Transformations Mediated by Palladium-(*N*-heterocyclic)Carbene Complexes

A thesis submitted in partial fulfilment of the requirements for the degree of

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By

ISRAEL CONESA LERMA

University College London
Christopher Ingold Laboratories
London
WC1H 0AJ

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

DECLARATION

I hereby declare that the work described in this thesis is the work of the author and has not been previously submitted to this or any other university for any other degree.

Israel Conesa Lerma

December 2007

ACKNOWLEDGEMENTS

I am finding most difficult to account for everyone that directly or indirectly have made this possible. Indeed, this is ultimately fruit of my own labour in the lab for the last three years, but I could only be writing these lines having been given the chance and an education to do so.

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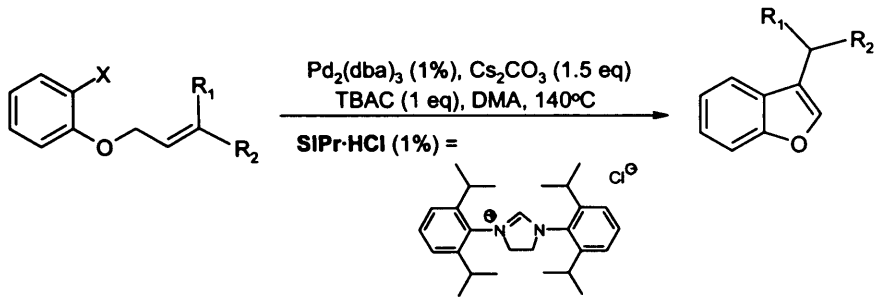
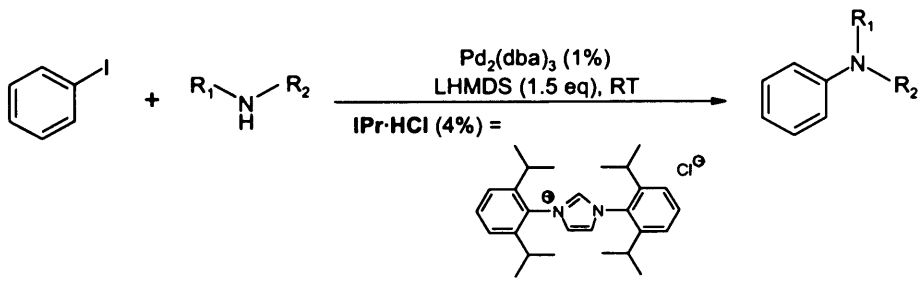
ABSTRACT

The synthesis of 3-substituted benzofurans by the intramolecular Heck cyclisation of 2-chlorophenyl allyl ethers has proved unsuccessful using a palladium/imidazolium salt protocol previously developed in our group. A palladium deallylation process was at play in this case, although both 2-iodo- and 2-bromophenyl derivatives do react under similar conditions. Similarly, the synthesis of indoles has been achieved with the same pattern of reactivity shown by benzofurans.



The mild amination of aryl iodides with a palladium/imidazolium system has been achieved using the hindered base lithium hexamethyldisilazide (LHMDS). In the first instance, only secondary amines were found to react, whilst a limited selection of primary amines investigated, either failed or needed more forcing conditions with concomitant formation of bisarylated by-product. Further optimisation studies were conducted with the aid of computer software for statistical design of experiments (DoE). A sterically hindered aryl iodide and a less demanding substrate were studied against *N*-methylbenzylamine. The resulting optimum conditions have benefited this protocol by allowing a primary amine, *N*-hexylamine, to react under mild conditions, although bisarylation was still observed.



CONTENTS

ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
DCM	Dichloromethane
dpe	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DMA	*N,N*-Dimethylacetamide
DME	Ethylene glycol dimethyl ether
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulphoxide
eq.	Equivalents
IAd·HCl	1,3-Bis(1-adamantyl)imidazolium chloride
I^{t}Bu·HCl	1,3-Bis-*tert*-butylimidazolium chloride
I^{t}BuPhe·HCl	1-*tert*-Butyl-3-phenethylimidazolium bromide
I^{t}BuPhp·HCl	1-*tert*-Butyl-3-(3-phenylpropyl)imidazolium bromide
IMes·HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
IPr·HCl	1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolium chloride
I^{i}Pr·HCl	1,3-Bis-*iso*-propylimidazolium chloride
KO^{t}Bu	Potassium *tert*-butoxide
KHMDS	Potassium hexamethyldisilazide
LHMDS	Lithium hexamethyldisilazide
MeOH	Methanol
MS	Mass Spectroscopy
m/z	Mass to Charge Ratio
NHCs	*N*-Heterocyclic carbenes
NHMDS	Sodium hexamethyldisilazide
NMP	*N*-Methyl-2-pyrrolidone
$Pd(SIPr)_2$	1,3-Bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazolyl palladium (0)
RT	Room Temperature
SIAd·HCl	1,3-Bis(1-adamantyl)-4,5-dihydroimidazolium chloride
SI^{t}Bu·HCl	1,3-Bis-*tert*-butyl-4,5-dihydroimidazolium chloride
SIMes·HCl	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride
$SIPr·BF_4$	1,3-Bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazolium tetrafluoroborate

SIPr·HCl	1,3-Bis(2,6-di-*iso*-propylphenyl)-4,5-dihydroimidazolium chloride
SI^{i}Pr·HCl	1,3-Bis-*iso*-propyl-4,5-dihydroimidazolium chloride
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TBAI	Tetrabutylammonium iodide
TBAN	Tetrabutylammonium nitrate
THF	Tetrahydrofuran
TLC	Thin layer chromatography

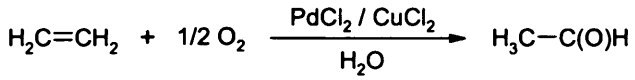
Chapter One : INTRODUCTION

Palladium (Pd) was discovered in 1803 by William Hyde Wollaston, who named it after the asteroid *Pallas*. Palladium is commercially extracted from nickel-copper deposits and has been found to have many technological applications ranging from catalytic converters in the automobile industry to components in electronic devices, as well as in utensils for dentistry and surgery.

Pd, atomic number 46, is a white/silver metal belonging to Group 10 of the Periodic Table, together with Ni and Pt. It is chemically inert except to strong acids such as sulphuric and nitric acid, and it has the ability to absorb 900 times its own volume of hydrogen at room temperature. The most abundant isotopes are; ^{105}Pd, ^{106}Pd and ^{108}Pd, although the total number of naturally occurring isotopes is six.

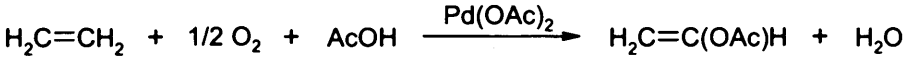
Pd generally prefers lower oxidation states [$Pd^{(0)}$, $Pd^{(II)}$ and $Pd^{(IV)}$], although a higher state, $Pd^{(VI)}$, has been achieved recently.[1] The ability to move between oxidation states is key for its catalytic properties.

For many years, the main application of Pd was as a heterogeneous catalyst for the hydrogenation of unsaturated bonds. The development of homogeneous Pd catalysts allowed for the discovery of new applications, most notably, the Wacker process (formation of acetaldehyde from ethylene) in 1959 (*Scheme 1.1.*).[2]



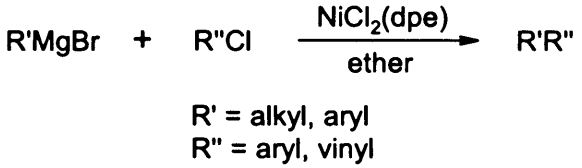
Scheme 1.1.

Soon after, in 1960, Moiseev discovered the formation of vinyl acetate by acetoxylation of ethylene, using $Pd(OAc)_2$ (*Scheme 1.2.*).



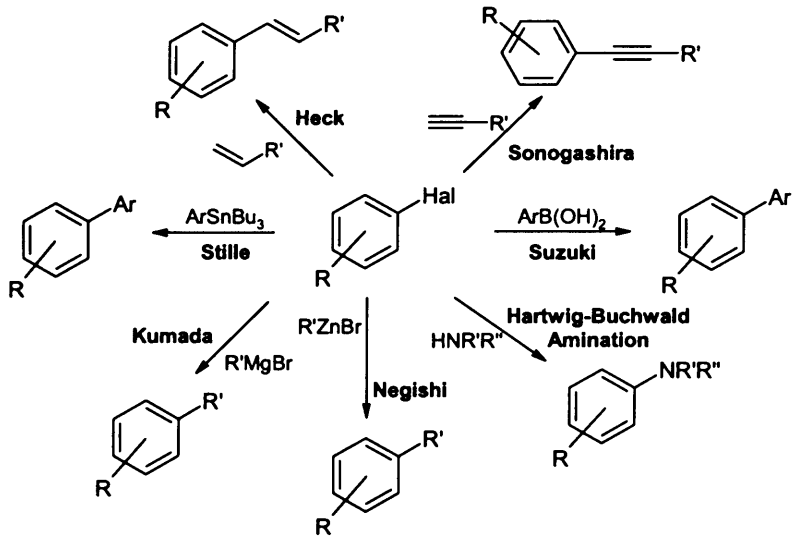
Scheme 1.2.

In the late 1960s and early 1970s, a new application for Pd was found away from reductions and oxidations and Pd catalysed cross-coupling and similar reactions were born. This was possible through previous work conducted by Kumada and Tamao on Ni catalysed cross-coupling reactions of Grignard reagents (*Scheme 1.3.*).[3-5]



Scheme 1.3. Original conditions found by Kumada and Tamao.

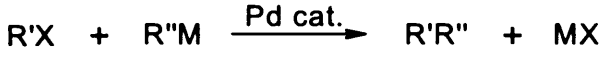
To this day, Pd has become a very powerful and versatile tool in organic chemistry not just because of the range of bond forming reactions it can promote, i.e. *C-C*, *C-N* and *C-O* (*Scheme 1.4.*), but also because it does so with great functional group tolerance allowing for the assembly of complex molecules featuring multiple functionalities.[6,7]



Scheme 1.4. Pd catalysed transformations.

1.1. *CROSS-COUPLING REACTIONS*

The term "cross-coupling" refers to the formation of *C-C* bonds and where one of the two reaction substrates is an organometallic species, RM, and the other contains a halide or *pseudo*-halide leaving group, X (*Scheme 1.5.*). Thus, strictly, the Heck and aryl amination reactions do not belong to this group of transformations, since an organometallic partner is not involved, yet they are often included due to their generally common mechanistic features.



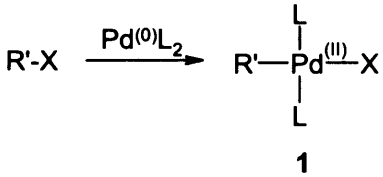
Scheme 1.5.

It must be emphasised that Ni, before Pd, served as a platform for what today is envisaged as a typical cross-coupling reaction, i.e. catalytic quantities of metal, with ligands in a mechanistic cycle, comprised of individual and well defined steps: oxidative addition, transmetalation and reductive elimination. Generally, Pd offers superior overall reactivity and stereoselectivity, reduced toxicity and is less prone to side reactions. Although Ni is less expensive and may be considered should reactivities be similar.

1.1.1. Catalytic Cycle

The general mechanistic vision of a Pd cross-coupling cycle consists of three main steps:

Oxidative Addition. A low valent and coordinatively unsaturated Pd species, typically $Pd^{(0)}$, reacts with an organic halide or *pseudo*-halide, R'X, cleaving this bond and forming two new ones (*Scheme 1.6.*). Two non-bonding orbitals of Pd are now involved, resulting in an increase of oxidation state of two. Thus the Pd centre becomes fully saturated.



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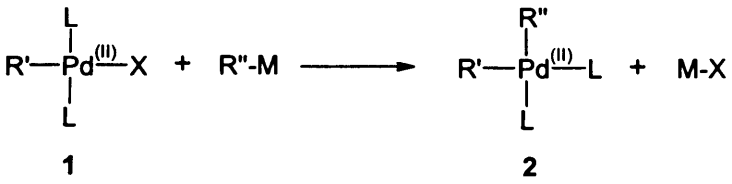
Scheme 1.6.

There are two mechanistic possibilities for oxidative addition which differ in the nature of the transition state. A one or two electron transfer from the Pd centre to the organic halide or pseudo-halide, in the form of a radical or nucleophilic attack, could give way to a charged ionic transition state, whilst a concerted mechanism could lead to a three-centre transition state.

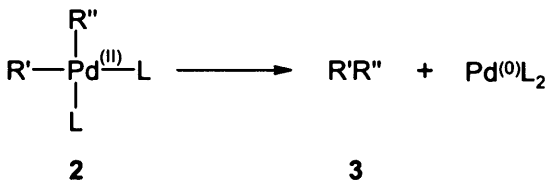
The order of reactivity ArI > ArBr > ArCl correlates with the strength of the Ar-X bond, thus chloroarenes are highly inert and reluctant to add to Pd centres through oxidative addition.[8]

Transmetallation. Intermediate **1** reacts with organometallic compounds or hydrides of main group metals, R"M or MH, exchanging R" or H for X (*Scheme 1.7.*). The driving force for this step is the difference in electronegativity between the metal and Pd.



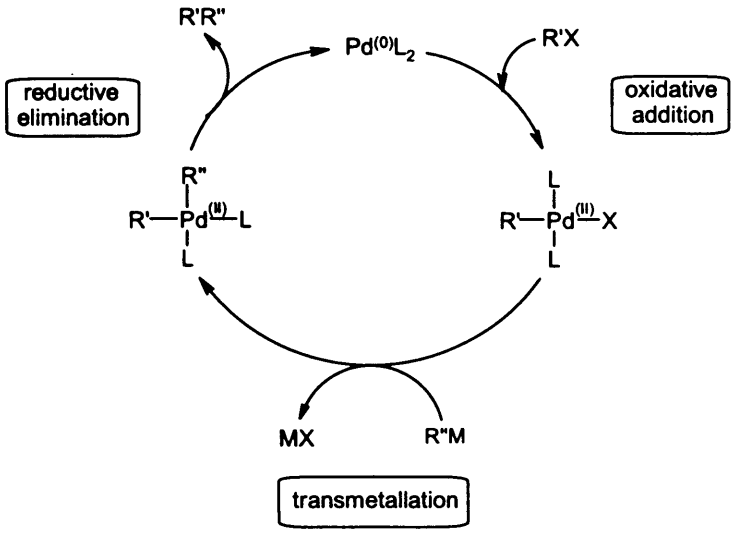
Scheme 1.7.

Reductive Elimination. R' and R" couple together forming the cross-coupled product **3** (*Scheme 1.8.*). For this to occur, these groups must be mutually *cis* but, if they are *trans* in the original complex **2**, rearrangement must take place prior to reductive elimination. Finally, the original $Pd^{(0)}$ species is liberated and able to restart the catalytic cycle.



Scheme 1.8.

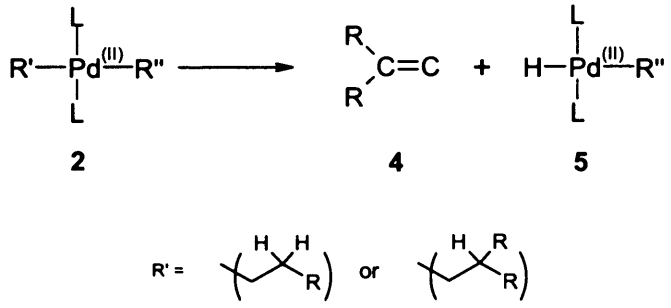
A representation of the full cycle is depicted below (*Scheme 1.9.*).



Scheme 1.9. Cross-coupling catalytic cycle.

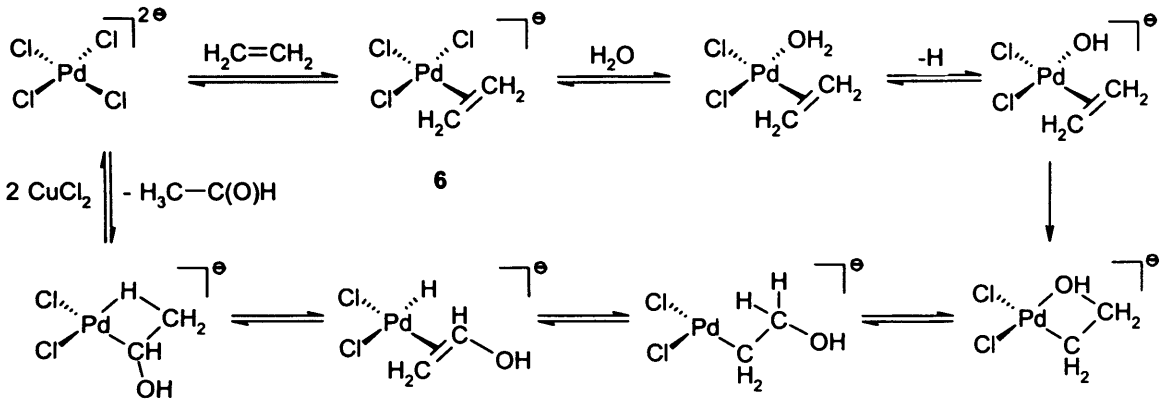
Two other reactions that may sometimes appear and interfere with the above cycle are:

β-Hydride Elimination. This is in direct competition with reductive elimination and occurs when the organic halide in complex **2** features a hydrogen atom on a carbon β to the metal (*Scheme 1.10.*). The result is an alkene **4** and a Pd hydride species **5**. The hydrogen atom must be *cis* to the metal and the reaction is favoured by *trans* geometries of the reactants in complex **2**. This reaction is partly responsible for making alkyl halides challenging substrates for cross-coupling reactions.



Scheme 1.10.

Nucleophilic attack to coordinated species. The effect of Pd on unsaturated compounds such as alkenes, arenes and alkynes renders them available for nucleophilic attack due to a decrease of their electron density. A typical example which exhibits this phenomenon has been already mentioned in the form of the Wacker process. The attack of the nucleophile (OH^-) on **6** occurs either internally or externally depending upon the concentration of chloride. The scheme below represents the former and is typical of the actual industrial process (*Scheme 1.11.*).

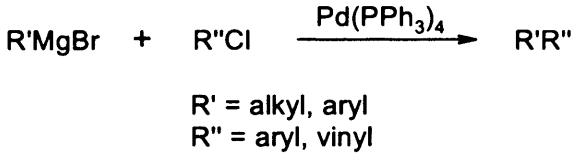


Scheme 1.11.

1.1.2. Examples of Palladium Catalysed Cross Coupling

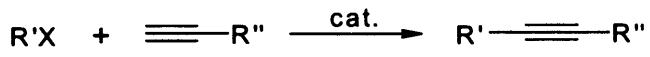
Cross-coupling reactions are varied and some of the most important ones are:

Kumada. First reported in 1972 using Ni by Kumada[3] and later extended to Pd by Murahashi,[9] this type of cross-coupling permits the coupling of organohalides to Grignard reagents. Its applicability is inferior to that of other cross-coupling reactions as it is incompatible with substrates bearing functionalities sensitive to Grignard reagents.



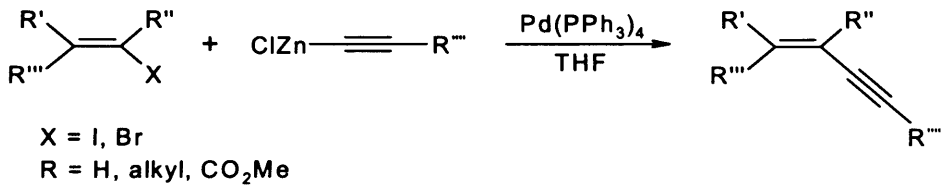
Scheme 1.12.

Sonogashira.[10] An organic halide reacts with a cupric alkyne, formed *in situ* from a terminal alkyne, a copper cocatalyst and a base, typically a tertiary amine (*Scheme 1.13.*).



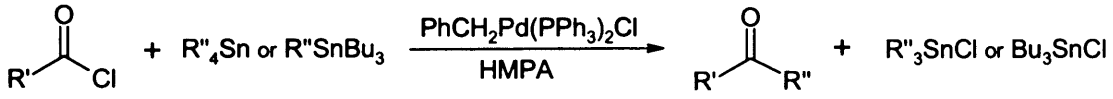
Scheme 1.13.

Negishi. First reported in 1977, this is a *C-C* bond forming reaction between an organozinc reagent and an organic halide (*Scheme 1.14.*).[11]



Scheme 1.14.

Stille. The organometallic species in this form of cross-coupling is an organostannane, often tributyltin, and it was discovered in 1978 by Stille (*Scheme 1.15.*).[12]

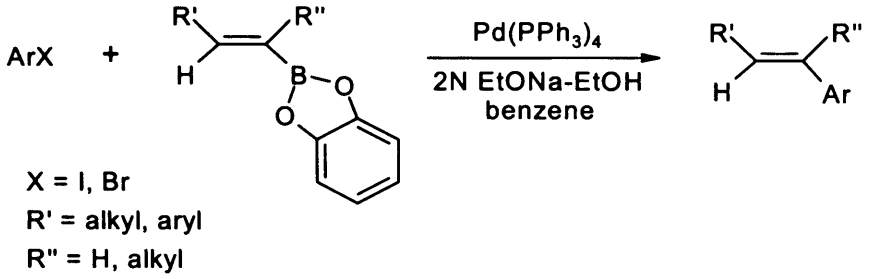


Scheme 1.15.

An excess of LiCl is frequently added to stabilise intermediates after oxidative addition and accelerate the reaction, whilst $Cu^{(I)}$ is employed as cocatalyst. This is truly a very versatile reaction, which allows for several types of organic electrophiles to be coupled successfully, from aryl and vinyl halides to acyl chlorides, benzyl and even

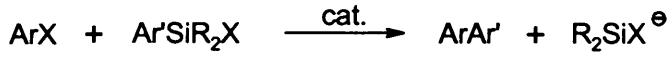
alkyl halides. Despite this, it suffers from two main drawbacks; one is the toxicity of organotin compounds and the other is the potential for homo coupling between the very reactive organostannanes.

Suzuki. In this case, the organometallic species is a boronate ester or a boronic acid. This reaction was first reported by Suzuki and Miyaura[13] in 1979 (*Scheme 1.16.*) and it has also been widely used whilst avoiding some of the drawbacks of the Stille reaction, particularly the issue of toxicity and robustness of the reaction conditions.



Scheme 1.16.

Hiyama.[14] Offering similar scope of substrates to the Suzuki coupling, this reaction involves organosilanes, requiring activation in the form of a fluoride ion (F^-) or a base.

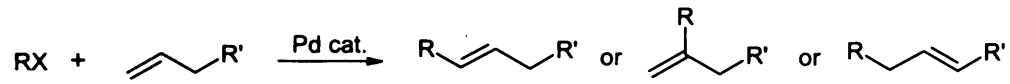


Scheme 1.17.

Organosilanes are interesting substrates due to their lack of toxicity and chemical stability and their importance has increased greatly ever since Hiyama's discovery. Numerous methods are available for both their preparation and their reaction with cross-coupling partners.[15]

1.2. *THE HECK REACTION*

Since the discovery in the late 1960s by Mizoroki[16] and Heck,[17] the Pd catalysed arylation or vinylation of an alkene or *Heck reaction* (*Scheme 1.18.*) has become one of the most important tools for the construction of *C-C* bonds.[18]



Scheme 1.18.

The one distinctive aspect of the Heck reaction is its versatility regarding substrates, reagents and conditions available to the experimentalist whilst, generally, cross-coupling reactions present a more specific set of conditions. A selected representation of the kind of substrates available for the Heck reaction is illustrated below (*Figure 1.1.*). Without a doubt, this range of potential starting materials together with the flexibility of reaction conditions, i.e. type of base, solvent, Pd source and ligands, has made the Heck reaction extremely valuable.

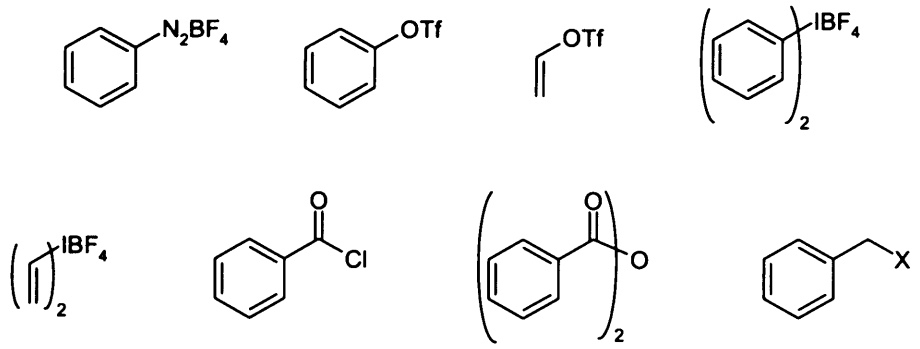


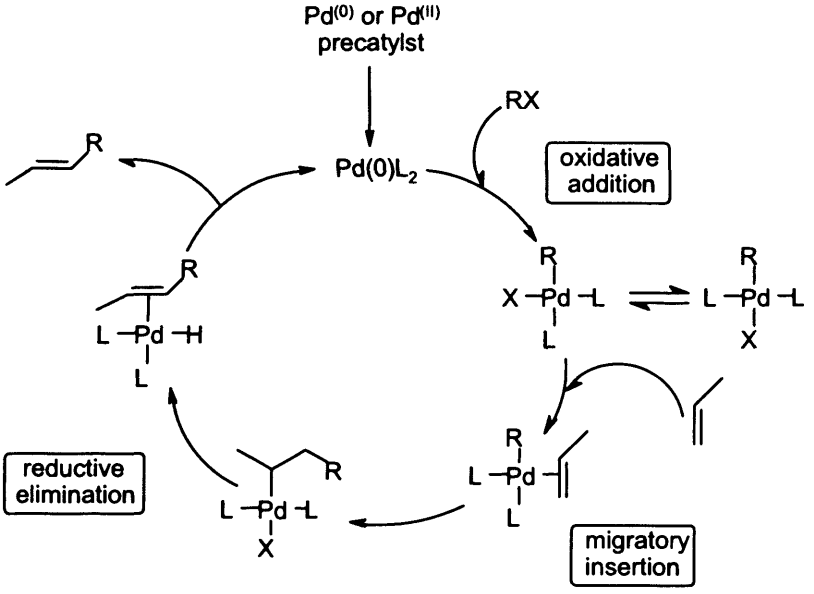
Figure 1.1.

Contemporary research in this area has been influenced by the chemical and pharmaceutical industries on two fronts, arguably interconnected. First, the most interesting class of substrate from the industrial point of view has been chloroarenes. Finding conditions suitable for the Heck reaction of these otherwise unreacting substrates has been a key aim for many research groups.[19] Aryl chlorides are relatively inexpensive when compared to aryl iodides and bromides and their widespread availability makes them amenable to large scale industrial applications.

The second aspect has had to do with the development of environmentally benign processes. For this reason, the Heck reaction has been investigated in media such as water[20] and ionic liquids,[21] thus reducing the amounts of organic solvents involved.

1.2.1. Catalytic Cycle

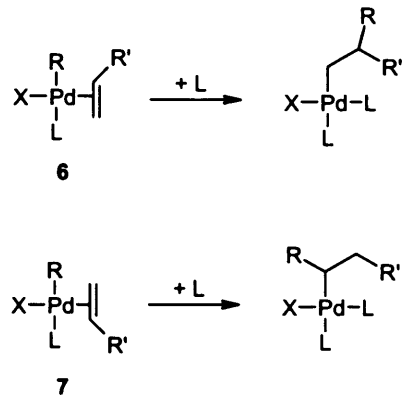
The catalytic cycle resembles that of cross-coupling reactions and comprises several key steps (*Scheme 1.19.*); oxidative addition, migratory insertion and reductive elimination.



Scheme 1.19. Traditional Heck catalytic cycle.

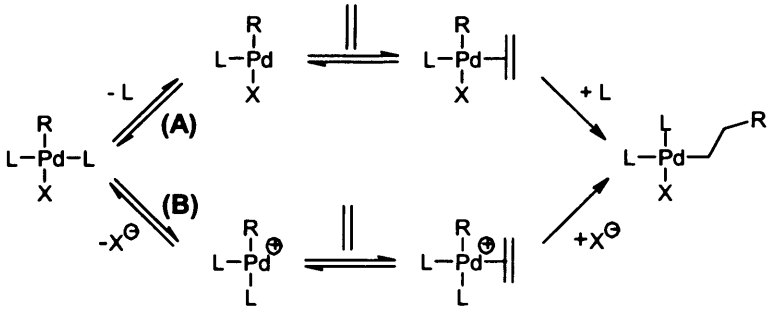
The **oxidative addition** of C-X bonds (X = halide or *pseudo*-halide) is a concerted process with simultaneous formation of M-C and M-X bonds. It is the *cis*-complex which enters the next stage of the cycle, although in most cases the isolable product possesses *trans*-geometry (thermodynamically more stable).

During **migratory insertion**, the alkene inserts into the Pd-R bond, through the intermediacy of a π-bond complex **6** or **7** (*Scheme 1.20.*), resulting in the formation of an unstable σ-bond. This step is the most likely responsible for the regio- and stereodiscrimination, as well as substrate selectivity.



Scheme 1.20.

A ligand must dissociate to make a coordination site available and depending upon the nature of the leaving group, two slightly different mechanisms have been proposed for this step (*Scheme 1.21.*).



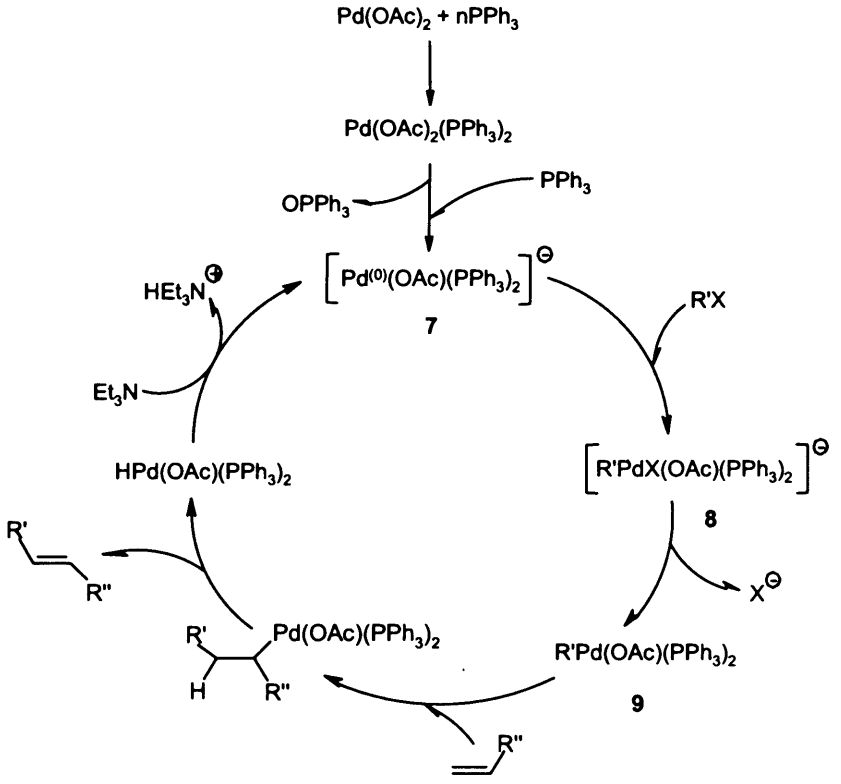
Scheme 1.21. The neutral and cationic pathways.

In the neutral pathway (A), typically followed by halides, the phosphine ligand dissociates prior to Pd-alkene coordination and insertion. The cationic pathway (B) is present when *pseudo*-halides such triflates are involved, resulting in the formation of a Pd cationic species.

Ultimately, the same product is achieved through both routes, which pathway is followed is highly dependent upon the reaction conditions, i.e. additives and alkene utilised.

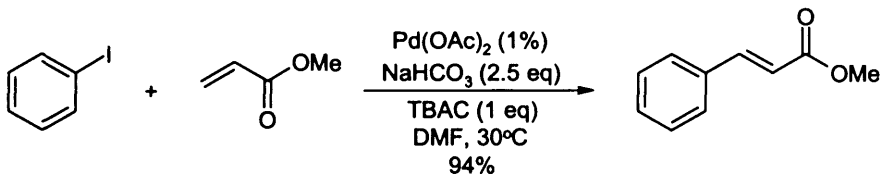
The cycle terminates with the **reductive elimination** to generate an alkene coordinated to Pd-H which is eliminated by a base via β-hydride elimination, leading to the formation of the final alkene and the regeneration of $Pd^{(0)}$.

Finding a unified mechanistic description for the Heck reaction is almost an impossible task as reagents, additives and reaction conditions have to be taken into account to describe the nature of the active catalytic species. Whilst most studies have been carried out with isolated species and for different stages of the catalytic cycle, Amatore and Jutand[22,23] have provided an alternative vision based on short-lived intermediates identified *in situ* through electrochemical techniques (*Scheme 1.22.*). By this interpretation, the catalytic species that initiates the cycle is a 16 electron complex, **7**, to which the aryl halide oxidatively adds, resulting in a short-lived pentacoordinated Pd species, **8**, and ultimately yielding oxidative addition product **9**.



Scheme 1.22. Amatore's proposed mechanism for the Heck reaction.

Jeffery was first to describe the positive role of tetrabutylammonium salts for the Heck reaction, in terms of acting as phase-transfer agents (*Scheme 1.23.*).[24-26]



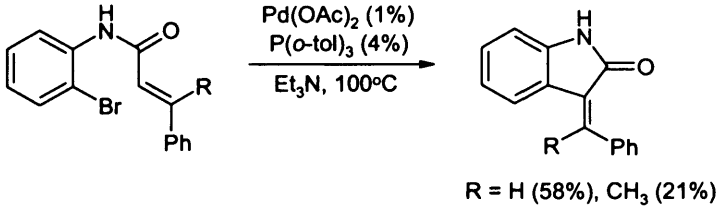
Scheme 1.23.

Salts of the type [^{n}Bu$_4$N]X have been attributed other roles by virtue of their decomposition product at high temperature, tri-butylamine, which acts as stabiliser for metal colloids formed *in situ* by preventing their aggregation to bigger and inactive particles[27] or as reducing agent for Pd(II) to Pd(0).[28]

1.2.2. The Intramolecular Heck Cyclisation

The intramolecular version of Pd catalysed transformations is of great utility, since both carbo- and heterocycles are at the core of many natural products and serve as target molecules for synthetic studies.[29-32]

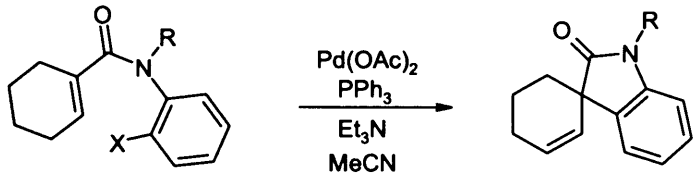
The first reports on intramolecular Heck cyclisations were published in the late 1970s, by the groups of Mori[33] and Heck[34] (*Scheme 1.24.*).



Scheme 1.24. First intramolecular reaction by Heck.

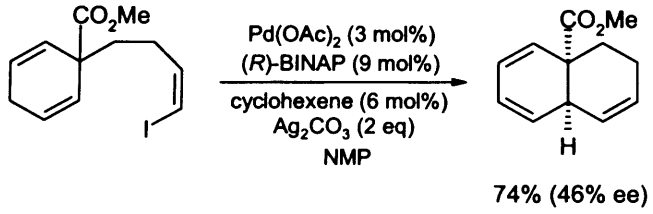
This work opened new routes for the preparation of heterocycles such as indoles[35] and carbazoles.[36] Moreover, Overman[37-39] deployed similar methodology for the

preparation of polycyclic systems and quaternary carbon centres in spiro compounds (*Scheme 1.25.*).



Scheme 1.25.

The true potential of the intramolecular Heck resides in the possibility for the construction of tertiary carbons with asymmetric induction. Since the first report by Shibasaki[40] in 1989 (*Scheme 1.26.*), the asymmetric intramolecular Heck cyclisation has been key for a number of natural products synthetic routes.[41]



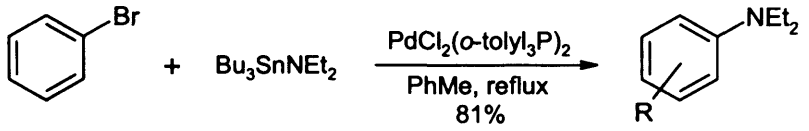
Scheme 1.26. First asymmetric intramolecular Heck cyclisation.

1.3. *HARTWIG-BUCHWALD AMINATION*

Arylamines are present in many areas of chemistry, from natural products and pharmaceuticals[42] to photographic and polymeric materials.[43] Traditional synthetic procedures suffered from a lack of functional group tolerance and relatively harsh conditions.[44,45] The introduction of Pd catalysed transformations overcame some of these drawbacks.

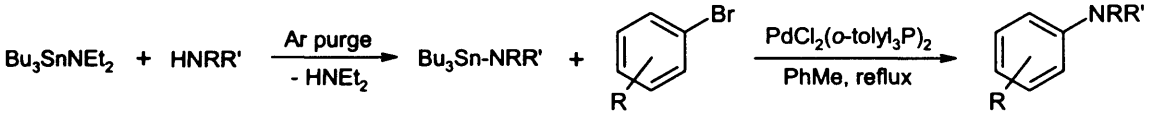
Initial efforts by Migita involved tin amides (*Scheme 1.27.*).[46] Albeit the clean and mild reactions achieved, this methodology presented several drawbacks due to the sensitivity and toxicity of tin reagents and narrow scope of substrates. Vinyl bromides

and aryl bromides containing electron donating or electron withdrawing groups gave products in low yields.



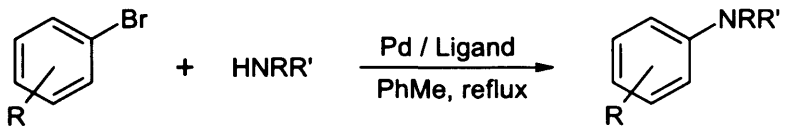
Scheme 1.27.

This work was independently adopted by Hartwig,[47] who looked for the first time at its mechanism, and by Buchwald,[48] who increased the scope of amines by the *in situ* formation of tin amides (*Scheme 1.28.*).



Scheme 1.28.

An important milestone was achieved by both with the departure from organostannane protocols. Buchwald[49] reported the synthesis of arylamines from aryl bromides and amines with catalytic Pd in the presence of NaO^{t}Bu. Concurrently, Hartwig[50] reported the use of LHMDS as base (*Scheme 1.29.*).

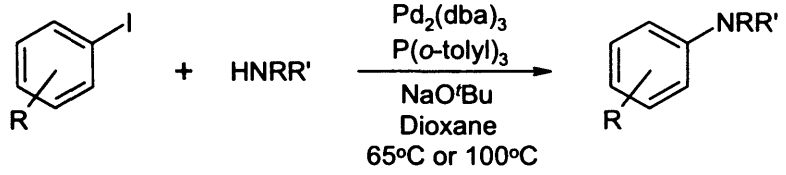


Hartwig's conditions: $PdCl_2(o\text{-tolyl}_3P)_2$, LHMDS
Buchwald's conditions: $Pd_2(dba)_3$, 2 P(o-tolyl)$_3$, NaO^{t}Bu

Scheme 1.29.

Contrary to the expected order of reactivity observed in the Heck reaction, aryl iodides were identified to be problematic substrates, particularly when coupled with primary amines. This was a common feature for both the Migita's tin protocol and the tin free procedures of Hartwig and Buchwald. At this point, it was attributed to a difference in the coordination chemistry of the oxidative addition products of aryl iodides and bromides.[51]

Despite Buchwald's breakthrough, primary amines, like hexylamine and aniline, reacted poorly under the same conditions that secondary amines, both with electron rich and electron poor aryl iodides (*Scheme 1.30.*).



Scheme 1.30.

Interestingly, aryl iodides offered better yields and milder conditions than their bromides counterparts in the intramolecular version of this transformation.[52]

Further developments in the nature of the phosphine ligands, i.e. the introduction of chelating ligands such as DPPF and BINAP, have allowed not only for a general protocol for the amination of aryl halides but also for its extension to other electrophiles like aryl triflates and tosylates or other nitrogen sources.[53-55]

1.4. *PHOSPHINE LIGANDS*

One of the most important factors in identifying successful conditions for palladium catalysed transformations is the choice of ligand and this thesis will focus on two classes of ligands.

Organophosphanes of the type PR_3 (phosphines) and $P(OR)_3$ (phosphites) are by far the most ubiquitous ligand partners employed in Pd catalysed cross-coupling, Heck and aryl amination reactions.

Phosphines and phosphites are electron neutral two electron donors capable of stabilising metal centres in low oxidation states, through their lone pair. In addition,

they are able to accept electrons from the metal by π-back donation depending upon the nature of R (*Figure 1.2.*). The more electronegative substituents R are, the higher its π-acidity is and the better acceptor for the metal it becomes (increased stabilisation for the metal).

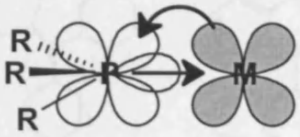


Figure 1.2. Schematic representation of σ and π back donation of *P*-M bonds.

The same substituent, R, plays another role in the overall properties of a phosphine ligand by virtue of its steric properties. In order to rationalise this effect, Tolman[56] introduced and quantified the term "cone angle" or angle spanning out by the ligand attached to the metal. The wider this angle is, the greater the steric hindrance over the metal centre. Some selected values are depicted below (*Figure 1.3.*). Also, related to this effect is the R groups' spatial arrangement, which may offer a chiral environment on the metal centre.

PH_3	PF_3	$P(OMe)_3$	PMe_3	PPh_3	$P(t\text{-}Bu)_3$
(87°)	(104°)	(107°)	(118°)	(145°)	(182°)

Figure 1.3. Cone angle values for some selected phosphines.

It has been long established that oxidative addition benefits from an electron rich Pd centre, resulting from the electron donor capabilities of phosphines. Whilst, the steric topography is the governing factor in the reductive elimination step.[57,58] Thus, their extensive presence in catalysis derives from the fact that both of these attributes, electronics and sterics, are tuneable by the appropriate manipulation of their R substituents.

Historically, PPh_3 was the ligand of choice for many of these transformations. However, new advances have been possible and gone hand in hand with the development of several new generations of these ligands, e.g. polydentate, chiral,

biphenyl, alkyl, palladacycles, etc (*Figure 1.4.*). This relationship goes as far as Pd itself being employed in the synthesis of phosphine ligands by *P-C* bond formation.[59]

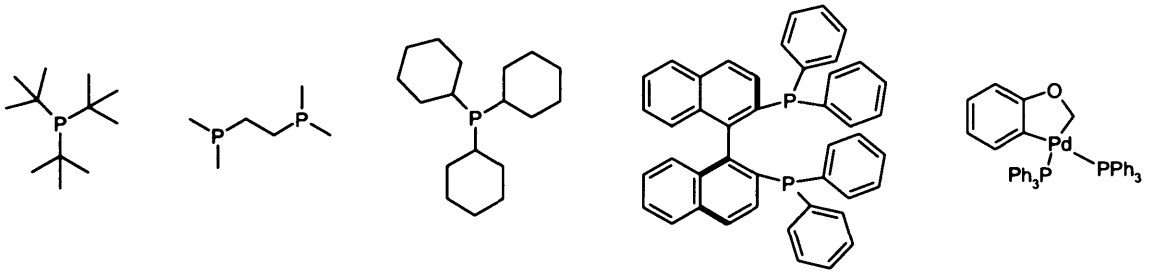
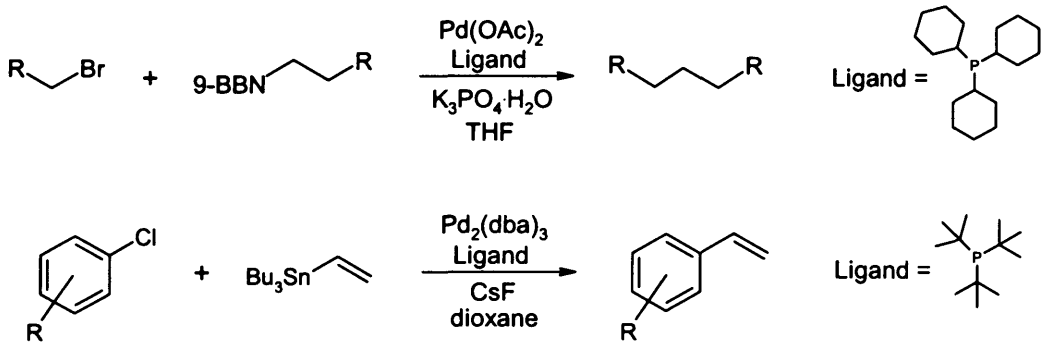


Figure 1.4. Recently developed phosphine ligands.

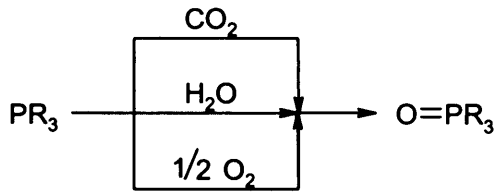
Two examples of the advances achieved with these new types of phosphines are connected to the kind of substrates traditionally demanding or out of reach for cross-coupling and other Pd catalysed transformations, i.e. alkyl electrophiles featuring β-hydrogens and chloroarenes (*Scheme 1.31.*).[60,61]



Scheme 1.31.

