New Palladium Catalysts

For Carbon-Carbon Bond Formation

A thesis presented for the degree of

Doctor of Philosophy

to the

University of St Andrews

by

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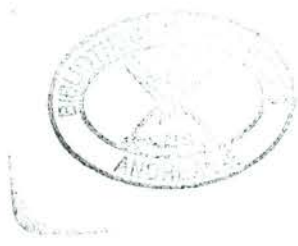
18th June 2001



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ACKNOWLEDGEMENTS

To my supervisor, Prof. David Cole-Hamilton, for his help, encouragement and guidance throughout the project.

To Dr. Doug Foster, for developing the chromatographic methods and running the countless GC and GC—MS analyses from which much of the data contained within this thesis is derived.

To the E.P.S.R.C. (Engineering and Physical Sciences Research Council) and Ineos Acrylics (formerly ICI Acrylics) for financial support (in the form of an Industrial CASE studentship).

To Dr. Phil Lightfoot, for performing the single crystal x-ray analyses.

To Mrs. Melanja Smith, for help and assistance in running NMR analyses and to Mrs. Sylvia Williamson, for performing microanalyses.

To Mr. Colin Smith, who used his glassblowing expertise to prepare the specialised glassware necessary for many of the preparations included within this thesis, and who repaired the said glassware on numerous occasions, and to Mr. Bobby Cathcart, for technical assistance.

To my parents, for their encouragement and financial support throughout my many years at University.

ABSTRACT

Palladium complexes prepared via the cyclometallation of phosphino ligands, commonly referred to as 'palladacycles', have recently been found to be convenient precursors to highly active catalysts for a variety of carbon—carbon bond forming, or 'cross-coupling', reactions.

The preparation of a range of novel cyclometallated palladium complexes based on bis(phosphinomethyl)benzene and benzylphosphine ligands was attempted. Only complexes obtained from benzylphosphine ligands were successfully isolated, and the reasons behind this are explained. It is shown that complexes with *tertiary*-butyl substituents on the phosphino moiety can be prepared via a number of alternative routes, while analogous compounds can only be obtained via the *ortho*-metallation of the aryl—bromine bond of the 2-bromobenzylphosphine ligand.

The catalytic properties of these complexes were investigated and the effectiveness of the compounds as catalysts in a variety of carbon—carbon bond forming reactions is discussed. In particular, the high catalytic activities observed by these palladium complexes towards the Heck and Suzuki cross-coupling reactions compare with those of the most active catalysts reported to date. These reactions are studied in detail, and explanations are given for the side-reactions and by-products observed when certain reaction conditions are employed.

CHAPTER 1

1. INTRODUCTION

The task of introducing a new chemical reaction to the industrial chemist's repertoire can be both frustrating and time-consuming. For a chemical process to be viable for use on an industrial scale, a number of criteria must first be satisfied. A reaction, which may be carried out in the laboratory as a matter of course, may not be considered viable due a number of economic or practical reasons.

Certain transformations may require conditions which either need expensive specialised equipment to obtain, or which cannot be obtained at all on a large scale. Many reagents and solvents have properties that immediately rule out their use on an industrial scale (such as high toxicity or flammability, corrosive or explosive properties) due to their potential effects on the industrial worker and the environment.

Perhaps equally restraining, given the economically driven competitiveness of the chemical industry, is that many laboratory processes are simply too inefficient, in terms of chemical yield, cost and time consumption, to even be considered for industrial scale-up.

It is for this reason that catalysis is becoming even more important in industrial chemistry. The discovery of a suitable catalyst can result in a successful chemical transformation that was previously inefficient, even impossible. Catalysis has, of course, been employed in the industry for decades. The use of iron as the catalyst in the Haber-Bosch synthesis for the production of ammonia, for example, which

converts an otherwise unreactive mixture of hydrogen and nitrogen, has been successfully used on an industrial scale since 1913.[1]

However, catalytic processes suffer from the same restrictions mentioned above. Some gas phase catalytic reactions require unrealistically high pressures and temperatures to proceed at an acceptable rate. Other processes use reagents so corrosive that all parts of the industrial plant in direct contact with the reaction mixture need to be constructed of expensive corrosion resistant alloys.

Even when a catalytic reaction is extremely efficient and can be performed at relatively benign reaction conditions, the high cost of the catalytic species is often the limiting factor. Many reactions are catalysed by very expensive semi-precious transition metals. Often these catalysts are not completely stable to the reaction conditions, the resulting decomposition making catalyst recovery difficult and very expensive, if not impossible. Should a reaction require a relatively high concentration (with respect to the amount of substrate used) of an expensive catalytic species that is difficult to recover, it is not difficult to appreciate that such a process would be quickly deemed non-viable on an industrial scale.

Unfortunately, there are many reactions catalysed by transition metal compounds that are efficient, selective and tolerant to a wide range of substrates, which have yet to be commonly used on an industrial scale. These reactions have enormous potential, but due to some limiting factors are not currently seen as being cost effective processes.

Recently, however, there has been a concentrated effort into the development of more efficient catalytic systems. Catalyst development can result in improved systems for existing industrial processes (for example, the introduction of BP's Cativa technology as a replacement for the BP/Monsanto acetic acid process),[2] or allow previously non-viable processes to be considered for use on an industrial scale.

Even when a process has been used efficiently on an industrial scale for a number of years, it is not uncommon for a company to continue to invest a large amount of resources in an effort to hold a competitive advantage, through the development of new catalytic systems.

1.1 Homogeneous Catalysis

Homogeneous catalysis has been an invaluable tool to the synthetic chemist, both in industry and in research institutions, for many decades. As society demands that chemical processes become more efficient, more cost effective and have less impact on the environment, the subject will only continue to increase in importance. Presently, the majority of pharmaceuticals and fine chemicals, as well as many starting materials and intermediates for chemical processes, are synthesised with catalysis being incorporated during at least some stage of their preparation. There is however, a constant drive in the search for new compounds which catalyse different reactions or which have improved efficiency over existing catalysts.

Chemists have a greater understanding of homogeneous catalysis (where the catalyst and the substrate are in the same phase) than its heterogeneous counterpart (where the catalyst is in a different phase from the substrate). Despite this, the majority of catalytic processes that are currently undertaken on an industrial scale are heterogeneous. The main reason for this is that, on the whole, heterogeneous catalysts are much more easily separated from the product mixture at the end of a reaction – often a simple filtration is all that is necessary. This obviously aids the potential recovery and reuse of the catalyst. If a catalyst can easily be recovered and reused repeatedly, with little or no decrease in activity, the initial expenditure in the catalytic technology can be recouped. Therefore, to date, heterogeneous catalysis has often been found to provide the more productive investment.

Due to the discrete nature of homogeneous catalyst complexes, the chemistry of such systems can usually be explained in a series of steps, which together form a catalytic cycle. The use of well established analytical techniques (such as nuclear magnetic resonance, infrared spectroscopy and mass spectrometry techniques) and isotopic labelling experiments can often confirm these steps unequivocally. Elucidation of the catalytic cycle of a homogeneous system can give a great understanding of not only the desired catalytic reaction, but also explain any instabilities of the system and possible reasons for the formation of undesirable side products.

As so often in chemistry, the development of a potentially useful catalytic system is an exercise in problem solving. For a reaction, catalytic or not, to be scaled-up for use in industry, all limiting factors must be overcome. In the case of a homogeneous catalytic system, these problems are varied. The catalyst must be extremely active at

practical reaction conditions, to allow suitable chemical conversions at relatively low catalyst concentrations. The catalytic transformation should ideally convert cheap, readily available starting materials into value added products selectively, in a reaction medium that is non-toxic and easily separable from the product. If that were not enough, the catalyst should be completely stable to the reaction conditions, easily separated from the product mixture, and, in a perfect world, be completely recovered to allow reuse.

1.2 Palladium Catalysed Reactions

Of all the transition metal catalysts, palladium compounds are arguably the most remarkable. Palladium has already been found to catalyse several diverse organic reactions and chemists in the future will undoubtedly discover that palladium compounds catalyse many more. It is possible for one particular palladium complex to catalyse a number of varied reactions, often with extremely high turnover rates and excellent product selectivities. For these reasons palladium catalysis is widely used in industrial processes, and new developments in the field are of great interest to the chemical industry.

Palladium on charcoal is a common heterogeneous system for the reduction of alkenes,[3] and the selective reduction of alkynes to *cis*-alkenes.[4] Carbonylation[5] and CO/ethylene oligomerisation,[6] in which perfectly alternating oligomers are formed, are just two examples of palladium-catalysed reactions involving gaseous substrates.

Oxidation,[7] molecular rearrangement[8] and cyclopropanation[9] are all possible by palladium catalysis. Such is the diversity of this range, one cannot begin to attempt to mention all of the reaction types. Across this portfolio of reactions, the palladium catalyst appears in many forms: as a heterogeneous solid, a discrete, monomeric complex, or compounds of higher nuclearity, such as dimers.

Many excellent textbooks have been dedicated solely to the subject of palladium catalysis in organic reactions,[10, 11] and the versatility of the metal will only be touched upon here. What will become apparent throughout this thesis, however, is that although a palladium compound may be a poor catalyst for one type of reaction, it may be an excellent catalyst in an entirely different type of reaction. Conversely, another palladium complex may be found to catalyse a whole range of mechanistically similar reactions.

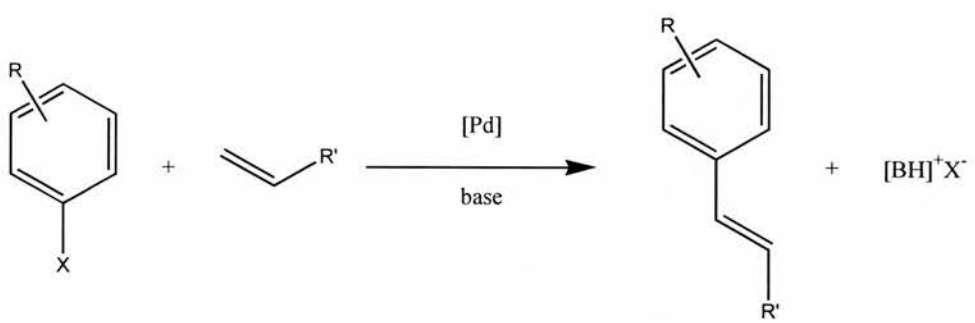
1.3 Literature Survey

To review the recent developments in all the many different areas of palladium catalysis would be an unrealistic goal. The following literature survey will be concerned mainly with palladium mediated cross coupling reactions, more specifically the Heck reaction, the Suzuki coupling of aryl boronic acids and the Stille reaction. These types of reaction have received a significant amount of attention in the literature in recent years, for reasons that will become clear. These types of

reaction have enormous potential, especially for use on an industrial scale, which is only beginning to be realised through recent developments in the area.

1.3.1 Vinylation of Aryl Halides - The Heck Reaction

The vinylation of aryl halides or triflates, now commonly referred to as the Heck reaction, was discovered independently by two groups in the early 1970s.[12, 13] This C—C coupling reaction involves the vinylic hydrogen of the alkene being replaced by an aryl group from the corresponding halide or related substrate, in the presence of a palladium catalyst and a stoichiometric amount of base. A general reaction scheme is shown below (scheme 1-1). Several groundbreaking developments have taken place in the area of Heck chemistry in recent years, and as a result, the reaction has been receiving a significant amount of attention in the literature.

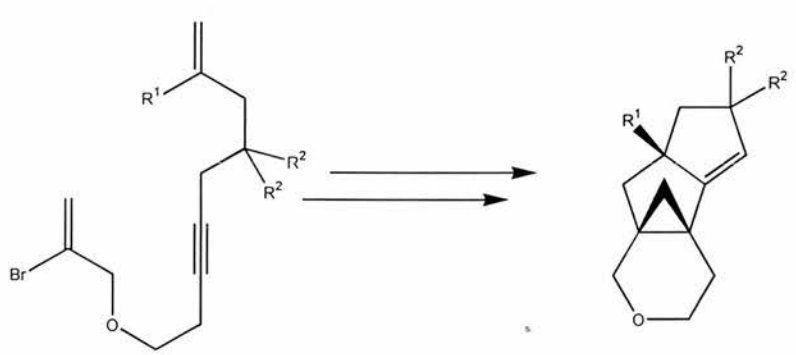


Scheme 1–1: The Heck Reaction

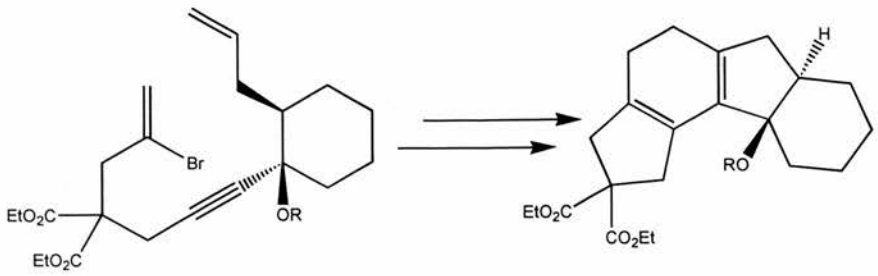
Interestingly, palladium is the only metal which will successfully catalyse this transformation, with other elements failing to give the desired product in acceptable

yield or selectivity. Inexpensive copper salts have been found to catalyse the vinylation of aryl iodides without additional ligands, but with turnover numbers of less than 10.[14] The use of nickel as a Heck catalyst has also been demonstrated, but a stoichiometric amount of zinc dust is required to complete the catalytic cycle.[15] Platinum displays inferior activity to palladium (TON < 50, TOF < 3 h^{-1}), and also catalyses the reductive dehalogenation of the aryl halide to a significant degree, which further decreases the metals suitability for Heck chemistry.[16]

The Heck reaction has found many applications over the past two decades and has proven to be an extremely versatile reaction. The reaction has proven to be selective, generally high yielding, and tolerant to a wide range of substrates. Literally hundreds, if not thousands, of research papers have been published reporting the use of a Heck reaction to selectively furnish products, often of staggering complexity, in good yields. Several examples involve intramolecular reactions or even cascade reactions, in which the product of an intramolecular Heck reaction undergoes further reaction to give a multi-cyclic product. An example of the formation of a 3-*exo-trig* ring as part of a Heck cascade cyclisation is shown in scheme 1-2.[17] Scheme 1-3 shows a similarly complex intra-intramolecular Heck cascade.[18]



Scheme 1-2: Example of a 3-*exo-trig* intramolecular Heck cascade



Scheme 1-3: Example of intra-intramolecular Heck cascade cyclisation

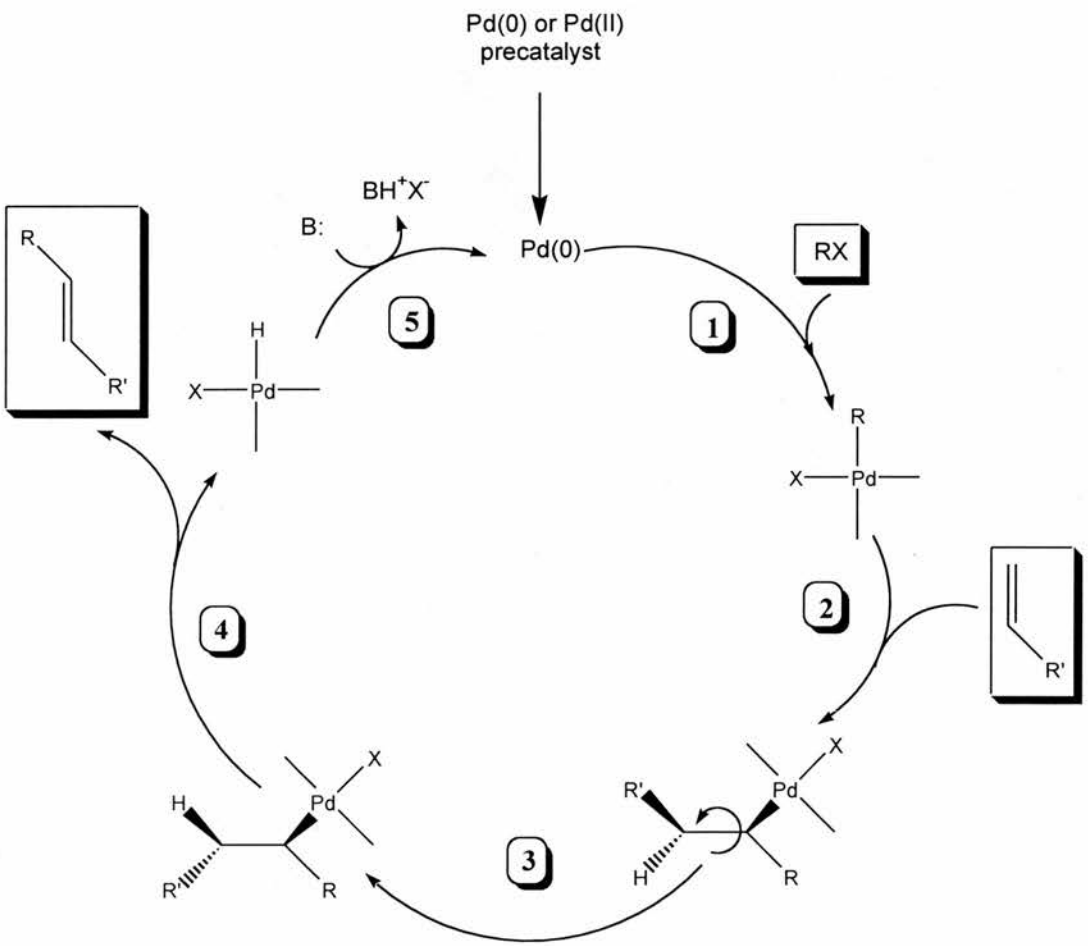
Throughout the past thirty years, the reaction has been widely reviewed, both in the literature and in many textbooks dedicated to the subject.[19] The reaction has often been described as one of the "true power tools" of the synthetic organic chemist due to its versatility.[19(c)] Despite this, it is only relatively recently that the potential of this reaction has begun to be realised, and Heck chemistry is finally being undertaken on an industrial scale. By analysing the 'traditional' Heck system, some of the disadvantages and limitations of this process become obvious, and the reasons why improvements have had to be made become clear.

1.3.1.1 The "Traditional" Heck System

1.3.1.1.1 Catalysts

The original Heck system[20] used palladium(II) acetate in the presence of two equivalents of triphenylphosphine to effectively yield coupling products from a variety of iodo- and bromoaromatic substrates. Since the early 1970s, a number of variations of the catalyst "cocktail" of palladium salt, phosphine ligand, base and

solvent have been used to varying degrees of success depending on the activity of the substrate being reacted. Often palladium acetate alone is enough to give excellent product yields, although phosphine ligands are usually required to prevent premature catalyst deactivation. The cheaper palladium salt, $PdCl_2$, can also be used, and a number of other commercially available palladium compounds are effective catalysts, including $Pd(PPh_3)_4$ and the air stable $Pd_2(dba)_3$.



Scheme 1-4: Heck reaction mechanism

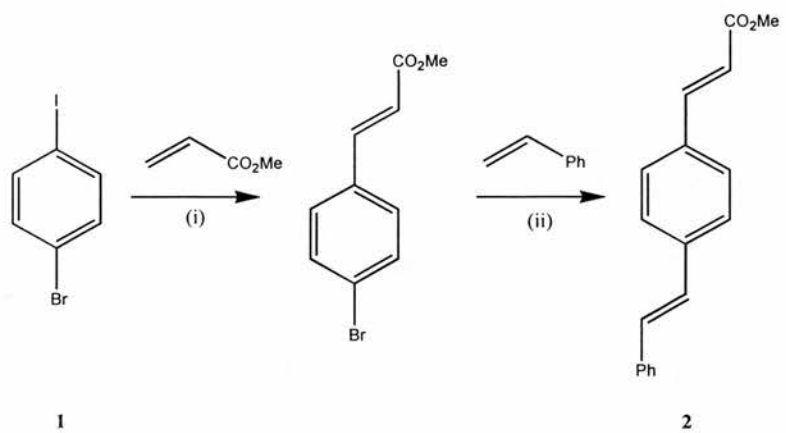
It has been widely regarded that the catalytic reaction cycle of the Heck reaction follows the mechanism outlined in scheme 1-4. If a Pd(II) precursor is used, it has generally been agreed that the Pd(II) compound undergoes a pre-activation reduction step *in situ*, to give the Pd(0) active species.[21] However, the precise mechanism of this pre-activation step is currently under debate, and may involve anionic intermediate complexes.[22] Beginning from a palladium(0) complex, the aryl halide, ArX, undergoes oxidative addition (step 1) to give a Pd(II) complex. The term oxidative addition describes the process of the addition of one molecule as two ligands on the metal centre with the cleavage of a covalent bond, in this case the aromatic-halogen bond. For this process to occur the metal must donate two electrons when accepting the ligands which leads to an increase in the oxidation state of the metal — hence *oxidative addition.* The cycle continues with coordination of the olefin and insertion to give a Pd(II)-alkyl intermediate (step 2). An internal rotation of the C—C bond then occurs (step 3), to allow the correct orientation (with at least one β-hydrogen synperiplanar) for the following β-hydrogen elimination (step 4). This generates the olefin product and a palladium hydride species. The final step, which makes the whole process catalytic by completing the cycle, is the dissociation of the alkene product and reductive elimination (essentially the opposite of the oxidative addition process) of HX with the use of a base, resulting in the reformation of the starting Pd(0) complex (step 5).

1.3.1.1.2 Substrates

It has been well reported that aryl iodides are more reactive Heck substrates than aryl bromides, and that aryl chlorides are unreactive, at least without the addition of promoting salts. This trend, I >> Br > Cl, follows the reactivity pattern of the aryl halide bond (Ar-I >> Ar-Br > Ar-Cl) and has led to the widely accepted hypothesis that the oxidative addition of the aryl halide (step 1, above) is the rate determining step of the catalytic cycle. Aryl bromides, and especially aryl iodides, are much more expensive than the corresponding chloro- analogue, and this is one of the main reasons why the Heck reaction has not been commonly used on a large scale. There has therefore been a great deal of effort spent on developing a system that allows the cheaper, but less reactive, aryl chloride to be used. However, most of the systems that do allow chloro- substrates to be processed with relative efficiency require much higher catalyst loadings and several more equivalents of expensive phosphine ligand to achieve acceptable product yields. Any economic gain by using the cheaper aryl chloride is quickly nullified by the high cost of the increased catalyst concentration, especially if the catalyst is unrecoverable. Recent developments, which attempt to address this problem, will be discussed later.

There are other classes of substrate which can be used in addition to haloarenes. Often overlooked is the aryl trifluoromethanesulfonate (or *triflate*), which although is less reactive than the iodide is more reactive then the corresponding aryl bromide. Substrates that are more reactive allow the use of milder conditions than the 120 — 150 °C required for the reaction of many aryl halides. Such compounds include

diazonium salts, such as aryldiazonium tetrafluoroborates.[23] These compounds allow Heck coupling to proceed at low temperatures without the need for base or phosphine ligands (the addition of such ligands leads to decomposition of the salt). Other leaving groups include hypervalent iodonium salts which, in a similar manner to diazonium salts, have a higher tolerance to bases, but are more troublesome to prepare.



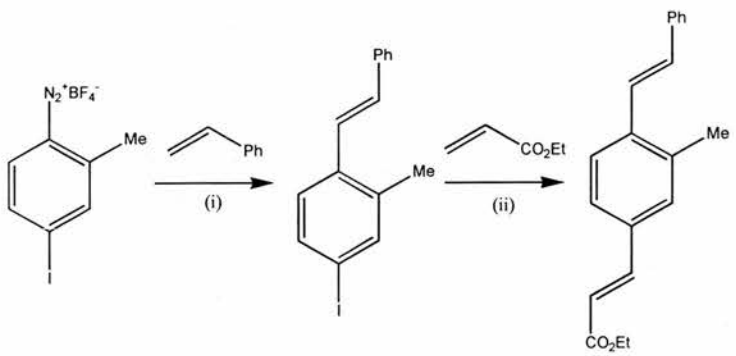
1 2

Scheme 1-5: Differential Heck reaction of bromoiodobenzene

(i) $Pd(OAc)_2$, Et_3N, 100 °C.
(ii) (ii) $Pd(OAc)_2$, PPh_3, Et_3N, 100 °C.

With a range of substrate classes of different reactivity available, differential Heck reactions can be performed, where complex molecules can be selectively synthesised in a stepwise manner by two consecutive, "back-to-back", Heck reactions. For example, as iodide is a more reactive leaving group than bromide, a Heck coupling of 1-bromo-4-iodobenzene **1** will result in exclusive reaction at the iodide. This allows the second coupling to take place at the bromide, to selectively yield the product **2** (scheme 1-5).[24] Similarly, as aryl iodides are more reactive than diazonium salts, the strategy can be employed with substrates incorporating both of these leaving groups.

This is particularly useful when high value products are involved, as both steps are high yielding. For example, the iodoarenediazonium salt **3** was first reacted with styrene then ethyl acrylate to give the product **4** in 55% yield (scheme 1-6).[25]



3 4

Scheme 1-6: Differential Heck reaction of an iododiazonium salt

(i) 2 mol % $Pd(OAc)_2$, EtOH, 80 °C.
(ii) 2 mol % $Pd(OAc)_2$, $NaHCO_3$, $NBu_4^+Cl^-$, DMF, 100 °C.

Just as the leaving group is important for high reactivity, so are the substituents on the aryl ring. A wide range of aryl substrates has been used in the Heck reaction, but the reactivity of these substrates varies with the electronic nature of the aromatic ring. Electron-withdrawing groups on the ring, such as formyl (COH) and acetyl ($COCH_3$), pull electron density away from the aryl-halide bond, increasing its activity and aiding the oxidative addition process. Such substrates, dubbed 'activated' aryl halides, are the most reactive in Heck catalysis, and give the highest yields and turnover numbers. Non-substituted aryl halides, such as bromobenzene are "non-activated", while substrates with electron-donating substituents, for example bromoanisole or bromotoluene, give additional electron density to the aryl-halide bond, have a detrimental effect on reactivity, and are classed as "deactivated". Only highly active catalytic systems allow these substrates to undergo efficient coupling.

The Heck reaction tolerates a range of alkene substrates as well as the range of aryl halides indicated above. As one would expect, the reactivity of the alkene towards Heck coupling is also dictated by the electronic effect of nearby substituents. In a similar manner to the aryl halide, the reactivity of the alkene is enhanced by the presence of electron withdrawing groups. Vinyl esters, or acrylates, and styrenes are among the most reactive substrates, while ethylene is non-activated and the relatively electron-rich 1-hexene is deactivated. Reports of effective couplings of aryl halides with such alkenes are rare. In addition to the electronic effect of sustituents, steric factors also have an influence on the activity of the alkene. Electron-withdrawing, mono-substituted alkenes (e.g. styrene) are more reactive than a 1,1-disubstituted substrate such as methyl methacrylate, for example. However, examples of the Heck reaction of tetrasubstituted carbon—carbon double bonds are known.[26, 27]

1.3.1.1.3 Solvents

Over the past 25 years, polar, aprotic solvents, such as *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethylsulfoxide (DMSO) and acetonitrile, have been shown to be the media of choice for the Heck reaction. Although their effectiveness is not in doubt, there are three reasons why these solvents are perhaps unsuitable for use on a large scale. Some are toxic, which necessitates costly disposal procedures. More importantly, most are high boiling (due to the necessary high reaction temperatures), and are therefore difficult to remove from the product mixture after reaction. Although a more reactive system would allow lower reaction

temperatures (and a different solvent), large-scale Heck reactions using these solvents require energy and time consuming extractions and distillations for solvent removal. These solvent systems also make catalyst recovery difficult, and a number of strategies, such as biphasic systems, have been developed to overcome this. The search for more environmentally friendly, easily separable media is ongoing, but this can only be successful with the combined development of more reactive systems to overcome the shortfalls of a less suitable solvent. Examples of potential alternative media are discussed below.

Water

There are no more environmentally friendly solvents than water. Water is also highly polar, and indeed there have been a number of instances of the Heck reaction being successfully performed in aqueous or mainly aqueous media.[28, 29] There is an additional benefit that many natural products are hydrophilic and reactions of such compounds are difficult to perform in organic reactions. The synthesis of combinatorial libraries of organic compounds involving the Heck reaction in water using immobilised iodoarenes as the substrates has been reported.[30]

Although organic substrates are often soluble in water, the catalyst is not. This problem can be overcome by employing water-soluble sulfonated phosphine ligands, for example TPPMS (triphenylphosphinemonosulfonate) and TPPTS (triphenylphosphinetrisulfonate). These ligands have been used successfully in a variety of reactions in aqueous media involving metals other than palladium.[28]

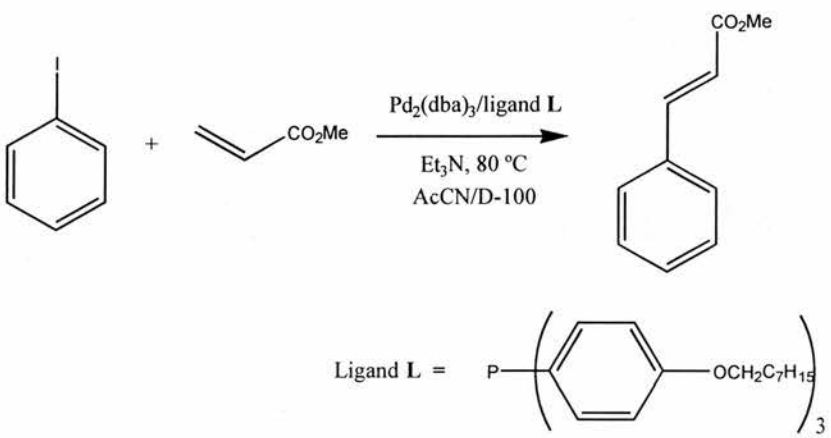
Casalnuovo *et al* have reported the use of $Pd(TPPMS)_3$ in the catalysis of a number of cross-coupling reactions in water/acetonitrile, including the Heck reaction, but a very high catalyst concentration (10 mol %) was used, which would negate any advantage gained by using water as the solvent.[31]

Biphasic Systems

The problem of catalyst recovery in a homogeneous system can be solved, to a certain extent, by the use of a biphasic system, where the catalyst remains in one phase, the substrates and product in another. Confusingly, the reaction does not take place at the interface, as the mass-transfer involved is too severe, but in the polar phase, with the reaction rate dependent on the solubility of the reagents in this layer. This would seem to go against the point of using two phases, but the products can easily be extracted from the phase at the end of the reaction, enabling the catalyst solution to be recycled.

Many solvents have been investigated for use as the immiscible phase including water, other hydroxylic solvents, of which ethylene glycol is one of the most common, and liquid CO_2. Perhaps one of the most promising media is the fluorous phase. Catalytic complexes have to be modified using a similar strategy to the hydrophilic catalysts mentioned above for use in aqueous systems. By adding long fluorinated tails to phosphine ligands, the solubility of palladium complexes in fluorous media, such as perfluorous octane (C_8F_{18}), can be significantly increased. Reaction then takes place in the fluorous phase and the product is extracted. This

system has been attempted with many catalytic reactions, most recently the Heck coupling. Iodobenzene was successfully reacted with methyl methacrylate in 89% yield in a system of acetonitrile and D-100 (a perfluorinated solvent consisting of mainly of C_8F_{18})(scheme 1-7).[32] Unfortunately, although this system allows reuse of the catalytically active fluorous layer, the product yields obtained drop significantly with each reuse, suggesting deactivation of the catalyst, or perhaps leaching of the catalyst into the organic layer. Although this medium shows potential for application in industry, further developments must be made to overcome these problems.



Scheme 1-7: Fluorous Biphasic Heck reaction system

Supercritical Fluids

Supercritical fluids, in particular supercritical carbon dioxide, represent alternative media that are receiving interest as potential new solvents for Heck reactions. Above the critical temperature and pressure of a substance (in the case of CO_2 these are relatively easily obtainable at 31.1 °C and 73.8 bar, respectively) that substance will

be in the *supercritical* phase, and possess hybrid properties of both a liquid and a gas. Supercritical CO_2 is an excellent solvent for organic compounds, although most palladium complexes are insoluble. However, $scCO_2$ exhibits similar solvent properties to those of fluorinated liquids, and therefore palladium complexes with ligands developed for the fluorous phase systems mentioned above are also soluble in carbon dioxide. The Heck reaction of iodobenzene and methyl acrylate in $scCO_2$ was achieved in excellent yield using 5 mol % $PdL_2(OAc)_2$ [L = $(C_6F_{13}CH_2CH_2)_2PPh$].[33]

The benefit of supercritical CO_2 as the reaction medium is apparent during reaction work-up. Rather than the laborious extractions and distillations to remove the high boiling solvents used in standard systems, the reaction medium is simply reverted to the gaseous state by manipulation of the vessel temperature and pressure and vented through a conventional solvent to trap the product mixture. The CO_2 can then be efficiently recycled, which enhances the attractiveness of the system, economically and environmentally. The process has been used with success in a number of catalytic processes, both homogeneous and heterogeneous, and the advantages of the system ensure that further investigations into the use of this medium as a solvent in the Heck reaction will be made.

The developments above indicate that significant progress has been made to ease catalyst recyclablity and make the process more environmentally appealing. However, despite the tremendous potential of the Heck reaction in synthetic organic chemistry the process has been largely ignored, and, until recently, the reaction has rarely been used industrially. This is due to a number of limitations of the conventional Heck system. The first is the relatively low thermal stability of the

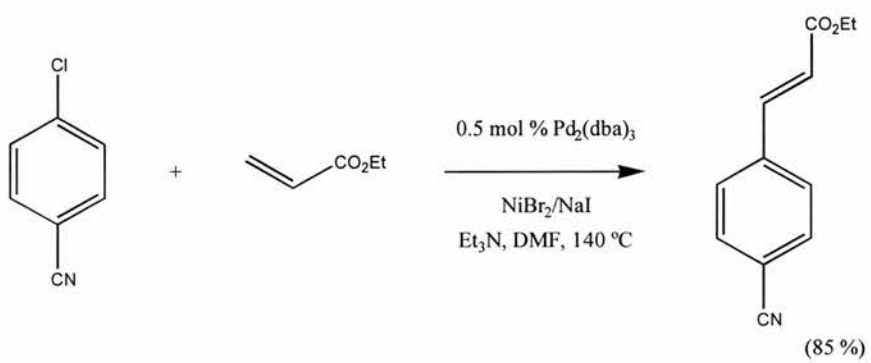
conventional Heck catalyst. With reaction temperatures often in the excess of 130 °C, catalyst decomposition and palladium precipitation with conventional *in situ* systems has been a common problem. Loss of such an expensive metal on an industrial scale is obviously unacceptable, and, as yet, there is no efficient method for recycling the decomposed catalyst. The use of several equivalents of phosphine ligand give added stability against palladium precipitation, but due the high cost of phosphines, this is often expensive. There is also significant evidence to suggest that a large excess of phosphine can greatly inhibit the rate of reaction. The conventional system may require a catalyst concentration of up to 1—5 mol % for reasonable substrate conversion, which relates to a maximum turnover number of only 20—100. This represents very poor activity on an industrial scale and this is emphasised if there is a problem with catalyst instability or lack of recovery.

Another problem with such catalytic systems is the phenomenon of 'aryl scrambling'. This is when the aryl group of the substrate is randomly substituted with that of the phosphine ligand (due to P—C bond cleavage of the catalyst), lowering the yield of the desired product. Conventional catalytic systems also require the relatively expensive aryl iodide or bromide as the substrate, and this can influence the economic viability of a process. Chloro- substrates are significantly less expensive than the corresponding bromo-, iodo- or triflate compounds which are required for successful reaction, but are notoriously unreactive using conventional Heck catalysts. There is little doubt that the Heck reaction would be more commonly used in industrial processes if the catalytic system allowed chloro- compounds to be used.

1.3.1.1.4 Developments to Traditional System

There have been several developments made to the traditional Heck system in an effort to optimise the process, and perhaps overcome some of the limitations mentioned above.

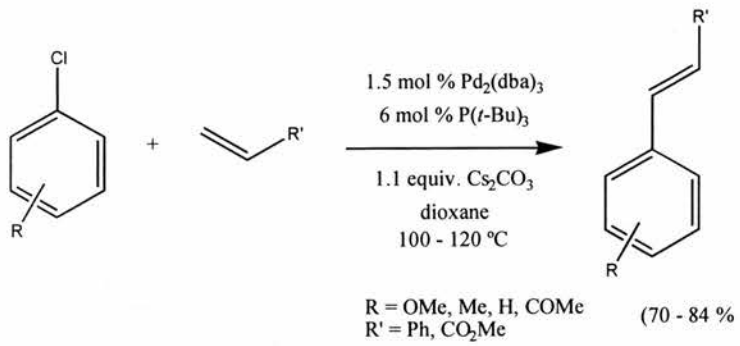
The unreactivity of chloroarenes as substrates in the Heck reaction is perhaps the problem that has received most attention. The financial benefits of 'opening the door' to the use of the cheaper chloroaromatics is an obvious goal. Several developments that specifically solve this problem have appeared in the recent literature.



Scheme 1-8: Bimetallic Heck reaction of Chloroarenes

The use of a bimetallic catalytic system seemed to be a novel solution. By converting the chloroarene to the corresponding iodoaromatic with $NiBr_2$/NaI, excellent yields were achieved with a variety of substrates (scheme 1-8).[34] Unfortunately, the system required more than a stoichiometric amount of nickel iodide, which somewhat detracted from the goal of making the Heck reaction more financially attractive.

However, there have been some major developments that have been made entirely through the use of more efficient ligand systems.

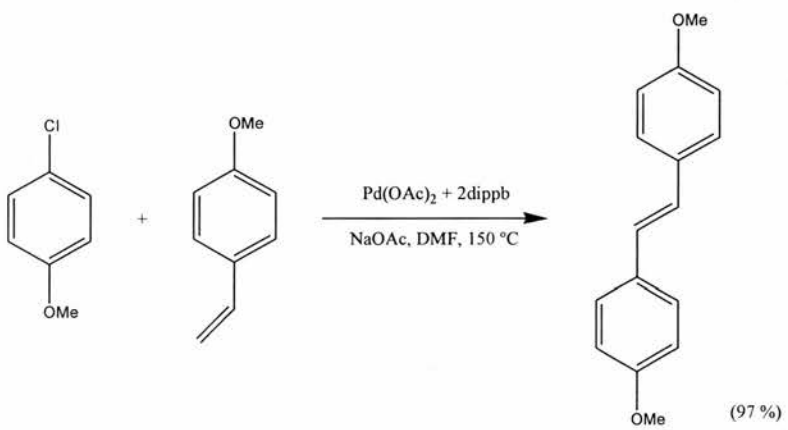


Scheme 1-9: Heck reaction of chloroarenes using (*t*-Bu)$_3$P as ligand

Perhaps the most interesting development is the use of the sterically hindered, electron-rich phosphine (*t*-Bu)$_3$P as the ligand, as reported by Fu (scheme 1-9).[35] The system allowed chlorobenzene and even the deactivated 4-chloroanisole to react in surprisingly high yields of 70 — 84 %, at the relatively low reaction temperature of 100 — 120 °C. However, using 1.5 mol % of catalyst limits the maximum achievable turnover number to less than 70. More recently, Beller has reported the use of di-1-adamantyl-*n*-butylphosphine as an efficient ligand for chloroaromatic Heck reactions.[36] Using a palladium concentration of 1 mol %, the deactivated substrate 4-chlorotoluene has been selectively coupled to styrene to afford the desired Heck product, 4-methylstilbene, in 98 % yield (TON = 98).

The use of phosphite ligands for the efficient conversion of aryl chlorides has also been reported by Beller.[37] The reaction of the electron deficient 4-trifluromethyl-chlorobenzene with styrene was achieved by employing an *in situ* system consisting of $Pd(OAc)_2$ and a range of alkyl and aryl phosphites. The best result, with a turnover

number of 15,000, was obtained with tris(2,4-di-*t*-butylphenyl)phosphite. The system was also effective when the deactivated 4-bromoanisole was used (TON 31,000), but the use of deactivated chloroaromatic substrates was not reported. The high activity of phosphorus amidites as monodentate phosphorus ligands has been reported by de Vries and van Leeuwen.[38] Reetz *et al* have reported excellent results for the reaction of chlorobenzene with styrene using a palladium catalyst with acetonitrile ligands.[39] Although six equivalents of tetraphenylphosphonium chloride are required for activity, excellent yields are obtained for the reaction. Reetz also reports an increase in product selectivity when a small amount of N,N-dimethylglycine (DMG) is added to the reaction mixture.



Scheme 1-10: Heck reaction of 4-chloroanisole using dippb as ligand

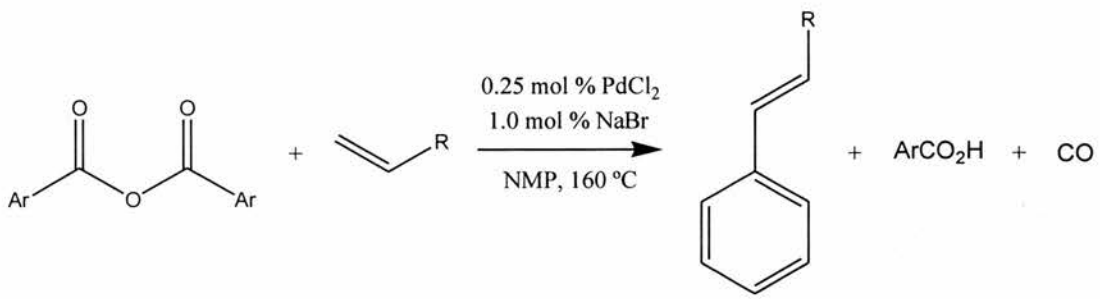
Although these recent developments are indeed impressive, the results of Milstein *et al* in 1992 are still noteworthy.[40] Using a range of chelating diphosphines as ligands, yields of 19 — 97 % were obtained using a range of chloroaromatic substrates. The chelate bite-angle of the diphosphine had a dramatic effect, with 1 mol % $Pd(OAc)_2$ in the presence of 2 mol % 1,4-bis(diisopropylphosphino)butane (dippb) giving the best results (scheme 1-10).

Base-free systems

Another drawback of the Heck system concerns the necessity for a stoichiometric amount of base to complete the catalytic cycle, via the reduction of the palladium(II) hydride to Pd(0) (see scheme 1-4, step 5, above). Not only is the need for base an economic concern, the production an equivalent of the conjugate base salt $[BH]^+X^-$ as a by-product creates a number of problems. Firstly, such an amount of by-product is expensive to dispose of on a large scale. More importantly, as the reaction progresses, more of this by-product is formed, and, depending on the base used, is often insoluble in the reaction medium. This results in the gradual change of the composition of the reaction mixture and the problems associated with it. The ionic strength of the medium changes, and this can lead to different solubility characteristics of the substrates and products. Salt precipitation can occur around the catalyst molecules, gradually 'capturing' the catalyst and preventing further reaction. Even if catalyst deactivation is a negligible issue, a decrease in rate as the reaction progresses is evident.

There have been a couple of examples of Heck systems that have attempted to overcome the problems stated above by avoiding the use of base entirely. The first 'base-free' alkene arylation was reported by Milstein,[41] employing a modified version of the chelate-assisted method mentioned previously. Interestingly, the chelating phosphine that gave the best results under basic conditions, dppb (scheme 1-10), was completely ineffective in the base-free system. Using the ligand dppp (1,3-bis(diisopropylphosphino)propane), however, gave a yield of 81 % for the coupling of

chlorobenzene and styrene. The only drawback was that 50 mol % of zinc was required to provide the reducing conditions necessary to regenerate the catalyst.

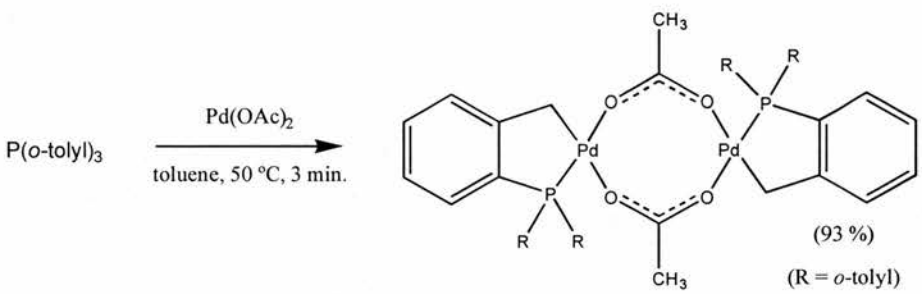


Scheme 1-11: Base-free Heck reaction using aryl anhydrides as substrates

An ingenious development to the base-free system has been the use of aromatic anhydrides as substrates (scheme 1-11).[42] The leaving group in this system is an aryl carboxylate, which can reduce the Pd—H intermediate itself, without the need for base or added reducing agents. The resulting arylcarboxylic acid can then be used to regenerate the anhydride in a separate procedure. Good yields were obtained for the reaction of benzoic anhydride with a range of olefins, using 0.25 mol % $PdCl_2$ as catalyst. Although 1.0 mol % NaBr was required, the system had the added economic benefit of being phosphine free.

1.3.1.2 'Palladacycle' Catalysts

The real explosion of interest in the Heck reaction began in 1995, when Herrmann reported the extraordinary catalytic activity of an orthometallated palladium complex **5**, which has since been commonly referred to as the Herrmann 'palladacycle'.[43, 44]



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Scheme 1-12: The Herrmann 'Palladacycle'

The complex, conveniently prepared in high yield from palladium(II) acetate and tris(*o*-tolyl)phosphine (scheme 1-12), has been found to catalyse the Heck coupling with turnover numbers of up to 1,000,000 (moles of product produced per mole of palladium) and turnover frequencies in the range of 5,000 to 20,000 (moles product produced per mole of palladium per hour). These values represented an improvement on the traditional system of an order of magnitude, as the previously highest recorded turnover number for the Heck reaction was 134,000.[45] Such a marked improvement in efficiency allows lower catalyst concentrations to be used, rather than the 1—5 mol % required for reasonable conversions with the traditional *in situ* system.

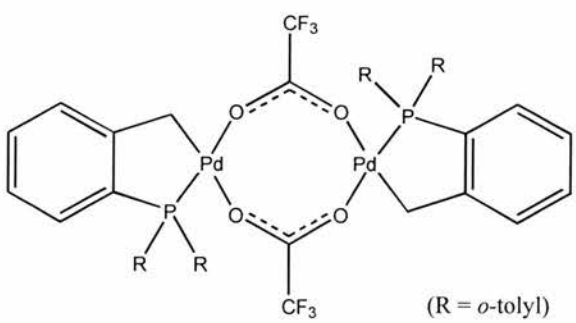
The Herrmann palladacycle **5** has been shown to be extraordinarily stable to both air and high temperatures. No degradation is seen after storage of the compound in air over a period of several months, and the complex can be heated under reflux in toluene for long periods with no palladium precipitation.

The Herrmann palladacycle has a number of distinct advantages over the *in situ* system, and as such could easily be described as one of the most significant developments in homogeneous catalysis of the past decade. The stability of the complex allows ease of handling (which is especially important on a large scale), and the implementation of higher reaction temperatures if necessary. There is no need for additional equivalents of expensive phosphine ligand in the reaction system to stabilise the catalyst. This adds to the activity of the system, as excess phosphine can occupy vacant reaction sites of catalytic intermediates during the reaction cycle. Such systems have since been termed *underligated*, but although higher activity levels are common, there is potential for premature catalytic deactivation. The lack of a defined ligand shell can cause the formation of inactive palladium compounds, including the precipitation of palladium black [ref. 19(d) and references therein].

However, the sheer activity of the Herrmann system can mean reactions are often complete before significant deactivation can occur. High yielding reactions can be achieved using lower catalyst loadings than ever before, and this, together with the fact that excess phosphines are not required, increases the potential economic attraction of the Heck reaction immeasurably. The yield-sapping problem of aryl-scrambling due to P—C bond cleavage of the catalyst seems to have been overcome with the Herrmann system also, as no aryl by-products are detected.

Such an advance in the reactivity of Heck catalysts would perhaps mean that chloroaromatics could now be processed easily. Unfortunately, this has not been the case, and although development of the Herrmann system for use with aryl chlorides has yielded reasonable results, they do not match the efficiency of those described above. With no additives of any kind, the Herrmann system achieves a yield of only 8 % for the reaction between the activated 4-chloroacetophenone and *n*-butyl acrylate.[43] However, the addition of 20 mol % tetrabutylammonium bromide furnishes the product in a yield of 40 %, corresponding to an impressive TON of 40,000.[44]

A number of developments to the Herrmann system have been made which allow application in some of the alternative media mentioned previously. For example, reaction of tris(*o*-tolyl)phosphine with $Pd(OCOCF_3)_2$ rather than $Pd(OAc)_2$, results in the fluorinated analogue of Herrmann's palladacycle, **6**, being formed, which can be used in supercritical CO_2. Interestingly this compound is catalytically active at lower temperatures than **5**, which requires temperatures above 100 °C.



