Synthesis of Novel *N*-Heterocyclic Carbene-Palladium Complexes and Their Catalytic Activity

Daniel P. Guest

Supervisor Dr O. Navarro

Submitted to the University of Sussex in part fulfilment of the requirements of the degree of Doctor of Philosophy, January 2017

Declaration

I hereby declare that the work presented in this thesis was carried out at the University of Sussex under the supervision of Dr O Navarro between the dates of September 2012 and April 2016. The work presented in this thesis is my own, unless otherwise stated, and has not been submitted in whole or in part form for award of another degree.

Daniel P. Guest

Acknowledgements

Firstly I would like to thank Prof. John Spencer for his guidance and constant enthusiasm throughout my Ph.D, also Dr. Oscar Navarro, my supervisor.

I would like to thank my fellow research group members past and present Chris Gallop, Irene Malenda, Melvin Ansell and Jose Gascon for their help, support and friendship in the laboratory, which made the Ph.D. a more enjoyable experience.

I would like to thank Adam Close, Tom Moore, Oran O'Doherty, Hayley Rand, Gavin Roffe, Rhiannon Jones, Katie Duffell, Jess Dwyer and Dave Neil-Hall for their general support, camaraderie and close friendship.

I would like to thank the staff within the chemistry department at University of Sussex. In particular Paul Andrews and Alex Burns for both tolerating my mess in their office when writing up and being generally excellent human beings. Dr. Alaa Abdul-Sada for performing mass spectrometry measurements, Dr. Iain Day for guidance and consultations with NMR spectroscopy.

The EPSRC National Mass Spectrometry Service of the University of Swansea and National X-Ray Diffraction Units of the University of Southampton are acknowledged for carrying out HRMS measurements and X-ray crystallographic measurements.

I would like to thank my upper school science teacher, Dr J. Maple, for igniting my interest in science, showing how fun and interesting chemistry can be.

Last, but by no means least, I would like to thank my family: Mum, Dad, my brother Oliver, grandparents Anna & Ron, and my partner Gemma, for their love and unconditional support throughout this process.

List of Symbols and Abbreviations

OAc	acetate, CH_3CO
AcOH	acetic acid, $C_2H_4O_2$
Bu	butyl, C_4H_9
COD	1,5-Cyclooctadiene
CMD	concerted metalation deprotonation
Cy	cyclohexyl
d	deuterated
DCM4	dichloromethane, CH_2Cl_2
DEA	diethylamine, $C_4H_{11}N$
DFT	density functional theory
DME	dimethoxyethane, $C_4H_{10}O_2$
DMF	dimethylformamide, C_3H_7NO
Dppp	1,3-Bis(diphenylphosphino)propane
Et	ethyl, CH_2CH_3
equiv	equivalent
EtOAc	ethyl acetate, $C_4H_8O_2$
EtOH	ethanol, C_2H_6O
h	hour
IPr	1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene
IPr^*	1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]imidazole-2-ylidene
IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene
IPent	1,3-bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene
Me	methyl, CH_3
MeCN	acetonitrile, C_2H_3N
MeOH	methanol, CH_3OH
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance

PEPPSI	pyridine enhanced pre-catalyst preparation stabilisation and initiation
Ph	phenyl, C_6H_5
py	pyridine, C_5H_5N
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazolidene
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidene
r.t.	room temperature
T	temperature
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
$NBu_4(OAc)$	tetrabutylammonium acetate
TEA	triethylamine, $C_6H_{15}N$
THF	tetrahydrofuran, C_4H_8O
tol	tolyl 4-MeC_6H_4
ν	frequency
δ	chemical shift
σ	sigma

Abstract

Chapter 1: Gives the reader a background on carbenes paying particular attention to N-heterocyclic carbenes (NHCs). The chapter describes NHC's electronic and structural properties and their behaviour as ligands. The recent usage of NHC-palladium complexes as catalysts for cross-coupling reactions is explored.

Chapter 2: Provides a background on NHC-palladium complexes bearing N-donors as throwaway ligands, highlighting the importance of throw-away ligands on catalytic activity. The chapter describes the preparation of a number of novel NHC-palladium complexes bearing throw-away ligands and the activity of (IPr*)$PdCl_2$(TEA) in Buchwald-Hartwig aminations is explored.

Chapter 3: Provides a background on the Mizoroki Heck reaction, focusing on the importance of charged intermediates in the process. Then reviews the current development of anionic NHC-palladium complexes in the literature. An account of the discovery and preparation of novel [(NHC)$PdCl_3$[TBA] complexes and the catalytic activity of [(SIPr)$PdCl_3$[TBA] in Mizoroki-Heck coupling reactions is given. A plausible Amotore-Jutand type mechanism is proposed which is supported by DFT calculations provided by research collaborators.

Chapter 4: Provides a background on C-H activation reactions catalysed by palladium compounds with particular focus on acetoxylation reactions. The chapter describes the synthesis of [(NHC)$PdCl_2$X][Y] complexes including the development of [(IMes)$PdCl_2$OAc][TBA] and its performance in acetoxylation reactions. A proposed mechanism for the reaction of [(IMes)$PdCl_2$OAc][TBA] is discussed, using experimental observations.

Contents

1 Introduction

1.1 Carbenes

Carbenes are neutral, divalent derivatives of carbon containing six valence electrons with a formal charge of zero. The existence of carbenes was first postulated in 1903 by Edward Buchner in cyclopropanation studies of ethyl diazoacetate with toluene, and the simplest carbene: methylene ($:CH_2$) was identified by Herzberg in 1959.[1] Although in the following decades some information regarding the synthetic utility of carbenes was obtained, it was not until 1988 when attempts to isolate them were successful.[2] The carbene moiety consists of two covalent bonds and two nonbonding electrons localised on the carbon (Table 1.1).

Table 1.1 Common reactive intermediates of carbon

Carbon reactive intermediates	Structure	Number of covalent bonds	Number of Valence electrons
Carbanions		3	8
Radicals		3	7
Carbenium ion		3	6
Carbenes		2	6

Carbenic carbons can exist with either a bent or linear geometry using differing amounts of hybridisation. Linear geometry would require a sp-hybridised carbon centre with two nonbonding degenerate orbitals (p_x and p_y). Bending the molecule involves the carbon adopting sp^2 hybridisation, removing the degeneracy of the orbitals resulting in one p orbital remaining the same (known as p_π) and the other adopting some s character (known as σ). The linear geometry is rare as most carbenes are bent with frontier orbitals systematically called p_π and σ. The frontier orbitals of the carbene could be filled in four possible ways (Figure 1.1) firstly with the two nonbonding electrons located in two

different orbitals with parallel spins, known as the triplet state **1a**, or spin paired in the same orbital known as singlet states **1b**, **1c** (with **1b** generally being the most stable) and finally spin paired in different orbitals **1d** known as an excited singlet state. This ground state spin multiplicity is an integral feature of carbenes and dictates their reactivity,[3] for example: triplet carbenes have two singly occupied orbitals and are therefore regarded to behave as diradicals, whereas singlet carbenes possess a filled and a vacant orbital and can be nucleophilic or electrophilic in nature.

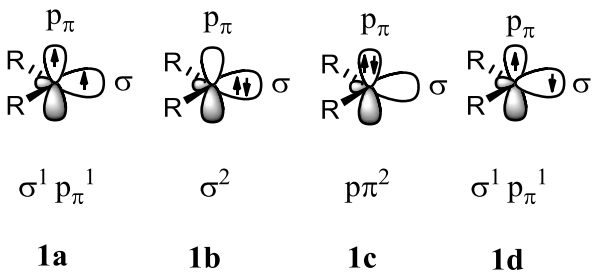


Figure 1.1 Electronic configurations of bent carbenes**.**

Theoretically almost all carbenes have the potential to exist in either the triplet or singlet state, however this ground state multiplicity is affected by the relative energy of the σ and p_π orbitals. If the difference in energy between the two orbitals is large (2 eV or more calculated by Hoffmann[4]) then the singlet state would be favoured, however if the σ-p_π energy separation is small, then the triplet state would be the more favoured electronic configuration due the reduced electron-electron repulsion generated. Since as mentioned above the carbene ground state multiplicity is dependent on the relative energies of the σ and p_π orbitals, it is not surprising that substituents on the carbene have an effect on this. This influence has been analysed in terms of electronic and steric effects.

1.2 Electronic Effects of Substituents on Carbene Multiplicity

1.2.1 Inductive Effects

Research in the 1970s by Harrison *et al.* showed that the ground states of carbenes could be altered when substituents were changed.[5] This work involved changing the substituents from electropositive lithium to hydrogen, then to electronegative fluorine

(although mesomeric effects also contribute to the latter), this established that σ- electron withdrawing substituents favour the singlet over the triplet state. These observations can be rationalised by considering perturbation of the orbital diagrams (C_{2v} symmetry) of the carbenes, as shown σ- electron withdrawing substituents inductively stabilize the σ nonbonding orbital thus increasing the σ-p_π energy gap and favouring the singlet state (Figure 1.2a), conversely σ- electron donating substituents induce a reduction of the σ-p_π gap resulting in the triplet state being favoured (figure 1.2b).

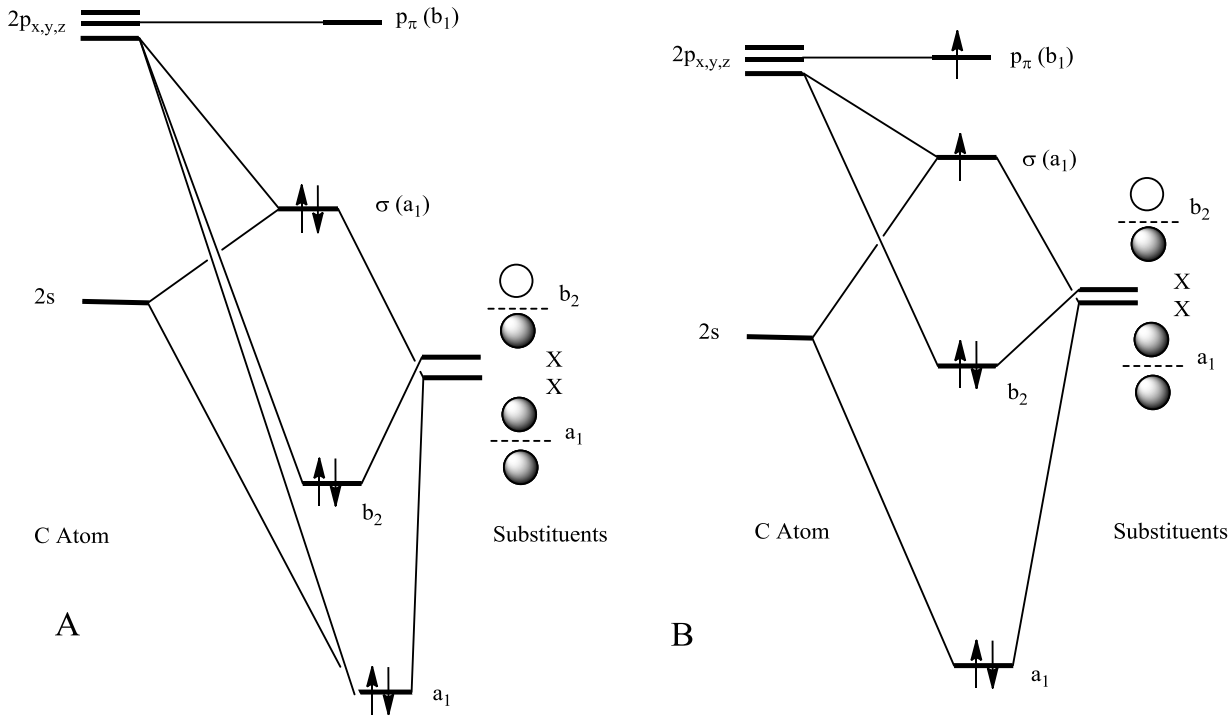


Figure 1.2 Inductive effect of substituents on σ-p_π energy gap (A) σ- electron withdrawing substituents. (B) σ- electron donating substituents.

1.2.2 Mesomeric Effects

While inductive effects do play a role in dictating the ground state multiplicity of carbenes, mesomeric effect contributions have been found to be more profound.[6] Substituents interacting with the carbenic centre can be placed in two classes: X substituents, which consist of π- electron donating groups such as halides, amines, phosphines, oxygen and sulphur and Z substituents which consist of π- electron withdrawing groups such as carbonyls, cyanide, boron containing substituents and

trifluoromethyl. Singlet carbenes can therefore be classified according to the type of substituent with three combinations possible (X-X), (Z-Z) or (X-Z) carbenes.

(X-X) carbenes: In this type of carbene the σ-p_π energy gap is increased via the increase in energy of the vacant p_π orbital of the carbenic carbon through interaction with the symmetric combination of the substituent lone pairs (Figure 1.3) therefore favouring the singlet state. Donation of the X substituents lone pairs results in the formation of a polarised four electron three centre π system. This interaction means the C-X bond show some multiple bond character therefore (X-X) carbenes are best described as two zwitterionic superimposed structures with a negative charge at the carbenic centre. They are predicted to exist as bent singlet carbenes.[7]

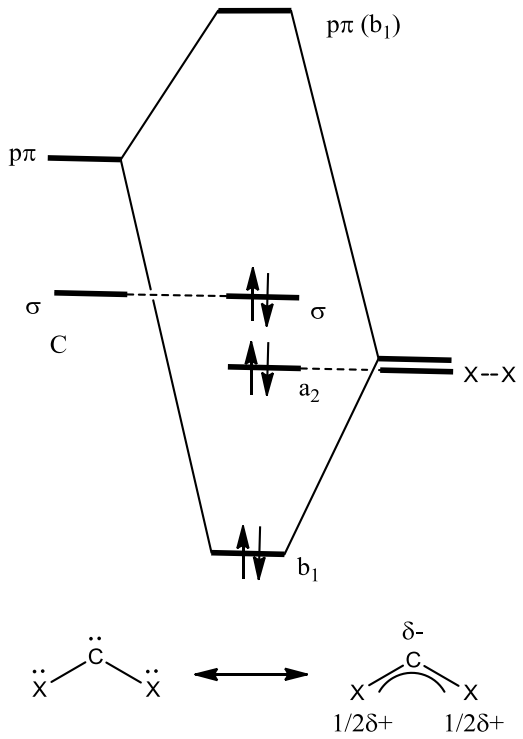


Figure 1.3 Perturbation of orbital diagram due to mesomeric effects of electron withdrawing groups.

(Z-Z) carbenes: This type of compound is predicted to exist as a linear singlet motif in which, the symmetric combination of the substituent vacant orbitals interacts with the filled p_y orbital of the carbenic carbon (Figure 1.4). Since only the p_y orbital has the correct spatial orientation (perpendicular to the valence plane) to interact with the vacant orbitals the p_x-p_y degeneracy is broken making these carbenes have a singlet state even

though they have a linear geometry. This substitution pattern results in the formation of a polarized two electron three centre π system, which is described as two zwitterionic superimposed structures with a positive charge at the carbenic centre.

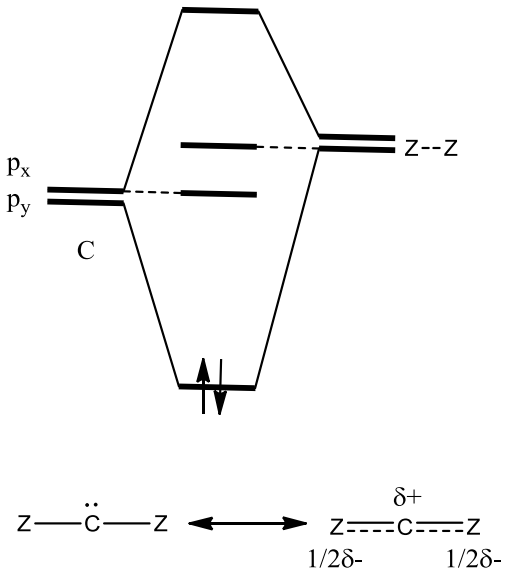


Figure 1.4 Perturbation of orbital diagram due to mesomeric effects of electron donating groups.

(X-Z) carbenes: This is the last possible electronic configuration which consists of a combination of X and Z substituents. In this format the X substituent lone pair interacts with the p_y orbital destabilising it, while the Z substituent vacant orbital interacts with the p_x orbital stabilizing it (Figure 1.5). Both of these interactions favour formation of the singlet state and result in a polarised allene-type system, which is pseudo linear.

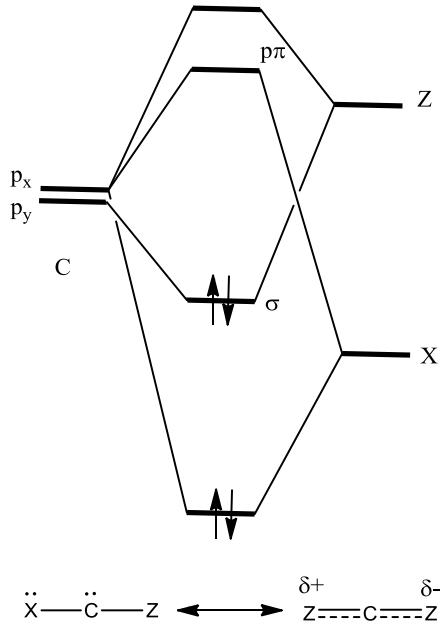


Figure 1.5 Perturbation of orbital diagram due to mesomeric effects of a combination electron donating and withdrawing groups.

1.3 Steric Effects of Substituents on Carbene Multiplicity

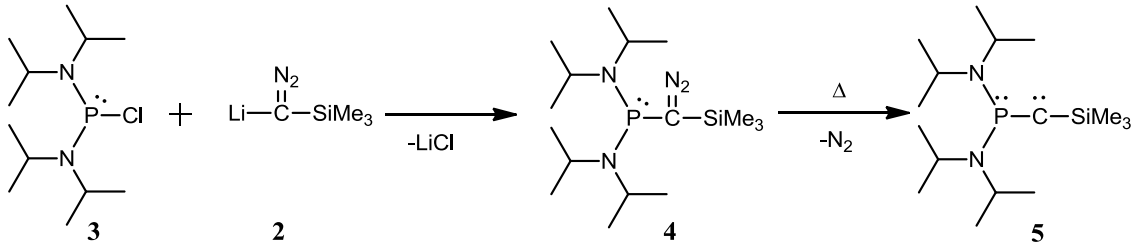
Although electronic effects are more significant, in cases where they are negligible, steric effects can dictate the ground state multiplicity of the carbene. Bulky substituents stabilise all types of carbenes to a certain extent by blocking reactants approach to the carbenic centre. However since increasing the steric bulk of the carbene substituents would result in a broadening of the carbenic angle leading to a more linear geometry, the triplet state which derives its electronic stability from the degeneracy of the frontier orbitals is more stabilised by this increase.

1.4 Persistent Singlet Carbenes: Synthesis and Stability

Most carbenes are very short lived (transient) and normally exist as reactive intermediates, however there is a class of these compounds known as persistent carbenes that are stable enough to be isolated.

1.4.1 Phosphinosilyl and Phosphinophosphonio Carbenes

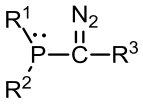
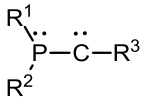
Stable phoshinocarbenes can be prepared via the decomposition of diazo compounds which is a classical method for the synthesis of many transient carbenes. The first reported method for the preparation of an α-diazophoshine **4** (Scheme 1.1) was in 1985 and was achieved via the reaction of the lithium salt of trimethylsilyldiazomethane **2** with one equivilant of bis(diisopropylamino)chlorophosphine[8] **3**. Further work by Betrand *et al.*[2] established that the corresponding phosphinosilylcarbene **5** could be formed from the α-diazophoshine via dinitrogen elimination by thermolysis (250 °C under vacuum) and that this compound which was isolated as a red oil in an 80% yield was stable for weeks at room temperature.



Scheme 1.1 First synthesis of phosphinosilylcarbene**.**

A number of phosphinosilylcarbenes have been prepared using the same procedure.[9,10] However, only a few of them were found to be stable at room temperature (Table 1.2). Studies have shown that bulky substituents kinetically stabilize phosphinosilylcarbenes but this stability is often inversely proportional to that of the diazo precursors.[11] It has also been reported that the silyl functionality at the carbenic centre can be replaced by an isoelectronic isovalent phosphonion substituent without any loss of stability.

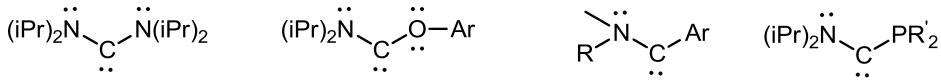
Table 1.2 Stability of a number of Phosphinosilyl and Phosphinophosphonio Carbenes and the Diazo-precursors.

 **4** and  **5**					
	R^1	R^2	R^3	Diazo Stability	Carbene Stability
4a,5a	*i*-Pr_2N	*i*-Pr_2N	$SiMe_3$	b.p 85-90 °C, 10^{-2} mmHg	b.p 75-80 °C, 10^{-2} mmHg Several weeks at 25 °C
4b,5b	Tmp[a]	*i*-Pr_2N	$SiMe_3$	Few minutes at 25 °C	Several weeks at 25 °C
4c, 5c	Tmp[a]	Me_2N	Si(*i*-Pr)$_3$	Several days at 25 °C 1 h at 35°C	Several weeks at 25 °C
4d, 5d	Tmp[a]	Me_2N	$SiMe_3$	Several days at 25 °C 1 h at 35°C	Several weeks at 25 °C
4e, 5e	Tmp[a]	Ph	$SiMe_3$	Few minutes at 25 °C	Few hours at 25 °C
4f, 5f	*c*-Hex_2N	*c*-Hex_2N	$SiMe_3$	Stable 24 h at 70 °C	Several weeks at 25 °C
4g, 5g	*i*-Pr_2N	*i*-Pr_2N	PR_2H[+b]	Not observed at 25 °C	m.p. 88°C indefinitely at 25 °C
4h, 5h	*i*-Pr_2N	*i*-Pr_2N	PR_2Cl[+b]	Not observed at 25 °C	Few days at 25 °C in solution

[a]Tmp = 2,2,6,6-tetramethylpiperidino; [b]R= N-*i*Pr_2.

Investigations into the nature of the bonding system in phosphinosilylcarbenes have been carried out using single-crystal X-ray analysis,[12] NMR spectroscopy, and theoretical calculations.[13] The results of these techniques suggest that phosphinosilyl and phosphinophosphonio carbenes exist as singlets wherein the phosphino group act as X substituents with their lone pair interacting with the carbenes vacant orbital, and the silyl or phosphonio groups act a Z substituents with the carbenic lone pair interacting with their low lying σ^* orbitals.

1.4.2 Acyclic Amino Carbenes



6 **7** **8** **11**

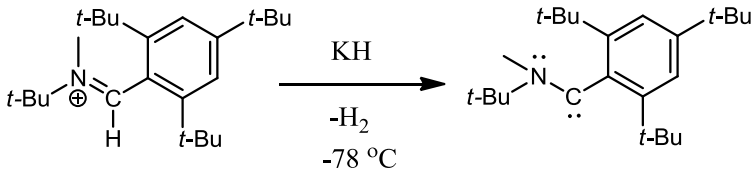
R = *t*-Bu, Ad, *i*-Pr
R' = *t*-Bu, N(iPr)$_2$, Ph

Figure 1.6 Acyclic amino carbenes.

With the aim of developing nucleophilic catalysts based on derivatives of imidazol-2-ylidenes the first acyclic diaminocarbene (Figure 1.6) **6** was isolated in 1996.[14] It was prepared as stable solid via the deprotonation of N,N,N' .N'-tetraisoproplyformamidinium chloride by lithium diisopropylamide (LDA). Analysis of this compound by single crystal X-ray diffraction showed that both C-N bonds have substantial double bond character implying an X-X carbene classification. Non cyclic X-X carbene system are rare probably due to their decreased stability and co-ordination ability when compared to their cyclic counterparts. In fact to date predominately diamocarbene **6** and amino-alkoxy carbene **7** have been used as ligands.[15] A Density Functional Theory (DTF) study of diaminocarbene **6** found that this carbene has a much smaller singlet-triplet energy gap and stronger nucleophilicity than cyclic analogues.[16]

Research by Bertrand in 2001 found that one amino substituent bonded to the carbenic carbon is sufficient to stabilise the system and permit isolation at room temperature.[17] The second substituent can be a spectator group that merely affords some degree of steric protection only. The first compound of this new class of carbenes (X-spectator) **8** was

prepared by the deprotonation of the iminium salt **9** with potassium hydride at 78°C in tetrahydrofuran (THF) under an argon atmosphere (Scheme 1.2). This amino-arylcarbene **10** was found to be stable for days at -50°C but only stable at room temperature for a few hours. Following the same procedure described above a number of amino-arylcarbenes have been synthesised.



9 **10**

Scheme 1.2 First synthesis of a stable amino-arylcarbene**.**

The aryl group's role as a spectator in the stabilisation of the carbenic centre was proven both by X-ray analysis and carbene reactivity. The X-ray structure of amino-arylcarbene **9**a showed that the N-C bond length was shorter (1.283 ± 0.003 Å) in comparison to diaminocarbenes, implying a stronger donation of the nitrogen lone pair into the vacant carbene orbital. Also the carbene to aryl carbon bond length was longer (1.453 ± 0.003 Å) and the carbene bond angle more acute (121.0° ± 0.2°) when compared to analogous X-Z carbenes such as phosphino-arylcarbenes. In terms of carbene reactivity, amino-arylcarbenes were found to undergo coupling reactions with *tert*-butyl isocyanide at room temperature, which is typical of transient singlet carbenes but not observed with X-X carbenes, demonstrating that in the case of amino-arylcarbenes the vacant carbene orbital remains accessible.

Later work by Bertrand and co-workers, aimed at exploiting the reactivity of the spectator substituent which is not electronically involved with the carbenes stability, led to the synthesis of amino-phoshinocarbene **11**.[18] In this molecule the phosphino groups retains it pyramidal geometry, due to it high planarization energy[19] and is therefore available for further co-ordination to a metal centre. As a consequence carbenes of this type can behave as α, β-bidentate ligands.

1.4.3 N-Heterocyclic Carbenes

N-heterocyclic carbenes are a specific type of persistent carbene where the carbenic carbon is located within an N-heterocyclic structural motif.[20] Over the last few decades they have become a dominate feature in the fields of organocatalysis,[21] and organometallic chemistry.[20] Imidazole and imidazoline 5-membered heterocycles are the most common and will be the focus of this section but other classes are known (Figure 1.7).

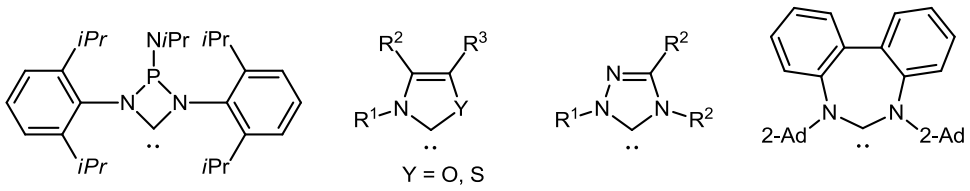
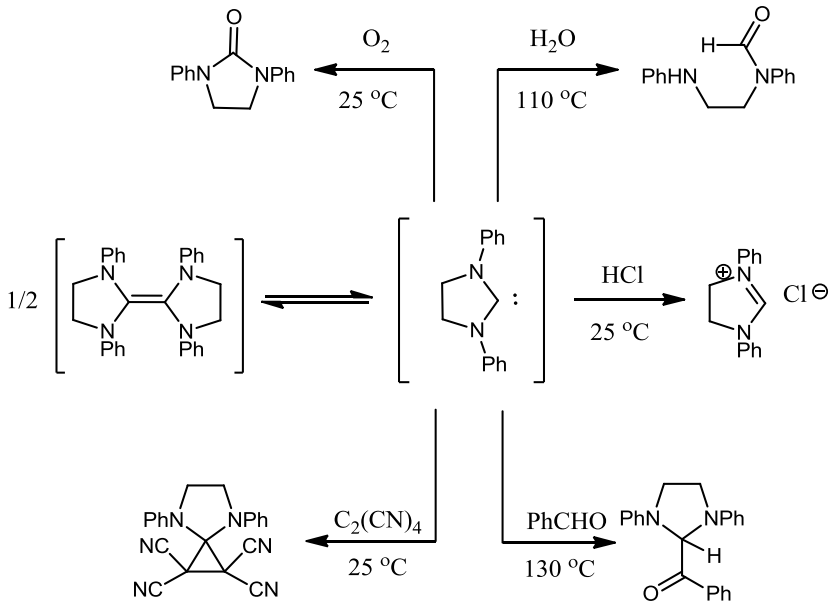


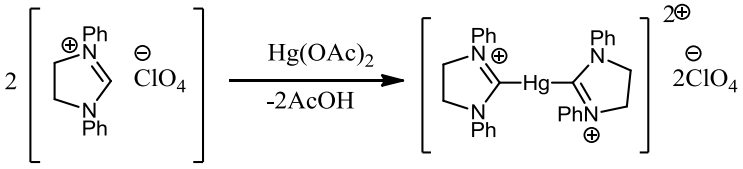
Figure 1.7 Examples of structural variety of NHCs.

Before the isolation of stable NHCs was achieved, research in the early 1960s by Wanzlick probed the reactivity of *in situ* generated NHCs (Scheme 1.3) and identified the nucleophilic nature of these reactive species.[22]



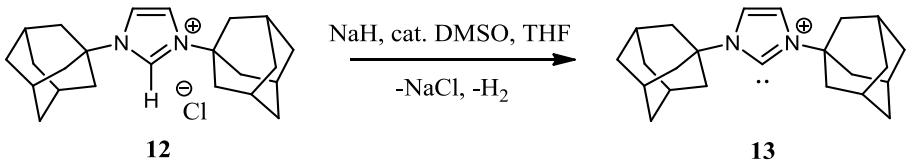
Scheme 1.3 Early reactivity studies of NHCs.

Based on these findings Wanzlick *et al*. described direct synthesis of metal-carbene complexes,[23] prepared without isolation of the free carbene (Scheme 1.4).



Scheme 1.4 Direct synthesis of NHC-metal complex

Despite these insights, the real potential of NHCs as ligands for transition metal chemistry was not realised until Arduengo *et al.* published the synthesis and high stability of the carbene IAd (**13)** in 1991 (Scheme 1.5). [24] This compound, which was generated via the reaction of imidazolium chloride **12** with NaH and catalytic DMSO in THF, was significant because its high stability allowed detailed characterisation of a free carbene for the first time.



12 **13**

Scheme 1.5 Synthesis of IAd.

Initially the stability of this carbene was thought to be purely a result of the sterically demanding N-substituents. A following publication from the same group reported the synthesis of a further four more analogous carbenes,[25] prepared via the same methodology which were far less sterically hindered but also relativity stable (Figure 1.8). After these findings attention naturally turned to identifying why some species were stable and isolatable while others were not.

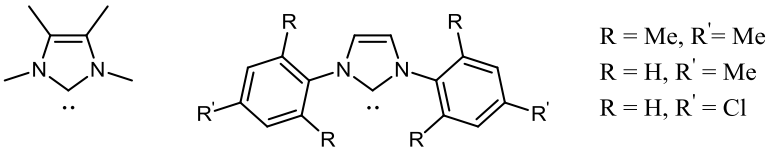


Figure 1.8 Stable NHCs isolated by Arduengo.

As mentioned earlier in this chapter a key factor in carbene stability is the size of the singlet-triplet energy gap (singlet species are more stable). NHCs are best described as X-X carbenes which are stabilised mesomerically, via the donation of electron density from adjacent lone pairs on the hetero atom to the empty ρ orbital of the carbene and inductively due to the electronegativity of the nitrogen groups relative to carbon. These systems are further stabilised due to their cyclic nature,[26] which constrains the spatial orientation of the carbenic carbon into a bent geometry favouring the singlet state (Figure 1.9). Other factors which can increase NHC stability include increasing the aromaticity of the heterocycle[27] and the use of sterically demanding N-substituents.[28]

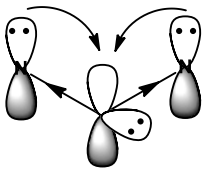
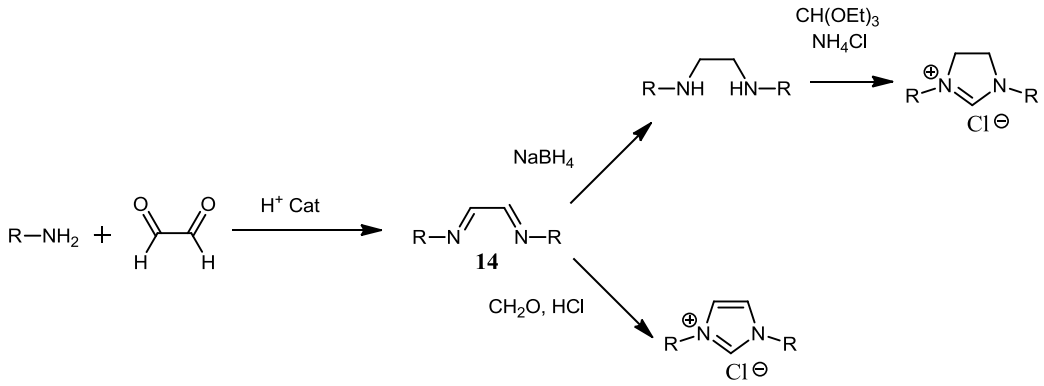


Figure 1.9 Bonding arrangement in NHCs.

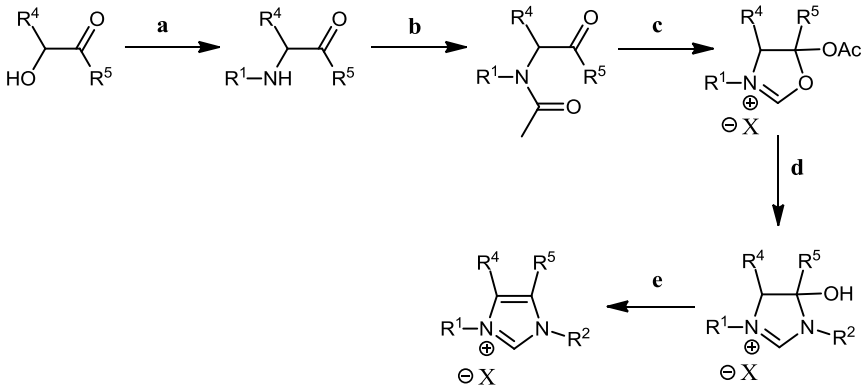
As interest in the chemistry of NHCs has grown, driven in part by their high utility as ligands for transition metal catalysts, numerous methods for their preparation have been developed. A full discussion of every synthetic route is beyond the scope of this chapter, however the earliest common route to the most utilised NHCs such as IMes, SMies, IPr and SIPr involves the deprotonation of the corresponding imidazolium salt using a strong

base, [29] typically NaH or KH in the presence of a catalytic amount of KO^{t}Bu (Scheme 1.6). The imidazolium salt precursor can be prepared in a multistep process beginning with the condensation of glyoxal with the corresponding aryl amine in the presence of an acid catalyst to produce the desired diazabutadiene **14** (DAD). The DAD can either be reduced using $NaBH_4$ or $LiAlH_4$ then ring closed with triethylorthoformate in the presence of an ammonium salt to yield the saturated precursor, or directly treated with paraformaldehyde under acidic conditions if the unsaturated precursor is required. This methodology is only suitable for synthesising symmetrical imidazolium salts, where the N-substituents are the same.



Scheme 1.6 Common route to symmetrical imidazolium and imidazolidinium salts.

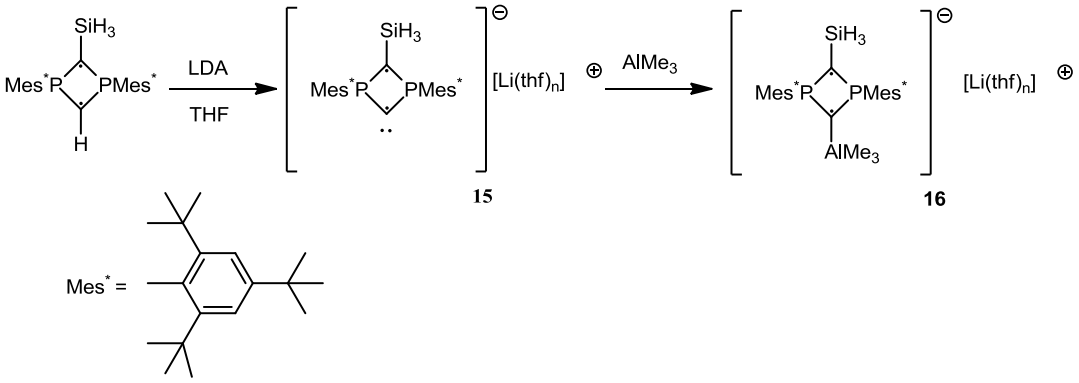
A versatile method for the preparation of unsymmetrical imidazolium salts,[30] was described in 2006 by Fürstner *et al.* (Scheme 1.7). The key feature of this synthetic route was the exchange of the oxygen in the oxazole heterocycle with various amine based reaction partners such as substituted anilines, primary and secondary amines, as this tolerance to many functional groups facilitated the preparation of many previously unattainable NHC precursors.



Scheme 1.7 Synthesis of unsymmetrical imidazolium salts. [a] R^1NH_2, HCl cat, toluene. [b] MeC(O)OC(O)H. [c] Ac_2O, HX. [d] R^2NH_2, toluene. [e] Ac_2O, HX cat.

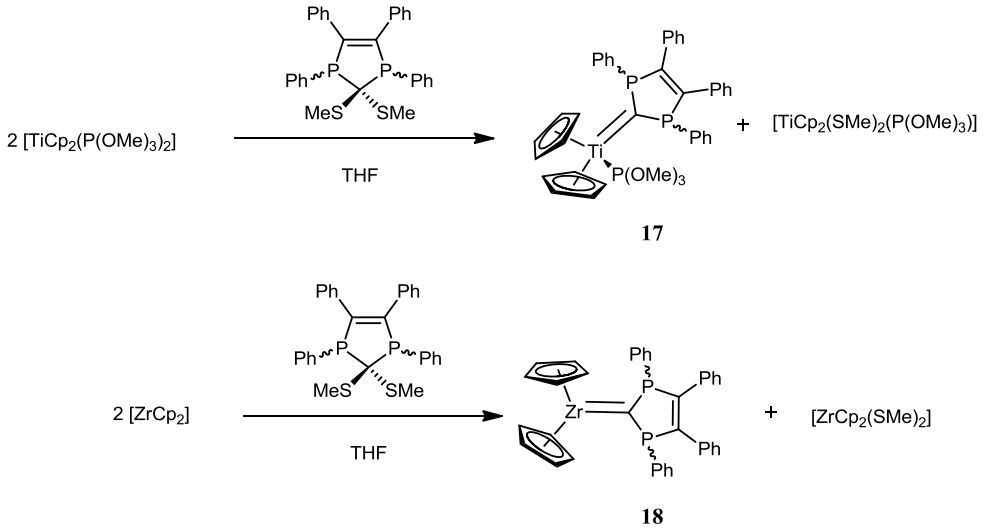
1.4.4 Cyclic Diphosphinocarbenes

In a 1996 seminal paper by Schleyer *et al.*[19] it was stated that the intrinsic π donor capacities of heavier elements such a phosphorus are as large or in some cases larger than those of their second row counterparts such a nitrogen, and that their apparent observed donor inferiority is a result of their difficulty in attaining the required planar configuration. This information coupled with the isolation of stable NHCs led other groups to research the synthesis of cyclic diphosphinocarbenes (PHCs) in the hopes of developing viable alternatives to NHCs in catalysis. The earliest example of a PHC was reported in 1999,[31] and reported the synthesis of 1-3-diphosphacyclobutane-2,4-diyl-ylidenides (**15**) via deprotonation using LDA (Scheme 1.8). It was found that this compound could be stored under inert atmosphere for some time without decomposition. Unfortunately ab initio calculations on model compounds, NBO analysis and X-ray data of its Lewis acid adduct **16** revealed significant pyramidalization of the phosphorus atoms which led to low singlet-triplet energy gap and would therefore imply poor performance as an NHC mimic.



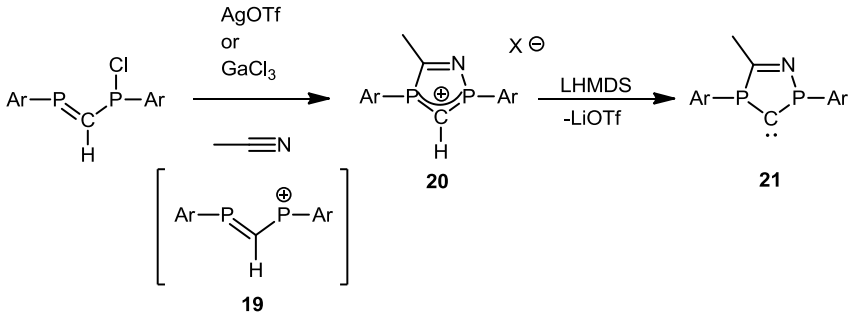
Scheme 1.8 First synthesis of PHC.

Later work reported the synthesis of complexes with titanocene (**17**) and zirconocene (**18**) containing a PHC as a ligand (Scheme 1.9).[32] These complexes were only able to be analysed spectroscopically and were found to be unstable in the absence of solvent. Preliminary DFT calculations confirmed the nucleophilic character of the carbenes in the complexes.



Scheme 1.9 Metal PHC complexes.

In 2005 the first synthesis of a stable isolatable PHC was reported.[33] This synthetic approach (Scheme 1.10) consisted of: a [3+2] cycloaddition of a diphosphallylic cation **19** with acetonitrile in the presence of silver trifluorometnesulfonate or gallium trichloride to produce the desired salt **20**, followed by deprotonation of the salt by lithium bis(trimethylsilyl)amide to yield the target free PHC **21**.

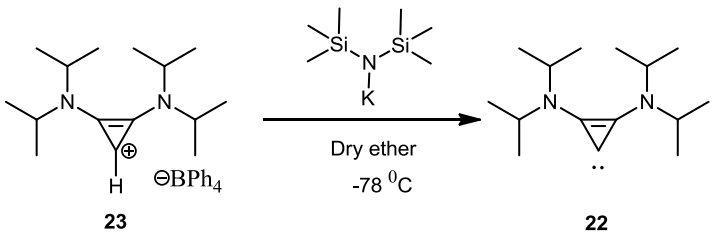


Scheme 1.10 Synthetic route to isolatable stable PHCs.

This carbene is the diphosphorus analogue of Enders' NHC and contains bulky P-substituents to attempt to sterically facilitate the planarization of the phosphorus atoms. The X-ray diffraction analyses of compounds **20** and **21** revealed that this was successful, as both molecules expressed an almost planar environment with regards to the phosphorus centres. As a consequence the calculated singlet-triplet gap was larger than all other PHCs reported though still not as large as Enders' NHC.

1.4.5 Cyclopropenylidene Carbene

The existence of cyclopropenyilidene was proven in 1985 by astronomical detection,[34] and has now been inferred to be the most abundant cyclic hydrocarbon observed in interstellar space.[35] Despite this fact, the isolation this class of molecule in the laboratory remained elusive until 2006 when it was reported by Bertrand and co-workers. [36] In this paper the bis(dialkylamino)cyclopropenylidene (**22**) was prepared by the deprotonation of the cyclopropenium salt (**23**) with potassium bis(trimethylsilyl)amide (Scheme 1.11).



Scheme 1.11 First Synthesis of Cyclopropenylidene carbene in the laboratory.

Single crystal X-ray diffraction analysis of the molecule found that the amino groups and ring were nearly coplanar which suggests interaction of the nitrogen lone pairs with the

electron deficient π system of the ring. This interaction coupled with the acute carbene angle induced by the three carbon ring and the sterically demanding N-substituents result in a large calculated singlet-triplet energy gap and therefore a more stable carbene. Molecule **22** was found to be air sensitive, but very thermally stable.

1.5 Bonding of NHCs to Metal Centres

As mentioned above in recent years NHCs have found considerable utility as ligands in transition metal catalysts. As a result of this, research into understanding the bonding nature of NHCs to metal centres and the influence of that bonding on the properties of the metal has been of great importance. NHCs were considered to behave as ligands in a similar fashion to phosphines, since both bind to metal centres via dative co-ordination using a lone pair of electrons. In fact in the early days of NHC development they were labelled as "phosphine mimics".[37] However as research continued the ligand properties of these two classes of compounds have diverged considerably.

1.5.1 Nature of the NHC-metal bond

The Tolman electronic parameter (TEP) is the most typically used method to determine the donating ability of NHCs.[38] This method was first designed to investigate the electronic properties of phosphanes[39], and involves the analysis of CO stretching frequencies of M-L complexes (Figure 1.10). The stretching of the CO bonds is derived from the π donation of electron density from the metal centre into the anti-bonding orbital of the CO bond and is dependent on how electron rich the metal is. Hence the degree of donation from the NHC ligand to the metal will have a correlation to the C-O bond distance and therefore the IR stretching frequency. A number of NHCs have been characterised in this manner,[40] and have been found to be strongly donating.

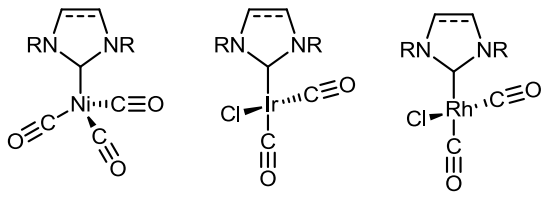


Figure 1.10 Systems commonly used for TEP analysis of NHCs.

NHCs were originally believed to be purely σ donors. However, later studies have shown that though the principal interaction between an NHC and a metal is σ donation, a degree of π bonding and π back-bonding is possible (Figure 1.11). For example in 2005 Nolan *et al.* reported that π donation from a NHC was responsible for the high stability of a low valent, 14 electron Ir complex.[41]

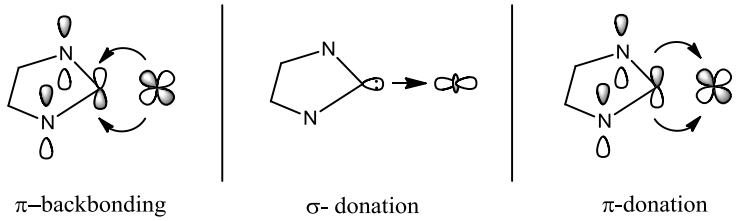


Figure 1.11 Contributions to metal-NHC bond.

The importance of π back-bonding was highlighted by Hu *et al*.[42] with the analysis of the NHC C-N bond lengths for a series of [Z(IMes)$_2$] (Z = Ni^0, Ag^1, I$^+$) complexes (Figure 1.12). In the nickel complex **23**, the metal is comparably electron rich and so donates electron density into the anti-bonding N-C orbital resulting in lengthening of the C-N bond. In the case of complex **24,** in which the metal centre is less electron rich, the back bonding potential is diminished and therefore the C-N elongation is less pronounced. The C-N bond is shortened further in the iodine complex **25** which has no filled d orbitals at all and consequently cannot back bond at all.

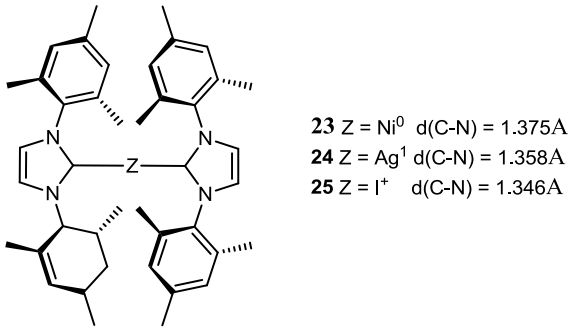
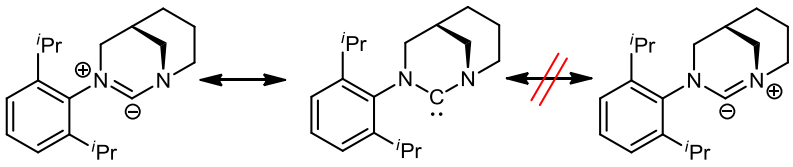


Figure 1.12 Effect of π back-bonding in bis(NHC) compounds.

Research by Bertrand and co-workers reported the synthesis of an NHC ligand **26**,[43] where one of the nitrogen atoms in the ring had a fixed orientation which prevented its donation of electron density into the carbenic carbons' empty p-orbital (Figure 1.13). This carbene was found to be still as nucleophilic and σ donating as other NHC analogs, however it had a smaller singlet- triplet energy gap and was more π-accepting.



26

Figure 1.13 Tuning the bonding nature of the NHC-metal bond via structural confinement.

As shown in the examples above, the bonding nature of NHCs to metals is a more nuanced affair then originally believed, and though σ donation is the most predominate mode of bonding, the amount of which these other bonding modes contribute to the overall strength of the metal-NHC bond is dependent on both the electronic arrangement of the metal and structure of the NHC.

1.5.2 Abnormal carbenes

The conventional bonding motif of NHCs to a metal centre involves co-ordination via the C2 position, however systems where binding occurs in the C4 or C5 positions have been synthesised (Figure 1.14). These compounds, known as abnormal NHCs (aNHCs) or mesoionic carbenes (MICs) exhibit different electronic properties as ligands, which naturally confers different reactivity when compared to the metal-NHC complexes.