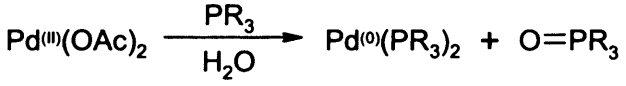
Despite all the advantages that older and newer generations of organophosphane ligands have brought to Pd catalytic transformations, they are prone to a number of side reactions leading to catalyst decomposition or unwanted by-products on many occasions.[62-64]

One reaction affecting phosphines is oxidation, leading to their analogous phosphine oxides (*Scheme 1.32.*). Thus, solvents and reagents must be carefully dried and degassed and reactions conducted under strict inert atmosphere, making it unfavourable for large scale industrial applications and presenting problems in terms of long-term storage.



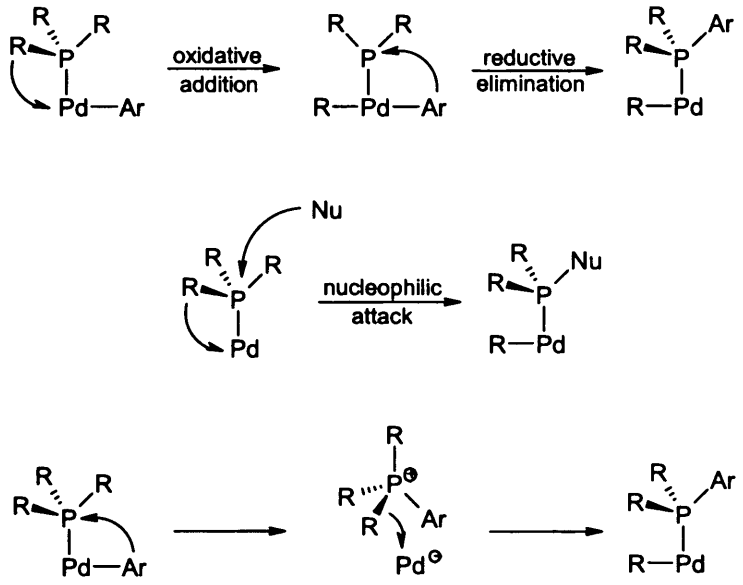
Scheme 1.32. Main oxidation agents for phosphines.

This process however is also necessary for the reduction of $Pd^{(II)}$ to $Pd^{(0)}$ (*Scheme 1.33.*). The excess of ligand typically required for optimum results is due to loss of phosphine.



Scheme 1.33.

Other important degradation processes of phosphines occur during coordination with metals. Three main mechanisms may be envisaged resulting in aryl migration from the phosphine to the metal. These are oxidative addition into the *P-C* bond, nucleophilic attack and aryl exchange via phosphonium salts (*Scheme 1.34.*).



Scheme 1.34.

1.5. *N-HETEROCYCLIC CARBENE LIGANDS*

Some of the drawbacks associated with the use of organophosphanes were mostly addressed with the introduction in catalysis of *N*-heterocyclic carbenes (NHCs) more than a decade ago. Initially termed "phosphine mimics" because of their similar electronic interactions with metal centres,[65,66] they have grown to supersede phosphines in many applications and being utilised in many other areas of chemistry.

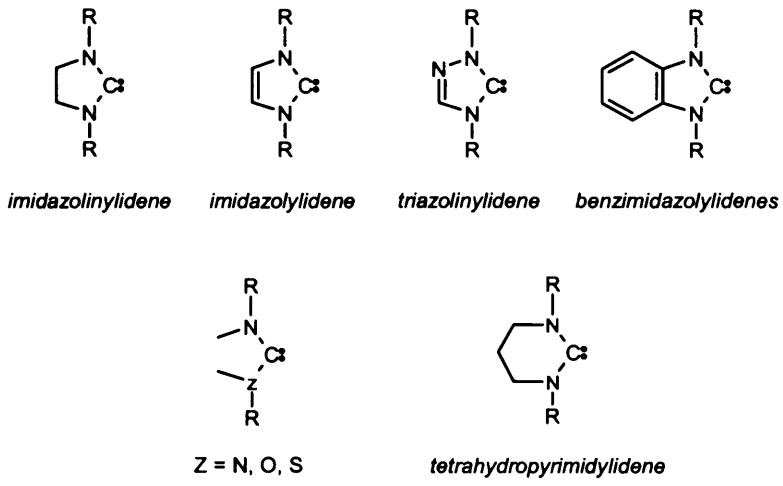
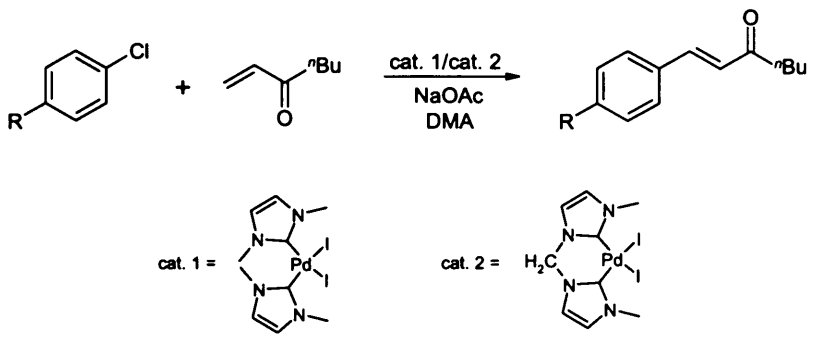


Figure 1.5. Structural diversity of some stable carbenes.

Since the first application by Herrmann in a catalytic process, namely a Heck reaction (*Scheme 1.35.*),[67] they have enriched the range of ligand partners available to Pd.

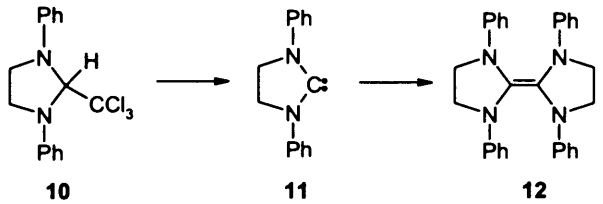


Scheme 1.35. Herrmann's application of a Pd-NHC complex in a Heck reaction.

NHCs present several advantages over phosphines. Firstly, their ease of access makes them a viable alternative to some of the more expensive and less accessible phosphines. Secondly, NHCs are somewhat stable and their precursors may be equally employed in Pd catalytic reactions. Thirdly, the steric and electronic properties may be tuned independently as the substituents are not directly attached to the carbene centre.

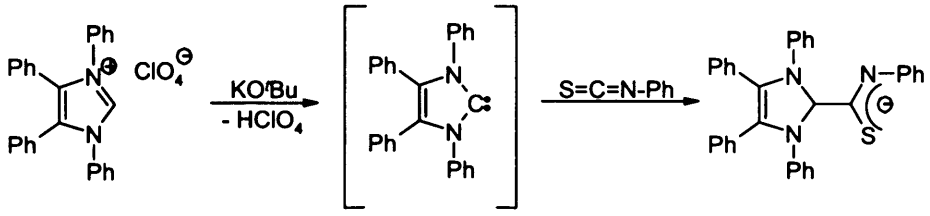
1.5.1. Historical Background of *N*-Heterocyclic Carbenes

Contemporary research in this area commenced in the 1960s when Wanzlick embarked upon a project to synthesise the free carbene **11** from **10** by thermal elimination of chloroform, although only the dimeric species **12** was isolated (*Scheme 1.36.*).[68-71]



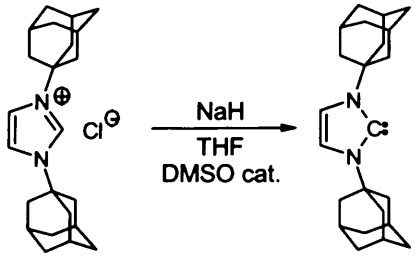
Scheme 1.36.

Nevertheless, reactivity consistent with the presence of a nucleophilic carbene was observed and Wanzlick demonstrated that imidazolium salts were deprotonated by KO^{t}Bu to furnish carbenes, which were trapped, but never isolated (*Scheme 1.37.*).[72]



Scheme 1.37.

A milestone in carbene chemistry was achieved with the first NHC **13** isolated by Arduengo and co-workers in 1991 (*Scheme 1.38.*).[73,74]



13

Scheme 1.38. Arduengo's first isolable *N*-heterocyclic carbene.

A plethora of research has been dedicated to this area since these original contributions, and much of this has been driven by the interest in the utility of NHCs in coordination and organometallic chemistry. However, NHCs have found applications in nucleophilic catalysis and as reagents in their own right.[75,76] In addition, some of their precursors, particularly imidazolium salts, are part of the extensive family of ionic liquids.[77]

An illustrative application of the potential general utility of the NHCs ligands in metal catalysed processes is in metathesis where Grubbs and co-workers have extensively utilised NHCs as a replacement for an organophosphane.[78]

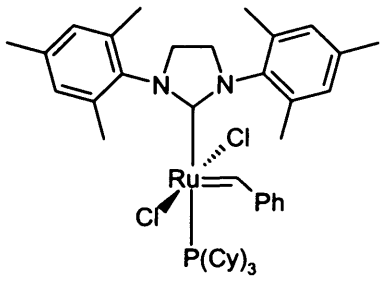


Figure 1.6. Second generation Grubbs' catalyst.

1.5.2. Electronic Properties

"Carbenes are compounds with a neutral dicoordinate carbon atom featuring either two singly occupied nonbonding orbitals (triplet state) or alternatively both a lone pair and an accessible vacant orbital (single state)".[79]

With regard to NHCs, it has been established that they display singlet state multiplicity, $^1A_1$ (*Figure 1.7.*), in agreement with prior theoretical calculations[80-82] and later structural investigations.[83,84]

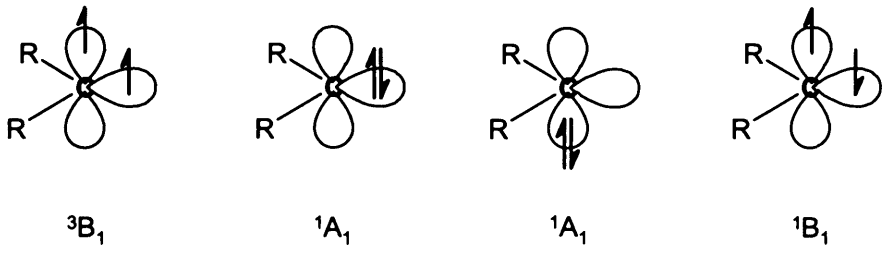


Figure 1.7. Electronic configurations in carbenes.

Pauling discerned that the ideal substitution pattern to stabilise a singlet carbene is one which preserves the electroneutrality of the carbene centre and, later, Wanzlick recognised the potential of the imidazole ring for this purpose. Consequently, in NHCs the carbene electron deficiency is reduced by the donation of the two nitrogen lone

pairs whilst the inductive effect of the more electronegative nitrogen atoms stabilises the carbene centre, i.e. *push,push* mesomeric-*pull,pull* inductive effect (*Figure 1.8.*).

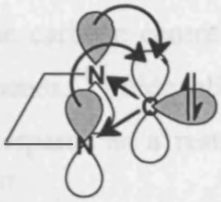


Figure 1.8.

Experimentally determined electron distribution has indicated that there is a high electron density at the carbene centre, as well as on the flanking nitrogen atoms, thus producing considerable repulsion to a potential nucleophile approaching above or below the molecular plane. This effect is responsible for reducing the expected ambiphilic character of NHCs.[85,86]

Arduengo initially postulated that π-delocalisation from the C_4-C_5 double bond played a fundamental role in stabilising imidazol-2-ylidenes. This was later refuted first in 1995, with the isolation of the first imidazolin-2-ylidene by Arduengo himself[87] and later, in 1996 when Heinemann[88] and Frenking[89] independently published their results based on thermodynamic, magnetic, structural and theoretical studies. All reports concluded that aromaticity brings an additional stabilisation to this system, although the aromatic character is less pronounced than for their imidazolium precursors. Those studies also agreed that resonance structure **A** (*Figure 1.9.*) is the dominant resonance canonical to describe NHCs but with an important contribution from **B** and **C**.

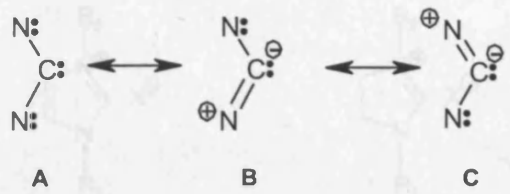


Figure 1.9.

1.5.3. Structural and Spectroscopic Features

The geometry of the central imidazole ring is hardly affected by a variety of substituents that have been investigated by Arduengo.[74]

The bond angle observed in the carbene centre (100-110°) is in good agreement with that expected for singlet carbenes.[74] Imidazolin-2-ylidenes present larger angles relative to their unsaturated counterparts, as a result of the strain introduced by the longer C_4-C_5 and $C_{4(5)}$-$N_{3(1)}$ bonds.[87]

For unsaturated NHCs, the nitrogen atoms are always in a planar environment, and the $C_{4(5)}$-$N_{3(1)}$ bond lengths are rather short (1.32-1.37 Å) whereas saturated NHCs present a "twisted" backbone.

The ^{13}C-NMR for the carbene centre is in the range 205-220 ppm for the unsaturated NHCs and, approximately, 15-20 ppm downfield for the saturated NHCs. Benzimidazol-2-ylidenes come into resonance at even lower fields.

1.5.4. Synthesis of Imidazolium Salts

The importance of imidazolium salts in contemporary organic chemistry is evident from the great deal of reports describing the discovery of new and reliable routes for accessing NHCs, their precursors and their complexes with metals.

A positive feature common across the whole range of NHC precursors is their ease of synthesis, therefore it is not surprising that the largest family of precursors corresponds to the imidazole group, i.e. imidazolium and imidazolinium salts (*Figure 1.10.*).

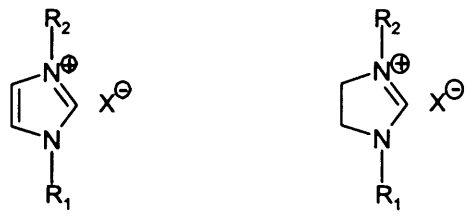
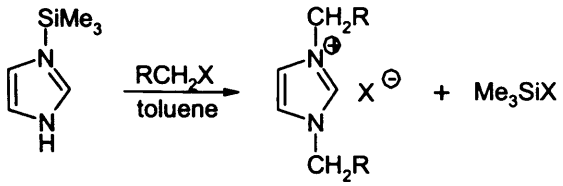


Figure 1.10. Imidazolium and Imidazolinium salts.

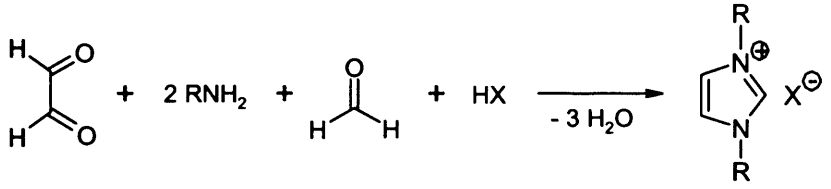
Alkylation of imidazole or *N*-substituted imidazoles offers a straightforward method for this purpose. The drawbacks associated with this route are the limited range of commercially available *N*-substituted imidazoles, although procedures for their preparation have been described,[90,91] and the substantial formation of elimination by-products with secondary and tertiary alkyl halides.[92]

Similarly, alkylation of commercially available *N*-trimethylsilylimidazole has proved successful with a variety of alkyl bromides and chlorides (*Scheme 1.39.*).[93]



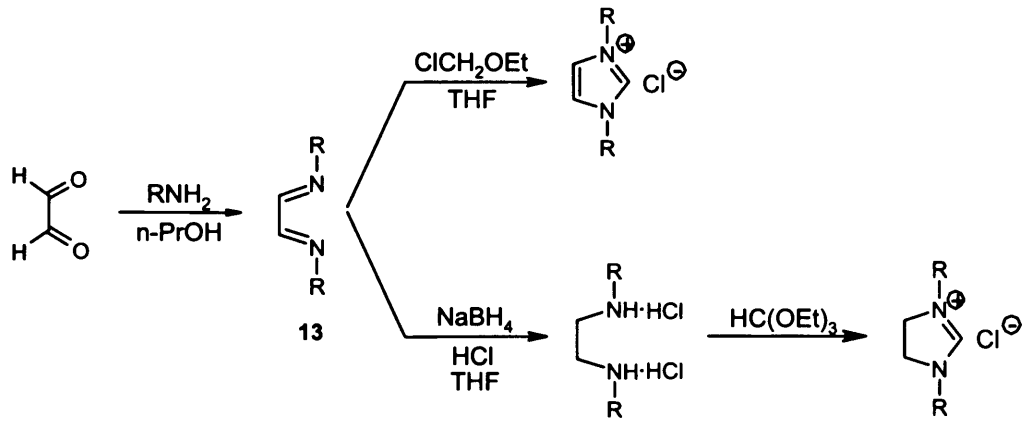
Scheme 1.39.

An alternative utilises a multi-component reaction which builds up the heterocycle with the relevant substituents in "one pot" (*Scheme 1.40.*).[94,95]



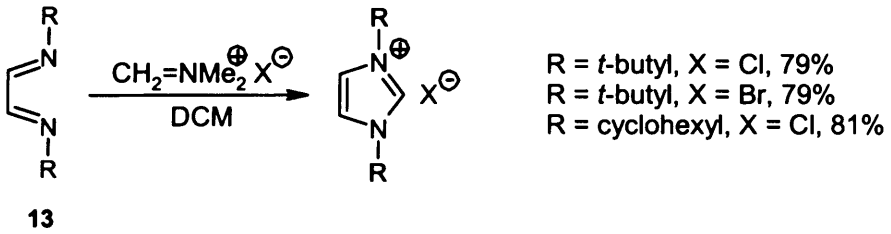
Scheme 1.40.

An important variation by Arduengo of the route above commences with the isolation of 1,4-diazadiene, **13**, derived from aqueous glyoxal and the required amines, in the presence of an acidic catalyst. This could be either cyclised to the imidazolium salt or turned into the imidazolinium salt, via reduction to ethylenediamine dihydrochloride and treatment with an orthoester (*Scheme 1.41.*).[96,97]



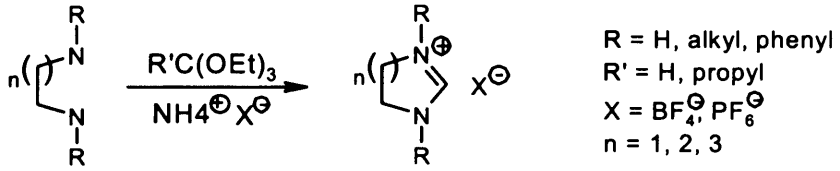
Scheme 1.41.

Other carbon electrophiles have served as alternatives to the frequently employed chloromethyl ethyl ether. For instance, a recent report has made use of dimethylmethyleneammonium salts (*Scheme 1.42.*).[98]



Scheme 1.42.

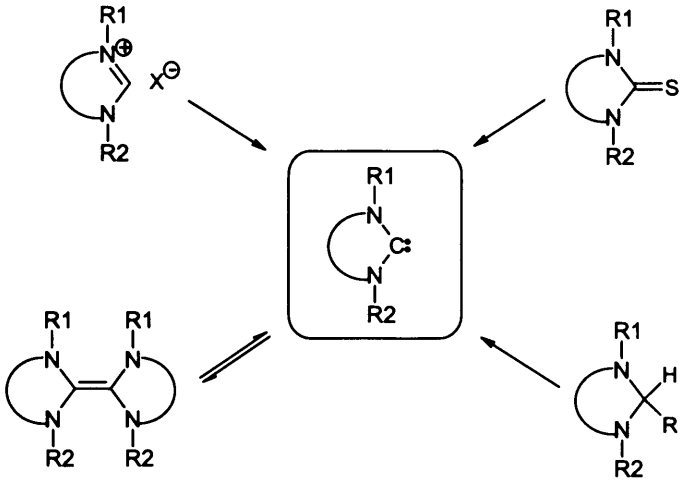
Imidazolinium (dihydroimidazolium, n=1), tetrahydropyrimidinium (n=2) and tetrahydro-1,3-diazepinium (n=3) salts are easily accessed by reaction of an orthoester and *N,N'*-dialkyl or *N,N'*-diaryldiamines (*Scheme 1.43.*).[99]



Scheme 1.43.

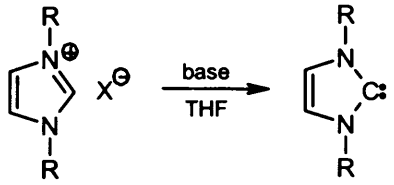
1.5.5. Isolation of NHCs

There are a variety of different methods used to form NHCs (*Scheme 1.44.*):



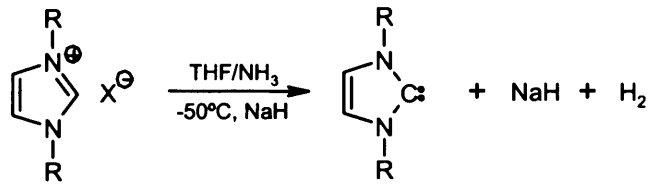
Scheme 1.44.

The most general method for the formation of NHCs is the deprotonation of imidazolium salts by bases such as NaH and KO^{t}Bu or dimsyl-anions (DMSO$^-$) in THF (*Scheme 1.45.*).[74]



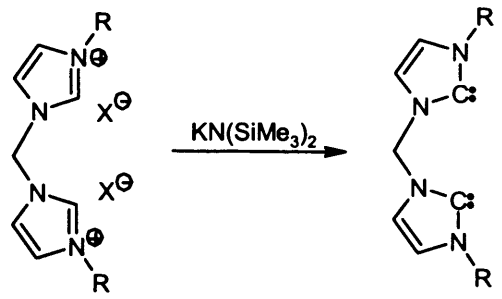
Scheme 1.45.

Herrmann developed an alternative large-scale synthesis of pure NHCs in which imidazolium salts were deprotonated smoothly and quantitatively in liquid ammonia or mixtures of liquid ammonia with organic amines (*Scheme 1.46.*).{Herrmann, 1996 180 /id}



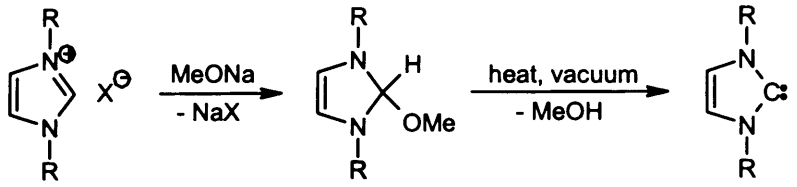
Scheme 1.46.

In the case of chelating dicarbenes, bases such as KHMDS or LDA were found to selectively deprotonate the azolium salts, leaving methylene and other hydrocarbon bridges intact (*Scheme 1.47.*).[101]



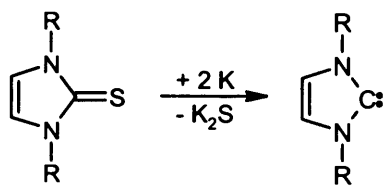
Scheme 1.47.

Vacuum thermolysis of small molecules methoxy, ethoxy or trichloromethyl derivatives also yields NHCs (*Scheme 1.48.*).[102,103]



Scheme 1.48.

Cyclic thiourea derivatives may be subject to desulfurisation by elemental potassium giving rise to the carbene (*Scheme 1.49.*).{Kuhn, 1993 128 /id;Hahn, 2000 4 /id;Hahn, 2003 159 /id}



Scheme 1.49.

1.5.6. Electronic and Structural Features of Pd-NHC Complexes

Herrmann first successful application of a Pd-NHC complex led him to describe them as "*a new structural principle of catalysts in homogeneous catalysis*".[67] In early work, he noted the pronounced σ donor similarities between NHCs and electron rich organophosphanes and, therefore, their potential as replacements or alternatives ligands.

Two types of complexes could be envisaged depending upon the nature of the Pd-carbene bond; Schrock and Fischer complexes. In Schrock complexes, the bond is essentially covalent and results from the interaction of a triplet carbene and a metal in a triplet state. The bond in Fischer complexes is more donor-acceptor in nature and results from σ-donation of carbene to metal and π-donation of metal to carbene.

Pd-NHC complexes are typically of the Fischer class, however, unlike them or organophosphane complexes, the π back bonding component from the metal centre to the NHC ligand is almost negligible (*Figure 1.11.*).[107,108]

Figure 1.11.

The electronic properties of NHCs have been found not to be significantly affected by *N*-substituents and remain strongly electron donors, for example more so than tertiary phosphines.[109,110]

The Pd-NHC bond is single in character and longer (typically 2 Å) than in Schrock and Fischer type complexes. In some cases, NHCs can rotate around the metal-carbon bond depending on the steric situation.

Upon coordination of NHCs to Pd, the planarity of the ring is affected by the substituents on the unsaturated imidazole nitrogens. With aromatic substituents the effect is negligible, but alkyl substituents induce an important torsion of the backbone ($N_1C_4C_5N_3$). Saturated imidazoles present a deviation from planarity as a consequence

of the two sp^3 carbons (C_4C_5). Upon coordination, the backbone angle slightly increases.[111]

The internal ring angle ($N_1C_2N_3$), 103-110°, at the carbon atom is slightly larger in coordinated carbenes than for free carbenes, although the difference is not as large as that observed in the related azolium salt. In addition, the C-N bond distances lie between those of the free carbenes and azolium salts.

Since the electronic properties do not vary significantly from one NHC to another, the difference in reactivity amongst Pd-NHC complexes must be sought within their topology. The term "cone angle", already described for phosphines, does not apply to NHC ligands as the *N*-substituents project forward creating a pocket surrounding the metal, rather than a cone away from it.

An attempt to rationalise the steric factor for Pd-NHC complexes was conducted by Nolan, with the introduction of the term "buried volume" or volume occupied by the ligand in a sphere of imposed radius (3 Å) centred on the palladium atom. ^{t}Butyl, adamantyl and 2,6-diisopropylphenyl ligands were identified as the most sterically demanding.[111]

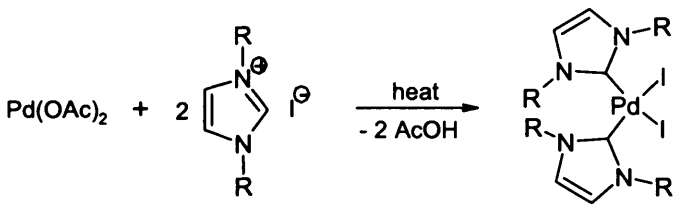
1.5.7. Synthesis of Pd-NHC Complexes

The synthesis of NHC complexes is mainly based on three routes:[79,112-114]

In situ deprotonation of ligand precursors

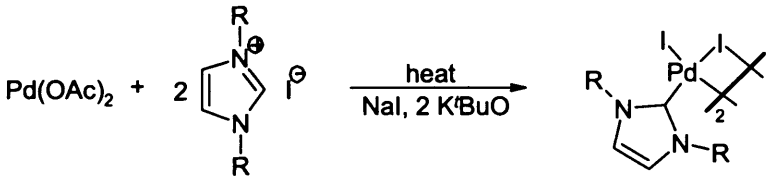
In cases where the carbene is unstable or difficult to handle, this may be the only method for preparation of the desired complex. When the azolium salt comprises a coordinating anion, e.g. I^-, this may be incorporated into the new complex. Using non-coordinating anions, e.g. ClO_4^-, PF_6^-, BF_4^-, avoids this incorporation.

Ligands in the Pd precursor itself could affect deprotonation of the azolium salt (*Scheme 1.50.*).



Scheme 1.50.

Employing external bases such as potassium or lithium *tert*-butoxide, triethylamine and butyl lithium also achieves the deprotonation of azolium salts and their complexation with transition metals. In some cases, this causes the formation of different products as compared with the method above (*Scheme 1.51.*).

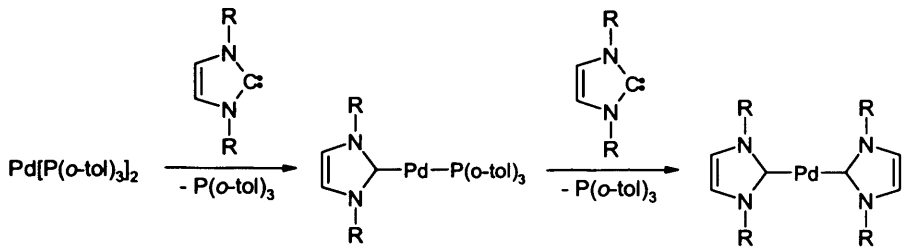


Scheme 1.51.

Complexation of the free, pre-isolated NHCs

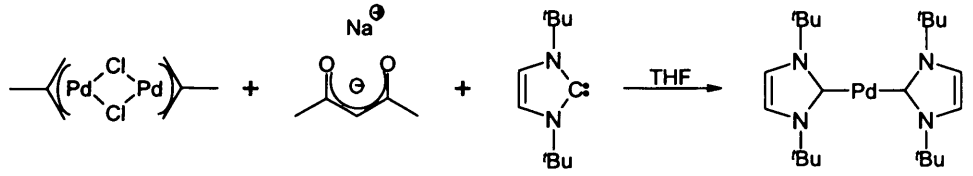
Isolation of free NHCs could be accomplished by any of the methods described in the previous section.

NHCs are able to exchange with phosphine and other ligands. This is a very important approach for the synthesis of $Pd^{(0)}$ complexes. Tri-*ortho*-tolylphosphine appears to be the ligand of choice in these cases, as others fail to give clean substitutions. Using sterically demanding NHCs results in mixed phosphine-NHC complexes (*Scheme 1.52.*).[115]



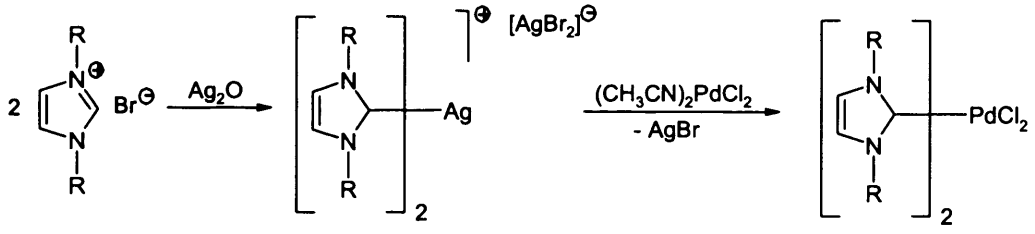
Scheme 1.52.

Caddick and Cloke[116] applied a known synthesis of zerovalent palladium-phosphine complexes by attack of a nucleophile to the allyl units of $[Pd(\eta^3\text{-}C_4H_7)Cl]_2$ and trapping of palladium(0) with phosphine ligand. In their methodology, sodium dimethylmalonate is added to $[Pd(\eta^3\text{-}C_4H_7)Cl]_2$, in the presence of 1,3-di-*N*-*tert*-butylimidazol-2-ylidene, leading to the formation of bis(1,3-di-*N*-*tert*-butylimidazol-2-ylidene)palladium(0) in "one pot" (*Scheme 1.53.*).



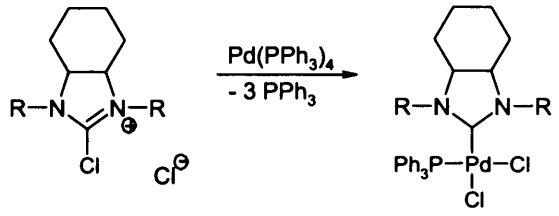
Scheme 1.53.

Other methods for the preparation of NHC-metal complexes include vapor-phase deposition[117] and ligand transfer from silver complexes.[118,119] The driving force for the latter is the precipitation of silver halide salts. In some cases the transfer reaction may be carried out from the $Ag^{(I)}$ complex, generated *in situ* from Ag_2O, in "one pot" (*Scheme 1.54.*).



Scheme 1.54.

Other alternative methods by Fürstner exploit the ease of oxidative addition of 2-chloro-1,3-disubstituted imidazolinium/imidazolium salts to metals (*Scheme 1.55.*).[120]



Scheme 1.55.

1.6. *APPLICATIONS OF NHCs IN PALLADIUM CATALYSIS*

From the point of view of catalysis, research on new organophosphanes and NHCs as ligands has moved beyond the common aim of high turnover activity and functional group sensitivity. Increasingly, catalytic systems are required to meet certain criteria, such as environmental economy, commercial availability or ease of synthesis and stability to the reaction conditions.

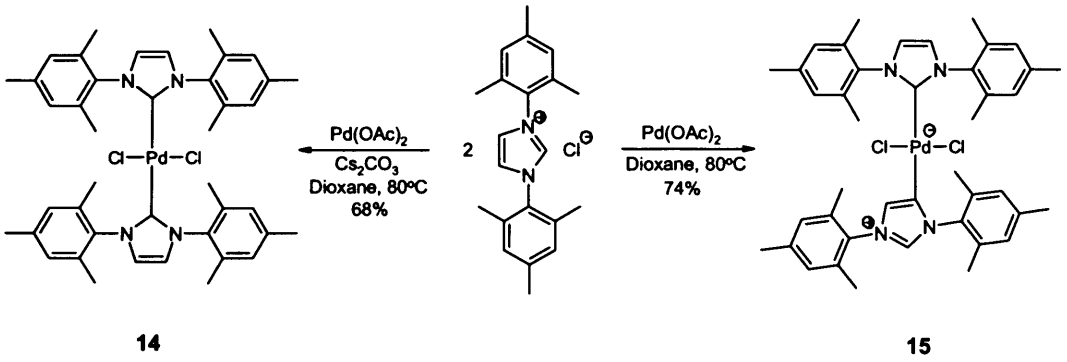
Arguably, NHCs have more rapidly and readily met these new standards than phosphanes. The ease of synthesis of both NHCs and their precursors has already been noted, and now they have started featuring in catalogues from main chemical suppliers. Their functionalisation may be easily achieved to offer new properties, e.g. asymmetric induction, water solubility, solid support fixation, etc. Finally, their stability towards air and moisture makes them amenable to large scale applications.

NHCs have been found to perform successfully in all the transformations described in this introduction, in some instances with enhanced efficiency (turnover, yield, etc.) or indeed by enabling coupling of difficult substrates, e.g. aryl chloride and alkyl halides.

Despite the plethora of research on their organometallic chemistry and catalytic activity, a question that remains unanswered has been over the true identity of the catalytic species. Very often, NHC precursors (typically azolium salts) are employed alongside a Pd source and a difference in reactivity has been observed when their

equivalent and well-defined Pd-NHC complexes are used instead. Nevertheless, this lack of understanding has not precluded their application in palladium catalysis.

A possible explanation could be the formation, depending upon the conditions, of metalation products through "unusual" binding sites.[121-123] A report by Nolan serves as a perfect illustration of the confusion surrounding this subject.[123] As depicted below (*Scheme 1.56.*), the presence or absence of base is critical in the formation of complexes **14** or **15**. Interestingly, Nolan noted how the "normal" complex **14** was inactive in a model Suzuki cross-coupling and Heck reaction. Complex **15** performed well in both cases, yet it was less efficient than the equivalent *in situ* generated catalytic system in the Suzuki cross-coupling.



14 **15**

Scheme 1.56.

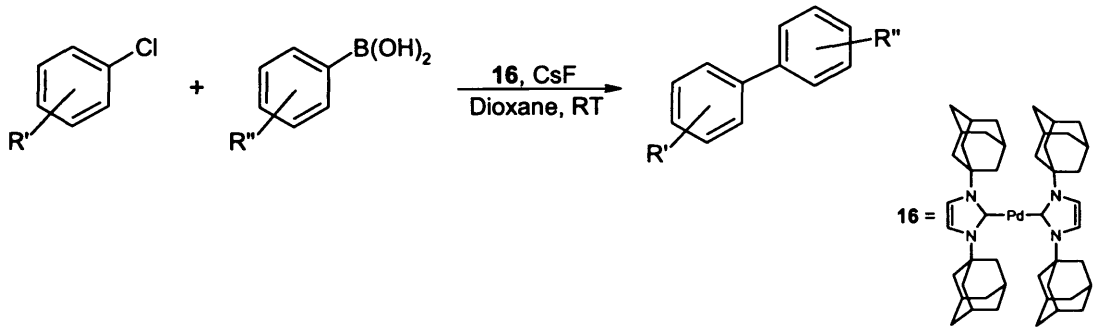
1.6.1. Cross-coupling Reactions

Since the first application in a catalytic Heck reaction by Herrmann,[67] numerous other researchers have recognised the potential of NHCs as ligands for palladium catalysed cross-coupling reactions. To enumerate all the work conducted in this field goes beyond the scope of this thesis, instead the Heck and aryl amination reactions will be subjected to a more detailed comment.

Numerous reviews have already been devoted to this area[124-126] and one and one of the key features which appears to be emerging is the ability of Metal-NHC complexes

to mediate coupling of more challenging partners. Chloroarenes, for instance, have been coupled successfully with boronic acids (Suzuki reaction)[127], organosilanes (Hiyama coupling)[128] and organostannanes (Stille coupling)[129] amongst others. All of these examples utilise a common method for generating the catalytic systems *in situ*, thus obviating an extra experimental step for the formation of the Pd-NHCs complexes.

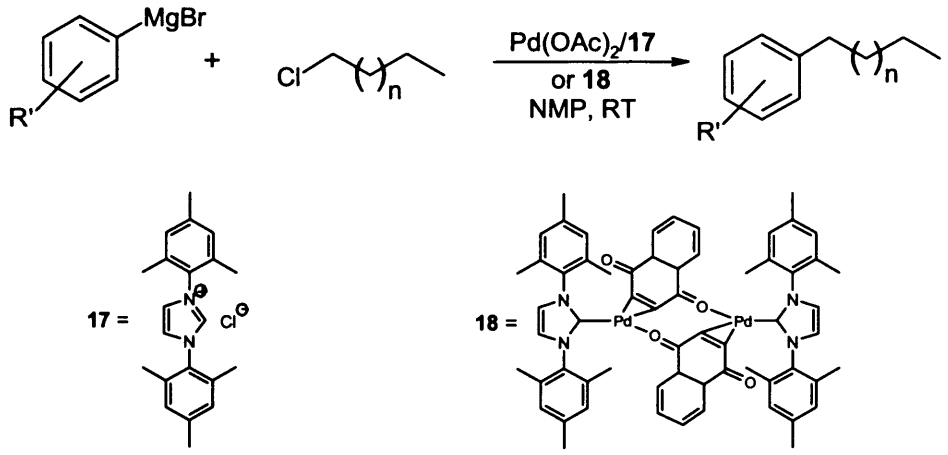
A remarkable advance with this kind of substrate was reported by Herrmann in Suzuki couplings conducted at room temperature.[130] In this case a well defined Pd-NHC complex was employed (*Scheme 1.57.*).



Scheme 1.57.

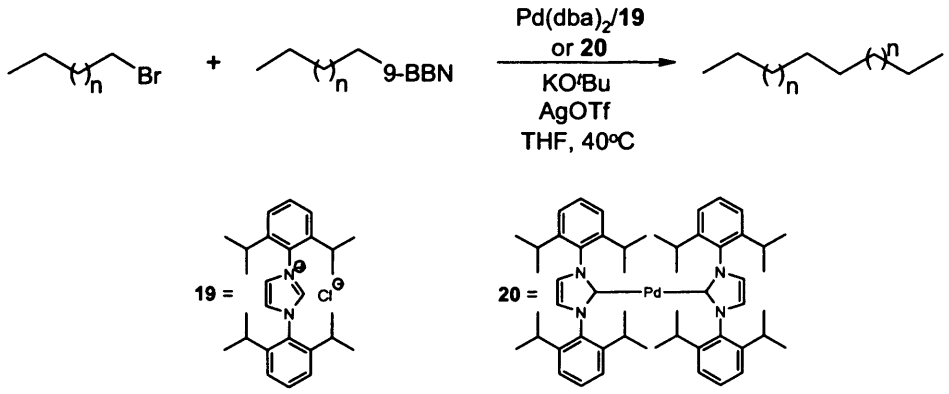
Recent advances with phosphines and NHC ligands have also permitted cross-coupling reactions with alkyl halides which intrinsically pose an extra level of complexity due to the potential for β-hydride elimination reactions along with slower rates of oxidative addition.

Beller[131] reported the first Kumada cross-coupling reaction conducted with NHC ligands employing both a catalytic system originated *in situ* from IMes·HCl **17** and a napthoquinone Pd-NHC complex **18** (*Scheme 1.58.*).



Scheme 1.58.

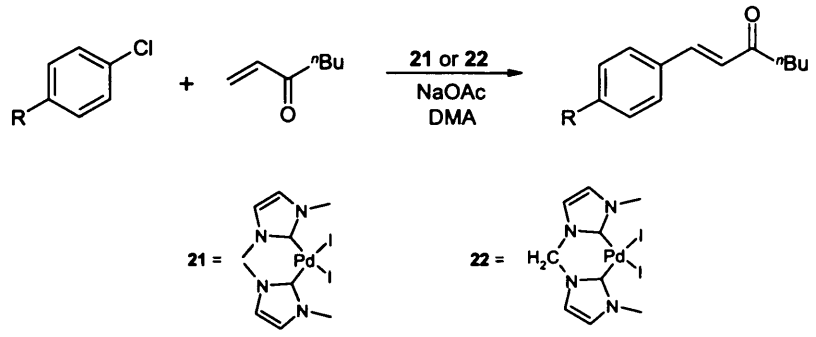
Our group has also reported a synthetic protocol for Suzuki cross-coupling of alkyl bromides with alkyl organoboranes (*Scheme 1.59.*).[132] Although yields were moderate, it demonstrated in principle the potential of an *in situ* catalytic system comprised of imidazolium salt IPr·HCl **19** and a Pd source. The equivalent Pd-NHC complex **20** was also tested and found to be less effective than the *in situ* protocol.



Scheme 1.59.

1.6.2. Heck Reactions

Early examples of Heck reactions employing Pd-NHC complexes were based on electron deficient substrates and relied on high temperatures and activated alkenes (*Scheme 1.60.*).[67,133-135]



Scheme 1.60.

The Caddick group reported the first examples of intramolecular Heck cyclisations of aryl halides using a Pd/imidazolinium salt protocol (*Table 1.1.*).[136]

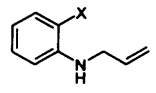
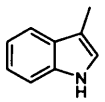
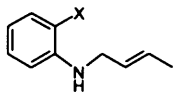
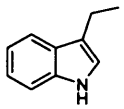
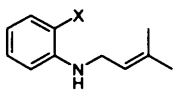
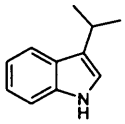
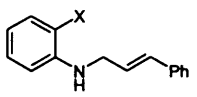
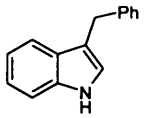
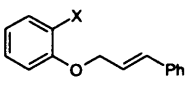
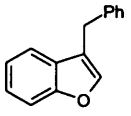
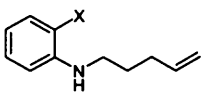
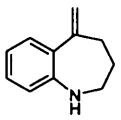
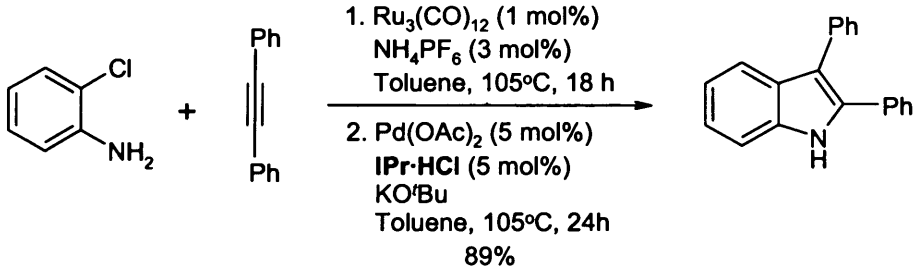
Entry	Substrate	Product	Yield
1 2 3			I: 81% Br: 77% Cl: 18%, 65%[a]
4 5 6			I: 82% Br: 71% Cl: 21%, 64%[a]
7 8 9			I: 76% Br: 56% Cl: 22%, 58%[a], 52%[b]
10 11 12			I: 78% Br: 71% Cl: 27%, 70%[a]
13 14 15			I: 84% Br: 61% Cl: 17%, 63%[c]
16 17 18			I: 82% Br: 60% Cl: 28%, 31%[d]

Table 1.1. Selected cyclisations performed by Caddick *et al.*[136]
(a) TBAB, (b) TBAN, (c) TBAC, (d) TBAI.