6

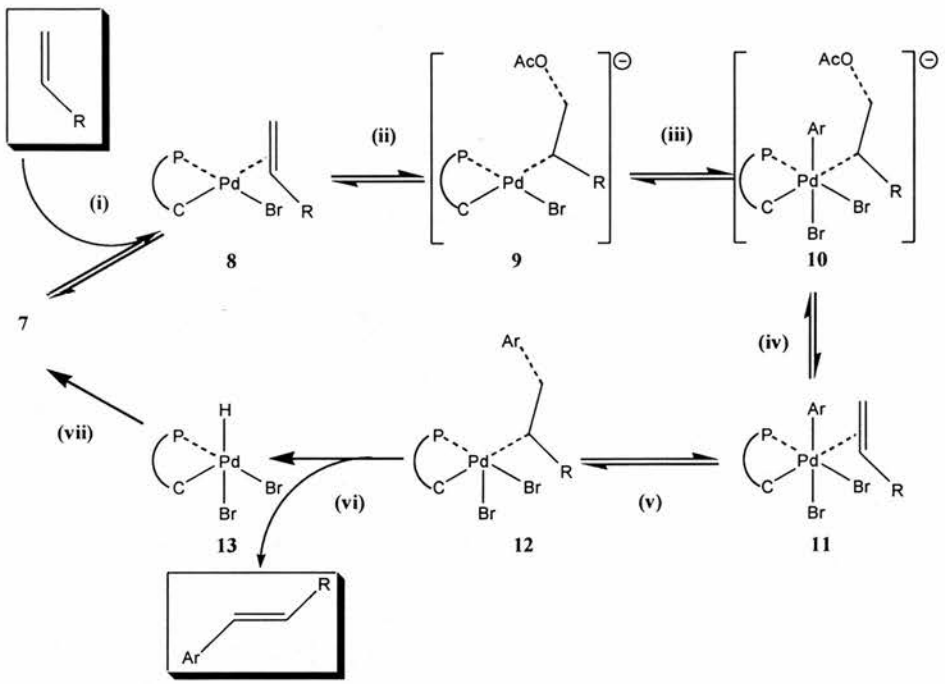
Extensive work has been done by the Herrmann group on the use of **5** in non-aqueous ionic liquids (NAILs).[46, 47] NAILs, or molten salts, are alternative reaction media that

offer the opportunity of recycling the catalyst. The salts, for example tetrabutylammonium bromide, are liquid at reaction temperature (typically 130 — 160 °C) but are of sufficiently high boiling point to allow separation of the products and starting materials from the catalyst solution by distillation. The added stabilisation effect of $[NBu_4]^+Br^-$ mentioned previously result in superior yields being obtained for reactions of aryl chlorides compared to those obtained in traditional molecular solvents.

The introduction of such a dramatically different complex as a Heck reaction catalyst, that is so much more active than previous systems, has predictably led to much speculation about the possibility of an alternative catalytic mechanism. Initially, Herrmann reported that the palladacycle **5** (in which palladium is in the +2 oxidation state) remained intact throughout the reaction, immediately suggesting that the catalytic cycle had to involve Pd(II) and uncommon (but not unheard of) Pd(IV) intermediates, rather than the accepted Pd(0)/Pd(II) mechanism. The first to publish a speculative mechanism incorporating this hypothesis was Shaw (scheme 1-13).[48, 49]

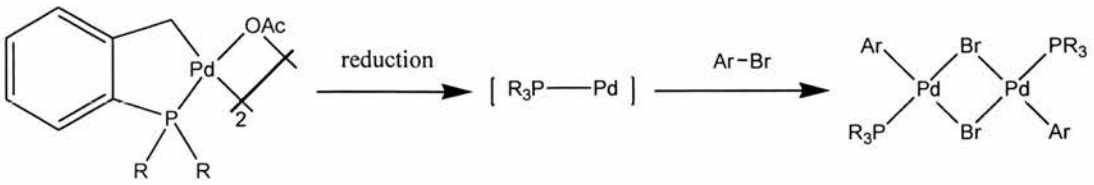
Working upon the experimental observation of the Herrmann group that no reaction involving the palladacycle **5** occurred until the alkene was added,[43, 44] Shaw suggested that the alkene coordinated to the palladium centre first (step i), and that this promoted oxidative addition of the aryl halide to a Pd(II) centre. The coordinated alkene is susceptible to attack by nucleophilic species, in this case the acetate ion (available from the bridging ligands or the base if NaOAc is used), and forms a σ-alkyl bond (step ii). The electron-donating effect of the two carbon atoms on palladium activate the complex towards oxidative addition of the aryl halide, giving

the Pd(IV) species **10** (step iii).



Scheme 1-13: Speculated mechanism for Heck reaction involving palladacycles

Removal of the acetate ion regenerates the coordinated alkene (step iv). Aryl migration (step v) is followed by β-hydride elimination of the alkene product (step vi). Regeneration of the active palladacycle **7**, unchanged except for bridging bromide ligands rather than acetate ligands is achieved by removal of HBr by base (step vii). This agrees with the original Herrmann report that the bromine-bridged analogue is isolated at the end of the reaction.[43]

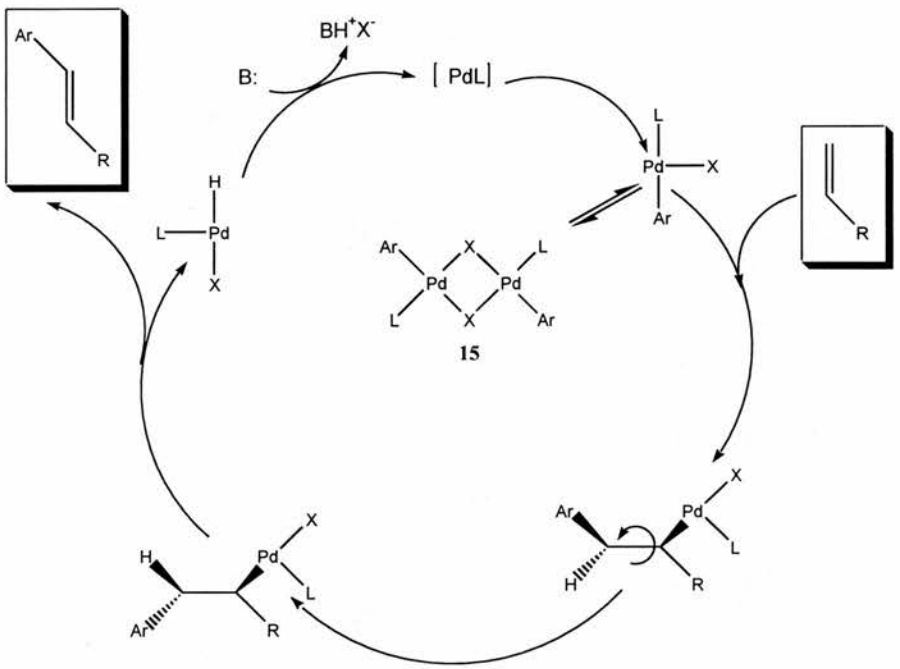


5 **14** **15**

Scheme 1-14: Postulated mechanism for reduction of palladacycle

However, this mechanism is in direct contradiction with the work of Hartwig,[50] who found that although **5** catalysed the amination of aryl halides, the palladacycle was broken down to the monophosphanepalladium(0) complex [PdP(*o*-tolyl)$_3$] during the reaction. Although this work was conducted while focussing on a different type of cross-coupling reaction, a similar postulated mechanism for the gradual reduction of the palladacycle to [PdP(*o*-tolyl)$_3$] **14** by an unnamed reducing agent was reported for the Heck arylation of 1,1-disubstituted alkenes by Beller (scheme 1-14).[51] Subsequent oxidative addition of an aryl bromide, for example, would give complex **15**, which was assumed to be the actual active intermediate. Evidence supporting this hypothesis was given when complex **15**, prepared by an alternative method,[52] gave the same product distributions as palladacycle **5** for the reaction of 1-bromo-4-chlorobenzene with α-methylstyrene. Palladacycle **5** was stabilised against reduction to [Pd{P(*o*-tolyl)$_3$}$_2$] when the coordinating amine diisopropylethylamine (DIPEA) was used as base, and therefore an induction period was observed. However, no such induction period was observed when complex **15** was used as catalyst, giving further evidence towards the case for this complex being the active species. A mechanism, supported by kinetic studies on a range of compounds of type **15**, was reported by de

Vries, van Leeuwen and co-workers (scheme 1-15).[38] The cycle is very similar to that of the traditional mechanism described previously (scheme 1-4).

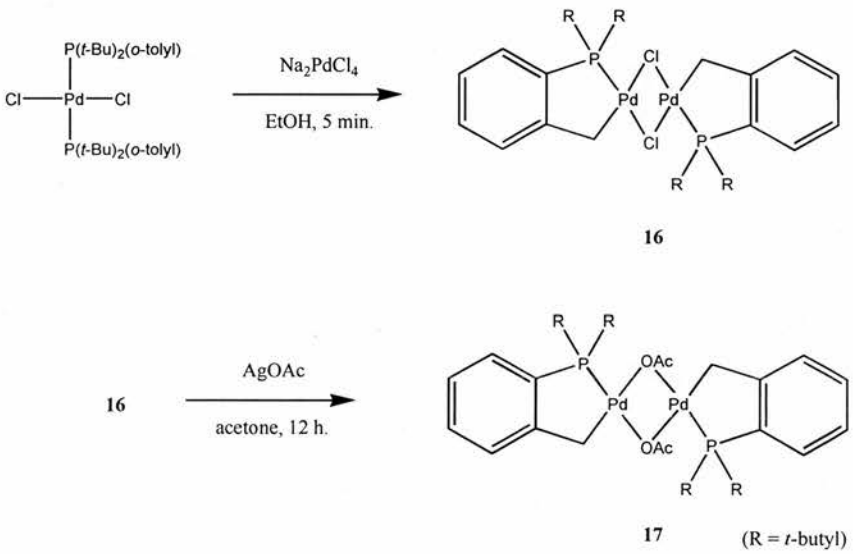


Scheme 1-15: Postulated Heck mechanism for complex 15

Although this hypothesis has not been proven unequivocally, it now seems most likely that palladacycle complexes are not active catalytic species, but rather easily handled precursors to underligated palladium catalysts. The active species then participate in a Pd(0)/Pd(II) catalytic cycle not dissimilar to that of the conventional system. The low phosphine-palladium ratio, or *underligation*, is responsible for the high catalytic activity of these systems. Although additional equivalents of phosphine stabilise the active species, they also retard activity. Thus, the success of a Heck catalytic system is a fine balance of activity and catalyst stability.

1.3.1.2.1 Other Palladacyclic Systems

Herrmann was not the first to prepare palladacyclic compounds of the type **5**. The di-*t*-butyl analogues **16** and **17**, for example, were first prepared by Shaw by heating the *trans*-dichlorobisphosphine palladium(II) complex in the presence of sodium tetrachloropalladate (scheme 1-16).[53] The acetate-bridged **17** was then obtained by shaking **16** with silver acetate. Several other complexes, such as the mixed *t*-butyl/*o*-tolyl analogue, were synthesised by a similar method. However, the catalytic activity of these complexes was not investigated.

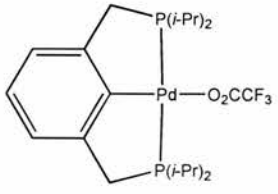


Scheme 1-16: Preparation of palladacycle analogues

Heck himself even detected the presence of the palladacycle **5** in his $Pd(OAc)_2$/tris(*o*-tolyl)phosphine *in situ* system, but explicitly dismissed the complex as an inactive

species, having no place in the reaction cycle.[54] Herrmann once disputed this statement,[46] but it seems that Heck's findings have turned out to be correct.

Nevertheless, it is for the recognition of the activity of the complex as a catalyst precursor for the Heck reaction that Herrmann deserves credit. By introducing the concept of palladacycle complexes as catalyst precursors for Heck reactions, a number of cyclometallated palladium complexes have appeared in the recent literature, showing similarly high, and often superior activity to **5**, in the Heck reaction and in other related couplings, some of which will be discussed later. Many of these complexes are direct analogues of the Herrmann compound, such as the fluorinated example mentioned previously, while others are novel compounds with related structures.



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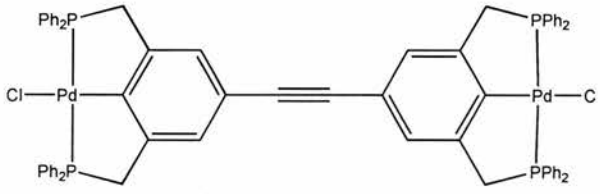
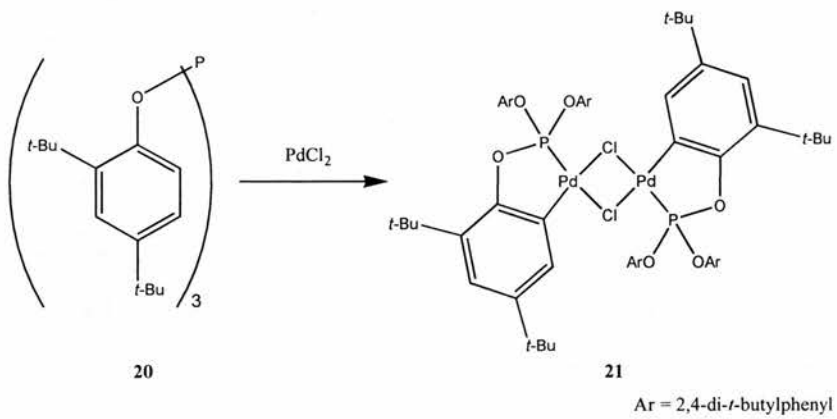


19

Milstein reported the orthometallated bisphosphines **18** in 1997,[55] which have become known as 'pincer' ligand complexes, due to the tridentate P,C,P' bonding effect of the 1,3-bis(phosphinomethyl)benzene ligand. Very high activity for the Heck reaction of a range of bromo- and iodoaromatics was reported, with turnover numbers in the range of 100,000 to 500,000 being achieved. Most recently Beletskaya *et al* have

reported a similar pincer compound **19** with high catalytic activity in which two P,C,P' units are tethered together by an acetylene based bridge.[56]

1.3.1.2.2 Orthopalladated phosphite ligands

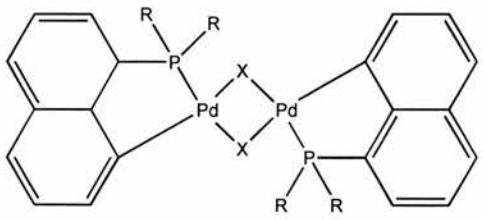


Scheme 1-17: Metallation of triarylphosphite ligand

The effectiveness of the ligand tris(2,4-di-*t*-butylphenyl)phosphite **20** in an *in situ* system was mentioned above. The orthopalladation of this ligand with $PdCl_2$ to form complex **21** was reported by Bedford (scheme 1-17).[57] This complex has been found to rival the Herrmann complex **5** in terms of activity, with the reaction of 4-bromoacetophenone and *n*-butyl acrylate going to completion within 6 hours at 160 °C, obtaining a turnover number of 1,000,000 (the Herrmann complex achieves 1,000,000 TON in 24 hours at 130 °C), without the need for promoting salts. A turnover of 5.75 million was achieved for the reaction of 4-bromoacetophenone and styrene at 160 °C, which, at the time, represented the highest reported turnover

number for any Heck reaction, although a "substantial" amount of polystyrene was formed as a side product.

A range of palladacycles derived from tri(1-naphthyl)phosphine (for example, **22**) has been reported by Shaw.[49] Another structure **23**, which looks like a phosphite analogue of the Milstein PCP' complex mentioned previously, was prepared by Shibasaki.[58]



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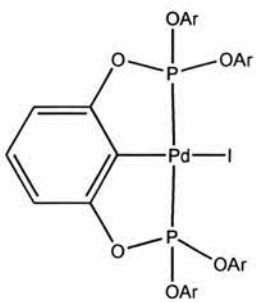


23

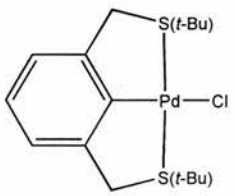
R = naphthyl
Ar = *p*-methoxypheny

Both have also proven to be excellent Heck catalysts, with turnovers of up to 1,120,000 and 8,900,000 respectively, although these were obtained using the more highly reactive iodoarenes as substrates.

1.3.1.2.3 S and N containing palladacycles

Many examples of palladacycles formed from phosphine and phosphite ligands have been reported. All of these have similar properties. All of the complexes mentioned

above are undoubtedly precursors to very active Heck catalysts, with relative activities being determined by the precise electronic and steric environments that these various ligands provide. There is evidence to suggest that palladacycles with certain ligand environments may give superior results than others for a given substrate. There have been developments to further vary the electronic environment of the palladium centre by metallating sulfur containing ligands[59] and imines.[60] Once again these compounds, **24** and **25**, are active Heck catalysts, achieving excellent yields and turnover numbers in the region of 1,500,000 with aryl iodides. Such examples show that the presence of a phosphorus atom in a palladacycle precursor is not essential for high activity.



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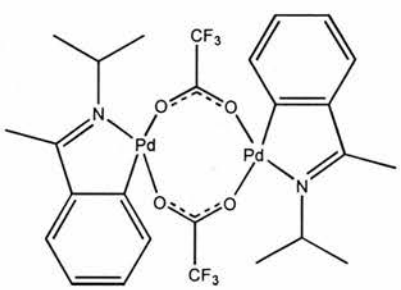

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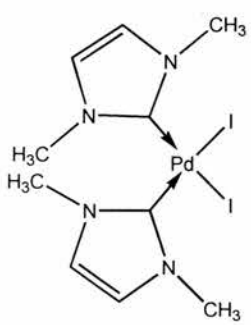
1.3.1.3 *Alternative Systems*

From the numerous examples given above, palladacycle chemistry has obviously had an enormous effect on the development of the catalytic system for the Heck reaction. However, despite the significant amount learned from the various research groups working in this area, the mechanistic details and the art of tailoring palladium

precursors to specific substrates to obtain optimum efficiency remain far off goals. In the meantime, developments have been made in alternative palladium systems for the Heck reaction. As these systems are beyond the scope of this thesis, they will be mentioned only briefly.

1.3.1.3.1 Carbenes

The development of *N*-heterocyclic carbenes as effective phosphine-free catalysts for Heck type reactions has been conducted by the Herrmann group in parallel to their studies on palladacyclic chemistry. Initial results were published around the same time as the groundbreaking discovery of the activity of palladacycle **5**,[43] and focussed on the two imidazole based carbene-palladium complexes **26** and **27**.[61]



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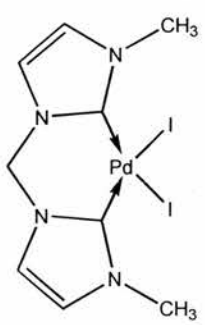


27

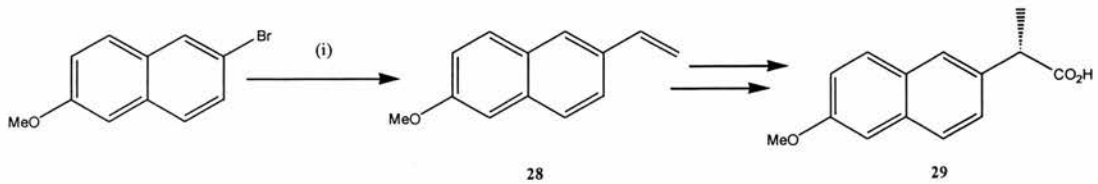
Complex **26** in particular displays superior thermal and air stability than even palladacycle **5**, and both complexes are active Heck catalysts. The complexes suffer from a long initiation period as the Pd(II) centre is reduced to the active Pd(0) species,

but this can be overcome by forming the active species *in situ* by adding the ligand to a Pd(0) precursor, such as $Pd(dba)_2$. Complex **27** was then shown to efficiently convert the deactivated 4-bromoanisole (95 %, TON 190) and the activated chloroarene 4-chloroacetophenone (60 %, TON 120) to Heck products.[62] Most recently, this system has been developed to allow attachment of the carbene complexes to a polymeric support, effectively heterogenising the system and allowing convenient catalyst recovery.[63] Turnovers of up to 5,000 have been obtained for Heck reactions in this instance. Although less active than palladacyclic systems, the superior stability of the carbene complex allows a greater range of application. Although the turnover numbers are low, the heterogenised example is perhaps more likely to find widespread use on an industrial scale due to its recyclability.

1.3.1.3.2 Palladium Colloids

There has been much debate as to whether palladium metal can catalyse the Heck reaction without the aid of stabilising ligands. Although there has been one report on the use of palladium black to process reactive aryl iodides,[64] Pd(0) is generally regarded as inactive towards the Heck reaction. However, the enormous activity shown by underligated palladium generated from palladacycles has led to investigations into colloidal palladium dispersions, stabilised only by tetraalkylammonium ions.[65] Although turnover numbers up to 1,900 were obtained, the reaction was not reproducible, and activity was poor for chloroaromatics and deactivated aryl bromides.

1.3.1.4 *Industrially Applied Processes*

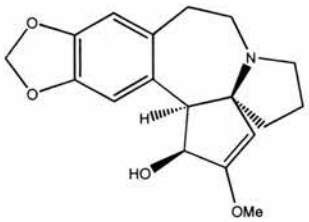


28 29

Scheme 1-18: Synthesis of Naproxen via an industrially feasible Heck reaction

(i) 20 bar ethylene, NaOAc, DMA, palladacycle **5**, 140 °C, 10 — 16 h.

With such focus on the Heck reaction over the past five years, and with many of the problems associated with the traditional system being overcome through the development on new, more active catalysts, there are finally more instances of the Heck reaction being used in industry. The use of the Herrmann complex **5** as the catalyst for a number of Heck reactions in the areas of industrial and applied chemistry has been reported.[66] An intermediate, **28**, of the non-steroid anti-inflammatory Naproxen **29** has been synthesised by the Heck coupling of ethylene with 2-bromo-6-methoxynaphthalene, for example (scheme 1-18).[67] Palladacycle **5** has also been used to mediate efficient couplings in the formation of cephalotaxine **30**,[68, 69] steroids of the type **31**,[70] and a blood coagulation enzyme inhibitor **32**.[71]



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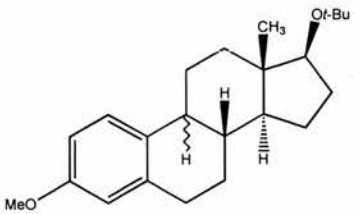

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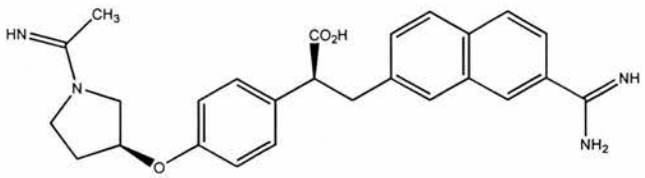
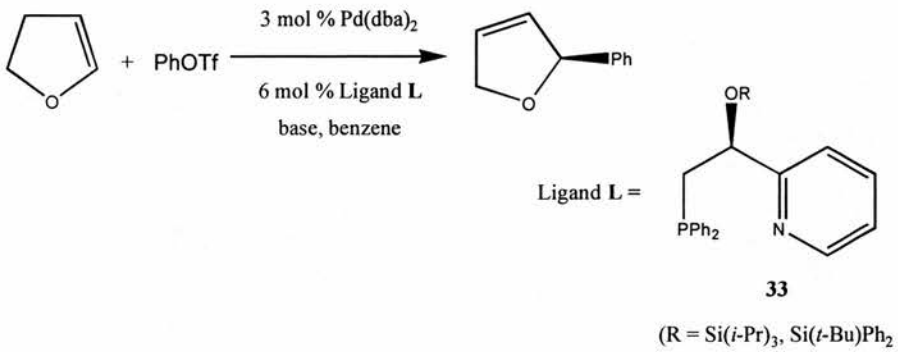


32

However, despite the improvements that have been made to the system, the chemical industry demands more. Catalyst activity and stability has still to reach a reliable level to lure industrial chemists away from tested heterogeneous methods. Catalyst recovery is still a problem, and with impurity specifications, especially in the pharmaceutical industry, at such infinitesimally low levels, toxic palladium precipitation or leaching cannot be tolerated.

We have also reached the time where the requirements of excellent chemoselectivity and regioselectivity, as well as high activity and mild reaction conditions are not enough. Many products must now be synthesised asymmetrically, or in enantio-pure form. The subject of asymmetric Heck chemistry falls out with the scope of this thesis, but is an area where there is much activity. Two recent reviews both cite the problem of product isomerisation, especially with a ligand commonly used in asymmetric synthesis, BINAP.[72, 73] The latter review, by Pfaltz *et al*,[73] described the

use effective use of chiral P,N-ligands of the type **33**, giving excellent enantiometric excesses in the region of 87—99 % and low levels of isomerisation (scheme 1-19).

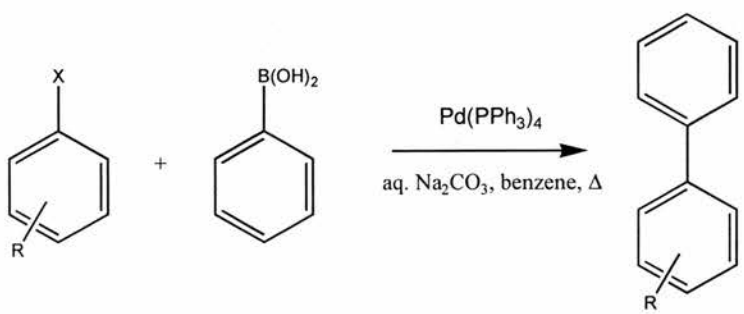


Scheme 1-19: Asymmetric Heck reaction using chiral P, N-ligands

It is obvious that a great deal of development has taken place in the area of Heck chemistry since the discovery of the reaction in the early 1970s. Many problems have been overcome, yet it seems as these are met, other challenges appear. The potential of the reaction is beginning to be fulfilled, but there is still much room for improvement.

1.3.2 Cross Coupling of Aryl Halides and Aryl Boronic Acids - The Suzuki Reaction

The coupling of arylboronic acids with aryl halides to yield biaryl compounds, the Suzuki reaction, was first reported in 1981 (scheme 1-20).[74]

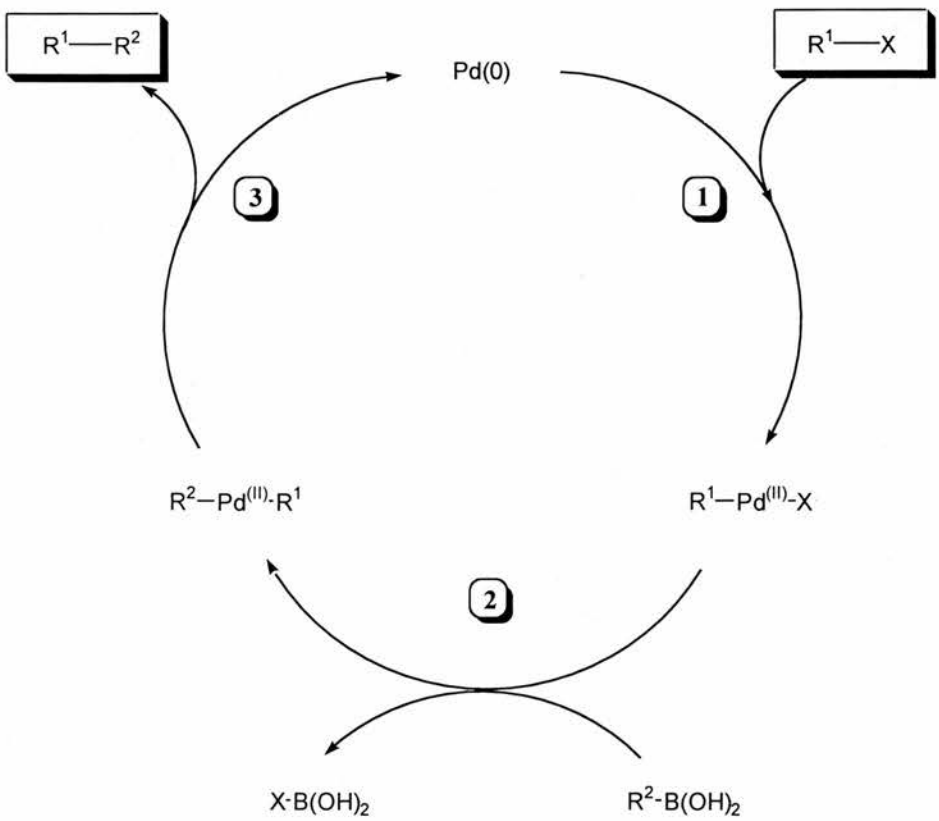


Scheme 1-20: The Suzuki Reaction

Substituted arylboronic acids are prepared straightforwardly from the corresponding Grignard or organolithium reagents, and thus the Suzuki coupling is an established and versatile method to substituted biaryls. Even *ortho*-substituted substrates can react in good yields (through the use of strong bases) despite the obvious steric hindrance factors, and therefore the coupling often provides the only practical pathway to such functionalised products. As a result, the reaction has been utilised on an industrial scale, and extensively in the synthesis of many natural products and pharmaceutical compounds.

A catalytic cycle for the Suzuki coupling is shown in scheme 1-21. The reaction is mechanistically similar to the Heck reaction (see scheme 1-4) with the oxidative

addition of the aryl halide being a key step (step 1). The most obvious difference, however, is a 'transmetallation' step (step 2), where the aryl group from the boronic acid is added to the palladium(II) intermediate with exclusion of the boronic halide salt $XB(OH)_2$.

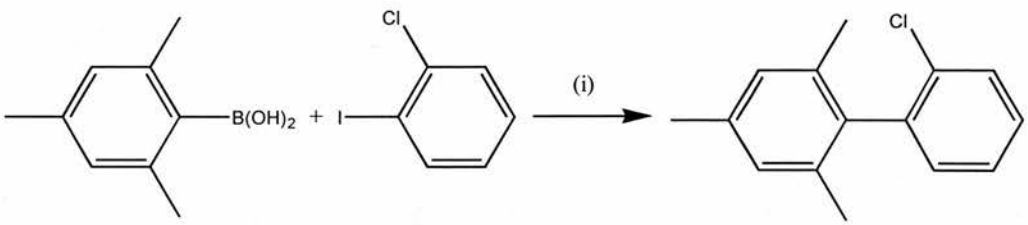


Scheme 1-21: Suzuki Reaction Mechanism

The most commonly used catalyst for this coupling to date has been $Pd(PPh_3)_4$, although suitable alternatives include $PdCl_2(PPh_3)_2$ and the *in situ* $Pd(OAc)_2/PPh_3$ system. As phosphines seem to inhibit the reaction, a similar trend to that seen in the Heck reaction is observed, with higher activity observed for $PdCl_2(PPh_3)_2$ than for $Pd(PPh_3)_4$, and in many cases superior yields being achieved with $Pd(OAc)_2$ alone.

The widespread commercial availability and relatively high thermal stability of $Pd(PPh_3)_4$ may have accounted for the compound being the catalyst of choice.

A similar range of aryl substrates to those used in the Heck reaction are suitable for Suzuki couplings. Aryl iodides and bromides are particular effective, with aryl chlorides being inert in most cases. The use of aryl triflates has been reported more recently, and these have been found to be particularly reactive.[75]



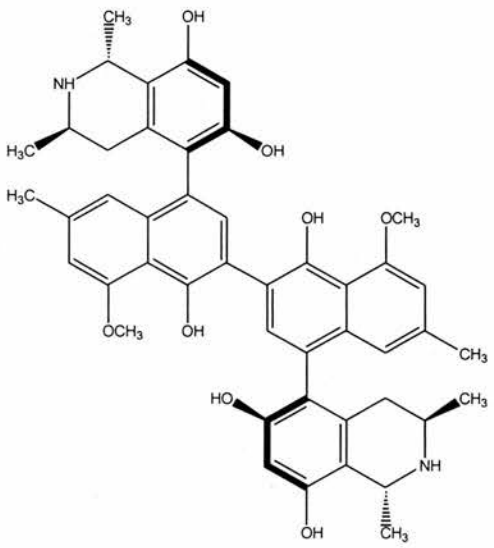
Scheme 1-22: Formation of highly substituted biaryls by the Suzuki coupling

(i) $Pd(PPh_3)_4$, aq. $Ba(OH)_2$, DME, 80 °C. (94 %)

A range of bases has been used, often in an aqueous solution. However, the use of aqueous conditions is unsuitable in many cases due to competitive hydrolytic deboronation of the arylboronic acid in this medium, with 2,6-dimethoxyphenylboronic acid being particularly prone to this problem.[76] Base sensitive substrates can still be processed through the 'heterogeneous' use of a K_2CO_3 suspension in toluene.[77] An alternative method is the use of essentially non-basic fluoride salt conditions (for example, CsF and $Bu_4N^+F^-$).[78] The use of strong bases, for instance NaOH or $Ba(OH)_2$, has an accelerating affect on the coupling, and, as

mentioned above, can be used to allow sterically hindered substrates, such as mesitylboronic acid, to be processed in high yield (scheme 1-22).[79]

The use of such conditions has allowed the convenient preparation of a number of highly substituted natural products and pharmaceutically active compounds.



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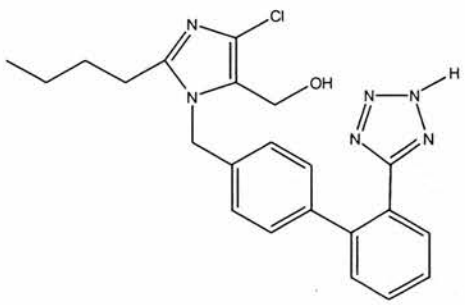


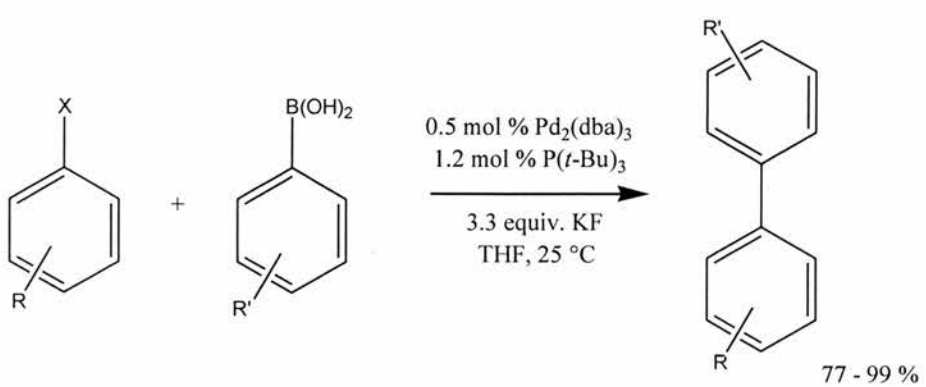
35

Michellamine **34**, which is a natural product with potential anti-HIV properties, is one example.[80] Meanwhile, less harsh conditions are required for the Suzuki coupling in the synthesis of Losartan **35**, a powerful angiotensin II receptor antagonist that is made on an industrial scale.[81]

1.3.2.1 Recent Developments

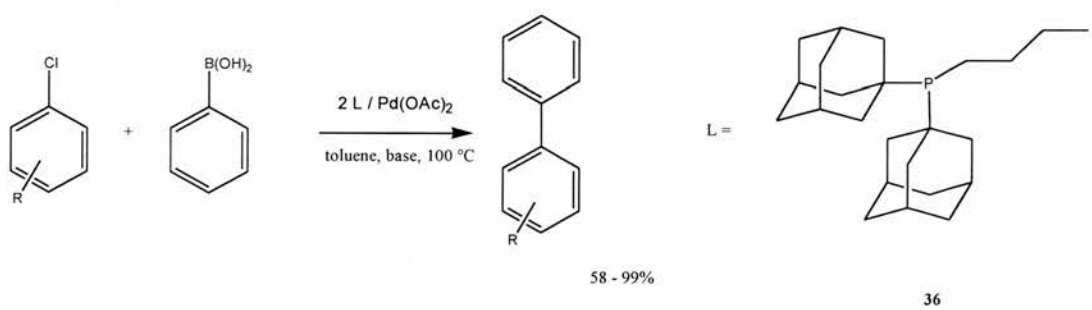
Due to the similarity of the Suzuki catalytic system to that of the Heck reaction, many of the developments that have been introduced to the Heck coupling in recent years have also been attempted on the Suzuki reaction. For example, the goal of optimising the system to allow the cheaper chloroaromatic to be used as a substrate would have considerable economic benefits for both reactions. As a result, a number of new Suzuki catalytic systems have appeared in the literature in an attempt to tackle this problem. Some of these have already been applied to the Heck reaction.

One such example is the use of the tri-*t*-butylphosphine as a ligand by Fu.[82] Using an almost identical system to the one that achieved such impressive results in processing aryl chlorides in the Heck reaction (see scheme 1-9), similarly high yields have been obtained for a range of chloroaromatic substrates in the Suzuki coupling.



Scheme 1-23: Room temperature Suzuki reactions with P(*t*-Bu)$_3$ ligand

The system has also allowed the reaction of iodo-, bromo- and even chloroaromatics to be conducted at room temperature (although only activated aryl chlorides were used, and fluoride salts were required) (scheme 1-23). The optimisation of the number of equivalents of phosphine ligand to palladium complex seems to be an important factor. For the Heck reaction, the best results were obtained using four equivalents of the sterically bulky phosphine. In the Suzuki coupling, 2.4 equivalents were used for the room temperature reactions (with 3.3 equivalents of KF), while 3 equivalents of the ligand was deemed necessary to obtain good yields with deactivated aryl chlorides at 70 °C. One example, the coupling of 2-chlorobenzonitrile with *p*-tolylboronic acid, using a catalyst loading of 0.01 mol % Pd, furnished the desired coupled product in 97 % yield at 90 °C, corresponding to a turnover number of 9,700.

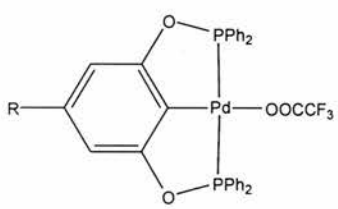


Scheme 1-24: Suzuki reaction of chloroaromatics using di-1-adamantyl-*n*-butylphosphine 36 as a ligand.

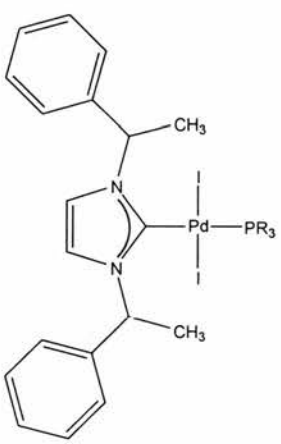
The use of di-1-adamantylalkylphosphines as effective ligands for the Heck coupling of aryl chlorides has been reported by Beller.[36] This catalytic system has recently been developed for use in Suzuki reactions, with outstanding results.[83] A range of chloroaromatics have been successfully converted to biphenyl products, using catalyst

concentrations as low as 0.005 mol % Pd and a relatively low reaction temperature of 100 °C (scheme 1-24). Impressive turnover numbers of up to 20,000 were achieved using di-1-adamantyl-*n*-butylphosphine **36** as the ligand, which are the highest obtained for the processing of aryl chlorides to date.

Less impressive results for chloroaromatics were obtained by Bedford, who used a phosphite analogue of the Milstein pincer type complex **37** as the catalyst for the Suzuki reaction of 4-chloronitrobenzene,[84] but it was argued that the catalyst was less expensive than the systems of Fu and Guram. The system yielded better results for aryl bromides, and although poor conversions were obtained when low catalyst concentrations (1×10^{-4} mol %) were used, this still equated to turnover numbers in the region of 150,000.



37 (R = H, CH)



38 (R = Ph, Cy)

An analogue of the *N*-heterocyclic carbene complex developed for use in the Heck reaction has been reported to be an active Suzuki catalyst for aryl bromides and chlorides by Herrmann.[85] The complex, **38**, achieved turnover numbers of up to

1,000 for activated aryl bromides and 90 for aryl chlorides. Notably, no activity was observed in the absence of the phosphine ligand.

Other interesting developments include a Suzuki coupling conducted in supercritical carbon dioxide. Yields of 49 — 52 % were obtained for aryl iodide substrates using the same system mentioned above for Heck reactions (5 mol % $PdL_2(OAc)_2$ [L = $(C_6F_{13}CH_2CH_2)_2PPh$]).[33]

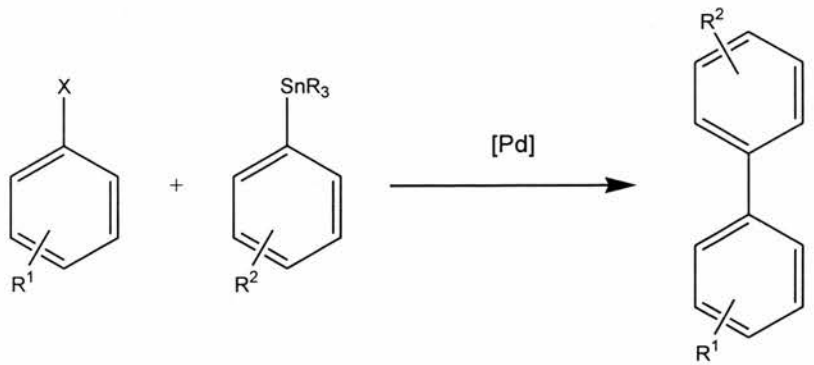
1.3.2.2 Palladacycle Precursors

It is obvious from the examples above, that, due to the similarities between the Heck and Suzuki couplings, a development in one reaction usually also has a beneficial effect on the other. The high turnovers obtained by palladacycle precursors in the Suzuki reaction has been touched upon above in the example of the phosphite pincer complex **37**. The activity of palladacycle **5** towards the Heck reaction and the Suzuki coupling was reported by Herrmann consecutively.[43, 86] Turnovers of up to 74,000 for the activated 4-bromoacetophenone and 2,100 for 4-chloroacetophenone have been obtained using this system.

Since then, several palladacyclic systems that exhibit high activity towards the Heck reaction have also been reported to be efficient Suzuki catalysts. The most notable example is the phosphite palladacycle of Bedford **21** (see scheme 1-17). The complex has proven to be a more active catalyst for the Heck reaction than the Herrmann

system, and indeed excellent turnover numbers of up to 1,000,000 (and incredibly high turnover frequencies of up to 870,000 h^{-1}) have been achieved for the Suzuki coupling of 4-bromoacetophenone and phenylboronic acid.[87]

1.3.3 Cross Coupling of Aryl Halides and Aryl Stannanes - The Stille Reaction



Scheme 1-25: Stille Coupling of an aryl halide and an aryl stannane

One of the most versatile palladium catalysed cross-coupling reactions is the coupling of tetraorganotin compounds with organic halides and triflates, or the Stille reaction, first reported in 1979.[88] Many substrates are tolerated, allowing alkyl, alkenyl, aryl and benzyl groups to be transferred from tin to carbon, generally in high yield. An example of the reaction of an aryl stannane with an aryl halide, a coupling analogous to the Suzuki reaction, is shown in scheme 1-25.

The reaction is well developed and is widely used to efficiently produce a variety of complex molecules. Advantages of the system include high chemoselectivity and base-free conditions, which is important for selective reactions with high value, base sensitive substrates. The tin compounds are prepared straightforwardly and, due to their inertness to air and moisture, are easily handled. Unfortunately, tin compounds are highly toxic, and due to extremely strict regulatory limits on heavy metal

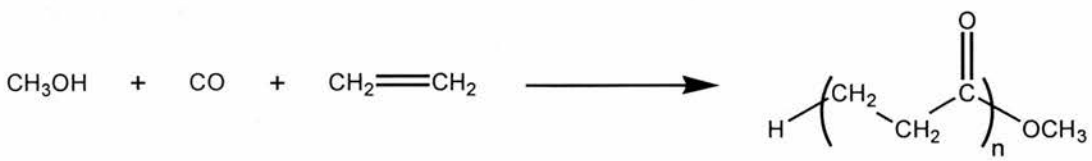
impurities in pharmaceutical products, the reaction is largely avoided in many areas of industry.

The catalysts of choice for the Stille reaction have been $Pd(PPh_3)_4$ and $PhCH_2PdCl(PPh_3)_2$. Other systems include $Pd_2(dba)_3$ with phosphine or arsine ligands. Relatively high concentrations (1—5 mol %) of these catalysts and lithium and copper salts are often necessary to obtain reasonable yields of product.[89]

Palladacycle catalyst precursors have recently been applied to the Stille reaction, with mixed results. Herrmann and Hartwig independently reported identical turnover numbers of 1,650 for the coupling of 4-bromoacetophenone with trimethyl(phenyl)tin, with much lower values (in the region of 10—50 TON) for more deactivated aryl halides, with palladacycle **5** as the catalyst.[66, 50] In contrast, Bedford has reported turnover numbers in excess of 800,000 for the same 4-bromoacetophenone coupling using the phosphite palladacycle **21**, and an impressive 840 turnovers with the deactivated 4-bromoanisole. Reasonable results have been obtained conducting the coupling reaction in supercritical carbon dioxide.[90] The reaction between iodobenzene and tributyl(vinyl)tin proceeded in high yield using $Pd_2(dba)_3$ with the CO_2-soluble ligand tris(3,5-bis(trifluoromethyl)phenyl)phosphine. However, the rate of reaction was such that the turnover frequency was less than 10 h^{-1}. To date, no system has allowed aryl chlorides to be processed in the Stille reaction with any degree of efficiency.

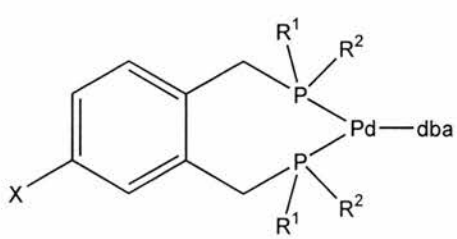
1.4 Aims of Project

Ineos Acrylics (formerly ICI Acrylics) has reported the use of an *in situ* palladium complex with a bidentate diphosphine ligand as a highly active, selective catalytic system for the methoxycarbonylation of ethene (scheme 1-26).[91]



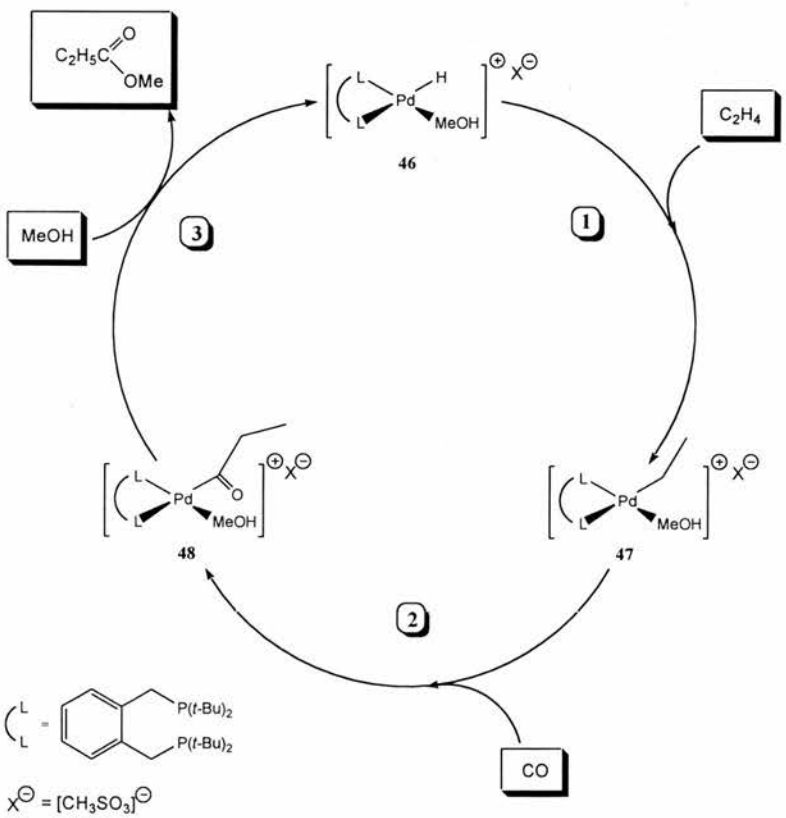
Scheme 1-26: Methoxycarbonylation of ethene

A variety of products is available from this reaction, ranging from high molecular weight polyketones, useful as thermoplastics, to methyl propanoate (n = 1 in scheme 1-26, above), which is used by Ineos Acrylics as a key intermediate in the manufacture of methyl methacrylate, an important monomer produced on a large scale world wide. Depending on the nature of the phosphine ligand used, the selectivity of the catalytic system can tailored, with monodentate phosphines usually producing methyl propanoate, and chelating bidentate phosphines giving higher molecular weight CO/ethene co-polymers.[92] However, the Ineos Acrylics system seems to contradict this trend.



