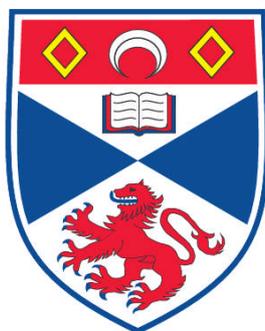


**MODIFICATION OF
BIS(DITERTIARYBUTYLPHOSPHINOMETHYL)BENZENE FOR
IMPROVED CATALYST SEPARATION AND STABILITY**

Benjamin Lee Parnham

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Bis(ditertiarybutylphosphinomethyl)benzene
for Improved Catalyst Separation and Stability**



A thesis presented by

Benjamin Lee Parnham

to the

University of St Andrews

in application of

THE DEGREE OF DOCTOR OF PHILOSOPHY

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Abstract

Palladium complexes of bis(*di-tert*-butylphosphinomethyl)benzene (DTBPMB) show remarkably high activity as alkene methoxycarbonylation catalysts, in addition to numerous other catalytic conversions, and are currently being commercialised by Lucite in ethene methoxycarbonylation to methyl propanoate. Any large-scale exploitation of this catalyst system for heavier products, however, is likely to be hindered by catalyst-product separation problems common to homogeneous catalysts; hence modification of this catalyst system to allow facile product separation was investigated.

Tethering of DTBPMB residues onto polystyrene *via* Suzuki-type coupling of suitable precursors onto bromopolystyrene and boronic acid functionalised polystyrene resins was investigated and the phosphine was successfully immobilised. Phosphination of the resins was not complete however and as such there is concern that other phosphine residues may be present which do not exhibit a bidentate binding motif. The synthesis of a potassium sulfonate derivative of DTBPMB (KBPMBS) was successful and immobilisation of this onto ion exchange resins was also investigated. Some preliminary results from studies into 1-octene methoxycarbonylation using palladium complexes of these resins were obtained.

Supporting of this diphosphine onto silica *via* a sol-gel co-condensation methodology was also investigated; the synthesis of a suitably functionalised precursor containing a sulfonamide linkage was successful *via* protection of the diphosphine using borane. Although formation of the silica support was successful, attempts to deprotect the phosphine-borane resulted in cleavage of the ligand from the support. An alternative route to this supported ligand was attempted and others discussed. Synthesis of a suitable sol-gel precursor *via* alkene hydrosilation was also attempted and is discussed. Supporting of the sulfonated phosphine, KBPMBS onto silica functionalised with imidazolium tethered residues was also investigated, although complete leaching of the phosphine from the support by methanol washing was observed.

Immobilisation of the synthesised KBPMBS ligand in an ionic liquid (IL) phase was investigated. Complex formation and catalytic activity were demonstrated and a positive effect on conversion was observed upon addition of carbon dioxide to the system;

possibly due to the increased CO solubility within the IL phase. Efficient product separation from the IL-immobilised catalyst system was demonstrated, both by organic extraction and using supercritical carbon dioxide flow. However, poor catalyst stability under these conditions appears to present a barrier to recycling this system, with loss of conversion observed on catalyst recycling.

Other attempts to immobilise the DTBPMB ligand are discussed and reduction of the sulfide derivative of DTBPMB was demonstrated using hexachlorodisilane, which could be used as a general synthetic strategy for protecting highly electron rich phosphines.

It is possible that increasing the bulk of the DTBPMB ligand may increase catalyst stability and result in catalyst systems with higher turnover numbers. Therefore syntheses of bulky ligands based on the DTBPMB backbone were investigated. 1,2,4,5-tetrakis(di(*tert*-butyl)phosphinomethyl)benzene was successfully synthesised although palladium complexes of this showed no activity in catalytic methoxycarbonylation. Attempts to synthesise a related biphenyl-based tetraphosphine is also discussed, although isolation of this in a pure form was not achieved. Routes toward tetraphenyl and dimethyl-diphenyl functionalised derivatives of DTBPMB have also been explored, although only a monophosphine was isolated due to difficulties in obtaining an intermediate di(chloromethyl) precursor in both synthetic pathways, although this now appears to have been overcome.

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Table of Abbreviations

| | |
|----------------------------------|--|
| [NTf ₂] ⁻ | Bis(trifluoromethanesulfonyl)imide |
| [RMIM] ⁺ | Alkylmethylimidazolium, [Et = Ethyl, Pr = Propyl, Pe = Pentyl, Oc = Octyl] |
| 4-DMAP | 4-dimethylaminopyridine |
| acac | Acetylacetonate |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BISBI | 2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl |
| C.I. | Chemical Ionisation |
| Cy | Cyclohexyl |
| dba | <i>trans-trans</i> -dibenzylideneacetone |
| DBPMB | 1,2-bis(di- <i>tert</i> -butylphosphinomethyl)benzene |
| DCM | Dichloromethane |
| DMF | N,N-dimethylformamide |
| DPPP | 1,3-bis(diphenylphosphino)propane |
| DTBPMB | 1,2-bis(di- <i>tert</i> -butylphosphinomethyl)benzene |
| E.I. | Electron Ionisation |
| <i>ee</i> | Enantiomeric excess |
| HLB | Hydrophilic lipophilic balance |
| ICP-AES | Inductively coupled plasma – atomic emission spectroscopy |
| ICP-MS | Inductively coupled plasma – mass spectrometry |
| IL | Ionic liquid |
| ¹ Pr | <i>iso</i> propyl |
| KBPMBS | Potassium 3,4-bis(di- <i>tert</i> -butylphosphinomethyl)benzenesulfonate |
| Lucite | Lucite International Ltd |
| MSA | Methanesulfonic acid |
| NBS | N-Bromosuccinimide |
| ⁿ BuLi | <i>n</i> -butyllithium |
| Ph | Phenyl |
| PS-TPP | Polystyrene – triphenylphosphine |
| scCO ₂ | Supercritical carbon dioxide |
| SCF | Supercritical fluid |

| | |
|-----------------|--|
| TBPBP | 3,3',4,4'-tetrakis(di- <i>tert</i> -butyl-phosphinomethyl)biphenyl |
| ^t Bu | Tertiary (<i>tert</i>) butyl |
| TEOS | Tetraethyl orthosilicate |
| TKPMB | 1,2,4,5-tetrakis(di(<i>tert</i> -butyl)phosphinomethyl)benzene |
| TMEDA | N,N,N',N',Tetramethylethylenediamine |
| TOF | Turnover frequency |
| TOF-MS | Time-of-flight mass spectrometry |
| TON | Turnover number |

1. Introduction

1.1 Homogeneous and Heterogeneous Catalyst Systems

A catalyst is a chemical substance that increases the rate of a reaction by accessing a more kinetically accessible route to a product without itself being consumed in the reaction. Effective catalysts are highly attractive to industry, not only allowing milder pressures and reaction temperatures to be used but also allowing the product distribution to be directed towards a desired product. As a result, over 80 % of all industrial chemical processes are catalytic and it has been estimated by the North American Catalysis Society that a massive 35 % of worldwide GDP depends on catalysis; and still the catalyst market is increasing at a rate of 5 % per annum. (2006)¹

Catalytic reactions are often classified by whether or not the compounds present in the system are in the same phase as the catalytic species. When this is the case, the system is described as homogeneous, otherwise it is a heterogeneous catalyst system. In Table 1-1, some of the main aspects of these two catalyst systems are compared.

| | Homogeneous | Heterogeneous |
|----------------------------|--------------------|----------------------|
| Active centres | All metal atoms | Surface atoms only |
| Concentration | Small | High |
| Diffusion Problems | Rarely present | Present |
| Catalyst Structure | Known | Poorly defined |
| Stoichiometry | Known | Unknown |
| Modification Scope | High | Low |
| Reaction Conditions | Mild | Severe |
| Catalyst Separation | Difficult | Easy |
| Application | Limited | Wide |

Table 1-1 - Comparison of homogeneous and heterogeneous catalyst systems²

1.1.1 Comparison

Heterogeneous catalysts are often metals or metal oxide materials, whereas homogeneous catalysts tend to be metals that are complexed by a variety of ligands. Comparison of the two catalyst systems highlights several advantages of homogeneous over heterogeneous systems.² Homogeneous catalysts are generally more active than their heterogeneous counterparts, having all of their active centres available for catalysis; whereas only surface atoms are generally active in the heterogeneous case. This results in greater catalytic efficiency, allowing lower catalyst loadings and milder conditions compared to heterogeneous systems. These properties result in practical advantages for industrial applications, such as lower process temperatures and pressures.

The complete dissolution of a homogeneous catalyst and reagents significantly reduces diffusion problems that can sometimes be problematic for heterogeneous systems, although gas transport to a homogeneous catalyst can sometimes present problems. The surface-only reactivity of heterogeneous catalysts makes them susceptible to poisoning, something which is less problematic with homogeneous systems. The well-defined structure of homogeneous catalysts has allowed them to be more fully characterised and allows an extensive mechanistic understanding of their catalytic processes, allowing catalytic cycles to be drawn up to describe the processes occurring.³ This mechanistic understanding has allowed to an extent “catalyst designing”, where the electronic and steric properties of a catalyst can be tuned in order to increase its efficiency or selectivity.

1.1.2 Limitations of Homogeneous Catalysis

Homogeneous catalysts are not without their problems, the catalysts may be based around expensive precious metals that are complexed to often elaborate ligands, making them particularly expensive to synthesise. The catalysts can be fairly sensitive, particularly to temperature - sometimes leading to unacceptably short catalyst lifetimes and low thermal stability.

Very often, the most significant barrier to more widespread use of homogeneous catalysts in industry is a lack of an efficient and economic catalyst separation method. The separation of solid-supported or suspended heterogeneous catalysts is, in contrast often trivial, simply requiring filtration of the catalyst to recover. For a homogeneous catalyst system to compete on economics, the high cost of the catalyst needs to be counteracted by a highly efficient catalyst / product separation technique, leading to minimal loss of the catalyst.

Occasionally such separation can be achieved by distillation of the reaction products. Chemistry where this is possible however is somewhat limited as the reaction products must be particularly volatile as the moderate thermal stability of many homogeneous catalysts can be restrictive on the temperatures that can be used. Even when this is possible, the additional cost of such a distillation can be high and will need to be considered in any overall process costing.

Despite these limitations, there are some major industrial processes that employ homogeneous catalysts. One of the first large-scale homogeneous processes developed was alkene hydroformylation (largely propene) known as the Oxo process. The bulk aldehyde produced here is a useful intermediate to many industrially important chemicals such as alcohols, acids, amines and esters.

Earlier processes, such as those operated by Ruhrchemie and BASF used cobalt hydridocarbonyl which was separated by thermal decomposition. A process developed by Shell however utilises the catalyst $[\text{HCo}(\text{CO})_3(\text{PR}_3)]$ where R is an alkyl.⁴ Here the catalyst is sufficiently thermally stable to allow separation by distillation. More recently developed processes use rhodium / triphenylphosphine such as the, “Low pressure oxo

process” developed and commercialised by Union Carbide / Davy Powergas / Johnson Matthey and independently by Celanese and BASF.⁵ In this a more active yet more expensive catalyst system and again separation is effected by distillation. Due to catalyst stability it is more ideally suited to ethylene feedstock, though is just economically viable with propene.

1.2 Lucite and Methyl Methacrylate Production

Lucite International (Lucite) is the largest worldwide manufacturer of methyl methacrylate (MMA). The majority of their sales are of the MMA monomer, although an increasingly significant part of their business comes from downstream products based on polymethyl methacrylate (PMMA) such as products for injection moulding, liquid crystal display backing materials, adhesives, coatings and trade named products such as *PlexiglasTM*, *PerspexTM* and *LuciteTM*.

In 1999, the worldwide production capacity for methyl methacrylate was 2.4×10^6 tonnes annually, of which Lucite (then known as Ineos Acrylics) owned 540,000 tonnes (2000 figures).⁶ The company hence has about a 25 % share in the global acrylics market and has been working to build on this with the development of a more efficient process for MMA manufacture using methanol, ethylene and carbon monoxide feedstocks. This new process, now dubbed the “alpha process” is estimated to give around a 20 % cost saving compared with the conventional acetone-cyanohydrin (ACH) route to MMA.⁷

1.2.1 The ACH Process

Up until recently, acetone cyanohydrin (ACH) has been the exclusive feedstock for all industrial manufacture of methacrylic acid derivatives. This process was first used for industrial manufacture in 1937 by Rohm and Haas and ICI. Manufacture of acetone cyanohydrin involves addition of hydrogen cyanide to acetone using a liquid-phase base as catalyst such as an alkali metal hydroxide at temperatures below 40 °C.⁶ (Figure 1-1)

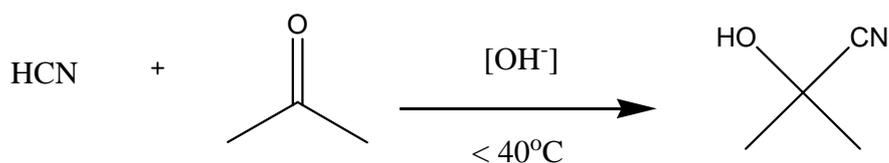


Figure 1-1 - Acetone cyanohydrin from hydrogen cyanide and acetone

This mild process produces ACH at a selectivity of 92-99 % (based on HCN). In the case of MMA manufacture the nitrile group of ACH then undergoes an acid catalysed hydration *via* an amide intermediate. This conversion is effected using 98 % sulfuric acid at 80-140°C, forming the methacrylic acid amide sulfate. This is then converted to MMA and ammonium bisulfate by reaction with methanol at either 80 °C or at 100-150 °C under pressure. (Figure 1-2)

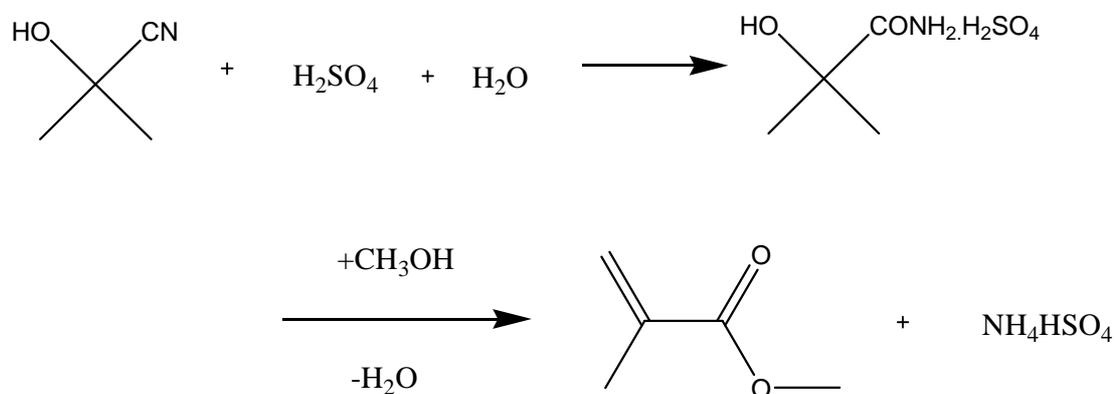


Figure 1-2 - Methyl methacrylate manufacture from acetone cyanohydrin

This process has an overall selectivity to MMA of about 77 %, based on acetone. Process improvements have been developed over the years and this classical methodology is still competitive, accounting for around 80 % of worldwide production capacity (2000 figures).⁶

Although this process is economically competitive when a cheap source of HCN is available, it is far from ideal. The large scale use of mineral acid and liquid phase base as well as the massive production and subsequent disposal of unwanted ammonium bisulfate has a significant environmental impact; 1.2 Tonnes of ammonium bisulfate co-product are produced for every tonne of MMA.⁸

The removal of these reagents and the unwanted side-product in a more atom-efficient process would hence lead to a process with a much lessened environmental impact and likely economic gain and hence has been an active area of research for numerous companies including BASF, MGC, Elf and Shell as well as Lucite.⁸

1.2.2 The Alpha Process

An alternative route to MMA has been developed at Lucite over recent years and has been recently termed the 'alpha' process.⁷ It essentially consists of two reactive stages followed by a series of separation steps to obtain MMA. The first stage takes methanol, ethylene and carbon monoxide (CO) in a methoxycarbonylation reaction over a palladium-based homogeneous catalyst system to give methyl propanoate (MeP). The reaction is highly active and selective towards the desired product to the extent that the product stream essentially requires no purification. (Figure 1-3)

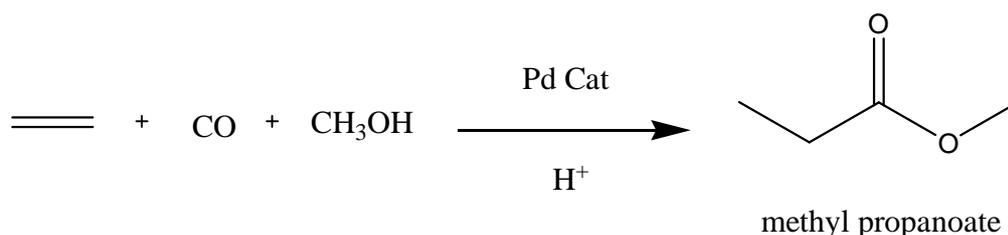


Figure 1-3 - Methyl propanoate from methoxycarbonylation of ethene

MeP is then combined with formaldehyde (obtained from methanol using the formalin process) in the gas phase over a fixed bed heterogeneous catalyst to give MMA. This is performed at 320 °C and 2 bar giving a selectivity to MMA of 95 %. Methanol is also added during the reaction and the water content is kept to a minimum to minimise the production of methacrylic acid. This is then taken through a series of somewhat complicated purification stages to give the final product.

It is the former, homogenous catalyst system that is the focus of this project and so is to be a major subject of discussion here.

1.3 Methoxycarbonylation of Alkenes

1.3.1 Catalysts Reported in the Literature

Early methoxycarbonylation catalysts were based on cobalt and nickel carbonyl compounds. More recent literature on this area however has concentrated largely on Pd-based carbonylation catalysts and to a lesser extent Pt, Rh and Ru, due to the better performance of these catalysts under more mild conditions. As well as the interest in ethylene methoxycarbonylation for MMA production, styrene methoxycarbonylation has a significant contribution in the literature due to its interest in routes to the drug ibuprofen.

1.3.2 Catalysis With DTBPMB / Palladium

Complexation of 1-2 bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) with a suitable palladium precursor such as tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) forms a species in which only one diphosphine ligand is bound in a *cis* coordination to the palladium centre. (Figure 1-4, species **1**) This is presumably due to the high steric bulk of the *tert*-butyl groups of the ligand. Addition of a weakly coordinating Brønsted acid, such as a sulfonic acid, produces the palladium hydride species (Figure 1-4, species **2**), which is considered to be the catalytically active species.

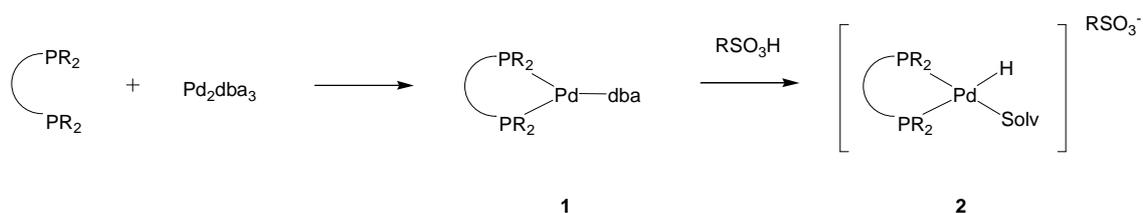


Figure 1-4 - Complexation of diphosphine to palladium and formation of palladium hydride

In general, bidentate complexes are highly active in the copolymerisation of CO and ethene, giving perfectly alternating polyketone product. (Figure 1-5) In fact there has been considerable interest in such catalytic systems for the production of this desirable material.⁹ Monophosphine ligands, such as triphenylphosphine, give the monomeric methyl propanoate product with high selectivity.¹⁰ Intermediate reactivity is observed

when hemilabile P,O or P,S diphosphine ligands are used, where unsaturated oligoketones are observed.¹¹

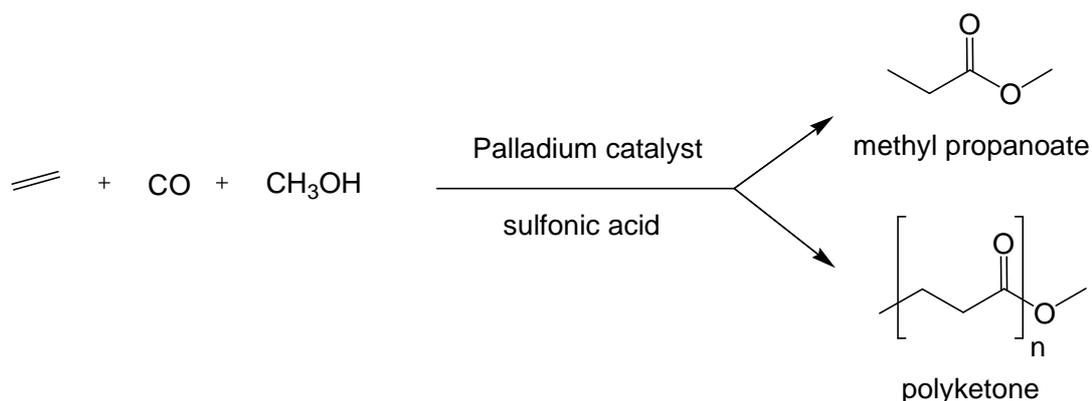


Figure 1-5 - Possible products from ethylene / CO / methanol reaction over palladium catalysts

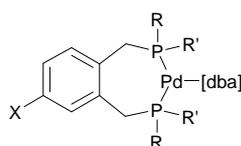
Complexes of DTBPMB however break this generalisation, giving exceptional selectivity to the methyl propanoate (MeP) monomer. When methanesulfonic acid (MSA) is used as the proton donor, the catalyst system has been reported to give a selectivity towards MeP of 99.98 % at a rate of consumption of 50, 000 mol of ethene per mol of palladium per hour (turnover frequency; TOF) under mild conditions (80 °C, 10 atm.) in batch reactions.¹²

The system also offers high stability, achieving total turnover numbers (total number of moles of product per mole of catalyst before unacceptable loss in activity; TON) in excess of 100,000. In contrast, catalysis with triphenylphosphine complexes achieved a modest 1,800 turnovers under these conditions. Due to these desirable properties, the use of this catalyst system for methyl propanoate synthesis has hence been patented by Lucite.¹³

The presence of the highly electron donating and bulky *tert*-butyl groups and the semi-rigid 4-carbon backbone of the diphosphine are thought to be important in effecting the observed catalysis. When this *cis* coordinating diphosphine is used, the steric bulk of the phosphine groups increases the rate of methanolysis, leading to monomer; whereas less bulky phosphines such as 1,3-bis(diphenylphosphino)propane (DPPP) prefer to coordinate further alkene, leading to polymerisation.¹⁴ The high stability of the system may also be attributed to the ligand; the large steric bulk would disfavour metal cluster formation and the highly electron donating ability of the phosphorous means the ligand

remains fully protonated under catalytic conditions. Phosphine quaternisation therefore is not a deactivating process for this system as protonated DTBPMB is also able to bind to the palladium centre.

Exchange of the *tert*-butyl groups with less electron donating and / or less bulky groups, such as phenyl or *iso*-propyl has a dramatic effect on the catalysis, giving reduced activity and a selectivity to MeP of around 20 %, with largely polymeric and oligomeric ketone products instead. (Figure 1-6, complexes **4-7**)



- 1** R = R' = ^tBu, X = H **5** R = R' = Cy, X = H
2 R = R' = ^tBu, X = NO₂ **6** R = R' = Ph, X = H
3 R = R' = ^tBu, X = OCH₃ **7** R = ^tBu, R' = Cy X = H
4 R = R' = ⁱPr, X = H

| Catalyst | TOF | Selectivity to MeP (%) ⁱ | P-Pd-P bite angle (°) ⁱⁱ |
|----------|---------|-------------------------------------|-------------------------------------|
| 1 | 12, 000 | 99.9 | 103.9 |
| 2 | 11, 500 | 99.9 | |
| 3 | 11, 800 | 99.9 | |
| 4 | 200 | 20 | 104.3 |
| 5 | 200 | 25 | 103.9 |
| 6 | 400 | 20 | 104.6 |
| 7 | 500 | 30 | |

Figure 1-6 - Catalytic results from DTBPMB derivatives 1-7¹²

(i) By GC; remainder oligomers and polymers, (ii) Where determined by X ray crystallography

Interestingly, substitution of the phenyl ring with electron withdrawing or donating groups such as NO₂ or OMe has very little effect on the catalytic properties. (Figure 1-6, complexes **2** and **3** respectively). In addition, studies on methoxycarbonylation of vinyl acetate using 1,2-bis(di-*tert*-butylphosphinomethyl)naphthalene and 2,3-bis(di-*tert*-butylphosphinomethyl)naphthalene at room temperature (3 hours) showed no difference in ester selectivity - only a reduction in conversion compared to DTBPMB,¹⁵ hence suggesting only a reduction in rate for these naphthyl derivatives.

1.4 Mechanism of Catalysis

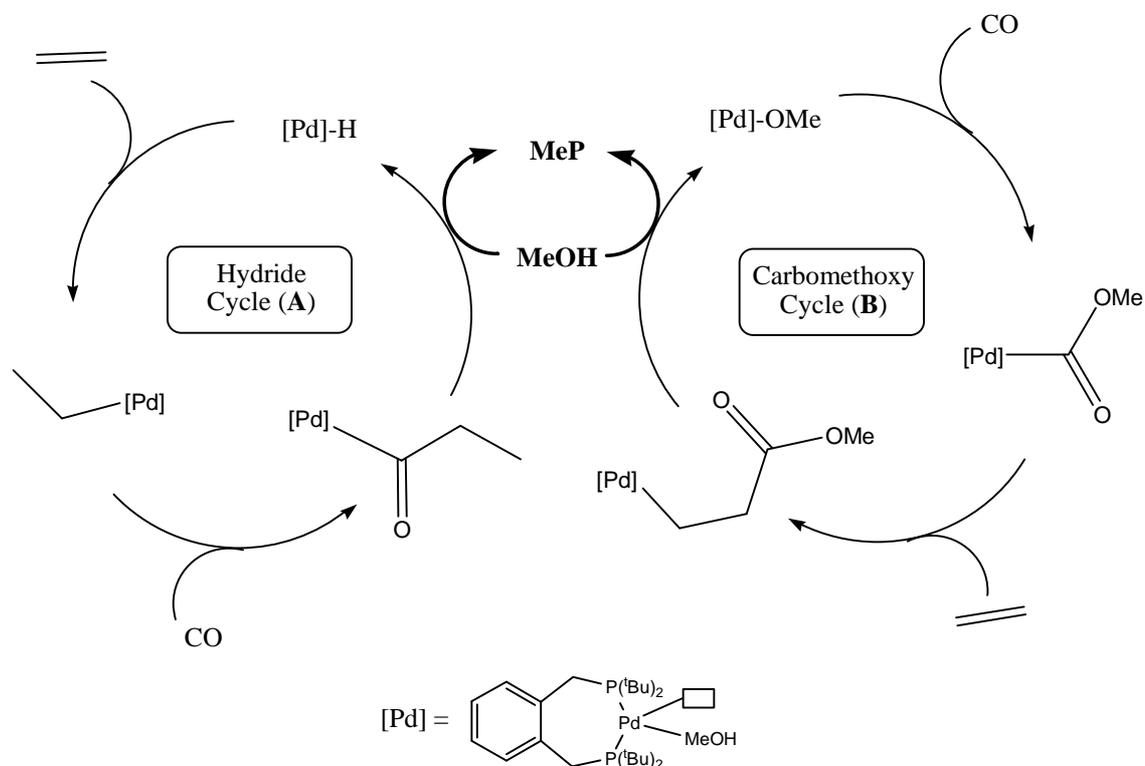


Figure 1-7 - Suggested mechanisms for ethene methoxycarbonylation

Two mechanisms have been proposed for ethene methoxycarbonylation by DTBPMB. They differ in whether the palladium complex initiates the catalytic cycle as either a hydride or a methoxide and are hence termed the “hydride cycle” or the “carbomethoxy cycle” respectively. (Figure 1-7, cycles A and B respectively) There have been several reports that have attempted to address which of these mechanisms operate in DTBPMB methoxycarbonylation.

In studies on the methoxycarbonylation of 1-octene, the hydride mechanism was demonstrated to be occurring through the use of deuterium labelled methanol.¹⁶ When 1-octene is used as substrate, rapid isomerisation of the alkene occurs due to chain propagation and β -hydride elimination of the substrate. This quickly forms an equilibrium distribution of isomerised octenes. CO insertion however, only occurs on the terminal alkene and so this equilibrium is pushed back as the reaction progresses.

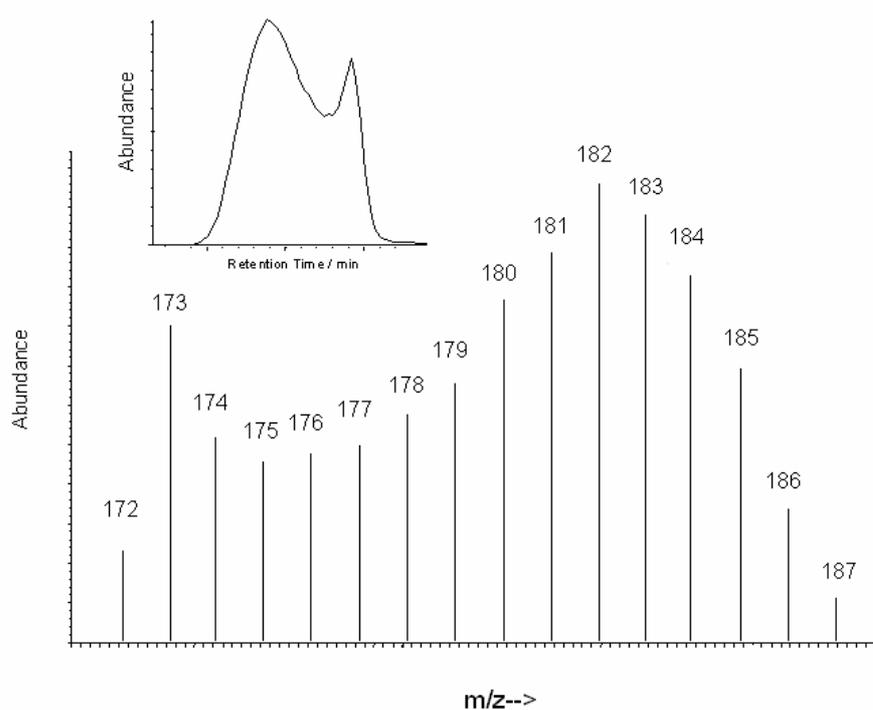


Figure 1-8 - Parent ions from methyl nonanoate formation in deuterated methanol¹⁶

When deuterated methanol is used as substrate, there is a distribution of deuterium content in the methyl nonanoate product (Figure 1-8). The peak of d₁ ester is due to the direct carbonylation of the substrate before the isomerisation equilibrium is set up. Most important is the presence of d₀ ester. In the carbomethoxy mechanism, there is no route by which such a product can be obtained, as the nucleophilic attack of the deuteromethanol would always give a deuterated product. The hydride mechanism however can rationalise this, as after β -hydride abstraction from the d₁ Pd-alkyl complex, unlabelled ethene can exchange with d₁ alkene and subsequent steps lead to d₀ ester, as is shown in Figure 1-9.

1.5 Other Conversions Demonstrated with DTBPMB Complexes

As discussed above, the methoxycarbonylation of higher alkenes, such as 1-octene has been demonstrated using DTBPMB and as such a patent has also been filed by Lucite.¹⁹ Due to the rapid thermodynamic equilibration of these alkenes during catalysis, the use of such internal alkenes as substrate has also been demonstrated.¹⁶ Such an observation has been made previously by Pringle *et. al.* using adamantyl cage diphosphines,²⁰ although superior rates and linear product selectivities were observed for DTBPMB complexes.

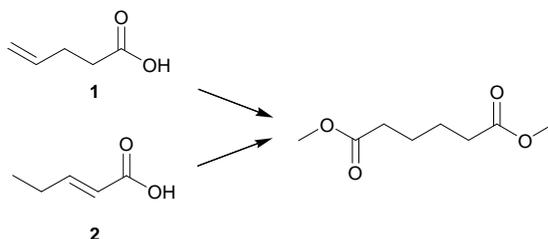


Figure 1-10 - Unsaturated pentanoic acids to dimethyl adipate

In addition, the carbonylation of unsaturated dicarboxylic acids and esters has been demonstrated using Pd complexes of DTBPMB.²¹ This conversion may be attractive as a route to making nylon 6,6 as well as dimethyl adipate, which is used as a plasticiser, in paint strippers and as a chemical intermediate. Dimethyl adipate can be formed catalytically by methoxycarbonylation of butadiene, although this is gaseous and hence more difficult to handle. Conversion of 4 and 2-pentenoic acid would give the required product, as shown in Figure 1-10, substrates **1** and **2** respectively. Conversion of **2** is particularly challenging due to the requirement to break conjugation. However, both substrates underwent complete conversion at 20 bar CO at 40 °C for 3 hours, with a selectivity of 96 / 97 % respectively.²²

Methoxycarbonylation of 1,3-butadiene was also attempted although yields here were disappointing. Another notable conversion that was not successful is that of allyl alcohols. Here it has been speculated that conversion is blocked by the formation of a stable 5-membered ring species in the catalytic cycle as is illustrated in Figure 1-11, below.²¹

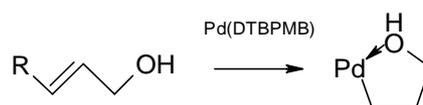


Figure 1-11 - Formation of 5-membered ring allyl alcohols

The use of Pd / DTBPMB complexes under basic conditions has also been found to be effective in the methoxycarbonylation of aryl chlorides, showing good selectivity for activated chloroaromatics such as 4-chloromethylbenzoate.²³ Surprisingly, when less activated chloroaromatics such as 4-chloroacetophenone are used, competition from nucleophilic aromatic substitution at the chloride occurs, forming additional methoxide co-products. When a less nucleophilic alcohol such as $\text{CF}_3\text{CH}_2\text{OH}$ is used with a weak base such as triethylamine, unactivated aromatic chlorides such as chlorobenzene could be carbonylated but reactions with deactivated aromatics such as 4-chloromethoxybenzene were not successful.

DTBPMB-palladium complexes have also been used in the synthesis of high value oxygenates from natural oils, which are produced in bulk as potential bio-fuels. These unsaturated oils contain a triglyceride ester terminus, from which one of a variety of unsaturated alkyl chains are present and can be produced so as to express high levels of a particular chain type, examples of such are given in Figure 1-12.

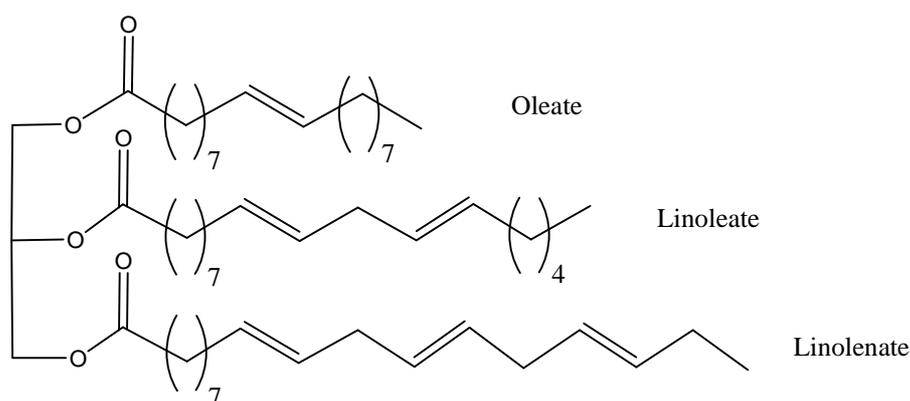


Figure 1-12 - Examples of natural oil ester chains

One feature common to these unsaturated chains is the 7-carbon alkyl chain between the carbonyl and the first alkene functionality. Jackson *et al.* have investigated tandem cross metathesis of these oils with a short chain alkene in order to cleave the ester chains at this position.²⁴ The use of the ruthenium-carbene based 2nd Generation Hoveyda-Grubbs

catalyst with an excess of *cis*-2-butene was most successful at achieving this.²⁵ The use of ethylene for this was poor as the resulting ruthenium-ethylene intermediate is unstable and leads to catalyst degradation; the presence of trace buta-1,3-diene also led to degradation of the catalyst. This procedure leads to efficient production of cleaved trimeric ester product, (at 97 % conversion) along with mixtures of cleaved internal alkenes, which could be easily separated (Figure 1-13).