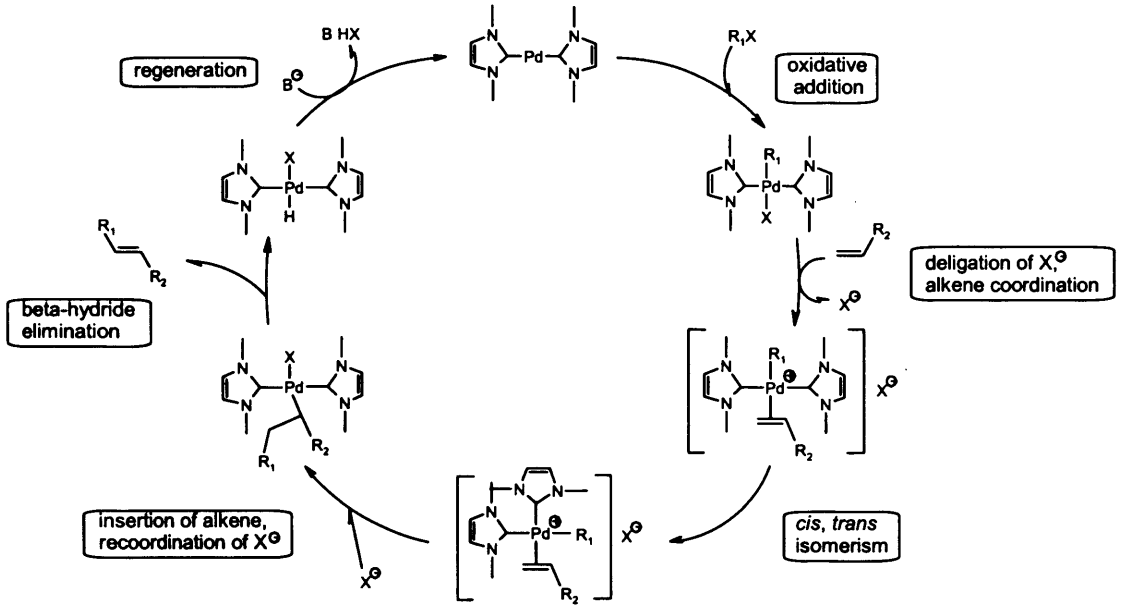
This work was particularly relevant due to the exploitation of aryl chlorides when, traditionally, they have been challenging substrates, yet more interesting from the economic point of view as a result of their widespread availability and relatively lower cost by comparison with aryl iodides or bromides.[137] Fundamental to this success was the addition of tetraalkylammonium salts which brought about a significant increase in yields for these substrates. This effect, also known as "Jeffery's effect" has already been described earlier in this introduction.

This work has made a contribution towards establishing imidazolium salts as a viable alternative for effecting intramolecular Heck cyclisations and encouraged others to investigate this protocol further. For example, a recent application made use 2-chloroanilines for the "one pot" formation of indoles (*Scheme 1.61.*).[138] Interestingly, ligand **IPr·HCl** was the ligand of choice in favour of **SIPr·HCl** which offered a much decreased yield (31%).



Scheme 1.61.

Initial mechanistic studies into the Heck reaction, both theoretical[139] and experimental,[140,141] appear to agree with the pathway depicted below (*Scheme 1.62.*).



Scheme 1.62.

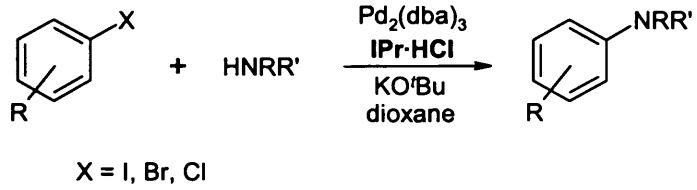
The active catalytic species is a linearly coordinated 14 electron Pd centre to which an aryl halide (R_1X) oxidatively adds. Deligation of a ligand, believed to be the halide due to the strength of the Pd-NHC bonds, occurs before alkene coordination to form a cationic Pd species. When the appropriate geometry in the complex is achieved, both NHC ligands are mutually *cis* and insertion of R_1 into the alkene as well as recoordination of the halide is made possible. The required product is released by β-hydride elimination, and the $Pd^{(0)}$ species is regenerated by reductive elimination of HX by a base.

However, it has been reported that NHC dissociation is more facile that originally envisioned,[142] with recent reports indicating the presence of a dissociative pathway resulting in a 12 electron mono-ligated palladium species.[143]

1.6.3. Hartwig-Buchwald Aminations

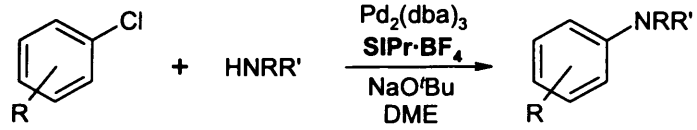
NHC precursors were first employed for the amination of aryl halides by Nolan. The system comprised by $Pd_2(dba)_3$ and IPr·HCl proved to be very efficient for the room temperature amination of aryl bromides and iodides. Chloroarenes were also successfully coupled with amines in good yields, including primary amines such as

hexylamine and aniline, although higher temperatures were required to effect coupling with the latter partners (*Scheme 1.63.*).[144]



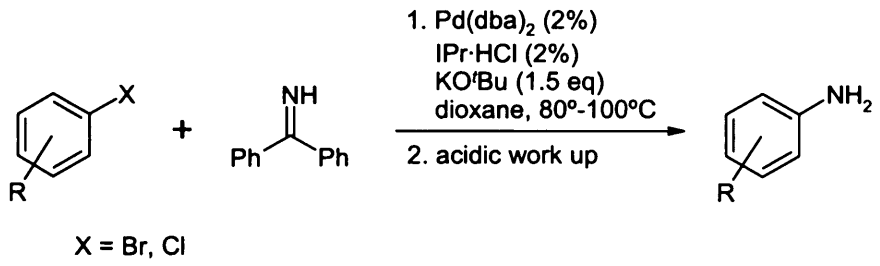
Scheme 1.63.

Hartwig also made use of NHC precursors for aminations of aryl chlorides, achieving some transformations at room temperature (*Scheme 1.64.*). A slower rate and decreased reactivity with primary amines, such *N*-hexylamine, was noted in accordance with the above report.[145]



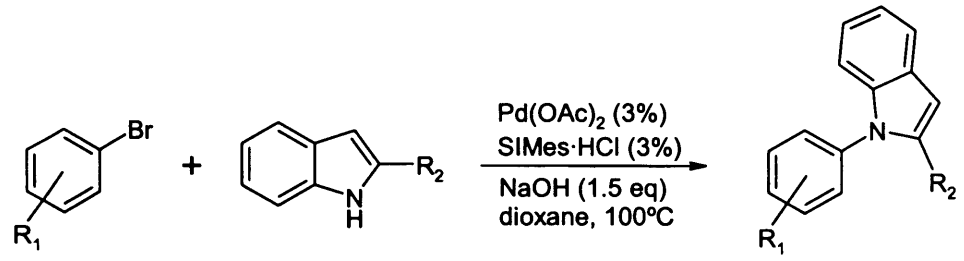
Scheme 1.64.

Nolan extended his protocol to other substrates. For instance, aryl bromides and chlorides were coupled with benzophenone imine as ammonia surrogate, producing *N*-unsubstituted anilines upon acidic work up (*Scheme 1.65.*).[146]



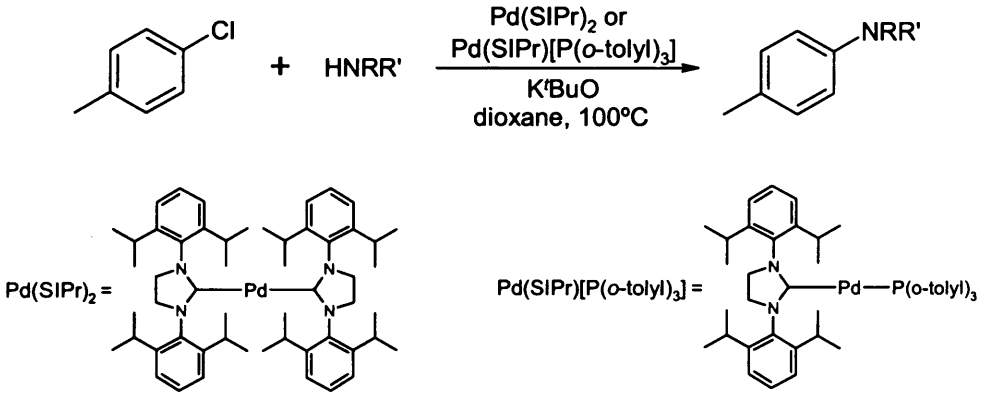
Scheme 1.65.

Additionally, Nolan successfully reacted bromo- and chloropyridines with amines in good to excellent yields, as well as employing indoles as coupling partners for aryl bromides with a change of ligand to a saturated imidazolium salt (*Scheme 1.66.*).[146]



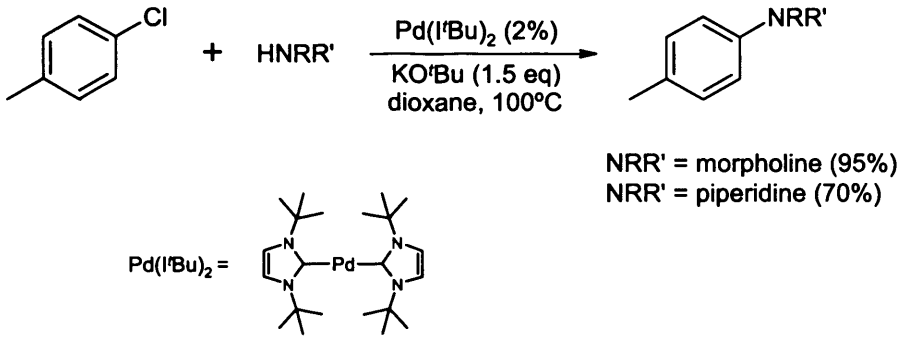
Scheme 1.66.

The Caddick group proved that amination of 4-chlorotoluene was feasible employing Pd bis-carbene, $Pd(SIPr)_2$, and mixed carbene-phosphine Pd(SIPr)[P(*o*-tolyl)$_3$] complexes, with a range of primary, secondary and aryl amines, although higher temperatures were needed (*Scheme 1.67.*). Moreover, during the course of this work, an unexpected lability of the Pd-carbene bond was observed.[142]



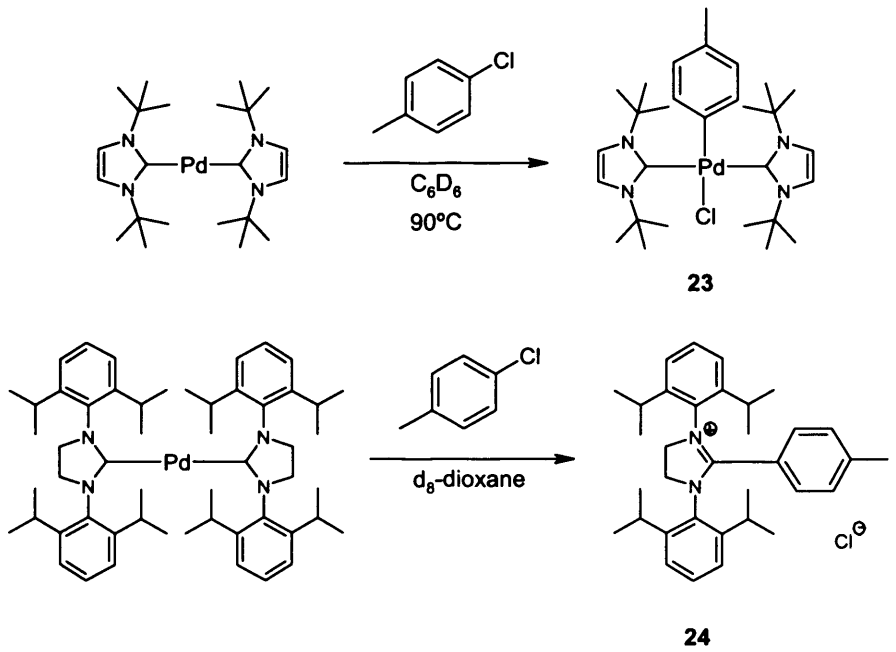
Scheme 1.67.

In addition to the above complexes, the Caddick group also reported an improved procedure for the synthesis of complex $Pd(I^tBu)_2$, which proved successful in the amination of 4-chlorotoluene with morpholine and piperidine (*Scheme 1.68.*).[116]



Scheme 1.68.

Soon after, a mechanistic study on the amination of 4-chlorotoluene with Pd(I^{t}Bu)$_2$ was reported, resulting in the isolation and characterisation of the first oxidative addition product **23** of an aryl chloride with a Pd bis-carbene complex (*Scheme 1.69.*). Curiously, a similar complex Pd(SIPr)$_2$ produced Pd black and arylated imidazolium salt **24**.[147]



Scheme 1.69.

Kinetic studies on aryl chlorides have shown that oxidative addition was the rate-determining step and it was influenced by the nature of the substituents on the aryl ring. This way, electron withdrawing groups favoured oxidative addition whilst the

opposite was observed for electron donating groups. The kinetic data was consistent with a mechanistic pathway featuring previous dissociation of a carbene ligand from the Pd-bis carbene complex prior to oxidative addition.[148]

Subsequent studies on the catalytic activity of Pd bis-carbene complexes versus the catalytic system generated *in situ*, proved the latter to be superior in amination of aryl chlorides. Of the Pd complexes studied, those with a saturated NHC backbone were more efficient than their unsaturated counterparts.[149]

New advances in this area have given rise to different Pd-NHC structural motifs or generations. For instance, Pd-NHC complexes bearing "dummy" ligands, such as allyl moieties, have been developed. Their ease of synthesis and the possibility of carefully controlling their electronic properties have made them interesting second generation catalyst in amination and Suzuki reactions (*Figure 1.12.*).[116,150]

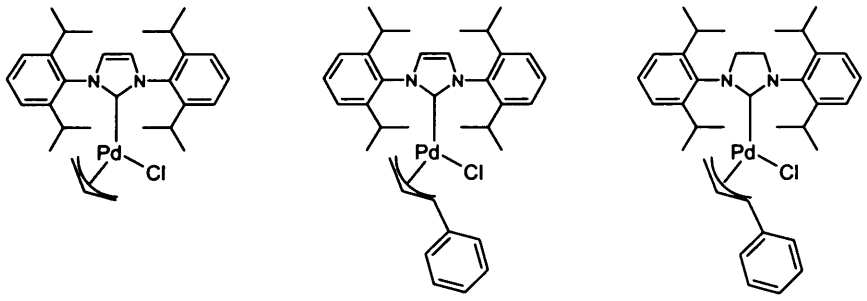
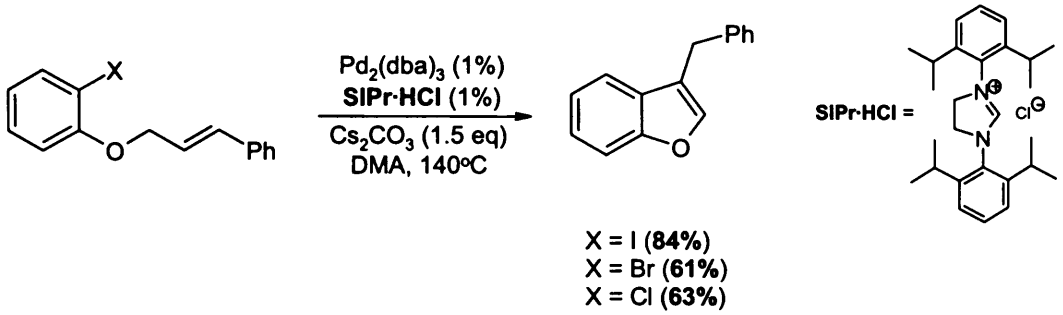


Figure 1.12. Second generation Pd-NHC complexes.

Chapter Two : INTRAMOLECULAR HECK CYCLISATIONS

2.1. *INTRODUCTION*

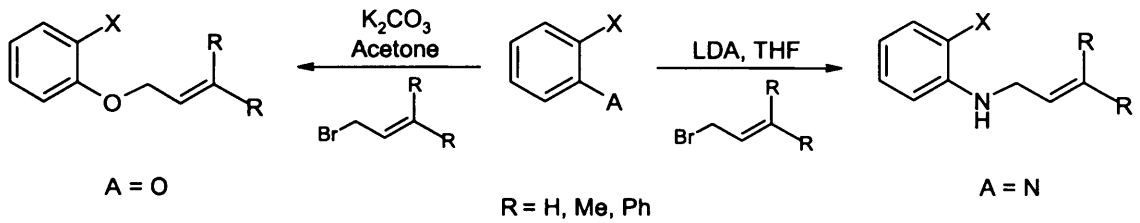
A previous report from our group was mainly focused on nitrogen containing heterocycles, prepared by intramolecular Heck reactions.[136] Only one instance with an oxygen containing substrate leading to a benzofuran was reported (*Scheme 2.1.*).



Scheme 2.1. Intramolecular Heck reported by Caddick *et al.*

Benzofurans and their derivatives are known to possess important biological properties. As such, we sought to extend that protocol to the preparation of other benzofurans. We were also particularly interested in utilising substrates where the halide was chlorine due to the wider availability and economic advantage of using aryl chloride precursors.

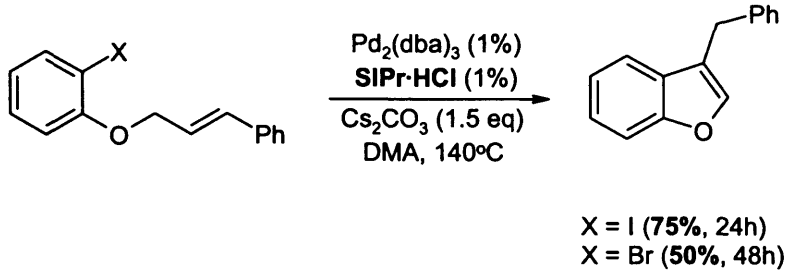
O- and *N*-allyl-*o*-halobenzenes were prepared using previous procedures employed by our group.[136] Typically, *o*-halobenzenes were treated in basic conditions with an allyl bromide (*Scheme 2.2.*) and full details are given in the experimental section.



Scheme 2.2. Preparation of *O*- and *N*-allyl-*o*-halobenzenes.

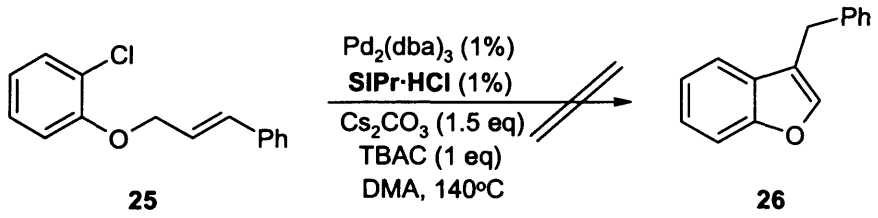
2.1. *RESULTS AND DISCUSSION*

Initially, the example in *Scheme 2.1* was replicated (*Scheme 2.3.*).[136] The reactivity pattern was in agreement to that reported of increasing reaction times moving from iodo- (24h) to the bromo-substrate (48 h).



Scheme 2.3.

Disappointingly, the formation of 3-benzylbenzofuran, **26**, from the chloro-derivative **25** proved unattainable (*Scheme 2.4.*). During the course of the reaction, disappearance of the starting substrate was not followed by the formation of the required product. This result led to a more thorough investigation into these reactions.



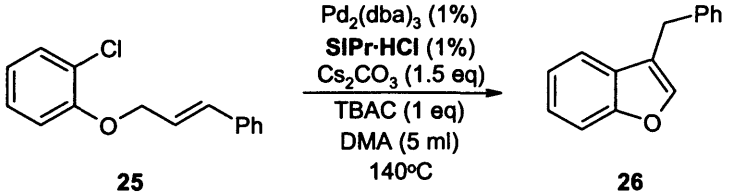
Scheme 2.4. Reported conditions for intramolecular Heck of substrate **25**.[136]

The optimum conditions previously reported by our group involved high temperatures, typically 140°C. This factor was revisited in different solvents; DMA, DMSO, DMF and dioxane. It was apparent that at room temperature or under mild heating, the reaction did not proceed or proceeded very slowly and starting material was the only component present in the mixture. The disappearance of starting material was only observed at temperatures above 100°C, which is within the range of typical temperatures necessary for the Heck reaction. Pd and ligand loadings were also increased from 1% to 10% in a bid to facilitate the transformation of our substrate into the required product without success.

Quaternary ammonium salts of the type TBAI, TBAB, TBAN and TBAC have proved fundamental additives in some Heck reactions as discussed in the introduction. However, they are known for their hygroscopicity, especially TBAC. Caddick's observations on intramolecular Heck cyclisations showed the dramatic effect on yields by comparison of the outcome of reactions involving chloride substrates with and without these additives.[136] In agreement with the "Jeffery's effect", in those reactions of chloro-substrate, **25**, proceeded to better yields when TBAC was present. Although this was not explicitly addressed in any previous work, we were concerned about a potential adverse effect of water and these salts were purified ahead of the experiments, according with literature procedures.[151] These freshly purified salts achieved the same degradation components in the reaction mixture.

Activated molecular sieves were also employed as an additive in order to ensure that conditions were totally free of adventitious water. This also led to a negative outcome on this reaction.

A summary of other studies is presented below (*Table 2.1*). In all cases, **25** was reacted in DMA with one or more of the reagents as indicated.



25 **26**

Experiment	Cs_2CO_3	$Pd_2(dba)_3$	SIPr·HCl	TBAC	Product	Recovered SM
A	-	-	-	-	No	Yes
B	√	-	-	-	No	Yes
C	-	√	-	-	No	Yes
D	-	-	√	-	No	Yes
E	-	-	-	√	No	Yes
F	-	√	√	-	No	No
G	√	√	√	-	No	No

Table 2.1.
Reactions were conducted on a 1 mmol scale of **25** for 24h.

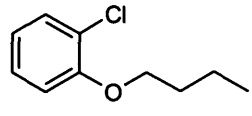
Several important observations were drawn solely on the basis of TLC analysis. Experiment A proved the thermal stability of **25** as no other component was observed

after 24h. Experiments B-E confirmed that the individual components in isolation and in the relevant quantities were not responsible for substrate degradation, including the Pd source. Equally important, the potential presence of moisture from its most likely source, i.e. TBAC, did not exert a negative effect. Only experiments containing the system Pd/**SIPr·HCl** afforded degradation products, confirming that was a Pd catalysed process in need of ligands. Finally, in the absence of TBAC, i.e. experiment G, the same degradation process was exhibited.

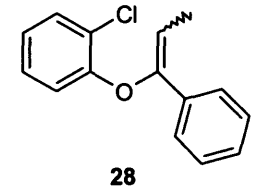
During the introduction, it has been discussed how the presence of the unsaturation brought additional, but far from vital, stability to the resulting carbene ligand. With that in mind, a straight switch of the **SIPr·HCl** employed for the imidazolium salt **IPr·HCl** was performed without any improvement in the outcome.

The nature of the base is known to exert profound effects on the Heck reaction and we wanted to examine how a stronger base such as KO^{t}Bu would perform against Cs_2CO_3. KO^{t}Bu has been often employed in catalytic processes involving carbene precursors, including the amination of aryl halides described in next chapter but, in our hands, it proved equally ineffective.

The identification and characterisation of the degradation products resulting from this reaction was complicated by the fact that it was difficult to resolve them by TLC, irrespective of the eluting solvent. Despite these difficulties, two main by-products, **27** and **28** (*Figure 2.1.*), could be identified on the basis of NMR and MS analysis (Appendix 1).



27

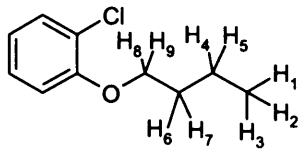


28

Figure 2.1.

Although the NMR spectra were not totally free of impurities, compound **27** (*Figure 2.2.*) presented a typical signal display for a *n*-butyl residue with a triplet (0.96-1.06 ppm, $H_{1,2,3}$) for the terminal methyl group, a sextet (1.48-1.57 ppm, $H_{4,5}$) and a quintet (1.77-1.84 ppm, $H_{6,7}$) for the internal two methylene groups and a triplet

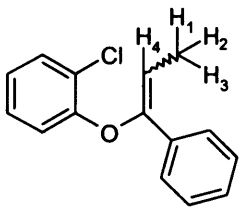
(4.00-4.03 ppm, $H_{8,9}$) for the methylene attached to oxygen. The aromatic region showed quite clearly a total of four protons, indicating the presence of two substituents in the phenyl ring and their pattern and multiplicity were indicative of an *ortho* arrangement. The HPLC chromatogram under UV detection presented two peaks at 6.38 and 7.47 min. of retention time.



27

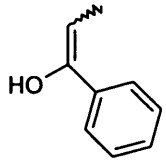
Figure 2.2.

As was the case with **27**, compound **28** (*Figure 2.3.*) could not be isolated cleanly. The HPLC chromatogram presented a main peak at 6.74 min, although there were minor impurities which included **27**. The molecular ion for that peak was 245/247 in a pattern typical for the presence of chlorine. A fragment of **28** could also be observed with a *m/z* (135) consistent with compound **29**. ^{1}H-NMR showed clear presence of **27** as an impurity. A doublet (1.75-1.77 ppm, $H_{1,2,3}$) corresponding with the methyl group protons could be observed, as well as a quartet (5.93-5.98 ppm, H_4) for a proton coupling with them. This pattern eliminated compound **30** which was isomeric with **28**, as the methyl protons would have not been able to couple with any other proton.



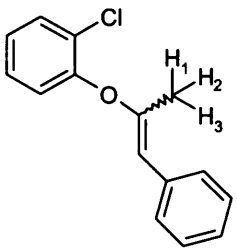
MWt=244

28



MWt=134

29



MWt=244

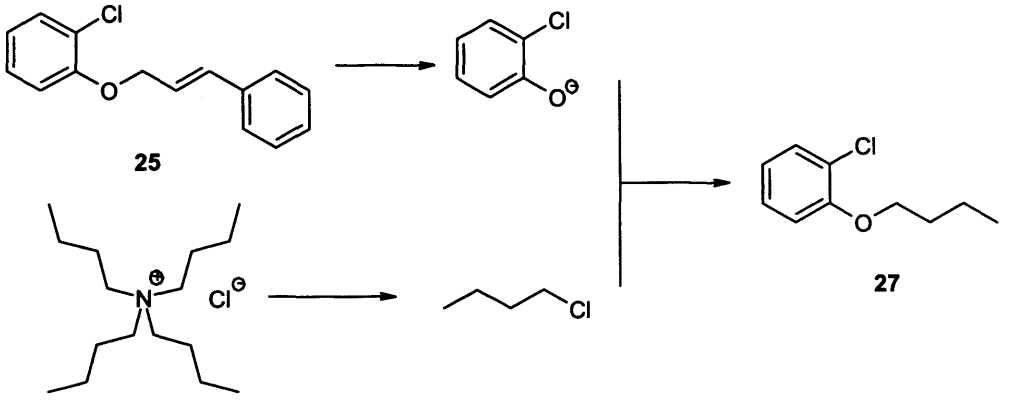
30

Figure 2.3.

The origin of this by-product formation was believed to be the loss of the allyl moiety by a Pd *O*-deallylation process. The allyl group is commonly used as a

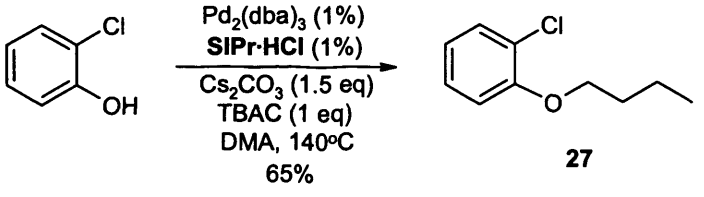
protecting group for alcohols, offering good stability towards mild acidic and basic conditions, and a good example of its importance is its role in the assembly of complex natural products.[152] Two main routes are open for its cleavage, either isomerisation of the double bond followed by acid hydrolysis or reaction with metals such as Pd, Rh and Ir in catalytic quantities.

A representation of the process leading to **27** is depicted below (*Scheme 2.5.*). After deallylation of **25**, the initial chlorophenol is obtained and, under the basic reaction conditions, is able to react with *n*-butyl chloride formed by substitution.



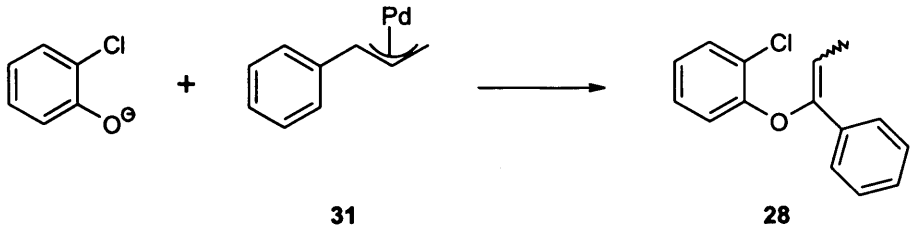
Scheme 2.5.

In order to prove the feasibility of this reaction, chlorophenol was subjected to the same conditions and led also to **27** (*Scheme 2.6.*).



Scheme 2.6.

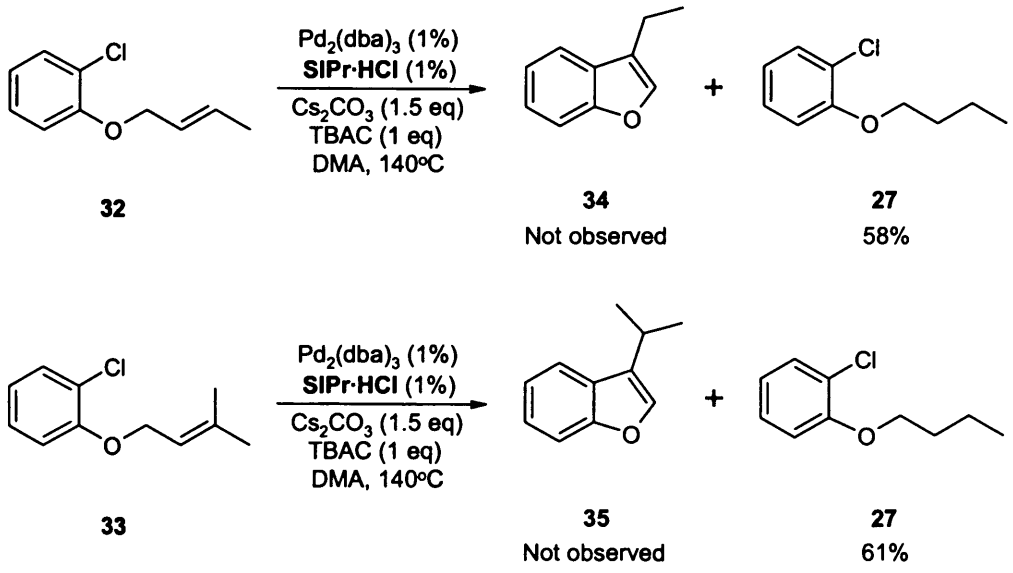
During the course of our studies, we showed that decomposition of **25** was possible without the presence of TBAC. We inferred that a separate reaction was taking place and giving rise to **28**. 2-Chlorophenol was able to react in the presence of Pd-allyl complex **31**, (*Scheme 2.7.*). MS evidence pointed to a chlorinated material of the expected *m/z* for **28**.



31 **28**

Scheme 2.7.

This behaviour was found to be not just characteristic of the cinnamyl containing substrate **25**, but also of similar allyl derivatives. Thus, substrates **32** and **33** could not be cyclised to **34** and **35**, respectively under the same conditions (*Scheme 2.8.*). In both cases, the disappearance of starting material was observed, but the required product was never formed. Instead, a similar deallylation process to the one described gave rise to compound **27** in both cases.

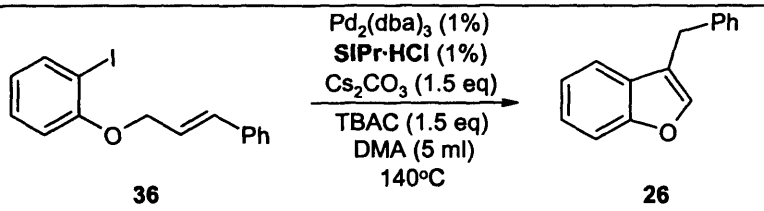


32 **34** Not observed **27** 58%

33 **35** Not observed **27** 61%

Scheme 2.8.

A similar study to the one conducted for the chloro-substrate **25** was applied to the iodo-substrate **36** (*Table 2.2.*). This was found to be stable to prolonged heating in the presence of base, ligand or $Pd^{(0)}$ source independently (*Table 2.2.*, Experiments B'-E'), as well as in the absence of them all (*Table 2.2.*,Experiment A').



36 **26**

Experiment	Cs_2CO_3	$Pd_2(dba)_3$	SIPr·HCl	TBAC	Yield
A'	-	-	-	-	-
B'	√	-	-	-	-
C'	-	√	-	-	-
D'	-	-	√	-	-
E'	-	-	-	√	-
F'	-	√	√	-	-
G'	√	√	√	-	75
H'	√	√	√	√	61[a]

Table 2.2.
Reactions were conducted on a 1 mmol scale of **36**.
(a) 1-Butoxy-2-iodobenzene was observed.

It is worth noting that the addition of ammonium salt TBAC to this reaction had a slightly detrimental effect (*Table 2.2.*, experiment H'). Minimal quantities (5%) of 1-butoxy-2-iodobenzene were observed as a result of the same process in operation during intramolecular reaction of **25**.

Another interesting finding had to do with the activity of the catalytic system. After the reaction was deemed complete by TLC, further amounts of both iodo-substrate **36** (1 mmol) and base (1.5 mmoles, 1.5 eq) were added in the same Schlenk tube resulting in subsequent conversion to product. The catalytic activity was still high up to the third run investigated.

Having established the validity of the standard protocol for the intramolecular Heck of aryl iodides, we proceeded to extending it further to other substrates, including bromo-substrates. The results are summarised below (*Table 2.3.*).

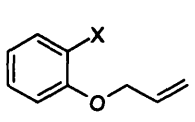
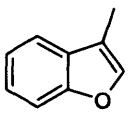
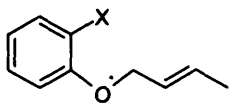
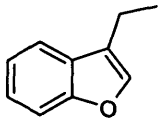
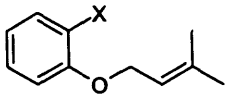
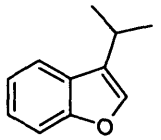
Entry	Substrate	Product	Yield[a]
1 2			I: 81% Br: 77%[b]
3 4			I: 82% Br: 71%[b]
5 6			I: 76% Br: 66%[b]

Table 2.3.
Conditions: 1 mmol of substrate, $Pd_2(dba)_3$ (1%), SIPr·HCl (1%), Cs_2CO_3 (1.5 mmoles), DMA (10 mL), 140°C, 24h. (a) Isolated yields. (b) 48h reaction time.

Finally, after the problems identified with *O*-allyl-*o*-chlorobenzene substrates, we wished to establish whether the deallylation process would occur with *N*-allyl-*N*-halobenzenes. As expected, the reactions of iodo- and bromo-substrates were successfully cyclised and this is consistent with previously reported results (*Table 2.4.*).[136]

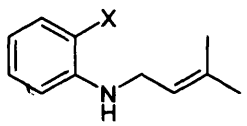
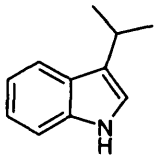
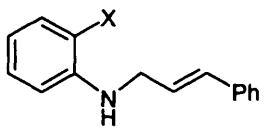
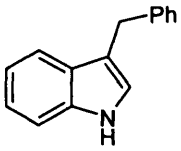
Entry	Substrate	Product	Yield[a]	Yield[b]
1 2 3			I: 76% Br: 56% Cl: 58%[c]	I: 79% Br: 62% Cl: 60%[c]
4 5 6			I: 78% Br: 71% Cl: 70%[c]	I: 75% Br: 62% Cl: 60%[c]

Table 2.4.
Conditions: 1 mmol of substrate, $Pd_2(dba)_3$ (1%), SIPr·HCl (1%), Cs_2CO_3 (1.5 mmoles), DMA (10 mL), 140°C, 24h. Reported (a) and isolated (b) yields. (c) TBAB added.

To our delight, the reaction of the chloro-substrate was also successful. Although the allyl group is also employed as a protecting group for nitrogen, under our conditions it was found not to be cleaved whilst still performing satisfactorily in an intramolecular Heck cyclisation.

2.2. *CONCLUDING REMARKS*

The synthesis of 3-substituted benzofurans following a palladium/imidazolium salt protocol has been achieved following a similar protocol to that reported previously in our group for the preparation of 3-substituted indoles.[136]

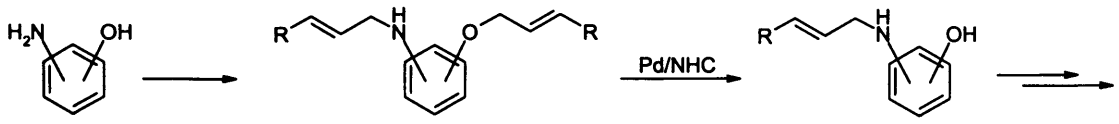
Although the concept of Pd catalysed intramolecular cyclisation is far from new, this work has introduced another protocol to the many other synthetic solutions, catalytic or otherwise, available for the preparation of both benzofurans[153-156] and indoles.[157-161] Its value is two fold; firstly, it has proved useful for the preparation of indoles from substrates with chlorine as halide which, for the aforementioned reasons, are interesting starting materials and, secondly, this protocol has proved that a catalytic system comprised of a Pd source and imidazolium salt is a good alternative to other protocols employing more expensive phosphines or difficult to handle catalytic systems.

However, aryl chlorides still remain challenging substrates for the Heck and other Pd catalysed reactions and the reactivity of Pd-NHC complexes, either pre-formed or formed *in situ*, is yet to match in some cases that of their phosphines counterparts.[162]

New advances in reaction conditions or structural variations around the NHC motifs may yet bring enhanced reactivity to aryl chlorides. To date and to the best of our knowledge, there have not been more reports on intramolecular Heck cyclisations using the protocol previously developed in our group or further extended in this thesis.

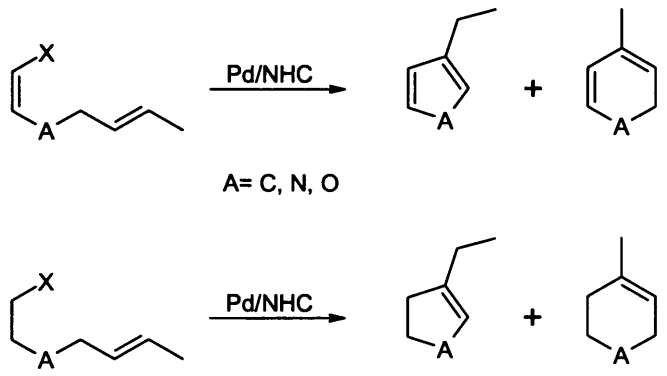
The main limitation encountered was the problems associated with forming 3-benzylbenzofurans employing chloride substrates. Instead, a process leading to the loss of the allyl moiety was observed. In stark contrast, this deallylation process was not observed using substrates containing chlorine and *N*-allyl moieties, consistent with a previous report in our group.[136]

Future work in this area should focus on identification of the factors responsible, on the one hand for cyclisation and for the other on deallylation. If the preference between *O*-deallylation over *N*-deallylation holds generally true, allyl groups might be employed as protecting groups for substrates containing both alcohol and amine functionalities. Deallylation under our conditions might avoid deprotection of the amine and expose the alcohol for further elaboration (*Scheme 2.9.*).



Scheme 2.9.

Another future line of research may choose to focus on intramolecular Heck cyclisations of vinyl or alkyl halides to provide both carbo- and heterocyclic structures (*Scheme 2.10.*). For those alkyl halides possessing hydrogen atoms at *beta* positions, the potential for β-hydride elimination must be addressed by this or future generations of Pd/NHC catalytic systems.



Scheme 2.10.

Chapter Three : AMINATION OF ARYL IODIDES

3.1. INTRODUCTION

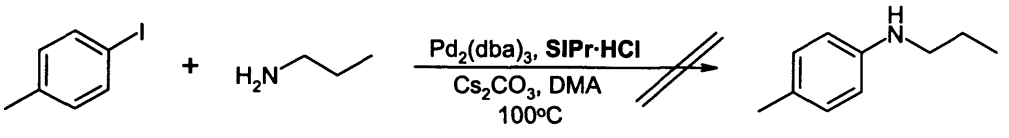
We also sought a general set of conditions for the Hartwig-Buchwald amination of aryl iodides, thus allowing for a catalytic system of general applicability across several Pd catalysed reactions.

Although aryl iodides have often been regarded as very reactive coupling substrates in comparison with aryl bromides and especially, chlorides, Pd/imidazolium salt protocols reported to date have suffered with limited applicability to electron rich aryl iodides and primary amines. In contrast, aryl chlorides and bromides have been used extensively using this catalytic system.

Finding a mild protocol for the amination of aryl iodides was still of great interest despite the advances in both NHCs and phosphine ligands. Furthermore, that protocol should prove universal for several types of amines, from reactive cyclic secondary cases through to primary amines or amides.

3.2. RESULTS AND DISCUSSION

The amination of 4-iodotoluene and *N*-butylamine was first attempted using the $Pd_2(dba)_3$/**SIPr·HCl** system from previous chapter (*Scheme 3.1.*).



Scheme 3.1.

Unexpectedly, upon isolation the product proved to be 4,4'-dimethylbiphenyl in 65% yield (Figure 3.1.), apparently the result of the Pd catalysed homocoupling of 4-iodotoluene.

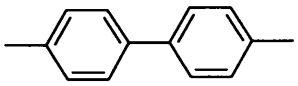
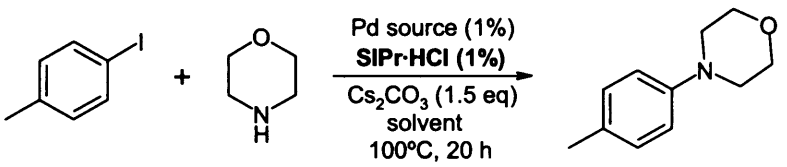


Figure 3.1. Homocoupling product.

A similar outcome was also found with a secondary amine such as morpholine (*Table 3.1.*). Four different Pd sources; $Pd_2(dba)_3$, $PdCl_2$, $Pd(dba)_2$ and $Pd(OAc)_2$ were screened in two different solvents (toluene and dioxane).

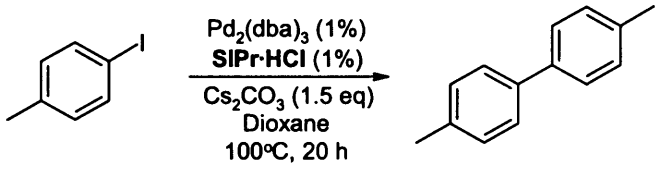


Experiment	Pd source	Solvent	Recovered SM	Product observed
A	$Pd_2(dba)_3$	Toluene	45%	Bitolyl
B	$Pd_2(dba)_3$	Dioxane	-	Bitolyl (65%)
C	$PdCl_2$	Toluene	57%	Bitolyl
D	$PdCl_2$	Dioxane	-	Bitolyl (55%)
E	$Pd(dba)_2$	Toluene	44%	Bitolyl
F	$Pd(dba)_2$	Dioxane	-	Bitolyl (61%)
G	$Pd(OAc)_2$	Toluene	51%	Bitolyl
H	$Pd(OAc)_2$	Dioxane	-	Bitolyl (59%)

Table 3.1.

Dioxane appeared to be a better solvent than toluene for promoting this reaction, as no unreacted starting material was isolated. However, in all cases none of the desired product was observed and bitolyl was the main component present in the mixture. The combination of these findings suggested at this stage that, independently of solvent, type of amine and Pd source, the homocoupling process was due to a combination of base and ligand **SIPr·HCl**.

An investigation into the stability and reactivity of the starting aryl iodide was conducted (*Table 3.2.*). Morpholine was not included as it was not believed to play a role in the homocoupling process.

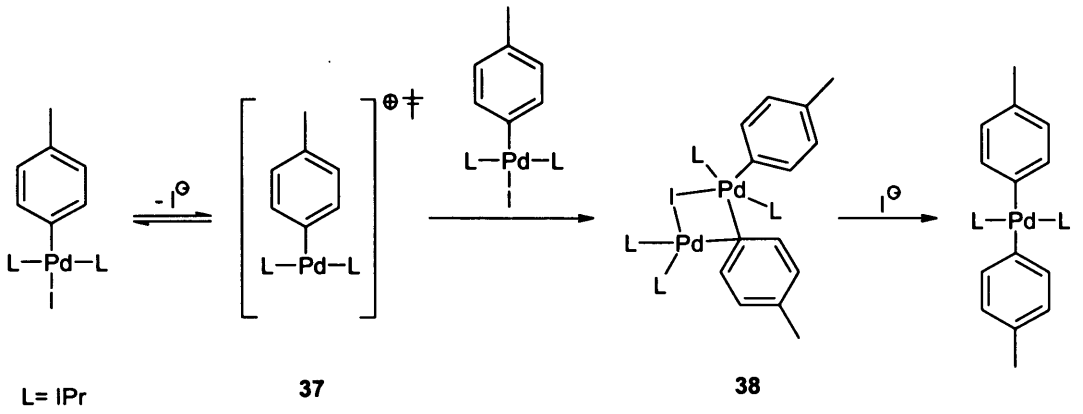


Experiment	Cs_2CO_3	$Pd_2(dba)_3$	SImid 1
A	-	-	-
B	√	-	-
C	-	√	-
D	-	-	√
E	√	√	√

Table 3.2.

In all cases unreacted starting material was the only component present by TLC after twenty hours. Intriguingly, upon addition of morpholine and with further heating, the appearance of the bitolyl compound was observed (experiment E, *Table 3.2.*).

