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PHD

Developments in supported aqueous-phase catalysis

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**DEVELOPMENTS IN SUPPORTED
AQUEOUS-PHASE CATALYSIS**

submitted by Amin Ruhul Mirza

for the degree of PhD

of the University of Bath

1999

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PhD.

Abstract

The original supported aqueous-phase, SAP, system of catalysis was based upon a water-soluble organometallic catalyst complex, being dissolved in a polar, hydrophilic film, supported upon high surface area glass beads whilst reactants and products were restricted to a non-miscible solvent phase. The approach assumed that interaction between the substrates and the catalyst complex occurred at the interface between the two phases. Hence, the high surface area afforded by the porous silica support maintained the activity that would be associated with reactions within a homogeneous system whilst reducing the potential for heavy metal contamination in the product.

Chapter 1 discusses the advantages and disadvantages of homogeneous and heterogeneous systems of catalysis. This follows onto a review of the use of SAP catalyst system over the past decade.

Chapter 2 describes the preparation of SAP catalysts and investigation of catalyst loadings, aryl phosphine ligands, ligand loadings, liquid-phase loadings, catalyst recycling, and affect upon catalyst leaching and reaction kinetics towards optimisation of SAP palladium catalysed Heck reactions on aryl halides.

Chapter 3 discusses the development of supported organic-phase, SOP, catalysts using silica derivatised with long chain alkyl silanes for use with hydrophilic substrates and the screening of solvents in this phase reversal of the SAP system.

Chapter 4 extends the application of SAP and SOP catalyst systems to chiral oxazoline ligands for allylic substitution reactions, transfer hydrogenation and to Heck reactions with substituted indoles.

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Abbreviations

AA	atomic absorption
Ac	acetate
Ac ₂ O	acetic anhydride
acac	acetylacetonate
Ar	aryl
atm.	atmosphere
BET	Brunauer-Emmett-Teller
BINAP	2,2'- <i>bis</i> (diphenylphosphino)-1,1'-binaphthyl
<i>t</i> -Bu	<i>tert</i> -butyl
cat.	catalytic
(<i>S,S</i>)-CHIRAPHOS	(2 <i>S</i> ,3 <i>S</i>)-(-)- <i>bis</i> (diphenylphosphino)butane
cm	centimetre
conv.	conversion
CPG	controlled pore glass
CP MAS	cross polarisation magic angle spinning
D.C.	dielectric constant
DCM	dichloromethane
DIOP	2,3- <i>o</i> -isopropylidene-2,3-dihydroxy-1,4- <i>bis</i> (diphenylphosphino)butane
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
D _p	pore diameter
E ⁺	electrophile
e.e.	enantiomeric excess

equiv.	equivalent
Et	ethyl
Et ₂ O	diethyl ether
g	gram
GC	gas chromatography
h	hour
HexDPPDS	hexyl- <i>bis</i> (sodium- <i>m</i> -sulfonatophenyl)phosphine
HPLC	high performance liquid chromatography
ICP	inductively coupled plasma
<i>i</i> -Pr	<i>iso</i> -propyl
IR	infra-red
L	ligand
LADH	liver alcohol dehydrogenase
Me	methyl
mg	milligram
min.	minute
ml	millilitre
M _w	relative molecular weight
NMR	nuclear magnetic resonance
nm	nanometre
Nuc ⁻	nucleophile
PEG	polyethylene glycol
Ph	phenyl
ppb	parts per billion
ppm	parts per million
rpm	revolutions per minute

r.t.	room temperature
SA	surface area
SAP	supported aqueous-phase
SHFC	supported homogeneous film catalyst
SLP	supported liquid-phase
SOP	supported organic-phase
TFA	trifluoroacetic acid
TGA	thermogravimetric analysis
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	turnover frequency
TPP	triphenylphosphine
TPPMS	monosulfonated triphenylphosphine
TPPTS	trisulfonated triphenylphosphine
UV	ultra-violet
V _p	pore volume
v/v	volume/volume
wt%	weight percent

CHAPTER 1
INTRODUCTION

Chapter 1: Introduction

1.1 Introduction

The synthesis of a wide variety of fine chemicals and pharmaceuticals is realised using homogeneous heavy metal catalyst systems.^{1,2} However, homogeneous systems often demand expensive separation of the catalyst from the desired product.³ This is particularly necessary and required by legislation for compounds to be used in the formulation of drugs or that are destined for human consumption.

To avoid this separation stage, efforts have been made to immobilise homogeneous catalysts upon suitable porous carriers.⁴ The aim being to maintain the activity and selectivity of a homogeneous system whilst avoiding or minimising the leaching of the catalyst into the product. A successful process would have the advantages of enhancing economic potential whilst reducing possible toxicity from transition metals in a synthetic procedure.⁵

The aim of this project was to develop a technique capable of a wide range of clean chemical transformations with low levels of catalyst leaching and which could readily be applied to continuous flow/loop processes in scale-up.

1.2 Homogeneous Catalysis

Homogeneous catalysts have the advantage of high activities and selectivity in mild conditions.¹ This is because every atom is available for reaction and the chemical reactivity can be easily modified by the addition of different ligands and solvents.

But they also have limitations; often there is contamination of the product with catalyst due to the difficulties inherent in separations. Also, homogeneous catalysts are usually limited to operations at relatively low temperatures in order to prevent solvent loss or complex decomposition. A comparison of the characteristic advantages and disadvantages of homogeneous and heterogeneous catalyst systems is illustrated in **Table 1**.

Many homogeneous reactions are not commercially feasible because of the problems of catalyst recovery. This has promoted research into new methods of immobilising catalytic organometallics. Catalyst separation in heterogeneous systems is generally simplified. Sometimes it can even be acceptable to 'lose' the catalyst in homogeneous systems. However, this is not so in cases when the catalyst is expensive or toxic. This is especially highlighted in continuous processes.

Table 1. Typical characteristics of homogeneous and heterogeneous catalyst systems.

	Homogeneous Catalyst	Heterogeneous Catalyst
Selectivity	High	Variable
Activity (relative to metal content)	High	Variable
Reaction conditions	Mild	High temperature/pressure often necessary
Recycling	Expensive separation	Simplified separation giving long catalyst service life
Diffusion problems	None	May be significant
Sensitivity towards poisoning	Low	High
Mechanistic understanding	Plausible under random conditions	Limited to model systems
Variability of steric/electronic properties	Possible	Not possible

1.3 Water-Soluble Catalysts

In the early 1970s, the economics of propylene hydroformylation made research into the development of new processes viable.

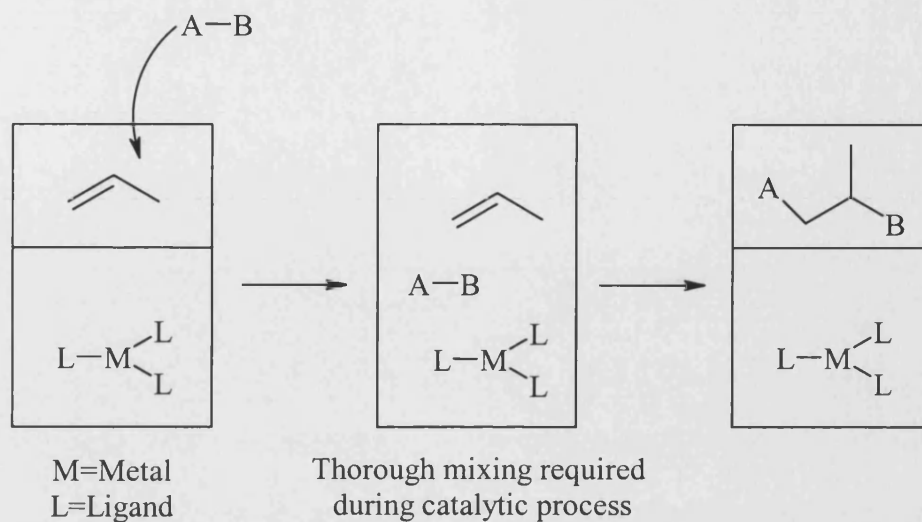
In 1973, a transition metal catalysed reaction in aqueous solution was attempted in the presence of a water-soluble hydroxymethyl substituted alkylphosphine.⁶ It was ascertained that many reactions catalysed by palladium, platinum or rhodium could be carried out without much care as to the solvent or reagent characteristics. This also implied that the hydroformylation of olefins could be performed in water. An approach to catalyst separation based on using water as a non-miscible solvent for hydroformylation was foreseen. This led to the search for new water-soluble ligands.^{3,4}

1.3.1 Biphasic Reactions

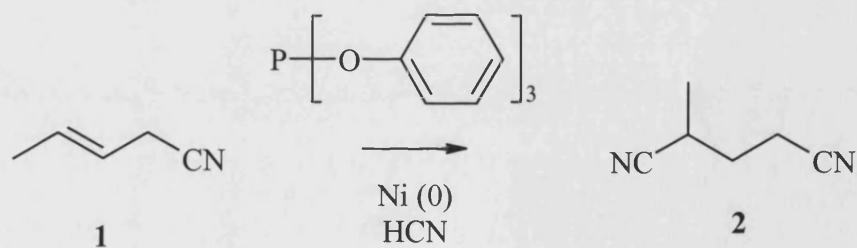
The separation of product phase from catalyst routinely includes operations which apply thermal stresses on the catalyst and can result in decomposition. Also, thermal separations rarely give quantitative recovery of catalyst.

Immobilisation methods which partition catalyst and reactant/product in different phases have seen some degree of success.^{1,2} This is illustrated by the nickel catalysed oligomerisation of ethylene to prepare linear α -olefins. Known as the Shell Higher Olefins Process, it is carried out in polar 1,4-butanediol, a poor solvent for α -olefins.^{4,7} This approach is limited, however, by the poor distribution factor of reagents and catalyst between two phases making continuous separation in the reactor difficult.^{8,9,10}

Figure 1. Principles underlying biphasic catalysis in water. Metal catalyst, M, solubilised by hydrophilic ligand, L, converts olefin and gaseous A-B to products which can be isolated from catalyst by phase separation.



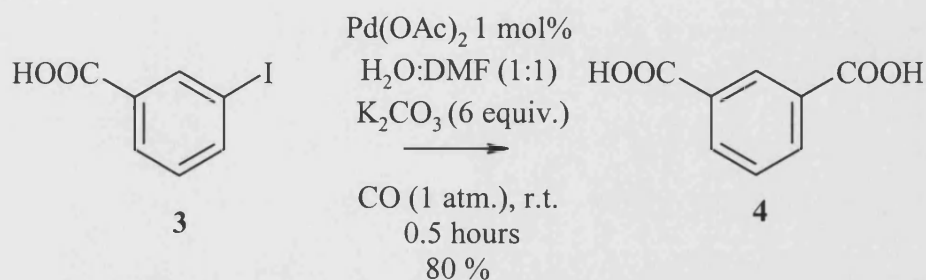
The synthesis of adiponitrile (**2**) using 3-pentene-nitrile (**1**) in the presence of nickel and arylphosphite is carried out in a polar solvent.³ The high boiling point of adiponitrile makes distillation unfeasible, therefore, the product is separated by liquid-liquid extraction with cyclohexane. The nickel catalyst used is maintained in the polar phase.



The Rhone-Poulenc hydroformylation process and the Union Carbide process use immobilised homogeneous catalyst systems in which the reactants and products are phases separate from the catalyst phase.^{3,11} As the reaction proceeds, a

hydrophobic phase is formed which is easily separated from the aqueous phase without major loss of catalyst.

Palladium catalysed carbonylations of aryl halides (3) have been demonstrated in both aqueous and organic solvents.^{12,13} In the aqueous system a mixture of H₂O:DMF (1:1 or 1:2, v/v) or water alone is used, depending upon the solubility of the substrate, at room temperature to yield the aromatic acid (4).



Generally, product separation is simplified for two-phase reactions with water-soluble catalysts and can be used to extend the active life of the catalyst by avoiding detrimental separation processes.^{4,10} For example, in a biphasic system with a hydrophilic organometallic catalyst complex the reaction occurs in the aqueous phase or at the phase interface. The water-soluble catalyst is insoluble in the organic product phase and can be easily separated after reaction. Also, the use of water as a solvent has the added environmental attraction.

However, the system is limited by a number of factors. Catalyst separation is difficult when water-soluble products are synthesised as in the case of the aromatic acid (4). Additionally the system is limited by the solubility of the substrates in the aqueous layer containing the catalyst. Also, the activity is significantly dependent upon the limited interfacial area between the different phases.¹⁴

1.3.2 Fluorous Biphasic Reactions

It is possible to overcome the problem of conventional biphasic catalyst systems by using an organometallic complex incorporating fluororous ligands and an immiscible fluororous phase which does not interfere with the synthesised products.^{15,16}

The fluororous phase in such biphasic systems has been compared to the aqueous medium in aqueous/organic reactions. In one such case, the fluorocarbon/hydrocarbon phases become miscible when heated to 37 °C to generate a homogeneous phase which re-separates on cooling to room temperature. The hydroformylation of 1-decene has been demonstrated with fluororous biphasic systems. By utilising a fluorinated phosphine ligand, $[P(CH_2CH_2(CF_2)_5CF_3)_3]$, prepared to electronically resemble a trialkylphosphine and $[Rh(CO)_2(acac)]$, a catalyst can be prepared which will facilitate the hydroformylation of 1-decene (CO:H₂, 1:1, 10 atm., 10 hours). The fluororous phase can then be separated, by cooling under nitrogen, and recycled with little loss of activity.

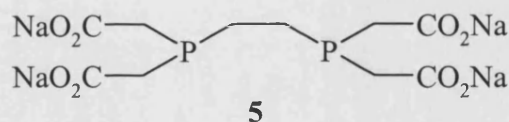
Much work has been carried out with the aim of applying this system, using different fluororous ligands, to reactions such as hydroboration and Stille couplings.^{17,18} Fluorous biphasic systems can also be applied to water-sensitive reactions.

1.3.3 Water-Soluble Phosphines

Phosphines are very useful for stabilising metal complexes. Therefore, techniques for altering the solubility of organometallic phosphine complexes by introducing hydrophilic moieties such as hydroxy, sulfonate, amino and carboxylic groups have been extensively researched.¹⁹

1.3.4 Carboxylated Phosphines

Carboxylated phosphines were among the first water-soluble ligands investigated and were being studied even as early as 1960. They can be produced by direct reaction of a secondary phosphine with a ω -bromoester to yield the ω -phosphinoesters. The phosphine analog of EDTA can be prepared as the air-stable monohydrate of the tetrasodium salt (**5**). Unfortunately, carboxylated phosphines are limited by their solubility in basic media.

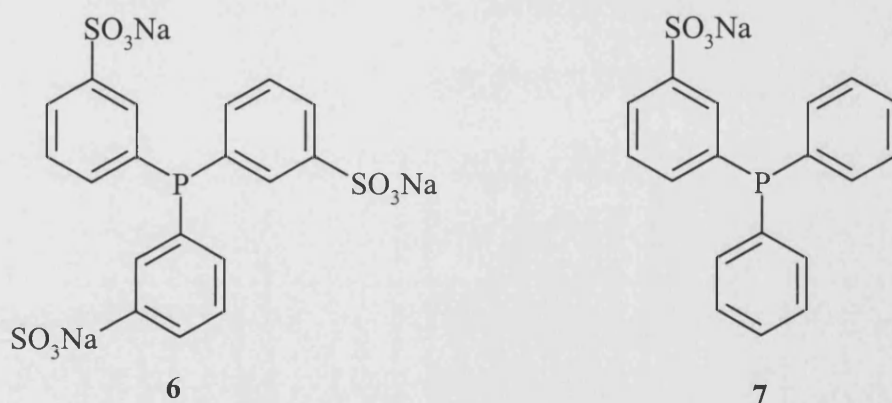


1.3.5 Aminated Phosphines

Aminated phosphines are commonly prepared by the quaternisation of amino-containing phosphine ligands. They, similarly to the carboxylated phosphines, are restricted by the fact that ligands containing amino groups of this type are only soluble in acidic media.¹⁹

1.3.6 Sulfonated Phosphines

It has been demonstrated as early as 1958 that the sulfonation of triphenylphosphine produces water-soluble ligands.²⁰ These have seen widespread use in the development of hydrophilic catalysts. In fact, sulfonated phosphines are the most commonly used type of ligands in aqueous organometallic chemistry.^{4,21,22} The preparation of such water-soluble catalysts has routinely been demonstrated by bonding with trisulfonated (6) or monosulfonated (7) ligands (TPPTS and TPPMS).^{23,24,25,25}

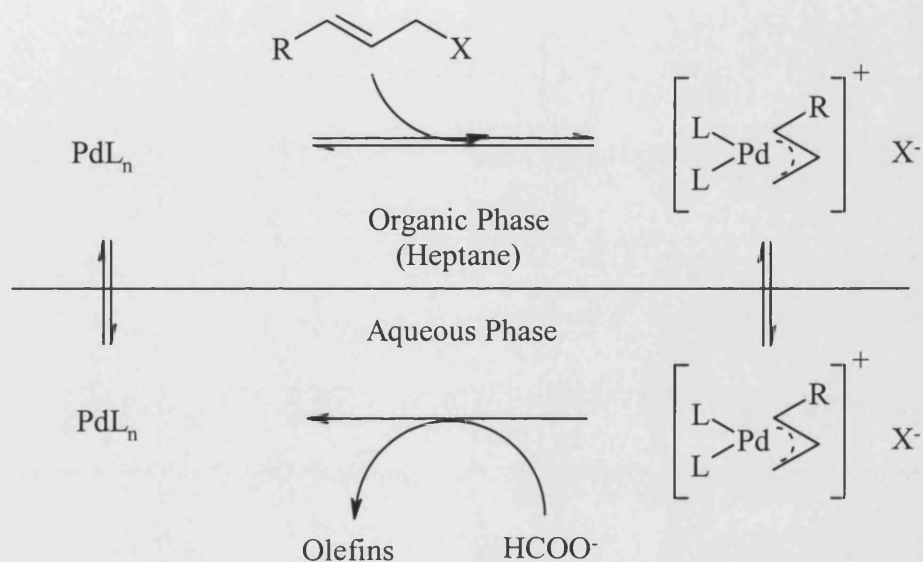


The solubilities of the trisodium salt of *tris(m-sulfonatophenyl)phosphine* Na-TPPTS and the monosodium salt of *mono(m-sulfonatophenyl)diphenylphosphine* Na-TPPMS have been determined in water as $\sim 1100 \text{ gL}^{-1}$ and $\sim 80 \text{ gL}^{-1}$, respectively.³ Sulfonated phosphines have been employed to enhance the hydrophilicity of catalysts in a number of important aqueous reactions including alkylation, cross-coupling reactions, hydrogenations, hydroformylation, carbonylation, and metathesis polymerisation.^{9,19,23,26}

Water-soluble TPPMS palladium-phosphine complexes, $[\text{PdCl}_2(\text{TPPMS})_2]$, have even been used as phase-transfer catalysts. They are able to facilitate the transport of allylic chlorides or acetates into the aqueous phase in heptane:water two-

phase systems so that reduction can be carried out by sodium formate to generate a mixture of 1- and 2-alkenes (**Figure 2**).^{26,27}

Figure 2. TPPMS complexes in phase-transfer catalysis.



TPPTS and TPPMS organometallic complexes have amphiphilic character due to the presence of the sulfonate and phenyl moieties in the molecules. This allows better movement between phases in biphasic systems. The ligands can even be modified to form surface-active micelles.²⁸

TPPTS has seen most widespread use in hydroformylation reactions. The rhodium catalysed hydroformylation of propene uses an equimolar mixture of hydrogen and carbon dioxide at 40 atm. and 125 °C in aqueous solution to generate butanal which can be easily decanted from the reaction mixture. The rhodium-TPPTS complex gives 99 % yield, compared to less than 90 % in the conventional cobalt catalysed system, and is less susceptible to poisoning or decomposition.³

Phosphine complexes such as $[\text{RhCl}(\text{TPPTS})_2]$ have also been seen to catalyse the hydrogenation of alkenes and carbonyl double bonds. It was also noted

that this complex was more active than $[\text{RhCl}(\text{TPPTS})_3]$.²⁹ This has been attributed to the rhodium (III) complex, used to form $[\text{RhCl}(\text{TPPTS})_3]$, catalysing oxygen transfer from water to yield the inactive oxide $[\text{TPPTS}=\text{O}]$.

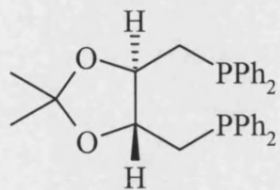
1.3.7 Other Water-Soluble Phosphines

Bicyclic and bidentate ligands for hydrogenation and hydroformylations have been prepared from maleic anhydride and maleic anhydride phosphine.³⁰ Hydroxyalkylphosphines have been produced by the condensation of primary or secondary alkyl- or arylphosphines with ketones or aldehydes in the presence of hydrochloric acid.¹⁹ Novel amphiphilic diphosphine rhodium complexes have also been demonstrated for use in hydroformylations.³¹

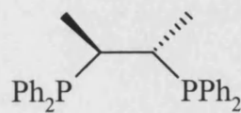
1.3.8 Enantiomerically Pure Phosphines

By introducing a polar functional group to an enantiomerically enriched diphosphine or by binding an enantiomerically pure moiety to a diphosphine ligand, enantiomerically pure phosphines such as 2,3-*o*-isopropylidene-2,3-dihydroxy-1,4-*bis*(diphenylphosphino)butane (8) DIOP, (2*S*,3*S*)-(-)-*bis*(diphenylphosphino)butane (9) (*S,S*)-CHIRAPHOS and (2*S*,4*S*)-(-)-4-(diphenylphosphino)-2-(diphenylphosphino methyl)pyrrolidine (10) can be prepared for use in aqueous or biphasic asymmetric catalysis.^{19,32}

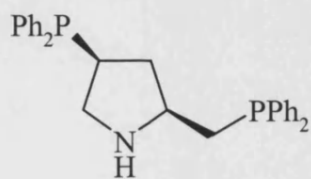
Such enantiomerically enriched ligands have shown good enantioselectivities in hydrogenation and hydroformylation reactions.^{10,33}



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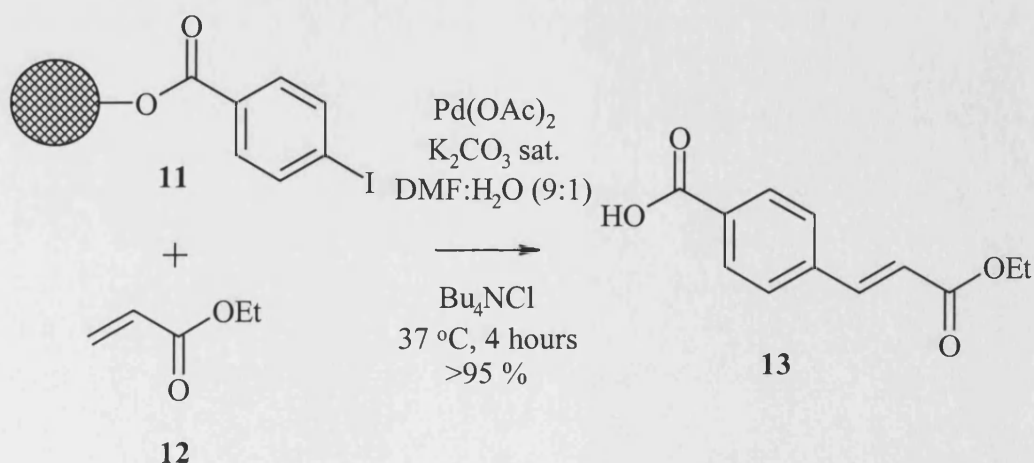
1.4 Heterogeneous Catalysis

Techniques that have been used in the past to separate products from catalyst include distilling the products from the reaction medium; co-ordinating the metal to a functionalised organic polymer or inorganic support; or using a semi-permeable membrane.³ Supports such as polymers, resins and silicas have been used to facilitate or eliminate catalyst recovery operations, and produce materials of unusual selectivity.

These supports have either been bound to the catalyst complex or attached directly to the substrate. The current interest in combinatorial chemistry has inspired much of the recent research into solid-phase organic chemistry by demonstrating the potential for supported reagents and catalysts in organic synthesis. However, these systems generally lack the combined activity/selectivity of analogous homogeneous catalysts at low temperatures.

1.4.1 Supported Substrates

Methodologies for solid supported syntheses are continuously being developed. This is often inspired by the potential for automated synthesis shown by many reactions with the target of producing chemical libraries of molecules such as ligands, which can be easily cleaved from supports after reaction.³⁴



A number of key synthetic reactions such as allylic substitutions, Heck, Stille, and Suzuki couplings have been effectively demonstrated using solid-phase syntheses to give good yield. For example, the palladium mediated coupling of ethyl acrylate (**12**) with 4-iodobenzoic acid (**11**), attached to commercially available hydroxyl functionalised TantaGel resin, has been demonstrated to give optimum conversion of >95 % at 37 °C after 4 hours. Subsequent detachment from the solid support was carried out using 0.1 M sodium hydroxide.³⁵

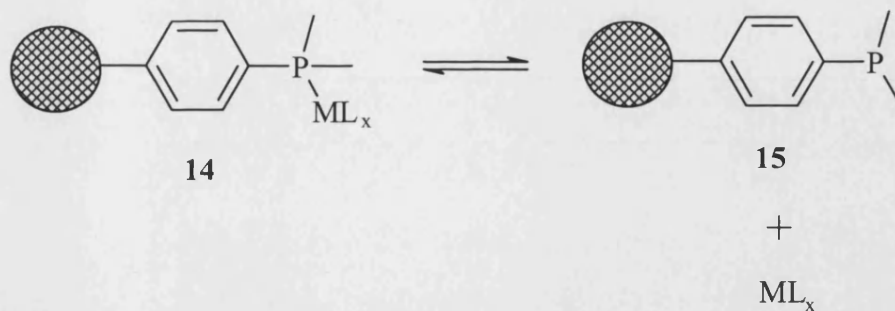
1.4.2 Supported Catalysts

Heterogeneous techniques have seen little success compared to homogeneous systems on an industrial scale.

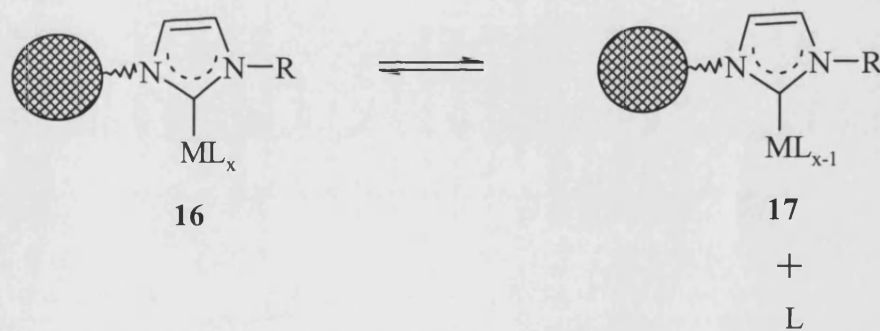
Immobilisation of the catalyst onto a stationary solid support by adsorption or by attachment to a support such as a polymer has exposed problems of either the catalyst continuously leaching, the possibility of polymer degradation, or reduced reaction rate due to decreased mobility of the catalyst. This is coupled with the additional time and expense of preparing a supported catalyst system. This is demonstrated by the Heck reaction of methyl acrylate and iodobenzene using a polymer-bound palladium-phosphine catalyst.³⁶

However, catalyst recycling in such systems is relatively convenient as the reaction solvent can sometimes be simply decanted from the reaction or the supported catalyst separated by filtration or centrifugation.^{37,38,39}

Dissociation of the metal from one of the anchored ligands is often the cause of leaching in such systems. Dissociation can also arise from structural changes with accompanying weakening of certain bonds during the catalytic cycle, while the metal co-ordination sphere undergoes continuous change.



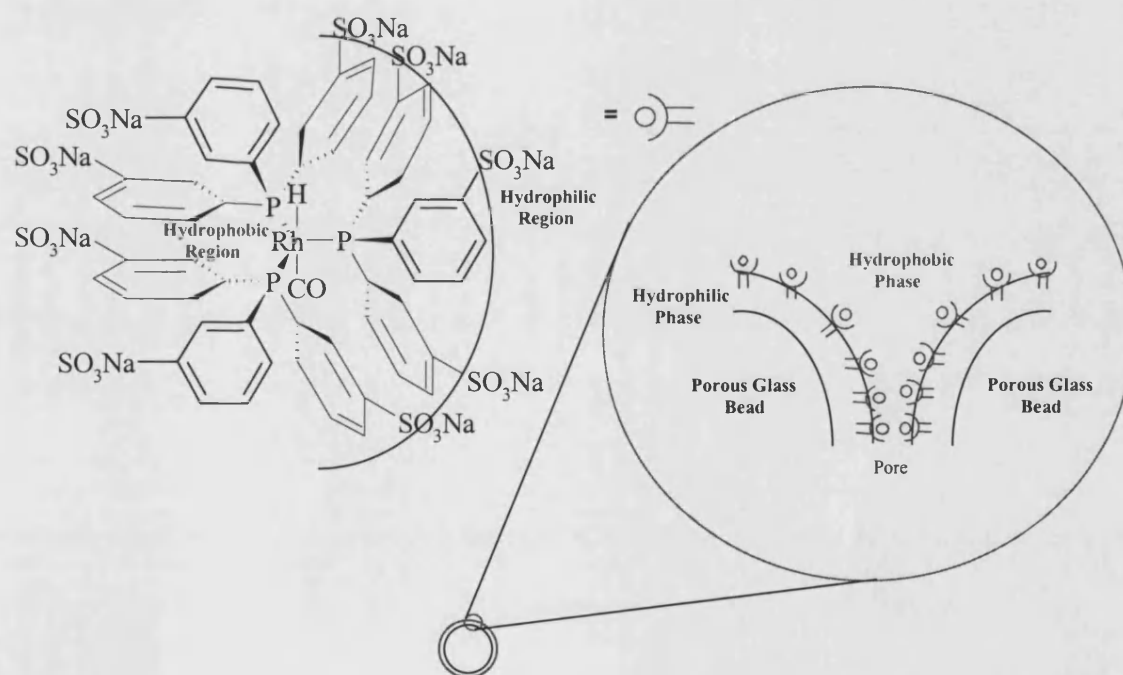
The long-term problem of metal leaching from an immobilised catalyst is especially highlighted in continuous flow systems where the metal concentration cannot attain an equilibrium. Leaching also occurs from systems, for example, with supported ligands. This can be costly especially if expensive ligands are employed. One solution to this is the use of *N*-heterocyclic carbenes (**16**) which effect catalytic C-C coupling reactions but unlike phosphines do not dissociate from the metal centre.⁴⁰



1.5 Supported Aqueous-Phase Catalysis

An adaptation of the biphasic approach is supported aqueous-phase (SAP) catalysis, described by Davis and demonstrated for use in the hydroformylation of higher alkenes.⁴¹ It is based upon supported liquid-phase (SLP) catalysis, a system in which a catalyst is deposited upon a high surface area porous support in a thin film of non-volatile solvent; reactants and products are limited to the surrounding gas phase. However, the SLP approach is limited to substrates and products in the gaseous phase.⁴²

Figure 3. The supported aqueous-phase (SAP) catalyst system.



SAP catalysis is based upon a water-soluble organometallic catalyst complex, originally $[\text{RhH}(\text{CO})(\text{TPPTS})_3]$, being dissolved in a polar, hydrophilic film supported upon high surface area glass beads whilst reactants and products are restricted to a non-miscible solvent phase (**Figure 3**).^{43,44} The approach assumes

that interaction between the substrates and the catalytic species occurs at the interface between the two phases. Hence, the high surface area afforded by the porous silica support maintains the activity that would be associated with reactions within a homogeneous system whilst reducing the potential for heavy metal contamination in the product. Also, crucially, the concept also eliminates the need for water-soluble reactants. The technique has also been extended to reactions such as asymmetric hydrogenation, Wacker oxidation, and hydroformylation of α,β -unsaturated esters.^{45,46,47,48}

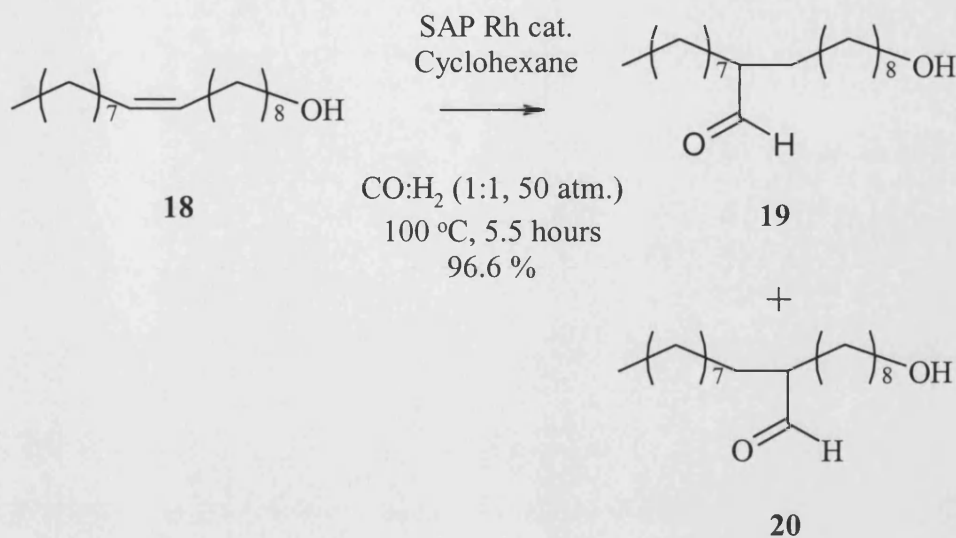
1.5.1 Rhodium Hydroformylation

In the early stages of development a high surface area silica, CPG-240 (surface area, SA= 77.5 m²g⁻¹), was contacted with water-soluble [RhH(CO)(TPPTS)₃], by aqueous-phase impregnation.

This was done by stirring an aqueous solution of the catalyst onto degassed CPG-240 along with excess TPPTS. After evacuation of the water to yield the 'dry' catalyst (water content = 2.9 % by TGA), exposure to vapour-phase water for fixed times allowed precise amounts of water to be condensed onto the silica surface by virtue of the hygroscopic nature of the complex.

The amount of water in the catalyst was found to greatly influence catalytic activity and selectivity. It was reported that the dried catalyst is more stable to storage. The catalyst was used to carry out the hydroformylation of oleyl alcohol (**18**) to the aldehydes (**19** and **20**) in cyclohexane (96.6 % conversion after 5.5 hours at 100 °C). The alcohol is insoluble in water and not subject to hydroformylation under usual biphasic conditions. The catalyst was also shown to be stable to recycling and the colourless filtrate after reaction was demonstrated to be inactive in further hydroformylation or hydrogenation indicating the absence of any leached rhodium

catalyst. This was confirmed by spectrophotometric and atomic absorption methods.^{44,37}



A new method of catalyst preparation by self-assembly was devised by loading $[Rh(acac)(CO)_2]$ in hexane onto CPG-240 by the incipient wetness technique and vacuum drying to remove solvent. This was then treated with an aqueous solution of 9 molar equivalents of TPPTS. The change of colour from white to yellow indicated rapid ligand exchange, minimising the possibility of catalyst deactivation by oxidation. The water was then removed under vacuum to yield a 'dried' supported aqueous-phase catalyst with a water content of 2.9 %. ^{31}P NMR confirmed the presence of the assembled catalyst complex and some oxidised phosphine. Hydration of the SAP catalyst was carried out by adding an amount of water, no more than the pore volume of the CPG, to a sample of pure CPG-240 which is 10 % of the weight to be used in reaction. The water was then allowed to equilibrate before being used in the hydroformylation reaction.

The presence of three equivalents of water-soluble phosphine to rhodium was reported to maximise catalyst stability. In the absence of solid support, decomposition of the homogeneous catalyst was observed and no hydroformylation of water-insoluble substrate was obtained. It was thus apparent that the stability of

[RhH(CO)(TPPTS)₃] was enhanced when adsorbed on glass surfaces as in a supported aqueous-phase catalyst.⁴¹

A catalyst was also prepared with the related silica CPG-350, such that the surface area available was equivalent to that when prepared with CPG-240. Similar conversions were attained with the catalyst and were consistent with the premise that the reaction was occurring at the interface and was proportional to the interfacial area in the reactor.⁴⁹

The influence of water content on the catalyst was also investigated. It was determined that maximum activity was at a loading of ~8 wt% water upon the supported catalyst. At this level, a high degree of mobility is possible whereas at low water content catalyst movement is suppressed. The turnover frequency, TOF, in the hydroformylation of 1-heptene increased by two orders of magnitude when the catalyst water content was increased from 2.9 wt% to 9 wt% without change in the selectivity. It was also suggested that catalyst stability was compromised, reflected by progressive darkening, under conditions of increased water loading and temperature. At high water content the catalyst was inactive, as it is less available to the water-insoluble substrate.⁴⁴

More recently, SAP catalysts were hydrated *in situ* under reaction conditions. Pure CPG-240, equivalent to 10 % of the amount to be used in the reaction, was impregnated with a specific amount of water, which was never more than the pore volume available. This was allowed to equilibrate within the pores whilst blending for half an hour. This was then loaded into the reactor along with dry solvent and olefin substrate. Then dried SAP catalyst was added. The total water in the system is the sum of residual water on the dry SAP catalyst (2.9 %) and the water on the wet CPG-240 (19 %). It was suggested that the water distributed over all solid particles, in the organic liquid and vapour phase.

Changes in the colour of the SAP catalyst during the course of the reaction were taken as an indication of catalyst degradation. SAP catalysts which are hydrated are less stable than those which are dried under reaction conditions. At high water levels, increased amounts of phosphine oxide were observed by ^{31}P NMR. The hydrated catalyst had an activity of at least two times that of the dried catalyst. In the best cases SAP catalysts were reportedly only 4 or 5 times slower than the equivalent homogeneous catalyst systems. Self-assembly tests indicated that the components of SAP catalyst were stable in the supported form. Therefore, the separation of the solution and complex from the support is unlikely under reaction conditions.^{41,50}

Hydroformylation of hept-1-ene yielded similar conversion and n:b (normal:branched) ratio as tetradec-1-ene and heptadec-1-ene using a SAP catalyst consisting $[\text{RhH}(\text{CO})(\text{TPPTS})_3]$ on CPG-240 (20 % conversion, in cyclohexane, $\text{H}_2:\text{CO}$, 1:1, 6.8 atm.).

A comparative study of the hydroformylation of olefins with a water-soluble rhodium complex was carried out with biphasic and supported aqueous-phase catalysts which suggested that the water is actually an immobilisation agent. In a continuous flow experiment it was found that, after 38 hours, water had leached from 3 g of supported aqueous-phase catalyst in a tubular trickle-bed reactor (at 100 °C and 52 atm., $\text{H}_2:\text{CO}$, 1:1) but no rhodium.⁵¹ From an initial high water loading the activity was seen to increase as water leached from the trickle-bed into the organic phase until water content was sufficient to supply no more than two mono-layers to the silica surface. This was attributed to the increased presence of the active site of the catalyst at the phase interface rather than in the aqueous solvent. It was also suggested that the glass support interacts with the water-soluble phosphines by hydrogen-bonding the hydrated sulfonate groups.

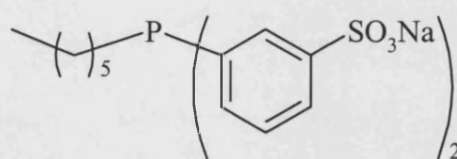
An investigation into the mechanism of the catalysis in the rhodium catalysed hydroformylation showed that the ratio of straight to branched (n:b) products was very different when using the SAP catalyst compared to the biphasic reaction. In the biphasic reaction the n:b ratio was high suggesting that $[\text{RhH}(\text{CO})(\text{TPPTS})_2]$ was the catalytic species with the two phosphines in the *trans* positions to each other. The n:b ratio with the SAP catalyst was only just higher than the homogeneous system in which the intermediate is either $[\text{RhH}(\text{CO})(\text{TPP})_2]$ or $[\text{RhH}(\text{CO})_2(\text{TPP})]$. Thus, it was suggested that the catalytic species is $[\text{RhH}(\text{CO})_2(\text{TPPTS})]$ in the SAP system. It was also noted that a species with two *cis* phosphines could be responsible.⁵¹ It was suggested that these observations could be as a result of either higher effective phosphine concentration or different catalytic species in the SAP system.^{45,52}

Structural elucidation was very difficult once the catalyst had been immobilised upon the bead. It was only possible to compare the activity observed with equivalent homogeneous and biphasic systems. Electron microprobe analysis performed indicated a uniform Rh:P distribution across the surface of the silica.⁴⁴ Infrared spectroscopy could only indicate a lack of rhodium carbonyls in reaction solution. Solid-phase ^1H or ^{31}P NMR on the dry catalyst confirmed the presence of the phosphine ligands. The $[\text{RhH}(\text{CO})(\text{TPPTS})_3]$ complex exists as a trigonal bipyramid, with the phosphines occupying the equatorial positions, in solution on the silica. CP MAS ^{31}P NMR showed that the phosphines were stationary when the catalyst was dry but mobile once hydrated by the supported solvent layer.⁵³

The co-deposition of alkali metal salts on the surface of the SAP catalyst (KCl:Rh, 2-10:1) before hydration was found to improve the activity and n:b ratios in hydroformylation of terminal alkenes.⁵⁴ This was attributed to the salt stabilising the

polar transition-state and increasing the steady-state concentration of the acyl intermediate thereby aiding CO insertion in alkyl ligands.

Lipophilic chains have been incorporated into sulfonated phosphine ligands to make hexyl-*bis*(sodium-*m*-sulfonatophenyl)phosphine, HexDPPDS (**21**). This was unsuccessful in that the aim was to increase surface activity in the SAP catalyst by positioning the metal centre nearer the phase interface. The catalyst did, however, exhibit similar n:b ratios to the TPPTS ligand and did not leach heavy metal.⁵⁵



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The hydroformylation of methyl acrylate was affected using SAP catalyst and was observed to exhibit average turnover frequencies, which were greater than ten times that in equivalent homogeneous or biphasic reactions. This was attributed to favourable interaction between the substrate, surface hydroxyls on the silica and the supported solvent.^{48,56}

Significant dependence on water content was observed. A study carried out on a number of alternative silicas e.g. silica gel (60 Å) showed that activity increased as the degree of pore filling (δ , calculated by dividing the volume of the coating added by the total pore volume of the solid) reached unity. It rapidly decreased above this level and became comparable to a biphasic system. It was also demonstrated that performance is independent of surface area and mean pore diameter. SAP catalysts prepared from CPG-240 (pore diameter, $D_p = 240$ Å), CPG-350 ($D_p = 350$ Å), alumina and molecular sieves exhibited lower activity compared to the cheaper silica analogues. In this case it was attributed to the higher surface area of the cheaper

analogues at full pore filling, $\delta=1$. Substrates, less polar than methyl acrylate, exhibited optimum activity at a low pore filling giving a large interfacial area.

The term supported homogeneous film catalysts (SHFC) has been coined by groups investigating alternatives for the water phase in hydroformylation. Polyethylene glycol was chosen for its high boiling point, ability to form films and immiscibility with the product/substrate phase. Addition of polyethylene glycol (PEG 600) until $\delta=0.5$ doubled (TOF 2.6 min^{-1}) the activity of the dry catalyst. The use of a 1:1 mixture of water and PEG 600 at $\delta=1.4$ increased (TOF 8.3 min^{-1}) the activity further. The hydroformylation of hex-1-ene was shown to give an activity of 24.7 min^{-1} and an n:b ratio of up to 6:1 (pore filling, $\delta=1.4$, at $100 \text{ }^\circ\text{C}$, and 6 atm.) which is comparable to the equivalent homogeneous reaction (TOF 68 min^{-1} , n:b 3).⁵⁷

Unlike in the homogeneous reaction the absence of bulk solvent was seen to be beneficial. The lower solubility of substrates such as oct-1-ene in the film was thought to contribute to reduction in activity. In such cases, the activity has been seen to increase through the course of the reaction. IR spectroscopy suggests that this is most likely due to product dissolution in the coating acting as a surfactant to increase transfer of substrate into the film. The implication that the reaction occurs in the film and that activity is dependent upon solubility of the substrate contradicts previous SAP catalyst studies. Unexpectedly, it has been shown that the use of the more viscous PEG 8000 slows reaction. Reducing viscosity of the film by dilution with water increases activity. This is in contradiction to the theory that the catalyst is active at the interface. By adding a surfactant the initial activity of the catalyst can be increased to match that after a prolonged reaction. Also optimum pore filling, $\delta=1.4$, which is much higher than the 0.06 for the original SAP catalyst and close to the level at which droplets form on the bead.