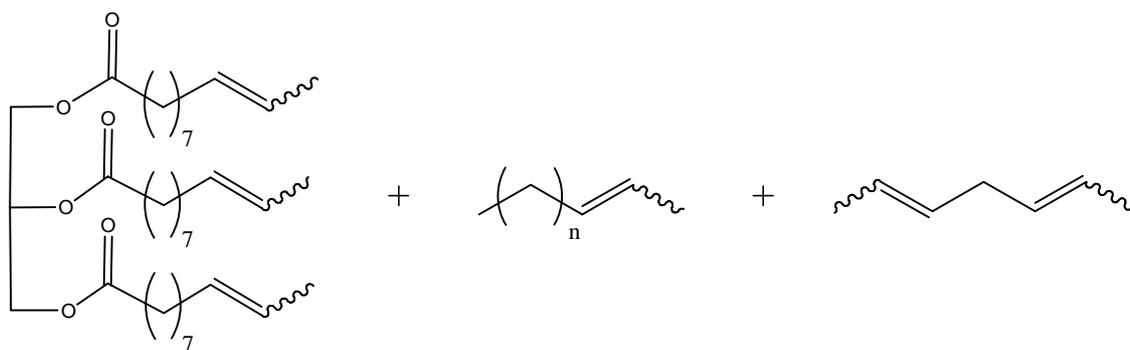


Figure 1-13 - Products from Grubbs-type cross metathesis of natural oils

Tandem isomerisation / methoxycarbonylation and transesterification of this unsaturated triester using Pd / DTBPMB complexes results in the highly selective production of dimethyl dodecanedioate in excess of 95 % selectivity, as shown in Figure 1-14. Conditions similar to those used for octene methoxycarbonylation were efficient here, although longer reaction times of 20 hours were required.²⁶ The group then followed on to demonstrate a one-pot metathesis-isomerisation-methoxycarbonylation-transesterification sequence, leading directly from the natural oil to terminal ester products in excess of 95 % selectivity.

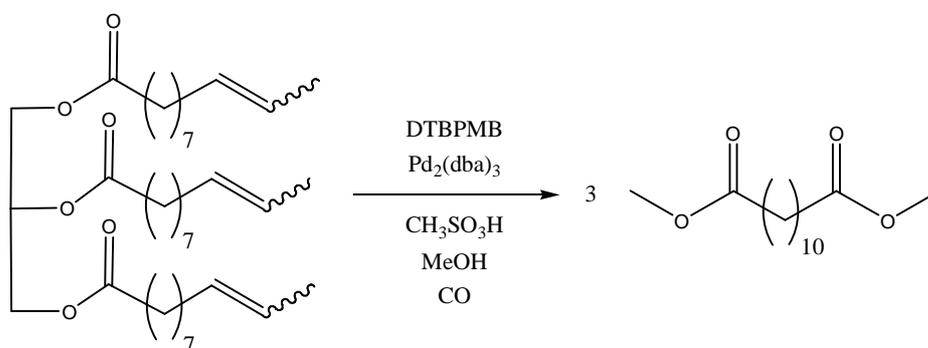


Figure 1-14 - Formation of dimethyl dodecanedioate using Pd-DTBPMB catalysis

1.6 Separation of Homogeneous Catalysts – An Overview

A major issue to address with any potential process development of the palladium / DTBPMB catalyst system, whether based on any of the transformations described previously or otherwise, would be that of catalyst separation. In the classical example of the Oxo hydroformylation process described, separation of the cobalt catalyst was effected by catalyst decomposition. This however is not a viable option when expensive ligands and precious metal catalysts are used, such as in this case.

Although product distillation can be viable, such as for ethene methoxycarbonylation and propene / butene hydroformylation, it fails for many heavier products due to the limiting thermal stability of the catalyst. For this reason, there has been intensive research into alternative strategies for homogeneous catalyst separation²⁷ for at least the last three decades¹ and so the major approaches taken to tackle this problem will be introduced here.

1.6.1 Biphasic Systems

This strategy involves modifying a catalyst system so as to be soluble in an immiscible phase to that containing the product; this is commonly achieved by the use of a sulfonated ligand system to create a water-soluble catalyst. The organic substrate can then be introduced within an organic phase and the reaction media efficiently mixed to allow reaction. The products can then be easily removed by decanting the organic phase, leaving the catalyst within the aqueous phase.

This strategy has been utilised commercially in the Ruhrchemie / Rhône-Poulenc process, where propene hydroformylation is performed using rhodium complexes of the trisodium salt of triphenylphosphine trisulfonate.²⁸ As the catalyst is present in the aqueous phase, this approach gives unacceptably low rates if the solubility of substrate is very poor in this phase. For this reason, commercialisation for larger substrates, such as those used to make detergent-grade aldehydes has not been performed.

The Shell Higher Olefins Process (SHOP) also exploits a biphasic system, here ethene is oligomerised to higher alkenes using a nickel catalyst which has been designed to be soluble in 1,4-butanediol. The heavy alkene products are immiscible in this highly polar solvent and so can be decanted.

1.6.2 Fluorous Systems

Fluorous systems attempt to overcome the problems of poor rates that can be associated with biphasic systems by exploiting the fact that fluorous solvents are generally miscible with organic solvents at typical catalytic reaction temperatures, yet phase separate at room temperature. To this end, 1-octene hydroformylation has been demonstrated in a perfluorocyclohexane / toluene using rhodium complexes of **3**.²⁹ (Figure 1-15)

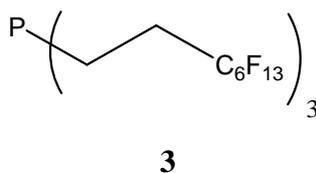


Figure 1-15 - Fluorinated ligand for fluorous biphasic catalysis

To allow separation, there is a requirement for a sample of the reaction mixture to stand in a “separation tank” in order to allow the mixture to cool and phase separate. This semi-continuous mode of operation, along with the high cost of the fluorinated solvents presents barriers to the large-scale use of this technique in bulk chemical processes.

Due to the scope of this project, the strategies of tethering homogeneous catalyst systems to insoluble supports and of product separation using ionic liquid / supercritical carbon dioxide flow systems will be discussed in more detail.

1.7 Supported Catalysis – Heterogenisation of Homogeneous Catalyst Systems

The concept of immobilising a homogeneous catalyst is relatively simple. The aim is simply to tether the homogeneous catalyst to an insoluble support and hence allow facile separation either by filtration or by the use of a fixed bed reactor.

Strategies for the immobilisation of homogeneous systems have taken one of four broad forms and these have been illustrated schematically in Figure 1-16. The idea of catalyst entrapment is probably the easiest strategy from a practical point of view as known catalysts can be used directly without the need for modification. Here, the catalyst is simply trapped within a polymer matrix. This form of immobilisation is highly likely to retain the catalytic activity of the complex but leaching of the complex from the support into the reaction solution is often unacceptably high.

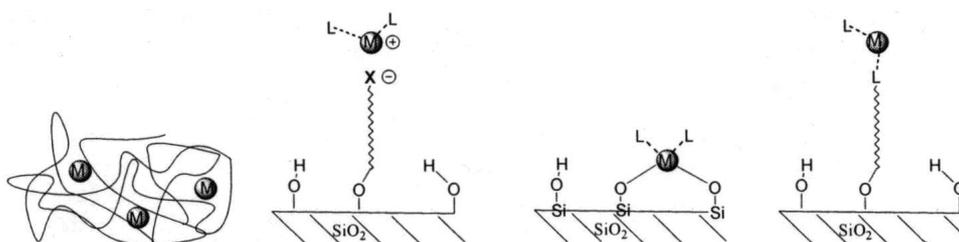


Figure 1-16 -Strategies for catalyst immobilisation; from left to right; catalyst entrapment, ion-pair interaction, metal anchoring to support and ligand anchoring to support. Adapted from ref. 30

It is therefore generally beneficial to have some form of interaction between the support and the catalyst. An ion-pair interaction between the support and complex is such an example, although this is often only suitable for ionic catalysts. Additionally, the catalytic activity may well be affected if the counter-ion is important. Leaching may also occur if the charge on the complex is lost during the catalytic cycle or salts are formed during the reaction.³⁰

By anchoring the complex to the support covalently, a much more robust link to the support is formed. This anchoring of the catalyst is ideally made through a ligand to the support. This however does involve the synthesis of a new ligand containing a suitable

binding motif to give a robust linkage and so inevitably involves additional development and cost.

1.7.1 Polystyrene Supports

Polystyrene-type polymers are the most investigated variety of organic support, both due to their ease of functionalisation and their relatively low cost. Their first major reported use was by Merrifield in his pioneering work on solid phase peptide synthesis.³¹ This work concerned the development of reversible linkages between the support and the peptide chain, an area that has continued to receive much interest and as such, many types of linkage have now been studied.³²

Supported catalysts of this form should not be confused with supported reagents of which there are many examples. There is a lot of interest in this field for developing novel solid supported synthetic methodologies and has been recently subject to a comprehensive review by Ley *et al.*³³ Supported reagents are immobilised reactive species (usually organic functionalities) that are generally used in stoichiometric quantities and then regenerated for subsequent recycles.

Polystyrene containing resins are generally synthesised by copolymerisation of styrene with a cross linker molecule such as divinylbenzene, (DVB) which is required to give the resin a 3-dimensional structure which prevents dissolution in organic solvents. The polymerisation process does not necessarily require a solvent, (*bulk polymerisation*) although due to the highly exothermic nature of the radical process, a solvent is generally used to act as a heat transfer agent.³⁴

A solvent compatible with the monomer can be used, (*solution polymerisation*) here the polymeric material will precipitate as it is formed. The most common synthetic technique however utilises a monomer-immiscible solvent, water for example, for styrene monomers. (*suspension polymerisation*, Figure 1-17) The mixture is efficiently stirred whilst radical initiation is effected, this results in the formation of spherical polymer beads or 'resins'. This synthetic technique could be easily modified to allow incorporation of functionalised groups such as phosphines by the copolymerisation of a vinyl or styryl functionalised derivative of the desired moiety.

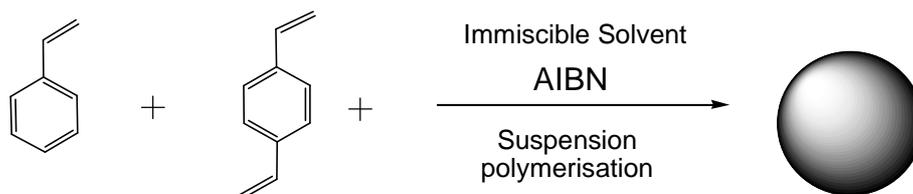


Figure 1-17 - Suspension polymerisation

For bulk chemical use however, polystyrene supports do have disadvantages; their organic nature means they are susceptible to thermal degradation, particularly if a reaction or reactor set-up is susceptible to the formation of hot-spots. Polymers that are lightly cross linked, (< 2 %) are known as *gel type* resins and swell significantly in organic solvents. This can lead to a support with a particularly poor mechanical strength, which can create practical issues. They are susceptible to physical break up in a reactor and can cause high resistance in fixed-bed type reactor setups.

Increasing the content of cross linker in the resin leads to enhanced mechanical strength but also significant chain entanglement, reducing the porosity of the resin. This porosity can be increased by the addition of inert solvents or diluents during polymerisation which template a rigid pore structure in the polymer and so swelling is less significant.³⁵ These resins are generally known as *macroporous* resins and are less susceptible to the physical break-up seen in *gel type* resins.

These resins are also more suited to polar solvents where *gel type* resins swell poorly. The more permanent porosity of *macroporous* resins means this is less of a problem. They can however suffer from lower loading capacities compared to *gel type* beads. Another approach is to modify *gel type* resins in order to increase their philicity to polar solvents by the grafting of polar poly(ethyleneglycol) onto the resin. ArgoGel and TentaGel are two commercially available supports in which this has been performed.³⁶

Even with these shortcomings, polystyrene resins have been used on large scales, especially in the application of ion-exchange processes. Polystyrene-based resins are popular for small to medium scale usage, such as in batch reactions and on laboratory scales. Here a wide range of supported catalysts for many reaction types have been explored; an area that has been the subject of recent reviews.^{37,38}

Triphenylphosphine-polystyrene (PS-TPP) was one of the first phosphine functionalised polystyrenes developed and is now available commercially. Initial syntheses of PS-TPP were by direct functionalisation of the resin by bromination and lithiation. The metallated polystyrene can then be quenched by diphenylchlorophosphine to give the supported ligand.

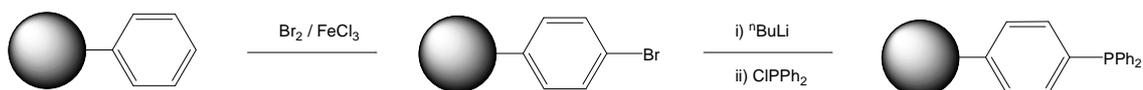


Figure 1-18 - Polystyrene-triphenylphosphine by direct resin functionalisation

Care must be taken in the comparison of conversions using resin-supported complexes due to the many different methodologies utilised in their synthesis and the lack of definitive characterisation of these catalysts. Treatment of polystyrene resins with metallating agents such as *n*-butyllithium can lead to side reactions and can contaminate the resins, affecting properties such as their swelling ability. This can also lead to a more poorly defined material and can affect reproducibility. An alternative therefore is to treat well-defined bromopolystyrene (ideally synthesised by *suspension copolymerisation* of styrene, bromostyrene and DVB) with a metallated phosphine, for example LiPR_2 or KPR_2 . This is the more common modern methodology for attaching a simple monodentate phosphine to polystyrene.³⁷

Supported metal complexes of these phosphines can then be synthesised from a suitable metal precursor or by ligand substitution with the analogous free phosphine complex. For example, the first palladium PS-TPP complexes were reported in the 1970's and were formed by ligand substitution from tetrakis(triphenylphosphine)palladium to PS-TPP, which was effected by heating (Figure 1-19).^{39,40}

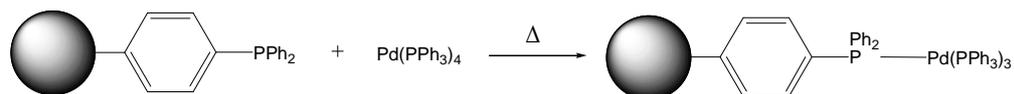


Figure 1-19 - Formation of palladium PS-TPP

Suzuki couplings with palladium complexes of PS-TPP were investigated by Le Drain *et al.*⁴¹ and were found to be very dependent on the palladium precursor used to make

the immobilised catalyst. Preformed tetrakis(triphenylphosphine)palladium was found to give significantly higher yields even at low metal loadings when compared to catalysts prepared from other metal precursors. (Table 1-2) Palladium leaching from these resins ranged from 0.60 - 0.65 mol % and the catalysts were stable to air and heat. They were also recycled 5 times with no observable loss in activity.

| Entry | Pd Source | Mol % Pd | Yield (%) |
|-------|---|----------|-----------|
| 1 | Pd(PPh ₃) ₄ | 3 | 94 |
| 2 | Pd(PPh ₃) ₄ | 0.1 | 90 |
| 3 | PdCl ₂ | 13.5 | 72 |
| 4 | Pd(CH ₃ CN) ₂ Cl ₂ | 4.4 | 85 |
| 5 | Pd(dba) ₂ | 1 | 90 |
| 6 | Na ₂ PdCl ₄ | 1 | 87 |

Table 1-2 - Effect of palladium precursor on coupling of phenylboronic acid to 4-bromopyridine

Grubbs *et. al* reported the first alkene hydrogenation catalyst based on an immobilised ruthenium complex.⁴² (Figure 1-20) Here the rate of reduction was found to be dependent on the size of the alkene and whether it is cyclic or acyclic. Going from acyclic to cyclic alkenes, or increasing the ring size of cyclic alkenes significantly affected the rate of catalysis. In both cases a drop in rate was observed and this was attributed to the catalysis largely taking place within the pores of the resin rather than on the surface. This catalyst was reused 10 times with a variation in activity of $\pm 10\%$.

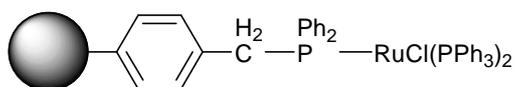


Figure 1-20 – Grubbs' alkene hydrogenation catalyst

Pitmann *et al.* found ruthenium complexes of PS-TPP and polystyrene-1,2-bis(diphenylphosphine)ethane (PS-DPPE) to be active in hydroformylation of 1-pentene. The supported catalysts were found to give a higher linear aldehyde selectivity compared to that of the homogeneous analogue. This selectivity was reduced as the loading of phosphine on the resin was lowered.

This can be rationalised by a concept known as “ligand matrix isolation”, first proposed by Grubbs *et al.* in 1977.⁴³ For the supported catalyst, there is effectively a higher concentration of phosphine than there is in an equivalent homogeneous system, as it is all concentrated on the resin beads. This higher effective phosphine concentration will result in a higher linear aldehyde selectivity in rhodium catalysed hydroformylation as has explained by Wilkinson *et al.*⁴⁴

The effective phosphine concentration in the matrix is a complex result of its structure; for example, a highly cross linked resin results in significant entanglement of the polymer chains. The pendant phosphines are therefore less mobile and so multiple phosphine complexation to rhodium is less favourable, hence resulting in a less selective catalyst.⁴⁵

The immobilisation of bidentate phosphines has attracted interest due to the superior ligating properties of these over monodentate phosphines. Diphosphines will usually adopt a bidentate binding motif and this should result in stronger binding to the metal centre due to the *chelate effect*.⁴⁶ This binding motif should significantly reduce the level of metal leaching from the support over that observed for monodentate ligands. Several groups have attempted immobilisation of the BINAP ligand, which was originally reported by Noyori for highly enantioselective hydrogenation reactions.⁴⁷

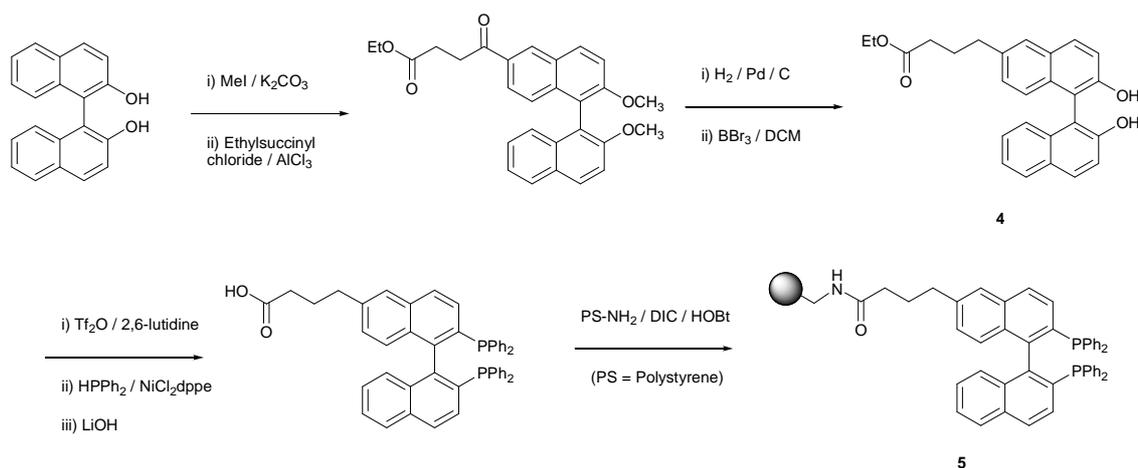


Figure 1-21 - Synthesis of an immobilised *R*-BINAP using amide linker⁴⁸

The diphosphine was originally immobilised by Bayston *et al.* using the synthetic scheme shown in Figure 1-21 above.⁴⁸ The phenol moieties of enantiomerically pure *R*-1,1'-Bi-2-naphthol (*R*-BINOL) were protected as their methyl esters, allowing acylation

and reduction of the resulting ketone to give **4**. This diphenol was then converted to the ditriflate and then catalytically phosphinated with two equivalents of diphenylphosphine using a nickel catalyst. This was then coupled to aminopolystyrene (amine loading - 0.21 mmol g^{-1}) under standard peptide coupling conditions to give the amide linked BINAP, **5** with a loading of immobilised ligand of 0.18 mmol g^{-1} . Ruthenium complexes of this material were synthesised from **6** (Figure 1-22) and these were tested in asymmetric hydrogenation reactions.

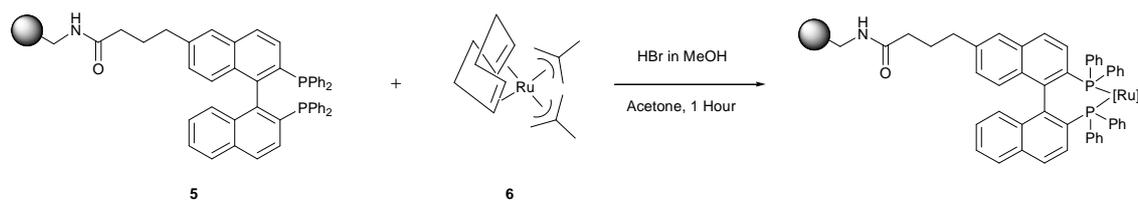


Figure 1-22 - Formation of immobilised R-BINAP-Ru complex

There were initial concerns that changing the symmetry of the BINAP molecule from C₂ to the pseudo-C₂ symmetry seen in the immobilised analogue would affect the enantioselectivity of this catalyst. However product *ee* was 97 %, dropping only slightly from the 99 % *ee* observed in the homogeneous case. For near quantitative hydrogenation, longer reaction times and temperatures were needed compared to the homogeneous catalyst and the immobilised system was reused 3 times with only a marginal loss of activity and selectivity. Ruthenium content of less than 1 mol % of that present in the supported resin was observed in the reaction products by inductively coupled plasma atomic emission spectroscopy (ICP-AES), hence leaching levels were low and the amide linker employed was demonstrated to be robust under the hydrogenation conditions applied.

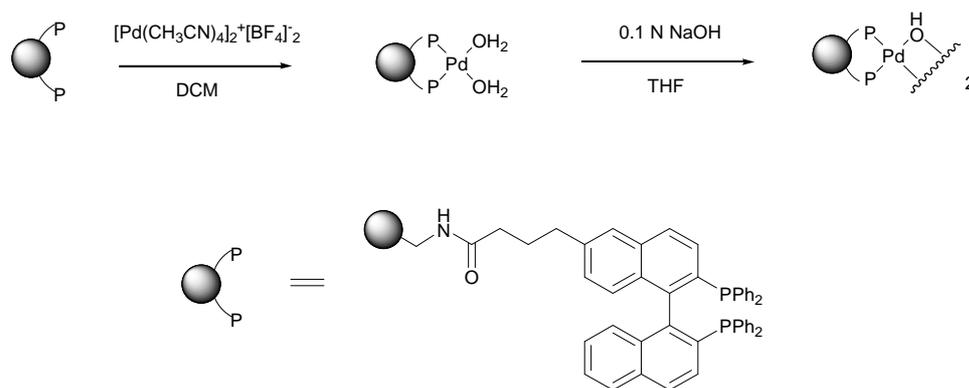


Figure 1-23 - Palladium complexes of immobilised R-BINAP

Two palladium complexes of **5** have also been reported as detailed in Figure 1-23; a di-aqua complex, **7** and a bridged di-hydroxo complex, **8**.⁴⁹ These have been found to be active in asymmetric aldol and Mannich type reactions respectively; although again there is a slight reduction in activity and selectivity on subsequent catalyst cycles.

Another rhodium based enantioselective hydrogenation catalyst has been reported by Nagel *et al.* for the hydrogenation of an α -(acetylamine)cinnamic acid.⁵⁰ (Figure 1-24) This ligand contains a carbon chain spacer between itself and the support and is also tethered by an amide functionality. The polymer backbone is optimised for the polar reaction environment with the use of a TentaGel resin. This optimisation gives observed rates and selectivities that are in line with those of the homogeneous analogue, demonstrating that with careful optimisation, supported catalysts can sometimes be as active as their homogeneous equivalents.

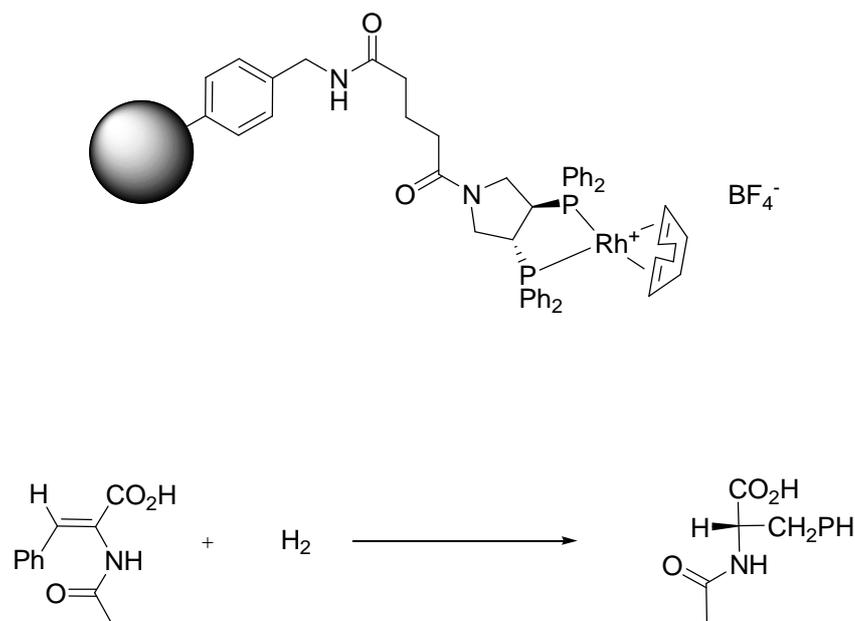


Figure 1-24 –Nagel catalyst (top) for enantioselective reduction of N-acetyldihydrophenylglycine (bottom)

1.7.2 Silica Supports

The use of silica as a support type for catalyst immobilisation has also been popular due to its high physical and chemical robustness. The first reports of silica immobilised catalysts appeared in the late 1970's. Such ligands were immobilised by functionalisation with alkoxy silane groups, these were then grafted to commercially available silicas *via* hydrolysis and subsequent condensation.⁵¹ (Figure 1-25, top scheme) Alternatively a silica surface is given a chloromethyl functionality and then all remaining silanol groups removed by reaction with excess trimethylchlorosilane (silylated). This material can then be coupled with KPR_2 to give a supported phosphine.⁵² These two methodologies are shown schematically in Figure 1-25.

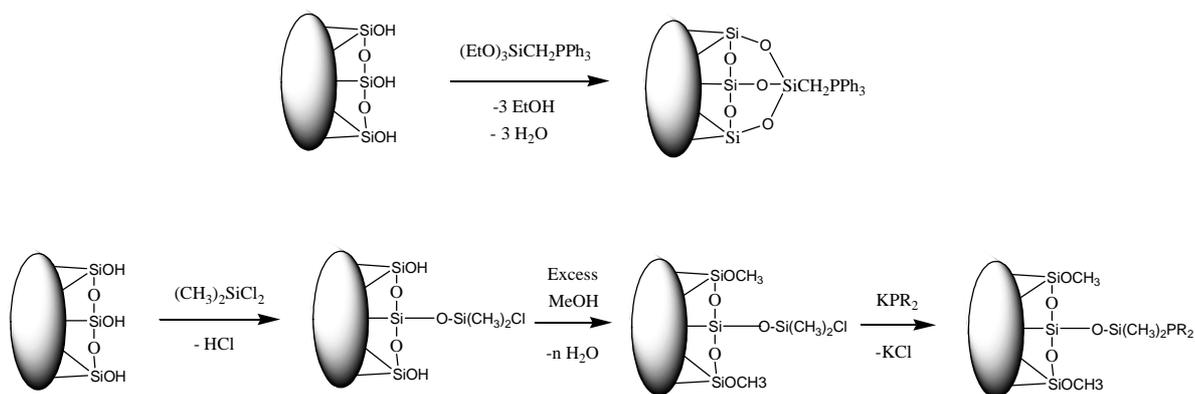


Figure 1-25 - Two methodologies for silica immobilisation of phosphine moieties^{51,52}

These early silica immobilised catalysts were active, although metal leaching was a severe problem, for example hydroformylation of 1-hexene was of poor selectivity using rhodium complexes of silica immobilised TPP.⁵³ This is thought to be due to free rhodium carbonyl species that had formed from metal leaching from the support. These complexes would effect rapid and unselective catalysis.

1.7.2.1 The Sol Gel Process

Another approach to the synthesis of silica supported catalysts was pioneered by Panster *et al.* and is known as the sol-gel process.⁵⁴ This process involves the hydrolysis of a tetraalkoxysilane to tetrahydroxysilane, which then undergoes a condensation-polymerisation to produce a polysilicate as shown in Figure 1-26.



Figure 1-26 - The sol gel condensation process

The mild conditions required and high homogeneity of the final product have made sol gel processing attractive for the synthesis of solid-state metal oxide materials such as ceramics.⁵⁵ These qualities make it equally attractive for the immobilisation of organic tethers, such as phosphine moieties to these oxide materials; in fact the procedure is mild enough to allow immobilisation of enzymes onto silica.⁵⁶ By exploiting the sol-gel procedure, with additional co-condensation of a trialkoxysilane functionalised monomer

of a phosphine; a silica polymer can be synthesised containing immobilised phosphines as pendant groups.

These sol-gel processed catalysts are remarkably active and stable. In 1-octene hydroformylation, Panster found no drop in catalyst performance over 1000 hours and almost no metal leaching – initial leaching of 2-3 ppm was reduced to 0.3 ppm after an initial start-up phase.⁵⁷ A relatively poor linear to branched ratio of products, of 1.5 was observed. Interesting, the ligands in these catalysts can be considered to be “site isolated”,⁵⁸ not showing the “ligand-matrix isolation” behaviour observed for polystyrene resins. This is thought to be due to the rigid structure of the polymeric backbone and so it is not possible for two phosphines to complex the same metal centre. This is the likely rationale for the low linear aldehyde selectivity observed for this catalyst.

Xanthene-based diphosphines have been shown to give high linear selectivity in alkene hydroformylation reactions and this is thought to be due to their large natural P-M-P bite angle.⁵⁹ Therefore van Leeuwen *et al.* synthesised polymeric silica structures containing related diphosphines using the sol-gel co-condensation technique.⁶⁰

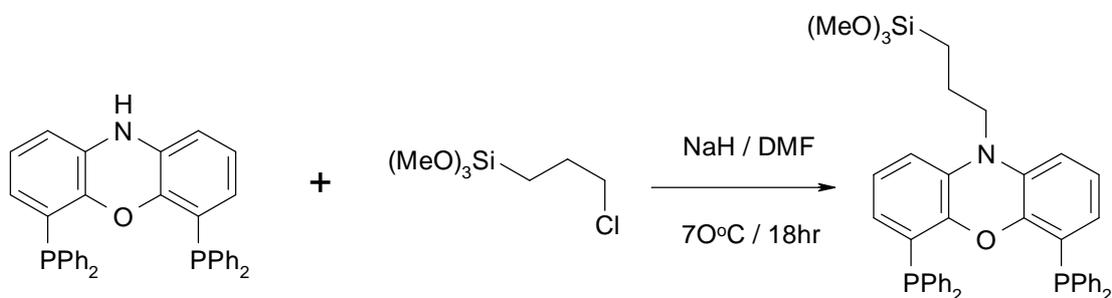


Figure 1-27 – Synthesis of a trimethoxysilane functionalised xanthene type ligand

N-(3-trimethoxysilane-n-propyl)-4,5-bis(diphenylphosphino)xanthene was given a trimethoxysilane functionality by coupling to 3-chloropropyltrimethoxysilane (Figure 1-27). The rhodium complex of this was then formed from reaction with the rhodium precursor, [Rh(acac)(CO₂)] prior to sol gel co-condensation. Interestingly this rhodium complex appeared to self-catalyse the sol-gel process, which normally requires addition of acid or base. Gelation occurred within an hour, compared to about 7 days in the absence of the complex⁶¹ to give the sol-gel immobilised complex illustrated schematically in Figure 1-28.

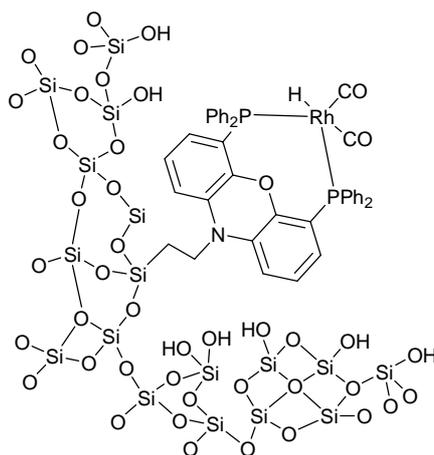


Figure 1-28 - Schematic representation of sol-gel immobilized rhodium-siloxantphos⁶¹

The performance of this catalyst in hydroformylation is good, giving 95 % linear aldehyde, which is comparable to the homogeneous system, the remainder being branched aldehyde and alcohol byproducts. Linear selectivity is also impressive with a linear to branched ratio of 65, over twice as high as is seen in the homogeneous system. The observed catalyst turn-over frequency (TOF) is about 15 % of that observed in the homogeneous system. The high linear selectivity was demonstrated to be due to the large natural bite angle of the ligand by comparison with sol gel immobilised N-(3-triethoxysilane-n-propyl)-N',N'-bis[2-(diphenylphosphanyl)-ethyl]-urea, (Figure 1-29 below); this gives a linear-to-branched ratio 15 times smaller.

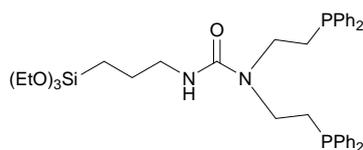


Figure 1-29 - N-(3-triethoxysilane-n-propyl)-N',N'-bis[2-(diphenylphosphanyl)ethyl]urea

The described method of preparation is important in obtaining this activity. If the Xanthene based diphosphine precursor is grafted onto a commercially available silica and then complexed to rhodium, a highly active yet poorly selective catalyst is formed. This is thought to be due to the formation of rhodium salts, from interactions with the slightly acidic surface silanols of the support. This would result in active and poorly selective rhodium catalysis by surface silanol complexes, such as SiO-Rh type complexes. Capping of these silanol groups was investigated, with the best results being

observed when triethylamine was used as a blocker. In this case, product selectivity was comparable to the homogeneous and sol-gel processed catalysts, although the rate was somewhat retarded, probably due to the coordinating ability of the amine.⁶²

Leaching from the sol-gel processed catalyst was not observed, being less than the detection limit of the ICP-AES technique of 1 ppm. There was also no observed deterioration of performance of the catalyst after 8 recycles or over repeated use over a 2 week period. The immobilised system is also an active hydrogenation catalyst, and so tandem hydroformylation-hydrogenation reactions have been demonstrated, converting alkenes to alcohols in one-pot with an overall selectivity to linear alcohol of 90 %.

Rationalisation as to why sol-gel processed catalysts show these significant improvements compared to conventionally grafted silicas has been attempted by Ciriminna *et al.*⁶³ They suggest several factors that are important to consider in catalysis within sol gel matrices. Sol-gel processing results in the catalyst moieties being entrapped deep within the pores of the silica matrix rather than largely on the surface of the support, as is the case for catalysts supported by grafting. In fact XPS analysis of the ruthenium-based catalyst, “Ormosil” was unable to detect any of the entrapped ruthenium after two minutes. This deep entrapment is thought to stabilise the catalyst moieties, both physically and chemically. In addition there is an increase in selectivity, as the pores are able to dictate the approach of incoming reactants to the active centre. The extreme dispersion of the catalyst in the matrix is also suggested to lead to the enhanced reactivity of these materials.