39 $R^1 = R^2 = t$-Bu, X = H
40 $R^1 = R^2 = t$-Bu, X = NO_2
41 $R^1 = R^2 = t$-Bu, X = OMe
42 $R^1 = R^2 = i$-Pr, X = H
43 $R^1 = R^2$ = Cy, X = H
44 $R^1 = R^2$ = Ph, X = H
45 $R^1 = t$-Bu, R^2 = Cy, X = H

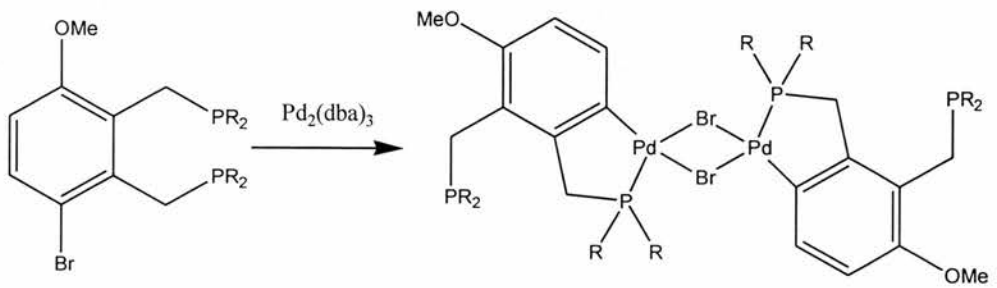
A number of complexes was synthesised, all based on a 1,2-bis(diphosphinomethyl)benzene ligand (**39** — **45**). Reaction of the complex **39** with methanesulfonic acid produces a system which achieves remarkable activity (turnover frequencies of up to 50,000 h^{-1}) and selectivity to methyl propanoate (99.98 %) at very mild conditions (80 °C and 10 bar combined pressure of CO and ethene). Comparable results were seen with complexes **40** and **41**. This shows that the nature of the phosphine moiety is an important factor in the activity of the catalyst, with the di-*t*-butylphosphine ligands exhibiting activity 60 times higher than other less sterically bulky, less electron donating phosphines. The similar activity of **39**, **40** and **41** also shows that the presence of electron withdrawing (X = NO_2, **40**) or electron donating (X = MeO, **41**) groups on the aryl ring of the ligand have no significant effect on either the activity or selectivity of the catalyst.



Scheme 1-27: Mechanism for methoxycarbonylation of ethene

It has recently been shown that the methoxycarbonylation of ethene is catalysed by these complexes via palladium hydride catalytic cycle shown (scheme 1-27).[93] The reaction of the complex **39** in methanol with acid (e.g. methanesulfonic acid), gives the palladium hydride solvento-cation **46**. Coordination and insertion of ethene gives the alkyl complex **47** (step 1). Coordination of carbon monoxide, followed by an alkyl migration results in the formation of the acyl intermediate **48** (step 2). The cycle is completed by alcoholysis by methanol to yield the product, methyl propanoate, with regeneration of the hydride active species (step 3). All of the above steps have been proven by identification of the intermediates by multinuclear NMR spectroscopy and isotopic labelling experiments.

A further range of bidentate ligand analogues was then synthesised with bromine groups on the aromatic linkage. Tethering the complex to a heterogeneous support, to aid catalyst recovery, was one of the aims. One such ligand was the 4-bromo-2,3-bis(di-*t*-butylphosphinomethyl)anisole analogue, **49**.



49 **50** R – *t*-butyl

Scheme 1-28: Metallation of bromo ligand 49

However, reaction of this ligand with the tris(dibenzylideneacetone)dipalladium(0) precursor gave an unexpected product. Rather than form the expected chelated complex of the type **39** (which had been observed for all other ligands based on the central *o*-xylyl moiety), the ligand **49** coordinated to palladium through one phosphine moiety only, and underwent *ortho*-metallation (via oxidative addition of the aryl—bromine bond) to form the dimeric palladacycle complex **50** (scheme 1-28). The second phosphine moiety did not coordinate to palladium in any way,[94] and will be referred to as the 'pendant' phosphine from hereon. This structure has been fully characterised and confirmed by a single crystal x-ray structure (figure 1-1).[95]

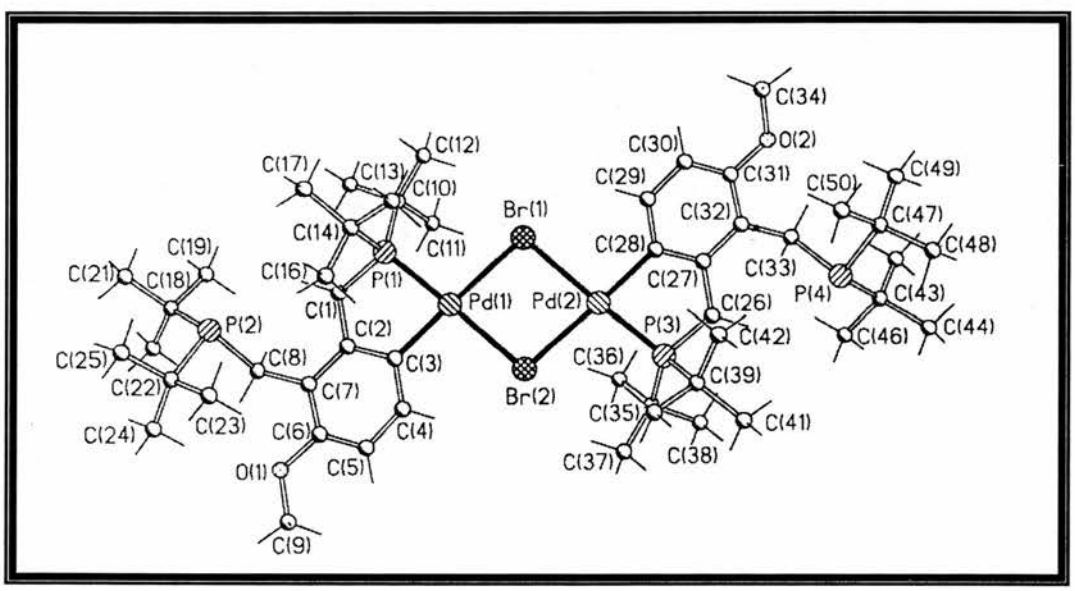


Figure 1-1: X-ray structure of dimeric palladacycle complex 50

Initial experiments at Ineos Acrylics showed this complex to also be an active catalyst towards the methoxycarbonylation of ethene, although of lower activity than the complexes of type **39**.[96]

Complex **50** is structurally similar to the Herrmann palladacycle **5**, and several comparisons can be made. For instance, both compounds have two five-membered palladium containing heterocycles, each with one palladium—carbon bond and one palladium—phosphorus bond. However, the linkages are different: the Herrmann palladacycle **5** contains a palladium—benzyl linkage and an aromatic—phosphorus—palladium linkage, while the Ineos heterocycle, **50**, comprises palladium—aromatic bonds and benzyl—phosphine—palladium linkages. Thus, the palladium atom in this 'isomeric' palladacycle ring has a significantly different electronic environment to that of the Herrmann complex, which may affect the catalytic activity of the complex. From x-ray crystallography data, the geometries of the two palladacycles are similar. The Pd—C bond lengths of both compounds are approximately 2.02 Å, while the palladium—phosphorus bond of the Herrmann compound is slightly shorter (2.22 Å) than that of the Ineos complex (2.23 Å). The carbon—palladium—phosphorus bond angles of both compounds are also similar (82.3° for **5**, 81.8° for **50**). It must be noted that as there are groups of different electronic character on the phosphorus atoms of these two complexes (electron-withdrawing *o*-tolyl groups on the Herrmann complex, electron-donating *t*-butyl groups on complex **50**), it is difficult to make any direct structural comparisons from the crystal data.

Before the commencement of this project, only a very small amount of complex **50** had been synthesised, using a method designed to produce chelate complexes. In addition, neither the cyclometallation process nor the catalytic properties of this complex had been thoroughly investigated. There were obviously many routes of investigation into this potentially exciting new compound. The initial aims of the

project were broad, and, predictably, changed significantly in the course of its three-year duration.

These were:

1. To develop an understanding of the alkene carbonylation reaction catalysed by the palladacycle complex.
2. To ascertain if the complex is active towards carbon—carbon bond formation (e.g. Heck reaction).
3. To synthesise analogues with different phosphine moieties in order to develop structure—property relationships.
4. Investigate the possibility of anchoring the complex to a polymeric support via the pendant phosphine groups.

The work done and the conclusions made during this project will now be discussed, keeping the objectives above in mind. However, as will become apparent, a number of factors arose which meant the focus of the project changed, with more time being spent exploiting the results of one investigation (objective 2, above), while it became impractical to investigate other areas (objective 4, above). These, of course, will be fully explained at the appropriate stage in the thesis.

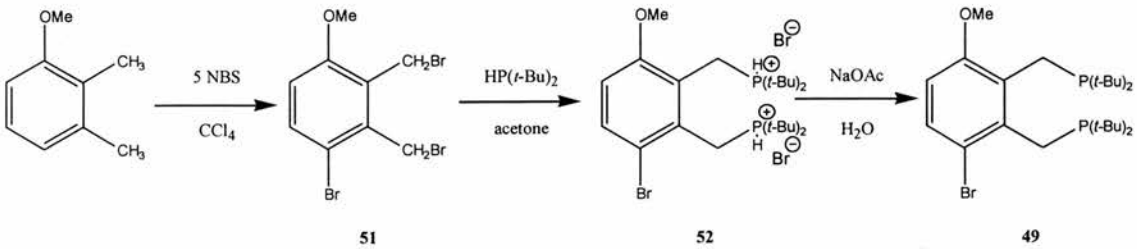
CHAPTER 2

2. SYNTHESIS OF LIGANDS AND POTENTIAL CATALYSTS

The first objective of the project was to successfully synthesise the benzylphosphine ligands necessary for the preparation of the target palladacycle complex previously prepared by Ineos and analogous compounds for catalytic investigation. This chapter will firstly be concerned with describing the methods used to synthesis the phosphine ligands and their intermediates, and the effectiveness of these methods.

For a number of reasons, the synthesis of the target ligand compound, 4-bromo-2,3-bis(di-*t*-butylphosphinomethyl)anisole, **49**, was more problematic than first anticipated, which led to a change of strategy, and ultimately a entirely different focus on the project. The rationale behind this approach will be explained. As a result of this development, alternative synthetic methods were attempted, first in an effort to prepare the target ligand by different means, then latterly to allow analogous palladium complexes to be prepared from alternative ligands. The outcome of these strategies will be reported. Finally, the metallation reactions of the successfully prepared phosphine ligands and the resulting palladium compounds will also be described.

2.1 Synthesis of Phosphine Ligands



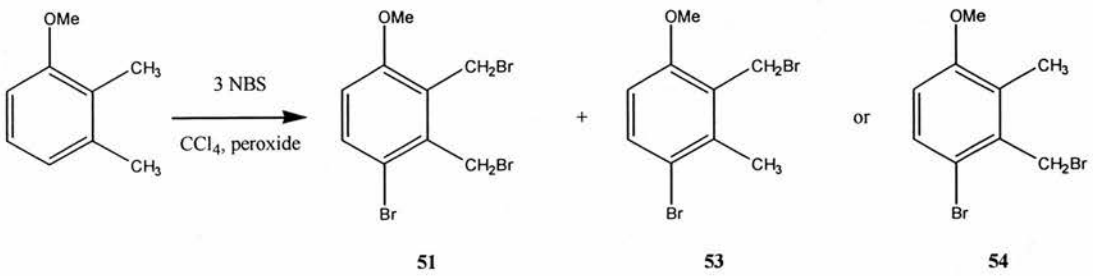
51 52 49

Scheme 2-1: Original scheme for preparation of ligand 49

The ligand 4-bromo-2,3-bis(di-*t*-butylphosphinomethyl)anisole, **49**, had been previously synthesised in three steps from the readily available substrate 2,3-dimethylanisole, via the specifically brominated 4-bromo-2,3-bis(bromomethyl)anisole **51** and the diphosphonium salt **52** (scheme 2-1).[94]

The first step, specific bromination of 2,3-dimethylanisole to 4-bromo-2,3-bis(bromomethyl)anisole **51**, was achieved by reacting the substrate with an excess (5 equivalents) of the brominating agent *N*-bromosuccinimide (NBS) in carbon tetrachloride. Reaction of **51** with di-*t*-butylphosphine in acetone gave the diphosphonium bromide **52**, which was reduced to the diphosphine ligand **49** by treatment with sodium acetate in water. The synthesis was a modified version of the preparation of the *para*-substituted ligand 1,3-bis(di-*t*-butylphosphinomethyl)benzene previously reported by Shaw.[97] Unfortunately, a number of problems were encountered following this scheme, which necessitated several developments to the process and a change in strategy before progress could be made.

2.1.1 Preparation of Brominated Aromatics



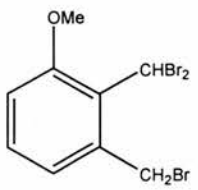
51 53 54

Scheme 2-2: Bromination of 2,3-dimethylanisole with 3 equivalents NBS

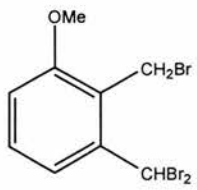
As the first intermediate of a three stage process, the brominated aromatic 4-bromo-2,3-bis(bromomethyl)anisole **51** had to be prepared using a reliable method, in good yield and quality. The compound had previously been prepared in reasonable yield at Ineos by the reaction of 2,3-dimethylanisole and five equivalents of NBS with dibenzoyl peroxide as a radical initiator. Using the stoichiometric three equivalents of the brominating agent did not fully brominate the anisole substrate at the 2-methyl or 3-methyl position, to give either 4-bromo-2-(bromomethyl)-3-methylanisole **53** or 4-bromo-3-(bromomethyl)-2-methylanisole **54** as a side product (analytical evidence was not conclusive as to which side product was formed)(scheme 2-2).

This result corresponds with the findings of Alper, who found that reaction of the dimethylanisole with two equivalents of NBS produced the dibrominated 4-bromo-2-(bromomethyl)-3-methylanisole **53** (which was confirmed by single crystal x-ray analysis) in 90 % yield.[98] Monitoring this reaction by GC and GC-MS revealed that bromination occurred on the aromatic ring before the 2-methyl position. Alper also

showed that 4-bromo-2,3-bis(bromomethyl)anisole **51** could be obtained directly from 2,3-dimethylanisole in 94 % yield by reaction with three equivalents of NBS.



55



56

However, these results could not be reproduced. Reaction of 2,3-dimethylanisole with five equivalents of NBS, as per the Ineos method, gave either 2-(dibromomethyl)-3-methylanisole **55** or 3-(dibromomethyl)-2-methylanisole **56** as the product (again, spectroscopic evidence was not conclusive as to which isomer was formed). When 3 equivalents of NBS were used, as per the Alper method, the same product (either **55** or **56**) was formed. It is important to note that no bromination occurred on the aromatic ring of the anisole substrate while trying to replicate these methods.

An encouraging breakthrough occurred upon the discovery that Bickelhaupt *et al* had observed similar results to our own for this reaction, which contradicted the findings of Alper.[99] Bickelhaupt reacted a range of methyl-substituted anisoles with various equivalents of NBS, the results of which yielded a number of conclusive trends.

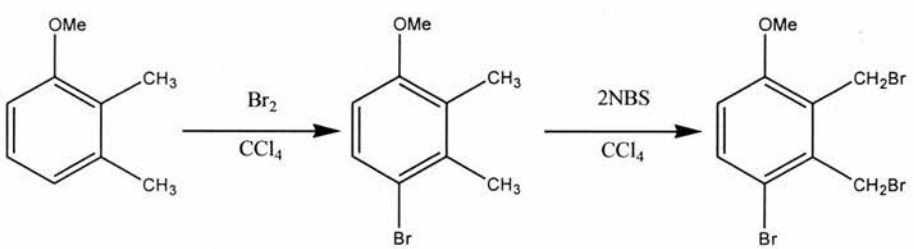
Firstly, there is a clear distinction in the mechanisms involved between the *para*-bromination on the aromatic ring and alkyl side-chain bromination. Nuclear

bromination, that is bromination on the aromatic ring, is an electrophilic aromatic substitution reaction, while bromination of the methyl groups by NBS, known as the Wohl-Zieler reaction, is a radical process. Under conditions favouring radical processes (irradiation by use of a high-powered lamp; it was stated that radical initiation is not reliable when a peroxide initiator is used) both reaction mechanisms can still take place, depending on the substitution pattern of the aromatic. For example, bromination of anisoles with *ortho*-methyl groups (2-methylanisole and 2,6-dimethylanisole) occurs exclusively on the methyl groups. Conversely, *meta*-substituted anisoles, such as 3,5-dimethylanisole are activated towards nuclear bromination and thus two products, 4-bromo-3,5-dimethylanisole and 3-(bromomethyl)-5-methylanisole are formed in a 3:1 ratio. When all *ortho*- and *meta*-positions are occupied (e.g. 2,3,5,6-tetramethylanisole) the activating effect of the *meta*- substituents overcomes the retarding effect of the *ortho*-substituents, and nuclear bromination is still observed at the 4- position.

Reaction of 2,3-dimethylanisole under these conditions gave almost exclusively the side-chain brominated product, with virtually no nuclear bromination. In contrast to the result of Alper, in which the first equivalent of NBS reacted exclusively at the *para*- position, reaction with one equivalent of NBS gave 2-(bromomethyl)-3-methylanisole and 3-(bromomethyl)-2-methylanisole as the brominated products in a 9:1 ratio. A further equivalent of NBS furnishes 2,3-bis(bromomethyl)anisole as the only product. This is in agreement with our result and is completely the opposite reaction to that observed by Alper.

There are several explanations for such a difference in reactivity. Alper assumed that by adding the radical initiator, benzoyl peroxide, to the reaction mixture, a radical mechanism would be induced. Bickelhaupt explains that (i) use of a radical initiator is not as reliable a method as irradiation for inducing radical reactions; (ii) the kinetic data reported by Alper does not suggest that a radical mechanism is occurring for his reaction (the reaction takes in excess of 24 hours in refluxing carbon tetrachloride to reach completion, while Bickelhaupt's irradiation reactions are complete within 30 minutes); (iii) if a radical mechanism were occurring in the Alper reaction, alkyl chain bromination would be the predominant reaction. To explain why we obtained results similar to Bickelhaupt for the reaction of 2,3-dimethylanisole with NBS, using reaction conditions similar to Alper, we have made the following conclusions. Despite using no additional irradiation source, we are confident a radical mechanism is still occurring in our reactions. Bickelhaupt has reported identical product ratios using thermal heating rather than irradiation, with daylight being the only light source, but the reaction times are longer. Our reactions needed 24 hours to reach completion (indicated by all of the suspended succinimide by-product floating in the CCl_4 solvent – NBS does not float in carbon tetrachloride), but no attempt was made to exclude light from the reaction mixture. In addition, the condition of the *N*-bromosuccinimide reagent is also important. As NBS is exposed to light, it gradually breaks down by a radical process to form a residual amount of elemental bromine. If the presence of bromine is high enough in the reaction mixture, electrophilic aromatic substitution will be a competing side-reaction, yielding nuclearly brominated products. We suggest that the NBS used by Alper and Ineos in the reaction of 2,3-dimethylanisole had a residual amount of bromine in the reaction mixture, and the radical bromination mechanism of NBS was not sufficiently induced.

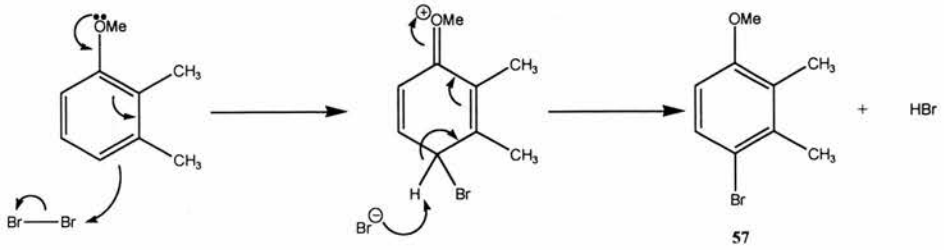
Further evidence in support of this theory was provided when it was found that *para*-bromination of 2,3-dimethylanisole in carbon tetrachloride could be achieved when one equivalent of Br_2 was added to the reaction mixture. As a result, careful addition of bromine to a solution of 2,3-dimethylanisole in CCl_4 (over-addition caused bromination to occur at the 6-position as well as the 4-position) yielded 4-bromo-2,3-dimethylanisole **57** in quantitative yield. This product could be isolated or reacted further *in situ* by addition of two equivalents of NBS to furnish the desired product, 4-bromo-2,3-bis(bromomethyl)anisole **51** (scheme 2-3). This product could also be formed in good yield by performing the NBS dibromination first, to yield 2,3-bis(bromomethyl)anisole, then the nuclear bromination by addition of bromine to this compound. The convenience and higher purity of product obtained by the former procedure made it the method of choice.



57 **51**

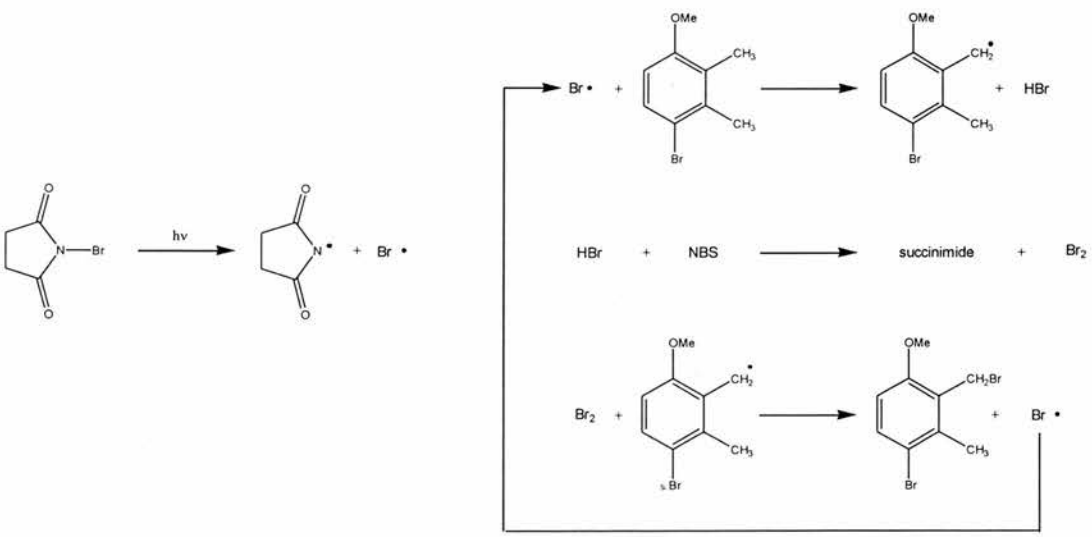
Scheme 2-3: Bromination method to synthesise 4-bromo-2,3-bis(bromomethyl)anisole

It should be noted that 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), a proven aromatic ring brominating agent,[100] was also successfully employed in the preparation of 4-bromo-2,3-dimethylanisole **57**, but the product yield and quality was inferior to that obtained with elemental bromine.



Scheme 2-4: Bromination by Electrophilic Aromatic Substitution

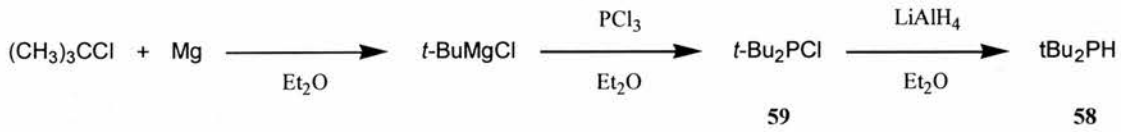
In summary, a method has been developed to synthesise 4-bromo-2,3-bis(bromomethyl)anisole **51** by the use of two types of bromination. Firstly, 2,3-dimethylanisole is brominated in the 4-position in quantitative yield by the addition of exactly one equivalent of elemental bromine. This reaction is an example of electrophilic aromatic substitution, and the mechanism for this reaction is shown is scheme 2-4. The desired product **51** was then formed by addition of two equivalents of *N*-bromosuccinimide, a reaction that involves a radical mechanism in which a bromide radical is the chain carrier (the mechanism for the first of the two brominations is shown in scheme 2-5).



Scheme 2-5: Bromination by radical mechanism

2.1.2 Preparation of Phosphines and Phosphonium Salts

With the brominated aromatic 4-bromo-2,3-bis(bromomethyl)anisole **51** successfully synthesised in high quality on a large (~50 g) scale, the secondary phosphine di-*t*-butylphosphine **58** had to be prepared reliably in similar amounts. The general outline for the synthesis of the phosphine, via di-*t*-butylchlorophosphine **59** is shown in scheme 2-6.



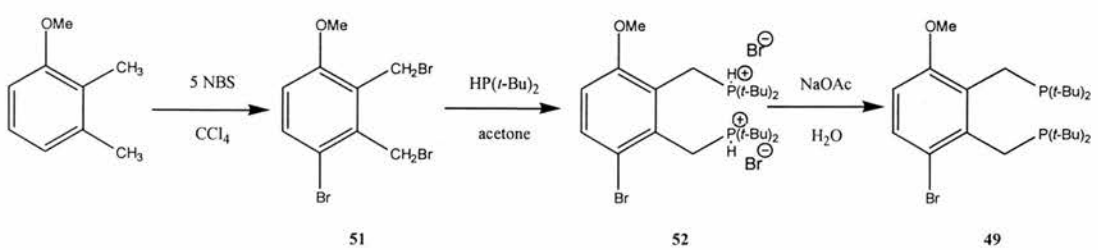
Scheme 2-6: Preparation of di-*t*-butylphoshine

The chlorophosphine **59**, prepared by the Grignard reaction of *t*-butylmagnesium chloride with phosphorus trichloride, would be reduced to the desired product **58** by reaction with lithium aluminium hydride. However, in a similar manner to the synthesis of the bromoaromatic **51**, the method used by Ineos for the preparation of phosphine **58** did not provide satisfactory product yield or quality. Referring to the literature, it appeared that optimisation of the molar ratios of the reagents used and isolating the chlorophosphine (which had previously been reduced to the phosphine *in situ*) was necessary.

The procedure reported by Scherer and Schieder for the preparation of di-*t*-butylchlorophosphine **59** was used as the basis for our method.[101] However, Scherer prepared the Grignard reagent from 1.2 equivalents of *t*-butyl chloride and one

equivalent of magnesium. In our hands, this resulted in reaction of the Grignard reagent with the excess *t*-butyl chloride, causing a precipitate to form before addition of the phosphorus trichloride. This resulted in the reaction solution becoming viscous and lowered the reaction yield (through loss of reagent and the difficulty of stirring the reaction mixture). Lowering the amount of *t*-butyl chloride to 1.06 equivalents per equivalent of magnesium prevented this from occurring while still ensuring complete formation of the Grignard reagent. The phosphorus trichloride was then added to three equivalents of the Grignard reagent. Such an excess of reagent was required to ensure that the disubstituted phosphine, rather than the monosubstituted *t*-butyldichlorophosphine, was the main product due to the added steric bulk of the *t*-butyl group. The Ineos procedure had only used 2.2 equivalents of the Grignard reagent, which did not produce reasonable yields of the desired product in our hands. The modified procedure gave di-*t*-butylchlorophosphine **59** in typical yields of 55 %.

As mentioned previously, superior results were obtained when the chlorophosphine **59** was isolated and purified by distillation before reduction to the phosphine. This reduction was effectively performed by lithium aluminium hydride following the procedure of Timmer *et al*,[102] which resulted in the pure phosphine **58** being obtained in 60 % yield.

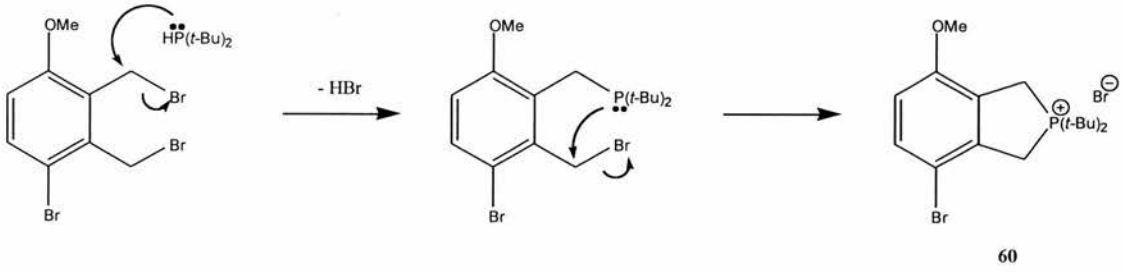


51 52 49

Scheme 2-7: Preparation of Ligand via Phosphonium Salt Formation

With the two ligand precursors, 4-bromo-2,3-bis(bromomethyl)anisole **51** and di-*t*-butylphosphine **58**, prepared in reasonable yield using a robust method, work on the ligand preparation could begin. Reaction of the bromoaromatic **51** with two equivalents of the phosphine in acetone was expected to yield the diphosphonium dibromide **52**, an air-stable intermediate which could be isolated or reduced to the desired ligand 4-bromo-2,3-bis(di-*t*-butylphosphinomethyl)anisole **49** by treatment with sodium acetate in water (scheme 2-7).

However, preparation of the desired ligand **49** was hampered by the formation of a heterocyclic by-product **60**, caused by one phosphine molecule reacting at both bromomethyl sites in turn. A possible mechanism for the formation of this by-product is shown in scheme 2-8.



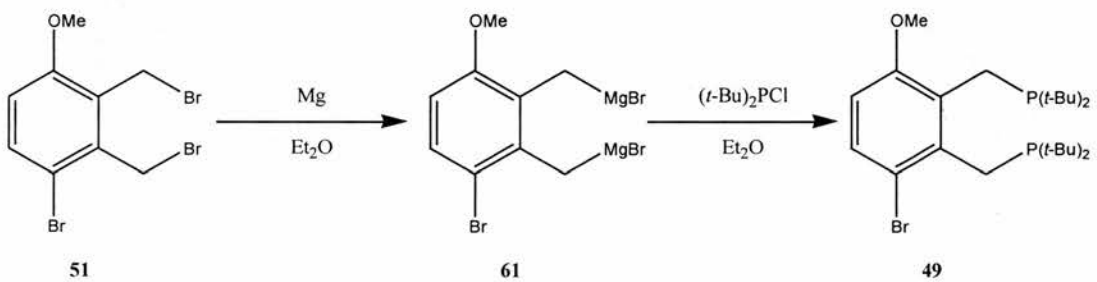
Scheme 2-8: Formation of heterocyclic by-product

Formation of a monophosphonium salt intermediate may be followed by reduction to the phosphine with extrusion of hydrogen bromide. The monophosphine is then free to react with the second bromomethyl group to yield the cyclic phosphonium bromide **60**. This by-product had previously been reported by the Ineos group, but the ratio of desired product to heterocyclic by-product had been ~3:1, which was considered

satisfactory. In our hands this ratio was in the region of 1:9, which meant steps had to be taken to minimise or prevent the formation of the by-product, as methods attempted by Ineos to ring-open the heterocycle had been unsuccessful.[94]

2.1.3 Alternative Ligand Preparation Strategies

A number of strategies were attempted in an effort to minimise or avoid preparation of the heterocyclic by-product **60**, with varied success. This included the attempted preparation of the di-Grignard reagent **61**, followed by reaction with the chlorophosphine (scheme 2-9).



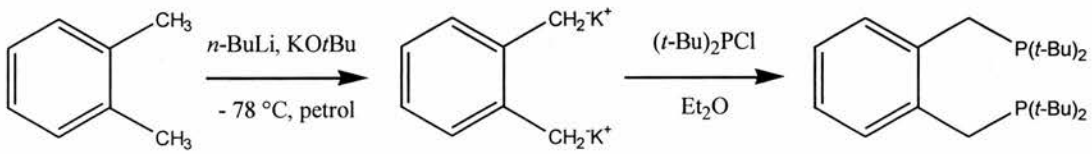
51 **61** **49**

Scheme 2-9: Preparation of ligand via di-Grignard reagent

A method analogous to the original Shaw preparation involving the more reactive iodoaromatic intermediate was attempted. Unfortunately, the preparation of 4-bromo-2,3-bis(iodomethyl)anisole via the reaction of 4-bromo-2,3-dimethylanisole **57** with iodosuccinimide was unsuccessful. As well as syntheses involving more reactive aromatic substrates, approaches in which a more reactive phosphine was used were attempted. However reactions of the potassium salt, $[t\text{-}Bu_2P]^-K^+$, and the lithium salt,

$[t\text{-}Bu_2P]^-Li^+$, with the aromatic 4-bromo-2,3-bis(bromomethyl)anisole **51**, were unsuccessful.

The successful linkage of two di-*t*-butylphosphines to a bis(bromomethyl)aromatic compound to form a diphosphine was achieved using a method developed by Edwards (scheme 2-10).[103]



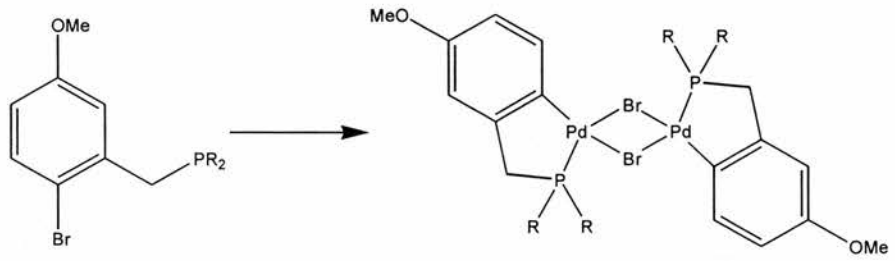
62 **63** **64**

Scheme 2-10: Diphosphine preparation via dipotassium salt

Reaction of *ortho*-xylene **62** with *n*-butyllithium in the presence of potassium *t*-butoxide yielded the dipotassium salt **63**, which was isolated and reacted with chlorodi-*t*-butylphosphine to yield 1,2-bis(di-*t*-butylphosphinomethyl)benzene **64**. However, ligand **49** required a methoxy group *ortho* to one phosphinomethyl substituent, and a bromine atom *ortho* to the other phosphinomethyl moiety. Introduction of the methoxy substituent by employing the above method with 2,3-dimethylanisole as the substrate was not successful, with the expected product, 2,3-bis(di-*t*-butylphosphinomethyl)anisole, not being obtained in good yield. In addition, subsequent bromination of the diphosphine **64** could not be performed selectively. The problem of lithium—halogen exchange by *n*-butyllithium prevented the introduction of the *ortho*-bromine before addition of the phosphines. Thus,

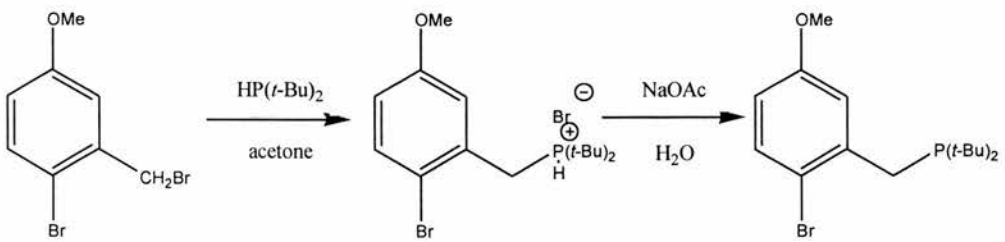
preparation of the dipotassium salt of 3-bromo-1,2-dimethylbenzene was not attempted.

With no ligands of the type **49** successfully synthesised, a complete change of strategy was required.



Scheme 2-11: Ligand simplification by removal of one phosphinomethyl group

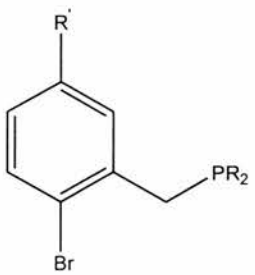
As the pendant phosphinomethyl group is not necessary for the actual formation of the palladacycle structure, the ligand synthesis could be simplified, and the possibility of cyclic side product **60** formation eliminated, by the removal of the phosphinomethyl group *ortho*- to the methoxy substituent (scheme 2-11). Should the pendant phosphines be found necessary for the catalytic activity of the complex, one would have to return the problem at a later stage.



67 66 65

Scheme 2-12: Preparation of monophosphine ligand

Formation of the monophosphine ligand **65** was achieved by the usual Shaw method, via the phosphonium salt **66** (scheme 2-12). The starting material 4-bromo-3-(bromomethyl)anisole **67** was cheap and readily available, but could alternatively be prepared from 4-bromo-3-methylanisole by bromination with NBS. Reaction of this bromoaromatic with di-*t*-butylphosphine gave the phosphonium salt **66** in quantitative yield as a white solid. This air-stable material could be isolated and stored until needed or reacted further to the phosphine **65**. Isolation of the phosphine, a high boiling point liquid, in high purity proved difficult, with Kugelrohr short-path distillation yielding the best product quality. Due to the high air-sensitivity of the compound, it was necessary to store the ligand under argon and process the compound further as soon as possible to minimise phosphine oxidation.

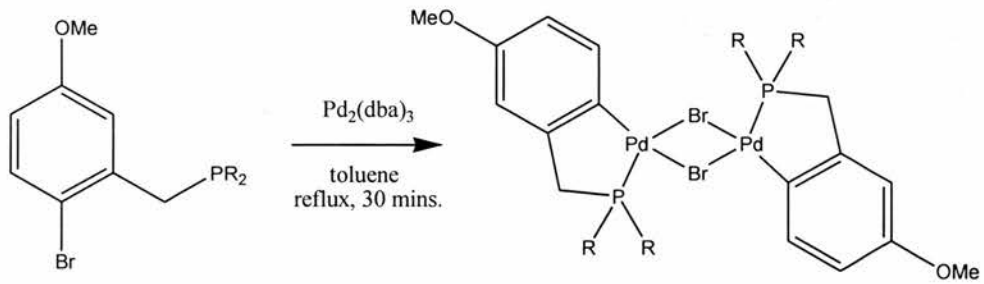


65 R = *t*-Bu, R' = OMe
68 R = *t*-Bu, R' = H
69 R = Et, R' = H
70 R = Ph, R' = H

A number of analogous ligands **68-70** were prepared in a similar manner. These compounds did not have the methoxy substituent *para-* to the bromine, in an effort to show that this group was not required for cyclometallation to palladium to occur. Variation of the phosphine moiety would also provide insight to the cyclometallation process and any potential properties of the complexes synthesised. Unlike all the other ligands synthesised, which were all clear oils, the phenyl derivative **70**, was a solid, which made isolation and purification much easier.

2.2 Cyclometallation of Phosphine Ligands: Preparation of 'Palladacycles'

The main precursor used for the cyclometallation of the *ortho*-bromobenzylphosphine ligands to form palladacycle complexes was tris(dibenzylideneacetone) dipalladium(0), which is a relatively cheap, air-stable, zerovalent palladium compound. Unfortunately, the precursor was not ideal for our purposes. Reaction of a ligand with the palladium precursor would yield large amounts of palladium metal precipitate, as well as the dibenzylideneacetone by-product, which would precipitate out of the reaction solution. These had to be separated before the desired product could be isolated.



65 **71** R = *t*-butyl

Scheme 2-13: Cyclometallation of *o*-bromobenzylphosphine ligand

A high reaction temperature, and thus a high boiling point solvent, was required for the cyclometallation to occur. However, this caused an increase in palladium metal precipitation, and thus the product yields were dramatically lowered. Reaction of the ligand 3-(di-*t*-butylphosphinomethyl)-4-bromoanisole **65** with $Pd_2(dba)_3$ in refluxing toluene eventually yielded the metallated complex **71** after several filtrations and

crystallisations (scheme 2-13). This structure has been fully characterised by ^{1}H and ^{31}P NMR, microanalysis and single crystal x-ray crystallography, an illustration of which is shown in figure 2-1.

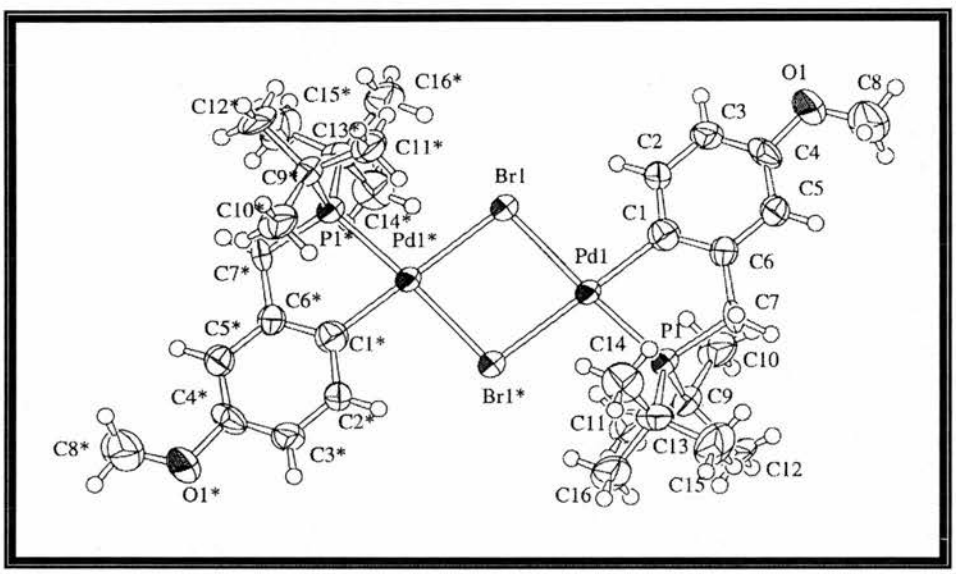
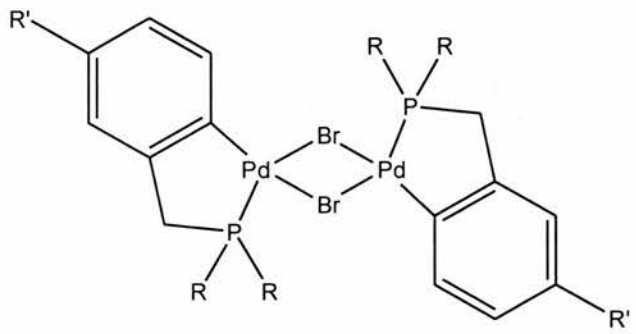


Figure 2-1: Single Crystal X-Ray Structure of Palladacycle 71

The structure of the palladacycle **71** is very similar to that of the Ineos Acrylics complex **50** (see figure 1-1) except for the absence of the pendant phosphinomethyl groups. As a result of this absence, complex **70** is indefinitely stable in air, in a similar manner to the Herrmann palladacycle, while the trivalent phosphorus atoms on the pendant groups of complex **50** are prone to oxidation. Comparison of the crystallographic data of the two compounds shows that loss of the pendant phosphine arm has not affected the structural parameters of palladacycle significantly. Both compounds have similar Pd—C (2.03 Å) and Pd—P (2.23 Å) bond distances and the

C—Pd—P 'bite-angle' of the palladacyclic rings are both around 81°. The distance between the two palladium atoms in both complexes is 3.80 Å.

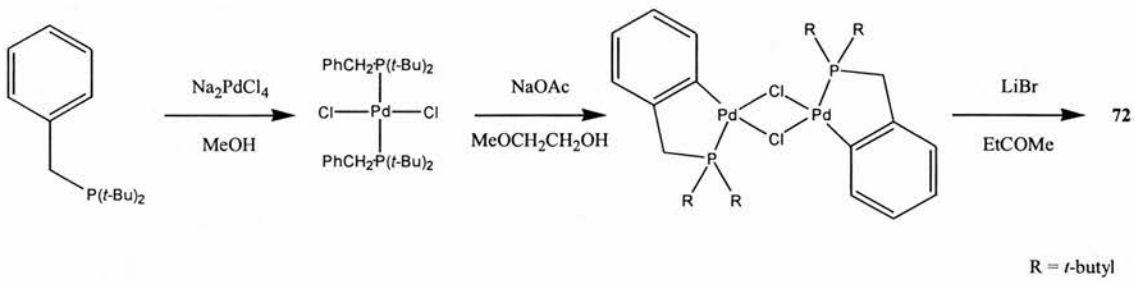


71 R = *t*-butyl; R' = OMe
72 R = *t*-butyl; R' = H
73 R = ethyl; R' = H
74 R = phenyl; R' = H

Metallation of the analogous ligands 2-(di-*t*-butylphosphinomethyl)bromobenzene **68**, 2-(diethylphosphinomethyl)bromobenzene **69** and 2-(diphenylphosphinomethyl) bromobenzene **70** were carried out in a similar manner, except that a higher reaction temperature was required. Mixed xylenes (b.p. 144-145 °C) were found to be an effective solvent for this purpose, to yield three further complexes **72-74**. The attempted preparations of (2-bromobenzyl)dibenzylphosphine, tri-(2-bromobenzyl) phosphine and (2-bromobenzyl)-di-(*o*-tolyl)phosphine (the latter in an attempt to synthesise a complex for direct comparison to the Herrmann complex **5**) for use as ligands were unsuccessful.

2.2.1 Alternative Cyclometallation Methods

Of the four complexes **71-74** synthesised by the above method, only compound **72** has been prepared previously, by Shaw,[104] although a very different method was used (scheme 2-14).



Scheme 2-14: Shaw Preparation of Palladacycle Complex 72

This involved the preparation of a chloro-bridged analogue of **72** via the reductive metallation of *trans*-bis(benzyldi-*t*-butylphosphine)dichloropalladium. This complex was then converted to the bromo-bridged complex **72** by treatment with lithium bromide.

2.2.2 Use of Alternative Palladium Precursors

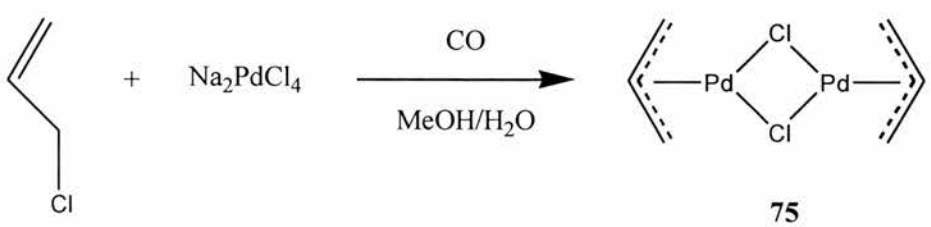
The inefficiency of tris(dibenzylideneacetone)dipalladium(0), $Pd_2(dba)_3$, as a palladium precursor for our metallation reactions has been mentioned previously.

However, a palladium(0) source was necessary, as the oxidative addition of the aryl bromide ligand across the metal centre forms a stable palladium(II) species. $Pd_2(dba)_3$ is a convenient Pd(0) source due to its high air-stability, especially in comparison to the only other commercially available Pd(0) source, tetrakis(triphenylphosphine)palladium(0). As a result, $Pd_2(dba)_3$ is often used as precursors to many catalytic compounds, and indeed is widely used as a catalyst in several reactions. However, the problem of degradation to palladium metal during the lengthy high temperature reactions necessary in the synthesis of compounds **71-74**, led us to investigate alternative, more efficient, methods to generate the palladacycle structure.

Examples of the metallation of phosphine ligands to form five-membered heterocyclic compounds, such as the palladium(II) complexes mentioned thus far, are more common for the related d^8 metals rhodium(I) and iridium(I). For metallation to palladium to occur, steric factors are very important. Most examples reported have bulky *t*-butyl or mesityl substituents on the phosphorus atom, in addition to the group to be metallated. These bulky groups force the carbon atom to be metallated sufficiently close to the palladium, and thus the metallation process is more likely to occur. In many examples, such as the Herrmann and Shaw complexes mentioned above, the palladation involves oxidative addition of a C—H bond, with subsequent elimination of AcOH or HCl respectively. However, the synthesis of our complexes **71-74** is much different. Oxidative addition of the aryl bromide of the phosphine ligand to $Pd_2(dba)_3$ is accompanied by dissociation of dibenzylideneacetone, a solid, non-volatile by-product, which must be extracted from the reaction mixture before the desired product can be isolated. The dba ligand does not aid the metallation process

in any way. Premature dissociation due to the high reaction temperatures involved causes underligation of the second palladium atom of the $Pd_2(dba)_3$ dimer to occur and the unstable palladium coagulates and precipitates out of the reaction solution as palladium black.

