Bipyridine Ligands for use in Polymer-Supported Iridium Catalyzed C-H Borylation

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Abstract

Polymer-supported catalysis has shown high recyclability of precious metal catalysts. This project explored several synthetic routes to make a polymer-support linker to use in organic synthesis.

Bipyridine ligands, such as 4, 4'-*tert*-butyl-bipyrine with an iridium precatalyst afford a highly efficient C-H borylation, but studies of polymer-supported bipyridine ligands have not been extensively researched. With an aim to exploring this approach to allow recycling of the expensive iridium catalysts synthesis of new bipyridine ligands were undertaken. A modular synthesis was envisaged using Stille cross-coupling to generate a model compound. However, no desired bipyridine compounds could be synthesized.

Alternative methods were then employed to synthesize the polymer-supported ligands. The initial aim was to couple two substituted pyridine to generate a bipyridine. Several methods have been investigated. The best route involved the cross-coupling of a pyridine N-oxide and 2-bromopyridine. However this only gave the desired product in low yield. Then attention turned to functionalize preformed 4, 4'-disubstitued-2, 2'-bipyridine, however, ligands suitable for immobilisation onto a polymer resin were not successful generated. Recently, excellent yields of pyridine containing biaryls through the direct addition of aryl lithiation to pyridines have been reported. This aroused interests for generating bipyridine ligands in an analogous fashion. Although this new route to synthesis bipyridine ligands was not completed, this showed a high possibility for the generation of polymer-supported ligands and is worthy of further study.

Full details of this research are presented in chapter 2. Experimental procedure and data is in chapter 4.

Contents

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First and foremost I would like to thank my supervisor, Dr Patrick G. Steel, whose encouragement, guidance and support from the initial to the final level enabled me to develop an understanding of the subject. Without his help and enthusiasm, this dissertation would not have been possible. Writing an 80-page paper in English is really a big project to me as an international student. It also means more time and energy needs to be paid than for other students.

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Last but not least, my biggest thanks go to my parents and my boyfriend. Without their support, I really don't think I can finish this. I love you all very much.

Terminology

aq.	Aqueous
Ar	Aryl
bpy	Bipyridine
B_2Pin_2	Bis (pinacolato) diboron
COD	1, 5-Cyclooctadiene
COE	Cyclooctene
DCM	Dichloromethane
DMAE	Dimethylamino ethanol
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dtbpy	4, 4'-di-tert-butyl-2, 2'-bipyridine
EDTA	Ethylenediaminetetraacetic acid
ES^+MS	Positive charge electrospray mass spectrometry
ES^-MS	Negative charge electrospray mass spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
eq.	Equivalents
GC-MS	Gas chromatography-mass spectrometry
HBcat	Catecholborane
HBPin	Pinacolborane

HPLC	High performance liquid chromatography
IR	Infra-red spectroscopy
m/z	Mass to charge ratio
MeCN	Acetonitrile
MeOH	Methanol
mg	milligram
mmol	millimole
mol	mole
MWI	Microwave Irradiation
MTBE	Methyl tert-butyl ether
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
NO_2	Nitro
Ph	Phenyl
rt	room temperature
sat.	saturated
^tBu	tert-butyl
THF	Tetrahydrofuran
TLC	Thin-layer Chromatography
TMSCl	Trimethylsilyl chloride

Chapter 1 Introduction

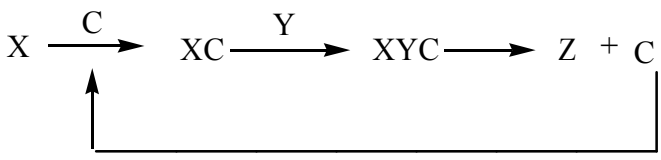
1.1 General Introduction

This dissertation describes research towards the synthesis of polymer-supported bipyridine ligands for iridium-catalysed C-H borylation. Bipyridine ligands, such as 4, 4'-di-tert-butyl-2, 2'-bipyridine, have been applied in iridium catalysed C-H aromatic borylation. Although the catalyst complex generated from bipyridine ligands and iridium precursor has attracted much attention, the area of supported catalysis using these ligands has not been extensively researched.

This chapter essentially consists of three short reviews concerning three main topics relevant to this project: cross-coupling reactions, polymer supported catalysis and C-H borylation. The other two chapters in this dissertation describe the results obtained and the details of experimental procedures used and characterisation, respectively.

1.2 Introduction to Catalysis

Catalysts are defined as materials which promote a change in the rate of chemical reactions without themselves undergoing change (Figure 1.1). They participate in a catalytic cycle that converts reactants, into products and regenerates the catalyst. Each cycle is called a turnover. A highly active catalyst has either or both a larger turnover number (*TON*: the number of moles of substrate that a mole of catalyst can convert before becoming inactivated) and turnover frequency (*TOF*: is used to refer to the turnover per unit time).



X, Y: reactants, C: catalysts, Z: product

Figure 1.1

Catalysts can be divided into three categories: Metal-based catalysts, organocatalysts, and enzymes. The metal-based catalysts can be further classified into two sorts, heterogeneous and homogeneous, depending on whether a catalyst exists in the same phase as the substrates or a different one (Figure 1.2).
The aim of this project was to focus on iridium-catalysed aromatic C-H borylation, thus the following section focuses on transition metal catalysis.

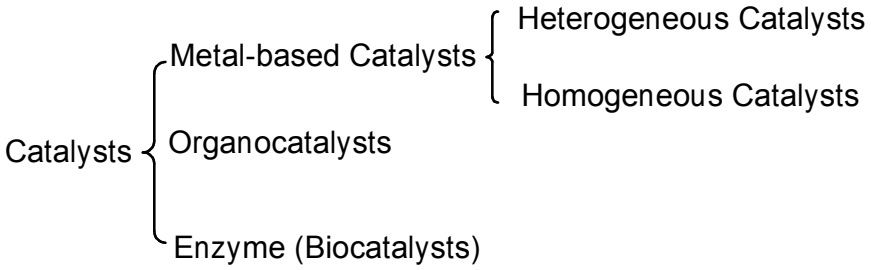
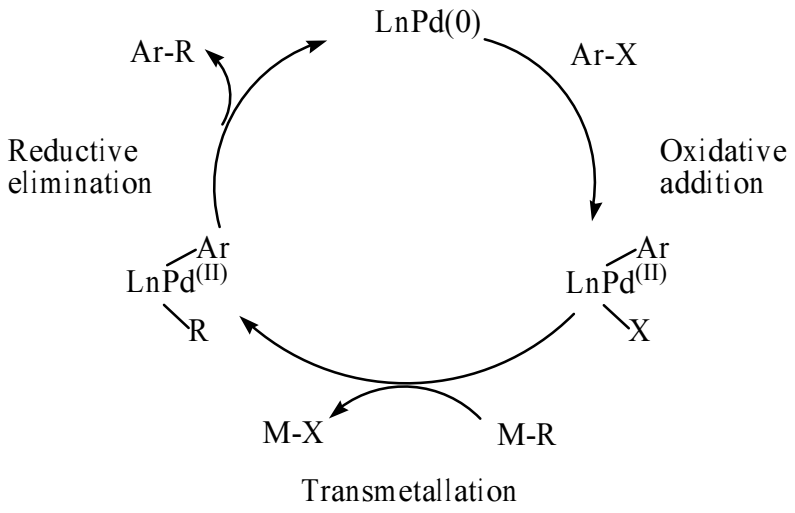


Figure 1.2

1.3 Palladium Catalysed Cross-Coupling Reaction

Palladium-catalysed cross-coupling is widely used to form C-C bonds, and therefore finds widespread application for the synthesis of molecules possessing interesting pharmacological or physical properties.[1] The cross-coupling reaction normally occurs by a sequence of steps, initiated by the oxidative addition of an organic halide and finished by reductive elimination (Scheme 1.1).



Scheme 1.1

The initial aim of our project was to synthesise a bipyridine ligand using palladium-catalysed cross-coupling techniques. The use of organotin (Stille), organoboranes (Suzuki-Miyaura), and organozinc (Negishi) reagents as nucleophiles have been comprehensively studied and provided a general way for formation new carbon-carbon bond. [2,5,9]

In this section, these three main palladium-catalysed cross-coupling reactions and their reaction mechanism will be introduced. All of these reactions have been used in this project.

1.3.1 Suzuki-Miyaura Cross-Coupling Reaction

1.3.1.1 Introduction of Suzuki Cross-Coupling

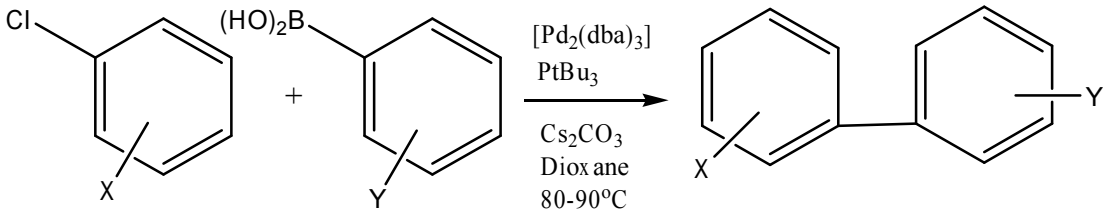
The Suzuki-Miyaura coupling reaction is one of the most useful carbon-carbon bond forming reactions in organic synthesis. Aryl- or vinyl boronic acids can react with aryl- or vinyl halides in the presence of a palladium catalyst and base to form C-C bonds (Equation 1.1).

$$R_1\text{-}BY_2 \quad + \quad R_2\text{-}X \xrightarrow[\text{Base}]{\text{Pd catalyst}} \quad R_1\text{-}R_2$$

Equation 1.1

This reaction has many attractive features including being largely unaffected by water, tolerating a broad range of functional groups, and generally proceeding with high regio- and stereoselectivity. In addition, the inorganic by-product is non-toxic and easily removed from the reaction mixture.[2]

In 1998, Littke and Fu demonstrated a general method for the Suzuki cross-coupling of aryl chlorides with arylboronic acids in the present of $Pd_2(dba)_3$, P^tBu_3 and Cs_2CO_3.[3]



Scheme 1.2

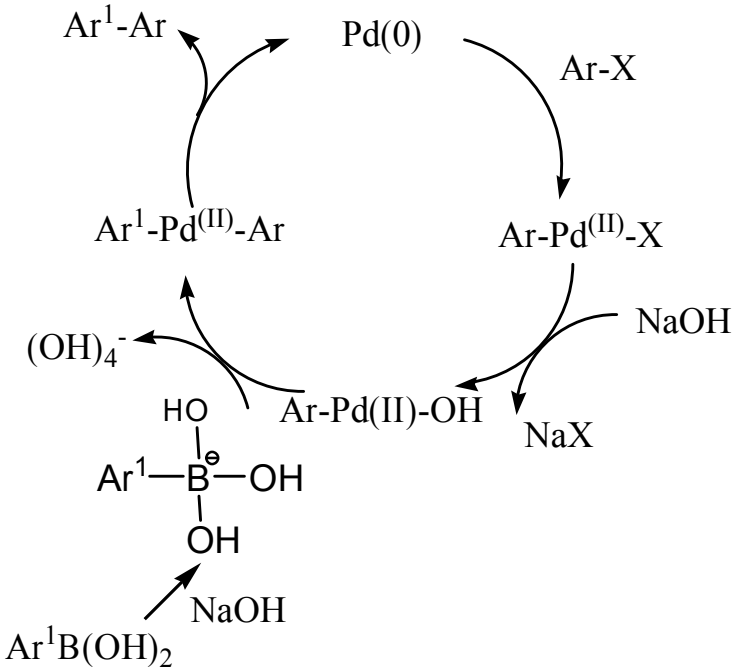
Table 1.1 Cross-coupling of arylchlorides with arylboronic acids

Entry	1	2	3	4	5	6	7	8
X	4-Me	4-MeCO	4-MeO	4-NH_2	4-Me	4-Me	2-Me	2-Me
Y	H	H	H	H	4-CF_3	4-OMe	H	2-Me
Yield (%)	87	91	89	92	86	82	90	87

Under these conditions, the cross-coupling reactions proceeds well regardless of whether the arylchloride contains electron-rich or electron-deficient substituents.

1.3.1.2 The Mechanism of Suzuki Cross-Coupling

The mechanism of the Suzuki reaction follows the general model for palladium-catalysed cross-coupling reactions and is described in Scheme 1.3. The first step is the oxidative addition of palladium to the aryl halide to form an organo-palladium species. Reaction with the base forms the intermediate Ar-$Pd^{(II)}$-OH, and subsequent transmetalation with the aryl boronate gives the organopalladium species Ar^1-$Pd^{(II)}$-Ar. Reductive elimination of the desired product regenerates the palladium (0) catalyst.[4]



Scheme 1.3

1.3.2 Stille Cross-Coupling

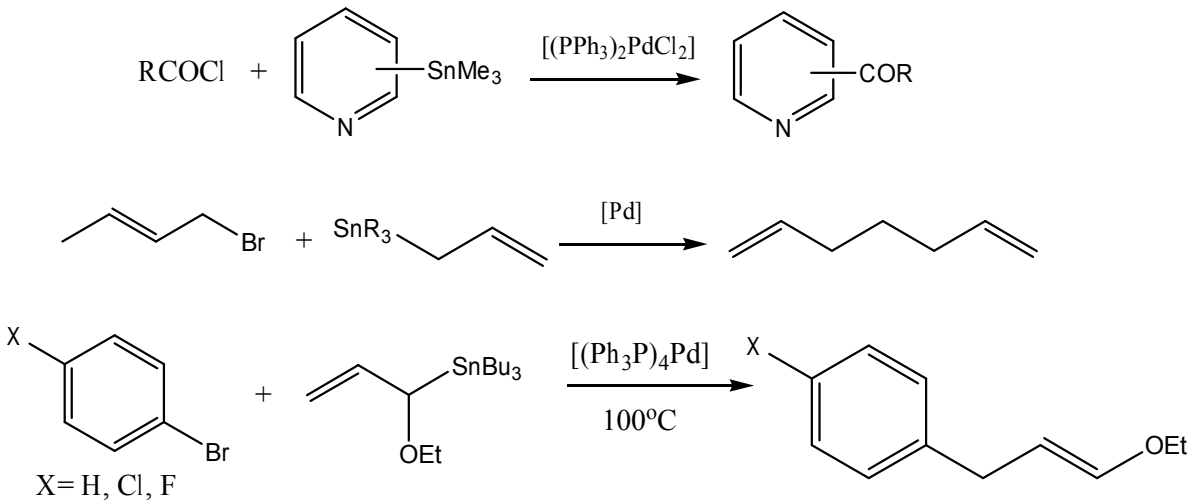
The Stille Coupling is a versatile C-C bond forming reaction between organo stannanes and organo-halides or pseudohalides, such as a triflate, CF_3SO_3.[5]

$$R_1\text{-}Sn(R)_3 + \quad R_2\text{-}X \xrightarrow{\text{Pd catalyst}} \quad R_1\text{-}R_2$$

R_1, R_2= Ar, Vinyl and Alkyl.

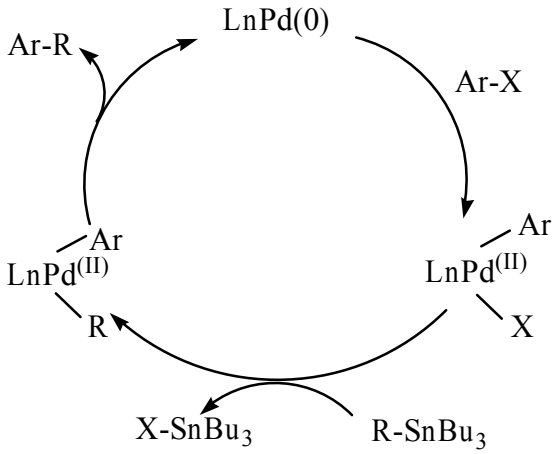
Equation 1.2

The organostannane may be aryl, vinyl or alkyl. Many electrophilic coupling partners have been employed, e.g.: acid chlorides, benzyl halides, allyl halides and acetates, substituted vinyl halides and triflates, aryl halides, α-haloketones and α-haloesters (Scheme 1.4).[6]



Scheme 1.4

The mechanism of Stille coupling is very similar to that observed for the Suzuki reaction.[7]



Scheme 1.5

1.3.3 Negishi Coupling

1.3.3.1 Introduction of Negishi Cross-Coupling

Despite the wide use of organo boronic acids in Suzuki-Miyaura cross-couplings a number of issues remain. For example, these include the frequent need for recrystallization of the arylboronic acid prior to use the propensity of aryl boronic acids to undergo competitive protodeboronation as well as problems involving the preparation and application of sterically hindered boronic acids.[8] Similarly, in the

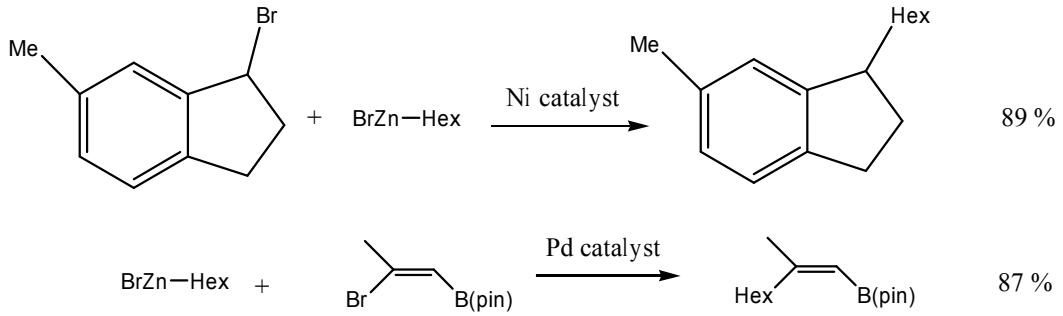
Stille reaction the less reactive aryltin reagents require the use of highly polar solvents and harsh reaction conditions. Moreover, organotin reagents are toxic compounds.[9] Those problems existing in Suzuki and Stille reactions can be often overcome by using Negishi reaction conditions.

The Negishi coupling was the first reaction that allowed the preparation of unsymmetrical biaryls (Equation 1.3).[8]

$$R_1\text{-}X_1 \quad + \quad R_2\text{-}Zn\text{-}X_2 \xrightarrow{MLn} R_1\text{-}R_2$$

Equation 1.3

The reaction can use either palladium or nickel based catalysts (Scheme 1.6).[10] In the second example shown, interesting chemoselectivity was observed with reaction occurring with the bromine atom rather than B(pin) group.



Scheme 1.6

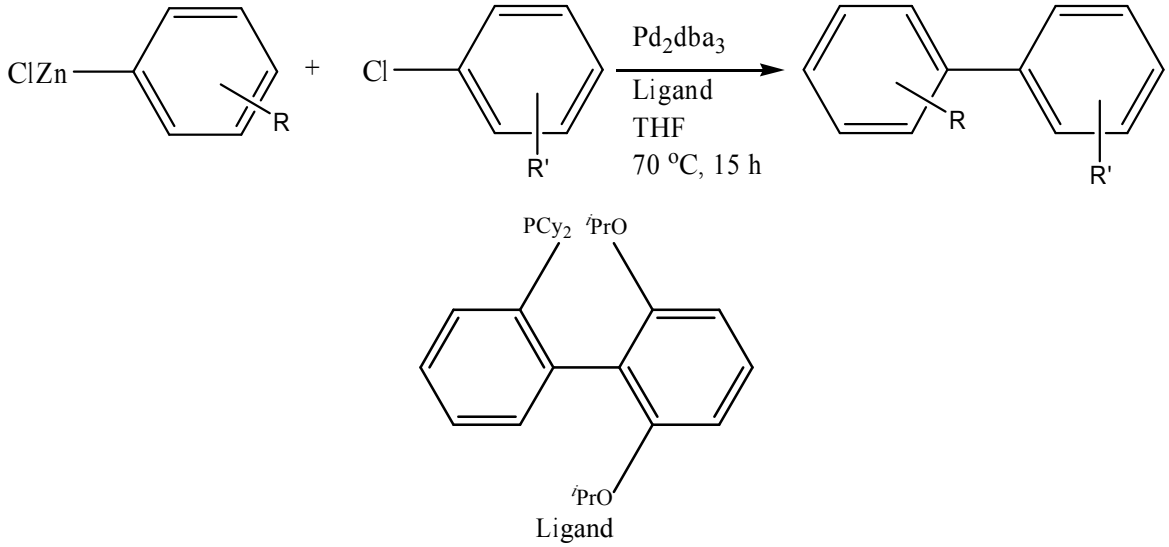
Dai and Fu reported a general protocol for the Negishi reaction by using commercially available $Pd(P^tBu_3)_2$ as a precatalyst.[11] This method could be employed to couple aryl- and alkylzinc reagents with aryl and vinyl chlorides in excellent yield.

$$R\text{-}ZnCl \quad + \quad R^1\text{-}Cl \xrightarrow[THF/NMP,\ 100^oC]{Pd(P(t\text{-}Bu)_3)_2} R\text{-}R^1$$

R=aryl, alkyl; R^1=aryl, heteroaryl, vinyl

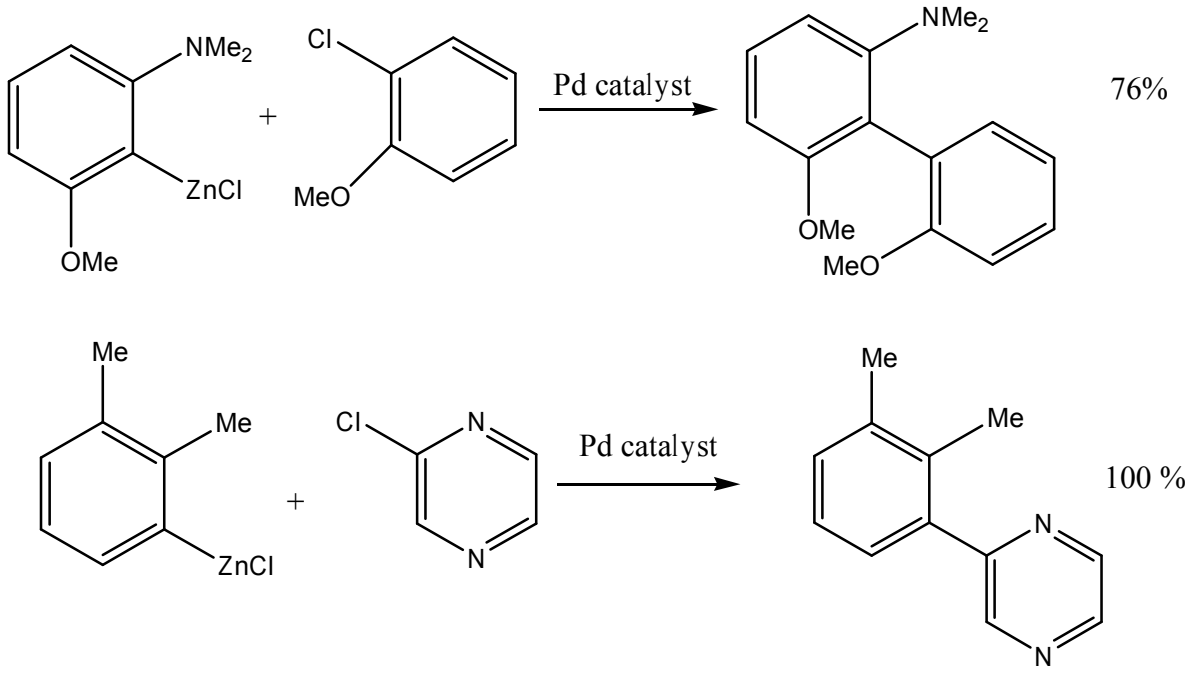
Equation 1.4

In 2004, Milne and Buchwald demonstrated a new, highly active and general catalyst system for the Negishi cross-coupling reaction.[12] (Scheme 1.7)



Scheme 1.7

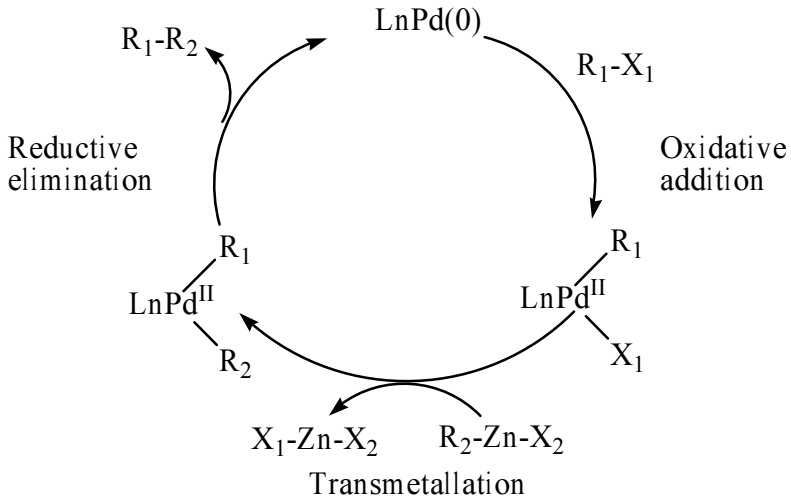
These new catalyst systems are particularly effective in promoting the Negishi cross-coupling reaction providing high turnover numbers, broad substrate scope and giving excellent yield. For example they can be used to couple both aryl and heteroaryl halides and to generate hindered biaryls (Scheme 1.8).