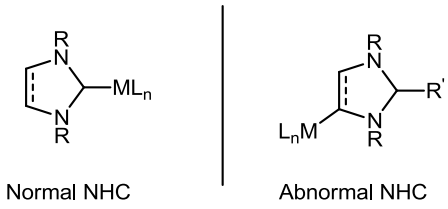
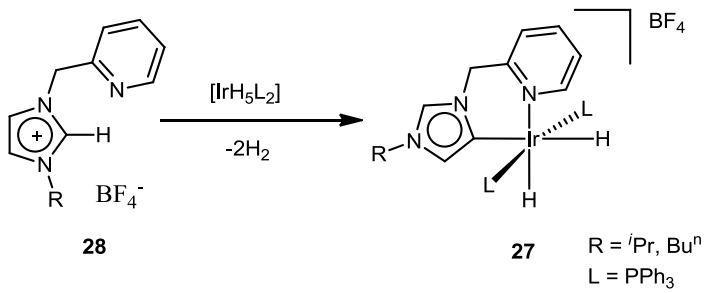


Figure 1.14 Normal vs abnormal bonding of NHCs to a metal centre.

The first example of an aNHC complex **27** was synthesised in 2001,[44] by the reaction of a pyridine-substituted imidazolium salt **28** with $IrH_5(PPh_3)_2$ (Scheme 1.12). Currently there are two main methods of the synthesis of aNHCs. The first method is via the deprotonation of the C4 or C5 position using a strong base.[45] Since the C2 proton of imidazolium salts is more acidic than the C4 or C5 protons, it must be blocked either by direct substitution at the C2 position,[46] or by careful selection of N substituents.[47] The second method is by the oxidative addition of the imidazolium salt to a low –valent group 10 metal such as Pd^0 or Pt^0 via an C-X bond (X=Br,I) on the C5 position in the ring.[48]



Scheme 1.12 First synthesis of an aNHC complex.

Abnormal carbenes have been found to more nucleophilic and more π-accepting than their NHC congeners, due to the absence of the second neighbouring electron withdrawing nitrogen.[49]

1.5.3 Tuning electronic effects of NHCs as ligands

The structural features of an NHC which can be modified to tune its electronic properties when co-ordinated to a metal centre are: i) the electronic nature of the C4-C5 backbone (saturated or unsaturated), ii) substitution on the carbon atoms in the NHC backbone and iii) variation of the N-substituents (Figure 1.15). As mentioned earlier, the key experimental parameter used in assessing the electronic properties of NHCs as ligands is measuring the CO stretching frequency ν_{av}, by IR spectroscopy. This methodology has been used to explore the effect of modifications on the three structural features outlined above.

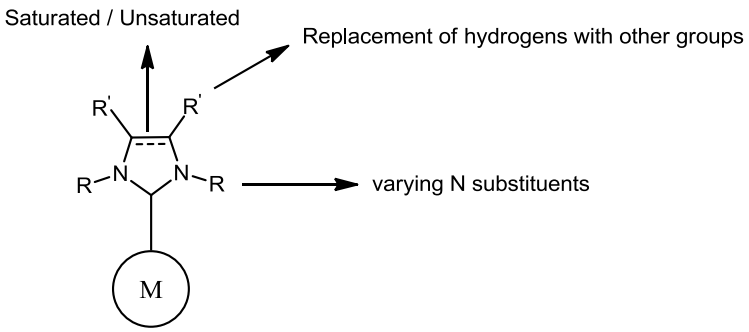
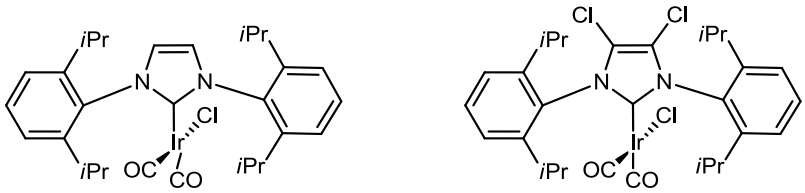


Figure 1.15 Handles for modification of a typical NHC for tuning its electronic properties as a ligand.

The electronic nature of the C4-C5 bridge was found to have a negligible effect on the binding properties of the NHC, only resulting in a 2-3 cm^{-1} variation in stretching frequency.[38] More impact has been observed when considering substitution on the C4 and C5 carbon atom. For example, replacement of the hydrogens on those carbon atoms of complex **28** with more electron withdrawing Cl atoms as in complex **29**, resulted in the average CO stretching frequency shifting from 2024 to 2028 cm^{-1} (Figure 1.16).[50] It has been reported that changing the nature of the N-substituents can have some effect on the NHCs electronic properties (less the 5 cm^{-1}).[50] In general alky N-substituents are better electron donors then aryl N-substituents.

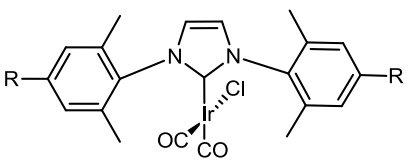


28 ν_{av}= 2024 cm^{-1}

29 ν_{av}= 2028 cm^{-1}

Figure 1.16 Tuning electronic properties of NHC through backbone modification.

The greatest impact on the electronic properties of NHC is derived from the modification of the *para* position of an aromatic N-substituent. Switching from a strongly electron donating group (NEt_2) to a strongly electron withdrawing group (SO_2-(*p*-tolyl)) results in the average CO stretching frequency increasing by 8 cm^{-1}(Figure 1.17).[51] Experimental testing and quantum mechanical calculations have been carried out to understand how these groups could influence the electronic properties of the NHC to such a great extent, despite being 7 σ bonds away from the metal. These studies concluded that this interaction occurs via a 'through space' donation from the C_{ipso} atom of the N-substituent either directly into the empty d orbitals of the metal or into an appropriately orientated electronically suitable group attached to the metal.[52]



R = NEt_2 ν_{av}= 2022 cm^{-1}
R = Me ν_{av} = 2025 cm^{-1}
R = SO_2-(p-tolyl) ν_{av}= 2030 cm^{-1}

Figure 1.17 Tuning electronic properties of a NHC through N-substituent modification.

1.5.4 Steric impact of NHC ligands

The steric properties of NHCs can have a significant effect on the catalytic performance of an NHC-metal complex. Conventional methods used to quantify the steric impact of phosphanes such as the Tolman cone angle,[39] proved to be insufficient for NHCs due their markedly different shapes (Figure 1.18).

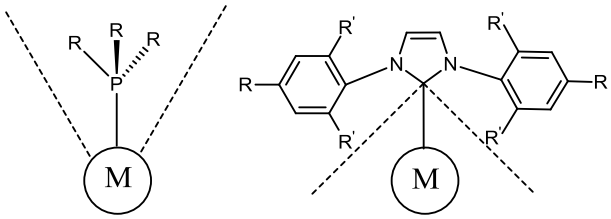


Figure 1.18 Difference in the steric environments imposed by phosphanes and NHCs.

Systems designed to more accurately describe NHCs steric qualities, such as the fence model, proved imprecise.[53] Then in 2010 the concept of percentage buried volume ($\%V_{bur}$) was introduced;[54] this system defines the fraction of the volume of a sphere, centred on the metal, which is occupied by the ligand (Figure 1.19). One of the major advantages of this methodology was its generality. The $\%V_{bur}$ calculations were found to accurately describe the steric properties of NHCs and other ligands such as phosphines, facilitating direct comparison for the first time.[38] Research by Nolan *et al*. found an almost linear correlation between experimental bond dissociation energy (BDE) and $\%V_{bur}$, with BDE increasing with reduction of steric bulk.[55] This highlighted the important role the steric bulk of the NHC has on their binding ability to transition metals. In the same publication the authors identified that saturated NHCs have a greater steric impact than their unsaturated analogs, and reasoned that was a result of the longer backbone imposing a greater N-C-N bond angle, directing the N-substituents closer to the metal centre.

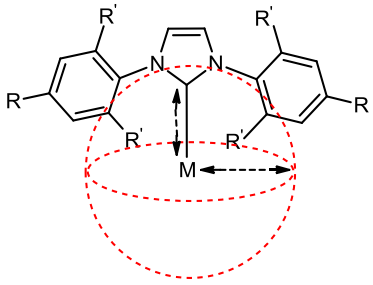
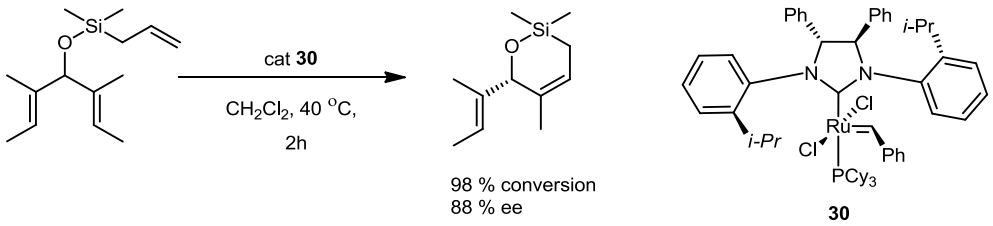


Figure 1.19 Diagram illustrating the $\%V_{bur}$ of an NHC ligand.

Analysis of the catalytic reactivity of NHC-metal complexes such as ruthenium complex **30** indicated that the steric pressure of the NHC ligand is not expressed evenly in the first co-ordination sphere of the metal (Scheme 1.13).[56] It was theorised that this variation in steric environment could result from an intrinsic flexibility around the N-substituent bond,[57] and that exploitation of this parameter could shape the co-ordination sphere around the metal, therefore improving the complex's catalytic performance.



Scheme 1.13 Experimental evidence for NHC steric flexibility.

This theory was confirmed by Cavallo *et al*. using *ab initio* molecular dynamics calculations of a series of NHC-Ru catalysts used for olefin metathesis (Figure 1.20).[58] This study found that the distribution of dihedral angles ϕ_1 and ϕ_2 around the N-substituent bonds are influenced by both the steric nature of the *ortho* groups on the N-substituents and the specific orientations of other ligands co-ordinated to the metal centre (Figure 1.21). Distribution of dihedral angles ϕ_1 and ϕ_2 in the SIMes complex **31** is centred at 90° with a restricted flexibility of ± 15°.

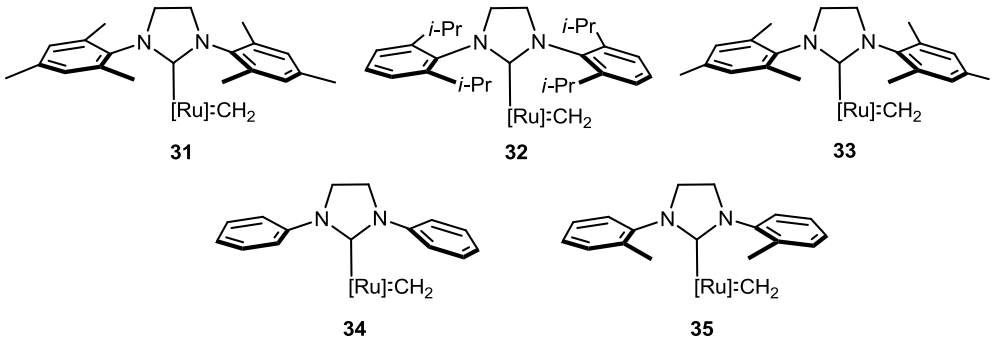


Figure 1.20 Series of NHC-Ru catalysts used for olefin metathesis.

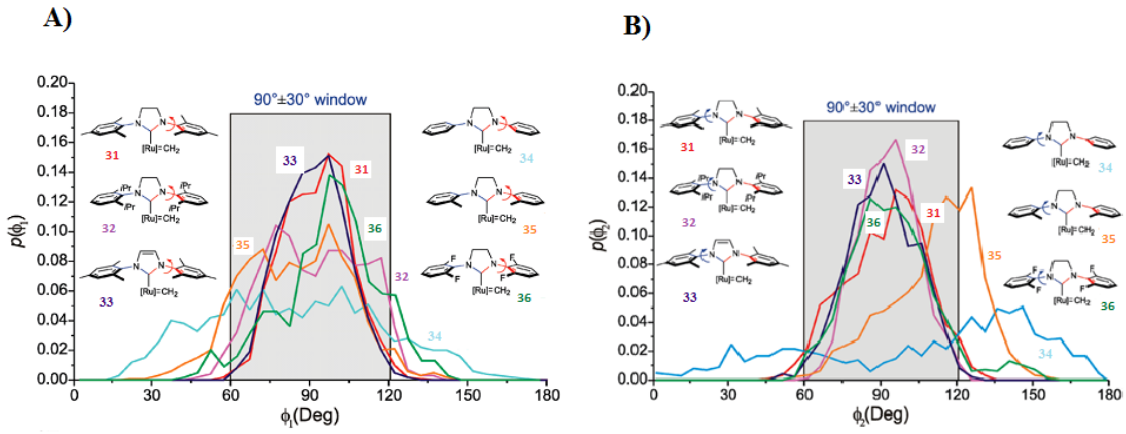


Figure 1.21 Distribution of the dihedral angles ϕ_1 (A) and ϕ_2 (B) in NHC-Ru pre-catalysts. [Ru] represents $Ru(Cl_2)(PMe_3)$ which were omitted for clarity.

In the case of the SIPr complex **32** the ϕ_2 distribution is similar to the SIMes analogue, however the ϕ_1 plot is comparatively broader and flatter as a result of steric interaction between the halide ligands and the larger *i*-Pr groups on the N-substituent. Both the ϕ_1 and ϕ_2 values for the sterically unhindered N-phenyl system **34** have very flat profiles with tails approaching 0-180 °C, indicating free rotation N-substituent bond. Geometries approaching 0-180 °C can have catalytic implications as N-substituents in those positions are predisposed to interact with the ylidene moiety via C-H activation, resulting in a loss of catalytic activity.[59] The NHC-Ru complex with a single *ortho* substituent **35** showed the largest difference between the ϕ_1 and ϕ_2 values. The ϕ_1 plot of this complex was found contain two major peaks: one around 90°, similar to the SIMes system; implying that the inclusion of a single methyl group on the N-substituent can impose a marked reduction in flexibility and the second at lower ϕ_1 values which indicates that the *o*-tolyl ring can twist to turn its unsubstituted side toward the Cl-Ru-Cl plane. Conversely the ϕ_2 distribution contains a well-shaped peak approximately 30° higher than the other complexes, this suggests the *o*-tolyl ring can assume a sterically preferential conformation derived from twisting the methyl-substituted side away from the crowded Cl-Ru-Cl plane.

The above rationalization on the nonhomogeneous distribution of the steric impact from NHCs as ligands led to the refinement of the $\%V_{bur}$ descriptor (which only measured the average of the steric properties) into topographic steric map systems that analysed the $\%V_{bur}$ in single quadrants around the metal centre. Topographic steric maps can be viewed

as chemical analogues to geographical maps, wherein different colours and lines indicate differing degrees of elevation. In the case of topographic steric maps $\%V_{bur}$ values are combined along the *z*-axis, which is the area the NHC ligand occupies in the first co-ordination sphere of the metal. Positive values of the isocontour lines refer to the top half of the sphere and negative the bottom. This system facilitates a three dimensional visualisation of the steric environment around the metal centre, highlighting the structural motifs of the NHC which exert the most steric pressure in a given complex. The topographic steric maps of the complexes **31**, **32** and **35** are shown below (Figure 1.22).

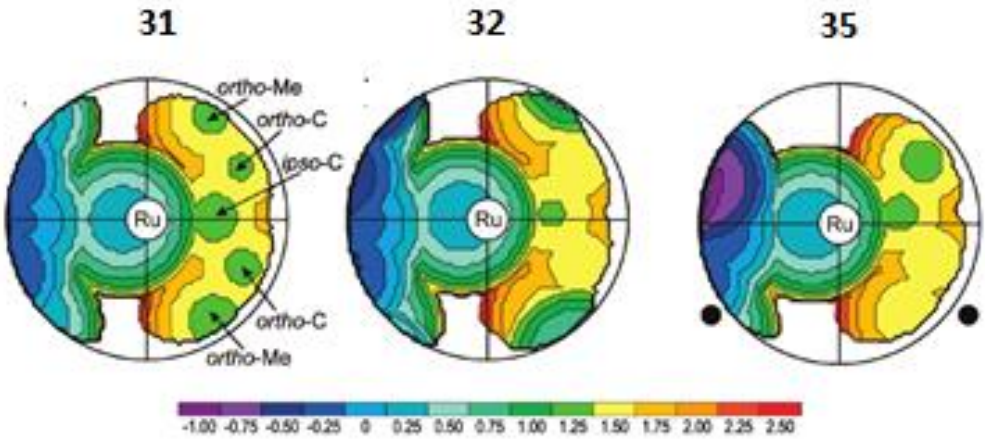


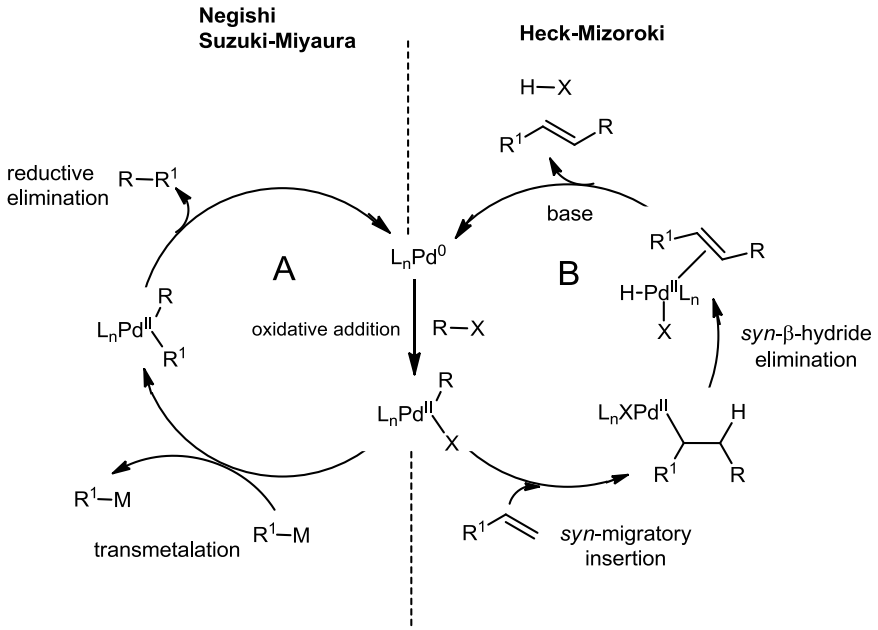
Figure 1.22 Steric maps of NHC-Ru complexes

In the SIMes-bearing complex **31**, the side of the NHC which occupies the space above the vacant Ru co-ordination position is shown to twist down (signified by the dark blue areas on the two left quadrants) sterically shielding that site. The other side of the NHC has less steric impact on the metal centre as it is competing with the methylidene for space, however the yellow band at 1.00-1.25 Å does suggest that the mesityl ring does impart some steric pressure on the Ru-methylidene bond, especially through the *ipso* and *ortho* carbon atoms of the ring (green imprints on steric map for **31**). The *ortho* methyl groups on the ring are also reported to have a small impact at the borders of the co-ordination sphere. The bulkier *i*-Pr groups of the IPr-Ru complex **32** are shown to exert more steric pressure at the borders of the co-ordination sphere then the SIMes counterpart **31** (darker areas in the corners of each quadrant). In order to relieve this steric pressure, the SIPr ligand is pushed away from the metal centre slightly; consequently the steric

impact of the SIPr ligand relating to the central zone, where the Ru-methylidene bond is orientated, is diminished. This is indicated by the absence of green spots characterising *ortho* C atoms in **32** when compared with **31**. This clear difference in steric environment imparted by the SIMes and SIPr NHCs to the Ru metal centre is not seen when using the simple $\%V_{bur}$ descriptor as they have similar average $\%V_{bur}$ values. In the case of the *ortho*-tolyl NHC-Ru complex **35** both sides of the NHC have rotated their N-substituent bonds to orientate their unsubstituted sides down towards the metal centre, minimising their steric impact. This results in a roughly C_s-symmetric map, with the bottom two quadrants more hindered and could explain the ability of the *ortho*-tolyl system to selectively form *cis* olefins when used as a catalyst.[60]

1.6 (NHC)-Palladium Complexes used in Cross Coupling Reactions

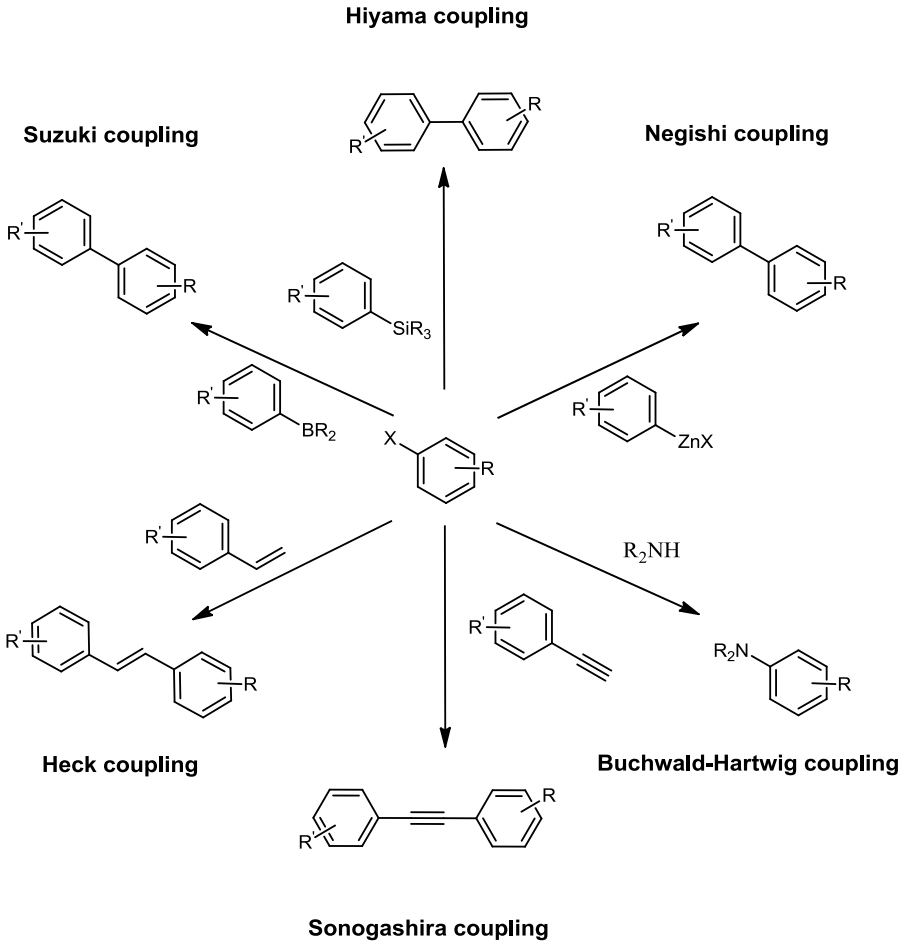
Transition metal catalysed cross-coupling has become one of the most predominant methods for carbon-carbon bond formation. Research by many groups in the late 1970s expanded the scope of palladium catalysis, to the point where currently, palladium mediated transformations are the most common form of cross coupling reaction. The significance of palladium catalysed reactions was acknowledged in 2010 when Richard Heck, Ei-ichi Negishi and Akira Suzuki were jointly awarded the Nobel Prize for their contribution to this field of chemistry. The Suzuki-Miyaura reaction is the most commonly utilised currently in the literature, followed by the Heck and Sonogashira coupling reactions. Generally the mechanisms for these palladium catalysed cross coupling reactions can be categorised into two pathways (Scheme 1.14). Both begin with the oxidative addition of an aryl halide (or pseudohalide) to the catalytically active L_nPd^0 species. At this point the processes diverge. In pathway A, the reaction progresses via transmetalation of an organometallic species, generating a Pd^{II} intermediate bearing the two organic coupling partners. This intermediate subsequently undergoes reductive elimination, forming the C-C bond between the partners and regenerating the Pd^0 species. Alternatively in pathway B the reaction progresses though co-ordination of an alkene to the Pd^{II} species, followed by *syn* migratory insertion. The insertion is regioselectively controlled by the nature of the alkene, the catalyst and reaction conditions. The generated organopalladium species then undergoes *syn* β-hydride elimination, releasing the coupled alkene product. The L_nPd^0 catalyst is then regenerated via base assisted elimination of H-X.



Scheme 1.14 The general catalytic mechanisms for Mizoroki-Heck, Suzuki-Miyaura and Negishi reactions.

Palladium cross coupling reactions are conventionally defined by the type of nucleophile that they couple with: the organic halogen or pseudo-halogen reagent (Scheme 1.15). These systems traditionally used tertiary phosphines as ligands, however, due to the fact that NHCs are more electron donating, form more stable metal complexes and are highly tuneable with regard to their steric and electronic properties, they have recently seen a high degree of utility as catalysts in cross coupling reactions. This is due to research in the early 2000s by the groups of Herrmann[62], Nolan[63], Beller[64] and Sigman[65] which identified that Pd-NHC complexes showed high activity, pioneering their use in Pd-catalysed cross-coupling reactions.

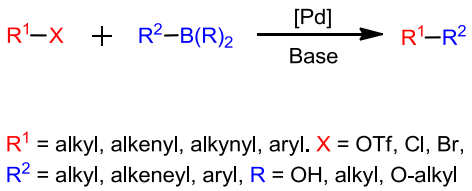
The aim of the rest of this section is to outline the recent developments in the design of (NHC)-palladium complexes in each category of cross-coupling reaction. Discussions of catalysts containing N-donors which function as throw-away ligands have been omitted from this section as they are described later in Chapter 2.



Scheme 1.15 Summary of palladium cross coupling reactions, classified by nucleophilic partner**.**

1.6.1 Suzuki-Miyaura Cross-Coupling

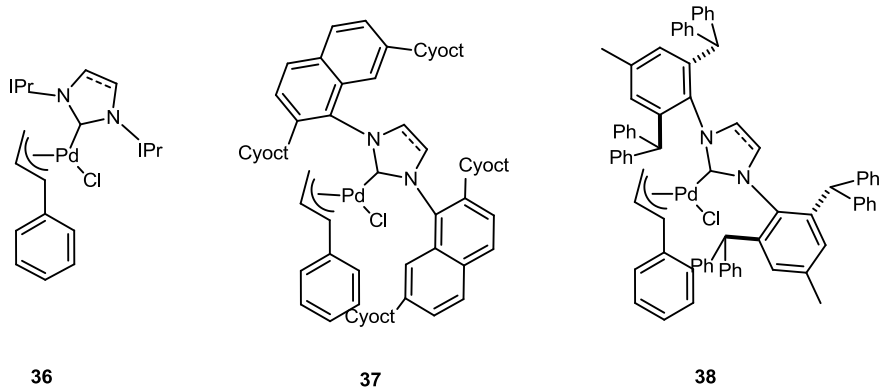
The Suzuki-Miyaura cross-coupling is the palladium catalysed coupling of organoboron compounds with organohalides (Scheme 1.16.) Among the plethora of cross-coupling reactions now available, the Suzuki-Miyaura reaction has emerged as one of the most versatile, finding use in the synthesis of many compounds such as polymers, agrochemicals and pharmaceuticals[61]. As a result of this high utility, the development of Pd-NHC complexes as catalysts for Suzuki-Miyaura coupling has been the focus of much research in the last two decades.



Scheme 1.16 General scheme for a Suzuki-Miyaura cross-coupling.

In 2006 Nolan and co-workers designed and fully characterised a series of (NHC)Pd(R-allyl)Cl complexes based on (NHC)Pd(allyl)Cl systems previously developed by this group and tested their use as catalysts for Suzuki cross coupling.[66] Comparison of these new complexes to the original (NHC)Pd(allyl)Cl systems found that substitution at terminal position of the allyl scaffolds favoured a more facile activation step. Of the complexes tested (IPr)Pd(cinnamyl)Cl (**36**) was reported to be the most effective, able to couple hindered substrates such as tri-ortho-substituted biaryls at room temperature.

The goal of designing a Pd-NHC catalyst which could facilitate the room temperature synthesis of highly desirable tetra-ortho-substituted biaryls by Suzuki-Miyaura coupling was first achieved in 2011 by Dorta *et al.*[67] The central feature of the catalyst used (**37**) was the introduction of a C_2-symmetric NHC ligand with appropriately substituted naphthyl side chains. Advanced DFT calculations showed how this ligand's symmetry induced steric properties and allowed a dramatic increase in the catalytic performance. Recent research into (NHC)-Pd(cinnamyl) complexes as catalysts led Nolan and co-workers to develop complex [Pd(IPr*)(cin)Cl] (**38**). This catalyst was found to show excellent catalytic activity in Suzuki-Miyaura cross coupling, allowing the generation of *tetra-ortho*-substitued biaryls at room temperature[68].

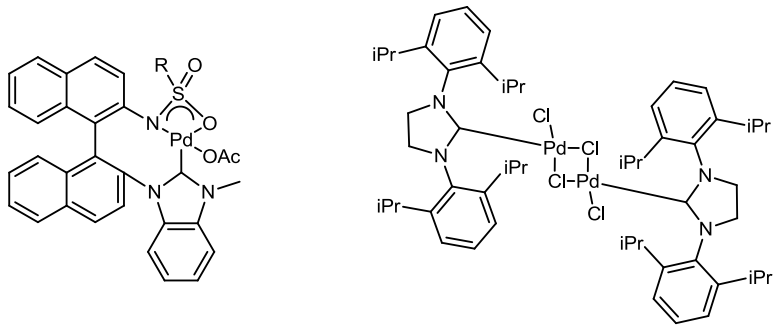


36 **37** **38**

Figure 1.23 NHC-palladium(allyl)Cl complexes used for Suzuki-Miyaura reactions

In 2008 the synthesis of a number NHC-Pd complexes were reported bearing a novel NHC-sulpthonamide ligand, derived from binaphthyl-2-2'-diamine (BINAM).[69] It was reported that of the six NHC-Pd(II) complexes tested, the two tridentate Pd complexes (**39**, **40**) bearing weakly co-ordinating acetate counterions proved the most effective in catalysing Suzuki-Miyaura cross-coupling reactions (Figure 1.24)

Research by Cazin *et al.* found that the easily prepared $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ dimer **41** could be used to good effect in Suzuki-Miyaura coupling reactions, mediating the synthesis of simple biaryls at low catalysts loadings and a room temperature.[70] Although **41** cannot compete in activity with non-dimeric NHC-Pd complexes it is worth mentioning as its development was a stepping stone to the much more effective mono NHC co-ordinated palladium catalysts**.**



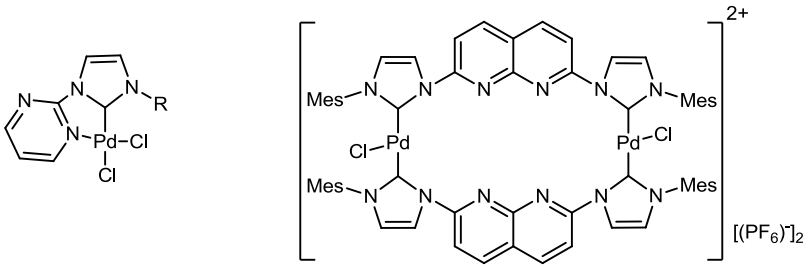
39 R= Me
40 R= PhMe

41

Figure 1.24 NHC-Pd catalysts used in Suzuki-Miyaura cross coupling.

In 2009 Chen and co-workers prepared a series of tetra and penta-coordinated Pd-NHC complexes bearing mono- and dicarbene ligands. [71] The complexes were prepared via transmetallation of corresponding *in situ* generated silver-carbene complexes to $Pd(cod)Cl_2$ and fully characterised by NMR, elemental analysis and X-ray single crystal diffraction. Testing of these compounds as catalysts for Suzuki coupling reactions found tetra-coordinated mono-NHC bearing complex **42** to be the most effective (Figure 1.25). The dicarbene palladium complexes were reported to be much less active than their mono-carbene counterparts, an observation rationalised by the authors who proposed that the blocking of one of the co-ordination sites at the metal by the additional donor inhibits the substrates approach to the Pd centre.

Recently the synthesis of palladium complexes based on 1,8-naphthridine functionalized NHC motifs have been reported.[72] One of these complexes, **43** was tested as a catalyst for Suzuki- Miyaura coupling reactions. It was reported to couple aryl bromides in ethanol under refluxing temperatures, but was found to be ineffective for activated or un-activated aryl chlorides.



42 R = 2, 4, 6-trimethylphenyl **43**

Figure 1.25 Example of NHC-Pd complexes with novel structural motifs.

Many NHCs are derived from imidazolium or 4,5-dihydroimidazolium salts and bind a metal at the C2 position, but it has been reported that metalation of the imidazolium salts can also take place at the C4 or the C5 position, known as abnormal N-heterocyclic carbenes (aNHCs). Early research has reported that aNHCs are even stronger donors then conventional NHC and could provide new opportunities in catalysis.[73]

In 2010 Hong and co-workers produced an aNHC **44** derived from a C2-protected imidazolium salt (Figure 1.26). This ligand then was used for the in situ generation of a Pd-aNHC catalyst for Suzuki-Miyuara coupling reactions.[74]Analysis of the results showed that abnormal NHC performed better when compared to their corresponding normal counter parts, suppressing homocoupling of arylboronic acids. Recently two halobridged dimers **45** containing aNHCs where synthesised, fully characterised and tested as catalysts for Suzuki coupling reactions[75]. These dimers were found to be able to cross-couple an array of aryl chloride at room temperature with very low catalyst loading.

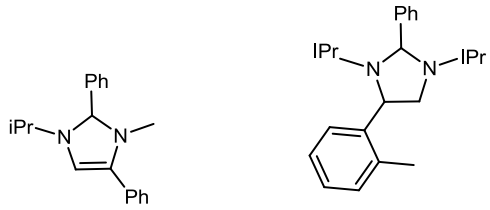


Figure 1.26 Abnormal NHCs which have been co-ordinated to Palladium for Suzuki-Miyuara cross coupling reactions.

Recently a number of groups have reported investigations into developing complexes consisting of both a phosphine and a NHC which have allowed access to stable chelate complexes with interesting electronic properties (Figure 1.27). In 2010 a number of air stable neutral (**46A**) and cationic Pd (**46B**) complexes bearing chiral phosphine-NHC ligands were prepared. They were designed to have planar chirality and characterised by NMR and X-ray diffraction. These complexes were shown to catalyse asymmetric Suzuki-Miyaura coupling reactions between aryl bromides and arylboronic acids with moderate enantioselectivites and yield utilising low catalyst loadings.

A series of mixed $P(OR)_3$/NHC Pd complexes (**47**) were synthesised and fully characterised in 2010.[76] X-ray analysis was used to computationally determine the steric properties of both carbene and phosphine ligands. It was reported that the NHCs modulate their bulkiness with respect to the steric requirements of the co-ligands. These complexes were tested as catalysts in Suzuki-Miyuara cross-coupling reactions and were found to be effective. Mechanistic analysis suggest that the presence of alkoxide groups is necessary for activation of the precatalysts to generate the catalytically active Pd(0) species.

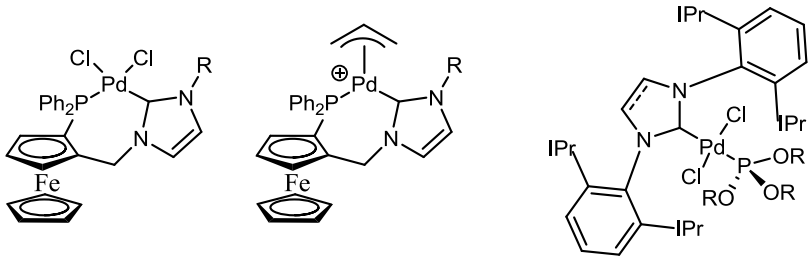
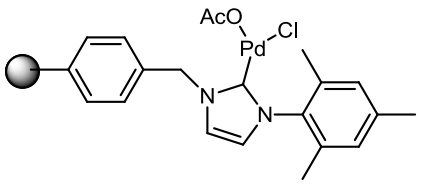


Figure 1.27 Mixed NHC, Phosphine palladium complexes used in Suzuki-Miyuara cross coupling.

Over the past few years Suzuki reactions of aryl chlorides have been successfully completed using homogenous Pd-NHC catalysts. However, homogenous catalysis has some inherent problems, such as the need to separate and recycle the catalyst and contamination from ligand residues in products. With this in mind a number of research groups have developed several types of heterogeneous NHC catalysts. One group developed an immobilized NHC- palladium catalyst **48** (Figure 1.28), prepared by reacting macroporous chloromethyl polystyrene with 1-mesitylimidazole.[77] This MPS-supported NHC complex was found to be an effective catalyst for the Suzuki reaction of aryl iodide and bromides at room temperature. This system could be even used for the coupling of aryl chlorides using elevated temperatures (100 ^{0}C).

Recently a novel IPr-functionalized mesoporous ethane-silica was synthesized via the co-condensation of IPr-bridged triethoxysilane and bis(triethoxysily)ethane.[78] This new mesoporus material containing an organic framework was found to have high surface area, large pore volume and good co-ordination capacity for Pd. As a result of these characteristics these materials showed remarkable catalytic activity for Suzuki cross coupling reactions. The surface NHC complexes with acetylacetonate (acac) ligands in particular could be reused 10 times without a significant decrease in activity and is the most efficient phosphine-free solid catalyst for coupling reactions.



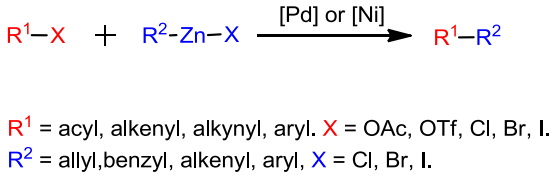
48

Figure 1.28 Example of an immobilized NHC-palladium catalyst.

1.6.2 Negishi Reaction

Extensive research by Negishi developed a synthetic pathway for the Pd- or Ni catalysed cross coupling of organozincs with aryl, alkenyl or alkynyl halides, a reaction now known as the Negishi cross coupling reaction[79] (Scheme 1.17). Traditionally the most common ligand co-ordinated to the Pd/Ni metal centre was PPh_3 but with the recent emergence of NHCs as effective ligands in many cross coupling reactions their use in Negishi couplings

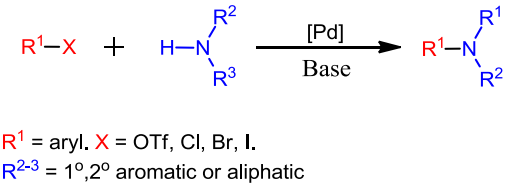
has increased. The most successful NHC-palladium complexes for catalysing Negishi reactions are based on PEPPSI systems and will be discussed in later chapter 2.



Scheme 1.17 General scheme for a Negishi cross-coupling.

1.6.3 Buchwald-Hartwig Aminations

Aryl amines have many varied applications in organic chemistry, industry and materials science,[80] and as such the field of research devoted to the development of efficient protocols for their synthesis is extensive. Since its inception in 1995 by the groups of Buchwald[81] and Hartwig[82] the use of Pd complexes to catalyse amination reactions between aryl halides and secondary amines has become one of the most prominent and powerful methodologies for C-N bond formation (Scheme 1.18). This is due to its selectivity, mild reaction conditions and high tolerance to other functionalities.[83]



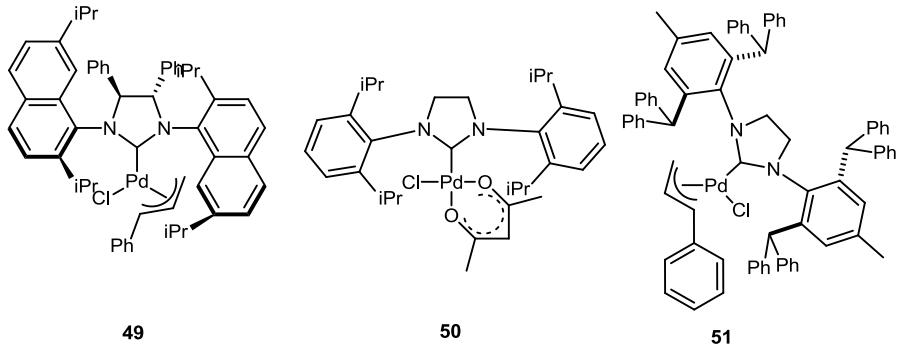
Scheme 1.18 General scheme for Buchwald-Hartwig aminations.

In 2008 Dorta and co-workers reported the development of a series of chiral (NHC)Pd(cin)Cl catalysts.[84] These complexes contained NHC ligands which were derived from C_2-symmetric diamines with napthyl side chains. The complexes were found to exist as a mixture of diastereomers that could be separated via column chromatography, allowing their absolute configurations to be assigned. Investigation into the effect of side chain orientation and their ease of rotation relative to the chiral NHC backbone in these Pd-NHC complexes revealed that these factors have dramatic effects on the selectivity and efficiency of these catalysts and lead to the identification of precatalyst [(R_a,R_a)-(4S,5S)-DiPhSIPrNap]Pd(cin)Cl (**49**) as the most effective complex.

This complex was reported to catalyze the preparation of the target oxindoles with ee's of 86% and percentage yields of up to 99% (Figure 1.29).

Work by Winkelmann *et al*. used X-ray crystallography and ^{1}H NMR spectroscopy to highlight the difference in catalytic performance in Buchwald-Hartwig aminations between (IPr)Pd(acac)Cl and its saturated counterpart (SIPr)Pd(acac)Cl. It was reported that the SIPr-bearing complex (**50**) performed better in this type of reaction and hypothesized that this greater efficiency was derived from the greater steric demand the SIPr ligand places on the metal center[85].

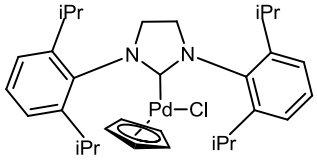
Very recently, Nolan and co-workers reported (IPr*)Pd(cinnamyl)Cl (**51**) as an excellent pre-catalyst for Buchwald–Hartwig amination reactions, with high efficiency for the coupling of numerous (hetero)-aryl chlorides, at room temperature.[86]



49 **50** **51**

Figure 1.29 NHC-palladium complexes used in amination reactions

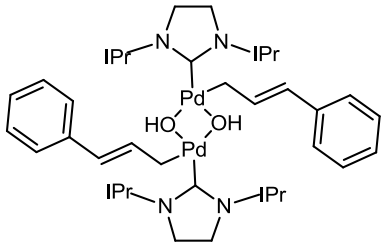
Research into the synthesis NHC-Pd catalysts bearing a cyclopentadiene (Cp) unit have been reported.[87] Aiming to exploit the extreme sensitivity of Cp rings to reductive removal from Cp-Pd complexes, resulting in the formation of active [(NHC)Pd(0)] species, this new class of NHC-Pd complexes were found to be air-stable and able to exhibit high catalytic activity for Buchwald-Hartwig aminations at room temperature. Of all the Cp-Pd complexes tested CpPd(SIPr)Cl (**52)** was found to be the most effective precatalyst (Figure 1.30)**.**



52

Figure 1.30 NHC-palladium complex with Cp ligand

In 2007 Yang and co-workers reported an efficient synthetic pathway for the preparation of tri-arylamines catalysed by the use of $Pd_2(dba)_3$ and IPr.HCl. This method is an efficient and convenient route to the target tri-arylamine compounds and is more convenient, economical and versatile when compared to other Pd/phosphine,[88] and Cu catalysed systems reported at the time. [89] Recently Nolan and co-workers tested the catalytic activity of the palladium hydroxide dimer **53** in amination reactions (Figure 1.31).[90] The complex proved to be a viable catalyst, facilitating the coupling between p-chloroanisole and morpholine at 50 °C with 99% conversion.



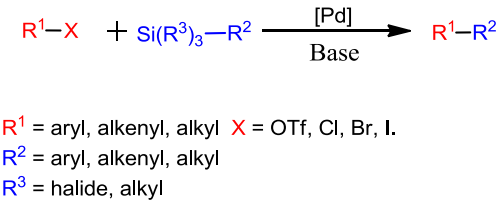
53

Figure 1.31 NHC-Palladium Hydroxide dimer

1.6.4 Hiyama Coupling

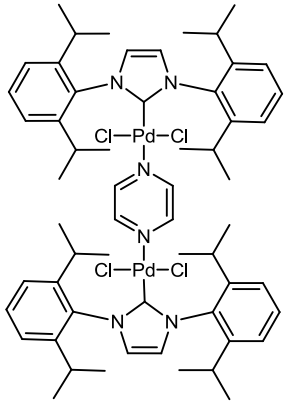
Although Suzuki-Miyaura cross-coupling is still the most prevalent transition metal coupling reaction for the construction of biaryl frameworks, over the last few decades Hiyama cross-coupling has become increasingly popular.[91] The Hiyama reaction utilises organosilicon compounds as organometallic nucleophiles in Pd catalysed cross-coupling reactions (Scheme 1.19). Organosilicon reagents are attractive substrates due to their environmentally benign nature, good stability and ease of availability. However their low nucleophilicity, which results from the small electronegativity difference between Si and C, means the reactions often requires the presence of an anionic activator such as a fluoride ion or a base.[92]

As a result of the growing success of Pd-NHC systems in analogues cross coupling methodologies such as Suzuki couplings, there has been increased interest in their utilisation in Hiyama cross-coupling reactions.



Scheme 1.19 General scheme for Hiyama coupling.

Very recently the preparation of four linear dinuclear NHC-Pd complexes was reported.[93] These novel complexes containing either pyrazine or DABCO bridging ligands were made through one pot reactions under mild conditions and fully characterised by NMR, FT-IR and elemental analysis. Testing of these Pd-NHC complexes as catalysts for Hiyama coupling reactions found that the more sterically bulker systems exhibited higher activity, with complex $[PdCl_2(IPr)]_2$(μ-pyrazine) (**54**) being the most effective (Figure 1.32).

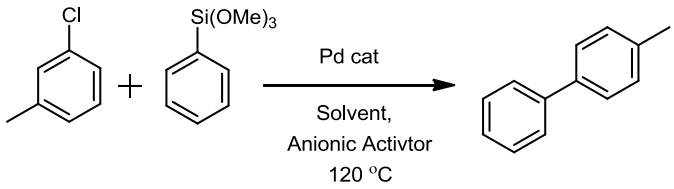


54

Figure 1.32 $[PdCl_2(IPr)]_2$(μ-pyrazine) catalyst

This complex (**54**) was reported to facilitate the coupling of aryl chlorides with aryltrialkyoxysilanes with good to moderate yields. A comparison of the activity of catalyst **54** compared to the very active $(IPr)PdCl_2(Im)$ complex is shown below (Table 1.3).

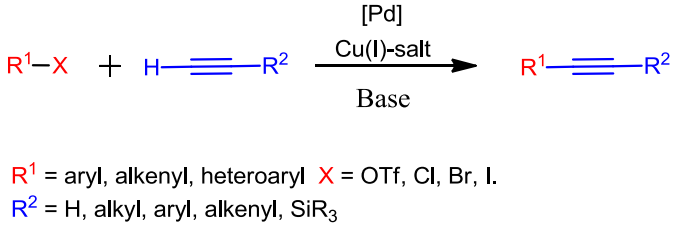
Table 1.3 Comparison of the catalytic activity of complex 54 vs (IPr)$PdCl_2$(Im)



Catalyst number and percentage loading	Solvent	Anionic Activator	Temperature ^0C	Time (h)	Yield (%)
(IPr)$PdCl_2$(Im) (1.0 mol %)	None	TBAF.$3H_2O$	120	3	68
54 (0.50 mol %)	Toluene	TBAF.$3H_2O$	120	5	80

1.6.5 Sonogashira Coupling

The Sonogashira coupling reaction is the most prevalent and effective method for the synthesis of sp2-sp2 carbon-carbon bond synthesis between terminal alkynes and organic halides (Scheme 1.20). Since compounds bearing carbon triple bonds are ubiquitous in pharmaceuticals and fine chemicals, protocols dedicated to their synthesis have been the subject of much scientific scrutiny. Although the classic methodology of using $Pd(PPh_3)_2Cl_2$ with a copper co-catalyst is still the most popular, the last decade has seen much interest in the development of palladium catalyst containing NHC ligands.



Scheme 1.20 General Scheme for Sonogashira coupling.

In 2006 the first Sonogashira coupling of alkynes with unactivated secondary alkyl bromides was reported.[94] This synthesis used bioxazoline derived NHC (IBiox) as ligands in Pd(NHC) dimer complexes, exploiting the ligands electron rich donor nature and steric

bulk to increase the complexes catalytic activity. Testing of the Pd-dimers in the Sonogashira coupling of cycloheptyl bromide and 1-octyne identified complex [IBiox7PdCl$_2$] (**55**) to be the most effective catalyst (Figure 1.33). This catalyst was reported to couple both secondary and primary alkyl bromides, tolerating a variety of functionalities on the alkyl halide component with good yields at 60^{0}C.

Research into another Pd-NHC dimer system, investigating the effect of the σ-donor nature of di-coordinated NHCs compared to mono-coordinated analogue's, led to the synthesis of two new N/O-functionalised NHC palladium complexes.[95] Theses complexes were trans-[(1-benzyl-3-(3,3-dimethyl-2-oxobutyl)$_2$PdBr$_2$] **(56),** and cis-[(1-benzyl-2-oxobutyl)imidazole-2-ylidene)$_2$PdBr$_2$] **(57)** (Figure 1.33). The unusual cis structure of complex **57** was proved by single crystal X-ray diffraction and was believed to result from hydrogen bonding between the amido N-H proton on the functionalised side group of one of the NHC ligands and the amido oxygen of the functionalised side arm of the other NHC ligand.