In contrast, in the synthesis of the Herrmann complex **5,** it is most probable that this very efficient metallation is actually aided by the ligands on the palladium precursor, $Pd_2(OAc)_2$, with extrusion of two moles of acetic acid occurring during the reaction. No added base is required to effect the cyclometallation of tris(*o*-tolyl)phosphine, but the two excess acetate anions from the palladium(II) acetate must aid the conversion process. It is not unusual for a reaction to be forced to completion when small, volatile by-products are formed during the reaction. By-products volatile enough to be removed from the reaction (in the form of a gas, for example) leads to a shift in the reaction equilibrium towards the products. This led us to investigate the use of alternative palladium precursors containing labile ligands in cyclometallation reactions, which would be extruded as volatile products upon reductive elimination, and aid complex formation in a similar manner.



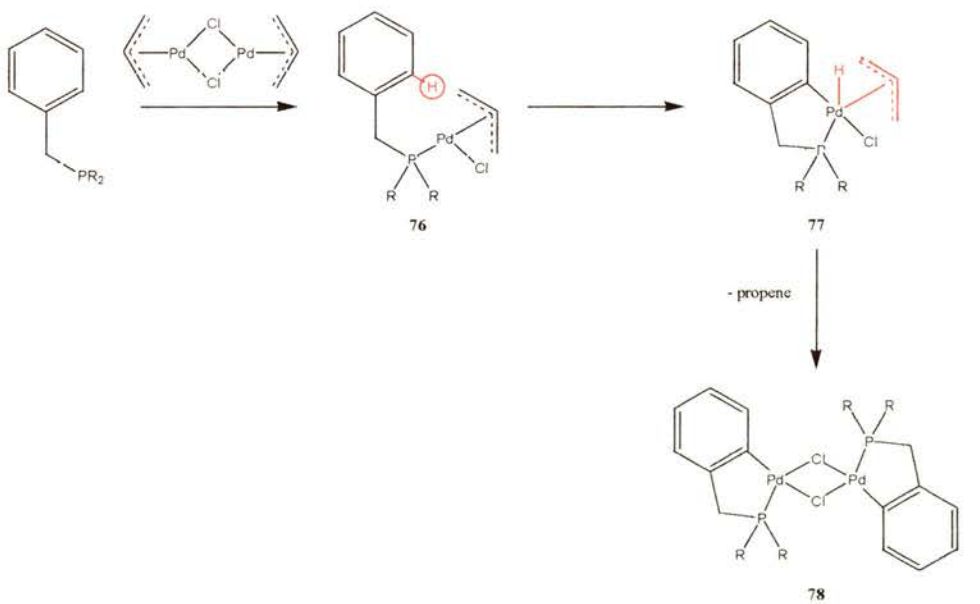
75

Scheme 2-15: Preparation of di-μ-chlorobis(η^3-allyl)dipalladium(II) 75

Many halogen-bridged dimeric palladium species have been reported in the literature which contain labile, unsaturated ligands. One such example is di-μ-chlorobis(η^3-allyl)dipalladium(II) **75** (scheme 2-15).

This complex is prepared by the reaction of allyl chloride with sodium tetrachloropalladate in methanol, using carbon monoxide as a reducing agent.[105] However, this synthesis proved unreliable, with the product often decomposing to palladium black upon aqueous workup. A more robust method involved first dissolving the palladate reagent in water before diluting the solution in methanol.[106]

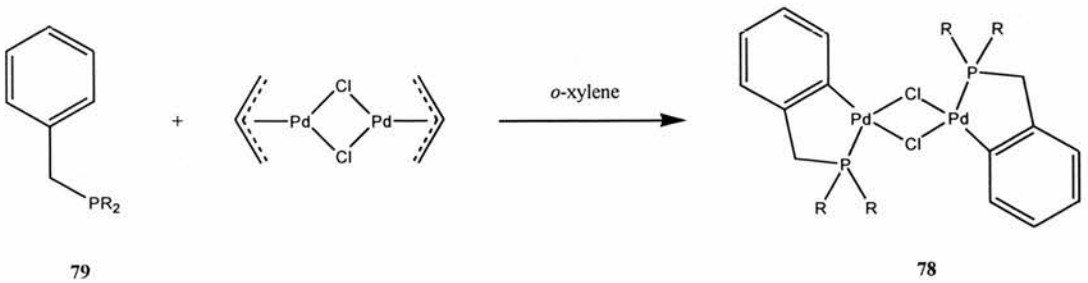
By using complex **75** as a palladacycle precursor, it was thought that the allyl ligands would be extruded as two mole equivalents of volatile propene gas during the formation of the product. A proposed mechanism to yield the chloro-bridged palladacycle product **78** is shown in scheme 2-16.



Scheme 2-16: Proposed mechanism for formation of palladacycle 78 from allyl precursor 75

The first step of the metallation is the coordination of one tertiary benzylphosphine per palladium atom of the dimer to form, via bridge splitting of the dimer, two equivalents of a monomeric allylchloropalladiumphosphine species **76**. This intermediate is then orientated in such a way that the *ortho*- aromatic C—H bond to be metallated (coloured in red) is in the vicinity of the palladium centre. This is favoured if sterically bulky groups are situated on the phosphine moiety. The next step, metallation to form a palladacyclic hydride monomer **77**, is the rate determining step of the mechanism. Formation of similarly unusual 14-electron palladium(IV) species have been previously reported to be necessary for cyclometallation to occur,[107] but in this instance oxidative addition of a relatively unreactive aromatic C—H bond across the palladium centre is a step dependent on the steric and electronic environment of the surrounding ligand shell. Extrusion of propene by the reductive elimination of the hydride and the allyl ligand from the reactive intermediate **77** is a much more favoured process, and the resultant underligated monomer is isolated as the stable chloro-bridged dimeric species **78**.

As mentioned above, for the metallation of the phosphine ligand to occur, the formation of the palladium(IV) species **77** is necessary. Unfortunately, due to the steric and electronic requirements, only certain ligands will undergo this transformation. Firstly, as for the metallation reaction reported above by Shaw,[104] only sterically bulky phosphines can force the required C—H bond into the conformation required for cyclopalladation. As a result, only benzyldi-*t*-butylphosphine **79** was found to successfully undergo metallation by this method (scheme 2-17).



79 78

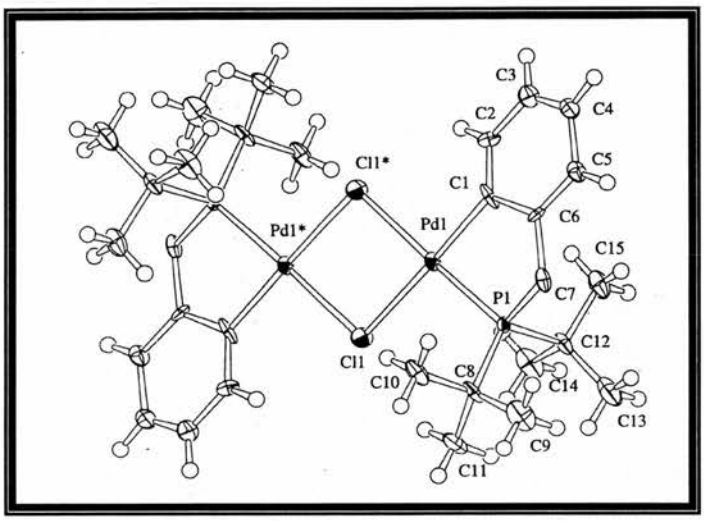
R = *t*-butyl

Scheme 2-17: Preparation of palladacycle by use of allyl precursor

The reactions of several other tertiary benzylphosphines with the allyl dimer **75** were attempted, including tribenzylphosphine, dibenzylphenylphosphine and benzyldiphenylphosphine, without success. This has led to the assumption that the substituents on the phosphorus atom must be electron-donating, as well as sterically bulky, for the metallation to proceed. The only product obtained when aromatic substituted (electron-withdrawing) tertiary phosphines were reacted was the dichlorobisphosphinopalladium species. Treating this compound with base (even a very strong base such as *n*-butyllithium), as per the Shaw method (see scheme 2-14), did not yield the desired cyclometallated product.

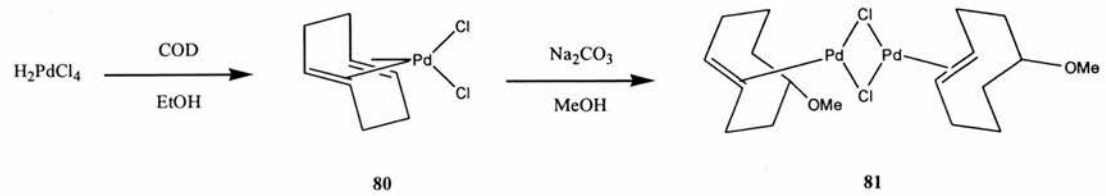
Although benzyldi-*t*-butylphosphine was the only ligand to successfully yield a cyclometallated product by this method, it does provide an elegant, one step synthesis (as compared to the two steps required to obtain the same compound by the Shaw method) to the palladacycle **78**. The identity of this product has been confirmed by x-ray crystallography (figure 2-2).

Figure 2-2: Single Crystal X-Ray Structure of Palladacycle 78



The x-ray crystal structure of this complex was similar to those of palladacycles **50** and **71**, with the palladium—phosphorus (2.23 Å) and palladium—carbon (2.03 Å) bond distances being virtually identical. However, the change of the bridging atoms from bromo- to chloro- are perhaps responsible for the slightly larger carbon—palladium—phosphorus angle (83.5° vs. 81° for **50** and **71**) and the shorter inter-palladium distance (3.65 Å compared to 3.80 Å).

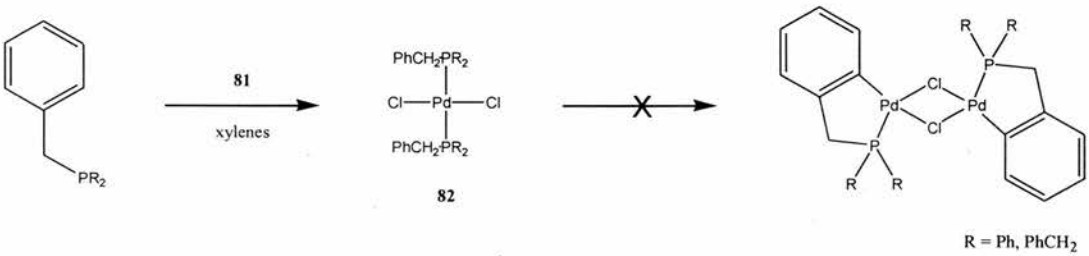
In order to attempt to induce the metallation of other benzyl phosphines, a second alternative palladium precursor was synthesised for use in a similar manner as the allyl palladium dimer **75**. The preparation of μ-dichlorobis(8-methyoxy-4-cycloocten-1-yl)dipalladium(II) **81** was prepared straightforwardly via dichloro(1,5-cyclooctadiene)palladium(II) **80** (scheme 2-18).[108]



80 81

Scheme 2-18: Preparation of cyclooctadiene(COD)-based dimer 81

A number of tertiary phosphines were reacted with this COD-based palladium precursor. Phosphines such as tribenzylphosphine and benzyldiphenylphosphine were chosen in an effort to produce palladacyclic compounds with substituent groups other than *t*-butyl on the phosphine moiety. However, reaction of these phosphines with complex **81** in refluxing xylene resulted only in the formation of the bisphosphino compound **82** (scheme 2-19).



82

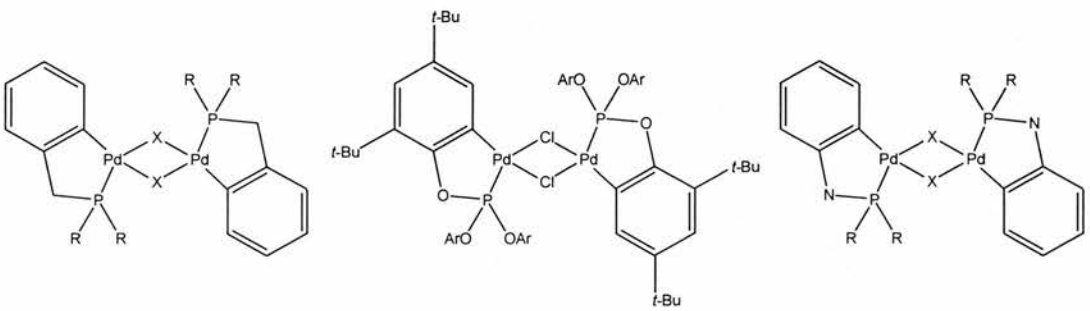
Scheme 2-19: Reaction of complex 81 with tertiary phosphines

These bisphosphino palladium complexes are similar to the intermediates formed in the Shaw preparation of palladacycles. However, as these compounds do not possess the sterically bulky (i.e. mesityl, *t*-butyl) groups on the phosphine moiety necessary

for palladation, conversion of these compounds to the corresponding palladacycle by, for example, the use of base (see scheme 2-14), was unsuccessful.

2.2.3 Aminophosphines Ligands – Attempted Preparation of N-Containing Palladacycle Complexes

The palladacycle complexes synthesised thus far have the general structure **83**, based on tertiary phosphine ligands with at least one benzyl group, which forms the palladacycle.

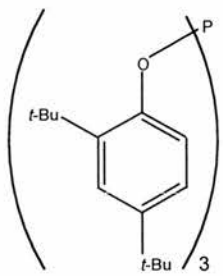


83 **21** **84**

Ar = 2,4-di-*t*-butylphenyl
X = Br, Cl

Comparing the structure of **83** with that of the phosphite-based complex of Bedford, **21** (see scheme 1-16), there are many similarities. The same 'benzyl' structural template is evident, with the CH_2 of **83** being replaced with the oxygen atom of the phosphite ligand in complex **21**. The high catalytic activity of the phosphite palladacycle **21** towards the Heck and Suzuki coupling reactions has been widely reported.[57, 87] It was thus decided to attempt the synthesis of an analogous nitrogen-containing palladacyclic complex of the general structure **84**, via the metallation of an aminophosphine ligand rather than a phosphine or phosphite. As complex **84** would have similar electronic properties to the active phosphite analogue **21**, an aminophosphine-based complex would be a promising candidate as a potential Heck

catalyst. This assumption can be further supported by the fact that the thiophosphine-based analogue has also been recently reported as an active coupling catalyst.[59]



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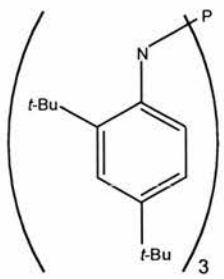
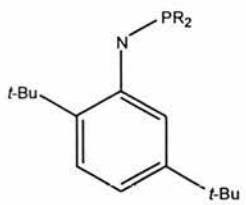


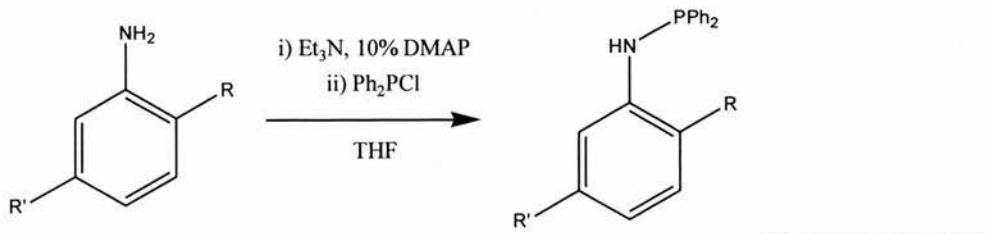
85



86

The Bedford complex **21** is prepared by the metallation of the commercially available trisphosphite ligand **20**. Synthesis of a direct aminophosphine analogue, tris(2,4-di-*t*-butylphenylamino)phosphine **85** would prove difficult due to the substituent pattern on the aromatic amine – the necessary 2,4-di-*t*-butylaniline starting material is not commercially available, and would require several steps to synthesise. The presence of the sterically bulky *t*-butyl groups on the aromatic ring are essential for the metallation of the phosphite **20** and thus would also be necessary on any aminophosphine analogue. However, a similar ligand, **86**, could be synthesised from 2,5-di-*t*-butylaniline, which *is* commercially available.

The linking of an amine to a chlorophosphine is a well known reaction.[109] However, even using a strong base, the yield obtained in the reaction of 2,5-di-*t*-butylaniline with chlorodiphenylphosphine was poor. This problem was overcome by the addition of a catalytic amount of *N,N*-dimethylaminopyridine (DMAP), which furnished (2,5-di-*t*-butylphenylamino)diphenylphosphine **86** in 51 % yield (scheme 2-20).

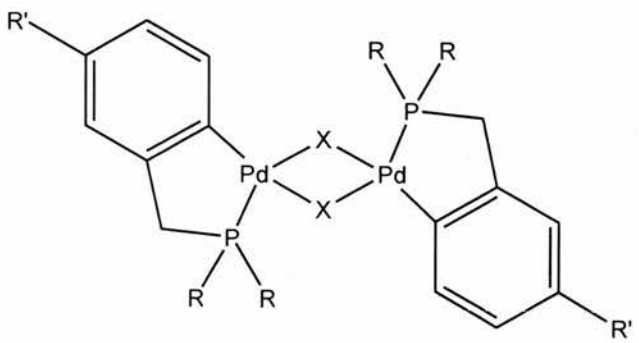


86 R = *t*-Bu, R' = *t*-Bu
87 R = Br, R' = H

Scheme 2-20: Preparation of Aminophosphine Ligands

Unfortunately, all attempts to cyclometallate this ligand failed. Before this approach can be fully dismissed the direct analogue of the Bedford ligand, tris(2,4-di-*t*-butylphenylamino)phosphine **85** must be prepared, but due to time constraints this was not attempted. In an alternative attempt to prepare nitrogen containing palladacycle analogues, through the oxidative addition of *ortho*-bromo ligands, (2-bromophenylamino)diphenylphosphine **87** was prepared in a similar manner to **86** in 61 % yield. Evidence of cyclometallation of this compound by reaction with $Pd_2(dba)_3$ in *o*-xylene was not conclusive - material of a suitable purity could not be isolated from the reaction liquors. At this point, attempts to prepare cyclometallated aminophosphine compounds were abandoned, and investigations were focussed on the catalytic activity of the cyclometallated benzylphosphine compounds.

2.3 Summary



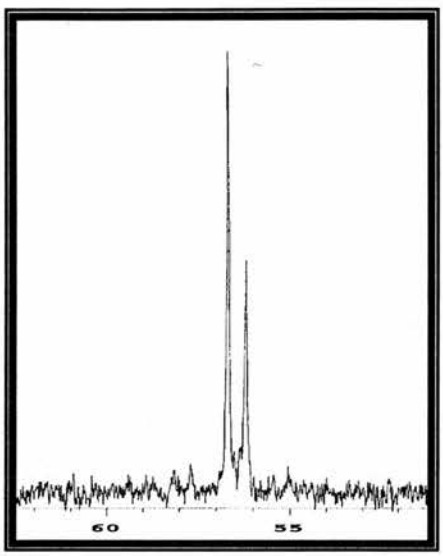
71 R = *t*-butyl; R' = OMe; X = Br
72 R = *t*-butyl; R' = H; X = Br
73 R = ethyl; R' = H; X = Br
74 R = phenyl; R' = H, X = Br
78 R = *t*-butyl; R' = H, X = Cl

In total, five complexes were synthesised, via three methods. Complexes **71-74** were prepared in the same way, via the oxidative addition of a *ortho*-bromobenzylphosphine ligand to a palladium(0) precursor ($Pd_2(dba)_3$) by refluxing in a high boiling solvent, such as xylene. The instability of the palladium precursor to the reaction conditions resulted in significant palladium precipitation (palladium black formation) and low yields of the desired complexes were obtained. The chloro-bridged complex **78** is identical to compound **72**, except for the difference in the nature of the bridging halogen ligands. This compound was prepared using two approaches – via the formation of the bisphosphinopalladium complex (see scheme 2-14), and in one step by the reaction of benzyldi-*t*-butylphosphine with the palladium(II) allyl dimer **75** (see scheme 2-17).

All five complexes are yellow, air-stable crystalline solids, although unfortunately, the crystals obtained from the ethyl and phenyl complexes (**73** and **74**) were unsuitable for single crystal x-ray analysis. The compounds have distinctive ^{31}P NMR spectra, and as a result the technique was used as an effective in-process check

to identify the presence of the desired product during cyclometallation reactions. The ^{31}P NMR spectrum of the phenyl complex **74**, along with resonance details of all five complexes, is shown in figure

2-3.

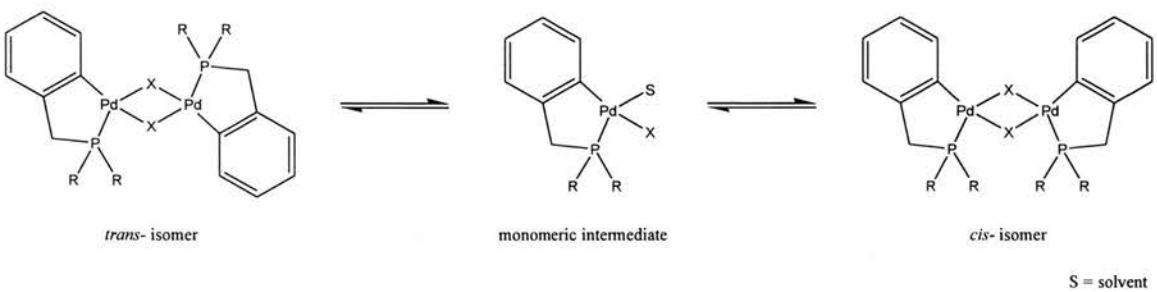


	δ_P (ppm)	δ_P (ppm) Free Ligand
71	**99.4(s), 99.6(s)**	**33.9(s)**
72	**95.0(s), 95.2(s)**	**34.6(s)**
73	**68.7(s), 70.1(s)**	**-13.6(s)**
74	**56.2(s), 56.7(s)**	**-12.3(s)**
78	**101.8(s), 102.2(s)**	**35.4(s)**

Figure 2-3: ^{31}P NMR Spectrum of Complex 74, with details of complexes in table

The ^{31}P NMR spectra of the complexes are all similar in that all of the compounds exhibit a characteristic pair of singlets at room temperature. The peaks of the complexes which possess substituents on the phosphorus atom which are more electron-donating (e.g. compound **72**, R = *t*-butyl, δ_P 95.0(s), 95.2(s)) appear more downfield than those with electron-withdrawing groups (compound **74**, R = phenyl, δ_P 56.2(s), 56.7(s)). The explanation behind the appearance of these two singlets is subject to debate. The phenomenon is also seen in similar compounds such as the Herrmann palladacycle **5**. Herrmann has suggested that they arise due to the complex existing as an equilibrium of monomeric and dimeric species in solution due to the

bridge-splitting effects of coordinating solvents. What seems more likely is that these complexes are mainly in the *trans*- conformation in solution at room temperature (giving rise to the larger of the two singlets in the ^{31}P NMR spectrum), with a small amount of the *cis*- isomer also present. These two conformations interconvert via monomeric intermediates at room temperature (scheme 2-21).



trans- isomer monomeric intermediate *cis*- isomer

S = solvent

Scheme 2-21: Proposed equilibrium of palladacyclic structure in solution

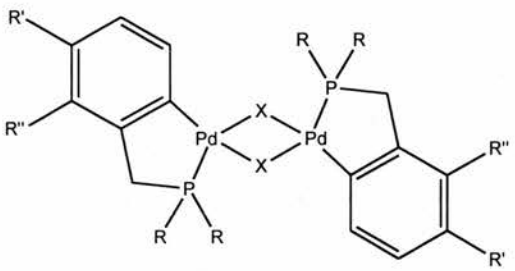
On cooling the complexes to temperatures below –40 °C only one singlet is observed in the ^{31}P spectrum, suggesting that only the kinetically stable *trans*- isomer is present at low temperatures. From x-ray crystallography data, it is clear that only the *trans*-conformer is present in the solid state.

Of the five complexes synthesised and described above, both the *t*-butyl compounds **72** and **78** have been synthesised previously, by a different method, by Shaw.[104] However, the compounds with substituents other than *t*-butyl on the phosphino moiety, **73** and **74**, and the methoxy- substituted **71**, are, to our knowledge, new compounds.

There is evidence to suggest that bulky, electron-donating substituents, such as the *t*-butyl group, are necessary, either on the aromatic ring or the phosphino moiety, to effect cyclometallation of benzyl-type ligands of this kind. However, by introducing a bromine atom in a position *ortho-* to the α-carbon, the *ortho*-metallation process can be facilitated by providing a bond more reactive than the aromatic-hydrogen linkage that is required to be broken in the oxidative addition process. In this instance, sterically bulky, electron-donating substituents are not required on the ligand, and analogues with electron-withdrawing aromatic groups on the phosphino moiety can be prepared. This is of particular importance, as it has been frequently reported that electron-withdrawing groups on the phosphorus enhance the catalytic activity of palladacyclic compounds in coupling reactions.

CHAPTER 3

3. CATALYTIC INVESTIGATION OF SYNTHESISED PALLADACYCLE COMPLEXES



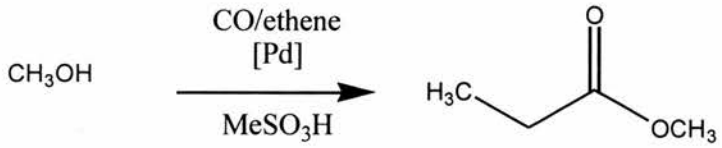
50 R = *t*-butyl; R' = OMe; R'' = $CH_2P(t\text{-Bu})_2$; X = Br
71 R = *t*-butyl; R' = OMe; R'' = H; X = Br
72 R = *t*-butyl; R' = H; R'' = H; X = Br
73 R = ethyl; R' = H; R'' = H; X = Br
74 R = phenyl; R' = H, R'' = H; X = Br
78 R = *t*-butyl; R' = H, R'' = H; X = Cl

As described in the previous chapter, five palladacycle complexes were synthesised (compounds **71**, **72**, **73**, **74** and **78**, above). Unfortunately, the target compound, complex **50**, which had previously been shown to be an active catalyst for the methoxycarbonylation of alkenes by Ineos,[94, 96] had not been successfully isolated. However, it was decided to continue with catalytic studies of the synthesised palladacycles that had been prepared. Results from these investigations would hopefully yield information on why complex **50** was catalytically active. For instance, were the phosphinomethyl 'pendant arms' on the Ineos complex necessary for catalysis, or would complex **71** (identical to **50** except for the pendant arms) exhibit similar activity? If so, this would have distinct advantages – in contrast to compound **50**, complex **71** is indefinitely air-stable. This is due to the absence of the phosphino pendant arms, which are prone to oxidation, and thus compound **71** is more convenient to handle. Similarly, if complex **71** was indeed found to be catalytically active, would the presence of the methoxy substituent on the aromatic ring of the palladacycle give the compound enhanced activity compared to an analogous complex

with no substituents (complex **72**)? What effect would varying the moiety on the metallated phosphorus atom have on the catalytic activity of the complex? Although some of these complexes had been characterised previously, results of catalytic investigations into this type of complex had not been reported. By attempting alkene carbonylation reactions using these compounds as catalysts, it was hoped that the trends observed from the experimental results would give an insight to the structural-property relationship of the palladacycle. In addition, due to the similarity of the complexes synthesised to that of the Herrmann compound **5**, it was intended to investigate the catalytic activity of these compounds towards carbon-carbon cross-coupling reactions, such as the Heck reaction.

3.1 Alkene Carbonylation

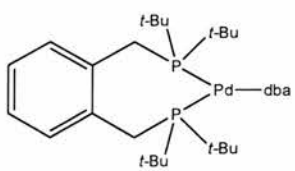
As the 'pendant-arm' complex **50** had not been successfully prepared, the original catalytic investigations performed by Ineos could not be confirmed. As a result of this, any comparisons to results obtained with the other complexes would be difficult to justify if any of the reaction conditions varied to those used in the original research. In an effort to minimise these variations, the catalytic investigations of the five palladacyclic compounds (**71-74**, **78**) towards alkene carbonylation were conducted at the Ineos laboratories, Wilton, UK, using the same reaction autoclave and conditions used in the original experiments with complex **50**.



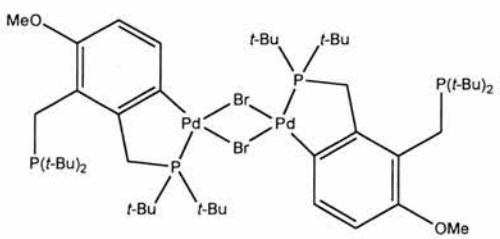
88

Scheme 3-1: Attempted methoxycarbonylation of ethene using palladacyclic complexes

The test reaction used was the methoxycarbonylation of ethene to form methyl propanoate **88** (scheme 3-1), a substance used by Ineos in the manufacture of methyl methacrylate (MMA), a polymer precursor. The effectiveness of the chelated bisphosphino complex **39** as a catalyst for this reaction has already been reported by Ineos.[91] The pendant-arm palladacycle complex **50** was also found to be catalytically active towards carbonylation, but significantly less active than complex **39**.[96]



39



50

For methoxycarbonylation reactions using complexes **39** and **50** as catalyst precursors, methanesulfonic acid was required to activate the catalyst. In a study conducted by Ineos,[94] it was found that for complex **50**, two equivalents of acid were required to achieve optimum activity, while too much acid significantly affects catalyst performance. However, the presence of acid is not vital for catalytic activity,

as reasonable performance was obtained when no acid was added. The precise mechanism for the activation of the catalyst, and the catalytic cycle itself, is unknown, but is assumed to occur via the rupture of the five-membered palladacycle. Indeed, an *in situ* ^{31}P NMR study showed that by using an excess of methanesulfonic acid, there was strong evidence to suggest that the palladacycle compound had been completely converted to a non-metallated intermediate. However, a more detailed study has been conducted into the mechanism of the more active chelate complex **39**, and the catalytic cycle of the carbonylation reaction using **39** as the catalyst has been proven by spectroscopic characterisation (see scheme 1-27).[93] This mechanism shows that the bisphosphino ligand remains chelated to the palladium atom throughout the reaction.

The catalytic activity of the closest analogue to the palladacycle **50**, complex **71**, was investigated first. Immediately an unexpected problem was encountered in that the palladium complex was completely insoluble in the reaction solvent, methanol. It was therefore necessary to dissolve the catalyst in a small amount of dichloromethane before charging the reaction solvent, thus changing the reaction conditions with respect to those used in the original investigations. Whether this change affected the following results is unknown. The catalyst solution was then treated with ten equivalents of methanesulfonic acid, and the reaction mixture heated to 90 °C. The two substrates, ethene and carbon monoxide, were then introduced to the reaction autoclave as a 1:1 gaseous mixture, at a pressure of 10 bar. After one hour no decrease in pressure had been observed, which would have indicated that reaction had occurred (due to two gaseous reagents forming one molar equivalent of liquid product), so the temperature was increased to 120 °C. After a total of 1.5 hours, no

reaction had been observed, so the experiment was ceased. Upon examination of the reaction mixture a large amount of palladium precipitate was observed, suggesting complete decomposition of the catalyst. Analysis of the reaction mixture by GC-MS revealed that only a trace amount of product, methyl propanoate, had been formed. The reaction was repeated using two equivalents of methanesulfonic acid, and then with no acid at all, and a similar result was obtained each time – large amounts of palladium precipitate, and only a trace of methyl propanoate produced.

Complexes **72**, **73**, **74** and **78** were investigated in a similar manner. In each case palladium precipitation was observed, with little or no product formed. A summary of these results is shown in table 3-1.

Table 3-1: Methoxycarbonylation reactions using palladacycle complexes as catalyst precursors

Run	Complex	Equivs. $MeSO_3H$	Time @ 90 °C (min)	Time @ 120 °C (min)	Pd ppt observed?	Product
1	**71**	10	60	30	Yes	Trace
2	**71**	0	60	220	Yes	Trace
3	**71**	2	60	0	Yes	Trace
4	**72**	2	60	0	Yes	Trace
5	**73**	2	60	0	Yes	Trace
6	**74**	2	60	0	Yes	Trace
7	**78**	2	80	0	Yes	Trace

Reaction conditions: 50 mg of complex dissolved in 5 cm^3 dichloromethane. 80 cm^3 methanol added, followed by acid (except entry 2). Autoclave heated to 90 °C, then pressurised with 10 bar 1:1 ethylene/carbon monoxide. Temperature maintained at 90 °C for at least 60 minutes, then heated to 120 °C (entries 1 and 2).

From this investigation it is clear that the five complexes tested are poor catalysts for the methoxycarbonylation of ethene under these reaction conditions. As the results for the reaction runs with and without methanesulfonic acid (runs 1 and 2) were similar, it is evident that it is not necessarily the acid that is responsible for the

decomposition of the catalyst. From the previous investigations of the Ineos complex **50**, should the hypothesis that the palladacycle ring is ruptured during the catalytic cycle be assumed true, one may suggest that the resultant non-metallated intermediate is stabilised by coordination of the free 'pendant' phosphine to the palladium. Although methanesulfonic acid is required for optimum performance, it can be assumed that the demetallation of the palladacycle can still occur in the absence of acid (thus accounting for the catalytic activity of **50** with no acid added) under these reaction conditions. However, with complexes **71**, **72**, **73**, **74** and **78**, no pendant phosphine is present, and thus no stabilisation can occur once the palladacycle is ruptured. Without the necessary phosphine ligands to stabilise the palladium complex, decomposition to palladium black is rapid.

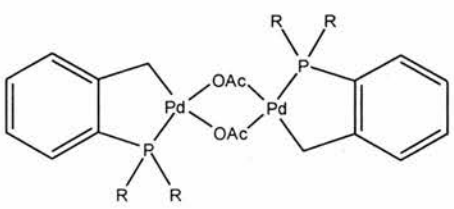
Evidence to support the above theory is provided by Herrmann, who reported that the Pd—C bond in the Herrmann palladacycle **5** can readily be cleaved by the insertion of CO, followed by reductive elimination, thus rendering the complex useless for carbonylation reactions.[66, 110] It seems reasonable to suggest that the reduction of other five-membered palladacycles, such as those tested for activity towards alkene methoxycarbonylation, to underligated palladium complexes also occurs readily in the presence of carbon monoxide. Although these underligated species are highly reactive catalysts in cross-coupling reactions such as the Heck reaction, they are obviously unstable under carbonylation reaction conditions, and rapidly decompose to palladium black. The precise mechanism for this decomposition is unknown.

In conclusion, it is evident that palladacyclic complexes such as compound **71** are not active methoxycarbonylation catalysts under the conditions investigated. This is in

contrast to the reasonable catalytic activity exhibited by complex **50** under near identical reaction conditions. Therefore the presence of the di-*t*-butylphosphinomethyl 'pendant-arms' on complex **50** must have a direct stabilising effect on the catalytic intermediates present in the reaction cycle, as complex **71** is identical to **50** except for the absence of these substituent groups. From experimental evidence and previous reports in the literature, we can assume that the palladacyclic ring is ruptured in the presence of carbon monoxide. We can also assume that although a certain amount of methanesulfonic acid is required for the optimum catalytic activity of complex **50**, the acid may contribute to catalyst decomposition. Upon breakdown of the palladacycle **50**, catalysis can occur via intermediates stabilised by coordination of the free pendant phosphino group. The mechanism of this reaction is not fully understood. Complexes without the pendant phosphino arm break down to give intermediates which are too unstable under these reaction conditions, and rapidly decompose to inactive palladium black.

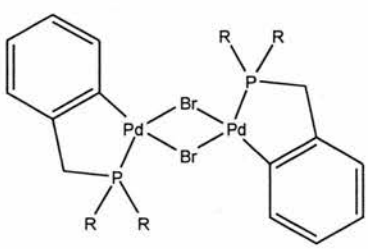
3.2 Arylation of Alkenes – The Heck Reaction

As mentioned previously, the Heck reaction is a highly versatile palladium catalysed cross-coupling reaction between alkenes and aryl halides or triflates. There have been a number of palladacycle compounds that have been recently reported to exhibit extraordinarily high activity towards the Heck reaction, for example, the complexes of Herrmann[43, 44] and Bedford.[57] Due to the structural similarities of these complexes to the metallated benzylphosphine complexes prepared by us, it was decided to investigate whether our complexes were also active Heck catalysts.



5

R = *o*-tolyl

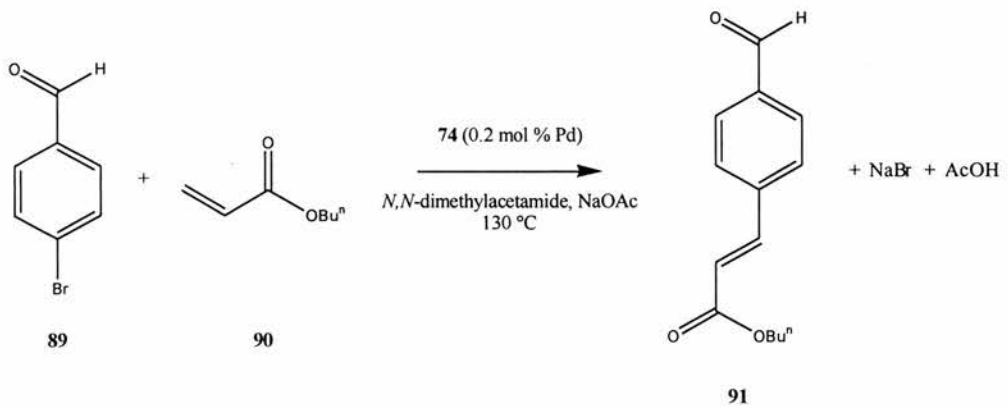


74

R = phenyl

Herrmann has reported that electron-withdrawing aryl substituents (e.g. *o*-tolyl, mesityl) on the phosphino moiety of palladacycle **5** gives superior catalytic performance in cross-coupling reactions than analogues with electron-donating alkyl groups (e.g. *t*-butyl).[66] With this in mind, the obvious choice for which of our compounds to investigate first was the phenyl-substituted palladacycle **74**, which was the only compound of the five complexes synthesised to possess electron-withdrawing

groups on the phosphorus. Most of the work discussed here will focus on this complex.



Scheme 3-2: **Heck coupling of 4-bromobenzaldehyde with *n*-butyl acrylate using complex 74 as catalyst**

The first investigative Heck reaction utilising complex **74** as the catalyst was the coupling between 4-bromobenzaldehyde **89** and *n*-butyl acrylate **90** (scheme 3-2). Both reagents are known to be highly active substrates in the Heck reaction, and were sensible choices for such an exploratory experiment, as a positive result (i.e. at least partial conversion of the reagents to the desired product, *n*-butyl (*E*)-4-formylcinnamate **91**) would occur quickly, if at all. A relatively high catalyst concentration (compared to the low concentrations stated in the literature for the Herrmann complex) was used in this first instance, so a positive result would hopefully be large enough to be easily measurable. Indeed this was found to be the case, with the bromobenzaldehyde **89** being completely converted to the cinnamate product **91** within 4 hours at 130 °C. No other product was obtained, even in trace quantities. Although this related to a turnover number (moles of product obtained per mole of palladium used) of only 500, the result showed that complex **74** exhibits

catalytic activity which was worthy of further investigation. By conducting further experiments using lower catalyst concentrations, the full potential of this type of palladium complex would be realised.

3.2.1 Measurement of Reaction Progress

Reactions can be followed in a number of ways, including *in situ* monitoring or sampling techniques. For our purposes, the measurement of the conversion of the reagents to reaction products was accurately yet conveniently obtained by gas chromatography (GC), although gas chromatography—mass spectrometry (GC-MS) was routinely used in addition to this technique to confirm the identity of the products and to aid the identification of any unexpected by-products. The main advantage of gas chromatography as a monitoring technique (or 'in-process check') for this type of catalytic reaction was that samples could be taken directly from an ongoing reaction to rapidly obtain an accurate composition of the reaction mixture. A sample of the reaction mixture would be taken immediately before the catalyst was added (a 't = 0' sample). This would give a starting ratio of the two reagents in the mixture. By noting the exact time at which the catalyst was added to the solution, the rate of the reaction could be calculated in terms of catalyst turnover numbers per hour (or turnover frequency) between t = 0 and the time the next sample was taken.

However, although GC can be a very accurate tool for obtaining *relative* ratios of components in a mixture, the technique cannot give the absolute measurement of the

quantity of the component in the entire reaction vessel. To obtain this, the ratio of the measured reagent to a non-reactive compound of known concentration in the mixture must be calculated. This technique is known as referring to an *internal standard.* By noting the starting ratio of the reagent to the internal standard, the consumption of the reagent (percentage conversion) and formation of products (percentage yield) can be accurately measured. The choice of the internal standard is very important. The compound must not react with any of the other reaction components (i.e. the reagents, the products, the catalyst or any solvent), as this would affect the ratio obtained. Neither must the standard interfere or inhibit the reaction, for example by altering the solubility properties of the reagents or the viscosity of the reaction mixture. Finally, the internal standard must be consistently detectable by GC, with as little deviation in retention time as possible, so that its identity is never in question. Compounds with excessively long retention times are poor references for this reason. Therefore, the standard must be reasonably volatile (so to have a short retention time), but completely unreactive in the reaction medium.

For our investigations, naphthalene was used as the internal standard. Herrmann had used diethyleneglycol di-*n*-butyl ether as the reference compound for much of his work. GC standardisation experiments showed that the concentration of naphthalene in the reaction medium could be detected with remarkable accuracy and consistency, and therefore the aromatic compound was chosen as the preferred internal standard.

The reaction mixtures were easily prepared by charging the solid reagents and the solvent to the reaction flask, degassing the mixture thoroughly by repeatedly evacuating the reaction vessel and purging with argon, then adding the more volatile

alkene reagent, which had been degassed previously, via syringe. This was done to ensure that none of the alkene was lost by evaporation during the degassing process. The internal standard, naphthalene, was added in an amount corresponding to 0.5 molar equivalents with respect to the aryl reagent. The mixture was then heated to the reaction temperature (usually 130 — 170 °C) and a 't = 0' sample taken immediately before the catalyst was injected as a solution via syringe. Samples were then taken at regular intervals: hourly, every three or four hours, or even every 12 hours, depending on the expected rate of reaction. By analysing the samples, the decrease in the ratio of aryl reagent to naphthalene could be measured, with the difference in this ratio expressed as a percentage (with respect to the starting ratio) giving the reagent conversion. Conveniently, from an analytical point of view, the catalyst **74** was shown to be completely inactive below 100 °C — therefore by removing a sample from the reaction flask, the reaction within that sample is effectively stopped immediately. This was shown to be the case when a sample was reanalysed several days after it was originally taken, and was found to give the same component ratio. As a result, the analyses were shown to be accurate representations of the reaction mixture at the time that the sample was taken, without any sort of quenching of the reaction mixture required when collecting the sample.

3.2.2 Heck Reaction of Bromoaromatic Substrates

With a confirmed Heck catalyst in complex **74** to investigate, and an accurate, convenient and reliable method with which to monitor reactions, it was important to set research objectives for this new development within the project. The original aim of developing a new catalyst for alkene carbonylation had been dispelled, and with a limited time constraint, parameters for this new investigation had to be chosen carefully.

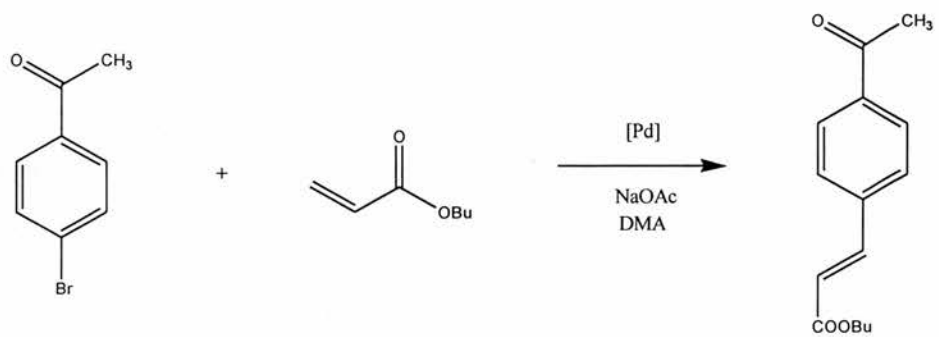
The variable reactivity of substrates in the Heck reaction is well known. For the aryl substrate, the nature of the aryl-halide bond is important in determining its reactivity. The aromatic C—I bond of aryl iodides is more reactive than the C—Br bond of aryl bromides. Both bonds are much more reactive than the corresponding carbon—chlorine bond of chloro analogues. This is where the challenge lies, as the unreactive chloroaromatics are significantly less expensive than the corresponding bromide or iodide analogue. As this is a potentially cheaper route to the same product, the successful utilisation of chloroaromatics as substrates in the Heck reaction is the 'holy grail' of chemists working in this area. Of course, a study would have to be conducted to investigate if the conversion of aryl chlorides to Heck products would take place in the presence of complex **74**. However, it was first necessary to thoroughly examine how efficient the catalyst is when aryl bromides are used as substrates, and how its performance compares with those of existing catalysts.

The reactivity of bromoaromatic compounds as Heck reaction substrates is determined by the nature of the substituent(s) on the aromatic ring. The most reactive reagents are compounds with electron-withdrawing substituents, such as formyl (-COH) and acetyl ($-COCH_3$), which pull electron density away from the aryl-halide bond, making the bond weaker, and more susceptible to oxidative addition across palladium — the widely acknowledged rate-determining step of the Heck reaction. Conversely, aromatics with electron-donating groups, such as alkyl or alkoxy, allow a high level of electron density to remain between the carbon and bromine atoms of the aryl-halide bond, effectively strengthening the bond and lowering the reactivity of the substrate.

As a result, 'activated' bromoaromatics (those with electron-donating substituent groups) give the most impressive results catalytically. Less catalyst is required to achieve complete reaction, and the rate of reaction is faster than when less active substrates are used. If a reaction can be completed with a lower catalyst concentration, impressive catalyst turnover numbers and turnover frequencies ensue. In the recent literature it has become common for the performance of Heck catalysts to be compared to one another by the turnover number achieved for a particular reaction involving two very reactive substrates – 4-bromoacetophenone and *n*-butyl acrylate. Herrmann has achieved turnover numbers of up to 1,000,000 (mol product/mol Pd) within 24 hours for this reaction using palladacycle **5** as catalyst, obtaining a product yield of 99 %, although 20 mol % of a promoting salt (tetrabutylammonium bromide) was used.[66] Using the Bedford catalyst **21**, the same result (100 % product yield, 1,000,000 turnover numbers) is obtained in 6 hours with no promoting salts, although a temperature of 160 — 165 °C is used compared to 130

°C in the case of the Herrmann example.[57] Both complexes are obviously very efficient catalysts, and the results are phenomenal due to the reactivity of the substrates used.

Table 3-2: Heck reaction of 4-bromoacetophenone with *n*-butyl acrylate



92

Entry	Catalyst (mol % Pd)	Additive (mol %)	Temp (°C)	Time (h)	Conversion (%)[a]	Yield (%)[b]	TON[c]
1[d]	0.0002	—	160	20	86	85	425,360
2	0.00002	—	160	144	82	72	3,590,400
3	0.0002	—	130	24	59	58	291,030
4	0.0002	—	130	143	89	88	442,270
5	0.00004	—	130	24	17	3	70,975
6	0.0001	—	150	20	40	33	332,000
7	0.0001	—	130	20	23	19	183,870
8	0.0001	Bu_4NBr (20)	130	20	22	16	161,330
9	0.0002	—	160	6	99	91	454,000
10	0.000002	—	160	72	42	2	972,750

Reaction conditions: 50 mmol aryl bromide, 100 mmol *n*-butyl acrylate, 25 mmol naphthalene, 50 cm^3 DMA, catalyst (complex 74) injected as a solution in DMA. [a]Determined by GC. [b]Determined by GC. [c]Moles of desired product per mol% Pd catalyst. [d]70 mmol *n*-butyl acrylate used.

To investigate how complex **74** compared to these two catalysts in terms of performance, a number of experiments were conducted using the same two substrates, base (sodium acetate), solvent (DMA) and reagent concentrations as both the

Herrmann and Bedford studies. A summary of the results obtained for this reaction, the coupling between 4-bromoacetophenone and *n*-butyl acrylate to form the cinnamate product **92**, is displayed in table 3-2.