Scheme 1.8

1.3.3.2 The Mechanism of Negishi Cross-Coupling

The mechanism of the reaction is shown below (Scheme 1.9). The reaction in general proceeds through an oxidative addition step of the organohalide followed by transmetallation with the zinc compound and then reductive elimination.



Scheme 1.9

1.4 Polymer-Supported Catalysis

One particular shortcoming in catalysis is the cost of the metal catalyst and associated ligands. On solution to this is to immobilise the catalyst onto a polymer. Such polymeric supported catalysts are easy to separate from reaction media and can be used repeatedly. In addition this method offers several other advantages when compared to non-supported catalysts including enhanced stability, easier handling, non-toxicity and lower cost. [13] Great efforts in polymer-supported catalysis research have been made in recent years and the following sections discuss some of these.

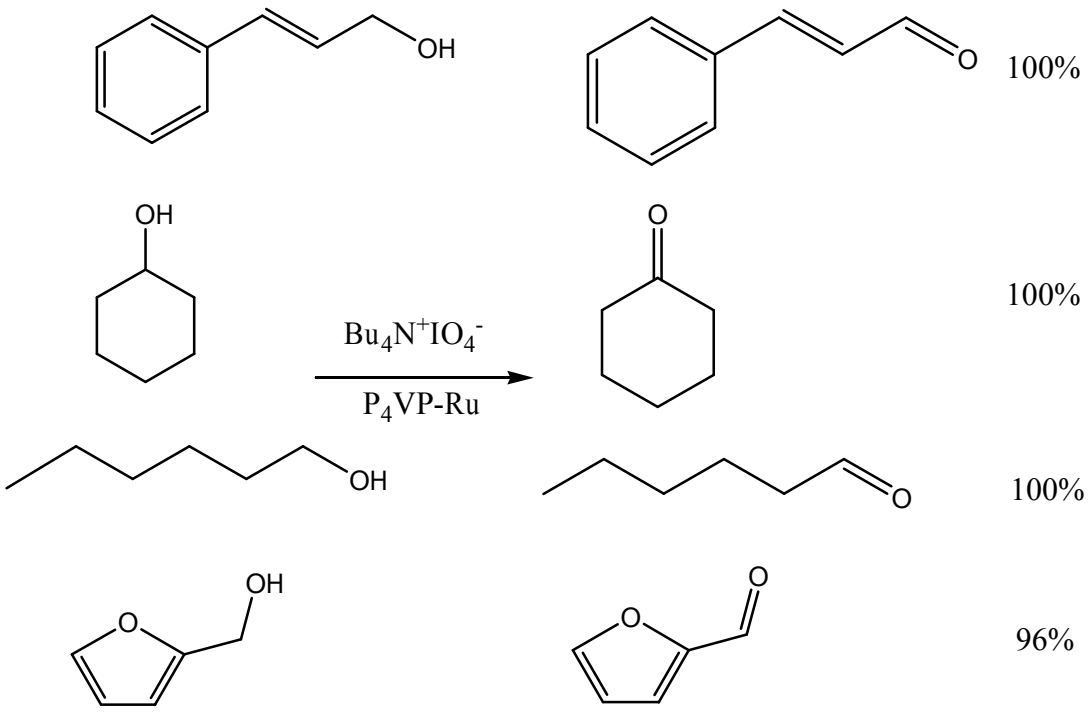
1.4.1 Applications of Polymer-Supported Catalyst

A wide number of organic transformations have been carried out using polymer-supported catalysts. These include oxidation, reduction, addition, cycloaddition, and transition metal-catalyzed carbon-carbon bond-forming reactions.[14] The following

sections will give examples of the application of polymer-supported catalysis to oxidation, reduction, and C-C bond forming reactions particularly focusing on those involving transition metal-catalyzed reactions.

1.4.1.1 Oxidation by Polymer-Supported Catalysts

Oxidation of primary and secondary alcohols to their corresponding aldehydes and ketones plays an important role in organic chemistry. Recently, Friedrich reported that poly (4-vinylpyridine)-supported sodium ruthenate provides an efficient and selective method for oxidation of benzylic and allylic alcohols to their corresponding oxidation products (Scheme 1.10).[15]



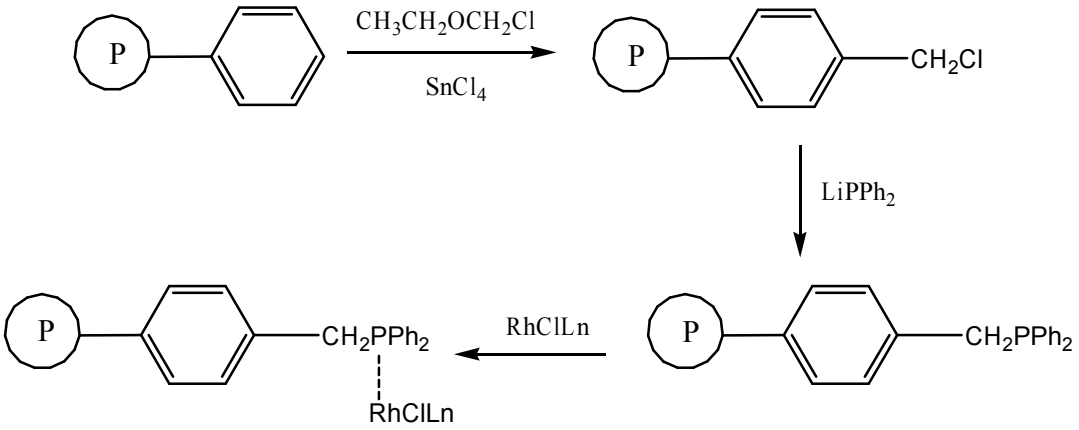
poly(4-vinylpyridine)/DVB(2%)= P_4VP

Scheme 1.10

These reactions proceed at room temperature without heteroatom oxidation, double bond isomerisation or cleavage. In addition, the catalyst can be recycled by filtration and used in another oxidation reaction, with little decrease in the yield observed for each subsequent reaction.

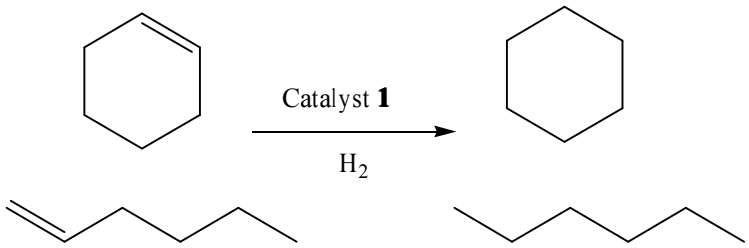
1.4.1.2 Reduction by Polymer-Supported Catalysts

One of earliest reports on the use of polymer supported catalysts for hydrogenation was reported by Grubbs.[16] Commercial polystyrene beads were first chloromethylated, then treated with lithiodiphenylphosphine for 1 day to replace the chlorines atoms with diphenylphosphine groups and then equilibrated with tris(triphenylphophine) chlororhodium(I) for 2-4 weeks to generate the desired polymer catalyst **1** (Scheme 1.11).



1 Scheme 1.11

This catalyst **1** could be used to hydrogenate a series of olefins. In addition, the catalyst **1** was easily recovered and could be reused more than 10 times (Scheme 1.12).

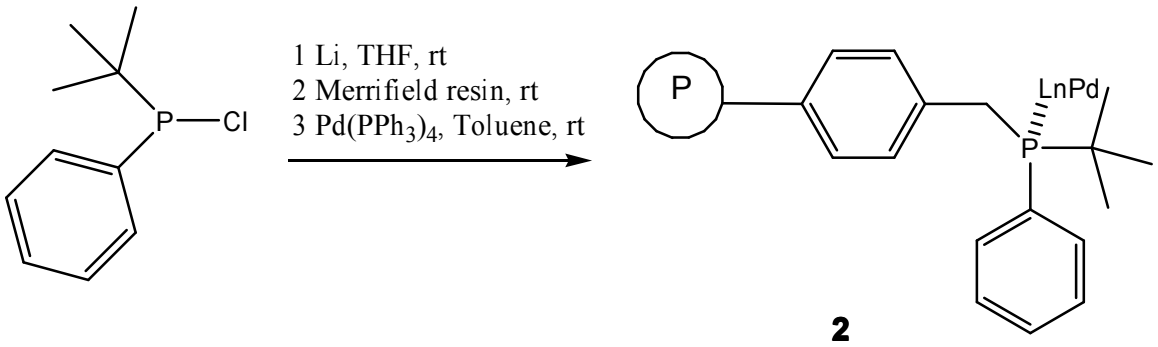


Scheme 1.12

1.4.1.3 Polymer-Supported Transition Metal-Catalyzed Carbon-Carbon Bond-Forming Reaction

Polymer supported transition metal-catalyzed reactions have been extensively studied. One successful example is that reported by Becht and co-workers which provides a general method for supported Suzuki-Miyaura reactions.[17] The polymer supported catalyst was prepared in three steps: lithiation of the (aryl-*tert*-butyl)-

chlorophosphine, followed by substitution of the halogen atoms, such as chlorine, of the polymer, and then introduction of the metal (Scheme 1.13).



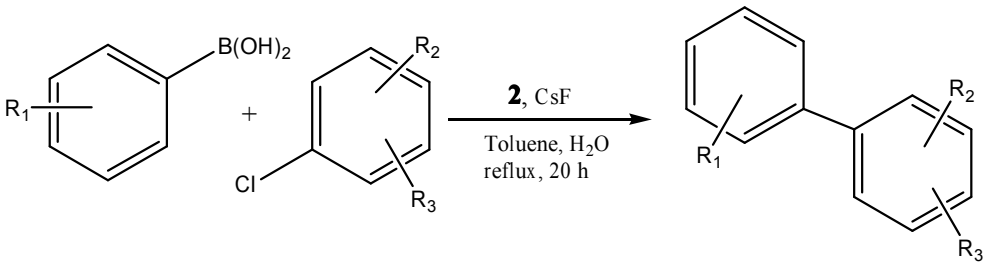
2

Scheme 1.13

The recyclability of these heterogeneous catalysts was then tested in the Suzuki-Miyaura reaction. The cross-coupling of various aryl chlorides with arylboronic acids were performed in the presence of catalyst **2** with very good yields being obtained with either electron-rich or electron-deficient substituent on each reactant (Scheme 1.14). In addition, the catalyst **2** was air- and moisture-stable, easy to recover and reuse. For example, after seven cycles a product yield of 98 % was obtained in the reaction of 4-chloroacetophenone and phenylboronic acid (Table 1.2). Moreover, the crude biaryls obtained contain only a negligible amount of Pd contaminants, which considerably simplified purification procedures.

Table 1.2 The test of recyclability of Catalyst **2**

Run	1	2	3	4	5	6	7
Yield (%)	99	95	99	98	99	98	98

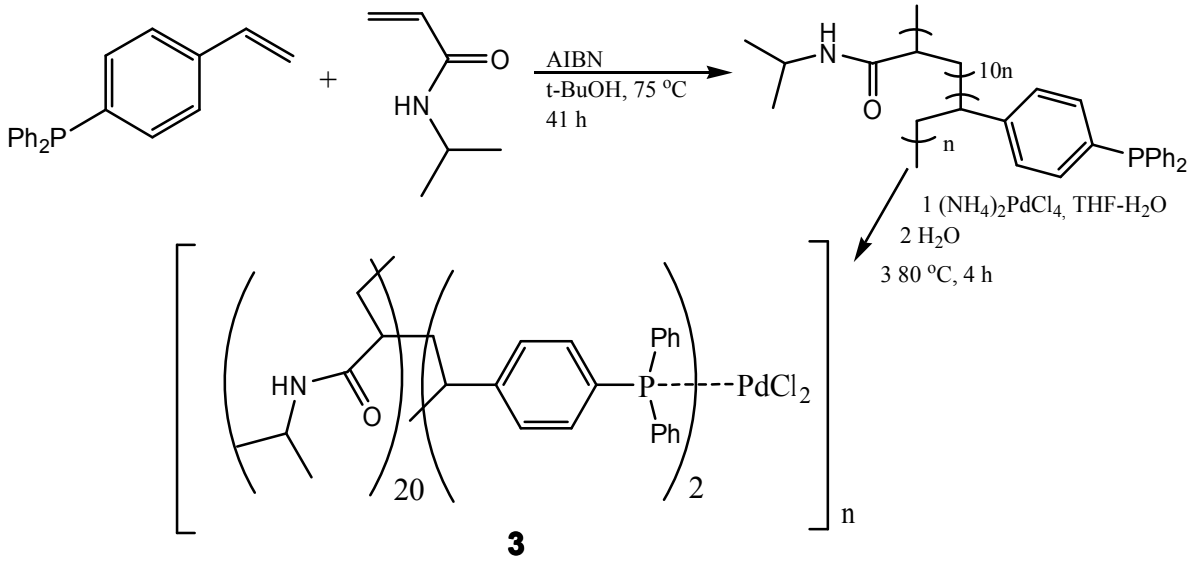


a: R_1=R_3=H, R_2= 4-Ac, 90%; b: R_1=R_3=H, R_2=4-Me, 86%;

c: R_1=2-Me, R_2=4-Ac, R_3=H, 86%; c: R_1=3-NO_2, R_2=4-Ac, R_3=H, 78%.

Scheme 1.14

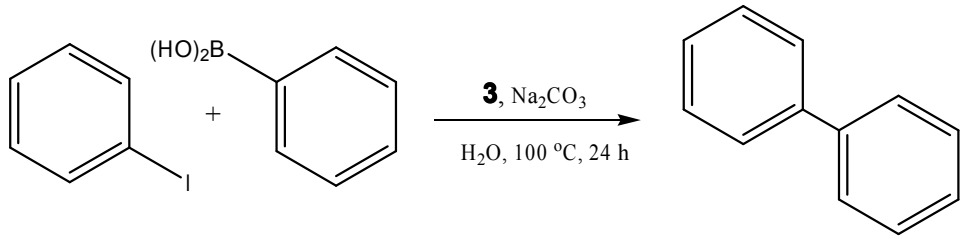
Ikegami and co-workers reported the use of another polymer supported palladium catalyst for the Suzuki cross coupling reaction which also showed high activity.[18] They developed an amphiphilic polymer-supported palladium catalyst **3**, which was insoluble in water and organic solvents. These properties facilitated easy recovery from the reaction system (Scheme 1.15).



3

Scheme 1.15

The coupling reaction of iodobenzene with phenylboronic acid was employed to test catalyst **3** (Scheme 1.16).



Scheme 1.16

Table 1.3 The test of recyclability of Catalyst **3**

Catalyst	1st use	10th use	1st-10th consecutive use
Yield (%)	95	93	av. 95

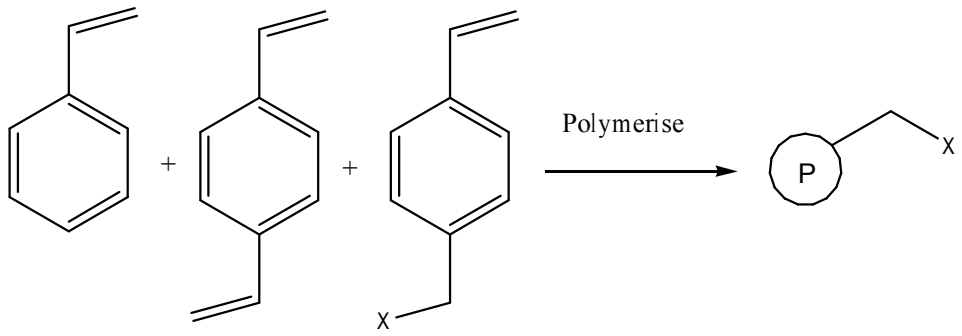
Using the reaction detailed in Scheme 1.16, the catalyst **3** was recycled 10 times without any loss of catalytic activity (Table 1.3). The catalyst was also applicable to the Suzuki-Miyaura coupling of both electron-rich or electron-deficient aryl bromides and triflates, giving with high yields of products. Ikegami also demonstrated that catalyst **3** retains its catalytic activity, even in water, eliminating the need for hazardous organic solvents. Consequently, this catalyst can be considered an environmentally friendly palladium catalyst. In addition it was effective in the Heck reaction as well as in Suzuki reactions.

1.4.2 Types of Polymer-Supported Catalysts

Polymer-supported catalysts have been divided into two categories: soluble and insoluble.

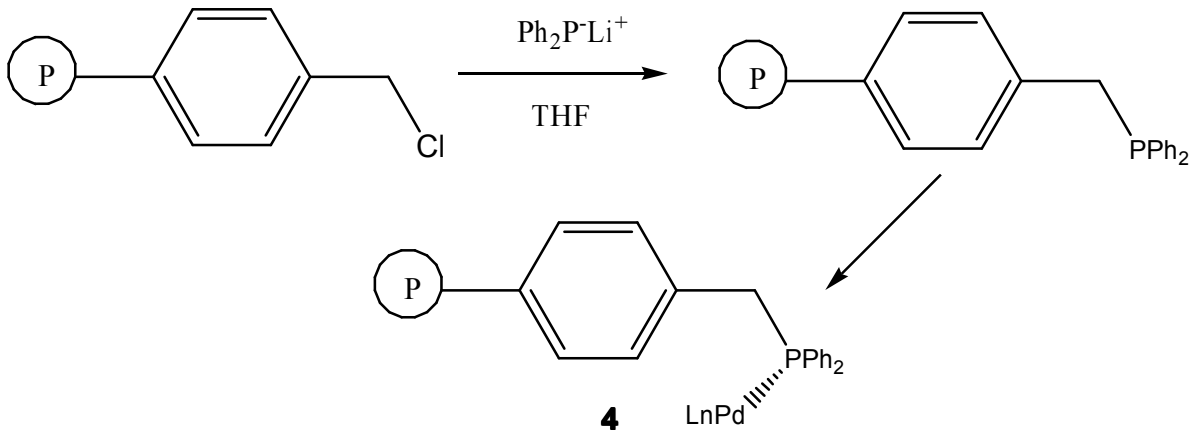
1.4.2.1 Insoluble Polymer-Supported Catalysts

The most commonly used insoluble polymer-supported in catalysis is cross-linked polystyrene, containing a reactive benzyl halide group, known as Merrifield resin, Scheme 1.17.[19]



Scheme 1.17

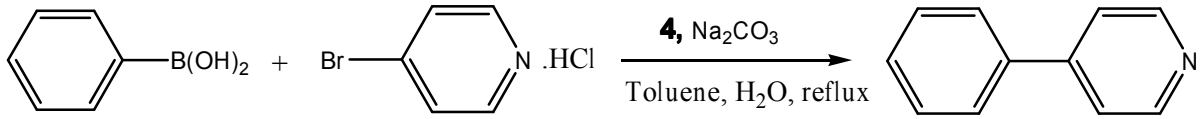
An early attempt to use functionalised polystyrene supported palladium catalysis was reported by Fenger and Drian.[20] The catalyst **4** was prepared in two steps from commercial chloromethyl Merrifield resin by substitution with Ph_2PLi, followed by an exchange reaction with Pd complex, such as $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd(dba)_2$ (Scheme 1.18).



Ln= $(PPh_3)_2Cl_2$; $(PPh_3)_4$; $(dba)_2$

Scheme 1.18

The activity of supported catalyst **4** was measured through the coupling of phenylboronic acid with 4-bromopyridine. Fenger stated that they could be reused more than five times without any decrease in activity (Scheme 1.19).



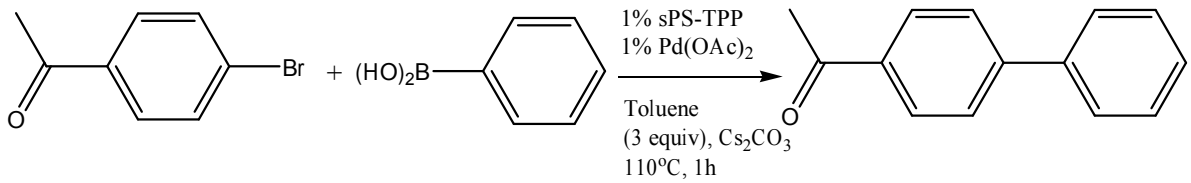
Scheme 1.19

1.4.2.2 Soluble Polymer-Supported Catalysts

Reflecting the benefit of simplified purification procedure and catalyst recovery when compared with traditional solution based catalysts, insoluble polymer-support catalysts have attracted much attention. However, the shortcoming to their use is that the diffusion of reagents and substrates into and out of an insoluble polymer matrix can seriously affect the catalyst's reactivity.[21] Since 1960s, soluble polymer-supports have generated increasing interest as an alternative answer to this challenge.[22] Such homogeneous catalysts generally show better selectivity and higher reactivity than heterogeneous counterparts.[23]

Among all the soluble polymer supports, poly(ethylene glycol) (PEG) and linear polystyrene (PS) are the most common supports used in organic synthesis. For example, PEG supports have many applications in catalysis including the immobilization of phase-transfer catalysts, metal based catalysts etc. For example, Ribière demonstrated that a PEG supported Pd catalyst, promotes a very efficient and selective intermolecular Heck reaction.[24] Blettner and co-workers studied using PEG as a soluble polymeric support in preparation of sterically hindered *(E)* and *(Z)*-3,3-diaryl acrylic acid esters and indicated the polymer support additionally improved the stereoselectivity of the Heck reaction. [25]

A modified polystyrene supported Pd catalyst in Shin's project showed excellent activity in Suzuki-Miyaura coupling of aryl halides (Scheme 1.20). The catalyst could be recovered quantitatively through a simple precipitation process and reused more than four times without significant loss of activity. [23]



Scheme 1.20

Table 1.4 The test of reusability of PS supported catalyst

Catalyst	1st use	2nd use	3rd use	4th use
Yield (%)	99	96	99	98

1.5 Introduction of Boronic Acids and Borylation Reaction

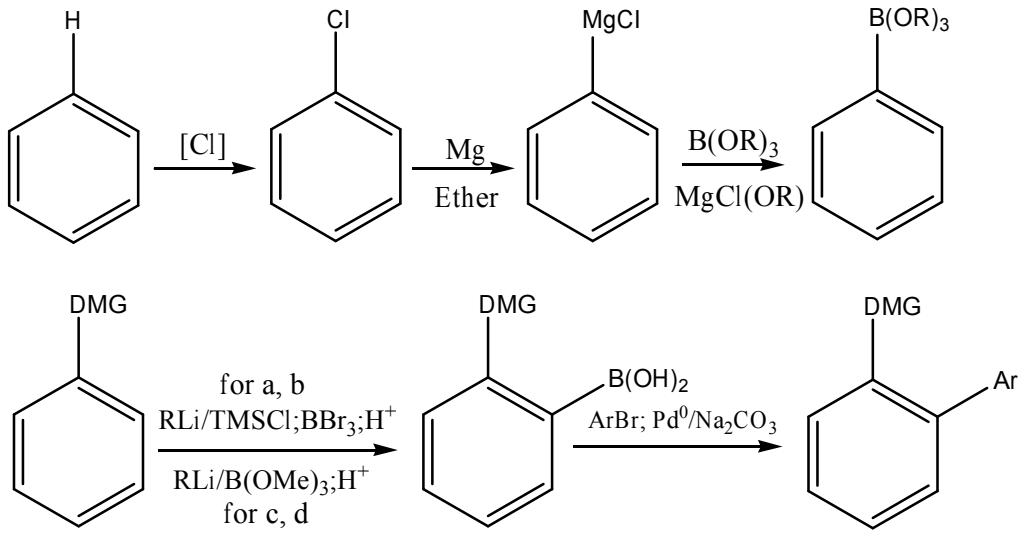
1.5.1 Introduction of Boronic Acids

Organoboronic acid are important reagents for organic synthesis. Most are very stable in air and at ambient temperature and the by-products from their use are generally non-toxic. These properties make them easy to handle during chemical synthetic processes. Whilst most commonly associated with Suzuki-Miyaura

reaction, they have found use in many other organic transformations including both C-C bond forming reactions and functional group interconversions.