The leaching of some of the PEG and not the metal into the bulk solvent implied that the coating has solubility, to some degree, in a concentrated solution of the aldehyde product. This could be limited by the addition of sodium sulfate to the film. Films consisting of polyvinylpyrrolidone, polyvinyl alcohol and polyethylene oxide have also been employed as alternatives with little or no success.

1.5.2 Cobalt Hydroformylation

The hydroformylation of 1-hexene was economically carried out using $[\text{Co}_2(\text{CO})_6(\text{TPPTS})_2]$, a cheap alternative to rhodium catalysts, under biphasic and SAP conditions (upon 3 g CPG-340, 50 ml toluene, $\text{H}_2:\text{CO}$, 1:1, 54 atm., 190 °C, 8 hours).²¹

Under biphasic conditions, the complex displayed lower activity and also high levels of leaching originating from the equilibria in which the catalyst most likely exists, with the organic-soluble dicobalt octacarbonyl $[\text{Co}_2(\text{CO})_8]$ and hydridocobalt tetracarbonyl $[\text{CoH}(\text{CO})_4]$ under high pressure in the reaction. The amount of cobalt leached was reduced ten-fold using the supported catalyst compared to the two-phase system. This was achieved with a two-fold excess of phosphine to complement the increase in phosphine concentration at the glass surface.

The activity of this system did not appear to be as dependent on water content as the rhodium based catalyst. This could imply that the substrate phase is homogeneous at the high reaction temperature or that the activity of the catalyst is not as dependent upon its mobility. The activity of the supported catalyst was seen to be independent of the level of cobalt present in the organic phase. This supports the theory that cobalt supported on the glass is the catalytic species and is backed up by the high n:b ratio seen in the reaction which is comparable to the equivalent

homogeneous reaction and double that observed for the biphasic system. This suggests that the reaction pathway is different than that for the biphasic system. It was also reported that the activity improved as cobalt loading was decreased, suggesting much of the cobalt becomes unavailable for catalysis at high loading in the supported system. The temperature used was significantly higher than in the rhodium system and thus there was some indication of decomposition of the cobalt complex to metal on the glass.

The same research group produced alkylphosphines with sulfonated aromatic phosphines acting as anchors. This was with the aim of reducing displacement of the phosphine ligands by CO which produces a less selective catalytic species.⁵⁵

1.5.3 Platinum Hydroformylation Catalysts

[Pt(TPPTS)₂Cl₂] has been demonstrated as an active catalyst in the hydroformylation of 1-hexene, on CPG-350, CPG-240 and under biphasic reaction conditions. Prior to this it was known that the unsulfonated complex [Pt(PPh₃)₂Cl₂] is inactive in homogeneous hydroformylation.

Analogies have been drawn from these observations suggesting that the sulfonate group acts as an activating ligand much like the addition of methanesulfonic acid in similar platinum complexes. The presence of tin (II) chloride as a co-catalyst usually increases the rate of hydroformylation and improves selectivity of the reaction. Due to the facile nature of the Pt-Sn bond for hydrolysis, it was considered inappropriate for an aqueous reaction. However, it was found that a minimal amount of water on the glass surface is permissible in order to carry out the reaction with tin (II) chloride co-catalyst under SAP catalyst conditions.

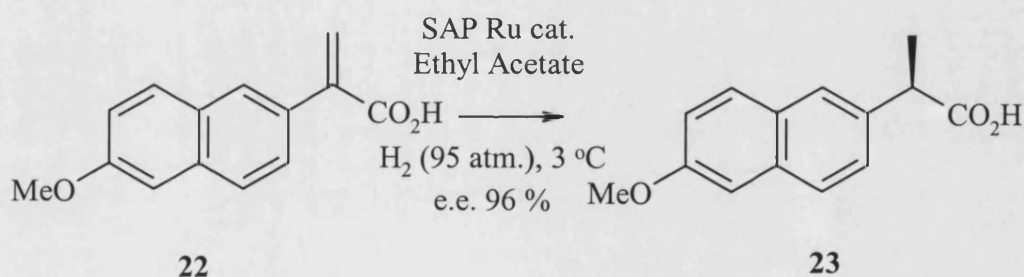
The supported catalyst was prepared by deposition of the *cis* isomer of [Pt(TPPTS)₂Cl₂] on to the silica. Treating the dried beads with two equivalents of tin

(II) chloride in dichloromethane followed by evaporation of the solvent resulted in a SAP catalyst with 1.4 % water content. The two SAP catalysts, one with and one without tin (II) chloride, exhibited similar activity but very different regioselectivity. The [Pt(TPPTS)₂Cl₂] complex gave products with an n:b ratio of 3.0:1 whereas the tin modified catalyst exhibited an n:b ratio of 11.5:1.²²

An enantiomerically pure platinum catalyst has also been employed in an asymmetric hydroformylation with some enantioselectivity.⁵⁵

1.5.4 Asymmetric Hydrogenation

[Ru(C₆H₆)(BINAP-4SO₃Na)Cl]Cl has been explored as a complex for asymmetric hydrogenation in homogeneous, heterogeneous and SAP catalyst systems. 2-(6-methoxy-2-naphthyl)acrylic acid (**22**) was chosen as substrate for hydrogenation to give the anti-inflammatory drug, (*S*)-Naproxen (**23**).⁴⁵



This was carried out on CPG-240 in ethyl acetate (3 °C). The homogeneous catalyst system proved to be the most active giving high enantioselectivity and demonstrating the need for freedom of mixing between the catalyst complex and substrate. The presence of triethylamine was shown to improve enantioselectivity. Carrying out the homogeneous reaction in a 1:1 methanol:water system reduced the enantioselectivity to 77.6 % e.e. compared to 87.5 % in methanol alone. This was thought to provide evidence of the significance of the easily displaced chloro ligand in enantioselectivity.

The addition of water to hydrate the dry inactive SAP catalyst raised the activity to fifty times greater than that of the biphasic system and just seven times slower than the homogeneous system. The extent of catalyst hydration was limited by the solubility of water in ethyl acetate. Although, increased water loading improved activity and enantioselectivity, the selectivity of the system still fell short of the heterogeneous system due to hydrolysis of the Ru-Cl bond. Enantioselectivity could be improved by decreasing reaction temperature but at the cost of turnover frequency.

Water was later substituted for ethylene glycol in hydrogenations with SAP catalysts. The integrity of the $[\text{Ru}(\text{C}_6\text{H}_6)(\text{BINAP-4SO}_3\text{Na})\text{Cl}]\text{Cl}$ complex appeared to be maintained (demonstrated by ^{31}P NMR) in a 1:1 mixture of ethylene glycol in methanol. However, introduction of water appeared to result in cleavage of the Ru-Cl bond. By stirring a solution of ethylene glycol in ethyl acetate with dry supported catalyst, the system was solvated. The activity was again seen to be dictated by the level of solvent loading on the bead. However, in this instance the enantioselectivity of the supported catalyst was similar to that of the homogeneous system. Also there was a three-fold increase in the activity compared to previous SAP catalyst systems, increasing to fifty-fold when using ethylene glycol/water in a biphasic system. However, a drawback to this modification was the observed leaching of ruthenium from the supported catalyst into the bulk organic solvent assumed to be as a result of the greater solubility of ethylene glycol in the organic phase.^{46,52}

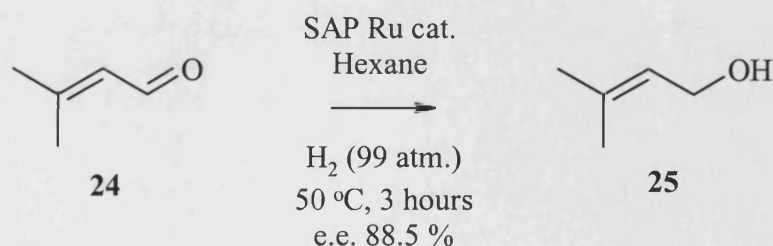
By separating the solvated beads from the bulk organic phase by filtration and vacuum drying, mass-transfer to the organic phase could be minimised by saturating the bulk solvent with ethylene glycol. By this procedure it was possible to carry out asymmetric hydrogenation with a SAP catalyst giving high activity and

selectivity (88.4 % versus 88.2 % compared to the homogeneous equivalent at room temperature).

Enantiomerically pure bidentate phosphine complexes of rhodium and platinum have been synthesised for asymmetric hydrogenation.^{55,58} Also, a new generation of asymmetric hydrogenation catalysts consisting of Rh (I), Ru (II), Ni (II), or Co (II) complexes anchored in modified USY zeolites has been reported. These exhibited a remarkable support effect on the enantioselectivity for the catalytic hydrogenation of prochiral alkenes. The system, however, was limited by the small pores (~8 Å) which only allowed small substrates to be reacted.⁴⁵

1.5.5 Hydrogenation of α,β -Unsaturated Aldehydes

[RuCl₂(TPPTS)₃] and [RuH₂(TPPTS)₄] complexes have been successfully used in the hydrogenation of α,β -unsaturated aldehydes to allylic alcohol with a SAP catalyst on Merck 60 silica. This process is important in the field of flavour and fragrance chemistry. 100 % conversion along with a selectivity of 88.5 % was seen with the supported catalyst in the hydrogenation of 3-methylbut-2-enal (**24**) to give 3-methylbut-2-enol (**25**) (hexane, 50 °C, 3 hours).⁵⁹



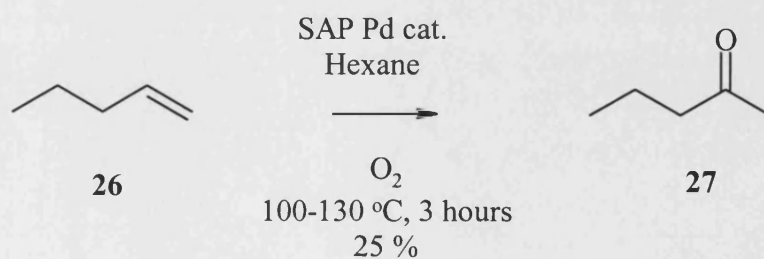
Recycling of the catalyst resulted in a reduction in yield attributed to catalyst poisoning by substrate. Substituting with polar solvents such as methanol reduced activity and caused visible leaching of the catalyst from the support. Reactions that were conducted in neat substrate gave good selectivity but poor yield.

1.5.6 Wacker Oxidation

A limiting factor in the Wacker oxidation of alkenes is that the reaction is routinely carried out in aqueous solvent. Although the oxidant in this palladium/copper catalysed reaction is molecular oxygen, the incorporated oxygen comes from the aqueous solvent. This retards the reaction of higher alkenes which are sparingly soluble in aqueous solvents.

It was hoped that the use of supported aqueous-phase catalysts would overcome these obstacles. The supported catalyst was prepared by deposition of a 1:1 ratio of the metals as their dichlorides from an aqueous solution. This was hydrated by transfer from controlled pore glass beads of known water content. This process proved superior to direct hydration as it does not appear to be as disruptive to the catalyst surface and the controlled nature of the water release from the saturated support to the unhydrated catalyst.⁴⁷

Oxidation of hept-1-ene (**26**) to heptanone (**27**) was carried out with this supported catalyst (PdCl₂-CuCl₂ on CPG-240, hexane, 3 hours) at temperatures of 100-130 °C and varying oxygen pressure. A much higher level of water loading was required for optimum activity compared to the hydroformylation reactions. This was attributed to the absence of hydrophilic ligands. Conversions of up to 25 % were reported under optimum conditions. Significant isomerisation of hept-1-ene to hept-2-ene and hept-3-ene was noted during reaction. An unusually high dependence on oxygen pressure was suggested to reflect difficulties in palladium re-oxidation in the supported aqueous-phase system.



The problems of isomerisation and loss of conversion at high temperatures (>100 °C) was more pronounced in the new supported catalyst system. Increased loading of palladium was reflected in increased levels of heptene conversion. Supernatants from reactions, filtered through a stainless steel HPLC sintered filter, were found to contain no traces of palladium or copper by atomic absorption spectrometry down to a sensitivity limit of 2 ppm and 1 ppm, respectively.

1.5.7 Enzymatic Catalysis

Supported aqueous-phase catalysts have also been extended to enzymatic systems.⁶⁰ Horse liver alcohol dehydrogenase (LADH) has been demonstrated catalysing the oxidation and reduction of alcohols and aldehydes, respectively, in organic media in a system based upon SAP catalysis.

The main limitation of LADH in organic solvents is the poor interaction between the enzyme and the organic-insoluble nicotinamide cofactor, (NADH). Enzyme immobilisation has, therefore, been utilised to promote enzyme-cofactor interaction. Prior to SAP catalysis, LADH and NADH have been co-immobilised onto non-porous glass in polar, water-immiscible solvents such as ethyl acetate and isopropyl ether. A 'micro-aqueous' environment was maintained on the glass bead surface by the presence of a saturating level of water in the solvent enabling the NADH and LADH to interact. However, due to the poor level of hydration and low interfacial area, reaction rates were slow.

Entrapping the enzyme and cofactor within an aqueous phase on porous supports (150 Å, SA=300 m²g⁻¹) ensured the enzyme existed in its proper hydration state for optimal catalysis. Using an optimal pore hydration equivalent to 70 % pore volume, rates six-fold higher than with non-porous glass were demonstrated as well as cofactor recycling numbers in excess of 10⁵.

1.6 Conclusion

Much of the work undertaken in the development of catalytic processes that are environmentally benign is primarily concerned with primary prevention, i.e. that does not pollute, rather than secondary prevention, i.e. clean-up.

The disposability of the catalyst system is, therefore, a high concern in the design of new catalyst systems. There is a definite trend away from liquid to solid catalyst systems. As catalysts become more sophisticated, the issue of cost becomes more profound. However, as environmental regulations are demanding higher standards of emissions, the choice is between more costly and sophisticated catalysts or more expensive and thorough cleanup processing. The attraction of supported aqueous-phase catalysis stems from the hybridisation of the principles underlying homogeneous and heterogeneous catalysis. The potential for modification and application is, therefore, quite diverse. Supported aqueous-phase catalysis has a significant role to play in the future of clean technologies.

CHAPTER 2

OPTIMISATION OF PALLADIUM BASED SUPPORTED

AQUEOUS-PHASE CATALYSIS

Chapter 2: Optimisation of Palladium Based Supported Aqueous-Phase

Catalysis

2.1 Introduction

Palladium compounds are extremely useful for C-C bond forming reactions. The catalyst precursor is commonly palladium (II) acetate, although palladium (II) chloride or even palladium on charcoal can be used to carry out vinylation of organic halides.

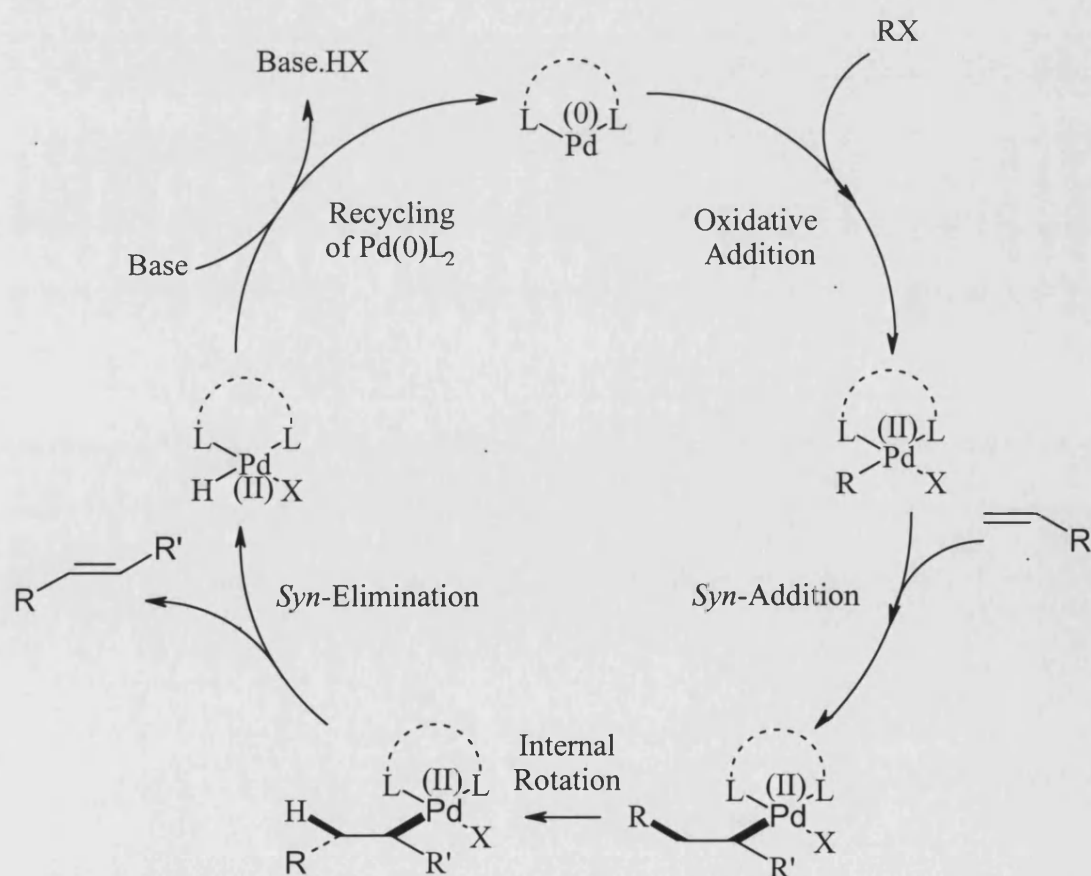
The reactions can be carried out homogeneously using common solvents such as acetonitrile, dimethylformamide, and methanol at temperatures between 50 °C and 160 °C to give good to excellent yields. The palladium (II) complexes must be reduced under reaction conditions, presumably by oxidising some of the olefin present, then react with the halide to form the organopalladium intermediate as a palladium (0) complex. The presence of a base is often necessary as the hydropalladium halide dissociates reversibly and the base shifts the equilibrium to the palladium (0) species.^{2,61,62}

2.2 The Heck Reaction

Palladium complexes are commonly used to carry out vinylation of organic halides. This can be done by refluxing under nitrogen, in common organic solvents, to give excellent yields.

The Heck reaction is a key example of such a coupling. The reaction can typically be carried out by heating the halide with 1 mol% palladium (II) acetate or palladium (II) chloride, 2 mol% triphenylphosphine (TPP), a slight excess of tertiary amine (e.g. triethylamine), and alkene in acetonitrile. The palladium (II) complex is assumed to be reduced *in situ* to palladium (0) by the phosphine, olefin, or triethylamine base during the catalytic cycle (**Figure 4**).²

Figure 4. General mechanism of the Heck reaction.

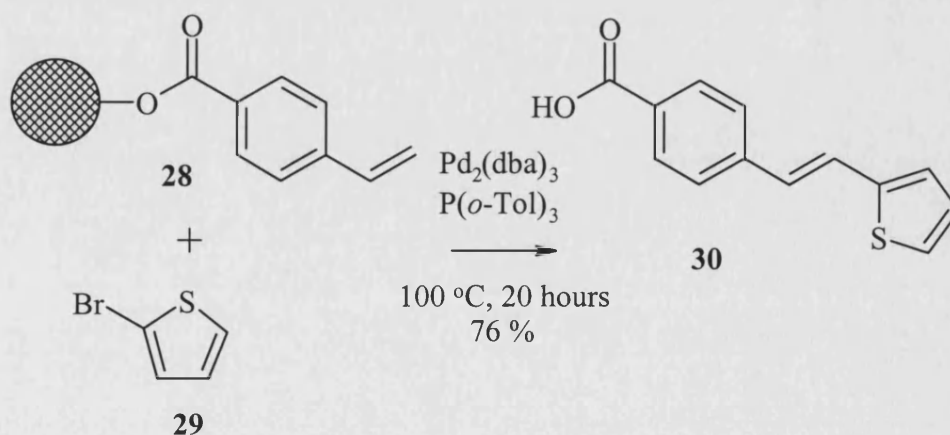


Because of the safety and economic significance, the use of aqueous conditions in such reactions has been studied using a number of homogeneous biphasic systems. These studies have centred on a number of approaches, having the catalyst and substrate both present in the aqueous phase, having a water-soluble catalyst with a hydrophobic substrate, or having a hydrophobic catalyst with a water-soluble substrate. These techniques are often, however, limited by the solubility of the olefin in the catalyst phase.^{63,64,65,66}

2.2.1 Heck Reactions on Solid Supports

The arylation of methyl acrylate with iodobenzene has been studied using heterogeneous catalysts upon modified silica supports. Promising results were obtained for a range of precursors screened for conversion, activity and stability.⁶⁷

Solid supports in the Heck reaction have the potential to offer advantages such as simplified separation and recyclability, thermal stability and high turnover numbers and moderate catalyst efficiency. For example, resin supported 4-vinylbenzoic acid (**28**) was coupled in Heck reactions with a number of substrates such as 2-bromothiophene (**29**). In this particular case it was possible to use harsher conditions than normal to attain good yields of product.



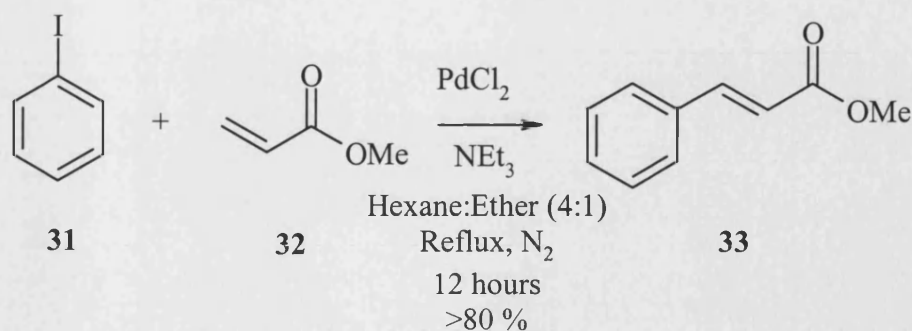
2.3 Factors in the Optimisation of Heck Reactions with SAP Catalysts

This chapter describes the preparation and use of the supported aqueous-phase system of catalysis and the efforts made to optimise and expand upon its use for palladium based reactions. Several factors in the preparation of the supported catalyst have been investigated with the aim of ensuring good assembly, distribution and immobilisation of the catalyst complex across the surface of the beads.

The thickness of the hydrophilic film upon the porous glass beads was varied. The hydrophilic nature of the ligand complex was studied using mono- and tri-sulfonated sodium and lithium salts of triphenylphosphine. The effect of level of catalyst loading and ligand/catalyst ratio upon leaching and activity were also examined. These factors were studied to establish optimum activity and minimum leaching and develop a better understanding of the catalysis occurring in supported aqueous-phase systems.

This is a continuation of the work that had been carried out by groups on using the system for rhodium hydroformylation and asymmetric hydrogenation, with the aim of easy separation of active catalyst from products in chemical processes.

2.3.1 The Vinylation of Iodobenzene



The Heck coupling between methyl acrylate (32) and iodobenzene (31) in the presence of triethylamine was chosen as the reaction for this study. The coupling was performed by heating under reflux with a solvent mixture of hexane:ether (4:1). Sulfonated phosphine ligands were chosen for their excellent solubility in water (e.g. $\sim 80 \text{ gL}^{-1}$ for Na-TPPMS and $\sim 1100 \text{ gL}^{-1}$ for Na-TPPTS).³ Palladium levels in the reaction supernatant were determined prior to and at the end of reactions.

2.3.2 Analysis of Silica Pore Size Distribution, Surface Area, Pore Volume and Adsorption Isotherm

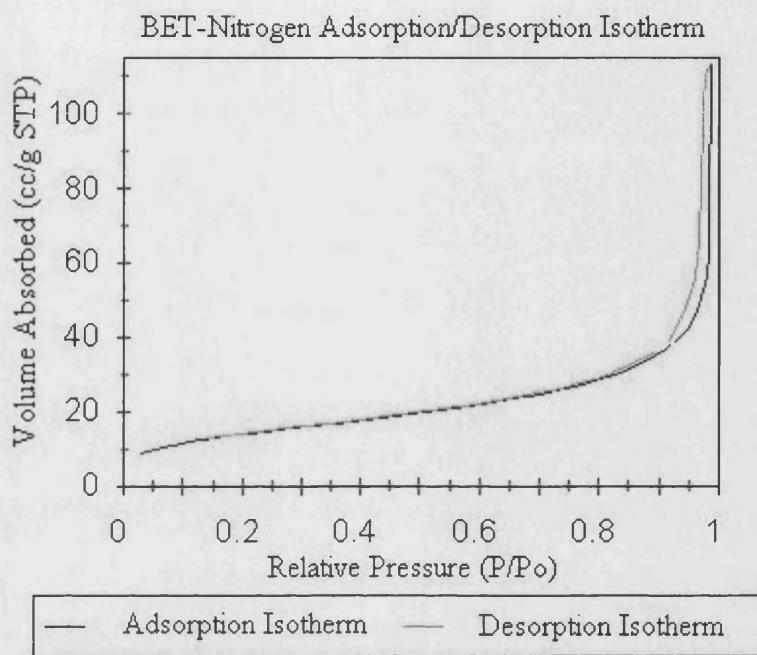
BET-N₂ adsorption/desorption analysis was carried out on the porous silicas to confirm reported pore size distribution, surface area and pore volume.

It was found that the porous glasses typically gave type IV isotherms with characteristic HI hysteresis loops associated with porous materials known to consist of uniform spheres in fairly regular array with narrow distributions of pore size (Figure 5).⁶⁸

Gas adsorption measurements are widely used for determining the surface area and pore size distribution of an extensive array of different solid materials. Adsorption is the enrichment of one or more components in an interfacial layer. The

relation, at constant temperature, between the amount adsorbed and the equilibrium pressure of the gas is the adsorption isotherm.

Figure 5. Typical BET-N₂ adsorption/desorption isotherm plot for CPG.

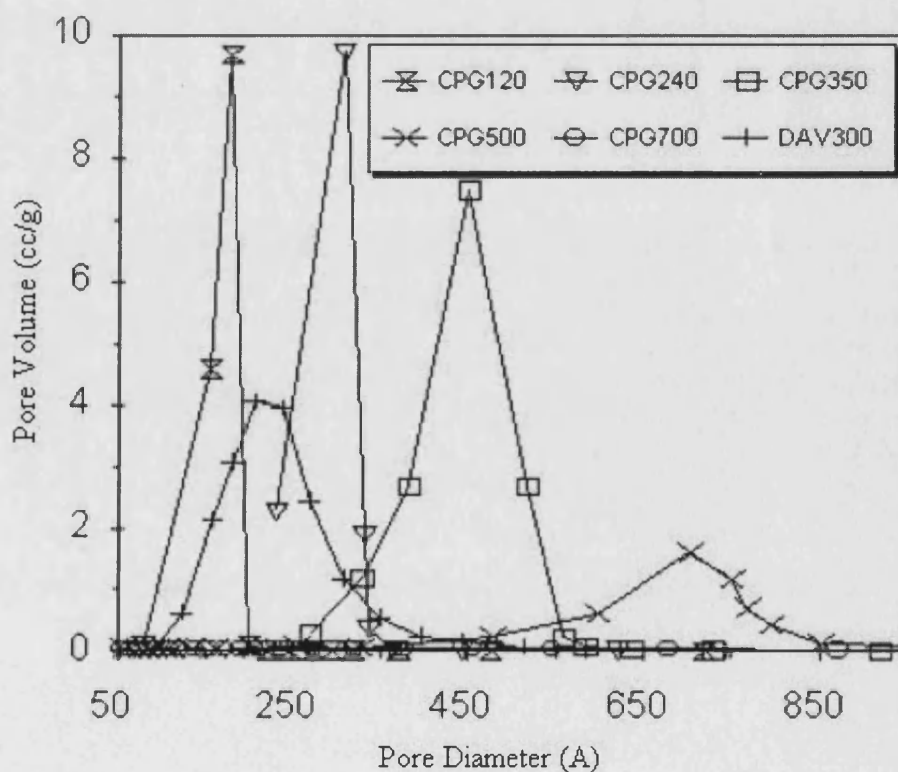


In the context of physisorption pores can be classified according to their sizes: macropores >50 nm, mesopores 2-50 nm, micropores <2 nm. Isotherms can generally be grouped into six types. Type I are given by microporous solids having small external surfaces e.g. activated carbons, and certain porous oxides. The reversible type II isotherm is obtained with non-porous or macroporous adsorbent. The reversible type III isotherm is not common, but is found in a number of cases e.g. nitrogen on polyethylene. Type IV isotherms are given by many mesoporous industrial adsorbents. Type V is uncommon but is obtained with certain porous adsorbents. Type VI isotherms are observed with argon or krypton on graphitised carbon blocks at liquid nitrogen temperature.

Shapes of hysteresis loops correspond to specific pore structures. Type HI is associated with porous materials consisting of agglomerates or compacts of uniform spheres in regular array, with narrow pore size distributions. Many porous adsorbents (e.g. inorganic oxide gels and porous glasses) tend to give type H2 loops, with the distribution of pore size and shape not well-defined. The type H3 loop is observed with aggregates of plate-like particles giving rise to slit-shaped pores. Similarly, the type H4 loop is often associated with narrow slit-like pores, but in this case the type I isotherm character is indicative of microporosity.

The Brunauer-Emmett-Teller (BET) gas adsorption method has become the most widely used standard procedure for the determination of the surface area of finely divided and porous materials, despite the over-simplification of the model on which the theory is based.

Figure 6. Pore size distributions for silicas CPG-120, CPG-240, CPG-350, CPG-500, CPG-700 and Davisil 300 (Calculated from BET-N₂ adsorption/desorption analysis).



The Controlled Pore Glasses, CPGs, were shown to possess narrow pore size distributions but also displayed many micro size pores (<2 nm). However, CPGs with greater average pore diameter, CPG-500 and CPG-700 exhibited greater deviation in pore size. This is illustrated by their proximity to the horizontal in the pore size distribution diagram, especially in the case of CPG-700 which appears indistinguishable from the baseline (Figure 6).

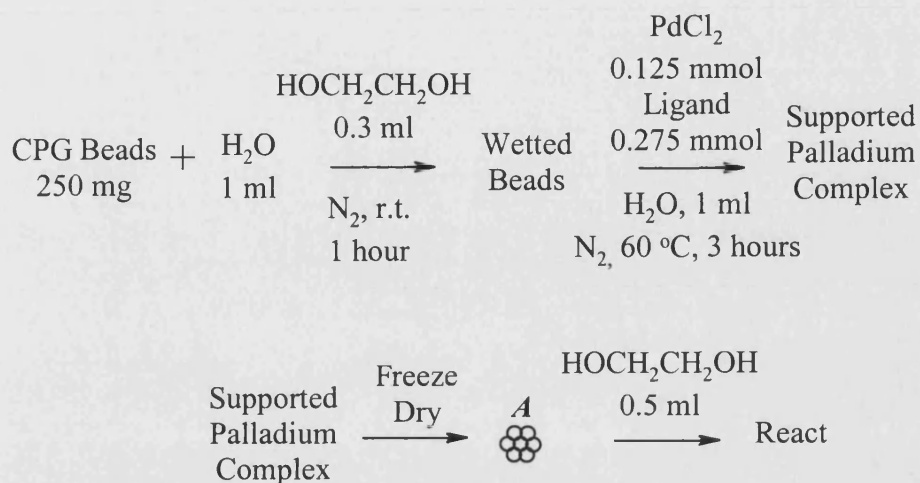
Beads with larger average pore size were disregarded for these studies as they were shown to exhibit greater deviation in physical characteristics. CPG-290B ($D_p=290 \text{ \AA}$; $SA=132 \text{ m}^2\text{g}^{-1}$), Siva Beads-soda glass ($D_p=60\text{-}300 \text{ microns}$; particle size=1-2 mm), Siva Beads-soda glass ($D_p=60\text{-}300 \text{ microns}$; particle size=0.4-1 mm), crushed foamed clay (particle size >0.125-0.7 mm), and foamed clay (particle size >2.8-3 mm) were eliminated as potential supports due to poor availability or detrimental solvent interactions. The porous silica, CPG-350, was chosen for study. It displayed similar deviation in pore size to Davisil 300, which is a cheap viable alternative for future large-scale operations. The two types of silica beads also have similar average pore diameter (350 \AA and 300 \AA , respectively). The properties of catalysts supported upon them were very similar despite the large difference in surface area. A previous study had shown pore diameter to be of greater importance in influencing these properties.⁴⁸

2.3.2 Immobilisation of Palladium Complex onto Porous Silica

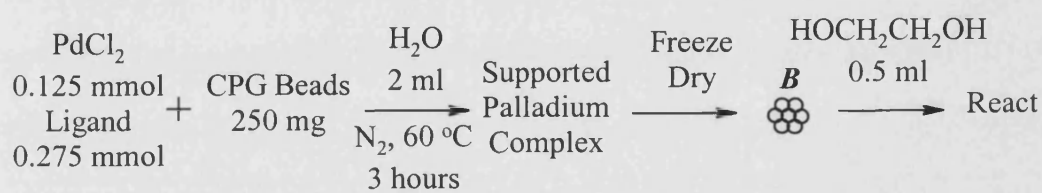
Several techniques were explored in order to optimise the assembly and immobilisation of the catalyst complex onto the porous glass beads (Figure 7). These different techniques of dried supported aqueous-phase catalyst preparation were seen to produce variations in activity and leaching.

Figure 7. Preparation of palladium SAP catalysts.

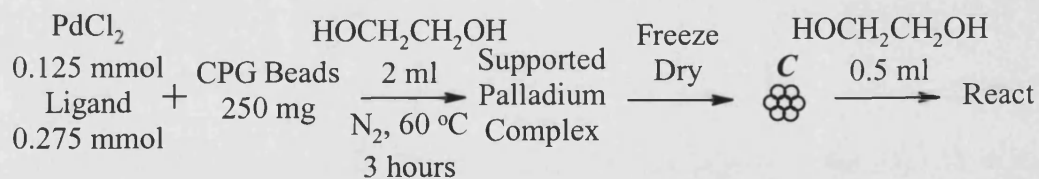
Method A



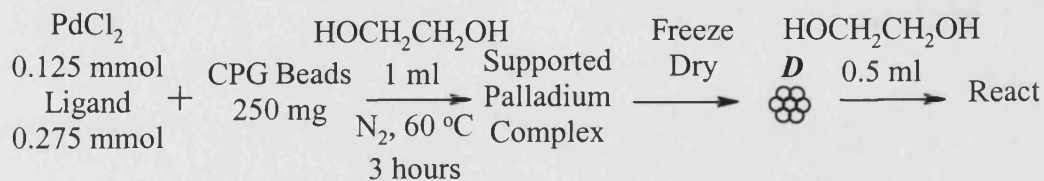
Method B



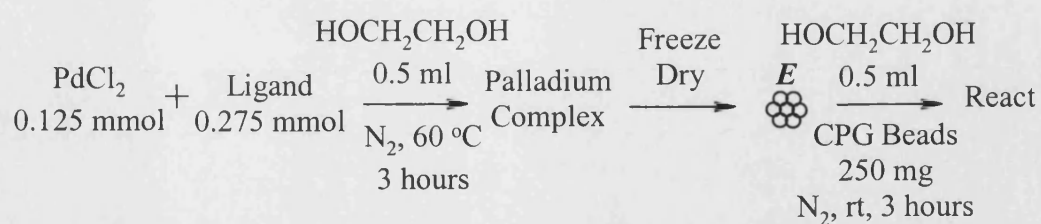
Method C



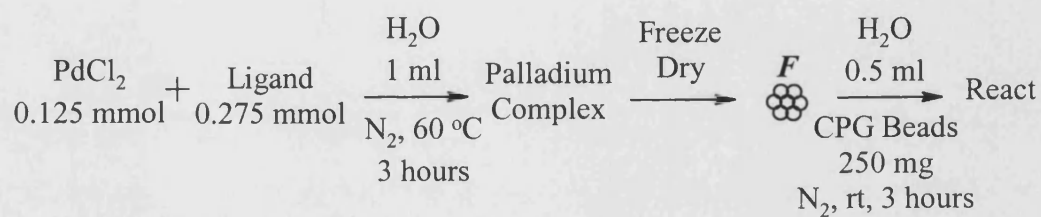
Method D



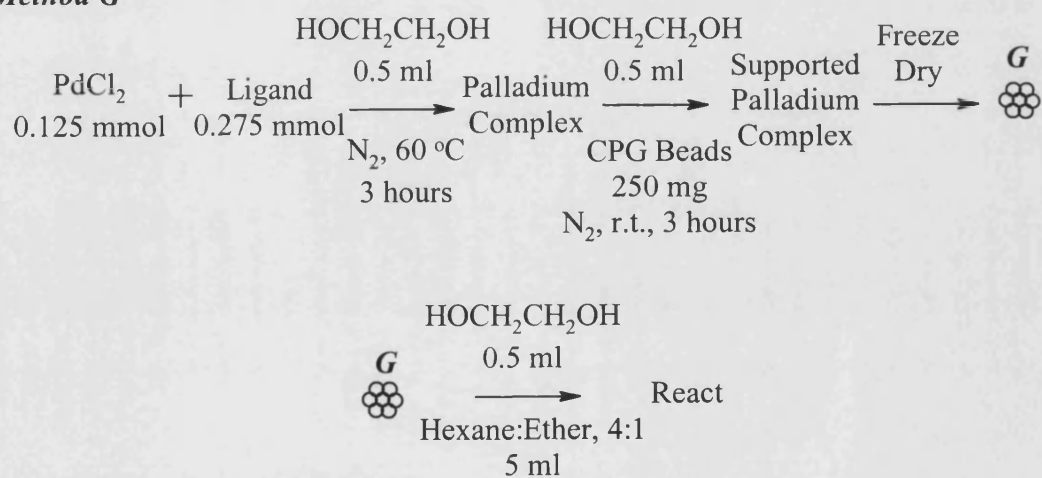
Method E



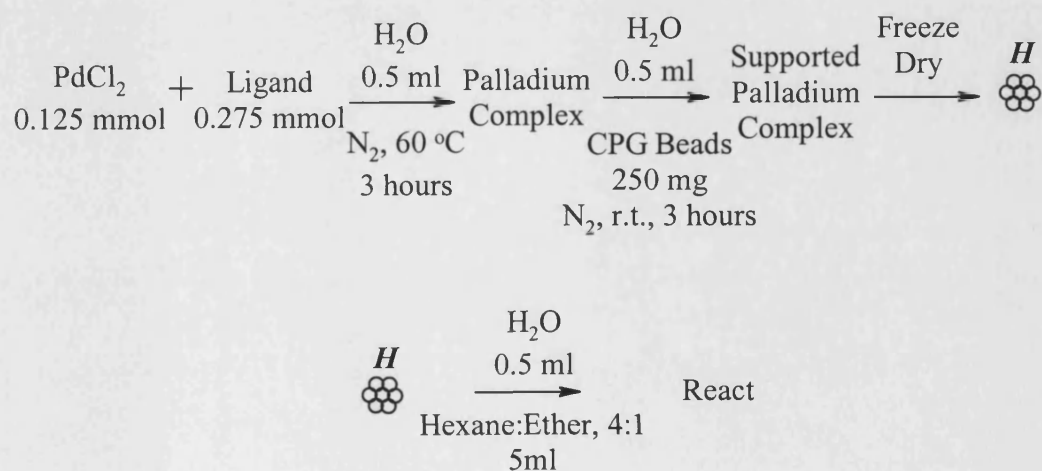
Method F



Method G



Method H



Solvent samples from before and after reaction were analysed to determine the extent of palladium leaching. Samples were vacuum filtered through a stainless steel Millipore in-line filter to remove solid particles. They were then evaporated at 400 °C and extracted into de-ionised water with a few drops of aqua-regia for atomic absorption spectrometry.

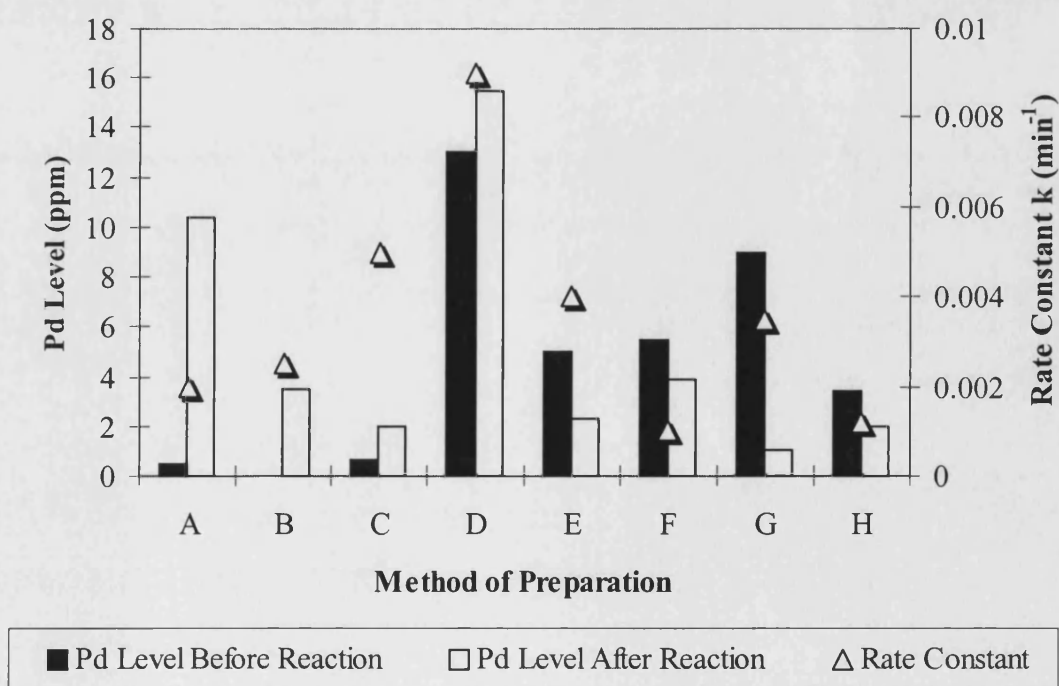
Initially a relatively cumbersome multi-step procedure, *A*, was used, involving separate formation of the palladium complex by stirring the palladium (II) chloride with ligand for 3 hours at 60 °C in water followed by introduction of silica which had been 'pre-wetted' by stirring in water, dosed with ethylene glycol, for 1 hour at room temperature. Further stirring was used to facilitate good distribution of the complex across the support over 3 hours before removing the solvent overnight by freeze-drying, producing a catalyst which exhibited poor activity ($1.9 \times 10^{-3} \text{ min}^{-1}$) and significant levels of palladium leaching during the course of the reaction (10.3 ppm).

Methods *B* and *C* were both disregarded despite their simplicity as they also produced a catalyst with which the equilibrium tended towards the catalyst gradually leaching into the bulk solvent. Reducing the level of ethylene glycol used in the catalyst preparation (method *D*) resulted in an unstable catalyst with very significant leaching of metal. However, it was noted that the activity of this catalyst was profoundly higher than with other preparations. The connection between these observations would later be investigated in more detail. It was noticed that preparations which involved the addition of dry silica beads during the latter stages of the process (methods *E-H*) produced catalysts in which the equilibrium tended towards a reduction of the level of metal in the bulk solvent during the course of the reaction, i.e. the catalyst complex was more stable. Methods *E* and *F*, however, produced catalysts with which the level of metal in the bulk solvent after reaction

was still significant. Also method *F*, which uses water as a coating, produced a catalyst which displayed poor activity in this reaction.