The results obtained for this reaction were varied, and the reasons for this were not immediately obvious. Take for example entries 1 and 2, in which the experiments differed only in the catalyst concentration used. As one may expect, the experiment with the lower catalyst concentration (entry 2) requires a much longer reaction time to reach a substrate conversion comparable to that obtained when more catalyst is used (entry 1). However, product selectivity is also sacrificed, so, despite a higher turnover number being achieved, this together with the long reaction time limited the practicality of using such a low catalyst concentration. Nevertheless, a turnover number of over 3.5 million (entry 2) exceeds any others that have been reported in the literature for this reaction.

A temperature dependence on the reaction rate was also observed, which is also what one may expect. Comparing entry 1 with entry 3, it is apparent that a higher substrate conversion (86 % vs. 59 %) is achieved at 160 °C than 130 °C when the same catalyst concentration is used. Entries 6 and 7 show the same trend.

No benefit is gained when tetrabutylammonium salts are added to the reaction mixture (see entries 7 and 8). Herrmann has reported that addition of these compounds have a stabilising effect on the palladacycle **5** and promote the reaction rate.[66]

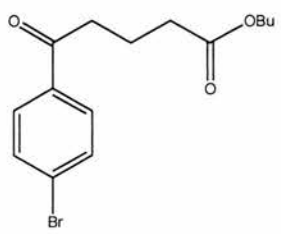
However, as mentioned above for entries 1 and 2, it is apparent that product selectivity is affected when a lower catalyst concentration is used — this effect is even more noticeable when lower reaction temperatures are employed in addition to low catalyst concentration. For example, at 130 °C, product selectivity is 99.5 % (by GC) in favour of the desired product, *n*-butyl (*E*)-4-acetylcinnamate **92**, when 0.0002 mol % catalyst is used (entry 3). This figure fell to 17 % when the catalyst concentration was reduced to 0.00004 mol % (entry 5).

It is also apparent that the concentration of the alkene reagent, *n*-butyl acrylate, also has an effect on the product yield and selectivity. When 1.4 molar equivalents of acrylate were added to the reaction mixture, a substrate conversion of 86 % was obtained within 20 hours (160 °C, 2×10^{-4} mol % Pd, entry 1). Increasing this concentration to 2.0 equivalents resulted in the bromoacetophenone being completely converted within 6 hours using the same reaction temperature and catalyst concentration (entry 9). This increase in reaction rate is what one would expect when the concentration of one reagent is increased with respect to the other. However, it appeared that the excess acrylate reacted further with the product, as the selectivity to the desired compound, *n*-butyl (*E*)-4-acetylcinnamate, suffered (99.5 % vs. 92 %).

Analysis of the product distribution from this and other bromoacetophenone coupling experiments led to the discovery that a secondary, competing side-reaction was occurring in addition to the desired Heck coupling reaction.

3.2.3 Product Selectivity of Acetophenone Reactions

The use of gas chromatography (GC) as an in-process reaction monitoring technique allowed the presence of any reaction by-products to be detected, accurately quantified and their relative concentrations monitored throughout the course of the reaction. Gas chromatography-mass spectrometry (GC—MS) was used in addition to this technique to aid the identification of these by-products. For the reaction between 4-bromoacetophenone and *n*-butyl acrylate, the two main by-products were identified as butyl 5-(4-bromophenyl)-5-oxopentanoate **93** and dibutyl 4-(4-bromobenzoyl)heptanedioate **94**, with butyl (2*E*)-3-[4-(5-butoxyl-5-oxopentanoyl)phenyl]-2-propenoate **95** observed in some instances.



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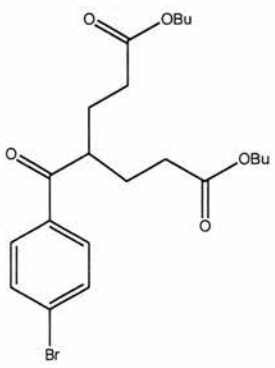

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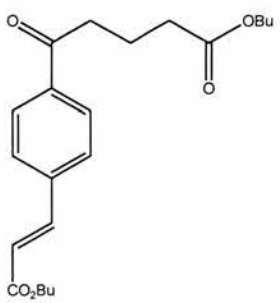
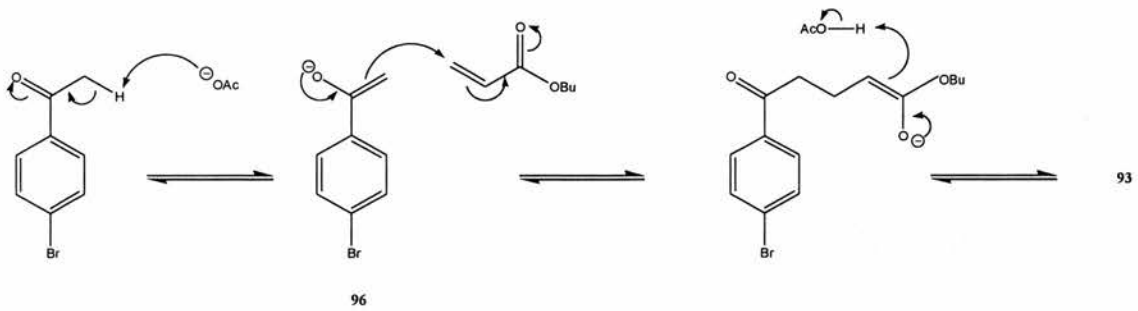


95

The formation of these three compounds is caused by the base catalysed reaction of 4-bromoacetophenone with *n*-butyl acrylate, for which a mechanism is shown in scheme 3-3. The protons alpha- to the carbonyl of the acetophenone substrate are acidic enough to be abstracted by the base, sodium acetate. The resultant enolate **96** can then react with the unsaturated acrylate to give the monoalkylated by-product **93**.

This reaction is known as Michael addition. At very low catalyst concentration and/or lower temperatures, Michael addition can predominate over the Heck reaction for these substrates.



Scheme 3-3: Mechanism for formation of by-product 93 via Michael addition

Although the remaining α-protons of compound **93** are less acidic than those of the acetophenone, the by-product can undergo a second Michael addition to form the dialkylated compound **94**. Under certain conditions, the desired Heck product *n*-butyl (*E*)-4-acetylcinnamate **92** can also undergo Michael addition to form butyl (2*E*)-3-[4-(5-butoxyl-5-oxopentanoyl)phenyl]-2-propenoate **95**. GC—MS analysis confirmed that this compound was produced in a significant amount when an excess of *n*-butyl acrylate was used in conjunction with a high reaction temperature and a relatively low catalyst concentration (table 3-2, entry 10). When the desired Heck product is present in a significant concentration, the high reaction temperature appears to facilitate a further Michael addition reaction.

To investigate the effect of this Michael side reaction, an experiment was conducted using identical reaction conditions to those used in the catalytic runs, but without any palladacycle **74** added. No reaction of any type was observed after 16 hours at 130 °C

in the absence of both catalyst and base. However, 24 hours after sodium acetate was added to the reaction mixture, a significant amount of both Michael addition products **93** and **94** were observed by GC—MS (the ratio of 4-bromoacetophenone:**93**:**94** was 79:11:10). Predictably, as no palladium catalyst had been added, no Heck product **92** was formed. After a further 72 hours at 130 °C in the presence of base, there was no further conversion of the 4-bromoacetophenone substrate to the alkylated products, suggesting that the three compounds (the substrate and the two Michael addition products **93** and **94**) exist in equilibrium under these conditions. Further evidence towards the reversibility of this reaction is obtained when the relative amounts of substrate, Heck product and Michael addition products are monitored throughout the course of a Heck reaction between 4-bromoacetophenone and n-butyl acrylate. An example is shown in Figure 3-1, using 1×10^{-4} mol % of complex **74** as the catalyst at 130 °C.

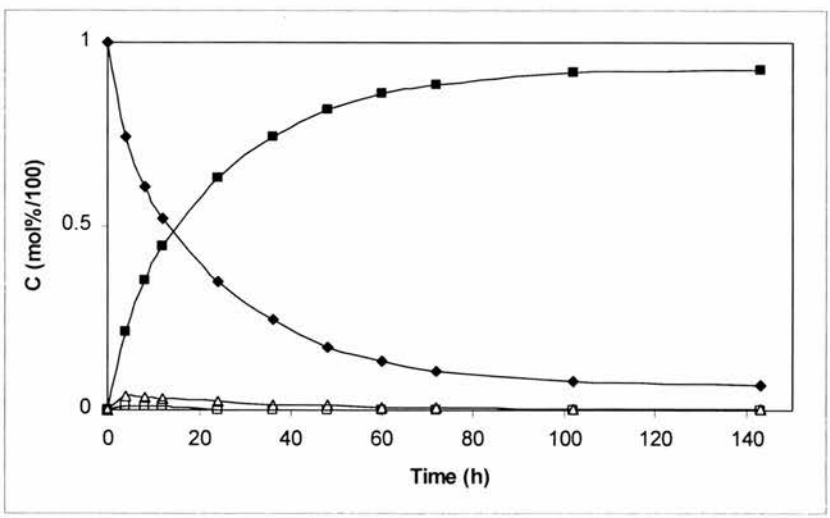
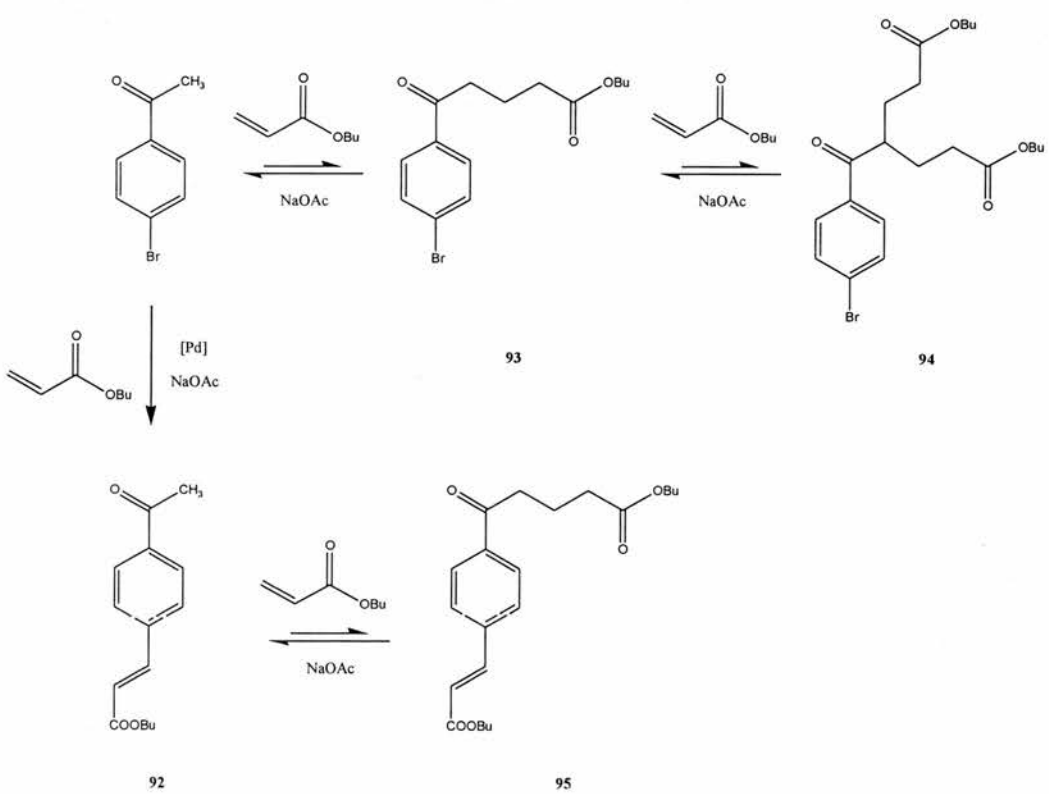


Figure 3-1: Diagram of the concentration (C in mol %/100) vs. reaction time of the Heck reaction of 4-bromoacetophenone (◆) with *n*-butyl acrylate at 130°C to form *n*-butyl (*E*)-4-acetylcinnamate 92 (■): catalyst 74 (0.0001 mol %, 0.0002 mol % Pd)(table 3-2, entry 4). Michael addition by-products (mono-alkylated 93, △, and di-alkylated 94 □) are also formed.

After 4 hours, 26 % of 4-bromoacetophenone was converted to form 21.1 % Heck product **92**, 3.7 % mono-alkylated Michael addition product **93** and 1.2 % di-alkylated Michael product **94**. From this point, the amounts of Michael by-products present in the reaction mixture decreased as the reaction continued. At the end of the reaction (143 hours at 130 °C) the by-products consisted of only 0.37 % of the mono- Michael product **93**, with no detectable amount of the di-alkylated product **94** observed. The final substrate conversion was 93.2 %, with 99.2 % selectivity to the desired Heck product. The equilibrium between 4-bromoacetophenone and the Michael addition by-products was dragged in favour of the 4-bromoacetophenone as the substrate was removed due to consumption in the ongoing Heck reaction. As a result, the amounts of these alkylated products decreased from the initial equilibrated levels before the Heck catalyst was added to the final observed amounts stated above.



Scheme 3-4: Proposed reaction scheme for the Heck reaction of 4-bromoacetophenone and *n*-butyl acrylate catalysed by complex 74

A hypothetical reaction scheme summarising the two reactions taking place in the 4-bromoacetophenone/*n*-butyl acrylate reaction mixture is shown in scheme 3-4. In the absence of palladium catalyst the base promoted Michael addition of the acetophenone to the acrylate occurs to form monoalkylated **93** and ultimately dialkylated **94**. Both steps are reversible, with the equilibria in both instances lying well to the left. As soon as the palladium catalyst is added to the reaction mixture the acetophenone is removed from this equilibrium system as it is consumed in the Heck reaction to form the cinnamate **92**. Removal of acetophenone moves the Michael reaction equilibria further to the left, with the affect of reversing the addition, and a decrease in alkylated by-products as the Heck reaction proceeds.

3.2.3.1 Effect of Temperature and Catalyst Concentration on Product Selectivity

As mentioned previously, the selectivity to the Heck reaction between 4-bromoacetophenone to the desired product *n*-butyl (*E*)-4-acetylcinnamate **92** varied significantly depending on the reaction conditions employed. Selectivity was seen to decrease when lower temperatures were used in conjunction with a low catalyst concentration. An extreme example of this effect is illustrated in figure 3-2. At a low catalyst concentration (1×10^{-5} mol % of complex **74**), complete conversion of the acetophenone substrate does not occur at 130 °C. After 144 hours, the substrate conversion is only 37 %, with 6.6 % Heck product **92**, 10.9 % monoalkylated Michael product **93** and 19.9 % dialkylated Michael product being formed.

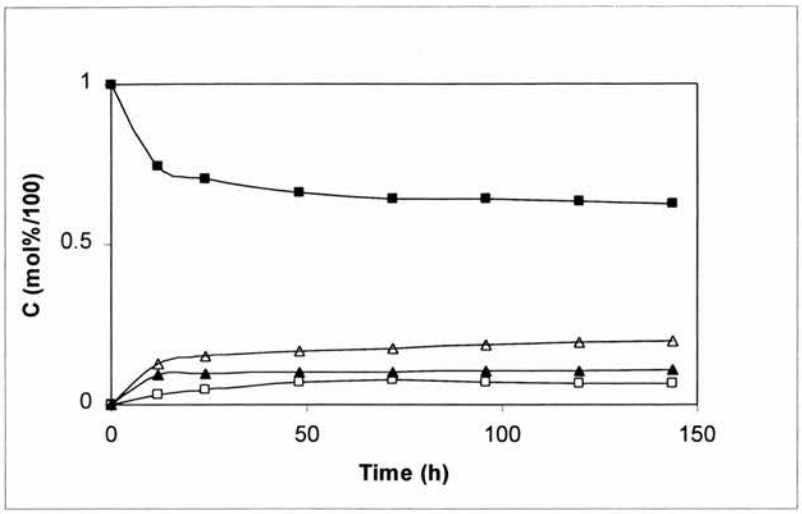
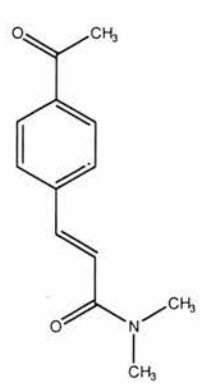


Figure 3-2: Diagram of the concentration (C in mol %/100) vs. reaction time of the Heck reaction of 4-bromoacetophenone (■) with *n*-butyl acrylate at 130°C with low catalyst concentration (0.00001 mol % 74, 0.00002 mol % Pd) to form *n*-butyl (*E*)-4-acetylcinnamate 92 (▲). Decreased product selectivity to yield higher levels of Michael addition by-products (mono-alkylated 93, △, and di-alkylated 94 □) is evident.

When the same reaction was performed at 160 °C with the same catalyst concentration, the substrate conversion and product ratio differed significantly (figure 3-3). After 144 hours at this temperature, 82.3 % of the bromoacetophenone had been converted, and the selectivity to the desired Heck product **92** was higher (63.5 %). The amount of Michael addition products **93** and **94** was lower (3.2 % **93**, 3.5 % **94**), but a significant amount of the Heck product **92** also underwent Michael addition to yield butyl (2*E*)-3-[4-(5-butoxyl-5-oxopentanoyl)phenyl]-2-propenoate **95** (6.9 %).



97

An additional impurity was also formed, the level of which steadily increased throughout the reaction to a final figure of 16 %. The mass spectrum of this impurity is consistent with that of 3-(4-acetylphenyl)-*N*,*N*-dimethylacrylamide **97** (F.W. = 217), suggesting that the Heck product is prone to nucleophilic attack by dimethylamine, a possible decomposition product of *N*,*N*-dimethylacetamide. However, this impurity was not isolated, and the identity of this compound has not been confirmed.

The Michael addition reaction, and hence the levels of the alkylated by-products **93** and **94**, can be minimised by the appropriate choice of catalyst concentration for the reaction temperature. If the catalyst concentration is suitably high, the desired Heck product will be formed exclusively, although a lower turnover will be obtained and the full potential of the catalyst will not be utilised.

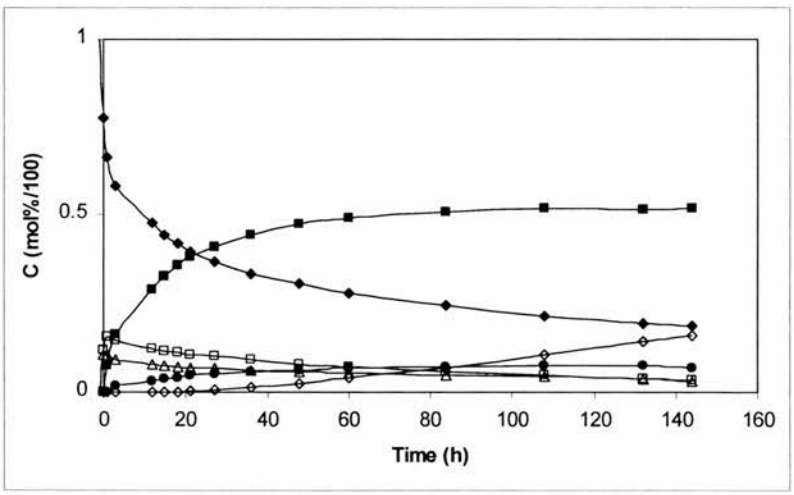


Figure 3-3: Diagram of the concentration (C in mol %/100) vs. reaction time of the Heck reaction of 4-bromoacetophenone (◆) with *n*-butyl acrylate at 160°C with low catalyst concentration (0.00001 mol % 74, 0.00002 mol % Pd) to form *n*-butyl (*E*)-4-acetylcinnamate 92 (■)(table 3-2, entry 2). Michael addition by-products mono-alkylated 93 (△), di-alkylated 94, (□), and Heck monoalkylated 95, (●) are also formed. An unidentified decomposition product (◇) grows in concentration throughout the reaction.

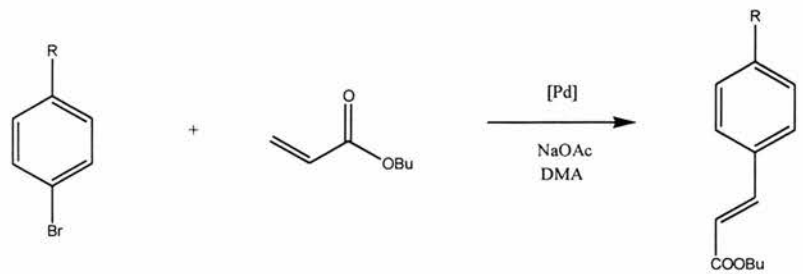
These trends can be summarised in terms of the reaction scheme shown above (scheme 3-4). With a low concentration of catalyst **74** the substrate 4-bromoacetophenone is not removed rapidly enough by participation in the Heck reaction to prevent the Michael addition from occurring. Higher temperatures aid the kinetics of the Heck coupling, which in turn improves substrate conversion and product selectivity, but decomposition can occur during prolonged reaction times. Higher catalyst concentration aids the Heck reaction at all temperatures, shortening the time necessary for acceptable conversions. Thus, it is apparent that the reaction mixture is a finely balanced equilibrium in which a slight change in the conditions can dramatically alter the kinetics of the two reactions taking place, and hence the product distributions obtained. Two examples illustrating the extremes of these variations, and perhaps the limitations of the catalytic system for this particular reaction, are shown in table 3-1 (entries 9 and 10). Using 1×10^{-4} mol % of complex **74**, complete conversion of the substrate occurred within 6 hours (entry 9). Selectivity to the Heck product **92** was 92 %, with the only by-product formed being the Michael addition compound of the Heck product, butyl (2*E*)-3-[4-(5-butoxyl-5-oxopentanoyl)phenyl]-2-propenoate **95**. Formation of this compound was probably due to using an excess (2 molar equivalents) of the butyl acrylate. This result corresponds to a turnover number of over 450,000 moles of product per mole of catalyst, and an average turnover frequency of over 75,000 h^{-1}. The higher reaction temperature (160 °C) obviously has a dramatic effect, as 143 hours were required to achieve a conversion of 89 % at 130 °C using the same catalyst concentration (entry 4). In contrast, using a very dilute catalyst concentration (1×10^{-6} mol % **74**), in an effort to obtain a turnover number in the order of 50,000,000 (entry 10), achieved a substrate conversion of only 42 % after 72 hours. However, Michael addition was the prominent reaction, with the product

distribution consisting of 22.5 % monoalkylated **93**, 72.8 % dialkylated **94** and only 4.7 % desired product **92**. Due to the extraordinarily low catalyst concentration, this still equates to a turnover number of nearly 1,000,000. However, the practical benefits, given the poor product selectivity, are limited.

3.2.3.2 Further Michael Addition By-Product Formation

The problem of poor product selectivity for the Heck reaction of 4-bromoacetophenone, for certain reaction conditions, was principally due to the substrate participating in a Michael addition reaction with the butyl acrylate. Protons acidic enough to be abstracted by the sodium acetate base are available *alpha-* to the carbonyl group of the acetophenone, which tautomerises to the enolate necessary for Michael addition (see scheme 3-3). The discovery and subsequent understanding that this was occurring in our experiments was made too late to thoroughly investigate and develop the catalytic system in an attempt to prevent this side-reaction. The fact that the Michael addition had not previously been reported as a competing reaction to this particular Heck coupling when similar palladacycle catalysts were used (e.g. the Herrmann and Bedford systems) is interesting. It is without doubt that the reaction temperature and catalyst concentration could be optimised to maximise catalyst efficiency and product selectivity for the acetophenone coupling. Perhaps a weaker base would prevent the Michael addition from occurring, by slowing the formation of the enolate intermediate **96**. However, it was observed that the Michael addition was not a side-reaction exclusive to the coupling of 4-bromoacetophenone.

Table 3-3: Attempted Heck reaction of various bromoaromatics with *n*-butyl acrylate

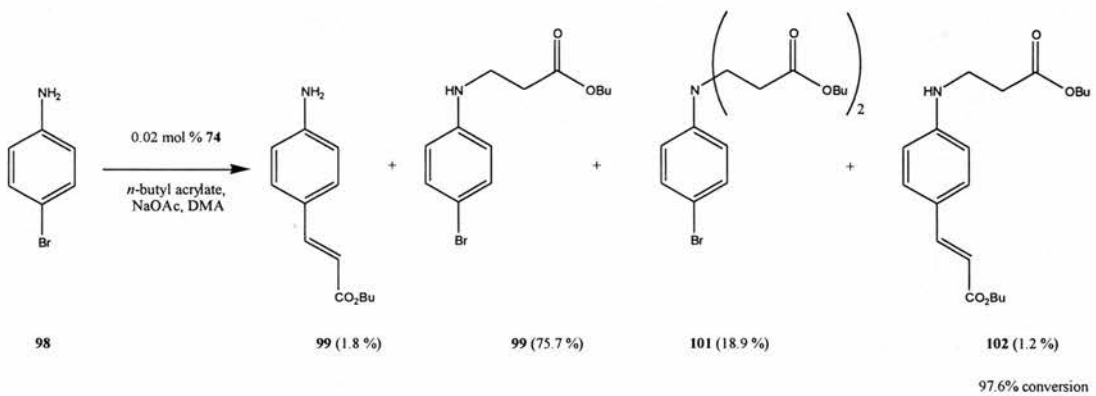


Entry	Substrate	Catalyst (mol % Pd)	Temp (°C)	Time (h)	Conversion (%)[a]	Yield (%)[b]	TON
1	R = *p*-NH_2	0.02	130	48	98	2	93
2	R = *p*-OH	0.02	130	24	21	20	1,055
3	R = *p*-NMe_2	0.01	130	48	24	24	2,440

Reaction conditions: 50 mmol aryl bromide, 70 — 100 mmol *n*-butyl acrylate, 25 mmol naphthalene, 50 cm^3 DMA, catalyst (complex 74) injected as a solution in DMA. [a] Determined by GC. [b] Yield of desired Heck product, determined by GC.

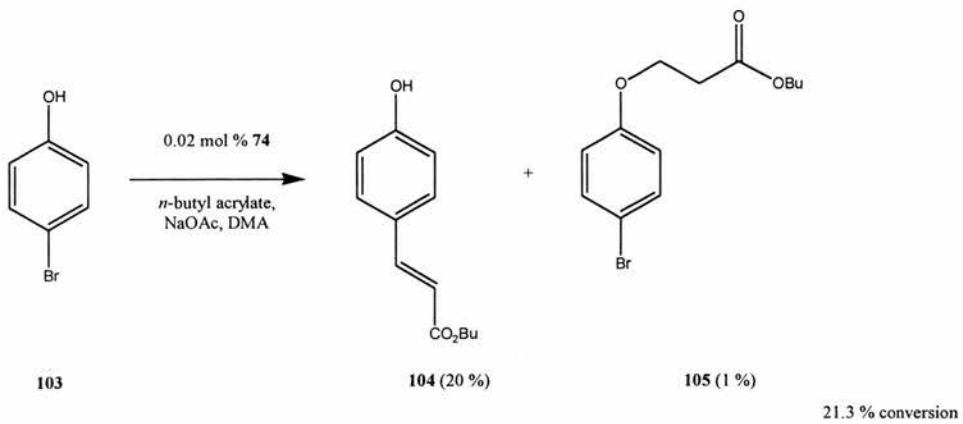
A variety of bromoaromatic substrates was investigated for activity in the Heck reaction using complex **74** as the catalyst, with various substituents on the aromatic ring. These were chosen in an attempt to investigate the effect of the electronic properties of the substituents on Heck reaction performance. The details of this investigation will be discussed later. In addition to 4-bromoacetophenone, significant amounts of Michael addition products were obtained when 4-bromoaniline **98** was used as the substrate (table 3-3, entry 1). In comparison to the 4-bromoacetophenone experiments, complete conversion of the substrate occurred, and despite a relatively high concentration of catalyst **74** being used, virtually no (~2 %) desired Heck product, butyl (2*E*)-3-(4-aminophenyl)-2-propenoate **99** was obtained. Instead, the Michael addition products *n*-butyl 3-(4-bromoanilino)propanoate **100** and 3-[(4-

bromophenyl)-(2-butoxycarbonyl-ethyl)-amino]-propionic acid butyl ester **101** were obtained in an 80:20 ratio (scheme 3-5). These compounds were identified by GC—MS, and these identities confirmed by ^{1}H NMR. A small amount of the alkylated Heck product (3-[4-(2-butoxycarbonyl-ethylamino)-phenyl]-acrylic acid butyl ester) **102** was also obtained. The route of formation to this product, i.e. either by alkylation of **99** or Heck reaction of **100**, was not determined.



Scheme 3-5: Attempted Heck reaction of 4-bromoaniline

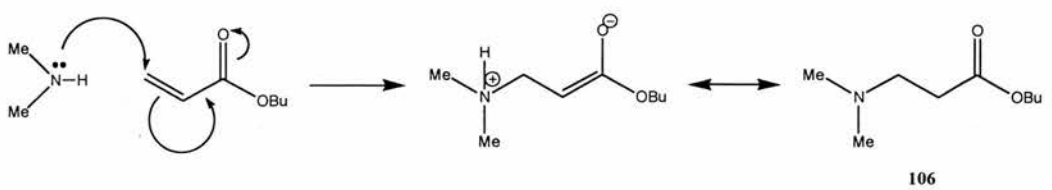
In direct comparison to the 4-bromoaniline substrate, the Heck reaction of 4-bromophenol **103** selectively produced the desired product butyl (2*E*)-3-(4-hydroxyphenyl)-2-propenoate **104** in 20 % yield after 48 hours using the same catalyst concentration (table 3-3, entry 2). The product selectivity was 95 %, with a relatively small amount of the Michael addition product butyl 3-(4-bromophenoxy)propanoate **105** being formed (scheme 3-6). Reaction of the substituted 4-bromo-*N,N*-dimethylaniline gave the desired Heck product in 24 % yield, with no Michael addition products being formed (table 3-3, entry 3).



Scheme 3-6: Heck reaction of 4-bromophenol

In addition to by-product formation due to Michael reactions occurring on the bromoaromatic substrate, problems were experienced when it was attempted to purify the *N,N*-dimethylacetamide solvent by distillation from barium oxide. During a period in the project when the reasons for the poor product selectivities obtained in the Heck reaction experiments were not fully understood, deciding to purify all the substrates and the solvent by crystallisation or distillation techniques was considered a logical step. If the by-products had been formed from impurities in the reaction mixture, purification seemed a likely cure to the problem. Distillation from barium oxide is an accepted literature procedure to purify the DMA solvent,[111] and was duly undertaken. However, the purified solvent was found to contain 1.6% dimethylamine, while the unpurified solvent (anhydrous DMA, purchased from Aldrich) was confirmed to be >99.95 % pure by GC. The high level of dimethylamine in the purified solvent could have been caused by one of two methods. Distillation of the unpurified solvent would have effectively concentrated the level of low boiling impurities, as these would have been collected first. Alternatively, the high temperature involved in the distillation process (b.p. DMA = 164.5 — 166 °C) may

have degraded the solvent, with one of the decomposition products being dimethylamine. As no dimethylamine was detected in the unpurified solvent, the second explanation seems more likely. Whatever the reason for the presence of dimethylamine in the reaction solvent, use of DMA contaminated with this impurity completely inhibits the Heck coupling by converting *n*-butyl acrylate to butyl 3-(dimethylamino)propanoate **106** via a Michael addition reaction (scheme 3-7). The butyl acrylate is completely consumed by dimethylamine before the palladium catalyst is added, thus prohibiting any reaction, Heck or Michael alkylation, from occurring with the aromatic substrate. The reaction to form **106** is facile as no *n*-butyl acrylate was found in the reaction mixture after stirring at ambient temperature.



Scheme 3-7: Reaction of dimethylamine with *n*-butyl acrylate

Although the formation of the Michael addition product between dimethylamine and butyl acrylate was found to inhibit the subsequent Heck reaction, the ease of identification of the dimethylamine impurity and the resultant product **106** by GC—MS provided rapid elucidation to the nature of the inhibition problem. From this discovery, the realisation that Michael addition to butyl acrylate was responsible for by-product formation in 4-bromoacetophenone Heck reactions (and subsequently in reactions involving other substrates, see above) was made. In summary, the failed attempt to purify the dimethylacetamide solvent resulted, somewhat fortuitously, in

the understanding of the nature of the by-product reaction in the Heck coupling of 4-bromoacetophenone with *n*-butyl acrylate. From this, the conclusion that the selectivity to the desired Heck product is dependent on the susceptibility of the substrate to undergo Michael addition with *n*-butyl acrylate can be made. Therefore, it can be deduced that this selectivity is directly dependent on the acidity of the protons on the substituents on the bromoaromatic substrate.

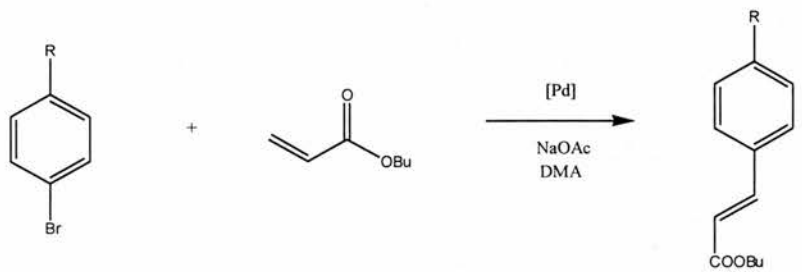
3.2.4 Alternative Bromoaromatic Substrates

Due to the two substrates, 4-bromoacetophenone and butyl acrylate, being highly activated towards Heck coupling, the reaction can be effectively mediated using reasonably low concentrations of 'traditional' *in situ* catalyst systems, with practical turnover numbers being achieved. For example, a turnover number of 134,000 has been obtained for a reaction between similarly activated substrates — 1-bromo-4-nitrobenzene and ethyl acrylate — using *in situ* palladium acetate and tri-*o*-tolylphosphine.[45] Although palladacycle type catalysts have improved the turnover numbers achievable when reactive substrates are used by an order of magnitude, the most important improvements from a practical point of view are those obtained when less activated aromatic substrates are used.

A variety of bromoaromatic compounds was investigated as Heck reaction substrates using our catalytic system, ranging from 'activated' electron-withdrawing compounds (4-bromoacetophenone, 4-bromobenzaldehyde) and the 'non-activated'

bromobenzene, to 'deactivated' electron-donating substrates (e.g. 4-bromoanisole)(table 3-4). The aim of our investigation was to determine whether non-activated substrates reacted, and if so to optimise the reaction conditions to maximise the turnover numbers obtained. A comparison of substrate performance for these compounds could then be made.

Table 3-4: Heck reaction of various bromoaromatics with *n*-butyl acrylate



Entry	Substrate	Catalyst (mol % Pd)	Temp (°C)	Time (h)	Conversion (%)[a]	Yield (%)[b]	TON
1	R = *p*-CHO	0.004	130	3	99	99	24,750
2	R = *p*-CHO	0.0005	130	5.5	67	67	133,500
3	R = *p*-CHO	0.00001	150	96	37	37	3,720,000
4	R = H	0.004	130	175	85	85	21,100
5	R = *p*-OMe	0.004	130	175	68	68	16,900
6	R = *p*-NH_2	0.02	130	48	98	2	93
7	R = *p*-OH	0.02	130	24	21	20	1,055
8	R = *p*-NMe_2	0.01	130	48	24	24	2,440
9	R = *m*-COMe	0.02	130	44	95	91	9,080
10	R = *m*-OMe	0.02	130	44	21	21	2,070

Reaction conditions: 50 mmol aryl bromide, 70 — 100 mmol *n*-butyl acrylate, 25 mmol naphthalene, 50 cm^3 DMA, catalyst (complex 74) injected as a solution in DMA. [a]Determined by GC. [b]Determined by GC.

The high activity of 4-bromoacetophenone as a Heck substrate was hindered by significant by-product formation due to Michael addition, depending on the reaction conditions used, as mentioned in detail above. It was assumed that by using the activated 4-bromobenzaldehyde, which does not possess *alpha-* protons such as those responsible for the Michael addition reaction on 4-bromoacetophenone, high turnover numbers would be obtained without the occurrence of side-reactions.

This was indeed found to be the case. In addition to the first exploratory experiment mentioned above (see scheme 3-2), in which a turnover of 500 was obtained, several further investigative catalytic runs were performed using 4-bromobenzaldehyde (table 3-4, entries 1—3). A turnover of 24,750 was easily achieved in three hours using 2×10^{-3} mol % **74** as catalyst (4×10^{-3} mol % Pd)(entry 1). An experiment using 5×10^{-4} mol% Pd was stopped prematurely, but a turnover in the excess of 130,000 was obtained in 5.5 hours (entry 2). In an effort to maximise the turnover number obtained, a lower catalyst concentration (1×10^{-5} mol % Pd) was used in combination with a higher temperature (entry 3). In this case, a turnover number of 3.7 million was obtained after 96 hours at 150 °C, although this corresponded to a substrate conversion of only 37 %. In each example the reaction is 100 % selective, with no by-products, such as Michael addition compounds, detected. Comparison of these results with those obtained from the 4-bromoacetophenone experiments show that although both compounds are highly active Heck reaction substrates, the presence of acidic *alpha-* protons hinders the selectivity of the acetophenone reaction (resulting in alkylation side-product formation) while the benzaldehyde reaction proceeds cleanly. The turnover number obtained for this reaction is amongst the highest yet observed for a Heck coupling reaction.

3.2.4.1 Non-activated and Deactivated Aryl Bromide Substrates

The impressive turnover numbers obtained using substrates such as 4-bromoacetophenone and 4-bromobenzaldehyde arise because of the 'activating' electron-withdrawing substituents on the aromatic ring. It was thus important to compare these values to those obtained with the non-activated bromobenzene and 'deactivated' substrates such as 4-bromoanisole.

Table 3-5:

Entry	Substrate	Catalyst (mol % Pd)	Temp (°C)	Time (h)	Conversion (%)[a]	Yield (%)[b]	TON
1	R = *p*-CHO	0.004	130	3	99	99	24,750
2	R = H	0.004	130	175	85	85	21,100
3	R = *p*-OMe	0.004	130	175	68	68	16,900
4	R = *m*-COMe	0.02	130	44	95	91	9,080
5	R = *m*-OMe	0.02	130	44	21	21	2,070

Reaction conditions: 50 mmol aryl bromide, 70 — 100 mmol *n*-butyl acrylate, 25 mmol naphthalene, 50 cm^3 DMA, catalyst (complex 74) injected as a solution in DMA. [a]Determined by GC. [b]Determined by GC.

A comparison of the conversion rates of 4-bromobenzaldehyde, bromobenzene and 4-bromoanisole for the Heck coupling with *n*-butyl acrylate using 0.002 mol % complex **74** as the catalyst at 130 °C (table 3-5, entries 1—3) is shown in figure 3-4.

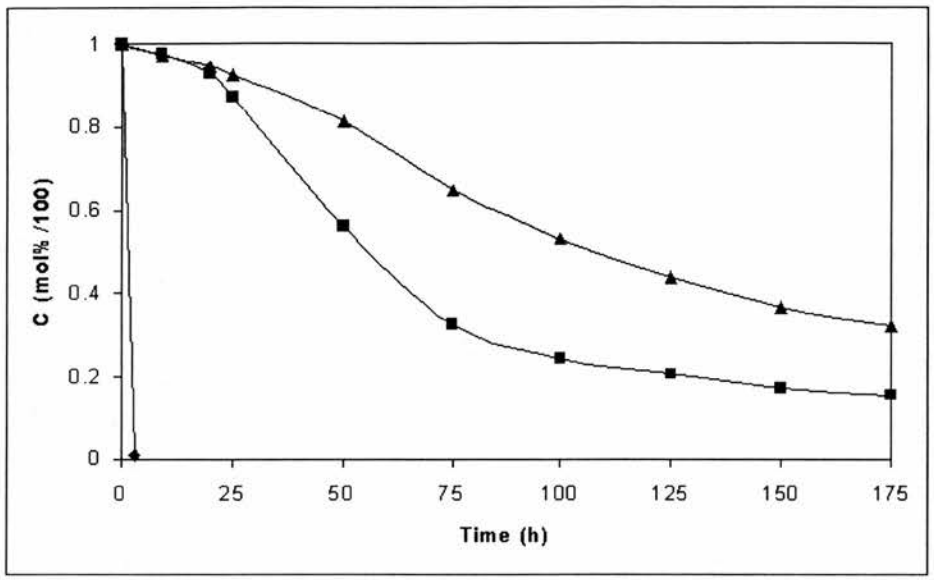


Figure 3-4: Conversion of aryl bromide substrates 4-bromobenzaldehyde (◆), bromobenzene (■) and 4-bromoanisole (▲) in Heck coupling with *n*-butyl acrylate at 130 °C using 0.002 mol % 74 as catalyst (table 3-5, entries 1, 2 and 3).

The activating effect of the aldehyde substituent on 4-bromobenzaldehyde is dramatic, with complete conversion being achieved within 3 hours. The reactivities of bromobenzene and 4-bromoanisole are more comparable, with rate of conversion of bromobenzene slightly higher than that of the more deactivated bromoanisole. A significant induction period is observed for both substrates, particularly bromobenzene. After 9 hours at 130 °C the conversions of both compounds are virtually identical (~2.5 %), after which time the bromobenzene begins to react at a much faster rate than 4-bromoanisole. Neither substrate is completely converted after 175 hours, although the turnover numbers achieved (21,100 and 16,900, respectively) are very impressive when compared to those reported in the literature for these substrates.

For example, using a catalyst concentration of 1 mol % of palladacycle **5** (2 mol % Pd), Herrmann obtained a conversion of 96 % for the reaction of bromobenzene with *n*-butyl acrylate after 48 hours at 140 °C, equating to a turnover number of just 48. By using 1 mol % tetraphenylphosphonium chloride as a stabilising additive, the catalyst concentration could be lowered to 0.02 mol % Pd to obtain a turnover number of 9,800 after 48 hours.[66] Using the Bedford complex **21**, a conversion of 51 % (TON = 255) was obtained after 18 hours for the same reaction using a catalyst concentration of 0.2 mol% Pd at 140 °C.[57] Even the best *in situ* catalyst system, $Pd(OAc)_2/4P(o\text{-tolyl})_3$, achieved a substrate conversion of only 65 % (TON = 6,500) for the Heck coupling of bromobenzene with ethyl acrylate at 130 °C.[45]

For the Heck coupling of the deactivated 4-bromoanisole, reaction conversions and turnover numbers quoted in the literature are, predictably, even lower than those obtained with bromobenzene. The Herrmann system achieved a turnover number of only 47, which was increased to 100 when 20 mol % tetrabutylammonium bromide was added as a promoting salt.[66] Using a lower concentration of the Bedford catalyst **21** (0.2 mol % Pd), a conversion of only 6 % (TON = 30) at 140 °C was obtained. Better results were obtained when a higher temperature (TON = 375 at 165 °C) or an alternative base (TON = 440 with K_2CO_3 at 160 °C) was used, however. By the addition of several equivalents of phosphite ligand a turnover number of 9,800 was achieved,[57] but this detracts from the aim of using palladacycle complexes as underligated catalyst precursors, which do not normally require additional equivalents of ligands for activity.

Although the results shown above for complex **74** cannot be directly compared to those obtained for other systems (due to, in many instances, a lower catalyst concentration and temperature being used, and hence a longer reaction time being necessary), the turnover numbers obtained with this catalyst show the activity of complex **74** is at least of the same order of magnitude as those of existing high performance Heck catalysts. Again, further optimisation of the reaction conditions is required to maximise the rate of reaction in an effort to obtain high product yields within a reasonable reaction time.

The performance of another similarly deactivated substrate, 4-bromoaniline, has been mentioned previously due to the tendency of the compound to undergo Michael addition rather than the desired Heck coupling (see table 3-3, entry 1). The fact that other substrates with electron-donating groups, for example 4-bromoanisole (table 3-4, entry 5), 4-bromophenol (table 3-4, entry 7) or 4-bromo(dimethyl)aniline (table 3-4, entry 8) yield the Heck product exclusively, with little or no Michael addition by-product formation, suggests that the acidity of protons on the substituent group dictate product selectivity in this catalytic system. Although these examples cannot be compared directly (due to a variation in the catalyst concentration used in each case), it is apparent that these three deactivated substrates are of similar reactivity.

3.2.4.1 Effect of Substituent Pattern on Substrate Activity

Thus far, aromatic substrates with substituents *para-* to the bromine have been studied. From the observed trends, it is evident that substrate activity is dependent on the electronic properties of the substituent in this position, with electron-withdrawing groups producing superior results. It was decided to investigate if altering the electronic environment of the substrate, by moving the substituent to the *meta-* position, would alter this trend. We did not study the activity of *ortho-* substituted substrates, as any effect of the electronic environment on the observed reactivity of the compound would be complicated by steric factors.

The two substrates investigated were 3-bromoacetophenone (table 3-5, entry 4) and 3-bromoanisole (table 3-5, entry 5). By moving the substituent to the *meta-* position, it was thought that the reactivity of these substrates would be significantly altered. Although the approach of the *meta-* substituted compound to the palladium reaction site should not be affected too significantly due to steric hindrance compared to the analogous *para-* substituted aromatic, it was assumed that the electronic character of the substrate would be appreciably different, and this would affect the reactivity exhibited by the *meta-* derivative. The hypothesis behind this thinking was that the electron-withdrawing effect of the acetyl- substituent and the electron-donating effect of the methoxy- substituent on the lability of the aromatic—halogen bond would both be diminished in the *meta-* position compared to the *para-* position. As a result, the reactivity of 3-bromoacetophenone should be lower than that of 4-

bromoacetophenone, while 3-bromoanisole should be more reactive than the *para*-substituted analogue.

The results obtained from these two substrates, using a relatively high catalyst concentration (0.02 mol % Pd), are interesting. Firstly, the reaction of 3-bromoacetophenone with *n*-butyl acrylate did not go to completion, but afforded 95 % of the desired product after 44 hours at 130 °C. With such an activated substrate, it would be expected that the coupling would have been completed in a much shorter time considering the high catalyst concentration used. It is noteworthy that no Michael addition products were observed for this reaction, which is a benefit of using a higher catalyst concentration. In contrast, a conversion of only 21 % was obtained for the reaction of 3-bromoanisole. These results, with the acetophenone exhibiting greater activity than the anisole, are what one may expect. However, due to time constraints, control experiments, in which couplings of 4-bromoacetophenone and 4-bromoanisole would have been attempted using the same catalyst concentrations as those used for the *meta*- substituted analogues, were not performed. As a result, direct observations on the effect of the position of the substituent on substrate reactivity cannot be made, and this investigation was not continued further. A similar study of the reactivity of the activated 2-, 3- and 4-bromobenzonitrile substrates with ethyl acrylate by Spencer showed that the *para*- substituted 4-bromobenzonitrile was the most reactive, as expected, while 2-bromobenzonitrile was found to be the least reactive.[45] The reasons given for the lower activity of the *ortho*- substituted compound are twofold — steric hindrance and possible coordination of the cyano-group to the palladium reaction centre.

3.2.5 Effect of the Phosphino Moiety on Catalyst Activity

The nature of the ligand coordinated to the metal centre can have a remarkable effect on the stability and lability of a transition metal complex. These properties can prove decisive in the suitability of such a complex as a potential catalyst.

For phosphine ligated complexes, the influence of the phosphino moiety can be exerted in a number of ways. Often the chemoselectivity, and even the stereoselectivity, of a catalytic process can be influenced by the use of sterically bulky phosphino ligands. The 'bulkiness' of a particular phosphine can be determined in terms of its Tolman cone angle, which is the angle at the apex of an imaginary cone which completely envelopes the ligand in its most extended form.[112]

In addition, the electronic inductive effect of the substituent group(s) on the phosphorus ligand can also influence the activity of a catalyst. Phosphines are σ-electron donors, but the extent of this electron donation can be altered depending on the nature of the substituent groups — alkyl groups, with a positive inductive effect, will enhance the electron donation of the ligand. However, groups with a negative inductive effect (i.e. electron withdrawing), such as aromatics, lessen the electron donation of the phosphine ligand as a whole. Depending on the catalytic reaction cycle, this can enhance or worsen the reaction kinetics of a particular process.