1.5.2 Developments in the Synthesis of Arylboronic Acids and Their Esters

Earlier work on the preparation of arylboronic acids or esters generally involves three steps: pre-functionalisation of the arene substrates, transmetallation, and reaction of the arylmetal intermediates with an electrophilic borate. [26,27]



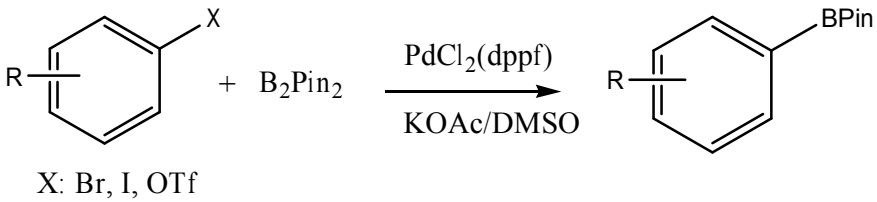
DMG=Direct Metallation Group a: $CON(^{i}Pr)_2$; b:$OCONEt_2$; c:OMOM; d: $NHCO_2$

Scheme 1.21

Whilst, such methods have been widely used there are problems, with this strategy. For example, although arylboronic esters can be synthesised using Grignard or lithium reagents they require the protection of functional groups sensitive to these reagents. Similarly, the *ortho*-transmetallation methods needs an *ortho*-directing groups as a prerequisite which may not be required in the final product. Overall, both of these pathways require several steps to achieve the desired product.

In 1995, Miyaura and co-workers described the palladium catalysed cross-coupling of bis(pinacolato)diboron (B_2pin_2) with aryl halides (Scheme 1.22).[28] Compared to the earlier methods, this methodology showed increased selectivity and efficiency. Furthermore, it can tolerate various functional groups and is a more linear

procedure to acquire the borylated product as only one step is required. In addition, the borylated products are very stable towards air and easy to work up by normal chromatography.



Scheme 1.22

However, even this method required pre-functionalisation of the arene substrate. In pursuit of a more general, milder and efficient method, attention has turned to direct C-H borylation. Although catalytic functionalization of inert C-H bonds is still a big challenge in organic synthesis, much progress has been made in recent years.

1.5.3 Catalytic C-H borylation

Recently, Rh, Ir, Pd and Re complexes have been explored to allow direct borylation of hydrocarbons via C–H activation. These are economical, efficient, and environmentally benign protocols for the synthesis of a variety of organoboron compounds.[29] Whilst this project concentrated on the synthesis of polymer-supported bipyridine ligands for iridium-catalysed C-H borylation, the evolution of the methods for iridium catalysed aromatic C-H borylation will be introduced.

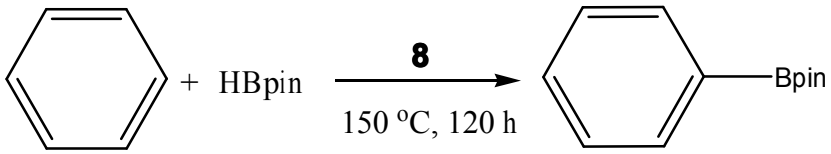
1.5.3.1 Development of Iridium-Catalysed C-H Borylation of Arenes

The first example of aromatic C-H borylation with Ir complexes was reported by Marder and co-workers in 1993 in a synthetic approach to making **6**. The reaction of HBCat with Ir complex was performed in toluene.[30] Unexpectedly, a small amount of **7** was observed. This was a significant discovery in the development of aromatic C-H borylation (Equation 1.5).

$$[Ir(\eta^5\text{-}C_9H_7)(COD)] + \text{excess HBCat} \longrightarrow \underset{\mathbf{6}}{[Ir(\eta^6\text{-}MeC_6H_5)(Bcat)_3]} + \underset{\mathbf{7}}{\text{tolyl-Bcat}}$$

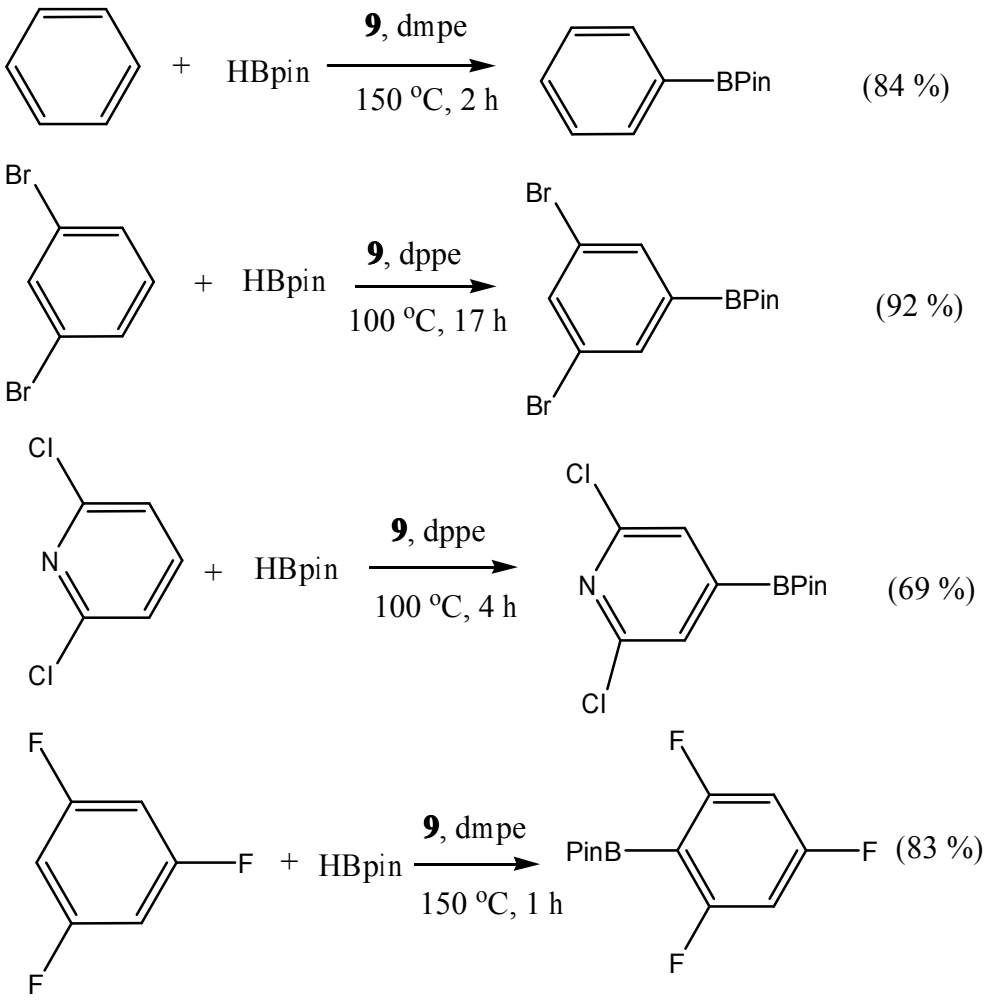
Equation 1.5

In 1999, Smith and co-workers demonstrated the first catalytic borylation reaction by using a [Cp*Ir(PMe)$_3$(H)(Bpin)] **8** (Cp*=C_5Me_5) in the presence of PMe_3.[31]



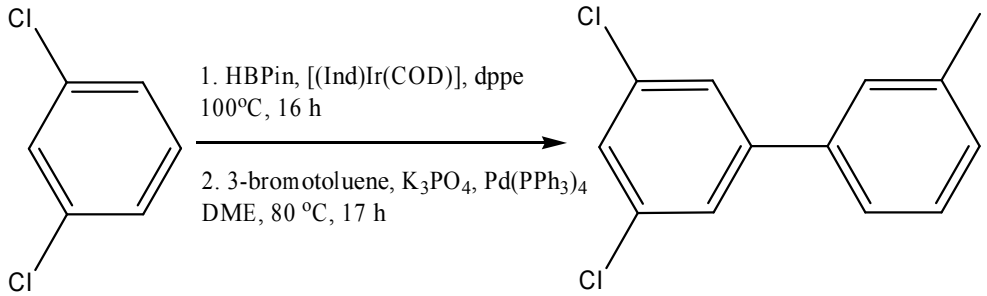
Scheme 1.23

Three years later, Smith further advanced this methodology showing that [(Ind) Ir (COD)] **9** (Ind= η^5-C_9H_7, COD=1, 5-cyclooctadiene), combined with dmpe (1, 2-bis (dimethylphosphino) ethane), had an effective TON of 4500. This was 1000 higher than precatalyst **8**. In addition, catalyst **9** could be generated easily from commercial available sources such as [IrCl(COD)]$_2$ **10**.Smith also reported that Ir complex **9** in combination with dppe (1,2-bis (diphenylphosphino)ethane) generated catalysts that are more selective for arene activation than Rh catalysts [Cp*Rh(η^4-C_6Me_6)] **11,** with the arene to benzylic selectivity exceeding 142: 1 compared to 7: 1 for **11**.[27] These new Ir catalysts **9** with a ligand of dmpe or dppe were employed with a range of arenes and showed good conversions (Scheme 1.24).



Scheme 1.24

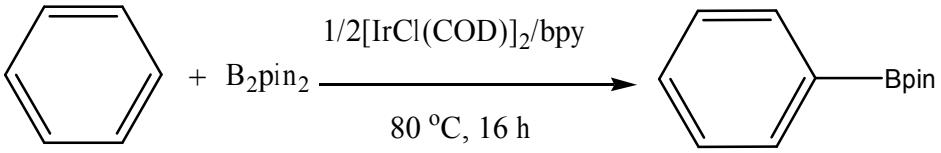
Furthermore, Smith explored the one-pot C-H activation and cross-coupling reactions. The desired product was obtained in 80% yield. This study indicated that Ir catalysts are compatible with Pd-catalyzed reactions (Scheme 1.25).



Yield = 80 %

Scheme 1.25

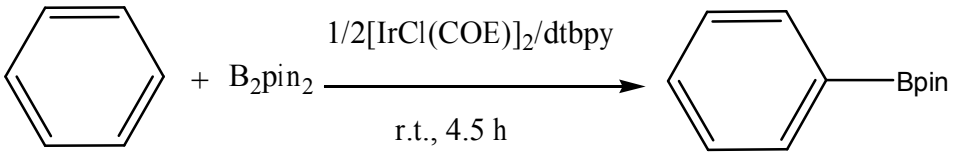
In the same year, Miyaura and co-workers disclosed that a combination of commercially available $[IrCl(COD)]_2$ **10** and 2,2'-bipyridine (bpy) formed complexes that enable the borylation of arenes by B_2pin_2 under mild conditions (Scheme 1.26).



Yield = 95 %

Scheme 1.26

In the same report, Miyaura's group revealed that $[IrCl(COE)]_2$ **12** (COE= cyclooctene) in conjunction with 4,4'-di-tert-butyl-2,2'-bipyridine (dtbpy) ligands could catalyse the C-H borylation at room temperature. The borylated product PhBpin was produced in 83 % yield (Scheme 1.27).[32]



Yield = 83 %

Scheme 1.27

The use of **10**/bpy and **12**/dtbpy, provides a simple and direct route for the synthesis of arylboronates. Furthermore, these discoveries made a significant contribution to the development of C-H borylation of arenes and heteroarenes.

1.5.3.2 Study on the $[IrX(COD)_2]$, bipyridine ligands, and solvent of Iridium-Catalysed C-H Borylation

After studying the effect of anionic ligands (X) on iridium precursors $[IrX(COD)_2]$, Miyaura and Hartwig *et al* demonstrated that iridium complexes possessing OPh, OMe or OH (entry 4, 5, 6) are more active for the borylation of benzene by B_2pin_2 at room temperature. The less-basic OAc, Cl and cationic BF_4 (entry 1, 2, 3) complexes containing a bpy ligand did not catalyze the reaction.[33]

Table 1.5

The effect of anionic ligands (X) on iridium precursors [IrX(COD)$_2$]

Entry	Ir precursor	Ligand	Time[h]	Conversion[%]	Yield [%]
1	[IrCl(COD)$_2$]	bipyridine	24	0	0
2	[Ir(OAc)(COD)$_2$]	bipyridine	24	19	1
3	[Ir(COD)$_2$]BF$_4$	bipyridine	24	3	0
4	[Ir(OPh)(COD)$_2$]	bipyridine	4	100	84
5	[Ir(OMe)(COD)$_2$]	bipyridine	4	100	90
6	[Ir(OH)(COD)$_2$]	bipyridine	4	100	88

The effects of substitution on the bipyridine ligand were evaluated using [Ir(OMe)(COD)]$_2$ **13** catalyst precursor. Catalysts derived from methylated analogues **14**, **15** and **16**. Figure 1.3, displayed moderate or good activity, but catalysts containing **17** and **18** showed little activity. Catalysts containing the 4,4'-di-tert-butyl-2,2'-bipyridine **19** exhibited the highest yield for aromatic C-H borylation.

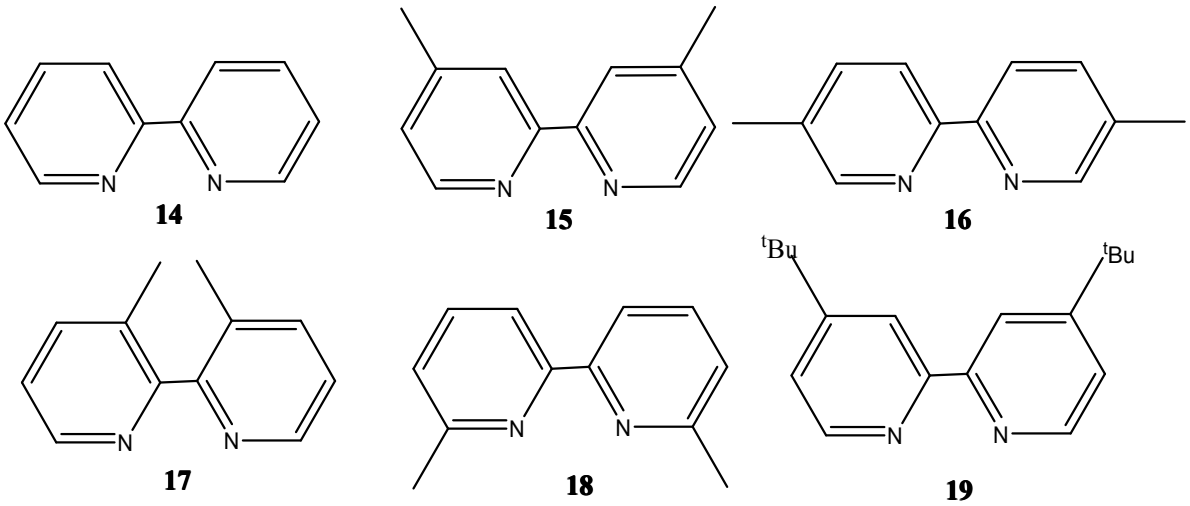
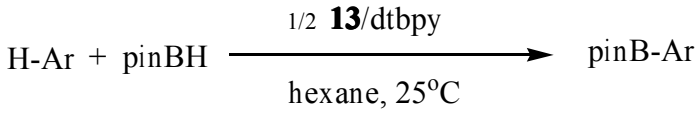


Figure 1.3

[Ir(OMe)(COD)]$_2$ **13** and 4,4'-di-tert-butyl-2,2'-bipyridine generated a Ir complex with the readily accessible and less expensive pinBH provided a convenient, economical and environmentally benign route for aryl- and heteroarylboronates.[34] (Scheme 1.28)

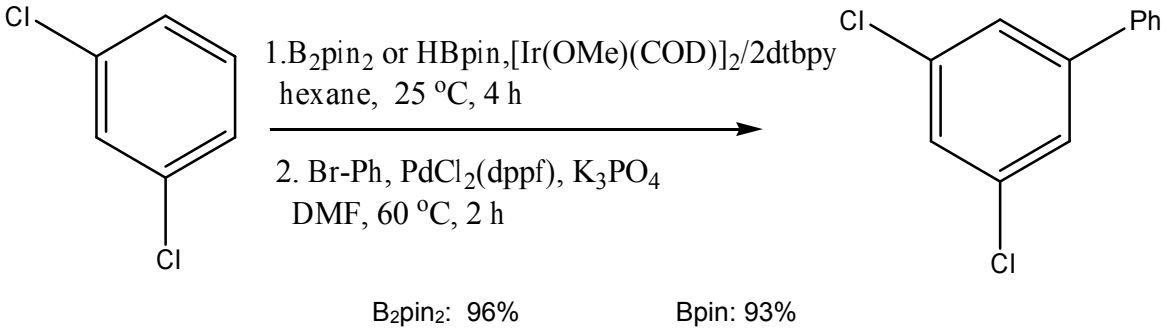
The choice of solvent is also very important for the reaction. In Miyaura's report the suitable solvent is hexane. More recently other more substrate tolerant solvents have been described notably THF and MTBE.



Scheme 1.28

1.5.3.3 One-Pot Borylation/ Suzuki-Miyaura Reaction

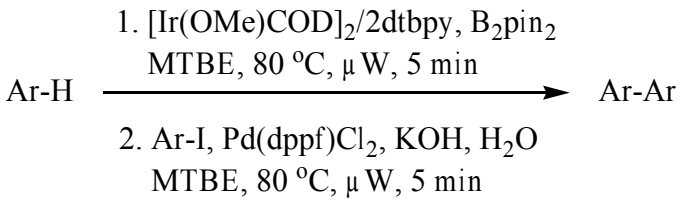
As the borylated compounds are important intermediates in organic synthesis, ideas of directly cross-coupling with aryl bromides to create a convenient one-pot procedure for the synthesis of unsymmetrical biaryls have attracted much attention.[35]



Scheme 1.29

Miyaura studied the dichlorobenzene as model reaction and obtained high yield of dichlorobiphenyl which revealed the optimal condition for cross-coupling was use the $PdCl_2$ (dppf) as catalyst, K_3PO_4 as base, DMF as solvent. Under these optimal conditions a series of C-H borylation have been employed and afforded excellent yield.

More recently, Harrisson *et al* has described a one-pot single version of this sequence which can be accelerated by using microwave irradiation with methyl tert-butyl ether (MTBE) as solvent.[36]

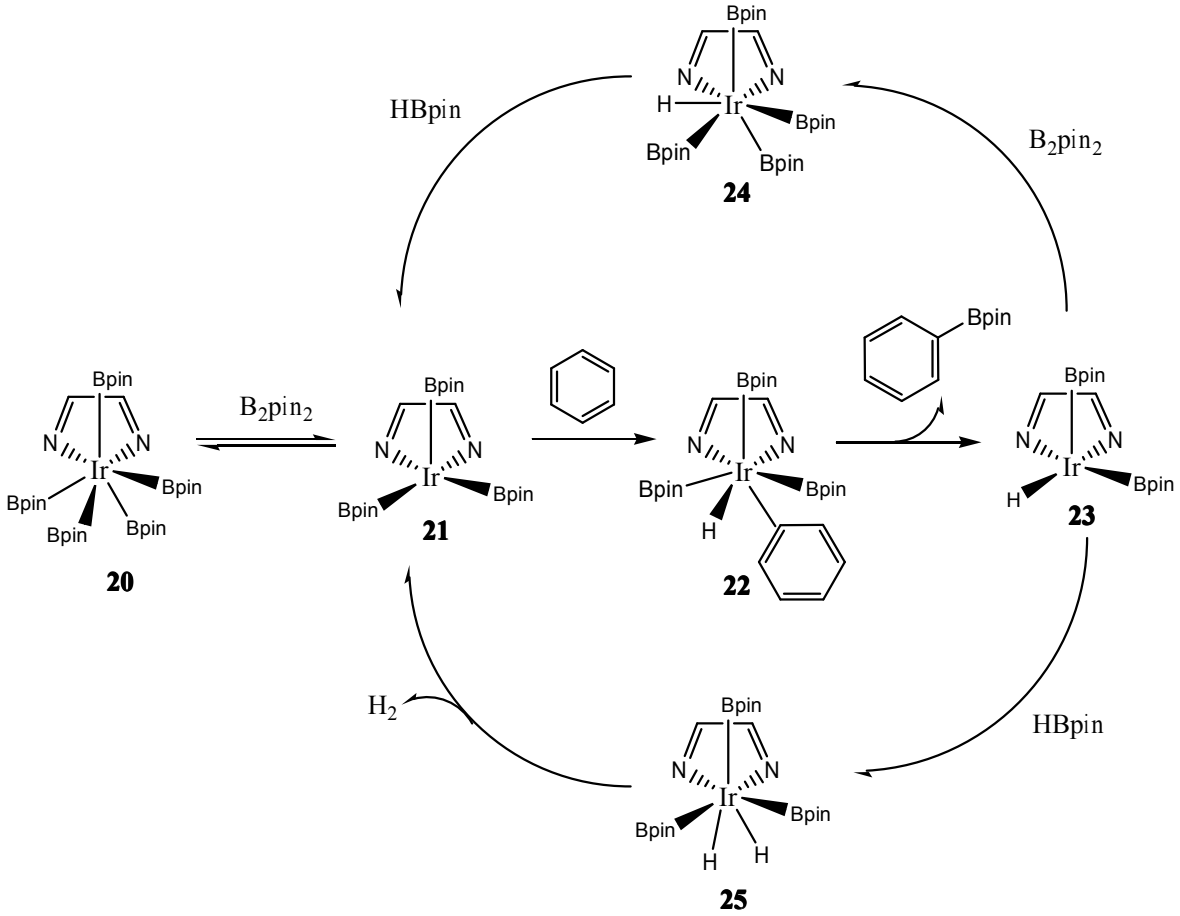


Scheme 1.30

This method provided an efficient mehod for the one-pot single solvent C-H borylation/ Suzuki-Miyaura cross-coupling sequence. Significantly with some substrate combinations the whole process can be completed in a matter of minutes.