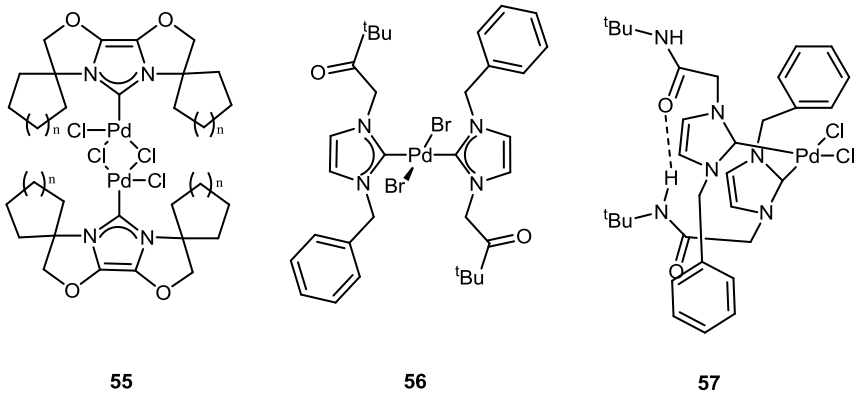


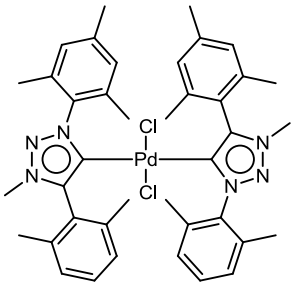
Figure 1.33 NHC-palladium dimers used in Sonogashira cross coupling

These complexes (**57**, **58**) were reported to be effective catalysts for the Sonogashira cross-coupling, coupling a range of aryl iodides with substituted acetylenes in air under amine free conditions. Comparative testing of these complexes against a PEPPSI based mono NHC co-ordinated system (discussed In chapter 2) showed they had higher activity; DFT studies showed this could be a due to the fact that the di-coordinated NHC systems cause a more electron rich metal centre.

Research in 2011 by Fukuzawa and co-workers, hoping to exploit the reported superior donor qualities of 1,2,3-triazol-ylidene when compared to imidazole-2-ylidenes resulted in the synthesis of a catalyst based on abnormal NHC ligands (Figure 1.34).[96] Of the

complexes prepared, $(TMes)_2PdCl_2$ (**58**) was found to be the most effective for Sonogashira cross-coupling reactions, however, its activity was reported to be limited to electron poor aryl halides only.

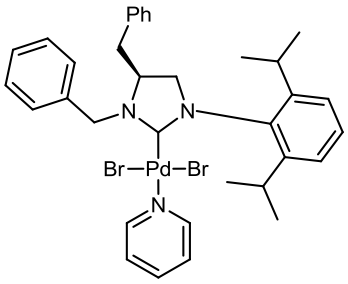
.



58

Figure 1.34 Abnormal NHC-palladium systems used for Sonogashira cross coupling reactions.

Very recently a series of chiral NHC-palladium complexes were prepared from l-phenlalanine and fully characterised by ^{1}H and ^{13}C- NMR spectroscopy and single crystal X-ray diffraction.[97] The catalytic activity of these complexes was tested in the Sonogashira coupling under copper free conditions in air. Analysis identified chiral Pd-NHC complex **59** to be the most efficient, coupling a range of aryl halides to phenylacetylene (Figure 1.35).

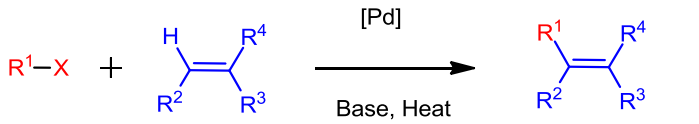


59

Figure 1.35 Example of a chiral NHC-palladium complex used in Sonogashira cross coupling reactions.

1.6.6 Heck-Mizoroki Cross-Coupling

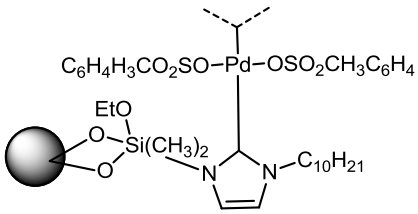
The palladium-catalysed Heck-Mizoroki cross-coupling reaction is a powerful and versatile method for arylation and vinylation of olefins using a hindered amine base, and a Pd(0) catalyst at elevated temperatures (Scheme 1.21). Since its discovery in the 1970s by T. Mizoroki and R. F. Heck it has become one of the most widely used catalytic carbon-carbon bond forming tools in organic chemistry. Although traditionally the Pd complexes contained phosphine based ligands, the observed high thermal stability of NHCs has led to a number of catalysts being reported which include NHCs as ligands instead.



R^1 = aryl, benzyl, alkenyl, alkyl (no β hydrogen) X = OTf, Cl, Br, I, OTs, N_2^+
R^2, R^3, R^4 = alkyl, aryl, alkenyl

Scheme 1.21 General Scheme for Heck reaction.

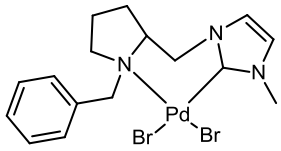
In 2007 Sen and co-worker reported the synthesis of imidazolium based NHC-Pd complexes which have been immobilized on 10 nm silica nanoparticles[98]. It was reported that due to the high surface area and small size, these nano-particles can remain suspended in a number of solutions, with their active site readily accessible to the reactants. Testing the catalytic activity of these immobilized NHC-Pd complexes in Heck reactions found complex **60** to be the most efficient (Figure 1.36). This complex was able to couple n-butyl acrylate to a number of iodo-aryls with excellent yield within two hours, however attempts to extend the protocol to the utilisation of bromo-aryl proved unsuccessful.



60

Figure 1.36 NHC-palladium complex bound to silica nanoparticles.

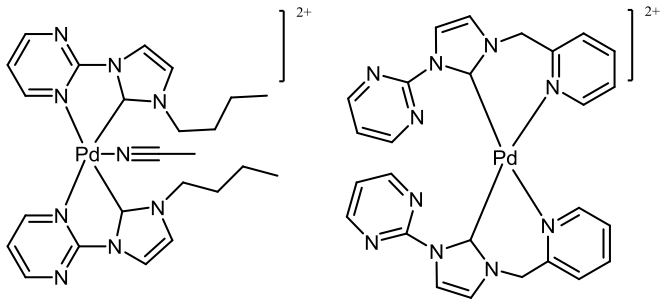
With the aim of developing NHC-Pd complex which are catalytically active for carbon-carbon bond formation in pure water, Shao and co-workers have reported the synthesis of a proline derived NHC-Pd complex **61** (Figure 1.37). This complex was found to be to a good catalyst of Heck reactions of aryl iodides and bromides in pure water.[99] Optimisation of this reaction found the systems activity to be heavily base dependant, KO^{t}Bu was identified as the ideal base for this protocol. Further testing showed that functionality of the aryl halides had some effect on activity of the catalyst, as aryl halides with electron donating groups were reported to have high yields compared to substrates with more electron deficient functionalities.



61

Figure 1.37 Water soluble NHC-palladium complex.

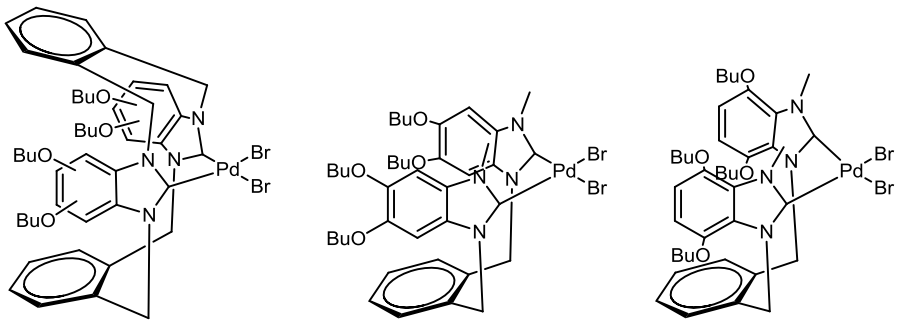
In 2008 Wang and co-workers reported the synthesis of two new palladium complexes containing pyrimidine functionalised NHC ligands: [Pd(1-n-butyl-3-(2-pyrimidly)imidazolylidne)$_2$(CH_3CN)](PF_6) (**62**) and [Pd(1-(2-picolyl)-3-(2-pyrimidyl)imidazolylidene)$_2$](PF_6) (**63**)**.** These complexes were fully characterised by ^{1}H, ^{13}C NMR spectroscopy, elemental analysis and single crystal X-ray diffractometry[100] (Figure 1.38). Testing revealed that both complexes were excellent catalysts for the Heck cross-coupling reactions of aryl bromides and activated aryl chlorides, resulting in the formation of target compounds in high yields with a very low catalyst loading of 0.01%. It is worth noting that complex **62** is unusual as it has a penta-coordinated palladium, where the metal centre is co-ordinated by two imidazolylidne, two pyridine motifs and one acetonitrile molecule forming a square-pyramidal molecular geometry.



62 **63**

Figure 1.38 Novel cationic NHC-palladium complexes.

Research by White and co-workers resulted in the synthesis and testing of catalysts in Heck cross-coupling reactions of a number of bis(benzimidazolin-2-ylidene based NHC-Pd complexes[101]. The NHCs moieties were joined by either one or two *o*-xylyl linkers, and contained butoxy groups. The inclusion of the butoxy groups was to serve a dual purpose, increasing electron density around the metal centre and helping complex solubilisation. The complexes were fully characterised by ^{1}H, ^{13}C- NMR spectroscopy and single crystal X-ray diffraction. The activity of four complexes **64a**, **64b**, **65** and **66** in Heck reactions was explored and compared to the well-known Heck catalyst: $Pd(OAc)_2$ (Figure 1.39). All of the new complexes proved more effective than $Pd(OAc)_2$, coupling iodo and bromo aryls to butyl acrylate with good yields in 24 hours. Of the four tested complexes **64b** and **65** were reported to be the most active in Heck reactions.



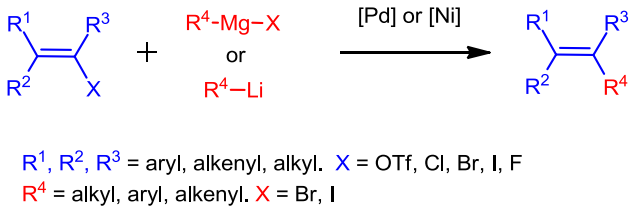
64a 5,6-BuO
64b 4,7-BuO

65 **66**

Figure 1.39 NHC-palladium complexes based on bis(benzimidazolin-2-ylidene)

1.6.7 Kumada-Corriu Cross-Coupling

In 1972 M. Kumada[102] and R.J.P Corriu[103] independently discovered methods for the steroeoselective cross-coupling of aryl/alkenyl halides with Grignard reagents, catalysed by the presence of nickel-phosphine complexes (Scheme 1.22). The scope and limitations of this reaction were further explored by Kumada and as a result this transformation is now known as Kumada cross-coupling. Recently a number of Pd-NHC complexes have been developed which can facilitate this coupling reaction.

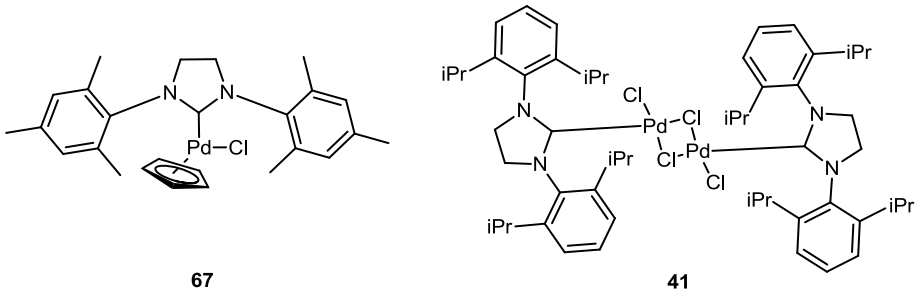


Scheme 1.22 General Scheme for Kumada-Corriu coupling.

Research by Cazin and co-workers investigated the activity of a series of Pd-NHC dimers as catalysts for Kumada coupling reactions[104]. Of the fours complexes tested (NHC= IPr, SIPr, IMes and SIMes) the SIPr based NHC-Pd complex $[Pd(\mu\text{-}Cl)(Cl)(SIPr)]_2$ **41** proved to be the most effective. It was reported to catalyse the coupling of tri, tetra-*ortho*-substituted and hetero atom containing aryl halides to Grignard reagents with good yields under relatively mild reaction conditions (Figure 1.40). It is worth noting that the use of Pd-NHC dimers in the Suzuki-Miyaura coupling of tetra-*ortho* substituted biaryl proved unsuccessful, highlighting the relevance of Kumada coupling reactions as a viable synthetic pathway for the preparation of these highly sort after compounds.

Recently the use of CpPd(NHC)Cl complexes as pre-catalysts for the coupling of aryl and heteroaryl chlorides with PhMgBr was reported.[105] The investigation into the electronic and steric effects of the NHC ligand on the CpPd(NHC)Cl complexes revealed that saturated NHCs with less bulky R substituents were the most effective catalyst in Kumada coupling reactions, opposite to the optimised steric requirements of Pd-NHC systems for Suzuki-Miyaura cross coupling reactions wherein bulkier R groups yielded

higher activity. The Complex CpPd(SIMes)Cl **67** was reported to be the most effective catalyst able to couple an array of aryl and heteroaryl chlorides with PhMgBr at room temperature with low catalyst loadings.



67 41

Figure 1.40 NHC-palladium complexes used in Kumada-Corriu Cross-Coupling reactions.

1.7 References

(1) Singh, M. S. *Reactive intermediates in organic chemistry: structure, mechanism, and reactions*; Wiley-VCH, 2014.

(2) Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, 6463–6466.

(3) Schuster, G. B. *Adv. Phys. Org. Chem* **1986**, *22*, 311.

(4) Stoker, H. *Org. Biomol. Chem* **1976**, *90*, 1475–1485.

(5) Harrison, J. F.; Liedtke, R. C.; Liebman, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 7162–7168.

(6) Baird, N. C.; Taylor, K. F. *J. Am. Chem. Soc.* **1978**, *100*, 1333–1338.

(7) Irikura, K. K.; Goddard, W.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 48–51.

(8) Baceiredo, A.; Bertrand, G.; Sicard, G. *J. Am. Chem. Soc.* **1985**, *107*, 4781–4783.

(9) Bertrand, G.; Reed, R. *Coord. Chem. Rev.* **1994**, *137*, 323–355..

(10) Bourissou, D.; Bertrand, G. *Adv. Organomet. Chem* **1999**, *44*, 175.

(11) Gregory R. Cillette, Antoine Baceiredo, and G. B. *Angew. Chem Int. Ed.*. **1990**, *29*, 1429–1431.

(12) Soleilhavoup, M.; Baceiredo, A.; Treutler, O.; Ahlrichs, R.; Nieger, M.; Bertrand, G. *J. Am. Chem. Soc.* **1992**, *114*, 10959–10961.

(13) Hoffmann, M. R.; Kuhler, K. *J. Chem. Phys.* **1991**, *94*, 8029.

(14) Alder, R. W.; Allen, P. R.; Murray, M.; Orpen. G. *Angew. Chemie Int. Ed.* **1996**, *35*, 1121–1123.

(15) Herrman, A. W.; Ofele, K.; Preysing, V, D.;Herdtweck, E. *Journal of Organometallic Chemistry* **2003**, 684 235–248.

(16) Lee, M.-T.; Hu, C.-H. *Organometallics* **2004**, *23*, 976–983.

(17) Solé, S.; Gornitzka, H.; Schoeller, W.; Bourissou, D.; Bertrand, G. *Science.* **2001**, *292*, 1901–1903.

(18) Merceron, N.; Miqueu, K.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **2002**, *124*, 6806–6807.

(19) Kapp, J.; Schade, C.; El-Nahasa, A. M.; von Ragué Schleyer, P. *Angew. Chem Int. Ed.* **1996**, *35*, 2236–2238.

(20) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.

(21) Bourissou, D.; Guerret, O.; Gabbaie, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.

(22) Park, R. B.; Within, N. G. P.; Technischen, O. I. D. E. R.; Berlin, U. *Angew. Chemie Int. Ed.* **1962**, 75–80.

(23) Wanzlick, H.-W.; Schönherr, H.-J. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 141–142.

(24) Arduengo, A. J.; Kline, M.; Harlow, R. L. *J. Am. Chem. Soc.* **1991**, 21, 363–365.

(25) Arduengo, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.

(26) Gleiter, R.; Hoffmann, R. *Org. Biol. Chem.* **1968**, *90*, 5457–5460.

(27) Boehme, C.; Frenking, G. *J. Am. Chem. Soc.* **1996**, *118*, 2039–2046.

(28) Denk, M. K.; Thadani, A.; Hatano, K.; Lough, A. J. *Angew. Chem. Int. Ed.* **1997**, *36*, 2607–2609.

(29) Bantreil, X.; Nolan, S. P. *Nat. Protoc.* **2011**, *6*, 69–77.

(30) Fürstner, A.; Alcarazo, M.; César, V.; Lehmann, C. W. *Chem. Commun.* **2006**, No. 20, 2176–2178.

(31) Niecke, E.; Fuchs, A.; Nieger, M.; Schmidt, O.; Schoeller, W. W. *Angew. Chem. Int. Ed.* **1999**, *38* (20), 3031–3034.

(32) Cantat, T.; Mézailles, N.; Maigrot, N.; Ricard, L.; Le Floch, P. *Chem. Commun.* **2004**, *2*, 1274–1275.

(33) Martin, D.; Baceiredo, A.; Gornitzka, H.; Schoeller, W. W.; Bertrand, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 1700–1703.

(34) Thaddues, P.; Vrtilek, J. M.; Gottlieb, C. A. *Astrophys. J.* **1985**, *299*, L63–L66.

(35) Kaiser, R. I. *Chem. Rev.* **2002**, *102*, 1309–1358.

(36) Lavallo, V.; Canac, Y.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science.* **2006**, *312*, 722–724.

(37) Green, J. C.; Scurr, R. G.; Arnold, P. L.; Cloke, F. G. N. *Chem. Commun.* **1997**, 20, 1963–1964.

(38) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485–2495.

(39) Tolman, C. *Chem. Rev.* **1977**, *77*, 313–348.

(40) Nelson, D. J.; Nolan, S. P. *Chem. Soc. Rev.* **2013**, *42*, 6723–6753.

(41) Scott, N.; Dorta, R.; Stevens, E.; Correa, A.; Cavallo, L.; Nolan, S. *J. Am. Chem. Soc.* **2005**, *127*, 3516–3526.

(42) Hu, X.; Castro-Rodriguez, I.; Olsen, K.; Meyer, K. *Organometallics* **2004**, *23*, 755–764.

(43) Martin, D.; Lassauque, N.; Donnadieu, B.; Bertrand, G. *Angew. Chemie - Int. Ed.* **2012**, *51*, 6172–6175.

(44) Gründemann, S.; Kovacevic, a; Albrecht, M.; Faller, J. W.; Crabtree, R. H. *Chem. Commun.*. **2001**, *4*, 2274–2275.

(45) Albrecht, M. *Chem. Commun.*. **2008**, 31, 3601–3610.

(46) Isomers, C. H.; Kaiser, R. I.; Ochsenfeld, C.; Lee, Y. T.; Suits, G. **2007**, *274*, 1508–1511.

(47) Bacciu, D.; Cavell, K. J.; Fallis, I.; Ooi, L. L. *Angew. Chemie - Int. Ed.* **2005**, *44* (33), 5282–5284.

(48) Kluser, E.; Neels, A.; Albrecht, M. *Chem. Commun.* **2006**, No. 43, 4495–4497.

(49) Ung, G.; Bertrand, G. *Chem. A. Eur. J.* **2011**, *17* (30), 8269–8272.

(50) Kelly, R. A.; Clavier, H.; Giudice, S.; Scott, N. M.; Stevens, E. D.; Bordner, J.; Samardjiev, I.; Hoff, C. D.; Cavallo, L.; Nolan, S. P. *Organometallics* **2008**, *27*, 202–210.

(51) Leuthauber, S.; Schwarz, D.; Plenio, H. *Chem. A. Eur. J.* **2007**, *13*, 7195–7203.

(52) Credendino, R.; Falivene, L.; Cavallo, L. *J. Am. Chem. Soc.* **2012**, *134*, 8127–8135.

(53) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674–2678.

(54) Clavier, H.; Nolan, S. P. *Chem. Commun.*. **2010**, *46*, 841–861.

(55) Hillier, A. C.; Sommer, W. J.; Yong, B. S.; Petersen, J. L.; Cavallo, L.; Nolan, S. P. *Organometallics* **2003**, *22*, 4322–4326.

(56) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840–1846.

(57) Costabile, C.; Cavallo, L. *J. Am. Chem. Soc.* **2004**, *126*, 9592–9600.

(58) Ragone, F.; Poater, A.; Cavano, L. *J. Am. Chem. Soc.* **2010**, *132*, 4249–4258.

(59) Mathew, J.; Koga, N.; Suresh, C. H. *Organometallics* **2008**, *27*, 4666–4670.

(60) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.

(61) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

(62) Frey, G. D.; Schu, J.; Herdtweck, E.; Herrmann, W. A.; Chem, C. J. O. *Organometallics* **2005**, *24*, 4416–4426.

(63) Navarro, O.; Marion, N.; Scott, N. M.; González, J.; Amoroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron* **2005**, *61*, 9716–9722.

(64) Frisch, A.; Jackstell, R.; Go, M.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Rˆttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 986–989.

(65) Jensen, D. R.; Schultz, M. J.; Mueller, J. a; Sigman, M. S. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 3810–3813.

(66) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.

(67) Wu, L.; Drinkel, E.; Gaggia, F.; Capolicchio, S.; Linden, A.; Falivene, L.; Cavallo, L.; Dorta, R. *Chem. Eur. J.* **2011**, *17*, 12886–12890.

(68) Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. *Chem. Eur. J.* **2012**, *18*, 4517–4521.

(69) Zhang, T.; Wang, W.; Gu, X.; Shi, M. *Organometallics* **2008**, 27, 753–757.

(70) Diebolt, O.; Braunstein, P.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.*. **2008**,. 27, 3190–3192.

(71) Zhang, Xiaoming Xia, Qinqin Chen, W. *Dalton Trans.* **2009**,35, 7045–7054.

(72) Chang, Y.-H.; Liu, Z.-Y.; Liu, Y.-H.; Peng, S.-M.; Chen, J.-T.; Liu, S.-T. *Dalton Trans.* **2011**, *40*, 489–494.

(73) Schuster, O.; Yang, L.; Raubenheimer, H. G.; Albrecht, M. *Chem. Rev.* **2009**, *109*, 3445–3478.

(74) Xu, X.; Xu, B.; Li, Y.; Hong, S. H. *Organometallics* **2010**, 29 6343–6349.

(75) Sau, S. C.; Santra, S.; Sen, T. K.; Mandal, S. K.; Koley, D. *Chem. Commun.*. **2010**, *48*, 555–557.

(76) Diebolt, O.; Cavallo, L.; Nolan, S. P.; Slawin, A. M. Z.; Cazin, C. S. J. **2010**, No. 10, 1443–1450.

(77) Lee, D.-H.; Kim, J.-H.; Jun, B.-H.; Kang, H.; Park, J.; Lee, Y.-S. *Org. Lett.* **2008**, *10* (8), 1609–1612.

(78) Li, G.; Yang, H.; Li, W.; Zhang, G. *Green Chem.* **2011**, *13*, 2939.

(79) Negishi, B. S. *J. Am. Chem. Soc.* **1976**, *98* , 6729–6731.

(80) Scarborough, C. C.; Bergant, A.; Sazama, G. T.; Guzei, I. a; Spencer, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084–5092.

(81) Guram, A. S.; Rennels, R. a.; Buchwald, S. L. *Angew. Chemie Int. Ed. English* **1995**, *34*, 1348–1350.

(82) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36* , 3609–3612.

(83) *Metal-Catalysed Cross-Coupling Reactions*; edited by Meijere, A. De; Diederich, F.2004; Vol. 1. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

(84) Luan, X.; Mariz, R.; Robert, C.; Gatti, M.; Blumentritt, S.; Linden, A.; Dorta, R. *Org. Lett.* **2008**, *10* , 5569–5572.

(85) Winkelmann, O. H.; Riekstins, A.; Nolan, S. P.; Navarro, O. *Organometallics* **2009**, *28*, 5809–5813.

(86) Anthony Chartoire, Xavier Frogneux, S. P. N. *Adv Synth Catal* **2012**, *354*, 1897.

(87) Jin, Z.; Guo, S.-X.; Gu, X.-P.; Qiu, L.-L.; Song, H.-B.; Fang, J.-X. *Adv. Synth. Catal.* **2009**, *351*, 1575–1585.

(88) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983–2990.

(89) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.

(90) Egbert, J. D.; Chartoire, A.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2011**, *30*, 4494–4496.

(91) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.

(92) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58–61.

(93) Yang, J.; Wang, L. *Dalton Trans.* **2012**, *41*, 12031–12037.

(94) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925–2928.

(95) Ray, L.; Barman, S.; Shaikh, M. M.; Ghosh, P. *Chemistry* **2008**, *14*, 6646–6655.

(96) Inomata, S.; Hiroki, H.; Terashima, T.; Ogata, K.; Fukuzawa, S. *Tetrahedron* **2011**, *67*, 7263–7267.

(97) Yang, L.; Guan, P.; He, P.; Chen, Q.; Cao, C.; Peng, Y.; Shi, Z.; Pang, G.; Shi, Y. *Dalton Trans.* **2012**, *41*, 5020–5025.

(98) Tandukar, S.; Sen, A. *J. Mol. Catal. A Chem.* **2007**, *268*, 112–119.

(99) Tang, Y.-Q.; Chu, C.-Y.; Zhu, L.; Qian, B.; Shao, L.-X. *Tetrahedron* **2011**, *67*, 9479–9483.

(100) Ye, J.; Chen, W.; Wang, D. *Dalton Trans.* **2008**, 30, 4015–4022.

(101) White, A. H.; Skelton, B. W.; Simpson, P. V.; Brown, D. H.; Baker, M. V. *Dalton Trans.* **2009**, 35, 7294–7307.

(102) Kumada, M.; Sumitani, K.; Tamao, K. *J. Am. Chem. Soc.* **1971**, *94*, 4374–4376.

(103) Corriu, J. P.; Masse, J. P. *J.C.S. Chem. Comm.*, **1972**, *144*, 7062.

(104) Hartmann, C. E.; Nolan, S. P.; Cazin, C. S. J. *Organometallics*. **2009**, *2*, 2915–2919.

(105) Jin, Z.; Gu, X.-P.; Qiu, L.-L.; Wu, G.-P.; Song, H.-B.; Fang, J.-X. *J. Organomet. Chem.* **2011**, *696*, 859–863.

2 N-Donors as Throw-away Ligands

2.1 Background

In order to avoid the rigorous anhydrous conditions required to handle free NHCs, prior to co-ordination to a Pd centre, a number of the earliest NHC-Pd catalysts used in cross coupling reactions were synthesised *in situ*. These protocols involved adding imidazolium salts with common palladium sources along with the coupling partners to the reaction mixture.[1] Optimisation of these systems were hampered by ambiguity over the stoichiometry, the composition of the active species and the rate and efficiency of forming these complexes in solution. To counter this problem, research groups like Nolan *et al.* developed well defined NHC-Pd(II) complexes which could behave as air stable pre-catalysts (Figure 2.1).[2]

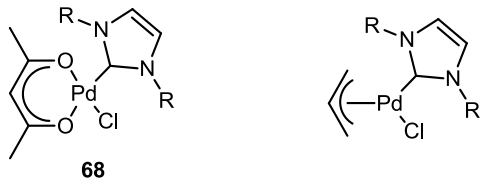
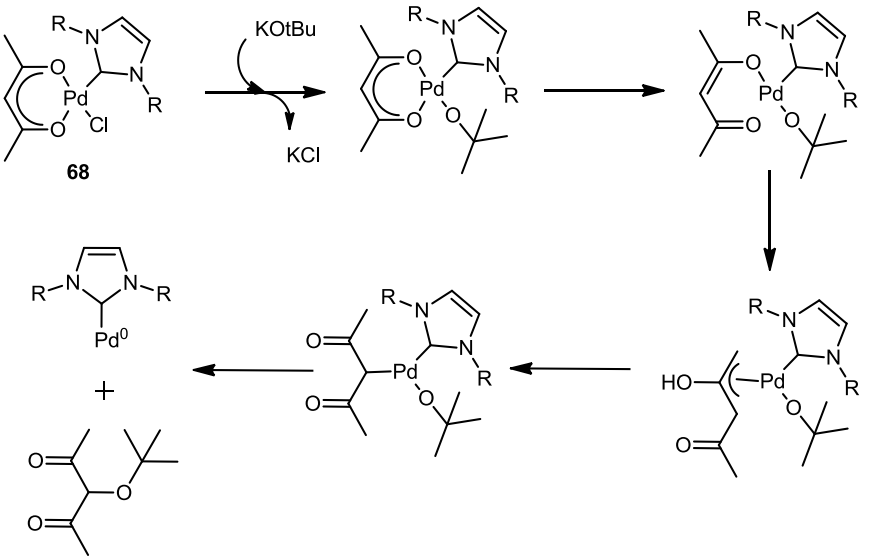


Figure 2.1 Examples of well-defined NHC-Pd(II) precatalysts.

This type of complex, such as (NHC)Pd(acac)Cl (**68**) could be reduced to form catalytically active NHC-Pd(0) species during the cross coupling reactions (Scheme 2.1**Error! Reference source not found.**).[3] The ease and speed that these precatalysts form the active Pd(0) species is an important factor in their catalytic activity.

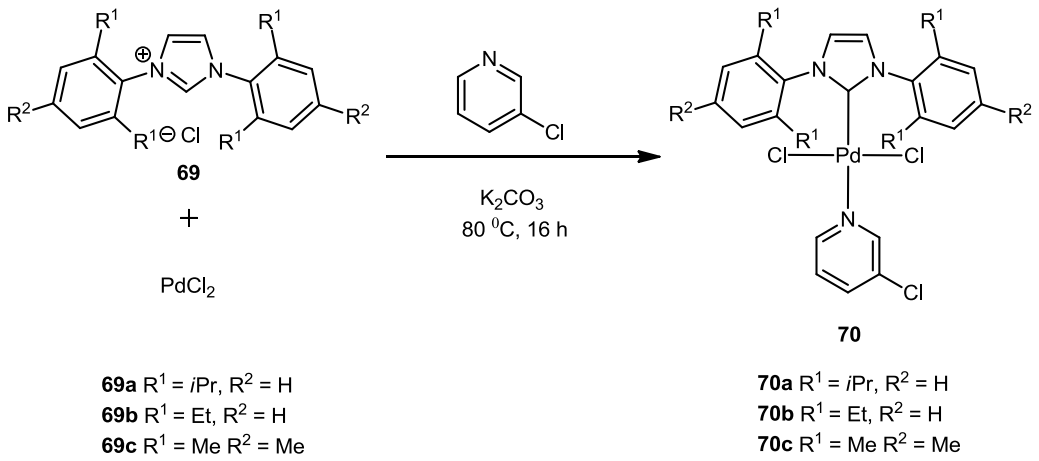


Scheme 2.1 Proposed mechanism for the activation of precatalyst (NHC)Pd(acac)Cl.

As result of this fact the development of NHC-Pd catalysts which contain labile ligands, known as "*throw-away ligands"* have been the focus of much research. One of the earliest and most prevalent examples of this class of complex are (NHC)$PdCl_2$(PEPPSI) systems (PEPPSI =pyridine-enhanced precatalysts, preparation, stabilisation, and initiation).

2.1.1 (NHC)$PdCl_2$(py) complexes

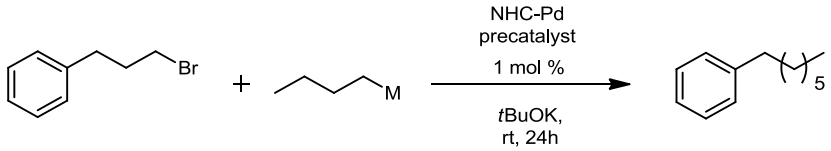
In 2006 Organ *et al.* reported the synthesis of a number of NHC-Pd complexes bearing one NHC ligand, two anionic ligands and 3-chloropyridine as the fourth throw-away ligand.[4] These compounds were analogous to complexes reported by Grubbs *et al.* in 2002 for ruthenium catalysed cross metathesis.[5] Organ's complexes were prepared by heating imidazolium salts with $PdCl_2$ and K_2CO_3 in neat 3-chloropyridine (Scheme 2.2) in air and resulted in formation of the target complexes in excellent yields.



Scheme 2.2 Synthesis of (NHC)$PdCl_2$(PEPPSI) complexes in air.

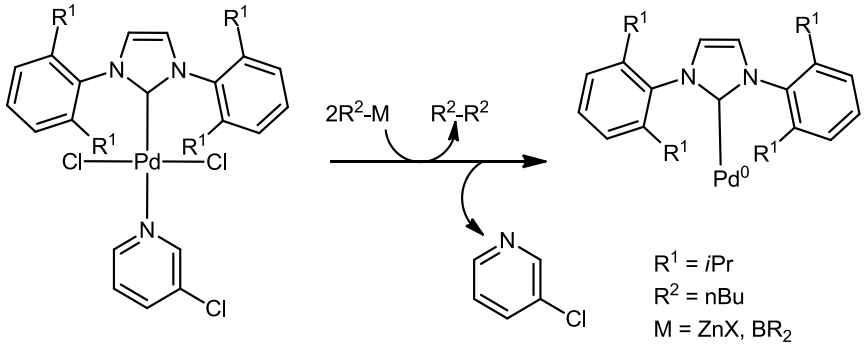
These complexes were tested as catalysts for alkyl-alkyl Negishi and Suzuki cross couplings (Table 2.1) and found that the most sterically bulky (IPr)$PdCl_2$(3-chloropyridine) complex was the most effective.

Table 2.1 Comparison of the catalytic activity of (NHC)$PdCl_2$(PEPPSI) complexes in alkyl-alkyl cross coupling reactions



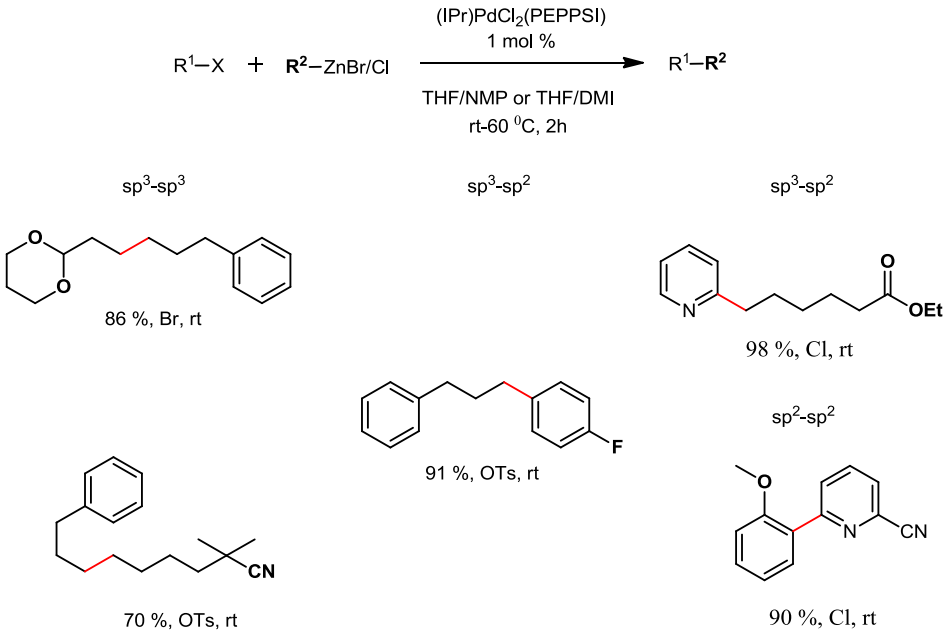
Entry	Organometallic reagent **M =**	GC yield of product (**70a** precatalyst)	GC yield of product using (**70b** precatalyst)	GC yield of product using (**70c** precatalyst)
1	ZnBr (1.3 equiv)	100	34	8.0
2	BBu_2 (1.2 equiv)	100	31	6.5

The activation of the Pd(II) precatalysts into the active Pd(0) species was proposed to operate through reduction by the organometallic reagent, followed by dissociation of the pyridine (Scheme 2.3). This hypothesis was supported the observation of *n*-tetradecane and 3-chloropyridine by GC/MS, in the reaction of (IPr)$PdCl_2$(3-chloropyridine) with two equivalents of *n*-heptyzinic bromide. The authors stated that the pyridine ligand in these complexes played an integral role in the synthesis and stabilisation of the Pd(II) precatalysts and aided catalyst activation by readily dissociating after its reduction to the active NHC-Pd^0 species. The importance of this step led to the adoption of the moniker PEPPSI (pyridine-enhanced precatalysts, preparation, stabilisation, and initiation) to describe this particular structural motif.



Scheme 2.3 Proposed mechanism of activation of (NHC)$PdCl_2$(PEPPSI) precatalysts.

A full exploration of (IPr)$PdCl_2$(PEPPSI) **70a** as a catalyst for Negishi coupling was carried out in 2006.[6] It was reported that under optimised conditions this complex was able to facilitate the coupling of all combinations of alkyl and aryl partners (Scheme 2.4). This system was also significant as it was the first NHC-Pd methodology which surpassed analogous phosphine-ligated Negishi protocols in both scope and activity.



Scheme 2.4 Examples of Negishi coupling products catalysed by (IPr)$PdCl_2$(PEPPSI) complex.

In 2008 complex **70** was found to catalyse the Suzuki-Miyaura coupling of sp^3-sp^3 and sp^3-sp^2 partners,[7] reacting unactivated alkyl bromides and aryl bromides/chlorides with alkyl-9-BBN at room temperature using a mild base (K_3PO_4) in good yields. Although the research mentioned above highlighted the catalytic efficiency of (NHC)$PdCl_2$(PEPPSI) complexes, a detailed study into the effect of the throw-away ligand moiety on catalytic activity was not undertaken until 2010.[8] In this study a number of NHC-Pd complexes bearing different pyridine congeners were synthesised (Figure 2.2), then subjected to structure-activity relationship (SAR) analysis. It was reported that variation of the throw-away ligand does have an effect on catalytic activity. For example complex **71** showed lower catalytic activity in simple sp^2-sp^2 Kumada Corriu cross coupling compared to complex **70** (Scheme 2.5A). This was rationalised to be a result of slower activation of the palladium pre-catalyst, derived from the stronger σ donating nature and steric bulk of lutidine compared to 3-chloropyridine ligand. Conversely, when exploring reactions between more challenging coupling partners (Scheme 2.5B) the catalysts with the more strongly bound throw-away ligands showed better activity, with complex **72** performing the best. It was suggested that this reversal in activity was due to the fact that the conversion of more challenging coupling partners required longer reaction times and therefore catalysts with lifetimes extended either by a slower release of the active Pd^0 complex or re-coordination of the throw away ligand to the active species would be more effective.

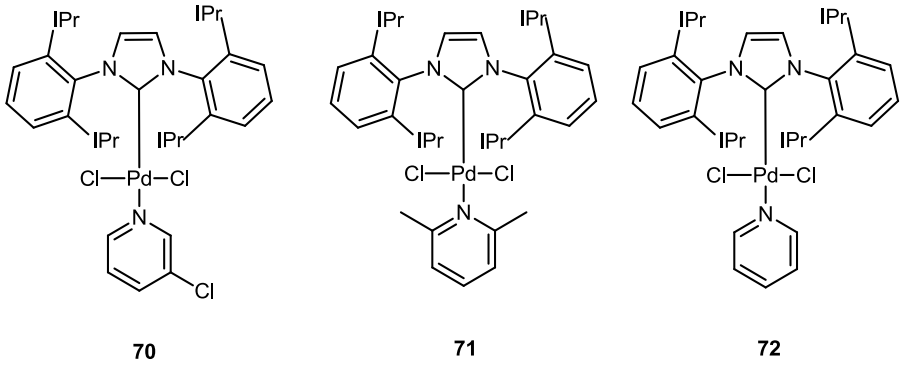
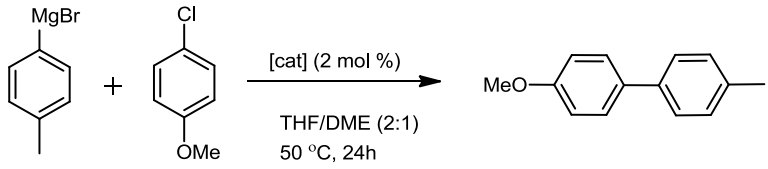
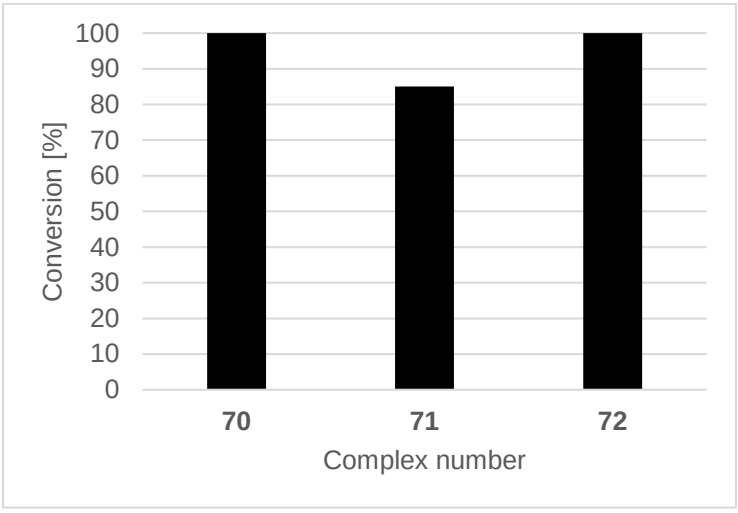


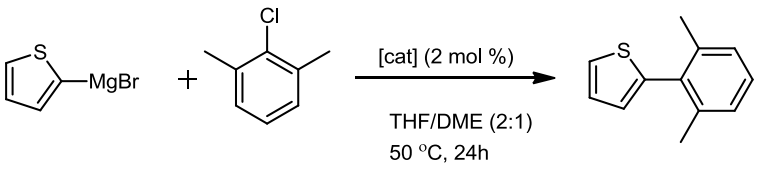
Figure 2.2 (IPr)$PdCl_2$(PEPPSI) complexes analysed in SAR study.

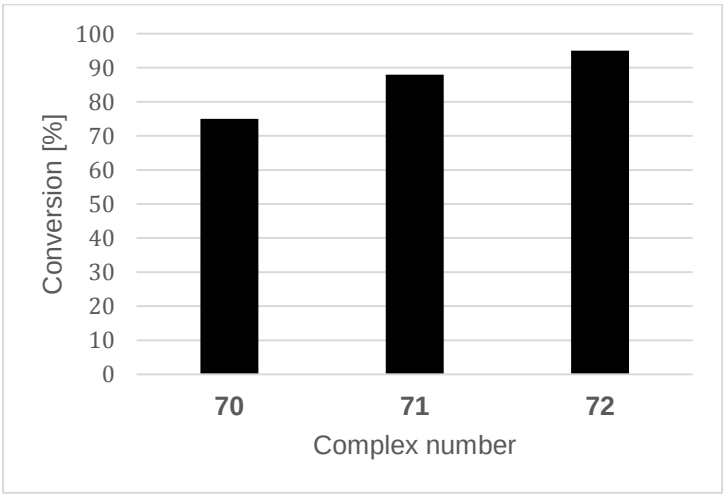
A]





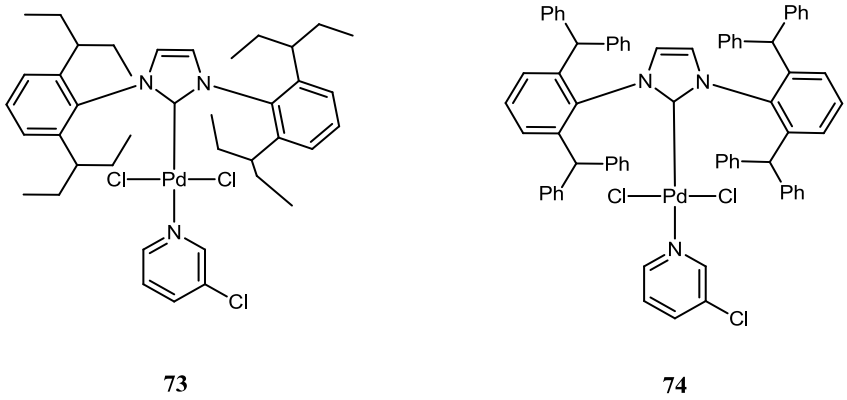
B]





Scheme 2.5 Effect of throw-away ligand on PEPPSI complexes in Kumada Corriu cross coupling.

Influenced by the "flexible steric bulk" concept first proposed by Glorius *et al*.[9] a number of research groups have focused on the inclusion of bulkier NHC ligands when designing new catalysts. This trend has been observed in the case of PEPPSI based NHC-Pd complexes, with the preparation of numerous pre-catalysts containing sterically demanding ligands, the most notable being IPent and IPr* (Figure 2.3). Complex **73**, first reported in 2009, was found to catalyse the coupling of challenging tetra-ortho-substituted biaryls.[10] This system facilitated these couplings at a lower temperature and with a greater scope of partners than the first reported NHC based procedure described by Gloruis *et al*. using IBox12 complex.[11]

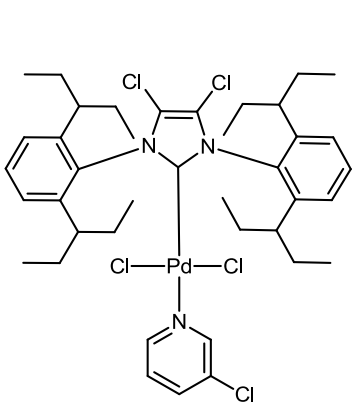


73 **74**

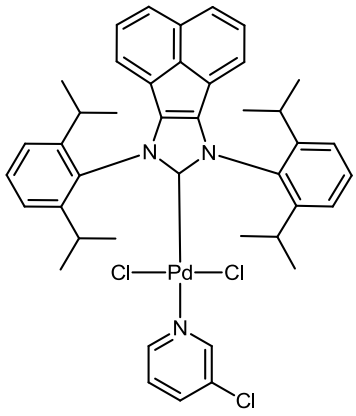
Figure 2.3 (NHC)$PdCl_2$(PEPPSI) complexes with flexible steric bulk.

In 2011 (IPent)$PdCl_2$(PEPPSI) complex (**73**) was reported to be a very effective catalyst in the Negishi cross coupling of secondary alklyzinic halides with aryl and hetero-aryl halides.[12] This complex enabled the coupling of sp^3-hybridised organometallics, suppressing the formation of the isomerised by-product which is formed via the competing β-hydride elimination/migratory insertion pathway. It was hypothesised that this selectivity was a more exaggerated form of the process described previously for the (IPr)$PdCl_2$(PEPPSI) complex[13]. In the case of (IPent)$PdCl_2$(PEPPSI) the high selectivity was reported to be derived from weak, fleeting through space (IPent)H-Pd interactions that guide the organometallic reactant to and from the metal centre, making the spatial orientation required for β-hydride elimination unfavourable. These through space (IPent)H-Pd interactions were believed to be integral to the reported high activity of complex **73** in the Buchwald-Hatwig amination of electronically deactivated and sterically hindered aryl chlorides to a wide array of secondary amines.[14] It was stated that

interactions between the hydrogens on the N-substituents of the NHC and the metal centre lead to an increase in positive charge on the metal and that this facilitates the rate determining deprotonation step in the cycle, improving catalytic activity. An analogous complex to (IPent)$PdCl_2$(PEPPSI) was developed in 2012 by Nolan *et al*.[15] This complex **74**, which contained the IPr^* NHC ligand, was proved to be highly active in Buchwald-Hartwig amination reactions, showing similar reactivity at room temperature to the IPent complex **73**, but much improved activity at high temperature and low catalyst loading. With the intention of further enhancing the catalytic activity of (NHC)$PdCl_2$(PEPPSI) complexes in Negishi coupling, Organ *et al*. prepared a series of complexes with a variety of substitution patterns on the NHC backbone.[10] From this series ($IPent^{Cl}$)$PdCl_2$(PEPPSI) **75** (Figure 2.4) performed the best, showing high reactivity, broad functional group tolerance and excellent selectivity for the desired non-rearranged product. The authors suggested that the higher selectivity imparted by NHC backbone substitution was steric in origin, as TEP analysis failed to yield consistent correlation between electronic ligand effects and selectivity. Later in 2012 the preparation of acenaphthoimidazolylidene palladium complex **76** was reported.[16] This complex was found to be an efficient catalyst for the Suzuki-Miyaura cross-coupling of sterically hindered partners, allowing successful coupling in excellent yields with low catalyst loading under mild reaction conditions.



