APPLICATIONS OF NOVEL SILICA SUPPORTED PALLADIUM CATALYSTS IN COUPLING REACTIONS

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August 2010

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Abstract

This work describes the preparation of a range of silica supported palladium catalysts and their testing in cross coupling reactions. A silica supported *bis*-phosphine palladium catalyst has been prepared and characterised using solid state ^{31}P NMR, TGA, elemental analysis and SEM. The evaluation of the catalyst in copper-free Sonogashira reactions is explored in some depth. Good to excellent conversion rates were observed throughout a wide range of substrates and the catalyst proved to be recyclable over 5 cycles. Also presented is the preliminary screening of the *bis*-phosphine palladium catalyst in Heck and Suzuki reactions and the first solvent and copper-free *5-endo-dig* cyclisation reaction of unprotected (2-phenylethynyl)aniline derivatives to yield 2-substituted indole derivatives.

The preparation of range of novel *bis*-NHC (*N*-heterocyclic carbene) palladium dichloride complexes is also reported. Due to the fact that the *bis*-NHC complexes are prepared prior to immobilisation, the precatalytic species could be well characterised by high-resolution mass spectrometry, ^{1}H and ^{13}C NMR. The silica supported *bis*-NHC complexes were generally capable of achieving good conversions in Suzuki reactions of aryl iodides and bromides with 0.2 mol% catalyst loading. The catalysts also showed modest levels of activity toward deactivated aryl chloride substrates. The steric properties of the *N*-substituents on the *bis*-NHC complexes proved to have a significant effect on catalytic activity. As observed in homogeneous catalysis, bulky NHC ligands such as *N*-mesityl and *N*-(2,6-diisopropyl)phenyl exhibit increased catalytic activity compared to the less-bulky *N*-benzyl ligand. This is significant because the use of sterically bulky NHC ligands in hybrid catalysis has received little attention in the scientific literature.

Finally, the preparation of a novel, silica supported iminoalkyl-NHC palladium complex has been explored. Although preparation of the iminoalkyl NHC complex proved problematic, the prototype catalyst displayed modest activity in allylic alkylation reactions (up to 24% conversion), which is apparently the first example of a heterogeneous NHC catalyst used for this process.

Abbreviations

Ac	Acyl
AES	Atomic Emission Spectroscopy
APS	3-Aminopropyl functionalised Silica
Ar	Aryl
BINAP	*Bis*-(1,1'-diphenylphosphine)binaphthalene
BPSRG	Biological and Pharmaceutical Science Research Group
BSA	*N,O-Bis*(trimethylsilyl)acetamide
Bz	Benzyl
CNF	Carbon nanofibre
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPP	Diphenylphosphine
DPPM	Diphenylphosphinomethanol
EDG	Electron Donating Group
ee	Enantiomeric Excess
EWG	Electron Withdrawing Group
GC-MS	Gas Chromatography-Mass Spectrometry
IMes	(*N,N-bis*-Mesityl)imidazol-2-ylidine
^{i}Pr	Isopropyl
I^{i}Pr	(*N,N-bis*-Diisopropylphenyl)imidazol-2-ylidine
L_n	Ligands
M	Metal
MCM-41	Mobil Composition of Matter (Mesoporous silica)
Me	Methyl
MeCN	Acetonitrile
Mol%	Molar percentage
MP	Melting Point
Ms	Mesyl (methanesulfonic acid)
^{n}Bu	Butyl

NHC	*N*-Heterocyclic Carbene
NOE	Nuclear Overhauser Effect
NMP	*N*-Methyl Pyrrolidinone
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
OAc	Acetate
OMe	Methoxy
OTf	Triflate (trifluoroacetate)
Pd/C	Palladium on Carbon
PEPPSI	Pyridine Enhanced Precatalyst Preparation Stabilisation and Initiation
Ph	Phenyl
PS	Polystyrene
PVI/PVC	Poly(*N*-vinylimidazole-*co*-vinylcaprolactam)
PYBOX	Phenyl-1,3-*bis*-oxazoline
RT	Room Temperature
SBA-15	Santa Barbara Amorphous material (Mesoporous silica)
SEM	Scanning Electron Microscopy
TBAB	Tetrabutylammonium Bromide
TBAF	Tetrabutylammonium Fluoride
^{t}Bu	Tertiary Butyl
TEM	Transmission Electron Microscopy
TGA	Thermogravimmetric Analysis
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl (4-toluenesufonic acid)
X	Halogen (or similar 1e ligand)
))))	Ultrasonic irradiation

Acknowledgments

The author wishes to thank Prof. Liz Tyrrell and Dr. Neil Williams, who have been a constant source of guidance and inspiration throughout this project. Also, thanks to the BPSRG and Kingston University for the funding that made this project possible. Thanks to my family for all their support and finally a big thank you to my friends and colleagues in the School of Pharmacy and Chemistry at Kingston, whose company, assistance and advice made this project all the more enjoyable and successful.

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1 Immobilised Transition Metal Complexes in Organic Synthesis

1.1 Introduction

Transition metal catalysts have found widespread applications in chemical syntheses in both academic and industrial communities. The economic and environmental benefits of catalytic reactions often include reduced energy input and materials costs, waste minimisation and recyclability: all of which are important concepts in green chemistry.[1] The efficiency of catalytic processes can be attributed to the ability of catalysts to perform specific chemical reactions over numerous cycles without being consumed in the process. By definition; a catalyst "increases the rate of attainment of chemical equilibrium without itself undergoing chemical change".[2]

Heterogeneous catalytic reactions are normally mediated by metallic elements. The transition metals such as platinum, palladium and ruthenium are especially useful, which is largely due to the fact that they can exist in a variety of stable oxidation states. This allows for the formation of intermediate complexes with organic substrates, subsequent elimination of the products and regeneration of the active catalyst (Figure 1).

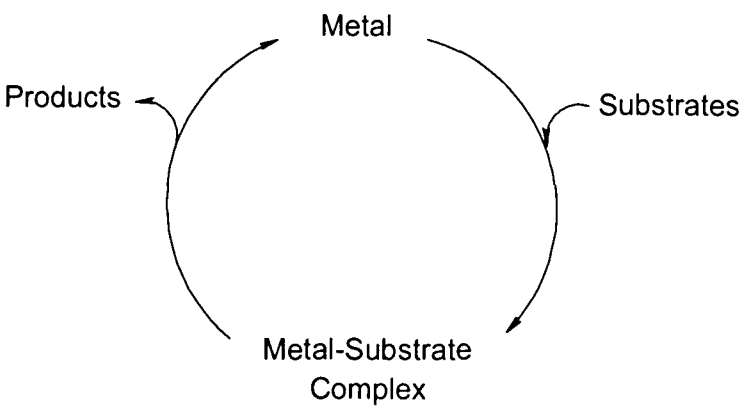


Figure 1 A general catalytic cycle.

The field of catalysis is conventionally divided into 3 main areas; heterogeneous, homogeneous and biocatalysis. Heterogeneous catalysis involves the use of catalytic materials that occupy a different phase to the reactants, in contrast with homogeneous catalysis where the catalyst and reactants are present in the same phase. Biocatalysis involves the use of enzymes and other naturally occurring biotechnology.

There are undoubtedly advantages associated with homogeneous catalysis; these include high levels of catalytic activity, selectivity and the fact that the catalyst is usually a well-defined chemical species (which may be studied using standard spectroscopic techniques). A major drawback of homogeneous catalysis, however, is that separation of the catalyst from reaction mixtures is often not trivial and may add to the overall cost of the process. The potential for recycling of homogeneous catalysts also tends to be rather limited, which represents another financial concern.

Heterogeneous catalysis goes some way towards addressing these issues. Because heterogeneous systems are insoluble in reaction mixtures, a simple filtration step can be employed to recover the catalyst, which can normally be re-used. Unfortunately, heterogeneous catalysts are generally less selective than their homogeneous counterparts, owing to the presence of numerous active species, which limits their synthetic utility somewhat. One relatively recent approach is the idea of hybrid or immobilised catalysis, which involves the anchoring of metal complexes to an insoluble support material. Theoretically this combines the properties of both heterogeneous and homogeneous catalysis. In practice however, hybrid catalysts often display markedly different behaviour and catalytic activity compared to homogeneous systems, and metal leaching from the support material is frequently observed.

Although this report will be centred on hybrid (immobilised) catalysis, it would be impossible to fully survey the literature without occasionally straying into the other, closely-related fields.

1.2 Heterogeneous Catalysis

Heterogeneous catalysis may be further divided depending on the nature of the catalyst. The most frequently encountered types of heterogeneous catalyst include simple metal compounds and immobilised organometallic species (hybrid catalysts). Each type of heterogeneous catalytic process has specific advantages and limitations associated with its use, some of which are briefly discussed.

1.2.1 Catalysis by Metal Compounds

This refers to reactions promoted by simple metal compounds such as pure metals or metal oxides. In an attempt to maximise catalyst surface area or minimise cost, elemental metals (nanoparticles) are often dispersed over robust, chemically inert support materials such as carbon or silica.[3] As one of the earliest known forms of catalysis, this is perhaps the best documented. A classic example is the Haber process, which is used for the conversion of elemental nitrogen to ammonia. This reaction usually employs a finely divided iron catalyst (magnetite ore, Fe_3O_4) and hydrogen and nitrogen in their gaseous states making it a truly heterogeneous process (Scheme 1).[4]

$$N{\equiv}N\ (g) + 3\ H{-}H\ (g) \xrightarrow[400\ ^{\circ}C,\ 150\text{-}300\ atm.]{Fe_3O_4\ (s)} 2\ NH_3\ (g)$$

Scheme 1 General description of the Haber process.

The basic mechanism for this catalytic process is considered to involve adsorption of N_2 and H_2 molecules onto the surface of metal particles. This has the effect of weakening the bonds in the substrate molecules, allowing for a lower energy reaction pathway (a faster reaction) than would take place in the absence of catalyst.[5]

Mechanisms behind heterogeneous catalytic reactions are often difficult to elucidate. The field of surface science has played a crucial role in revealing the mechanisms behind heterogeneous reactions like the Haber process. These reactions have been studied extensively by surface spectroscopic techniques including Scanning Electron Microscopy (SEM), which have contributed to the

idea that active sites of the catalysts usually consist of corners, steps and crystal defects on the metal particles.[4,6] However there exists ongoing controversy over the idea that these reactions are truly heterogeneous, i.e. does the reaction actually occur on the surface of the metal, or is the metal particle simply acting as a reservoir for smaller, solution phase (homogeneous) entities?[7-8]

Palladium on carbon is a common example of a simple metal compound dispersed over a solid support material. Despite its rudimentary nature, this catalyst continues to find application in industrially important processes including hydrogenations of unsaturated compounds and C-C bond forming reactions.[9-11] The key aspect of this type of supported catalysis is that the metal particles (in their elemental form) are simply dispersed throughout the solid material, not bonded by covalent or ionic means. As such, metal leaching into reaction mixtures is often observed during reactions, and again the question of true heterogeneity arises.

1.2.2 Hybrid (Immobilised) Catalysis

Immobilisation of metal complexes by tethering or grafting to an inert support material (e.g. polystyrene, carbon or silica) may be regarded as 'heterogenisation' of homogenous catalysts. In theory, this method combines the stability and recyclability of heterogeneous catalysis with the activity and selectivity associated with homogeneous catalysis. In practice however, catalysts supported in this way often display different activity to their homogeneous counterparts (e.g. lower activity).[12] This method does offer the advantage of simplified processing, allowing catalysts to be separated from reaction mixtures by a simple filtration step and potentially recycled.

Catalysts immobilised in this way suffer the drawback of limited characterisation of the catalytically active species (due to their insoluble nature) and catalyst degradation and/or leaching from the support is an ongoing problem. Nonetheless, much research has been devoted to the grafting or tethering of metal complexes onto solid supports. In fact, it represents the central theme of this project.

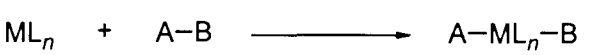
1.3 Catalytic Reactions: A Review

Advances in the field of organometallic chemistry have aided our understanding of catalysis. The presence of organic ligands co-ordinated to the metal centre to form a complex is now known to be an extremely useful method of 'tuning' the steric and electronic properties of the catalyst. Thus, the design of the ligand-metal complex allows catalysts to be tailored to some extent for a particular reaction.

Transition metals are known to form complexes with organic compounds where the metal (M) accepts electron density from a number of ligands (L_n) in an attempt to fill its outer-shell *d*-orbitals. These complexes make catalytic reactions possible by forming transient intermediates with the substrates, which undergo a series of processes whilst coordinated to the metal, yielding the product and regenerating the catalyst. The series of mechanistic steps in converting substrates to products is known as the catalytic cycle. Some of the common organometallic reactions encountered in typical catalytic cycles are briefly summarised.[13]

1.3.1 Oxidative Addition

Many catalytic processes begin with the insertion of a metal atom into a covalent bond on an organic molecule. This reaction is termed oxidative addition and usually results in the formation of a metal-carbon bond (Scheme 2). The oxidation state, co-ordination number and total electron count of the metal in the resulting complex increase by two units.

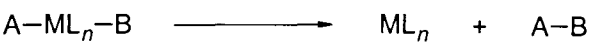


Scheme 2 Formation of a metal alkyl.
A-B = R_3C-H (where R = alkyl- or aryl-), R-X, RCO-X, H-H, Cl-Cl etc.[13]

Oxidative addition is regarded as the rate-determining step in catalytic reactions such as Sonogashira coupling and the product (the σ-alkyl or σ-aryl metal complex) is recognised as an intermediate of fundamental importance in numerous C-C bond forming reactions.[14]

1.3.2 Reductive Elimination

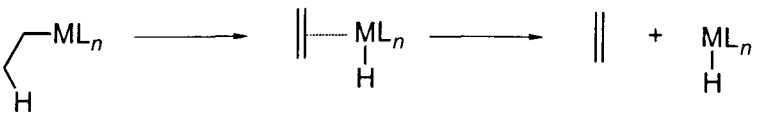
Reductive elimination is the reverse of oxidative addition. As the name suggests, the metal is reduced (i.e. oxidation state, coordination number and electron count decrease by 2). This is often the product-forming step in a catalytic cycle (Scheme 3).



Scheme 3 Reductive elimination.[13]

1.3.3 β-Elimination

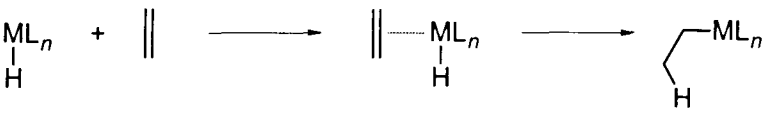
When a metal alkyl bears a β-hydrogen substituent and there is an empty *d*-orbital (vacant site) on the metal capable of forming an M-H σ-bond, β-elimination can occur (Scheme 4). This reaction requires the alkyl ligand to adopt a conformation such that the β-hydrogen is within bonding distance of the metal *d*-orbitals.



Scheme 4 β-Elimination. A hydrogen atom β- to the metal centre is transferred to the metal and the product (ethene in this case) then dissociates.[13]

1.3.4 Insertion

Insertion is the reverse of an elimination reaction. It involves the introduction of an alkenyl moiety into a M-X bond and often results in the formation of a metal alkyl (Scheme 5). The product may then be released from the complex by β-elimination. The coordination number, oxidation state and electron count of the metal remain unchanged in this reaction.



Scheme 5 Insertion of an alkenyl fragment into the M-H bond.[13]

1.3.5 Transmetallation

Many catalytic reactions require the presence of a second metal species (a co-catalyst). Transmetallation describes the exchange of ligands between two different metal complexes (Scheme 6). This process lies at the heart of numerous catalytic processes including Suzuki coupling reactions.

Scheme 6 Transmetallation, the exchange of ligands between metal-alkyl complexes.[13]

1.4 Solid Supported Transition Metals in Catalysis

As a truly multidisciplinary field, heterogeneous catalysis combines the study of surface science with organometallic chemistry. Therefore two distinct methodologies for the improvement of catalytic performance are apparent; variation of the active metal complex component and variation of the solid support material.

1.4.1 Types of Ligand

The stereoelectronic properties of the ligands coordinated to the metal centre are a major factor in determining the catalytic activity of the immobilised complex. Phosphine and *N*-heterocyclic carbene (NHC) ligands have received the most attention in the scientific literature and their merits and drawbacks have been reviewed.[15] Although both phosphines and NHCs are neutral, 2 electron donor ligands, they display markedly different geometries and electronic character.

1.4.1.1 Steric Factors

The architecture of the NHC ligand (Figure 2) is such that the -R substituents point toward the metal centre creating a 'pocket' around the active site. Phosphine ligands, being tetrahedral, necessarily direct the sterics of the substituents away from the metal.

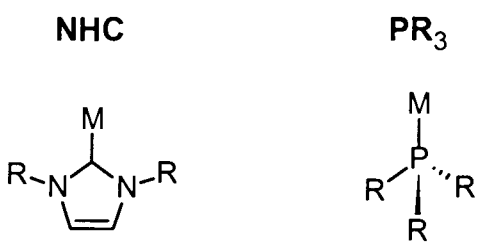
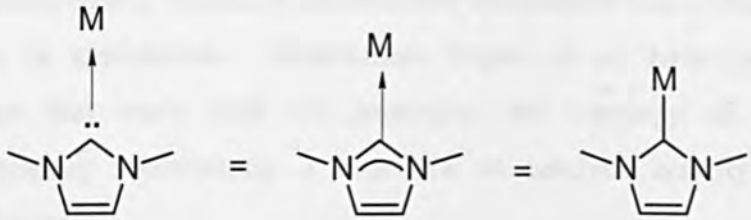


Figure 2 Structure of phosphine and NHC donor ligands.

Note that the structure shown in Figure 2 is a representation of the *N*-heterocyclic carbene nucleus; an sp^2 hybridised, neutral, 2 electron donor ligand coordinating to a metal via its lone pair. This structure may be portrayed in a number of

different ways as shown in Scheme 7, but for convenience, will be shown as above (Figure 2) throughout this report.



Scheme 7 Structural representations of the NHC ligand.

The steric properties of phosphines were first quantified by Tolman in 1970 with the introduction of the 'cone angle' concept (Figure 3).[16] The cone angle has been used to rationalise the higher activity of bulkier alkylphosphine-metal complexes in numerous catalytic reactions, with varying levels of agreement with empirical data.[17] However, the different topology of NHC ligands requires a more complex model, namely the steric parameter $\%V_{bur}$ coined by Nolan *et al.*,[18] which measures the space occupied by ligands in a sphere of 3 Angstrom radius surrounding the metal centre.

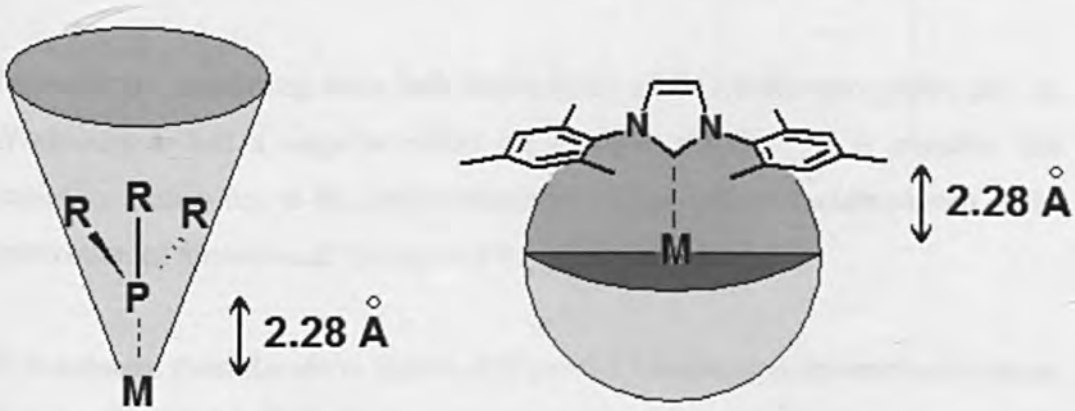
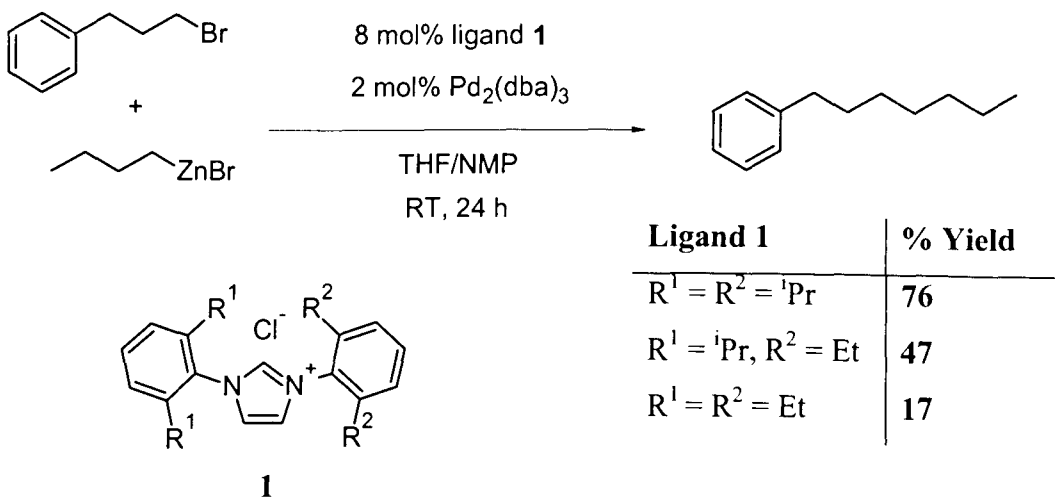


Figure 3 Schematic representation of cone angle measurement of phosphines (left) and $\%V_{bur}$ parameter of NHCs (right).

In a combined experimental and computational study, Organ *et al.* documented the effect of increasing steric bulk present on the N-aryl substituents of the NHC in alkyl-alkyl Negishi coupling reactions.[19] It has been suggested that a certain amount of steric bulk is helpful in the reductive elimination step of the mechanism, though this is speculative. Nonetheless Organ *et al.* have unequivocally demonstrated that steric bulk (in particular, the topology of the *N*-(2,6-diisopropylphenyl) substituents) is beneficial to catalytic activity in Negishi reactions (Scheme 8).



Ligand 1	% Yield
$R^1 = R^2 = {}^iPr$	**76**
$R^1 = {}^iPr$, $R^2 = Et$	**47**
$R^1 = R^2 = Et$	**17**

Scheme 8 Steric evaluation of *N*-arylimidazol-2-ylidene ligands in Negishi reactions.[19]

Interestingly, increasing steric bulk beyond that of *N*-(2,6-diisopropylphenyl), i.e. *N*-adamantyl, had a negative effect on catalytic activity. It is possible this inhibition occurs due to the steric obstruction of the oxidative addition step or the prevention of formation of the active Pd-NHC complex.

It is apparent from the above results that the *N*-2,6-(diisopropylphenyl) substituent is indeed a privileged structure, a concept which is revisited later in the present study. Although numerous studies on steric effects comparable to the work of Organ *et al.* are available in the literature for homogeneous catalysis, the phenomenon seems relatively unexplored in heterogeneous catalysis.

1.4.1.2 Electronic Factors

The differences in the electronic nature of the above classes of ligand arise from their ability to participate in back-bonding. Phosphines bind to metals through a strong σ-bond and the metal responds by donating significant amounts of electron density from its d_π orbitals into the vacant σ* or d_π orbital. This is known as back-bonding (Figure 4 - left).[13] NHCs are also strongly σ-donating ligands, but are generally believed to accept relatively less electron density through back-bonding than phosphines.[20] This has been the subject of much debate, as numerous experimental and computational studies have arrived at values for the π-backbonding component of the NHC-metal bond ranging from 10-40% of the total orbital interaction.[21] The NHC-metal bond length (typically 1.9-2.1 Angstroms), as determined by X-ray diffraction and infrared studies also suggests the presence of a π-component.[22]

NHC-metal complexes display sp^2 hybridised geometry around the carbene carbon. The remaining p-orbital is believed to accept electron density from the adjacent nitrogen atoms, and perhaps the entire π system of the imidazolylidene backbone,[23] in order to stabilise the carbene carbon. This is thought to prevent meaningful back-bonding contributions to the NHC-metal bond (Figure 4 - right).

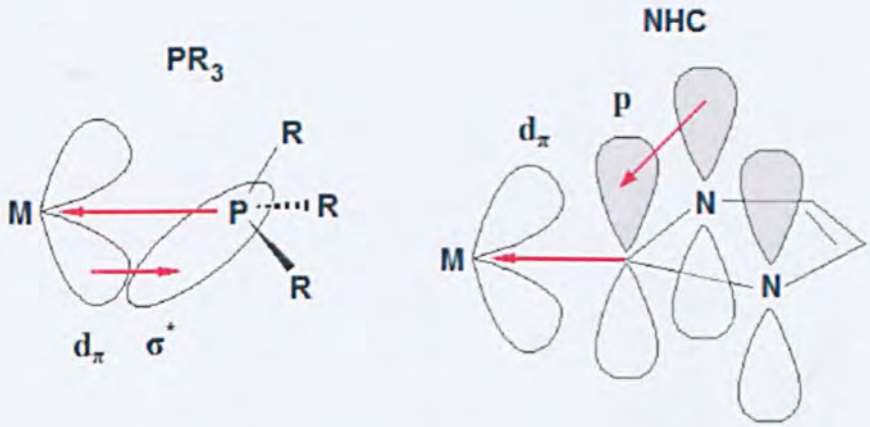


Figure 4 Difference in back bonding between phosphines and NHCs. Phosphines (left) form strong σ-bonds with the metal centre and in turn receive a back bonding contribution via the σ* orbital. The back bonding component in NHCs (right) is understood to be limited due to occupation of the carbene p-orbital by the electrons in the π system of the imidazolylidene.

This is in fact a somewhat simplified representation of the bonding situation in NHCs considering the $2p_z$ orbital of the carbene is known to participate in back bonding to some extent (depending very much on the NHC skeleton, the metal and other coordinated ligands).[24] Other factors to be considered include π-donation from the NHC to the metal and the likelihood of an electrostatic component of the NHC-metal bond.[25] However, the fact that NHCs, in general, participate in back bonding to a lesser extent than phosphines suggests a greater electron density at the metal centre. This may explain the superior performance of NHCs in numerous catalytic reactions. The most notable example of this is the inclusion of an NHC ligand into second generation Grubbs catalyst, with significant improvements observed in catalytic activity.[26]

The potential of NHC complexes in catalysis is indeed being realised in the research community. Their high levels of catalytic activity and stability not only render them excellent alternatives to phosphines, but also make them ideal candidates for immobilisation.

1.4.2 Types of Support

A diverse range of support materials for heterogeneous catalysis have been explored. Not only does the support material have dramatic implications for the physical handling of the immobilised catalyst, the choice of support may influence factors such as catalyst stability, reactivity, catalyst loading and cost (all of which are vital considerations for commercial applications). The fact that relatively few solid supported catalysts have actually found their way into industrial syntheses, despite the potential recognised by the research community suggests that the efficiency of these catalysts, in terms of production costs and recyclability, must be improved if their potential is to be realised.

The most popular support materials in the scientific literature are undoubtedly carbon and polystyrene, of which numerous examples may be cited.[30,31,42] However, various novel organic polymers and natural materials are now being employed as catalyst supports.[27] Of particular interest in this report is silica (of the general formula SiO_2) on account of its high thermal stability, versatility, and relatively low cost. Although silica occurs naturally in a plethora of different forms, much work has been published on the manufacture of various synthetic mesoporous silicas such as SBA-15 and MCM-41. Micelle templating procedures allow for highly accurate control over particle size distribution and pore size (which are of fundamental importance in catalysis).[28]

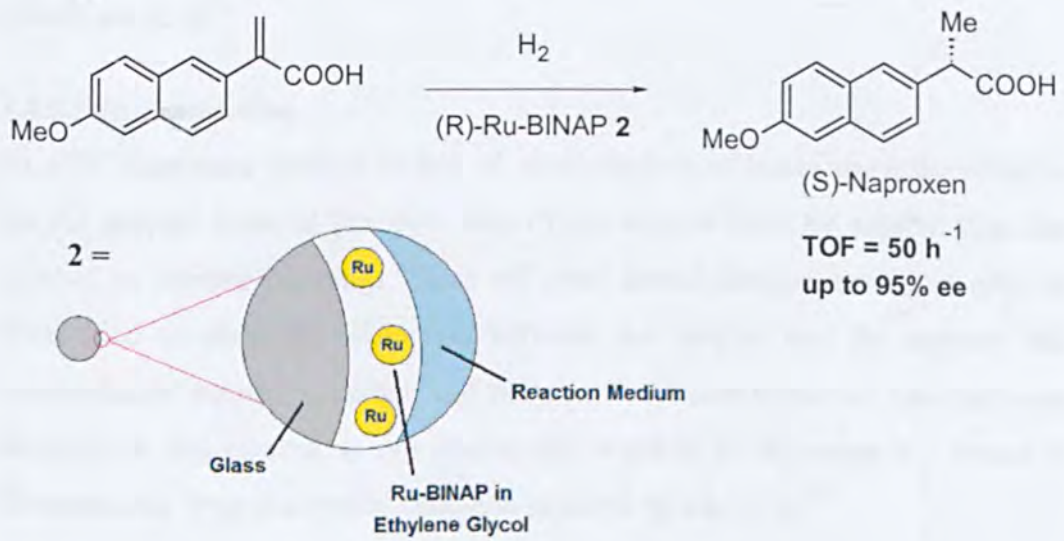
Silica also lends itself to chemical modification through surface silanol groups (Si-OH). Since, the silanol moiety displays similar reactivity to tertiary alcohols (R_3C-OH), organic linker groups may be easily tethered to the silica surface, which may be used as ligands to stabilise active metal complexes.

1.4.3 Methods of Immobilisation

1.4.3.1 Dispersion

As found with palladium on carbon and related catalysts, the dispersion technique is perhaps one of the best documented methods of immobilisation. Metal particles or complexes are simply adsorbed onto the surface of the support material and remain there by relatively weak Van der Waals and hydrogen bonding interactions. Examples of this type of immobilisation may be found in the work of Djakovitch *et al.*[10] Although one of the most straightforward methods of preparing a heterogeneous catalyst, the dispersion technique is limited somewhat by the fact that metal particles tend to leach into reaction mixtures, contaminating products and often preventing efficient recycling.

A variation on this technique can be found in biphasic heterogeneous catalysis, where the catalyst is contained within a liquid phase and the reactants are present in an immiscible solvent. This method was exemplified by Davis *et al.* who used catalyst **2**, a chiral ruthenium complex within an ethylene glycol layer on porous glass, to facilitate the synthesis of Naproxen® by asymmetric hydrogenation (Scheme 9).[29]



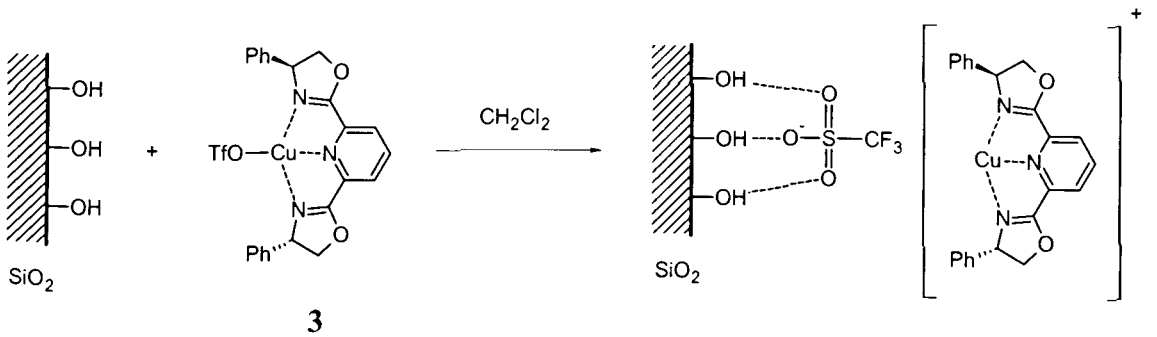
Scheme 9 Use of a biphasic heterogeneous Ru-BINAP catalyst in the synthesis of Naproxen®.

Using this technique, the authors reported very low levels of leached metal (as low as 32 ppb) and high levels of enantioselectivity. The reaction rates were

lower than that of the corresponding homogeneous catalyst by around 50%, which is typical of heterogeneous catalyst systems.

1.4.3.2 Electrostatic Immobilisation

Metals may also be attached to the surface of a support by means of ionic interactions. This strategy has been recently demonstrated by O'Leary *et al.*[30-31] in the immobilisation of asymmetric *bis*-oxazoline ligand **3** on silica (Scheme 10).



Scheme 10 Electrostatic immobilisation of PYBOX ligands on silica.

Interestingly, this catalyst system was tested on asymmetric alkynylation of imines and showed comparable activity to the corresponding homogeneous catalyst. The catalyst was also recyclable over three cycles showing only slight reductions in ee.[31]

1.4.3.3 Encapsulation

Another interesting method is that of encapsulation of metal particles within a porous support material (the pore size of the support must be smaller than the catalyst to prevent leaching). Since all other immobilisation strategies rely on some kind of chemical interaction between the catalyst and the support, the encapsulation method is unique and perhaps the closest mimic of homogeneous catalysis as the catalyst is not chemically attached to the support. Figure 5 illustrates the 'ship in a bottle' synthesis reported by Mei *et al.*[32]

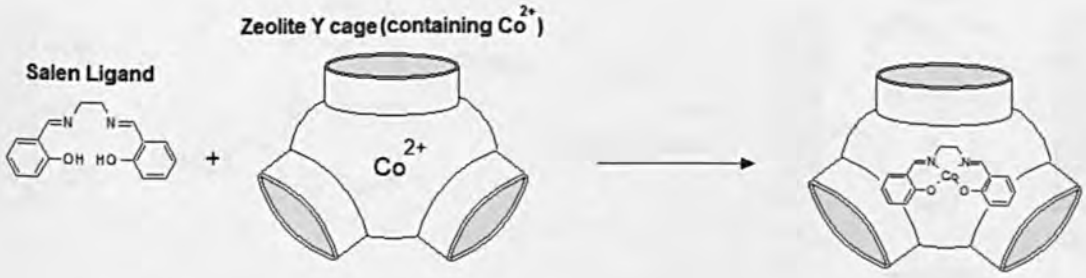


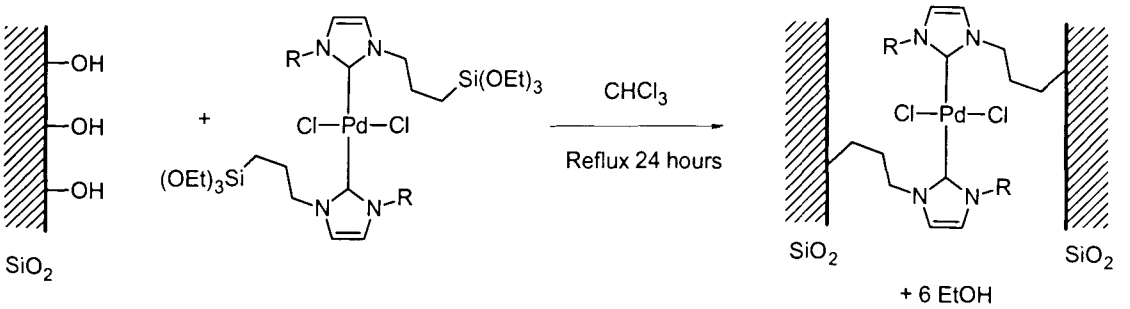
Figure 5 Ship in a bottle synthesis of Co(II) Salen complexes encapsulated in zeolite Y.

This catalyst showed modest yields and high selectivity in the oxidative carbonylation of aniline and was highly recyclable over five cycles.

Although catalyst systems of this type show high levels of recyclability and negligible levels of leaching, their synthesis is often fraught with difficulties. The preparation of encapsulated catalysts must be highly efficient due to the fact that purification of encapsulated intermediates is largely impossible. This may be avoided by polymerising the support around the preformed catalyst, as in the work Jamis *et al.*, however the metal complex used must be robust enough under the polymerisation conditions for this to be considered viable[33].

1.4.3.4 Covalent Immobilisation

One of the most popular methods for immobilisation of metal complexes is through the use of a covalently bound organic linker. The sheer number of covalently anchored heterogeneous catalysts found in the literature is a testament to the versatility of this method.[34] A recent and relevant example is found in the work of Artok *et al.*[35] The authors employed silica as their support material, taking advantage of the facile reaction between surface bound silanol groups and alkoxysilanes (Scheme 11).



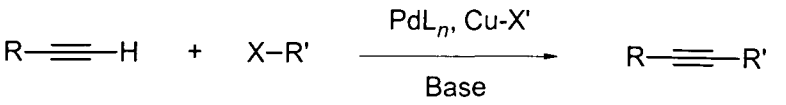
Scheme 11 Anchoring of NHC complexes to silica via condensation of alkoxysilanes with surface silanol groups. R = Bz or 2,4,6-trimethylbenzyl.

Aside from the simplicity and efficiency of this immobilisation procedure, the catalysts produced in this case proved highly active in Heck reactions and showed recyclability over 10 cycles (although successively longer reaction times were required).[35]

1.5 Cross-Coupling Reactions

1.5.1 Sonogashira Coupling

First reported in 1975,[36-38] this reaction describes the cross-coupling of a terminal alkyne with an aryl, alkenyl or alkyl halide (or triflate) (Scheme 12). Palladium and a copper co-catalyst are usually required for this reaction although variants using other metals have been described.



Scheme 12 Sonogashira cross-coupling reaction.
R / R' = Aryl, Alkyl, Alkenyl and X/ X' = Cl, Br, I or OTf.

Although this reaction represents an extremely versatile route to functionalised internal alkynes, it has yet to gain popularity in industrial processes. The presence of copper-based impurities in reaction mixtures represents a significant drawback in terms of industrial processing, necessitating additional purification steps, especially if products are being used for fine chemical or pharmaceutical applications.

Mechanistically, the Sonogashira reaction begins with oxidative addition of the organic halide to a palladium(0) species, the rate-determining step, to form a palladium(II) intermediate. This undergoes transmetallation (ligand exchange) with the copper acetylide (Figure 6, iii), which results in the formation of an intermediate σ-alkynyl complex. Reductive elimination forms the new C-C bond and regenerates the active palladium(0) complex.[36]

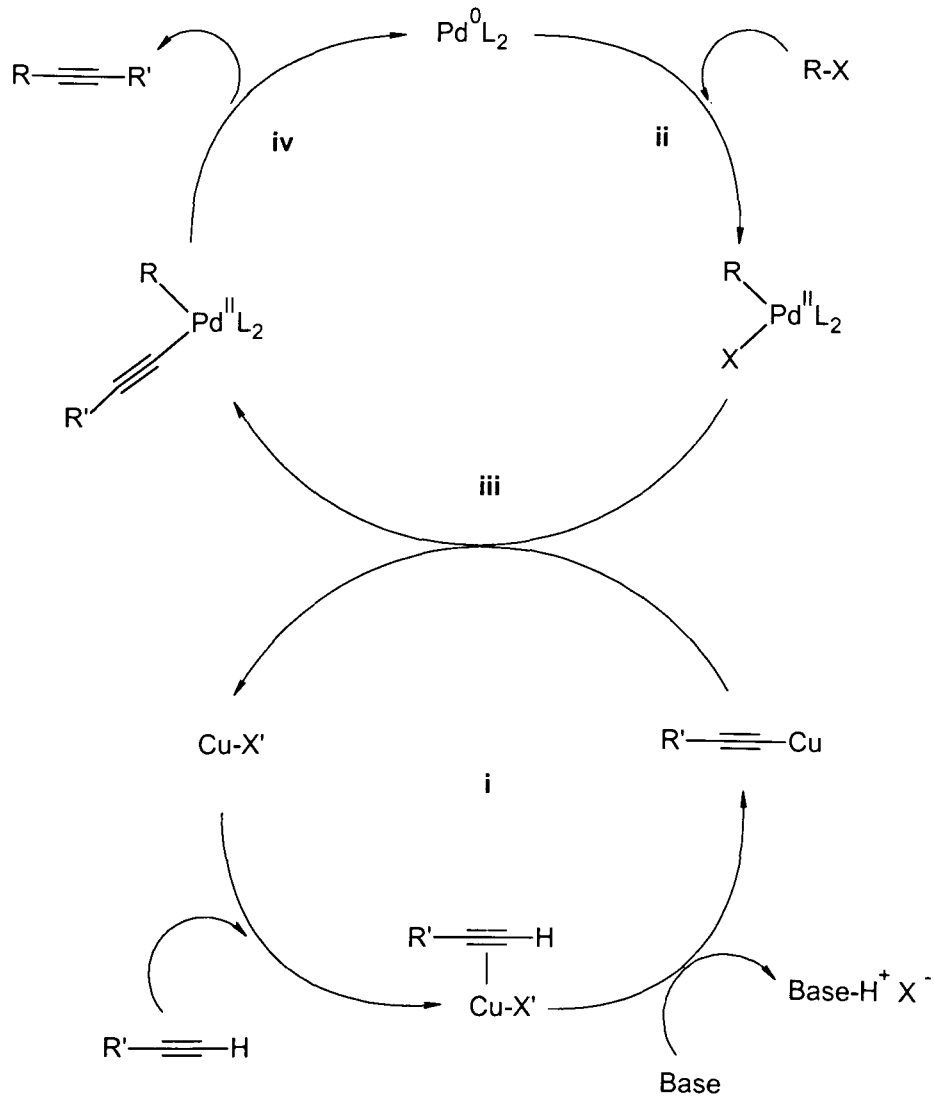
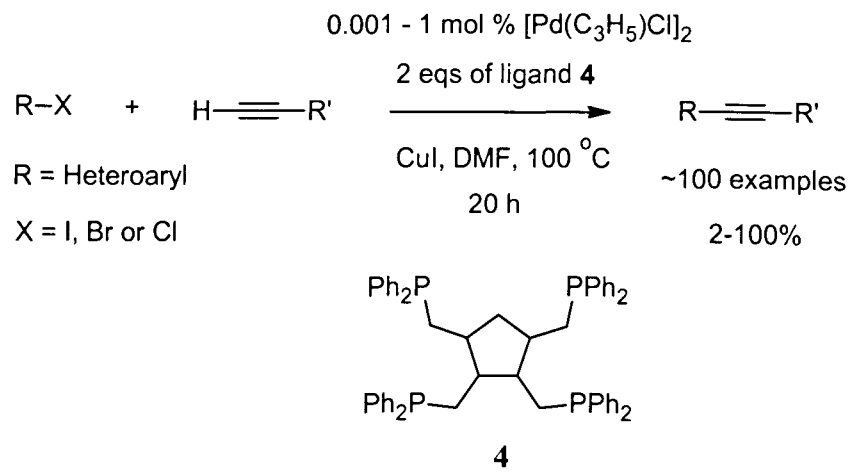


Figure 6 Established mechanism for the palladium and copper co-catalysed Sonogashira cross- coupling reaction.[36]

1.5.1.1 Homogeneous Sonogashira Coupling

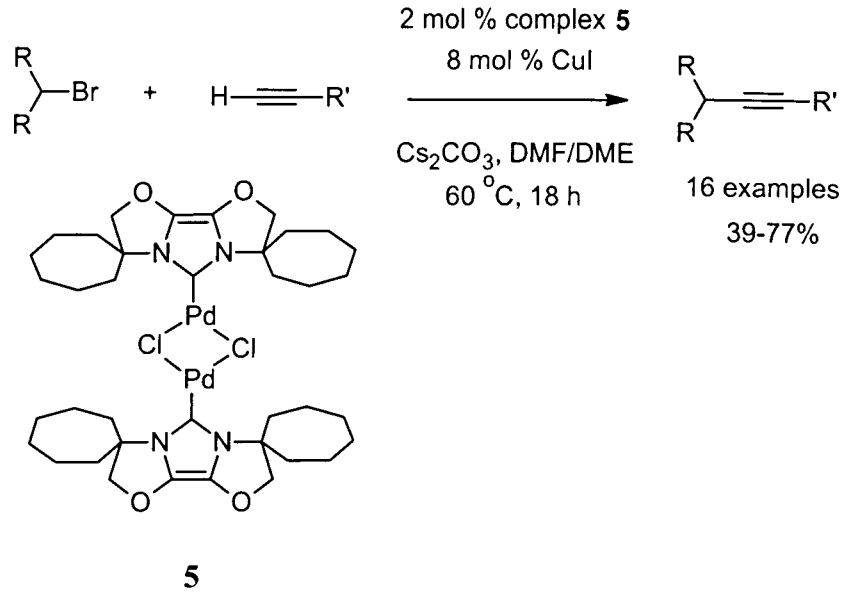
Significant advances in the area of homogeneous Sonogashira reactions include the use of bromide and chloride substrates, which are deactivated toward the initial oxidative addition step of the reaction compared to iodides. The use of aryl bromides and chlorides has been demonstrated by the groups of Leadbeater *et al.*[39], Wu *et al.*[40], and Hua *et al.*[41] to name but a few. Feuerstein and co-workers have had particular success in this area owing to the use of 'Tedicyp' **4**, a flexible *tetra*-phosphine ligand, in the coupling of heteroaryl halides with terminal alkynes (Scheme 13). Excellent yields were observed throughout, including >90% yields for chloride substrates using 1 mol % of palladium.[42-43]



Scheme 13 Feuerstein's impressive system for homogeneous Sonogashira coupling of heteroaryl iodides, bromides and chlorides.[42-43]

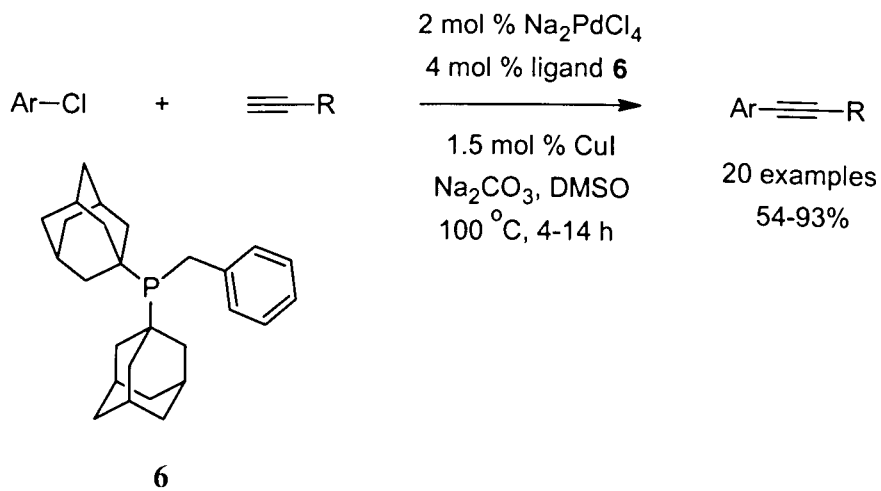
Glorius *et al.* have contributed to the broadening of the substrate profile for homogeneous Sonogashira reactions.[44] In 2006, they reported the use of their 'IBiox' series of *N*-heterocyclic carbene ligands (NHCs) for use in Sonogashira coupling of unactivated secondary alkyl bromides (Scheme 14). Good yields were reported, which have been attributed to the flexible steric properties of the IBiox NHC ligand **5**. Interestingly, when applied to an optically pure, secondary alkyl bromide, the stereochemical information was completely lost with the formation of product. This confirms that in the presence of **5**, the reductive elimination (product forming) step is non-selective. However, inclusion of a

suitably chiral ligand might result in the first enantioselective Sonogashira coupling reaction.



Scheme 14 Sonogashira coupling of secondary alkyl bromides.[44]

More recently, several groups have optimised the reaction conditions specifically for Sonogashira coupling of aryl chlorides, which are attractive substrates due to their availability, low cost and low environmental impact. Plenio *et al.* demonstrated excellent conversions throughout a range of aryl chlorides using bulky, adamantyl phosphine ligands **6** (Scheme 15).[45]

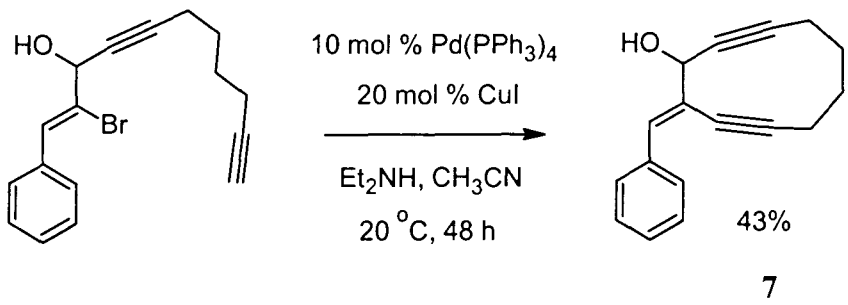


Scheme 15 Activation of the C-Cl bond for Sonogashira coupling of a range of substrates.[45]

Compounds **4**, **5** and **6** are among the most active catalysts in Sonogashira reactions to found in the literature and all employ ligands with considerable steric bulk. This concept will be frequently encountered throughout this work.

1.5.1.2 Intramolecular Sonogashira Coupling

Examples of intramolecular Sonogashira reactions can also be found in the literature, such as the work of Dai *et al.*[46] who constructed a highly strained 10-membered ring skeleton **7** as a precursor to the ene-diyne motif present in calicheamicin-type anticancer compounds. This group used commercially available *tetrakis*-triphenylphosphine palladium and CuI under mild conditions to facilitate 43% conversion to the ene-yne product (Scheme 16).



Scheme 16 Intramolecular Sonogashira reaction.[46]

1.5.1.3 Copper-Free Sonogashira Reactions

More recently, a copper-free variant of the Sonogashira reaction has found its way into the scientific literature.[47] Although these processes tend to require harsher conditions and suffer lower conversion rates, they represent a more environmentally friendly route to functionalised alkynes. Much progress has been made over the last decade and a mechanism for the copper-free Sonogashira reaction has been proposed (Figure 7).[48]

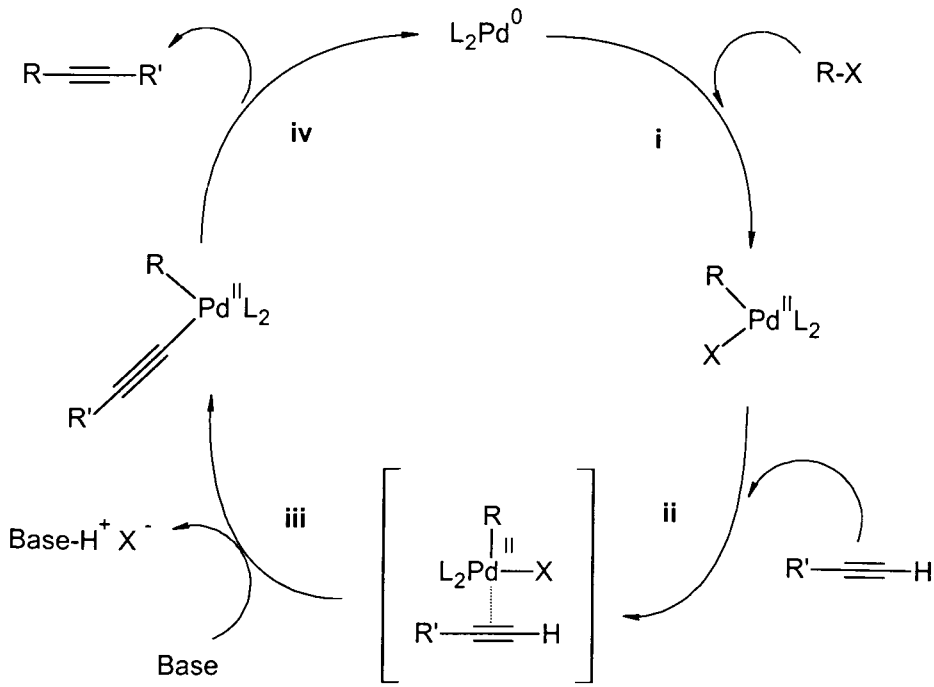
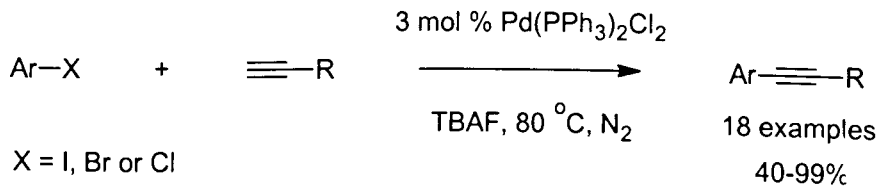


Figure 7 Proposed mechanism for the copper-free Sonogashira cross coupling reaction.[48] i) Oxidative addition ii) Association of the alkyne with the palladium (II) species iii) Deprotonation iv) Reductive elimination.