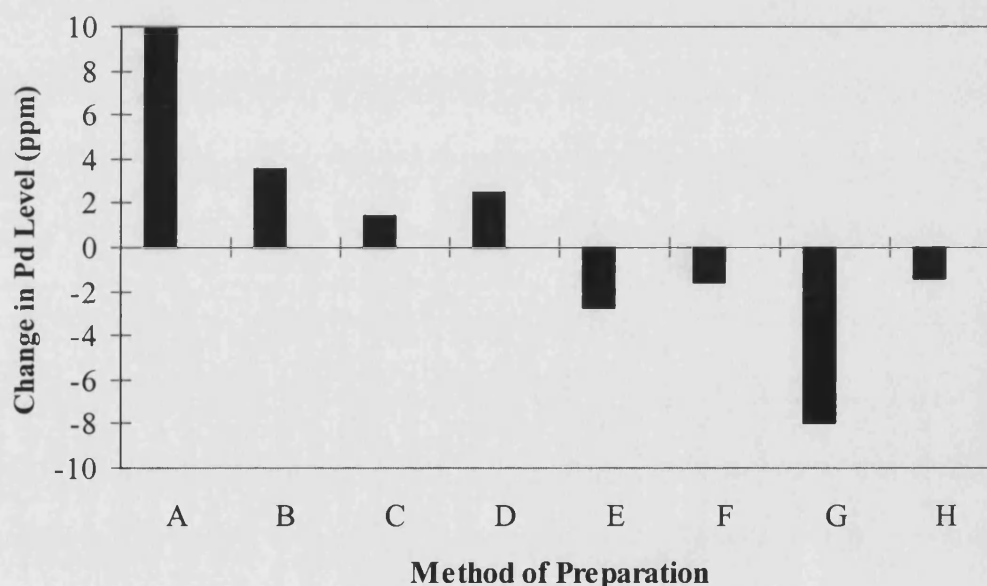
A more convenient procedure, *G*, was developed which gave a much reduced level of leaching (1.0 ppm) with greater activity ($3.4 \times 10^{-3} \text{ min}^{-1}$). Water had been substituted with ethylene glycol as it was seen to have a detrimental effect (method *H*). Procedures which involved the use of water in preparation produced catalysts with low activity. Substitution with ethylene glycol tripled activity of the supported catalyst and halved the level of palladium leached after reaction (Figure 8). The preparation, *G*, involved the palladium (II) chloride and ligand being stirred for 3 hours at 60 °C in 0.5 ml ethylene glycol. Dry CPG-350 and 0.5 ml of ethylene glycol were then introduced and the mixture stirred for a further three hours at room temperature before freeze-drying until constant mass. The hydrophilic ethylene glycol coating was introduced by stirring within the hexane:ether (4:1) reaction solvent prior to the reaction.

Figure 8. Methods of SAP catalyst preparation and effect upon activity and leaching.



The procedure gave the lowest level of palladium leaching from the supported catalyst preparation coupled with a reasonable activity and was, thus, used in subsequent studies. Comparison of the palladium levels present in the supernatant before and after reaction revealed an active uptake of the palladium onto the supported aqueous-phase catalyst i.e. self-assembly of the supported catalyst was occurring (**Figure 9**).

Figure 9. Methods of SAP catalyst preparation and effect upon change in palladium level during course of reaction.

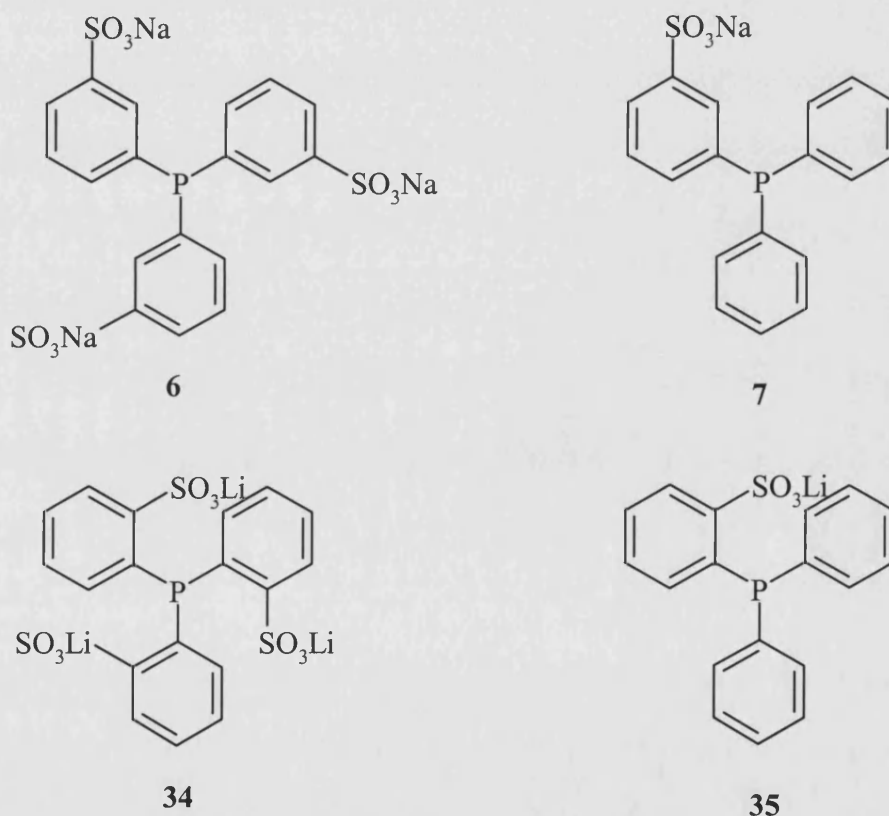


2.3.3 Hydrophilic Nature of Ligand

Alternative sulfonated triphenylphosphine ligands, Na-TPPMS; monosodium *mono(m-sulfonatophenyl)diphenylphosphine* (7), Na-TPPTS; trisodium *tris(m-sulfonatophenyl)phosphine* (6), Li-TPPMS; monolithium *mono(o-sulfonatophenyl)diphenylphosphine* (35), Li-TPPTS; trilithium *tris(o-sulfonatophenyl)phosphine* (34), were used in the catalyst preparation by procedure

G to determine whether the hydrophilicity of the ligand could be used as a tool for manipulating the efficiency of the catalyst system.

It was evident from the study that the *tris*(sulfonatophenyl)phosphine ligands (**6** and **34**) gave reduced levels of palladium leaching from the supported aqueous-phase catalyst, compared to the *mono*(sulfonatophenyl)diphenylphosphines (**7** and **35**), but markedly reduced the activities observed in the reactions (**Figure 10**). Also, carrying out the reaction with the lithium analogues of the ligands (**34** and **35**) there was a significant decrease in reactivity whilst leaching of the palladium from the support was observed to increase.

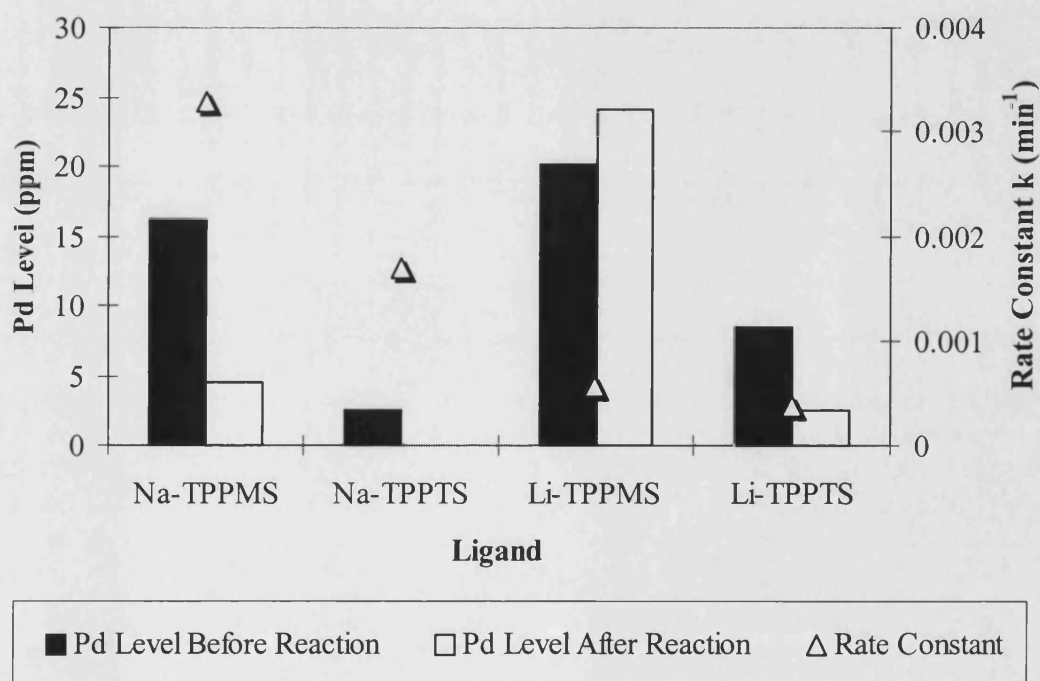


These observations can be explained in terms of the interaction between the hydrophilic moiety of the catalyst complex and the molecules of the hydrophilic phase. The more hydrophilic *tris*(sulfonatophenyl)phosphine ligands (Na-TPPTS and

Li-TPPTS) are more strongly held in this interaction. This slows the reaction, as seen in heterogeneous systems, whilst reduces leaching.

Also with the lithium ligands the sulfonato group is more hindered as it is *ortho*-substituted. This makes the complex less soluble in the hydrophilic phase and can disrupt the catalyst system across the phase interface. In addition, the *ortho*-substitution alters the activity of the resultant metal complex. The higher levels of palladium in the organic phase coupled with low activity in reaction are evidence of this.

Figure 10. Effect of ligand upon activity and level of palladium leached in SAP catalysts. (Na-TPPMS; monosodium *mono(m-sulfonatophenyl)diphenylphosphine*, Na-TPPTS; trisodium *tris(m-sulfonatophenyl)phosphine*, Li-TPPMS; monolithium *mono(o-sulfonatophenyl)diphenylphosphine*, Li-TPPTS; trilithium *tris(o-sulfonatophenyl)phosphine*).



2.3.4 Catalyst Loading

Having decided that the Na-TPPMS ligand gave the best compromise between hydrophilicity, activity and leaching, the optimum loading of the catalyst onto the support was sought. This served to demonstrate the efficiency of the support in limiting leaching.

As anticipated, there was a linear increase in activity with the level of palladium (II) chloride loading onto the support (Figures 11, 12, and 13). It is suggested that there is a direct relationship between activity observed and the level of palladium present in the reaction solvent. It was suspected that the activity could derive from homogeneous palladium complexes. The supernatant was filtered off at different stages during reaction and allowed to continue reacting whilst comparing with an unfiltered control.

Figure 11. Effect of palladium catalyst loading upon activity and leaching in SAP catalysts (carried out using ethylene glycol, $\delta=2$, upon CPG-350).

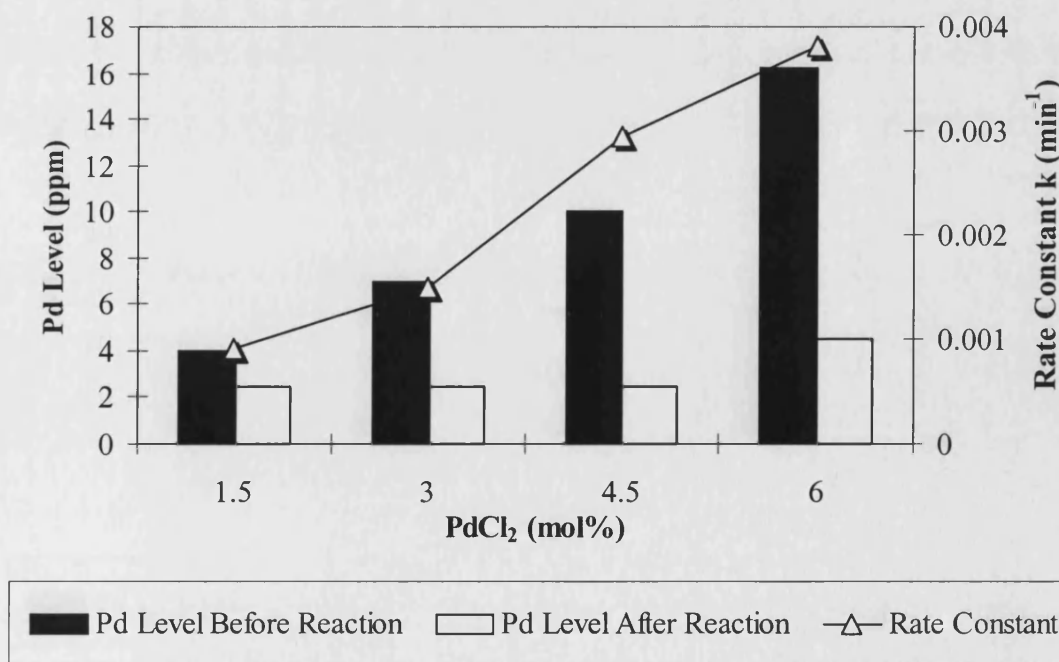


Figure 12. Effect of palladium catalyst loading upon activity and leaching in SAP catalysts (carried out using ethylene glycol, $\delta=2$, upon Davisil 300).

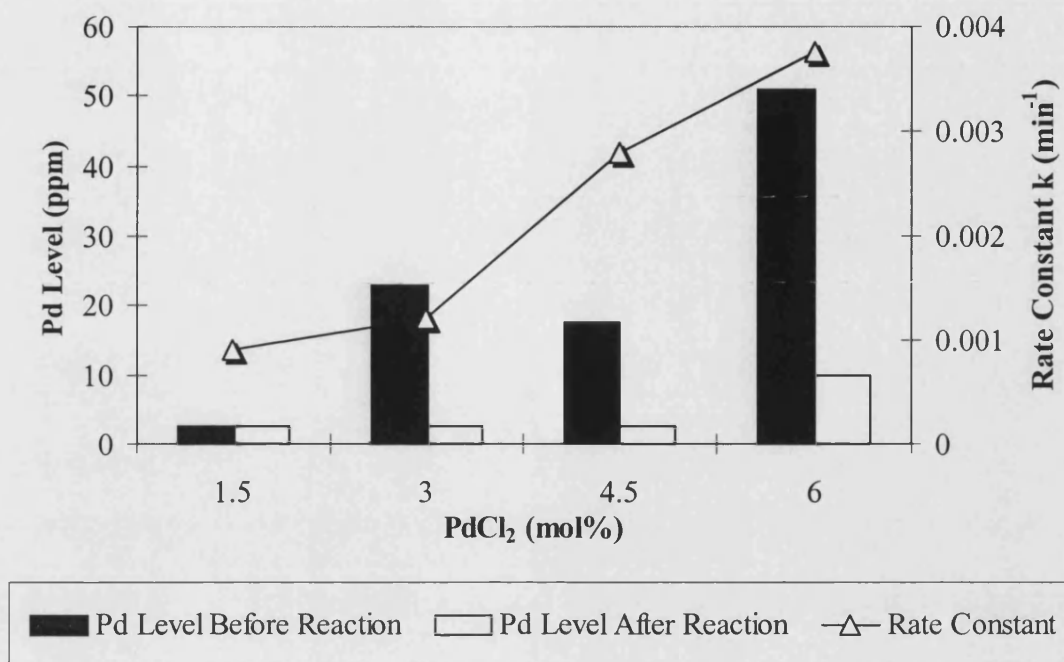


Figure 13. Effect of palladium catalyst loading upon activity and leaching in SAP catalysts (carried out using ethylene glycol, $\delta=0.1$, upon CPG-350).

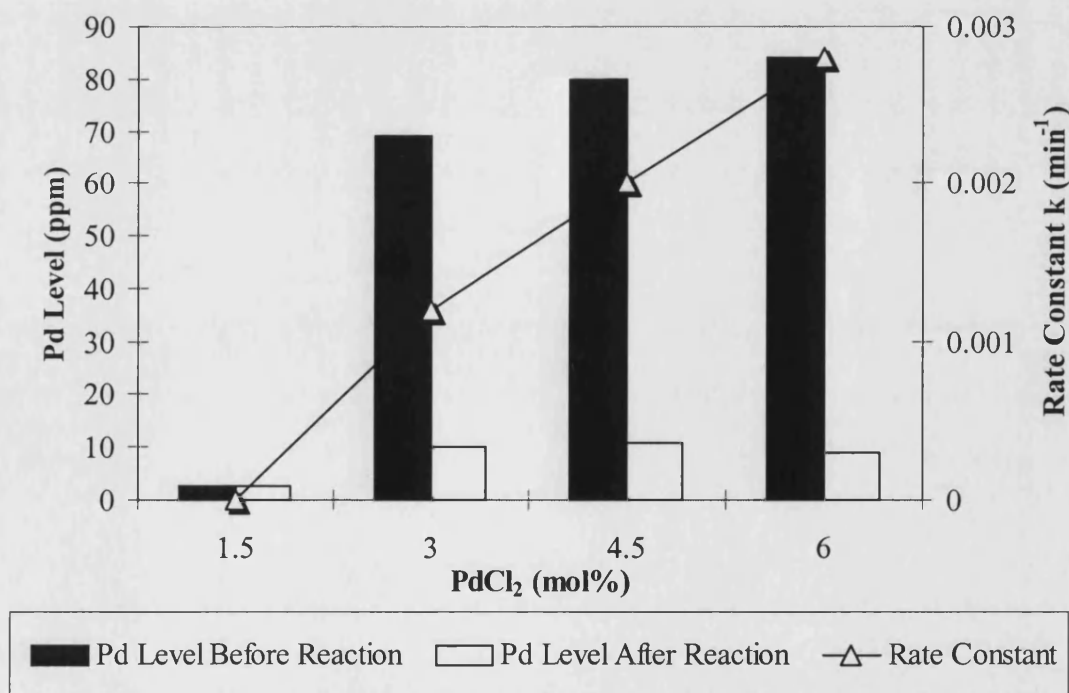
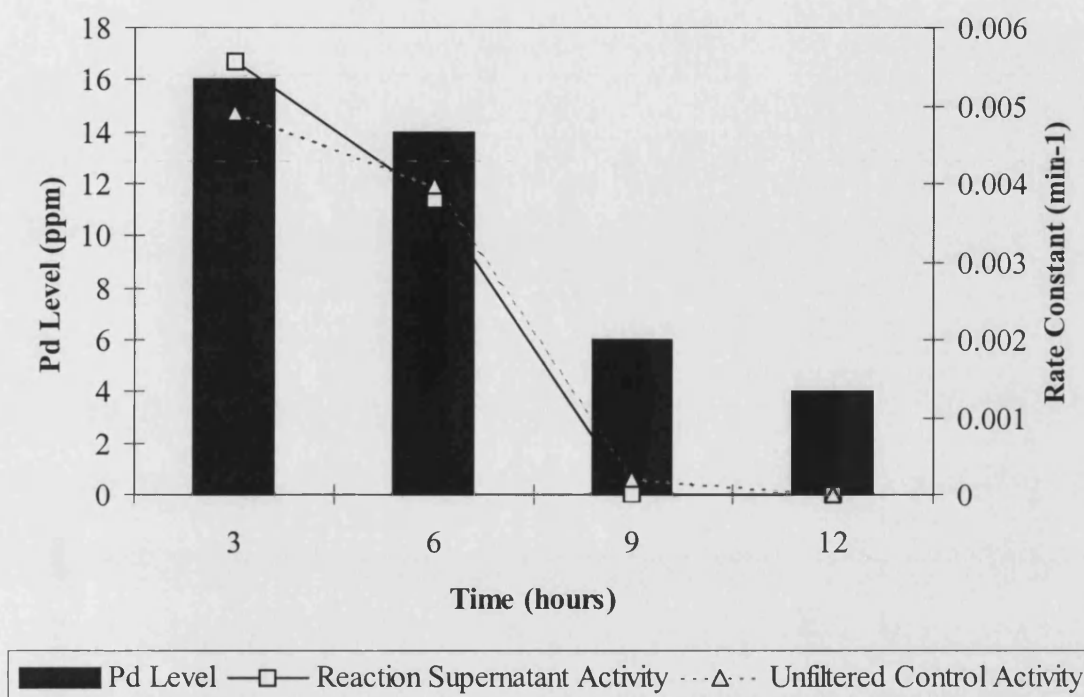


Figure 14. Comparison of activity of SAP catalyst and palladium level throughout reaction profile (carried out using ethylene glycol, $\delta=2$, and PdCl₂, 4.5 mol%, upon CPG-350).

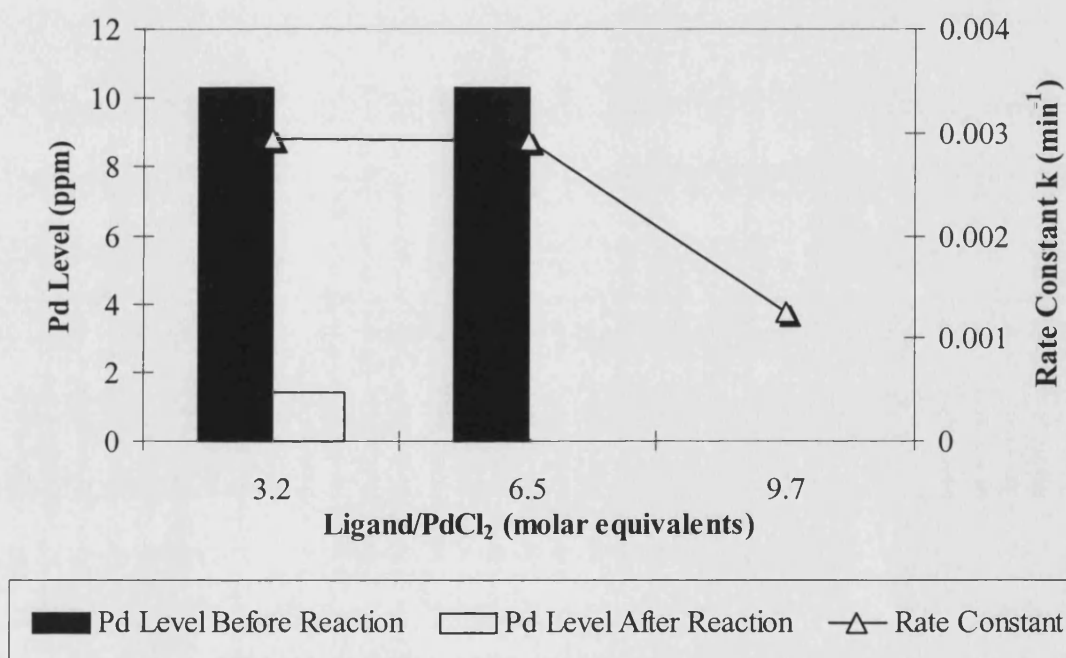


It was established that greater than 85 % of the activity was derived from organic-soluble palladium complexes during the course of the reaction. The palladium level throughout the reaction profile mirrors the level of activity of the catalyst in the reaction (**Figure 14**). This suggests that the reaction is predominantly homogeneous. However, there was uptake of palladium during the course of the reaction. The low levels attained after reaction was completed demonstrate that the system is potentially very useful. As has been reported in past works, the filtered supernatant after reaction was not seen to be active to fresh substrate.

2.3.5 Catalyst/Ligand Ratio

Having determined that 4.5 mol% of palladium supported upon silica gave sufficient activity without significantly contributing to leaching, the amount of ligand used in reactions was varied. This was to assess whether this was a factor that could be successfully used to limit the level of catalyst leaching during the reaction.

Figure 15. Effect of excess Na-TPPMS ligand upon activity and palladium leaching in SAP catalysts.

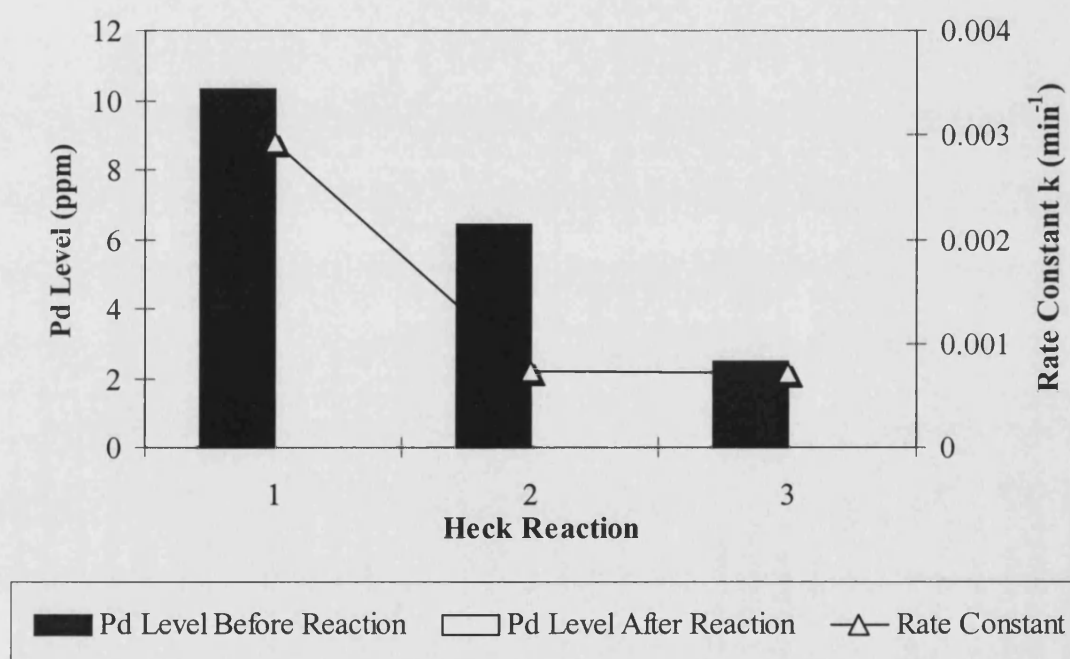


Excess ligand significantly retarded the reaction at 9.7 molar equivalents of Na-TPPMS to palladium (II) chloride (**Figure 15**). However, it was seen that addition of 6.5 molar equivalents of ligand eliminated the palladium leaching from the silica observed after reaction. This would be of vital significance for any proposed industrial process.

2.3.6 Catalyst Recycling

It was necessary to determine how robust the supported catalyst was to degradation. Thus experiments were carried out to study the viability for recycling and re-use of the catalyst in an industrial process.

Figure 16. Effect of recycling upon activity and palladium leaching from supported aqueous-phase catalysts in consecutive Heck reactions.



It was observed that the activity of the supported aqueous-phase catalyst decreased significantly after recycling (Figure 16). As reactions were repeated, decreasing levels of palladium were observed in the solvent prior to use suggesting gradual leaching of the palladium from the support. However, there was no detectable level of palladium present in the supernatant after reaction or in the solvent rinse prior to reaction, therefore, there could be no significant loss of catalyst. High levels of non-active oxidised phosphine were observed by ^{31}P NMR suggesting

catalyst deactivation, coupled with interaction between the deactivated complex and the support, leading to decreased leaching.

The reappearance of palladium in the supernatant when reaction solvent and substrate were recharged into the vessel was quite unexpected. The addition of fresh substrate, particularly iodobenzene, in subsequent reactions is evidently drawing palladium off the support at the beginning of couplings by the formation of a less polar intermediate in the catalytic cycle. As this substrate is consumed during reaction we again see total uptake of the palladium onto the support. The characteristic solubilities of the substrates, including bases, can interfere with the phase separation in supported aqueous-phase catalysts resulting in temporary leaching.

2.3.7 Hydrophilic Phase Loading

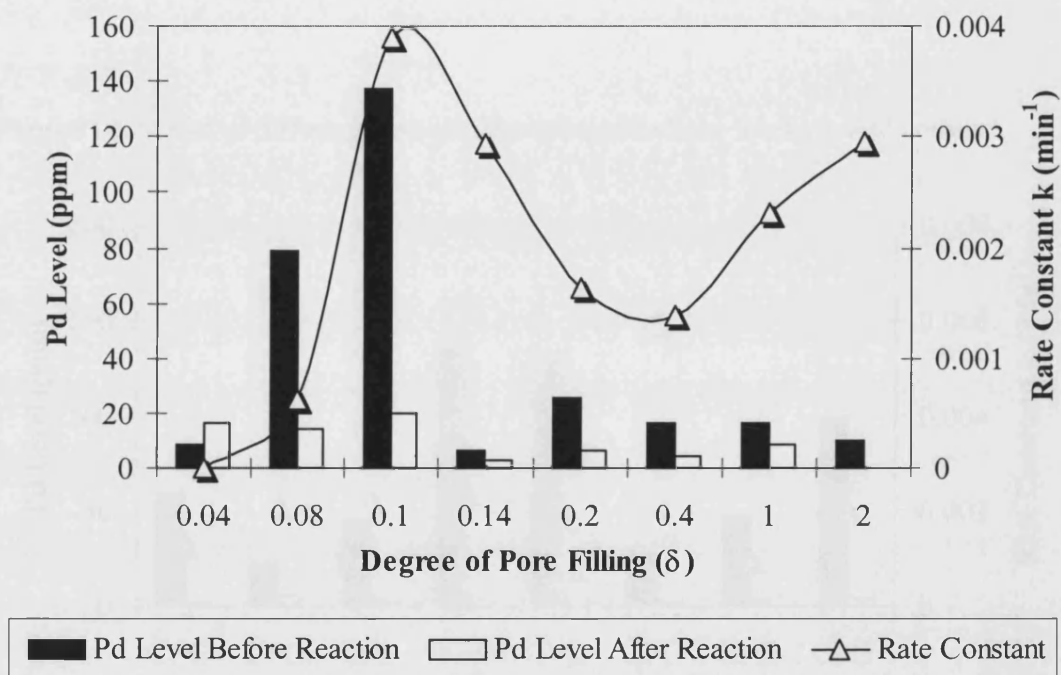
Before using the porous silicas the level of residual water was thermogravimetrically determined.

It was found that up to 3 wt% water was present in the pores. Therefore, silicas were oven dried (200 °C) for six hours before use. The influence of the level of hydrophilic phase, ethylene glycol, loading onto the catalyst upon activity and leaching was studied. The thickness of the coating would determine the mobility of the catalyst complex in the system and, therefore, be significant in dictating the activity of the supported catalyst.

The effect of the level of solvation of the SAP catalyst upon activity proved to be significant (**Figure 17**). Maximum activity was repeatedly attained at a degree of pore filling of $\delta=0.1$ (theoretical film thickness=16 Å). At very low pore filling, i.e. $\delta=0.04$, no activity was observed indicating the lack of mobility of the catalyst complex within a 6.5 Å film. Above $\delta=0.1$, analysis of the graph suggested that the

activity decreased as the pores were being filled due to diminishing interfacial area. It then increased again as the thickness of the coating around the silica increased thereby increasing the area of the interface.

Figure 17. Effect of degree of pore filling with ethylene glycol upon activity and palladium leaching in SAP catalysts.

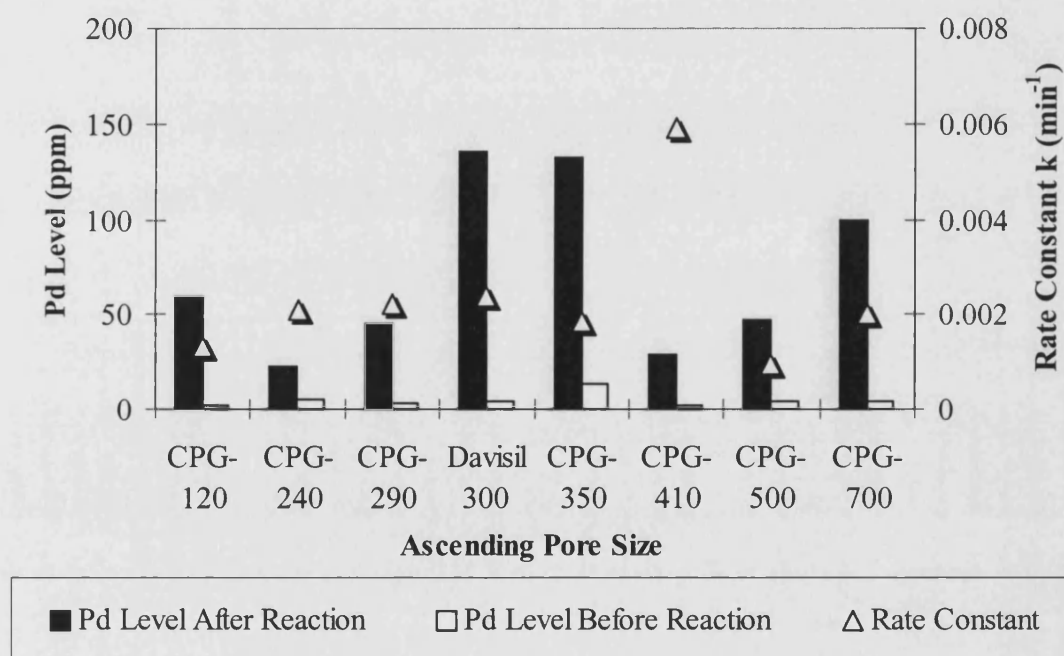


Molecular modelling of the Na-TPPMS catalyst complex ascertained that the average diameter of the catalyst structure was 11 Å (largest diameter; 15 Å, total volume; 590 Å³). It can thus be assumed that the thickness of the coating at pore filling of $\delta=0.1$ (16 Å) is adequate for a mono-layer of the catalyst complex. Below this level of loading it was observed that leaching prior to reaction increased. At low levels the coating across the surface was likely to be discontinuous resulting in leaching of both unsolvated palladium and catalyst dissolved in micelles of ethylene glycol from the silica. As ethylene glycol was increased up to a certain level instead of increasing the film thickness, surface-tension could have served to spread the film further across the surface, resulting in actual thinning of the coating.

2.3.8 Different Pore Glass Characteristics

So far it had been ascertained that a combination of Na-TPPMS (29 mol%) and palladium (II) chloride (4.5 mol%) supported upon CPG-350 (250 mg) solvated with ethylene glycol (0.025 ml; $\delta=0.1$) using method *G* produces a palladium supported aqueous-phase catalyst with optimum activity and leaching.

Figure 18. Effect of differing pore glasses upon palladium leaching and activity.

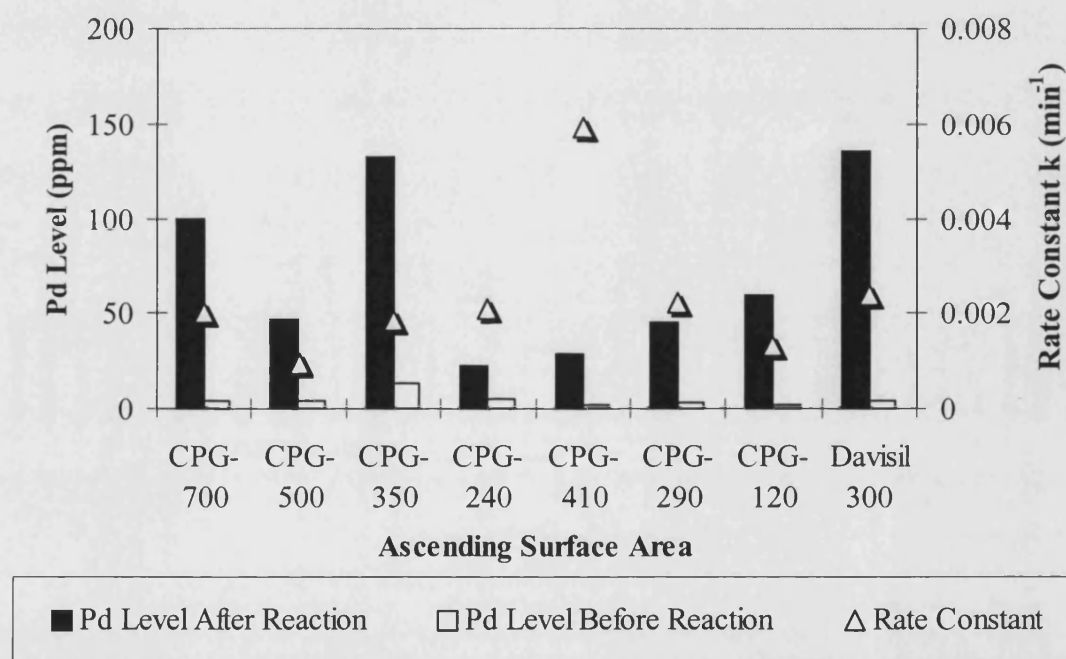


The influence of the type of porous glass support used in the catalyst preparation was studied to see how different characteristics such as pore size, surface area and pore volumes could influence kinetics and leaching in the reaction. Experiments were conducted with hydrophilic phase loading equivalent to $\delta=1$. From experiments, it was evident that the pore glasses exhibited very similar activity in reaction. Davisil 300 and CPG-350 exhibited very high levels of leaching prior to the

reaction but this was found to have significantly decreased by the end of the study (Figure 18).

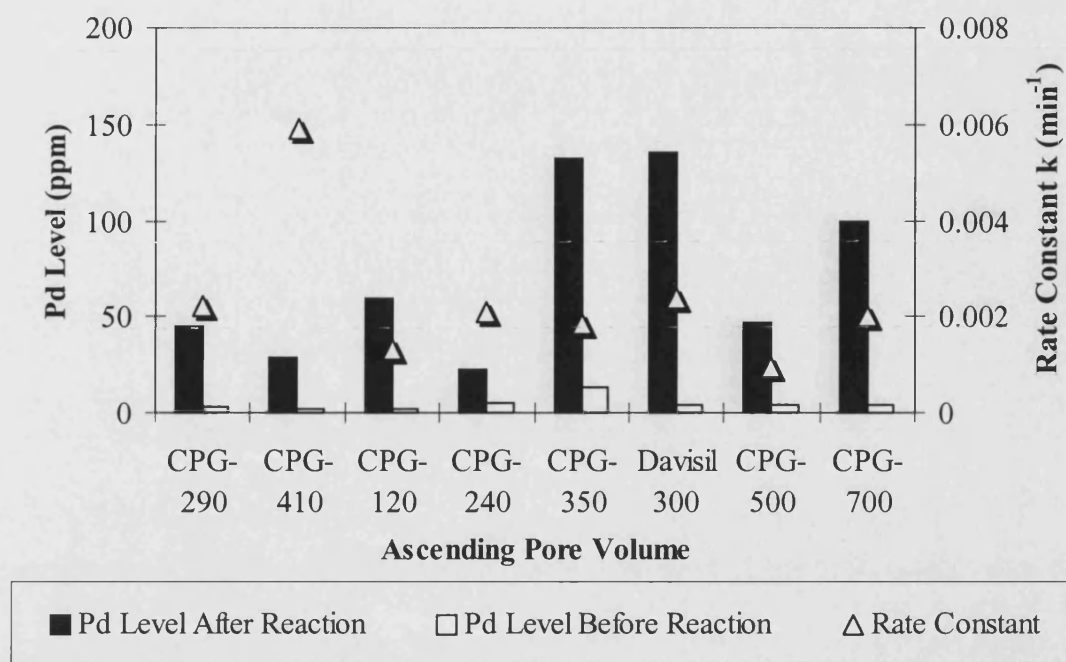
Arranging the activity/leaching data in order of ascending surface area, greatest activity was observed with CPG-410 characterised by a surface area of $96 \text{ m}^2\text{g}^{-1}$ (Figure 19). Therefore, this corresponds to the surface area which produces a coating of optimum thickness when $\delta=1$.

Figure 19. Effect of increasing surface area upon palladium leaching and activity.



Arranging the pore glasses in order of ascending pore volume, V_p , very little correlation between the pore volume of the pore glasses and the activity was evident (Figure 20).

Figure 20. Effect of increasing pore volume upon palladium leaching and activity.



2.4 Summary of Conclusions

The Na-TPPMS ligand offers low levels of leaching without retarding catalyst activity. Therefore, the combination of Na-TPPMS (29 mol%) and palladium (II) chloride (4.5 mol%) supported upon CPG-350 (250 mg) solvated with ethylene glycol (0.025 ml; $\delta=0.1$) produces a supported aqueous-phase catalyst with optimum activity whilst eliminating leaching to the limits of detection.

The method, *G*, developed for preparation of the SAP catalysts, and outlined earlier, is a convenient procedure for producing large quantities for reaction. The catalyst thus prepared is stable and can be stored dry for a number of weeks. Ethylene glycol as a coating would not be an ideal choice for an industrial process. Its viscosity and poor mass-transfer properties result in comparatively low activity as witnessed in this supported aqueous-phase system compared to an equivalent homogeneous catalyst system. In a biphasic solvent system, i.e. without the high surface area silica support, we see a much reduced activity for the catalyst, compared to a single-phase homogeneous system, due to poor mass-transfer of the catalyst into the substrate phase.

Water would be preferable for solvating the supported catalyst. However, as this is seen to degrade the catalyst complex and has also been shown in the past to leach from the silica, it also has its own disadvantages.^{48,41,69}

With the SAP system described in these studies <0.3 wt% of palladium used was observed to have leached into the solvent after reaction (10 ppm in 5 ml). The optimisation that has been carried out can be used successfully to reduce this down to a traceable level of 250 ppb. An outline of these findings has been published in the literature.^{70,71} This is a remarkable reduction when compared with the levels of heavy metal contamination seen in homogeneous systems. The convenience offered by this system of catalysis for heavy metal separation is very significant. The catalyst

can simply be filtered away from the reaction solvent. With regards to the nature of the catalysis occurring within the system evidence suggests that the catalysis is predominantly homogeneous via the formation of a organic-soluble catalyst-substrate adduct. The high surface area interface between the support coating and the bulk reaction solvent facilitates efficient transfer and removal of the heavy metal complex after completion of the reaction.

The recycling of the catalyst must be made efficient if it is to have any likelihood of competing with homogeneous systems on a commercial scale. To this end the nature and cause of the deactivation was further investigated. Impurities in starting materials may be responsible for the observed poisoning. The system has also been studied in continuous flow reactions. Theoretically, as the supported catalyst is exposed to a much higher level of stabilising phosphines the catalyst complex should be much more robust than in the homogeneous system.

In addition to this, the sulfonated aryl phosphines themselves are very hydrophilic, therefore, there is very little risk of the product being contaminated with leached phosphine. This was confirmed by atomic absorption spectrometry. Other such uses were sought for this technology and work done to expand upon the understanding of the nature of the catalysis in such systems with the aim of achieving a highly active, selective and re-usable system of catalysis for large-scale reactions.

CHAPTER 3

SUPPORTED ORGANIC-PHASE CATALYSIS ON REVERSE-PHASE GLASS BEADS

Chapter 3: Supported Organic-Phase Catalysis on Reverse-Phase Glass Beads

3.1 Introduction

The aim of this study was to investigate this new approach to supported homogeneous catalysis, and the factors that would affect its use in a variety of palladium catalysed coupling reactions.

It is a reversal of the previously studied supported aqueous-phase and liquid-phase catalysis systems in which a hydrophilic catalyst complex is held in solution upon a high surface area silica whilst substrates and products are restricted to a hydrophobic organic solvent. The term supported organic-phase (SOP) catalysis was coined to describe the system.

In this system a lipophilic catalyst complex is held onto a high surface area, porous silica bead by its affinity to the alkyl silane derivatisation of the surface of the glass. The substrates in the reaction are restricted to a bulk polar solvent allowing efficient catalysis without leaching of the heavy metal into the reaction solvent.

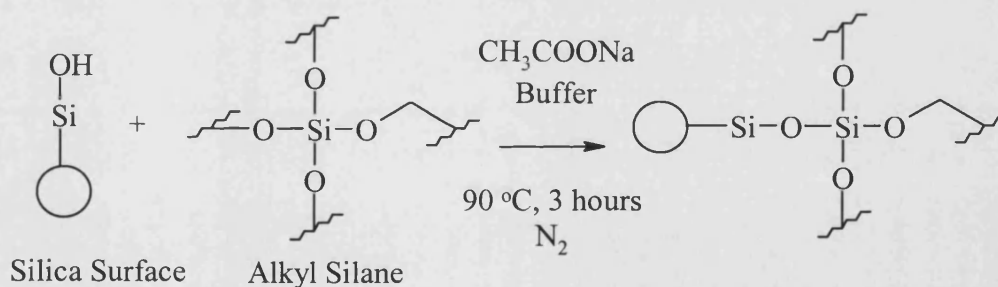
3.2 Preparation of Supported Organic-Phase, SOP, Catalysts

3.2.1 Procedures for Derivatisation of Silica

Davisil 300 silica was chosen as the support material due to previous success of its use in supported aqueous-phase catalysis. It is relatively cheap, has a high surface area ($150\text{-}170\text{ m}^2\text{g}^{-1}$) and a good pore size distribution around 300 \AA . Initially, two methods of derivatising the surface of the glass with alkyl silanes were devised.

