium carbonate and aqueous benzene, but 99 % yield with Ba(OH)\textsubscript{2} in aqueous DME (Table 2.1 Entry 1 and 7).

![Equation 2.1](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Solvent/H\textsubscript{2}O</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na\textsubscript{2}CO\textsubscript{3}</td>
<td>benzene</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>NaOH</td>
<td>benzene</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>Ba(OH)\textsubscript{2}</td>
<td>benzene</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Na\textsubscript{2}CO\textsubscript{3}</td>
<td>DME</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>K\textsubscript{3}PO\textsubscript{4}</td>
<td>DME</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>NaOH</td>
<td>DME</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>Ba(OH)\textsubscript{2}</td>
<td>DME</td>
<td>99</td>
</tr>
</tbody>
</table>

| Table 2.1 Selected results in Suzuki coupling. |

19
The change of solvent from benzene to DME doubled the yield for this coupling reaction. These interesting results proved that the reaction was dependent on the base and solvent. (Table 2.1 Entry 1 and 4)

Under Suzuki's conditions it is possible to make certain tri-ortho substituted biaryls. Reactions require 80-100 °C for 4-8 h for an efficient coupling. Recently Uemura et al. published some atropisomer selective Suzuki-type coupling reactions at these temperatures, using planar chiral tricarbonyl(arene)chromium complexes (42). The reaction requires the preparation of optically pure isomers of arene-chromium complexes (42a and b) (Scheme 2.1) by resolution and finally the chromium has to be removed from coupled product.

Scheme 2.1 Selected results in Suzuki coupling.

In our plan to achieve atropisomer selective biaryl coupling we were concerned that these sort of temperatures could racemise any atropisomer selection given in
the coupling reaction by the use of chiral ligands on Pd(O). Mild conditions, however would not destroy a stereo selective Suzuki biaryl coupling. To this end we have tried to reduce the activation energy of the reaction in order that the reaction could be carried out at ambient temperature or below.

First we looked at the effect of the base on Kishi's work had shown that using TIOH as a base, Suzuki coupling reactions between vinylic boronic acids (43) and vinylic iodides (44) were dramatically accelerated to such an extent that the reaction could be run at room temperature (Table 2.2). It was thought, perhaps, Tl(I) could form insoluble salts with the halide, and give a more reactive palladium species (Ar-Pd(PPh3)2) for the transmetallation step.

\[
\begin{align*}
\text{B(OH)}_2 + \text{Pd(PPh}_3\text{)}_4 & \rightarrow \text{(45)} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Pd(PPh$_3$)$_4$ mol%</th>
<th>Temp. °C</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOH</td>
<td>25</td>
<td>50</td>
<td>30 min</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>KOH</td>
<td>25</td>
<td>RT</td>
<td>30 min</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>TIOH</td>
<td>25</td>
<td>RT</td>
<td>&lt;&lt; 30 s</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>TIOH</td>
<td>3</td>
<td>RT</td>
<td>30 min</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Ag$_2$O</td>
<td>25</td>
<td>RT</td>
<td>5 min</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 2.2 Kishi's results for vinylic boronic acid and vinylic halide.
We investigated a fairly hindered Suzuki coupling reaction between mesitylboration (39) and iodobenzene (40) using various bases at ambient temperature (Equation 2.3). We found Suzuki's conditions very low yielding, but 10 % TIOH(aq) was a very effective base in comparison.

Table 2.3 demonstrates some selected results of Suzuki biaryl coupling reactions, with various bases, in DMF at ambient temperature.

\[ B(OH)_2 \quad K_3PO_4 \quad I \quad Ba(OH)_2 \quad Cs_2CO_3 \quad Pd(PPh_3)_4 / DMF \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base(aq)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cs_2CO_3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>K_3PO_4</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>Ba(OH)_2</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>NaOH</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>TIOH*</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>Tl_2CO_3</td>
<td>11</td>
</tr>
</tbody>
</table>

*10% TIOH(aq)

Table 2.3 Ambient temperature Suzuki biaryl coupling reaction in DMF.

As seen from the Table 2.3 entry 5, TIOH gives a remarkable increase in yield, and, we believe, in the rate of reaction.
The effectiveness of the concentrations of TlOH(aq) was investigated next.

\[
\text{B(OH)}_2 + \text{I} \rightarrow 1.5 \text{ mol \% Base} \rightarrow \text{Pd(PPh}_3)_4 / \text{DMF} \rightarrow \text{Yield} \%
\]

\[
\begin{array}{|c|c|c|}
\hline
\text{Entry} & \%\text{TlOH(aq)} & \text{Yield} \% \\
\hline
1 & 10 & 54 \\
2 & 2 & 39 \\
3 & 5 & 30 \\
4 & 20 & 27 \\
5 & \text{TlOH(s)}^a & >5 \\
6 & \text{Tl}_2\text{CO}_3(s)^a & >2 \\
\hline
\end{array}
\]

\(\text{a-Using non-aqueous solid base}\)

**Table 2.4**  Concentration effect of TlOH(aq) in Suzuki biaryl coupling

From Table 2.4, while 10 % TlOH(aq) yielded 54 % product (Entry 1), higher or lower concentrations did not give any increase in yields. TlOH(s) gave very poor yields.
2.2 Solvent Effects in the Suzuki Biaryl Coupling Reaction

Suzuki had shown that these type of reactions were solvent dependent so we next investigated the solvent affect in our TIOH promoted reactions. We first coupled mesityl boronic acid and iodobenzene (Equation 2.5) in the presence of Pd(PPh₃)₄ with 10% aq. TIOH in various solvents at room temperature. From the solvents screened only dimethyl acetamide (DMA) gave good yields of coupled products (Table 2.5, Entry 1). At present we can offer no reasoning why DMA should give better yields in this reaction compared to DMF. Mesityl boronic acid (39) gave slightly superior yields (8 to 20 %) to those of the corresponding di-n-butylboronate ester (46) and mesityl-trimethylene boronate ester (47) (Fig. 2.1).

![Figure 2.1](image)

Our new conditions enabled the coupling to be performed at room temperature (Table 2.5, Entry 1) and compared very favourably in terms of yield with the best from Suzuki's protocol, where reactions are performed at elevated temperature. With Suzuki's methods, the highest yield of (41), at room temperature, that we could prepare was never more than 36%.
Chapter Two

**Base, Solvent, Pd-complex effects**

\[
\text{B(OH)}_2 \quad \text{I} \quad \text{Pd(PPh}_3\text{)}_4 \\
10\% \text{aq. TIOH} \\
\text{Solvent} \quad 20 \degree \text{C} \\
12 \text{h.}
\]

\[
\text{Equation 2.5}
\]

\[
\text{(39) } \quad \text{B(OH)}_2 \quad \text{I} \quad \text{(40)} \quad \text{Pd(PPh}_3\text{)}_4 \\
10\% \text{aq. TIOH} \\
\text{Solvent} \quad 20 \degree \text{C} \\
12 \text{h.}
\]

\[
\text{(41) }
\]

\[
\text{(Equation 2.5)}
\]

\[
\text{Table 2.5 Effect of solvent on Suzuki coupling reaction with TIOH base}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield(^\text{a})%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMA</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>DMPU</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>NMP</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>Benzene</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>DME</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^\text{a}\) Isolated yields of pure products based on iodobenzene

The addition of equivalent amounts of KBr, LiBr or NH\(_4\)Br reduced the yield of the reaction between mesityl boronic acid and iodobenzene, in DMA, with 10%
TlOH(aq), to 60%. It could be because of the formation of insoluble thallium salts between TlOH and MX. This important piece of evidence indicated that Tl\(^{+}\) probably helps the reaction, as well as \(\cdot\)OH.

After optimisations of base and solvent we could couple mesityl boronic acid and iodobenzene in 92 % isolated yield.

We next probed the electronic and steric limits of this reaction by performing the coupling reaction with some ortho- and para- substituted aryl halides.

Selected results from this study\(^{35}\) are described in Table 2.6

The yields for the formation of tri-ortho substituted biaryls were moderate to good. An o-nitro substituent did not affect yields, whereas o-methoxy and o-methylcarboxylate gave only moderate yields and peculiarly an o-methyl substituent had a very deleterious affect on yield. This suggests a subtle balance of sterics at this position.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>% Yield</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>x=Br, p=NO₂</td>
<td>77</td>
<td>(41a)</td>
</tr>
<tr>
<td>2</td>
<td>x= Br, p=CO₂Me</td>
<td>90</td>
<td>(41b)</td>
</tr>
<tr>
<td>3</td>
<td>x= I , p=OMe</td>
<td>71</td>
<td>(41c)</td>
</tr>
<tr>
<td>4</td>
<td>x= I , p=Cl</td>
<td>61</td>
<td>(41d)</td>
</tr>
<tr>
<td>5</td>
<td>x= I , p=CO₂Me</td>
<td>73</td>
<td>(41b)</td>
</tr>
<tr>
<td>6</td>
<td>X= Br, o=NO₂</td>
<td>83</td>
<td>(41f)</td>
</tr>
<tr>
<td>7</td>
<td>X=I, o=NO₂</td>
<td>78</td>
<td>(41f)</td>
</tr>
<tr>
<td>8</td>
<td>X=I, o=OMe</td>
<td>49</td>
<td>(41g)</td>
</tr>
<tr>
<td>9</td>
<td>X=I, o=CO₂Me</td>
<td>35</td>
<td>(41h)</td>
</tr>
<tr>
<td>10</td>
<td>X=Br, o=Me</td>
<td>10</td>
<td>(41i)</td>
</tr>
</tbody>
</table>

Table 2.6  Synthesis of substituted biaryls from mesitylboronic acid.
The coupling reaction was little affected by either electron withdrawing or donating substituents (Table 2.6, Entries 1-5). The yield of coupled product (41h) between methyl-4 iodobenzoate and mesityl boronic acid (Table 2.6, Entry 5, 73%) was comparable to known mild procedures involving heat (81%)\(^3\), indicating that under these ambient conditions there was little hydrolysis of the base sensitive ester functionality.

We also tried Suzuki couplings between 1-napthylboronic acid (48), di-n butyl-1-naphtylboronic acid ester (49), naphthalenboronic acid-tri-methylene glycol-ester (50), 2-methyl-naphthalenboronic acid (51) (Fig2.2), and 2-methyl-di-n-butyl-naphthalenboronic acid ester (52) with some aryl halides (Equation 2.7). Similarly to the mesitylboronic acid (39) and its esters (47) and (47), 1-naphtylboronic acid (48) and 2-methyl-naphthalenboronic acid (51) yielded better than their esters (49, 50, 52) (Table 2.7).mentioned above.

Table 2.7 demonstrates some results of this study.

![Figure 2.2](image-url)
Arylboronic acid  +  Aryl halide \[ \xrightarrow{2 \text{ mmol Pd(PPh}_3)_4 / \text{DMA}} \text{Base / Time / Temperature} \]

Equation 2.7

<table>
<thead>
<tr>
<th>Boronic acid</th>
<th>Arylhalide</th>
<th>Condition</th>
<th>Yield%</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(48) Mes-Br</td>
<td>10%TlOH 12h / RT</td>
<td>65 (25)\textsuperscript{a}</td>
<td>(53)</td>
<td></td>
</tr>
<tr>
<td>(49) Mes-I</td>
<td>10%TlOH 12h / RT</td>
<td>34\textsuperscript{b}</td>
<td>(53)</td>
<td></td>
</tr>
<tr>
<td>(50) Mes-I</td>
<td>10%TlOH 12h / RT</td>
<td>22</td>
<td>(53)</td>
<td></td>
</tr>
<tr>
<td>(48) Ph-I</td>
<td>2(eq) Et\textsubscript{3}N 12 h / RT</td>
<td>0</td>
<td>(53)</td>
<td></td>
</tr>
<tr>
<td>(48) Mes-Br</td>
<td>10%TlOH 12h / RT</td>
<td>0</td>
<td>(53)</td>
<td></td>
</tr>
<tr>
<td>(48) Mes-I</td>
<td>Ba(OH)\textsubscript{2} / 8h / 80°C</td>
<td>0</td>
<td>(53)</td>
<td></td>
</tr>
<tr>
<td>(51) Ph-I</td>
<td>Ba(OH)\textsubscript{2} / 6h / 80°C</td>
<td>44</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>(52) Ph-I</td>
<td>10%TlOH 12h / RT</td>
<td>37</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>(51) I-OMe</td>
<td>Ba(OH)\textsubscript{2} 12 h / 80°C</td>
<td>28</td>
<td>(55)</td>
<td></td>
</tr>
<tr>
<td>(51) CN-I</td>
<td>Ba(OH)\textsubscript{2} 12 h / 80°C</td>
<td>87</td>
<td>(56)</td>
<td></td>
</tr>
<tr>
<td>(51) Br</td>
<td>Ba(OH)\textsubscript{2} 12h / 80°C</td>
<td>0</td>
<td>(53)</td>
<td></td>
</tr>
</tbody>
</table>

Mes=2,4,6-trimethylphenyl-, Ph= Phenyl\textsuperscript{a} excess of PPh\textsubscript{3} (2 mmol) was used
\textsuperscript{b}reaction proceeded in Et\textsubscript{3}N as a solvent.

Table 2.7 Miscellaneous Suzuki couplings of napthylboronic acid derivatives.
As seen from the results in table 2.7, while tri-o-substituted biaryls were obtained in reasonable yields, changes to the reaction conditions reduced yields or stopped the reaction. Tetra ortho-substituted variants could not be detected.

2.3 The effects of Pd-sources and ligands in Suzuki biaryl coupling reaction

Tetrakis-triphenylphosphine palladium is a commonly used catalyst in Suzuki and Stille biaryl syntheses. It is one of a range of commercially available zerovalent complexes. However the investigation of ligand effect has shown that different catalysts may give better reactions for different coupling partners. For instance tri-2-furylphosphine (TFP) has been shown to be highly advantageous in the coupling between iodobenzene and vinyltributyltin and triphenylarsine was found to be the best ligand for use with Pd(0) in the coupling of aryl triflates with tetramethyltin, and between arylstannanes with vinyl triflates.28

These interesting studies prompted us to examine different ligands such as triphenylphosphine, trimethylphosphite, triphenylphosphite, triphenylarsine, tri-n-butylphosphine, tri-2-furylphosphine, bis-diphenylphosphinoferrocene (dppf), diphenylphosphinoethane (dppe), in the Suzuki biaryl coupling reaction between arylboronic acids and aryl halides, in DMA with TIOH as a base (Table 2.8).

Pd(dba)2 & Pd2(dba)3. solvent are convenient sources of Pd(0)-complexes that can be used with most other ligands as dba is easily displaced. There are also examples where they have been used effectively, without addition of any ligand, in cross-coupling reactions.37
In our experiments for the investigation of ligand effects in coupling, two equivalents of ligand were introduced \textit{in situ} to the weakly co-ordinated \textit{tris}-
(dibenzylideneacetone)palladium(0) \( \text{Pd}_2\text{dba}_3(\text{CHCl}_3) \) or \( \text{Pd(dba)}_2 \) \cite{36,19} to prepare coordinately unsaturated species and four equivalents of ligand where introduced to prepare coordinately saturated Pd(0)-species (Fig. 2.3). Each case after the addition of ligand, the solution turned from the specific purple colour of dba substituted Pd-complex to a yellow colour which is indicative of free dba.

### 2.3.1 Sources of ligands on the Pd(0) species

\[ \text{Pd(dba)}_2 \quad \text{or} \quad \text{Pd}_2\text{(dba)}_3, \text{solvent} \]

\[
\begin{align*}
\text{Solvent} & \\
2L & \quad \text{or} \quad 4L \\
\text{PdL}_2 & \\
\text{or} & \\
\text{PdL}_4
\end{align*}
\]

\( L = \) PPh\(_3\), P(MeO)\(_3\), P(PhO)\(_3\), AsPh\(_3\), Bu\(_3\)P

TFP -(tri-2-furylphosphine),
dppf -(Bis-diphenylphosphino)ferrocene
dppe -(diphenylphosphinoethane)

\textbf{Figure 2.3}

The oxidative addition of aryl halide occurs on the coordinately unsaturated palladium species Pd(PPh\(_3\))\(_2\), but very little is known about the ligand effects on
cross-coupling reactions. It can effect the reaction due to steric and electronic factors, though it is difficult to distinguish between these. A detailed paper about effects of ligand on the palladium catalysed Stille coupling reactions has been published by Farina.28

Four equivalents of ligand triphenylphosphine and tri-2-furylphosphine were used to good effect in our standard Suzuki coupling reaction. Phosphine ligand free Suzuki-Type coupling of allylbromides with arylboronic acids have recently been published37 and biaryl coupling at 65 °C in aqueous acetone in good, mostly >98 % yields.38

![Equation 2.8](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield % Pd:L 1: 2</th>
<th>Yield % Pd:L 1: 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>------</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>AsPh₃</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Tri-2-furylphosphine</td>
<td>32</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>dppf</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>6</td>
<td>P₆Bu₃</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>7</td>
<td>dppe</td>
<td>36</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>P(OPh)₃</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>9</td>
<td>Ph₂PdC₆F₅</td>
<td>----</td>
<td>00</td>
</tr>
</tbody>
</table>

Table 2.8 Ligand effect in Suzuki biaryl coupling
Our experiments without addition of any ligand to the Pd$_2$(dba)$_3$.CHCl$_3$ did not give satisfactory yield of the desired biaryl (41) (Table 2.9, Entry 1). Coordinately unsaturated PdL$_2$ never gave satisfactory yields either. PPh$_3$ was found to be the best ligand, to use with coordinately unsaturated complexes giving a 61 % yield. This is low compared to the saturated complex that gave a 97 % yield (Table 2.8, Entry 2). In the case of bidentate ligands dppe gave 36 % with 2 eq. of ligand and 76 % with 4 eq. of ligand (Table 2.8, Entry 7). Diphenylphosphinoferrocene did not give any coupling product in either ratios. When the reaction did not work, starting halides were observed in the NMR spectra. Triphenylarsine gave the related product in 51 % maximum yield (Table 2.8, Entry 3). Tri-n-butylphosphine, triphenylphosphate and Ph$_2$Pd-C$_6$F$_5$, did not give related biaryls at all.

Some of our results on the ligands effect do not match with Farina's research. His examinations were mostly with vinyltributyltin as the electrophile which is believed to form a π-complex (57) with the Pd(II) intermediate (Fig. 2.4).

![Figure 2.4](image)

No such step has been postulated for the formation of biaryls and little is known about the transmetallation step.
We conducted similar research to the palladium(0)(dba) complexes, using Na$_2$PdCl$_4$ and PdCl$_2$ complexes with the addition of triphenylphosphine ligand (Table 2.9).

![Chemical reaction](Equation 2.9)

**Table 2.9**  Pd(II) complex and ligand effect in Suzuki coupling

In the absence of PPh$_3$, mesitylboronic acid (39) and iodobenzene (40) did not give the desired product using Na$_2$PdCl$_4$ or PdCl$_2$ complexes. The addition of two equivalents of ligand PPh$_3$ gave the coupled product (41) in less than 5 % yield, whilst four equivalents of ligand gave 66 % yield. It seemed that the reaction slowed down with excess of ligand as 6 equivalents only resulted in 42% yield. This could suggest inhibition of the reaction by the phosphine ligand.
2.4 Conclusion

Our investigations into the effect of base, solvent, ligand on palladium and substituents showed that all components affect the Suzuki biaryl coupling reaction.

We developed a reliable, ambient temperature method for the coupling of tri-ortho-substituted biaryls by using TIOH as the base and DMA as the solvent.

Investigation of ligand effects on the palladium complex proved that tetrakis-triphenylphosphine was the best. In situ preparation from Pd2(dba)3.CHCl3 and four equivalent triphenylphosphine gave a slight increase in yield of of the product (41). Tri-2-furylphosphine gave similar results to triphenylphosphine. So due to economics triphenylphosphine was preferable.

The investigation of the substituents effect raised interesting results. We have no summarisation or generalisation of the substituent effects on both components. Considering the suggested nucleophilic reaction during the oxidative addition step electron withdrawing substituents may be preferable on the electrophilic (aryl halide) partner, and electron donating substituents on the nucleophilic (arylboronic acid) partner. Also the oxidative addition step seems independent of substituents, maybe because it is believed to be the first step of the catalytic cycle.