Some authors have found it possible to carry out Sonogashira couplings without the need for copper or organic solvent. The inspirational work of Li *et al.* demonstrates that aryl iodides, bromides and chlorides can be efficiently employed in Sonogashira coupling reactions under environmentally benign conditions (Scheme 17).[49]



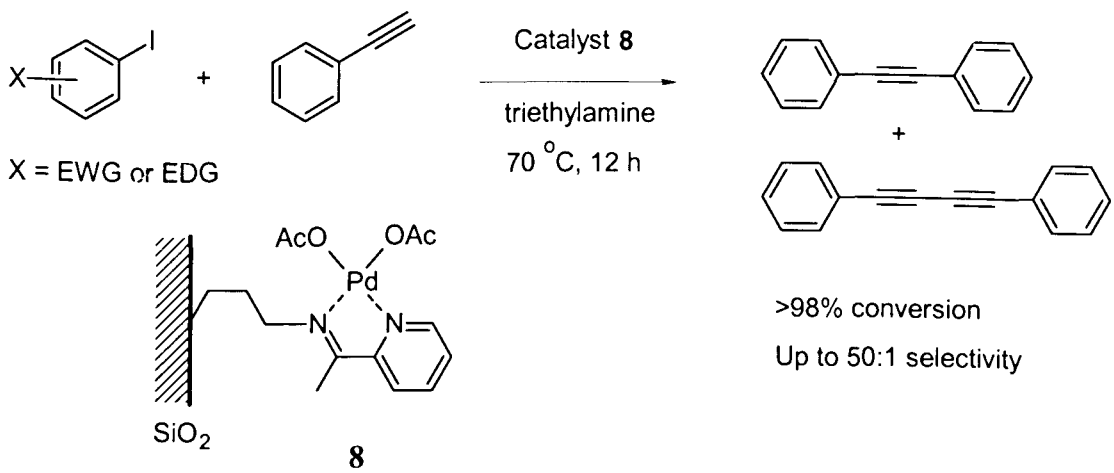
Scheme 17 Sonogashira cross coupling, which does not require copper or organic solvent.[49]

Their success can mainly be attributed to the tetrabutylammonium fluoride additive (TBAF - an ionic liquid) and strictly anhydrous experimental conditions. The authors propose a mechanism for the process which is very similar to the

copper-free mechanism (Figure 8), but with TBAF acting as a base to deprotonate the alkyne (they also alluded to the idea of TBAF acting as a phase transfer catalyst, which may be partly responsible for the high activities observed).

1.5.1.4 Heterogeneous Sonogashira Coupling

Following the pattern of increasingly environmentally-friendly Sonogashira couplings, the next logical step was to perform the reaction using a heterogeneous (recyclable) catalyst. Originally the reaction was reported as a homogeneous process (using *bis*-(triphenylphosphine)palladium dichloride and copper iodide), however numerous heterogeneous variants have now been reported. In 2005, Macquarrie *et al.* reported the synthesis and testing of silica-bound, *N,N*-chelated palladium complex **8** (Scheme 18) in copper-free Sonogashira reactions.[48] The authors were particularly interested in the selectivity of the catalyst for the cross-coupled product (in contrast to the alkyne-alkyne homocoupling side reaction first documented by Glaser[50]).



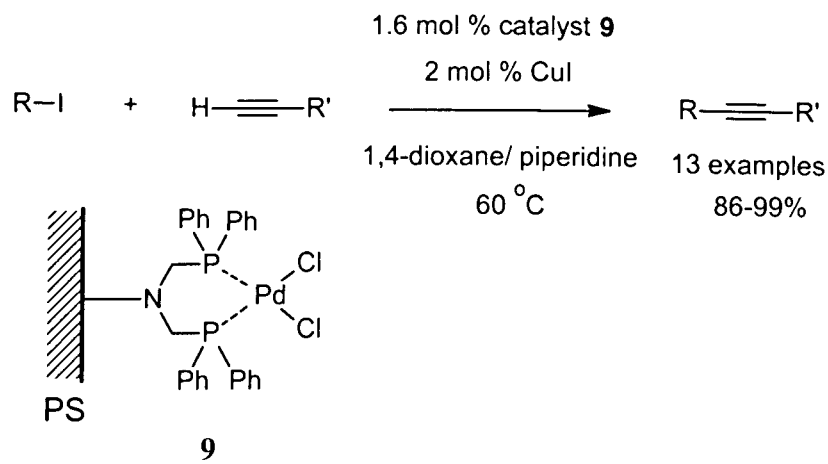
Scheme 18 An investigation into the selectivity of a silica supported palladium catalyst in Sonogashira reactions.[48]

Macquarrie *et al.* found that the selectivity observed was related to the electronic nature of the aryl iodide employed. Substrates bearing electron-withdrawing groups (EWGs) reacted faster and with superior selectivity when compared to substrates containing electron-donating groups (EDGs). Although this work is not particularly groundbreaking, the catalyst and conditions used are relatively 'green' and it does address the issue of the formation of unwanted side products.

Homocoupling of alkynes only appears to become significant when electronically deactivated substrates are used, which tend to undergo oxidative addition less readily. The low activity of this catalyst might be attributed to the relatively weak σ-donating properties of iminopyridine ligand **8** (compared with phosphines or NHCs).

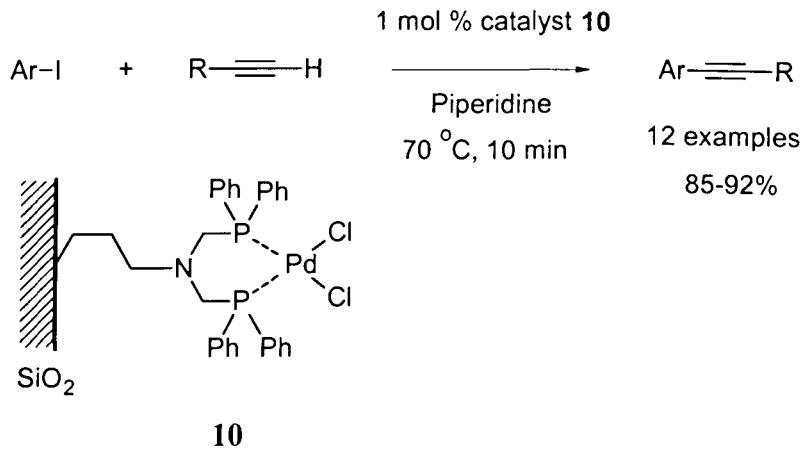
Already we note a trade-off between high catalytic activity and environmental concerns. There remains room for improvement as far as environmentally benign, heterogeneous Sonogashira reactions are concerned and numerous research groups have focussed upon just that.

Breinbauer *et al.* have reported the use of a palladium(II) *bis*-phosphine complex **9** immobilised on polystyrene (Scheme 19).[51] These authors found that the catalyst could be used in four consecutive cycles and obtained quantitative conversions throughout, although an increased amount of catalyst (5 mol %) and long reaction times (>12 h) were required. A major drawback associated with their protocol is the use of 2 mol % of copper(I) iodide, which not only appears as a contaminant in products, but is also implicated in the alkyne-alkyne homocoupling reaction to which the authors made no reference.



Scheme 19 Polystyrene supported catalyst used for Sonogashira coupling of iodoarenes with alkynes.[51]

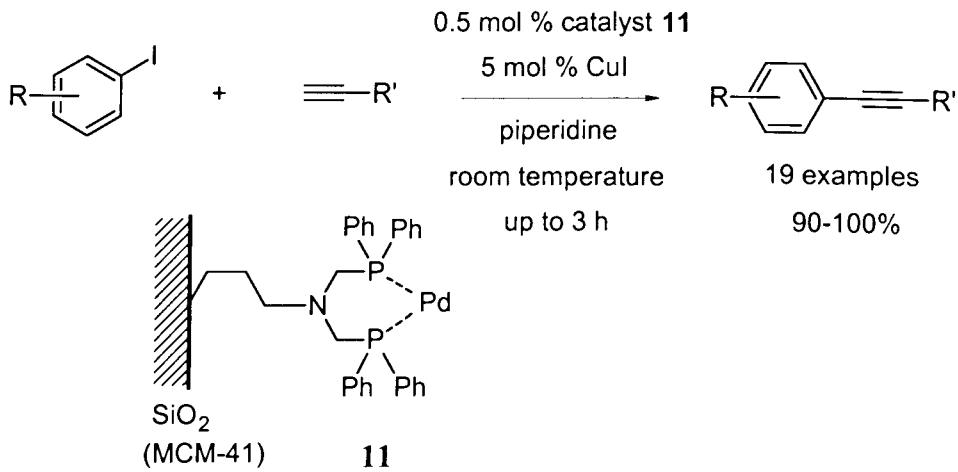
Tyrrell *et al.* reported a solid supported palladium phosphine complex **10** in 2005,[52] which was structurally similar to that of Breinbauer *et al.*[51] Their support material of choice however was commercially available silica gel. The low cost, thermal stability and chemically inert nature of silica give it advantages over other support materials and, unlike polystyrene and related organic polymers, the material does not require 'preswelling' in organic solvent. Tyrrell *et al.* reported the synthesis and testing of this catalyst in Sonogashira coupling reactions of aryl iodides as shown in Scheme 20.



Scheme 20 Silica supported catalyst used for Sonogashira coupling of iodoarenes with alkynes.[52]

This catalyst showed good activity in the Sonogashira reactions, furnishing excellent conversions in minutes, and was shown to be recyclable (though this resulted in lower rates of conversion). However, the catalyst was only tested on aryl iodides with limited functionalities and its reactivity towards aryl bromides or indeed other catalytic reactions was not explored.

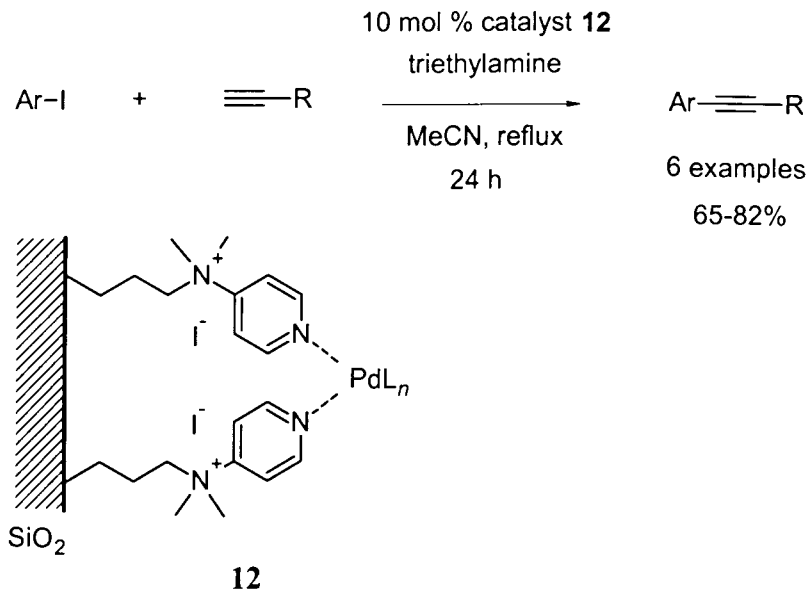
Recently, the group of M. Cai *et al.* have reported the synthesis and catalytic activity of MCM-41-supported phosphine **11**[53] and thioether[54] complexes of palladium in a range of catalytic processes. Their phosphine based catalyst furnished excellent yields in Sonogashira couplings for a wide range of aryl iodides (Scheme 21).



Scheme 21 MCM-41 supported *bis*-phosphine palladium catalyst used by Cai *et al.*[53]

Reactions were carried out at room temperature with low catalyst loadings and required only 3 h reaction time (at most). The catalyst exhibited a remarkable degree of recyclability, with near-quantitative conversions over 10 cycles. Unfortunately the authors did use 5 mol % of copper(I) iodide and made no reference to the activity of the catalyst towards aryl bromide substrates. This *bis*-(diphenylphosphine)palladium motif has been encountered several times already in this review. Although the phosphine ligand is easily oxidised in the presence of air, Cai *et al.* demonstrated impressive reusability of the catalyst (compared with the groups of Tyrrell and Breinbauer). This may be due to the fact that they employed highly regular, nanostructured silica (MCM-41) or perhaps because they preformed the active palladium(0) species (rather than *in situ* reduction) and took extreme precaution against exposing the catalyst to oxygen between cycles.

More recently, Polshettiwar *et al.* published an account of their investigations into preparation of catalyst support materials containing pyridyl ligands **12**.[55] Notably, they obtained highly regular nanostructured supports via template-assisted condensation of triethoxysilylated precursors. The group obtained respectable yields in Sonogashira couplings without the need for a copper source (Scheme 22), and went on to demonstrate good catalytic activity in Heck and Cyanation reactions.



Scheme 22 Palladium catalyst supported on nanostructured silica prepared using micelle-templating methods.[55]

It is evident from the scientific literature that protocols for Sonogashira coupling reactions have evolved considerably over the last few decades. The development of highly active catalysts capable of turning over even the most deactivated halide substrates is of great industrial significance, as is the appearance of numerous immobilised catalysts, which may be removed from reaction vessels by filtration and recycled. However, a catalytic system combining both of these attractive features has yet to be reported for Sonogashira reactions.

1.5.2 Suzuki-Miyaura Coupling Reactions

The Suzuki-Miyaura reaction describes the coupling of a boronic acid (or ester) with an aryl, alkenyl or alkyl halide (or triflate). The reaction between phenylboronic acid and a range of aryl bromides using a homogeneous palladium catalyst, *tetrakis*-(triphenylphosphine)palladium(0), was first reported in 1979[56] and has attracted considerable attention in the scientific community since then as it arguably represents the most efficient and versatile route to the commercially important biaryl motif.[57] The mechanism is reported to proceed via oxidative addition of the palladium(0) catalyst to the halide substrate followed by transmetallation with the boronate salt and finally reductive elimination to yield the product and regenerate the active palladium(0) species (Figure 8).[58]

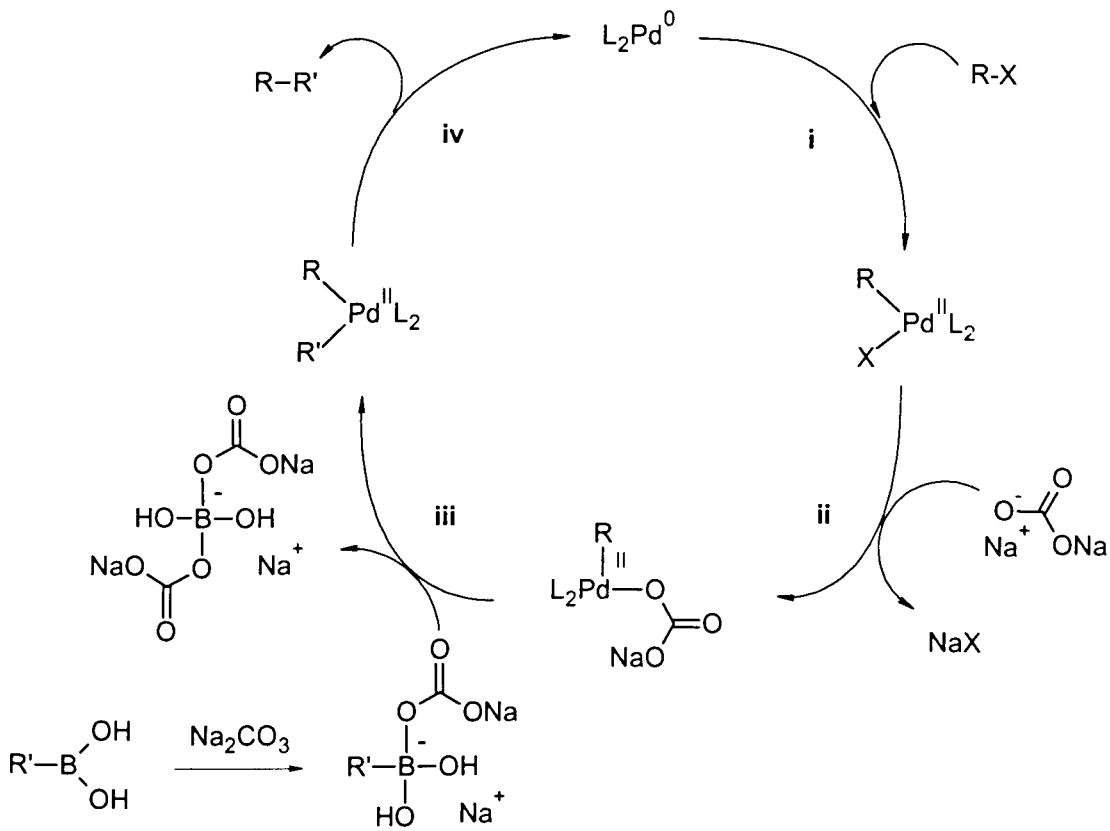


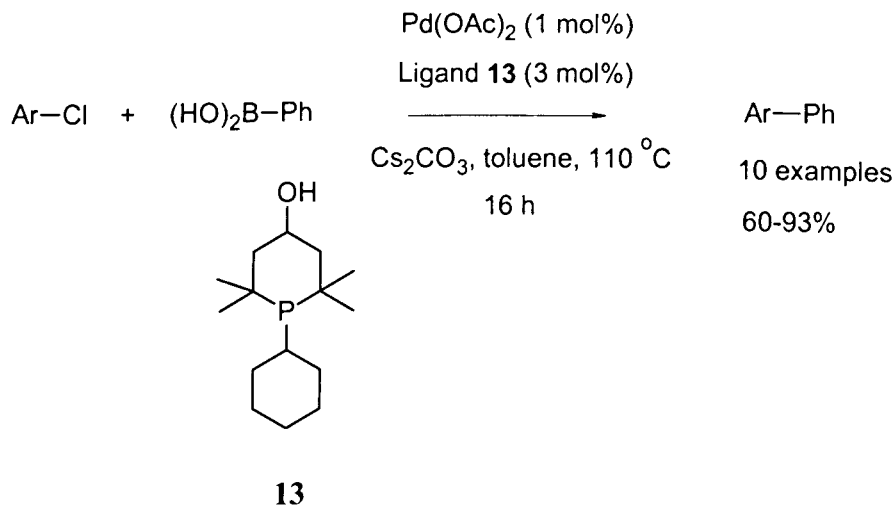
Figure 8 Proprosed mechanism for the Suzuki-Miyaura cross coupling reaction.[58]
i) Oxidative Addition, ii) Coordination of base, iii) Transmetallation iv) Reductive Elimination.

Protocols have now been developed for efficient coupling of chloride substrates under mild conditions, including sterically hindered or electronically deactivated substrates.

1.5.2.1 Suzuki Coupling of Aryl Chorides

Recent examples of Suzuki reactions using challenging substrates employ mainly alkyl phosphine and *N*-heterocyclic carbene ligands although numerous other catalyst systems have been developed. Much of the recent work revolves around catalysts for the coupling of chloride substrates and/or catalysts which can operate under milder conditions. This material has been extensively reviewed.[59]

A recent example of the application of bulky, alkyl phosphine ligands to the Suzuki coupling of challenging electron-rich or *ortho*- substituted aryl chlorides is demonstrated in the work of McNulty *et al.*[60] The mixed donor P-, O- ligand **13** shown in Scheme 23 proved to be the most effective in their range of ligands screened.



Scheme 23 Coupling of challenging chloride substrates.[60] Ar = Ph; 2-OMe; 2,4-OMe; 2-NH_2 etc.

Although the presence of a remote hydroxyl group would be expected to stabilise the palladium complex, these authors postulated that the active catalyst actually consisted of the mono-dentate palladium(0) complex **14**, formed by a conformational change in the cyclohexyl subunit (Figure 9). The idea of formation of a more reactive *mono*-ligated palladium species from a *multi*-ligated complex *in situ* is a concept which has been used to explain increased activity for a range of catalysts with bulky substituents.[61]

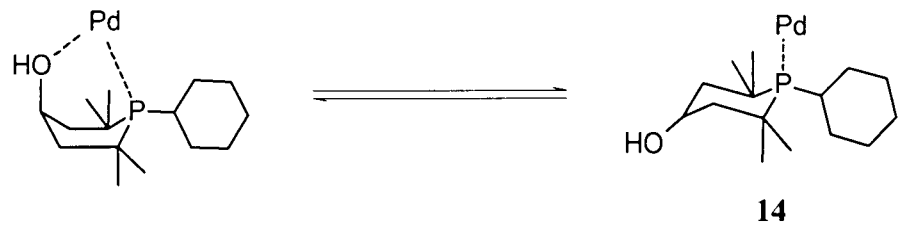
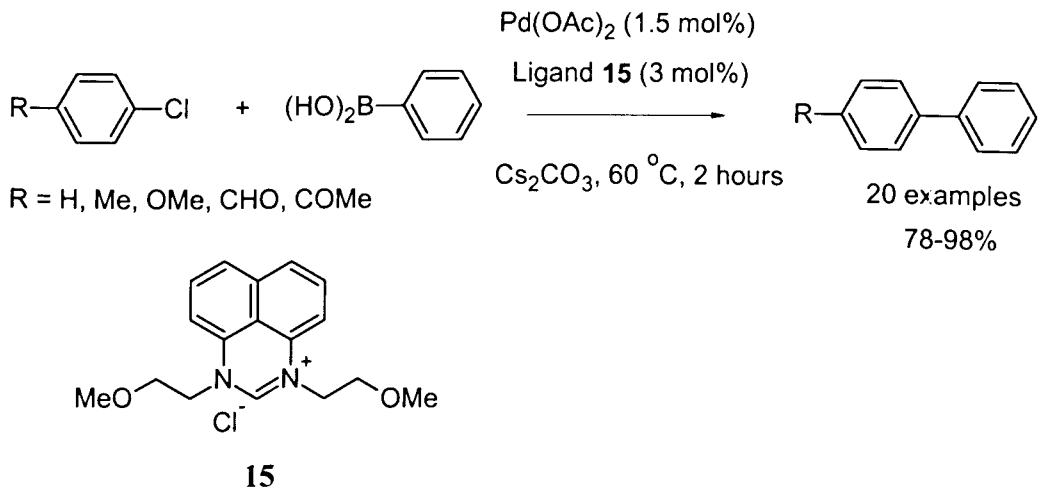


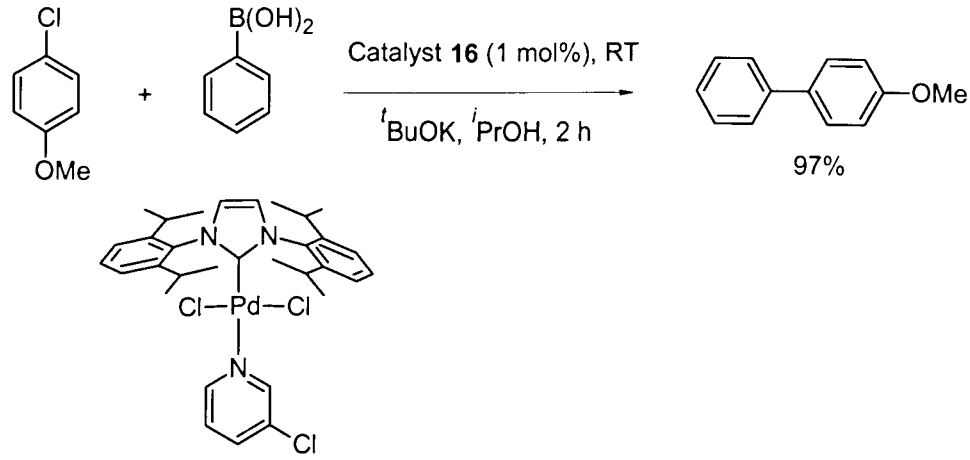
Figure 9 Proprosed *in situ* activation of *P*-, *O*- mixed donor Pd complex.[60]

Ozdemir *et al.*[62] demonstrated highly efficient couplings at 60 °C using a range of 1,3-dialkyl pyrimidin-2-ylidium NHC ligand precursors such as **15** (Scheme 24). Most notably, this catalyst system was reported to be fully air stable, a feature that may prove crucial for commercial applications (simplified operating conditions and recycling etc.).



Scheme 24 Use of pyrimidin-2-ylidene NHC ligands for Suzuki coupling of aryl chlorides under mild conditions.[62]

Another important class of NHC ligands being employed in various organometallic reactions (including Suzuki couplings) was developed by the Organ group at York University (Canada) and is known as 'PEPPSI' (Pyridine Enhanced Precatalyst Preparation Stabilisation and Initiation). PEPPSI.IPr **16** has been successfully applied to the Suzuki reaction[63] (Scheme 25), and is currently finding applications in numerous other catalytic reactions,[64] often displaying superior activity to analogous *in situ* prepared NHCs.



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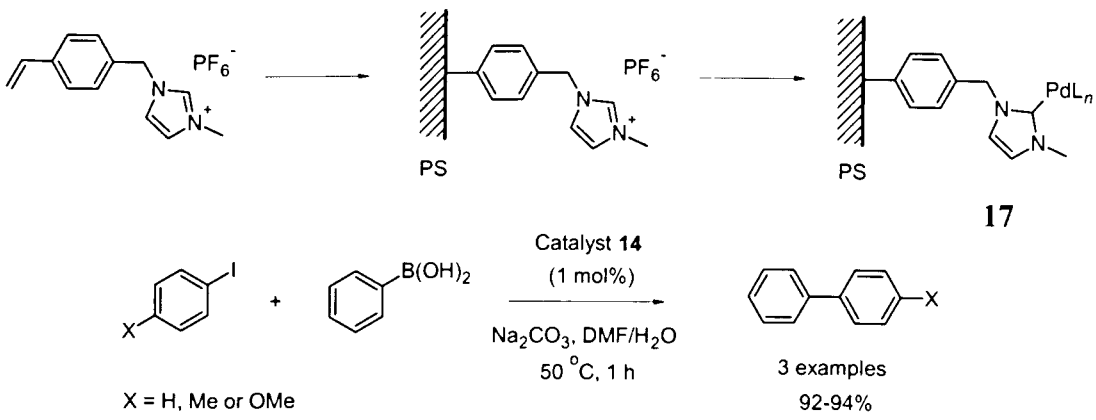
Scheme 25 Testing of PEPPSI.IPr in Suzuki coupling of a deactivated aryl chloride.[63]

Crucial to the success of this catalyst was the incorporation of a sterically bulky NHC ligand which is strongly σ-donating (e.g. IMes, IPr etc.) and a 3-chloropyridine 'throw-away' ligand, which is labile and designed for rapid *in situ* generation of catalytically active species (the Pd^0 complex). As well as demonstrating the near-quantitative conversion of 4-chloroanisole at room temperature (Scheme 25), the authors applied the catalyst to the synthesis of various sterically hindered and electronically deactivated substrates, including heterocyclic compounds, reporting excellent yields throughout.

PEPPSI is reported to be stable to air and moisture which is a key advantage over numerous existing NHC catalyst systems which tend to require handling under an inert atmosphere. In fact no stages in the preparation of this catalyst require a protective environment as the authors amply demonstrated in their 'coffee cup' synthesis.[64] The high activity and versatility of this class of catalyst, coupled with the low environmental impact and the ease of handling, is likely to make it appear attractive to industry. However, as yet PEPPSI is not recyclable.

1.5.2.2 Heterogeneous Suzuki Coupling

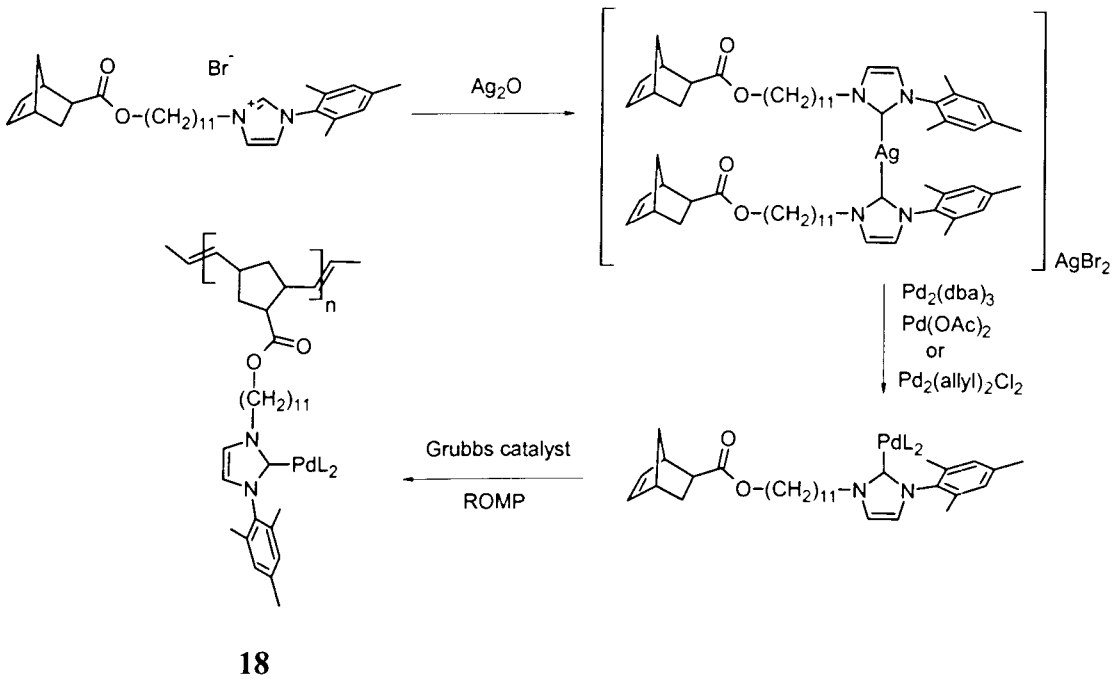
Of particular interest are the recent attempts at immobilising various NHC complexes of palladium for use in heterogeneous Suzuki couplings. A relatively early attempt at such a process was accomplished by Lee *et al.* in 2004.[65] This group prepared a styrene monomer containing an imidazolium salt moiety, which could be polymerised and then metallated to yield NHC complex **17** supported on the surface of a polystyrene resin (Scheme 26). The group went on to demonstrate the activity of the catalyst system in Suzuki reactions, which appeared to be limited to aryl iodides (not a particularly impressive feat). However, the catalyst did exhibit some level of reusability, as it could be reused under the same conditions with only small (less than 10%) decreases in conversion rates.



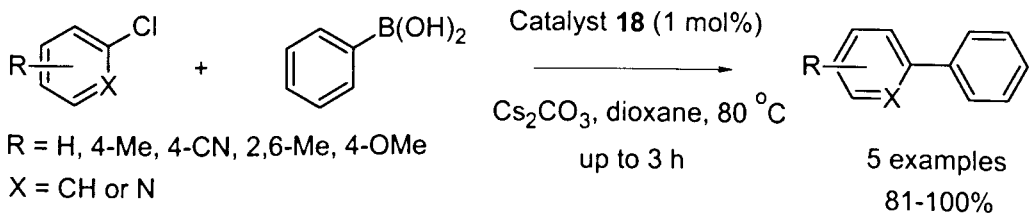
Scheme 26 Preparation and testing of polystyrene-supported NHC-Pd complex.[65]

Since then, immobilised catalysts have been reported for Suzuki coupling reactions which have much higher activity and thus a broader substrate scope. A shining example of immobilised NHC catalysts for Suzuki reactions can be found in the work of Sommer and Weck.[66] This group prepared a poly(norbornene)-supported NHC palladium complex **18** (Scheme 27). Because the monomeric complex was prepared prior to polymerisation and was soluble in chloroform, NMR and mass spectrometry could be used to elucidate the structure of the precatalyst. This catalyst system may be considered immobilised, but perhaps not truly heterogeneous (due of the fact that the polymer is soluble in the reaction

mediums used - this is debatable). The catalyst performed exceptionally well in Suzuki coupling reactions, turning over even the most challenging substrates in under 3 h (Scheme 28). Most notably, 2,6-dimethylchlorobenzene was successfully arylated in 90% yield using only 1 mol% of their poly(norbornene)-supported catalyst. The authors also carried out extensive leaching investigations using atomic emission spectroscopy to confirm that the reaction was, at least predominantly, taking place on the tethered palladium complex as opposed to in solution.



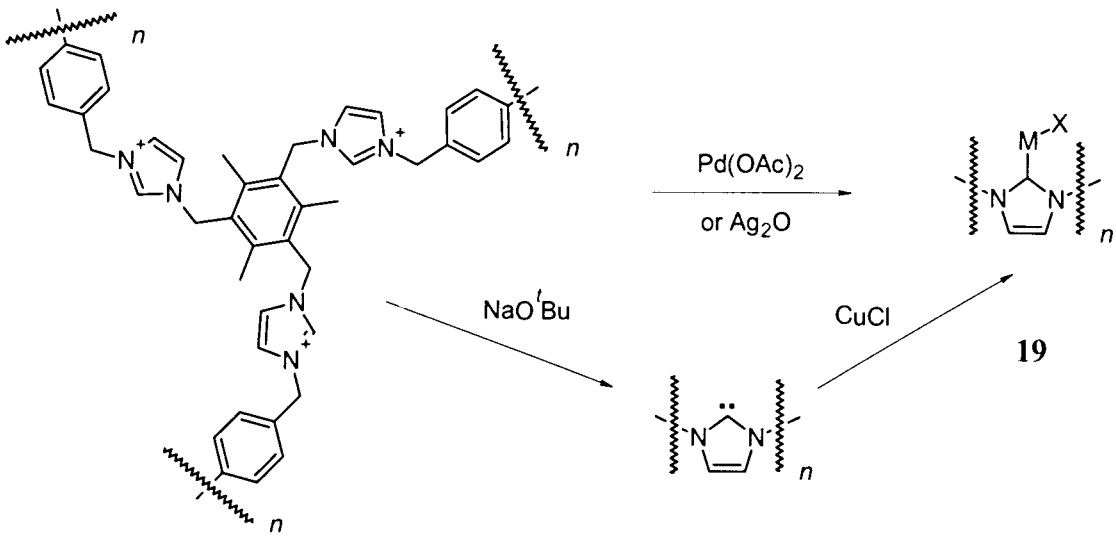
Scheme 27 Preparation of poly(norbornene)-supported Pd NHC complex.[66]



Scheme 28 Testing of poly(norbornene)-supported catalyst **18** in Suzuki coupling of aryl chlorides.[66]

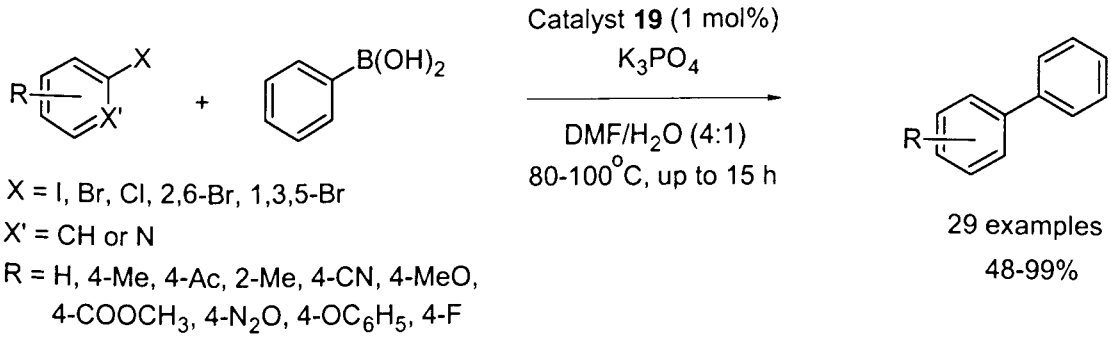
Attempted recycling showed a sharp decrease in catalytic activity (with conversions dropping to 44% at the third cycle), which is proposed to be related to the reduced solubility of catalysts recovered from reaction mixtures.

A promising strategy for supporting NHC complexes was recently illustrated in the work of Ying *et al.*[67] Their support material was composed of poly(imidazolium salts), which could be converted to the corresponding NHC-metal complex by treatment with the appropriate agent (Scheme 29).



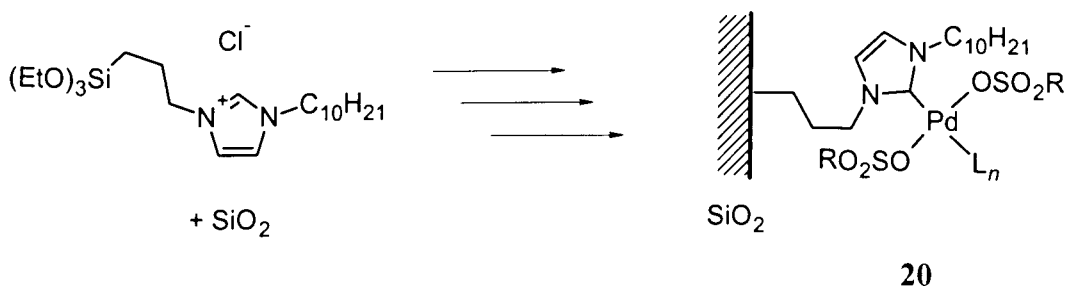
Scheme 29 Preparation of imidazol-2-ylidene supported *N*-aryl NHC complexes.[67] M = Pd, Ag or Cu.

The imidazol-2-ylidene-supported catalyst **19** proved to be highly efficient, accomplishing the coupling of activated aryl chlorides in near-quantitative yields with a catalyst loading of 2 mol% (Scheme 30). The group went on to demonstrate recycling of the catalyst over six consecutive cycles in the reaction between 4-chlorobenzonitrile and phenylboronic acid (>95%). Recycling of catalysts in Suzuki reactions of aryl chlorides is indeed an impressive feat, very few examples of this can be found in the scientific literature. Interestingly, the reusability of the catalyst was only realised by treating the poly(imidazolium salt) precursor for two days at 120 °C. This apparently increased the amount of crosslinking in the polymer network and thus the stability of the immobilised complex was greatly improved.

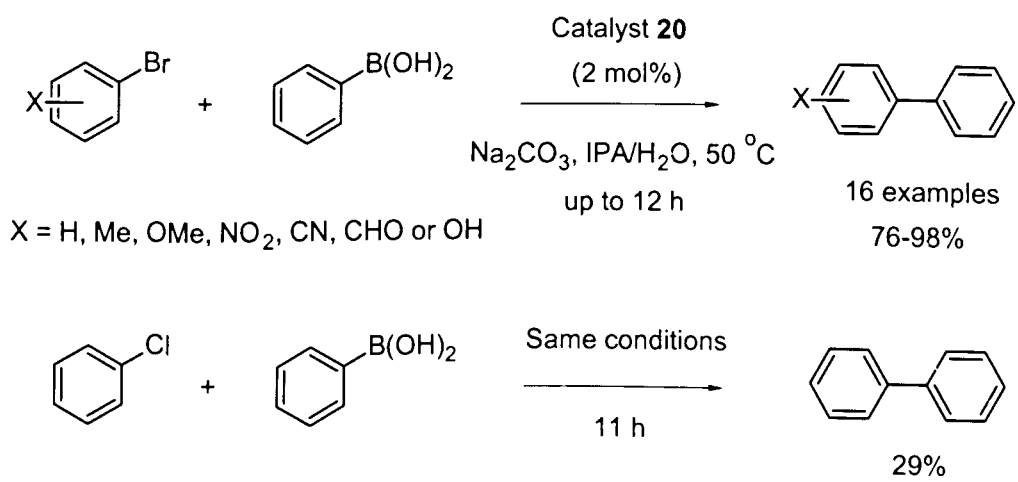


Scheme 30 Testing of imidazol-2-ylidine supported *N*-aryl NHC Pd complex **19**.[67]

In 2007, Sen and Tandukar published their work detailing preparation of a silica-supported NHC Palladium catalyst **20** and its testing in Suzuki and Heck reactions (Scheme 31 and 32).[68] A wide range of biaryls were prepared in good yields from aryl bromide substrates and the catalyst showed some activity for chloride substrates.



Scheme 31 Preparation of silica supported *N*-alkyl NHC-Pd catalysts. R = $C_{12}H_{25}$ or $C_6H_4CH_3$.[68]

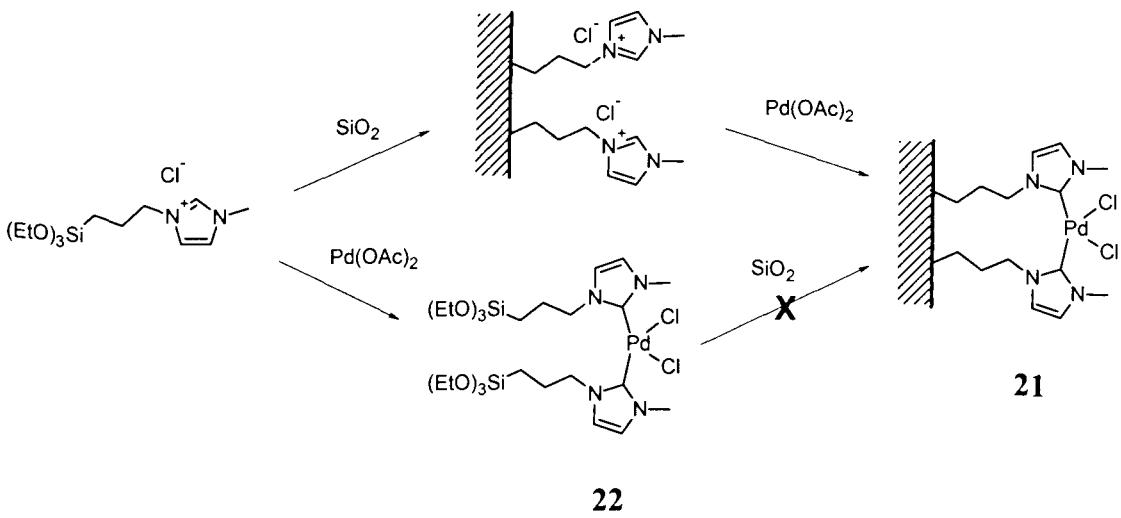


Scheme 32 Suzuki coupling reactions using a silica-supported NHC-Pd catalyst **20**.[68]

This paper was significant as it was among the first successful applications of silica-supported palladium-NHC complexes to Suzuki coupling of aryl bromide substrates. This catalyst was shown to be tolerant of a wide range of functionalised aryl bromides and even showed some activity in the reaction of chlorobenzene with phenylboronic acid, apparently a first for NHC-palladium catalysts immobilised on silica (Scheme 32).

Unfortunately, the symmetry of the biphenyl product obtained from the reaction between chlorobenzene and phenylboronic acid prevents the authors from being able to distinguish the cross-coupling reaction from boronic acid homocoupling. The catalyst was apparently inactive when other chloride substrates were employed, which is only evident due to the absence of such data.

The group of Myung-Jong Jin *et al.* reported similar findings that same year using the *N*-methyl NHC derivative **21**.[69] Rather than just grafting the imidazolium salt precursor to the silica support with subsequent metallation, this group also attempted the synthesis of the entire *bis*-NHC palladium complex **22** prior to immobilisation (Scheme 33).

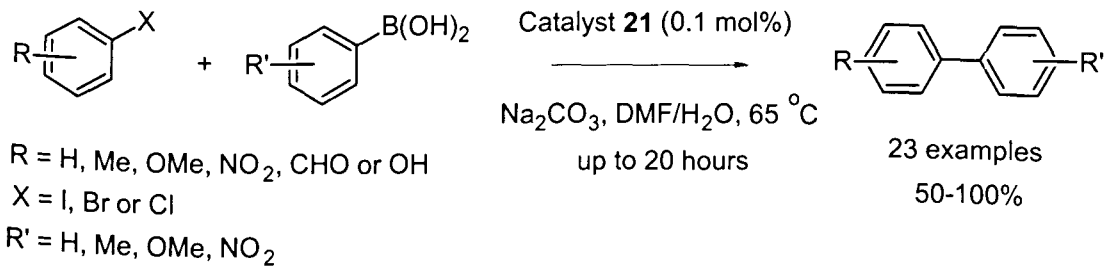


Scheme 33 Preparation of silica supported *bis*-NHC Pd complex **21**. Only the above route was feasible due to insolubility of the triethoxysilated *bis*-NHC complex **22** in organic solvents.[69]

The main advantage associated with the latter synthetic route is that complex **22** should be soluble in organic solvents, which would allow for characterisation by NMR and mass spectrometry (mass spectrometry would be particularly useful as

it may indicate whether the *mono-* or *bis*-NHC species was present). Unfortunately, the authors reported that immobilisation of the preformed *bis*-NHC complex was impossible due to solubility issues, which is surprising, and did not include characterisation data for the intermediate *bis*-NHC complex **22**.

Despite the lack of characterisation, their catalyst proved to be extremely effective for Suzuki couplings of iodides and bromides, which were coupled in near quantitative conversions in under 1 h using only 0.1 mol% of catalyst (Scheme 34).

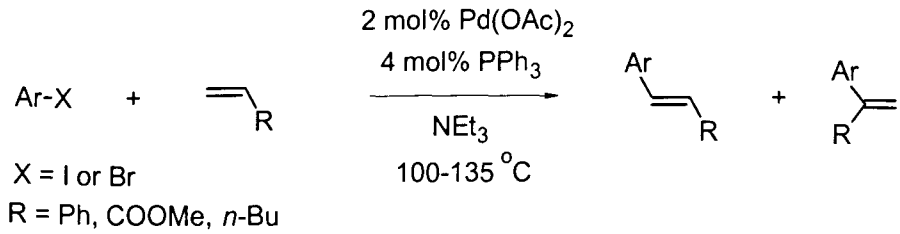


Scheme 34 Suzuki couplings of aryl iodides, bromides and chlorides using silica supported *bis*-NHC Pd catalyst **21**.[69]

Interestingly, three aryl chloride substrates were included in their testing range. Conversions of these substrates were modest (50-66%), required between 12 and 20 h and significant amounts of homocoupling side products were observed; nonetheless, it illustrates that silica-supported NHC-Pd complexes do have potential in this area. Another noteworthy feature of this work was the recycling studies carried out. The catalyst could be reused up to six times for couplings of iodides and activated bromides with negligible decrease in conversion rate. However, closer scrutiny of the results reveals that the catalyst loading was increased to 0.2 mol% for these studies and the time taken to achieve these very high conversions was not reported.

1.5.3 Heck Reaction

The arylation of alkenes using transition metal complexes was first documented by Heck in 1968,[70] however the process required stoichiometric amounts of palladium complex (Ar-Pd-Cl) derived from the *in situ* reaction between Ar-Hg-Cl and $PdCl_2$. Mizoroki *et al.* later reported the catalytic process employing iodobenzene, substituted alkenes and 10 mol% $PdCl_2$, which bears more of a resemblance to the modern Mizoroki-Heck reaction.[71] This protocol was limited to aryl iodides until 1974, when Heck *et al.* reported the use of triphenylphosphine as an additive (Scheme 35) which allowed for the use of aryl bromide substrates (aryl chlorides remained unreactive in these studies).[72] The proposed mechanism is outlined in Figure 6.



Scheme 35 The Mizoroki-Heck reaction reported in 1974.[72]

The reaction has enjoyed continued popularity amongst synthetic chemists and, due to its efficacy and versatility, has found application in the synthesis of commercially important molecules.[73] The Heck reaction remains one of the methods of choice for selective Csp^2-Csp^2 bond formation, and recent efforts have focussed on activation of aryl chloride substrates and making the reaction more attractive from an economical point of view.

The Heck reaction is understood to proceed via oxidative addition of the halide to the metal centre followed by insertion of the alkene into the Pd-C bond and subsequent β-hydrogen elimination (Figure 10).

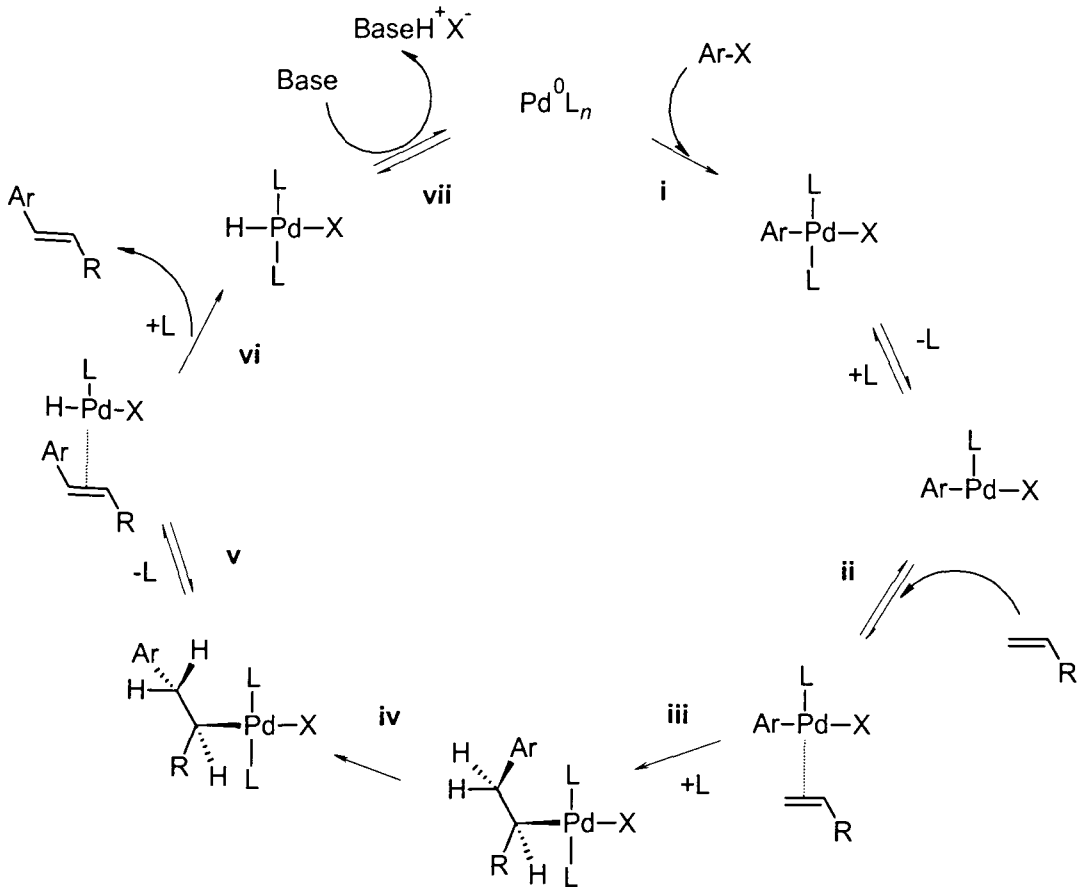
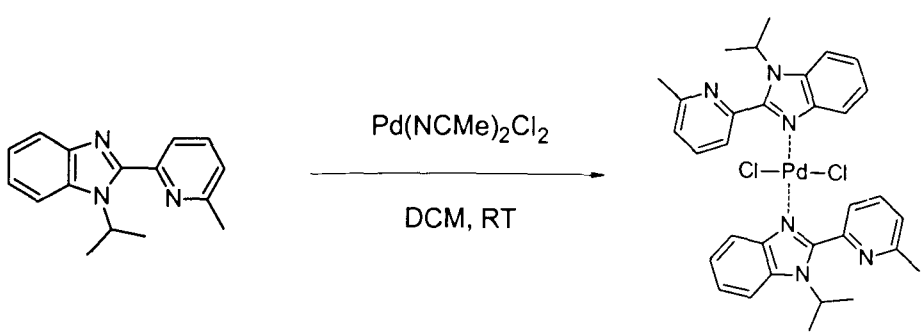


Figure 10 The reaction mechanism proposed by Heck *et al.*[72] i) Oxidative addition, ii) Coordination of the alkene, iii) *Syn*-insertion of the alkene into the Pd-C bond, iv) C-C bond rotation, v) β-Hydride elimination, vi) Reductive elimination, vii) Deprotonation.

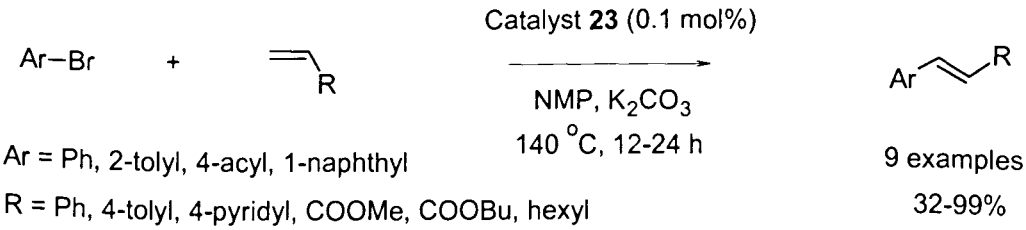
Recent incarnations of the Heck reaction employ sophisticated palladium complexes, usually bearing sterically bulky ligands. This is illustrated in the work of Chen *et al.*[74] who evaluated a range of novel *bis*-(2-pyridyl)benzimidazole complexes of palladium **23** in the Heck coupling of aryl bromides and various alkenes (Schemes 36 and 37).