The HLB system is commonly used to assess surfactant materials, and is a measure of the relative percentage of hydrophilic and lipophilic regions on a molecule or material.⁶⁴ The HLB concept also becomes important for assessing sol gel catalysts due to the deep encapsulation of the active sites. A good balance between the hydrophilic matrix, the often hydrophobic reagents and the products is essential for efficient conversions by a sol-gel catalyst. For example catalytic hydrogenation using a sol gel entrapped rhodium catalyst has been shown to require a 5 % methyl modified silica for conversion.⁶⁵ If the catalyst is made more hydrophobic, the matrix retains the reagents / products within the pores and if no methyl modification is performed there is no conversion, possibly as the matrix is too polar to attract reagents into the pores.

1.7.3 [Other Support Strategies]

1.7.3.1 Supported Aqueous Phase Catalysis

An interesting strategy for catalyst immobilisation was developed by Davis and Hanson.⁶⁶ The concept, known as Supported Aqueous Phase Catalysis (SAPC) exploits the fact that in a biphasic system, reactions will largely take place at the phase boundary. Therefore by increasing this phase boundary, a more efficient catalyst system can be developed.

The concept involves using an insoluble support which has a narrow pore-size distribution and a hydrophilic surface; such supports are commercially available. To this is adhered a thin layer of aqueous solution containing a water-soluble catalyst; in this example, rhodium complexes of sodium tri(phenylphosphine-3-sulfonate) were used. These particles (shown schematically in Figure 1-30) are then used in an organic solution containing the reactants.

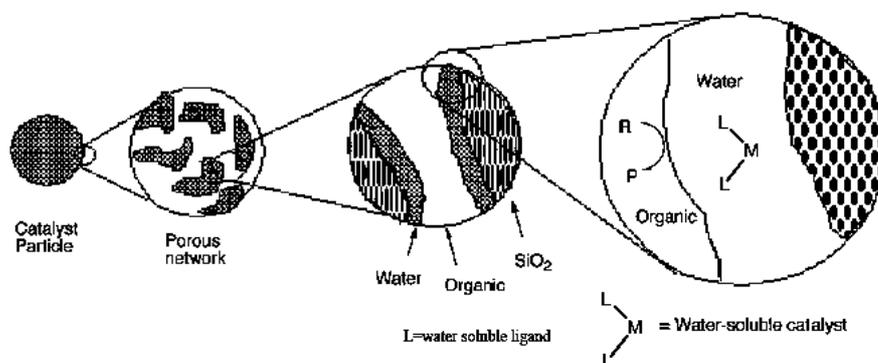


Figure 1-30 - Schematic representation of a supported aqueous phase catalyst from reference 30

This SAPC was shown to be active in 1-heptene hydroformylation, although the rate was highly dependent on the water content of the catalyst – if this is too small then a decrease in catalyst mobility causes low activity, if it is too high the reagent has to diffuse through the aqueous layer and so causes poor rates. This dependency on water content adds an additional level of complexity to an otherwise attractive concept.

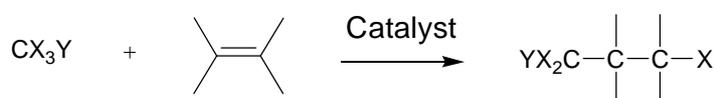
No reports of carbonylation catalysts utilising this technique could be located, although the use of sulfonated xanthene-type diphosphines for highly selective linear hydroformylation has been investigated.⁶⁷ A continuous flow system has also been demonstrated; here water leaches from the catalyst and so needs to be continuously replenished, although no metal appears to leach from the support.⁶⁸

1.7.3.2 Soluble Supports and Dendrimers

Soluble supports have attracted interest, as their increased homogeneity may overcome the observed loss in activity that is observed when immobilising onto insoluble supports. These soluble supports do show enhanced activity although separation can be more difficult with entanglement of the support leading to inefficient catalyst recovery.

Dendrimers are relatively well defined hyper-branched polymers which maintain a globular structure in solution. Their name is derived from the Greek *dendra* meaning tree as they have been described as having tree-like structures. Their good definition and relatively large size means separation can be effected using size-exclusion filtration techniques.

Dendrimers were first reported as catalyst supports by Van Koten *et al.*,⁶⁹ where a nickel pincer complex was immobilised onto the periphery of a siloxane dendrimer. This catalyst was shown to be effective at performing a Kharasch addition reaction, (Figure 1-31), which is the addition of a polyhalogenalkane over a double bond.



X = Halogen, Y = H, Halogen or electronegative group

Figure 1-31 - Kharasch addition

The dendritic catalyst was found to have a drop in activity of only 20-30 %, compared to its homogeneous analogue, and the dendrimer was found to have a retention of 99.8 % during nanofiltration. In continuous use however, deactivation occurred rapidly. As the dendrimer was clearly being retained efficiently, it was suggested that this loss in

activity was due to catalyst degradation to form an insoluble and inactive nickel(III) complex.⁷⁰

As well as acting as a support, immobilisation onto dendrimers can have an effect on the catalysis. Cole-Hamilton and co-workers reported that 1-octene hydroformylation using diphenylphosphine functionalised polyhedral oligomeric silsesquioxane (POSS) based dendrimers gave an enhanced linear selectivity compared to the individual dendron building blocks. This, “positive dendritic effect” was attributed to the increased steric crowding within the dendrimer, making bidentate coordination to the ruthenium more favourable.⁷¹

1.8 Catalyst Separation Using Ionic Liquids

1.8.1 Ionic Liquids – Properties and Applications

Ionic liquids (IL's) are low melting points salts; a definition that is generally regarded to include salts with a melting point of less than 100 °C.⁷² The existence of IL's has been known for a long time, with the first IL being reported in 1914 by Walden, who described the synthesis of ethylammonium nitrate (Figure 1-32); having a melting point of 12 °C.⁷³

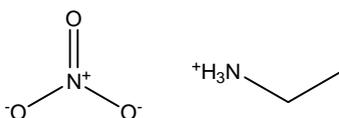
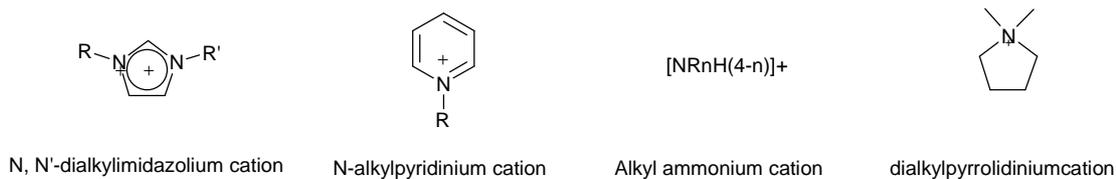


Figure 1-32 - Ethylammonium nitrate – the first reported ionic liquid

Since then, there had only been a handful of publications on IL's, primarily concerning their electrochemical properties up until the 1980's, when they were first proposed as solvents for organic synthesis.⁷⁴ Since then and notably in the last 7 years, there has been a boom of research interest into the properties and uses of these molten salts for a wide variety of applications. One of the defining properties of IL's has been their lack of a detectable vapour pressure. Recent work however has shown that some common IL's can be distilled without decomposition at reduced pressures.⁷⁵

IL's are generally made from two components (*binary ionic liquids*); one anion and one cation. One or both of these components is often bulky and poorly coordinating, hence giving them their characteristic low melting points. Some common anions and cations are illustrated in Figure 1-33. Physical properties, such as melting point, solvating properties and viscosity vary dramatically, depending on which combination of ions is used. This versatility has led to terms such as “designer solvents” being used to describe IL's.⁷⁶

Some Common Ionic Liquid Cations



Some Common Ionic Liquid Anions

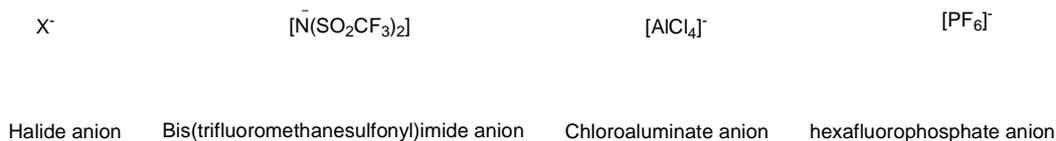


Figure 1-33 – Some common ionic liquid ions

R and R` = alkyl

IL's are of particular industrial interest due to their good, tailorable solvating properties,⁷⁷ non-flammability and extremely low vapour pressures; hence they may well offer a viable alternative to volatile organic solvents. They have often been termed “green solvents”, although there is still some dispute over this.⁷⁸ They are generally synthesised from petroleum derived feedstocks and initial toxicology studies have shown several imidazolium and quaternary ammonium based IL's to be more ecologically toxic than many common organic solvents.⁷⁹

Generalisations such as this are difficult to make over an entire class of material; however a major route of exposure to the toxic effects of solvents is through inhalation and the negligible vapour pressures of IL's prevent this problem. If utilised in efficient and highly recyclable processes, the environmental impact of processes utilising IL's can be significantly less than those based on conventional technologies.⁷⁴

1.8.2 Industrial Applications

Processes utilising IL's, either in a developmental stage or in commercial processes exist; examples of which follow. One of the first to be demonstrated is a biphasic process known as the Difasol process; developed by L'Institut Français du Pétrole (IFP).⁸⁰ Here the dimerisation of butenes takes place in a biphasic system where a nickel salt catalyst is immobilised in an imidazolium chloroaluminate based IL. (Figure 1-34) This is able to solubilise the butene substrate to a suitable degree, but has a poor solubility for the octene products and so these form a separate layer above the IL.

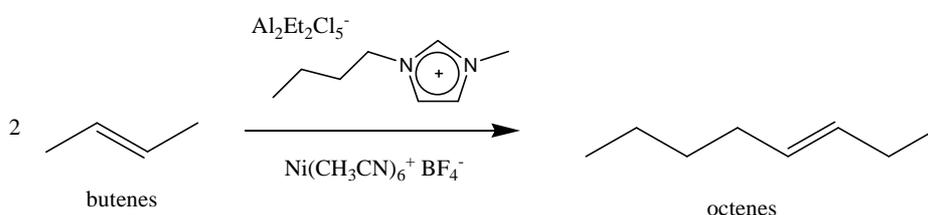


Figure 1-34 - Difasol process

In continuous flow mode, conversions to octenes of 70-80 % are reported with easy product separation by decanting in a separate settling tank. This reaction system has also been demonstrated to be effective in other organic transformations.⁸¹ This technology has now been developed and is considered the, “best technology choice” for this reaction type.⁸³ It is available for license but has not as yet been taken further than a pilot plant stage.

Eastman-Kodak operated a process involving a Lewis acid rearrangement reaction in an IL solvent.⁸² The process was in commercial operation for 8 years before being stopped in 2004 due to a general reduction in demand for the product.⁸³ It concerns the rearrangement of 3,4-epoxybutane (produced by Eastman by the vapour phase oxidation of 1,3-butadiene over a silver-alumina catalyst⁸⁴) to 2,5-dihydrofuran, which is used as a versatile chemical intermediate. Preceding literature had shown Lewis acid based homogeneous catalysts with iodide anions to be promising candidates for this conversion.⁸⁵ (Figure 1-35, below)

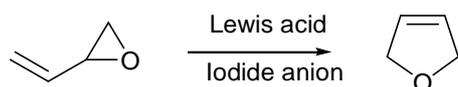


Figure 1-35 - Eastman-Kodak process for isomerisation of 3,4-epoxybutane to 2,5-dihydrofuran

Long alkyl chain phosphonium iodide IL's were found to be ideal solvents for this conversion, showing a good solubility for the reaction components. When used with an equimolar ratio of trioctyltin iodide as the Lewis acid, a stable system was set up in which efficient conversions were obtained. In laboratory scale experiments, product extraction was performed in batch using *n*-octane; on scale-up, a Continuously Stirred Tank Reactor (CSTR) and Karr extraction column were successfully utilised.⁸⁶

More recently, BASF have commercialised a process known as “Biphasic Acid Scavenging using Ionic Liquids” (BASIL).⁸⁷ The specific application of the commercial process is the removal of waste hydrogen chloride in the synthesis of alkoxyphenylphosphines, (Figure 1-36) which are important precursors for photoinitiators for printing inks and wood coatings.

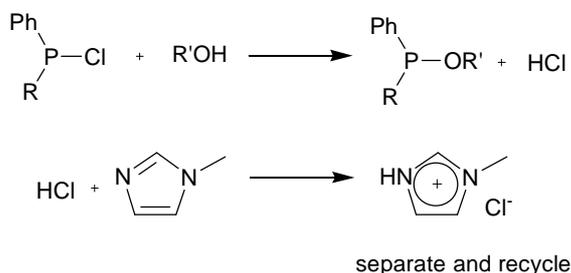


Figure 1-36 - BASIL process for acid scavenging

This acid is traditionally removed by neutralisation by a simple base and filtered; the BASIL process utilises 1-methylimidazole as base, creating a biphasic system where the newly generated IL can be separated gravimetrically. Although more expensive than simple bases, it can be regenerated and recycled and the gravimetric separation method is cheaper than filtration and so this process has been proven to be more economic. The generality of the BASIL process is particularly impressive and it could be applied to many other processes where waste acid is produced; silylations, esterifications (with acid chlorides) and eliminations (of HX) are just examples.⁸⁸

1.8.3 Ionic Liquid / Supercritical Carbon Dioxide Flow systems

A supercritical fluid is, “the defined state of a compound, mixture or element above its critical pressure (p_c) and critical temperature (T_c) but below the pressure required to condense it into a solid”.⁸⁹ For pure carbon dioxide, the supercritical phase is entered above a critical temperature of 304.3 K and a pressure of 73.8 bar, as is highlighted in its phase diagram. (Figure 1-37)

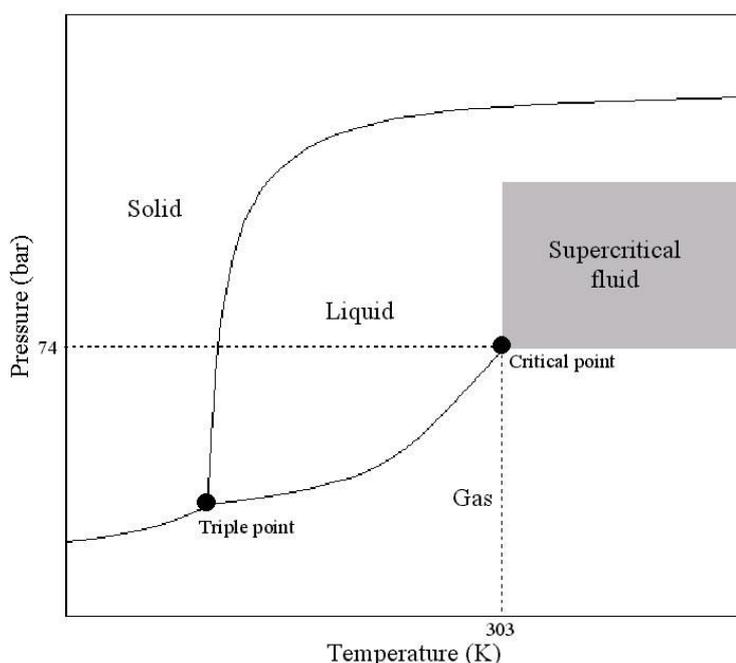


Figure 1-37 - Phase diagram for carbon dioxide⁸⁹

The properties of supercritical fluids (SCF's) have been described as being between those of liquids and gases.⁹⁰ SCF's have gas-like viscosities and diffusional properties, such as the ability to occupy all available volume, yet at the same time have liquid-like densities and as such, are able to efficiently solubilise liquids and solids. Supercritical carbon dioxide (scCO₂) has been widely used in research due to the relative ease of accessibility of its critical point, its relatively low cost and its lack of flammability and toxicity. These properties have also made its use on a large scale attractive and commercial applications for scCO₂ have been wide ranging, from natural product extraction⁹¹ to wood conservation⁹² and dry cleaning.⁹³

The decaffeination of coffee is probably the most well known commercial process utilising scCO_2 .⁹⁴ Here scCO_2 is used as an extraction solvent for caffeine. This is a viable alternative to conventional methods, which use ethyl acetate-water or dichloromethane-water extractions from the coffee beans. Thomas Swan (UK) has recently developed a commercial heterogeneous plant able to perform a variety of processes ranging from gram to tonne scales. The plant uses a scCO_2 flow extraction technique for processes such as hydrogenations and alkylations.⁹⁵

DuPont has developed a process for the synthesis of fluoropolymers, such as their Teflon™ brand product which utilises scCO_2 solvent as an alternative to a traditional aqueous *suspension polymerisation* preparation.⁹⁶ This process avoids the requirement to use environmentally damaging chlorofluorocarbons (CFC's) as well as providing advantages in polymer isolation and drying. The process has been commercialised in a \$40 million plant at Fayetteville, USA and a further \$235 million facility is planned.⁹⁷

A supercritical fluid / ionic liquid (SCF/IL) flow system puts a slightly different spin on these conventional supercritical fluid extraction techniques. In this concept, the aim is to immobilise a homogeneous catalyst by exploiting the combined properties of scCO_2 with those of IL's. It had been observed by Brennecke *et al.*⁹⁸ that scSO_2 is surprisingly soluble in certain IL's, reaching a mole-fraction of 0.6 at 8 MPa, yet the reverse is not the case, with generally no detectable IL solubility in pure scCO_2 observed.⁹⁹ Even when a relatively large amount of co-solvent is present, IL solubility remains low at significantly less than 10^{-4} mole fraction when 10-30 mol % of co-solvent is present.¹⁰⁰ The SCF and IL therefore form a biphasic system with the IL remaining at the bottom. The group were successful in using scCO_2 to extract naphthalene from 1-butyl-3-methylimidazolium hexafluorophosphate, ([BMIM][PF₆]) with no detectable IL present in the extract.

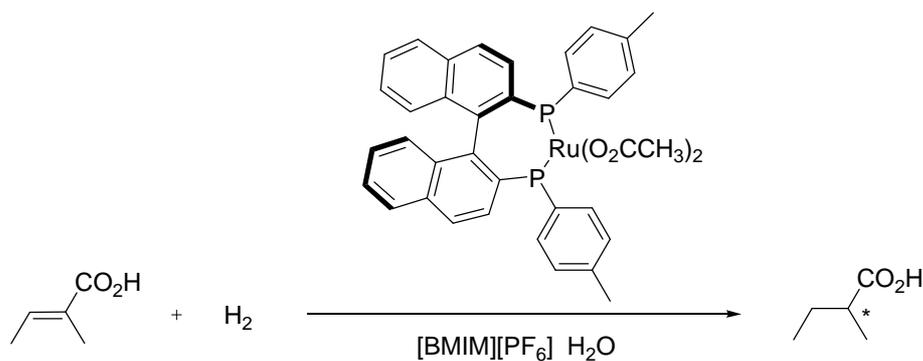


Figure 1-38 - Enantioselective hydrogenation of tiglic acid in [BMIM][PF₆]

Jessop *et al.*¹⁰¹ demonstrated that this concept could be used to perform repeated asymmetric hydrogenation reactions in batch mode, with product extraction using scCO₂. Here Tiglic acid was hydrogenated with high enantioselectivity using Ru(O₂CMe)₂((*R*-tolBINAP) in [BMIM][PF₆] (Figure 1-38). The same catalyst solution was recycled 5 times with no observed reduction in conversion or *ee*.

Webb *et al.* demonstrated the use of this technique in a continuous flow mode for hydroformylation reactions.¹⁰³ Initially utilising phosphite complexes but later with the 1-propyl-3-methylimidazolium salt of triphenylphosphine monosulfonate [PrMIM][TPPMS] on rhodium, continuous-flow hydroformylation of 1-octene was demonstrated. Here the octene reagent, along with synthesis gas and CO₂ were continuously flowed into a CSTR containing the IL immobilised catalyst. Extraction was effected by the scCO₂ flow and products isolated from this by decompression. This causes transition of the supercritical fluid into the gaseous phase, precipitating the previously solubilised organic products. A scheme of the reactor setup used is shown in Figure 1-39.

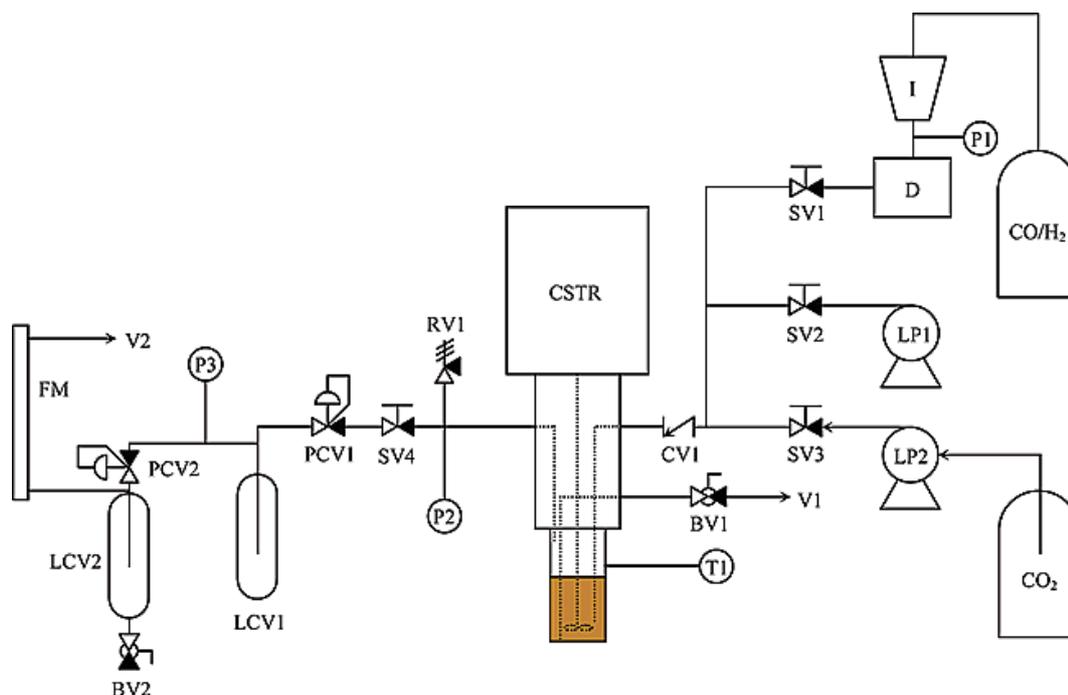


Figure 1-39 - Reactor setup for continuous flow hydroformylation¹⁰⁵

CSTR Continuously stirred tank reactor, CV Check valve, D Dosimeter, FM Flow meter, I Intensifier, LCV Liquid collection vessel, LP Liquid pump, P Pressure transducer, PCV Pressure control valve, RV Relief

Hexafluorophosphate and tetrafluoroborate based IL's were used initially and although they demonstrated proof of the concept, the results were poor.¹⁰² This was thought to be due to catalyst decomposition by small amounts of hydrogen fluoride, which is generated from the hydrolysis of these anions. Better results were observed using the sulfonamide based IL, 1-Octyl-3-methylimidazolium bis(trifluoromethanesulfonyl)-imide, ([OMIM][NTf₂]) under the optimised conditions detailed in Figure 1-40.¹⁰³

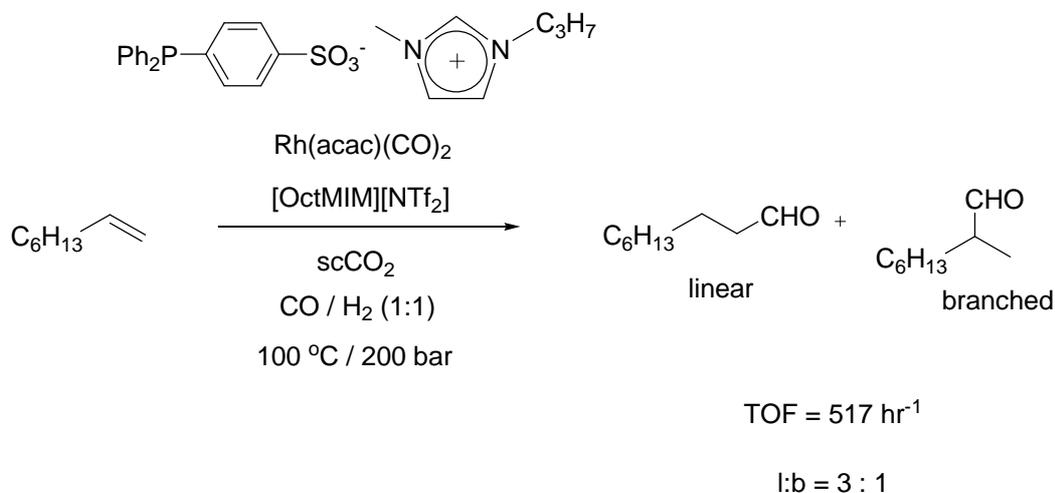


Figure 1-40 - Conditions for continuous flow hydroformylation of 1-octene

The increased solubility of octene in the long alkyl chain solvent, along with the increased stability of the anion is thought to be responsible for the increased performance of this system. Conversions of up to 87 % with catalyst turnovers of up to 500 hr⁻¹ were observed with rhodium leaching as low as 12 ppb, although this was significantly higher when the partial pressure of synthesis gas was low. The catalyst could be used for several weeks without visible performance loss. Deactivation was found to be due to phosphine oxidation, leading to the formation of [Rh₄(CO)₁₂]. This in turn leaches into the scCO₂ phase.

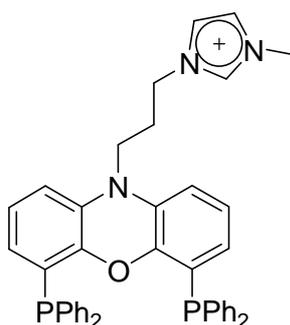


Figure 1-41 - Imidazolium functionalised xanthene ligand

Several modifications to this system have also been reported. The ligand was replaced with an imidazolium-functionalised Xanthene-based ligand, (Figure 1-41) as this ligand family has been shown to give high linear selectivities in hydroformylation reactions.¹⁰⁴ With this ligand, a higher linear-to-branched ratio of 40 was achieved, although catalyst TOF was lower and rhodium leaching was higher. A system containing only imidazolium salts of TPPMS and no IL solvent was also investigated, with the catalyst being dissolved in the reaction product. Here operating pressures could be reduced to 125 bar and conversions remained efficient.¹⁰⁵ The extent of rhodium leaching was found to be dependent on the alkyl chain length of the imidazolium cation but was generally higher than for the scCO₂ / IL system.

Processes based on these separation techniques have been compared to current commercial octene and propene hydroformylation processes. On an initial evaluation they appear to fare well.¹⁰⁶ One concern with the present scCO₂ / IL process is the high pressure required; whereas the scCO₂ / catalyst only process currently has high levels of

rhodium leaching. A fully recyclable, “green” process based on this type of separation has been proposed and is shown schematically in Figure 1-42.

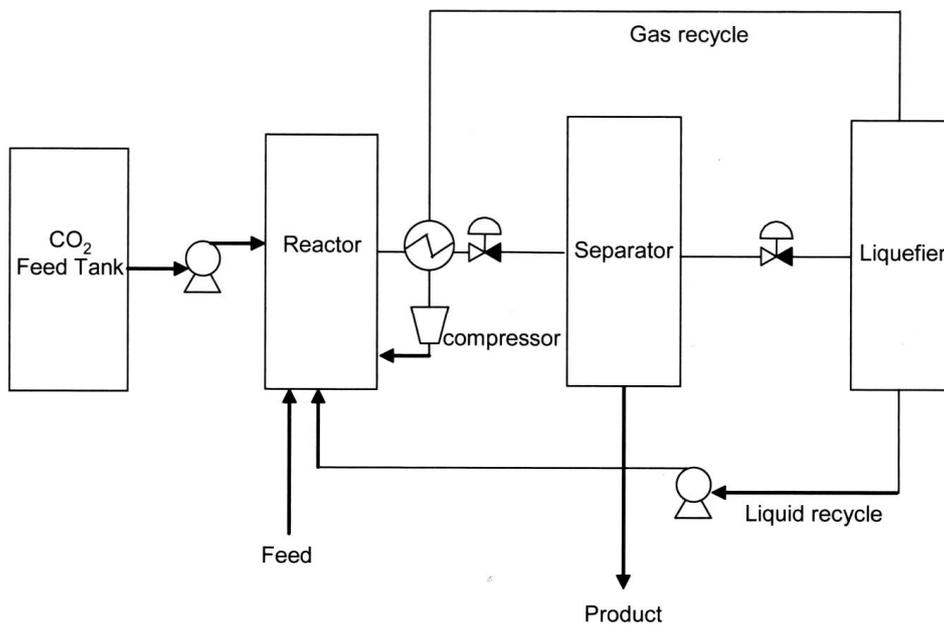


Figure 1-42 - Schematic for a recyclable IL/scCO₂ flow hydroformylation process¹⁰⁶

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2. Aims and Scope

The aim of this project was to investigate alternative separation techniques for methoxycarbonylation catalysts based on the 1,2-bis(di-*tert*-butylphosphinomethyl)-benzene (DTBPMB) ligand structure. To this end, the synthesis of immobilised systems using both polystyrene and silica as insoluble supports, where the ligand is strongly bound to the support in question has been attempted.

Adaptation of the DTBPMB ligand for use in a SCF / IL flow system has also been investigated as another possible technique for catalyst / product separation. For this, the synthesis of an ionic derivative of the DTBPMB ligand was attempted and the catalytic performance of palladium complexes of this ligand investigated, both in IL solvent and in an IL / SCF flow system.

A secondary aim was to investigate whether the addition of further bulk to the DTBPMB ligand could increase the stability of the resulting catalyst system. This would allow the development of methoxycarbonylation catalysts with higher TON's; the economic benefits of which are clear. This subject was not discussed in the introduction chapter as it forms its own story and will instead be introduced along with the subsequent results in Chapter 8.

3. General Methods and Terminology

3.1 Reagents and Experimental Environment

When experimental work was performed with the exclusion of air and / or moisture, standard Schlenk techniques were utilised to manipulate reagents within an argon or nitrogen atmosphere. The gas was passed through a column of silica to which Cr^(II) was adsorbed prior to use, in order to ensure its dry and anaerobic properties. All glassware was oven-dried, pumped and back-filled with argon 3 times prior to use.

When dried and / or deoxygenated solvents were used, dichloromethane (DCM) and N,N-dimethylformamide (DMF) were dried over calcium hydride and methanol over magnesium turnings and stored over pre-dried 4 Å molecular sieves. These were then distilled in an argon atmosphere prior to use. Petroleum ether (40-60 °C fraction), tetrahydrofuran (THF), diethyl ether and toluene were dried and deoxygenated using activated alumina and a copper catalyst using a solvent purification system (manufactured by Innovative Technologies, UK) of which water content was determined to be below 5 ppm (below 10 ppm for THF) by Karl-Fisher titration.

For all other solvents, drying was achieved using 4 Å molecular sieves (dried at 120 °C under high vacuum for 2 hours prior to use) and deoxygenation was generally accomplished by bubbling a steady stream of argon through a Schlenk tube containing the solvent for at least 30 minutes. For more volatile solvents, (for example deuteriochloroform) degassing was achieved after drying over 4 Å molecular sieves, by at least 3 freeze-pump-thaw cycles using liquid nitrogen / argon.

3.1.1 Purification of 1-Octene Feedstock

Before use, 1-octene was treated to remove any trace peroxide impurities using the following procedure;

Under anaerobic conditions, 1-octene (Alfa-Aesar, 500 cm³) was vigorously mixed with an aqueous solution of ferrous ammonium sulfate and left overnight. The alkene

was then washed with water ($3 \times 500 \text{ cm}^3$) and passed through a column of alumina before drying over 4 \AA molecular sieves. The octene was then degassed using argon by needle bubbling and stored under argon, in the dark until required.

3.2 Analytical Techniques

3.2.1 Solution state NMR

Liquid-phase NMR spectroscopy was performed on Bruker Advance™ 300 or Varian Gemini™ 2000 spectrometers equipped with quad probes for ^1H , ^{13}C , ^{31}P and ^{19}F observation. Both machines operate at 300 MHz for ^1H , 75.5 MHz for ^{13}C and 121.5 MHz for ^{31}P observation. ^{31}P -NMR spectra were run with proton decoupling unless otherwise stated. All NMR samples were measured in $> 99.9 \%$ deuterated chloroform (Aldrich) at 298 K unless otherwise stated. ^{13}C nuclei were collected using the Bruker, “PENDANT” pulse sequence which allows differentiation of resonance multiplicities. Residual deuterated solvent peaks were used as an internal reference for ^1H and ^{13}C NMR spectra with tetramethylsilane at 0 ppm and ^{31}P -NMR spectra were referenced to 85 % H_3PO_4 at 0 ppm.

3.2.2 Solid State NMR

Solid state ^{31}P -NMR were obtained from the EPSRC national solid state NMR service located at the University of Durham, UK, where spectra were referenced to 85 % H_3PO_4 .

3.2.3 Gas Chromatography

GC-MS analysis was performed on a Hewlett Packard 6890 series GC system fitted with both a flame-ionisation detector (FID) and a HP 5973 Mass Selective Detector (Electron Impact, EI). The GC employed a Supelco™ Meridian MDN-35 low polarity, cross-linked phase comprised of a (35 % phenyl)-methylpolysiloxane fused silica

capillary column (30 m x 0.25 mm x 0.25 mm). Data analysis was performed using HP-Chemstation™ G1701AA software version A.03.00.

The following method was used for analysis of GC-FID samples:

Start 50 °C, hold (4 min.), ramp at 20 °C min⁻¹ to 130 °C, hold (2 min.), ramp 20 °C min⁻¹ to 240 °C and hold (14.5 min.).

The following method was used for analysis of GC-MS samples:

Start 50 °C, hold (12 min.), ramp at 20 °C min⁻¹ to 160 °C, hold (8 min.), ramp 20 °C min⁻¹ to 320 °C and hold (30 min.)

3.2.4 C, H, N, S Elemental Microanalysis

Elemental microanalyses for atomic compositions of carbon, hydrogen, nitrogen and sulfur were carried out using the in-house service at St. Andrews by Ms. S. Williamson using a Carlo Erba 1106 Elemental Analyser.

3.2.5 Mass Spectrometry

Electron Ionisation (EI) mass spectra from GC samples were collected as described in section 3.2.2; all Time-Of-Flight (TOF), electrospray and Chemical Ionisation (C.I.) mass spectrometry were carried out by Ms Caroline Horsburgh at the in-house service at St Andrews.

3.2.6 Scanning Electron Microscopy (SEM) / Energy Dispersive X-Ray Analysis (EDS)

These analyses were performed at the St Andrews electron microscope facility using a JSM 5600 SEM fitted with an EDS (Energy Dispersive X-rays) system for analytical elemental analysis, on a SEM 5600 Inca Energy System for data collection and interpretation.

3.2.7 FT-IR Spectroscopy

IR spectra were recorded using a Perkin Elmer Spectrum GX-FTIR system, with measurements being taken in the mid-IR region (4000 – 600 cm⁻¹)

3.2.8 ICP-MS

Palladium ICP-MS determinations were performed at St. Andrews by Ms S. Williamson using an Agilent 7500 series ICP-MS spectrometer to analyse organic matrix samples and using palladium(II) acetate (Aldrich) as a palladium standard.

3.2.9 X-Ray Crystallography

X-ray crystal data collections and structure determinations were performed within the in-house facility at St Andrews University by Prof. A.M.Z. Slawin. Data were obtained using a Rigaku Mo MM007 (dual port) high brilliance generator with a Saturn 70 and Mercury CCD detectors incorporating two X-Stream LT accessories.

3.3 Definitions of Terms Used

Numerous catalytic terms are utilised throughout this thesis and although many are in common use in the literature, some can at times be ambiguous. Therefore for clarity, their meanings within this text are defined below. Reference to 1-octene methoxycarbonylation is made as this is the general reaction used throughout this thesis.

1. Conversion / %

The number of moles of substrate converted to reaction products. Isomerised alkenes are considered as substrates rather than products for this.