75

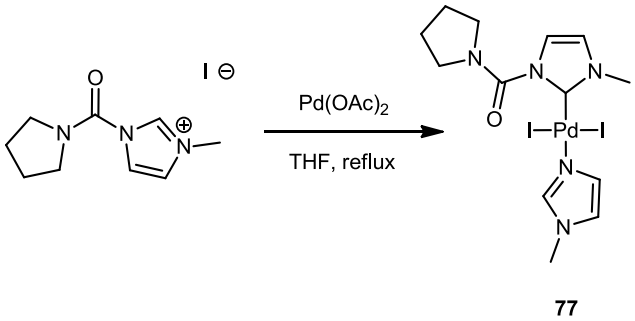


76

Figure 2.4 Sterically bulky (NHC)$PdCl_2$(PEPPSI) with modified back bones.

2.1.2 (NHC)$PdCl_2$(Im) complexes

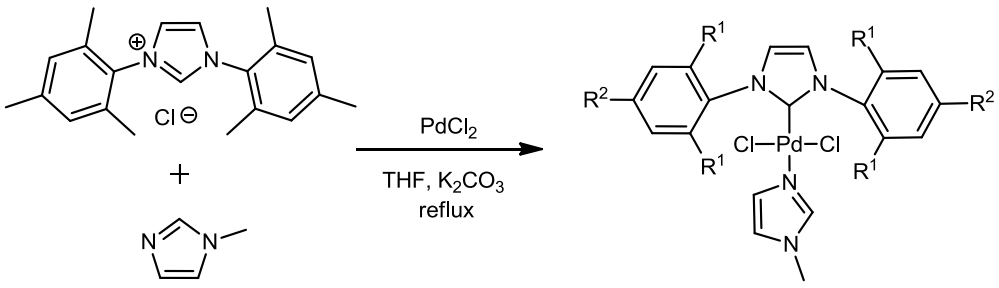
A highly effective protocol for Sonogashira coupling reactions was reported in 2002.[17] The pre-catalyst was an N-carbamoyl-substituted heterocyclic carbene Pd complex **77**, which contained N-methylimidazole as a throw-away ligand. This complex **77**, prepared via the reaction of two equivalents of carbamoyl imidazolium salt with $Pd(OAc)_2$ (Scheme 2.6), was found to couple aryl iodides with a variety of alkyne partners at room temperature with excellent yields. Modification of the protocol; increasing the temperature to 80 °C and changing the base to Cs_2CO_3 allowed the coupling of more challenging aryl bromides.



77

Scheme 2.6 First synthesis of an (NHC)$PdCl_2$(Im) complex

In further studies Shao *et al*. prepared the IMes and IPr derivatives of the (NHC)$PdCl_2$(Im) complex, using the same protocol as that in the preparation of the PEPPSI systems (Scheme 2.7).[18]



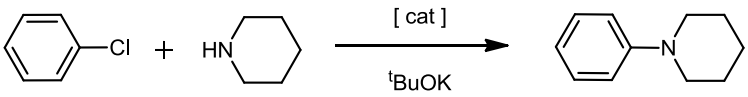
78 = R^1 = ^{i}Pr R^2 = H
79 = R^1 = CH_3 R^2 = CH_3

Scheme 2.7 Synthesis of IMes and IPr (NHC)$PdCl_2$(Im) complexes**.**

Single crystal X-ray analysis of **78** revealed that compared to the PEPPSI derivative the N-methylimidazole complex has a shorter Pd-N bond, due to its stronger σ-donor properties. This factor could perturb the complexes catalytic activity. Indeed a

comparison of complexes **72** and **78** performance in the Buchwald-Hatwig reaction of chlorobenzene with piperidine showed the methylimidazole based complex required a higher temperature to operate (Table 2.2).[18,19] Research by Lu *et al.* in 2012 reported the use of (IPr)$PdCl_2$(Im) **78** in Hiyama coupling.[20] In this study aryl chlorides were coupled with arylsiloxanes in good yields using 1 mol% of the palladium precatalyst at 120 °C in toluene.

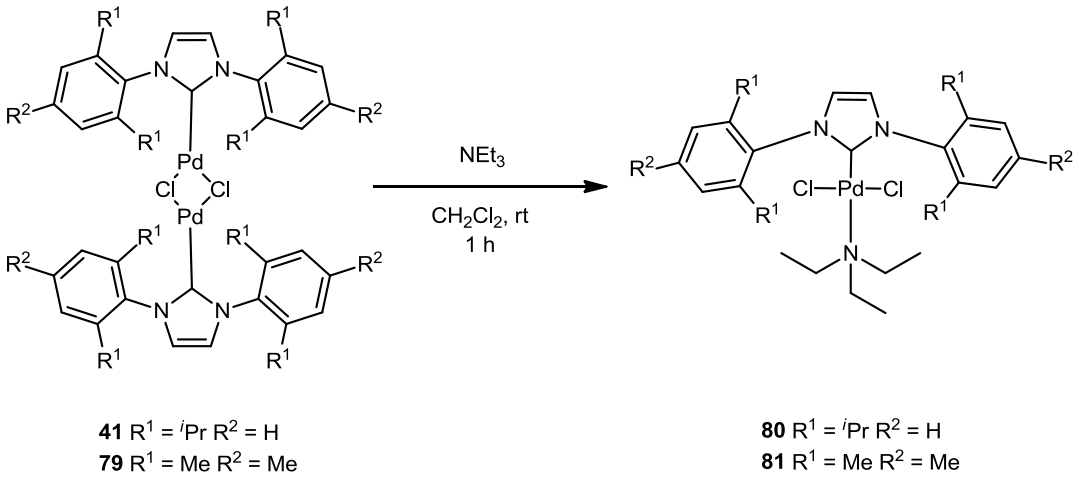
Table 2.2 Catalytic activity of complexes 72 and 78 in Buchwald-Hartwig amination.



Catalyst	Mol %	Solvent	Reaction Time/ (h)	Temperature / (°C)	% Yield
(IPr)$PdCl_2$(py) **72**	2	DME	24	30	83
(IPr)$PdCl_2$(Im) **78**	1	Dioxane	3	90	89

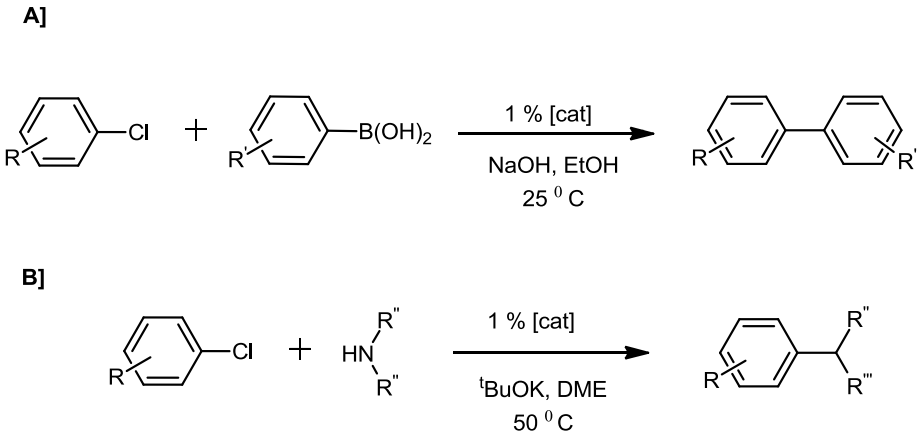
2.1.3 (NHC)$PdCl_2$(TEA) complexes

Research by Navarro *et al.* in 2011 reported the preparation of novel complexes containing triethylamine (TEA) as a throw away ligand.[21] These complexes were prepared by the reaction of the corresponding $[(NHC)PdCl_2]_2$ dimer with an excess of triethylamine in dichloromethane (DCM) at room temperature (Scheme 2.8). The TEA throw away ligand was selected due to both its σ-donor capabilities and low steric demand.



Scheme 2.8 Synthesis of (NHC)$PdCl_2$(TEA) complexes.

The (IPr)$PdCl_2$(TEA) complex **80** was shown to be an effective precatalyst in both Suzuki-Miyaura cross-coupling and Buchwald-Hartwig aminations (Scheme 2.9), showing higher activity at lower temperatures then the PEPPSI based analogue. Single crystal X-ray diffraction analysis of the (IPr)$PdCl_2$(TEA) **80** complex revealed a Pd-N bond distance significantly longer than the (IPr)$PdCl_2$(PEPPSI) **70** complex. This difference was attributed to the π-acceptor character of 3-chloropyridine ligand. The authors suggested that the higher activity of the TEA complex at lower temperatures was a result of either or a combination of both: the longer Pd-N bond aiding formation of the Pd^0 catalyst and the stronger σ-donor characteristics of the TEA ligand that facilitate re-coordination, increasing the active catalyst life time.



Scheme 2.9 A] Reaction conditions used for Suzuki-Miyaura cross coupling catalysed by (IPr)$PdCl_2$(TEA). B] Reaction conditions used for Buchwald-Hartwig aminations catalysed by (SIPr)$PdCl_2$(TEA).

2.2 Results and Discussion

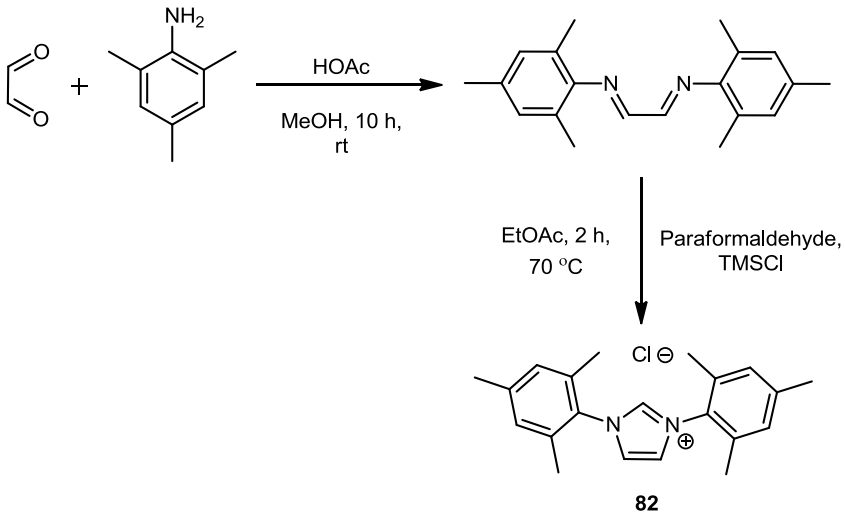
Due to the success of the NHC palladium precatalysts containing N-donors, the aim of this investigation was to synthesise a series of novel NHC palladium complexes containing a nitrogen co-ordinated throw-away ligand, and test the most promising complexes as a precatalysts for cross-coupling reactions.

2.2.1 Synthesis of novel (NHC) palladium complexes with N-donors as throw away ligands.

2.2.1.1 (IMes)$PdCl_2$(2-phenylpyridine)

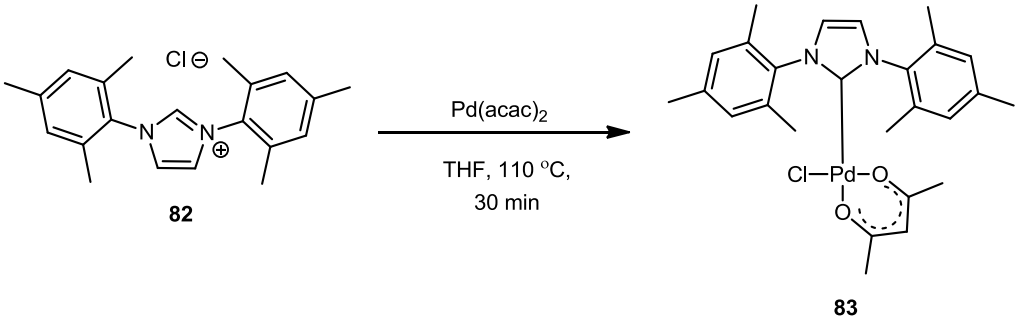
Inspired by the success of the (NHC)$PdCl_2$(PEPPSI) complexes reported above, we decided to investigate the synthesis of novel complexes containing a pyridine based throw away ligand. We selected 2-phenylpyridine as an alternative to the 3-chloropyridine of the PEPPSI based systems, believing that the increased steric bulk could facilitate easier de-coordination of the throw away ligand, improving catalytic performance.

The IMes.HCl salt **82** was prepared using the protocol described in 2007 by Hintermann (Scheme 2.10).[22] It begins with the reaction between glyoxal with 2,6-dimethylaniline catalysed by acetic acid, resulting in the formation of 1,4-diaryl-1,4-diazadiene (DAD). This DAD was then reacted with paraformaldehyde and chlorotrimethylsilane (TMSCl) yielding the target IMes.HCl salt in a good yield (67 %).



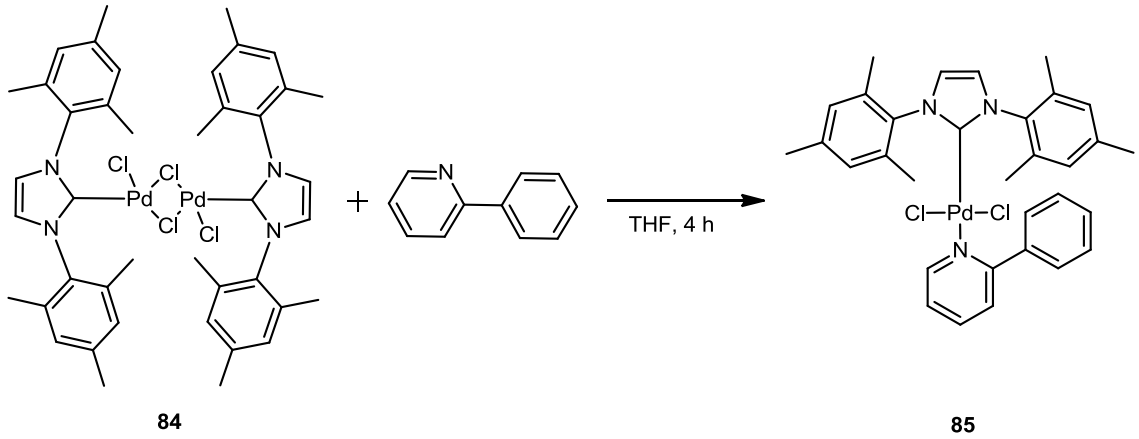
Scheme 2.10 Synthesis of IMes HCl.

The IMes salt was then reacted with palladium acetylacetonate in a process reported by Navarro *et al.*[23] by heating to 110 °C with microwave irradiation for 30 min, resulting in the formation of the (IMes)Pd(acac)Cl complex **83** (Scheme 2.11). The $[(IMes)PdCl_2]_2$ dimer **84** was prepared by stirring the (IMes)Pd(acac)Cl complex with an excess of HCl in dioxane for 6 h at room temperature.



Scheme 2.11 Synthesis of (IMes)Pd(acac)Cl via microwave irradiation.

Stirring the $[(IMes)PdCl_2]_2$ dimer **84** with 2-phenylpyridine for 4 h at room temperature in tetrahydrofuran (THF) resulted in the solution changing colour from orange to yellow. Removal of the solvent in vacuo, yielded a yellow solid which was found to be the desired $(IMes)PdCl_2$(2-phenylpyridine) complex **85** (Scheme 2.12). This new complex was fully characterised by means of elemental analysis, ^{1}H and ^{13}C NMR spectroscopy. The solid state structure was unambiguously determined by X-ray single crystal diffraction (Figure 2.5).



84 85

Scheme 2.12 Reaction between $[(IMes)PdCl_2]_2$ and 2-phenylpyridine.

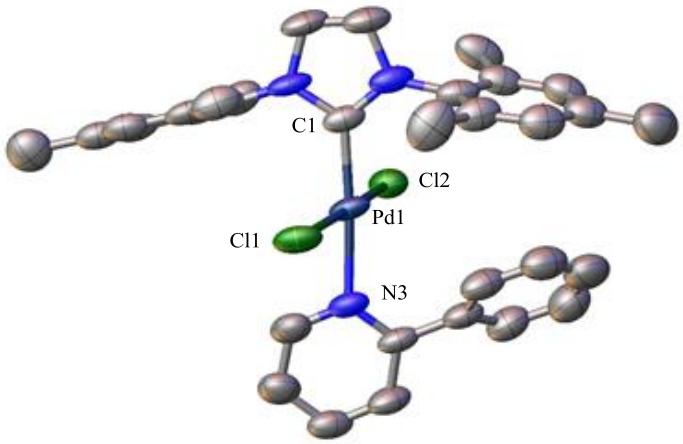
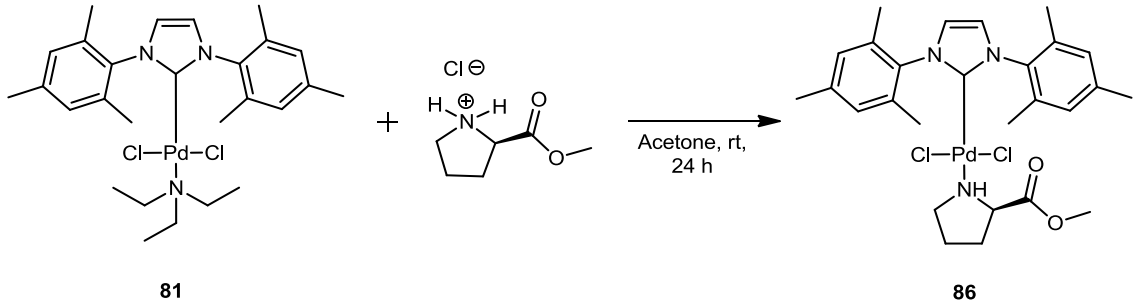


Figure 2.5 X-ray structure of $(IMes)PdCl_2$(2-phenylpyridine). Thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1-C1: 1.972(5), Pd-Cl1: 2.337(11), Pd-Cl2: 2.291(13), Pd-N3: 2.124(4), C1-Pd1-Cl1: 92.3(3), C1-Pd1-Cl2: 91.20(16), N3-Pd1-Cl2: 89.32(13), N3-Pd1-Cl1: 92.3(3).

The complex was found to have a distorted square planar geometry with the 2-phenylpyridine *trans* to the IMes ligand. Unfortunately the Pd-N bond length was found to be very similar to the PEPPSI derived system; therefore increasing the steric bulk of the throw-away ligand is unlikely to affect the ease of activation of the palladium precatalyst and thus improve the complexes performance in cross coupling reactions. However since the bulky phenyl group does occupy the co-ordination sphere of the metal centre, it could be beneficial in palladium (II)-palladium (IV) systems such as acetoxlaytion reactions. This hypothesis has been tested and results reported in a later chapter (Chapter 4).

2.2.1.2 (IMes)$PdCl_2$(S-methyl-pyrrolidine-2-carboxylate)

Aiming to explore alternative N donor ligands in NHC palladium precatalysts, we identified l-proline methyl ester hydrochloride as a potential candidate. The compound was chosen due to its availability, cheap price, interesting chiral properties and weaker σ-donor ability compared to TEA. An initial attempt to synthesis the target compound by reacting the $[(IMesPdCl_2]_2$ dimer with l-proline methyl ester hydrochloride proved unsuccessful. However, running the reaction under the same conditions but replacing the dimer with (IMes)$PdCl_2$(TEA) complex generated (IMes)$PdCl_2$(S-methyl-pyrrolidine-2-carboxylatye) in quantitative yields (Scheme 2.13). This complex was fully characterised by means of elemental analysis, ^{1}H and ^{13}C NMR spectroscopy. The solid state structure was unambiguously determined by X-ray single crystal diffraction (Figure 2.6). The complex was found to have a distorted square planar geometry with the l-proline methyl ester *trans* to the IMes ligand. The Pd-N distance was found to be shorter than the TEA counterpart; this could be explained by an enhancement of the σ-donor character of the nitrogen facilitated by intramolecular hydrogen bonding between the pyrrolidine and one of the chlorines attached to the palladium. This hypothesis is plausible as the H-Cl distance (2.58 Å) is shorter than the sum of the van der Waals radii of H and Cl atoms, 2.95 Å. A similar effect was observed with the (NHC)$PdCl_2$(DEA) complexes (DEA = diethylamine) reported by Navarro *et al.* in 2011. [24] They found that the complexes bearing the DEA functionality had a shorter Pd-N bond then their TEA analogues, resulting from intramolecular hydrogen bonding. It was reported that these (NHC)$PdCl_2$(DEA) complexes performed comparatively worse in the Suzuki-Miyaura cross coupling of 2,6-dimethylphenyl chloride with phenylboronic acid. The performance difference was attributed to the slower activation of the precatalyst, resulting from slower disassociation of the throw away ligand. Due to this observation, we believe the (IMes)$PdCl_2$(S-methyl-pyrrolidine-2-carboxylate) complex is unlikely to provide higher activity in cross coupling reactions then the TEA ligated compounds, but due to its chiral properties may find use in Pd(II) catalysed stereoselective reactions.



81 86

Scheme 2.13 Synthesis of (IMes)$PdCl_2$(S-methyl-pyrrolidine-2-carboxylate)

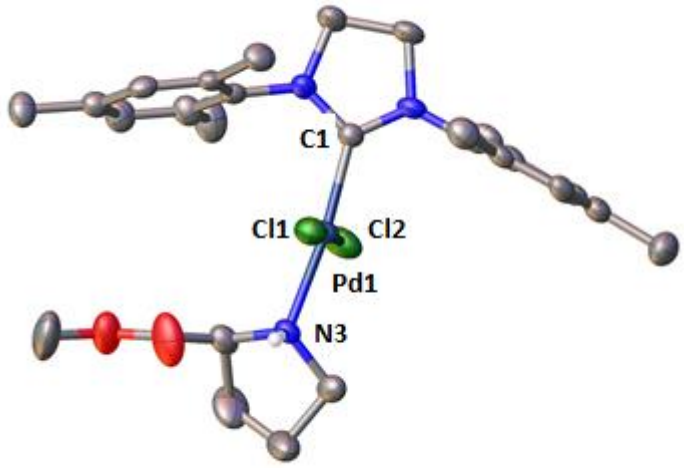
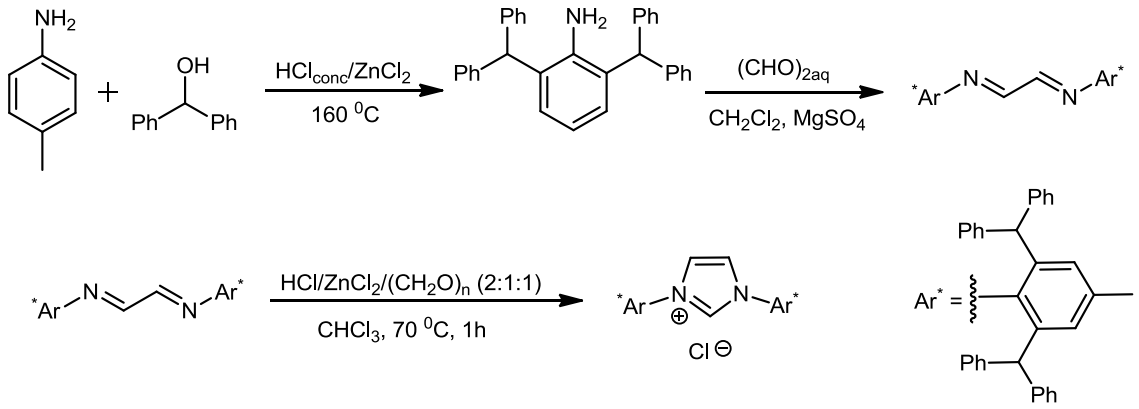


Figure 2.6 X-ray structure of (IMes)$PdCl_2$(S-methyl-pyrrolidine-2-carboxylate). Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1-C1: 1.971(6), Pd-Cl1: 2.3006(17), Pd-Cl2: 2.2945(16), Pd-N3: 2.119(5), C1-Pd1-Cl1: 89.56(19), C1-Pd1-Cl2: 94.02(19), N3-Pd1-Cl2: 85.32(14), N3-Pd1-Cl1: 91.36(14).

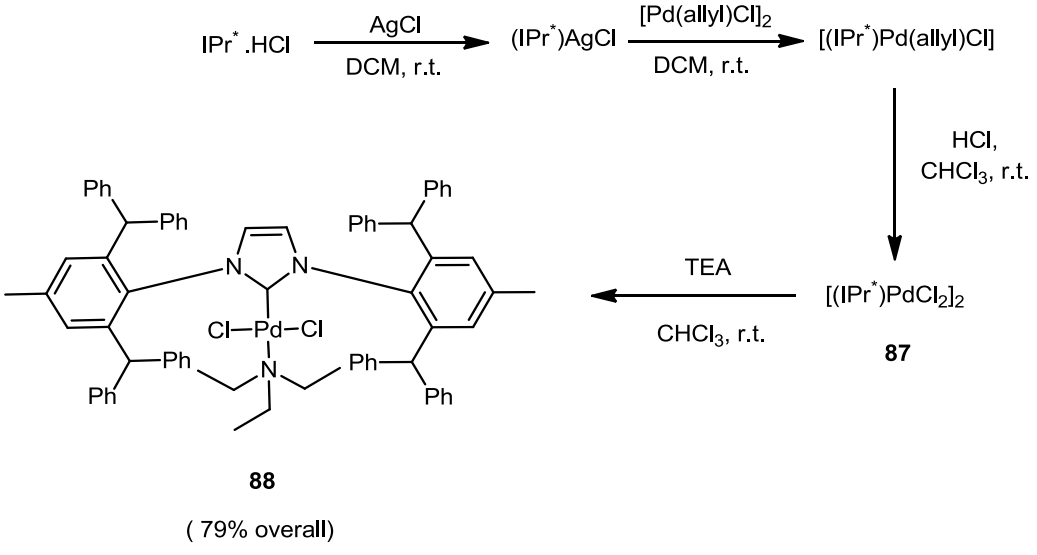
2.2.1.3 (IPr*)$PdCl_2$(TEA)

Intending to explore the potential further enhancement of catalytic activity of these TEA containing NHC-palladium complexes, we decided to synthesise the (IPr*)$PdCl_2$(TEA) complex. The imidazolium salt IPr*.HCl was prepared by the following literature procedure and its identity confirmed by ^{1}H NMR spectroscopy (Scheme 2.14).[25]



Scheme 2.14 Synthesis of IPr*. HCl.

This imidazolium salt was then used to prepare the target (IPr*)$PdCl_2$(TEA) complex in a procedure depicted below (Scheme 2.15).[26] This procedure begins with the reaction of the IPr*.HCl with AgCl under conditions reported in the literature to yield the corresponding (IPr*)AgCl complex. This was followed by transmetalation with $[Pd(allyl)Cl]_2$. Without isolation of the intermediate complex, the crude reaction mixture was treated with 4 M HCl in dioxane to generate the dimer $[(IPr^*)PdCl_2]_2$ **87**. Finally, the dimer was reacted with an excess of TEA to yield the target (IPr*)$PdCl_2$(TEA) **88** complex in an overall yield of 79 %. Both the $[(IPr^*)PdCl_2]_2$ and (IPr*)$PdCl_2$(TEA) complexes were fully characterised by ^1H, ^{13}C NMR spectroscopy and elemental analysis.



Scheme 2.15 Synthesis of (IPr*)$PdCl_2$(TEA).

A slow recrystallization of (IPr*)$PdCl_2$(TEA) in chloroform/hexane mixture yielded crystals suitable for X-ray diffraction analysis. As expected, the molecular structure shows a square planar Pd centre with the NHC and TEA *trans* to each other (Figure 2.7). The bond lengths from the metal were of a similar range to that of the IPr-bearing complex. The Pd-N bond was found to be significantly longer than the (IPr*)$PdCl_2$(PEPPSI) analogue, suggesting a weaker interaction between the Pd and the throw away ligand and therefore an easier activation process.

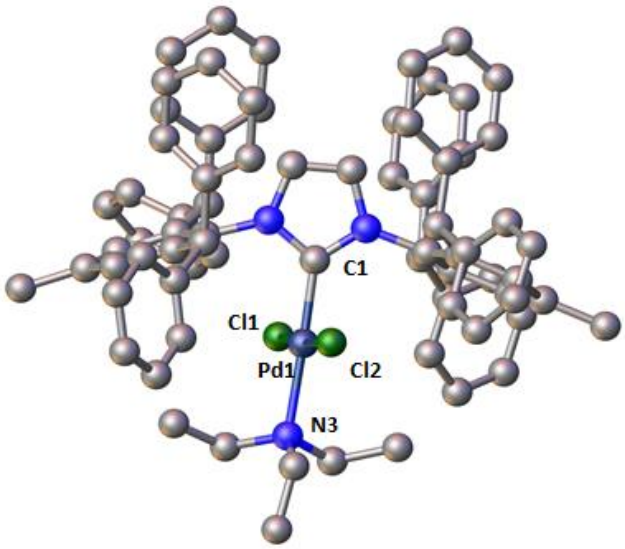


Figure 2.7 X-ray structure of (IPr*)$PdCl_2$(TEA). Hydrogen atoms are omitted for clarity . Selected bond lengths [Å] and angles [°]: Pd1–C1 1.960(6), Pd1–N3 2.179(5), Pd–Cl1 2.2989(17), Pd–Cl2 2.3041(17), C1–Pd1–Cl1 86.15(17), C1–Pd1–Cl2 89.35(17), N3–Pd1–Cl1 94.11(16), N3–Pd1–Cl2 90.41(16).

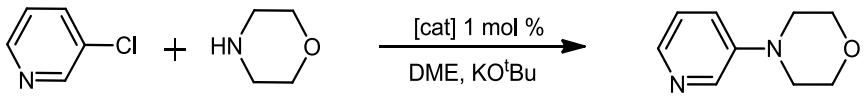
After analysing the structures of the three novel complexes prepared, we identified the (IPr*)$PdCl_2$(TEA) complex to be the best candidate for catalysing cross-coupling reactions. As a result of this the (IPr*)$PdCl_2$(TEA) complex was tested as a catalyst for Buchwald-Hartwig amination reactions.

2.2.2 Comparative testing of (IPr*)$PdCl_2$(TEA) as a precatalyst in Buchwald-Hartwig aminations

In order to facilitate a direct comparison between the catalytic activity of (IPr*)$PdCl_2$(TEA), (SIPr)$PdCl_2$(TEA) and (IPr*)$PdCl_2$(PEPPSI) complexes, we used the same base and solvent system (KO^{t}Bu, DME) that was reported for these catalysts in the literature. The (IPr*)$PdCl_2$(TEA) complex was found to be air and moisture stable, therefore the coupling reactions were set up and performed in open air.

In a direct comparison of (IPr*)$PdCl_2$(TEA) and (SIPr)$PdCl_2$(TEA) in the Buchwald-Hartwig coupling between 3-chloropyridine and morpholine (Table 2.3), the IPr* bearing complex showed a clear improvement in activity, enabling the coupling reaction to occur in a good yield at room temperature. This difference in activity is probably a result of the flexible steric bulk of the IPr* carbene adjusting towards incoming substrates and thus applying steric pressure during the reductive elimination step.

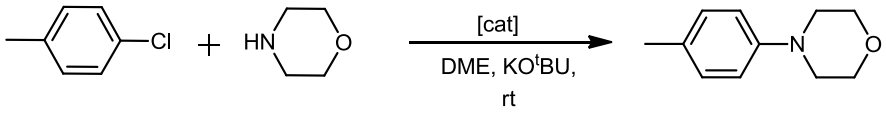
Table 2.3 Comparative catalytic activity of (SIPr)$PdCl_2$(TEA) and (IPr*)$PdCl_2$(TEA) complexes.



Catalyst	Conditions	Temperature /(°C)	Time /(h)	% yield
(SIPr)$PdCl_2$(TEA)	glovebox	50	3.5	77
(IPr*)$PdCl_2$(TEA)	in air	room temperature	26	91

The significance of the TEA throwaway ligand was highlighted in the comparison of the catalytic performance of (IPr*)$PdCl_2$(PEPPSI) and (IPr*)$PdCl_2$(TEA) in the Buchwald-Hartwig coupling of 1-chloro-4-methylbenzene and morpholine (Table 2.4). The TEA ligated complex was able to couple the substrates in a shorter time, with a better yield and half the catalyst loading.

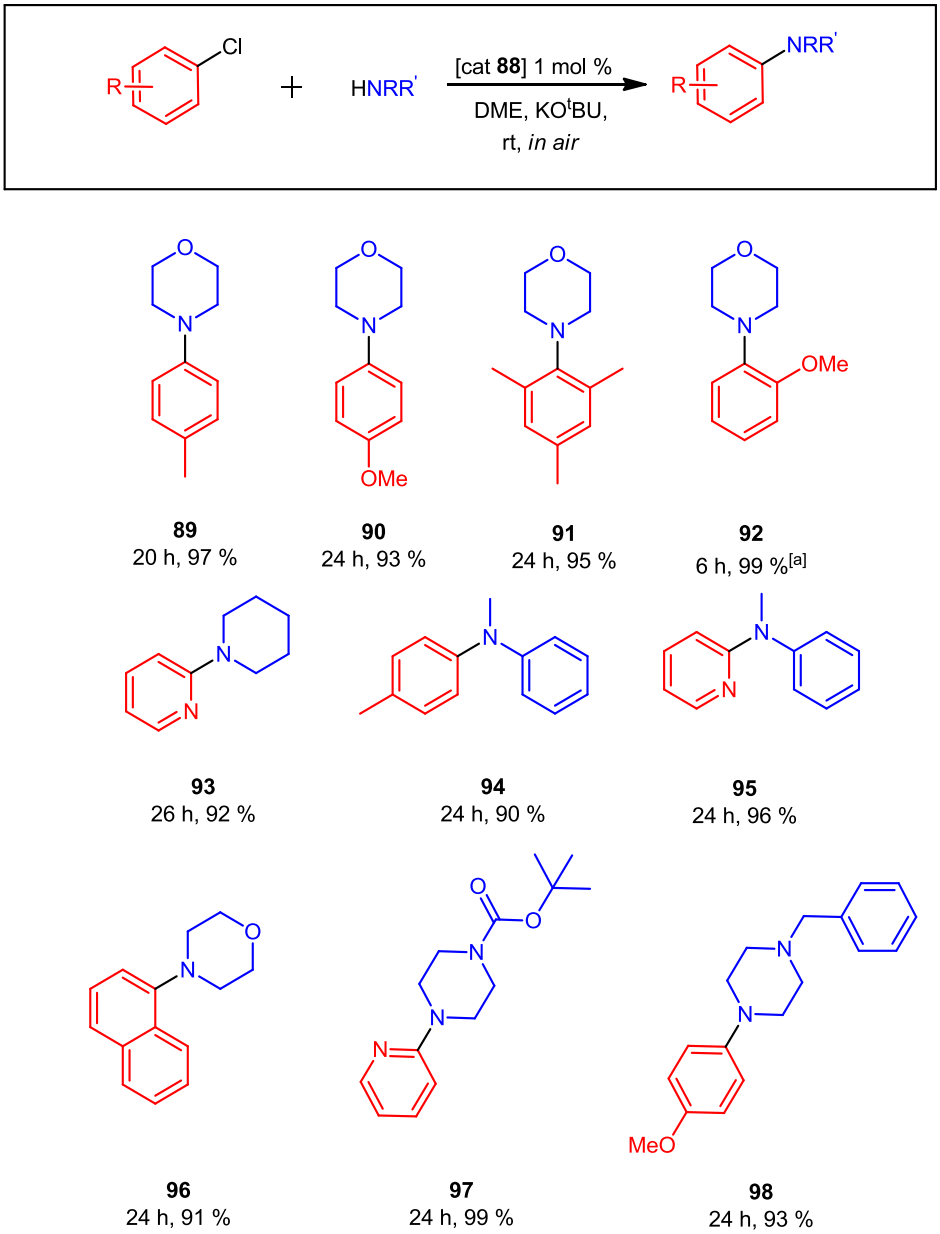
Table 2.4 Comparative catalytic activity of (IPr^*)$PdCl_2$(TEA) and (IPr^*)$PdCl_2$(PEPPSI) complexes.



Catalyst	Conditions	Catalyst loading (mol %)	Time /(h)	% yield
(IPr^*)$PdCl_2$(PEPPSI)	glovebox	2	24	94
(IPr^*)$PdCl_2$(TEA)	in air	1	20	97

2.2.3 Scope of reactivity

The scope of this pre-catalyst in Buchwald-Hartwig aminations was then investigated. The complex was found to catalyse the coupling of a number of aryl chlorides and secondary amines, without the need to set up or perform the reactions under an inert atmosphere (Scheme 2.16). The use of more sterically demanding aryl chlorides had no significant effect on reaction times or yields. Unsurprisingly less time was needed when the chlorine was replaced with bromine. Two piperazine based compounds were successfully synthesised, including the 1-benzyl-4-(4-methoxyphenyl)piperazine **98**, which has displayed selective potency at the D_4 receptor and is a benchmark for the development of compound libraries for potential schizophrenia treatment.



Scheme 2.16 Room temperature Buchwald Hartwig couplings catalysed by (IPr*)$PdCl_2$(TEA). Reaction conditions: aryl chloride (1 mmol), amine (1.1 mmol), KO^{t}Bu (1.1 mmol), DME (1 ml). The yield is the average of two runs. [a] 2-bromo anisole used. Yields given are isolated pure compounds.

2.3 Conclusion

The aim of this chapter was to design a novel (NHC)-palladium catalyst bearing an N-donor throw away ligand and test its activity in cross-coupling reactions. We have reported the preparation of three new NHC palladium complexes, and the best candidate: (IPr*)$PdCl_2$(TEA) has been tested in Buchwald Hartwig amination reactions. The complex was found to facilitate the coupling of aryl chlorides and bromides to secondary amines with excellent yields under mild, and user friendly conditions.

2.4 Experimental

General Considerations

Unless otherwise noted, all manipulations were performed in air. All solvents and reagents were used as received with the exception of KOtBu, which was flame-dried prior to use. The reagents were purchased from Sigma Aldrich, Fluorochem and Alfa Aesar. The imidazolium salt IPr*·HCl and complex (IPr*)AgCl were prepared by following literature procedures and their identity and purity was confirmed by ^{1}H NMR spectroscopy.[25] The $[(IMes)PdCl_2]_2$ and (IMes)$PdCl_2$(TEA) complexes were prepared by following reported literature procedures and their identity and purity confirmed by ^{1}H NMR spectroscopy.[21]

Synthesis of $[(IPr^*)PdCl_2]_2$ (87)

In a vial equipped with a magnetic stir bar, (IPr*)AgCl (2.38 g, 2.25 mmol) and $[Pd(allyl)Cl_2]_2$ (0.42 g, 1.15 mmol) were dissolved in dichloromethane, and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo and triturated with hexane to afford an off-white solid (2.06 g). This solid was re-dissolved in chloroform (10 mL), and 4 n HCl in diox-ane (1 mL) was added. The solution was allowed to stir at room temperature for 4 h and was then concentrated in vacuo and tritu-rated with hexane to afford a pale yellow solid, yield 2.0 g (94%). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ = 2.16 (s, 12 H), 4.57 (s, 4 H,), 6.13 (s, 8 H,), 6.58 (d, J = 6, 15 H), 6.70 (s, 8 H), 6.99–7.08 (m, 25 H,), 7.21 (t, J = 7.5, 10 H), 7.29 (t, J = 7.5, 15 H,), 7.38 (d, J =6,15 H) ppm. ^{13}C{^{1}H} NMR [$(CD_3)_2SO$, 75 MHz]: δ

= 21.4, 50.1, 126.4, 127.9, 128.2, 128.7, 129.9, 130.1, 134.5, 137.9, 141.4, 143.4, 143.8. Anal. Calcd for $C_{138}H_{112}Cl_4N_4Pd_2$ (2181.04): C 75.99, H 5.18, N 2.57; found C 75.71, H 4.95, N 2.64.

Synthesis of (IPr*)$PdCl_2$(TEA) (88)

In a vial equipped with a magnetic stirbar, $[(IPr^*)PdCl_2]_2$ (545 mg, 0.25 mmol) was suspended in chloroform (1 mL), and an excess of triethylamine (0.5 mL) was added. The solution was stirred at room temperature for 2 h. The removal of the solvent afforded a pale yellow solid, which was washed with hexane, yield 532 mg (89%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.95 (t, J =7.5Hz,9H), 2.23 (s, 6H), 2.77 (q, J =7 Hz, 6H), 4.44 (s, 2 H), 6.07 (s, 4 H),6.70 (m, 8 H, ArH), 6.81 (s, 4 H), 7.01 (m, 12 H), 7.25(m, 14 H), 7.48 (d, J = 6 Hz, 6 H,). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 9.6, 21.8, 22.3, 46.5, 50.9, 123.1, 125.8 , 126.0, 127.8, 127.9, 129.3, 129.6, 130.1, 134.6, 138.3, 142.8, 143.7, 145.6, 152.5 Anal. Calcd for $C_{75}H_{71}Cl_2N_3Pd$ (1191.71): C, 75.59, H 6.01, N 3.53; found C75.45, H 6.33, N 3.44.

Synthesis of (IMes)$PdCl_2$(2-phenylpyridine) (85)

In a vial equipped with a magnetic stirbar, $[(IMes)PdCl_2]_2$ (100 mg, 0.104 mmol) was dissolved in THF (5 mL), the solution was stirred until the complex dissolved. Then 2-phenylpyridine (15 μL, 0.104mmol) was added via a micro pipette, and the reaction left to stir for 4 hours at room temperature. Once the reaction had finished the solvent was removed under vacuum. The product was then recrystallized in benzene and hexane in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 7.3 Hz, 2H), 7.61 (td, J = 7.7, 1.4 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.27 (s, 1H), 7.20 (t, J = 7.7 Hz, 2H), 7.17 – 7.10 (m, 1H), 7.07 (s, 2H), 7.04 (s, 2H), 7.02 (d, J = 1.5 Hz, 1H), 6.93 – 6.88 (m, 1H), 2.51 (s, 3H), 2.40 (s, 3H), 2.34 (s, 6H), 2.16 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6): δ = 160.6, 155.4, 151.0, 139.3, 138.9, 138.3, 137.2, 136.3, 136.1, 135.3, 134.9, 129.2, 128.9, 128.0, 125.2, 123.8, 122.3, 21.01, 19.0, 18.6. Anal. Calcd for $C_{32}H_{33}Cl_2N_3Pd$: C, 60.34; H, 5.22; N, 6.66. Found: C, 60.42; H, 5.21; N, 6.52. CCDC number: 1473490.

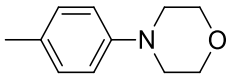
Synthesis of (IMes)$PdCl_2$(methyl pyrrolidine-2-carboxylate) (86)

In a vial equipped with a magnetic stirbar, (IMes)$PdCl_2$(TEA) (100 mg, 1.715 mmol) was dissolved in dry acetone (5 mL). Then L-proline methyl ester hydrochloride (0.28, 1.715 mmol) was added, and the reaction was left to stir overnight. The solvent was then removed in vacuo and the product then purified by recrystallization in a benzene and hexane mixture in a quantitative yield. ^{1}H NMR (399 MHz, benzene-d_6) δ 6.85 (s, 4H), 6.14 (s, 2H), 4.20 (dt, *J* = 9.3, 6.1 Hz, 1H), 3.83 – 3.64 (m, 1H), 3.10 (s, 3H), 3.00 – 2.77 (m, 1H), 2.56-2.51 (m, 1H), 2.48 (s, 12H), 2.10 (s, 6H), 1.79 – 1.55 (m, 1H), 1.32 – 1.16 (m, 1H), 1.16 – 1.01 (m, 1H), 0.74 (dt, *J* = 12.4, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 172.3, 156.8, 138.5, 136.3, 135.5, 129.1, 129.0, 60.5, 51.2, 49.2, 29.8, 23.9, 20.7, 19.0. Anal. Calcd for $C_{27}H_{36}Cl_2N_3O_2Pd$: C, 53.00; H, 5.93; N, 6.87. Found C, 52.68; H, 5.95; N, 6.81. CCDC number: 1504858.

General Procedure for Buchwald-Hartwig amination reactions

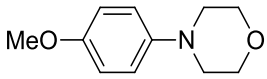
Complex **88** (1 mol %), KO^{t}Bu (1.1 mmol) aryl halide (1 mmol) amine (1.1 mmol) and DME (1 ml) were added in turn to a vial equipped with a magnetic stir bar. The solution was then stirred at room temperature and monitored by gas chromatography. Once the reaction was finished, the solution was poured into distilled water (5 mL) and the organics extracted three times with ethyl acetate (10 mL). The organic portions were combined, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The products were isolated by flash chromatography using the solvent systems described below. The amount of product shown is the average of two runs.

4-Methylbenzyl)morpholine.[27] **(89)**



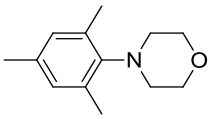
The procedure afforded, after purification (Petroleum ether/EtOAc = 90/10), 172 mg (97 %) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, J = 9.3 Hz, 2H), 6.84 (d, J = 9.3 Hz, 2H), 3.87 (t, J = 4.5 Hz, 4H), 3.12 (t, J = 4.5 Hz, 4H), 2.29 (s, 3H).

4-(4-Methoxyphenyl)morpholine.[27] **(90)**



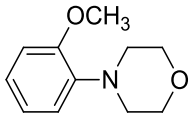
The procedure afforded, after purification (Petroleum ether/EtOAc = 98/2), 180 mg (93 %) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93-6.83 (m, 4H), 3.86 (t, J = 4.5 Hz, 4H), 3.78 (s, 3H), 3.06 (t, J = 4.5 Hz, 4H).

4-Mesitylmorpholine.[27] **(91)**



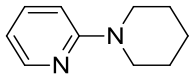
The procedure afforded, after purification (Petroleum ether/EtOAc = 80/20), 195mg (95 %) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 2H), 3.79 (t, J = 4.5 Hz, 4H), 3.08 (t, J = 4.5 Hz, 4H), 2.31 (s, 6H), 2.24 (s, 3H).

4-(2-Methoxyphenyl)morpholine.[28] **(92)**



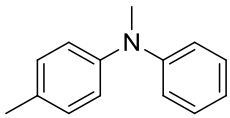
The procedure afforded, after purification (Petroleum ether/EtOAc = 90/10), 191 mg (99 %) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06-6.99 (m, 1H), 6.96-6.92 (m, 2H), 6.90-6.86 (m, 1H), 3.90 (t, J = 4.5 Hz, 4H), 3.87 (s, 3H), 3.07 (t, J = 4.5 Hz, 4H).

2-(Piperidin-1-yl)pyridine.[27] **(93)**



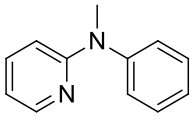
The procedure afforded, after purification (Petroleum ether/EtOAc = 99/1), 149 mg (92 %) of the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20-8.14 (m, 1H), 7.47-7.39 (m, 1H), 6.63 (d, J = 8.4 Hz, 1H), 6.57-6.51 (m, 1H), 3.51 (s, broad, 4H), 1.63 (s, broad, 6H).

N,4-dimethyl-N-phenylaniline.[27] **(94)**



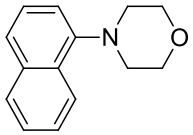
The procedure afforded, after purification (Petroleum ether/EtOAc = 80/20), 178 mg (90 %) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.356 (m, 2H), 7.23-7.16 (d, 2H), 7.11-7.06 (d, 2H), 7.04-6.99 (m, 2H), 6.99-6.92 (m 1H), 3.36 (s, 3H), 2.41 (s, 3H).

N-Methyl-N-phenylpyridin-2-amine.[28] **(95)**



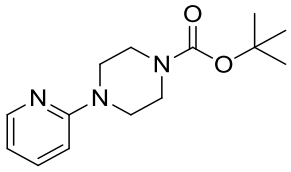
The procedure afforded, after purification (Petroleum ether/EtOAc = 80/20), 177mg (96 %) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (m, 1H), 7.40 (m, 2H), 7.30 (m, 2H), 7.21 (m, 2H), 6.60 (td, J = 6.0, 0.9 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 3.48 (s, 3H).

4-(Naphthalen-1-yl)morpholine.[29] **(96)**



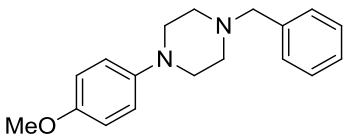
The procedure afforded, after purification (Petroleum ether/EtOAc = 90/10), 194 mg (91 %) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (t, J = 4.6 Hz,4H,), 4.03 (t, *J* = 4.6 Hz, 4H), 7.13 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.47 (t, *J* = 8.2 and 7.4 Hz, 1H), 7.50−7.59 (m, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.90 (m, 1H), 8.30 (m, 1H).

***Tert*-butyl 4-(pyridin-2-yl)piperazine-1-carboxylate.**[30] **(97)**



The procedure afforded, after purification (Petroleum ether/EtOAc = 98/2), 234 mg (99 %) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 3.47 (m, 8H), 6.54-6.61 (m, 2H), 7.40-7.46 (m, 1H), 8.11-8.14 (s, 1H).

1-benzyl-4-(4-methoxyphenyl)piperazine.[31] **(98)**



The procedure afforded, after purification (Petroleum ether/EtOAc = 98/2), 263 mg (93 %) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60–2.63 (m, 4H), 3.08–3.11 (m, 4H), 3.57 (s, 2H), 3.76 (s, 3H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 1H), 7.26–7.36 (m, 5H).

2.5 References

(1) O'Brien, C. J.; Kantchev, E. A. B.; Chass, G. a.; Hadei, N.; Hopkinson, A. C.; Organ, M. G.; Setiadi, D. H.; Tang, T. H.; Fang, D. C. *Tetrahedron* **2005**, *61*, 9723–9735.

(2) Viciu, M. S.; Germaneau, R. F.; Navarro-Fernandez, O.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2002**, *21*, 5470–5472.

(3) Navarro, O.; Marion, N.; Scott, N. M.; González, J.; Amoroso, D.; Bell, A.; Nolan, S. P. *Tetrahedron* **2005**, *61*, 9716–9722.