In traditional Heck catalyst systems, where the palladium centre is stabilised by several equivalents of phosphine ligands, a triarylphosphine is deemed necessary for reasonable substrate conversions.[20] However, problems involving quaternisation of

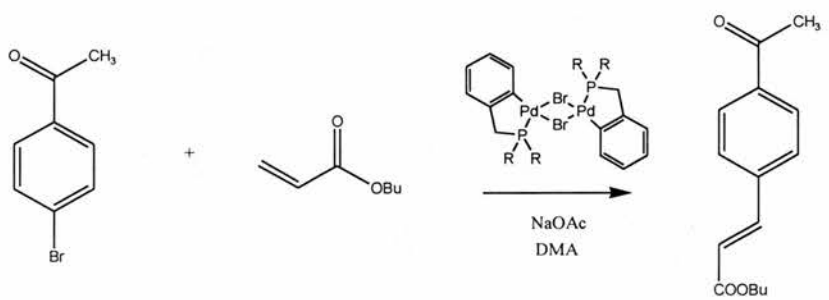
the phosphine by reaction with the bromoaromatic substrate to form tetraarylphosphonium bromides have been reported. Heck found that the sterically hindered tris(*o*-tolyl)phosphine successfully inhibited this reaction and also enhanced the desired coupling reaction (with respect to triphenylphosphine), unless the substrate is also sterically hindered.[113] As a result, tris(*o*-tolyl)phosphine has commonly been used as an effective ligand, and the highest turnover numbers for the Heck coupling using a traditional *in situ* catalyst have been obtained using this phosphine.[45]

For the use of palladacyclic complexes as Heck catalyst precursors, a similar trend is seen. From kinetic studies, Herrmann first made the observation that aryl substituted palladacycles, such as the *o*-tolyl palladacycle **5**, and also phenyl and mesityl substituted analogues, are superior Heck catalysts than those with alkyl groups (for example *t*-butyl and cyclohexyl).[66] Herrmann has rationalised these findings on the basis of the basicities of the respective phosphorus atoms, the steric effect of the ligand, and the thermal stability of the complex. All three of these factors can be influenced by the phosphino substituent. For example, the basicity of the P atom is obviously affected by the electronic nature of the groups bonded to it.

It is perhaps not by coincidence that many other active Heck catalysts for the processing of aryl bromides reported in the recent literature also have arylphosphino ligands, for example those of Bedford[57] and Shaw.[49] However, as this project has also focussed on catalysts for alkene carbonylation, which comprised of metallated alkylphosphino ligands, a range of palladacyclic compounds with different substituents on phosphorus had been synthesised. It was decided to investigate if

these complexes were also Heck catalysts, and if so, would the observations made by Herrmann be confirmed, with alkyl substituted palladacycles being of lower activity than an aryl substituted analogue. By comparing the performance of the *t*-butyl and ethyl substituted analogues **72** and **73** with that of the phenyl substituted complex **74**, upon which all of the cross-coupling investigations had thus far centred, it was hoped that a trend would be observed that would relate catalytic activity to the electronic nature of the phosphino moiety.

Table 3-6: Effect of phosphino moiety on catalyst performance



Entry	Catalyst	Concentration (mol % Pd)	Temp (°C)	Time (h)	Conversion (%)[a]	Yield (%)[b]	TON
1	**72** (R = *t*-Bu)	0.02	130	24	99	98	4,900
2	**72** (R = *t*-Bu)	0.0002	130	24	17	10	51,100
3	**73** (R = Et)	0.0002	130	24	31	25	125,300
4	**74** (R = Ph)	0.0002	130	24	52	50	248,700

Reaction conditions: 50 mmol 4-bromoacetophenone, 100 mmol *n*-butyl acrylate, 25 mmol naphthalene, 50 cm^3 DMA, catalyst injected as a solution in DMA. [a]Determined by GC. [b]Determined by GC.

The findings of the investigation into this effect are summarised in table 3-4. An initial experiment showed that the *t*-butyl palladacycle **72** is also an effective Heck catalyst (table 3-6, entry 1). Using a relatively high catalyst concentration (0.02 mol % Pd), 4-bromoacetophenone is completely converted to the desired product within

24 hours. The Heck reaction of 4-bromoacetophenone and *n*-butyl acrylate was then attempted using three different palladacycles **72**, **73** and **74** as catalyst precursors, which differed only in the nature of the phosphino moiety. All other reaction variables (temperature, catalyst concentration, substrate concentration) were kept constant (table 3-6, entries 2, 3 and 4). By comparing the performance of the three complexes **72**, **73** and **74**, it appears that the activity exhibited is dictated by the nature of the phosphino moiety, with a trend of activity in the order of Ph > Et > *t*-Bu, which follows the electron-withdrawing character of the substituent. However, the difference in activity is not significantly large. For instance, a catalyst concentration of 2×10^{-4} mol % Pd is insufficient to completely convert the bromoacetophenone substrate within 24 hours 130 °C for all three examples. The highest conversion, 52 %, is obtained with the phenyl catalyst **74**, with the *t*-butyl complex **72** only achieving a conversion of 17 % after 24 hours. It was also evident that the reaction was more selective as the activity of the catalyst increased, with significant levels Michael addition by-products observed after 24 hours, particularly in the case of the *t*-butyl analogue **72**.

A comparison of the conversion of 4-bromoacetophenone to the coupling product *n*-butyl (*E*)-4-acetylcinnamate for the three complexes is illustrated in figure 3-5. It is interesting to observe that both the alkyl substituted catalysts **72** and **73** show higher initial activity than the phenyl complex **74** — after 4 hours, the substrate conversion is 26 % for the ethyl complex **73**, 17 % for the *t*-butyl analogue **72**, and only 14 % for the phenyl catalyst **74**. However, after this time the reactions with the alkyl catalysts seem to stall, while the phenyl complex continues to convert the bromoacetophenone at an approximately constant rate throughout the first 24 hours, and on to a final

conversion of 89 % after 143 hours (table 3-2, entry 4). From these observations, one may assume that the alkyl substituted catalysts are more active than the phenyl compound **74**, but are much less stable. Catalyst decomposition quickly occurs, and as a result the reaction stalls and no further conversion occurs. In contrast, the phenyl complex is more stable and is able to catalyse the reaction without decomposition for a prolonged period of time.

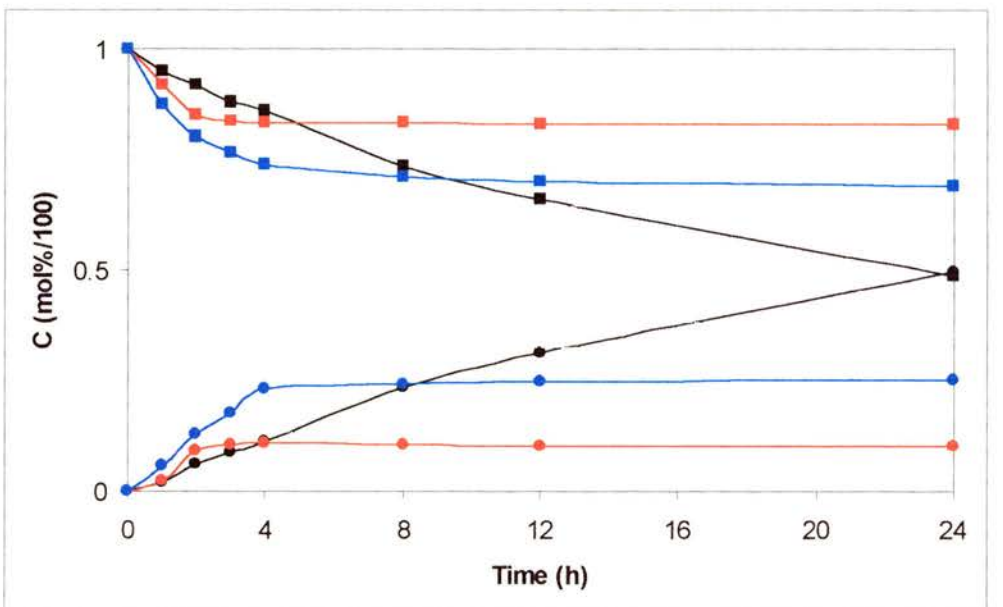


Figure 3-5: Diagram of the concentration (C in mol %/100) vs. reaction time of the Heck reaction of 4-bromoacetophenone (■) with *n*-butyl acrylate at 130°C to form *n*-butyl (*E*)-4-acetylcinnamate (●), using three catalysts 72 (R = *t*-butyl, red), 73 (R = ethyl, blue) and 74 (R = phenyl, black) (0.0002 mol% Pd) (table 3-6, entries 2, 3, and 4).

3.2.6 Alternative Alkene Substrates

The Heck reactions described thus far have concentrated on the coupling of various bromoaromatics with *n*-butyl acrylate. In a similar vein to the aryl bromide substrate, the alkene can be activated or deactivated according to the substituent groups attached to the C—C double bond. The Heck reaction of 1,1-disubstituted alkenes are known. Acrylates, which have electron-withdrawing ester groups, are amongst the most active substrates, and as a result are commonly used in reported examples of very active Heck systems in an effort to achieve the highest possible turnover numbers. The coupling of the activated 4-bromoacetophenone with *n*-butyl acrylate has frequently been used as a 'benchmark' reaction with recently reported systems, for this reason. The conversions achieved using palladacycle **74** as the catalyst with these substrates and the problems encountered with the reaction selectivity have been described above.

Table 3-7: Heck Reaction of Alternative Alkene Substrates

Entry	Aryl Bromide	Alkene	Catalyst (mol% Pd)	Base	T (°C)	Time (h)	Conv. (%)[†]	TON[‡]
1	4-bromoacetophenone	styrene[a]	0.00002	NaOAc	130	40	0	0
2	4-bromoacetophenone	hex-1-ene[a]	0.01	NaOAc	150	72	0	0
3	4-bromoacetophenone	MMA[b]	0.002	NaOAc	130	48	96[e]	48,200
4	4-bromoacetophenone	MMA[b]	0.002	DIPEA	130	48	27[e]	13,450
5	4-bromoacetophenone	ethene[c]	0.02	NaOAc	130	2.5	1	50
6	2-bromo-6-methoxy-naphthalene	ethene[d]	0.05	NaOAc	140	11	68	1,350
7	2-bromo-6-methoxy-naphthalene	ethene[d]	0.01	NaOAc	140	24	56	5,550

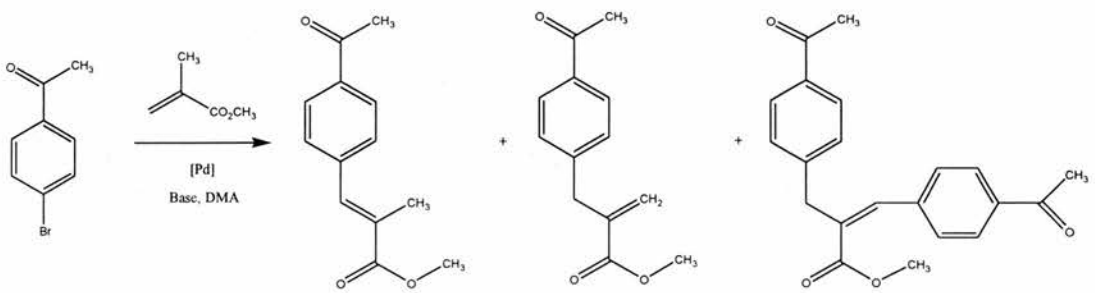
Reaction conditions: One equivalent aryl bromide, alkene ([a]2 equivalents, [b]1.5 equivalents, [c]9 bar, [d]20 bar), 1.1 equivalents base, DMA, catalyst 74 injected as a solution in DMA. [e]3 products formed. [†]Conversion of aryl bromide, determined by GC. [‡]Moles Heck product per mole catalyst.

Heck couplings using a range of alternative alkene substrates were attempted in addition to *n*-butyl acrylate. These ranged from the activated, phenyl substituted, styrene, to 1-hexene, which is deactivated due to the inductive effect of the alkyl chain. The results from these experiments are shown in table 3-7.

The reaction with the styrene was disappointing (entry 1). The electron-withdrawing phenyl group should activate the alkene towards the Heck coupling reaction, but after 40 hours at 130 °C the 4-bromoacetophenone was completely unreacted. However, after this time no styrene was observed in the reaction mixture by GC—MS. Instead, a viscous polymeric material was formed in the reaction flask, which was assumed to be polystyrene. Bedford experienced a 'substantial' amount of polystyrene formation during the attempted coupling of 4-bromoacetophenone and styrene catalysed by 1×10^{-5} mol % of complex **21**, but this still suggests that the substrate was at least partially converted to the desired Heck product, with a turnover number of 5,750,000 being achieved (although this number is in terms of the styrene converted, not product obtained).[57] Selectivity was much improved when the catalyst concentration was increased to 1×10^{-4} mol %, with a 96 % conversion to the coupled product, 4-acetostilbene. The lack of any desired Heck coupling when complex **74** was used was probably due the catalyst concentration being too low, and the palladium catalysed polymerisation becoming the predominant reaction. Similarly, the attempted reaction of the deactivated substrate hex-1-ene was unsuccessful due to an insufficient amount of catalyst **74** being employed (entry 2). However, the catalyst concentration used (0.01 mol % Pd) was considered sufficient for any reaction to be observed if it were to occur. It is apparent that a much higher concentration is required for the efficient

processing of such deactivated substrates, and it was decided not to pursue this avenue further.

Methyl Methacrylate

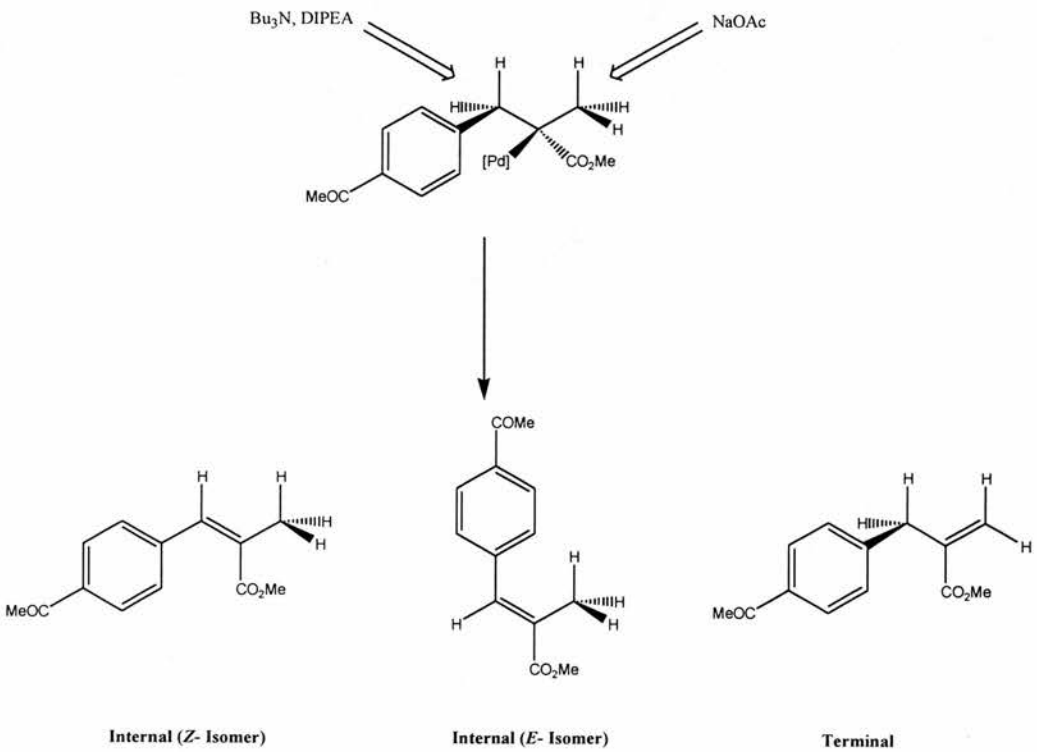


Scheme 3-8: Reaction of 4-bromoacetophenone with methyl methacrylate

The reaction of the 1,1-disubstituted alkene methyl methacrylate (MMA) was more successful (entries 3 and 4). The Heck coupling of this type of alkene to form trisubstituted aromatic olefins has been made more efficient with the introduction of palladacyclic catalyst precursors.[114] The electron-withdrawing ester group of the MMA ensures that the substrate is suitably activated towards the coupling. The additional methyl group lowers the activity of the substrate in two ways, alkyl electron-donation and steric hindrance. Using 0.002 mol % Pd of complex **74**, this substrate was successfully converted in 95 % yield. However, reaction can occur at either end of the double bond, to produce both the internal alkene, methyl 3-(4-acetylphenyl)-2-methylpropenoate **107**, and the terminal alkene, methyl 2-(4-acetylbenzyl)acrylate **108**. In addition, it is possible that the terminal alkene can react

further to produce the disubstituted product, methyl 2-(4-acetylbenzyl)-3-(4-acetylphenyl)acrylate **109** (scheme 3-8).

The product distribution and rate of this reaction appears to be dependent on the base used. During a similar investigation carried out by Beller using the Herrmann complex **5** as the catalyst,[51] the use of sodium acetate favoured the production of the terminal alkene, resulting in the formation of a significant amount of the diarylated product. However, when a more coordinating base was employed, such as tributylamine or diisopropylethylamine (DIPEA), the internal olefin was favoured.



Scheme 3-9: Effect of base on product selectivity

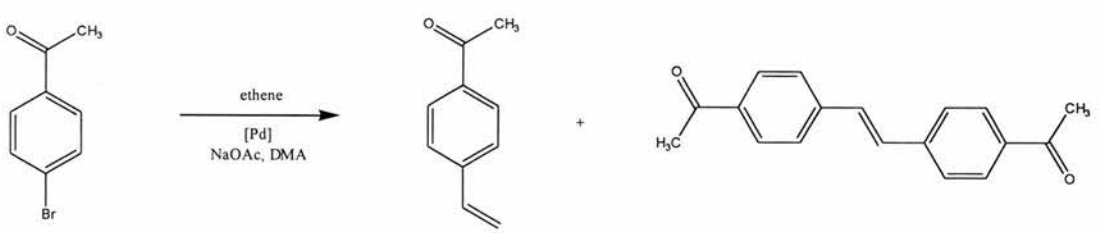
This effect is due to a variation in the mechanism of the final β-hydride elimination step of the catalytic cycle, depending on the base used (scheme 3-9). For the amine-assisted reaction, the most acidic proton is abstracted (which happens to be *alpha-* to the aryl substituent) and thus the internal olefin product is favoured (the ratio of internal to terminal and doubly arylated products was approximately 80:20). Less coordinating bases (i.e. NaOAc) are not assumed to be directly involved in the reductive elimination of HX from H—Pd—X, so a near statistical distribution of internal:terminal products was obtained in these cases (a ratio of ~40:60). In addition, use of coordinating amines appeared to slow the rate of reaction significantly. For example, the coupling of 1-bromo-4-fluorobenzene with butyl methacrylate proceeded to 83 % conversion in 24 hours with 0.01 mol % catalyst and NaOAc base, while a conversion of only 36 % was achieved using DIPEA base during the same period.

Our results compare reasonably with the findings of Beller. Using a lower catalyst concentration (0.002 mol %), a conversion of 87 % is obtained for the coupling of 4-bromoacetophenone with methyl methacrylate within 24 hours, when NaOAc is used as the base. The final conversion for this reaction is 96 % (TON = 48,200) after 48 hours (table 3-7, entry 3), which suggests that our catalyst system is approximately five times more efficient than the Herrmann complex, **5**. When DIPEA is used, a conversion of only 33 % is achieved after 144 hours (table 3-7, entry 4). However, the effect of base on product distribution is less dramatic than in Beller's study. With NaOAc as base the ratio of internal:terminal products is 76:24. By employing DIPEA, this ratio is improved to 89:11. It is interesting to note that the internal

product is favoured in both cases, and, in contrast to the Beller observations, no diarylated product is formed with either base.

Ethene

An exploratory Heck reaction was attempted using ethene gas as the alkene substrate. However, after 2.5 hours at 130 °C, 4-bromoacetophenone was only 1 % converted to 4-acetylstyrene **110** in the presence of 9 bar ethene (table 3-5, entry 5). It was evident that a higher catalyst concentration and pressure of ethene would be required to achieve acceptable results. It was also anticipated that due to the product, 4-acetylstyrene, being more activated towards the Heck reaction than ethene, the formation of 4,4'-diacetylstilbene **111** would be a potential problem (scheme 3-10). As Herrmann had previously experienced success with the coupling of ethene with 2-bromo-6-methoxynaphthalene (see scheme 1-17),[66, 67] it was decided instead to compare the performance of our catalyst system in this reaction with his results.



110 111

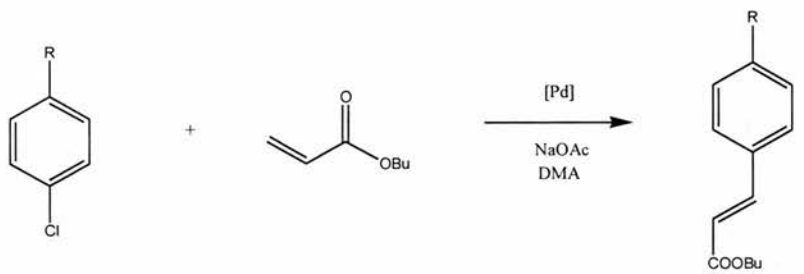
Scheme 3-10: Reaction of 4-bromoacetophenone with ethene

The experimental reactions of 2-bromo-6-methoxynaphthalene with ethene were conducted in a specially constructed autoclave using 20 bar ethene. The kinetics of the reaction were easily followed by the observation of the decrease in pressure in a 'ballast vessel' which was used to fill the reaction vessel by means of a pressure transducer, which kept the reaction pressure constant. Using 0.05 mol % of complex **74** as the catalyst, and a reaction temperature of 140 °C, a conversion of 68 % to 2-methoxy-6-vinylnaphthalene **28** was achieved within 11 hours (table 3-7, entry 6). Decreasing the catalyst concentration to 0.01 mol % allowed a turnover number of 5550 to be achieved in 24 hours (56 % conversion). According to experimental results reported in a patent, Herrmann has achieved turnover numbers of around 950 using identical reaction conditions and up to 10,000 for this reaction when the ethene pressure is increased to 30 bar.[67]

3.2.7 Chloroaromatic Substrates

A number of experiments using the less expensive, and thus commercially important, chloroaromatic substrates in the Heck coupling with *n*-butyl acrylate, were attempted. The results from these experiments are displayed in table 3-8.

Table 3-8: Heck reaction of chloroaromatic substrates

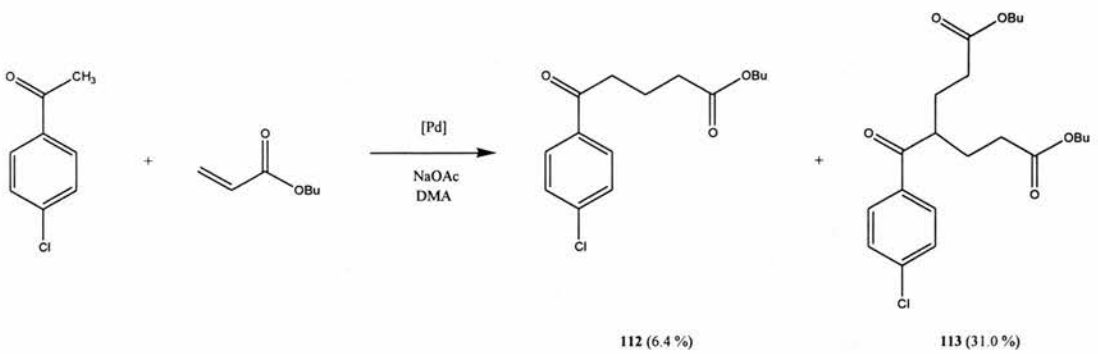


Entry	Aryl Chloride	Catalyst (mol % Pd)	Additive (mol %)	Temp (°C)	Time (h)	Conversion (%)†	TON
1[a]	R = COMe	**74** (0.1)	—	130	144	37	~0
2[a]	R = H	**74** (0.1)	—	130	144	60	~0
3	R = COMe	**74** (0.1)	—	150	18	0	0
4	R = CHO	**74** (0.01)	—	130	72	0	0
5	R = CHO	**74** (0.01)	Bu_4NBr (10)	130	72	1	110
6	R = CHO	**72** (0.01)	—	130	72	0	0
7	R = CHO	**72** (0.01)	Bu_4NBr (10)	130	72	1	90

Reaction conditions: One equivalent aryl chloride, 2 equivalents butyl acrylate (except [a]1.4 equivalents used), 1.1 equivalents base, DMA, catalyst injected as a solution in DMA. †Conversion of aryl chloride, determined by GC.

The results are generally poor. The reaction of 4-chloroacetophenone at 130 °C (entry 1) gave only the Michael addition products butyl 5-(4-chlorophenyl)-5-oxopentanoate **112** and dibutyl 4-(4-chlorobenzoyl)heptanedioate **113** (scheme 3-11), similar to those obtained from some of the bromoacetophenone reactions described

above. When the reaction temperature was increased to 150 °C (entry 3) only palladium black was observed, indicating rapid decomposition of the catalyst.



112 (6.4 %) **113** (31.0 %)

Scheme 3-11: Attempted reaction of 4-chloroacetophenone with *n*-butyl acrylate

Although chlorobenzene appeared to have been 60 % converted by GC at 130 °C (entry 2), no coupled product was observed, and this result must be treated as anomalous. Successful conversion of aryl chloride substrates have only been possible with very high catalyst concentrations or with the use of stabilising salts such as tetrabutylammonium bromide. For example, the coupling of 4-chloroacetophenone with *n*-butyl acrylate has been achieved in 40 % yield using the Herrmann palladacycle **5** and 20 mol % NBu_4Br (TON = 40,000).[66] In addition, the groups of Beller and Fu have found success when electron-donating phosphine ligands have been employed.[35-37] We decided to incorporate these ideas into our own investigation by comparing the performance of the phenyl palladacycle **74** with the electron-donating *t*-butyl analogue **72**, both with and without the use of added stabilising salt. These results of these experiments showed little improvement upon the previous attempts (entries 4-7). It was concluded that the addition of 10 mol % of

tetrabutylammonium bromide did have a beneficial effect on the reaction as no palladium precipitate was observed for these experiments (entries 5 and 7). However, only a trace of the desired Heck product was obtained in each case. No product was observed in the absence of the promoting salt. The activity of these systems were so low that it was not clear if the presence of the *t*-butyl group was having a positive effect on the reaction rate or not. It was decided that significant activity towards the Heck reaction of chloroaromatics would not be observed for this system unless extremely high catalyst concentrations were used.

3.2.8 Heck Reaction — Conclusions

Through our investigations into the carbonylation of alkenes, we have successfully synthesised a series of palladacyclic compounds, some of which, although being poor carbonylation catalysts, have been shown to be precursors to highly active underligated Heck catalysts.[115] In particular, di-μ-bromobis[(diphenyl-phosphinomethylphenyl)-α,P)palladium(II)] **74** shows remarkable activity, comparable to, and in many cases exceeding, the performance of the most highly active Heck catalysts reported to date.

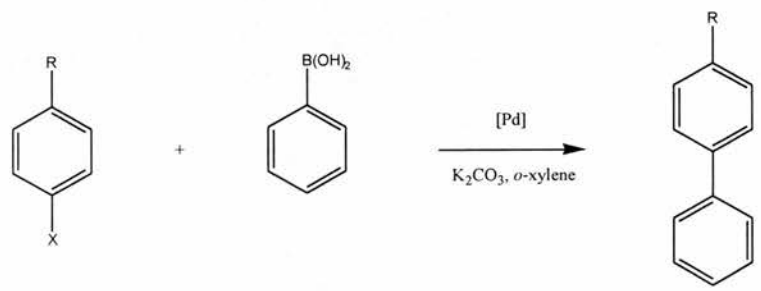
A number of bromoaromatic substrates have been successfully converted to Heck products using this catalyst. For a number of these substrates the product selectivity can be affected via the formation of Michael addition by-products. The factors influencing this side reaction were investigated. The presence of electron-

withdrawing phenyl substituents on the phosphino moiety (i.e. complex **74**) was found to increase catalyst stability and thus catalyst activity in comparison to electron-donating substituents. A range of unsaturated substrates was investigated using this new catalyst system, including 1,1-disubstituted alkenes and gaseous ethene. Finally, the possibility of processing of industrially desirable chloroaromatic substrates was investigated, with poor results.

3.3 Cross-Coupling of Aryl Halides and Aryl Boronic Acids — The Suzuki Reaction

Many of the recently reported palladacyclic catalyst systems developed for the Heck coupling of aryl halides with alkenes have also shown catalytic activity towards the Suzuki reaction. Therefore, it seemed a logical step to investigate whether complex **74** or its analogues, which have been proven to be highly active Heck catalysts (see above),[115] also exhibited activity towards the mechanistically similar coupling of aryl halides with arylboronic acids.

Table 3-9: Suzuki coupling of aryl halides with phenylboronic acid

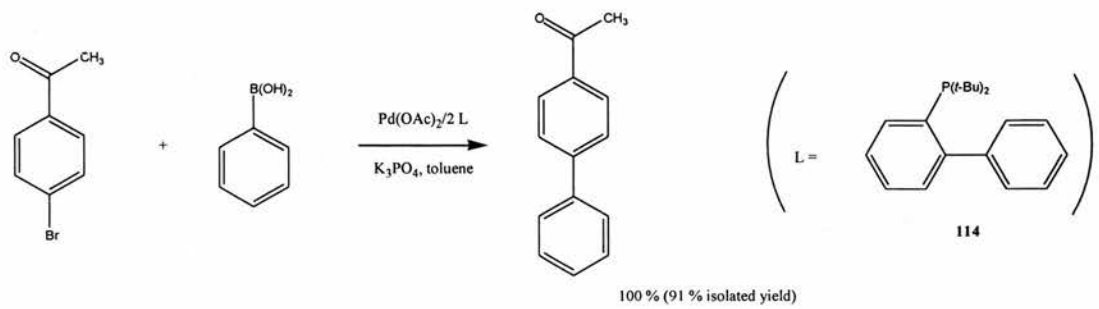


Entry	Aryl Halide	Catalyst (mol % Pd)	Temp (°C)	Time (h)	Conversion (%)[a]	TON
1	4-Bromoacetophenone	**74** (0.002)	130	20	100	49,750
2	4-Bromoacetophenone	**74** (0.001)	130	24	97	96,600
3	4-Bromoacetophenone	**74** (0.0002)	130	24	67	334,500
4[b]	4-Bromoacetophenone	**74** (0.0001)	110	24	6	61,000
5	4-Chloroacetophenone	**74** (0.02)	130	48	0	0
6	4-Chlorobenzaldehyde	**72** (0.01)	130	24	83	2,720[c]

Reaction conditions: 50 mmol aryl halide, 75 mmol phenylboronic acid, 100 mmol K_2CO_3, 150 cm^3 *o*-xylene, catalyst injected as a solution in *o*-xylene. [a]Determined by GC. [b]Toluene solvent. [c]Other products are (4-chlorophenyl)phenylmethanol (37 %) and (4-biphenyl)phenylmethanol (19 %).

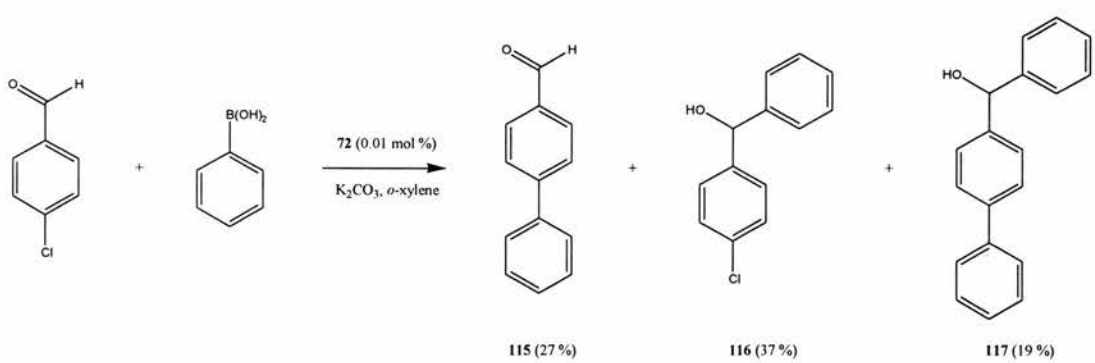
A summary of the results obtained from the Suzuki coupling reaction of phenylboronic acid with activated bromo- and chloro- aromatics is shown in table 3-9. An initial experiment using 0.02 mol % of the phenyl palladacycle **74** as the catalyst precursor quickly confirmed that the complex was indeed an active Suzuki catalyst, with 4-acetylbiphenyl being formed exclusively from 4-bromoacetophenone (entry 1)(TON = 49,750). Halving the catalyst concentration gave a similar result after 24 hours at 130 °C, effectively doubling the turnover number obtained (entry 2)(TON = 96,600). The limit of the catalyst is approached when the concentration is reduced to 2×10^{-4} mol % (entry 3), when the substrate conversion is only 67 % after 24 hours. However, this corresponds to a turnover number of over 330,000, which surpasses the performance of the Herrmann catalyst **5** for this reaction (TON = 74,000).[66, 86]

Bedford has achieved superior performance for this Suzuki coupling reaction using complex **21** as the catalyst, with turnover numbers of up to 1,000,000 being obtained.[87] Interestingly, the reaction rate achieved with this complex was strongly influenced by the choice of solvent and base, with toluene and K_2CO_3 giving the best results. When reaction conditions identical to those used by Bedford were employed, with 1×10^{-4} mol % of complex **74** as the catalyst (entry 4), a substrate conversion of only 6 % was obtained after 24 hours. Using the same catalyst concentration, Bedford achieved complete conversion within 2.25 hours with the metallated phosphite complex **21**, which corresponds to a turnover number of 1,000,000 and a turnover frequency in excess of 440,000 h^{-1}. The performance of this system has since been surpassed by Buchwald *et al*, who have achieved a turnover number of 1×10^{8} for the reaction of 4-bromoacetophenone with phenylboronic acid using an *in situ* *o*-(di-*t*-butylphosphino)biphenyl **114**/palladium acetate catalyst (scheme 3-12).[116]



Scheme 3-12: Suzuki coupling using *o*-(di-*t*-butylphosphino)biphenyl 114 as a ligand

Attempts to couple chloroaromatics with phenylboronic acid using the palladacyclic complex **74** as the catalyst were unsuccessful. Using a relatively high catalyst concentration (0.02 mol %), no conversion of the activated 4-chloroacetophenone was observed after 48 hours at 130 °C (table 3-9, entry 5). Following the high activity observed using catalyst ligands with electron-donating *t*-butylphosphino groups (for example the systems of Fu[82] and Buchwald[116]) it was decided to investigate if the *t*-butyl palladacycle analogue **72** showed catalytic activity towards the Suzuki coupling of an aryl chloride substrate.



Scheme 3-13: Attempted Suzuki coupling of 4-chlorobenzaldehyde

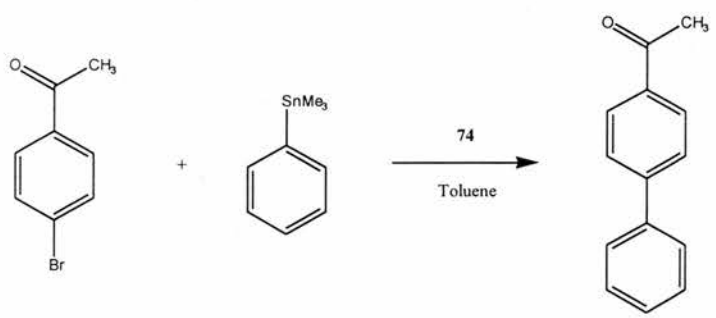
The coupling of the activated substrate 4-chlorobenzaldehyde with phenylboronic acid using 0.01 mol % of the *t*-butyl substituted complex **72** as the catalyst was partially successful (scheme 3-13). After 24 hours at 130 °C, the chlorobenzaldehyde was 83 % converted. Unfortunately, the reaction did not yield the desired product 4-formylbiphenyl **115** selectively. Two by-products, (4-chlorophenyl)phenylmethanol **116** and (4-biphenyl)phenylmethanol **117**, were identified by GC-MS. In addition, no further reaction was observed after 24 hours. The reason for this apparent catalyst deactivation was not clear. The product mixture was not separated, as therefore the identities of the by-product compounds could not be confirmed. Should these structures of the generated by-products be assumed correct, it appears that a competing side-reaction, in which the aryl group of the substrate nucleophilically attacks the carbonyl group of a second molecule, occurs. The first by-product **116** is formed by nucleophilic attack on the 4-chlorobenzaldhyde starting material, while the larger compound **117** arises from attack of the formyl group of the desired product 4-formylbiphenyl **115**.

Although the Grignard-type side reaction results in a yield of only 27 % of the desired compound **115** (TON = 2720), it should be noted that (4-biphenyl)phenylmethanol **117**, which is formed in a yield of 19 %, is generated from subsequent Suzuki coupling of the desired product. Thus, the total yield of Suzuki coupled products is 46 %, which corresponds to a turnover number of 4,600. This is similar to the highest turnover number obtained for chloroaromatic Suzuki couplings for the *o*-(di-*t*-butylphosphino)biphenyl ligand system reported by Buchwald.[116] However, these results are inferior to those of Fu, who obtained a turnover number of 9,700 for the coupling of 2-chlorobenzonitrile with *p*-tolylboronic acid.[82]

3.4 Cross Coupling of Aryl Halides and Aryl Stannanes — The Stille Reaction

The palladacyclic complexes of Herrmann (**5**) and Bedford (**21**), both highly active catalysts for the Heck and Suzuki coupling reactions, have also been reported as being active towards the coupling of aryl halides with aryl stannanes, commonly referred to as the Stille reaction (see scheme 1-25).[66, 87]

A brief attempt was made at investigating the activity of the metallated benzylphosphino palladacycle complex **74** towards the Stille coupling, as this compound had also been shown to be an active Heck and Suzuki catalyst (see above).



Scheme 3-14: Stille coupling of 4-bromoacetophenone with trimethyl(phenyl)tin

Although Herrmann has achieved a maximum turnover number of 1,650 for the coupling of 4-bromoacetophenone and trimethyl(phenyl)tin using palladacycle **5** as the catalyst,[66] Bedford has achieved a turnover number of 830,000 for a similar reaction catalysed by 1×10^{-4} mol % Pd of complex **21**.[87] Using identical reaction conditions and catalyst concentration to that used by Bedford, the coupling of 4-bromoacetophenone and trimethyl(phenyl)tin was attempted using di-μ-

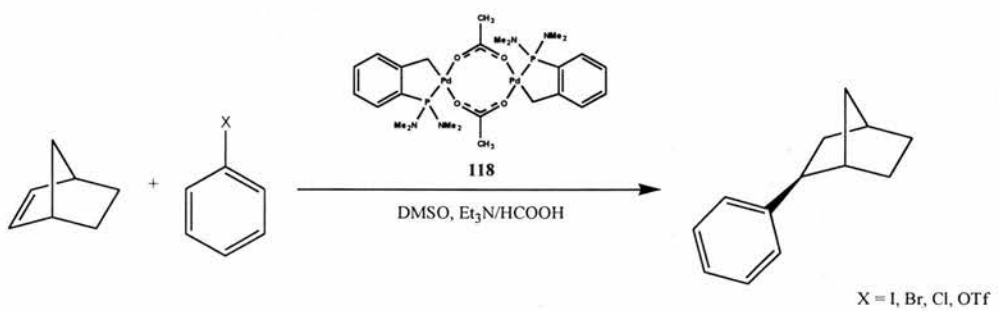
bromobis[(diphenylphosphinomethylphenyl)-α,P)palladium(II)] **74** (scheme 3-14). After 24 hours at 110 °C, no conversion of the 4-bromoacetophenone substrate was observed by GC, suggesting the catalyst concentration used was insufficient to effect reaction. Increasing the concentration to 0.01 mol % Pd was beneficial, with a conversion of 35 % obtained after 6 hours at 110 °C, corresponding to a turnover number of 3,520. Unfortunately, although the desired product, 4-acetylbiphenyl, was formed selectively, no further reaction occurred after the initial 6 hours. No reason for this sudden catalyst deactivation was obvious.

Although this result showed that complex **74** is an active Stille coupling catalyst, no further investigative work was conducted on this reaction. The first experimental reaction, using 1×10^{-4} mol % Pd of complex **74**, showed that the catalyst system is not as active as the Bedford complex **21**, as no product was formed. Using a much higher concentration afforded reasonable catalytic activity, superior to that of the Herrmann catalyst **5**. However, the higher cost of the stannane substrate with respect to the boronic acid analogue used to make the same product via the Suzuki coupling,[i] the lower catalytic activity, and the high toxicity of the organotin substrate and the by-product salt led to the conclusion that further development on this reaction was of limited value.

[i] Aldrich Chemical Company catalogue; trimethyl(phenyl)tin currently costs £15.30/g, while phenylboronic acid costs £1.62/g.

3.5 Hydroarylation and Heck Reaction of Norbornene Substrates

An analogue of the Herrmann palladacycle **5** has recently been shown to catalyse the hydroarylation of norbornene with remarkable efficiency (scheme 3-15).[117] Through metallation of bis(dimethylamino)-*o*-tolylphosphine, the dimethylamino substituted palladacycle analogue **118** is formed in high yield. This complex successfully catalyses the hydroarylation reaction, in which the norbornene substrate is coupled to an aryl halide with subsequent saturation of the C—C double bond, with turnover numbers of up to 1.58×10^{10} being achieved when aryl iodides are used.

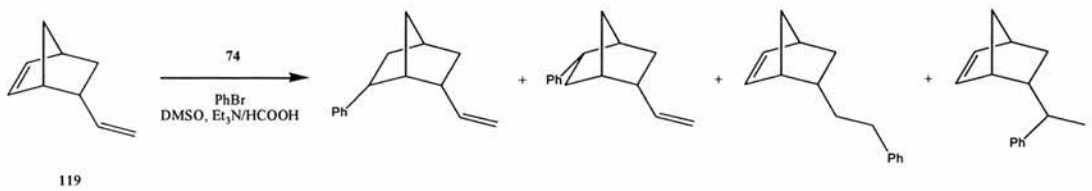


Scheme 3-15: Hydroarylation of norbornene

Although the turnover numbers obtained for this reaction using the above catalyst system are exceptional, the performance is much lower when alkyl bromide substrates are employed (e.g. TON = 196,000 for bromobenzene).

The hydroarylation of norbornene with bromobenzene was attempted using palladacycle complex **74** as the catalyst. With a catalyst concentration of 0.006 mol % Pd, norbornene was 57 % converted to 2-phenylnorbornane in 12 hours (TON =

9,500), although the reaction appeared to stall after this time. No reaction was observed when a lower catalyst concentration (4×10^{-4} mol % Pd) was used.



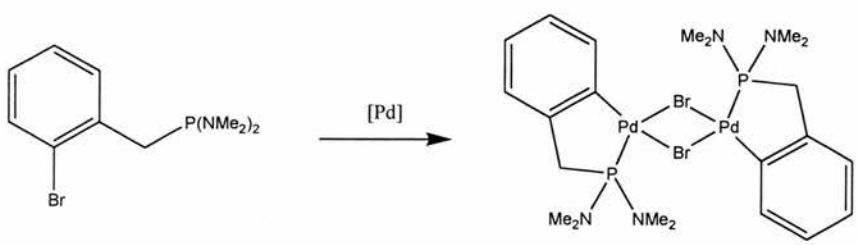
Scheme 3-16: Attempted hydroarylation of 5-vinylnorborn-2-ene

The hydroarylation of 5-vinylnorborn-2-ene **119** with bromobenzene (scheme 3-16) showed that the reaction is not particularly selective, as the reaction produced a mixture of the four possible isomeric products (detected by GC-MS), with arylation occurring at both ends of the two C—C double bonds. In addition, the total yield of all four products was only 6.4 %, even when a relatively high concentration of complex **74** (0.02 mol % Pd) was used, indicating that the presence of the vinyl group deactivates the substrate, possibly both sterically and electronically.

An attempt to synthesise substituted norbornenes via the Heck reaction catalysed by palladacycle **74** was unsuccessful. Even with a catalyst concentration as high as 0.01 mol % Pd, no desired products were detected by GC-MS for the reactions of norbornene or 5-vinylnorborn-2-ene with bromobenzene. This is most probably due to the C—C double bonds of both substrates being electronically deactivated. The norbornene double bond is deactivated by a positive inductive effect from both ends (other internal alkenes, for example cyclohexene and but-2-ene, are similarly deactivated, and as such the Heck reactions of these substrates are not known). The

double bond of the vinyl group of 5-vinylnorborn-2-ene, although more activated than the internal double bond, is also deactivated from one end due to the positive inductive effect of the norbornene ring. The terminal alkene hex-1-ene is similarly deactivated for this reason and has already been shown to be a poor Heck substrate with this catalyst system (see table 3-7, entry 2).

The high activity observed in the hydroarylation reaction for the alkylamino substituted palladacycle **118** catalyst system is certainly due to the effect of the aminophosphine ligand. A comparison of the performance of this system with that of the Herrmann palladacycle **5** for this reaction showed that the *o*-tolyl substituted Herrmann compound was significantly less active than the alkylamino compound.[117] Ideally, the performance of complex **118** would be directly compared to an analogous compound based on palladacycle **74** synthesised via the metallation of 2-bromo[bis(dimethylamino)phosphinomethyl]benzene **120** (scheme 3-17).



120

Scheme 3-17: Proposed synthesis of alkylamino substituted palladacycle

CHAPTER 4

4. CONCLUSIONS

During the course of the three year duration of this project, the aims and objectives of the work undertaken developed significantly. Originally devised as an investigation into the catalytic activity of a new class of palladacyclic complex towards alkene carbonylation, it eventually became apparent, after a considerable amount of time and effort, that the target complex (palladacycle **50**) would not be easily prepared. A change of strategy allowed a number of analogous compounds to be synthesised (**71**, **72**, **73**, **74** and **78**), which all comprised of the same palladacyclic backbone as compound **50**, but did not possess the 'pendant' phosphinomethyl group, which was later shown to be essential for carbonylation activity.

However, a number of the synthesised complexes were shown to be highly active Heck catalysts, in particular the phenyl substituted palladacycle di-μ-bromobis[(diphenylphosphinomethylphenyl)-α,P)palladium(II)] **74**. The activity of this complex as a Heck catalyst was thoroughly investigated, with a variety of substrates and reaction conditions attempted. The tendency of certain aryl halide substrates, in particular bromo- and chloroacetophenone, to undergo a Michael addition side-reaction with *n*-butyl acrylate, was discovered, and an attempt to optimise the reaction conditions to minimise the effect of this reaction was made.

In addition to Heck reaction activity, complex **74** exhibits very high catalytic activity towards the Suzuki reaction, and to a lesser extent, the Stille coupling and the hydroarylation reaction. Most notably, use of the electron rich *t*-butyl analogue di-μ-

bromobis[(di-*t*-butylphosphinomethylphenyl)-α,P)palladium(II)] **72** has allowed the economically favourable chloroaromatic substrates to be efficiently processed in the Suzuki coupling reaction.[115]

Had more time been available, a number of further aims may have been achieved. Firstly, it would have been desirable to optimise the catalyst concentration and reaction conditions for each substrate used in the Heck reaction in an effort to maximise both catalyst efficiency and the product yield obtained. Unfortunately, in many examples the catalyst concentration used was insufficient to effect complete conversion of the aryl halide substrate to the desired coupled product. In other examples, efficiency may have been improved by increasing the reaction temperature, reducing the catalyst concentration or further investigating the effect of stabilising additives (for example tetrabutylammonium or phosphonium salts).

Secondly, the preparation of the metallated benzylphosphine palladacycles described above is not as efficient as many alternative palladacyclic catalysts described in the literature, most notably the Herrmann complex **5** (which is synthesised in high yield from the reaction of the commercially available tris(*o*-tolyl)phosphine with palladium(II) acetate)[43] and the Bedford compound **21** (similarly prepared from tris(2,4-di-*t*-butylphenyl)phosphite and palladium(II) chloride).[87] In contrast, the benzylphosphino ligands required for the preparation of the palladacycle complexes investigated above are not readily available, and are not straightforwardly prepared. Many of the reagents and intermediates are highly unstable in air, and some are relatively expensive. In addition, the synthetic steps to these ligands, and the metallation of the ligand to form the palladacyclic complex itself, are non-robust and

low yielding. Further work is required to develop a more efficient route to these complexes, possibly using an alternative palladium precursor to tris(dibenzylideneacetone)dipalladium(0). Presently, the potential application of the phenyl complex di-μ-bromobis[(diphenylphosphinomethylphenyl)-α,P)palladium(II)] **74** as a Heck catalyst is inhibited by the difficulty of preparation and relatively high cost of the complex in comparison to alternative catalysts reported in the literature.

