Novel N-heterocyclic carbine ligands for use in supported catalysis

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Department of Chemistry

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Contents

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Chris

Abstract

Novel N-Heterocyclic carbene ligands for use in supported catalysis

Christopher William Thomas Teasdale

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Ligands involving CNC structures have been of intense interest in research. With an aim to investigating this area, a modular synthesis was developed using condensation reactions between a base unit of 2,6-dichloroisonicotinic acid and *N*-alkyl imidazoles to provide a range of 2,6-bis(imidazolium) salts. From this point several methods were available to incorporate an active metal centre, however, state of the art microwave-accelerated synthesis was found to be the most successful technique in forming the tridentate palladium complexes.

Several strategies were investigated to attach these complexes to polymer resins, exploring a range of linking groups, coupling procedures and resins. The most effective strategy involved forming an acid functionalised palladium complex to allow loading onto an amino-functionalised resin. Although several reagents were investigated it was found that the commercially available reagent PyBop® was the most effective in forming the stable amide bond from the palladium complex to the polymer resin. By using an excess of coupling reagent and an excess of the acid functionalised palladium complex complete loading onto an amino functionalised resin could be achieved.

The supported complexes were found to be highly stable catalysts in Heck, Suzuki-Miyaura and Stille reactions, and capable of cross-coupling a range of aryl iodides in very high yields. The active catalysts showed very little leaching of palladium (ICP-MS) and could be recycled up to fourteen times with no loss of activity. Long reaction times were overcome using tetra-*n*-butylammonium bromide as an additive or by using microwave irradiation.

Following these catalytic studies and with an aim to using less active electrophiles, several strategies were investigated to develop enhanced activity catalysts. These strategies involved replacing one of the *N*-Heterocyclic carbene ligands with either an "inert" bulky group or with another alternative ligand.

Full details of this research are presented in chapters 2 to 5.

Terminology

AAS	Atomic absorbtion spectroscopy
AcOH	Acetic acid
Ad	Adamantyl
Ar	Aryl
Bn	Benzyl
BnOH	Benzyl alcohol
Boc	*t*-Butyloxy carbonyl
Cy	Cyclohexyl
DCM	Dichloromethane
DFT	Density functional theory
DIC	N,N'-Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine (Hunig's base)
DMA	Dimethylacetamide
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
dppe	1,2 bis(diphenylphosphine)ethane
dppf	1,1' bis(diphenylphosphine)ferrocene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ES^+MS	Positive charge electrospray mass spectrometry
ES^-MS	Negative charge electrospray mass spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
eq.	Equivalents
FCC	Flash column chromatography
GC	Gas chromatography
ICP-MS	Inductively coupled plasma mass spectrometry
IMes	1,3-Bis(Mesityl)imidazol-2-ylidene
IPr	1,3-Bis(2,6-di-*iso*-propylphenyl)imidazol-2-ylidene
^{i}Pr	*i*-Propyl
^{i}PrOH	*i*-Propyl alcohol
IR	Infra-red spectroscopy
KHMDS	Potassium hexamethyl disilylamide
LiDMAE	Lithium dimethyl amino ethoxide
LiHMDS	Lithium hexamethyl disilylamide
m/z	Mass to charge ratio
MeCN	Acetonitrile
MeOH	Methanol
Mes	Mesityl (2,4,6-trimethylphenyl)
n-Bu	*n*-Butyl
NMR	Nuclear magnetic resonance
NHC	*N*-Heterocyclic carbene
OAc	Acetate
Pd/C	Palladium adsorbed on carbon
Ph	Phenyl
RCM	Ring closing metathesis
ROM	Ring opening metathesis
ROMP	Ring opening metathesis polymerisation
rt	Room temperature

^{t}Bu	*t*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri-*i*-propylsilyl
Tol	Tolyl
TPPTS	Triphenylphosphine trisulphonate sodium salt
TsOH	Toluene sulphonic acid
XPS	X-ray photoelectron spectroscopy

Chapter 1

Introduction

1.0- General Introduction

This thesis describes research concerning the chemistry of *N*-Heterocyclic carbene ligands and their respective palladium complexes. *N*-Heterocyclic carbenes show similarity with electron-rich organophosphines in terms of their metal coordination chemistry. Consequently, the literature on this class of ligand and their use in catalysis has grown enormously with several reviews detailing their synthesis, physical characteristics and application in catalysis.[1,2,3,4,5,6] Although the use of *N*-Heterocyclic carbene ligands in palladium catalysis has attracted much interest, the area of supported catalysis using these ligands has not been researched extensively.

This chapter essentially consists of three mini reviews concerning three main topics covered in this thesis: supported catalysis, palladium-catalysed cross-coupling reactions and *N*-Heterocyclic carbenes. Chapters 2 to 4 present and rationalise results, chapter 5 presents conclusions and future work and chapter six details experimental procedures.

1.1- Introduction to catalysis

In chemistry, a catalyst can be defined as a substance that accelerates a reaction, but undergoes no net chemical change. It operates by lowering the overall activation energy of a reaction by providing an alternative reaction pathway. This pathway will avoid the slow, rate-determining step of the uncatalysed reaction. The result is a greater reaction rate at the same temperature.[7]
Catalysts can be classified as *homogeneous* if they are in the same phase as the reagents and *heterogeneous* if they are in a different phase.

Catalysts essentially participate in *catalytic cycles* that consume reactants, form products and regenerate the catalytic species. At the end of the cycle the catalyst is regenerated so that it may go through another cycle. Each cycle is known as a *turnover*, and an effective catalyst may undergo hundreds or thousands of turnovers before decomposing.

1.1.1- Kinetics and terminology

For a reaction to occur, the energy of the system must be greater than or equal to the initial activation energy (E^A) of the reaction. If the activation energy is high, at normal temperatures only a small proportion of molecular collisions will result in reaction. The catalyst lowers the E^A by providing an alternative reaction route that avoids the previous slow, rate determining step and offers a higher rate of reaction at the same temperature.

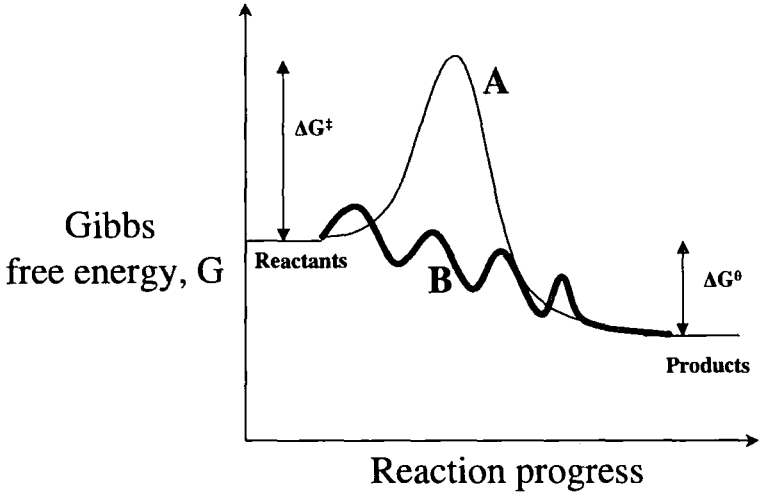


Figure 1.1

Consider the energy profile of a reaction, figure 1.1; the reaction will have an overall Gibbs free energy, $\Delta G^{\ominus}$. G is a path function and depends only on the current state of the system in question, not on the path that led to that state. The thin curve **A** represents the uncatalysed reaction. This profile has a higher Gibbs energy of activation $\Delta G^{\ddagger}$ than any step in the catalysed reaction shown by the thick curve **B**. The Gibbs free energy of reaction ΔG^{θ} from reactants to products is unchanged from **A** to **B**. Therefore, it is true to say that thermodynamically unfavourable reactions cannot be made favourable by catalysis.

A catalyst does not appear in the stoichiometric equation for an overall reaction, however it is directly involved in the conversion and appears both in individual mechanistic steps, and in the kinetic rate law. Thermodynamic law states that the

position of equilibrium is unchanged by the presence of a catalyst; however, the rate at which equilibrium is attained will be much greater.

Generally a catalyst is used to increase the rate of a desired reaction; however, there are several properties a catalyst must possess to be truly useful:

i) Turnover number

An efficient catalyst should complete a reaction cycle (turnover) rapidly. Strictly speaking, the turnover number, N is often used to express the efficiency of a catalyst. For the conversion of A into B, catalysed by Q proceeding at rate v:

$$A \xrightarrow{Q} B \qquad v = \frac{d[B]}{dt}$$

the turnover number is given by

$$N = \frac{v}{[Q]}$$

if the rate of the uncatalysed reaction is negligible. A highly active catalyst that produces a large reaction rate even at low concentrations has a large turnover number. This number should ideally be as large as possible.

ii) Turnover number (TON) vs. turnover frequency (TOF)

In organometallic literature a simpler definition of turnover number is used. The turnover number (TON) of a catalyst can be described as the number of molecules that react per molecule of catalyst, whilst the turnover frequency (TOF) of a catalyst can be described as the number of molecules that react per

molecule of catalyst per unit time. In order to be concise, these definitions of TON and TOF will be followed in this thesis.

iii) Stability

A catalyst should ideally last indefinitely. However, in reality this does not happen, as a catalyst may be destroyed by side reactions to the main catalytic cycle or poisoned by impurities in the starting materials. An effective catalyst should undergo hundreds or thousands of turnovers before decomposition. Decomposition can occur under harsh reaction conditions, such as very high temperature.

iv) Selectivity

A selective catalyst yields a high proportion of the desired product with minimum amounts of side products. The presence of a catalyst can allow the preferential formation of a product that may be less stable thermodynamically than another. There are different types of selectivity, which can take place: chemoselectivity, where a reaction occurs only at one functional group in the reactant; regioselectivity, where one regioisomer forms preferentially over another; stereoselectivity, where there is catalytic formation of one stereoisomer over another.

1.2- Supported catalysis

Homogeneous transition metal catalysis is traditionally accomplished through metal choice, ligand design, and fine tuning. On a small scale, homogeneous transition metal catalysts are ideal for controlling reactivity and selectivity. However, on a large scale, these catalysts can be difficult to separate from the product. In addition many homogeneous transition metal catalysts are unstable at high temperatures and contain expensive precious metal centres. Furthermore the cost of the ligand system employed (especially in asymmetric catalysis) often far exceeds that of the precious metal centre.

Heterogeneous catalysts, on the other hand, are more desirable for use in industrial processes because they can be readily separated and reused, and because they are amenable to continuous flow operations. Despite the preferred use of heterogeneous catalysts, they can be difficult to synthesise, characterise, and optimise - making rational catalyst design challenging and thereby forcing the researcher to rely more on empiricism.

Consequently, to overcome these problems one approach is to attach a homogenous catalyst to a support of some kind, essentially to heterogenise the homogeneous catalyst, thus combining the positive attributes of both kinds of catalysts. This technique makes it possible to first optimise a catalyst's reactivity and selectivity under controllable conditions, and then support it on media suitable for the intended application.

1.2.1- Types of catalyst support

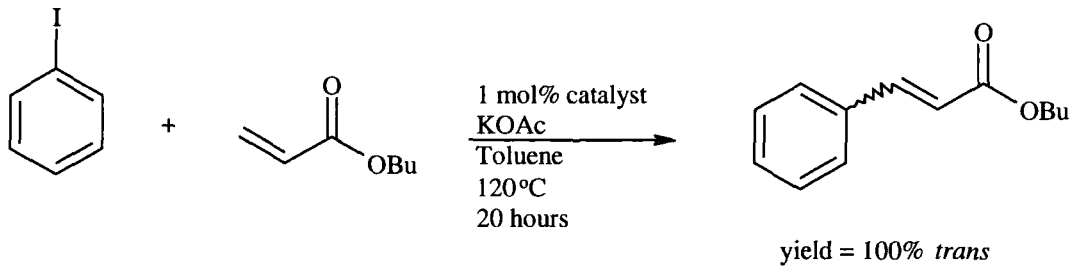
With reference to the catalytic reactions discussed in chapters 2 and 3 and to demonstrate the large number of techniques available, this section will mainly focus on the development of supported palladium catalysts for use in cross-coupling reactions (these reactions are discussed in further detail in sections 1.3-1.3.3).

The palladium-catalysed coupling of aryl halides by Heck, Suzuki, Sonogashira and Stille type reactions is a well established methodology in organic synthesis. Typically the reactions are carried out homogeneously using a palladium source (for example $Pd(OAc)_2$, $Pd_2(dba)_3$, $PdCl_2(MeCN)_2$ and $PdCl_2(PPh_3)_2$), an additional phosphine ligand (for example PPh_3, P^tBu_3, dppf and dppe) and a base. However, the reactions suffer limitations that have so far prevented their wide-spread industrial application. For example relatively large amounts of catalyst are needed for reasonable conversions and catalyst recycling is hampered by the early precipitation of palladium black. A few approaches have been described in the literature to improve these homogeneous catalyst systems: the use of bulky phosphine ligands; the use of a large excess of ligand; and

using high pressure conditions.[8,9,10,11,12] With regard to industrial applications, however, the use of heterogeneous or supported catalysts may be of the most practical use.

There have been numerous reports in the literature detailing a wide variety of strategies and structures in supported palladium catalysis, examples of which are discussed below.

Bhanage *et al.* reported the Heck coupling of iodobenzene and butyl acrylate using a heterogeneous catalyst system, scheme 1.1.[13] This system was comprised of a palladiumtriphenylphosphine trisulphonate sodium salt complex immobilised in an ethylene glycol film on a silica particle, figure 1.2.



Scheme 1.1

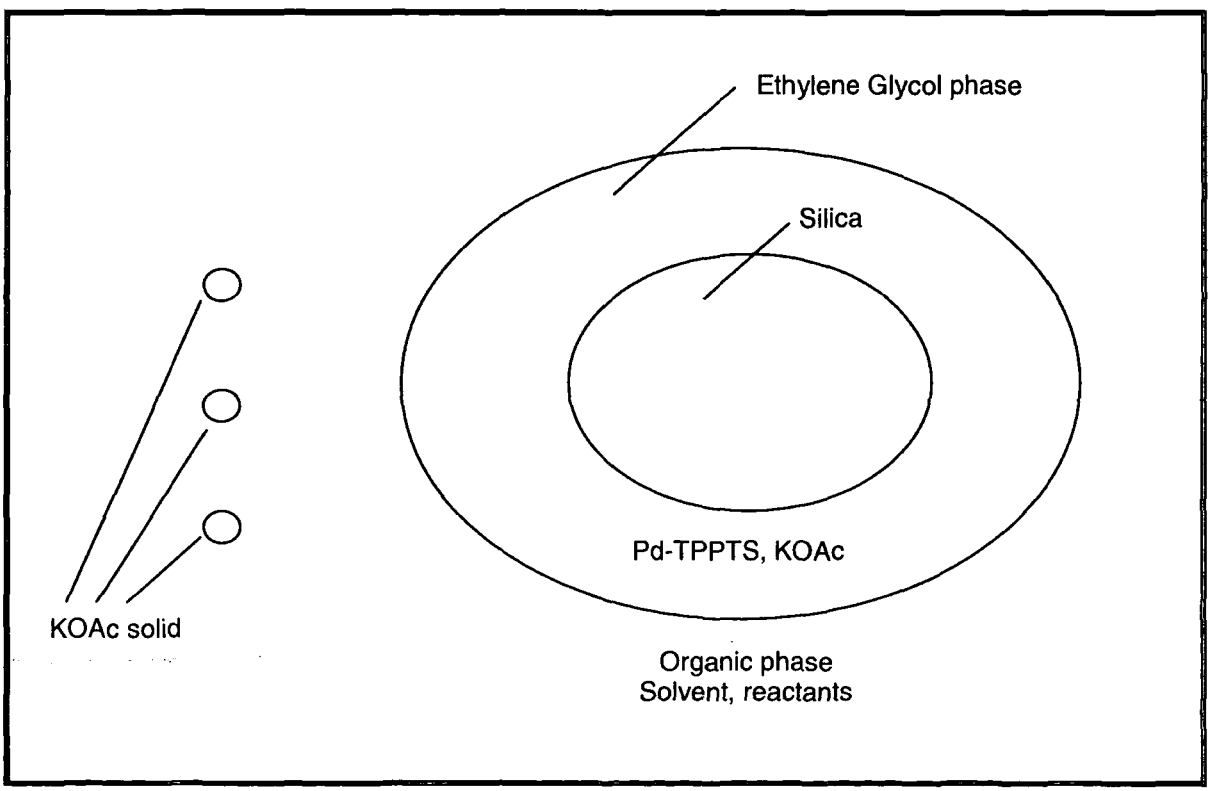


Figure 1.2

The catalyst was prepared by the dissolving $Pd(OAc)_2$, TPPTS and KOAc in ethylene glycol. This solution was stirred with silica gel and toluene for 24 hours and then vacuum dried to give the heterogeneous catalyst. Bhanage *et al.*. commented that the catalyst could be reused up to 5 times before a regeneration procedure using fresh silica and ethylene glycol was required. Whilst selectivity and substrate conversions were excellent, the catalyst was very sensitive to the choice of solvent and base used. Solvents that were miscible with ethylene glycol resulted in palladium leaching as did the use of NEt_3 as a base.

In an attempt to develop a phosphine-free recyclable heterogeneous catalytic system Choudary *et al.*. immobilised nanopalladium particles on basic Mg-Al layered double hydroxide.[14] Choudary *et al.*. commented that this support provided adequate electron density to the anchored Pd^0 species to facilitate the oxidative addition of the deactivated electron-rich chloroarenes. The layered double hydroxide consisted of alternating cationic Mg^{II}, Al^{III} and anionic $Cl^-.H_2O$ layers. $PdCl_4^{2-}$ was exchanged onto the chloride saturated layered double hydroxide to give the desired catalyst, figure 1.3.

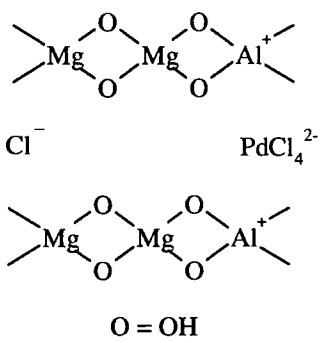
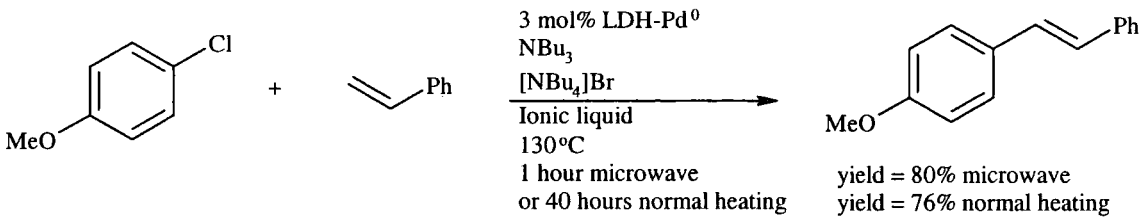


Figure 1.3

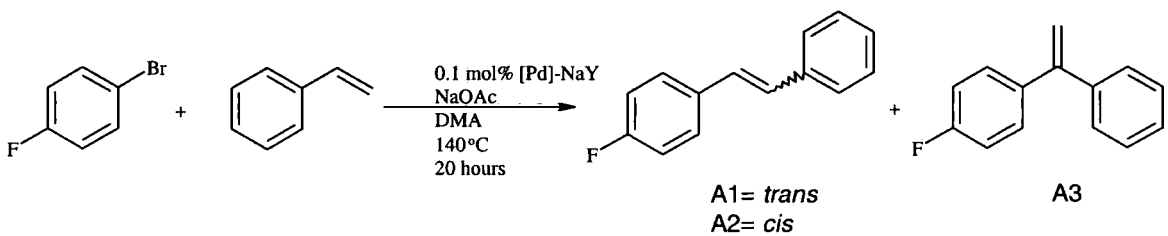
Choudary *et al.*. used the immobilised catalyst in the Heck coupling of 4-chloroanisole and styrene, scheme 1.2. The *trans*-stillbene product was isolated in high yield in only 1 hour under microwave-accelerated conditions. The catalyst was recycled and the reaction repeated five times with no observable decrease in yield.



Scheme 1.2

Djakovitch and Koehler reported the use of palladium-modified zeolites in Heck cross-coupling reactions.[15,16] These catalysts were prepared by ion exchange of a NaY zeolite with an aqueous solution of $[Pd(NH_3)_4]Cl_2$. The zeolites then underwent calcination with O_2 to form the $[Pd^{II}]$-NaY zeolite and subsequent reduction with H_2 gave the $[Pd^0]$-NaY zeolite.

These zeolite catalysts were then investigated for activity and selectivity in the Heck reaction of 4-bromofluorobenzene with styrene, scheme 1.3.



Isolated Yields:

[Pd°]-NaY	A1= 89% , A2 = 1% , A3 = 8%
$[Pd^{II}]$-NaY	A1 = 90% , A2 = 1% , A3 = 8%
$[Pd(NH_3)_4]^{2+}$-NaY	A1 = 93% , A2 = 1% , A3 = 6%

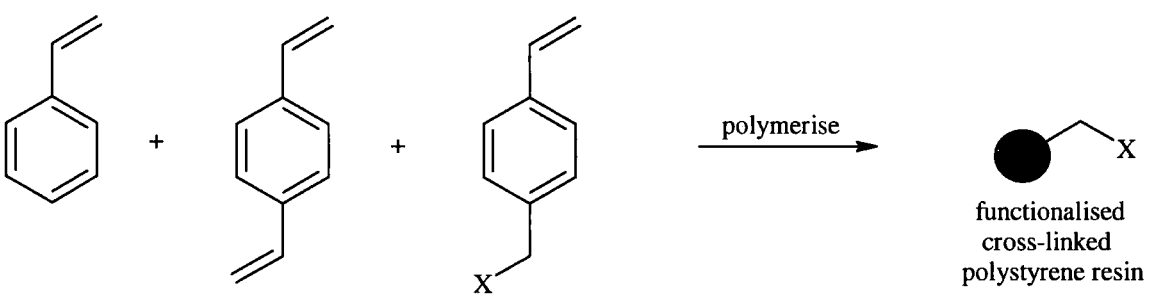
Scheme 1.3

Analysis of the reaction mixture (after removal of the catalyst by filtration) by AAS revealed no leaching of palladium from the Pd^0 and Pd^{II} zeolite catalysts, however, leaching was detected with the $[Pd(NH_3)_4]^{2+}$ zeolite catalyst. Whilst all three of the catalysts could be reused in a second Heck reaction, the $[Pd(NH_3)_4]^{2+}$ zeolite catalyst lost activity rapidly after the first reaction run. Whilst Djakovitch and Koehler had addressed the problem of palladium leaching and demonstrated catalyst recycling to a certain extent, their system could only cross couple activated aryl bromides. The

catalytic system would be difficult to tune to use the less active but industrially important aryl chlorides.

In all three examples of supported catalysis described above one common limitation was observed. Although studies the reactions were investigated extensively by a variety of spectroscopic techniques, no conclusive evidence was found to support whether the cross-coupling reactions proceeded homogenously or via a heterogeneous mechanism. Consequently tuning of the catalytic systems would be much more difficult.

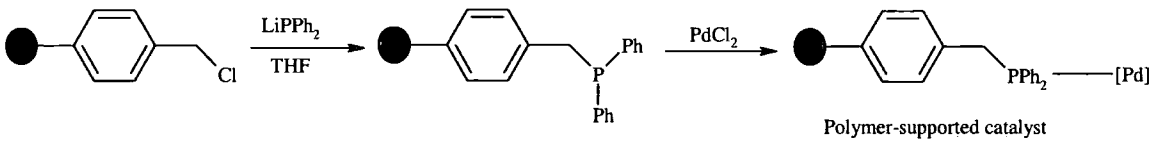
As homogeneous palladium catalysts have been used and studied extensively in cross-coupling reactions, *e.g.* $Pd(PPh_3)_4$, their mechanism is often well known and understood. In addition homogeneous catalysts can be studied easily by standard spectroscopic techniques. In many cases, the most successful strategy is to link an established solution phase catalysts to a functionalised polymeric support to allow for recovery and reuse by simple filtration procedures. Since Merrifield's report of peptide synthesis on polymer support, the most commonly used support in catalysis is cross-linked polystyrene, scheme 1.4.[17]



Scheme 1.4

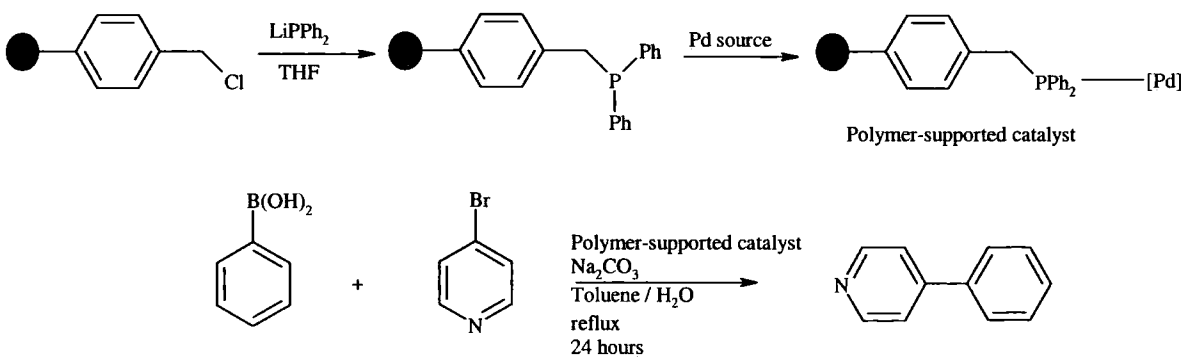
A number of functionalised polymer resins are now commercially available. Alternative linking strategies can be investigated depending on the functional group on the cross-linked polystyrene resin. In addition, the use of PEG and different polymerisation methods provides resins which swell in a variety of solvents. However, it is apparent, especially in asymmetric catalysis, that the catalytic activity and/or stereoselectivity found in the solution phase does not always correlate with that in the supported phase.[18]

One of the first examples of cross linked polystyrene in catalysis was by Trost who prepared a polymer-supported analogue of triphenylphosphine from Merrifield resin (chloromethyl cross-linked polystyrene), scheme 1.5.[19]



Scheme 1.5

In another paper, Fenger and Le Drian further investigated the effect of the choice of palladium source on catalytic activity in the Suzuki coupling of phenylboronic acid and 4-bromopyridine, scheme 1.6.[20]



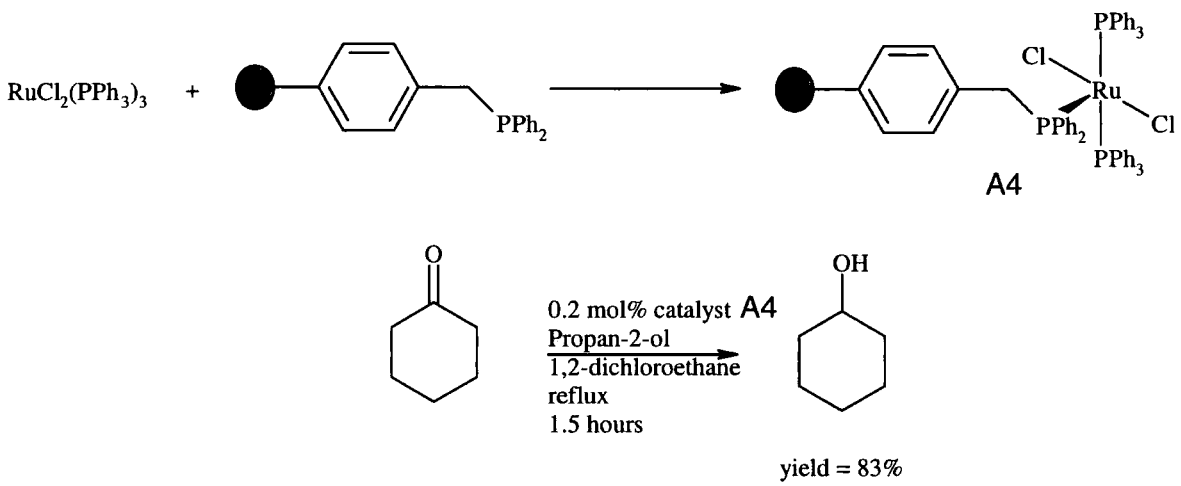
Scheme 1.6

Fenger and Le Drian commented that the Pd/P ratio had no influence on the activity of the catalyst, however, yields of the cross coupled product varied significantly upon varying the palladium source. Catalysts prepared with $PdCl_2$ and $PdCl_2(MeCN)_2$ required approximately 20 mequiv. of palladium in the reaction to achieve yields of between 60-78%. As all these catalysts contained a Pd^{II} species; Fenger and Le Drian also reduced one of the catalysts with hydrazine in the presence of PPh_3 to generate the Pd^0 catalyst. The cross-coupled product was still only formed in 71% yield after using 145 mequiv. of palladium. Curiously, however, when $Pd(PPh_3)_4$ was used as the metal source the catalyst activity increased dramatically with only 1 mequiv of palladium required to produce the cross-coupled product in 90% yield. The catalysts could be

recycled up to five times without an observed decrease in activity; however, palladium leaching was detected, with a 0.6% decrease in the catalyst mass after every run.

From these examples it is clear that a major drawback is that once the solution phase catalyst is attached to the polymer-support it is difficult to fully characterise the catalytic species. Whilst methods such as elemental analysis and IR spectroscopy provide some information, ^{1}H and ^{13}C NMR spectroscopy prove difficult. However, the use of polymer resins containing PEG, for example tentagel® have addressed this problem.

As a convenient ligand system, polymer-supported triphenylphosphine (strictly speaking polymer supported benzyldiphenylphosphine) has been used in numerous reactions involving other transition metals. For example Leadbetter prepared the resin-bound ruthenium phosphine complex **A4** for use in transfer hydrogenation reactions, scheme 1.7.[21]



Scheme 1.7

Whilst yields were much higher when the homogeneous catalyst $RhCl_2(PPh_3)_3$ was used (95%), Leadbetter found that the resin-bound catalyst could be recycled successfully up to four times without observing a decrease in yield.

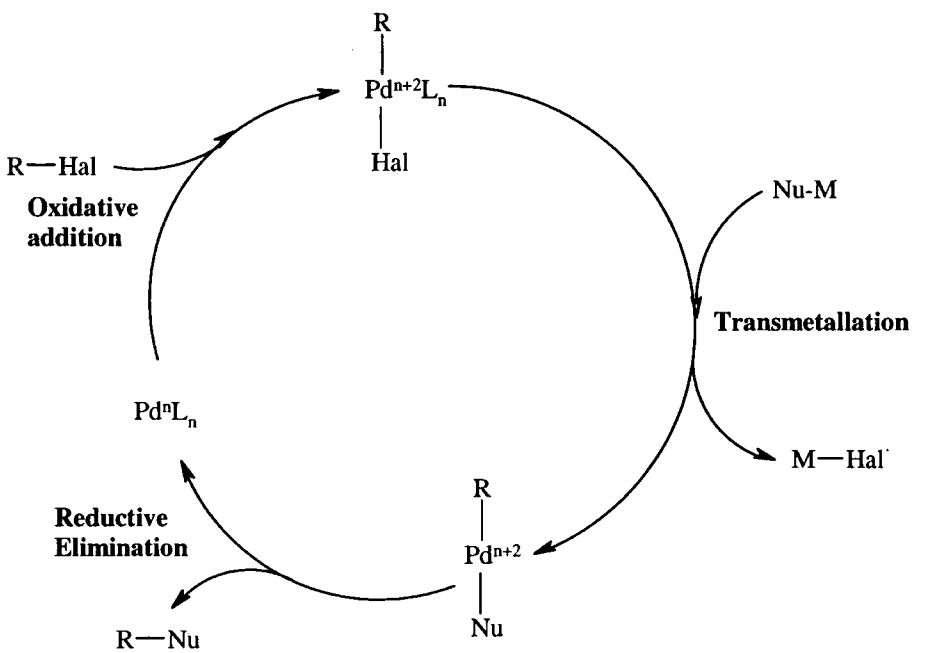
Other types of catalyst support are described in section 1.5.6.5.

1.3- Palladium-catalysed cross-coupling reactions

Palladium catalysts have provided a plethora of new methodologies for synthetic organic chemistry. The palladium-catalysed cross-coupling of aryl halides (or halide analogues) with nucleophiles has been firmly established as one of the most important methods available for carbon-carbon and carbon-heteroatom bond formation.

Palladium-catalysed cross-coupling reactions can be separated into three distinct classes: those involving transmetallation, Hartwig-Buchwald type heteroatom cross-couplings, and the Heck reaction.

With the exception of the Heck reaction and the copper-free Sonogashira reaction, all of these coupling reactions follow the same general catalytic cycle, scheme 1.8. Several named reactions may be performed by varying the nucleophile used in catalysis, table 1.1.



Scheme 1.8

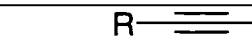
Reaction	Nucleophilic reagent, [M]-Ar'
Suzuki-Miyaura	R'-BX_2
Negishi	R'-ZnX
Kumada	R'-MgX
Stille	R'-SnR''_3
Sonogashira	
Hiyama	R'-$Si(OR'')_3$
Hartwig-Buchwald amination	R_2NH
Hartwig-Buchwald amidation	RCONHR'
Hartwig-Buchwald	RSH
Hartwig-Buchwald	ROH

Table 1.1

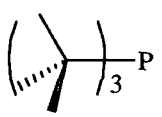
All of the reactions shown in table 1.1 can be catalysed by a great variety of palladium complexes. Many of these complexes are now commercially available to the organic chemist for use in homogeneous catalysis, for example $Pd(OAc)_2$ or $Pd(C_3H_5)(\mu\text{-}Cl)_2$. However, only reactive electrophiles tend to undergo coupling and substrate conversion is usually rather limited. On the other hand as a great number of ligands are either commercially available or can be easily synthesised; simple ligand exchange allows the formation of a new complex with enhanced properties such as improved thermal stability, resistance to oxidation, increased activity with certain substrates and enantioselectivity.

It is thought that the reactions in table 1.1 involve a catalytically active Pd^0 species, followed by oxidative addition of R-Hal to generate an R-Pd^{II}-Hal intermediate. However there have been reports in literature suggesting Pd^{II}-Pd^{IV} catalytic cycles.[22,23]

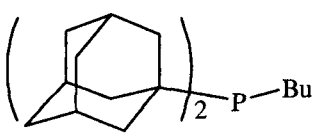
The R group involved in oxidative addition normally has to be an aryl or vinyl group; otherwise rapid β-hydride elimination can cause decomposition of the required R-Pd intermediate. However, recent work by Fu *et al.*. has shown examples of Suzuki, Sonogashira, and Stille couplings of alkyl halides which can be achieved by using moderately bulky, electron rich alkylphosphines or *N*-Heterocyclic carbenes.[24,25,26,27,28,29]

The general order of reactivity of aryl electrophiles in cross-coupling reactions is Ar-I > Ar-Br > Ar-OTf > Ar-OTs > Ar-Cl.[5]

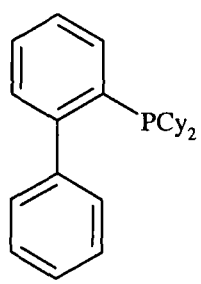
Whilst for several years aryl bromides and iodides have been preferably used as substrates in palladium-catalysed cross-coupling reactions, the availability, low cost and facile modification of phenols to aryl triflates or tosylates has generated interest in these substrates. Aryl iodides will undergo oxidative addition at room temperature or just above in the presence of triphenylphosphine ligands. Aryl bromides typically require temperatures between 80-150°C. The far more readily available and industrially important aryl chlorides are typically transformed very slowly by standard palladium/ arylphosphine catalysts. The use of sterically demanding alkylphosphines such as **B1**, **B2** and **B3** has allowed aryl bromides to couple at room temperature and aryl chlorides to be coupled under milder temperatures. [30, 31, 32]



B1



B2



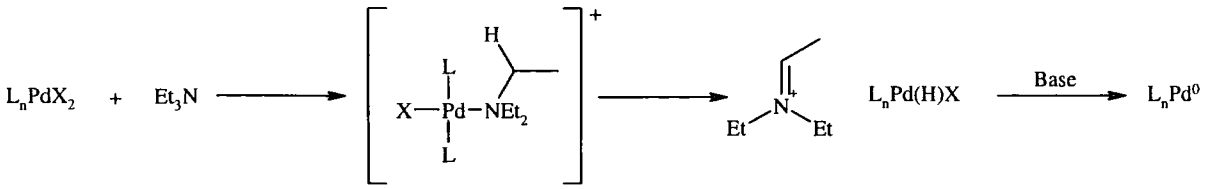
B3

More electron-rich ligands are expected to accelerate the oxidative addition step by making the catalyst's metal centre itself more electron-rich. This increased electron density is particularly important for less reactive aryl chlorides in overcoming the high strength of the C-Cl bond.

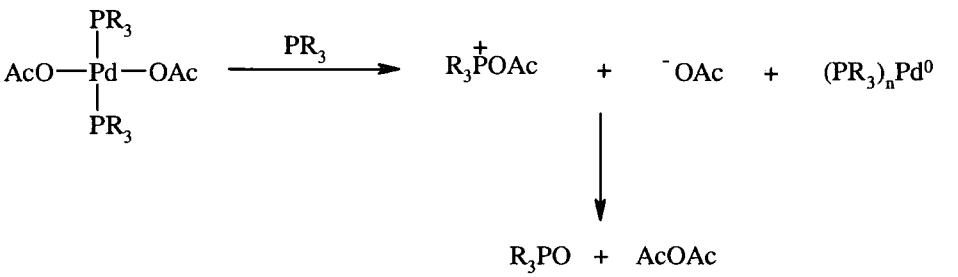
Whilst both Pd^0 and Pd^{II} sources can be used, the active species is generally thought to be Pd^0. The reduction of Pd^{II} to Pd^0 can occur by a variety of mechanisms depending on the reaction conditions: reduction by alkylation, scheme 1.9; reduction by amines or alcohols, scheme 1.10; or reduction by phosphine, scheme 1.11.[33]

$$L_nPdX_2 + 2RM \xrightarrow{-2\,MX} L_nPdR_2 \longrightarrow L_nPd^0 + R{-}R$$

Scheme 1.9



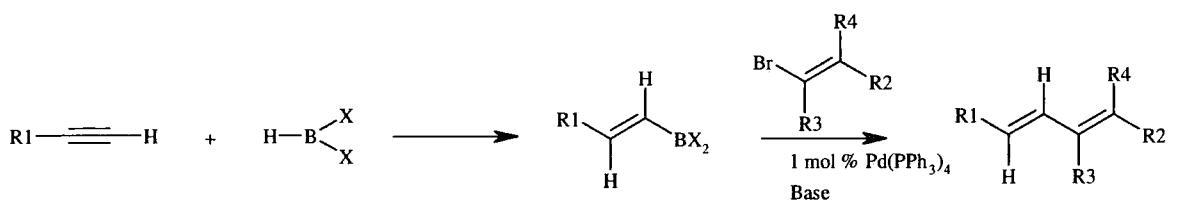
Scheme 1.10



Scheme 1.11

Palladium is one of the most versatile metals used by synthetic chemists because it promotes a myriad of transformations. There are a great number of literature publications concerning palladium-catalysed reactions, the vast majority of which are beyond the scope of this thesis. Consequently this thesis concerns palladium-catalysed cross-coupling reactions only, and in particular those that are described in chapters 2 and 3 - the Suzuki-Miyaura, Stille and Heck cross-coupling reactions.

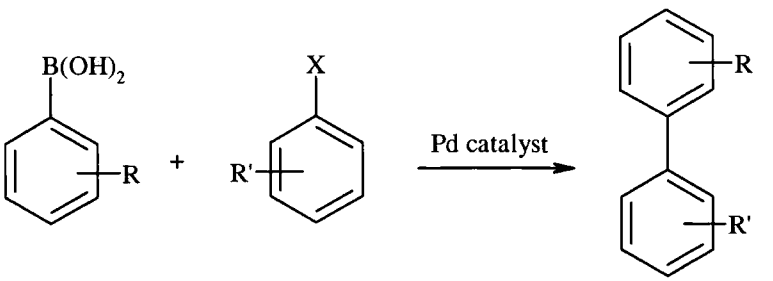
1.3.1- The Suzuki-Miyaura reaction



Scheme 1.12

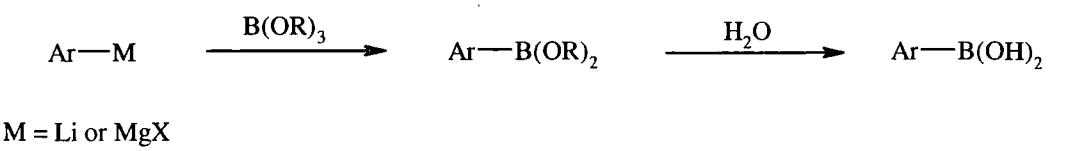
Suzuki and Miyaura first reported the palladium-catalysed cross-coupling of alkenylboranes and alkenyl halides in 1979, scheme 1.12.[34,35] Since then the reaction

has grown in terms of substrate and catalyst scope. Today the coupling reaction of aryl- and heteroaryl-boronic acids with aryl and heterocyclic electrophiles has become a powerful method for preparing various biaryl systems and is widely used in synthesising natural products, scheme 1.13.[36]

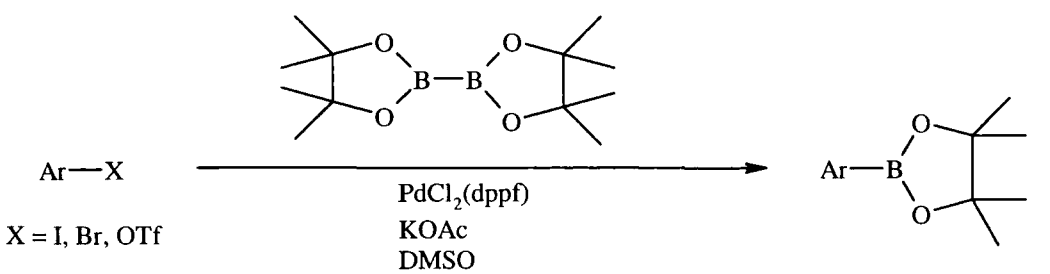


Scheme 1.13

Although boronic acids are typically reported in Suzuki-Miyaura couplings in the literature, boronate esters have also been used. Both species can be easily prepared from trialkyl boronates, scheme 1.14.[33]



Scheme 1.14

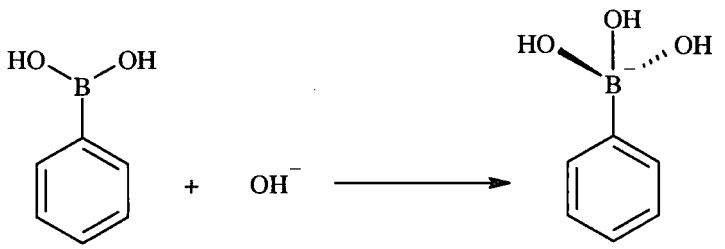


Scheme 1.15

Miyaura *et al.* also reported the preparation of arylboronates from aryl halides or triflates using bis(pinacolate)diboron, scheme 1.15.[37]

Organoboranes or boronates are only weakly nucleophilic, hence they are stable to water and oxygen. This low nucleophilicity means that they do not undergo transmetallation with palladium halides, except in the presence of oxygen or fluoride Lewis bases. Therefore, typical Suzuki coupling conditions either involve aqueous hydroxide or fluoride salts in organic solvents.

One explanation for this base-accelerating effect is that tetrahedral boron-ate complexes are formed. In fact it has been shown in the literature that boronic acids, which are typically used in Suzuki coupling reactions, form tetrahedral boron-ate species in the presence of hydroxide or fluoride, scheme 1.16.[38,39]

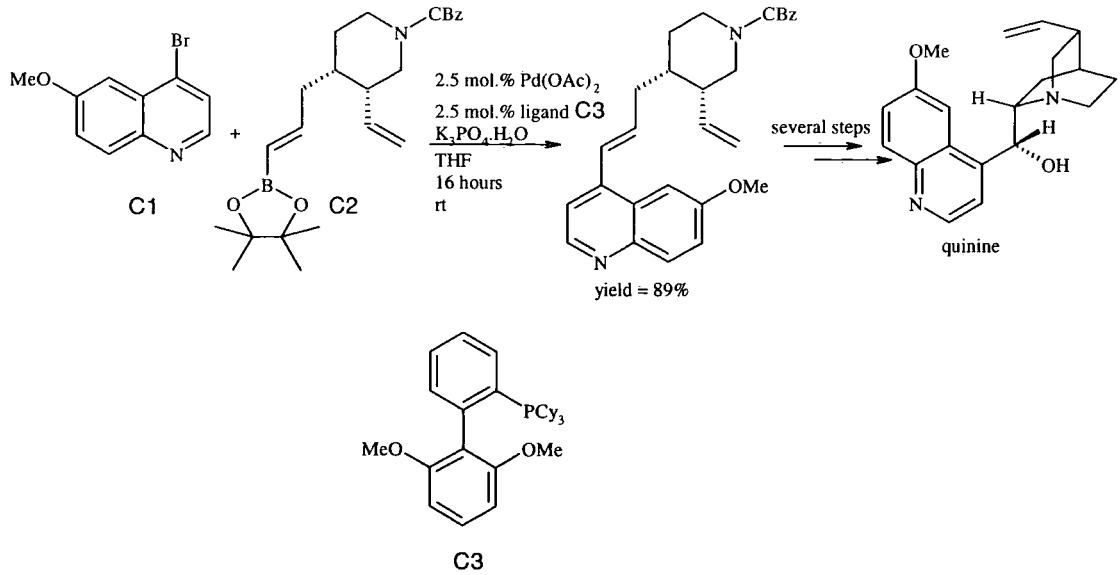


Scheme 1.16

On a commercial scale the Suzuki-Miyaura reaction is usually preferred to other carbon-carbon bond- forming processes since organoboronic acids are conveniently synthesised reagents and are generally thermally stable to water and oxygen.

On a laboratory scale the Suzuki-Miyaura cross-coupling reaction has been used in a wide variety of carbon-carbon bond formations. This has been underscored by the large volume of literature that has been published, for example several reviews of the Suzuki-Miyaura reaction are available covering the many reaction conditions and substrates available to the synthetic chemist.[40,41]

Due to its versatility, several groups have used the Suzuki-Miyaura reaction in the total synthesis of natural products. For example Jacobsen *et al.* used a Suzuki-Miyaura coupling reaction using methodology developed by Buchwald in the first catalytic total synthesis of quinine.[42,43] Successful cross-coupling of boronate ester **C1** and bromoquinoline **C2** was achieved at room temperature with 2.5 mol.% catalyst loading producing exclusively the *trans*-olefin in 89% yield, scheme 1.17.



Scheme 1.17

Nicolau *et al.* used a Suzuki-Miyaura cross-coupling reaction in the total synthesis of vancomycin.[44] Whilst synthesising the vancomycin aglycon fragment, figure 1.4, Nicolau *et al.* coupled a boronic acid derivative and an aryl iodide with bulky *ortho*-substituents, scheme 1.18. Two atropisomers, **C4** and **C5** were formed in high yield and carried through several steps of the synthesis until being separated by chromatography.

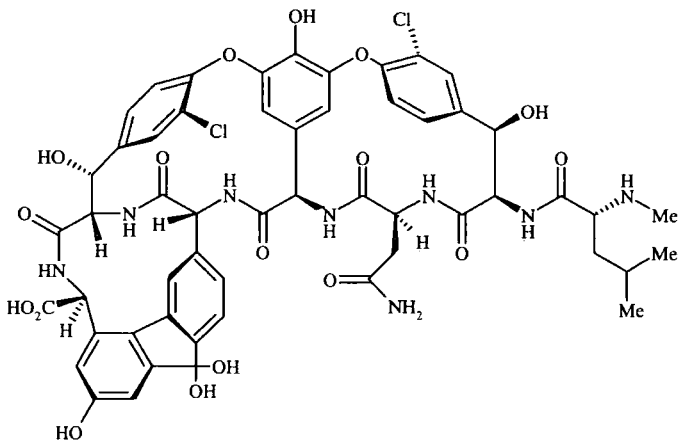
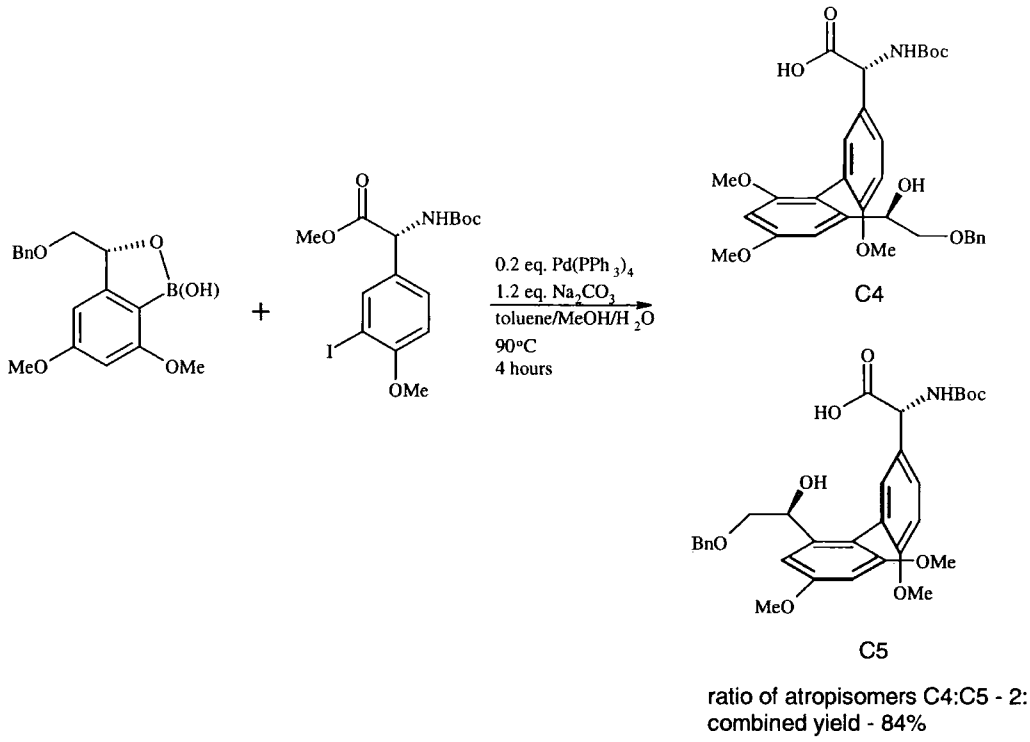
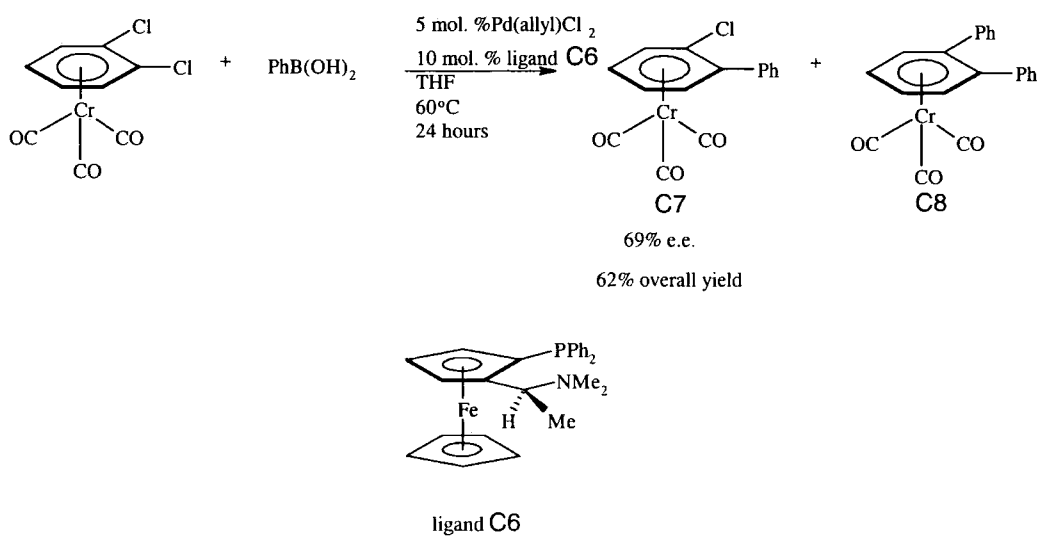


Figure 1.4



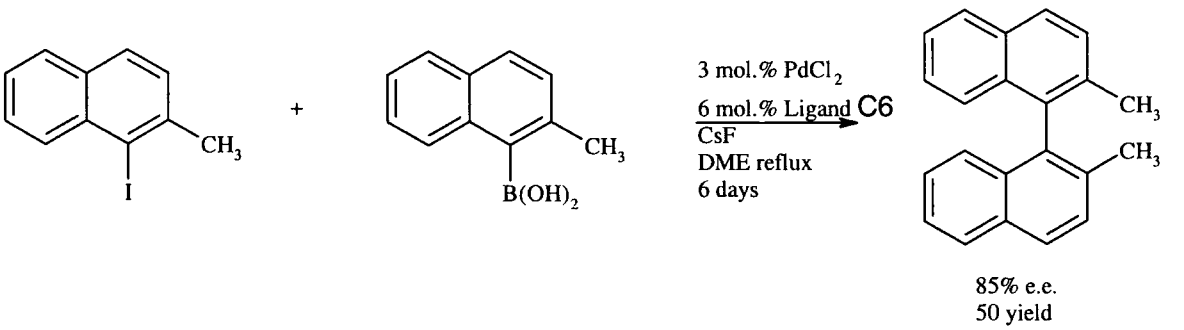
Scheme 1.18

Several groups have performed asymmetric Suzuki-Miyaura cross-coupling reactions. For example Uemura and Hayashi studied the desymmetrisation of planar-prochiral compounds, scheme 1.19.[45,46] When a palladium catalyst with chiral ligand **C6** was used; planar-chiral **C7** was obtained with 69% e.e. together with a small amount of the achiral bis(coupled) product **C8**. The reaction was found to be very sensitive to electronic effects, and the use of the more electron-rich 4-methoxyphenyl boronic acid caused a decrease in enantioselectivity together with a dramatic reduction in the reaction rate.



Scheme 1.19

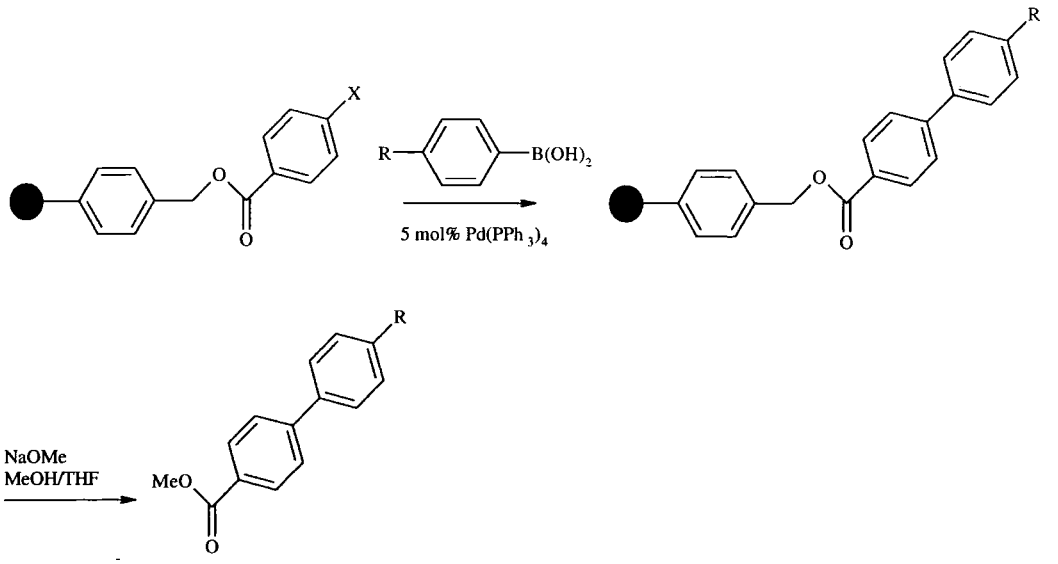
Biaryl systems where rotation is restricted between the two aryl centres are in fact chiral systems. Cammidge and Crépy reported the Suzuki-Miyaura coupling of aryl boronates to give axially-chiral biaryls, scheme 1.20.[47] Although several chiral ligands were investigated, the greatest enantioselectivities were obtained using the same ligand as Uemura and Hayashi, **C6**.



Scheme 1.20

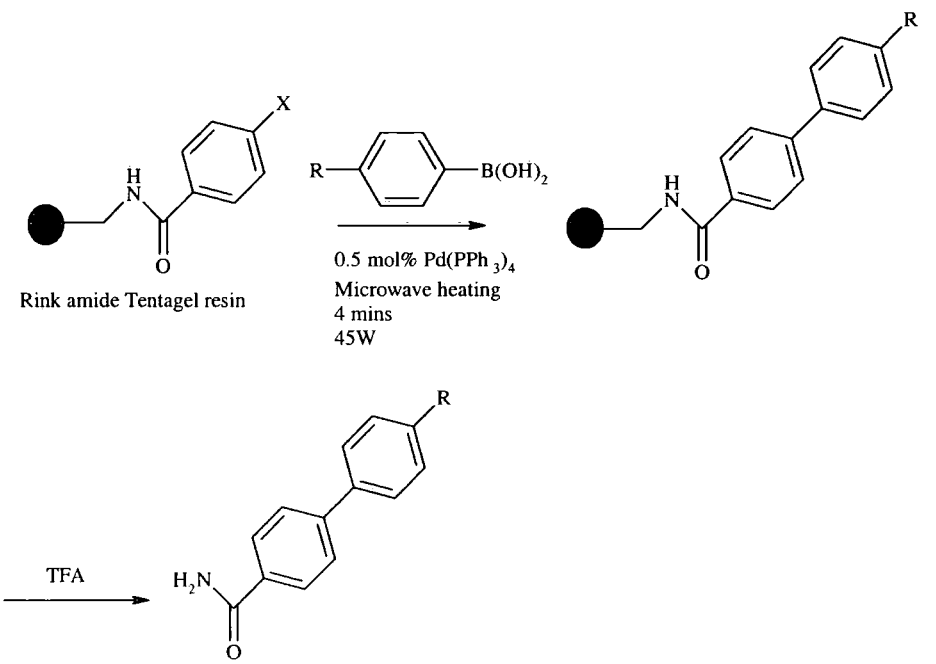
As a versatile method of forming carbon-carbon bonds, and as the reaction generally results in an excellent yield at relatively mild temperatures, several groups have adapted the reaction for use in combinatorial chemistry.

Frenette and Friesen reported the first supported Suzuki-Miyaura reaction between Merrifield-bound aryl iodides and aryl boronic acids.[48] Simple transesterification was sufficient to release the biaryl products after the reaction, scheme 1.21.



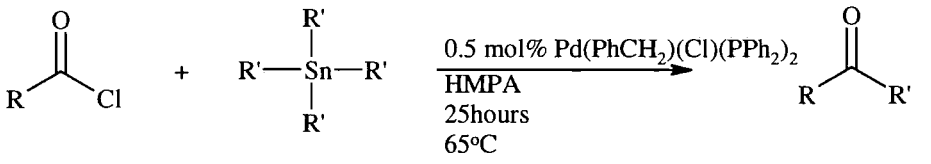
Scheme 1.21

Larhed *et al.* reported the cross-coupling of aryl halides bound to Rink amide tentagel® resin with a variety of aryl boronic acids under microwave radiation-accelerated conditions, scheme 1.22.[49] Very high conversions were achieved after only four minutes of heating with only 1 eq. of boronic acid and small quantities of catalyst. The biaryl products were isolated in high yield (80-95%) after cleavage from the resin using TFA. Following this publication several groups have reported that the Suzuki-Miyaura reaction can be accelerated using microwave radiation.[50,51]



Scheme 1.22

1.3.2- The Stille reaction



R= Ph, Me, *t*-Bu

R' = Me, Ph, *n*-Bu, $PhCH_2$

73-99% yield

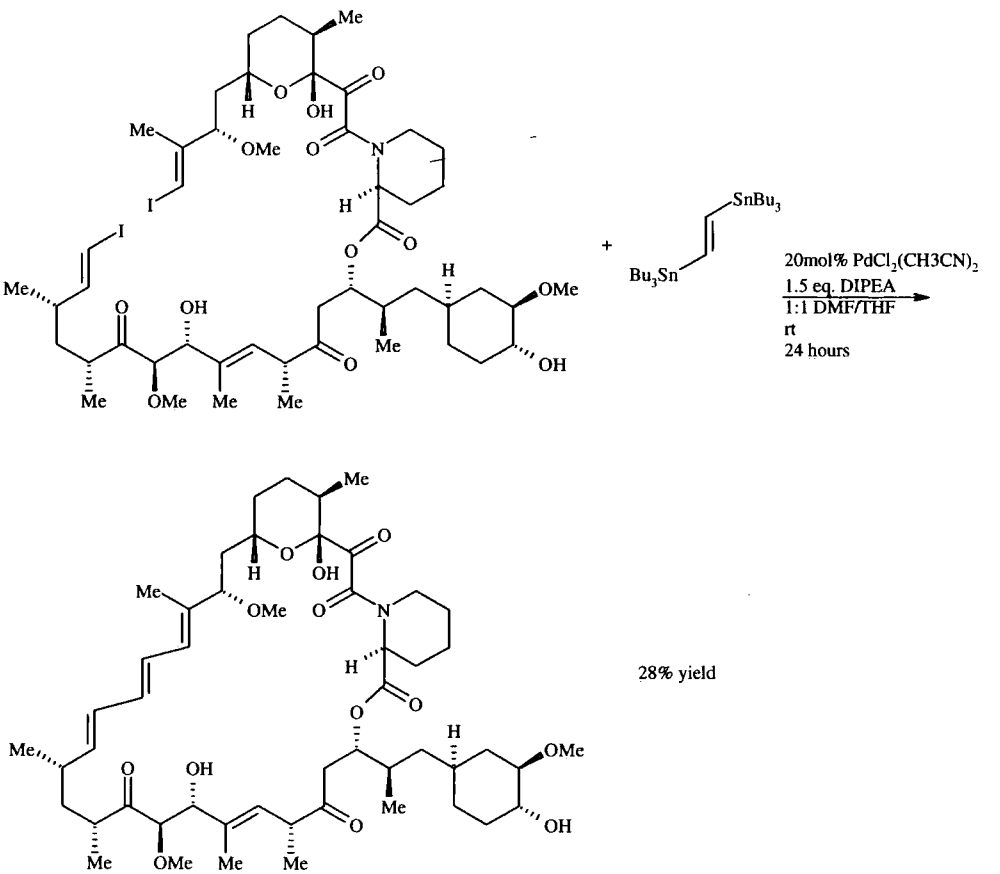
Scheme 1.23

Stille and Milstein reported the first palladium-catalysed cross-coupling with organostannane compounds in 1978, scheme 1.23.[52] Whilst Stille and Milstein originally used an acid chloride electrophile, the use of several different types of electrophile has been reported in the literature since then, with the most common being an aryl or vinyl halide.[53,54]

Mechanistically the Stille coupling reaction is very similar to the Suzuki-Miyaura reaction. However the major difference is that the metallic nucleophile does not require preactivation with base. The mechanism involves oxidative addition of the vinyl or aryl halide or equivalent by a palladium (0) catalyst. The palladium (II) intermediate can then undergo a transmetallation reaction with the organostannane. Reductive elimination then completes the cycle to release the product and regenerate the palladium (0) catalyst, (see scheme 1.8 above, section 1.3).

Since its first reported use in 1978, the Stille reaction has been very popular in organic synthesis and has been widely used for the coupling of both aromatic and vinylic systems and several reviews have been published covering the multitude of synthetic applications; although the Suzuki-Miyaura reaction has more recently become the preferred cross-coupling reaction as the boron-containing side products are non-toxic.[33,53,54] However, the ease with which the necessary organostannanes can be prepared and their stability often exceed the disadvantages of the significant toxicity and the difficulty in separating organostannanes from the organic product.

As a result of these factors the Stille reaction has been used extensively in total synthesis. For example Nicolau *et al.* used a double Stille coupling reaction in the final macrocyclisation of rapamycin, scheme 1.24.[55]

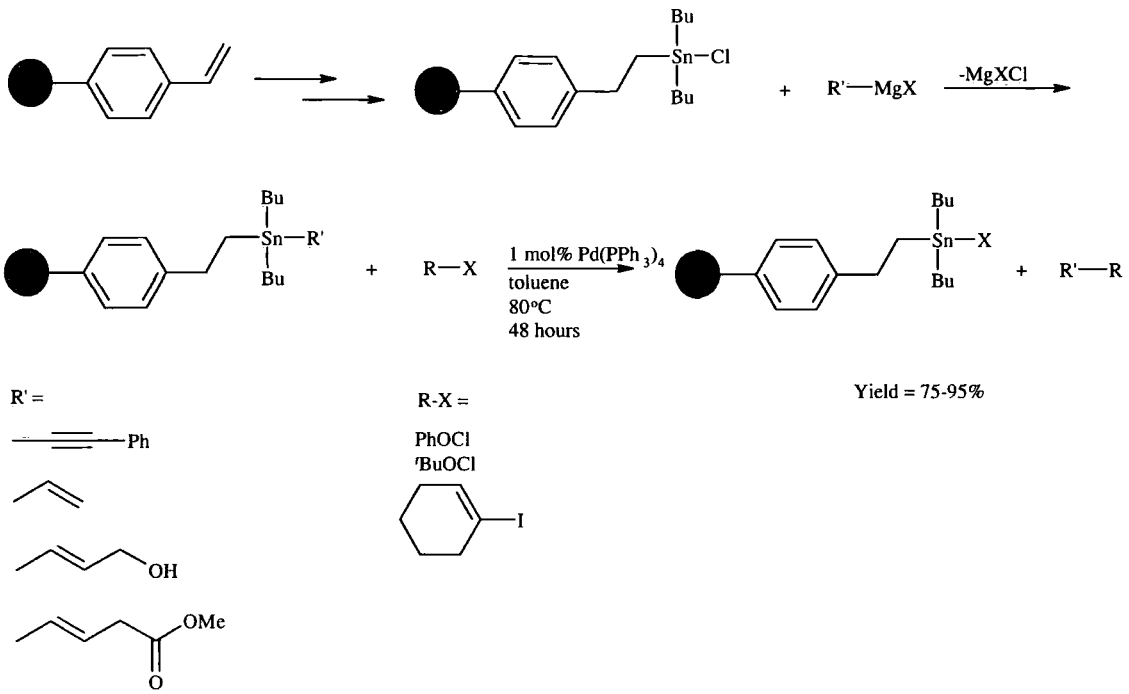


Scheme 1.24

Whilst the coupling of *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene and the di-iodo rapamycin precursor was successful, the final rapamycin product was isolated in only 28% yield. However, this synthesis demonstrates the exceptionally high tolerance of the Stille coupling reaction to other functional groups present in the molecule.

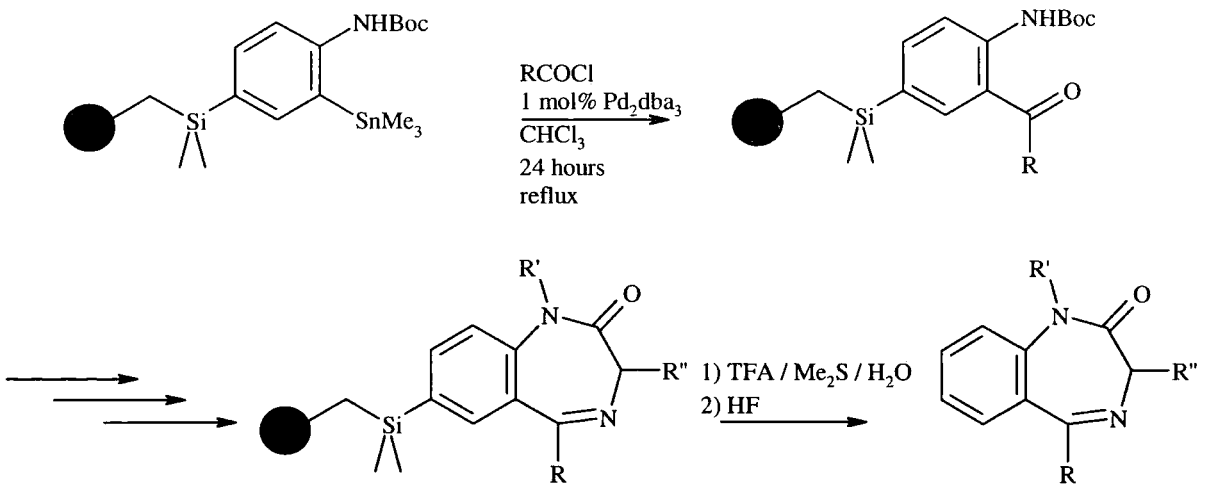
Neumann *et al.* developed a simple strategy to generate polymer-supported organostannanes in an attempt to overcome the disadvantage of equimolar amounts of trialkyltin by-products that often contaminate the desired product at the end of a Stille cross-coupling reaction, scheme 1.25.[56] Using an organotin chloride attached to cross-linked polystyrene resin, a range of desired organostannanes could be generated by a reaction with Grignard reagents. The reactive polymer could then undergo Stille cross-couplings with organic electrophiles. The polymer-supported organotin by-product

could be easily separated by filtration and recycled by another reaction with a Grignard reagent. Neuman *et al.* reported that the desired products were free of tin compounds to within the limit of a few ppm and there was no measurable decrease in yield in subsequent regeneration cycles using the recycled supported organostannanes. One disadvantage of this system, however, was that the Stille couplings required considerably longer reaction times than with analogous solution phase reagents.[88]



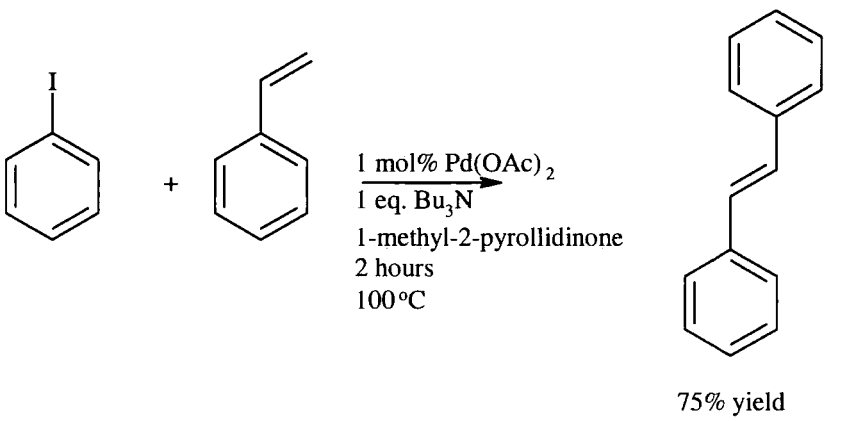
Scheme 1.25

Ellman and Plunkett reported a polymer-supported Stille coupling in the synthesis of a range of 1,4-benzodiazepine derivatives, scheme 1.26.[57] Their method was advantageous because it allowed the formation of a ketone in one easy step; could be driven to completion by use of excess acid chloride; and would not be affected by other functional groups.