(4) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. a; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.Eur. J.* **2006**, *12*, 4743–4748.

(5) Love, J. A; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4035–4037.

(6) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem.Eur. J.* **2006**, *12*, 4749–4755.

(7) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C.; Organ, M. G. *Chem. Commun.* **2008**, 6, 735–737.

(8) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. *Chem.Eur. J.* **2010**, *16*, 10844–10853.

(9) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chemie - Int. Ed.* **2003**, *42*, 3690–3693.

(10) Pompeo, M.; Froese, R. D. J.; Hadei, N.; Organ, M. G. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 11354–11357.

(11) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.

(12) Çalimsiz, S.; Organ, M. G. *Chem. Commun.* **2011**, *47*, 5181–5183.

(13) Chass, G. A; Brien, C. J. O.; Hadei, N.; Kantchev, E. A. B.; Mu, W.; Fang, D.; Hopkinson, A. C. *Chem.Eur. J.* **2009**, *15*, 4281–4288.

(14) Hoi, K. H.; Çalimsiz, S.; Froese, R. D. J.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2011**, *17*, 3086–3090.

(15) Chartoire, A.; Frogneux, X.; Boreux, A.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2012**, 6947–6951.

(16) Tu, T.; Sun, Z.; Fang, W.; Xu, M.; Zhou, Y. *Org. Lett.* **2012**, *14*, 4250-4253.

(17) Batey, R. a; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4* , 1411–1414.

(18) Zhu, L.; Gao, T. T.; Shao, L. X. *Tetrahedron* **2011**, *67*, 5150–5155.

(19) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. *Chemistry* **2008**, *14*, 2443–2452.

(20) Gu, Z.-S.; Shao, L.-X.; Lu, J.-M. *J. Organomet. Chem.* **2012**, *700*, 132–134.

(21) Chen, M.; Vicic, D. A.; Turner, M. L.; Navarro, O. *Organometallics*. **2011**, *2*, 5052–5056.

(22) Hintermann, L. *Beilstein J. Org. Chem.* **2007**, *3*, 2–6.

(23) Winkelmann, O. H.; Navarro, O. *Adv. Synth. Catal.* **2010**, *352*, 212–214.

(24) Chen, M.; Vicic, D. A.; Chain, W. J.; Turner, M. L.; Navarro, O. *Organometallics*. **2011**, *2*, 6770–6773.

(25) Berthon-Gelloz, G.; Siegler, M. a; Spek, A. L.; Tinant, B.; Reek, J. N. H.; Markó, I. E. *Dalton Trans.* **2010**, *39*, 1444–1446.

(26) Guest, D.; Chen, M. T.; Tizzard, G. J.; Coles, S. J.; Turner, M. L.; Navarro, O. *Eur. J. Inorg. Chem.* **2014**, *2*, 2200–2203.

(27) A. Chartoire, X. Frogneux, A. Boreux, A. Slawin and S. P. Nolan, *Organometallics* **2012**, *31*, 6947-6951.

(28) S. Meiries, A. Chartoire, A. Slawin and S. P. Nolan, *Organometallics* **2012**, *31*, 3402-3409.

(29) S. Meiries, K. Speck , D. Cordes, A. Slawin and S. P. Nolan, *Organometallics* **2013**, *32*, 330–339.

(30) R. Varala, S. Nuvula and S. Adapa, *J. Org. Chem*. **2006**, *71* , 8283–8286.

(31) K. Hodgetts, A. Kieltyka, R. Brodbeck, J. Tran, J. Wasley and A. Thurkauf, *Bioorg. Med. Chem*. **2001**, *9*, 3207–3213.

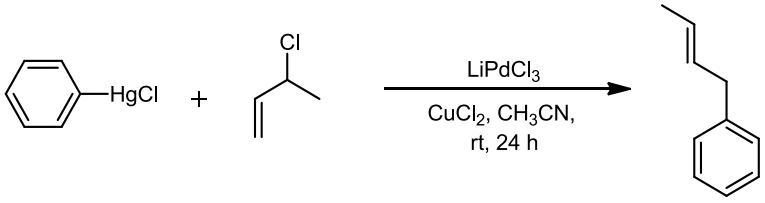
3 [(NHC)PdCl$_3$][TBA] complexes as catalysts for the Mizoroki-Heck Reaction

3.1 Background

The formation of new C-C bonds is vital to the synthesis of pharmaceuticals, natural products and material science. In the pursuit of these endeavours the Mizoroki-Heck reaction is a uniquely attractive process among cross-coupling reactions, due to its direct formation of C-C bonds from the comparatively inert vinylic C-H bonds of α-olefins.[1] This inertness, compared to substrates required for other coupling reactions, is advantageous as it means that fewer steps are required in its installation and maintenance throughout a synthetic procedure.

3.1.1 Discovery of the Mizoroki-Heck reaction

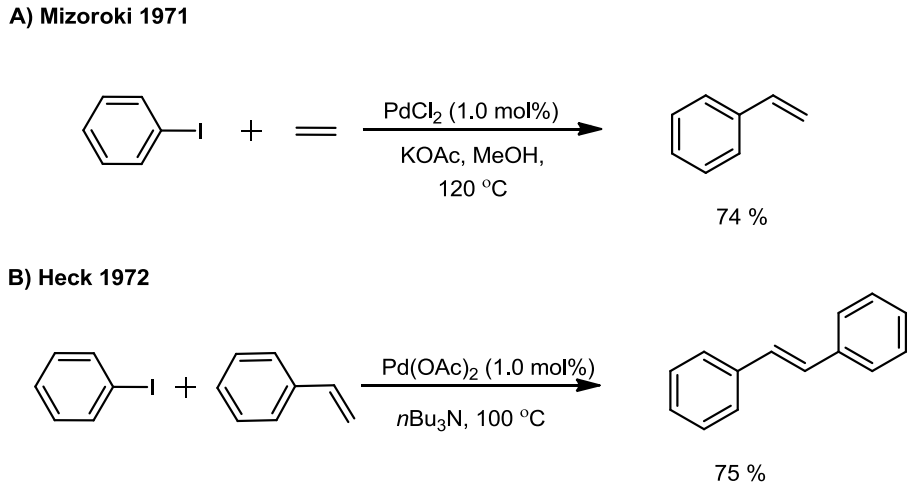
The basis for the modern day Mizoroki-Heck reaction was reported in a series of monographs by Heck in the late 1960s.[2-3] They described the formation of arylated alkenes by the reaction of alkenes with a stoichiometric amount of [Ar-Pd-X] (X = Cl or OAc), which was generated in situ by reacting ArHgX (X = Cl or OAc) with LiPdCl$_3$ (Scheme 3.1). Although this methodology was an effective method for the preparation of arylated alkenes, the utilisation of toxic arylmercury reagents rendered this process undesirable for widespread adoption.



Scheme 3.1 Stoichiometric coupling of arylmetallic reagent with 3-chloro-1-butene

In 1968 Fitton and co-workers reported that Pd(PPh$_3$)$_4$ a palladium(0) complex can undergo oxidative addition with chloroolefins, alkyhalides and arylhalides;[4] this observation showed that mercury reagents were not required to facilitate the oxidative addition step. Based on this study, procedures that utilised the oxidative addition of ArX directly to a palladium (0) species were reported independently by Mizoroki and Heck in

1971 and 1972 respectively,[5,6] (Scheme 3.2). These reactions, which were found to work faster when a base was added, were the earliest examples of a new reaction later called the Mizoroki-Heck reaction.



Scheme 3.2 Early examples of palladium (II) cross coupling reaction.

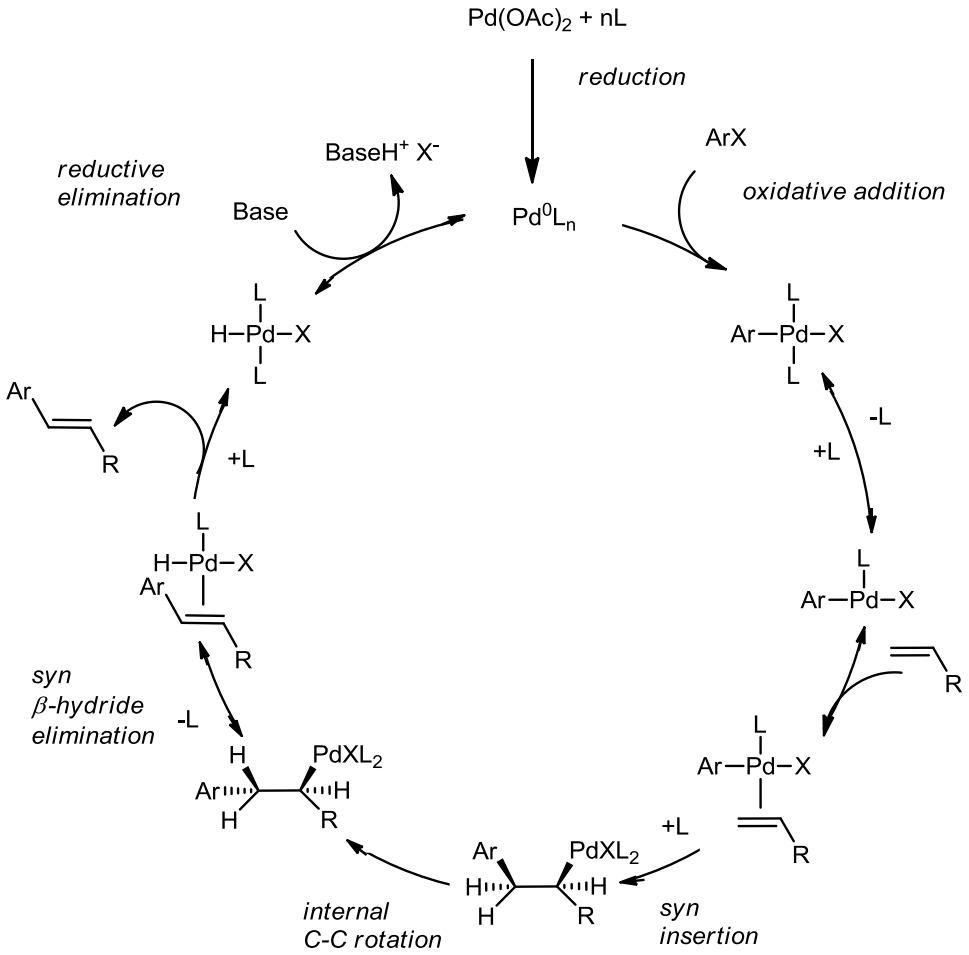
Mizorki and co-workers further developed their preliminary work in 1973,[7] extending the scope of reactivity to include bromobenzene. In this study the use of a phosphine ligand PPh_3 was found to slightly increase the yield.

3.1.2 Mechanism

The first full mechanism for the reaction between iodobenzene and styrene catalysed by $Pd(OAc)_2$ was reported in 1972 by Heck and Nolley.[6] They proposed the oxidative addition of the aryl halide to palladium metal, which had been formed in situ by the reduction of $Pd(OAc)_2$ by the alkene. The newly formed organopalladium halide then underwent an addition reaction with the olefin, which then decomposed by eliminating hydridopalladium halide to form the target substituted olefinic compound. It was then suggested that the hydridopalladium halide species further decomposes into hydrogen halide and palladium which can then re-enter the cycle.

In 1974 the usage of PPh_3 as the ligand associated with $Pd(OAc)_2$ was reported by Dieck and Heck.[8] The addition of the ligand was found to have little effect when using aryl iodides, but its inclusion allowed the procedure to couple aryl bromides at temperatures in the range of 100-135 °C. The mechanism for reactions catalysed by $Pd(OAc)_2$

associated with monophosphine ligand was proposed in this monograph. This mechanism, described by Heck as successive reactions, is presented in a cyclic format below (Scheme 3.3).



Scheme 3.3 Proposed mechanism when the precursor is $Pd(OAc)_2$ and a monophosphine ligand.

In this cycle the following steps were postulated:

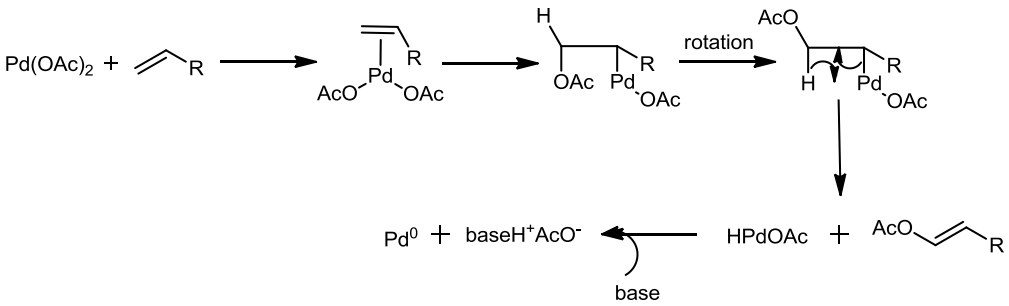
I. A loosely defined reduction process of palladium(II) species to palladium(0)
II. The oxidative addition of the aryl halide to a palladium (0) complex
III. The dissociation of one phosphine from the generated σ-aryl-palladium(II) halide, followed by η-2 co-ordination of the alkene.
IV. *Syn* insertion of the alkene, generating a σ-alkyl-palladium(II) halide.
V. An internal C-C rotation which places a sp^3 β hydrogen in a *syn* position relative to the palladium. This facilitates a *syn* *β*-hydride elimination resulting in a hydridopalladium(II) halide with a co-ordinated arylated alkene.

VI. Dissociation of the arylated alkene followed by a reversible reductive elimination of hydrogen halide regenerating the Pd(0) complex which continues the cycle.

The reactions described above formed the bases of the textbook mechanism for the Mizoroki-Heck reaction, of which many of the steps have been proved correct. However over the last thirty years, with the advent of new analytical techniques and the identification of novel ligand systems, there have been many gains in knowledge pertaining to i) the intermediate palladium species in the cycle, ii) the reduction pathways of the palladium(II) species and iii) the factors which control the regioselectivity of the Mizoroki-Heck reaction.

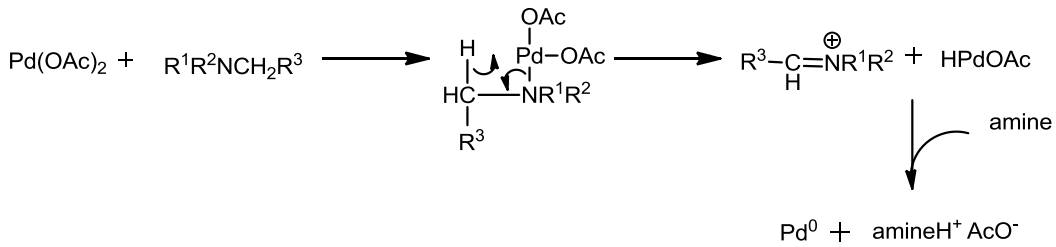
3.1.2.1 Catalyst activation pathways

The suggested pathways for reduction of the palladium(II) precatalyst are varied and dependant on the reaction conditions. In the case of ligand free systems three possible mechanisms have been proposed. The first, suggested by Heck, involved the alkene acting as a reducing agent (Scheme 3.4).[9] This requires an intramolecular nucleophilic attack of the acetate onto the alkene, followed by *β*-hydride elimination leading to the formation of HPdOAc which then undergoes a base promoted reductive elimination yielding Pd(0).



Scheme 3.4 Reduction of the Pd(II) reagent by alkene.

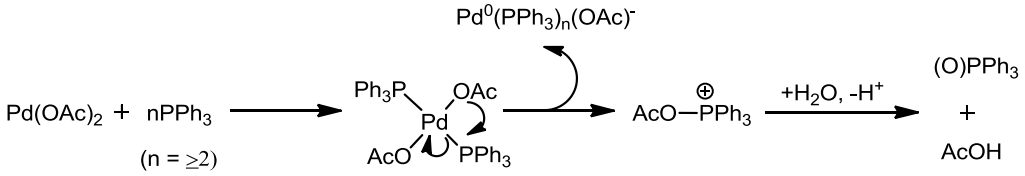
It has been proposed that when amines are used as the base they can also act as a reducing agent (Scheme 3.5). In this case, after co-ordination to the palladium metal centre, a β-hydride elimination may take place resulting in the formation of HPdOAc which then undergoes reductive elimination to produce the active Pd(0) species.



Scheme 3.5 Reduction of the Pd(II) reagent by amine base.

In 2000 Reetz and Westermann realised that in Mizoroki-Heck reactions performed in the absence of phosphine ligands, additives such as ammoniums salts can facilitate the thermolytic decomposition of $Pd(OAc)_2$ at 100-130 °C.[10] The cleavage of the Pd-OAc bond generates Pd(0) nanoparticles stabilised by $R_4N^+X^-$, which then act as the active catalyst for the reaction.

In catalytic systems, when a monophosphine such as PPh_3 is used in conjunction with a divalent palladium species containing an oxygenated ligand (AcO^-, NO_3^-, $CF_3CO_2^-$), the palladium(II) compound is proposed to be reduced by the phosphine ligand. This hypothesis was developed by Jutand and co-workers in 1992,[11] and was based on electrochemical analysis and ^{31}P NMR spectroscopy. They reported that in DMF, mixtures of $Pd(OAc)_2$ and $nPPh_3$ ($n \geq 2$) rapidly react to produce $Pd(OAc)_2(PPh_3)_2$, which slowly forms $Pd(PPh_3)_n(OAc)^-$ and phosphine oxide via an intramolecular reduction (Scheme 3.6). Further studies by Amatore and Jutand investigated the kinetics of the reduction process.[12] They reported that the reduction of the Pd(II) by the phosphine is much faster than by the alkene or amine. It was also determined that the reduction process is sensitive to electronic and steric factors with more electron poor phosphines reacting faster.



Scheme 3.6 Reduction of $Pd(OAc)_2$ by monophosphine PPh_3.

The composition of the palladium complex formed post reduction is dependent on the equivalents of phosphine used. When 2 equivalents of PPh_3 are added to $Pd(OAc)_2$, only

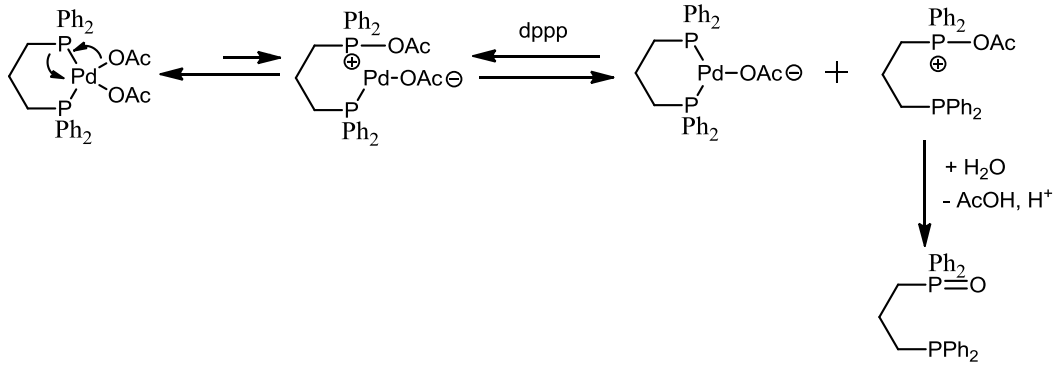
one PPh_3 is available to stabilise the resulting Pd(0) complex since the other is used in the reduction process. This would imply that the complex would have the formal structure $[Pd^0(PPh_3)(OAc)^-]$. However, because the ^{31}P NMR spectra of this species showed two singlets of similar magnitude a bridged dimeric *cis*- and *trans*-$[Pd^0(OAc)(\mu\text{-}OAc)(PPh_3)]_2^{4-}$ complex has been proposed.

When three equivalents of PPh_3 are mixed with $Pd(OAc)_2$ the anionic 16 electron species $Pd^0(PPh_3)_2(OAc)^-$ is formed. This complex is unstable and could be rendered more so via the interaction of its acetate ligand with protons generated by the hydrolysis of the phosphonium, as this would result in the formation of a more naked $Pd^0(PPh_3)_2$ complex. However this interaction is prevented by the capture of the protons by the base, which is used in Mizoroki-Heck reactions to help regenerate the catalyst after completing the cycle.

When more than 3 equiv of PPh_3 are mixed with $Pd(OAc)_2$ a saturated stable 18 electron $Pd^0(PPh_3)_3(OAc)^-$ complex is formed, which exists in equilibrium with $Pd^0(PPh_3)_2(OAc)^-$ (Scheme 3.7).

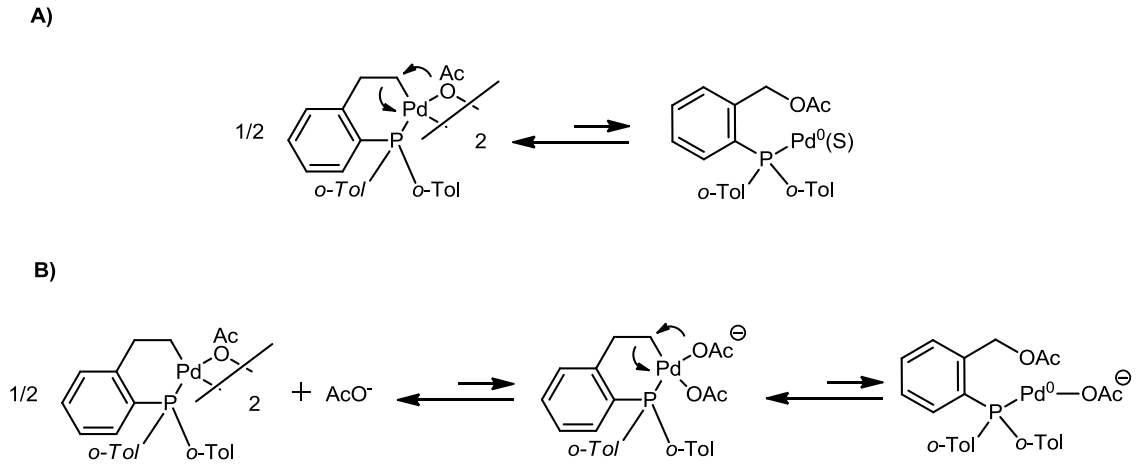
Scheme 3.7 Equilibrium between the active 16 electron species and the inactive 18 electron species when more than three equiv of PPh_3 is used.

In catalytic systems, when a bisphosphine such as dppp is used in conjunction with a divalent palladium species containing an oxygenated ligand, the catalyst activation pathway is proposed to be slightly different from monophosphine systems.[13] This is due to the fact that the phosphonium formed from the reductive elimination step is still ligated to the palladium via the second phosphine and is therefore vulnerable to fast intermolecular oxidative addition back to the starting material. In order to drive the equilibrium to favour formation of the anionic Pd(0) complex, a second equivalent of dppp is added. This ligand co-ordinates to the palladium centre, substituting the mono-ligated $P\text{^}P^+$ which is then hydrolysed to form the hemioxide dppp(O) (Scheme 3.8). The reversibility of the first step means that the formation of the Pd(0) species is slower for bisphosphine species when compared to their monophosphine counterparts. The addition of three equivalents of dppp results in the formation of a stable, catalytically inactive $Pd^0(dddp)_2$ complex.



Scheme 3.8 Reduction by two equivalents of bisphosphine ligand.

In 2005 the mechanism for the generation of a Pd^0 complex from P,C-palladacycles with bridging acetates in the absence of any reducing agent was explored by Jutand *et al.*[14] It was reported that the palladacycle acted as a reservoir for the generation of monophosphine-Pd^0 complex, which was formed via a reductive elimination between the *o*-benzyl moiety and an adjacent $^-$OAc ligand (Scheme 3.9a). As with the bisphosphine complexes described above, the formation of the Pd^0 species is reversible, as the backward oxidation pathway is intramolecular. The use of an acetate derived base can favourably affect the equilibrium by ligating to the palladium centre, forming a monomeric anionic P,C-palladacycle (Scheme 3.9b).

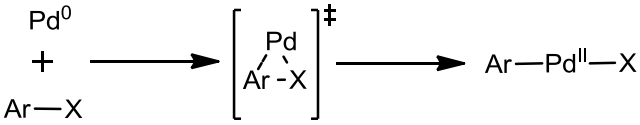


Scheme 3.9 Reduction of P,C-palladacycles A) without the presence of acetate ions (S = DMF) B) in the presence of acetate ions.

These anionic species are deviations from the textbook Mizoroki-Heck pathway, which suggested that the Pd complex that reacts with the aryl halide is a neutral species with two L ligands.

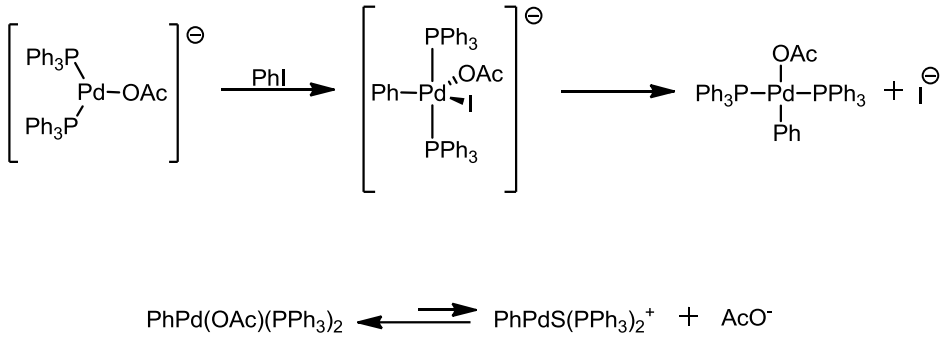
3.1.2.2 Oxidative Addition

The textbook mechanism for the oxidative addition process in the Mizoroki-Heck reaction is generally excepted to occur between a neutral palladium(0) species and the aryl halide or pseudohalide via the cleavage of the C-X bond and the formation of new Pd-X and Ar-Pd bonds (Scheme 3.10).[15] However as described above, in a number of protocols the active palladium species may be anionic in nature which can affect the palladium(II) complex generated.



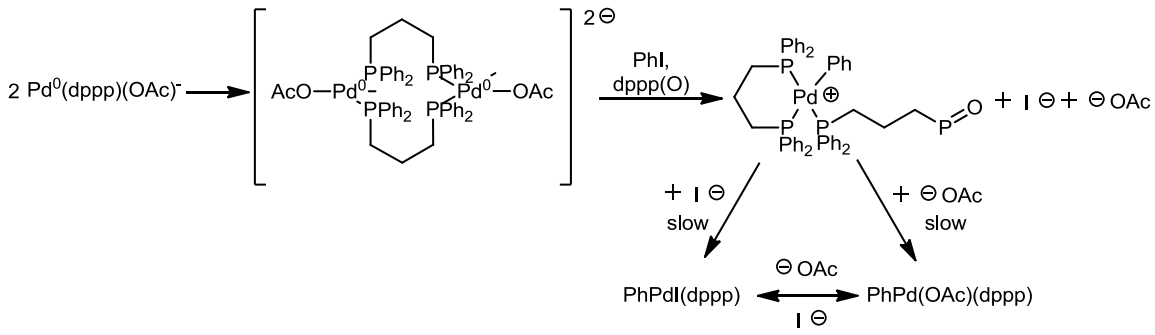
Scheme 3.10 Concerted oxidative addition step with neutral palladium species. X = halide or pseudohalide**.**

In the reaction between $Pd(OAc)_2$ and three equivalents of PPh_3, the anionic complex $Pd^0(PPh_3)_2(OAc)^-$ is proposed to be the only reactive species. The reaction of this complex with PhI was investigated electrochemically by Amatore *et al*.[16] They reported that the product of this reaction was not the expected *trans*-$PhPdI(PPh_3)_2$, but instead *trans*-$PhPd(OAc)(PPh_3)_2$ (Scheme 3.11). This complex was postulated to be synthesised via a short lived 18-electron penta-coordinated anionic complex $[PhPdI(OAc)(PPh_3)_2]^-$. The new complex exists in equilibrium with a cationic complex *trans*-$PhPdS(PPh_3)_2^+$ (S = solvent).



Scheme 3.11 Oxidative addition step between PhI and the anionic complex generated from $Pd(OAc)_2$ and three equivalents of PPh_3. S = DMF.

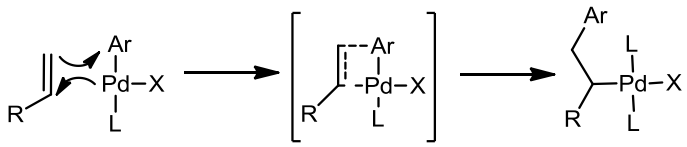
When $Pd(OAc)_2$ and two equivalents of a bisphosphine such as dppp are used in Mizoroki-Heck reactions they form the anionic species $Pd^0(dppp)(OAc)^-$ and dppp(O), the former of which is proposed to dimerise forming $[Pd^0(dppp)(OAc)]_2^{2-}$. This complex was reported to react with PhI to yield the cationic $PhPd(dppp)(dppp(O))^+$, in which the palladium is ligated by both a dppp ligand and the hemioxide acting as a monodentate ligand. This cationic species then slowly reacts with iodide or acetate to give either PhPdI(dppp) or PhPd(OAc)(dppp) respectively. These two complexes are hypothesised to exchange their anions in a reversible reaction (Scheme 3.12) and exist in equilibrium with $PhPdS(dppp)^+$.[13] Due to the slow substitution by the acetate or iodide, the overall reaction is slower by a factor of 300 compared to monophosphines under identical temperatures and concentration of PhI and NEt_3.



Scheme 3.12 Oxidative addition step between PhI and the anionic complex generated from $Pd(OAc)_2$ and two equivalents of dppp.

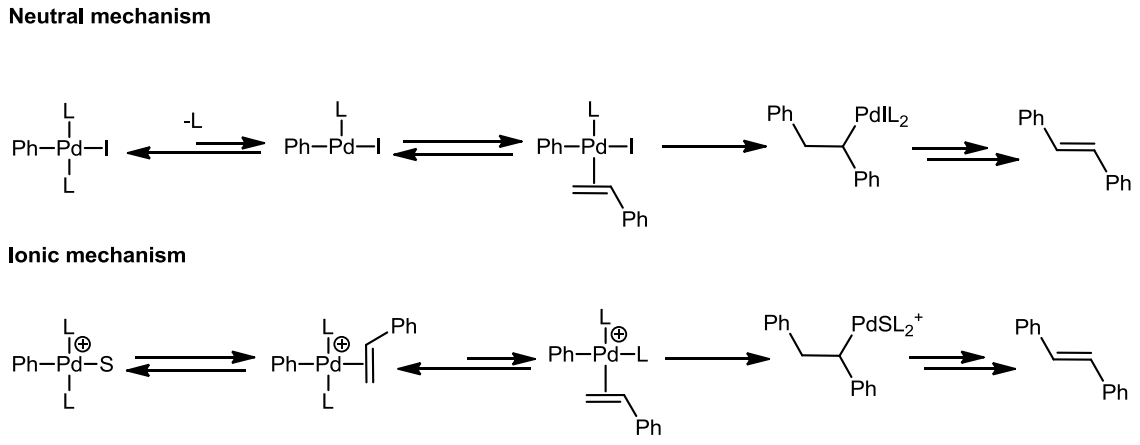
3.1.2.3 Complexation/Insertion

The migratory insertion process is the most important step in the Mizoroki-Heck cycle as it is crucial in the determination of the regio- and stereo chemistry of the products. The insertion reaction can occur in three ways. [15] The first case treats the organopallladium species as the nucleophile in which the organic moiety is a carbanion existing with a metal-based cation. The second possibility is the reverse situation wherein the alkene is the nucleophile which then attacks the electrophilic Pd species. The third and most likely pathway is a concerted four centre process wherein the bond breaking and new bond formation are synchronous (Scheme 3.13).



Scheme 3.13 Most likely pathway for the migratory insertion of the alkene.

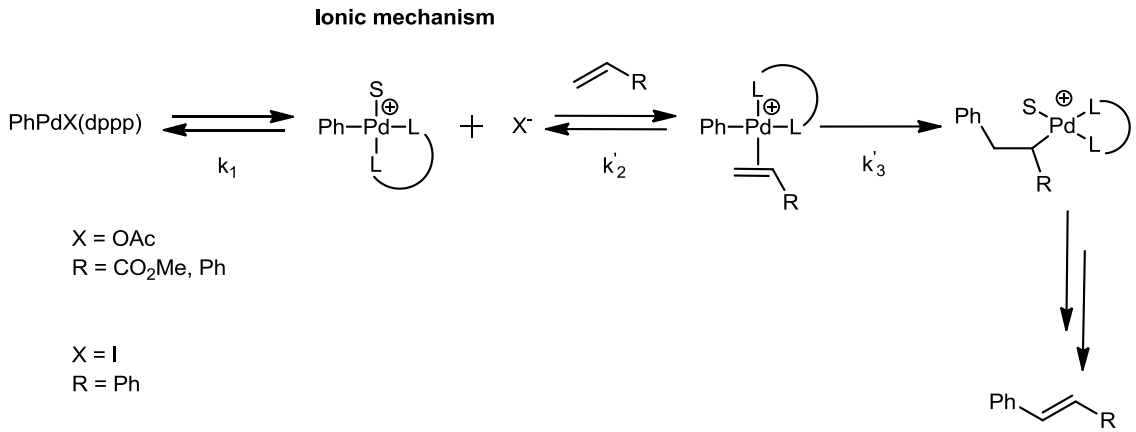
In order for the migratory insertion step to take place a co-ordination site on the metal must first be made available. For this to occur a ligand must disassociate from the palladium complex. Two different routes have been proposed depending on whether an L or X ligand deco-ordinates, known as the neutral or the ionic mechanism (Scheme 3.14). The neutral mechanism is initiated by the deco-ordination of a neutral L ligand and the ionic, deco-ordination of an anionic X^- ligand. The pathway favoured is dependent on both the ligands used, the nature of the substrate coupled being and is major factor in the determination of the product's regio-chemistry. The neutral mechanism is proposed to be more sensitive to steric factors, leading to a preferential migration of the aryl group onto the less substituted carbon of the alkene, favouring the synthesis of linear alkenes. The ionic mechanism is stated to be more sensitive to electronic factors, so it will favour the selective migration of the aryl moiety onto the most charge deficient carbon, which in some substrates (electron rich alkenes) would be the alpha carbon, leading to the generation of a branched alkene product.[17]



Scheme 3.14 Possible pathways for the co-ordination of the alkene.

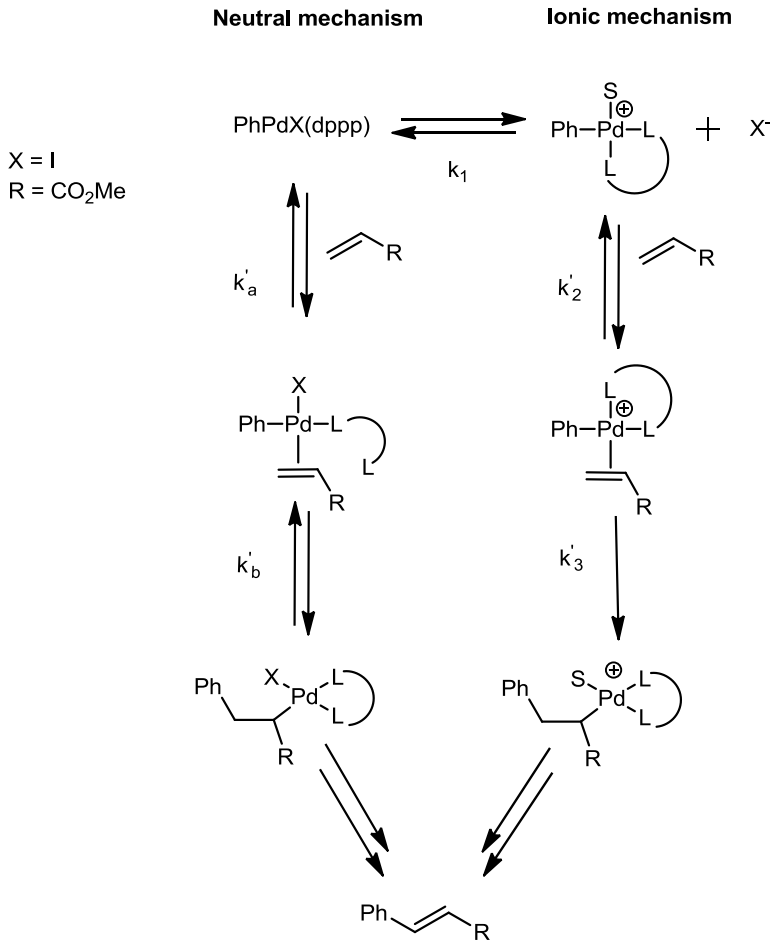
In the case when 3 equivalents of monophosphine PPh_3 and $Pd(OAc)_2$ are used, the species formed after the oxidative addition of phenyliodide are proposed to be *trans*-$PhPd(OAc)(PPh_3)_2$ and *trans*-$PhPdS(PPh_3)_2^+$, both existing in equilibrium. Reactivity studies between the two species revealed that the $PhPd(OAc)(PPh_3)_2$ complex reacts with styrene faster than *trans*-$PhPdS(PPh_3)_2^+$, revealing that in this case the neutral pathway is dominant.[12] This difference in rate was rationalised by both the faster dissociation of PPh_3 facilitated by the bidentate character of the acetate ligand and the insertion of the alkene being slowed in the ionic pathway by the need for an endergonic *trans/cis* isomerisation step.

As described above, Amatore, and Jutand postulated that when bisphosphine ligands such as dppp are used with $Pd(OAc)_2$, the species formed after the oxidative addition of phenyliodide are PhPdI(dppp), PhPd(OAc)(dppp) and the cationic species $PhPdS(dppp)^+$ which they exist in equilibrium with.[13] Consequently there are three potential candidates for the reaction with alkenes in this system, two neutral and one cationic. A kinetic study reported in 2007 on the reaction of isolated PhPdX(dppp) (X = I, OAc) with electron-deficient, neutral and electron rich alkenes in the absence of base revealed that the mechanism of reaction is substrate dependant with the majority of reactions proceeding via the ionic mechanism (Scheme 3.15).[18]



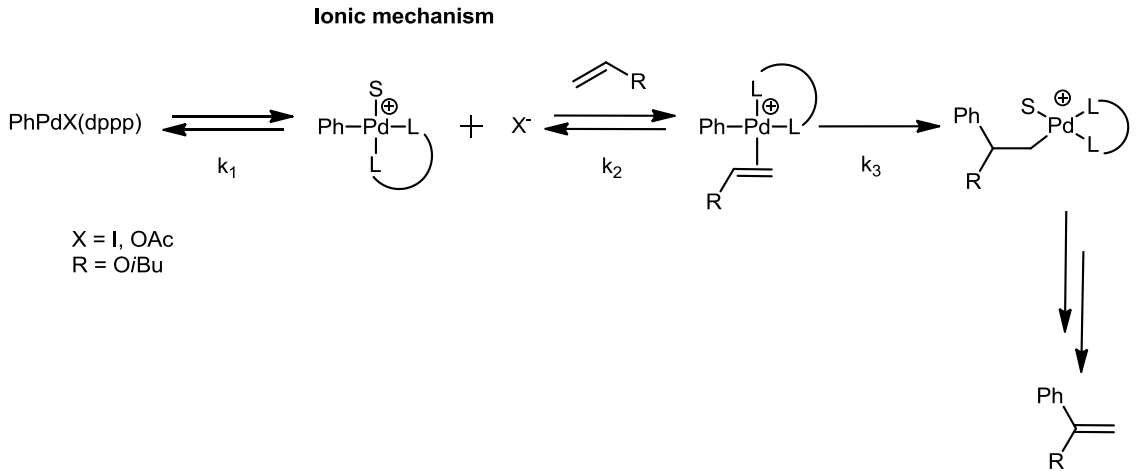
Scheme 3.15 Reactive species, preferred pathway and regiochemistry for insertion of neutral and electron-deficient alkenes from kinetic data. S = DMF.

Of the reactions tested only the reaction of PhPdI(dppp) with the electron deficient alkene methyl acrylate proceed by both neutral and ionic pathways (Scheme 3.16).



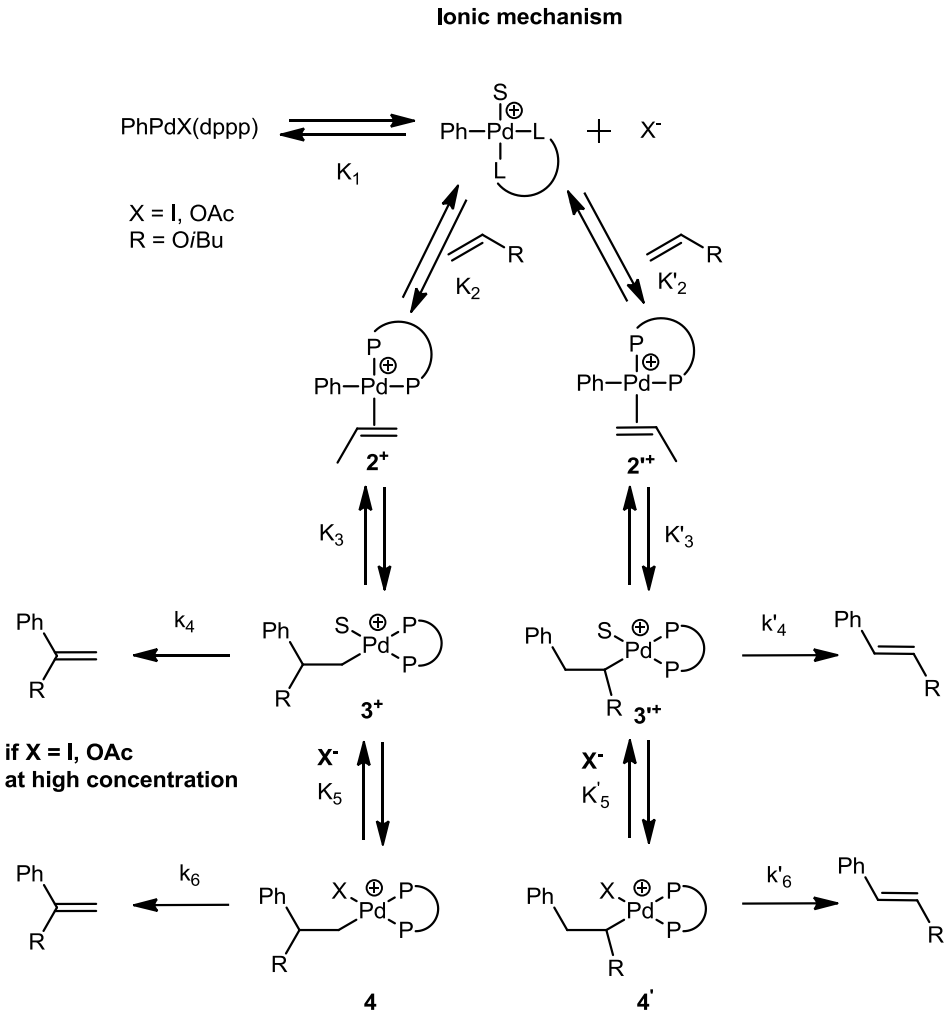
Scheme 3.16 Reactive species, preferred pathways and regiochemisty for insertion of electron-deficient alkene methyl acrylate when the palladium complex is PhPdI(dppp) from kinetic data. S = DMF.

Unsurprisingly, the stereochemistry of the products in these reactions was also found to be substrate dependant. The linear product was the only product in the reaction between PhPdX(dppp) (X = I, OAc) and methyl acrylate, and the major product for styrene (80% selectivity). However when the electron rich alkene isobutyl vinyl ether was used the major product was the branched alkene (Scheme 3.17).



Scheme 3.17 Reactive species, preferred pathway and regiochemistry for insertion of electron-rich alkene: isobutyl vinyl ether when the palladium complex is PhPdI(dppp) from kinetic data. S = DMF.

These mechanisms adequately explain the regioselectivity of the alkene products in relation to the electronic properties of the starting materials. However cannot explain the high dependence of regioselectivity on experimental conditions. For example, studies by Xiao and co-workers revealed that Mizoroki-Heck reactions using the same catalyst, the reactions between n-butylvinyl ether and aryl halides in DMF resulted in a mixture of branched and linear products,[19] whereas in ionic liquids exclusively the branched product was synthesised.[20] This observation was problematic for the proposed model, since whatever the reaction medium, in reactions with electron rich alkenes the reactive complex should be the same ($PhPdS(dppp)^+$) and so consequently so should the regioselectivity. This observation was rationalised in a mechanism proposed by Jutand and co-workers (Scheme 3.18).[18]



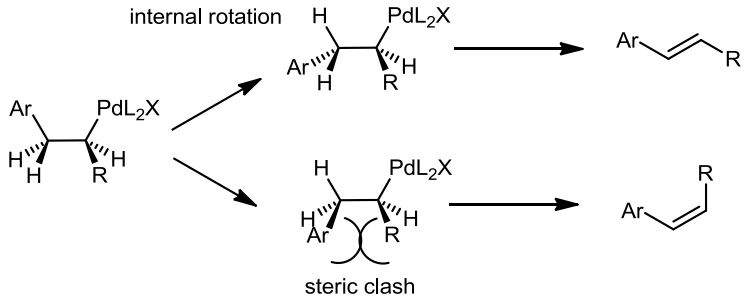
Scheme 3.18 Mechanism which rationalizes the dependence of regioselectivity with changing reaction conditions. S = solvent.

In this mechanism the insertion steps are reversible and in situations where the anion X^- (I, AcO^-) is present at high concentrations the cationic complexes **3**$^+$ and **3'**$^+$ can be reversibly quenched by the anion to form the neutral complexes **4** and **4'**. Therefore, taking an electron rich alkene as an example, the branched product will be formed as a major product when route **a** is faster than route **b** ($K_2K_3k_4$ » $K'_2K'_3k'_4$). However the linear product will be formed as the major product whenever route **b'** is faster than **a** ($K'_2K'_3K'_5k'_6[X^-]$ » $K_2K_3k_4$) or when route **b'** is faster than route **a'** ($K'_2K'_3K'_5k'_6$ » » $K_2K_3K_5k_6$ if $K_5k_6[X^-]$ » k_4). This mechanism can explain the results reported in the catalytic reaction of Xiao and co-workers because in DMF the halide ions released over the course of the reaction react with the cationic complexes **3+** and **3'+** giving complexes **4** and **4'** and resulting in the formation of a mixture of branched and linear products. In conditions with high ionic strength, such as ionic liquids, the reaction of the halides with

the cationic species is inhibited, slowing the formation of **4** and **4'** thus allowing the reaction to proceed by route **a**, resulting in the branched alkene as the major product.

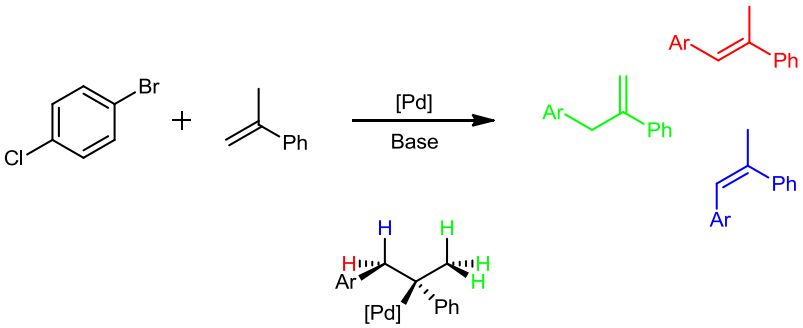
3.1.2.4 β-hydride Elimination

The next step in the cycle is the β-hydride elimination process, wherein a hydrogen atom is transferred to the palladium centre, the double bond is reformed and the sigma bond between the product and the palladium is broken. In order for this to occur an internal rotation must take place resulting in a β hydrogen *syn* to the palladium. Two conformations are possible for the *syn*-elimination leading to two possible products with (*E*) and (*Z*) stereochemistry. However in the case of mono substituted alkenes the conformer resulting in the (*Z*) is higher in energy due to steric interactions between the R and aryl groups and is therefore less favoured (Scheme 3.19). This accounts for the experimentally observed high stereoselectivity for (*E*)-alkenes in Mizoroki-Heck reactions.



Scheme 3.19 Stereoselectivity at the β-hydride elimination step.

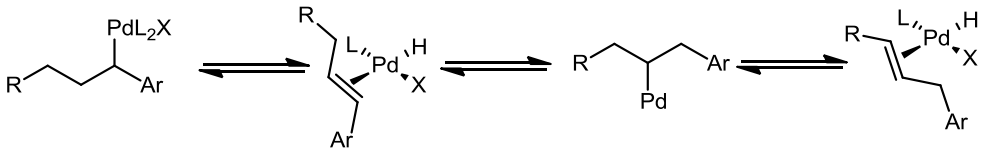
When 1,1 di-substituted alkenes are used as starting materials, the elimination step is complicated by the presence of more β hydrogens, thus the stereochemistry of the product is non-trivial to predict. For example, a study 1998 reported the Mizoroki Heck reaction between α-methyl styrene and aryl bromides resulted in a mixture of *(E)* and *(Z)* isomers and the terminal alkene (Scheme 3.20).[21] Interestingly the authors reported that the ratio of the products was affected by the base used, and hypothesised that this was a consequence of the weaker organic bases abstracting a hydrogen from the more acidic benzylic group in an apparent E2 type elimination. However a recent publication has suggested a more likely explanation derived from isomerisation during the reductive elimination process which will be discussed below.[15]



Scheme 3.20 Products in the reaction between α-methyl styrene and 1-bromo-4-chlorobenzene.