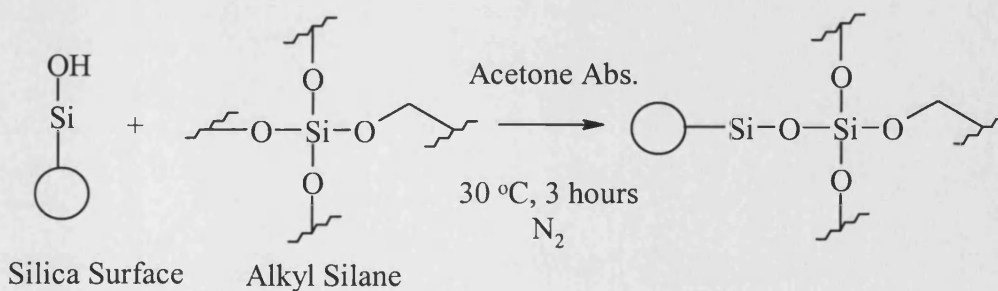
The first was adapted from a literature procedure, method *A*, which was reported to give a theoretical coverage of $2.5\text{ }\mu\text{mol m}^{-2}$ (**Figure 21**).⁷²

Figure 21. Method *A* for reverse-phase derivatisation of silica.



A second procedure was later derived, method *B*, from Schott Engineering which gave a theoretical coverage of $20\text{ }\mu\text{mol m}^{-2}$.

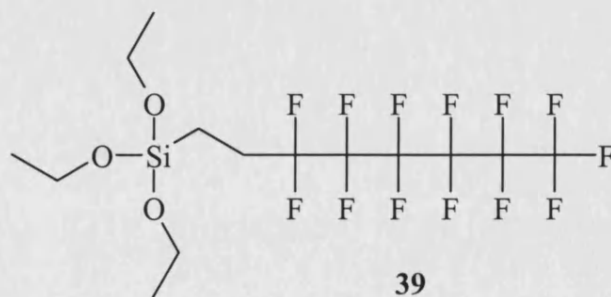
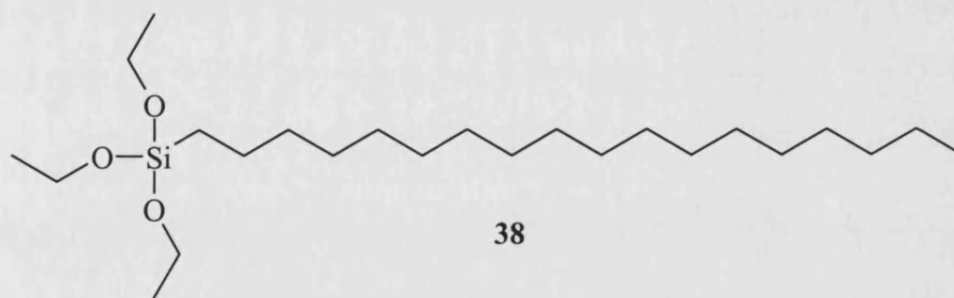
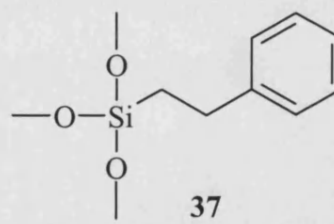
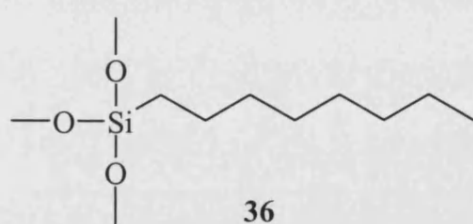
Figure 22. Method *B* for reverse-phase derivatisation of silica.



It was possible to confirm the presence of the alkyl groups upon the surface of the silica. The change in the degree of vibration of protons along the alkyl carbon chain with distance from the binding silica atom could be observed using solid-state NMR techniques.

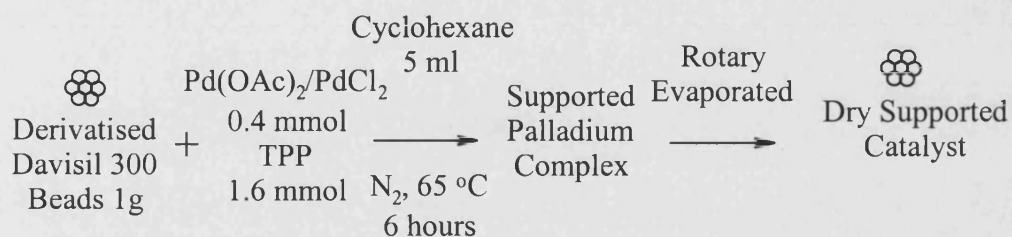
3.2.2 Alkyl Silanes

The abilities of a number of different alkyl silanes; octyltrimethoxysilane (**36**), 2-phenylethyltrimethoxysilane (**37**), *n*-octadecyltriethoxysilane (**38**), and 1H, 1H, 2H, 2H perfluorooctyltriethoxysilane (**39**) to impart lipophilic characteristics to the silica beads were investigated.

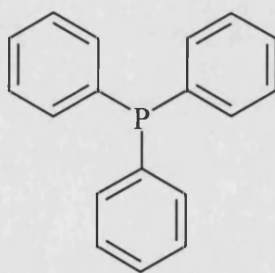


3.2.3 Immobilisation of Catalyst Complex

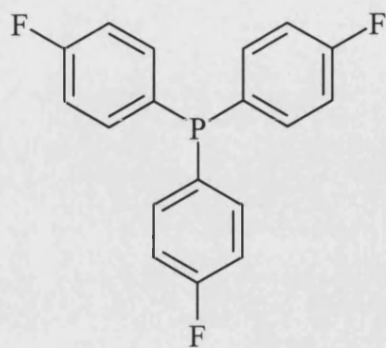
The supported organic-phase catalysts were prepared by stirring the derivatised beads with palladium (II) acetate or palladium (II) chloride and, optionally, triphenylphosphine, TPP (40), in cyclohexane. Rotary evaporation was then used to yield the dried supported catalyst.



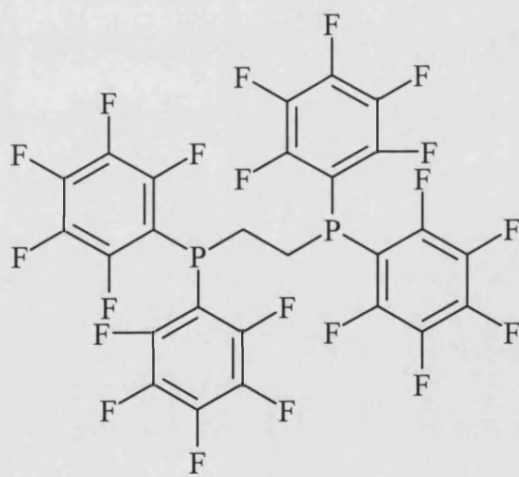
The perfluoro silane derivatised beads were complexed with palladium (II) acetate and fluorinated phosphines; *tris*(4-fluorophenyl)phosphine (41) and 1,2-*bis*(dipentafluorophenyl)phosphine (42). Supported catalysts were also prepared using underivatised beads and employed as controls.



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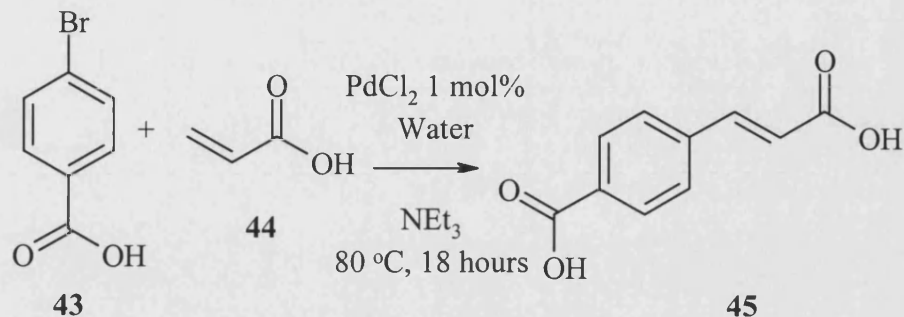
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3.3 Preliminary Studies with Supported Organic-Phase Catalysts

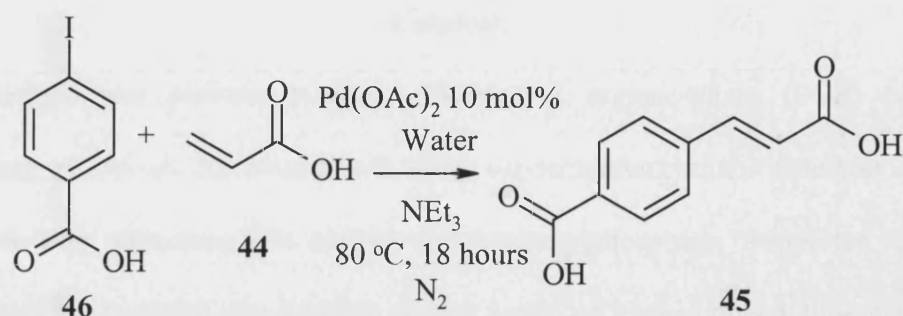
3.3.1 Heck Coupling of 4-Bromobenzoic Acid and Acrylic Acid



Having derivatised the beads it was necessary to nominate a control reaction upon which to test the supported catalyst system on. The coupling of 4-bromobenzoic acid (43) and acrylic acid (44) to produce 4-carboxycinnamic acid (45) was attempted in the presence of triethylamine, using palladium (II) chloride (1 mol%) in water at 80 °C.⁷³

However, the reaction proved unsuccessful with just 6 % conversion after 18 hours. The addition of TPP (20 mol%) did not improve the situation (0.5 % conversion after 18 hours). The reaction in the presence of palladium (II) chloride (1 mol%) and TPP (20 mol%) was repeated using ethylene glycol as solvent. This gave 18.5 % conversion after 18 hours. However, ethylene glycol is primarily not a solvent of choice for this system. Its poor mass-transfer properties do not promote high catalyst activity as previously illustrated by SAP catalyst systems.

3.3.2 Heck Coupling of 4-Iodobenzoic Acid and Acrylic Acid



Due to the poor success with 4-bromobenzoic acid, the coupling of 4-iodobenzoic acid (46) and acrylic acid (44) was attempted.

The reaction was carried out with palladium (II) acetate (10 mol%) and triethylamine in water at 80 °C. This gave a conversion of 66 % after 18 hours. The addition of triphenylphosphine (20 mol%) to the reaction increased conversion to 97 % after 18 hours.

3.3.3 Potassium Carbonate as Base

Replacing triethylamine with potassium carbonate in the reaction increased conversion to >98 % in the phosphine-free reaction. This was so even when catalyst was reduced to 1 mol% to reproduce, as closely as possible, literature conditions.

Unlike the reactions using triethylamine as base, the presence of triphenylphosphine was seen to heavily retard conversion in the homogeneous system with potassium carbonate (25 %). It is believed that the triethylamine base promotes association of the polar substrates with the organic-soluble catalyst complex. However, due to the high conversions observed, potassium carbonate was used as a base in subsequent reactions.

3.3.4 Heck Coupling of 4-Iodobenzoic Acid and Acrylic Acid with an SOP

Catalyst

The reaction was performed using a supported organic-phase (SOP) catalyst, consisting of Davisil 300 derivatised using octyltrimethoxysilane (Method *A*) and prepared with palladium (II) acetate and triphenylphosphine. Supported catalyst equivalent to 10 mol% of palladium and 40 mol% of triphenylphosphine was used and solvated with cyclohexane equivalent to $\delta=1$.

Using the SOP catalyst system, 99 % conversion was attained at 18 hours. The level of palladium leaching observed in the solid product was found to be 114 ppm by ICP analysis compared to 293.9 ppm in the equivalent homogeneous reaction (without triphenylphosphine).

The homogeneous reaction with triphenylphosphine was heavily retarded and only attained 15 % conversion. The level of supported catalyst was reduced to 2 mol% and even as low as 1 mol% with very little or no decrease in activity and subsequent reduction of palladium leaching into the aqueous supernatant.

3.3.5 The Effect of Triphenylphosphine upon Activity

Initially it was observed that the SOP catalyst (octyltrimethoxysilane derivatised) had lower activity compared to the homogeneous system (**Figures 23**).

The presence of triphenylphosphine in the SOP catalyst significantly increased its activity above that of the homogeneous reaction, with low palladium leaching (2.4 ppm). The underivatised supported catalyst behaved similarly to the homogeneous catalyst system in that its activity was evidently retarded by the presence of triphenylphosphine (**Figures 24**). In this study, the supported catalysts did not possess a cyclohexane coating. The action of the supported catalyst upon the rate of reaction was very encouraging and signifies the potential of SOP catalysis.

Figure 23. Activity of homogeneous and SOP catalyst systems in arylation of 4-iodobenzoic acid.

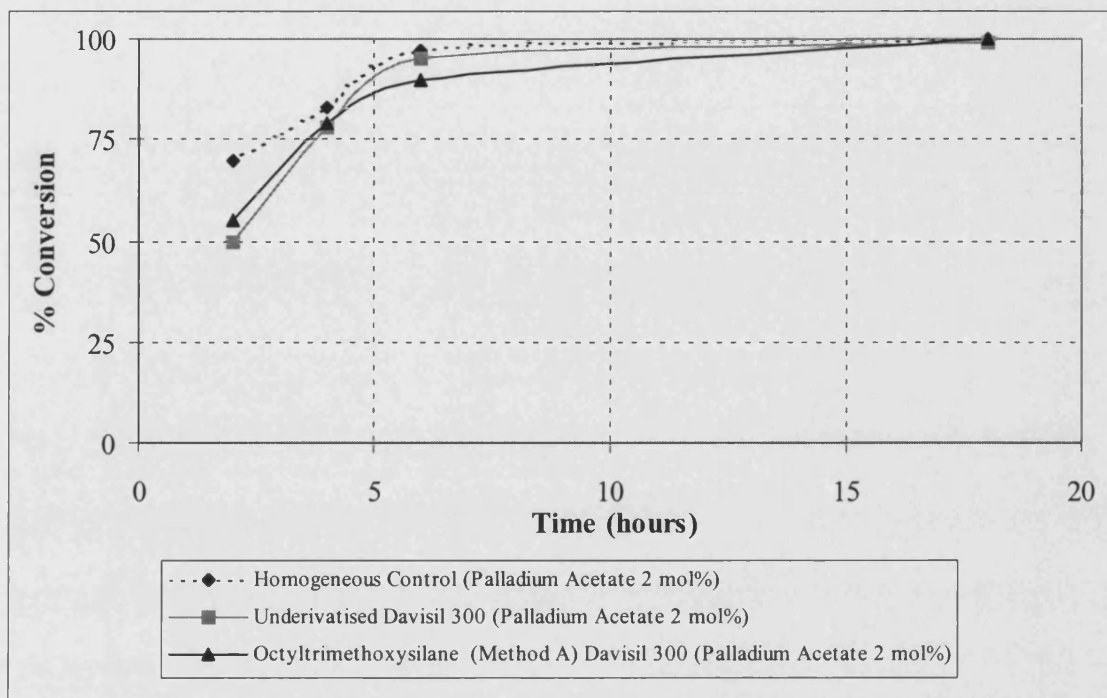
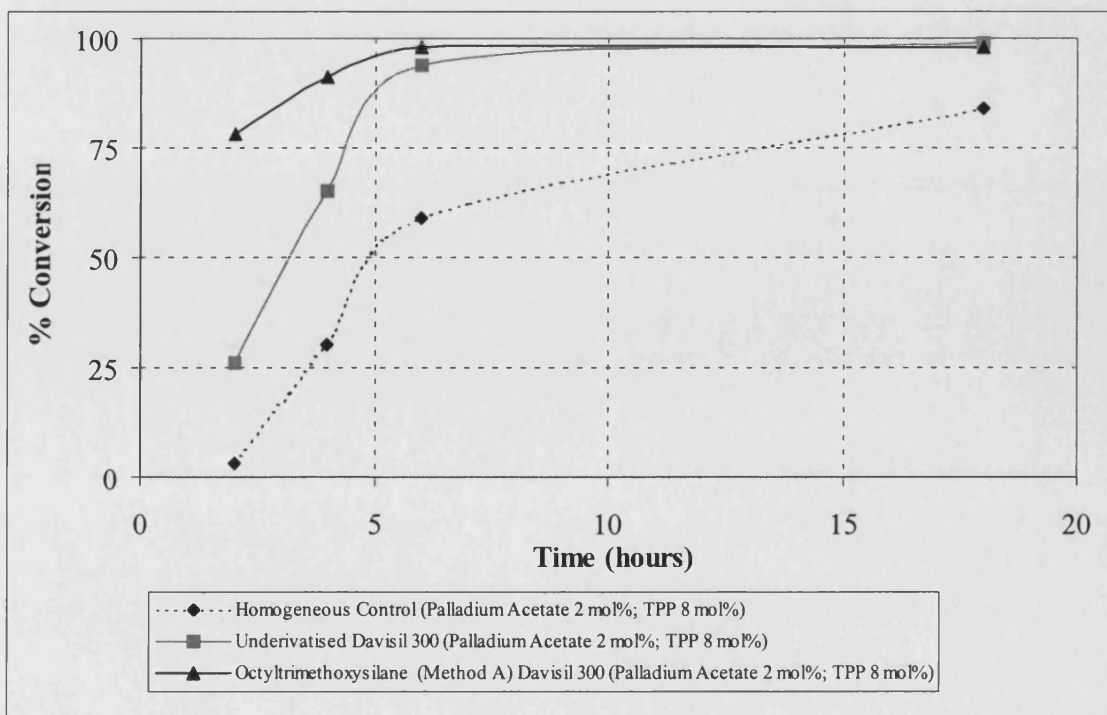


Figure 24. Activity of homogeneous and SOP catalyst systems in arylation of 4-iodobenzoic acid in presence of triphenylphosphine.



3.4 Automation

The reaction was adapted for automation using a Gilson 233 Auto-Sampler, Stem Hi Heater/Stirrer Reaction Station and DART Operating System. This allowed the screening of large numbers of reactions to investigate the application of SOP catalytic systems.

The 4-iodobenzoic acid substrate and potassium carbonate base were prepared as standard aqueous solutions which were dosed, along with acrylic acid, directly into reaction tubes containing pre-weighed catalyst. Due to the poor solubility of the 4-iodobenzoic acid, excess potassium carbonate was added (15 mmol; 3.75 equiv.) to maintain it in solution as it was pumped through the HPLC auto-dosing/sampling system. As a consequence of this, it was observed that reaction rate was greatly enhanced (100 % conversion after 2 hours at 80 °C).

3.5 Studies into Factors Effecting Level of Leaching from SOP Catalyst Systems

3.5.1 The Effect of Cyclohexane Coating upon Palladium Leaching

It was demonstrated that palladium leaching into the reaction supernatant was significantly reduced by the use of supported organic-phase catalyst systems (Figures 25i and 25ii). In the homogeneous systems with potassium carbonate, reductions in leaching level resulting from the presence of triphenylphosphine were accompanied by retardation of the reaction (Figure 24).

It was seen that the addition of the surface coating to the silica ($\delta=1$) prior to reaction led to a small increase in the level of palladium leaching into the reaction supernatant (Figures 25i, 25ii and 26). Such an influence was expected as cyclohexane would theoretically increase mobility of the alkyl chains holding the palladium complex on the silica surface significantly. For example, a decrease in palladium leaching from 24.1 ppm to 0.74 ppm was observed when triphenylphosphine was introduced into the homogeneous system in the presence of cyclohexane (Figure 25i). Repeating the experiments without cyclohexane we saw a decrease from 15.8 to 0.3 ppm (Figure 25ii).

A palladium level of 8.7 ppm was attained, with the presence of triphenylphosphine and cyclohexane in the reaction, with catalyst supported on underivatized Davisil 300. The absence of cyclohexane reduced the level to 7.3 ppm. With catalyst supported on octyltrimethoxysilane derivatized (Method A) Davisil 300, in the presence of triphenylphosphine and a cyclohexane coating, a palladium leaching level of 7.7 ppm was observed. This was reduced to 0.4 ppm in the absence of cyclohexane. A palladium leaching level of 0.5 ppm was observed using catalyst

supported on 2-phenylethyltrimethoxysilane derivatised (Method A) Davisil 300 with triphenylphosphine and in the absence of cyclohexane.

Figure 25i. Effect of cyclohexane coating upon level of palladium leaching (carried out in the presence of substrates).

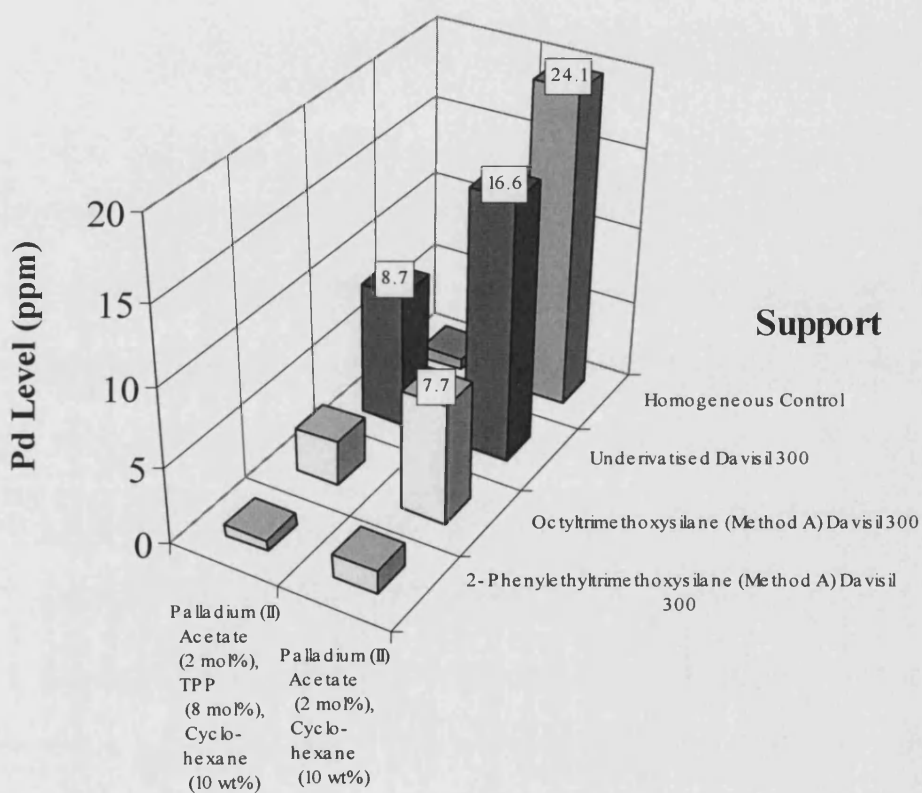
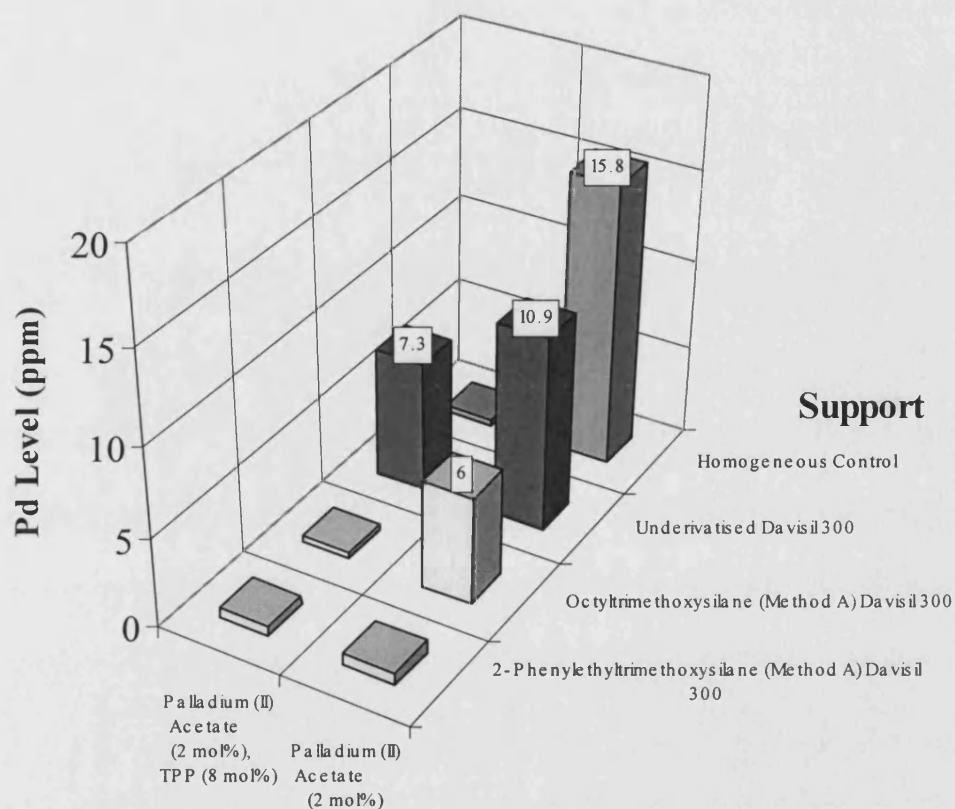


Figure 25ii. Effect of absence of cyclohexane coating upon level of palladium leaching (carried out in the presence of substrates).



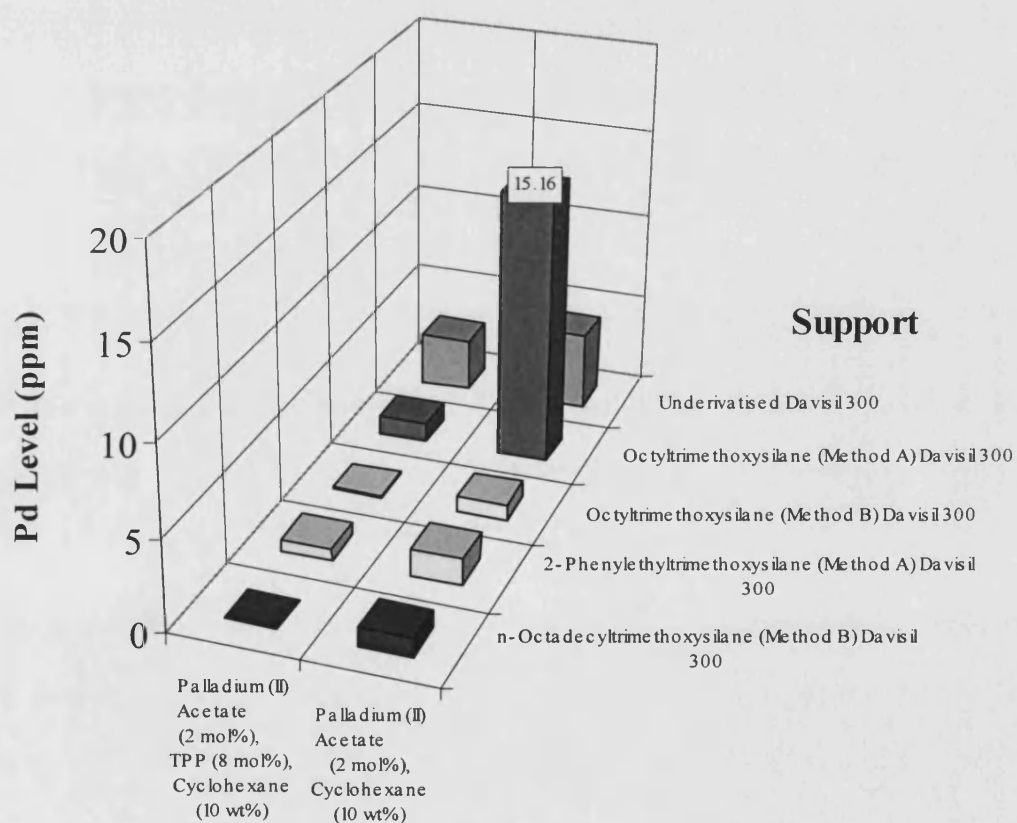
3.5.2 The Effect of Type of Derivatisation on Level of Palladium Leaching

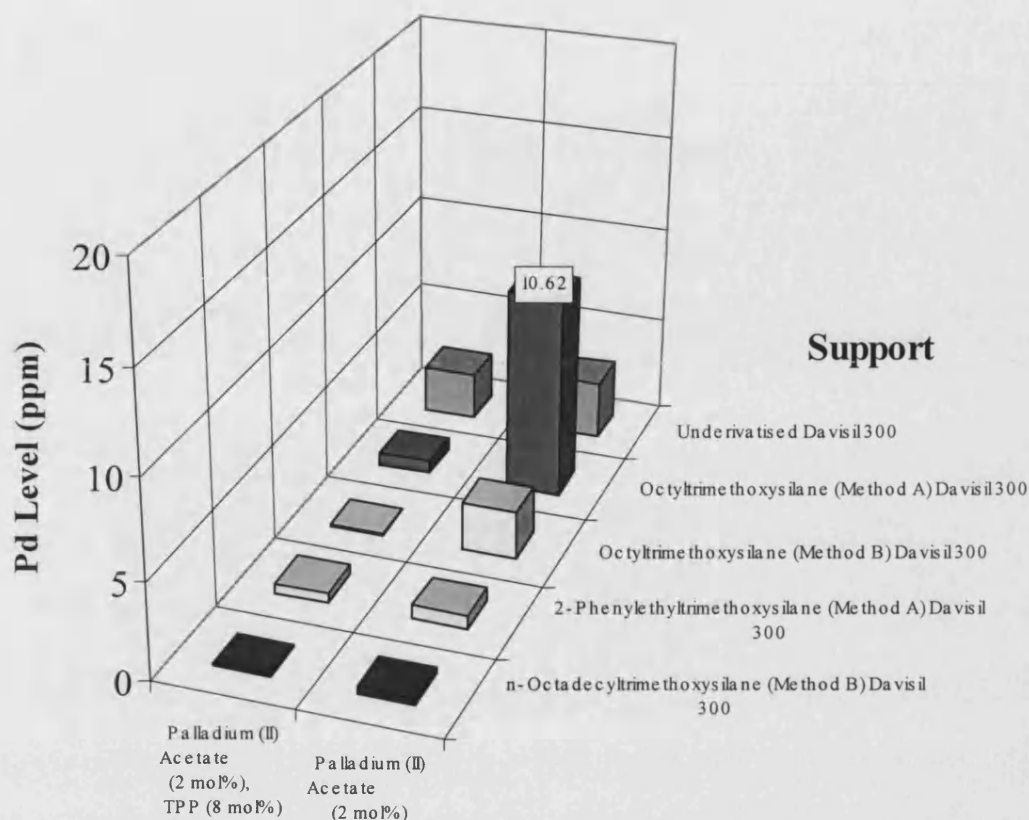
A study was conducted, in the absence of substrates, to compare the effect of the derivatisation upon the level of palladium leaching.

It appears the *n*-octadecyltriethoxysilane (**38**) derivatisation (method **B**) of the silica surface produces a catalyst which performs best, overall, with lowest levels of catalyst leaching (**Figure 26**). This is attributed to the greater degree of lipophilicity imparted by its alkyl chain compared to the shorter alkyl chain of octyltrimethoxysilane (**36**). Also, in the case of the 2-phenylethyltrimethoxysilane

derivatisation (method *A*) the aryl ring is held away from the silane functionality allowing efficient performance without inhibiting the mobility of the catalyst complex. However, as the performance of the octyltrimethoxysilane is comparable with the larger silanes when method *B* is employed as the derivatisation procedure, and because of the restraints of cost, this SOP catalyst system was chosen for use in preliminary research.

Figure 26. Effect of derivatisation upon the level of palladium leaching (study performed in the absence of substrates).





3.5.3 The Effect of Triphenylphosphine upon Palladium Leaching

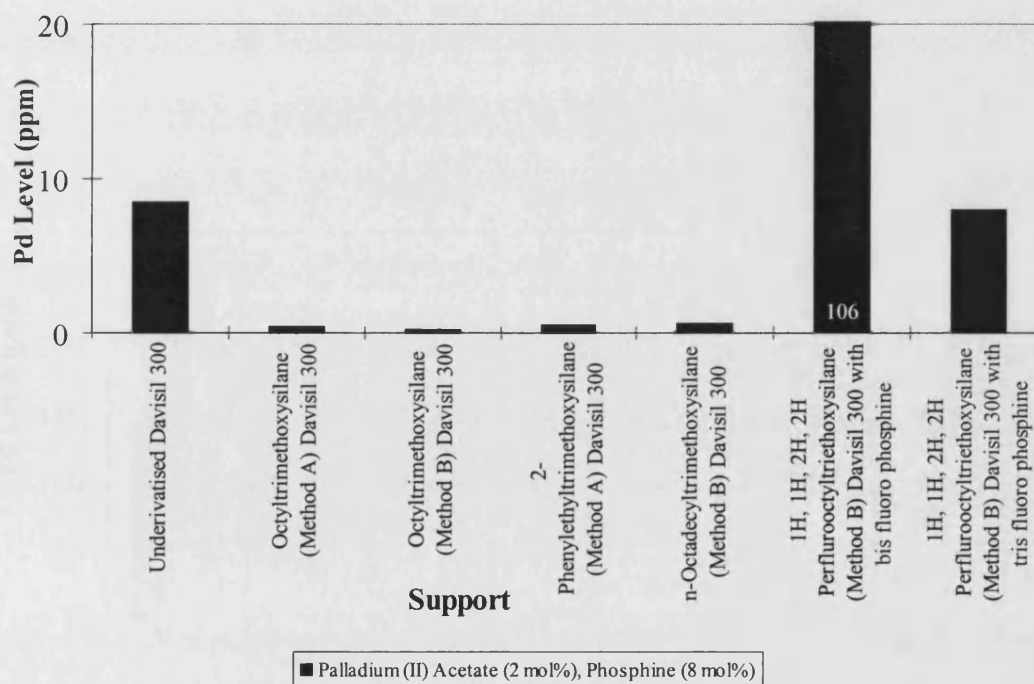
It is apparent that the presence of triphenylphosphine upon the supported system and in the homogeneous system reduces the level of palladium leaching witnessed in the supernatant (**Figures 25 and 26**).

The relationship between the palladium acetate and phosphine complex requires more investigation as it may be that the acetate groups alone may have sufficient affinity to the hydrophobic silica when the level of derivatisation is high (method **B**). The variable factors are the degree of hydrophobicity imparted by the method of derivatisation i.e. the theoretical coverage and level imparted by the length of the alkyl chain. The extent of this effect has been seen to vary between solvents.

3.5.4 Method of Silica Derivatisation and its Effect upon Level of Palladium Leaching

Derivatisation of the silica support with alkyl silanes results in lower levels of palladium leaching into the reaction solvent. It was found that the method of derivatisation (*A* or *B*) plays an important role in dictating the efficiency of the supported catalyst system for immobilising the palladium complex (**Figure 27**).

Figure 27. Comparison of silica derivatisation procedures and effect upon leaching (carried out in the presence of substrates and triphenylphosphine).



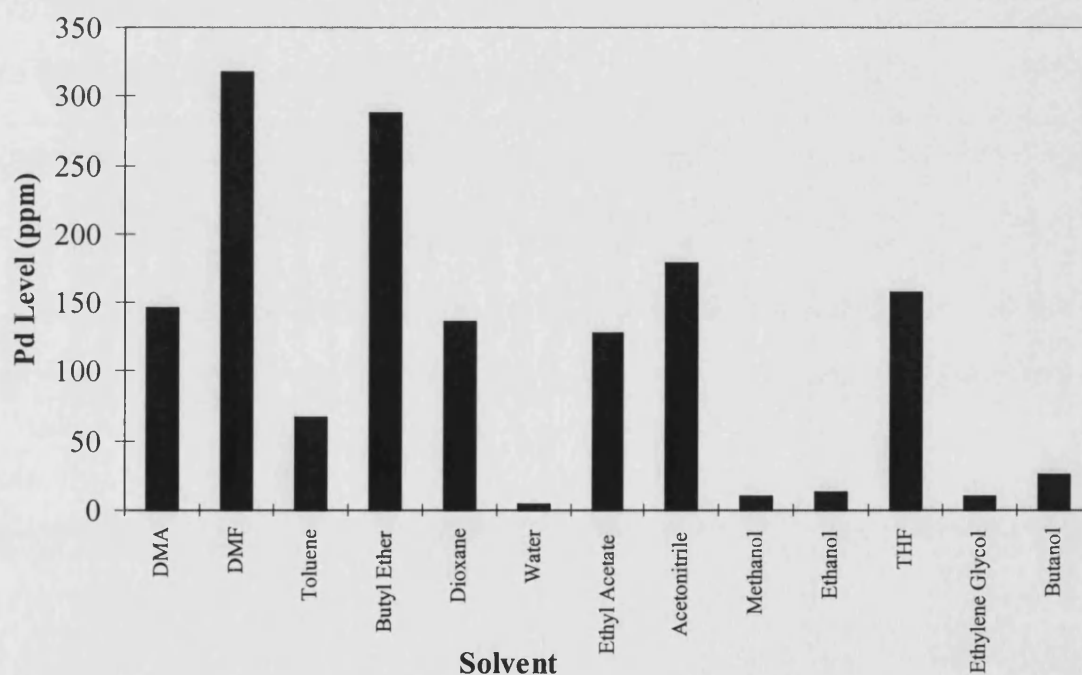
With method *B* there is better silane coverage of the glass surface generally leading to superior anchoring of the complex to the beads. The least leaching was surprisingly attained with method *B* octyltrimethoxysilane derivatised Davisil 300. This apparently contradicts the observations made earlier when investigating which silane derivatisation gave the best performance. However, this study was performed

in the presence of substrates which are known to alter the leaching characteristics of the supported catalysts. Therefore, when considering new reactions modification of the catalyst may be justified to attain a more efficient system.

3.5.5 Effect of Solvent upon Palladium Leaching

Several solvents were screened for compatibility with the supported organic-phase catalyst system.

Figure 28. Solvent screening for compatibility with SOP octyltrimethoxysilane (Method *B*) derivatised Davisil 300 catalyst system (carried out in the presence of triphenylphosphine and in the absence of substrates).

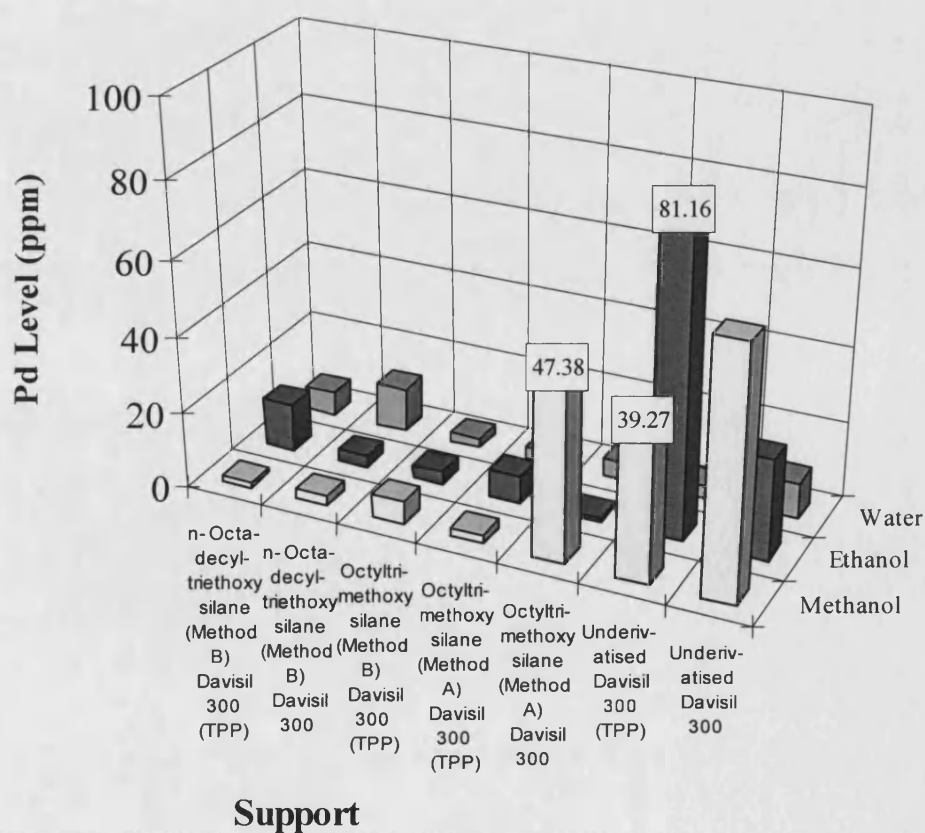


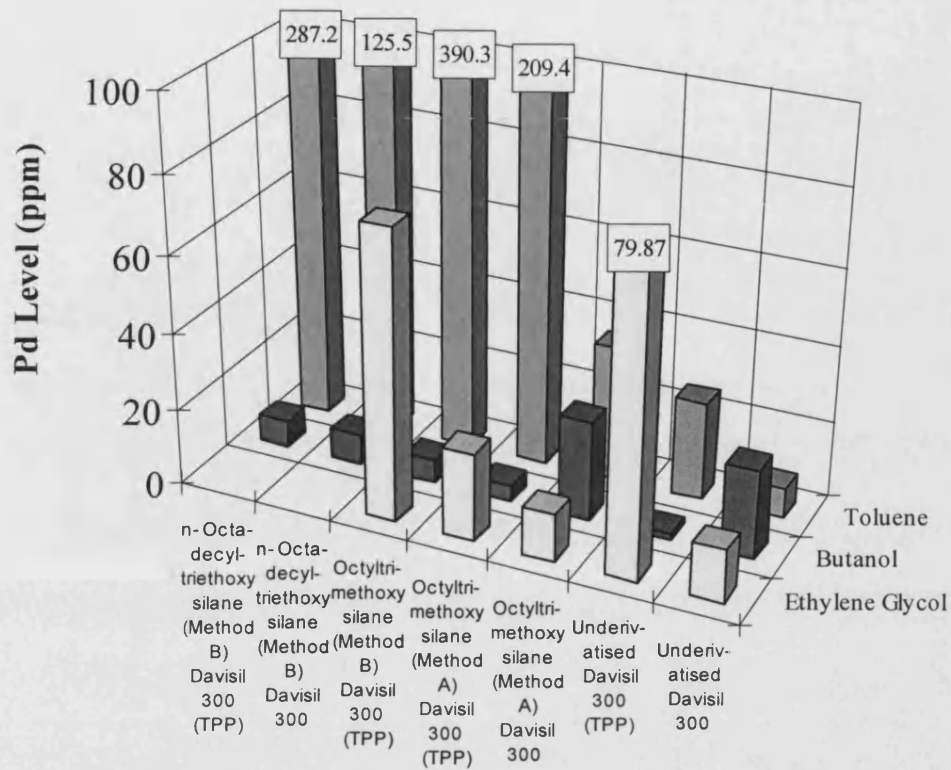
DMF, DMA, toluene, dioxane, ethyl acetate, butyl ether, acetonitrile and THF were eliminated due to the high levels of leaching observed in these solvents (**Figure 28**). Triphenylphosphine is known to be soluble to some degree in these solvents which may explain this result. Comparatively low levels were seen with

water, methanol, ethanol, ethylene glycol and butanol. It is known that triphenylphosphine has very poor solubility in these solvents.

The different supported catalysts were screened in these solvents, and with toluene for comparison. For example, in water, the octyltrimethoxysilane (Method *B*) derivatised Davisil 300 catalyst prepared with TPP gave the best results (**Figure 29**). In methanol, the octyltrimethoxysilane (Method *A*) derivatised Davisil 300 catalyst prepared with TPP displayed the lowest levels of leaching. Information gained from this study would be useful when considering SOP catalyst options for different substrates/reactions.

Figure 29. Solvent screening of different derivatised supports for compatibility with SOP catalyst system (carried out in the absence of substrates).