23

Scheme 36 Synthesis of *bis*-(pyridyl)benzimidazole Pd complexes (most active complex shown).[74]

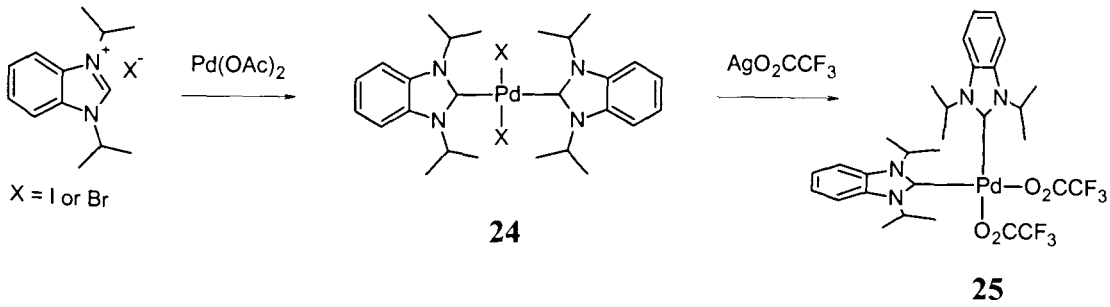
The authors found that the *bis*-benzimidazole complex **23** was usually formed as long as the pyridyl ring was suitably substituted and that when no substituent was present, the bidentate, *mono*-ligated complex was formed (which proved to be less active in Heck reactions).



Scheme 37 Testing of *bis*-(pyridyl)benzimidazole palladium complex **23**.[74]

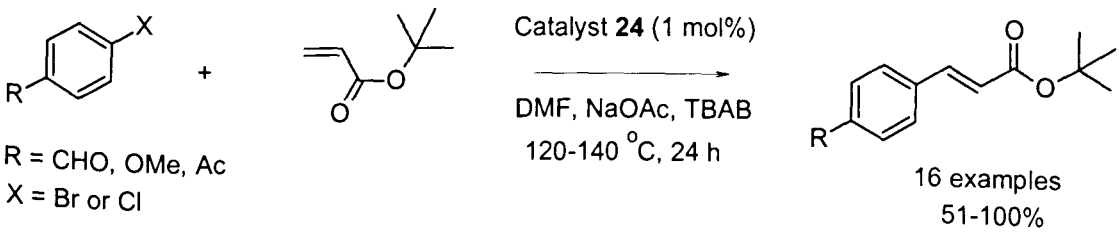
1.5.3.1 Heck Coupling of Aryl Chlorides

Recently, numerous examples of Heck reactions employing aryl chlorides have appeared in the literature. Vinh Huynh *et al.* demonstrated the efficacy of various *N*-isopropyl substituted, benzannulated NHC complexes of palladium.[75] Interestingly, the group were able to prepare both *trans*- and *cis*-isomers (**24** and **25**) of the NHC complexes (Scheme 38).



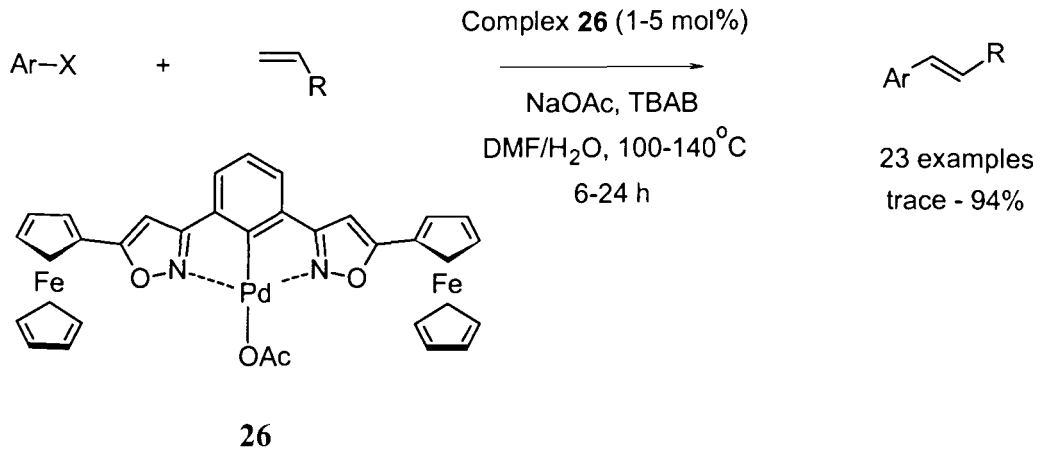
Scheme 38 Synthesis of *trans*- and *cis*- *bis*-NHC palladium complexes.[75]

The catalysts were tested on a modest range of aryl bromide and chloride substrates and the *trans*-isomer showed superior catalytic activity in all cases. Chloride substrates were converted to the desired Heck product in high yields, however long reaction times and temperatures as high as 140 °C were required to effect the desired transformations (Scheme 39).



Scheme 39 Testing of the *trans*- *bis*-NHC palladium complex **24**.[75]

Shang *et al.* also attempted the Heck coupling of aryl chloride substrates using the ferrocene-containing, *N,C,N*-pincer palladium complex **26** developed in their laboratories (Scheme 40).[76] This catalyst system coupled bromide substrates in a very efficient manner, however yields for couplings employing aryl chlorides were modest (at best, 78% for activated aryl chlorides) and required higher catalyst loadings and extended reaction times.



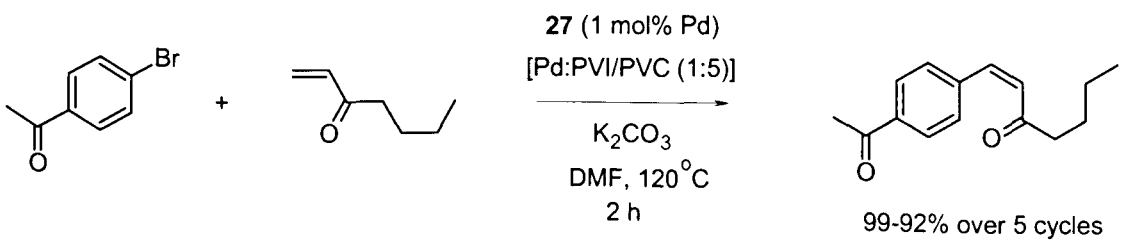
Scheme 40 Testing of *N,C,N*-pincer complex **26**.[76] X = Br or Cl.

The authors also mentioned that recovery of the palladium complex was possible due to its low solubility in organic solvents, however no mention of the reusability of the catalyst appeared in the article.

1.4.3.2 Heterogeneous Heck Reactions

Many solid-supported catalysts for Heck reactions have been reported and indeed been applied to industrial-scale chemical synthesis.[73] However, one of the main challenges in this respect is the development of heterogeneous catalysts which exhibit comparable activity and selectivity to the numerous homogeneous catalysts which are available. Palladium on carbon (10% wt) was found, by Hagiwara *et al.*,[77] to be active in Heck couplings of aryl iodides (with dramatic reductions in yield observed when the protocol was applied to aryl bromides). This catalyst was shown to be recyclable over 5 cycles, however efficient conversion of more demanding substrates (i.e. aryl bromides and chlorides) requires a more sophisticated catalyst system.

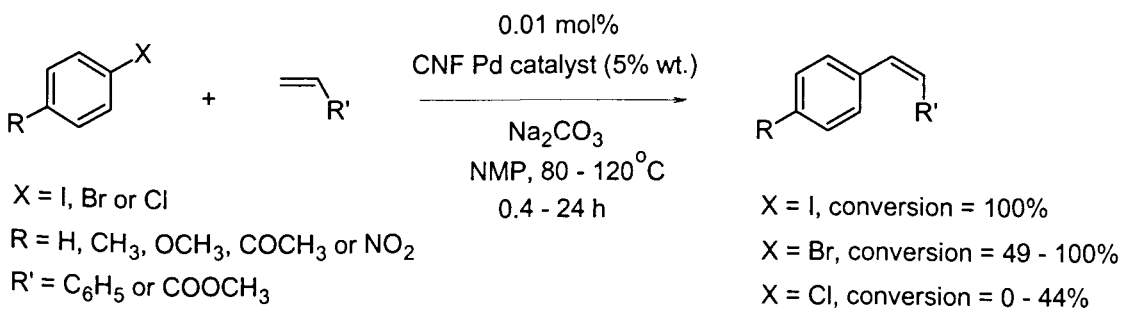
Beletskaya *et al.*[78] explored the immobilisation of palladium onto poly(*N*-vinylimidazole) and poly(*N*-vinylimidazole-*co*-vinylcaprolactam) based supports for heterogeneous Heck reactions. Interestingly, these functionalised polymers were not intended to be converted into poly(*N*-heterocyclic carbene) complexes (although the formation of NHC species *in situ* cannot be ruled out due to the presence of K_2CO_3). Rather the authors aimed to produce palladium nanoparticles dispersed throughout the polymer network, with varying ratios of $PdCl_2$: polymer. It was established that a 1:5 ratio of $PdCl_2$: poly(*N*-vinylimidazole-*co*-vinylcaprolactam) **27** gave the most satisfactory catalytic activity in Heck couplings of aryl iodides and activated aryl bromides with *n*-butyl acrylate, with yields ranging from 83 - 95% using 1 mol% [Pd] catalyst. Electron microscopy (TEM) analysis of this material revealed evenly dispersed palladium nanoparticles (8-10 nm in diameter). This catalyst system was recyclable over 5 cycles with a small decrease in activity (Scheme 41).



Scheme 41 Reusability of a '$PdCl_2$ / poly(*N*-vinylimidazole-*co*-vinylcaprolactam)' catalyst.[78]

In an analogous study Li *et al.* prepared Pd nanoparticles dispersed over a mesoporous silica support (SBA-15).[79] This catalyst system was tested in Heck reactions of aryl iodides and activated aryl bromides and facilitated excellent yields throughout, using a palladium loading of only 0.04 mol%. This seems to suggest that metal particles supported on silica display superior catalytic activity to metals supported on other polymers (based on a comparison with the work of Beletskaya *et al.*[78]). This could be attributed to the controlled pore size of the silica-support increasing the accessibility of active sites. This silica supported catalyst was of comparable recyclability to Beletskaya's organic co-polymer supported catalyst, with conversions dropping to 90% by the fifth cycle (accompanied by small amounts of leached palladium in reaction mixtures).

More recently Chen *et al.* applied carbon nanofibres (CNFs) as support materials for palladium nanoparticles.[80] These catalytic materials showed exceptional catalytic activity in the Heck reaction of aryl iodides, bromides and even activated aryl chlorides (Scheme 42), making it one of the most active heterogeneous palladium catalysts for Heck reactions reported to date.

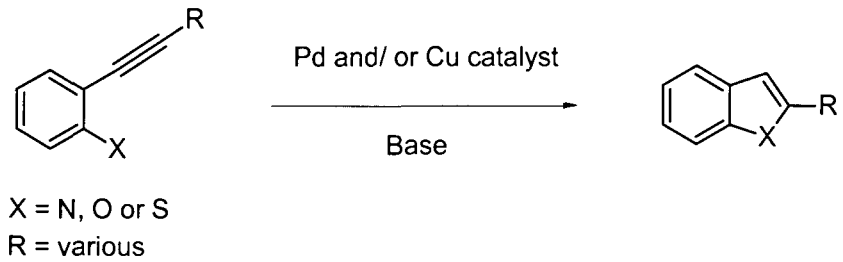


Scheme 42 Testing of palladium on carbon nanofibres (CNFs) (5% wt.) catalyst.[80]

This catalyst was also shown to be recyclable over 7 cycles in the reaction between iodobenzene and styrene (100% conversions throughout) and over 4 cycles for the reaction of bromobenzene with styrene (conversions in this reaction dropped from 80% to 57% by the 3rd reuse). Again, this catalyst system seems to be amongst the most efficient reported to date, emphasizing the importance of a well-defined support material. Due to its total lack of reactivity towards deactivated aryl chlorides (containing EDGs), certain aspects of this catalyst may be improved upon.

1.4.4 '5-*Endo-dig*' Cyclisation Reactions

The palladium-mediated intramolecular addition of amines to alkynes (Scheme 43) (or '5-*endo-dig*' cyclisation according to Baldwin's rules[81]) was first reported in the late 1980s[82] and due to the synthetic utility of the reaction (i.e. in the preparation of enamines, indoles and benzofurans), it has enjoyed continued popularity amongst organic chemists and has been extensively reviewed.[83]



Scheme 43 Generalised 5-*Endo-dig* cyclisation reaction.

The reaction is proposed to proceed via co-ordination of the alkyne to the metal species allowing nucleophilic attack on the alkyne and the formation of a C-X bond (Figure 11),[84-86] although variations on this idea do exist.

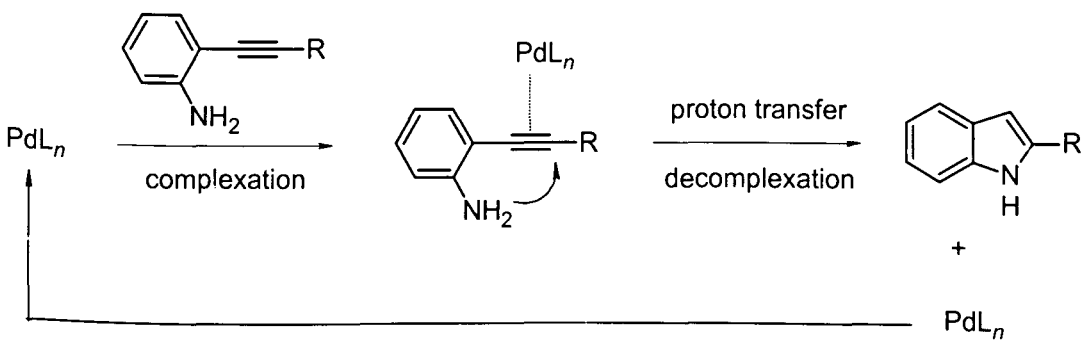
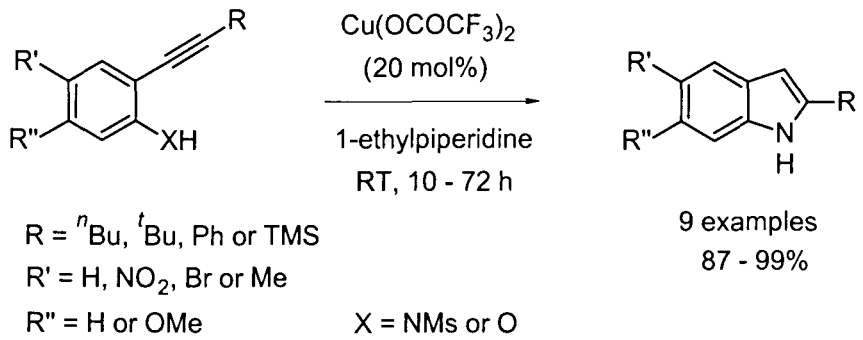


Figure 11 The reported mechanism for the palladium mediated cyclisation reaction.[84-86]

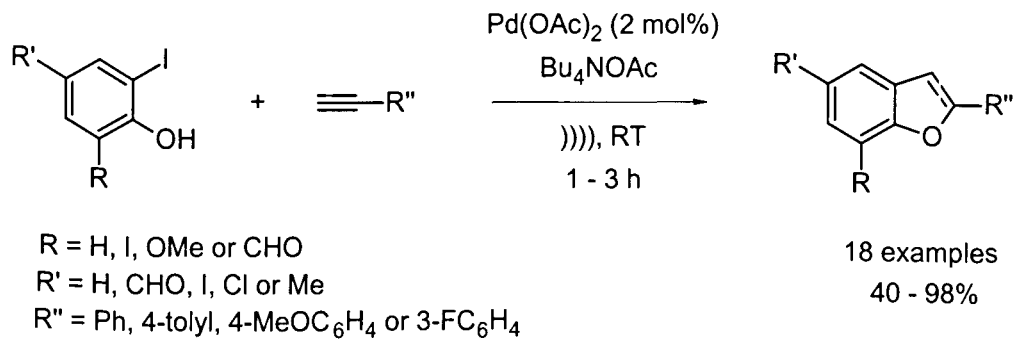
The intramolecular reaction of 2-(ethynyl)aniline derivatives represents a convenient route to 2-substituted indoles, and is normally carried out using homogeneous conditions. Hiroya *et al.*[85] employed large amounts of copper trifluoroacetate and achieved excellent yields across a range of substituted 2-(ethynyl)aniline derivatives and one 2-(ethynyl)phenol substrate (Scheme 44). The authors discovered that derivatisation of the amino substituents (to the *N*-

methylsulfonate) was necessary for the reaction to take place under their conditions. The free amine was unreactive in these studies. This reaction is also relatively environmentally friendly as it employs an aqueous solvent at room temperature and the copper catalyst was shown to be reusable over three cycles.



Scheme 44 Cyclisation of 2-(ethynyl)aniline derivatives using copper(II) trifluoroacetate.[85]

Srinivasan *et al.* recently demonstrated the tandem Sonogashira coupling-5-*endo-dig* cyclisation of substituted phenols using palladium acetate and ultrasonic irradiation (Scheme 45).[86]

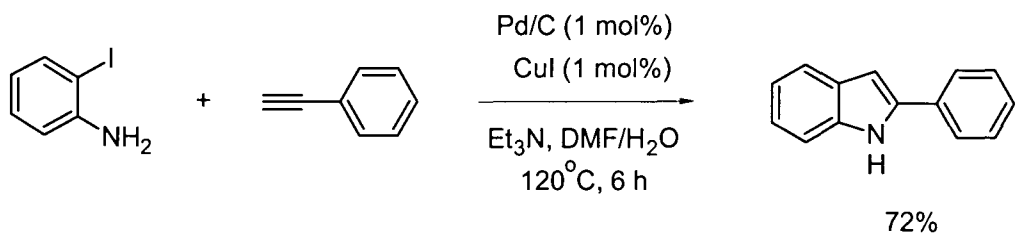


Scheme 45 Ultrasound promoted one-pot Sonogashira-5-*endo-dig* cyclisation reaction.[86]

In this study, a range of 18 substituted benzofurans were prepared in good yields. The authors noted that ultrasound had a dramatic effect on the rate of reaction (for example, increasing the conversion from 60% in 24 h to 91% in 1 h). Also noted was the fact that substrates bearing electron withdrawing substituents underwent faster reaction than electron rich or unsubstituted substrates.

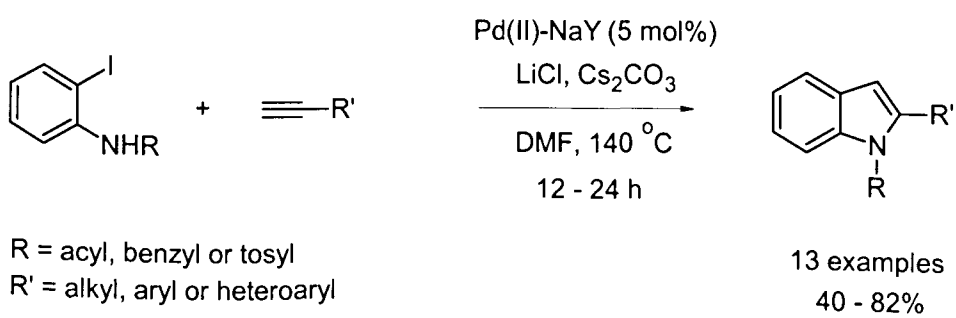
1.4.4.1 5-*Endo-Dig* Cyclisations using Heterogeneous Catalysis

The use of heterogeneous palladium catalysts for this reaction has received considerably less attention. Djakovitch *et al.* accomplished the tandem Sonogashira coupling and 5-*endo-dig* cyclisation[10] using palladium on carbon and copper iodide (Scheme 46). The authors noted that without the copper co-catalyst, the reaction proceeded slowly, yielding only 25% of 2-phenylindole after 24 h, which suggests that the copper co-catalyst is implicated in the initial coupling reaction and/or the heteroannulation.



Scheme 46 One-pot Sonogashira coupling and heteroannulation using palladium on carbon.[10]

Hong *et al.* also investigated the use of heterogeneous catalysts for the synthesis of 2-substituted indoles from iodoanilides.[87] Of the range of palladium doped zeolites tested, zeolite 'NaY' doped with palladium(II) proved to be the most efficient system, furnishing the desired cyclisation products in respectable yields (Scheme 47). Again, the authors found that derivatisation of the amino substituents was necessary, although no copper co-catalyst was required when using this catalyst system. This heterogeneous catalyst also showed good recyclability, furnishing the cyclised product over six consecutive cycles, however longer reaction times and lower yields were noted.



Scheme 47 Application of palladium-modified zeolite catalyst to 5-*endo-dig* cyclisations.[87]

The sheer lack of published literature on intramolecular 5-*endo-dig* cyclisations promoted by heterogeneous palladium catalysts leaves this area very much open for development.

1.5.5 Asymmetric Allylic Alkylation Reactions

The palladium catalysed alkylation of substrates bearing allylic leaving groups (the Tsuji-Trost reaction) was first described in the late sixties.[88] Because of the wide variety of allylic substrates and different nucleophiles tolerated by the reaction, it became the focus of much research in the synthetic community. It was not until 1977 that Trost and co-workers attempted an asymmetric version of the reaction.[89] A generalised catalytic cycle for this process is illustrated in Figure 12.

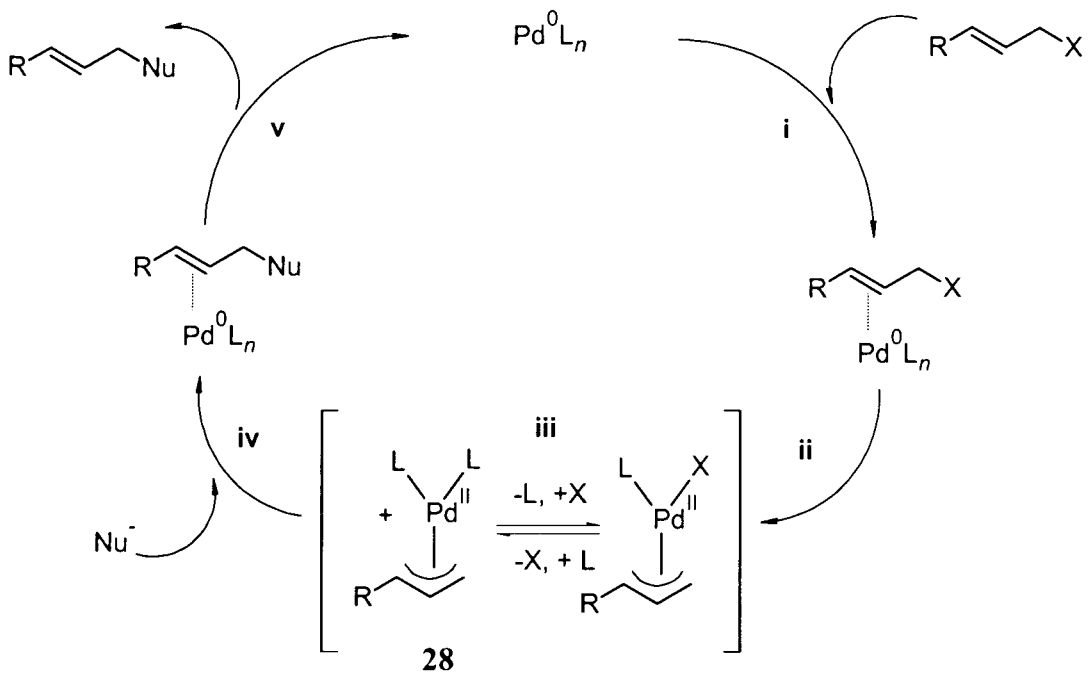


Figure 12 Mechanism of allylic alkylation; i) Complexation, ii) Oxidative addition, iii) Ligand exchange, iv) Nucleophilic attack and reductive elimination and v) Decomplexation.

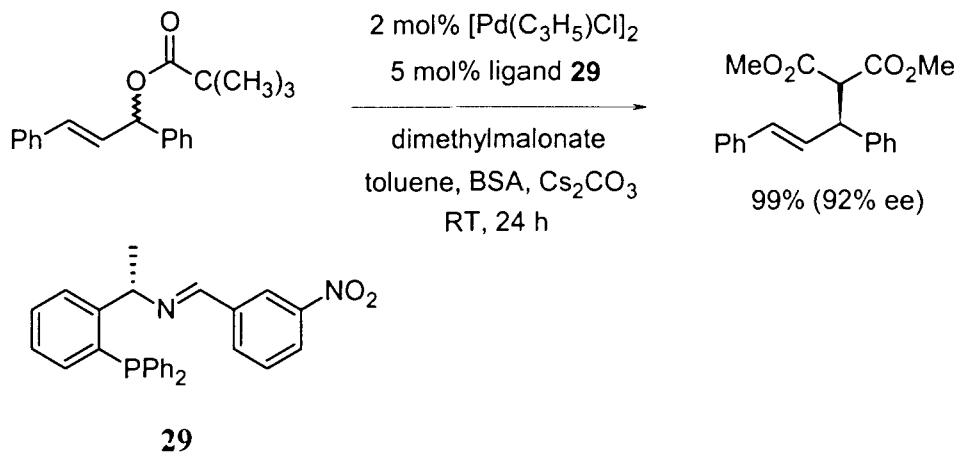
The regioselectivity of the reaction is determined mainly by the steric effects of substituents on the allylic substrate, nucleophillic attack tends to take place on the least hindered terminus of π-allyl complex **28**.

When the allylic leaving group is attached to a chiral centre, the reaction results in the formation of enantiomers, the relative enantiomeric excesses observed are largely dependant upon the nature of the nucleophile. The initial oxidative addition step results in an inversion of the stereochemistry, much like an S_N2 reaction. Soft nucleophiles then attack the π-allyl palladium complex **28** from the opposite side of the complex leading to another inversion of the configuration,

whereas hard nucleophiles attack the metal centre, undergoing transmetallation and leading to retention of the stereochemical information. Furthermore, enantiodiscrimination may also arise from numerous steps in the process.[90] In general, for the reaction to achieve useful enantioselectivities, the environment around the metal must be chiral. This is usually achieved by the use of chiral ligands.

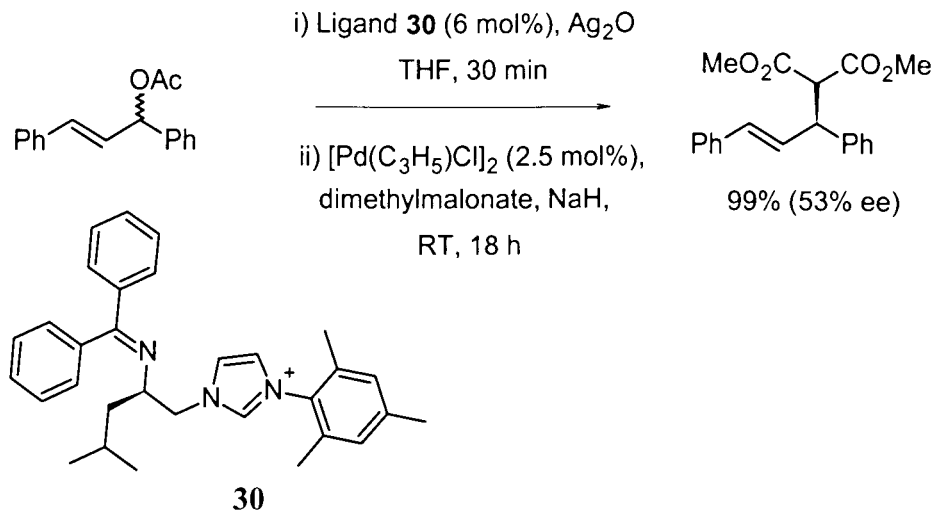
1.5.5.1 Homogeneous Allylic Alkylation

After much optimisation, Huang *et al.*[91] are one of many groups to accomplish the asymmetric allylic alkylation of 1,3-diphenylpropenyl pivilate using a bidentate imino-phosphine ligand **29** (Scheme 48).



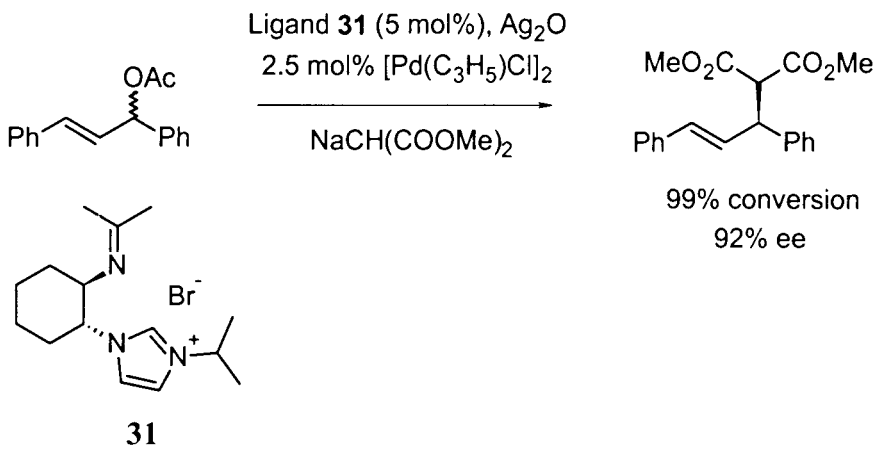
Scheme 48 Optimised conditions for allylic alkylation of 1,3-diphenylpropenyl pivilate using chiral imino-phosphine ligand system **29**.[91]

Williams *et al.* have recently explored the use of imino-NHC mixed donor ligands in this reaction (Scheme 49).[92] Their catalyst system was formed *in situ* from the corresponding iminoalkyl imidazolium salt **30**, Ag_2O (as an NHC transfer agent) and $[Pd(C_3H_5)Cl]_2$. The group achieved high conversion rates in the benchmark reaction of 1,3-diphenylpropenyl acetate with the anion of dimethylmalonate, but enantiomeric excesses were modest, which seems to be contemporary with this type of catalyst system.



Scheme 49 Allylic alkylation of 1,3-diphenylpropenyl acetate using imino-NHC ligand **30**.[92]

Douthwaite *et al.*, had varying success using a similar ligand precursor (**31**). Although some examples gave excellent conversions and enantioselectivities (Scheme 50), most of the wide range of ligands based on 1,2-diaminocyclohexane resulted in modest ees of under 50%.[93]

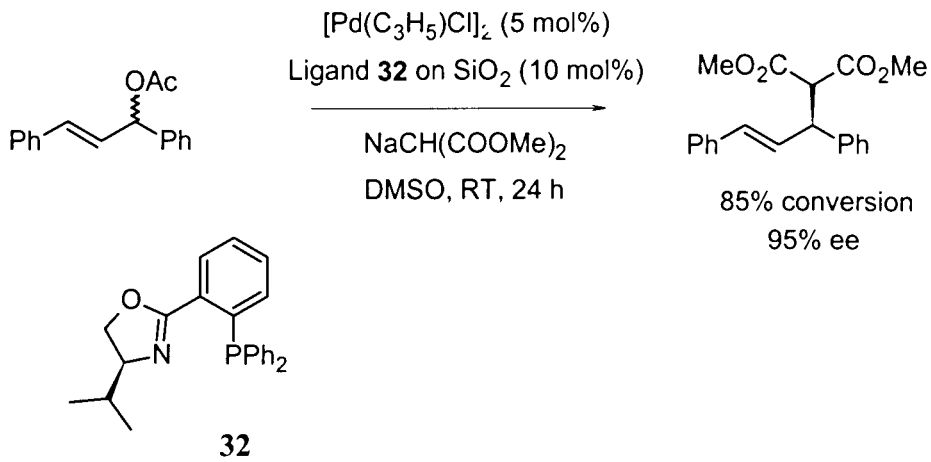


Scheme 50 Allylic alkylation using imino-NHC ligands based on 1,2-diaminocyclohexane.[93]

NHC ligands, which have been heralded as a convenient alternative to phosphines, do indeed show potential for asymmetric reactions although the field is very much still in its infancy.

1.4.5.2 Heterogeneous Asymmetric Allylic Alkylation

Examples of immobilised catalysts used for asymmetric allylic alkylation reactions in the scientific literature are surprisingly scarce. However, one example could be found in the work of Williams *et al.*, who employed chiral phosphine ligand **32** adsorbed on reversed phase silica beads to achieve good conversions and very high enantiomeric excesses (Scheme 51).[94]

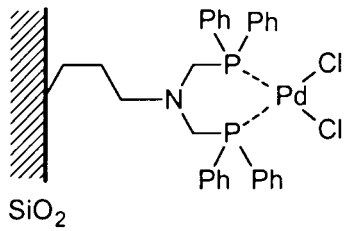


Scheme 51 Heterogeneous asymmetric allylic alkylation - the only example to date?[94]

Although the asymmetric ligand was not covalently attached to the silica surface, the authors reported only low levels of palladium leaching during the reaction (0.02% based on the amount of palladium used). However, recycling of this catalyst system was apparently not attempted. In terms of conversion and enantioselectivity, this catalyst is exceptional although there remains room for development with regard to recyclability of the system. Immobilisation of chiral NHC complexes for asymmetric allylic alkylation remains completely unexplored.

1.6 Aims of the Project

Although the preparation of silica-supported *bis*-phosphine palladium catalyst **10** (Figure 13) was previously reported by Tyrrell *et al.* in 2005,[52] several important aspects including characterisation and catalytic testing remain unexplored.



10

Figure 13 Silica-supported phosphine catalyst for Sonogashira reactions.

The initial aim of this work was to fine-tune the synthesis of **10** and characterise it as fully as possible with techniques such as TGA, elemental analysis and solid-state NMR, in order to establish reproducible protocol for its preparation. Furthermore, since previous studies had focussed upon Sonogashira coupling of relatively undemanding substrates (namely aryl iodides), there was an opportunity to establish the limitations of the catalyst in Sonogashira couplings and also to assess its potential for other palladium-mediated transformations.

Another aim of the project was to attempt the immobilisation of *N*-heterocyclic carbene-based palladium catalysts of the general structure shown in Figure 14.

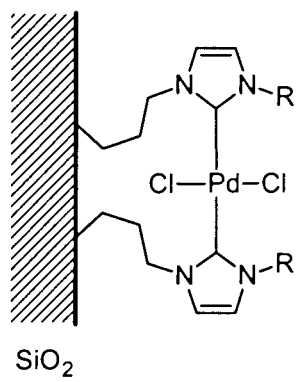


Figure 14 Supported NHC catalyst. R = methyl, benzyl, mesityl etc.

In particular, the incorporation of steric bulk into the NHC backbone was especially attractive. It is been demonstrated that bulky *N*-substituted NHC-metal complexes exhibit superior catalytic activity under homogeneous conditions,[19] this phenomenon remains relatively unexplored in heterogeneous catalysis.

Continuing the theme of immobilisation of NHC complexes of palladium, another somewhat ambitious aim was to attempt the synthesis of immobilised mixed donor iminoalkyl-NHC complexes for allylic alkylation reactions (Figure 15). This chemistry is normally accomplished using homogeneous systems and the notable lack of scientific literature on immobilised catalysts for allylic alkylations may give some hint as to the challenges associated with such a process. Ultimately, the goal would be to incorporate a chiral moiety into the ligand structure allowing for enantioselective allylic alkylation reactions.

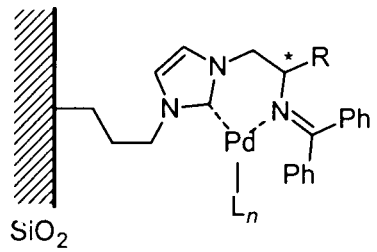
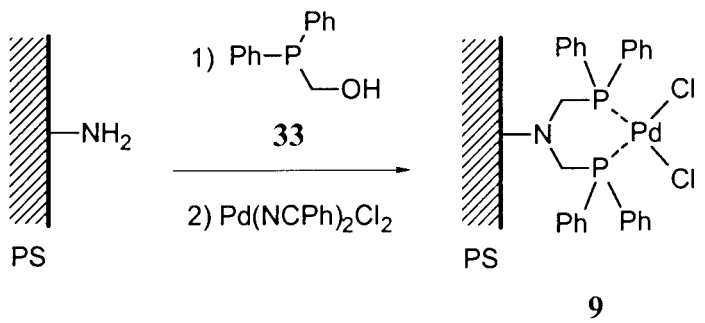


Figure 15 Supported iminoalkyl NHC catalyst. Initially R = H, however replacing it with a chiral, bulky group (eg. isopropyl) may result in an enantioselective catalyst.

2 Preparation of Immobilised *Bis*-Phosphine Palladium Catalyst

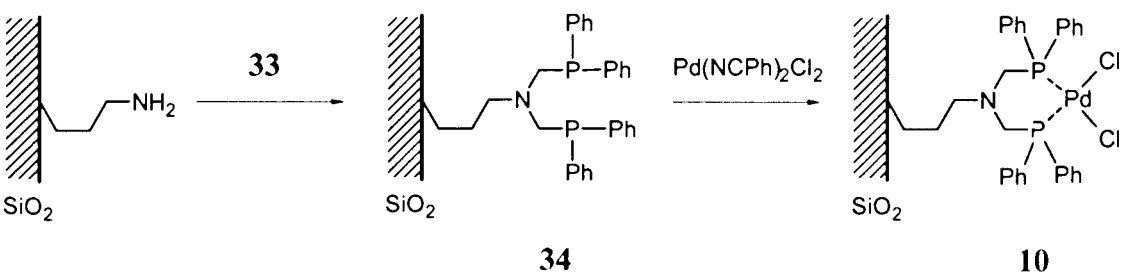
2.1 Introduction

The concept of heterogenisation of a homogeneous catalyst system was aptly illustrated by Breinbauer *et al.* in 2003. This polystyrene supported *bis*-phosphine palladium complex **9** showed good catalytic activity in Sonogashira coupling reactions and exhibited high levels of recyclability.[51] The preparation of this catalyst consisted of tethering diphenylphosphinomethanol **33** to aminomethyl-functionalised polystyrene followed by sustitution with $Pd(NCPh)_2Cl_2$ (Scheme 52).



Scheme 52 Preparation of polystyrene supported *bis*-phosphine palladium complex **9**.[51]

The use of silica as a catalyst support offers certain advantages over polystyrene including its thermal stability and the fact that it does not require pre-swelling in organic solvent. With this in mind, Tyrrell *et al.* prepared the silica-supported analogue of complex **9** using 3-aminopropylfunctionalised silica (APS) (Scheme 53).[52]



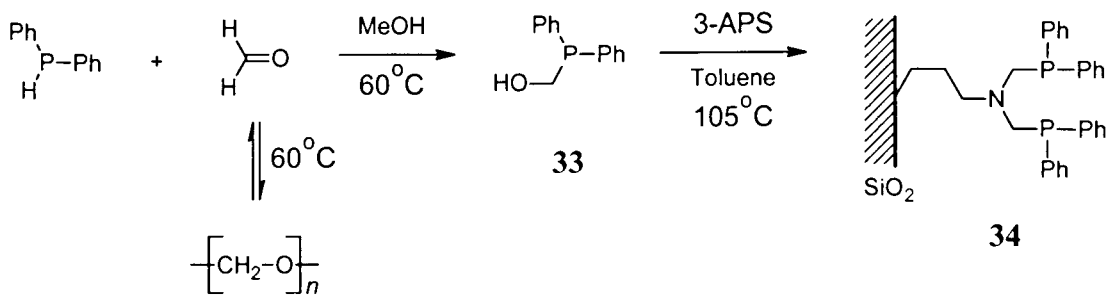
Scheme 53 Synthetic route to silica supported *bis*-phosphine palladium catalyst **10**.[52]

Although catalyst **10** showed comparable activity to the polystyrene supported analogue in Sonogashira coupling reactions and was shown to be recyclable,[52] further investigation was required to establish its composition, synthetic potential and its limitations in terms of substrate tolerance.

The following chapter focuses on the preparation of catalyst **10**, an investigation of its structure, thorough testing in Sonogashira reactions and preliminary screening for activity in other catalytic reactions. One of the major challenges associated with this synthesis, aside from the oxygen sensitive nature of the phosphine ligand, was characterising the inherently insoluble immobilised species **34** and **10**. This study therefore employed techniques such as thermal analysis (TGA), solid-state NMR and elemental analysis in an attempt to investigate the composition of the catalyst.

2.2 Synthesis of Immobilised *Bis*-Phosphine Ligand 34

The initial reaction between diphenylphosphine and formaldehyde was carried out under an inert atmosphere using degassed, anhydrous solvents (Scheme 54). As in previous studies,[51-52] little effort was made to characterise the oxygen-sensitive intermediate species, diphenylphosphinomethanol **33**.



Scheme 54 Preparation of silica-supported *bis*-phosphine ligand **34**.[51-52]

The formation of a colourless solution from a white suspension is reported as an indicator for the progress of this reaction.[51] After 48 h, the colourless solution was obtained and **33** was detected by GC-MS (17.1 min, m/z 216 [M^+]) along with various by-products, the latter possibly due to oxidation of the product in the GC injector. Due to its sensitivity to oxygen, purification and further characterisation of this species was not attempted.

A solution of the crude product was then added to commercially available 3-aminopropyl silica (3-APS, 1.0 mmol/g) and the mixture refluxed in dry, degassed toluene to facilitate immobilisation of the aryl phosphine species, affording **34** (*bis*-diphenylphosphinomethyl-3-aminopropyl functionalised silica) as a yellow solid.

2.2.1 TGA Analysis of Immobilised *Bis*-Phosphine Ligand 34

Thermogravimmetric analysis (TGA) was used to investigate the percentage of organic material present in immobilised phosphine **34**. Since the silica support is involatile at the temperatures used (up to 650 °C), loss of mass can be attributed to organic moieties tethered to the support. By comparing the TGA profile of the starting material (3-aminopropyl silica) with that of **34**, the relative increase of organic material on the support may be determined.

3-Aminopropyl functionalised silica was purchased from Sigma-Aldrich ltd. (with a loading of 1.0 mmol/g) and would be expected to lose 5.8% of its mass due to the aminopropyl fragments (RMM: 58). The observed loss of mass for this material was actually 9.1% (Figure 16), indicating that some other organic species is present. A major factor in the thermal analysis of 3-APS and related types of silica is the condensation of surface silanol groups, which occurs at temperatures exceeding 200 °C.[95] The water eliminated by this process undoubtedly adds to the observed loss of mass.

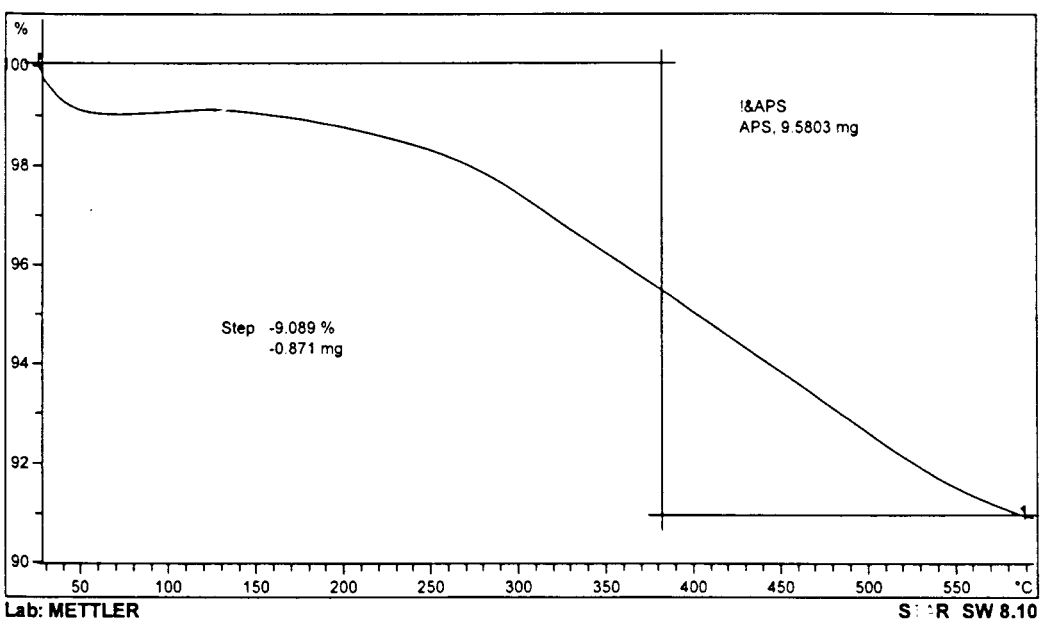
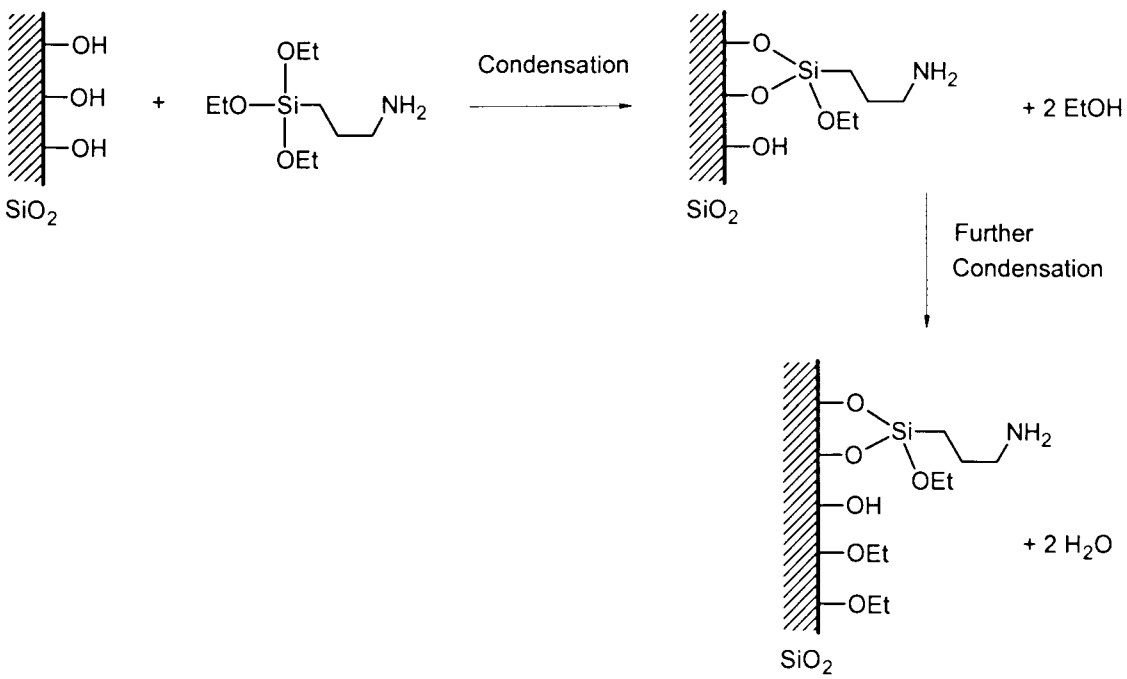


Figure 16 TGA of 3-aminopropyl functionalised silica. Temperature program: 20 °C/ min.

Another possibility is the presence of adsorbed water, although drying under vacuum at 80 °C over phosphorous pentoxide for 24 h is expected to remove the majority of this moisture.[96] Owing to the hygroscopic nature of silica, some amount of water is likely to be present in all samples.

Determination of the loading of the 3-APS by TGA may be further complicated by the presence of ethoxysilyl groups, which are a likely contaminant from the commercial synthesis of this starting material (Scheme 55). Using solid state ^{13}C NMR, Blumel *et al.* demonstrated that all of the ethoxy groups displaced from the trialkoxysilane undergo condensation with silanol groups on the silica surface.[97] These surface bound alkyl groups could be responsible for some of the excess organic material observed in the TGA of 3-APS (Figure 16).



Scheme 55 Formation of ethoxysilane in the synthesis of commercially available 3-APS.[97]

If every tethered amino group was successfully reacted with aryl phosphine **33** (100% immobilisation), a loss of 28.4% would be expected in the TGA of **34**. However, a loss of around 23% was observed (Figure 17). The 23% volatile material observed in this study would also include loss of adsorbed water and condensation of silanol groups, which suggests that the reaction did not go to completion. Taking into account the original aminopropyl loading of 9.1%,

compound **34** contains only 13.7% more organic matter than the aminopropyl functionalised starting material. When compared with the theoretical mass increase (for 100% immobilisation), this indicates only 28% of the surface amino groups have reacted with phosphine ligand. Considering that TGA confirms a less than complete reaction with DPPM, the immobilised *mono*-phosphine species **34b** (Figure 18) might be expected as a side-product along with unreacted aminopropyl groups.

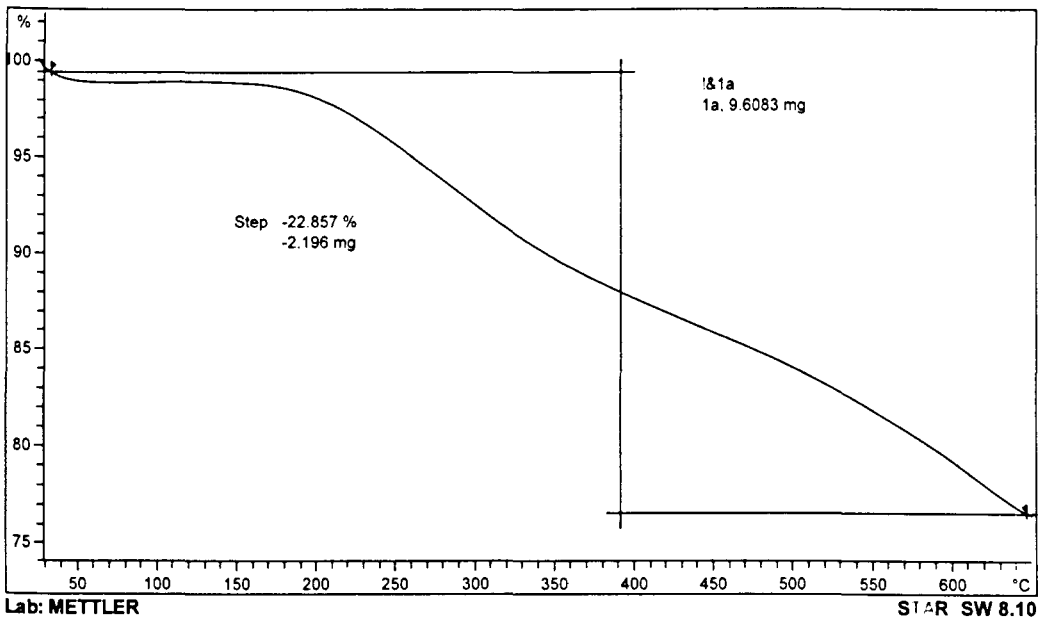
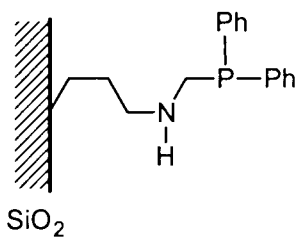


Figure 17 TGA of tethered phosphine species **34**.



34b

Figure 18 Proposed structure of immobilised *mono*-phosphine species **34b**.

2.2.2 Solid State ^{31}P NMR Analysis of *Bis*-Phosphine Ligand 34

The ^{31}P NMR spectrum of immobilised phosphine ligand **34** reveals a large peak at δ -27 ppm for the diphenylphosphine species (Figure 19), which correlates extremely well with the literature value.[51,98] Also present in this spectrum is a smaller, broader peak (or possibly two small overlapping peaks) at around 25 ppm, which was originally assigned to the surface-bound phosphorus (V) oxide **35a** or **35b** resulting from exposure to oxygen (Figure 20).

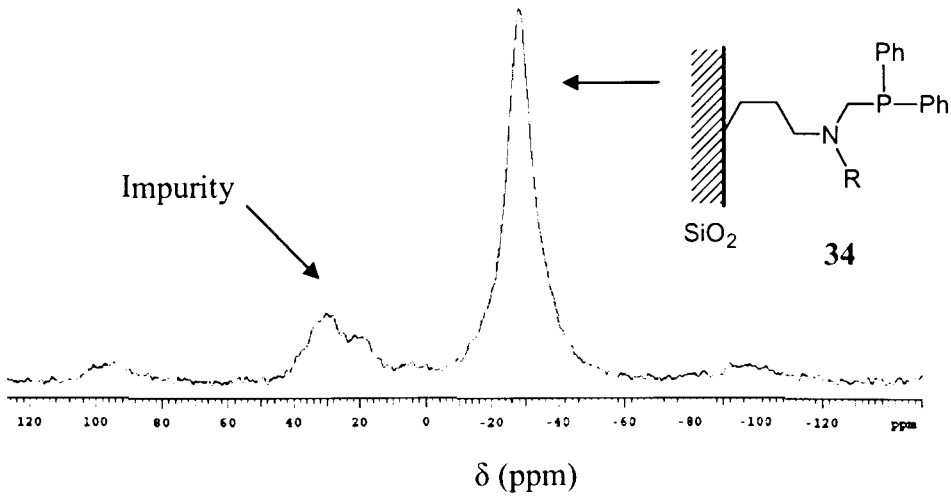


Figure 19 Solid-state ^{31}P NMR spectrum of silica supported diphenylphosphine ligand **31**. R = $P(Ph_2)$ or H.