3.1.2.5 Reductive Elimination

After the β-hydride elimination step, the η^2 co-ordinated alkene product deco-ordinates leaving a Pd-H species, which can then undergo reductive elimination and re-enter the catalytic cycle. The reductive elimination step is proposed to be facilitated by the presence of the base which sequesters the HX generated. If the Pd-H species does not undergo the reductive elimination quickly then re-addition to the alkene is possible. This could result in the reformation of the pre β-hydride elimination species or the formation of new isomers (Scheme 3.21).



Scheme 3.21 Isomerisation of the Mizoroki-Heck product.

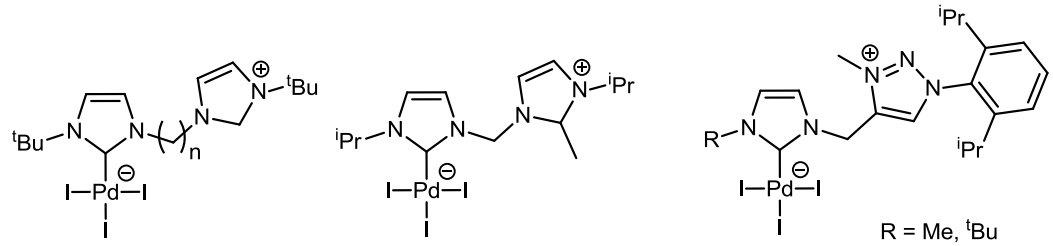
Since the strength of the base used would have an effect on the lifetime of the Pd-H species, Beletskaya and Cheprakov reasoned that this isomerisation was responsible for the observed effect that different bases had on the ratio of alkene products,[15] not the E2-type elimination suggested previously. They suggested that the hindered organic base would be less effective at facilitating the reductive elimination step, therefore allowing the system to equilibrate and result in the preferential formation of the most stable internal olefin products.

The research described above highlights the significance of anionic species in the activity of Pd complexes when used in Mizoroki-Heck reactions. With this in mind, when considering the design of new (N-heterocyclic carbene)-palladium complexes the development of species bearing a negative charge could be beneficial.

3.1.3 Anionic (N-Heterocyclic Carbene) palladium complexes

A review of the literature showed that the development of anionic N-heterocyclic carbene (NHC) bearing palladium complexes is quite limited. In this section the existing complexes are described. To the best of our knowledge, the use of these complexes in catalytic processes has not been reported.

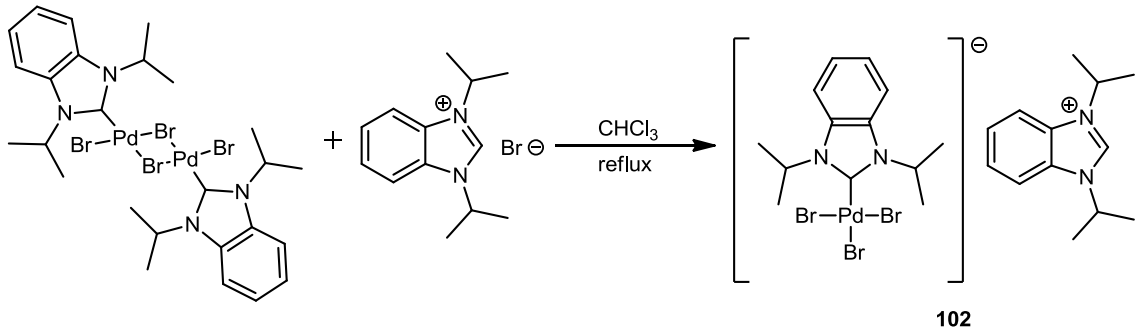
The first of these anionic NHC-Pd complexes was reported in 1999 by Herrman *et al*.[22] This complex consisted of an ionic palladium co-ordinated to two iodides, one acetate and an NHC with a pendant imidazolium substituent (**99**) (Figure 3.1). It was reported as an isolated intermediate in the formation of a sterically demanding bis(NHC) palladium complex. Later, when exploring the palladation of diimidazolium salts in the C4 position, Albrecht and co-workers reported an anionic NHC-Pd complex analogous to the species identified by Herrmann.[23] This complex contained a diimidazolium with isopropyl groups as N substituents and a functionalised C2 position on the pendant imidazolium (**100**) .
In 2012 Cowie *et al.* reported the synthesis of an anionic NHC-Pd complex bearing a triazolium N-substituent (**101**).[24] This complex was an isolated intermediate in the generation of dicarbene-bridged mixed metal complexes.



99 Herrman, 1999 **100** Albrecht, 2008 **101** Cowie, 2012

Figure 3.1 Examples of zwitterionic NHC-Pd complexes.

The first anionic NHC-Pd complex where the negative charge was not neutralised by a pendent substituent but instead by a detached cationic fragment was reported by Huynh and co-workers in 2006 (**102**).[25] This complex was formed by reaction of a Pd-dimer with the quaternary ammonium salt: 1,3-diisopropylbenzimidazolium bromide (Scheme 3.22). The authors suggested that this reaction may be reversible and hypothesized that this species may be present in the catalytic cycle when the Pd-dimer is used in cross-coupling reactions.

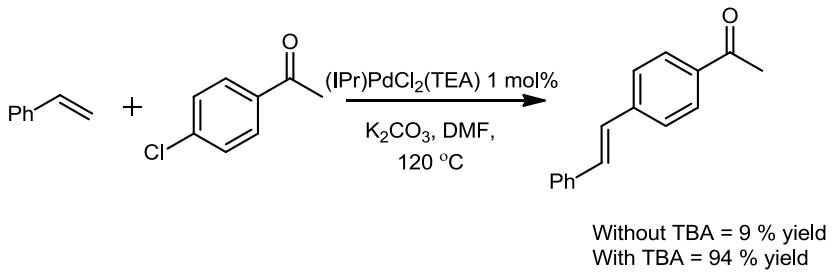


102

Scheme 3.22 Synthesis of [(NHC)$PdBr_3$][1,3-diisopropylbenzimidazlium] complex.

3.1.4 Investigation Aim

Recently in the Navarro group, we published the catalytic activity of (NHC)$PdCl_2$(TEA) complexes in Mizoroki-Heck reactions. In this publication the quaternary ammonium salt tetrabutylammonium bromide (TBAB) was used as an additive, as per successful conditions published in the literature by other groups. Interestingly it was observed that the absence of TBAB led to very poor conversion (Scheme 3.23). Taking into account the findings by Huynh and co-workers described above, it was theorised that maybe the (NHC) $PdCl_2$(TEA) complex was not the active precatalyst in these reactions as previously assumed, and instead it may be another species consisting of an anionic palladium with the TBA as a counter ion. The aim of this investigation was to test this hypothesis, isolate these new potential complexes and explore their reactivity in Mizoroki-Heck reactions.

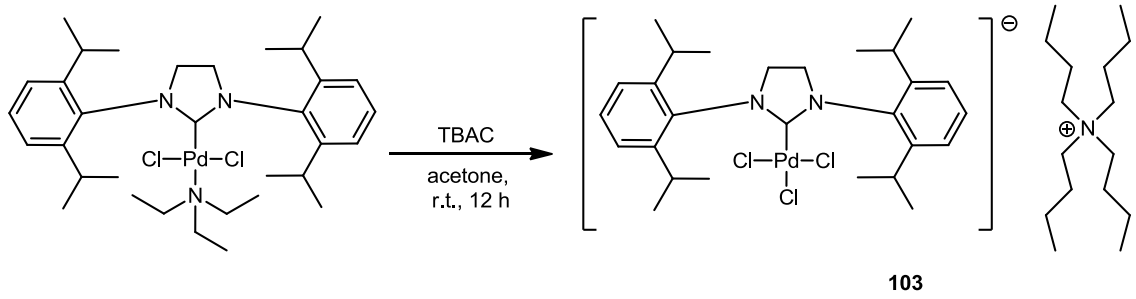


Scheme 3.23 Effect of TBA on conversion in the Mizoroki-Heck reaction catalysed by (IPr)$PdCl_2$(TEA).

3.2 Discussion and Results

3.2.1 Synthesis of [TBA][(NHC)$PdCl_3$] complexes

In order to ascertain if any reaction occurs between (NHC)$PdCl_2$(TEA) and a quaternary ammonium salt, complex (SIPr)$PdCl_2$(TEA) was stirred at room temperature with tetrbutylammonium chloride (TBAC) in dry acetone for 5 hours. TBAC was selected as a model quaternary ammonium salt over TBAB in order to simplify the characterisation of the product complex with respect to potential *cis-trans* isomerisation. The reaction led to the formation of a novel ionic complex [TBA][(SIPr)$PdCl_3$] (**103)** in a 88% yield (Scheme 3.24).



103

Scheme 3.24 Synthesis of [TBA][(SIPr)$PdCl_3$].

When the reaction time was extended to 12 h the reaction proceeded in a quantitative fashion. This new complex was fully characterised by ^{1}H, ^{13}C NMR spectroscopy and elemental analysis, with crystals suitable for X-ray diffraction grown from a slow evaporation of a concentrated solution of acetone and hexane. X-ray analysis revealed the complex adopted the expected square planar geometry with the Pd-Cl bond *trans* to the NHC longer than the other two Pd-Cl bonds. The shortest separation distance in the solid

state between the cationic quaternized nitrogen and a chlorine on the anionic palladium complex was measured to be 4.62 Å (Figure 3.2).

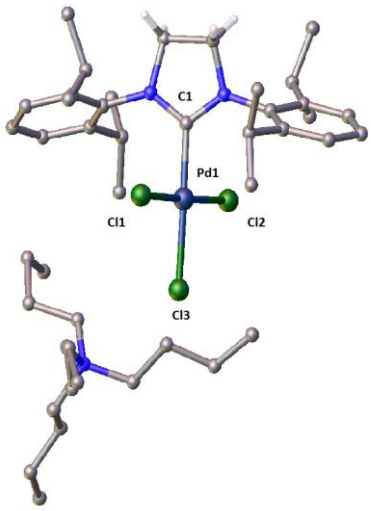
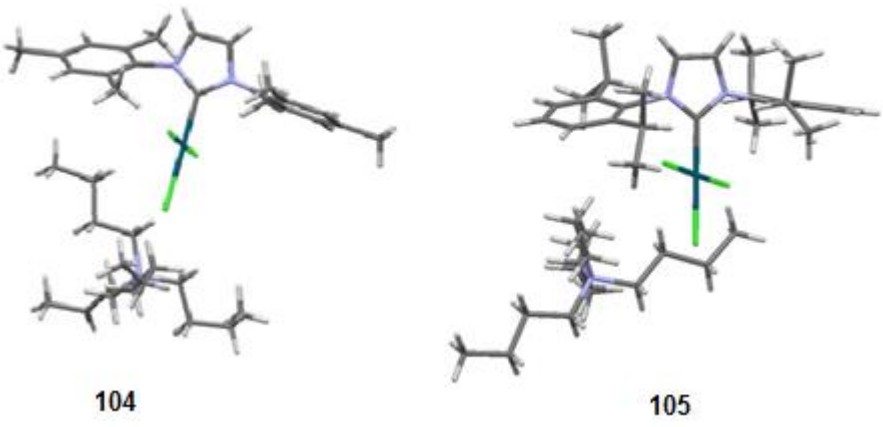
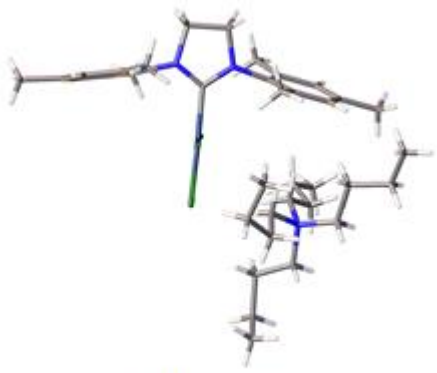


Figure 3.2 Crystal structure of [TBA][(SIPr)$PdCl_3$] Hydrogen atoms are omitted for clarity except those in the backbone of the NHC. Selected bonds (Å) and angles (deg): C1−Pd1: 1.959(2); Pd1−Cl2: 2.3770(7); Pd1−Cl1: 2.3020(6); Pd1−Cl3: 2.3080(6); C1−Pd1−Cl1: 89.89(6); C1−Pd1− Cl3: 88.61(6)

The reaction with TBAC was also carried out with (IPr), (IMes) and (SIMes)$PdCl_2$(TEA) complexes respectively. In each case the corresponding [TBA][(NHC)$PdCl_3$] complex was formed in excellent yields (**104**,**105**, **106**). The same structural motifs observed with the [TBA][(SIPr)$PdCl_3$] complex were observed in the IPr, IMes, and SIMes derivatives (Figure 3.3). Attempts to prepare these complexes directly by reacting TBAC with their respective dimers, thus removing an additional reaction step, proved unsuccessful.





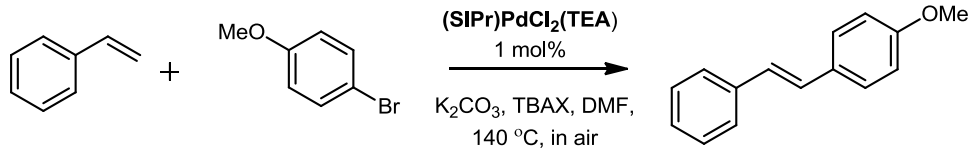
106

Figure 3.3 Crystal structures of [TBA][(IMes)$PdCl_3$] [TBA][(IPr)$PdCl_3$] and [TBA][(SIMes)$PdCl_3$].

3.2.2 Catalyst optimisation

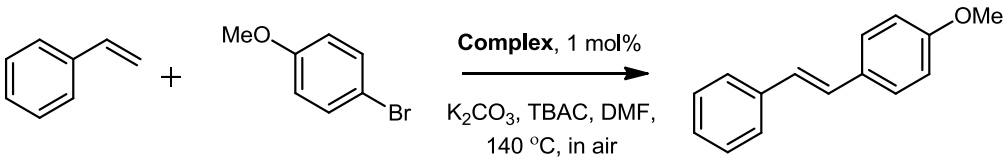
The protocol developed for the synthesis of the novel [TBA][(SIPr)$PdCl_3$] complex proved that conversion of the (SIPr)$PdCl_2$(TEA) species to this complex in the presence of TBAC is possible. Before any conclusions on the identity of the active species in the original protocol could be made, we reasoned that the effect of changing the halide from bromine to chlorine in the quaternary salt should be determined. To that end the activity of (SIPr)$PdCl_2$(TEA) in the coupling of 4-Br-anisole and styrene with TBAB and TBAC as an additive was compared (Table 3.1). The results showed that changing the quaternary salt from TBAB to TBAC had a negligible effect on catalyst activity, therefore any observed difference in activity between the two procedures should be a result of the palladium complexes only.

Table 3.1 Effect of changing the quaternary ammonium salt on the activity of (SIPr)$PdCl_2$(TEA) in the Mizoroki-Heck coupling of 4-Br-anisole and styrene.



Entry	Quaternary Ammonium Salt	Yield (%)	Time (min)
1	TBAB	92	60
2	TBAC	93	75

The next step in testing the hypothesis that these anionic species were the real catalyst precursors was to compare the activity of (NHC)$PdCl_2$(TEA) and [TBA][(NHC)$PdCl_3$] in Mizoroki-Heck reactions. [TBA][(SIPr)$PdCl_3$] was selected, as (SIPr)$PdCl_2$(TEA) was reported to be the most active complex tested in the previous study. The coupling of 4-Br-anisole and styrene was used as the model reaction, following standard Jeffery conditions.[26] The results showed that the two complexes had almost identical activity, suggesting that the active catalyst was the same in each case (Figure 3.4).

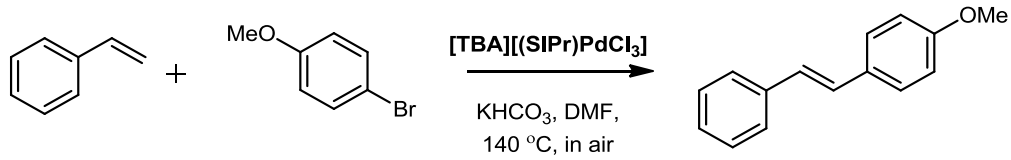


Entry	Complex (1 mol%)	Yield (%)	Time (min)
1	(SIPr)$PdCl_2$(TEA)	93	75
2	[TBA][(SIPr)$PdCl_3$]	91	75

Figure 3.4 Comparison of catalytic activity between NHC-palladium complexes, (SIPr)$PdCl_2$(TEA) and [TBA][(SIPr)$PdCl_3$] in Mizoroki-Heck couplings.

Running the same coupling reaction between 4-Bromoanisole and styrene with [TBA][(SIPr)$PdCl_3$] in the absence of a quaternary salt resulted in no change in either product yield or reaction time, suggesting that the role of the ammonium salt in the early protocol was exclusively to facilitate the formation of the [TBA][(SIPr)$PdCl_3$] complex. Changing the base from K_2CO_3 to the less basic $KHCO_3$ increased the catalyst's activity, allowing the catalyst loading to be reduced by half without diminishing the yield of the desired product (Table 3.2). Having developed an optimised protocol for the [TBA][(SIPr)$PdCl_3$] catalysed coupling of 4-Bromoanisole with styrene, we then proceeded to test this system with other substrates.

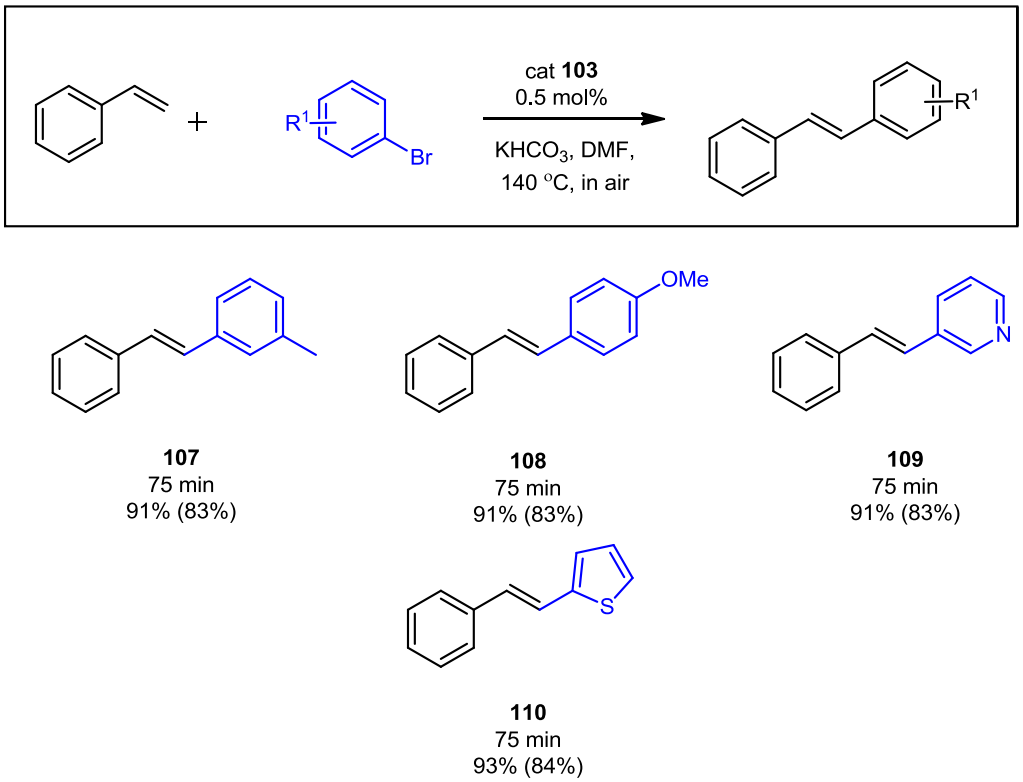
Table 3.2 Optimised protocol for Mizoroki Heck couplings catalysed by [TBA][(SIPr)$PdCl_3$].



Entry	Catalyst loading (mol%)	Yield (%)	Time (min)
1	1	94	30
2	0.5	97	75

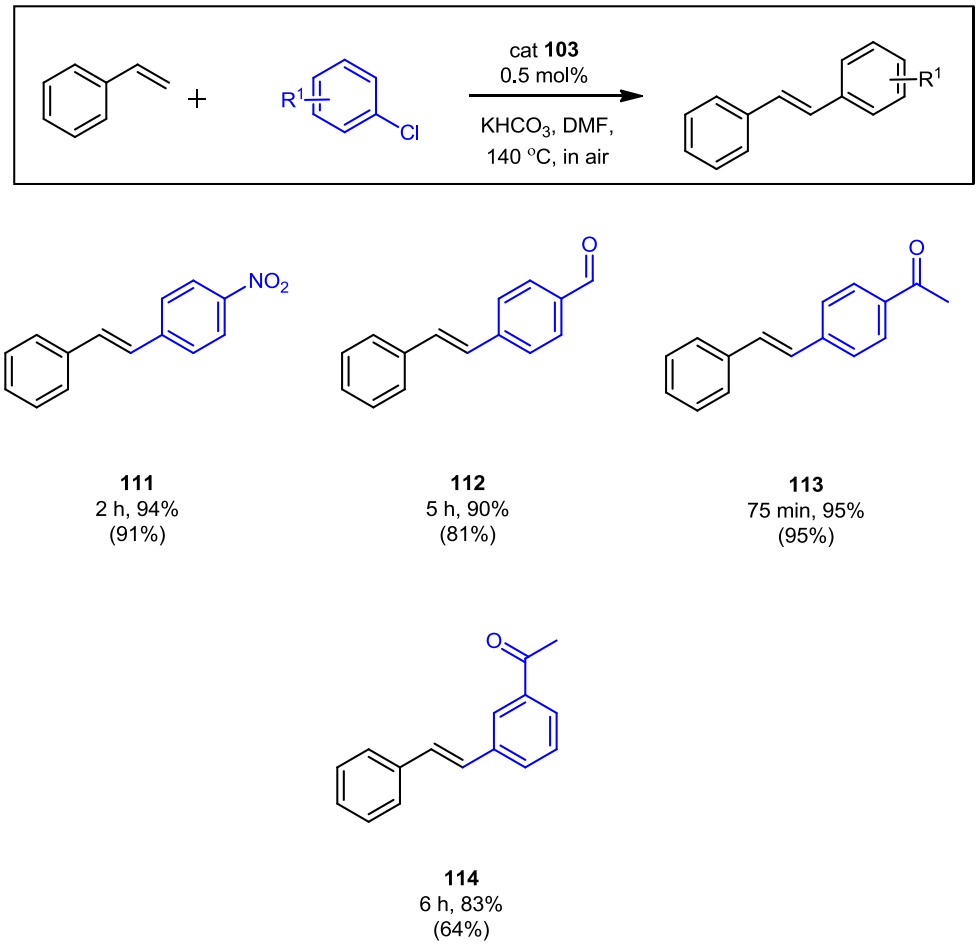
3.2.3 Scope of reactivity

Under these optimised conditions [TBA][(SIPr)$PdCl_3$] was found to catalyse the coupling of styrene to a number of unactivated aryl bromides in excellent yields and short reaction time (Scheme 3.25). The protocol was shown to be tolerant to electron rich aryl groups as well as heteroaromatic species. In all cases the yields obtained were equal or higher than those reported for the (SIPr)$PdCl_2$(TEA)/TBAB protocol with comparable reaction times.



Scheme 3.25 Mizoroki-Heck coupling of aryl bromides with styrene. Yields of the (SIPr)$PdCl_2$(TEA)/TBAB protocol are shown in parentheses.

When considering the coupling of activated chlorides, the same pattern of improvement when compared to the original procedure was observed (Scheme 3.26). As with the (SIPr)$PdCl_2$(TEA)/TBAB protocol the *meta*-substituted aryl chloride gave a lower yield compared to the *para* isomer. Unsurprisingly, the reaction times needed for the coupling of chlorides were longer than those for the bromides.

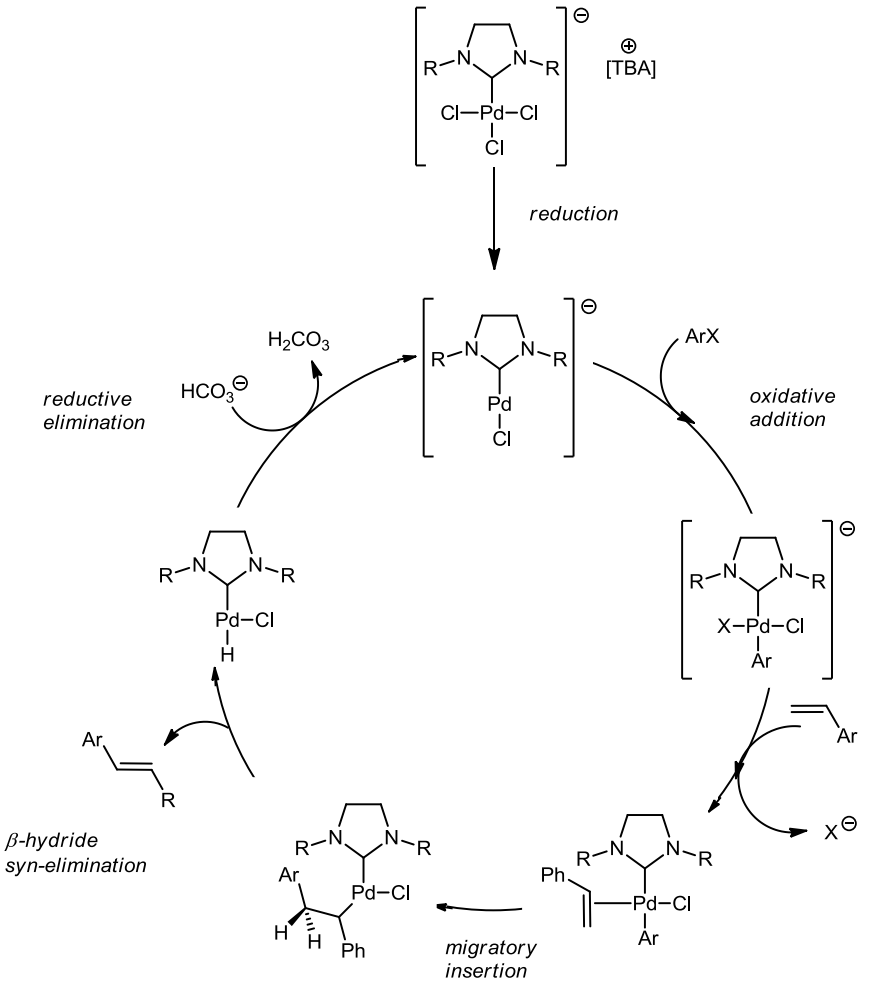


Scheme 3.26 Mizoroki-Heck coupling of aryl chlorides with styrene. Yields of (SIPr)PDCl$_2$(TEA)/TBAB protocol are shown in parentheses.

3.2.4 Mechanism

We proposed that the [TBA][(NHC)PdCl$_3$] complex catalyses Mizoroki-Heck reactions via an Amotore-Jutand mechanistic pathway (Scheme 3.27), in which the active species is the 14-electron anionic species [(NHC)Pd^{0}Cl]$^-$ This active species is generated by the *in situ* reduction of the anionic precatalyst. The identity of the reducing agent in this protocol is ambiguous but could be the alkene coupling partner, an amine derived from the thermal decomposition of the TBA counter ion or DMF. This active species then undergoes oxidative addition with the aryl halide to form [Ar(NHC)PdClX]$^-$. After deco-ordination of X$^-$ it reacts with styrene, first via η^2-co-ordination, then migratory insertion of the Ar group followed by β-hydride *syn* elimination resulting in the formation of the coupled product. Once the alkene deco-ordinates, the active anionic Pd^0 species is regenerated by the abstraction of the proton from the resultant palladium hydride complex

by the base. The validity of this proposed mechanism was explored computationally by our collaborators using DFT calculations and was found to be plausible, having a smooth downhill relative energy profile.[27]



Scheme 3.27 Proposed mechanism for the Mizoroki-Heck reaction catalysed by [TBA][(SIPr)$PdCl_3$].

3.3 Conclusion

The aim of this chapter was to test the hypothesis that the (NHC)$PdCl_2$(TEA) complex may not be the active precatalyst in the protocol reported by Navarro *et al*. as previously assumed, but may instead be another species consisting of an anionic palladium with the TBA as a counter ion. This hypothesis has been proved true and has led to the synthesis and identification of a novel class of anionic palladium NHC complexes: [TBA][(NHC)$PdCl_3$]. The catalytic activity of the SIPr bearing derivative in the Mizoroki-Heck coupling of aryl halides to styrene has been explored and a plausible Amotore-Jutand type mechanism has been proposed.

3.4 Experimental

General Considerations

All reagents and solvents were purchased from commercial suppliers and used without further purification unless noted. (NHC)$PdCl_2$(TEA) complexes were prepared following literature procedure.

Synthesis of [(SIPr)$PdCl_3$][TBA] (103)

A reaction vial was loaded with a magnetic stirring bar, (SIPr)$PdCl_2$(TEA) (502 mg, 0.75 mmol), tetrabutylammonium chloride (231 g, 0.83 mmol) and 2 mL of dry acetone. The solution was allowed to stir at room temperature overnight. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (613 mg, 97%). ^{1}H NMR (500 MHz, C_6D_6); δ 7.28-7.20 (m, 6H), 3.88-3.79 (m, 4H), 3.55 (s, 4H), 3.16-3.09 (m, 8H), 1.77 (d, J = 6.5 Hz, 12H), 1.46-1.37 (m, 8H), 1.33−1.25 (m, 8H), 1.21 (d, J = 6.5 Hz, 12H), 0.95 (t, J = 7.3 Hz, 12H). ^{13}C {^{1}H} NMR (100 MHz, C_6D6): δ 190.4, 147.6 , 136.5 , 128.5, 124.7, 58.2, 53.5, 27.4, 26.6, 23.9, 25.2, 19.1, 13.9. Anal. Calcd for $C_{43}H_{74}Cl_3N_3Pd$: C, 61.06; H, 8.82; N, 4.97. Found: C, 60.94; H, 8.77; N, 4.94.

Synthesis of [(IMes)$PdCl_3$][TBA] (104)

A reaction vial was loaded with a magnetic stirring bar, (IMes)$PdCl_2$(TEA) (200 mg, 0.344mmol), tetrabutylammonium chloride (105 mg, 0.377 mmol) and 2 mL of dry benzene. The solution was allowed to stir at room temperature overnight. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (256 mg, 98%).^{1}H NMR (500 MHz, C_6D_6) δ 6.88 (s, 4H), 6.14 (s, 2H), 3.22 – 3.12 (m, 8H), 2.56 (s, 12H), 2.24 (s, 6H), 1.50 (m, 8H), 1.37 (m, 1H), 1.00 (t, J = 7.2 Hz, 12H).^{13}C NMR (100 MHz, C_6D_6): δ 157.5, 137.9, 136.7, 136.3, 128.9, 122.9, 58.5, 24.1, 20.9, 19.8, 19.5, 13.8. . Anal. Calcd

for $C_{37}H_{60}N_3Pd$: C, 58.50; H, 7.96; N, 5.53. Found: C, 58.29; H, 8.06; N, 5.39. CCDC number 1473488.

Synthesis of [(IPr)$PdCl_3$][TBA] (105)

A reaction vial was loaded with a magnetic stirring bar, (IPr)$PdCl_2$(TEA) (200 mg, 300mmol), tetrabutylammonium chloride (105 mg, 0.377 mmol) and 2 mL of dry benzene. The solution was allowed to stir at room temperature of 12h. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (243mg 96%).^{1}H NMR (500 MHz, C_6D_6) δ 7.39 – 7.24 (m, 6H), 6.60 (s, 2H), 3.54 (p, *J* = 6.7 Hz, 4H), 3.26 – 3.13 (m, 8H), 1.69 (d, *J* = 6.5 Hz, 12H), 1.48 (m, 8H), 1.35 (m, 8H), 1.11 (d, *J* = 6.9 Hz, 12H), 1.00 (t, *J* = 7.3 Hz, 12H). ^{13}C {^{1}H} NMR (100 MHz, C_6D_6): *δ* 160.7, 147.8, 134.5 , 129.1, 124.1, 58.3, 53.3, 28.6, 26.6, 24.7, 24.0, 19.7, 13.9. Anal. Calcd for $C_{43}H_{74}Cl_3N_3Pd$: C, 61.20; H, 8.60; N, 4.98. Found: C, 61.44; H, 8.61; N, 5.01.

Synthesis of [(SIMes)$PdCl_3$][TBA] (106)

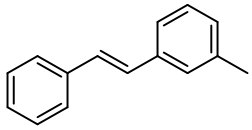
A reaction vial was loaded with a magnetic stirring bar, (SIMes)$PdCl_2$(TEA) (200 mg, 0.342mmol), tetrabutylammonium chloride (105 mg, 0.377 mmol) and 2 mL of dry benzene. The solution was allowed to stir at room temperature overnight. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (253mg, 97%). ^{1}H NMR (500 MHz, C_6D_6): δ 6.89 (s, 4H), 3.20 (s, 4H), 3.16 (m, 8H), 2.73 (s, 12H), 2.22 (s, 6H), 1.49 (m, 8H), 1.40 – 1.31 (m, 8H), 1.00 (t, *J* = 7.3 Hz, 12H). ^{13}C NMR (100 MHz, C_6D_6): δ 188.1, 137.5, 137.1, 136.2, 129.2, 58.5, 50.3, 24.1, 20.9, 19.8, 19.7, 13.8. Anal. Calcd for $C_{37}H_{62}Cl_3N_3Pd$: C, 58.34; H, 8.20; N, 5.52. Found: C, 58.44 H, 8.27; N, 5.61.

General Procedure for Heck reactions

A 4 mL screw-capped vial equipped with a magnetic stirring bar was charged with potassium carbonate (1 mmol), TBAB (0.5 mmol), aryl halide (0.5 mmol), complex, anhydrous DMF (1 mL) and the alkene (0.55 mmol). The vial was sealed with a screw-cap fitted with a septum and the reaction mixture allowed to stir at 140 °C and monitored by GC. When the reaction was complete or there was no further increase in conversion,

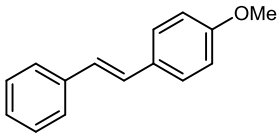
it was cooled down to room temperature, poured into water (10 mL) and extracted with Et_2O or EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The resultant solution was concentrated onto celite under reduced pressure for purification by column chromatography. All reported yields are an average of two runs.

(*E*)-1-Methyl-3-styrylbenzene.[28] **(107)**



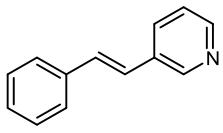
Product obtained as a white solid (176 mg, 91%). Eluent: 40/60 petroleum ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, J = 6.9 Hz, 2H), 7.55 – 7.47 (m, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.3 – 7.20 (m, 3H), 2.54 (s, 3H).

(*E*)-1-Methoxy-4-styrylbenzene.[29] **(108)**



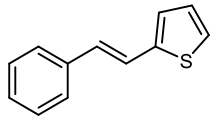
Product obtained as a white solid (204 mg, 97%). Gradient eluent: 0 : 1 to 2 : 8. EtOAc : 40/60 petroleum ether. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52 – 7.44 (m, 3H), 7.35 (t, J = 7.7 Hz, 2H), 7.39 – 7.20 (m, 2H), 7.08 (d, J = 16.3 Hz, 1H), 6.99 (d, J = 16.3 Hz, 1H), 6.94 – 6.89 (m, 2H), 3.84 (s, 3H).

(E)-3-Styrylpyridine.[29] **(109)**



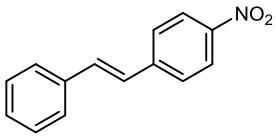
Product obtained as a pale yellow solid (165 mg 91%). Eluent gradient: 5 : 95 to 40 : 60. 40/60 petroleum ether : Et_2O. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.74 (br.s 1H), 8.50 (m, 1H), 7.85 – 7.82 (m, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.34 – 7.218 (m, 2H), 7.18 (d, J = 16.4 Hz, 1H), 7.08 (d, J = 16.4 Hz, 1H).

(E)-2-Styrylthiophene.[28] **(110)**



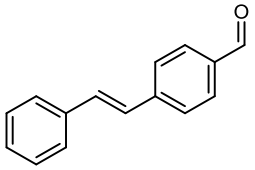
Product obtained as a yellow solid (173 mg, 93%). Eluent gradient: 0 : 1 to 5 : 95 Et_2O : 40/60 petroleum ether. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.46 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.31 – 7.19 (m, 3H), 7.13-7.08 (m, 1H), 7.06-7.01 (m, 1H), 6.96 (d, J = 16.1 Hz, 1H).

4-Nitrostilbene.[30] **(111)**



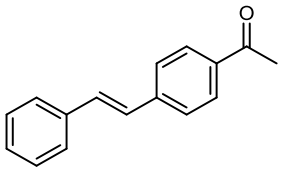
Product obtained as a yellow solid (200 mg, 94%). Eluent: 99 : 1 40/60 petroleum ether : Et_2O. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.23 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 7.4 Hz, 2H), 7.45 – 7.30 (m, 3H), 7.29 (d, J = 16.3 Hz, 1H), 7.16 (d, J = 16.3 Hz, 1H).

4-Styrylbenzaldehyde.[31] **(112)**



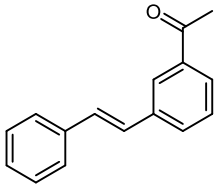
Product obtained as a yellow solid (187 mg, 90%).Eluent: 95:5 40/60 petroleum ether : Et_2O. ^1H NMR (500 MHz, $CDCl_3$) δ = 10.00 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 7.9 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 16.3 Hz, 1H), 7.15 (d, J = 16.3 Hz, 1H).

1-(4-Styrylphenyl)ethanone..[29] **(113)**



Product obtained as a pale yellow solid (211 mg, 95%). Eluent gradient: 5 : 95 to 20 : 80. Et_2O : 40/60 petroleum ether. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.39 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 16.3 Hz, 1H), 7.14 (d, J = 16.3 Hz, 1H), 2.61 (s, 3H).

1-(3-Styrylphenyl)ethanone.[32] **(114)**



Product obtained as a pale yellow solid (184 mg, 83%). Eluent gradient: 10 : 90 to 35 : 65. Et_2O : 40/60 petroleum ether. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.10 (s, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 2H), 7.29 (t, J = 7.3 Hz, 1H), 7.20 (d, J = 16.4 Hz, 1H), 7.14 (d, J = 16.3 Hz, 1H), 2.65 (s, 3H).

3.5 References

(1) Uni, V.; Champaign, U.; Mathews, S.; Delcamp, J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270–11271.

(2) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526.

(3) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531–5534.

(4) Fitton, P.; Johnson, M. P.; McKeon, J. E. *Chem. Commun.* **1968**, 1, 6.

(5) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581–581.

(6) Nolley, J. P.; Heck, R. F. *J. Org. Chem.* **1972**, *37*, 2320–2322.

(7) Mori, K.; Mizoroki, T.; Ozaki, A. *Bull Chem Soc Jpn*. 1973, 46, 1505–1508.

(8) Dieck, H. ; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133–1136.

(9) Heck, R. F. *J. Am. Chem. Soc.* **1969**, *91*, 6707–6714.

(10) Reetz, M. T.; Westermann, E. *Angew. Chemie - Int. Ed.* **2000**, *39*, 165–168.

(11) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009–3013.

(12) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818–1826.

(13) Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics* **2001**, *20*, 3241–3249.

(14) D'Orlyé, F.; Jutand, A. *Tetrahedron* **2005**, *61*, 9670–9678.

(15) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

(16) Amatore, C.; Came, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605–5614.

(17) Von Schenck, H.; Åkermark, B.; Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503–3508.

(18) Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Organometallics*. **2007**, *26*, 1757–1761.

(19) Mo, J.; Xiao, J. *Angew. Chemie - Int. Ed.* **2006**, *45*, 4152–4157.

(20) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751–760.

(21) Beller, M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, *1998*, 29–35.

(22) Herrmann, W. A.; Gardiner, M. G. *Organometallics*. **1999**, 18, 4082–4089.

(23) Heckenroth, M.; Kluser, E.; Neels, A.; Albrecht, M. *Dalton Trans.* **2008**, 44, 6242–6249.

(24) Zamora, M. T.; Ferguson, M. J.; McDonald, R.; Cowie, M. *Organometallics* **2012**, *31*, 5463–5477.

(25) Huynh, H. V.; Han, Y.; Ho, J. H. H.; Tan, G. K. *Organometallics* **2006**, *25*, 3267–3274.

(26) Jeffery, T. *Chem. Commun.* **1984**, 1287–1289.

(27) Guest, D.; Menezes Da Silva, V. H.; De Lima Batista, A. P.; Roe, S. M.; Braga, A. C.; Navarro, O. *Organometallics* **2015**, *34*, 2463–2470.

(28) Lee, J.-Y.; Cheng, P.-Y.; Tsai, Y.-H.; Lin, G.-R.; Liu, S.-P.; Sie, M.-H.; Lee, H. M. *Organometallics* **2010**, *29*, 3901–3911.

(29) Tessin, U. I.; Bantreil, X.; Songis, O.; Cazin, C. S. J. *Eur. J. Inorg. Chem.* **2013**, 2013, 2007–2010.

(30) Gao, T.; Jin, A.-P.; Shao, L.-X. *Beilstein J. Org. Chem.* **2012**, *8*, 1916–1919.

(31) Sawoo, S.; Srimani, D.; Dutta, P.; Lahiri, R.; Sarkar, A. *Tetrahedron* **2009**, *65*, 4367– 4374.

(32) Wang, W.; Yang, Q.; Zhou, R.; Fu, H.-Y.; Li, R.-X.; Chen, H.; Li, X.-J. *J. Organomet. Chem.* **2012**, *697*, 1–5.

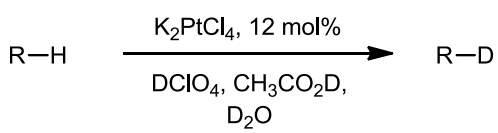
4 Synthesis of [(NHC)PdCl$_2$OAc][TBA] complexes and activity in acetoxylation reactions.

4.1 Background

The selective functionalisation of C-H bonds is an attractive prospect in many areas of chemistry. Initially most research was focused on the conversion of light alkenes to alcohols, methane in particular as its conversion to methanol would allow its transportation without the expense and danger associated with liquefying it.[1] Although a commercially viable methodology to achieve this goal remains elusive, the knowledge obtained from these studies with regards to the mechanisms by which a C-H bond can be cleaved using transition-metal compounds,[2] has led to a paradigm shift from the standard logic in synthetic organic chemistry. Instead of depending on the arrangement of selective reactions at functional groups, reactions can also occur by controlled functionalisation of specific C-H bonds. The classical organic chemistry route for the cleavage of non-activated C-H bonds is by radical based processes. These systems are often quite unselective because although there is some preference between tertiary, secondary and primary C-H bonds, distinction between C-H of the same type is low.[3] Through the advances made in organometallic chemistry, C-H functionalisation is now a viable strategy in the synthesis of complex molecules, and has been utilised in the preparation of numerus natural products.

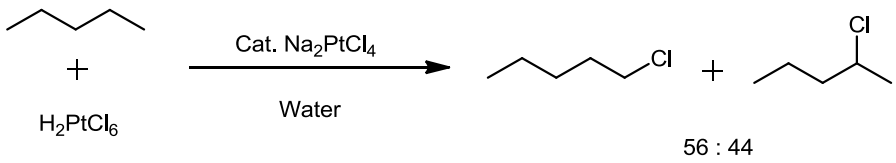
4.1.1 Origins of transition metal catalysed C-H functionalisation

Some of the earliest evidence that transition metal complexes could be utilised for the catalytic selective cleavage of C-H bonds of alkanes was reported by Shilov and co-workers in 1969 and the early 1970s.[4] They showed that Hydrogen/Deuterium exchange would occur between alkanes and a deuterated acid in the presence of a platinum(II) catalyst (Scheme 4.1).



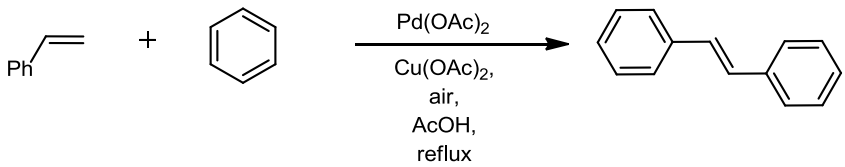
Scheme 4.1 Platinum catalysed H/D exchange.

Further work by Shilov reported that the halogenation of alkenes by platinum(II) catalysts was possible, when $[Pt(IV)Cl_6]^{2-}$ was used as an oxidant (Scheme 4.2). These reactions resulted in the formation of a mixture of alkyl halides, with higher selectivity for the linear product. This was significant, as it contrasted with standard organic reactions which react via radicals or carbonium ions and therefore favour the most highly substituted position. These reactions showed that transition metal catalysts could affect the site selectivity of C-H bond activation. The high cost of the needed Pt(IV) oxidant rendered the commercial application of this procedure impractical however, these results motivated a large number of groups to research the development of transition metal complexes for the selective activation of C-H bonds in alkanes.



Scheme 4.2 Regioselectivity in the halogenation of pentane catalysed by Na_2PtCl_4.

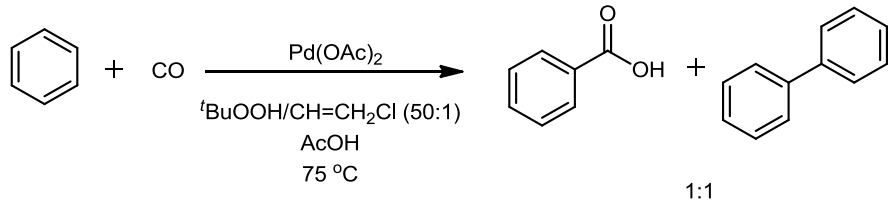
Simultaneously to Shilov's publications, Fujiwara and co-workers reported the aromatic substitution of a styrene-palladium chloride complex in the presence of acetic acid.[5] Further research by the same group a year later reported that the aromatic substitution of styrene would still take place when the styrene-palladium complex was replaced with $Pd(OAc)_2$ and styrene.[6] Soon after, a methodology which made this process catalytic with respect to palladium by the inclusion of oxidants such as cupric or silver acetate and air was developed.[7] This oxidative coupling of an arene with an alkene became known as the Fujiwara reaction (Scheme 4.3).



Scheme 4.3 C-H bond functionalisation via the Fujiwara reaction.

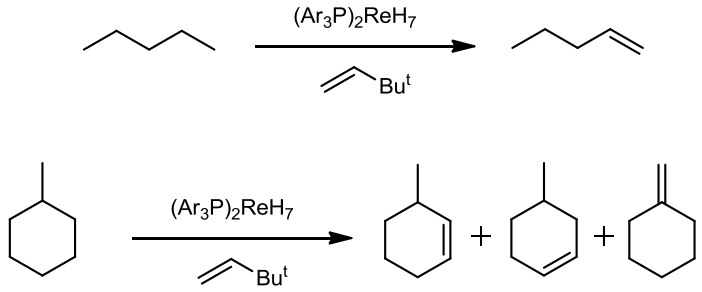
In 1980 Fujiwara and co-workers studied the carboxylation of arenes. Palladium acetate was found to promote the direct formation of aryl carboxylic acids from arenes with

carbon monoxide (15 atm),[8] experimental data suggested the reaction was electrophilic in nature and could be made catalytic with respect to palladium by the addition of *t*-BuOOH and allyl halides (Scheme 4.4).[9]



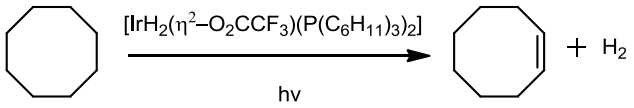
Scheme 4.4 Carboxylation of benzene catalysed by Palladium acetate.

In the 1980s the earliest research into the heterogeneous dehydrogenation of alkanes to form alkenes by transition metal complexes was pioneered concurrently by the two research groups of Felkin and Crabtree. Felkin and co-workers developed a number of rhenium heptahydrides with the general formula $(Ar_3P)_2ReH_7$. These complexes, when used in conjuction with 3,3-dimethylbutene as a hydrogen acceptor, were found to convert n-pentane into pent-1-ene, [10] and cycloalkanes into cycloalkenes (Scheme 4.5).[11]



Scheme 4.5 Dehydrogenation of alkanes and cycloalkanes by $(Ar_3P)_2ReH_7$.

Crabtree and co-workers reported the preparation of a number of iridium based complexes which selectively dehydrogenate linear and cyclic alkanes to their corresponding alkenes, either thermally or photochemically (254 nm). When photochemical irradiation was used, a sacrificial hydrogen acceptor was not required (Scheme 4.6).[12] Both groups provided evidence to support the hypothesis that the catalysts were reacting homogeneously.



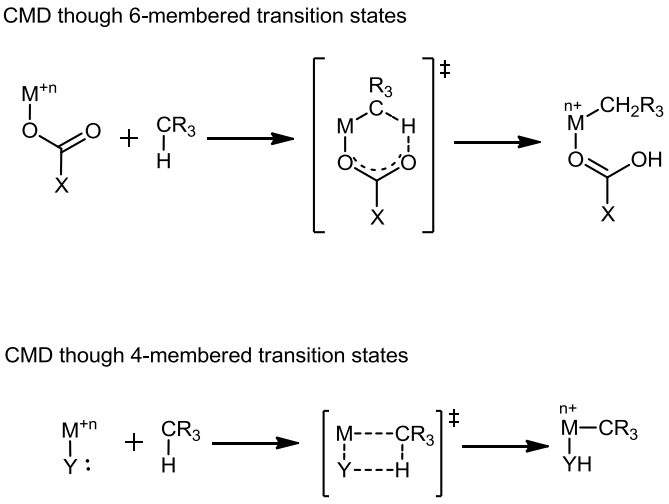
Scheme 4.6 Photochemical activation of cyclo-octane by iridium complexes.