1.5.3.4 Mechanism of Iridium-Catalysed C-H Borylation of Benzene

The mechanism of $[IrCl(COD)_2]$/bpy-catalyzed borylation of benzene with diboron compound was studied computationally by Sakaki and co-workers.[37]



Scheme 1.31

This suggested that the iridium(III) tris (boryl) complex **21** was the active species. The oxidative addition of benzene affords iridium(V) species **22** and reductive elimination of phenylborane takes place from **22** with concomitant formation of the iridium(III) complex **23**. Complex **23** then reacts with B_2pin_2 to give iridium(V) complex **24** with an activation barrier of 8.0 kcal/mol. Subsequent reductive elimination of borane then regenerates the active species **21**. After all the B_2Pin has been consumed, **23** can react with HBpin generated from **24**. This ''second cycle'' has a considerable larger activation barrier 21.3Kcal/mol for the formation of **25**.

From this analysis, Sakaki and co-workers concluded that the trisboryl iridium(III) complex **21** represented the key catalytically active species. This suggestion was subsequently corroborated experimentally by Hartwig *et al*.

1.6 Conclusions

As can be seen from this short and highly selective review both metal based catalysis and polymer supported catalysis are important areas of organic synthesis. Iridium catalysed arene C-H borylation chemistry has become an important method for organic synthesis providing access to boronic acids widely used in the Suzuki Miyaura reaction. The combination of C-H borylation chemistry and polymer supported chemistry has not been well described. The aim of this project is to generate polymer-supported bipyridine ligands for use in the iridium-catalysed C-H borylation reaction. The work towards this goal is described in more details in the following chapter.

Chapter 2 Results and Discussion

2.1 Introduction

Iridium-catalyzed C-H borylation provides a powerful synthetic tool for generating organoboron derivatives. However whilst the reaction conditions are much safer and milder than traditional methods the high cost of Iridium catalysts limits their use on industrial-scale. Although these problems might be overcome by recovery and re-use, the unstable and highly soluble nature of the Ir complex makes this challenging. However, by attaching the catalyst to an insoluble polymer support facilitates easy recovery and reuse of the precious iridium catalysts. As discussed in the previous chapter, there is an underlying increased interest on polymer supported catalysts and their reusable properties. The work described below discusses several methods to generate a polymer supported ligands for iridium catalysed C-H borylation.

2.2 Project Strategy

A polymer supported Ir-catalyst can be divided into three parts: a suitable polymer, for example commercially available Merrifield resin, the iridium complex, such as [IrCl(COD)$_2$] or [IrOMe(COD)$_2$]; and the ligands. Whilst 4, 4'-di-tert-butyl-2, 2'-bipyridine is the most common ligands for iridium borylation, it requires modification for use in polymer supported catalysts. The best ligands should be easy to attach to the polymer. In addition, since the immobilization to a polymer can decrease the reactivity of catalysts, it is necessary to form more reactive ligands. Taking those factors into account the ideal ligand complex can be drawn as shown in Figure 2.1.

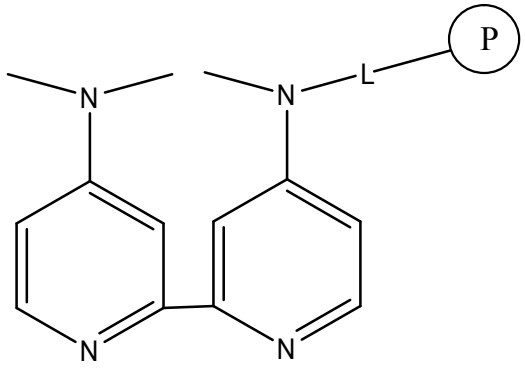
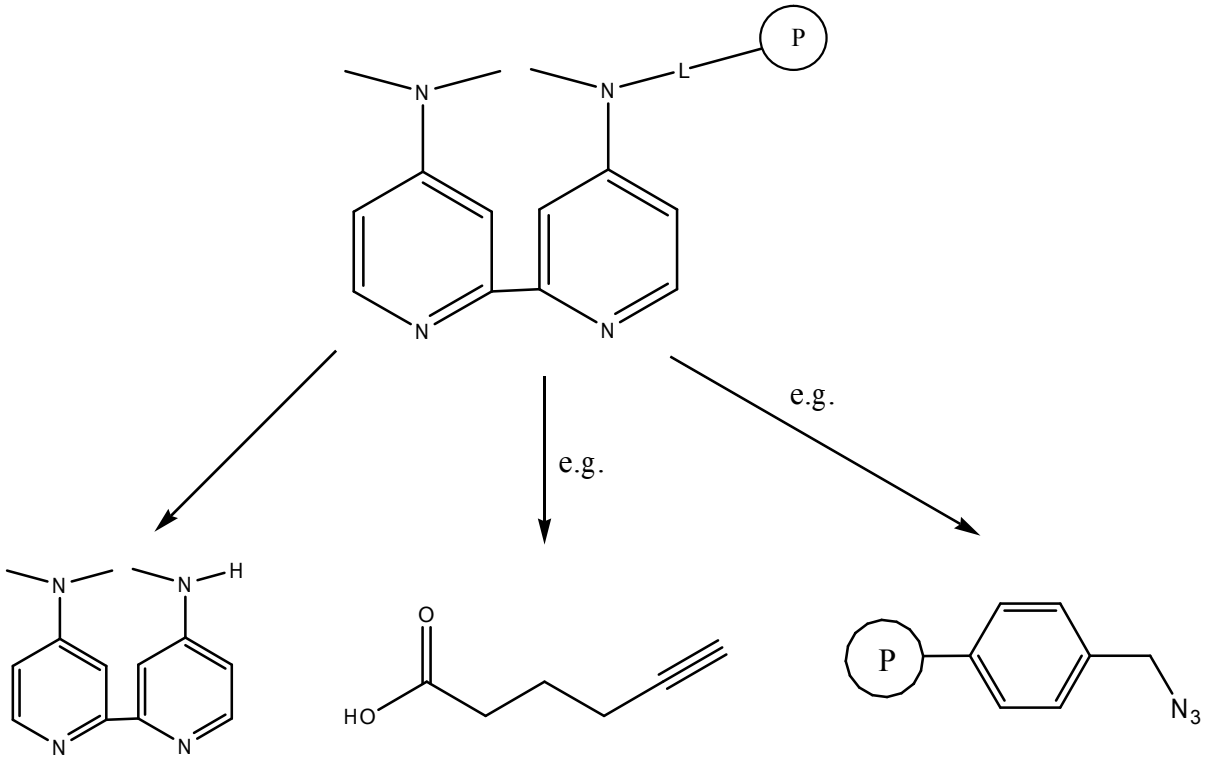


Figure 2.1

The reason for this is that dimethylamino groups are more electron-donating than the tert-butyl groups, which are used in most C-H borylation bipyridine ligands found to-date. Consequently, the dimethylamino group can increase the activity of the polymer bonded complex. Furthermore the amine group is easy to combine with other functional groups. The disconnection of the ligand complex could then be simplified to that shown in Figure 2.2.

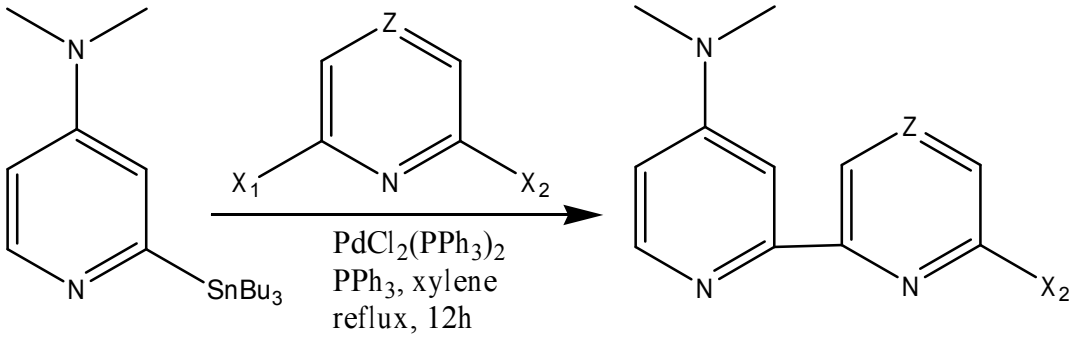


26 **27** **28**

Figure 2.2

Azide **28** corresponds to a suitably modified polymer support. It was planned to use the mild conditions of the azide alkyne Huisgen cycloaddition to couple the ligand to the polymer. This required an alkyne and azide to be attached to the ligands and polymer, respectively. The linker component can be obtained from commercial available acid **27**. The non-symmetrical ligand **26** can be further disconnected into two 4-substituted pyridines.

With these points in mind attention was drawn to a report by Fort and co-workers detailing the synthesis of disubstituted 2, 2'-bipyridines (Scheme 2.1). [38]



a: X_1=Br X_2=H Z=CH, 72%; b: X_1=Cl X_2=H Z=N, 85%

c: X_1=Br X_2=H Z=$CNMe_2$, 60%; d: X_1=X_2= Br Z=CH, 91%

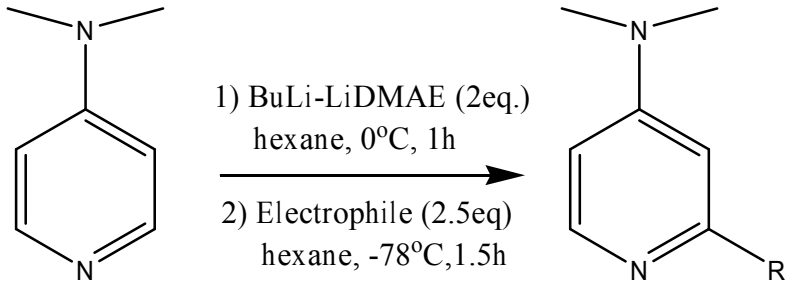
Scheme 2.1

With the structure shown in figure 2.2 and the reaction paths in scheme 2.1 in mind, several strategies could be investigated to generate a polymer-supported complex.

2.3 Synthesis of 4, 4'-(Dimethylamino)-2, 2'-bipyridine as Model Ligands

2.3.1 Preparation of 2-Substituted-4-DMAP

4-(Dimethylamino) pyridine (DMAP) has been used extensively as a powerful ligand for transition metals. The modification of the 4-aminogroup has considerable precedent,[39] but only a few papers focusing on the pyridine ring have been published. The first direct lithiation of 2-DMAP was reported by Fort and co-workers. According to Fort's report the use of a BuLi-Me_2N $(CH_2)_2OLi$ (BuLi-LiDMAE) combination lead to the selective monolithiation of the 2-position of DMAP (Scheme 2.2). The resulting anion could be then combined with a range of electrophiles as shown in Table 2.1.

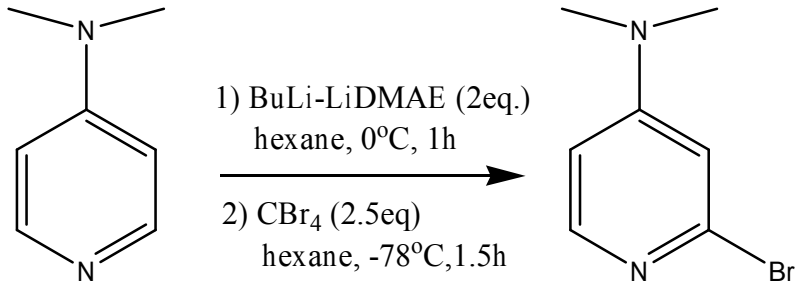


Scheme 2.2

Table 2.1 Synthesis of 2-Substituted-4-DMAP

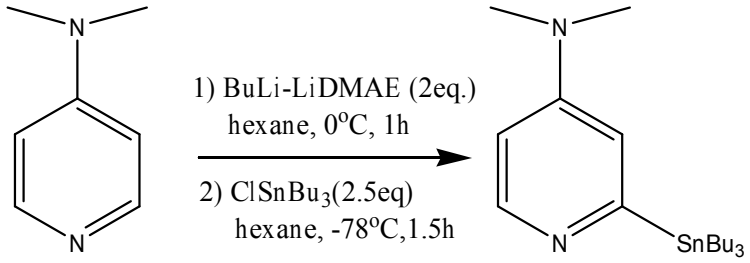
Electrophile	**R**	**Isolate Yield (%)**
$PhCONMe_2$	PhCO	65
$ClPPh_2$	PPh_2	90
CBr_4	Br	94
$ClSnBu_3$	$SnBu_3$	70

This approach of selective functionalisation of the C-2 position of DMAP provided a simple way to synthesize bromide **30**, which was required for the cross-coupling (Scheme 2.3). Consequently this process was explored. In this two equivalents of BuLi-LiDMAE were added to DMAP at 0°C to form the anion and then the reaction mixture was cooled to -78 °C and a solution of CBr_4 as the electrophile in hexane was added. Following quenching by addition of water and work up, examination of the crude product by ^{1}H-NMR spectra showed four peaks at δ 7.96 (d, 1H), 6.66 (d, 1H), 6.45 (dd, 1H), and 3.00 (s, 6H) which are consistent with expected C6, C3, C5 and NMe_2 signals. This was further confirmed by the characteristic 1:1 bromine isotope pattern in the mass spectra corresponding to the molecular ion of 201(M^+, Br^{79}) and 203(M^+, Br^{81}). Following chromatography (50% EtOAc in hexane) the pure bromide **30** was obtained in 75% yield.



29 Yield= 75% **30**

Scheme 2.3

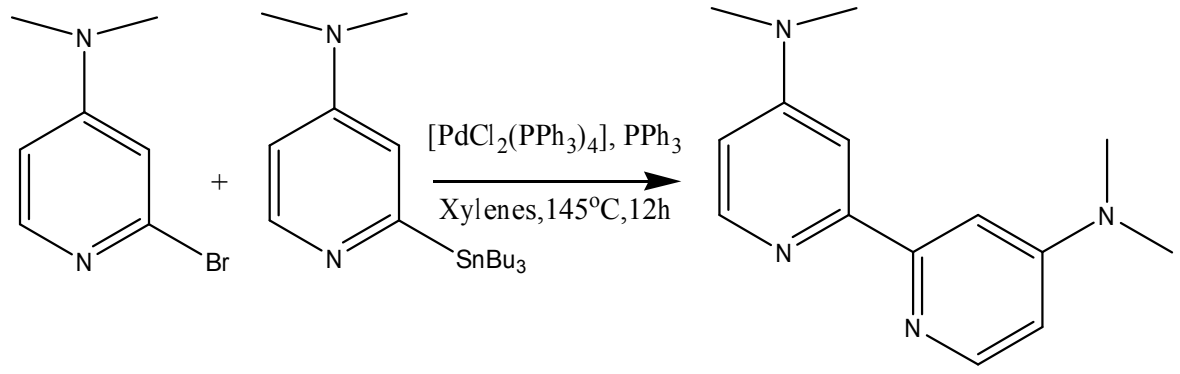


29 Yield= 80% **31**

Scheme 2.4

After that attention then turned to the preparation of 2-tributylstannyl-4-dimethylamino pyridine **31**. Using the same procedure as the bromide but with $SnBu_3Cl$ as the electrophile was equally successful. Examination of the ^{1}H-NMR spectra showed three peaks at δ 8.38 (d, 1H), 6.67(d, 1H) and 6.40 (dd, 1H), which are consistent with expected the C6, C3, and C5 signals. The formation of the desired stannane was further confirmed by the characteristic tin isotope pattern in the mass spectra corresponding to the molecular ion of 413.3 (M^+, Sn 120), 411.3(M^+, Sn 118). 409.3(M^+, Sn 116). The isolated yield was 80%. The availability of the tin derivative offered a possibility to prepare new 2, 2'-bipyridine ligands by Stille cross-coupling.

2.3.2 Stille Cross-Coupling of 2-Substituted-4-DMAP

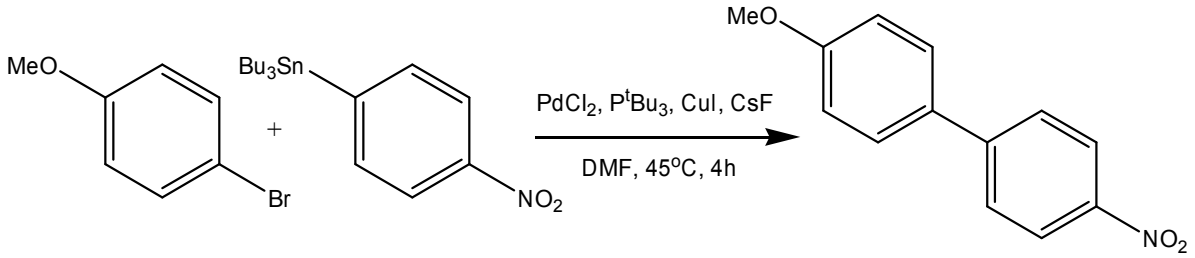


Yield= 60 % **32**

Scheme 2.5: Synthesis of bipyridine as reported by Fort[39]

With **30** and **31** in hand, we started our investigation on generating the bipyridine **32**, through a Stille reaction using the procedure taken from Fort and co-workers' report (Scheme 2.5).[39] In this, $PdCl_2(PPh_3)_4$, PPh_3 and **30** were added into a solution of **31** in degassed xylene and the reaction mixture was heated to 145°C under argon atmosphere. After heating under reflux for 12 h, the reaction mixture was allowed to reach room temperature and the black mixture was filtered over a pad of Celite. Unfortunately, examination of the crude reaction mixture by ^{1}H-NMR spectra, revealed no signals that suggested the formation of **32**.

Following this unsuccessful reaction an extensive study of the Stille coupling was undertaken.



33 **34** Yield= 92 % **35**

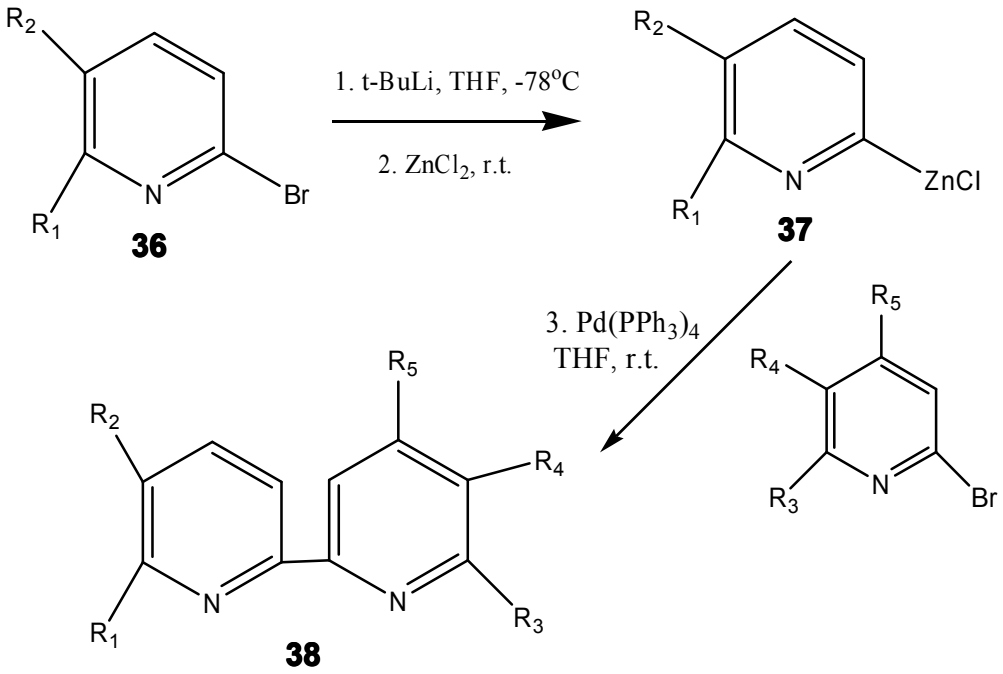
Scheme 2.6: Stille Cross-coupling as reported Baldwin[41]

A search of literature revealed a report by Baldwin,[40] in which a combination of a copper (I) salt with fluoride ions proved to have a remarkable effect on the Stille coupling (Scheme 2.6). The beneficial effects of Cu (I) has been well documented. Stille and Scott[41] have observed that fluoride ion can increase the rate of palladium-catalyzed coupling reactions and that the Bu_3SnCl by-product could be removed by

transformed into insoluble Bu_3SnF. Baldwin and coworkers demonstrated that the use of a $PdCl_2/P^tBu_3$ catalytic system with CuI and CsF in DMF was the optimal conditions when coupling aryl bromides. Consequently, this method was attempted for the cross-coupling of **30** and **31.** However, analysis of the crude product using ^{1}H-NMR spectra showed that a considerable amount of DMAP had been regenerated but gave no evidence for the formation of the desired bipyridine.

2.3.3 Negishi Cross-coupling of 2-Substituted-4-DMAP

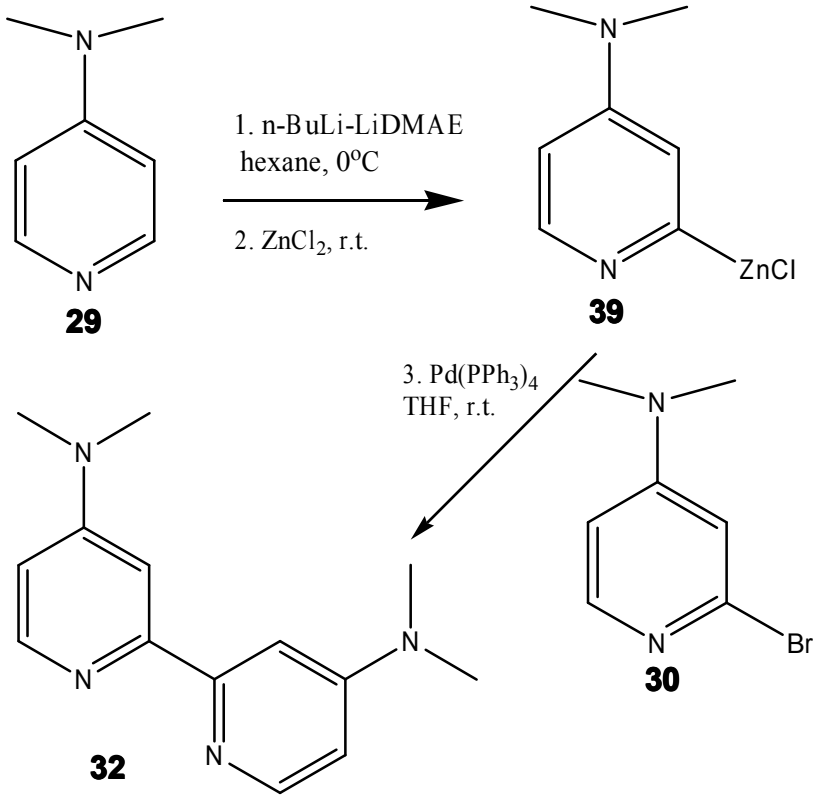
There are three common methods to achieve the cross coupling of two different pyridine derivatives. There are the Stille, Suzuki and Negishi reactions. The unsuccessful generation of **32** by the Stille reaction prompted us to explore the alternative reactions. Given that organozinc compounds are reported to provide better transmetalation activity than organoboron reagents, coupled with the known difficulties in making 2-pyridine boronates, we opted to explore the Negishi reaction. Recently, Lützen[42] had reported a one-pot reaction for the synthesis of various mono- and disubstituted 2, 2'-bipyridines. This modified Negishi cross-coupling strategy uses a relatively inexpensive, commercially available catalyst tetrakis (triphenylphosphine) palladium(0). (Scheme 2.7)



Scheme 2.7

The mechanism of cross-coupling reaction proceeds through the oxidative addition of the organic bromide, followed by transmetallation with the arylzinc compound and reductive elimination.