The transmetallation steps are sensitive to the steric environment of the oxidative addition product. In our examinations, while the coupling of mesityl boronic acid and iodobenzene under our improved method gave 92% yield, the corresponding coupling reaction of phenyl boronic acid with iodomesitylene, which gave the same product, proceeded in 65% yield.
3

Oxidative addition
3 Oxidative addition

Many synthetic metal catalysed reactions require an oxidative addition process. The accepted first step of the catalytic cycle in the palladium catalysed cross-coupling reactions previously mentioned, is the oxidative addition of the aryl electrophile to palladium(0), with conversion of organic substrates into the intermediate organometallic palladium (II) species shown (Eq. 3.1).

\[
\text{Ar-}X + M(0) \rightarrow \text{R-M}^{\text{II}}X
\]

Equation 3.1

Although the oxidative addition products are well characterised\textsuperscript{39,2a,43} the exact mechanism is still debated, with many different mechanisms being suggested.\textsuperscript{40,23b} It is possible to divide them in to two main mechanisms involving ionic, or non ionic intermediates. (Fig. 3.1)
Zerovalent metals such as nickel, palladium, etc. are prepared as tetra-substituted stable complexes, $\text{ML}_4$. Whereas the active form is the coordinately unsaturated $\text{ML}_2$ complex.$^{41}$

Fitton and Johnson observed iodobenzene reacted rapidly at room temperature with $\text{tetrakis}(\text{triphenylphosphine})\text{palladium(0)}$.$^{42}$ Later they showed that the oxidative addition rate of halobenzenes to $\text{tetrakis}(\text{triphenylphosphine})$-palladium(0) decreased in the order $\text{I}>\text{Br}>>\text{Cl}$ in benzene. Iodobenzene reacts spontaneously at room temperature, whilst bromobenzene gives no reaction at room temperature, and requires about 80 °C heat to start the smooth reaction to give the desired bromo(phenyl)$_2$-(triphenylphosphine)palladium(II) in good yield. Chlorobenzene did not give any oxidative addition even at 130 °C,$^{43}$ although the decomposition of the palladium complex started to occur at this high temperature. Importantly after oxidative addition, the Pd-aryl halide complex reactivity order should be $\text{Cl}>>\text{Br}>>\text{OTf}>>\text{I}$.

Although different mechanisms have been proposed for oxidative addition, the above results suggest a sequence that requires carbon halogen bond breaking to occur to an appreciable extent in the rate determining transition state of the reaction ionic pathway. However, results suggest$^{23b}$ that the non ionic pathway (Scheme 3.1) is the favoured mechanism.
Substituent effect of halobenzenes on the oxidative addition showed chlorobenzenes substituted with electron-donating groups are inactive. Thus $p$-chloroanisole gave no product with $tetrakis$(triphenylphosphine)palladium (0) even after heating at 135°C for 16 h. On the other hand, chlorobenzene with electron-withdrawing substituents are considerably more reactive than chlorobenzene itself. For example, while chlorobenzene was unreactive at 135°C, $p$-chlorobenzonitrile gave 97% yield of adduct at 100°C. The reactivity of substituted chlorobenzenes parallels the electron-withdrawing power of the substituents.

In order to generate aryl palladium (II) chloride intermediates (60) Stille developed an alternative approach with LiCl to make the reactive Pd-Cl complexes (Eq. 3.2).
Using LiBr, which gave arylpalladium (II) bromide intermediates \((61)\), did not give as high a yield as LiCl (Eq. 3.3).

\[
\begin{align*}
\text{(59)} & \quad \text{OTf} + \text{Pd(PPh}_3\text{)}_2 & \text{LiBr} \quad \text{Pd(PPh}_3\text{)}_2 + \text{Br} \\
\text{(61)} & \quad \text{PPh}_3 \\
\end{align*}
\]

**Equation 3.3**

The mechanism was suggested as below (Eq. 3.4),

\[
\begin{align*}
\text{(52)} & \quad \text{CF}_3 \quad \text{O} \quad \text{O} \\
\text{(55)} & \quad \text{Pd(PPh}_3\text{)}_2 + \text{OTf} \\
\end{align*}
\]

**Equation 3.4**

In THF, a less dissociating and co-ordinating solvent than DMF, the ionic species which result from the oxidative addition are partially ion paired.

The rate of oxidative addition to the zerovalent palladium, in toluene, was found to be first order with respect to iodobenzene and palladium, and an inverse first order dependence with respect to the ligand triphenylphosphine. The reactive palladium intermediate is assumed to be the coordinately unsaturated \(\text{Pd(PPh}_3\text{)}_2\) or \(\text{Pd(PPh}_3\text{)}_3\) species.
Solvents were also found to effect the rate of oxidative addition. It is a fact that the
dissociation of coordinately saturated Pd(PPh₃)₄ to Pd(PPh₃)₂ depends on the
coordination properties of the solvent.

After the first triphenylphosphine ligand has dissociated (Eq. 3.5), two pathways
can follow:-

Equation 3.5.

1: direct dissociation of a second triphenylphosphine ligand (Eq. 3.6),

\[
Pd(PPh₃)₃ \rightarrow Pd(PPh₃)₂ + PPh₃
\]

Equation 3.6.

2: coordination of solvent and then dissociation of a second triphenylphosphine
ligand (Eq. 3.7). Dissociation of solvent finally gives the (Eq. 3.8) di-substituted
Pd(0) species.

\[
S + Pd(PPh₃)₃ \rightarrow S\rightarrow Pd(PPh₃)₂ + PPh₃
\]

Equation 3.7
Equation 3.8

Coordinately unsaturated PdL₂ species are electron rich in comparison to the solvent coordinated species and should be more reactive. But, in polar solvents, tri-substituted species (solvent coordinated) were also observed as a reactive oxidative addition intermediate.¹⁴,⁵¹

Cationic (σ-aryl)palladium complexes (62) were also observed on the oxidative addition of aryltriflate (59) with Pd(PPh₃)₄ (Eq. 3.9).⁴⁰ₐ

Equation 3.9

3.1 Aryltriflates in oxidative addition

The use of aryltriflates in the Suzuki coupling reaction is unusual, possibly due to some triflates being base sensitive.⁴⁶ However some Suzuki coupling reactions with triflates have been examined.⁴⁷ Couplings were made in dioxane, with powdered K₃PO₄ and addition of 1.1 equivalent KBr. LiCl and KI were not very
effective, which is opposite to that found in related Stille couplings employing triflate species. The reactivity of the triflate, in comparison to aryl halides, was suggested as \( \text{I} > \text{Br} > \text{OTf} > \text{Cl} \). This particular process, then only seems useful if the aryl-halide coupling partner can not be obtained. Also the use of an aryl-triflate precursor, with added salt, does not give a better reaction, but merely enables the formation of the aryl-palladium-(II)-halide intermediate.

We attempted to couple phenyltriflate \((59)\), mesitylboronic acid \((39)\) and -ester \((46)\) (Eq. 3.10), under variety of conditions, as shown in Table 3.1, unfortunately no coupling products were obtained.

![Equation 3.10]

Table 3.1 Attempt to couple arylboronic acid and aryltriflate
Using the DMA, TIOH conditions, that have been successful for arylhalides, (Eq. 2.6), no coupling was seen with aryltriflates. It could be because of the reaction between TIOH and potassium or sodium, salts to form insoluble TIX (Eq. 3.11-a) before oxidative addition of aryltriflate to the palladium(0). Another factor could be the degradation of the triflate to the alcohol, which would not give oxidative addition (Eq. 3.11-b). The use of solid TIOH (entry 4 and 5) did not give any coupling products either. This suggested, once again, the formation of insoluble TIX salts.

\[
\begin{align*}
\text{Ar-OTf} & + \text{Ar-B(OH)}_2 & \xrightarrow{\text{Pd(PPh}_3\text{)}_4} & \text{Pd(arylidene)}_2 \\
\text{LiCl} & + 10\% \text{TIOH(aq)} & & \text{LiOH} + \text{TlCl}
\end{align*}
\]

Equation 3.11

\[
\begin{align*}
\text{a- LiCl} & + \text{TIOH} & \rightarrow & \text{LiOH} + \text{TlCl} \\
\text{b- Ar-OTf} & + \text{TIOH} & \rightarrow & \text{Ar-OH} + \text{Tl-OTf}
\end{align*}
\]

3.2 Aryldiazonium salts in oxidative addition

Reaction of arenediazonium cation with functional groups is an effective method for regioselective aromatic substitution reactions. It was successfully used in Gomberg-Bochman reactions (Eq. 1.7) for symmetrical and unsymmetrical biaryl syntheses, and prompted chemists to improve the reaction conditions by eliminating side reactions through the use of more soluble BF\textsubscript{4}\textsuperscript{-}, and BF\textsubscript{6}\textsuperscript{-} species
or phase transfer variants. Oxidative addition of arenediazonium salts to palladium has also been applied in synthetic chemistry.

Palladium catalysed reactions of arenediazonium salts with Me₄Sn in acetonitrile afforded the methylnarene with evolution of gas, presumably methane. Addition of LiCl to the reaction mixture to form Me₃SnCl decreased the yield dramatically.

The adaptation of this reaction to prepare biaryls, using ArN₂Cl and ArSnBu₃ gave desired products in satisfactory yields. This reaction also gave undesired byproducts, resulting from homo coupling. Using 1 eq. of the transition metal complex Pd(dba)₂ under nitrogen was found to be the most satisfactory (Scheme 3.2), comparison with Pd(OAc)₂, (65)=11%, (66)=59%, (67)=7% and Pd(OAc)₂(PPh₃)₂ with (65)=21%, (66)=23%, (67)=7% yields.

![Scheme 3.2 Pd-catalysed coupling of aryldiazonium with arylstannane](image-url)
Diazonium salts have also been coupled with alkyltin reagents and used in the palladium catalysed carbonylative coupling of arenediazonium salts with organotin reagents, with in good yields. Kikukawa's method can be seen as an aryldiazonium salt version of the aryltriflate used in Stille's couplings.

The diazonium method has disadvantages, when compared to Stille triflate couplings (Eq. 1.12), due to the formation of byproducts and the, stability, at room temperature, of the arene diazonium halide.

The carbonylative coupling of aryldiazonium salts and aryltin compounds did give good yields of desired unsymmetrical ketone (Scheme 3.3). However no biaryl formation, or symmetrical ketone derived from the diazonium species was reported, although there was a small amount of the symmetrical ketone (69), derived from the aryltin species as a by product.

\[
\text{Scheme 3.3 Formation of unsymmetrical ketone from the diazonium salt}
\]
The mechanism of this reaction is suggested as a catalytic cycle involving palladium, similar to that proposed for the Suzuki and Stille methodologies (Scheme 3.4)

Scheme 3.4 Proposed catalytic cycle for Kikukawa's diazonium coupling.

We thought that by using aryldiazonium salts we may reduce the activation energy required for oxidative addition of the aryl group to palladium. This assumes that oxidative addition is rate determining step. We attempted the formation of Pd species (60) directly from diazonium halides (Eq. 3.12) or other diazonium species (71), and (72) plus halide salts (Eq. 3.13).
Unfortunately both conditions were unsuccessful. Furthermore we failed, to couple any of the aryldiazonium salts with any aryl boronic acids, or esters, at all. (Table 3.2)
Table 3.2. Attempts of Suzuki cross-coupling between aryl boronic acid and aryl diazonium salts.

These negative results could possibly be attributed to the decomposition of the diazonium salts in the presence of aqueous base, required for the Suzuki coupling reaction (see chapter 1, Scheme 1.6, (36)).
3.3 Tricarbonyl(arene)chromium complex in oxidative addition

The coupling of tricarbonyl(arene)chromium complexes with arylboronic acids\textsuperscript{31} as the first stereoselective example of a Suzuki biaryl coupling reaction, attracted our attention. When the aryl halides have two differing \textit{ortho-} or \textit{meta-} substituents, then reaction with hexacarbonyl chromium gives two enantiomers of the tricarbonyl(arene) chromium complex (42a) and (42b), due to planar chirality. (Eq. 3.14)

\begin{equation}
\text{Equation 3.14}
\end{equation}

It has been noted that oxidative addition of aryl-Cl to zerovalent palladium complexes is usually difficult (Scheme 3.1 and Eq. 3.2). The coordination of an electron withdrawing group to the aryl ring, in this case Cr(CO)\textsubscript{3}, allows more facile oxidative addition to the Ar-Cl bond. The coupling of tricarbonyl(arene)-chromium complexes, with arylboronic acids, in the presence of catalytic Pd(PPh\textsubscript{3})\textsubscript{4} and a chiral phosphine ligand, were first reported in 1994,\textsuperscript{31a} Later an improved procedure\textsuperscript{31b} found that the coupling of an (arylhalide)Cr(CO)\textsubscript{3} was very effective, (Scheme 3.5), whilst the coupling of an (arylmetal)Cr(CO)\textsubscript{3} with an aryl halide was not satisfactory. In the presence of Pd(PPh\textsubscript{3})\textsubscript{4}, the reactions of (arylmetal)-Cr(CO)\textsubscript{3} (metal= -MgBr, -ZnCl, -B(OH)\textsubscript{2}, -SnBu\textsubscript{3}) with bromobenzene gave demetaleted (arene)-Cr(CO)\textsubscript{3} as the major product, along with very small amounts of coupled products.
Scheme 3.5 The coupling of tricarbonyl(arylhalide)chromium complex with boronic acid.

Axial stereochemistry of the coupled products was controlled by the steric bulk of the ortho-substituents adjacent to the coupling position. While sometimes only a trace of CO insertion product were observed, a 1,3-dioxolane substituted arenechromium complex (79) and o-(hydroxymethyl)phenylboronic (80) acid formed the CO-inserted product (81) predominantly without the formation of mono-Cr(CO)₃-complexed biaryl (Scheme 3.6).
However using this method requires planar, chiral tricarbonyl(arene)chromium complexes. Thus optical resolution of the tricarbonyl(arene)chromium complexes is necessary if two ortho-substituted, or an ortho and para-substituted, aryl halide is used.

We attempted the coupling of iodo- and bromomesitylene (83) with mesitylboronic acid (39) or esters under our standard conditions. None of our attempts were successful. However standard coupling of iodo- or bromomesitylene, with phenylboronic acid (73), or the coupling of mesitylboronic acid (39) with iodo- or bromobenzene (40) were successful in very good yields (Table 2.6). We tried the more hindered coupling between mesitylboronic acid (39) and tricarbonyl(bromomesitylene)-chromium complex (82), with Uemura's \(^{31b}\) conditions. Bimesitylene (13) was not detected from the variety of different reaction conditions (Table 3.3).

**Scheme 3.6** CO-insertion in Uemura's tricarbonyl(arene)chromium methodology
Table 3.3 Coupling attempts of mesitylboronic acid and tricarbonyl(bromomesitylene) chromium complex with TIOH base.

We also tried the *in situ* reaction of mesitylboronic acid (39) and bromomesitylene (83) in acetonitrile, with the addition of 1 eq. Cr(CO)$_6$, TIOH as the base and Pd(PPh$_3$)$_4$ as the catalyst (Eq. 3.16).

![Equation 3.16](image)

Most of these reactions gave bromomesitylene back with no observation of bimesitylene (13). The problem here would seem to be the huge steric hindrance of four *ortho* methyl groups, hindering the reaction during the transmetallation or reductive elimination steps.

3.4 Using chiral or coordinating substituents on the aryl halide.

3.4.1 o- Oxazoline substituted aryl halide
Transferring chirality from another substituent to the biaryl axis had not been attempted in previous Suzuki or Stille coupling reactions. We wanted to examine the effect of such a chiral substituent on the atropisomer selection in an asymmetric Suzuki coupling reaction. We chose the oxazoline function as it has been used to good effect by Meyers and can be made chiral. It is also easily transformed to many other functional groups.

Chiral aryloxazolines were used by Meyers to form biaryls,\textsuperscript{51} where the oxazoline promoted the substitution of an $o$-OMe group with an aryl group from its corresponding Grignard reagents (Eq. 3.17).

\begin{center}
\textbf{Equation 3.17}
\end{center}

\begin{center}
\begin{align*}
\text{Ar} & \quad \text{OMe} + \text{Ar} & \quad \text{OMe} \quad \text{Mg,THF} \quad \Delta \\
(84) & \quad (85) & \quad (86)
\end{align*}
\end{center}

For the synthesis of some pharmacologically active biaryls a combination of aryloxazolines, with different characteristics, were exploited: Directed ortho-metalation of aryl oxazolines with n-BuLi and transmetallation with Zn; followed by the addition of a palladium catalyst and aryl halide gave corresponding biaryl oxazolines (Scheme 3.7).\textsuperscript{52}
Scheme 3.7 *Ortho*- directed / transmetallated / palladium catalysed couplings of aryloxazolines

However, the organolithium reagents required are detrimental towards some functionalities, and lengthy protection / deprotection sequences are sometimes needed.

Palladium mediated *ortho*-alkylation of aryloxazolines,\(^{53c}\) has also been accomplished, in good yields (Eq. 3.19). This method, however, does not use organolithium reagents, but requires an excess of alkylhalide (15 equivalent for mono o- substituted product) and an equivalent amount of palladium. (Eq. 3.19).
 Though, the cyclo palladated complexes of aryloxazoline, and the oxidative addition of \( o \)-halo-aryloxazoline, has been widely investigated\(^5\), the catalytic coupling reaction of an \( o \)-oxazoline- substituted arylhalide or \( o \)-oxazoline- substituted arylboronic acid, had not been investigated.

The literature describes an oxidative addition product of \textit{ortho}-bromophenyl-oxazoline (91) to Pd(dba)\(_2\), which gave di-\( \mu \)-bromobis[2-(4',4'-dimethyl-2'-oxazoliny1)phenyl-1-C,3'-N] dipalladium(II) (92) (Eq. 3.20).
We thought that we could use this reaction in a catalytic sequence involving Pd(0). If the oxidative addition product (92) could enter a catalytic cycle, then transmetallation could occur with a boronic acid and subsequent reductive elimination would give biaryls and regenerate Pd(0). The coordination of nitrogen to the palladium centre may give certain structural constraints to the complex, and this coordination may accelerate the transmetallation. Stille coupling of vinylstannanes and vinyl halides have been shown to be accelerated by this kind of chelation. Eventually, using a chiral aryloxazoline we may get diastereoselective C-C bond formation to produce one atropisomer predominantly, or even exclusively. Thus we prepared some aryl oxazolines and attempted the Suzuki coupling reaction under various conditions. Table 3.4 demonstrates some selected results from this work.
As seen from table 3.4, under none of the usual conditions were we able to couple aryl oxazolines with mesityl- or phenylboronic acids. In all cases work up gave the boronic acids and aryl oxazolines back. Traces of the coupling product were not observed from crude spectroscopic data.
We thought perhaps that the methyl groups may have caused some steric effect that inhibited the coordination of the nitrogen to the palladium, or that they may have prevented the complex from undergoing the desired transmetallation reaction. Accordingly we prepared the unsubstituted aryloxazoline (93) and tried to couple this under similar conditions (Eq. 3.22). Once again, no related biaryls were detected and unreacted starting materials were recovered (Table 3.5).

![Equation 3.22]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Boronic acid</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mes-B(OH)(_2)</td>
<td>DMA</td>
<td>10% TiOH(aq)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Mes-B(OH)(_2)</td>
<td>DMA</td>
<td>Et(_3)N</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Mes-B(OH)(_2)</td>
<td>DMF</td>
<td>Ba(OH)(_2)·8H(_2)O</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ph-B(OH)(_2)</td>
<td>DMA</td>
<td>Ba(OH)(_2)·8H(_2)O</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ph-B(OH)(_2)</td>
<td>Benzene</td>
<td>Ba(OH)(_2)·8H(_2)O</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ph-B(OH)(_2)</td>
<td>DMA</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Ph-B(OH)(_2)</td>
<td>DMA</td>
<td>10% TiOH (^a)(aq)</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Reaction carried out at room temperature

**Table 3.5** Attempts to couple mesityl and phenyl boronic acids with aryloxazoline (93)
In order to investigate this reaction further, we prepared the oxidative addition complex (94) (Eq. 3.23). This would at least show us whether the oxidative addition step was working.

\[ \text{Equation 3.23} \]

The related cyclopalladated complex (92) was also successfully prepared by using 1 equivalent of Pd(dba)_3.CHCl_3 and oxazoline (91).

\[ \text{Equation 3.24} \]

This verified that there was no problem in forming the oxidative addition complex. We then examined the stoichiometric coupling of this complex with aryl boronic acids (Eq. 3.25 and 3.26). Unfortunately, no related biaryls were formed from these reactions. After work up we were able to recover the boronic acid but
not the initial complex. A small amount (~9%) of unidentified products were also isolated.

\[ \text{Equation 3.25} \]

\[
\begin{align*}
\text{Pd} & \text{N O} \text{Br}_2 + \text{B(OH)}_2 \\
& \text{Benzene} \\
& \text{Ba(OH)}_2 \cdot 8 \text{H}_2\text{O} \\
& 80^\circ \text{C} \text{12h}
\end{align*}
\]

Finally, we tried coupling with Grignard reagents, in case our boronic acids were not reactive enough. The cross coupling of (92) with mesityl magnesiumbromide did not give any of the related biaryl.

\[ \text{Equation 3.26} \]

\[
\begin{align*}
\text{THF/ Reflux} \\
\text{Overnight}
\end{align*}
\]
Chapter Three

Oxidative Addition

Equation 3.27

The failure of these reactions could be due to the strong coordinating ability of the nitrogen to the palladium. Consequently we set out to prepare some complexes containing a less coordinating atom. Instead of a 1,3-oxazoline, we decided to prepare the 1,3-oxolane, which again could ultimately be prepared chirally and be transformed to many functional groups.