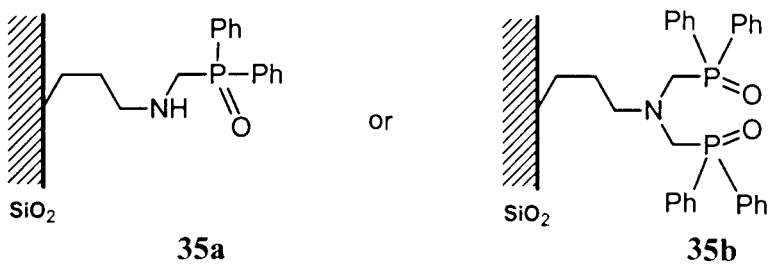


Figure 20 Possible identities of the impurity present in **34**, resulting from reaction with oxygen.

There is another possibility for the structure of the impurity (Figure 19, 25 ppm). Solid state ^{31}P NMR data reported by Blumel *et al.* in 2008 closely resembles the spectrum of immobilised phosphine **34**, including the presence of an impurity at around 25 ppm (Figure 21).[97]

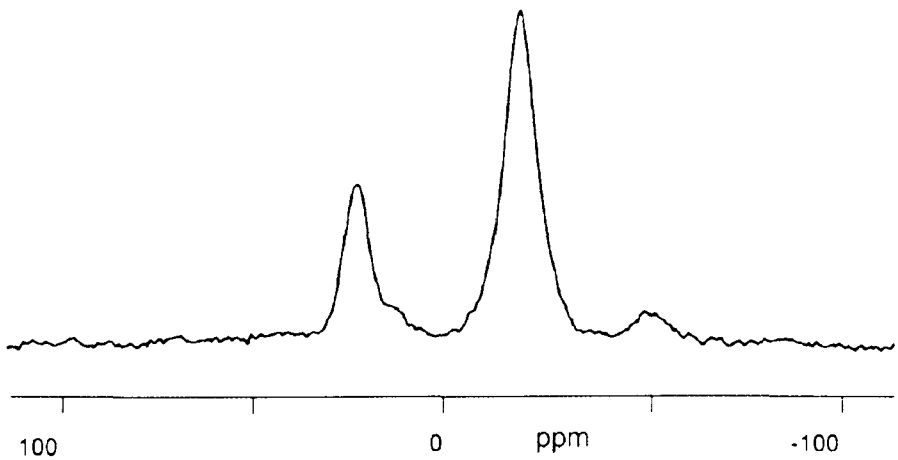
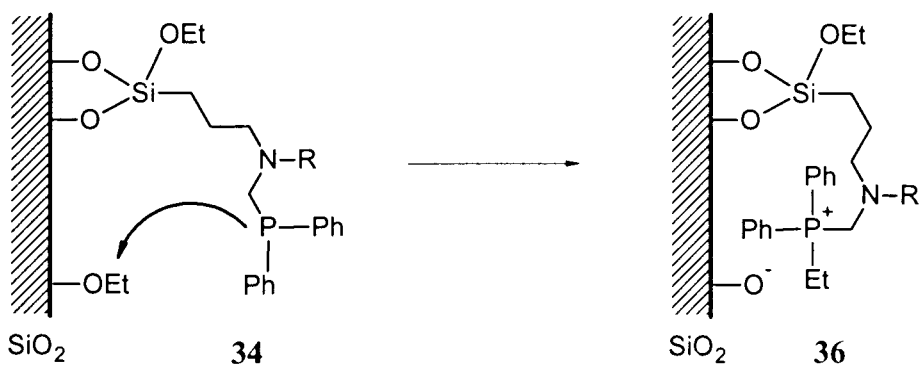


Figure 21 Solid state ^{31}P NMR spectrum of silica supported diphenylphosphine ligand **34** reported by Blumel *et al.*[97] showing an impurity at 25 ppm.

The alkylphosphonium salt **36**, as proposed by Blumel *et al.*[98] could result from the reaction between immobilised phosphine **34** and a surface bound ethoxy group (Scheme 56).

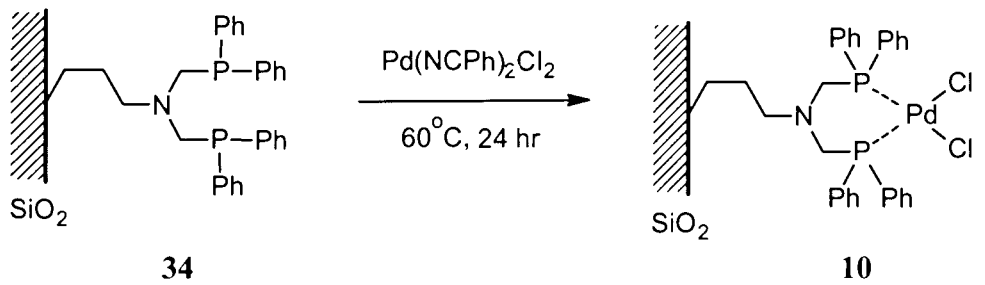


Scheme 56 Formation of an alkylphosphonium salt on the silica surface.[98] R = H or $P(Ph)_2$.

The presence of impurity **36** would not be considered beneficial to the catalyst performance. Although the ionic interaction may enhance the stability of the ligand on the support, the oxidised alkylphosphonium salt would not be expected to co-ordinate to palladium due to its lack of a lone pair.

2.3 Synthesis of Immobilised *Bis*-Phosphine Palladium Catalyst 10

The immobilised phosphine species **34** was treated with *bis*-(benzonitrile)palladium dichloride as shown (Scheme 57) to yield catalyst **10**. The brown-coloured product was simply filtered off under nitrogen and washed with dry THF and DCM.



Scheme 57 Synthesis of catalyst **10** by ligand sustitution.

GC-MS analysis of the washings confirmed the presence of benzonitrile, which suggested ligand substitution had taken place. The amount of catalyst recovered after drying corresponded to a 97% yield by mass.

2.3.1 TGA Analysis of Catalyst 10

Complete complexation of the immobilised phosphine species **34** with palladium dichloride would be expected to result in a significantly different TGA profile. This is due to the fact that palladium metal is involatile at the temperatures used in the TGA experiments (up to 650 °C). The chloride ligands are expected to be volatile, theoretically adding 4.5% to the expected mass loss. However, the presence of the expected amount of palladium (6.7%) lowers the total theoretical mass loss to 20.5%.

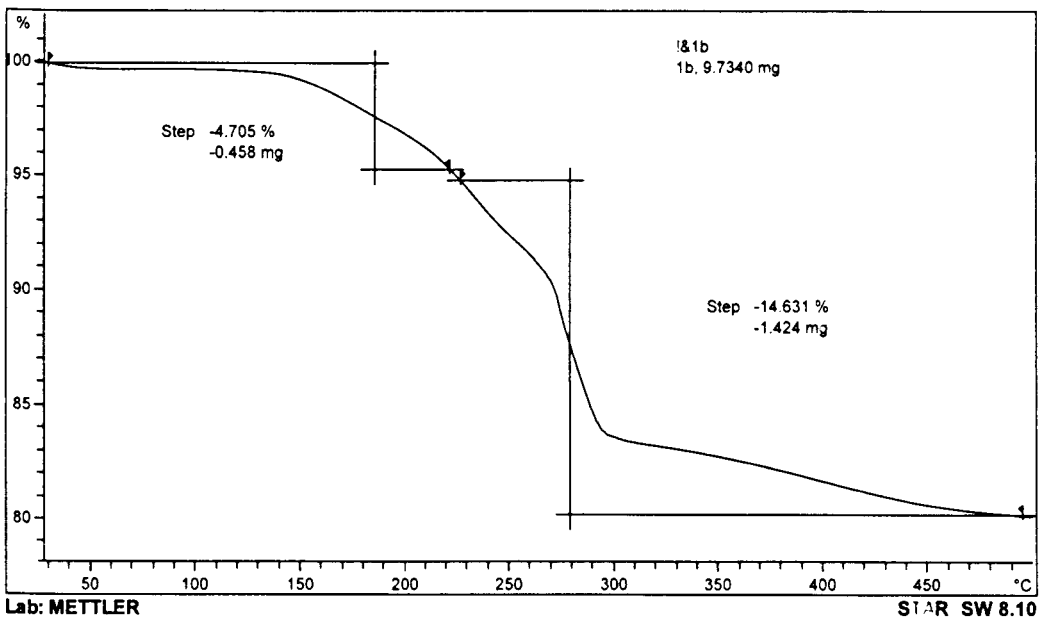


Figure 22 TGA of catalyst **10**.

Indeed, a loss of only 19% was observed for catalyst **10** (Figure 22) (compared with 23% for the precursor **34**), suggesting that more palladium has been immobilised than was expected.

2.3.2 Solid State ^{31}P NMR Analysis of Catalyst 10

Solid state ^{31}P NMR (Figure 23) agreed with the literature value for phosphorus (III) species co-ordinated to palladium (a large peak at δ 10 ppm).[30,97] In addition, ^{31}P NMR analysis also indicated the presence of the same impurity noted in the spectrum of immobilised phosphine **34** (Figure 19, δ 25 ppm), which is assigned to impurity **35** or **36** (Figure 20 and Scheme 56). The fact that the same impurity is present supports the idea that it is indeed the phophonium salt or a phosphorous oxide species, which would be incapable of coordinating to palladium.

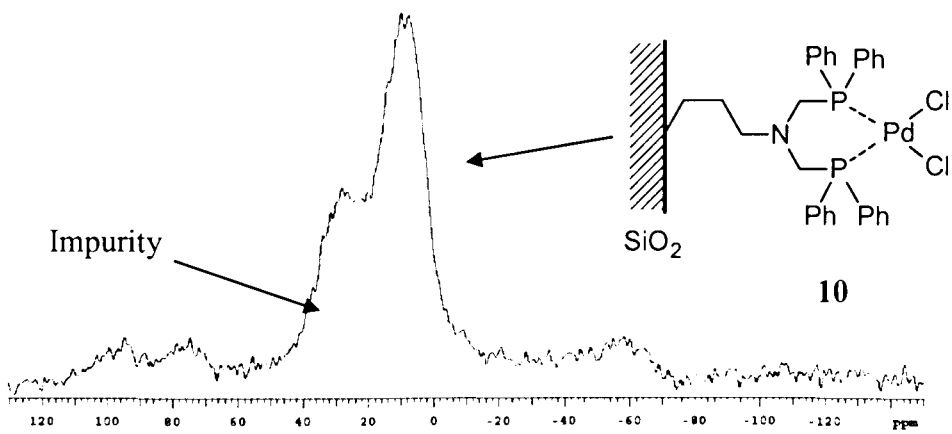


Figure 23 Solid-state ^{31}P NMR spectrum of Catalyst **10**.

Gratifyingly, no peak at δ -27 ppm corresponding to immobilised phosphine **34** is visible, which suggests all of the tethered diaryl phosphine species present on the silica are co-ordinated to palladium. The NMR signal for the expected diphenylphosphine palladium complex **10** integrates for around 67% of the total phosphorus content. The majority of immobilised phosphine species therefore correspond to the expected product.

2.3.3 Elemental Analysis of Catalyst 10

Elemental analysis (Table 1) of a digested sample of immobilised phosphine catalyst **10** reveals 6.8% palladium content (very close to the theoretical loading of 6.7%) and 1.7% phosphorus (less than half expected amount).

Table 1 Elemental analysis of catalyst **10**

ELEMENT	C	H	N	P	Pd
% Theory[a]	21.88	1.90	0.88	3.94	6.73
% Theory[b]	13.84	1.35	1.00	2.11	7.64
% Found 1	14.49	2.06	1.34	1.68	6.81
% Found 2	14.49	2.17	1.32	1.66	6.87

[a] Theoretical elemental percentages assuming 100% conversion to the *bis*-phosphine palladium complex. [b] Theoretical elemental percentage assuming 100% conversion to the proposed *mono*-phosphine palladium complex.

The most surprising feature of the elemental analysis of catalyst **10** was that it did not correspond to the expected elemental ratios of the *bis*-phosphine complex. Nor did it correspond to the proposed *mono*-phosphine complex. The ratio of nitrogen to phosphorus should theoretically be 1:4.48. The observed ratio is a mere 1:1.25, confirming that the initial reaction between 3-aminopropyl functionalised silica and diphenylphosphinomethanol (Scheme 54) did not go to completion. In fact, based on the observed and theoretical elemental ratios, only 27.9% of the expected amount of phosphorus is present on the silica support. This figure is supported by TGA analysis (a 28% increase in organic material compared with the 3-APS starting material- see Figure 17).

Due to the relatively high palladium content, the sample must contain palladium species which are not ligated by phosphorus. A strong possibility is the formation of metal nano-particles on the support material.

2.3.4 SEM Analysis of Catalyst 10

In order to investigate the hypothesis that palladium nanoparticles had formed on the surface of catalyst **10** during its preparation, a sample was analysed by SEM. Figure 24 confirms the presence of surface-bound species ranging from 20 nm to 200 nm in diameter. The morphology of these structures is similar to literature examples of immobilised palladium nanoparticles (Figure 25),[99-100] prepared by reacting palladium(II) chloride with silica. Although further studies would be required to establish the composition of the spherical particles, Figure 25 at least serves as a useful comparison between batches of catalyst.

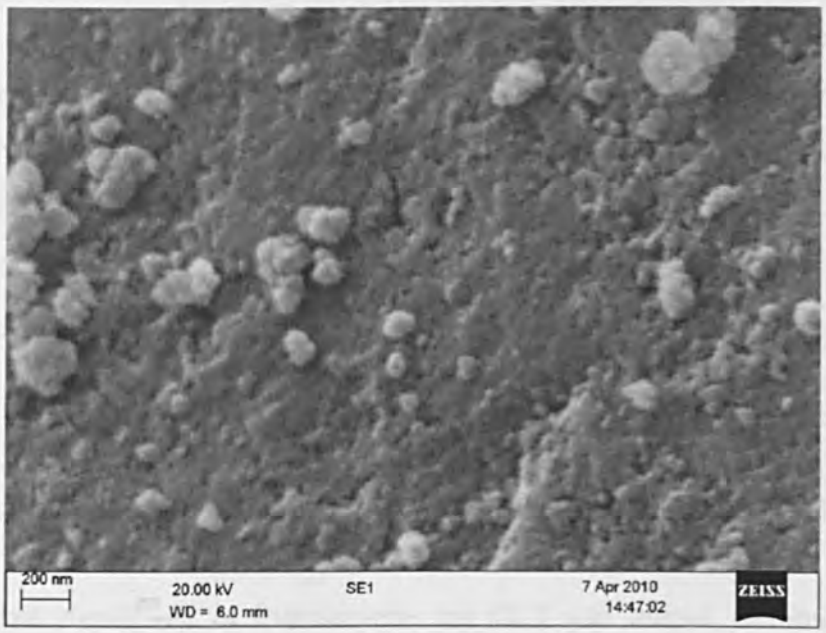


Figure 24 SEM image of catalyst **10**.

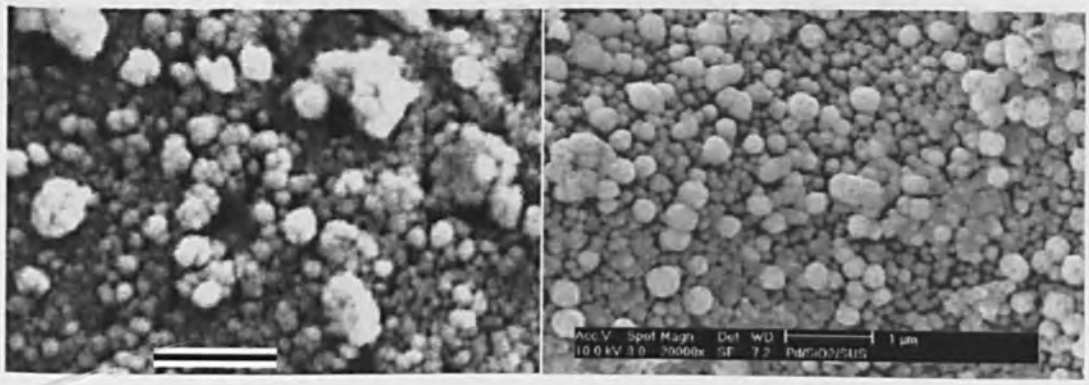


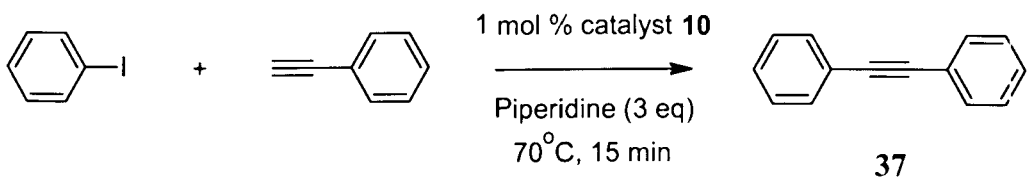
Figure 25 SEMs of two different silica-supported palladium nanoparticle catalysts.[99-100]

2.4 Catalytic Testing of Immobilised *Bis*-Phosphine Catalyst 10

2.4.1 Sonogashira Reactions

As the catalytic activity of the silica-supported catalyst **10** in copper-free Sonogashira cross-coupling reactions had been established to some extent,[52] the aim of this study was to test the activity of the catalyst across a wider range of substrates. The main criteria being assessed were functional group tolerance, activity toward sterically and electronically demanding substrates, recyclability and activity in other catalytic reactions.

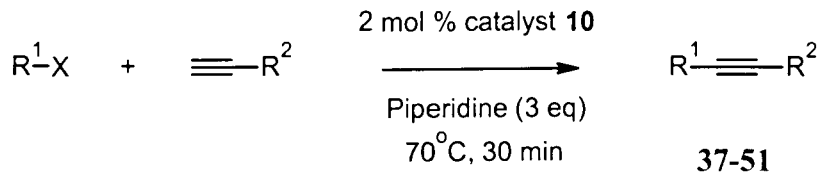
Firstly, the catalyst was tested in a standard copper-free Sonogashira reaction to confirm that it was of comparable activity to the catalyst in the original publication.[52] The cross-coupling of iodobenzene and phenylacetylene was previously accomplished in >99% conversion in 15 min. The result obtained in this study (Scheme 58) was highly encouraging.



Scheme 58 Confirmation of the catalytic activity of **10** in a standard Sonogashira reaction.

Quantitative conversion of iodobenzene (by GC) was indeed facilitated in 15 minutes. Actually, complete solidification of the reaction mixture due to the formation of piperidinium salt occurred in less than 5 minutes. The product, diphenylacetylene **37**, was isolated in 88% yield by column chromatography (using hexane as the eluent). This confirmed that the catalyst used in this investigation was at least of comparable activity to the original batch reported in 2005.[52]

The same methodology was applied to a range of aromatic halides and alkynes bearing different functional groups. Reactions employing halide substrates with electron donating groups (e.g. 4-iodoanisole) or steric restrictions (e.g. 2-iodotoluene) proceeded more slowly. As a result, the catalyst loading and reaction time were increased to make the process more generally applicable (Scheme 59).



Scheme 59 Modified Sonogashira conditions.

The modified conditions were used with a wide range of halides and alkynes to demonstrate the synthetic utility of catalyst (Table 2).

Table 2 Sonogashira cross-coupling reactions.

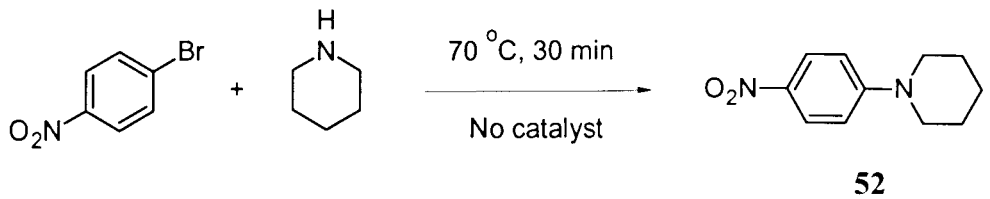
Entry (name)	X	R^1	R^2	Conversion[a]	Yield[b]
1 (37)	I	Ph	Ph	>99	88
2 (38)	I	Ph	4-$MeOC_6H_4$	98	80
3 (39a)	I	2-$NH_2C_6H_4$	Ph	78	60
4 (39b)	I	Ph	2-$NH_2C_6H_4$	95	80
5 (40)	I	4-$MeCOC_6H_4$	Ph	>99	81
6 (41)	I	2-MeC_6H_4	Ph	63	52
7 (42)	I	2-BrC_6H_4	Ph	65	59
8 (43)	I	4-BrC_6H_4	Ph	96	82
9 (44)	I	Ph	$C(Me)_2NH_2$	45	34
10 (45)	I	2-$NH_2C_6H_4$	2-$NH_2C_6H_4$	>99	74
11 (46)	I	4-$MeCOC_6H_4$	2-$NH_2C_6H_4$	>99	82
12 (47)	I	2-$NH_2C_6H_4$	4-$MeOC_6H_4$	85	60
13 (48)	I	4-$MeCOC_6H_4$	4-$MeOC_6H_4$	>99	80
14 (49)	I	2-NH_2, 5-CNC_6H_3	Ph	>99	76
15 (50)	I	2-NH_2, 5-CNC_6H_3	4-$MeOC_6H_4$	95	65
16 (37)	Br	Ph	Ph	32	10
17 (51)	Br	4-$NO_2C_6H_4$	Ph	89	30
18 (40)	Br	4-$MeCOC_6H_4$	Ph	40	17

[a]The % conversion of the halide substrate was determined by GC. [b]Figures represent % yield isolated by column chromatography.

Good to excellent conversion rates were observed throughout the range of aryl iodides tested. Some notable exceptions include electron-rich aryl iodides e.g. 2-iodoaniline (entries 3 and 12), which would be expected to be somewhat electronically deactivated to the initial oxidative addition step and would experience some steric hindrance. 2-Iodotoluene (entry 6), would also be subject to these stereoelectronic effects. 1,1-dimethylaminoethyne (entry 9) was coupled in less than 50%, confirming that aromatic alkynes were preferred in this study over aliphatic alkynes.

As expected, substrates containing more than one halide substituent, e.g. 1,2- and 1,4-bromoiodobenzene (entries 7 and 8) underwent further reaction to furnish small amounts of the corresponding *bis*-Sonogashira products (1,2- and 1,4-*bis*-phenylethynylbenzene). This result was particularly encouraging as it confirmed that catalyst **10** was capable of turning over the less reactive aromatic aryl bromide substrates to some extent. Examples, in the scientific literature, of heterogeneous catalyst systems employing aryl bromides in Sonogashira reactions are scarce.

The more challenging aryl bromide substrates (entries 16, 17 and 18) furnished only modest amounts of cross-coupled product, confirming the idea that they are deactivated towards oxidative addition (the rate-determining step), compared to aryl iodides.[101] Significant amounts of alkyne-alkyne homocoupling were identified in these reaction mixtures by GC-MS. 4-Nitrobromobenzene, an electronically activated aryl bromide, was used in an attempt to increase the % conversion. Interestingly, this substrate preferentially reacts with piperidine under these conditions to form 1-(4-nitrophenyl)piperidine **52**. Initially, this was thought to be the result of a Buchwald-Hartwig type C-N coupling,[102] which has not yet been reported for this particular catalyst. However, by carrying out the reaction without any catalyst, it was established that the substrate is activated (by the electron-withdrawing effects of the nitro- and bromo- substituents) toward a non-catalytic nucleophillic aromatic *ipso*- substitution reaction (Scheme 60), for which there is already literature precedent.[103]



Scheme 60 Non-catalytic *ipso*- substitution, the dominant process throughout Sonogashira reactions involving 4-nitrobromobenzene. 99% conversion observed by GC.

Following a literature search, it appears that most groups avoid 4-nitrobromobenzene as a substrate in the testing of heterogeneous palladium catalysts in Sonogashira reactions. This is most likely due to this prominent side reaction and suggests that the rate of oxidative addition of aryl bromides to catalyst **10** is slow enough to allow this non-catalytic process to dominate. It may be possible to suppress this undesirable process by using a less nucleophilic base (e.g. TEA), though this was not attempted.

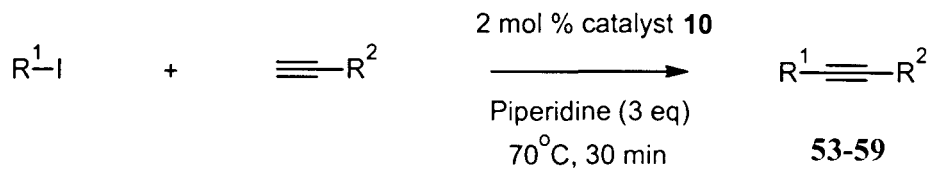
The activity observed in Sonogashira coupling reactions using catalyst **10** is highly comparable with that of similar heterogeneous palladium catalysts reported in the literature. Breinbauer *et al.* used the polystyrene supported analogue of **10**, and obtained near-quantitative conversions throughout a range of functionalised aryl iodides.[51] However, the authors did use 2 mol% of copper iodide as a co-catalyst. Unfortunately no data regarding the activity of Breinbauer's catalyst toward aryl bromide substrates or in copper-free reactions appeared in the article.

More recently, Cai *et al.* used an MCM-41 supported thioether palladium complex to achieve very similar yields in copper-free Sonogashira coupling reactions.[54] The authors found it possible to perform the reaction under aerobic conditions using aqueous solvent, which is a distinct commercial advantage and is possible only due to the phosphine-free catalyst system employed. The phosphine-based palladium catalyst also reported by this group[53] required 10 mol% copper iodide as a co-catalyst to achieve excellent conversions.

The versatile silica supported *bis*-pyridine palladium complex reported by Polshettiwar *et al.*[55] actually required 5x the catalyst loading to produce similar results in Sonogashira coupling reactions to those presented in this study.

These studies have shown that aryl bromides are not very reactive under these conditions. Increasing reaction temperatures and prolonging reaction times only led to catalyst decomposition with little improvement in yield of cross-coupled product. This is not surprising considering high yielding Sonogashira reactions of aryl bromides using heterogeneous palladium catalysis are a rarity in the scientific literature.[66]

The same reaction conditions were successfully applied to a range of heterocyclic aryl iodide substrates (Scheme 61, Table 3). Excellent conversions were noted throughout, which implies that the presence of a heteroatom in the aromatic ring has no noticeable effect on the yield; making this process attractive for synthesis of heterocyclic molecules.



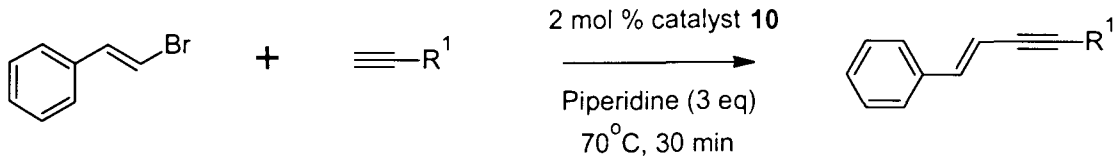
Scheme 61 Sonogashira coupling of heteroaromatic iodides.

Table 3 Sonogashira cross-coupling of heterocyclic aromatic iodides

Entry (name)	R^1	R^2	Conversion[a]	Yield (%)[b]
1 (53)	2-thiophenyl	Ph	>99	76
2 (54)	3-pyridinyl	Ph	>99	73
3 (55)	5-indolyl	Ph	92	76
4 (56)	2-thiophenyl	3-thiophenyl	>99	63
5 (57)	2-thiophenyl	2-$NH_2C_6H_4$	95	72
6 (58)	2-NH_2,5-ClC_6H_3	3-thiophenyl	95	76
7 (59)	5-indolyl	2-$NH_2C_6H_4$	96	80

[a]The % conversion of the halide substrate was determined by GC. [b]Figures represent % yield isolated by column chromatography.

The coupling of alkenyl halides is also possible under our standard conditions. β-Bromostyrene proved to be an ideal substrate, furnishing the expected ene-yne products in high yields (Scheme 62, Table 4).



60-64

Scheme 62 Sonogashira coupling of β-Bromostyrene.

Table 4 Sonogashira cross-coupling of β-Bromostyrene

Entry (name)	R^1	Conversion[a]	Yield (%)[b]
1 (60)	Ph	98	85
2 (61)	$2\text{-}NH_2C_6H_4$	99	87
3 (62)	cyclopentyl	77	51
4 (63)	3-thiophenyl	95	66
5 (64)	TMS	81	65

[a]The % conversion of the halide substrate was determined by GC. [b]Figures represent % yield isolated by column chromatography.

Few examples of Sonogashira coupling of alkenyl bromides using heterogeneous palladium catalysts exist in the literature. Those that could be identified used homogeneous palladium catalysts with copper co-catalysts to achieve high conversions.[46] Therefore the use of a heterogeneous, copper-free catalyst system represents another novel synthetic application of catalyst **10**.

2.4.2 Recycling Studies

Using a higher catalyst loading (4 mol%, as used in recycling studies of comparable catalysts in the scientific literature[51-53]), it was established that catalyst **10** could indeed be recycled. Conversion of the halide substrate was monitored by GC-MS using an internal standard. For each cycle, the catalyst was removed from the reaction by filtration, washed with DCM and dried under vacuum. (Figure 26).

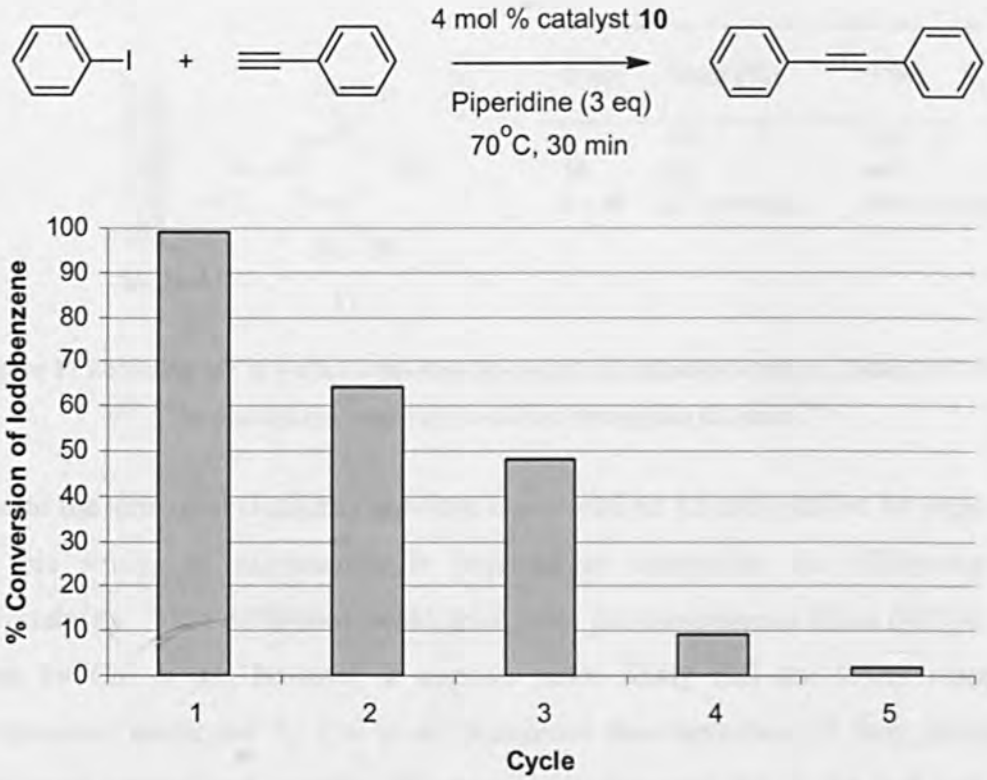
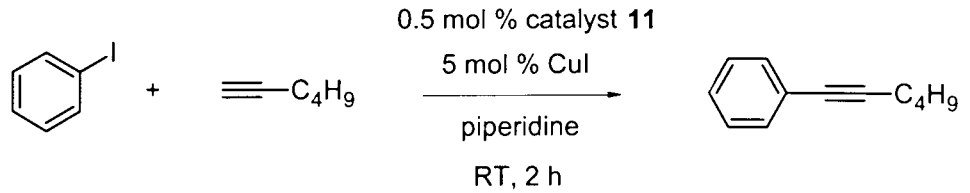
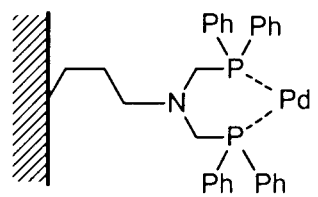


Figure 26 Chart showing consecutive re-uses of catalyst **10** in Sonogashira coupling of iodobenzene and phenylacetylene. The % conversion of iodobenzene was established by GC using an internal standard.

A steady decrease in conversion rate was observed in this study. Compared with Breinbauer's polystyrene supported analogue **9**, which was capable of four consecutive Sonogashira couplings (quantitative yields observed throughout),[30] catalyst **10** appears considerably less stable. However, close scrutiny of Breinbauer's results reveals that reactions were carried out overnight (as opposed to over 30 minutes). Therefore, Breinbauer *et al.* did not accurately measure the decrease in activity upon recycling, only that the recycled catalyst eventually reached 99% conversion.

Cai *et al.* however presented a highly recyclable catalyst system **11**.[53] By keeping the reaction time constant, these authors were able to demonstrate near-quantitative conversions over ten cycles with negligible decrease in turnover number, although 5 mol % copper iodide was required (Figure 27).





MCM-41

11

Cycle	Yield (%)	TON
1	98	196
10	96	192
1 - 10	97 (average)	194 (average)

Figure 27 Recycling of Cai's silica supported *bis*-phosphine palladium catalyst. Based on TONs, the reaction rate remained consistent throughout the study.[53]

Due to the structural similarity between Cai's catalyst **11** and catalyst **10** prepared in this study, an explanation is required to rationalise the difference in recyclability. This difference could arise from the mesoporous silica (MCM-41) used by Cai *et al.*, however it appears more likely that the lower reaction temperature employed by Cai *et al.* prevented decomposition of their catalyst. The room temperature reaction was possible in this case due to the fact that the active palladium(0) species was preformed (by reduction of the palladium(II) chloride complex with hydrazine monohydrate). Catalyst **10**, used in the present study, relies upon *in situ* reduction, which requires higher temperatures.

As in the work of Breinbauer *et al.*,[51] increasing the reaction time resulted in increased % conversion, confirming that the catalyst was actually slowing down (as opposed to dying completely). It is postulated that that leaching of palladium into reaction mixtures or the formation of catalytically inactive palladium complexes on the support may be responsible for this progressive deactivation of the catalyst.

2.4.3 '5-*Endo-Dig*' Cyclisation Reactions

During the testing of 2-amino substituted aryl iodides in Sonogashira coupling reactions (Table 2, entries 3, 4, 10, 11, 12, 14 and 15), an interesting side reaction was observed. GC-MS analysis of these reaction mixtures indicated the presence of an isomer of the expected product in small amounts (Figure 28).

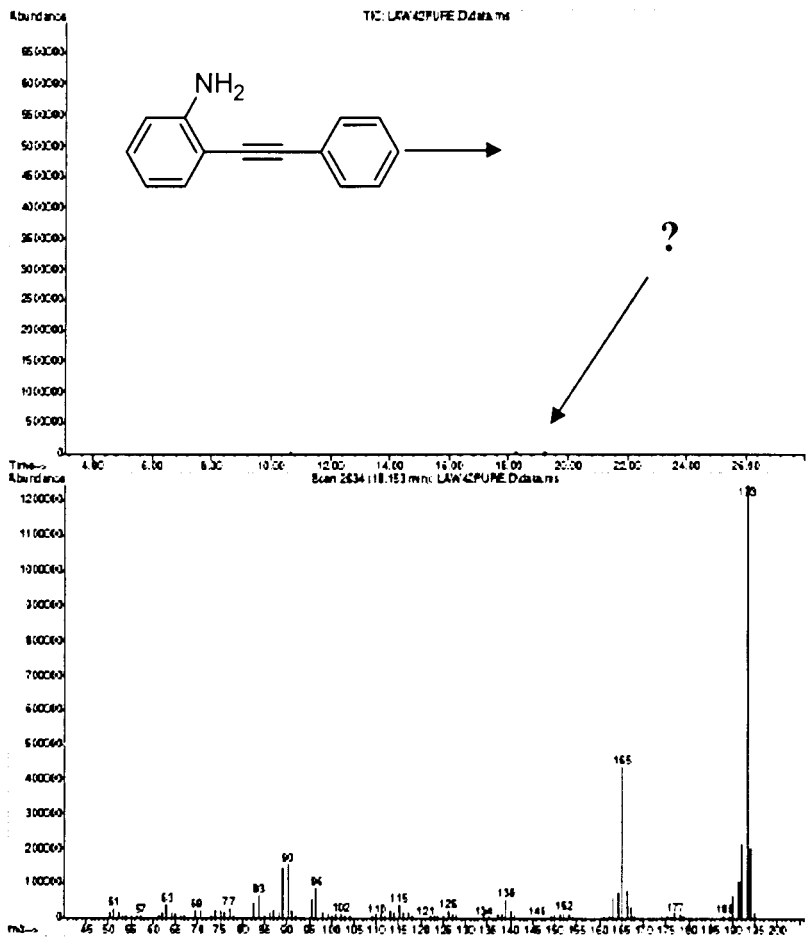
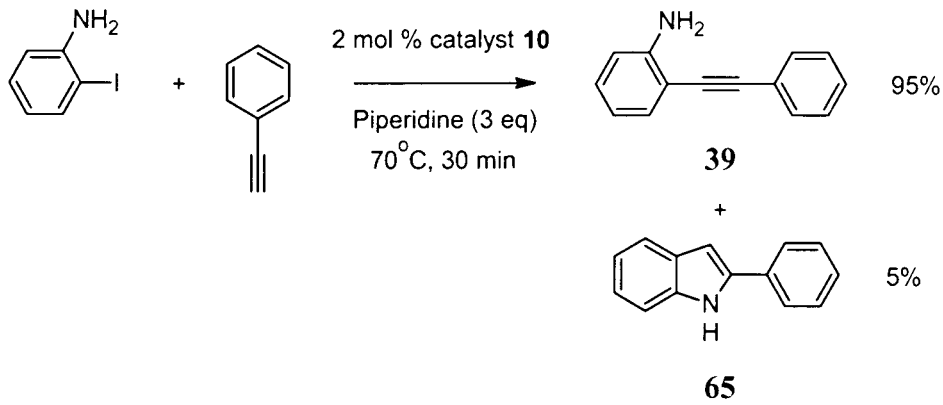


Figure 28 GC-MS showing the expected product (18 min) and its isomer (19 min).

It was reasoned that the 'impurity' was actually the cyclised product. This idea was confirmed by isolation of the side product by column chromatography and subsequent NMR analysis. This finding prompted the investigation into the application of catalyst **10** to the synthesis of 2-substituted indoles.

Literature precedent (albeit recent) does exist for the use of supported palladium catalysts for the synthesis of 2-substituted indoles from 2-ethynylanilines. Djakovitch *et al.* used palladium on carbon with a copper co-catalyst,[10] others

groups including Wu *et al.*[84] and Srinivasan *et al.*[105] performed the reaction under copper-free conditions but found that *N*-protection of the amino group (e.g. *N*-tosyl or *N*-mesyl) was necessary for the reaction to take place. It was then realised that the first copper-free '5-*endo-dig*' cyclisation of 2-(phenylethynyl)aniline (the free amine) using a supported palladium catalyst had occurred, by chance, in our laboratory (Scheme 63).



Scheme 63 Sonogashira coupling to yield 2-(phenylethynyl)aniline and 2-phenylindole.

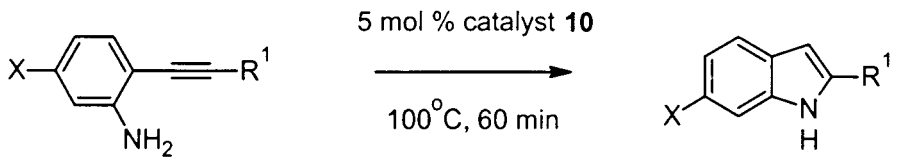
All initial attempts at modifying the Sonogashira conditions to favour the formation of the cyclisation product were unsuccessful, despite the existence of a one-pot procedure using palladium on carbon and a copper co-catalyst, reported by Djackovitch *et al.*[10] Increased catalyst loading, temperature and prolonged reaction time seemed to have little effect on the product distribution. After much experimentation, it was realised that isolating the Sonogashira product and treating it with fresh catalyst at 100 °C afforded indole **65** in quantitative fashion (Table 5).

Table 5 Optimising the heteroannulation reaction to yield 2-phenylindole using catalyst **10**.

Entry	Cat. Loading (mol %)	Temp. (°C)	Time (min)	Conversion[a]
1	10	160	20	>99
2	10	120	20	>99
3	10	100	20	96
4	10	90	20	67
5	4	100	20	12
6	4	100	180	68
7	2	100	20	27
8	2	100	60	63
9	5	100	20	77
10	5	100	60	>99

[a]The % conversion of 2-(phenylethynyl)aniline was determined by GC.

Having optimised the reaction conditions, a small range of suitable substrates were tested (Scheme 64). Excellent yields were observed throughout (Table 6)



65-68

Scheme 64 *5-endo-dig* cyclisation of 2-(ethynyl)aniline derivatives.

Table 6 Synthesis of 2-substituted indoles from 2-(ethynyl)aniline derivatives

Entry (name)	R^1	X	Conversion[a]	Yield (%)[b]
1 (65)	Ph	H	>99	96
2 (66)	5-indolyl	H	>99[c]	91
3 (67)	3-thiophenyl	Cl	98[c]	89
4 (68)	2-thiophenyl	H	98[c]	90

. [a]The % conversion of the halide substrate was determined by GC. [b]Figures represent % yield isolated by column chromatography. [c]DMF (1 mL) used as solvent.

Due to the low melting point of 2-(phenylethynyl)aniline **39**, the reaction proceeded without the need for solvent (entry 1, Table 6). Substrates with higher melting points were solubilised with DMF. In comparison to some literature procedures, this process is extremely efficient as it does not require a copper co-

catalyst or derivatisation of the amino group and in some cases, proceeds without solvent. Based on its simplicity and efficiency, this process could possibly lend itself to large scale synthesis of indole-containing products which are ubiquitous throughout the scientific literature.[104]

The fact that the reaction proceeds in the absence of solvent, co-catalyst or external base raised a question about the mechanism. The reported mechanism (summarised in Figure 29) involves co-ordination of the alkyne with the metal centre, followed by nucleophilic attack (by the amino group) on the activated alkyne.[106-107]

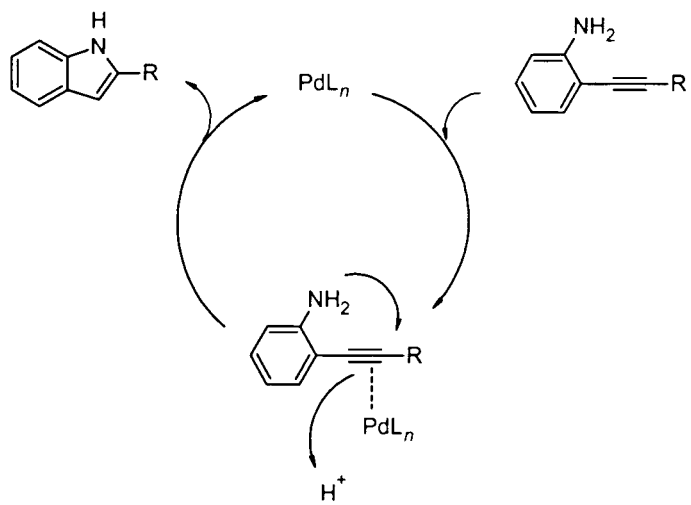


Figure 29 Literature mechanism for the 5-*endo-dig* cyclisation of ethynylaniline derivatives.[106-107]

This mechanism does not account for the necessary proton transfer, a process which is probably assisted by the presence of base. In the absence of base, however we proposed an alternative mechanism based upon oxidative addition of the N-H bond (Figure 30). This mechanistic idea was in fact published in 2005 - see appendix. Oxidative addition of the N-H bond has previously been described[108] and the formation of a 6-membered palladacycle by insertion of the alkyne into the Pd-H bond seems reasonable (similar 4-membered palladacycles have been prepared from *ortho*-haloanilines[109]).

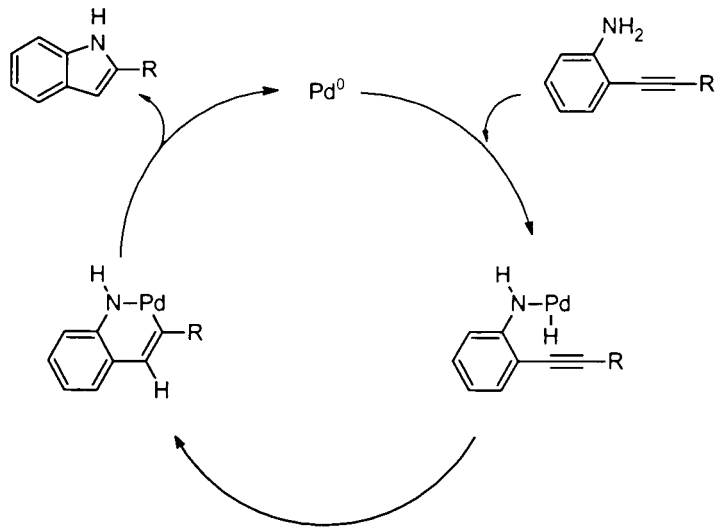
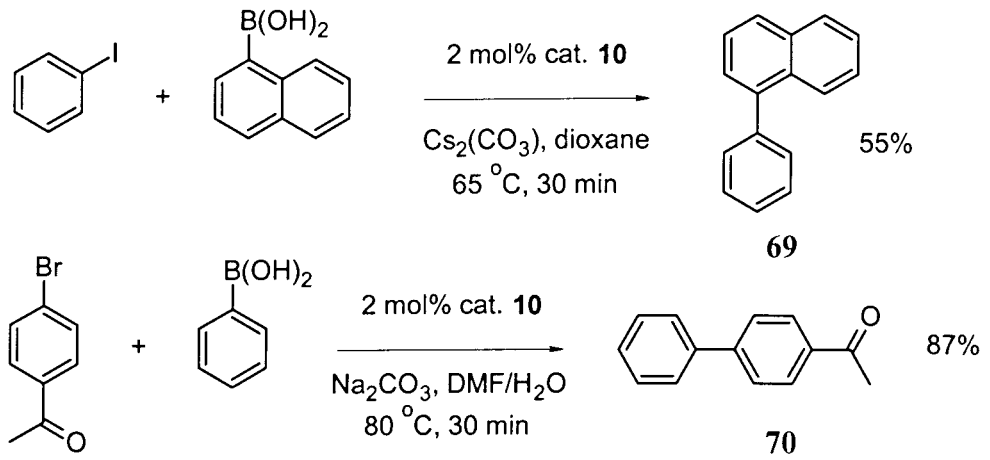


Figure 30 Proposed alternative mechanism for 5-*endo-dig* cyclisation reactions.

2.4.4 Suzuki Reactions

Although it was not the main focus of this investigation, preliminary screening for activity in Suzuki coupling reactions was carried out using catalyst **10**. Under two different literature conditions (designed for reactions of aryl iodides and bromides)[110] 2 mol% of catalyst **10** furnished respectable conversions of iodobenzene and 4-bromoacetophenone to the Suzuki products **69** and **70**, which were isolated in 55% and 87% yield respectively (Scheme 65).



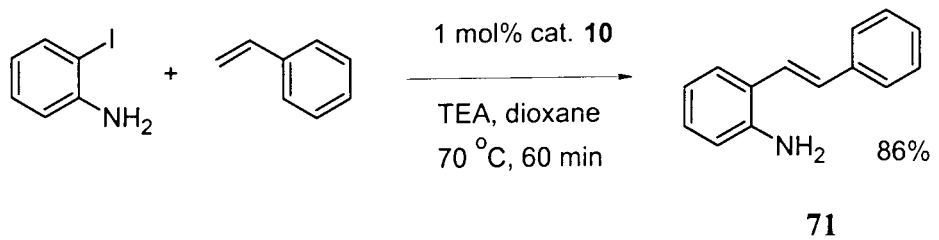
Scheme 65 Testing of catalyst **10** in Suzuki coupling reactions.

The fact the catalyst showed some activity without optimisation studies was encouraging, suggesting the catalyst may be quite versatile in nature. However in comparison to existing heterogeneous catalysts, the conversion rate is low.[67-69]

Catalyst **10** performed much better when aqueous DMF was used as solvent. This may be related to the increased solubility of the reactants in this solvent system. Iodobenzene is known to be a reactive substrate and should present no problems to a competent catalyst. Although optimisation of the reaction conditions may have improved upon the yields, the testing was not taken further in this study.

2.4.5 Heck Reaction

Catalyst **10** also showed some promising activity in the Heck reaction (Scheme 66).



Scheme 66 Testing of catalyst **10** in Heck coupling of 2-iodoaniline.

The reaction reached 86% conversion in 1 h. Small amounts of an isomeric side product presumably resulting from *anti*- insertion of the alkene, were identified in the product mixture by GC-MS (Figure 31, 19 min).

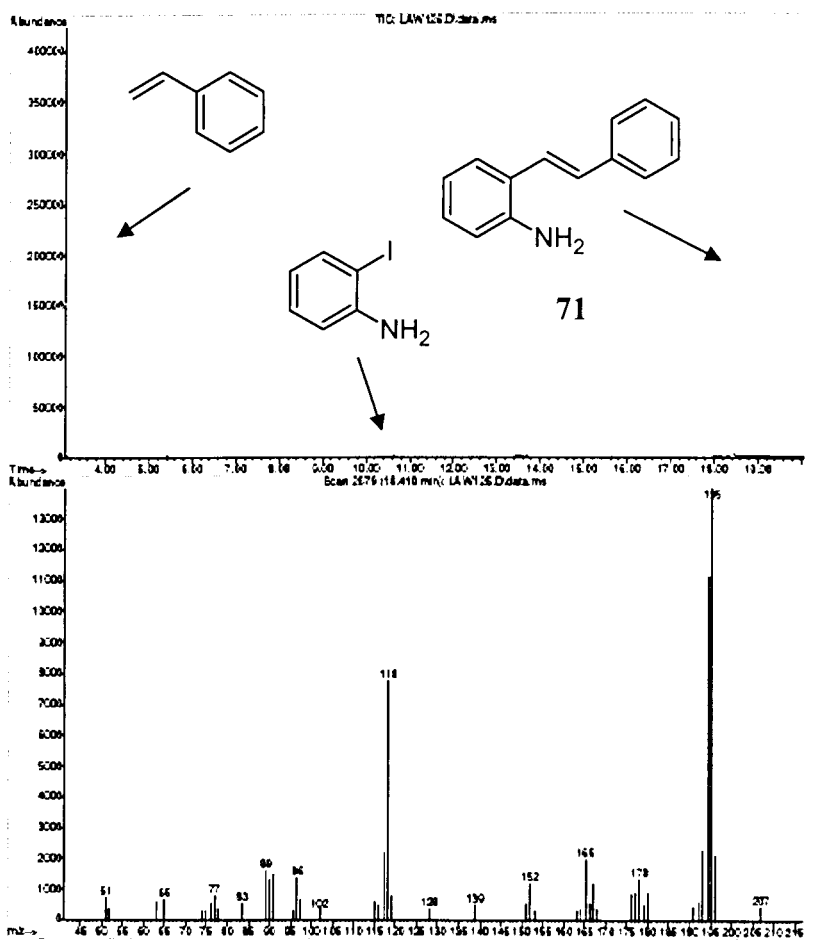


Figure 31 GC-MS of the crude Heck reaction mixture showing 86% conversion of the iodide substrate.

Considering that 2-iodoaniline is a relatively activated substrate, the catalyst shows inferior activity to some recently reported heterogeneous palladium complexes. For example Li *et al.* achieved higher conversion rates using palladium on SBA-15 with a palladium loading of only 0.04 mol%.[79]

The testing of catalyst **10** in Heck reactions was not explored further in this work. Having established activity in Sonogashira reactions and conducted preliminary screening in 5-*endo-dig* cyclisations, Suzuki and Heck coupling reactions, the focus of the project shifted towards the development of novel silica-supported catalysts.

2.5 Conclusions and Future Work

The initial aim of this work was to fine tune the synthesis of catalyst **10** and characterise it as fully as possible in order to establish a reproducible protocol. Another aim was to explore in greater depth the scope of its application in palladium catalysed transformations. The following conclusions may be drawn.

Catalyst **10** performed extremely well in Sonogashira coupling reactions throughout a range of substrates including alkenyl bromides and heterocyclic aryl iodides. The copper-free, solvent-free protocol lends itself to industrially feasible applications. Removal of catalyst from reaction mixtures by simple filtration is a definite advantage over most homogeneous methodologies, although the limited recyclability of the catalyst would reduce its commercial viability somewhat. Since only modest yields were obtained for attempted couplings of aryl bromide substrates, the catalytic activity observed is comparable to most existing solid-supported palladium phosphine complexes.[51-53] These results exemplify the dramatic difference in reactivity between heterogeneous and homogeneous catalyst systems (the latter being capable of turning over aryl bromide and even aryl chloride substrates under mild conditions).[42-45]

Importantly, throughout the six batches of catalyst **10** prepared in this study, consistent results were obtained in terms of TGA profiles, catalytic activity and recyclability. This confirms that the protocol is indeed reproducible, which was not reported previously.[31]

The 5-*endo-dig* cyclisation process (a serendipitous discovery) used to prepare 2-substitued indole derivatives is highly efficient and could potentially lend itself to industrial applications. It is interesting to note that a 'one-pot' Sonogashira-cyclisation reaction was not possible in this study, the Sonogashira product must be isolated and then treated with fresh catalyst to achieve meaningful conversions. Quite possible is the idea that the one-pot process is hindered by the presence of piperidinium hydroiodide (a normal by-product of the Sonogashira reaction),

which above all else causes the reaction mixture to solidify, preventing adequate stirring. Thus perhaps the one-pot process is simply impeded by mass transport. Analysis of catalyst **10** has revealed certain previously unknown features regarding its composition. Most notable of which is the fact that the catalyst consists of several species including the expected *bis*-phosphine palladium complex and palladium metal particles (Figure 32).