We started our investigation by exploring the generation of the required dimethylamino-2-pyridyl zinc reagent. Since the selective 2-lithiation of DMAP, following Fort's procedure, had proved to be successful it was proposed that simple transmetallation of the pyridyl lithium might generat the required organozinc reagent.

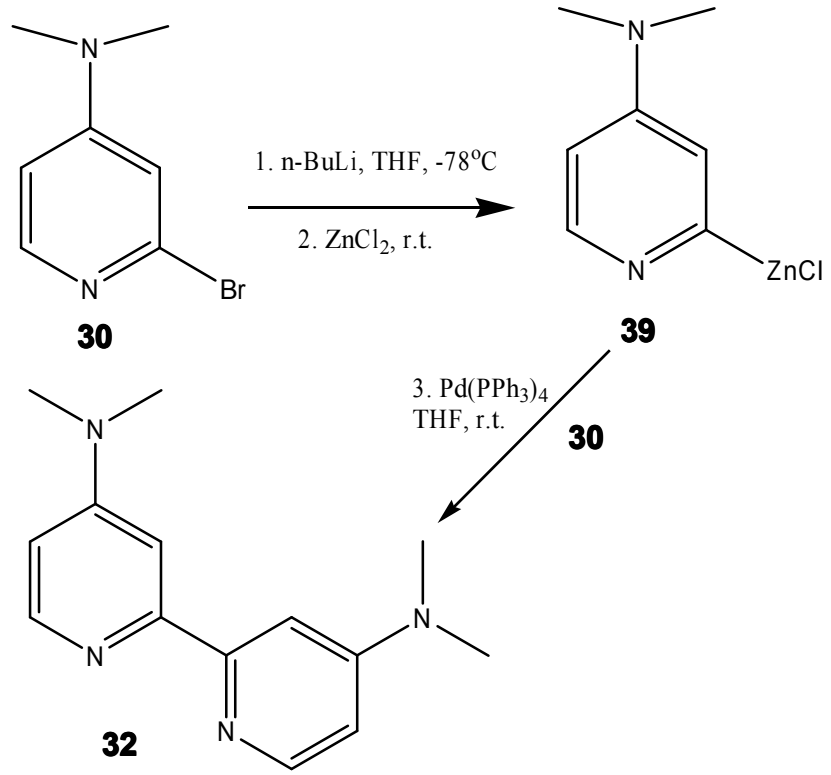


29 **39** **30** **32**

Scheme 2.8

These 'one-pot' reactions are described in Scheme 2.8. Following lithiation as before $ZnCl_2$ was then added and the solution stirred for 2 h when a solution of **30** and Pd $(PPh_3)_4$ in THF was added. After stirring for a further 18 h at room temperature, the reaction was quenched by the addition of sat. aq. EDTA. Disappointingly, the crude ^{1}H-NMR spectra only showed three peaks at δ 7.88 (d), 6.59 (d), 6.38 (dd), and two, δ 8.19 (d), 6.45 (d), which correspond to **30** and **29**, respectively.

It is possible that the DMAE inhibited the formation of the organzinc reagent. Consequently, an attempt to start the reaction from bromide **30** by lithium-halogen exchange was carried out. (Scheme 2.9)



Scheme 2.9

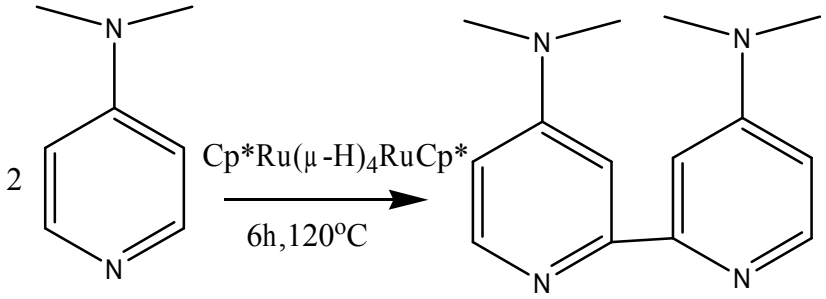
Following addition of BuLi to a solution of bromide **30** in THF at -78 °C, 2.4 equiv. of $ZnCl_2$ was added to the reaction mixture. Subsequently, another portion of bromide and the Pd catalyst were added. Examination of the crude reaction mixtures by ^{1}H-NMR spectra, revealed signals for the **30** and three multiple peaks between δ 7.2 to δ 7.8. Following chromatography, it was found that a byproduct co-eluted with the DMAP. However, analysis of GC-MS spectroscopy data did not enable this product to be identified. Moreover, no evidence for the formation of the desired bipyridine could be found.

2.3.4 Conclusion

In conclusion, even though **30** and **31** were successfully synthesized in very good yield, attempts to cross- couple them to give the desired bipyridine by either Stille or Negishi conditions failed.

The reason for the failure of this synthesis of 4, 4'-(dimethylamino)-2, 2'-bipyridine is not clear. One possibility might be that the two dimethylamino groups are too electron donating for effective oxidative addition during the palladium catalytic cycle.

An alternative way to synthesize **32** was reported by Suzuki (Scheme 2.10)[43]. This called dehydrogenative coupling, uses bimetallic ruthenium complexes to cross coupling two DMAPs. However, the low yield made this procedure unattractive and other methods were considered.



Yield = 32 % (^{1}H NMR analysis, lit.[44])

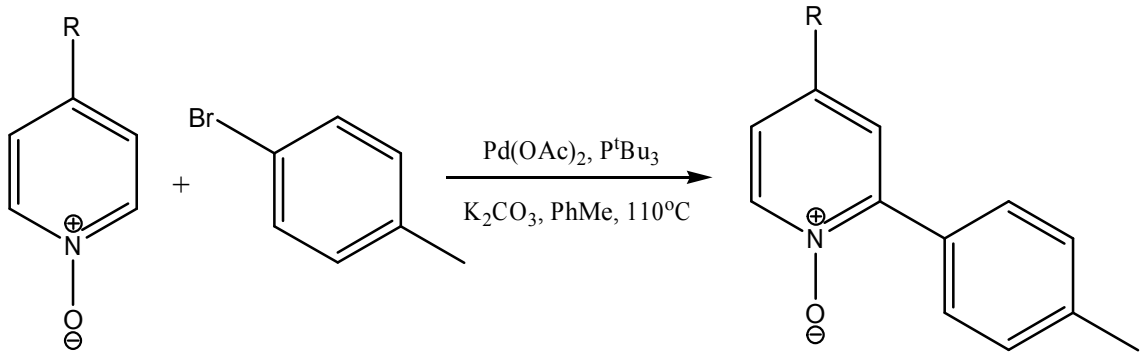
Scheme 2.10

2.4 Synthesis of Bipyridine N-oxide

2.4.1 Introduction of Bipyridine N-oxide

As the synthesis of the model ligand 4, 4'-(dimethylamino)-2, 2'-bipyridine **32** using classical cross coupling reactions had failed, alternative approaches were considered. Fagnou[44] had demonstrated the direct arylation of pyridine N-oxides with a wide range of aryl bromides. This occurred with complete selectivity of the 2-position (Scheme 2.11). Both electron-donating and electron –withdrawing groups were acceptable substrates.In addition, the pyridine N-oxides are commercially available and inexpensive. Moreover, the presence of a nitro group provides a

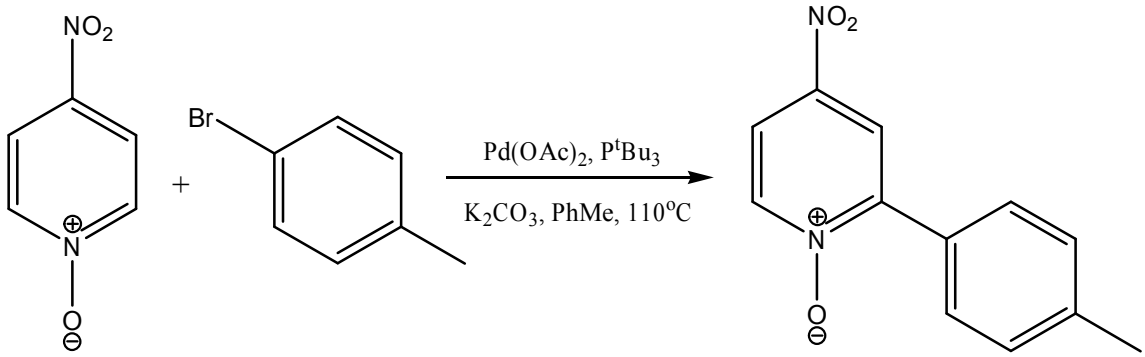
convenient handle to generate the connection to the polymer. Consequently, this approach appeared to have great potential for making the desired bipyridine and was therefore selected for further study.



R= NO_2, Yield= 78 % (lit.); R=OMe, Yield= 80 % (lit.)

Scheme 2.11: Cross-coupling as reported Fagnou[45]

According to Fagnou's report, 4 equiv. of pyridine N-oxide, 2 equiv. of K_2CO_3, 0.05 equiv. palladium acetate in combination with 0.15 equiv. of tri-tert-butylphosphine represented the optimal conditions. The unreacted N-oxide could be recovered by silica gel flash column chromatography.



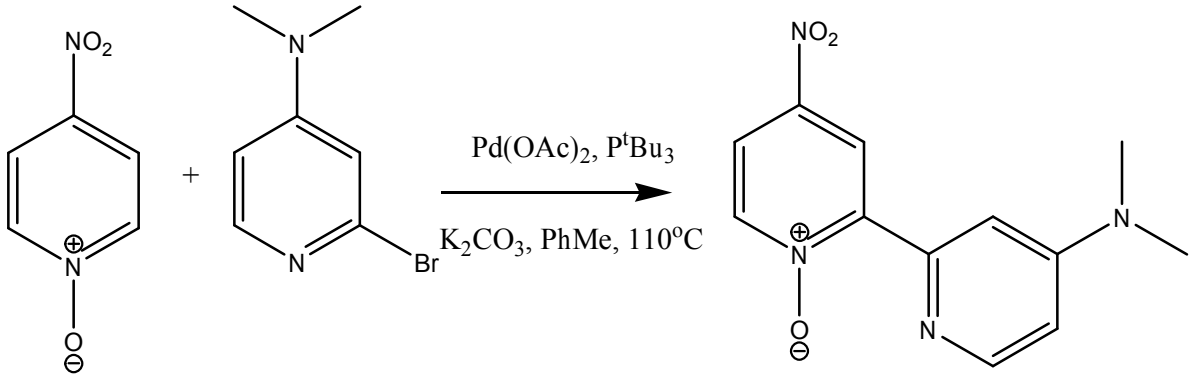
40 **41** Yield = 43 % **42**

Scheme 2.12

Initially a model study was carried out repeating the same reaction described by Fagnou (Scheme 2.10). A solution of P^tBu_3 and **41** in toluene was added to a solution of **40**, $Pd(OAc)_2$, K_2CO_3 in toluene. The reaction mixture was then heated at 110 ^oC and stirred for 20 h. Following work up, examination of the ^1H-NMR spectra showed three peaks at δ 8.38 (d, 1H), 8.30 (d, 1H) and 8.03 (dd, 1H), which are consistent with expected C6, C3, and C5 signals. This was further

confirmed by the mass spectra which revealed a molecular ion at 231.1 (MH^+). Flash chromatography then gave **42** in 43% yield (Scheme 2.12).

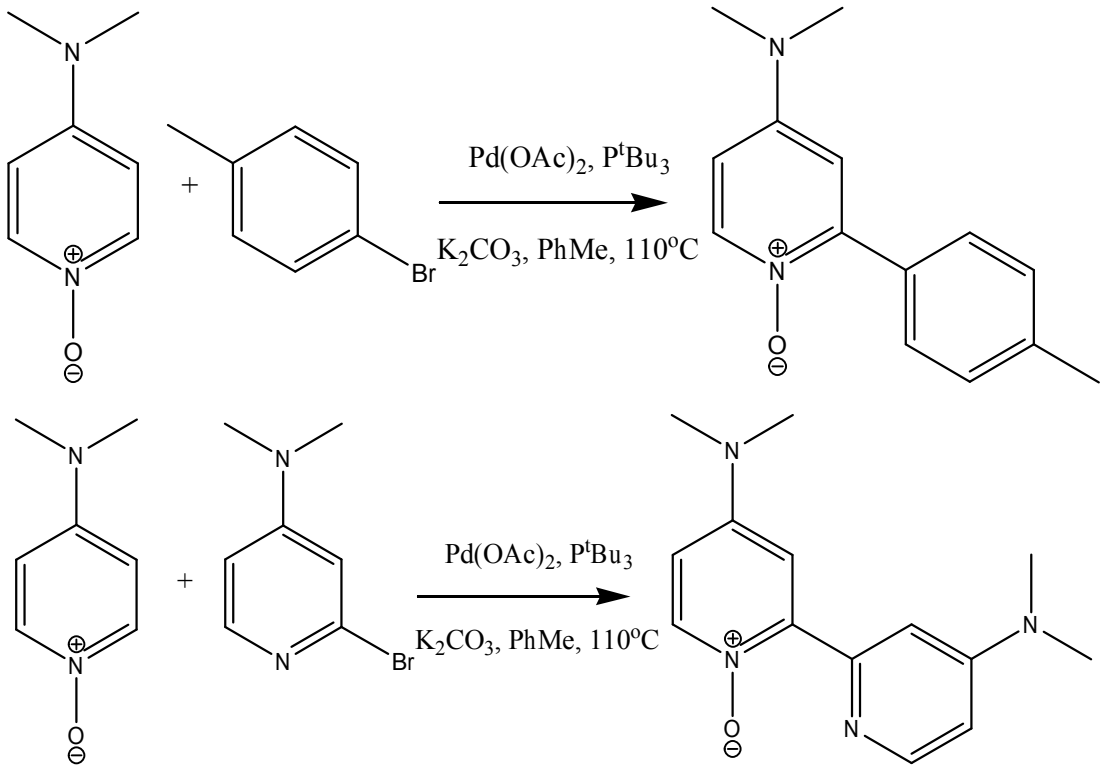
Having demonstrated that the method worked, the reaction was then repeated using bromide **30** instead of **41**. Initial analysis by mass spectra, revealed a molecular ion at 261.1(MH^+) confirmed the loss of bromine and formation of **43**. However, the isolated yield was only 8% (Scheme 2.13).



40 **30** Yield = 8 % **43**

Scheme 2.13

Interestingly, both reactions were also performed with DMAP N-oxide (Scheme 2.14). However neither of the two reactions generated any desired product after work up.



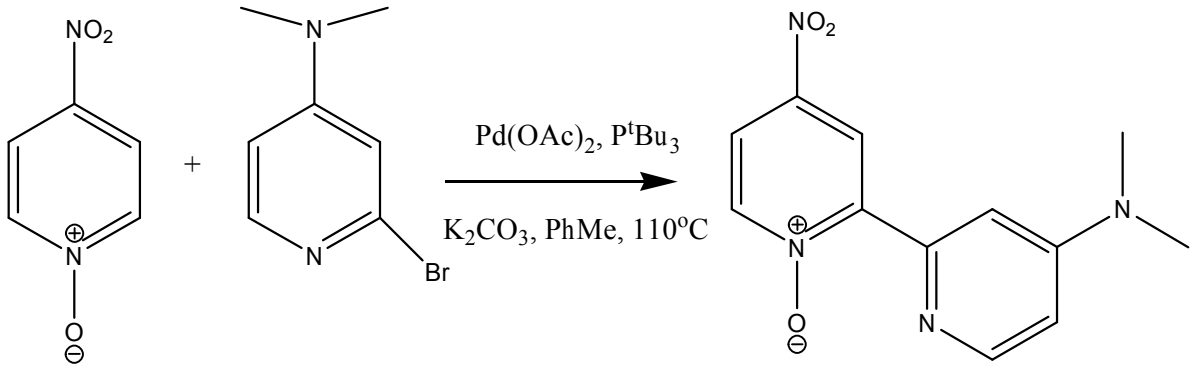
Scheme 2.14

Comparing with the two groups of reactions, the only difference is in the 4-substitution group of the pyridine N-oxide. One is an electron deficient, nitro group, and the other is an electron donating, dimethylamino group. These results provided further evidence the dimethylamino group hinders the cross-coupling reaction.

The initial aims of the project were to develop a bisubstituted 2, 2'-pyridine suitable for immobilization onto a polymer resin. As the **43** potentially meets this requirement, further investigation was under taken.

2.4.2 Investigation of 4'-Dimethylamino-4-nitro-2, 2'-bipyridine N-oxide

Although the synthesis of the bipyridine derivatives was successful, the low yield limited further application. Analysis of the crude reaction mixture by ^{1}H-NMR spectra revealed significant amount of unreacted bromide **30**. Anticipating that the reaction had not finished in 22 h, longer reaction times were employed.



40 **30** Scheme 2.15 **43**

Disappointingly, the isolated yield showed no difference after 96 h when compared with 22 h suggesting that the catalyst had decomposed during the reaction. Consequently an investigation of the catalyst loading was undertaken. The studies of catalyst loading are shown in Table 2.2. When using 5% Pd $(OAc)_2$ the isolated yield was 8 %, when the catalyst loading was increased to 20%, the yield was correspondingly up to 31%. However, when 0.5 equiv. catalyst were employed, no product was obtained. The reasons for these results are not obvious and need further study.

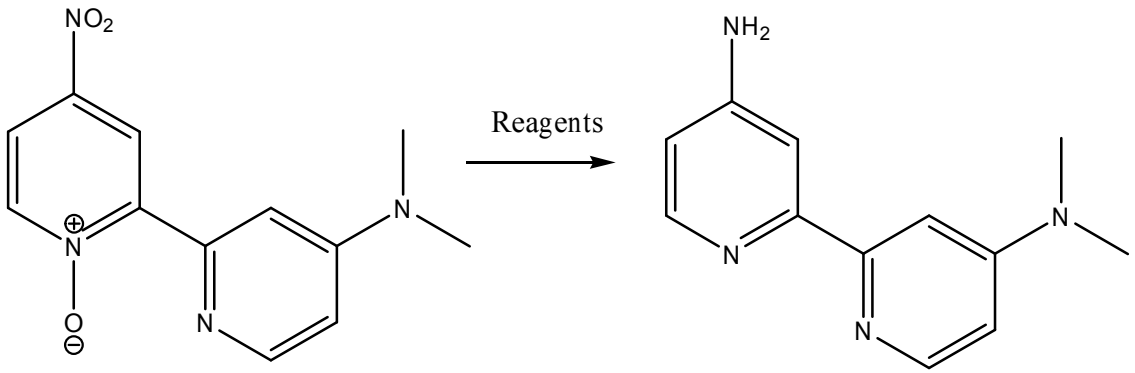
Table 2.2

Catalysis ($Pd(OAc)_2$)	5%	20%	50%
Isolated yield/%	8	31	0

From this, it can be concluded that the optimal conditions for making 4'-dimethylamino-4-nitro-2, 2'-bipyridine N-oxide **43** involved using 4 equiv. of pyridine N-oxide, 1 equiv. of bromide **30**, 2 equiv. of K_2CO_3, 0.20 equiv. palladium acetate in combination with 0.60 equiv of tri-tert-butylphosphine in toluene heated under reflux for a reaction time of 22 h.

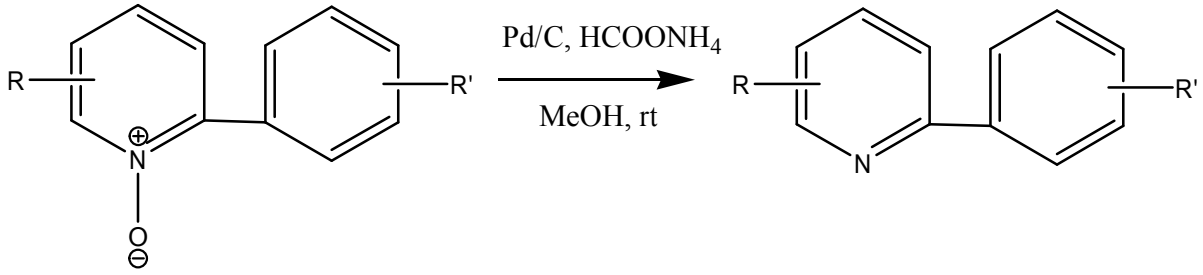
2.4.3 Reduction of Bipyridine N-oxide

With a successful route for making 2, 2'-bipyridine N-oxide, the next step was the reduction of the N-oxide and nitro group to generate **44** (Scheme 2.16).



43 Scheme 2.16 **44**

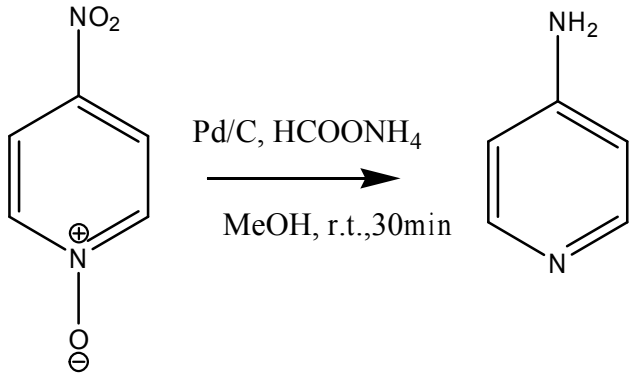
A well-established catalytic method for reduction of pyridine N-oxide is using Pd/C and ammonium formate as reductant. Significantly, Fagnou had demonstrated that biaryl pyridine N-oxides can be deoxygenated via palladium-catalyzed reduction with ammonium formate (Scheme 2.17). Because **45** (Scheme 2.18) has the same functional groups as does with **43**, and is commercially available, the study on the reduction began by replicating this process with **45** as a model substrate.



a: R= H R'= 4-CH_3, 95%; b: R=H R'=3-OMe, 87%
c: R=4-OMe R'=4-CH_3, 84%; d: R=H R'=4-CO_2CH_3, 87%

Scheme 2.17

Ammonium formate was added to a solution of **45**, Pd/C in MeOH under an inert atmosphere and followed by GC-MS. Following complete consumption of the starting materials, analysis of GC-MS data, showed the formation of a product with molecular ion at 94 (M^+) corresponding to **46** (Scheme 2.18). This model study therefore suggested that reduction of **43** would be successful. However, in view of the low yield of **43**, alternative pathways were explored and these experiments remain to be undertaken.