Scheme 1.26

1.3.3- The Heck reaction



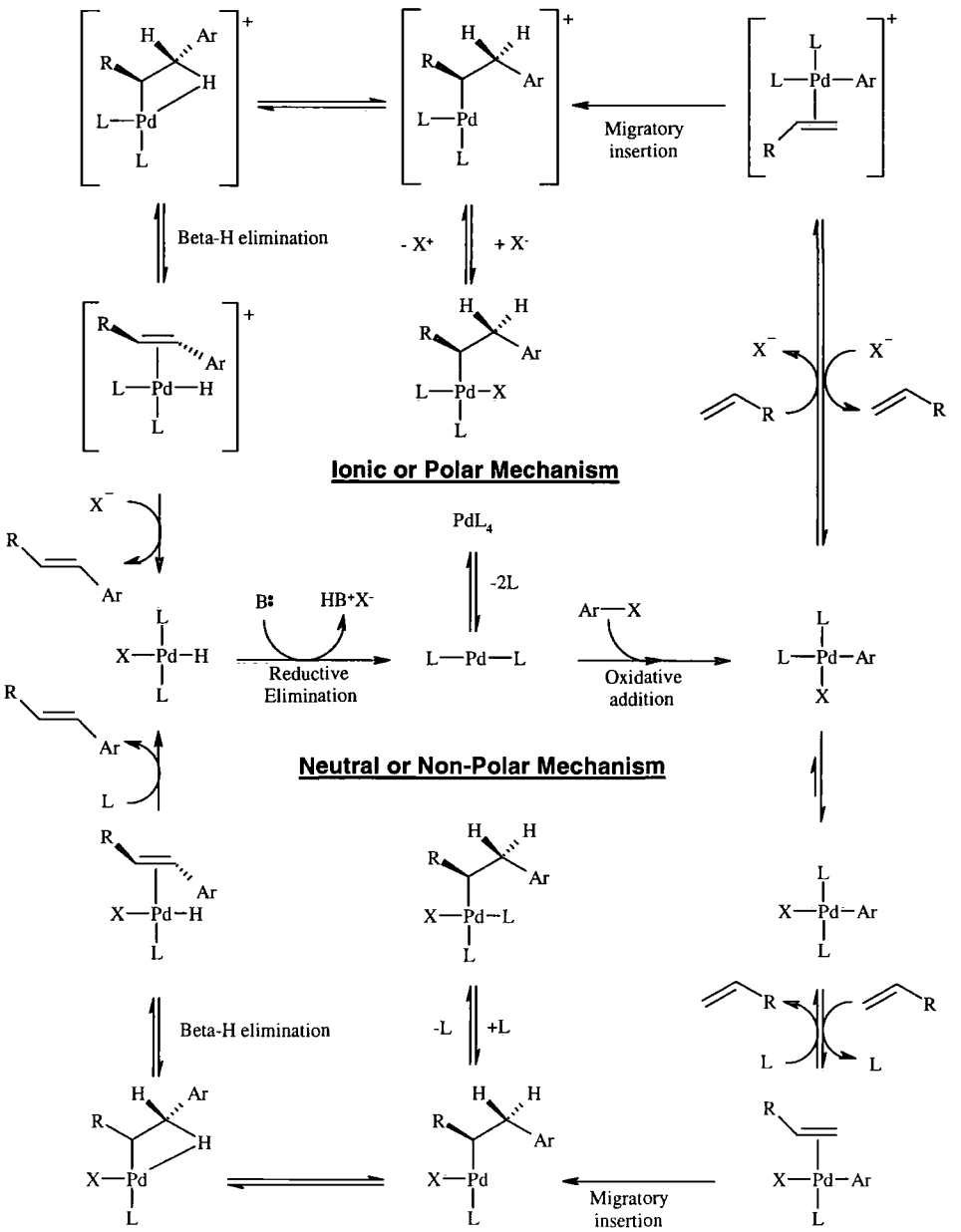
75% yield

Scheme 1.27

Since its first reported use in 1972, scheme 1.27, the Heck reaction has become one of the most widely used palladium-catalysed carbon-carbon bond forming reactions in organic synthesis.[58] Compared to the vinyl/aryl metal compounds that are employed in other cross-coupling reactions, functional group tolerance and the ready availability and low cost of simple olefins contribute to the extensive use of the Heck reaction.

In contrast to the other palladium-catalysed cross-coupling reactions discussed earlier, the Heck reaction proceeds *via* a slightly different reaction cycle. Whilst the other cross-coupling reactions involve a transmetallation step, the Heck reaction does not and instead involves an alkene insertion step. The actual C-C bond forming reaction is a

migratory insertion not a reductive elimination. A β-hydride elimination step is required to generate a carbon-carbon double bond before reductive elimination of the final product. A base is also required in the reaction media in order to regenerate the active catalyst for another catalytic cycle.

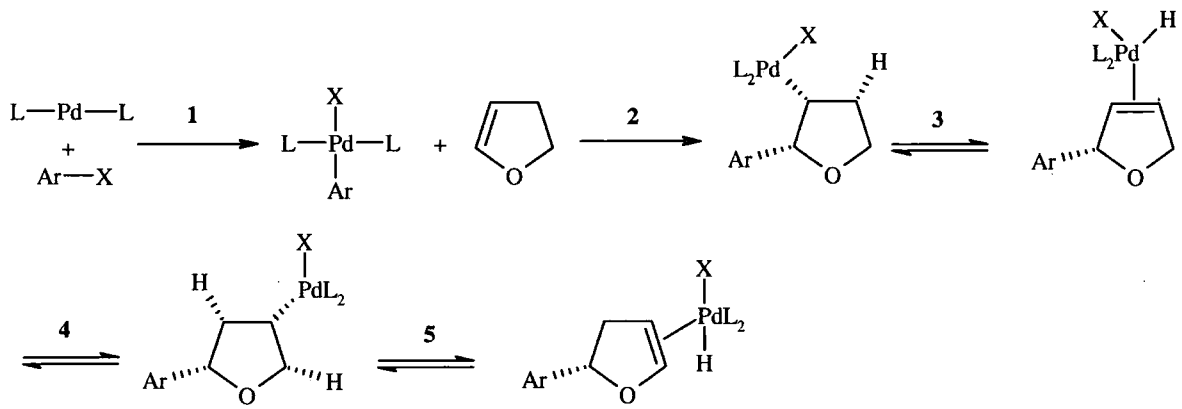


Scheme 1.28

The key step in the Heck reaction is ligand coordination of the alkene to the palladium complex *via* an associative ligand substitution mechanism. As either a neutral ligand, such as a phosphine, or an anionic ligand may be the leaving group, two reaction cycles - neutral or ionic, scheme 1.28 can occur.[59] The ionic mechanism becomes more

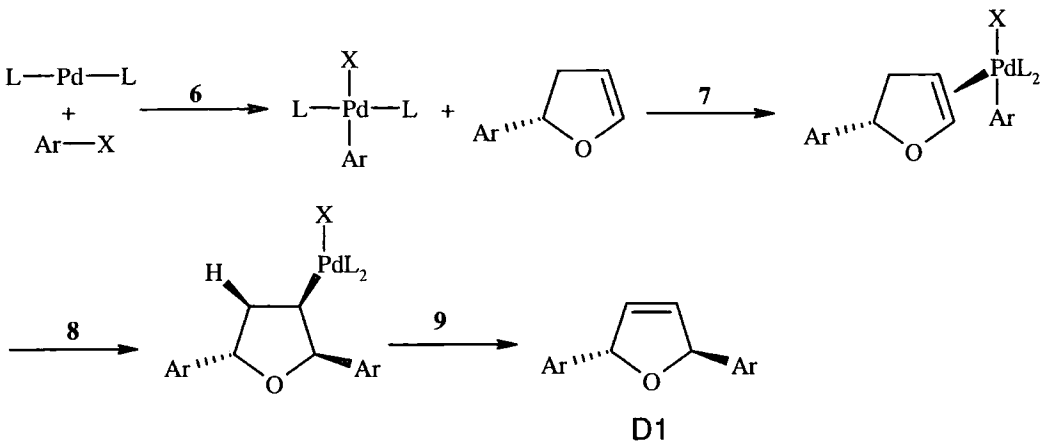
important when X is a good leaving group such as I^- or OTf^- or when a chelating ligand is used. The neutral pathway is more common with non-chelating neutral ligands such as monophosphines.

Evidence suggests that the migratory insertion step is concerted, however, with more electrophilic palladium centres and electron-rich alkenes, a cationic mechanism may be possible, in which the palladium adds to the alkene electrophilically before delivering the aryl nucleophile.[59]



Scheme 1.29

The synthesis of a *trans*-dihydrofuran for example involves all of these steps, scheme 1.29.[33] Alkene isomerisation can occur during the Heck coupling reaction as the β-hydride elimination step is reversible. This allows the most stable alkene to be formed by hydropalladation-dehydropalladation. Oxidative addition of the aryl halide to the palladium (0) complex (**step 1**) is followed by insertion of the palladium (II) complex into the furan double bond. Carbopalladation on the electron-rich alkene proceeds to give the substituted product in a *syn* fashion (**step 2**). β-Hydride elimination must occur away from the aryl group to form the alkene as there is no *syn* hydrogen on the other side (**step 3**). Hydropalladation can then form a new σ complex (**step 4**). β-Hydride elimination of the hydrogen closest to the oxygen atom gives the enol ether, which is the most stable alkene possible due to conjugation (**step 5**).

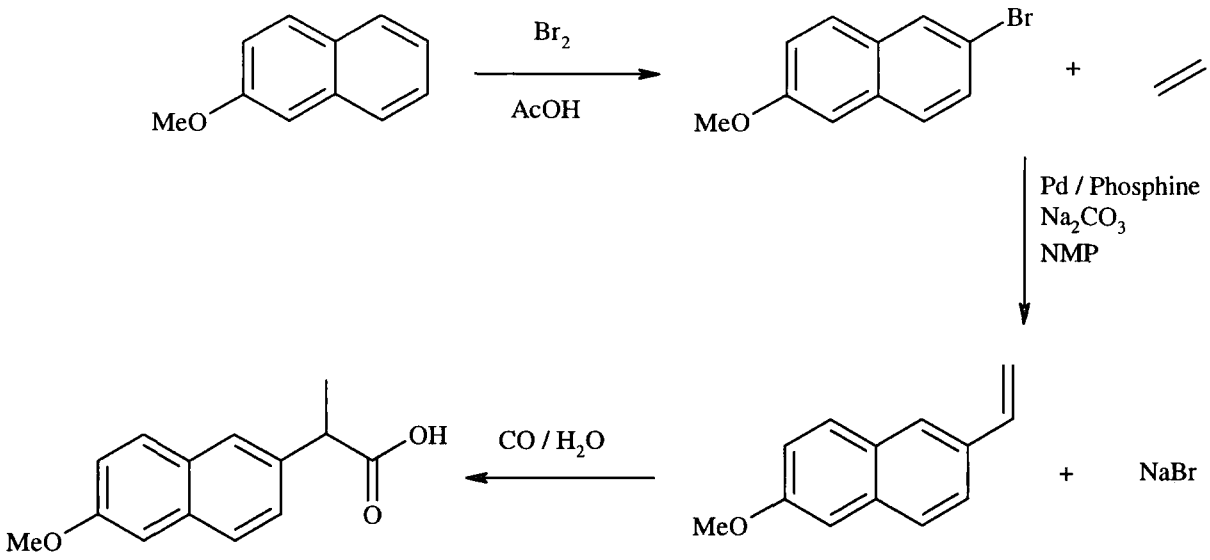


Scheme 1.30

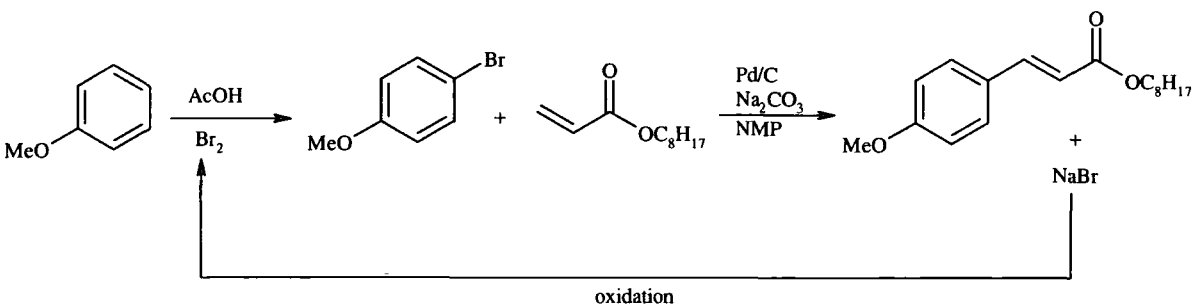
A second Heck reaction can now occur, scheme 1.30, with oxidative addition of the aryl halide to form another palladium (II) complex (**step 6**). However, the enol ether now has two diastereotopic faces: *syn* or *anti* to the aryl group introduced in the first sequence. As palladium (II) is a large ion and is sensitive to steric effects, coordination of the palladium (II) intermediate occurs on the face of the enol ether *anti* to the first aryl group (**step 7**). This in turns controls all the subsequent steps which must be *syn* (**steps 8 and 9**) allowing the formation of the *trans* product **D1**. All of these isomerisation processes, however, can be prevented by the addition of strong base which will remove hydrogen halide from the palladium complex as soon as it is formed.

The choice of reaction substrates in Heck reactions is limited to aryl, heteroaryl, vinylic and benzylic electrophiles, because the presence of an sp^3 carbon in the β position carrying hydrogen would result rapidly in β-hydride elimination. Whilst recent work by Fu *et al.* has shown that substrates containing sp^3 carbons carrying hydrogen can be used in other cross-coupling reactions under carefully controlled conditions, unfortunately they cannot be used in the Heck reaction.[28,29,30]

Whilst palladium cross-coupling reactions are usually of most use in small scale laboratory synthesis, the Heck reaction has recently been used in large scale industrial synthesis. For example the synthesis of the anti-inflammatory drug Naproxen by Albemarle, scheme 1.31, and the production of the sunscreen agent octyl methoxycinnamate by DSM Catalytica Pharmaceuticals, scheme 1.32.[60]

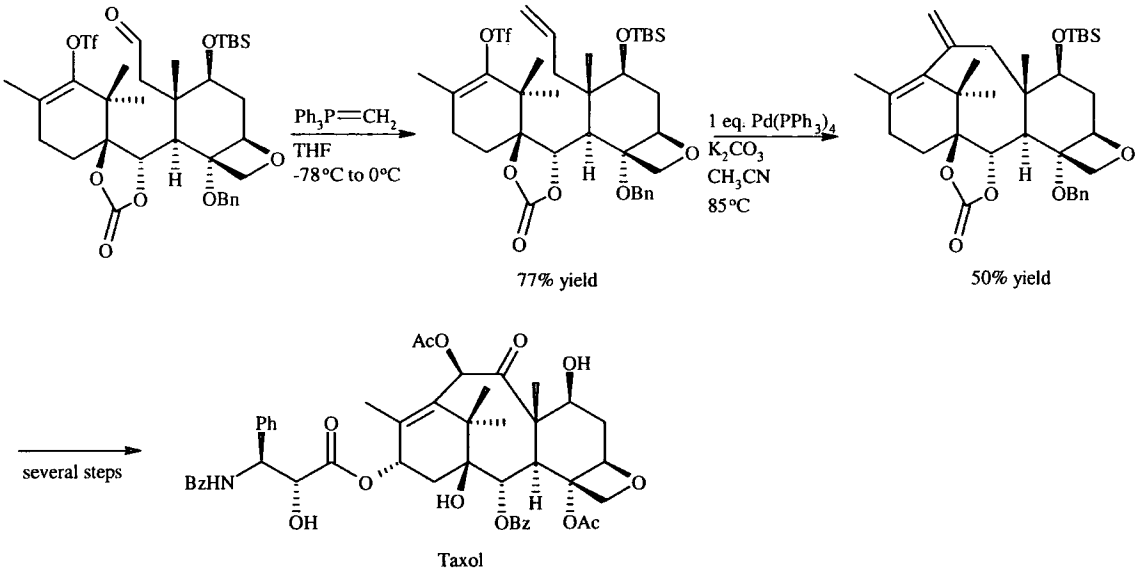


Scheme 1.31



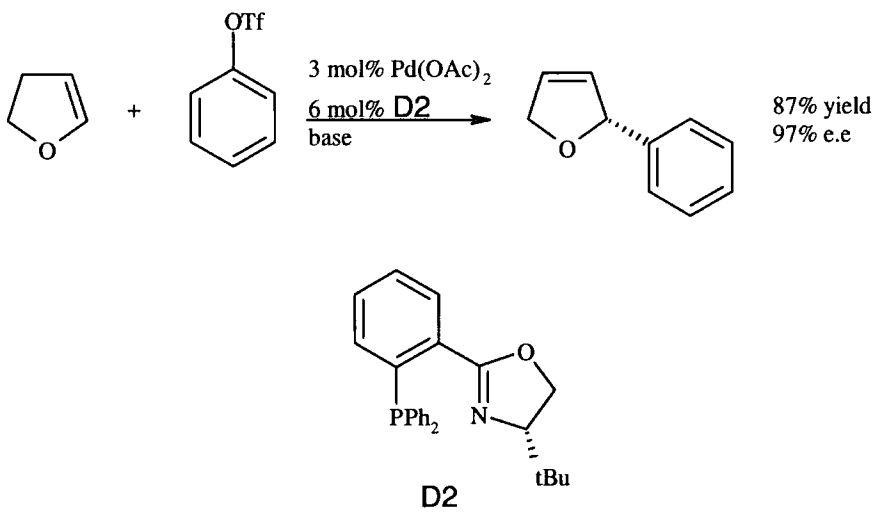
Scheme 1.32

As an important method of functionalising alkenes, the Heck reaction has been reported in the literature in the total synthesis of several large molecules. For example, Danishefsky *et al.* performed an intramolecular Heck coupling in the synthesis of the antitumour reagent Taxol, scheme 1.33.[61] Initial studies generated low yields of the Heck coupled product, with large amounts of palladium black precipitating during the reaction. Consequently stoichiometric amounts of the palladium catalyst were required to form the coupled product in adequate yield. It was proposed that the main difficulty in the reaction seemed to arise from the olefin insertion-elimination steps. Reaction times of several days were required, which was thought to reflect the strain of the bridgehead olefin in the cyclised diene.

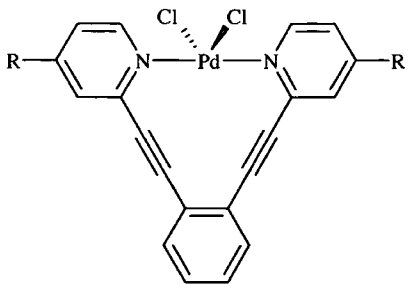


Scheme 1.33

The Heck reaction can be enantioselective when chiral ligands are used. For example Pfaltz *et al.* used the chiral PHOX ligand, **D2** to control the enantioselectivity in the Heck reaction of dihydrofuran and phenyl triflate, scheme 1.34.[62]



Scheme 1.34

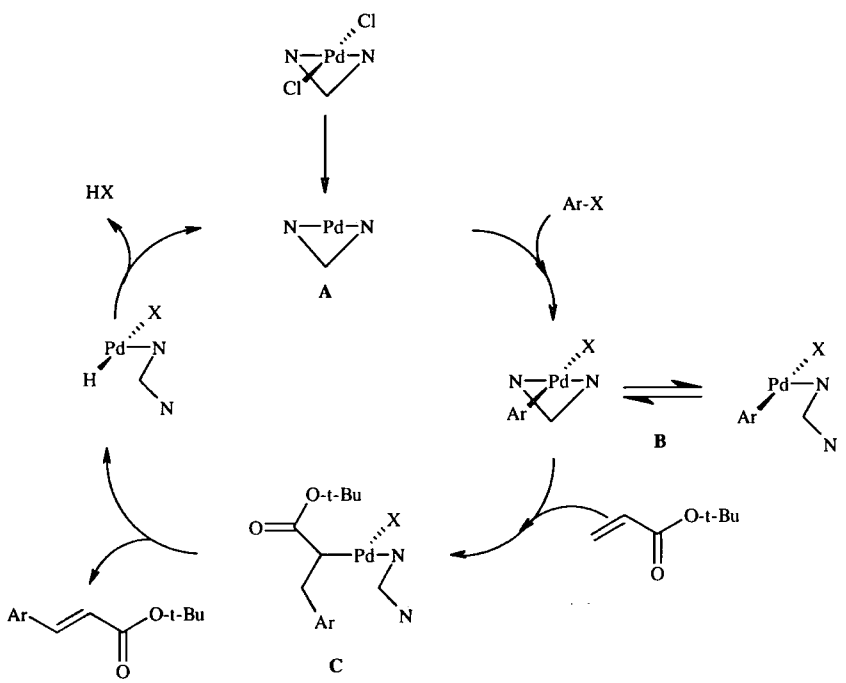


D3

R= H, Me

With reference to the ligands described and investigated in chapters 2 and 3, an interesting catalyst was reported by Kawano *et al.*.[63] The novel complex **D3** effectively catalysed the Heck coupling of aryl iodides with *tert*-butyl acrylate with large TON and in high yield. The catalyst, which featured a rigid *trans*-bidentate pyridine ligand was thought to act *via* an interesting mechanism, scheme 1.35.

Oxidative addition of the aryl halide probably occurs *via* Pd^0 complex A which is obtained by preactivation of complex **D3**. Following oxidative addition the complex formed contains the coordinated pyridine ligand in a *trans*-configuration. Migratory insertion of the olefin is associated with the chelate opening in B as the rigidity of the ligand structure makes *trans* to *cis* isomerisation of the left hand complex B impossible. This process allows production of complex C. β-hydride elimination and chelate closure completes the catalytic cycle.



Scheme 1.35

1.4- Carbenes: an introduction

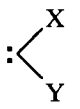


Figure 1.5

The word carbene stems from the name given to free, disubstituted carbon compounds with the general structure shown in figure 1.5. Because the carbon atom does not possess an octet of electrons, free carbenes are electron deficient and are therefore extremely reactive. They are so reactive that some carbenes are able to insert into C-H alkane bonds or react with alkenes to form cyclopropanes, scheme 1.36.[64]

Scheme 1.36

Free carbenes exist in two different electronic states: singlet and triplet, figure 1.6. The singlet state has one lone electron pair, whilst the triplet state has two unpaired electrons. In terms of hybridised orbitals, the singlet state of a free carbene has three sp^2 orbitals, one of which is doubly occupied and is non-bonding and an empty, $2p$ orbital perpendicularly situated. A triplet carbene, however, has two non-bonding, singly occupied, orthogonal $2p$ orbitals and two sp orbitals that are involved in bonding to substituents.

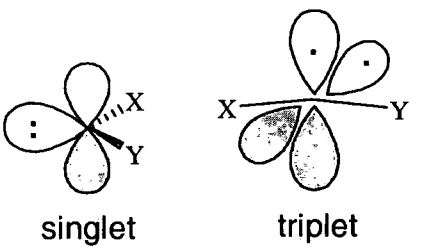


Figure 1.6

Whether a free carbene exists in the ground state as a singlet or as a triplet depends on the nature of the substituents X and Y that are attached to the carbon atom. When X and

Y are alkyl groups or hydrogen then the triplet state is usually the ground state. On the other hand, when X and Y are heteroatoms such as N, O, S or a halogen, the heteroatom donor groups on a carbene centre render the originally degenerate orbitals on the carbene carbon unequal in energy. This enhances the nucleophilicity and thermodynamic stability of the carbon atom and a singlet state occurs, figure 1.7.

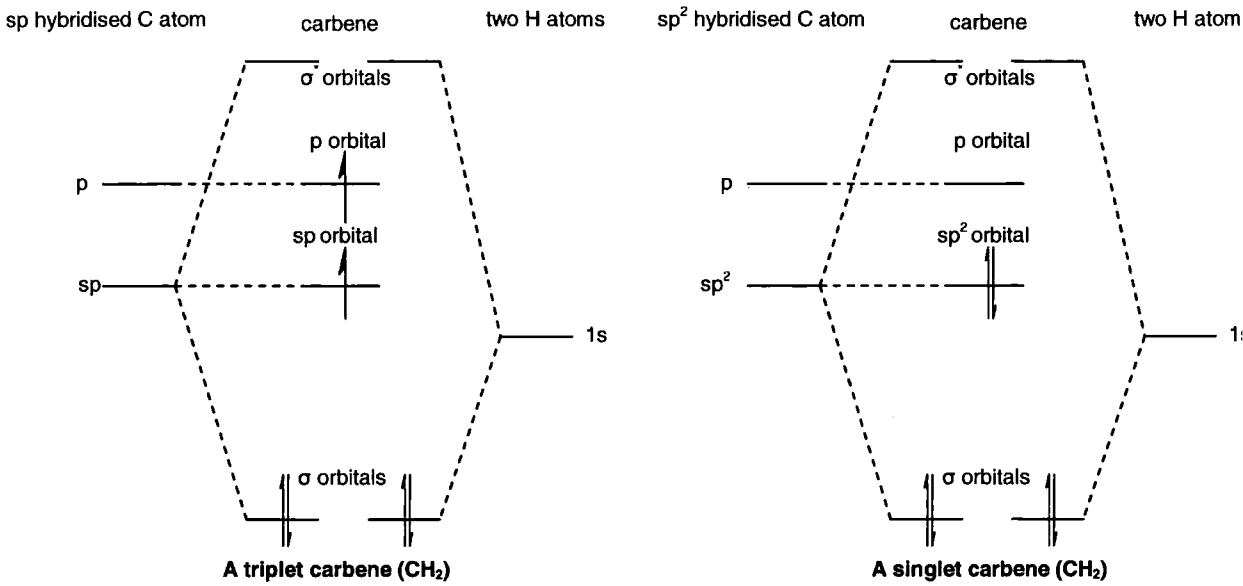
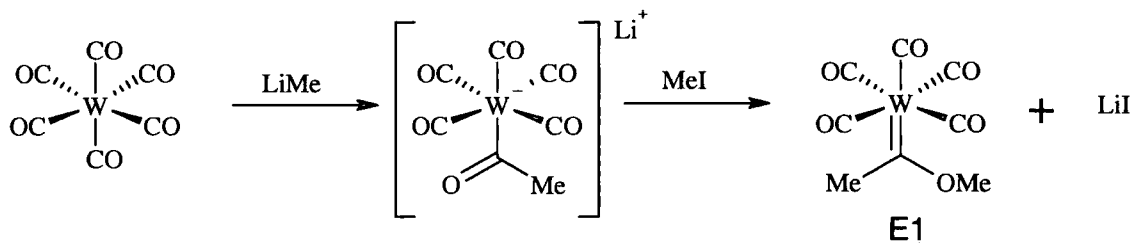


Figure 1.7

Carbenes were first observed in metal complexes, the first of which, **E1** was discovered by Fischer in 1964.[65] The singlet carbene complex **E1** was formed by the attack of an alkyllithium on a metal carbonyl followed by methylation, scheme 1.37.



Scheme 1.37

Just as there are two types of free carbene, there are two types of metal-carbene complex. As with free carbenes, the two varieties of metal-carbene complex depend upon the nature of substituents on the carbene carbon.

Carbene complexes, $L_nM=CR_2$, containing low oxidation state, late transition metals and having π-donor substituents R, such as -OMe or $-NMe_2$, on the carbene carbon are called Fischer carbenes. The carbene behaves as if it carries a δ+ charge, i.e. it is electrophilic.

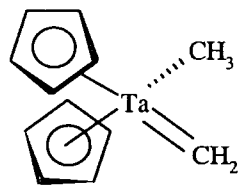
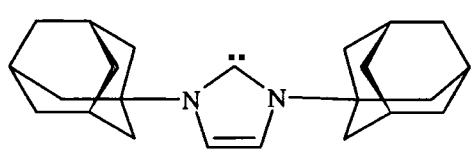


Figure 1.8

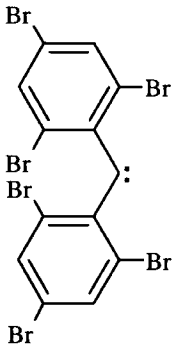
Several years after Fischer discovered complexes of type **E1**, Schrock *et al.* discovered another type of carbene in which the substituents attached to the carbene carbon were hydrogen or an alkyl group, figure 1.8.[66] Unlike previous Fischer-type carbene containing complexes, Schrock-type complexes were found to be nucleophilic and tended to contain early, high oxidation state, transition metals.

It was originally thought that carbenes were far too reactive to be isolated as free unligated compounds. However, in 1991 Arduengo *et al.* demonstrated how the combination of sterics and strong π donor substituents can stabilise a metal free singlet carbene, **E2** sufficiently to make it isolable.[67,68]



E2

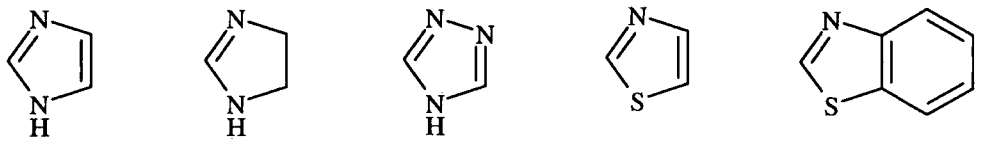
Soon afterwards, Tomioka *et al.* successfully isolated 2, 2', 4, 4', 6, 6'-hexabromodiphenylcarbene, **E3** and in so doing, demonstrated that carbenes with substituents that are not electron donors could be isolated.[69] As these triplet carbenes cannot be stabilised through thermodynamic effects, Tomioka *et al.* rendered the carbene unreactive by steric protection. The triplet state was confirmed by ESR spectroscopy.



E3

1.5- N-Heterocyclic carbenes

The following sections describe selected aspects of *N*-Heterocyclic carbene ligands and their chemistry.



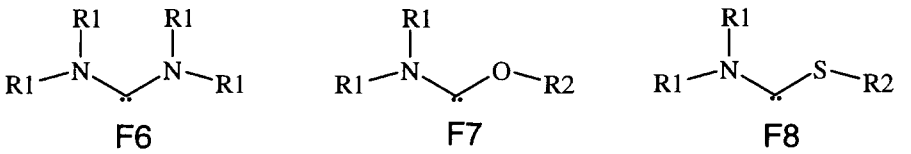
F1 F2 F3 F4 F5

Whilst the most common *N*-Heterocyclic carbenes are derived from imidazole, **F1**, several variants have been reported in the literature. Carbenes derived from imidazolidene, **F2** posses a smaller singlet-triplet gap, since the five-centre six-electron π delocalisation as a stabilising factor is no longer possible. Consequently carbenes derived from **F2** tend to be stronger σ donors.

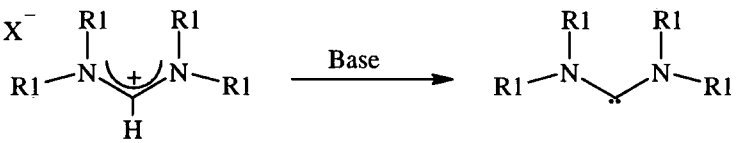
Carbenes derived from triazole, **F3** have been synthesised by endothermic elimination of methanol from the corresponding 5-methoxytriazole (*c.f.* scheme 1.49).

Thiazole (**F4**) and benzothiazole (**F5**) derived carbenes have recently been of great interest in ionic liquid applications and enzymatic studies.[70, 71] In the latter, thiazole-

derived carbenes are close analogues of the intermediate involved in enzymatic C-C bond forming and breaking transformations catalysed by thiamine.

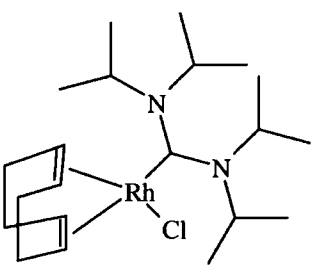


R1= $(CH_3)_2CH$, piperidyl
R2= aryl



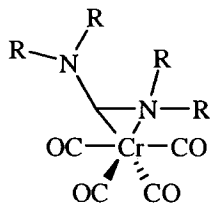
Scheme 1.38

Open chain acyclic bis(amino)carbenes have been reported by Alder *et al.*.[72] They can be prepared from the corresponding formamidinium salts, scheme 1.38. Several metal complexes have been synthesised with these ligands such as rhodium complex **F9**. Complexes containing the aminooxy- or aminothio-carbene ligands, **F7** and **F8**, however, have been reported to be closer in behaviour to classic Fischer-type carbene complexes.[73]



F9

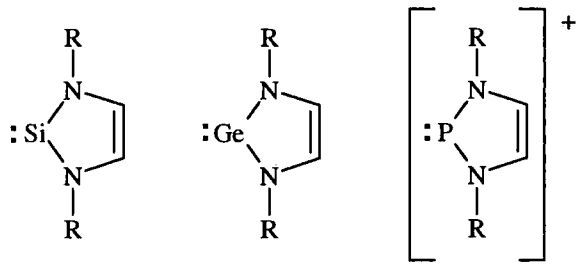
Bis(amino)carbenes can, however, (side on) coordinate to transition metals, that is to say metal complexes can contain a η^2 (C,N) bis(amino)carbene, for example chromium complex **F10**. According to Alder *et al.* this effect may stabilise the under-coordinated "resting state" of *N*-Heterocyclic carbene-based catalysts.[72]



F10

R= ^{i}Pr

Finally, the homologous and isoelectronic heavier congeners of *N*-Heterocyclic carbenes, **F11**, **F12** and **F13** are also known and their synthesis has been reported in literature.[74,75] C-C saturated derivatives of the silylenes and germylenes have also been reported. However, there are very few reports of this field in organometallic chemistry.[76]



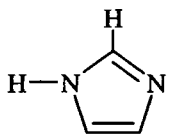
F11 F12 F13

Although several different types of *N*-Heterocyclic carbene and their analogues have been described here, this thesis will be predominantly concerned with *N*-Heterocyclic carbenes derived from imidazoles.

1.5.1- Nomenclature

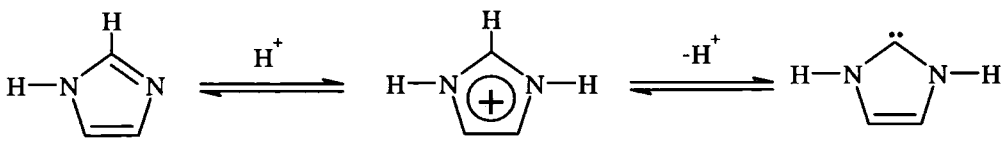
The suffixes of the systematical names of heterocyclic compounds are determined by the nature of the heteroatoms in the ring. The first differentiation is made between a ring containing at least one nitrogen atom and all other heterocyclic rings. Five-membered rings containing at least one nitrogen atom have the suffixes -olidine (saturated ring systems), -oline (ring containing one double bond), and -ole (ring containing the maximum number of double bonds).

The *N*-Heterocyclic ylidenes first isolated by Arduengo are formal tautomers of 1*H*-imidazole **A**.



A

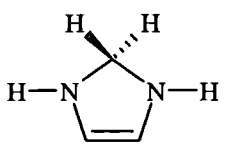
Protonation of 1*H*-imidazole at the basic N3 position and subsequent deprotonation of the resulting 1,3-dihydroimidazolium ion **B** at the C2 centre yields the 1,3-dihydrosubstituted ylidene **C,** scheme 1.39.



A B C

Scheme 1.39

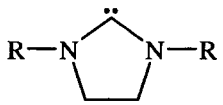
The number of π electrons (6) remains unchanged. The addendum -ylidene refers to compounds in which two hydrogen substituents are replaced by two electrons or one pair of electrons. The parent compound of **C** is unequivocally described as 2,3-dihydro-1*H*-imidazole **D**.



D

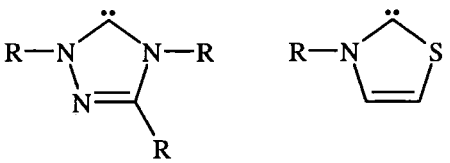
Thus **C** is called 2,3-dihydro-1*H*-imidazol-2-ylidene. As **D** represents a ring system with only one double bond, it may also be called an imidazoline. Although the name imidazoline by itself comprises other tautomers, 1,3-di-R-imidazoline-2-ylidene is

unequivocal for compounds of type **C**. The names 1,3-di-R-2,3-dihydro-1*H*-imidazol-2-ylidene and 1,3-di-R-imidazoline-2-ylidene are synonymous here because of the substitution pattern of imidazole-derived carbenes with (organic) substituents in positions 1 and 3, and the carbonic centre at the C2 atom. *N*-Heterocyclic ylidenes of type **E** with a saturated C-C bond are correctly called 1,3-di-R-2,3,4,5-tetrahydro-1*H*-imidazol-2-ylidenes or 1,3-di-R-imidazolidine-2-ylidenes.



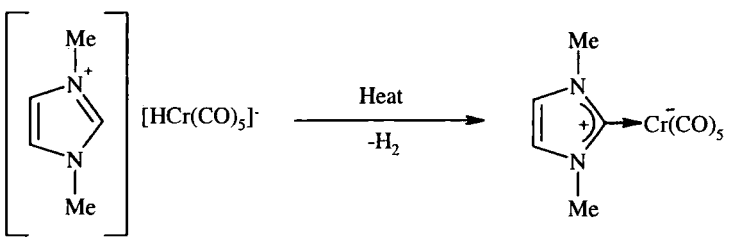
E

Triazole-derived carbenes of type **F** are called 1,3,4-tri-(R)-4,5-dihydro-1*H*-triazol-5-ylidenes, and thiazole-derived are called 2,3-dihydro-thiazol-2-ylidenes **G**.



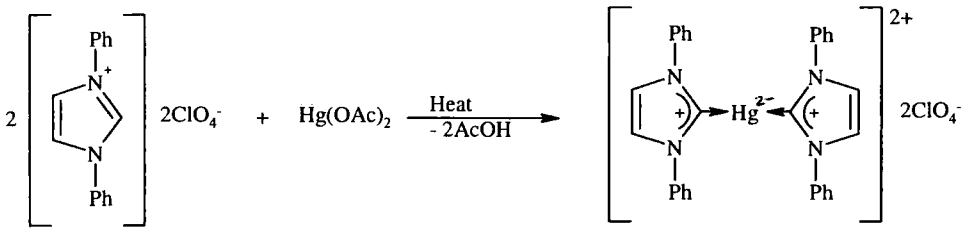
F G

1.5.2- The History of N-Heterocyclic Carbenes



G1

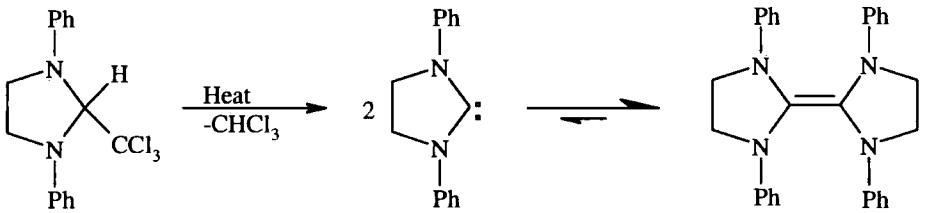
Scheme 1.40



G2

Scheme 1.41

Soon after the discovery of metal-carbene complexes of type **E1** by Fischer, Öfele (**G1**) and Wanzlick (**G2**) independently published the synthesis of metal complexes with novel *N*-Heterocyclic carbenes as ligands.[77,78] Öfele was originally trying to obtain dihydro-complexes from heterocyclic salts; however, when using imidazolium salts, Öfele noticed a side reaction and isolated complex **G1**, scheme 1.40. Wanzlick on the other hand synthesised complex **G2** by treating an imidazolium salt with a metal salt containing basic ligands, scheme 1.41. Öfele's chromium complex **G1** was prepared from a hydrocarbonylmetalate whilst Wanzlick's mercury complex **G2** was prepared simply from the metal acetate.



G3 G4 G5

Scheme 1.42

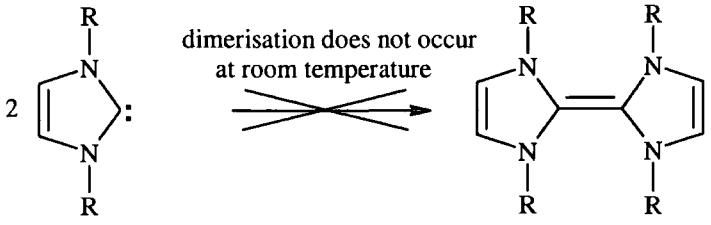
Wanzlick *et al.* were the first to investigate the synthesis of saturated and unsaturated heterocyclic carbenes.[79,] In an attempt to generate imidazolin-2-ylidene, **G4**, imidazoline **G3** underwent thermal α-elimination of chloroform; however, the resulting product dimerised to yield the electron rich olefin **G4**, scheme 1.42. Wanzlick *et al.* originally thought that monomeric carbene **G4** had been formed. However, cross-coupling experiments with differently substituted dimers indicated that olefin **G5** appeared not to be in equilibrium with its monomers.

Although Öfele and Wanzlick published several reports discussing unsuccessful attempts to isolate a free carbene, it was not until Arduengo *et al.* proved that *N*-Heterocyclic carbenes are in principle thermodynamically stable that this research area started to accumulate interest.[67]

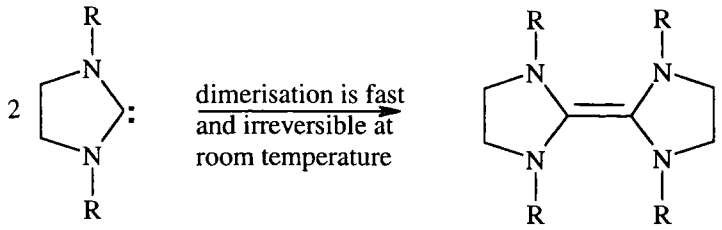
Herrmann *et al.* were the first to suggest that bulky *N*-Heterocyclic carbenes, such as Arduengo's carbene **E2,** could also bind extremely well to low valent metals with ligand properties that were similar to that of electron-rich phosphines. Herrmann *et al.* concluded that an equally rich coordination and catalysis chemistry would arise from this "novel" class of ligands.

1.5.3- Hybridisation and Structure of N-Heterocyclic singlet carbenes

Singlet-triplet splitting correlates with increasing electronegativity of the π donor substituents X and Y in carbenes of the type :CXY.[80] Whilst several combinations of heteroatoms are conceivable only singlet carbenes with two nitrogen atoms have been isolated as crystalline compounds so far. These singlet carbenes have a pronounced low energy HOMO and a high energy LUMO. Because of the lower electronegativity of carbon, they are stronger electron-pair donors than amines. Since the amino groups are π-donating and σ-withdrawing, 2,3-dihydro-1*H*-imidazol-2-ylidenes benefit from a "push-pull" stabilising effect.[5,6,64]



Scheme 1.43



Scheme 1.44

Dimerisation of unsaturated imidazol-ylidenes is estimated to be enthalpically favourable by approximately 4kcal/mol, but this apparently does not offset the unfavourable entropic consideration, scheme 1.43.[3] Conversely imidazolin-ylidenes will dimerise rapidly and irreversibly to form electron-rich alkenes, scheme 1.44, unless the carbene carbon is shielded by large bulky substituents.[3] The difference in the tendencies of imidazol-ylidenes and imidazolin-ylidenes to dimerise has been attributed to several factors including the aromaticity of the former and the (calculated) smaller singlet ground state to triplet excited state energy difference for the latter (~80kcal/mol for imidazol-ylidenes and ~70kcal/mol imidazolin-ylidenes).[3]

1.5.4- Coordination

It has been known for some time that organophosphines and *N*-Heterocyclic carbenes are very similar with regard to their metal coordination chemistry, electronic properties and in metal complex synthesis. NHCs are typical σ-donor ligands and can substitute other classical two-electron donor ligands such as amines, ethers and phosphines to form NHC metal complexes.

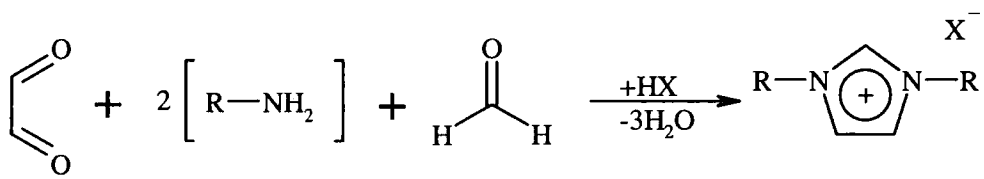
Öfele and Herrmann described spectroscopic studies comparing NHCs and organophosphines, both of which are pronounced σ-donor ligands with little backbonding.[81] This is due to the fact that the proximal nitrogen atoms donate electron density into the empty orbital on the carbon atom.

Nolan later reported that NHC ligands generally behave as better donors than the best phosphine donor ligands with the exception of the sterically demanding adamantyl carbene, **E2**.[82]

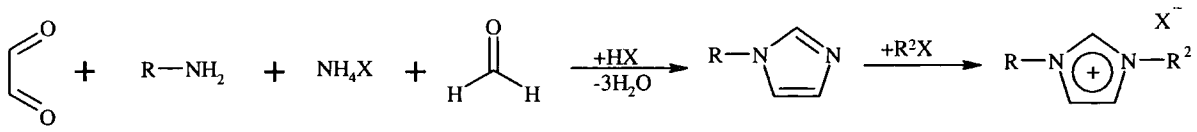
Single crystal X-ray diffraction studies of NHC-metal complexes have shown little difference in ligand geometry from case to case.[1] NHC-metal bonds (>210pm) are longer than in Fischer or Schrock-type complexes, (<200pm). This is due to the pronounced backbonding in Fischer or Schrock type complexes, which significantly shortens the metal-ligand bond length. Therefore allowing for sterics, NHCs can in effect rotate around the metal-carbon axis.

1.5.5- Synthesis

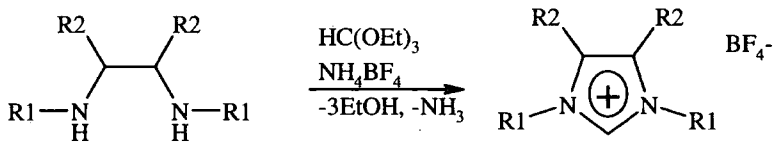
Of all stable *N*-Heterocyclic carbenes, the most easily available are derived from imidazole as many imidazolium precursors can be made without difficulty.[1,83] For example, a one-pot synthesis using glyoxal, primary amine and formaldehyde exists, scheme 1.45. A slight variation allows the preparation of unsymmetrical *N*-substituted derivatives, scheme 1.46. 1,2-diamines can be converted into an imidazolium precursor *via* an orthoformate route, scheme 1.47. These three methods provide a synthetic route to an imidazolium precursor. The imidazolium salt may then be deprotonated using a variety of bases to generate the free carbene. Whilst a free carbene can be generated *via* treatment with a strong base, such as NaOMe or KO^{t}Bu, metal complexes can be generated by heating the imidazolium salt in the presence of a metal salt containing ligands of sufficient basicity, *e.g.* OAc, acac. Harsher techniques, such as desulphurisation of a cyclic thiourea, scheme 1.48, and vacuum thermolysis of methoxy derivatives, scheme 1.49, have been described in literature.[84,85]



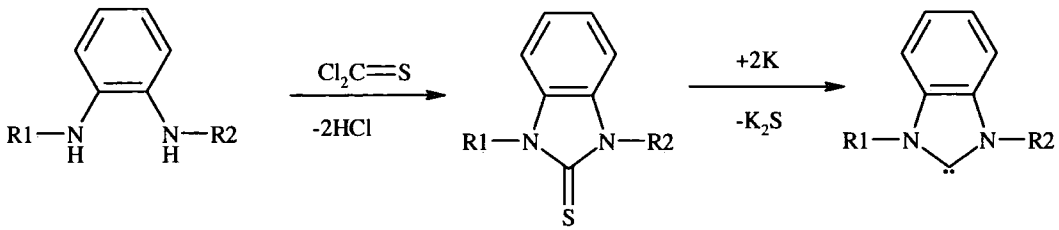
Scheme 1.45



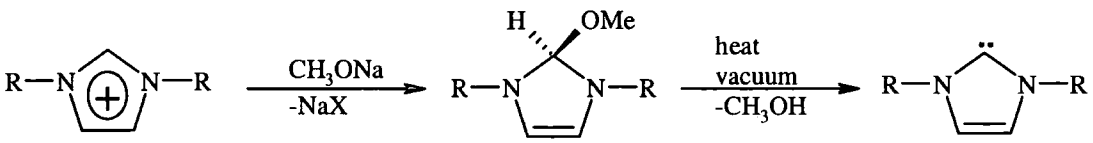
Scheme 1.46



Scheme 1.47



Scheme 1.48



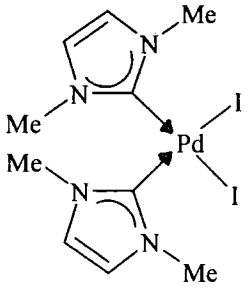
Scheme 1.49

1.5.6- NHCs in catalysis

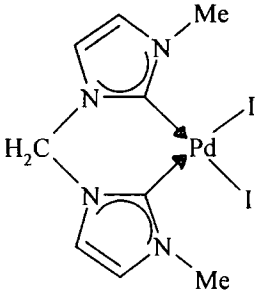
To date there is a great multitude of publications reporting transition-metal-catalysed reactions involving *N*-Heterocyclic carbene ligands. The following sections present a brief discussion of recent highlights and developments in four major areas: palladium-catalysed cross-coupling reactions; olefin metathesis; transition-metal-catalysed reactions of industrial importance; asymmetric catalysis; and other uses of *N*-Heterocyclic carbenes.

1.5.6.1- Palladium-catalysed cross-coupling reactions

After the initial patent reports of *N*-Heterocyclic carbenes in catalysis, the first publication was by Herrmann *et al.* in 1995 communicating the Heck coupling of aryl bromides and aryl chlorides with complexes **H1** and **H2**.[86] Several advantages over traditional phosphine ligands were described: high thermal stability and hydrolytic durability resulting from exceptionally stable Pd-C bonds; easy accessibility; and no need for an excess of the ligand. Almost full conversion of the halide substrate was reported by using only 0.001mol% catalyst for aryl bromides and 0.1-1mol% for aryl chlorides. Herrmann *et al.* further proposed in this report that this novel class of ligand could be modified to provide water-soluble, two-phase catalysts; immobilised onto a solid support; or possibly chirally modified to permit asymmetric synthesis.

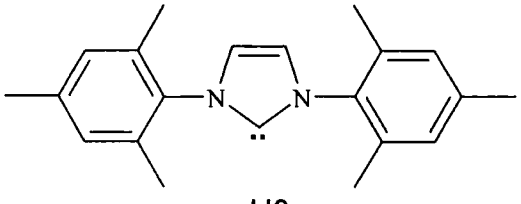


H1



H2

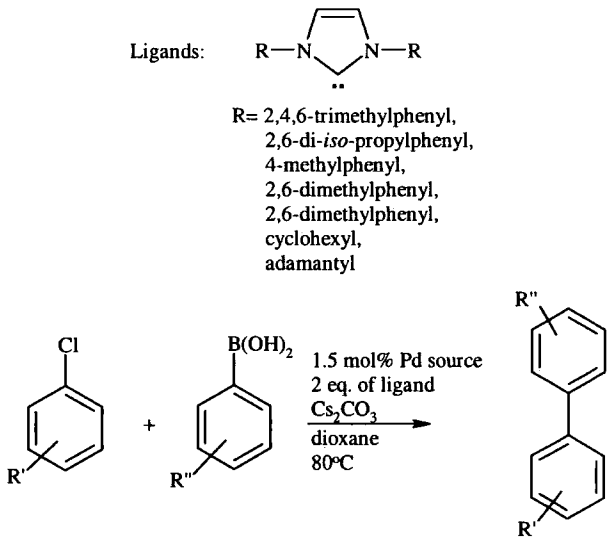
Following Herrmann's report several groups reported the use of *N*-Heterocyclic carbene ligands in palladium-catalysed Suzuki-Miyaura cross-coupling reactions. Nolan *et al.* have published a significant number of reports detailing the use of the carbene, IMes, **H3** and analogues in palladium-catalysed cross-coupling reactions.[87]



H3

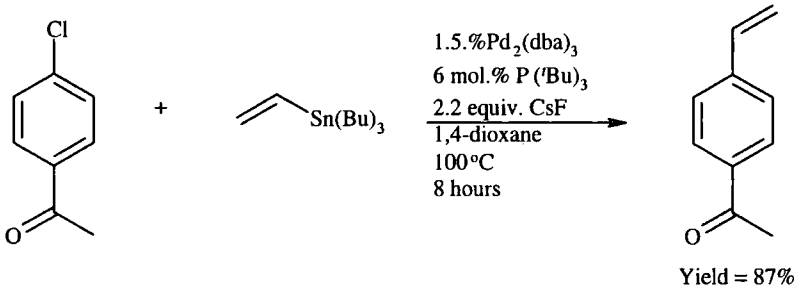
The ligands employed were found to be exceptionally tolerant to functional groups in Suzuki-Miyaura cross-coupling reactions and were even capable of coupling

deactivated aryl chlorides with boronic acids in high yield after heating for only 2 two hours or less, scheme 1.50. In accordance with other groups, slightly lower yields were observed for sterically hindered *ortho*-substituted reagents.

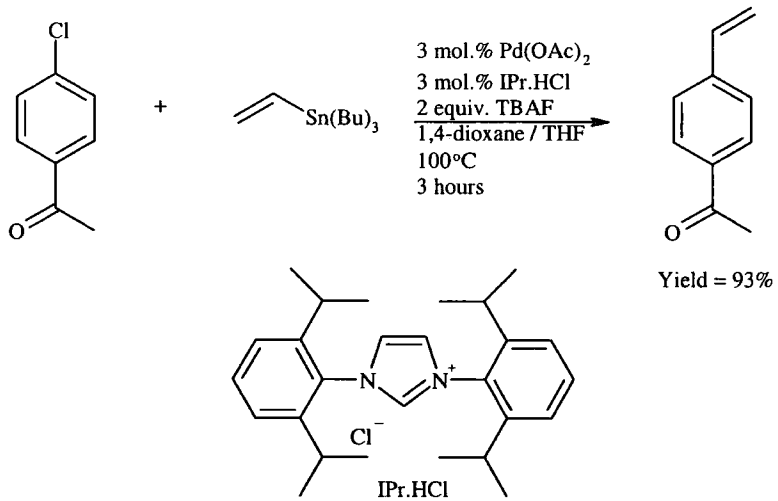


Scheme 1.50

Nolan *et al.* also performed several other types of palladium-catalysed cross-coupling reactions (Stille, Heck, Kumada, Hiyama, and Sonogashira) using the *N*-Heterocyclic carbene ligand, IMes and its analogues.[87] The reactivity of these systems surpassed that previously observed with phosphine ligands. For example Fu *et al.* investigated the Stille coupling of 4-acetylchlorobenzene and tributylvinyltin using the strongly electron-donating ligand P(^{t}Bu)$_3$, scheme 1.51.[88] The styrene product was isolated in 87% yield after 8 hours heating. Nolan *et al.*, after investigating the same reaction using the NHC ligand IPr (generated in situ from IPr.HCl), isolated the styrene product in 93% yield after only 3 hours heating, scheme 1.52.[87]

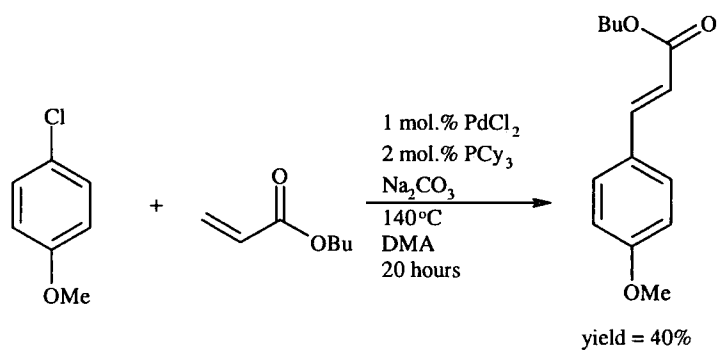


Scheme 1.51

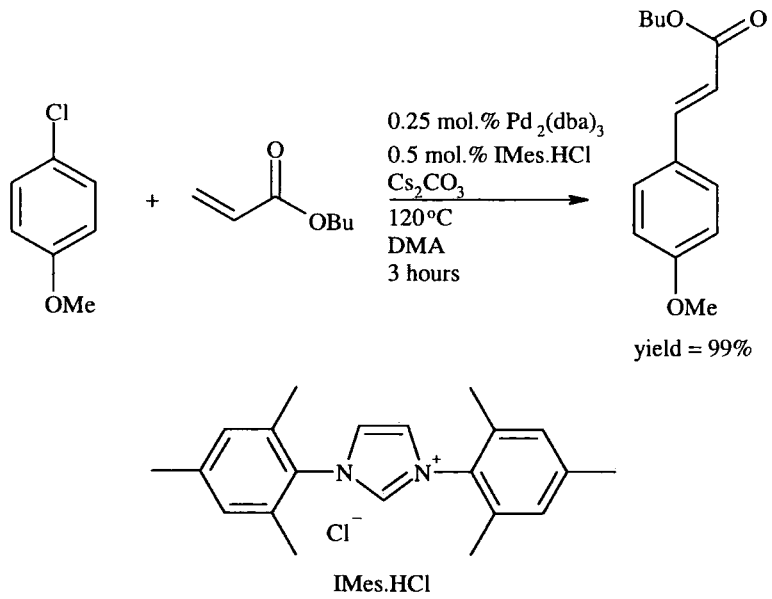


Scheme 1.52

In another example, the Heck coupling of 4-chloroanisole and butyl acrylate had been previously investigated by Schynder *et al.* using the monophosphine ligand PCy_3, scheme 1.53.[89] The *trans*-cinnamate product was isolated in only 40% yield after twenty hours of heating. Nolan *et al.* on the other hand used the NHC ligand IMes (generated in situ from IMes.HCl), scheme 1.54.[87] The *trans*-cinnamate product was isolated in 99% yield after only three hours heating. Whilst the shorter reaction time may in part be attributed to the use of a Pd^0 source (removing the time lag to reduce the Pd^{II} precatalyst to the active Pd^0 species), the use of a NHC ligand did have a dramatic effect on the activity of the catalytic system.



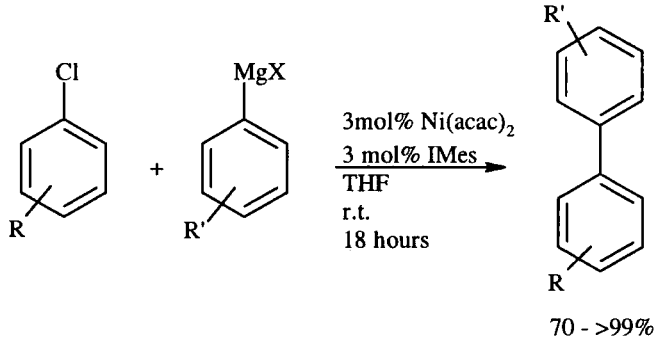
Scheme 1.53



IMes.HCl

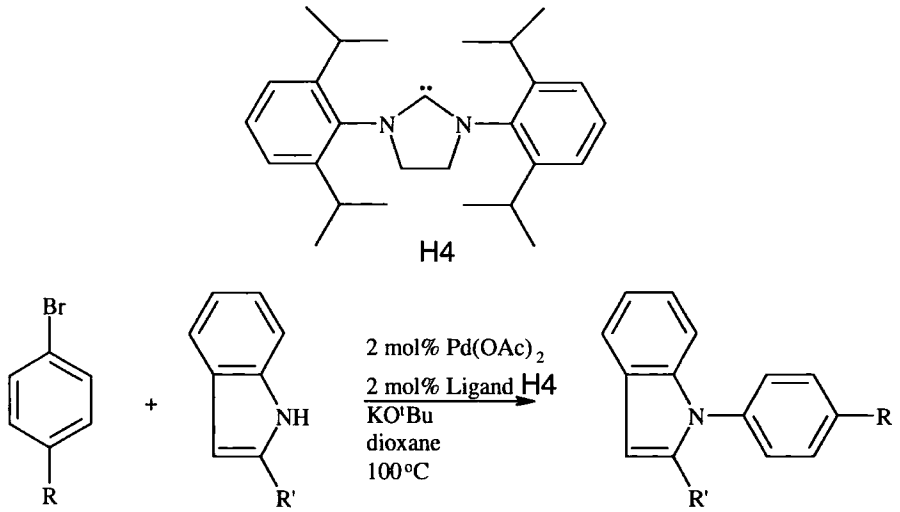
Scheme 1.54

In all of the other cases described by Nolan *et al.* the highest conversions of substrate occurred where the NHC was comprised of bulky *ortho*-substituted aryl groups, such as 2,4,6-trimethylphenyl, 2,6-di-isopropylphenyl and 2,6-dimethylphenyl. This indicated that steric factors dictate the effectiveness of the catalytic system (see also section 4.1).



Scheme 1.55

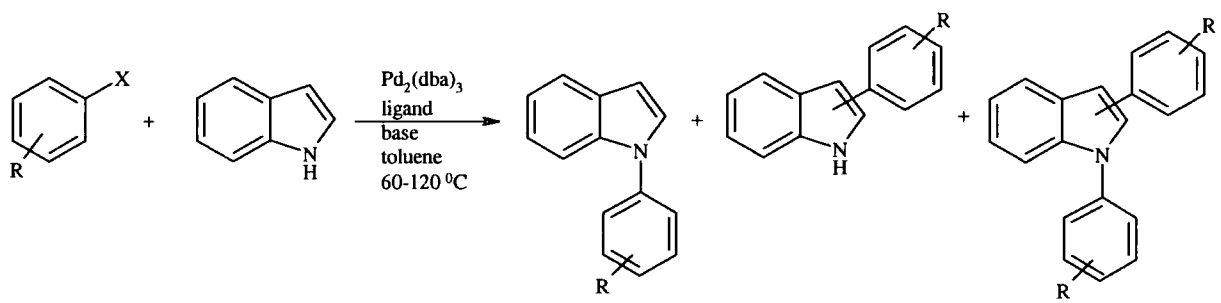
Whilst Nolan *et al.* used IMes and $Pd(OAc)_2$ in Kumada coupling reactions with aryl Grignard reagents, Herrmann *et al.* reported that $Ni(acac)_2$, IMes systems were more effective allowing lower temperatures and shorter reaction times, scheme 1.55.[90] As a consequence of these milder conditions, problems associated with palladium catalysts (such as homocoupling of the Grignard substrates and over-reduction of palladium) were overcome.



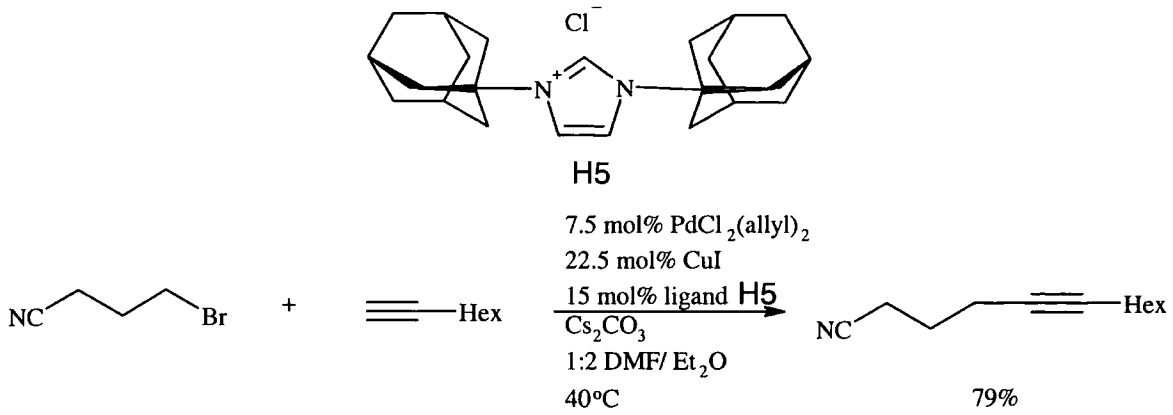
Scheme 1.56

Interestingly Nolan *et al.* further investigated the use of NHCs in Hartwig-Buchwald amination reactions.[87] Although the use of unsaturated 2,3-dihydro-imidazol-2-ylidenes was effective in most cases, these ligands were ineffective at the *N*-arylation of aryl indoles. Good results were obtained, however, when the saturated 1,3-di-(2,6-di-isopropylphenyl)-imidazolidin-2-ylidene, **H4** was used, scheme 1.56.

Hartwig and Buchwald both reported that often a mixture of three products were produced during the *N*-arylation of indoles: C-arylated products, *N*-arylated products and N,C-doubly arylated products, scheme 1.57.[91,92] However, according to Nolan by using **H4** as a ligand, only the *N*-arylated indole was formed.



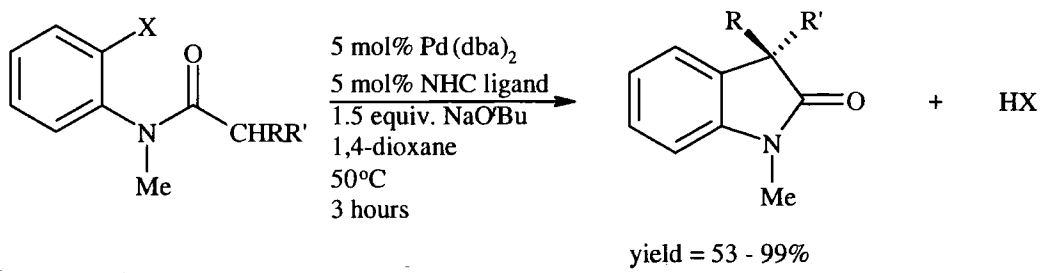
Scheme 1.57



Scheme 1.58

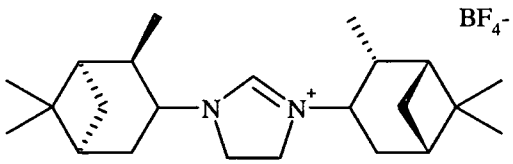
Recent work by Fu *et al.* has shown that by carefully controlling the reaction conditions Suzuki-Miyaura, Stille and Sonogashira couplings of alkyl halides are possible. This is great importance as traditionally cross-coupling reactions have always involved the coupling of two sp^2 centres, as β-hydride elimination is possible when sp^3 centres are used, also oxidative addition to a sp^3 centre is relatively slow compared to a sp^2 centre. Although much of the work involved the use of bulky phosphine ligands, one report described the use of *N*-Heterocyclic carbene ligands in Sonogashira coupling reactions, scheme 1.58.[93] Yields as high as 79% were achieved after 16 hours heating. However, the catalytic system was highly dependent on the choice of ligand and palladium source used. In addition, attempts to perform copper-free Sonogashira coupling were unsuccessful.

Hartwig and Lee demonstrated that sterically hindered NHCs can be used effectively in Hartwig-Buchwald amidation reactions.[94] In an extensive study with the NHC ligand IMes, **H3** excellent conversions and high yields were achieved in cyclic amidation reactions to form oxindoles, scheme 1.59.



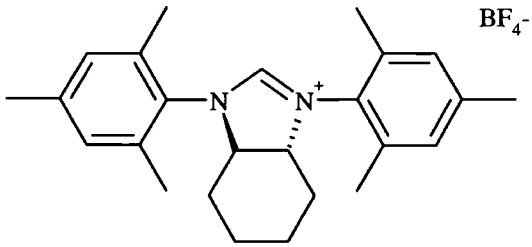
Scheme 1.59

In addition Hartwig and Lee extensively studied the asymmetric synthesis of oxindoles where R ≠ R'. Although a plethora of chiral phosphine ligands were investigated, the most effective ligands were chiral NHCs. Enantiomeric excesses of up to 76% were recorded in some cases. Interestingly Hartwig and Lee commented that it was desirable to locate the stereogenic centre as close as possible to the reacting centre, as ligand **H6** with chiral *N*-substituents provided greater enantioselectivity than ligand **H7** with a chiral backbone.



H6

76% e.e.

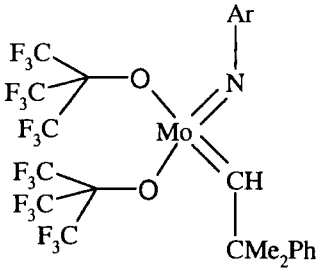


H7

<46% e.e.

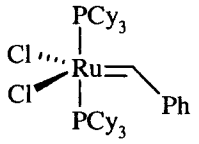
1.5.6.2 - Olefin metathesis

Olefin metathesis is one of the most original and unusual transformations in chemistry. Remarkably, the strongest bond in the olefin, the C=C double bond, is broken during the reaction. The resulting RHC= fragments are exchanged between the olefins that participate in the reaction. Metathesis reactions were originally applied to simple olefins because early catalysts such as Schrock's molybdenum derived catalyst, **J1** were intolerant of functionality.[95] Grubbs later developed the much more useful ruthenium-derived catalyst, **J2** which was much more tolerant of organic functionality.[96] As **J1** and **J2** are not regenerated at the end of a catalytic cycle the complexes are not true catalysts, and therefore can be more accurately described as reaction initiators.



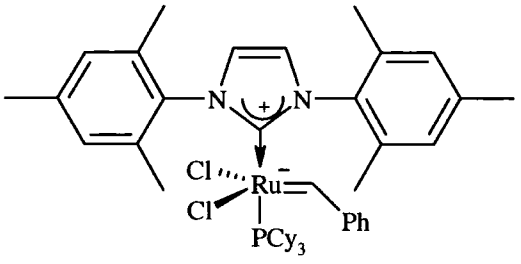
Ar = $C_6H_3(2,6\text{-}i\text{-}Pr)_2$

J1

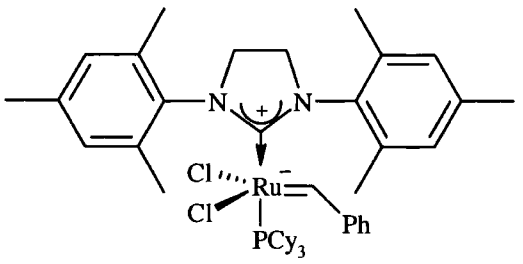


J2

Soon after the reports of NHCs in palladium-catalysed cross-coupling reactions, next generation olefin metathesis initiators were reported. The mixed-ligand olefin metathesis initiators **J3** and **J4** first appeared in a patent by Herrmann *et al.*[97] Grubbs and Nolan soon followed publishing papers in this area.[98, 99]



J3



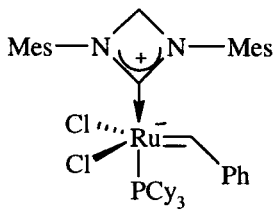
J4

Two excellent reviews of the area have now been written by Grubbs and Fürstner.[100, 101]One important conclusion from these reviews is that "no single catalyst outperforms all others in all possible applications". Consequently the structural versatility of *N*-Heterocyclic carbene ligands is all the more important.

DFT studies of **J3** and **J4** suggested that NHC ligands had much higher dissociation energies compared to a typical phosphine ligand.[102]

In a series of ligand exchange studies Grubbs revealed that phosphine dissociation is facile in bis(phosphine) complex **J2**.[103] The resulting fourteen electron complex will then bind to an olefin much better than to a phosphine. However, NHC complexes **J3** and **J4** strengthen binding of the olefin to the metal, which is thought to account for the enhanced activity of these catalysts.

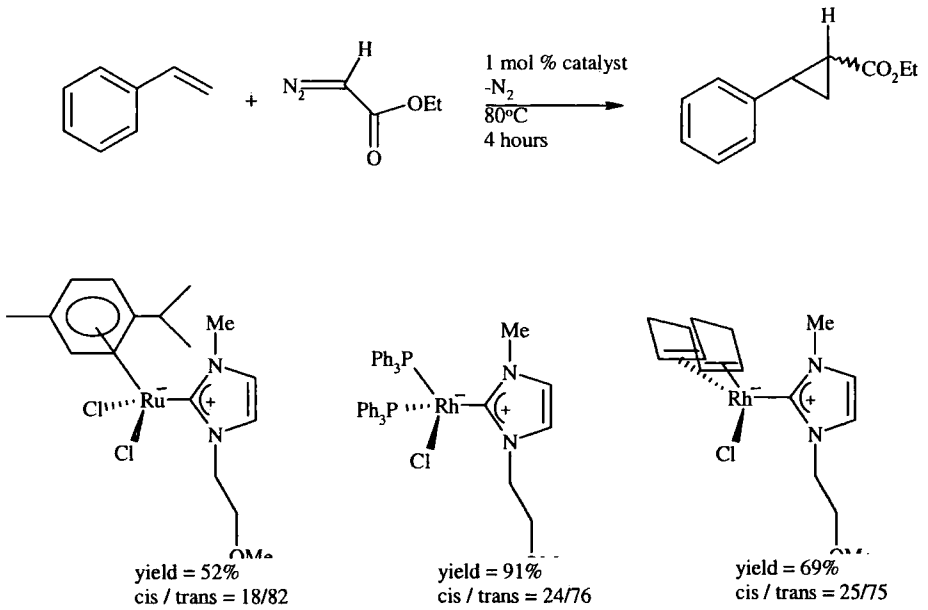
Ruthenium-based metathesis catalysts containing unusual NHC ligands were presented at the 14th International Symposium on Homogeneous Catalysis. Complex **J5** was of great interest as it showed significantly greater activity under mild conditions compared to **J3** and **J4** in preliminary studies.[104, 105] However, no data was given regarding the longevity and substrate tolerance of complex **J5**.