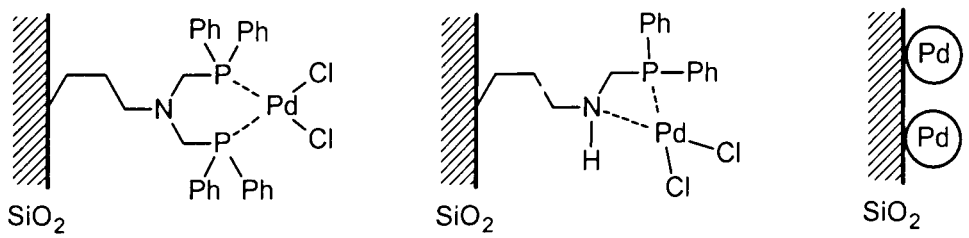


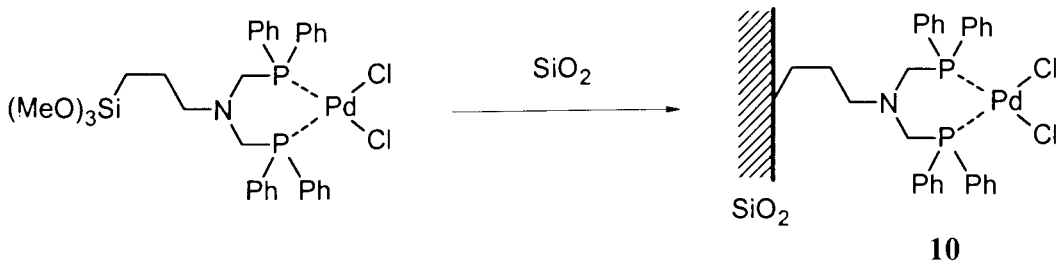
Figure 32 Potentially catalytically active species present in catalyst **10**. The expected *bis*-phosphine species (left), proposed *mono*-phosphine species (middle) and palladium metal particles (right) due to insufficient amounts of immobilised phosphine ligand.

The activity of solid-supported palladium nanoparticles in Sonogashira coupling reactions is well documented. Wang *et al.* demonstrated the efficiency of colloidal palladium(0) supported on poly(vinylpyrrolidone), which displayed superior activity in the Sonogashira coupling of aryl bromides, compared to catalyst **10**.[111] Therefore it is entirely possible that palladium nanoparticles are responsible for some of the observed catalytic activity. Although not necessarily a disadvantage in terms of catalyst performance, the presence of more than one active species generally complicates the analysis of the catalyst and prevents reliable fine-tuning experiments involving the variation of ligand structure.

The fact that modest activity in unoptimised Suzuki and Heck reactions was also established is an encouraging indication of the versatility of catalyst **10**. However further studies would be required to optimise these processes.

The main problem identified in the synthesis of catalyst **10** was in the preparation and immobilisation of diphenylphosphinomethanol **33**. The oxygen-sensitive nature of this species prevented isolation and characterisation, resulting in a low yield which led to an incomplete immobilisation step (calculated at 28% based on

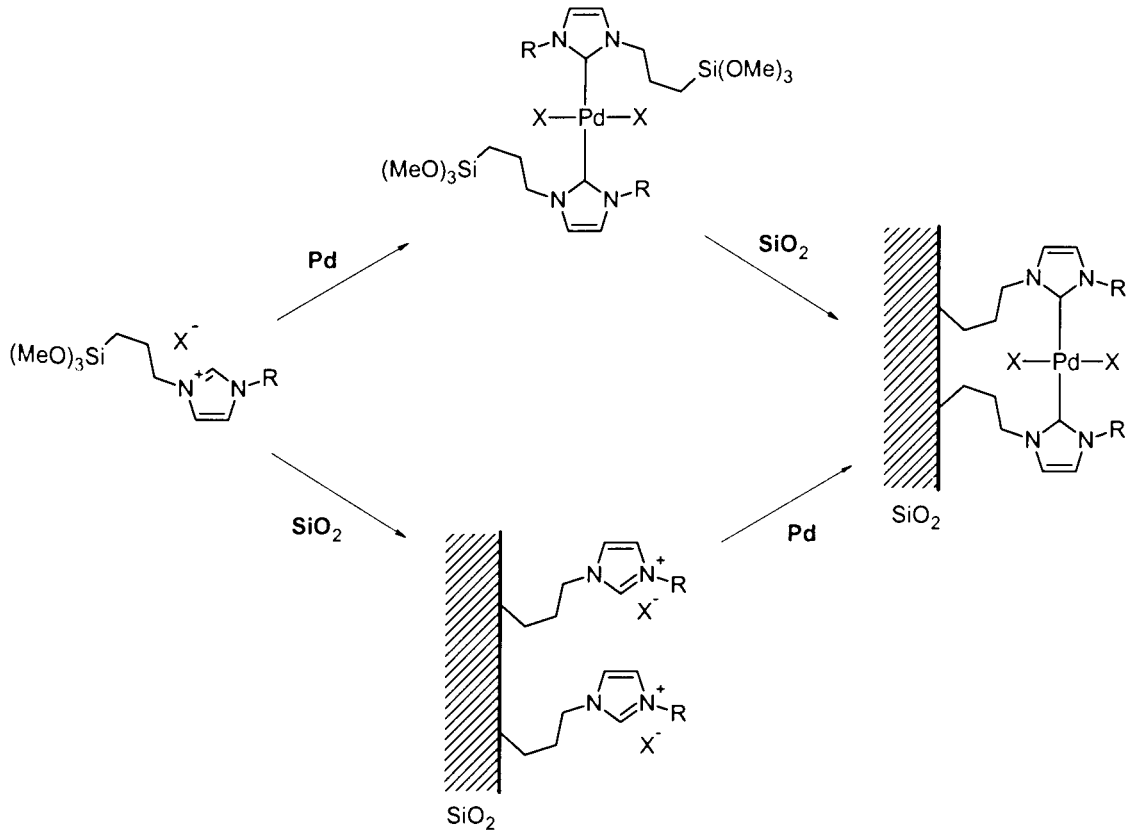
TGA and elemental analyses). Although this literature method produced a highly active catalyst, it would seem that a more reliable approach would be to generate and characterise the entire metal complex prior to immobilisation such as in Scheme 67. Moreover, this method would facilitate precise control of catalyst loading resulting in a more uniform, well-defined catalyst.



Scheme 67 An alternative approach to the preparation of catalyst **10**.

Rather than exploring alternative syntheses of catalyst **10**, we turned our attention to the heterogenisation of a new and exciting class of organometallic ligand, *N*-heterocyclic carbenes (NHCs). Since NHC-palladium complexes are known to be more stable than their phosphine counterparts, they provide an opportunity to prepare silica-supported catalysts by two different methodologies i.e. immobilisation of ligand followed by complexation and synthesis of the entire NHC complex followed by immobilisation (Scheme 68).

This methodology allows for the characterisation of the metal complex prior to immobilisation and, by careful choice of ligand, allows for an investigation into the effects of steric crowding around the metal centre.



Scheme 68 Strategies for the preparation of silica-supported NHC-palladium complexes.

3 Preparation of Immobilised *Bis*-NHC Catalysts

3.1 Introduction

N-Heterocyclic carbene complexes of palladium have recently found numerous applications in both homogeneous and heterogeneous catalysis. Often described as phosphine mimics, the use of NHCs has increased in popularity in recent years due to certain inherent advantages over phosphine ligands. They are generally more air-stable than phosphines which makes them ideal candidates for heterogenisation and thus potentially very interesting from an industrial perspective. Another apparent advantage associated with NHCs is their relatively environmentally benign nature (compared with phosphine precursors which are hazardous and unpleasant to work with). This move towards development of novel NHC palladium catalysts is therefore in keeping with our 'green' approach to catalyst design.

Further benefits of NHCs as ligands include the fact that steric and electronic properties are isolated such that the steric bulk of the ligand may be varied without directly affecting the electron-donating ability of the ligand (Figure 33). This allows for more reliable investigation into the steric effects on catalytic activity. Also, unlike phosphines which direct their substituents away from the metal centre, the steric bulk of NHC ligands is necessarily pointing toward the metal, forming a 3-dimensional pocket. This suggests that the *N*-substituents of NHCs may exert a more pronounced steric effect on the active site than substituents on phosphine ligands, which may be beneficial to catalytic activity.

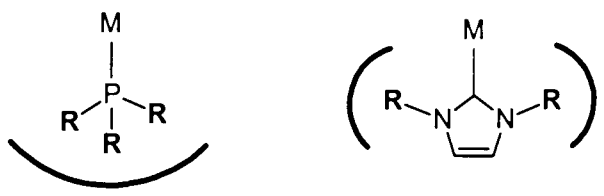


Figure 33 Fundamental structural differences between phosphines, where steric bulk is directly attached to the co-ordinating phosphorus atom (left) and NHCs, where steric bulk is not attached to the co-ordinating carbon atom (right).

Numerous research groups have focussed on the development of silica-supported NHC complexes in hope of combining the attractive properties of NHC ligands with the practical advantages associated with heterogeneous catalysis. Progress in this field has been recently reviewed.[112-113]

The majority of silica-supported NHC-palladium complexes found in the scientific literature are of the general structure shown in Figure 34.

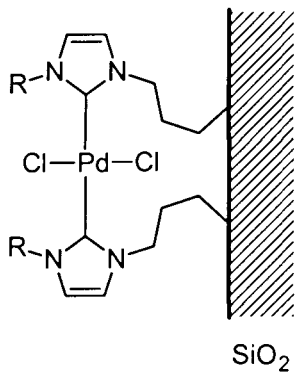


Figure 34 General structure of reported silica-supported NHC-palladium complexes. R = -alkyl, -benzyl, -CH_2(2,4,6-trimethyl)phenyl.[67-69]

Solid-supported *N*-alkyl and *N*-benzyl NHC palladium complexes have been reported and generally show good activity in cross-coupling reactions.[67-69] Interestingly, heterogeneous catalysts containing the bulkier *N*-aryl NHC ligands have received little attention in the literature. The phenomenon of bulky ligands having beneficial effects on catalytic activity in homogeneous reactions is well documented.[19] This suggests that silica-supported, sterically bulky NHC complexes may exhibit increased catalytic activity and would therefore represent ideal targets in the context of this work.

This study will therefore focus on the synthesis of a range of sterically bulky silica supported NHC-palladium complexes (including *N*-mesityl and *N*-(diisopropyl)-phenyl NHC ligands) in order to investigate the effect of increasing steric bulk around the metal centre on catalytic activity.

3.1.1 Synthetic Approaches to Immobilised *Bis*-NHC Palladium Complexes

The target molecule was disconnected as shown (Figure 35). As in the work of Enders *et al.*[108] the synthesis may be approached in two directions; by immobilisation of the imidazolium salt on silica followed by deprotonation and complexation with palladium and by forming the *bis*-NHC complex prior to immobilisation.

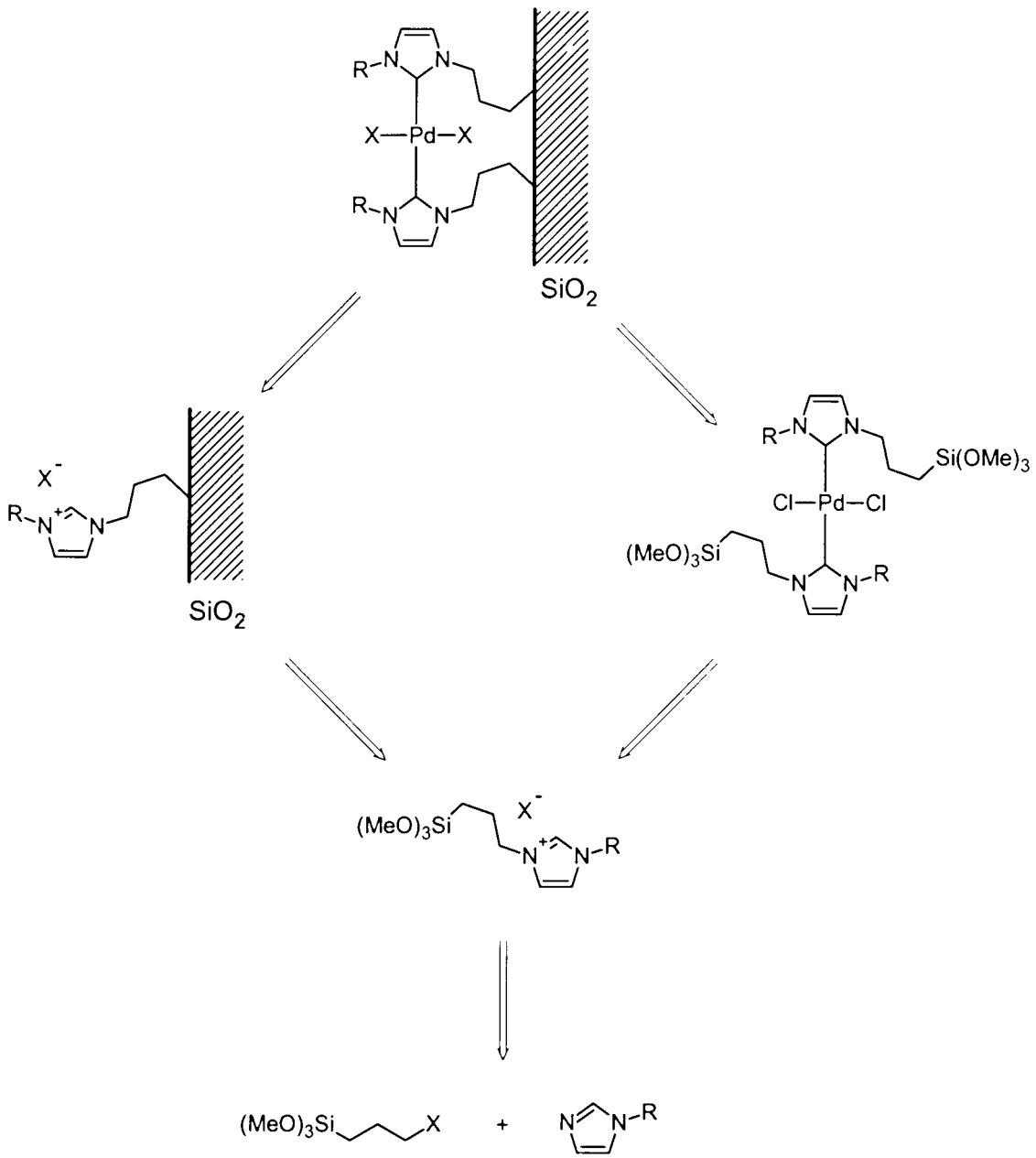
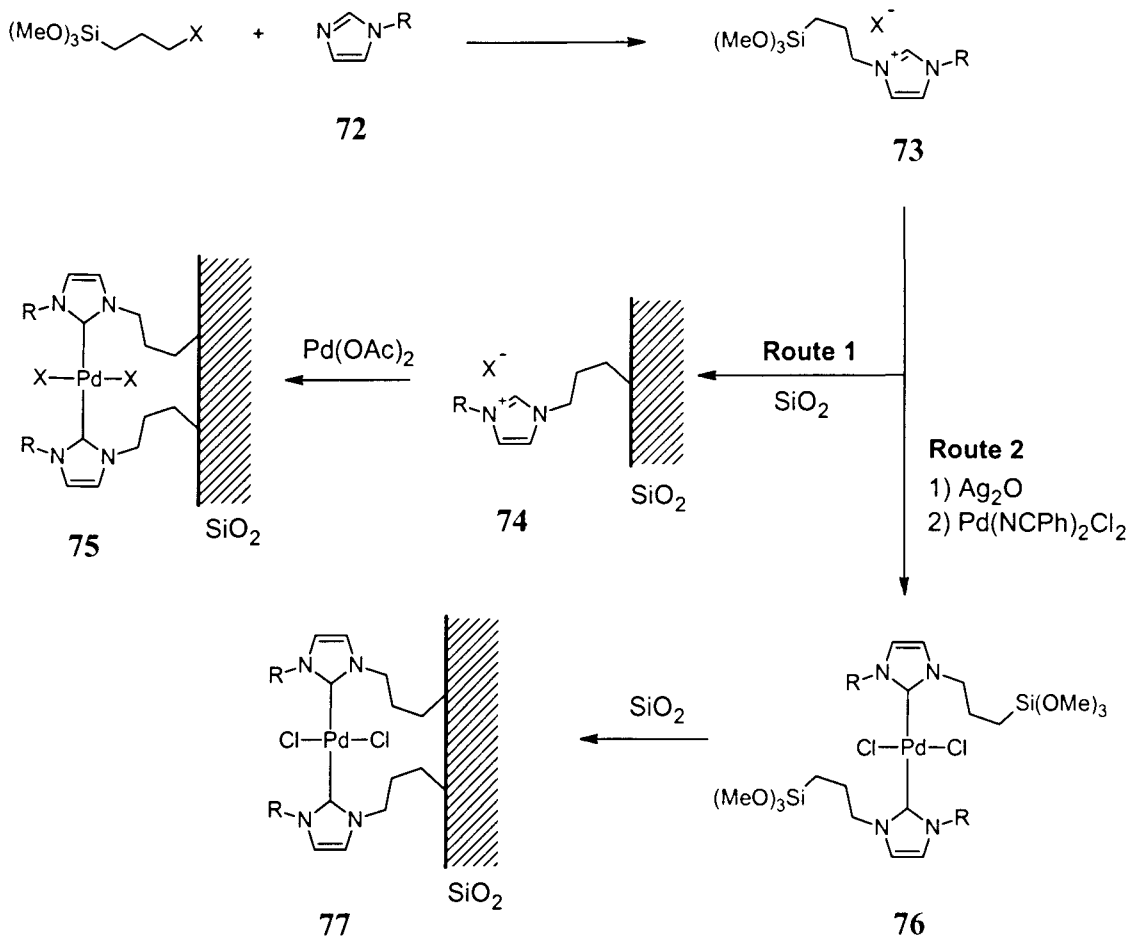


Figure 35 Two possible synthetic routes to silica-supported *Bis*-NHC complexes of palladium.

The imidazolium salts based on **73** are common intermediates for both strategies, and may be prepared by *N*-alkylation of substituted imidazoles with commercially available trialkoxysilyl alkyl bromides (Scheme 69).



Scheme 69 Preparation of *bis*-NHC precatalysts.
R = benzyl-, mesityl- and 2,6-(diisopropyl)phenyl-, X = I or Br.

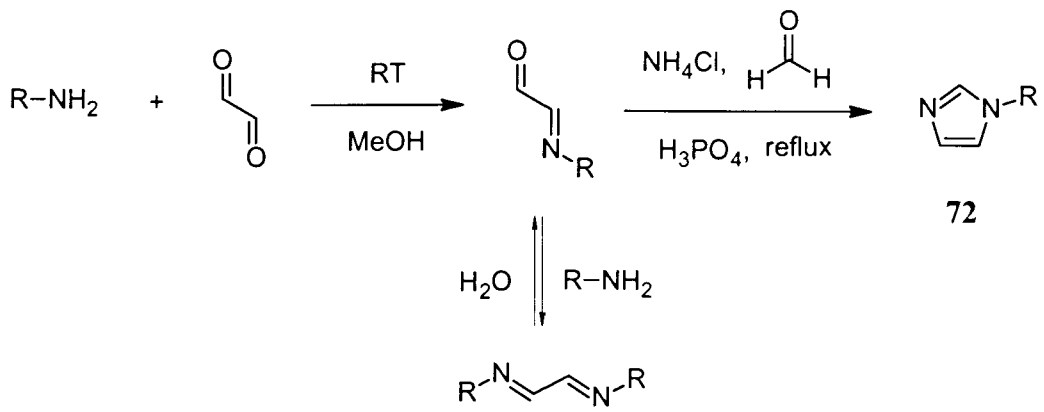
Route 1 is analogous to the synthetic route of *bis*-phosphine catalyst **10** in that the catalyst is assembled sequentially on the silica support. A similar procedure was recently employed by Sen *et al.* in the synthesis of immobilised NHCs bearing *N*-decyl groups.[68] The second approach is a particularly attractive route as it should allow for full characterisation of the palladium complex prior to immobilisation, as in the work of Polshettiwar *et al.*[115] If successful, the resulting catalysts obtained from routes 1 and 2 should be very similar, which may allow for a direct comparison between synthetic methodologies.

3.2 Synthesis of *N*-Substituted Ligand Precursors

N-Alkyl and *N*-benzyl imidazoles are commercially available and relatively inexpensive, however the sterically demanding *N*-aryl imidazoles are not. Several literature methods exist for the preparation of sterically hindered *N*-aryl imidazoles although yields are generally poor.[116] Liu *et al.* reported an improved method for *N*-mesityl and *N*-(diisopropyl)phenylimidazole, which resulted in a modest 40 and 43% yield respectively.[117]

3.2.1 Synthesis of *N*-Substituted Imidazoles

N-mesityl and *N*-(diisopropyl)phenylimidazole, **72a** and **72b**, were prepared by Liu's method,[117] which consisted of condensation of anilines, glyoxal, ammonium chloride and formaldehyde (Scheme 70, Table 7). The proposed *N*-(tritertiarybutyl)phenyl imidazole (**72c**) could, unfortunately, not be prepared by this method.



Scheme 70 Synthesis of *N*-aryl substituted imidazoles. R = mesityl- **72a**, 2,6-(diisopropyl)phenyl- **72b** and 2,4,6-(tritertiarybutyl)phenyl- **72c**.

Table 7 Summary of yields of *N*-aryl imidazoles obtained.

Entry (Name)	R	Yield (%)[a]
1 (72a)	mesityl-	43
2 (72b)	2,6-(diisopropyl)phenyl-	30
3 (72c)	2,4,6-(tritertiarybutyl)phenyl-	0 (90)[b]

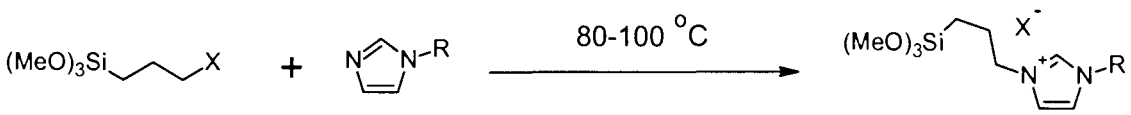
[a] Isolated by column chromatography and recrystallisation. [b] Isolated yield of diimine intermediate.

The low yields were, at first, attributed to the significant steric hindrance around the amino group. However GC-MS analysis of reaction mixtures of the initial condensation after 16 h revealed only small amounts of the expected imine intermediate (Scheme 70) and the diimine (the result of nucleophilic attack on both carbonyl groups of glyoxal) as the major product. This implies that the diimine must first be hydrolysed back to the imine before cyclisation can take place. This is possibly significant as it may explain the low yields as most of the starting material could be lost in the form of a diimine adduct, though this is speculative.

It would appear that optimising this particular reaction may be of value, considering the vast amounts of scientific literature being devoted to NHCs as catalysts. Perhaps very careful control over the rate of addition of the aniline derivative would favour formation of the mono-imine intermediate and increase the % conversion to the imidazole? Unfortunately, this remains the least efficient synthetic step in the entire synthesis of the silica-supported NHC catalysts and optimisation was not explored in this work.

3.2.2 Synthesis of Trimethoxysilyl Imidazolium Salts

Imidazolium salts **73a-g** were prepared by heating an *N*-substituted imidazole with 3-(bromo/iodopropyl)trimethoxysilane at 80-100 °C. The trialkoxysilyl group allows for facile tethering to silica via condensation with surface silanol groups.[97-98] All imidazole reagents employed were molten at the reaction temperature, meaning no solvent was required for this transformation (Scheme 71). Reactions were monitored by TLC and in all cases the imidazolium salt was detected on the baseline within 20 h accompanied by the complete disappearance of the imidazole starting material. Furthermore, imidazolium salts were isolated in high yields with trituration in diethylether being the only purification step required (Table 8).



72 **73**

Scheme 71 Preparation of imidazolium salts. R = methyl-, benzyl-, mesityl- and 2,6-(diisopropyl)phenyl-, X = I or Br.

Table 8 Synthesis of imidazolium salts **73a-g**.

Entry (name)	X	R	Temperature (°C)	Yield (%) [a]
1 (73a)	Br	Methyl-	80	85
2 (73b)	I	Methyl-	80	87
3 (73c)	Br	Benzyl-	80	79
4 (73d)	I	Benzyl-	80	98
5 (73e)	Br	Mesityl-	80	86
6 (73f)	Br	2,6-(Diisopropyl)phenyl-	100	76[b]
7 (73g)	I	2,6-(Diisopropyl)phenyl-	100	96

[a] All products were isolated by trituration with diethyl ether. [b] Due to the appearance of several imidazolium-based side products, the reaction was carried out in refluxing acetonitrile.

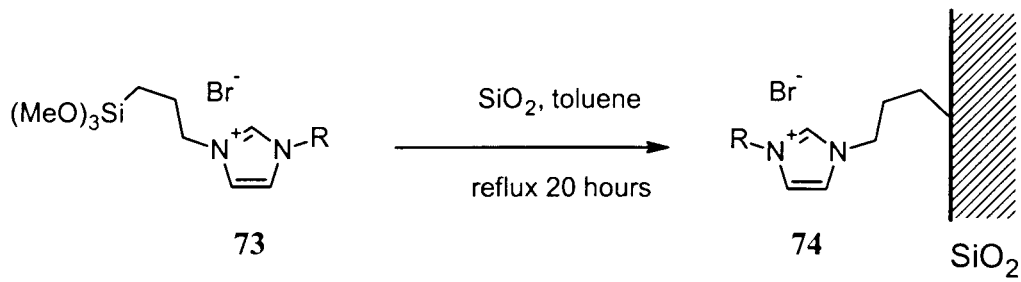
3-iodopropyltrimethoxysilane (entries 2, 4 and 7) was apparently more reactive than the bromide meaning the reaction times could be reduced to 2 h. This could be attributed to the increased leaving ability of the iodide ion.

Due to the higher melting point of **72b** the reaction was carried out at 100 °C. This furnished the expected species and several impurities, which could not be easily identified or removed. ^{1}H NMR spectrum of the product mixture showed several other peaks in around δ 9-10 ppm corresponding to N-C*H*-N protons. It was eventually established that using refluxing acetonitrile as a solvent eliminates the formation of side products (entry 6). In all examples, ^{1}H NMR analysis confirmed the presence of the imidazolium N-C*H*-N proton at δ 9-10 ppm.

With methoxysilyl alkyl imidazolium salts **73** in hand, the preparation of silica-supported *bis*-NHC palladium complexes could be attempted by two different synthetic routes.

3.3 Route 1: Immobilisation of Imidazolium Salts

Route 1 involved the immobilisation of imidazolium salts according to the literature procedure (Scheme 72).[68] The amount of imidazolium salt employed determines the catalyst loading, and in this case it was designed to be 1.0 mmol/g, which is identical to the loading of the 3-aminopropyl functionalised silica starting material (used in the making of catalyst **10**). The immobilisation procedure proved to be highly efficient (Table 9). In fact in both cases, washings of the silica supported product **74** contained no detectable amounts of imidazolium salt by ^{1}H NMR, indicating quantitative conversions throughout.



Scheme 72 Immobilisation of imidazolium salts to yield modified silica **74**.

Table 9 Yields of immobilised imidazolium salts **74a** and **b** expressed as a weight percentage.

Entry (Name)	R =	Yield (wt. %)
1 (74a)	Benzyl-	95
2 (74b)	Mesityl-	97

3.3.1 Complexation of Immobilised Imidazolium Salts

Conversion of the immobilised imidazolium salts **74a-b** to palladium-NHC complexes **75a-b** (Scheme 73) was accomplished with palladium(II) acetate, which serves a dual role. The acetate ligand acts as a base, deprotonating the imidazolium salt (acetic acid is eliminated from the complex) and the resulting NHC then coordinates directly to the metal centre.[118]

Scheme 73 Deprotonation of imidazolium salts and complexation with palladium in one synthetic step. R = benzyl (**75a**) or mestiyl (**75b**).

The analysis of catalysts **75a-b** was unfortunately complicated by the presence of residual DMSO which proved impossible to remove.

Elemental analysis of catalyst **75b** (R = mesityl) shows an excess of palladium (Table 10), suggesting the presence of other palladium species. Formation of palladium black (palladium nanoparticles) at some stage in the synthesis is a strong possibility and would explain the dark colour of the catalyst. It appears the excess palladium (used to ensure complete reaction of all imidazolium salt moieties on the catalyst precursor) could not be removed from the support material by simple washing steps alone. Also, the amount of carbon and nitrogen observed is lower than expected, which suggests an incomplete reaction between the NHC precursor and the silica support.

Table 10 Elemental analysis of catalyst **75b** (R = 2,4,6-Mesityl).

ELEMENT	C	H	N	Pd
% Theory	16.20	1.80	2.52	4.77
% Found 1	14.60	2.16	1.32	6.86
% Found 2	14.59	2.15	1.33	6.89

SEM analysis indicates the presence of surface debris in catalyst **75b**, reminiscent of the SEM images of the phosphine catalyst **10**, which are expected to be composed of palladium nanoparticles (Figure 36).

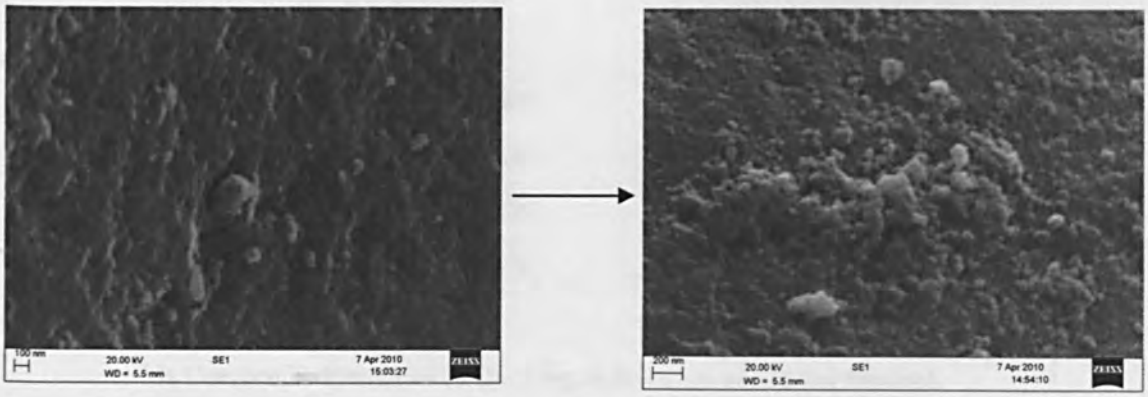
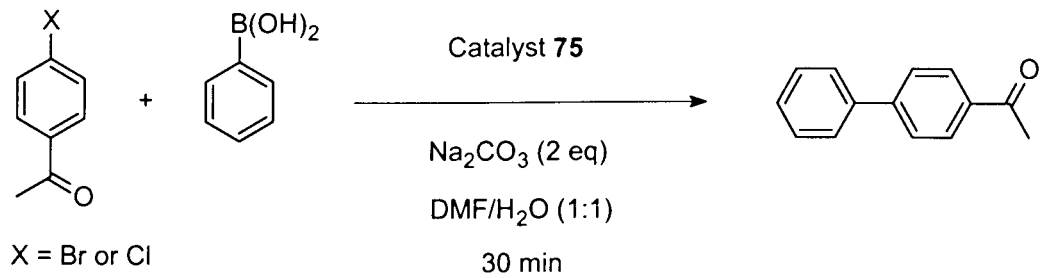


Figure 36 SEM images of supported imidazolium salt **74b** (left) and supported NHC catalyst **75b** (right)

Despite the limited characterisation of catalysts **75a** and **b**, they provide a basis for comparison with the other silica supported NHC catalysts presented in this study. They are expected to be active in Suzuki coupling reactions as they are structurally comparable to several heterogeneous catalysts reported in the literature.[119-120]

3.3.2 Preliminary Screening of NHC Catalysts - Suzuki Coupling

Catalysts **75a** and **b** (prepared using the *N*-benzyl and *N*-mesityl substituted imidazolium salts respectively) were tested for activity in a standard Suzuki reaction. (Scheme 74, Table 11).



Scheme 74 Standard Suzuki reaction conditions[110]

Table 11 Screening for activity in Suzuki reaction of 4-haloacetophenones and phenylboronic acid.

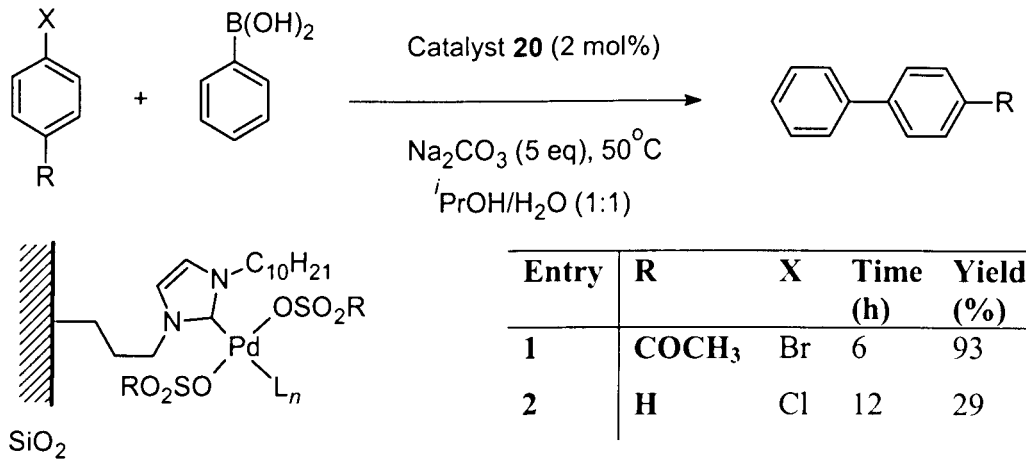
Entry	Catalyst (loading)	X	Temperature (°C)	Conversion (%)[a]
1	**75a** (0.2 mol%)	Br	80	79
2	**75b** (0.2 mol%)	Br	80	84
3	**75a** (2 mol%)	Cl	100	4[b]
4	**75b** (2 mol%)	Cl	100	7[b]

[a] % Conversion determined by GC using dodecane as an internal standard.
[b] Reaction time increased to 60 minutes.

The most significant aspect of these results is the fact that the mesityl-NHC catalyst **75b** was more active than the benzyl-NHC catalyst **75a**. This suggests that increased steric bulk around the metal centre does indeed have a positive effect on catalytic activity, in agreement with the observation by Organ *et al.* (amongst others) in steric investigations of homogeneous NHC-palladium complexes.[19]

The level of catalytic activity observed is more than satisfactory. The fact that a low catalyst loading of 0.2 mol% can achieve good conversions of aryl bromide

substrates is comparable with numerous silica-supported NHC-Palladium catalysts. In fact, the silica-supported alkyl NHC catalyst reported by Sen *et al.* (Scheme 75) required 10x the catalyst loading and a reaction time of 6 h to achieve comparable conversions of bromide substrates.[68]



Entry	R	X	Time (h)	Yield (%)
1	$COCH_3$	Br	6	93
2	H	Cl	12	29

Scheme 75 Suzuki coupling of aryl halides reported by Sen *et al.*[68]

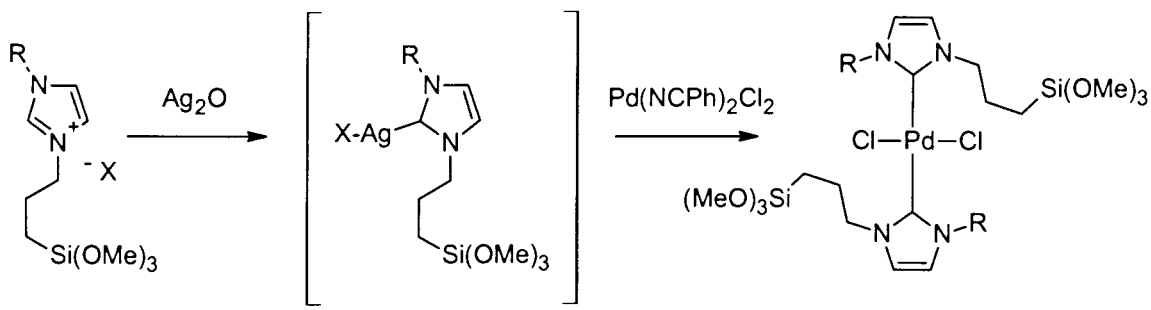
The same authors quoted a yield of 29% for the reaction between chlorobenzene and phenylboronic acid. However, no attempt was made to differentiate the biphenyl product from the boronic acid homocoupling side reaction which was frequently observed during reactions employing aryl chlorides in the present study.

Rather than exhaustive testing using catalysts **74**, the alternative synthesis (involving preparation of the entire *bis*-NHC palladium complex prior to immobilisation) was explored in order to establish the preferred synthetic route.

3.4 Route 2: Synthesis of *Bis*-NHC Palladium Complexes

Silver-NHC complexes represent convenient precursors to palladium NHCs. Originally reported by Lin *et al.*, NHC complexes of silver may be prepared from imidazolium salts and silver(I) oxide and employed as carbene transfer reagents.[121]

Route 2 consists of the preparation of *bis*-NHC-palladium complexes **76** and subsequent tethering to silica. In this method, silver(I) oxide is used to deprotonate the imidazolium salt, forming the silver-NHC complex (not isolated) (Scheme 76).



73 **76**

Scheme 76 Synthesis of *bis*-NHC complexes via a silver carbene intermediate.

The silver complex then undergoes ligand exchange with the palladium source. The yields obtained varied depending on the imidazolium salt used and are summarised in Table 12.

Table 12 Yields of *bis*-NHC palladium complexes **76**.

Entry (Name)	Imidazolium Salt (R =)	X	Yield (%) [a]
1 (76a)	Benzyl-	Br	56
2 (76b)	Mesityl	Br	50
4 (76c)	2,6-(Diisopropyl)phenyl-	Br	47
5 (76d)	2,6-(Diisopropyl)phenyl-	I	35 [b]

[a] Obtained by trituration in hexane and/or diethylether. [b] The complex mixture of products was unidentifiable using NMR and mass spectrometry and later showed lower activity in Suzuki coupling reactions.

The key advantages of this method are that the *bis*-NHC palladium complexes **76a-c** were isolated and analysed by conventional means. Furthermore, the process is carried out at ambient temperature and the silver salt by-products may be removed by filtration. In each case the product was isolated by trituration in cold diethyl ether.

Unfortunately the imidazolium iodide salts **73b, d** and **g** were found to be unsuitable for this process. It is likely that the intermediate silver carbene complex(es) formed from imidazolium iodides adopt a different structure to the one shown in Scheme 76. Possibilities include the structures illustrated in Figure 37.[122]

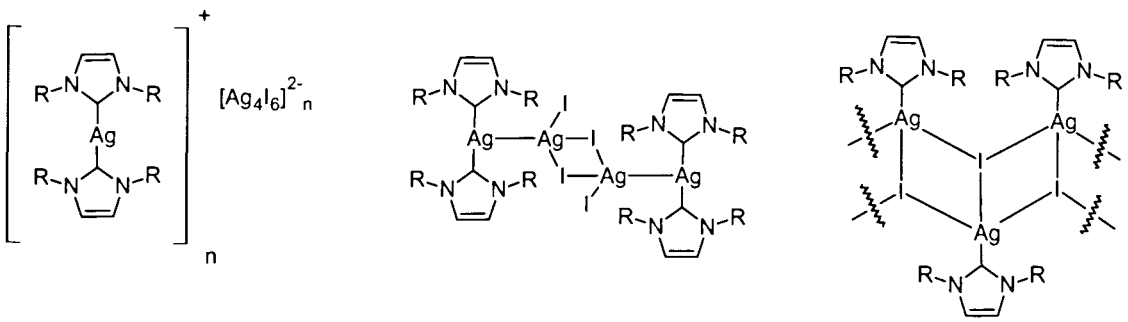


Figure 37 Silver-NHC complexes prepared from imidazolium iodide precursors.[122]

All catalysts prepared from imidazolium iodides have significantly different and more complicated NMR spectra and have proven to be less active in Suzuki coupling reactions, meaning that the bromide salt is necessary to generate the expected *bis*-carbene palladium complex **76**. These complexes are soluble in polar organic solvents and were characterised using mass spectrometry and ^{1}H / ^{13}C NMR.

3.4.1 Mass Spectrometric Analysis of *Bis*-NHC Palladium Complexes 76a-c

In each case, chemical ionisation methods allowed the molecular ion of the *bis*-NHC palladium complex **76** to be measured (Figure 38 and Table 13).

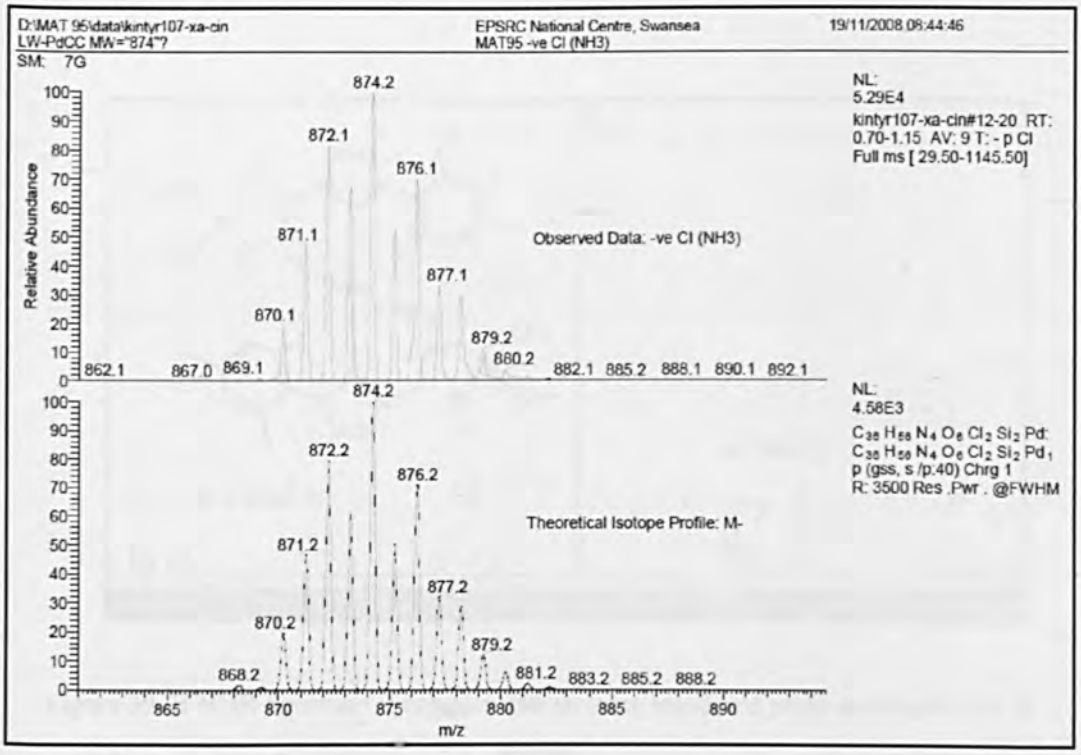


Figure 38 Low-resolution mass spectrum of *bis*-[1-mesityl-3-(trimethoxysilyl)propyl-imidazolylidine]palladium dichloride **76b** showing theoretical and observed isotope profiles.

Table 13 High-resolution mass spectrometry of *bis*-NHC complexes **76a-c**.

Entry (Name)	Molecular Formula	R	RMM (theory)	RMM (observed)
1 (76a)	$C_{32}H_{48}O_6N_4Si_2Cl_2Pd$	benzyl-	814.1535	814.1537
2 (76b)	$C_{36}H_{56}O_6N_4Si_2Cl_2Pd$	mesityl-	870.2161	870.2161
3 (76c)	$C_{42}H_{68}O_6N_4Si_2Cl_2Pd$	diisopropylphenyl-	954.3089	954.3090

The observation of near-perfect theoretical isotope profiles and highly accurate molecular ion peaks provides unequivocal evidence for the presence of the *bis*-NHC palladium complexes, as opposed to the *mono*-NHC or dimeric species.

3.4.2 NMR Analysis of *Bis*-NHC Palladium Complexes 76a-c

NMR spectra of *bis*-NHC palladium complexes are generally complicated and often difficult to interpret. Numerous signals of the *bis*-NHC complex **76b** are duplicated in both ^{1}H and ^{13}C NMR (Figures 39 and 40).

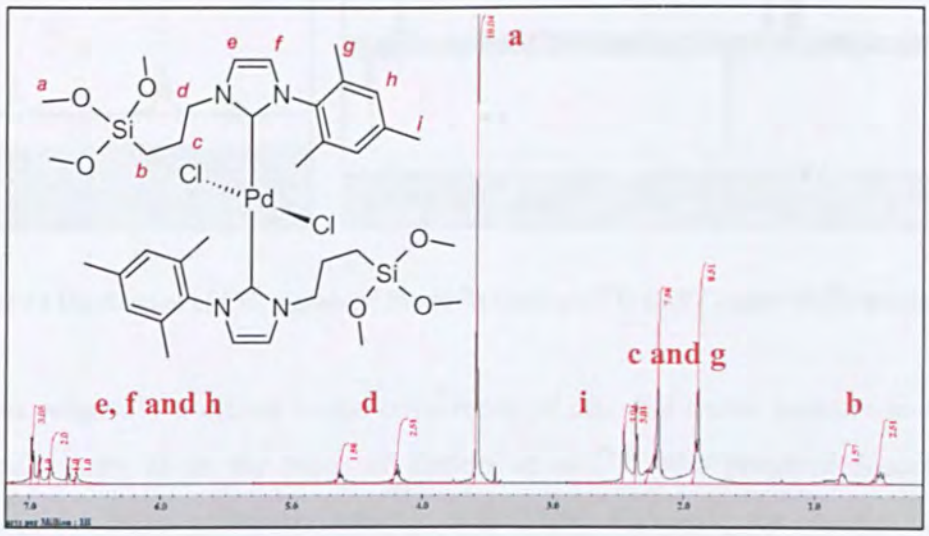


Figure 39 ^{1}H NMR Spectrum of complex **76b** showing broadened peaks and duplication of signals.

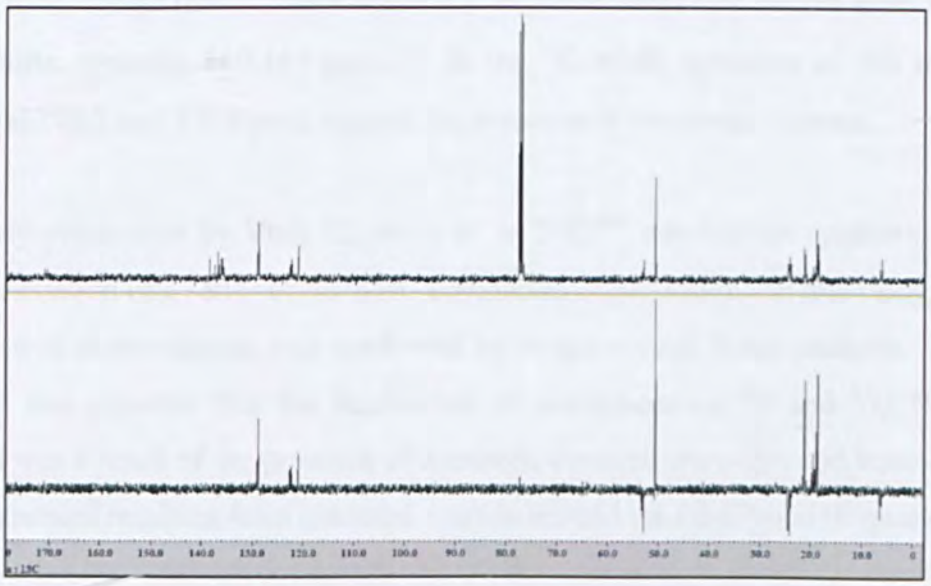


Figure 40 ^{13}C spectrum (top) and ^{13}C DEPT (bottom) of complex **76b**.

These spectra suggest the presence of two closely-related species, which is particularly evident from the NMR signals of the propyl chain in the ^{1}H and ^{13}C DEPT NMR (Figure 41).

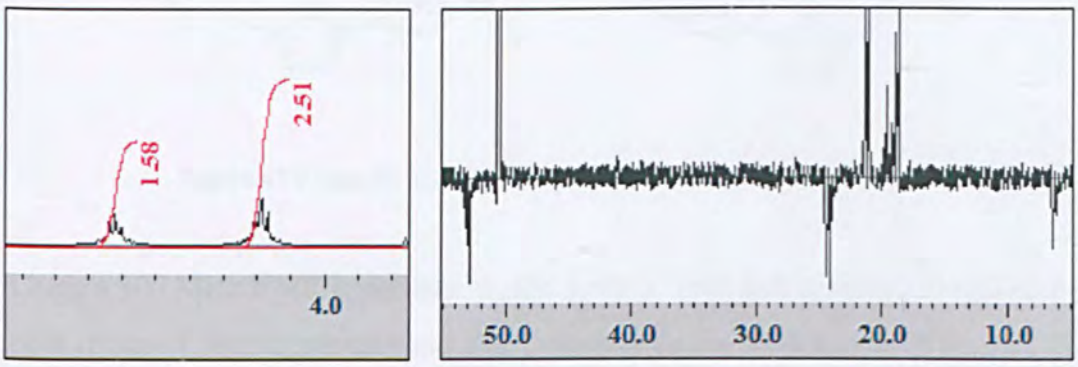


Figure 41 Duplication of CH_2 signals of **76b** in ^{1}H (left) and ^{13}C DEPT (right) NMR spectra.

This was originally ascribed to the occurrence of *cis*- and *trans*- isomers around the metal centre as in the work of Enders *et al.*,[114b] who prepared *N*-methyl substituted *bis*-NHC palladium complexes in 2006. However, the occurrence of *cis*- isomers seemed unlikely considering the steric bulk of NHC complex **76b**.

In fact, *cis*- and *trans-bis*-NHC palladium complexes can be distinguished by the ^{13}C resonances for the carbene carbon. *Trans*- carbene complexes usually have δ values in the range 168-172 ppm whilst *cis*- carbene complexes exhibit more high field shifts, typically 160-165 ppm.[123] In the ^{13}C NMR spectrum of **76b** the δ values at 170.5 and 170.9 ppm suggest the presence of two *trans*- isomers.

A timely publication by Vinh Huynh *et al.* in 2009[124] detailed the synthesis and characterisation of a series of *bis*-NHC complexes of palladium. In this study, the presence of *trans*-isomers was confirmed by single crystal X-ray analysis. The authors also reported that the duplication of resonances on ^{1}H and ^{13}C NMR spectra was a result of the presence of rotameric isomers, *trans-syn* and *trans-anti* configurations resulting from hindered rotation around the Pd-C bond (Figure 42).

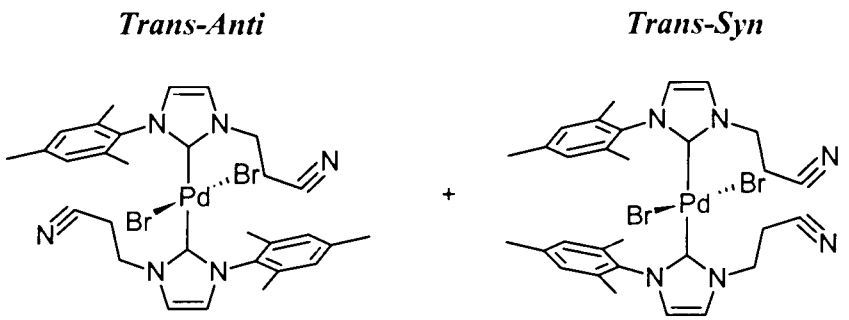


Figure 42 Rotamers of complexes prepared by Vinh Huynh *et al.*[124]

Using a 500 MHz NMR spectrometer, the authors were able to assign the peaks of both rotamers unambiguously and also demonstrate the coalescence of the signals when the temperature of the NMR study was increased.

The protons of the propyl chain in these complexes experience some degree of shielding from the bulky aromatic group in the *trans-anti* rotamer, as a result their signals appear slightly upfield with respect to the *trans-syn* rotamer. Vin Huynh reports a ratio of 1: 2 for the complexes shown in Figure 41. Based on the integration of the remarkably well separated $-CH_2$ ^1H NMR signals, complex **76b** exists in a ratio of roughly 1: 1.67 *trans-syn*: *trans-anti* in solution at room temperature.