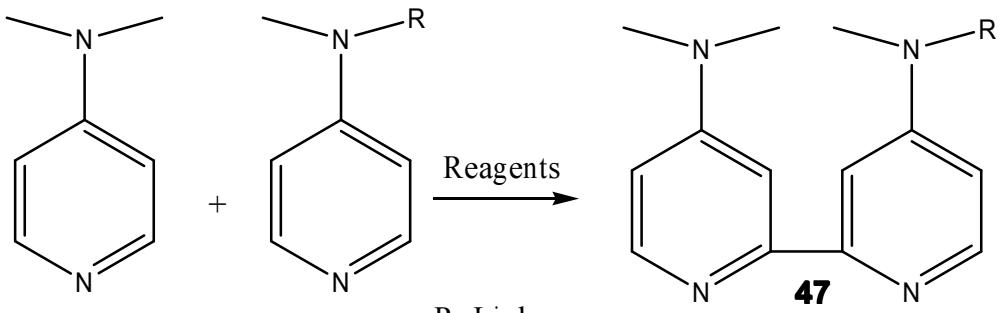
45 Scheme 2.18 **46**

2.4.4 Conclusion

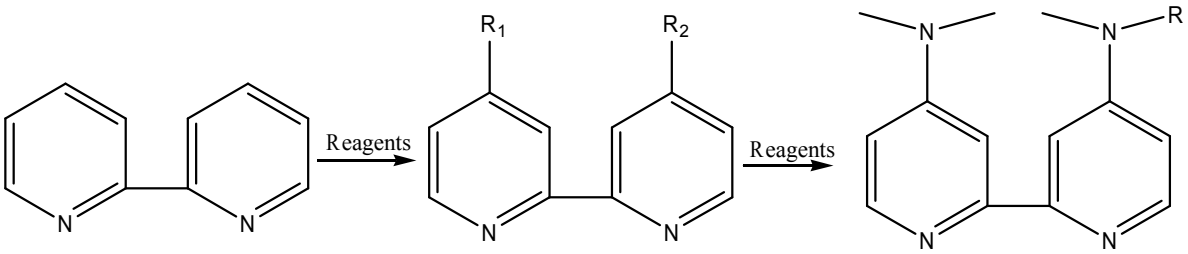
The cross-coupling reaction pyridine N-oxide **40** and bromide **30** afforded the desired bipyridine **43**. In addition, the subsequent reduction reaction proved very successful. However, the low yield in cross-coupling reaction limits the use of the sequence for the ligand synthesis and alternative methods were then examined. Theses are described in the following sections.

2.5 Synthesis of Bipyridine N-oxide Ligands

In view of the difficulties with the early attempts to cross-couple two 4-substituted pyridine derivatives, an alternative strategy exploring the direct functionalization of the 4 position of a preformed bipyridine was then investigated (Scheme 2.19).



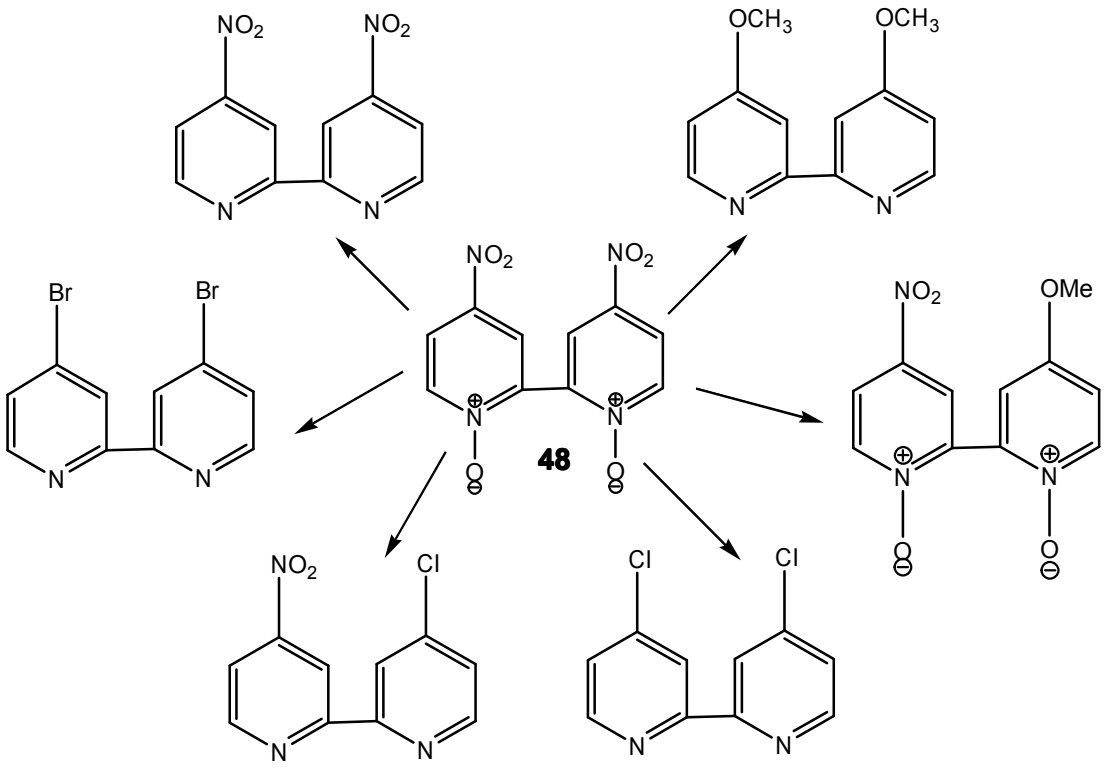
Initial attempts to generate **47** by cross-coupling



New route for generating **47** though functionalize bipyridine derivatives

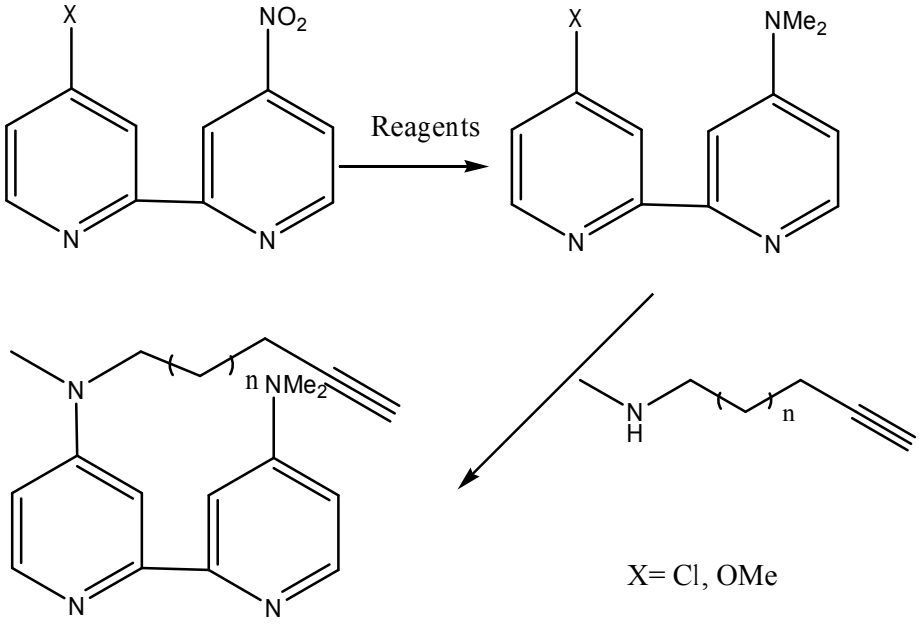
Scheme 2.19

Attention was drawn to a report by Wenkert and Woodward[45], who had demonstrated that 4, 4'-dinitro-2, 2'-bipyridine N, N'-dioxide **48** could be converted into a various 4, 4'-disubstituted bipyridines (Scheme 2.20).



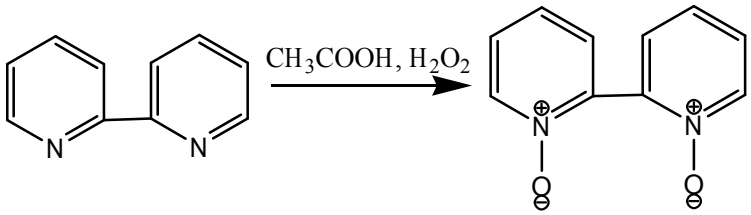
Scheme 2.20

In particular, the synthesis of the unsymmetrically substituted analogues, 4-nitro-4'-chloro-2, 2'-bipyridine **49** and 4-methoxy-4'-nitro-2, 2'-bipyridine N, N'–dioxide **50** indicated great potential for generating polymer enhanced ligands through the possible synthetic pathways described in Scheme 2.21.



Scheme 2.21

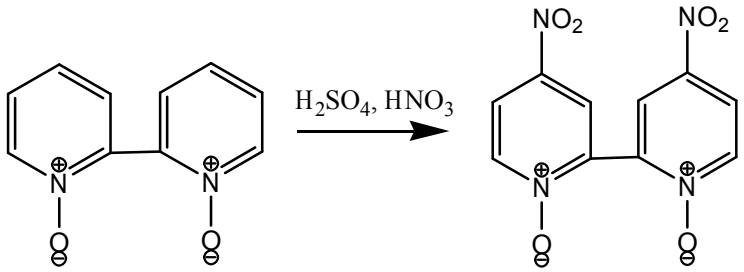
2.5.1Generating 4, 4'-Dinitro-2, 2'-bipyridine N, N'- dioxide



Yield= 90% **51**

Scheme 2.22

The procedure for making 2, 2'-bipyridine N, N'- dioxide was repeating Clennan's methods[46]. A commercial solution of H_2O_2 was added to a solution of 2, 2'-bipyridine in glacial acetic acid. After stirring for 5 h, another portion of H_2O_2 was added. After stirring for 16 h at 75°C, acetone was added to precipitate the desired **51**. Examination of mass spectra revealed a molecular ion m/z (ES^+) 189.1(MH^+). This was further confirmed by a peak in the IR spectrum at 1253 cm^{-1} indicating an N-O absorption band. The yield of pure product **51** was 90 % (Scheme 2.22).



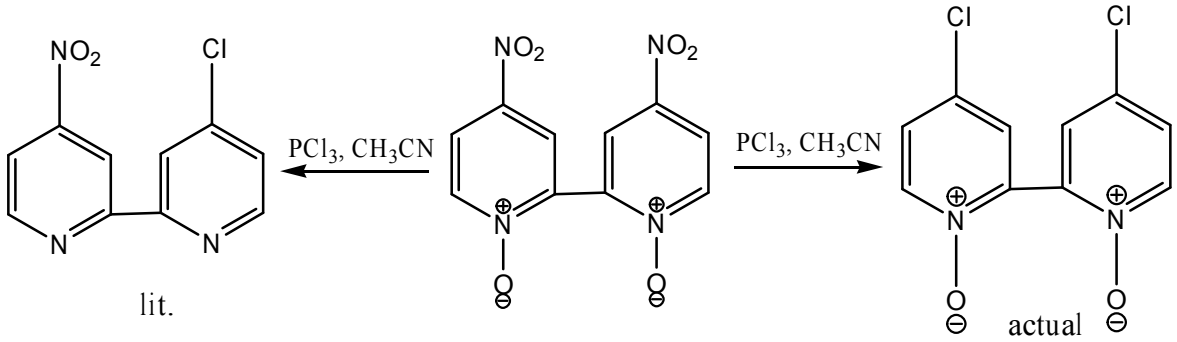
Yield= 45% **48**

Scheme 2.23

With **51** in hand, attention was turned to generate **48**. Following a report by Kavanagh and Leech[47], the preparation of **48** was achieved by nitration of **51** with a combination of sulfuric acid and nitric acid. After the reaction mixture was heated at 96°C for 20 h, the acidic mixture was poured onto a stirred ice-water mixture, causing the desired product **48** to precipitate as a yellow solid. Examination of the mass spectra revealed a molecular ion m/z (ES^+) 279.1(MH^+) confirming the formation of **48**. ^{1}H-NMR spectra only showed three peaks at δ 8.70 (d), 8.60 (d),

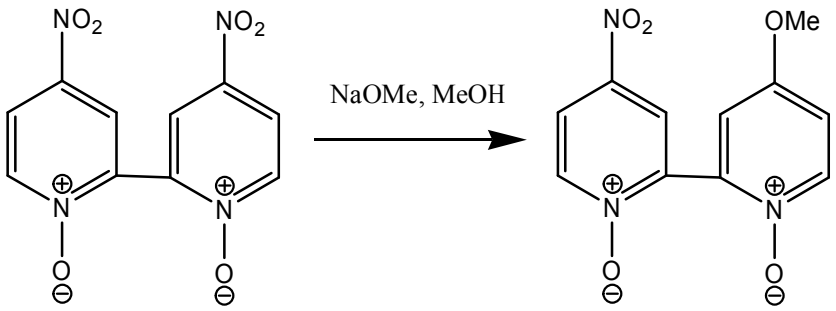
and 8.38 (dd) which are consistent with the expected C3, C6, and C5 signals and suggested a high pure product. Consequently, no further purification was attempted. The yield of the product was 45 %.

2.5.2 Synthesis of Bipyridine Derivatives



49 Scheme 2.24 **52**

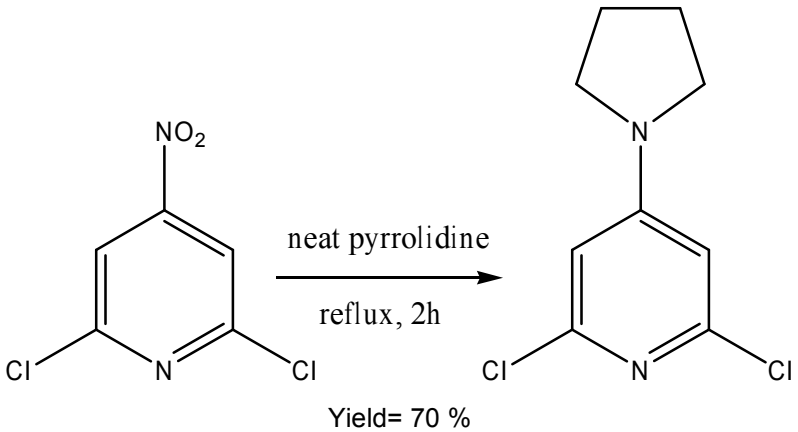
With **48** in hand, we started our investigation to generate 4-chloro-4'-nitrobipyridine **49** using the same conditions as described by Wenkert and Woodward. In their report, this reaction has two products, one is the desired mono chloropyridine **49**, yield 42 %, and the other is 4, 4'-dichloro-2, 2'-bipyridine with a yield 33 %. Repeating the reaction **48** and PCl_3, were heated under reflux in dry acetonitrile for 1.75 hours. Following cooling, an aqueous work up and extraction, examination of the crude product by mass spectra, revealed a characteristic 9: 6: 1 chlorine isotope pattern corresponding to a molecular ion of 257.1(MH^+, Cl^{35}), 259.1(MH^+, Cl^{35}, Cl^{37}), 261.1 (MH^+, Cl^{37}). This suggested the formation of 4, 4'-dichloro-2, 2'-bipyridine N, N'-dioxide **52**. The isolated yield, of this transformation was 20 %. With none of the desired **49** being isolated, our attention turned to another way to generate suitable bipyridine derivatives.



Scheme 2.25 **50**

The second attempt to generate 2, 2'-bipyridine derivatives was again based on a procedure from Wenkert and Woodward's report. **48** was stirred in a solution of NaOMe in dry MeOH under argon for 19 h. Disappointingly, only unchanged starting materials were recovered and none of the desired product could be detected after work up.

Following these unsuccessful reactions an extensive study on generating 2, 2'-bipyridine compounds was undertaken. Angiolini's report attracted our attention, which demonstrated 4-nitro pyridine can undergo nucleophilic substitution in the presence of neat pyrrolidine affording 4-pyrrolidine pyridine in good yield (Scheme 2.26). [48]

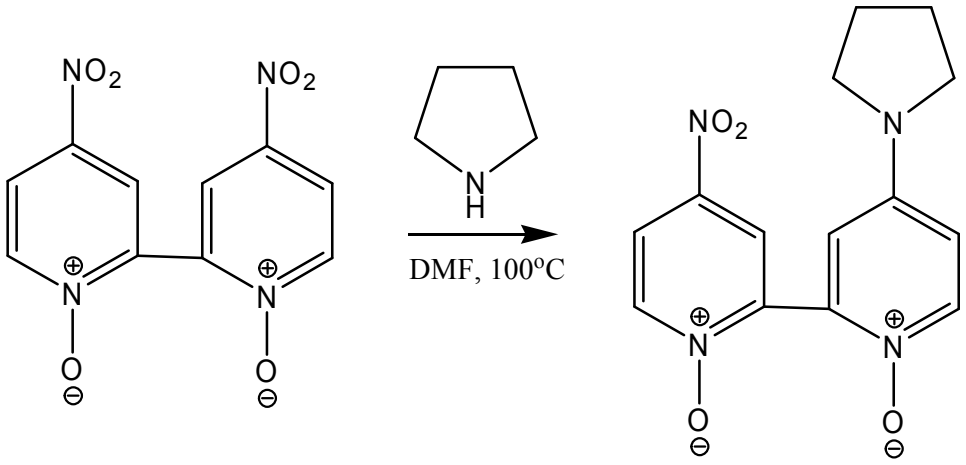


Yield= 70 %

53 Scheme 2.26 **54**

Following this idea **48** and pyrrolidine were dissolved in DMF and heated in a microwave reactor. After 10 minutes at 100°C, the reaction mixture was diluted in DCM, followed by washing with Na_2CO_3 solution, water, brine, combine organic

layer, filtration and concentration. However, analysis by GC-MS only unchanged starting materials was detected.



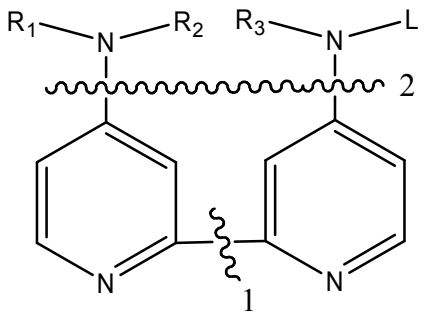
Scheme 2.27 **55**

2.5.3 Conclusion

Although the synthesis of 4, 4'-dinitro-2, 2'-bipyridine N, N'- dioxide was successful, the generating of 2, 2'-bipyridine derivatives, suitable for a insoluble polymer-supported ligand, remained a challenge.

2.6 Synthesis of 2, 2'-bipyridine ligands 56

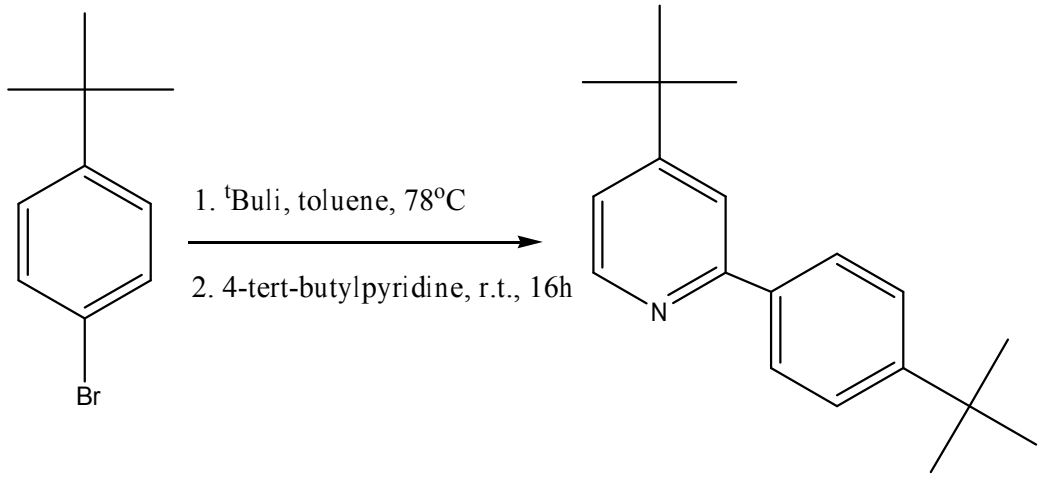
Several attempts have tried to synthesis of the bipyridine ligand **56**, disappointing, none of those methods provide a good route for making the ligands and an alternative strategy was sought.



56

Figure 2.3

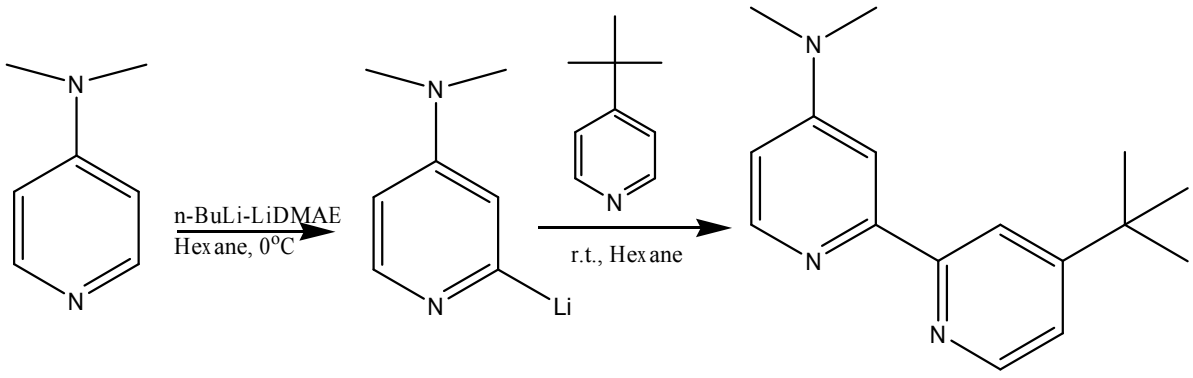
Recently, Andrew Beeby's group (Durham University) has synthesized pyridine containing biaryls. The reaction involved directed ortho addition of an aryl lithium, generated by lithium halogen exchange to 4-*tert*-butylpyridine (Scheme 2.28). However, they hadn't yet attempted the coupling of two pyridines. The making of **57** in 73 % suggested a high possibility for a successful synthesis of the desired bipyridine derivatives.



Scheme 2.28 **57**

2.6.1 Model reaction: Synthesis of 4-Dimethylamino-4'-^{t}Butyl -2, 2'-bipyridine

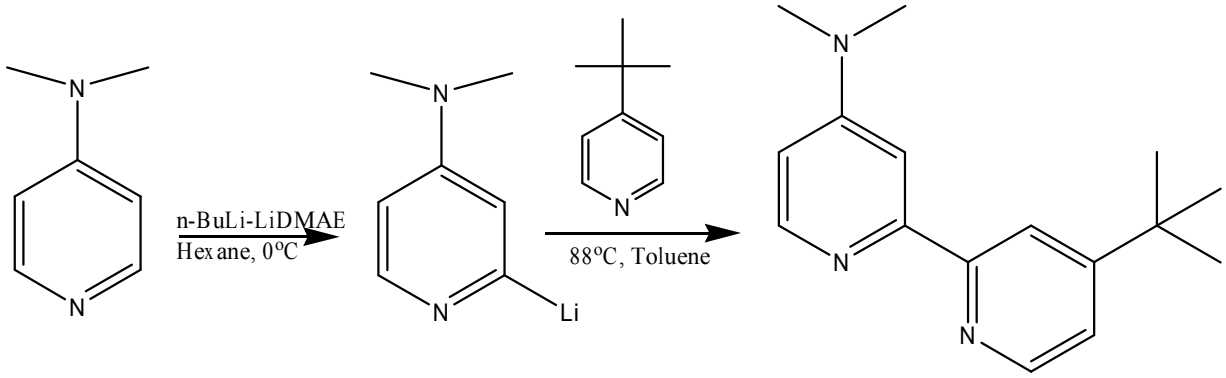
Based on Beeby *et al*'s procedure and the initial synthesis of 2-bromo-4-dimethylamino pyridine, the synthesis of **58** was carried out (Scheme 2.29).



29 Scheme 2.29 **58**

As previously, two equivalent of BuLi-LiDMAE were added to DMAP in hexane at 0°C to form the anion and then the reaction mixture was allowed to warm to room temperature and 4-^{t}butyl pyridine was added as electrophile. After stirring at room temperature for 22 h, the reaction was quenched by an addition of water. However, following examination of the crude product mixture by GC-MS, no molecular ion corresponding to the desired product could be detected.

Given the precedents described above the lack of reaction was surprising and a second attempt was made but with increased reaction temperature.