J5

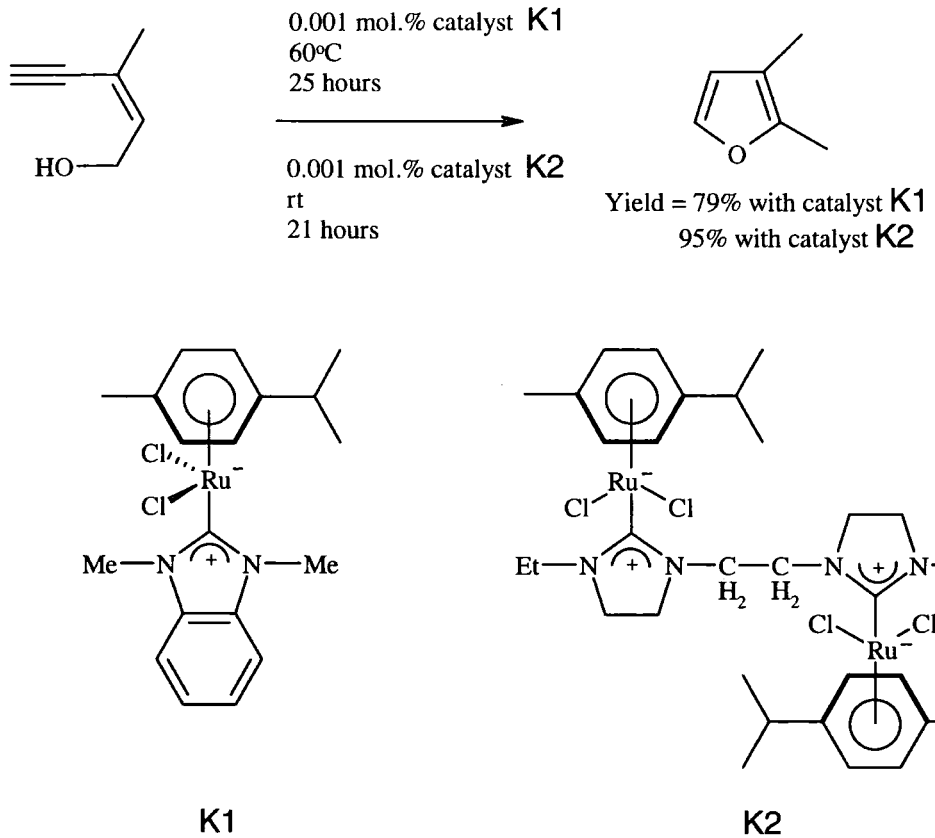
1.5.6.3- Other transition metal-catalysed reactions involving N-Heterocyclic carbenes

Catalytic cyclopropanation of olefins with diazoalkanes is of use in the industrial synthesis of insecticides. Ruthenium (II) and rhodium (I) NHC-containing complexes were prepared by Dixneuf *et al.* and investigated for catalytic activity in this reaction, scheme 1.60.[106] The NHC ligands used contained CH_2CH_2OMe coordinating "side arms" which could potentially act as hemilabile ligands upon elimination of PPh_3, COD or arene. Dixneuf *et al.*, however, did not suggest possible structures of the catalytic species involved in this reaction.



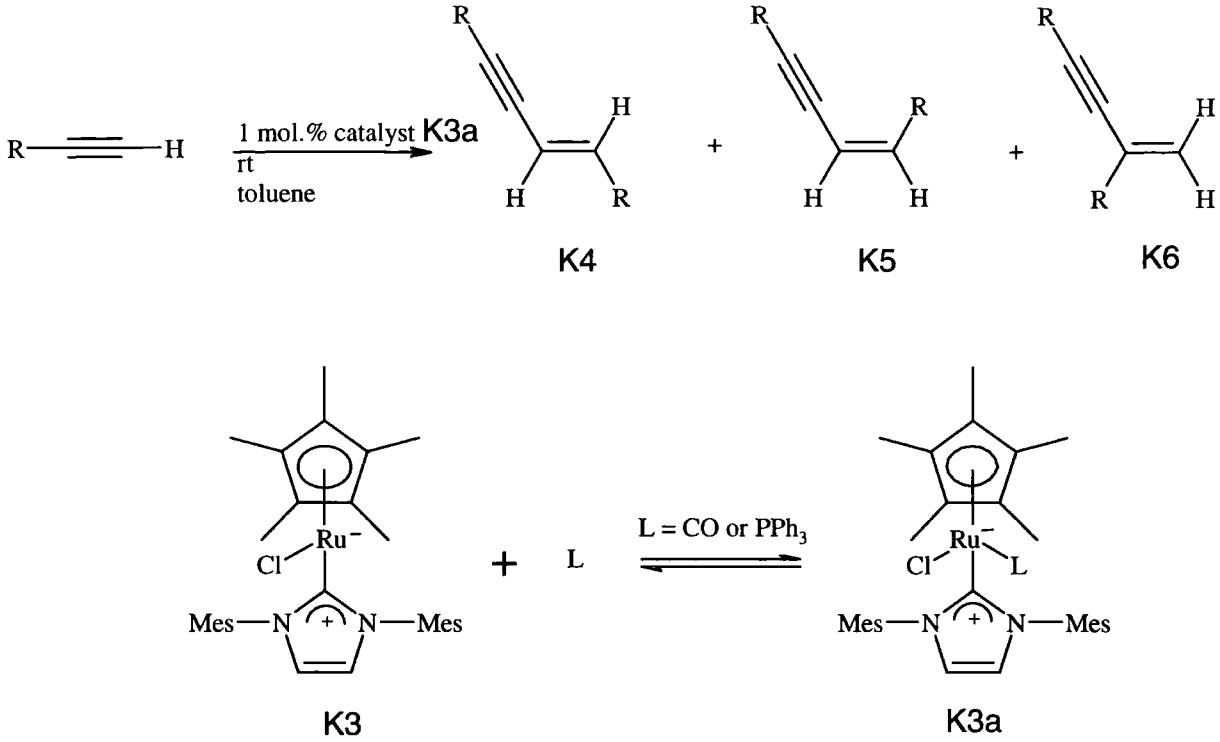
Scheme 1.60

Dixneuf *et al.* discovered that ruthenium (II) phosphine complexes could act as catalysts for the activation of (Z)-2-en-4-yn-1-ols towards their intramolecular cyclisation into furans.[106] An improved catalytic furan synthesis was reported using the benzimidazolin-2-ylidene-containing ruthenium complex, **K1**, scheme 1.61.[107] Yields and catalytic activity were improved in a subsequent report featuring ruthenium complex **K2** containing a stronger electron-donating imidazolin-2-ylidene ligand.[108]



Scheme 1.61

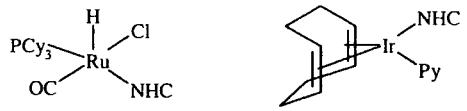
Herrmann *et al.* reported a general alkyne coupling reaction using ruthenium as the mediating metal, scheme 1.62.[109] The NHC complex, **K3** was used as a catalyst precursor which formed the tetracoordinate catalytic complex **K3a** upon addition of a two-electron ligand such as PPh_3 or CO. Conversions as high as 99% were observed when R = Ph, tolyl, and $SiMe_3$ within five to ten minutes at room temperature. The *trans*-coupling product **K4** was formed almost exclusively, apart from when R = $SiMe_3$ where the α-olefin, **K6** was obtained in 92% yield.



Scheme 1.62

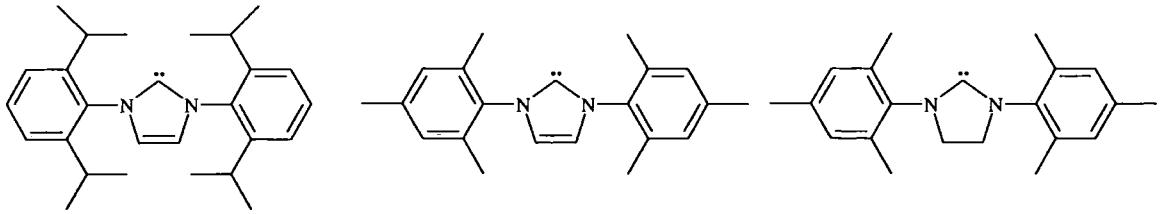
Nolan *et al.* investigated the hydrogenation of 1-hexene, cyclohexene and other simple alkenes using ruthenium and iridium catalysts, **K7** and **K8**.[110] Whilst hydrogenation was successful with complexes **K7** and **K8**, elevated temperatures were required. This is in contrast to traditional hydrogenation catalysts, such as Wilkinson's catalyst ($RhCl(PPh_3)_3$) and Crabtree's iridium catalyst ($[Ir(cod)(py)(PCy_3)]PF_6$), which successfully hydrogenate simple alkenes at room temperature.

Nolan *et al.* commented that whilst iridium catalyst **K8** was less efficient than Crabtree's catalyst at room temperature (which may be attributed to the larger steric bulk of the NHC ligand compared to that of PCy_3), it displayed a higher activity under a mild pressure of hydrogen at 50°C. This is in contrast to the activity of Crabtree's catalyst, which is significantly less active under the same conditions.

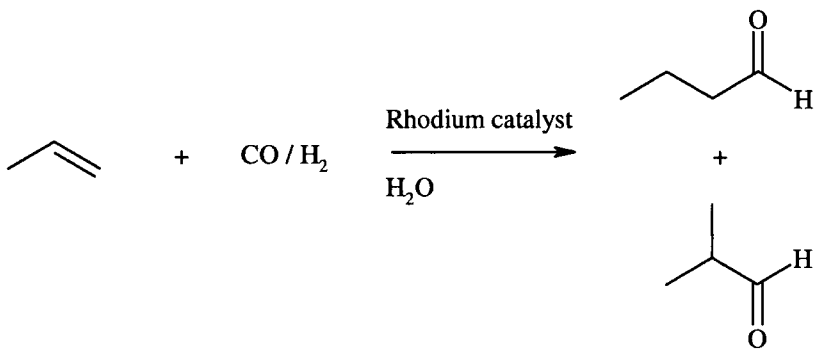


K7 K8

NHC=



The hydroformylation reaction is one of the most important catalytic reactions in industry. For example the conversion of propylene into butanal, scheme 1.63.[111] Butanal can then be used to prepare several other products, including paint solvents and plasticisers.



Scheme 1.63

Crudden *et al.* reported the first example of a rhodium *N*-Heterocyclic carbene complex for the hydroformylation reaction.[112] The report described the hydroformylation of styrene and styrene derivatives, scheme 1.64. Such substrates are of significance as the resulting aldehydes may be oxidised to provide 2-arylpropanoic acids, such as ibuprofen, figure 1.9.

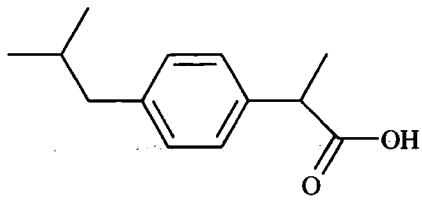
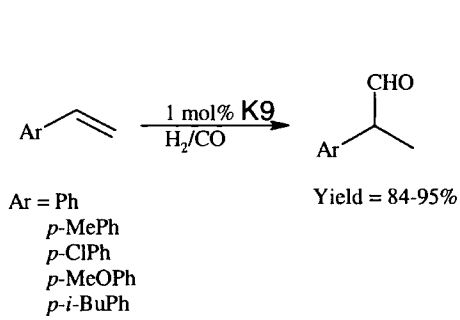
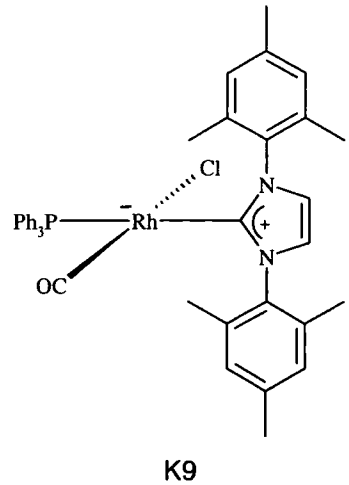


Figure 1.9

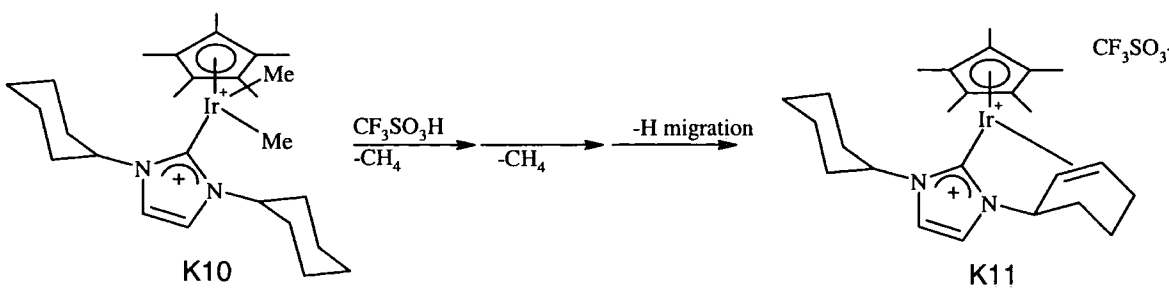




K9

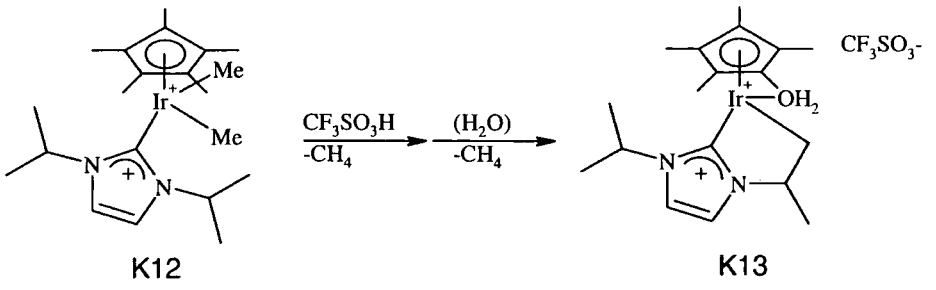
Scheme 1.64

Depending on the application, achieving a high selectivity for either the branched or linear isomer is critical. Complex **K9** was reported as highly selective in the hydroformylation of styrene derivatives giving up to 50:1 selectivity for the branched isomer depending on the styrene substrate. Complex **K9** was prepared by ligand exchange with IMes, **H3** and Wilkinson's catalyst ($Rh(PPh_3)_3Cl$). Simple substitution of one of the phosphine ligands by the NHC provided complex **K9** in high yield (87%). Although the product yields and selectivity reported were high, the catalytic activities of **K9** were still low (TOF < 10 hours^{-1}) suggesting that the increased catalyst stability was at the expense of activity.



K10 K11

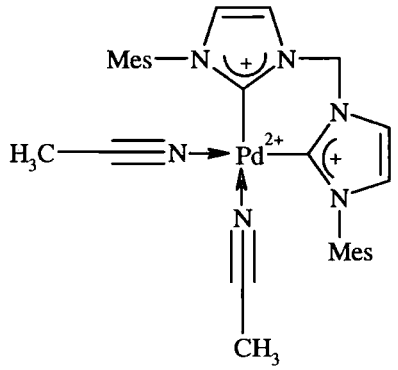
Scheme 1.65



K12 K13

Scheme 1.66

Alkanes are notably very unreactive compounds and are amongst the most difficult compounds for activation. NHC complexes of iridium, however, have a strong tendency to undergo C-H activation, scheme 1.65. Herrmann *et al.* discovered iridium complex **K10** undergoes loss of methane under acidic conditions to form π-cyclohexene complex **K11**.[113] Further investigation showed that a related process occurs when an *iso*propyl derivative, **K12** is used, scheme 1.66.[114]



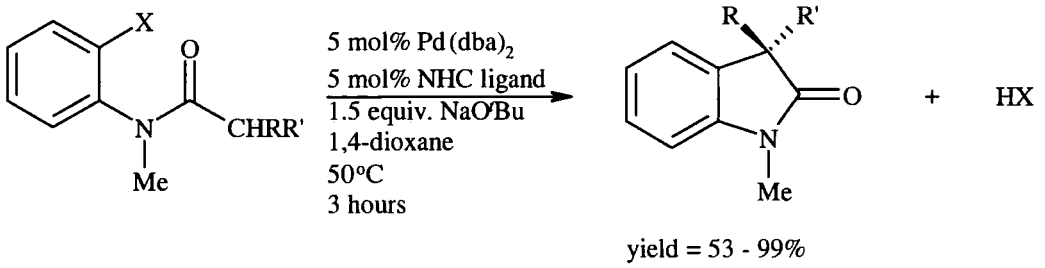
K14

Dicationic palladium NHC complexes such as **K14** were recently reported by Herrmann *et al.* in the copolymerisation of ethylene and carbon monoxide to give high molecular weight, strictly alternating poly(C_2H_4-alt-CO) under mild conditions and low pressure.[115] Complex **K14** reportedly gives greater TON without the addition of *p*-benzoquinine than catalysts previously reported in the literature.[116,117] The polymerisation of ethylene and carbon monoxide is of great interest and has been commercially exploited by Shell as part of their CARILON® polymers business.

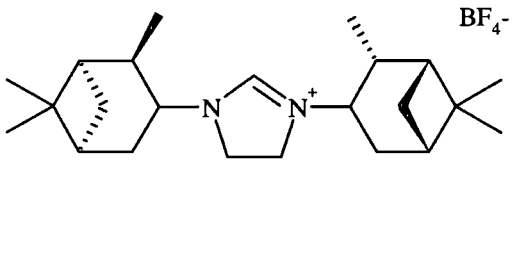
1.5.6.4- N-Heterocyclic carbenes in asymmetric catalysis

There are very few catalytic processes in which chiral *N*-Heterocyclic carbene ligands have provided high enantioselectivities: palladium-catalysed oxindole synthesis; iridium-catalysed hydrogenation of unfunctionalised alkenes using imidazol-2-ylidene ligands and ruthenium-catalysed desymmetrising metathesis reactions using saturated imidazolin-2-ylidene ligands. Furthermore, whilst asymmetric rhodium-catalysed hydrosilation reactions have been reported, only moderate enantiomeric excesses have been achieved.

As discussed previously (section 1.5.6.1), Hartwig and Lee successfully synthesised chiral oxindoles using chiral NHC ligand **H6** in high yield and enantiomeric excess, scheme 1.67.[94]

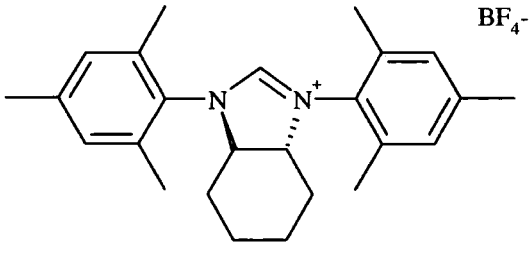


Scheme 1.67



H6

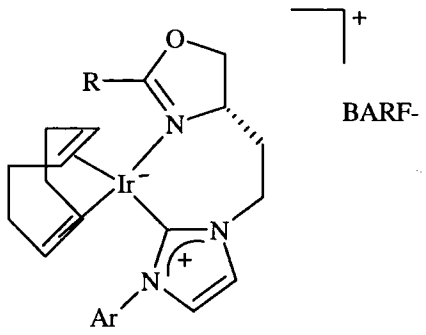
76% e.e.



H7

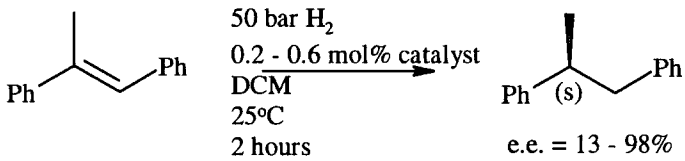
<46% e.e.

Burgess *et al.* synthesised the chiral iridium complex **L1** for use in asymmetric hydrogenation of trisubstituted alkenes, scheme 1.68.[118] The highest enantiomeric excess (98%) was achieved using the 1-adamantyl version of catalyst **L1**.



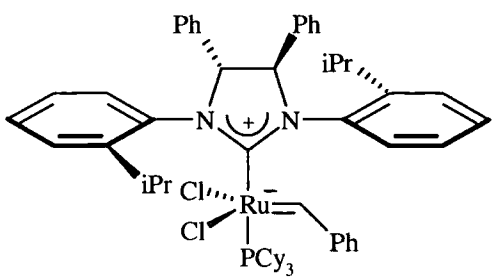
L1

R=Ph, $CHPh_2$, ^tBu, 1-Ad
Ar= 2,6-$(^iPr)_2C_6H_3$
BARF = tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate

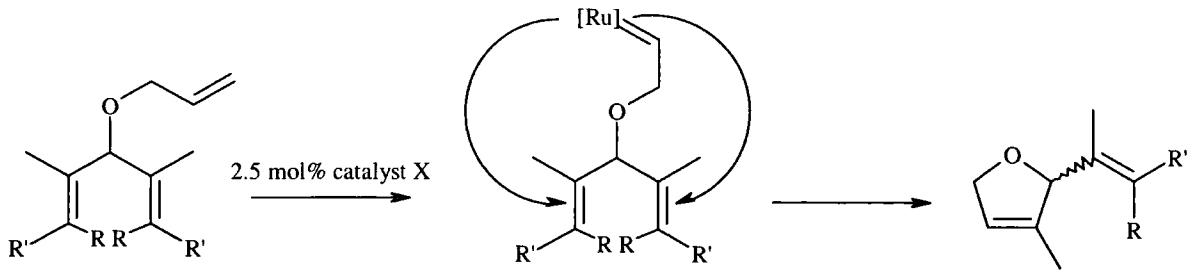


Scheme 1.68

Grubbs *et al.* successfully demonstrated the asymmetric ring-closing metathesis of achiral trienes using the chiral ruthenium complex **L2**, scheme 1.69.[119] Mono-*ortho*-substituted aryl groups on the imidazolin functional group effectively transferred the stereochemistry of the ligand nearer to the metal centre as the *ortho*-substituents of the aryl groups are placed *anti* to the substituents on the imidazolin ring. High enantioselectivities were observed (up to 90% e.e.) with near quantitative conversion of the starting triene substrate.

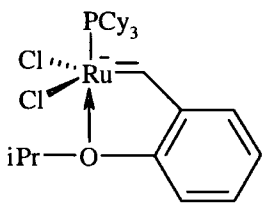


L2

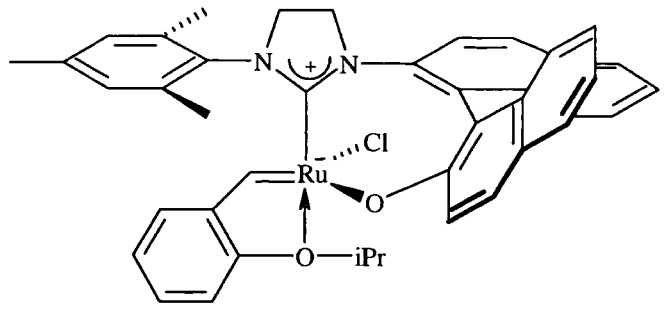


Scheme 1.69

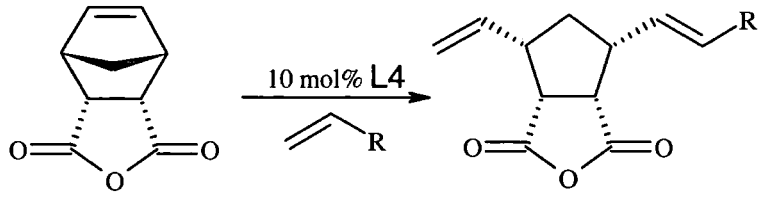
Previous work by Hoveyda *et al.* demonstrated the activity and recyclability of a ruthenium complex containing an alkoxide ligand, **L3**.[120, 121] Having successfully demonstrated that the alkoxide ligand system improved catalyst stability and longevity, Hoveyda *et al.* adapted this system to include a chiral NHC ligand in order to investigate asymmetric ROM/CM reactions of norbornenes and to assess recyclability, scheme 1.70.[122] Very high enantioselectivities and substrate conversions were observed after only 1.5 hours heating at 50°C with complex **L4**. In addition approximately 95% of the catalyst could be recovered at the end of the reaction for further use without any loss in activity in a repeat run.



L3



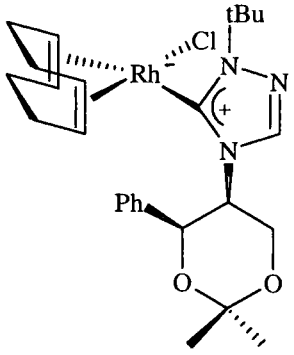
L4



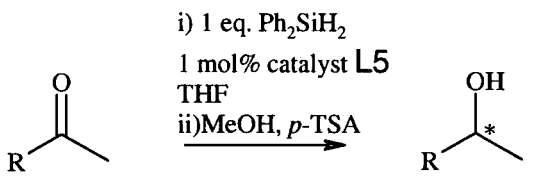
>98% e.e.
> 98% conversion

Scheme 1.70

Enders *et al.* have published several reports regarding the synthesis of chiral rhodium and palladium complexes containing NHC ligands.[123,124,125,126] Rhodium complex **L5** was used in the catalytic asymmetric hydrosilylation of methyl ketones, scheme 1.71. The resulting alcohols were formed in high yield (80-90%) although enantioselectivity varied from moderate to poor (43-19% e.e.). However, this represents a good result for a non-chelating ligand, with asymmetric activity most probably caused in part by the axis of chirality.



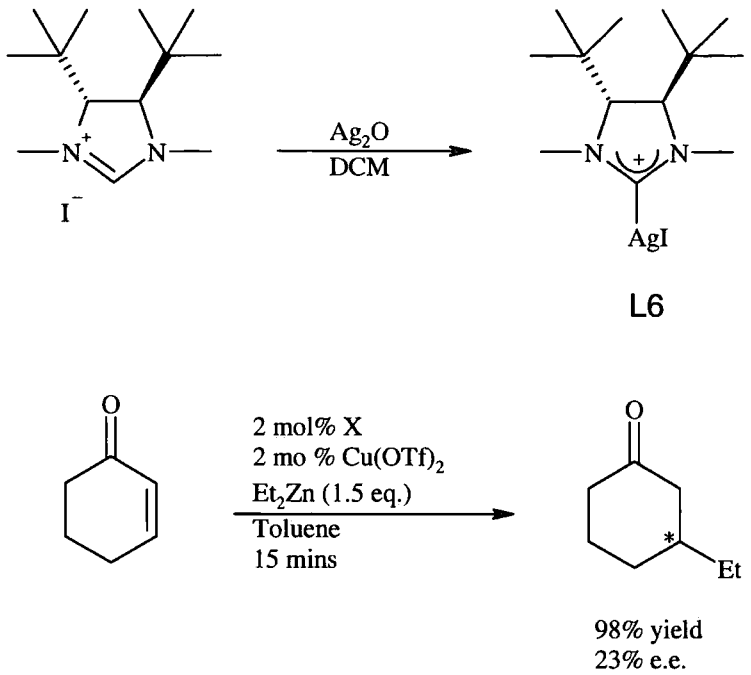
L5



19-43% e.e.
80 -90% yield

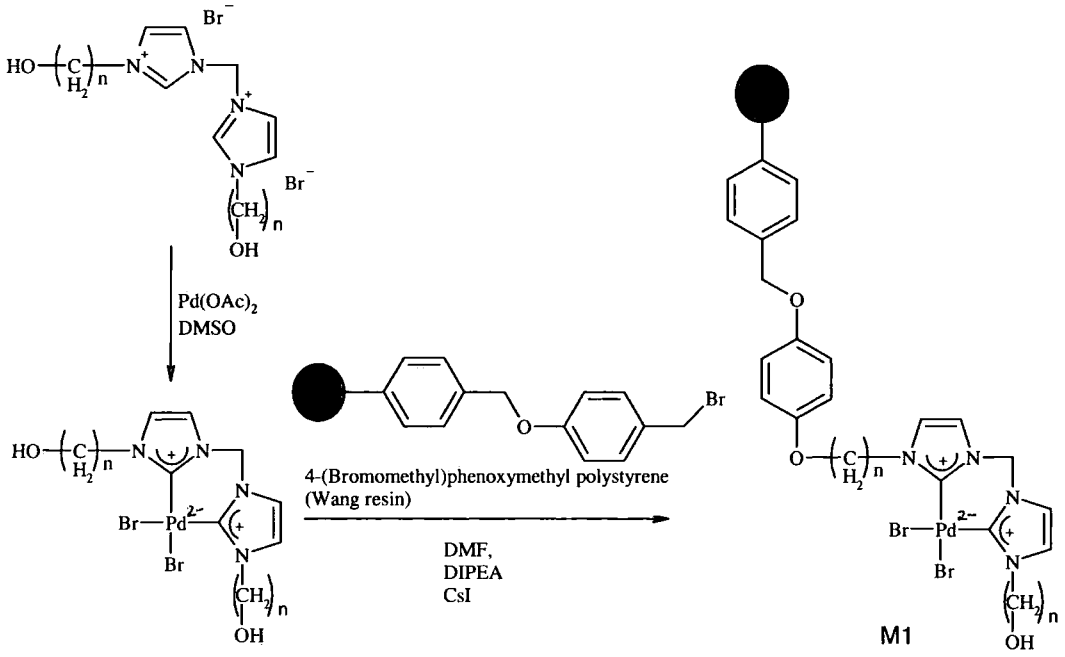
Scheme 1.71

Silver (I) NHC complexes can be prepared from imidazolium salts and Ag_2O. These silver complexes can be treated with metal salts and used as NHC transfer agents to provide a range of metal complexes (this area is discussed further in section 4.2). Woodward *et al.* used this technique to prepare copper complexes containing the NHC ligand IMes **H3**.[127] Woodward *et al.* went on to report ligand accelerated catalysis with a NHC in copper-catalysed conjugate addition.[127] Mangeney *et al.* adapted this technique to report the enantioselective conjugate addition of diethylzinc to cyclohexenone using the chiral silver (I) diaminocarbene **L6** and $Cu(OTf)_2$, scheme 1.72.[128] Although the enantioselectivity was not high, the easy generation of the catalyst provides a route for further research.



Scheme 1.72

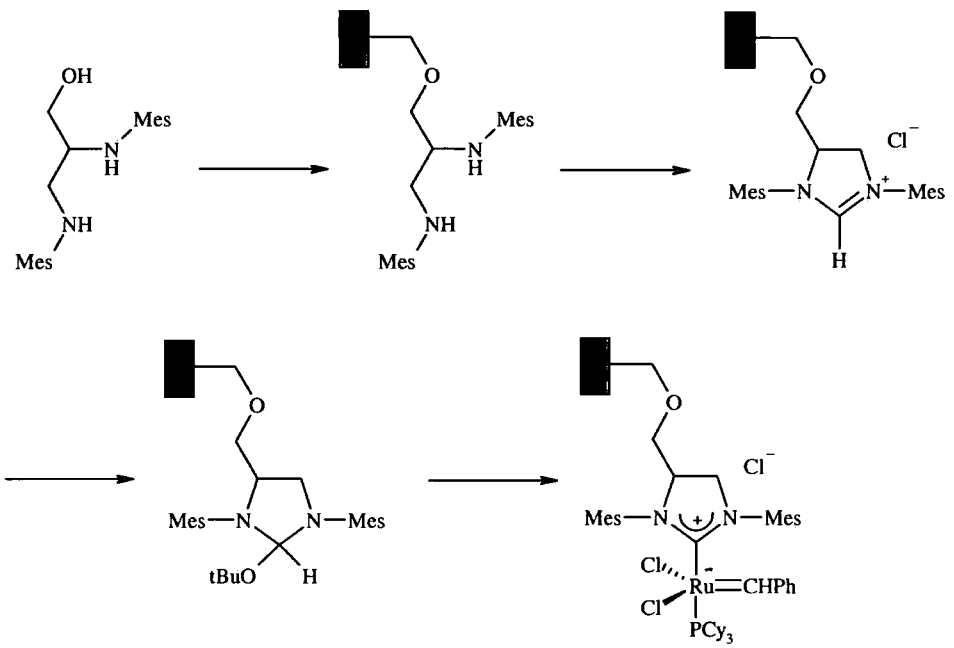
1.5.6.5- Supported catalysis involving N-Heterocyclic carbenes



Scheme 1.73

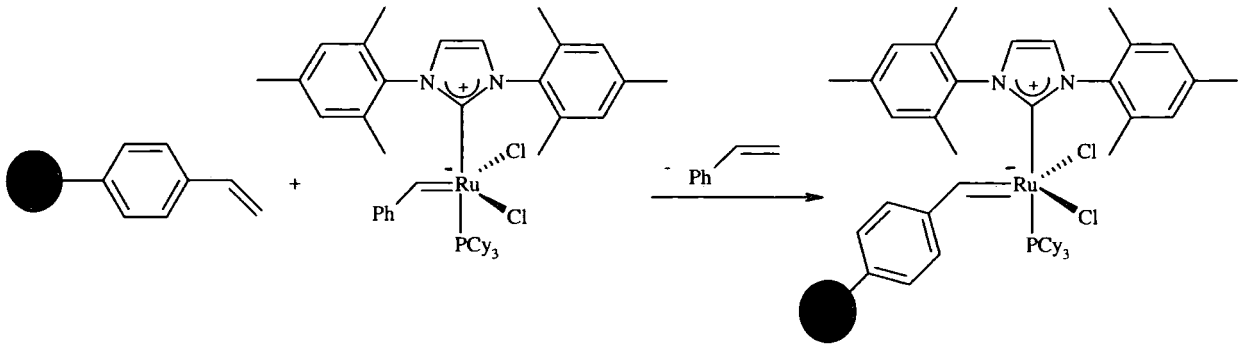
In 2000 several reports published the synthesis and use of polymer-supported NHC catalysts. For example Herrmann *et al.* published the synthesis of supported complex

M1.[129] The complex was formed by reacting N,N'-di-imidazololylmethane with alkyl bromides to form a range of 1,1'-di(alkyl)-3,3'-methylenediimidazolium dihalide salts. The salts were heated in the presence of $Pd(OAc)_2$ to generate bis(carbene) palladium (II) dibromide complexes. Nucleophilic substitution on bromo-Wang resin afforded the supported complex, scheme 1.73. Herrmann *et al.* used **M1** to catalyse the arylation of olefins with aryl bromides. The catalyst was used fifteen times without detectable loss of activity. Elemental analysis of the used catalyst showed a significant decrease in palladium content after the first run. However, elemental analysis of the same catalyst after four runs showed essentially the same palladium content. The Heck couplings did, however, require high temperatures and long reaction times compared to enhanced activity catalysts that have been reported recently.[30,32,130]



Scheme 1.74

Blechart *et al.* published the synthesis of a polymer-supported olefin metathesis catalyst.[131] An alternative strategy was pursued where the polymer-anchored ligand precursor was first synthesised and then treated with a ruthenium compound to generate the supported catalyst, scheme 1.74. The catalyst showed high activity in both ring-closing and ring-opening metathesis, with *cis/trans* ratios in the polymeric products corresponding exactly to what is observed with homogeneous versions of the catalyst.



Scheme 1.75

Barrett *et al.* demonstrated that a "boomerang" metathesis catalyst could be used in four consecutive RCM steps.[132] Using a cross metathesis step the complex is anchored to the traditional carbene that initiates the reaction, which is itself bound to a vinylated polystyrene resin, scheme 1.75. In accordance with enhanced activity initiators developed by Grubbs *et al.*, this catalyst was more efficient than traditional bis(phosphine) ruthenium complexes in olefin metathesis reactions.[96] Although the catalyst functioned by the release of the complex into solution, metal leaching was minimised by the recovery of the complex by the vinyl polystyrene resin.

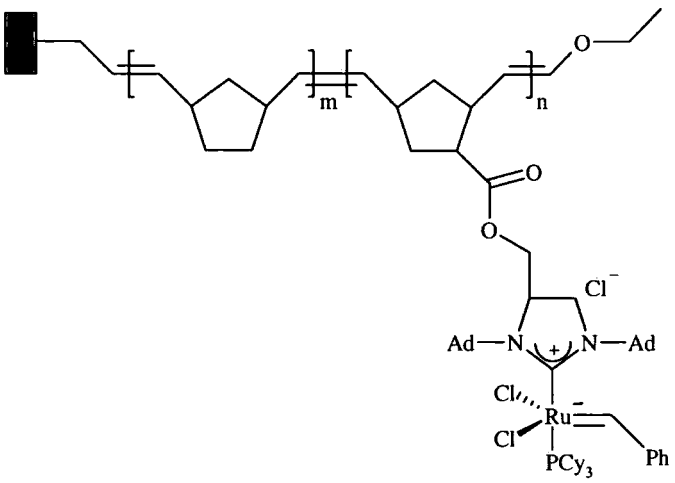
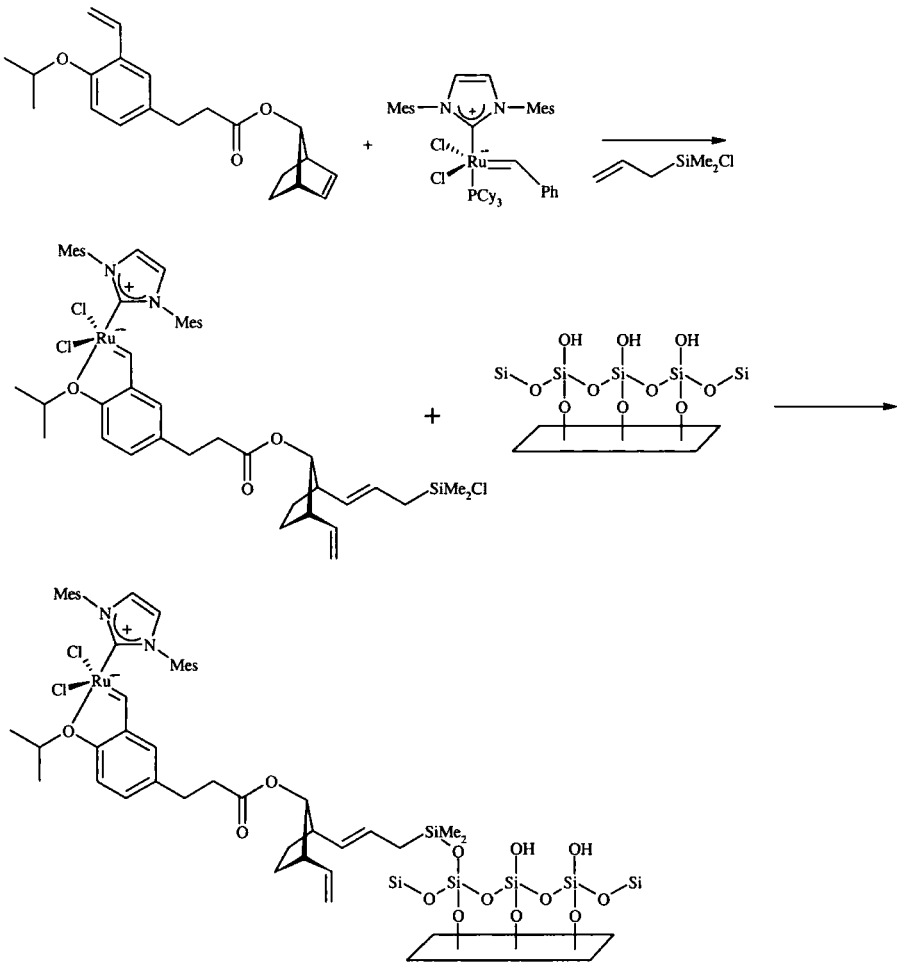


Figure 1.10

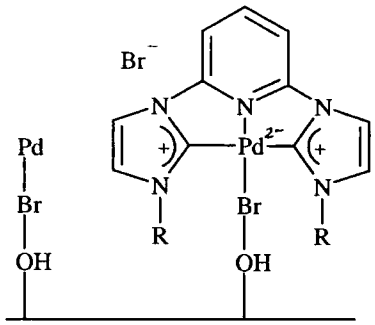
Buchmeister *et al.* prepared an immobilised metathesis catalyst by initial metathetic copolymerisation of olefins to produce a monolithic material with a controlled pore diameter.[133] The monolithic carrier was functionalised by living NHC-ruthenium termini (from an imidazolium precursor and Grubb's ruthenium metathesis catalyst),

figure 1.10. The catalyst was highly active in RCM and ROM reactions giving the same *cis/trans* ratios as homogeneous counterparts.



Scheme 1.76

Hoveyda *et al.* developed an alternative concept for the immobilisation of olefin metathesis NHC catalysts.[134] Ruthenium complexes were supported by monolithic samples of porous sol-gel glass *via* the technique shown in scheme 1.76. The catalyst retained its activity after multiple recycles (>15), affording products without recourse to any purification steps.



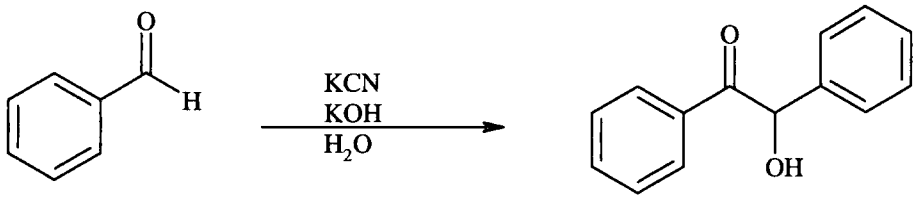
R= n-Bu, -CH_2Ph, p-CH_2PhNO_2

Figure 1.11

Peris *et al.* successfully immobilised a series of CNC tridentate bis(carbene) palladium complexes onto montmorillonite K-10 clay, figure 1.11.[135] The very stable pincer-type ligand provided stability even when the reaction was carried out at elevated temperatures (140-180°C). Analysis of the catalyst after a Heck cross-coupling reaction by XPS revealed negligible metal leaching. As a result the catalyst could be reused at least ten times without significant loss in activity. A further report detailed the use of these supported catalysts in Sonogashira coupling reactions.[136]

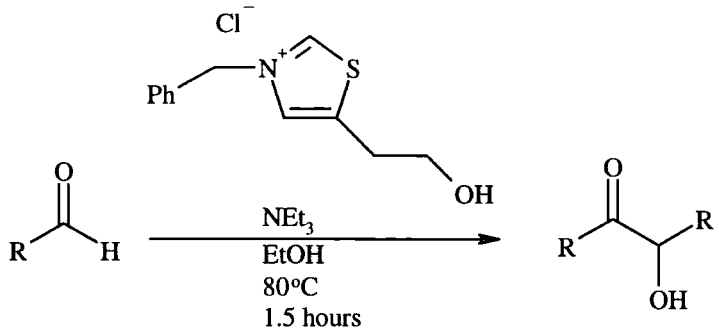
1.5.6.7- Other uses of N-Heterocyclic carbenes

It has been known for some time that certain nucleophiles can act as catalysts in condensation reactions involving acyl anions. These condensation reactions are examples of an umpolung addition. For example Lapworth reported the formation of benzoin by the cyanide-catalysed condensation of benzaldehyde in alkaline solution in 1903, scheme 1.77.[137]



Scheme 1.77

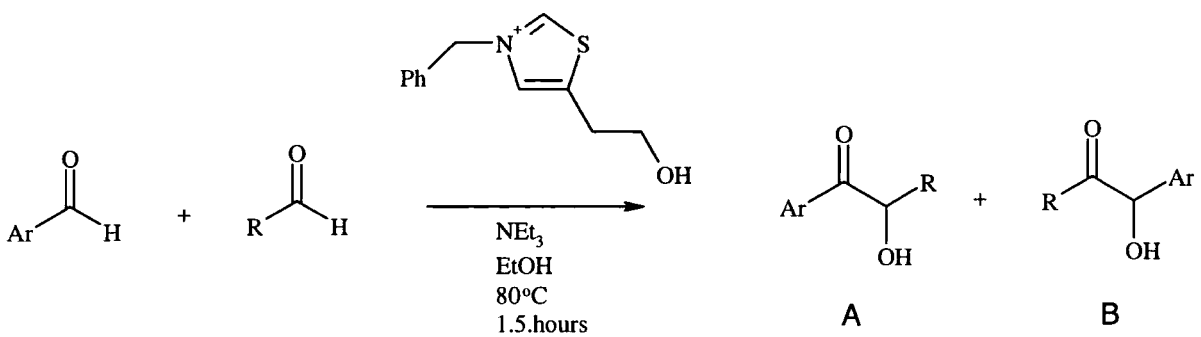
Following a report by Dokowa *et al.* describing the synthesis of thiazolium salts, Breslow successfully replaced catalytic cyanide with thiazolium derived carbenes in the benzoin condensation reaction.[138,139] Almost twenty years later Stetter *et al.* reported the use of thiazolium derived carbenes in other acyloin condensation reactions, scheme 1.78.[140]



$R = CH_3$	Yield =68%
$R = C_2H_5$	Yield =67%
$R = C_9H_{19}$	Yield =88%
$R = TIPSO(CH_2)_3$	Yield = 71%

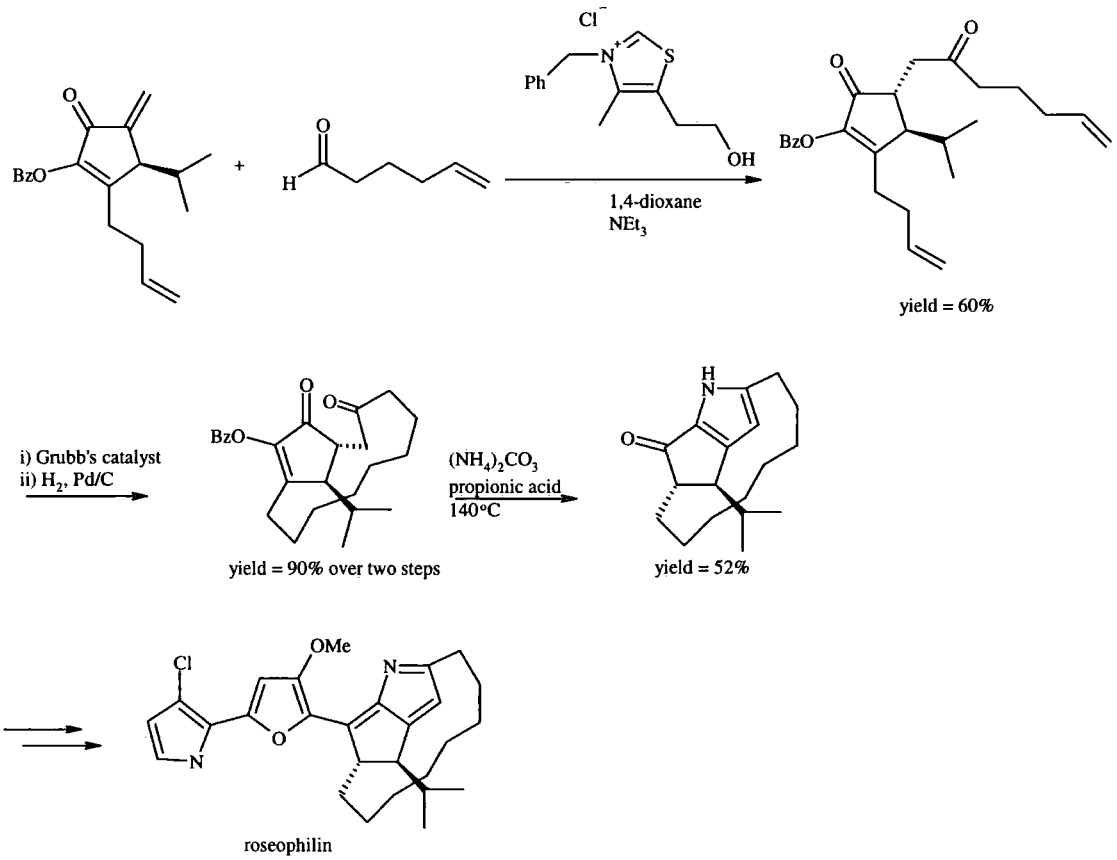
Scheme 1.78

In a further report Stetter reported a cross-acyloin condensation reaction using mixtures of different aldehydes, scheme 1.79.[141] In these cross-condensation reactions, the selectivity for reaction product A or B arises from the reaction of the most stable acyl anion reacting with the most reactive aldehyde.

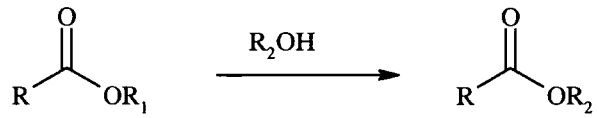


Scheme 1.79

Stetter also reported that the aldehyde nucleophile could add to another aldehyde or a conjugate acceptor.[141] This second process, known as the Stetter reaction, is a very useful method of preparing 1,4-dicarbonyl compounds and has been used in several synthetic applications. For example Harrington *et al.* reported the total synthesis of roseophilin (a sub-micromolar inhibitor of several cancer cell lines) featuring a Stetter reaction, scheme 1.80.[142]



Scheme 1.80

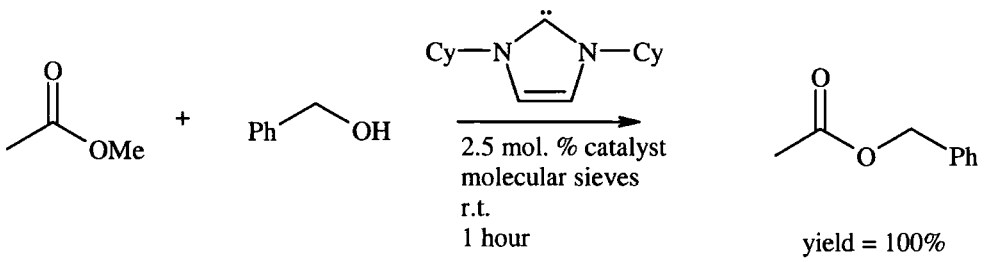


Scheme 1.81

The ester functional group represents one of the most ubiquitous groups in chemistry playing a key role in biology and as a key intermediate or protecting group in organic transformations.[143] Consequently methods to synthesise different esters are very useful. Transesterification by exchange of an alkoxy moiety, scheme 1.81, can be performed by a variety of techniques such as using enol esters as acylating agents.[144,145,146] Readily

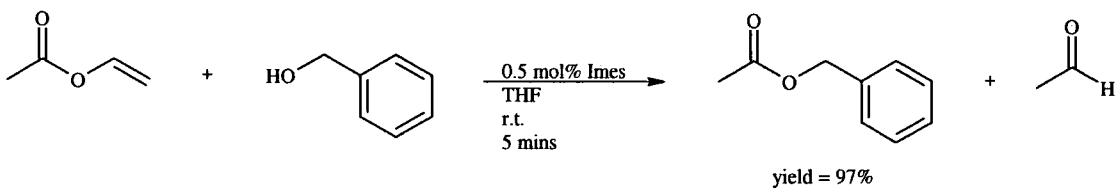
available methyl esters, however, require harsh conditions to enable alcohol deprotection and rarely undergo transesterification to higher homologues due to the reversibility of the reaction.

Nolan *et al.* reported that *N*-Heterocyclic carbenes, imidazol-2-ylidenes in particular, are efficient catalysts in the transesterification between esters and alcohols.[147] Nolan *et al.* successfully converted methyl esters in the presence of alkyl-substituted NHCs into higher homologues in very short reaction times, scheme 1.82.



Scheme 1.82

In an additional reaction, Nolan *et al.* also demonstrated that only very low catalyst loadings of aryl or alkyl substituted NHC catalysts were required to mediate the acylation of alcohols with vinyl acetate at room temperature, scheme 1.83.[147]



Scheme 1.83

Room-temperature ionic liquids have been utilised as clean solvents and catalysts for green chemistry and as electrolytes for batteries, photochemistry and electrosynthesis. They have no significant vapour pressure and thus create no volatile organic components. They also allow for easy separation of organic molecules by direct distillation without loss of the ionic liquid. Their liquid range can be as large as 300° C allowing for large kinetic control of the reaction, which, coupled with their good solvent properties, allows small reactor volumes to be utilised.

Salts based upon poor nucleophilic anions such as $[BF_4]^-$, $[PF_6]^-$, $[CF_3CO_2]^-$, $[CF_3SO_3]^-$, etc, are water- and air-insensitive and possess remarkably high thermal stability. Many of these materials are based around imidazolium cations, figure 1.12.

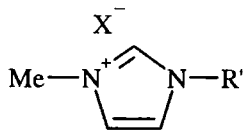
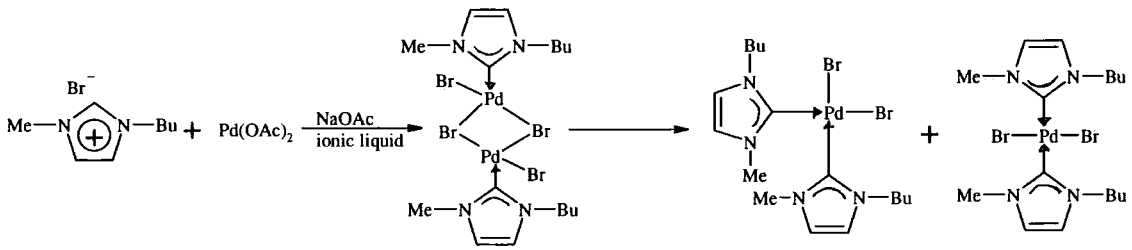


Figure 1.12

By changing the anion or the alkyl chain on the cation, a wide variation in properties such as hydrophobicity, viscosity, density and solvation can be obtained. For example, they will dissolve a wide range of organic molecules to an appreciable extent, the solubility being controlled by the nature of the counter-anion.

The beneficial effects in catalytic processes may in part be due their easy conversion into NHC-metal complexes. Other ligands that are present in the reaction may be sufficiently basic to induce deprotonation and form the respective *N*-Heterocyclic carbene.

Xiao *et al.* performed Heck reactions in the ionic liquid 1-butyl-3-methylimidazolium bromide.[148] The ionic liquid reacted readily with $Pd(OAc)_2$ to yield dialkylimidazol-2-ylidene complexes which were characterised by ^1H and ^{13}C NMR spectroscopy, scheme 1.84.



Scheme 1.84

The NMR studies showed that interconversion between the different isomers occurred at high speed at moderate temperature.

Chapter 2

CNC bis(carbene) ligands and synthesis of a polymer-supported palladium complex

2.0- Project strategy

Homogeneous catalysis now provides a powerful synthetic tool for the organic chemist. However, the high cost of many catalytically active complexes and difficulties separating them from reaction products often limits their use, especially on a large scale. By attaching the catalyst to a polymer support to permit recycling, some of these problems can be dealt with.

As discussed in the previous chapter, in the last decade, the incorporation of *N*-Heterocyclic carbenes in a variety of transition metal complexes has provided a series of enhanced catalysts. These often show greater versatility, activity and stability than their phosphine counterparts.

Before the design of any metal complex for this project, there were certain key factors that had to be taken into account. The metal complex/es must feature:

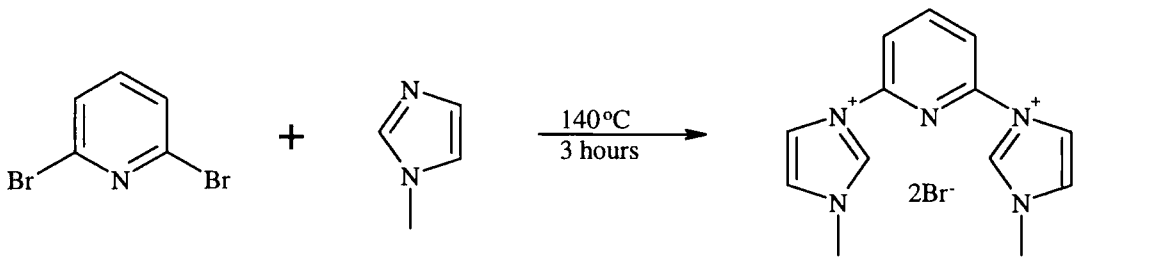
i) *N*-Heterocyclic carbene ligands in order to give greater stability and increased catalytic activity to any complex made.

ii) A functional group or site which would allow coupling to a polymer support of some kind. This would allow simple separation of the catalyst from the reaction media by filtration and would ultimately permit recycling of the catalyst.

iii) A versatile modular ligand system which would permit tuning of the electronic and steric properties of any catalyst made and ultimately offer the possibility of performing asymmetric catalysis.

iv) A C_2 symmetric ligand system. If enantioselective catalysis was to be investigated the catalyst would ideally be C_2 symmetric. The reason for this is to reduce the number of possible isomeric metal complexes, as well as the number of different substrate–catalyst arrangements and reaction pathways, when compared with a nonsymmetrical ligand. The consequence of C_2 symmetry can have a beneficial effect on enantioselectivity because the competing less-selective pathways are possibly eliminated. Because fewer reaction intermediates must be taken into account, C_2 symmetry is of particular advantage in mechanistic studies because it facilitates analysis of the ligand–substrate interactions that may be responsible for enantioselection. [149,150]

With these points in mind attention was drawn to a report by Chen and Lin detailing the synthesis of bis(imidazolium) salt **1a**, scheme 2.1. [151]



Scheme 2.1

This report offered a potentially facile method for synthesising a stable tridentate CNC ligand system. As discussed in chapter one, several techniques are available for preparing a metal - NHC complex from an imidazolium salt. Based on Chen and Lin's report and the methods available for incorporating a metal centre, the general desired structure of the supported catalyst could be envisaged, figure 2.1.

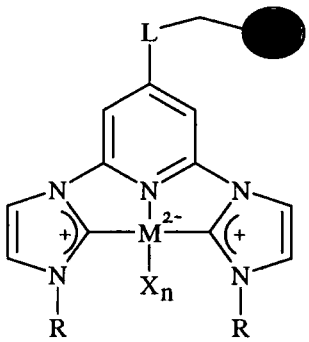


Figure 2.1

Using a core pyridine unit, a linker or spacer unit would be incorporated at C4 (L - see below for further discussion); *N*-Heterocyclic carbene functionality would be incorporated at C2 and C6. It is predicted that the strong binding to the metal of the tridentate ligand system featuring two *N*-Heterocyclic carbene ligands in combination with the strong σ donation onto a metal centre would provide a stable and highly active catalytic system. Further tuning of physical characteristics and catalytic activity could be done by varying the N substituents (R); a range of metal centres (M) could be incorporated to catalyse a range of synthetic reactions. Further tuning of the catalytic

system can occur by using a variety of polymer supports, *e.g.* cross-linked polystyrene, silica and controlled pore glass.

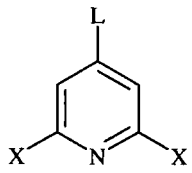
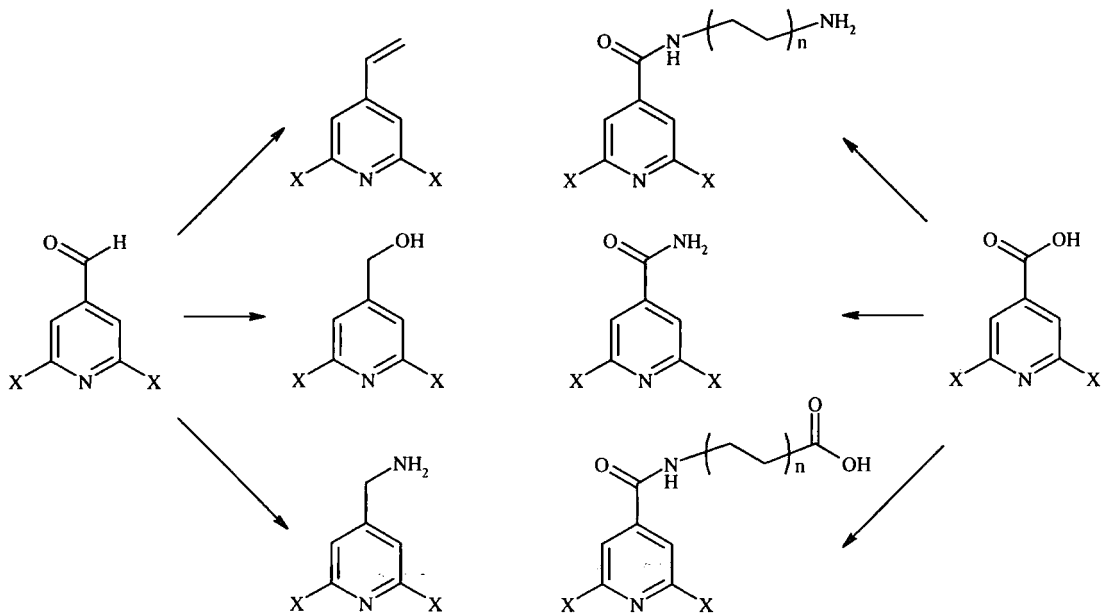


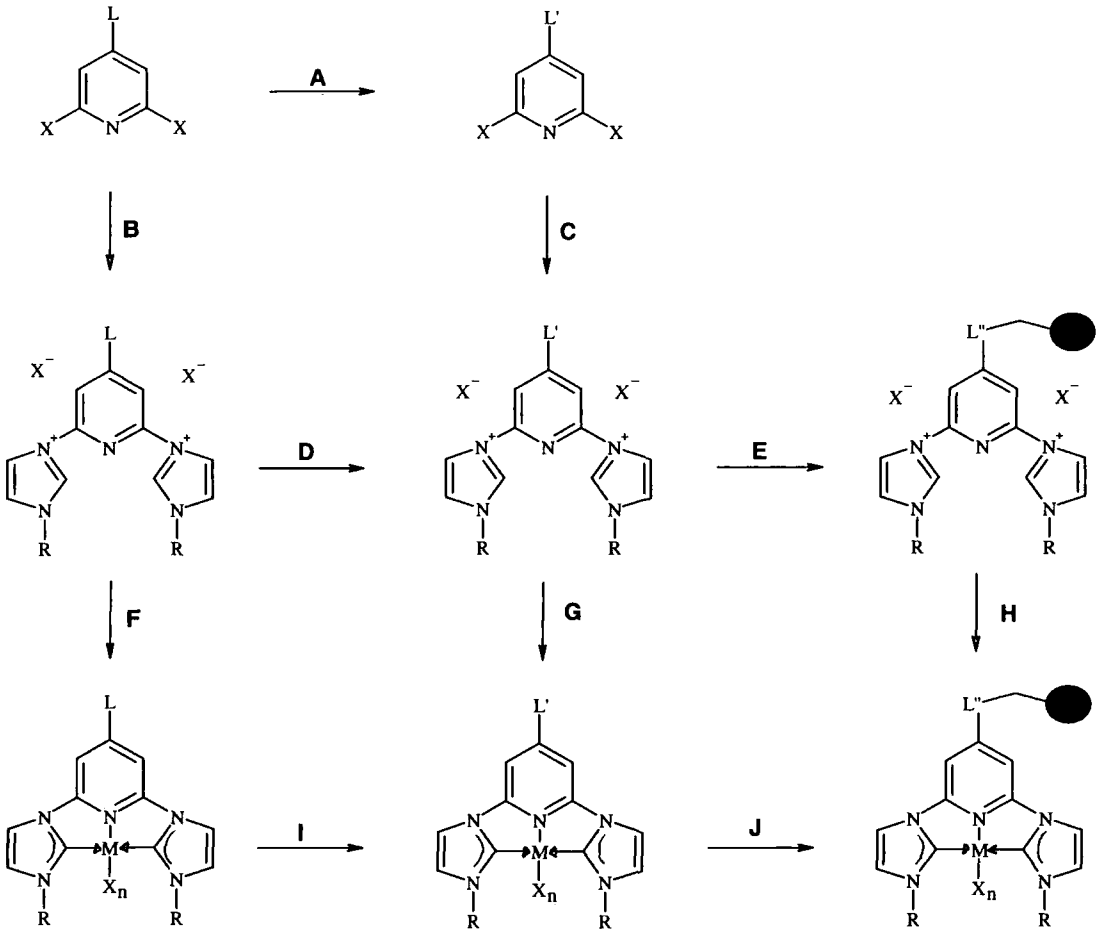
Figure 2.2

With the structure shown in figure 2.1 in mind a modular strategy could be devised based around the core pyridine unit. Using a functionalised pyridine as a starting material, figure 2.2 would permit polymer attachment at C4, whilst metal-binding functionality could be incorporated at C2 and C6. This core unit would also permit the synthesis of next generation complexes with C_2 symmetry for use in enantioselective catalysis.

A range of pyridines are commercially available that would allow studies on the synthesis of a polymer-supported bis(carbene) complex. However modification of the C4 functional group may be required before attachment to a polymer support. These modifications would also alter the electronic properties of the pyridine ring, scheme 2.2.



Scheme 2.2



Scheme 2.3

With the core unit in hand, several reaction paths and strategies could be investigated to generate a polymer-supported complex, scheme 2.3:

A - Further modification of C4 functionality may be required in order to modify physical characteristics such as solubility; to attach a spacer unit (a spacer unit or linker would hopefully enhance the homogeneous characteristics of the catalytic complex by increasing the distance of the complex from the stationary support); or to permit a specific method of attachment to a polymer support (for example conversion of an aldehyde into an alkene so that a complex may undergo ROMP).

B & **C** - Metal-binding functionality can be incorporated at C2 and C6 of the pyridine unit by substitution of X with *N*-alkyl or *N*-aryl imidazoles allowing the formation of a bis(imidazolium) salt.

D - Further modification of pyridine C4 functionality may be performed upon formation of the bis(imidazolium) salt.

E - The bis(imidazolium) salt may be attached to a polymer support before incorporation of a metal centre.

F - Methods can be investigated for incorporating a metal centre (see chapter 1). The bis(imidazolium) salt can be treated with strong base to generate the bis(carbene). After isolating the bis(carbene), ligand exchange with a metal source would generate the tridentate CNC metal complex. Alternatively a one-pot strategy may be undertaken using a metal source which contains ligands of sufficient basicity to deprotonate the bis(imidazolium) salt and generate the metal complex in one step.

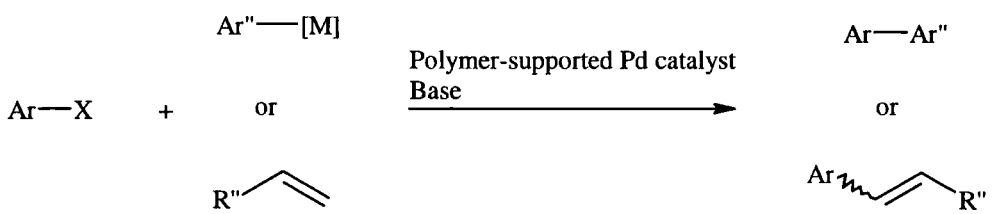
G - Modification of the pyridine C4 functionality may be required before methods can be investigated for incorporating a metal centre. Certain methodologies for incorporating the metal centre may not tolerate certain functional groups and as a consequence the synthetic strategy would have to be modified.

H - With a polymer-supported bis(imidazolium) salt in hand methods can be investigated to incorporate a metal centre.

I - Further modification of the pyridine C4 functionality may be required to permit attachment to a polymer support.

J - With a tridentate CNC complex in hand, strategies can be investigated to attach the complex to a polymer support.

As some functional groups may not be stable to certain reaction conditions or interfere during synthesis, several alternative strategies must be available in order to synthesise the polymer-supported CNC complex.



Scheme 2.4

Whilst it can be envisaged that a number of different metal centres could be incorporated into the ligand system, this project focused on the formation of a palladium complex for use in palladium-catalysed cross-coupling reactions, scheme 2.4. The reasons for this were:

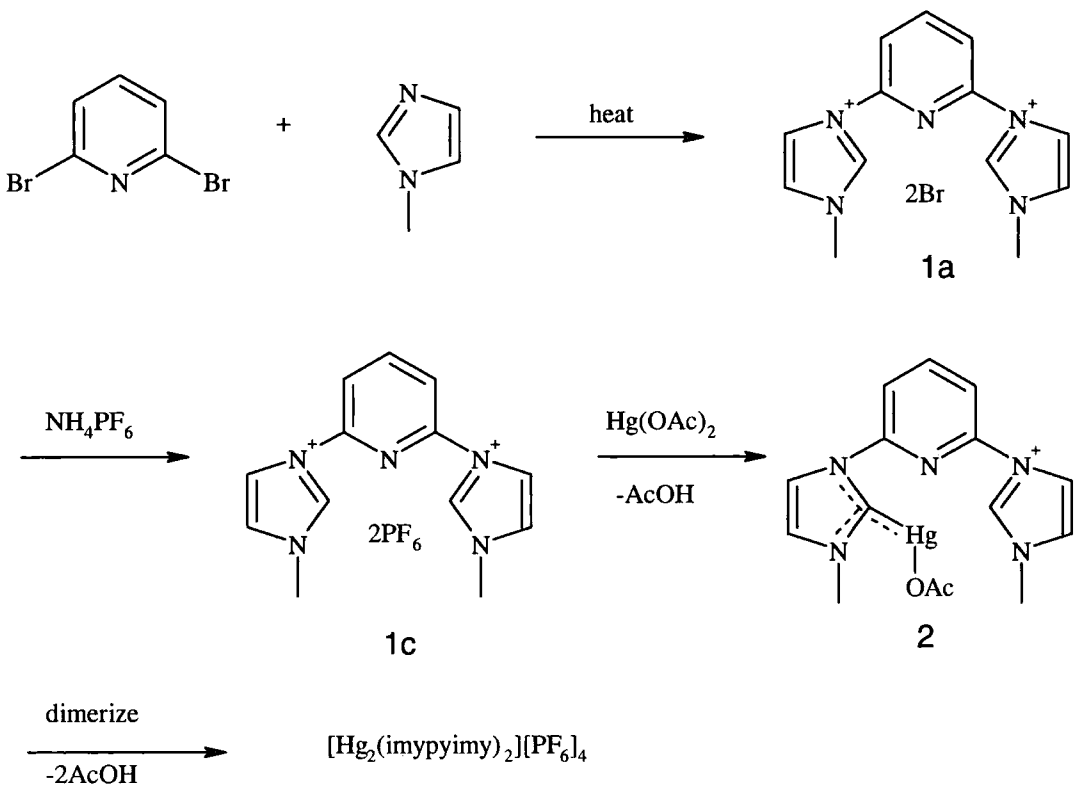
i) to establish a tried and trusted methodology for the incorporation of a metal centre;

ii) to compare catalytic activity with other supported palladium catalysts that have been reported in the literature;

iii) to try to establish the key features of a catalyst in palladium-catalysed cross-coupling reactions in order to generate an enhanced activity supported catalyst.

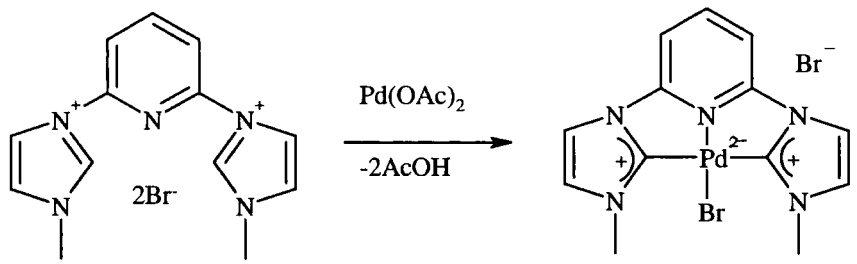
2.1- CNC bis(carbene) ligand systems

The initial aims of the project were to develop the synthesis of a metal complex featuring *N*-Heterocyclic carbene ligands suitable for immobilisation onto a polymer resin. In this context a report by Chen and Lin describing the synthesis of a novel ligand system, **1a** was interesting for several reasons, scheme 2.5.[151] Firstly, the synthesis appeared straightforward. Secondly, the tridentate CNC ligand system should provide thermal stability which would permit recycling. Finally, the ligand system was C_2 symmetric which could be beneficial to the development of enantioselective variants.