3.4.2.1 HETCOR NMR Experiments

The palladium complex **76b** was subjected to HETCOR experiments in hope of unambiguously assigning the ^{1}H and ^{13}C spectra (Figure 43).

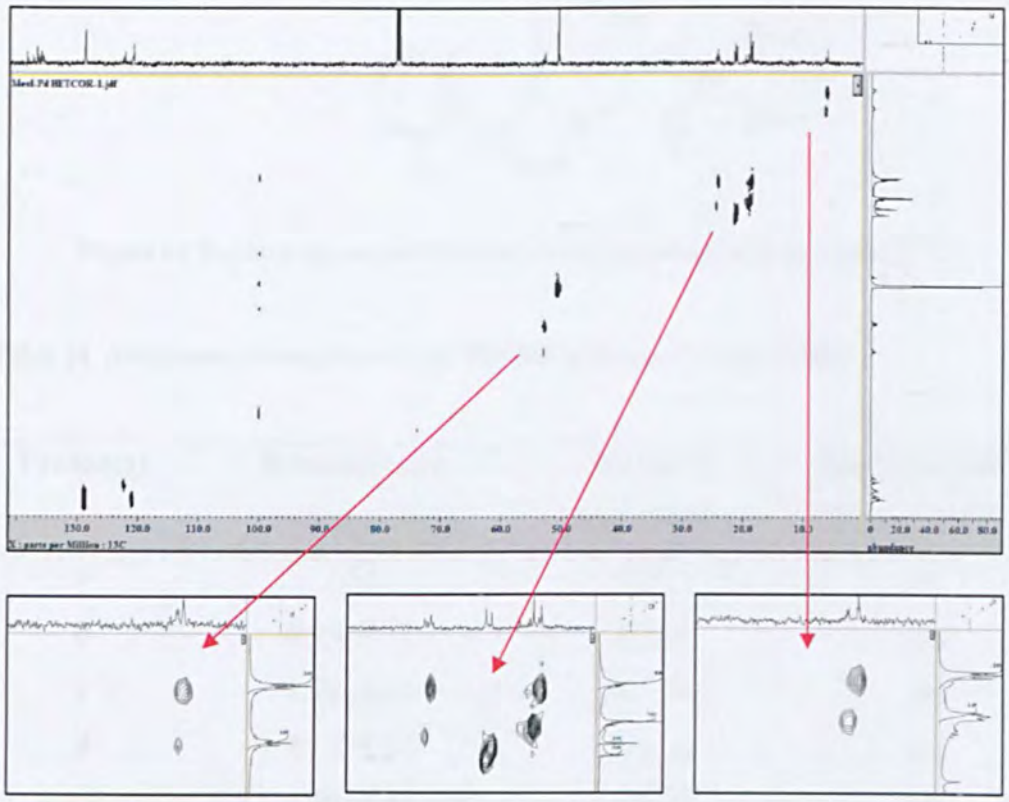


Figure 43 HETCOR NMR spectrum of complex **76b** showing C-H connectivity. Cross-peaks for the alkyl CH_2 groups have been expanded.

The heteronuclear correlation experiment reveals the alkyl CH_2 groups which are obscured in the ^{1}H spectrum by the *ortho*-methyl groups of the mesityl substituents (Figure 43, central expansion). The following assignments can now be attributed to the ^{1}H (Figure 44, Table 14) and ^{13}C NMR data (Figure 45, Table 15).

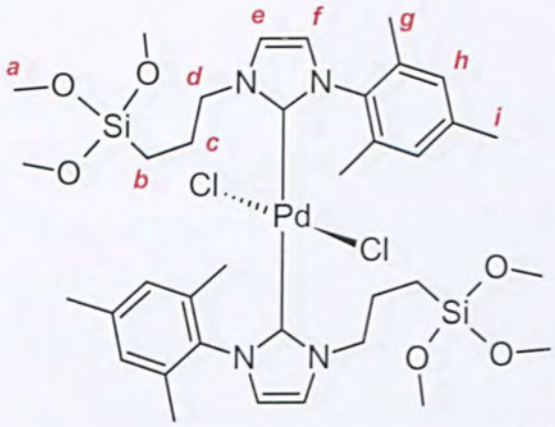


Figure 44 The main proton environments present in palladium NHC complex **76b**.

Table 14 Assignment of resonances in the ^{1}H NMR spectrum of complex **76b**.

Proton(s)	Resonance(s) (δ, ppm)	Integral, Multiplicity	Duplicate Peaks Observable? [a]
a	3.58	18H, s	no
b	0.49, 0.78	4H, m	yes
c	1.90, 2.21	4H, m	yes
d	4.18, 4.62	4H, m	yes
e and *f*	6.64, 6.70, 6.92, 6.97	4H, m	no
g	1.87, 2.19	12H, s	no
h	6.84, 6.98	4H, s	yes
i	2.36, 2.46	6H, s	no

[a] In cases where duplicate peaks are not observable, peaks are broad and unresolved.

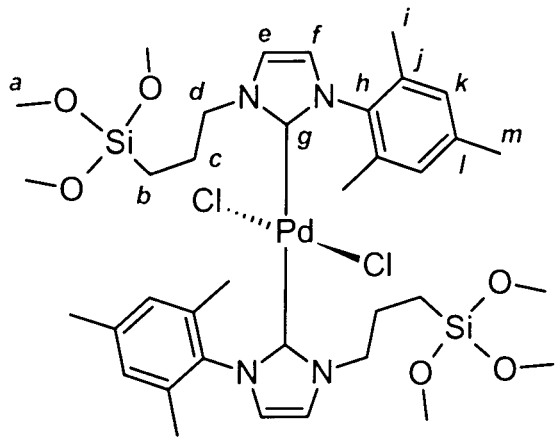


Figure 45 Carbon environments present in palladium NHC complex **76b**.

Table 15 Assignment of resonances in the ^{13}C NMR spectrum of complex **76b**

Carbon(s)	Resonance(s) (δ, ppm)	Duplicate Peaks Observable? [a]
a	50.7	no
b	6.07, 6.13, 6.39, 6.44	yes
c	24.0, 24.1, 24.3, 24.45	yes
d	52.87, 53.03, 53.1, 53.28	yes
e and ***f***	120.75, 120.85, 120.9, 121.0, 122.25, 122.4, 122.55, 122.65	yes
g	170.5, 170.9	yes
h, j and ***l***	135.6, 135.7, 136.0, 136.2, 136.5, 136.8, 136.9, 137.4, 137.5, 138.4	yes
i	18.55, 18.7, 18.88, 18.95, 19.0, 19.13, 19.23, 19.65	yes
k	128.88, 128.83, 128.79, 128.75	yes

. [a] In cases where duplicate peaks are not observable, peaks are unresolved.

3.4.2.2 NOESY NMR

NOESY NMR analysis of complex **76b** confirmed the presence of two chemically distinct species (Figure 46). The cross-peaks relating to the N-CH_2 protons, for example, show no enhancement with the equivalent protons in the other isomer, suggesting these protons are not spatially close to each other.

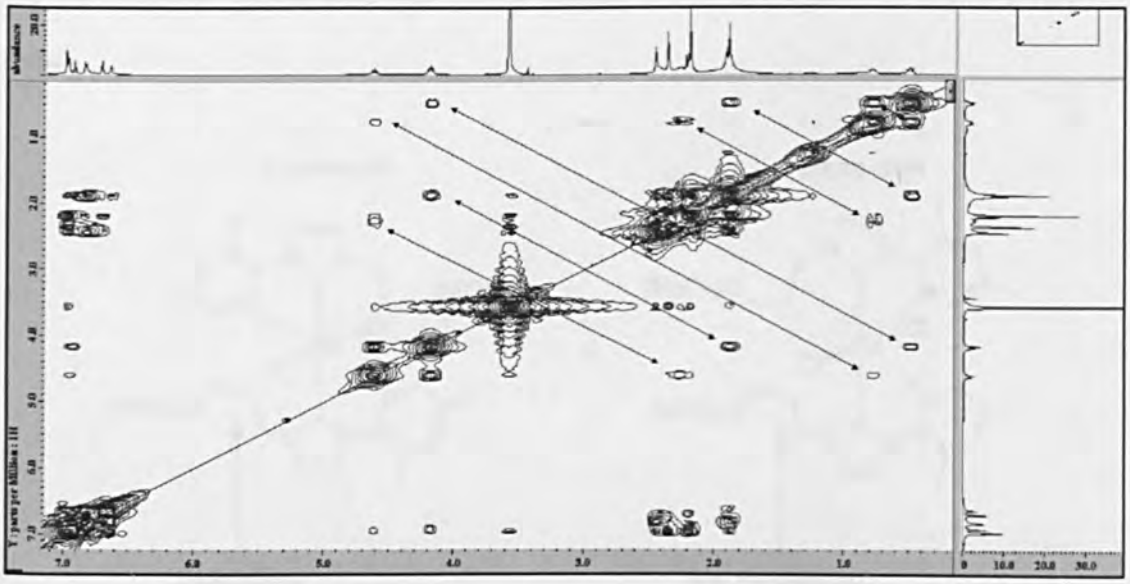


Figure 46 NOESY NMR spectrum of complex **76b**. Cross-peaks (indicated by double-headed arrows) show protons in spatial proximity to eachother.

The lack of cross-peaks between the alkyl CH_2 protons and the aromatic mesityl protons in either isomer does not really support the idea of rotamers. However, it is entirely likely that the distance between the alkyl and aromatic protons in the *trans-anti* isomer is simply too large to observe NOE effects.

It may be tentatively concluded from the above NMR data that complex **76b** exists as a mixture of rotameric isomers (Figure 47) as in the work of Vinh Huynh *et al.*[124] The most compelling evidence of this is the duplication and wide separation of peaks for the methylene protons, which is expected to be the result of a shielding effect by the aromatic mesityl group in the *trans-anti* isomer. It stands to reason that rotation around the palladium-carbon bond may be hindered by the chloride ligands although further studies would be required to confirm this idea.

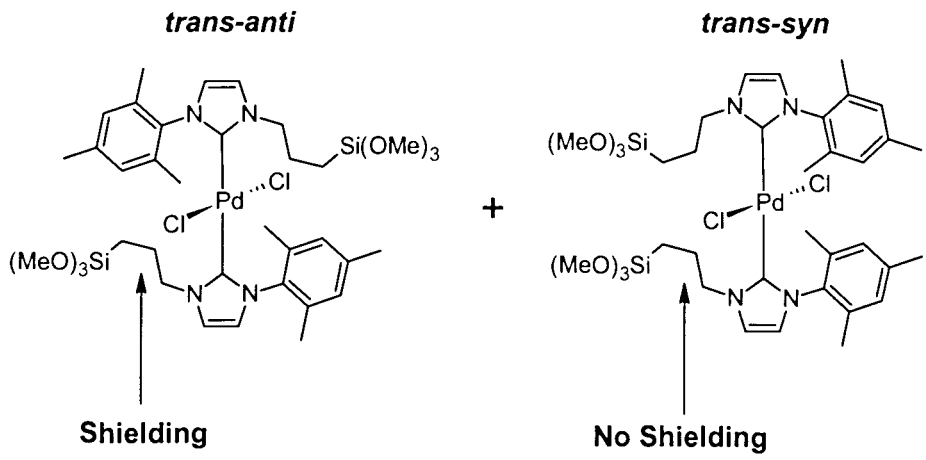


Figure 47 Proposed configuration of *bis*-NHC palladium complex **76b**.

3.4.3 Elemental Analysis of *Bis*-NHC Complex 76b

Elemental analysis of complex **76b** reveals that although the elemental ratios are quite close to theoretical values, the compound cannot be considered absolutely pure (Table 16).

Table 16 Elemental analysis of complex **76b**.

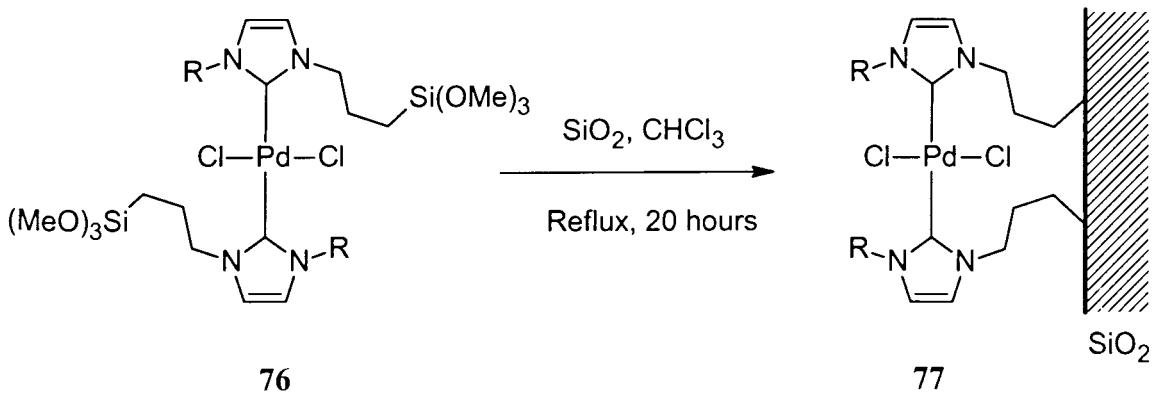
ELEMENT	C	H	N	Pd
% Theory	49.45	6.46	6.40	12.17
% Found 1	47.75	6.19	7.02	11.51
% Found 2	47.83	6.41	6.93	11.67

The presence of impurities is not surprising considering purification was limited to trituration in diethyl ether. Column chromatography using oxide supports such as silica is not possible (the complex becomes immobilised onto to the stationary phase even at room temperature). And despite numerous attempts, recrystallisation of complexes **76a-c** only resulted in the precipitation of the product (with little or no improvement in chemical purity).

Although the elemental analyses of complex **76b** may appear unconvincing, when combined with the NMR and mass spectral data, these species are remarkably well-characterised. Especially when compared with the *bis*-phosphine catalyst **10**[32] and numerous other similar heterogeneous precatalysts in the scientific literature.

3.4.4 Immobilisation of *Bis*-NHC Palladium Complexes

Tethering of the palladium complexes **76a-c** to silica to form the supported palladium complexes **77a-c** was accomplished by refluxing in chloroform overnight (Scheme 77). One striking feature of this reaction is that no trace of the bright yellow coloured palladium complex remained in the reaction mixture after filtration. The product, in the form of a pale yellow powder was simply filtered off and washed with chloroform and dichloromethane. No trace of the complex was detected in the NMR spectrum of the washings, again indicating a highly efficient immobilisation process.



Scheme 77 Immobilisation of complexes **76a-c** to give catalysts **77a-c**.

Table 17 Yields of immobilised *bis*-NHC palladium complexes (**77a-c**).

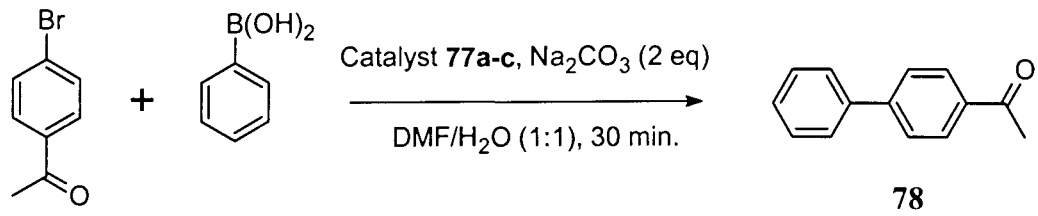
Entry (Name)	R =	Yield (wt. %) [a]
1 (77a)	Benzyl-	94
2 (77b)	Mesityl-	95
3 (77c)	2,6-(Diisopropyl)phenyl-	95

[a]Yields expressed as a percentage of the theoretical mass.

3.5 Catalytic Testing of *Bis*-NHC Complexes 77

3.5.1 Suzuki Reactions

Complexes **77a-c** were tested for activity in Suzuki cross coupling reactions. Using one of the many available literature methods,[110] the catalysts showed promising activity in the Suzuki coupling of 4-bromoacetophenone with phenylboronic acid (Scheme 78, Table 18), even when used in low loadings.



Scheme 78 Suzuki coupling of 4-bromoacetophenone with phenylboronic acid.

This reaction was used as a benchmark to compare catalysts **77a-c** and to optimise the required catalyst loading (Table 18).

Table 18 Optimisation of Suzuki coupling reactions.

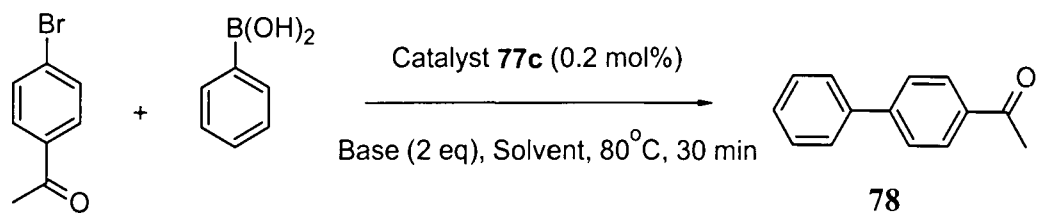
Entry	Catalyst	R =	Loading (mol%)	Temperature (°C)	Conversion (%)[a]
1	**77a**	benzyl	1	80	>99
2	**77b**	mesityl	1	80	>99
3	**77c**	dipp	1	80	>99
4	**77a**	benzyl	0.2	80	81
5	**77b**	mesityl	0.2	80	90
6	**77c**	dipp	0.2	80	>99
7	**77c**	dipp	0.2	60	28
8	**77c**	dipp	0.1	80	80
9	**77c**	dipp	1	RT	trace
10	**77c**	dipp	0.2	RT	12[b]

[a] % Conversion based on the halide substrate, determined by GC using dodecane as an internal standard. [b] Reaction time extended to 24 h. Dipp = 2,6-(diisopropyl)phenyl.

Results show that a loading of 1 mol% catalyst is more than enough to facilitate quantitative conversions (entries 1-4), however when the loading is reduced to 0.2 mol% a slight difference in activity between the catalysts becomes apparent (entries 5-8). As expected, catalysts containing bulkier NHC ligands **77b** and **77c** show superior activity in Suzuki coupling reactions. This phenomenon is well established in homogeneous catalysis,[19] but to the best of our knowledge has not been investigated to this extent in heterogeneous catalysis employing NHC ligands.

One possible reason for the increased catalytic activity of the sterically bulkier catalysts may reside in the idea that the presence of bulky groups facilitates the departure of the chloride ligands to form the proposed active palladium(0) species.

In an attempt to further optimise the reaction conditions, a modest range of bases and solvents were employed (Scheme 79, Table 19).



Scheme 79 Attempted optimisation of Suzuki reaction conditions.

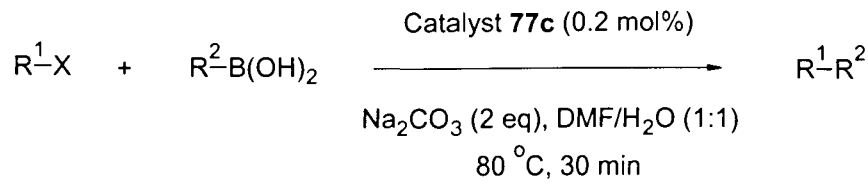
Table 19 Optimisation of base and solvent for Suzuki coupling reactions.

Entry	Base	Solvent	Conversion (%)[a]
1	DMF/H_2O (1:1)	Na_2CO_3	98
2	DMF/H_2O (1:1)	Cs_2CO_3	85
3	Acetonitrile	Na_2CO_3	74
4	Morpholine	Morpholine	trace
5	DMF	Na_2CO_3	54
6	DMF/H_2O (10:1)	Na_2CO_3	89

[a] % Conversion based on the halide substrate, determined by GC using dodecane as an internal standard.

Modifying the base and solvent conditions had no beneficial effect on conversion rate. Having established the optimum reaction conditions, the catalysts were

tested on a range of aryl halide and boronic acid substrates in order to assess the functional group tolerance and activity towards electronically deactivated and sterically hindered substrates (Scheme 80, Table 20).



Scheme 80 Testing of catalyst **77c** on a range of substrates.

Table 20 Results of Suzuki coupling reactions.

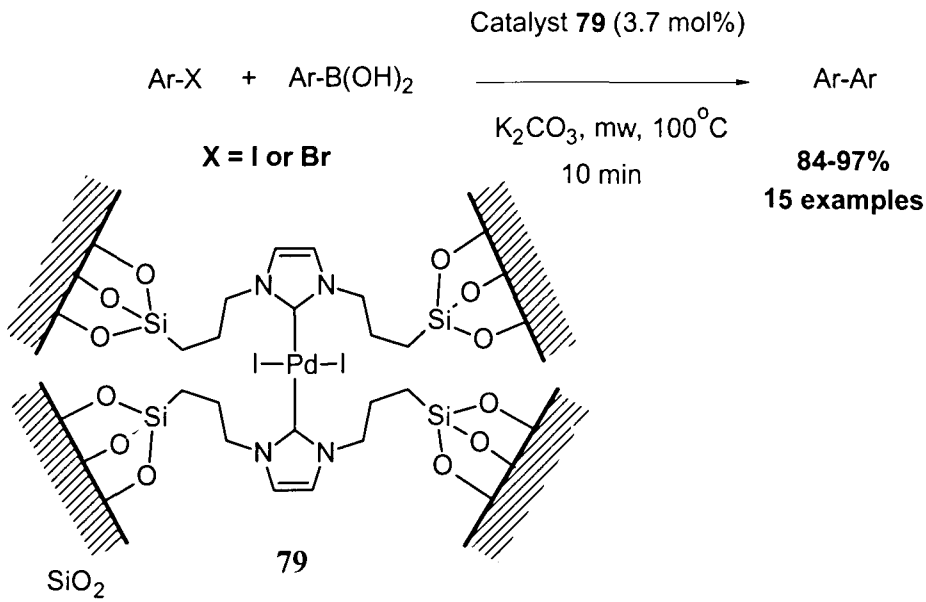
Entry	R^1	X	R^2	Conversion (%)[a]
1	C_6H_5	I	C_6H_5	>99 (89)
2	2-(Me)C_6H_5	I	C_6H_5	67
3	3-C_5H_4N	I	C_6H_5	48
4	C_6H_5	Br	C_6H_5	>99
5	4-(MeCO)C_6H_4	Br	C_6H_5	98 (90)
6	C_6H_5	Br	3-C_5H_4N	<1
7	C_6H_5	Br	4-C_5H_4N	<1
8	4-(O_2N)C_6H_5	Br	C_6H_5	69
9	4-(MeO)C_6H_4	Br	C_6H_5	35 (29)
10	4-(MeCO)C_6H_5	Br	2-C_4H_3S	<1
11	C_6H_5	Cl	C_6H_5	52[b]
12	C_6H_5	Cl	$C_{10}H_7$	40[b]
13	4-(MeCO)C_6H_4	Cl	C_6H_5	30[b]
14	4-(O_2N)C_6H_5	Cl	C_6H_5	13[b]
15	4-(MeO)C_6H_4	Cl	C_6H_5	4[b]

[a] % Conversion of the aryl halide was established by GC-MS using dodecane as an internal standard. Numbers in parentheses represent % yield isolated by column chromatography. [b] Temperature increased to 100 °C, catalyst loading increased to 1 mol %, reaction time increased to 60 min.

Several interesting conclusions may be drawn from these results. It is apparent that sterically hindered substrates such as 2-iodotoluene (entry 2) experience lower conversion rates. Heterocyclic halides (entry 3), although tolerated, suffer lower conversion rates and heterocyclic boronic acids were not tolerated in these studies (entries 6, 7 and 10), which was completely unanticipated.

Finally, and most impressively, aryl chloride substrates furnished modest amounts of cross-coupled product in this study (entries 11-15). Only a handful of silica-supported NHC palladium catalysts in the scientific literature are capable of turning over these deactivated substrates.[68] However, conversion rates were low and could not be improved upon with increased time or temperature. In fact, Suzuki coupling of aryl chlorides always resulted in decomposition of the catalyst accompanied by the appearance of palladium black in the reaction mixture.

For comparison, let us consider silica-supported *N*-alkyl NHC complex **79** prepared by Polshettiwar *et al.* in 2008.[115] This catalyst showed excellent activity toward aryl iodide and bromide substrates using 3.7 mol% catalyst under microwave irradiation (Scheme 81).



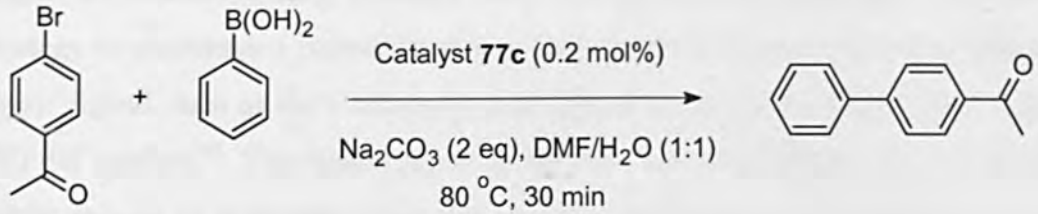
Scheme 81 Testing of *N*-alkyl NHC palladium complex on silica by Polshettiwar *et al.*[115]

Although Polshettiwar reported excellent conversion rates, there was no evidence of aryl chlorides being employed in Suzuki reactions. Perhaps the lack of steric bulk around the NHC nucleus was a major factor in determining the activity of catalyst **79**? Overall, the yields obtained by Polshettiwar *et al.* for Suzuki coupling of aryl bromides and iodides were superior to those presented in Table 20, however it is entirely likely that the increased catalyst loading and microwave irradiation contributed to the higher conversions observed.

Catalyst **77c** compares very well with most silica-supported NHC-palladium catalysts in the literature, outperforming the systems reported by Sen *et al.*,[68] Jin *et al.* [69] and Polshettiwar *et al.*[115] in Suzuki coupling reactions. However, several heterogeneous NHC catalysts display superior activity to catalyst **77c**. These include the poly(norbornene)-supported *N*-mesityl NHC complex reported by Weck *et al.*[66] and the poly(imidazolylidine)-supported *N*-mesityl NHC complex prepared by Ying *et al.*[67] (both were detailed in the literature review in the introduction section). These support materials, however are much more challenging, time-consuming and expensive to prepare than the commercially available silica gel used in this study.

3.5.2 Recycling Studies

The recyclability of catalyst **77c** in Suzuki coupling reactions (Scheme 82) was limited to four consecutive cycles and, as with the phosphine catalyst **10** a steady decrease in activity was observed (Figure 48).



Scheme 82 Recycling studies using catalyst **77c**.

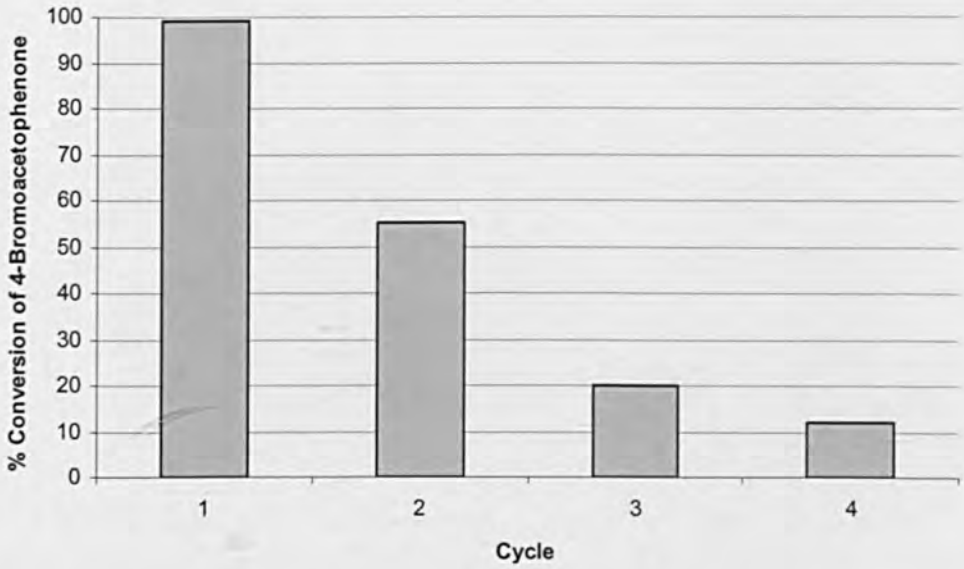


Figure 48 Recyclability of catalyst **77c** in the Suzuki coupling of 4-bromoacetophenone and phenylboronic acid.

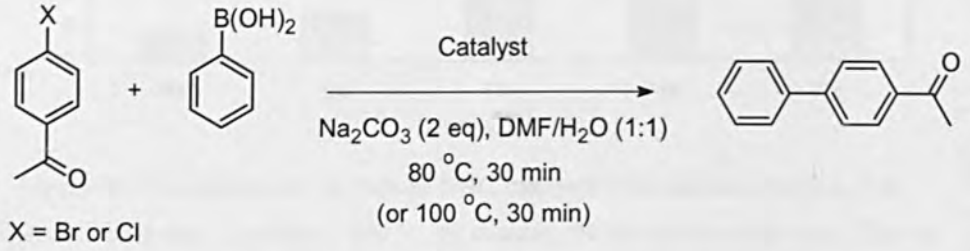
There are examples of heterogeneous catalysts in the literature that exhibit twice this level of recyclability, such as the poly(imidazolylidene)-supported NHC reported by Ying *et al.*[67]

One possibility for the comparatively low recyclability observed in this study is the lack of a suitable resting state. In a typical Suzuki coupling reaction, the active catalytic species is expected to be the palladium(0) complex, which is susceptible to oxidation upon exposure to air. Upon completion of the reaction

cycle, it is entirely likely that a large portion of the catalyst becomes oxidised and is therefore inactive for the subsequent cycles. One method of avoiding this deactivation may be to take extreme precautions against exposure to air between reactions, which has undoubtedly been adopted by numerous research groups in the literature. However, in terms of commercial applications, the necessity of an argon atmosphere during filtration may be considered infeasible. Another strategy to encourage a reversible resting state might involve the use of a 'throw away' ligand, such as the 3-chloropyridine ligand employed by Organ *et al.* with PEPPSI catalyst.[63] This ligand serves to stabilise the palladium(0) species, yet is labile enough to dissociate under the reaction conditions. The inclusion of a throw away ligand may be an attractive strategy for future investigations.

3.5.3 The Effect of Steric Bulk on Catalytic Activity

Having prepared *bis*-NHC palladium complexes by two different routes, it is possible to compare their catalytic activity directly. All NHC catalysts; **75a** and **b** (made by route 1) and **77a-c** (route 2), at equivalent palladium loading were submitted to two standard Suzuki reactions (Scheme 83, Figures 49 and 50).



Scheme 83 Head-to-head comparison of the catalystic activity of NHC catalysts **75** and **77**.

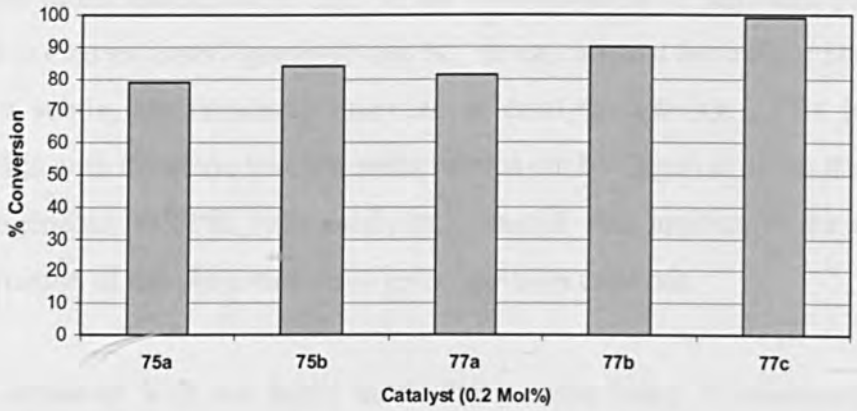


Figure 49 Performance of the various NHC catalysts in the Suzuki coupling of 4-bromoacetophenone. Conditions: 80 °C, 30 minutes. % Conversion of the aryl bromide determined by GC analysis.

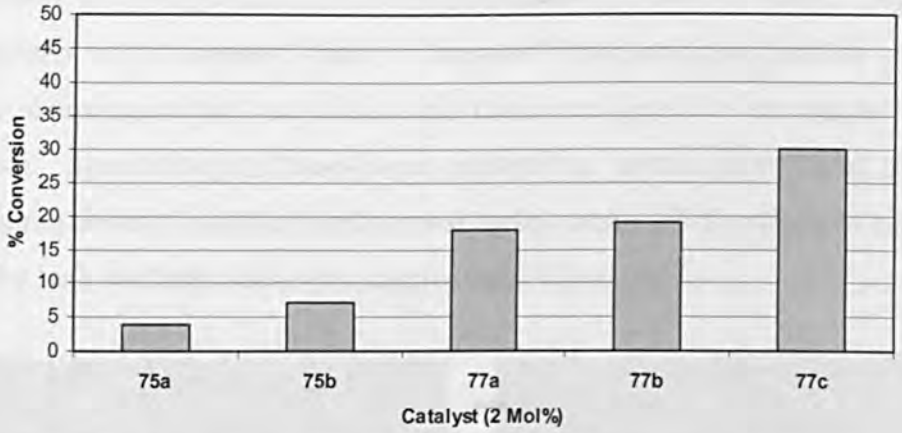


Figure 50 Performance of the various NHC catalysts in the Suzuki coupling of 4-chloroacetophenone. Conditions: 100 °C, 60 minutes. % Conversion of the aryl chloride determined by GC analysis.

The effect of increasing steric bulk on the *N*-substituents on the NHC palladium complex is evident from Figures 49 and 50. It appears that the bulkier complexes exhibit a subtle, yet noticeable increase in catalytic activity. This is highly comparable with the steric investigations carried out by Organ *et al.* on their range of homogeneous PEPPSI type catalysts,[19] though this appears to be the first documentation of the phenomenon in heterogeneous catalysis.

This is consistent with our initial thesis that a more bulky *N*-substituent would result in a more active immobilized catalyst for Suzuki coupling, as is seen in homogenously catalysed cross-coupling reactions. Early work by Nolan *et al.*[125] demonstrated that *N*-mesityl and *N*-diisopropyl(phenyl) substituted imidazolylidenes were more active (53-99% conversion) than *N*-alkyl substituted imidazolylidenes (14-16% conversion) for the palladium catalysed Suzuki cross-coupling of aryl chlorides with arylboronic acids. This work also indicated that, the diisopropyl(phenyl) substituted imidazolylidene ligand gave a slightly higher conversion (95%) than the *N*-mesityl substituted imidazolylidene (90%) when using $Pd_2(dba)_3$ as a palladium source. Similar behaviour has been seen for other palladium catalysed cross-coupling reactions such as Negishi Coupling Buchwald-Hartwig coupling and the arylation of ketones.[126-131]

A slight difference in reactivity was observed between the catalysts which were complexed with palladium prior to immobilisation (**77a-c**) and those assembled sequentially on the support (**75a-b**). Catalysts **77a-c** performed slightly better in Suzuki coupling of aryl bromides, this could be related to the purity of the catalysts. Since catalysts **75a-b** were expected to contain particles of metallic palladium (evident from their dark-brown appearance), SEM analysis of catalysts made by both synthetic routes was carried out (Figure 51).

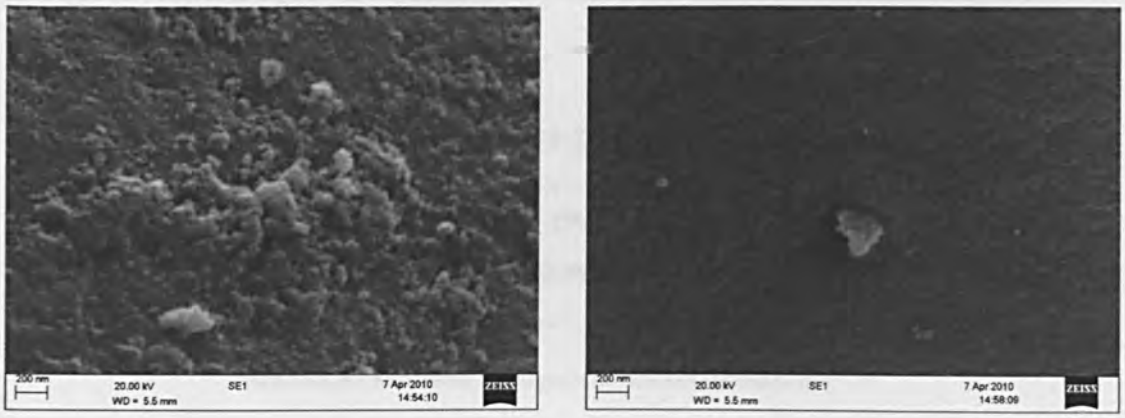
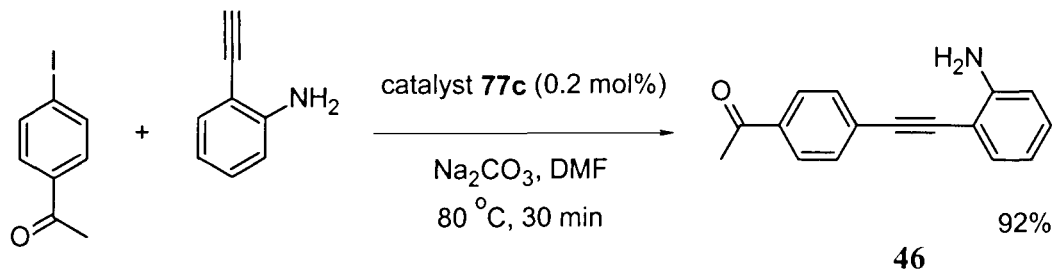


Figure 51 SEM images of catalysts prepared by stepwise immobilisation (**75b** - left) and by formation of the *bis*-NHC complex prior to immobilisation (**77b** - right).

Considering both synthetic routes were expected to produce the same catalyst, a stark difference becomes apparent at x80,000 magnification. The morphology of catalyst **75b** indicates the presence of metallic particles, similar to the *bis*-phosphine catalyst **10**, whereas catalyst **77b** appears much more uniform. Although some debris is present on the surface of catalyst **77b**, there is now no doubt as to which of the synthetic routes is preferable.

3.5.4 Sonogashira Reaction

When catalyst **77c** was screened for activity in Sonogashira reactions under the same conditions used with the *bis*-phosphine catalyst **10**, no reaction occurred. This was unexpected. It was presumed that catalyst **77c** was not being reduced to its active palladium(0) state under these conditions. Since the catalyst was known to be active under the conditions used in Suzuki coupling reactions, sodium carbonate was employed with excellent results (Scheme 84).



Scheme 84 Modified Sonogashira reaction conditions.

This result suggests that catalyst **77c** is considerably more active than *bis*-phosphine catalyst **10** (which required 10x the loading to achieve a similar conversion rate). Unfortunately catalyst **77c** showed negligible activity in Sonogashira couplings of aryl bromides and chlorides, which indicates that its scope of application is similar to that of catalyst **10**.

Aside from the extremely low catalyst loading required and the copper-free protocol, the reaction appears to proceed in a much cleaner fashion compared to that of catalyst **10**, which required 3 equivalents of piperidine. Unfortunately, purification by column chromatography was necessary to separate the Sonogashira product from a small amount of alkyne-alkyne homocoupling product which was also present. Nonetheless, use of catalyst **77c** and sodium carbonate represent a valuable improvement on the Sonogashira coupling protocol used earlier in this study.

3.6 Conclusions and Future Work

The synthetic route for catalysts **77a-c** has several advantages over the method used to prepare *bis*-phosphine palladium catalyst **10**. Firstly, being able characterise the palladium complex prior to immobilisation allows for a much better estimation of the catalyst loading and fine structure of its active sites. The synthesis of the imidazolium salt precursors **73** is a high-yielding, solvent-free reaction which requires only one simple purification step. The imidazolium salts and NHC palladium complexes are solid at room temperature and, unlike the *bis*-phosphine catalyst precursors, do not smell and pose minimal chemical hazards to the user.

The range of *bis*-NHC palladium catalysts **77a-c** have proven to be highly active in Suzuki coupling of aryl iodides and bromides (affording excellent conversions of selected substrates), and have shown modest activity in reactions involving aryl chlorides. Their reactivity is at least comparable to that of several contemporary heterogeneous NHC catalysts.[52,68-69] However, catalysts **77a-c** do appear to be more sensitive to the presence of other functionalities on the aromatic halide substrate when compared with selected literature examples.

The preliminary activity observed in Sonogashira reactions is also encouraging. A loading of 0.2 mol% of catalyst **77c** was enough to furnish excellent conversions within 30 minutes, which is comparable to numerous publications and roughly 10 times the activity of the *bis*-phosphine catalyst **10**.[51, 52, 54] Also, due to the fact that sodium carbonate could be used as a base, a much more efficient, amine-free Sonogashira coupling reaction is presented here compared to the standard conditions used in chapter 2.3.1 of this work.

The level of reusability exhibited by the silica-supported catalysts **77a-c** was relatively low (limited to four consecutive uses with a steady decrease in turnover rate). This is a stability concern which is also reflected in the fact that the catalysts degrade over a period of months if not stored under an inert atmosphere and probably relates to their exposure to oxygen, although the possibility of some

kind of unfavourable interaction with the silica surface cannot be ruled out. Although NHC-palladium complexes **76** are fairly robust (i.e. they do not require handling under inert atmosphere), the immobilised palladium complexes **77** are not stable to air and moisture unlike some similar catalysts reported in the literature.[54]

The head-to-head comparison of catalysts **75a-b** and **77a-c** illustrates a slight difference in activity in Suzuki coupling reactions. It is clear that the catalysts which were complexed with palladium prior to immobilisation show slightly higher activity compared to those assembled on the support. This could be related to the purity of the catalysts. If palladium black (nanoparticles) are indeed the major contaminant in catalysts **75** (as indicated somewhat from the SEM analysis), then a significant amount of the catalyst in the reaction mixture may be composed of elemental palladium, which would be expected to exhibit lower activity in Suzuki coupling reactions.[132] Synthetic route 2 is therefore preferred over route 1 as it makes better use of the precious metal source.

Secondly, we note that catalysts bearing the more bulky substituents exhibit a higher rate of conversion. The order of activity in Suzuki coupling reactions is illustrated in Figure 52.

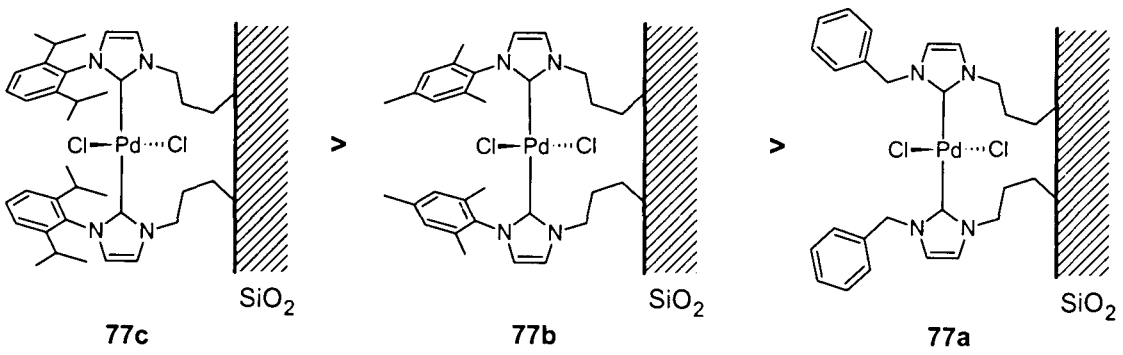


Figure 52 Order of reactivity of silica-supported *bis*-NHC palladium catalysts prepared in this study.

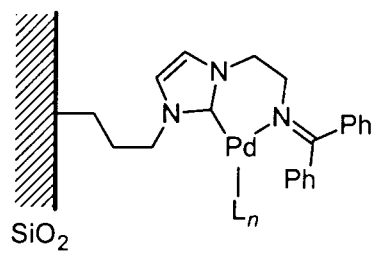
Clearly, steric bulk around the metal centre has a positive effect on catalytic activity, just as in homogeneous catalysis.[19] It is possible that the steric crowding simply serves to facilitate the departure of the chloride ligands to form the active

palladium(0) complex during Suzuki coupling reactions, though this is entirely speculative.

4 Preparation of Immobilised Iminoalkyl-NHC Catalyst

4.1 Introduction

The next area to be explored was the development of a silica-supported iminoalkyl NHC catalyst for allylic alkylation reactions. The use of chiral phosphine ligands is well established for homogeneous asymmetric allylic alkylations, however recently NHC ligands have been employed and in some cases display comparable activity and enantioselectivity.[133] As previously mentioned, NHCs are gaining popularity due to their enhanced stability, convenient stereoelectronic modification and environmentally benign nature compared with phosphines. That said, the aim was to prepare a mixed donor iminoalkyl NHC complex **80** (Figure 53) covalently anchored to silica for environmentally sound allylic alkylation reactions, which would be completely novel. Ultimately, chiral iminoalkyl NHC catalysts, derived from amino acids, would be employed in the hope of achieving enantioselection in these reactions. The initial pilot study presented here however will employ non-chiral ligands.



80

Figure 53 Iminoalkyl NHC catalyst structure.

4.2 Attempted Synthesis of Ligand Precursor 81

As with the preparation of the *bis*-NHC complexes (Chapter 3), the synthesis may be approached from two different perspectives, i.e. the preparation of the entire complex with subsequent immobilisation (route 1) or the stepwise immobilisation of the various moieties, building the catalyst onto the support in a sequential manner (route 2).

4.2.1 Route 1: Non-Chiral Ligand Synthesis

Figure 54 shows retrosynthetic analysis of the iminoalkyl imidazolium salt target molecule **81**.

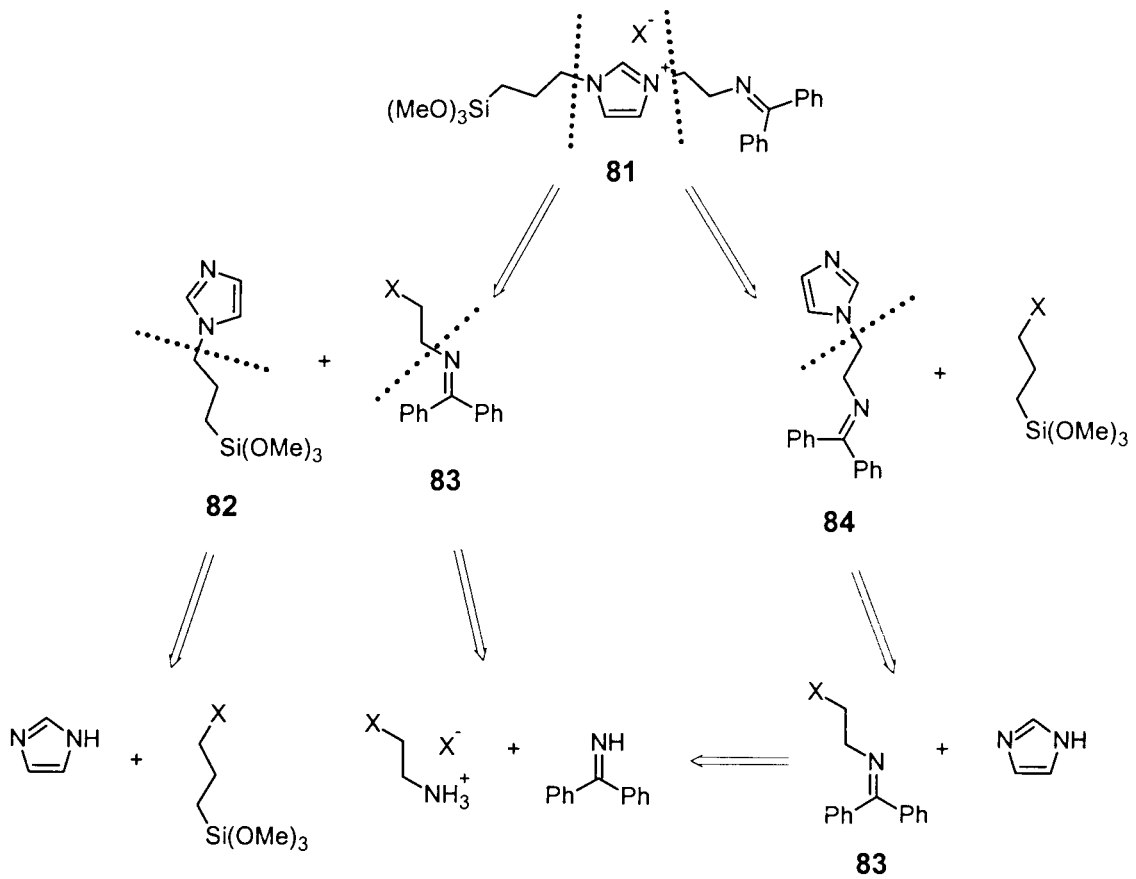
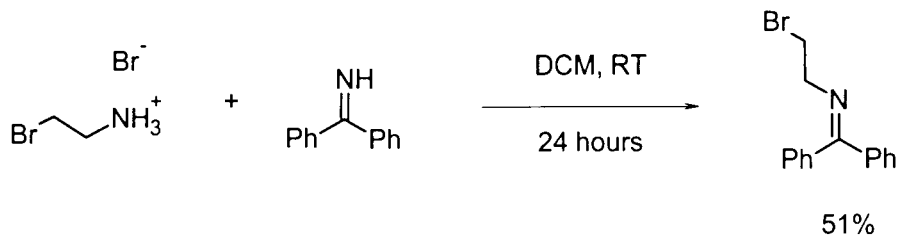


Figure 54 Disconnecting the target molecule.

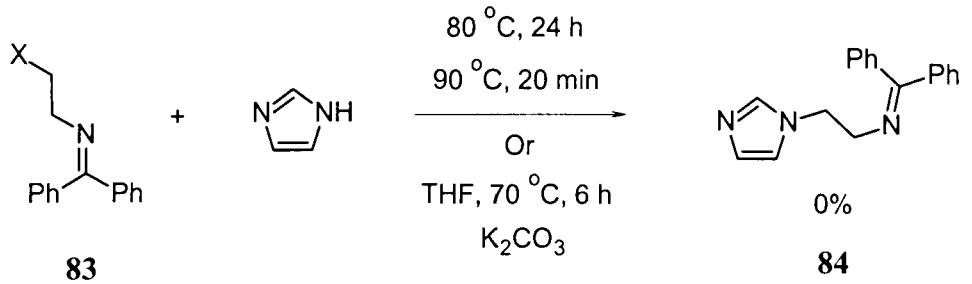
It was anticipated that the trimethoxysilyl unit would be subject to hydrolysis and condensation. As such, the most logical route would involve the introduction of this sensitive group towards the end of the synthesis. Therefore it was decided to

first approach the preparation of iminoalkyl imidazole **84**, which was carried out in accordance with the literature procedure (Scheme 85).[134] This presented no problems, other than a modest yield. The product **83** was isolated in 51% yield after recrystallisation.



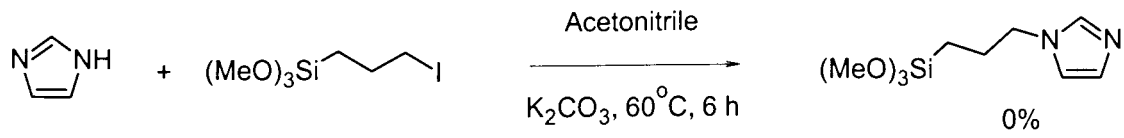
Scheme 85 Preparation of iminoalkyl bromide **83**. **83**

With iminoalkyl bromide **83** in hand, the next step would involve the alkylation of imidazole, a seemingly straightforward process. However, despite several attempts employing different solvents and temperatures, this reaction resulted in the formation of a dark, tarry substance whose identity could not be confirmed by NMR (Scheme 86).



Scheme 86 Attempted *N*-Alkylation of imidazoles to form iminoalkyl imidazole **84**. X = I or Br.

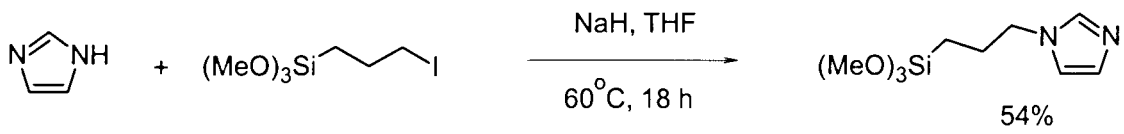
As an alternative, the preparation of *N*-propyl-(trimethoxysilyl)imidazole **82** was carried out. The standard literature method (Scheme 87)[135] for this reaction unfortunately led to the formation of 'brick dust', a white precipitate insoluble even in boiling DMSO! In an attempt to increase the rate (and thus selectivity) of the reaction, the bromide **83** was converted to the iodide, using the Finkelstein reaction.[136] Although the conversion of **83** to the iodide was accomplished in quantitative fashion, the iodide substrate experienced the same problem with polymerisation.