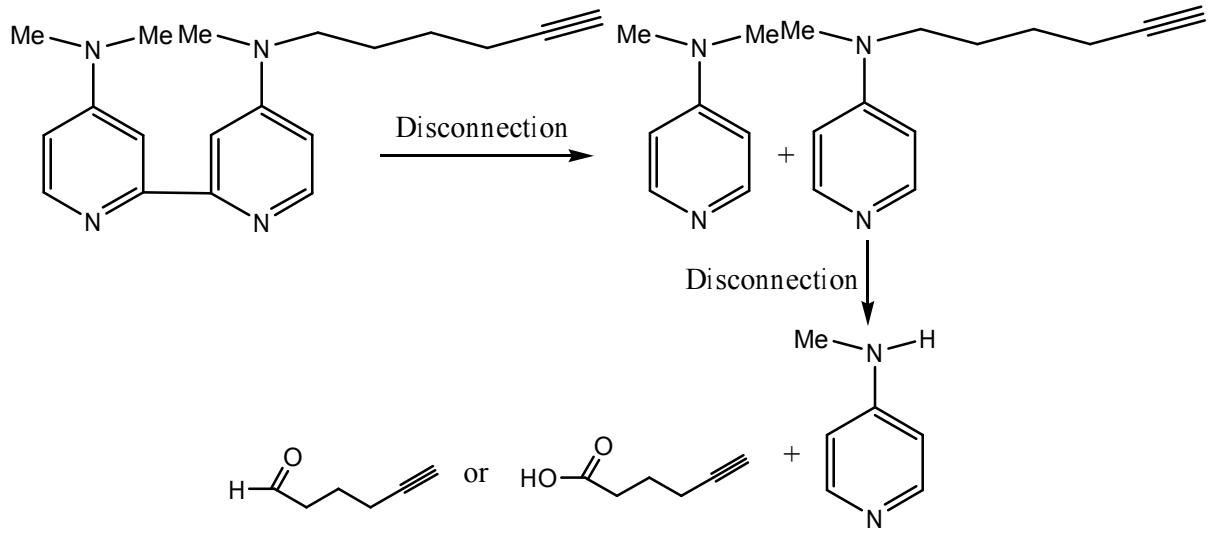
Yield = 32 %

Scheme 2.30

A solution of 4-^{t}butyl pyridine in toluene instead of hexane was added to the preformed 2-lithium-pyridine and the mixture then heated to 88°C. After stirring at 88 °C for 22 h, the reaction was quenched by an addition of water. Examination of the crude mixture by GC-MS showed a molecular ion 255 (M^{+}) corresponding to the desired product **58**. This indicated the exchange of lithium and pyridine happened when heated up. The isolated yield was 32 %. The low yield reflected difficulties in purification as several methods: normal silica chromatography, aluminum chromatography, reversed phase chromatography, were required. Finally the pure product could be obtained by using high performance liquid chromatography.

2.6.2 Synthetic pathway

Based on this model reaction and initial strategy (Figure 2.2), the design of synthesis polymer suitable ligands **56** can be disconnected as shown in Scheme 2.31.

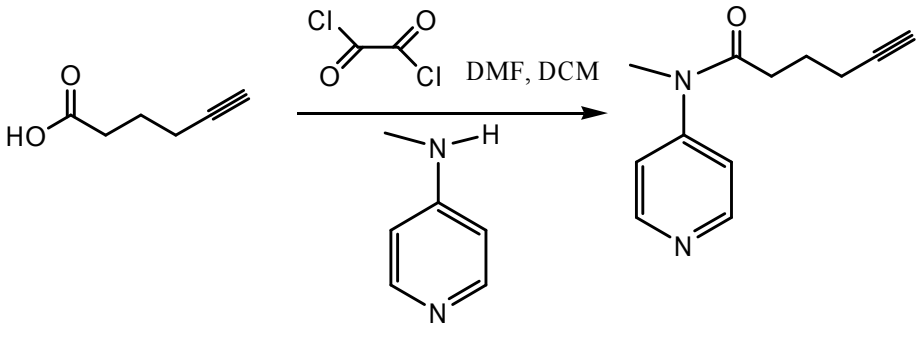


60 **27** **59**

Scheme 2.31

The disconnection of the desired polymer suitable ligand led to DMAP and an alkyne containing amino pyridine. Further analysis of the latter suggested two possible synthetic routes that could be employed. The first one involved reation of amine **59** with acid **27** to generate the amide **61** which could then be reduced to the amine **62.** The second approach used aldehyde **60** whhich could be combined with amine **59** in a direct reductive amination procedure.

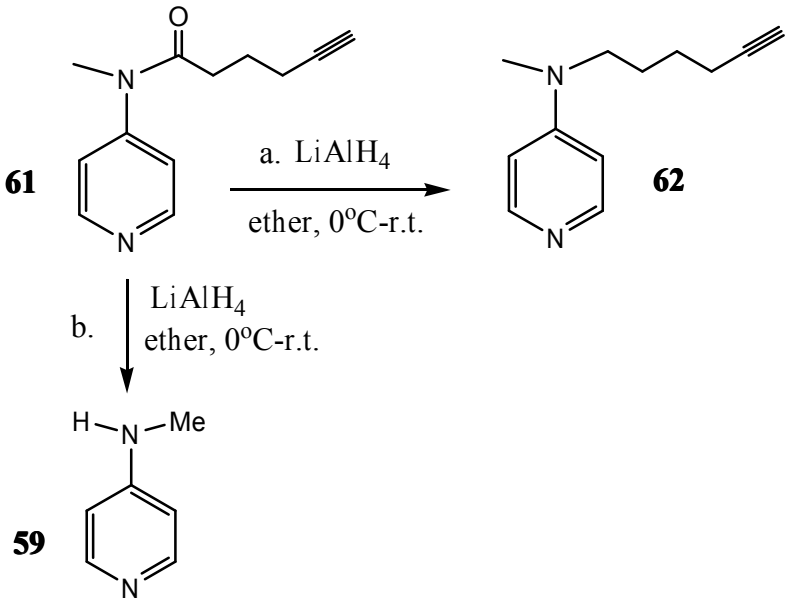
2.6.2.1 Route 1



27 Yield = 67 % **61**

Scheme 2.32

The initial step involved generating the amide **61**. This reaction was carried out by using 1.5 equiv. of oxalyl chloride, a drop of DMF as catalyst to generate the acid chloride from the 5-hexynoic acid, subsequently reacted with amine to give amide **61**. Examination of the crude mixture by GC-MS showed a molecular ion at 203.2 (MH^+). The formation of the desired amide **61** was further confirmed by the IR peak at 1670 cm^{-1} consistent with an amide C=O stretch. The isolated yield was 67%.

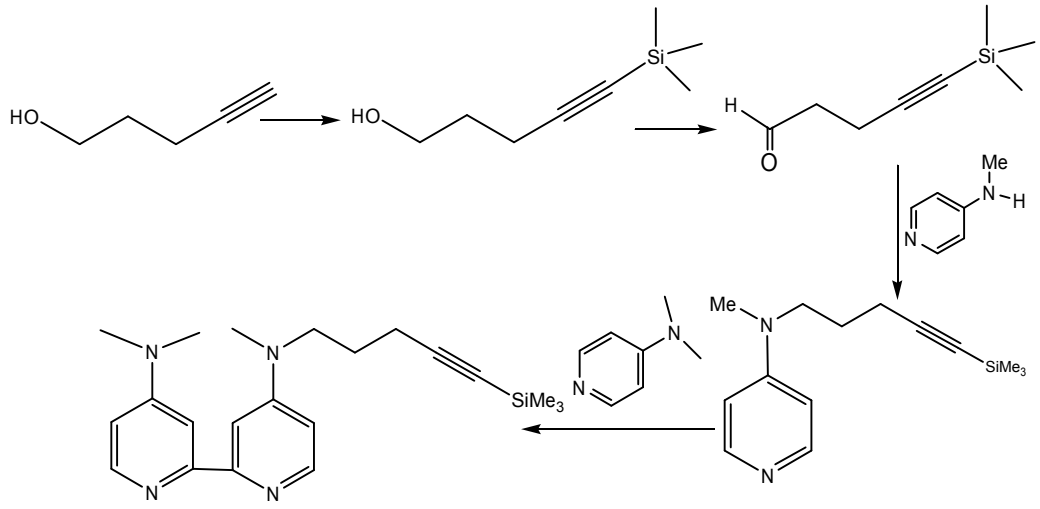


Scheme 2.33 a. ideal route; b. actual route

With **61** in hand, attention turned to the reduction of the carbonyl group. This step utilised lithium aluminium hydride as the reducing agent. The reaction was quenched by an addition of water, NaOH, and another portion of water, followed by filtration and concentration. However, analysis of the product by GC-MS showed only a molecular ion at 108 (M^+) correspond to the amine **59** and none of the desired product could be detected.

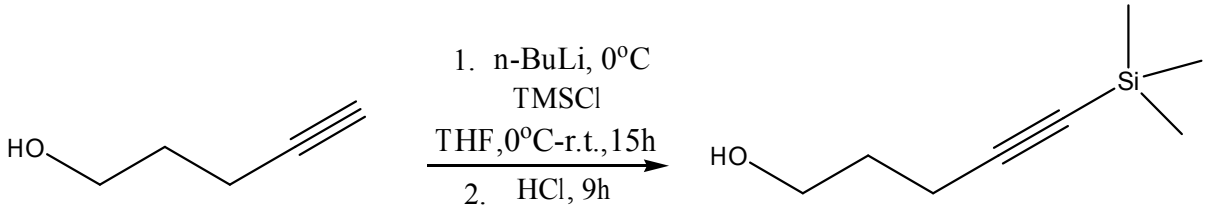
2.6.2.2 Route 2

After the failed reduction of the amide **61**, attention was turned to route 2. Since pent-4-ynal **60** is not commericial available, our study began from 4-pentyn-1-ol **63** as described in Scheme 2.34.



Scheme 2.34

The first step involved protection of the terminal alkyne. A solution of BuLi in hexane was added to 4-pentyn-1-ol in THF at 0 ^{o}C and the mixture stirred for 3h, TMSCl was then added followed by warming to room temperature and stirring for 15 h. Aqueous HCl was then added to hydrolyse the silyl ester. After stirring for 9 h the reaction was worked up in the normal fashion. Examination of the crude mixture by GC-MS showed a molecular ion at 157.2 (MH^+) and ^{1}H-NMR indicated four peaks at 3.62 (t, 2H), 2.21(t, 2H), 1.63(quin, 2H), 0.00 (9H) corresponding to the desired product **64**. Following chromatography **64** was obtained in 40 % yield.

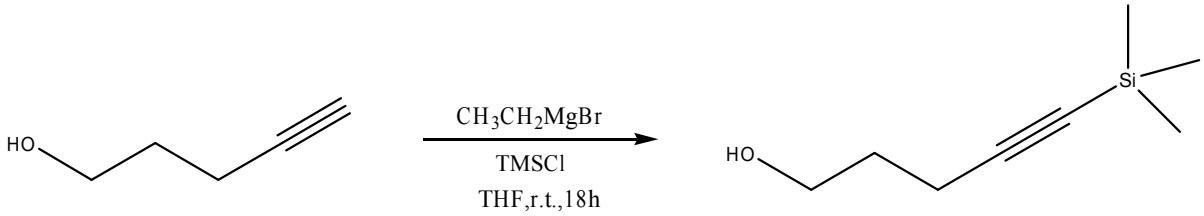


63 Yield = 40 % **64**

Scheme 2.35

However, the low yield was disappointing and a second reaction following Hiroi's[49] procedure provided better yield and shorter reaction time. In this, 3 equiv. of CH_3CH_2MgBr were combined with 4-pentyn-1-ol, followed by adding TMSCl. After 18 h stirred at room temperature, the reaction was quenched by addition of 10 %

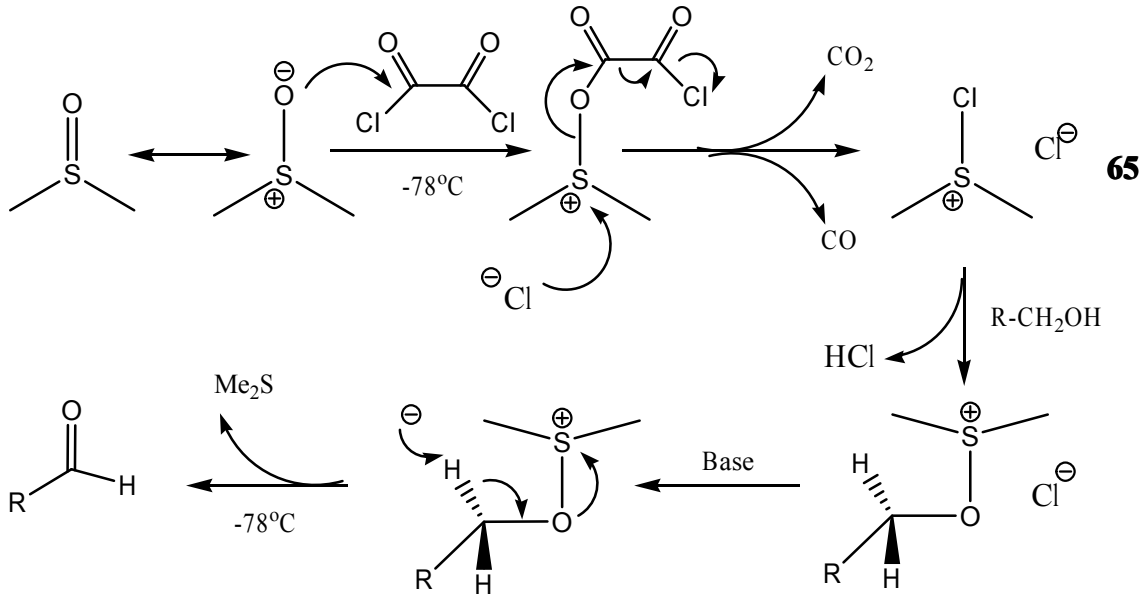
aqueous HCl. Following work up and chromatography **64** was obtained in 68 % yield.



Yield = 68 %

Scheme 2.36

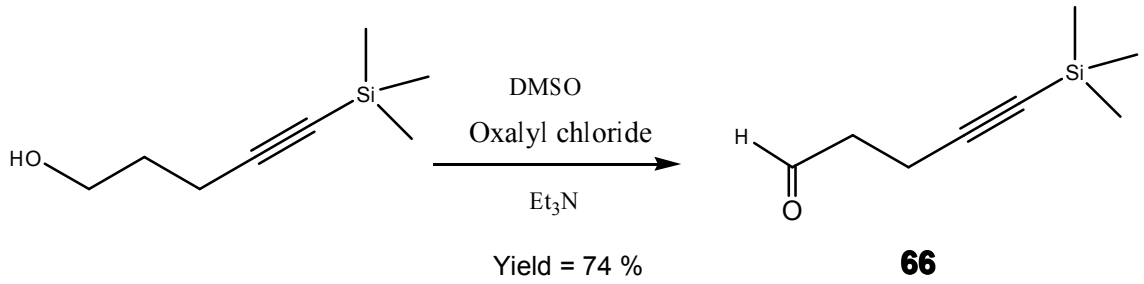
With **64** in hand, an attempt to oxidise the alcohol was carried out. The reaction was using Malacria's[50] procedure for the Swern oxidation. In this, the DMSO reacted with oxalyl chloride to give off CO_2 and CO to form **65.** Alcohol **64** and Et_3N were then added to generate the desired aldehyde **66** (Scheme 2.37).



R=$CH_2CH_2CH{\equiv}CSi(Me)_3$

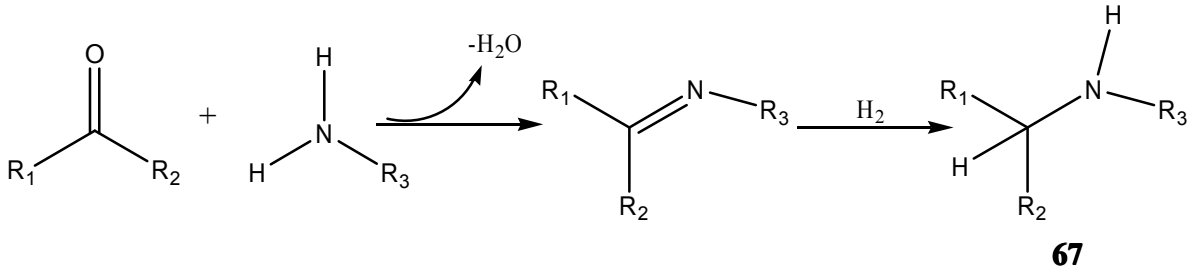
Scheme 2.37: Mechanism of the Swern Oxidation

Following work up analysis by GC-MS, revealed a peak with a molecular ion at 139 (M^+-15) and an absorption band in the IR spectrum at 1728 cm^{-1} (C=O stretch, aldehyde) corresponding to the desired product **66**. After purification, the isolated yield of desired **66** was 74%.



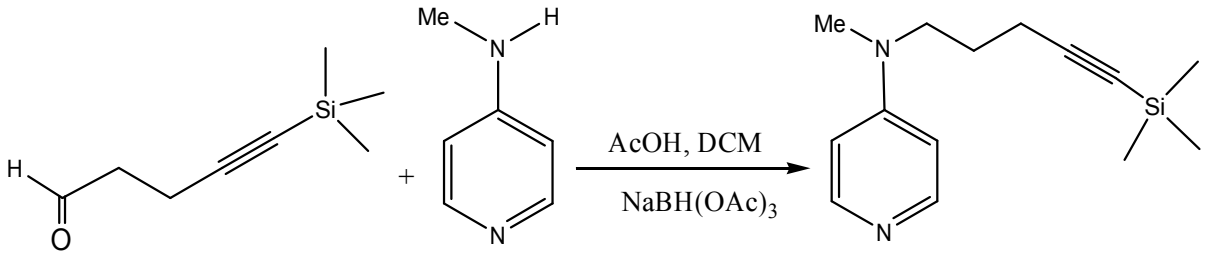
Scheme 2.38

The third step was the reductive amination reaction. In this the carbonyl group, aldehyde or ketone, react with an amine to give an intermediate imine which undergoes reduction with reductant to give the amine **67**.



Scheme 2.39

The procedure for this reaction was taken from a report by Abdel-Magid.[51] Aldehyde **66**, amine **59**, acetic acid were mixed in DCM and then sodium triacetoxyborohydride was added. The reaction was then stirred at room temperature and followed by TLC. After 2 h, a new spot was observed but plenty of starting materials remained. However, even after 96 h the two starting materials could still be detected. Following addition of NaOH, work up and chromatography, analysis of the purified product by ^{1}H-NMR spectra revealed the proton peak at 3.62 (t, 2H), 2.21(t, 2H), 1.62(quin, 2H), 0.01 (9H) corresponding to the alcohol **64**.



66 **59** **68**

Scheme 2.40

Disappointingly, no desired product was generated following Abdel-Magid's methods. According to the reaction results, it can be concluded that the rate of sodium triacetoxyborohydride reduction of the aldehyde was much quicker than imine formation. A potential solution to it is problem could be to carry out the reaction of **66** and **59** to form the imine before adding the $NaBH(OAc)_3$. However, due to a lack of time, this experiment remains to be undertaken.

2.6.3 Conclusions

It is very exciting to say that we have success generated a bipyridine ligands **58**. Even though the yield was not satisfied, with further study on the purification, it is very possible to find a better way to isolation.

Although the routes try to making polymer suitable ligands have not finished because we don't have enough time, they provided a new thinking and direction to generate bipyridine derivatives.

Chapter 3 Conclusion and Future Work

3.1 Conclusion

The research described in this dissertation has involved several routes that may lead to the synthesis of polymer-supported bipyridine ligands.

The first route involved the synthesis of two substituted pyridine and then coupling them to give the desired bipyridine. However, both Stille and Negishi conditions failed to obtain the desired product. The failure of the synthesis of 4, 4'-(dimethylamino)-2, 2'-bipyridine provided one possibility that two dimethylamino group are too electron donating for effective oxidative addition during the palladium catalytic cycle. Although the successful cross-coupling of a pyridine N-oxide and 2-bromopyridine provided a suitable synthetic strategy, the yield could not be optimised to a good level.

The second route attempted to functionalize preformed 4, 4'-disustituted 2, 2'-bipyridine. However, the generation of 2, 2'-bipyridine derivatives suitable for elaboration into a polymer support remained a challenge.

In the third route explored was generated a new unsymmetrical bipyridine ligand, 4-dimethylamino-4'-tert-butyl-2, 2'-bipyridine. Even though the yield was not optimal, with further study on the purification, this approach represented is very exciting. Although these routes to make polymer suitable ligands are not complete, they have provided new thinking and direction to generate bipyridine derivatives.

3.2 Future Work

Future work would include developing the 4-nitro-4'-dimethylamino-2, 2'-bipyridine N-oxide. This would involve reduction of the nitro and N-oxide group and then coupling to a linker to connect to a polymer. Finally convert the ligand into iridium precatalyst to test their recyclability.

A second task would be to test the efficiency of 4-dimethylamino-4'-tert-butyl -2, 2'-bipyridine in the iridium catalytic C-H borylation. In particular the effect of having unsymmetrical ligands will be of great interest.

The third area would be to build on the direct lithiation approach. This requires efficient access to an acceptor pyridyl unit. Two approaches could be explored to build on the studies undertaken. First the amide **61** (section 2.6.2.1) could be reduced with different reductant, such as BH_3 before coupling with DMAP. Alternatively, to explore more efficient protocols using N-methyl pyridine before undertaking the coupling with lithiated DMAP.

Chapter 4 Experimental Procedures and Data

4.1 General Experimental Procedures

All of the reagents were commercially available and were used without further purification. Dry solvents were obtained from Innovative Technology Solvent Purification System (SPS) as per standard procedures within the department and stored under nitrogen before use. In the cases where mixtures of solvents were used, ratios were calculated based on volumes used. All reactions were carried out under an atmosphere of argon, unless otherwise stated.

Chromatography

All reactions were monitored by thin layer chromatography (TLC, 60 F_{254}) using normal phase silica plates. Compound were visualized by UV radiation at 254 nm or by staining (e.g. PMA 1 g/100 mL EtOH, Potassium Permanganate 0.5 g KMO_4 /100 mL water) and revealed by heating.
Flash column chromatography was carried out using normal phase silica gel (40-63u 60A) with an appropriate eluent. High performance liquid chromatography (Waters MDAP system, UK, Ltd) was carried out by Durham University Chromatography service.

IR Spectroscopy

Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 series FT-IR Spectrometer with ATR (attenuated total reflection) attachment. Absorption maxima are reported in wavenumbers (cm^{-1}).

NMR Spectroscopy

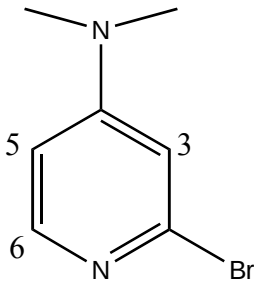
^{1}H NMR and ^{13}C NMR spectra were acquired in $CDCl_3$, unless otherwise stated, on a Bruker Avance-400 (^{1}H at 400MHz, ^{13}C at 100MHz), Varian VNMRS-700 (^{1}H at 700 MHz, ^{13}C at 176 MHz) or INOVA-500 (^{1}H at 500 MHz, ^{13}C at 126 MHz). Spectra were reported as follows: chemical shift δ (ppm) (multiplicity, coupling constant *J* (Hz), number of protons, assignment). The residual protic solvent was used as the internal reference: $CDCl_3$ δ_H = 7.26 ppm; δ_C = 77.0 ppm.

Mass Spectrometry

Gas-Chromatography Mass Spectra (GC-MS: EI, CI) were taken using a Thermo-Finnigan Trace with a 25 cm column connected to a VG Mass Lab Trio 1000. Electrospray mass spectra (ES) were obtained on a Micromass LCT Mass spectrometer carried by Durham University Mass Spectrometry service.