Scheme 2.5

Preliminary work in the group had investigated the versatility of this ligand system by forming the tridentate palladium complex **4**, scheme 2.6. Concurrent with this research, Crabtree and Peris published the synthesis of **4** and demonstrated the potential catalytic activity of **4** in Heck coupling reactions.[152]



4

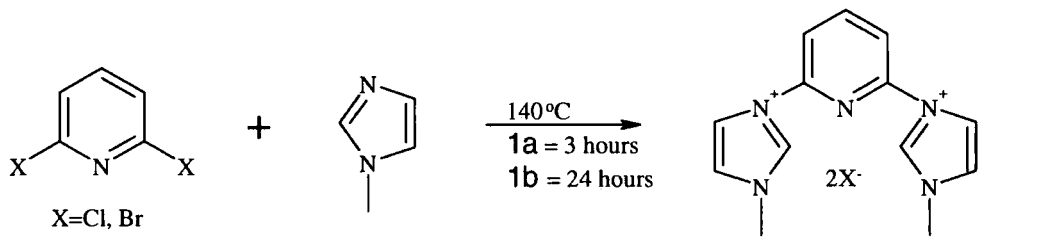
yield = 70%

Scheme 2.6

The initial goals of the project were: to replicate the ligand synthesis described by Chen and Lin; to replicate the complex synthesis by Crabtree and Peris; to evaluate the catalytic activity of complex **4**; finally to determine a strategy to immobilise an analogue or derivative on a polymer support.

2.2- Investigation of the bis(imidazolium) unit

As discussed above the initial aim was to fully evaluate the synthesis of the CNC ligand previously reported by Chen and Lin.

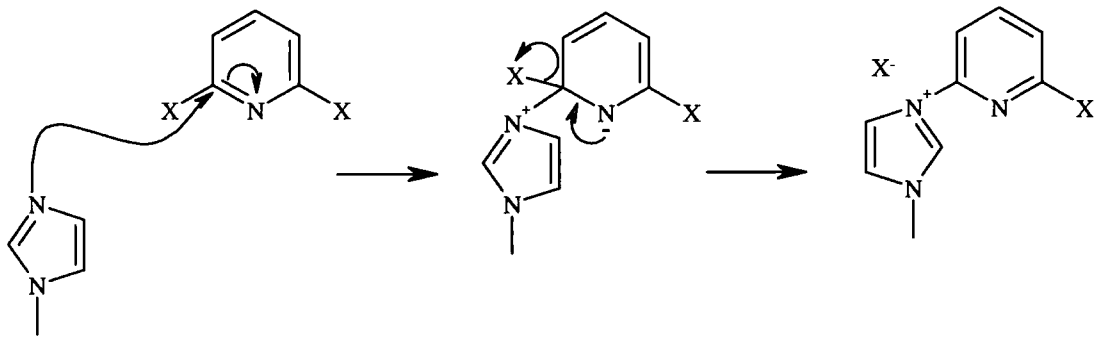


1a X=Br yield = 91%

1b X=Cl yield = 15%

Scheme 2.7

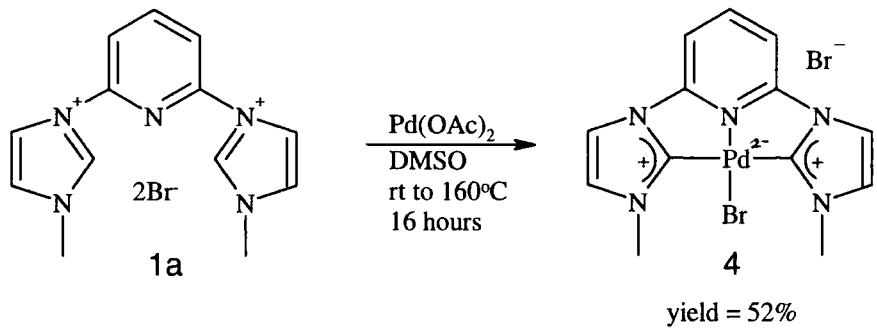
Bis(imidazolium) salt **1a** was synthesised in the literature from 2,6-dibromopyridine. Early experiments investigated the treatment of commercially inexpensive 2,6-dichloropyridine with 1-methylimidazole heating at 140°C for 24 hours, scheme 2.7. Yields for compound **1b** were unexpectedly low (~15%). Examination of ^{1}H NMR spectra revealed a large quantity of unreacted starting materials present in the crude reaction mixture. Consequently the synthesis was repeated with 2,6-dibromopyridine forming salt **1a** in high yield (91%) in only 3 hours, scheme 2.7. This observation is in contrast to traditional aromatic substitution of a pyridine ring - a proposed reaction mechanism postulated that the higher reactivity of 2,6-dibromopyridine over its dichloropyridine counterpart was due to the rate determining step of halide anion elimination. The effect of bromide as a better leaving group is rate determining rather than the initial attack of the nucleophile at the δ^{+} carbon, scheme 2.8.[153]



Scheme 2.8

Examination of the product by ^{1}H NMR spectroscopy revealed a characteristic peak at δ 10.24 (2H) due to the deshielded NCHN imidazolium protons, which suggested formation of the bis(imidazolium) salt. So with ligand **1a** in hand attention turned to incorporating a palladium metal centre.

2.3- Generating a palladium complex



Scheme 2.9

In their work Crabtree and Peris explored direct thermal complexation using $Pd(OAc)_2$ to generate tridentate bis(carbene) palladium complex **4**, scheme 2.9. Crabtree and Peris reported that complex **4** suffered from poor solubility with only polar solvents such as DMSO and hot MeOH proving useful. Repeating the conditions described by Crabtree and Peris, however, yielded **4** in only moderate yields (52%) accompanied by considerable amounts of palladium black. Consequently full air sensitive technique in Schlenk apparatus was followed. However, this did not prevent palladium black formation.

Of all the analytical techniques available, ES^+MS proved the most effective method to determine whether complexation was successful. Analysis of complex **4** by this technique revealed a characteristic set of peaks. This set was due to the 6 naturally abundant isotopes of palladium producing several molecular ion signals, figure 2.1.

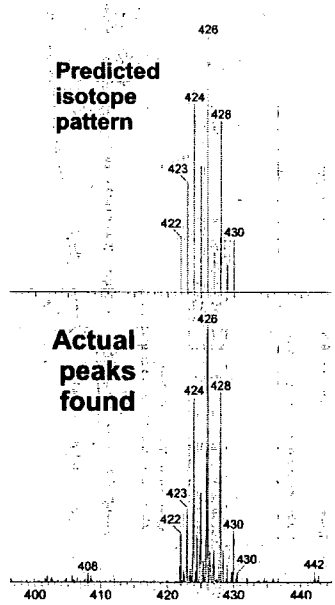
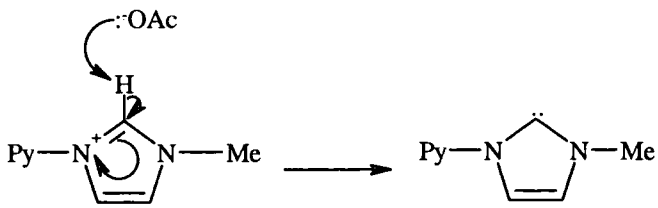


Figure 2.3

Examination by ^{1}H NMR spectroscopy recorded the disappearance of the NCHN imidazolium signals at δ10.24 suggesting the formation of the bis(carbene). In addition the characteristic sharp doublets of the NCHCHN backbone in bis(imidazolium) salt **1a** shifted significantly upon carbene generation from δ8.12 and δ8.82 to δ7.65 and δ8.43. This is characteristic of the change from an imidazolium ionic salt to a neutral carbene, scheme 2.10. Successful synthesis of complex **4** permitted studies to evaluate catalytic activity which will be discussed later.



Scheme 2.10

2.3.1- Microwave-accelerated synthesis

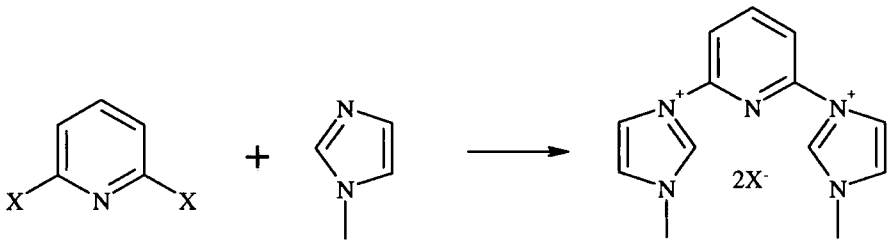
Although the synthesis of the bis(imidazolium) ligands and palladium complexes described above was successful, certain limitations were observed:

i) Ligand synthesis was successful with 2,6-dibromopyridine only.

ii) Complexation using $Pd(OAc)_2$ was slow and gave only moderate yields

iii) Excess $Pd(OAc)_2$ was required as significant quantities of palladium black were formed.

As discussed previously in chapter one it is known that ionic liquids can absorb microwave radiation in a very efficient manner to allow microwave-accelerated synthesis.[1,148] Considering that many ionic liquids are based on an imidazolium salt unit, it was postulated that the synthesis of both bis(imidazolium) salt **1a** and complex **4** could be accelerated under microwave radiation and the reaction limitations overcome. Consequently a variety of conditions varying temperature and heating time were investigated, scheme 2.11 and table 2.1.



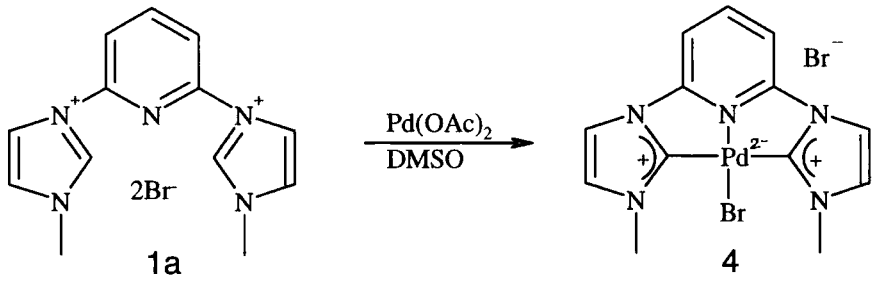
Scheme 2.11

Entry	Compound (X=)	Duration of heating (mins)	Power (W)	Temperature (°C)	Yield (%)
1	Cl	5	25	130	0
2	Br	5	25	130	0
3	Cl	8	25	150	47
4	Br	8	25	150	91
5	Br	13	25	150	92

Table 2.1

Early attempts to synthesise the bis(imidazolium) salts **1a** and **1b** were unsuccessful (entries 1 and 2). No crystalline product was isolated upon work up; however, analysis of the crude reaction mixtures by ^1H NMR spectroscopy recorded a characteristic imidazolium proton signal at ~δ10. However, a large number of signals between δ7.0 and δ10.0 suggested a mono-substituted product had been formed. Anticipating the

formation of a mono-substituted product, longer reaction times and higher temperature were employed. This approach provided crystalline products in significantly shorter reaction times and reproducibly higher yields than conventional heating (entries 3, 4, 5). In accordance with previous findings, substitution of bromide was much faster than chloride.



Scheme 2.12

Generation of complex **4** was also investigated, scheme 2.12. It was postulated that with both a polar solvent and a metal salt present in the reaction mixture, efficient absorbance of microwave radiation would occur. Consistent with this hypothesis and in contrast to conventional synthesis of **4** described above (section 2.3), **4** was isolated in 95% yield after only 15 minutes of heating at 165°C. In addition very little or no palladium black was formed even though air sensitive techniques were not followed.

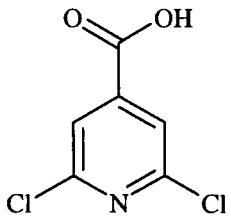
Curiously it was discovered that the synthesis of tridentate CNC palladium complexes using this method was very sensitive to temperature control. If the reaction temperature exceeded 165°C for several minutes the isolated yields fell dramatically.

Synthesis of the CNC ligand **1a** and complex **4** was established using methodology developed by Crabtree and Peris. Further enhancement using microwave technology has provided a fast, efficient route to compounds **1a** and **4** with significant increases in isolated yields.

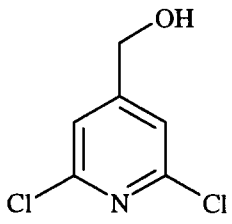
2.4- Synthesis of functionalised CNC ligands

Having established enhanced methodology for preparing pyridyl bis(carbene) CNC palladium complexes, attention now turned to the synthesis of functionalised CNC ligands.

In accordance with the project strategy a linker unit was to be incorporated into the CNC ligand system. In order to maintain overall C_2 symmetry the linker unit would be incorporated at the C4 position of the pyridine ring.



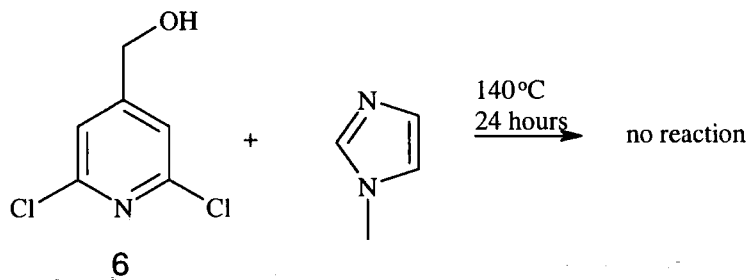
5a



6

Two strategies to incorporate a linker unit were investigated using two commercially available compounds: 2,6-dichloroisonicotinic acid, **5a** and 2,6-dichloropyridine-4-methanol, **6**. Conversion of 2,6-dichloroisonicotinic acid to an amide or ester offered one route to immobilisation. On the other hand 2,6-dichloropyridine-4-methanol provided another route by forming an ether linkage to a polymer support. The two different strategies also offered the potential to tune the electronic characteristics of the pyridine ring.

2.4.1- 2,6-dichloropyridine-4-methanol, 6 as a core unit

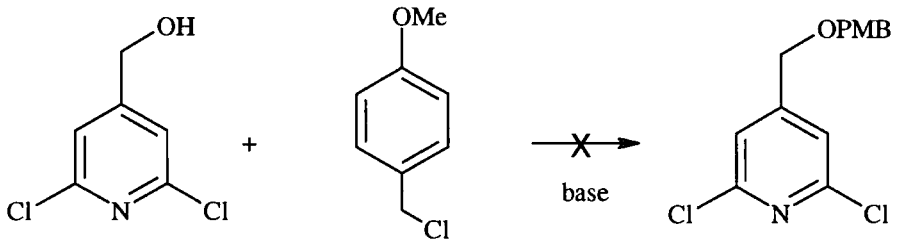


6

Scheme 2.13

Initial attempts at heating **6** with 1-methylimidazole did not yield the desired bis(imidazolium) product and starting materials were recovered, scheme 2.13. It was postulated the electron donating functionality at C4 hindered attack at C2 and C6 by a nucleophile or that the terminal hydroxyl group interfered with the substitution reaction. Assuming the latter protection of the hydroxyl group was investigated.

Although numerous strategies for the protection of alcohols exist, attention focused on the formation of a benzyl ether. Formation of the benzyl ether would initially act as a model study for attachment to a functionalised resin, *e.g.* Merrifield resin (cross linked chloromethyl polystyrene), whilst permitting synthesis of the ligand unit. Secondly, benzyl ethers may be easily cleaved *via* palladium catalysed hydrogenolysis.



Scheme 2.14

Initial efforts involved prior treatment of **6** with DIPEA and subsequent addition of PMB chloride in the presence of a small amount of KI, scheme 2.14. TLC and analysis by ^{1}H NMR spectroscopy only revealed a mixture of starting materials. Even increasing the number of DIPEA equivalents and using longer reaction times were unsuccessful in yielding the desired protected product.

2,6-Dichloropyridine-4-methanol was treated with the stronger base, NaH in THF. Although a colour change took place suggesting deprotonation, after the addition of PMB chloride no product was detected by TLC or, after work up, by ^{1}H NMR spectroscopy. Finally the same method was repeated in DMF; however, once again no product was detected.

It was postulated that the target compound could be not formed due to nucleophilic attack by the nitrogen on the pyridine ring. This rapid quarternisation of the pyridine nitrogen would hinder nucleophilic attack by the hydroxyl group.

Concurrent with protecting studies of **6**, novel linking strategies using 2,6-dichloroisonicotinic acid, **5a** were more successful, therefore further work using **6** was abandoned.

2.4.2- 2,6-dichloroisonicotinic acid, 5a as a core unit

The initial strategy using **5a** was to bind a linker or polymer via an amide bond to the pyridine core. An amide linkage was preferred for several reasons: the fact that amides are more stable than their ester equivalents, the availability of literature procedures and the possibility of alternative electronic effects through reduction of the amide linkage.

As discussed previously, in order to link the ligand or complex to a polymer, the ligand precursor must include a secondary functional group, Z, as a site for attachment, figure 2.4.

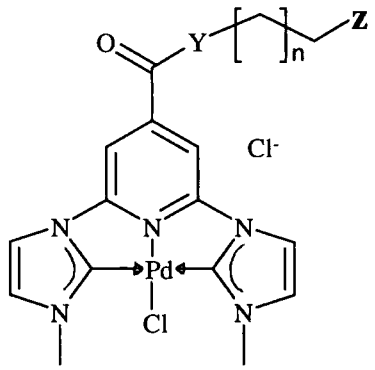
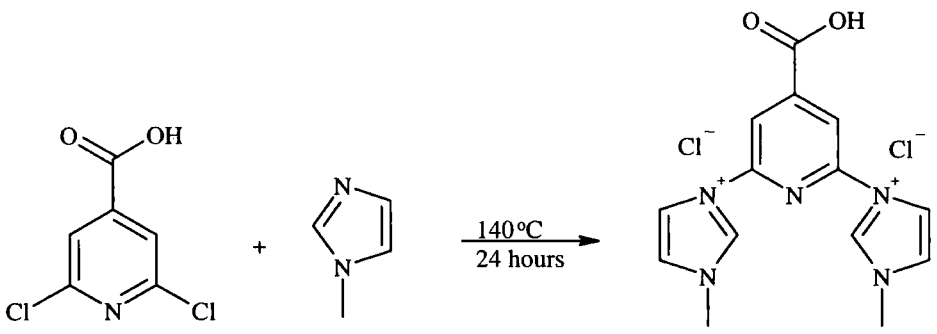


Figure 2.4

Initial studies, however, started with the synthesis of a model ligand system without any secondary site for polymer attachment. This model system was investigated to see what effect the amide bond had on solubility and activity.

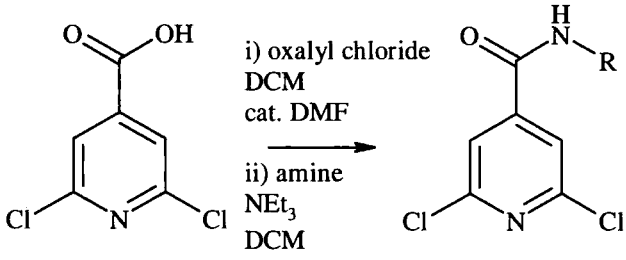
2.4.3- 2,6-dichloroisonicotinic amide derivatives



5a 7

Scheme 2.15

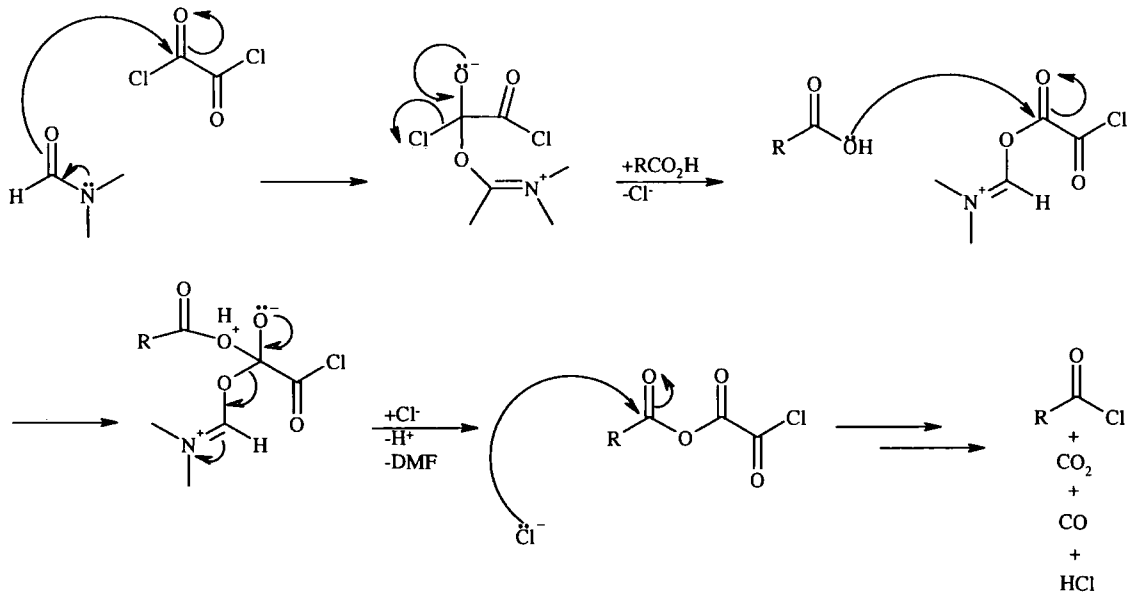
Previous work in the group had investigated substitution of 2,6-dichloroisonicotinic acid, **5a** with 1-methylimidazole under the previously established reaction conditions developed in section 2.2. A red/brown crystalline material was isolated; however, analysis was frustrated by very poor solubility. Although formation of a polymer was suggested, it was postulated that bis(imidazolium) salt **7** was the most likely product, scheme 2.15. Salt **7** is highly conjugated and planar allowing close intermolecular packing. This may explain the very poor solubility and as a result further modification of **7** was not possible. Therefore amide functionality must be incorporated before treatment with 1-methylimidazole.



Scheme 2.16

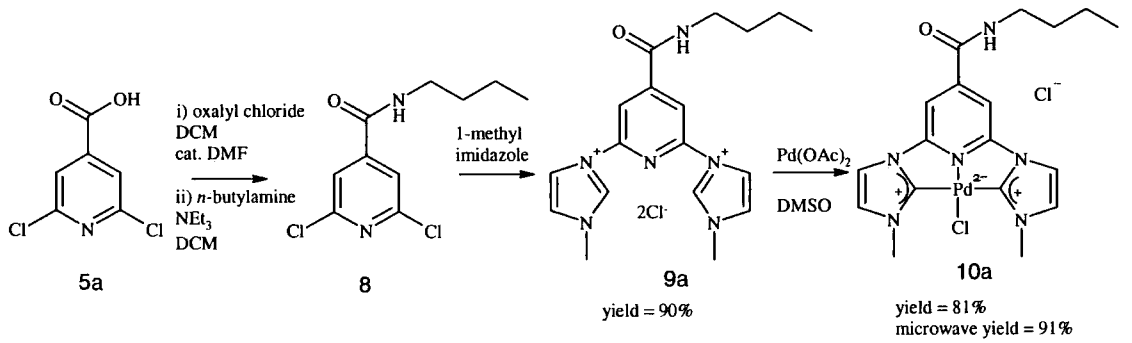
A literature investigation revealed a patent by Horrom detailing the facile synthesis of 2,6-dichloroisonicotinic amide derivatives to investigate their use as potential sedatives.[154,155] The amide could be easily formed from the respective acid chloride and an amine, scheme 2.16.

Following this precedent, addition of oxalyl chloride to 2,6-dichloroisonictinic acid, **5a** in the presence of a small quantity of DMF produced 2,6-dichloroisonicotinoyl chloride, **5b**. DMF is known to catalyse the formation of acid chlorides from oxalyl chloride, scheme 2.17.



Scheme 2.17

Characteristic IR absorptions at 1781cm^{-1} and 733cm^{-1} confirmed conversion to the acid chloride. The crude product was subsequently treated with *n*-butylamine in the presence of NEt_3 to yield **8** in high yield (70%) after work up and purification. Analysis by ^{1}H NMR spectroscopy revealed a NH peak at δ6.19 which disappeared upon addition of D_2O. Further analysis by IR spectroscopy revealed the characteristic amide carbonyl absorption at 1647cm^{-1}.



Scheme 2.18

Treatment of **8** with 1-methylimidazole yielded bis(imidazolium) salt **9a** in high yield (90%), scheme 2.18. The characteristic NCHN proton signal at δ10.64 confirmed synthesis of the target compound. Subsequent treatment of **9a** with $Pd(OAc)_2$ under Crabtree and Peris' conditions produced complex **10a** in 81% yield. As before, complexation under microwave-accelerated conditions formed **10a** in higher yield, 91%. ES^+MS confirmed the incorporation of the palladium centre detecting the 6 different palladium isotope mass ions (478-484).

Incorporation of the amide functionality had a beneficial effect on solubility. In contrast to the unfunctionalised counterpart **4**, complex **10a** was soluble in EtOH and $CHCl_3$. This change is probably due to the butyl chain removing the compound's planarity and breaking up intermolecular stacking.[156]

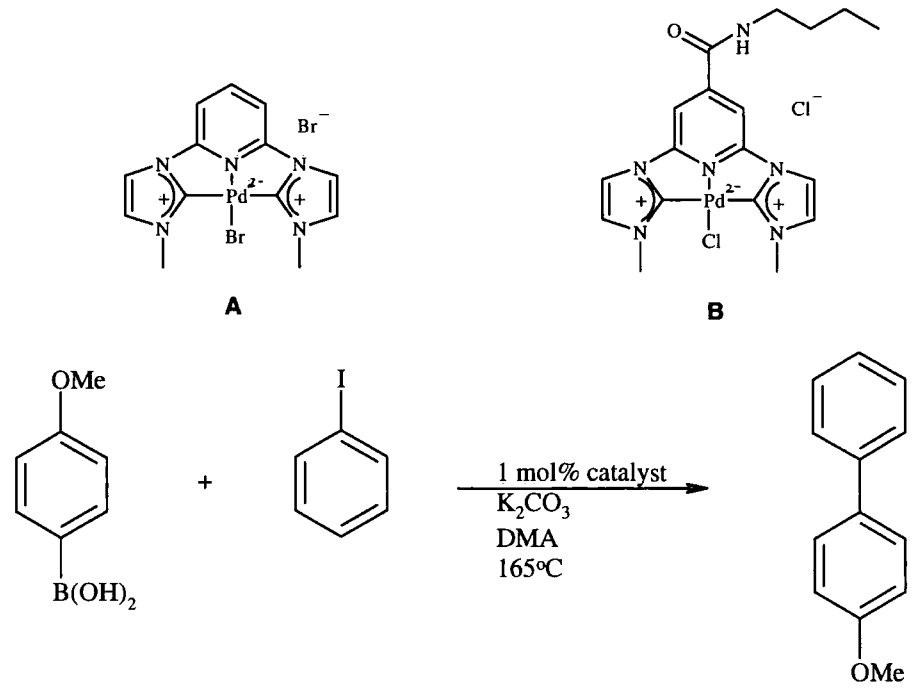
The successful synthesis of the model complex permitted studies to evaluate catalytic activity to be undertaken. These studies involved a comparison of the novel functionalised complex **10a** with the reported complex **4**.

2.4.4- Catalytic activity

Previous work by Crabtree and Peris demonstrated that complex **4** was an effective catalyst in Heck cross-couplings.[152,156] However, due to poor catalyst solubility, cross-coupling reactions were performed using only DMA as solvent. Crabtree and Peris further investigated the use of pyridyl bis(carbene) CNC ligands in Suzuki cross-coupling reactions.[156] With a view to evaluating what effect functionalisation of the pyridine ring had on catalytic activity, catalytic studies were performed. Using conditions established by Crabtree and Peris, the Suzuki cross-coupling reaction between 4-methoxybenzene boronic acid and iodobenzene was investigated, scheme 2.19. Iodobenzene and product concentrations were monitored by GC with diethyleneglycol di-*tert*-butyl ether as an internal standard and commercially available samples were used to establish retention time. Yields were determined from the average of two runs, table 2.2.

The presence of the amide linker appeared to reduce catalytic activity to a limited extent; however, the high thermal stability of **10a** would permit significant recycling when the complex is attached to a polymer support. Furthermore incorporation of amide functionality improves solubility which may prove useful in later stages of the synthetic strategy.

As a result of the successful studies of the model system, bifunctional linker units could now be investigated.



Scheme 2.19

Percentage yields (GC) of cross coupled product over time

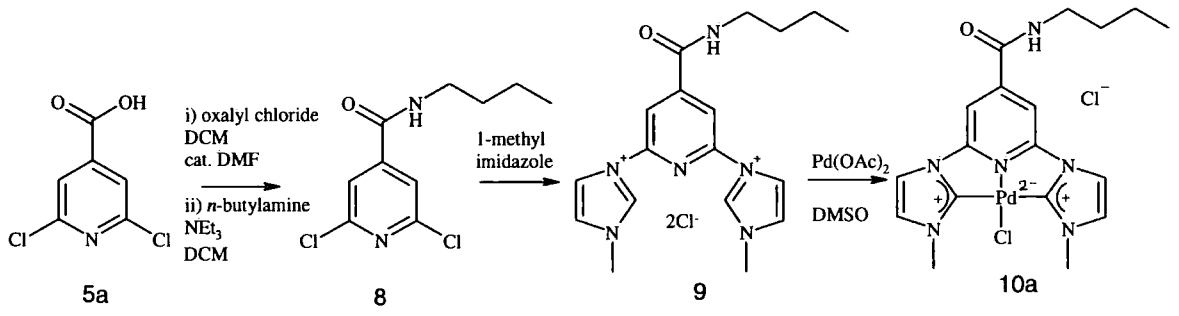
Time	1hr	4hrs	8hrs	12hrs	16hrs	24hrs	36hrs
Catalyst A	9	36	79	90	95	100	100
Catalyst B	7	20	64	76	87	96	100

Table 2.2

2.5 - Bifunctional linker units

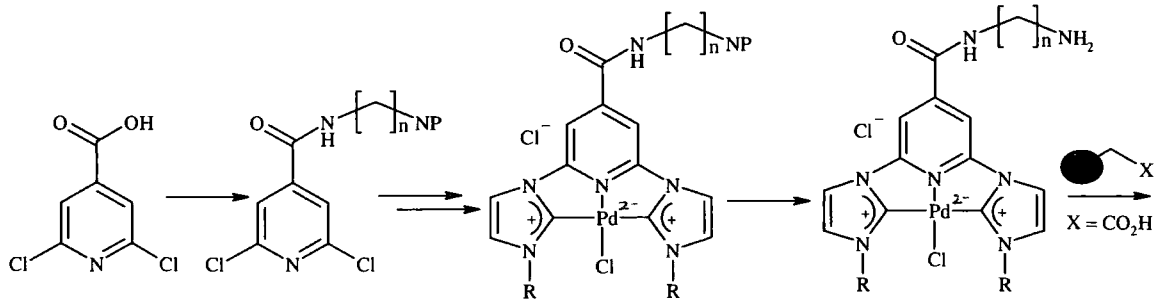
The synthesis of **10a** succeeded in demonstrating that functionality can be incorporated and tolerated at the C4 position of the pyridine ring. As discussed previously a secondary site of reactivity is required at the end of the amide alkyl chain for attachment to a polymer support. Therefore several linker strategies were investigated.

2.5.1- Diamine linkers



Scheme 2.20

Methodology developed by Horrom to functionalise 2,6-dichoroisonicotinic acid was successfully applied to the preparation of intermediates in the synthesis of complex **10a**, scheme 2.20. From this it was suggested that similar techniques would permit attachment to a functionalised polymer bead via an amide bond, scheme 2.21.

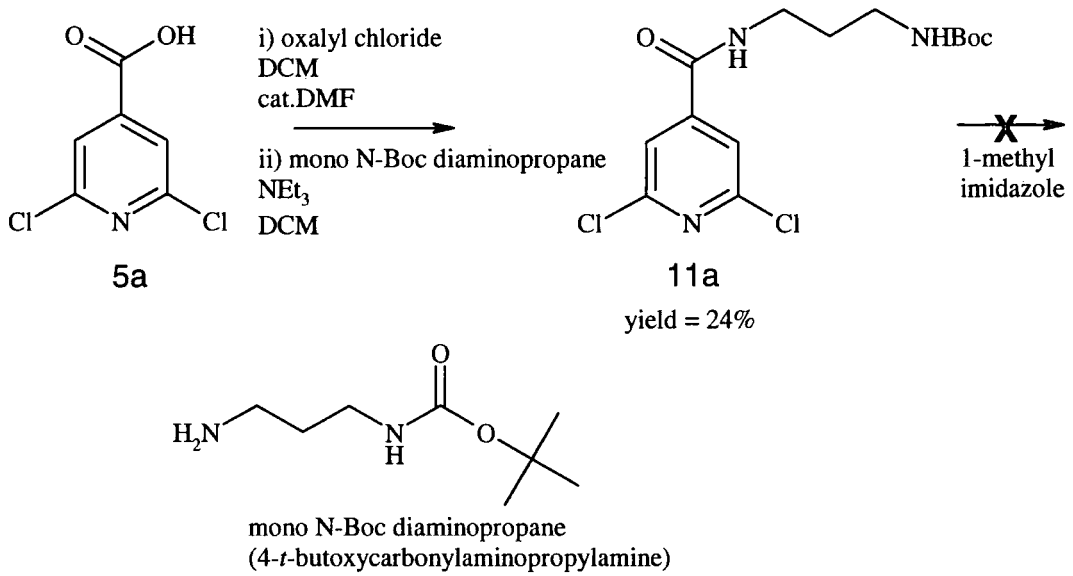


Scheme 2.21

By attaching a protected diamine to the pyridine core, an analogue of complex **10a** could be synthesised. Sequential adding of metal binding functionality and incorporation of a metal centre would generate a novel complex. Subsequent deprotection of the amine would provide the secondary reactive site for immobilisation. Attachment techniques could then be investigated.

2.5.2- Mono(*N*-Boc)diaminopropane as a linker unit

Initial studies of incorporating a secondary functional site started with the commercially available mono(*N*-Boc)diaminopropane. Following Horrom's procedure compound **11a** was isolated as analytically pure product, albeit in only 24% yield, scheme 2.22.

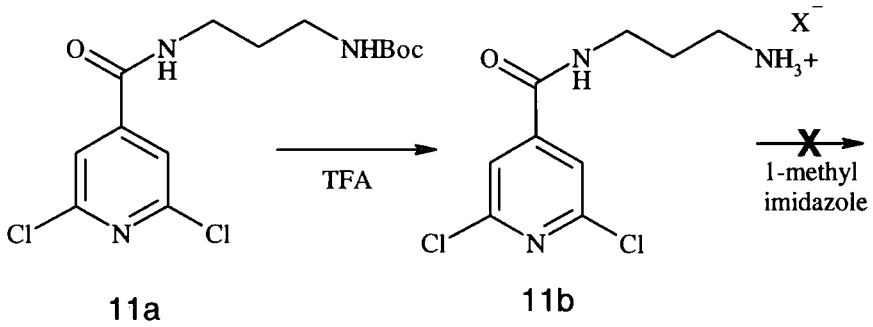


Scheme 2.22

Compound **11a** was identified by ^{1}H NMR spectroscopy. Two broad triplets at δ8.86 and δ6.83 with equal integration corresponded to the 2 NH protons showing amide formation had taken place; a singlet at δ1.37 (9H) showed that the Boc protecting group was still intact. ES$^+$MS showed two peaks at 370 and 372 (isotopes of $[M+Na^+]^+$). Further optimisation of reaction conditions to improve yields was inhibited by the high cost of the starting material. Treatment of **11a** with 1-methylimidazole using established conditions was frustrated by the poor stability of the Boc protecting group. A black crystalline solid was isolated after work up. Analysis by ^{1}H NMR spectroscopy

of this solid detected characteristic imidazolium proton signals at ~δ10, however, no signal was seen for the Boc protecting group. Varying the temperature from reflux to 90°C and shortening the reaction time was of no benefit and each time the Boc group was lost. Therefore considering the instability at high temperature, subsequent complexation with $Pd(OAc)_2$ was not attempted.

An alternative strategy was then investigated. Deprotection of **11a** with TFA gave amino salt **11b**. However, substitution with 1-methylimidazole was unsuccessful, scheme 2.23 and given the expense of mono *N*-Boc diaminopropane and the lability of the Boc protecting group, alternative linker units were then considered.

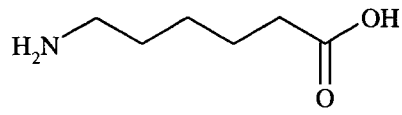


Scheme 2.23

2.5.3- Caproate linkers

In view of the difficulties with the diamine species described above, an alternative linker was sought. It was thought that a carboxylic acid at the end of the linker unit could be used to attach the ligand/complex to a polymer support. The acid could be converted and protected as an ester in order not to interfere with synthesis of the ligand system. Unlike a Boc protected amine in the previous section, it was thought that ester functionality would be stable to the high temperatures involved in ligand synthesis. Functional group interconversion of the ester into its carboxylic acid would then permit coupling to a functionalised polymer resin using peptide coupling techniques.

A search of commercially available amino acids led to the commercially inexpensive material 6-aminocaproic acid, **12**.

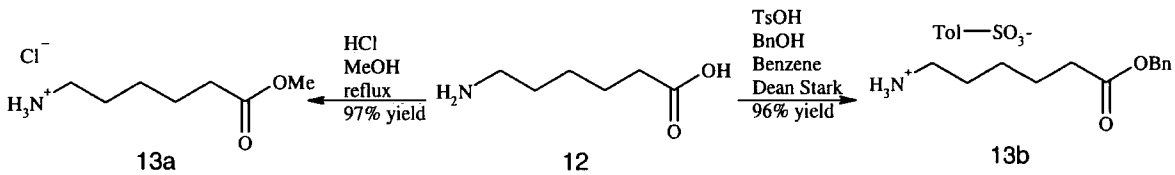


12

Simple esterification could produce a range of compounds offering different synthetic routes, *e.g.* methyl, benzyl, *t*-butyl. Whilst all esters can be converted into carboxylic acids by base-catalysed hydrolysis, *t*-butyl esters can undergo acid-catalysed hydrolysis and benzyl esters offer the option of palladium-catalysed hydrogenolysis.

2.5.4- Esterification of 6-aminocaproic acid

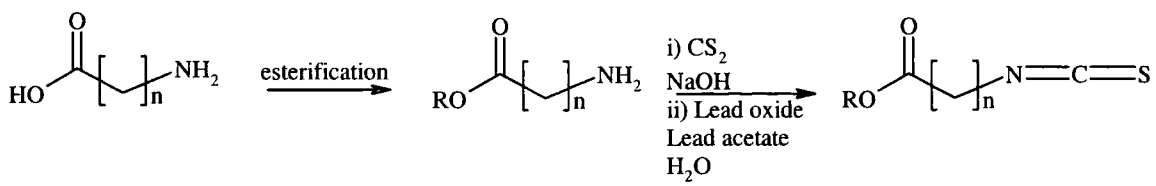
To assess the stability of ester functionality in CNC ligand and metal complex synthesis two esters were investigated, compounds **13a** and **13b**, which would provide alternative methods for conversion into a carboxylic acid, scheme 2.24.



13a 12 13b

Scheme 2.24

A literature search revealed previous work by McKay *et al.* describing the preparation of carbalkoxyalkyl isothiocyanates from methyl esters of amino acids, scheme 2.25.[157] The report also described esterification procedures for a range of amino acids including 6-amino caproic acid.

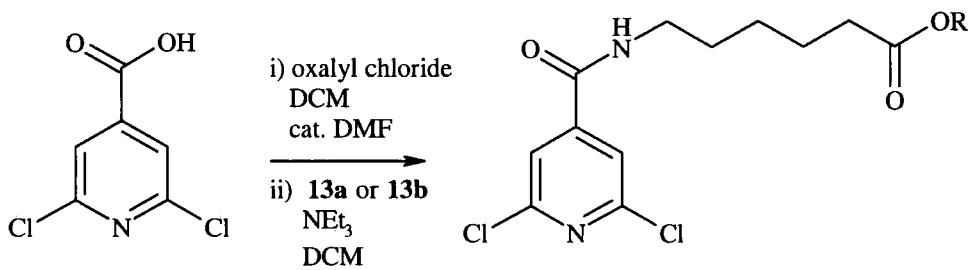


Scheme 2.25

Due to difficulties in determining the quantities of HCl required, early attempts to repeat the reaction conditions described in the report by McKay *et al.* produced **13a** in only moderate yields. Synthetic yields were improved by using an alternative method to prepare the acidified solution of MeOH necessary for esterification. The solution was prepared by careful addition of acetyl chloride to a large excess of dry MeOH. Subsequent addition of 6-aminocaproic acid and heating to reflux generated methyl ester **13a** in 24 hours (97%), scheme 2.24. A characteristic IR absorbtion of the ester carbonyl at 1735cm^{-1} confirmed preparation of an ester.

Previous work by Boxus was used in the preparation of benzyl ester **13b**, scheme 2.24.[158] Boxus prepared **13b** under Dean Stark conditions using benzene as the solvent. Further investigation of literature procedures reported the use of toluene. However, esterification required heating for longer and generated ~20% lower yields than those reported by Boxus. Repeating the procedure by Boxus was successful, isolating benzyl ester **13b** in 96% yield. Characteristic IR absorbtion of the ester carbonyl at 1738cm^{-1} confirmed generation of an ester. Both compounds **13a** and **13b** were isolated as their protonated amino salts to prevent formation of the lactam.

2.5.5– Attachment to the core pyridine unit



14a R = Me yield = 75%
14b R = Bn yield = 79%

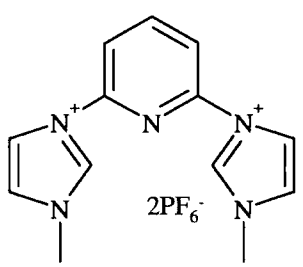
Scheme 2.26

With the two esters **13a** and **13b** in hand, studies to generate the CNC ligand unit could be undertaken. Compounds **13a** and **13b** were coupled to the pyridine core unit using the previously established methodology developed by Horrom *et al.*, scheme 2.26. The substituted pyridines **14a** and **14b** were isolated in high yields (75% and 79%

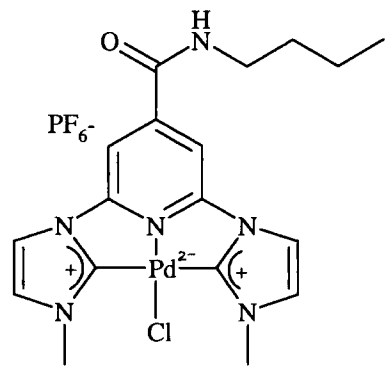
respectively). Both compounds recorded a characteristic broad triplet using ^{1}H NMR spectroscopy (X= δ8.84, X= δ8.83) suggesting that coupling between the free amine and the acid chloride had taken place. IR spectroscopy recorded the ester carbonyl absorptions (**13a**= 1739 cm^{-1}, **13b**= 1729 cm^{-1}) and the amide carbonyl absorbtions (**13a**= 1635 cm^{-1}, **13b**= 1640 cm^{-1}). Both compounds were shown to be analytically pure by C, H and N analysis to permit studies to generate the respective bis(imidazolium) salts.

2.5.6- Bis(imidazolium) salt synthesis A

With the functionalised pyridines **14a** and **14b** in hand, attempts were then made to generate their respective bis(imidazolium) salts. Whilst these salts were previously prepared using 1-methylimidazole, our attention was drawn to a report by Crabtree and Peris describing the use of 1-*n*-butylimidazole.[156] In this report Crabtree and Peris suggested that the poor solubility of 2,6-bis(imidazolium) pyridine salts was due to structural planarity leading to intermolecular stacking in the solid state. Chen and Lin overcame the solubility issue by treating these salts with NH_4PF_6 in an ion exchange reaction. The two PF_6^- counterions provided a ligand which was soluble in MeCN and acetone. Compounds **1c** and **10b** were prepared by this method.



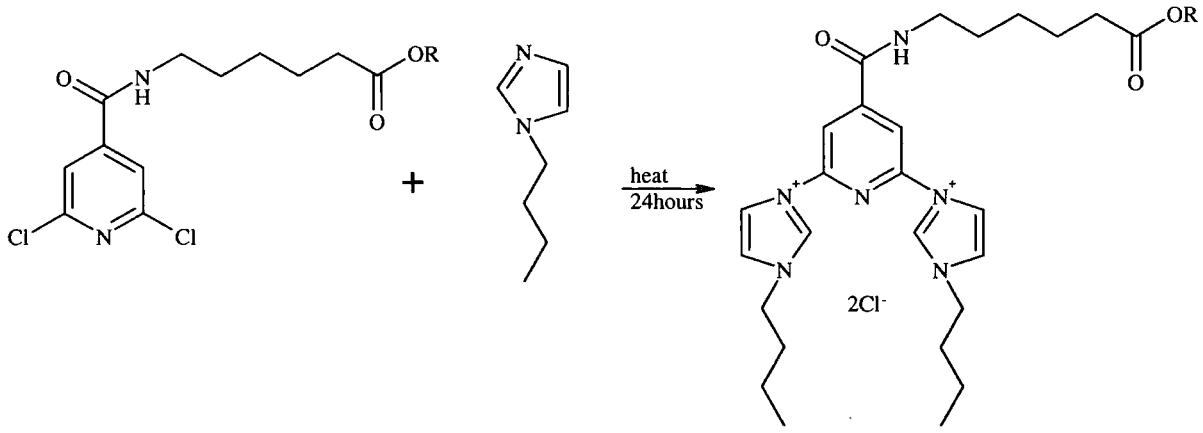
1c



10b

Crabtree and Peris reported later that using longer chain alkyl imidazoles improves solubility by breaking up intermolecular stacking. Therefore in order to evaluate the

reported effect on solubility, pyridines **14a** and **14b** were treated with 1-*n*-butylimidazole under conditions described by Crabtree and Peris, scheme 2.27.



14a R=Me
14b R=Bn

15a R=Me not isolated
15b R=Bn yield = 89%

Scheme 2.27

Methyl ester **15a** was not successfully isolated upon work-up. The solid rapidly turned brown on drying in air. Benzyl ester **15b**, however, was successfully isolated, albeit in only moderate yield initially. The technique was optimised on increasing the reaction temperature to 160°C to give bis(imidazolium) salt **15b** in 89% yield.

Analysis of **15b** by ^{1}H NMR spectroscopy recorded a shift from δ7.58 for the NCHN protons in uncoupled 1-*n*-butylimidazole to δ11.29 in product **15b** suggesting formation of the bis(imidazolium) salt. Structurally the rest of the compound was intact - the amide proton producing a characteristic broad triplet at δ9.91 and the large multiplet at δ7.31 and singlet at δ5.06 implied that the benzyl ester was stable to the reaction conditions.

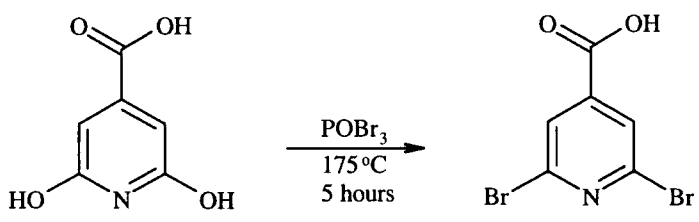
Attempts to further improve the synthesis using the microwave-accelerated methodology were unsuccessful. After heating in the microwave cavity the crude reaction was a dark brown colour. Analysis recorded numerous sp^2 aromatic and sp^3 alkyl proton signals by ^{1}H NMR spectroscopy. It was thought that 1-*n*-butylimidazole might have decomposed possibly by a β-hydrogen elimination mechanism catalysed by the chloride anion, however this hypothesis was not investigated further.

Concurrent with optimisation studies to synthesise **15b** described above, another strategy was investigated as initial results utilising 1-*n*-butylimidazole were disappointing.

As discussed previously, 2,6-dibromopyridine undergoes substitution by an imidazole more rapidly than its chlorinated counterpart. It was anticipated that 2,6-dibromoisonicotinic acid, **5d**, could be manipulated in the same manner as 2,6-dichloroisonicotinic acid; however, substitution by 1-methylimidazole or 1-*n*-butylimidazole would occur much faster.

As discussed above, it was anticipated that 2,6-dibromoisonicotinic acid would be a useful pyridine core unit. The carboxylic acid could be functionalised for attachment to a polymer support whilst metal binding functionality could be incorporated easily upon substitution with an *N*-alkylimidazole.

An investigation of literature procedures produced only one result - previous work by Fallahpour described the synthesis of 2,6-dibromoisonicotinic acid for use in palladium-catalysed Stille couplings.[159] Fallahpour heated citrazinic acid, **5c** in the presence of $POBr_3$ in an autoclave to give **5d**, scheme 2.28.



5c → 5d

yield = 57%

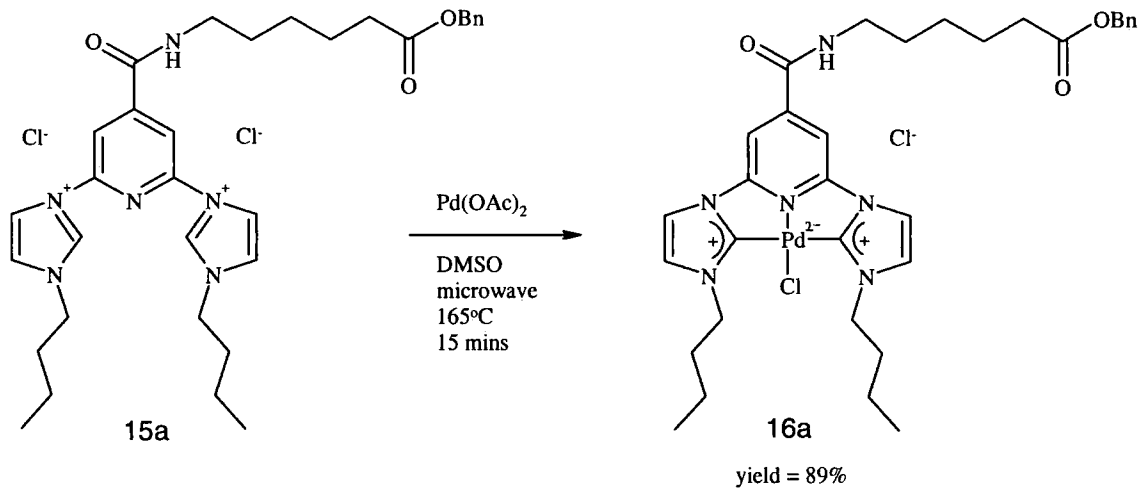
Scheme 2.28

Repeating Fallahpour's procedure gave **5d** in 57% yield. ES^+MS detected three peaks characteristic of 2 bromine atoms in the molecule: 282 (M^++2Br^{81}), 280 (M^++Br^{79}&Br^{81}), 278 (M^++2Br^{79}). Synthesis of **5d**, however, was inhibited by the expensive quantities $POBr_3$ required giving moderate yields and the hazardous work up involving HBr. Therefore after successfully optimising the synthesis of bis(imidazolium) salt **15b** from 2,6-dichloroisonicotinic acid **5a** further studies of 2,6-

dibromoisonicotinic acid were discontinued. Studies then focused on incorporating the palladium metal centre.

2.5.7- Generating palladium complex 16

With bis(imidazolium) salt **15b** in hand, complexation studies were undertaken. It was found that treating **15b** with $Pd(OAc)_2$ using the previously established microwave protocol successfully formed complex **16a** in high yield (89%), scheme 2.29.



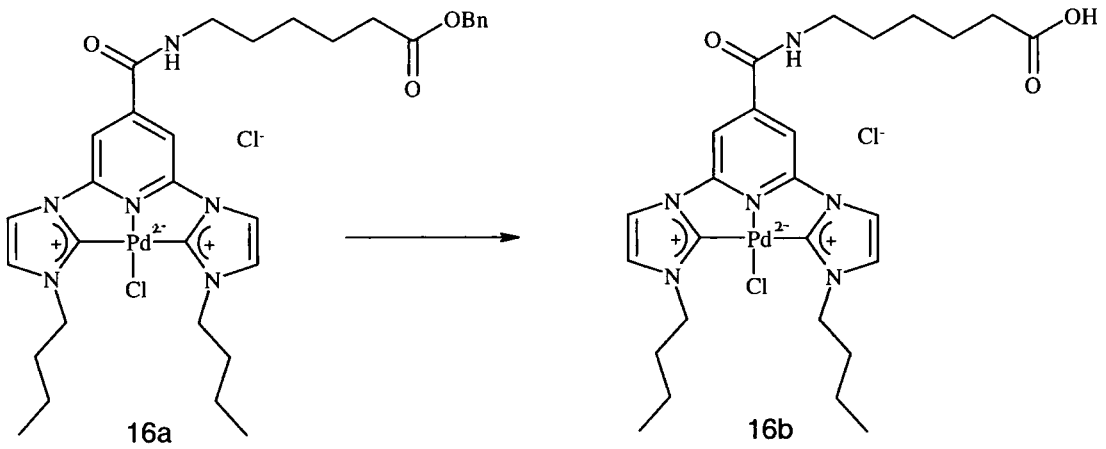
Scheme 2.29

The loss of the deshielded NCHN proton signal confirmed formation of the 1-butyl-3-pyridyl-imidazol-2-ylidene or carbene by ^1H NMR spectroscopy. Incorporation of palladium was confirmed by ES^+MS detecting the characteristic isotope signals from *m/z* 709 to 716.

Given that complex **16a** was successfully synthesised without degradation of any of the functional groups, studies could be undertaken to provide the carboxylic acid functionality required for attachment to a polymer resin.

2.5.8- Conversion of 16a into a carboxylic acid

In accordance with the synthetic strategy, base-catalysed hydrolysis or palladium-catalysed hydrogenolysis would convert **16a** into its respective carboxylic acid **16b**, scheme 2.30. This conversion would permit attachment to a functionalised polymer using peptide coupling techniques.



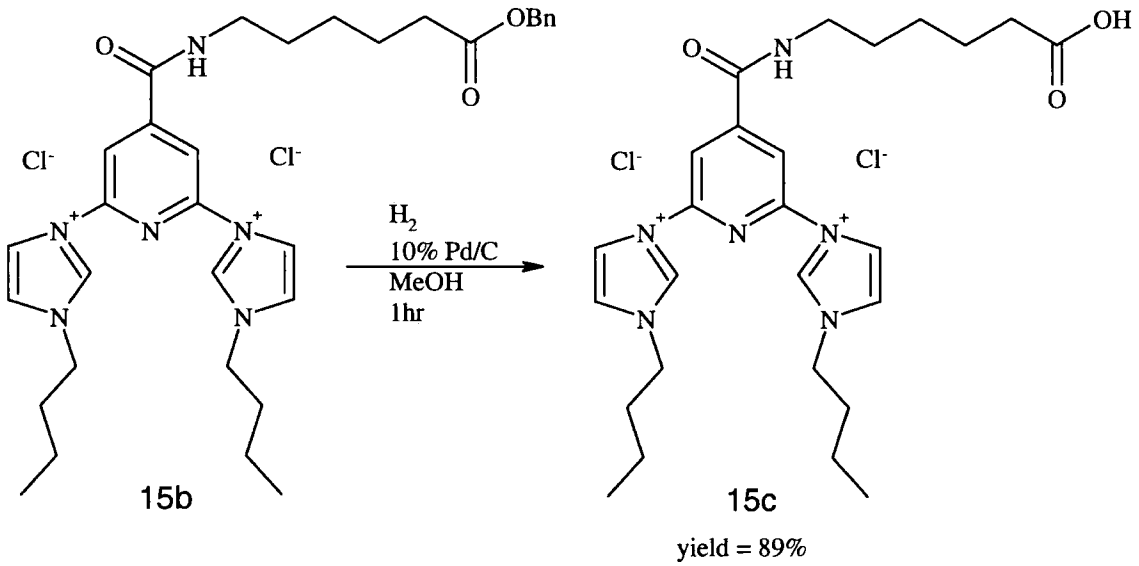
Scheme 2.30

An initial attempt to hydrolyse ester **16a** with 2N NaOH (aq) in THF resulted in the deposition of considerable amounts of Pd^0 in the reaction flask and the formation of a number of unknown products. These products could not be determined using ES^+MS and ^1H NMR spectroscopy. Therefore an alternative conversion method involving hydrogenolysis was investigated using 10% Pd/C in MeOH under 1atm H_2. However, after only 30 minutes Pd^0 deposition was observed. ES^+MS analysis confirmed imidazolium salt **15b** had in fact been regenerated and the benzyl ester was intact. Consequently a variety of conditions were subsequently investigated. Disappointingly the use of other catalysts, Wilkinson's catalyst, 5% Pt/C and complex **16** itself were all ineffective at removing the benzyl ester without Pd^0 deposition. Furthermore, the milder deprotection method of transfer hydrogenation was investigated using ammonium formate with 10% Pd/C. However, this method was also unproductive. As a result of these investigations the strategy was revised and the synthesis of bis(imidazolium) salt **15c** investigated.

2.5.9- Hydrogenolysis of bis(imidazolium) salt 15b

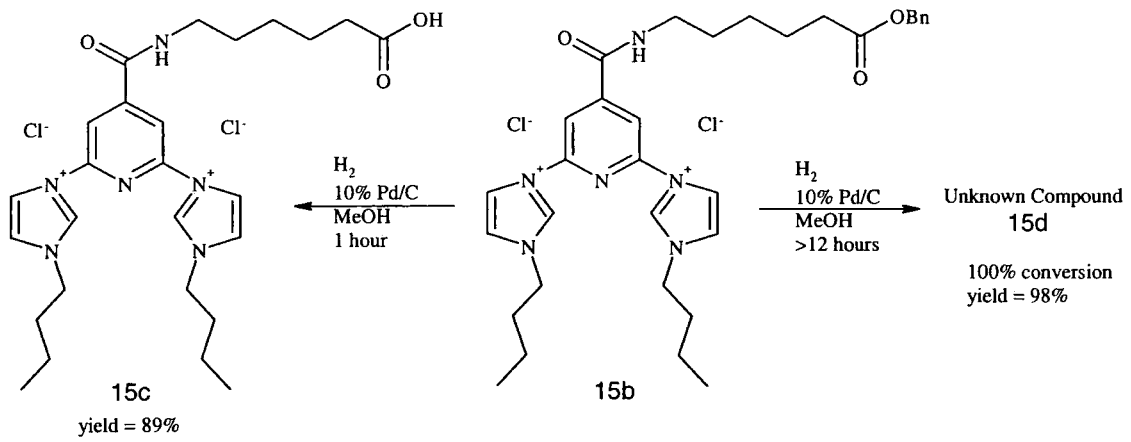
From the studies described above in order to avoid Pd^0 decomposition, carboxylic acid functionality must be generated before incorporation of the palladium centre. Consequently hydrogenolysis of bis(imidazolium) salt **15b** was investigated, scheme 2.31.

Hydrogenolysis of **15b** occurred successfully in only 1 hour yielding acid **15c** in high yield (89%). Analysis by ^1H NMR spectroscopy of the recrystallised product revealed a broad singlet at δ12.00 and the loss of the benzyl protons at δ7.31 and δ5.06. The IR spectrum of acid **15c** recorded a new carbonyl absorption peak at 1717cm^{-1} with loss of the peak at 1748cm^{-1}.



Scheme 2.31

Initial attempts to debenzylate **15b** via hydrogenolysis were performed for longer periods of time (12-18 hours) and gave an unexpected result, scheme 2.32.

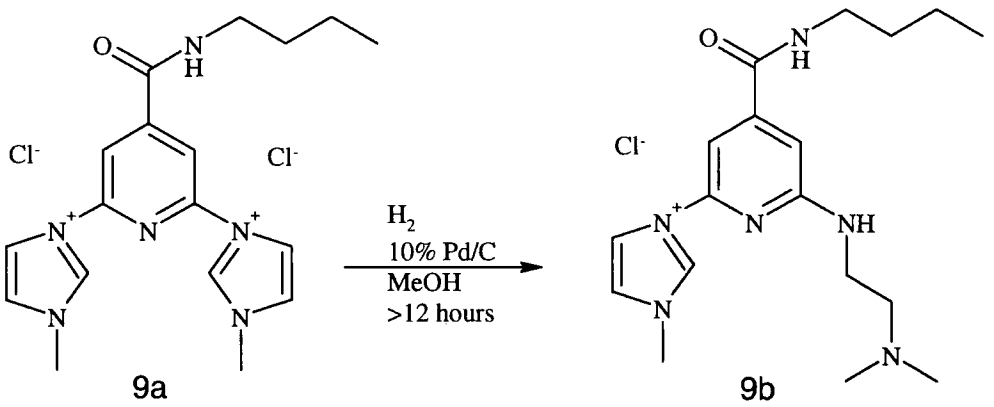


Scheme 2.32

Analysis of this crude reaction mixture by ^{1}H NMR spectroscopy was very complex. Although the benzyl ester signals (δ7.31 and δ5.06) were not present, resolving the product or products was frustrated by the large number of overlapping signals between 6 and 8 ppm and below 3 ppm. A crystalline solid was isolated after workup, however, the solid rapidly picked up atmospheric moisture forming a viscous yellow oil. Repeat recrystallisations provided a pure product by LC analysis. All methods of structural analysis were investigated. $ES^{+}MS$ showed a pure product with *m/z* 487, compound **15c**, however, has *m/z* 482. The unknown product was five mass units higher than expected. Rationalising the structure of compound **15d** by ^{1}H and ^{13}C NMR spectroscopy was hindered by the immense number of peaks.

As rationalisation of the structure was frustrated due to the compound's size and complexity especially from the *n*-butyl alkyl chains, it was thought that a smaller analogue would undergo the same transformation.

2.5.10- Hydrogenolysis of bis(imidazolium) salt 9a



Scheme 2.33

As discussed in the previous section initial attempts at debenzylation via the hydrogenolysis of bis(imidazolium) salt **15b** were obstructed by the formation of an unidentified product **15d**. To solve the structure of this product the short chain analogue **9a** derived from *N*-methylimidazole was subjected to the identical reaction conditions, scheme 2.33. It was thought that no transformation would occur as there was no benzyl ester present in the structure. Curiously after subjecting **9a** to the same conditions as **15b** ES^+MS detected a compound that was 5 mass units heavier than starting compound **9a**. Analysis by ^1H NMR spectroscopy recorded a complex spectrum similar to **15d** with several overlapping signals between 6 and 9 ppm and below 3ppm.

Like **15d**, the new product **9b** was a crystalline solid which rapidly picked up atmospheric moisture to form a viscous yellow oil; however, single crystals of **9b** were successfully isolated to permit X-ray structural analysis. The results of this analysis are shown below, figure 2.5.

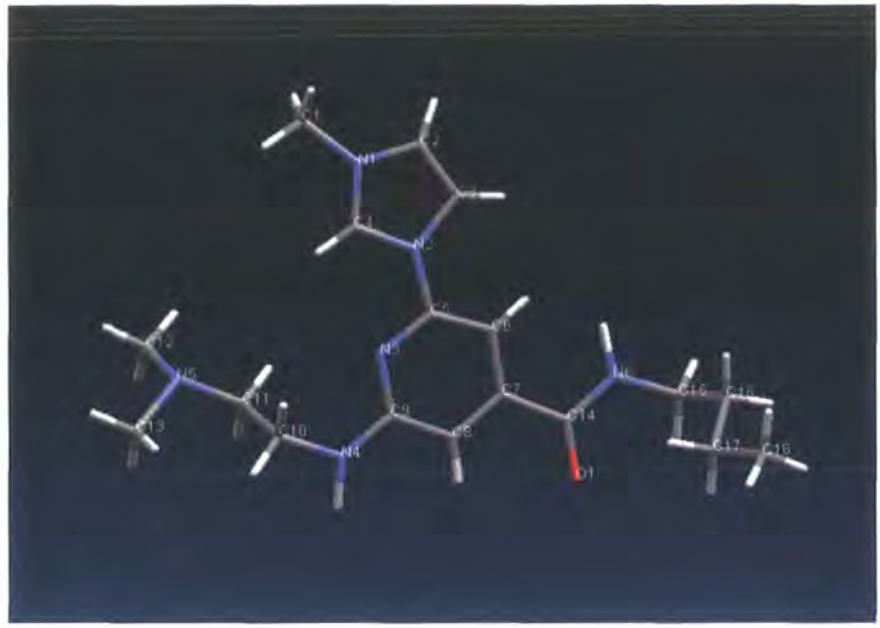
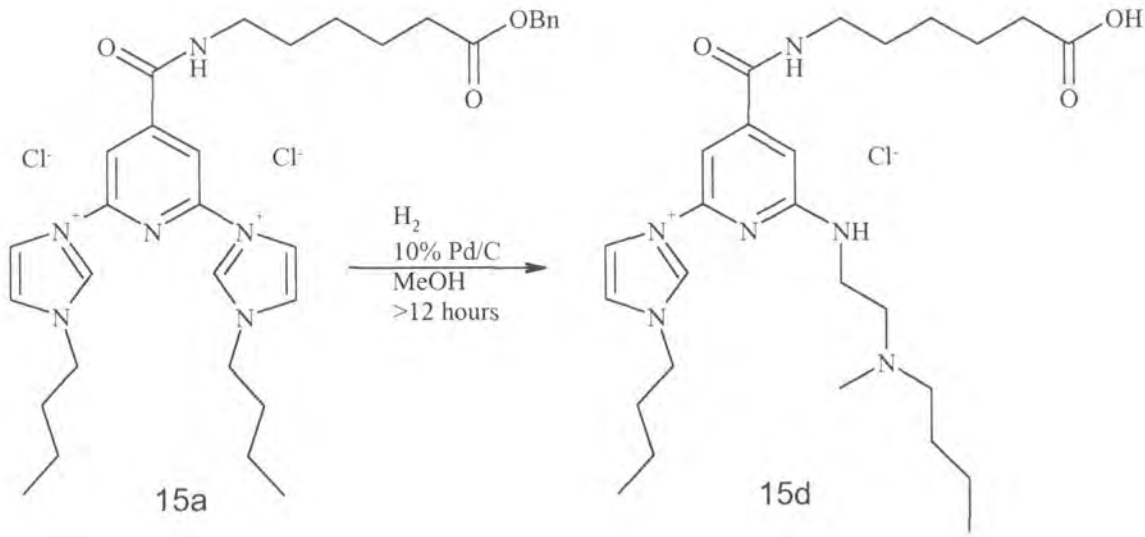


Figure 2.5

Subjecting **9a** to hydrogenolysis conditions had succeeded in breaking open one of the imidazolium rings to generate **9b**.



Scheme 2.34

Using the X-ray crystal structure of **9b** as a guide the unknown product **15d** was characterised and found to have undergone the same transformation, scheme 2.34. Subsequent studies with other bis(imidazolium) salts were of further interest. The basic unfunctionalised bis(imidazolium) salt, **1a** did not undergo the transformation under hydrogenolysis conditions suggesting that an electron donating functionality was

required at C4. However, the transformation did tolerate other groups on the imidazolium ring e.g. phenyl, benzyl and *n*-butyl, figure 2.6. In all cases only one imidazolium ring was reduced, therefore it was postulated that longer reaction times would successfully reduce both imidazolium rings.

After solving the structures of these reduced compounds and successfully isolating bis(imidazolium) salt **15c**, which could be attached to a polymer support, studies focused on incorporating the palladium metal centre.

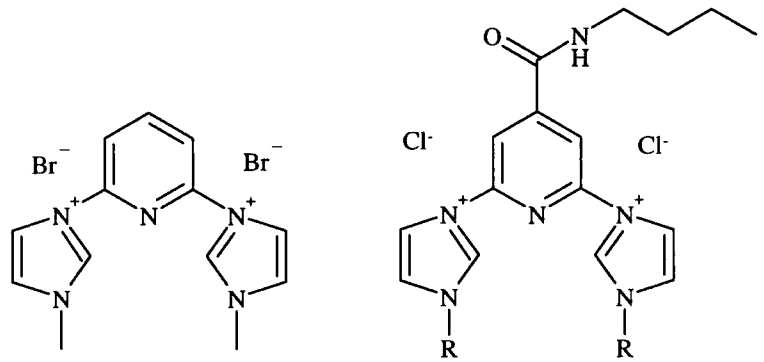
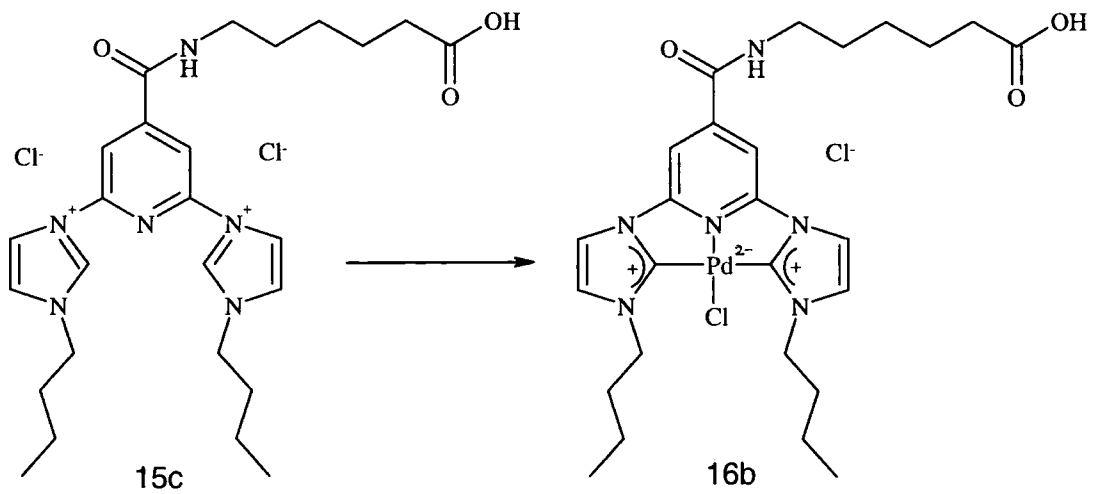


Figure 2.6

2.6- Methods for synthesising a polymer-supported complex

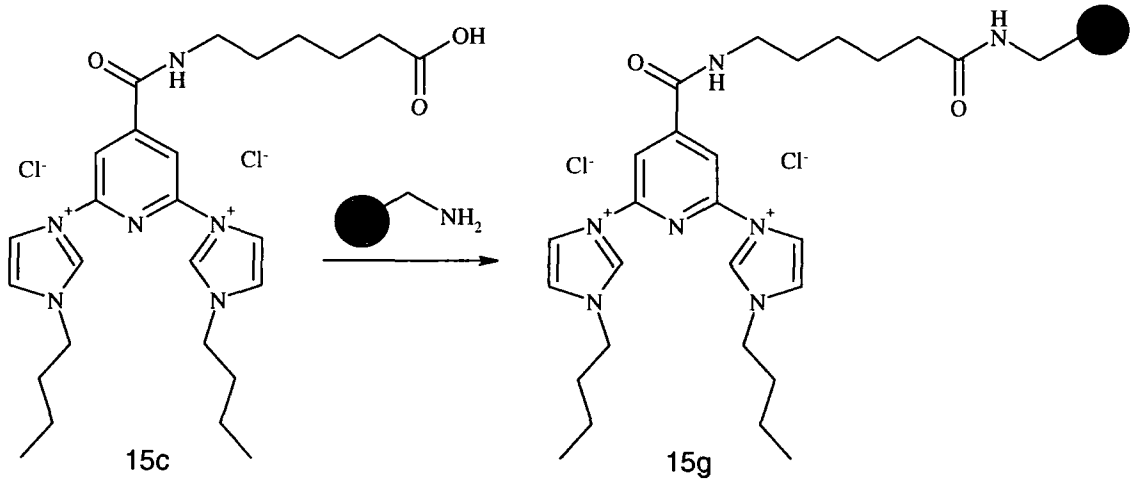


Scheme 2.35

With **15c** in hand, methods for generating complex **16b** were investigated, scheme 2.35. Attempts to generate **16b** with $Pd(OAc)_2$ using the previously established microwave assisted technique were unsuccessful, and it appeared that the acid functionality prevented complexation. Although other complexation techniques were available for example generating a silver bis(carbene) complex with Ag_2O, they were not investigated.[160]

Failure to generate complex **16b** necessitated modifying the synthetic strategy. It was proposed that **15c** could be attached to a polymer resin using peptide coupling techniques to provide an immobilised CNC ligand. Different techniques could subsequently be investigated to incorporate the palladium metal centre.