Support

3.6 Fluorous SOP Catalyst Systems

Preliminary experiments were conducted to investigate the SOP catalyst system for use with fluorous silanes and fluorinated phosphines.

The fluorous silane systems gave clear post-reaction supernatant when prepared with the *tris*(4-fluorophenyl)phosphine (41). With the 1,2-*bis*(dipentafluorophenyl)phosphine ethane (42), however, high levels of leaching were observed (**Figure 27**). It is anticipated that ligands with fluorous ponytails (e.g. $\text{P}[\text{CH}_2\text{CH}_2(\text{CF}_2)_n\text{CF}_3]_3$) would perform more effectively and it is suggested that future investigations should consider this possibility for reactions in fluorous phase.

3.7 Prep-Scale Reaction with Supported Organic-Phase Catalyst

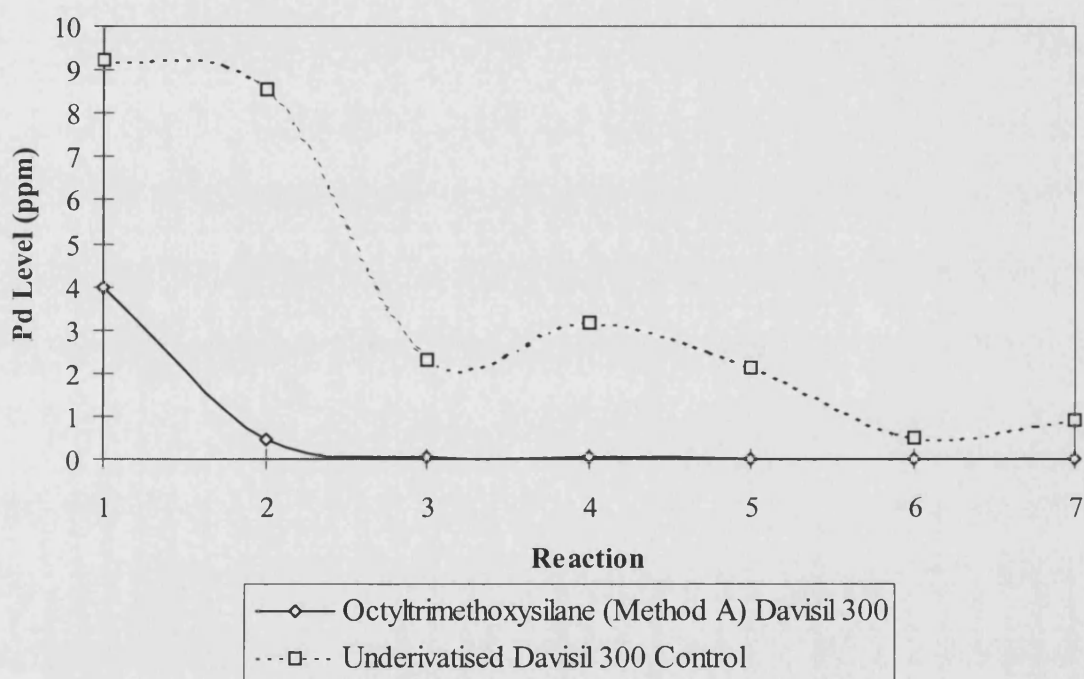
A prep-scale reaction was carried out using 4-iodobenzoic acid and acrylic acid using an octyltrimethoxysilane derivatised Davisil 300 supported organic-phase catalyst.

100 % conversion by HPLC was achieved in under 2 hours with a crude yield of 90 % and recrystallised yield of 81 %. Product purity was greater than 98+ % with the main impurity being water. The level of palladium in the solid sample was also 39.6 ppm compared to 293.9 ppm in the equivalent homogeneous reaction without triphenylphosphine.

3.8 The Re-Use of Supported Organic-Phase Catalysts

The recycling of the SOP catalysts was investigated to see if there was any deterioration in catalyst activity or the efficiency of the support in limiting leaching during re-use.

Figure 30. Level of palladium leaching from SOP catalyst during re-use.



The supported catalysts were found to stay active for seven cycles of re-use after they had been rinsed and dried under vacuum. Also, after an initial loss of palladium from the support the leaching witnessed in re-use was of part per billion level (**Figure 30**). The actual physical appearance of the catalyst also indicated that it was stable after recycling. This is a significant improvement on the supported aqueous-phase system.

3.9 Summary of Conclusions from Preliminary SOP Catalyst Studies

Initial studies have yielded promising results for the future application of supported organic-phase catalysis systems. From these experiments we can draw some general conclusions as guidelines for further investigations into this novel system of supported catalysis.

The use of inorganic bases such as sodium/potassium acetates, carbonates and bicarbonates is preferential as commonly used organic bases such as secondary or tertiary amines appear to promote leaching using this system of catalysis. Early experiments indicated less than half the level of palladium contamination in the solid product when using SOP catalysts compared to the equivalent homogeneous systems. This was quickly improved to less than one eighth in test prep-scale reactions. The presence of triphenylphosphine was surprisingly seen to promote the activity of the SOP catalyst to a level above that of the homogeneous system, whilst dramatically reducing the level of palladium leaching from the derivatised support. However, in the case of the homogeneous reactions and the underderivatised silica support used as a control experiment, the presence of triphenylphosphine, whilst reducing leaching, retarded catalyst activity.

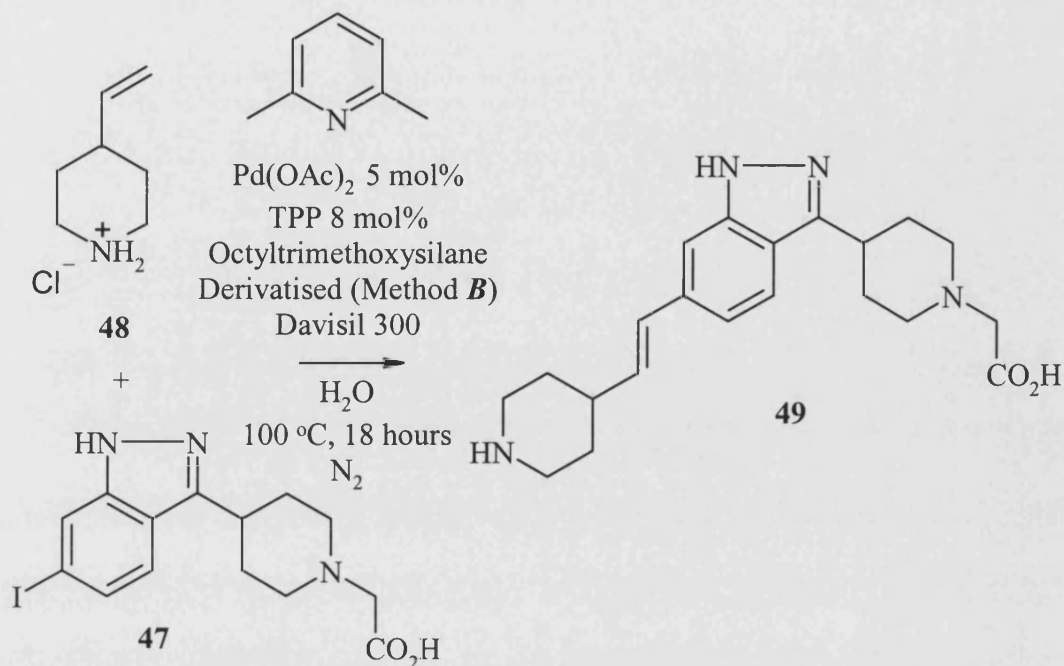
The presence of cyclohexane as a coating was seen to slightly increase the level of metal leaching into the bulk solvent. The principle intention of the coating had been to increase mobility of the supported catalyst complex allowing greater activity and selectivity. However, its absence from reactions using SOP catalysts does not appear to be detrimental to the action of the catalyst. Generally, it was observed that derivatisation using larger silanes, such as *n*-octadecyltriethoxysilane and 2-phenylethyltrimethoxysilane, produces a more efficient catalyst for minimising metal loss. Also, it was shown that method **B** for the derivatisation of the surface of

the silica resulted in better silane coverage and, thereby, produced a more effective catalyst support.

Preliminary studies into the use of fluoruous phosphines and fluoruous silanes have demonstrated that the system is potentially an alternative approach for 'heterogenising' homogeneous catalysts. It was also noted that solvents in which triphenylphosphine displays poor solubility are fair candidates for reactions using SOP catalyst systems, taking into consideration that it may be advantageous to modify the catalyst or support derivatisation for different substrate reactions. SOP catalysts have also been demonstrated to be active for at least seven cycles of re-use with leaching at ppb levels. Subsequent research centred upon the application of the SOP catalyst system to simple synthetic steps to further demonstrate the usefulness of this approach in clean technology.

3.10 Application of the SOP System of Catalysis

3.10.1 Coupling of Vinyl Piperidine and GW292715A (Iodoindazole)

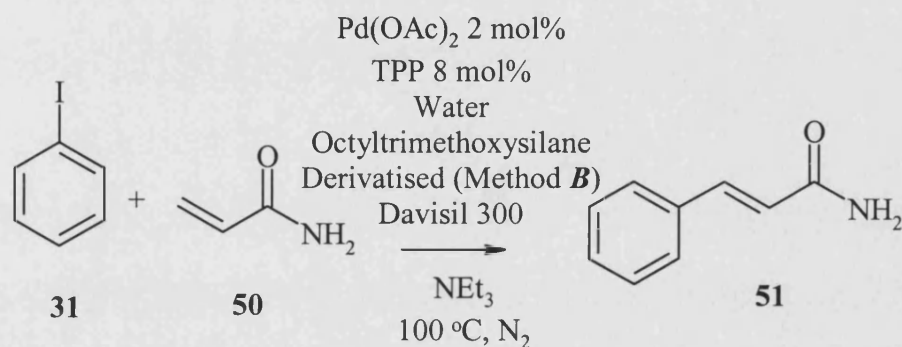


The coupling of GW292715A (**47**) with vinyl piperidine (**48**) was carried out in water using a supported organic-phase catalyst, consisting of octyltrimethoxysilane derivatised Davisil 300 (method *B*) with palladium (II) acetate and triphenylphosphine. This was done in the presence of triethylamine as a substitute for the more routinely used base 2, 6-lutidine.

The reaction was judged complete after 18 hours by TLC. The filtered and evaporated reaction mixture was analysed by ¹H NMR and found to contain the desired GR233548X product (**49**) as well as significant impurities including vinyl piperidine and triethylamine. There was also the presence of the methylene impurity. Analysis by HPLC gave the ratio of desired product compared to amination, methylene and cis impurities as 12.4:0.1:2.3:0.4, respectively.

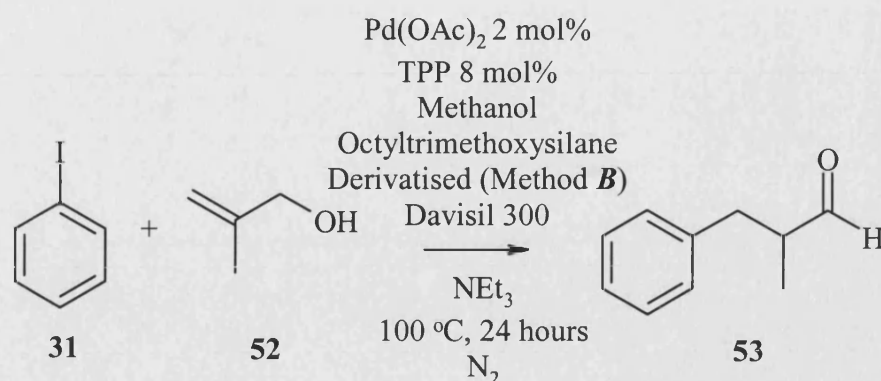
However, the level of palladium leached was very high. This was attributed to the presence of triethylamine as base. The potential exists for this reaction to be explored further using an alternative base and a lower level of vinyl piperidine substrate.

3.10.2 Heck Coupling of Iodobenzene and Acrylamide



The coupling of iodobenzene (**31**) with acrylamide (**50**) was attempted in water using a supported organic-phase catalyst, composing octyltrimethoxysilane derivatised Davisil 300 (method **B**) with palladium (II) acetate and triphenylphosphine, in the presence of triethylamine as base. However, due to the poor solubility of the substrates and products in water this was abandoned. It was suggested that the reaction may be repeated in the future using methanol as the reaction solvent.

3.10.3 Heck Coupling of Iodobenzene and 2-Methyl-2-propen-1-ol

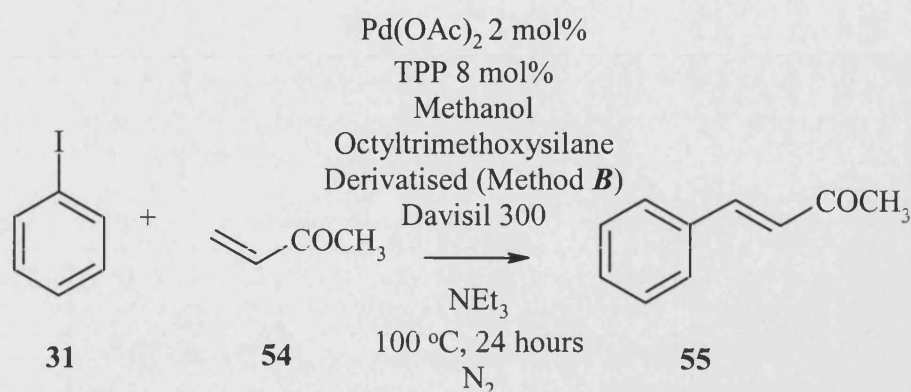


The coupling of iodobenzene (**31**) with 2-methyl-2-propen-1-ol (**52**) was carried out in methanol using out using a supported organic-phase catalyst, composing octyltrimethoxysilane derivatised Davisil 300 (method **B**) with palladium (II) acetate and triphenylphosphine.

The reaction was observed to be complete by TLC at 24 hours. ¹H NMR analysis on the filtered and evaporated reaction mixture showed the presence of the α -methyl hydrocinnamaldehyde product (**53**) but also large amounts of triethylamine, water and phosphine impurities. Also the isolated crude solid contained a high level of leached palladium.

A crude yield of 61 % was obtained. Stirring the product with a small amount of uncomplexed, octyltrimethoxysilane derivatised silica was successful in reducing the level of leached palladium from 1011 ppm to 59.7 ppm.

3.10.4 Heck Coupling of Iodobenzene and Methyl Vinyl Ketone

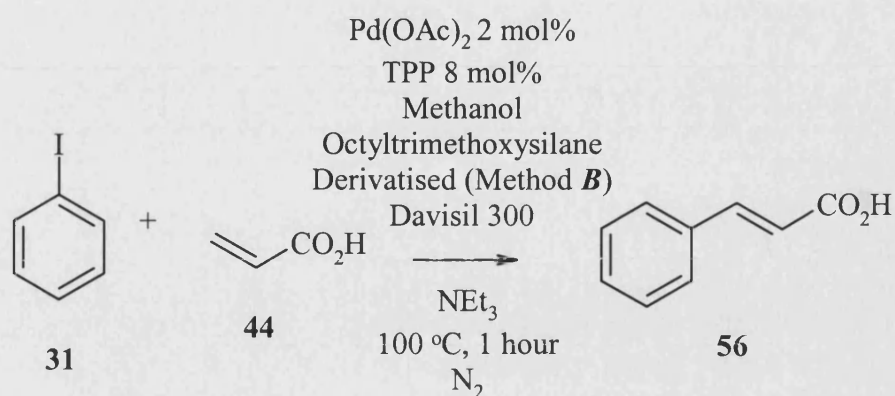


The coupling of iodobenzene (**31**) with methyl vinyl ketone (**54**) was carried out in methanol in the presence of triethylamine using a supported organic-phase catalyst composing octyltrimethoxysilane derivatised Davisil 300 (method **B**) with palladium (II) acetate and triphenylphosphine.

The reaction was observed to be complete at 24 hours by TLC. ^1H NMR analysis of the filtered and evaporated reaction mixture showed the presence of the benzalacetone product (**55**) but also large amounts of triethylamine, water and phosphine impurities. Also, the solid crude isolated contained a high level of leached palladium.

Water and triethylamine were removed by separation with ethyl acetate. A crude yield of 68 % was obtained. Stirring the product with a small amount of uncomplexed, octyltrimethoxysilane derivatised silica was successful in reducing the level of leached palladium from 301 ppm to 23.7 ppm.

3.10.5 Heck Coupling of Iodobenzene and Acrylic Acid



The coupling of iodobenzene (**31**) with acrylic acid (**44**) was carried out in methanol in the presence of triethylamine using a supported organic-phase catalyst composing octyltrimethoxysilane derivatised Davisil 300 (method *B*) with palladium (II) acetate and triphenylphosphine.

The reaction was complete after 1 hour. ^1H NMR analysis of the filtered and evaporated reaction mixture showed the presence of the cinnamic acid product (**56**) (64 % yield) but also large amounts of triethylamine, water and phosphine impurities. Also, the solid crude isolated contained a high level of leached palladium.

3.11 Triethylamine as Base

These studies emphasise the potential for high levels of palladium leaching when triethylamine is utilised as the base in reactions carried out in methanol.

In a control experiment with octyltrimethoxysilane derivatised Davisil 300 (method *B*) supporting palladium (II) acetate and triphenylphosphine it was observed that leaching into the reaction solvent (water/methanol) was increased by a factor of 100-200 times in the presence of triethylamine. The implication that more suitable bases are required is further reinforced by these findings. Methanol was used as the solvent in a number of reactions as it was found that iodobenzene was immiscible with water. However, potassium carbonate, used in previous reactions, is also insoluble in methanol. Therefore, a more suitable alkali metal salt is sought.

3.12 Discussion

It is apparent from these studies that at present there is no fixed rule for carrying out supported organic-phase catalysis but rather there are a number of approaches available which are dictated by solvent and substrate compatibility of the reaction with the catalyst system.

For example, it appears that the effect of triphenylphosphine in reducing leaching is reversed in a number of solvents; toluene, ethylene glycol and ethanol (**Figure 29**). In addition, there is the fluorosilane and fluorinated phosphine approach to be researched. Another aspect of the system that warrants further investigation is the enhanced activity demonstrated by the supported catalyst. This is unusual for heterogeneous systems. However, it highlights the principles underlying systems where the catalyst is not covalently bonded to a support, in which the stereoselectivity and activity as displayed by homogeneous systems is not compromised.

The coupling of an iodindazole with vinyl piperidine has been demonstrated with some success to produce an intermediate for a drug molecule in the early stages of manufacture. The coupling of iodobenzene has been carried out with 2-methyl-2-propen-1-ol and methyl vinyl ketone using SOP catalysis in methanol. However, again a more appropriate base is required to prevent the leaching resulting from the triethylamine. This will be explored further in the next chapter. However, it has been demonstrated for the first time that by stirring product mixtures with a small quantity of uncomplexed silane derivatised silica, the support can be effectively used as a sponge to absorb leached metal catalyst. Research has also been extended in this area with promising results.⁷⁴

The potential for this system of catalysis is extremely promising and more research is required to perfect it. If all the potentials are fulfilled i.e. creating a

catalyst system that has negligible heavy metal leaching into the product, competes with the activity and selectivity of its homogeneous counter-parts, and can be recycled without loss of activity, the implications for heterogeneous catalysis systems will be far reaching. For the immediate future, research focuses upon extending the system for use with asymmetric ligand complexes.

CHAPTER 4

FURTHER APPLICATIONS OF SOP AND SAP

CATALYST SYSTEMS

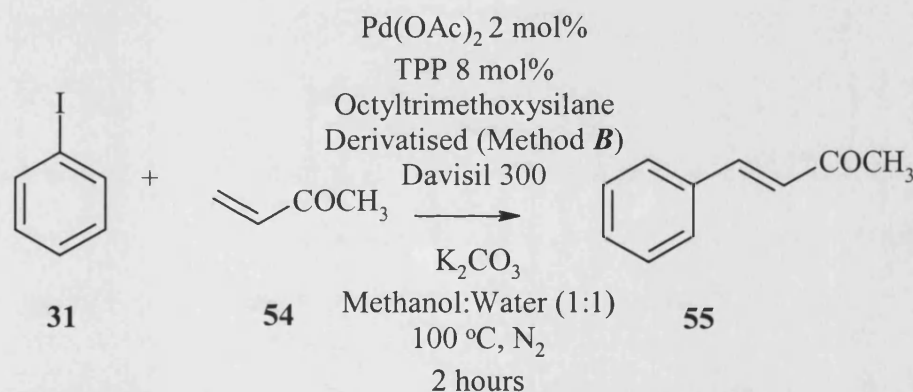
Chapter 4: Further Applications of SOP and SAP Catalyst Systems

4.1 Introduction

In this chapter, modifications of the SOP and SAP systems of catalysis are explored with the aim of extending their application to key synthetic reactions.

Approaches for the substitution of tertiary amines with inorganic bases are described with the aim of improving leaching levels from initial studies conducted using SOP catalysts. The supported catalysts are demonstrated for use in enantioselective allylic substitution. The approach is also adapted for a preliminary study into transfer hydrogenation. Finally, further efforts to use the system in couplings towards the synthesis of drug molecules are outlined.

4.2 Heck Coupling of Iodobenzene with Methyl Vinyl Ketone

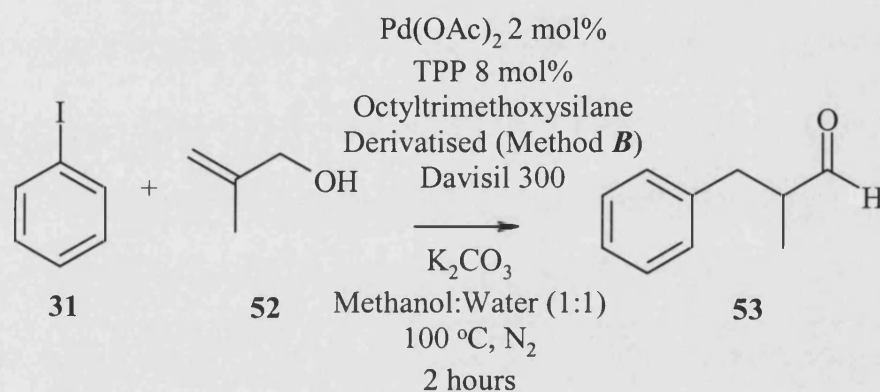


The coupling of iodobenzene (31) with methyl vinyl ketone (54) was re-investigated using palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) upon octyltrimethoxysilane derivatised Davisil 300 (method *B*).

Previously, problems were encountered when the reaction was carried out with triethylamine base, leading to high levels of palladium leaching from the support into the methanol solvent. This was attributed to the formation of methanol-soluble adducts of the catalyst complex with the triethylamine. The reaction was

performed in the presence of potassium carbonate in the place of triethylamine. By modifying the solvent composition of the system to methanol:water, 1:1, potassium carbonate could be dissolved. The reaction was shown to be complete in 2 hours by monitoring with TLC to give a 97 % crude yield. The level of palladium leaching had been reduced from 301 ppm to 16 ppm by the absence of triethylamine from the reaction.

4.3 Heck Coupling of Iodobenzene with 2-Methyl-2-propen-1-ol



The coupling of iodobenzene (31) with 2-methyl-2-propen-1-ol (52) was also repeated using palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) upon octyltrimethoxysilane derivatised Davisil 300 (method **B**).

The reaction was performed with potassium carbonate replacing triethylamine. A methanol:water, 1:1, solvent mix allowed the use of potassium carbonate. In this case, by monitoring by TLC, the reaction was shown to be complete in 2 hours and gave a 71 % crude yield. The level of palladium leaching had been reduced from 1011 ppm to 20 ppm by this modification.

4.4 Discussion

Returning to methanol as the reaction solvent, the couplings of methyl vinyl ketone and 2-methyl-2-propen-1-ol were attempted in the presence of different bases (triethanolamine, sodium methoxide and sodium *t*-butoxide).

The reactions were seen, however, to be incomplete after 48 hours and the level of palladium leached into the methanol was measured and found to be significantly high. It is apparent that there is a conflict between phase separation in the supported catalyst system and the use of these liquid bases.

For the present, we appear to have overcome the solubility of potassium carbonate by the use of solvent mixtures. The resulting catalyst system offers a clean and efficient approach to facilitate the Heck reaction of aryl halides with low levels of leaching and a proven recyclability.

4.5 Allylic Substitution

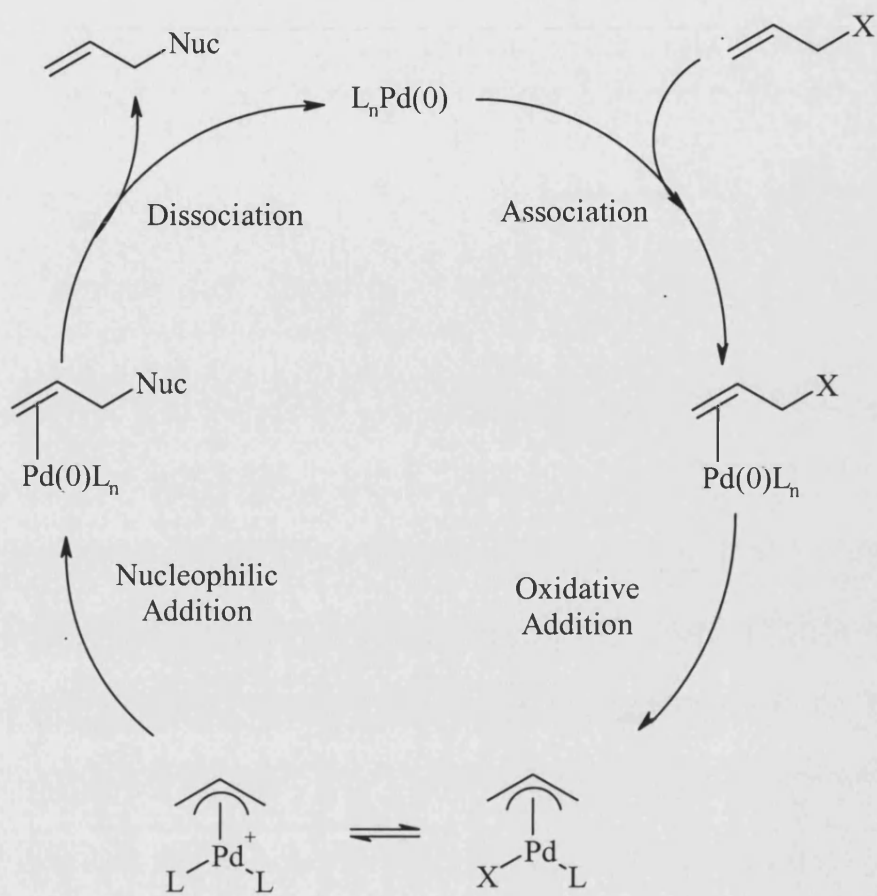
4.5.1 Introduction

Palladium catalysed allylic substitutions are versatile reactions encompassing a wide range of allyl systems and their nucleophilic partners. They have been used to provide chemo-, regio-, diastereo- and enantioselectivity in synthetic processes.

As early as 1965, the reaction of a range of nucleophiles with palladium allyl complexes was demonstrated.⁷⁵ The allylic substitution reaction was developed throughout the early 1970's into a catalytic process. The basic process involved the reaction of allyl acetate with the sodium salt of dimethyl malonate in the presence of catalytic palladium and phosphine. This was carried out in a polar solvent such as THF to afford the product in good yield and with high turnover. A range of leaving groups can be effectively utilised included halides, sulfones, carbonates, epoxides and phosphates.⁷⁶

In the past, this group has demonstrated the application of this chemistry to synthesise α and β -amino acids for use in the pharmaceutical industry. The stereochemical control exerted by oxazolines in auxiliary based reactions is generally excellent and has found numerous applications in such asymmetric synthesis. For example, the use of (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline (**62**) has been demonstrated in palladium catalysed enantioselective allylic amination.⁷⁷

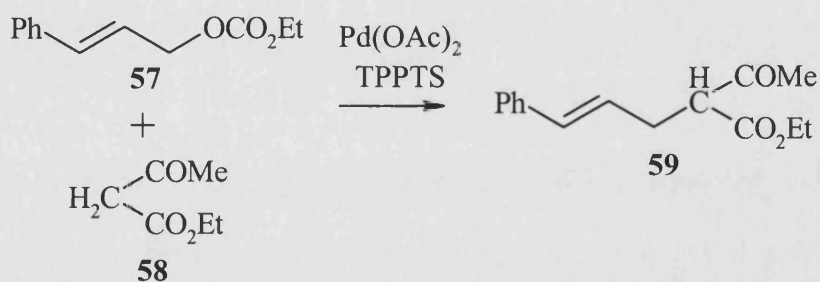
Figure 31. General mechanism for palladium catalysed allylic substitution.



4.5.2 Supported Catalysis

Phosphine stabilised palladium (0) has been demonstrated to catalyse the allylic alkylation of (*E*)-cinnamyl ethyl carbonate (**57**) by carbonucleophiles such as ethyl acetoacetate (**58**) (Trost-Tsuji reaction) using a silica supported aqueous-phase.⁷⁸

The palladium catalyst was solubilised in water using the trisodium salt of *tris*(*m*-sulfonatophenyl)phosphine, TPPTS. The aqueous phase was supported upon porous silica (Grace, SA=185 m² g⁻¹, D_p=240 Å) and used in a water/nitrile system. Optimum conditions for this system were compared with the equivalent 'monophasic' system (water and acetonitrile are miscible).⁷⁹ The catalyst complex was shown to be more stable under SAP conditions than under homogeneous conditions. The monophasic system was also demonstrated to result in the formation of significant amounts of cinnamyl alcohol by-product. It was suggested that the activities and recyclability of these catalytic systems were dependent on various factors such as palladium/TPPTS ratio, the nature of the organic phase, the miscibility of the nitrile and aqueous phase, and the water content of the silica in the SAP catalyst system.

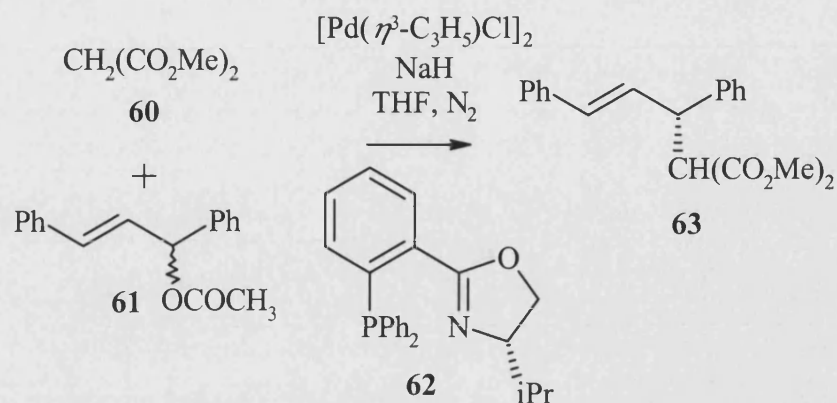


A more recent study confirmed that supported aqueous-phase methodology is well-adapted to the heterogenisation of truly biphasic water/nitrile systems (e.g. water/benzonitrile).⁸⁰ This led to a catalyst more active than the corresponding biphasic system, regardless of water content. This was attributed to the enhancement in interphase surface area. Optimum activity for this system was observed with a

water content of ca. 50 wt% (i.e. full pore filling). This ensured mobility of the catalyst complex. Above 50 wt% of water, a drop in activity was seen, accompanied by agglomeration of the solid, the formation of the cinnamyl alcohol by-product, and palladium and water leaching. With the water/acetonitrile system, the SAP catalyst was demonstrated to have lower activity than when the same solvent system is employed under homogeneous conditions.

Overall, the SAP catalyst was reported to be more stable towards degradation to metallic particles. The selectivity of the catalyst under SAP conditions was higher than under biphasic (water/benzonitrile) or monophasic (water/acetonitrile) homogeneous conditions. In the latter system, 50 % cinnamyl alcohol was produced by hydrolysis of the carbonate, a reaction favoured by high temperature and the presence of large amounts of water. The enhanced selectivity of the supported catalyst for the desired monoalkylated product (**59**) was correlated to the low levels of water required to obtain an active catalyst. It was also noted that the supported catalysts progressively lose part of their activity after several recyclings. This was attributed to the leaching of water from the support into the organic phase, although it was acknowledged that degradation of the catalytically active species may be responsible. It was concluded that the optimum level of water was a compromise between the mobility of the complex, solubility of the reactants and leaching into the organic phase.

4.5.3 Allylic Substitution with Supported Organic-Phase Catalyst



To further the investigation of this system of catalysis in asymmetric synthesis, the palladium catalysed allylic alkylation of *rac*-(*E*)-1,3-diphenylprop-2-enyl acetate (**61**) was studied using dimethyl malonate (**60**) as a nucleophile. $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (2.5 mol%) was present as well as a chiral oxazoline ligand (10 mol%) (**62**). Methodology was adapted from reported experimentals.⁸¹

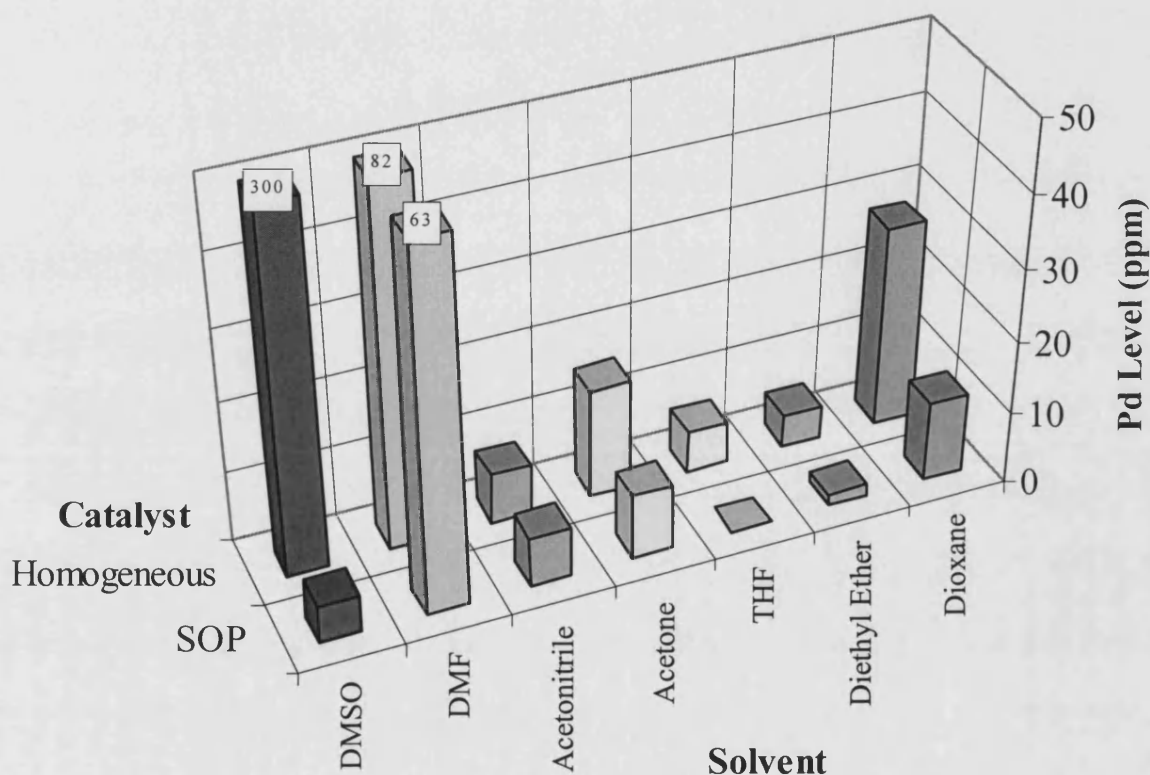
Adapting the reaction for supported organic-phase catalysis, a reduction in the level of palladium leaching from 5.9 ppm to 0 ppm was observed when the reaction was performed in the presence of octyltrimethoxysilane derivatised (method **B**) Davisil 300, compared to the homogeneous reaction. Yields were in excess of 50 % for both catalytic systems.

4.5.4 The Effect of Solvents on Palladium Leaching in Allylic Substitution

Reaction

The SOP catalysed allylic substitution reaction was investigated using a variety of polar solvents with differing dielectric constants (D.C.).

Figure 32. Effect of different solvents on palladium leaching in allylic substitution reaction.



Reactions were carried out using $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (2.5 mol%), oxazoline ligand (10 mol%), and optionally octyltrimethoxysilane derivatised (Method *B*) Davisil 300, in 1 ml of reaction solvent. Generally, excellent enantiomeric excesses (>80 %) and reduced levels of leaching were observed when using the SOP catalyst compared to the homogeneous reaction (**Figure 32**). In the most extreme case, the level was reduced from 300 ppm to 5.4 ppm when the reaction was carried out in DMSO. It was also interesting to note that the sodium hydride base used to prepare

the malonate salt did not detrimentally effect the stability of the supported catalyst or promote leaching.

4.6 Ruthenium Catalysed Transfer Hydrogenation

4.6.1 Introduction

Transfer hydrogenation is the reduction of multiple bonds with the aid of a hydrogen donor. The process involves catalytic abstraction of the hydrogen from the donor followed by addition to the unsaturated functional group of the substrate. Ketones, α,β -unsaturated carbonyl compounds, α,β -unsaturated acids and esters, imines and nitro compounds have been successfully reduced by transfer hydrogenation.⁸²

The advantage of transfer hydrogenation is that it avoids the risks and precautions necessary when using molecular hydrogen. The rate and selectivity can also be optimised by selecting appropriate hydrogen donors. Hydrogen sources that have been employed include unsaturated hydrocarbons such as cyclohexane or cyclohexadiene, primary or secondary alcohols and even formic acid and its salts.

However, hydrogen transfer has attracted less attention than homogeneous hydrogenation in the past because of the low activities exhibited by early catalysts, such as $[\text{RuCl}_2(\text{PPh}_3)_3]$, and the high temperatures required for reaction. Advances have led to the development of more active catalysts and more efficient hydrogen donors, as well as extended the range of potential substrates. Now, enantiomeric excesses for asymmetric hydrogen transfer can be quoted at the same level as asymmetric hydrogenation.⁸³

4.6.2 Mechanism

Two general reaction paths can be proposed for transfer hydrogenation. The step-wise or 'hydridic route' involves the intermediate formation of a metal hydride derivative by the interaction of the catalyst and hydrogen donor. This is followed by hydride transfer to the substrate. The 'direct hydrogen transfer' process suggests that the hydrogen is transferred to the substrate in a concerted process.⁸⁴

4.6.3 Hydrogen Donors

Alcohols are the most commonly employed hydrogen donors. This includes chiral alcohols and even formic acid. The dehydrogenation of formic acid is an irreversible and exothermic process resulting in the formation of carbon dioxide. This often overcomes the energetic requirement of the reduction.

Secondary alcohols have seen widespread use even in the reduction of ketones. In particular, propan-2-ol is an inexpensive and readily available choice. It has an appropriate boiling point and solubility. Upon dehydrogenation it forms acetone which can be easily removed from the reaction.

4.6.4 Substrates

The majority of research into transfer hydrogenation has been concerned with the reduction of ketones, mainly aryl ketones, and activated carbon-carbon bonds in α,β -unsaturated acids.

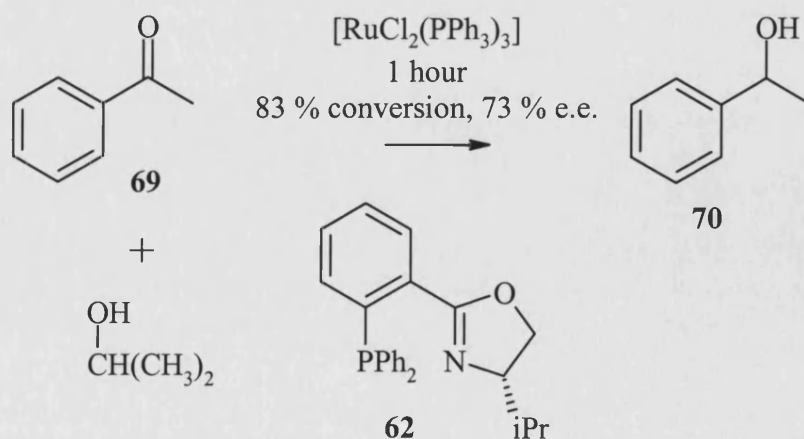
It is well known that the reduction of carbon-carbon double bonds by alcohols and formic acid is thermodynamically favoured and can be carried out in a variety of conditions. However, with the reduction of ketones the equilibrium of hydrogen transfer reduction by alcohols is thermodynamically unfavourable and lies

to the left. Therefore, appropriate reaction conditions and hydrogen donors are necessary to facilitate high conversion.

4.6.5 Catalysts

Ru (II), Rh (I), and Ir (I) complexes with chiral phosphorus and nitrogen ligands have been successfully employed in promoting enantioselective transfer hydrogenations.

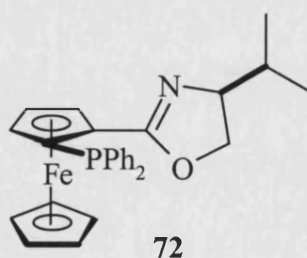
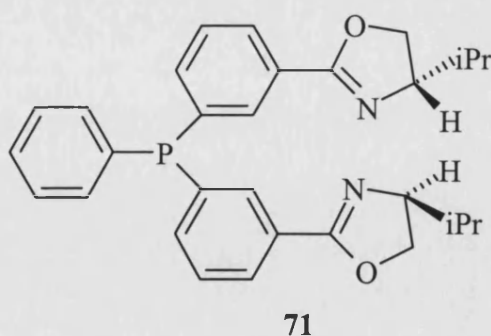
Ruthenium (II) complexes of $[\text{RuCl}_2(\text{PPh}_3)(\text{L})]$, where L is a tridentate ligand with P, N, and O donor atoms, have been employed as efficient catalysts for transfer hydrogenation of cyclic ketones. However, when L was optically active no significant e.e. was observed.⁸⁵ Sometimes strong bases such as sodium hydroxide are used as promoters in the reaction. For example, $[\text{NiCl}_2(\text{PPh}_3)_2]$ catalysed transfer hydrogenation of acetophenone in propan-2-ol has been demonstrated with an 82 % yield in the presence of sodium hydroxide.⁸⁶ β -amino alcohols have also been shown to exhibit a high ligand acceleration effect even at room temperature in the reduction of aromatic ketones in propan-2-ol.⁸⁷



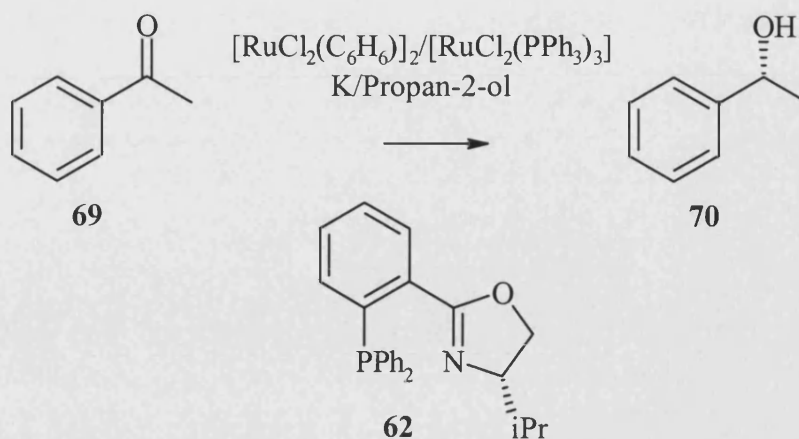
Of particular interest is the transfer hydrogenation of alkyl aryl ketones such as acetophenone (69) with propan-2-ol catalysed by ruthenium complexes of chiral

phosphinooxazolines, demonstrated with excellent turnover and yielding products with up to 94 % enantiomeric excess.^{88,89} Prior to this, high enantioselectivities have been limited to a small set of aryl ketones or subject to low turnover. With this complex the reaction is unaffected by the steric bulk of the substrate indicating a potentially broad scope for use. Chiral NPN-type tridentate ligands containing two oxazoline rings (**71**) have also been used in ruthenium (II) complexes. High activities and enantioselectivities (up to 92 %) were reported in reactions with aryl alkyl and dialkyl ketones.⁹⁰

Interestingly, nickel stabilised zirconia ($Zr_{0.8}Ni_{0.2}O_2$) has been demonstrated as a re-usable, solid catalyst for the reduction of nitroarenes, aldehydes and ketones giving yields as high as 96 % using potassium hydroxide and propan-2-ol.⁹¹ Recently much attention has centred around the use of chiral ferrocene ligands to facilitate a variety of enantioselective transformations. In the field of transfer hydrogenation, ligands such as (*S,S*)-(4,5-dihydro-4-isopropyl-2-oxazolyl)-2-diphenylphosphino ferrocene (**72**) have been used to perform enantioselective reduction of aryl alkyl ketones.^{92,93}



4.6.6 Ru Catalysed Transfer Hydrogenation of Acetophenone



An investigation was carried out into the potential for using the supported aqueous-phase or organic-phase catalyst system for enantioselective transfer hydrogenation with the aim of initiating future research. The study was based upon past research into the application of oxazoline ligands for asymmetric transfer hydrogenation.⁸⁸

The transfer hydrogenation of acetophenone (69) was attempted using catalyst complexes formed from $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ or $[\text{RuCl}_2(\text{PPh}_3)_3]$ (2.5 mol% ruthenium) and (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline ligand (3 mol%) (62) in propan-2-ol.