4.2 Experimental Methods and Data

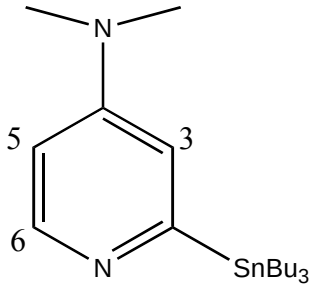
2-Bromo-4-dimethylamino pyridine **30**



A solution of 2-dimethylaminoethanol (0.8 mL, 8 mmol) in hexane (10 mL) was cooled to -5 ^{o}C under argon. nBuLi (1.6 M in hexane, 10 mL, 16 mmol) was added dropwise. After 30 mins at -5 ^{o}C, 4-dimethylamino pyridine (488 mg, 4 mmol) was added as solid in a single portion. After 1h at -5 ^{o}C, the solution was cooled to -78 ^{o}C and then a solution of CBr_4 (3.34 g, 10 mmol) in hexane (20 mL) was added dropwise. After 1.5 h of stirring at -78 ^{o}C. The reaction was quenched by addition of H_2O (5 mL). The mixture was separated and the aqueous layer extracted by diethyl ether (3 x 20 mL) and dichloromethane (3 x 20 mL). Combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (50 % EtOAc in hexane) to afford 2-bromo-4-dimethylamino pyridine as brown solid (0.60 g, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.0, 1H, 6-H), 6.66 (d, J = 2.4, 1H, 3-H), 6.45 (dd, J = 2.4, 6.0, 1H, 5-H), 3.01 (s, 6H, NMe_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 149.3, 143.1, 109.2, 106.2, 39.3; m/z (ES^+) 201(M^+, Br^{79}) 203(M^+, Br^{81}); ν_{MAX} (neat) 2368, 1910, 1614, 1552, 1439, 1250 (aromatic C-N), 1174 (aliphatic C-N), 1121, 968, 822, 197, 720, 688 (C-Br) cm^{-1}.

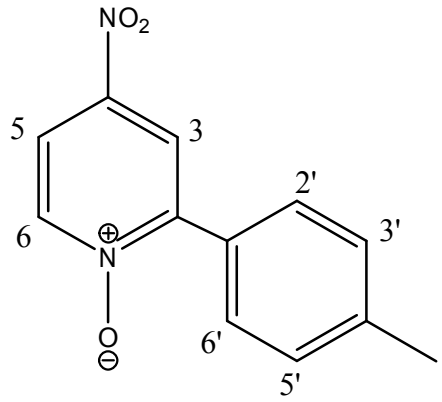
2-Tributylstannyl-4-dimethylamino pyridine **31**



A solution of 2-dimethylaminoethanol (0.8 mL, 8 mmol) in hexane (10 mL) was cooled to -5 ^{o}C under argon. nBuLi (1.6 M in hexane, 10 mL, 16 mmol) was added dropwise. After 30 mins at -5 ^{o}C, 4-dimethylamino pyridine (488 mg, 4 mmol) was added as solid in a single portion. After 1h at -5 ^{o}C, the solution was cooled to -78 ^{o}C and then a solution of $ClSnBu_3$ (3.26 g, 10 mmol) in hexane (20 mL) was added dropwise. After 1.5 h of stirring at -78 ^{o}C. The reaction was quenched by addition of H_2O (5 mL). The mixture was separated and the aqueous layer extracted by diethyl ether (3 x 20 mL) and dichloromethane (3 x 20 mL). Combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (Et_3N: Hexane: EtOAc= 10: 45: 45) to afford 2-tributylstannyl-4-dimethylamino pyridine as brown gummy solid (1.30 g, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 6.0, 1H, 6-H), 6.67 (d, *J* = 2.8, 1H, 3-H), 6.40 (dd, *J* = 2.9, 5.9, 1H, 5-H), 3.00 (s, 6H), 1.63 – 1.52 (m, 6H), 1.35 (m, *J* = 7.3, 14.7, 6H), 1.15 – 1.08 (t, 6H), 0.90 (t, *J* = 5.7, 8.9, 9H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.8, 152.1, 145.0, 115.5, 105.4, 38.8, 29.1, 27.3, 13.8, 9.8; m/z (ES^{+}) 413.3 (M^{+}, Sn 120, 100%), 411.3(M^{+}, Sn 118, 80%). 409.3(M^{+}, Sn 116, 40%); v_{MAX} (neat) 2954, 2922, 2870, 1579 (aromatic C-N), 1464, 1443, 1364, 1275, 1215, 1128, 1070, 982 (aliphatic C-N), 806 cm^{-1}.

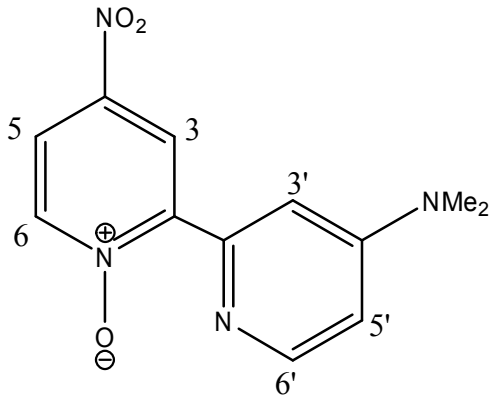
2-(4’-Methyl phenyl)-4-nitropyridine N-oxide **42**



4-Nitropyridine N-oxide (560 mg, 4 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), K_2CO_3 (276 mg, 2 mmol) were placed in a round bottom flask. The flask then was fitted with a reflux condenser capped with a rubber septa and purged with argon. A solution of P^tBu_3 (0.15 mL, 0.15 mmol) and 4-bromo toluene (170 mg, 1 mmol) in toluene (10 mL) was added by syringe. The mixture was heated to 110 ^oC and stirred for 20 h. After cooling to room temperature, the reaction was filtered through celite, washed with MeOH and DCM, and concentrated. The crude product was purified by silica gel flash column chromatography (5 % Acetone in DCM) to afford the 2-(4’-methyl phenyl)-4-nitropyridine N-oxide as yellow powder (0.10 g, 43 %).

^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 7.2, 1H, 6-H), 8.30 (d, J = 3.2, 1H, 3-H), 8.03 (dd, J = 3.2, 7.2,1H, 5-H), 7.75 (d, J = 8.2, 2H, 2’-H, 6’-H), 7.36 (d, J = 7.9, 2H, 3’-H, 5’-H), 2.35 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.4, 142.0, 141.3, 141.2, 129.3, 129.0, 127.7, 121.3, 118.1, 21.5; m/z (ES^+) 231.1 (MH^+); v_{MAX} (neat) 3082, 1504 (NO_2), 1336 (NO_2), 1275 (N-O), 1243 (N-O), 1104, 824, 658 cm^{-1}.

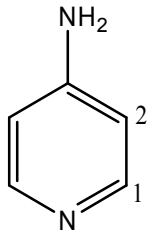
4’-Dimethylamino-4-nitro-2, 2’-bipyridine N-oxide **43**



4-Nitropyridine N-oxide (280 mg, 2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), K_2CO_3 (276 mg, 2 mmol) were placed in a round bottom flask. The flask then was fitted with a reflux condenser capped with a rubber septa and purged with argon. A solution of P^tBu_3 (0.15 mL, 0.15 mmol) and 2-bromo-4-dimethylamino pyridine (100 mg, 0.5 mmol) in toluene (5 mL) was added by syringe. The mixture was heated to 110 ^oC and stirred for 20 h. After allowed to cool to room temperature, the reaction mixture was filtered through celite, washed with MeOH and DCM, and concentrated. The crude product was purified by column chromatography (10 % Acetone in DCM) to afford the 4’-dimethylamino-4-nitro-2,2’-bipyridine N-oxide as yellow solid (40 mg, 31 %).

^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (d, J = 3.3, 1H, 3-H), 8.36 (dd, J = 6.6, 13.7, 2H, 6-H, 6’-H), 8.23 (d, J = 2.6, 1H, 5-H), 8.03 (dd, J = 3.3, 7.2, 1H, 3’-H), 6.59 (dd, J = 2.7, 6.0, 1H, 5’-H), 3.11 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 149.9, 149.4, 147.7, 142.7, 142.1, 123.0, 118.7, 108.6, 107.7, 39.6; m/z (ES^+) 261.1(MH^+); v_{MAX} (neat) 3022, 2400, 1598, 1522 (NO_2), 1487, 1425, 1342 (aromatic C-N), 1217 (N-O), 1019 (aliphatic C-N) cm^{-1}.

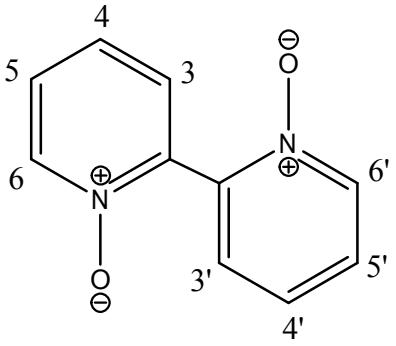
4-Amino pyridine **46**



Ammonium formate (3.2 g, 50 mmol) and Pd / C (0.053 g, 0.5 mmol) were added into a stired solution of 4-nitro pyridine N-oxide (0.7 g, 5 mmol) in MeOH (10 mL) at room temperature under argon. After 30 mins, the reaction was filtered through celite, washed with DCM, and concentrated to afford the 4-amino pyridine as light brown powder (0.40 g, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 5.3 Hz, 2H, 1-H), 6.45 (d, J = 6.2 Hz, 2H, 2-H), 4.05 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 150.5, 109.5; GC-MS (EI) 94; v_{MAX} (neat) 3434 (N-H stretch), 3074, 1645 (N-H bend), 1597 (N-H bend), 1505, 990, 821, 675 (N-H wag) cm^{-1}.

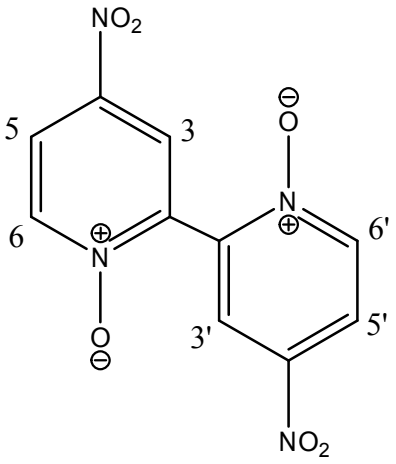
2, 2'-Bipyridine N, N-dioxide **51**



H_2O_2 (27.5 % in water, 15 mL) was added to a solution of 2, 2'-bipyridine (6 g, 38.4 mmol) in glacial acetic acid (40 mL) at 75 °C. After stirring for 5 h, another portion of H_2O_2 (10 mL) was added and the solution was stirred for another 8 h. The reaction was allowed to cool to room temperature and then acetone (400 mL) was added and the precipitate formed was filtered and air-dried to afford the 2,2'-bipyridine N,N-dioxide as white powder (6.50 g, 90 %).

^{1}H NMR (400 MHz, D_2O) δ 8.39 (dd, *J* = 2.9, 5.2, 1H, 6-H), 7.75 (dd, 1H, 4-H), 7.67 (m, 2H, 3-H, 5-H); ^{1}H NMR (400 MHz, DMSO) δ 8.34 (d, *J* = 6.4, 1H, 6-H), 7.63 (d, *J* = 7.8, 1H, 3-H), 7.51 (t, *J* = 7.7, 1H, 5-H), 7.41 (t, *J* = 7.7, 1H, 4-H); ^{13}C NMR (101 MHz, D_2O) δ 141.8, 139.7, 131.5, 128.8, 128.4; m/z (ES^+) 189.1 (M^+), 210.9(MNa^+), 399.1(M_2Na^+); v_{MAX} (neat) 3039, 1473, 1427, 1253 (N-O), 1147, 1118, 1022, 960, 838, 765, 724 cm^{-1}.

4, 4'-Dinitro-2, 2'-bipyridine N, N-dioxide **48**

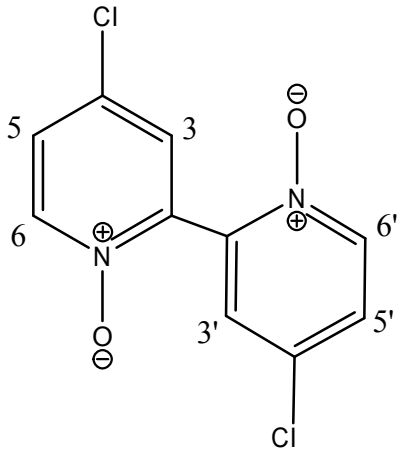


Concentrated sulfuric acid (98 %, 7.2 mL) was added to 2, 2'-bipyridine N-oxide (1.5 g, 8 mmol). The mixture was cooled to 0 °C before adding fuming nitric acid (>90 %, 2.5 mL), and then heated to reflux (97 °C) for 20h. The reaction mixture was allowed to room temperature and then poured onto a stirred ice-water mixture (-40 °C, made of liquid nitrogen and 40 mL of water). The solution became green with liberation of N_2O_4. Upon standing, a bright yellow precipitate come out and keep stirring at -40

^{o}C (maintained by adding liquid nitrogen) for 1 h. The product was collected by filtration, washed with water (3 x 25 mL) and dried in air to afford 4,4'-dinitro-2,2'-bipyridine N,N-dioxide as yellow powder (1.0 g, 45 %).

^{1}H NMR (400 MHz, DMSO) δ 8.70 (d, *J* = 3.3, 1H, 3-H), 8.60 (d, *J* = 7.2, 1H, 6-H), 8.38 (dd, *J* = 3.3, 7.3, 1H, 5-H); ^{13}C NMR (176 MHz, DMSO) δ 142.6, 141.6, 140.9, 124.2, 122.4; m/z (ES^{+}) 279.1(MH^{+}); ν_{MAX} (neat) 3087 (C-H),1602, 1574, 1506 (NO_2), 1336, 1286 (N-O),1239, 1114, 908, 838, 748, 650 cm^{-1}.

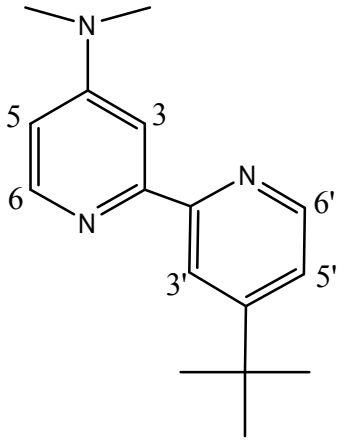
4, 4'-Dichloro-2, 2'-bipyridine N, N'-dioxide **52**



A solution of 4, 4'-dinitro-2, 2'-bipyridine N, N'-dioxide (327 mg, 1.175 mmol) and PCl_3 (1.2 mL, 13.75 mmol) were refluxed in 30 mL of dry acetonitrile for 2.5 h. The solution was allowed to cool to room temperature and stirred for another 20 h. Ice water (15 ml) was added into the reaction mixture. The organic layer was then evaporated in *vacuo* and the aqueous phase basified to pH 11 and then exhaustively extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (2.5-50 % EtOAc in hexane) to afford the 4, 4'-dichloro-2, 2'-bipyridine N, N'-dioxide as yellow solid (60 mg, 20 %).

^{1}H NMR (400 MHz, DMSO) δ 8.37 (d, J = 7.0, 2H, 6-H, 6'-H), 7.93 (d, J = 3.1, 2H, 3-H, 3'-H), 7.68 (dd, J = 3.1, 7.0, 2H, 5-H, 5'-H); ^{13}C NMR (176 MHz, DMSO) δ 143.0, 140.7, 128.9, 128.9, 127.7; m/z (ES^+) 257.1(MH^+); v_{MAX} (neat) 3037, 1600, 1451, 1240, 827 cm^{-1}.

4-Dimethylamino-4'-tert-butyl -2, 2'-bipyridine **58**

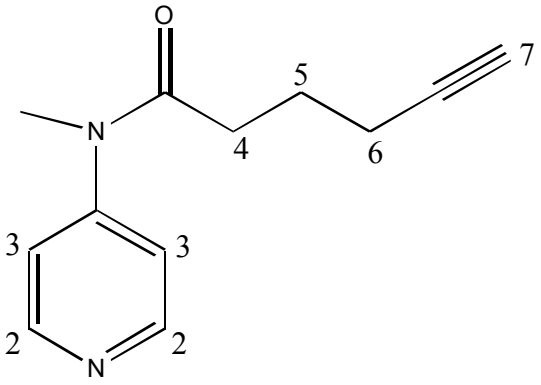


A solution of 2-dimethylamino ethanol (0.8 mL, 8 mmol) in hexane (10 mL) was cooled to -5 ^{o}C under argon atmosphere. nBuLi (1.6 M in hexane, 10 mL, 16 mmol) was added as dropwise. After 30 mins at -5 ^{o}C, 4-dimethylamino pyridine (488 mg, 4 mmol) was added as a solid in a single portion. After 1h at -5 ^{o}C, 4-tert-butylpyridine (0.7 mL, 4.8 mmol) and toluene (20 mL) was added. After 22 h of stirring at 88 ^{o}C, the reaction was quenched by addition of H_2O (10 mL). The colour of the mixture suddenly changed from red to orange. The mixture was separated and the aquerous layer extracted with diethyl ether (3 x 20 mL) and dichloromethane (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by HPLC to afford the 4-dimethylamino-4'-tert-butyl -2, 2'-bipyridine as brown gummy liquid (326 mg, 32 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 5.2, 1H, 6'-H), 8.46 (d, J = 6.6, 1H, 6-H), 8.39 (s, 1H, 3'-H), 7.65 (d, J = 2.7, 1H, 3-H), 7.38 (dd, J = 1.8, 5.2, 1H, 5'-H), 6.65 (dd, J = 2.8, 6.6, 1H, 5-H), 3.21 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

161.2, 156.8, 156.6, 155.6, 149.2, 149.0, 120.9, 118.6, 106.8, 104.3, 39.6, 35.3, 31.2; m/z (ES^+) 256.26 (M^+), 257.26 (MH^+); v_{MAX} (neat) 2962 (C-H),1637, 1587, 1556, 1417, 1342 (aromatic C-N), 1223 (aliphatic C-N), 990, 844, 809, 728 cm^{-1}.

4-(N-methyl-N-hex-5-ynamide) pyridine **61**

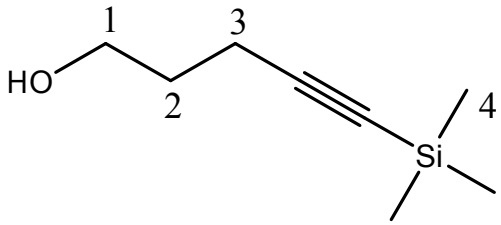


A drop of DMF was added into a solution of 5-hexynoic acid (0.11 mL, 1 mmol) in dry DCM (5 mL) at room temperature under argon. Then oxalyl chloride (0.13 mL, 1.5 mmol) was added dropwise with the evolution of a gas. After the reaction mixture had ceased bubbling, the solution was concentrated. Dry toluene (10 mL) was added into reaction flask and the solution was re-concentrated. Another portion of DCM (8 mL) was added and the reaction was cooled to 0°C. A solution of trimethylamine (0.28 mL, 2 mmol) and 4-(methylamino) pyridine (97 mg, 0.9 mmol) in DCM (10 mL) was added. The mixture was allowed to warm to ambient temperature and followed by TLC. The mixture was neutralized by adding $NaHCO_3$ and then separated. The aqueous layer extracted by ethyl acetate (2 x 30 mL). Combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (50 % EtOAc in hexane) to afford the 4-(N-methyl-N-hex-5-ynamide) pyridine as white powder (0.12 g, 67 %).

^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 1.6, 4.5, 2H, 2-H), 7.12 (dd, *J* = 1.6, 4.6, 2H, 3-H), 3.25 (s, 3H), 2.32 (t, *J* = 7.2, 2H, 4-H), 2.16 (tb, *J* = 2.6, 6.8, 2H, 6-H), 1.84 – 1.74 (m, 3H, 5-H, 7-H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 167.8, 147.4, 147.3,

117.3, 79.4, 65.1, 32.8, 28.8, 19.9, 13.8; m/z (ES^+) 203.2 (MH^+), 225.2 (MNa^+); v_{MAX} (neat) 3203, 2910, 1670 (C=O amide), 1592, 1380, 1316 (aromatic C-N), 1231 (C-N), 1210, 1123, 830, 704 (RC≡CH, C-H bend) cm^{-1}.

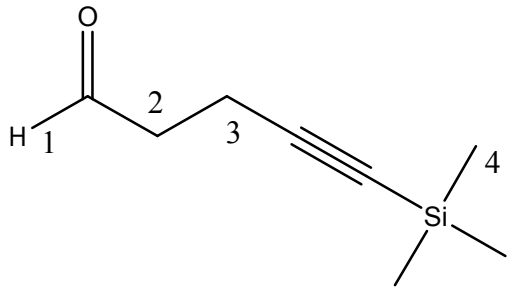
5-(Trimethylsilyl) pent-4-ol **64**



A 3.0 M diethyl ether solution of ethyl magnesium bromide (10 mL, 30 mmol) was added at 0 °C to a solution of 4-pentyn-1-ol (0.92 mL, 10 mmol) in THF, and the mixture was stirred at room temperature for 1 h. TMSCl (3.81 mL, 30 mmol) was added to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature and stirred for another 18 h. The reaction was quenched by addition of 10% aqueous HCl. The mixture was diluted with ether, separated and the organic layers was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10-30 % EtOAc in hexane) to afford the 5-(trimethylsilyl) pent-4-ol as colourless liquid (1.06 g, 68 %).

^1H NMR (400 MHz, $CDCl_3$) δ 3.62 (t, *J* = 4.3, 7.9, 2H, 1-H), 2.21 (t, *J* = 6.9, 2H, 3-H), 1.63 (quin, *J* = 6.5, 13.0, 2H, 2-H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.6, 85.2, 61.8, 31.1, 16.4, 0.0; m/z (ES^+) 157.2 (MH^+); v_{MAX} (neat) 3352 (O-H, stretch), 2956 (-CH_2-, stretch), 2174 (-C≡C-, stretch), 1413 (-CH_2-, bend), 1248 (Si-CH_3), 1052 (C-O, alcohol) cm^{-1}.

5-(Trimethylsilyl)-4-pentyn-1-al **66**



A solution of dimethyl sulfoxide (0.51 mL, 7.2 mmol) in DCM (25 mL) was added at -78 °C to a solution of oxalyl chloride (0.33 mL, 3.6 mmol) in DCM (15 mL) and the mixture was stirred at -78 °C for 15 min. 5-(trimethylsilyl) pent-4-ol (468 mg, 3 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture at -78 °C. After stirred for 20 min, triethylamine (2.1 mL, 15 mmol) was added. Then the reaction was allowed to warm to room temperature and keeping stirring for 3 h. The mixture was diluted with diethyl ether (50 mL), washed with saturated solutions of NH_4Cl (50 mL), $CuSO_4$ solution (2 x 50 mL), and brine (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (10-20 % EtOAc in hexane) to afford the 5-(trimethylsilyl)-4-pentyn-1-al as colourless liquid (0.34 g, 74 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, J = 1.2 Hz, 1H), 2.73 – 2.65 (t, 2H, 2-H), 2.61 – 2.51 (t, 2H, 3-H), 0.19 – 0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 104.7, 85.8, 42.5, 13.1, 0.13; GC-MS (EI) 139 (M^+-15); ν_{MAX} (neat) 2959, 2177(-C≡C-, stretch), 1728 (C=O stretch, aldehyde), 1249 (Si-CH_3), 1056 cm^{-1}.

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