4.1.2 Mechanisms of C-H activation by transition metal complexes

As interest in C-H functionalisation catalysed by transition metals has grown, a number of mechanisms by which the C-H bond is cleaved have been identified.

4.1.3 Concerted metalation-deprotonation (CMD)

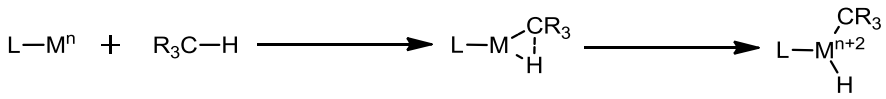
This process involves the base assisted concerted cleavage of two sigma bonds and the formation of two new sigma bonds (Scheme 4.7). It has been named concerted metalation deprotonation (CMD) by Fagnou *et al.*[13] or ambiphilic metal ligand activation (AMLA) by Macgregor and co-workers.[14] C-H cleavage via either 6-membered or 4-membered transition states are the most common for this pathway, although larger seven membered systems have been proposed. On the surface the CMD mechanism via a 4-membered transition state may seem identical to sigma bond metathesis, however computational analysis suggests that these two pathways are distinctly different when the orbitals involved are compared. In the case of CMD the Y-H bond formed is not based on the same orbital as the breaking M-Y bond, which is the case in sigma bond metathesis. Another difference between the two mechanisms is the nature of the ligand involved: in the case of CMD, Y is typically a heteroatom with a lone pair, while in sigma bond metathesis the ligand is normally an alkyl or aryl group. Typically the CMD mechanism is an inner sphere (vide supra) process with the basic moiety co-ordinated to the metal, yet recently outer sphere cases have been discovered.[15]



Scheme 4.7 C-H activation via CMD. X= alkyl, OH, O^- Y = OR, NR_2

4.1.4 Oxidative addition

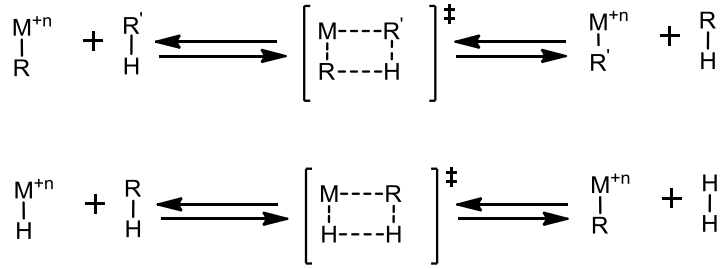
The oxidative addition of a C-H results in the breaking of one sigma bond and the formation of two new sigma bonds to the metal centre; this process increases the formal oxidation state of the metal by two and proceeds via a three-membered transition state (Scheme 4.8). The Oxidative addition pathway is typically observed in complexes containing low valent, electron rich metals such as Re, Fe, Ru, Ir, Pt.[14]



Scheme 4.8 C-H activation via Oxidative addition.

4.1.5 Sigma-bond metathesis

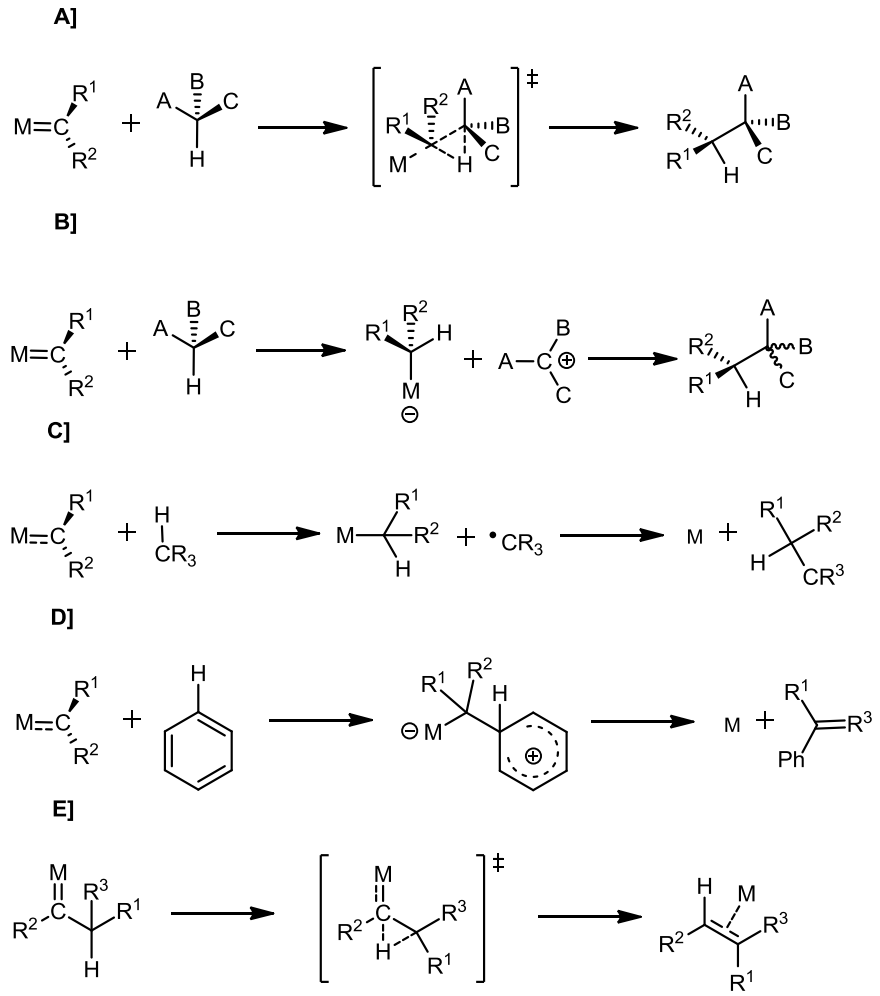
When complexes containing early transition metals with d^0 electronic configuration and alkyl or hydride ligands are used, activation via sigma bond metathesis is possible (Scheme 4.9). This mechanism is commonly observed for group 3 metals, though some examples involving groups 4 and 5 are known.[16] The C-H group is proposed to act as an electron donor in an interaction with the electron deficient metal centre leading to the formation of a 4-membered transition state.[17]



Scheme 4.9 C-H activation via sigma bond metathesis. R and R' are most commonly both alkyl groups.

4.1.6 Transition metal carbene mediated C-H activation

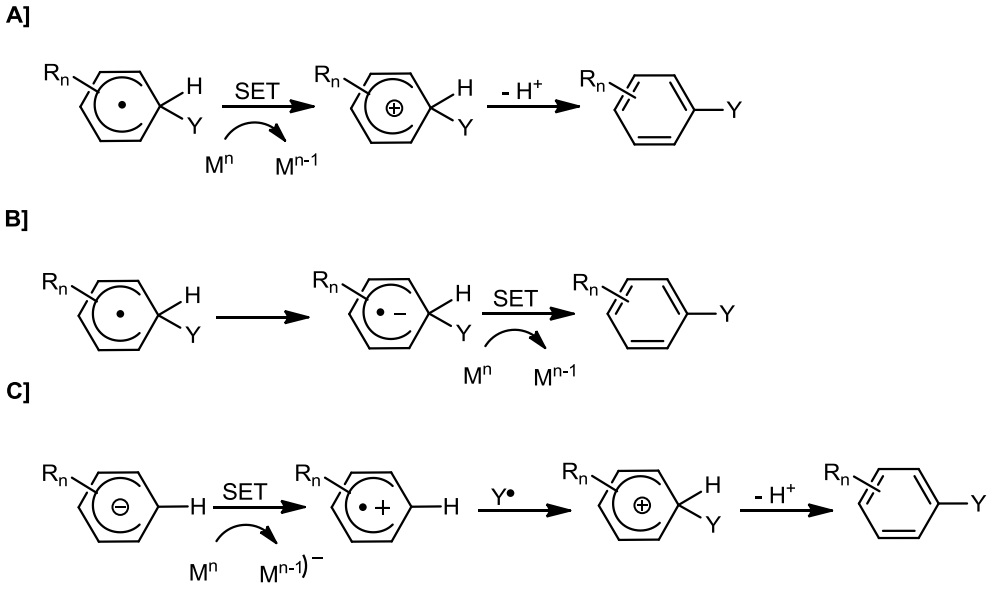
In the current literature, five possible mechanisms for transition metal carbene mediated C-H activation have been reported. The most likely pathway for any given reaction is dependent on many factors and since the formation of the metal-carbene bond is commonly the rate limiting step in these reactions, gaining experimental mechanistic information after this step is difficult. Due to this the majority of mechanistic insight is often gained through computational studies. Intrinsic to all these mechanisms is the insertion of the carbene unit into the alkyl C-H bond occurs without the formation of a metal-carbon bond from the substrate. The most common pathway is the insertion of the carbene unit into an sp^3 hybridised C-H bond; this process can be concerted, via a three membered transition state (Scheme 4.10A) or stepwise (Scheme 4.10B) depending on the strength of activation on the C-H bond or how well the carbenium intermediate can be stabilised.[18] A third much less common pathway for the activation of sp^3 hybridised C-H bonds involves the generation of a carbenoid and the use of a non-innocent ligand acting as a one electron oxidant, leading to the abstraction of a hydrogen atom (Scheme 4.10C).[19] Recently a mechanism for transition metal carbene C-H insertion into a sp^2 hybridised system was proposed. This process suggested a nucleophilic attack of the aryl group at an *in situ* generated carbeniod, followed by an intramolecular hydrogen transfer (Scheme 4.10D).[20] The final possible mechanism is the formation of alkenes from alkanes by the inducement of a 1,2-H shift (Scheme 4.10E).[21]



Scheme 4.10 C-H activation via transition metal carbene mediation.

4.1.7 Single electron transfer-involved deprotonation

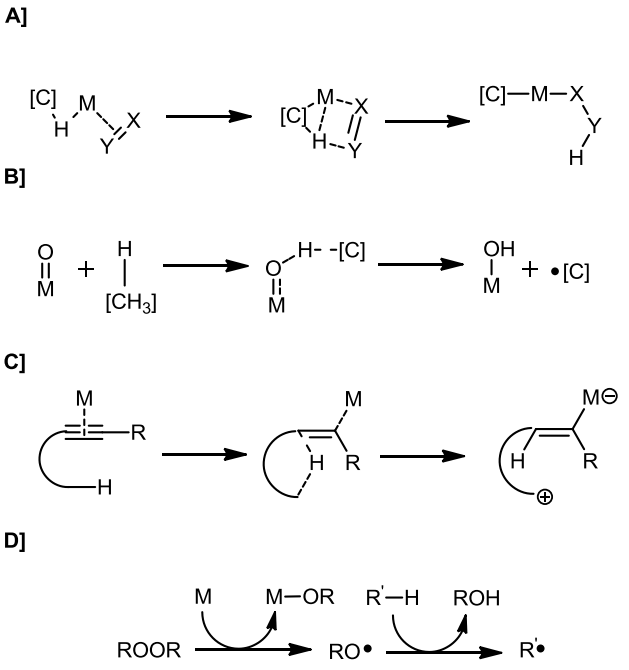
Single electron transfer (SET)-involved deprotonations are mechanistic pathways primarily proposed for the functionalisation of aromatic C-H bonds. In these cases the metal complexes are proposed to act as single electron catalysts reacting with radical intermediates. The SET process can occur either before deprotonation, generating a cationic intermediates (Scheme 4.11A), or after via a radical anion (Scheme 4.11B). Recently a more complex mechanism has been proposed wherein the SET of anionic intermediates is followed by atom (or ligand) transfer, then deprotonation (Scheme 4.11C).[22,23]



Scheme 4.11 C-H activation via SET-involved deprotonation**.**

4.1.8 Hydrogen atom transfer

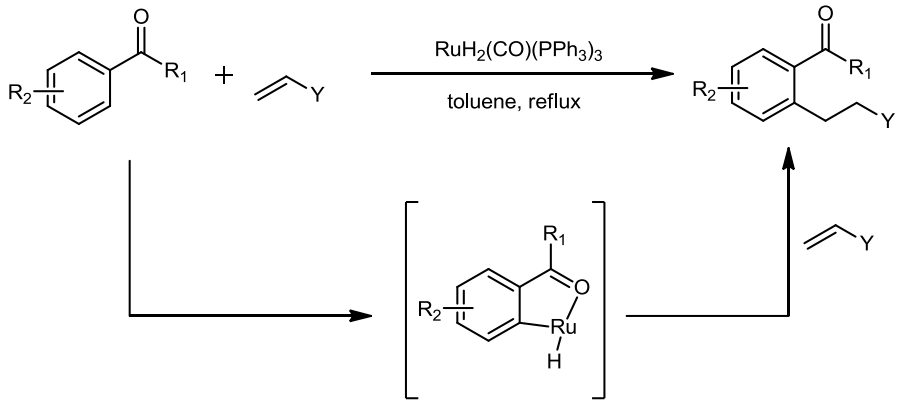
Currently four mechanisms of hydrogen transfer have been proposed. The first is known as ligand-to-ligand transfer (LLHT) and is a combination of oxidative addition and migratory insertion. This process leads to the formal transfer of hydrogen, without the formation of a hydride intermediate (Scheme 4.12A).[24] The second mechanism specific to transition metal-oxo complexes is the abstraction of hydrogen, leading to the formation of alkyl radicals (Scheme 4.12B). These radical species can then rapidly react with the resulting hydroxo ligand in a "rebound" step, forming the alcohol product.[25] The third method is nucleophilic carbon to carbon hydrogen transfer (Scheme 4.12C) in which electron deficient transition metal complexes activate unsaturated compounds.[26] This process is known as hydride transfer or hydrogen shift, in this case the catalyst is proposed to be behaving as a Lewis acid and does not change oxidation state. The final type of hydrogen atom transfer is known as transition metal induced hydrogen abstraction. In these cases, the metal catalyst reacts with an oxidant to generate oxygen radicals which then abstract the hydrogen atom (Scheme 4.12D).[27]



Scheme 4.12 C-H activation via hydrogen atom transfer.

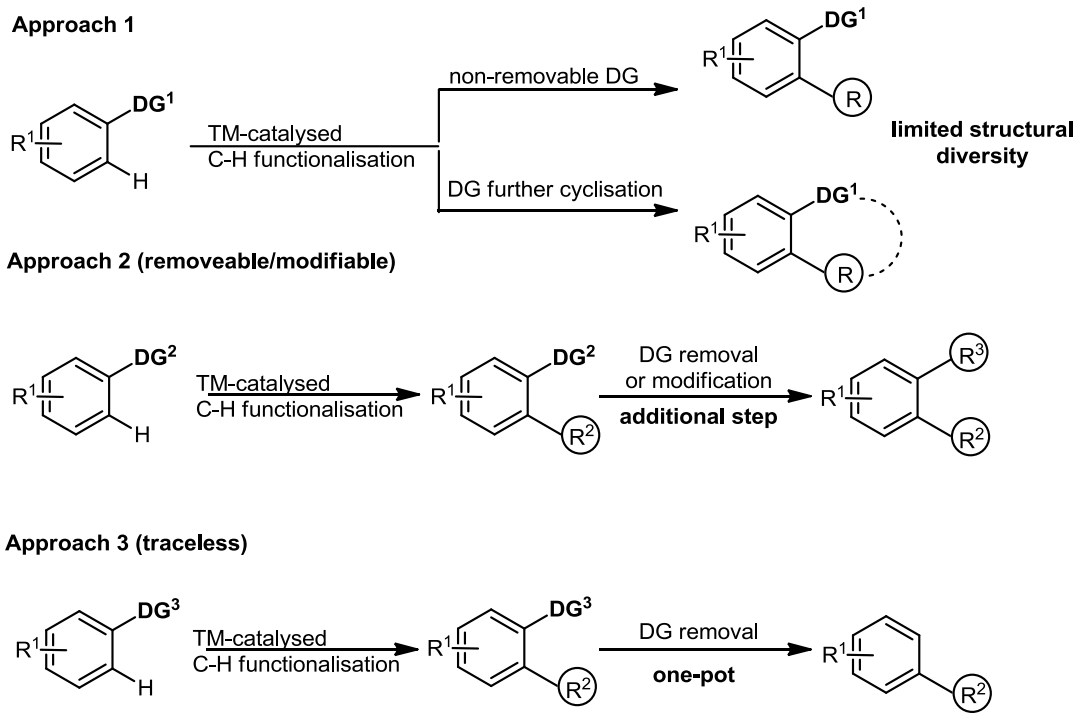
4.1.9 Directed C-H functionalisation of aromatic compounds

Before C-H functionalisation methods could find broad utility in the field of synthetic chemistry, methods to address the critical requirement of site selectively had to be developed, as most compounds contain multiple C-H bonds of the same type. The most successful approach has been the use of directing groups, first reported in the pioneering work of Murai and co-workers in the 90s.[28] In this work, the carbonyl functionality of aromatic ketones was used to direct their *ortho*-alkylation with olefins, catalysed by a ruthenium complex co-ordinating to the metal centre (Scheme 4.13).



Scheme 4.13 Catalytic C-H activation using a directing group by Murai and co-workers.

Since their seminal work, the development of directing group strategies has become extremely active, with various directing groups such as heterocycles, amines, alcohols and carbonyl-related functional groups reported in the literature. These systems can be categorised into three different approaches (Scheme 4.14).

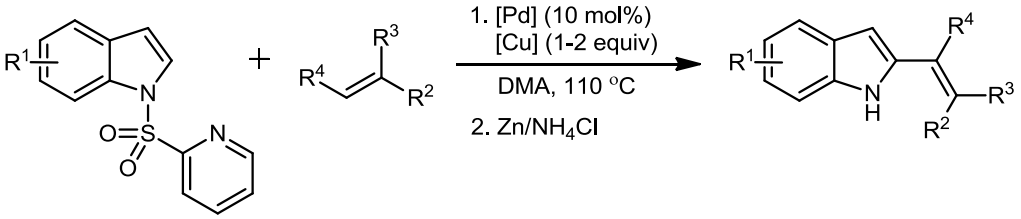


Scheme 4.14 Three approaches to transition metal catalysed C-H activation using directing groups.

Approach 1 was the earliest methodology, in which after C-H functionalisation the directing group either remains part of the product or undergoes cyclisation to form a heterocycle. In these cases the structural diversity of the products are limited, as the directing group cannot be conveniently removed or undergo versatile transformation.

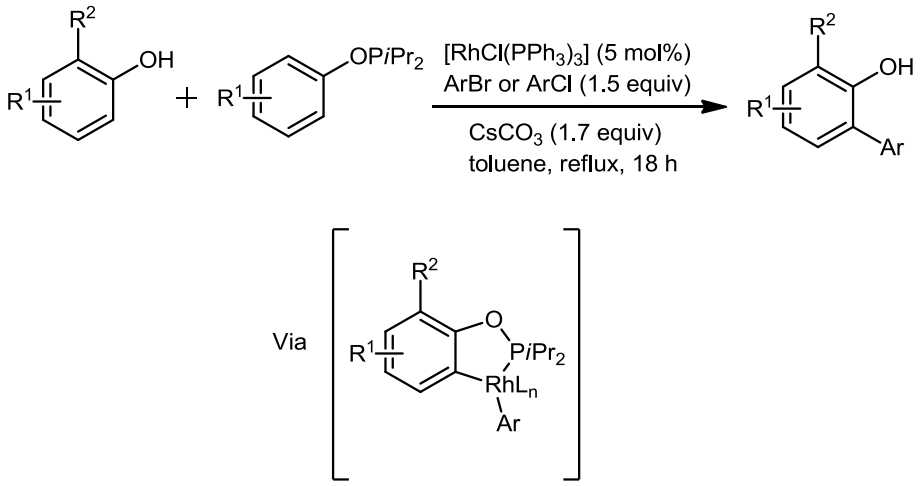
These simple motifs are still useful when exploring the activity of new potential catalysts. These directing groups consist of a strongly co-ordinating nitrogen-containing functionality such as pyridine.[29]

In approach 2 the directing group can be readily removed or further modified post C-H functionalisation by additional steps to yield the functionalised product.[30] An excellent example of this kind of strategy is the use of N-(2-pyridyl)sulfonyl as a removable directing group in the palladium catalysed alkenylation of indoles and pyrroles by Carretero and co-workers in 2009 (Scheme 4.15).[31] After functionalisation, the removal of the directing group was readily achieved by reductive cleavage with Zn or Mg to yield the 2-alkenyl or alkyl-substituted indoles and pyrroles, respectively.



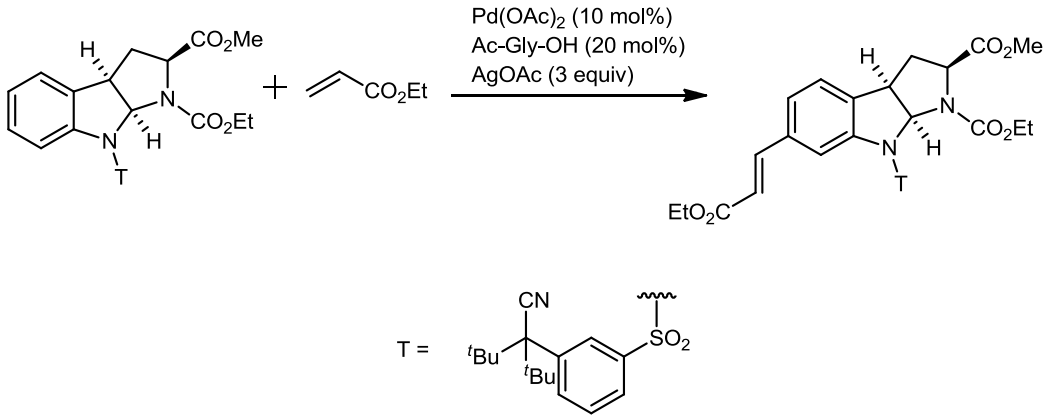
Scheme 4.15 Alkenylation of indoles using a removable directing group.

Approach 3 describes the newest strategy in which the C-H functionalisation of the substrate and removal of the directing group can be carried out in one-pot. In some cases the introduction procedure can also be done in the same pot; these types of directing groups are classified as traceless.[32] A recent example of this strategy is the first catalytic intermolecular one-pot synthesis of *ortho*-arylated phenols developed by Bedford and co-workers.[33] In this procedure a phosphinite cocatalyst acts as a tether between the phenol group and the Rh catalyst, forming a five-membered metallacycle, which then undergoes subsequent reductive elimination, regenerating the active Rh catalyst and liberating 2-arylated dialkylphoshinite. This compound then undergoes catalytic transesterification with the starting phenol to regenerate the co-catalyst and release the 2-arylated phenol product (Scheme 4.16).

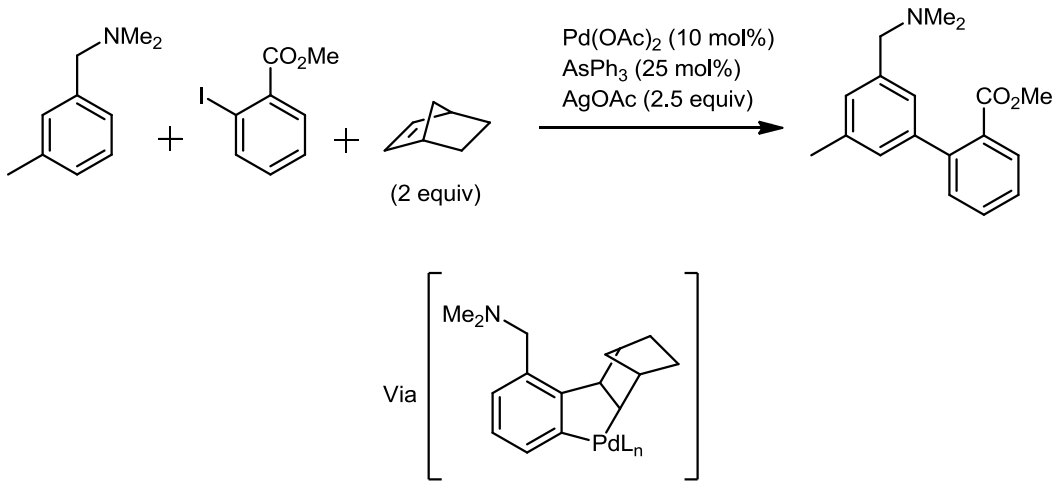


Scheme 4.16 Catalytic ortho-arylation of phenols using traceless a directing group.

While *ortho* selective arene functionalisation has been the most extensively developed area of research, in recent years there has been a growing interest in designing new directing groups which will enable C-H functionalisation at other positions.[34] Notable strategies include the development of U-shaped templates for the *meta* selective functionalisation of 2,3-dihydroindoles, designed in a collaborative project between the Yu and Movassaghi groups (Scheme 4.17).[35] Also the *meta* selective arylation through the combining of an *ortho* directing group with a norbornene-induced organometallic relay, demonstrated by Dong and co-workers (Scheme 4.18).[36]



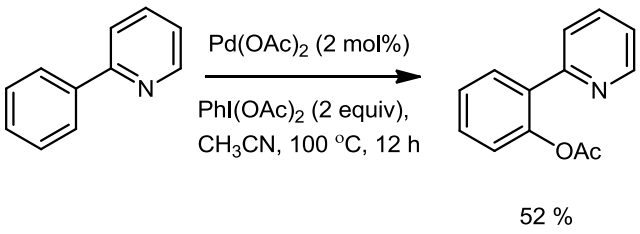
Scheme 4.17 *meta*-Selective C-H functionalisation using U shaped directing group T.



Scheme 4.18 *meta*-Selective C-H functionalisation using an *ortho* directing group in conjunction with norbornene.

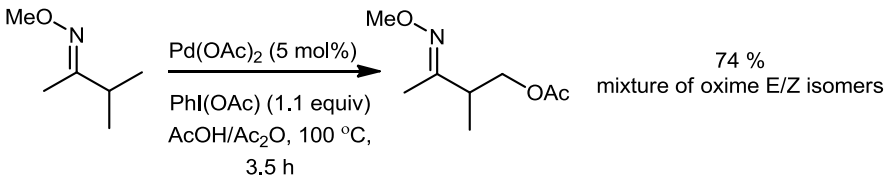
4.1.10 Palladium catalysed acetoxylation reactions

In 1966 the first Pd-catalysed aromatic C-H acetoxylation reaction was reported.[37] Later oxidants such as $K_2Cr_2O_7$, $Pb(OAc)_4$ and N_2O_2 in acetic acid were found to aid the preparation of phenyl acetate from benzene under Pd catalysis.[38] In 1996 Crabtree and co-workers identified $PhI(OAc)_2$ as a cheap, mild and effective terminal oxidant for the acetoxylation of arenes, which functions simultaneously as both an oxidant and a source of acetate.[39] Encouraged by the successes in the use of directing groups for other C-H functionalisation reactions described above, the groups of Sanford and Yu pioneered directed C-H acetoxylation reactions employing $Pd(OAc)_2$ as the catalyst. In 2004 Sanford and co-workers reported the first chelate-directed oxidation of sp^2 and sp^3 bonds using $PhI(OAc)_2$ as the oxidant and pyridine as the directing group (Scheme 4.19),[40] and the range of potential substrates was expanded further in a follow up publication in 2005.[41]



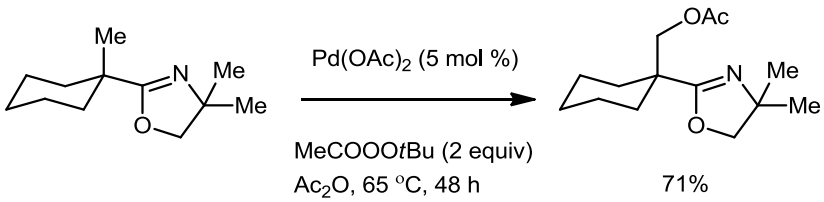
Scheme 4.19 Acetoxylation of 2-phenylpyridine catalysed by $Pd(OAc)_2$ with $PhI(OAc)_2$.

Sanford and co-workers also reported the oxidation of unactivated sp^3 C-H bonds, using *O*-methyl oxime as a directing group (Scheme 4.20).[42]



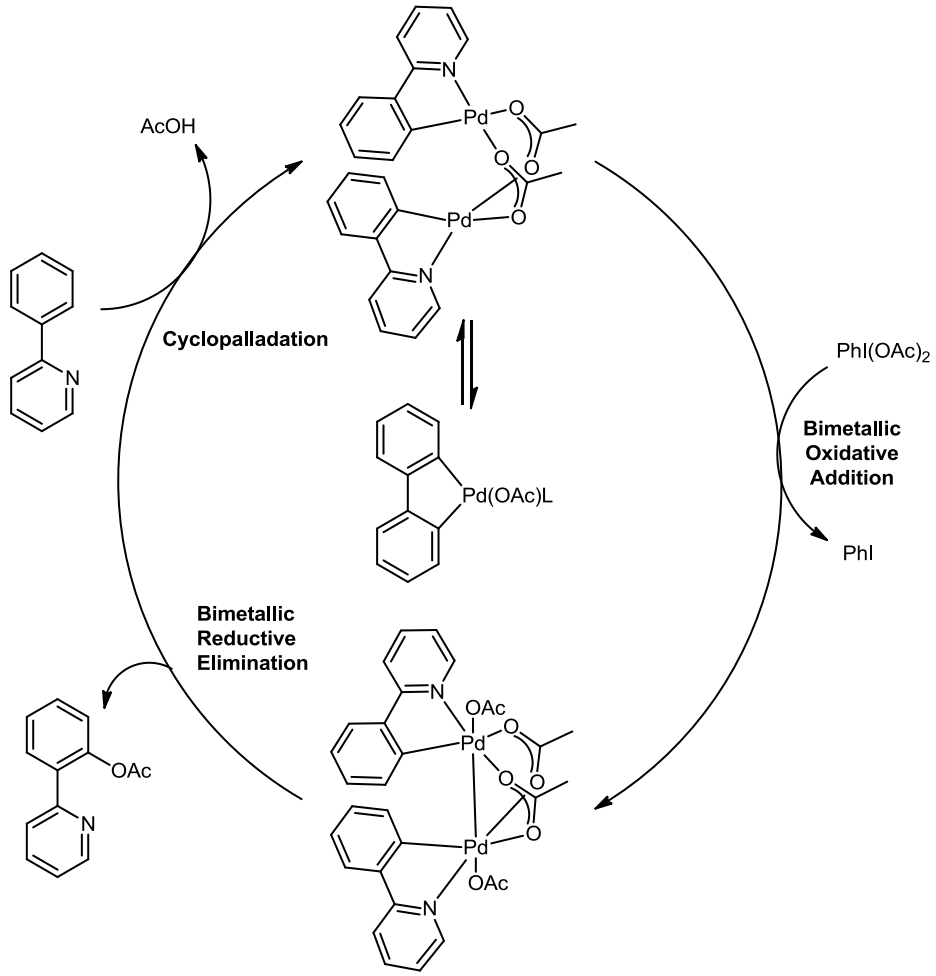
Scheme 4.20 Acetoxylation using oxime directing group**.**

In 2005 Yu and co-workers reported the oxidation of unactivated C-H bonds using MeCOOO*t*Bu as an oxidant and 2-substituted 4,4-dimethyloxazoline functionality as the directing group (Scheme 4.21).[43]



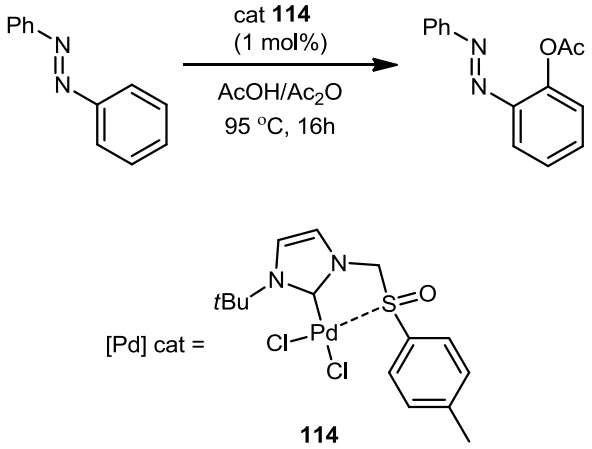
Scheme 4.21 Acetoxylation using MeCOOO*t*Bu as oxidant and 4,4-dimethyloxazoline as directing group.

It has been proposed that CMD is the most likely mechanism of C-H activation in reactions catalysed by $Pd(OAc)_2$, resulting from a low energy pathway evaluated by density functional theory (DFT).[13] Initially, Sanford and co-workers proposed a Pd(II)/Pd(IV) mechanism. Further work by Ritter *et al.* suggested a pathway involving a discrete bimetallic Pd(III) intermediate (Scheme 4.22).[44]



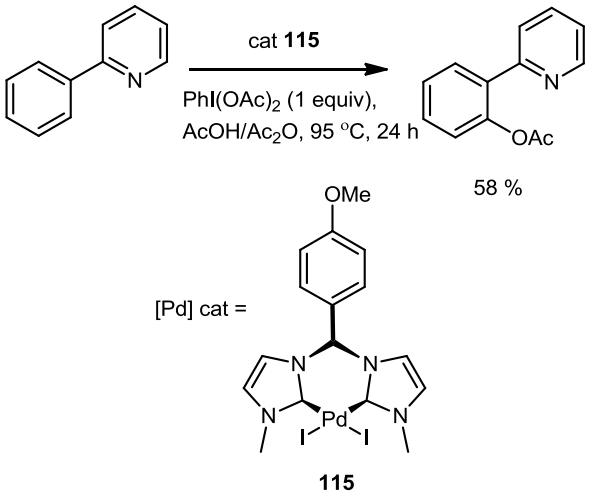
Scheme 4.22 Proposed bimetallic Pd(II)/Pd(III) catalytic cycle.

Although $Pd(OAc)_2$ catalysed acetoxylation is a useful methodology, its yield is hampered by a tendency to undergo dioxidation, resulting in the formation of the diacetoxylated product. Due to this, research continues to find more selective catalytic systems. In 2013 the synthesis of a series of novel NHC-Pd complexes bearing sulfoxide functionalities were reported, and their behaviour as catalysts in arene C-H bond oxidative activation was explored.[45] Of the catalysts tested the NHC-Pd complex (**114**) bearing a *t*-Bu R group was the most effective, facilitating the acetoxylation of a number of arenes (Scheme 4.23).



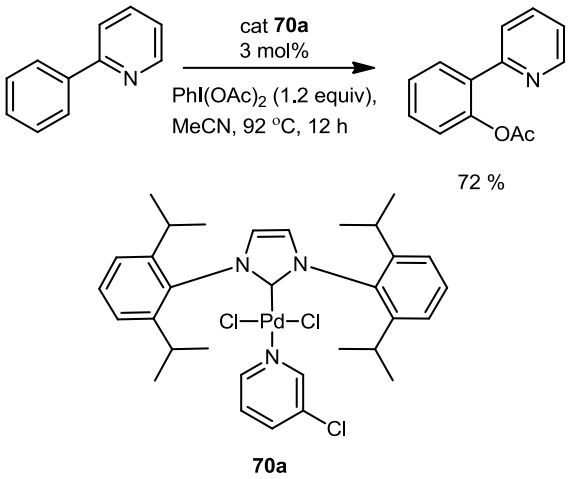
Scheme 4.23 Acetoxylation catalysed by novel NHC-Pd complex.

The authors provided evidence which suggested the C-H activation step occurs at the Pd(IV) rather than Pd(II) intermediates. In 2015 the first C-H bond oxidative activation catalysed by a bis NHC-Pd complex (**115**) was reported (Scheme 4.24).[46] In this study a series of control experiments were undertaken designed to elucidate the reaction mechanism, which suggested the involvement of a Pd(II)/Pd(IV) cycle in this case.



Scheme 4.24 Acetoxylation catalysed by bis NHC-Pd complex.

Very recently the use of the complex (IPr)$PdCl_2$(py) (**70a**) in C-H oxidative functionalisation has been reported (Scheme 4.25).[47] This methodology was found to have improved selectivity compared to the analogous system using $Pd(OAc)_2$ developed by Sanford and co-workers with up to 96% yield for the monoacetoxylated product.



Scheme 4.25 Acetoxylation catalysed by Pd-PEPPSI- type complexes.

4.1.11 Investigation Aims

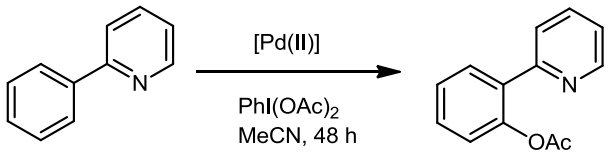
The aim of this investigation is to explore the catalytic activity of the novel anionic NHC palladium complexes [TBA][(NHC)$PdCl_3$] for directed C-H bond oxidative activation and to investigate if modification of the anionic motif can affect catalyst performance. Also use stoichiometric experiments to elucidate a probable reaction mechanism.

4.2 Discussions and Results

4.2.1 Initial testing

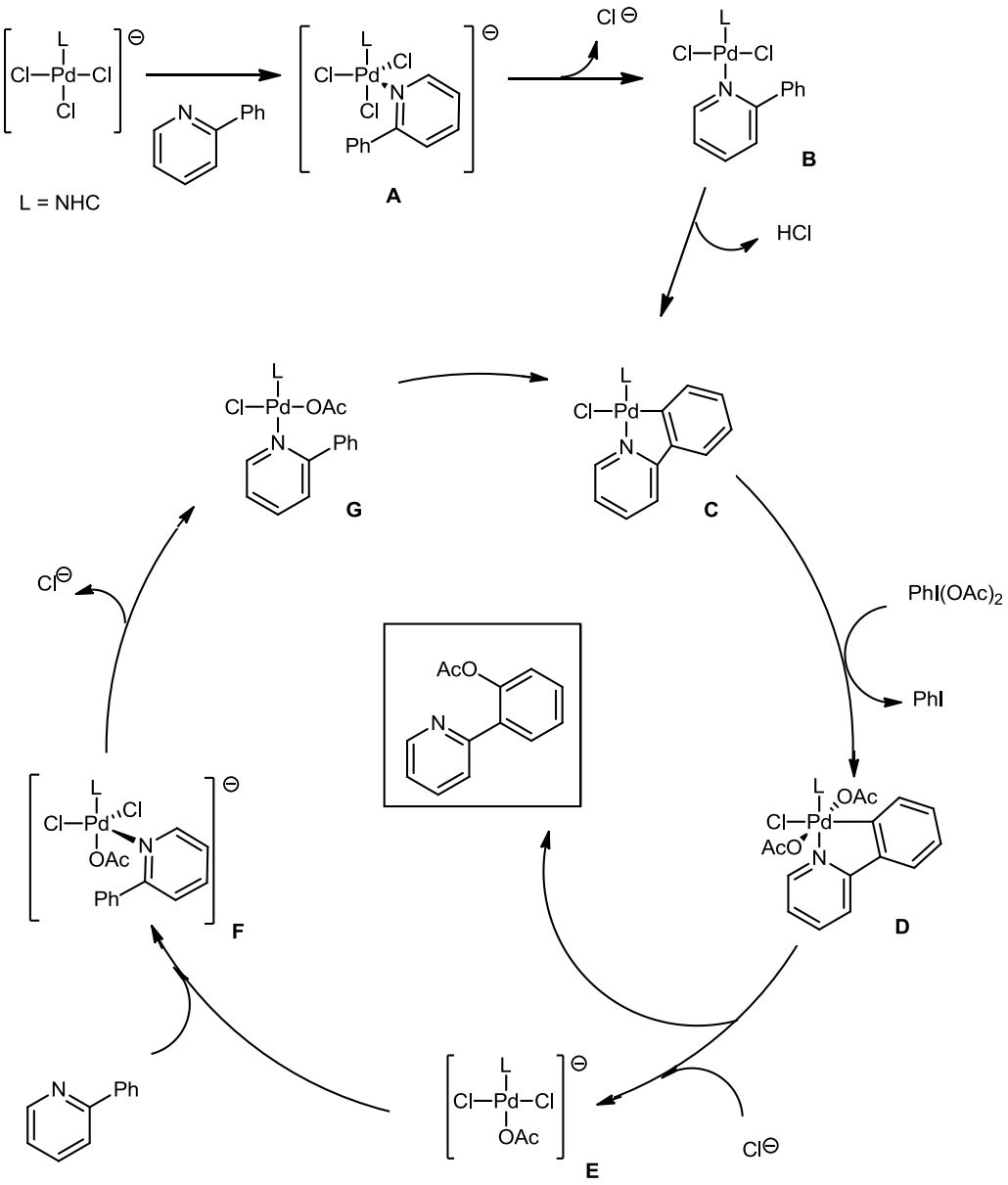
In order to benchmark our novel catalysts, the substrate chosen for the initial studies was 2-phenylpyridine, oxidised using conditions reported by Sanford and co-workers regarding solvent (MeCN) and oxidant ($PhI(OAc)_2$).[41] Comparative testing of the anionic complexes [TBA][(SIPr)$PdCl_3$], [TBA][(IMes)$PdCl_3$] with $Pd(OAc)_2$ under these conditions were very promising, with the anionic complexes able to produce the target mono-acetoxylated product in higher yields, at a lower temperature with decreased catalyst loading. The yield was found to be increased further when the equivalents of $PhIOAc_2$ were increased to two (Table 4.1).

Table 4.1 Comparative acetoxylation of 2-phenylpyridine.



[Pd(II)]	$PhI(OAc)_2$ (equiv)	Temperature (°C)	Yield (%)
$Pd(OAc)_2$, 10 mol%	1.05	100	52
[TBA][(SIPr)$PdCl_3$], **(103)** 2 mol%	1	75	74
[TBA][(SIPr)$PdCl_3$], **(103)** 2 mol%	2	75	85
[TBA][(IMes)$PdCl_3$], **(104)** 2 mol%	2	75	89

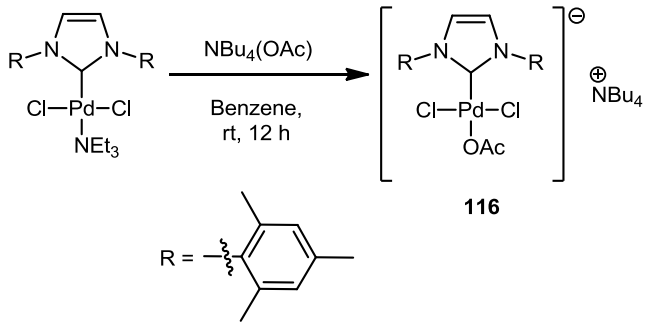
Before undertaking experiments to ascertain the substrate scope for these complexes, we decided to consider their possible mechanism of action in order to identify possible means to improve their activity. Based on a review of the literature regarding directed C-H bond oxidation described above, we proposed a Pd(II)/Pd(IV) pathway shown below (Scheme 4.26). In this proposed mechanism 2-phenylpyridine co-ordinates the palladium, leading to the formation of an unstable anionic 18 electron pentaco-ordinated species **A**. Complex **A** then gains net neutrality by losing a chloride forming complex **B**. This complex then undergoes C-H activation, via concerted metalation-deprotonation yielding palladacycle **C**. The reaction of **C** with the oxidant ($PhI(OAc)_2$) results in the oxidative addition of two acetates to the metal centre, producing the 18 electron species **D**. This species can then release the desired acetoxylated product by reductive elimination. Co-ordination of a chloride could generate the 16 electron Pd(II) species **E**, which would then act as the catalyst in the following cycles. It would be likely that this complex **E** would react faster than **B** due to a faster CMD step because of an easier elimination of HOAc compared to HCl**.** In order to test this hypothesis we decided to prepare the anionic NHC-palladate [TBA][(IMes)$PdCl_2OAc$] and test its activity compared to its tri-chloro analogue.



Scheme 4.26 Initially proposed mechanism for C-H bond oxidative activation using NHC-palladate complexes.

4.2.2 Synthesis of [TBA][(NHC)PdCl$_2$OAc] complexes

The preparation of the [TBA][(IMes)PdCl$_2$OAc] complex (**116)** was attempted using the same procedure used for the synthesis of [TBA][(NHC)PdCl$_3$], with the substitution of tetrabultyammonium chloride for tetrabutylammonium acetate (Scheme 4.27).



Scheme 4.27 Synthesis of [TBA][(IMes)PdCl$_2$OAc].

Pleasingly the reaction yielded the target complex cleanly in high yield, allowing after recrystallization the full characterisation of the product by ^{1}H, ^{13}C NMR spectroscopy, EA and single crystal X-ray diffraction. As expected, the crystal structure featured a square planer palladium centre with the NHC *trans* to an O-bond acetate moiety. The Pd-Cl bond distances perpendicular to the NHC were similar in both the [TBA][(IMes)PdCl$_2$OAc] and [TBA][(IMes)PdCl$_3$], however the Pd-C$_{carbene}$ distance was slightly shorter in the [TBA][(IMes)PdCl$_2$OAc] complex, due to the better π-acceptance of the acetate moiety (Figure 4.1). In order to test the tolerance of this methodology to other NHCs, the preparation of [TBA][(IPr)PdCl$_2$OAc] (**117**) was attempted using the same procedure. This reaction proceeded cleanly, also yielding the target complex, which was fully characterised by ^{1}H, ^{13}C NMR spectoscopy, EA and single crystal X-ray diffraction.

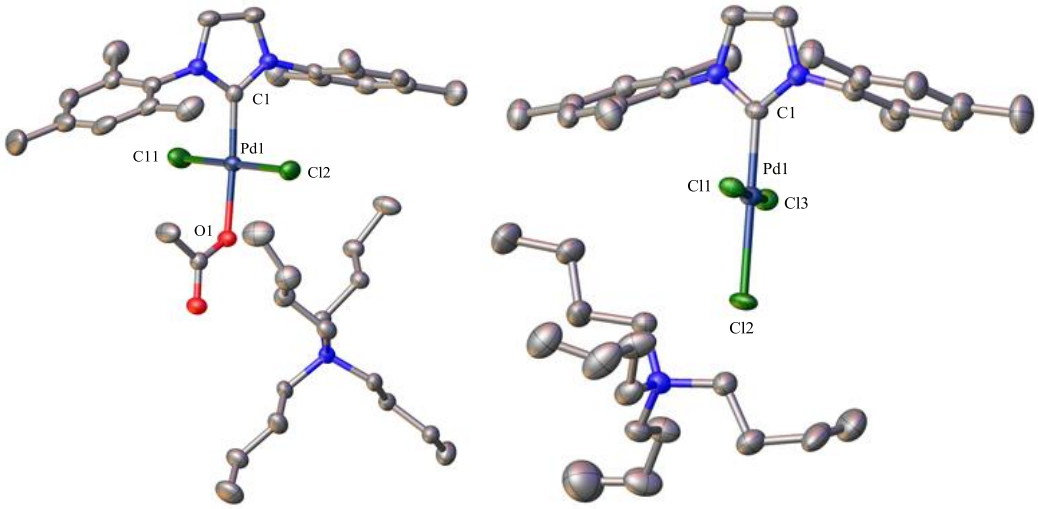
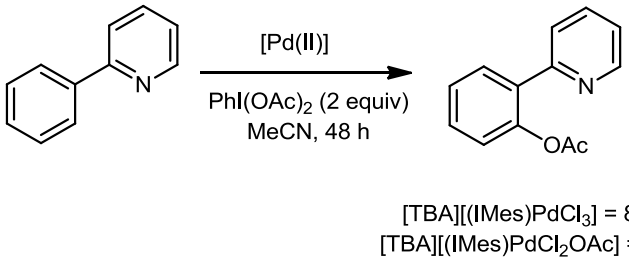


Figure 4.1 X-ray structure of [TBA][(IMes)PdCl$_3$] and [TBA][(IMes)PdCl$_2$OAc] with thermal ellipsoids at 50% probability level. Hydrogens are omitted for clarity. [TBA][(IMes)PdCl$_2$OAc] Selected bond lengths [Å] and angles [°]: Pd1-C1: 1.957(3), Pd-Cl1: 2.3023(8), Pd-Cl2: 2.3105(8), Pd-O1: 2.0922(18), C1-Pd1-Cl1: 90.67(8), C1-Pd1-Cl2: 90.12(8), O1-Pd1- Cl2: 90.24(6), O1-Pd1-Cl1: 89.27(6). [TBA][(IMes)PdCl$_3$] Selected bond lengths [Å] and angles [°]: Pd1-C1: 1.973(5), Pd-Cl1: 2.3740(11), Pd-Cl2: 2.4240(11), Pd-Cl3: 2.3159(13), C1-Pd1-Cl3: 91.06(4), C1-Pd1-Cl1: 89.04(15), Cl3- Pd1-Cl2: 91.06(4), Cl2-Pd1-Cl1: 91.56(4).

When the [TBA][(IMes)PdCl$_2$OAc] complex was tested for the C-H bond oxidation of 2-phenypyridine, our hypothesis on its higher activity compared to its tri-chloro analogue proved correct (Scheme 4.28). Due to this higher activity we decided to optimise the reaction for this complex.



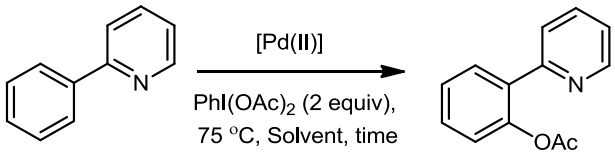
Scheme 4.28 Comparative of [TBA][(IMes)PdCl$_3$] and [TBA][(IMes)PdCl$_2$OAc] in the C-H bond activation of 2-phenylpyridine.