The formation of bis-aryls is of great importance in many areas of Chemistry and numerous palladium-based protocols have been developed to address this synthetic problem.[163,164] In mechanistic terms one possibility is that such reactions proceed via a $Pd^{(IV)}$ complex, although this has been discounted by Cavell based on his spectroscopic studies on a similar system.[141] Based on the assumption that the carbene ligands would not dissociate, Cavell postulated that iodine would become the leaving group therefore generating a three coordinated Pd transition state **37**, which exchanges to form an aryl bridged Pd dimer **38**. Final reductive elimination would afford the homocoupling product (*Scheme 3.2.*).



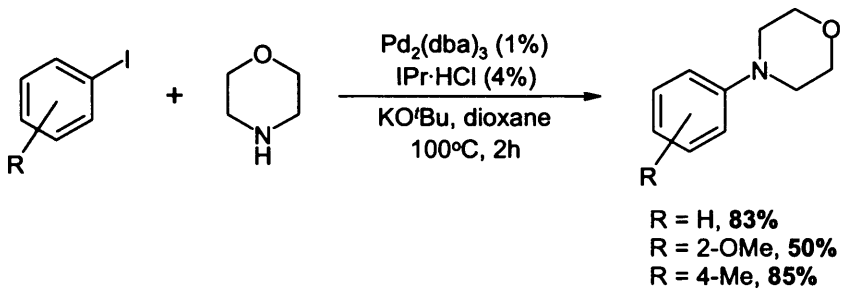
L= IPr 37 38

Scheme 3.2.

Contrary to our initial assumption, the role of amine was found to be crucial in this bis-arylation process, although the above hypothesis by Cavell obviated its participation. We inferred that this reaction was due to a combined effect of amine as well as base, since our later work under similar conditions but utilising a stronger alkoxide base afforded the desired product and no bis-arylation. Identifying the exact nature of this phenomenon was beyond the scope of our studies. We can only speculate that the presence of a weak base favours a situation in which the amine might coordinate to Pd before oxidative addition of the aryl iodide. Another molecule of aryl iodide might then undergo further oxidative addition to the resulting complex.

Isolation of the homocoupling product in a separate preparative scale reaction and under the conditions of experiment E (*Table 3.2.*), afforded 65% yield. Although the yield was satisfactory, this compound was still considered a by-product of the reaction of interest and further studies into the optimisation of these reactions were not pursued.

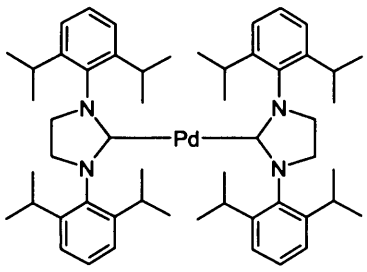
The conditions previously reported by Nolan were then revisited utilising the unsaturated ligand **IPr·HCl** and employing an alkoxide base (*Scheme 3.3.*).[146] It was gratifying to obtain the desired products in moderate to excellent yields and after a relatively short reaction time.



Scheme 3.3.

After adopting the reaction of iodobenzene and morpholine as a benchmark, several observations were made upon changes to the experimental parameters. A larger excess of amine did improve the yield when heating but only slightly to 89%. At ambient temperature, the final yield decreased to 41% after 24h. Only after prolonging the reaction time to 48h, the yield increased to 53%.

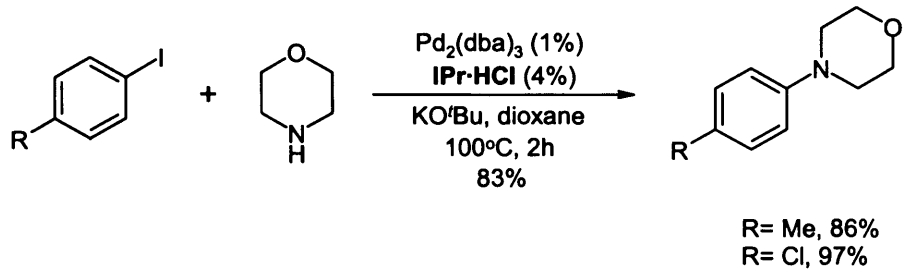
Two other catalysts systems were screened; **SIPr·HCl** offered a lesser yield (77%), whilst the complex **Pd(SIPr)$_2$** (*Figure 3.2.*), resulted in a 73% yield. This was another example of the difference of reactivity, between the *in situ* generated ligand and the preformed, well-defined Pd-NHC complex.



Pd(SIPr)$_2$

Figure 3.2.

The validity of these conditions was confirmed when changing from iodobenzene to 4-iodotoluene and 4-chloro-iodobenzene (*Scheme 3.4.*).

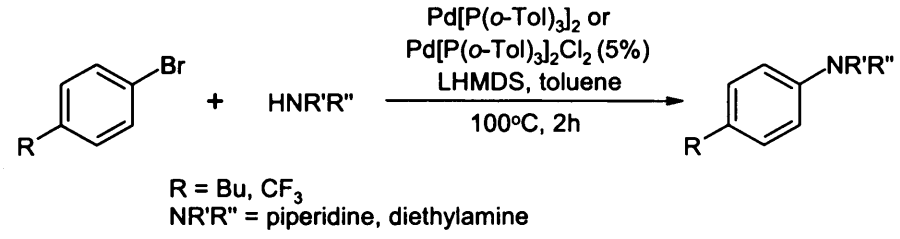


Scheme 3.4.

Despite the good yields presented, this protocol had several drawbacks. Firstly, these reactions only afforded moderate yields at ambient temperature. Secondly, it was reliant on the use of KO^{t}Bu as base which has been recommended to be stored and used under anhydrous conditions, typically in a dry box, for optimal results.[146] Additionally, the presence of KO^{t}Bu made it incompatible with functional groups such as triflates, ketones or phenols.

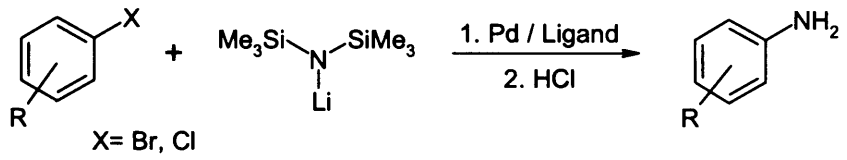
In the pursuit for even milder and more amenable laboratory conditions, the hindered base LHMDS came across as a potential substitute for alkoxide bases. LHMDS is commercially available either as a solid which must be handled under a dry atmosphere or more conveniently as stock solutions in THF, dioxane and toluene.

Herrmann first employed both KHMDS and LHMDS for the isolation of NHCs from their salt precursors in liquid ammonia.[101] With regards to Pd catalysed aminations, LHMDS had already been introduced as a base by Hartwig (*Scheme 3.5.*).[50]



Scheme 3.5.

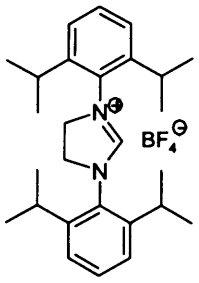
Brüning[165] employed LHMDS for the catalytic transformation of allyl chloride into allyl bis(trimethylsilyl)amine and, later Hartwig[166] and Buchwald[167] utilised it as an ammonia surrogate for the formation of anilines (*Scheme 3.6.*).



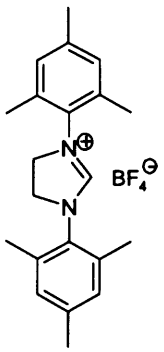
Buchwald's conditions: $Pd_2(dba)_3$, (biphen)PCy_2, toluene
Hartwig's conditions: $Pd(dba)_2$, P(*t*-Bu)$_3$, toluene

Scheme 3.6.

It is worth noting how the presence of NHC precursors in Hartwig's work, i.e. imidazolinium salts **SIPr·HBF$_4$** and **SIMes·HBF$_4$** (*Figure 3.3.*), did not lead to efficient transformations into the aryl bis-(trimethylsilyl)amine.



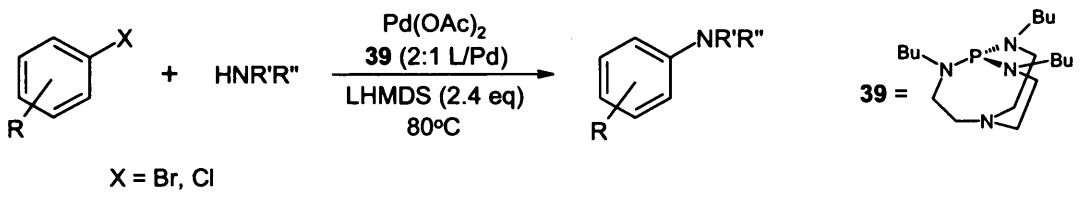
SIPr·HBF$_4$



SIMes·HBF$_4$

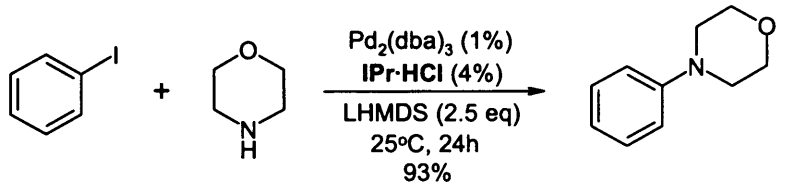
Figure 3.3

LHMDS has also been utilised as an effective base with a novel kind of proazaphosphatrane ligand **39** for the amination of aryl bromides and chlorides (*Scheme 3.7.*). Furthermore, it is compatible with alcohol, amide and ketone functionalities on the initial aryl halide. The limitations were also reported; intolerance to amines bearing these functionalities, incompatibility with *ortho* substitution and with primary and acyclic amines.[168]



Scheme 3.7.

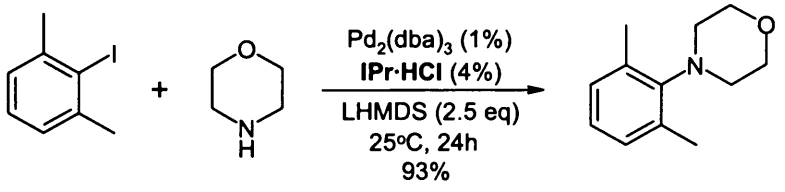
Following that report, a first attempt was conducted with an imidazolium salt **IPr·HCl** as ligand. LHMDS (1M solution in THF) was employed without added co-solvent, thus doubling as a reaction medium (*Scheme 3.8.*).



Scheme 3.8.

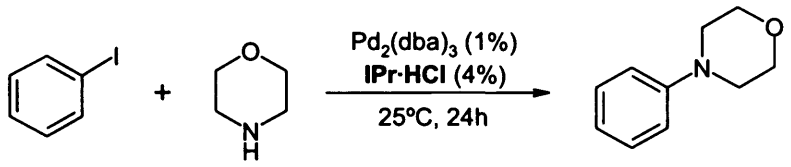
To the best of our knowledge, this was the first time that LHMDS was employed in this way with a NHC precursor, and it gave rise to the amination product in excellent yield and under mild reaction conditions.

Several reactions were conducted to ascertain the catalytic nature of this system. In this manner, $Pd_2(dba)_3$ and **IPr·HCl** were omitted in separate experiments with no product formation. The possibility of a reaction path involving benzyne was ruled out by using a substrate which avoided its formation (*Scheme 3.9.*).



Scheme 3.9.

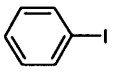
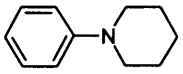
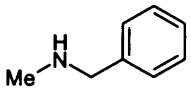
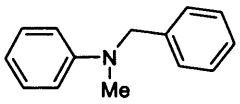
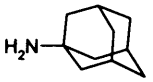
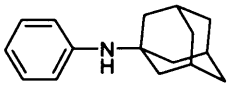
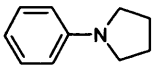
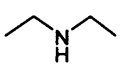
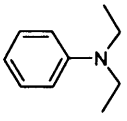
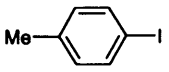
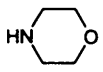
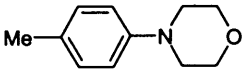
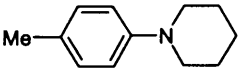
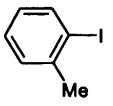
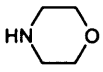
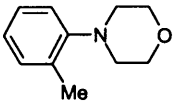
As discussed earlier, LHMDS is a member of a triad of commercially available trimethylsilylamide bases, which also features KHMDS and NHMDS. After screening these bases in our benchmark reaction (*Scheme 3.10.*), a significant decrease in yield was observed. This difference in reactivity was consistent with the original report that inspired the utilisation of LHMDS as base.[168]



NHMDS (2.5 eq, 1M in THF) = 13% yield
KHMDS (2.5 eq, 0.5M in toluene) = 42% yield

Scheme 3.10.

With this procedure in hand, other reactions of this kind were subsequently conducted in order to investigate its scope (*Table 3.3.*).

Entry	Ar-I	HNR'R''	Ar-NR'R''	Yield (%)[a]
1				81
2				89
3				70
4				88
5				27
6				90
7				83
8				92

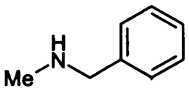
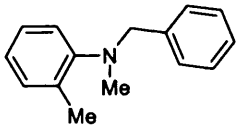
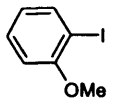
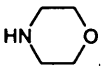
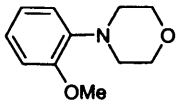
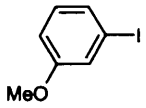
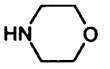
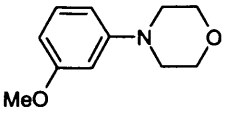
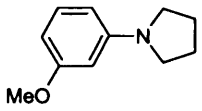
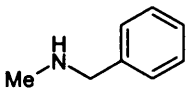
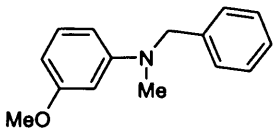
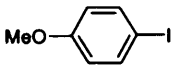
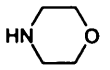
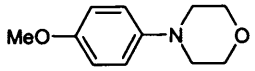
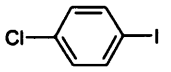
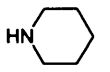
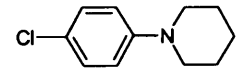
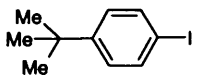
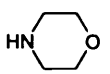
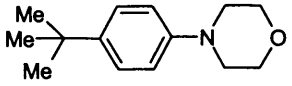
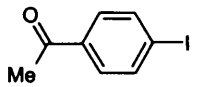
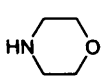
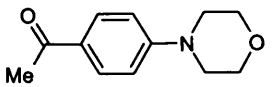
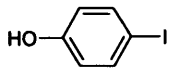
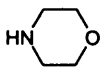
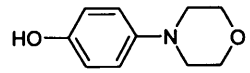
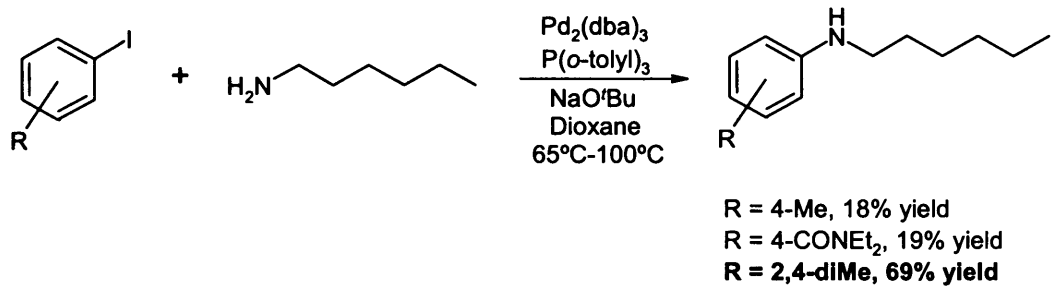
Entry	Ar-I	HNR'R''	Ar-NR'R''	Yield (%)[a]
9				82
10				78
11				79
12				78
13				88
14				96
15				85
16				89
17				66
18				20

Table 3.3.

Conditions: 1 mmol of aryl iodide, 1.2 eq. of amine, $Pd_2(dba)_3$ (1%), IPr·HCl (4%) and 2.5 eq. of LHMDS (1M in THF), 25°C, 24h. Reactions times were not optimised. (a) Isolated yields.

As it can be seen from the table, all but one of the amines featured were secondary ones. Our attempts of coupling primary amines, with the exception of adamantanamine, were unsuccessful.

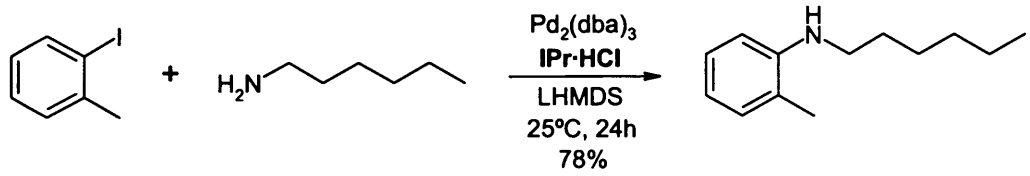
Primary amines, were identified as particularly problematic substrates when the first Pd catalysed protocols were reported; "*In the case of primary amines, including aniline, acceptable yields are only realised when there is a substituent ortho to the iodide*", Buchwald.[51] Indeed, this author presented low yields of coupling product when using *N*-hexylamine as coupling partner. However, when the aryl iodide featured an *ortho* substituent, a good yield was achieved (*Scheme 3.11.*).



Scheme 3.11. Reactions reported by Buchwald.[51]

Even after further developments in this area by Buchwald, which included a newer generation of phosphine ligand, heating was still required.[169]

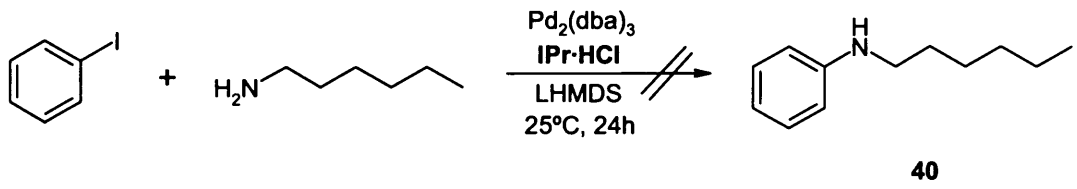
With this precedent in mind, we were able to perform a similar reaction under our RT protocol in good yield (*Scheme 3.12.*), obviating the heating conditions.



Scheme 3.12.

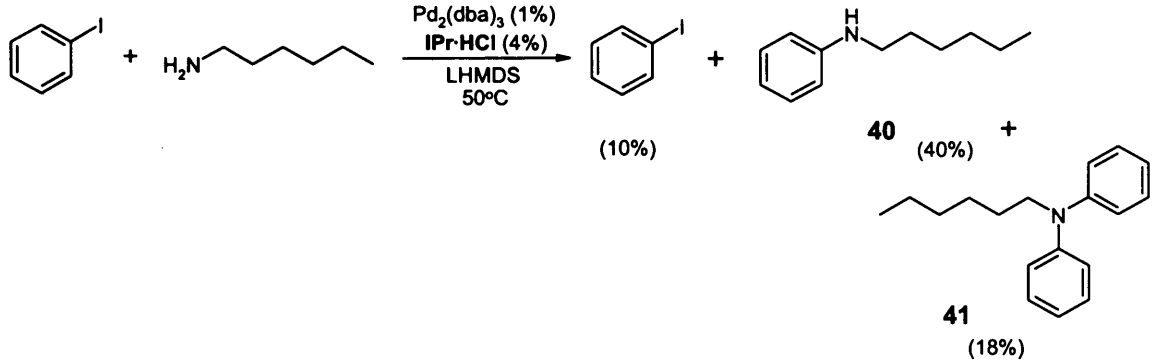
Two precedents of a similar reaction conducted by Hartwig on 2-chlorotoluene still required heating, as opposed to our RT protocol.[170,171]

Much experimentation was directed towards studying the reactivity of an aryl iodide lacking an *ortho* substituent, i.e. iodobenzene, with *N*-hexylamine (*Scheme 3.13.*).



Scheme 3.13.

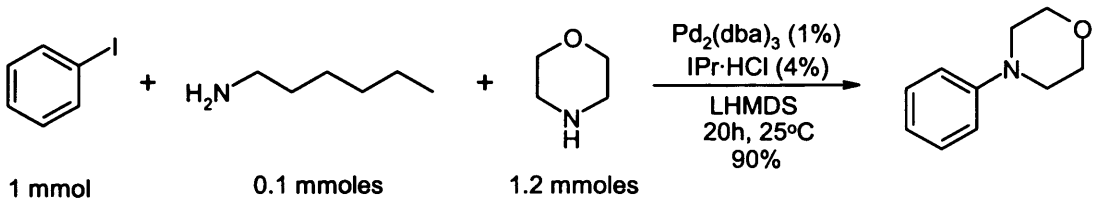
- Under our protocol, the starting iodobenzene did not react at all and no other apparent component was present in the reaction mixture. This result was consistent with the original report by Verkade which inspired our RT protocol.[168]
- An excess of amine (2 eq) resulted in the deposition of Pd black.
- Heating (50°C) was only partially successful with some starting material disappearing in favour of the required product **40** although the bis-arylation product **41** was also observed (*Scheme 3.14*).



Scheme 3.14.
Percentages in parenthesis indicate recoveries.

- Prolonged reaction times at higher temperature (60-70°C) did not appear to improve the consumption of starting material.
- An investigation into the order of addition of reagents followed and completion was achieved under very specific conditions, i.e. simultaneous dropwise addition of both iodobenzene and amine over a preheated (60°C) mixture containing base, Pd and ligand. However, the presence of bis-arylation (compound **41**) was unavoidable indicating that the mono-arylated product **40** (secondary amine) was in direct competition with *N*-hexylamine.
- In contrast, dropwise addition of iodobenzene to the preheated (60°C) mixture of all other reagents resulted in no reaction.
- The catalytic system proved to be active when our protocol was followed for the amination of iodobenzene with morpholine and a substoichiometric quantity of *N*-hexylamine (10 molar%). Although the yield was comparable with previous results,

the effect on rate was noticeable and reaction times increased from 30 min, with no added *N*-hexylamine, to 20 hours (*Scheme 3.15.*).



Scheme 3.15.

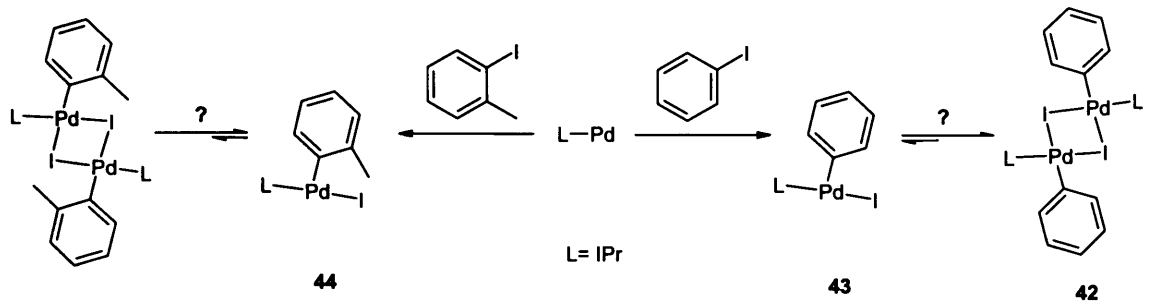
All the above results as a whole suggested that the amine played a key and as yet undefined role rather than simply acting as coupling partner during the catalytic cycle.

An understanding of the mechanism of this transformation has been sought for the last decade with mixed results. Initially, Hartwig[50] through his use of LHMDS postulated a cycle for aryl bromides initiated by oxidative addition and formation of a dimeric palladium species, coordination of the amine with subsequent deprotonation by base and reductive elimination which renders the aryl amination product and the active catalyst. A lower reactivity was noted for aryl iodides which was consistent with earlier reports by Migita[46] with his tin procedure and later by Buchwald with palladium. The latter first attributed it to a difference in the oxidative addition products obtained from aryl iodides in comparison to aryl bromides.[51]

The introduction of a second generation of bidentate phosphine ligands, such as BINAP and DPPF, brought an increased generality of both the aryl halides and amines that could be successfully coupled. On the other hand, they also introduced an extra level of complexity on the determination of the mechanistic cycle which still lasts to this date. For instance, both Hartwig and Buchwald proposed two separate mechanisms which differed, in gross terms, in the timing in which amine and base joined the cycle and, therefore, their exact role.[172,173] Very recently, the same authors together with Blackmond,[174] produced a revised view of the mechanism which took into account all the previous information gathered up to date and complemented it with other analytical

techniques, such as calorimetric analysis. An important conclusion was that the amine was not involved in the oxidative addition step.

As mentioned previously in this thesis, it is now accepted that the palladium species entering the cycle is a monoligated Pd-NHC complex. Oxidative addition of iodobenzene could potentially give rise to dimeric species **42**, via **43** (*Scheme 3.16.*), whilst a more sterically hindered aryl iodide such as 2-iodotoluene may not permit the same arrangement altogether, thus favouring complex **44**.



Scheme 3.16.

In this scenario, it is conceivable that a primary amine may find difficult to coordinate to complex **43** due to its low availability, whilst the opposite effect is observed with complex **44**. Bulkier phosphines, as previously described, do produce good yields of amination products with primary amines possibly due to the fact that their steric properties do not allow systems like **42** to form.

In the instance where we described the successful coupling of iodobenzene and *N*-hexylamine under heating, the dropwise addition of these two substrates meant that a higher concentration of **43** might have been present to react with the amine rather than with our previous order of addition, where the amine was added in one portion over the aryl iodide. However, once the product was formed, the secondary amine thus generated successfully competed with *N*-hexylamine, generating the bis-arylation adduct.

Our RT protocol could not be transferred successfully to aryl chlorides, described in previous chapter as less reactive but very interesting substrates from the economic point of view (*Table 3.4.*). Better yields were previously achieved by the Caddick group for entries 2 and 4, 97% and 58% respectively.[175]

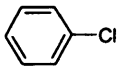
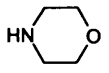
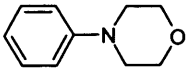
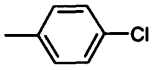
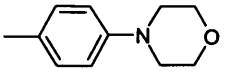
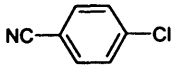
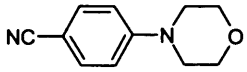
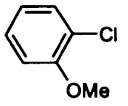
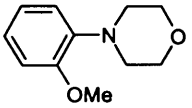
Entry	Ar-Cl	HNR'R''	Ar-NR'R''	Yield (%)[a]
1				43
2				8
3				10
4				8

Table 3.4.

Conditions: 1 mmol of aryl chloride, 1.2 eq. of amine, $Pd_2(dba)_3$ (1%), IPr·HCl (4%) and 2.5 eq. of LHMDS (1M in THF), 25°C, 24h. Reactions times were not optimised. (a) Isolated yields.

3.3. *STATISTICAL AIDED OPTIMISATION OF CONDITIONS*

3.3.1. Introduction

Design of experiments (DoE) may be defined as a statistical aided approach for the rational collection and evaluation of data.

DoE originated in the 1920s with the pioneering work of Fisher[176] and it has evolved and been refined considerably since then. Although predominantly exploited by R&D departments in industry, the last few years have seen a small but steady introduction of such methodology in academia, normally due to collaborations like the one which has made this work possible.

DoE has found applications in the formulation of products in the food, health care and pharmaceutical industries, as well as in the optimisation of analytical instruments and manufacturing processes.

For the purpose of the work described herein, optimising reaction conditions means obtaining the highest response, i.e. yield of the required product and minimising, if present, any by-products.

The traditional approach when presented with a piece of chemistry for optimisation has been the discrete changes of separate factors one at a time. There are two main disadvantages associated with this approach. Firstly and most importantly, it might not lead to a real optimum as potential interactions amongst factors are missed. Secondly, it requires many more runs than a well designed DoE and does not cover appropriately the experimental space, thus making it unappealing from the economic point of view.

The DoE approach allows for several factors to be measured simultaneously and initial substrates, products and impurities can be modelled at no extra experimental cost. Aided by computer software, a DoE provides a robust framework in which the aforementioned experimental space may be covered with a relatively small number of experiments, detecting the dominant factors.

Finally, inherently to all experimentation there is an issue of variability. Using DoE, one can take into account variability in the system and minimise it, offering a more robust set of results.

In common to any approach used to study and optimise a chemistry method, some previous consideration of what is known and what is hoped to achieve is crucial. One may consider focusing on a selected number, rather than all factors, and the minimum and maximum levels of each. These levels could be dictated by a number of reasons, e.g. experimental constraints, economic or environmental issues, etc. In addition, results or responses have to be measurable. Also, often overlooked, the experimental logistics require some attention with regards to the number of experiments that could realistically be conducted, time invested, need for replicates, etc.

With a design in place, the next stage requires gathering the responses (e.g. yields) and fitting them to a mathematical model (*Figure 3.4.*). If an appropriate fit is found, the true power of DoE comes into play, as the model permits the identification of optimum conditions and making predictions based on changes on any of the factors. Should the data not fit a model, it may still be used by reverting back to the design stage and performing modifications, usually by collecting more data.

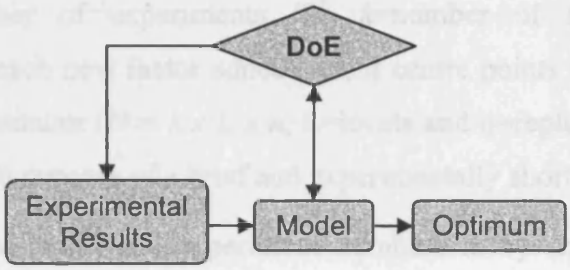


Figure 3.4.

Nowadays, there are a number of commercial, software applications that facilitate the work of the experimenter when dealing with a DoE, from inception to final results. These are highly important since they have brought the usage of statistic tools to non-statisticians, often discouraged by its complexity and they offer a simple user interface with a great deal of online help for interpretation of data and diagnostic tools. The DoE work described in this thesis was conducted with Design Expert® v6 by State-Ease Inc.

3.3.2. Types of Designs

Depending upon the objective of the study, there are two main groups of designs; Factorial and Response Surface Method designs.

The ***Factorial*** design is primarily used for screening of significant factors, although it can be refined to optimise a process. It may also provide information about the interaction between factors and the robustness of a method. A Full Factorial design involves all the factors, typically at two levels, i.e. a high (+1) and a low (-1) level. This way, a matrix of experiments for a two level full factorial design of two factors could be represented as depicted below (*Table 3.5.*).

	Factor 1	Factor 2
Experiment 1	+1	-1
Experiment 2	+1	+1
Experiment 3	-1	-1
Experiment 4	-1	+1

Table 3.5.
A design matrix.

The total number of experiments (2^k, k=number of factors) would grow exponentially with each new factor added and, if centre points and replications are to be conducted, this number ($N = k \times L \times n$, L=levels and n=replications) would further increase and defy the purpose of a brief and experimentally short study.

A way of cutting down the experiment numbers is by employing a Fractional Factorial design, which only takes a fraction of the numbers whilst maintaining a reasonably good resolution. The trade-off is that some interaction effects might be aliased or confounded with other effects.

Both types of designs are graphically represented below for an instance of three factors and two levels (*Figure 3.5.*). Each factor takes up an axis and its value change from the lowest (-) to the highest (+), thus, the origin of coordinates (---) represents the lowest level of all three factors. Measuring all points (full factorial) allows for a better depiction of the design space, whilst the fewer measurements of a fractional factorial design do not strictly cover such space.

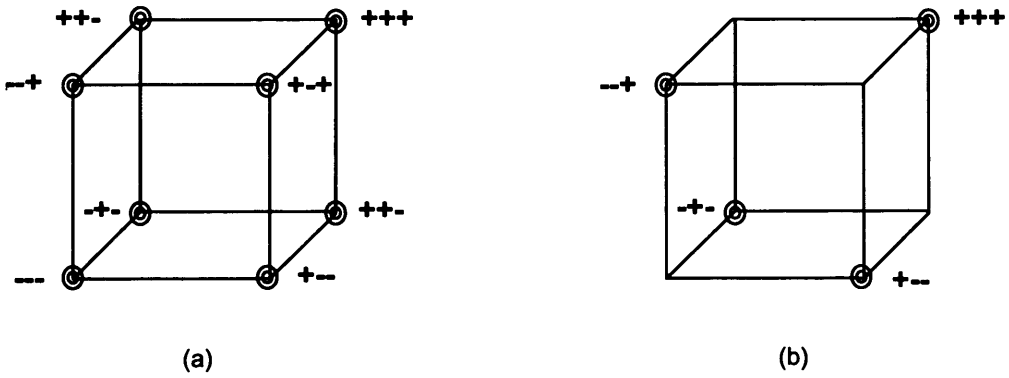


Figure 3.5. Factorial designs; (a) full and (b) fractional.

Response Surface Methods, RSM, comprise a number of statistical and mathematical techniques employed to optimise a process by finding a region of the design space were a certain response is optimal and then developing a mathematical model to explain it.

Firstly, a first order polynomial model may be employed, such as those of factorial designs. A two variable (x_1 and x_2) first order polynomial model acquires the form depicted below (*Equation 1.*), where η represents the response function and β's are unknown parameters which must be estimating by collecting data. The last term

represents interactions between the two variables. This is only a first approximation to the true function which is unknown and possibly more complex. In other systems of higher number of variables, the main ones are highlighted and other less important variables might be obviated.

$$\eta = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} x_1 x_2$$

Equation 1.

Where there is a curvature in the response function, a second order or quadratic model is required (*Equation 2.*).

$$\eta = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{11} x_1^2 + \beta_{22} x_2^2 + \beta_{12} x_1 x_2$$

Equation 2.

Often quadratic models are enough to explain most problems but, if a stronger curvature is present, a third order or cubic model may be employed.

3.3.3. Analysis of Variance (ANOVA)

After the design has been selected and experiments conducted, statistics help us to understand whether a suitable model has been found which fits the results.

The purpose of ANOVA is to test for differences between means for statistical significance by splitting the total variance into a component due to true error and a component due to the difference between means. Two main statistical functions within ANOVA help us to determine whether the model is significant. First, the **F value** or ratio between the model mean square, which in turn depends on the sum of squares and degrees of freedom of the system, and the error mean square. Large F values (>> 1) indicate that the variance is significantly larger than the error. Second, the **Prob > F** value is the probability that there is not a factor effect on the response, therefore low values, i.e. typically less than 0.05, indicate that the effect is significant.

Validation of the model could be conducted numerically through the R-Squared, Adjusted R-Squared and Predicted R-Square terms which are all also related to the sum of squares both of the model and the residual (difference between the observed

value and the predicted by the model). These terms must have values similar to each other and close to 1 for a good fit of the data to the model.

Another way of performing this validation is by graphical means, i.e. plots, which in the case of Design Expert® are all presented with minimal effort and in a way that is intuitive for the non-statistician. Most of these plots display the studentised form of residuals, these are; the residual divided by the estimated deviation of that residual.

- Normal probability; points in the plot should form an approximate straight line. It does normally inform us of a potential deviation from normality.
- Residuals vs. Predicted; as the name suggest, the studentised residuals are plotted against their predicted response values. A random scatter of plots is ideal and indicates that there is not an association between these variables.
- Residuals vs. Run; the studentised residuals are plotted against the experiment number. Any trend in the plot could indicate a time-dependent variable, hence the importance of randomising the experiments.
- Residuals vs. Factor; plot of residuals against the factors of study. Again, a random spread is desirable. It looks at the variance not accounted for in the model at different levels of each factor.
- Cook's distance: Provide information about individual runs being statistically different from the mean. Values close to 0 are preferable, with no points deviating significantly from the trend.

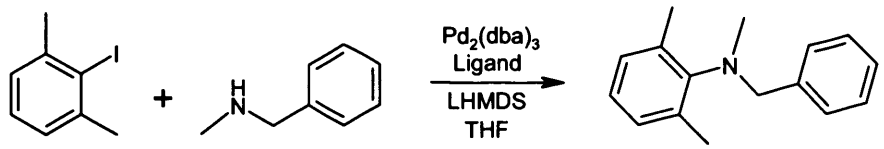
3.4. DoE STUDIES ON HARTWIG-BUCHWALD AMINATIONS

Having found a mild protocol for the amination of aryl iodides, a study focused on the optimisation of the reaction conditions was conducted. The aim was twofold; "fine-tune" the conditions for increased yields and gaining some insight into the mechanism of these transformations.

According to the requirements of the DoE study, we needed to carry out the following: selection of an appropriate reaction; evaluation of the number of factors of interest and their levels; choice of a design; experimental work; validation of the model.

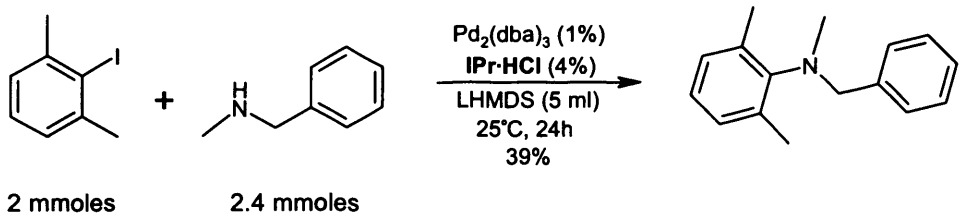
Initial DoE on a sterically encumbered system

N-Methylbenzylamine was chosen to be reacted with a sterically hindered aryl iodide (*Scheme 3.17*). It was hoped that by finding the optimum conditions for this benchmark reaction, it could be generalised to sterically less demanding substrates.



Scheme 3.17.

A certain amount of the required product was prepared in order to analyse its response and that of other components by HPLC in the reaction mixture. Thus, a reaction was conducted under our standard protocol (*Scheme 3.18.*), only to afford a low yield of the required product and, therefore, corroborating our initial assumption of a sterically challenging system.



Scheme 3.18.

Both TLC (Hex/EtOAc 1%) and HPLC analyses of the mixture after 24h, still presented evidence of unreacted starting material. At this stage, this was not an issue since the aim was to perform a HPLC profile with pure product together with starting material at different concentrations. Moreover, this made a stronger case for further optimisation for an enhanced conversion into product.

After these preliminary studies the individual factors and their levels were next evaluated (*Table 3.6*).

Factor	Units	Low	High
A: Amine	eq.	1.05	2
B: Palladium	mol %	0.5	2
C: Temperature	°C	25	50
D: Base	eq.	1.05	2.5
E: Volume	vols.	2.5	5
F: Ligand ratio	Ratio	1	3
G: Type of Ligand	-	Ligand 1 to 5	

Table 3.6.

Amine. The top value of 2 eq. was considered artificially high from the economic point of view in order to take into account potentially more expensive amines.

Palladium. For similar reasons, the Pd loadings were capped at only 2%.

Temperature. With the lowest level (25°C) being the temperature of the protocol already established, it was of great interest to investigate its effect at moderately higher values.

Base. The amount of base it was also considered an important factor not only on its own right, but also because of its inseparable relation to the volume of the reaction mixture. As our standard protocol was based on 2.5 eq. of base, the effect of lower amounts had to be investigated to make a case for an economically benign and mild conditions protocol.

Volume. The total volume in our previously found protocol was given by the amount of base (1M in THF). It was considered appropriate to study the effect of higher dilutions by the addition of extra THF. Hereafter, *volume* refers to the total volume of THF present in the reaction mixture, whatever its source.

Ligand ratio. It has been the subject of much speculation due to contradictory reports on the most effective ratio to Pd. The usually found 1:1 and 1:2 Pd/ligand ratios were investigated, as well as a further excess of a 1:3 ratio.

Type of Ligand. This was the only categorical factor included in this study, whilst all the above were numerical. Five ligands were chosen at this stage (*Figure 3.6.*), as they featured recurrently in the literature. Ligands 1 and 2 presented us with the opportunity for a direct comparison between the unsaturated and saturated imidazolium salts.

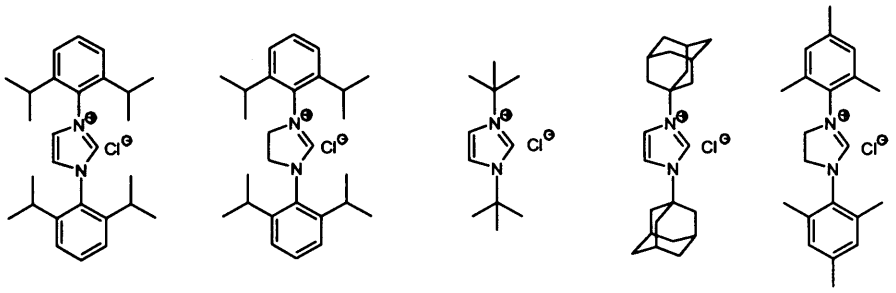
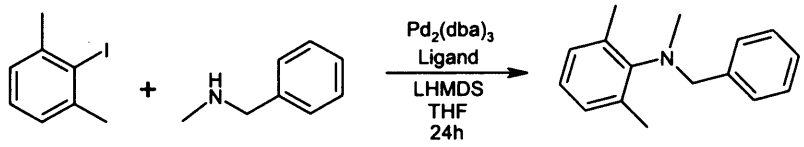


Figure 3.6. Ligands surveyed for DoE study.

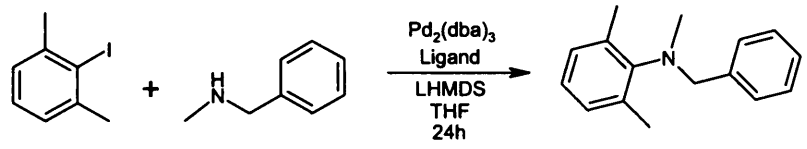
A RSM such as a D-Optimal design with a quadratic model was utilised in this study. Optimal designs perform algorithmic optimisations based on a model that will be fit, in our case; a quadratic one. They are normally employed in cases where the standard factorial or fractional designs require far too many runs or there are factor levels which are not feasible in a particular experimental setup. It starts by producing a table of reactions with all the factors as in a regular full factorial design, then, the experimenter decides on the number of design points and the computer produces a candidate set whose aim is complying with the optimality criteria.

The results of this study are presented in *Table 3.7.*



2 mmoles 2.4 mmoles

Run	Factor A Amine eq	Factor B Pd mol %	Factor C Temp. °C	Factor D Base eq	Factor E Volume vols	Factor F Ligand ratio	Factor G Ligand type	Response Product % a/a	Response Start Mat % a/a
1	2.00	0.50	50.00	1.05	2.50	3.00	Ligand 5	20.48	61.35
2	1.05	0.50	25.00	1.05	5.00	3.00	Ligand 1	4.35	77.36
3	2.00	2.00	50.00	1.77	5.00	3.00	Ligand 5	32.96	23.81
4	2.00	2.00	50.00	2.50	5.00	1.00	Ligand 3	11.93	0
5	2.00	0.50	50.00	1.05	2.50	1.00	Ligand 2	19.39	71.26
6	2.00	1.25	50.00	1.05	5.00	3.00	Ligand 1	0	78.72
7	1.05	2.00	25.00	2.50	2.50	2.00	Ligand 3	7.48	85.13
8	2.00	2.00	25.00	2.50	5.00	1.00	Ligand 4	38.22	53.43
9	2.00	2.00	50.00	1.05	5.00	1.00	Ligand 2	19.13	80.87
10	1.05	2.00	50.00	2.50	2.50	1.00	Ligand 2	40.27	0
11	2.00	0.50	37.50	2.50	2.50	3.00	Ligand 1	25.66	0
12	1.05	0.50	50.00	1.05	5.00	1.00	Ligand 2	14.21	85.79
13	1.05	2.00	25.00	2.50	2.50	2.00	Ligand 3	31.42	38.1
14	1.05	2.00	25.00	1.05	5.00	1.00	Ligand 3	12	75.65



2 mmoles 2.4 mmoles

Run	Factor A Amine eq	Factor B Pd mol %	Factor C Temp. °C	Factor D Base eq	Factor E Volume vols	Factor F Ligand ratio	Factor G Ligand type	Response Product % a/a	Response Start Mat % a/a
15	2.00	2.00	50.00	1.05	2.50	1.00	Ligand 4	26.84	53.75
16	1.05	2.00	50.00	2.50	2.50	3.00	Ligand 1	22.88	0
17	2.00	2.00	50.00	2.50	2.50	1.00	Ligand 5	45.31	0
18	1.05	0.50	25.00	2.50	5.00	1.00	Ligand 2	6.12	88.22
19	2.00	0.50	50.00	1.05	5.00	3.00	Ligand 4	4.15	95.85
20	1.52	1.25	25.00	1.77	3.75	2.00	Ligand 5	15.81	67.61
21	2.00	2.00	25.00	1.05	5.00	2.00	Ligand 4	11.49	88.51
22	1.05	0.50	50.00	2.50	5.00	3.00	Ligand 5	17.28	66.67
23	1.05	0.50	25.00	1.05	5.00	1.00	Ligand 4	0	100
24	1.52	1.25	37.50	1.05	3.75	2.00	Ligand 5	33.23	35.28
25	2.00	0.50	25.00	1.05	2.50	2.00	Ligand 4	4.74	95.26
26	1.05	0.50	50.00	1.05	2.50	3.00	Ligand 3	6.03	90.44
27	1.05	2.00	25.00	2.50	5.00	3.00	Ligand 2	20.51	27.09
28	1.05	0.50	25.00	1.05	2.50	1.00	Ligand 5	3.49	93.02
29	1.05	0.50	50.00	2.50	2.50	1.00	Ligand 5	20.15	69.53
30	1.05	2.00	50.00	2.50	5.00	3.00	Ligand 4	6.81	86.77
31	2.00	2.00	25.00	2.50	5.00	3.00	Ligand 1	16.12	20.87
32	1.05	0.50	50.00	2.50	2.50	3.00	Ligand 4	5.06	94.94
33	1.52	2.00	25.00	1.05	5.00	1.00	Ligand 1	8.24	69.48
34	1.52	0.50	25.00	2.50	5.00	3.00	Ligand 3	0	100
35	2.00	1.25	50.00	2.50	2.50	3.00	Ligand 3	19.99	63.06
36	1.05	2.00	50.00	1.05	2.50	1.00	Ligand 1	12.02	63.49
37	1.05	2.00	37.50	2.50	5.00	1.00	Ligand 1	23.75	27.24
38	1.05	2.00	50.00	1.05	5.00	1.00	Ligand 5	30.39	38.73
39	2.00	0.50	25.00	1.77	5.00	1.00	Ligand 1	5.17	80.98
40	2.00	2.00	25.00	1.05	2.50	3.00	Ligand 3	4.04	86.56
41	1.05	0.50	25.00	2.50	2.50	1.00	Ligand 1	9.99	69.46
42	1.05	0.50	25.00	2.50	2.50	3.00	Ligand 2	24.69	69.88
43	2.00	0.50	25.00	1.05	5.00	3.00	Ligand 2	5.67	87.19
44	2.00	0.50	50.00	2.50	5.00	3.00	Ligand 2	61.19	12.51
45	1.05	2.00	25.00	2.50	2.50	3.00	Ligand 5	25.56	42.13
46	2.00	2.00	50.00	2.50	2.50	1.00	Ligand 1	28.25	0
47	1.05	0.50	50.00	2.50	5.00	1.00	Ligand 3	7.88	86.33
48	1.52	2.00	50.00	1.05	2.50	3.00	Ligand 2	18.47	78.1
49	1.05	2.00	25.00	1.05	3.75	1.00	Ligand 2	17.25	82.75
50	1.05	2.00	25.00	1.05	2.50	3.00	Ligand 4	6.17	86.65
51	2.00	0.50	25.00	2.50	2.50	1.00	Ligand 3	3.52	96.48
52	2.00	0.50	50.00	1.05	5.00	2.00	Ligand 3	10.27	79.02
53	2.00	2.00	25.00	1.05	2.50	1.00	Ligand 5	31.04	36.53
54	2.00	0.50	25.00	2.50	5.00	1.00	Ligand 5	0	93.4
55	1.52	0.50	50.00	2.50	5.00	1.00	Ligand 1	31.08	30.79
56	1.05	0.50	50.00	1.05	2.50	1.00	Ligand 4	16.85	78.78
57	2.00	2.00	25.00	2.50	3.75	3.00	Ligand 4	10.7	89.3
58	2.00	2.00	25.00	2.50	2.50	1.00	Ligand 2	53.95	0
59	2.00	0.50	25.00	1.77	5.00	1.00	Ligand 1	5.68	84.08
60	2.00	0.50	50.00	2.50	5.00	1.00	Ligand 4	13.05	81.48
61	1.05	2.00	50.00	1.05	5.00	3.00	Ligand 3	4.72	84.37

Table 3.7.