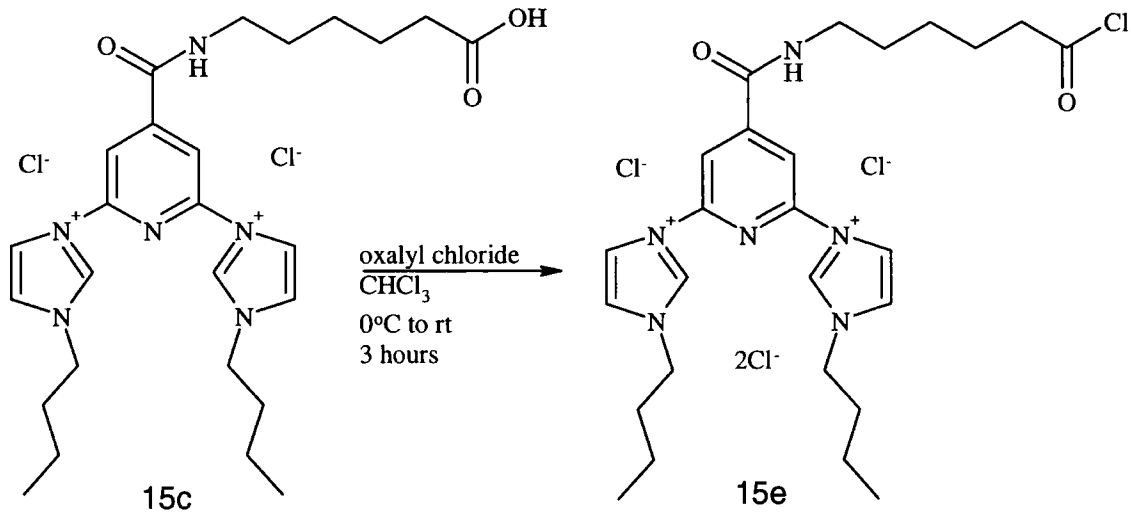
2.6.1- Immobilisation of a bis(imidazolium) salt for complexation studies



Scheme 2.36

Following the success of using an amide bond to attach a linker to the core pyridine unit, it was decided that bis(imidazolium) salt **15c** would be loaded onto an amino-functionalised resin, scheme 2.36. Consequently a range of peptide coupling techniques were investigated.

Initial attempts to load **15c** onto a low loading amino tentagel® resin with DIC or EDCI using literature techniques were only moderately successful.[161] Determining resin loading by mass was frustrated by difficulties in drying the Tentagel® resin. Complete loading determined by bromophenol blue stain was not possible even after repeating the loading procedure three times.[162] As a result it was proposed that generating the activated substrate, acid chloride **15e** would provide a more successful route for immobilisation.



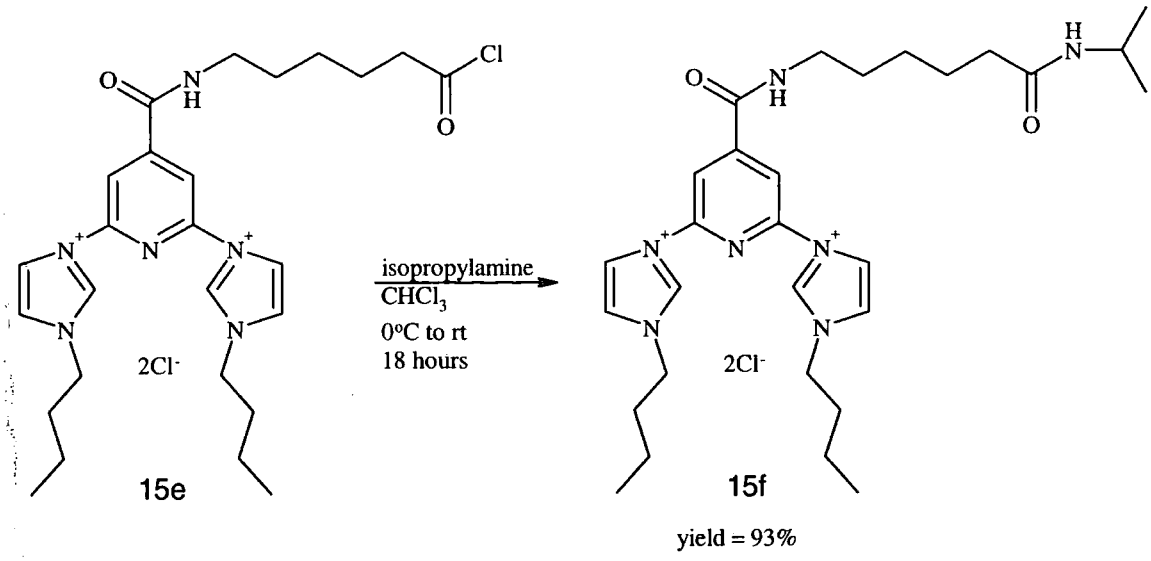
15c

15e

100% conversion

Scheme 2.37

Treatment of **15c** with oxalyl chloride gave acid chloride **15e**, scheme 2.37. IR absorbance at 1802cm^{-1} and disappearance of the carboxylic acid peak (δ12.00) by ^{1}H NMR spectroscopy confirmed 100% conversion to the acid chloride. Subsequent addition of isopropyl amine using previously described conditions (section 2.4.3) generated amide **15f** in high yield (93%), scheme 2.38.



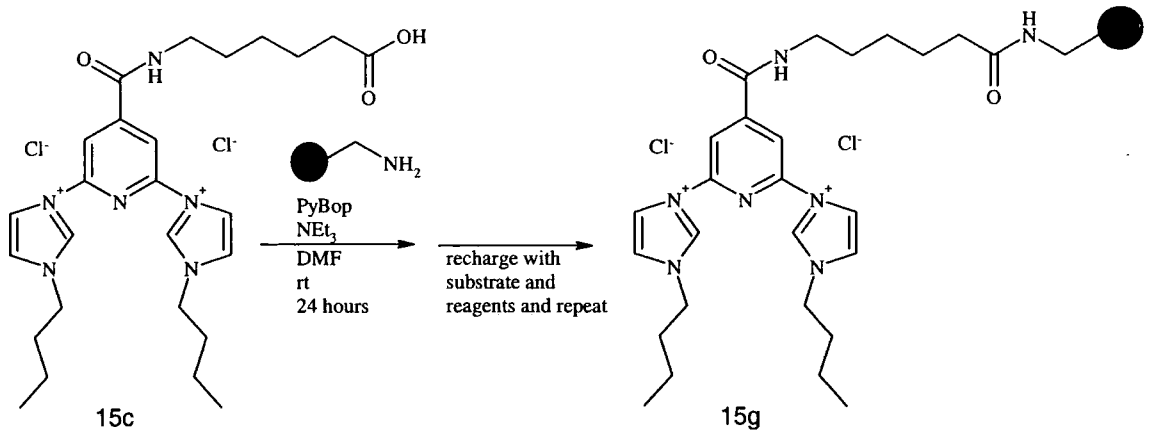
15e

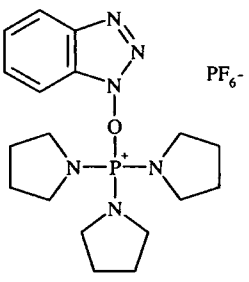
15f

yield = 93%

Scheme 2.38

Formation of **15f** was used to determine reaction conditions necessary for polymer attachment. Repeating these conditions with amino Tentagel® resin using NEt_3 as base did generate the polymer supported CNC ligand **15g** from acid chloride **15e**. However, determination of loading by mass suggested loading was minimal even after the coupling conditions were repeated.





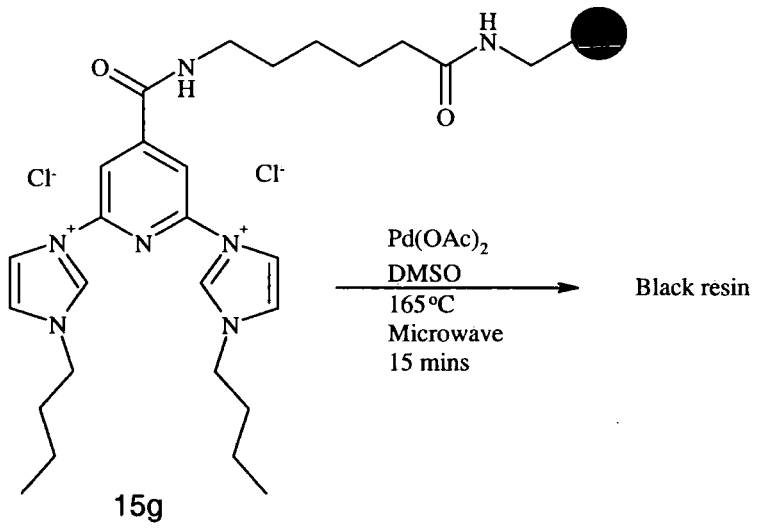
Scheme 2.39

Effective loading onto the amino resin to produce **15g** was finally accomplished by the use of PyBop® coupling reagent (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and NEt_3. Although complete loading of the resin was not accomplished at first, it was found that simply recharging the reaction tube with substrate **15c** and reagents and repeating the procedure gave 100% loading of the resin as determined by bromophenol blue stain, scheme 2.39. Methods to incorporate the palladium metal centre could now be investigated.

2.6.2- Complexation studies of a polymer-supported CNC ligand

With the immobilised CNC ligand **15g** in hand, attention turned to generating the polymer-supported palladium complex. Treatment of **15g** with $Pd(OAc)_2$ using the previously established microwave-assisted technique (section 2.3.1) appeared unsuccessful as considerable amounts of Pd^0 were deposited over the polymer resin,

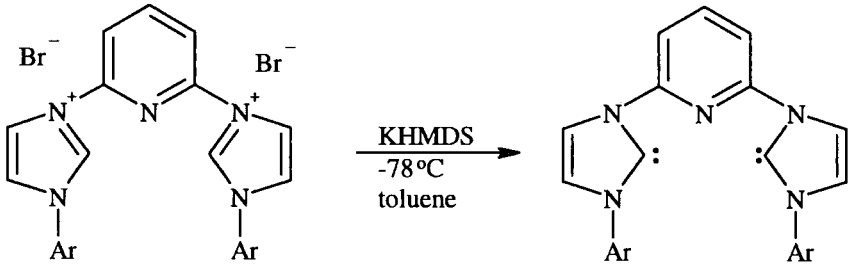
scheme 2.40. The modified resin did not swell in the solvent and therefore could not be purified. As a result further investigation of this method was discontinued.



15g

Scheme 2.40

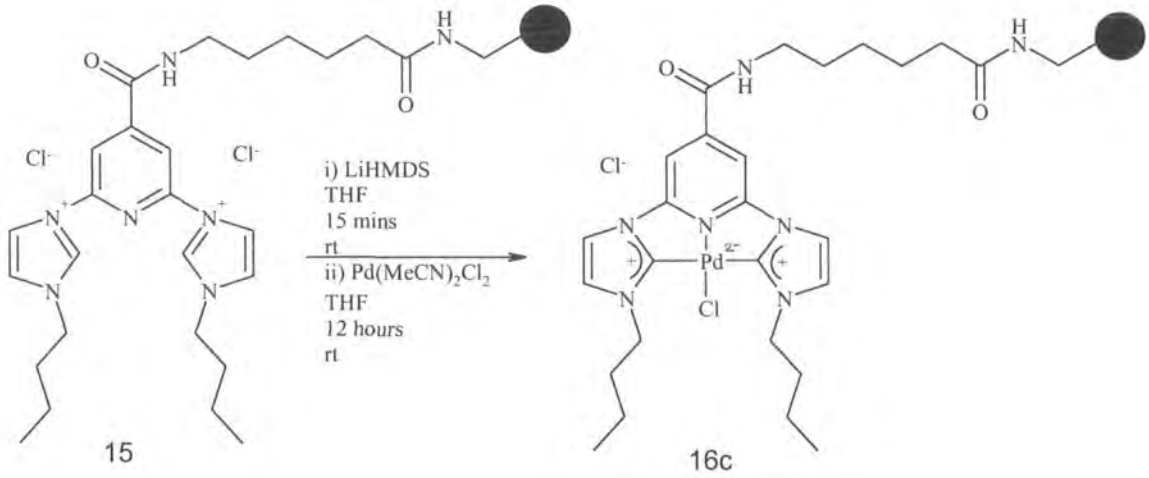
Following these difficulties attention was drawn to a report by Danopoulos *et al.* detailing the synthesis and isolation of a free bis(carbene) **18**, scheme 2.41.



17 18

Scheme 2.41

Danopoulos treated bis(imidazolium) salt **17** with the strong base KHMDS at low temperature. The resulting bis(carbene) **18** was isolated and purified by recrystallisation from toluene. The carbene was stable indefinitely at -20°C under argon and stable for 2-3 hours at room temperature.



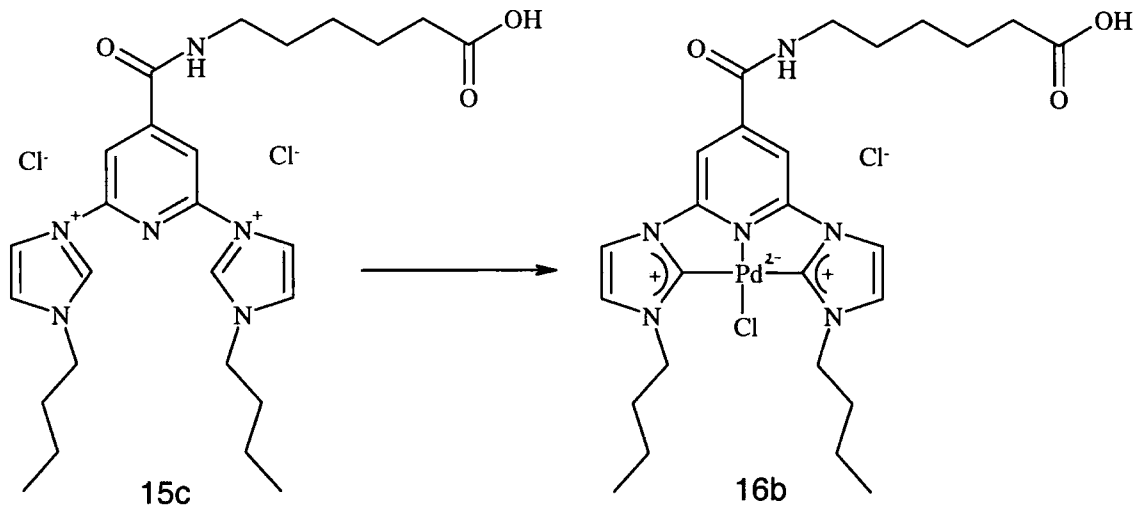
Scheme 2.42

As a result of this report, supported bis(imidazolium) salt **15g** was treated with LiHMDS and then immediately treated with a solution of $PdCl_2(MeCN)_2$ in THF, scheme 2.42. Full air sensitive techniques were maintained throughout. Unlike the previous strategy, resin **16c** swelled in solvent permitting washing and analysis. However, the black colour suggested Pd^0 was adsorbed on the resin, (*top*) figure 2.7. Analysis and catalytic activity studies of resin **16c** will be discussed in chapter 3.

Figure 2.7

2.7- Generating a polymer-supported palladium complex

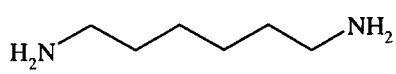
The appearance of resin **16c** suggested that considerable amounts of Pd^0 were suspended on the polymer bead. As a result alternative strategies were investigated that would permit generation of the bis(carbene) palladium complex before attachment to the polymer.



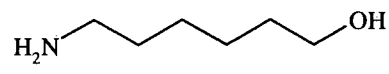
Scheme 2.43

Using bis(imidazolium) salt **15c**, methods for generating complex **16b** were investigated, scheme 2.43. However, attempts to generate **16b** with $Pd(OAc)_2$ using previously established methodology were all unsuccessful. It appeared that the acid functionality prevented complexation. Although other complexation techniques were available they were not investigated.[1]

Failure to generate complex **16b** necessitated modifying the synthetic strategy. Alternative caproate- based linkers **19** and **20** were considered, which would involve different protecting group strategies.

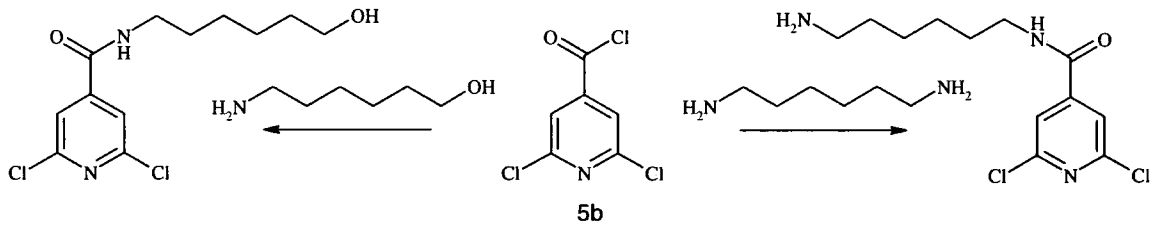


19



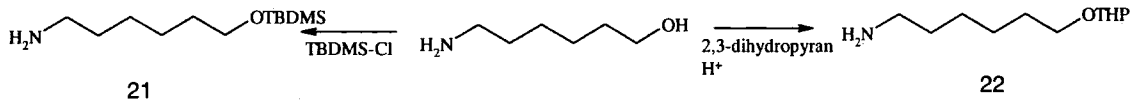
20

It was envisaged that careful control of coupling conditions with acid chloride **5b** would form only the mono-amide, scheme 2.44. However, attempts to couple **5b** with linkers **19** and **20** with high solvent dilution were unsuccessful in preventing coupling at both ends of the linker unit.



Scheme 2.44

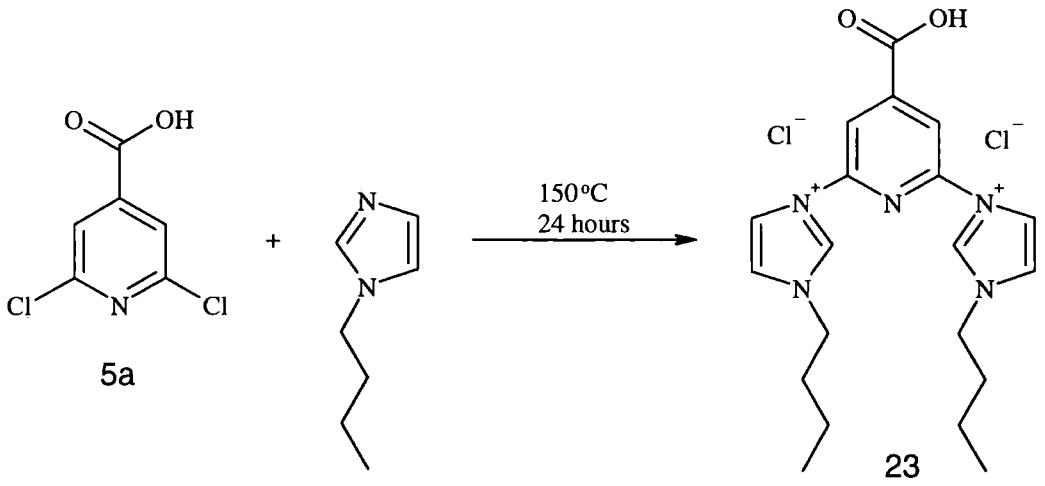
As a result, methods to protect one of the linker's functional groups were investigated. Studies focused on protecting the hydroxyl group of linker **20** by conversion to a silyl or THP ether, scheme 2.45. However, isolation and analysis of **21** and **22** was frustrated by difficulties removing unreacted starting material.



Scheme 2.45

Concurrent with the protection studies of linker **20**, another strategy to generate a functionalised palladium complex was more successful. As a result protection studies were discontinued.

2.8 Bis(imidazolium) salt synthesis B

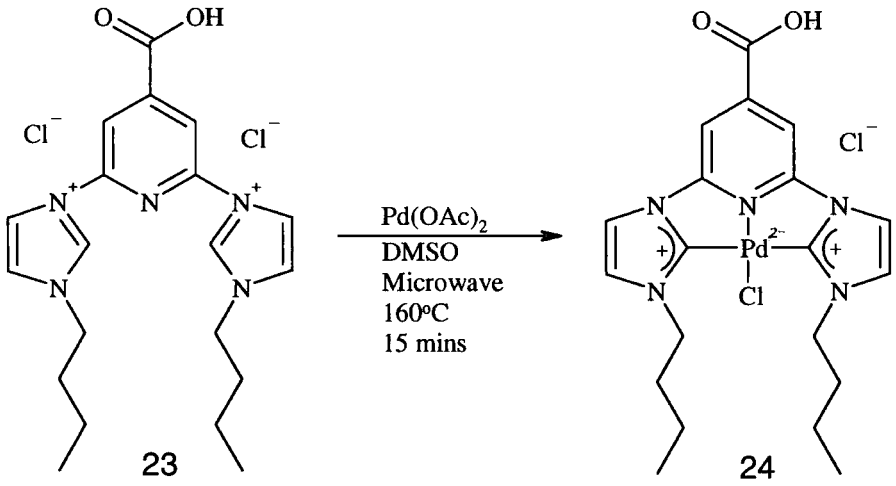


Scheme 2.46

Concomitant with protection studies involving linker unit **20**, an alternative strategy to generate a functionalised CNC bis(carbene) palladium complex was investigated. Previous work had shown that treatment of 2,6-dichloroisonicotinic acid **5a** with 1-methylimidazole generated the proposed product **7**, scheme 2.15. Further modification of **7** was hindered by poor solubility. However, Crabtree and Peris demonstrated that treatment of 2,6-dibromopyridine with 1-*n*-butylimidazole produced a bis(imidazolium) salt soluble in a range of organic solvents. As a consequence, treatment of 2,6-dichloroisonicotinic acid **5a** with 1-*n*-butylisonicotinic acid was investigated, scheme 2.46. Bis(imidazolium) salt **23** was successfully isolated after 24 hours heating at 150°C in moderate yield. Salt **23** was soluble in MeOH and could be successfully recrystallised from hot ^{i}PrOH to yield analytically pure product. Analysis of **23** by ^{1}H NMR spectroscopy recorded the deshielded NCHN proton signals at δ10.99. Although the carboxylic acid proton was not observed using ^{1}H NMR spectroscopy, the deshielded carbon signal was observed at δ164 by ^{13}C NMR spectroscopy. In addition the broad absorbance at 3100cm^{-1} using IR spectroscopy confirmed the presence of carboxylic acid functionality.

With **23** in hand, attention turned to incorporating the palladium metal centre.

2.8.1 Synthesis of complex 24



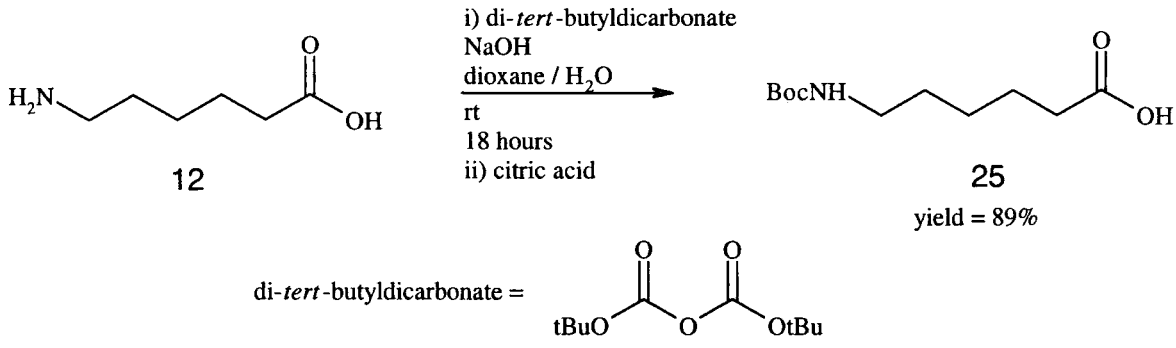
Scheme 2.47

Methods to incorporate the palladium metal centre into ligand **23** were investigated. Although alternative methods were considered initial attempts at complexation involved treatment of **23** with $Pd(OAc)_2$. Using the previously established microwave protocol, complex **24** was successfully isolated in 61% yield, scheme 2.47. Interestingly the carboxylic acid functionality at C4 did not prevent complexation unlike the results obtained during studies of salt **15c**. Analysis by ^1H NMR spectroscopy recorded the disappearance of the imidazolium NCHN proton signals indicating formation of the bis(carbene). ES^+MS detected the characteristic palladium isotope signals suggesting complexation was successful (*m/z* 506-512). Given the successful synthesis of complex **24**, a novel strategy for attachment to a functionalised resin was investigated.

2.9- (*N*-Boc)-6-aminocaproic acid

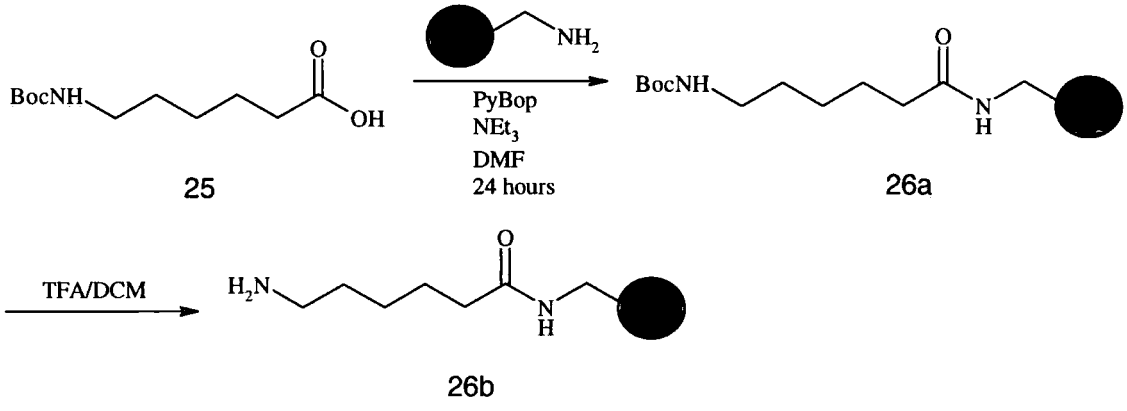
Previous strategies to attach a CNC bis-carbene palladium complex to a polymer support involved attaching a linker/spacer unit to the pyridine core. The new strategy involved attaching a linker/spacer unit to the polymer resin, then coupling complex **24** onto the modified resin. As described earlier, studies involved the use of 6-aminocaproic acid as a linker unit. In order to prevent competing polymerisation reactions during modification of the polymer resin, the linker unit 6-aminocaproic acid

12 was to be converted to its protected form, (*N*-Boc)-6-aminocaproic acid **25**, scheme 2.48.



Scheme 2.48

A search of literature procedures revealed a report by McKay *et al.* describing the preparation of *N*-Boc protected amino acids using di-*tert*-butyldicarbonate and the modification of the carboxylic acid group.[157] Their procedure was successfully employed isolating **25** in high yield (89%). Analysis of **25** confirmed successful conversion to the carbamate by observation of the singlet at δ1.44 using ^{1}H NMR spectroscopy and the strong absorbance at 1683cm^{-1} using IR spectroscopy.



Scheme 2.49

With **25** in hand, attention turned to modifying the polymer resin. Using the peptide coupling methodology previously described (2.6.1), **25** was successfully loaded onto amino Tentagel® resin to generate resin **26a**, scheme 2.49. IR spectroscopy of resin **26a** confirmed the Boc protecting group was still present by absorption at 1690cm^{-1}. The

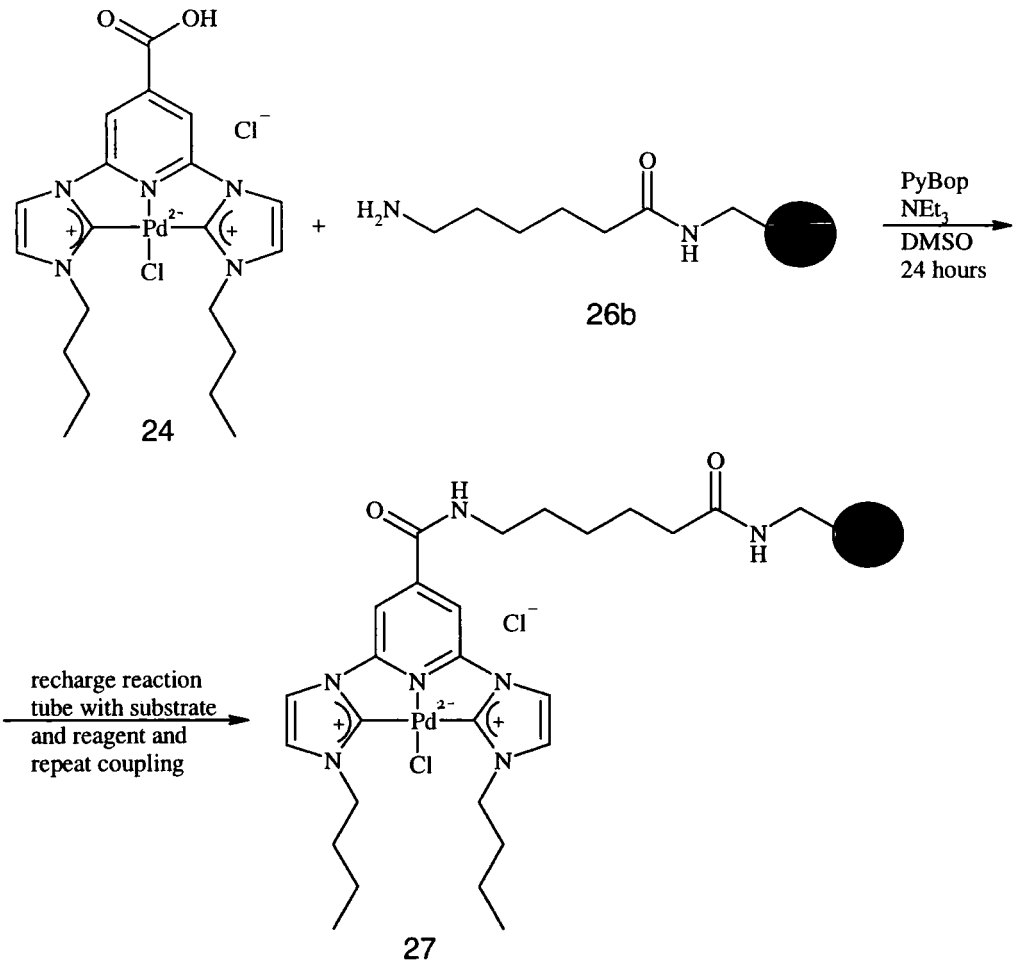
characteristic carbonyl absorption from the new amide group was observed at 1655cm^{-1} suggesting attachment to the polymer support had taken place. Complete loading of the resin was determined by bromophenol blue stain.

In order to load palladium complex **24** onto the modified resin, the Boc group was removed by shaking resin **26a** in excess TFA/DCM (1:1) for 2 hours to yield resin **26b**. Analysis of resin **26b** by IR spectroscopy recorded the disappearance of the carbamate absorption at 1690cm^{-1} and the appearance of a broad absorption at 3336cm^{-1}.

With the modified resin **26b** in hand, loading of complex **24** on the resin could be investigated.

2.9.1- Synthesis of polymer-supported complex 27

Previous work had shown how bis(imidazolium) salt **15c** could be loaded onto amino tentagel® resin using the PyBop® coupling reagent, scheme 2.39. Repeating the procedure with complex **24** and modified resin **26b** was unproductive as complex **24** was not sufficiently soluble in DMF to allow loading onto the polymer resin. However, repeating the procedure using dry DMSO as solvent was successful in partially loading the resin (determined by mass). However, repeating the procedure by recharging the reaction tube with substrate and reagents was necessary to complete full loading of the resin (determined by bromophenol blue stain) and thus generate **27**, scheme 2.50.



Scheme 2.50

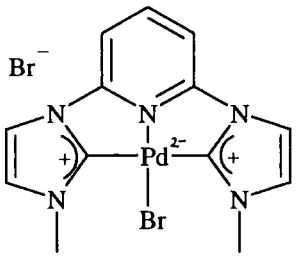
Analysis of **27** by magic angle ^{1}H NMR spectroscopy was unsuccessful. Although analysis of supported bis(imidazolium) salt **15g** was successful using this technique, the presence of the palladium centre prevented tuning of the NMR probe. As a result the most useful analytical technique was determination of palladium content by mass using ICP-MS. Although this technique did not provide information regarding the coordination of the palladium it did confirm that no excess palladium was present on the resin (0.22mmolg^{-1}, 3.04% Pd [theoretical maximum 3.05%]).

With supported complex **27** in hand, studies focused on evaluating the catalytic activity and recyclability of the resin. These studies will be discussed in the next chapter.

Chapter 3

Catalytic studies of polymer-supported CNC bis(carbene) palladium complexes

3.0- Catalysis using CNC bis(carbene) palladium complexes



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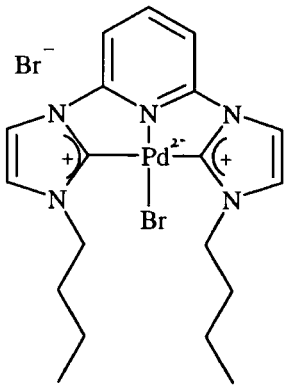
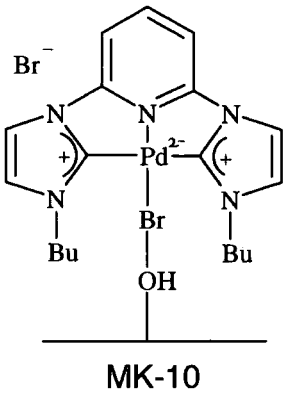


28



29

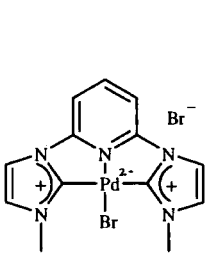
Previous work by Crabtree and Peris evaluated the catalytic activity of complexes **4** and **28**.[152,156] Further work by Peris described the immobilisation of **28** onto a commercial montmorillonite MK-10 clay support to generate **29**.[135] Peris demonstrated that **29** could be reused up to 10 times in Heck cross-coupling experiments with no loss in yield. Consequently initial studies focused on assessing the catalytic activity of the non-supported palladium complexes described in the previous chapter, complexes **4**, **10a** and **16a**. These complexes were used in cross-coupling experiments to establish optimum reaction conditions and to assess catalyst activity and stability.

3.1- Suzuki cross-coupling reactions with homogeneous catalysts

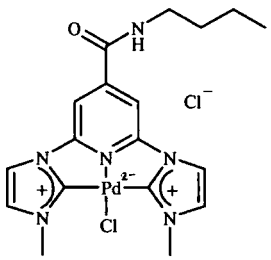
As described in the previous chapter (section 2.4.4), studies to investigate catalytic activity and the effect of functionalisation at C4 were performed. For simplicity the Suzuki coupling between 4-methoxybenzene boronic acid and iodobenzene was selected as commercially available products were available to aid analysis, scheme 3.1. Furthermore reaction conditions developed by Crabtree and Peris were employed.[156]

Although yields were determined from the average of only two runs, the amide linker in complex **10a** did appear to reduce catalytic activity (section 2.4.4). This observation conflicts with findings by Van Koten *et al.* who proposed that substitution of a phenyl

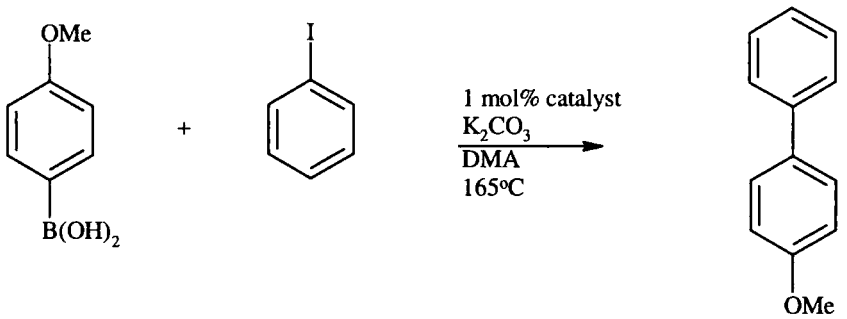
ring at the C4 position would have a negligible effect on catalytic activity.[163,164,165] Van Koten *et al.* used DFT calculations to investigate the electronic influences of the *para* substituents on the Lewis acidity of the palladium (II) centre in cationic catalyst precursors, figure 3.1.



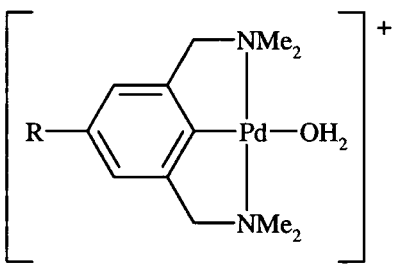
A



B



Scheme 3.1



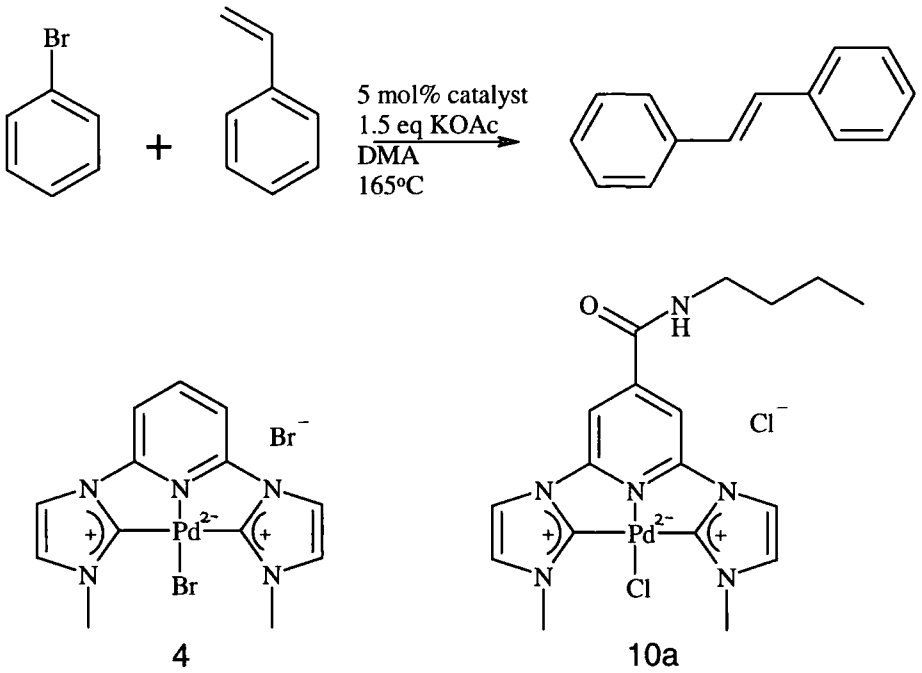
R= H
NO_2
NMe_2
C(O)Me
OCH_2Ph
Ph
$SiMe_3$

Figure 3.1

Van Koten *et al.* calculated from the Mulliken charge at the palladium (II) centres and from the Pd-OH_2 and Pd-C(aryl) distances that *para*-substituents R have only a minor electronic influence on the palladium centre and thus on its Lewis acidity. However, further practical experiments by Van Koten *et al.* suggested that the *para*-substituents alter the relative magnitude of the rate constants of the individual mechanistic steps and thus change the rate-determining step of a given reaction. Given these findings

alternative cross-coupling reactions were investigated to evaluate the effect of an amide linker unit on catalytic activity.

3.2- Heck cross-coupling reactions with homogeneous catalysts



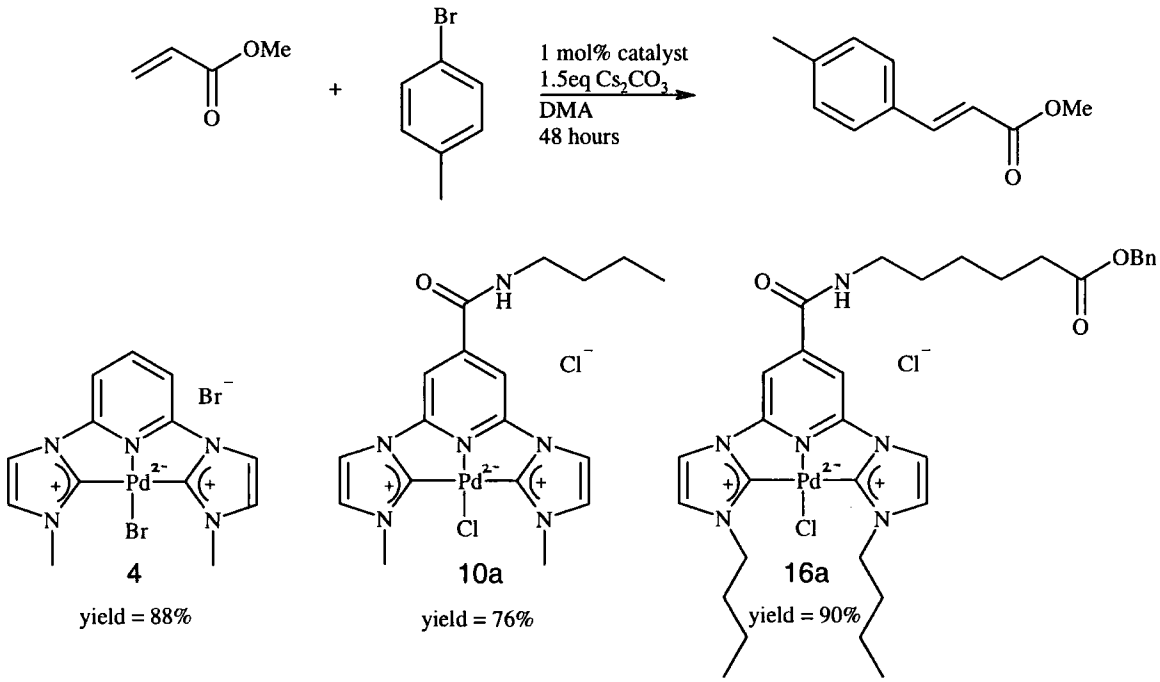
Scheme 3.2

After studies of the bis(carbene) catalysts **4** and **10a** in Suzuki reactions, alternative cross-coupling reactions were investigated to evaluate catalytic activity.

Previous work by Crabtree and Peris had shown that complex **4** was catalytically active in Heck reactions.[152] Consequently the catalytic activity of functionalised complex **10a** was evaluated using the same conditions developed by Crabtree and Peris. Catalysts **4** and **10a** were both evaluated in the Heck reaction between bromobenzene and styrene, scheme 3.2. The reaction was followed by GC using commercially available *trans*-stilbene to establish retention time. Both catalysts were catalytically active achieving full conversion of starting material in 48 hours. Isolation of the product / products, however, was hindered by difficulties in chromatography. As a result an alternative Heck reaction was investigated using bromotoluene and methyl methacrylate as substrates, scheme 3.3. On following the reaction by GC, however, full conversion of

substrate was not achieved within 48 hours. Nevertheless the *trans*-cinnamate product was successfully isolated after chromatography in high yield.

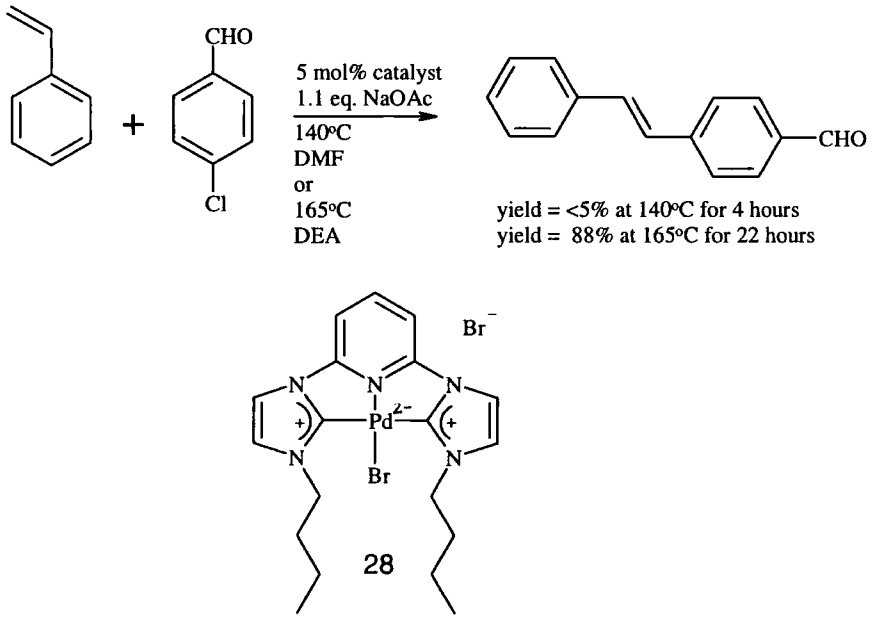
From scheme 3.3, functionalised complex **10a** was not as effective as the original complex **4** developed by Crabtree and Peris. Interestingly, however, the caproate-functionalised complex **16a** was the most active catalyst in this reaction. It was proposed that the longer *N*-alkyl chain would increase the electron-donating character of the ligand system and as a result improve catalytic activity. On the other hand the enhanced solubility of **16a** due to its longer alkyl chain may have been the determining factor for its greater catalytic activity.



Scheme 3.3

From these studies certain limitations were observed. Although yields were high in both the Suzuki and Heck reactions, studies were hindered by the poor solubility of the CNC bis(carbene) complexes. As a result only DMA was an effective solvent for the cross-coupling reactions. The use of DMF was investigated; however, no cross coupled product was detected. It was suggested that the lower boiling point of DMF hindered the reaction. Therefore the Heck reaction in scheme 3.3 was repeated using catalyst **4** but at the lower temperature of 145°C. No cross coupled product was detected by GC.

Interestingly these findings conflict with those by Crabtree and Peris who used the CNC bis(carbene) complex **28** in the Heck reaction between *para*-chlorobenzaldehyde and styrene.[156] The stilbene product was formed, albeit in low yield, even when the reaction was run at 140°C, scheme 3.4. Crabtree and Peris then investigated the same reaction using DEA as solvent under non-reflux conditions at 165°C. The cross coupled product was formed in high yield even though no measures were taken to exclude air or moisture from the system. From this research it was determined that high temperatures are necessary when using tridentate CNC bis(carbene) palladium complexes as catalysts for cross-coupling reactions.



Scheme 3.4

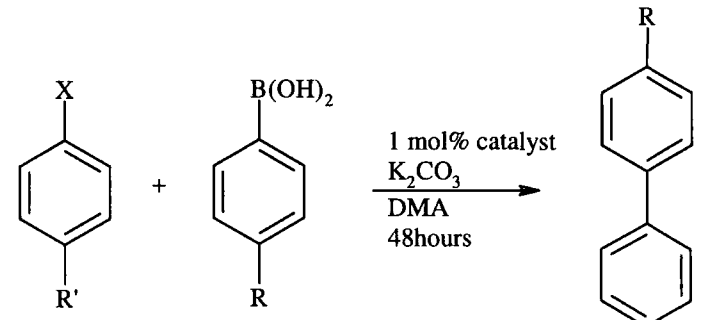
Following the research by Crabtree and Peris who successfully used aryl chlorides in Heck reactions, the Heck reaction in scheme 3.4 was repeated using chlorobenzene and catalyst **16a**. Unfortunately no coupled product was formed even after heating for 72 hours. Further investigation using activated aryl chlorides was not pursued.

After successfully establishing the required reaction conditions for Suzuki and Heck reactions involving the palladium catalysts **4**, **10a** and **16a**, the catalytic activity of the supported catalysts developed in the previous chapter was then evaluated.

3.3- Polymer-supported palladium catalysis

Following successful studies with homogeneous tridentate CNC bis(carbene) catalysts, the catalytic activity of supported complexes **16c** and **27** was investigated. The two alternative syntheses of these polymer-supported CNC bis(carbene) palladium complexes were described in the previous chapter (sections 2.6.2 and 2.9.1). Polymer-supported complex **16c** was formed by complexation of a solid-supported ligand, scheme 2.38, whilst polymer supported-complex **27** was formed by attachment of a palladium complex to a solid support, scheme 2.46.

3.3.1- Suzuki cross-coupling reactions using supported catalysts 16c and 27



Scheme 3.5

Initial studies focused on evaluating the catalytic activity of polymer-supported complexes **16c** and **27** in Suzuki cross-coupling reactions, following the reactions by GC, scheme 3.5. Yields were determined by GC using diethylene glycol di-*tert*-butyl ether as an internal standard and are shown below, table 3.1.

Entry	R=	R'=	X=	Catalyst	Yield (%)
1	Me	H	Cl	**16c**	0
2	Me	H	Cl	**27**	0
3	Me	H	Br	**16c**	55

4	Me	H	Br	**27**	61
5	OMe	H	Br	**16c**	55
6	OMe	H	Br	**27**	57
7	OMe	H	I	**16c**	56
8	OMe	H	I	**27**	95
9	OMe	COOMe	I	**27**	98
10	OMe	NMe_2	I	**27**	98
11	OMe	Br	I	**27**	93*

*= yield based on boronic acid

Table 3.1

As expected, the polymer-supported catalysts were unable to catalyse the cross-coupling with chlorobenzene, entries 1 and 2. This follows the similar observation when homogeneous catalysts were investigated (section 3.2). However when the more active bromobenzene was used, the cross-coupling reaction did occur, albeit in moderate yield only, entries 3 - 6. Interestingly when iodobenzene was used (which is a more reactive electrophile in cross-coupling reactions), yields only increased when catalyst **27** was used, entries 7 and 8.

With the aim of assessing the versatility of the catalytic system, several aryl iodides were investigated. Surprisingly the activated aryl iodide, entry 9, and deactivated aryl iodide, entry 10, were both converted to the biphenyl product in exactly the same yield. However, it was thought that 1-bromo-4-iodobenzene would undergo cross-coupling at the iodine position only, entry 11. Analysis of the isolated product by GCMS revealed a 1:1 ratio of two biphenyls, figure 3.2.

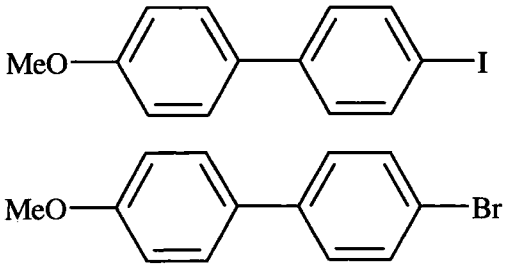
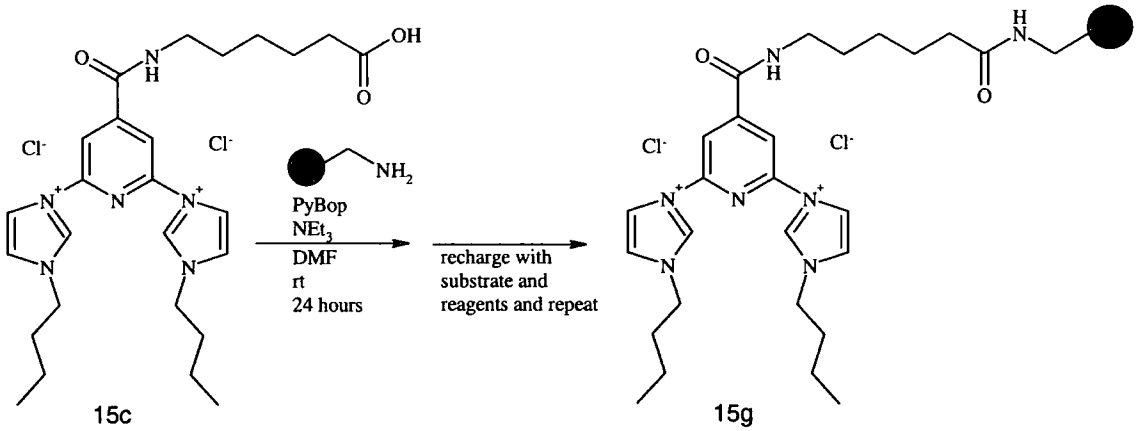


Figure 3.2

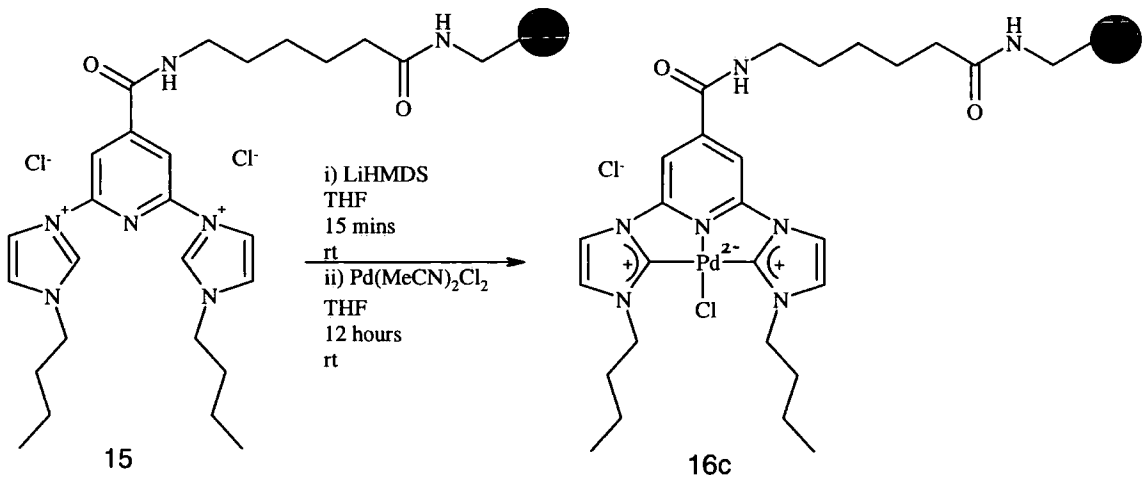
The enhanced activity of catalyst **27** over catalyst **16c** can be explained by the difference in how the two catalysts were synthesised. Catalyst **16c** was prepared by

attaching bis(imidazolium) salt **15c** to an amino-functionalised resin to give the immobilised bis(imidazolium) salt **15g**, scheme 3.6. **15g** was then treated with base to generate the supported free carbene and subsequently treated with a solution of $PdCl_2(MeCN)_2$. Simple ligand exchange would generate the palladium complex **16c**, scheme 3.7.



100% loading as determined by bromophenol blue

Scheme 3.6

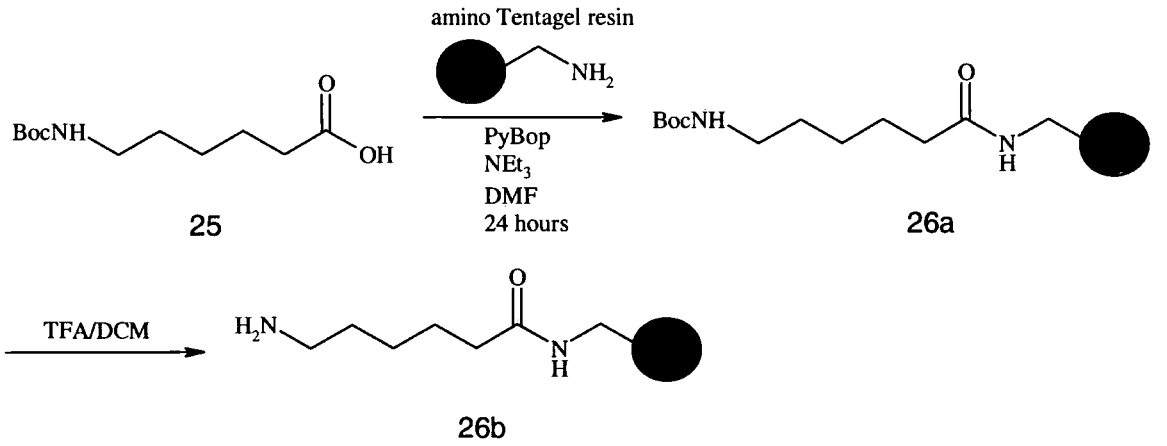


conversion and yield not determined

Scheme 3.7

Although analysis of immobilised bis(imidazolium) salt **15g** was successful using magic angle ^1H NMR spectroscopy, analysis of catalyst **16c** using the same technique was unsuccessful. However, elemental analysis determined the palladium content of catalyst **16c** to be significantly higher than expected (found 5.09%, calculated 3.04%).

This observation suggested that significant quantities of Pd^0 were deposited throughout the resin indicating that catalyst **16c** was essentially free Pd^0 absorbed on an amino functionalised resin. On the other hand, elemental analysis of catalyst **27** showed exactly the correct palladium content suggesting no excess Pd^0 was absorbed on the resin. Analysis of catalyst **27** by magic angle ^1H NMR spectroscopy was again unsuccessful, although the technique was successful in analysing all of the synthetic modifications to the amino-functionalised resin, scheme 3.8.

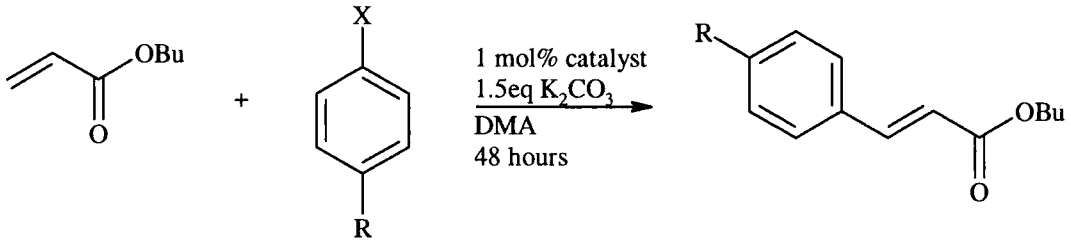


Scheme 3.8

Analysis of the catalyst precursor, the unbound CNC bis(carbene) palladium complex **24** was successful, however, by ^1H NMR spectroscopy and ES^+MS, suggesting that a palladium centre was successfully bound by the CNC bis(carbene) ligand system. These observations are clear to see on looking at the physical appearance of the two catalysts, figure 2.7. Catalyst **16c** is the black coloured resin at the top of the picture whilst catalyst **27** is the yellow resin at the bottom.

After successful studies of Suzuki cross-coupling reactions the Heck cross-coupling reaction was then investigated.

3.3.2- Heck cross-coupling reactions using supported catalysts 16c and 27



X=Br, I
R=H, COOMe, NMe_2, Br

Scheme 3.9

As discussed previously (section 3.2), the Heck cross-coupling reaction was investigated using homogeneous CNC bis(carbene) catalysts. However, initial attempts to repeat reaction conditions in scheme 3.3 with polymer-supported catalysts **16c** and **27** were unsuccessful in forming the cinnamate product. Consequently the system was modified using the less volatile *n*-butylacrylate as substrate and K_2CO_3 as base, scheme 3.9. As a result of these modifications the catalytic activity of catalysts **16c** and **27** could be successfully investigated, table 3.2. The reactions were followed by GC and all products underwent purification by FCC with silica gel to determine isolated yields.

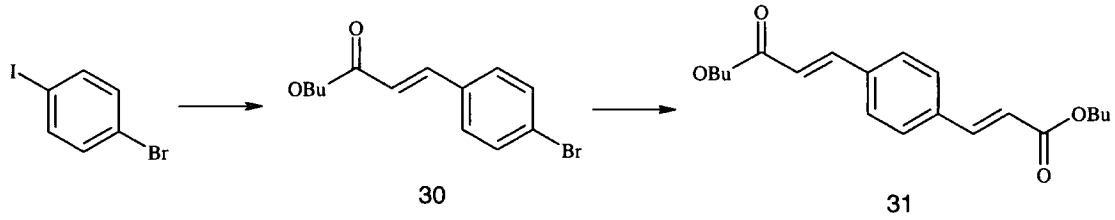
Entry	R	X	Catalyst	Yield (%)
1	H	Br	**16c**	31
2	H	Br	**27**	70
3	H	I	**16c**	53
4	H	I	**27**	87
5	COOMe	I	**27**	94
6	NMe_2	I	**27**	93
7	Br	I	**27**	97*

* = yield based on *n*-butylacrylate

Table 3.2

To isolate the cinnamate product in high yield it was necessary to use more active aryl iodides as yields were significantly lower with aryl bromides, entries 1 and 2. In

accordance with studies of the Suzuki reaction, no difference was observed in the cross-coupling of activated and deactivated aryl iodides, entries 5 and 6.



Scheme 3.10

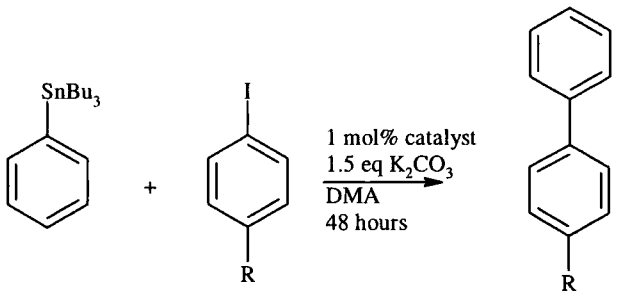
Interestingly, when 1-bromo-4-iodobenzene was used, the monocoupled product **30** was not isolated as had been predicted. In fact the doubly substituted compound **31** was isolated upon reaction work-up. Rationalising the formation of this product can be done by considering the formation of the bromocinnamate **30**, scheme 3.10. At first, Heck coupling will occur at the reactive iodine moiety of 1-bromo-4-iodobenzene. The resulting cinnamate **30** is in fact an activated aryl bromide, consequently the molecule immediately undergoes a second Heck coupling reaction to form compound **31**.

In accordance with studies of the Suzuki reaction in the previous section, catalyst **27** was significantly more active than its counterpart catalyst **16c**.

To further evaluate the catalytic activity of the polymer-supported catalysts, the Stille reaction was then investigated.

3.3.3- Stille cross-coupling reactions using supported catalysts 16c and 27

Studies to investigate catalytic activity in Stille cross-coupling reactions were performed using the same reaction conditions developed in previous cross-coupling reactions (sections 3.3.1 and 3.3.2). However, as a result of the poor activity of catalyst **16c** in previous studies, catalytic studies of the Stille reaction were investigated using catalyst **27** only.



R= COOMe, NMe_2, Br

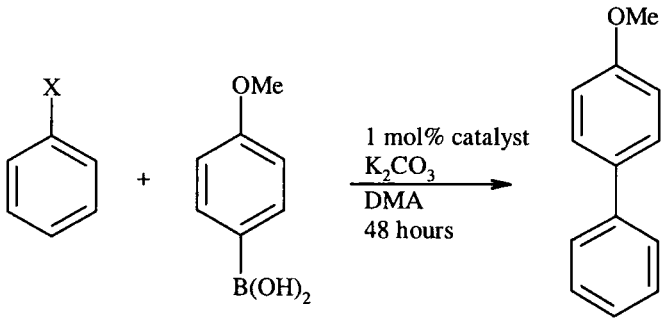
Scheme 3.11

After heating for 48 hours the reaction mixtures underwent an aqueous work-up and treatment with KF to remove tin residues. In all cases isolating the pure cross-coupled product was hindered by separating the large number of products with very similar R_f values. Consequently isolated yields were not determined. Further analysis of the reaction mixtures by GCMS showed significant quantities of the homocoupled biphenyl product. Whilst the desired biphenyl products had been formed, they were only present in minor to moderate quantities. As a result of these poor results further optimisation of the reaction conditions was discontinued and attention turned to investigating the longevity of the polymer-supported catalysts.

3.4- Recycling studies with supported catalysts 16c and 27

As discussed in chapter 1 the main purpose of developing a supported catalyst is that it can be easily separated from the reaction media and recycled. Therefore attention turned from investigating different substrates to evaluating the longevity and recyclability of the polymer-supported catalysts. Initial studies concentrated on evaluating catalyst longevity in Suzuki cross-coupling reactions.

3.4.1- The reuse of polymer-supported catalysts in successive Suzuki reactions



Scheme 3.12

Having demonstrated that catalytic activity remained after immobilising the CNC bis(carbene) palladium complex, attention turned to investigating the viability of recycling and reuse of the polymer-supported catalysts in Suzuki cross-coupling reactions, scheme 3.12. The results of these studies are shown below, table 3.3. The yield shown is the average from repeat runs before a 5% loss in overall yield.

Entry	X	Catalyst	Recycles[a]	Yield (%)[b]
1	Br	16c	2	55[c]
2	Br	27	4	55[c]
3	I	16c	2	56[c]
4	I	27	5	95[c]
5	I	27	>14	95[d]
6	I	27	>4	98[e]
7	I	27	>12	95[f]

[a] Recycles before >5% drop in isolated yield

[b] Yield of purified product after chromatography

[c] Reactions carried out in air

[d] Reactions carried out under argon

[e] Reactions carried out in 24 hours with 20 mol% NBu_4Br added

[f] Reactions carried out using microwave heating, 170°C, 10 mins, 30W

Table 3.3

Following heating for 48 hours, the reaction mixture was filtered and the catalytic resin washed with THF and water (1:1) to remove excess substrate and any precipitated salts. The resin was then dried under vacuum before reuse in a successive Suzuki reaction. Initial studies ran the reaction under an atmosphere of air, however only limited repeat reactions were possible before the overall yield began to fall, entries 1-4. It was

consequently found that purging the reaction mixture with argon for approximately 30 minutes prior to heating circumvented this problem. Under the modified conditions catalyst **27** was far more robust with no drop in activity after 14 recycles, entry 5. However, at this point certain limitations were observed: the lower activity of aryl bromides and the apparent need for high temperatures and long reaction times. To overcome the long reaction time, two alternative methods were investigated.

Previous reports in literature have highlighted the use of alkylammonium bromides as additives in cross-coupling reactions involving aryl chlorides.[27,28,29,156] According to the literature; the use of these additives significantly increases the activity of the catalytic system allowing high turnovers with aryl chlorides. With this in mind it was thought that the addition of 20 mol% NBu_4Br may facilitate the Suzuki reaction of aryl iodides. Indeed after modification the reaction was complete in only 24 hours and no homocoupling of the boronic acid substrate was observed, entry 6.

Considering the choice of solvent and the presence of an organometallic component in the catalytic system, it was proposed that the system would be accelerated under microwave radiation. Consequently the reaction was subjected to microwave heating forming the biphenyl product in high yield after only 10 minutes (heating at 170°C), entry 7. The reaction was subsequently repeated reusing the catalyst with no diminution in yield even after a minimum of 12 recycles.

Throughout the investigation 1 mol% catalyst was used. This reflects the ease in handling the quantity of resin (~50mg) on the scale of the reactions investigated. However, microwave-accelerated Suzuki reactions were repeated three times using lower catalyst loadings (0.5%, 0.1%) with no loss in yield and apparent recyclability.

During recycling studies, table 3.3, the product mixtures (entries 4 and 5) were analysed by ICP-MS in order to determine levels of palladium leaching, the results of which are shown below in tables 3.4 (entry 4 from table 3.3) and 3.5 (entry 5 from table 3.3).

	Run 1	2	3	4	5
Pd detected (ppb)	3.10		1.96		0.16
Final conc. ng/ml	1548		979		82

Suzuki reaction performed in air

Table 3.4

	Run 1	2	3	4	5	6	7
Pd detected (ppb)	0.90	0.62		0.30		0.07	
Final conc. ng/ml	450	312		152		36	
	8	**9**	**10**	**11**	**12**	**13**	**14**
Pd detected (ppb)		0.06		0.04		0.05	
Final conc. ng/ml		28		22		23	

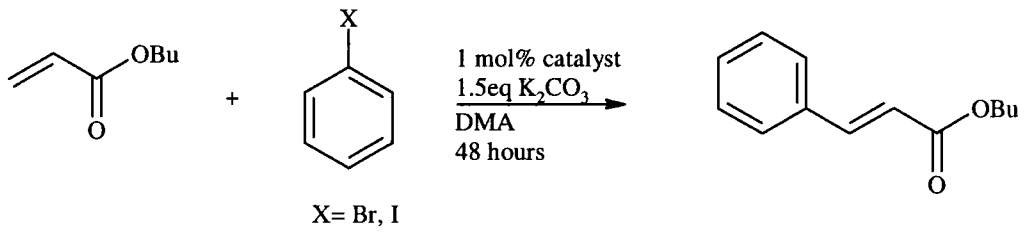
Suzuki reaction performed under argon

Table 3.5

The greatest levels of palladium leaching were after the initial run (~0.9-3.0ppb) with consequent runs showing only minor levels of leaching (~0.05ppb).

Following evaluation of catalyst longevity in Suzuki cross-coupling reactions attention turned to investigating the Heck olefination of aryl halides using the polymer-supported catalysts **16c** and **27**.

3.4.2- The recycling of supported catalysts in successive Heck reactions



Scheme 3.13

Having successfully investigated the viability of recycling and reuse of the polymer-supported catalysts in Suzuki cross-coupling reactions, attention turned to investigating the same factors in Heck cross-coupling reactions, scheme 3.13. The results of these

studies are shown below, table 3.6. The yield shown is the average from repeat runs before a 5% loss in overall yield.

Compared to studies of the Suzuki reaction in the previous section, the yields in Heck reaction studies were lower, necessitating the use of aryl iodides for successful formation of the cinnamate product. In addition in all Heck reactions only the *trans*-cinnamate product was observed.
Following heating for 48 hours, the reaction mixture was filtered and the catalytic resin washed with THF and water (1:1) to remove excess substrate and any precipitated salts. The resin was then dried under vacuum before reuse in a successive Heck reaction.

In accordance with studies of the Suzuki reaction, in initial studies the reaction was run under an atmosphere of air, however only limited repeat reactions were possible before the overall yield began to fall, entries 1-4. In line with Suzuki studies it was consequently found that purging the reaction mixture with argon for approximately 30 minutes prior to heating circumvented this problem. Under the modified conditions catalyst **27** was far more robust with no drop in activity after 14 recycles, entry 5.

Entry	X	Catalyst	Recycles[a]	Yield%[b]
1	Br	**16c**	2	27[c]
2	Br	**27**	3	66[c]
3	I	**16c**	3	53[c]
4	I	**27**	8	82[c]
5	I	**27**	>14	83[d]

[a] Recycles before >5% drop in isolated yield

[b] Yield of purified product after chromatography

[c] Reactions carried out in air

[d] Reactions carried out under argon

Table 3.6

With the aim of reducing the relatively long reaction time the reaction was subjected to microwave heating. However, whilst the technique was successful with Suzuki cross-couplings, microwave heating was unproductive in Heck cross-couplings.

In accordance with studies in the previous section, during these recycling studies, table 3.6, the product mixtures (entries 4 and 5) were analysed by ICP-MS in order to determine levels of palladium leaching, the results of which are shown below in tables 3.7 (entry 4 from table 3.6) and 3.8 (entry 5 from table 3.6).

	Run 1	2	3	4	5	6	7	8
Pd detected (ppb)	3.59		1.92		0.33		0.15	
Final conc. ng/ml	1795		961		166		73	

Heck reaction performed in air

Table 3.7

	Run 1	2	3	4	5	6	7
Pd detected (ppb)	0.88	0.86		0.29		0.05	
Final conc. ng/ml	442	432		145		23	
	8	**9**	**10**	**11**	**12**	**13**	**14**
Pd detected (ppb)		0.04		0.04		0.03	
Final conc. ng/ml		20		21		16	

Heck reaction performed under argon

Table 3.8

In accordance with recycling studies of the Suzuki reaction discussed above, the greatest levels of palladium leaching were after the initial run (~0.9 – 3.5ppb) with minor levels of leaching in consequent runs (~0.04ppb).

Further analysis of the catalytic studies will be discussed in the next section.