3.4.2 o-Chiral-1,3-dioxolane substituted aryl halides

Using 1,3-dioxolane as a protecting group for aldehydes or ketones is well established. We prepared the desired 1,3-oxolanes (Fig. 3.2) by the reaction of o-halo benzaldehydes with the diols, and a catalytic amount of p-TsOH.

![Figure 3.2](image)

In the literature however there were no reports of 2-(o-haloaryl)-1,3-dioxolane palladium complexes, even from oxidative addition reactions. Thus we had no idea if the oxygen would coordinate with the palladium to give the related
cyclopalladated complex (96) (Fig. 3.3) and thus assist in accelerating the transmetallation step.

![Figure 3.3](image)

We prepared 2-(o-bromo and -iodophenyl)-1,3-dioxolane (97) and (98) (Fig. 3.4) in 88 % and 85 % yield respectively.

The Suzuki coupling reaction of (97) and (98) with mesityl-(39) and phenyl boronic acids (73) showed some promising results (Scheme 3.8).
With these excellent results in hand, we than started to think about, how we could make biaryls diastereoselectively by employing chirality on any part of the 1,3-dioxolane.

After our initial encouraging results we carried out the coupling reaction with various racemic substituted dioxolane systems, prepared in an analagous fashion to 97 and 98 in good yields, (Fig. 3.5) with various arylboronic acid and -esters.(Fig. 3.6)
The attempted coupling reactions are summarised in Table 3.6. Surprisingly, it seems additional -CH₃ substituents on the dioxolane moiety slows down the reaction and gave low yields of coupled products. Additionally in some cases the reaction ceased all together.
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Oxidative Addition

Table 3.6 NMR judged yields of coupling between arylboronic acids and 2-aryl-1,3-dioxolanes.

<table>
<thead>
<tr>
<th>Run</th>
<th>Arylboronic acid</th>
<th>Arylacetylene</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39</td>
<td>101</td>
<td>A</td>
<td>(104)</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>101</td>
<td>B</td>
<td>(104)</td>
<td>&gt;10</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>102</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(104)</td>
<td>&gt;10</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>102</td>
<td>B</td>
<td>(104)</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>101</td>
<td>A</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>102</td>
<td>B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>101</td>
<td>A</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>102</td>
<td>A</td>
<td>(105)</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>73</td>
<td>103</td>
<td>A&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(106)</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>103</td>
<td>A</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>103</td>
<td>C</td>
<td>Trace</td>
<td>Trace</td>
</tr>
<tr>
<td>12</td>
<td>48</td>
<td>102</td>
<td>A</td>
<td>Trace</td>
<td>Trace</td>
</tr>
</tbody>
</table>

<sup>a</sup) Solid TIOH was used.  <sup>b</sup) 2 eq. Boronic acid and 2.5 eq. base were used.  <sup>c</sup) 1 equivalent Pd(PPh₃)₄ was used.

While the unsubstituted 1,3-dioxolane substituent (97 or 98) allowed biaryl bond formation ortho to it, one methyl substituent on the dioxolane (101) caused a
dramatic reduction in yields with mesityl boronic acid \((39)\) (entry 1, 2). Good yields were only obtained with the unhindered phenyl boronic acid \((73)\) (entry 8), while the dimethyl substituted dioxolane \((103)\) only yielded biaryl with \((73)\) when stoichiometric palladium was employed (entry 9).

In all of the coupling attempts between 4-(substituted)aryl-1,3-dioxolanes and arylboronic acids, we isolated the corresponding biaryls contaminated with the starting dioxolanes. The polarity of \(o\)-arylhalo-1,3-dioxolanes were so close to that of the coupled biaryls, we were not able to separate them by flash chromatography. The yields given in Table 3.6 are NMR estimated yields of product.

Additional modifications like using the corresponding esters of arylboronic acids \((47), (49), (50), (52)\) or using different base such as \(\text{Li}_2\text{CO}_3\) or \(\text{Et}_3\text{N}\) did not give the desired biaryls in any better yields.

3.5 Conclusion

Our attempts at affecting the oxidative addition step of the Suzuki reaction in order to increase the rate of the reaction or control the stereoselectivity of the aryl bond formation have been met with a frustrating lack of success.

We believe decomposition of the starting materials under the reaction conditions was responsible for the failure of aryl triflates to undergo a Suzuki coupling reaction. Although there has been some success with tricarbonyl (arene) chromium complexes, we found that more hindered couplings were unsuccessful. \textit{Ortho} oxazoline substituents on the aryl halide coupling partner, far from accelerating the
coupling reaction formed a stable cyclopalladated intermediate that was fairly inert
to the coupling reaction. Our only success was with the use of an ortho 1,3-
dioxolane substituent on the aryl halide coupling partner, which did not affect the
yield of the biaryl bond formation even with a hindered boronic acid. However,
introducing chirality on to the dioxolane substituent dramatically reduced the
yields and disheartened us from further diastereoselective couplings.

At this stage we decided to turn our attention to the transmetallation step of the
suggested catalytic cycle.
4

Transmetallation
Transmetallation is one of the two important steps in palladium catalysed cross-coupling reactions. Most organometallics transmetallate the oxidative addition product (85), formed from the insertion of Pd(0) between a C-X bond. Organometallic reagents transfer their organic group to palladium in exchange for the halide or triflate, which produces a dialkyl or diarylpalladium(II) complex (108) and a main group metal halide or triflate (Eq. 4.1). Transmetallation from Li, Mg, Zn, B, Al, Sn, Si, Ge, Hg, Tl, Cu, etc. have been widely studied. However, Sn, B and Zn have emerged as the most popular. Transmetallations occur from more electropositive to more electronegative metals, but this may be effected by changing coordinating ligands, thus altering the electronegativity of metals. Transmetallations are an equilibrium and only a small equilibrium constant is required for the whole coupling reaction to proceed. Fast reductive elimination follows cis-trans isomerisation and delivers the coupled product (Scheme 1.5).

\[
\text{transmetallation} \\
\text{R-Pd-X + R'M} & \rightarrow & \text{R-Pd-R' + MX} \\
(107) & & (108)
\]

\textbf{Equation 4.1}

Palladium catalysed cross coupling reactions of vinyl or aryl halides were looked at with Grignard reagents and organolithiums. Initially, Ni-catalysed\textsuperscript{56} cross-coupling reactions of Li and Mg reagents were somewhat more widely
investigated than Pd-catalysed cross-coupling reactions. Unfortunately the reactivity of these reagents, meant that functional groups such as carbonyl could not be tolerated and often homo coupling of the organic halide was isolated as a substantial byproduct.

Organometallic reagents in which the metals have intermediate electropositive character generally lead to higher yields of the coupled products, by giving fewer by products and tolerating a wide range of functional groups in either, or both of the coupling partners. Accordingly, organozinc, organotin and organoboron compounds are particularly useful. Allyl and aryl Li and Mg reagents are used to synthesise the more electropositive metal species such as Zn, Sn, B compounds by transmettalations. However, it should be appreciated that each metal reagent has its own optimum conditions and different results may be obtained under different reaction conditions. Although there have been many improvements on the more modern methods mentioned above, there still does not exist a general catalytic method for the syntheses of hindered biaryls and many chemists are trying hard to develop such a method.

4.1 Organozinc compounds

Organozinc compounds can easily be prepared from main group organometallics, by simple addition of anhydrous zinc chloride in THF. Direct insertion of activated zinc metal to the carbon-halide bond,\(^{57}\) is also possible. These species are used successfully in many Pd-catalysed cross-coupling reactions,\(^{14}\) and allow many functionalities, in both coupling partners, such as esters, ketones and nitriles to be present without protection. (Eq. 4.2).
An example is the palladium catalysed cross coupling of p-cyanophenylzinc bromide with p-iodobenzoic acid ethyl ester, affording product \((114)\) in 82% yield\(^{58}\) (Eq. 4.3).

4.2 Organotin and -boron compounds

More popular organometallics, for biaryl formations, are organotin (Stille) and organoboron compounds (Suzuki). Transmetallation from tin and boron to palladium is a highly developed and extensively utilised process in organopalladium chemistry.\(^{59}\)
Carbonylative cross-coupling of stananes and boron regents has been extensively investigated.\textsuperscript{60} For most cases transmetallation is suggested as the rate limiting step. This may be due to the low nucleophilic nature of arylboronic acid, and that is why a CO insertion to the oxidative addition product, followed by transmetallation can give carbonylative coupled products. These reactions seem to be easier and cleaner than the corresponding biaryl couplings. The reason for this could be that there is either less steric hindrance when comparing aryl-aryl to aryl-alkyl compounds, or carbonylative oxidative addition products (115) are more reactive than arylpalladium(II) halide complexes (107).

\begin{equation}
\text{R–Pd–X} \xrightarrow{\text{CO insertion}} \text{R–C–Pd–X} + \text{RM} \xrightarrow{\text{Transmetallation}} \text{R–C–Pd–R} + \text{MX}
\end{equation}

\begin{equation}
\text{R–C–R} \xrightarrow{\text{Reductive eliminations}} \text{R–Pd–X} \xrightarrow{\text{CO insertion}} \text{R–C–Pd–X} + \text{RM} \xrightarrow{\text{Transmetallation}} \text{R–C–Pd–R} + \text{MX}
\end{equation}

\begin{equation}
\text{R–C–R}
\end{equation}

\textbf{Scheme 4.1.} Palladium catalysed carbonylative coupling

It is important that both the transition metal and the main group partner, involved in the transmetallation, benefit from the process energetically. Triflates in Stille couplings with organotin reagents sometimes fail since the resultant tin triflate is not stable. The reaction proceeds well with the addition of lithium chloride,
permitting the production of the more stable organotin chloride (119), rather than triflate (118) (Eq. 4.4).

\[
\text{R–Pd–OTf} + \text{R’SnR}_3 \rightarrow \text{R–Pd–R’} + \text{R}_3\text{SnOTf} \\
\text{R–Pd–OTf} + \text{R’SnR}_3 + \text{LiCl} \rightarrow \text{R–Pd–R’} + \text{R}_3\text{SnCl} + \text{Pd OTf R R}
\]

Equation 4.4

Similarly, transmetallations from boron to palladium were not successful until stable organoboranates were generated, by reaction in the presence of base or alkoxide to produce stable B-O compounds (121) (Eq. 4.5).

\[
\text{R–Pd–X} + \text{RB(OR)}_2 \rightarrow \text{R–Pd–R’} + \text{XB(OR)}_2 + \text{Pd X R R}
\]

Equation 4.5

The use of TIOH provides a low temperature, fast route to the formation of coupled products. It is postulated that TIOH leads to insoluble TIX salts, during the process, and this help the transmetallation process in this way.\(^{33,35}\)

The reactive boron species which undergoes transmetallation is said to be a boronate anion. However, phenyl-di-n-butyl boronate (122-a) did not couple,
using triethylamine as a base, whilst the related boronic acid (73) gave a 98 % yield of coupled product (124). 61

For this reason, under non aqueous conditions, arylboronate dianion (125) was suggested as the reactive organometallic species which undergoes transmetallation.61

Equation 4.6

The base may play another role, reacting with the arylpalladium(II) halide complex, to give an arylpalladium(II) hydroxide species (126) (Fig. 4.1), which should be then more reactive, as oxygen is more electronegative than the bromine or iodine.
Transmetallation from boron to palladium has been expanded, with directed ortho-metalation of benzamide derivatives (127) by Snieckus (Eq. 4.7).

\[
\begin{align*}
(R')\text{NOC} & \rightarrow \left[ \begin{array}{c}
\text{O} \\
N(R')_2 \\
\text{RLi}_n \\
\end{array} \right]_n \\
\rightarrow & \left[ \begin{array}{c}
\text{O} \\
N(R')_2 \\
\text{RLi}_n \\
\end{array} \right]_n
\end{align*}
\]

Equation 4.7
Benzamide 2-boronic acid derivatives (128) are more reactive than related boronic acids. However it was not mentioned by Snieckus whether coordination of the amide nitrogen to the palladium may be responsible, or the influence that the amide group may have as an electronegative substituent.

There is little doubt that steric hindrance around the newly formed C-C bond, and electronic effects, of substituents on both components, play major roles in the efficiency of biaryl cross-coupling reactions. The extent with which these factors are important are still under investigation.

In our observations of coupling to mesitylboronic acid, the use of an unsubstituted aryl halide, usually iodobenzene, gave higher yields of coupled products, when compared with ortho- or para- substituted arylhalides.

While the first considerations for donating higher yields in cross coupling reactions, is due to little steric hindrance, there is another approach. Facile aryl-aryl exchange may occur at the palladium center between the aryl moiety and a phenyl group from triphenylphosphine, and this may increase the coupled product from halobenzenes. When Pd(PPh3)2(C6H4-p-CH3)I complex (130), prepared from the oxidative addition of p-iodotoluene to Pd(PPh3)4, was heated at...
50-60 °C in THF or chloroform, a regiospecific exchange between the aryl on the palladium centre, and a phenyl from the phosphine was observed\textsuperscript{63} (Scheme 4.2).

Scheme 4.2 Aryl scrambling from the triphenylphosphine.

More experiments with o-iodoanisole and deuterated phosphine complexes have showed similar results.\textsuperscript{64} The exchange reaction was found to be sensitive to air and free phosphine ligand. While in the presence of air, an unknown decomposition was observed, the addition of 1 equiv. of PPh\textsubscript{3} inhibited the aryl exchange and it was thought that a reactive, coordinatively unsaturated palladium species was the reason for aryl exchange. Coupled aryl exchange products have been identified.

A good example is the Suzuki coupling of 2,3,4-trimethoxyphenylboronic acid (134) with 4-bromo-1,2-methylenedioxybenzene (135). This reaction gave 3,4-
methylene dioxy-2',3',4'-trimethoxybiphenyl (136) in 54% isolated yield, with 27% of the scrambled product 2,3,4-trimethoxybiphenyl (137) (Scheme 4.3).65

\[
\text{MeO} \quad \text{B(OH)}_2 + \begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\xrightarrow{\text{Pd(PPh}_3)_4} \begin{array}{c}
\text{Br} \\
\text{O}
\end{array}
\xrightarrow{\text{DME/EtOH}} \begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array} + \begin{array}{c}
\text{MeO} \\
\text{MeO} \\
\text{OMe}
\end{array}
\]

(Scheme 4.3) Aryl scrambling in Suzuki coupling reaction.

Using 1 mole % of catalyst or tris-substituted-arylphtines, such as tris(2-methoxyphenyl)phosphine was found to increase the desired product ratio.

Chenard et al.66 also showed that scrambling can occur during the Stille coupling reaction. The reaction of 6-methoxy-2-(trimethylstannyl)naphthalene (138) with \( p \)-substituted bromobenzene (139), in various solvents was studied. The undesired scrambling products (141) were isolated in between 20-55 % yield (Scheme 4.4).
They also found solvent polarity and substituents on the arylhalide had a relatively small effect on the ratio of scrambling products. The yields of undesired product decreased in less polar solvents and with electron withdrawing substituents on the aryl halide. While 74% of available phenyl groups were transferred from triphenylphosphine, those of triphenylarsine were transferred quantitatively. These results support the work of Cheng et al. and suggest that using less catalyst would reduce the yields of scrambled products.

If it is considered that, as discussed in this thesis, palladium catalysed cross-coupling reactions are affected by: the type and amount of ligand on the Pd-complexes; the solvent; halide on the electrophilic partner; metal on the nucleophilic partner; reaction temperature; additional base in Suzuki couplings or main group salts in Stille couplings, then we can see how a generalisation or even classification of this reaction is quite difficult.
4.3 Using chiral cyclic boronic acid esters

Hydrolytic deboronation of the boronic acid was, sometimes, an undesirable side effect in the Suzuki biaryl coupling, under aqueous conditions. Therefore non-aqueous conditions and the use of boronic acid esters were developed by Suzuki.\textsuperscript{30} Thus, the yields of coupled product (143) from the 2-formylphenylboronic acid with 2-iodotoluene was increased from 54\% (Eq. 4.9) to 89\%, (Eq. 4.10), by switching from formylphenylboronic acid and aqueous sodium carbonate, to formylphenylboronic acid dimethylester and powdered potassium phosphate.

\[ \text{Equation 4.9} \]

\[
\begin{align*}
\text{(77)} & \quad \text{B(OH)}_2 \quad \text{CHO} \\
& \quad \text{H}_3\text{C} \quad \text{I} \quad \text{CHO} \quad \text{H}_3\text{C} \\
& \quad \text{Pd(PPh}_3)_4 \quad \text{DME/H}_2\text{O} \\
& \quad \text{Na}_2\text{CO}_3(\text{aq}) \quad 80^\circ\text{C} \\
\rightarrow & \quad \text{(143)} \quad \text{CHO} \quad \text{H}_3\text{C} \quad 54\% \\
& \quad \text{(142)} \quad + \quad \text{(144)} \quad \text{CHO} \\
& \quad \text{H}_3\text{C} \quad 39\%
\end{align*}
\]
When this in mind, we thought that maybe we could achieve atropisomer selective biaryl coupling via cyclic chiral arylboronic acid esters (146). If we place bulky substituents on the boronic ester it could react with the oxidative addition product the σ-arylpalladium(II) complex, in a particular orientation due to the proposed transmetallation transition state shown in Fig. 4.2. In this figure the orientation of the group R$_2$ will be dictated by the steric bulk of the cyclic chiral arylboronic acid ester.
General preparation of arylboronic acids was from the arylboronic-di-alkyl-esters, by basic hydrolysis. (See experimental chapter). Suzuki coupling conditions require base, so it was not known if the chiral arylboronic esters (146) would hydrolyse under the reaction conditions (Eq. 4.12).

\[ \text{Equation 4.12} \]

A mesityltrimethylene glycol ester (47) was prepared, and a coupling attempted under Suzuki's reaction conditions using TIOH in the absence of palladium (Eq. 4.13).

\[ \text{Equation 4.13} \]
Unfortunately mesitylboronic ester (47) and iodobenzene (40) under TIOH / DMA condition showed predominantly a hydrolysis reaction. (Eq 4.13).

As using base is necessary for transmetallation from boron to palladium, this approach appeared doomed to failure and we turned our attentions elsewhere.

4.4 Using arylthallium compounds

TIOH as a base in Suzuki biaryl couplings accelerated the reaction and gave good yields at ambient temperature. There is a suggestion that thallium makes insoluble salts and affects the transmetallation equilibrium (Eq.. 4.14).33

Thus, we had the idea that using arylthallium compounds instead of arylboronic acid and TIOH as a base could have a similar effect. If arylthallium compounds allowed transmetallation to the oxidative addition product (35). Formation of insoluble thallium salts could then drive the transmetallation. (Eq. 4.15)
Aromatic organothallium compounds have been used for coupling with olefins successfully in around 60% yield\textsuperscript{67} (Eq. 4.16).

\[
\text{ArTlX}_2 \text{ or Ar}_2\text{TlX} + \text{RCH=CHR}^* \xrightarrow{\text{Li}_2\text{PdCl}_4} \text{ArCR=CHR}^* + \text{HPdX}
\]

\[X=\text{OCOCF}_3, \text{CN}, \text{Cl}\]

Equation 4.16

The oxidative dehydrodimerization of aromatic compounds to biaryls is very successful with thallium(III)trifloroacetate.\textsuperscript{10} Control of regioselectivity and unwanted product formation are the main problems. In the synthesis of aromatic carbonyl compounds \textit{via} thallation carbonylation of arenes, the transmetallation of arylthallium to Pd(II) (Eq. 4.17) has been suggested.\textsuperscript{68}

\[
\text{ArTlX}_2 \xrightarrow{[\text{PdX}_4]} [\text{ArPdX}_3]^{-2} + \text{TiX}_3
\]

\[
[\text{ArPdX}_3]^{-2} + \text{CO} \xrightarrow{-2} [\text{ArCOPOdX}_3]^{-2}
\]

\[
[\text{ArCOPOdX}_3]^{-2} + \text{ROH} \rightarrow \text{ArOO}_2\text{R}
\]

Equation 4.17
Symmetrical, sterically non-hindered biaryls were also synthesised, in excellent yields, by treating arylthallium bis(trifluoroacetates) (107) with a catalytic amount (10 mol % eq) of lithium tetrachloropalladate (Li₂PdCl₄) (Table 4.1). Unfortunately reactions failed when there was an ortho- substituent present.⁶⁹

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>H</td>
<td>i-Pr</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>(CH₂)₃CO₂H</td>
<td>H</td>
<td>90</td>
</tr>
</tbody>
</table>

**Table. 4.1** Coupling of arylthallium bis(trifluoroacetates) with lithium tetrachloropalladate.⁶⁹

The reaction tolerated air, moisture, and even carboxyl groups (Table. 4.1 entry 5). While ρ-thallated chlorobenzene gave a low yield of coupled product (entry 4), thallated bromo and iodobenzene were even less productive.