83b **82**

Scheme 87 Attempted *N*-Alkylation of imidazole.

Finally, using a different literature procedure reported by Neouze *et al.*,[137] compound **82** was prepared from 3-iodopropyltrimethoxysilane **83b** (Scheme 88). Use of the iodide and deprotonation using sodium hydride resulted in formation of the product in acceptable yield.

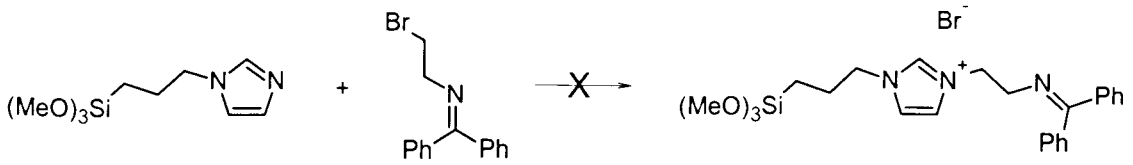


83b **82**

Scheme 88 Successful *N*-alkylation of imidazole. The reaction was monitored by GC-MS.

Unfortunately, NMR analysis using a 400 MHz instrument revealed the presence of more than one species. Multiple peaks were observed for the methoxy groups, which when integrated together added up to the correct number of protons. This observation was not reported by Neouze *et al.*,[137] probably due to the low resolution of their 60 MHz NMR spectrometer. Distillation of the product under reduced pressure had little or no effect on its purity as determined by NMR analysis, and so it was reasoned that the product could be carried forward. The possibility of some kind of unusual NMR effect, perhaps inter- or intramolecular co-ordination of the imidazolyl nitrogen to the silane thus changing the chemical environment of the methoxy groups, has not been ruled out since the compound was shown to be pure by GC-MS.

With iminoalkyl bromide **83** and trimethoxysilylalkyl imidazole **82** in hand, all that remained was another apparently simple *N*-alkylation reaction to form the target imidazolium salt (Scheme 89).



82 **83** **81**

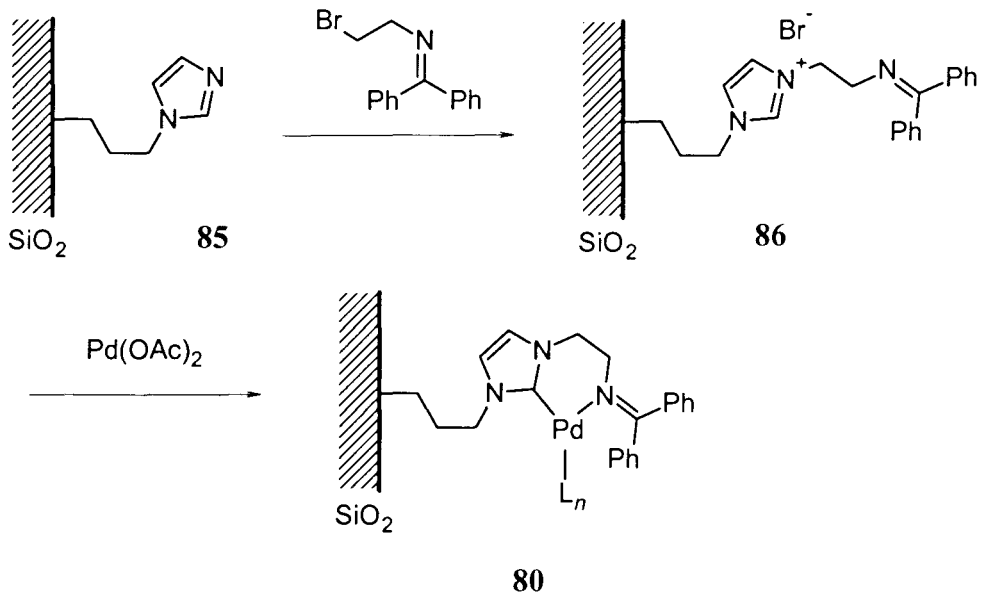
Scheme 89 The final step required to prepare the iminoalkyl imidazolium salt.

Unfortunately, standard solvent-free conditions led to the formation of numerous imidazolium-based products. One of these products was suspected to be our target molecule, however it proved to be inseparable from the side products. Tweaking the reaction conditions with various temperatures and solvents either resulted in similar product distributions or the formation of the, now familiar, insoluble 'brick dust' suggesting some kind of polymerisation.

Alas, despite being tantalisingly close to preparation of the iminoalkyl imidazolium salt **81**, the devotion of any further time and effort could not be justified.

4.2.2 Route 2: Immobilisation of Non-Chiral Ligand

Since the source of complication in the synthesis of imidazolium salt **81** seemed to involve the trimethoxysilyl group, it was reasoned that the problems encountered could be avoided if the ligand precursor was first attached to the silica support as in Scheme 90. The supported iminoalkyl imidazolium salt **86** was obtained as a yellow powder.



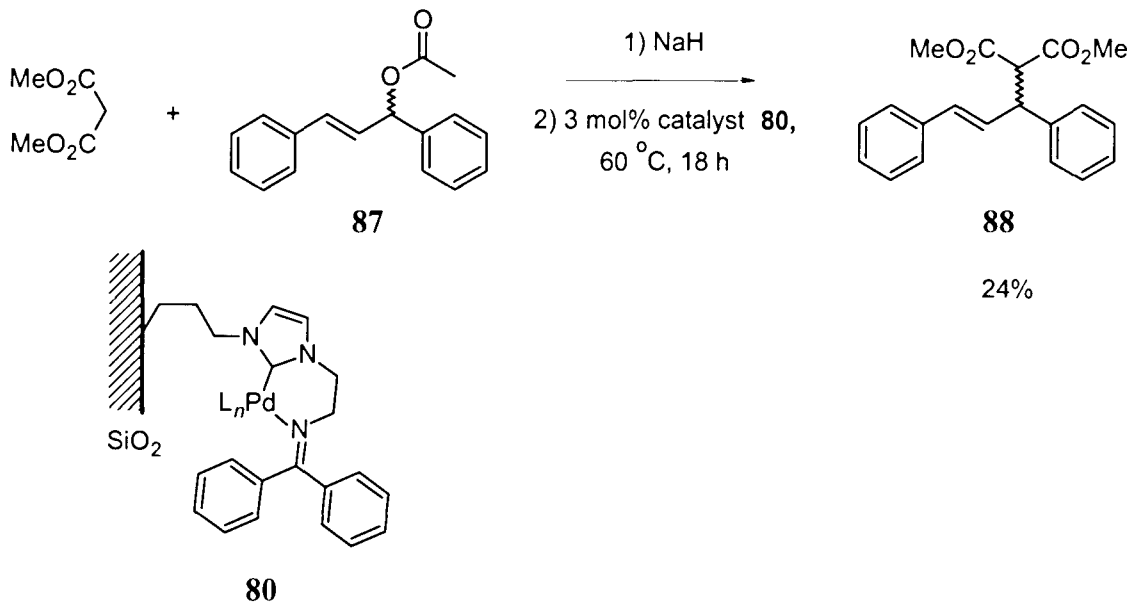
Scheme 90 Alternative synthetic route to catalyst **80**.

As previously mentioned, the main drawback associated with this synthetic route is the fact that NMR and mass spectrometry analysis of the catalyst and precursor will not be possible due to solubility issues.

The strategy of using silver(I) oxide to form the intermediate silver-NHC complex becomes redundant due to the production of insoluble silver bromide (which, as the catalyst is totally insoluble, could not be removed by the usual filtration step). And so precursor **86** was treated with $Pd(OAc)_2$ according to the literature method.[118] In this reaction, the acetate ligand serves to deprotonate the imidazolium salt and the *N*-heterocyclic carbene produced coordinates directly to the palladium atom.

4.3 Heterogeneous Allylic Alkylation

The silica-supported iminoalkyl-NHC catalyst **80** was tested for activity in the allylic alkylation of 1,3-diphenylpropenyl acetate with dimethylmalonate (Scheme 91).

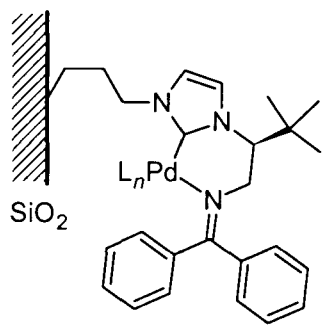


Scheme 91 Preliminary screening of iminoalkyl NHC palladium catalyst **80** in allylic alkylation of 1,3-diphenylpropenyl acetate using dimethyl malonate.

After 18 h, the alkylated product **88** was detected by GC-MS (21.1 min, M^+: 324). Purification by column chromatography (eluting with hexane : ethyl acetate, 8.5 : 1.5) resulted in a modest isolated yield of 24%.

4.4 Conclusions and Future Work

This appears to be the first application of a silica-supported iminoalkyl-NHC catalyst to allylic alkylation. Optimisation of the reaction conditions may lead to improvements in yield. Importantly, the inclusion of a chiral moiety into the catalyst structure (such as Figure 55) could potentially lead to enantioselectivity in the reaction, which would be a worthwhile endeavour for future investigations...



89

Figure 55 Immobilised chiral iminoalkyl-NHC catalyst structure.

Also, the synthesis of imidazolium salt **81** may indeed be feasible if a method of selective *N*-alkylation could be developed (i.e. suppressing side reactions such as oligomerisation/ polymerisation). This would allow for NMR/ mass spectrometric analysis of the iminoalkyl-NHC complex prior to immobilisation and thus, greater control over the catalyst loading and fine structure.

4.5 Concluding Remarks

Overall, this work provides evidence of the application of various hybrid catalysts to a wide range of potentially useful chemical processes. The portfolio of reactions catalysed by silica-supported phosphine **10** has been considerably expanded to include Sonogashira reactions of substituted aryl halides, heteroaryl iodides and alkenyl bromides. Most notably, a procedure has been developed allowing for the intramolecular cyclisation of unprotected 2-ethynylaniline derivatives, yielding 2-sustituted indoles in high yields, without the need for a copper co-catalyst. Preliminary studies on the activity of **10** in Heck and Suzuki reactions are also presented. The structure of catalyst **10** has now been investigated by solid state ^{31}P NMR, SEM and TGA, revealing that the catalyst is actually composed of several active species, which was previously not known.

The series of novel silica-supported *bis*-NHC catalysts **77a-c** presented in Chapter 3 showed excellent activity in Suzuki coupling reactions of aryl halides, most notably achieving modest conversions of chloride substrates, which is contemporary with numerous existing hybrid catalysts in the literature. A clean, environmentally-sound procedure for the use of catalysts **77a-c** in Sonogashira couplings has also been developed. This procedure, which involved the use of sodium carbonate as opposed to traditional amine bases, is highly efficient and warrants further investigation. Also, the design of the synthesis of catalysts **77a-c** allows for characterisation of the NHC complexes prior to immobilisation. The presence of the expected *bis*-NHC palladium (II) chloride complexes was confirmed by solution-phase ^{1}H and ^{13}C NMR analysis and high-resolution mass spectrometry. The speculation that this synthetic route would lead to a more well-defined catalyst structure and minimised amounts of surface-associated palladium (0) metal is supported by SEM analysis.

Importantly, the use of bulky *N*-mesityl and *N*-diisopropylphenyl NHC ligands lead to increased conversion rates in Suzuki coupling reactions compared with *N*-benzyl substituted ligands. This is apparently the first example of the

phenomenon of bulkier NHC ligands exhibiting increased catalytic activity in heterogeneous catalysis.

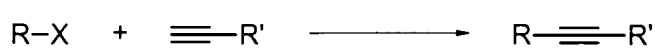
Finally, silica-supported iminoalkyl-NHC complex **80** has demonstrated modest activity in allylic alkylation reactions. This is the first application of such a catalyst to the heterogeneous version of the reaction. The modular design of the ligands employed facilitates modifications to include a chiral moiety for asymmetric heterogeneous allylic alkylations - a worthwhile endeavour for future studies.

5 Experimental

All coupling reagents and general laboratory chemicals (including anhydrous solvents) were purchased from Sigma-Aldrich ltd. and were used without further purification. All NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a Jeol Eclipse^{+} 400 NMR spectrometer using Jeol Delta version 4.3.6 control and processing software. Chemical shifts are reported in ppm, referenced to residual solvent peaks (acetone, chloroform or DMSO). MS were recorded using a Varian CP-3800 Gas Chromatograph with Varian 1200L Quadrupole Mass Spectrometer controlled using Varian Saturn GC/MS System Control Version 6.41. Melting point determinations were recorded using a Stuart Scientific SMP3 digital melting point apparatus and are uncorrected.

5.1 General Experimental procedures

Sonogashira Coupling

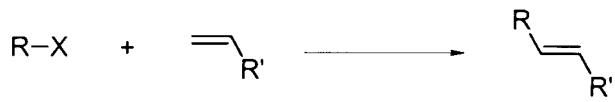


A dry Shlenk tube under nitrogen was charged with the aryl (or alkenyl) halide (1 mmol) and catalyst **10** (31.4 mg, 2 mol%). To this was added the alkyne (1.4 mmol) and piperidine (3 mmol) and the mixture was heated at 70 °C (with stirring) for 30 minutes by which point solidification had usually occurred. After cooling to room temperature, the mixture was diluted with ether (20 mL), filtered and the solvent removed (*in vacuo*). The crude product was purified by column chromatography and/or recrystallisation. Sonogashira coupling was also accomplished using catalyst **77c** (2 mol%) using sodium carbonate (3 eq) as the base.

5-*Endo-dig* Cyclisation Reactions

A dry Shlenk tube containing 2-(phenylethynyl)aniline (1 mmol, 193 mg), or a derivative thereof, and catalyst **10** (5 mol%, 78 mg) was heated at 100 °C for 60 minutes. Substrates with melting points >100 °C were solubilised with DMF (1 mL). The reaction mixture (now solid) was extracted into ethyl acetate (20 mL), filtered, washed with water (3x 20 mL) and the solvent removed *in vacuo*. This furnished the cyclised product, which was purified by column chromatography.

Heck Reaction

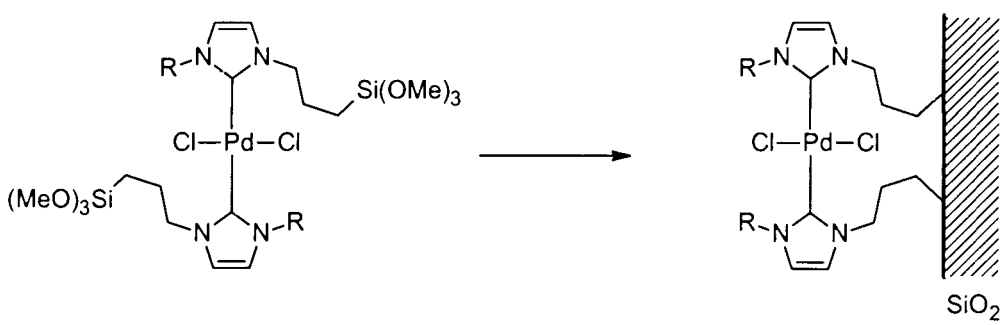


A dry Shlenk tube under nitrogen was charged with the aryl halide (2 mmol), catalyst **10** (62.8 mg, 1 mol%), alkene (4 mmol) and triethylamine (6 mmol) and the mixture was heated at 75 °C for 6.5 h. After cooling to room temperature, the mixture was extracted into diethyl ether (30 mL), washed with water (2x 20 mL) and then concentrated *in vacuo*. The resulting residue was chromatographed over silica to afford the purified product.

Suzuki Coupling

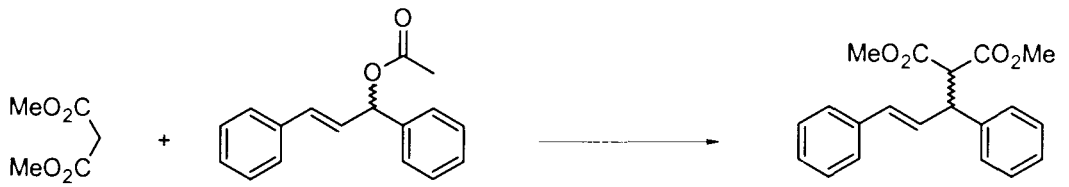
The aryl iodide or bromide (1 mmol) and catalyst **10** (2 mol%) were added to a dry Shlenk tube under nitrogen, followed by caesium carbonate (2 mmol), the boronic acid (1.4 mmol) and 1,4-dioxane (3 mL). This mixture was heated at 65 °C for 30 minutes, cooled to room temperature, diluted with acetone (10 mL) and filtered. The internal standard (dodecane, 1 mmol) was added the solution was analysed by GC-MS (EI, single ion monitoring mode). Suzuki coupling of aryl bromides and iodides was also accomplished using catalyst **77c** (0.2 mol%), sodium carbonate (2 mmol) and DMF/H_2O (1:1, 2 mL). Aryl chlorides could also be employed, however the catalyst loading was increased to 1 mol%, temperature was increased to 100 °C and the reaction time increased to 60 minutes.

Immobilisation of *Bis*-NHC Palladium complexes 70a-c



A solution of the *bis*-NHC complex **76a-c** in anhydrous chloroform (20 mL) was refluxed for 20 h with silica gel (amorphous, 0.035-0.070 nm). At this point, no visible trace of the complex remained in solution. After cooling to room temperature, the mixture was filtered under a cone of nitrogen and washed with anhydrous chloroform (3x 50 mL) and anhydrous dichloromethane (4x 50 mL). The yellow solid was dried under reduced pressure and stored under nitrogen at -4 °C. The washings were concentrated under reduced pressure and analysed by ^{1}H NMR, which showed no trace of the complex.

Allylic Alkylation Reaction

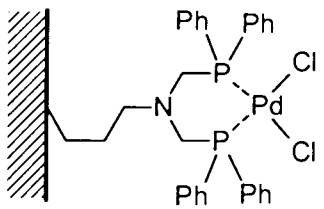


NaH (60% dispersion in mineral oil, 0.085 g, 2 mmol) was washed with hexane and suspended in anhydrous THF (2 mL). Dimethylmalonate (0.228 mL, 2 mmol) was added slowly and when effervescence had ceased, the mixture was added to a Shlenk tube containing catalyst **80** (0.0415 g, 3 mol%) and a further 2 mL THF. This mixture was stirred for 30 minutes at room temperature, then heated at 60 °C for 18 h. After cooling to room temperature, the crude product was chromatographed over silica (eluting with hexane : ethyl acetate, 8.5 : 1.5) to yield the alkylated product.

5.2 Synthetic Procedures and Analytical Data

(New compounds are indicated by an asterisk)

[1] Synthesis of silica-supported palladium catalyst 10*

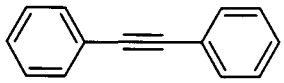


3-Aminopropyl functionalised silica (2.36 mmol, 2.36 g) was dried over phosphorous pentoxide at 80 °C for 48 h, then suspended in toluene and degassed by sonication (30 minutes) and nitrogen flow overnight. Under nitrogen, in a separate vessel, paraformaldehyde (9.44 mmol, 0.28 g) was suspended in MeOH (25 mL) and refluxed for 2 h. Then diphenylphosphine (9.44 mmol, 1.73 mL) was added and the mixture was heated at 90 °C for 44 h. The solvent was removed from the mixture (now a colourless solution) and the resulting clear viscous oil was added to the silica suspension. This mixture was refluxed (130 °C oil bath temperature) with a Dean-Stark trap for 24 h. The resulting mixture was filtered under nitrogen and washed sequentially with toluene (2x 50 mL), DCM (2x 50 mL) and again with toluene (2x 50 mL) and dried *in vacuo* to yield a pale yellow solid (2.87 g). This solid was reacted with $(C_6H_5CN)_2PdCl_2$ (2.4 mmol, 0.93 g) in chloroform (30 mL) at 60 °C for 24 h. This mixture was filtered and washed with DCM (3x 100 mL), ether (3x 50 mL), THF (3x 50 mL) and finally DCM again (3x 50 mL). Finally, the resulting brown solid (3.16 g) was dried *in vacuo* overnight.

^{31}P NMR (121 MHz, H_3PO_4): δ 10.35 (s, Ar-P co-ordinated with Pd), 29.84 (s, impurity, probably $R_3P{=}O$).

Elemental analysis: see appendix. TGA: see appendix.

[2] Synthesis of diphenylacetylene 37



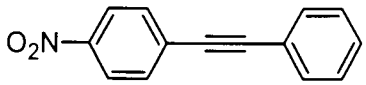
A dry Shlenk tube under nitrogen was charged with catalyst **10**, (2 mol%, 31.4 mg), iodobenzene (1 mmol, 0.204 mL), phenylacetylene (1.4 mmol, 0.154 mL) and piperidine (3 mmol, 0.297 mL). This mixture was heated at 70 °C for 30 minutes by which point solidification, due to the presence of piperidine hydroiodide, had occurred. After cooling to room temperature, the mixture was diluted with ether (20 mL), filtered and the solvent removed (*in vacuo*). The crude product was purified by column chromatography (hexane) to yield diphenylacetylene (157 mg, 88%) as a colourless crystalline solid (MP: 60-62 °C, lit. 59-61 °C).[53]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.57 (m, 4H, Ar-H), 7.32-7.39 (m, 6H, Ar-H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 131.7, 128.4, 128.3, 123.4, 89.5.
MS (EI) m/z: 178 (M^+).

[3] Recycling of Catalyst 10

The above procedure was repeated 4 times using the same catalyst. For each cycle, the catalyst was removed by filtration, washed with ether (10 mL), dried *in vacuo* and transferred to the next reaction vessel. Percent conversion of iodobenzene was determined by GC analysis of crude product with dodecane as an internal standard. A fairly steady decrease in conversion rate was noted. The following conversions were observed; cycle 1: 99%, cycle 2: 64%, cycle 3: 48%, cycle 4: 9%, cycle 5: 2%.

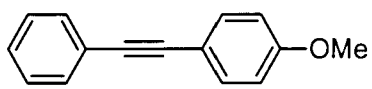
[4] Synthesis of (4-phenylethynyl)nitrobenzene 51



The reaction was carried out using the conditions outlined in experiment 2 except 4-nitrobromobenzene (202 mg, 1 mmol) was used as the aryl halide. Purification by column chromatography (hexane: ethyl acetate, 9: 1) yielded (4-phenylethynyl)- nitrobenzene (67 mg, 30%) as a yellow solid (MP: 116-118 °C, lit.: 120-121 °C).[53]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, 2H, J = 8.8 Hz, Ar-H), 8.01 (d, 2H, J = 8.4 Hz, Ar-H), 7.58-7.64 (m, 1H, Ar-H), 7.41-7.53 (m, 4H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.0, 196.0, 147.2, 142.1, 136.3, 133.8, 130.7, 129.0, 128.5, 123.9. MS (EI) m/z: 223 (M^+).

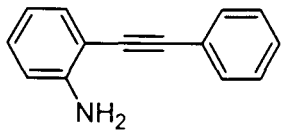
[5] Synthesis of (4-phenylethynyl)anisole 38



The reaction was carried out using the conditions outlined in experiment 2 except 4-Ethynylanisole (1.4 mmol, 182 mL) was used as the alkyne. Purification by column chromatography (9:1 hexane: ethyl acetate) yielded (4-phenylethynyl)anisole (167 mg, 80%) as a pale orange solid (MP: 55-56 °C, lit.: 56-58 °C).[53]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.52 (m, 2H, Ar-H), 7.46-7.48 (d, 2H, J = 8.8 Hz, Ar-H), 7.31-7.36 (m, 3H, Ar-H), 6.87-6.89 (d, 2H, J = 8.8 Hz, Ar-H), 3.83 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 133.1, 131.5, 128.4, 128.0, 123.5, 115.4, 114.1, 89.4, 88.1, 55.4. MS (EI) m/z: 208 (M^+).

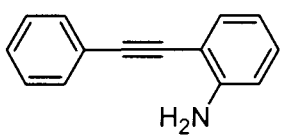
[6] Synthesis of (2-phenylethynyl)aniline 39a



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodoaniline (1 mmol, 219 mg) was used as the aryl halide. Purification by column chromatography (chloroform) yielded (4-phenylethynyl)aniline (116 mg, 60%) as a pale orange solid (MP: 89-91 °C, lit,: 85-86 °C).[106]

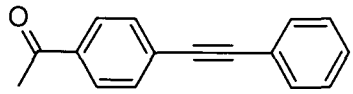
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.55 (m, 2H, Ar-H), 7.33-7.39 (m, 4H, Ar-H), 7.13-7.17 (m, 1H, Ar-H), 6.79 (t, J = 7.7 Hz, 2H, Ar-H), 4.28 (s, 2H, -NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 132.2, 131.5. 129.8, 128.4, 128.3, 123.4, 118.1, 114.4, 108.0, 94.8, 85.9. MS (EI) m/z: 193 (M^+).

[7] Synthesis of (4-phenylethynyl)aniline 39b



The reaction was carried out using the conditions outlined in experiment 2 except 2-ethynylaniline (1.4 mmol, 159 mL) was used as the alkyne. Purification by column chromatography (9:1 hexane: ethyl acetate) yielded (4-phenylethynyl)aniline (154 mg, 80%) as a pale orange solid. Analytical data: see **39a**.

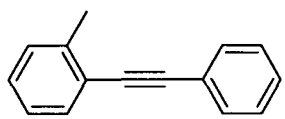
[8] Synthesis of 4-(phenylethynyl) acetophenone 40



The reaction was carried out using the conditions outlined in experiment 2 except 4-iodoacetophenone (1 mmol, 246 mg) was used as the aryl halide. Purification by column chromatography (9:1 hexane : ethyl acetate) yielded 4-(phenylethynyl) acetophenone as a pale yellow crystalline solid (178 mg, 81%), MP: 99-101 °C (lit.: 94-96 °C).[106]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.95 (d, 2H, J = 8.1 Hz, Ar-H), 7.60-7.62 (d, 2H, J = 8.1 Hz, Ar-H), 7.54-7.57 (m, 2H, Ar-H), 7.35-7.39 (m, 3H, Ar-H), 2.61 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 136.2, 131.8, 131.7, 128.9, 128.5, 128.4, 128.3, 122.7, 92.8, 88.7, 26.7. MS (EI) m/z: 220 (M^+).

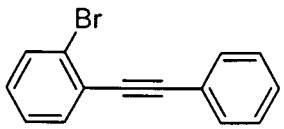
[9] Synthesis of 2-(phenylethynyl)toluene 41



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodotoluene (1 mmol, 128 mL) was used as the aryl halide. Purification by column chromatography (hexane) yielded 2-(phenylethynyl)toluene as a colourless oil (100 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.55 (m, 3H, Ar-H), 7.30-7.38 (m, 3H, Ar-H), 7.21-7.24 (m, 2H, Ar-H), 7.13-7.20 (m, 1H, Ar-H), 2.49-2.52 (s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 131.9, 131.6, 129.6, 128.5, 128.4, 128.2, 125.7, 123.6, 123.1, 93.4, 88.4, 20.9. MS (EI) m/z: 192 (M^+).

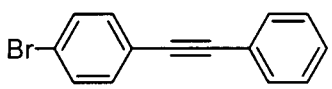
[10] Synthesis of 2-(phenylethynyl)bromobenzene 42



The reaction was carried out using the conditions outlined in experiment 2 except 2-bromoiodobenzene (1 mmol, 128 mL) was used as the aryl halide. Purification by column chromatography (hexane) yielded 2-(phenylethynyl)bromobenzene as a red/ orange oil (151 mg, 59%). *bis*-Sonogashira side product, 1,2-(diphenylethynyl)benzene, also isolated.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.65 (m, 4H, Ar-H), 7.34-7.40 (m, 3H, Ar-H), 7.27-7.32 (m, 1H, Ar-H), 7.15-7.22 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.3, 132.5, 131.8, 129.5, 128.7, 128.5, 127.1, 125.7, 125.5, 123.0, 94.0, 88.1. MS (EI) m/z: 256/258 (M^+).

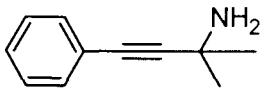
[11] Synthesis of 4-(phenylethynyl)bromobenzene 43



The reaction was carried out using the conditions outlined in experiment 2 except 4-bromoiodobenzene (1 mmol, 283 mg) was used as the aryl halide. Purification by column chromatography (hexane) yielded 4-(phenylethynyl)bromobenzene (210 mg, 82%)as a colourless crystalline solid, (MP: 80-82 °C, lit.: 82-84 °C).[111] *Bis*-Sonogashira side product, 1,4-(diphenylethynyl)benzene, also isolated.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.55 (m, 2H, Ar-H), 7.46-7.50 (d, 2H, J = 8.8 Hz, Ar-H), 7.37-7.40 (d, 2H, J = 8.6 Hz, Ar-H), 7.33-7.36 (m, 3H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.1. 131.7, 131.6, 128.6, 128.5, 123.0, 122.5, 122.3, 90.6, 88.4.
MS (EI) m/z: 256/258 (M^+).

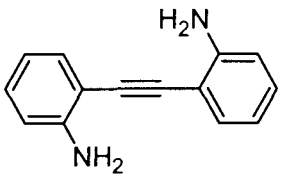
[12] Synthesis of 2-phenylethynyl-2-amino-2-propane 44



The reaction was carried out using the conditions outlined in experiment 2 except 2-Methyl-2-aminobut-3-yne (1.4 mmol, 147 mL) was used as the alkyne. Purification by column chromatography (7:3 ethyl acetate: methanol) yielded 2-phenylethynyl-2-amino-2-propane (154 mg, 80%) as a light-brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.43 (m, 2H, Ar-H), 7.22-7.29 (m, 3H, Ar-H), 4.74 (s, 2H, $-NH_2$), 1.63 (s, 6H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8, 128.4, 128.3, 122.6, 93.2, 82.6, 47.7, 30.7. MS (EI) m/z: 159 (M^+).

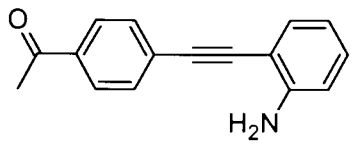
[13] Synthesis of 1,2-*bis*-(2-aminophenyl)ethyne 45



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodoaniline (1 mmol, 219 mg) was used as the aryl halide and 2-ethynylaniline (1.4 mmol, 159 mL) was used as the alkyne. Purification by recrystallisation (chloroform) yielded 1,2-*bis*-(2-aminophenyl)ethyne (154 mg, 74%) as a light-green crystalline solid (MP: 154-155 °C, lit.: 154 °C).[138]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.40 (m, 2H, Ar-H), 7.12-7.17 (m, 2H, Ar-H), 6.69-6.77 (m, 4H, Ar-H), 4.27 (s, 4H, $-NH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 132.1, 129.8, 118.1, 114.5, 108.2, 91.2. MS (EI) m/z: 208 (M^+).

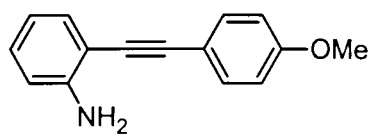
[14] Synthesis of 2-(4'-acetophenylethynyl)aniline 46



The reaction was carried out using the conditions outlined in experiment 2 except 4-Iodoacetophenone (1 mmol, 246 mg) was used as the aryl halide and 2-ethynylaniline (1.4 mmol, 159 mL) was used as the alkyne. Purification by recrystallisation (methylated spirit) yielded 2-(4-acetophenylethynyl)aniline as an off white solid (194 mg, 82%) MP: 114-116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 2H, J = 8.6 Hz, Ar-H), 7.60 (d, 2H, J = 8.6 Hz, Ar-H), 7.35-7.41 (m, 1H, Ar-H), 7.14-7.20 (m, 1H, Ar-H), 6.70-6.77 (m, 2H, Ar-H), 4.23-4.36 (s, 2H, $-NH_2$), 2.60-2.63 (s, 3H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.2, 179.7, 171.9, 136.2, 132.4, 131.6, 130.4, 128.4, 128.3, 118.2, 114.6, 100.0, 94.1, 26.8. MS (EI) m/z: 236 (M^+).

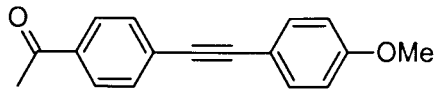
[15] Synthesis of 2-(4'-methoxyphenylethynyl)aniline 47



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodoaniline (1 mmol, 219 mg) was used as the aryl halide and 4-ethynylanisole (1.4 mmol, 0.182 mL) was used as the alkyne. Purification by recrystallisation (methylated spirit) yielded 2-(4'-methoxyphenylethynyl)aniline as a light orange crystalline solid (142 mg, 60%) MP: 99-102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.50 (d, 2H, J = 8.8 Hz, Ar-H), 7.34-7.38 (m, 1H, Ar-H), 7.10-7.16 (m, 1H, Ar-H), 6.88 (d, 2H, J = 9.0, Ar-H), 6.70-6.76 (m, 2H, Ar-H), 4.25-4.30 (s, 2H, $-NH_2$), 3.81-3.86 (s, 3H, O-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 147.7, 133.0, 132.1, 129.5, 118.0, 115.5, 114.4, 114.1, 108.4, 94.7, 84.5, 55.4. MS (EI) m/z: 233 (M^+).

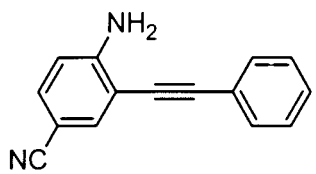
[16] Synthesis of 4-(4'-acetophenylethynyl)anisole 48



The reaction was carried out using the conditions outlined in experiment 2 except 4-iodoacetophenone (1 mmol, 246 mg) was used as the aryl halide and 4-ethynylanisole (1.4 mmol, 0.182 mL) was used as the alkyne. Purification by column chromatography (chloroform) yielded 4-(4'-acetophenylethynyl)anisole (200 mg, 80%) as a pale yellow solid (MP: 129-131 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, 2H, J = 8.2 Hz, Ar-H), 7.57 (d, 2H, J = 8.2 Hz, Ar-H), 7.49 (d, 2H, J = 8.6 Hz, Ar-H), 6.89 (d, 2H, J = 8.6 Hz, Ar-H), 3.82-3.85 (s, 3H, O-CH_3), 2.59-2.62 (s, 3H, -$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 160.2, 136.0, 133.4, 131.5, 128.7, 128.3, 114.8, 114.2, 93.1, 87.7, 55.3, 26.7. MS (EI) m/z: 250 (M^+).

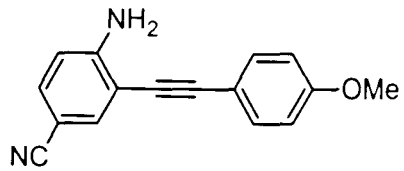
[17] Synthesis of 2-(phenylethynyl)-4-amino benzonitrile 49*



The reaction was carried out using the conditions outlined in experiment 2 except 4-amino-3-iodobenzonitrile (1 mmol, 244 mg) was used as the aryl halide. Purification by column chromatography (chloroform) yielded 2-(phenylethynyl)-4-amino benzonitrile (175 mg, 80%) as an off-white crystalline solid (MP: 88-89 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7,65 (m, 1H, Ar-H), 7.50-7.55 (m, 2H, Ar-H), 7.35-7.40 (m, 4H, Ar-H), 6.70-6.74 (d, 1H, J = 8.6 Hz, Ar-H), 4.75-4.81 (s, 2H, -NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 136.4, 133.3, 131.7, 129.0, 128.6. 122.4, 119.5, 114.0, 108.2, 100.2, 96.3, 83.5. MS (EI) m/z: 218 (M^+). HRMS (EI): calculated for $C_{15}H_{10}N_2$; 218.0838, Found: 218.0837.

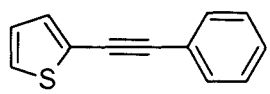
[18] Synthesis of 2-(4'-methoxyphenylethynyl)-4-aminobenzonitrile 50*



The reaction was carried out using the conditions outlined in experiment 2 except 4-amino-3-iodobenzonitrile (1 mmol, 244 mg) was used as the aryl halide and 4-ethynylanisole (1.4 mmol, 0.182 mL) was used as the alkyne. Purification by column chromatography (chloroform) yielded 2-(4'-methoxyphenylethynyl)-4-aminobenzonitrile (161 mg, 65%) as a pale-yellow crystalline solid (MP: 147-149 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.63 (m, 1H, Ar-H), 7.46 (d, 2H, J = 9.0 Hz, Ar-H), 7.35 (m, 1H, Ar-H), 6.9 (d, 2H, J = 9.0 Hz, Ar-H), 6.68-6.73 (d, 1H, J = 8.4 Hz, Ar-H), 4.72-4.85 (s, 2H, $-NH_2$), 3.82-3.85 (s, 3H, $-OCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 150.9, 136.2, 136.1, 133.2, 133.0, 114.4, 114.2, 114.0, 108.7, 100.2, 96.4, 82.1, 55.4. MS (EI) m/z: 248 (M^+). HRMS (EI): calculated for $C_{16}H_{12}O_1N_2$; 248.0944, Found: 248.0945.

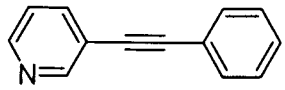
[19] Synthesis of 2-(phenylethynyl)thiophene 53



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodothiophene (1 mmol, 0.110 mL) was used as the aryl halide. Purification by column chromatography (hexane) yielded 2-(phenylethynyl)thiophene (140 mg, 76%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.50-7.56 (m, 2H, Ar-H), 7.27-7.39 (m, 5H, Ar-H), 7.00-7.04 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.6, 132.0, 131.5, 128.5, 127.3, 127.2, 123.4, 123.0, 92.3, 82.7. MS (EI) m/z: 184 (M^+).

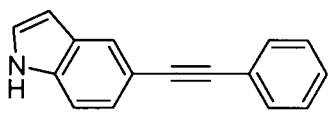
[20] Synthesis of 3-(phenylethynyl)pyridine 54



The reaction was carried out using the conditions outlined in experiment 3-iodopyridine (1 mmol, 205 mg) was used as the aryl halide. Purification by column chromatography (3.5: 1 diethylether: hexane) yielded 3-(phenylethynyl)pyridine (130 mg, 73%) as an orange crystalline solid (MP: 51-53 °C, lit.: 50-51 °C).[139]

^{1}H NMR (400 MHz, $CHCl_3$): δ 8.75-8.79 (s, 1H, Ar-H), 8.55 (d, J = 4.9 Hz, 1H, Ar-H), 7.81 (d, J = 7.9 Hz, 1H, Ar-H), 7.52-7.58 (m, 2H, Ar-H), 7.35-7.40 (m, 3H, Ar-H), 7.29 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 148.7, 138.5, 131.8, 128.9, 128.5, 123.1, 122.6, 120.6, 92.7, 86.0. MS (EI) m/z: 179 (M^+).

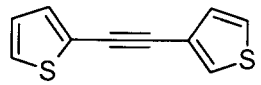
[21] Synthesis of 3-(phenylethynyl)indole 55



The reaction was carried out using the conditions outlined in experiment 5-iodoindole (1 mmol, 243 mg) was used as the aryl halide. Purification by column chromatography (3.5 : 1 ether : hexane) yielded 3-(phenylethynyl)indole (205 mg, 73%) as a yellow oil.

^{1}H NMR (400 MHz, $CHCl_3$): δ 8.02-8.24 (s, 1H, N-H), 7.78-7.82 (s, 1H, Ar-H), 7.45-7.50 (m, 2H, Ar-H), 7.23-7.31 (m, 4H, Ar-H), 7.14-7.18 (m, 2H, Ar-H), 6.47-6.50 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 131.6, 128.4, 127.8, 126.4, 125.8, 125.1, 124.8, 124.1, 114.5, 111.2, 103.0, 91.1, 87.1. MS (EI) m/z: 217 (M^+).

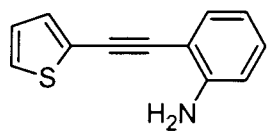
[22] Synthesis of 3-(2'-thiophenylethynyl)thiophene 56



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodothiophene (1 mmol, 0.110 mL) was used as the aryl halide and 3-ethynylthiophene (1.4 mmol, 0.137 mL) was used as the alkyne. Purification by column chromatography (hexane) yielded 3-(2'-thiophenylethynyl)thiophene (119 mg, 63%) as a colourless crystalline solid (MP: 97-100 °C lit. 92-93 °C).[140]

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.48 (dd, J = 1.2 Hz, 1H, Ar-H), 7.20-7.26 (m, 3H, Ar-H), 7.14 (m, 1H, Ar-H), 6.96 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.9, 129.8, 128.9, 127.3, 127.2, 125.6, 123.3, 122.0, 88.3, 82.2. MS (EI) m/z: 190 (M^+).

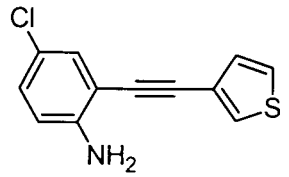
[23] Synthesis of 2-(2'-aminophenylethynyl)thiophene 57



The reaction was carried out using the conditions outlined in experiment 2 except 2-iodothiophene (1 mmol, 0.110 mL) was used as the aryl halide and 2-ethynylaniline (1.4 mmol, 0.159 mL) was used as the alkyne. Purification by column chromatography (hexane) yielded 2-(2'-aminophenylethynyl)thiophene (143 mg, 72%) as a yellow solid (MP: 63-64 °C).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.25 (d, J = 5.2 Hz, 1H, Ar-H), 7.08 (d, J = 3.6 Hz, 1H, Ar-H), 7.01 (d, J = 7.7 Hz, 1H, Ar-H), 6.81-6.88 (m, 2H, Ar-H), 6.54 (d, J = 8.2 Hz, 1H, Ar-H), 6.35 (t, J = 7.5 Hz, 1H, Ar-H), 4.77-4.99 (s, br, 2H, Ar-NH_2). ^{13}C NMR $(CD_3)_2CO$): δ 149.5, 131.9, 131.8, 130.1, 127.6, 127.4, 123.3, 117.0, 116.6, 106.3, 90.1, 87.0. MS (EI) m/z: 199 (M^+).

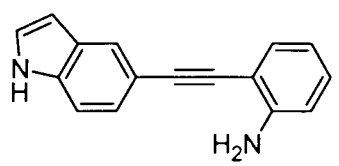
[24] Synthesis of 3-(5'-chloro-2'-aminophenylethynyl)thiophene 58*



The reaction was carried out using the conditions outlined in experiment 2 except 5-chloro-2-iodoaniline (1 mmol, 253 mg) was used as the aryl halide and 3-ethynylthiophene (1.4 mmol, 0.137 mL) was used as the alkyne. Purification by column chromatography (1 : 5 ethyl acetate : hexane) yielded 3-(5'-chloro-2'-aminophenylethynyl)thiophene (177 mg, 76%) as a light brown solid (MP: 107-110 °C).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.69-7.71 (m, 1H, Ar-H), 7.48-7.51 (m, 1H, Ar-H), 7.20-7.23 (m, 2H, Ar-H), 6.8 (d, J = 2.0 Hz, 1H, Ar-H), 6.57 (dd, J = 2.0 Hz, 1H, Ar-H), 5.30-5.45 (s, 2H, NH_2). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 150.6, 134.8, 133.1, 129.8, 128.8, 126.0, 122.3, 116.3, 113.4, 105.6, 90.1, 84.6. MS (EI) m/z: 233 (M^+).

[25] Synthesis of 5-(2'-aminophenylethynyl)indole 59*

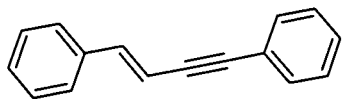


The reaction was carried out using the conditions outlined in experiment 2 except 5-iodoindole (1 mmol, 243 mg) was used as the aryl halide and 2-ethynylaniline (1.4 mmol, 0.159 mL) was used as the alkyne. Purification by column chromatography (chloroform) yielded 5-(2'-aminophenylethynyl)indole (185 mg, 80%) as a pale yellow crystalline solid (MP: 183-184 °C).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10.29-10.51 (s, br, 1H, indolyl N-H), 7.75-7.78 (m, 1H, Ar-H), 7.38-7.41 (m, 1H, Ar-H), 7.33-7.35 (t, J = 2.8 Hz, 1H, Ar-H), 7.20-7.27 (m, 2H, Ar-H), 6.99-7.04 (m, 1H, Ar-H), 6.71-6.75 (dd, 1H, J = 8.2 Hz,

8.1 Hz, Ar-H), 6.52-6.57 (m, 1H, Ar-H), 6.44-6.46 (m, 1H, Ar-H), 4.99-5.09 (s, 2H, $-NH_2$). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 149.2, 136.0, 131.6, 129.1, 128.2, 126.1, 124.8, 123.9, 116.5, 114.0, 113.9, 111.5, 107.8, 101.8, 96.1, 83.5. MS (EI) m/z: 232 (M^+). HRMS (EI): calculated for $C_{16}H_{12}N_2$: 232.0995, found: 232.0995.

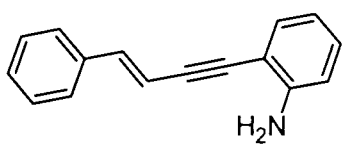
[26] Synthesis of β-(phenylethynyl)styrene 60



The reaction was carried out using the conditions outlined in experiment 2 except β-bromostyrene (1 mmol, 0.128 mL) was used as the aryl halide. Purification by recrystallisation (methylated spirits) yielded β-(phenylethynyl)styrene (173 mg, 85%) as a colourless crystalline solid (MP: 102-103 °C, lit.: 96 °C).[141]

^1H NMR (400 MHz, $CDCl_3$): δ 7.27-7.52 (m, 10H, Ar-H), 7.02-7.09 (d, 1H, J = 16.3 Hz, alkenyl-H), 6.36-6.43 (d, 1H, J = 16.3 Hz, alkenyl-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 136.4, 131.6, 128.8, 128.7, 128.4, 128.3, 126.4, 123.5, 108.2, 91.8, 89.0. MS (EI) m/z: 204 (M^+).

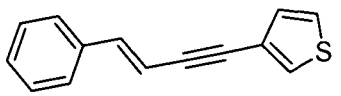
[27] Synthesis of β-(2-aminophenyl- ethynyl)styrene 61



The reaction was carried out using the conditions outlined in experiment 2 except β-bromostyrene (1 mmol, 0.128 mL) was used as the aryl halide and 2-ethynylaniline (1.4 mmol, 0.159 mL) was used as the alkyne. Purification by column chromatography (1 : 4 ethyl acetate : hexane) yielded β-(2-aminophenyl-ethynyl)styrene (165 mg, 87%) as a dull yellow crystalline solid (MP: 111-112 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.46 (m, 2H, Ar-H), 7.27-7.39 (m, 4H, Ar-H), 7.10-7.16 (m, 1H, Ar-H), 7.04 (d, 1H, J = 16.3 Hz, alkenyl-H), 6.67-6.75 (m, 2H, Ar-H), 6.44 (d, 1H, J = 16.1 Hz, alkenyl-H), 4.15-4.37 (s, 2H, $-NH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 140.8, 136.4, 132.2, 129.7, 128.8, 128.7, 126.3, 118.1, 114.4, 108.2, 108.1, 94.3, 88.3. MS (EI) m/z: 219 (M^+).

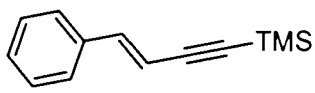
[28] Synthesis of β-(3'-thiophenylethynyl)styrene 63



The reaction was carried out using the conditions outlined in experiment 2 except β-bromostyrene (1 mmol, 0.128 mL) was used as the aryl halide and 2-ethynylaniline (1.4 mmol, 0.159 mL) was used as the alkyne. Purification by column chromatography (hexane) yielded β-(3'-thiophenylethynyl)styrene (MP: 89-91 °C).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.64-7.67 (m, 1H, Ar-H), 7.49-7.55 (m, 3H, Ar-H), 7.27-7.39 (m, 3H, Ar-H), 7.17 (m, 1H, Ar-H), 7.04 (d, J = 16.3 Hz, 1H, alkenyl-H), 6.53 (d, J = 16.3 Hz, 1H, alkenyl-H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 141.1, 136.4, 129.6, 128.8, 128.8 (overlapping), 128.7, 126.4, 126.2, 122.5, 108.0, 88.3, 86.8. MS (EI) m/z: 210 (M^+).

[29] Synthesis of β-(trimethylsilylethynyl)styrene 64

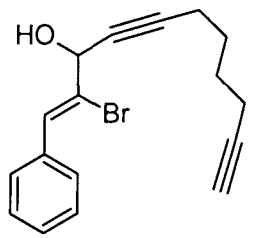


The reaction was carried out using the conditions outlined in experiment 2 except β-bromostyrene (1 mmol, 0.128 mL) was used as the aryl halide and trimethylsilylacetylene (2.5 mmol, 0.352 mL) was used as the alkyne.

Purification by column chromatography (hexane) yielded β-(trimethylsilylethynyl)styrene (130 mg, 65%) as a yellow oil.

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.48-7.52 (m, 2H, Ar-H), 7.30-7.37 (m, 3H, Ar-H), 7.00 (d, J = 16.5 Hz, 1H, Alkenyl C-H), 6.35 (d, J = 16.5 Hz, 1H, Alkenyl C-H), 0.18-0.22 (s, 9H, Si-CH_3). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 142.4, 128.9, 128.8, 126.5, 108.1, 104.8, 96.2, -0.4, -0.7. MS (EI) m/z: 200 (M^+).

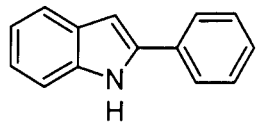
[30] Synthesis of 2-Bromo-1-phenylundec-1-ene-4,10-diyn-3-ol



Under an inert atmosphere, a stirred solution of 1,7-octadiyne (30 mmol, 3.98 mL) in anhydrous THF (15 mL) was cooled to -78 °C. To this, a solution of n-butyllithium (30 mmol in 18.75 mL hexane) was added and the mixture was allowed to stir for 10 minutes (a pale-yellow precipitate was noted). A solution of α-bromocinnamaldehyde (15 mmol, 3.165 g) in anhydrous THF (15 mL) was added dropwise, at which point the precipitate dissolved to form a yellow solution. This solution was stirred for 30 minutes. The reaction was then quenched with HCl (15% v/v, 25 mL) and the organic phase dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (1 : 9 ethyl acetate : toluene) to yield a yellow oil (2.89 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.66 (m, 2H, Ar-H), 7.31-7.40 (m, 3H, Ar-H), 7.23-7.25 (s, 1H, C=C-H), 5.05-5.09 (d, J = 7.0 Hz, 1H, -OH), 2.50-2.53 (d, J = 7.5 Hz, 1H, H*), 2.29-2.34 (m, 2H, alkyl-H), 2.21-2.26 (m, 2H, alkyl-H), 1.94-1.97 (t, J = 2.6 Hz, 1H, alkynyl-H), 1.65-1.70 (m, 4H, alkyl-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8, 129.3, 129.2, 128.5, 128.3, 126.3, 87.8, 84.0, 78.4, 68.9, 68.7, 27.5, 27.3, 18.4, 18.0. MS (EI) m/z: 318 (M^+).

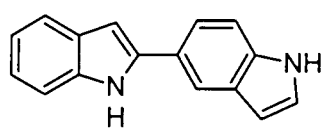
[31] Synthesis of 2-Phenylindole 65



A dry Shlenk tube containing 2-(phenylethynyl)aniline **39** (1 mmol, 193 mg, from expt. 7) and catalyst **10** (5 mol%, 78 mg) was heated at 100 °C for 60 minutes. The reaction mixture (now solid) was extracted into ethyl acetate (20 mL), filtered, washed with water (3x 20 mL) and the solvent removed *in vacuo*. This furnished 2-Phenylindole (185 mg, 96%) as an off-white solid (MP: 191-193 °C, lit.: 188-190 °C).[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.40 (s, br, 1H, indolyl N-H), 7.61-7.70 (m, 3H, Ar-H), 7.39-7.48 (m, 3H, Ar-H), 7.30-7.35 (m, 1H, Ar-H), 7.17-7.23 (m, 1H, Ar-H), 7.10-7.15 (m, 1H, Ar-H), 6.82-6.85 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.9, 132.5, 129.4, 129.1, 127.8, 125.3, 122.5, 120.8, 120.5, 111.0, 100.1. MS (EI) m/z: 193 (M^+). HRMS (EI): calculated for $C_{14}H_{11}N_1$: 193.0886, found: 193.0888.