Finally, the syntheses of a number of further palladacycle analogues were attempted without success. These included the attempted metallations of more easily available ligands, such as tribenzylphosphine and tris(*o*-bromobenzyl)phosphine. The successful synthesis of *o*-tolyl and dimethylamino derivatives of the phenyl complex **74** would have been desirable for comparison purposes (against the Herrmann complex **5** and the hydroarylation catalyst **118**, respectively). In addition, attempts to metallate synthesised arylaminophosphine ligands were also unsuccessful. It was expected that the resultant nitrogen-containing palladacycle compounds would have exhibited a catalytic activity similar to that of the electronically similar phosphite palladacycles of Bedford,[57, 87] which are more active than the metallated benzylphosphine complexes discussed above. Development of these syntheses may have resulted in the successful isolation of further palladacycle complexes with potential catalytic properties.

In conclusion, rather than the investigation and optimisation of a potential alkene carbonylation catalyst, the focus of this project, as a result of a number of factors, instead concentrated on the synthesis of a series of palladium complexes, many of which are novel, and the subsequent investigation of the catalytic properties of these

compounds. As a result, the discovery was made that several of these 'palladacycle' compounds were convenient, air-stable precursors to highly active underligated carbon—carbon bond forming catalysts, exhibiting activity that compares with, and in several example exceeds, that of existing systems.

CHAPTER 5

5. EXPERIMENTAL

5.1 Symbols and Abbreviations

The following common acronyms will be used in this section with further definition:

Ac	acetyl
Ar	aryl
Bn	benzyl
b.p.	boiling point
t-Bu	*tert*-butyl
δ	chemical shift in parts per million
dba	dibenzylideneacetone
DCM	dichloromethane
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
eq.	molar equivalent
Et	ethyl
GC	Gas Chromatography
GC—MS	Gas Chromatography—Mass Spectrometry
h, min	hours, minutes
J	spin-spin coupling constant in Hertz
LAH	lithiumaluminium hydride

M	mol dm^{-3}
Me	methyl
mol	moles
mmol	millimoles
m.p.	melting point
NBS	*N*-bromosuccinimide
NMR	Nuclear Magnetic Resonance
Ph	phenyl
r.t.	room temperature
s, d, t, q, m, br	singlet, doublet, triplet, quartet, multiplet, broad
THF	tetrahydrofuran
TMS	trimethylsilane

5.2 Instrumentation and General Techniques

5.2.1 NMR Spectroscopy

^{1}H NMR spectra were recorded at a frequency of 299.988 MHz using either a Varian Gemini 2000 or Bruker AM300 spectrometer at ambient temperature unless otherwise stated. TMS was used as an internal reference. Deuterated solvents were degassed and stored over molecular sieves before use.

^{13}C NMR spectra were recorded at 75.440 MHz also using either a Varian Gemini 2000 or Bruker AM300 spectrometer at ambient temperature unless otherwise stated.

^{31}P NMR spectra were recorded at 121.436 MHz with ^{1}H decoupling on a Varian Gemini 2000 spectrometer at ambient temperature unless otherwise stated. H_3PO_4 was used as an external reference.

5.2.2 GC and GC—MS

Gas chromatographic analyses were carried out on a Hewlett-Packard 5890 Series Gas Chromatograph equipped with both a flame ionisation detector (GC-FID) (for quantitative analyses) and a Hewlett-Packard 5890 Series mass selective detector (for qualitative analyses). The gas chromatograph was interfaced with a Hewlett-Packard Chemstation for the determination of peak areas by electronic integration. Both analysis methods employed a Supelco MDN-35 [bonded and crosslinked phase with 35 % phenyl and 65 % methylpolysiloxane] fused silica capillary column (30 m × 0.25 mm × 0.25 mm film thickness). For ease of identification, the GC-FID and GC-MS methods were specifically developed not only for clean separation of all reaction products, but also so that the retention time for each reaction product was very similar while employing either detection method. The GC-FID analysis method employed an oven temperature of 120 °C for 7.5 min. followed by a ramp of 20 °C min^{-1} to 280 °C and held. The flow of helium carrier gas through the column was constant at a flow rate of 2.0 cm^3 min^{-1} (initial inlet pressure = 25.3 psi), giving an initial linear gas velocity through the column of 45 cm s^{-1}. The GC-MS analysis method employed the

same oven temperature profile but with a constant helium carrier gas flow rate of 1.7 cm^3 min^{-1} (initial inlet pressure = 19.6 psi), giving an initial linear gas velocity through the column of 49 cm s^{-1}.

5.2.3 X-Ray Crystallography

Single-crystal x-ray crystallographic analyses of palladium complexes di-μ-bromobis[(di-*t*-butylphosphinomethyl-(3-methoxyphenyl))-α,P)palladium(II)] **71** and di-μ-chlorobis[(di-*t*-butylphosphinomethylphenyl)-α,P)palladium(II)] **78** were performed by Dr. Phil Lightfoot. For experimental details and x-ray data see Appendix I.

5.2.3 Elemental Analysis

CHN elemental analysis was performed on a Carlo-Erbo EA1110 or a Carlo-Erbo EA1106 apparatus by Mrs Sylvia Williamson.

5.2.4 Melting Point Determination

Melting points were determined using a Gallenkamp melting point apparatus, and are uncorrected.

5.2.5. Drying and Evaporation of Organic Solutions

Organic solutions were often dried by stirring with anhydrous magnesium or sodium sulfate for a period of at least 30 minutes then filtering the spent drying agent. This technique will be referred to as 'drying over magnesium/sodium sulfate'. Evaporation of organic solutions was often achieved by the use of a Buchi Rotavapor apparatus. This technique will be referred to as 'evaporating to dryness'.

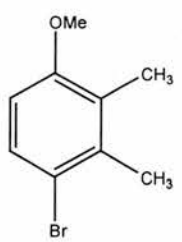
5.2.6 Drying and Purification of Organic Solvents

Organic solvents (e.g. toluene, ether, DCM, petroleum ether b.p. 40-60 °C, THF) were routinely dried according to standard procedures. These solvents were then stored over molecular sieves. Anhydrous DMA was purchased from Aldrich. All solvents were degassed and purged with argon prior to use.

5.3 Preparation of Phosphine Ligands

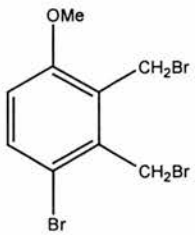
Except for the work-up of reaction mixtures, all operations were carried out under argon. 2,3-dimethylanisole, 4-bromo-3-methylanisole, 2-bromotoluene, 2,5-di-*t*-butylaniline and 2-bromoaniline were purchased from Aldrich or Lancaster. Di-*t*-butylphosphine and 2-bromobenzyl bromide were purchased from Aldrich or prepared according to the procedure below. Other phosphine compounds were purchased from Strem or Fluka or prepared according to the procedures below.

4-Bromo-2,3-dimethylanisole 57



2,3-dimethylanisole (27.24 g, 27.7 cm^3, 0.2 mol) was added to a flask and dissolved in carbon tetrachloride (150 cm^3). The flask was then covered to eliminate light (in an effort to discourage the radical mediated side-chain bromination reaction). To the stirred mixture was added dropwise a solution of bromine (32.0 g, 10.3 cm^3, 0.2 mol) in carbon tetrachloride (50 cm^3). The mixture was then stirred under reflux for 18 hours. The product solution was not isolated but analysed by ^1H NMR and used directly in next stage. $\delta_H(CDCl_3)$ 2.22 (3H, s, C(2)Me), 2.39 (3H, s, C(3)Me), 3.80 (3H, s, OMe), 6.60 (1H, d, *J* 9, C(6)H), 7.35 (1H, d, *J* 9, C(5)H).

4-Bromo-2,3-bis(bromomethyl)anisole **51**



A mixture of 4-bromo-2,3-dimethylanisole **57**, NBS (64.08 g, 1.8 eq.) and dibenzoyl peroxide (1.0 g, ~1 mol %) in carbon tetrachloride (150 cm^3) was heated at reflux for 18 hours and cooled. The succinimide by-product was removed by filtration and the solvent evaporated. The resultant yellow solid was recrystallised from hot hexane yielding the product as a white crystalline solid. (52.3 g, 70.1 % from 2,3-dimethylanisole), m.p. 99-100 °C (Found: C, 28.91; H, 2.20 %. $C_9H_9Br_3O$ requires C, 28.99; H, 2.43 %); $\delta_H(CDCl_3)$ 3.89 (3H, s, OMe), 4.74 (2H, s, C(2)CH_2Br), 4.78 (2H, s, C(3)CH_2Br), 6.76 (1H, d, *J* 8, C(6)H), 7.51 (1H, d, *J* 8, C(4)H); $\delta_C(CDCl_3)$ 23.8 (C(2)CH_2Br), 29.3 (C(3)CH_2Br), 56.1 (OMe), 112.9 (C(6)H), 116.3 (*C*(2)CH_2Br), 127.4 (*C*(3)CH_2Br), 134.1 (C(5)H), 136.9 (CBr), 157.3 (*C*OMe).

Di-t-butylchlorophosphine **59**

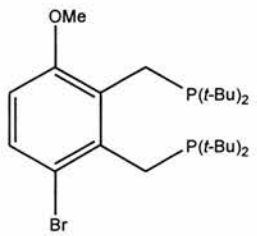
A solution of *t*-butyl chloride (59.3 g, 69.7 cm^3, 0.64 mol, 3.2 eq.) in diethyl ether (350 cm^3) was added to clean, dry magnesium turnings (14.6 g, 0.6 mol, 3 eq.). The dark grey Grignard solution was then heated under reflux for 2 h. A solution of phosphorus trichloride (27.5 g, 17.5 cm^3, 0.2 mol, 1 eq.) in diethyl ether (150 cm^3) was then added, dropwise with cooling and vigorous stirring, to the Grignard solution, over a period of 30 min. The reaction mixture was heated under reflux for a further 2

h., cooled to room temperature and allowed to settle overnight. The magnesium chloride precipitate was filtered, the solvent evaporated and the resulting residue subjected to vacuum distillation to yield the product as a clear liquid (19.72 g, 55 %)(b.p. 32 °C, 1 mmHg). $\delta_P(CDCl_3)$ 146.9 (s).

Di-t-butylphosphine **58**

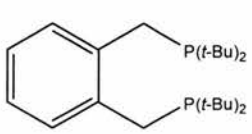
A solution of di-*t*-butylchlorophosphine **57** (19.0 g, 20 cm^3, 105.3 mmol) in diethyl ether (40 cm^3) was added, dropwise with vigorous stirring, to a chilled solution of LAH (4.2 g, 110.8 mmol) in diethyl ether (110 cm^3). The mixture was then heated under reflux for 1 h, cooled to 0 °C and hydrolysed with H_2O (4.2 cm^3) in THF (10 cm^3) and 5 % NaOH(aq) solution (17 cm^3). The mixture was stirred under reflux for a further 3 h. and allowed to cool overnight. By distillation at 0.1 mm Hg all components distilling between 20 °C and 80 °C were collected at –78 °C (acetone/CO_2 bath). The organic layer was then separated, dried ($MgSO_4$) and the solution evaporated to dryness. The crude product was then distilled to yield the product as a clear liquid (6.99 g, 60 %) (b.p. 22 °C, water pump vac.). $\delta_P(CDCl_3)$ 20.1 (s)(lit., $\delta_P(CDCl_3)$ 20.1(s)).[118]

Attempted synthesis of 4-*Bromo*-2,3-*bis(di-t-butylphosphinomethyl)anisole* 49



4-Bromo-2,3-bis(bromomethyl)anisole **51** (6.34 g, 17 mmol) was dissolved in the minimum amount of acetone (25 cm^3). Di-*t*-butylphosphine **58** (5.0 g, 34 mmol) was added to the stirred solution over period of 30 min. and the reaction mixture stirred at r.t. for 24 h. A solution of sodium acetate (9 g) in water (30 cm^3) was added to the mixture which was stirred for a further 24 h. The mixture was then extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness to yield a yellow-white solid, which was recrystallised from hexane/ether (1:1). ^{31}P NMR analysis showed the resultant solid to be a mixture of the desired product **49** (δ_P 33.6 (s), 35.5 (s)) and the heterocyclic by-product **60** (δ_P 67.5). The experiment was abandoned.

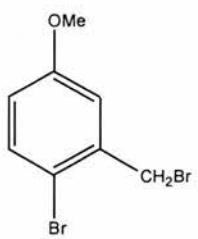
1,2-*Bis(di-t-butylphosphinomethyl)benzene* 64



n-Butyllithium (1.6 M in hexanes, 48.4 cm^3, 77.5 mmol) was added to a mixture of *o*-xylene (3.72 g, 35 mmol) and potassium *t*-butoxide (8.7 g, 77.5 mmol) in petrol ether

(40-60 °C)(175 cm^3) at –78 °C. The temperature of the mixture was allowed to rise to room temperature, then the orange-red mixture was heated under reflux for 1 h. The mixture was cooled to r.t., and the resultant brick-red solid filtered and washed with light petroleum (2 × 50 cm^3). The solid was cooled to –78 °C and diethyl ether (175 cm^3) added. Neat di-*t*-butylchlorophosphine **59** (14.0 g, 77.5 mmol) was added by syringe to the solution. The temperature of the mixture was allowed to rise to r.t. and the mixture was stirred overnight. The mixture was filtered and the filtrate hydrolysed with degassed water (2.0 cm^3). Filtration and solvent evaporation yielded an oily liquid. Crystallisation from methanol at –78 °C eventually yielded a small amount of a white crystalline solid (3.10 g, 32 %), δ_H ($CDCl_3$) 1.15 (36H, m, 4 × *t*-C_4H_9), 3.02 (4H, s, 2 × CH_2), 7.05 (2H, t, 2 × CH), 7.54 (2H, d, 2 × CH); δ_P ($CDCl_3$) 27.8 (s), 66.3 (s)(oxide).

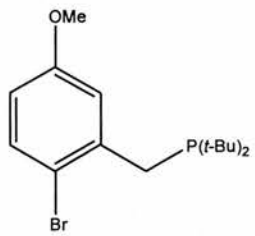
***4-Bromo-3-(bromomethyl)anisole* 67**



A mixture of 4-bromo-3-methylanisole (10.05 g, 11cm^3, 50 mmol), NBS (8.90 g, 50 mmol) and dibenzoyl peroxide (100 mg) in carbon tetrachloride (70 cm^3) was stirred under reflux for 18 h. The succinimide by-product was filtered and the solvent evaporated to yield a yellow oil which rapidly crystallised to give a white/yellow solid. Recrystallisation from hexane yielded the pure product as white needle crystals

(9.98g, 71 %). $\delta_H(CDCl_3)$ 3.80 (3H, s, OMe), 4.56 (2H, s, CH_2Br), 6.74 (1H, d, *J* 8, C(6)H), 7.00 (1H, s, C(2)H), 7.45 (1H, d, *J* 8, C(5)H); $\delta_C(CDCl_3)$ 35.5 (CH_2Br), 55.7 (OMe), 114.9 (*C*CH_2Br), 116.6 (C(6)H), 116.7 (C(2)H), 134.1 (C(5)H), 138.0 (CBr); 159.5 (*C*OMe).

***4-Bromo-3-(di-t-butylphosphinomethyl)anisole* 65**

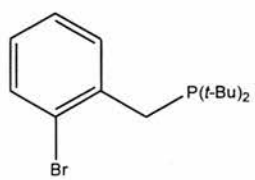


Neat di-*t*-butylphosphine **58** (4.0 cm^3, 21.4 mmol) was added to a solution of 4-bromo-3-(bromomethyl)anisole **67** (6.0 g, 21.4 mmol) in acetone (20 cm^3). The mixture was heated under reflux for 45 min. then cooled. Evaporation of the solvent yielded the phosphonium salt as a white solid. The salt was then dissolved in water (25 cm^3), and the solution treated with a solution of sodium acetate (5.5 g, 67 mmol) in water (13 cm^3). The mixture was stirred for 2 h. then extracted with diethyl ether (3 × 50 cm^3). Drying the organics ($MgSO_4$) and evaporation to dryness yielded a clear oil. Fractional distillation (Kugelrohr, 160 °C, ~1 mmHg) eventually afforded the product as a clear oil in only moderate purity (~57 %) by ^{31}P NMR. δ_P ($CDCl_3$) 33.9 (s)(product), 48.6 (s)(minor imp.), 60.7 (s)(oxide).

2-Bromobenzyl bromide

A mixture of 2-bromotoluene (68.4 g, 0.4 mol) and NBS (99.7 g, 0.56 mol) in carbon tetrachloride (480 cm^3) was treated with dibenzoyl peroxide (0.8 g) and heated under reflux for 4 h. The succinimide was filtered and the solvent evaporated to yield a yellow oil. Crystallisation of the product from petroleum ether (40 – 60 °C) was achieved by cooling to –20 °C to yield the product as a colourless solid (45.5 g, 45 %); δ_H ($CDCl_3$) 4.30 (2H, s, CH_2Br), 7.16 (1H, t, *J* 9, C(4)H), 7.29 (1H, t, *J* 7, C(5)H), 7.45 (1H, d, *J* 8, C(6)H), 7.58 (1H, d, *J* 12, C(3)H); δ_C ($CDCl_3$) 33.5 (CH_2Br), 124.8 (CBr), 128.1, 130.5, 131.7, 133.7, 137.3 (CCH_2Br).

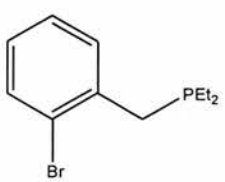
2-Bromobenzyldi-t-butylphosphine **68**



Di-*t*-butylphosphine **58** (5.0 g, 34.2 mmol) was added dropwise via syringe to a solution of 2-bromobenzyl bromide (8.55 g, 34.2 mmol) in acetone (20 cm^3). The mixture was heated under reflux for 45 min., during which time a white precipitate formed. The solvent was removed by filtration to yield 2-bromobenzyldi-*t*-butylphosphonium bromide (δ_P 31.7), which was dissolved in water (25 cm^3) and

treated with a solution of sodium acetate (7.0 g) in water (25 cm^3) and stirred at room temperature overnight. The mixture was extracted with diethyl ether (3 × 30 cm^3) and the combined organics dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled to yield the product as a clear liquid (7.3 g, 67 %), b.p. 102 – 106 °C, 0.2 mm Hg; δ_H ($CDCl_3$) 1.1–1.3 (18H, m, 4 × *t*-C_4H_9), 2.99 (2H, br s, CH_2P), 6.97 (1H, t, *J* 9, C*4*-H), 7.19 (1H, t, *J* 7, C*5*-H), 7.45 (1H, d, *J* 9, C*6*-H), 7.63 (1H, d, *J* 10, C*3*-H); δ_C ($CDCl_3$) 15.3 (CH_2), 27.9 ($C(CH_3)_3$), 29.7 (CH_3), 32.0 ($C(CH_3)_3$), 125.1 (CBr), 127.2 (CH), 127.3 (CH), 132.3 (CH), 132.9 (CH), 141.1 (CCH_2); δ_P ($CDCl_3$) 34.7 (s).

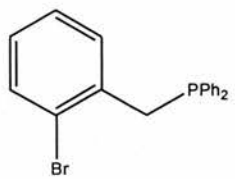
(2-Bromobenzyl)diethylphosphine 69



Diethylphosphine (5.0 g, 55.5 mmol) was added to a solution of 2-bromobenzyl bromide (13.87 g, 55.5 mmol) in diethyl ether (40 cm^3). The resultant precipitate (2-bromobenzyl)diethylphosphonium bromide (δ_P 18.7) was collected by filtration and dissolved in water (50 cm^3). The solution was treated with aqueous sodium acetate (10 g in 50 cm^3 water) and the mixture stirred at r.t. overnight. The mixture was then extracted with diethyl ether (3 × 50 cm^3), dried ($MgSO_4$), evaporated to dryness and distilled (Kugelrohr, b.p. 125 °C, ~1 mm Hg) to obtain the product as a clear oil (3.17 g, 22 %), δ_H ($CDCl_3$) 1.05 (6H, t, *J* 6, 2 × CH_3), 1.45 (4H, q, *J* 6, 2 × CH_2CH_3), 2.92 (2H, s, CH_2Ar), 6.98 (1H, t, *J* 9, Ar), 7.18 (2H, m, Ar), 7.50 (1H, d, *J* 7.5, Ar); δ_C

($CDCl_3$) 9.6 (CH_3), 18.9 (CH_2CH_3), 34.1 (CH_2Ar), 124.6 (CBr), 127.3, 130.9, 133.0, 138.8 (CCH_2P); δ_P ($CDCl_3$) –13.6 (s).

(2-Bromobenzyl)diphenylphosphine 70



Diphenylphosphine (4.4 g, 23.6 mmol) was added to solution of 2-bromobenzyl bromide (6.71 g, 26.7 mmol) in ether (15 cm^3). The mixture was stirred under reflux for 30 min. and cooled overnight. A white solid (phosphonium bromide, δ_P –1.6) was filtered (cannula) and dried *en vacuo*. The salt was dissolved in water (35 cm^3) and treated with a solution of sodium acetate (5.0 g) in water (25 cm^3). The mixture was heated at 70 °C and cooled. The solution was then extracted with diethyl ether (3 × 30 cm^3). The combined organic layers were dried ($MgSO_4$), evaporated and the resultant solid recrystallised from ethanol to yield white needles (2.70 g, 32 %), δ_H ($CDCl_3$) 3.55 (2H, s, CH_2P), 6.82 (2H, d, *J* 7.5, Ar), 7.02 (2H, m, Ar), 7.37 (10H, m, PPh_2), 7.56 (1H, d, *J* 9, Ar); δ_P ($CDCl_3$) –12.4 (s).

Benzyldi-t-butylphosphine 79

Neat di-*t*-butylphosphine **58** (5.0 g, 34.2 mmol) was added to a solution of benzyl bromide (5.85 g, 34.2 mmol) in acetone (20 cm^3). The solution was heated under reflux for 45 min., then cooled to 5 °C to yield a white precipitate. The solvent was

removed *in vacuo* and a sample of the phosphonium salt removed for NMR analysis (δ_P 33.3(s)). The salt was dissolved in water (25 cm^3) and treated with a solution of sodium acetate (7.0 g) in water (25 cm^3) and the mixture stirred overnight. The mixture was extracted with diethyl ether (3 × 30 cm^3), dried ($MgSO_4$) and evaporated. Distillation yielded the product as a clear liquid (4.8 g, 59 %); b.p. 126 – 130 °C, 0.25 mm Hg; ^{31}P NMR ($CDCl_3$) δ_P 35.4 (s).

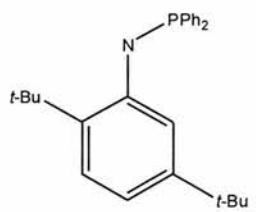
Benzyldiphenylphosphine

Benzyl magnesium chloride was prepared by adding a solution of benzyl chloride (6.96 g, 55 mmol) in diethyl ether (60 cm^3) to magnesium turnings (1.7 g, 70 mmol). After the reaction had ceased, the mixture was heated under reflux and cooled. A solution of chlorodiphenylphosphine (10.0 g, 45.3 mmol) in diethyl ether (50 cm^3) was added, dropwise with stirring at 0 °C to the Grignard solution. The reaction mixture was stirred at ambient temperature for 2 h. and allowed to settle overnight. The resultant mixture was hydrolysed with ammonium chloride solution (100 cm^3, 1 mol dm^{-3} in water). The hydrolysed solution was filtered twice, separated and the organic layer filtered again. The filtrate was then dried ($MgSO_4$) and evaporated to dryness. The resultant white solid was recrystallised twice (EtOH) to eventually yield the product as a white solid (1.2 g, 9.6 %) in 82 % purity (by ^{31}P NMR). δ_H ($CDCl_3$) 3.35 (2H, s, CH_2Ph), 6.95–7.70 (15H, m, 3 × Ph); δ_P ($CDCl_3$) –9.4 (product), 30.0 (oxide).

Dibenzylphenylphosphine

Benzyl magnesium chloride was prepared by adding a solution of benzyl chloride (17.0 g, 134 mmol) in diethyl ether (140 cm^3) to magnesium turnings (3.91 g, 156 mmol). After reaction, the mixture was heated under reflux for 1 h. and cooled to 0 °C. A solution of dichlorophenylphosphine (10.0 g, 55.9 mmol) in diethyl ether (65 cm^3) was added, dropwise with stirring at 0 °C, to the Grignard solution. The mixture was heated under reflux for 1 h. and allowed to cool and settle overnight. The mixture was hydrolysed with ammonium chloride solution (200 cm^3, 1 mol dm^{-3} in water), the organic layer separated, dried ($MgSO_4$) and evaporated to dryness. The resultant white solid was recrystallised (EtOH) to yield the product in 81 % purity (by ^{31}P NMR) (3.7 g, 23 %). δ_H ($CDCl_3$) 3.0 (4H, s, 2 × CH_2Ph), 6.9 – 7.4 (15H, m, 3 × Ph); δ_P ($CDCl_3$) –12.2 (product), 35.7 (oxide).

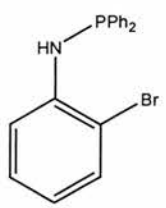
(2,5-Di-t-butylphenylamino)diphenylphosphine **86**



Anhydrous triethylamine (7.0 cm^3, 50 mmol) and DMAP (0.62 g, 5 mmol) were added to a solution of 2,5-di-*t*-butylaniline (10.0 g, 48.7 mmol) in THF (180 cm^3). The mixture was cooled to 0 °C and neat chlorodiphenylphosphine (8.8 cm^3, 48.7 mmol) added. The mixture was stirred at r.t. for 24 h. and the resultant triethylamine hydrochloride precipitate filtered and washed with THF (2 × 50 cm^3). The filtrate and

washings were then evaporated to dryness and cooled to yield a yellow-white solid. Recrystallisation from ethanol yielded the product as a white powder (13.44 g, 71 %), m.p. 107-109 °C, (Found: C, 81.06; H, 8.38; N, 3.67 %. $C_{26}H_{32}NP$ requires C, 80.17; H, 8.28; N, 3.60 %); δ_H ($CDCl_3$) 1.20 (9H, s, *t*-C_4H_9), 1.35 (9H, s, *t*-C_4H_9), 6.82 (1H, dd, *J* 4 and 8.5, Ar), 7.20 (1H, d, *J* 9,Ar), 7.29 (1H, dd, *J* 3 and 5.5, Ar), 7.37—7.50 (10H, m, PPh_2); δ_C ($CDCl_3$) 30.6 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 33.8 ($C(CH_3)_3$), 34.4 ($C(CH_3)_3$), 114.6, 114.9, 126.2, 128.8, 128.9, 129.3, 131.5, 131.8, 133.0, 140.6, 140.8, 144.5, 150.2; δ_P ($CDCl_3$) 29.7 (s).

(2-Bromophenylamino)diphenylphosphine **87**

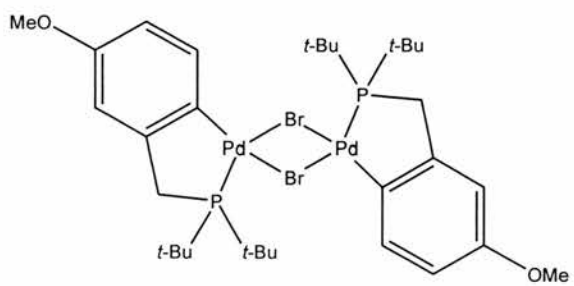


Anhydrous triethylamine (8.5 cm^3, 60 mmol) and DMAP (0.73 g, 6 mmol) were added to a solution of 2-bromoaniline (10.0 g, 58.1 mmol) in THF (200 cm^3). The mixture was cooled to 0 °C and neat chlorodiphenylphosphine (10.5 cm^3, 58.1 mmol) added. The mixture was stirred at r.t. for 24 h. and the resultant triethylamine hydrochloride precipitate filtered. The filtrate was cooled in the freezer to yield a yellow solid which was recrystallised from ethanol to yield the product as an off-white powder (12.71 g, 61 %), m.p. 48-49 °C, (Found: C, 60.93; H, 4.16; N, 3.99 %. $C_{18}H_{15}BrNP$ requires C, 60.70; H, 4.24; N, 3.93 %); δ_H ($CDCl_3$) 6.69 (1H, t, *J* 6.5, Ar), 7.18 (1H, t, *J* 8.5, Ar), 7.36-7.54 (12H, m, Ar); δ_P ($CDCl_3$) 29.5 (s).

5.4 Preparation of Palladium Complexes

Sodium tetrachloropalladate, palladium chloride, palladium acetate and tris(dibenzylideneacetone)dipalladium were purchased from Aldrich or Lancaster. The Herrmann palladacycle **5**, [43] dichloro(1,5-cyclooctadiene)dipalladium(II) **80**[108] and di-μ-dichlorobis(8-methoxy-4-cycloocten-1-yl)dipalladium **81**[109] were prepared according to literature procedures.

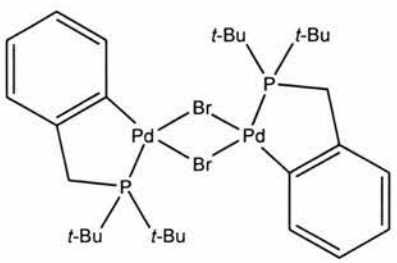
Di-μ-bromobis[(di-t-butylphosphinomethyl(-3-methoxyphenyl))-α,P)-palladium(II)] **71**



Tris(dibenzylideneacetone)dipalladium(0) (1.80 g, 1.96 mmol) was added to a solution of impure 4-bromo-3-(di-*t*-butylphosphinomethyl)anisole (5.0 g, corrected to 2.75 g, 8.0 mmol, 4 eq.) in toluene (50 cm^3). The mixture was then heated under reflux for 30 min. and cooled. The mixture was reduced to ¼ volume and *n*-hexane (50 cm^3) added which yielded a pale green precipitate. The precipitate was filtered and washed with diethyl ether (100 cm^3). The resultant grey-green solid was heated in DCM and subjected to hot filtration. The yellow filtrate was evaporated to dryness and the resultant yellow solid recrystallised from DCM/diethyl ether to yield the

product as yellow crystals (0.40 g, 23 %), (Found: C, 42.63; H, 5.78 %. $C_{32}H_{52}Br_2O_2P_2Pd_2$ requires C, 42.55; H, 5.80 %); mp 230 - 232 °C; δ_H ($CDCl_3$) 1.41 (36H, m, 4 × *t*-C_4H_9), 3.19 (4H, d, *J* 13, 2 × CH_2P), 3.73 (6H, s, 2 × OMe), 6.51 (2H, d, *J* 4, 2 × CH), 6.64 (2H, s, 2 × CH), 7.83 (2H, d, *J* 4, 2 × CH); δ_C ($CDCl_3$) 29.7, 24.6 (d, *J* 29, CH_2P), 36.5, 109.3, 109.6, 111.1, 139.0, 139.4, 157.8; δ_P ($CDCl_3$) 99.6 (s)(*trans*-), 99.4 (s)(*cis*-).

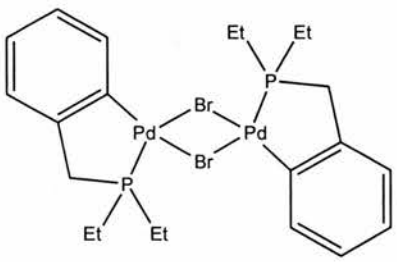
***Di-μ-bromobis[(di-t-butylphosphinomethylphenyl)-α,P)palladium(II)]* 72**



A solution of tris(dibenzylideneacetone)dipalladium(0) (5.28 g, 5.8 mmol) in xylenes (40 cm^3) was treated with 2-bromobenzyldi-*t*-butylphosphine **68** (4.0 g, 12.7 mmol, 2.2 eq.). The mixture stirred at room temperature overnight, and then heated under reflux for 3 h. and cooled. Palladium metal precipitate was removed by filtration. The filtrate was evaporated to dryness and the resultant yellow solid redissolved in DCM. The dibenzylideneacetone by-product was precipitated by addition of hexane (50 cm^3) and removed by filtration. The filtrate was then evaporated to dryness and the solid recrystallised from DCM/hexane to finally yield the product as an orange crystalline solid (1.85 g, 38 %), δ_H ($CDCl_3$) 1.41 (36H, m, 4 × *t*-C_4H_9), 3.22 (4H, d, *J* 13, 2 × CH_2P), 6.82 (2H, t, *J* 4, 2 × CH), 6.95 (2H, t, *J* 4, 2 × CH), 7.02 (2H, d, *J* 4, 2

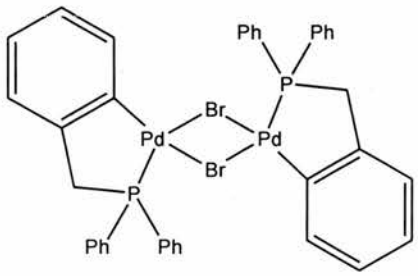
× CH), 7.92 (2H, d, *J* 5, 2 × CH); δ_C ($CDCl_3$) 29.7, 34.7 (d, *J* 28, CH_2P), 36.5, 123.3, 123.5, 125.2, 125.4, 138.7, 139.0; δ_P ($CDCl_3$) 101.2 (s)(*trans*-), 101.0 (s)(*cis*-).

Di-μ-bromobis[(diethylphosphinomethylphenyl)-α,P)palladium(II)] **73**



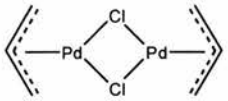
A solution of tris(dibenzylideneacetone)dipalladium(0) (4.48 g, 4.9 mmol) in xylenes (80 cm^3) was treated with 2-bromobenzyldiethylphosphine **69** (3.1 g, 10.8 mmol, 2.2 eq.). The mixture was stirred for 30 min. at r.t., 1 h. at 100 °C, and then 3 h. at 120 °C. The cooled mixture was then filtered to remove the palladium metal precipitate and the resultant filtrate reduced to ¼ volume. Addition of hexane (80 cm^3) yielded a yellow precipitate which was filtered and recystallised from DCM/hexane to yield the product as yellow crystals (1.22 g, 34 %), (Found: C, 35.87; H, 4.25 %. $C_{22}H_{32}Br_2P_2Pd_2$ requires C, 36.15; H, 4.41 %); mp 225 - 227 °C; δ_H ($CDCl_3$) 1.42 (12H, t, *J* 6, 4 × CH_3), 3.26 (4H, d, *J* 13, 2 × CH_2P), 3.48 (8H, q, *J* 9, 4 × CH_2), 6.96 (2H, t, *J* 4, 2 × CH), 6.97 (2H, t, *J* 4, 2 × CH), 7.08 (2H, d, *J* 10, 2 × CH), 7.85 (2H, d, 2 × CH); δ_C ($CDCl_3$) 9.0, 20.3, 20.6, 37.2 (d, *J* 34, CH_2P), 124.3, 124.6, 125.5, 125.8, 138.5; δ_P ($CDCl_3$) 70.1, (s)(*trans*-), 68.7 (s)(*cis*-).

***Di-μ-bromobis[(diphenylphosphinomethylphenyl)-α,P)palladium(II)]* 74**



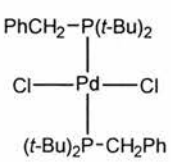
A solution of tris(dibenzylideneacetone)dipalladium(0) (7.64 g, 8.3 mmol) in xylenes (120 cm^3) was treated with 2-bromobenzyldiphenylphosphine **70** (6.52 g, 18.4 mmol, 2.2 eq.). The mixture was heated at reflux for 3 h. and cooled. The mixture was then filtered to remove palladium precipitate and filtrate reduced to ¼ volume. Addition of hexane (100 cm^3) yielded the dba by-product as a yellow precipitate which was removed by filtration. The filtrate was evaporated to dryness and the resultant solid recrystallised twice by DCM/hexane to yield the product as a yellow crystalline solid (dichloromethane hemi-solvate)(0.50 g, 6 %). Further material was obtained from a second crop (total yield 1.16 g, 15 %), mp > 200 °C (Found: C, 47.90; H, 3.33 %. $C_{32}H_{52}Br_2O_2P_2Pd_2.0.5CH_2Cl_2$ requires C, 47.88; H, 3.44 %); δ_H ($CDCl_3$) 3.83 (4H, d, *J* 13, 2 × CH_2P), 6.85 (2H, t, *J* 8, 2 × CH), 6.99 (2H, m, 2 × CH), 7.13 (2H, d, *J* 7, 2 × CH), 7.3—7.9 (20H, m, 2 × PPh_2), 8.07 (2H, br d, 2 × CH); δ_C ($CDCl_3$) 43.6 (d, *J* 37, CH_2P), 124.4, 125.7, 125.9, 129.0, 131.4, 133.3, 133.4, 138.7; δ_P ($CDCl_3$) 56.7 (s)(*trans*-), 56.2 (s)(*cis*-).

***Di-μ-chlorobis(η^3-2-propenyl)dipalladium(II)* 75**[106]



Methanol (17 cm^3) was added to a solution of sodium tetrachloropalladate (2.0 g, 6.8 mmol) in water (2.8 cm^3). Allyl chloride (1.5 cm^3, 18.2 mmol) was then added to the solution. The solution was then stirred at ambient temperature with carbon monoxide bubbling for 1 h. after which the resultant green mixture was poured into degassed water (80 cm^3) and shaken well. The mixture was extracted into DCM (2 × 30 cm^3). The combined organic layers were then washed with water (2 × 45 cm^3) and dried ($MgSO_4$). Evaporation to dryness yielded the desired product as a yellow crystalline solid (0.97 g, 78 %), (Found: C, 19.54; H, 2.57 %. $C_6H_{10}Cl_2Pd_2$ requires C, 19.70; H, 2.76 %); δ_H ($CDCl_3$) 2.98 (4H, d, *J* 14, 2 × CH_3), 4.04 (4H, d, *J* 10, 2 × CH_3), 5.39 (2H, sp, *J* 7, 1 × CH); δ_C ($CDCl_3$) 63.0 (CH_3), 111.3 (CH).

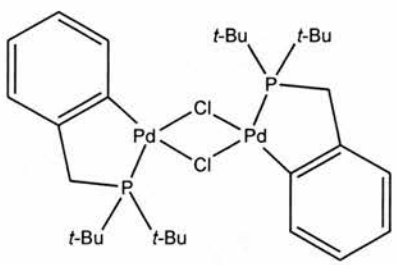
Bis(benzyldi-t-butylphosphine)palladium(II) dichloride[104]



Benzyldi-*t*-butylphosphine **79** (1.8 g, 7.6 mmol) was added via syringe to a solution of sodium tetrachloropalladate (1.0 g, 3.4 mmol) in methanol (16 cm^3) and the solution stirred at room temperature overnight. The resultant yellow precipitate was filtered via cannula, washed with water then ethanol, dissolved in DCM, dried ($MgSO_4$) and

evaporated to yield an orange solid. Recrystallisation (DCM/methanol) yielded the product as orange crystals (0.58 g, 26 %), δ_H ($CDCl_3$) 1.58 (36H, m, 4 × *t*-C_4H_9), 3.75 (4H, t, *J* 7, 2 × CH_2P), 7.20—7.35 (10H, m, 2 × Ph); δ_P ($CDCl_3$) 43.0 (s).

***Di-μ-chlorobis[(di-t-butylphosphinomethylphenyl)-α,P)palladium(II)]* 78**



A solution of benzyldi-*t*-butylphosphine **79** (0.16 g, 2 equiv) in *o*-xylene (10 cm^3) was added via syringe to a solution of di-μ-chlorobis(η^3-2-propenyl)dipalladium(II) **75** (100 mg, 0.27 mmol) in *o*-xylene (30 cm^3). The mixture was stirred overnight at r.t. then heated under reflux for a further 4 h. Evaporation to dryness yielded a solid which was recrystallised (DCM/hexane) to yield the product as a single yellow crystal (0.16 g, 77 %), (Found: C, 48.06; H, 6.46 %. $C_{30}H_{48}Cl_2P_2Pd_2$ requires C, 47.76; H, 6.41 %); m.p. 222 – 224 °C (dec.); δ_H ($CDCl_3$) 1.46 (36H, m, 4 × *t*-C_4H_9), 3.22 (4H, d, *J* 13, 2 × CH_2P), 6.83—7.03 (6H, m, 6 × CH), 7.80 (1H, m, CH); δ_C ($CDCl_3$) 29.5, 34.0 (d, *J* 30, CH_2P), 36.2, 123.2, 123.5, 125.1, 125.4, 137.1, 137.5; δ_P ($CDCl_3$) 102.2 (s)(*trans*-), 101.8 (s)(*cis*-).

Alternatively, the product **78** was obtained by treating a solution of *trans*-dichlorobis(benzyldi-*t*-butylphosphine)palladium(II) (0.58 g, 0.89 mmol) in 2-

methoxyethanol (40 cm^3) with sodium acetate (2.58 g, 30.5 mmol) and heating the resultant mixture under reflux for 2 h. The mixture was then treated with water (75 cm^3), and the resultant precipitate filtered and recrystallised (DCM/petroleum ether) to yield the product as yellow crystals (0.13 g, 38 %), δ_P ($CDCl_3$) 102.1 (s)(*trans*-), 101.7 (s)(*cis*-).

5.5 Catalysis

5.5.1 Alkene Carbonylations — General Procedure

Alkene carbonylation reactions were attempted at the catalyst development laboratories at Ineos Acrylics, Wilton, UK, with the help of Dr. Graham Eastham.

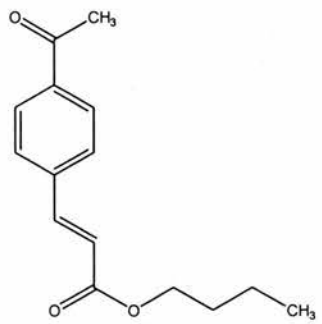
The palladium complex to be tested (50 mg) was dissolved in DCM (5.0 cm^3) and the solution diluted with methanol (80 cm^3). Methane sulfonic acid (0 — 10 eq.) was added to the solution and the mixture transferred to a 250 cm^3 glass autoclave. The autoclave was then charged with 10 bar 1:1 ethene/carbon monoxide and heated to the reaction temperature. After 2-5 hours the vessel was depressurised and a sample of the reaction mixture taken for GC/GC—MS analysis.

5.5.2 Heck Reactions — General Procedure

A suspension of the aryl halide (50 mmol), naphthalene (25 mmol) and base (55 mmol) in DMA (50 cm^3) was degassed and purged with argon several times. The alkene (70-100 mmol) was then added to the suspension and the reaction mixture heated. When the reaction temperature was obtained, the catalyst was added as a solution in DMA. The reaction was then monitored by GC/GC—MS by withdrawing samples at regular intervals. The product was isolated by washing the cooled reaction mixture with 5 % HCl solution, extraction with DCM (3 × 50 cm^3), drying the

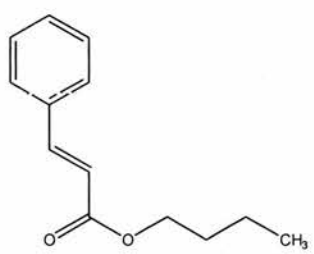
organics over $MgSO_4$ and evaporation to dryness. The crude product was then purified by distillation or recrystallisation.

***n-Butyl (E)-4-acetylcinnamate* 92**



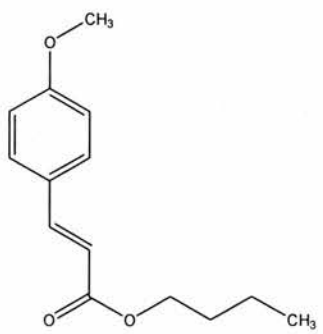
δ_H ($CDCl_3$) 0.95 (3H, t, *J* 9, CH_2CH_3), 1.40 (2H, m, *J* 8, CH_2CH_3), 1.67 (2H, m, *J* 8, $CH_2CH_2CH_3$), 2.59 (3H, s, $COCH_3$), 4.19 (2H, t, *J* 8, $CH_2CH_2CH_2CH_3$), 6.48 (1H, d, *J* 17, COC*H*=CH), 7.57 (2H, d, *J* 9, 2 × CH), 7.65 (1H, d, *J* 17, ArC*H*=CH), 7.92 (2H, d, *J* 9, 2 × CH); δ_C ($CDCl_3$) 13.8 (CH_2CH_3), 19.3 (CH_2CH_3), 26.8 ($COCH_3$), 30.9 ($CH_2CH_2CH_3$), 64.9 ($CH_2CH_2CH_2CH_3$), 121.1 (COCH=CH), 128.4, 129.1, 138.3, 139.1, 143.3 (ArCH=CH), 167.0 (CO_2Bu), 197.7 ($COCH_3$).

n-Butyl (E)-4-cinnamate



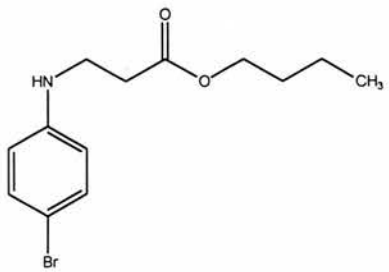
δ_H ($CDCl_3$) 0.96 (3H, t, *J* 7, CH_2CH_3), 1.40 (2H, m, *J* 7, CH_2CH_3), 1.67 (2H, m, *J* 7, $CH_2CH_2CH_3$), 4.20 (2H, t, *J* 7, $CH_2CH_2CH_2CH_3$), 6.45 (1H, d, *J* 16, COC*H*=CH), 7.35 (1H, t, *J* 3.5, CH), 7.52 (2H, t, *J* 3.5, CH), 7.69 (1H, d, *J* 16, ArC*H*=CH), 7.82 (2H, d, *J* 3.5, 2 × CH); δ_C ($CDCl_3$) 13.7 (CH_2CH_3), 19.2 (CH_2CH_3), 30.8 ($CH_2CH_2CH_3$), 64.5 ($CH_2CH_2CH_2CH_3$), 118.5 (COCH=CH), 125.9, 128.1, 128.2, 129.0, 130.4, 134.7 (CCH=CH), 144.7 (ArCH=CH), 167.3 (CO_2Bu).

n-Butyl (E)-4-methoxycinnamate



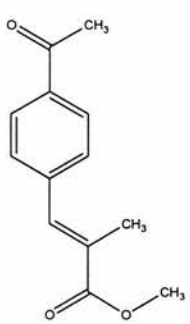
δ_H ($CDCl_3$) 0.95 (3H, t, *J* 7.5, CH_2CH_3), 1.43 (2H, m, *J* 7.5, CH_2CH_3), 1.67 (2H, m, *J* 7.5, $CH_2CH_2CH_3$), 3.79 (3H, s, OCH_3), 4.17 (2H, t, *J* 7, $CH_2CH_2CH_2CH_3$), 6.30 (1H, d, *J* 16, COC*H*=CH), 6.86 (2H, d, *J* 7, 2 × CH), 7.44 (2H, d, *J* 7, 2 × CH), 7.63 (1H, d, *J* 16, ArC*H*=CH); δ_C ($CDCl_3$) 13.7 (CH_2CH_3), 19.2 (CH_2CH_3), 30.9 ($CH_2CH_2CH_3$), 55.3 (OCH_3), 64.3 ($CH_2CH_2CH_2CH_3$), 114.5, 115.9 (COCH=CH), 127.4 (CCH=CH), 129.8, 144.4 (ArCH=CH), 161.6 ($COCH_3$), 167.6 (CO_2Bu).

***n-Butyl* 3-*(4-bromoanilino)propanoate* 98**



Isolated by distillation (b.p. 125 °C, 1 mm Hg). δ_H ($CDCl_3$) 0.96 (3H, t, *J* 7, CH_3), 1.39 (2H, m, *J* 8, CH_2CH_3), 1.62 (2H, m, *J* 8, $CH_2CH_2CH_3$), 2.65 (2H, t, *J* 6.5, CH_2CO_2Bu), 3.45 (2H, t, *J* 6.5, $NHCH_2$), 4.12 (2H, t, *J* 6.5, $CH_2CH_2CH_2CH_3$), 6.60 (2H, d, *J* 6.5, 2 × CH), 7.30 (2H, d, *J* 8.5, 2 × CH); δ_C ($CDCl_3$) 13.8 (CH_3), 19.2 (CH_2CH_3), 30.7 ($CH_2CH_2CH_3$), 33.6 (CH_2CO_2Bu), 40.4 ($NHCH_2$), 64.9 ($CH_2CH_2CH_2CH_3$), 110.8 (CBr), 115.8, 132.4, 145.9 (CNH), 172.5 (CO).

***Methyl* 3-*(4-acetylphenyl)*-2-*methylpropenoate* 105**

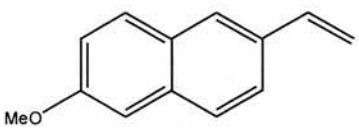


Isolated by column chromatography (ethyl acetate/hexane 1:8). δ_H ($CDCl_3$) 2.12 (3H, s, $C=CCH_3$), 2.61 (3H, s, $COCH_3$), 3.82 (3H, s, $COOCH_3$), 7.47 (2H, d, *J* 8, 2 × CH), 7.69 (1H, s, C*H*=C), 7.98 (2H, d, *J* 4.5, 2 × CH); δ_C ($CDCl_3$) 14.3, ($C=CCH_3$), 26.8

($COCH_3$), 52.4 ($COOCH_3$), 128.7, 130.0, 130.8, 136.8, 137.9, 140.9, 169.1 ($COOCH_3$), 197.9 ($COCH_3$).