2. Selectivity / (%)

The number of moles of desired products obtained, over the number of moles of all products identified by GC, not including isomerised alkenes or known contaminants. For 1-octene methoxycarbonylation this refers to the *total* amount of methyl ester product produced; i.e. the linear ester (methyl nonanoate) as well as the branched. (methyl 2-methyloctanoate) Attempts are made to identify any major side products by GC-FID / GC-MS.

3. Linear to Branched Ratio (l:b)

The ratio of the generally more desirable linear ester (methyl nonanoate) present over that of the branched ester (methyl 2-methyloctanoate).

4. Isomerisation / %

In palladium catalysed methoxycarbonylation of linear C₃₊ alkenes, isomerisation of the original terminal alkene is rapid¹ and so the presence of other positional isomers of the alkene are observed. The isomerisation refers to the number of moles of *all* octene isomers observed (including 1-octene) over the number of moles of the original 1-octene substrate.

5. Turnover Frequency (TOF) / hr⁻¹

Refers to the activity of the catalyst; the number of moles of substrate converted to total ester product per mole of catalyst per unit time. No detailed kinetic studies were undertaken and so this number refers to the mean observed TOF.

6. Turnover Number (TON)

Is the total number of moles of product obtained per mole of catalyst performed by a given catalyst before activity is lost. Rather than defined as the point of total activity loss, this often refers to catalyst activity dropping below an acceptable threshold.

¹ C. Jimenez-Rodriguez, D.F. Foster, G.R. Eastham and D.J. Cole-Hamilton, *Chem. Commun.*, 2004, 1720.

4. Immobilisation onto Polystyrene

4.1 Covalent immobilisation

The use of polystyrene as a support has been discussed in Chapter 1 and, in this chapter, attempts to immobilise the 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) backbone onto such a support will be discussed. A robust covalent linkage is attractive and in order to create such a linkage, suitable functionalisation of the DTBPMB molecule will be required. In the triphenylphosphine-polystyrene (TPP-PS) based systems discussed in Chapter 1, metal leaching is relatively high, being in the region of 1-5 %, so too high for any bulk chemical application.¹ It is hoped however, that this bidentate binding ligand will reduce leaching due to chelation of the metal centre.

4.1.1 Potential Anchoring Sites for the DTBPMB Molecule

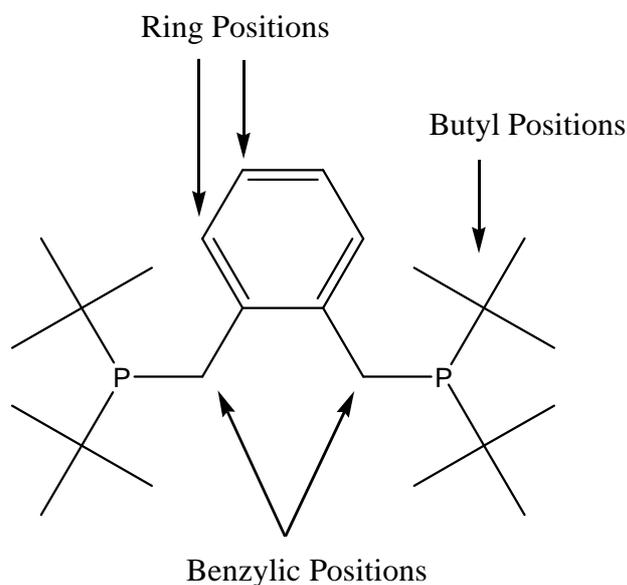


Figure 4-1 - Potential anchoring sites for DTBPMB

The DTBPMB molecule has three general sites at which a tether could be attached; at the benzylic carbons, the butyl positions and through the ring carbons. These are illustrated above in Figure 4-1. The benzylic positions are attractive from a synthetic point of view due to their inherent acidity, allowing relatively easy deprotonation here. Work at Lucite, however, has shown that substitution here has a detrimental effect on

the catalytic properties of the diphosphine.² On substitution of one of these positions with a methyl group, a significant reduction in the activity of the catalyst is observed; on methyl substitution at both benzylic positions no catalysis is observed. This dramatic effect may be because the semi-rigid backbone of the DTBPMB molecule is essential for its catalytic properties or it could be due to the change in the electronic environment of the phosphines, as the ³¹P-NMR signals are deshielded by approximately 20 ppm in the modified diphosphines.²

The *tert*-butyl groups have also been demonstrated to be essential in maintaining the catalytic properties of the molecule, as is discussed in detail in chapter 1. Ethene methoxycarbonylation is very poor, giving low rates and poor ester selectivities when the *tert*-butyl groups are substituted for less electron rich or less bulky groups, such as *iso*-propyl or phenyl groups.³ Functionalisation at the ring positions therefore presents the most attractive strategy for immobilisation of this molecule. Substitution here would be unlikely to affect the catalytic activity of the diphosphine, being remote from the molecule's active site. The methyl bridge protons also offer significant shielding of the aromatic system from the phosphorus positions, so any change in the ring electronics by substitution is unlikely to significantly affect the electronic environment of the phosphorus sites and hence the catalytic properties of the molecule.

4.1.2 Reported syntheses of DTBPMB

Before discussing the synthetic routes attempted to tether this molecule, it is useful to look at synthetic methodologies utilised to obtain DTBPMB itself. Preparation of DTBPMB in the open literature⁴ is performed *via* the deprotonation of *ortho*-xylene using *n*-butyllithium (ⁿBuLi), N,N,N',N'-tetramethylethylenediamine (TMEDA) and potassium *tert*-butoxide (KO^tBu) to obtain the corresponding dipotassium salt. This is then combined with two equivalents of di-*tert*-butylchlorophosphine (ClP^tBu₂) to obtain the desired diphosphine (Figure 4-2) with yields ranging from 31 – 69 % depending on conditions. Formation of the product *via* the di-Grignard of 1,2-bis(chloromethyl)benzene and subsequent quenching with ClP(^tBu)₂ has also been reported to give a 55 % yield.⁵

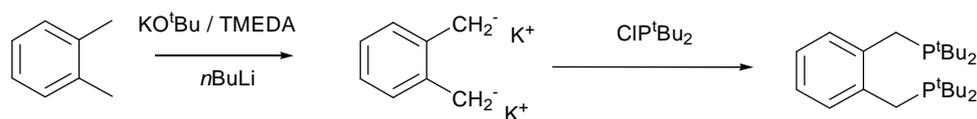


Figure 4-2 - Synthesis of DTBPMB via metallation of *ortho*-xylene

Good yields are obtained when two equivalents of $\text{LiP}(\text{tBu})_2$ (produced by $n\text{BuLi}$ metallation of the corresponding secondary phosphine) or are coupled with 1,2-bis(halomethyl)benzene.⁶ One problem with this synthetic route, however, is the production of significant quantities (ca 40 %²) of a cyclic phosphonium salt by-product, which is not observed for the 1,3-diphosphine where quantitative yields are reported.⁷ The phosphonium salt is thought to be formed in this case because of an intramolecular reaction of the monosubstituted phosphine intermediate. The lone pair of phosphorus is thought to perform an attack onto the nearby electrophilic benzylic carbon, forming a stable 5-membered ring phosphonium salt; (Figure 4-3) in fact, the use of dimethylchlorophosphine has been reported for the synthesis of such cyclic phosphonium salts.⁸ Attempts at Lucite to cleave this ring have been unsuccessful.²

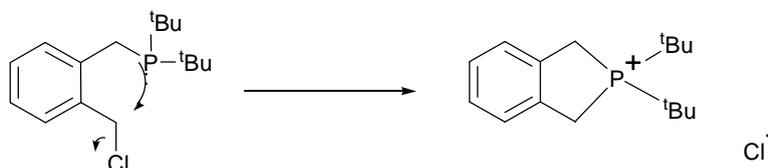


Figure 4-3 - Formation of a stable 5-membered ring phosphonium salt

To overcome this, Lucite has developed a more efficient route to DTBPMB by using a boron protected secondary phosphine. This can be synthesised in a relatively high yield from the corresponding chlorophosphine using sodium borohydride. $\text{HP}(\text{tBu})_2(\text{BH}_3)$ is then lithiated using $n\text{BuLi}$ and quenched using 1,2-bis(chloromethyl)benzene; as summarised in Figure 4-4.

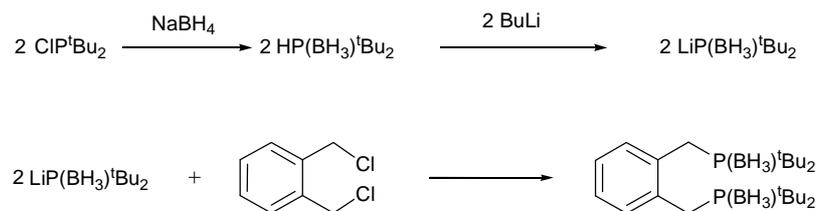


Figure 4-4 - DTBPMB via a boron protected secondary phosphine

Deprotection of boron protected phosphines such as this can be performed by the addition of a base, such as diethylamine⁹ or morpholine;¹⁰ however this is an equilibrium reaction and gives only moderate yields in this case, probably due to the high basicity of these phosphines. Lucite has therefore developed a more efficient method of deboration by conversion of the phosphine-borane to protonated phosphonium using 3 equivalents of the strong protic acid, methanesulfonic acid. This is then subsequently deprotonated by neutralisation using an ethanolic sodium hydroxide solution to yield the free phosphine, as is shown in Figure 4-5. This strategy has been reported to give clean deprotection in high yields in other phosphine syntheses.¹¹

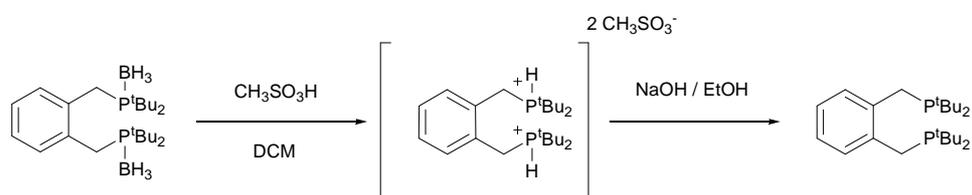


Figure 4-5 - Deboration of DTBPMB-BH₃ adduct

In the chapters that follow, a combination of these synthetic strategies will be utilised in attempts to synthesise immobilised derivatives of DTBPMB.

4.1.3 Immobilisation *via* Suzuki Coupling to Polystyrene

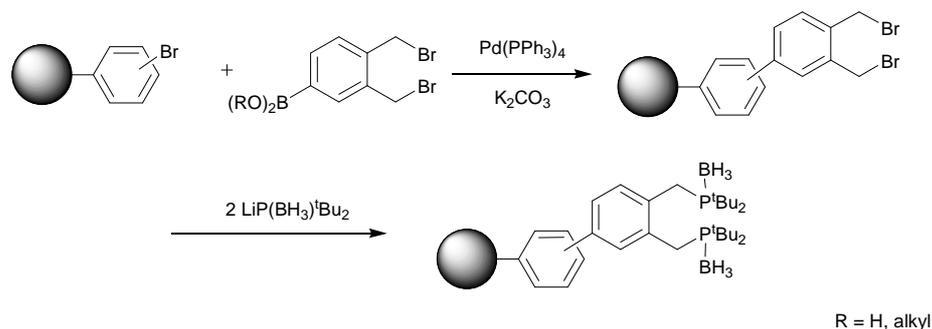


Figure 4-6 - Proposed synthesis of polystyrene-immobilised DTBPMB *via* Suzuki coupling (Route 1)

Immobilisation of DTBPMB was proposed by coupling of bromopolystyrene with a suitable boronate containing bis(methylhalide) groups in an *ortho* configuration. This product could then be reacted with $\text{LiP}(\text{BH}_3)^t\text{Bu}_2$ to produce the desired diphosphine, as is summarised in Figure 4-6. There was concern that reactivity of the benzylic bromides, although these would readily oxidatively add to the palladium (0) centre, reported Suzuki coupling of these functionalities appear to require slightly more forceful conditions.¹² The use of boron-protected phosphine was chosen to avoid cyclic phosphonium salt formation, as such side-products would be bound to the resin and so could not be simply washed away, as in the case of the free phosphine synthesis.

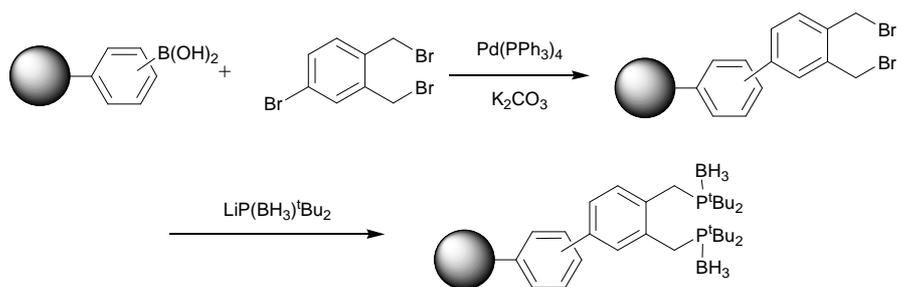


Figure 4-7 - Proposed synthesis of polystyrene-immobilised DTBPMB *via* Suzuki coupling (Route 2)

As a variant of this route, the use of immobilised boronic acid, along with a suitably functionalised aromatic bromide was also investigated, as shown in Figure 4-7. (Route 2) Although such a functionalised resin is not commercially available, its synthesis has been reported.²³ This second route has potential advantages over the first as this precursor should be more readily accessible, synthetically. In addition, the use of

polystyrene-immobilised boronic acid has been reported to produce cleaner functionalisation of the resin in Suzuki-type couplings compared to bromopolystyrene, as the palladium catalyst used for the Suzuki coupling is thought to ‘clean up’ any unreacted boronic acid moieties to hydrogen functionalities when longer reaction times are used.¹³

4.1.4 Synthesis of Boronate Precursor for Route 1

Synthesis of a suitable boronate precursor was based on a literature preparation of a related *para*-tolyl derivative.¹⁴ This involved converting *para*-bromotoluene to the corresponding Grignard and quenching with tri-*iso*-propyl boronate. The use of 4-bromo-*o*-xylene in this related conversion was attempted under the conditions described. (Figure 4-8)

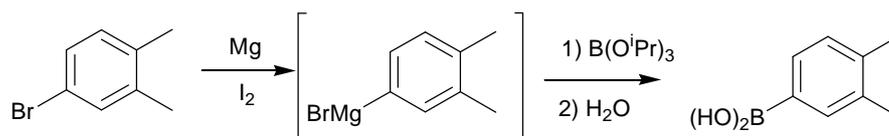


Figure 4-8 - Boronate preparation from 4-bromo-*o*-xylene

Following this procedure, attempts to crystallise the product led to the slow formation (4 – 5 days) of a highly crystalline solid that lacked the expected *iso*-propyl signals by ¹H-NMR. High-resolution time-of-flight mass spectrometry (TOF-MS) identified this as the boroxirane trimer of the desired boronate; such boroxiranes have been observed before in similar preparations.¹⁵ A reference to this product, where it had been synthesised by hydrolysis and subsequent oxidation of the corresponding dichloroborane was located, although only microanalysis and melting point were reported in its characterisation.¹⁶ This boroxirane was converted to the pinacol boronate in high yield by acid hydrolysis and subsequent esterification using pinacol by a published method for a related aromatic boroxirane.¹⁵ (Figure 4-9)

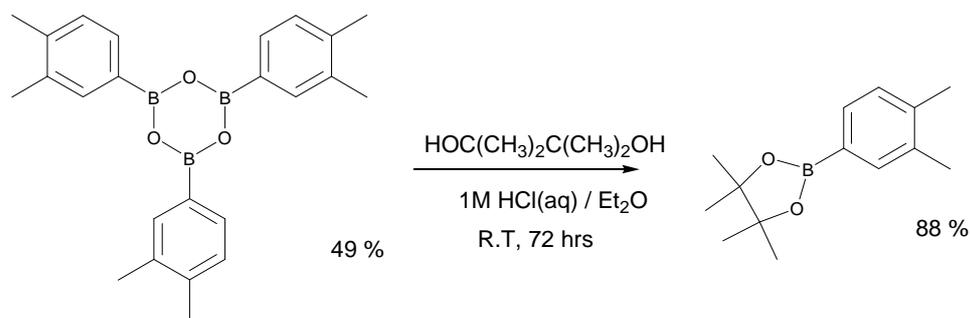


Figure 4-9 -Hydrolysis of boroxirane and formation of corresponding pinacol ester

The benzylic methyl groups of this pinacol ester were successfully brominated by radical bromination using 2.2 equivalents of N-bromosuccinimide, (NBS) using benzoyl peroxide as a radical initiator.¹⁷ This procedure produced crystalline bis(bromomethyl) functionalised product in a moderate (39 %) yield (Figure 4-10).

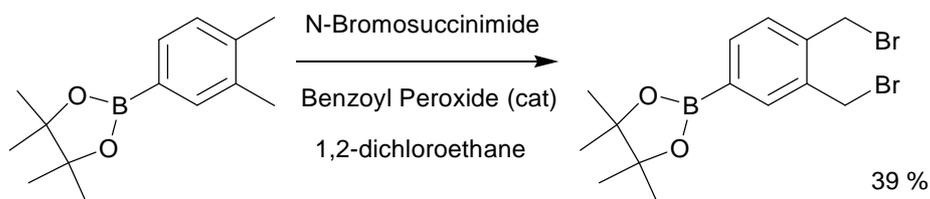


Figure 4-10 - NBS Bromination to suitable boronate precursor

4.1.5 Synthesis of Aryl Bromide Precursor for Route 2

The aryl bromide precursor required for route 2 was also successfully prepared from NBS bromination of commercially available 4-bromo-*o*-xylene in 48 % yield. (Figure 4-11) Several preparations of the related *m*-xylyl compound have been previously reported by such a route.¹⁸ Preparations by bromination of 4-bromo-*o*-xylene using elemental bromine and ultraviolet irradiation in carbon tetrachloride¹⁹ and water²⁰ have also been reported; although this conversion was successfully reproduced using 1,2-dichloroethane as solvent, the resulting oil was more difficult to purify.

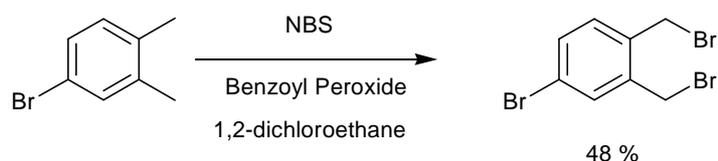


Figure 4-11 - Preparation of 1,2-bis(bromomethyl)-4-bromobenzene

Preparation by ring bromination of 1,2-bis(bromomethyl)benzene was also considered. Although halomethyl substituents deactivate ring systems towards electrophilic aromatic substitution,²¹ sodium bromate with sodium bisulfite has been described as a powerful brominating agent for such conversions.²² The use of the described conditions gave no conversion for 1,2-bis(bromomethyl)benzene and although bromination of 1,2-benzenedimethanol (as reported)²² followed by conversion to the desired product using, for example, PBr_3 , could be envisaged; this was not attempted, as the successful one step preparation was likely to be more efficient.

4.1.6 Polystyrene-Boronic Acid for Route 2

The preparation of polystyrene-boronic acid for use in Suzuki-type couplings has been described by Kell *et al.*¹³ by metallation of bromopolystyrene, followed by addition of tri(isopropyl)boronate and subsequent hydrolysis. Thomas *et al.*²³ claim *iso*-propyldi(*n*-butyl)magnesium lithium (${}^i\text{Pr}({}^n\text{Bu})_2\text{MgLi}$) as a superior metallating agent for bromopolystyrene compared to *n*-butyllithium, leading to higher conversions and better defined catalysts.

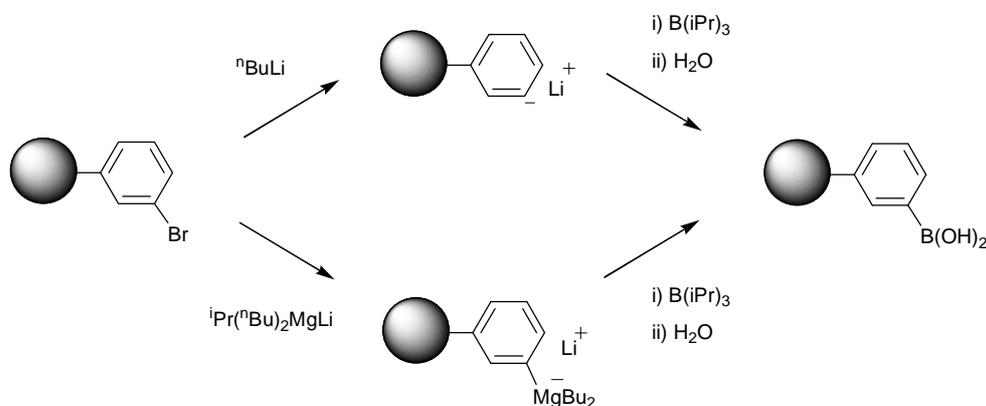
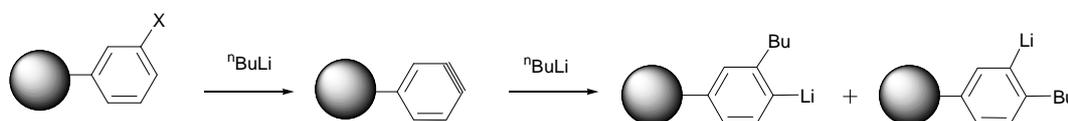


Figure 4-12 - Two reported preparations of polystyrene-boronic acid

It is suggested that $i\text{Pr}(\text{}^n\text{Bu})_2\text{MgLi}$, (also known as Oshima's complex after its original developer²⁴) does not cluster like *n*-butyllithium and so is more able to diffuse through the polystyrene network; hence allowing more complete exchange of bromine moieties that reside deep within the pores. The reagent could also be less susceptible to unwanted side reactions that can occur between *n*-butyllithium and polystyrene resins such as the formation of benzyne, which can lead on to butyl-substituted rings and the coupling of lithiated rings to nearby halogenated rings. (Wurtz coupling) Both of these side reactions would consume more butyllithium than has been accounted for, as is illustrated in Figure 4-13.²⁵

Benzyne Formation



Wurtz Coupling

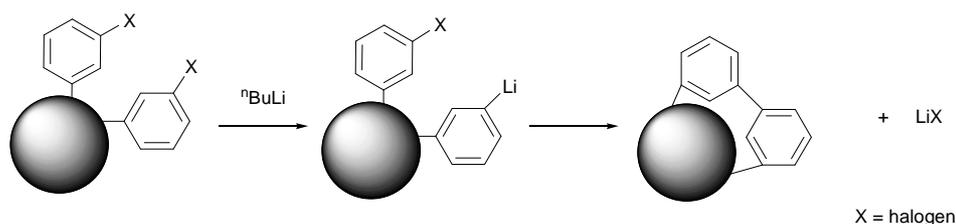


Figure 4-13 - Possible side reactions when metallating halopolystyrenes using ${}^n\text{BuLi}$ ²⁵

$i\text{Pr}(\text{}^n\text{Bu})_2\text{MgLi}$ is easily prepared from $i\text{PrMgCl}$ and two equivalents of ${}^n\text{BuLi}$ ²⁴ (Figure 4-14) and so syntheses of polystyrene-boronic acid using this reagent and with ${}^n\text{BuLi}$ were compared. Commercially available, bromopolystyrene of an intermediate bromine loading (2.5 mmol g^{-1}) was used and the resulting resins washed extensively in THF using a Soxhlet apparatus overnight.



Figure 4-14 - Preparation of $i\text{Pr}(\text{}^n\text{Bu})_2\text{MgLi}$

The reported preparations on polystyrene-boronic acid use boron microanalysis to characterise the products.^{13,23} However, this was not readily accessible and therefore

conversion of these resins was analysed by determination of their residual bromine content. This was achieved using by a back-titration method originally described by Volard.²⁶ This determination requires all material to be in solution and so in order to homogenise organic samples; these are generally digested in concentrated nitric acid prior to the analysis. However, heating of these resins to 130 °C in concentrated nitric acid, followed by mixing overnight did not digest the beads and the resulting mixture gave no precipitate upon addition of silver nitrate.

As an alternative therefore, the beads were decomposed in a closed oxygen atmosphere and the residue subsequently absorbed into a suitable solvent following a documented method.²⁷ Full details of this digestion and the Volard back-titration methods are given in Section 4.3.6. The bromine levels of the ⁿBu(ⁱPr)₂MgLi and ⁿBuLi processed resins, as determined by this method, are shown in Table 4-1.

| Sample | Br Concentration / mmol g ⁻¹ | Conversion / % |
|--|--|-------------------|
| bromopolystyrene | 2.23 | n/a |
| ⁿ BuLi processed | 1.02 | 54.4 |
| ⁱ Pr(ⁿ Bu) ₂ MgLi processed | 0.04 | 98.1 |

Table 4-1 - Bromine content on polystyrene resins by Volard titration
Bromine concentrations calculated as the mean of at least 2 consistent (+/- 0.05 mmol g⁻¹) titrations

The commercial bromopolystyrene was analysed to verify the analytical method, this commercial sample is reported to have a bromine loading of approximately 2.5 mmol g⁻¹ and the loading level determined here was used to calculate the conversions for the other two resins. The significant improvement in conversion when using ⁱPr(ⁿBu)₂MgLi is clear from this analysis, with almost complete conversion of the bromine functionalities in this case.

EDS analysis of the resin was also performed; with peaks observed for C, Br and O; (Table 4-2) unfortunately boron determination was not possible here due to significant overlap of the K_α energies of boron with those of the significant carbon content of the resin. The loss of bromine from the samples is however apparent when compared to the oxygen content which was assumed to be from boronate moieties. From the determined

atomic ratios of O and Br, a conversion of 98.4 % is calculated. As this technique observes only surface atoms, the values obtained cannot be generally be considered quantitative; however the good agreement of this data to that obtained from the Voldhart analysis does suggest that this conversion has occurred fairly homogenously throughout the beads, rather than primarily on the surface.

| Element | C | O | Br |
|-----------------|----------|----------|-----------|
| Weight % | 74.75 | 23.36 | 1.89 |
| Atomic % | 80.75 | 18.95 | 0.31 |

Table 4-2 - EDS analysis for PS-B(OH)₂ – C,O,Br normalised to 100 %*

* Mean results from analysis of 5 different bead samples

4.1.7 Suzuki Coupling and Phosphination to Resins

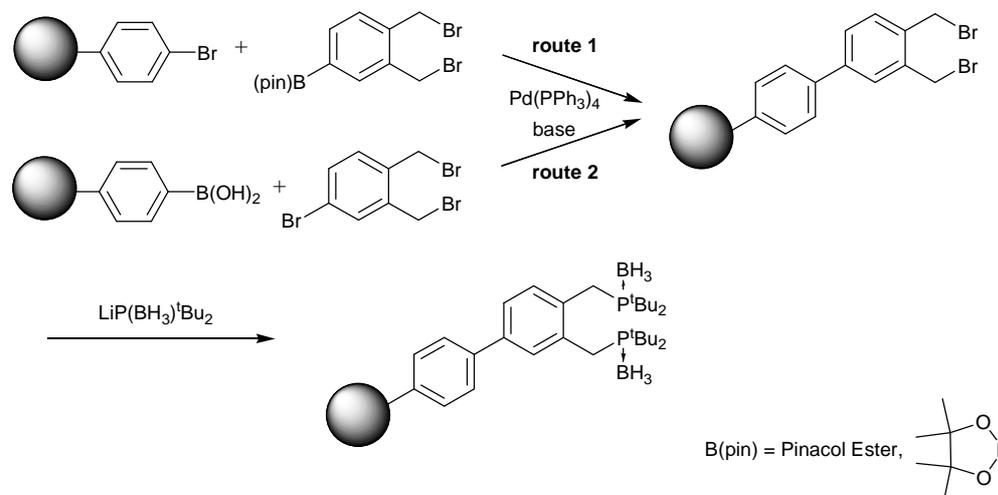


Figure 4-15 - Two preparative routes investigated using Suzuki couplings

Suzuki couplings were performed using the aryl bromides and boronates prepared, giving the two preparative routes illustrated in Figure 4-15. The coupling method employed was based on a literature preparation;²⁸ where dimethoxyethanolamine (DME) solvent was used with 6 mol % of tetrakis(triphenylphosphine) palladium ($\text{Pd}(\text{PPh}_3)_4$) and potassium carbonate as base. The solubility of the bis(bromomethyl)benzene substrates was poor in DME alone and so a DME / THF solvent mixture was used instead. The reaction mixtures were generally heated to 80 °C for 92 hours with gentle mixing using a small magnetic follower, to minimise physical degradation of the beads.

A concern with route 1 was that homocoupling of this species might be possible; Suzuki-type couplings to benzylic bromide substrates have been reported and as such, there could be potential for this substrate to couple to itself.¹² In the described preparation, a slight excess of boronic acid was used in the couplings to maximise yield, though this was reduced to 1.1 equivalents here.

The intermediate beads were washed with copious amounts of THF and DCM and were not analysed. They underwent subsequent phosphination with $\text{LiP}(\text{BH}_3)(\text{tBu})_2$ which was made *in situ* immediately prior to the phosphination reactions. The reactions were generally performed in DMF solvent, DMF was chosen as the lithiated phosphine was

known to be soluble in this; it is insoluble in solvents such as diethyl ether and hexane and so the use of such solvents would be likely to lead to reactivity problems, as both reagents would then be in the solid state. After phosphination, the resin beads were continuously washed with DCM overnight using a Soxhlet apparatus and then analysed.

³¹P-NMR analysis of the resulting beads gave broad peaks in one of two regions, being centered around 30 and 45 ppm. The latter signal is similar in shift to that for the borane adduct of DTBPMB. (49 ppm) The reaction conditions and characterisation data obtained for the reactions are summarised in Table 4-3.

| Reaction | a | b | c | d | e | f | g | h |
|--|---------------------|-------------|----------------------|--------|--------|--------|--------|--------|
| Preparative Route | No coupling | No coupling | 2 | 2 | 1 | 1 | 1 | 1 |
| Coupling Reaction Time | - | - | 92 hrs | 92 hrs | 72 hrs | 92 hrs | 92 hrs | 92 hrs |
| Coupling Reaction Temperature | - | - | 80 | 80 | 50 | 80 | 80 | 80 |
| Phosphination Solvent | DMF | THF | DMF | DMF | DMF | DMF | THF | THF |
| Equivalents of LiP(^t Bu ₂)(BH ₃) | 1.1 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 2.2 | 4.4 |
| Phosphination Reaction Time | 18 hrs | 48 hrs | 18 hrs | 18 hrs | 18 hrs | 18 hrs | 18 hrs | 48 hrs |
| Atomic P ratio (wrt Br) by EDS / % [†] | 2 % | 4 % | 0 % | 1 % | 8 % | 11 % | 28 % | 49 % |
| ³¹ P-NMR –ca. 45 ppm integral | No signal | | | | Minor | 91 % | Major | 69 % |
| ³¹ P-NMR – 25 - 35 ppm region integral | No signal | | | | Major | 9 % | - | 31 % |
| Comments | Trace phosphination | | Trace bromine by EDS | | | | | |

Table 4-3 – Compiled data for Suzuki coupling – phosphination reactions onto polystyrene resins

[†] Mean value of elemental compositions of 6 different beads by EDS; normalised result from total bromine and phosphorus content (atomic %)

The resins were initially screened for phosphorus at St Andrews using EDS and solution-state ^{31}P -NMR, which was performed in toluene / d^6 benzene (9 : 1) for a lock signal. No magic angle spinning (MAS) was performed and so broad signals were obtained but the spectra were of acceptable quality to initially screen for the presence of phosphorus and gave an approximate shift range. No phosphorus content was observed on samples prepared *via* route **2** (routes **c** and **d**) and trace bromine was observed on these samples by EDS. Oxygen levels were comparable to the prepared polystyrene-boronic acid (Table 4-2) which suggests that the initial Suzuki coupling reaction has failed here.

Due to the concerns about homocoupling of the substrate in route **1**, relatively mild conditions were employed initially for the Suzuki coupling. (reaction **e**) Subsequent phosphination led to 2 very weak signals in the solution-state ^{31}P -NMR spectrum, with the major being at around 35 ppm; the other, which occurs at approximately 45 ppm being slightly sharper. Conversion of the available bromine sites here was particularly poor, with only 8 % phosphorus observed by EDS relative to bromine. When a higher temperature of 80 °C was used for the coupling (as was described in the method followed²⁸) and a longer reaction time of 92 hours utilised, a slight improvement in the conversion to 11 % was observed by EDS. More significantly however was the ^{31}P -NMR analysis of this polystyrene, where the signal at approximately 45 ppm was now major.

It is possible that the low conversions observed on these resins are due to the DMF solvent that is utilised. Although a highly polar solvent is required here, such solvents are generally poor solvents for gel-type polystyrene beads, causing the pores of these to collapse in upon themselves and so significantly reduce their available surface area for reactions. As such, less polar solvents such as toluene are generally recommended for conversions on lightly crosslinked polystyrenes to avoid this.²⁹ $\text{LiP}^t\text{Bu}_2(\text{BH}_3)$ is, however, insoluble in toluene but was found to be soluble in THF and so the use of this solvent as a possible alternative was investigated for the phosphination reactions, the results of which are detailed as reactions **g** and **h**. This resulted in an improvement in the observed phosphorus levels of 28 % relative to bromine. (sample **g**) The use of longer reaction times and a 2-fold excess of $\text{LiP}^t\text{Bu}_2(\text{BH}_3)$ improves this further to 49 %. (sample **h**)

Combined ^{31}P Solid State NMR data for samples f, g and h

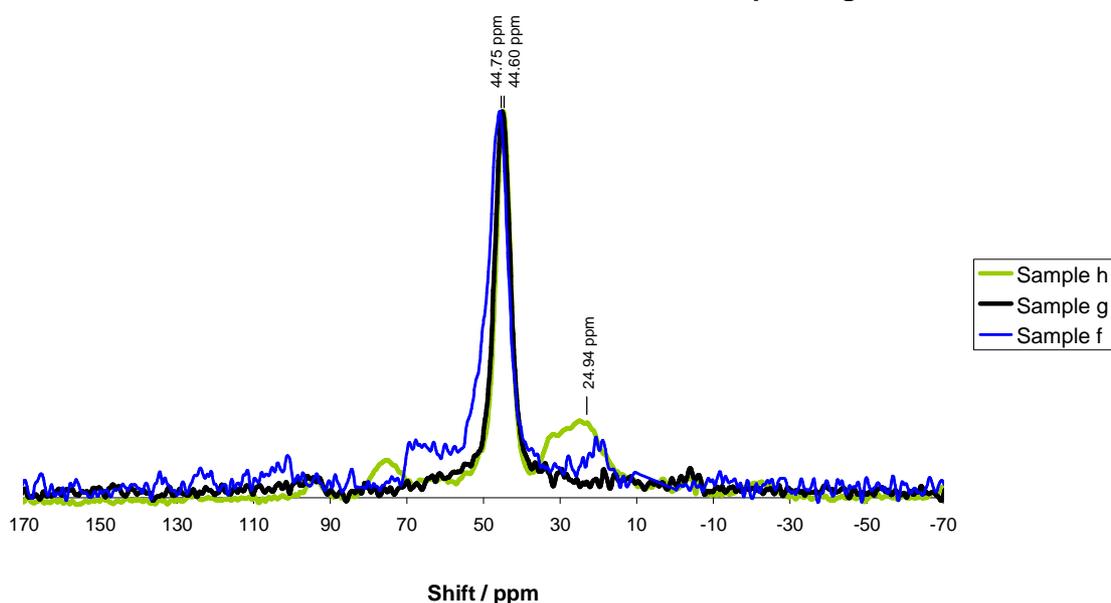


Figure 4-16 – Solid state ^{31}P -NMR spectra for resins f, g and h

Solid state ^{31}P -NMR spectra for samples **f**, **g** and **h** are illustrated in Figure 4-16 and all show a strong signal at 45 ppm; this is similar to, although slightly shifted from that of the free borane adduct of DTBPMB which occurs at 51 ppm. Sample **g** shows little evidence of any other phosphorus environments, although in sample **h** and to a lesser extent in sample **f**, there appears to be a broad signal in the range 22-37 ppm, which, judging by its shape, appears to be a composite of several peaks – particularly so in sample **h**.