Responses were measured by peak area%. See experimental section for details.

After ANOVA calculations the best model that could be fit to the data for the product response was a linear one and several factors were highlighted as significant; B (palladium), C (temperature), D (base) and G (type of ligand). These are all factors which are key to almost any Pd catalysed reaction, so their significance did not come as a surprise.

The trend observed was of increased product formation with increasing values of Pd, temperature and base (*Figure 3.7.*). The only factor with a value common to our standard RT protocol was base (2.5 eq.), although it could be appreciated that for this particular system, conversion to product did not change extremely with the other factor levels. This possibly indicated that our initial RT protocol conditions were not far from the optimum level.

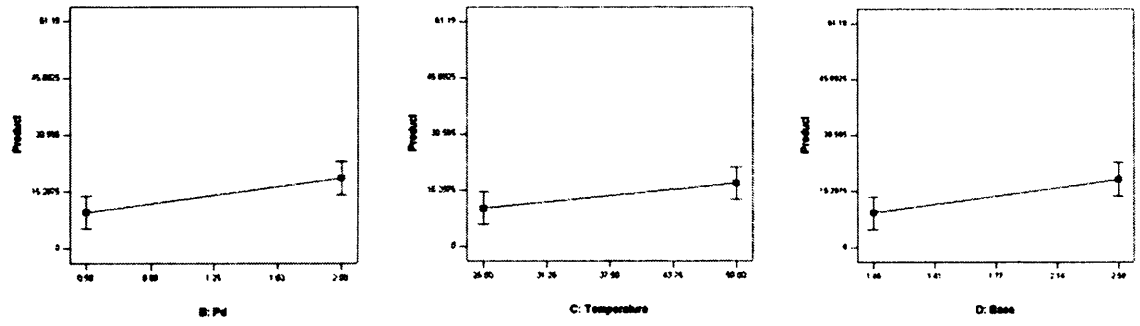


Figure 3.7.

The type of ligand (factor G), was also expected to play a fundamental role for the conversion into product. After all, the whole catalysed process was reliant on the ability of the ligand to interact effectively with Pd and, based on our limited number of ligands for this study, it appeared that saturated imidazolium salts performed better than unsaturated ones, including the ligand in our standard RT protocol, i.e. Ligand 1 or IPr·HCl (*Figure 3.8.*). As discussed during the introduction chapter the presence of a double bond in the imidazole ring has some energetic and structural consequences, which manifested themselves in this system with an inferior conversion to product.

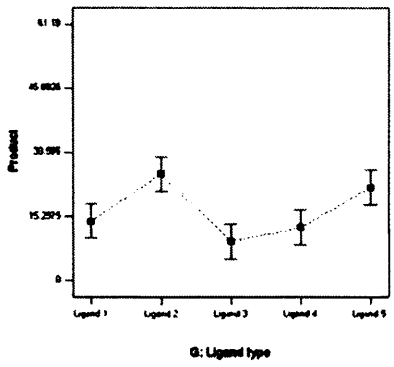


Figure 3.8.

A difference between *N*-alkyl and *N*-aryl substitution was also discerned, with a preference for the latter and a reminder that both electronic and structural properties were at play. Ligands 1 (IPr·HCl) and 2 (SIPr·HCl) have been widely used in this area as their isopropyl residues appeared to provide the right steric properties when compared to ligand 5 (SIMes·HCl), although in our system the presence of *N*-aryl substituents was more important.

Disappearance of starting material did follow a reverse trend to that observed for the conversion to product (*Figure 3.9.*), underpinning the trends previously described for the formation of the latter.

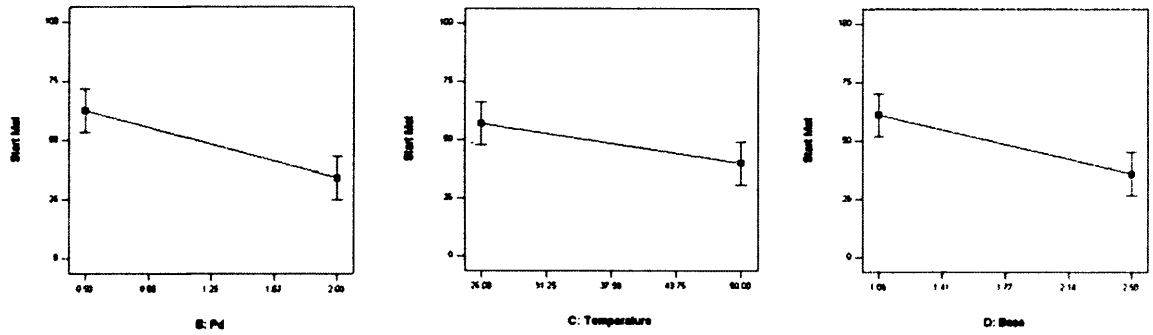
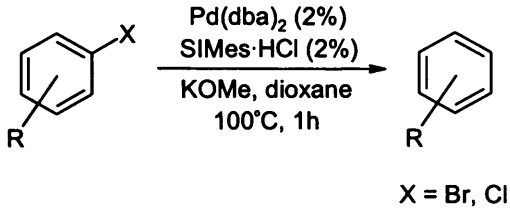


Figure 3.9.

An important caveat found upon completion of the required experiments was the observation of *m*-xylene as a by-product, due to dehalogenation of the starting 2-iodo-*m*-xylene. It was suspected that incomplete conversion of starting material alone, could not totally account for the low yield, but the difficulty to identify this by-product was due to the fact that it was not easily observed by TLC and it was never isolated after

chromatography of the crude mixture. Moreover, the HPLC system employed for this DoE did not resolve *m*-xylene from IPr·HCl, thus co-eluting together in a single peak.

Nolan devoted a report on dehalogenation of aryl bromides and chlorides with a Pd/imidazolium salt system (*Scheme 3.19.*).[177] In this report, dehalogenation of aryl bromides was described as more facile than that of their chloride counterparts.



Scheme 3.19.

Nolan postulated a mechanism for which the alkoxide base would attack the oxidative addition product of a Pd-carbene complex to an aryl halide, removing the halide and with subsequent elimination of an aldehyde. Finally, the reductive elimination step would regenerate the catalyst and afford the arene.

Aryl iodides were not explicitly mentioned, although we inferred that their dehalogenation would be even more facile than that of aryl bromides and chlorides, under similar conditions. However, our system differed from that reported in that there was a coupling partner, i.e. *N*-methylbenzylamine, to which 2-iodo-*m*-xylene could react to form the amination product.

Although experimentation had already concluded at this stage, it was sought to add the *m*-xylene response to our design and model it similarly to that of product and starting material. The number of data points was limited and the only way to handle the results for reactions conducted with IPr·HCl (ligand 1) was to disregard its contribution to the *m*-xylene peak area percentage. Upon analysis (see Appendix 2), several significant factors and interactions were found; A (amine), E (Volume), BG (palladium/ligand type), CG (temperature/ligand type) and EF (volume/ligand ratio).

Whilst *m*-xylene formation slightly increased with higher loadings of amine, a more pronounced and opposite effect was observed with volume (*Figure 3.10.*).

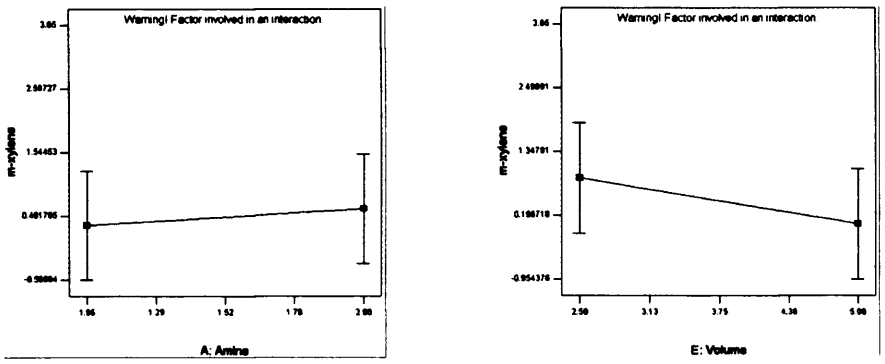


Figure 3.10.

At middle values of ligand ratio, there were not preferential trends for the formation of *m*-xylene, from low to high Pd loadings. For instance, whilst IPr·HCl (ligand 1) favoured an increase, its saturated version, SIPr·HCl, did so similarly. In contrast, another saturated ligand, SIMes·HCl, showed a decrease (*Figure 3.11.*).

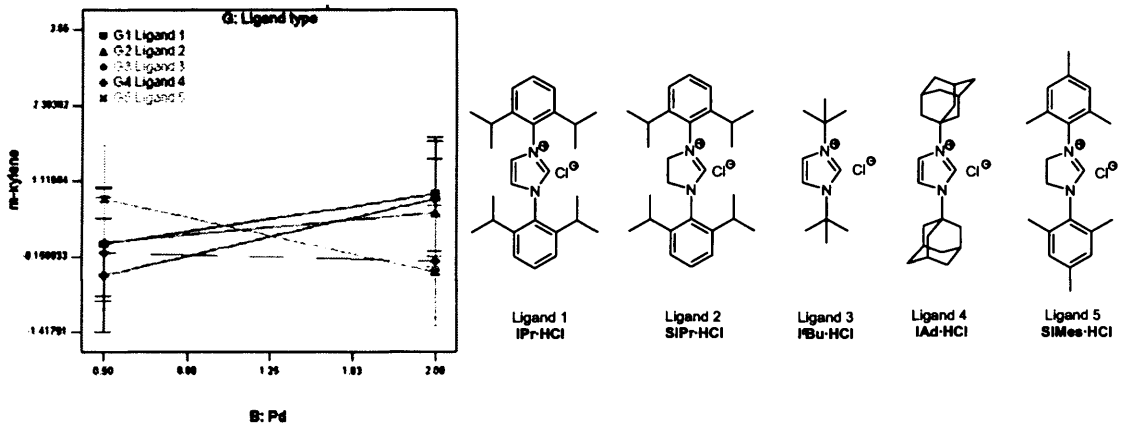


Figure 3.11.
Effect of Pd/ligand type interaction on the formation of *m*-xylene.

Nolan's report on dehalogenation highlighted SIMes·HCl (ligand 5) as the best ligand for the dehalogenation of 4-chlorotoluene to toluene, followed by SIPr·HCl (ligand 2).[177] In our system, ligand 5 or SIMes·HCl certainly appeared to perform well at low Pd loadings and sharply decreased its efficiency at higher ones, although this could be also due to the fact that the ligand ratio was fixed at its middle value and, therefore, did not change accordingly with Pd loadings. Ligands 1 and 2 performed equally well at low Pd loadings but improved at higher ones, with a small preference

for the former. In this case, the presence of unsaturation had a positive effect. Ligands 3 and 4 were the worst performers, although the former was insensitive to Pd loadings and the latter sharply improved the conversions to *m*-xylene.

Interestingly, both SIPr·HCl (ligand 2) and SIMes·HCl (ligand 5) were also the best ligand performers for the formation of product in our DoE system. This proved that in order to discriminate between the required product and the by-product, the best conditions had to be found on the right combination of all the other factors.

The ligands also appeared to be sensitive to the reaction temperature (*Figure 3.12.*), although no clear generalisations could be made on their efficiency based on their structural features, as with the interaction described above.

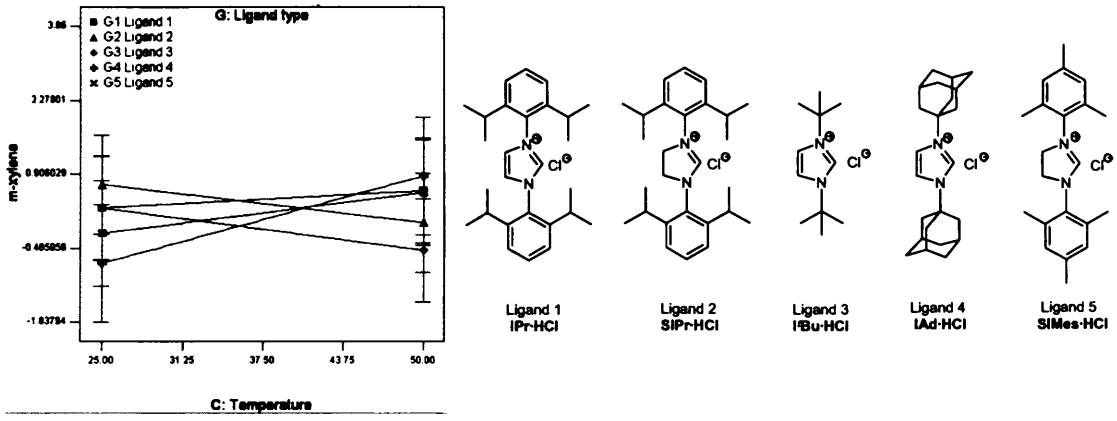


Figure 3.12.
Effect of temperature/ligand type interaction on the formation of m-xylene.

Finally, the other main interaction highlighted, i.e. volume/ligand ratio (*Figure 3.13.*), indicated an enhanced conversion to *m*-xylene with the highest Pd/ligand ratio (1:3) at low dilutions. The minimum Pd/ligand ratio (1:1) performed quite well in this transformation and was not significantly sensitive to the concentration of the reaction mixture even at high dilutions. Diminution of *m*-xylene formation could be achieved by increasing both the volume and the Pd/ligand ratio in the mixture.

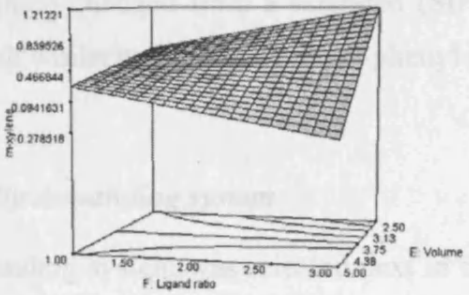


Figure 3.13.

With the aid of Design-Expert®, it was possible to obtain a numerical optimisation of the reaction conditions required for the formation of both product and by-product (*Table 3.8.*).

Factor	Standard RT protocol conditions	Optimised DoE conditions (product)	Optimised DoE conditions (*m*-xylene)
A: Amine (eq.)	1.2	1.05	1.05
B: Pd (mol%)	1	0.50	0.50
C: Temperature (°C)	25	31	25
D: Base (eq.)	2.5	1.05	1.05
E: Volume (vols.)	-	2.94	4.43
F: Ligand ratio (ratio)	2	3	2.55
G: Ligand type (type)	1	5	5

Table 3.8.

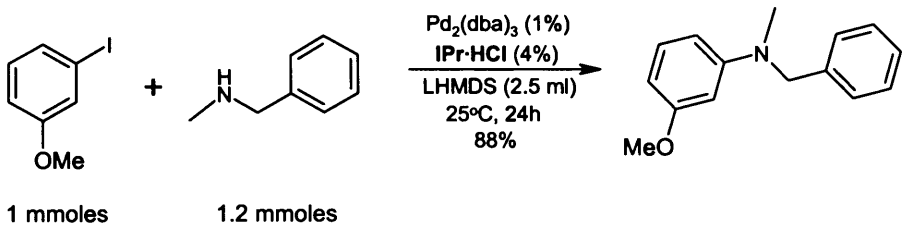
These conditions did not appear to differ substantially from one another. On the whole, this meant two things regarding by-product formation; firstly, that it was unavoidable in our system and, secondly, that it was significant due to the low yields of required product achieved, even when total conversion of starting material was observed.

From the above conditions, it would appear that slightly higher concentration, temperature and ligand ratio values played in favour of the required product, minimising the by-product.

Similarly, there were minimal differences to our initially found RT protocol, except on the type of ligand, which changed from a saturated (SIPr·HCl) to an unsaturated imidazolium (IPr·HCl) salt whilst still retaining the *N*-phenyl substitution.

DoE on a less sterically demanding system

A less sterically demanding system was selected next in order to conduct a similar DoE exercise. The amine had already been employed in the previous design and was reacted with 3-iodoanisole under the conditions of our standard RT protocol (*Scheme 3.20.*). The good yield was consistent with similar reactions of other secondary amines described previously in this chapter.



Scheme 3.20.

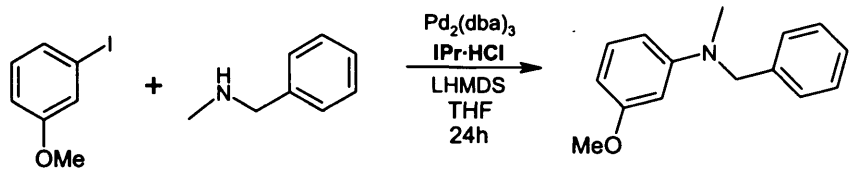
In this occasion, a simpler Fractional Factorial Design was selected and the factors from previous DoE revisited (A-F, *Table 3.9.*). The categorical factor, i.e. type of ligand, was excluded from the study at this stage and, therefore, all reactions were conducted with **IPr·HCl** as a carbene ligand precursor, due to its extensive application across this area of research.

Factor	Units	Low	High
A: Amine	eq.	1.05	2
B: Palladium	mol %	0.5	2
C: Temperature	°C	25	50
D: Base	eq.	1.05	2.5
E: Volume	vols.	2.5	5
F: Ligand ratio	ratio	1	3

Table 3.9.

The design was comprised of 16 experiments with an additional 2 experiments acting as centre points. Introducing centre points in a factorial design permits to estimate the error and the presence of curvature in the design.

The reactions were conducted on a 2 mmole scale of 3-iodoanisole and yields of *N*-(3-Methoxyphenyl)-*N*-Methylbenzylamine are tabulated below (*Table 3.10.*). Full experimental details are given in the experimental section.



Run	Factor 1 Amine (eq)	Factor 2 Pd (mol%)	Factor 3 Temp (°C)	Factor 4 Base (eq)	Factor 5 Vol (ml)	Factor 6 Ligand/Pd (ratio)	ISOLATED YIELDS (%)
1	1.05	2	25	2.5	5	1	**61**
2	1.05	2	25	1.05	5	3	**45**
3	1.525	1.25	37.5	1.775	3.75	2	**75**
4	2	0.5	25	1.05	5	1	**13**
5	2	2	25	2.5	2.5	1	**64**
6	1.05	2	50	2.5	2.5	3	**80**
7	1.05	0.5	50	1.05	5	3	**14**
8	2	2	50	1.05	5	1	**11**
9	1.525	1.25	37.5	1.775	3.75	2	**83**
10	1.05	0.5	50	2.5	5	1	**36**
11	2	0.5	25	2.5	5	3	**18**
12	1.05	0.5	25	2.5	2.5	3	**16**
13	2	0.5	50	2.5	2.5	1	**9**
14	2	0.5	50	1.05	2.5	3	**49**
15	1.05	0.5	25	1.05	2.5	1	**47**
16	2	2	50	2.5	5	3	**73**
17	2	2	25	1.05	2.5	3	**44**
18	1.05	2	50	1.05	2.5	1	**40**

Table 3.10.
Factorial DoE. Centre points (Runs 3 and 9).

The results showed a good spread of yields (9% to 83%). The two centre points, i.e. runs 3 and 9, afforded 75 and 83% respectively under identical reaction conditions and were relatively close in value. However, it is worth noting that these two yields were amongst the highest and that centre points are precisely that; middle values between the highest and lowest values for a factor. The implication for our study was clear; the optimum conditions were located around the middle points where a lesser number of data points were available.

A logit transformation was chosen for fitting the data (*Equation 3*). This kind of transformation is useful for responses whose values have a finite range, e.g. yield of product. These values must fall within the boundaries of the lower and upper limits, i.e. 0% and 100%.

$$\text{Logit (Y)} = \log_e \{\text{Y} - \text{lower limit} / \text{upper limit} - \text{Y}\}$$

Equation 3

It was still possible to discern main factors and interactions with the aid of a Half Normal Probability plot (*Figure 3.14.*). Large values are shown in the upper right-hand corner of the graph and, on moving from right to left the importance of a factor or interaction of factors decreases. The triangle denotes the size of the error associated with the design, therefore, those factors closing zero or to its left may be disregarded, as their effect is no bigger than such error.

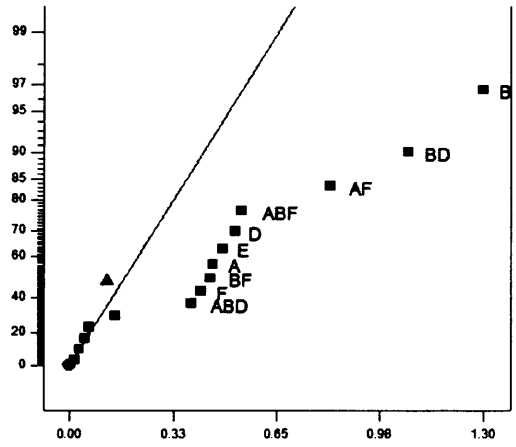


Figure 3.14.
Main factors and interactions marked with squares.
y axis; %probability, x axis; [effect].

According with the above plot the most important factor was Pd loading (factor B). This was not surprising as an active form of Pd is vital for catalysis and it was always expected to be a main factor. With the exception of temperature (factor C), all other single factors were highlighted by the design.

A two factor interaction such as Pd/base (BD) was also singled out. The role of base is fundamental for amination reactions, but in this context it was also associated

inseparably to solvent and, therefore, with the volume or dilution factor. Another main interaction appeared to be amine/ligand ratio (AF), which may have indicated a possible competition of amine against ligand for Pd coordination sites. Finally, as it was expected, the interaction Pd/ligand ratio (BF) was significant.

Although three factor interactions are rare, this design signalled two; amine/Pd/ligand ratio (ABF) and amine/Pd/base (ABD) coinciding with main two factor interactions.

Aliasing of terms was observed amongst two factor interactions and between main effects and three factor interactions. The alias list within Design-Expert® reported that BD was aliased with CF (temperature/ligand ratio). As the latter contained a factor which was not significant, i.e. C, it was likely that BD (Pd/base) was the correct alias since both B and D were important factors. Similarly, the interaction BF (Pd/ligand ratio) appeared the correct alias when compared with the term CD (temperature/base). Unfortunately, the same argument could not be applied for the alias between terms AF and DE (base/volume) as their single factors were all significant and of similar magnitude, thus they had to be taken into consideration.

Regarding the three factor interactions already described, the term ABF was aliased with ACD, BDE and CEF, whilst ABD was aliased with ACF, BEF and CDE. These could be also narrowed down by removing terms containing C (temperature).

Once the selection of main factors and aliases was made, it was possible to examine the ANOVA. Firstly, the values for the F (52.21) and Prob>F (<0.0001) indicated that our model was significant. All the factors and interactions mentioned above, i.e. A, B, D, E, F, AF, BD, BF, ABF and BEF, were also significant model terms. R-Squared (0.9886), Adjusted R-Squared (0.9697) and Predicted R-Square (0.9400) were all in good agreement. All the ANOVA calculations and Diagnostic plots are shown in Appendix 3.

Although a factor which is involved in an interaction can not be evaluated individually, its gross trend may still give some useful information. This way, the following trends were observed:

- The amount of amine needed to be low (1.05 eq).
- The loading of Pd needed to be high (2 %), consistent with an increased availability of catalyst.
- The amount of base needed to be high (2.5 eq).
- The total volume needed to be low (2.5 vols.), consistent with an increased concentration of all reagents.
- The ligand ratio needed to be high (3).
- The amine/ligand ratio interaction (*Figure 3.15.*) indicated a significant detrimental yield for product at low ligand ratio and with increased amine. Whilst at high ligand ratio, the effect of amine was not as pronounced.

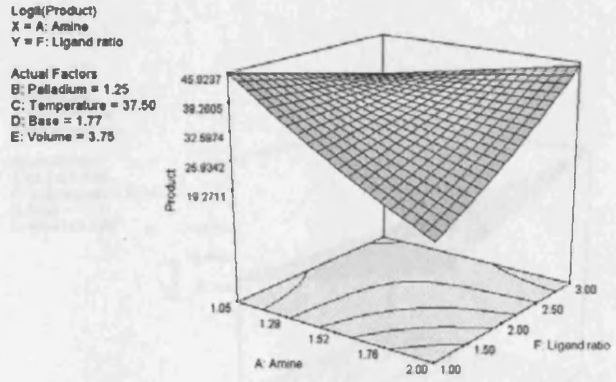


Figure 3.15.
Model graph for the amine/ligand ratio interaction.

- The Pd/base interaction (*Figure 3.16.*) offered a better yield of product when both factors where high, whilst at low base levels, the Pd loading was not relevant.

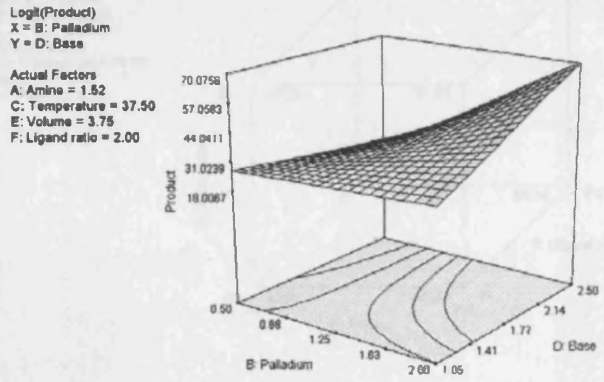


Figure 3.16.
Model graph for the Pd/base interaction.

- The Pd/ligand ratio interaction (*Figure 3.17.*) showed that an increased yield of product was achieved at high levels of both, whilst at low level of Pd the ligand ratio did not significantly modify the yield.

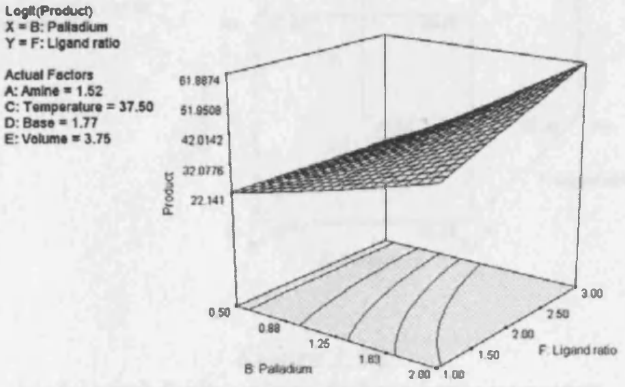


Figure 3.17.
Model graph for the Pd/ligand ratio interaction.

- The first of the three factors interactions was amine/Pd/ligand ratio (*Figure 3.18.*). This was consistent with the two factors interactions previously discussed, i.e. Pd/ligand ratio and amine/ligand ratio. The best conversion to product was achieved at high values of all three factors, although low values of amine loadings was most favourable.

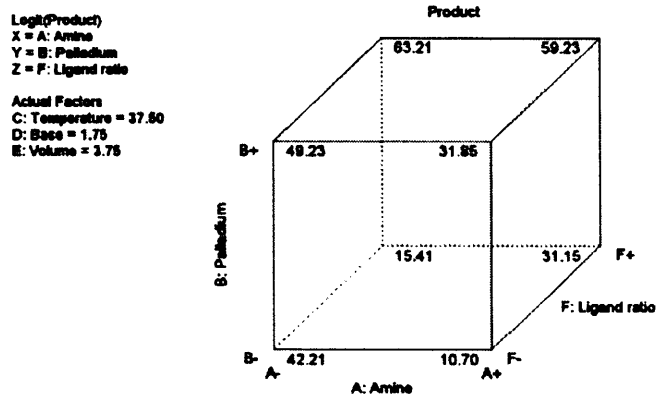


Figure 3.18.
Model graph for the amine/Pd/ligand ratio interaction.

- The last three factors interaction was volume/Pd/ligand ratio (*Figure 3.19.*). This showed increased yields with high values of ligand ratio and palladium loadings. The total volume had little effect on the yields.

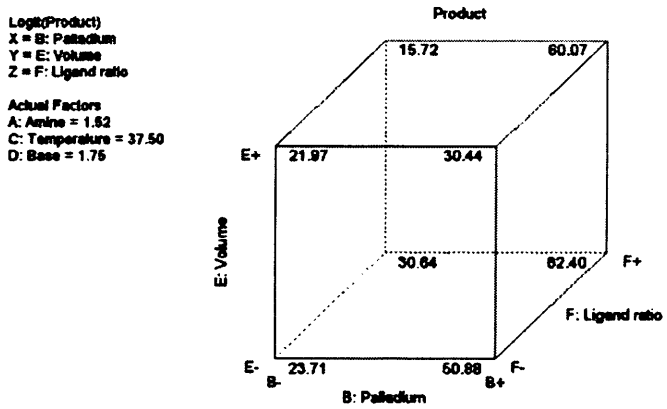


Figure 3.19.
Model graph for the volume/Pd/ligand ratio interaction.

It must be emphasised that all this information only represents gross trends since, strictly, the model was not able to perform predictions based on the initial data. During the early analysis of this DoE, it was found that the highest yields resided in the centre points. This implied that our model deviated from linearity in or around the centre point conditions. In order to refine our model, a RSM was conducted which allowed for further measurements around these points and to obtain the curvature and the factors responsible for it.

The type of RSM chosen was a Central Composite Design (CCD), which typically contains an imbedded two level factorial design as the one employed above, plus further axial and centre points. These axial, or sometimes called start points, depend upon the number of factors and the properties sought for the design.

Two factors; amine and temperature, were kept constant at their middle values as they were found not to effect a significant influence, thus aiding to reduce the number of experiments (*Table 3.11.*).

Factor	Units	Low	High
A: Palladium	mol %	0.5	2
B: Base	eq.	1.05	2.5
C: Volume	vols.	2.5	5
D: Ligand ratio	ratio	1	3
E: Amine	eq.	1.525	
F: Temperature	°C	37.5	

Table 3.11.
Factors investigated in the new CCD.
Factors E and F were kept constant.

A further 10 experiments were conducted to enhance the previous design (*Table 3.12.*).

Run	Factor 1 Amine (eq)	Factor 2 Pd (mol%)	Factor 3 Temp (°C)	Factor 4 Base (eq)	Factor 5 Vol (ml)	Factor 6 Ligand/Pd (ratio)	ISOLATED YIELDS (%)
1	1.05	2	25	2.5	5	1	**61**
2	1.05	2	25	1.05	5	3	**45**
3	1.525	1.25	37.5	1.775	3.75	2	**75**
4	2	0.5	25	1.05	5	1	**13**
5	2	2	25	2.5	2.5	1	**64**
6	1.05	2	50	2.5	2.5	3	**80**
7	1.05	0.5	50	1.05	5	3	**14**
8	2	2	50	1.05	5	1	**11**
9	1.525	1.25	37.5	1.775	3.75	2	**83**
10	1.05	0.5	50	2.5	5	1	**36**
11	2	0.5	25	2.5	5	3	**18**
12	1.05	0.5	25	2.5	2.5	3	**16**
13	2	0.5	50	2.5	2.5	1	**9**
14	2	0.5	50	1.05	2.5	3	**49**
15	1.05	0.5	25	1.05	2.5	1	**47**
16	2	2	50	2.5	5	3	**73**
17	2	2	25	1.05	2.5	3	**44**
18	1.05	2	50	1.05	2.5	1	**40**
19	1.525	2	37.5	1.775	3.75	2	**86**
20	1.525	1.25	37.5	2.5	3.75	2	**83**
21	1.525	1.25	37.5	1.775	5	2	**84**
22	1.525	1.25	37.5	1.775	2.5	2	**78**
23	1.525	1.25	37.5	1.775	3.75	2	**86**
24	1.525	0.5	37.5	1.775	3.75	2	**81**
25	1.525	1.25	37.5	1.775	3.75	3	**84**
26	1.525	1.25	37.5	1.775	3.75	2	**86**
27	1.525	1.25	37.5	1.775	3.75	1	**84**
28	1.525	1.25	37.5	1.05	3.75	2	**79**

Table 3.12.
Factorial DoE (runs 1-18) enhanced with a CCD (runs 19-28).

Unsurprisingly, the new set of experiments afforded good yields as they were based around the centre points. Two of these new centre points, i.e. runs 23 and 26, offered the best yields (86%).

The quadratic model selected to fit the data was significant according with the calculations of ANOVA; F and Prob>F values, 10.64 and <0.0001 respectively. Adjusted R-Squared (0.7876) and Predicted R-Square (0.5479) were not as close as it should have been desired. This, although not ideal, was no deterrent for navigating the design space. The diagnostic plots (Appendix 4) were also consistent with a good choice of model.

From the one factor plots (*Figure 3.20.*), it could be observed that the deviation from linearity was due to palladium (factor A), base (factor B) and volume (factor C).

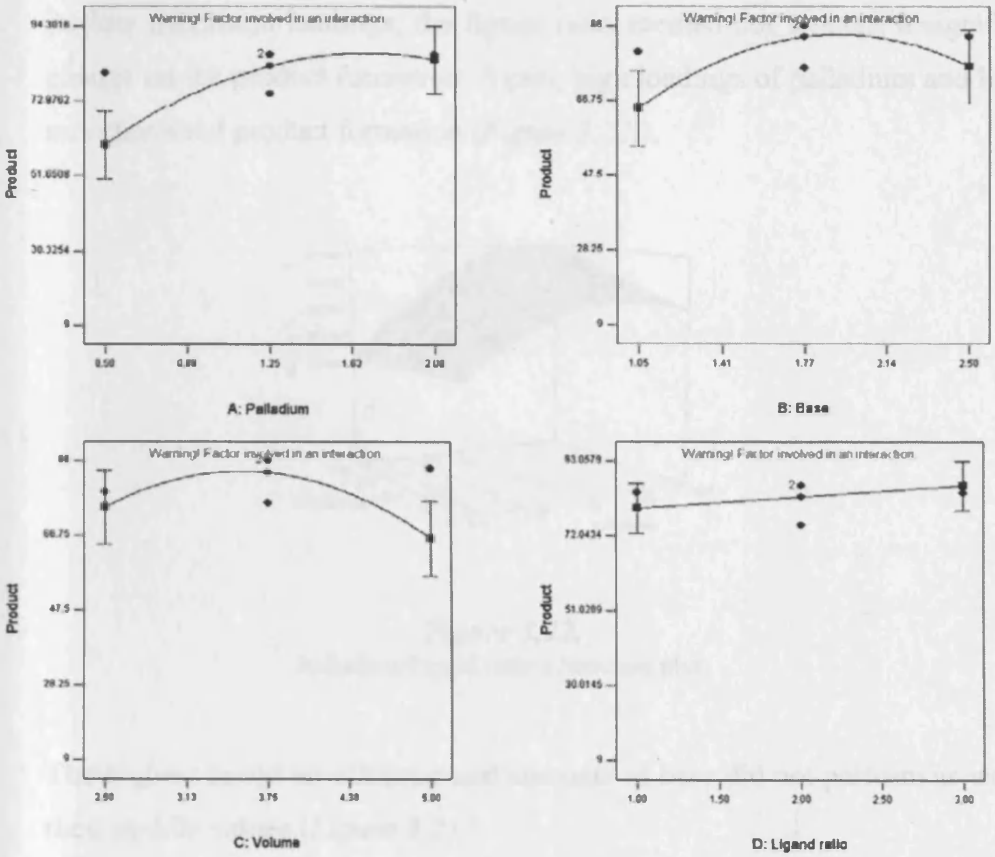


Figure 3.20.
One factor plots for; A: Palladium, B: Base,
C: Volume, D: Ligand ratio.

- Similarly to the findings in the factorial design, both the palladium and base loadings needed to be high for maximum product formation (*Figure 3.21.*).

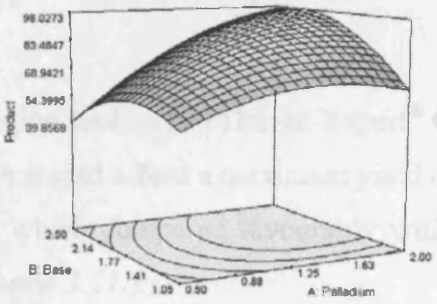


Figure 3.21.
Palladium/base interaction plot.

- At low palladium loadings, the ligand ratio seemed not to exert a significant change on the product formation. Again, high loadings of palladium and ligand ratio favoured product formation (*Figure 3.22.*).

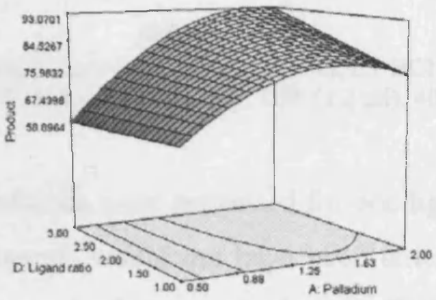


Figure 3.22.
Palladium/ligand ratio interaction plot.

- The highest or lowest dilutions and amounts of base did not perform as well as their middle values (*Figure 3.23.*).

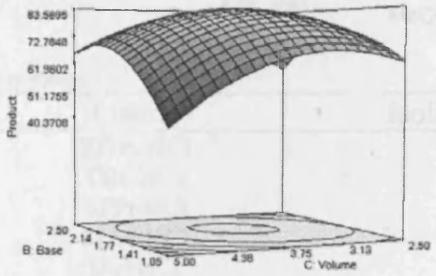
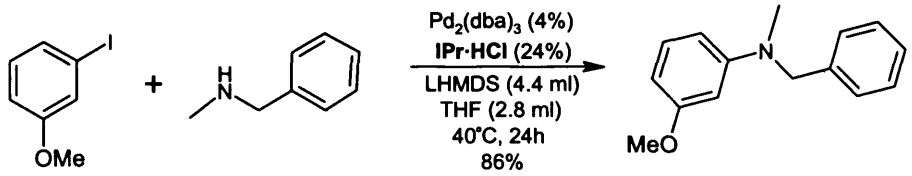


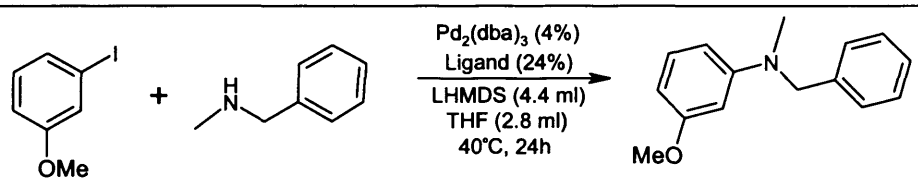
Figure 3.23.
Base/volume interaction plot.

Employing the optimisation tool within Design-Expert® we were able to obtain the values of each factor which would afford a maximum yield of product. In our case, the predicted yield was 90%, which compared favourably with the 86% of a validation reaction that followed (*Scheme 3.21.*).



Scheme 3.21.
Optimised conditions: $Pd_2(dba)_3$ (2%), IPr·HCl (12%), LHMDS (1M in THF, 2.2 eq), THF (1.2 ml), 40°C, 24h.

These newly found conditions were optimised for one ligand only, i.e. IPr·HCl, and their extension to other ligands would not have been strictly valid. However, it was considered to be a good comprise between a robust DoE study and a more traditional approach of changing one factor at the time and, with that in mind, a ligand screening was conducted (*Table 3.13.*).



Entry	Ligand	Isolated yield (%)
1	SI^{t}Bu·HCl	4
2	I^{t}Bu·HCl	31
3	SI^{i}Pr·HCl	31
4	SIAd·HCl	4
5	IAd·HCl	31
6	I^{t}BuPhp·HBr[a]	43
7	I^{t}BuPhe·HBr[a]	34
8	SIMes·HCl	58
9	IMes·HCl	65
10	SIPr·BF_4[b]	75
11	SIPr·HCl	75
12	$Pd(SIPr)_2$[c]	56

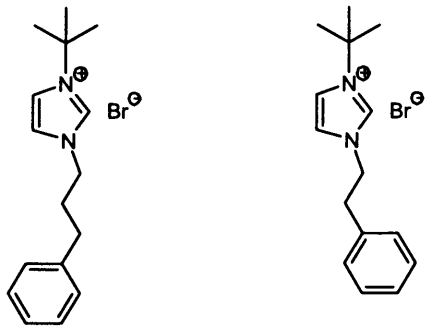
Table 3.13.
Reactions were conducted in groups of three, with a fourth reaction as a control experiment with IPr·HCl. (a) See *Figure 3.24.* (b) Prepared from SIPr·HCl by stirring in aqueous NH_4BF_4. (c) Conducted on a ¼ of scale. Low yielding reactions presented unreacted starting material.

The above ligand screening proved that IPr·HCl (86% yield) still outperformed the rest of ligands, although it was closely followed by it saturated version, i.e. SIPr·HCl. Saturated imidazolium salts have been described as better electron donors than

unsaturated ones.[178] However, their increased electron rich character did not translate into a better performance, quite the opposite, saturated imidazolium salts performed worse in other ligand pairs, such as; SI^{t}Bu·HCl/I^{t}Bu·HCl (entries 1 and 2), SIAd·HCl/IAd·HCl (entries 4 and 5) and SIMes·HCl/IMes·HCl (entries 8 and 9).

Additionally, the difference in substitution pattern in the imidazolium ring indicated that phenyl substitution was preferable (entries 8-11) over alkyl one (entries 1-5). This again manifested the electronic and structural subtleties present in these systems, as alkyl substitution was expected to afford a richer electron donating ligand.

Ligands I^{t}BuPhp·HBr and I^{t}BuPhe·HBr (entries 6 and 7) could be also regarded as alkyl disubstituted imidazolium salts, with a distinguishing terminal phenyl ring in one of the *N*-alkyl groups (*Figure 3.24.*). This made an interesting departure from the usual symmetric ligands on study and produced slightly better yields than other alkyl substitutions in the series (entries 1-5). In both instances, the terminal phenyl ring was believed to be far enough from the imidazolium ring not to influence its electronics. The fact that I^{t}BuPhp·HBr offered an increased yield was attributed to a lesser steric crowding at the carbene centre.



I^{t}BuPhp·HBr I^{t}BuPhe·HBr

Figure 3.24.

Electronics aside, the structural properties could be partially isolated and analysed in several instances. Ligands IPr·HCl and IMes·HCl (entry 9), as well as SIMes·HCl and SIPr·HCl (entries 8 and 11), highlighted the importance of the *ortho*-isopropyl residue by potentially rendering extra protection to the palladium centre. This seemed to contravene what had been described for I^{t}BuPhp·HBr but, in fact, emphasises that the "right" sterics must be in place to protect the metal centre from becoming inactive, whilst still allowing it to coordinate with the aryl iodide.

With SIPr·BF_4 (entry 10) in hand, the opportunity materialised to study the potential effect of the counterion, which concluded with the same isolated yield that its HCl version (entry 11).

From the results presented above it was concluded that the best NHC ligands were those with the following two main features; unsaturation and *N*-phenyl substitution. Differences in reactivity observed amongst this group of NHC ligands were based on the nature of the alkyl residues and their position in the phenyl rings.