5.5.3 Heck Reactions with Ethene

2-*Methoxy*-6-*vinylnaphthalene* 28



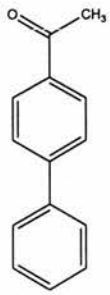
A mixture of 2-bromo-6-methoxynaphthalene (2.37 g, 10 mmol), naphthalene (0.64 g, 5 mmol) and the catalyst **74** (1×10^{-2} mol % Pd) in DMA (10 cm^3) was degassed and purged with argon several times. Sodium acetate (0.90 g, 11 mmol) was charged to the autoclave, which was evacuated and purged with argon several times. The reaction mixture was transferred to a 50 cm^3 autoclave via syringe and the autoclave evacuated and purged three times with 10 bar ethene. The autoclave was then sealed under ca. 2 bar ethene, and rapidly heated to 140 °C. Once the temperature had stabilised the autoclave was opened to a ballast vessel containing ethene which was connected to the autoclave via a mass-flow controller set at 20 bar. The mixture was stirred maintaining 140 °C and 20 bar pressure for 24 hours. The reaction progress was monitored by observing the pressure drop in the ballast vessel over time. After 24 h., the vessel was depressurised and the reaction mixture analysed by GC/GC—MS. The mixture was washed with water (50 cm^3), extracted into DCM (3×50 cm^3), dried over magnesium sulfate and evaporated to dryness to yield the product, 2-methoxy-6-vinylnaphthalene, **28**; δ_H ($CDCl_3$) 3.82 (3H, s, OCH_3), 5.20 (1H, d, *J* 11,

CH=CH*H*), 5.74 (1H, d, *J* 17.5, CH=C*H*H), 6.77 (1H, dd, *J* 12 and 16, C*H*=CH_2), 7.08 (1H, dd, *J* 3 and 9, CH), 7.44 (1H, d, *J* 3, CH), 7.60 (1H, d, *J* 3, CH), 7.62 (1H, d, *J* 7, CH), 7.74 (1H, d, *J* 5, CH), 7.77 (1H, d, *J* 3, CH); δ_C ($CDCl_3$) 55.4 (OCH_3), 106.0, 113.2 (CH=*C*H_2), 120.0, 124.0, 126.0, 126.3, 127.2, 128.1, 128.7, 129.7, 137.1 (*C*H=CH_2), 158.2 (*C*OCH_3).

5.5.3 Suzuki Reactions — General Procedure

A suspension of the aryl halide (50 mmol), phenylboronic acid (75 mmol), naphthalene (25 mmol) and potassium carbonate (100 mmol) in *o*-xylene (150 cm^3) was degassed and purged with argon several times. The reaction mixture was heated to the reaction temperature and the catalyst added as a solution in *o*-xylene. The reaction was followed by GC/GC—MS by withdrawing samples at regular intervals. The product was isolated by washing the reaction mixture with water (2 × 100 cm^3), drying the organics over $MgSO_4$ and evaporating to dryness. The product was then purified by recrystallisation.

4-Acetylbiphenyl



Isolated by recrystallisation from ethanol. δ_H ($CDCl_3$) 2.60 (3H, s, $COCH_3$), 7.39 (1H, t, *J* 7, CH), 7.41 (2H, t, *J* 7, 2 × CH), 7.59 (2H, d, *J* 9, 2 × CH), 7.63 (2H, d, *J* 7, 2 × CH), 7.99 (2H, d, *J* 9, 2 × CH); δ_C ($CDCl_3$) 26.8 ($COCH_3$), 126.1, 127.5, 127.6, 128.2, 128.5, 129.2, 129.3, 136.2 ($CCOCH_3$), 140.2, 146.1, 198.1 ($COCH_3$).

5.5.4 Stille Reactions — General Procedure

A solution of the aryl halide (8 mmol) and naphthalene (4 mmol) in toluene (40 cm^3) was degassed and purged with argon several times. Trimethyl(phenyl)tin (10 mmol) was then added to the solution via syringe. The mixture was degassed once more, heated to the reaction temperature and the catalyst added as a solution in toluene. The reaction was monitored by GC/GC—MS by withdrawing samples at regular intervals. The product was identified by GC—MS, but was not isolated.

4.5.5 Hydroarylation Reactions — General Procedure

A solution of the norbornene (100 mmol), the aryl halide (300 mmol), naphthalene (50 mmol), triethylamine (350 mmol) and formic acid (300 mmol) in DMSO (130 cm^3) was degassed and purged with argon several times. The mixture was then heated to the reaction temperature and the catalyst injected as a solution in DMSO. The reaction was followed by GC/GC—MS by withdrawing samples at regular intervals. The product(s) were not isolated.

4.5.6 Attempted Heck Reaction of 5-Vinylnorborn-2-ene — General Procedure

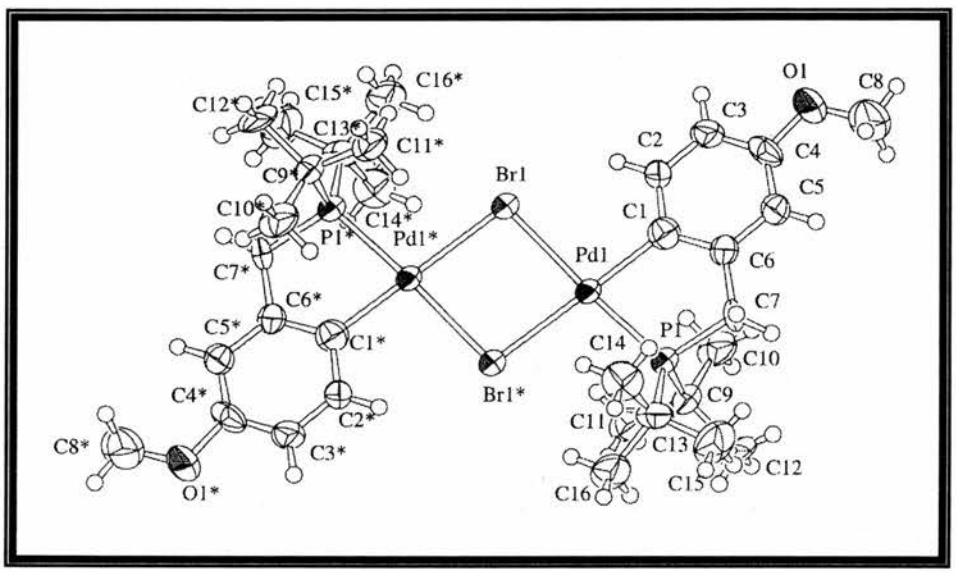
A suspension of 5-vinylnorbor-2-ene (50 mmol), the aryl halide (75 mmol), naphthalene (25 mmol) and sodium acetate (55 mmol) in DMA (50 cm^3) was degassed and purged with argon several times. The mixture was heated to the reaction temperature and the catalyst injected as a solution in DMA. The reaction was followed by GC/GC—MS by withdrawing samples at regular intervals. The reaction was unsuccessful in every case and no products were isolated.

APPENDIX I

X-RAY CRYSTALLOGRAPHY

X-Ray Crystallography

***Di-μ-bromobis[(di-t-butylphosphinomethyl(-3-methoxyphenyl))-α,P)-palladium(II)]* 71**



Experimental

Data Collection

A yellow block crystal of $C_{32}H_{52}Br_2O_2P_2Pd_2$ having approximate dimensions of 0.40 × 0.35 × 0.35 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo—Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the

range $24.25 < 2\theta < 24.88°$ corresponded to a primitive orthorhombic cell with dimensions:

$a = 18.24(1)$ Å

$b = 15.607(7)$ Å

$c = 12.989(6)$ Å

$V = 3672(5)$ Å^3

For $Z = 8$ and F.W. = 903.36, the calculated density is 1.63 g/cm^3. The systematic absences of:

0kl: $k \neq 2n$

h0l: $l \neq 2n$

hk0: $h \neq 2n$

uniquely determine the space group to be:

Pbca (#61)

The date were collected at a temperature of 20 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 50.0 °. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.29 ° with a take-off angle of 6.0°. Scans of $(1.63 + 0.35 \tan \theta)°$ were made at a speed of 16.0 °/min (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans)

and the counts accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 235 mm. The computer controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 3898 reflections which were collected, 3471 were unique (R_{int} = 0.033). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Mo—Kα radiation is 32.3 cm^{-1}. An empirical absorption correction using the program DIFABS[119] was applied which resulted in transmission factors ranging from 0.61 to 1.00. The data were corrected for Lorentz and polarisation effects. A correction for secondary extinction was applied (coefficient = 3.40458e-07).

Structure Solution and Refinement

The structure was solved by and expanded using Fourier techniques.[120] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[121] was based on 2173

observed reflections ($I > 300\sigma(I)$) and 182 variable parameters and converged (last parameter shift was 0.02 times its esd) with unweighted agreement factors of:

$$R = \sum || Fo | - | Fc || / \sum | Fo | = 0.062$$

$$R_{\omega} = \sqrt{(\sum \omega (| Fo | - | Fc |)^2 / \sum \omega Fo^2))} = 0.066$$

The standard deviation of an observed unit weight[122] was 5.48. The weighting scheme was based on counting statistics and included a factor (p = 0.005) to downweight the intense reflections. Plots of $\sum \omega (| Fo | - | Fc |)^2$ versus $| Fo |$, reflection order in data collection, $\sin \theta / \lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map correspond to 1.40 and –1.28 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[123] Anomalous dispersion effects were included in Fcalc;[124] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[125] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[126] All calculations were performed using the teXsan[127] crystallographic software package of Molecular Structure Corporation.

Experimental Details

A. Crystal Data

Empirical Formula	$C_{32}H_{52}O_2P_2Pd_2Br_2$
Formula Weight	903.36
Crystal Colour, Habit	yellow, block
Crystal Dimensions	0.40 × 0.35 × 0.35 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections used for Unit Cell Determination (2θ range)	25 (24.3 – 24.9°)
Omega Scan Peak Width at Half-height	0.29°
Lattice Parameters	a = 18.24(1)Å
	b = 15.607(7)Å
	c = 12.898(6)Å
	V = 3672(5)Å^3
Space Group	Pbca (#61)
Z value	8
D_{calc}	1.634 g/cm^3
F_{000}	1808.00
μ(MoKα)	32.34 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	MoKα (λ = 0.71069Å)
	graphite monochromated
Attenuator	Zr foil (factor 8.53)
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	235 mm
Temperature	20.0 °C
Scan Type	ω-2θ
Scan Rate	16.0 °/min (in ω) (up to 4 scans)
Scan Width	(1.63 + 0.35 tan θ)°
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 3839
	Unique: 3471 (R_{int} = 0.033)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.6101 – 1.000)
	Secondary Extinction
	(coefficient: 3.40458 e^{-07})

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function minimised	$\sum\omega(\|Fo\|-\|Fc\|)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)}=\frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.0050
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2173
No. Variables	182
Reflection/Parameter Ratio	11.94
Residuals: R; R_ω	0.062; 0.066
Goodness of Fit Indicator	5.48
Max. Shift/Error in Final Cycle	0.02
Maximum peak in Diff. Map	1.40 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-1.28 $e^-/Å^3$

Table 1. Atomic Coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
Pd(1)	0.04401(6)	0.08414(7)	0.58726(7)	2.82(2)
Br(1)	0.05340(8)	0.03278(10)	0.3997(1)	4.14(4)
P(1)	0.0360(2)	0.1396(2)	0.7465(3)	3.15(9)
O(1)	0.2951(6)	0.3454(8)	0.5342(9)	5.8(3)
C(1)	0.1256(6)	0.1721(7)	0.5775(9)	2.3(3)
C(2)	0.1784(7)	0.1662(9)	0.498(1)	3.2(3)
C(3)	0.2345(8)	0.2232(10)	0.488(1)	4.0(4)
C(4)	0.2396(8)	0.289(1)	0.557(1)	4.2(4)
C(5)	0.1919(8)	0.2963(10)	0.639(1)	4.0(4)
C(6)	0.1360(7)	0.2357(10)	0.648(1)	3.6(4)
C(7)	0.0817(8)	0.2428(9)	0.738(1)	4.0(4)
C(8)	0.3004(9)	0.417(1)	0.600(1)	7.7(6)
C(9)	0.0900(8)	0.0733(10)	0.843(1)	3.8(4)
C(10)	0.1718(9)	0.083(1)	0.813(1)	5.5(5)
C(11)	0.0677(8)	-0.021(1)	0.835(1)	4.8(4)
C(12)	0.0806(9)	0.109(1)	0.956(1)	6.0(5)
C(13)	-0.0576(9)	0.1704(10)	0.793(1)	4.5(4)
C(14)	-0.1007(9)	0.204(1)	0.700(1)	5.7(5)
C(15)	-0.0576(10)	0.234(1)	0.876(1)	7.8(6)
C(16)	-0.1005(8)	0.090(1)	0.837(1)	6.1(5)

Table 1. Atomic Coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(1)	0.1748	0.1205	0.4500	3.7955
H(2)	0.2693	0.2173	0.4335	4.8384
H(3)	0.1968	0.3413	0.6880	4.7652
H(4)	0.0470	0.2868	0.7243	4.8460
H(5)	0.1068	0.2550	0.8007	4.8460
H(6)	0.3093	0.3987	0.6696	9.3096
H(7)	0.3393	0.4530	0.5784	9.3096
H(8)	0.2558	0.4488	0.5983	9.3096
H(9)	0.2016	0.0546	0.8626	6.6041
H(10)	0.1798	0.0590	0.7465	6.6041
H(11)	0.1844	0.1424	0.8116	6.6041
H(12)	0.0179	-0.0279	0.8546	5.8009
H(13)	0.0739	-0.0404	0.7654	5.8009
H(14)	0.0978	-0.0550	0.8795	5.8009
H(15)	0.1126	0.0787	1.0016	7.1766
H(16)	0.0921	0.1680	0.9574	7.1766
H(17)	0.0314	0.1005	0.9782	7.1766
H(18)	-0.0778	0.2540	0.6739	6.8417
H(19)	-0.1017	0.1612	0.6473	6.8417
H(20)	-0.1494	0.2168	0.7207	6.8417

Table 1. Atomic Coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(21)	-0.0316	0.2120	0.9341	9.4027
H(22)	-0.0345	0.2848	0.8524	9.4027
H(23)	-0.1067	0.2462	0.8957	9.4027
H(24)	-0.1490	0.1068	0.8549	7.2870
H(25)	-0.1022	0.0466	0.7858	7.2870
H(26)	-0.0762	0.0692	0.8969	7.2870

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pd(1)	0.0350(6)	0.0474(7)	0.0247(5)	-0.0067(6)	-0.0016(5)	-0.0015(5)
Br(1)	0.059(1)	0.066(1)	0.0314(8)	-0.0244(9)	0.0060(8)	-0.0081(7)
P(1)	0.042(2)	0.049(2)	0.029(2)	-0.006(2)	0.001(2)	-0.003(2)
O(1)	0.058(8)	0.09(1)	0.073(9)	-0.036(7)	-0.003(6)	0.001(7)
C(1)	0.037(7)	0.012(6)	0.039(7)	-0.024(6)	-0.007(7)	0.010(6)
C(2)	0.042(9)	0.040(9)	0.038(8)	-0.006(8)	-0.0003(7)	-0.001(7)
C(3)	0.041(10)	0.07(1)	0.045(9)	-0.008(9)	0.005(8)	0.001(8)
C(4)	0.030(9)	0.07(1)	0.06(1)	-0.017(8)	-0.010(8)	0.022(9)
C(5)	0.052(10)	0.06(1)	0.039(9)	-0.014(9)	-0.014(8)	0.008(8)
C(6)	0.036(8)	0.06(1)	0.036(8)	-0.010(8)	-0.011(7)	0.000(7)
C(7)	0.062(10)	0.042(9)	0.050(9)	-0.029(8)	-0.002(8)	-0.013(8)
C(8)	0.07(1)	0.13(2)	0.09(2)	-0.03(1)	-0.01(1)	0.01(2)
C(9)	0.054(10)	0.06(1)	0.032(8)	-0.005(9)	-0.003(8)	-0.006(7)
C(10)	0.05(1)	0.12(2)	0.041(9)	0.00(1)	-0.014(8)	0.00(1)
C(11)	0.08(1)	0.06(1)	0.041(9)	-0.003(10)	-0.004(9)	0.000(8)
C(12)	0.08(1)	0.13(2)	0.017(7)	-0.02(1)	-0.010(8)	0.008(9)
C(13)	0.06(1)	0.06(1)	0.046(9)	-0.006(9)	0.017(9)	0.005(8)
C(14)	0.06(1)	0.07(1)	0.08(1)	0.01(1)	0.00(1)	0.00(1)
C(15)	0.09(1)	0.13(2)	0.08(1)	0.00(1)	0.03(1)	-0.05(1)
C(16)	0.05(1)	0.12(2)	0.07(1)	-0.01(1)	0.018(9)	-0.02(1)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*cU_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
Pd(1)	Br(1)	2.554(2)	Pd(1)	Br(1)	2.553(2)
Pd(1)	P(1)	2.234(4)	Pd(1)	C(1)	2.03(1)
P(1)	C(7)	1.82(1)	P(1)	C(9)	1.90(1)
P(1)	C(13)	1.87(2)	O(1)	C(4)	1.37(2)
O(1)	C(8)	1.41(2)	C(1)	C(2)	1.41(2)
C(1)	C(6)	1.36(2)	C(2)	C(3)	1.36(2)
C(3)	C(4)	1.37(2)	C(4)	C(5)	1.37(2)
C(5)	C(6)	1.39(2)	C(6)	C(7)	1.53(2)
C(9)	C(10)	1.55(2)	C(9)	C(11)	1.54(2)
C(9)	C(12)	1.57(2)	C(13)	C(14)	1.53(2)
C(13)	C(15)	1.46(2)	C(13)	C(16)	1.58(2)

Table 4. Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
C(2)	H(1)	0.95	C(3)	H(2)	0.95
C(5)	H(3)	0.95	C(7)	H(4)	0.95
C(7)	H(5)	0.95	C(8)	H(6)	0.95
C(8)	H(7)	0.95	C(8)	H(8)	0.95
C(10)	H(9)	0.95	C(10)	H(10)	0.95
C(10)	H(11)	0.95	C(11)	H(12)	0.95
C(11)	H(13)	0.95	C(11)	H(14)	0.95
C(12)	H(15)	0.95	C(12)	H(16)	0.95
C(12)	H(17)	0.95	C(14)	H(18)	0.95
C(14)	H(19)	0.95	C(14)	H(20)	0.95
C(15)	H(21)	0.95	C(15)	H(22)	0.95
C(15)	H(23)	0.95	C(16)	H(24)	0.95
C(16)	H(25)	0.95	C(16)	H(26)	0.95

Table 5. Bond Angles (Å)

atom	atom	atom	angle	atom	atom	atom	angle
Br(1)	Pd(1)	Br(1)	83.38(6)	Br(1)	Pd(1)	P(1)	175.5(1)
Br(1)	Pd(1)	C(1)	96.0(4)	Br(1)	Pd(1)	P(1)	99.8(1)
Br(1)	Pd(1)	C(1)	176.9(3)	P(1)	Pd(1)	C(1)	81.0(4)
Pd(1)	Br(1)	Pd(1)	96.62(6)	Pd(1)	P(1)	C(7)	104.9(5)
Pd(1)	P(1)	C(9)	111.1(5)	Pd(1)	P(1)	C(13)	117.0(5)
C(7)	P(1)	C(9)	106.6(7)	C(7)	P(1)	C(13)	102.2(7)
C(9)	P(1)	C(13)	113.7(7)	C(4)	O(1)	C(8)	115(1)
Pd(1)	C(1)	C(2)	120.2(9)	Pd(1)	C(1)	C(6)	123(1)
C(2)	C(1)	C(6)	116(1)	C(1)	C(2)	C(3)	122(1)
C(2)	C(3)	C(4)	118(1)	O(1)	C(4)	C(3)	112(1)
O(1)	C(4)	C(5)	125(1)	C(3)	C(4)	C(5)	121(1)
C(4)	C(5)	C(6)	118(1)	C(1)	C(6)	C(5)	122(1)
C(1)	C(6)	C(7)	118(1)	C(5)	C(6)	C(7)	119(1)
P(1)	C(7)	C(6)	106.3(10)	P(1)	C(9)	C(10)	106(1)
P(1)	C(9)	C(11)	110.0(10)	P(1)	C(9)	C(12)	111(1)
C(10)	C(9)	C(11)	109(1)	C(10)	C(9)	C(12)	107(1)
C(11)	C(9)	C(12)	112(1)	P(1)	C(13)	C(14)	107.7(10)
P(1)	C(13)	C(15)	114(1)	P(1)	C(13)	C(16)	111(1)
C(14)	C(13)	C(15)	110(1)	C(14)	C(13)	C(16)	107(1)
C(15)	C(13)	C(16)	105(1)				

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	C(2)	H(1)	188.6	C(3)	C(2)	H(1)	118.5
C(2)	C(3)	H(2)	120.7	C(4)	C(3)	H(2)	120.8
C(4)	C(5)	H(3)	120.8	C(6)	C(5)	H(3)	120.8
P(1)	C(7)	H(4)	110.2	P(1)	C(7)	H(5)	110.3
C(6)	C(7)	H(4)	110.2	C(6)	C(7)	H(5)	110.3
H(4)	C(7)	H(5)	109.5	O(1)	C(8)	H(6)	109.4
O(1)	C(8)	H(7)	109.7	O(1)	C(8)	H(8)	109.6
H(6)	C(8)	H(7)	109.3	H(6)	C(8)	H(8)	109.2
H(7)	C(8)	H(8)	109.6	C(9)	C(10)	H(9)	109.5
C(9)	C(10)	H(10)	109.5	C(9)	C(10)	H(11)	109.6
H(9)	C(10)	H(10)	109.3	H(9)	C(10)	H(11)	109.5
H(10)	C(10)	H(11)	109.4	C(9)	C(11)	H(12)	109.6
C(9)	C(11)	H(13)	109.5	C(9)	C(11)	H(14)	109.6
H(12)	C(11)	H(13)	109.3	H(12)	C(11)	H(14)	109.5
H(13)	C(11)	H(14)	109.3	C(9)	C(12)	H(15)	109.4
C(9)	C(12)	H(16)	109.5	C(9)	C(12)	H(17)	109.4
H(15)	C(12)	H(16)	109.5	H(15)	C(12)	H(17)	109.4
H(16)	C(12)	H(17)	109.5	C(13)	C(14)	H(18)	109.4
C(13)	C(14)	H(19)	109.3	C(13)	C(14)	H(20)	109.4
H(18)	C(14)	H(19)	109.6	H(18)	C(14)	H(20)	109.7

Table 6. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
H(19)	C(14)	H(20)	109.4	C(13)	C(15)	H(21)	109.6
C(13)	C(15)	H(22)	109.5	C(13)	C(15)	H(23)	109.5
H(21)	C(15)	H(22)	109.4	H(21)	C(15)	H(23)	109.4
H(22)	C(15)	H(23)	109.4	C(13)	C(16)	H(24)	109.6
C(13)	C(16)	H(25)	109.4	C(13)	C(16)	H(26)	109.6
H(24)	C(16)	H(25)	109.3	H(24)	C(16)	H(26)	109.6
H(25)	C(16)	H(26)	109.3				

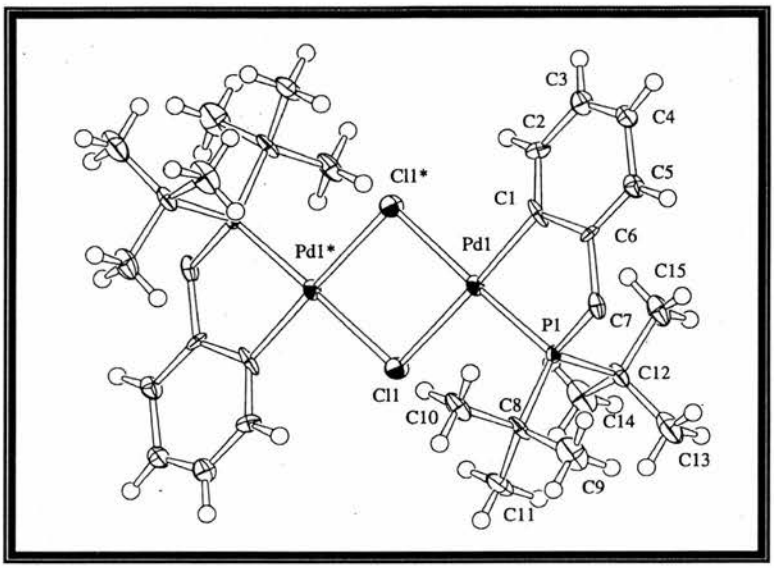
Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Pd(1)	Br(1)	Pd(1)	Br(1)	0.0	Pd(1)	Br(1)	Pd(1)	P(1)	-176.8(10)
Pd(1)	Br(1)	Pd(1)	C(1)	78(6)	Pd(1)	Br(1)	Pd(1)	Br(1)	0.0
Pd(1)	Br(1)	Pd(1)	P(1)	135(1)	Pd(1)	Br(1)	Pd(1)	C(1)	-177.0(3)
Pd(1)	P(1)	Pd(1)	P(1)	-25.3(10)	Pd(1)	P(1)	C(9)	C(10)	66(1)
Pd(1)	P(1)	C(9)	C(11)	-51(1)	Pd(1)	P(1)	C(9)	C(12)	-176.5(9)
Pd(1)	P(1)	C(13)	C(14)	-35(1)	Pd(1)	P(1)	C(13)	C(15)	-157(1)
Pd(1)	P(1)	C(13)	C(16)	82(10	Pd(1)	C(1)	C(2)	C(3)	-179(1)
Pd(1)	C(1)	C(6)	C(5)	-178(1)	Pd(1)	C(1)	C(6)	C(7)	-2(1)
Br(1)	Pd(1)	Br(1)	Pd(1)	0.0	Br(1)	Pd(1)	P(1)	C(7)	-28(1)
Br(1)	Pd(1)	P(1)	C(9)	-143(1)	Br(1)	Pd(1)	P(1)	C(13)	84(1)
Br(1)	Pd(1)	C(1)	C(2)	-20(1)	Br(1)	Pd(1)	C(1)	C(6)	164(1)
Br(1)	Pd(1)	Br(1)	Pd(1)	0.0	Br(1)	Pd(1)	P(1)	C(7)	163.5(5)
Br(1)	Pd(1)	P(1)	C(9)	-81.7(5)	Br(1)	Pd(1)	P(1)	C(13)	51.2(6)
Br(1)	Pd(1)	C(1)	C(2)	-57(6)	Br(1)	Pd(1)	C(1)	C(6)	117(6)
P(1)	Pd(1)	C(1)	C(2)	163(1)	P(1)	Pd(1)	C(1)	C(6)	-12(1)
P(1)	C(7)	C(6)	C(1)	19(1)	P(1)	C(7)	C(6)	C(5)	-163(1)
O(1)	C(4)	C(3)	C(2)	-175(1)	O(1)	C(4)	C(5)	C(6)	176(1)
C(1)	Pd(1)	P(1)	C(7)	19.5(6)	C(1)	Pd(1)	P(1)	C(9)	-95.3(6)
C(1)	Pd(1)	P(1)	C(13)	131.8(7)	C(1)	C(2)	C(3)	C(4)	0(2)
C(1)	C(6)	C(5)	C(4)	-2(2)	C(2)	C(1)	C(6)	C(5)	5(2)

Table 7. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(2)	C(1)	C(6)	C(7)	-177(1)	C(2)	C(3)	C(4)	C(5)	2(2)
C(3)	C(2)	C(1)	C(6)	-3(2)	C(3)	C(4)	O(1)	C(8)	176(1)
C(3)	C(4)	C(5)	C(6)	-1(2)	C(4)	C(5)	C(6)	C(7)	-179(1)
C(5)	C(4)	O(1)	C(8)	-1(2)	C(6)	C(7)	P(1)	C(9)	92(1)
C(6)	C(7)	P(1)	C(13)	-147.9(9)	C(7)	P(1)	C(9)	C(10)	-47(1)
C(7)	P(1)	C(9)	C(11)	-165(1)	C(7)	P(1)	C(9)	C(12)	69(1)
C(7)	P(1)	C(13)	C(14)	78(1)	C(7)	P(1)	C(13)	C(15)	-43(1)
C(7)	P(1)	C(13)	C(16)	-163(1)	C(9)	P(1)	C(13)	C(14)	-166(1)
C(9)	P(1)	C(13)	C(15)	70(1)	C(9)	P(1)	C(13)	C(16)	-49(1)
C(10)	C(9)	P(1)	C(13)	-158(1)	C(11)	C(9)	P(1)	C(13)	82(1)
C(12)	C(9)	P(1)	C(13)	-42(1)					

Di-μ-chlorobis[(di-t-butylphosphinomethylphenyl)-α,P)palladium(II)] 78



Experimental

Data Collection

A yellow block crystal of $C30H48Cl_2P_2Pd_2$ having approximate dimensions of 0.25 × 0.20 × 0.08 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo—Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centred reflections in the range $15.00 < 2\theta < 25.00°$ corresponded to a primitive orthorhombic cell with dimensions:

$a = 14.151(9)$ Å

$b = 13.53(1)$ Å

$c = 16.833(10)$ Å

$V = 3222(3)$ Å^3

For Z = 4 and F.W. = 754.36, the calculated density is 1.55 g/cm^3. The systematic absences of:

0kl: $k \neq 2n$

h0l: $l \neq 2n$

hk0: $h \neq 2n$

uniquely determine the space group to be:

Pbca (#61)

The date were collected at a temperature of 150 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 50.0 °. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.05 ° with a take-off angle of 6.0°. Scans of (1.00 + 0.35 tan θ)° were made at a speed of 16.0 °/min (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting to background counting time was 2:1. The diameter of the incident beam collimator was

1.0 mm and the crystal to detector distance was 235 mm. The computer controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

Data Reduction

Of the 4367 reflections which were collected, 3679 were unique (R_{int} = 0.057). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Mo—Kα radiation is 14.0 cm^{-1}. An empirical absorption correction using the program DIFABS[119] was applied which resulted in transmission factors ranging from 0.77 to 1.00. The data were corrected for Lorentz and polarisation effects.

Structure Solution and Refinement

The structure was solved by direct methods[128] and expanded using Fourier techniques.[120] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[121] was based on 2354 observed reflections ($I > 300\sigma(I)$) and 163 variable parameters and converged (last parameter shift was 0.01 times its esd) with unweighted agreement factors of:

$$R = \sum || Fo | - | Fc || / \sum | Fo | = 0.057$$

$$R_{\omega} = \sqrt{(\sum \omega (| Fo | - | Fc |)^2 / \sum \omega Fo^2))} = 0.116$$

The standard deviation of an observed unit weight[122] was 3.28. The weighting scheme was based on counting statistics and included a factor (p = 0.039) to downweight the intense reflections. Plots of $\sum \omega (| Fo | - | Fc |)^2$ versus $| Fo |$, reflection order in data collection, sin θ / λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map correspond to 1.29 and –2.03 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[123] Anomalous dispersion effects were included in Fcalc;[124] the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley.[125] The values for the mass attenuation coefficients are those of Creagh and Hubbel.[126] All calculations were performed using the teXsan[127] crystallographic software package of Molecular Structure Corporation.

Experimental Details

A. Crystal Data

Empirical Formula	$C_{30}H_{48}Cl_2P_2Pd_2$
Formula Weight	754.36
Crystal Colour, Habit	yellow, plate
Crystal Dimensions	0.25 × 0.20 × 0.08 mm
Crystal System	orthorhombic
Lattice Type	Primitive
No. of Reflections used for Unit Cell Determination (2θ range)	25 (15.0 – 25.0°)
Omega Scan Peak Width at Half-height	0.05°
Lattice Parameters	a = 14.151(9)Å
	b = 13.53(1)Å
	c = 16.833(10)Å
	V = 322(3)Å^3
Space Group	Pbca (#61)
Z value	4
D_{calc}	1.555 g/cm^3
F_{000}	1536.00
μ(MoKα)	14.00 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	MoKα (λ = 0.71069Å)
	graphite monochromated
Attenuator	Zr foil (factor 8.53)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	235 mm
Temperature	150.0 °C
Scan Type	ω-2θ
Scan Rate	16.0 °/min (in ω) (up to 4 scans)
Scan Width	(1.00 + 0.35 tan θ)°
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 4367
	Unique: 3679 (R_{int} = 0.057)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.7717 – 1.000)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function minimised	$\sum\omega(\mid Fo \mid - \mid Fc \mid)^2$
Least Squares Weights	$\frac{1}{\sigma^2(Fo)} = \frac{4Fo^2}{\sigma^2(Fo^2)}$
p-factor	0.0390
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2354
No. Variables	163
Reflection/Parameter Ratio	14.44
Residuals: R; R_ω	0.057; 0.116
Goodness of Fit Indicator	3.28
Max. Shift/Error in Final Cycle	0.01
Maximum peak in Diff. Map	1.29 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-2.03 $e^-/Å^3$

Table 1. **Atomic Coordinates and B_{iso}/B_{eq}**

atom	x	y	z	B_{eq}
Pd(1)	0.42177(6)	0.08221(6)	0.94443(5)	1.10(2)
Cl(1)	0.5379(2)	0.0927(2)	1.0522(2)	2.05(7)
P(1)	0.3792(2)	0.2407(2)	0.9392(2)	0.94(6)
C(1)	0.3277(8)	0.0679(10)	0.8544(6)	1.6(3)
C(2)	0.3285(8)	-0.0069(8)	0.8026(7)	1.3(3)
C(3)	0.2622(10)	-0.0149(9)	0.7415(7)	1.9(3)
C(4)	0.1961(9)	0.0516(10)	0.7299(7)	1.7(3)
C(5)	0.1935(9)	0.1415(9)	0.7803(7)	1.6(3)
C(6)	0.2597(9)	0.1479(8)	0.8416(7)	1.2(3)
C(7)	0.2612(9)	0.2385(9)	0.8929(7)	1.6(3)
C(8)	0.3597(10)	0.301(1)	1.0368(6)	1.7(3)
C(9)	0.294(1)	0.389(1)	1.0281(8)	3.3(4)
C(10)	0.3143(10)	0.226(1)	1.0908(7)	2.2(3)
C(11)	0.453(1)	0.338(1)	1.0757(8)	2.4(3)
C(12)	0.4587(9)	0.3138(10)	0.8714(7)	1.6(3)
C(13)	0.439(1)	0.425(1)	0.8722(9)	3.1(4)
C(14)	0.5616(9)	0.291(1)	0.8945(8)	2.6(3)
C(15)	0.4437(9)	0.275(1)	0.7856(8)	2.3(3)
II(1)	0.3758	-0.0565	0.8079	1.5612
H(2)	0.2667	-0.0699	0.7069	2.2631

Table 1. Atomic Coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(3)	0.1500	0.0420	0.6893	2.0629
H(4)	0.1489	0.1927	0.7715	1.8884
H(5)	0.2125	0.2351	0.9328	1.8282
H(6)	0.2505	0.2970	0.8619	1.8282
H(7)	0.3217	0.4371	0.9945	3.9953
H(8)	0.2352	0.3679	1.0058	3.9953
H(9)	0.2820	0.4174	1.0790	3.9953
H(10)	0.3545	0.1709	1.0972	2.6882
H(11)	0.2556	0.2051	1.0684	2.6882
H(12)	0.3021	0.2552	1.1413	2.6882
H(13)	0.4402	0.3657	1.1262	2.8650
H(14)	0.4817	0.3863	1.0425	2.8650
H(15)	0.4955	0.2836	1.0820	2.8650
H(16)	0.3762	0.4375	0.8559	3.7888
H(17)	0.4486	0.4502	0.9243	3.7888
H(18)	0.4817	0.4576	0.8367	3.7888
H(19)	0.5725	0.3139	0.9471	3.0668
H(20)	0.6027	0.3235	0.8589	3.0668
H(21)	0.5715	0.2217	0.8924	3.0668
H(22)	0.4864	0.3077	0.7508	2.7220

Table 1. Atomic Coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(23)	0.4549	0.2060	0.7843	2.7220
H(24)	0.3806	0.2883	0.7695	2.7220

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Pd(1)	0.0086(5)	0.0175(6)	0.0157(5)	0.0011(4)	-0.0046(4)	0.0027(4)
Cl(1)	0.023(2)	0.021(2)	0.034(2)	0.003(1)	-0.018(2)	0.000(1)
P(1)	0.012(1)	0.012(1)	0.012(1)	0.000(1)	-0.002(1)	0.003(1)
C(1)	0.007(6)	0.046(9)	0.007(6)	-0.004(6)	-0.001(5)	0.008(6)
C(2)	0.012(6)	0.015(6)	0.022(7)	-0.002(5)	0.005(6)	-0.005(5)
C(3)	0.027(7)	0.018(7)	0.018(7)	0.001(6)	0.000(6)	0.001(6)
C(4)	0.021(8)	0.028(7)	0.016(7)	-0.013(6)	-0.003(6)	0.004(5)
C(5)	0.014(7)	0.027(7)	0.018(6)	-0.006(6)	-0.004(6)	0.004(5)
C(6)	0.019(7)	0.004(6)	0.023(7)	-0.002(5)	0.001(6)	0.000(5)
C(7)	0.014(7)	0.027(7)	0.018(7)	0.007(6)	-0.003(5)	0.013(5)
C(8)	0.021(7)	0.035(8)	0.007(6)	0.005(6)	-0.002(5)	-0.002(5)
C(9)	0.05(1)	0.05(1)	0.027(8)	0.030(9)	-0.002(7)	-0.010(7)
C(10)	0.026(8)	0.047(10)	0.012(6)	0.006(7)	0.003(6)	-0.002(6)
C(11)	0.035(9)	0.039(9)	0.016(7)	0.003(7)	-0.009(6)	-0.006(6)
C(12)	0.014(7)	0.034(8)	0.012(6)	-0.007(6)	-0.003(6)	0.006(6)
C(13)	0.037(9)	0.06(1)	0.022(7)	-0.014(8)	-0.011(7)	0.008(7)
C(14)	0.013(7)	0.06(1)	0.025(8)	-0.006(7)	0.003(6)	0.005(7)
C(15)	0.025(8)	0.047(9)	0.015(7)	-0.002(7)	0.002(6)	0.007(6)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*cU_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
Pd(1)	Cl(1)	2.452(3)	Pd(1)	Cl(1)	2.435(3)
Pd(1)	P(1)	2.228(3)	Pd(1)	C(1)	2.03(1)
P(1)	C(7)	1.84(1)	P(1)	C(8)	1.86(1)
P(1)	C(12)	1.88(1)	C(1)	C(2)	1.34(2)
C(1)	C(6)	1.46(2)	C(2)	C(3)	1.39(2)
C(3)	C(4)	1.32(2)	C(4)	C(5)	1.48(2)
C(5)	C(6)	1.40(2)	C(6)	C(7)	1.50(2)
C(8)	C(9)	1.52(2)	C(8)	C(10)	1.51(2)
C(8)	C(11)	1.55(2)	C(12)	C(13)	1.53(2)
C(12)	C(14)	1.54(2)	C(12)	C(15)	1.55(2)

Table 4. Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
C(2)	H(1)	0.95	C(3)	H(2)	0.95
C(4)	H(3)	0.95	C(5)	H(4)	0.95
C(7)	H(5)	0.96	C(7)	H(6)	0.96
C(9)	H(7)	0.95	C(9)	H(8)	0.95
C(9)	H(9)	0.95	C(10)	H(10)	0.95
C(10)	H(11)	0.96	C(10)	H(12)	0.95
C(11)	H(13)	0.95	C(11)	H(14)	0.95
C(11)	H(15)	0.95	C(13)	H(16)	0.95
C(13)	H(17)	0.95	C(13)	H(18)	0.96
C(14)	H(19)	0.95	C(14)	H(20)	0.94
C(14)	H(21)	0.95	C(15)	H(22)	0.95
C(15)	H(23)	0.95	C(15)	H(24)	0.95

Table 5. Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
Cl(1)	Pd(1)	Cl(1)	83.3(1)	Cl(1)	Pd(1)	P(1)	98.8(1)
Cl(1)	Pd(1)	C(1)	177.7(4)	Cl(1)	Pd(1)	P(1)	177.7(1)
Cl(1)	Pd(1)	C(1)	94.4(4)	P(1)	Pd(1)	C(1)	83.5(4)
Pd(1)	Cl(1)	Pd(1)	96.7(1)	Pd(1)	P(1)	C(7)	104.2(4)
Pd(1)	P(1)	C(8)	115.5(4)	Pd(1)	P(1)	C(12)	111.5(4)
C(7)	P(1)	C(8)	104.3(6)	C(7)	P(1)	C(12)	107.1(5)
C(8)	P(1)	C(12)	113.1(6)	Pd(1)	C(1)	C(2)	123.7(10)
Pd(1)	C(1)	C(6)	118.1(9)	C(2)	C(1)	C(6)	118(1)
C(1)	C(2)	C(3)	122(1)	C(2)	C(3)	C(4)	122(1)
C(3)	C(4)	C(5)	119(1)	C(4)	C(5)	C(6)	117(1)
C(1)	C(6)	C(5)	120(1)	C(1)	C(6)	C(7)	120(1)
C(5)	C(6)	C(7)	119(1)	P(1)	C(7)	C(6)	105.7(8)
P(1)	C(8)	C(9)	110.6(8)	P(1)	C(8)	C(10)	107.4(9)
P(1)	C(8)	C(11)	112.8(9)	C(9)	C(8)	C(10)	108(1)
C(9)	C(8)	C(11)	108(1)	C(10)	C(8)	C(11)	108(1)
P(1)	C(12)	C(13)	113.7(10)	P(1)	C(12)	C(14)	108.0(8)
P(1)	C(12)	C(15)	107.7(9)	C(13)	C(12)	C(14)	111(1)
C(13)	C(12)	C(15)	108(1)	C(14)	C(12)	C(15)	107(1)

Table 6. Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	C(2)	H(1)	118.7	C(3)	C(2)	H(1)	118.8
C(2)	C(3)	H(2)	119.0	C(4)	C(3)	H(2)	118.7
C(3)	C(4)	H(3)	120.3	C(5)	C(4)	H(3)	120.3
C(4)	C(5)	H(4)	121.8	C(6)	C(5)	H(4)	121.0
P(1)	C(7)	H(5)	110.8	P(1)	C(7)	H(6)	111.0
C(6)	C(7)	H(5)	110.7	C(6)	C(7)	H(6)	111.0
H(5)	C(7)	H(6)	107.6	C(8)	C(9)	H(7)	109.5
C(8)	C(9)	H(8)	109.5	C(8)	C(9)	H(9)	109.5
H(7)	C(9)	H(8)	109.6	H(7)	C(9)	H(9)	109.7
H(8)	C(9)	H(9)	109.1	C(8)	C(10)	H(10)	110.2
C(8)	C(10)	H(11)	109.5	C(8)	C(10)	H(12)	109.6
H(10)	C(10)	H(11)	109.3	H(10)	C(10)	H(12)	109.6
H(11)	C(10)	H(12)	108.6	C(8)	C(11)	H(13)	110.1
C(8)	C(11)	H(14)	109.5	C(8)	C(11)	H(15)	109.8
H(13)	C(11)	H(14)	109.3	H(13)	C(11)	H(15)	109.2
H(14)	C(11)	H(15)	108.9	C(12)	C(13)	H(16)	110.1
C(12)	C(13)	H(17)	109.8	C(12)	C(13)	H(18)	109.4
H(16)	C(13)	H(17)	109.6	H(16)	C(13)	H(18)	109.2
H(17)	C(13)	H(18)	108.8	C(12)	C(14)	H(19)	108.8
C(12)	C(14)	H(20)	109.4	C(12)	C(14)	H(21)	109.1

Table 6. Bond Angles (°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
H(19)	C(14)	H(21)	109.9	H(19)	C(14)	H(21)	109.4
H(20)	C(14)	H(21)	110.2	C(12)	C(15)	H(22)	109.1
C(12)	C(15)	H(23)	109.5	C(12)	C(15)	H(24)	109.2
H(22)	C(15)	H(23)	109.8	H(22)	C(15)	H(24)	109.5
H(23)	C(1 5)	H(24)	109.9				

Table 7. Torsion Angles (°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
Pd(1)	Cl(1)	Pd(1)	Cl(1)	0.0000(1)	Pd(1)	Cl(1)	Pd(1)	P(1)	155(2)
Pd(1)	Cl(1)	Pd(1)	C(1)	-179.5(3)	Pd(1)	Cl(1)	Pd(1)	Cl(1)	0.0000(1)
Pd(1)	Cl(1)	Pd(1)	P(1)	-179.0(1)	Pd(1)	Cl(1)	Pd(1)	C(1)	12(8)
Pd(1)	P(1)	C(7)	C(6)	-27.8(8)	Pd(1)	P(1)	C(8)	C(9)	-156.0(9)
Pd(1)	P(1)	C(8)	C(10)	-37.3(10)	Pd(1)	P(1)	C(8)	C(11)	82.6(9)
Pd(1)	P(1)	C(12)	C(13)	-174.0(8)	Pd(1)	P(1)	C(12)	C(14)	-49.8(10)
Pd(1)	P(1)	C(12)	C(15)	65.6(9)	Pd(1)	C(1)	C(2)	C(3)	180.0(9)
Pd(1)	C(1)	C(6)	C(5)	180.0(9)	Pd(1)	C(1)	C(6)	C(7)	1(1)
Cl(1)	Pd(1)	Cl(1)	Pd(1)	0.0	Cl(1)	Pd(1)	P(1)	C(7)	-157.2(4)
Cl(1)	Pd(1)	P(1)	C(8)	-43.5(5)	Cl(1)	Pd(1)	P(1)	C(12)	87.6(4)
Cl(1)	Pd(1)	C(1)	C(2)	-9(8)	Cl(1)	Pd(1)	C(1)	C(6)	175(7)
Cl(1)	Pd(1)	Cl(1)	Pd(1)	0.0000(1)	Cl(1)	Pd(1)	P(1)	C(7)	1(3)
Cl(1)	Pd(1)	P(1)	C(8)	-112(2)	Cl(1)	Pd(1)	P(1)	C(12)	116(2)
Cl(1)	Pd(1)	C(1)	C(2)	22(1)	Cl(1)	Pd(1)	C(1)	C(6)	-162.6(8)
P(1)	Pd(1)	C(1)	C(2)	158(1)	P(1)	Pd(1)	C(1)	C(6)	-16.4(8)
P(1)	C(7)	C(6)	C(1)	19(1)	P(1)	C(7)	C(6)	C(5)	-159.9(9)
C(1)	Pd(1)	P(1)	C(7)	23.2(5)	C(1)	Pd(1)	P(1)	C(8)	137.0(6)
C(1)	Pd(1)	P(1)	C(12)	-92.0(5)	C(1)	C(2)	C(3)	C(4)	0(2)
C(1)	C(6)	C(5)	C(4)	0(1)	C(2)	C(1)	C(6)	C(5)	4(1)
C(2)	C(1)	C(6)	C(7)	-174(1)	C(2)	C(3)	C(4)	C(5)	4(1)

Table 7. Torsion Angles (°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(3)	C(2)	C(1)	C(6)	-5(1)	C(3)	C(4)	C(5)	C(6)	-4(1)
C(4)	C(5)	C(6)	C(7)	178(1)	C(6)	C(7)	P(1)	C(8)	-149.3(8)
C(6)	C(7)	P(1)	C(12)	90.5(9)	C(7)	P(1)	C(8)	C(9)	-42(1)
C(7)	P(1)	C(8)	C(10)	76.4(10)	C(7)	P(1)	C(8)	C(11)	-163.7(9)
C(7)	P(1)	C(12)	C(13)	72.6(10)	C(7)	P(1)	C(12)	C(14)	-163.2(9)
C(7)	P(1)	C(12)	C(15)	-47(1)	C(8)	P(1)	C(12)	C(13)	-41(1)
C(8)	P(1)	C(12)	C(14)	82(1)	C(8)	P(1)	C(12)	C(15)	-162.1(9)
C(9)	C(8)	P(1)	C(12)	73(1)	C(10)	C(8)	P(1)	C(12)	-167.5(9)
C(11)	C(8)	P(1)	C(12)	-47(1)					