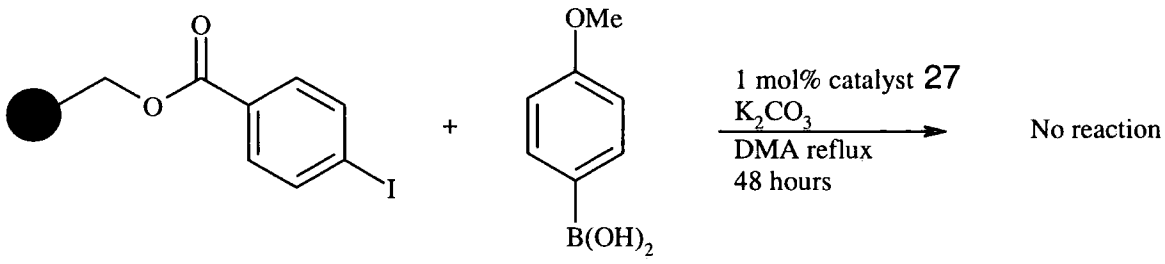
3.4.3- Conclusions

As discussed above the catalytic activity of two supported palladium catalysts was investigated. These catalysts were prepared using two distinct strategies - complexation of a polymer-supported ligand, catalyst **16c** and immobilisation of a palladium

complex, catalyst **27**. During the course of these studies it was rapidly noticed that catalyst **16c** was significantly less active than its counterpart catalyst **27**. For example whilst both catalysts successfully completed cross-coupling reactions with aryl bromides and iodides, there was a disparity in isolated yields, tables 3.3 and 3.6. Likewise during recycling studies it was noticed that the lifetime of catalyst **16c** was significantly shorter than that of catalyst **27**. From these observations and the physical appearance of catalyst **16c**, figure 3.3 it was suggested that there were significant quantities of Pd^0 adsorbed on the polymer resin with little or none of the CNC bis(carbene) palladium complex present. Without the thermally stable ligand system it would be likely that significant palladium leaching would occur. Consequently the longevity of catalyst **16c** would be poor.

As discussed above during recycling studies (sections 3.4.1 and 3.4.2) the product mixtures were analysed by ICP-MS in order to determine levels of palladium leaching. In recycling studies of both the Suzuki and Heck reactions, the greatest levels of palladium leaching were after the initial run with consequent runs showing only minor levels of leaching. Furthermore the palladium content of catalyst **27** was analysed after successfully completing 14 recycles, tables 3.3 and 3.6. It was found that the palladium content had fallen to 3.02% (starting content 3.04%) in both cases.

In order to confirm that the active catalyst remained bound to the polymer support during the cross-coupling reactions, two experiments were investigated. In the first experiment the reaction mixture was filtered after approximately 24 hours (~50% conversion by GC) to remove the catalytic resin. No further conversion occurred despite heating for a further 48 hours. Furthermore a second experiment following a procedure developed by Davies and Lipschutz was investigated.[166,167] Using a polymer-supported iodide (4-iodobenzoic acid attached to Wang resin - 2.7mmolg^{-1}), polymer-supported catalyst **27** and 4-methoxyboronic acid, a three phase test was performed, scheme 3.14.



Scheme 3.14

After treatment of the Wang resin with NaOMe, analysis of the cleaved material revealed no Suzuki coupled product had been formed. In addition Davies *et al.* reported that the addition of iodobenzene to the reaction mixture would cause desorption of the Pd(II) species following oxidative addition. The Ph-Pd-I species then enters a conventional catalytic cycle generating a soluble Pd(0) catalyst. Consequently, the reaction shown in scheme 3.14 was repeated with the addition of 1 eq. of iodobenzene. 4-methoxybiphenyl was successfully isolated upon work up, however, no cross coupled product was detected (GC) upon cleavage of the polymer-bound substrate. Therefore it can be assumed that the active catalytic species is in fact polymer-bound and catalyst **27** does not function via a *release* and *capture* mechanism.

The catalytic studies described above have shown that polymer-supported CNC systems are very effective ligands, showing high levels of stability and maintaining high levels of activity even at low catalyst loadings. However, limitations were observed. The systems were inactive with aryl chlorides, showed only moderate activity with aryl bromides and therefore required the use of reactive aryl iodides for successful cross-coupling. It was proposed that there was a difference in the rate determining step between aryl iodides and bromides resulting in the variation of catalyst turnover. From the literature it is known that the rate of oxidative addition is much greater with aryl iodides. In addition high activation temperatures and long reaction times were necessary to form the cross coupled product in high yield. However, the use of NBu_4Br and microwave heating did overcome these final two limitations.

As a consequence of these limitations the ligand system was reviewed and studies undertaken to develop novel enhanced activity catalysts. These studies are described in the next chapter.

CHAPTER 4

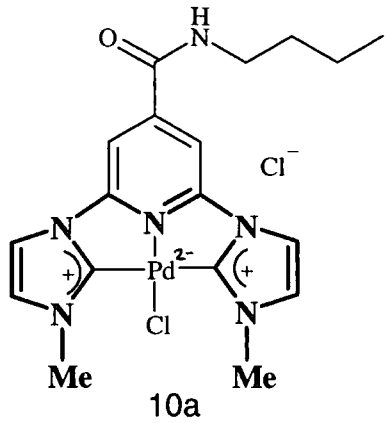
Development of enhanced activity ligand systems

4.0- Enhanced ligand system design

The strong and inert metal-carbene σ bond, which has been compared to metal-trialkylphosphine bonding, in combination with the numerous opportunities for electronic and steric ligand tuning have permitted the development of novel transition metal catalysts.[1]

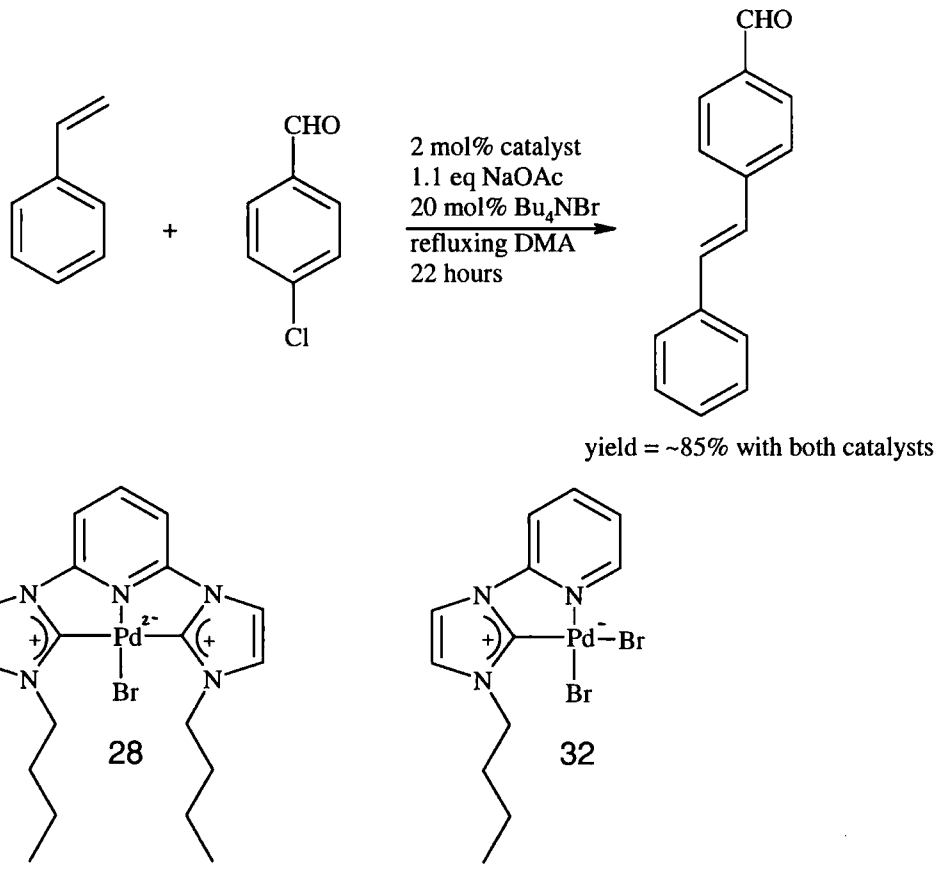
In the previous chapter several CNC bis(carbene) palladium complexes were investigated for catalytic activity. It was found that these complexes were effective catalysts for cross-coupling reactions, showing high levels of stability and maintaining high levels of activity even at low catalyst loadings. In addition these catalysts were capable of being recycled upon immobilisation onto a polymer support. Limitations were observed, however. The systems were inactive with aryl chlorides, showed only moderate activity with aryl bromides and therefore required the use of reactive aryl iodides for successful cross-coupling. In addition high activation temperatures and long reaction times were necessary to form the cross coupled product in high yield. It was proposed that the very strong binding and chelation of the ligand system was responsible for these limitations.

With respect to the tridentate the CNC bis(carbene) complexes discussed in the previous two chapters, it was thought that the high levels of thermal stability are due to the chelation and strong metal binding of the tridentate pincer ligand system (shown in bold in complex **10a** below). Whilst the nature of the ligand system is beneficial to thermal stability and catalyst longevity, catalytic activity is reduced, however. As high temperatures for successful cross-coupling are required, it was proposed that one of the imidazol-2-ylidene ligands must dissociate to provide a coordinatively unsaturated metal centre during the catalytic cycle.



10a

It was thought that removing one of the imidazol-2-ylidene ligands would increase catalytic activity, although the thermal stability and longevity of the catalyst would suffer as a result. However, the increased catalytic activity would permit lower reaction temperatures and shorter reaction times to overcome this limitation.



Scheme 4.1

This hypothesis has been proposed in the literature; consequently attention was drawn to previous work by Peris and Crabtree, who demonstrated that the mono-carbene

palladium complex **32** (where one of the imidazol-2-ylidene ligands had been replaced by hydrogen) catalysed the Heck reaction of chlorobenzaldehyde and styrene, scheme 4.1.[156] Peris and Crabtree also suggested that the high temperatures required by catalytic tridentate CNC pincer complexes were necessary to promote dissociation of one of the carbene ligands. They postulated that complex **32** would promote catalysis at a lower temperature if this was indeed the case. However, on carrying out the reaction at 145°C no product was detected. Interestingly, upon heating the reaction to 165°C, the cross coupled product was formed at the same rate as with complex **28**. The results of these experiments were not clear, neither confirming nor invalidating the hypothesis concerning high reaction temperatures and dissociation of the imidazol-2-ylidene ligands.

However, using information from other literature reports it was possible to postulate the requirements of a novel ligand system.[1,2,3,168,169,170,171,172] It was proposed that the strong electron donating effect of the NHC ligand was responsible for the high levels of thermal stability and resistance to oxidation, compared to phosphine ligand counterparts. The higher rates of palladium catalysis observed when NHC ligands are used are most probably due to the strong electron-donating effect improving the rate of oxidative addition in a catalytic cycle.

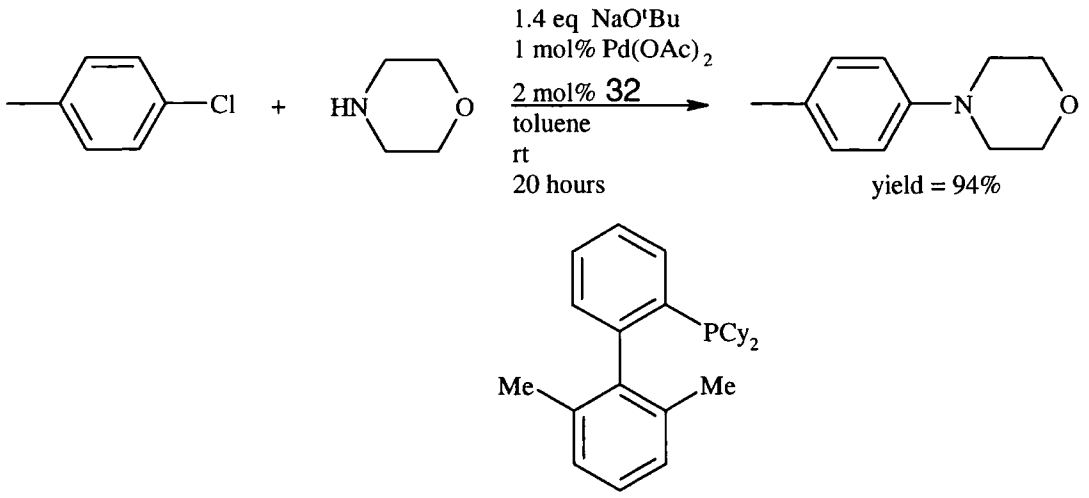
Towards this end, ligand designs incorporating the *N*-Heterocyclic carbene donor connected by suitable linkers to other classical heteroatom donors seemed attractive, because they could combine strong spectator characteristics of the *N*-Heterocyclic carbene ligand with functional groups of diverse σ and π bonding, softness and size, providing control over the coordination environment of the metal and possibly its catalytic activity.

With reference to several ligand systems that have been recently reported in literature, novel *N*-Heterocyclic carbene ligand systems were designed and investigated.

4.1- Strategies towards phenylpyridine mono-imidazolium salts

Previous work by Buchwald *et al.* showed that replacing traditional phosphine ligands such as PPh_3 or PBu_3 with large bulky ligands such as the biaryl monophosphine **32**

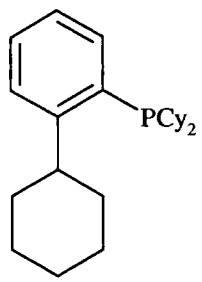
significantly improved catalytic activity in palladium-catalysed amination reactions, scheme 4.2.[173,174]



32

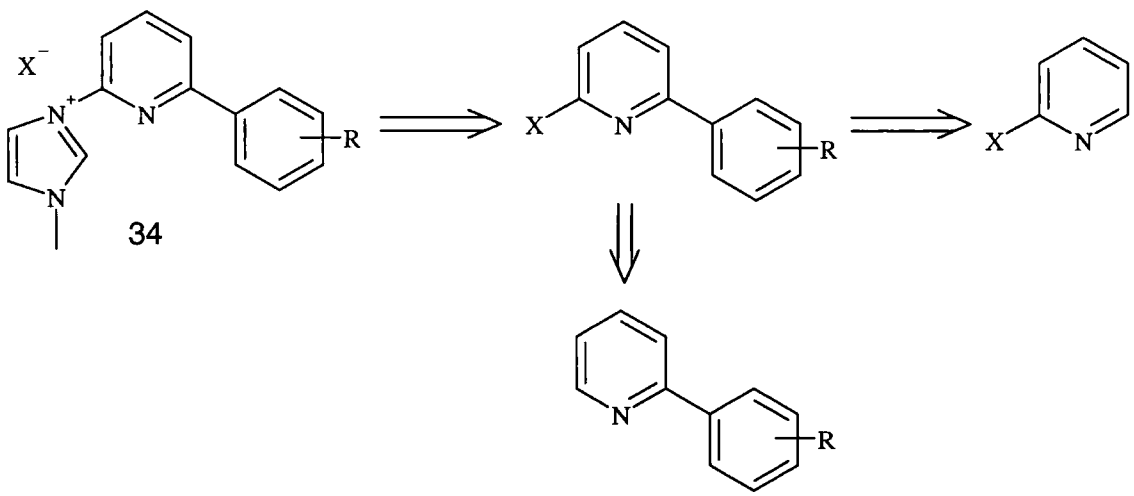
Scheme 4.2

Buchwald *et al.* suggested that the increased activity was due to the increased steric bulk of ligand **32** which accelerated the rate of C-N bond-forming reductive elimination as well as promoting the rate of N-Pd bond formation via the formation of (monophosphine)palladium complexes. In addition Buchwald *et al.* proposed that the π-system of the *ortho* aromatic group may participate in an interaction with the unoccupied metal d-orbital.[175] Further evidence for this was provided by the fact that room temperature reactions conducted with ligand **33** were much less efficient than those employing ligand **32**.



33

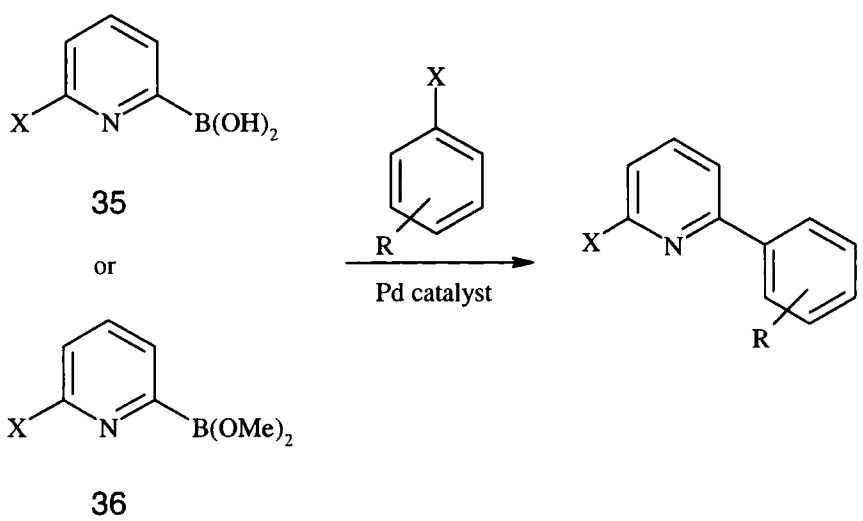
With this information in mind it was suggested that replacing one of the imidazol-2-ylidene ligands from the tridendate CNC pincer carbene complexes, discussed in the previous two chapters, with a large bulky group would improve catalytic activity.



Scheme 4.3

Initial studies concentrated on incorporating a phenyl group into the ligand system, **34**. In order to do this a retrosynthetic strategy was developed focusing on synthesising the functionalised halogenated pyridine, scheme 4.3. This compound could then undergo substitution with an *N*-alkyl imidazole to incorporate the required metal binding functionality.

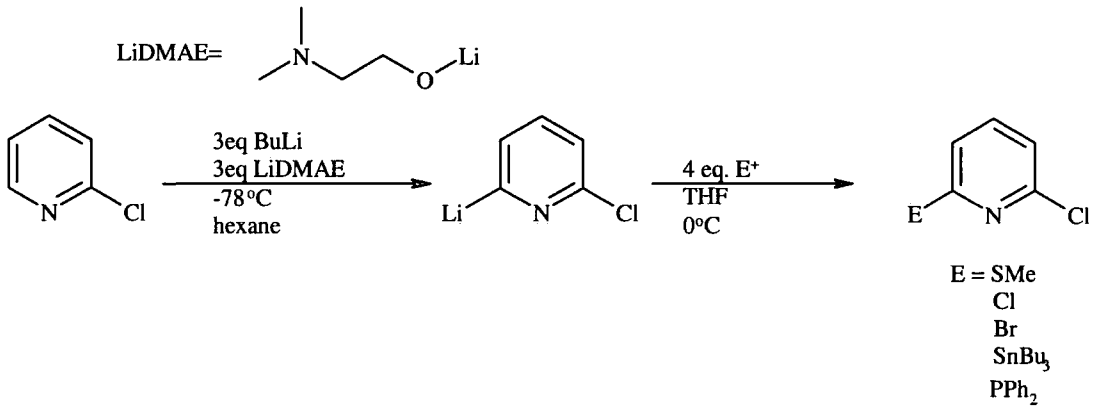
From scheme 4.3 a proposed route was to use a halopyridyl boronic acid, **35** or methyl ester, **36** which could undergo a Suzuki coupling with an appropriate electrophile to generate the desired functionalised pyridine, scheme 4.4.



Scheme 4.4

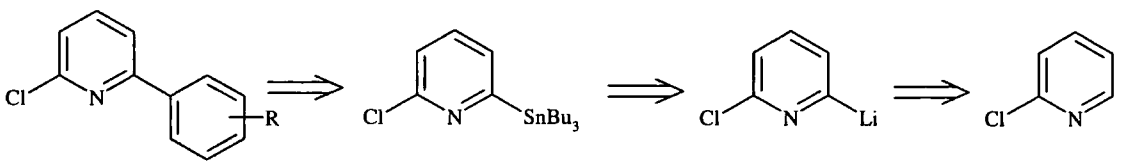
However compared to 3- or 4-pyridyl boronic acid, commercially available 2-pyridyl boronic acid is very expensive. The reason for this is that 2-pyridyl boronic acid or its methyl ester are highly susceptible to hydrolytic protodeboronation and are consequently very difficult to handle and synthesise.[176] In addition a report by Miyaura *et al.* detailing the synthesis of several types of pyridyl boronic acids stated that 2-pyridyl boronic acid could not be isolated in a pure form.[177]

With this in mind an alternative strategy involving a Stille coupling was investigated. Consequently attention was drawn to a report by Fort *et al.* detailing regioselective lithiation techniques to synthesise a variety of functionalised halopyridines.[178] Fort *et al.* regioselectively metalated 2-chloropyridine at the unusual C6 position using a new superbase, LiDMAE, scheme 4.5. Treatment of the pyridyllithium intermediate with different electrophiles generated a range of substituted chloropyridines.

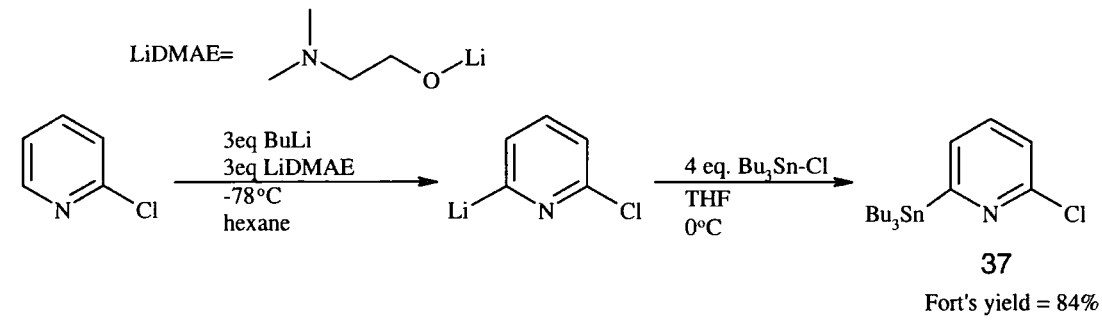


Scheme 4.5

From this a retrosynthetic strategy was devised - selective lithiation of 2-chloropyridine would permit generation of a stannylpyridine. Palladium-catalysed Stille coupling with an aryl halide would generate the desired phenylpyridine, scheme 4.6.

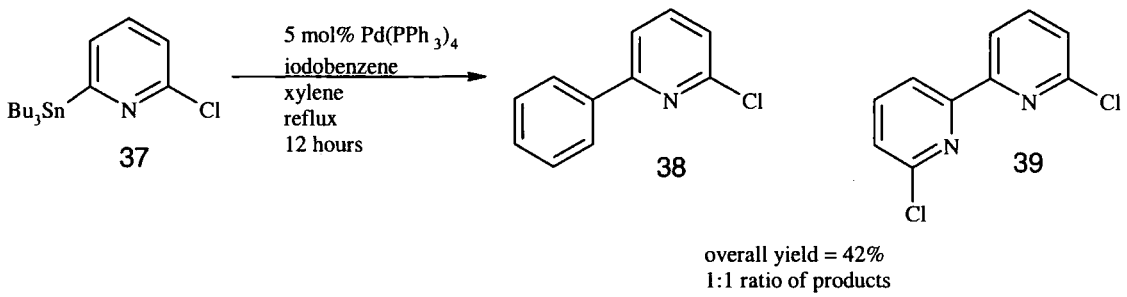


Scheme 4.6



Scheme 4.7

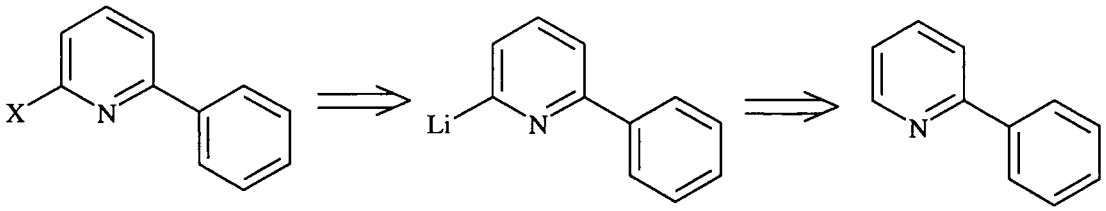
Unfortunately whilst Fort *et al.* reported isolating tributyl(6-chloro-2-pyridyl)stannane **37** in 84% yield, scheme 4.7, initial attempts to repeat this procedure were unsuccessful using the quantities of reagents described by Fort *et al.*. However, on repeating the procedure using 5 eq. of *n*-BuLi and 4 eq. of LiDMAE stannane **37** was successfully formed, however, only in moderate yield (~40%). Unfortunately chromatography of **37** was hindered by the presence of tin contaminants preventing isolation of the pure product.



Scheme 4.8

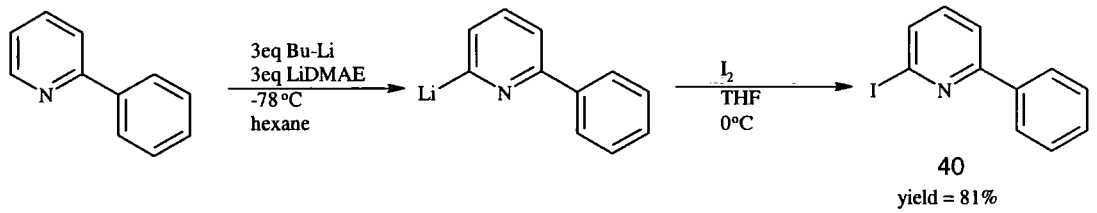
However, crude stannane **37** was used in a model study of the Stille coupling to form 2-chloro-6-phenylpyridine **38** using reaction conditions previously described by Fort *et al.*, scheme 4.8. After heating for twelve hours, analysis of the Stille reaction mixture by GCMS revealed a 1:1 ratio of the desired pyridine **38** and the undesired homocoupled product **39**.

As a consequence of the poor overall yields this synthetic strategy was not investigated further.



Scheme 4.9

Following these poor results further investigation of literature revealed previous work by Fort *et al.* detailing that the superbase BuLi-LiDMAE also mediated and stabilised the formation of phenylpyridyllithium species.[179] These species could then be treated with an appropriate electrophile to yield the desired functionalised phenylpyridine. Based on this work an alternative synthetic strategy was developed, scheme 4.9.

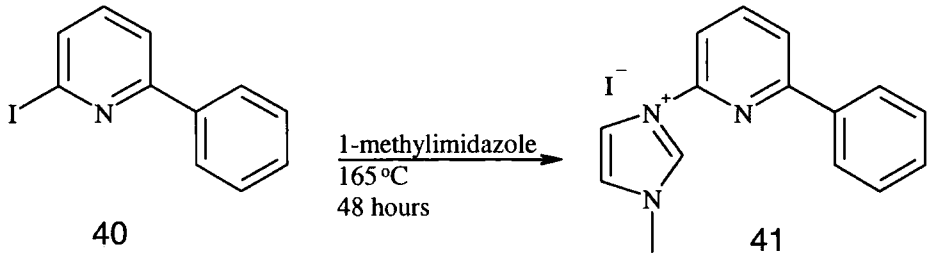


Scheme 4.10

Following Fort *et al.'s* procedure, 2-phenylpyridine underwent selective lithiation upon treatment with the superbase BuLi-LiDMAE. The pyridyllithium was subsequently treated with iodine to yield 2-iodo-6-phenylpyridine in high yield (81%), scheme 4.10. Analysis by GCMS successfully detected the molecular ion at *m/z* 281 and the fragmented molecular ion minus iodine at *m/z* 154. Excess iodine was easily removed by washing the product mixture with saturated sodium thiosulphate solution. After successfully synthesing 2-iodo-6-phenylpyridine, the synthesis of chloro and bromo variants was investigated. Whilst attempts to form these halogenated phenylpyridines using C_2Cl_6 and CBr_4 permitted identification of the crude products by ^1H NMR spectroscopy and EIMS, isolation of the pure products was hindered by difficulties in removing excess quantities of the electrophile.

With the phenylpyridine **40** in hand, attention turned to forming the mono-imidazolium salt necessary for complexation studies.

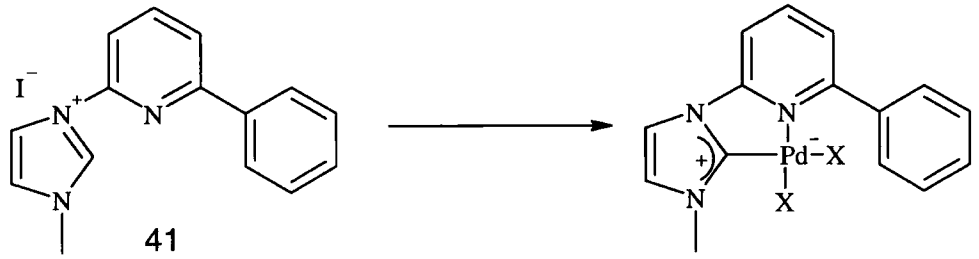
4.2- Synthesis of 2-phenyl-6-N-methylimidazolium pyridine iodide



Scheme 4.10

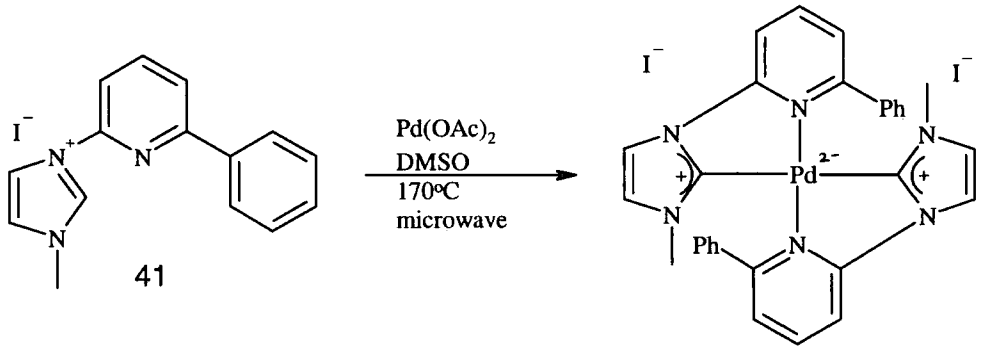
Phenylpyridine **40** was treated with 1-methylimidazole using the procedure described in the two previous chapters. Analysis of the crude reaction mixture after heating for forty eight hours by ^{1}H NMR spectroscopy revealed a characteristic peak at δ10.16 suggesting formation of the imidazolium salt. However, isolation of the product was frustrated by the enhanced solubility characteristics of the mono-imidazolium product. In contrast to the formation of poorly soluble bis(imidazolium) salts described in the previous two chapters, simple precipitation of salt **41** in non-polar solvents was unsuccessful. Consequently the synthetic procedure was modified using Kugelröhr distillation to remove excess 1-methylimidazole at the end of the reaction. This modification permitted the isolation of mono-imidazolium salt **41** in high yield (87%), scheme 4.10.

Therefore with this material in hand, studies to incorporate a palladium centre were undertaken, scheme 4.11.



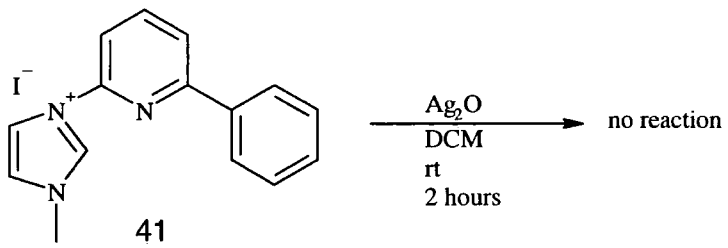
Scheme 4.11

Initial attempts to incorporate the palladium centre investigated the use of $Pd(OAc)_2$ and the previously established microwave-assisted methodology (section 2.3.1). However, analysis of the crude reaction mixture by ES^+MS did not reveal the presence of any mono-carbene complexes although LCMS (ES^+) did reveal the formation of one product with *m/z* 578. Further inspection of the mass spectrum indicated the product contained palladium due to the characteristic isotopic signals present. Further analysis by ^1H and ^{13}C NMR spectroscopy was hindered by the small quantity of product that was isolated. However, from the data available it was speculated that the bis(carbene) dimer **42** had been formed, scheme 4.12. The formation of this product could be rationalised by there being too few coordinating ligands present in the reaction mixture for formation of a mono-carbene palladium complex. So as not waste the limited quantities of starting material (for reasons described below) this complexation technique was not investigated further and alternative complexation techniques were considered.



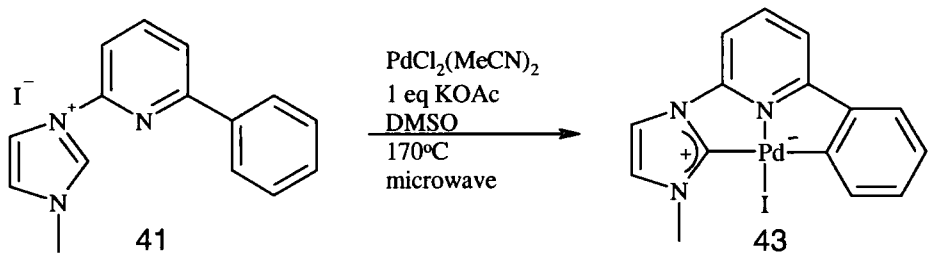
Scheme 4.12

A report by Wang and Lin described how Ag_2O can be used to prepare silver *N*-Heterocyclic carbene complexes.[180] These complexes can be used as carbene transfer agents when treated with a palladium metal source. Consequently mono-imidazolium salt **41** was treated with Ag_2O in order to synthesise the silver complex, scheme 4.13. Unfortunately analysis of the crude reaction mixture by ES^+MS revealed none of the desired complex had been formed. As a result this technique was not investigated further.



Scheme 4.13

As attempts to generate the desired mono-carbene complex using $Pd(OAc)_2$ were unsuccessful it was thought that the microwave-assisted technique may be successful if alternative palladium sources were investigated. Consequently mono-imidazolium salt **41** was heated for 10 minutes with the non-basic salt $PdCl_2(MeCN)_2$ and in the presence of 1 equiv. of KOAc, scheme 4.14.



Scheme 4.14

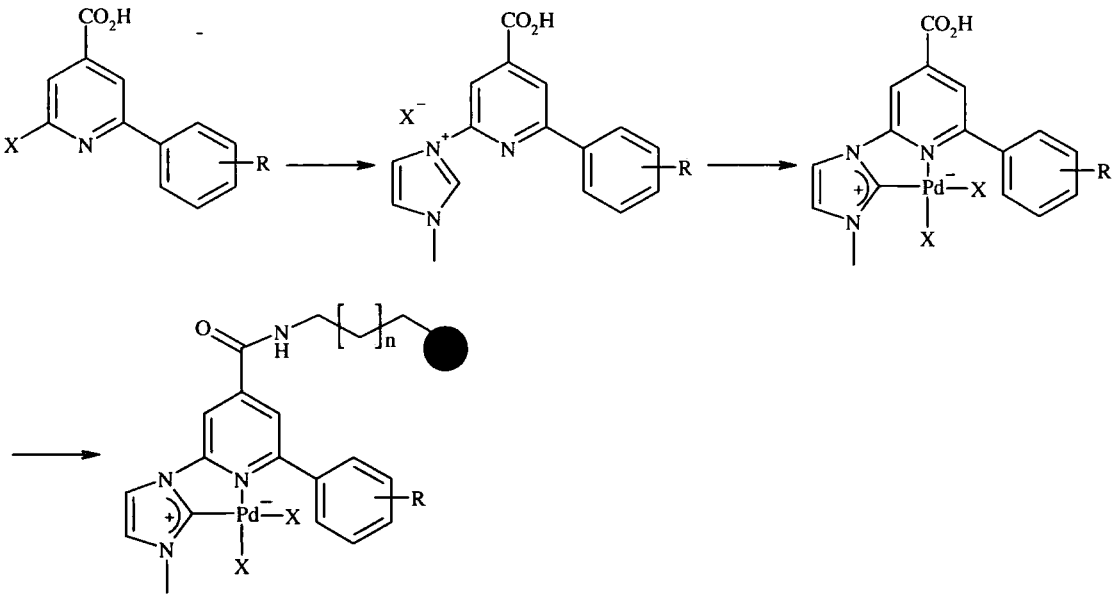
After heating the crude reaction mixture was analysed by LCMS. A large quantity of unreacted starting material was present; however, an unknown product containing palladium (*m/z* 427 plus palladium isotopes) was detected. Analysis of the crude reaction mixture by ^1H NMR spectroscopy was frustrated by the small quantities of the product formed, however, another signal was observed at δ4.05 close to the N-$C\underline{H}_3$ signal (δ3.98) of the imidazolium salt starting material. Although this observation suggested the formation of a new product, the large number of overlapping aromatic proton signals prevented full structural characterisation. Based on the mass spectrometry data it was suggested that the mono-carbene complex **43** had been formed. The crude reaction mixture was analysed by HRMS to provide further evidence for the formation of this product (*m/z* 466.91107).

Although there was no firm evidence for the formation of complex **43**, this transformation is not unknown as metal complexes have been reported in literature containing *ortho*-metallated PPy ligands.[181,182,183]

Unfortunately whilst mono-imidazolium salt **41** was successfully synthesised twice to permit further studies, all further attempts to repeat the synthesis were unsuccessful. Consequently several factors were investigated such as the purity of the starting materials, temperature, heating time and the quantity of 1-methylimidazole used. To date the repetition of the formation of salt **41** has not been successful and the reasons for this are still unknown.

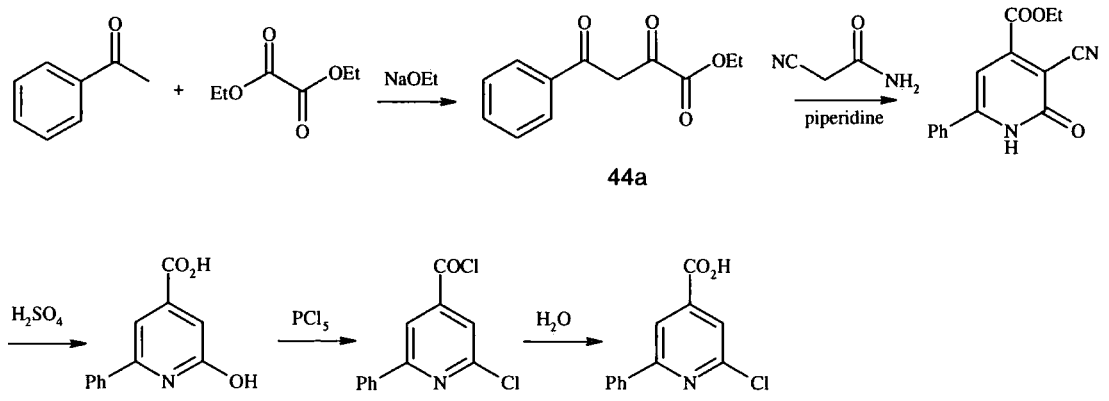
Whilst all attempts to reproduce the synthesis of mono-imidazolium salt **41** were unsuccessful, sufficient material was successfully isolated and collected to permit initial complexation studies; however, complete structural analysis and isolation of complexes **42** and **43** as pure compounds was prevented due to the limited quantity of salt **41** available.

Concurrent with studies to synthesise mono-imidazolium salt **41**, strategies were investigated to synthesise a mono-imidazolium salt capable of being attached to a polymer support.
Following the success of using 2,6-dichloroisonicotinic acid **5a** and peptide coupling techniques in previous studies (section 2.6.1 to 2.9.1), a similar strategy was proposed, scheme 4.15.



Scheme 4.15

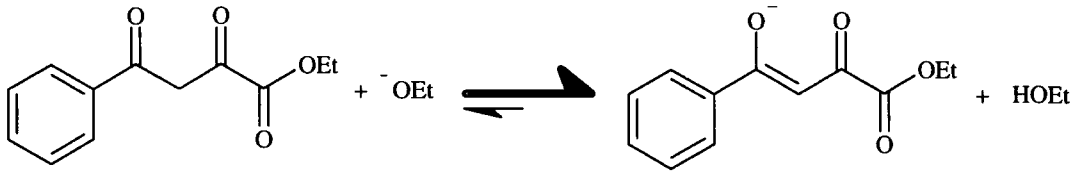
However, this strategy required an acid-functionalised phenylpyridine as a starting material and unfortunately no compounds fitting this requirement were commercially available. Consequently attention was drawn to a patent report by Liberman describing the synthesis of isonicotinic thioamides.[184] In this patent Liberman described the synthesis of several 2-chloroisonicotinic acid derivatives with various substituents at the 6 position. With the information from this patent in hand a synthetic route was proposed, scheme 4.16.



Scheme 4.16

2,4-Dioxo-4-phenyl-butyric acid ethyl ester **44a** was formed by Claisen condensation of acetophenone and diethyl pyruvate in moderate yield (55%).[185] Analysis of the product by ^{1}H NMR spectroscopy revealed the product had been isolated as the β-keto ester

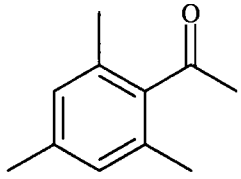
sodium salt **44b** (a broad singlet at δ14.07 and a singlet at δ7.09). This is due to the pK_a of the first α proton in product **44a** being much lower than the pK_a of ethanol, scheme 4.17.



44a 44b

Scheme 4.17

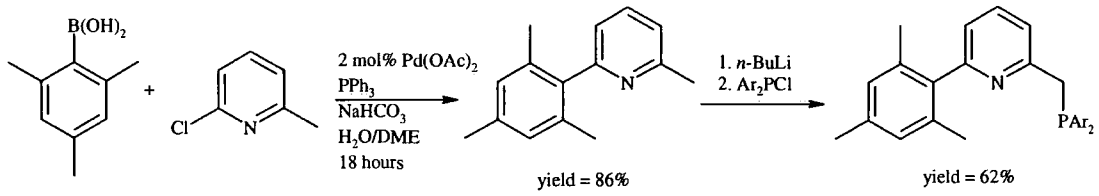
With the β-keto ester in hand next step of the synthetic route could be investigated. However, concomitant with these studies it became apparent that 2-phenylpyridine was not a suitable ligand as the phenyl group could bind to a palladium centre via *ortho*-metallation. To prevent this alternative aryl groups lacking *ortho* hydrogens must be used in the ligand system. With this in mind the synthetic route described above was revised.



45

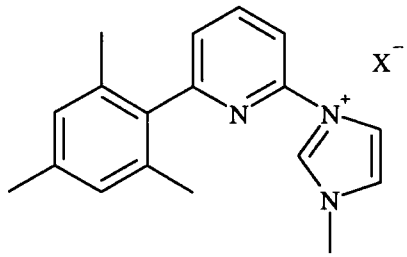
It was suggested that the synthetic route could be repeated using ketone **45** which lacked *ortho* hydrogens. However, as β-keto ester **44b** was only synthesised in moderate yield and given the high cost of ketone **45** this synthetic route was deemed impractical and studies were discontinued.

Following these results attention turned to a report by Liu *et al.* describing the synthesis of a bulky phosphino-pyridine ligand system, scheme 4.18.[186] These ligands readily formed palladium and nickel complexes upon treatment with (COD)PdCl(Me) and (DME)$NiBr_2$. Liu *et al.* investigated these complexes for use in polymerisation and oligomerisation of ethylene.



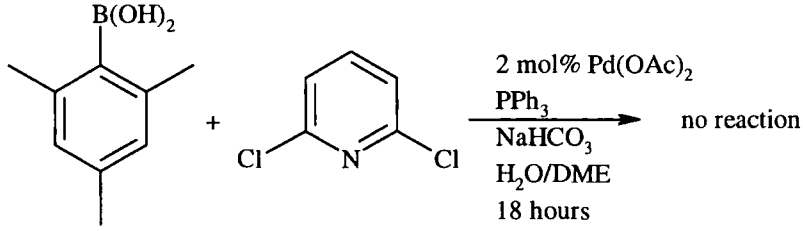
Scheme 4.18

This report was of interest because it provided a method of incorporating a trimethylphenyl group into the mono-carbene ligand system. The trimethylphenyl group would provide steric bulk, however, in contrast to the phenyl system described above it would not undergo *ortho*-metallation and bind to the metal centre. As a result it was hoped that the proposed ligand **46** would provide greater levels of catalytic activity.



46

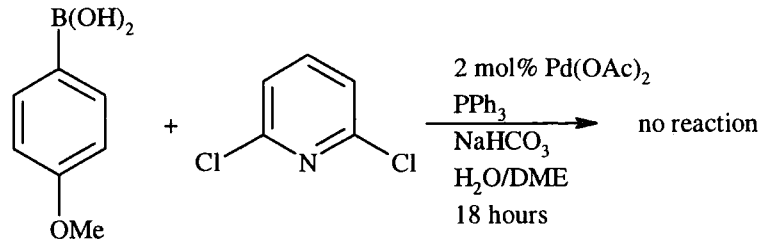
Initial studies focused on repeating the reaction conditions described by Liu *et al.* using 2,6-dichloropyridine with an equimolar amount of 2,4,6-trimethylphenyl boronic acid, scheme 4.19. Unfortunately no cross coupled product was detected by GC.



Scheme 4.19

Suzuki cross-coupling reactions involving sterically hindered substrates often occur in low to moderate yields according to literature reports.[87,172,173] Consequently the reaction was repeated using the activated boronic acid, 4-methoxybenzene boronic acid, scheme

4.20. However, once again no cross coupled product was detected by GC using Liu *et al.'s* reaction conditions.

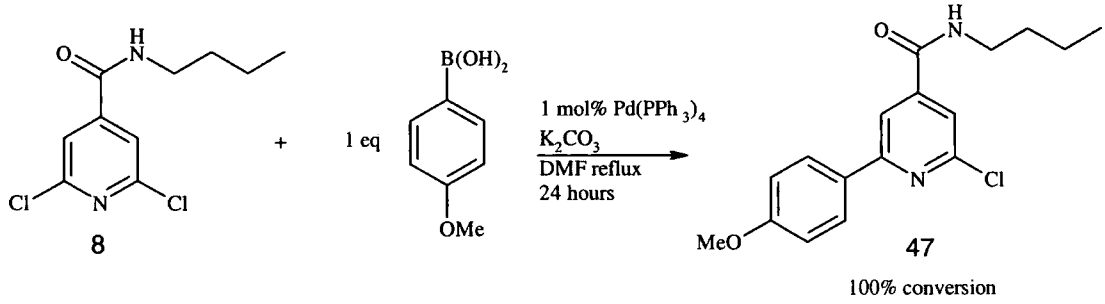


Scheme 4.20

It was suggested that although studies had focused on a simple unfunctionalised model system, using 2,6-dichloroisonicotinic acid, **5a** as substrate would in fact be more useful. The electron withdrawing functionality of this substrate (compared to 2,6-dichloropyridine) should activate **5a** in Suzuki cross-coupling reactions. This work would also be of great interest as it provided a potential strategy to develop a mono-carbene complex that could be attached to a polymer support via an amide linkage of the type described in chapters 2 and 3.

In order to follow reaction progress 2,6-dichlorisonicotinic-4-butylamide, **8** was used as a substrate so that reactions could be analysed by GC.

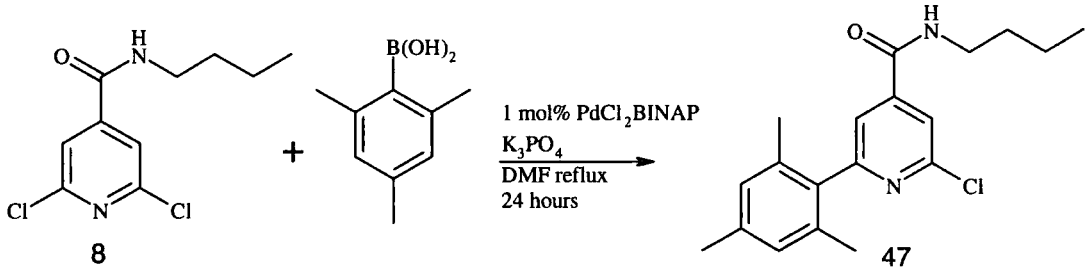
Liu *et al.'s* reaction conditions were modified so as to create more forceful reaction conditions for successful cross-coupling, using the preformed catalyst $Pd(PPh_3)_4$; the slightly stronger base K_2CO_3; and the higher boiling point solvent DMF, scheme 4.21.[87]



Scheme 4.21

After heating for 24 hours, the crude reaction mixture was analysed by GC indicating full conversion of the starting material and the cross coupled product was identified by ES^+MS (*m/z* 318 $[M^+ {}^{35}Cl]$, 320 $[M^+ {}^{37}Cl]$, 341 $[M^{35}Cl + Na]^+$, 343 $[M^{37}Cl + Na]^+$).

In order to prevent *ortho*-metallation of the palladium centre the aryl group must not contain any *ortho* hydrogens. Therefore studies were undertaken to repeat the Suzuki coupling with 2,4,6-trimethylphenylboronic acid. However, using the reaction conditions described in scheme 4.21 no cross coupled product was detected and starting materials were recovered. Therefore a parallel screening array of 24 Suzuki reactions to determine optimal reaction conditions was investigated. The protocol for this array is described in appendix 1.



Scheme 4.22

All of the individual reactions were analysed by GC after addition of diethyleneglycol di-*tert*-butyl ether as an internal standard in order to assess conversion of the starting material. As a result of this analysis one set of reaction conditions was chosen and subsequently scaled up and repeated to allow further analysis, scheme 4.22.

After heating and aqueous work up to remove inorganic salts, the crude product was analysed by GC (after addition of diethyleneglycol di-*tert*-butyl ether as an internal standard). It was determined that the starting material had undergone only ~50% conversion to an unknown product. Consequently the product mixture was further analysed by GCMS (CI). Analysis by this technique suggested cross coupled product **37** had indeed been formed (*m/z* 331 $[M^{35}Cl + H^+]^{\cdot+}$, 333 $[M^{37}Cl + H^+]^{\cdot+}$). However, purification proved difficult. Visualisation of the TLC plate by UV revealed three spots, one of which was the starting material **8** which was easily removed by FCC. However, two inseparable spots remained which appeared as a single product by GC. Further

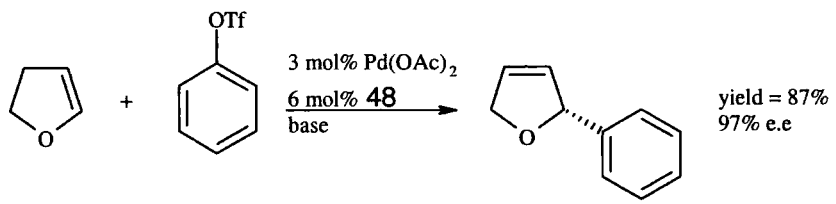
analysis of these products by ^{1}H NMR spectroscopy was frustrated by the number of overlapping signals. It was suggested that the presence of the two *ortho* methyl groups on the phenyl ring prevented rotation between the two aromatic rings. Consequently 2 atropisomers could be formed as a result of the Suzuki cross-coupling.

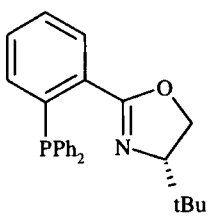
Due to the time constraints of this project, product **47** was not successfully isolated as a pure compound and fully characterised; however, studies are ongoing within the Steel research group.

4.3- Oxazoline ligand systems

Asymmetric catalysis is of great importance in synthesis. Several recent publications detailing the total synthesis of natural compounds such as Danishefsky *et al.'s* synthesis of taxol have been facilitated by the use of asymmetric catalysis.[61]

Focusing on palladium cross-coupling reactions, asymmetric versions of the Suzuki and Heck coupling reactions have been reported.[47,62] For example Pfaltz *et al.* used the chiral PHOX ligand **48** in the Heck coupling of dihydrofuran and phenyltriflate to lead to asymmetric induction with high enantiomeric excess, scheme 4.23.



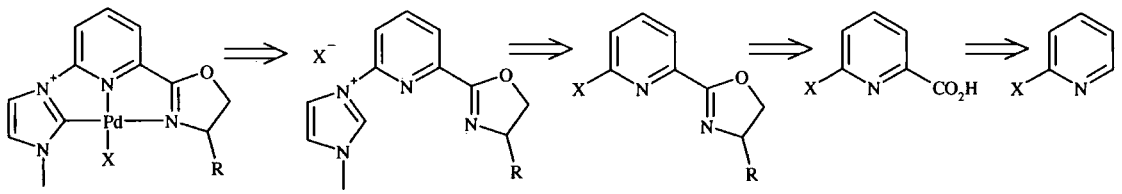


48

Scheme 4.23

Several *N*-Heterocyclic carbene ligand systems have been reported in asymmetric catalysis and many of these contain an additional oxazoline ligand unit possessing a chiral centre. However, according to a review by Burgess no asymmetric palladium

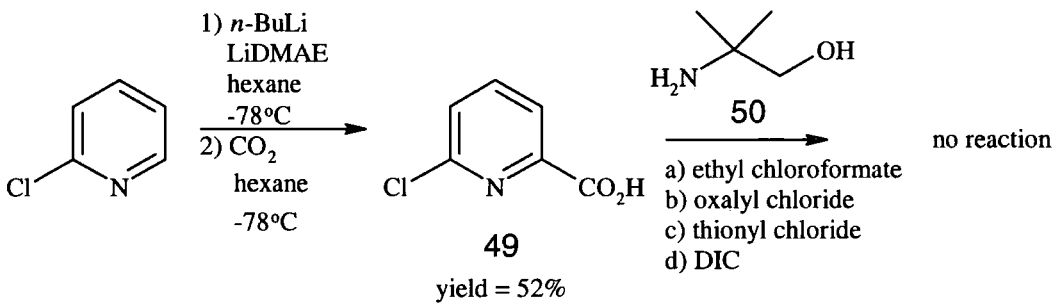
cross-coupling reactions have been reported using chiral *N*-Heterocyclic ligands.[3] Therefore, with a view to developing a ligand system capable of asymmetric catalysis, studies were undertaken to incorporate an oxazoline ligand into the core pyridine unit. The following studies were performed in collaboration with an undergraduate summer student, Graham Patterson.



Scheme 4.24

Initial studies focused on synthesising a core pyridine unit to which metal binding functionality could be attached, scheme 4.24.

Following the successful lithiation and functionalisation of 2-chloropyridine (section 4.1) 2-chloropyridine was treated with BuLi-LiDMAE to generate the pyridyllithium species. This was subsequently treated with dry ice to yield carboxylic acid **49** in moderate yield (52%), scheme 4.25.

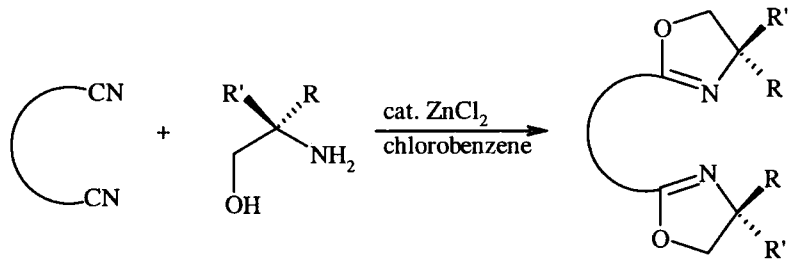


Scheme 4.25

Analysis of carboxylic acid **49** by IR spectroscopy revealed a characteristic broad absorption at 3057cm^{-1} for the hydroxyl group. ES$^-$MS confirmed formation of the chlorine-containing carboxylic acid with the detection of 2 signals *m/z* 157, 159 (3:1).

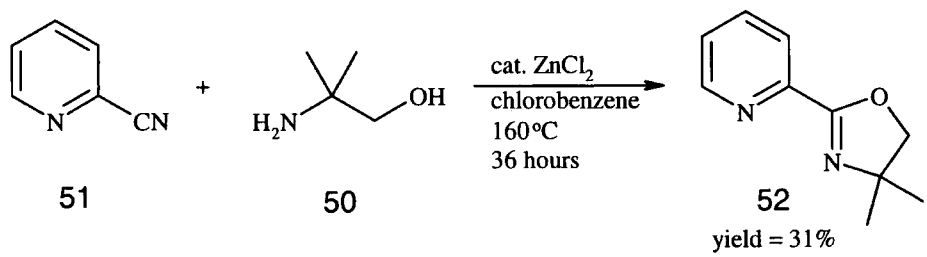
In order to assess the synthetic strategy, the inexpensive achiral aminoalcohol **50** was chosen to develop a model oxazoline ligand system.

Several literature procedures were investigated to form the oxazoline ligand from carboxylic acid **49** and aminoalcohol **50**.[187,188,189] However, all attempts to couple these two compounds via activation of the acid or by use of peptide coupling reagents were unsuccessful and consequently this route was discontinued. As result of this synthetic failure, attention was drawn to a report by Bolm *et al.* revealing how dinitrile compounds could be converted to bis(oxazolines) by treatment with $ZnCl_2$ and an aminoalcohol, scheme 4.26.[190]



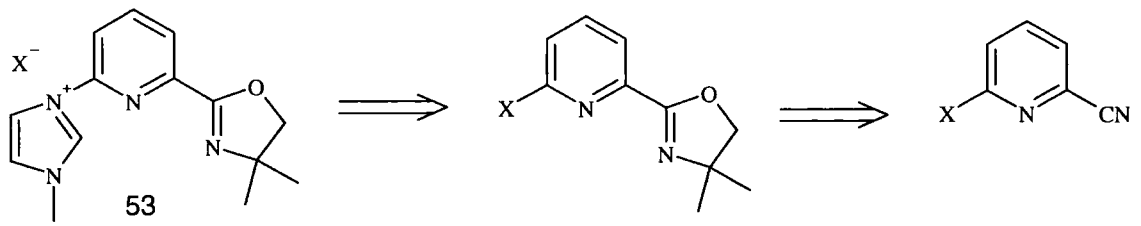
Scheme 4.26

Following this report model studies were undertaken to assess the application of this reaction. Commercially available 2-cyanopyridine, **51**, 2-amino-2-methylpropan-1-ol, **50** and $ZnCl_2$ were heated to reflux in chlorobenzene to yield oxazoline **52** in 31% yield, scheme 4.27. Synthesis of the oxazoline product was confirmed by the change in the aromatic proton chemical shifts from carboxylic acid **49** (δ 8.10, δ 7.84, δ 7.50) to oxazoline **52** (δ 8.63, δ 7.94, δ 7.68) and by detection of the molecular ions by ES^+MS (176 $[M^+]$, 177 $[MH^+]$, 199 $[M+Na]^+$, 200 $[MH+Na]^+$).



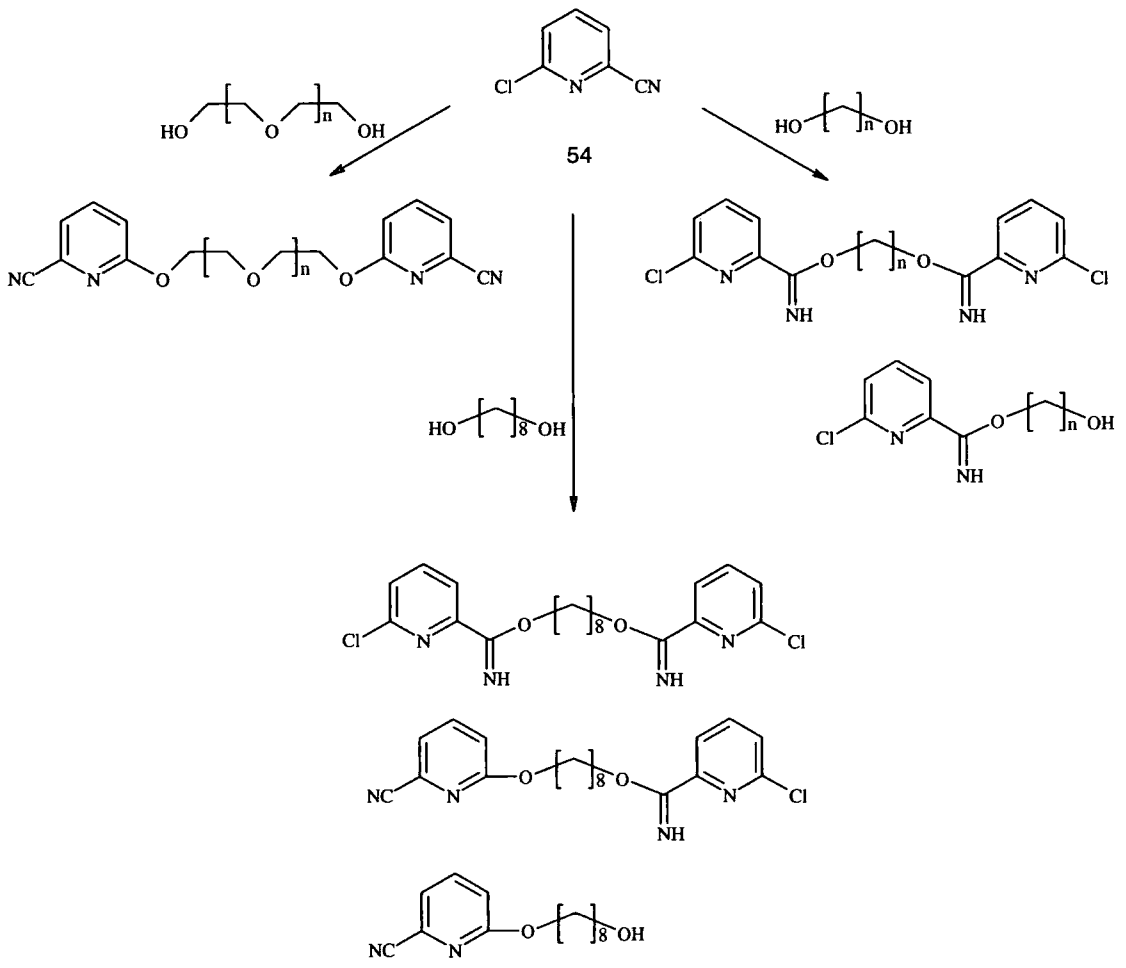
Scheme 4.27

However, in order to form the imidazolium salt **53**, a 2-cyano-6-halopyridine is required as a starting material, scheme 4.28.



Scheme 4.28

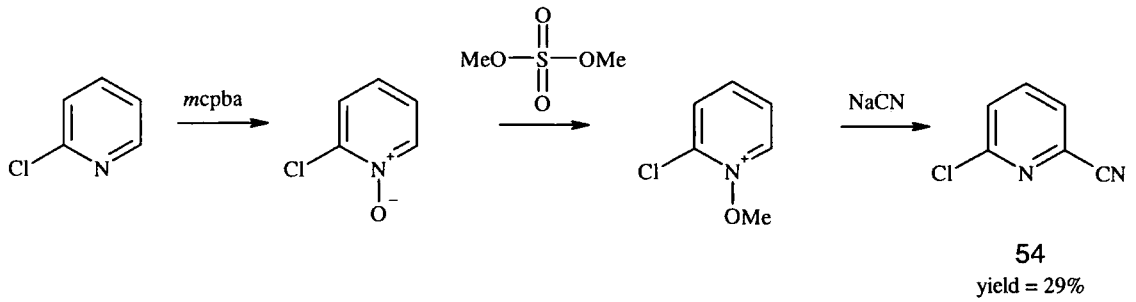
Unfortunately a search revealed that no 2-cyano-6-halopyridines are commercially available. Consequently attention was drawn to a report by Elman describing the synthesis of 2-chloro-6-cyanopyridine and reactions with various diols in order to form metal scavenging reagents, scheme 4.29.[191]



Scheme 4.29

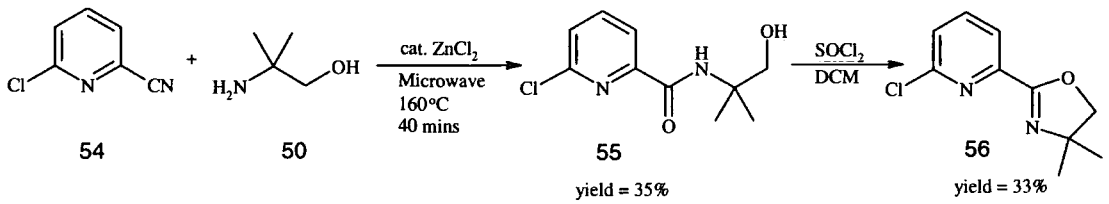
Following the procedure in this report 2-chloro-6-cyanopyridine **54** was synthesised in 29% yield after three steps from 2-chloropyridine, scheme 4.30. Incorporation of the

nitrile group was confirmed by the strong absorption at 2239cm^{-1} using IR spectroscopy and the detection of 2 molecular ion signals by EIMS (*m/z* 138 [M^{+35}Cl], 140 [M^{+37}Cl]).



Scheme 4.30

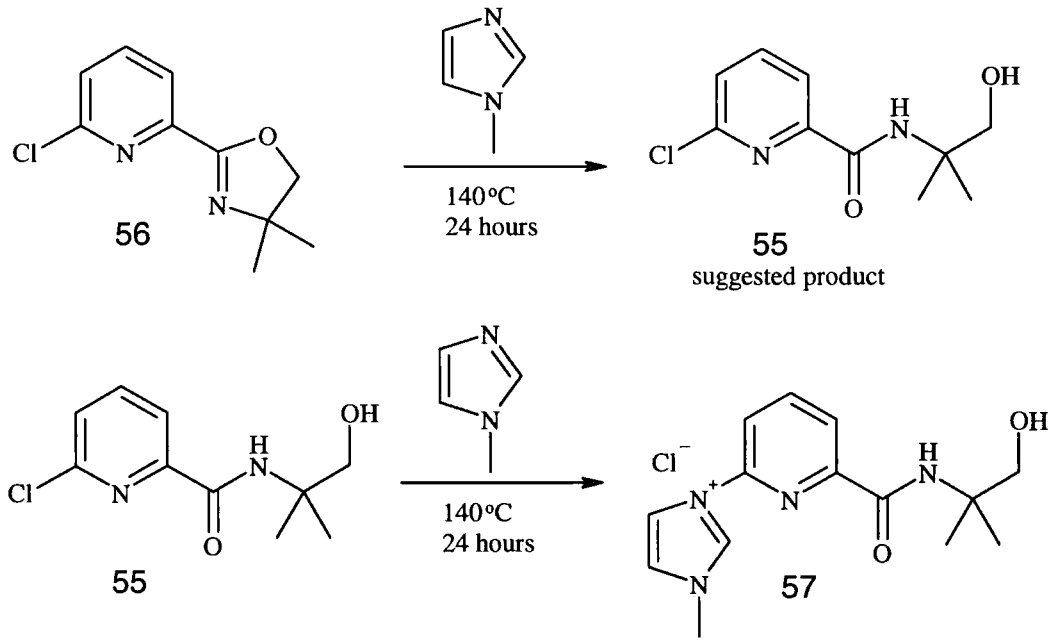
Attention was drawn to report by Clarke and Wood reporting how the synthesis of oxazolines with $ZnCl_2$ could be significantly accelerated using microwave radiation.[192] Consequently with 2-chloro-6-cyanopyridine **54** in hand, studies to form the oxazoline with 2-amino-2-methyl-propan-1-ol **50** were undertaken, scheme 4.31.



Scheme 4.31

2-chloro-6-cyanopyridine **54**, 2-amino-2-methyl-propan-1-ol **50** and catalytic $ZnCl_2$ were heated using microwave radiation in the absence of solvent. Unexpectedly, following work up only amide **55** was isolated in low yield (35%) not the expected oxazoline product. Amide **55** was identified by the characteristic carbonyl absorption (1665cm^{-1}) by IR spectroscopy, ^{1}H NMR spectroscopy (broad singlet at δ7.83) (and by detection of two molecular ions by EIMS (m/z 230 [M^{37}Cl$^+$] and 228 [M^{35}Cl$^+$]).

Cyclisation did occur upon further treatment of amide **55** with $SOCl_2$, however, oxazoline **56** was only isolated in low yield (33%). Formation of the oxazoline was confirmed by the disappearance of the carbonyl signal in amide **55** (δ 163) by ^{13}C NMR spectroscopy suggesting cyclisation had occurred and by detection of the two molecular ions by EIMS (*m/z* 212 [M^{37}Cl$^+$] and 210 [M^{35}Cl$^+$]).



Scheme 4.32

With oxazoline **56** in hand attention turned to forming the imidazolium salt, scheme 4.32. However, treatment of oxazoline **56** with 1-methylimidazole was not successful. Analysis of the crude mixture by ^{1}H NMR spectroscopy suggested the oxazoline ring had opened during heating and reformed the amide precursor **55** (broad singlet δ7.85). $ES^{+}MS$ of the crude reaction mixture revealed two peaks (m/z 230 and 228) suggesting formation of amide **55**. The desired imidazolium oxazoline product (*m/z* 257) was not detected.

Although 1-methylimidazole had been dried and distilled beforehand, it is still a hydroscopic compound and consequently the necessary water for the hydrolytic transformation of oxazoline **56** to amide **55** from may have been present.

Whilst the reaction conditions appeared to cause degradation of the oxazoline ring, it was suggested that amide **55** would be stable to the reaction conditions. Consequently amide **55** was treated with 1-methylimidazole under the same conditions as oxazoline **56**.

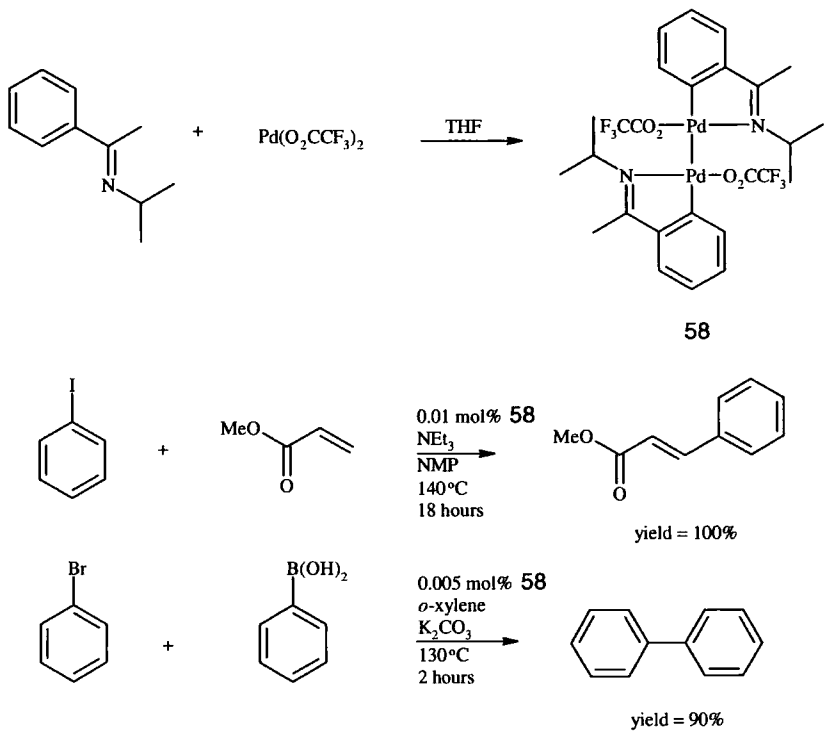
Following removal of excess 1-methylimidazole by Kugelröhr distillation the crude product was analysed by LCMS. Significant quantities of the amide starting material

were still present (*m/z* 230 and 228); however, a small signal (*m/z* 275) suggested that a small quantity of imidazolium salt **57** had been formed. Isolating this material proved extremely difficult as the material could not be purified by chromatography and proved very difficult to recrystallise.

Due to time constraints these results were not investigated further and whilst the yields reported in the synthesis of the oxazoline ligands **52** and **56** were rather low, current work in the Steel research group is focusing on optimising the synthetic procedures.

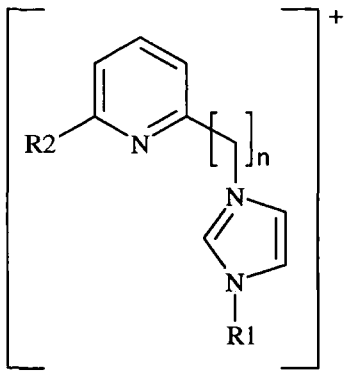
4.4- Imino and alkoxide ligand systems

Attention was drawn to two reports by Milstein *et al.* describing the catalytic activity of complex **58** in Heck and Suzuki cross-coupling reactions.[193,194] Very high TON were reported and in some cases exceeded 10^6, scheme 4.33.