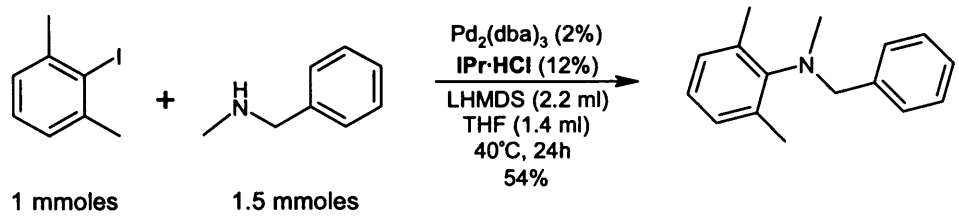
A comparison of the conditions firstly found with LHMDS as base and IPr·HCl as ligand and how they evolved with subsequent DoE studies on a hindered (1st DoE) and unhindered system (2nd DoE) is depicted below (*Table 3.14.*).

Factor	Standard RT protocol conditions	Optimised 1st DoE conditions	Optimised 2nd DoE conditions
A: Amine (eq.)	1.2	1.05	1.5
B: Pd (mol%)	1	0.50	2
C: Temperature (°C)	25	31	40
D: Base (eq.)	2.5	1.05	2.2
E: Volume (vols.)	-	2.94	1.4
F: Ligand ratio (ratio)	2	3	3
G: Ligand type (type)	IPr·HCl	SIMes·HCl	IPr·HCl

Table 3.14.

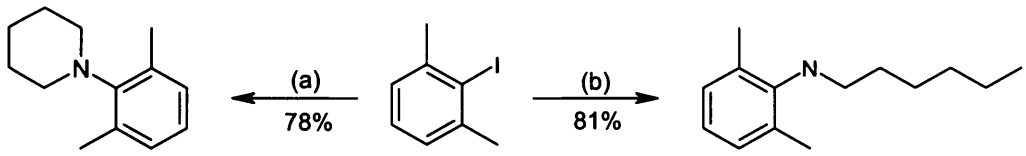
Our second DoE system was the one that approached the closest to the type of substrates employed under the RT protocol, i.e. coupling of unhindered aryl iodides with secondary amines. The conditions thereafter called for an slight increase in amine (1.2 to 1.5 eq.), Pd loadings (1 to 2 molar%) and Pd/ligand ratio (1:2 to 1:3). The temperature changed sharply (25°C to 40°C), whilst there was a small decrease in base loadings (2.5 to 2.2 eq). Overall, it could be said that our standard RT protocol was not too dissimilar to newly found conditions, yet DoE allowed for a more rigorous and systematic route to these.

The application of the DoE model and conditions in "real life" was the most important task left facing at this stage. The very sterically hindered system chosen in our first DoE was revisited with slightly improved results (*Scheme 3.22.*).



Scheme 3.22.

Two other reactions were conducted with 2-iodo-*m*-xylene to further probe its reactivity or lack of it with both a primary and a secondary amine (*Scheme 3.23.*). The presence of the *ortho-* substituents allowed *N*-hexylamine to couple in good yield and did not offer much hindrance for the coupling with piperidine.



Scheme 3.23.
Conditions: 2-iodo-*m*-xylene (1 mmol), amine (1.5 mmoles), $Pd_2(dba)_3$ (2%), IPr·HCl (12%), LHMDS (2.2 ml), THF (1.4 ml), 40°C, 24h. (a) piperidine. (b) *N*-hexylamine.

Finally, several reactions were conducted with other aryl halides and *pseudo*-halides to investigate the scope of our conditions (*Table 3.15.*).

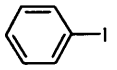
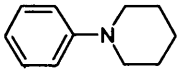
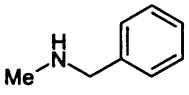
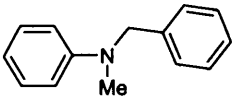
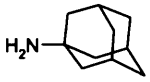
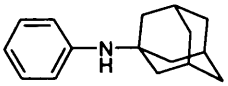
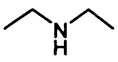
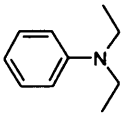
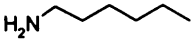
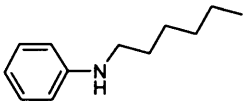
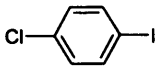
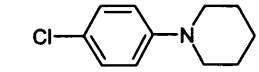
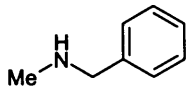
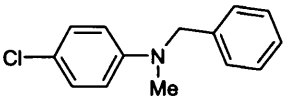
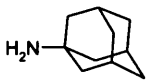
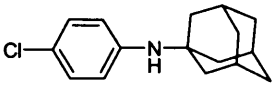
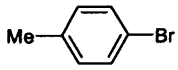
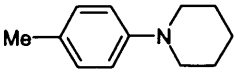
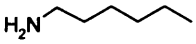
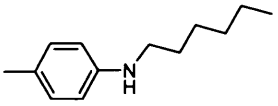
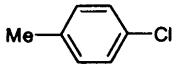
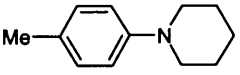
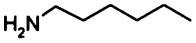
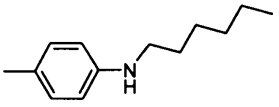
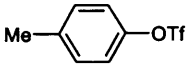
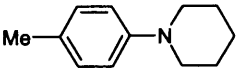
Entry	Ar-X	HNR'R''	Ar-NR'R''	Yield (%)
1				84 (81)
2				94 (89)
3				89 (70)
4				36 (27)
5				66 (40[a])
6				86 (85)
7				81
8				74
9				88
10				39[b]
11				32
12				3[c]
13				68

Table 3.15.

Conditions: aryl halide (1 mmol), amine (1.5 mmoles), $Pd_2(dba)_3$ (2%), IPr·HCl (12%), LHMDS (2.2 ml), THF (1.4 ml), 40°C, 24h.
Yields in parenthesis represent previous results pre-optimisation (*Table 3.3.*). (a) Calculated yield. (b) bisarylation present. (c) unreacted starting material present.

Entries 1-4 and 6 in the above table allowed for a direct comparison to the conditions first employed upon establishing LHMDS as our base of choice. Overall, there was a slight improvement on those yields consistent with the conclusions elucidated from our DoE, i.e. our RT protocol was not far from the optimum.

Significantly, we were able to achieve a higher conversion to product utilising a primary amine, e.g. *N*-hexylamine (entry 5). Our investigations, previous to this latest optimisation, resulted in the formation of the required product together with the bis-arylation by-product. In entry 5, we present the formation of *N*-phenylhexylamine as a single product in good yield. An aryl bromide (entry 10) and chloride also afforded the required coupling product with *N*-hexylamine, although conversions paralleled those of aryl bromides and chlorides.

Yields decreased on moving from an aryl bromide (entry 9 and 10) to an aryl chloride (entry 11 and 12), which was also consistent with the reactivity pattern described in a previous chapter on intramolecular Heck cyclisations.

Finally, aryl triflates have been found to perform in several palladium catalytic reactions, including aminations. We wished to screen a representative of their kind in the form of 4-methylphenyl triflate (entry 13) and under our protocol a moderate yield was obtained.

3.5. *CONCLUDING REMARKS*

Our first attempts to transfer the conditions employed for the intramolecular Heck cyclisations in previous chapter did not allow the Hartwig-Buchwald amination of aryl iodides either at RT or under heating. Instead, the homo-coupling of these substrates to form bis-arylated species was observed.

Additionally, earlier precedents for the amination of aryl iodides at RT, using NHC ligand precursors and alkoxide bases could not be reproduced and heating was required. With a similar palladium/imidazolium salt catalytic system and a change of base to the hindered LHMDS, we were able to establish a truly mild protocol for this transformation. Strictly inert atmospheres or the need for a dry-box were unnecessary, with reaction times ranging from 30 minutes to 24 hours.

Secondary amines, especially cyclic ones, offered good to excellent yields. At this stage, primary amines, with the exception of adamantanamine, could not be coupled effectively under our protocol. Interestingly, the presence of an *ortho-* substituent in the aryl iodide permitted a primary amine, such as *N*-hexylamine, to be coupled successfully.

Further optimisation of our RT protocol was sought with the aid of statistical design of experiments (DoE), for which the computer software Design-Expert® was employed. The final model acquired differed slightly to our original protocol and brought some improvement to the reaction yields. This approach permitted a more rational search for the optimum conditions which, otherwise might have been missed with a traditional approach of changing one factor at a time, due to the number of variables to be studied concurrently. Additionally, information about several interactions of amongst variables was also gained.

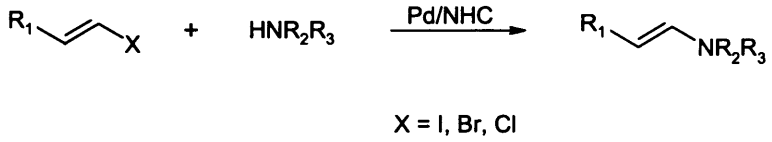
More importantly, *N*-hexylamine was successfully reacted with iodobenzene in good yield and without observing the bis-arylation by-product, thus opening the way for future coupling attempts with other primary amines.

No explicit attempts were conducted to investigate the mechanism of these transformations, although DoE studies afforded an insight into the best type of ligand. This information combined with previous observations on the reactivity of primary amines may call for a mechanistic pathway highly dependant of structural factors. These observations may have also revealed that amines, in general, and primary amines, in particular, were more than coupling partners and they may actively being involved in the mechanism.

When our optimised protocol was applied to an aryl bromide and an aryl chloride, decreased yields were observed on moving from the former to the latter. This is a pattern also observed in other palladium catalysed reactions. Future work in this area may choose to investigate a catalytic system capable of coupling aryl chlorides under the same mild conditions that we achieved with aryl iodides.

Another task to be undertaken might focus in extending the applicability of our protocol to substrates such as aryl triflates and tosylates which share ease of synthesis and wide availability with aryl chlorides. Only one instance of coupling an aryl triflate and piperidine has been described in this thesis with a moderate yield. It would be of great interest to reveal the full scope of these substrates.

In addition, our protocol could be employed as a starting point for the study of amination of vinyl halides (*Scheme 3.24.*).



Scheme 3.24.

Chapter Four : EXPERIMENTAL

4.1. *GENERAL INFORMATION*

Reactions were carried out with oven dried glassware and magnetic stirring, under an argon or nitrogen atmosphere. All solvents were reagent grade. DCM, toluene, diethyl ether, THF and acetonitrile were distilled from calcium hydride under argon or obtained from a solvent purification system. Anhydrous DMA was purchased from Aldrich. All other reagents were used "as received" from manufacturers, unless otherwise indicated.

Imidazolium IAd·HCl, IMes·HCl, IPr·HCl and imidazolinium salts SI^{t}Bu·HCl, SIMes·HCl, SIPr·HCl, SI^{i}Pr·HCl were prepared following literature procedures.[96,97,149] Salts I^{t}Bu·HCl, I^{t}BuPhe·HBr, I^{t}BuPhp·HBr, as well as palladium complex Pd(SIPr)$_2$ were obtained by members of our group.

Precoated silica gel plates (254 μm) with a fluorescent indicator (Merck) were used for analytical TLC. Plates were initially examined under UV light and then developed with aqueous potassium permanganate stain. Flash chromatography was carried out with Kiesegel (230-400 mesh) silica gel. ^{1}H NMR and ^{13}C NMR spectra were acquired at 300 MHz and 75 MHz, respectively, with a Bruker AMX 300. Chemical shifts (δ values) are reported in parts per million and coupling constants (*J* values) are quoted in Hertz. Melting points were measured in a Gallenkamp apparatus and are uncorrected. Mass spectra were obtained on a VG70-SE mass spectrometer. Elemental analyses were performed at the Department of Chemistry, University College London.

HPLC analysis were obtained with a Phenomenex Luna C18(2), 3μm column (50mm x 2.00mm), running a gradient mobile phase at 1 mL/min.

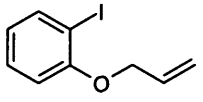
Unless otherwise specified, all compounds presented in this chapter have been previously reported in the literature and their references provided for comparison of analytical data.

4.2. *INTRAMOLECULAR HECK CYCLISATIONS*

4.2.1. Synthesis of *O*-allylhalobenzenes

A mixture of 2-halophenol (13.0 mmoles), allyl bromide (15.0 mmoles), potassium iodide (0.530 g, 3.2 mmoles) and potassium carbonate (3.6 g, 26.0 mmoles) was heated in acetone (75 mL) at reflux for 3h. After cooling at ambient temperature, the mixture was filtered through celite, with several washes of acetone, and the solvent evaporated *in vacuo*. The residue was redissolved in ether (70 mL) and washed with water (3x20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude material that was purified by flash chromatography on silica gel, eluting with increasing amounts of Et_2O in Petrol.

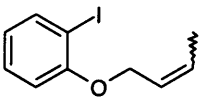
2-Allyloxy-2-iodobenzene[179]



The general procedure was followed with 2-iodophenol and allyl bromide to afford a colourless oil, 2.5 g, 74% yield.

δ_H ($CDCl_3$); 4.58 [d, 2H, CH_2CHCH, *J* 4.8], 5.31 [dd, 1H, CH_2CHCH, *J* 1.6, 10.8], 5.50 [1H, dd, CH_2CHCH, *J* 1.6, 17.2], 6.02-6.10 [m, 1H, CH_2CHCH], 6.70 [t, 1H, Ar**H**, *J* 7.4], 6.83 [d, 1H, Ar**H**, *J* 7.2], 7.28 [t, 1H, Ar**H**, *J* 7.4], 7.78 [d, 1H, Ar**H**, *J* 7.4]. **δ_C ($CDCl_3$)**; 69.45, 86.10, 112.30, 118.00, 122.35, 129.32, 132.28, 139.40, 156.67. **m/z** (EI); 258. **HRMS** (CI); C_9H_9IO, Required 259.9699, Found 259.9697. **Elemental Anal.** Calc.: C (41.56), H (3.49). Found: C (41.52), H (3.45).

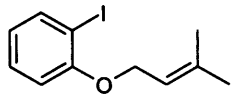
3-Methyl-2-allyloxy-2-iodobenzene[179]



The general procedure was followed with 2-iodophenol and crotyl bromide to afford a colourless oil, 3.0 g, 84% yield.

δ_H ($CDCl_3$); 1.72 [d, 3H, CH_3, *J* 1.5], 1.84 [d, 3H, CH_3, *J* 1.5], 4.47 [d, 1H, $CHCH_3$, *J* 5.2], 4.61 [d, 1H, $CHCH_3$, *J* 4.1], 5.62-5.87 [m, 1H, CHCH], 6.53 [dt, 1H, CH_2, *J* 1.5, 7.8], 6.78 [dd, 1H, CH_2, *J* 1.5, 7.8], 7.21-7.27 [m, 1H, ArH], 7.72 [dd, 1H, CH_2, *J* 1.5, 7.8]. **δ_C ($CDCl_3$);** 12.72, 15.87, 64.74, 68.99, 85.92, 122.48, 125.52, 125.85, 127.81, 129.39, 130.02, 138.92, 156.87. **LC/MS (EI);** 274. **HRMS** (EI); $C_{10}H_{11}IO$, Required 273.9856, Found 273.9853. **Elemental Anal.** Calc.: C (43.82), H (4.05). Found: C (43.80), H (4.01).

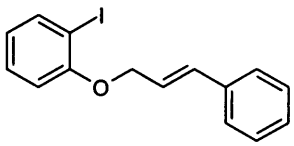
3,3-Dimethyl-2-allyloxy-2-iodobenzene[179]



The general procedure was followed with 2-iodophenol and 4-bromo-2-methyl-2-butene to afford a yellow oil, 3.0 g, 80% yield.

δ_H ($CDCl_3$); 1.72 [s, 3H, CH_3], 1.76 [s, 3H, CH_3], 4.60 [d, 2H, OCH_2, *J* 6.4], 5.52-5.59 [m, 1H, CH_2CH], 6.68 [td, 1H, ArH, *J* 1.1, 7.8], 6.87 [dd, 1H, ArH, *J* 7.9], 7.16-7.40 [m, 1H, ArH], 7.56 [d, 1H, ArH, *J* 7.9]. **δ_C ($CDCl_3$);** 18.42, 25.87, 66.30, 87.02, 112.82, 119.64, 122.52, 129.43, 137.96, 139.54, 157.58. **LC/MS** (EI); 288. **HRMS** (EI); $C_{11}H_{13}IO$, Required 288.0012, Found 288.0011. **Elemental Anal.** Calc.: C (45.86), H (4.55). Found: C (45.82), H (4.48).

3-Phenyl-2-allyloxy-2-iodobenzene[180]

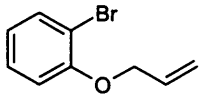


The general procedure was followed with 2-iodophenol and cinnamyl bromide to afford a colourless oil, 3.6 g, 82% yield.

δ_H ($CDCl_3$); 4.76 [d, 2H, CH_2CHCH, *J* 5.4], 6.42 [dt, 1H, CH_2CHCH, *J* 5.6, 16], 6.72 [2H, app. t, ArH, *J* 7.2], 6.89 [d, 1H, CH_2CHCH, *J* 16], 7.25-7.36 [m, 4H, ArH],

7.41 [d, 2H, Ar**H**, *J* 7.6], 7.78 [d, 1H, Ar**H**, *J* 7.6]. **δ_C ($CDCl_3$)**; 69.77, 87.00, 112.79, 122.79, 123.95, 126.64, 127.92, 128.61, 129.44, 132.93, 136.47, 139.59, 157.25, 154.17. **m/z** (EI); 178, 232, 335. **HRMS** (CI); $C_{15}H_{13}IO$, Required 336.0011, Found 336.0009. **Elemental Anal.** Calc.: C (53.59), H (3.90). Found: C (53.52), H (3.82).

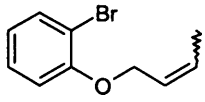
2-Allyloxy-2-bromobenzene[181]



The general procedure was followed with 2-bromophenol and allyl bromide to afford a colourless oil, 2.1 g, 76% yield.

δ_H ($CDCl_3$); 4.52 [d, 2H, CH_2CHCH, *J* 4.8], 5.23 [dd, 1H, CH_2CHC**H**, *J* 1.6, 10.8], 5.45 [1H, dd, CH_2CHC**H**, *J* 1.6, 17.2], 6.00-6.05 [m, 1H, CH_2C**H**CH], 6.78 [m, 1H, Ar**H**], 6.83 [d, 1H, Ar**H**, *J* 7], 7.17 [m, 1H, Ar**H**], 7.48 [d, 1H, Ar**H**, *J* 7]. **δ_C ($CDCl_3$)**; 68.15, 85.30, 112.13, 117.89, 122.16, 129.30, 131.79, 137.42, 155.09. **m/z** (EI); 212. **HRMS** (CI); C_9H_9BrO, Required 211.9837, Found 211.9832. **Elemental Anal.** Calc.: C (50.73), H (4.26). Found: C (50.79), H (4.22).

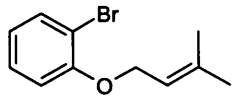
3-Methyl-2-allyloxy-2-bromobenzene[182]



The general procedure was followed with 2-bromophenol and crotyl bromide to afford a colourless oil, 2.4 g, 81% yield.

δ_H ($CDCl_3$); 1.68 [d, 3H, CH_3, *J* 1.5], 1.79 [d, 3H, CH_3, *J* 1.5], 4.27 [d, 1H, C**H**CH_3, *J* 5.2], 4.48 [d, 1H, C**H**CH_3, *J* 4.1], 5.52-5.65 [m, 1H, C**H**CH], 6.51 [dt, 1H, CH_2, *J* 1.5, 7.8], 6.69 [dd, 1H, CH_2, *J* 1.5, 7.8], 7.13-7.19 [m, 1H, Ar**H**], 7.58 [dd, 1H, CH_2, *J* 1.5, 7.8]. **δ_C ($CDCl_3$);** 12.08, 15.34, 63.99, 66.33, 85.10, 121.78, 124.52, 125.10, 127.32, 128.84, 139.96, 137.88, 155.83. **m/z** (EI); 227. **HRMS** (EI); $C_{10}H_{11}BrO$, Required 225.9993, Found 225.9981. **Elemental Anal.** Calc.: C (52.89), H (4.88). Found: C (52.76), H (4.72).

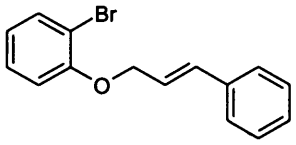
3,3-Dimethyl-2-allyloxy-2-bromobenzene[183]



The general procedure was followed with 2-bromophenol and 4-bromo-2-methyl-2-butene to afford a yellow oil, 2.5 g, 80% yield.

δ_H ($CDCl_3$); 1.68 [s, 3H, CH_3], 1.73 [s, 3H, CH_3], 4.54 [d, 2H, OCH_2, *J* 6.4], 5.36-5.45 [m, 1H, CH_2CH], 6.83 [td, 1H, Ar**H**, *J* 1.1, 7.8], 6.79 [dd, 1H, Ar**H**, *J* 1.1, 7.9], 7.19-7.33 [m, 1H, Ar**H**], 7.49 [d, 1H, Ar**H**, *J* 7.9]. **δ_C ($CDCl_3$)**; 18.44, 25.15, 66.08, 111.90, 116.36, 119.16, 122.53, 129.32, 133.47, 137.65, 155.52. **m/z** (EI); 241. **HRMS** (EI); $C_{11}H_{13}BrO$, Required 240.0150, Found 240.0139. **Elemental Anal.** Calc.: C (54.79), H (5.43). Found: C (54.69), H (5.40).

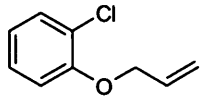
3-Phenyl-2-allyloxy-2-bromobenzene[180]



The general procedure was followed with 2-bromophenol and cinnamyl bromide to afford a colourless oil, 2.9 g, 77% yield.

δ_H ($CDCl_3$); 4.68 [d, 2H, CH_2CHCH, *J* 5.5], 6.36 [dt, 1H, CH_2CHCH, *J* 5.6, 16], 6.72 [1H, app. t, Ar**H**, *J* 7.2], 6.89 [d, 1H, CH_2CHCH, *J* 16], 7.15-7.32 [m, 5H, Ar**H**], 7.31 [d, 2H, Ar**H**, *J* 7.6], 7.49 [d, 1H, Ar**H**, *J* 7.6]. **δ_C ($CDCl_3$)**; 69.89, 112.80, 114.15, 122.38, 124.29, 127.12, 128.14, 128.90, 129.10, 133.29, 133.79, 136.67, 155.40. **m/z** (EI); 288, 290. **HRMS** (EI); $C_{15}H_{13}BrO$, Required 288.01502, Found 288.01510. **Elemental Anal.** Calc.: C (62.30), H (4.53). Found: C (62.19), H (4.45).

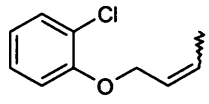
1-Allyloxy-2-chlorobenzene[184]



The general procedure was followed with 2-chlorophenol and allyl bromide to afford a colourless oil, 1.6 g, 73% yield.

δ_H ($CDCl_3$); 4.59 [dd, 2H, CH_2CHCH, *J* 1.3, 4.8], 5.29 [d, 1H, CH_2CHCH, *J* 10.8], 5.48 [1H, d, CH_2CHCH, *J* 1.5], 6.02-6.05 [m, 1H, CH_2CHCH], 6.85 [m, 1H, ArH], 7.15 [m, 1H, ArH], 7.32-7.34 [m, 2H, ArH, *J* 7.1]. **δ_C ($CDCl_3$)**; 69.51, 112.52, 121.33, 124.00, 127.83, 132.21, 155.12, 119.23, 131.15. **m/z** (EI); 169. **HRMS** (CI); C_9H_9ClO, Required 168.0342, Found 168.0335. **Elemental Anal.** Calc.: C (64.11), H (5.38). Found: C (64.03), H (5.40).

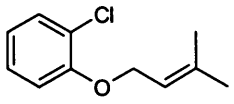
3-Methyl-2-allyloxy-2-chlorobenzene



The general procedure was followed with 2-chlorophenol and crotyl bromide to afford a colourless oil, 1.7g, 72%.

δ_H ($CDCl_3$); 1.65 [d, 3H, CH_3, *J* 1.6], 1.78 [d, 3H, CH_3, *J* 1.6], 4.23 [d, 1H, $CHCH_3$, *J* 5.0], 4.42 [d, 1H, $CHCH_3$, *J* 4.3], 5.45-5.53 [m, 1H, CHCH], 6.53 [dt, 1H, CH_2, *J* 1.6, 7.8], 6.23 [dd, 1H, CH_2, *J* 1.6, 7.8], 7.08-7.11 [m, 1H, ArH], 7.39 [dd, 1H, CH_2, *J* 1.6, 7.8]. **δ_C ($CDCl_3$);** 12.08, 15.34, 63.99, 66.33, 85.10, 121.78, 124.52, 125.10, 127.32, 128.84, 139.96, 137.88, 155.83. **m/z** (EI); 183. **HRMS** (CI); $C_{10}H_{11}ClO$, Required 182.0498, Found 182.0481. **Elemental Anal.** Calc.: C (65.76), H (6.07). Found: C (65.81), H (5.95).

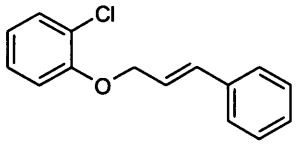
3,3-Dimethyl-2-allyloxy-2-chlorobenzene[185]



The general procedure was followed with 2-chlorophenol and 4-bromo-2-methyl-2-butene to afford a colourless oil, 2.3 g, 90%.

δ_H ($CDCl_3$); 1.59 [s, 3H, CH_3], 1.68 [s, 3H, CH_3], 4.37 [d, 2H, OCH_2, *J* 6.5], 5.22-5.32 [m, 1H, CH_2CH], 6.62 [td, 1H, ArH, *J* 1.0, 7.8], 6.81 [dd, 1H, ArH, *J* 1.0, 7.9], 7.20-7.41 [m, 1H, ArH], 7.21 [d, 1H, ArH, *J* 7.8]. **δ_C ($CDCl_3$)**; 18.30, 24.82, 65.19, 111.73, 115.11, 117.54, 119.67, 127.92, 130.32, 133.55, 149.30. **m/z** (EI); 197. **HRMS** (CI); $C_{11}H_{13}ClO$, Required 196.0654, Found 196.0632. **Elemental Anal.** Calc.: C (67.18), H (6.66). Found: C (67.01), H (6.54).

3-Phenyl-2-allyloxy-2-chlorobenzene[180]



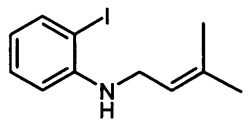
The general procedure was followed with 2-chlorophenol and cinnamyl bromide to afford a white solid, 2.8 g, 90% yield.

δ_H ($CDCl_3$); 4.80 [d, 2H, CH_2CHCH, *J* 5.6], 6.44 [dt, 1H, CH_2CHCH, *J* 5.6, 16], 6.80 [d, 1H, CH_2CHCH, *J* 16], 6.91 [app. t, 1H, ArH, *J* 7.8], 7.00 [d, 1H, ArH, *J* 8.2], 7.21-7.43 [m, 7H, ArH]. **δ_C ($CDCl_3$)**; 69.70, 114.01, 121.64, 123.15, 123.93, 126.65, 127.69, 128.00, 128.62, 130.41, 133.21, 136.36, 154.1. **m/z** (EI); 117, 91. **HRMS** (CI); $C_{15}H_{13}ClO$, Required 244.0654, Found 244.0649. **Elemental Anal.** Calc.: C (73.62), H (5.35). Found: C (73.59), H (5.30).

4.2.2. Synthesis of *N,N*-allylhalobenzenes

A solution of LDA, prepared from *N,N*-diisopropylamine (1.4 mL, 20.0 mmoles) and n-BuLi (2.5 M in hexanes, 8.4 mL, 21.0 mmoles) in THF (30 mL) at -78°C, was slowly added whilst stirring to a solution of 2-haloaniline (13.0 mmoles) in THF (75 mL) at -78°C. The reaction mixture was stirred at ambient temperature for 20 min. and cooled down to -78°C before adding the allyl bromide (15.0 mmoles). After 18h at ambient temperature, a saturated solution of NH_4Cl (75 mL) was added and the mixture extracted with EtOAc (3x30 mL). The combined organic phases was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a crude material that was purified by flash chromatography over silica gel, eluting with increasing amounts of Et_2O in Petrol.

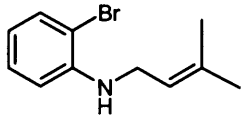
2-Iodophenyl-(3-methyl-2-butenyl)amine[180]



The general procedure was followed with 2-iodoaniline and 4-bromo-2-methyl-2-butene to afford the title compound as a yellow oil, 2.1 g, 56% yield.

δ_H ($CDCl_3$); 1.54 [s, 3H, CH_3], 1.57 [s, 3H, CH_3], 3.21 [d, 2H, NCH_2, *J* 6.5], 3.89 [s, 1H, NH], 5.04 [t, 1H, CH_2CH, *J* 6.5], 6.25 [t, 1H, ArH, *J* 8.0], 6.31 [d, 1H, ArH, *J* 8.0], 7.00 [t, 1H, ArH, *J* 8.0], 7.39 [d, 1H, ArH, *J* 8.0]. **δ_C ($CDCl_3$)**; 18.01, 25.66, 41.72, 84.39, 111.30, 117.01, 119.13, 127.74, 129.42, 136.03, 144.19. **m/z** (EI); 288. **HRMS** (CI); $C_{11}H_{14}IN$, Required 287.0172, Found 287.0165. **Elemental Anal.** Calc.: C (46.01), H (4.91), N (4.88). Found: C (46.02), H (4.88), N (4.92).

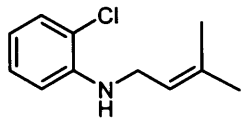
2-Bromophenyl-(3-methyl-2-butenyl)amine[180]



The general procedure was followed with 2-bromoaniline and 4-bromo-2-methyl-2-butene to afford the title compound as a yellow oil, 2.4 g, 76% yield.

δ_H ($CDCl_3$); 1.65 [s, 3H, CH_3], 1.67 [s, 3H, CH_3], 3.52 [d, 2H, NCH_2, *J* 6.5], 4.15 [s, 1H, NH], 5.22 [t, 1H, CH_2CH, *J* 6.6], 6.40 [t, 1H, ArH, *J* 7.8], 6.49 [d, 1H, ArH, *J* 7.8], 7.01 [t, 1H, ArH, *J* 7.8], 7.25 [d, 1H, ArH, *J* 7.8]. **δ_C ($CDCl_3$)**; 18.31, 26.16, 41.99, 109.20, 110.01, 117.83, 119.97, 126.78, 131.00, 135.43, 145.19. **m/z** (EI); 69, 171, 241. **HRMS** (CI); $C_{11}H_{14}BrN$, Required 239.0310, Found 239.0313. **Elemental Anal.** Calc.: C (55.02), H (5.88), N (5.83). Found: C (55.00), H (5.84), N (5.82).

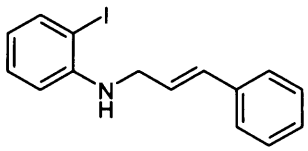
2-Chlorophenyl-(3-methyl-2-butenyl)amine[180]



The general procedure was followed with 2-chloroaniline and 4-bromo-2-methyl-2-butene to afford the title compound as a yellow oil, 1.9 g, 74% yield.

δ_H ($CDCl_3$); 1.74 [s, 3H, CH_3], 1.77 [s, 3H, CH_3], 3.68 [d, 2H, NCH_2, *J* 6.5], 4.23 [s, 1H, NH], 5.35 [t, 1H, CH_2CH, *J* 6.5], 6.64 [t, 1H, ArH, *J* 8.5], 7.14 [d, 1H, ArH, *J* 8.5], 7.24 [t, 1H, ArH, *J* 8.5], 7.51 [d, 1H, ArH, *J* 8.5]. **δ_C ($CDCl_3$)**; 18.24, 25.50, 42.67, 110.98, 117.39, 119.77, 121.82, 127.32, 129.49, 135.12, 145.10. **m/z** (EI); 69, 196. **HRMS** (CI); $C_{11}H_{14}ClN$, Required 195.0814, Found 195.0810. **Elemental Anal.** Calc.: C (67.51), H (7.21), N (7.16). Found: C (67.49), H (7.18), N (7.12).

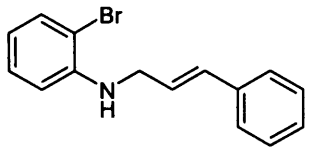
2-Iodophenyl-(3-phenylallyl)amine[180]



The general procedure was followed with 2-iodoaniline and cinnamyl bromide to afford the title compound as a yellow oil, 2.4 g, 55% yield.

δ_H ($CDCl_3$); 4.02 [d, 2H, CH_2CHCH, *J* 5.4], 4.41 [s, 1H, N**H**], 6.19 [dt, 1H, CH_2CHCH, *J* 5.6, 16.0], 6.25-6.34 [m, 1H, Ar**H**], 6.37-6.49 [m, 1H, Ar**H**], 6.49 [d, 1H, CH_2CHCH, *J* 16.0], 7.06-7.15 [m, 2H, Ar**H**], 7.21-7.43 [m, 4H, Ar**H**], 7.60-7.69 [m, 1H, Ar**H**]. **δ_C ($CDCl_3$)**; 46.40, 82.78, 111.12, 118.95, 126.19, 126.41, 127.64, 127.82, 128.58, 129.45, 131.87, 132.90, 135.47, 139.07, 143.83. **m/z** (EI); 130, 336. **HRMS** (CI); $C_{15}H_{14}IN$, Required 335.0172, Found 335.0165. **Elemental Anal.** Calc.: C (53.75), H (4.21), N (4.18). Found: C (53.72), H (4.18), N (4.15).

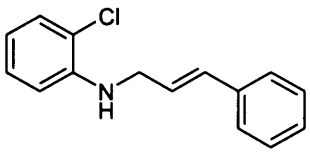
2-Bromophenyl-(3-phenylallyl)amine[180]



The general procedure was followed with 2-bromoaniline and cinnamyl bromide to afford the title compound as yellow/brown oil, 2.2 g, 58% yield.

δ_H ($CDCl_3$); 3.86 [dd, 2H, CH_2CHCH, *J* 1.3, 5.4], 4.60 [s, 1H, N**H**], 6.29 [dt, 1H, CH_2CHCH, *J* 5.4, 16.0], 6.61-6.68 [m, 2H, Ar**H**], 6.74 [dd, 1H, CH_2CHCH, *J* 1.3, 16.0], 7.07-7.14 [m, 2H, Ar**H**], 7.22-7.39 [m, 4H, Ar**H**], 7.57 [m, 1H, Ar**H**]. **δ_C ($CDCl_3$)**; 45.32, 109.72, 116.00, 118.14, 125.65, 125.33, 127.20, 127.69, 128.32, 128.72, 131.89, 130.41, 135.63, 143.63. **m/z** (EI); 117, 288. **HRMS** (CI); $C_{15}H_{14}BrN$, Required 287.0310, Found 287.0306. **Elemental Anal.** Calc.: C (62.52), H (4.90), N (4.86). Found: C (62.50), H (4.87), N (4.90).

2-Chlorophenyl-(3-phenylallyl)amine[180]



The general procedure was followed with 2-chloroaniline and cinnamyl bromide to afford the title compound as a yellow oil, 2.7 g, 85% yield.

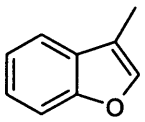
δ_H ($CDCl_3$); 3.72 [dd, 2H, CH_2CHCH, *J* 1.5, 5.5], 4.32 [s, 1H, **NH**], 6.19 [dt, 1H, CH_2CHCH, *J* 5.5, 16.0], 6.21-6.45 [m, 2H, Ar**H**], 6.93 [dd, 1H, CH_2CHCH, *J* 1.5, 16.0], 7.18-7.27 [m, 2H, Ar**H**], 7.31-7.39 [m, 4H, Ar**H**], 7.39 [m, 1H, Ar**H**]. **δ_C ($CDCl_3$)**; 40.98, 107.21, 113.67, 115.39, 121.15, 121.33, 125.89, 126.16, 127.18, 128.55, 129.55, 129.99, 132.22, 140.00. **m/z** (EI); 177, 244. **HRMS** (CI); $C_{15}H_{14}ClN$, Required 243.0814, Found 243.0809. **Elemental Anal.** Calc.: C (73.92), H (5.79), N (5.75). Found: C (73.88), H (5.82), N (5.74).

4.2.3. Synthesis of Benzofurans and Indoles

Representative procedure for iodo- and bromo-substrates.

N,N-allylhalobenzene or *O*-allylhalobenzene (1.00 mmol), Cs_2CO_3 (488 mg, 1.50 moles), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmoles) and imidazolinium salt **SIPr·HCl** (4.2 mg, 0.01 mmoles) were loaded into a Schlenk flask and purged with nitrogen and vacuum. DMA (10 mL) was added and the mixture heated at 140°C. Upon disappearance of starting material by TLC, the mixture was allowed to cool down to ambient temperature, diluted with Et_2O (20 mL) and filtered through celite with several portions of Et_2O. The filtrate was washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude residue was chromatographed over silica gel, eluting with increasing volumes of Et_2O in petrol.

3-Methylbenzofuran[186]

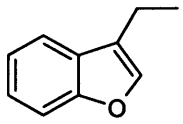


The procedure for iodo- and bromo-substrates was followed to afford the title compound as pale brown oil; 107 mg, 81% yield (from iodo-substrate) or 101 mg, 77% yield (from bromo-substrate).

δ_H ($CDCl_3$); 2.16 [s, 3H, CH_3], 7.18-7.27 [m, 5H, Ar**H**]. **δ_C ($CDCl_3$)**; 7.71, 107.98, 113.24, 117.39, 121.36, 122.57, 127.48, 138.16, 154.49. **m/z** (EI); 133. **HRMS** (EI);

C_9H_8O, Required 132.0575, Found 132.0569. **Elemental Anal.** Calc.: C (81.79), H (6.10). Found: C (81.68), H (5.97).

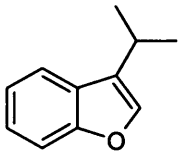
3-Ethylbenzofuran[187]



The procedure for iodo- and bromo-substrates was followed to afford the title compound as pale brown oil; 120 mg, 82% yield (from iodo-substrate) or 104 mg, 71% yield (from bromo-substrate).

δ_H ($CDCl_3$); 1.13 [t, 3H, CH_2CH_3, *J* 7.1], 2.63 [q, 2H, CH_2CH_3, *J* 7.1], 6.65 [s, 1H, Ar**H**], 7.01 [dd, 2H, Ar**H**, *J* 7.1, 7.9], 7.25 [d, 1H, Ar**H**, *J* 7.9], 7.49 [d, 1H, Ar**H**, *J* 7.9]. **δ_C ($CDCl_3$)**; 13.24, 16.89, 108.87, 115.32, 115.92, 117.62, 118.21, 121.20, 126.23, 137.15. **m/z** (EI); 147. **HRMS** (EI); $C_{10}H_{10}O$, Required 146.0731, Found 146.0727. **Elemental Anal.** Calc.: C (82.16), H (6.89). Found: C (82.13), H (6.81).

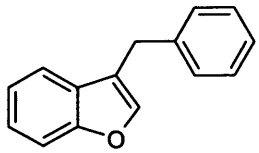
3-Isoproylbenzofuran[188]



The procedure for iodo- and bromo-substrates was followed to afford the title compound as colourless oil; 121 mg, 76% yield (from iodo-substrate) or 105 mg, 66% yield (from bromo-substrate).

δ_H ($CDCl_3$); 1.32 [d, 6H, CH_3, *J* 7], 3.02 [sept, 1H, C**H**], 6.67 [s, 1H, Ar**H**], 7.05 [dd, 2H, Ar**H**, *J* 7.1, 7.9], 7.19 [d, 1H, Ar**H**, *J* 7.9], 7.45 [d, 1H, Ar**H**, *J* 7.9].. **δ_C ($CDCl_3$)**; 21.92, 23.42, 112.11, 118.93, 121.33, 123.08, 126.75, 126.98, 138.68, 156.62. **m/z** (EI) 161. **HRMS** (EI) $C_{11}H_{12}O$; Requires 160.0888, Found 160.0884. **Elemental Anal.** Calc.: C (82.46), H (7.55). Found: C (82.40), H (7.59).

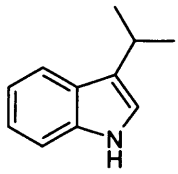
3-Benzylbenzofuran[180]



The procedure for iodo- and bromo-substrates was followed to afford the title compound as a yellow solid; 156 mg, 75% yield (from iodo-substrate) or 104 mg, 50% yield (from bromo-substrate).

δ_H ($CDCl_3$); 4.03 [s, 2H, CH_2Ph], 7.18-7.30 [m, 7H, Ar**H**], 7.37-7.60 [m, 3H, Ar**H**]. **δ_C ($CDCl_3$)**; 30.00, 111.43, 119.72, 119.88, 122.34, 124.21, 126.36, 127.00, 128.51, 128.64, 139.14, 142.13. **m/z** (EI) 209. **HRMS** (EI) $C_{15}H_{12}O$; Requires 208.0888, Found 208.0889. **Elemental Anal.** Calc.: C (86.51), H (5.81). Found: C (86.48), H (5.85).

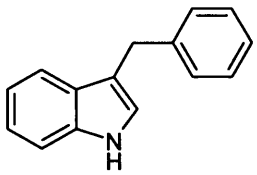
3-*Iso*-propyl-1*H*-indole[180]



The procedure for iodo- and bromo-substrates was followed to afford the title compound as a brown oil; 125 mg, 79% yield (from iodo-substrate); 98 mg, 62% yield (from bromo-substrate) or 95 mg, 60% yield (from chloro-substrate).

δ_H ($CDCl_3$); 1.19 [s, 3H, $CHCH_3$], 1.22 [s, 3H, $CHCH_3$], 3.05 [sept, 1H, $CHCH_3$, *J* 7], 6.63 [s, 1H, Ar**H**], 7.12 [dd, 2H, Ar**H**, *J* 7.5, 7.8], 7.19 [d, 1H, Ar**H**, *J* 7.8], 7.47 [d, 1H, Ar**H**, *J* 7.8], 7.69 [broad s, 1H, N**H**]. **δ_C ($CDCl_3$)**; 23.67, 25.87, 52.99, 111.76, 118.54, 118.95, 119.56, 121.11, 122.21, 123.78, 127.03, 135.66. **m/z** (EI) 159, 115. **HRMS** (EI) $C_{11}H_{13}N$; Requires 159.1048, Found 159.1045. **Elemental Anal.** Calc.: C (82.97), H (8.23), N (8.80). Found: C (82.93), H (8.20), N (8.76).

3-Benzyl-1*H*-indole[180]

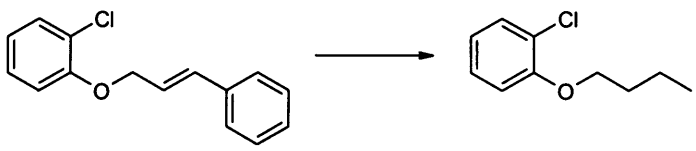


The procedure for iodo- and bromo-substrates was followed to afford the title compound as colourless oil, 155 mg, 75% yield (from iodo-substrate); 128 mg, 62% yield (from bromo-substrate) or 124 mg, 60% yield (from chloro-substrate).

δ_H ($CDCl_3$); 4.91 [s, 2H, CH_2Ar], 6.77 [s, 1H, Ar**H**], 7.01 [dd, 2H, Ar**H**, *J* 7.6, 8], 7.05-7.21 [m, 5H, Ar**H**], 7.21 [m, 5H, Ar**H**]. **δ_C ($CDCl_3$)**; 30.76, 109.50, 115.13, 119.01, 119.73, 120.66, 121.99, 125.67, 126.99, 128.12, 128.88, 135.13, 140.15. **m/z** (EI) 208, 130. **HRMS** (EI) $C_{15}H_{13}N$; Requires 207.1048, Found 207.1043. **Elemental Anal.** Calc.: C (86.92), H (6.32), N (6.76). Found: C (86.87), H (6.27), N (6.69).

4.2.4. Experiment Leading to the Deallylation Process

O-Allylhalobenzene **25** (1.00 mmol), Cs_2CO_3 (488 mg, 1.50 moles), $Pd_2(dba)_3$ (9.1 mg, 0.01 mmoles) and imidazolinium salt **SIPr·HCl** (4.2 mg, 0.01 mmoles) were loaded into a Schlenk flask and purged with nitrogen and vacuum. DMA (10 mL) was added and the mixture heated at 140°C. Upon disappearance of starting material by TLC, the mixture was allowed to cool down to ambient temperature, diluted with Et_2O (20 mL) and filtered through celite with several portions of Et_2O. The filtrate was washed with water (10 mL), brine (10 mL) and dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude residue was chromatographed over silica gel, eluting with increasing volumes of Et_2O in petrol.



25 **27**

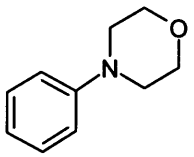
The above procedure was followed to obtain a 65% recovery of **27**. See Appendix 1 for spectroscopic evidence.