[32] Synthesis of 2-(5'-Indolyl)indole 66*

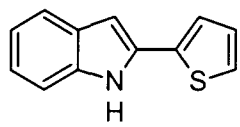


A dry Shlenk tube containing 5-(2'-aminophenylethynyl)indole **59** (0.25 mmol, 58 mg, from expt. 25), DMF (2 mL) and catalyst **10** (5 mol%, 19 mg) was heated at 100 °C for 60 minutes. The reaction mixture was diluted with ethyl acetate (20 mL), filtered, washed with water (3x 20 mL) and the solvent removed *in vacuo*. This yielded 2-(5'-indolyl)indole (53 mg, 91%) as a light brown solid (MP: 146 °C - decomposed).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10.41-10.59 (s, br, 1H, indolyl N-H), 10.17-10.35 (s, br, 1H, indolyl N-H), 7.97-7.98 (m, 1H, Ar-H), 7.54-7.57 (dd, J = 1.7

Hz, 1.8 Hz, 1H, Ar-H), 7.39-7.46 (m, 2H, Ar-H), 7.27-7.33 (dd, J = 0.9 Hz, 0.9 Hz, 2H, Ar-H), 7.26-7.29 (m, 1H, Ar-H), 6.88-6.98 (m, 2H, Ar-H), 6.68-6.71 (dd, J = 0.7 Hz, 0.7 Hz, 1H, Ar-H), 6.41-6.45 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 140.1, 137.4, 136.1, 129.8, 128.6, 125.8, 124.2, 120.9, 119.8, 119.7, 119.4, 116.9, 111.8, 110.9, 102.0, 97.5. MS (EI) m/z: 232 (M^+). HRMS (EI): calculated for $C_{16}H_{12}N_2$; 232.0995, found: 232. 0996.

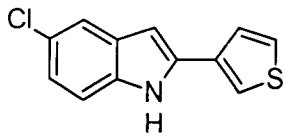
[33] Synthesis of 2-(2'-Thiophenyl)indole 67



A dry Shlenk tube containing 3-(2'-aminophenylethynyl)thiophene **57** (1 mmol, 220 mg, from expt. 23), DMF (1 mL) and catalyst **10** (5 mol%, 39 mg) was heated at 100 °C for 60 minutes. The reaction mixture was diluted with ethyl acetate, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1 : 5 ethyl acetate : hexane) to yield 2-(2'-Thiophenyl)indole (179 mg, 90%) as an off-white solid (MP: 168-171 °C).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.10-8.30 (s, br, 1H, N-H), 7.57-7.61 (d, J = 8.6 Hz, 1H, Ar-H), 7.3-7.38 (d, J = 8.2 Hz, 1H, Ar-H), 7.23-7.29 (m, 2H, Ar-H), 7.16-7.21 (t, J = 8.2 Hz, 1H, Ar-H), 7.06-7.14 (m, 2H, Ar-H), 6.72-6.74 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 136.6, 135.7, 132.4, 129.1, 128.0, 124.7, 123.0, 122.6, 120.6, 120.5, 110.9, 100.5. MS (EI) m/z: 199 (M^+).

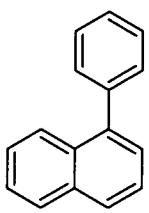
[34] Synthesis of 2-(3'-Thiophenyl)-5-chloroindole 68



A dry Shlenk tube containing 3-(5'-chloro-2'-aminophenylethynyl)thiophene **58** (116 mg, 0.5 mmol), DMF (1 mL) and catalyst **10** (5 mol%, 39 mg) was heated at 100 °C for 60 minutes. The reaction mixture was diluted with ethyl acetate, filtered and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (1:5, ethyl acetate:hexane) to yield 2-(3'-Thiophenyl)-5-chloroindole (103 mg, 89%) as an off-white solid (MP: 155-162 °C).

^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 10.64-10.82 (s, 1H, indolyl-H), 7.70-7.73 (m, 1H, Ar-H), 7.47-7.54 (m, 2H, Ar-H), 7.42-7.46 (m, 1H, Ar-H), 7.29-7.32 (s, 1H, Ar-H), 6.91-6.96 (dd, J = 1.8 Hz, 1H, Ar-H), 6.69-6.72 (m, 1H, Ar-H). ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 137.5, 135.5, 134.1, 128.0, 126.8, 125.8, 121.3, 120.1, 119.8, 113.4, 110.7, 99.1. MS (EI) m/z: 233 (M^+).

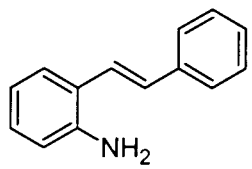
[35] Synthesis of 1-(Phenyl)naphthalene



Iodobenzene (1 mmol, 0.204 mL) and catalyst **10** (2 mol%, 62.8 mg) were added to a dry Shlenk tube under nitrogen, followed by caesium carbonate (2 mmol, 615 mg), 1-naphthylboronic acid (1.4 mmol, 240 mg) and 1,4-dioxane (3 mL). This mixture was heated at 65 °C for 30 minutes, cooled to room temperature, diluted with acetone (10 mL) and filtered. The residue was chromatographed over silica (hexane) to yield the title compound as a colourless oil (112 mg, 55%).

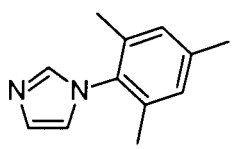
^{1}H NMR (400 MHz, $CHCl_3$): δ 7.89-7.78 (m, 3H, Ar-H), 7.45-7.34 (m, 9H, Ar-H). ^{13}C NMR (100 MHz, $CHCl_3$): δ 140.8, 140.3, 133.8, 131.7, 130.0, 128.2, 128.1, 127.6, 127.2, 126.9, 126.0, 125.9, 125.7, 125.3. MS (EI) m/z: 204 (M^+).

[36] Preparation of 2-Aminostilbene 71



A dry Shlenk tube under nitrogen was charged with 2-iodoaniline (438 mg, 2 mmol), catalyst **10** (43 mg, 1 mol%), styrene (416 mg, 4 mmol) and triethylamine (606 mg, 6 mmol) and the mixture was heated at 75 °C for 6.5 h. After cooling to room temperature, the mixture was extracted into diethyl ether (30 mL), washed with water (2x 20 mL), dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The crude product was analysed by GC-MS.
MS (EI) m/z: 195 (M^+).

[37] Synthesis of *N*-(2,4,6-Trimethylphenyl)imidazole 72b

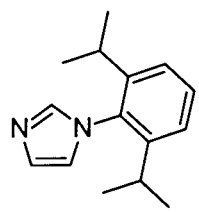


2,4,6-Trimethylaniline (25 mmol, 3.37 g), methanol (35 mL) and glyoxal (40% solution in water, 25 mmol, 3.63 mL) were added to a round-bottomed flask and stirred for 16 h. At this point the intermediate diimine condensation product was identified by tlc and GC-MS. To this suspension was added ammonium chloride (50 mmol, 2.67 g), formaldehyde solution (37%, 50 mmol, 4.05 mL) and methanol (140 mL). This solution was refluxed at 80 °C for 1 h, by which point a red solution had formed. After cooling to room temperature, phosphoric acid (85%, 3.50 mL) was then added dropwise and the mixture was refluxed for a further 4 h. The solvent was removed *in vacuo* and the viscous liquid was poured over ice (100 g), basified to pH 9 using sodium hydroxide and then extracted into

diethyl ether (3x 35 mL) and washed with water (3x 300 mL) and brine (3x 300 mL). The dark coloured solution was dried over anhydrous magnesium sulfate and the solvent removed once again leaving a viscous paste. The crude product was chromatographed over silica (1:1, ethyl acetate:petroleum spirit) to furnish the highly purified title compound as an off-white crystalline solid, 1.81 g (43%) MP: 116-118 °C, (lit.: 116-117 °C).[117]

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.33-7.37 (s, 1H, Ar-H), 7.13-7.17 (s, 1H, Ar-H), 6.88-6.92 (s, 2H, Ar-H), 6.80-6.83 (s, 1H, Ar-H), 2.25-2.28 (s, 3H, Ar-CH_3), 1.90-1.93 (s, 6H, Ar-CH_3). ^{13}C NMR (100 MHz, $CHCl_3$): δ 138.8, 137.5, 135.4, 133.4, 129.6, 129.0, 120.1, 21.0, 17.3. MS (EI) m/z: 186 (M^+).

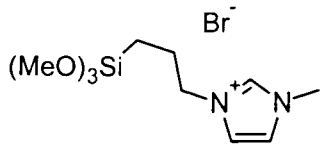
[38] Synthesis of *N*-(2,6-diisopropylphenyl) imidazole 72c



The procedure used was identical to experiment 37 (above) except 2,6-(diisopropyl)aniline (4.43 g, 25 mmol) was used in place of mesitylamine. Purification by column chromatography (1:1, ethyl acetate:petroleum spirit) yielded the product as light brown crystals, 1.71 g (30%) MP: 118-122 °C, (lit.; 122-123 °C).[117]

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.40-7.47 (m, 2H, Ar-H), 7.22-7.26 (m, 3H, Ar-H), 6.92-6.94 (t, J = 1.3 Hz, 1H, Ar-H), 2.33-2.44 (septet, J = 6.8 Hz, 2H, alkyl-CH), 1.09-1.14 (d, J = 6.8 Hz, 12H, alkyl-CH_3). ^{13}C NMR (100 MHz, $CHCl_3$): δ 146.6, 138.5, 129.9, 129.4, 123.8, 121.6, 28.2, 24.5, 24.4. MS (EI) m/z: 228 (M^+).

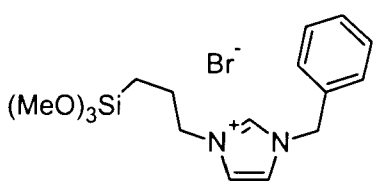
[39] 1-(Trimethoxysilyl)propyl-3-methylimidazolium bromide 73a



N-methylimidazole (0.410 g, 5 mmol) was added to a dry, round-bottomed flask under nitrogen followed by 3-(bromopropyl)trimethoxysilane (1.215 g, 5 mmol). This mixture was heated at 80 °C overnight with vigorous stirring. After cooling to room temperature, the mixture (now solid) was triturated in diethyl ether (3x 50 mL) to yield the product as a pale-yellow, viscous oil (1.377 g, 85%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 10.41-10.45 (s, 1H, Ar-H), 7.39-7.43 (s, 1H, Ar-H), 7.30-7.34 (s, 1H, Ar-H), 4.29-4.35 (t, J = 7.3 Hz, 2H, N-CH_2), 4.09-4.14 (s, 3H, N-CH_3), 3.56 (s, 9H, O-CH_3), 1.96-2.06 (p, J = 7.7 Hz, 2H, alkyl-CH_2), 0.59-0.67 (t, J = 7.7 Hz, 2H, Si-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 138.0, 123.3, 121.9, 51.9, 50.9, 36.9, 24.2, 6.0.
HRMS (EI): calculated for $C_{10}H_{21}N_2O_3Si$; 245.1316, found: 245. 1315.

[41] 1-(Trimethoxysilyl)propyl-3-benzylimidazolium bromide 73c

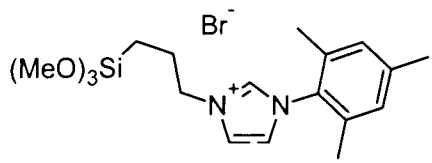


The procedure used for experiment **[39]** was followed except *N*-benzylimidazole (316 mg, 2 mmol) was used as the imidazole and the corresponding amount of 3-(bromopropyl)trimethoxysilane (482 mg, 2 mmol) was used. Trituration in diethyl ether (3x 50 mL) yielded the product as a colourless viscous oil (630 mg, 79%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 10.44-10.47 (s, 1H, Ar-H), 7.44-7.49 (m, 3H, Ar-H), 7.37-7.39 (m, 1H, Ar-H), 7.29-7.33 (m, 2H, Ar-H), 5.56-5.59 (s, 2H, benzyl-H), 4.22-4.27 (t, J = 7.3 Hz, 2H, N-CH_2), 3.47-3.50 (s, 9H, -OCH_3), 1.89-1.99 (p,

J = 7.9 Hz, 2H, alkyl-CH_2), 0.53-0.59 (t, J = 7.9 Hz, 2H, Si-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 136.9, 133.2, 129.5, 129.1, 122.2, 65.9, 53.2, 51.9, 50.7, 24.1, 15.3, 5.9. MS (ES): 321 m/z (M^+-Br).

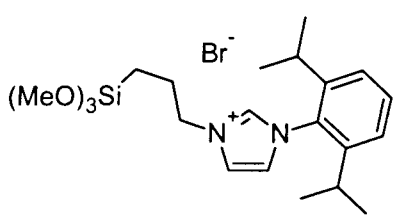
[43] 1-(Trimethoxysilyl)propyl-3-mesitylimidazolium bromide 73e*



Procedure was carried out as in experiment **[39]** except *N*-mesitylimidazole (0.930 g, 5 mmol) used as the imidazole. Trituration in diethyl ether (3x 50 mL) yielded the product as an off-white solid (MP: 120-123°C, 1.846 g, 86%).

^1H NMR (400 MHz, $CHCl_3$): δ 10.05-10.09 (s, 1H, Ar-H), 7.88-7.91 (m, 1H, Ar-H), 7.19-7.21 (m, 1H, Ar-H), 6.82-6.85 (s, 2H, Ar-H), 4.50-4.56 (t, J = 7.0 Hz, 2H, N-CH_2), 3.38-3.42 (s, 9H, O-CH_3), 2.16-2.19 (s, 3H, -CH_3), 1.88-1.99 (m, 8H, alkyl-CH_2 and Ar–CH_3 overlapping), 0.48-0.55 (t, J = 8.1 Hz, 2H, Si-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 141.1, 137.6, 134.1, 130.7, 129.8, 123.6, 123.5, 51.9, 50.7, 24.3, 21.1, 17.6, 5.6. MS (ES): 349 m/z (M^+-Br). HRMS (EI): calculated for $C_{18}H_{29}O_3N_2Si$; 349.1942, found: 349.1939.

[44] 1-(Trimethoxysilyl)propyl-3-(2',6'-diisopropylphenyl) imidazolium bromide 73f*

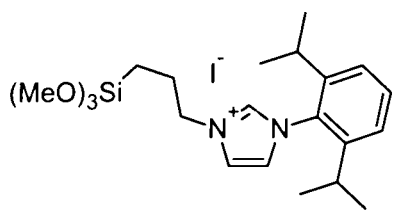


N-(2,6-diisopropylphenyl)imidazole (764 mg, 3.2 mmol) in acetonitrile (20 mL) was added to a dry, round-bottomed flask under nitrogen followed by 3-(bromopropyl)trimethoxysilane (684 mg, 3.2 mmol). This mixture was heated at 100 °C overnight. After cooling to room temperature, the solvent was removed *in*

vacuo and the crude product (now solid) was triturated in diethyl ether (3x 50 mL) to yield the product as an off-white solid (MP: 116-118°C, 1.17 g, 76%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 10.30-10.36 (s, 1H, Ar-H), 7.91-7.94 (s, 1H, Ar-H), 7.47-7.55 (m, 1H, Ar-H), 7.25-7.30 (m, 2H, Ar-H), 7.19-7.22 (m, 1H, Ar-H), 4.74-4.81 (t, J = 7.0 Hz, 2H, N-CH_2), 3.52-3.57 (s, 9H, O-CH_3), 2.19-2.30 (septet, J = 7.0 Hz, 2H, alkyl-CH), 2.04-2.14 (quintet, J = 8.1 Hz, 2H, alkyl-CH_2), 0.63-0.69 (t, J = 8.1 Hz, 2H, Si-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 145.4, 138.4, 132.0, 130.2, 124.8, 124.2, 123.2, 52.1, 50.8, 28.8, 24.5, 24.5 (shoulder), 24.2, 5.6. MS (ES): 391 m/z (M^+-Br). HRMS (EI): calculated for $C_{19}H_{35}O_3N_2Si$; 391.2411, found: 391.2401.

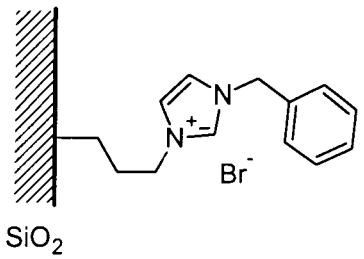
[45] 1-(Trimethoxysilyl)propyl-3-(2',6'-diisopropylphenyl)imidazolium iodide 73g*



Procedure was carried out as in experiment 44 except 3-iodopropyl trimethoxysilane (3.2 mmol, 1 eq) was employed instead of the bromide. The title compound was isolated as an orange oil (1.38 g, 96%).

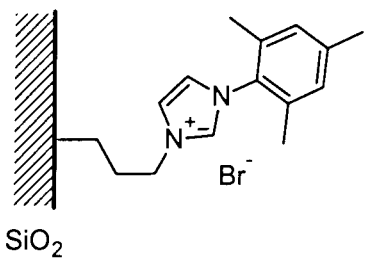
^{1}H NMR (400 MHz, $CHCl_3$): δ 9.87-9.91 (s, 1H, Ar-H), 8.01-8.05 (s, 1H, Ar-H), 7.43-7.51 (m, 1H, Ar-H), 7.20-7.27 (m, 3H, Ar-H), 4.64-4.71 (t, J = 7.0 Hz, 2H, N-CH_2), 3.46-3.54 (s, 9H, O-CH_3), 2.14-2.26 (septet, J = 6.8 Hz, 2H, alkyl-CH), 1.99-2.09 (quintet, J = 8.1 Hz, 2H, alkyl-CH_2), 1.05-1.17 (m, 12H, -CH_3), 0.57-0.65 (t, J = 8.1 Hz, 2H, Si-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 145.1, 137.0, 131.7, 129.7, 124.4, 124.3, 123.6, 51.8, 50.6, 28.4, 24.3, 24.2, 24.0, 5.2. MS (ES): 391 m/z (M^+-I).

[46] Synthesis of immobilised 1-propyl-3-benzylimidazolium bromide 74a



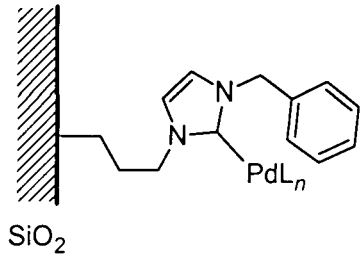
Under nitrogen, a dry round-bottomed flask was charged with 1-(Trimethoxysilyl)propyl-3-benzylimidazolium bromide **73c** (490 mg, 1.08 mmol), anhydrous toluene (60 mL) and silica gel (pre-dried, 972 mg, 16.2 mmol). The mixture was fitted with a Dean-Stark trap and refluxed for 24 h. After cooling to room temperature, the mixture was filtered and washed with anhydrous dichoromethane (3x 50 mL). The resulting white solid was dried *in vacuo* at 60 °C over phosphorous pentoxide (24 h) to yield 1.385 g of material (95 % by weight). ^{1}H NMR analysis of the dichloromethane washings showed no trace of the imidazolium salt starting material, indicating near-quantitative immobilisation. TGA analysis: see appendix.

[47] Synthesis of immobilised 1-propyl-3-mesitylimidazolium bromide 74b*



The procedure used was identical to experiment 46 except 1-(Trimethoxysilyl)propyl-3-mesitylimidazolium bromide **72e** (0.90 g, 3 mmol) was used with 2.70 g dry silica (45 mmol). The product took the form of a pale-yellow solid (3.49 g, 97% by weight). Again ^{1}H NMR confirmed the complete consumption of the imidazolium salt, indicating near-quantitative immobilisation. TGA analysis: see appendix.

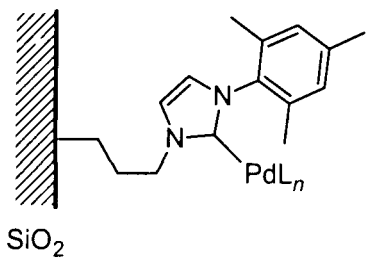
[48] Synthesis of *Bis*-benzyl NHC Catalyst 75a



Immobilised 1-propyl-3-benzylimidazolium bromide **74a** (1.00 g, 0.9 mmol) was suspended in dimethylsulfoxide (4.5 mL) and to this was added palladium (II) acetate (0.101 g, 0.045 mmol). This mixture was stirred at 60 °C for 4 h, then the temperature was increased to 100 °C for a further 30 minutes, then the mixture was allowed to cool to room temperature. The mixture was filtered, washed with dichloromethane (4x 50 mL) and finally dried *in vacuo* at 60 °C over phosphorous pentoxide (48 h) to yield a brown solid (1.04 g, 99% by weight).

TGA analysis: see appendix.

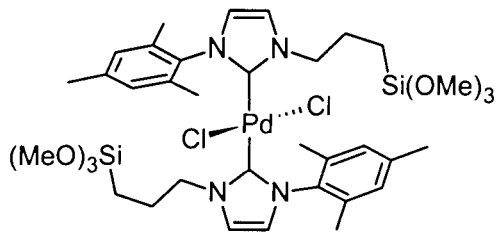
[49] Synthesis of *Bis*-mesityl NHC Catalyst 75b*



The procedure used was identical to experiment 48 except 1-(Trimethoxysilyl)propyl-3-mesitylimidazolium bromide **74b** (1.00 g, 0.72 mmol) was employed as the starting material. A brown solid (1.015 g, 97% by weight) was obtained.

TGA analysis: see appendix.

[50] *Bis*-1-[(trimethoxysilyl)propyl]-3-mesitylimidazol-2-ylidene palladium dichloride 76b*

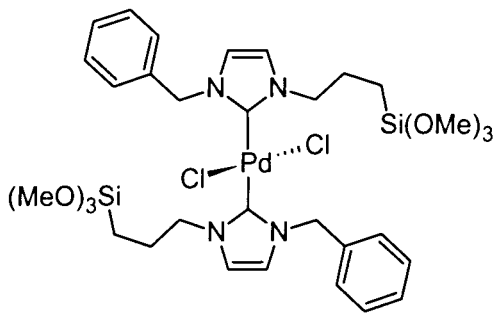


1-(Trimethoxysilyl)propyl-3-mesitylimidazolium bromide (1.287 g, 3 mmol) was added to a dry, light-protected Shlenk tube under nitrogen. To this was added silver (I) oxide (0.348 g, 1.5 mmol) and anhydrous chloroform (7.5 mL) and the resulting mixture was stirred at room temperature overnight. The mixture was carefully removed under continuous nitrogen flow, by pipette and filtered through celite directly into another dry, light-protected Shlenk tube under nitrogen (an extra 2.5 mL of anhydrous chloroform was used to dissolve any product remaining in the original vessel). The white precipitate was discarded. *Bis*-(benzonitrile)palladium (II) dichloride (0.504 g, 1.3 mmol) was added gradually and the mixture was stirred overnight. The mixture (now bright-yellow) was again filtered through celite and the solvent removed *in vacuo* to yield the crude product. Purification was accomplished by trituration with anhydrous diethyl ether (3x 20 mL), yielding the title compound as a yellow solid (0.530 g, 47%, mixture of *trans-syn-* and *trans-anti-* rotamers).

^{1}H NMR (400 MHz, $CHCl_3$): δ 6.95-7.00 (m, 3H, Ar-H), 6.91-6.93 (m, 1H, Ar-H imid.), 6.81-6.86 (m, 2H, Ar-H), 6.69-6.72 (m, 1H, Ar-H), 6.62-6.66 (m, 1H, Ar-H), 4.54-4.70 (m, 2H, alkyl-CH_2, *syn-* isomer), 4.11-4.26 (m, 2H, alkyl-CH_2, *anti-*isomer), 3.56-3.60 (s, 18H, OCH_3), 2.41-2.48 (s. 3H, p-CH_3, *syn*-isomer), 2.34-2.38 (s, 3H, p-CH_3, *anti*-isomer), 2.15-2.30 (m, 8H, alkyl-CH_2, *syn*-isomer and o-CH_3, *syn*-isomer overlapping), 1.85-1.94 (m, 8H, alkyl-CH_2, *anti*-isomer and o-CH_3, *anti*-isomer overlapping), 0.79-0.95 (m, 2H, alkyl-CH_2, *syn*-isomer), 0.45-0.53 (m, 2H, alkyl-CH_2, *anti*-isomer). ^{13}C NMR (100 MHz, $CHCl_3$): δ 170.9, 170.5, 138.4, 137.5, 137.4, 136.9, 136.8, 136.5, 136.2, 136.0, 135.7, 135.6, 128.88, 128.83, 128.79, 128.75, 122.65, 122.55, 122.4, 122.25, 121.0, 120.9, 120.85, 120.75, 53.28, 53.1, 53.03, 52.87, 50.7, 24.45, 24.3, 24.1, 24.0, 21.35, 21.08,

19.65, 19.23, 19.13, 19.0, 18.95, 18.88, 18.7, 18.55, 6.44, 6.39, 6.1, 6.07. Note: duplication of all signals observed as a result of *syn*- and *anti*-isomerism. MS (EI) m/z: 835 (M^+-Cl). HRMS (EI): calculated for $C_{36}H_{56}O_6N_4Si_2Pd$; 870.2161, found: 870.2161.

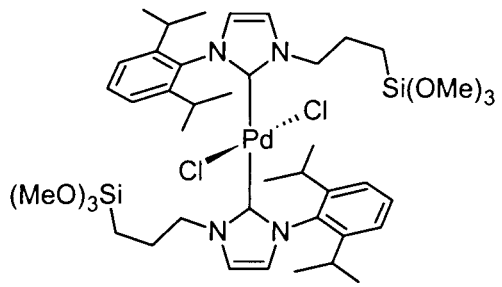
[51] *Bis*-1-[(trimethoxysilyl)propyl]-3-benzylimidazol-2-ylidene palladium dichloride 76a*



As experiment 50 except 1-(trimethoxysilyl)propyl-3-benzylimidazolium bromide **73b** (0.399 g, 1 mmol) was used as the imidazolium salt (adjusting the quantities of the other reagents according to this stoichiometry). The title compound was obtained as a bright yellow solid (0.205 g, 56%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.15-7.50 (m, 14H, Ar-H), 5.49-5.82 (m, 4H, benzyl-CH_2, *syn*- and *anti*-isomers), 4.32-4.49 (m, 4H, alkyl-CH_2, *syn*- and *anti*-isomers), 3.39-3.55 (m, 18H, -OCH_3, several overlapping signals), 2.02-2.35 (m, 4H, alkyl-CH_2, *syn*- and *anti*-isomers), 0.63-0.89 (m, 4H, alkyl-CH_2, *syn*- and *anti*-isomers). ^{13}C NMR: Not reported. HRMS (EI): calculated for $C_{32}H_{48}O_6N_4Si_2Pd$; 814.1535, found: 814.1537.

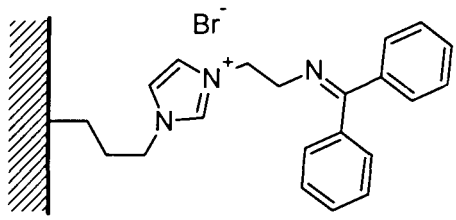
[52] *Bis*-1-[(trimethoxysilyl)propyl]-3-(2',6'-diisopropylphenyl)imidazol-2-ylidene palladium dichloride 76c*



As experiment 50 except 1-(trimethoxysilyl)propyl-3-(2',6'-diisopropylphenyl) imidazolium bromide **73f** (0.235 g, 0.5 mmol) was used as the imidazolium salt (adjusting the quantities of the other reagents according to this stoichiometry). The title compound was obtained as a dull-yellow solid (0.112 g, 47%).

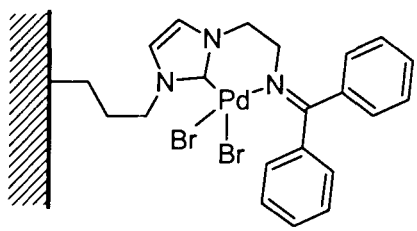
^{1}H NMR (400 MHz, $CHCl_3$): δ 7.26-7.36 (m, 6H, Ar-H), 6.89-7.08 (m, 2H, Ar-H), 6.65-6.81 (m, 2H, Ar-H), 4.67-4.89 (m, 2H, alkyl-CH_2, *syn*-isomer), 4.05-4.39 (m, 2H, alkyl-CH_2, *anti*-isomer), 3.43-3.63 (m, 18H, -OCH_3), 2.80-3.01 (m, 2H, alkyl-CH_2, *syn*-isomer), 2.52-2.73 (m, 2H, alkyl-CH_2, *anti*-isomer), 2.20-2.38 (m, 2H, alkyl-CH, *syn*-isomer), 1.73-1.84 (m, 2H, alkyl-CH, *syn*-isomer), 0.75-1.41 (m, 28H, alkyl-CH_3 and alkyl-CH_2). ^{13}C NMR: Not reported. HRMS (EI): calculated for $C_{42}H_{68}O_6N_4Si_2Pd$; 954.3089, found: 954.3090.

[53] Synthesis of supported iminoalkyl NHC catalyst precursor 86*



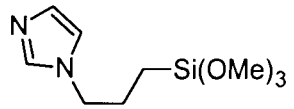
3-*N*-propylimidazole-functionalised silica gel (1.00 g, 1 mmol/ g) was dried at 60 °C over phosphorous pentoxide under reduced pressure and then suspended in anhydrous toluene (30 mL). To this was added *N*-(bromoethyl)diphenyl imine **83** (0.288 g, 1 mmol) and the mixture was refluxed for 20 h. After cooling to room temperature, the mixture was filtered under nitrogen and washed with anhydrous chloroform (3x 50 mL) and anhydrous dichloromethane (4x 50 mL) and dried under reduced pressure at 60 °C over phosphorous pentoxide for 24 h. The product appeared as a yellow solid (86% by weight).

[54] Synthesis of supported iminoalkyl NHC catalyst 80*



To a suspension of immobilised iminoalkyl imidazolium salt **86** (0.302 g, 0.25 mmol) in dry, degassed acetonitrile (5 mL) was added palladium (II) acetate (0.070 g, 0.31 mmol). The mixture was refluxed overnight, then cooled to room temperature, filtered under nitrogen and washed with dry chloroform (3x 10 mL) and dry dichloromethane (3x 10 mL) to yield the metallated complex **72** (0.316g) as a black solid.

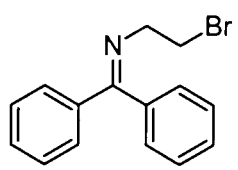
[55] *N*-(trimethoxysilyl)propylimidazole 82



Sodium hydride (60% dispersion in mineral oil, 0.80 g, 20 mmol) was washed with anhydrous hexane (3x 20 mL) and then suspended in anhydrous tetrahydrofuran (30 mL) in a round-bottomed flask under nitrogen and cooled to 0 °C. To this a solution of imidazole (1.36 g, 20 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise and the mixture was allowed to warm up to room temperature with stirring, until no more effervescence was observed. Then 3-iodopropyltrimethoxysilane (3.91 mL, 20 mmol) was added dropwise and the mixture was allowed to stir at room temperature for 20 h. The mixture was concentrated *in vacuo*, then dissolved in dichloromethane (40 mL) and filtered through celite. The solvent was removed *in vacuo*, chloroform (40 mL) was added and the mixture was once again filtered through celite. The product was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to yield a pale-yellow oil (2.25 g, 54%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.43-7.47 (s, 1H, Ar-H), 7.01-7.05 (s, 1H, Ar-H), 6.86-6.90 (m, 1H, Ar-H), 3.84-3.95 (m, 2H, alkyl-CH_2), 3.42-3.55 (s, 9H, -OCH_3), 1.75-1.90 (m, 2H, alkyl-CH_2), 0.45-0.59 (m, 2H, alkyl-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 137.2, 129.3, 118.8, 50.6, 49.1, 24.7, 6.1. MS (ES): 230 m/z (M^+).

[56] *N*-(Bromoethyl)diphenyl imine 83

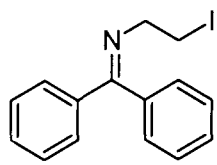


Bromoethylamine hydrobromide (10 g, 48.8 mmol) was added to a solution of benzophenone imine (8.85 g, 48.8 mmol) in anhydrous dichloromethane (200 mL)

and the mixture was stirred at room temperature for 24 h. After filtration, the resulting solution was combined with sodium bicarbonate (10 % w/v, 200 mL) and the emulsion was filtered under gravity. The organic layer was removed and the aqueous layer washed with dichloromethane (2x 50 mL). The organic layers were combined, washed with water (2x 50 mL), dried over anhydrous magnesium sulfate and then concentrated *in vacuo* to yield the title compound as a colourless crystalline solid (7.15 g, 51%), MP: 66-67 °C (lit.: 67 °C).[134]

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.61-7.66 (m, 2H, Ar-H), 7.31-7.50 (m, 6H, Ar-H), 7.17-7.21 (m, 2H, Ar-H), 3.76-3.82 (t, J = 5.7 Hz, 2H, alkyl-CH_2), 3.66-3.71 (t, J = 5.7 Hz, 2H, alkyl-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 170.1, 139.6, 136.7, 130.4, 128.8, 128.7, 128.6, 128.2, 127.9, 55.3, 33.6. MS (EI) m/z: 288 (M^+).

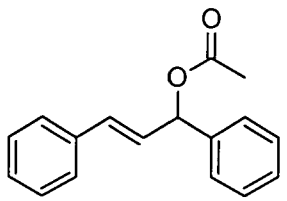
[57] *N*-(Iodoethyl)diphenyl imine 83b



Potassium iodide (2.32 g, 20 mmol) was suspended in acetone (50 mL) in a round bottomed flask. Then *N*-(Bromoethyl)diphenyl imine (0.576 g, 2 mmol) was added sequentially. The mixture was then heated at reflux for 24 h, allowed to cool to room temperature, filtered through celite and concentrated *in vacuo* to yield the title compound as a pale-yellow oil (0.63 g, 94%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.67-7.72 (m, 2H, Ar-H), 7.33-7.52 (m, 6H, Ar-H), 7.19-7.23 (m, 2H, Ar-H), 3.79-3.84 (t, J = 6.4 Hz, 2H, alkyl-CH_2), 3.45-3.51 (t, J = 6.4 Hz, 2H, alkyl-CH_2). ^{13}C NMR (100 MHz, $CHCl_3$): δ 169.6, 139.6, 136.6, 130.4, 128.8, 128.75, 128.7, 128.3, 127.9, 55.6, 7.6. MS (EI) m/z: 335 (M^+).

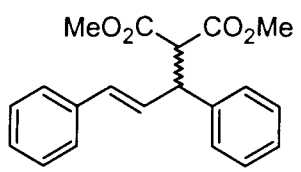
[58] 1,3-Diphenyl-2-propenyl acetate 87



Diphenylprop-1-enol (4.45 g, 21.15 mmol), dimethylaminopyridine (1 crystal, cat.), and pyridine (10 mL) were added to a round-bottomed flask and cooled to 0 °C with stirring. To this was added dropwise acetic anhydride (6 mL, 63.45 mmol) and the mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed with sodium bicarbonate (sat., 3x 200 mL) and water (2x 100 mL) and the solvent removed under reduced pressure. The resulting viscous oil was purified by column chromatography (1:20, ethyl acetate:pertroleum spirit) to yield a colourless oil (4.45 g, 84%).

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.25-7.49 (m, 10H, Ar-H), 6.66-6.72 (d, J = 15.7 Hz, 1H, vinyl C-H), 6.49-6.50 (d, J = 7.1 Hz, 1H, alkenyl C-H), 6.37-6.44 (q, J = 15.7 Hz, 1H, alkenyl C-H), 2.17-2.18 (s, 3H, acetyl-CH_3). ^{13}C NMR (100 MHz, $CHCl_3$): δ 169.9, 139.1, 136.0, 132.5, 128.55, 128.5, 128.1, 128.0, 127.4, 126.95, 126.6, 76.1, 21.3. MS (EI) m/z: 252 (M^+).

[59] 1,3-Diphenylprop-1-enyl dimethylmalonate 88



Sodium hydride (60% dispersion in mineral oil, 0.085 g, 2 mmol) was washed with anhydrous hexane (2x 5 mL) and then suspended in anhydrous tetrahydrofuran (5 mL) in a round-bottomed flask under nitrogen and cooled to 0 °C. To this was added a solution of dimethylmalonate (0.264 g, 2 mmol) in anhydrous THF (5 mL). After effervescence had ceased, the sodium salt of dimethylmalonate was transferred to a dry Shlenk tube containing catalyst **80**

(0.041 g, 3 mol%) and 1,3-diphenyl-2-propenyl acetate in THF (5 mL) under nitrogen. This mixture was heated at 60 °C for 18 h and then analysed by GC-MS, which confirmed the presence of the title compound (21.1 min, M^+: 324). Purification was then achieved by column chromatography (eluting with hexane and ethyl acetate - 8.5: 1.5) to yield 1,3-Diphenylprop-1-enyl-3-dimethylmalonate **79** as a pale yellow oil (0.078 g, 24%).

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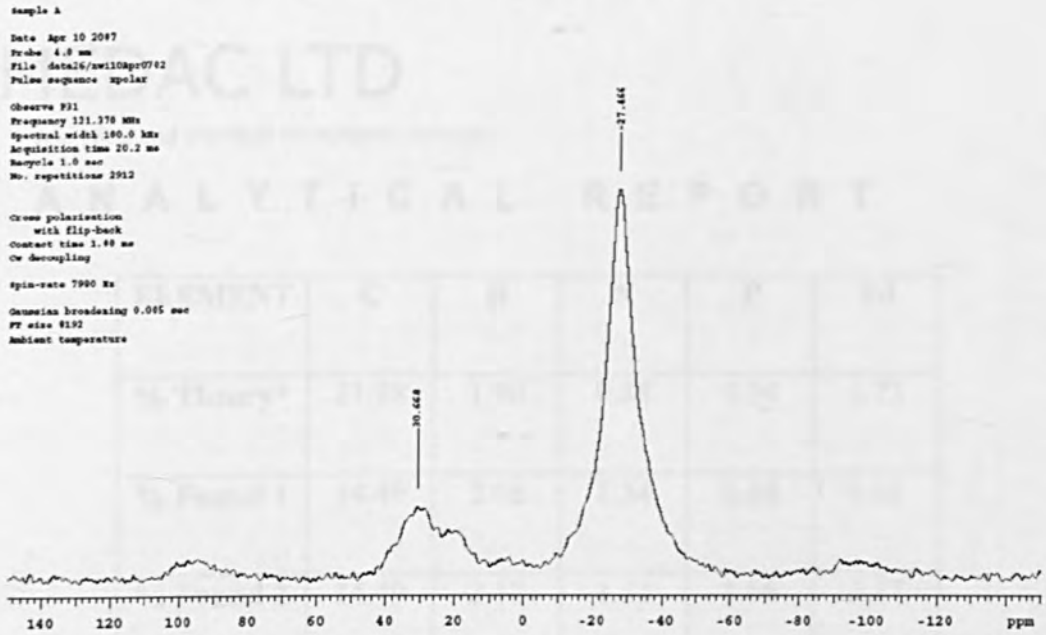
Appendices

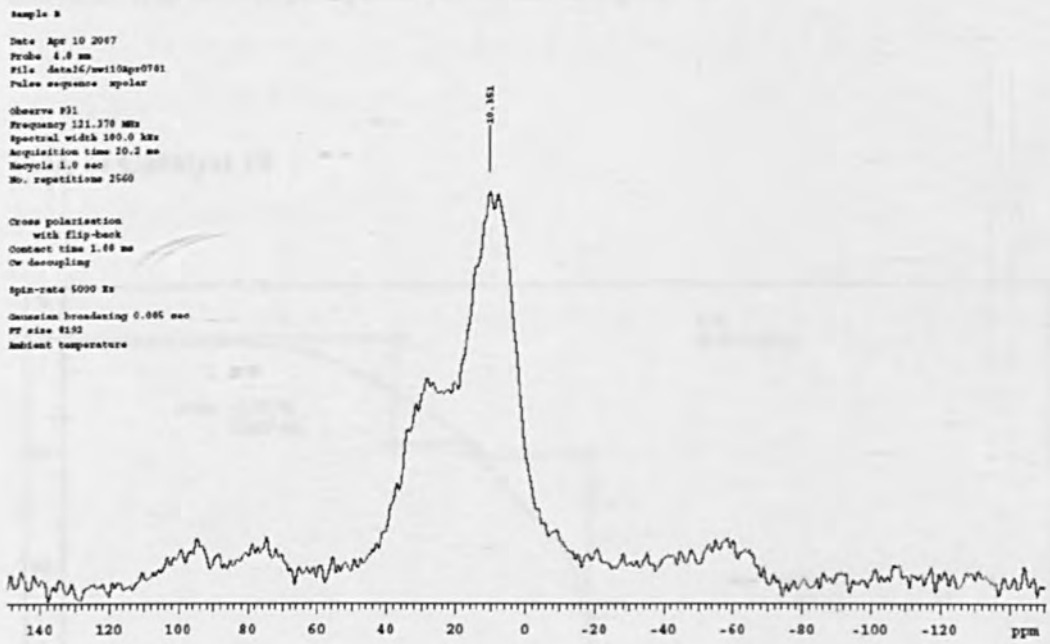
Contents

Published Work;

Solid State ^{31}P NMR Analysis Immobilised Phosphine 34



Solid state ^{31}P NMR Analysis of Catalyst 10



Elemental Analysis of Catalyst 10

MEDAC LTD

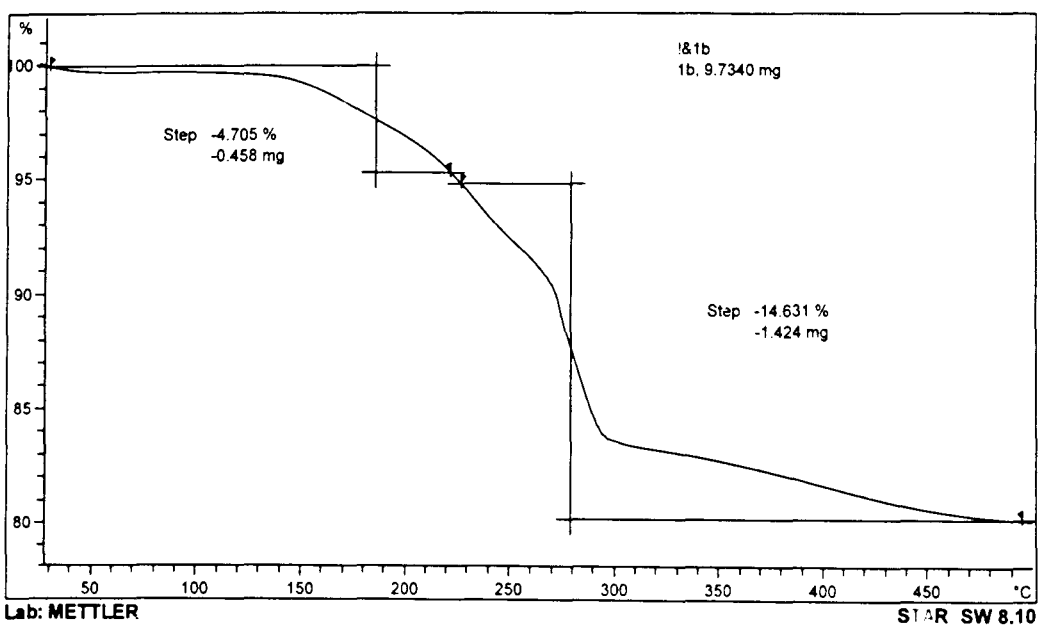
Analytical and chemical consultancy services

A N A L Y T I C A L R E P O R T

ELEMENT	C	H	N	P	Pd
% Theory*	21.88	1.90	0.88	3.94	6.73
% Found 1	14.49	2.06	1.34	1.68	6.81
% Found 2	14.49	2.17	1.32	1.66	6.87

* Theoretical ratios based on 100% immobilisation of ligand **34** and 100% conversion to the *bis*-phosphine palladium complex **10**.

TGA of Catalyst 10



Elemental Analysis of Catalyst 75b

MEDAC LTD

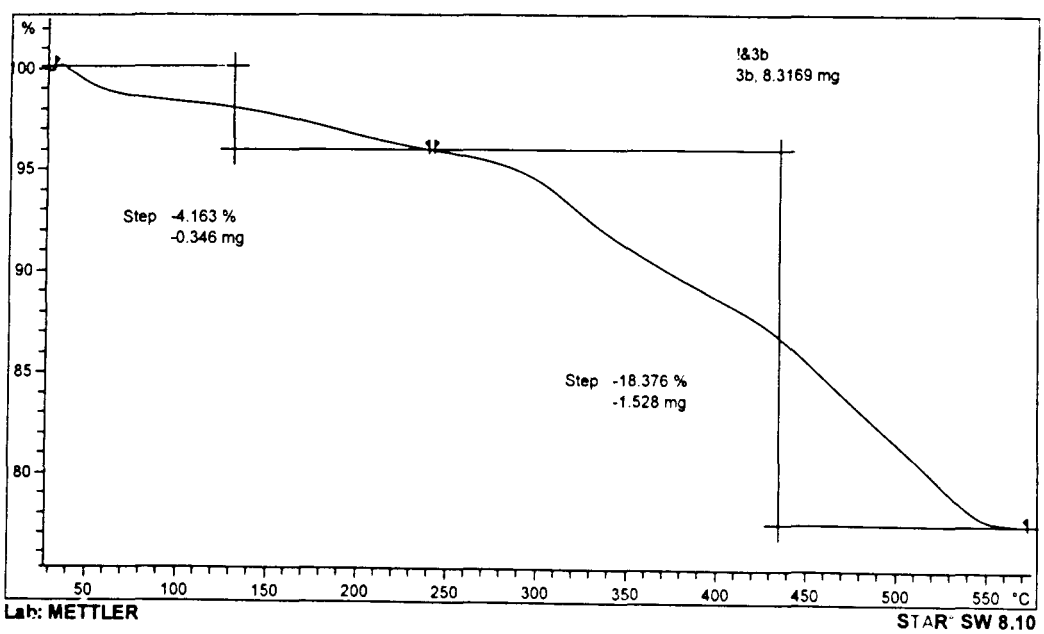
Analytical and chemical consultancy services

A N A L Y T I C A L R E P O R T

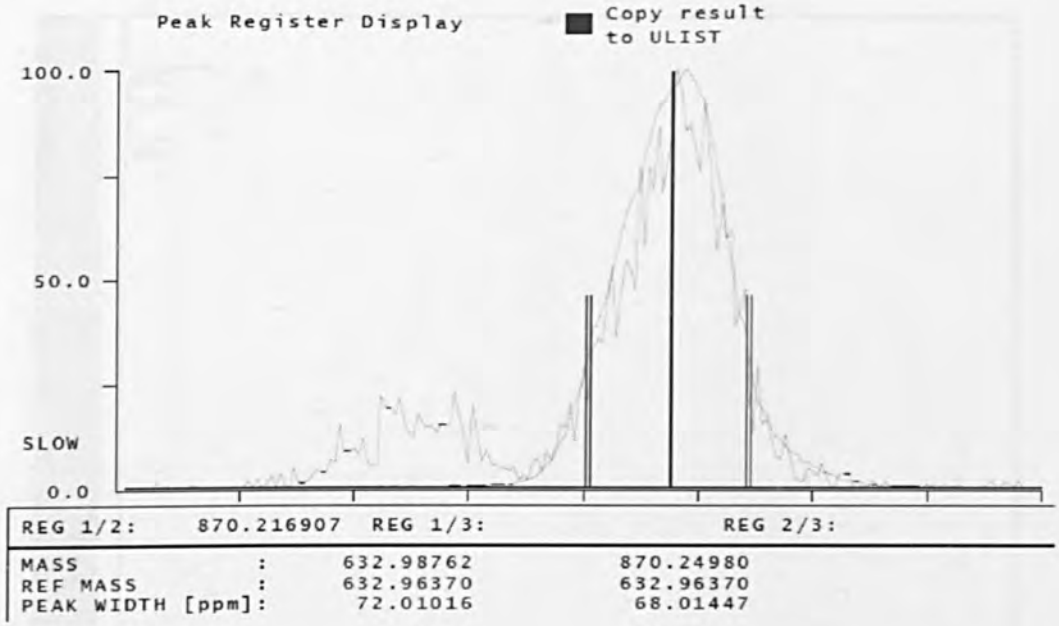
ELEMENT	C	H	N	P	Pd
% Theory*	16.20	1.80	2.52		4.77
% Found 1	14.60	2.16	1.32		6.86
% Found 2	14.59	2.15	1.33		6.89

* Theorectical ratios ased on 100% immobilisation of ligand **73b** and 100% conversion to *bis*-NHC complex **75b**.

TGA of Catalyst 75b



HRMS of Catalyst 77b



Mass	Theoretical Mass	Delta [ppm]	RDB	Composition
870.2161	870.2161	-0.0	7.0	$C_{32}H_{50}C_{11}N_2Cl_1{}^{104}Pd_1Si_3$
	870.2161	0.0	12.5	$C_{31}H_{53}C_6N_8Cl_1{}^{104}Pd_1Si_3$
	870.2161	0.0	25.0	$C_{47}H_{43}C_{11}N_4Cl_1Si_2$
	870.2161	-0.0	30.0	$C_{46}H_{40}C_6N_6Cl_2Si_1$
	870.2161	0.0	30.5	$C_{41}H_{37}C_6N_{11}Cl_1Si_2$
	870.2161	0.0	27.0	$C_{44}H_{47}C_7N_6{}^{104}Pd_1$
	870.2161	-0.0	17.5	$C_{36}H_{50}C_7N_{11}Cl_2{}^{104}Pd_1Si_2$
	870.2161	-0.0	12.0	$C_{36}H_{56}C_6N_4Cl_2{}^{104}Pd_1Si_2$

Elemental Analysis of Catalyst 77b

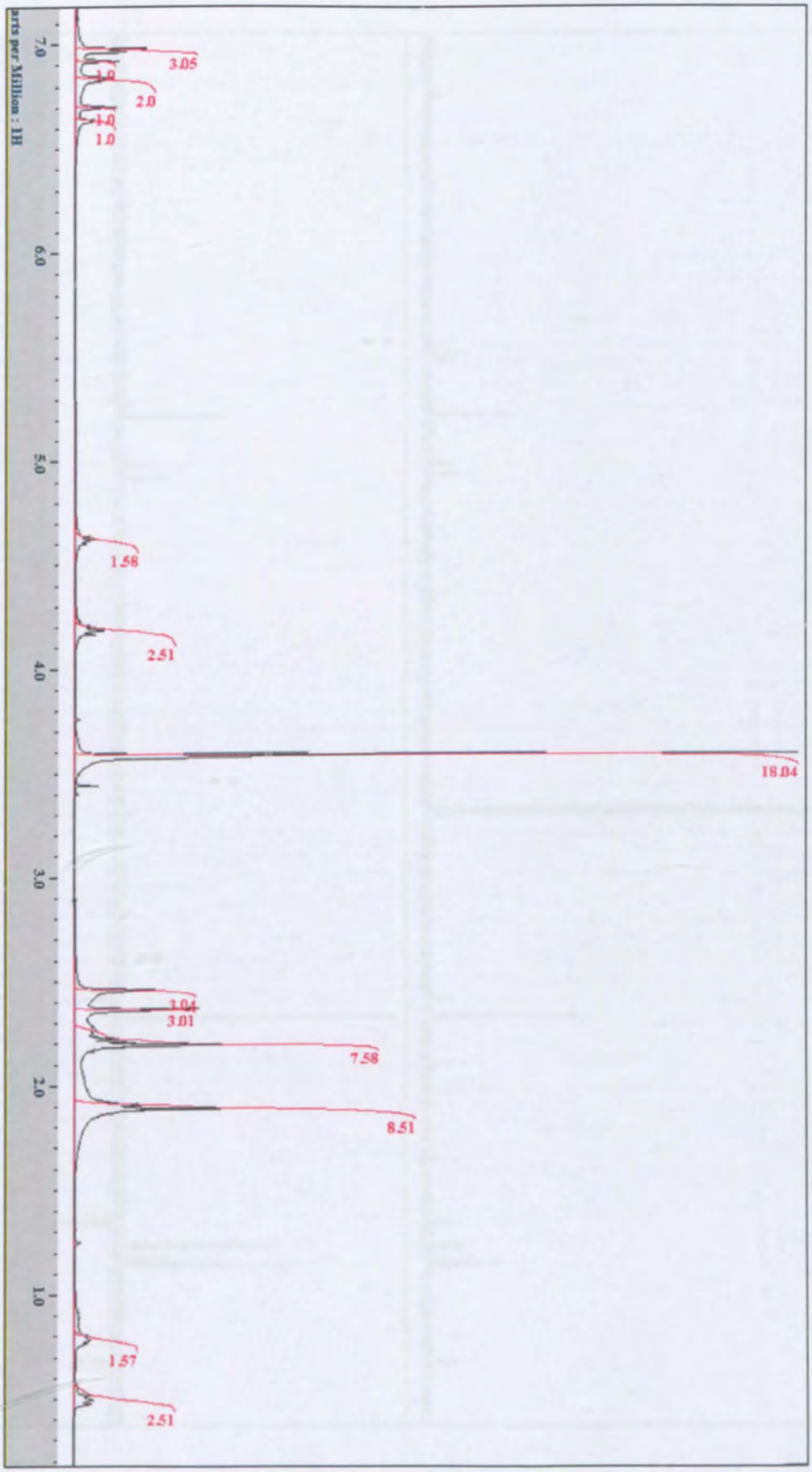
MEDAC LTD

Analytical and chemical consultancy services

A N A L Y T I C A L R E P O R T

ELEMENT	C	H	N	Pd
% Theory	49.45	6.46	6.40	12.17
% Found 1	47.75	6.19	7.02	11.51
% Found 2	47.83	6.41	6.93	11.67

^{1}H NMR of Catalyst **77b**



^{13}C and ^{13}C DEPT NMR of Catalyst **77b**