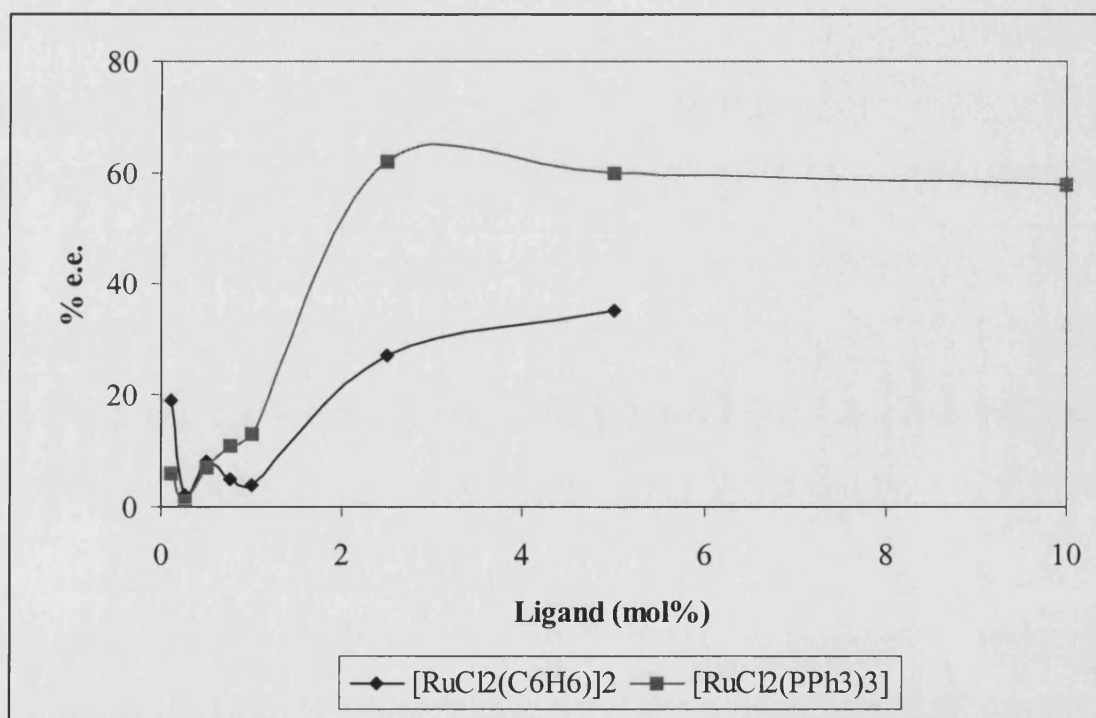
Initial reactions compared the activity of $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ and $[\text{RuCl}_2(\text{PPh}_3)_3]$ at room temperature and under reflux conditions. An optimal yield of 74 % was attained using $[\text{RuCl}_2(\text{PPh}_3)_3]$ with the (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline (62) ligand as a catalyst complex, after refluxing for 18 hours. This was coupled with a reasonable enantiomeric excess of 76 %.

The reactions were repeated in the presence of very low levels of ruthenium catalyst (0.2 mol%). If possible, this would make the approach more attractive for commercial processes. It was observed that the yields of the phenethyl alcohol (70) were maintained and even slightly increased when refluxing with 0.2 mol% of

ruthenium catalyst, $[\text{RuCl}_2(\text{PPh}_3)_3]$. However, the enantiomeric excess deteriorated significantly as a result of the low levels of the chiral ligand.

Reactions using $[\text{RuCl}_2(\text{C}_6\text{H}_6)_2]$ (0.5 mol%) were conducted with varying levels of oxazoline ligand (**62**) to investigate if enantiomeric excesses using this complex could be improved by altering the catalyst/ligand ratio. Although, high levels of conversion were achieved, enantiomeric excesses observed were poor (**Figure 33**).

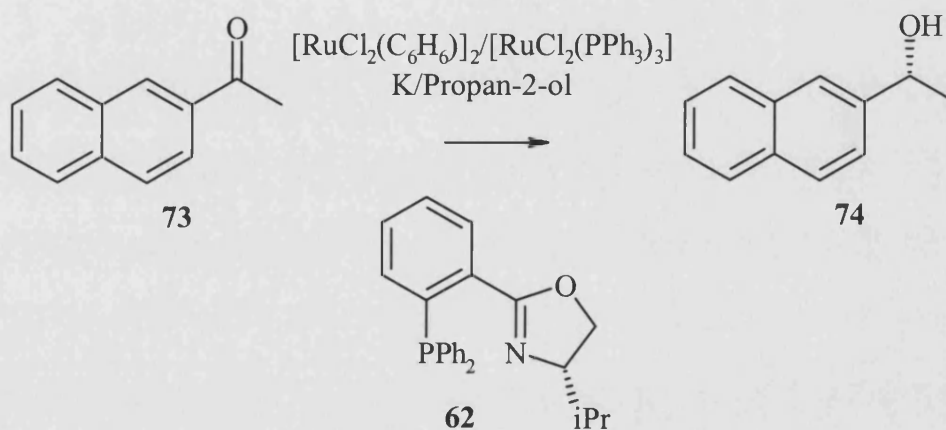
Figure 33. Effect of (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline ligand level on enantiomeric excess.



The study was, therefore, repeated using the catalyst $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.5 mol%). It appears that highest levels of enantiomeric excess are attained as the level of ligand approaches 3 mol% (76 % from earlier study and 62 % using 2.5 mol% ligand from this investigation). These observations were taken into account when attempting to immobilise the catalyst system. It was also noted that in some cases

enantiomeric excess decreased during the course of the reaction. As transfer hydrogenation is a reversible reaction, complete conversion is prevented. The reverse process frequently deteriorates enantiomeric purity of the alcohol product. Therefore, low substrate concentrations are required and unnecessarily long exposure to reaction mixture should be avoided. However, this must be balanced with the time required for optimal conversion of the substrate.^{88,94}

4.6.7 Ru Catalysed Transfer Hydrogenation of 1-Acetonaphthone



The reduction of 1-acetonaphthone was also explored with the $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2/[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.2 mol% ruthenium) -oxazoline (0.26 mol%) catalyst complexes.

In both cases the yields were relatively poor compared to the acetophenone reaction. It was noted, however, that the better results were again obtained when using the $[\text{RuCl}_2(\text{PPh}_3)_3]$ oxazoline complex (40 % ee, 54 % yield). Therefore, it was decided that attempts would be made to employ this catalyst upon a supported system.

4.6.8 Ru Catalysed Transfer Hydrogenation of Acetophenone with Supported Catalysts

The reduction of acetophenone was attempted using supported catalyst complexes; SOP catalyst *SCI* ($[\text{RuCl}_2(\text{PPh}_3)_3]$ with triphenylphosphine on octyltrimethoxysilane derivatised Davisil 300), SAP catalyst *SC2* ($\text{RuCl}_2[\text{PPh}_2(\text{C}_6\text{H}_4\text{SO}_3\text{Na})]_3$ on Davisil 300) and a homogeneous control *HCI* ($[\text{RuCl}_2(\text{PPh}_3)_3]$ equivalent to 0.1 mol% ruthenium with 0.18 mol% triphenylphosphine,).

Levels of conversion comparable to the homogeneous control *HCI* were seen when using the SOP catalyst *SCI*. Also, levels of leaching into the substrate phase were below 1 ppm for both the supported catalysts compared to 31 ppm for the homogeneous control which also showed signs of containing metallic ruthenium. These results were very promising and bode well for the asymmetric reaction with an oxazoline ligand.

A preliminary reaction carried out, as above, using the SOP catalyst complex *SCI* in the presence of oxazoline (**62**) (0.125 mmol) gave a conversion of 63 % with an enantiomeric excess of 32 %. Future work will attempt to optimise these preliminary reactions and expand upon this system of catalysis in the field of transfer hydrogenation.

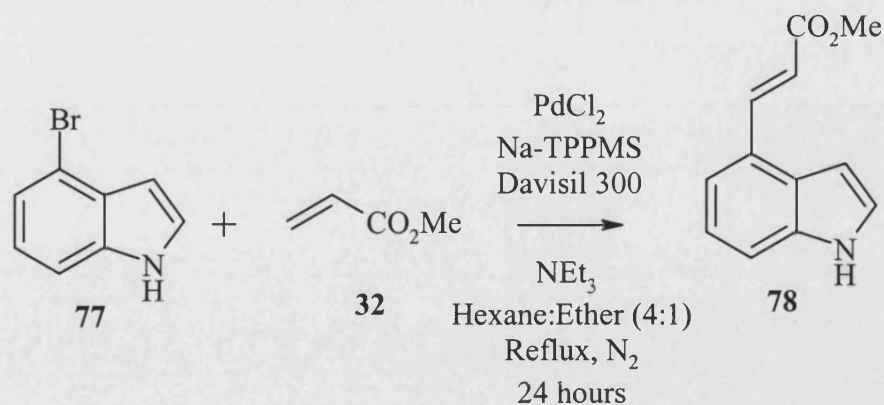
4.7 Heck Coupling on a Substituted Indole

4.7.1 Introduction

4-Bromoindole is a versatile starting material for the synthesis of ergot alkaloids such as Chanoclavine-I.^{95,96}

In the past the synthesis of indoles has been widely reported. Procedures have been described which employ supported catalysts and even solid supported substrates.^{97,98} Recently the synthesis of *N*-anilino-2,3-diphenylindole from the reaction of azobenzene and diphenylacetylene was reported using a supported aqueous-phase catalyst. The catalyst was shown to have fair activity and demonstrated to be partially recyclable.⁹⁹ This is evidence of the widespread interest in this area of heterocyclic chemistry and has inspired study into the application of supported aqueous-phase catalysis for reactions on a substituted indole.

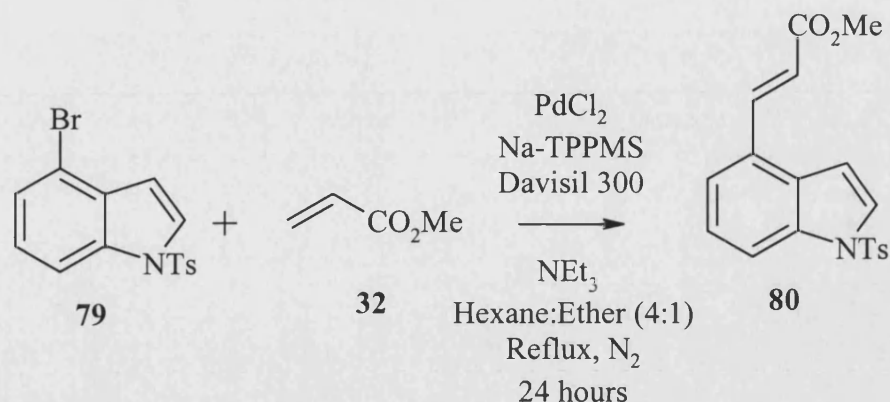
4.7.2 Heck Coupling to 4-Bromoindole



The reaction of 4-bromoindole (**77**) with methyl acrylate (**32**) was attempted using palladium (II) chloride (4.25 mol%) and Na-TPPMS (0.28 mol%) in hexane:ether (5 ml, 4:1) supported upon Davisil 300 with a coating of ethylene glycol.

Unfortunately, TLC analysis indicated that much of starting material was still present even after 24 hours. Analysis by ¹H NMR confirmed the absence of the desired product in the reaction mixture. However, it was noted that less than 1 ppm palladium had leached into the organic solvent. It was suggested that protection of the nitrogen on the indole may aid the reaction by eliminating possible by-products. Therefore, a tosyl group was introduced to form 4-bromo-1-tosylindole (**79**).

4.7.3 Heck Coupling to 4-Bromo-1-tosylindole



Having protected the indole nitrogen from potential side reactions, the coupling to methyl acrylate was re-attempted using palladium (II) chloride (4 mol%) and Na-TPPMS (28 mol%) supported on Davisil 300 with a coating of ethylene glycol.

A control reaction was also performed in the absence of Davisil 300 and ethylene glycol. However, analysis by ¹H NMR again confirmed the absence of any of the desired product in the reaction mixtures.

It was suggested that a more appropriate phosphine may be required for reaction, therefore, the above coupling was attempted using palladium (II) acetate (4 mol%) with tri-*o*-tolylphosphine, P(*o*-Tol)₃, (28 mol%) and optionally octyltrimethoxysilane derivatised Davisil 300 (method **B**) (250 mg). The reactions were performed neat in the presence of methyl acrylate and triethylamine. Analysis by TLC confirmed that no indole starting material remained after 6 hours (both >81 % yield). However, levels for palladium leaching were lower in the reaction containing the derivatised support (3 ppm compared to 22 ppm for the homogeneous control). It appears that the coupling cannot be carried out at present using the triphenylphosphine ligands. Promising results are expected for future investigations in this area.

4.8 Conclusions

The use of solvent mixtures to overcome solubility problems may become a useful tool in the application of supported organic-phase catalysis in a variety of basic synthetic transformations. The SOP catalyst system has been demonstrated as a new and efficient approach to facilitating Heck couplings on aryl halides, with low levels of catalyst leaching, excellent activity and effective recycling characteristics.

The SOP catalyst system has been applied to the allylic substitution reaction and has demonstrated rates of conversion comparable to a homogeneous system, whilst eliminating palladium leaching into the substrate phase. The supported catalyst has been used in variety of solvents, giving high levels of enantiomeric excess and in many cases dramatically reducing the level of leached metal.

The transfer hydrogenation of aryl alkyl ketones and Heck coupling to a substituted indole have been demonstrated using an SOP catalyst system. Levels of conversion similar to the homogeneous system were witnessed when using catalyst supported on silane derivatised Davisil 300. This was again accompanied by the reduction in level of catalyst leaching. Results for these preliminary investigations were promising and signify the potential for this catalyst system. It is further anticipated that highly enantioselective transfer hydrogenation using an SOP catalyst is possible in the presence of a chiral ligand.

4.9 Outlook

Supported aqueous-phase catalysis has been applied to a variety of transitional metal catalysed processes over the years. Realisation of the full potential outlined by the principles behind this system of catalysis has yet to be achieved i.e. maintaining the activity and selectivity of a homogeneous system whilst eliminating the need for catalyst separation. However, our understanding of the factors governing the behaviour of these catalysts is continually increasing. A number of possible avenues for future investigations have been initiated and uncovered from this research. It is hoped that this work forms the basis for the development of a breed of new, versatile supported catalysts.

CHAPTER 5
EXPERIMENTAL

Chapter 5: Experimental

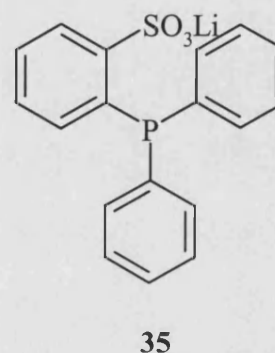
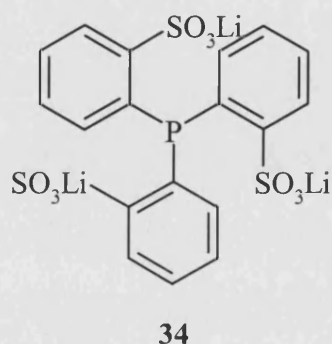
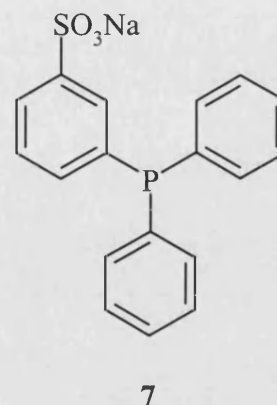
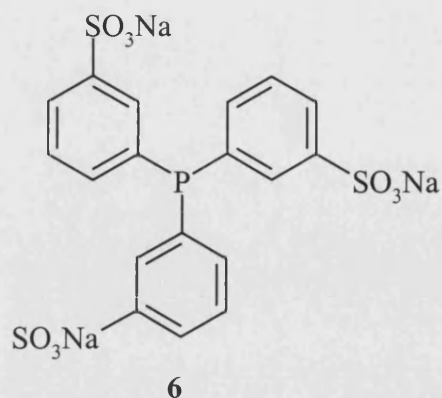
5.1 Factors in the Optimisation of Heck Reactions with SAP Catalysts

5.1.1 Materials

Iodobenzene (98 %), methyl acrylate (99 %), palladium (II) chloride (99 %), triphenylphosphine (99 %), triethylamine (99.5 %), palladium AAS standard solution (1000 $\mu\text{g ml}^{-1}$ in 5 wt% HCl), ethylene glycol (99.8 %), and phosphorus trichloride (98 %) were used as purchased from Aldrich. Hexane (95+ %), ethyl acetate (99.8 %), tetrahydrofuran (99.9+ %), diphenylphosphine chloride, and diethyl ether (99.8 % anhydrous) were purchased with the least level of water content from Aldrich. Oleum and *n*-butyllithium solutions (titrated prior to use with 1,3 diphenyl-2-propanone-*p*-toluene sulfenyl hydrazone) were purchased from Fluka. The lithium salt of benzenesulfonic acid was prepared as described in the literature.¹⁰⁰ In all operations requiring water, Millipore de-ionised water was used. Aqua-regia was prepared as required (3:1 conc. HCl:HNO₃).

Davisil 300 Å 653XWP (pore diameter, $D_p=300$ Å; surface area, SA=160 m^2g^{-1}) was purchased from Supelco Inc. Controlled pore glasses (CPG Inc.), CPG-120B ($D_p=128$ Å; SA=141 m^2g^{-1}), CPG-240B ($D_p=239$ Å; SA=82 m^2g^{-1}), CPG-290B ($D_p=290$ Å; SA=132 m^2g^{-1}), CPG-350B ($D_p=348$ Å; SA=62 m^2g^{-1}), CPG-410B ($D_p=410$ Å; SA=96 m^2g^{-1}), CPG-500B ($D_p=513$ Å; SA=51 m^2g^{-1}), and CPG-700B ($D_p=697$ Å; SA=39 m^2g^{-1}) were obtained from Cambio Limited and donated by GlaxoWellcome. All porous silicas were vacuum dried overnight at 200 °C before use to remove residual moisture.

5.1.2 Preparation of Mono- and Trisulfonated Triphenylphosphines



Monosodium *mono(m-sulfonatophenyl)diphenylphosphine*

Monosodium *mono(m-sulfonatophenyl)diphenylphosphine* (7) (Na-TPPMS; $M_w = 364.312$) was prepared by the drop-wise addition of oleum (25 % sulfur trioxide - in sulfuric acid) (0.5 ml) to triphenylphosphine (80 g, 305 mmol) suspended in concentrated sulfuric acid (36 ml).²⁰

More oleum (165 ml) was added to the cooled solution, and stirred at room temperature for 3 hours, before being poured onto ca. 2 kg of stirred ice. The emulsion was stirred for 5 minutes and extracted with ethyl acetate (2x500 ml). It was then extracted with 6 % aqueous sodium hydroxide solution (150 ml). The extract was neutralised with concentrated sulfuric acid and evaporated to give a white solid which was dried, then refluxed in methanol (750 ml). This was hot-

filtered, reduced to 200 ml and cooled. The resulting slurry was filtered and washed with methanol (3x20 ml). ^{31}P NMR, (161.98 MHz, $\text{DMSO-}d_6$) δ_{p} -6 ppm [$\text{PPh}_2(\text{C}_6\text{H}_4\text{SO}_3\text{Na})$], suggested the product was >99 % pure (yield 25.4 g, 23 %) after a single recrystallisation from water. Mass spectroscopy suggested that the main impurity was the disodium salt.

Trisodium *tris(m-sulfonatophenyl)phosphine*

Trisodium *tris(m-sulfonatophenyl)phosphine* (6) (Na-TPPTS ; $M_w=568.396$) was prepared by the slow addition of triphenylphosphine (10 g, 38.1 mmol) to oleum (100 ml) at 0 °C. After allowing to warm to room temperature the reaction was continued for ca. 150 hours.

It was then neutralised at 0 °C with 20 % aqueous sodium hydroxide and the volume reduced to 200 ml. This was refluxed with methanol (1000 ml) and hot-filtered. The solid was further extracted with hot methanol (500 ml) and the combined extracts were reduced to 200 ml in volume. Addition of acetone (800 ml) precipitated the product (75-85 % purity, the main impurity being Na-TPPTS oxide). A number of techniques were available for purification. This was achieved by extraction with acetone/methanol/water (10:5:1, 300 ml) followed by repeated dissolution, re-precipitation and extraction.²⁴ After two repetitions, 97 % purity (yield 14.2 g, 66 %) was determined by ^{31}P NMR (161.98 MHz, D_2O) δ_{p} -4.31 ppm [$\text{P}(\text{C}_6\text{H}_4\text{SO}_3\text{Na})_3$].

Monolithium *mono(o-sulfonatophenyl)diphenylphosphine*

Monolithium *mono(o-sulfonatophenyl)diphenylphosphine* (35) (Li-TPPMS ; $M_r=348.262$) was prepared from the lithium salt of benzenesulfonic acid (1.804 g, 11 mmol) in tetrahydrofuran (15 ml).

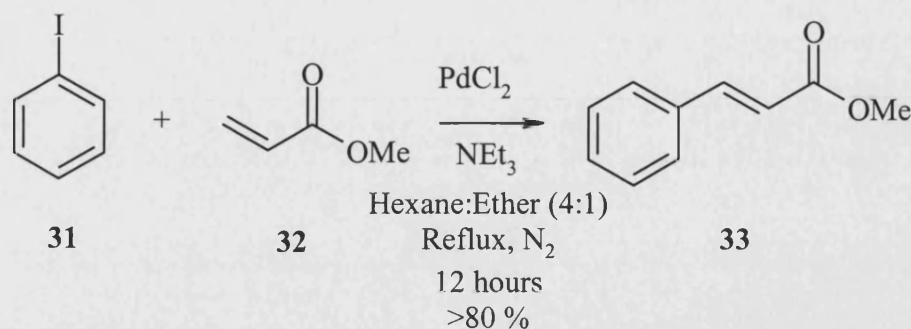
Having cooled the mixture to 0 °C, *n*-butyllithium (8 ml, 12 mmol, 1.5 M solution in hexanes) was added and allowed to stir for 20 minutes. Diphenylphosphine chloride (1.79 ml, 10 mmol) was added drop-wise, the reaction allowed to warm to room temperature and stirred for 1 hour. The product was poured onto water (100 ml) and light petroleum ether (bp 40-60 °C, 200 ml). The water was washed with diethyl ether (100 ml) and the aqueous layer was then evaporated at 150 °C by Kugelrohr to dryness (bp diphenylphosphine chloride ca. 135 °C at 1 mmHg). Purity was determined by ³¹P NMR δ_p (D₂O, 90 MHz, -7.24 ppm) to be >90 % (yield 1.9 g, 55 %).

Trilithium *tris*(*o*-sulfonatophenyl)phosphine

Trilithium *tris*(*o*-sulfonatophenyl)phosphine (**34**) (Li-TPPTS; M_r=520.246) was prepared from the lithium salt of benzenesulfonic acid (3.936 g, 24 mmol) in tetrahydrofuran (30 ml).

The solution was cooled to 0 °C, then *n*-butyllithium (17.6 ml, 26.4 mmol, 2.7 M solution in heptane) was introduced and allowed to stir for 25 minutes. Phosphorus trichloride (0.348 ml, 4 mmol) in tetrahydrofuran (6 ml) was added and the mixture stirred for 1 hour. The reaction mixture was filtered through cotton wool and the solvent removed *in vacuo* to give the yellow powdered product >90 % purity (yield 1.4 g, 67 %) by ³¹P NMR δ_p (D₂O, 90 MHz, -9 ppm). The main impurity from the reaction was identified as the lithium benzenesulfonate. Full characterisation of the lithium salts of sulfonated triphenylphosphines will be described, as well as techniques for purification in a publication scheduled for the near future.

5.1.3 The Vinylation of Iodobenzene



Methyl acrylate (**32**) (5.49 mmol) was added to iodobenzene (**31**) (1.88 mmol) in the presence of triethylamine (5.49 mmol) at reflux. The coupling was performed in a solvent mixture of hexane:ether (4:1, 5 ml) under nitrogen.

The 'dry' palladium sulfonated triphenylphosphine complex supported upon silica was re-solvated with hydrophilic phase mixed with the reaction solvent prior to the reaction. Palladium levels in the reaction supernatant were determined prior to and at the end of reactions.

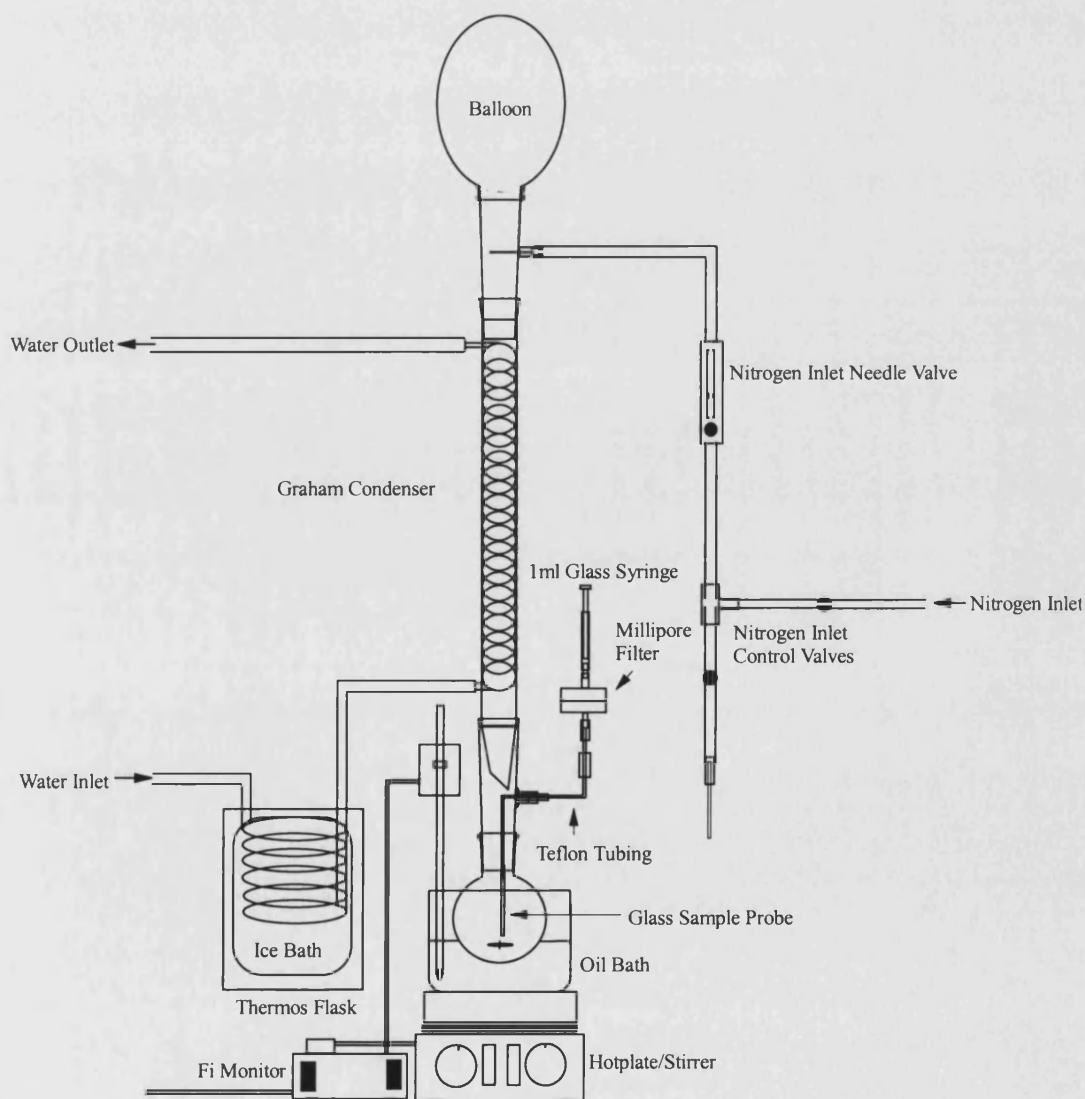
Conversion of the iodobenzene starting material into the methyl-*trans*-cinnamate product was monitored by gas liquid chromatography at regular intervals during the course of the experiment over 12 hours. The solvent was removed *in vacuo* and methyl-*trans*-cinnamate purified by 'flash' column chromatography (eluant, light petroleum:ether 4:1). Yields in excess of 80 % were obtained after completion. δ_{H} (250 MHz, CDCl₃) 7.69 (1H, d, *J* 16.1, ArCH=CH), 7.49 (2H, m, ArH), 7.34 (3H, m, ArH), 6.41 (1H, d, *J* 16.1, =CHCO₂CH₃), 3.77 (3H, s, CH₃CO). δ_{C} (62.5 MHz, CDCl₃) 165.0 (C=O), 141.3 (CH=CHCO₂CH₃), 134.9 (ArC), 128.4 (ArCH), 127.7 (ArCH), 126.2 (ArCH), 119.4 (=CHCO₂CH₃), 50.5 (CH₃). *m/z* (EI) 162 (M⁺, 85 %), 131 (100), 103 (68), 91 (15), 77 (45), 51 (28), 43 (18), 29 (14). mp 36-38 °C. bp 260-262 °C. ν_{max} (CH₂Cl₂)/cm⁻¹ 2930 (CH₃), 2885 (CH), 1745 (CO₂CH₃).

5.1.4 Apparatus and Instrumentation

Reaction Apparatus

All couplings were performed under an atmosphere of nitrogen. Batch reactions were carried out at 100 °C in 25 ml round-bottomed flasks fitted with a condenser.

The flasks were heated in an oil-bath upon a stirrer/hotplate with automatic temperature control. Sampling for gas liquid chromatography and atomic absorption spectrometry was conducted via a Teflon/glass sample-probe fitted with an in-line Millipore filter and syringe.



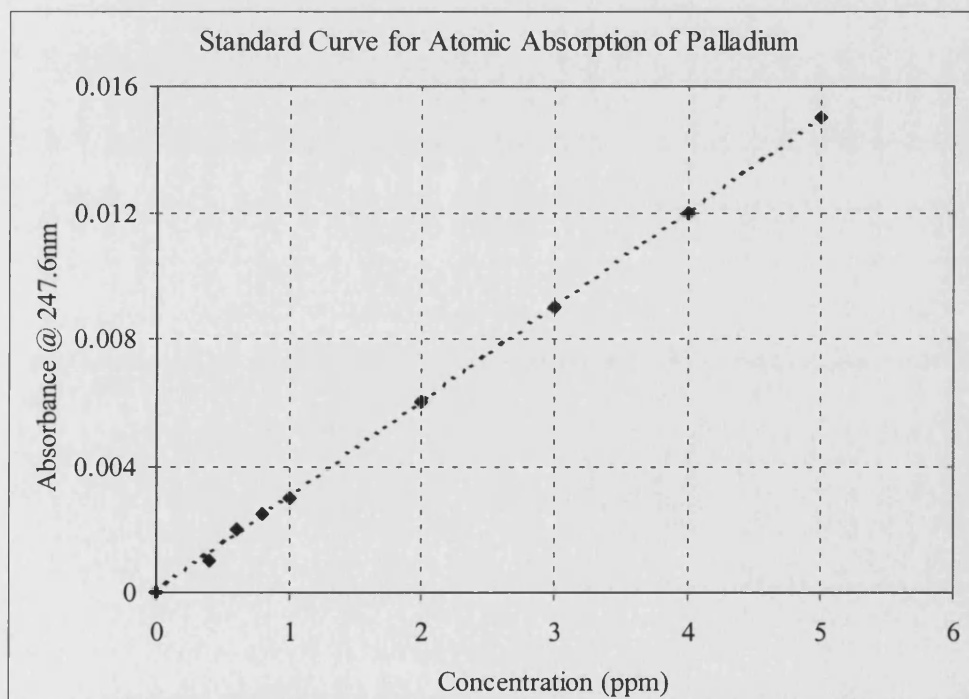
BET/N₂ Adsorption/Desorption Isotherms

BET-N₂ adsorption/desorption analysis carried out on porous glasses was performed on a Micromeritics ASAP2000, out-gassing to 10 mPa at 22 °C.

Atomic Absorption Spectrometry

Palladium atomic absorption analysis of reaction filtrates was performed on a Perkin-Elmer 1100B Spectrometer.

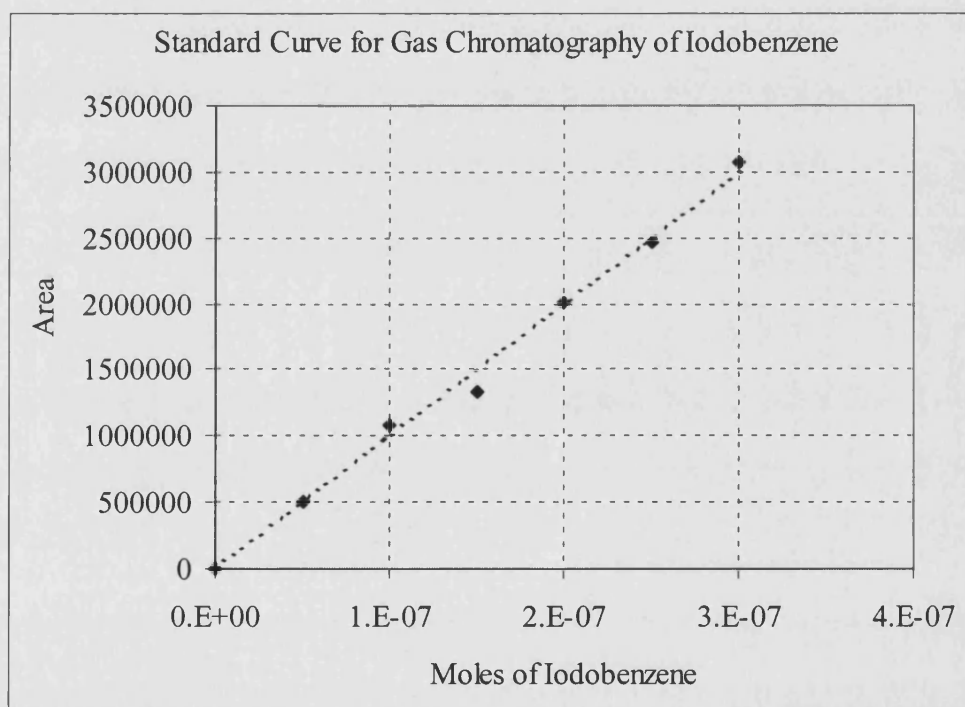
Samples were vacuum filtered to remove solid particles using a stainless steel Millipore in-line filter. They were then evaporated at 400 °C and extracted into 3 ml of de-ionised water with a few drops of aqua-regia. Flame (sensitivity; 250 ppb fuel lean flame) and graphite furnace (sensitivity; 100 ppb) techniques were employed using an S+S Juniper palladium hollow cathode lamp, HGA700 graphite furnace and AS70 Auto-Sampler.



Absorption levels were compared with a standard solution diluted to 0.4, 0.6, 0.8, 1.0, 2.0, 3.0, 4.0, and 5.0 ppm. Solvent samples from before and after reaction were analysed to determine the extent of palladium leaching. Comparative studies of palladium and phosphine levels were performed using ICP spectrometry on a Varian Liberty 200 instrument with samples prepared in DMSO (2 % HCl).

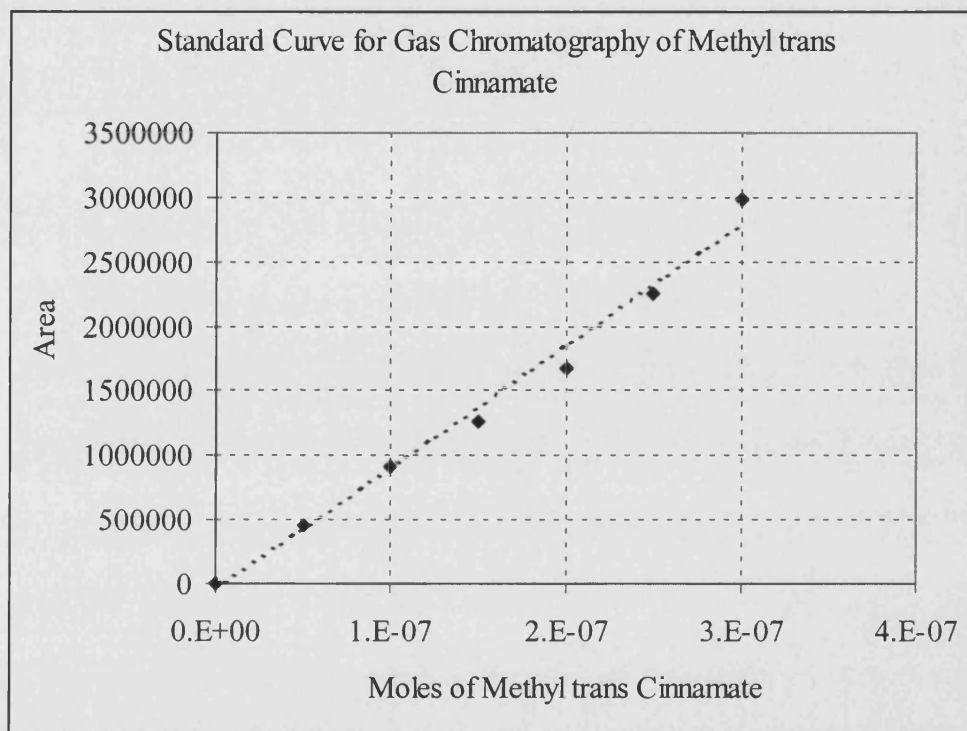
Reaction Kinetics

The extent of reaction was monitored on a Pye Unicam Series 304 gas chromatograph and a Perkin Elmer GC8700, with FID and Supelco SP2330 vitreous silica column, using iodobenzene and methyl-*trans*-cinnamate internal standards.



It was interesting to note that the reaction displayed pseudo first-order kinetics with respect to the methyl acrylate substrate being present in excess. Activities quoted were obtained from linear conversions graphs of $\ln[(M-X_A)/M(1-X_A)]$ against time. $M=C_{B0}/C_{A0}$; C_{A0} being initial concentration of substrate A and C_{B0} being initial concentration of substrate B. Fractional conversion of substrate A,

$X_A = (N_{AO} - N_A) / N_{AO}$; N_{AO} being initial number of moles of A whilst N_A is the number of moles of A at any given time. Similar observations have been made in reactions with a tri-phase catalysis system.¹⁰¹



Thin Layer Chromatography

Analytical TLC was performed using pre-coated aluminium-backed silica plates (Merck Kieselgel 60 GF₂₅₄). Plates were visualised using ultraviolet light (254 nm) and by staining with potassium permanganate solution or iodine, followed by heating.

'Flash' Chromatography

'Flash' chromatography was performed using Merck Kieselgel 60 H silica gel. Pressure was applied at the column head using manual bellows. Samples were

introduced as a saturated solution in an appropriate solvent. Column samples were monitored by TLC and collected.

Infrared Spectrometry

Infrared spectra were recorded as solutions in dichloromethane or as thin films, on a Nicolet FT-205 spectrometer and a Perkin Elmer 1600 series FT-IR with internal calibration, in the range 4000-600 cm^{-1} .

Elemental Analysis

Elemental analysis was performed on a Carlo Erba 1106 Elemental Analyser.

Melting Point

Melting points were recorded on an electrothermal digital melting point apparatus and are uncorrected.

Mass Spectrometry

High and low resolution mass spectra were recorded on a Kratos MS80 instrument and a Micromass Autospec.

NMR Spectra

^1H and ^{13}C NMR spectra were analysed using a Bruker AC-250 and DPX 400 instrument and on a Jeol JNM-GX270 and Ex-400. Chemical shifts were recorded as parts per million (ppm) downfield of trimethylsilane (singlet at 0 ppm, TMS) for proton resonances and referenced to the central peak of the triplet of CDCl_3 (977 ppm) for ^{13}C resonances. Multiplicities are represented as singlet (s), broad singlet

(br s), doublet (d), double doublet (dd), broad doublet (br d), double triplet (dt), apparent triplet (app t), triplet (t), quartet (q), and multiplet (m).

Solvent Evaporation

An Edwards Modulyo Pirani 10 freeze-drier was used in the preparation of the supported catalysts.

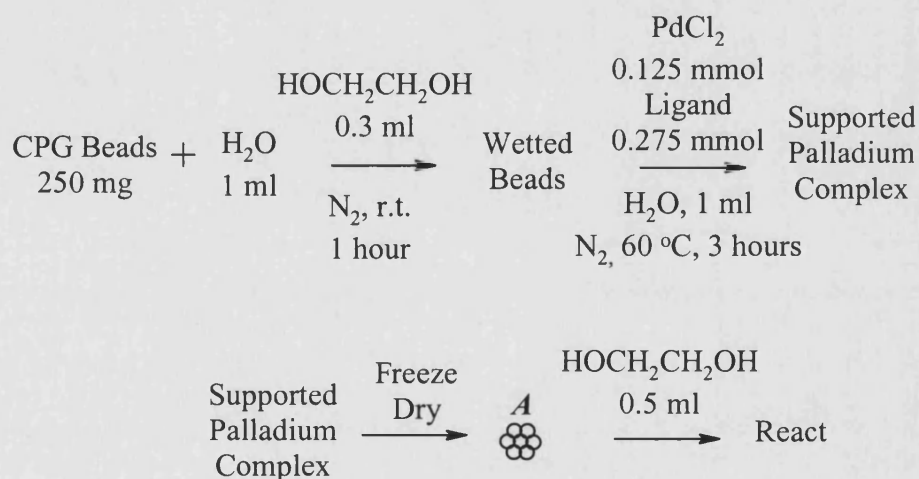
5.1.5 Immobilisation of Palladium Complex onto Porous Silica

The dried supported catalysts were re-solvated with ethylene glycol/water (0.5 ml per 250 mg silica) added to the organic phase, by stirring for 1 hour, prior to reaction. The level of solvation with hydrophilic phase, expressed in terms of the degree of pore filling, $\delta=2$.

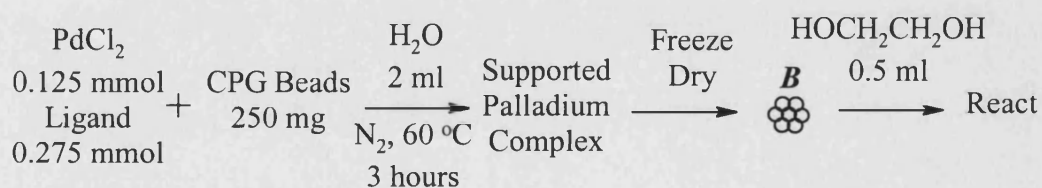
$$\text{Degree of pore filling } \delta = \frac{\text{Volume of the coating added (} 5 \times 10^{-7} \text{ m}^3 \text{)}}{\text{Total pore volume of solid (} V_p = 2.5 \times 10^{-7} \text{ m}^3 \text{)}}$$

The amount of silica and hydrophilic phase used was determined by comparison with work done previously by this and other groups. All manipulations were performed under nitrogen atmosphere or a vacuum. Palladium (II) chloride (6.6 mol% with respect to iodobenzene) and Na-TPPMS ligand (14.6 mol%) was used in each preparation. The complexes were supported onto CPG-350 (250 mg).