The mechanism of the reaction is not known but it has been suggested to involve a diaryl palladium species which after subsequent reductive elimination gave the
desired biaryl and Pd(0). The catalyst could then be regenerated from zerovalent palladium by the reduction of part of the Thallium(III) (Eq. 4.19)

\[
Pd^0 + \text{Tl}^{+3} \rightarrow Pd^{II} + \text{Tl}^{+1}
\]

Equation 4.19

We prepared mesitylthallium(III) acetate (153) and bis(trifluoroacetate) (154) and attempted to couple with aryl halides.

![Chemical structures](image)

Figure 4.3

The couplings attempted with aryl halides did not give any desired biaryls even when using iodobenzene (Table 4.2). Altering solvents, temperature, and palladium source did not give any promising results either. Our attempts are presented in Table 4.2.
The preparation of arylthallium (III) compounds has been widely studied.\textsuperscript{70} Besides the high toxicity of arylthallium compounds, there are other problems concerned with their manipulation. This could in part, account for the lack of success in these reactions.

We have also prepared the corresponding arylthallium halides (155) and (156) to couple with aryl halides.

![Chemical structure](image)

Table 4.2 Coupling attempts between arylthallium compound and aryl halides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Arylthallium</th>
<th>Arylhalide</th>
<th>Pd-Comp.</th>
<th>Solvent</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>153 M es-I</td>
<td>Pd(PPh\textsubscript{3})\textsuperscript{a}</td>
<td>Benzene</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>154 M es-Br</td>
<td>Pd(PPh\textsubscript{3})\textsuperscript{a}</td>
<td>THF</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>153 Ph-I</td>
<td>Pd(PPh\textsubscript{3})\textsuperscript{a}</td>
<td>Benzene</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>154 Ph-I</td>
<td>Pd(PPh\textsubscript{3})\textsuperscript{a}</td>
<td>THF</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>154 Ph-I</td>
<td>Na\textsubscript{2}PdCl\textsubscript{4} \textsuperscript{b}</td>
<td>DMA</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>154 Ph-I</td>
<td>—</td>
<td>Et\textsubscript{2}O</td>
<td>00</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>154 Ph-I</td>
<td>Na\textsubscript{2}PdCl\textsubscript{4} \textsuperscript{b}</td>
<td>MeOH</td>
<td>00</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} reaction was tried with Na\textsubscript{2}PdCl\textsubscript{4} as well.
\textsuperscript{b} excess of PPh\textsubscript{3} was added.
These attempts could not yield any coupled biaryls from the reaction of (155) and (156) with aryl halides as well. (Table 4.3)

![Chemical Reaction](image)

Table 4.3 Coupling attempts of arylthallium (III) halides with aryl halides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Ar'</th>
<th>Pd-Comp</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mes-</td>
<td>Ph-</td>
<td>Pd(PPh₃)₄</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Mes-</td>
<td>Ph-</td>
<td>Na₂PdCl₄</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Ph-</td>
<td>Mes-</td>
<td>Pd(PPh₃)₄</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Ph-</td>
<td>Mes-</td>
<td>Na₂PdCl₄</td>
<td>0</td>
</tr>
</tbody>
</table>

Mes=(Mesityl), 2,4,6-trimethylphenyl, Ph=Phenyl

Aryl thallium compounds have the following problems,⁶⁹,⁷⁰a,b for the preparation, purification and spectroscopic data.

1. **Solubility:** Arylthallium compounds are not soluble in most organic solvents. (Some are just soluble in boiling pyridine)

2. **Stability:** Arylthallium compounds differ in stability. For example, in water on heating disproportionation can give Mixture of Tl(I) and Tl(III) compounds.⁷⁰f
Isolation of pure thallium compounds from these mixtures is very difficult. We tried to make arylthalliums by the following related literature procedures and used products as crude compounds without recording any spectroscopic data, mainly, due to solubility, and mixtures were undoubtedly formed.

4.5 Dihydrobenzoboradiazoles as boronic acid derivatives

Arylboronic acids are not nucleophilic enough for an efficient transmetallation to palladium. Arylboronic acids, and their esters, need to be activated by the addition of base to the reaction media. We wondered how the nitrogen analogue of the boronic acid would react and decided to prepare some 2-aryl-dihydrobenzoboradiazoles (Scheme 4.5). We then examined the palladium catalysed coupling of these compounds with aryl halides. Although the preparation of the 2-phenyl-1,3-dihydro-2,1,3-benzoboradiazole was known (Eq. 4.20),

\[
\begin{align*}
2\text{PhTlX}_2 & \ = \ \text{Ph}_2\text{TlX} + \text{TlX}_3 \\
5\text{PhTlX}_2 & \ = \ 5\text{TlX} + 5\text{Ph-X} \\
\text{ArTlX}_2 + \text{ArTl} & \ = \ \text{Ar-Ar} + 2\text{TlX}
\end{align*}
\]

Equation 4.20

\[
\begin{align*}
\text{B(OH)}_2 + \text{H}_2\text{N} & \ \xrightarrow{\text{Toluene, reflux}} \ \text{B(\text{NH})}_2
\end{align*}
\]
The reaction of phenylboronic acid with ethylenediamine (Eq. 4.21) gave unidentified products of empirical formula $C_{20}H_{23}O_3N_2B_3$.\textsuperscript{71} Recrystallization gave unidentified decomposition product.

\begin{center}
\begin{align*}
\text{Equation 4.21}
\end{align*}
\end{center}

Our repetition of these experiments gave similar results. While the reaction of phenyl- and mesitylboronic acids with the ethylenediamine gave a mixture of compounds. The distillation of thick yellowish oily mixture resulted with the well known\textsuperscript{72} trimerisation product (160) and (161) (Eq. 4.22).

The preparation of mesityl and phenyl dihydrobenzoboradiazoles (158) and (162) was successful.

\begin{center}
\begin{align*}
\text{Equation 4.22}
\end{align*}
\end{center}
Unfortunately, the coupling attempts of 2-phenyl-(158) and 2-mesityl-
dihydrobenzoboradiazole (162) with iodobenzene (40) were not successful. (Eq. 4.23)

\[
\text{Ar-$B$N$\rightarrow$N$\rightarrow$I} \quad \text{Pd(PPh$_3$)$_4$} \quad \text{Solvent} \\
\text{Ar=Phenyl (158)} \\
\text{Ar=Mesityl (162)} \\
\text{Base $80^\circ C$} \\
\text{Solvent= Benzene, DMA,} \\
\text{Base= Ba(OH)$_2$·8 H$_2$O, Et$_3$N,} \\
\]

Equation 4.23

4.6 The use of co-catalyst

Organotin and organoboron compounds are less reactive, and more stable, than the corresponding Grignard reagents or organolithium reagents, which are commonly used in organic synthesis. While lower reactivity leads to the tolerance of functional groups on both components, stability makes them commercially available and easily handled as starting materials. Sometimes, however, they are not reactive enough for efficient transmetallation, and transmetallation is usually suggested as the rate determining step of these reactions.²⁸ As a solution to this problem CuI has been successfully employed as a cocatalyst in biaryl synthesis,⁷³
via Stille methodology. The effect of the CuI has led to plausible organocopper species being postulated.

We have tried CuI as a cocatalyst in Suzuki coupling reaction between mesitylboronic acid (39) and iodobenzene (40) in DMA (Eq. 4.24).

Equation 4.24

In contrast with the Stille coupling, the use of CuI as a cocatalyst, gave lower yields than our standard condition. While in the absence of CuI, the coupling of mesityl boronic acid and iodobenzene gave 92% yield (Equation 2.6), addition of CuI (4 equivalent to Pd-catalyst) reduced the yield of coupled product (38) to 23%. Repetition of the reaction with o-bromoanisole, p-bromonitrobenzene and o-bromotoluene yielded less than 10% of coupled product. Buchecker74 et. al. has observed similar opposite effect for the coupling of aryltriflates with boronic acid.
4.7 Using chiral 2-(o-phenylboronic acids)-1,3-dioxolane, or the corresponding ester

As discussed in chapter (3.4.2) in this thesis, due to the impracticalities of preparing biaryls from chiral 2-(o-haloaryl)-1,3-dioxolane (95), which could have transferred chirality from the electrophilic component to the biaryl axis, we decided to position the chirality ortho to the arylboronic acids or esters. e.g., (163) and (164) (Fig. 4.4).

![Figure 4.4](image)

However it is known that the preparations of 2-phenyl-2-oxazoline boronic acid (167) fails because of a strong and deleterious N-B interaction, \(^{75}\) (Fig. 4.5).
Metallation of 2-(o-bromophenyl)-4,4-dimethyl oxazoline (165) occurred very fast, via lithium halogen exchange at -75 °C, leading to yellow-brownish complex (166) which was quenched with an excess of trimethylborate. The resulting intermediate, 2-oxazolinylphenyl boronic acid dimethyl ester (167), was detected in the NMR and mass spectrum of the crude product mixture prior to hydrolysis. It was found that (167) was very sensitive to nucleophilic ring opening and the addition of water at room temperature gave carboxamido group (168). Thus, desired o-oxazoline phenylboronic acid gave an undesired decomposition product.

We were able to prepare 2-(o-phenylboronic acid esters)-1,3-dioxolane (164) by using the method outlined in (Fig. 4.5). The preparation of o-bromophenyl-1,3-dioxolane (97) and (102) was provided by refluxing equivalent mixtures of o-bromobenzaldehyde with the appropriate diols as in chapter three, Fig. 3.4.
Forming the o-1,3-dioxolane phenylboronic acids were problematical. The 1,3-dioxolane was removed under the reaction conditions to give 2-formylphenylboronic acid (77). (Eq. 4.26)

The preparation of 2-phenylboronic acid di-n-butylester-1,3-dioxolanes (169) and (171) were possible by the reaction of Grignard reagents derived from (97) and (102) with tri-n-butylborate at -78 °C.
The desired 2-phenylboronic acid dimethylene ester-1,3-dioxolanes (170) and (172), were prepared by either of two ways. Firstly the reaction of o-formylboronic acid with 2 equivalents of the appropriate diol afforded (170) and (172) in moderate yields.
Secondly, the reaction of 2-(phenylboronic acid di-n-butyl ester)-1,3-dioxolanes (169) and (171) with three equivalents of the appropriate diol afforded (170) and (172) in good yields.

![Figure 4.7](image_url)

Palladium catalysed coupling reactions were attempted with iodobenzene and this time pure coupled products could be cleanly isolated as there was a large difference in Rf between the aryl-boron partners and the coupled products, (Table 4.4). These results are in direct contrast to having the-1,3-dioxolane on the aryl halide mentioned in chapter three (3.4.2).
As seen from the table 4.4, palladium catalysed coupling of 2-(o-phenylboronic acid ester)-1,3-dioxolanes with iodobenzene (40) gave moderated to good yields of biaryls. The more hindered aryl halide 1-bromonaphtalane gave reduced yields with a diastereo selection of 5:4. The storeoselection indicates that this process may not be that useful.

Due to time constraints, the above reactions were not elaborated using enantiomerically pure 1,3-dioxolane to assess any stereoselectivity.

**4.8 Conclusions**

We have shown that trying to effect stereoselection through the use of chiral cyclic boronic acid esters is futile as they are readily hydrolysed under the reaction conditions. Building upon our TlOH work the direct use of aryl thalliums yielded no useful products. In addition the use of aryl thalliums have their own inherent problems. Finally the initial studies to use a chiral o-substituent in an aryl boronic acid derivative to control the stereoselectivity of the aryl bond formation was successful, but time constraints stopped any further work.
5

*Cis-trans* isomerisation and reductive elimination
5 Cis-trans isomerisation and reductive elimination

In the proposed mechanism of Suzuki cross-coupling reactions (Scheme 1.6), oxidative addition of an arylhalide to tetrakis triphenylphosphine gives a trans-aryl palladium halide complex (37). Transmetallation of this oxidative addition product produces a trans-diaryl palladium species (126), which can then give carbon-carbon coupling by a reductive elimination reaction that regenerates Pd(0). PdL₂R₂ complexes are square-planar complexes and may exist as cis- or trans-isomers. (Fig. 5.1)

![Figure 5.1](image)

Stille and Gill\textsuperscript{76} found that only the cis-isomer (173), of bis(triphenylphosphine), dimethyl palladium underwent reductive elimination. This meant that the trans- complex (174), which is produced after transmetallation, must first isomerise to the cis-isomer, before being able to reductively eliminate. Cis-isomers of diaryl- or dialkyl palladium complexes are often more favoured due to the avoidance of placing two ligands, with high trans influence (the alkyl or aryl group), opposite to each other.

Many mechanisms have been suggested for trans-cis isomerisation. These are affected by solvent, free phosphine ligand and the nature of transmetallating reagents. A polar solvent is necessary to stabilise the cis complex and a polar,
coordinating solvent is necessary for the isomerisation of a trans complex to the cis complex. However some trans-dialkyl palladium complexes do not isomerise, and give reductive elimination in relatively non polar solvents such as perdeutereobenzene and tetrachloroethane, when heated up to 50 °C.\(^\text{76a}\)

This probably accounts for the effect of solvents on the yields of coupled products (see Chapter 3-solvent effect in this thesis). It is common to use polar, coordinating solvents in Suzuki and Stille coupling reactions. DMF, DME, DMA and THF, are often used, most probably to assist in the rearrangements prior to reductive elimination.

Even though cis-trans isomerisation and reductive elimination have been widely investigated and reported,\(^\text{77}\) the suggested mechanisms require further elaboration in order to explain new observations and developments. Many suggested pathways can be summarised in one of three ways:

a) an associative mechanism, where a ligand or solvent coordination gives a five coordinated Pd-complex. Elimination of one of the ligands, after rearrangement, produces a four coordinated isomerised complex (Fig. 5.2).

![Figure 5.2](image-url)  
**Figure 5.2** Associative mechanism in cis-trans isomerisation.
b) a *dissociative mechanism*, where dissociation of one of the ligands, produces a tri-coordinate Pd-complex. Polar coordinating solvent maybe required to stabilise this coordinately unsaturated intermediate, before and after rearrangement. Re-coordination of a ligand produces the tetra coordinate, isomerised complex. (Fig. 5.3)

**Figure 5.3** Dissociative mechanism in *cis-trans* isomerisation.

c) promoted *trans-cis* isomerisation *via* binuclear palladium intermediate (Fig. 5.4), has also been suggested. While *trans*-complexes isomerise slowly, the addition of *cis*-complexes (180) can accelerate the isomerisation. The Pd<sup>a</sup>-Me, as opposed to the Pd<sup>b</sup>-Me<sup>'</sup> bond, breaks so as to avoid two ligands, of strong *trans* influence, being *trans* to each other in the final complexes (125') and (126').

**Figure 5.4** *Cis-* isomer promoted isomerisation of *trans*-dimethyl palladium complexes.
This mechanism may also occur between two trans complexes as shown in Figure 5.5. In this instance two trans complexes are converted into one cis and one trans complex, as an endothermic reaction.

**Figure 5.5**

Grignard or alkylithium transmetallation reagents effect trans-cis isomerisation. Below is the commonly suggested pathway for this type of isomerisation. (Fig. 5.6)

This proposed mechanism may explain why aryllithium or Grignard reagents give homo coupling as a by product in cross coupling reactions. The reactive aryllithium or Grignard reagent could react with the di-aryl substituted Pd(II) species and give a tri-aryl substituted intermediate (188). Elimination may then occur in one of two ways, regenerating the Mg or Li reagent or leading to Grignard derivatives of the initial aryl halide, and a new substituted Pd(II)
This latter route would give homo coupling of Grignard reagents (Fig. 5.7).

It is difficult to get experimental evidence to prove or disprove these proposed isomerisation mechanisms. It seems possible that different pathways exist for *trans-cis* isomerisations in the same reactions. Isomerisation may occur via one or a combination of the above-mentioned pathways.

Similar studies have been investigated concerning biaryl formation from the *cis*-diphenyl bis(triphenylphosphino)platinate(II) and the resulting observations led the authors to propose the following:-

a) *Trans -cis* isomerisation is necessary for reductive elimination.

b) Isomerisation may occur by the reorganisation of planar tetragonal structures to tetrahedral structures leading to a more stable *cis* isomer.
c) The coordination of triphenylphosphine to a planar tetragonal structure may give a trigonal bipyramidal structure. Dissociation of one of the ligands can then produce the more stable cis isomer.

The uncatalysed trans-cis isomerisation of Bis(pentafluorophenyl)bis-(tetrahydro-thiophene) palladium(II) complexes, in CDCl₃ or C₆D₆, supports a dissociative mechanism (Fig. 5.8).⁷⁹

![Figure 5.8](image)

Minniti observed that the cis- isomer (193) showed two IR. bands at 789 and 780 cm⁻¹ whereas the trans-isomer (190) showed a single band at 722 cm⁻¹. The ¹H NMR spectrum of trans-[Pd(C₆F₅)₂(tht)₂] in CDCl₃ showed a multiplet at δ 2.68 (-CH₂S-) and a multiplet at δ 1.86 (-CH₂- ). The corresponding multiplets for the methylene groups of the tht ligand, in the spectrum of the cis-isomer, were at δ 2.91 and 1.88. He found that this trans-cis isomerisation was an equilibrium and that the equilibrium lies on the side of the cis form.
Scheme 5.1 demonstrates the summarised pathways for cis-trans isomerisation, and reductive elimination of biaryls from the trans-diaryl palladium complex, produced from the transmetallation step of a palladium catalysed cross coupling reaction. In Suzuki and Stille cross-coupling reactions it is common to use polar coordinating solvents, and usually \( o \)-substituted aryl rings. Thus, in Suzuki and Stille methods, a dissociative mechanism (pathway A) is more likely, than the corresponding associative mechanism (pathway B), as polar solvents can stabilise coordinately unsaturated species, (195) and (196).

Scheme 5.1 Plausible trans-cis isomerisation of diaryl palladium complexes.
5.1 Atropisomerism and atropisomerisation of biaryls by reductive elimination from Pd(II) complexes

There are numerous molecules not containing an asymmetric carbon atom that show optical activity. However in such compounds that do not possess a centre of symmetry, they must have a plane of symmetry or an alternating axis of symmetry. It is the asymmetric character of the whole molecule, that we are concerned with. Thus, we can say that the asymmetric carbon atom is only one of a special case of asymmetric classes.

Among all the known types of molecules not containing asymmetric carbon atoms which may exist in optically active forms, the one which has been most extensively investigated is that of biaryl derivatives. Until 1907 it was believed that the two benzene rings of biaryl derivatives were extended and coplanar (Fig. 5.9).

![Figure 5.9](image_url)

In 1922 Christie and Kenner suggested co-axial but non-coplanar rings, comparable to allenic systems. The molecule now has two non-superimposable mirror images (Fig. 5.10).
Actually the delocalisation energy is at a maximum when the two aromatic rings are coplanar, but the steric interaction of the substituents on the 2, 2', 6 and 6' positions is also at a maximum. During rotation around the C(1)-C(1') bond, steric interactions decrease but delocalisation of the \( \pi \)-electrons also decreases. The molecule therefore adopts a conformation which is a compromise between these two opposing factors and the molecule exhibits atropisomerism. The term atropisomerism means optical isomers brought about by hindered rotation. In its original meaning the term was coined to encompass the optical isomers of the biphenyls.

Crystalline biphenyls contain a planar structure, but in the vapour phase the angle (\( \Phi \)) between the two aromatic rings is about 45\(^\circ\). The angle between the two aromatic rings plane is defined in figure 5.11.
Rotation around the sigma bond between the two aromatic rings gives a maximum energy at $\Theta = 0^\circ$, $180^\circ$ and $360^\circ$ because of steric interaction between the ortho hydrogen atoms. At $\Theta = 90^\circ$ and $270^\circ$ there are two smaller energy maximums which correspond to the conjugation minimum.

The steric interaction increases greatly when large ortho substituents are present. Isolation of the two enantiomeric conformations of biaryls is then possible.

According to the extend of the energy barrier to rotation, some of the biaryls give optically stable enantiomers at room temperature. The first isolated enantiomers, by Christie and Kenner were of 6, 6'-dinitrodiphenic acid. (Fig. 5.13)
Some biaryls that are optically active at room temperature when heated in solution may racemise and lose optical activity.  