Scheme 4.33

In addition previous work by Danopoulos *et al.* described the synthesis of various pyridine functionalised *N*-Heterocyclic carbenes, figure 4.1.[170]



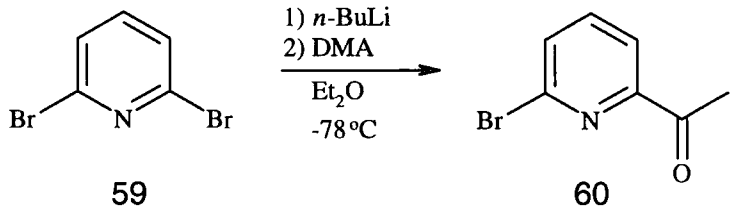
R1 = ^{t}Bu, mesityl, 2,6-^{i}Pr$_2$C$_6$H$_3$

R2 = TMS, H, CH_3

n = 1, 2, 3

Figure 4.1

It was suggested that these two strategies could be combined to form a mixed ligand system whose properties could be tuned using different imines. Consequently attention was drawn to a report by Holm *et al.* investigating the synthesis of new 2,6-disubstituted pyridine derivatives using 6-bromo-2-lithiopyridine as an intermediate.[195] One of the derivatives described was 2-bromopyridine-6-methylketone **59** which was prepared via monolithiation of 2,6-dibromopyridine and DMA, scheme 4.34.



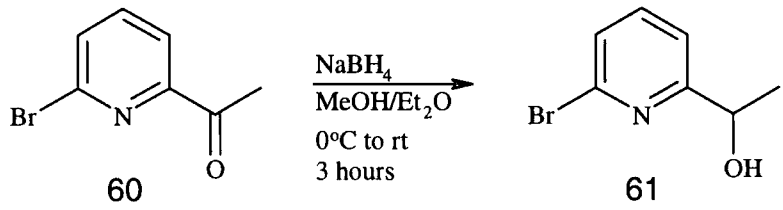
59 60

yield = 81%

Scheme 4.34

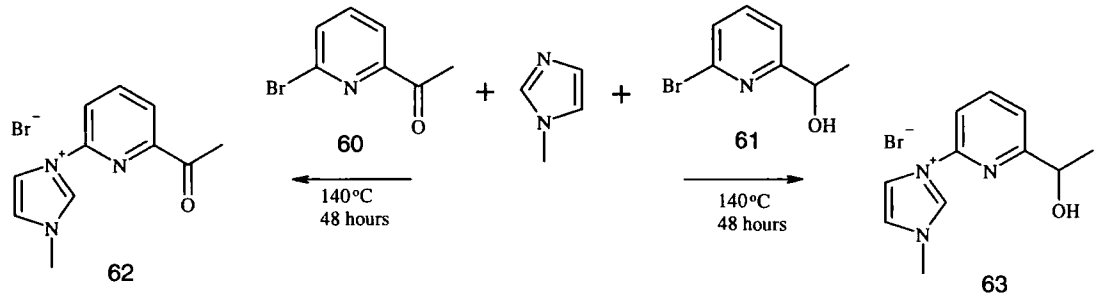
Following Holm *et al.'s* literature procedure afforded the substituted pyridine product in 81% yield after chromatography. Analysis of the product by IR spectroscopy showed a strong absorption at 1699cm^{-1} suggesting a carbonyl group was now present. Analysis by EIMS confirmed only one bromine atom was present (*m/z* 201 and 199). In addition the product was confirmed as analytically pure by C, H and N elemental analysis.

In order to synthesise an alternative alkoxide ligand system reduction of ketone **60** was investigated. It was found that ketone **60** could be easily reduced to alcohol **61** upon treatment with $NaBH_4$, scheme 4.35.



Scheme 4.35

In order to incorporate the NHC metal binding functionality ketone **60** and alcohol **61** were both treated with 1-methylimidazole to form their respective mono-imidazolium salts **62** and **63**, scheme 4.36. After removal of excess 1-methylimidazole by Kugelröhr distillation the crude reaction mixtures were analysed by ^1H NMR spectroscopy.



Scheme 4.36

Characteristic NCHN proton signals were observed at δ10.27 (ketone **62**) and δ10.15 (alcohol **63**) suggesting that incorporation of the imidazolium unit. The reaction appeared not to have interfered with the ketone or alcohol functionality as the CH_3 protons were still observed at δ2.80 (ketone **62**) and δ1.79 (alcohol **63**). The hydroxyl proton of alcohol **63** was observed at δ4.02. Unfortunately, difficulties in purification hindered further analysis of these products. Both of these compounds proved extremely difficult to recrystallise and due to their ionic nature could not be purified by chromatography. Consequently the reactions were repeated. However, the conversion of ketone **60** and alcohol **61** to imidazolium salts **62** and **63** was very poor (<10% by ^1H NMR spectroscopy). Due to time constraints of this project these reactions were not

optimised. However, these findings are currently under investigation within the Steel research group.

Chapter 5

Conclusions

and future work

5.0- Conclusions

The research described in this thesis has involved the development of polymer-supported bis(*N*-Heterocyclic carbene) palladium complexes. Whilst novel *N*-Heterocyclic carbene palladium complexes have been synthesised and evaluated for catalytic activity by several research groups, the polymer-supported complexes developed in this thesis have not been previously reported in literature. Consequently the research described in this thesis presents several synthetic techniques that may lead to the development of a range of enhanced activity supported catalysts.

In summary N-alkyl and aryl imidazoles have been used to form bis(imidazolium) salts which were the necessary precursors for *N*-Heterocyclic carbene generation.

Novel, facile techniques have been developed and rationalised to synthesise pyridine bis(imidazolium) salts and their respective bis(imidazol-2-ylidene) palladium complexes. In addition the synthetic efficiency of these techniques was dramatically improved using microwave-assisted techniques, section 2.3.1.

A variety of combinatorial techniques were investigated to immobilise functionalised bis(imidazolium) salts and bis(imidazol-2-yl) palladium complexes onto functionalised resins. This investigation revealed that PyBop® is the most suitable reagent for coupling acid functionalised compounds onto amino functionalised resins, section 2.6.1.

Two methods were developed to generate a polymer-supported palladium complex - complexation of a polymer-supported ligand and immobilisation of a palladium complex. These complexes **16c** and **27** were fully evaluated for catalytic activity and longevity in a series of cross-coupling reactions. Very high yields were reported and one catalyst in particular, **27** was capable of being recycled in excess of 14 times with no apparent loss in yield or activity, tables 3.3 and 3.6.[196]

A three phase test developed by Davies and Lipschutz was performed and suggested that the active catalytic species was polymer-bound throughout the entire catalytic cycle, scheme 3.14.

Following catalytic studies of the polymer-bound catalysts, limitations were observed. Consequently, enhanced ligand systems are under development.

It has been reported in the literature that no one ligand or small class of ligands is capable of handling all possible substrate combinations.[172] On this note the facile method of attachment to a polymer support described in chapter 2 and the novel ligand systems under development in chapter 4 could be combined to provide a broad range of polymer-supported ligand systems. This would permit facile screening of catalyst activity and introduces the concept of supported asymmetric catalysis, figure 5.1.

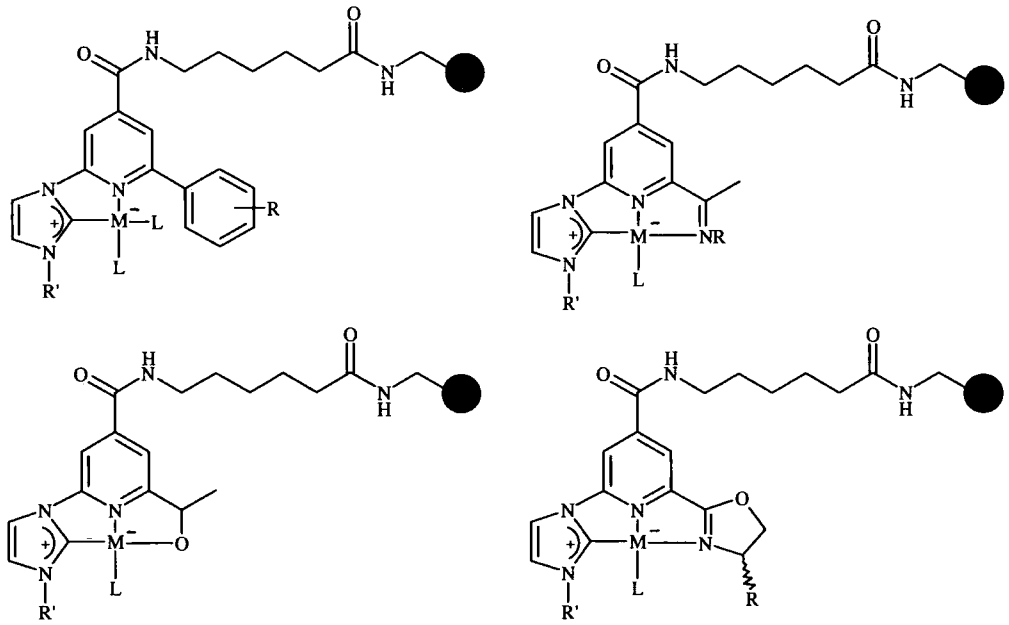
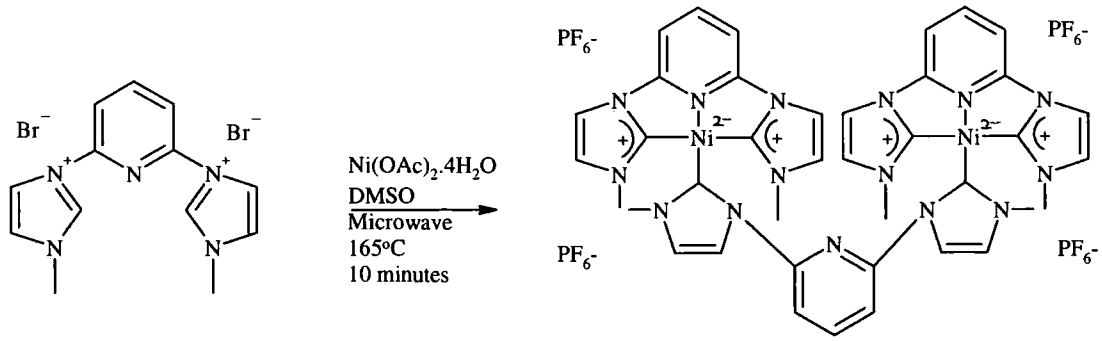


Figure 5.1

Finally it was shown in section 2.3.1 that treatment of bis(imidazolium) salts with $Pd(OAc)_2$ under microwave radiation generated the respective bis(carbene) palladium complexes in high yield. These complexes were investigated for activity in Pd-catalysed cross-coupling reactions. However, a plethora of alternative catalytic reactions could be investigated by varying the transition metal centre. The transition metal centre may be incorporated by varying the metal acetate used in synthesis. On this note the synthesis of several different CNC tridentate complexes was investigated using the microwave assisted methodology described in section 2.3.1. Commercially available first row transition metal acetates (Cr, Mn, Fe, Co, Ni, Cu) were investigated as metal sources. However, only the novel nickel complex **64** was isolated during these studies. Complex **64** from the reaction bis(imidazolium) salt **1a** and $Ni(OAc)_2.4H_2O$.

Interestingly although equivalent quantities of the bis(imidazolium) salt and $Ni(OAc)_2.4H_2O$ were used, a dinickel tri-*N*-Heterocyclic carbene complex was isolated and ultimately characterised by X-ray structural analysis, scheme 5.1 and figure 5.2.[197] Electrochemical studies of complex **64** are currently under investigation within the Steel research group.



Scheme 5.1

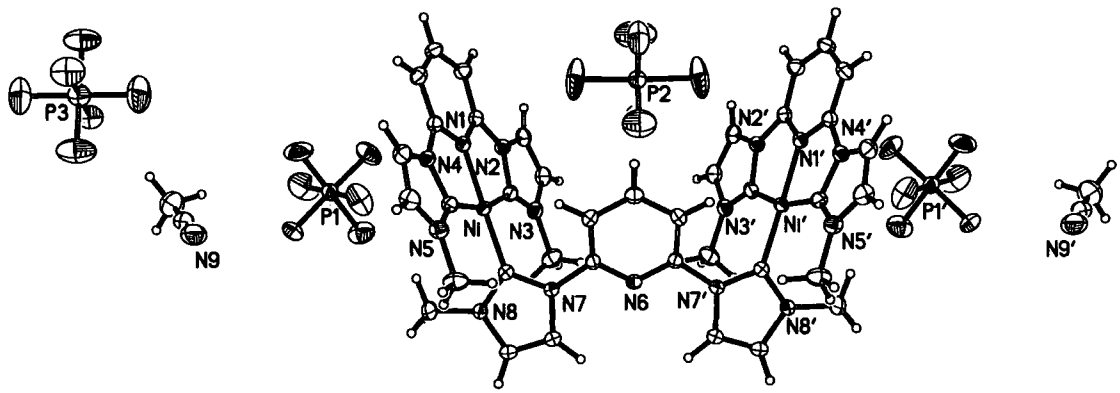


Figure 5.2

Chapter 6

Experimental procedures and data

6.1- General procedures

All reactions were carried out under an atmosphere of argon unless otherwise stated.

Solvents

Petroleum ether 40/60 refers to the fraction of petroleum ether that boils in the range 40 to 60°C. This was redistilled prior to use in all cases.

Solvents were distilled from the following reagents under a nitrogen atmosphere prior to use in all cases: Et_2O and THF (sodium benzophenone ketyl); DCM (calcium hydride); $CHCl_3$ (phosphorus pentoxide); MeOH (magnesium methoxide).

DMSO and NMP were distilled from calcium hydride under reduced pressure and stored over 4Å molecular sieves.

In the cases where mixtures of solvents were used, ratios given refer to the volumes used.

Reagents

1-methylimidazole and 1-*n*-butylimidazole were distilled from calcium hydride under reduced pressure.

In all other cases reagents were used as supplied.

Chromatography

Analytical thin layer chromatography (TLC) was carried out on aluminium, plastic or glass backed sheets of silica gel 60 F_{254}. Materials were visualized by UV radiation at 254nm, by development in potassium permanganate, in aqueous sodium carbonate, or in phosphomolybdic acid in ethanol.

Flash column chromatography was carried out using silica gel 40-60μ 60Å.

Microwave-accelerated synthesis

Reactions were carried out in either a CEM Discover® or a Biotage Initiator sixty™ microwave oven.

Gas chromatography

Gas chromatography was carried out on a Hewlett-Packard 5890 series II fitted with a 25m column. Detection was by flame ionization.

Mass spectrometry

Low resolution mass spectra (EI or CI) were obtained on VG Analytical 7070E or VG Autospec Organic mass spectrometers. Gas chromatography-mass spectra (GCMS, EI or CI) were obtained using a Hewlett Packard 5890 Series II gas chromatography equipped with a 25 m column connected to a VG Trio-1000. Electrospray mass spectra (ES) were obtained on a Micromass LCT Mass spectrometer. High resolution mass spectra were performed on a Micromass Autospec mass spectrometer in Durham. Inductively coupled plasma mass spectrometry (ICP-MS) was carried out using a Perkin Elmer Sciex Elan 6000 spectrometer.

IR spectroscopy

Infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrometer using either thin films between NaCl discs (liquids and oils); discs formed by compression with KBr (solids); use of a Diamond ATR (attenuated total reflection) accessory (Golden Gate) (liquids, oils and solids) or by liquid film using a semi peron cell type 1011 with 0.1mm path-length and KBr windows (liquids, oils and solids).

NMR spectroscopy

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or d_6-DMSO on Varian Mercury – 200, Varian Unity – 300, Bruker Avance – 400, Varian Mercury – 400 and Varian Inova – 500 spectrometers respectively. Spectra are reported as follows: chemical shift δ (ppm) (number of protons, multiplicity, coupling constant J (Hz), assignment). All chemical shifts are quoted in parts per million relative to tetramethylsilane ($\delta_H = 0.00$).

N.B. With compounds **14a** and **14b** one peak was obscured by the carbon peaks from the d_6-DMSO solvent using ^{13}C NMR spectroscopy. With compounds **15c**, **15e** and **16a** one peak was obscured by peaks from residual H_2O/HOD in the d_6-DMSO solvent using ^{1}H NMR spectroscopy.

6.2- Experimental methods and data

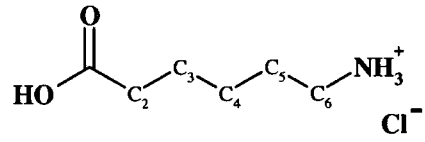
Synthesis of bis(acetonitrile) palladium dichloride [198]

$Pd(MeCN)_2Cl_2$

Dry palladium dichloride (2.0g, 0.011mol) was stirred in dry MeCN (20ml) at room temperature under argon for 12 hours. After filtration of the orange slurry, an orange/yellow solid was collected and dried. $Pd(MeCN)_2Cl_2$ was collected in 100% yield.

M.p. = >250°C; found C, 18.59, H, 2.40, N, 10.99%, $C_4H_6N_2PdCl_2$ requires C, 18.53, H, 2.32, N, 10.81%

Synthesis of 6-aminohexanoic acid hydrochloride [199]



6-Aminohexanoic acid (11.30g, 0.086mol) was stirred in water (15ml) containing concentrated HCl solution (15ml) under an argon atmosphere. The solution was heated to reflux and stirred for 3 hours. After cooling, the solution was concentrated *in vacuo* and diluted with acetone (50ml). A white precipitate was formed which was filtered and dried to yield a white crystalline solid (14.30g, 99% yield).

M.p. 130-132°C; Literature m.p. 132-133°C [199]; δ_H (300MHz, D_2O): 2.80 (2H, t, J= 7.5Hz, C(6)H), 2.00 (2H, t, J= 7.2Hz, C(2)H), 1.43 (4H, m, C(3)H and C(5)H), 1.18 (2H, m, C(4)H); *m/z* (ES^+): 172 $[(M^+)+H+K^+]^{\cdot+}$, 132 $[M^+]$

General procedure for attachment of a carboxylic acid onto an amino-functionalised resin such as amino Tentagel® or aminomethyl polystyrene

Amino-functionalised resin (Xg, N mmol.g^{-1}), carboxylic acid (3 equiv. = 3(X . N mmol)), PyBop® coupling reagent (5 equiv. = 5(X . N mmol)), dry NEt_3 (6 equiv. = 6(X . N mmol)) were all measured into a fritted solid phase reaction tube. Sufficient dry DMF was added to dissolve all of the carboxylic acid substrate and other reagents. The reaction tube was sealed with a rubber bung and taped shut with parafilm®. The reaction tube and its contents were shaken vigorously for 24 hours after which time the modified resin was drained and the reaction tube recharged with substrate, reagents and solvent. The reaction tube was once again sealed and shaken for another 24 hours. After which time the modified resin was then drained and washed with i) DCM (5 x 20ml), ii) DMF (5 x 20ml), iii) DCM and MeOH (alternate 5 x 20ml each), iv) Et_2O (5 x 10ml). The modified resin was then blown dry with argon and dried *in vacuo* at 60°C to constant mass before analysis.

General procedure for Suzuki catalysis

The reactions for Suzuki coupling studies were typically conducted as follows: catalyst (1 mol%), K_2CO_3 (270mg, 1.95mmol), boronic acid (1.50mmol), aryl halide (1.31mmol), diethylene glycol di-*tert*-butyl ether (323µl, 1.31mmol, GC standard), dry DMA (10ml) and a magnetic stirrer were added to a Radley's™ parallel synthesis carousel reaction tube. The tube was sealed with a Teflon screw cap. The reaction mixture was optionally degassed by bubbling argon through the reaction tube contents for 30 minutes prior to use. The reaction tube was placed in the carousel on top of a stirrer hotplate and heated to the desired temperature for the appropriate length of time of the experiment. After cooling to room temperature the reaction contents were filtered and the supported catalyst washed with DCM (30ml). For GC analysis the filtrate was measure into a 50ml standard volumetric flask and made up to the required volume with DCM. A small aliquot was taken for GC analysis of the reaction. For an isolated yield the organic filtrate was extracted with water (3 x 20ml) and dried with $MgSO_4$.

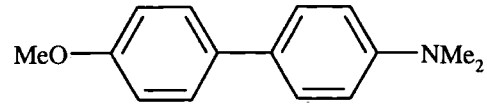
The mixture was filtered and solvent removed *in vacuo*. FCC (9:1 petroleum ether 40/60/EtOAc) afforded a white crystalline solid. The catalyst was washed further with THF/H_2O (1:1, 3 x 30ml) and Et_2O (3 x 10ml) and dried *in vacuo* for further use. All products were characterised by comparing with data available from commercially available samples.

General procedure for Heck catalysis

The reactions for Heck coupling studies were typically conducted as follows: catalyst (1 mol%), K_2CO_3 (610mg, 4.41mmol), acrylate (3.14mmol), aryl halide (2.23mmol), dry DMA (10ml) and a magnetic stirrer were added to a Radley's™ parallel synthesis carousel reaction tube. The tube was sealed with a Teflon screw cap. The reaction mixture was optionally degassed by bubbling argon through the reaction tube contents for 30 minutes prior to use. The reaction tube was placed in the carousel on top of a stirrer hotplate and heated to the desired temperature for the appropriate length of time of the experiment. After cooling to room temperature the reaction contents were filtered and the supported resin washed with DCM (30ml). The organic filtrate was extracted with water (3 x 20ml) and dried with $MgSO_4$. The mixture was filtered and solvent removed *in vacuo*. FCC (15:1 *n*-hexane/EtOAc) afforded a colourless oil. The catalyst was washed further with THF/H_2O (1:1, 3 x 30ml) and Et_2O (3x 10ml) and dried *in vacuo* for further use. All products were characterised by comparing with data available from commercially available samples.

Cross-coupling reaction products:

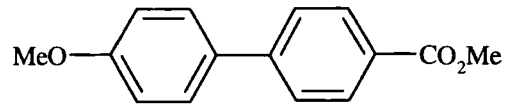
4-methoxy-4'-N,N-dimethylaminobiphenyl [200]



M.p. = 157-158°C; Literature m.p. = 157-159°C [200]; ν_{MAX} (ATR): 2268, 2117, 2067 cm^{-1}; δ_H (300MHz, $CDCl_3$) 7.51 (4H, m, Ar-H), 7.00 (2H, d, J= 8.8Hz, Ar-H), 6.85 (2H, d,

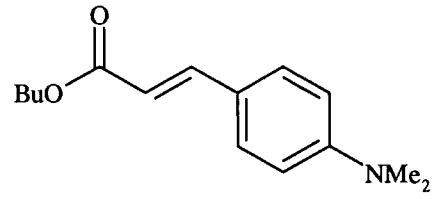
J= 8.8Hz, Ar-H), 3.87 (3H, s, OCH_3), 3.01 (6H, s, $N(CH_3)_2$); *m/z* (EI): 212.1 (100), 227.1 (95) [M^+]

4'-methoxy-biphenyl-4-carboxylic acid methyl ester [201]



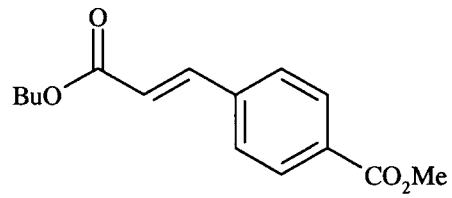
M.p. = 172-173°C; Literature m.p. = 172-174°C [201]; ν_{MAX} (ATR): 2245, 2130, 2079, 2032, 1705 (s) cm^{-1}; δ_H (300MHz, $CDCl_3$): 8.10 (2H, d, J= 8.4Hz, Ar-H), 7.64 (2H, d, J= 8.4Hz, Ar-H), 7.59 (2H, d, J= 8.4Hz, Ar-H), 7.02 (2H, d, J= 8.4, Ar-H); δ_C (100MHz, $CDCl_3$): 233.1, 167.3, 160.1, 145.4, 132.6, 130.3, 128.6, 126.7, 114.6, 55.6, 52.3; *m/z* (EI): 139.1 (100), 242.1 (70) [M^+]

3-(4-dimethylamino-phenyl)acrylic acid butyl ester [202]



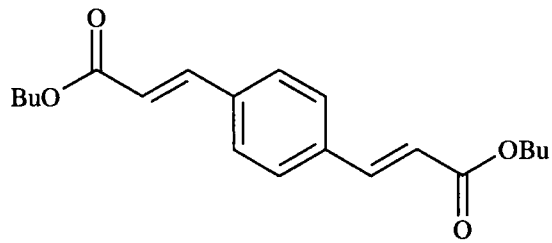
ν_{MAX} (ATR): 2252, 2116, 2090, 1998, 1898, 1715 (s), 1638 (w) cm^{-1}; δ_H (300MHz, $CDCl_3$): 7.65 (1H, d, J= 15.8, CH=C<u>H</u>), 7.43 (2H, d, J= 8.5Hz, Ar-<u>H</u>), 6.67 (2H, d, J= 8.5Hz, Ar-<u>H</u>), 6.26 (1H, d, J= 15.8Hz, C<u>H</u>=CH), 4.19 (2H, t, J= 7.1Hz, $OC\underline{H}_2CH_2CH_2CH_3$), 3.00 (6H, s, $NC\underline{H}_3$), 1.69 (2H, m, $OCH_2C\underline{H}_2CH_2CH_3$), 1.45 (2H, m, $OCH_2CH_2C\underline{H}_2CH_3$), 0.97 (3H, t, J= 7.1Hz, $OCH_2CH_2CH_2C\underline{H}_3$); δ_C (100Mhz, $CDCl_3$): 168.3, 151.9, 145.3, 129.9, 122.5, 112.79, 112.02, 64.2, 40.4, 31.1, 19.5, 14.0; *m/z* (EI):174.0 (100), 247.1 (90) [M^+]

4-((E)-2-butoxycarbonyl-vinyl)benzoic acid methyl ester [203]



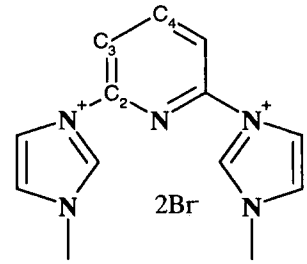
ν_{MAX} (ATR): 2240, 2097, 2005, 1720 (s), 1705 (s); δ_H (300MHz, $CDCl_3$): 8.06 (2H, d, J= 8.2Hz, Ar-H), 7.72 (1H, d, J= 16.1Hz, C<u>H</u>=CH), 7.59 (2H, d, J= 8.2Hz, Ar-H), 6.55 (1H, d, J= 16.1Hz, CH=C<u>H</u>), 4.22 (2H, t, J= 6.6Hz, OC<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 3.93 (3H, s, $CO_2C\underline{H}_3$), 1.69 (2H, m, $OCH_2C\underline{H}_2CH_2CH_3$), 1.45 (2H, m, $OCH_2CH_2C\underline{H}_2CH_3$), 0.97 (3H, t, $OCH_2CH_2CH_2C\underline{H}_3$); δ_C (100MHz, $CDCl_3$): 166.9, 166.7, 143.3, 138.9, 131.5, 130.3, 128.1, 120.9, 64.9, 52.5, 30.9, 19.4, 14.0; *m/z* (EI): 102.0 (100), 262.1 (10) [M^+]

<u>1,4-di-(2-n-butylcarbonyl-trans-vinyl)benzene [204]</u>



ν_{MAX} (ATR): 2269, 2123, 2085, 1998, 1850, 1718 (s); δ_H (300MHz, $CDCl_3$): 7.62 (2H, d, J= 16.2Hz, C<u>H</u>=CH), 7.47 (4H, s, Ar-<u>H</u>), 6.43 (2H, d, J= 16.2Hz, CH=C<u>H</u>), 4.15 (4H, t, J= 7.2Hz, OC<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.63 (4H, m, $OCH_2C\underline{H}_2CH_2CH_3$), 1.38 (4H, m, $OCH_2CH_2C\underline{H}_2CH_3$), 0.90 (6H, t, J= 7.2Hz, $OCH_2CH_2CH_2C\underline{H}_3$); *m/z* (EI): 41.1 (100), 273.1 (5) $[(M^+)\text{-}CH_2CH_2CH_2CH_3]^{+}$, 330.2 (5) [$M^+$]

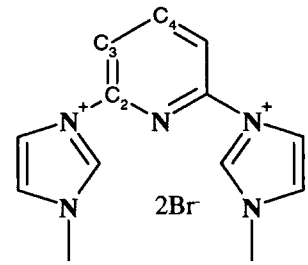
Synthesis of 2,6-bis[*N*-methylimidazolium]pyridine dibromide, **1a** [151, 152]



A mixture of 2,6-dibromopyridine (4.00g, 0.017mol) and *N*-methylimidazole (2.77g, 0.034mol) was heated at 150°C under N_2 in a round-bottomed flask fitted with a reflux condenser for 3 hours in the absence of solvent to yield a brown/yellow precipitate. The reaction mixture was cooled to room temperature and filtered. The precipitate was washed with DCM. After drying a white solid was collected (6.13g, 91% yield).

M.p. = > 250°C; Literature m.p. = >250°C [151]; found C 38.95, H 3.82, N 17.27%, $C_{13}H_{15}N_5Br_2$ requires C 38.90, H 3.74, N 17.45%; δ_H (250MHz, d_6-DMSO): 10.24 (2H, s, NC<u>H</u>N), 8.80 (2H, d, J= 1.8 Hz, NC<u>H</u>CHN); 8.61 (1H, t, J= 8.0Hz, C(4)<u>H</u>); 8.21 (2H, d, J= 8.0Hz, C(3)<u>H</u> and C(5)<u>H</u>); 8.09 (2H, d, J= 1.8Hz, NC<u>H</u>CHN); 4.01 (6H, s, NC<u>H</u>$_3$); *m/z* (ES^+): 184 $[(M^+)\text{-}H]^+$

General microwave procedure for synthesis of a tridentate CNC ligand such as **1a**

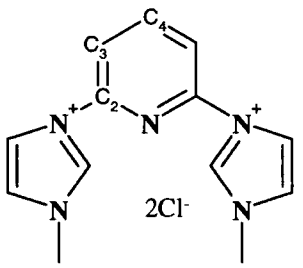


A mixture of 2,6-dibromopyridine (0.80g, 0.004mol) and *N*-methylimidazole (0.54ml, 0.0084mol) was stirred in a thick-walled glass microwave heating tube and degassed using argon. The reaction tube was sealed with a metal cap and placed inside the

microwave oven. After setting parameters for stirring, cooling, ramp time of 3 minutes, and heating for 10 minutes at 140°C, heating was started. After heating, the microwave oven underwent a cooling cycle for 5 minutes and the reaction tube was removed. After filtration of the tube contents, a precipitate was collected which was washed with DCM to yield a white crystalline solid. After drying the solid was collected (1.63g, 91% yield).

M.p. = >250°C; found C, 38.76, H, 3.75, N, 17.41%, $C_{13}H_{15}N_5Br_2$ requires C, 38.90, H, 3.74, N, 17.45%; δ_H (250MHz, d_6-DMSO): 10.24 (2H, s, NCHN); 8.80 (2H, broad t, J=1.8 Hz, NCHCHN); 8.61 (1H, t, J= 8.1Hz, C(4)H); 8.21 (2H, d, J= 8.1Hz, C(3)H and C(5)H); 8.09 (2H, broad t, J= 1.8Hz, NCHCHN); 4.01 (6H,s, N-CH_3); *m/z* (ES^+): 184 $[(M^+)-H]^+$

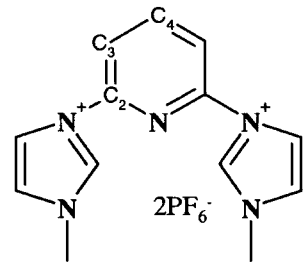
Synthesis of 2,6-bis[*N*-methylimidazolium]pyridine dichloride, **1b**



A mixture of 2,6-dichloropyridine (5.00g, 0.034mol) and *N*-methylimidazole (4.63g, 0.068mol) was heated at 150°C under N_2 in a round-bottomed flask fitted with a reflux condenser, in the absence of solvent for 24 hours to yield a brown precipitate. The reaction mixture was cooled to room temperature and filtered. The brown precipitate was washed with DCM to yield a crude brown solid. Recrystallisation of the crude product (MeOH/DCM) yielded an off white solid (1.56g, 14.7% yield).

M.p. = >250°C; found C 50.16, H 4.62, N 22.22%, $C_{13}H_{15}N_5Cl_2$ requires C 50.00, H 4.80, N 22.43%; ν_{MAX} (ATR): 2970 (w), 2360 (w), 1740 (s), 1336 (m), 1222 (m), 1217(m) cm^{-1}; δ_H (250MHz, d_6-DMSO): 10.76 (2H, s, NCHN), 8.82 (2H, d, J= 1.8Hz, NCHCHN); 8.60 (1H, t, J= 8.1Hz, C(4)H); 8.22 (2H, s, C(3)H and C(5)H); 8.12 (2H, d, J= 1.8Hz, NCHCHN); 4.10 (6H, s, NCH_3); δ_C (100MHz, d_6-DMSO): 145.9, 145.6, 137.0, 125.7, 119.8, 114.7, 37.2; *m/z* (ES^+): 184 $[(M^+)-H]^+$

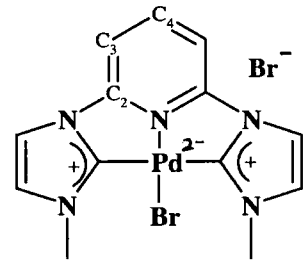
Conversion of 2,6-bis[*N*-methylimidazolium] pyridine dibromide into 2,6-bis[1-methylimidazolium] pyridine di(hexafluorophosphate), **1c**



2,6-bis[1-methylimidazolium-3-yl]pyridine dibromide (0.20g, $4.9x10^{-4}$mol) was dissolved in MeOH (15ml). This solution was added dropwise to a saturated solution of NH_4PF_6 in MeOH (50ml). A white precipitate was seen to form and the solution was left overnight. After the precipitate had settled, the solution was decanted and the precipitate was collected by centrifuge. The precipitate was washed three times in MeOH and each time collected by centrifuge. Recrystallisation of the precipitate (MeCN) yielded a white solid (0.26g, 99% yield).

M.p. = 244-246°C; found C 29.35, H 2.86, N 13.58%; Br content 0.14%, $C_{13}H_{15}N_5P_2F_{12}$ requires C 29.39, H 2.83, N 13.19%, Br content 0.00%

Synthesis of 2,6-bis[*N*-methylimidazol-3-ylidene]pyridine palladium bromide, **4** [152]

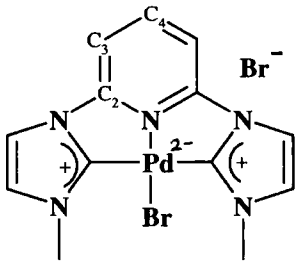


A mixture of $Pd(OAc)_2$ (0.50g, 0.002mol) and 2,6-bis[*N*-methylimidazolium]pyridine dibromide (0.90g, 0.002mol) was stirred in degassed DMSO (5ml) in a Schlenk tube under N_2 at room temperature for 3 hours, 50°C for 15 hours and finally at 160°C for 3

hours. A yellow precipitate was formed which was collected by filtration and washed with MeCN and DCM. Recrystallisation of the solid (DMSO/DCM) yielded a yellow/green solid (0.52g, 52% yield).

M.p. = >250°C; Literature m.p. = >250°C [152]; found C 30.55, H 2.61, N 13.69%, $C_{13}H_{13}N_5PdBr_2$ requires C 30.86, H 2.57, N 13.80%; ν_{MAX} (KBr): 3208 (m), 3067 (m), 2867 (m), 1810 (m), 1729 (s), 1656 (s), 1577 (s), 1489 (s), 760 (s) cm^{-1}; δ_H (250MHz, d_6-DMSO): 8.58 (1H, t, J= 8.0Hz, C(4)H); 8.43 (2H, d, J= 1.8Hz, NCHCHN); 8.00 (2H, d, J= 8.0Hz, C(3)H and C(5)H); 7.65 (2H, d, J= 1.8Hz, NCHCHN); 4.04 (6H, s, NCH_3); δ_C (125MHz, d_6-DMSO): 167.1, 151.8, 148.0, 126.4, 119.1, 110.0, 38.6; *m/z* (ES^+): 426 [M^+ $^{106}Pd^+$], 427 [M^+ ^{106}Pd-H]$^+$

General microwave procedure for synthesis of a tridentate CNC bis(carbene) complex such as **4**

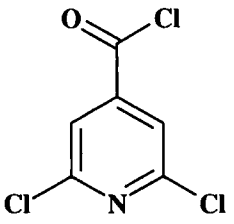


A mixture of 2,6-bis[*N*-methylimidazolium]pyridine dibromide (0.22g, 0.0005mol) and $Pd(OAc)_2$ (0.12g, 0.0005mol) was stirred in dry DMSO (2ml) inside a thick walled glass microwave heating tube and degassed using argon. The reaction tube was sealed with a metal cap and placed inside the microwave oven. After setting parameters for stirring, cooling, ramp time of 3 minutes, and heating for 5 minutes at 160°C, heating was started. After heating, the microwave oven underwent a cooling cycle for 5 minutes and the reaction tube was removed. After filtration of the tube contents, a precipitate was collected which was washed with DCM to yield a pale green solid (0.26g, 95% yield).

M.p. = >250°C; found C, 30.55.05, H, 2.63, N, 13.43%, $C_{13}H_{13}N_5PdBr_2$ requires C, 30.86, H, 2.57, N, 13.8%; ν_{MAX} (KBr): 3208 (m), 3067 (m), 2867 (m), 1810 (m), 1729 (s), 1656 (s), 1577 (s), 1489 (s), 760 (s); δ_H (250MHz, d_6-DMSO): 8.58 (1H, t, J= 8.1Hz, C(4)H); 8.43 (2H, broad t, J= 1.8Hz, NCHCHN); 8.00 (2H, d, J= 8.1Hz, C(3)H

and C(5)H); 7.65 (2H, broad t, J= 1.8Hz, NCHCHN); 4.04 (6H, s, N-CH_3); δ_C (125MHz, d_6-DMSO): 167.1, 151.8, 148.0, 126.4, 119.1, 110.0, 38.6; *m/z* (ES^+): 426 [M^+ ^{106}Pd], 427 [(M^+ ^{106}Pd)-H]$^{+}$

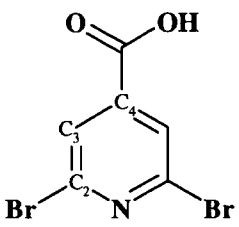
Synthesis of 2,6-dichloroisonicotinic acid chloride, **5b**



2,6-dichloroisonicotinic acid (1.25g, 0.006mol) was suspended in dry DCM (10ml) at 0°C under argon. Oxalyl chloride (0.85ml, 1.5 eq) was added dropwise and a catalytic amount of dry DMF (0.05ml) was added. The reaction mixture was stirred for 3 hours until no more effervescence was seen. The reaction mixture was concentrated *in vacuo* to yield a crude yellow solid. The crude solid was used immediately in later stages of synthesis.

ν_{MAX} (ATR): 3089 (w), 1771 (s), 1576 (s), 1543 (s), 1360 (s) cm^{-1}

Synthesis of 2,6-dibromoisonicotinic acid, **5d** [159]

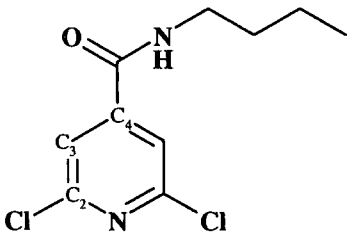


Citrazinic acid (8.56g, 0.055mol) and $POBr_3$ (25.00g, 0.086mol) were heated at 175°C in an autoclave for 5 hours. The autoclave was cooled down over a period of 12 hours. The autoclave was cautiously opened and an acidic gas was released. This was treated by passing through a glass bubbler containing aqueous NaOH. Water (500ml) was cautiously added to the black product inside the autoclave and filtered. The brown

aqueous phase was extracted five times with DCM. The black residue was continuously extracted in a Soxhlet extractor with DCM for 15 hours and the brown solution obtained was combined with the previous organic extracts. The organic phase was dried ($MgSO_4$) and solvent removed *in vacuo*. The brown residue was recrystallised from DCM to obtain a very pale yellow solid (8.90g, 57% yield).

M.p. = 186-188°C. Literature m.p. = 184-185°C [159]; found C, 25.64, H, 1.25, N, 4.97%, $C_6H_3Br_2NO_2$ requires C, 25.65, H, 1.08, N, 4.99%; ν_{MAX} (KBr): 3104 (br), 1725 (s), 1540 (s), 1413 (m), 675 (s) cm^{-1}; δ_H NMR (300MHz, $CDCl_3$): 8.06 (2H, s, C(3)H and C(5)H); δ_C (100MHz, $CDCl_3$): 167.3, 142.7, 141.2, 127.1; *m/z* (ES^+): 234 $[(M^+ 2Br^{79})-CO_2H]^{+}$, 236 $[(M^+ Br^{79}\&Br^{81})-CO_2H]^{+}$, 238 $[(M^+ 2Br^{81})-CO_2H]^{+}$, 278 $[M^+ 2Br^{79}]$, 280 $[M^+Br^{79}\&Br^{81}]$, 282 $[M^+2Br^{81}]$

Synthesis of *N*-butyl-2,6-dichloroisonicotinamide, **8** [154]

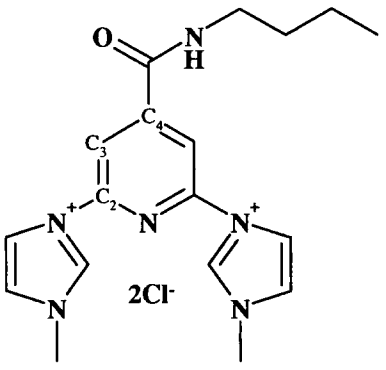


2,6-dichloroisonicotinic acid (0.20g ,0.001mol) was stirred in dry DCM (2ml) at -78°C under N_2. Oxalyl chloride (0.13g, 1 eq) was added dropwise over 5 minutes. DMF (1 drop) was carefully added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred for 1 hour. Solvent and volatile by products were removed *in vacuo* and the resulting precipitate was dissolved in dry DCM (2ml) and stirred under N_2 at –78°C. A solution of butylamine (1.5 eq), NEt_3 (1.5 mol. 1 eq) and DMAP (5mg) was prepared in dry DCM (5ml). This "basic" solution was added dropwise over 5 minutes to the dissolved precipitate at –78°C and stirred for 30 minutes. The reaction mixture was warmed to room temperature and stirred for one hour. The reaction mixture was washed with water (5ml) and the organic layer collected. The organic layer was further washed with $NaHCO_3$ solution (5ml, 10%). The organic layer was extracted and dried ($MgSO_4$). Residual solvent was removed *in*

vacuo to yield a pale white solid (0.26g). Recrystallisation of the solid (EtOAc/petroleum ether 40/60) yielded an off white solid (0.19g, 70% yield).

M.p. = 92-94°C. Literature m.p. = 93-94°C [151]; found C 49.01, H 4.92, N 11.50%, $C_{10}H_{12}N_2OCl_2$ requires C 48.58, H 4.85, N 11.34%; ν_{MAX} (KBr): 3293 (m), 2923 (br), 1647 (s), 1558 (m), 1460 (s), 1376 (s), 1165 (m), 810 (m), 723 (m) cm^{-1}; δ_H (300MHz, $CDCl_3$): 7.49 (2H, s, C(3)H and C(5)H), 6.19 (1H, broad s, CONH); 3.44 (2H, m, $NHCH_2CH_2CH_2CH_3$); 1.56 (2H, m, $CH_2CH_2CH_2CH_3$); 1.35 (2H, m, $CH_2CH_2CH_2CH_3$); 0.92 (3H, t, J= 6.3Hz, $CH_2CH_2CH_2CH_3$); δ_C (65MHz, d_6-DMSO): 163.8, 151.9, 148.0, 120.6, 40.0, 31.4, 20.0, 13.7; *m/z* (CI, NH_3): 245 (42) $[(M^+)-H]^+$, 246 (100) $[M^+]$

Synthesis of 2,6-bis[*N*-methylimidazolium]isonicotin-4-*n*-butylamide dichloride, **9**

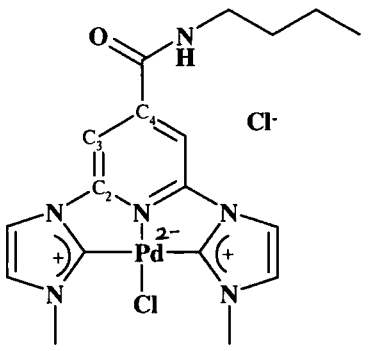


A mixture of 2,6-dichloropyridine-4-*n*-butylamide (0.15g, 0.001mol) and *N*-methylimidazole (0.10g, 2 eq) was heated under N_2 in the absence of solvent at 150°C for 21 hours. The reaction mixture was allowed to cool and the solution was filtered. A brown precipitate was collected which was washed with DCM. The brown precipitate was heated with decolourising charcoal in methanol at 50°C for 20 minutes. Filtration and evaporation of the solute yielded a yellow/white solid (0.24g, 90% yield).

M.p.= >250°C; found C 52.58, H 5.77, N 20.13%, $C_{18}H_{24}N_6OCl_2$ requires C 52.50, H 5.83, N 20.04%; ν_{MAX} (ATR): 2970 (w), 2361 (m), 2349 (m), 1739 (s), 1365 (m), 1229 (m), 1222 (m) cm^{-1}; δ_H (300MHz, d_6-DMSO): 10.64 (2H, s, NCHN), 9.50 (1H, t, J= 5.7Hz, CONH), 8.92 (2H, d, J= 2.0Hz, NCHCHN), 8.83 (2H, s, C(3)H and C(5)H), 8.10 (2H, d, J= 2.0Hz, NCHCHN), 4.05 (6H, s, NCH_3), 3.40 (2H, m, $NHCH_2CH_2CH_2CH_3$), 1.59 (2H, m, $CH_2CH_2CH_2CH_3$), 1.38 (2H, m, $CH_2CH_2CH_2CH_3$);

0.94 (3H, t, J= 7.2Hz, $CH_2CH_2CH_2C\underline{H}_3$); *m/z* ($ES^+$): 283 $[(M^+)\text{-}CH_2CH_2CH_2CH_3]^{\cdot+}$, 340 $[M^+]$

Synthesis of 2,6-bis[*N*-methylimidazol-3-ylidene]isonicotin-4-*n*-butylamide palladium chloride, **10a**

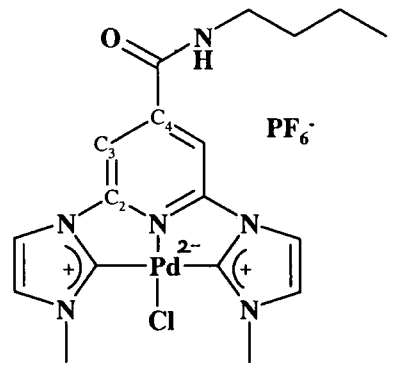


A mixture of 2,6-bis[*N*-methylimidazolium-3-yl]isonicotin-4-*n*-butylamide dichloride (0.99g, 0.002mol) and $Pd(OAc)_2$ (0.56g, 0.002mol) was stirred in degassed DMSO (5ml) in a Schlenk tube under N_2, at room temperature for 3 hours. The temperature was raised to 50°C and the reaction mixture stirred for 12 hours and finally at 160°C for 3 hours.

The reaction mixture was cooled to room temperature and filtered. A brown precipitate was collected which was washed with MeCN and DCM to yield a crude green solid. Recrystallisation of the solid (DMSO/DCM) yielded a pale green solid (1.14g, 81% yield).

M.p.= >250°C; found C 38.68, H 4.63, N 14.76%, $C_{18}H_{22}N_6PdOCl_2$ requires C 41.90, H 4.27, N 16.3%; ν_{MAX} (ATR): 2979 (w), 2354 (m), 1743 (s), cm^{-1}; δ_H (400MHz, d_6-DMSO): 9.13 (1H, t, J= 2.5Hz, CON$\underline{H}$); 8.48 (2H, d, J= 2.0Hz, NC$\underline{H}$CHN); 8.41 (2H, s, C(3)$\underline{H}$ and C(5)$\underline{H}$); 7.71 (2H, d, J= 2.0Hz, NCHC$\underline{H}$N); 4.07 (6H, s, $NC\underline{H}_3$), 3.49 (2H, m, $NHC\underline{H}_2CH_2CH_2CH_3$); 1.58 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$); 1.40 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$); 0.93 (3H, t, J= 7.2Hz, $CH_2CH_2CH_2C\underline{H}_3$); δ_C (100MHz, d_6-DMSO): 167.2, 163.2, 151.4, 126.2, 118.9, 108.0, 37.4, 31.6, 20.3, 14.4; *m/z* (ES^+): 481 $[M^+$ $^{106}Pd]$, 482 $[(M^+\,^{106}Pd)+H]^{\cdot+}$

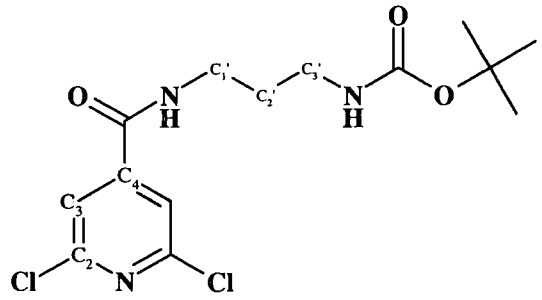
Conversion of 2,6-bis[*N*-methylimidazol-3-ylidene]isonicotin-4-*n*-butylamide palladium chloride to 2,6-bis[*N*-methylimidazol-3-ylidene] isonicotin-4-*n*-butylamide palladium chloride hexafluorophosphate, **10b**



2,6-bis[*N*-methylimidazol-3-ylidene]isonicotin-*n*-butylamide palladium chloride (0.10g, 0.00019mol) was dissolved in the minimum amount of MeOH (~25ml). This solution was added dropwise to a saturated solution of NH_4PF_6 in MeOH (100ml). A green/white precipitate slowly formed which was allowed to settle overnight. Most of the liquid phase was separated off and the solid collected by centrifugation. The solid was washed 3 times with MeOH and each time the solid collected by centrifuge or by settling overnight. The solid was recrystallised (MeCN/DCM) and the solution filtered to yield a light green solid (0.11g, 94% yield).

M.p.= >250°C; found C 34.19, H 3.28, N 13.69%, $C_{18}H_{22}N_6OClPdPF_6$ requires C 34.58, H 3.52, N 13.45%.

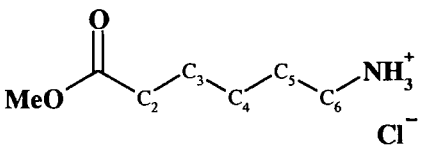
Synthesis of *N*-4'-*t*-butoxycarbonylaminopropyl-2,6-dichloroisonicotinamide, **11a**



2,6-Dichloroisonicotinic acid (3.00g, 0.015mol) was stirred in dry DCM (10ml) under N_2. Oxalyl chloride (1.98g, 1 eq) was added dropwise slowly over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 1 hour and volatile products were removed *in vacuo*. NEt_3 was added until no more precipitate was formed. Excess NEt_3 was removed *in vacuo* and dry DCM was added. The reaction mixture was stirred and cooled to –78°C. A solution of *N*-Boc-mono-protected diaminopropane (2.72g, 1 eq), NEt_3 (1.5 eq) and DMAP (2mg) was prepared in dry DCM (10ml). This basic solution was added dropwise to the reaction mixture over 5 minutes and the mixture stirred for 30 minutes. After this time the reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was washed with water and the organic layer separated. This layer was further washed with $NaHCO_3$ solution (10%). The organic layer was collected and dried ($MgSO_4$). Residual solvent was removed *in vacuo* to yield a brown precipitate. Recrystallisation of the solid product (EtOAc/petroleum ether 40/60) yielded a pale yellow solid (1.30g, 24% yield).

M.p. 120-124°C; found C, 48.30, H, 5.58, N, 11.87%, $C_{14}H_{19}N_3O_3Cl_2$ requires C, 48.27, H, 5.46, N, 12.07%; δ_H (300MHz, d_6-DMSO): 8.86 (1H, t, J= 5.7Hz, CONH); 7.87 (2H, s, C(3)H); 6.83 (1H, t, J= 5.7Hz, NHCOO^{t}Bu); 3.26 (2H, m, C(1')H); 2.98 (2H, m, C(3')H); 1.63 (2H, m, C(2')H); 1.37 (9H, s, $C(CH_3)_3$); δ_C (125MHz, d_6-DMSO): 161.9, 155.6, 149.8, 147.8, 121.5, 77.5, 37.6, 37.4, 29.0, 28.3; *m/z* (ES^+): 347 [M^+ $2^{35}Cl$], 349 [M^+ ^{35}Cl&^{37}Cl], 351 [M^+ $2^{37}Cl$]

Synthesis of 6-aminohexanoic acid methyl ester hydrochloride, **13a** [157, 199]

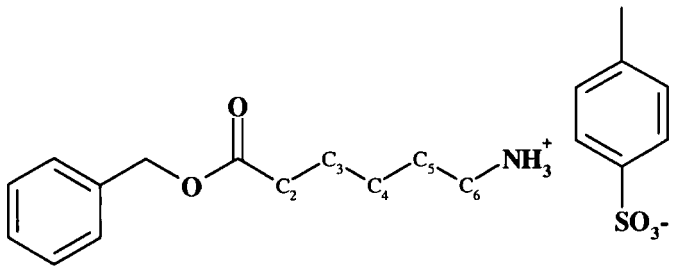


6-Aminocaproic acid hydrochloride (3.00g, 0.017mol) was stirred in dry MeOH (10ml). In a separate reaction flask, acetyl chloride (10ml) was added dropwise at 0°C to a stirred volume of dry MeOH (50ml). Once effervescence had finished, the solution

of 6-aminocaproic acid hydrochloride was added dropwise to the acetyl chloride at room temperature. The reaction mixture was heated to reflux and stirred for 48 hours. After cooling, solvent was removed *in vacuo* to yield a pale yellow solid. Recrystallisation of the solid ($MeOH/Et_2O$) yielded a white crystalline solid (3.17g, 97% yield).

M.p. 120-122°C; Literature m.p. 121-122.5°C [157,199]; ν_{MAX} (KBr): 3601 (br), 2527 (m), 2447 (m), 2353 (m), 1950 (m), 1735 (s), 1622 (s) cm^{-1}; δ_H (300MHz, D_2O): 4.63 (3H, s, $OC\underline{H}_3$), 2.81 (2H, t, J= 7.8Hz, C(6)$\underline{H}$), 2.25 (2H, t, J= 7.5Hz, C(2)$\underline{H}$), 1.48 (4H, m, C(3)$\underline{H}$ and C(5)$\underline{H}$), 1.21 (2H, m, C(4)$\underline{H}$); δ_C (125MHz, d_6-DMSO): 173.9, 51.9, 39.2, 33.7, 27.3, 26.0, 24.6; *m/z* (ES^+): 146 [M^+], 186 [$MH+K^+]^+$

Synthesis of 6-aminohexanoic acid benzyl ester hydro-*p*-toluenesulphonate, **13b** [158]

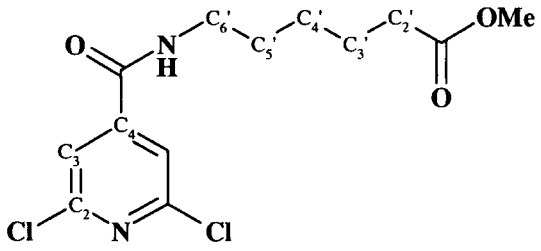


A mixture of 6-aminocaproic acid (2.00g, 0.015mol), benzyl alcohol (10ml) and *p*-toluenesulphonic acid (3.35g, 1.1 eq) in benzene (200ml) was heated to reflux for 3 hours (azeotropic distillation with Dean Stark apparatus). The solution was cooled to room temperature and stirred overnight. After addition of Et_2O (200ml), a white precipitate started to form and the solution was placed in a freezer for 48 hours. The mixture was filtered and a white crystalline solid collected, this was washed with cold Et_2O. After drying a white crystalline solid was collected (5.74g, 96% yield).

M.p. = 106-107°C. Literature m.p. = 106-107°C [158]; ν_{MAX} (KBr): 3465 (br), 2943, 2869, 2041, 1738 (s), 1626 (m), 1482 (w) cm^{-1}; δ_H (300MHz, d_6-DMSO): 7.70 (3H, broad s, $N\underline{H}_3^+$), 7.48 (2H, d, J= 8.0Hz, Ph(SO_3)-$\underline{H}$), 7.37 (5H, m, Ph-$\underline{H}$), 7.13 (2H, d, J= 8.0Hz, Ph(CH_3)-$\underline{H}$), 5.09 (2H, s, $C\underline{H}_2Ph$), 2.74 (2H, m, C(6)$\underline{H}$), 2.36 (2H, t, J= 7.2Hz, C(2)$\underline{H}$), 2.29 (3H, s, Ph-$C\underline{H}_3$), 1.52 (4H, m, C(3)$\underline{H}$ and C(5)$\underline{H}$), 1.29 (2H, m, C(4)$\underline{H}$); δ_C (125MHz, $CDCl_3$): 173.01, 141.02, 140.76, 135.91, 128.97, 128.44, 128.09, 128.04,

125.74, 66.02, 39.55, 33.71, 26.92, 25.65, 24.02, 21.17; *m/z* (ES^+): 222 [M^+], 262 [$MH+K^+]^+$

Synthesis of (2,6-dichloropyridine-4-carbonyl)-6'-aminohexanoic acid methyl ester, **14a**

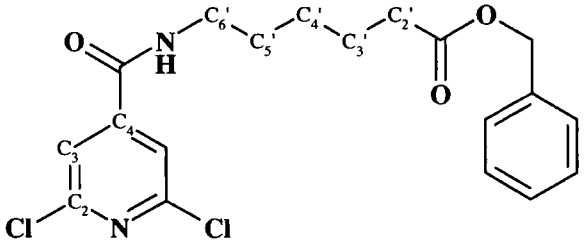


2,6-Dichloroisonicotinic acid (1.25g, 0.006mol) was suspended in dry DCM (10ml) at 0°C under argon. Oxalyl chloride (0.85ml, 1.5 eq) was added dropwise, followed by a catalytic amount of dry DMF (0.05ml). The reaction mixture was stirred for 3 hours until no more effervescence was seen. The reaction mixture was concentrated *in vacuo*. Dry $CHCl_3$ was added (15ml) and the reaction mixture stirred. 6-aminocaproic methyl ester hydrochloride (1.29g, 1.1 eq) and a catalytic amount of DMAP (0.02g) were added. Dry NEt_3 (2.26ml, 2.5 eq) was slowly added to the reaction mixture whilst stirring. The reaction mixture was warmed to room temperature and stirred overnight for 12 hours. The reaction mixture was washed with water (50ml) and the organic layer extracted with EtOAc. This organic layer was further washed with saturated aqueous $NaHCO_3$ and the organic layer extracted. After drying ($MgSO_4$) solvent was removed *in vacuo* to yield a crude yellow oil. Filtration through silica gel (100% EtOAc) yielded a pale yellow oil after the solvent was removed *in vacuo*. Petroleum ether 40/60 was added to the oil and the mixture was placed in the refrigerator. After 3 hours, filtration of the mixture yielded a pale yellow solid. After drying, a cream coloured, crystalline solid was collected (1.50g, 75% yield).

M.p. = 75-77°C. Found C, 50.0, H, 5.3, N, 8.9%; $C_{13}H_{16}N_2O_3Cl_2$ requires C, 48.9, H, 5.0, N, 8.8%; ν_{MAX}(ATR): 3310 (w), 2970 (w), 2360 (w), 1739 (s), 1640 (m), 1534 (m), 1365 (s), 1217 (m) cm^{-1}; δ_H (300MHz, d_6-DMSO): 8.84 (1H, t, J= 5.1Hz, CONH), 7.83 (2H, s, C(3)H and C(5)H), 3.22 (2H, m, C(6')H), 3.54 (3H, s, OCH_3), 2.27 (2H, t, J= 7.5Hz, C(2')H), 1.50 (4H, m, C(5')H and C(3')H), 1.29 (2H, m, C(4')H); δ_C (125MHz,

d_6-DMSO): 174.0, 162.6, 150.5, 148.5, 122.3, 51.9, 33.9, 29.0, 26.5, 24.8; *m/z* (ES^+): 345 [M^+ $2^{35}Cl$], 347 [M^+ $^{35}Cl\&^{37}Cl$], 349 [M^+ $2^{37}Cl$]

Synthesis of 6-(2,6-dichloropyridine-4-carbonyl)-6'-aminohexanoic acid benzyl ester, **14b**

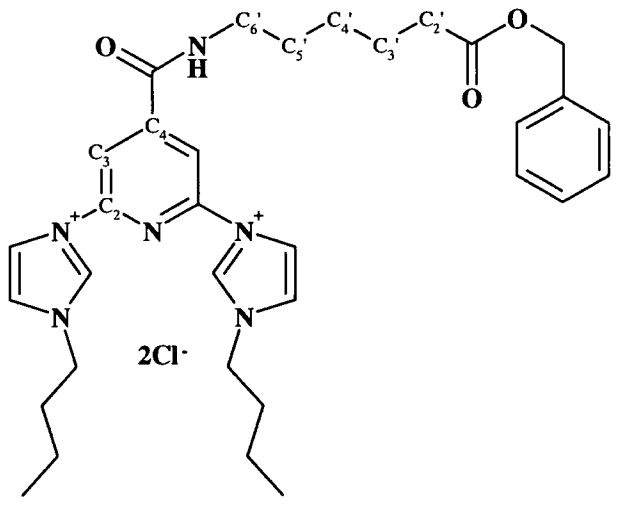


2,6-Dichloroisonicotinic acid (1.25g, 0.006mol) was suspended and stirred in dry DCM (10ml) under argon. Oxalyl chloride (0.85ml, 1.5 eq) was added dropwise at –78°C. The reaction mixture was stirred and 2 drops of dry DMF were added. The reaction mixture was allowed to warm to room temperature and stirred for 5 hours. Excess reagent and solvent were removed *in vacuo* to yield a pale yellow oil. 6-aminohexanoic acid benzyl ester *p*-toluenesulphonate (2.80g, 1.1 eq), DMAP (10mg) and dry DCM (10ml) were added to the oil at –78°C and the mixture stirred under argon.The reaction mixture was warmed to 0°C and dry NEt_3 (1.8ml, 2.5 eq) was added cautiously to the reaction mixture with stirring. The reaction mixture was warmed to room temperature and stirred for 48 hours. The reaction mixture was washed with water twice and the organic layer extracted (EtOAc). This organic layer was washed three times with saturated aqueous bicarbonate solution and the organic layer extracted (EtOAc). After drying ($MgSO_4$), the solvent was removed *in vacuo* to yield a yellow oil. FCC (50/50 EtOAc/petroleum ether 40/60) and removal of solvent *in vacuo* yielded analytically pure product as a pale yellow oil (2.03g, 79% yield).

M.p. = 84-85°C. Found C, 57.79, H, 5.11, N, 7.06%, $C_{19}H_{20}N_2O_3Cl_2$ requires C, 57.72, H, 5.06, N, 7.09%; ν_{MAX} (ATR): 3320 (w), 1729 (s), 1641 (s), 1526 (s), 1358 (m), 1280 (w), 1164 (s), 808 (m), 756 (m), 700 (m) cm^{-1}; δ_H (300MHz, d_6-DMSO): 8.83 (1H, t, J= 5.4Hz, CONH), 7.83 (2H, s, C(3)H and C(5)H), 7.30 (5H, m, Ph-H), 5.04 (2H, s, CH_2Ph), 3.22 (2H, m, C(6')H), 2.32 (2H, t, J= 7.2Hz, C(2')H), 1.51 (4H, m, C(5')H

and C(3')H), 1.27 (2H, m, C(4')H); δ_C (100MHz, d_6-DMSO): 173.4, 162.4, 150.5, 136.9, 129.1, 128.6, 128.5, 122.1, 66.0, 50.0, 34.0, 29.0, 26.5, 24.8; *m/z* (ES^+): 394 [M^+ $2^{35}Cl$], 395 [(M^+ $2^{35}Cl$)+H]$^+$, 396 [M^+ ^{35}Cl&^{37}Cl], 397 [(M^+ ^{35}Cl&^{37}Cl)+H]$^+$, 398 [M^+ $2^{37}Cl$], 399 [(M^+ $2^{37}Cl$)]$^+$

Synthesis of (2,6-bis(*N*-*n*-butyl-imidazolium)pyridine-4-carbonyl)-6'-aminohexanoic acid benzyl ester, **15a**

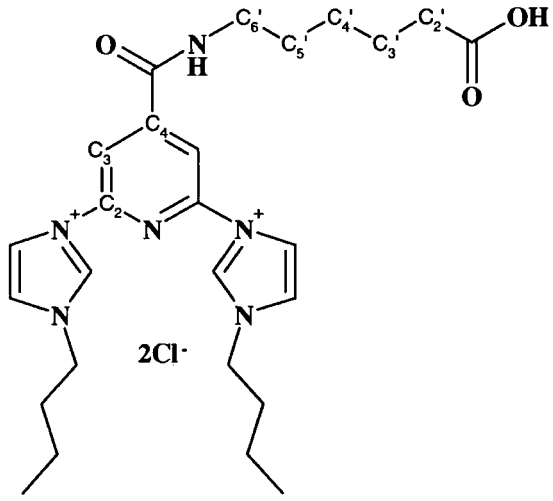


(2,6-Dichloropyridine-4-carbonyl)-6'-aminohexanoic acid benzyl ester (2.03g, 0.005mol) and *N*-*n*-butylimidazole (1.7ml, 1.60g, 2.5 eq) were measured into a round-bottom flask with a reflux condenser and then degassed using argon. The reaction mixture was heated to 160°C and stirred for 36 hours. After cooling, the mixture was filtered and a brown solid was collected. The solid was washed with cold Et_2O (5ml) to yield a cream coloured solid. Recrystallisation of the solid ($CHCl_3$) yielded analytically pure product as an off white solid (2.95g, 89% yield).

M.p. = >250°C; found C=61.65, H=6.94, N=13.24, $C_{33}H_{44}N_6O_3Cl_2$ requires C, 61.58, H, 6.84, N, 13.06%; ν_{MAX} (ATR): 2902 (w), 2348 (m), 1748 (s), 1645 (s), 1539 (m), 1222 (m) cm^{-1}; δ_H (400MHz, d_6-DMSO): 11.29 (2H, s, NCHN), 9.91 (1H, t, J= 5.6Hz, CONH), 9.10 (2H, d, J= 1.8Hz, NCHCHN), 9.05 (2H, s, C(3)H), 8.18 (2H, d, J= 1.8Hz, NCHCHN), 7.31 (5H, m, Ph-H), 5.06 (2H, s, CH_2Ph), 4.36 (4H, t, J= 6.8Hz, $NCH_2CH_2CH_2CH_3$), 3.34 (2H, m, C(6')H), 2.35 (2H, t, J= 7.6Hz, C(2')H), 1.92 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.59 (4H, m, C(5')H and C(3')H), 1.33 (6H, m,

$NCH_2CH_2C\underline{H}_2CH_3$ and C(4')H), 0.92 (6H, t, J= 7.2Hz, $NCH_2CH_2CH_2C\underline{H}_3$); δ_C (100MHz, d_6-DMSO): 173.4, 162.3, 149.7, 146.6, 137.1, 136.9, 129.1, 128.6, 128.5, 124.4, 120.3, 112.9, 65.9, 50.0, 34.0, 31.7, 29.0, 26.5, 24.8, 19.4, 14.0; *m/z* (ES^+): 571 $[(M^+)-H]^+$, 607 $[(M^+)+^{35}Cl^-]$, 609 $[(M^+)+^{37}Cl^-]$

Synthesis of (2,6-bis(*N*-*n*-butylimidazolium)pyridine-4-carbonyl)-6'-aminohexanoic acid, **15c**

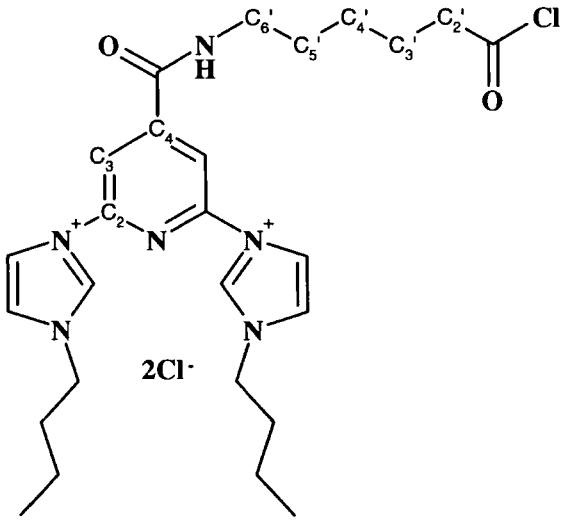


(2,6-bis(*N*-*n*-Butylimidazolium-3-yl)pyridine-4-carbonyl)-6'-aminohexanoic acid benzyl ester (3.00g, 0.004mol) and Pd (10%) on carbon catalyst (0.10g) were measured into a round bottom flask under an atmosphere of argon. Dry MeOH (20ml) was added and a hydrogenation tap fitted. The reaction mixture was stirred and repeatedly evacuated and flushed with hydrogen from a balloon. The reaction mixture was stirred under an atmosphere of hydrogen for 80 minutes. The reaction mixture was filtered and concentrated *in vacuo*. Fresh catalyst (Pd (10%) on carbon (0.10g)) and solvent (dry MeOH) were added and the hydrogen evacuation – flushing process repeated. The reaction mixture was stirred under an atmosphere of hydrogen for another 80 minutes. Following work-up by filtration and solvent removal *in vacuo* an orange/brown crystalline solid was formed. Recrystallisation (^{i}PrOH) gave a white crystalline solid (2.30g, 89% yield).

M.p. = >250°C; found: C, 56.05, H, 6.69, N, 15.01%, $C_{26}H_{38}N_6O_3Cl_2$ requires C, 56.42, H, 6.87, N, 15.19%; ν_{MAX} (KBr): 3566 (br), 3214 (m), 1717 (s), 1654 (s), 1541 (m),

1229 (m) cm^{-1}; δ_H (200 MHz, d_6-DMSO): 12.00 (1H, s, $CO_2\underline{H}$), 10.94 (2H, s, NC$\underline{H}$N), 9.70 (1H, t, J= 5.2Hz, CON$\underline{H}$), 8.99 (2H, d, J= 1.8Hz, NCHC$\underline{H}$N), 8.93 (2H, s, C(3)$\underline{H}$), 8.16 (2H, s, J= 1.8Hz, -NC$\underline{H}$CHN), 4.34 (4H, t, J= 7.0Hz, NC$\underline{H}_2$$CH_2CH_2CH_3$), 2.20 (2H, t, J= 7.2Hz, C(2')$\underline{H}$), 1.92 (4H, m, $NCH_2C\underline{H}_2CH_2CH_3$), 1.57 (4H, m, C(5')$\underline{H}$ and C(3')$\underline{H}$), 1.33 (6H, m, $NCH_2CH_2C\underline{H}_2CH_3$ and C(4')$\underline{H}$), 0.93 (6H, t, J= 7.2Hz, $NCH_2CH_2CH_2C\underline{H}_3$); δ_C (125 MHz, d_6-DMSO): 175.1, 162.6, 149.9, 146.6, 137.1, 124.5, 120.3, 113.1, 50.2, 34.3, 31.7, 31.4, 29.2, 26.7, 24.9, 19.5, 14.0; *m/z* (ES^+): 481 $[M-H]^+$

Synthesis of (2,6-bis(*N*-*n*-butylimidazolium)pyridine-4-carbonyl)-6'-aminohexanoic acid chloride, **15e**

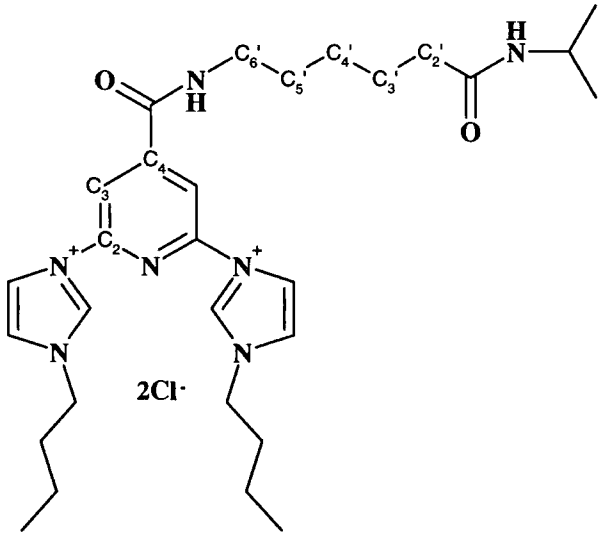


(2,6-bis(*N*-*n*-Butylimidazolium-3-yl)pyridine-4-carbonyl)-6'-aminohexanoic acid (0.70g, 0.001mol) was stirred in dry $CHCl_3$ (20ml) under an atmosphere of argon at 0°C. Oxalyl chloride (0.4ml, 3 eq) was added and the solution stirred and allowed to warm to room temperature. After stirring for 3 hours all effervescence had finished; excess reagent and solvent were removed *in vacuo* to yield a cream coloured crystalline solid. ^1H NMR spectroscopy confirmed 100% conversion to the acid chloride. Recrystallisation of the solid ($CHCl_3$) provided analytically pure material.