4.3. *AMINATION OF ARYL IODIDES*

4.3.1. Typical Procedure for the RT Protocol

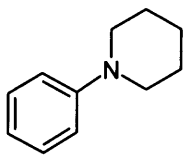
An oven-dried Schlenk tube was charged with $Pd_2(dba)_3$ (9 mg, 0.01 mmol), 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride **IPr·HCl** (17 mg, 0.04 mmol) and a magnetic stirrer bar. The flask was evacuated and backfilled with nitrogen three times, after which the aryl iodide (1.0 mmol) and amine (1.2 mmol) were added, followed by LHMDS (1M solution in THF, 2.5 mL). The mixture was maintained at 25°C and stirred for 20 hours (reaction times were not optimised). After dilution with DCM, it was absorbed straight onto silica and purified by flash chromatography on silica gel eluting with increasing amounts of ether in hexane.

***N*-Phenylmorpholine**[171]



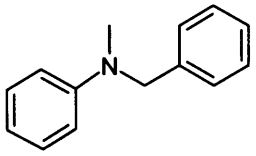
δ_H ($CDCl_3$); 3.15-3.18 [m, 4H, CH_2NCH_2], 3.85-3.89 [m, 4H, CH_2OCH_2], 6.86-6.92 [m, 3H, ArH], 7.25-7.29 [m, 2H, ArH]. **δ_C ($CDCl_3$);** 49.43, 66.91, 114.42, 115.79, 120.18, 129.21, 151.23. **m/z** (EI); 164. **HRMS** (EI) $C_{10}H_{13}NO$; Requires 163.0997, Found 163.0989. **Elemental Anal.** Calc.: C (73.59), H (8.03), N (8.58). Found: C (73.49), H (8.21), N (8.50).

***N*-Phenylpiperidine**[189]



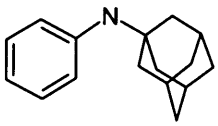
δ_H ($CDCl_3$); 1.55-1.63 [m, 2H, $CH_2CH_2CH_2$], 1.69-1.76 [m, 4H, $CH_2CH_2CH_2$], 3.15-3.18 [m, 4H, CH_2NCH_2], 6.81-6.86 [m, 1H, ArH], 6.96-6.97 [m, 2H, ArH], 7.23-7.29 [m, 2H, ArH]. **δ_C ($CDCl_3$);** 24.32, 25.97, 50.73, 116.56, 119.21, 129.02, 152.29. **m/z** (EI); 162. **HRMS** (EI) $C_{11}H_{15}N$; Required 161.1204, Found 161.1210. **Elemental Anal.** Calc.: C (81.94), H (9.38), N (8.69). Found: C (81.91), H (9.28), N (8.65).

***N*-Benzylmethylphenylamine**[171]



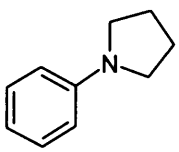
δ_H ($CDCl_3$); 2.99 [s, 3H, NCH_3], 4.55 [s, 2H, NCH_2], 6.70-6.78 [m, 3H, ArH], 7.21-7.27 [m, 5H, ArH], 7.31-7.36 [m, 2H, ArH]. **δ_C ($CDCl_3$);** 38.51, 56.60, 112.31, 116.59, 126.73, 126.88, 128.51, 129.29, 139.05, 149.74. **m/z** (EI); 105, 120, 197. **HRMS** (EI) $C_{14}H_{15}N$; Required 197.1204, Found 197.1209. **Elemental Anal.** Calc.: C (85.24), H (7.66), N (7.10), Found: C (85.18), H (7.52), N (7.14).

***N*-Phenyladamantanamine**[190]



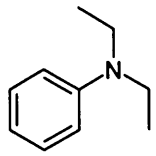
δ_H ($CDCl_3$); 1.62-1.63 [m, 6H, CH_2CH_2], 1.87-1.88 [m, 6H, CH_2CH_2], 2.10 [app. s, 3H, CH_2CHCH_2], 6.76-6.82 [m, 3H, ArH], 7.12-7.18 [m, 2H, ArH]. **δ_C ($CDCl_3$);** 29.72, 36.42, 43.43, 52.31, 119.29, 128.73. **m/z** (EI); 135, 170, 227. **HRMS** (EI) $C_{16}H_{21}N$; Required 227.1673, Found 227.1668. **Elemental Anal.** Calc.: C (84.53), H (9.31), N (6.16). Found: C (84.47), H (9.35), N (6.07).

***N*-Phenylpyrrolidine**[189]



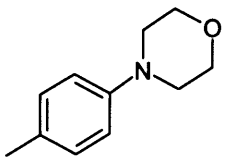
δ_H ($CDCl_3$); 2.00-2.04 [m, 4H, CH_2CH_2], 3.25-3.33 [m, 4H, CH_2NCH_2], 6.58-6.61 [m, 2H, Ar**H**], 6.68-6.71 [m, 1H, Ar**H**], 7.23-7.29 [m, 2H, Ar**H**]. **δ_C ($CDCl_3$);** 25.55, 47.65, 111.62, 115.31, 129.19, 148.02. **m/z** (EI); 91, 104, 147. **HRMS** (EI) $C_{10}H_{13}N$; Required 147.1047, Found 147.1039. **Elemental Anal.** Calc.: C (81.59), H (8.90), N (9.51). Found: C (81.49), H (8.93), N (9.48).

Diethyl phenylamine[189]



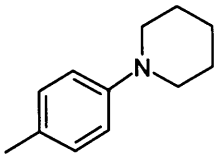
δ_H ($CDCl_3$); 1.20 [t, 6H, NCH_2CH_3, *J*], 3.30 [q, 4H, NCH_2CH_3, *J*], 6.53-6.60 [m, 3H, Ar**H**], 7.34-7.45 [m, 2H, Ar**H**]. **δ_C ($CDCl_3$);** 12.50, 44.25, 111.69, 115.74, 129.11, 147.91. **m/z** (EI); 149. **HRMS** (EI) $C_{10}H_{15}N$; Required 149.1204, Found 149.1201. **Elemental Anal.** Calc.: C (80.48), H (10.13), N (9.39). Found: C (80.42), H (10.07), N (9.34).

***N*-(4-Methylphenyl)morpholine**[171]



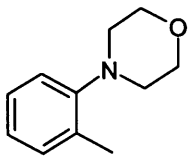
δ_H ($CDCl_3$); 2.28 [s, 3H, $ArCH_3$], 3.09-3.12 [m, 4H, CH_2NCH_2], 3.84-3.88 [m, 4H, CH_2OCH_2], 6.82 [d, 2H, Ar**H**, *J* 8.5], 7.08 [d, 2H, Ar**H**, *J* 8.6]. **δ_C ($CDCl_3$);** 20.42, 49.99, 67.01, 116.01, 129.73, 146.82, 149.18. **m/z** (EI); 178. **HRMS** (EI) $C_{11}H_{15}NO$; Required 177.1153, Found 177.1145. **Elemental Anal.** Calc.: C (74.54), H (8.53), N (7.90). Found: C (74.53), H (8.59), N (7.81).

***N*-(4-Methylphenyl)piperidine**[146]



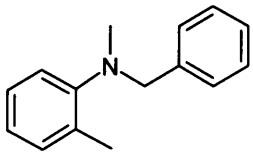
δ_H ($CDCl_3$); 1.52-1.56 [m, 2H, $CH_2CH_2CH_2$], 1.66-1.76 [m, 4H, $CH_2CH_2CH_2$], 2.27 (s, 3H, $ArCH_3$), 3.08-3.11 [m, 4H, CH_2NCH_2], 6.86 [d, 2H, Ar**H**, *J* 8.7], 7.05 [d, 2H, Ar**H**, *J* 8.7]. **δ_C ($CDCl_3$);** 20.44, 24.39, 25.93, 51.31, 116.90, 129.54, 150.05. **m/z (EI):** 91, 119, 174, 212. **HRMS** (EI) $C_{12}H_{17}N$; Required 175.1360, Found 175.1355. **Elemental Anal.** Calc.: C (82.23), H (9.78), N (7.99). Found: C (82.20), H (9.70), N (7.95).

***N*-(2-Methylphenyl)morpholine**[171]



δ_H ($CDCl_3$); 2.33 [s, 3H, $ArCH_3$], 2.91-2.94 [m, 4H, CH_2NCH_2], 3.85-3.88 [m, 4H, CH_2OCH_2], 6.97-7.04 [m, 2H, Ar**H**], 7.15-7.21 [m, 2H, Ar**H**]. **δ_C ($CDCl_3$);** 17.9, 52.3, 67.5, 118.9, 123.4, 126.7, 131.2, 132.6, 151.3. **m/z** (EI); 178. **HRMS** (EI) $C_{11}H_{15}NO$; Required 177.1153, Found 177.1158. **Elemental Anal.** Calc.: C (74.54), H (8.53), N (7.90). Found: C (73.88), H (8.62), N (7.43).

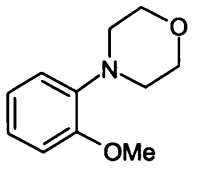
***N*-(2-Methylphenyl)-*N*-methylbenzylamine**



δ_H ($CDCl_3$); 2.43 [s, 3H, $ArCH_3$], 2.61 [s, 3H, NCH_3], 4.06 [s, 2H, NCH_2], 7.01-7.09 [m, 1H, Ar**H**], 7.12-7.14 [m, 1H, Ar**H**], 7.21-7.42 [m, 7H, Ar**H**]. **δ_C ($CDCl_3$);** 18.49, 40.90, 60.72, 120.00, 123.01, 126.43, 126.92, 128.30, 128.37, 131.16, 132.86, 139.12, 152.43. **m/z** (EI); 91, 120, 211. **HRMS** (EI) $C_{15}H_{17}N$; Required 211.1360,

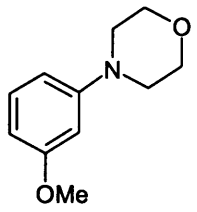
Found 211.1351. **Elemental Anal.** Calc.: C (85.26), H (8.11), N (6.63). Found: C (85.20), H (7.96), N (6.58).

***N*-(2-Methoxyphenyl)morpholine**[169]



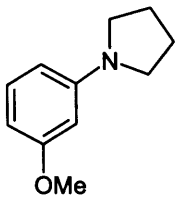
δ_H ($CDCl_3$); 3.05-3.08 [m, 4H, CH_2NCH_2], 3.86 [s, 3H, OCH_3], 3.88-3.91 [m, 4H, CH_2OCH_2], 6.87-6.89 [m, 1H, ArH], 6.93-6.94 [m, 2H, ArH], 7.00-7.04 [m, 1H, ArH]. **δ_C ($CDCl_3$);** 51.21, 55.42, 67.29, 111.33, 118.00, 121.02, 123.26, 141.15, 153.02. **m/z** (EI); 120, 135, 193. **HRMS** (EI) $C_{11}H_{15}NO_2$; Required 193.1102, Found 193.1109. **Elemental Anal.** Calc.: C (68.37), H (7.82), N (7.25). Found: C (67.98), H (7.75), N (7.27).

***N*-(3-Methoxyphenyl)morpholine**[191]



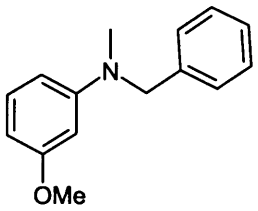
δ_H ($CDCl_3$); 3.13-3.17 [m, 4H, CH_2NCH_2], 3.79 [s, 3H, OCH_3], 3.83-3.87 [m, 4H, CH_2OCH_2], 6.43-6.46 [m, 2H, ArH], 6.52-6.55 [m, 1H, ArH], 7.16-7.22 [m, 1H, ArH]. **δ_C ($CDCl_3$);** 49.32, 55.22, 66.99, 102.26, 104.74, 108.55, 129.99, 152.71, 160.64. **m/z** (EI); 135. **HRMS** (EI) $C_{11}H_{15}NO_2$; Required 193.1102, Found 193.1094. **Elemental Anal.** Calc.: C (68.37), H (7.82), N (7.25). Found: C (68. 28), H (7.82), N (7.20).

***N*-(3-Methoxyphenyl)pyrrolidine**[192]



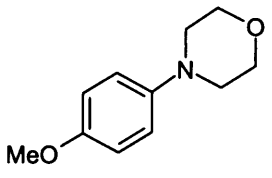
δ_H ($CDCl_3$); 1.94-2.02 [m, 4H, CH_2CH_2], 3.26-3.30 [m, 4H, CH_2NCH_2], 3.80 [s, 3H, OCH_3], 6.11-6.13 [m, 1H, Ar**H**], 6.19-6.27 [m, 2H, Ar**H**], 7.11-7.18 [m, 1H, Ar**H**]. **δ_C ($CDCl_3$);** 25.50, 47.73, 55.12, 97.91, 100.56, 104.90, 129.88, 149.33, 160.74. **m/z** (EI); 121, 177. **HRMS** (EI) $C_{11}H_{15}NO$; Required 177.1153. Found 177.1151. **Elemental Anal.** Calc.: C (74.54), H (8.53), N (7.90). Found: C (73.92), H (8.64), N (7.23).

***N*-(3-Methoxyphenyl)-*N*-methylbenzylamine**[193]



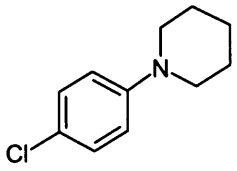
δ_H ($CDCl_3$); 3.01 [s, 3H, NCH_3], 3.73 [s, 3H, OCH_3], 4.30 [s, 2H, NCH_2], 6.21-6.43 [m, 2H, Ar**H**], 6.49-6.52 [m, 1H, Ar**H**], 7.18-7.22 [m, 1H, Ar**H**], 7.30-7.39 [m, 5H, Ar**H**]. **δ_C ($CDCl_3$);** 37.81, 55.43, 56.18, 99.32, 100.18, 105.33, 125.33, 126.62, 127.22, 129.25, 138.18, 150.39, 158.87. **m/z** (EI); 228. **HRMS** (EI) $C_{15}H_{17}NO$; Required 227.1310. Found 227.1308. **Elemental Anal.** Calc.: C (79.26), H (7.54), N (6.16). Found: C (79.23), H (7.55), N (6.13).

***N*-(4-Methoxyphenyl)morpholine**[171]



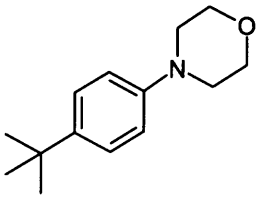
δ_H ($CDCl_3$); 3.04-3.07 [m, 4H, CH_2OCH_2], 3.63 [s, 3H, OCH_3], 3.77-3.85 [m, 4H, CH_2NCH_2], 6.83-6.91 [m, 4H, ArH]. **δ_C ($CDCl_3$);** 50.82, 55.61, 67.12, 114.56, 117.88, 145.62, 153.99. **m/z** (EI); 120, 135, 178, 193. **HRMS** (EI) $C_{11}H_{15}NO_2$; Required 193.1102, Found 193.1100. **Elemental Anal.** Calc.: C (68.37), H (7.82), N (7.25). Found: C (68.37), H (7.99), N (7.17).

***N*-(4-Chlorophenyl)piperidine**[146]



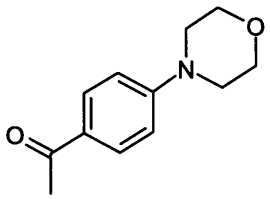
δ_H ($CDCl_3$); 1.50-1.60 [m, 2H, $CH_2CH_2CH_2$], 1.66-1.73 [m, 4H, $CH_2CH_2CH_2$], 3.13-3.18 [m, 4H, CH_2NCH_2], 6.89 [d, 2H, ArH, *J* 8.6], 7.16 [d, 2H, ArH, *J* 8.6]. **δ_C ($CDCl_3$);** 24.21, 25.72, 50.79, 117.61, 128.42. **m/z** (EI); 111, 139, 194. **HRMS** (EI) $C_{11}H_{14}ClN$; Required 195.0814, Found 195.0809. **Elemental Anal.** Calc.: C (67.51), H (7.21), N (7.16). Found: C (67.38), H (7.21), N (7.09).

***N*-(4-*t*-Butylphenyl)morpholine**[194]



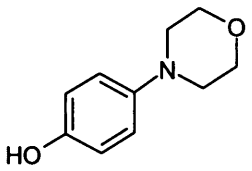
δ_H ($CDCl_3$); 1.30 [s, 9H, CH_3], 3.14-3.16 [m, 4H, CH_2OCH_2], 3.85-3.88 [m, 4H, CH_2NCH_2], 6.86 [d, 2H, ArH, *J* 8.8], 7.30 [d, 2H, ArH, *J* 8.8]. **δ_C ($CDCl_3$);** 31.55, 33.93, 49.61, 67.03, 115.49, 126.04, 142.53, 148.82. **m/z** (EI); 146, 176, 204, 219. **HRMS** (EI) $C_{14}H_{21}NO$; Required 219.1623, Found 219.1617. **Elemental Anal.** Calc.: C (76.67), H (9.65), N (6.39). Found: C (76.31), H (9.79), N (6.38).

***N*-(4-Acetylphenyl)morpholine**[195]



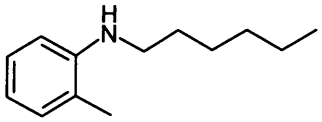
δ_H ($CDCl_3$); 2.39 [s, 3H, CH_3], 3.17-3.19 [m, 4H, CH_2OCH_2], 3.82-3.87 [m, 4H, CH_2NCH_2], 6.84 [d, 2H, Ar**H,** *J* 8.6], 7.54 [d, 2H, Ar**H**, *J* 8.6]. **δ_C ($CDCl_3$);** 25.72, 46.33, 65.87, 112.39, 128.15, 128.29, 153.21, 194.76. **m/z** (EI); 205. **HRMS** (EI) $C_{12}H_{15}NO_2$; Required 205.1102, Found 205.1099. **Elemental Anal.** Calc.: C (70.22), H (7.37), N (6.32). Found: C (70.19), H (7.36), N (6.33).

***N*-(4-Hydroxyphenyl)morpholine**[168]



δ_H ($CDCl_3$); 3.00-3.09 [m, 4H, CH_2OCH_2], 3.82-3.86 [m, 4H, CH_2NCH_2], 5.02 [s, 1H, O**H**], 6.45 [d, 2H, Ar**H,** *J* 8.7], 6.63 [d, 2H, Ar**H**, *J* 8.7]. **δ_C ($CDCl_3$);** 50.29, 68.35, 115.89, 117.21, 143.45, 152.11. **m/z** (EI); 179. **HRMS** (EI) $C_{10}H_{13}NO_2$; Required 179.0946, Found 179.0945. **Elemental Anal.** Calc.: C (67.02), H (7.31), N (7.82). Found: C (67.00), H (7.29), N (7.82).

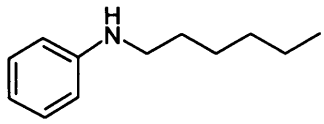
***N*-(2-Methylphenyl)hexylamine**[171]



δ_H ($CDCl_3$); 0.98 [t, 3H, CH_3, *J* 7.0], 1.31-1.45 [m, 6H, $CH_2CH_2CH_2CH_3$], 1.60 [quintet, 2H, $NCH_2CH_2CH_2$, *J* 7.10], 2.15 [s, 3H, $ArCH_3$], 3.19 [t, 2H, NCH_2, *J* 7.15], 6.97-7.04 [m, 2H, Ar**H**], 7.15-7.21 [m, 2H, Ar**H**]. **δ_C ($CDCl_3$);** 14.18, 16.28, 21.45,

25.82, 29.33, 32.15, 44.67, 108.21, 115.02, 122.79, 129.33, 131.15, 147.32. **m/z** (EI); 192. **HRMS** (EI) $C_{13}H_{21}N$; Required 191.1674, Found 191.1677. **Elemental Anal.** Calc.: C (81.61), H (11.06), N (7.32). Found: C (81.58), H (11.04), N (7.35).

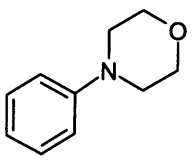
***N*-Phenylhexylamine[171], 40**



Reaction followed the general procedure but the mixture was heated at 50°C. Starting material was recovered (10%) as well as product (compound **40**, 40%) and bisarylated by-product (compound **41**, 18%). Recoveries of compounds **40** and **41** were calculated from the ^{1}H-NMR spectrum.

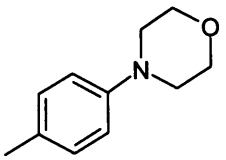
δ_H ($CDCl_3$); 0.84 [t, 3H, CH_2CH_3, *J* 6.9], 1.20-1.28 [m, 6H, $CH_2CH_2CH_2$], 1.58 [q, 2H, $NHCH_2CH_2CH_2$], 3.09 [t, 2H, NCH_2CH_2, *J* 7.1], 3.42 [broad s, 1H, $NHCH_2$], 6.60-6.65 [m, 2H, Ar**H**], 6.65-6.67 [m, 1H, Ar**H**], 7.19-7.25 [m, 2H, Ar**H**]. **δ_C ($CDCl_3$);** 14.1, 22.3, 25.9, 28.9, 31.7, 45.0, 112.2, 118.2, 130.5, 147.6. **δ_H ($CDCl_3$)** for bisarylated by-product **41**; 0.89 [t, 3H, CH_2CH_3, *J* 6.8], 1.17–1.24 [m, 6H, $CH_2CH_2CH_2$], 1.67 [q, 2H, $NHCH_2CH_2CH_2$, *J* 7.3], 3.62 [t, 2H, Ar**H**, *J* 7.6], 6.87 [dt, 2H, Ar**H**, *J* 1.1, 7.3], 6.91 [d, 4H, Ar**H**, *J* 7.6], 7.29 [t, 4H, Ar**H**, *J* 7.5].

***N*-Phenylmorpholine[171]**



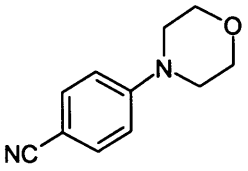
The general procedure was followed starting from chlorobenzene to afford a 43% yield. Spectroscopic analyses were consistent with previously isolated compound.

***N*-(4-Methylphenyl)morpholine**[171]



The general procedure was followed starting from 4-chlorotoluene to afford an 8% yield. Spectroscopic analyses were consistent with previously isolated compound.

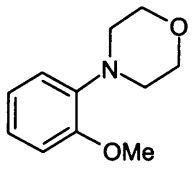
***N*-(4-Cyanophenyl)morpholine**[196]



The general procedure was followed starting from 4-chlorobenzonitrile to afford a 10% yield.

δ_H ($CDCl_3$); 3.19-3.27 [m, 4H, CH_2OCH_2], 3.83-3.86 [m, 4H, CH_2NCH_2], 6.82 [d, 2H, Ar**H**, *J* 8.9], 7.49 [d, 2H, Ar**H**, *J* 8.9]. **δ_C ($CDCl_3$);** 45.18, 62.24, 100.21, 112.79, 118.32, 131.24, 153.11. **m/z** (EI); 189. **HRMS** (EI) $C_{11}H_{12}N_2O$; Required 188.0949, Found 188.0941. **Elemental Anal.** Calc.: C (70.19), H (6.43), N (14.88). Found: C (70.14), H (6.37), N (14.82).

***N*-(2-Methoxyphenyl)morpholine**[169]



The general procedure was followed starting from 2-chloroanisole to afford an 8% yield. Spectroscopic analyses were consistent with previously isolated compound.

4.3.2. Typical Procedure for First DoE.

Reactions were conducted at GSK Tonbridge on a SK233 system, allowing for up to 10 reactions to be carried out in parallel with individual control of temperature and stirring, as well as automated sampling into an Agilent 1100 HPLC system with UV detection (220 nm). Mobile phase A was 0.05% TFA in water and mobile phase B was 0.05% TFA in acetonitrile. The gradient consisted on 0-95% phase B over 8 min and 0% phase B over 2 min, at 1 ml/min flow rate. The column was a Phenomenex Luna 3μ C18(2), 50 x 20 mm, kept at 40°C.

Reaction vessels were initially charged with $Pd_2(dba)_3$ and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride **IPr·HCl**. Liquids were dispensed by a robotic arm in the following order: 2-iodo-*m*-xylene, *N*-methylbenzylamine, LHMDS (1M solution in THF) and THF. After heating at the required temperature for 24 hours, samples were automatically submitted to the HPLC system. Responses, including those of *m*-xylene, are presented in Appendix 2.

4.3.3. Typical Procedure for Second DoE.

Reactions were conducted in a Radleys Carousel™ reaction station, using standard magnetic stirring under an inert atmosphere of Nitrogen. Amounts of reagents, conditions employed and results were listed in *Table 3.10* and *Table 3.12*.

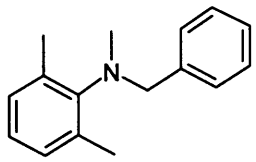
Radleys tubes were initially charged with $Pd_2(dba)_3$ and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride **IPr·HCl**, followed by 3-iodoanisole, *N*-methylbenzylamine and LHMDS (1M solution in THF). After heating at the required temperature for 24 hours, the mixtures were allowed to cool down to RT before diluting with DCM and pre-absorbing in silica gel for column chromatography eluting with increasing amounts of ether in hexane.

4.3.4. Typical Procedure for the Optimised Conditions Resulting from Second DoE.

A Radleys tube was initially charged with $Pd_2(dba)_3$ (2 molar%) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride **IPr·HCl** (12 molar%), followed by the aryl iodide (1.00 mmol), amine (1.50 mmoles), THF (1.4 mL) and LHMDS (2.20 mL, 1M solution in THF). After heating at 40°C for 24 hours, the mixtures were allowed to cool down to RT before diluting with DCM and pre-absorbing in silica gel for column chromatography eluting with increasing amounts of ether in hexane.

The ligand screening reported was conducted as above by changing the nature of the ligand.

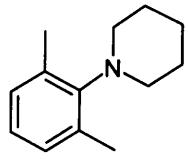
***N*-(2,6-Dimethylphenyl)piperidine**



The procedure described above was followed to afford the title compound in 54% yield.

δ_H ($CDCl_3$); 2.41 [s, 6H, Ar**C**H_3], 3.05 [s, 3H, N**C**H_3], 4.30 [s, 2H, N**C**H_2], 6.86 [d, 1H, Ar**H**, *J* 8.4], 7.11 [d, 1H, Ar**H**, *J* 8.4], 7.20 [m, 1H, Ar**H**], 7.31-7.37 [m, 5H, Ar**H**]. **δ_C ($CDCl_3$);** 55.43, 56.18, 99.32, 100.18, 105.33, 125.33, 126.62, 127.22, 129.25, 138.18, 150.39, 158.87. **m/z** (EI); 225. **HRMS** (EI) $C_{16}H_{19}N$; Required 225.1517, Found 225.1511. **Elemental Anal.** Calc.: C (85.29), H (8.50), N (6.22). Found: C (85.23), H (8.52), N (6.21).

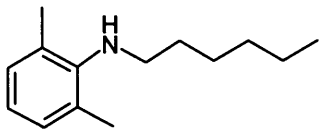
***N*-(2,6-Dimethylphenyl)piperidine**



The procedure described above was followed to afford the title compound in 78% yield.

δ_H ($CDCl_3$); 1.47-1.55 [m, 2H, $CH_2CH_2CH_2$], 1.60-1.68 [m, 4H, $CH_2CH_2CH_2$], 2.40 [s, 6H, $ArCH_3$], 3.15-3.22 [m, 4H, CH_2NCH_2], 6.85 [d, 1H, ArH, *J* 8.4], 7.11 [d, 1H, ArH, *J* 8.4], 7.19 [m, 1H, ArH]. **δ_C ($CDCl_3$);** 24.19, 25.86, 51.11, 117.33, 118.62, 133.01. **m/z** (EI); 189. **HRMS** (EI) $C_{13}H_{19}N$; Required 189.1517, Found 189.1514. **Elemental Anal.** Calc.: C (82.48), H (10.12), N (7.40). Found: C (82.46), H (10.13), N (7.43).

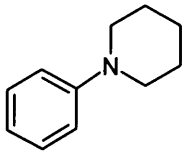
***N*-(2,6-Dimethylphenyl)hexylamine**



The procedure described above was followed to afford the title compound in 81% yield.

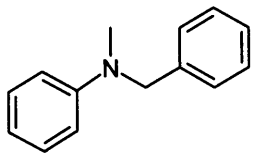
δ_H ($CDCl_3$); 1.00 [t, 3H, CH_3, *J* 7.0], 1.28-1.39 [m, 6H, $CH_2CH_2CH_2CH_3$], 1.65 [quintet, 2H, $NCH_2CH_2CH_2$, *J* 7.08], 2.19 [s, 6H, $ArCH_3$], 3.07 [t, 2H, NCH_2, *J* 7.05], 6.88 [m, 1H, ArH], 7.11 [m, 2H, ArH]. **δ_C ($CDCl_3$);** 16.11, 21.25, 25.42, 29.63, 32.05, 44.37, 108.91, 115.12, 122.19, 129.43, 147.52. **m/z** (EI); 205. **HRMS** (EI) $C_{14}H_{23}N$; Required 205.1830, Found 205.1829. **Elemental Anal.** Calc.: C (81.89), H (11.29), N (6.82). Found: C (81.85), H (11.30), N (6.80).

***N*-Phenylpiperidine**[189]



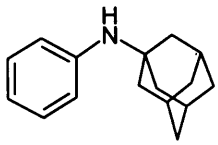
The procedure described above was followed to afford the title compound in 84% yield. Spectroscopic analyses consistent with previously synthesised compound.

***N*-Benzylmethylphenylamine[171]**



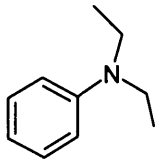
The procedure described above was followed to afford the title compound in 94% yield. Spectroscopic analyses consistent with previously synthesised compound.

***N*-Phenyladamantanamine[190]**



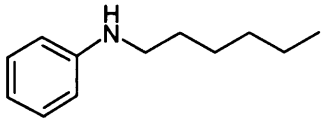
The procedure described above was followed to afford the title compound in 89% yield. Spectroscopic analyses consistent with previously synthesised compound.

Diethyl phenylamine[189]



The procedure described above was followed to afford the title compound in 36% yield. Spectroscopic analyses consistent with previously synthesised compound.

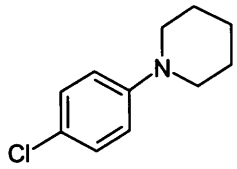
***N*-Phenylhexylamine[171], 40**



The procedure described above was followed to afford the title compound in 66% yield. Spectroscopic analyses consistent with previously synthesised compound.

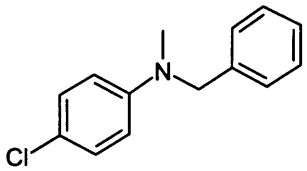
δ_H ($CDCl_3$); 0.84 [t, 3H, CH_2CH_3, *J* 6.9], 1.20-1.28 [m, 6H, $CH_2CH_2CH_2$], 1.58 [q, 2H, $NHCH_2CH_2CH_2$], 3.09 [t, 2H, NCH_2CH_2, *J* 7.1], 3.42 [broad s, 1H, $NHCH_2$], 6.60-6.65 [m, 2H, Ar**H**], 6.65-6.67 [m, 1H, Ar**H**], 7.19-7.25 [m, 2H, Ar**H**]. **δ_C ($CDCl_3$);** 14.1, 22.3, 25.9, 28.9, 31.7, 45.0, 112.2, 118.2, 130.5, 147.6. **m/z** (EI); 178. **HRMS** (EI) $C_{12}H_{19}N$; Required 177.1517, Found 177.1512. **Elemental Anal.** Calc.: C (81.30), H (10.80), N (7.90). Found: C (81.26), H (10.77), N (7.92).

N-(4-Chlorophenyl)piperidine[146]



The procedure described above was followed to afford the title compound in 86% yield. Spectroscopic analyses consistent with previously synthesised compound.

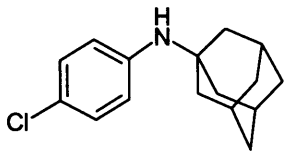
N-(4-Chlorophenyl)-*N*-methylbenzylamine



The procedure described above was followed to afford the title compound in 81% yield.

δ_H ($CDCl_3$); 3.15 [s, 3H, NCH_3], 4.17 [s, 2H, NCH_2], 6.33-6.49 [m, 2H, Ar**H**], 6.67-6.78 [m, 2H, Ar**H**], 7.55-7.76 [m, 5H, Ar**H**]. **δ_C ($CDCl_3$);** 55.67, 56.22, 99.87, 101.02, 105.13, 126.01, 126.72, 128.18, 150.12, 159.00. **m/z** (EI); 232. **HRMS** (EI) $C_{14}H_{14}ClN$; Required 231.0814, Found 231.0809. **Elemental Anal.** Calc.: C (72.57), H (6.09), N (6.04). Found: C (72.55), H (6.02), N (6.03).

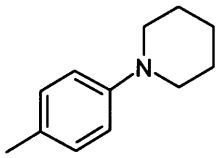
***N*-(4-Chlorophenyl)-*N*-adamantylamine**



The procedure described above was followed to afford the title compound in 74% yield.

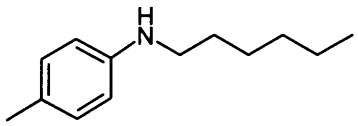
δ_H ($CDCl_3$); 1.58-1.62 [m, 6H, CH_2CH_2], 1.85-1.89 [m, 6H, CH_2CH_2], 2.11 [app. s, 3H, CH_2CHCH_2], 6.35-6.42 [m, 2H, ArH], 6.58-6.78 [m, 2H, ArH]. **δ_C ($CDCl_3$);** 30.12, 35.41, 43.22, 51.77, 119.88, 128.21, 131.16. **m/z** (EI); 262. **HRMS** (EI) $C_{16}H_{20}ClN$; Required 261.1284, Found 261.1276. **Elemental Anal.** Calc.: C (73.41), H (7.70), N (5.35). Found: C (73.45), H (7.72), N (5.31).

***N*-(4-Methylphenyl)piperidine[146]**



The procedure described above was followed using 4-bromotoluene to obtain 88% yield. Spectroscopic analyses were consistent with previously synthesised compound.

***N*-(4-Methylphenyl)hexylamine[171]**

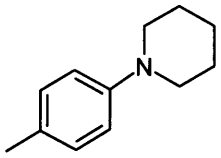


The procedure described above was followed using 4-bromotoluene to obtain 39% yield.

δ_H ($CDCl_3$); 0.80 [t, 3H, CH_2CH_3, *J* 6.9], 1.18-1.27 [m, 6H, $CH_2CH_2CH_2$], 1.52 [q, 2H, $NHCH_2CHCH_2$], 2.16 [s, 3H, $ArCH_3$], 3.13 [t, 2H, NCH_2CH_2, *J* 7.1], 3.39 [broad s, 1H, $NHCH_2$], 6.55 [d, 2H, ArH, *J* 8.2], 6.87 [d, 2H, ArH, *J* 8.2]. **δ_C ($CDCl_3$);** 14.1, 20.6, 22.9, 25.8, 28.7, 32.1, 45.2, 113.5, 127.8, 130.2, 145.9. **m/z** (EI); 192. **HRMS**

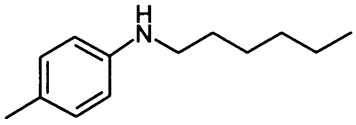
(EI) $C_{13}H_{21}N$; Required 191.1674, Found 191.1666. **Elemental Anal.** Calc.: C (81.61), H (11.06), N (7.32). Found: C (81.56), H (11.09), N (7.28).

***N*-(4-Methylphenyl)piperidine**[146]



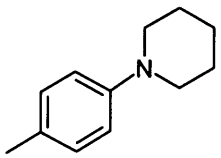
The procedure described above was followed using 4-chlorotoluene to obtain 32% yield. Spectroscopic analyses were consistent with previously synthesised compound.

***N*-(4-Methylphenyl)hexylamine**



The procedure described above was followed using 4-chlorotoluene to obtain 3% yield. Spectroscopic analyses were consistent with previously synthesised compound.

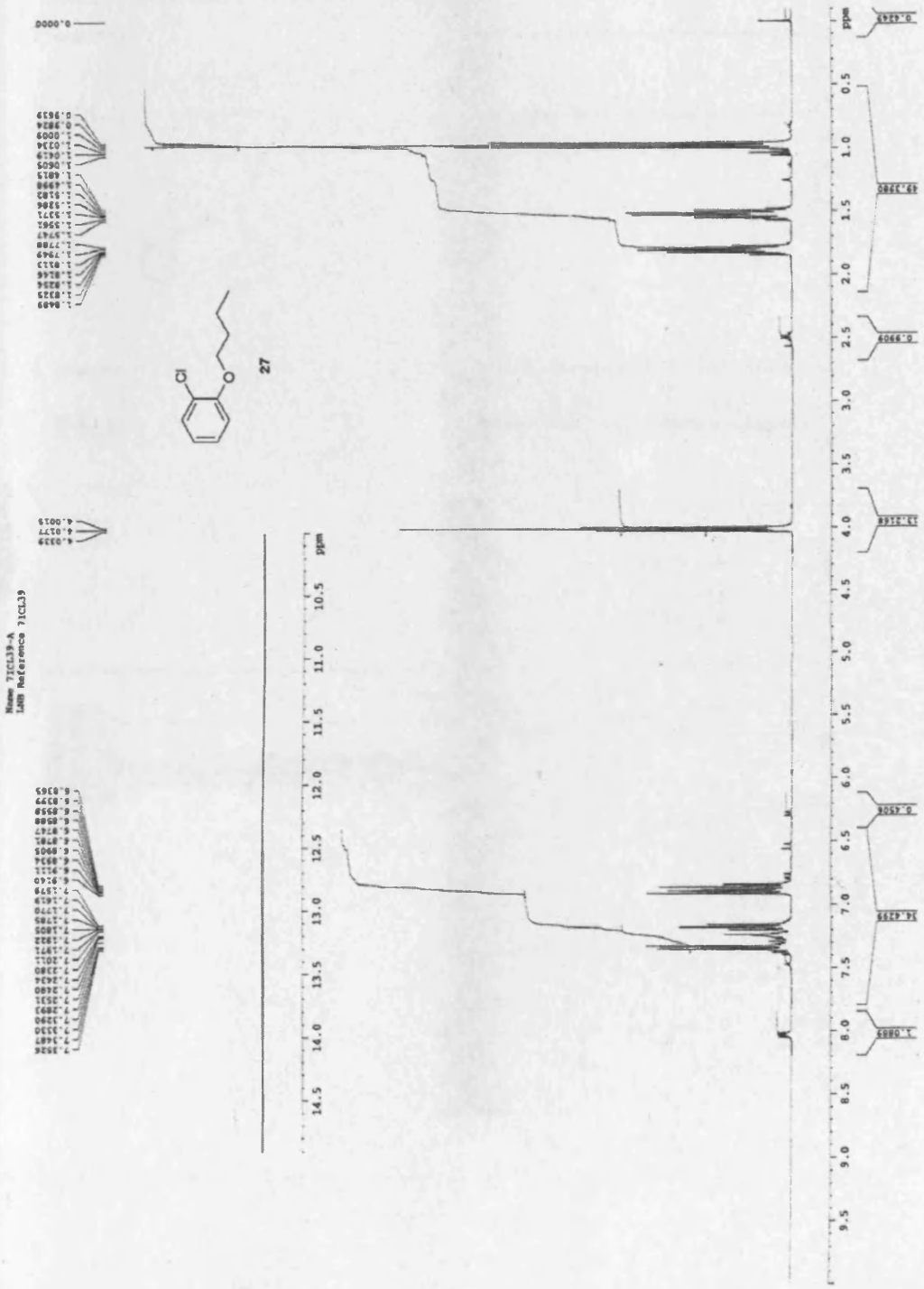
***N*-(4-Methylphenyl)piperidine**[146]

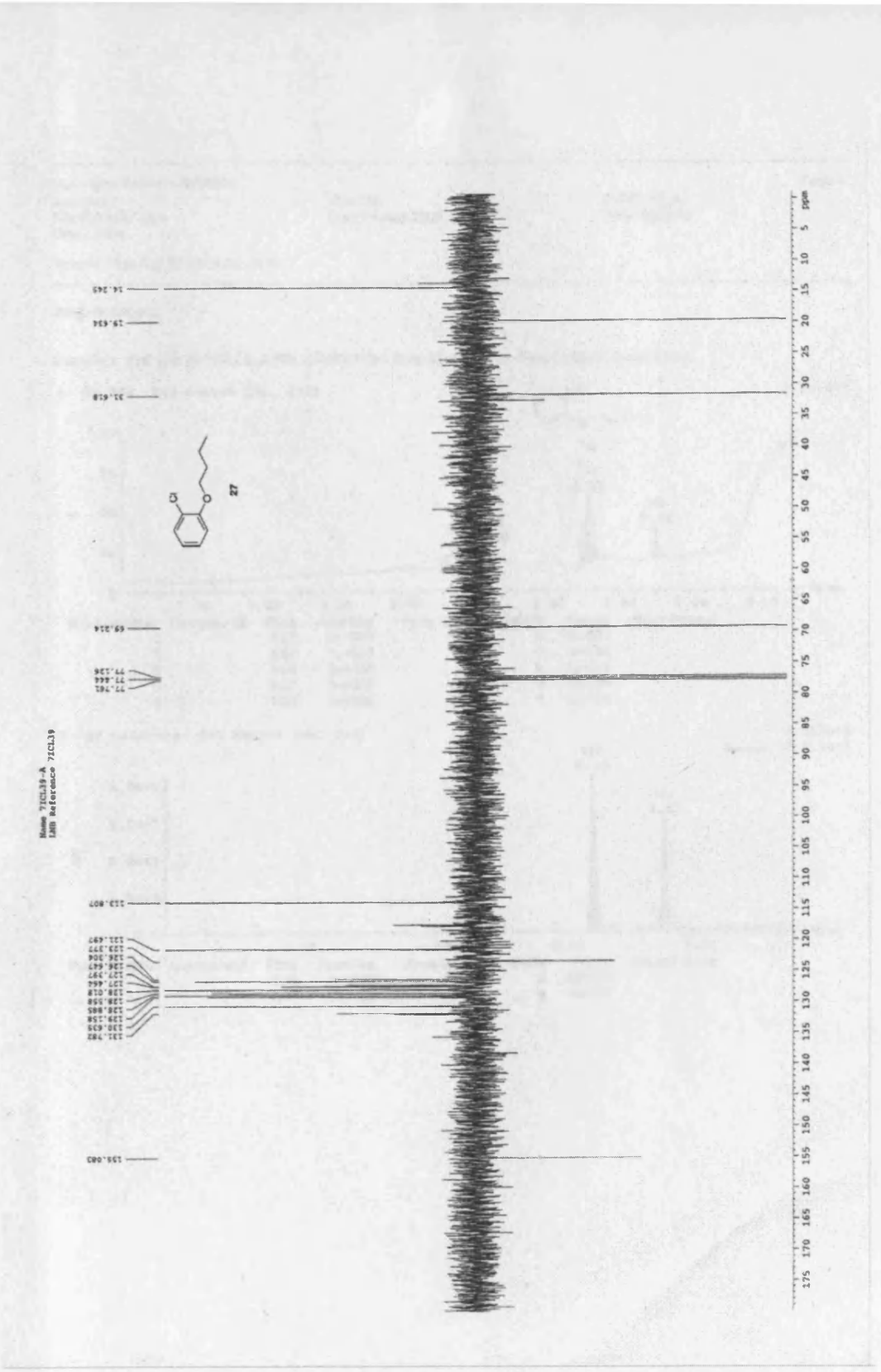


The procedure described above was followed using *p*-tolyl trifluoromethanesulfonate instead of 4-iodotoluene, to obtain 68% yield. Spectroscopic analyses were consistent with previously synthesised compound.

APPENDIX

APPENDIX 1: SPECTROSCOPIC EVIDENCE FOR COMPOUNDS 27 & 28.