To attempt to obtain further evidence for the identity of the signals at near δ 30, a sample of bromopolystyrene was subjected to direct phosphination (sample **a**) and the resulting resin analysed by ^{31}P -NMR. Under the described conditions, phosphination did not appear to take place readily, with trace phosphine found on the beads by EDS. Longer reaction times and the use of an excess of phosphine in THF (Sample **b**) also resulted in poor phosphine loadings and no strong phosphine signal was observed by ^{31}P -NMR. Although a very weak signal may be present in the baseline of sample **b** at approximately 38 ppm, the signal to noise ratio is too poor to be conclusive. As an alternative therefore, LiP^tBu_2 was coupled with 4-bromo-*o*-xylene in hexanes and the

resulting crude oil gave good NMR evidence for that of the expected aromatic phosphine-borane. The observed ^{31}P -NMR shift of 42.1 ppm is 7.1 ppm lower than that of the di-*tert*-butylphosphine-borane substrate. (Figure 4-17) On the bromopolystyrene resin, a mixture of products would be expected by this route as the arylbromide residues would be present in a mixture of *ortho* and *para* positions.

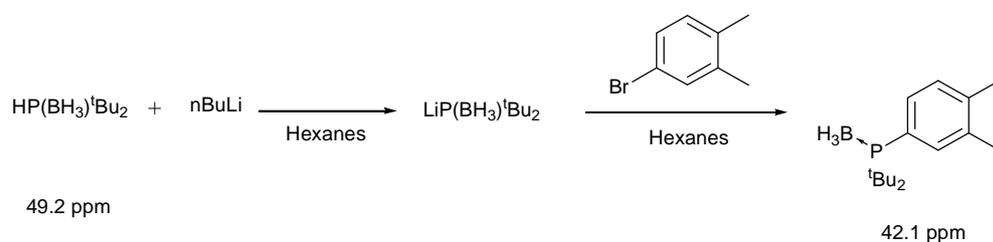


Figure 4-17 - Phosphination of 4-bromo-*o*-xylene

The evidence suggests that two types of products are forming; both the expected methylene bridged phosphines as well as aromatic phosphine species. There is however, a difference in shift from the solution state species compared to those on the polystyrene support of approximately 5-6 ppm. This could be explained by a solvent shift occurring due to the solution state samples being swollen in toluene / d^6 -benzene to allow for a lock signal. A solvent shift is observed for polystyrene-triphenylphosphine in the solid state compared to the solution state (in CDCl_3) of between -1 and -2 ppm, depending on the nature of the polystyrene support.³⁰ The larger shift here may be due to the different solvent used and the different nature of the phosphorus as a phosphine-borane in this case.

An attempt was made to obtain further evidence for the presence of CH_2P proton environments in the resins **g** and **h** using solid state ^1H -NMR; these are present at 3.0 ppm in DTBPMB. However, even with rapid MAS (25 kHz); the spectrum is dominated by the aromatic signals of the polystyrene protons, although shoulders are present at 5.2, 4.0 and 1.5 ppm and possibly more. Better data may be obtainable here using a solution state MAS-probe and d^6 -toluene solvent to allow efficient swelling of the resin.

4.2 Ionic Functionalisation

4.2.1 Sulfonation of DTBPMB

Direct sulfonation of DTBPMB would provide an attractive route for ionic immobilisation of the ligand onto an ionic support. Sulfonated phosphines are also interesting as they often result in water soluble catalysts which can be used in aqueous biphasic systems to effect product separation, as discussed in chapter 1.

The DTBPMB molecule is set up well for sulfonation. Difficulties can sometimes arise when attempting to sulfonate certain aromatic phosphines due to the strongly deactivating nature of the protonated phosphorus on the electrophilic aromatic substitution reaction.⁴¹ Such difficulties can be overcome with the use of carbon spacer groups on the rings, insulating a more distant aromatic system. An example where this has been successfully utilised is reported by Hanson^{31,32} in the production of the sulfonated Xantphos derivative below. (Figure 4-18)

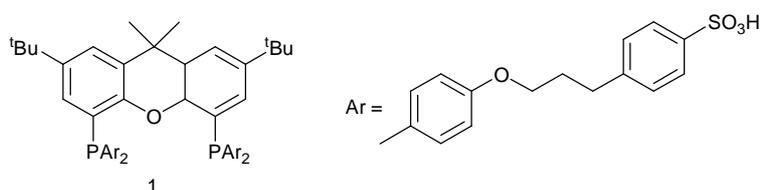


Figure 4-18 - Phosphine Sulfonation using spacer groups

DTBPMB already has suitable spacer groups in the form of the methylene bridges between the phosphorus and the aromatic system, resulting in effective insulation of the aromatic system from the phosphorus atoms. Sulfonation is a reversible process and is classically achieved with the use of strong or fuming sulphuric acid.³³ The reaction follows the standard two-step electrophilic aromatic substitution mechanism where the sulfonating agent is either SO₃ or a HSO₃⁺ species,³⁴ as shown in Figure 4-19, below.

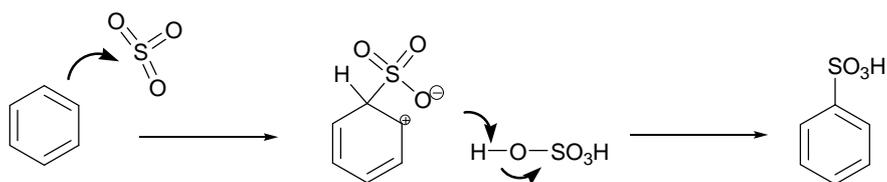


Figure 4-19 - Electrophilic aromatic substitution for aromatic sulfonation

Sulfonation of DTBPMB was successful based on a method described by Joó *et al.*³⁵ Here the ligand was subjected to fuming sulphuric acid (20 % free SO₃ content) for 4 hours, after which the solution was carefully hydrolyzed over degassed ice. Complete conversion to the sulfonated form was verified by ³¹P-NMR, showing two inequivalent phosphine environments at 50.0 and 50.7 ppm.

Although the sulfonation is efficient and practically simple, separation of this sulfonated product is not so trivial and is in fact a recognised general concern in the preparation of sulfonated phosphines.⁴¹ After neutralisation of the acid, a large volume of inorganic sulfate impurity is present and extraction of the phosphine from this is generally difficult due to their similar solubility properties.

Neutralisation of the sulphuric acid will generally result in saturation of the aqueous solution. In some cases, if this is performed carefully and repeatedly,³⁶ it is possible to precipitate the sulfonated phosphine before the inorganic sulfate, hence allowing separation. Several attempts at this were performed for the DTBPMB case; with neutralisation using aqueous sodium hydroxide solution. The initial precipitate isolated had only a trace ³¹P-NMR signal, suggesting it consisted largely of sodium sulfate rather than phosphine.

Therefore, as an alternative, the hydrolyzed solution was taken to pH 8-10 (at which the phosphine was fully deprotonated by ³¹P-NMR) and all the water was removed *in vacuo*. This was a slow process, particularly as it had to be performed at 40 °C to minimise frothing, which is thought to be due to the surfactant-like nature of the sulfonated phosphine. This was best achieved using an in-line liquid nitrogen cold trap on a Schlenk line.

The resulting solid was then extracted with warm methanol for 30 minutes, filtered and the methanol removed. The resulting white solid was produced in too high a mass to be free of sodium sulfate impurity; when neutralisation was effected using potassium sulfate, significantly less mass remained after the methanol extraction. This may be attributed to the lower solubility of potassium sulfate in methanol compared to that of

sodium sulfate.³⁷ Microanalysis of the solid showed poor results and it is suggested therefore, that potassium sulfate impurity was still present in the solid.

Purification of this crude compound posed a challenge for some time, although this was finally overcome using a chromatographic separation. This technique was not considered initially due to the expected high affinity of the sulfonate group for silica gel. de Vries *et al.*³⁸ successfully reported such a method to isolate sulfonated phosphines with differing degrees of sulfonation using the highly polar solvent system of ethyl acetate, methanol, acetic acid and water to elute the desired product from the column. This solvent system successfully eluted the pure potassium salt of the sulfonated DTBPMB; Potassium 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonate. (KBPMBS) A small amount of methanol was still observed both by NMR and in the microanalysis, even after extended drying *in vacuo*. Evidence for sulfonation at the 4-position can be seen in the aromatic region of the ¹H-NMR, where a singlet and AB-split signal with an integration of 1H and 2H respectively are observed.

4.2.1.1 Crystal Structure for 3,4-bis(di-tert-butylphosphino-methyl)benzenesulfonic Acid

Slow recrystallisation of KBPMBS gave crystals suitable for X-ray diffraction from THF-water. Interestingly the crystals obtained were of the acid rather than the potassium salt and the structure acquired is illustrated in Figure 4-20. The hydrogens shown were not resolved and are in idealised positions.

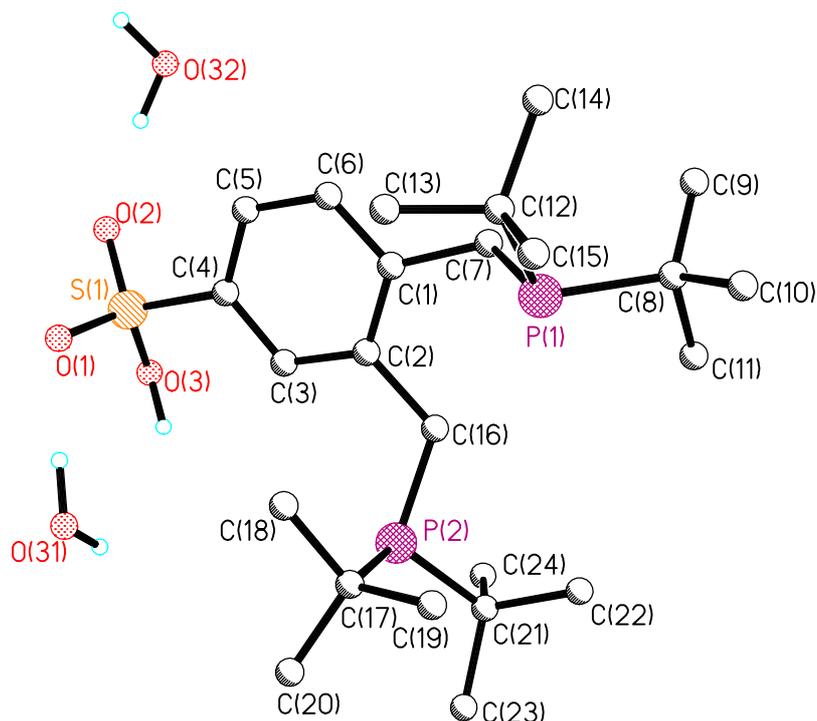


Figure 4-20 - X ray crystal structure of 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonic Acid

The structure clearly shows the substitution in the 4-position as expected, along with two waters of crystallisation around the sulfonate group. Of particular note in this structure is the difference in the bond lengths around the phosphorus atoms, as highlighted in Figure 4-21. The substituent *para* to the sulfonate group (P(1)) has a weaker P-C bond at 1.859 Å compared to the P-C bond in the *meta* substituent (P(2)) at 1.795 Å; in addition the bond to the *tert*-butyl groups attached to P(1) are weaker than those attached to P(2).

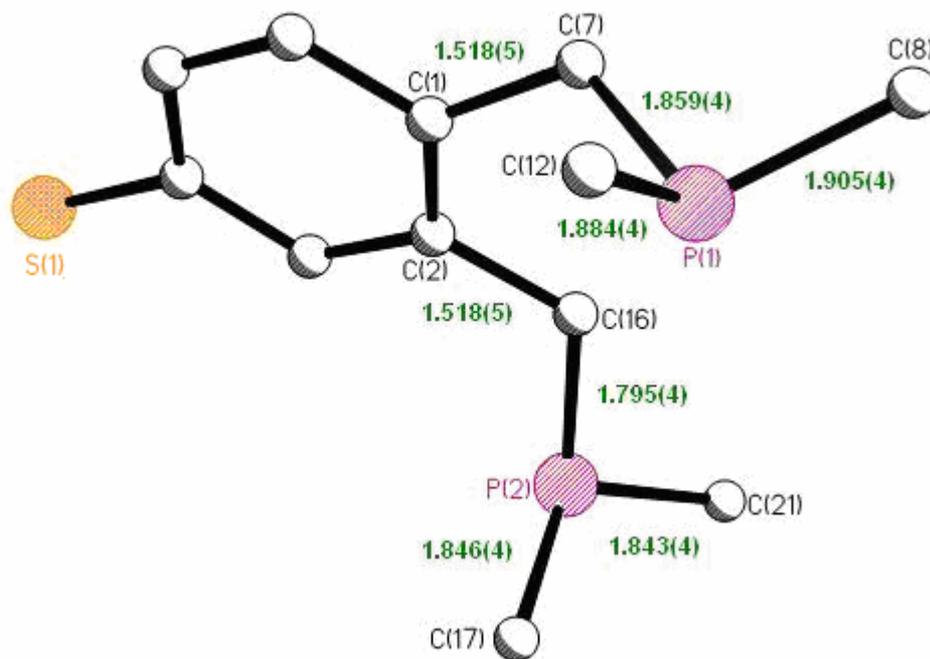


Figure 4-21 - Selected bond lengths for 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonic Acid; bond lengths (green) in Å with standard deviational errors in parentheses

The standard deviational errors in the bond distances are detailed in parentheses in Figure 4-21 and are relatively low. The standard deviational errors in the bond lengths displayed are as calculated from the crystal structure data. Two bond lengths can be considered different within experimental error if there is still a difference in length when a 3-fold multiplication of this error is applied (+/-) to both bond distances.

Hence, the difference in the phosphorus-methylene carbon distances (*i.e.* P(1) – C(7) and P(2) – C(16)) is significant within experimental error. Whereas, the difference in the *tert*-butyl bond distances are not significant within groups bound to the same phosphorus, although the difference in the bonding of the *tert*-butyl groups bound to P(1) is significantly different to those bound to P(2).

To investigate whether this bond distance difference was also present in the diphosphine-Pd(dba) complex, crystals of this were grown from hexane / methanol by vapour diffusion, unfortunately the crystals obtained were not of sufficient quality to obtain an X ray structure from the in-house service.

4.2.1.2 Other Strategies for Isolation of Potassium 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonate.

Although a preparation of KBPMBS has been developed and a successful separation method developed, it is not ideal. The necessity to remove large quantities of water from the crude mixture is a slow and inefficient step and makes even modest scale up of this preparation difficult. For a 17 g (substrate scale) preparation, the removal of this solvent took over 10 hours due to the necessity to perform this on a Shlenk line at 40 °C to minimise excessive frothing, with regular blocking of the in-line cold trap.

This separation problem has been acknowledged previously by other groups and studies into alternative isolation techniques have been reported. Herrmann *et al.*³⁹ successfully utilised an “extraction-reextraction” technique which was initially reported in the patent literature⁴⁰ and subsequently utilised by the group for the isolation of sulfonated 2,2'-bis(diphenylphosphinomethyl)-1,1'-biphenyl. (BISBI) The technique involves creating an organic-soluble salt of the sulfonated species by quaternisation with the long chain amine, triisooctylamine. The large alkane groups of the resulting ammonium salt allow it to be extracted into an organic phase, leaving the inorganic sulfate in the aqueous phase. Separation and neutralisation of the salt with sodium hydroxide then yields the water-soluble sodium salt of the sulfonated phosphine (Figure 4-22).

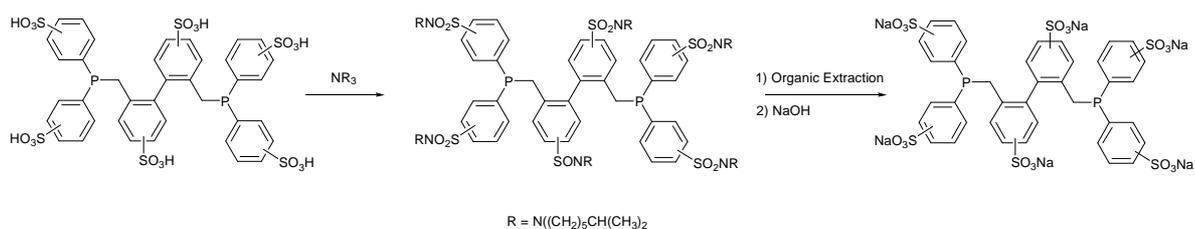


Figure 4-22 - Successful isolation of BISBI using extraction-reextraction technique

This methodology was attempted for separation of KBPMBS. Formation of the triisooctylamine salt of the product and rapid extraction into DCM was successful when the pH of the acidic aqueous layer was raised to six. After washing the DCM layer, re-extraction of the product back into an aqueous layer as its sodium salt was not successful, even under strongly basic (pH 14) conditions with vigorous stirring overnight. After sonication of the mixture for an hour, the diphosphine remained

exclusively in the DCM layer. To speculate, the failure of this technique for KBPMBS could be attributed to the relatively low water solubility of the diphosphine.

Another interesting technique for isolating sulfonated phosphines has been reported by Mul *et al.*,⁴¹ who report precipitation of sulfonated products directly after reaction and prior to any neutralisation, this was achieved by mixing the acid solution with a specific ratio of water and cooling to -10 °C or -20 °C for up to a week. This isolation technique was successfully demonstrated for a range of sulfonated phosphines including derivatives of xantphos and BINAS.

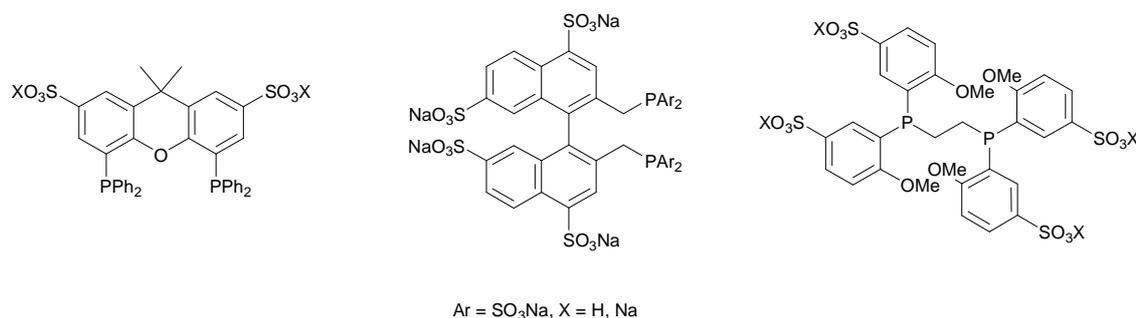


Figure 4-23 - Examples of sulfonated ligands isolated by direct precipitation⁴¹

This strategy was therefore attempted for the direct isolation of KBPMBS. After repeated attempts however no precipitate was observed, even after storage for over 2 weeks at -20 °C. To speculate, this may be due to the large difference in the degree of sulfonation of the products reported by Mul *et al.* and that of KBPMBS. KBPMBS contains only one sulfonate group and hence still retains a significant organic character owing to its four *tert*-butyl groups. All of the examples given in the paper have a much higher degree of sulfonation, with as many as eight sulfonic acid groups per molecule and only one of the products has any aliphatic component. This difference in the degree of polarity of KBPMBS compared to these related ligands is therefore likely to be why these alternative isolation techniques fail for this ligand.

Later work with the KBPMBS ligand had found it to have an appreciable, although not overly high solubility in DCM. This observation may form the basis for a more efficient isolation technique for obtaining this sulfonated molecule in its pure form.

4.2.2 Immobilisation Using Ion Exchange Resins

Some work was done on immobilisation of KBPMBS onto a strongly acidic ion exchange resin. The resin, Amberlite IRA400 was chosen for this; which is a polystyrene-divinylbenzene crosslinked resin containing quaternary ammonium chloride functionality and so ionic tethering through the sulfonate functionality should be possible here, as is shown in Figure 4-24.

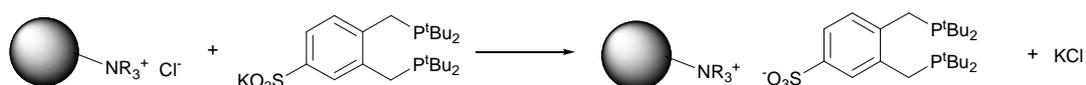


Figure 4-24 - Immobilisation of KBPMBS onto Amberlite IRA400 resin

A recent report by Tanaka *et al.*⁴² describes supported sulfonic acid on polystyrene resins for styrene methoxycarbonylation using phosphine-palladium complexes, with DTBPMB being reported as the ligand of choice out of those screened. The reaction was particularly sensitive to the loading of sulfonic acid on these resins with a PS-SO₃H : Pd ratio of 4.5 giving 97 % conversion to esters with an 88 % branched selectivity, whereas trace conversion was observed when this ratio was increased to 5.3; commercial sulfonic acid resins also showed poor activity. The catalyst was recycled 4 times without activity loss in vinyl acetate methoxycarbonylation by stripping the system of all volatiles then reusing the resin; and so catalyst leaching is not reported.

Immobilisation of KBPMBS onto Amberlite IRA400 was initially attempted using a column immobilisation technique; this however resulted in poor loadings of phosphine onto the support and significantly higher loading levels were achieved using a batch technique,⁴³ where ligand and resin were heated for 12 hours in an acetone / water solution (1 : 1 by vol). Analysis of these beads by EDS, along with a typical SEM image is given in Figure 4-25.

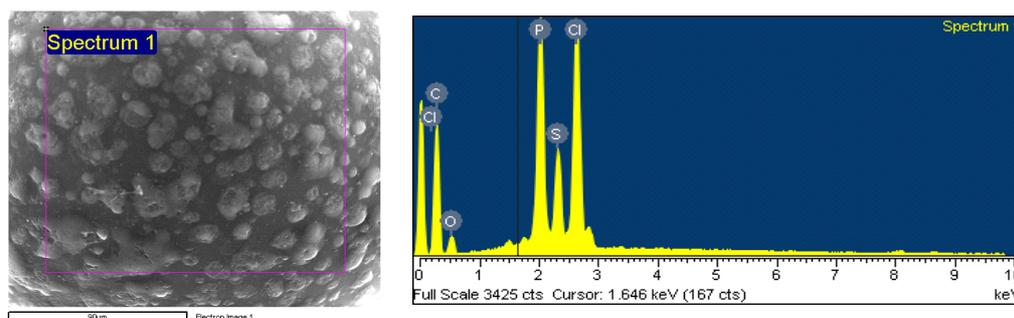


Figure 4-25 - SEM Image and typical EDS analysis

| Element wt % | | | | | | |
|--------------|------|-----|-----|-----|----------------|-----------------|
| C | O | P | S | Cl | P : S (atomic) | Cl : S (atomic) |
| 74.5 | 11.9 | 4.6 | 2.4 | 6.6 | 2.0 | 2.3 |

Table 4-4 – EDS summary on phosphine-immobilised resin

Mean results from analysis of 5 different samples

EDS analysis shows a perfect correlation of the P : S ratios at 2.0 as expected. The S : Cl ratio at 2.3 suggests that approximately 1 in 3 of the available basic sites on the resin are occupied by phosphine. Sulfur microanalysis shows 1.18 wt % of sulfur[‡] present on the resins, which assuming a 1 : 2 stoichiometry equates to a 7.21 wt % loading of the phosphine or 0.14 mmol g⁻¹ of the diphosphine. Solid state ³¹P-NMR of the beads shows a relatively sharp signal around 28 ppm; almost identical to that observed for the free phosphine though the resolution does not allow differentiation of the two similar phosphine environments.

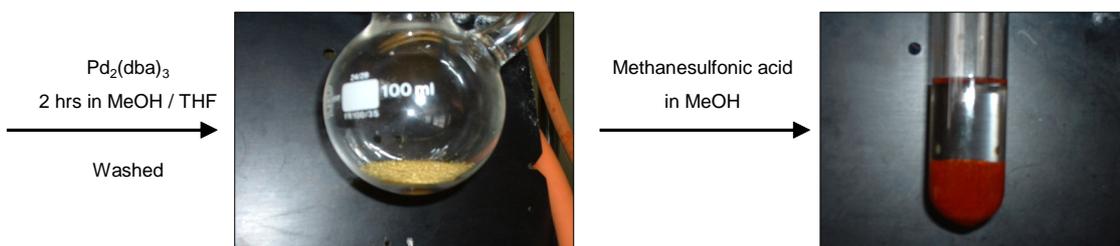


Figure 4-26 - Treatment of resin with palladium precursor (left) followed by methanesulfonic acid (right)

[‡] Considering a background sulfur reading on the beads of 0.04 wt %

Treatment of these beads with Pd₂(dba)₃ for two hours, followed by washing and subsequent treatment with methanesulfonic acid led to vibrant colour changes similar to those observed in the homogenous system and no large-scale (visible) leaching of the catalyst into the organic phase (Figure 4-26, right). Performance of these beads in 1-octene methoxycarbonylation (discussed more fully in Chapter 6) was assessed and the results obtained detailed in Table 4-5.

| CO Pressure | P ratio [§] | Time | Temp. | Conversion | Selectivity | L:B Ratio |
|-------------|----------------------|-------|-------|------------|-------------|-----------|
| bubbling | 1 | 2 hrs | 24 °C | trace | - | - |
| 30 bar | 1 | 3 hrs | 80 °C | 12 % | 95 % | 20 |
| 30 bar | 2.5 | 3 hrs | 80 °C | 0 % | - | - |

Table 4-5 – Summary of 1-octene methoxycarbonylation experiments using resin supported catalyst

After trace conversion was observed with bubbling CO, longer reaction times and higher temperatures and pressures were used resulting in a reasonable 12 % conversion to esters. However, reducing the ligand : palladium ratio to that used more generally³ resulted in complete loss of catalyst activity. It is possible that the activity observed may be due to homogeneous catalyst that has leached into the methanol phase, although accurate ICP determinations of palladium levels were not performed.

[§] With respect to atomic palladium

4.2.3 Discussion

Immobilisation of DTBPMB-type residues through strong carbon-carbon bond linkages has been attempted *via* Suzuki-type coupling both to bromopolystyrene and polystyrene-boronic acid using suitably functionalised precursors. The bromopolystyrene route has resulted in the immobilisation of phosphine, although the identity of this species is not conclusive. ³¹P-NMR evidence suggests that the expected phosphine environment exists, although the levels are not high, as determined by EDS. This appears to be the only environment present in the sample when a 28 % conversion of the available bromine sites is achieved. When longer reaction times, THF solvent and an excess of phosphine are used in the resin phosphination, a higher loading of phosphorus is achieved, although new signals in the ³¹P-NMR appear in the 22-37 ppm region, which are proposed to arise from aryl phosphine-boranes. This suggests that the Suzuki coupling reaction does not give quantitative yields, resulting in a mixture of species on the resin. Higher levels of phosphination may be possible using highly crosslinked, macroporous polystyrene resins, these have a more rigid pore structure and so these pores do not collapse in poor solvents like gel type resins do. They are, however, more susceptible to physical breakdown compared to gel type resins.

A problem with this strategy appears to be the use of a step that does not result in near quantitative yields and so this would lead to a less well defined catalyst. In light of the successful formation of the sulfonated derivative of DTBPMB; KBPMBS, along with subsequent work which will be described in chapter 5 on the formation of a sulfonyl chloride derivative of this molecule, allows consideration of another immobilisation strategy.

Organosulfur reagents have been recently shown to be effective in a range of transition metal catalysed carbon-carbon bond forming reactions, such as Heck and Suzuki-type couplings,⁴⁴ in which they are reported to be more active than their corresponding bromides and chlorides. This chemistry may therefore present a more efficient method for immobilising the sulfonyl chloride functionalised diphosphine to the prepared boronic acid functionalised polystyrene. (Figure 4-27)

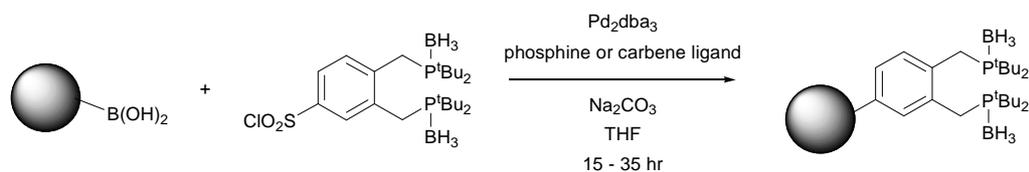


Figure 4-27 - Possible coupling of sulfonyl chloride functionalised DTBPMB derivative

An initial attempt at this conversion was undertaken using ((di-*o*-tolylphosphino)benzyl)dipalladium(II) under the reported conditions.⁴⁵ After washing *via* Soxhlet, there was an observed conversion of ca. 3 % of the bromine sites to phosphorus (by EDS). This conversion is of course too low to be useful, although optimisation of these reaction conditions or the use of alternative catalysts may give better results. In the coupling of *p*-tolylsulfonylchloride with *m*-nitrobenzeneboronic acid; Pd(PPh₃)₄ was found to be the best phosphine based ligand giving 55 % conversion, with more electron rich phosphines performing poorly.⁴⁵ Carbene-based systems were also investigated. They, in general, performed even better.

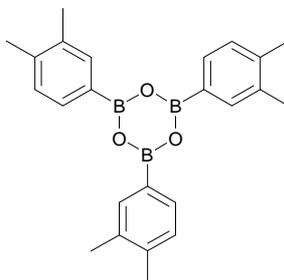
Sulfonation of DTBPMB has successfully produced the sulfonated ligand, KBPMBS. Preliminary work into immobilisation of this ligand onto a strongly basic ion exchange resin shows promise with no significant leaching from this support by solvent washing. Activity in 1-octene methoxycarbonylation is only observed when an equimolar palladium to phosphine ratio is used and as such, it is possible that the activity observed here is due to homogeneous catalysis. Further investigation of this system is needed – it may be possible that the high levels of chlorine on the support retard the catalysis by competitive complexation to the palladium centres; as may be also the case in the system reported by Tanaka *et al.*⁴² when high levels of supported acid are present on the resins. It would therefore be interesting to investigate supports with lower loadings of functionality and / or to exchange the chloride residues on these resins. For example quantitative conversion of the chloride form of Amberlite IRA400 was successful (by EDS) by treatment with a concentrated methanesulfonic acid solution in DCM by column.

Another interesting approach could be to combine the features of this supported system with that reported by Tanaka *et al.*⁴² Resins that contain both acidic and basic sites are commercially available and so to functionalise these with both sulfonic acid residues (as Tanaka) and KBPMBS-complexes (as here) may present an interesting catalyst system

which may have no need for excess free acid to be present and could in turn lead to higher catalyst activity and lower leaching levels.

4.3 Experimental

4.3.1 Synthesis of (3,4-dimethylphenyl)boroxirane



Under a dry and anoxic atmosphere, a 500 cm³ round bottom flask fitted with a reflux condenser was charged with fresh magnesium turnings (Alpha Aesar, 2.52 g, 105 mmol) in dry THF (100 cm³) and a single crystal of iodine. To this was added a solution of 3,4-dimethylbromobenzene (Alpha Aesar, 18.4 g, 100 mmol) in dry THF (100 cm³) drop wise at a rate sufficient to maintain gentle reflux. After addition was complete, reflux was maintained for a further 90 minutes resulting in a dark green / grey coloured suspension.

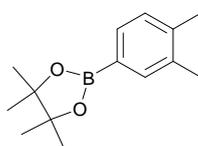
To a second 500 cm³ round bottomed flask was added tri(*iso*-butyl)boronate (Acros, 21.35 g, 110 mmol) in dry THF (100 cm³) and the solution was cooled to -10 °C with a ice-salt bath. The above prepared Grignard mixture was added dropwise to this solution over 10 minutes with efficient stirring and the solution was maintained at -10 °C for a further 60 minutes. 10 % v/v sulphuric acid (75 cm³) was then added to hydrolyse any excess Grignard and the mixture extracted with ether (3 x 100 cm³). The combined organic phase was dried over magnesium sulfate and the solvent removed *in vacuo* to give an oily solid. This was slowly crystallised from methanol at -20 °C to yield the title compound as colourless crystals. (11.59 g, 49 %)

Characterisation

TOF-MS Requires $M^+ = 396.224 \text{ g mol}^{-1}$; Found $M^+ = 396.224 \text{ g mol}^{-1}$. **¹H-NMR:** δ [ppm] = 2.37 (s, 3H, BCCHC(CH₃)C(CH₃)), 2.40 (s, 3H, BCCHC(CH₃)C(CH₃)), 7.28 (d, 1H, BCCHC(CH₃)C(CH₃)), 7.99 (m, 2H, BCCHCH); **¹³C-NMR:** δ [ppm] = 19.8 (s,

BCCHC(CH₃)C(CH₃), 20.3 (s, BCCHC(CH₃)C(CH₃)), 129.4 (s, BCCHCH), 133.4 (s, BCCHC(CH₃)C(CH₃)), 136.0 (s, BCCHC(CH₃)C(CH₃)), 136.8 (s, BCCHCH), 141.6 (s, BCCHC(CH₃)C(CH₃));** **Mpt:** 244 – 246 °C (Lit = 244-245 °C)⁹; **Microanalysis:** Requires - C = 72.81 %, H = 6.87 %, Found - C = 72.46 %, H = 7.19 %. Literature data available for melting point only and is comparable.¹⁶

4.3.2 Preparation of 2-(3,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a 250 cm³ round bottomed flask fitted with an air condenser and magnetic follower was added (3,4-dimethylphenyl)boroxirane (11.0 g, 27.8 mmol), and pinacol (2,3-dimethylbutane-2,3-diol, Aldrich, 11.8 g, 33.4 mmol), diethyl ether (150 cm³) and hydrochloric acid solution (1 mol dm⁻³, 150 cm³). The biphasic solution was then stirred at room temperature for 72 hours.

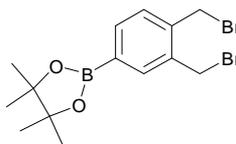
The aqueous layer was then taken to a pH of 9 using saturated sodium carbonate solution, the organic layer separated and the aqueous layer further extracted with diethyl ether. (3 x 100 cm³) The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo* (40 °C) to yield the title compound as a yellow oil. (16.9 g, 88 %). Attempts to crystallise from hexanes (slowly cooled then at -20 °C) were unsuccessful.

** No ¹³C-NMR signal for carbon (BC) is observed even at high concentration after 6000 scans; no signal for this carbon is reported in literature data either.⁴⁶

Characterisation

¹H-NMR:^{††} δ [ppm] = 1.37 (s, 12H, BOC(CH₃)₂C(CH₃)₂), 2.31 (s, 3H, BCCHC(CH₃)C(CH₃)), 2.35 (s, 3H, BCCHC(CH₃)C(CH₃)), 7.22 (d of d, 1H, BCCHCH), 7.58 (1H, m, BCCHCH), 7.62 (1H, s, BCCHC(CH₃)); ¹³C-NMR: δ [ppm] = 19.4 (s, BCCHC(CH₃)C(CH₃)), 19.9 (s, BCCHC(CH₃)C(CH₃)), 24.7 (s, BOC(CH₃)₂C(CH₃)₂), 83.5 (s, BOC(CH₃)₂C(CH₃)₂), 129.1 (s, BCCHCH), 132.6 (s, BCCHCH), 135.9 (s, BCCHC(CH₃)C(CH₃)), 140.0 (s, BCCHC(CH₃)C(CH₃)), 140.8 (s, BCCHC(CH₃)C(CH₃));^{‡‡} **Microanalysis:** Requires; C = 72.44 %, H = 9.12 %, Found; C = 72.54 %, H = 8.89 %. **Mpt:** 28 – 32 °C. Analysis comparable with literature data.⁴⁶

4.3.3 Preparation of 2-(3,4-bis(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a 250 cm³ round bottomed flask fitted with a reflux condenser and magnetic follower was added 2-(3,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10 g, 43.1 mmol), N-bromosuccinimide (Aldrich, 16.9 g, 95.0 mmol), 1,2-dichloroethane (Fluka, 150 cm³) and benzoyl peroxide. (Aldrich, ca. 100 mg) The slurry was stirred and heated to 95 °C for 5 hours. (Caution - rapid exotherm on radical initiation)

The orange solution was cooled and the resulting succinimide precipitate filtered. Diethyl ether (100 cm³) was added and the organic phase washed with water (3 x 100 cm³) and dried over magnesium sulfate (Caution, highly lachrymatory solution). The solution was then passed through a plug of diatomaceous earth, followed by a plug of silica and the solvents removed *in vacuo* to yield a crude yellow solid. This was

^{††} Spectra corrected to residual diethyl ether signal present.