M.p. = >250°C; found: C, 54.19, H, 6.73, N, 14.98%, $C_{26}H_{37}N_6O_2Cl_3$ requires C, 54.59, H, 6.47, N, 14.70%; ν_{MAX} (KBr) 1802 (s), 1653 (s), 1539 (s), 1446 (s), 1225 (m) cm^{-1};

δ_H (500 MHz, $CDCl_3$) 11.33 (2H, s, NCHN), 9.95 (1H, t, J= 5.0Hz, CONH), 9.16 (2H, d, J= 1.8Hz, NCHCHN), 9.09 (2H, s, C(3)H), 8.21 (2H, d, J= 1.8Hz, NCHCHN), 4.40 (4H, t, J= 6.5Hz, $NCH_2CH_2CH_2CH_3$), 2.22 (2H, t, J= 7.0Hz, C(2')H), 1.95 (4H, m, $NCH_2CH_2CH_2CH_3$), 1.63 (2H, m, C(5')H), 1.54 (2H, m, C(3')H), 1.35 (6H, m, $NCH_2CH_2CH_2CH_3$ and C(4')H), 0.95 (6H, t, J= 7.5Hz, $NCH_2CH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 175.1, 162.3, 149.8, 146.6, 137.2, 124.4, 120.3, 113.0, 50.1, 34.3, 31.7, 31.3, 29.1, 26.7, 24.9, 19.47, 14.0; *m/z* not possible due to reactivity with solvent.

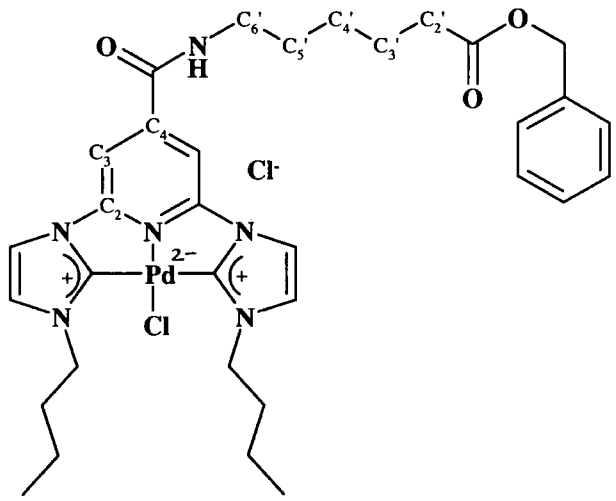
Synthesis of (2,6-bis(*N*-*n*-butyl-imidazolium)pyridine-4-carbonyl)-6'-aminohexanoic isopropyl amide, **15f**



(2,6-bis(*N*-*n*-Butylimidazolium-3-yl)pyridine-4-carbonyl)-6'-aminohexanoic acid chloride (0.50g, 0.91mmol) was stirred in dry $CHCl_3$ (30ml) under an argon atmosphere at 0°C. Isopropylamine (0.20ml, 2.5 eq) in dry $CHCl_3$ (10ml) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* to yield a red/brown precipitate. ^1H NMR spectroscopy showed isopropylamine hydrochloride was present. The precipitate was dissolved in MeOH (10ml) and anhydrous K_2CO_3 added. The suspension was stirred vigorously for 10 minutes, filtered, and solvent removed *in vacuo*. A yellow precipitate was collected. Recrystallisation ($MeOH/Et_2O$) afforded the product as a pale yellow crystalline solid (0.48g, 93% yield).

M.p. = >250°C; found: C, 58.41, H, 7.30, N, 16.27%, $C_{29}H_{45}N_7O_2Cl_2$ requires C, 58.59, H, 7.58, N, 16.50; ν_{MAX} (KBr): 1659 (s), 1640 (s), 1543 (m), 1227 (m) cm^{-1}; δ_H (500MHz, d_6-DMSO): 12.18 (2H, s, NC<u>H</u>N), 9.92 (1H, t, J= 5.2Hz, CON<u>H</u>), 9.27 (2H, d, J= 1.8Hz, NCHC<u>H</u>N), 9.17 (2H, s, C(3)<u>H</u>), 7.48 (2H, d, J= 1.8Hz, NC<u>H</u>CHN), 6.02 (1H, d, J= 8.0Hz, CON<u>H</u>), 4.54 (4H, t, J= 7.0Hz, NC<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 4.03 (1H, m, CH$_3$C<u>H</u>CH$_3$), 3.52 (2H, m, C(6')<u>H</u>), 2.03 (2H, t, J= 7.0Hz, C(2')<u>H</u>), 1.94 (4H, m, NCH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.63 (2H, m, C(5')<u>H</u>), 1.52 (2H, m, C(3')<u>H</u>), 1.34 (6H, m, NCH$_2$CH$_2$C<u>H</u>$_2$CH$_3$ and C(4')<u>H</u>), 1.01 (6H, d, J= 6.5Hz, C<u>H</u>$_3$CHC<u>H</u>$_3$), 0.95 (6H, t, J= 7.0Hz, NCH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (125 MHz, d_6-DMSO) 172.9, 161.8, 150.9, 146.3, 137.8, 123.2, 120.7, 113.2, 51.0, 44.7, 41.3, 40.4, 36.9, 32.3, 28.5, 26.4, 25.5, 23.0, 19.7, 13.7; *m/z* (ES^+): 560 $[M+^{37}Cl^-]^{\cdot+}$, 558 $[M+^{35}Cl^-]^{\cdot+}$, 522 $[M-H]^+$, 261 $[M^{2+}]$.

<u>Synthesis of (2,6-bis(1-*n*-butyl-imidazol-3-yl)pyridine-4-carbonyl)-6'-aminohexanoic acid benzyl ester palladium dichloride, **16a**</u>

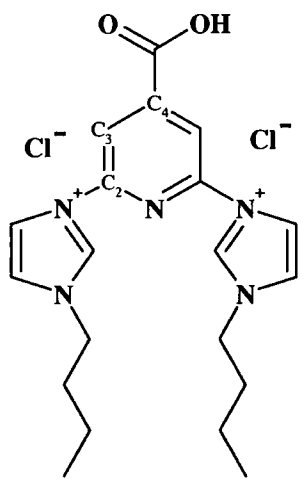


A mixture of (2,6-bis(1-methylimidazolium)pyridine-4-carbonyl)-6'-aminohexanoic acid benzyl ester dibromide (0.50g, 0.77mmol) and $Pd(OAc)_2$ (0.18g, 0.77mmol) was stirred in dry DMSO (3ml) inside a thick-walled glass microwave heating tube and degassed using argon. The reaction tube was sealed with a metal cap and placed inside the microwave oven. After setting parameters for stirring, cooling, ramp time of 5 minutes, and heating for 15 minutes at 165°C, heating was started. After heating, the microwave oven underwent a cooling cycle for 5 minutes and the reaction tube was

removed. After filtration of the tube contents, a precipitate was collected which was washed with DCM to yield a crude green solid. Recrystallisation (EtOH/petroleum ether 40/60) of the crude solid provided analytically pure product as a pale green crystalline solid (0.51g, 89% yield).

M.p. = >250°C; found C, 53.49, H, 6.01, N, 11.64%, $C_{33}H_{42}N_6O_3Cl_2Pd$ requires C, 53.05, H, 5.63, N, 11.25%; ν_{MAX} (ATR): 2929 (w), 2366 (m), 1728 (m), 1654 (s), 1577(s), 1542 (s), 1473 (s) cm^{-1}; δ_H (500MHz, d_6-DMSO): 9.22 (1H, t, J= 5.0Hz, CONH), 8.51 (2H, d, J= 2.25Hz, NCHCHN), 8.49 (2H, s, C(3)H), 7.81 (2H, d, J= 2.25Hz, NCHCHN), 7.35 (5H, m, Ph-H), 5.09 (2H, s, CH_2Ph), 4.50 (4H, t, J= 7.0Hz, $NCH_2CH_2CH_2CH_3$), 2.39 (2H, t, J= 7.5Hz, C(2')H), 1.79 (4H, m, NCH2CH2CH2CH3), 1.61 (4H, m, C(5')H and C(3')H), 1.34 (6H, m, C(4')H and $NCH_2CH_2CH_2CH_3$), 0.92 (6H, t, J= 7.5Hz, $NCH_2CH_2CH_2CH_3$); δ_C (125MHz, d_6-DMSO): 173.5, 166.9, 151.8, 151.5, 147.0, 137.0, 129.1, 129.7, 128.6, 124.8, 119.1, 108.0, 66.1, 49.5, 40.8, 34.1, 33.1, 29.1, 26.5, 24.9, 19.7, 14.3; *m/z* (ES^+): 711 $[M^{+106}Pd +^{35}Cl]^+$, 713 $[M^{+106}Pd +^{37}Cl]^+$

Synthesis of 2,6-bis(*N*-*n*-butylimidazolium)pyridine-4-carboxylic acid dichloride, **23**

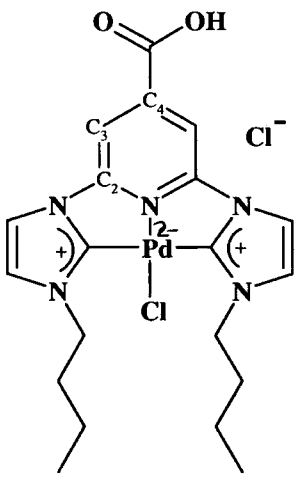


2,6-dichloroisonicotinic acid (3.50g, 18mmol) was stirred in neat *N*-*n*-butylimidazole (10ml) at 150°C for 24 hours under an argon atmosphere. The solution turned brown on heating and a brown precipitate was seen on cooling to room temperature. The precipitate was dissolved in the minimum quantity of hot MeOH (~50ml). This solution

was added slowly to a large stirred excess of Et_2O (1L). A light brown precipitate was formed and collected by filtration. The solid was washed with DCM and Et_2O. After drying a light brown crystalline solid was collected. (5.5g, 69% yield). An analytically pure product was prepared by recrystallising the light brown solid from hot ^{i}PrOH to give a cream coloured crystalline solid.

M.p. = >250°C; found: C, 54.33, H, 6.27, N, 15.74%, $C_{20}H_{27}N_5O_2Cl_2$ requires C, 54.55, H, 6.14, N, 15.74; ν_{MAX} (ATR) 3100 (br), 3050 (s), 1695 (s), 1543 (m) cm^{-1}; δ_H (300MHz, d_6-DMSO): 10.99 (2H, s, NC<u>H</u>N), 9.01 (2H, s, NC<u>H</u>CHN), 8.56 (2H, s, C(3)<u>H</u>), 8.17 (2H, s, NCHC<u>H</u>N), 4.36 (4H, t, J= 6.9Hz, NC<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.93 (4H, m, NCH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.34 (4H, m, NCH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 0.95 (6H, t, J= 6.9Hz, NCH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (125 MHz, d_6-DMSO): 164.4, 150.8, 146.4, 137.2, 124.4, 120.4, 114.3, 40.5, 31.8, 19.5, 13.9; *m/z* (ES^+): 369 [M^+], 368 [(M^+)-H]$^+$, 324 [(M^+)-CO_2H]$^+$, 200 [(M^{2+})+MeOH]$^+$

<u>Synthesis of 2,6-(*N*-*n*-butylimidazol-2-ylidene)pyridine-4-carboxylic acid palladium dichloride, **24**</u>

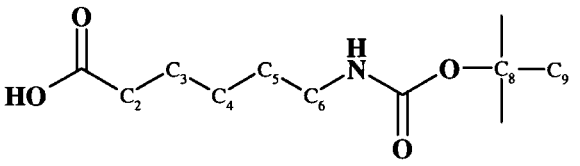


2,6-bis(*N*-*n*-butylimidazolium)pyridine-4-carboxylic acid dichloride (1.00g, 2.27mmol) and $Pd(OAc)_2$ (0.51g, 2.27mmol) were measured into a microwave heating tube. The tube was sealed and flushed with argon. Dry DMSO (7ml) was added and the tube contents degassed by bubbling argon through the solution for 15 minutes. The reaction tube was thoroughly shaken to ensure a homogenous solution and placed inside the

microwave reactor. The reaction solution was heated for 15 minutes at 160°C and 50W of power with continuous stirring. After cooling the reaction solution was left for 20 minutes until a dark precipitate was seen to form. The reaction solution was diluted with DCM (20ml) and the resulting precipitate collected by filtration. The precipitate was washed with DCM and Et_2O to yield a crude orange solid. This solid was recrystallised from hot ^{i}PrOH and the precipitate filtered and washed with Et_2O. After drying a pale orange crystalline solid was collected (0.75g, 61% yield).

M.p. = >250°C; found C, 44.60, H, 4.71, N, 12.81, Pd, 19.02%, $C_{20}H_{25}N_5O_2Cl_2Pd$ requires C, 44.16, H, 4.60, N, 12.88, Pd, 19.40%; ν_{MAX} (ATR): 3120 (br), 3086 (m), 1689 (s), 1573 (s), 1465 (s) cm^{-1}; δ_H (300MHz, d_6-DMSO): 8.66 (2H, s, NC<u>H</u>CHN), 8.35 (2H, s, C(3)<u>H</u>), 7.77 (2H, s, NCHC<u>H</u>N), 4.48 (4H, t, J= 7.2Hz, NC<u>H</u>$_2$CH$_2$CH$_2$CH$_3$), 1.78 (4H, m, NCH$_2$C<u>H</u>$_2$CH$_2$CH$_3$), 1.32 (4H, m, NCH$_2$CH$_2$C<u>H</u>$_2$CH$_3$), 0.92 (6H, t, J= 7.2Hz, NCH$_2$CH$_2$CH$_2$C<u>H</u>$_3$); δ_C (100MHz, d_6-DMSO): 166.8, 151.9, 151.3, 137.2, 124.5, 119.3, 109.1, 40.5, 33.1, 19.6, 14.2; *m/z* (ES^+): 510 [M^+ $^{106}Pd^{35}Cl$], 512 [M^+ $^{106}Pd^{37}Cl$]

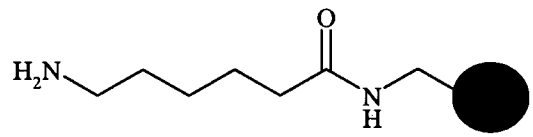
Synthesis of *N*-Boc-6-aminohexanoic acid, **25**



A solution of di-*tert*-butyldicarbonate (18.3g, 83.8mmol) in 1,4-dioxane/H_2O (2:1, 120ml) was added dropwise to a stirred solution of 6-aminocaproic acid (10.0g, 76.2mmol) in 1,4-dioxane / H_2O (2:1, 120ml) at 0°C at such a rate that pH 9-10 (pH meter) was maintained by careful addition of 1N NaOH (aq). The mixture was warmed to room temperature and the pH checked periodically and maintained at 9-10. The reaction mixture was stirred overnight and the solvent removed *in vacuo*. The residual oil was taken up in H_2O and the solution extracted with Et_2O. The aqueous phase was acidified with citric acid (pH 3) and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. Recrystallisation of the crude product (EtOAc/petroleum ether 40/60) yielded a white crystalline solid (15.5g, 89% yield).

M.p. = 139-141°C; found C, 57.52, H, 9.01, N, 6.34%, $C_{11}H_{21}NO_4$ requires C, 57.14, H, 9.09, N, 6.06%; ν_{MAX} (ATR): 3367 (br), 1715 (s), 1683 (s), 1520 (m), 1250 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$): 5.62 (1H, broad s), 4.56 (1H, broad s), 3.11 (2H, s, C(2)H), 2.34 (2H, t, J= 7.5Hz, C(6)H), 1.64 (2H, m, C(5)H), 1.49 (2H, m, C(3)H), 1.44 (9H, s, C(9)H), 1.37 (2H, m, C(4)H); δ_C (125MHz, $CDCl_3$): 178.9, 167.5, 79.2, 40.3, 33.8, 29.7, 28.4, 26.2, 24.3; *m/z* (ES^+): 254 $[(M^+)+Na]^{+}$, 198 $[((M^+)-^tBu)+Na]^{+}$

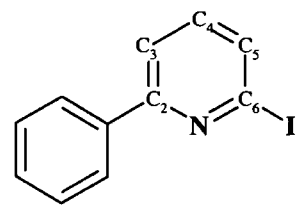
Synthesis of 6-aminocaproic acid supported on amino tentagel resin, **26b**



Resin **26a** (1.0g) was weighed into a fritted solid phase reaction tube. TFA/DCM (1:1) (20ml) was added and the reaction tube sealed with a rubber bung. The reaction tube and its contents were shaken vigorously for 3 hours. After which time the modified resin was then drained and washed with i) DCM (5 x 20ml), ii) DMF (5 x 20ml), iii) DCM and MeOH (alternate 5 x 20ml each), iv) Et_2O (5 x 10ml). The resin was then blown dry with argon and dried *in vacuo* at 60°C to constant mass before analysis.

ν_{MAX}: 3352 (br), 1658 (s); δ_H (500MHz, $CDCl_3$): 5.6, 3.1, 2.3, 1.6

Synthesis of 2-phenyl-6-iodopyridine, **40**

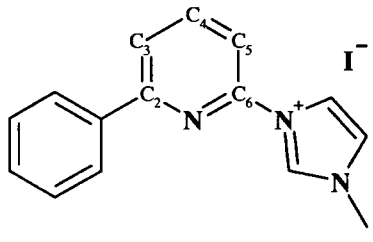


A solution of 2-dimethylaminoethanol (9.6ml, 96mmol) in dry hexane (120ml) was cooled to -5°C and treated dropwise with *n*-BuLi (120ml, 192mmol) under an

atmosphere of argon. After 1 hour at -5°C, a solution of 2-phenylpyridine (4.94g, 31.92mmol) in dry hexane (60ml) was added dropwise. After 1 hour at -5°C, the red/brown solution was cooled to -78°C and treated with a solution of iodine (28.00g, 110mmol) in dry THF (60ml). After 1 hour at -78°C, the reaction mixture was allowed to warm to room temperature. Hydrolysis was performed at -5°C with H_2O (40ml). The reaction mixture was washed with saturated NaS_2O_4 solution (2 x 400ml) and the organic layer collected (Et_2O). The aqueous layer was further extracted with DCM and the organic layer collected. The organic layers were combined, washed with H_2O, and extracted with DCM and dried over $MgSO_4$. Solvent was removed *in vacuo* to yield a crude orange/brown crystalline solid. Purification by FCC (gradient, i) petroleum ether 40/60, ii) petroleum ether 40/60/EtOAc 98:2) yielded a cream coloured crystalline solid (7.24g, 81% yield).

M.p. = 80-81°C; found: C, 46.94, H, 2.39, N, 15.01%, $C_{11}H_8NI$ requires C, 46.98, H, 2.85, N, 14.98%; ν_{MAX} (ATR) 3050 (w), 1568 (m), 1541 (m), 1422 (m), 1383 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$): 7.97 (2H, d, J= 8.5Hz, Ph-H), 7.69 (1H, d, J= 7.7Hz, C(3)H / C(5)H), 7.65 (1H, d, J= 7.7Hz, C(3)H / C(5)H), 7.45 (3H, m, Ph-H), 7.37 (1H, broad t, J= 7.7Hz, C(4)H); δ_C (125MHz, $CDCl_3$): 159.3, 138.3, 138.0, 133.4, 129.8, 129.0, 127.2, 119.6, 118.5; *m/z* (E.I.) 281.0 [M^+], 282.0 [M^+C^{13}], 154.0 [M-I]$^+$, 127.9 [I^+]

Synthesis of 2-phenyl-6-(*N*-methylimidazolium)pyridine iodide, **41**

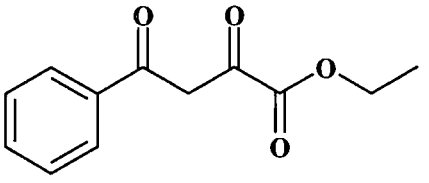


A solution of 2-phenyl-6-iodopyridine (1.00g, 3.56mmol) in *N*-methylimidazole (10ml) was stirred at 160°C for 48 hours under an atmosphere of argon. The reaction was allowed to cool to room temperature and excess *N*-methylimidazole removed *in vacuo* using a Kugelröhr vacuum distillation oven. A brown/black precipitate was collected.

Recrystallisation of the precipitate ($MeOH/Et_2O$) yielded a white crystalline solid (1.12g, 87% yield).

M.p. = >250°C; found C, 49.27, H, 3.59, N, 11.82%, $C_{15}H_{14}N_3I$ requires C, 49.58, H, 3.86, N, 11.57%; ν_{MAX} (ATR) 2966 (m) Ar-H, 1221 (s) cm^{-1}; δ_H (300MHz, d_6-DMSO): 10.16 (1H, broad s, NCHN), 8.62 (1H, broad t, J= 2.0Hz, NCHCHN), 8.27 (3H, m, C(4)H and Ph-H), 8.21 (1H, d, J= 7.8Hz, C(5)H), 7.98 (1H, broad t, J= 2.0Hz, NCHCHN), 7.94 (1H, d, J= 7.8Hz, C(3)H), 7.54 (3H, m, Ph-H), 3.98 (3H, s, N-CH_3); δ_C (125MHz, d_6-DMSO): 156.4, 146.9, 142.4, 137.2, 136.3, 131.1, 129.7, 127.7, 125.5, 121.7, 119.8, 113.0, 37.1; *m/z* (ES^+) 236.1 [M^+]

Synthesis of 2,4-dioxo-4-phenyl-butyric acid ethyl ester, **44a** [185]

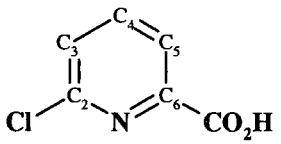


Dry EtOH (300ml) was stirred at 0°C in a two-necked round bottom flask under an atmosphere of argon. Small pre-cut pieces of sodium metal (2.50g) were added carefully to the EtOH and the mixture rapidly stirred. Once all the sodium had reacted with the EtOH, acetophenone (58.3ml, 0.5mol) and diethyl oxalate (68ml, 0.5mol, 1 eq) were run in slowly from a dropping funnel over one hour. The reaction was allowed to warm to room temperature and a yellow precipitate could be clearly seen to form after only one hour. The reaction mixture was stirred rapidly overnight. The reaction mixture was cooled to 0°C and concentrated hydrochloric acid (15ml) in water (100ml) was rapidly added to the reaction mixture. The mixture was extracted three times with DCM (3 x 50ml) and the organic layers collected, combined, dried ($MgSO_4$) and concentrated *in vacuo*. Unreacted acetophenone and diethyl oxalate were removed by distillation under reduced pressure to yield a crude orange/red liquid. This liquid was cooled to 0°C. On cooling a precipitate was formed which was collected by filtration to yield the crude product as an orange coloured crystalline solid. Analytical quality product was

obtained by recrystallisation (EtOH/petroleum ether 40/60) to yield the product as a cream coloured crystalline solid (55.2g, 55% yield).

M.p. = 43-44°C. Literature m.p. = 43-44°C [185]; δ_H (300MHz, d_6-DMSO), 14.07 (1H, broad s, O<u>H</u>), 8.05 (2H, d, J= 7.5Hz, Ph-<u>H</u>), 7.68 (1H, t, J= 7.5Hz, Ph-<u>H</u>), 7.55 (2H, t, J= 7.5Hz, Ph-<u>H</u>), 7.09 (1H, s, PhCOHC<u>H</u>CO), 4.30 (2H, q, J= 6.5Hz, 13.2Hz, C<u>H</u>$_2$CH$_3$), 1.29 (3H, t, J=6.5Hz, CH$_2$C<u>H</u>$_3$); *m/z* (ES$^+$): 243 [(M$^+$)+Na]$^{\cdot+}$, 275 [(M$^+$)+MeOH+Na]$^{\cdot+}$

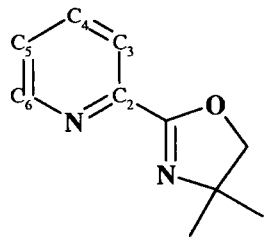
<u>Synthesis of 2-chloropyridine-6-carboxylic acid, **49** [205]</u>



A solution of 2-dimethylaminoethanol (6.38ml, 0.063 mol) in dry hexane (40ml) was cooled to -5°C under argon. *n*-BuLi (50.4ml, 0.13mol) was added slowly with stirring, as not to allow a build-up of gas. 2-Chloropyridine (2ml, 0.021 mol) in dry hexane (18ml) was added slowly. The solution turned a brown-red colour after the addition of 2-chloropyridine. In a separate flask solid CO_2 (4.62g, 0.11mol) was added to dry hexane (20ml) at -78°C. The lithiated chloropyridine was then transferred to the CO_2 flask by cannular under an argon atmosphere. The reaction mixture was stirred overnight and was then made alkaline to pH9 by the addition of sat. $NaHCO_3$, extracted with chloroform (3 x 20ml) and the aqueous layer collected. The aqueous layer was then acidified to pH1 by the addition of conc. HCl and extracted again with chloroform (2 x 20ml). The organic layer was collected and the solvent removed *in vacuo* to yield a crude brown precipitate. Recrystallisation from hexane yielded the title compound as a cream solid (1.57g, 52% yield).

M.p. = 191-192°C; Literature m.p. = 193°C [205]; ν_{MAX} (ATR): 3057 (br), 2359, 1692 (s), 1562, 1452, 1417, 1290, 1259 cm^{-1}; δ_H (400 MHz, $CDCl_3$): 8.10 (1H, d, J=9.1Hz, C(3/5)H), 7.85 (1H, t, J= 9.1Hz, C(4)H); 7.50 (1H, d, J= 9.1Hz , C(3/5)H); δ_C (500 MHz, $CDCl_3$), 163.6, 151.7, 147.2, 141.3, 130.1, 123.0; *m/z* (ES$^-$): 157 [(M^{35}Cl)-H]$^-$, 159 [(M^{37}Cl)-H]$^-$

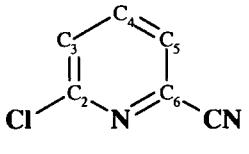
Synthesis of 2-(4',4' dimethyl-4,5-dihydro-oxazo-2-yl)pyridine, **52** [190]



$ZnCl_2$ (0.034g, 0.25mmol) was heated under high vacuum, melted to remove any water and then allowed to cool under argon. Chlorobenzene (15ml) was added, followed by 2-cyanopyridine (0.52g, 5mmol) and 2-amino-2-methyl-propan-1-ol (1.24ml, 15mmol). The reaction mixture was then heated under reflux at 160°C for 36 hours. After this time the solvent was evaporated *in vacuo*. The residue was taken up in DCM (20ml) and extracted with water (3 x 15ml). The aqueous layer was extracted with DCM (2 x 15ml). The organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude residue was purified by flash column chromatography (3:2 EtOAc/petroleum ether (40/60) with 1% NEt_3 added). This yielded the title compound as a colourless oil (0.27g, 31%).

ν_{MAX} (ATR): 2966, 1692, 1639, 1569, 1462, 1415, 1357 cm^{-1}; δ_H (400MHz, $CDCl_3$): 8.63 (1H, d, J = 4.3Hz, C(2/5)H), 7.94 (1H, d, J= 8.5Hz, C(2/5)H), 7.68 (1H, t, J= 8.5Hz, C(3/4)H), 7.30 (1H, t, J= 6.4Hz, C(3/4)H), 4.12 (2H, s, $OCH_2C(CH_3)_2$), 1.34 (6H, s, $C(CH_3)_2$); *m/z* (ES^+): 176 $[M^+]$, 177 $[(M^+)+H]^{\cdot+}$, 199 $[(M^+)+Na]^{\cdot+}$, 200 $[(M^+)+H+Na]^{\cdot+}$

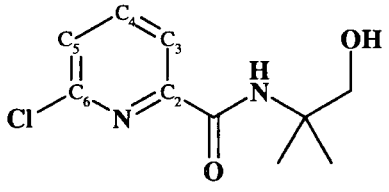
Synthesis of 2-chloro-6-cyanopyridine, **54** [191]



Meta-chloroperbenzoic acid (29.60g, 0.13 mol) was dissolved in dry DCM (25ml) under argon. 2-Chloropyridine (8.3ml, 0.088 mol) was added dropwise, and the mixture was stirred at room temperature for 20 hours. After this time, ammonia gas was bubbled through the mixture for several minutes and the mixture filtered to remove the ammonium salts formed. The resulting filtered solution was concentrated in vacuo, producing a crude brown solid (2-chloropyridine-N-oxide). The solid was then added to neat dimethyl sulfate (8.8ml, 0.088mol) in small portions with stirring, keeping the temperature below 40°C. The mixture was stirred under argon overnight to allow complete crystallisation. The crystals were washed (Et_2O), then dissolved in water (70ml) and transferred to a dropping funnel. NaCN (12.95g, 0.26 mol) in water (70ml) was stirred in a 2-armed flask under argon. The solution was cooled to -10°C and the methylated N-oxide was added dropwise from the funnel. A brown precipitate formed immediately, which was filtered off and washed with water. This was then dried and recrystallised from hexane, yielding the title compound as a light pink solid (3.57g, 29%).

M.p = 84-85°C; Literature m.p =85-87°C [191]; ν_{MAX} (ATR): 2234 (s), 1558, 1431, 1144 cm^{-1}; δ_H (400MHz, $CDCl_3$): 7.84 (1H, t, J= 9.8Hz, C(4)H), 7.68 (1H, d, J= 6.1Hz, C(3/5)H), 7.58 (1H, d, J= 9.2Hz, C(3/5)H); δ_C (125MHz, $CDCl_3$): 153.3, 140.6., 134.2, 129.5, 128.1, 116.8; *m/z* (EI): 138.0 (65) [M^+ ^{35}Cl], 140.0 (23) [M^+ ^{37}Cl], 103 (100) [(M^+)-Cl]

Synthesis of 6-chloropyridine-2-carboxylic acid-(2'-hydroxy-1',1'-dimethyl-ethyl)amide, **55**

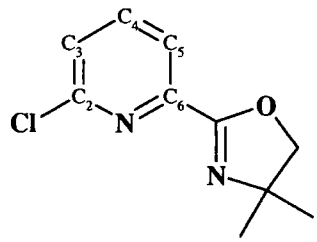


$ZnCl_2$ (0.2g, 1.47mmol), 2-chloro-6-cyanopyridine (1g, 7.22mmol) and 2-amino-2-methyl-propan-1-ol (3.8ml, 39.4mmol) were measured into a microwave reaction vessel. The vessel was capped and sealed shut, then irradiated in a microwave oven at

160°C for 40 minutes, giving a green solution. This was taken up into sat. ammonium chloride (10ml), and extracted with ethyl acetate (3 x 10ml). The organic layer was washed with brine (10ml), dried ($MgSO_4$), filtered and evaporated in vacuo. The pure amide was then obtained by flash column chromatography (1:1 EtOAc/petroleum ether (40/60) and 1% NEt_3), to give the title compound as a white solid (0.57g, 35%).

M.p. = 135-137°C; ν_{MAX} (ATR): 3352 (br), 3036 (w) , 2853 (w), 1732 (s), 1571, 1461, 1410, 1349 cm^{-1} ;δ_H (400MHz, $CDCl_3$): 8.00 (1H, d, J= 9.9Hz, C(3/5)H), 7.74 (1H, t, J= 6.3Hz, C(4)H), 7.36 (1H, d, J= 9.0Hz, C(3/5) H), 3.63 (2H, s, $C(CH_3)_2CH_2OH$), 1.32 (6H, s, CH_3); δ_C (125MHz, $CDCl_3$): 163.4, 161.5, 160.2, 140.7, 127.4, 121.3, 71.4, 56.8, 24.6; *m/z* (ES^+) 253 $[M^{+37}Cl + Na]^+$, 251 $[M^{+35}Cl + Na]^+$

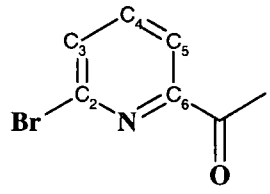
Synthesis of 2-chloro-6-(4',4'-dimethyl-4',5'-dihydro-oxazo-2'-yl)pyridine, **56**



The amide **55** previously synthesized (0.6g, 2.63mmol) was taken up in dry DCM (5ml) and stirred with thionyl chloride (0.19ml, 2.63mmol) under argon for 20 mins. The reaction mixture was quenched with water (5ml) and 2.5M NaOH (5ml) while cooling in ice. The aqueous and organic layers were separated and the aqueous layer extracted with EtOAc (3 x 5ml). The organic layers were combined, dried ($MgSO_4$) and the solvent removed in vacuo. The product was obtained by flash column chromatography (1:1 EtOAc : Petroleum ether (40/60) + 1% NEt_3), yielding the title compound as a colourless oil (0.18g, 33%).

ν_{MAX} (ATR): 2968, 1641, 1567, 1443, 1362, 1324 cm^{-1}; δ_H (400MHz, $CDCl_3$): 7.92 (1H, d, J= 9.3Hz, C(3/5)H), 7.67 (1H, t, J= 9.3Hz, C(4)H), 7.35 (1H, d, J= 9.3Hz, C(3/5)H), 4.14 (2H, s, $OCH_2C(CH_3)_2$), 1.34 (6H, s, CH_3); δ_C (125MHz, $CDCl_3$): 160.8, 152.4, 148.8, 140.1, 127.6, 123.2, 80.7, 69.9, 29.4; *m/z* (EI): 195 (100), 210 (19) $[M^{+35}Cl]$, 212 (6) $[M^{+37}Cl]$.

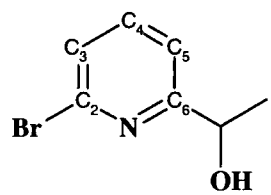
Synthesis of 2-bromopyridine-6-methylketone, **60** [195]



N,N-dimethylacetamide (16.3ml, 0.13mol) was added at -78°C to 6-bromo-2-lithiopyridine (prepared from 2,6-dibromopyridine (29.7g) and *n*-BuLi solution (78.3ml, 1.6M)) in Et_2O (300ml). The solution was stirred for 2 hours and then hydrolysed with saturated aqueous NH_4Cl (50ml). The aqueous layer was separated, washed twice with Et_2O (2 x 20ml) and the organic layers combined. The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo* to yield a crude brown solid. The solid was purified by FCC (9:1 petroleum ether 40/60/EtOAc) to yield a white crystalline solid, (20.3g, 81% yield).

M.p. = 55-56°C. Literature m.p. = 54-55°C [195]. Found C, 42.37, H, 3.09, N, 7.46. C_7H_6NOBr requires C, 42.00, H, 3.00, N, 7.00; ν_{MAX} (ATR): 2931 (w), 1699 (s), 1552 (w), 1362 (w) cm^{-1}; δ_H (500MHz, $CDCl_3$): 7.99 (1H, d, J= 8.0Hz, C3H), 7.70 (1H, t, J= 8.0Hz, C4H), 7.66 (1H, d, J= 8.0Hz, C5H), 2.71 (3H, s, CH_3); δ_C (125MHz, $CDCl_3$): 198.9, 154.5, 141.6, 139.4, 132.0, 120.7, 26.0; *m/z* (EI): 120 (100) [(M^+)-Br], 199 (10) [M^+ Br^{79}], 201 (10) [M^+ Br^{81}]

Synthesis of 2-bromopyridine-6-ethan-1-ol, **61**

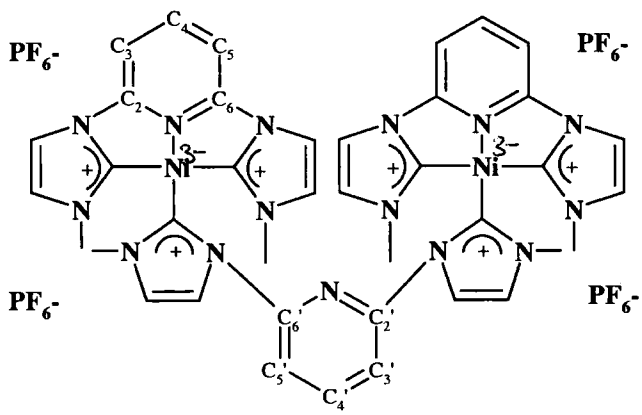


2-bromopyridine-6-methylketone (1.00g, 0.005mol) and $NaBH_4$ (0.57g, 3eq) were weighed into a round bottom flask. The flask contents were flushed with argon and

cooled to 0°C. A solution of dry MeOH/Et_2O (1:1, 20ml) was added slowly and the reaction mixture stirred. After 30 minutes the reaction mixture was warmed to room temperature. After stirring for 3 hours TLC (9:1 petroleum ether 40/60/EtOAc) confirmed no starting material was present. H_2O (10ml) was added cautiously to the reaction mixture and the reaction mixture extracted with DCM (2 x 25ml). The organic layer was collected, dried ($MgSO_4$), and solvent removed *in vacuo* to yield a colourless oil (0.97g, 96% yield).

Found C, 41.67, H, 3.87, N, 6.99%, C_7H_8NOBr requires C, 41.58, H, 3.96, N, 6.93%; ν_{MAX} (ATR) 3354 (br), 1582 (m), 1554 (m), 1431 (m), 1405 (m) cm^{-1}; δ_H (500MHz, $CDCl_3$): 7.56 (1H, t, J= 8.0Hz, C4H), 7.40 (1H, d, J= 8.0Hz, C3H), 7.30 (1H, d, J= 8.0Hz, C5H), 4.88 (1H, q, J= 7.0Hz, $CHCH_3$), 3.33 (1H, broad s, -OH) 1.51 (3H, d, J= 7.0Hz, CH_3); δ_C (125MHz, $CDCl_3$): 165.5, 141.3, 139.5, 126.9, 118.8, 69.4, 24.3; *m/z* (ES^+): 184 $[(M^+Br^{79})\text{-}OH]^{\cdot+}$, 186 $[(M^+Br^{81})\text{-}OH]^{\cdot+}$, 201 $[M^+Br^{79}]$, 203 $[M^+Br^{81}]$, 224 $[(M^+Br^{79})+Na]^+$, 226 $[(M^+Br^{80})+Na]^{\cdot+}$

Synthesis of tri-(2,6-bis(1-methylimidazol-2-ylidene)pyridine)dinickel tetrahexafluorophosphate, **64**



A mixture of 2,6-bis[1-methyl-imidazolium]pyridine dibromide (0.22g, 0.5mmol) and $Ni(OAc)_2.4H_2O$ (0.12g, 0.5mmol) was stirred in dry DMSO (2ml) inside a thick-walled glass microwave heating tube and degassed using argon. The reaction tube was sealed with a metal cap and placed inside the microwave oven. After setting parameters for stirring, cooling, ramp time of 3 minutes, and heating for 5 minutes at 160°C,

heating was started. After heating, the microwave oven underwent a cooling cycle for 5 minutes and the reaction tube was removed. After filtration of the tube contents, a precipitate was collected which was washed with DCM to yield a crude orange solid. This solid was dissolved in the minimum amount of MeOH (~15ml). This solution was added dropwise to a saturated solution of NH_4PF_6 in MeOH (75ml). A yellow precipitate slowly formed which was allowed to settle overnight. Most of the liquid phase was separated off and the solid collected by centrifugation. The solid was washed 3 times with MeOH and each time the solid collected by centrifuge or by settling overnight. The solid was recrystallised (MeCN/DCM) and the solution filtered to yield a light green solid (0.21g, 92% yield).

M.p. = >250°C. Found C, 47.29, H, 4.07, N, 21.62, $C_{39}H_{39}N_{15}Ni_2P_4F_{24}$ requires C, 47.75, H, 3.98, N, 21.43; ν_{MAX} (ATR): 2970 (m), 2361 (m), 1739 (s), 1366 (s), 1229 (s) cm^{-1}; δ_H (300MHz, CD_3CN): 8.71 (2H, d, J= 8.0Hz, C(3')H and C(5')H), 8.47 (2H, t, J= 8.5Hz, C(4)H), 8.24 (1H, t, J= 8.0Hz, C(4')H), 7.92 (2H, d, J= 2.0Hz, NCHCHN), 7.91 (2H, d, J= 2.0Hz, NCHCHN), 7.67 (4H, d, J= 8.5Hz, C(3)H and C(5)H), 7.49 (4H, d, J= 2.0Hz, NCHCHN), 7.22 (4H, d, J= 2.0Hz, NCHCHN), 4.20 (6H, s, CH_3), 2.82 (12H, s, CH_3); δ_C (125MHz, CD_3CN): 229.5, 229.5, 167.4, 166.1, 148.6, 127.5, 122.2, 108.7, 78.2, 77.9, 39.1, 36.2, 30.2; *m/z* (ES^+): 1273.2 $[(M^{4+})+3PF_6^-]^+$, 563.3 $[(M^{4+})+2PF_6^-]^+$

Chapter 7

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APPENDIX 1

SUZUKI ARRAY PROTOCOL

A1 Protocol for Suzuki Arrays in Greenhouse

The protocol used to carry out arrays of 24 Suzuki reactions using a Radley Technologies Greenhouse Parallel Synthesizer is described in this Appendix. This procedure was adapted from one developed by Mr Ian B. Campbell of GlaxoSmithkline, Stevenage, UK and acknowledgement is made to him for the original protocol.

The conditions cover a range of catalysts, ligands, bases and solvents which have been employed regularly in Suzuki cross-coupling reactions. Arrays were carried out in a 24 array Greenhouse and followed by GC and GCMS. The reactions were carried out on either 0.1 mmol scale or 0.05 mmol scale as described.

A1.1- Reaction Conditions

Greenhouse Tube	Catalyst	Ligand	Base	Solvent
A1	$Pd(PPh_3)_4$		Cs_2CO_3	DMF
A2	$Pd(PPh_3)_4$		K_3PO_4	DMF
A3	$Pd(PPh_3)_4$		Na_2CO_3	DME / H_2O
A4	$Pd(PPh_3)_4$		$NaHCO_3$	DME / H_2O
A5	$Pd(PPh_3)_4$		$Ba(OH)_2$	DME / H_2O
A6	$Pd(PPh_3)_4$		NaOH	DME / H_2O
B1	$Pd(OAc)_2$		K_2CO_3	DME / H_2O
B2	$Pd(OAc)_2$	IMES	Et_3N	Toluene
B3	$Pd(OAc)_2$	IMES	Et_3N	DMF
B4	$Pd_2(dba)_3$	IMES	Et_3N	MeCN
B5	$Pd_2(dba)_3$	IMES	Et_3N	Dioxane / H_2O
B6	$Pd(OAc)_2$	PPh_3	$NaHCO_3$	DME / H_2O
C1	$Pd(OAc)_2$	$(2\text{-furan})_3P$	Et_3N	DMF
C2	$Pd(OAc)_2$	Dppe	Et_3N	DMF
C3	$Pd(OAc)_2$	Dppb	Et_3N	DMF
C4	$Pd(OAc)_2$	Dppf	Et_3N	DMF
C5	$Pd(OAc)_2$	*	K_3PO_4	EtOH / H_2O
C6	$Pd(OAc)_2$	*	K_3PO_4	Toluene
D1	$Pd_2(dba)_3$		KOAc	Toluene/EtOH
D2	$Pd_2(dba)_3$	IMES	Cs_2CO_3	Dioxane
D3	$Pd_2(dba)_3$	Dppf	Cs_2CO_3	DMF
D4	$PdCl_2(Binap)$		$NaHCO_3$	DME / H_2O
D5	$PdCl_2(Binap)$		K_3PO_4	DMF
D6	$PdCl_2(Binap)$		CsF	THF / H_2O

Total: 4 catalysts, 7 ligands, 10 bases, 8 solvents, 1 boronic acid and 1 aryl halide require dispensing.

24 Reactions on 0.1 mmol scale. 3% catalysts, 6% ligands, 3 equivalents base.

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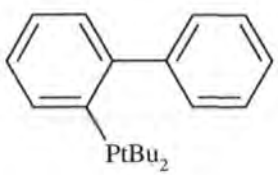

A1.2- Dispense List

A1	Aryl Halide	0.2 M in THF	
A2	Boronic Acid	0.2 M in THF	
A3	$Pd(PPh_3)_4$	0.01 M in THF	11.55 mg/ml
A4	Pd(OAc)2	0.01 M in THF	2.24 mg/ml
A5	$Pd_2(dba)_3$	0.01 M in THF	9.14 mg/ml
A6	$Pd(Binap)Cl_2$	0.01 M in THF	8.0 mg/ml
B1	IMES	0.01 M in THF	2.02 mg/ml
B2	dppm	0.01 M in THF	3.85 mg/ml
B3	$(2\text{-furan})_3P$	0.01 M in THF	2.32 mg/ml
B4	dppe	0.01 M in THF	3.98 mg/ml
B5	dppb	0.01 M in THF	4.26 mg/ml
B6	dppf	0.01 M in THF	5.54 mg/ml
B7	*	0.01 M in THF	2.98 mg/ml
C1	Na_2CO_3	1.0 M in H_2O	106 mg/ml
C2	$NaHCO_3$	1.0 M in H_2O	84 mg/ml
C3	NaOH	1.0 M in H_2O	40 mg/ml
C4	Et_3N		
C5	K_2CO_3	1.0 M in H_2O	138 mg/ml
C6	K_3PO_4	1.0 M in H_2O	203 mg/ml
C7	CsF	1.0 M in H_2O	151 mg/ml
D1	DMF		
D2	DME		
D3	PhMe		
D4	MeCN		
D5	Dioxane		
D6	H_2O		
D7	EtOH		
D8	THF		

A1.3- Solid Samples

Cs_2CO_3	3 x 97.5 mg
K_3PO_4	3 x 60.9 mg
$Ba(OH)_2$	1 x 51.3 mg
KOAc	1 x 29.4 mg

A1.4- Protocol

500 µl A1 to vessels A1 – D6	(24 dispenses)
500 µl A2 to vessels A1 – D6	(24 dispenses)
500 µl A3 to vessels A1 – A6	(3 dispenses)
500 µl A4 to vessels B1 – C6 (Not B4 and B5)	(10 dispenses)
500 µl A5 to vessels D1 – D3, B4 and B5	5 dispenses)
500 µl A6 to vessels D4 – D6	(3 dispenses)
500 µl B1 to vessels B2 – B5 and D2	5 dispenses)
500 µl B2 to vessel B6	(1 dispense)
500 µl B3 to vessel C1	(1 dispense)
500 µl B4 to vessel C2	(1 dispense)
500 µl B5 to vessel C3	(1 dispense)
500 µl B6 to vessels C4 and D3	(2 dispenses)
500 µl B7 to vessels C5 and C6	(2 dispenses)

STOP

EVAPORATE THF (Genevac 12 minutes full power)

A1.5- Protocol

300 µl C1 to vessel A3	(1 dispense)
300 µl C2 to vessels A4, D4, and B6	3 dispenses)
300 µl C3 to vessel A1	(1 dispense)
50 µl C4 to vessels B2 – C4 NOT B6	8 dispenses)
300 µl C5 to vessel B1	(1 dispense)
300 µl C6 to vessel C5	(1 dispense)
300 µl C7 to vessel D6	(1 dispense)
1000 µl D1 to vessels A1, A2, B3, B7 – C4, D3, D5	9 dispenses)
700 µl D1 to vessel B1	(1 dispense)
700 µl D2 to vessels A3 – A6, B6 and D4	6 dispenses)
1000 µl D3 to vessels B2 and C6	(2 dispenses)
500 µl D3 to vessel D1	(1 dispense)
1000 µl D4 to vessel B4	(1 dispense)
500 µl D5 to vessel B5	(1 dispense)
1000 µl D5 to vessel D2	(1 dispense)
300 µl D6 to vessels A3 – A6, B1, B5, B6, C5, D4 and D6	10 dispenses)
700 µl D7 to vessel C5	(1 dispense)
700 µl D8 to vessel D6	(1 dispense)

Add Cs_2CO_3 97.5 mg to vessels A1, D2 and D3

Add K_3PO_4 60.9 mg to vessels A2, C6 and D5

Add $Ba(OH)_2$ 51.3 mg to vessel A5

Add KOAc 29.4 mg to vessel D1

A1.6- protocol

Reactions are heated at 100°C for 24 h and analysed by GC and GCMS

Appendix 2

Crystal structure and data refinement

Crystal data and structure refinement for nickel complex **64**

Identification code	CWT/Ni	
Empirical formula	$[C39\ H39\ N15\ Ni2]^{4+}\ (P\ F6^{-})_4 \cdot 2(C2\ H3\ N)$	
Formula weight	1497.26	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pnma* (No. 62)	
Unit cell dimensions	a = 12.692(1) Å	□= 90°
	b = 29.643(2) Å	□= 90°
	c = 15.058(1) Å	□ = 90°
Volume	5665.3(7) $Å^3$	
Z	4	
Density (calculated)	1.755 g/cm^3	
Absorption coefficient	0.909 mm^{-1}	
F(000)	3016	
Crystal size	0.24 × 0.13 × 0.09 mm^3	
□ range for data collection	1.37 to 27.49°.	
Index ranges	$-16 \leq h \leq 16, -38 \leq k \leq 38, -19 \leq l \leq 19$	
Reflections collected	61163	
Independent reflections	6632 [R(int) = 0.0681]	
Reflections with I>2□(I)	4938	
Completeness to □ = 27.49°	100.0 %	
Absorption correction	Integration	
Max. and min. transmission	0.9316 and 0.8350	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6632 / 97 / 484	
Largest final shift/ e.s.d. ratio	0.002	
Goodness-of-fit on F^2	1.031	
Final R indices [I>2□(I)]	R1 = 0.0355, wR2 = 0.0897	
R indices (all data)	R1 = 0.0540, wR2 = 0.0985	
Largest diff. peak and hole	0.626 and -0.397 $e.Å^{-3}$	

Disorder. In the $P(1)F_6$ anion all atoms [P(1), F(1) to F(6)] are disordered between positions A (80%) and B (20%). The $P(2)F_6$ anion is disordered between two positions (*i* and *ii*), both having mirror symmetry. The F(11) atom retains the same position (on the *m* plane), the rest of the anion librating around it. Position (*i*) (overall occupancy 60%) comprises the P(2A), F(7A), F(8A), F(9A) atoms on the *m* plane and F(6A) in a general position. Position (*ii*) (occupancy 40%) comprises the P(2B) and F(9B) atoms on the *m* plane and F(6B) and F(7B) in general positions.

Table 2. Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2 \times 10^4$) for 04srv216. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Ni	73081(2)	38938(1)	9102(2)	1713(8)
N(1)	68858(14)	40838(6)	20417(11)	1850(40)
N(2)	83499(14)	37298(6)	24770(12)	2000(40)
N(3)	93660(15)	34272(6)	15130(12)	2260(40)
N(4)	55332(14)	43833(6)	13022(12)	2000(40)
N(5)	53802(15)	42719(6)	-956(12)	2420(40)
N(6)	77100(20)	25000	-4386(16)	1820(50)
N(7)	77374(15)	32745(6)	-5559(12)	2000(40)
N(8)	82912(16)	39464(6)	-8004(12)	2280(40)
C(1)	74549(16)	39702(7)	27508(14)	1930(40)
C(2)	71600(18)	40898(8)	36026(15)	2430(50)
C(3)	62479(19)	43458(8)	36846(15)	2530(50)
C(4)	56527(18)	44707(7)	29501(15)	2420(50)
C(5)	60017(17)	43256(7)	21356(14)	2010(40)
C(6)	84642(17)	36589(7)	15762(14)	2050(40)
C(7)	91614(18)	35334(7)	29564(15)	2350(50)
C(8)	98007(18)	33475(8)	23495(15)	2490(50)
C(9)	60243(17)	41879(7)	5825(14)	2080(40)
C(10)	45907(18)	45827(8)	10599(16)	2570(50)
C(11)	44941(19)	45103(8)	1821(16)	2830(50)
C(12)	98552(19)	32702(9)	6864(16)	3110(60)
C(13)	55420(20)	41239(9)	-10180(15)	3300(60)
C(14)	72717(17)	28822(7)	-1686(13)	1820(40)
C(15)	64240(18)	29057(7)	4087(15)	2320(50)
C(16)	60070(30)	25000	7030(20)	2430(70)
C(17)	77587(17)	36978(7)	-2045(14)	1920(40)
C(18)	86260(20)	36813(8)	-15092(15)	2800(50)
C(19)	82853(19)	32630(8)	-13572(15)	2670(50)
C(20)	85070(20)	44282(8)	-7157(17)	3130(60)
P(1A)	81433(13)	53730(5)	15350(11)	2550(30)
F(1A)	90520(30)	56663(11)	19517(17)	7440(90)
F(2A)	82461(18)	50137(8)	23319(16)	4480(60)
F(3A)	90195(17)	50987(8)	9846(13)	4820(50)
F(4A)	80290(30)	57110(11)	7295(15)	4530(80)
F(5A)	72820(30)	56394(12)	20642(19)	8330(120)

F(6A)	72682(18)	50574(8)	10930(17)	5430(60)
P(1B)	80560(60)	53420(30)	17120(40)	3000(200)
F(1B)	92650(60)	54480(30)	19410(60)	3600(200)
F(2B)	79660(70)	50910(30)	26260(50)	3600(300)
F(3B)	84130(70)	48900(30)	12530(60)	5600(200)
F(4B)	81570(110)	55950(40)	7930(80)	8500(800)
F(5B)	77620(80)	57980(30)	21760(80)	6500(400)
F(6B)	68680(60)	52360(30)	15220(50)	4300(200)
P(2A)	22848(14)	25000	15806(14)	2080(40)
F(7A)	22490(30)	30358(11)	15880(40)	6340(150)
F(8A)	27180(40)	25000	25770(30)	7500(160)
F(9A)	34580(30)	25000	12450(40)	5020(120)
F(10A)	18310(40)	25000	6170(30)	5620(110)
P(2B)	23250(20)	25000	18230(20)	2160(70)
F(7B)	22490(30)	28721(16)	25540(30)	5270(120)
F(8B)	23540(50)	28940(30)	10950(50)	8200(300)
F(9B)	35660(50)	25000	18390(60)	5150(190)
F(11)	10711(17)	25000	18718(19)	5120(70)
P(3)	46455(7)	75000	22792(6)	3220(20)
F(12)	46563(16)	69635(6)	22830(16)	6930(60)
F(13)	33877(18)	75000	22624(17)	5670(70)
F(14)	46910(20)	75000	12346(16)	6760(80)
F(15)	59123(17)	75000	23089(14)	3980(50)
F(16)	46250(20)	75000	33353(16)	6050(80)
N(9)	61620(20)	65165(9)	1054(16)	4950(70)
C(21)	67880(30)	66564(9)	5705(19)	4150(70)
C(22)	75990(30)	68307(11)	11610(20)	5630(90)

Table 3. Bond lengths [Å] and angles [°] for 04srv216

Ni-C(17)	1.866(2)	P(1A)-F(4A)	1.580(3)
Ni-N(1)	1.8727(17)	P(1A)-F(6A)	1.597(3)
Ni-C(6)	1.909(2)	P(1A)-F(3A)	1.608(3)
Ni-C(9)	1.913(2)	P(1A)-F(2A)	1.610(2)
N(1)-C(1)	1.332(3)	P(1B)-F(6B)	1.566(9)
N(1)-C(5)	1.339(3)	P(1B)-F(5B)	1.567(10)
N(2)-C(6)	1.380(3)	P(1B)-F(2B)	1.568(9)
N(2)-C(7)	1.386(3)	P(1B)-F(3B)	1.574(10)
N(2)-C(1)	1.403(3)	P(1B)-F(4B)	1.580(11)
N(3)-C(6)	1.338(3)	P(1B)-F(1B)	1.604(10)
N(3)-C(8)	1.395(3)	P(2A)-F(10A)	1.561(4)
N(3)-C(12)	1.467(3)	P(2A)-F(9A)	1.573(5)
N(4)-C(9)	1.378(3)	P(2A)-F(7A)	1.589(3)
N(4)-C(10)	1.383(3)	P(2A)-F(7A)#1	1.589(3)
N(4)-C(5)	1.399(3)	P(2A)-F(8A)	1.598(5)
N(5)-C(9)	1.332(3)	P(2A)-F(11)	1.602(3)
N(5)-C(11)	1.392(3)	P(2B)-F(7B)	1.562(4)
N(5)-C(13)	1.471(3)	P(2B)-F(7B)#1	1.562(4)
N(6)-C(14)#1	1.326(2)	P(2B)-F(9B)	1.576(7)
N(6)-C(14)	1.326(2)	P(2B)-F(11)	1.593(3)
N(7)-C(17)	1.362(3)	P(2B)-F(8B)#1	1.601(5)
N(7)-C(19)	1.393(3)	P(2B)-F(8B)	1.601(5)
N(7)-C(14)	1.429(3)	P(3)-F(14)	1.574(3)
N(8)-C(17)	1.343(3)	P(3)-F(16)	1.590(2)
N(8)-C(18)	1.392(3)	P(3)-F(12)	1.5906(19)
N(8)-C(20)	1.460(3)	P(3)-F(12)#2	1.5906(19)
C(1)-C(2)	1.382(3)	P(3)-F(13)	1.597(2)
C(2)-C(3)	1.390(3)	P(3)-F(15)	1.608(2)
C(3)-C(4)	1.390(3)	N(9)-C(21)	1.138(4)
C(4)-C(5)	1.373(3)	C(21)-C(22)	1.454(5)
C(7)-C(8)	1.341(3)		
C(10)-C(11)	1.345(3)		
C(14)-C(15)	1.385(3)		
C(15)-C(16)	1.387(3)		
C(16)-C(15)#1	1.387(3)		
C(18)-C(19)	1.333(3)		
P(1A)-F(5A)	1.566(3)		
P(1A)-F(1A)	1.575(3)		

C(17)-Ni-N(1)	178.56(9)	N(3)-C(6)-Ni	143.84(17)
C(17)-Ni-C(6)	97.08(9)	N(2)-C(6)-Ni	112.33(15)
N(1)-Ni-C(6)	81.48(8)	C(8)-C(7)-N(2)	105.5(2)
C(17)-Ni-C(9)	99.84(9)	C(7)-C(8)-N(3)	107.8(2)
N(1)-Ni-C(9)	81.60(8)	N(5)-C(9)-N(4)	104.29(18)
C(6)-Ni-C(9)	163.07(9)	N(5)-C(9)-Ni	143.72(17)
C(1)-N(1)-C(5)	120.32(18)	N(4)-C(9)-Ni	111.97(15)
C(1)-N(1)-Ni	119.87(15)	C(11)-C(10)-N(4)	105.7(2)
C(5)-N(1)-Ni	119.80(14)	C(10)-C(11)-N(5)	107.6(2)
C(6)-N(2)-C(7)	111.70(18)	N(6)-C(14)-C(15)	124.1(2)
C(6)-N(2)-C(1)	116.83(18)	N(6)-C(14)-N(7)	113.38(19)
C(7)-N(2)-C(1)	131.45(19)	C(15)-C(14)-N(7)	122.45(19)
C(6)-N(3)-C(8)	111.16(18)	C(14)-C(15)-C(16)	117.0(2)
C(6)-N(3)-C(12)	125.82(19)	C(15)#1-C(16)-C(15)	120.3(3)
C(8)-N(3)-C(12)	123.02(19)	N(8)-C(17)-N(7)	104.83(17)
C(9)-N(4)-C(10)	111.31(18)	N(8)-C(17)-Ni	125.74(16)
C(9)-N(4)-C(5)	117.51(18)	N(7)-C(17)-Ni	129.07(16)
C(10)-N(4)-C(5)	131.02(19)	C(19)-C(18)-N(8)	107.2(2)
C(9)-N(5)-C(11)	111.13(19)	C(18)-C(19)-N(7)	106.72(19)
C(9)-N(5)-C(13)	125.6(2)	F(5A)-P(1A)-F(1A)	91.7(2)
C(11)-N(5)-C(13)	123.22(19)	F(5A)-P(1A)-F(4A)	90.40(16)
C(14)#1-N(6)-C(14)	117.4(3)	F(1A)-P(1A)-F(4A)	91.30(17)
C(17)-N(7)-C(19)	110.44(18)	F(5A)-P(1A)-F(6A)	91.3(2)
C(17)-N(7)-C(14)	126.83(18)	F(1A)-P(1A)-F(6A)	176.9(2)
C(19)-N(7)-C(14)	122.69(18)	F(4A)-P(1A)-F(6A)	89.31(15)
C(17)-N(8)-C(18)	110.84(18)	F(5A)-P(1A)-F(3A)	179.5(2)
C(17)-N(8)-C(20)	124.93(19)	F(1A)-P(1A)-F(3A)	88.73(18)
C(18)-N(8)-C(20)	124.22(19)	F(4A)-P(1A)-F(3A)	89.33(17)
N(1)-C(1)-C(2)	122.2(2)	F(6A)-P(1A)-F(3A)	88.28(16)
N(1)-C(1)-N(2)	109.37(18)	F(5A)-P(1A)-F(2A)	90.63(17)
C(2)-C(1)-N(2)	128.5(2)	F(1A)-P(1A)-F(2A)	90.51(16)
C(1)-C(2)-C(3)	116.6(2)	F(4A)-P(1A)-F(2A)	177.89(17)
C(2)-C(3)-C(4)	121.8(2)	F(6A)-P(1A)-F(2A)	88.82(14)
C(5)-C(4)-C(3)	116.9(2)	F(3A)-P(1A)-F(2A)	89.63(15)
N(1)-C(5)-C(4)	122.2(2)	F(6B)-P(1B)-F(5B)	91.5(6)
N(1)-C(5)-N(4)	109.07(18)	F(6B)-P(1B)-F(2B)	89.7(5)
C(4)-C(5)-N(4)	128.7(2)	F(5B)-P(1B)-F(2B)	90.0(6)
N(3)-C(6)-N(2)	103.77(18)	F(6B)-P(1B)-F(3B)	91.5(5)

F(5B)-P(1B)-F(3B)	177.0(7)
F(2B)-P(1B)-F(3B)	90.2(5)
F(6B)-P(1B)-F(4B)	90.8(6)
F(5B)-P(1B)-F(4B)	90.0(6)
F(2B)-P(1B)-F(4B)	179.5(8)
F(3B)-P(1B)-F(4B)	89.8(6)
F(6B)-P(1B)-F(1B)	178.1(6)
F(5B)-P(1B)-F(1B)	87.8(5)
F(2B)-P(1B)-F(1B)	88.6(5)
F(3B)-P(1B)-F(1B)	89.2(5)
F(4B)-P(1B)-F(1B)	91.0(6)
F(10A)-P(2A)-F(9A)	92.9(3)
F(10A)-P(2A)-F(7A)	89.8(2)
F(9A)-P(2A)-F(7A)	91.70(15)
F(10A)-P(2A)-F(7A)#1	89.8(2)
F(9A)-P(2A)-F(7A)#1	91.70(15)
F(7A)-P(2A)-F(7A)#1	176.6(3)
F(10A)-P(2A)-F(8A)	178.5(3)
F(9A)-P(2A)-F(8A)	88.6(3)
F(7A)-P(2A)-F(8A)	90.2(2)
F(7A)#1-P(2A)-F(8A)	90.2(2)
F(10A)-P(2A)-F(11)	84.3(2)
F(9A)-P(2A)-F(11)	177.1(3)
F(7A)-P(2A)-F(11)	88.30(15)
F(7A)#1-P(2A)-F(11)	88.29(15)
F(8A)-P(2A)-F(11)	94.2(2)
F(7B)-P(2B)-F(7B)#1	89.9(4)
F(7B)-P(2B)-F(9B)	92.9(3)
F(7B)#1-P(2B)-F(9B)	92.9(3)
F(7B)-P(2B)-F(11)	84.6(2)
F(7B)#1-P(2B)-F(11)	84.6(2)
F(9B)-P(2B)-F(11)	176.4(4)
F(7B)-P(2B)-F(8B)#1	177.2(4)
F(7B)#1-P(2B)-F(8B)#1	88.2(4)
F(9B)-P(2B)-F(8B)#1	89.3(3)
F(11)-P(2B)-F(8B)#1	93.1(3)
F(7B)-P(2B)-F(8B)	88.2(4)
F(7B)#1-P(2B)-F(8B)	177.2(4)
F(9B)-P(2B)-F(8B)	89.3(3)
F(11)-P(2B)-F(8B)	93.1(3)
F(8B)#1-P(2B)-F(8B)	93.6(7)
P(2B)-F(11)-P(2A)	13.22(11)
F(14)-P(3)-F(16)	178.83(15)
F(14)-P(3)-F(12)	90.19(9)
F(16)-P(3)-F(12)	89.80(9)
F(14)-P(3)-F(12)#2	90.19(9)
F(16)-P(3)-F(12)#2	89.80(9)
F(12)-P(3)-F(12)#2	178.93(17)
F(14)-P(3)-F(13)	91.18(15)
F(16)-P(3)-F(13)	89.99(14)
F(12)-P(3)-F(13)	90.50(8)
F(12)#2-P(3)-F(13)	90.50(8)
F(14)-P(3)-F(15)	89.50(14)
F(16)-P(3)-F(15)	89.33(13)
F(12)-P(3)-F(15)	89.50(8)
F(12)#2-P(3)-F(15)	89.50(8)
F(13)-P(3)-F(15)	179.32(14)
N(9)-C(21)-C(22)	179.2(4)

Symmetry transformations used to generate equivalent atoms: #1 x,-y+1/2,z #2 x,-y+3/2,z

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^4$) for 04srv216. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Ni	183(1)	170(1)	162(1)	-17(1)	10(1)	14(1)
N(1)	191(9)	178(9)	186(9)	-6(7)	2(7)	8(7)
N(2)	198(9)	202(9)	201(9)	-1(7)	2(7)	13(7)
N(3)	219(9)	201(9)	257(10)	-9(8)	10(8)	17(8)
N(4)	206(9)	198(9)	197(9)	-4(7)	8(7)	31(7)
N(5)	236(10)	271(10)	219(9)	12(8)	-19(8)	21(8)
N(6)	204(12)	187(12)	155(12)	0	-13(10)	0
N(7)	252(9)	179(9)	169(8)	-11(7)	40(8)	-6(8)
N(8)	295(10)	168(9)	222(9)	-11(7)	66(8)	-13(8)
C(1)	201(11)	173(10)	207(10)	-6(8)	-3(8)	-11(8)
C(2)	271(12)	259(11)	198(11)	-11(9)	-5(9)	-11(9)
C(3)	306(13)	254(11)	200(11)	-57(9)	55(9)	-14(10)
C(4)	232(11)	228(11)	265(12)	-39(9)	26(9)	26(9)
C(5)	212(10)	178(10)	212(10)	-8(8)	12(9)	-7(8)
C(6)	207(11)	183(10)	224(11)	-18(8)	19(9)	0(9)
C(7)	240(11)	202(11)	262(11)	22(9)	-49(9)	12(9)
C(8)	217(11)	218(11)	312(12)	7(9)	-39(10)	12(9)
C(9)	224(11)	203(10)	196(10)	0(9)	8(9)	-14(9)
C(10)	214(11)	261(12)	297(12)	19(10)	8(9)	46(9)
C(11)	228(12)	329(13)	293(12)	48(10)	-37(10)	51(10)
C(12)	255(12)	351(14)	327(13)	-55(11)	32(10)	83(10)
C(13)	324(13)	474(16)	193(11)	-4(11)	-28(10)	32(12)
C(14)	212(10)	172(10)	162(9)	-7(8)	-35(8)	-13(8)
C(15)	266(11)	194(11)	235(11)	-33(9)	29(9)	22(9)
C(16)	226(16)	261(16)	241(16)	0	44(13)	0
C(17)	208(10)	184(10)	184(10)	-11(8)	7(9)	1(9)
C(18)	376(14)	260(12)	204(11)	-12(9)	106(10)	0(10)
C(19)	387(14)	218(11)	196(11)	-19(9)	71(10)	11(10)
C(20)	411(14)	187(11)	340(13)	-18(10)	102(11)	-76(10)
P(1A)	335(6)	223(6)	206(6)	27(5)	-34(5)	15(4)
F(1A)	1050(20)	740(20)	443(14)	-82(15)	-164(14)	-535(19)
F(2A)	414(13)	525(14)	405(13)	231(11)	-46(11)	64(11)
F(3A)	417(12)	622(14)	407(11)	-14(10)	11(10)	224(11)
F(4A)	735(19)	368(13)	255(12)	128(9)	61(10)	95(13)
F(5A)	1160(30)	830(20)	514(16)	198(16)	479(18)	660(20)

F(6A)	468(13)	530(14)	631(15)	140(12)	-281(12)	-181(11)
F(7A)	233(16)	221(14)	1450(50)	-150(20)	120(20)	-35(12)
F(8A)	610(30)	1230(50)	410(30)	0	-80(20)	0
F(9A)	210(20)	410(20)	890(40)	0	140(30)	0
F(10A)	570(30)	740(30)	380(20)	0	-110(20)	0
F(7B)	390(20)	510(30)	690(30)	-270(20)	40(20)	-80(20)
F(8B)	400(30)	1000(60)	1060(60)	820(50)	250(40)	220(40)
F(9B)	200(30)	360(30)	990(60)	0	30(40)	0
F(11)	251(11)	305(12)	980(20)	0	171(12)	0
P(3)	300(5)	380(5)	286(5)	0	-76(4)	0
F(12)	655(13)	388(10)	1036(17)	-42(10)	-35(12)	-87(9)
F(13)	305(12)	870(20)	528(15)	0	-104(11)	0
F(14)	538(16)	1190(30)	296(12)	0	-117(12)	0
F(15)	310(11)	510(14)	375(12)	0	-61(9)	0
F(16)	442(15)	1070(20)	307(12)	0	-10(11)	0
N(9)	703(19)	456(15)	327(13)	-43(11)	83(13)	-147(13)
C(21)	640(20)	290(14)	309(14)	-14(12)	170(14)	-49(14)
C(22)	780(20)	440(18)	467(18)	-105(15)	14(17)	-107(17)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 04srv216.

	x	y	z	U(iso)
H(2)	7563	4001	4113	29
H(3)	6023	4438	4265	30
H(4)	5023	4648	3006	29
H(7)	9239	3527	3590	28
H(8)	10448	3191	2466	30
H(10)	4105	4739	1440	31
H(11)	3920	4608	-186	34
H(121)	9768	3494	225	44(5)
H(122)	10601	3215	769	44(5)
H(123)	9525	2992	493	44(5)
H(131)	5574	3798	-1049	59(6)
H(132)	4961	4227	-1379	59(6)
H(133)	6192	4246	-1253	59(6)
H(15)	6143	3191	598	28
H(16)	5421	2500	1107	29
H(18)	9020	3781	-2016	34
H(19)	8392	3004	-1729	32
H(201)	8162	4545	-196	66(6)
H(202)	9254	4476	-665	66(6)
H(203)	8248	4584	-1232	66(6)
H(221)	7269	7027	1604	113(10)
H(222)	8112	7005	815	113(10)
H(223)	7959	6581	1463	113(10)