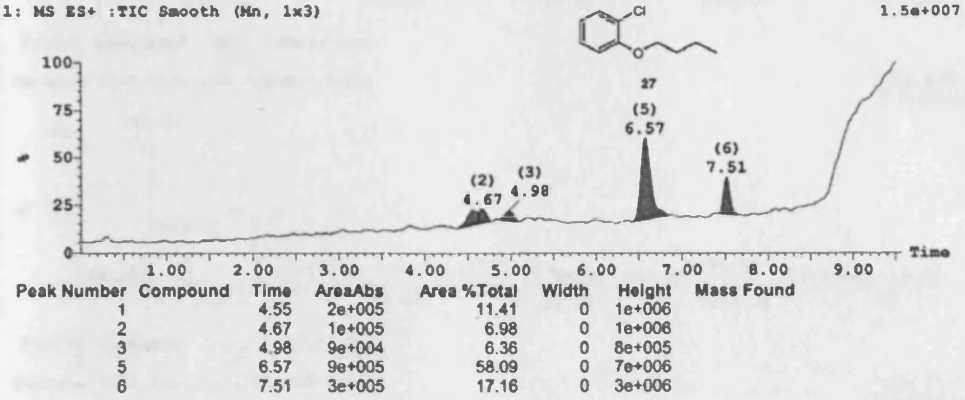

Name 7ICL39-A
Exp Reference 7ICL39
27
ppm

Openlynx Report - ISRAEL1 Page 1
Sample: 1 Vial:1:56 ID:7ICL39_A
File:ISRAEL118-1 Date:22-Aug-2005 Time:15:08:16
Description:

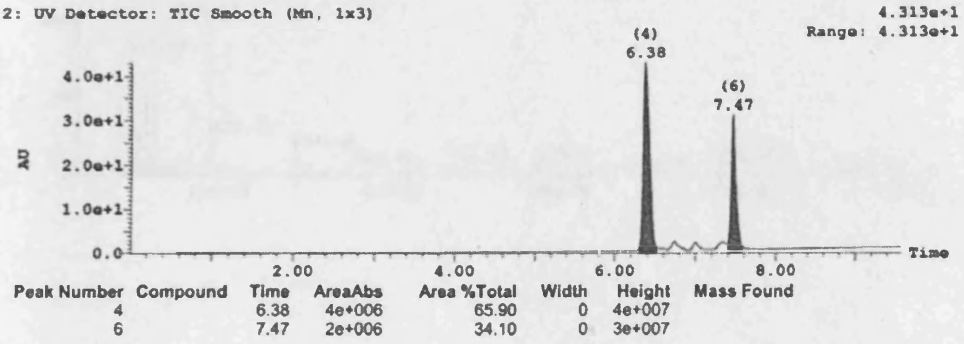
Printed: Mon Aug 22 15:21:34 2005

Sample Report:

Sample 1 Vial 1:56 ID 7ICL39_A File ISRAEL118-1 Date 22-Aug-2005 Time 15:08:16 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.55	2e+005	11.41	0	1e+006	
2		4.67	1e+005	6.98	0	1e+006	
3		4.98	9e+004	6.36	0	8e+005	
5		6.57	9e+005	58.09	0	7e+006	
6		7.51	3e+005	17.16	0	3e+006	



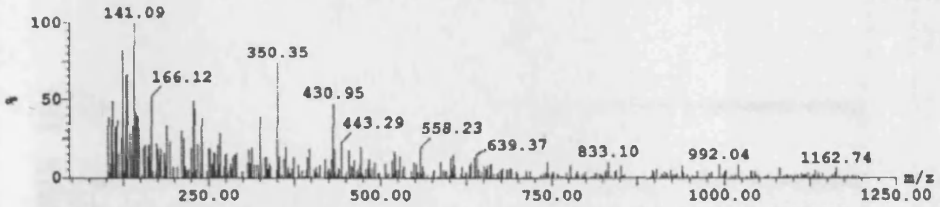
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
4		6.38	4e+006	65.90	0	4e+007	
6		7.47	2e+006	34.10	0	3e+007	

Sample Report (continued):

Peak ID	Compound	Time	Mass Found
4		6.38	

Combine (625:635-(608:613+654:659))

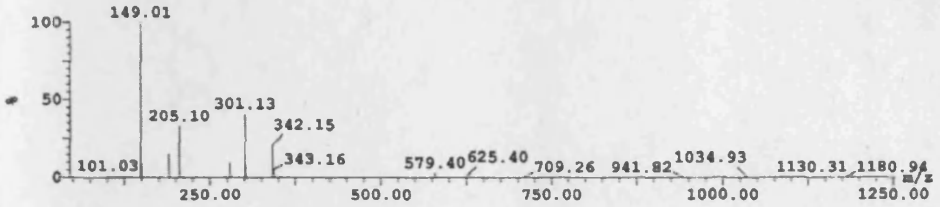
1:MS ES+
1.7e+004



Peak ID	Compound	Time	Mass Found
5		6.57	

Combine (644:654-(620:625+687:692))

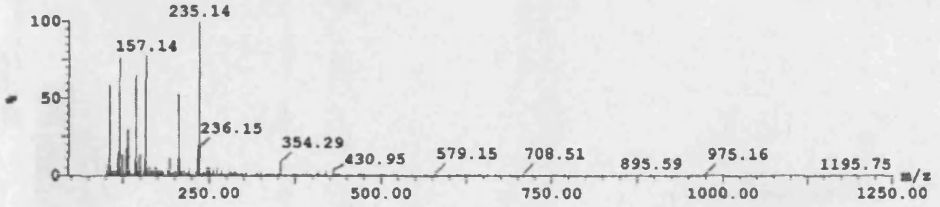
1:MS ES+
2.2e+006

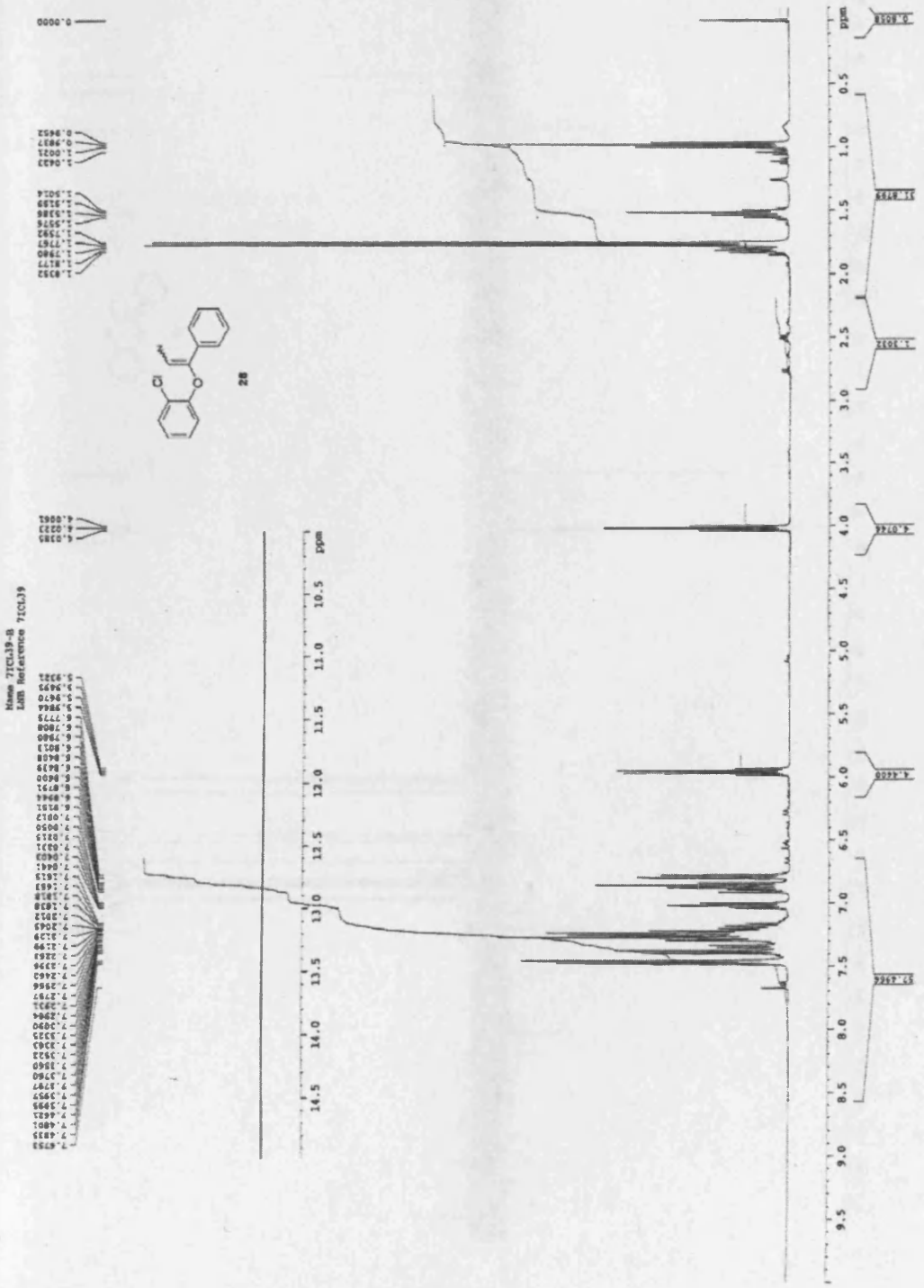


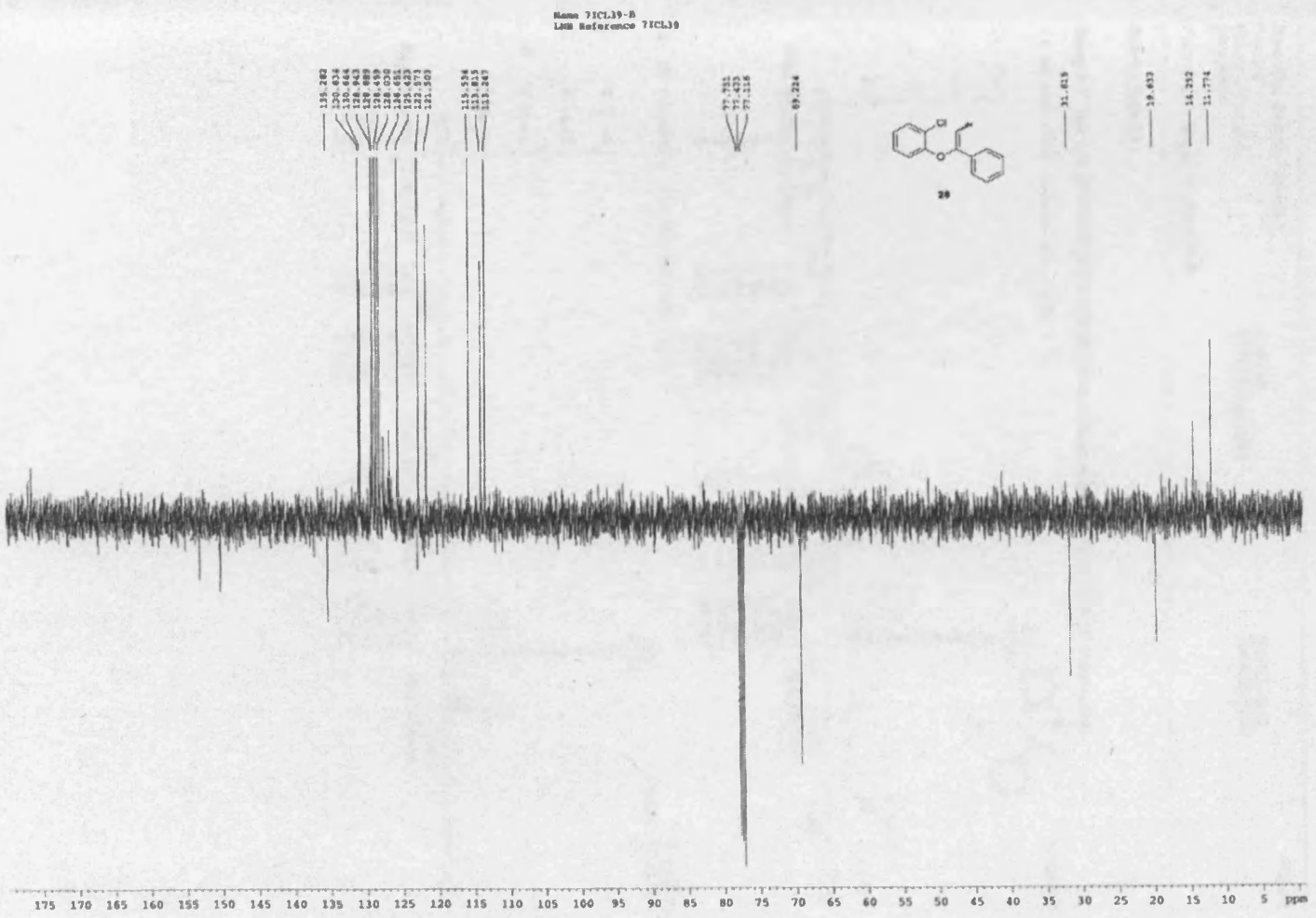
Peak ID	Compound	Time	Mass Found
6		7.51	

Combine (733:743-(716:721+758:763))

1:MS ES+
2.1e+005




Name 7ICL39-B
Exp# Reference 7ICL39
2B
ppm


Name 7ICL39-B
LMB Reference 7ICL39
77.251
77.453
77.116
69.224
31.619
19.633
14.292
11.774
20
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 ppm

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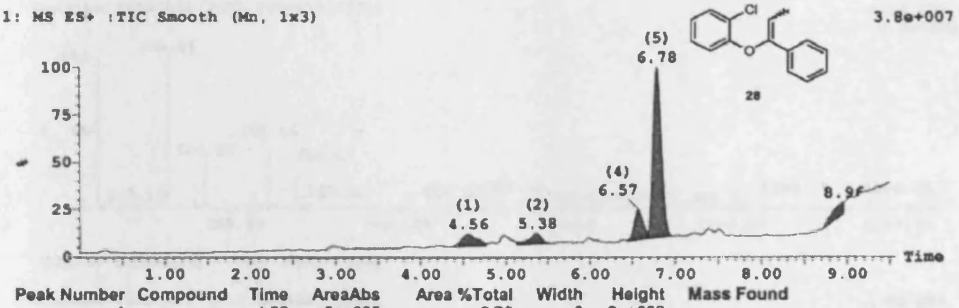
Sample: 1 Vial:1:57 ID:7ICL39_B
File:ISRAEL119-1 Date:22-Aug-2005 Time:15:21:34
Description:

Printed: Mon Aug 22 15:34:52 2005

Sample Report:

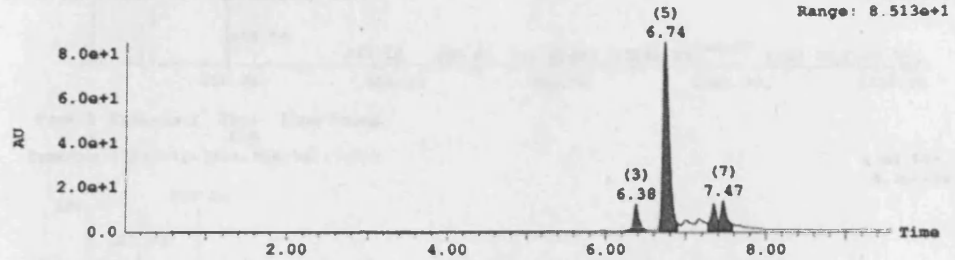
Sample 1 Vial 1:57 ID 7ICL39_B File ISRAEL119-1 Date 22-Aug-2005 Time 15:21:34 Description

1: MS ES+ :TIC Smooth (Mn, 1x3) 3.8e+007



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.56	5e+005	8.76	0	3e+006	
2		5.38	4e+005	6.40	0	2e+006	
4		6.57	7e+005	12.31	0	6e+006	
5		6.78	4e+006	65.63	0	3e+007	
8		8.96	4e+005	6.90	0	2e+006	

2: UV Detector: TIC Smooth (Mn, 1x3) 8.513e+1
Range: 8.513e+1

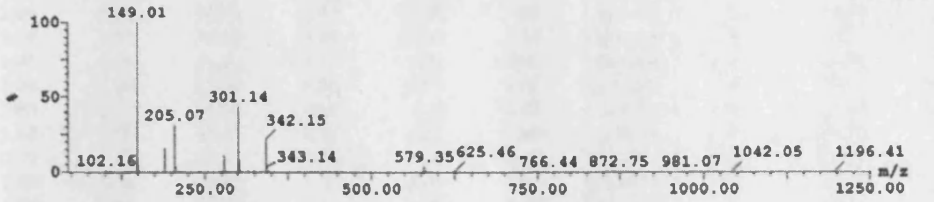


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
3		6.38	8e+005	9.10	0	1e+007	
5		6.74	7e+006	77.15	0	8e+007	
6		7.35	6e+005	6.25	0	9e+006	
7		7.47	7e+005	7.50	0	1e+007	

Sample Report (continued):

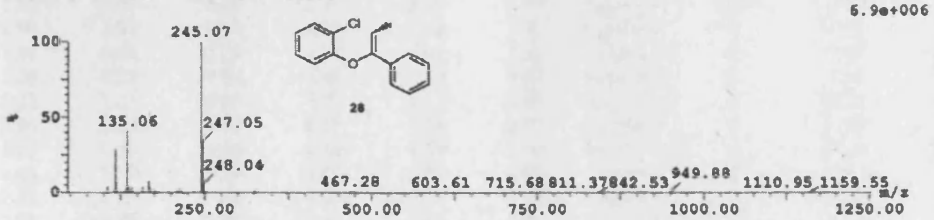
Peak ID	Compound	Time	Mass Found
4		6.57	

Combine (644:654-(621:626+670:675)) 1:MS ES+ 2.0e+006



Peak ID	Compound	Time	Mass Found
5		6.78	

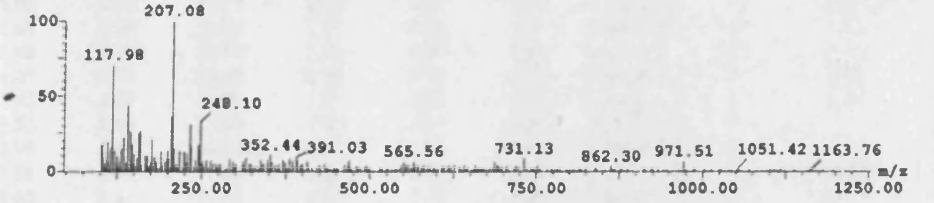
Combine (661:671-(643:648+690:695)) 1:MS ES+ 6.9e+006



28

Peak ID	Compound	Time	Mass Found
6		7.35	

Combine (721:731-(704:709+742:747)) 1:MS ES+ 6.7e+004



APPENDIX 2: TABLE OF CONDITIONS EMPLOYED AND RESULTS FOR DoE 1.

Run	Factor A Amine eq	Factor B Pd mol %	Factor C Temp. °C	Factor D Base eq	Factor E Volume vols	Factor F Ligand ratio	Factor G Ligand type	Response m-xylene % a/a	Response Product % a/a	Response Start Mat % a/a
1	2.00	0.50	50.00	1.05	2.50	3.00	Ligand 5	3.1	20.48	61.35
2	1.05	0.50	25.00	1.05	5.00	3.00	Ligand 1	0	4.35	77.36
3	2.00	2.00	50.00	1.77	5.00	3.00	Ligand 5	0	32.96	23.81
4	2.00	2.00	50.00	2.50	5.00	1.00	Ligand 3	0	11.93	0
5	2.00	0.50	50.00	1.05	2.50	1.00	Ligand 2	0	19.39	71.26
6	2.00	1.25	50.00	1.05	5.00	3.00	Ligand 1	0	0	78.72
7	1.05	2.00	25.00	2.50	2.50	2.00	Ligand 3	0	7.48	85.13
8	2.00	2.00	25.00	2.50	5.00	1.00	Ligand 4	0	38.22	53.43
9	2.00	2.00	50.00	1.05	5.00	1.00	Ligand 2	0	19.13	80.87
10	1.05	2.00	50.00	2.50	2.50	1.00	Ligand 2	0	40.27	0
11	2.00	0.50	37.50	2.50	2.50	3.00	Ligand 1	0	25.66	0
12	1.05	0.50	50.00	1.05	5.00	1.00	Ligand 2	0	14.21	85.79
13	1.05	2.00	25.00	2.50	2.50	2.00	Ligand 3	0	31.42	38.1
14	1.05	2.00	25.00	1.05	5.00	1.00	Ligand 3	0	12	75.65
15	2.00	2.00	50.00	1.05	2.50	1.00	Ligand 4	2.96	26.84	53.75
16	1.05	2.00	50.00	2.50	2.50	3.00	Ligand 1	2.38	22.88	0
17	2.00	2.00	50.00	2.50	2.50	1.00	Ligand 5	0	45.31	0
18	1.05	0.50	25.00	2.50	5.00	1.00	Ligand 2	0	6.12	88.22
19	2.00	0.50	50.00	1.05	5.00	3.00	Ligand 4	0	4.15	95.85
20	1.52	1.25	25.00	1.77	3.75	2.00	Ligand 5	0	15.81	67.61
21	2.00	2.00	25.00	1.05	5.00	2.00	Ligand 4	0	11.49	88.51
22	1.05	0.50	50.00	2.50	5.00	3.00	Ligand 5	0	17.28	66.67
23	1.05	0.50	25.00	1.05	5.00	1.00	Ligand 4	0	0	100
24	1.52	1.25	37.50	1.05	3.75	2.00	Ligand 5	0	33.23	35.28
25	2.00	0.50	25.00	1.05	2.50	2.00	Ligand 4	0	4.74	95.26
26	1.05	0.50	50.00	1.05	2.50	3.00	Ligand 3	0	6.03	90.44
27	1.05	2.00	25.00	2.50	5.00	3.00	Ligand 2	0	20.51	27.09
28	1.05	0.50	25.00	1.05	2.50	1.00	Ligand 5	0	3.49	93.02
29	1.05	0.50	50.00	2.50	2.50	1.00	Ligand 5	0	20.15	69.53
30	1.05	2.00	50.00	2.50	5.00	3.00	Ligand 4	0	6.81	86.77
31	2.00	2.00	25.00	2.50	5.00	3.00	Ligand 1	0	16.12	20.87
32	1.05	0.50	50.00	2.50	2.50	3.00	Ligand 4	0	5.06	94.94
33	1.52	2.00	25.00	1.05	5.00	1.00	Ligand 1	0	8.24	69.48
34	1.52	0.50	25.00	2.50	5.00	3.00	Ligand 3	0	0	100
35	2.00	1.25	50.00	2.50	2.50	3.00	Ligand 3	0	19.99	63.06
36	1.05	2.00	50.00	1.05	2.50	1.00	Ligand 1	0	12.02	63.49
37	1.05	2.00	37.50	2.50	5.00	1.00	Ligand 1	0	23.75	27.24
38	1.05	2.00	50.00	1.05	5.00	1.00	Ligand 5	0	30.39	38.73
39	2.00	0.50	25.00	1.77	5.00	1.00	Ligand 1	0	5.17	80.98
40	2.00	2.00	25.00	1.05	2.50	3.00	Ligand 3	1.11	4.04	86.56
41	1.05	0.50	25.00	2.50	2.50	1.00	Ligand 1	0	9.99	69.46
42	1.05	0.50	25.00	2.50	2.50	3.00	Ligand 2	0	24.69	69.88
43	2.00	0.50	25.00	1.05	5.00	3.00	Ligand 2	0	5.67	87.19
44	2.00	0.50	50.00	2.50	5.00	3.00	Ligand 2	0	61.19	12.51
45	1.05	2.00	25.00	2.50	2.50	3.00	Ligand 5	0	25.56	42.13
46	2.00	2.00	50.00	2.50	2.50	1.00	Ligand 1	2.71	28.25	0
47	1.05	0.50	50.00	2.50	5.00	1.00	Ligand 3	0	7.88	86.33
48	1.52	2.00	50.00	1.05	2.50	3.00	Ligand 2	0	18.47	78.1
49	1.05	2.00	25.00	1.05	3.75	1.00	Ligand 2	0	17.25	82.75
50	1.05	2.00	25.00	1.05	2.50	3.00	Ligand 4	0	6.17	86.65
51	2.00	0.50	25.00	2.50	2.50	1.00	Ligand 3	0	3.52	96.48
52	2.00	0.50	50.00	1.05	5.00	2.00	Ligand 3	0	10.27	79.02
53	2.00	2.00	25.00	1.05	2.50	1.00	Ligand 5	0	31.04	36.53
54	2.00	0.50	25.00	2.50	5.00	1.00	Ligand 5	0	0	93.4
55	1.52	0.50	50.00	2.50	5.00	1.00	Ligand 1	0	31.08	30.79
56	1.05	0.50	50.00	1.05	2.50	1.00	Ligand 4	0	16.85	78.78
57	2.00	2.00	25.00	2.50	3.75	3.00	Ligand 4	0	10.7	89.3
58	2.00	2.00	25.00	2.50	2.50	1.00	Ligand 2	3.65	53.95	0
59	2.00	0.50	25.00	1.77	5.00	1.00	Ligand 1	0	5.68	84.08
60	2.00	0.50	50.00	2.50	5.00	1.00	Ligand 4	0	13.05	81.48
61	1.05	2.00	50.00	1.05	5.00	3.00	Ligand 3	0	4.72	84.37

Response: m-xylene

ANOVA for Response Surface 2FI Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	37.66	49	0.77	2.05	0.0984	Not significant
A	*4.00*	*1*	*4.00*	*10.67*	*0.0075*	
B	*1.21*	*1*	*1.21*	*3.23*	*0.0999*	
C	*0.32*	*1*	*0.32*	*0.86*	*0.3736*	
D	*0.089*	*1*	*0.089*	*0.24*	*0.6367*	
E	*2.42*	*1*	2.42	*6.45*	*0.0275*	
F	*0.054*	*1*	*0.054*	*0.14*	*0.7115*	
G	*1.17*	*4*	*0.29*	*0.78*	*0.5620*	
AB	*0.85*	*1*	*0.85*	*2.26*	*0.1606*	
AC	*0.13*	*1*	*0.13*	*0.36*	*0.5616*	
AD	*0.18*	*1*	*0.18*	*0.47*	*0.5082*	
AE	*1.66*	*1*	*1.66*	*4.41*	*0.0595*	
AF	*0.57*	*1*	*0.57*	*1.52*	*0.2435*	
AG	*1.78*	*4*	*0.44*	*1.18*	*0.3703*	
BC	*0.031*	*1*	*0.031*	*0.083*	*0.7790*	
BD	*1.43*	*1*	*1.43*	*3.81*	*0.0768*	
BE	*1.07*	*1*	*1.07*	*2.84*	*0.1199*	
BF	*0.46*	*1*	*0.46*	*1.24*	*0.2897*	
BG	*6.09*	*4*	*1.52*	*4.06*	*0.0293*	
CD	*0.041*	*1*	*0.041*	*0.11*	*0.7485*	
CE	*0.091*	*1*	*0.091*	*0.24*	*0.6321*	
CF	*0.28*	*1*	*0.28*	*0.74*	*0.4088*	
CG	*5.66*	*4*	*1.41*	*3.77*	*0.0363*	
DE	*1.37*	*1*	*1.37*	*3.64*	*0.0829*	
DF	*0.14*	*1*	*0.14*	*0.36*	*0.5599*	
DG	*4.23*	*4*	*1.06*	*2.82*	*0.0782*	
EF	*2.05*	*1*	*2.05*	*5.46*	*0.0394*	
EG	*1.96*	*4*	*0.49*	*1.30*	*0.3273*	
FG	*2.02*	*4*	*0.50*	*1.34*	*0.3147*	
Residual	4.13	11	0.38			
Lack of Fit	*4.13*	*9*	*0.46*			
Pure Error	*0.000*	*2*	*0.000*			
Cor Total	41.79	60				

The Model F-value of 2.05 implies there is a 9.84% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

In this case A, E, BG, CG, EF are significant model terms.

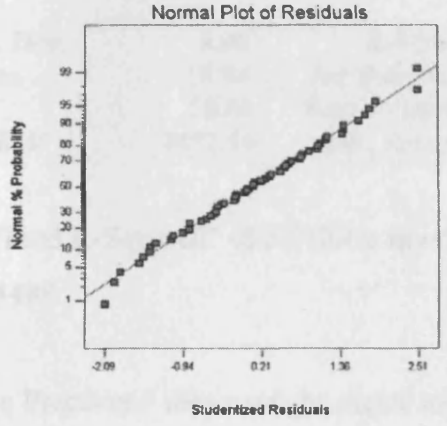
Values greater than 0.1000 indicate the model terms are not significant.

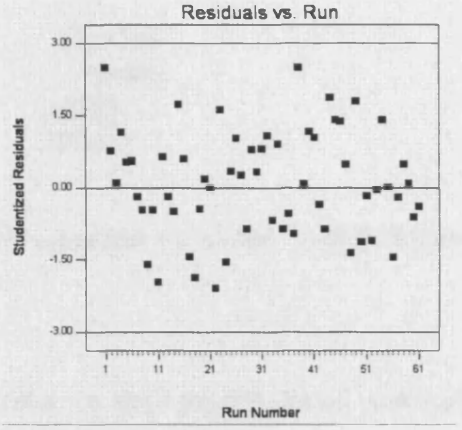
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Std. Dev.	0.61	R-Squared	0.9012
Mean	0.26	Adj R-Squared	0.4612
C.V.	234.85	Pred R-Squared	-4.7192
PRESS	238.98	Adeq Precision	7.342

A negative "Pred R-Squared" implies that the overall mean is a better predictor of your response than the current model.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 7.342 indicates an adequate signal. This model can be used to navigate the design space.





Response: Product

ANOVA for Response Surface Linear Model

Analysis of variance table [Partial sum of squares]

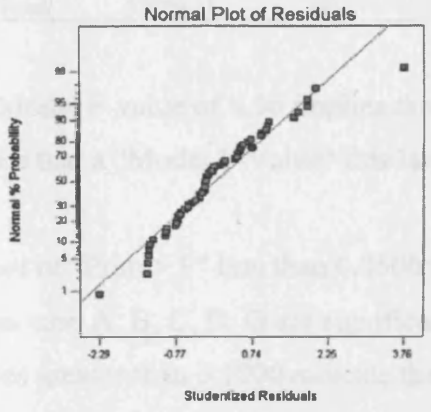
Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	5843.08	10	584.31	5.88	< 0.0001	significant
A	*393.23*	*1*	*393.23*	*3.96*	*0.0521*	
B	*1210.14*	*1*	*1210.14*	*12.19*	*0.0010*	
C	*660.61*	*1*	*660.61*	*6.65*	*0.0129*	
D	*1133.64*	*1*	*1133.64*	*11.42*	*0.0014*	
E	*276.17*	*1*	*276.17*	*2.78*	*0.1016*	
F	*114.64*	*1*	*114.64*	*1.15*	*0.2878*	
G	*2180.30*	*4*	*545.07*	*5.49*	*0.0010*	
Residual	4964.91	50	99.30			
Lack of Fit	*4678.22*	*48*	*97.46*	*0.68*	*0.7601*	Not significant
Pure Error	*286.69*	*2*	*143.35*			
Cor Total	10807.99	60				

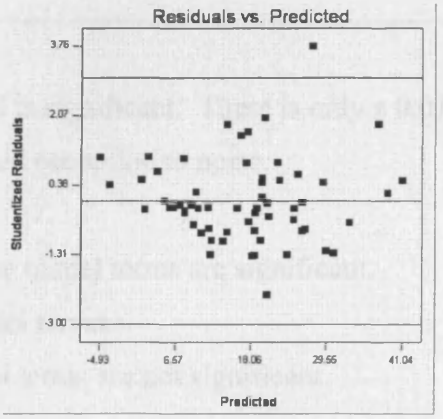
The Model F-value of 5.88 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case B, C, D, G are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. The "Lack of Fit F-value" of 0.68 implies the Lack of Fit is not significant relative to the pure error. There is a 76.01% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

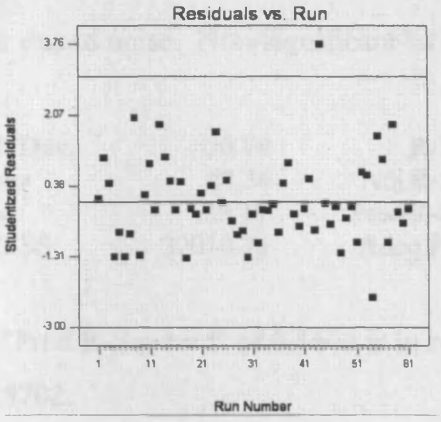
Std. Dev.	9.96	R-Squared	0.5406
Mean	16.94	Adj R-Squared	0.4488
C.V.	58.84	Pred R-Squared	0.3123
PRESS	7432.54	Adeq Precision	10.864

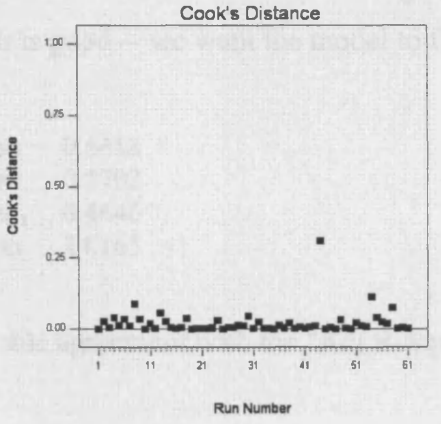
The "Pred R-Squared" of 0.3123 is in reasonable agreement with the "Adj R-Squared" of 0.4488.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 10.864 indicates an adequate signal. This model can be used to navigate the design space.









Response: **Start Mat**

ANOVA for Response Surface Linear Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	38375.55	10	3837.55	8.96	< 0.0001	significant
A	*1891.41*	*1*	*1891.41*	*4.42*	*0.0407*	
B	*11320.97*	*1*	*11320.97*	*26.43*	*< 0.0001*	
C	*4174.93*	*1*	*4174.93*	*9.75*	*0.0030*	
D	*8767.67*	*1*	*8767.67*	*20.47*	*< 0.0001*	
E	*913.35*	*1*	*913.35*	*2.13*	*0.1505*	
F	*62.49*	*1*	*62.49*	*0.15*	*0.7041*	
G	*10720.29*	*4*	*2680.07*	*6.26*	*0.0004*	
Residual	21414.76	50	428.30			
Lack of Fit	*20304.04*	*48*	*423.00*	*0.76*	*0.7215*	*not significant*
Pure Error	*1110.72*	*2*	*555.36*			
Cor Total	59790.31	60				

The Model F-value of 8.96 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B, C, D, G are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

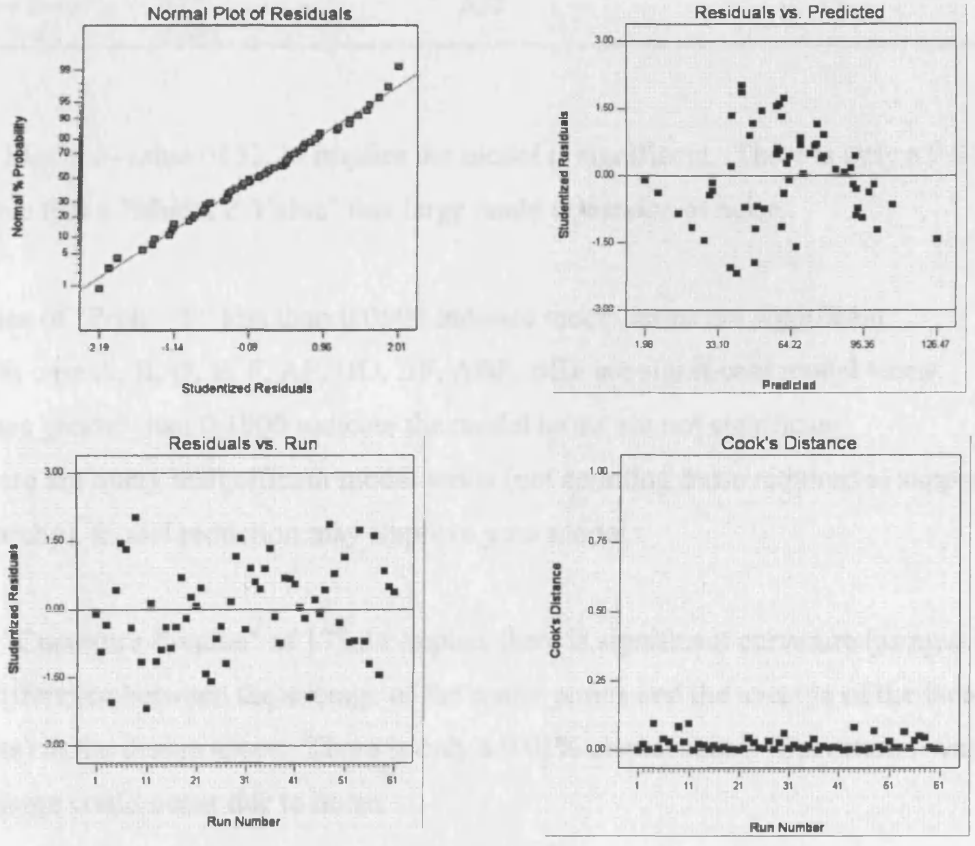
The "Lack of Fit F-value" of 0.76 implies the Lack of Fit is not significant relative to

the pure error. There is a 72.15% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Std. Dev.	20.70	R-Squared	0.6418
Mean	62.36	Adj R-Squared	0.5702
C.V.	33.19	Pred R-Squared	0.4646
PRESS	32010.73	Adeq Precision	14.165

The "Pred R-Squared" of 0.4646 is in reasonable agreement with the "Adj R-Squared" of 0.5702.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 14.165 indicates an adequate signal. This model can be used to navigate the design space.



APPENDIX 3: ANOVA CALCULATIONS & DIAGNOSTIC PLOTS FOR DoE 2.

Response: Product

ANOVA for Selected Factorial Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Model	20.01	10	2.00	52.21	< 0.0001	significant
A	*0.81*	*1*	*0.81*	*21.03*	*0.0037*	
B	*6.77*	*1*	*6.77*	*176.56*	*< 0.0001*	
D	*1.08*	*1*	*1.08*	*28.14*	*0.0018*	
E	*0.92*	*1*	*0.92*	*24.05*	*0.0027*	
F	*0.68*	*1*	*0.68*	*17.68*	*0.0057*	
AF	*2.69*	*1*	*2.69*	*70.20*	*0.0002*	
BD	*4.55*	*1*	*4.55*	*118.61*	*< 0.0001*	
BF	*0.78*	*1*	*0.78*	*20.35*	*0.0041*	
ABF	*1.16*	*1*	*1.16*	*30.31*	*0.0015*	
BEF	*0.58*	*1*	*0.58*	*15.20*	*0.0080*	
Curvature	6.65	1	6.65	173.54	< 0.0001	
Residual	0.23	6	0.038			
Lack of Fit	*0.11*	*5*	*0.022*	*0.19*	*0.9309*	*not significant*
Pure Error	*0.12*	*1*	*0.12*			
Cor Total	26.89	17				

The Model F-value of 52.21 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case A, B, D, E, F, AF, BD, BF, ABF, BEF are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The "Curvature F-value" of 173.54 implies there is significant curvature (as measured by difference between the average of the center points and the average of the factorial points) in the design space. There is only a 0.01% chance that a "Curvature F-value" this large could occur due to noise.

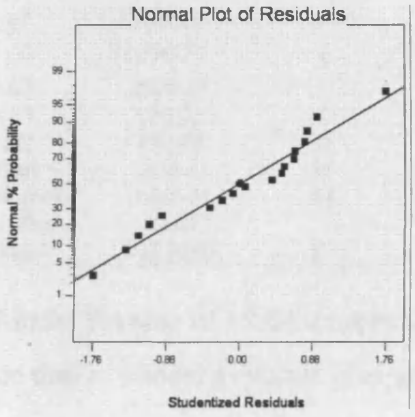
The "Lack of Fit F-value" of 0.19 implies the Lack of Fit is not significant relative to the pure error. There is a 93.09% chance that a "Lack of Fit F-value" this large could

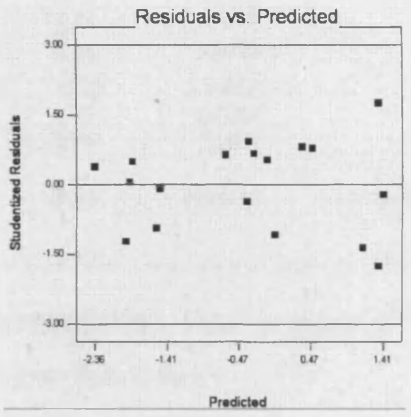
occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

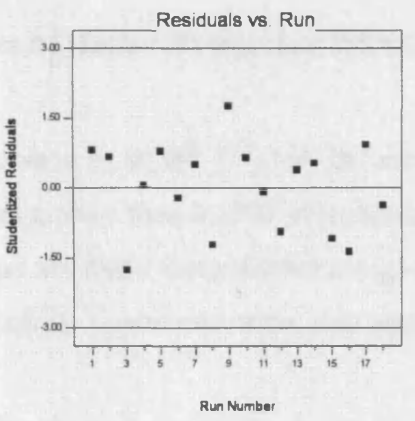
Std. Dev.	0.20	R-Squared	0.9886
Mean	-0.38	Adj R-Squared	0.9697
C.V.	-51.90	Pred R-Squared	0.9400
PRESS	1.61	Adeq Precision	23.561

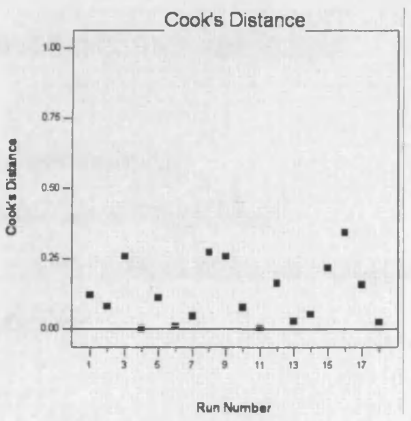
The "Pred R-Squared" of 0.9400 is in reasonable agreement with the "Adj R-Squared" of 0.9697.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 23.561 indicates an adequate signal. This model can be used to navigate the design space.









APPENDIX 4: ANOVA CALCULATIONS & DIAGNOSTIC PLOTS FOR DoE 2 (CCD ENHANCED).

Response: Product

ANOVA for Response Surface Reduced Quadratic Model

Analysis of variance table [Partial sum of squares]

Source	Sum of Squares	DF	Mean Square	F Value	Prob > F	
Block	10222.95	1	10222.95			
Model	9668.58	10	966.86	10.64	< 0.0001	significant
A	*2713.39*	*1*	*2713.39*	*29.87*	*< 0.0001*	
B	*533.56*	*1*	*533.56*	*5.87*	*0.0276*	
C	*288.00*	*1*	*288.00*	*3.17*	*0.0940*	
D	*186.89*	*1*	*186.89*	*2.06*	*0.1707*	
A^2	*279.69*	*1*	*279.69*	*3.08*	*0.0984*	
B^2	*430.11*	*1*	*430.11*	*4.73*	*0.0449*	
C^2	*430.11*	*1*	*430.11*	*4.73*	*0.0449*	
AB	*2070.25*	*1*	*2070.25*	*22.79*	*0.0002*	
AD	*342.25*	*1*	*342.25*	*3.77*	*0.0701*	
BC	*841.00*	*1*	*841.00*	*9.26*	*0.0078*	
Residual	1453.43	16	90.84			
Lack of Fit	*1421.43*	*14*	*101.53*	*6.35*	*0.1443*	*not significant*
Pure Error	*32.00*	*2*	*16.00*			
Cor Total	21344.96	27				

The Model F-value of 10.64 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise.

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

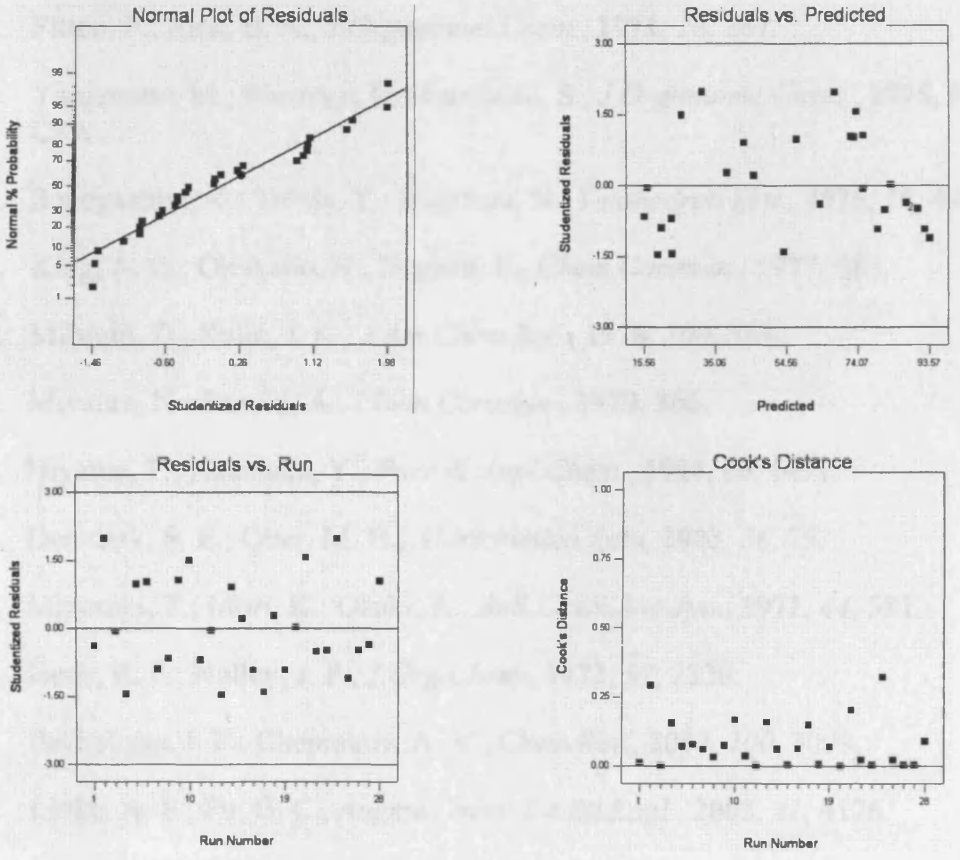
In this case A, B, B^2, C^2, AB, BC are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The "Lack of Fit F-value" of 6.35 implies the Lack of Fit is not significant relative to the pure error. There is a 14.43% chance that a "Lack of Fit F-value" this large could occur due to noise. Non-significant lack of fit is good -- we want the model to fit.

Std. Dev.	9.53	R-Squared	0.8693
Mean	57.46	Adj R-Squared	0.7876
C.V.	16.59	Pred R-Squared	0.5479
PRESS	5028.24	Adeq Precision	12.503

The "Pred R-Squared" of 0.5479 is not as close to the "Adj R-Squared" of 0.7876 as one might normally expect. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response tranformation, outliers, etc.

"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 12.503 indicates an adequate signal. This model can be used to navigate the design space.



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