Atropisomerisation, by controlled reductive elimination, from the diaryl Pd(II) species, is the main goal in Suzuki and Stille coupling. These coupling reactions work well for sterically non-hindered molecules. More hindered biaryl systems, especially with four $o$-substituents, could not be prepared under these conditions. This limitation is the main problem in investigating atropisomer selective reactions using transition metal catalysis.

5.2 Atropisomer selective palladium catalysed biaryl coupling

Despite the abundance of work with Suzuki and Stille biaryl coupling reactions, studies for atropisomer selective variants are still scarce. Godard et al. explain low yields in the formation of bulky biaryls, due to the unfavourable interaction between $o$-substituents on the boronic acids and $o$-substituents on the aryl halide, in the transmetallation, transition state (Figure 5.14).

![Figure 5.14](image-url)
Earlier, a similar transition state was proposed by Widdowson et al.\textsuperscript{86} for the palladium catalysed cross-coupling of aryl halide with aryl Grignard reagents.

Uemura has recently attempted some atropisomer selective Suzuki cross-coupling reactions between tricarbonyl(arene)chromium complexes and aryl boronic acids,\textsuperscript{31} or aryl Grignard reagents.\textsuperscript{87} It is known that oxidative addition of the carbon-halogen bond of the aryl halide to the palladium(0) is accelerated by coordination of an electron withdrawing tricarbonylchromium species. The reaction of tricarbonyl(2,6-disubstituted-1-bromobenzene)- chromium with \textit{ortho}-substituted arylboronic acids, in the presence of Pd(0) complexes gave mono Cr(CO)\textsubscript{3} complexes of biaryls, with extremely high stereo selectively, depending on the steric bulkiness of the \textit{ortho} substituents.

This method allowed the preparation of both axially chiral biaryls starting from a single, planar, chiral(arene)chromium complex. (Scheme 5.2)

\begin{center}
\textbf{Scheme 5.2} Synthesis of both Atropisomers of Axial biphenyls.
\end{center}
Uemura rationalised these atropisomer selective couplings as arising from cis-diarylpalladium complexes. Trans-diarylpalladium(II) complex \( \text{205} \) may give two possible conformations of the cis-isomer according to the substituents on the biaryl rings. (Scheme 5.3)

![Scheme 5.3. Proposed transition states for cross coupling.](image)

In the cis-isomer \( \text{206} \) sterically bulky L substituent standing face to face with the R substituent on the other aryl rings. The alternative cis-complex \( \text{207} \) which has the sterically bulky L substituent is syn-to the H atom, is less hindered.

Meyers version of the reaction has been studied by the same authors\textsuperscript{87} and it has been found that the diastereoselective synthesis of axially chiral biaryls via nucleophilic addition to (arene)chromium complexes with Grignard reagents is also possible. (Scheme 5.4)
The diastereoselectivity of the reaction was found to be dependent on the reaction temperature. Higher boiling solvents produce the sterically unfavoured syn-isomer (\ref{211}) predominantly, while lower temperature solvents produce the thermodynamically controlled anti-isomer (\ref{210}). The plausible reaction mechanism for this highly diastereoselectively process, is suggested to be similar to the proposed model by Meyers (Scheme 1.3) shown in scheme 5.5.

Scheme 5.4. Nucleophilic substitution of (arene)chromium complexes with aryl Grignard.
**Scheme 5.5** Proposed mechanism of nucleophilic substitution of (arene)-
chromium complexes with aryl Grignard.

There are not many examples of catalytic stereoselective biaryl couplings in the
literature. Hayashi has reported a nickel catalysed atropisomer selective biaryl
coupling between napthyl magnesium and napthyl halide, by the use of chiral ligands. The use of reactive Grignard reagents once again limited the reaction and only certain substrate combinations were possible (Scheme 5.6). Applications of this methodology to the coupling of complex functionalised aromatic compounds such as those found in natural products has not been reported.

**Scheme 5.6** Catalytic asymmetric synthesis of 1,1'-Binaphthyls.

Even after these results, the isomerisation, and the mechanism of the transition metal catalysed coupling reactions could not be fully elucidated and warrant further investigation.
6

Experimental
6 Experimental

6.1 General Experimental

(DCM) Dichloromethane was purified by distillation over calcium hydride at 38-39 °C before use.

(DMA) N,N-Dimethylacetamide was stored over molecular sieves under nitrogen.

(DMF) N,N-Dimethylformamide was stored over molecular sieves under nitrogen.

(IR) Infrared spectroscopy was detected as solutions in DCM by using Perkin Elmer 160 FT-IR spectrometer and thin films by using Perkin Elmer Paragon 100 spectrometer.

(MS) Mass spectroscopy was performed using a Kratos MS-25 spectrometer, and accurate mass were obtained using a Kratos MS-80 HR spectrometer.

(THF) Tetrahydrofuran was freshly distilled from potassium benzophenone ketyl before use.

10% TIOH(aq) was stored in a round bottom flask with a septum inlet, under a positive nitrogen atmosphere and removed via syringe by pressure of nitrogen.

1H-NMR (nuclear magnetic resonance spectra) were detected by using a Bruker AC 250 MHz spectrometer at 250 MHz. In the presentation of NMR data, spectra were recorded in CDCl₃ unless otherwise stated. Abbreviation δ represents chemical shift in ppm, s (singlet), d (doublet), t (triplet), m (multiplet). All coupling constants were measured in Hz.
Benzene was kept over sodium wire for a day before use.

Elemental analyses were performed using a Perkin Elmer 2400 CHN elemental analyser.

Ethane-1,2-diol was distilled at 90-92 °C (25 mmHg) before use.

Ethyl acetate was purified by distillation at 77-78 °C.

Flash column chromatography was performed using Merck 9385 60 silica gel, eluting with redistilled ethyl acetate / petroleum ether unless otherwise stated.

Melting points were determined using a Kofler hot stage apparatus.

p-Toluenesulfonic acid was dried by azeotroping with dry benzene, and vacuum dried, to give a brown solid mp. 38 °C.

Palladium catalysed coupling reactions were carried out under positive nitrogen pressure unless otherwise stated.

Petroleum ether was purified by distillation at 40-60 °C.

Purified compounds from the flash column chromatography were kept under high vacuum for 4-5 h before spectroscopic measurements, unless otherwise stated.

Pyridine was freshly distilled from calcium hydride at 114-116 °C before use.

Temperatures of -78°C was achieved using a solid carbon dioxide acetone slush bath, and of 80 °C controlled by a magnetic stirrer thermostat and oil bath.

Thallium compound reactions were manipulated in an efficient fume hood. Rubber gloves were worn at all times. The residues were collected in a glass bottle with addition of NaCl, because of the toxic nature of many thallium compounds.
Thin layer chromatography (TLC) was performed on Merck 5554 60F silica gel coated aluminium plates and detection was effected by dipping the plates in a ceric ammonium sulphate solution, and ultraviolet light.

Tri-n-butylborate was distilled under reduced pressure into a dry flask and kept under nitrogen pressure.

Triethylamine was freshly distilled from calcium hydride before use.

Triphenylphosphine was heated at 80 °C under water pump vacuum overnight before use.

Zinc chloride was crystallised from dioxane and stored over P₂O₅ in a dessicator.
6.2 Preparation of palladium(0) complexes.

6.2.1 Preparation of tetrakis(triphenylphosphine)palladium(0)\textsuperscript{88}

\[ \text{PdCl}_2 + 4 \text{PPh}_3 + \text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O} \rightarrow \text{Pd(PPH}_3)_4 \]

\[ \text{C}_{72}\text{H}_{60}\text{PdP}_3 = 1155 \text{ g mol}^{-1} \]

A mixture of palladium dichloride (0.70 g, 3.95 mmol), triphenylphosphine (5.25 g, 20 mmol) was warmed in DMSO (20 ml) under an atmosphere of nitrogen until dissolution had occurred. (oil bath ~140 °C). The reaction was removed from the bath and hydrazine hydrate (0.8 g, 16 mmol) added rapidly with vigorous stirring which was accompanied by the evolution of nitrogen. On cooling the yellow crystals were filtered under a nitrogen atmosphere, washed successively with two cold portions of EtOH (1 ml), then Et\(_2\)O (2 ml) and then dried under high vacuum to yield (4.1 g, 90\%). The complex was kept under nitrogen in the fridge due to its sensitivity to air and moisture. It can be handled for a short time in an oxygen atmosphere. A greenish colour shows the decomposition of the complex.

6.2.2 Preparation of dibenzylideneacetone (dba)\textsuperscript{89}
One half of a mixture of benzaldehyde (6.1 g, 0.05 mol) and acetone (4.6 g, 0.1 mol) was added to a cooled (20-25 °C) solution of NaOH (20 g, 0.5 mol) in water (50 ml) and ethanol (25 ml), stirring being maintained by the use of an a over head stirrer. In the first 2-3 mins a flocculent yellow precipitate developed. After 15 mins, the rest of the benzaldehyde/acetone mixture was added and vigorous stirring continued for 1.5 h. The precipitate was then isolated by filtration, washed with cold distilled water and then vacuum dried at room temperature. The crude material (8.2 g, 68 %) was recrystallised from hot ethyl acetate to yield (7.9 g, 67 %) as a yellow crystals. (mp. 110°C , Lit.89. 104-107 °C)

6.2.3 Preparation of bis(dibenzylideneacetone) palladium(0)\textsuperscript{36}

Sodium acetate was added to a hot \textit{(ca} 60 °C) methanolic solution of sodium chloropalladate and an excess of dibenzylideneacetone, (dba / Pd ≥ 3), and the mixture was allowed to cool, with stirring. A brownish crystalline complex,
(PhCH=CH-CO-CH=CHPh)₂-Pd, was precipitated, removed by filtration and washed successively with water and acetone. The dark brown-black complex was obtained in quantitative yield.

### 6.2.4 Preparation of tris(dibenzylideneacetone)dipalladium chloroform

\[
Pd(dba)₂ \xrightarrow{CHCl₃} Pd₂(dba)₃.CHCl₃
\]

C₂₂H₄₃O₃Pd₂Cl₃=1035 g.mol⁻¹

Recrystallization of \( Pd(dba)₂ \) from chloroform gave the above complex in 95-98% yield as a dark violet complex.

### 6.3 General methods for the preparation of arylboronic acids and derivatives

#### 6.3.1 Preparation of mesityl di-n-butylboronic acid ester (46)

\[
\text{A portion (8-10 ml) of bromomesitylene (20 g, 0.1 mol) in anhydrous THF (50 ml) was added from a dropping funnel to dry magnesium turnings (2.5 g, 0.11 mol) in}
\]
anhydrous THF (100 ml), under positive N₂ pressure in order to initiate a gentle reflux. The remaining bromomesitylene solution was then added dropwise, with stirring, so as to maintain a gentle reflux (~30 min). After complete addition and the spontaneous reaction had subsided, the mixture was refluxed for 1 hour, by which time most of the magnesium had reacted. After cooling to -78°C a solution of tri-n-butyl borate (35.0 ml, 0.13 mol) in anhydrous THF (50 ml) was added dropwise under nitrogen. After complete addition the mixture was warmed to room temperature and poured into ice-water and carefully neutralised with HCl 1 mol. dm⁻³ whilst maintaining the temperature at 0°C. The mixture was extracted with Et₂O and the combined etheral layers washed once with cold water, dried over MgSO₄, filtered and evaporated to give the ester (46), (24.5 g, 89 %) as a yellowish liquid.¹⁰

**1H-NMR** δ 6.8 (2H, s, H-3 and -5); 3.7 (4H, t, J=6.4, H-7); 2.6 (6H, m, 2×o-CH₃); 2.5 (3H, s, p-CH₃), 1.5 (4H, m, H-8); 1.3 (4H, m, H-9); 0.9 (6H, m, H-10), (MS EI+), 276 (M⁺) 220 (-Bu), 203, 162, 130, 119, 104. δmax., 3614, 2933, 2873, 1608, 1464, 1318, 1216, 1067, 1026 cm⁻¹

*NOTE:* Aryl -di-n-butylboronic acid esters are slightly air sensitive and hydrolyse to the related boronic acids.

The following aryldi-n-butylboronic acid esters were prepared by using the same method.

### 6.3.2 Phenyl-di-n-butylboronate (122a)

C₁₄H₂₃BO₂ = 234 g.mol⁻¹
(122a) was isolated as a yellowish liquid, 85%. **1H-NMR** \( \delta \ 7.75-7.45 \) (5H, m, ArH); \( \delta \ 3.64 \) (4H, t, J= 6.4 Hz, H-7); **170-130** (8H, m, H-8 and -9); \( \delta \ 0.94 \) (6H, t, J=7.0 Hz, H-10. **MS(EI+)**  234 (M\(^+\)), 177, 130, 116, 88,77. \( \nu_{\text{max.}} \), 3623, 2687, 1560, 1438, 1348, 1316, 1105, 1073, 1026 cm\(^{-1}\).

### 6.3.3 Preparation of mesitylboronic acid(39)

![Diagram of the preparation of mesitylboronic acid](image)

\( C_9H_{13}BO_2=164 \text{ g.mol}^{-1} \)

To stirred mesityl di-n-butyl boronic acid ester (46) was added dropwise 2M KOH(aq) until pH≥ 8. The resultant oily white precipitate was stirred for 15 min, before butanol was distilled off under vacuum. HCl (1N) was added dropwise to the residue in the distillation flask until pH 6, and the mixture left overnight at 4 °C to give a precipitate. The solid mesitylboronic acid (39) was filtered off, and recrystallised from water to give white crystals 75%, mp. 145-147 °C; (lit.\(^9\), 64%, 143-145 °C). **1H-NMR** \( \delta \ 6.8 \) (2H, s, H-3 and -5); **4.6** (2H, s, BOH); **2.4** (6H, s, 2xCH\(_3\)), **2.3** (3H, s, p-CH\(_3\)). **MS (EI+)**; 164 (M\(^+\)), 146 (-H\(_2\)O), 131 (-CH\(_3\)), 120, 105, 91. \( C_9H_{13}BO_2 \) requires 164.100 found 164.101 \( \nu_{\text{max.}} \), 3623, 3594, 2920, 2859, 1610, 1359, 1330, 1276, 1270, 1170, 1078 cm\(^{-1}\)

The following boronic acids were prepared by using the same method as for the preparation of mesitylboronic acid from mesityl-di-n-butylboronic acid ester.
6.3.4 Phenylboronic acid (73)

Phenylboronic acid (73) was isolated as white crystals, yield 60%, mp 217-219 (lit.93, 60%, 214-216 °C) 1H-NMR δ 7.75−7.40 (5H, m, ArH), 4.73 (2H, s, BOH). MS (EI+) (M+) 122 (m+), 104 (-H2O), 88, 77. υmax., 3642,1602, 1494, 1441, 1348, 1275, 1252, 1180, 1087 cm⁻¹

6.3.5 Preparation of 1-naphthylboronic acid (48)

The preparation of 1-naphthyl (48) and 2-methyl napthyl boronic acid and (51) were identical to that for mesityl boronic acid-di-n-butyl ester except that after the addition of n-butyl borate, the mixture was stirred at room temperature for 5 h. The mixture was then hydrolysed by the dropwise addition of HCl (1N) until pH 2. Extracted with diethyl ether (2 X 75 ml) and the combined ethereal layers washed
with water, dried over MgSO₄, filtered and evaporated to give the naphthylboronic acid (48). Which was recrystallised from water and isolated as yellowish crystals, yield 55% mp, 226°C, (lit², 219-225 °C), 1H-NMR δ 7.80 (3H, dd., J=8.0, 1.5 Hz, H-2, H-3 and H-4); 7.50-7.27 (4H, m, from H-6, to -9); 5.00 (2H, brs, BOH). MS (EI+) 172 (M⁺), 154 (-OH), 128 (-BOH), 115, 102, 77. C₁₀H₁₁BO₂ requires 173.0773 found 173.0786. υmax, 3683, 3591, 1507, 1348, 1322, 1274, 1210, 1143 cm⁻¹

6.3.6 Preparation of 2-methyl-1-naphthylboronic acid(51)

2-methyl-1-naphthylboronic acid (51) was prepared by using the same method as above

(51) was isolated as a yellowish crystals, yield, 68%, mp, 130 °C (lit, 125-127°C)³. 1H-NMR δ 7.80 (2H, dd., J=8.0, 1.7 Hz, H-3 and H-4); 7.50-7.27 (4H, m, H-6, -7, -8, and -9); 4.93 (2H, s, BOH), 2.58 (3H, s, CH₃), MS (EI+) 186 (M⁺), 169 (-OH), 141 (-BOH), 115. C₁₁H₁₁BO₂ requires 186.085 found 186.085. υmax, 3630, 3589, 1508, 1358, 1302 1274, 1215, 1145 cm⁻¹.
6.3.7 Preparation of 2-formylphenylboronic acid (77)\[^{94}\]

\[
\begin{align*}
\text{C}_7\text{H}_7\text{BO}_3 & \equiv 150 \text{ g mol}^{-1} \\
\end{align*}
\]

To a slight excess of Mg (2.4 g, 99 mmol) was added dropwise 2-(o-bromophenyl)-1,3-dioxolane (20.5 g, 90 mmol) under nitrogen in dry THF. The reflux was maintained for an additional 45 min, after the addition, with an oil bath. The cooled solution was transferred to a degassed solution of tri-n-butyl borate (40.51 g, 176 mmol) in dry THF (200 ml) at -78 °C. The reaction was stirred for 2 hours and then allowed to warm to room temperature before it was hydrolysed with 4 N HCl (200 ml). The solvent was removed and the milky precipitate was taken up in water (200 ml) and ether (200 ml). The organic phase was then extracted twice with 1 M NaOH (200 ml). The combined aqueous extracts were acidified to pH 1 with concentrated HCl before extraction with two portions of ether. The combined ethereal layers were dried over MgSO\(_4\), filtered and evaporated to give a 55%, mp. 112°C (lit.\[^{94}\] 65% ; 108-110°C) of the boronic acid (77) as a white foam. If necessary, white crystals could be obtained from cold CH\(_2\)Cl\(_2\). \textbf{\(^1\text{H NMR}\)} \textbf{8.98} (1H, s, CHO), \textbf{8.30} (1H, dd., J=8.0, 0.7 Hz, H-6 or H-3), \textbf{7.90} (1H, dd., J=7.3, 0.7 Hz, H-3 or H-6), \textbf{7.20} (2H, m, H-4 and H-5), \textbf{6.00} (2H, s, BOH), \textbf{MS(EI+)} 150 (M\(^+\)), 132(-OH), 104 (- BOH), 77 (-CHO). C\(_7\)H\(_7\)BO\(_3\) requires C, 56.37, H 4.69, found C 56.28, H4.69.\(\nu\) max, 3620, 3062, 1695, 1568, 1311 cm\(^{-1}\).
6.3.8 Preparation of mesitylboronic acid tri-methylene glycol ester\textsuperscript{90b} (47)

A mixture of mesityl-di-n-butyl borate (13.8 g, 50 mmol) and propane-1,3-diol (3.9 g, 50 mmol) was stirred at room temperature for 30 min. The milky white mixture was distilled under reduced pressure. After all the butanol had distilled, the product mesitylboronic acid trimethylene glycol ester was then distilled bp. 61°C, 5 mmHg, to give a colourless creamy solid 84%, mp, 39-40°C, \textbf{1H-NMR} \(\delta\) 6.77 (2H, s, ArH-3 and -5); 4.18 (4H, t, J=6.9 Hz, -H-4 and H-6); 2.32 (6H, s, 2x-o-CH3); 2.23 (3H, s, p-CH3); 2.09 (2H, m, H-5). \textbf{MS (EI\textsuperscript{+})} 204 (M+), 162, 146, 131, 120, 105. \(\nu\text{max}\), 3084, 1596, 1521, 1342 cm\(^{-1}\).

6.3.9 Preparation of napthylboronic acid dimethylene glycol ester.(2-naphthalene-1-yl-1,3,2-dioxaborinane)(50)

\(C_{13}H_{13}BO_2 = 212\ \text{g.mol}^{-1}\)
(50) was prepared using the same method as above and was isolated as a colourless liquid, 75%. 1H-NMR δ 7.73 (4H, m, ArH-6, -7, -8, and -9) 7.40-7.35 (3H, m, ArH-2, -3, and -4); 4.12 (4H, m, H-4 and H-6); 1.82 (2H, m, H-5) MS(EI+) 212(M+); 154 (M+-C3H6O); 127(M+-C3H6BO2). C13H17BO2 requires 212.1321 found 212.1320. υ max, 3082, 1584, 1525, 1248 cm⁻¹.