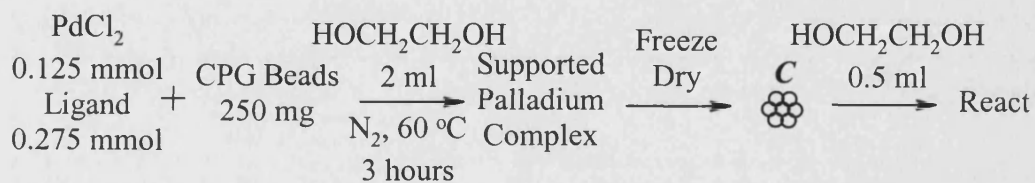
Method A



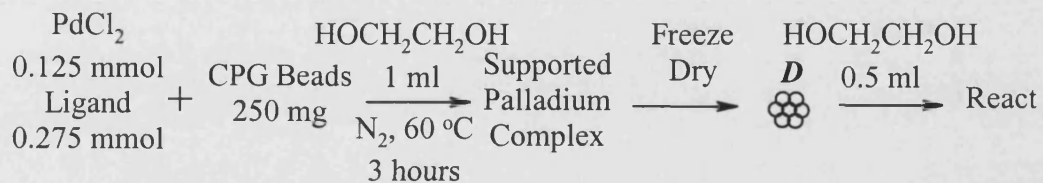
Method B



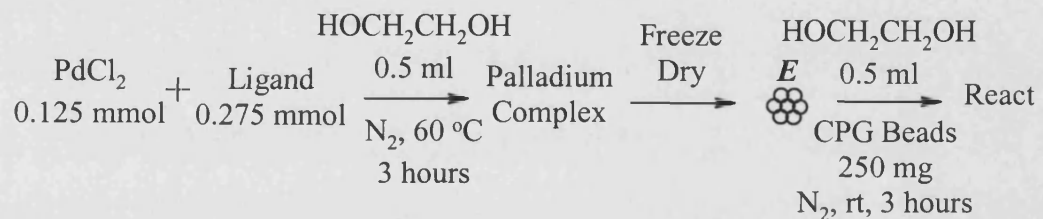
Method C



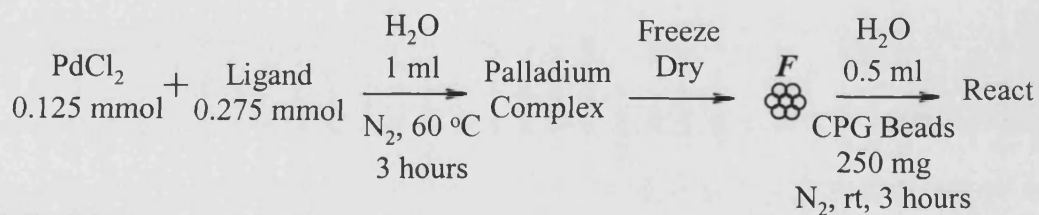
Method D



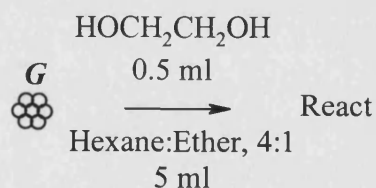
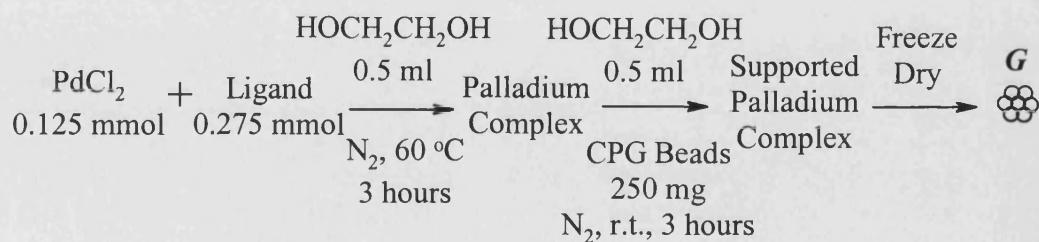
Method E



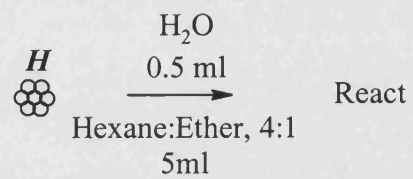
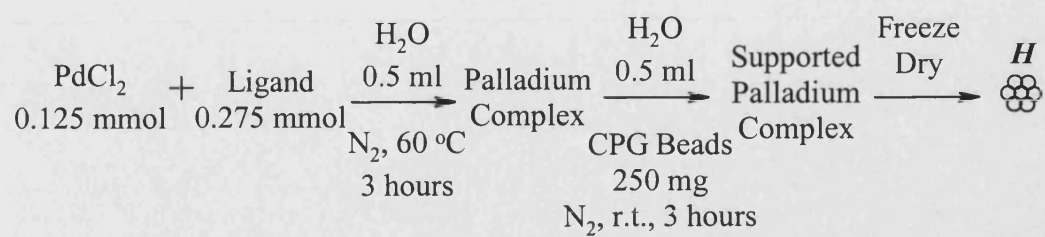
Method F



Method G



Method H



5.1.6 Hydrophilic Nature of Ligand

Each reaction was carried out using palladium (II) chloride (6 mol%), and CPG-350 (250 mg) hydrated with ethylene glycol ($\delta=2$).

To each was added ligand (Na-TPPMS (7); monosodium *mono(m-sulfonato phenyl)diphenylphosphine*, Na-TPPTS (6); trisodium *tris(m-sulfonatophenyl) phosphine*, Li-TPPMS (35); monolithium *mono(o-sulfonatophenyl) diphenylphosphine*, Li-TPPTS (34); or trilithium *tris(o-sulfonatophenyl)phosphine* (14.6 mol%).

PdCl ₂ (mol%) (mol)	Ligand (mol)	Ligand Type	Ethylene Glycol (ml)	Glass Beads (mg)	Bead Type
6 1.13x10 ⁻⁴	2.75x10 ⁻⁴	Na- TPPMS	0.5	250	CPG-350
6 1.13x10 ⁻⁴	2.75x10 ⁻⁴	Na- TPPTS	0.5	250	CPG-350
6 1.13x10 ⁻⁴	2.75x10 ⁻⁴	Li- TPPMS	0.5	250	CPG-350
6 1.13x10 ⁻⁴	1.75x10 ⁻⁴	Li- TPPTS	0.5	250	CPG-350

5.1.7 Catalyst Loading

Reactions using Na-TPPMS (2.5 molar equivalents with respect to catalyst) were performed with varying amounts of palladium (II) chloride (1.5 mol%, 3 mol%, 4.5 mol%, and 6 mol%).

These studies used standard conditions of ethylene glycol ($\delta=2$) upon CPG-350 and Davisil 300 (250 mg). The study was later repeated using the optimum level of pore filling ($\delta=0.1$) with ethylene glycol.

PdCl ₂ (mol%) (mol)	TPPMS (mol)	Ethylene Glycol (ml)	Glass Beads (mg)	Bead Type
1.5 2.82×10^{-5}	7.05×10^{-5}	0.5	250	CPG-350
3 5.64×10^{-5}	1.41×10^{-4}	0.5	250	CPG-350
4.5 8.46×10^{-5}	2.12×10^{-4}	0.5	250	CPG-350
6 1.13×10^{-4}	2.83×10^{-4}	0.5	250	CPG-350
1.5 2.82×10^{-5}	7.05×10^{-5}	0.5	250	Davisil 300
3 5.64×10^{-5}	1.41×10^{-4}	0.5	250	Davisil 300
4.5 8.46×10^{-5}	2.12×10^{-4}	0.5	250	Davisil 300

6		0.5	250	Davisil 300
1.13×10^{-4}	2.83×10^{-4}			
1.5		0.025	250	CPG-350
2.82×10^{-5}	7.05×10^{-5}			
3		0.025	250	CPG-350
5.64×10^{-5}	1.41×10^{-4}			
4.5		0.025	250	CPG-350
8.46×10^{-5}	2.12×10^{-4}			
6		0.025	250	CPG-350
1.13×10^{-4}	2.83×10^{-4}			

5.1.8 Catalyst/Ligand Ratio

Palladium (II) chloride (4.5 mol%) with CPG-350 (250 mg) and ethylene glycol ($\delta=2$) was used in each of these reactions.

The amount of Na-TPPMS added was varied in each case (3.2 molar equivalents with respect to catalyst, 6.5 molar equivalents, and 9.7 molar equivalents).

PdCl ₂ (mol%) (mol)	TPPMS (equiv.) (mol)	Ethylene Glycol (ml)	Glass Beads (mg)	Bead Type
4.5 8.46×10^{-5}	3.2 2.75×10^{-4}	0.5	250	CPG-350
4.5 8.46×10^{-5}	6.5 5.49×10^{-4}	0.5	250	CPG-350
4.5 8.46×10^{-5}	9.7 8.23×10^{-4}	0.5	250	CPG-350

5.1.9 Catalyst Recycling

In this study palladium (II) chloride (4.5 mol%) was used with Na-TPPMS (29.2 mol%), CPG-350 (250 mg) and ethylene glycol ($\delta=2$).

Filtered aliquots (0.3 ml) of reaction supernatant were removed at the initial stages of and after each reaction for palladium level determination. After each reaction the supported catalyst was rinsed with reaction solvent (2x5 ml) and the reactor recharged with substrates. The coupling was repeated three times using the same preparation of catalyst.

5.1.10 Hydrophilic Phase Loading

Prior to these experiments the degree of pore filling, $\delta=2$, had been used in the catalyst preparations. In this study, Na-TPPMS (29.2 mol%) and palladium (II) chloride (4.5 mol%) was used with CPG-350 (250 mg).

The degree of pore filling with hydrophilic phase, ethylene glycol, onto CPG-350 (250 mg, total $V_p=0.25 \text{ cm}^3$, $SA=15.5 \text{ m}^2$) was varied. Calculation of the film thickness was based upon a perfect flat surface area.

Ethylene Glycol Loading (ml = $\times 10^{-6} \text{ m}^3$)	Degree of Pore Filling, δ	Theoretical Thickness of Phase Coating (\AA)
0.01	0.04	6.5
0.02	0.08	13
0.025	0.1	16
0.035	0.14	23
0.05	0.2	32
0.1	0.4	65
0.25	1.0	160
0.5	2.0	320

PdCl ₂ (mol%) (mol)	TPPMS (mol)	Ethylene Glycol (ml)	Glass Beads (mg)	Bead Type
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.01	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.02	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.025	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.035	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.05	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.1	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.25	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.5	250	CPG-350

5.1.11 Different Pore Glasses Characteristics

Using method **G**, palladium (II) chloride (4.5 mol%) with TPPMS (14.6 mol%) was used in each preparation. Into each preparation pore glass (250 mg) was added along with enough ethylene glycol to fill the pore volume, $\delta=1$.

PdCl ₂ (mol%) (mol)	TPPMS (mol)	Ethylene Glycol (ml)	Glass Beads (mg)	Bead Type
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.2	250	CPG-120
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.21	250	CPG-240
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.20	250	CPG-290
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.25	250	CPG-350
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.20	250	CPG-410
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.29	250	CPG-500
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.31	250	CPG-700
4.5 8.46x10 ⁻⁵	2.75x10 ⁻⁴	0.3	250	Davisil 300

5.2 Supported Organic-Phase Catalysis on Reverse-Phase Glass Beads

5.2.1 Materials

Sodium acetate buffer (0.1 M; pH 5.5) was prepared using sodium acetate (99+ %) as purchased from BDH dissolved in water and adjusted with acetic acid (99.8 %) from Aldrich. All operations requiring water were carried out using water (HPLC grade) purchased from Aldrich. Methanol (99.9+ % HPLC grade), octyltrimethoxysilane (96 %), acetone (99.9+ %), cyclohexane (99.9+ % HPLC grade), 4-bromobenzoic acid (98 %), palladium (II) acetate (98 %), potassium carbonate (99 %), ammonium hydrogen phosphate (99 %), acetonitrile (99.93+ % HPLC grade), 2-methyl-2-propen-1-ol (99 %), methyl vinyl ketone (99 %), DMF (99.9+ % HPLC grade), DMA (99.93 % HPLC grade), toluene (99.8 % HPLC grade), butyl ether (99.3 %), dioxane (99.9 % HPLC grade), ethyl acetate (99.98 % HPLC grade), acetonitrile (99.93+ % HPLC grade), ethanol (90 %), THF (99.9 % HPLC grade), butanol (99.8 % HPLC grade), acrylamide (97 %), 2,6-lutidine (99+ %), *tris*(4-fluorophenyl)phosphine (99 %), acrylic acid (99 %), vinyl piperidine and *t*-butyl ammonium hydroxide were used as purchased from Aldrich. *n*-Octadecyl triethoxysilane and 1,2-*bis*(dipentafluorophenylphosphine) ethane were purchased from Lancaster in the purest available form. 1H, 1H, 2H, 2H perfluorooctyl triethoxysilane was purchased from Fluorochem. 2-Phenylethyl trimethoxysilane was used as purchased from Fluka.

5.2.2 Reaction Analysis

Conversion

It was necessary to develop a HPLC method which could be used to follow the progress of the reaction. This was facilitated by an eluant, composed of 0.05 M ammonium hydrogen phosphate and acetonitrile (3:1) adjusted to pH 4.5. As separation was performed upon an Inertsil ODS-2 column ($\lambda=240$ nm) it was necessary to add *t*-butyl ammonium hydroxide as an ion-pair reagent, to create a concentration of 25 mmol, to the eluant. Using a 15 cm column and a flow rate of 1.5 ml/min chromatography time was reduced to 15 minutes.

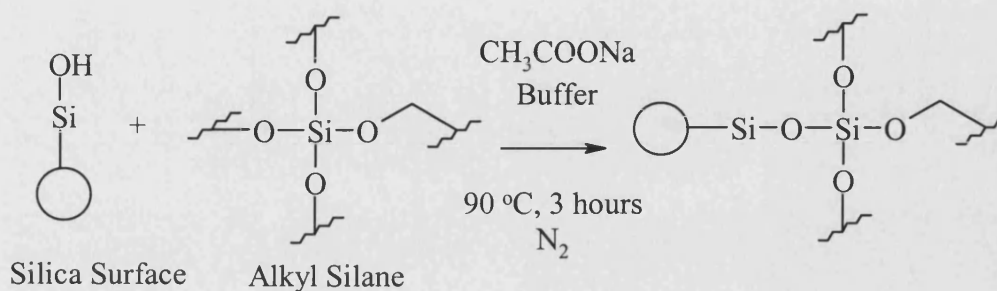
Elemental Analysis

The level of heavy metal leaching from supported and homogeneous catalysts was measured using upon a Varian 100 Liberty ICP spectrophotometer. This was done using water and DMSO as solvents and with the aid of quality control standards.

5.2.3 Preparation of Supported Organic-Phase, SOP, Catalysts

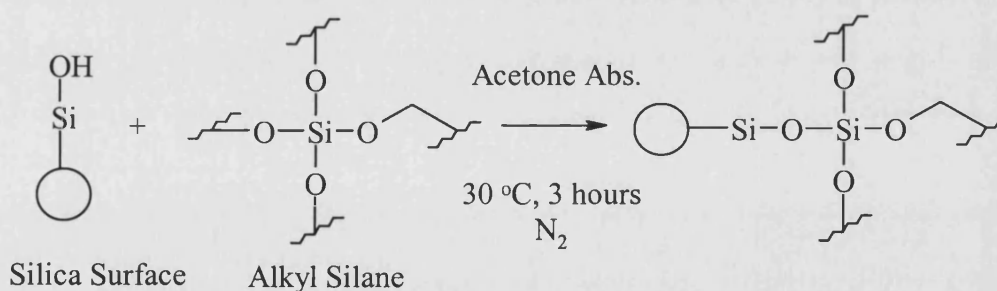
Procedures for Derivatisation of Silica

Method A



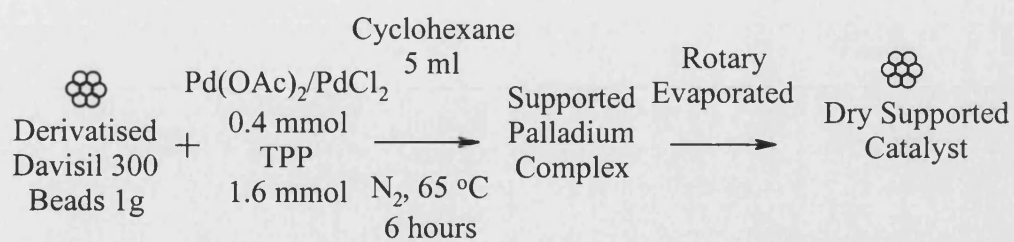
Davisil 300 silica (2 g) in 0.1 M sodium acetate buffer (8 ml), adjusted to pH 5.5, was sonicated under vacuum in a round-bottomed flask to degas. Alkyl silane (0.8 mmol) was then introduced and the mixture stirred, at $90\text{ }^\circ\text{C}$ for 5 hours under nitrogen. The silica was then washed twice with water (2x20 ml), then twice with methanol (2x20 ml), through a fine glass sinter funnel. After washing, the derivatised silica was dried for 12 hours at $70\text{ }^\circ\text{C}$ in a vacuum oven.

Method B



Davisil 300 silica (10 g) was sonicated under vacuum with absolute acetone (50 ml) in a 100 ml round-bottomed flask to degas. Alkyl silane (32 mmol) was then introduced and the mixture stirred at $30\text{ }^\circ\text{C}$ for 3 hours, under nitrogen. The silica was then washed with acetone (20 ml) through a fine glass sinter funnel. After washing, the derivatised silica was dried for 12 hours at $80\text{ }^\circ\text{C}$ in a vacuum oven.

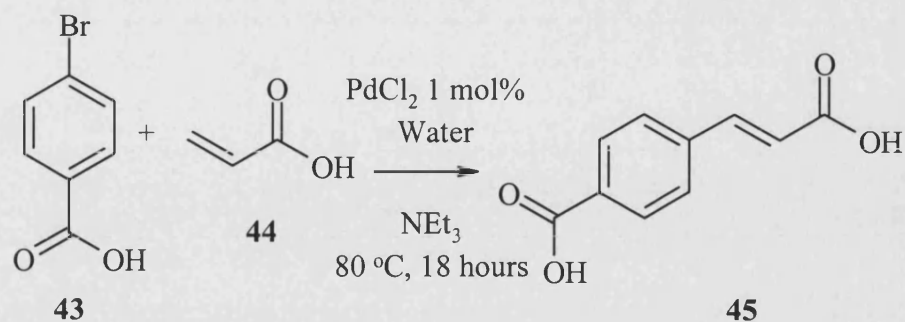
Immobilisation of Catalyst Complex



The supported organic-phase catalysts were prepared by stirring the derivatised beads (1 g) with palladium (II) acetate or palladium (II) chloride (0.4 mmol) and, optionally, triphenylphosphine, TPP, (1.6 mmol) in cyclohexane (5 ml) at 65 °C for 6 hours. This was performed under nitrogen followed by rotary evaporation to give the dried supported catalyst.

5.2.4 Preliminary Studies with Supported Organic-Phase (SOP) Catalysts

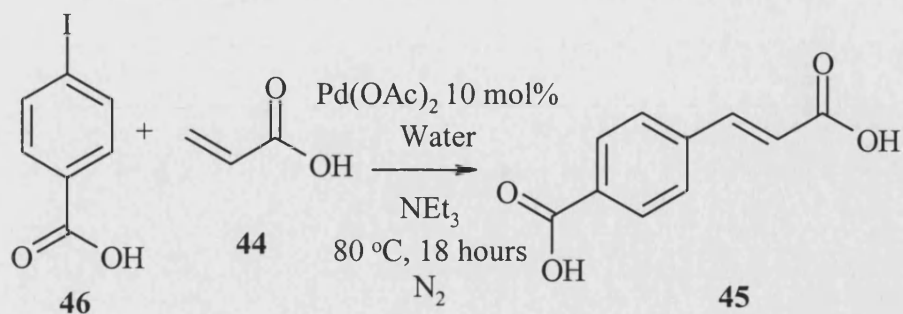
Heck Coupling of 4-Bromobenzoic Acid and Acrylic Acid



Reactions were performed with 4-bromobenzoic acid (**43**) (2 mmol), acrylic acid (**44**) (4 mmol), and triethylamine (6 mmol) catalysed by palladium (II) chloride (1 mol%) under nitrogen.

TPP (mol%)	Reaction Solvent	% Conversion (18 hours)
--	4 ml Water	6
20	4 ml Water	0.5
20	4 ml Ethylene Glycol	18.5

Heck Coupling of 4-Iodobenzoic Acid and Acrylic Acid



Reactions were performed using 4-iodobenzoic acid (**46**) (2 mmol), acrylic acid (**44**) (4 mmol), and triethylamine (6 mmol) catalysed by palladium (II) acetate (10 mol%) in water (4 ml) under nitrogen. Yields in excess of 65 % were obtained after completion. δ_{H} (250 MHz, DMSO-*d*₆) 7.97 (2H, d, *J* 8.1, ArH), 7.80 (2H, d, *J* 8.3, ArH), 7.65 (1H, d, *J* 16.2, HC=C), 6.65 (1H, d, *J* 16.2, C=CH). δ_{C} (62.5 MHz, DMSO-*d*₆) 167.47, 167.00, 142.79, 138.49, 131.99, 129.9, 128.39, 121.72. mp >300 °C. bp 260-262 °C. ν_{max} (CH₂Cl₂)/cm⁻¹ 1688 (C=O).

TPP (mol%)	% Conversion (18 hours)
--	66
20	97

Potassium Carbonate as Base

Reactions were performed with 4-iodobenzoic acid (1 mmol), acrylic acid (1.5 mmol), and potassium carbonate (1.5 mmol) under nitrogen.

Pd(OAc) ₂ (mol%)	TPP (mol%)	Reaction Solvent	% Conversion (18 hours)
10	--	2 ml Water	98
10	40	2 ml Water	25
1	--	10 ml Water	99

Heck Coupling of 4-Iodobenzoic Acid and Acrylic Acid with a SOP Catalyst

Reactions were performed with 4-iodobenzoic acid (1 mmol), acrylic acid (1.5 mmol), and potassium carbonate (1.5 mmol) catalysed by palladium (II) acetate (10 mol%) in water (4 ml) under nitrogen.

Support	TPP (mol%)	Cyclohexane (ml)	Pd Level in Solid (ppm)	% Conversion (18 hours)
Octyltrimethoxysilane (Method A) Davisil 300	40	0.3 $\delta=1$	114.4	99
Homogeneous Control	--	--	293.9	85

The Effect of Triphenylphosphine upon Activity

Reactions were performed with 4-iodobenzoic acid (4 mmol), acrylic acid (6 mmol), and potassium carbonate (6 mmol) catalysed by palladium (II) acetate (2 mol%) in water (8 ml) under nitrogen. In this study, the supported catalysts did not possess a cyclohexane coating.

Support	TPP (mol%)	Pd Level (ppm) Supernatant
Homogeneous Control	--	37.5
Underivatized Davisil 300	--	26.3
Octyltrimethoxysilane (Method A) Davisil 300	--	25.2
Homogeneous Control	8	3.3
Underivatized Davisil 300	8	3.3
Octyltrimethoxysilane (Method A) Davisil 300	8	2.4

5.2.5 Automation

Reactions were adapted for automation using a Gilson 233 Auto-Sampler, Stem Hi Heater/Stirrer Reaction Station and DART Operating System. 4-Iodobenzoic acid substrate and potassium carbonate base were prepared as standard aqueous solutions (based on reactant and solvent quantities as expressed below) which were dosed, along with acrylic acid, directly into reaction tubes containing pre-weighed catalyst. Reactions were monitored, stirring at 80 °C, under a nitrogen blanket, over 2 hours.

5.2.6 Studies into Factors Effecting Level of Leaching from SOP Catalyst Systems

The Effect of Cyclohexane Coating upon Palladium Leaching

Reactions were performed with 4-iodobenzoic acid (4 mmol), acrylic acid (6 mmol), and potassium carbonate (15 mmol) catalysed by palladium (II) acetate (2 mol%) in water (12 ml) under nitrogen.

Support	TPP (mol%)	Cyclohexane (ml)	Pd Level in Solid (ppm)
Homogeneous Control	--	0.2	24.1
As Above	8	0.2	0.74
As Above	--	--	15.8
As Above	8	--	0.3
Underivatised Davisil 300	--	0.2	16.6
As Above	8	0.2	8.7
As Above	--	--	10.9
As Above	8	--	7.3
Octyltrimethoxysilane (Method A) Davisil 300	--	0.2	7.7
As Above	8	0.2	2.9
As Above	--	--	6.0
As Above	8	--	0.4
2-Phenylethyltrimethoxysilane (Method A) Davisil 300		0.2	1.5

As Above	8	0.2	0.7
As Above	--	--	0.7
As Above	8	--	0.5

The Effect of Type of Derivatisation on Level of Palladium Leaching

Studies were performed, in the absence of substrates, using palladium (II) acetate (2 mol%) in water (12 ml) under nitrogen.

Support	TPP (mol%)	Cyclohexane (ml)	Pd Level in Solid (ppm)
Underivatised Davisil 300	--	0.2	4.31
As Above	8	0.2	2.92
As Above	--	--	3.06
As Above	8	--	2.48
Octyltrimethoxysilane (Method <i>A</i>) Davisil 300	--	0.2	0.82
As Above	8	0.2	0.14
As Above	--	--	2.46
As Above	8	--	0.04
Octyltrimethoxysilane (Method <i>B</i>) Davisil 300	--	0.2	15.16
As Above	8	0.2	0.14
As Above	--	--	10.62

As Above	8	--	0.65
2-Phenylethyltrimethoxysilane (Method <i>A</i>) Davisil 300	--	0.2	1.46
As Above	8	0.2	0.67
As Above	--	--	0.68
As Above	8	--	0.51
<i>n</i> -Octadecyltrimethoxysilane (Method <i>B</i>) Davisil 300	--	0.2	0.99
As Above	8	0.2	0.08
As Above	--	--	0.35
As Above	8	--	0.07

**The Method of Silica Derivatisation and its Effect upon Level of
Palladium Leaching**

Reactions were performed using 4-iodobenzoic acid (4 mmol), acrylic acid (6 mmol), and potassium carbonate (15 mmol) catalysed by palladium (II) acetate (2 mol%) in water (12 ml) under nitrogen.

Support	Pd(OAc) ₂ (mol%)	TPP/Ligand (mol%)	Pd Level in Solid (ppm)
Underivatised Davisil 300	2	8	8.47
Octyltrimethoxysilane (Method <i>A</i>) Davisil 300	2	8	0.4
Octyltrimethoxysilane (Method <i>B</i>) Davisil 300	2	8	0.16
2-Phenylethyltrimethoxysilane (Method <i>A</i>) Davisil 300	2	8	0.5
<i>n</i> -Octadecyltriethoxysilane (Method <i>B</i>) Davisil 300	2	8	0.6
1H, 1H, 2H, 2H Perfluorooctyltriethoxysilane (Method <i>B</i>) Davisil 300	2	8 mol% 1,2- <i>bis</i> (dipenta fluorophenyl phosphine)ethane	106
1H, 1H, 2H, 2H Perfluorooctyltriethoxysilane (Method <i>B</i>) Davisil 300	2	8 mol% <i>tris</i> (4-fluoro phenyl)phosphine	8.03

The Effect of Solvent upon Palladium Leaching

Studies were performed with palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) upon (octyltrimethoxysilane Method *A* derivatised) Davisil 300 coated with cyclohexane ($\delta=1$) in 12 ml of solvent under nitrogen.

Solvent	Pd Level in Supernatant (ppm)
DMF	146.4
DMA	316.8
Toluene	67.2
Butyl Ether	287.5
Dioxane	135.5
Water	4.8
Ethyl Acetate	127.7
Acetonitrile	178.2
Methanol	9.3
Ethanol	12.8
THF	157.3
Ethylene Glycol	9.8
Butanol	25.8

Screening of solvents for compatibility with SOP catalyst was carried out in the presence of palladium (II) acetate (2 mol%) and cyclohexane ($\delta=1$) under nitrogen.

Support	TPP (mol%)	Solvent (12 ml)	Pd Level in Solid (ppm)
Underivatized Davisil 300	--	Ethylene Glycol	14.05
As Above	--	Water	9.56
As Above	--	Ethanol	26.13
As Above	--	Methanol	64.95
As Above	--	Butanol	23.20
As Above	--	Toluene	7.96
Underivatized Davisil 300	8	Ethylene Glycol	79.87
As Above	8	Water	3.31
As Above	8	Ethanol	81.16
As Above	8	Methanol	39.27
As Above	8	Butanol	1.54
As Above	8	Toluene	25.37
Octyltrimethoxysilane (Method A) Davisil 300	--	Ethylene Glycol	12.45
As Above	--	Water	4.54
As Above	--	Ethanol	1.08
As Above	--	Methanol	47.38
As Above	--	Butanol	25.8

As Above	--	Toluene	35.3
Octyltrimethoxysilane (Method <i>A</i>) Davisil 300	8	Ethylene Glycol	23.01
As Above	8	Water	2.99
As Above	8	Ethanol	7.02
As Above	8	Methanol	2.36
As Above	8	Butanol	4.05
As Above	8	Toluene	209.4
Octyltrimethoxysilane (Method <i>B</i>) Davisil 300	8	Ethylene Glycol	75.15
As Above	8	Water	2.45
As Above	8	Ethanol	3.58
As Above	8	Methanol	6.14
As Above	8	Butanol	6.15
As Above	8	Toluene	390.30
<i>n</i> -Octadecyltriethoxysilane (Method <i>B</i>) Davisil 300	--	Ethylene Glycol	--
As Above	--	Water	11.71
As Above	--	Ethanol	3.0
As Above	--	Methanol	2.77
As Above	--	Butanol	8.04
As Above	--	Toluene	125.50
<i>n</i> -Octadecyltriethoxysilane (Method <i>B</i>) Davisil 300	8	Ethylene Glycol	--
As Above	8	Water	6.32

As Above	8	Ethanol	12.71
As Above	8	Methanol	1.51
As Above	8	Butanol	7.18
As Above	8	Toluene	287.2

5.2.7 Prep-Scale Reaction with Supported Organic-Phase Catalyst

4-Iodobenzoic acid (20.0 mmol) was added to acrylic acid (30.0 mmol) in water (60 ml) with potassium carbonate (75 mmol) in a 100 ml round-bottomed flask fitted with reflux condenser. The mixture was stirred in the presence of supported organic-phase catalyst (octyltrimethoxysilane derivatised Davisil 300), equivalent to triphenylphosphine (8 mol%) and palladium (II) acetate (2 mol%), under an atmosphere of nitrogen at 100 °C for 2 hours.

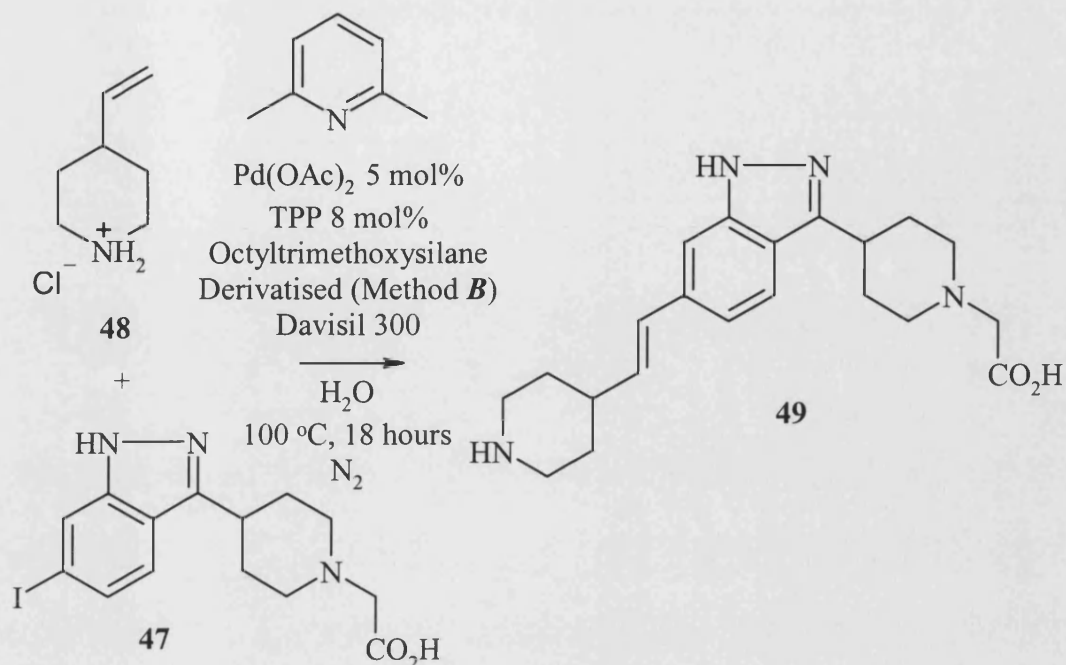
5.2.8 The Re-Use of Supported Organic-Phase Catalysts

Reactions were performed with 4-iodobenzoic acid (4 mmol), acrylic acid (6 mmol), and potassium carbonate (15 mmol) catalysed by palladium (II) acetate (2 mol%), triphenylphosphine (8 mol%) with a cyclohexane coating ($\delta=1$) in water (12 ml) under nitrogen. The supported catalysts were filtered off after each reaction, rinsed with water (2x10ml) and immediately re-used.

Reaction	Pd Level Supernatant (ppm)	Pd Level Supernatant (ppm)
	Octyltrimethoxysilane (Method A) Davisil 300	Underivatised Davisil 300
1	3.972	9.234
2	0.4414	8.533
3	0.0351	2.316
4	0.0322	3.155
5	0.0140	2.127
6	0.0	0.5112
7	0.0	0.927

5.2.9 Application of the SOP System of Catalysis

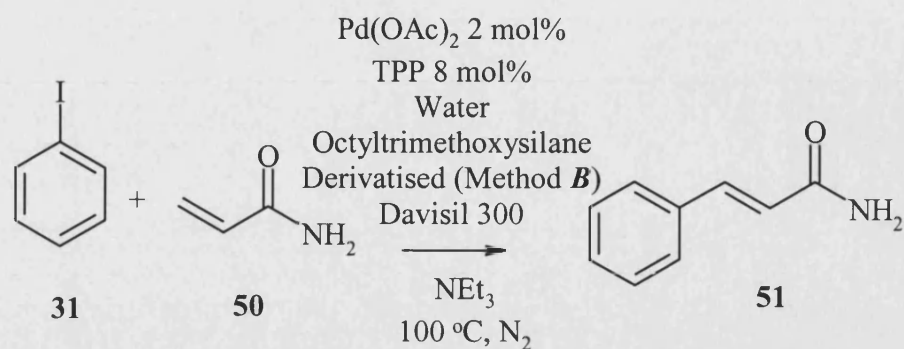
Coupling of Vinyl Piperidine and GW292715A (Iodoindazole)



GW292715A (**47**) (0.47 mmol) was added to vinyl piperidine (**48**) (1.175 mmol) in the presence of a supported organic-phase catalyst consisting of octyltrimethoxysilane derivatised (method **B**) Davisil 300, supporting palladium (II) acetate (equivalent to 5 mol%) and triphenylphosphine (8 mol%).

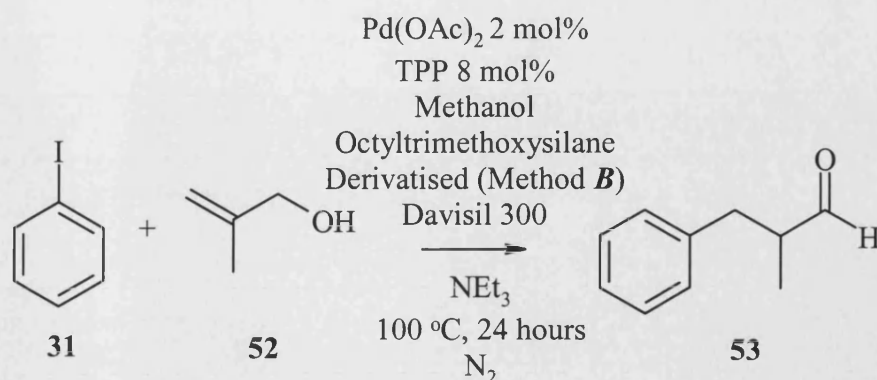
The reaction was performed with triethylamine base (2.82 mmol) in water (2 ml) stirring under nitrogen at 100 °C for 18 hours. The reaction was monitored by TLC at 2, 4, 6, 12, and 18 hours for the presence of iodobenzene starting material. After completion, the mixture was cooled, filtered through a glass sinter and washed with water (2x50 ml). Solvent was removed *in vacuo* to leave a light brown solid analysed by HPLC and ICP (GR233548X, purity 12.43 %). Palladium level in the solid was measured at 234.2 ppm (high). Nominal yield for the reaction is 37 %. Details of the analytical methodology are held at GlaxoWellcome MRC, Stevenage.

Heck Coupling of Iodobenzene and Acrylamide



Iodobenzene (**31**) (6.5 mmol) was added to acrylamide (**50**) (17.4 mmol) and triethylamine (8.1 mmol) in 5 ml water. This was performed in the presence of a supported organic-phase catalyst composing octyltrimethoxysilane derivatised (method *B*) Davisil 300, with palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) at 100 °C under nitrogen.

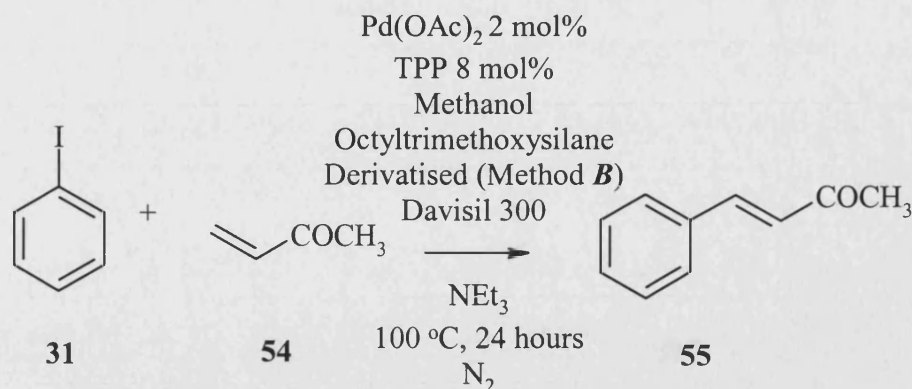
Heck Coupling of Iodobenzene and 2-Methyl-2-propen-1-ol



Iodobenzene (**31**) (6.455 mmol) was added to 2-methyl-2-propen-1-ol (**52**) (8.05 mmol) in the presence of a supported organic-phase catalyst composing octyltrimethoxysilane derivatised Davisil 300 (method **B**), supporting palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) under nitrogen.

The mixture was stirred in 5 ml methanol in the presence of triethylamine (8.05 mmol) at 100 °C for 24 hours. The reaction was monitored by TLC. Water and triethylamine impurities after reaction were separated by washing with ethyl acetate (2x40 ml) and 2N HCl (2x10 ml). The organic phase was then washed with brine (20 ml) and dried over magnesium sulfate. A crude yield of 61 % of 2-methyl-3-phenylpropanal (**53**) was obtained. The palladium level in reaction supernatant was very high (1011 ppm) but was reduced, by stirring with derivatised Davisil 300 (0.5 g in 5 ml methanol), to 59.7 ppm. δ_{H} (250 MHz, CDCl₃) 9.70 (1H, d, CHO), 7.20 (5H, m, ArH), 3.10 (1H, br m, CHCHO), 2.9 (2H, m, PhCH₂), 1.15 (3H, d, CH₃CHCHO). mp 120-123 °C. ν_{max} (neat)/cm⁻¹ 3020, 2950, 2700, 1715, 1600, 1490, 1445, 920, 740, 700.

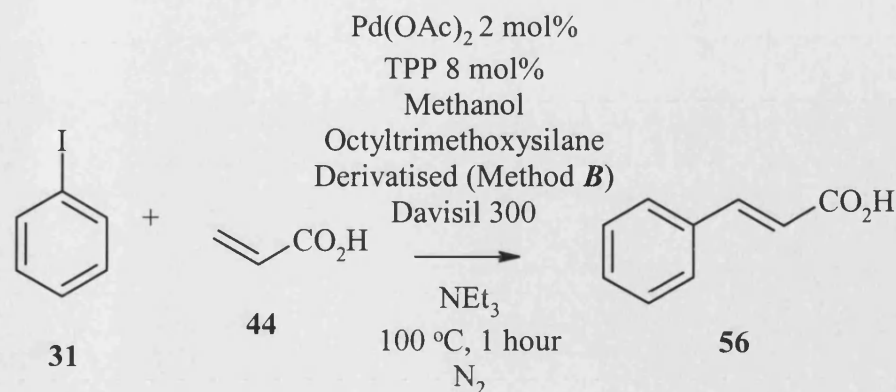
Heck Coupling of Iodobenzene and Methyl Vinyl Ketone



Iodobenzene (**31**) (6.455 mmol) was added to methyl vinyl ketone (**54**) (8.05 mmol) with a supported organic-phase catalyst composing octyltrimethoxysilane derivatised Davisil 300 (method **B**), supporting palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) under nitrogen.

The mixture was stirred in 5 ml methanol in the presence of triethylamine (9.185 mmol) at 100 °C for 24 hours. The reaction was monitored by TLC. Water and triethylamine impurities were removed after reaction by washing with ethyl acetate (2x40 ml), then 2N HCl (2x10 ml) and separating. The organic phase was washed with brine (20 ml) and dried over magnesium sulfate. A crude yield of 70 % of *trans*-4-phenyl-3-buten-2-one (**55**) was obtained. The palladium level in the reaction supernatant was very high (301 ppm) but was reduced by stirring with derivatised Davisil 300 (0.5 g in 5 ml methanol) to 23.7 ppm. δ_{H} (250 MHz, CDCl₃) 7.4 (5H, m, ArH), 7.20 (1H, d, *J* 16, =CHCO), 6.62 (1H, d, *J* 16, PhCH=), 2.32 (3H, s, CH₃). δ_{C} (60 MHz, CDCl₃) 198.46, 143.42, 133.69, 130.55, 128.85, 128.26, 127.60, 27.50. mp 32-34 °C.

Heck Coupling of Iodobenzene and Acrylic Acid



Iodobenzene (**31**) (4.0 mmol) was added to acrylic acid (**44**) (6.0 mmol) along with a supported organic-phase catalyst composing octyltrimethoxysilane derivatised Davisil 300 (method **B**) supporting palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) under nitrogen.

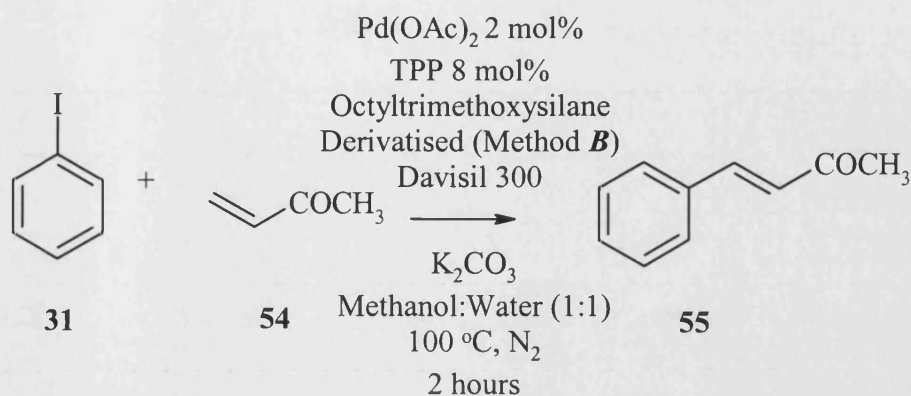
The mixture was stirred in 12 ml methanol in the presence of triethylamine (6.0 mmol) at 100 °C for 1 hour. The reaction was monitored by TLC. There was no indication of the iodobenzene starting material after 1 hour. The reaction mixture was filtered through a glass sinter and dried *in vacuo* (64 % yield). The palladium level in the supernatant was recorded, 176 ppm (high). δ_{H} (250 MHz, CDCl₃) 12.67 (1H, br s, CO₂H), 7.83 (2H, m, ArH), 7.63 (1H, d, *J* 15.8, =CH), 7.44 (1H, t, *J* 7.7, ArH), 7.16 (1H, dt, *J* 7.7, 1.5, ArH), 6.42 (1H, d, *J* 15.8, CH=). mp 130-132 °C.