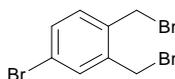
^{‡‡} No ¹³C-NMR signal for carbon (BC) is observed even at high concentration after 6000 scans; no signal for this carbon is reported in literature data either.⁴⁶

recrystallised from DCM / methanol (slowly then at -20 °C for 48 hours) to yield the title compound as colourless needles (5.24 g, 39 %)

Characterisation

¹H-NMR; δ [ppm] = 1.27 (s, 12H, BOC(CH₃)₂C(CH₃)₂), 4.59 (s, 2H, BCCHC(CH₂Br)C(CH₂Br)), 4.60 (s, 2H, BCCHC(CH₂Br)C(CH₂Br)), 7.30 (d, 1H, BCCHCH), 7.65 (d of d, 1H, BCCHCH), 7.72 (1H, s, BCCHC(CH₂Br)); **¹³C-NMR;** δ [ppm] = 25.2 (s, BOC(CH₃)₂C(CH₃)₂), 30.2 (s, BCCHC(CH₂Br)C(CH₂Br)), 30.5 (s, BCCHC(CH₂Br)C(CH₂Br)) 84.5 (s, BOC(CH₃)₂C(CH₃)₂), 130.9 (s, BCCHCH), 136.3 (s, BCCHCH), 137.8 (s, BCCHC(CH₃)C(CH₃)), 139.7 (s, BCCHC(CH₃)C(CH₃)), 139.0 (s, BCCHC(CH₃)C(CH₃)); **Microanalysis:** Requires; C = 43.12 %, H = 4.91 %, Found; C = 43.35, H = 5.10 %. **Mpt:** 133 – 134 °C. No literature data available for comparison.

4.3.4 Preparation of 3,4-bis(bromomethyl)bromobenzene



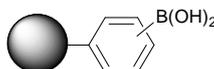
To a 250 cm³ 3-necked round bottomed flask fitted with a dropping funnel and a magnetic follower was added 3,4-dimethylbromobenzene (Alfar Aesar; 97 %, 18.06 g, 98.0 mmol) in 1,2-dichloroethane (Fluka, 100 cm³). Added to this was N-bromosuccinimide (Aldrich, 40.13 g, 225.4 mmol) and benzoyl peroxide (Fluka, 0.20 g, 0.95 mmol). The reaction mixture was heated to 100 °C and stirred under reflux for 5 hours. (Caution - rapid exotherm on radical initiation)

The reaction flask was cooled and the crystallised succinimide filtered, the solvent removed *in vacuo* and the resulting orange oil redissolved in diethyl ether. (50 cm³) This was washed with water (2 x 50 cm³) sodium thiosulfate solution (ca. 1 mol dm⁻³, 50 cm³) and dried over magnesium sulfate. The solvents were then removed *in vacuo* and the crude orange oil slowly crystallised from hot methanol (slowly cooled then at -20 °C overnight) to yield the title compound as colourless to beige solid (16.0 g, 48 %)

Characterisation

¹H-NMR: δ [ppm] = 4.59 (d, 4H, $J_{\text{HH}} = 4.3$ Hz, CH_2Br), 7.26 (m, 1H, $\text{CHCHC}(\text{CH}_2\text{Br})$), 7.43 (m, 1H, $\text{CHCHC}(\text{CH}_2\text{Br})$), 7.52 (s, 1H, $\text{CBrCHC}(\text{CH}_2\text{Br})$); **¹³C-NMR:** δ [ppm] = 29.1 (CH_2Br), 125.5 (CBr), 132.9 ($\text{CH,CH,C}(\text{CH}_2\text{Br})$), 133.0 ($\text{CH,CH,C}(\text{CH}_2\text{Br})$), 134.3 ($\text{CBrCHC}(\text{CH}_2\text{Br})$), 136.0 ($\text{CBrCHC}(\text{CH}_2\text{Br})$), 139.0 ($\text{CH,CH,C}(\text{CH}_2\text{Br})$); **Microanalysis,** Requires; C = 28.03 %, H = 2.06 %, Found; C = 27.81 %, H = 1.91 %. **Mpt:** 58 – 60 °C. Only boiling point available in literature, which was not compared (130 - 145 °C at 0.3 mm).¹⁹

4.3.5 Synthesis of Polystyrene-Arylboronic Acid



i) Synthesis of Oshima's Complex; *i*-Pr(*n*-Bu)₂MgLi

The following was performed immediately prior to use of the *i*-Pr(*n*-Bu)₂MgLi complex and follows a described method.²³ With the exclusion of air and moisture, a 2-necked 100 cm³ round bottomed flask fitted with a Young's tap and magnetic follower was cooled to 0 °C *via* an ice water bath and *i*-propylmagnesium chloride (1 equivalent, Aldrich, 2 mol dm⁻³ in THF) added in dry THF. *n*-butyllithium (2 equivalents, Aldrich, 2.5 mol dm⁻³ in hexanes) was then added *via* syringe over 5 minutes. The resulting solution was stirred for a further 30 minutes before being used directly in the preparation below.

ii) Polystyrene Manipulation

To a 100 cm³ 2-necked round bottomed flask fitted with Young's tap and magnetic follower was added bromopolystyrene (*ca.* 2.5 mmol Br g⁻¹, Fluka, 0.50 g) in dry THF and allowed to swell for 15 minutes; then cooled to 0 °C *via* an ice-water bath. Preformed *i*-Pr(*n*-Bu)₂MgLi solution (1.5 mmol) in THF (20 cm³) was then added and the mixture allowed to warm to room temperature then stirred gently for at 80 °C for 6 hours.

The mixture was cooled to 0 °C and trimethylboronate (Acros, 0.204 g, 2 mmol) was added *via* syringe. The mixture was allowed to warm to room temperature and stirred gently overnight. The beads were then filtered and washed with copious amounts of THF and DCM before being continuously washed in THF using a Soxhlet apparatus for 16 hours. The beads were then filtered and dried *in vacuo*, to yield the title compound as beige beads. (0.524 g)

Characterisation – See main text and Section 4.3.6, below.

4.3.6 Bromine Determination on Polystyrene Resins

This method for halogen determination, originally described by Volhard²⁶ allows determination of bromine content in solution. Therefore the polystyrene resin samples required digestion prior to this analysis, which was successfully achieved by decomposition in a closed oxygen atmosphere following a documented method.²⁷ Here the beads were contained within a parcel of ashless paper in a platinum gauze basket, which was suspended within a closed flask. (Figure 4-28). The flask contains an aqueous hydroxide and peroxide solution to absorb any resulting halide.

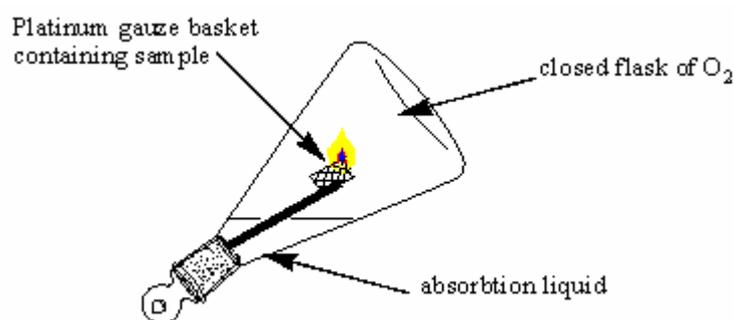


Figure 4-28 - Oxygen combustion for digestion of polystyrene beads

After combustion, the resulting solution is titrated by treatment with a known excess of silver nitrate. The residual silver content is then determined by titration with thiocyanate using iron ammonium sulfate as indicator. For the case of chloride, the titration is somewhat complicated by the incomplete precipitation of AgCl, hence resulting in consumption of the thiocyanate. (Figure 4-29)



Figure 4-29 - Thiocyanate consumption by solvated silver chloride

This can be overcome by removal of the silver salt by filtration or by reversing the reaction and complexing out all the residual thiocyanate with an excess of the Fe(III) indicator.⁴⁷ In the case of bromide however, the resulting silver salt is too insoluble to effect thiocyanate consumption and hence reaction Figure 4-30 can be assumed to be exclusive.



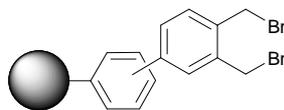
Figure 4-30 - Consumption of silver nitrate by thiocyanate

Procedure

All apparatus was thoroughly rinsed with distilled water prior to analysis. To a 250 cm³ ground stoppered conical flask was added distilled water (5 cm³), sodium hydroxide solution (0.5 mol dm⁻³, 5 cm³) and hydrogen peroxide. (*ca.* 30 % v/w, 10 drops) The flask was then purged with a rapid flow of oxygen for three minutes and stoppered. An accurately weighed sample of 30-50 mg was wrapped in ashless paper and placed within the platinum gauze basket with a paper taper. The taper was ignited and the suspended gauze immediately placed within the flask, turned upside down and held behind a blast shield whilst the flask contents were allowed to combust.

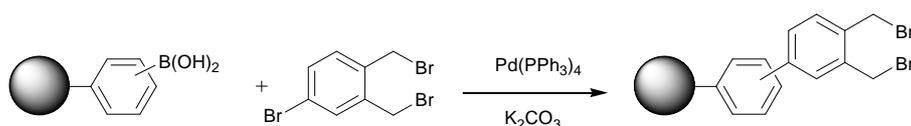
After combustion was complete, the flask was agitated to absorb all halide into the solution. The solution was then acidified with nitric acid (69 %, 15 cm³) and a slight stoichiometric excess of silver nitrate solution added. (0.01 mol dm⁻³, *ca.* 1.25 equivalents) The solution is then titrated against standardised KSCN using iron(III) alum as indicator; with the endpoint being determined by the first permanent red-brown coloration. This procedure was repeated at least three times until two consistent bromine determinations ($\pm 0.05 \text{ mmol g}^{-1}$) were made.

4.3.7 Suzuki Coupling to Bromopolystyrene (Route 1) (General)



Under a nitrogen atmosphere, to a 100 cm³ round bottomed flask fitted with a Young's tap, reflux condenser and oil bubbler was added tetrakis(triphenylphosphine)palladium (0.06 equivalents) and bromopolystyrene (Fluka, 100-400 mesh, *ca.* 2.5 mmol g⁻¹, 1 equivalent) in degassed DME / THF (1 : 1 by vol., 30 cm³) and the mixture gently stirred for 30 minutes. Degassed potassium carbonate solution (*ca.* 16 equivalents in 10 cm³) was then added to the mixture followed by 2-(3,4-bis(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 1.1 equivalents) as a solid. The mixture was heated to the desired temperature for the specified time and allowed to cool to room temperature. After cooling, the orange beads were filtered and washed with copious volumes of water, acetone, THF and finally DCM and oven dried (80 °C, 4 hrs) before undergoing the phosphination reaction

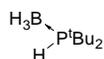
4.3.8 Attempted Suzuki Coupling to Polystyrene-Boronic Acid (Route 2) (General)



Under a nitrogen atmosphere, to a 100 cm³ round bottomed flask fitted with a Young's tap, reflux condenser and oil bubbler was added tetrakis(triphenylphosphine)palladium (0.06 equivalents) and 3,4-bis(bromomethyl)bromobenzene (1.1 equivalents, *ca.* 2.5 mmol g⁻¹) in degassed DME / THF (1 : 1 by vol., 30 cm³) and the mixture gently stirred for 30 minutes. To a separate 100 cm³ round bottomed flask was added polystyrene-boronic acid (*ca.* 2.5 mmol g⁻¹, 1 equivalent) and degassed potassium carbonate solution (16 equivalents in 20 cm³ and gently stirred as the contents of the former flask were added by syringe. The mixture was heated to the desired temperature for the specified time and allowed to cool to room temperature. After cooling, the yellow beads were

filtered and washed with copious volumes of water, acetone, THF and finally DCM and oven dried (80 °C, 4 hrs) before undergoing the phosphination reaction.

4.3.9 Preparation of Di-*tert*-butylphosphine-BH₃ Adduct



Under anerobic conditions in an argon atmosphere, to a 3-necked, 250 cm³ round bottomed flask fitted with a Young's tap, a pressure equalising dropping funnel and a magnetic follower was added sodium borohydride (2.67 g, 70.6 mmol) and dry DMF (ca. 50 cm³) to afford a clear solution. The solution was cooled *via* an ice-water bath and with vigorous stirring, di(*tert*-butyl)chlorophosphine (Aldrich, 10.0 g, 55.4 mmol) was added over 20 minutes using a pressure-equalising dropping funnel. The solution was allowed to warm to 25 °C and stirred for 2 hours. More than 98 % conversion was verified by ³¹P-NMR and so a small amount of sodium borohydride (0.5 g, 13.2 mmol) was added and the solution stirred for a further 30 minutes.

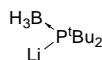
Now treated as air-stable, water (50 cm³) was added dropwise to produce a colourless precipitate. This was extracted into diethyl ether (3 x 50 cm³) and the organic phase washed with water (2 x 50 cm³) and brine (1 x 50 cm³). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo* to yield crude product as a colourless solid. This was recrystallised from hot hexanes and dried in air overnight to afford the title compound as colourless crystals. (6.40 g, 72 %)

Characterisation

MS: (EI, low res.) Requires M⁺ = 160, found M⁺ = 160; **¹H-NMR:** δ [ppm] = 0.92 (**q**, 3H, J_{BH} = 317.5 Hz, P-BH₃) 1.32 (**d**, 18H, J_{PH} = 14.0 Hz, P(C(CH₃)₃)₂), 4.10 (**d of q**, 1H, J_{PH} = 347 Hz, PH); **¹³C-NMR:** δ [ppm] = 28.9 (**d**, J_{CP} = 1.13Hz, P(C(CH₃)₃)₂), 30.5 (**d**, J_{CP} = 27.7 Hz, P(C(CH₃)₃)₂); **³¹P-NMR:** δ [ppm] = 49.2 (**m**,⁴⁸ P-BH₃); **Microanalysis:** Requires C = 60.00 %, H = 13.86 %, Found C = 59.76 %, H = 14.28 %; **Mpt:** 65 – 66 °C. Only ³¹P-NMR data available in literature and is comparable.⁴⁹

4.3.10 In situ Preparation of Lithium Di-tert-butylphosphine-BH₃

Adduct

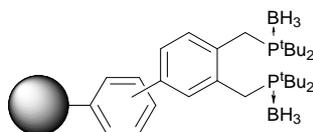


Under dry and anerobic conditions, to a 100 cm³ round bottomed flask fitted with Young's tap and magnetic stirrer was added di-*tert*-butylphosphine-BH₃ and the desired reaction solvent. (DMF / THF / diethyl ether or petroleum spirit). *n*-butyllithium (Aldrich 2.5 mol dm⁻³ in hexanes, 1.1 equivalents) was then added *via* syringe to the reaction mixture and stirred for 30 minutes, after which conversion to the lithiated phosphine was confirmed by ³¹P-NMR spectroscopy. For diethyl ether or petroleum solvents, the product precipitated from solution and so was filtered and washed with further solvent, this was not possible for DMF or THF and so the product solution was used directly in these cases.

Characterisation

³¹P-NMR (*in situ*), δ [ppm] = 1.02 (m, ⁴⁸ P-BH₃).

4.3.11 Phosphination of Functionalised Polystyrenes (4.3.7 and 4.3.8)



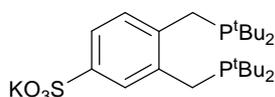
Under anhydrous conditions in a nitrogen atmosphere, the polystyrene substrate was added to a 100 cm³ round bottomed flask fitted with Young's tap and magnetic follower. The desired reaction solvent (DMF or THF, 10 cm³) was added to allow the beads to swell for 15 minutes. Preformed LiP(^tBu)₂(BH₃) in DMF or THF was then added from a separate round bottomed flask by cannula and the mixture gently mixed at room temperature for the desired time. After the reaction, water (10 cm³) was added to the mixture and the beads filtered and washed with copious amounts of water, acetone

and finally DCM. The beads were then continuously washed overnight in DCM using a Soxhlet apparatus.

Characterisation

See Table 4-3 and associated discussion (Page 70)

4.3.12 Preparation of Potassium 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonate



The following was undertaken in a dry and inert atmosphere throughout. To a 3-necked, 250 cm³ round bottomed flask fitted with a Young's tap, reflux condenser, oil bubbler and a magnetic follower was added DTPBMB (Lucite, 8.05 g, 20.4 mmol) and the flask cooled to 0 °C using an ice-water bath. Degassed sulfuric acid (5 cm³) was added slowly to mostly dissolve the DTBPMB. With rapid stirring, fuming sulphuric acid (Aldrich, 20 % free SO₃ content, 25 cm³) was added dropwise over 15 min, not to exceed a temperature of 5 °C. After which the mixture was heated to 80 °C for 4 hours and stirred at room temperature overnight.

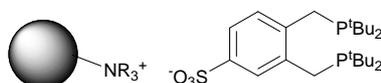
The solution was then transferred slowly *via* cannula to a 1 litre round bottomed flask fitted with a Young's tap and containing approximately 50 g of degassed ice to hydrolyse the acid. With ice-water cooling, the solution was then taken to a pH of 8-10 by the slow drop wise addition of potassium hydroxide solution (30 % v/w) resulting in the precipitation of the sulfonated phosphine within a large mass of potassium sulfate. The water was then removed *in vacuo* carefully at 40 °C (due to the surfactant-type nature of the product) with the water being collected using an in-line cold trap. The resulting mixture was resuspended in methanol (100 cm³) and stirred for 1 hour at 40 °C before filtering. The methanol was removed from the filtrate *in vacuo* and the resulting solid again resuspended in methanol (50 cm³) and filtered. The solvent was again removed *in vacuo* to yield crude product as a white solid.

The removal of the final inorganic sulfate impurity was achieved by passing a methanolic solution of the crude product through a silica plug (60 Å, 7 cm x 2 cm diam.) with elution of the desired phosphine from this being achieved using a mixture of ethyl acetate, methanol, acetic acid and water. (12 : 6 : 1 : 1 by volume) The solvents were removed *in vacuo* to yield the title compound as a colourless solid (6.86 g, 13.4 mmol, 66 %). Even after drying for 6 hrs; (60 °C, *in vacuo*) methanol (ca. 2 equivalents) was still present by ¹H-NMR.

Characterisation

¹H-NMR (CD₃OD): δ [ppm] = 1.07 (d, 36H, J_{PH}=11.4 Hz, t-butyl CH₃), 3.05 (4H, br. s, methylene CH₂), 7.45 - 7.50 (d of d, 2H, (aromatic AB pattern), KO₃SC-CH-CH-C), 7.96 (1H, s, KO₃S-CH-C); Contaminant peak present at δ = 4.85 ppm for methanol. **¹³C-NMR (CD₃OD):** δ [ppm] = 27.9 (d, P-C-(CH₃)₃), 30.7 (d, J_{CP} = 13 Hz, *butyl* C-CH₃), 33.3 (d, J_{CP} = 22 Hz, methylene -CH₂-P), 124.5 (s, KO₃S-C), 129.9 - 132.45 (m, CH-C(SO₃K)-CH-CH), 143.0 (P-CH₂-C-C-CH₂P); **³¹P-NMR (CD₃OD):** δ = [ppm] 26.1 (1P), 27.3 (1P); **Microanalysis:** Requires C = 56.22 %, H = 8.45 %, S = 6.25 %, For C₂₄H₄₃P₂KSO₃ : 2 CH₃OH; Requires, C = 54.14 %, H = 8.92 %, S = 5.56, Found; C = 53.75 %, H = 9.12 %, S = 5.61 %. No literature data available for comparison.

4.3.13 Immobilisation of Potassium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate onto Amberlite IRA400



To a 100 cm³ round bottomed flask fitted with Young's tap, reflux condenser, oil bubbler and magnetic follower was added Amberlite IRA400 (chloride form), Potassium 3,4-bis(di-*tert*-butylphosphino-methyl)benzenesulfonate (1.6 g, 3.12 mmol), acetone (15 cm³) and water. (15 cm³) The mixture was then heated to 80 °C for 8 hours, then allowed to cool. The beads were filtered, the resulting filtrate still containing phosphine

by ^{31}P -NMR. The beads were washed with acetone (3 x 25 cm³) and THF (3 x 25 cm³) and then dried *in vacuo*.

Characterisation

See main text for details.

4.4 Notes and References

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5. Immobilisation onto Silica

The use of silica as a support is attractive due to the high chemical and physical robustness of this material. As traditional methods of grafting organic moieties onto preformed silicas can suffer from poor loading levels and high levels of leaching, particular focus was therefore taken on the use of sol-gel processing as a synthetic methodology towards a supported system. This follows on from the observed advantages of increased specificity and undetectable leaching levels reported by van Leeuwen *et al.*¹ in hydroformylation reactions using a modified xantphos-type sol-gel supported system, as discussed in detail in section 1.7.2.1.

5.1 Immobilisation via Sulfonamide Linkage

Catalyst immobilisation *via* the sulfonated phosphine diphosphine, potassium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate (KBPMBS) is a particularly attractive proposition. Firstly, this functionalisation of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) has been successful and if immobilisation through this functionality is demonstrated, this could present a more general method for immobilisation due to the large number of sulfonated phosphines that have been reported in the literature.² It was proposed that immobilisation through a sulfonate group could be achieved by formation of a sulfonamide linkage. Sulfonamide linkages are relatively robust, being formed under and are stable in basic conditions.³ (Figure 5-1) They are also resistant to hydrolysis, with efficient cleavage requiring heating to 160 °C in 80 % sulphuric acid.⁴

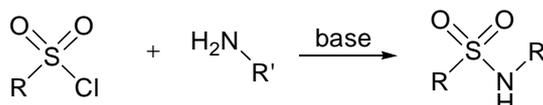


Figure 5-1 - Sulfonamide formation from sulfonyl chloride and amine

The bulk of research into sulfonamide-functionalised molecules is medicinal and is largely concerned with their antibacterial properties.⁵ They are generally formed by reaction of a sulfonyl chloride with an amine;⁶ although other methods exist, such as the

recently reported direct use of sulfur dioxide.⁷ The formation of a sulfonamide from KBPMBS, using the commercially available, 3-(triethoxysilyl)propan-1-amine would give a compound suitable for sol gel processing; (Figure 5-2) thus allowing immobilisation by hydrolysis and polymerisation of the triethoxysilyl functionality.

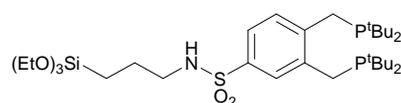


Figure 5-2 – Sulfonamide-based target compound for sol-gel processing

In order to allow formation of this sulfonamide, therefore, conversion of KBPMBS to the corresponding sulfonyl chloride was necessary. This can be achieved by treatment with thionyl chloride⁸ (SOCl₂) or phosphorus pentachloride.⁹ (PCl₅) Unfortunately, direct treatment of KBPMBS with SOCl₂ led to the rapid formation of a phosphorus adduct, giving a sharp ³¹P-NMR resonance at 82.1 ppm. Attempts to convert this adduct back to the free phosphine both using strongly basic or acidic conditions, even under reflux were unsuccessful. Likewise, the use of PCl₅ in POCl₃ solvent⁹ resulted in the formation of a phosphorus species giving a ³¹P-NMR resonance at 5.6 ppm. Hydrolysis and neutralisation of the reaction mixture resulted in a species with a ³¹P-NMR signal at 72.6 ppm and again, treatment with strong acid or base did not alter the nature of this phosphorus environment.

Although the identity of these phosphorus environments is unknown, in both cases they appear in the same general ³¹P-NMR shift region for observed phosphorus (V) derivatives of DTBPMB, such as the di(oxide) at 64.3 ppm and the di(sulfide) at 79.9 ppm. Most importantly however, these conversions appear to be difficult to reverse and so are not suitable for use here.

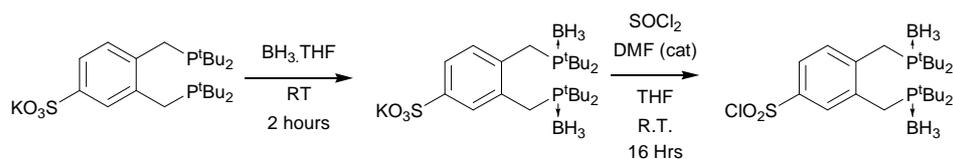


Figure 5-3 - Synthesis of sulfonyl chloride of KBPMBS *via* borane protection

Therefore protection of KBPMBS *via* its borane adduct was employed to allow conversion to the sulfonyl chloride. Borane protection was achieved in quantitative yields by treating a THF solution of KBPMBS with a slight excess of borane-THF complex at room temperature, which resulted in formation of the bis(borane) adduct. Conversion of this to the corresponding sulfonyl chloride was successful using thionyl chloride and a catalytic amount of DMF at room temperature, with a 47 % yield obtained, the loss being attributed to an unidentified insoluble dark solid, which slowly precipitated during the reaction.

This crude material still showed between 15 and 25 % of the phosphorus-thionyl chloride adduct, which could be attributed to deboronation by HCl that may form from decomposition of the SOCl_2 . Attempts to recrystallise this were unsuccessful, although a crude yellow solid was precipitated from warm acetonitrile and used directly. Although little evidence for the conversion can be obtained from NMR data, the sample shows a strong absorbance in the IR at 1170 cm^{-1} , as is expected for this functionality.¹⁰ This is also present in the sulfonyl chloride product, centred around 1122 cm^{-1} ; more convincing, however, is the observation of an additional sharp absorbance for the sulfonyl chloride at 1308 cm^{-1} which is in the expected region for a covalent $\text{SO}_2\text{-R}$ stretch.¹⁰ These conversions are summarised in Figure 5-3. Hence the borane has been shown to protect the phosphorus sites from attack, although an amount of the thionyl chloride-adduct product was still present in the obtained crude solid.

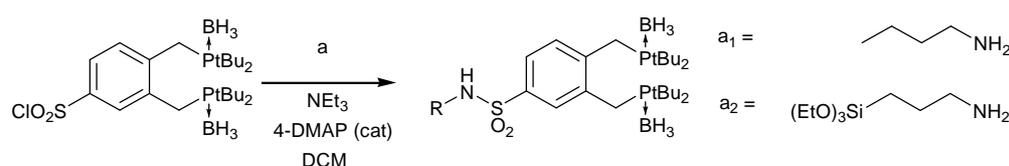


Figure 5-4 - Formation of sulfonamides

In order to verify this synthetic procedure and to confirm that the reaction conditions utilised were adequate, coupling of this sulfonyl chloride was first attempted on a small scale using butylamine rather than a silane-functionalised amine. (Figure 5-4, amine a_1) The conditions for the coupling were based on a reported synthesis¹¹ and these resulted in successful formation of the desired sulfonamide. Column chromatography isolated pure *n*-butylsulfonamide with crystals suitable for X ray diffraction. The X ray structure obtained is illustrated in Figure 5-5.

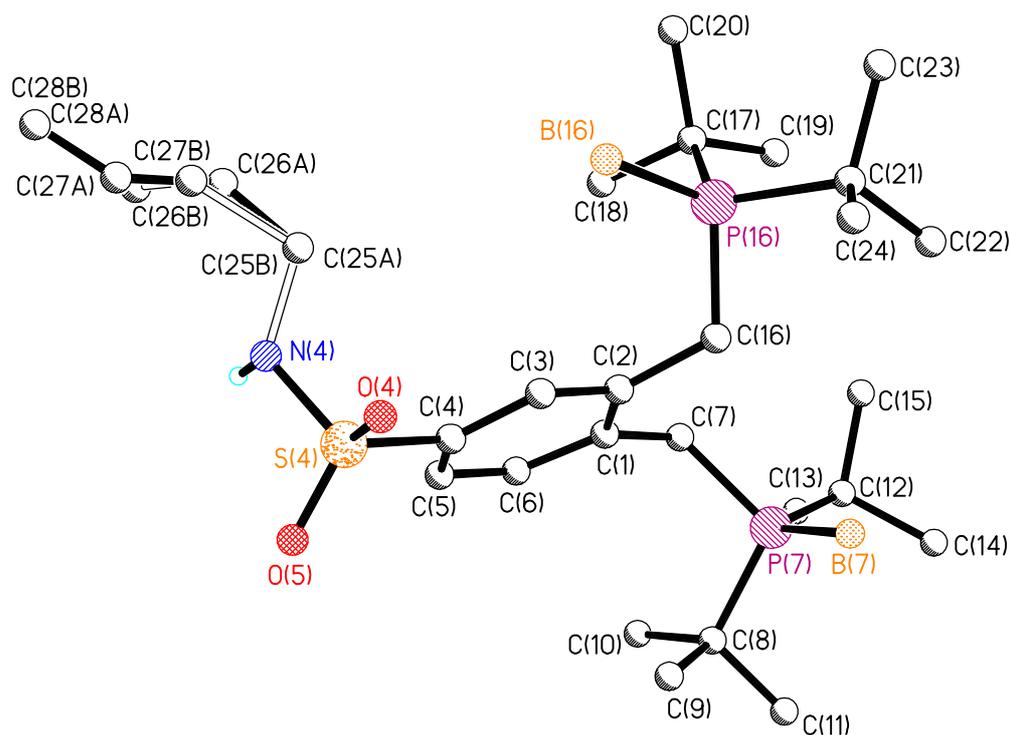


Figure 5-5 - Crystal structure for *n*-butyl-3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonamide-bis(borane) adduct

Hydrogen bonding details for this structure were not obtainable; this is probably due to the large steric bulk of the molecule. The structure clearly shows the sulfonamide bond formation at the 4-ring position, the butyl chain is somewhat disordered as is represented by the two plots for carbons 26 and 27. Interestingly, in contrast to the structure obtained for KBPMBS, the bond distance differences between the ring-to-methylene-bridge carbons (C2 to C16 and C1 to C7) are insignificant in this case, being within one standard deviational error of each other. This is presumably due to the different nature of the sulfur substituent.

This synthetic procedure was repeated using (triethoxysilyl)propan-1-amine to form the desired sulfonamide. In this case, the crude solid obtained was used directly in a sol-gel co condensation (Figure 5-6). Conditions similar to those described for condensation of Siloxantphos co-condensation were used.¹ To a solution of the sulfonamide in THF was added, triethylamine and tetraethoxysilane in methanol (required to maintain phase homogeneity) and this was treated with water and a trace of 4-DMAP at room

temperature. Rapid gelation of the solution occurred to the extent that magnetic stirring was no longer possible after 2 minutes.

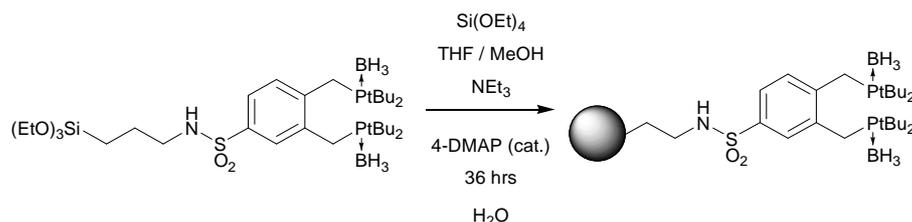


Figure 5-6 - sol gel co-condensation of 3,4-bis(di-*tert*-butylphosphinomethyl)-N-(3-(triethoxysilyl)propyl)benzenesulfonamide-bis(borane) adduct

The resulting silica gel was washed with copious amounts of THF and DCM and further washed with THF using a Soxhlet apparatus for 12 hours and dried *in vacuo*. The resulting free flowing silica gave a ^{31}P -NMR signal at 51 ppm, similar, albeit slightly broader than that for the free phosphine. Deprotection of the phosphine was attempted initially with triethylamine; however, even when heated under reflux for 14 hours, no cleavage of the borane group was observed by ^{31}P -NMR spectroscopy. In contrast, deprotection of DTBPMB-bis(borane) adduct was successful under these conditions, giving 68 % conversion to the free phosphine by ^{31}P -NMR integrals of the reaction mixture.

Therefore, an alternative deprotection was attempted, where the phosphine-borane is cleaved with a protic acid and the free phosphine obtained by subsequent neutralisation. The method utilised was based on that used by Lucite for deboronation of DTBPMB-borane adduct.¹² Treatment with 9 equivalents of methanesulfonic acid (MSA) in DCM (5 hours at reflux) appeared to lead to cleavage of the phosphine from the support, with no ^{31}P -NMR signal being observed on analysis of the silica after this procedure. An alternative synthetic methodology was attempted to try and prepare the free immobilised phosphine, as is outlined in Figure 5-7.

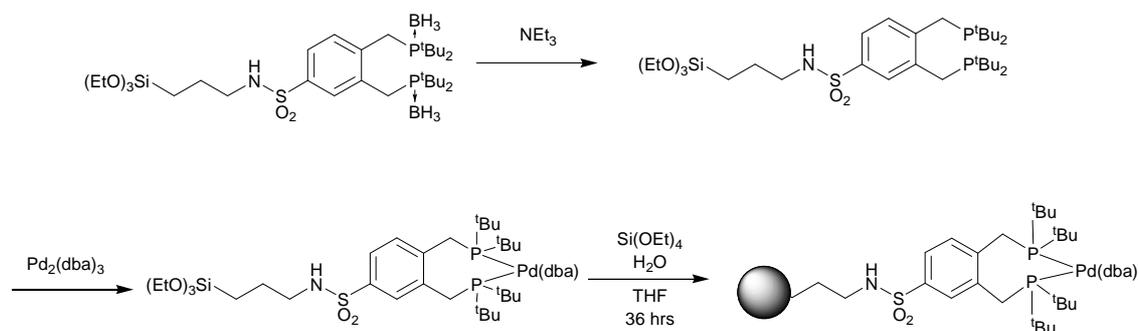


Figure 5-7 –Alternative preparation of sol-gel sulfonamide catalyst

This route necessitates the synthesis of the sulfonamide *via* borane protection at phosphorus (as before) and deprotection of the phosphine prior to the sol gel processing. This methodology allows metal complexation before sol-gel processing which may well result in superior catalyst selectivity, as was found for sol gel immobilised Siloxantphos.¹

The sulfonamide-linked borane adduct was synthesised as described previously to yield a colourless crude paste as before. Triethylamine deprotection had been attempted on this crude material after extensive drying, although resulted largely in formation of the thionyl chloride type adduct, presumably due to residual thionyl chloride within this crude paste. The conversion was attempted on a subsequent sample where this was stirred in methanol (room temperature, overnight) in an attempt to hydrolyse any residual thionyl chloride. Attempted triethylamine deprotection of this sample resulted in the same adduct being formed and so this route has currently resulted in no success. This route still shows promise if further purification is performed prior to the deboronation. The use of chromatography may be hindered by the triethoxysilane functionality here. In addition, any presence of water would probably result in attack of the hydrolytically unstable triethoxysilane functionality.

5.2 Immobilisation via Alkene Hydrosilylation

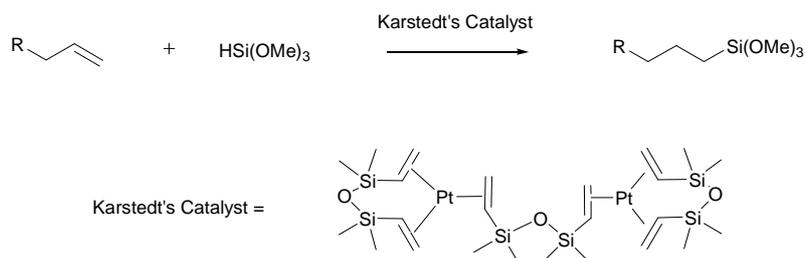


Figure 5-8 - Alkene hydrosilylation using Karstedt's catalyst¹⁴

Another attractive method for immobilisation would be to hydrosilate an alkene functionalised derivative of DTBPMB using a substrate such as trialkoxysilane. Hydrosilylation reactions are commonly and efficiently catalysed by platinum catalysts such as the Speier catalyst,¹³ Karstedt's catalyst¹⁴ (Figure 5-8), and more recently by Pt-carbene complexes.¹⁵ Such a transformation could be exploited to produce a precursor suitable for sol-gel processing as is proposed in Figure 5-9

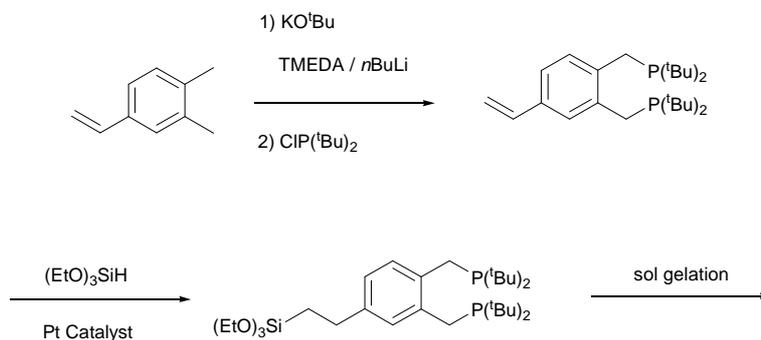


Figure 5-9 - Immobilisation via alkene hydrosilylation

This styrene functionalised ligand could also be used in a direct co-polymerisation with styrene and divinylbenzene to form a polystyrene-type resin through a *suspension polymerisation* technique. (Figure 5-10) This would be attractive, although due to the requirement for specialist glassware, mixing equipment and techniques to perform such polymerisations, this was not investigated.