4.2.3 Reaction optimisation

Solvent screening revealed that the reaction works much better in polar solvents, probably due to the higher stability of charged intermediates in polar solvents (Table 4.2). When the reaction was carried out in a mixture of DMF/Ac$_2$O (2:1) the reaction yielded a quantitative amount of product in less than a quarter of the time. The same pattern of reduced reaction time was observed with the other NHC-palladate complexes when using

this solvent system although the yields were still lower than the [TBA][(IMes)$PdCl_2OAc$] complex. Interestingly, the use of $Pd(OAc)_2$ with this solvent system and the same catalyst loading consumed all of the starting material in only an hour, yielding the di-*ortho*-acetoxylated substrate as the major product (84%). Attempts to modify the reaction conditions to favour the $Pd(OAc)_2$ catalysted production of the *mono*-*ortho*-acetoxylated product in this solvent system by reducing the reaction time or temperature proved unsuccessful, always resulting mixtures of mono and di-substituted substrates.

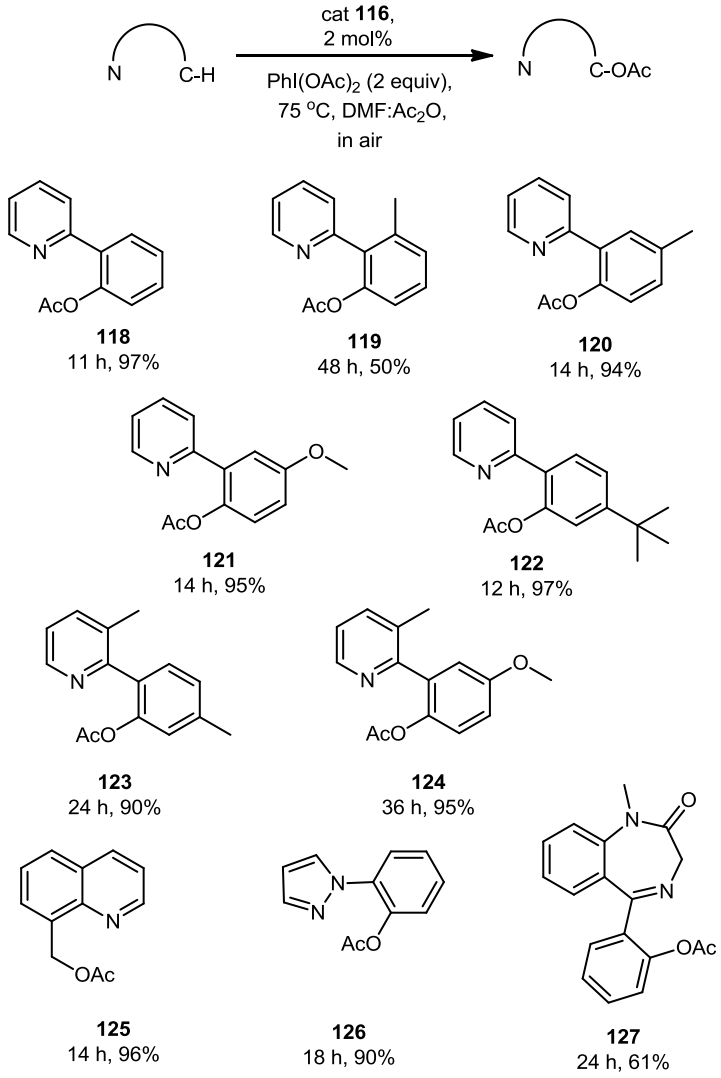
Table 4.2 Reaction optimisation catalyst loading, 2 mol%; PhI(OAc)2, 2 equiv.; solvent, 1.5 mL. *a)* Yield of monoacetylat-ed product, diacetylated product and remaining starting material. *b)* 1 equiv. of PhI(OAc)2. *c)* 25 °C.



entry	Pd complex	solvent	time (h)	yield (%)
1	[TBA][(IMes)$PdCl_2OAc$]	MeCN	48	94
2	[TBA][(IMes)$PdCl_2OAc$]	toluene	48	18
3	[TBA][(IMes)$PdCl_2OAc$]	1,4-dioxane	48	12
4	[TBA][(IMes)$PdCl_2OAc$]	2-Me-THF	48	15
5	[TBA][(IMes)$PdCl_2OAc$]	benzene	48	13
6	[TBA][(IMes)$PdCl_2OAc$]	DMF	24	68
7	[TBA][(IMes)$PdCl_2OAc$]	DMF/Ac_2O (2:1)	11	97
8	[TBA][(IMes)$PdCl_3$]	DMF/Ac_2O (2:1)	11	77
9	[TBA][(SIPr)$PdCl_3$]	DMF/Ac_2O (2:1)	11	75
10	$Pd(OAc)_2$	DMF/Ac_2O (2:1)	1	12,84,0[a]
11[b]	$Pd(OAc)_2$	DMF/Ac_2O (2:1)	1	32,49,18[a]
12[c]	$Pd(OAc)_2$	DMF/Ac_2O (2:1)	48	29,14,53[a]

4.2.4 Substrate scope

Under these optimised conditions, a series of substrates were *ortho*-acetoxylated (Scheme 4.29). When considering the substrates containing the 2-phenylpyridine moiety (**118-124**), the protocol showed good tolerance for *meta* and *para* substitution on the phenyl ring, however, *ortho* substitution seems to be more significant, resulting in both longer reaction times and lower yields (**119**). Ortho substitution on the pyridine ring also effects the rate of reaction but does not appear to affect the overall yield (**123**,**124**). Other directing scaffolds such as pyrazol **126** and the more challenging sp^3 C-H bond of quinoline **125** were also well tolerated. Finally, aiming to test our protocol on a more challenging motif we attempted the acetoxylation of a valium like benzodiazepine **127**, obtaining the target product in good yield.



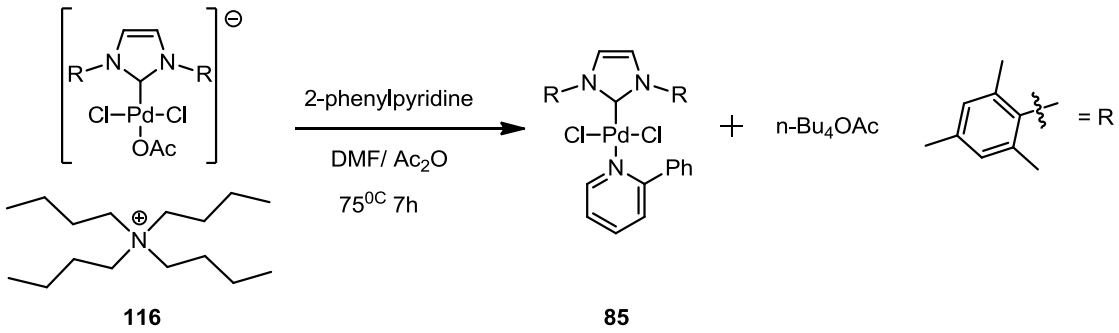
Scheme 4.29 Exploration of substrate scope.

4.2.5 Mechanistic insight

Aiming to elucidate the mechanism of reaction under the new optimised conditions, we undertook a number of experiments, beginning with stoichiometric reactions of the novel complexes with 2-phenylpyridine.

4.2.5.1 Stoichiometric reaction of [TBA][(IMesPdCl$_2$X] complexes with 2-phenylpyridine.

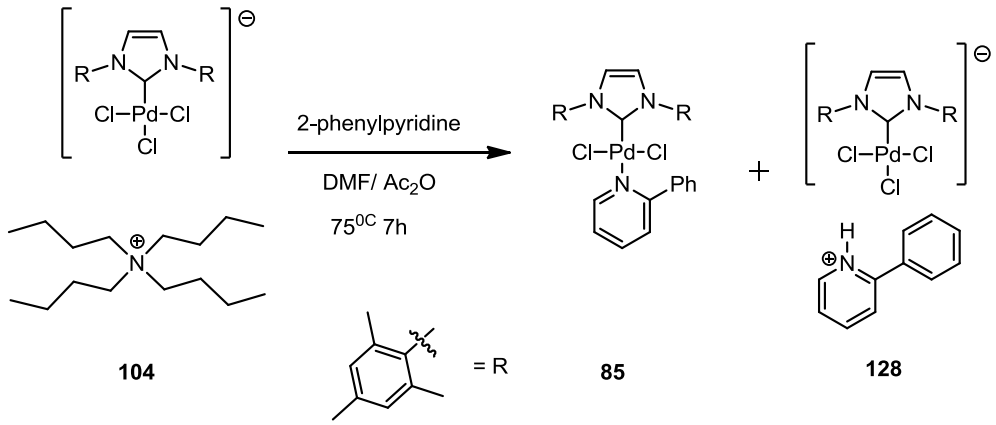
The reaction between [TBA][(IMes)PdCl$_2$OAc] and 2-phenylpyridine occurred cleanly and resulted in the formation of the expected (IMes)PdCl$_2$(2-phenylpyridine) complex in a quantitative yield (Scheme 4.30). The complex was fully characterised by ^{1}H, ^{13}C NMR spectroscopy, EA and single crystal X-ray diffraction.



Scheme 4.30 Reaction between [TBA][(IMes)PdCl$_2$OAc] and 2-phenylpyridine under reaction conditions.

Interestingly when the same reaction was carried out with the [TBA][(IMes)PdCl$_3$] after the same time, two products were observed in the ^{1}H NMR spectra. One pertaining to the neutral 2-phenylpyrdine co-ordinated complex and another which we believed to be the anionic trichloro palladium complex with the protonated 2-phenylpyridine as the cation (Scheme 4.31). The identity of this new salt was confirmed and by comparison with the results of its independent synthesis (Figure 4.2). The independent synthesis of this complex was achieved via the direct reaction of protonated 2-phenylpyridine with (IMes)PdCl$_2$(TEA) in benzene. Under these conditions the target complex precipitated

out of solution as it is insoluble in the chosen solvent. The new salt was fully characterised by ^{1}H, ^{13}C NMR spectroscopy, EA and single crystal X-ray diffraction (figure 4.3). Attempts to independently synthesis the acetate analogue [2-phenyl-1-pyridinium][(IMes)$PdCl_2$(OAc)] proved unsuccessful, always resulting in the formation of the co-ordinated 2-phenylpyridine complex (IMes)$PdCl_2$(2-phenylpyridine).



Scheme 4.31 Reaction between [TBA][(IMes)$PdCl_3$] and 2-phenylpyridine under reaction conditions.

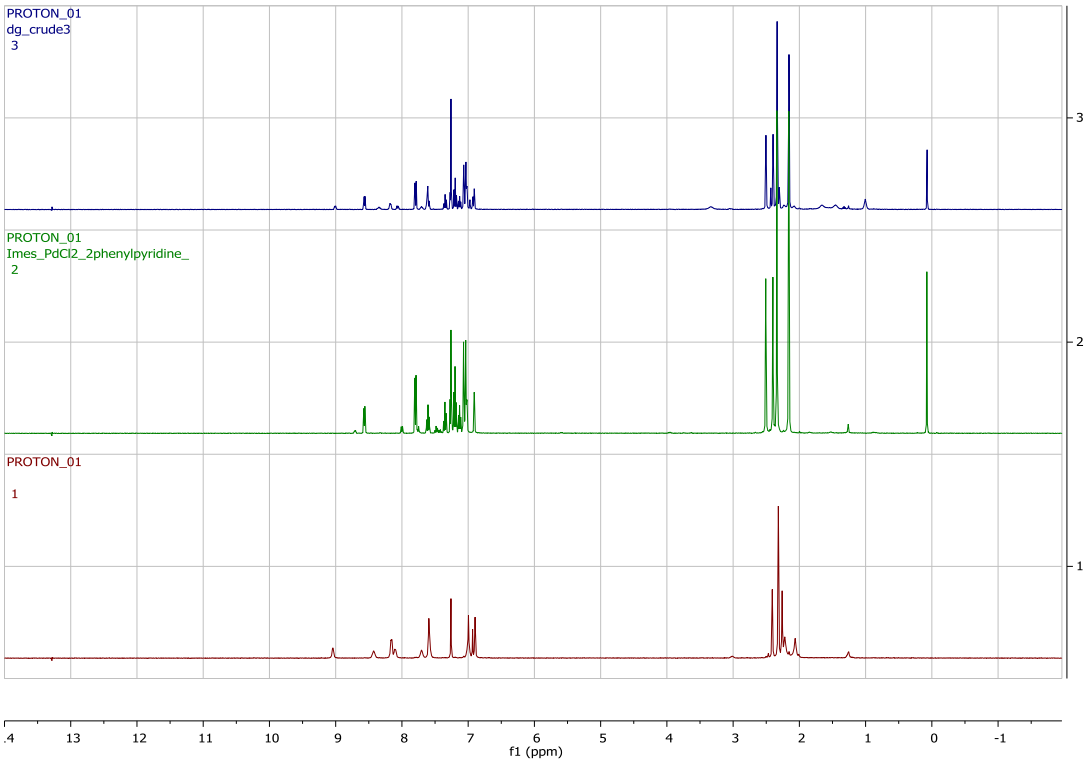


Figure 4.2 Identification of [2-phenyl-1-pyridinium][(IMes)$PdCl_3$] in the reaction between [TBA][(IMes)$PdCl_3$] and 2-phenylpyridine by ^{1}H NMR. Spectrum 1 (red) [2-phenylpyridin-1-ium][(IMes)$PdCl_3$] independently synthesised. Spectrum 2 (green) (IMes$PdCl_2$(2-phenylpyridine). Spectrum 3 (blue) crude NMR.

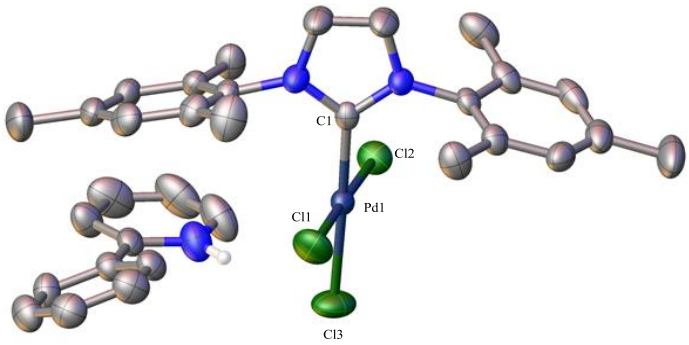
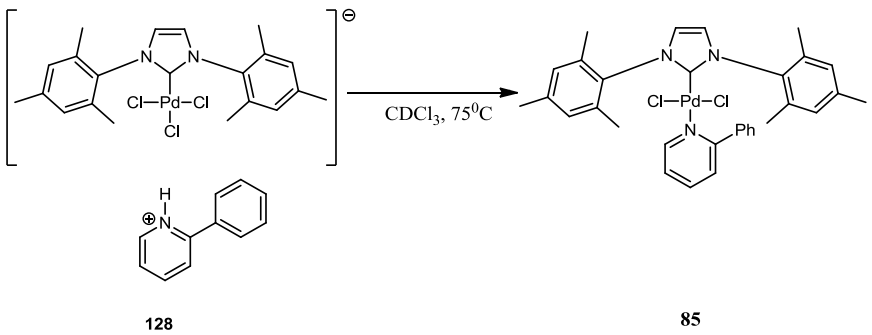


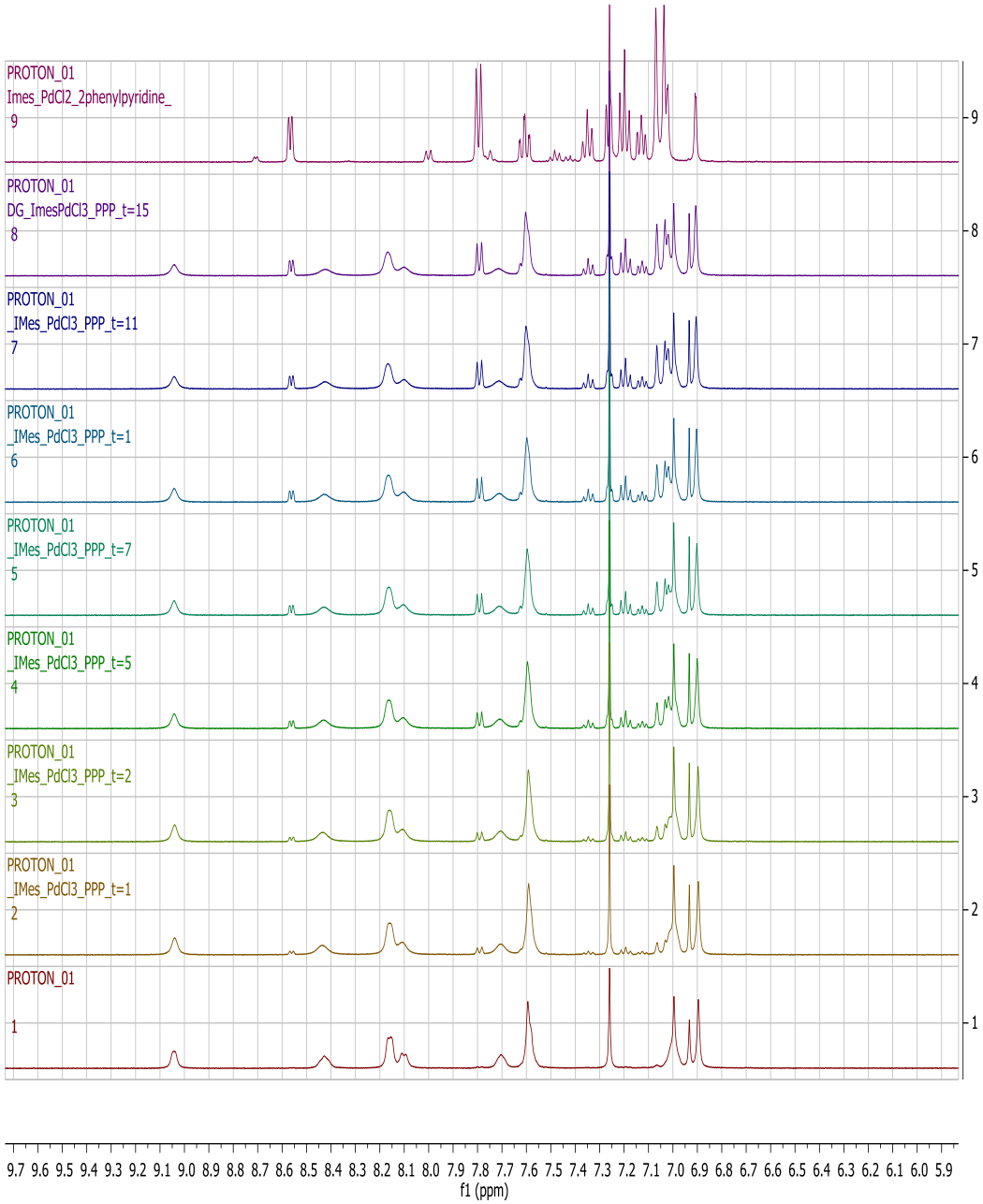
Figure 4.3 Molecular structure of [2-phenyl-1-pyridinium][(IMes)$PdCl_3$] with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1-C1: 1.980(4), Pd-Cl1: 2.2918(11), Pd-Cl2: 2.3019(12) , Pd-Cl3: 2.3716(12), C1-Pd1-Cl1: 89.31(10), C1-Pd1-Cl2: 90.64(10), Cl3- Pd1-Cl2: 89.89(5), Cl3-Pd1-Cl1: 90.21(5).

4.2.5.2 Thermal stability of [2-phenyl-1-pyridinium][(IMes)$PdCl_3$] in solution

Although the [2-phenyl-1-pyridinium][(IMes)$PdCl_3$] complex was found to be stable as a solid, in solution at 75 °C and even at room temperature the complex was found to slowly convert into the co-ordinated 2-phenylpyridine complex (IMes)$PdCl_2$(2-phenylpyridine) (Scheme 4.32). These results suggest that under our optimised reaction conditions the substrate is protonated by the reaction medium, then exchanges position with the TBA cation. Once this has occurred the substrate undergoes intramolecular deprotonation and co-ordination to the palladium centre. This accounts for the difference in activity observed between the [TBA][(IMes)$PdCl_3$] and [TBA][(IMes)$PdCl_2$OAc] catalysts as the acetate complex forms the substrate co-ordinated complex faster, revealed by their stoichiometric reactions with 2-phenylpyridine.



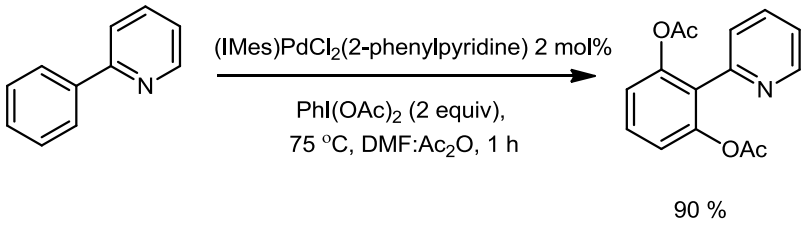
128 **85**



Scheme 4.32 Conversion of [2-phenyl-1-pyridinium][(IMes)$PdCl_3$] to (IMes)$PdCl_2$(2-phenylpyridine) over time monitored by ^{1}H NMR. t = time in hours.

4.2.5.3 Reactions with (IMes)$PdCl_2$(2-phenylpyridine)

Hoping to thermally induce the C-H activation of the co-ordinated 2-phenylpyridine, the (IMes)$PdCl_2$(2-phenylpyridine) complex was heated at 75 °C for up to 48 hours in the solvent mixture used in our catalytic protocol. This complex remained unaltered with no trace of the target palladacycle observed by NMR, indicating that either the presence of $PhI(OAc)_2$ is required for the CMD step to occur or the C-H activation is reversible.
When (IMes)$PdCl_2$(2-phenylpyridine) was used as a catalyst for the acetoxylation of 2-phenylpyridine using our reaction conditions, the reaction occurred faster than with [TBA][(IMes)$PdCl_2$OAc], using all the starting material within 1 hour, though with a much lower selectivity as the major product was the diacetoxylated product (Scheme 4.33). This suggests that the high selectivity observed for the [TBA][(IMes)$PdCl_2$OAc) complex is derived from the slow release of the active (IMes)$PdCl_2$(2-phenylpyridine) catalyst with the palladate acting as a reservoir, leading to longer reaction times but improved selectively.

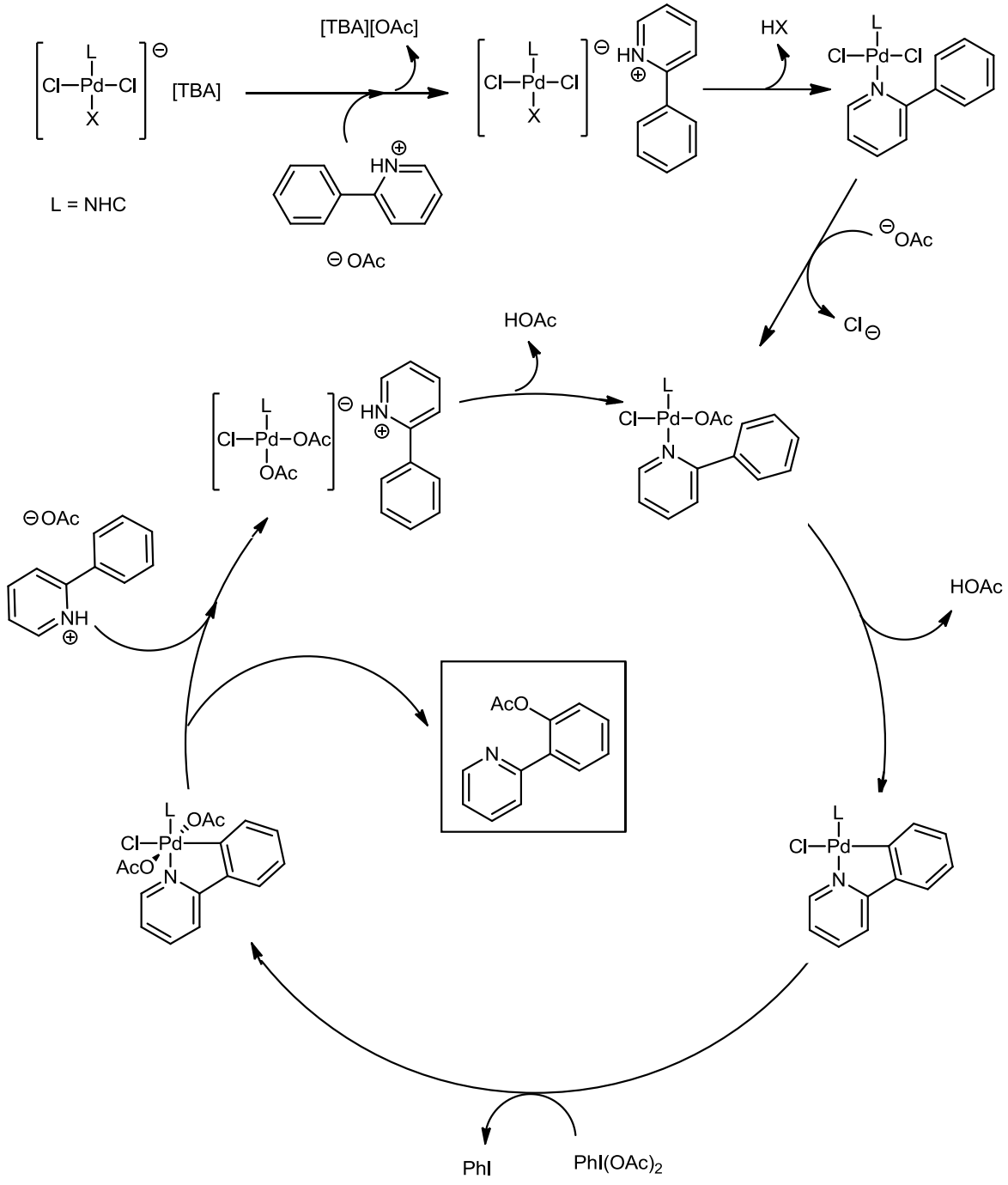


90 %

Scheme 4.33 Acetoxylation of 2-phenylpyridine by (IMes)$PdCl_2$(2-phenylpyridine).

4.2.5.4 Proposed mechanism under optimised conditions.

Using this information, we propose a plausible catalytic cycle for this reaction (Scheme 4.34). Key modifications when compared to our original are: the formation of the 2-pheny-1-pyridinium palladate intermediates and their corresponding intramolecular deprotonations and an extra step, when a chloride ligand is exchanged for an acetate, accounting for the required involvement of $PhI(OAc)_2$ in the C-H activation process leading to the formation of the palladacycle.



Scheme 4.34 Proposed mechanism for the acetoxylation of 2-phenylpyridine using (IMes)-palladate complexes.

4.3 Conclusion

In conclusion, a number of novel palladium complexes [TBA][(NHC)$PdCl_3$] were tested for directed C-H bond oxidative activation. [TBA][(IMes)$PdCl_3$] was found to be the most effective. Exploration of this complex's activity led to the development of the novel complex [TBA][(IMes)$PdCl_2OAc$] which was found to be more active than its trichloro analogue. Reaction condition optimisation for [TBA][(IMes)$PdCl_2OAc$] resulted in the development of a protocol able to catalyse the acetoxylation of a number of substrates with a better selectivity compared to $Pd(OAc)_2$ and other NHC-palladium complexes currently reported in the literature. Further experiments allowed for the observed difference in activity between [TBA][(IMes)$PdCl_3$] and [TBA][(IMes)$PdCl_2OAc$] to be rationalized and a plausible mechanism proposed.

4.4 Experimental

General Considerations

All reagents and solvents were purchased from commercial suppliers and used without further purification unless noted. The (NHC)$PdCl_2$(TEA) complexes were prepared following the procedures in the literature. Chromatography was performed using a Biotage isolera prime system with silica gel cartridges (P60-37-70 µm). NMR spectra were recorded on a Varian 500 or 400 MHz spectrometer. CHN elemental analysis was carried out at London Metropolitan University.

Synthesis of (IMes)$PdCl_2$(2-phenylpyridine) (85)

A reaction vial was loaded with a magnetic stirring bar, [(IMes)$PdCl_2OAc$][TBA] **(3)** (50mg, 0.06 mmol), 2-phenylpyridine (0.01ml, 0.07 mmol) Dimethylformamide (1ml) and acetic anhydride (0.5ml). The vial was sealed with a screw cap fitted with a septum and the reaction was allowed to stir at 75 °C for 8 hours. The solvent was then removed using a shlenk line and the product extracted from the reaction mixture with benzene and triturated with hexane to yield the title compound in a quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 6.0 Hz, 1H), 7.80 (d, J = 7.3 Hz, 2H), 7.61 (td, J = 7.7, 1.4

Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.27 (s, 1H), 7.20 (t, J = 7.7 Hz, 2H), 7.17 – 7.10 (m, 1H), 7.07 (s, 2H), 7.04 (s, 2H), 7.02 (d, J = 1.5 Hz, 1H), 6.93 – 6.88 (m, 1H), 2.51 (s, 3H), 2.40 (s, 3H), 2.34 (s, 6H), 2.16 (s, 6H). ^{13}C NMR (100 MHz, C_6D_6): δ = 160.6, 155.4, 151.0, 139.3, 138.9, 138.3, 137.2, 136.3, 136.1, 135.3, 134.9, 129.2, 128.9, 128.0, 125.2, 123.8, 122.3, 21.01, 19.0, 18.6. Anal. Calcd for $C_{32}H_{33}Cl_2N_3Pd$: C, 60.34; H, 5.22; N, 6.66. Found: C, 60.42; H, 5.21; N, 6.52. CCDC number: 1473490.

Synthesis of [(IMes)PdCl$_3$][TBA] (105)

A reaction vial was loaded with a magnetic stirring bar, (IMes)PdCl$_2$(TEA) (200 mg, 0.344mmol), tetrabutylammonium chloride (105 mg, 0.377 mmol) and 2 mL of dry benzene. The solution was allowed to stir at room temperature overnight. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (256 mg, 98%).^{1}H NMR (500 MHz, C_6D_6) δ 6.88 (s, 4H), 6.14 (s, 2H), 3.22 – 3.12 (m, 8H), 2.56 (s, 12H), 2.24 (s, 6H), 1.50 (m, 8H), 1.37 (m, 1H), 1.00 (t, *J* = 7.2 Hz, 12H).^{13}C NMR (100 MHz, C_6D_6): δ 157.5, 137.9, 136.7, 136.3, 128.9, 122.9, 58.5, 24.1, 20.9, 19.8, 19.5, 13.8. . Anal. Calcd for $C_{37}H_{60}N_3Pd$: C, 58.50; H, 7.96; N, 5.53. Found: C, 58.29; H, 8.06; N, 5.39. CCDC number 1473488.

Synthesis of [(IMes)PdCl$_2$OAc][TBA] (116)

A reaction vial was loaded with a magnetic stirring bar, (IMes)PdCl$_2$(TEA) **(1)** (200 mg, 0.343 mmol), tetrabutylammonium acetate (114 mg, 0.377 mmol) and 2 mL of dry benzene. The solution was allowed to stir at room temperature overnight. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (261 mg, 97%). ^{1}H NMR (500 MHz, C_6D_6): *δ* 6.92 (s, 4H), 6.15 (s, 2H), 2.97-2.90 (m, 8H), 2.54 (s, 12H), 2.46 (s,3H), 2.23 (s, 6H) 1.46-1.36 (m, 8H), 1.35−1.25 (m, 8H), 0.95 (t, *J* = 7.2 Hz, 12H). ^{13}C NMR (100 MHz, C_6D_6):*δ* 177.5, 155.7, 138.1, 136.8, 136.0, 128.8, 122.9, 58.0, 27.7, 23.7, 20.7, 19.6, 19.3, 13.7. Anal. Calcd for $C_{39}H_{63}N_3O_2Pd$: C, 59.65; H, 8.26; N, 5.29. Found: C, 59.71; H, 8.19; N, 5.27. CCDC number: 1435153.

Synthesis of [(IPr)PdCl$_2$OAc][TBA] (117)

A reaction vial was loaded with a magnetic stirring bar, (IPr)PdCl$_2$(TEA) (200 mg, 300 mmol), tetrabutylammonium acetate (114 mg, 0.377 mmol) and 2 mL of dry benzene. The solution was allowed to stir at room temperature overnight. Removal of the solvent in vacuo afforded a yellow oil, which was dissolved in ethyl acetate and triturated with hexane to yield the title compound as a pale yellow solid (256 mg, 98%).^{1}H NMR (500 MHz, C_6D_6) δ 7.39 – 7.27 (m, 6H), 6.63 (s, 2H), 3.49 (hept, J = 6.5 Hz, 4H), 3.19 – 3.09 (m, 8H), 2.31 (s, 3H), 1.65 (d, J = 6.4 Hz, 12H), 1.52-1.41 (m, 8H), 1.36 – 1.25 (m, 8H), 1.09 (d, J = 6.8 Hz, 12H), 0.98 (t, J = 7.2 Hz, 12H) .^{13}C {^{1}H} NMR (100 MHz, C_6D_6) δ 147.6, 136.4, 130.1, 124.9, 124.0, 58.0, 29.0, 26.7, 24.3, 23.5, 20.1, 14.3. Calcd for $C_{45}H_{75}Cl_2N_3O_2Pd$: C, 62.31; H, 8.71; N, 4.84. Found: C, 62.41; H, 8.67; N, 5.91.

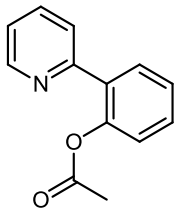
Synthesis of [(IMes)PdCl$_3$][2-phenylpyridin-1-ium] (128)

A reaction vial was loaded with a magnetic stirring bar, 2-phenylpyridine (0.123ml, 0.857 mmol) an excess of conc HCl (0.2 ml) and 2ml of dry benzene. The solution was allowed to stir at room temperature for 1 hour. Then (IMes)PdCl$_2$(TEA) **(1)** (100 mg, 0.172 mmol) was added to the reaction vial and the reaction was left to stir overnight at room temperature at which time a yellow precipitate had formed. This precipitate was then collected by filtration then washed twice with benzene (5ml) and once with ether (5ml) and was found to be the title compound (97mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.10 – 8.98 (m, 1H), 8.48 – 8.36 (m, 1H), 8.16 (d, *J* = 7.2 Hz, 2H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.74 – 7.66 (m, 1H), 7.59 (s, 3H), 7.00 (bs, 3H), 6.93 (s, 1H), 6.90 (s, 2H), 2.41 (s, 3H), 2.32 (s, 6H), 2.26 (s, 3H), 2.14 (d, *J* = 63.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.44, 145.54, 144.98, 142.70, 139.15, 138.64, 135.40, 134.40, 132.78, 129.94, 129.49, 129.32, 129.06, 128.58, 124.60, 124.44, 124.10, 123.96, 21.24, 21.2, 19.2, 18.8. Anal. Calcd for $C_{32}H_{43}Cl_3N_3Pd$: C, 57.07; H, 5.09; N, 6.24. Found: C, 56.93; H, 5.17; N, 6.18. CCDC number: 1473489

General Procedure for Acetoxylation reactions

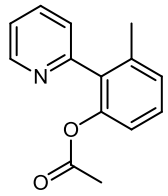
A 4 mL screw-capped vial equipped with a magnetic stirring bar was charged with (Diacetoxyiodo)benzene (1 mmol), Biphenylpyridine (0.5 mmol), complex **2**, N,N-dimethylformamide (1 mL) and acetic anhydride (0.5 mL). The vial was sealed with a screw-cap fitted with a septum and the reaction mixture allowed to stir at 75 °C and monitored by GC. When the reaction was complete or there was no further increase in conversion, it was cooled down to room temperature, poured into water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. The resultant solution was concentrated onto celite under reduced pressure for purification by column chromatography. All reported yields are an average of two runs.

2-(Pyridin-2-yl)phenyl acetate.[48] (**118)**



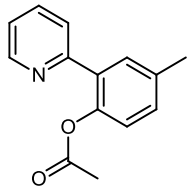
The reaction mixture was heated at 75ºC for 11 hr. The product was obtained as a clear oil (103 mg, 97%). A small amount of the diacetate compound was isolated (3mg, 2%) Eluent: Hexane/ ethyl acetate. 0-10% over 12mins, isocratic 10% for 6 mins, 10-50% over 7mins, isocratic 50% for 7mins.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72-8.67 (m, 1H), 7.74-7.76 (m, 2H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.25-7.21 (m, 1H), 7.16 (d, *J* = 8 Hz, 1H), 2.15 (s, 3H).

3-Methyl-2-(pyridin-2-yl)phenyl acetate.[49] **(119)**



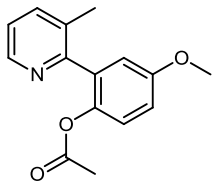
The reaction mixture was heated at 75ºC for 48 hr. The product was obtained as a pale yellow oil (57 mg, 50%). Eluent: Hexane/ ethyl acetate 10% isocratic.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75-8.71 (m,1H), 7.81-7.75 (m,1H), 7.35-7.25 (m,3H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 2.16 (s, 3H), 1.95 (s, 3H).

4-Methyl-2-(pyridin-2-yl)phenyl acetate.[50] (**120)**



The reaction mixture was heated at 75ºC for 14 hr. The product was obtained as a clear oil (107 mg, 94%) only one regioisomer observed by NMR and GC. Eluent: Hexane/ ethyl acetate 10% isocratic.^{1}H NMR (400 MHz, d6-acetone) δ = 8.68-8.65 (m, 1H), 7.84 (td, *J* = 7.8, 1.9 Hz, 1H), 7.65 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.32 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.27-7.24 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 2.39 (s, 3H), 2.14 (s, 3H).

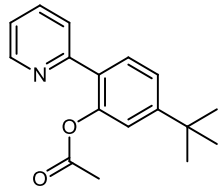
4-Methoxy-2-(3-methylpyridin-2-yl)phenyl acetate. (121)



The reaction mixture was heated at 75ºC for 36 hr. The product was obtained as an orange oil (122mg, 95%). Eluent: Hexane/ ethyl acetate 10% isocratic.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58-8.54 (m, 1H), 7.73-7.68 (m, 1H), 7.34-7.29 (m, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.98 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.90 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 2,26 (s, 3H), 1.96 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ = 169.1, 157.1, 154.9, 146.2, 141.6, 138.4, 133.5, 132.5, 123.5, 122.7, 115.2, 114.9, 55.7, 20.5, 19.0. HRMS (EI):

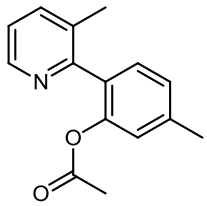
Calcd for $C_{15}H_{15}NO_3$ m/z 258.1125, Observed m/z 258.1118. IR (ATR): 2944.2, 1760.18, 1583.04.

5-(tert-Butyl)-2-(pyridin-2-yl)phenyl acetate. (122)



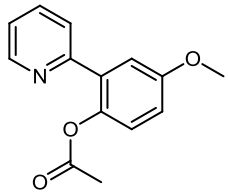
The reaction mixture was heated at 75ºC for 12 hr. The product was obtained as an orange oil (124 mg, 97%). A small amount of the diacetate compound was isolated (7mg, 4%) Eluent: Hexane/ ethyl acetate. 0-10% over 12mins, isocratic 10% for 6mins, 10-50% over 7mins, isocratic 50% for 7mins.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76-8.69 (m, 1H), 7.80 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.61-7.56 (m, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.33-7.27 (m, 1H), 7.17 (s, 1H), 2.19 (s, 3H), 1.35 (s, 9H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ = 169.3, 155.1, 154.2, 148.5, 147.9, 137.5, 137.4, 130.3, 123.8, 123.6, 122.2, 120.2, 34.8, 31.1, 21.0. HRMS (EI): Calcd for $C_{17}H_{20}NO_2$ m/z 270.1489, Observed m/z 270.1488. IR (ATR): 2963.43, 1763.60, 1587.29.

5-Methyl-2-(3-methylpyridin-2-yl)phenyl acetate. (123)



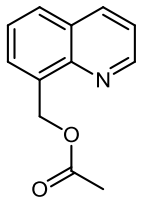
The reaction mixture was heated at 75ºC for 24 hr. The product was obtained as a pale yellow oil (109 mg, 90%). Eluent: Hexane/ ethyl acetate 10% isocratic.^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.51-8.45 (m,1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H) 7.00 (s, 1H), 2.4 (s, 3H), 2.19 (s, 3H), 1.95 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$):δ = 173.6, 168.9, 155.4, 147.9, 146.3, 139.6, 138.1, 132.4, 130.1, 126.6, 123.1, 122.4, 21.2, 20.6, 19.0. HRMS (EI): Calcd for $C_{15}H_{16}NO_2$ m/z 242.1176, Observed m/z 242.1170. IR (ATR): 2921.92, 1619.31, 1577.36.

4-Methoxy-2-(pyridin-2-yl)phenyl acetate.[48] **(124)**



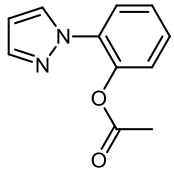
The reaction mixture was heated at 75ºC for 14 hr. The product was obtained as a yellow oil (115 mg, 95%) only one regioisomer observed by NMR and GC. A small amount of the diacetate compound was isolated (5mg, 3%) Eluent: Hexane/ ethyl acetate. 0-10% over 12mins, isocratic 10% for 6mins, 10-50% over 7mins, isocratic 50% for 7mins.[1]H NMR (400 MHz, d6-acetone) δ = 8.70-8.66 (m, 1H), 7.86-7.81 (m, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.36 (d *J* = 3.0 Hz, 1H), 7.34-7.30 (m, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 8.8, 3.0 Hz, 1H), 3.85 (s, 3H), 2.14 (s, 3H).

Quinolin-8-ylmethyl acetate.[51] **(125)**



The reaction mixture was heated at 75ºC for 14 hr. The product was obtained as a yellow oil (97 mg, 96%). Eluent: Hexane/ ethyl acetate 10% isocratic.[1]H NMR (400 MHz, $CDCl_3$) δ = 8.97-8.92 (m, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.82-7.74 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45-7.40 (m, 1H), 5.86 (s, 2H), 2.15 (s, 3H).

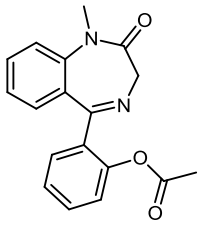
2-(1H-Pyrazol-1-yl)phenyl acetate.[51] **(126)**



The reaction mixture was heated at 75ºC for 18 hr. The product was obtained as a clear oil (91 mg, 90%). Eluent: Hexane/ ethyl acetate 10% isocratic.[1]H NMR (400 MHz,

$CDCl_3$) δ = 7.75-7.70 (m, 2H), 7.62-7.58 (m, 2H), 7.39-7.30 (m, 2H), 7.23-7.19 (m, 1H), 6.44-6.40 (m, 1H), 2.19 (s, 3H).

2-(1-Methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)phenyl acetate. (127)



The reaction mixture was heated at 75ºC for 24 hr. The product was obtained as a pale yellow solid (94 mg, 61%). Eluent: Hexane/ ethyl acetate 10% isocratic.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76-7.69 (m, 1H), 7.64-7.57 (m, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.43-7.34 (m, 2H), 7.25-7.22 (m, 1H), 7.21-7.14 (m, 1H), 4.91 (d, *J* = 9.6 Hz, 1H), 3.80 (d, *J* = 9.6 Hz, 1H), 3.46 (s, 3H), 1.72 (s, 3H).). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ = 169.6, 169.0, 168.0, 148.8, 143.3, 132.6, 132.3, 132.0, 130.5, 129.8, 128.5, 126.2, 124.7, 123.3, 121.2, 55.3, 35.3, 20.1. HRMS (EI): Calcd for $C_{18}H_{17}N_2O_3$ m/z 309.1234, Observed m/z 309.1231.IR (ATR): 2927.39, 2855.22, 1728.49, 1673.86.

4.5 References

(1) Arndtsen, B. a.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154–162.

(2) Labinger, J.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.

(3) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic chemistry*, 1st ed.; Oxford University Press: Oxford, 2000.

(4) Shilov. *Coord. Chem. Rev.* **1977**, *24*, 97–143.

(5) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1967**, *8*, 1119–1122.

(6) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *9*, 633–636.

(7) Fujiwara, Y.; Noritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

(8) Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc. Chem. Commun.* **1980**, 5, 220.

(9) Jintoku, T.; Fujiwara, Y.; Kawata, I.; Kawauchi, T.; Taniguchi, H. *J. Organometallic Chem.* **1990**, *385*, 297–306.

(10) Baudry, D.; Ephritikhine, M.; Felkin, H.; Zakrzewski, J. *J. Chem. Soc. Chem.Commun.* **1982**, 1235–1236.

(11) Baudry, D.; Ephritikhine, M.; Felkin, H.; Holmes-Smith, R. *J. Chem. Soc. Chem. Commun.* **1983**, 14, 788–789.

(12) Burk, M. J.; Crabtree, R. H. *J. Am. Chem. Soc* **1987**, *109*, 8025–8032.

(13) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

(14) Boutalda, Y.; Davies, D. L.; Poblador-Bahamonde, A.; Macgregor, S. A. *Dalton. Trans.* **2009**. 30, 5820–5831.

(15) Ajitha, M. J.; Huang, K.-W.; Kwak, J.; Kim, H. J.; Chang, S.; Jung, Y. *Dalton. Trans.* **2016**, *45*, 7980–7985.

(16) Rothwell, I. P. *Acc. Chem. Res.* **1988**, *21*, 153–159.

(17) Waterman, R. *Organometallics* **2013**, *32*, 7249–7263.

(18) Boultadakis-Arapinis, M.; Gandon, V.; Prost, E.; Micouin, L.; Lecourt, T. *Adv. Synth. Catal.* **2014**, 356,2493-2505.

(19) Varela-Álvarez, A.; Musaev, D. G. *Chem. Sci.* **2013**, *4*, 3758.

(20) Liu, H.; Duan, J. X.; Qu, D.; Guo, L. P.; Xie, Z. Z. *Organometallics* **2016**, *35*, 2003–2009.

(21) Batiste, L.; Chen, P.*J. Am. Chem.Soc.* **2014,** 136, 9296-9307. .

(22) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797–9804.

(23) Guo, X.-K.; Zhang, L.-B.; Wei, D.; Niu, J.-L. *Chem. Sci.* **2015**, *6*, 7059–7071.

(24) Xiao, L. J.; Fu, X. N.; Zhou, M. J.; Xie, J. H.; Wang, L. X.; Xu, X. F.; Zhou, Q. L. *J. Am. Chem. Soc.* **2016**, *138*, 2957–2960.

(25) Sun, X.; Sun, X.; Geng, C.; Zhao, H.; Li, J. *J. Phys. Chem. A.* **2014,** 118, 7146-7158.

(26) Li, Z. F.; Fan, Y.; Deyonker, N. J.; Zhang, X.; Su, C. Y.; Xu, H.; Xu, X.; Zhao, C. *J. Org. Chem.* **2012**, *77*, 6076–6083.

(27) Novμk, P.; Correa, A.; Gallardo-donaire, J.; Martin, R.. *Org. Lett.* **2014**, 16, 3404-3407..

(28) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531.

(29) Chen, X.; Engle, K. M.; Wang, D. H.; Jin-Quan, Y. *Angew. Chemie - Int. Ed.* **2009**, *48*, 5094–5115.

(30) Rousseau, G.; Breit, B. *Angew. Chemie - Int. Ed.* **2011**, *50*, 2450–2494.

(31) García-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chemie - Int. Ed.* **2009**, *48*, 6511–6515.

(32) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906–6919.

(33) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Synthesis* . **2003**, 1, 112–114.

(34) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343–350.

(35) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.; Movassaghi, M.; Yu, J. *J. Am. Chem. Soc.* **2014**, *136* , 10807.

(36) Dong, Z.; Wang, J.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 5887–5890.

(37) Davidson, J. .; Triggs, C. *Chem.ind* **1966**, 457.

(38) Tisue, T.; Downs, J.*Chem Commun.* **1969**, *11*, 410.

(39) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A Chem.* **1996**, *108*, 35–40.

(40) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301.

(41) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149–4152.

(42) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543.

(43) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q. *Angew. Chemie - Int. Ed.* **2005**, *44*, 7420–7424.

(44) Powers, D. C.; Geibel, M. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050–17051.

(45) Tato, F.; García-Domínguez, A.; Cárdenas, D. J. *Org. Lett.* **2013**, *32*, 7487–7494.

(46) Desai, S. P.; Mondal, M.; Choudhury, J. *Organometallics* **2015**, *34*, 2731–2736.

(47) Bolbat, E.; Wendt, O. F. *European J. Org. Chem.* **2016**, *2016*, 3395–3400.

(48) Dick, A. R.; Hull, K. L.; Sanford, M.S. *J. Am. Chem. Soc.*, **2004**, *126*, 2300–2301.

(49) Ye, Z.; Wang, W,; Luo, F.; Zhang, S.; Cheng, J. *Org. Lett.*, **2009**, *11*, 3974–3977.

(50) Kalyani, D.; Sanford, M. S. *Org. Lett.*, **2005**, *7*, 4149–4152.

(51) Chen, M. T.; Vicic, D. A.; Turner, M. L.; Navarro, O. *Organometallics*, ***2011***, 30, 5052-5065.