5.3 Further Applications of SOP and SAP Catalyst Systems

5.3.1 Materials

Triethanolamine (99 %), ruthenium AAS standard solution (1000 $\mu\text{g ml}^{-1}$ in 5 wt% HCl), potassium diphenylphosphide (99.8 %), sodium hydride (60 % oil suspension, washed with hexanes), acetophenone (99 %), 1-acetonaphthone (99 %), *o*-flourobenzonitrile (99 %), DMF-dimethyl acetal (99 %), acetic anhydride (99.8 %), 2-bromo-6-nitrotoluene (98 %), potassium metal, zinc dust, and pyrrolidine (99.9 %) were purchased from Aldrich Limited. Tosyl chloride, sodium methoxide, sodium *t*-butoxide, dimethyl sodium malonate, and zinc chloride were purchased from Acros Limited in their purest available form. $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, cerium (III) chloride heptahydrate, *trans*-chalcone, DMAP, $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$, $[\text{RuCl}_2(\text{PPh}_3)_3]$, sodium borohydride, and valinol were donated from various collaborations with the pharmaceutical industry.

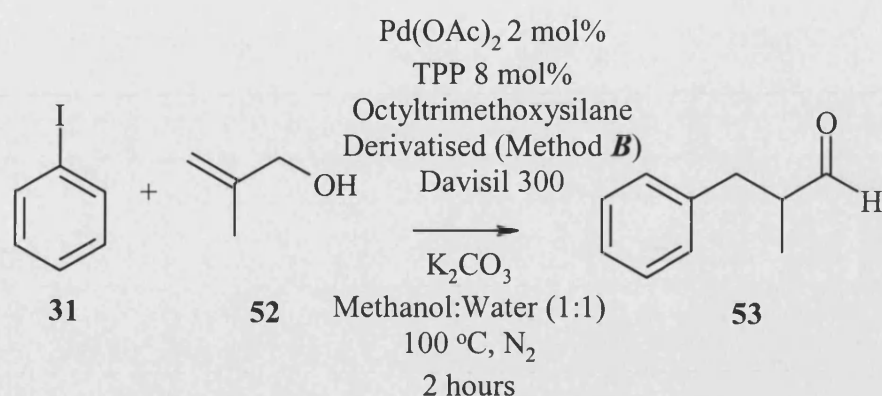
5.3.2 Heck Coupling of Iodobenzene with Methyl Vinyl Ketone



The coupling of iodobenzene (**31**) (6.5 mmol) with methyl vinyl ketone (**54**) (9.2 mmol) was carried out in the presence of palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) upon octyltrimethoxysilane derivatised Davisil 300 (method *B*) under nitrogen.

The reaction was performed using potassium carbonate (8 mmol) in the place of triethylamine. The solvent composition of the system was modified to methanol: water (5 ml, 1:1) allowing dissolution of the potassium carbonate. Monitoring by TLC, the reaction was judged to be complete after 2 hours and gave a 97 % crude yield of the desired product. The level of palladium leaching was reduced from 301 ppm to 16 ppm by the absence of triethylamine. δ_{H} (250 MHz, CDCl_3) 7.4 (5H, m, ArH), 7.20 (1H, d, J 16, =CHCO), 6.62 (1H, d, J 16, PhCH=), 2.32 (3H, s, CH₃). δ_{C} (60 MHz, CDCl_3) 198.46, 143.42, 133.69, 130.55, 128.85, 128.26, 127.60, 27.50. mp 32-34 °C.

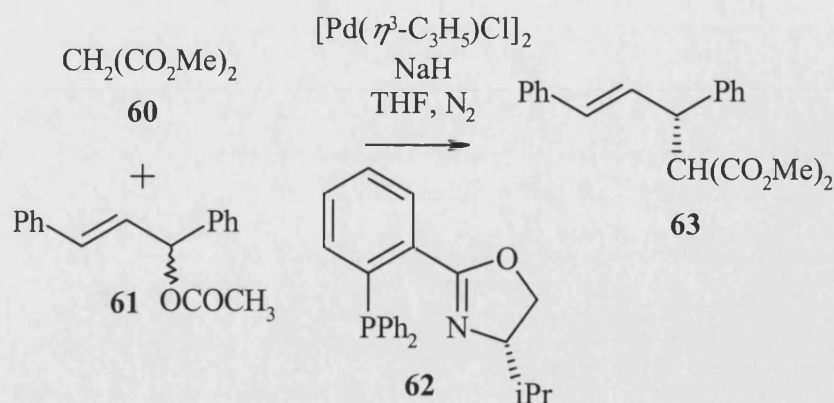
5.3.3 Heck Coupling of Iodobenzene with 2-Methyl-2-propen-1-ol



The coupling of iodobenzene (**31**) (6.5 mmol) with 2-methyl-2-propen-1-ol (**52**) (8.1 mmol) was carried out using palladium (II) acetate (2 mol%) and triphenylphosphine (8 mol%) upon octyltrimethoxysilane derivatised Davisil 300 (method **B**) under nitrogen.

The reaction was performed in the presence of potassium carbonate (8 mmol) in methanol: water (5 ml, 1:1). The coupling was judged to be complete in 2 hours by monitoring with TLC and gave a 71 % crude yield of the aldehyde (**53**). The level of palladium leaching was reduced from 1011 ppm to 20 ppm by the absence of triethylamine. δ_{H} (250 MHz, CDCl₃) 9.70 (1H, d, CHO), 7.20 (5H, m, ArH), 3.10 (1H, br m, CHCHO), 2.9 (2H, m, PhCH₂), 1.15 (3H, d, CH₃CHCHO). mp 120-123 °C. ν_{max} (neat)/cm⁻¹ 3020, 2950, 2700, 1715, 1600, 1490, 1445, 920, 740, 700.

5.3.4 Allylic Substitution with Supported Organic-Phase Catalyst



Allylic acetate (**61**) (0.4 mmol) along with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (2.5 mol%), oxazoline ligand (**62**) (10 mol%), and optionally octyltrimethoxysilane derivatised (Method **B**) Davisil 300, were dissolved in dry THF (1 ml) and stirred for 15 minutes at room temperature under a nitrogen pressure. A solution of dimethyl malonate (0.5 mmol) and sodium hydride (0.6 mmol) in THF (3 ml) which had been stirred together for 5 minutes was injected into the round-bottomed flask containing the acetate solution.

The reaction mixture was then stirred at room temperature until TLC analysis (light petroleum:ether 3:1) indicated that no starting material remained (30 hours). A 0.5 ml sample was removed for AAS analysis for level of palladium present. The remaining reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (2x20 ml) and extracted with dichloromethane (2x20 ml). The combined organic layers were then dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a straw coloured oil. Purification by flash column chromatography (eluant, light petroleum: ether 5:1) gave dimethyl (1,3-diphenylprop-2-enyl) malonate (**63**) as a pale yellow solid (yields >50 %). δ_{H} (250 MHz, CDCl_3) 7.44-7.15 (10H, m ArH), 6.48 (1H, d, J 15, PhCH=CH), 6.32 (1H, dd, J 15, 8, HC=CHPh), 4.27 (1H, dd, J 11, 8, PhCH), 3.95 (1H, d, J 11, CHCO₂CH₃), 3.70 (3H, s, CO₂CH₃), 3.53 (3H, s, CO₂CH₃). δ_{C} (62.5MHz, CDCl_3) 168.1 (C=O),

167.7 ($\underline{\text{C}}\text{O}$), 140.1 ($\text{Ar}\underline{\text{C}}$), 136.8 ($\text{Ar}\underline{\text{C}}$), 131.8 ($\text{HC}=\underline{\text{C}}\text{Ar}$), 129.1 ($\text{Ar}\underline{\text{C}}\text{H}$), 128.7 ($\text{Ar}\underline{\text{C}}\text{H}$), 128.4 ($\text{Ar}\underline{\text{C}}\text{H}$), 127.8 ($\text{Ar}\underline{\text{C}}\text{H}$), 127.5 ($\text{Ar}\underline{\text{C}}\text{H}$), 127.1 ($\text{Ar}\underline{\text{C}}\text{H}$), 126.3 ($\text{Ar}\underline{\text{C}}\text{H}$), 57.6 ($\underline{\text{C}}\text{H}(\text{CO}_2\text{Me})_2$), 52.6 ($\underline{\text{C}}\text{H}_3\text{CO}_2$), 52.4 ($\underline{\text{C}}\text{H}_3\text{CO}_2$), 49.1 ($\underline{\text{C}}\text{HPh}$).

Adapting the reaction for supported organic-phase catalysis, a decrease in the level of palladium leaching from 5.9 ppm to 0 ppm was observed when the reaction was performed in the presence of the octyltrimethoxysilane derivatised (method **B**) Davisil 300.

$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (mol%) (mol)	Oxazoline Ligand 62 (mol%) (mol)	Solvent	Octyltrimethoxysilane Derivatised (Method B) Davisil 300 (mg)	Pd Level (ppm)
2.5 1.0×10^{-5}	10 4×10^{-5}	THF	--	5.9
2.5 1.0×10^{-5}	10 4×10^{-5}	THF	100	0

The Effect of Solvents on Palladium Leaching in Allylic Substitution Reaction

Reactions were carried out by the addition of the allylic acetate (**61**) (0.4 mmol) along with $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (2.5 mol%), oxazoline ligand (**62**) (10 mol%), and optionally octyltrimethoxysilane derivatised (Method **B**) Davisil 300, to the reaction solvent (1 ml).

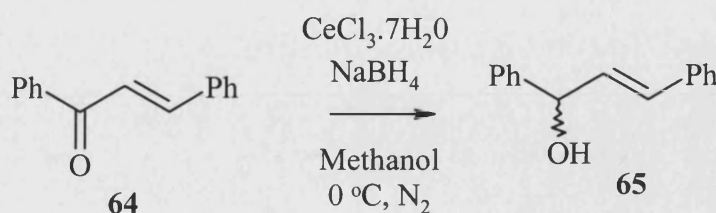
The mixture was stirred for 15 minutes at room temperature under a nitrogen pressure. A solution of dimethyl malonate (0.5 mmol) and sodium hydride (0.6 mmol) in THF (3 ml) which had been stirred together for 5 minutes was injected into the round-bottomed flask containing the acetate solution. The reaction was then allowed to continue at room temperature until TLC analysis indicated that no starting material remained.

Enantiomeric excesses was ascertained by HPLC on a Chiracel OD column (hexane:propan-2-ol 99:1, 1 ml min⁻¹, 254 nm, R_T 9.6 and 10.3 minutes).

$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (mol%) (mol)	Oxazoline Ligand 62 (mol%) (mol)	Solvent (D.C.)	Octyltrimethoxysilane Derivatised (Method B) Davisil 300 (mg)	Pd Level (ppm)	% e.e.
2.5 1.0x10 ⁻⁵	10 4x10 ⁻⁵	Dioxane 2.21	--	28.0	81
2.5 1.0x10 ⁻⁵	10 4x10 ⁻⁵	Dioxane 2.21	200	11.4	85
2.5 1.0x10 ⁻⁵	10 4x10 ⁻⁵	Diethyl Ether 4.3	--	4.8	86

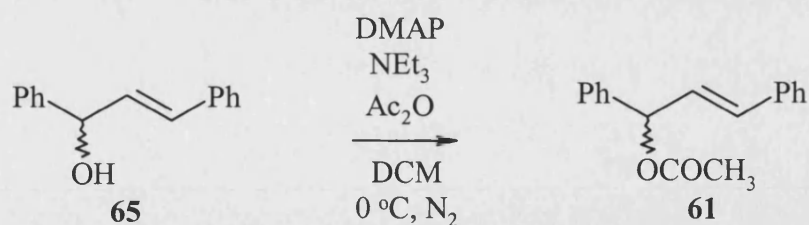
2.5	10	Diethyl	200	1.6	92
1.0x10 ⁻⁵	4x10 ⁻⁵	Ether 4.3			
2.5	10	THF 7.6	--	5.9	91
1.0x10 ⁻⁵	4x10 ⁻⁵				
2.5	10	THF 7.6	200	0	92
1.0x10 ⁻⁵	4x10 ⁻⁵				
2.5	10	Acetone	--	15.5	92
1.0x10 ⁻⁵	4x10 ⁻⁵	20.7			
2.5	10	Acetone	200	9.2	94
1.0x10 ⁻⁵	4x10 ⁻⁵	20.7			
2.5	10	Aceto-	--	7.0	86
1.0x10 ⁻⁵	4x10 ⁻⁵	nitrile 35.7			
2.5	10	Aceto-	200	6.8	95
1.0x10 ⁻⁵	4x10 ⁻⁵	nitrile 35.7			
2.5	10	DMF	--	82	94
1.0x10 ⁻⁵	4x10 ⁻⁵	37.6			
2.5	10	DMF	200	63	94
1.0x10 ⁻⁵	4x10 ⁻⁵	37.6			
2.5	10	DMSO	--	300	95
1.0x10 ⁻⁵	4x10 ⁻⁵	46.2			
2.5	10	DMSO	200	5.4	95
1.0x10 ⁻⁵	4x10 ⁻⁵	46.2			

Preparation of Rac-(*E*)-1,3-diphenyl-3-acetoxy-1-propene



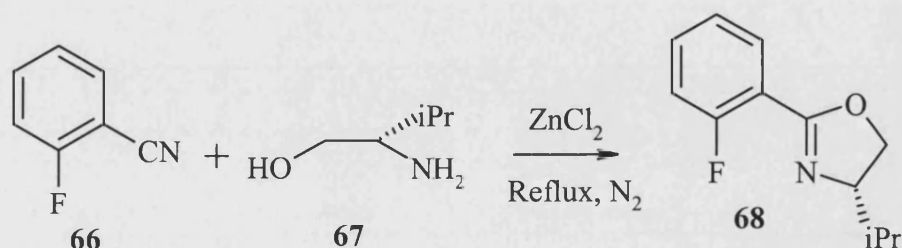
Cerium (III) chloride heptahydrate (48 mmol) and *trans*-chalcone (**64**) (47.9 mmol) were dissolved in methanol (100 ml) and stirred at 0 °C under nitrogen in a three-necked round-bottomed flask. NaBH₄ (57.5 mmol) was added portion-wise whilst maintaining the internal reaction temperature below 20 °C. The reaction mixture was then stirred for a further hour and allowed to gradually warm to room temperature.

The reaction was monitored by TLC (light petroleum:ether, 4:1) for the presence of starting material. The mixture was then diluted with water (50 ml) and extracted with ethyl acetate (3x50 ml). The organic layers were combined, dried over magnesium sulfate and filtered. Solvent was removed *in vacuo* to leave a cream white solid. Purification by flash chromatography (eluant, light petroleum:ether, 4:1) gave (*E*)-1,3-diphenylprop-2-en-1-ol (**65**) (87 % yield). δ_{H} (250 MHz, CDCl₃) 7.58-7.17 (10H, m ArH), 6.64 (1H, d, *J* 15.8, PhCH=CH), 6.32 (1H, dd, *J* 15.8, 6.4, CH=CHPh), 5.31 (1H, d, *J* 6.4, CHPh), 2.46 (1H, br s, OH). δ_{C} (62.5MHz, CDCl₃) 143.5 (ArC), 136.7 (ArC), 131.5 (CH=CH), 130.5 (CH=CH), 128.6 (ArCH), 128.5 (ArCH), 127.8 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 126.4 (ArCH), 75.1 (CHPh). mp 76-78 °C.



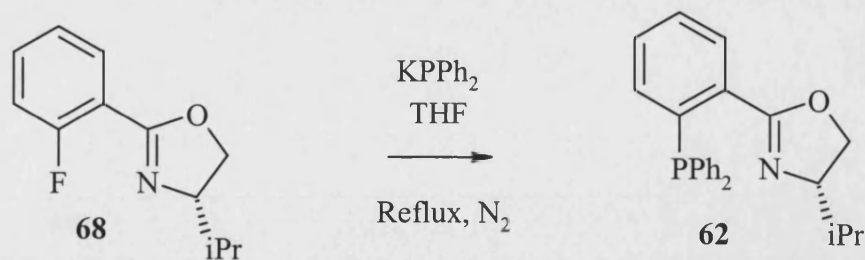
The alcohol (**65**) (15.76 mmol) and triethylamine (23.7 mmol) were dissolved in dichloromethane (30 ml) along with DMAP (0.32 mmol) and stirred at 0 °C under nitrogen. Acetic anhydride (17.34 mmol) was then added drop-wise over a 45 minute period. After addition was complete, the reaction was warmed to room temperature. TLC analysis indicated that starting material had been consumed after 2 hours (light petroleum:ether 4:1). The reaction was washed with 2 M sodium hydroxide solution (40 ml), to give a basic solution, and water (20 ml). The organic layer was then dried over magnesium sulfate, filtered and concentrated *in vacuo* to yield a pale yellow oil, (*E*)-1,3-diphenylprop-2-enyl acetate (**61**) (98% yield). δ_{H} (250 MHz, CDCl_3) 7.42-7.20 (10H, m ArH), 6.63 (1H, d, J 15, $\text{PhCH}=\text{CH}$), 6.42 (1H, dd, J 15, 6.5, $\text{CH}=\text{CHPh}$), 6.33 (1H, d, J 6.9, CHOCOCH_3), 2.12 (3H, s, OCOCH_3). δ_{C} (62.5MHz, CDCl_3) 169.9 ($\text{C}=\text{O}$), 139.2 (ArC), 136.1 (ArC), 132.5 ($\text{CH}=\text{CH}$), 128.6 ($\text{CH}=\text{CH}$), 128.5 (ArCH), 128.1 (ArCH), 128.0 (ArCH), 127.5 (ArCH), 127.0 (ArCH), 126.7 (ArCH), 76.1 (CHPh), 21.3 (OCOCH_3).

Preparation of iPr Oxazoline Ligand



The asymmetric ligand was prepared as reported in the literature.^{102,103}

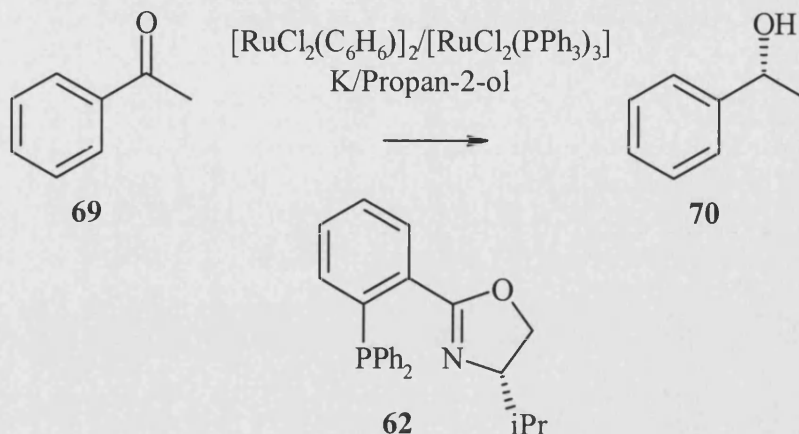
Zinc chloride (1.65 mmol), charged into a schlenk flask, was melted under a high vacuum and cooled under nitrogen for several cycles. After cooling to room temperature, *o*-fluorobenzonitrile (**66**) (33.0 mmol) was syringed into the flask followed by valinol (**67**) (42.9 mmol). The mixture was then refluxed under nitrogen for 48 hours. The reaction mixture was diluted with dichloromethane (100 ml) and washed with water (3x100 ml). The aqueous extracts were washed with dichloromethane (3x50 ml). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a pale brown oil. Purification by flash column chromatography (eluant, light petroleum: ether 5:1) gave the (4*S*)-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazoline (**68**) as a pale yellow solid (yield 48 %). δ_{H} (250 MHz, CDCl₃) 7.09-7.88 (4H, m, ArCH), 4.38 (1H, m, CHN), 4.14 (2H, m, CH₂O), 1.89 (1H, m, CH(CH₃)₂), 1.01 (3H, d, *J* 6.9, CHCH₃), 0.91 (3H, d, *J* 6.9, CHCH₃). δ_{C} (62.5MHz, CDCl₃) 163.0 (C=N), 132.0 (ArCH), 131.0 (ArCH), 123.7 (ArCH), 116.7 (ArCH), 116.3 (ArCH), 71.3 (CH₂O), 69.0 (CHN), 31.0 (CH(CH₃)₂), 17.4 (CH₃), 16.6 (CH₃). *m/z* (EI) 207.1058 (M⁺). ν_{max} (CH₂Cl₃)/cm⁻¹ 1651. $[\alpha]_{\text{D}}^{25}$ -62 (c=0.5, CHCl₃).



Potassium diphenylphosphide (20 mmol) as a solution in tetrahydrofuran (0.5 M) was added via syringe to a dried schlenk flask and heated under reflux for 30 minutes. The fluoro-oxazoline (**68**) (20 mmol) was then added as a solution in tetrahydrofuran (25 ml), and the mixture refluxed for 3 hours under a nitrogen atmosphere. The reaction mixture was diluted with dichloromethane (100 ml) and washed with water (100 ml). The organic phase was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a pale yellow oil. Purification by flash column chromatography (eluant, light petroleum: ether 5:1) gave the (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline (**62**) as a pale white solid (yield 74 %). δ_{H} (250 MHz, CDCl_3) 7.92 (1H, m, ArCH), 7.20-7.70 (12H, m, ArCH), 6.89 (1H, m, ArCH), 4.10 (1H, m, CHN), 3.80 (2H, m, CHN and CH_2O), 1.52 (1H, m, $\text{CH}(\text{CH}_3)_2$), 0.80 (3H, d, J 6.9, CH_3), 0.69 (3H, d, J 6.7, CH_3). δ_{C} (62.5MHz, CDCl_3) 162.9.0 ($\text{C}=\text{N}$), 127.9-138.1 (ArCH), 72.9 (CHN), 69.7 (CH_2O), 32.7 ($\text{CH}(\text{CH}_3)_2$), 18.7 (CH_3), 18.2 (CH_3). m/z (EI) 373.1597 (M^+). ν_{max} (CH_2Cl_2)/ cm^{-1} 1651. $[\alpha]_{\text{D}}^{25}$ -40 ($c=0.5$, CHCl_3). mp 84-86 °C.

5.3.5 Ruthenium Catalysed Transfer Hydrogenation

Ru Catalysed Transfer Hydrogenation of Acetophenone



An isopropoxide ion solution of 1 M concentration was prepared by slowly adding potassium metal (100 mmol) to propan-2-ol (100 ml).

The catalyst complexes were prepared by refluxing [RuCl₂(C₆H₆)₂] or [RuCl₂(PPh₃)₃] with the oxazoline ligand (62) in a round-bottomed flask with propan-2-ol (2 ml) for 1 hour under nitrogen. To the flasks were added acetophenone (69) (2.9 mmol) and isopropoxide solution (3 ml). Reactions were carried out under nitrogen and monitored by TLC (light petroleum:ethyl acetate 9:1). The reactions were quenched with 2N hydrochloric acid (2 ml), washed with water (50 ml) followed by saturated sodium sodium carbonate solution (100 ml), brine (100 ml) and then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Enantiomeric excess was ascertained by HPLC on a Chiracel OD column (hexane:propan-2-ol 99:1, 1 ml min⁻¹, 254 nm, R_T 25 and 32 minutes). δ_H (250 MHz, CDCl₃) 7.25-7.37 (5H, m, ArH), 4.88 (1H, m, CHOH), 2.02 (1H, s, OH), 1.48 (3H, d, J 6.6, CH₃). δ_C (100MHz, CDCl₃) 146.02, 128.70, 127.67, 125.59, 70.61, 25.35. [α]_D²⁵ +45.9 (c=0.5, CH₂Cl₂).

Initial reactions were carried out using catalyst complexes prepared by refluxing $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ (0.037 mmol) or $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.074 mmol) with oxazoline ligand (**62**) (0.088 mmol) in a round-bottomed flask with propan-2-ol (2 ml) for 1 hour under nitrogen. To the flasks were added acetophenone (**69**) (2.9 mmol) and isopropoxide solution (3 ml).

Catalyst (mol% Ru)	Ligand mol%	Reaction Temperature	% e.e.	% Yield
$[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ 2.5	3	R.T.	--	0
$[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ 2.5	3	Reflux	10	2
$[\text{RuCl}_2(\text{PPh}_3)_3]$ 2.5	3	R.T.	--	0
$[\text{RuCl}_2(\text{PPh}_3)_3]$ 2.5	3	Reflux	76	74

The reactions were repeated using catalyst complexes prepared with $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ (0.005 mmol) or $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.01 mmol) with oxazoline ligand (**62**) (0.013 mmol) refluxed in a round-bottomed flask with propan-2-ol (20 ml) for 1.5 hour under nitrogen. Acetophenone (**69**) (5 mmol) and isopropoxide solution (0.3 ml) were added to the flask and the mixture stirred for 24 hours. The aim was to investigate whether the reaction could be carried out using low levels of ruthenium catalyst (0.2 mol%).

Catalyst (mol% Ru)	Ligand mol%	Reaction Temperature	% e.e.	% Yield
[RuCl ₂ (C ₆ H ₆) ₂] 0.2	0.26	R.T.	--	0
[RuCl ₂ (C ₆ H ₆) ₂] 0.2	0.26	Reflux	5.5	12.2
[RuCl ₂ (PPh ₃) ₃] 0.2	0.26	R.T.	--	0
[RuCl ₂ (PPh ₃) ₃] 0.2	0.26	Reflux	21.5	80

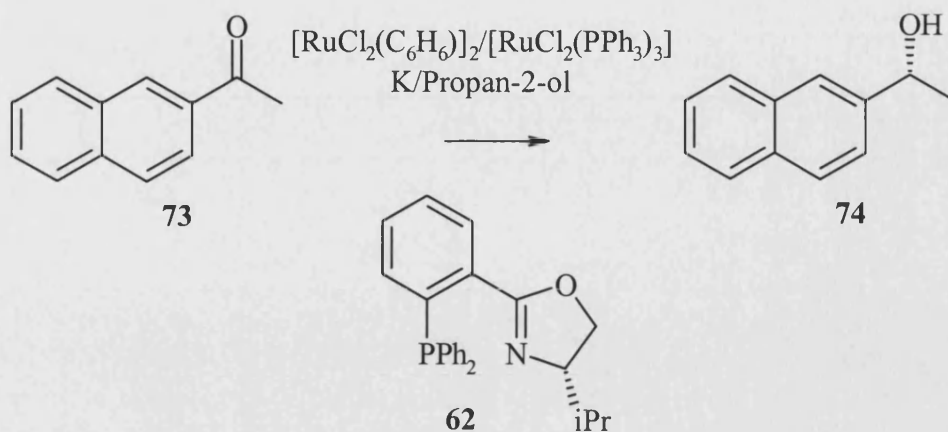
Reactions using [RuCl₂(C₆H₆)₂] (0.0125 mmol) were conducted with varying levels of oxazoline ligand (**62**) (0.005, 0.0125, 0.025, 0.0375, 0.05, 0.125, 0.25 mmol). Complexes were refluxed in a round-bottomed flask with propan-2-ol (10 ml) for 1.5 hour under nitrogen. To the flasks were added acetophenone (**69**) (5 mmol) and isopropoxide solution (0.3 ml). The reaction mixtures were refluxed for 24 hours under a nitrogen atmosphere.

Catalyst (mol% Ru)	Ligand mmol mol%	% e.e.	% Conversion
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.005 0.1	19	89
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.0125 0.25	2	95
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.025 0.5	8	94
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.0375 0.75	5	97
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.05 1.0	4	95
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.125 2.5	27	90
[RuCl ₂ (C ₆ H ₆) ₂ 0.5	0.25 5.0	35	91

The study was repeated using the catalyst [RuCl₂(PPh₃)₃] (0.025 mmol) and varying levels of oxazoline ligand (**62**) (0.005, 0.0125, 0.025, 0.0375, 0.05, 0.125, 0.25, 0.5 mmol). Complexes were refluxed in a round-bottomed flask with propan-2-ol (10 ml) for 1.5 hour under nitrogen. To the flasks were added acetophenone (**69**) (5 mmol) and isopropoxide solution (0.3 ml). The reaction mixtures were refluxed for 24 hours under a nitrogen atmosphere.

Catalyst (mol% Ru)	Ligand mmol mol%	% e.e.	% Conversion
[RuCl ₂ (PPh ₃) ₃] 0.5	0.005 0.1	6	94
[RuCl ₂ (PPh ₃) ₃] 0.5	0.0125 0.25	1	99
[RuCl ₂ (PPh ₃) ₃] 0.5	0.025 0.5	7	96
[RuCl ₂ (PPh ₃) ₃] 0.5	0.0375 0.75	11	98
[RuCl ₂ (PPh ₃) ₃] 0.5	0.05 1.0	13	99
[RuCl ₂ (PPh ₃) ₃] 0.5	0.125 2.5	62	97
[RuCl ₂ (PPh ₃) ₃] 0.5	0.25 5.0	60	86
[RuCl ₂ (PPh ₃) ₃] 0.5	0.5 10.0	58	88

Ru Catalysed Transfer Hydrogenation of 1-Acetonaphthone



Catalyst complexes were prepared by refluxing $[\text{RuCl}_2(\text{C}_6\text{H}_6)]_2$ (0.005 mmol) or $[\text{RuCl}_2(\text{PPh}_3)_3]$ (0.01 mmol) with oxazoline ligand (**62**) (0.013 mmol) in a round-bottomed flask with propan-2-ol (10 ml) for 1.5 hour under nitrogen. To the flasks were added 1-acetonaphthone (**73**) (5 mmol) and isopropoxide solution (0.3 ml). Reactions were carried out under nitrogen and monitored by TLC (light petroleum:ethyl acetate 9:1) for 24 hours.

The reactions were quenched with 2N hydrochloric acid (2 ml), washed with water (50 ml) followed by saturated sodium carbonate solution (100 ml), brine (100 ml) and then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Enantiomeric excess was ascertained by HPLC on a Chiracel OD column (hexane:propan-2-ol 95:5, 1 ml min⁻¹, 254 nm, R_T 9 and 15 minutes). δ_{H} (250 MHz, CDCl₃) 7.79-7.83 (4H, m, ArH), 7.45-7.51 (3H, m, ArH), 5.05 (1H, dq, *J* 3.5, CHOH), 1.92 (1H, d, *J* 3.5 OH), 1.57 (3H, d, *J* 6.4, CH₃). δ_{C} (100MHz, CDCl₃) 143.395, 133.55, 131.14, 128.54, 128.15, 127.89, 126.37, 126.1, 124.03, 70.76, 25.36. $[\alpha]_{\text{D}}^{25} +39.2$ (c=0.5, CH₂Cl₂).

Catalyst (mol% Ru)	Ligand mol%	Reaction Temperature	% e.e.	% Yield
[RuCl ₂ (C ₆ H ₆) ₂] 0.2	0.26	Reflux	1	2
[RuCl ₂ (PPh ₃) ₃] 0.2	0.26	Reflux	40	54

Preparation of Sulfonated RuCl₂(PPh₃)₃

RuCl₃.xH₂O (0.96 mmol) was dissolved in methanol (50 ml) and added to Na-TPPMS (4.6 mmol) in a 100ml round-bottomed flask. The mixture was refluxed under nitrogen for 18 hours. The methanol was then removed *in vacuo* to leave a light brown crystalline solid, RuCl₂[PPh₂(C₆H₄SO₃Na)]₃.

Immobilisation of [RuCl₂(PPh₃)₃] and RuCl₂[PPh₂(C₆H₄SO₃Na)]₃

[RuCl₂(PPh₃)₃] (0.005 mmol) along with triphenylphosphine (0.0088 mmol) were stirred with octyltrimethoxysilane derivatised Davisil 300 (method **B**) (250 mg) in hexane (5 ml) for 3 hours at 65 °C under nitrogen. The hexane was then removed *in vacuo* to yield a light brown powder of the SOP catalyst complex, **SC1**.

RuCl₂[PPh₂(C₆H₄SO₃Na)]₃ (0.005 mmol) was stirred with Davisil 300 (250 mg) in methanol (5 ml) for 3 hours at 65 °C under nitrogen. The methanol was then removed *in vacuo* to yield a light brown powder of the SAP catalyst complex, **SC2**.

The supported catalysts were equivalent to a ruthenium catalyst level of 0.1 mol% and phosphine ligand level of 0.5 mol%.

Ru Catalysed Transfer Hydrogenation of Acetophenone with Supported Catalysts

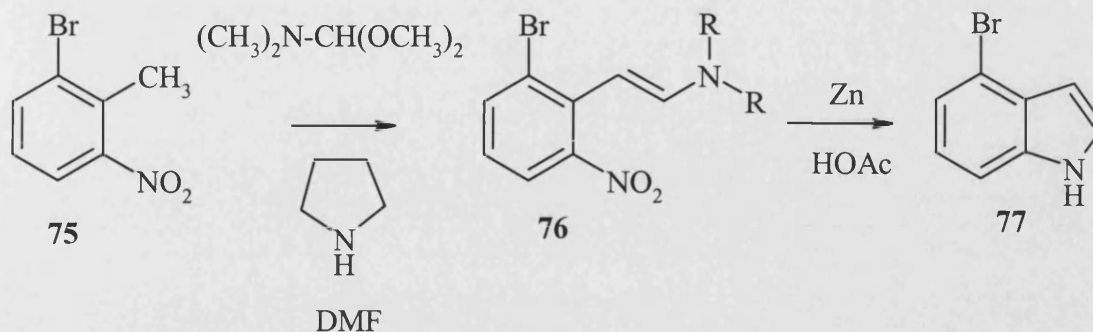
The reduction of acetophenone was carried out by addition of supported catalyst complex *SC1*, *SC2* or a homogeneous control *HCl* ($[\text{RuCl}_2(\text{PPh}_3)_3]$, 0.005 mmol, with triphenylphosphine, 0.0088 mmol) to acetophenone (5 mmol) and isopropoxide solution (0.3 ml).

This was stirred in propan-2-ol or toluene solvent (5 ml) for 24 hours at 100 °C under nitrogen. Reactions were monitored by HPLC for conversion and enantiomeric excess. Samples were also analysed for levels of ruthenium leaching.

Catalyst (mol% Ru)	Reaction Solvent	Catalyst Coating	Ru Level (ppm)	% Conversion
<i>SC1</i> 0.1	Propan-2-ol	Toluene 0.025ml	0.4	43
<i>SC2</i> 0.1	Toluene	Water 0.025 ml	0.8	15
<i>HCl</i> 0.1	Propan-2-ol	--	31.3	52

5.3.6 Heck Coupling on a Substituted Indole

Preparation of 4-Bromoindole



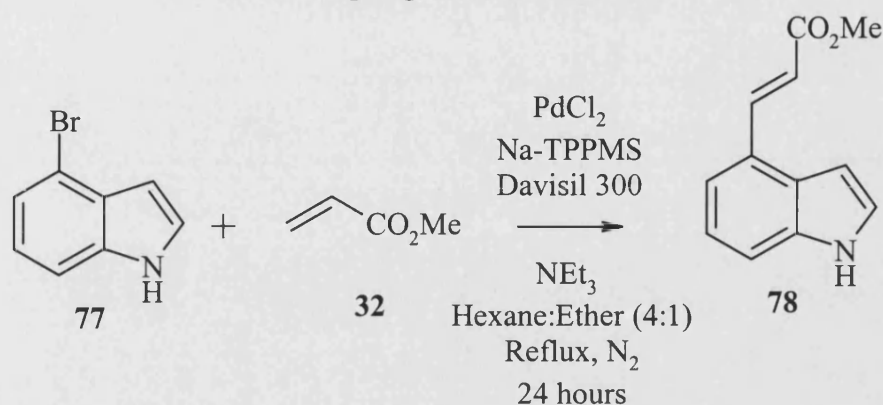
4-Bromoindole was prepared as described by a routinely used literature procedure.¹⁰⁴

To 2-bromo-6-nitrotoluene (**75**) (15 mmol) in dry DMF (30 ml) was added DMF-dimethyl acetal (45 mmol) and pyrrolidine (15 mmol). The solution was heated at 110°C for 3 hours under nitrogen. TLC analysis showed complete consumption of the bromonitrotoluene. The dark red solution was cooled, diluted with ether (100 ml), and washed with water (2x100 ml). The combined aqueous extracts were further extracted with ether (100 ml). After drying the organic phase over sodium sulfate, the solvent was evaporated *in vacuo*.

The crude enamine (**76**) was dissolved in 80 % aqueous acetic acid (100 ml) and heated to 75 °C in a 150 ml round-bottomed flask. Zinc dust (130 mmol) was then added portion-wise over 1 hour. The reaction temperature was raised to 85 °C and the reaction allowed to continue for 2 hours. The mixture was then cooled and filtered. The filtrate was diluted with ether (50 ml), washed with water (50 ml) and saturated sodium carbonate solution (50 ml) and then dried over sodium sulfate. The solvent was then removed *in vacuo* and the residue purified by flash column chromatography (eluant, hexane:ethyl acetate, 10:1) to give 4-bromoindole (**77**) (ca.

70 % yield). δ_{H} (250 MHz, CDCl_3) 8.24 (1H, br s), 7.30 (2H, m), 7.21 (1H, m), 7.04 (1H, t, J 7.8), 6.60 (1H, t, J 2.3).

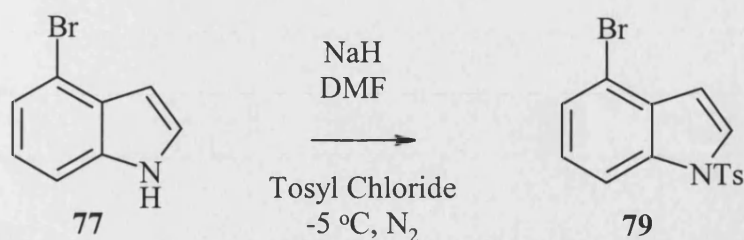
Heck Coupling to 4-Bromoindole



The reaction of 4-bromoindole with methyl acrylate was attempted using palladium (II) chloride and Na-TPPMS supported upon Davisil 300 with a coating of ethylene glycol.

Palladium (II) chloride (0.02 mmol) and Na-TPPMS (0.14 mmol) was added to a pressure tube containing Davisil 300 (250 mg) with ethylene glycol (0.025ml) and hexane:ether (5 ml, 4:1). The tube was sealed with nitrogen and the mixture stirred for 3 hours at 65 °C. Methyl acrylate (1.4 mmol) and 4-bromoindole (77) (0.47 mmol) were then added to the vessel along with triethylamine (1.4 mmol). The tube was resealed with nitrogen and stirred for 24 hours at 100 °C. TLC analysis indicated that much of starting material was still present. Analysis by ^1H NMR suggested the absence of the desired product in the reaction mixture. Less than 1 ppm palladium had leached into the organic solvent.

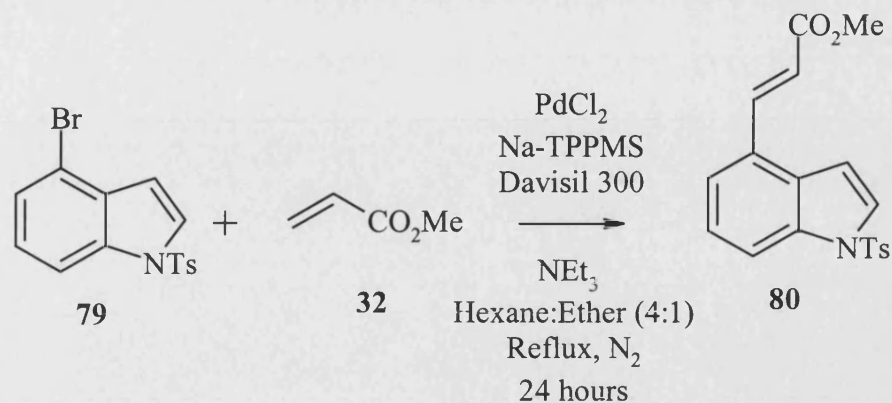
Protection of Nitrogen on 4-Bromoindole



To a suspension of sodium hydride (6.88 mmol) in DMF (30 ml) under nitrogen, at 5 °C, was carefully added a solution of 4-bromoindole (**77**) (6.25 mmol) in DMF (20 ml) over 1 hour. After addition was complete the mixture was stirred for a further 2 hours, maintaining the temperature at -5 °C. A nitrogen saturated solution of tosyl chloride (6.25 mmol) in DMF (25 ml) was introduced drop-wise to the reaction over a 1 hour period whilst maintaining the temperature.

The reaction was allowed to continue for a further 2 hours before combining with ice water (300 ml) and extracting with ether (3x100 ml). The organic extracts were washed with water (50 ml) and saturated sodium chloride solution (50 ml). They were then dried over magnesium sulfate and filtered. The solvent was removed *in vacuo* and the product 4-bromo-1-tosylindole (**79**) recrystallised from hexanes (ca. 65 % yield). δ_{H} (250 MHz, CDCl_3) 7.95 (1H, d, J 8, indole 7H), 7.76 (2H, d, J 8, tosyl H next to sulfonyl), 7.62 (1H, d, J 4, indole 2H), 7.39 (1H, d, J 8, indole 5H), 7.24 (2H, d, J 8, tosyl H next to CH_3), 7.17 (1H, t, J 8, indole 6H), 6.73 (1H, d, J 4, indole 3H), 2.35 (3H, s, CH_3). mp 118-120 °C.

Heck Coupling to 4-Bromo-1-tosylindole



Palladium (II) chloride (0.02 mmol) and Na-TPPMS (0.14 mmol) was added to a pressure tube containing Davisil 300 (250 mg) with ethylene glycol (0.025ml) and hexane:ether (5 ml, 4:1). A control reaction was also performed in the absence of Davisil 300 and ethylene glycol.

The tubes were sealed with nitrogen and the mixture stirred for 3 hours at 65 °C. Methyl acrylate (0.625 mmol) and 4-bromo-1-tosylindole (**79**) (0.5 mmol) were then added to the vessels along with triethylamine (0.625 mmol). The tubes were resealed with nitrogen and stirred for a further 24 hours at 100 °C. Analysis by ¹H NMR again confirmed the absence of any of the desired product in the reaction mixture.

It was suggested that a more appropriate phosphine may be required for reaction, therefore, the above coupling was attempted using palladium (II) acetate (0.02 mmol) with tri-*o*-tolylphosphine (0.14 mmol) and optionally octyltrimethoxysilane derivatised Davisil 300 (method **B**) (250 mg). The reaction was performed neat in the presence of methyl acrylate (0.625 mmol), 4-bromo-1-tosylindole (0.5 mmol) and triethylamine (0.625 mmol). The tubes were sealed with nitrogen and stirred for 6 hours at 100 °C.

Analysis by TLC confirmed that no starting material remained after 6 hours. The reaction mixture was diluted with dichloromethane (50 ml) and washed with

water (3x50 ml), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield the crude product 4-(2-carbomethoxyethen-1-yl)-1-tosylindole (**80**) as brown crystals (81% yield). δ_{H} (250 MHz, CDCl_3) 8.02 (1H, d, *J* 8, indole 7H), 7.97 (1H, d, *J* 16, =CHCO₂Me), 7.78 (2H, d, *J* 8, tosyl H next to sulfonyl), 7.67 (1H, d, *J* 4, indole 2H), 7.48 (1H, d, *J* 8, indole 5H), 7.36 (1H, t, *J* 8, indole 6H), 7.24 (2H, d, *J* 8, tosyl H next to CH₃), 6.88 (1H, d, *J* 4, indole 3H), 6.53 (1H, d, *J* 16, CH=CHCO₂Me), 3.81 (3H, s, CO₂CH₃), 2.35 (3H, s, CH₃).

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