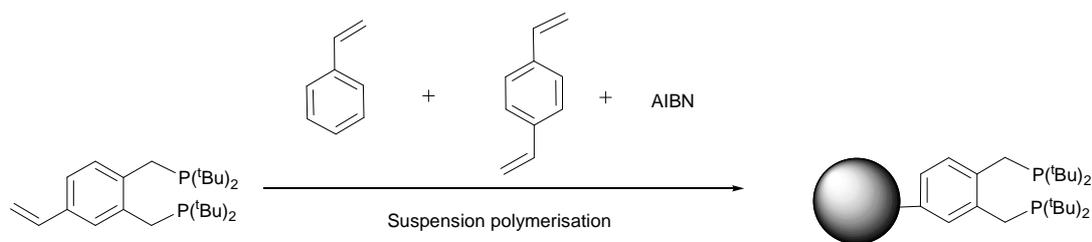


Figure 5-10 - Suspension polymerisation immobilisation of styrene functionalised DTPBMB

Initially, 3,4-dimethylstyrene was identified as a useful starting point for the procedure and several routes to its preparation were identified and investigated. The first preparation investigated was to perform a Wittig-type reaction on the corresponding aldehyde using methyltriphenylphosphonium bromide and *n*-butyllithium as base.¹⁶ An alternative was to perform a somewhat unusual Heck-type coupling on the corresponding acyl chloride using ethylene substrate.¹⁷ (Figure 5-11) In addition, Stille coupling of aryl bromides¹⁸ and more recently aryl chlorides¹⁹ using palladium-phosphine complexes were considered.

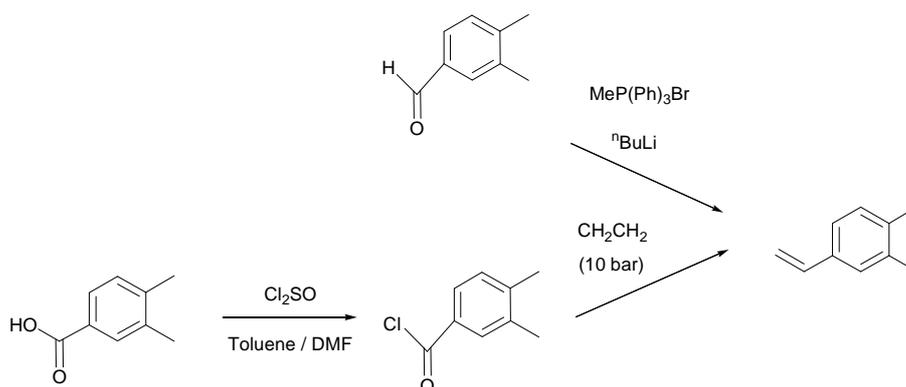


Figure 5-11 - Proposed routes to 3,4-dimethylstyrene

As detailed in the figure above, the Wittig type route results in a good (71 %) isolated yield of the desired styrene. Although preparation of the acyl chloride in the alternative route was efficient by a literature method,²⁰ at 88 % isolated yield; the subsequent Heck coupling only resulted in a 34 % yield of the styrene product. This is likely therefore to be a less efficient route, although the high cost of the 3,4-dimethylbenzaldehyde would have to be considered to determine this precisely.

In both cases, isolation of the desired product required column chromatography. The Stille-type coupling route reported by Fu *et al.*¹⁹ was not performed; the high cost of

catalyst makes this route less attractive, particularly when the requirement for a high (6 mol %) loading of the palladium-tri(*tert*-butylphosphine) based catalyst is considered. Stille coupling to aryl bromides using less expensive palladium-triphenylphosphine may give another viable route to these styrene products however.¹⁸

Phosphination of this compound by direct metallation was unsuccessful, leading to a large number of products (by TLC) and with many ³¹P-NMR resonances present in addition to a complex ¹H-NMR spectrum for the resulting crude oils. To speculate as to why, it could be envisaged that charge delocalisation of the intermediate could take place, (Figure 5-12) which could lead to a mixture of products being formed.

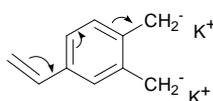


Figure 5-12 - Possible charge delocalisation for dimetallated intermediate

Bromination of the 3,4-dimethylstyrene using NBS was attempted using the methodology reported for dibromination of 4-bromo-*o*-xylene. (Section 4.3.4) This yielded a dark, sticky and poorly soluble material for which no interpretable NMR data could be obtained. It is possible that the radical bromination conditions could have led to polymerisation of the styrene functionality here. In addition, no literature preparations of such a compound or any of its isomeric derivatives could be located.

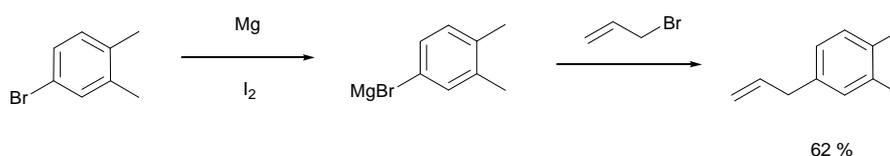


Figure 5-13 - Synthesis of 4-allyl-*o*-xylene

To try and overcome these problems, the use of an allyl functionalised xylene was investigated; the presence of the methyl spacer here may suppress the possible reactivity of the alkene functionality. This molecule was successfully prepared *via* a Grignard route from 4-bromo-*o*-xylene. Grignard formation was successful following a literature procedure,²¹ although the addition of iodine was required to initiate this metallation. Quenching with allyl bromide gave the desired allylxylene, (Figure 5-13) which was isolated in 62 % yield by reduced pressure distillation.

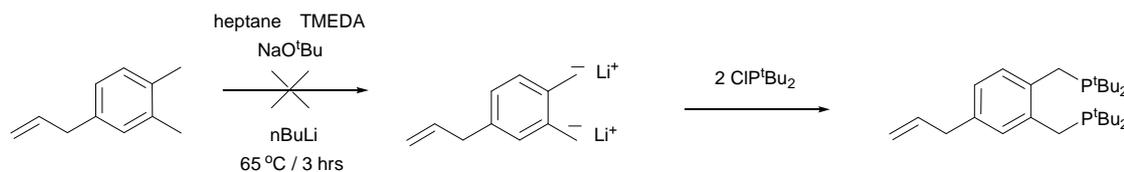


Figure 5-14 - Attempted diphosphination of 4-allyl-o-xylene

Attempted diphosphinations on this molecule using the general conditions filed by Lucite²² (Figure 5-14) led to the production of an orange-brown oil. The ³¹P-NMR spectrum for this oil shows three major signals at 33.0 and 27.3 ppm as well as a broad region around 45.7 ppm. All three are in approximately equal integrals along with numerous other minor peaks. The most significant feature of the ¹H-NMR spectrum is the complete loss of the characteristic alkene resonances, suggesting the reaction conditions have caused reaction of this functionality. It is possible that the acidity of the allylic CH₂ protons may cause *n*BuLi to deprotonate here, resulting in three possible sites for the phosphination to occur. The use of 3 equivalents of base, followed by quenching with only 2 equivalents of chlorophosphine was attempted in the hope that this would lead to better selectivity due to the high steric bulk of the electrophile; although there was little change in the observed product mixture when this was tried.

In an attempt to reduce the acidity of this benzylic CH₂ site, the synthesis of the longer chain derivative, 4-(hex-5-enyl)-o-xylene was successful using the same conditions as for the 4-allyl-o-xylene. Attempted diphosphination on this molecule resulted in the formation of an oil from which crystals could not be obtained. In this case, the ³¹P-NMR spectrum was significantly cleaner, showing just two major peaks in the expected region at 27.2 and 28.0 ppm.

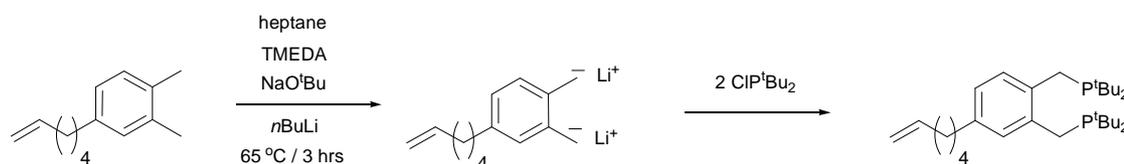


Figure 5-15 - Attempted diphosphination on 4-(hex-5-enyl)-o-xylene

The ¹H-NMR spectrum however, again shows complete loss of the alkene protons, with the observed alkyl chain signals approximately integrating to 12H; although this is

difficult to determine precisely due to overlap with the *tert*-butyl signals. Two sets of doublets are present around 3.0 ppm (4H combined integral), which are characteristic of the two CH₂P methylene resonances and hence suggest phosphination of this molecule has been successful. It therefore appears that the use of a longer alkyl chain spacer between the ring and the desired alkene functionality results in cleaner phosphinated product. The loss of alkene group under the reaction conditions however has not been overcome and so the desired functionalised DTBPMB derivative has not been successfully synthesised.

5.3 Immobilisation Using Imidazolium-Tethered Silica *via* a Sol-Gel Co-Condensation.

The possible supporting of KBPMBS onto a silica supported ionic liquid (IL) phase was investigated. Mehnert *et al.*²³ have reported the use of silica with anchored imidazolium groups, as supports for rhodium complexes of the sulfonated phosphines, tri(*m*-sulfonyl)triphenylphosphine trisodium salt (tppts) and tri(*m*-sulfonyl)triphenylphosphine tris(1-butyl-3-methylimidazolium) salt. (tppti) Both supported catalyst systems showed superior performance in 1-hexene hydroformylation (TOF = 65 and 56 min⁻¹ respectively) compared to the aqueous biphasic system, (TOF = 2 min⁻¹) which suffers from poor solubility of the 1-hexene in the aqueous phase.

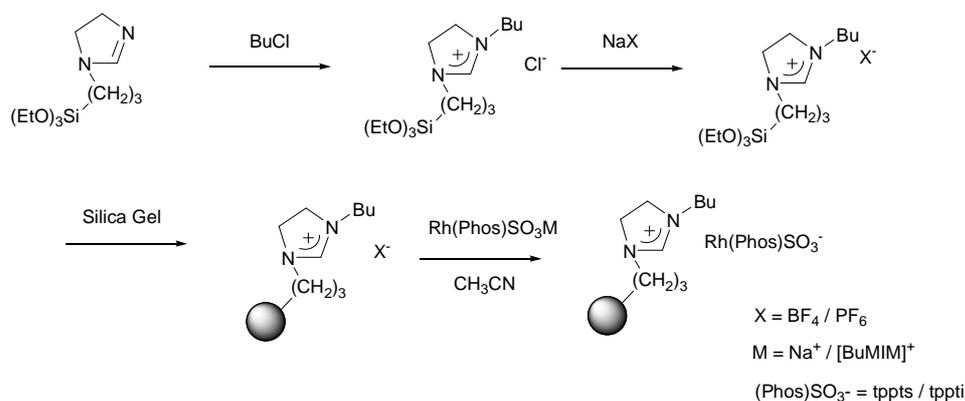


Figure 5-16 - Immobilisation of sulfonated phosphines onto imidazolium tethered silica²³

The supported phase was synthesised from a triethoxysilyl functionalised imidazole, which was converted to the imidazolium tetrafluoroborate or hexafluorophosphate salt. This salt was subsequently tethered to preformed silica *via* condensation and the catalyst loaded by evaporating an acetonitrile solution of the complex onto the silica. A preparation based on this was investigated for the KBPMBS ligand system, where the support was synthesised *via* a sol-gel co-condensation. Two preparative techniques were attempted as shown in Figure 5-17, where the sol gelation was performed before the complex was added, (route **a**) and where the complex was added prior to the sol gelation. (route **b**)

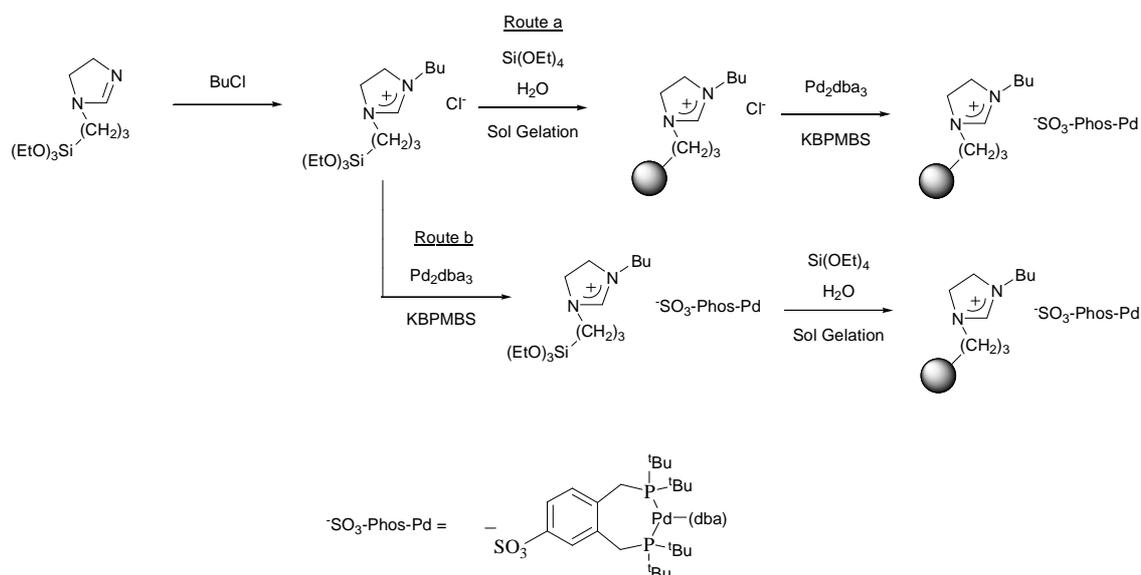


Figure 5-17 - Preparative route to SILP-type catalyst

The synthesis of the functionalised imidazolium chloride was successful following the preparation of Meinhert *et al.*²³ and subsequent gelation (route **a**) resulted in the formation of a free flowing colourless silica. Subsequent treatment of this with a solution of Pd_2dba_3 and KBPMBS (2.5 : 1 ratio) gave an orange-coloured silica. Following route **b**, addition of Pd_2dba_3 and KBPMBS (2.5 : 1 ratio) to the molecular imidazolium precursor in acetonitrile resulted in the formation of a fine precipitate which was filtered. The orange solution then underwent sol gelation to also obtain an orange free flowing silica.

In both cases however, washing of the silica with methanol resulted in orange to yellow coloured washings, which contained the expected palladium complex by $^{31}\text{P-NMR}$. (See section 6.3) These methanol washings were continued and resulted in coloured washings and both silica samples becoming colourless; suggesting that complete leaching from the support had occurred in both cases. Initial tests on these silicas showed no conversion in 1-octene methoxycarbonylation (20 bar CO , 80 °C, 3 hrs); again suggesting that none of the complex had remained on the support after washing with methanol.

5.4 Discussion

Formation of a catalytically active sulfonamide-linked silica supported material has been difficult and not successful here. The formation of a sulfonamide-linked derivative of DTBPMB has been demonstrated, however attempts to deboronate the corresponding sol-gel immobilised phosphine-borane with the use of acid led to cleavage of the catalyst from the support. This observation may suggest that the sulfonamide linkage is too weak for the intended purpose; especially as the alkene methoxycarbonylation catalysis requires acidic conditions.

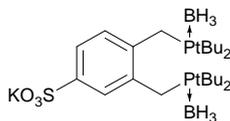
However, if deprotection were successful without cleavage, then investigations using low acid levels could be undertaken. It may be possible that no acid is required for catalysis here, as the acidity of the surface silanols may be sufficient to form the palladium-hydride species necessary for the reaction. If this supported catalyst were found to be too acid sensitive, it may still be useful in the methoxycarbonylation of aryl chlorides,²⁴ which is performed under basic conditions, and so the sulfonamide linkage should remain highly stable.⁴

Immobilisation onto silica *via* alkene hydrosilation is particularly attractive as this route would result in very strong C-C linked functionalities. Although several potentially suitable xylyl precursors were synthesised, subsequent phosphination of these did not lead to isolation of desired products. The use of a methyl spacer between the alkene and the aromatic ring appears to be necessary for preventing the formation of large numbers of side products. If this spacer is too short (allyl), it is possible that phosphination at the spacer carbon could be taking place due to its enhanced acidity, allowing one of the CH₂ protons to be abstracted. A longer spacer appears to suppress this, however there is complete loss of the alkene functionality in the resulting crude material and so the resulting product lacks the desired functionality to allow hydrosilation.

An alternative would be to exploit the reported use of Heck-type couplings on sulfonyl chlorides.²⁵ One possibility would be to couple to a suitable silane-functionalised styrene precursor, such as p-vinylphenyltrimethoxysilane, the synthesis of which has been described.²⁶ This could be coupled to the synthesised sulfonyl chloride derivative

5.5 Experimental

5.5.1 Synthesis of Potassium 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonate-bis(borane) adduct

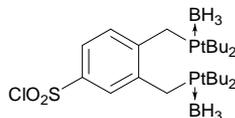


With the exclusion of air and moisture, to a 2 necked 100 cm³ round bottomed flask fitted with Young's tap, reflux condenser, bubbler and magnetic follower was added potassium 3,4-bis(di-tert-butylphosphino-methyl)benzenesulfonate (0.50 g, 0.975 mmol) in THF. (30 cm³) Borane-THF complex (Acros, 1 mol dm⁻³ in THF, 1.95 cm³, 1.95 mmol) was then added dropwise at room temperature *via* syringe over 5 minutes. The solution was then stirred at room temperature for a further 2 hours, after which ³¹P-NMR spectroscopy showed complete conversion to the bis(borane) adduct. The solvent was removed *in vacuo* and further THF added, (30 cm³) this was also removed *in vacuo* (in order to remove any remaining borane component) to yield the target compound as a colourless solid (0.521 g, 99 %)

Characterisation

¹H-NMR: δ [ppm] = 0.10 – 1.30 (m, 6H, J_{PB} = 230 Hz, PBH₃), 1.16 (m, 36H, P(C(CH₃)₂)₂), 3.31 (m, 4H, PCH₂CCCH₂P), 7.52 - 7.55 (m, 2H, O₂SCCHCHC), 7.99 (s, 1H, SO₃CH); ¹³C-NMR: δ [ppm] = 27.2 – 27.3 (m, PC(CH₃)₂)₂), 28.9 (br. d, J = 4 Hz, PC(CH₃)₂)₂), 33.5 (d of d, J = 20 Hz, 5 Hz, CH₂P), 124.4, 130.2, 132.5, 134.3, 137.9, 143.0 (6 x s, aromatic C); ³¹P-NMR: δ [ppm] = 51.4, 51.5 (2 x br. m); FT-IR: (Nujol Mull): 3280 br., 2726 w., 2382 m., 1581 m., 1170 s., 1070 br. s., 1041 s., 813 w., 721 s. cm⁻¹, Microanalysis: Requires; C = 53.15 %, 9.48 %, found; C = 52.75 %, H = 9.66 % Mpt: > 280 °C. No literature data available for comparison.

5.5.2 Synthesis of 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonyl chloride-bis(borane) adduct



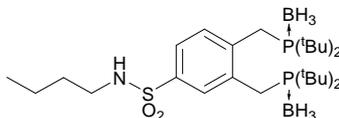
With the exclusion of air and moisture, a 2 necked 100 cm³ round bottomed flask fitted with Young's tap, reflux condenser, bubbler and magnetic follower was charged with potassium 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonate-bis(borane) adduct (0.521 g, 0.965 mmol) and THF (30 cm³) and cooled to 0 °C *via* an ice-water bath. With stirring, a solution of thionyl chloride (Fisher, 0.465 g, 0.28 cm³, 1.95 mmol) and DMF (1 drop) in THF (5 cm³) was added dropwise *via* syringe over 1 minute.

The solution was stirred at room temperature for a further 2 hours resulting in the formation of a colourless sticky precipitate. The solvent was removed *in vacuo* and the resulting sticky solid redissolved in THF. (30 cm³) The solvent was removed *in vacuo* and again redissolved in hot ethanol (ca. 30 cm³) and filtered. The solvent was removed from the filtrate *in vacuo* to yield the crude title compound as a yellow-brown solid. (0.239 g, 47 %)

Characterisation

¹H-NMR: δ [ppm] = 0.10 – 1.30 (m, 6H, J_{PB} = ca. 230 Hz, PBH_3), 1.14 (m, 36H, $P(C(CH_3)_3)_2$), 3.29 (m, 4H, PCH_2CCH_2P), 7.50 - 7.55 (m, 2H, $SO_2CCHCHC$), 8.00 (s, 1H, O_2SCCHC); **¹³C-NMR:** δ [ppm] = 27.0 – 27.3 (m, $PC(CH_3)_3$), 28.9 (d, $J = 4$ Hz, $PC(CH_3)_2$), 33.6 (m, CH_2P), 124.1, 130.0, 131.9, 134.0, 137.5, 143.0 (6 x s, aromatic C); **³¹P-NMR:** δ [ppm] = 51.4 (br. m); **FT-IR: (Nujol Mull):** 3270 br., 2750 m., 2180 m., 1591 s., 1308 s., 1122 m., 1059 s., 842 m., 675 w. cm⁻¹. No literature data available for comparison.

5.5.3 Synthesis of N-butyl-3,4-bis((di-tert-butyl)phosphino)methyl)benzenesulfonamide-bis(borane) adduct



Under anhydrous conditions, to a 100 cm³ round bottomed flask was added 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonyl chloride-bis(borane) adduct (0.250 g, 0.48 mmol) and *n*-butylamine (Eastman, 37 mg, 0.5 mmol) in dry DCM (20 cm³) and cooled to 0 °C using an ice-water bath. In a separate 100 cm³ round bottomed flask was added triethylamine, (Fluka, 0.3 cm³ 2.15 mmol) and 4-DMAP (Aldrich, ca. 10 mg, 0.05 mmol) in DCM. (20 cm³) The contents of this flask were then added dropwise to the initial flask over 5 minutes and the resulting solution stirred for 1 hour at room temperature.

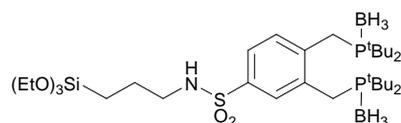
The solvents were then removed *in vacuo* and the resulting crude solid purified by column chromatography (silica, hexane : ethyl acetate 2 : 1, R_f = 0.52) and the product containing fractions recrystallised from DCM / hexane to yield the title compound as colourless needles. (0.113 g, 42 %)

Characterisation

¹H-NMR: δ [ppm] = 0.85 (t, 3H, J_{HH} = 15 Hz, CH₃CH₂CH₂CH₂NH), 1.26 (d, 36H, J_{PH} = 11.1 Hz, P(C(CH₃)₃)₂), 0.12 – 1.20 (q, 2H, J_{PB} = 330 Hz, PBH₃), 1.36 - 1.50 (m, 4H, CH₂CH₂CH₂NH), 1.57 (s, 1H, CH₂NHSO₂), 2.90 (q, 2H, J_{HH} = 21 Hz, CH₂NH), 3.41 (d of d, 4H, J_{HH} = 12 Hz / 4 Hz, PCH₂CCH₂P), 7.63 - 7.77 (m, 2H, SO₂CCHCHC), 8.11 (s, 1H, SO₂CCHC); **¹³C-NMR:** δ [ppm] = 13.6 (s, CH₃CH₂CH₂CH₂NH), 19.7, 24.7, 43.1 (3 x s, CH₃CH₂CH₂CH₂NH), 28.0 (d, J = 26 Hz, PC(CH₃)₃)₂), 28.5 (d, J = 12 Hz, PC(CH₃)₃)₂), 33.2 (d, J = 20 Hz, CH₂P), 125.0, 127.5, 130.7, 132.7, 135.2, 138.6 (6 x s, aromatic C); **³¹P-NMR:** δ [ppm] = 53.1 (br. m); **Microanalysis:** Requires C = 60.33 %, H = 10.67 %, N = 2.51 %, found C = 59.96 %, H = 10.35 %, N = 2.45 %.

Mpt: 193 - 195 °C. X ray structure details in main text. No literature data available for comparison.

5.5.4 Synthesis of 3,4-bis((di-*tert*-butyl-phosphino)methyl)-N-(3-(triethoxysilyl)propyl)benzenesulfonamide-bis(borane) adduct

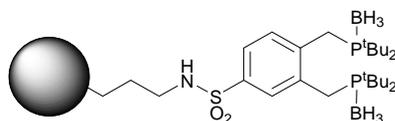


The procedure described above (Section 5.5.3) was followed using (triethoxysilyl)propan-1-amine (Aldrich, 0.113 g, 0.119 cm³, 0.48 mmol) in place of *n*-butylamine. Purification by column chromatography was not attempted and the resulting crude paste was analysed and used directly in subsequent reactions. (0.273 g, 81 %)

Characterisation

¹H-NMR: δ [ppm] = 0.12 – 1.20 (q, 6H, J_{PB} = ca. 350 Hz, PBH₃), 0.62 (m, 3H, SiCH₂), 1.24 (m, 45H, P(C(CH₃)₂)₂); 3 x OCH₂CH₃), 1.53 (m, 2H, SiCH₂CH₂), 1.53 (s, 1H, CH₂NHSO₂), 2.83 (m, 2H, CH₂NH), 3.35 (m, 4H, PCH₂CCCH₂P), 3.86 (q, 6H, J_{HH} = 26 Hz, 3 x OCH₂CH₃), 7.61 - 7.81 (m, 2H, SO₂CCHCHC), 8.10 (s, 1H, SO₂CCHC); **¹³C-NMR:** δ [ppm] = 8.1 (s, SiCH₃), 18.8 (s, 3 x SiOCH₂CH₃), 26.3, 44.7 (2 x s, SiCH₂CH₂CH₂NH), 27.9 (d, J_{CP} = 27 Hz, PC(CH₃)₂), 28.4 (d, J_{CP} = 12 Hz, PC(CH₃)₂), 33.2 (d, J_{CP} = 20 Hz, CH₂P), 58.3 (s, SiOCH₂) 125.1, 127.6, 130.4, 133.0, 135.0, 138.6 (6 x s, aromatic C); **³¹P-NMR:** δ [ppm] = 52.4 (br. m); No literature data available for comparison.

5.5.5 Sol Gel Co-Condensation of 3,4-bis(di(*tert*-butyl)phosphinomethyl)-N-(3-(triethoxysilyl)propyl)benzenesulfonamide-bis(borane) adduct

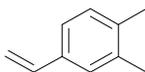


To a 100 cm³ round bottomed flask fitted with a Young's tap and magnetic follower was added crude 3,4-bis(di(*tert*-butyl)phosphinomethyl)-N-(3-(triethoxysilyl)propyl)-benzenesulfonamide bis(borane) adduct (0.339 g, 0.48 mmol) in dry THF (9 cm³) and methanol (3 cm³). Dry triethylamine (0.3 cm³, 2.17 mmol) and tetraethyl orthosilicate (Aldrich, 4 cm³, 18.0 mmol) was then added and the solution stirred well whilst water (4 cm³) was added *via* syringe which effected rapid gelation of the solution. The resulting gel was left to stand for 48 hours before being diluted with THF (50 cm³) and filtered. The resulting colourless free flowing silica was washed with copious amounts of water, methanol, THF and DCM before being continuously washed with THF in a Soxhlet apparatus for 16 hours and dried *in vacuo* to leave a colourless free-flowing silica. (2.06 g)

Characterisation

³¹P-NMR: δ [ppm] = 51.9 (br. m; ca. 82 % by integral), 81.1 (br. m; ca. 18 % by integral). See main text for suggested assignments.

5.5.6 Synthesis of 3,4-dimethylstyrene (via Wittig route)



Under an argon atmosphere, a 250 cm³ 2-necked round bottomed flask fitted with a Young's tap, reflux condenser and a pressure equalising dropping funnel was added triphenylmethylphosphonium bromide (Aldrich, 12.80 g, 37.44 mmol) in diethyl ether

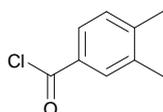
(100 cm³). The solution was stirred and cooled to 0 °C using an ice-water water bath and *n*-butyllithium (Aldrich, 2.5 mol dm⁻³ in hexanes, 14.98 cm³, 37.44 mmol) was added dropwise over 20 minutes. The mixture was then stirred at room temperature for 5 hours after which 3,4-dimethylbenzaldehyde (Aldrich, 5.00 g, 37.3 mmol) in diethyl ether (100 cm³) was added dropwise over 2 hours, resulting in the formation of a colourless precipitate.

The mixture was heated to reflux for 22 hours, filtered and the filtrate dried over magnesium sulfate. The solvent was removed carefully *in vacuo* at 20 °C to yield a yellow oil which was purified by column chromatography using silica gel (60 Å) eluting hexane : ethyl acetate (10 : 1) to give the title compound as a colourless oil. (3.49 g, 71 %)

Characterisation

MS (EI): Requires M⁺ = 132, Found M⁺ = 132; **¹H-NMR:** δ [ppm] = 2.16 (s, 3H, CH₃C), 2.17 (s, 3H, CH₃C), 5.08 (d, 1H, J_{HH} = 14.5 Hz, HHC=CHC), 5.59 (d, 1H, J_{HH} = 14.5 Hz, HHC=CHC), 6.58 (m, 1H, H₂C=CHC) 6.92 – 7.19 (m, 3H, aromatic CH); **¹³C-NMR:** δ [ppm] = 20.0, 20.2 (2 x s, C(CH₃)C(CH₃)), 113.0 (s, CH₂CHC) 124.1, 127.9, 130.2 (3 x s, aromatic CH), 135.7, 136.8, 137.0 (3 x s, aromatic C), 137.3 (s, CH₂CH); **Microanalysis:** Requires H = 9.15 %, C = 90.85 %, found H = 9.36 %, C = 91.01 %. Only boiling point and mass spectrum available in literature,²⁷ of which (bpt) was not compared.

5.5.7 Synthesis of 3,4-dimethylbenzoyl chloride



To a 250 cm³ round bottomed flask fitted with a reflux condenser and magnetic follower was added 3,4-dimethylbenzoic acid, (Avocado, 50 g, 0.33 mol), and thionyl chloride (Alfa, 55 g, 0.46 mol) in toluene (100 cm³). With efficient stirring, 2 drops of DMF were added to initiate a vigorous reaction. When the reaction had subsided somewhat,

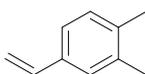
the mixture was heated to 65 °C for 3 hours, cooled and the solvent removed *in vacuo*. Complete conversion to the acid chloride was shown by ¹H-NMR, where complete loss of the acidic proton signal at 12.10 ppm was observed.

The crude product was redissolved in diethyl ether, (250 cm³) washed with water (2 x 250 cm³) and dried over magnesium sulfate before removal of the solvent *in vacuo*. The crude material was then crystallised from hexanes at -20 °C overnight. The crystals were rapidly filtered before they redissolved, and recrystallised from hexanes to yield the title compound as low-melting colourless crystals (42.6 g, 88 %)

Characterisation

¹H-NMR: δ [ppm] = 2.31 (s, 3H, CH₃C), 2.34 (s, 3H, CH₃C), 7.22 (m, 2H, CCHCHC), 7.61 (m, 1H, CHC); ¹³C-NMR: δ [ppm] = 19.2, 19.8 (2 x s, C(CH₃)C(CH₃)), 129.2, 131.4, 135.4 (5 x s, Aromatic C), 133.4 (s, CCOCl), 168.4 (s, COCl); **Microanalysis:** Requires C = 64.11 %, H = 5.38 %, found C = 65.30 %, H = 5.78 % **Mpt:** approximately room temperature. Only boiling point available in literature, which was not compared.²⁸

5.5.8 Synthesis of 3,4-dimethylstyrene (via Heck coupling)



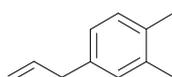
Under an argon atmosphere, a 100 cm³ hastelloy autoclave fitted with a pressure gauge and magnetic follower was charged with 3,4-dimethylbenzoyl chloride (Alfa Aesar, 8.6 g, 51.0 mmol), N-benzyl dimethylamine (Aldrich, 7.24 g, 53.6 mmol), palladium acetate (Aldrich, 0.113 g, 0.19 mmol) and toluene (100 cm³). The autoclave was then purged with ethylene and taken to 5 bar of ethylene pressure. The autoclave was heated, with stirring to 100 °C at which point further ethylene was added to give a total pressure of 10 bar. The autoclave was kept at this temperature for 4 hours before cooling and venting.

The mixture was washed with hydrochloric acid (ca. 2 mol dm⁻³, 2 x 50 cm³), sodium hydroxide (2 x 50 cm³) and water (2 x 50 cm³), dried over magnesium sulfate and the solvent removed. The crude product was purified by silica gel chromatography (60 Å) eluting with DCM to yield the title compound as an oil with a pale red colouration (2.2 g, 34 %). A trace of palladium contaminant is thought to be responsible for the slight colouration.

Characterisation

Analytically identical to 5.5.6.

5.5.9 Preparation of 4-allyl-1,2-dimethylbenzene



Under anhydrous conditions, to a 500 cm³ round bottomed flask fitted with a Young's tap, reflux condenser and magnetic follower and charged with magnesium turnings (Acros, 13.3 g, 0.28 mol) and a single crystal of iodine was added 4-bromo-o-xylene (Acros, 50 g, 0.27 mol) in diethyl ether (150 cm³). The mixture was heated to a gentle reflux for 3 hours after which it had taken on a dirty red-green colouration.

To a separate 500 cm³ round bottomed flask fitted with a Young's tap, reflux condenser and magnetic follower was added allyl bromide (Aldrich, 33.8 g, 0.28 mol) in dry diethyl ether. (100 cm³) Whilst stirring in a room temperature oil bath, the Grignard was added portionwise to this solution over 60 minutes and the resulting solution heated to gentle reflux for 2 hours, resulting in a colour change from dark green to yellow. The reaction solution was cooled with an ice-water bath and quenched by the careful addition of water (30 cm³) resulting in significant salt formation.