6.3.10 Preparation of o-(1,3-dioxolane-2-)phenyl-dimethylene-boronic acid ester (170)

\[
\text{CHO} \quad \begin{array}{c}
\text{HO} \\
\text{OH}
\end{array} \quad \text{HO} \\
\text{OH} \\
\text{B(O\text{\text{\text{\text{\text{\text{\text{Bu}}}}}}})_2}
\]

\[
\begin{array}{c}
\text{CHO} \\
\text{OH}
\end{array} \quad \text{HO} \\
\text{OH} \\
\text{B(O\text{\text{\text{\text{\text{\text{\text{Bu}}}}}}})_2}
\]

C11H13BO4= 220 g mol⁻¹

\( o\)-(1,3-Dioxolane-2-)phenyl-dimethylene-boronic acid ester (170) was prepared by two methods.

**Method 1:** To \( o\)-Formylphenylboronic acid (77) (0.75 g, 5 mmol) in benzene (30 ml) was added 1,2-ethanediol (0.68 g, 11 mmol). After stirring for 30 min at room temperature, the mixture was refluxed for 4 h, with water removal provided by a Dean-Stark apparatus. The cooled mixture was then filtered through silica and evaporation of the solvent yielded the product as a colourless liquid (0.89 g, 80%). 1H-NMR δ 7.78 (1H, dd., J=8.0, J'=1.0 Hz, ArH-2 or -5); 7.61 (1H, dd., J=7.6, J'= 0.6 Hz, ArH-5 or H-2); 7.45 (1H, td, J=7.3 Hz, J'= 1.5 Hz. ArH-3 or -4); 7.37, (1H,
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td, J=7.3, 1.5 Hz, ArH-4 or -3); 6.37 (1H, s, H-2); 4.35 (4H, s, H-4 and -5); 4.15-3.98 (4H, m, H-7 and -8), MS (EI+) 220 (M⁺), 192 (-CH₂CH₂-), 175 (-CH₂CH₂O), 160 (-CH₂CH₂O₂-), 148 (-dioxolane), 133, 118, 105. υ max, 3640, 2873, 1692, 1593, 1488, 1356, 1316, 1217, 1071 cm⁻¹

Method 2: To the o-(1,3-dioxolane-2-) phenyl-di-n-butylboronic acid ester (169) (5 g, 16 mmol) was added ethane-1,2-diol (1.25 g, 20 mmol). After stirring overnight the butanol was distilled under vacuum and the residue filtered through silica using ethyl acetate as the eluant. Evaporation of the solvent gave (170) 2.7 g, 75% yield as a colourless liquid. The spectral data were identical to that above.

6.3.11 Preparation of (o-4-methyl-1,3-dioxolane-2-)phenyl-4'-methyl-dimethylene-boronic acid ester (172)

(172) was prepared according to method 2 above, as a 1:1 mixture of diastereoisomers from commercial 1,2-propanediol.

\[
\begin{align*}
\text{C}_{13}\text{H}_{17}\text{BO}_{4} &= 248 \text{ g.mol}^{-1} \\
\end{align*}
\]

Isolated as a colourless liquid. 1H-NMR $\delta$ 7.94 (1H, dd., J= 6.4, J'= 2.1 Hz, ArH-2 or -5); 7.86 (1H, dd., J=6.10, 2.10 Hz, ArH-5 or -2); 7.60-7.53 (2H, m, ArH-3 and H-4); 6.45 and 6.39 (1H, s, H-2); 4.83-4.61 (2H, m, H-4 and H-5a or 5b), 4.5-4.3, 4.00-3.8 and 3.62-3.5 (4H, m, H-5a or -5b, H-7 and H-8), 1.45-1.30 (6H, m, 2x-
CH₃). MS (EI⁺) (M⁺), 248 (-CH₂CHCH₃), 189 (-OCH₂CHCH₃), 174 (C₃H₆O₂), 163, (C₃H₆BO₂), 146, 133, 117, 105. υₓ max, 2901, 2687, 1692, 1593, 1489, 1445, 1377, 1356, 1316, 1217 cm⁻¹.

6.3.12 Preparation of o- (4-methyl-1,3-dioxolane)phenyl-di-n-butylboronic acid ester(171)

A similar method to that used for the synthesis of 2-formylphenylboronic acid was followed, using 4-methyl-2-bromophenyl-1,3-dioxolane (22.9 g, 90 mmol) and after mixing with tri-n-butyl borate at -78°C, the reaction was stirred for 5 hours at this temperature. The mixture allowed to warm to (~ -10, -5 °C) and then poured onto ice cold water and extracted immediately with Et₂O (2 x 100 ml) while still cold. *

The combined ethereal layers were dried over MgSO₄, and filtered through a short plug of silica (10 g). Evaporation of the solvent yielded 23 g, 80% of the boronic acid ester (171) as a yellowish oil. (An analytical sample was prepared via flash column chromatography eluting with EtOAc). 1H-NMR 8 7.75-7.25 (4H, m, ArH-2 to -5), 6.05, 5.95 and 5.87 (1H, s, H-2), 4.45-4.00 (3H, m, H-4 and H-5); 3.80-3.45 (4H, m. H-7), 1.60-1.30 (8H, m, H-8 and H-9), 0.95-1.05 (9H, m, 3x-CH₃). MS (EI⁺) 319 (M⁺), 263 (-Bu), 205 (-Bu), 189 (-OH). 174 (-OH), 162 (-B), 149,
133, 105. $\nu_{\text{max}}$, 3614, 2873, 1692, 1593, 1488, 1356, 1274, 1204, 1119, 1071, 1038 cm$^{-1}$.

*NOTE:* Di-n-butylboronate ester was not stable to water at room temperature, slow hydrolysis was observed when it was extracted at ambient temperature.

\[
\begin{align*}
\text{B(O\text{Bu})}_3\text{H} & \xrightarrow{\text{Mg/THF}} \text{B(O\text{Bu})}_2\text{H} \xrightarrow{\text{RT}} \text{H}_2\text{O} \xrightarrow{\text{CHO}} \text{H}_2\text{O} \xrightarrow{\text{CHO}} \text{H}_2\text{O} \xrightarrow{\text{CHO}} \text{H}_2\text{O} \\
\end{align*}
\]

**6.3.13 Preparation of 2-(o-phenyl-boronic acid-di-n-butyl ester)-1,3-dioxolane(169)**

\[
\begin{align*}
\text{C}_{17}\text{H}_{27}\text{B} \xrightarrow{\text{Mg/THF}} \text{C}_{17}\text{H}_{27}\text{B} \xrightarrow{\text{B(O\text{Bu})}_3/-78^\circ C} \text{C}_{17}\text{H}_{27}\text{B} \\
\end{align*}
\]

2-(o-phenyl-boronic acid-di-n-butyl ester)-1,3-dioxolane was prepared *via* the above method to yield 169 as a yellowish liquid 21.5 g. 78 %. $1\text{H}-\text{NMR}$ $\delta$ 7.54 (2H, dt, J=8.0, 1.0 Hz, ArH-3 and -4) 7.30 (1H, dd, J=8.0, 1.0 Hz, ArH-2 or H-5); 7.18 (1H, dd, J=8.0, 1.0 Hz ArH-5 or H-2); 6.12 (1H, s, H-2); 4.18 (4H, m, H-4 and -5); 3.58 (4H, t, J=4.5 Hz, H-7); 1.49 (4H, m, H-8), 1.32 (4H, m, H-9); 0.94 (6H, t, J=6.0 Hz, 2x-CH$_3$), MS (EI$^+$) 261 (M$^+$ -CH$_2$CH$_2$O-), 205 (-Bu),189 (-BuO), 149, 133, 105. $\nu_{\text{max}}$, 3110, 3089, 1621, 1376, 1121 cm$^{-1}$.
6.4 Preparation of phenyltriflate (59)\textsuperscript{44}

\[
\text{C}_7\text{H}_5\text{SO}_3\text{F}_3= 226 \text{ g.mol}^{-1}
\]

To a solution of phenol (9.49 g, 0.1 mol), in anhydrous pyridine (50 ml) was slowly added trifluoromethanesulfonic anhydride (0.1 mol) at 0 °C. The resultant mixture was stirred at 0 °C for 5 min. and then allowed to warm to room temperature and stirred at this temperature for 25 h. The mixture was poured into water and extracted with ether. The ether extract was washed sequentially with water, 10 % aqueous hydrochloric acid solution and brine. Dried over MgSO\textsubscript{4} and concentrated to yield an oil (85%)

The spectroscopic data was in full agreement with the literature.\textsuperscript{44}.

6.5 Preparation of aryldiazonium salts

6.5.1 Preparation of phenyldiazonium fluoroborate (72)\textsuperscript{95}

A mixture of concentrated HCl (0.4 ml) and 48% hydrofluoric acid (0.05 g) were placed in a plastic flask which stood in an ice-salt bath (−10 to -15 °C). After the slow addition of freshly distilled aniline (0.93 g, 10 mmol), the solution was diazotized with sodium nitrite (0.7 g), with stirring, while the temperature was kept at around 0°C. When all the sodium nitrite had been added, boron trifluoride from a
cylinder was introduced, via syringe until precipitation of the diazonium fluoroborate was completed. When the temperature increased, dry ice was added to the solution to control the temperature. The diazotized solution was filtered through a cold sintered glass filter. The precipitate was washed with ice water (1 ml) and ice-cold methanol (1 ml), followed by several washing with cold ether before drying under vacuum to give a yellowish crystalline compound (72), that was kept in the fridge.

6.5.2 Preparation of phenyldiazonium chloride (70)\textsuperscript{96}

\[
\text{NH}_2 \quad \text{N}_2^+ \quad \text{Cl}^- \\
\begin{array}{c}
\text{NaNO}_2, 3 \text{HCl} \\
\text{H}_2\text{O}
\end{array}
\]

A solution of freshly distilled aniline (0.102 g, 1.1 mmol) in dioxane was added dropwise to an ice-salt cooled flask containing conc. HCl (2 ml) and AcOH (2 ml) with stirring. The solution was diazotized with the slow addition of sodium nitrite (0.103 g, 1.5 mmol). The mixture was stirred for 15 mins at this temperature and then either a) or b) was followed:

a) Dry dioxane (15 ml) was added and the phenyldiazonium chloride precipitate was filtered before immediate coupling attempts with aryl boronic acids.

b) The solution was used directly in Suzuki coupling reactions.
6.5.3 Preparation of phenyldiazonium bisulphate

A solution of sodium nitrite (0.138 g, 20 mmol) in concentrated H$_2$SO$_4$ (3 ml) was added to a solution of freshly distilled aniline (0.140 g, 1.5 mmol) in AcOH (20 ml) cooled in an ice-salt bath with vigorous stirring. Then either a) or b) was followed:

a) The cold solution was filtered from sodium bisulphate and immediately used in coupling reactions.

b) The solution was used directly in Suzuki coupling reactions.

6.6 Preparation of dihydrobenzoboradiazoles.

6.6.1 2-Phenyl-1,3-dihydro-2,1,3-benzoboradiazole(158)

Equimolar amounts of phenylboronic acid (73) (2.42 g, 2 mmol) and phenylenediamine (2.16 g, 2 mmol) were dissolved in toluene (30 ml) and heated to 110 °C. The water was removed with a Dean-Stark apparatus. After all the water had been removed, excess toluene was distilled at reduced pressure. The product was filtered, washed with pentane, and recrystallized from carbon tetrachloride to give greenish crystals, yield 90%, mp, 218 °C, (lit. 98 204 to 216 °C) $^1$H NMR $\delta$ 7.6-7.3
(5H, m, ArH-10 to -14), 6.75 (4H, s, ArH-5 to -8), 3.39 (2H, s, 2x-NH), MS (EI+)
194 (M+), 173, 166, 132, 108, 97, $\nu_{\text{max}}$, 3474, 1514, 1360, 1274, 1256, 1016 cm$^{-1}$

### 6.6.2 2-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-benzo-1,3,2-
diazaborole (162)$^{72b}$

2-(2,4,6-trimethyl-phenyl)-2,3-dihydro-1H-benzo-1,3,2-diazaborole was prepared in
a similar fashion to the above method and isolated as yellowish crystals, yield 45%,
mp. 145 °C, (lit.$^{72b}$ 141°C), $^1$H NMR $^6$81 (2H, s, H-11 and -13), 6.74 (4H, s, H-5
to -8), 3.34 (2H, s, 2x-NH), 2.33 (6H, s, 2x-CH$_3$), 2.25 (3H, s, p-CH$_3$), MS (EI+)
236 (M$^+$), 220 (-15), 205 (-30), 164, 146, 108, 91. $\nu_{\text{max}}$ 3426, 3348, 2356, 1622,
1503, 1274, 1256 cm$^{-1}$.
6.7 General preparation of tricarbonyl(arene)-chromium complexes$^{99,87}$

A mixture of bromomesitylene (2.0 g, 10 mmol) and Cr(CO)$_6$ (3.3 g, 15 mmol) in dibutyl ether (50 ml), CH$_3$CN (1 ml), THF (5 ml) was heated to reflux for 48 h under nitrogen. After cooling room to temperature the mixture was filtered to remove unreacted Cr(CO)$_6$ and solvents evaporated to give crude (82) (40%) (the remaining hexacarbonylchromium was removed by distillation). The crude product was purified by column chromatography ethyl acetate / petroleum ether (1:3) as the eluant to give (82) (28 %) as a greenish crystals. 1H NMR $\delta$ 6.90 (2H, brs, H-3 and -5), 2.36 (6H, brs, 2xo-CH$_3$), 2.22 (3H, brs, p-CH$_3$). MS (EI+) 287 (M+ -2CO), 233, 198, 119, 93, 52
6.8 Preparation of N-co-ordinated oxidative addition products

6.8.1 Di-µ-bromobis[2-(4',4'-dimethyl-2'-oxazolinyl) phenyl, 1-C,3'-N]dipalladium (92) \(^{53a}\)

Ortho-bromophenyl-4,4-dimethyl oxazoline (0.76 g, 3 mmol) and Pd\(_2\)(dba)\(_3\).CHCl\(_3\) (3.1 g, 3 mmol) were dissolved in dry degassed benzene (25 ml), and the brownish solution kept at 60 °C for 30 mins. under nitrogen. After cooling to room temperature the resultant precipitate was filtered, washed with petroleum. ether and vacuum dried. Yield 1.85 g, 85%. (lit.\(^{53a}\) 92%). \(\text{\textit{\textbf{1H NMR}}} \delta 7.60 \) (1H, dd, J=8.0, 0.6 Hz, ArH-3 or -6), 7.29 (1H, dd, J= 8.0, 0.6 Hz H-6 or H-3), 7.05 (2H, m, H-4 and H-5), 4.35 (2H, s, H-5), 1.54 (6H, s, 2x-CH\(_3\)), MS (EI+) 721 (M+), 641 (- Br), 535 (2x Br), 460, 391, 307, 280, 254. \(\text{\textit{\textbf{\upsilon max}}} 2966, 1628, 1596, 1579, 1482,1458, 1437, 1405, 1368, 1330, 1253, 1220.\)
6.8.2 Preparation of bromo[2-oxazolinyl]phenyl, 1-C, 3'-N]palladium (II) triphenylphosphine (94)

A mixture of tetrakis(triphenylphosphine)palladium (0), (2.31 g 2 mmol) and ortho-bromophenyl oxazoline (0.46 g 2 mmol) in dry degassed benzene (30 ml) was heated overnight in a sealed tube. After cooling to room temperature, the solvent was evaporated, and the remaining solid was washed with a little cold ether\textsuperscript{101} to yield (94) 1 g 88%. \textsuperscript{1}H NMR \textit{δ} 7.75 (6H, m, PhH), 7.40-7.22 (9H, m, Ph- H), 6.90 (1H, dt, J= 8.0, 0.6 Hz, ArH -4 or -5), 6.16 (1H, dt, J=8.0, 0.6 Hz, ArH-5 or -4), 6.40 (2H, dd, J= 7.2, 1.0 Hz, ArH-3 and -6), 4.72 (2H, t, J=9.0 Hz, ArH-5), 4.30 (2H, t, J=9.0 Hz H-4), MS (EI+) 595 (M\textsuperscript{+}), 514 (- Br), 460 (-ox.), 443, 408, 391, 367, 339.
6.9 Preparation of 2-(o-halo phenyl)-1,3-dioxolanes

6.9.1 Preparation of 2-(o-bromophenyl)-1-3-dioxolane 97

A mixture of 2-bromobenzaldehyde (23.5 ml, 203 mmol), ethylene glycol (13.5 ml, 240 mmol), and p-toluene sulfonic acid (1.9 g, 10 mmol) in benzene (150 ml) was refluxed for 6 h, water removal being supplied by a Dean Stark apparatus. Evaporation of the solvent and filtration of the crude product over silica gel yielded (40.7 g, 179 mmol, 88%) of compound (97) as a yellowish oil. \( \text{\textsuperscript{1}H NMR} \ \delta 7.60 \text{ (1 H, dd, } J=8.0, 1.0 \text{ Hz, ArH-3 or H-6); 7.55 \text{ (1 H, dd, } J=8.0, 1.0 \text{ Hz, H-6 or ArH-3); 7.32 \text{ (1H, td, } J=8.0, 0.5 \text{ Hz, ArH-4 or -5); 7.21 \text{ (1 H, td, } J=8.0, 0.5 \text{ Hz, ArH-5 or -4); 6.10 \text{ (1H, s, H-2); 4.20-4.00 \text{ (4H, m, H-4 and -5), MS (EI\textsuperscript{+}), 229(M+)\textsuperscript{+}}; 185 \text{ (M\textsuperscript{+}-CH\textsubscript{2}-CH\textsubscript{2}-O-), 156 (-dioxolane), 149 (-Br).} \) \ \text{\textsuperscript{\nu}max} \ 1274, 1188, 1117, 1074 \text{ cm\textsuperscript{-1}}.

The following related compounds were prepared under similar reaction conditions as mixtures of diastereoisomers.
6.9.2 4-methyl-2-(o-bromophenyl)-1,3-dioxolane (102)

(102) Was isolated as a yellowish oil (85%) in a diastereomeric mixture 1:1, \( ^1H \) NMR, \( \delta \) 7.67 (1H, dd, J=7.6, 1.8 Hz, ArH-3 or -6); 7.55 (1H, dd, J=9.2, 1.2 Hz ArH-6 or -3); 7.37-7.29 (1H, m, ArH-4 or -5); 7.24-7.16 (1H, m, ArH-5 or -4); 6.25 and 6.12 (1H, s, H-2); 4.44-4.33 (1H, m, H-4); 4.29 (0.5H, d, J=8.0, H-5a or H-5b); 4.15 (0.5H, dd, J=8.0, 2.4 Hz, H-5a or H-5b); 3.62 (1H, s, H-5a or H-5b) 1.39 and 1.37 (3H, d, J=8.0 Hz, -CH₃). \( \text{MS(EI}^+ \text{)} \) 243 (M⁺); 183(M⁺-CH₃CHCH₂O); 105. \( \text{C}_{10}\text{H}_{11}\text{O}_2\text{Br} \) requires 243.0020 found 243.0023. \( \nu \text{max.} \), 3684, 1592, 1571, 1471, 1443, 1379, 1275, 1256, 1210, 1125, 1094 cm⁻¹.

6.9.3 4-methyl-2-(o-iodophenyl)-1,3-dioxolane (101)
(101) Was isolated as a yellowish oil (86%) in a diastereomeric mixture (1:1). $^1$H NMR, $\delta$ 7.67 (1H, dd, J=8.0, 1.0 Hz, ArH-3 or -6); 7.57 (1H, dd, J=8.0, 1.0 Hz ArH-6 or -3); 7.34-7.22 (2H, m, ArH-4 and -5); 6.25 and 6.15 (1H, s, H-2), 4.42-4.40 (1H, m, H-4); 4.28 - 4.15 (1H, m, H-5a or -5b); 3.62 (1H, m, H-5b or -5a), 1.42 and 1.40 (3H, d, J=9.0 Hz, -CH$_3$). MS (EI$^+$) 290 (M$^+$), 231 (-C$_3$H$_6$O), 222, 152 (-Br), 128,119, 104. C$_{10}$H$_{11}$O$_2$I requires 289.9805 found 289.9803. $\nu_{\text{max}}$, 3683, 3582, 2931, 2880, 1697, 1585, 1379, 1276, 1211, 1122, 1090, 1013 cm$^{-1}$.

6.9.4 4,5-dimethyl-2-(o-bromophenyl)-1,3-dioxolane (103)

(103) Was isolated as a colourless liquid in a diastereomeric mixture (1:2:1). $^1$H NMR- $\delta$ 7.64 (1H, dd, J=7.6, 1.8 Hz, ArH-6 or -3); 7.54 (1H, dd, J=7.3 , 1.2 Hz, ArH-3 or -6); 7.33 (2H, td, J=7.3, 2.0 Hz ArH-5 and -4); 6.37, 6.25 and 6.14 (1H, s, H-2); 4.35 (0.5H, m, H-4 or H-5); 4.15 (0.5H, m, H-5 or H-4); 3.27 (1H, m, H-5 or H-4), 1.39, 1.33 and 1.25 (6H, 3xd, J=5.8 and 6.10 Hz cis-and trans-2x-CH$_3$), MS (EI$^+$) 257 (M$^+$), 185 (-C$_4$H$_8$O$_2$), 177 (-Br), 157, 133, 105. C$_{11}$H$_{13}$O$_2$Br requires 257.0177 found 257.0180. $\nu_{\text{max}}$, 2886, 1571, 1439, 1379, 1274, 1210, 1094, 1040 cm$^{-1}$.
6.9.5 4,5-dimethyl-2-(o-iodophenyl)-1,3-dioxolane

\[
\begin{align*}
\text{CHO} & \quad \text{HO} \quad \text{OH} \\
\text{Dean Stark / Benzene} & \quad \text{cat. TsOH}
\end{align*}
\]

\[C_{11}H_{13}O_2I=304 \text{ g.mol}^{-1}\]

1H-NMR- \(\delta\) 7.80 (1H, dd, J=8.0, 1.5 Hz, ArH-6 or -3); 7.60 (1H, dd, J=8.0, 2.0 Hz, ArH-3 or -6); 7.35 (1H, td, J=8.0, 2.0 Hz, ArH-4 or -5); 7.10 (1H, td, J=8.0, 1.5 Hz ArH-5 or -4), 6.05 and 5.93 (1H, 2xs, H-2); 4.38-4.27 (1H, m, H-4 or H-5); 4.23-4.14 (1H, m, H-5 or H-4), 1.35, 1.30 and 1.22 (6H, 3xd, J=6.0 and 7.2 Hz cis- trans-2x-CH3), MS (EI\(^+\)) 304 (M\(^+\)), 248 (-CH3-CH-CH-CH3), 232, 216, 204, 121, 89, 77.

6.9.6 4,6-dimethyl-2-(o-bromophenyl)-1,3-dioxane

\[
\begin{align*}
\text{CHO} & \quad \text{HO} \quad \text{OH} \\
\text{Dean Stark / Benzene} & \quad \text{cat. TsOH}
\end{align*}
\]

\[C_{12}H_{15}O_2Br= 271 \text{ g.mol}^{-1}\]

4,6-dimethyl-2-(o-bromophenyl)-1,3-dioxane was isolated as a colourless liquid in 82% yield. 1H-NMR-\(\delta\) 7.76 (1H, dd, J=7.9, 1.8, ArH-6 or -3); 7.53 (1H, dd, J= 7.9, 1.8 Hz, ArH-3 or -6); 7.34 (1H, td, J=7.3, 0.9 Hz, ArH-4 or ArH-5), 7.17 (1H, td,
J=7.6, 1.8 Hz, ArH-5 or ArH-4), 6.12 and 5.79 (1H, 2xs, H-2); 5.53-5.40 and 4.30-4.18 (1H, m, H-4 or H-6), 4.60-3.90 (1H, m, H-6 or H-4); 1.66-1.40 (2H, m, H-5); 1.34 and 1.32 (6H, 2xd, J=7.4 Hz 2x-CH3).

MS (EI+), 271(M+), 185(M+ -C5H10O), 157, 115, 105. C12H15O2Br requires 271.0333 found 271.0330. \( \nu_{\text{max}} \), 2934, 2688, 1697, 1594, 1571, 1376, 1350, 1336, 1274, 1174, 1131, 1067, 1019 cm\(^{-1}\).

6.10 Preparation of aryloxazolines.

6.10.1 2-(o-bromophenyl)-2-oxazoline (93)\(^{18}\)

\[
\begin{align*}
\text{CN} & \quad \text{HO} \\
\text{Br} & \quad \text{H}_2\text{N} \\
\text{C}_6\text{H}_5\text{Cl} / \text{reflux} & \quad \text{cat. ZnCl}_2 \\
\end{align*}
\]

\[
\text{C}_9\text{H}_8\text{NOBr}=226 \text{ g.mol}^{-1}
\]

2-Bromobenzonitrile (5.13 g, 0.028 mol) was added to a solution of ethanol amine (3 g, 0.05 mol) in chlorobenzene (25 ml) with a catalytic amount of ZnCl\(_2\) (1.1 mg, 0.077 mmol). The reaction was brought to reflux for 18 h. The chlorobenzene was removed by evaporation to yield a brown oil. The residue was chromatographed on silica gel with dichloromethane as eluant to yield (93) as a colourless oil.\(^{102}\) (4.2 g, 65 %) 1H-NMR. \( \delta \) 7.7-7.57 (2H, m, ArH-6 and ArH-3), 7.35-7.24 (2H, m, ArH-4 and ArH-5); 4.42 (2H, t, J=8.0 Hz, H-5); 4.08 (2H, t, J=8.0 Hz, H-4), MS (EI+), (M\(^+\)) 226, 195, 183,169,155, 116, 102, C\(_9\)H\(_8\)NOBr requires 225.9867 found 225.9863, \( \nu_{\text{max}} \), 1650, 1357, 1266, 1240, 1189, 1119, 1094, 1025 cm\(^{-1}\).
6.10.2 2-(o-Bromophenyl)-4,4-dimethyl-2-oxazoline (91)

\[
\begin{align*}
\text{CN} & \quad \text{HO}-
\begin{array}{c}
\text{NH}_2 \\
\text{cat.} \text{ZnCl}_2
\end{array}

c_6h_5cl / \text{reflux}
\end{align*}
\]

\[C_{11}H_{12}NOBr= 254 \text{ g.mol}^{-1}\]

2(o-Bromophenyl)-4,4-dimethyl-2-oxazoline was prepared using a similar method to that above, using 2-amino-2-methylpropanol and was isolated as a colourless oil (76%). 1H-NMR δ 7.59 (2H, dd, J=7.6, 1.8 Hz, H-6 and ArH-3), 7.26 (2H, td, J= 7.3, 1.5, ArH-4 and ArH-5); 4.10 (2H, s, H-5); 1.37 (6H, s, 2x-CH3). MS (EI+), 254 (M+), 238 (M+ - Me), 223 (M+ -2 x Me), 210, 182, 155. [C_{11}H_{12}NOBr]H+ requires 254.0180 found 254.0179, \upsilon_{\text{max}} , 3663 2326, 2230, 1934, 1818, 1958, 1588, 1469, 1385, 1313, cm\text{^{-1}}.

6.11 Preparation of 10%TIOH(aq)

\[
\begin{align*}
\text{TIOCOH} & \quad \text{KOH} \\
\rightarrow & \text{TIOH}
\end{align*}
\]

Thallium (I) hydroxide was precipitated from an approximately 6 N solution of thallium (I) formate (2.5 g, 10 mmol) in freshly distilled degassed water (1.70 ml) by the slow addition of approximately 10 N potassium hydroxide solution (1.2 g, 30 mmol) in distilled water (3 ml) freed from carbonate by bubbling nitrogen through the solution. The mixture was stirred until the flask had cooled to room temperature (~30 mins, external cooling also possible) to give a yellow crystalline precipitate.
The precipitate was sinter filtered under a nitrogen atmosphere, washed with a small portion of cold water (0.5 ml) to yield (1.66 g, 7.5 mmol) of yellow crystalline TlOH(s). A 10 % (aq.) solution was made immediately with freshly distilled water, degassed and kept under nitrogen.¹⁰³

NOTE: After a week a precipitate would develop in this solution and yields were affected. Consequently degassed solutions were kept for no longer than 1 week.

*During these studies, when thallium compounds were involved, all experiments were performed in an efficient fume hood and rubber gloves were worn, because most thallium compounds are toxic. Work up residues were collected in a glass bottle and sent for disposal.

6.12 Preparation of arylthallium compounds.

6.12.1 Dimesitylthallium bromide (156b)¹⁰⁴

![Chemical Reaction Diagram]

A solution of mesityl magnesium bromide, prepared from bromomesitylene (2.4 g, 12 mmol) and magnesium turnings (0.35 g, 14 mmol) in ether (25 ml) was added to thallium (III) chloride (1.56 g, 5 mmol) in ether (15 ml) with stirring at room temperature. The mixture was allowed to stir overnight. After removal of solvent
and addition of dilute acetic acid the separated solid was extracted with hot pyridine. Evaporation gave crude dimesitylthallium bromide as a white powder, 80% (mp. 160-180 °C, decomp.)

*Preparation of same molecule using mesityl magnesium bromide and thallium(I) chloride, Goddard's method 70b was attempted and gave a similar results.

6.12.2 Diphenylthallium bromide (156a)

\[
\text{MgBr}_2 \xrightarrow{\text{TlBr}_2 \text{ or TlBr}_3} \text{Ph}_2\text{TiBr}_2
\]

Diphenylthallium bromide was prepared in a similar procedure to that described above using phenyl magnesiumbromide. The component (156a) was isolated as a yellowish crystalline solid (78%), mp 150-160 °C, decomp.(lit.103 176 °C)

6.12.3 Preparation of arylthallium(III) chlorides

6.12.4 Phenylthallium dichloride (155a) 70c

\[
\text{Ph}_2\text{B(OH)}_2 \xrightarrow{\text{TlCl}_3} \text{Ph}_2\text{TiCl}_2
\]
A solution of phenylboronic acid (39) (1.0 g, 8.2 mmol), TlCl₃ (7.5 g, 24 mmol), in water (15 ml) were held at 100 °C for ca. 2 min. The resulting white precipitate was filtered, washed with water, and dried under vacuum to give (155a) as a white powder, (80 %), mp: 239 °C, decomp. (lit. 70 %, 235°C).

6.12.5 Mesitylthallium(III) chloride (155b), 70e

\[
\begin{align*}
\text{B(OH)₂} & \xrightarrow{TlCl₃} \text{TlCl}_₂
\end{align*}
\]

Mesitylthallium(III) chloride (155b) was prepared in a similar procedure to that above. The component (155b) was isolated as a white powder in 55 % yield. mp., 210 °C, decomp.

6.12.6 Mesitylthallium(III) acetate, 70e(153)

\[
\begin{align*}
\text{TlCl}_₂ & \xrightarrow{\text{AgOAc}} \text{TlOAc}_{2}
\end{align*}
\]

An excess of AgOAc (4 g, 11.4 mmol), was slowly added to a solution of (155b), (1.0 g, 2.54 mmol), contained in MeOH (35 ml), and the mixture was stirred for 5 h at ambient temperature. After filtration, removal of the solvent under vacuum yielded a white powder (35%).

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6.12.7 Mesitylthallium di-trifluoroacetate (154).

Mesitylene (1.2 g, 10 mmol) was added slowly to a stirred solution of thallium(III) trifluoroacetate (5.5 g, 10 mmol) in trifluoroacetic acid (15 ml) at room temperature. After stirring for two hours the white solid was filtered, washed with a little 1,2-dichloroethane (1 ml), and vacuum dried. (4.4 g, 85%) yield (lit.\textsuperscript{70c}, 94%).
6.13 General procedure for palladium catalysed coupling reactions of aryl electrophiles with aryl nucleophiles

*Spectroscopic data for all coupled biaryls are given in 6.13.

6.13.1 General procedure for Suzuki coupling reactions

A solution of tetrakis-triphenylphosphinepalladium(0) (0.023 g 0.02 mmol), haloarene (1 mmol) and base (1.5 mmol) were stirred in solvent (8 ml) for 5 mins, before the addition of solution of aryl boronic acid, in solvent(2 ml) via syringe through a septum inlet.

The mixture was heated in an oil bath at 80 °C with stirring usually for 6 h. The flask was cooled to room temperature, the product extracted with benzene, washed with brine, and dried over MgSO4. Finally, the product was isolated by silica gel column chromatography using ethyl acetate / petroleum ether as eluant.
6.13.2 General procedure for the study of *base effects at ambient temperature* in the Suzuki coupling reactions (for Table 2.3, pg. 22)

The above Suzuki coupling reaction procedure was followed, but without heating up to 80 °C. The reaction was allowed to run at room temperature in DMF as solvent for 12 h with the inclusion of various bases.

In the case of 10 % TIOH(aq) (Table 2.3, page 22), base (3.5 ml) was added after the addition of DMF, dropwise through a septum inlet with a syringe and additional water was not employed.
6.13.3 General procedure for the study of concentration effects of TlOH(aq) at ambient temperature (for Table 2.4, pg. 23)

A solution of Pd(PPh₃)₄ (0.023 g, 0.02 mmol), haloarene (1 mmol), arylboronic acid (1.1 mmol) and solvent (8 ml) under positive nitrogen pressure, were stirred for 5 min, before the dropwise addition of n% TlOH(aq), (~1 min) through the septum inlet with a syringe. The mixture was allowed to stir for 12 h at room temperature. The mixture was extracted with benzene (2 x 25 ml), washed with brine, and dried over MgSO₄. Finally, solvent was evaporated and the product was isolated by silica gel column chromatography using ethyl acetate / petroleum ether an eluant.

In solid base cases, base was added to the flask containing the aryl halide and arylboronic acid. Additional water was not employed.
**6.13.4 General procedure for the study of TIOH promoted coupling of aryl halide with mesityl boronic acid, in DMA** (For table 2.6, pg. 27)

![Chemical reaction diagram](image)

To a stirred solution of Pd(PPh$_3$)$_4$ (0.023 g, 0.02 mmol), iodobenzene (0.204 g, 1 mmol) and mesityl boronic acid (0.180 g, 1.1 mmol) in DMA (6 ml) was slowly added 10% TIOH(aq) (3.5 ml) through a septum inlet with a syringe, under nitrogen. The heterogeneous reaction mixture was allowed to stir overnight (16 h) at room temperature. The biaryl product was extracted with benzene, washed with brine and dried over MgSO$_4$. Purification by silica gel chromatography using 10:90 ethyl acetate / petroleum ether as eluant, gave (38) in 92% yield.
6.13.5 General coupling procedure for the study of *solvent effect* with 10% TlOH(aq) at ambient temperature (for Table 2.5, pg. 25)

![Chemical Reaction Diagram]

The 10% TlOH(aq) promoted coupling procedure above was followed, with the substitution of various solvents for DMA.

6.13.6 General procedure for the *ligand effects* in the coupling of iodobenzene with mesityl boronic acid at ambient temperature (For Table 2.8, pg. 32)

![Chemical Reaction Diagram]

A mixture of Pd$_2$(dba)$_3$.CHCl$_3$ (0.021 g, 0.02 mmol), haloarene (1 mmol), arylboronic acid (1.1 mmol) and ligand (0.04 mmol for coordinatively unsaturated complexes or 0.08 mmol for coordinatively saturated complexes) was dissolved in DMA (6 ml) under nitrogen and stirred for 5 mins before the addition of 10% TlOH(aq) (3.5
ml) (~1 min) through a septum inlet with a syringe. The heterogeneous mixture was allowed to stir for 12 h at room temperature. Finally, the standard work up was repeated.

**6.13.7 General procedure for the coupling attempts of phenyltriflate with mesityl boronic acid at ambient temperature (For Table 3.1, pg. 42)**

```
B(OH)₂ + OTf⁻
3% Pd(PPh₃)₄
Base / RT / 12 h
```

A mixture of mesitylboronic acid (0.180 g, 1.1 mmol), phenyltriflate (0.023 g, 1 mmol) Pd(PPh₃)₄ (0.035 g, 0.03 mmol) and MX salt (1.5 mmol) in solvent (6 ml) was stirred for 5 min, before the slow addition of 10% TlOH (3.5 ml) through a septum inlet. The mixture was stirred for 16 h before standard work up.

* The reaction in the absence of any salt was also examined under the same reaction condition.

**6.13.8 General procedure for ArN₂-X and arylboronic acids coupling attempts (for Table 3.2, pg. 48)**

```
Ar-B(OH)₂ + N₂-X
Pd(O) or Pd(II)
```
To a stirred solution of an aryldiazonium salt (1.1 mmol) was added a palladium catalyst (0.02 mmol) and an arylboronic acid (1 mmol) in DMA (8 ml) at room temperature, under positive nitrogen pressure. After stirring overnight, the reaction was worked up according to the standard procedure.

### 6.13.9 General procedure for tricarbonyl(arene)chromium and mesitylboronic acid coupling attempts (for Table 3.3, pg. 52)

**Method a.** A mixture of tricarbonyl(bromomesitylene)chromium (0.37 g, 1.1 mmol), mesitylboronic acid (0.180 g, 1.1 mmol), Pd(PPh₃)₄, 10% TIOH (aq) (3.5 ml) and benzene (6 ml) was heated at 80 °C for 8 h under a nitrogen atmosphere. After cooling to room temperature, the standard work up was performed.

**Method b:** (Ambient Temperature), A mixture of tricarbonyl(bromomesitylene)chromium (0.37 g, 1.1 mmol), mesitylboronic acid (0.180 g, 1.1 mmol), a Pd(0) or Pd(II) complex (0.02 mmol) in solvent (6 ml) was stirred for 10 mins under positive nitrogen pressure, before the dropwise addition of 10% TIOH through a septum inlet. The mixture was stirred for 12 h at ambient temperature, before the standard work up was performed.
**Method c:** *(In Situ)* A mixture of tricarbonyl(bromomesitylene)chromium (0.36 g, 1 mmol), mesitylboronic acid (0.180 g, 1.1 mmol), Pd(PPh₃)₄ (0.023 g, 0.02 mmol), Cr(CO)₆ (0.220 g, 1 mmol) in acetonitrile (8 ml) was heated to reflux for 5 h under positive nitrogen pressure. The flask was allowed to cool to room temperature and standard work up was performed.

**6.13.10 General procedure for coupling attempts of aryloxazolines with arylboronic acids (Table 3.4 and 3.5, pg. 57 and 58)**

![Chemical structure](image)

**Method 1:** A solution of aryl oxazoline (1 mmol), arylboronic acid (1.1 mmol), Pd(PPh₃)₄ and base (1.5 mmol) in solvent (6 ml) was stirred for 10 min before the addition of water (1 ml) through the septum inlet and the mixture heated to 80 °C by means of an oil bath for 6-12 h. The flask was allowed to cool to room temperature, and the mixture extracted with benzene. The combined organics were washed with brine, dried over MgSO₄ and the solvent evaporated. The crude was product purified by flash chromatography using ethyl acetate / petroleum ether as eluant.

**Method 2:** The ambient temperature reaction using TIOH (pg. 146) was attempted.

**Method 3:** A solution of the oxidative addition product *(92)* (1 mmol), mesitylboronic acid (0.246 g, 1.5 mmol), base (1.5 mmol) water (1 ml) and benzene
(8 ml) was kept at 80 °C for 12 h with stirring under nitrogen. After cooling to room temperature the standard work up procedure was performed.

* In method 3, when the base was Et₃N, no water was added.

**Method 4: (Using Grignard Reagents)**

![Chemical Reaction Diagram]

A freshly prepared solution of mesityl magnesium bromide (1.1 mmol) prepared from bromomesitylene (0.219 g, 1.1 mmol) and magnesium turnings (0.037 g 1.5 mmol) in THF (10 ml), was transferred to a stirred solution of complex (92) (0.361 g, 0.5 mmol) in THF (5 ml) by canula under nitrogen. After stirring for 15 mins. at ambient temperature, the mixture was brought to reflux for 4 h. Standard work up was repeated after cooling to room temperature.
6.13.11 General procedure for coupling of 2-(o-haloaryl)-1,3-dioxolane with arylboronic acid (Scheme 3.8 and Table 3.6, pg. 63 and 65)

\[
\text{B(OH)}_2 + \text{Br} \xrightarrow{\text{Pd(PPh}_3\text{)}_4} \xrightarrow{\text{DMA}} \xrightarrow{\text{Ba(OH)}_2.8\text{H}_2\text{O}, \text{H}_2\text{O / 80 °C}} \xrightarrow{\text{product (99)}}
\]

A mixture of 2-(o-bromophenyl)-1,3-dioxolane (0.252 g, 1 mmol), Pd(PPh₃)₄ (0.023 g, 0.02 mmol), phenylboronic acid (0.180 g, 1.1 mmol) and Ba(OH)₂·8H₂O (0.5 g, 1.6 mmol) in DMA (8 ml) was stirred for 10 min, before water (1 ml) was added slowly through a septum inlet with a syringe. The mixture was heated to 80 °C for 12 h and then allowed to cool to room temperature. Finally the standard work up was performed to give product (99) in 90% yield as a white crystalline solid.

* In the TlOH case, the 10 % TlOH promoted coupling procedure was followed.

**In the K₃PO₄ case, the Suzuki coupling procedure was followed.
6.13.12 Assessment of the stability of cyclic-boronate esters towards base in the Suzuki coupling reaction

A mixture of mesitylboronic acid-trimethylene-glycol ester (47) (0.224 g, 1.1 mmol), and iodobenzene (0.204 g, 1 mmol), in DMA (8 ml) was stirred for 5 min at room temperature, before 10% TlOH(aq) (3.5 ml) was added dropwise through a septum inlet to the reaction mixture via syringe. After stirring for 12 h at room temperature, the standard work up procedure gave mesitylboronic acid (0.135 g, 0.732 mmol) in 75% yield. Spectral and physical data were identical to that prepared previously.

6.13.13 General procedure for coupling attempt of arylthallium compounds with aryl halides (for Table 4.2 and 4.3, pg. 86 and 87)
To mesitylthallium dichloride (155b) (0.434 g, 1.1 mmol) was added iodomesitylene (0.246 g, 1 mmol), and Pd(PPh₃)₄ (0.023 g, 0.02 mmol) in benzene (8 ml) under nitrogen. The mixture was brought to 80 °C by heating with an oil bath. The heterogeneous mixture was allowed to stir for 12 h at this temperature. The flask was then cooled to room temperature and the standard work up procedure was performed. *In other experiments Na₂PdCl₄ (5.88 mg, 0.02 mmol), together with PPh₃ (21 mg 0.08 mmol) was employed as the Pd-catalyst.

6.13.14 General procedure for coupling attempt of aryl-dihydrobenzoboradiazoles with aryl halides

![Chemical reaction]

A mixture of phenyldihydrobenzoboradiazole (0.202 g, 1.1 mmol), iodobenzene (0.204 g, 0.1 mmol), Pd(PPh₃)₄ (0.023 g, 0.02 mmol), and Ba(OH)₂·8H₂O (0.5 g, 1.6 mmol), in benzene (6 ml) was stirred for 5 mins under nitrogen before water (1 ml) was added through a septum inlet. The mixture was brought to 80 °C and stirred at this temperature for 12 h. The flask was cooled to room temperature and the standard worked up procedure repeated.
6.14 General spectroscopic data for coupled biaryls.

Determination of the coupled product from mesitylboronic acid with aryl electrophiles was most easily carried out by NMR. The ortho- methyl signals in the mesitylboronic acid at 2.4 ppm move upfield by between 0.4-0.5 ppm in the coupled product, due to the shielding effect of the coupled aromatic ring.\textsuperscript{105}

See appendix NMR-1 and NMR-2

2,4,6-trimethylbiphenyl (41)

\[
\begin{array}{c}
\text{C}_15\text{H}_{16}=196 \text{ g.mol}^{-1} \\
\end{array}
\]

Isolated as colourless oil. \textbf{1H-NMR }\delta \text{ 7.51-7.33 } (3\text{H}, \text{ m, H-3', -4' and -5'}); \text{ 7.15 } (2\text{H}, \text{ dd, J=8.0, 1.5 Hz, H-2' and -6'}); \text{ 6.89 } (2\text{H, s, H-3 and -5}), \text{ 2.43 } (3\text{H, s, p- CH}_3); \text{ 2.10 } (6\text{H, s, 2xo- CH}_3), \text{ MS (E}1^+)\text{, 196 (M+), 181 (-CH}_3\text{), 165 (-2xCH}_3\text{), 152, 115, 77. C}_{15}\text{H}_{16} \text{ requires 196.1252 found 196.1261. }\nu_{\text{max}} \text{ (thin film) 3057, 3021, 2948, 2918, 2857, 1613, 1475, 1442, 1376, 1071 cm}^{-1}.
2,4,6-trimethyl-4'-nitro-biphenyl (41f)

![Diagram of 2,4,6-trimethyl-4'-nitro-biphenyl (41f)]

\[ C_{15}H_{15}NO_{2} = 241 \text{ g/mol} \]

Isolated as yellowish crystals. mp 96-97 °C (lit. 106-94 °C), \textbf{1H-NMR \( \delta \) 8.27 (2H, d, J=8.1 Hz, H-3' and -5'); 7.31 (2H, d, J=8.0 Hz, H-2' and -6'); 6.95 (2H, s, H-3 and -5); 2.33 (3H, s, p-CH\textsubscript{3}); 1.96 (6H, 2x o-CH\textsubscript{3}), \textbf{MS (EI\textsuperscript{+})} 241(M\textsuperscript{+}), 226 (CH\textsubscript{3}), 194 (-NO\textsubscript{2}), 180 (-CH\textsubscript{3}), 165, 152, 89. \( C_{15}H_{15}NO_{2} \) requires 241.1102, found 241.1109. \( \nu_{\text{max}} \), 1601, 1521, 1474, 1348, 1261, 1173, 1107, 1068, 1011 cm\textsuperscript{-1}.

2,4,6-trimethyl-2'-nitro-biphenyl (41a)

![Diagram of 2,4,6-trimethyl-2'-nitro-biphenyl (41a)]

\[ C_{15}H_{15}NO_{2} = 241 \text{ g/mol} \]

Isolated as yellowish crystals (mp. 47 °C). (lit.\textsuperscript{107} 42-44 °C), \textbf{1H-NMR \( \delta \) 7.98 (1H, dd, J= 8.0, 0.6 Hz, H-2'); 7.65 (1H, td, J=8.7, 1.0 Hz, H-4'); 7.50 (1H, td, 8.7, 1.0 Hz, H-3'); 7.19 (1H, dd, J= 8.0, 0.6 Hz, H-5'); 6.92 (2H, s, H-3 and -5); 2.30 (3H, s, p-CH\textsubscript{3}); 1.93 (6H, s, 2x o-CH\textsubscript{3}), \textbf{MS (EI\textsuperscript{+})} 241 (M\textsuperscript{+}), 226 (-CH\textsubscript{3}), 210 (-O\textsubscript{2}), 194, 179 , 165, 121, 89, 76. \( C_{15}H_{15}NO_{2} \) requires 241.1102, found 241.1111. \( \nu_{\text{max}} \) (thin film) 3088, 2863, 1585, 1528, 1463, 1436, 1361, 1294, 1258, 1148, 1042 cm\textsuperscript{-1}.
2,4,6-trimethyl-biphenyl-4'-carboxylic acid methyl ester (41h)

![Chemical Structure](image)

\[ C_{17}H_{18}O_2 = 254 \text{ g.mol}^{-1} \]

Isolated as white crystals mp. 125-127 °C, (lit.\textsuperscript{107} 124 °C). \textbf{1H-NMR} \( \delta \): \( 8.10 \) (2H, d, \( J = 8.0 \) Hz, H-3' and H-5'); \( 7.14 \) (2H, d, \( J = 8.0 \) Hz, H-2' and H-6'); \( 6.34 \) (2H, s, H-3 and H-5); \( 3.85 \) (3H, s, OCH\(_3\)); \( 2.26 \) (3H, s, p-CH\(_3\)); \( 1.91 \) (6H, s, 2\( \times \)o-CH\(_3\)). \textbf{MS (EI\textsuperscript{+})} 254 (M\textsuperscript{+}), 239 (-CH\(_3\)), 223 (-OCH\(_3\)), 195 (-COOCH\(_3\)), 180, 165, 141, 119, 104. \( C_{17}H_{18}O_2 \) requires 254.1306 found 254.1310. \( \nu_{\text{max}} \), 3052, 1720, 1611, 1436, 1285, 1256, 1191, 1102, 1007 cm\(^{-1}\).

2,4,6-trimethyl-4'-methoxy-biphenyl (41g).

![Chemical Structure](image)

\[ C_{16}H_{18}O = 226 \text{ g.mol}^{-1} \]

Isolated as yellowish solid, mp 74 °C. (lit.\textsuperscript{107} 71-75 °C). \textbf{1H-NMR} \( \delta \): \( 7.14 \) (2H, d, \( J = 8.0 \) Hz, H-3' and 5'); \( 6.93 \) (2H, d, \( J = 8.0 \) Hz, H-2' and 6'); \( 6.34 \) (2H, s, H-3 and H-5); \( 3.96 \) (3H, s, OCH\(_3\)); \( 2.31 \) (3H, s, p'-CH\(_3\)); \( 2.00 \) (6H, s, 2\( \times \)o'-CH\(_3\)). \textbf{MS (EI\textsuperscript{+})} 226
(M$^+$), 211 (- CH$_3$), 196 (-OCH$_3$), 181, 165, 150, 141, 128, 113, 105. $\nu_{\text{max}}$ (thin film) 2886, 2746, 2358, 2336, 1727, 1611, 1569, 1473, 1445, 1389, 1258, 1071 cm$^{-1}$.

2,4,6-trimethyl-2'-methoxy-biphenyl (41c)

\[
\text{C}_{16}\text{H}_{18}\text{O}= 226 \text{ g.mol}^{-1}
\]

Isolated as a colourless solid, mp 59°C. (lit.$^{107}$ 53-56 °C). $^{1}$$H$-NMR \( \delta \) 7.24 (2H, m, H-3' and H-6'); 6.92 (2H, m, H-4' and H-5'); 6.37 (2H, s, H-3 and H-5); 3.65 (3H, s, OCH$_3$), 2.25 (3H, s, p- CH$_3$); 1.89 (6H, s, 2xo- CH$_3$). $\text{MS (EI+)}$ 226 (M$^+$), 211 (- CH$_3$), 195 (-OCH$_3$), 180, 165, 152, 105, 92, C$_{16}$H$_{18}$O requires 226.1357, found 226.1367. $\nu_{\text{max}}$ 2993, 2953, 2834, 1608, 1584, 1572, 1515, 1468, 1459, 1286, 1245, 1174 cm$^{-1}$. 
**2,4,6-trimethyl-2'-chloro-biphenyl (41d)**

Isolated as slightly yellowish crystals. 1H-NMR δ 7.42 (1H, dd, J= 8.0, 1.0 Hz, H-3' or H-6'); 7.30 - 7.21 (2H, m, H-4' and H-5'); 7.08 (1H, dd, J=8.0, 1.0 Hz, H-6' or H-3'); 6.88 (2H, s, H-3 and H-5); 2.27 (3H, s, p-CH₃); 1.90 (6H, s, 2x o-CH₃). MS (EI⁺) 230 (M⁺), 215 (-CH₃), 195 (-Cl), 180, 165, 152, 115, 96, 89. C₁₅H₁₅Cl requires 230.0862 found 230.0748. vₘₐₓ (thin film) 2919, 2856, 1733, 1699, 1613, 1559, 1464, 1436, 1376, 1263, 1070, 1033 cm⁻¹.

**2,4,6-trimethyl-2'-cyano-biphenyl (41j)**

Isolated as a white solid mp. 110 °C. 1H-NMR δ 7.77 - 7.56 (2H, m, H-3' and H-6'); 7.49 - 7.42 (2H, m, H-4' or H-5'); 6.95 (2H, s, H-3 and H-5); 2.32 (3H, s, p-CH₃); 1.92 (6H, s, 2x o-CH₃). MS (EI⁺) 221 (M⁺), 206 (-CH₃), 194 (-N), 179, 165, 103, 96, 89. vₘₐₓ (thin film) 2918, 2227, 1733, 1653, 1612, 1468, 1435, 1377, 1258, 1199, 1095 cm⁻¹.
2-methyl-1-phenynaphthalane (54)

\[ C_{17}H_{14} = 218 \text{ g.mol}^{-1} \]

Isolated as yellowish creamy oil (lit.\textsuperscript{108} mp 44 °C). \textbf{1H-NMR} \( \delta \) 7.77 (2H, J= 8.0, 1.2 Hz H-2' and H-6'); 7.45-7.15 (9H, m, ArH); 2.17 (3H, s, CH\(_3\)). \textbf{MS (EI+)} 218 (M\(^+\)), 203 (-CH\(_3\)), 142 (-Ph), 115, 10. \( \nu_{\text{max}} \) (thin film) 3056, 2921, 1733, 1716, 1683, 1652, 1558, 1506, 1436, 1192, 1119 cm\(^{-1}\).

\[ C_{18}H_{13}N = 243 \text{ g.mol}^{-1} \]

2-methyl-1-(o-cyanophenyl)naphthalene (56)

Isolated as a yellowish solid mp. 95°C. \textbf{1H-NMR-} \( \delta \) 7.79 (2H, dd, J= 8.3 , 1.4, H-3' and H-6'); 7.7 (1H, td, J=6.7, 0.9 Hz, H-5'); 7.43 (1H, m, Naph-H); 7.33 (5H, m, Naph-H); 7.07 (1H, d, J= 9.1 Hz, H-3); 2.17 (3H, s, -CH\(_3\)). \textbf{MS (EI+)} 243(M\(^+\)), 227 (-CH\(_3\)), 214 (-N), 158, 141. 121 115, 108. \( \nu_{\text{max}} \), 3012, 2948, 2276, 1564, 1432, 1108 cm\(^{-1}\).
2-methyl-1-(4'-methoxyphenyl)naphthalene (55)

Isolated as a white solid mp. 110-115 °C(lit. 109-108 °C). 1H-NMR δ 7.84 (2H, d, J= 8.7 Hz, H-2' and H-6'), 7.77 (2H, d, J= 8.7, H-4' and H-5'); 7.48 - 7.32 (4H, m, Naph-H); 7.20 (2H, d, J = 9.3, Naph-H); 3.93 (3H, s, OCH₃), 2.27 (3H, s, -CH₃).

MS (EI+) 248 (M⁺), 234 (-CH₃), 219, 191, 127, 92. \( \nu_{\text{max}} \), 2942, 1611, 1556, 1312, 1176 cm⁻¹.

2'-(4,6-dimethyl-1,3-dioxane)-2-biphenyl

Isolated as a yellowish oil as a mixture of 4 diastereoisomers (ratio 1:2:1:1). 1H-NMR δ 7.82 (1H, dd, J= 8.1, 1.2 Hz, ArH-3'); 7.43 (5H, s, ArH-2 to -6); 7.22 (3H,
m, ArH-4', 5' and 6'); 6.1, 5.78, 5.74 and 5.36 (1H, 4xs, H-2); 4.45, 3.98 and 3.24 (2H, m, H-5); 2.00 and 1.50 (2H, m, H-4 and H-6); 1.25 (6H, m, 2x-CH3).M (EI+) 268 (M+), 198 (-C5H10), 181, 152, 115, 105, [C18H20O2]H+ requires 269.1541 found 269.1548. $\nu_{\text{max.}}$, 2783, 1603, 1314, 1232, 1074 cm$^{-1}$.

2,4,6-trimethyl-2'-(1,3-dioxolane-2-)biphenyl (99)

Isolated as white solid. mp 107-108 °C. 1H-NMR, δ 7.61 (1H, dd, J= 9.1, 3.6 Hz, H-3'); 7.40-7.35 (2H, m, H-4' and H-5'); 7.12 (1H, dd, J=6.5 , 1.5 Hz, H-6'); 6.90 (2H, 2xs, ArH-3 and -5); 5.40 (1H, s, H-2); 4.10 (2H, m, H-4a and H-5a); 3.80 (2H, m, H-5b and H-4b); 2.33 (3H, s, p- Me); 1.94 (6H, s, o- Me). MS (EI+) 268 (M+), 253 (-Me), 223 (-2 x Me), 207 (M+ -Oxazoline), 192, 179, 165, 148. [C18H21O2]H+ requires 269.1541 found 269.1540. $\nu_{\text{max.}}$, (nujol) 2752., 1611. 1259, 1202, 1117, 1075 cm$^{-1}$.
2,4,6-trimethyl-2’-(4-methyl-1-3-dioxolane-2-)biphenyl (104).

Isolated as white solid as a mixture of 2 diastereoisomers (ratios 1:1). **1H-NMR**

$\delta$ 7.62 (1H, dd, J= 7.2, 0.6 Hz, H-3'); 7.34 (2H, m, H-4' and -5'); 6.92 (1H, dd, J=7.0, 0.9 Hz , H-6'); 7.27 (2H, s, ArH-3 and -5); 5.42 and 5.29 (1H, 2xs, H-2); 4.10 (1H, m, H-4); 3.82, 3.40 and 3.25 (2H, 3xdd, J= 9.0, 0.5 Hz, H-5a and H-5b); 2.25 (3H, s, p- Me); 1.9 (6H, s, 2xo- Me); 1.25 and 1.15 (3H, 2xd, J= 7.5 Hz, -CH$_3$). **MS** (EI$^+$) 282 (M$^+$), 267 (-CH$_3$), 223(-C$_3$H$_6$), 207, 192, 176, 165, 104. [C$_{19}$H$_{22}$O$_2$]H$^+$ requires 283.1698 found 283.1697. ν$_{\text{max}}$ 3059, 2973, 2873, 2361, 1694, 1598, 1482, 1473, 1379, 1266, 1202, 1068 cm$^{-1}$.

2’-(1,3-dioxolane-2-)biphenyl (105)

$\delta$ 7.83 (1H, dd, J= 6.6, 2.0 Hz, H-3'); 7.38 (2H, m, H-4' and -5'); 6.92 (1H, dd, J=6.8, 1.0 Hz, H-6'); 7.29 (2H, s, ArH-3 and -5); 5.46 and 5.30 (1H, 2xs, H-2); 4.10 (1H, dd, J= 9.0, 0.5 Hz, H-5a and H-5b); 2.24 (3H, s, p- Me); 1.9 (6H, s, 2xo- Me); 1.25 and 1.15 (3H, 2xd, J= 7.5 Hz, -CH$_3$). **MS** (EI$^+$) 226 (M$^+$), 211 (-CH$_3$), 169, 154, 104. [C$_{15}$H$_{14}$O$_2$]H$^+$ requires 226.1612 found 226.1611. ν$_{\text{max}}$ 3062, 2921, 2843, 2361, 1694, 1599, 1473, 1379, 1263, 1202, 1068 cm$^{-1}$.
Isolated as yellowish oil. **1H-NMR** δ **7.66** (4H, m, H-3' to -6'); **7.45-7.20** (7H, m, ArH-2 to -6 and (H4' and -5')); **5.54** (1H, s, H-2); **4.40** (2H, m, H-4a and H-5a); **3.91** (1H, m, H-4b and H-5b), **MS (EI+)** 226 (M⁺), 198 (-CH₂CH₂-), 181, 165, 153, 115, 73, [C₁₅H₁₄O₂]H⁺ requires 227.1072 found 227.1064. \( \nu_{\text{max}} \) 3059, 2885, 2360, 1611, 1474, 1391, 1258, 1117, 1074 cm⁻¹.

**2’-(4-methyl-1,3-dioxolane-2)-1-napthylbenzene (173)**

\[
\text{C}_{20}\text{H}_{18}\text{O}_2 = 290 \text{ g mol}^{-1}
\]

Isolated as reddish crystals as a mixture of diastereoisomers. (ratio 1:1) **1H-NMR** δ **7.93 - 7.74** (4H, m, H-3' to 6'); **7.57 - 7.34** (7H, m, Naph-H); **5.16** and **4.83** (1H, 2xs, H-2); **4.37 - 4.00** (2H, m, H-5a or H-5b and H-4), **3.82, 3.43** and **3.25** (1H, 3xdd, J= 9.0, 3.1 Hz H-5a or H-5b), **1.35** and **1.12** (3H, 3xd, J=6.2 Hz, -CH₃), **MS (EI+)** 290 (M⁺), 248 (-C₃H₆), 231 , 215, 202, 185, 137, 128, [C₂₀H₁₈O₂]H⁺ requires 291.1385 found 291.1363. \( \nu_{\text{max}} \), (KBr, thin film) 3058, 2973, 2878, 2360, 2341, 1592, 1506, 1438, 1393, 1378 cm⁻¹
2-(4-methyl-1.3-dioxolane-2)-biphenyl (84).

\[
\text{C}_{16}\text{H}_{16}\text{O}_2 = 240\text{g.mol}^{-1}
\]

Isolated as yellowish oil as a mixture of 2 diastereoisomers (ratios 2:1). \textit{H-NMR} \delta 7.80-7.70 (2H, m, H-3' and -6'); 7.46-7.36 (5H, m, H-2 to -6); 7.31-7.27 (2H, m, H-4' and -5'); 5.81 and 5.72 (1H, 2xs, H-2); 4.50-4.10 (1H, m, H-4); 4.04, 3.63 and 3.46 (2H, 3xt, J=7.3 Hz, H-5a and H-5b); 1.43 and 1.28 (3H, 2xd, 6.1 Hz, -CH₃). \textit{MS (EI⁺)} 240 (M+), 198 (-C₃H₆), 181, 165 153 139, 127, 115, 105, [C₁₆H₁₆O₂]⁺ requires 241.1229 found 241.1234. \textit{υmax} (thin film) 3059, 2974, 2875, 1684, 1653, 1598, 1482, 1455, 1379, 1265, 1202, 1121, 1067 cm⁻¹.
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Appendix