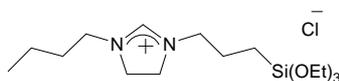
The resulting salt was dissolved by addition of further water, (100 cm³) the organic layer separated and the aqueous phase further extracted with diethyl ether (3 x 100 cm³). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo* at 40 °C to yield a crude oil. This was purified by reduced pressure

distillation to obtain the title compound as a colourless fraction. (62-64 °C at 0.1 mm Hg) This colourless oil was stored at 4 °C in the dark until required, slight discolouration was observed on storage after 3-4 weeks. (24.3 g, 62 %)

Characterisation

MS(EI): Requires $M^+ = 146$, Found $M^+ = 146$; **$^1\text{H-NMR}$:** δ [ppm] = 2.45 (s, 3H, CH_3C), 2.47 (s, 3H, CH_3C), 3.59 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 5.35 (m, 2H, $\text{CH}=\text{CH}_2$), 6.24 (m, 1H, $\text{CH}=\text{CH}_2$) 7.11 – 7.45 (m, 3H, aromatic CH); **$^{13}\text{C-NMR}$:** δ [ppm] = 19.8, 20.1 (2 x s, $\text{C}(\text{CH}_3)\text{C}(\text{CH}_3)$), 40.3 (s, $\text{CCH}_2\text{CH}=\text{CH}_2$), 115.8 (s, $\text{CH}_2=\text{CH}$), 126.1, 127.4, 128.9 (3 x s, aromatic CH), 135.7, 136.8, 140.0 (3 x s, aromatic C), 137.4 (s, $\text{CH}_2=\text{CH}$); **Microanalysis:** Requires H = 9.65 %, C = 90.35 %, found H = 9.91 %, C = 90.19 %. **Bpt:** 62 - 64 °C at 0.1 mm Hg. Only boiling point available in literature, which was not compared.²⁹

5.5.10 Preparation of 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium chloride²³

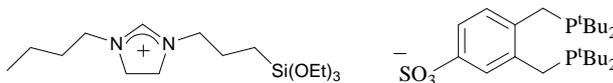


To a 250 cm³ round bottomed flask was added dried 1-chlorobutane (Aldrich, 25.4 g, 0.27 mol), N-(3-triethoxysilylpropyl)-4,5-dihydroimidazole (Fluorochem, 25.0 g, 91.2 mmol) and a magnetic follower. A reflux condenser and silica-drying tube were fitted and the mixture was heated to reflux for 20 hours. The volatile components were then removed *in vacuo* and the resulting oil washed with hexane (3 x 100 cm³) and dried *in vacuo* at 60 °C for 5 hours. The oil was then extracted into DCM and filtered through alumina and activated carbon yielding the title compound as a yellow solid after removal of the DCM solvent, which was stored in a glove box until required. (31.9 g, 95 %)

Characterisation

$^1\text{H-NMR}$ (CD_3CN): δ [ppm] = 0.62 (m, 2H, $\text{CH}_2\text{CH}_2\text{Si}$), 0.95 (tr, 3H, $J_{\text{HH}} = 7$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.20 (tr, 9H, $J_{\text{HH}} = 7$ Hz, 3 x OCH_2CH_3), 1.38 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.69 (m, 4H, $\text{CH}_2\text{CH}_2\text{Si}$; $\text{CH}_2\text{CH}_2\text{CH}_3$), 3.70 (m, 4H, $\text{SiCH}_2\text{CH}_2\text{CH}_2\text{NCH}_2$), 3.85 (m, 6H, 3 x OCH_2CH_3), 4.15 (m, 4H, $\text{CH}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 10.46 (s, 1H, NCHN); $^{13}\text{C-NMR}$ (CD_3CN): δ [ppm] = 7.6 (s, SiCH_2), 14.0 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 18.9 (s, OCH_2CH_3), 19.7 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 20.0 (s, SiCH_2CH_2), 29.5 (s, $\text{CH}_2\text{CH}_2\text{CH}_3$), 47.7, 48.9, 49.2, 50.2 (4 x s, $\text{CH}_2\text{NCH}_2\text{CH}_2\text{NCH}_2$), 58.7 (s, OCH_2CH_3), 159.1 (s, NCHN). Characterisation in good agreement to literature data.²³

5.5.11 Preparation of 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium 3,4-bis(di-tert-butylphosphinomethyl)benzenesulfonate



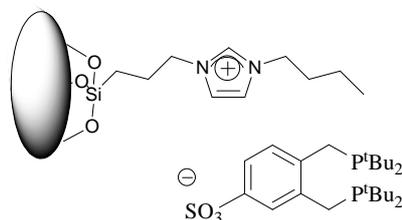
Under anhydrous and anaerobic conditions, to a solution of 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium chloride (0.500 g, 1.37 mmol) in acetonitrile (10 cm^3) was added 3,4-bis(di-tert-butylphosphinomethyl)benzenepotassium sulfonate (0.702 g, 1.37 mmol) in acetonitrile (10 cm^3). The resulting slurry was stirred for 5 days at room temperature. The precipitate was then removed by filtration through celite and the solvent removed *in vacuo*. The resulting orange oil was dissolved in DCM and filtered through activated carbon and alumina before removal of the solvent *in vacuo* yielding the title compound as a sticky orange-brown solid. (0.59 g 67 %). This was stored in a glove box until required.

Characterisation

$^1\text{H-NMR}$: δ [ppm] = 0.59 (br. m, 2H, $\text{CH}_2\text{CH}_2\text{Si}$), 0.95 - 1.08 (m, 39H, $\text{CH}_2\text{CH}_2\text{CH}_3$; 2 x $\text{P}(\text{C}(\text{CH}_3)_3)_2$), 1.20 (m, 9H, 3 x OCH_2CH_3), 1.15 (br. m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.69 (br. m, 4H, $\text{CH}_2\text{CH}_2\text{Si}$; $\text{CH}_2\text{CH}_2\text{CH}_3$), 2.99 (br. s, 4H, methylene CH_2), 3.61 (m, 4H,

SiCH₂CH₂CH₂NCH₂), 3.75 (br. m, 6H, 3 x OCH₂CH₃), 4.05 (m, 4H, CH₂NCH₂CH₂CH₂CH₃), 7.40-7.62 (m, 2H, KO₃SC-CH-CH-C), δ = 7.90 (s, 1H, KO₃SC-CH-C), 10.01 (s, 1H, NCHN); ¹³C-NMR: δ [ppm] = 7.4 (s, SiCH₂), 14.0 (s, CH₂CH₂CH₃), 19.9 (s, CH₂CH₂CH₃), 20.5 (s, SiCH₂CH₂), 22.9 (s, OCH₂CH₃), 27.5 (s, P-C-(CH₃)₃), 29.6 (s, CH₂CH₂CH₃), 30.2 (d of d, J_{CP} = 13 Hz / 7 Hz, *butyl* C-CH₃), 33.3 (d of d, J_{CP} = 22 Hz / 3 Hz, methylene -CH₂-P), 48.2, 48.8, 50.1, 50.5 (4 x s, CH₂NCH₂CH₂NCH₂), 119.5 (s, KO₃S-C), 122.9, 128.6, 131.1 (3 x s, CH-C(KSO₃)-CH-CH), 143.5 (P-CH₂-C-C-CH₂P) 176.1 (s, NCHN); ³¹P-NMR: δ [ppm] = 27.2, 28.1 (2 x s); No literature data available for comparison. On addition of Pd₂(dba)₃ (0.4 equivalents) in THF and stirring for 2 hours, two additional broad singlet's were observed in the ³¹P-NMR spectrum at 66.0 and 66.2 ppm, which are in the expected region for the dba complex.³⁰

5.5.12 Sol-Gel Co-Condensation of 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate



To a 100 cm³ round bottomed flask fitted with a Young's tap and magnetic follower were added 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate (0.59 g, 0.913 mmol) in dry THF (12 cm³) and methanol. (6 cm³) Dry triethylamine (0.6 cm³, 4.33 mmol) and tetraethyl orthosilicate (Aldrich, 8 cm³, 35.9 mmol) was then added and the solution stirred well whilst water (8 cm³) added. This effected rapid gelation of the solution, becoming too viscous to stir after 2 minutes. The resulting gel was left to stand for 48 hours before being washed with THF (3 x 50 cm³) and dried to leave a free flowing colourless silica gel. This was washed with methanol on a Soxhlet apparatus for 16 hours.

The above procedure was also followed using the $\text{Pd}_2(\text{dba})_3$ complex of 1-butyl-3-(3-triethoxysilylpropyl)-4,5-dihydroimidazolium 3,4-bis(di-*tert*-butylphosphinomethyl)-benzene sulfonate. (1 : 2.5 molar ratio with respect to palladium) This resulted in an orange coloured free flowing silica. Rather than wash on a Soxhlet apparatus, this sample was repeatedly washed in a Schlenk using portions (50 cm^3) of methanol and subsequent filtration. The filtrate took on a yellow colour on washing, eventually (after 6 washes) leaving the silica colourless. After this treatment the silica showed no ^{31}P -NMR resonances and the methanol washings contained weak ^{31}P -NMR signals at $\delta = 28.5, 29.4 \text{ ppm}$ (the free phosphine) and $\delta = 66.0, 66.2 \text{ ppm}$. (the expected palladium-dba complex)

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6. Catalysis in Ionic Liquids

6.1 Introduction

Investigation of an ionic liquid based separation technique led on from a preliminary study of an aqueous biphasic separation system for 1-octene hydroxycarbonylation. Hydroxycarbonylation of 1-octene has previously been reported by Jimenez¹ using unmodified 1,2-bis(*di-tert*-butylphosphinomethyl)benzene (DTBPMB) but due to the insolubility of the diphosphine in water itself, a two-solvent system with acetone was necessary to bring all the components into one phase.

Reaction times reported for this conversion were 20 hours, significantly longer than those reported in general. This is thought to be due to the poor nucleophilicity of water relative to alcohols and the low water concentration, which was necessary to overcome solvation problems. At high conversions, prop-1-en-2-yl nonanoate was observed, which is thought to have arisen from nucleophilic attack of the enolic form of acetone, which would be present due to keto-enol tautomerism. (Figure 6-1) Most importantly however, the catalyst was found to be stable under these conditions and selectivities were very good, generally being around 98 %.

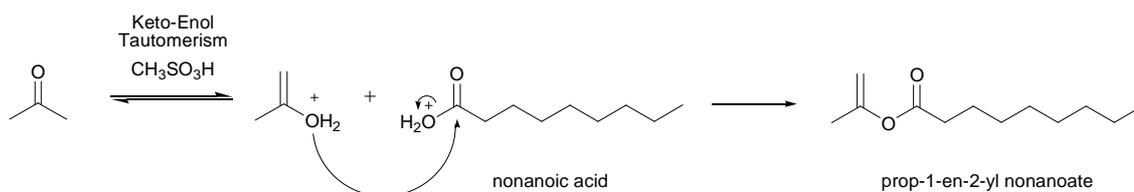


Figure 6-1 - Formation of 1-prop-1-en-2-yl nonanoate in the presence of acetone

As protonated potassium 3,4-bis(*di-tert*-butylphosphinomethyl)benzenesulfonate (KBPMBS) was known to be water soluble, a biphasic water-organic system was investigated for separation and whilst conversions looked promising. (Table 6-1) The catalyst resided primarily in the organic phase after reaction (visually and by ³¹P-NMR) and some palladium black was observed after reaction. The selectivity loss was primarily due to the formation of a compound which had a GC retention time of 18.9 minutes and remains unidentified, although by GC-MS has an *m/z* = 236 and a significant fragment at 131.

| CO Pressure | Conversion | Selectivity | L:B Ratio |
|-------------|------------|-------------|-----------|
| 4 bar | 10 % | 94.5 % | 249 |
| 40 bar | 52 % | 95.0 % | 193 |

Table 6-1 - Summary of biphasic hydroxycarbonylation experiments

Conditions - Pd₂dba₃ (0.1 mmol), KBPMBS (0.5 mmol), MSA (1 mmol), 1-octene (2 cm³), water (10 cm³), 80 °C, 3 hours.

On addition of an aqueous K₂PdCl₄ solution to an aqueous solution of KBPMBS and methanesulfonic acid (MSA), a colourless precipitate began to form. This suggests that, although the protonated KBPMBS ligand is water soluble, the resulting palladium complex appears not to be (Figure 6-2), which may explain its preference for an organic phase. Also, the relatively poor stability may be due to cluster formation in the high catalyst concentration in the smaller organic phase volume. This therefore led onto the investigation of ionic liquids as alternative solvents for catalyst-product separation.

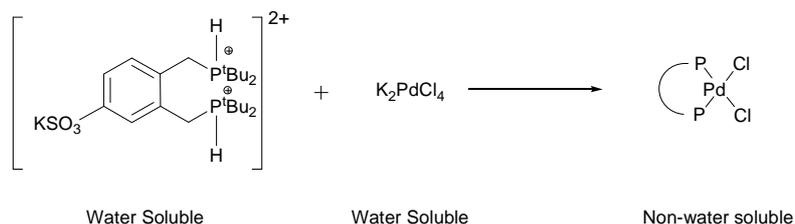


Figure 6-2 - KBPMBS complex formation in water

6.2 Ionic Liquids for Separation

Catalysis in ionic liquid (IL) phases was introduced in chapter 1, along with some of the potential advantages that such systems might bring with regard to assisting in catalyst-product separation. Therefore, assessment of the performance of the synthesised KBPMBS ligand in IL solvents will be discussed; leading on to investigation of IL-organic phase extractions and an IL-supercritical fluid (IL-SCF) extraction system as a means of effecting product separation.

Palladium catalysed methoxycarbonylation of 1-octene (Figure 6-3) was used as the reaction system and the conditions used were generally based on those described by Jimenez.¹ Here, Pd₂(dba)₃ was used as the palladium precursor with a 2.5 molar excess of ligand to palladium and a 10-fold molar excess of MSA with respect to palladium.²

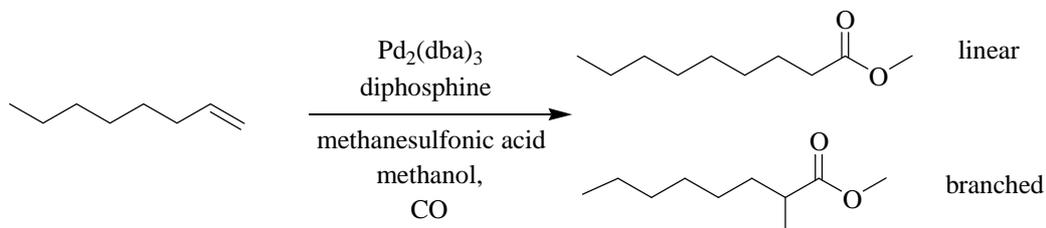


Figure 6-3 – Methoxycarbonylation of 1-octene by palladium – MSA complexes

6.2.1 1-Octene Methoxycarbonylation in Ionic Liquid Solvents

1-Octene methoxycarbonylation using palladium complexes of KBPMBS ligand was investigated based on the IL-based separation method employed by Webb *et al.*³ for 1-octene hydroformylation. This uses rhodium complexes of triphenylphosphine monosulfonate (TPPMS) for efficient separation of the aldehyde product by a flow of scCO₂, as is discussed more completely in section 1.8.3.

For this purpose, it is important that the IL has a high temperature stability, good solubility for the reagents and a low viscosity to allow manipulation using Schlenk techniques. Fortunately the ease and modular nature of IL synthesis means there are literally thousands of IL combinations already synthesised and investigated.⁴ A promising group of IL's for this task are based on the bis(trifluoromethanesulfonyl)imide ([NTf₂]⁻) anion. Bônhoté *et al.*⁵ found these [NTf₂]⁻ based imidazolium salts generally to have low melting points and low viscosities when coupled with an unsymmetrical cation. They are thermally stable up to 400 °C,⁵ above which they rapidly decompose to their corresponding 1-alkylimidazole derivatives.⁶

Their relatively low polarities give them a hydrophobic character, although they may still contain an appreciable water content. For example, [BuMIM][NTf₂] has a water content of 1.4 mass % at its saturation point; yet even after a vigorous drying procedure

it still contains 474 ppm water,⁷ although this is significantly less than the corresponding chloride salt, which contains 2200 ppm water after the same drying procedure. Although immiscible with water, [NTf₂]⁻ based imidazolium IL's are generally miscible with solvents with medium to high dielectric constants, such as DCM, THF and short-chain alcohols and ketones. They are generally immiscible with medium to low polarity solvents such as alkanes, toluene and diethyl ether.⁵

As a suitable cation for this work, 1-octyl-3-methylimidazolium ([OcmIM]⁺) was chosen; it has been suggested³ that the octyl chain here would assist in the solubility of the low polarity octene substrate within the IL. The methanol substrate should be highly soluble in this solvent, as discussed above and this IL has demonstrated good results in the IL/SCF described previously.³

6.2.2 Syntheses of Ionic Liquids

The preparation of imidazolium based IL's is practically straightforward and high yielding. In general, the halide salt is accessed initially by reaction of the desired alkyl halide with alkyl imidazole. If, as in this case, a different anion is then desired, a metathesis reaction with a suitable salt is subsequently performed. This is summarised in Figure 6-4 for the general synthesis of [alkylMIM][NTf₂].

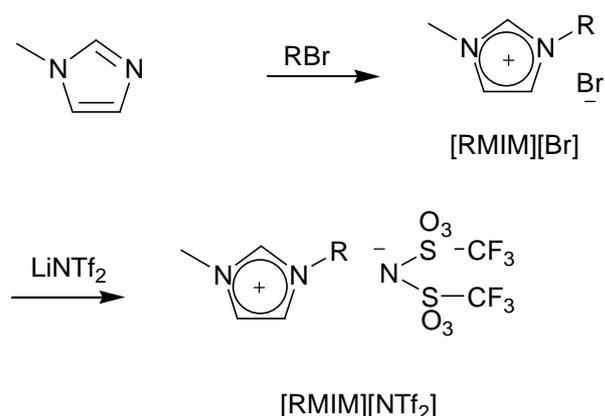


Figure 6-4 - General method for the formation of alkylimidazolium bis(trifluoromethanesulfonyl)imide ionic liquids, R = alkyl

1-[Octyl, Pentyl and Propyl]-3-methylimidazolium triflamides of the above form; ([OcMIM][NTf₂], ([PeMIM][NTf₂], ([PrMIM][NTf₂], respectively) were synthesised by this route in relatively high yield using literature preparations.^{§§} In all cases these products were colourless to tan coloured oils with characterisation in good agreement with literature data.^{§§}

6.3 Studies on Complex Formation in IL solvent

Initial tests were carried out to verify the solubility of the KBPMBS in the IL and to see whether formation of palladium complexes of the ligand was successful in the IL medium. KBPMBS (0.197 g) was mixed in [OctMIM][NTf₂] (5 cm³) at room temperature. Although dissolution did occur to a large extent, the solution was still somewhat cloudy after mixing for 2 hours; heating to 80 °C removed this cloudiness, indicating an acceptable, albeit not overly high solubility of the ligand in [OctMIM][NTf₂], with improved solubility observed at catalytically relevant temperatures.

The formation of palladium complexes of KBPMBS was then studied in the IL solvent by ³¹P-NMR at room temperature. Formation of these complexes was also attempted in methanol under identical conditions for comparison; in both cases a 1:1 ratio of ligand to palladium was used and d₄-methanol was added prior to analysis to obtain a lock signal. These data are tabulated, along with data reported by Eastham from a similar study on DTBPMB complex formation in methanol⁸ in Table 6-2.

^{§§} See experimental section of this chapter for specific references

| Ligand | DTBPMB ⁸ | KBPMBS | KBPMBS |
|---|---|--------------------------------------|---|
| Solvent | MeOH | MeOH | [OcMIM][NTf ₂] |
| Free phosphine. Signals observed / ppm | 28.4 | 23.0, 24.3 | 26.0, 27.5 |
| Addition of Pd ₂ dba ₃ (1 eq), after ca. 30 min. Signals observed / ppm | 48.0 (br), 50.0 (br); “analysed immediately” | 23.0, 24.3, 46.5 (br), 51.1 (br), | 43.7 (br), 47.8 (br), 52.0 (br); (1 : 2 : 1) |
| Above, after 1 hour. Signals observed / ppm | | 46.5 (br), 51.1 (br) (1 : 1) | 43.7 (br), 47.8 (br), 52.0 (br); (1 : 2 : 1) |
| Above plus MSA (5 eq), 30 min. Signals observed / ppm | 40.0 (br), 63.0 (br); “analysed immediately”; 67.5 only after 24 hours | 69.3 (br), 69.4 (br) | 69.1 (br), 69.5 (br) |

Table 6-2 – Summary of ³¹P-NMR data for palladium diphosphine complexes in [OcMIM][NTf₂] and methanol solvent

The data suggest that complex formation has successfully occurred for KBPMBS, both in methanol and [OcMIM][NTf₂]. The likely rationale for the observed broad signals for the dba complex is that there are several conformational binding motifs for dba to the palladium which cannot be resolved on the NMR timescale. Eastham has performed low temperature ³¹P-NMR studies to further investigate these for the DTBPMB complex.⁸

The signals observed for KBPMBS complexes follow the same trend as for DTBPMB complexes, with more peaks observed due to the inequivalency of the phosphorus sites in KBPMBS. Complex formation for KBPMBS in methanol appears to be somewhat retarded compared to DTBPMB, with signals for the free phosphine still observed after 30 minutes, although these are no longer present after 1 hour; interestingly this is not the case for KBPMBS complex formation in [OcMIM][NTf₂] solvent.

Another notable difference for the KBPMBS complexes is the difference in the observed signals soon after addition of 5 equivalents of MSA. Eastham reports two broad signals at 40 and 63 ppm which disappear to give just a signal at 67.5 ppm after 24 hours. The former signals are not observed in these cases after 30 minutes and only signals around 69 ppm are observed both in methanol and [OcMIM][NTf₂] solvents.

6.4 Batch Catalysis Experiments

6.4.1 Autoclave Setup

Reactions were performed in a 20 cm³ stainless steel CSTR fitted with a variable speed T-bar stirrer. Temperature control was achieved by an external heating jacket and internal thermocouple and was controlled using a Eurotherm™ temperature control box. Pressure was monitored by a digital pressure transducer and over-pressure protection was achieved using a bursting disc set to 230 bar.

Gas pressure could be introduced to the autoclave *via* a ball valve using high-pressure gas heads and Swagelok™ pressure tubing. Manipulation of air-sensitive liquids could be performed using an inlet which can be attached directly to a Schlenk line for access to vacuum and argon. Liquids could be introduced *via* a septum, either by cannula or syringe. A schematic diagram of the reactor setup is shown in Figure 6-5.

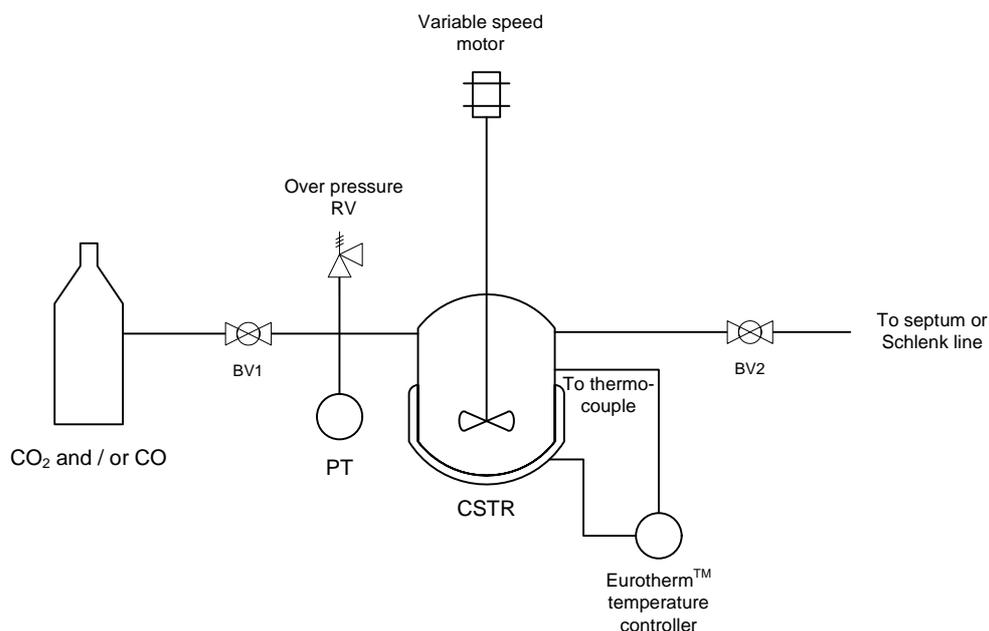


Figure 6-5 – Schematic of batch autoclave setup

**CSTR = Continuously Stirred Tank Reactor, RV = Release Valve,
PT = Pressure Transducer, BV = Ball Valve**

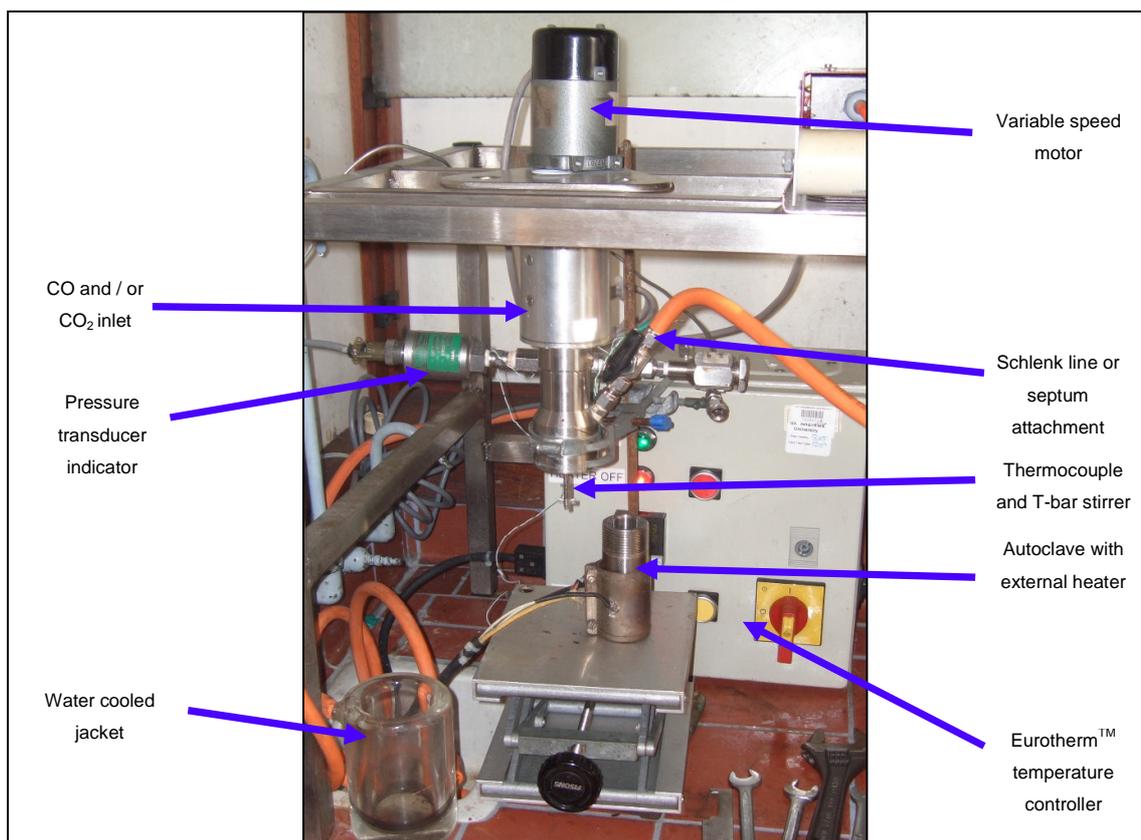


Figure 6-6 - Photograph of batch autoclave reactor setup

6.5 Catalysis Compared with Unmodified DTBPMB

As both KBPMBS and DTBPMB were soluble in methanol, an initial comparison of the catalytic performance of these two ligands in methoxycarbonylation was performed. The catalytic conditions used were based on those reported by Jimenez *et al.*² for 1-octene methoxycarbonylation. The data obtained are shown in Table 6-3.

| Ligand | Conversion | Selectivity | L:B Ratio | Mean TOF |
|--------|------------|-------------|-----------|----------------------|
| DTBPMB | 99.5 % | 98.6 % | 38 | 158 hr ⁻¹ |
| KBPMBS | 72.1 % | 97.5 % | 22 | 114 hr ⁻¹ |

Table 6-3 - Batch reactions in methanol with KBPMBS and DTBPMB ligands
 Conditions, Pd₂dba₃ (0.05 mmol), diphosphine (0.25 mmol), MSA (0.5 mmol), 1-octene (2 cm³),
 methanol (10 cm³), CO (30 bar), 80°C, 3 hrs

Mean turnover frequency (TOF) values are given to allow comparison with data presented later. Both catalyst systems appeared to be stable under these conditions, resulting in yellow solutions after catalysis. DTBPMB catalysis compares well with results obtained by Jimenez,¹ with high 1 : b selectivity. Both catalysts appeared to be stable under these reaction conditions, giving yellow-orange solutions after catalysis with no indication of palladium-black formation. There does appear to be a retardation in the rate of catalysis for KBPMBS as well as a slightly poorer 1 : b ratio of esters; however, the selectivity both toward general ester formation and to linear ester is good in both cases.

6.6 Catalysis in IL Solvent

Catalysis was attempted using 5 cm³ of [OcmIM][NTf₂] as solvent. A 2-fold molar excess of methanol to 1-octene was used with an initial 1-octene loading of 2 cm³. After reaction, the IL phase was extracted with an organic solvent. Unsaturated hydrocarbons have an appreciable solubility in imidazolium-based IL's, with aromatic hydrocarbons showing particularly high solubilities,⁹ so extraction with such solvents would be likely to lead to considerable leaching. This could be attributed to strong interactions between the π -system of the aromatic solvent with the imidazolium cation, which have been reported.¹⁰ For this reason the medium polarity, solvent diethyl ether was selected for extraction of products.

To determine the efficiency of the diethyl ether extractions, a catalytic [OcmIM][NTf₂] phase (1 cm³) containing both 1-octene and methyl nonanoate product was extracted several times with diethyl ether (4 cm³) and analysed by GC using nonane (Aldrich) as an internal standard.

| Extract | Normalised 1-Octene Content | Normalised Methyl Nonanoate Content |
|---------|-----------------------------|-------------------------------------|
| 1 | 96.2 % | 75.9 % |
| 2 | 1.7 % | 12.4 % |
| 3 | 1.7 % | 6.4 % |
| 4 | 0.5 % | 4.9 % |

Table 6-4 – Product extraction using diethyl ether

As can be seen by the data in Table 6-4, diethyl ether is efficient at extracting 1-octene, although somewhat less so for the more polar ester product. From these results it was decided that the IL phase would be extracted two times with ether for analysis, although it should be noted that this method is likely to slightly underestimate the conversions, as methyl nonanoate is incompletely extracted from the IL at this point. It is important to note that this extraction appears to result in significant leaching of the catalyst phase into the extract; resulting in yellow extracts. Four extracts of the same 1 cm³ sample resulted in reduction of the catalyst phase to ca. 0.35 cm³ and hence this would be a poor choice of extraction solvent for product-catalyst separation.

Under a CO pressure of 4 bar at 80 °C, no detectable conversion to ester was observed by GC after 2 hours. Isomerisation of the 1-octene had occurred however with 56 % of the total octene content being other isomers. The presence of isomerised octenes suggests that the catalyst has been active, although appears to either be starved of CO or otherwise CO insertion into the substrate has not occurred. This is possibly due to a poor solubility of CO in the IL phase.

6.6.1 Carbon Monoxide Solubility in Ionic Liquids.

Studies into gas solubility in IL's have been undertaken on a variety of synthetically important gases.¹¹ With the notable exception of CO₂, many gases show a relatively poor solubility in IL's, with a pattern which correlates well with polarizability of each gas.

Only relatively recently has any detailed study been undertaken on the solubility of carbon monoxide in IL's.¹² Here, the solubility of carbon monoxide in a series of IL's was investigated using high pressure ¹³C NMR spectroscopy in order to ascertain trends in the solubility. The anion was found to play an important role in the solvating ability, with the series [BF₄]⁻ < [PF₆]⁻ < [SbF₆]⁻ < [CF₃CF₂]⁻ < [Tf₂N]⁻ being established. This correlates with increasing size and decreasing π*-character of the anion giving better solubility.¹³

In the case of pyridinium and imidazolium based IL's, the CO solubility is also increased by lengthening in the substituent alkyl chain on the cation. The addition of a benzyl group to this chain decreases the solubility – again correlating to a decrease in CO solubility as the π*-character of the IL increases.¹⁴

With this in mind, consideration of CO solubility in [OctMIM][NTf₂] suggests that this IL is already well designed for CO solubility. The anion has been reported to play the most significant role in CO solvation ability and for this, the NTf₂⁻ ion has been shown to be the most effective of the reported anions. The alkyl chain length on the cation is already long at eight carbons and the synthesis of IL's with significantly longer chain lengths would become increasingly synthetically difficult and would be likely to give only a small increase in CO solubility if the trend in the reported Henry's constants is to be extrapolated.¹²

Another potential method for significantly increasing the CO solubility in IL's is based on a report by Leitner *et al.*¹⁵ on the enantioselective hydrogenation of *N*-(1-phenylethylidene)aniline in [EMIM][NTf₂]. Here a significant increase in the solubility of H₂ was observed by high-pressure ¹H-NMR upon the addition of various CO₂ pressures at a constant partial pressure of H₂, as detailed in Figure 6-7. This significant increase in H₂ solubility was reflected in an increase of conversion to the desired hydrogenation product from 3 % to 100 % over 22 hours at 40 °C.

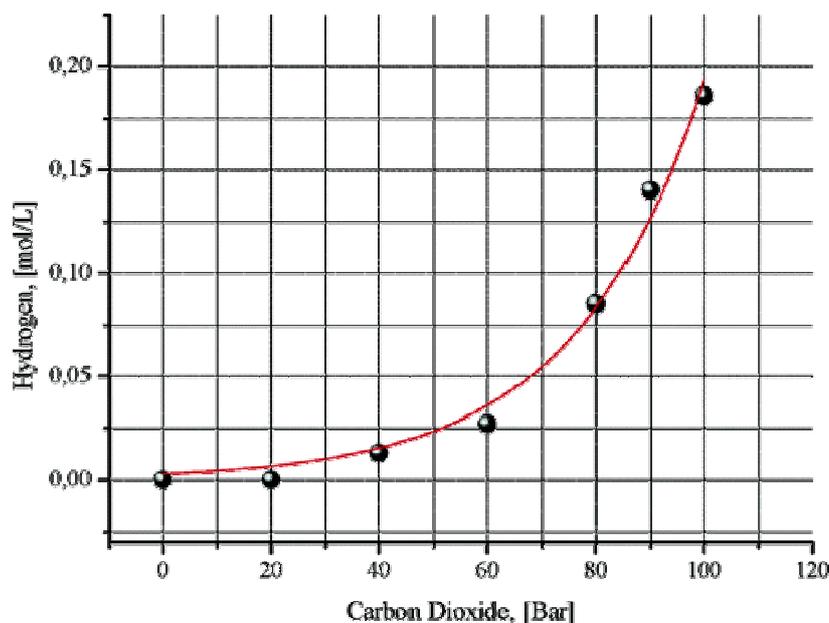


Figure 6-7 - Hydrogen solubility in [EtMIM][NTf₂] as a function of CO₂ Pressure¹⁵

The IL under 30 bar of H₂ did not show any detectable dihydrogen peak in the ¹H-NMR spectrum but when CO₂ was added to make up a total pressure of 120 bar, the IL became significantly less viscous and the dihydrogen peak was clearly visible. Integration of this peak gave an estimated concentration of H₂ in the IL of 0.14 mol dm⁻³ which is comparable to H₂ solubility in common organic solvents under similar conditions. Error! Bookmark not defined.

The use of an additional CO₂ pressure in this form for the methoxycarbonylation system was therefore considered. Direct observation of the CO solubility in the IL was considered using high pressure ¹³C-NMR, however this would not be trivial as the poor natural abundance and long relaxation times of the ¹³C nucleus would make quantification of CO content difficult. However consequential evidence for this occurring may well be observed in the form of increased ester conversions in the catalytic process.

6.7 Batch Reactions With and Without Addition of CO₂

Carbon dioxide was delivered in liquid form and so was dispensed into the autoclave directly at a maximum of 60 bar at 15 °C. Delivering CO₂ to the reactor at a higher

pressure than this would require a HPLC pump. For this reason, the CO₂ pressure was kept at a constant 59 bar (+/- 1 bar) - its room temperature liquid pressure. An additional CO pressure of between 10 and 40 bar was then added. Supercritical fluid chromatography grade (BOC-Gases, SFC grade) CO₂ was used as this higher purity grade gas contained minimal water (<2 vpm) and oxygen (<5 vpm) impurities. The data obtained are shown in Table 6-5.

| Gas Pressure | Conversion | Selectivity | L:B ratio | Mean TOF |
|--|------------|-------------|-----------|---------------------|
| 10 bar (CO) | 0.0 % | - | - | - |
| 20 bar (CO) | 0.0 % | - | - | - |
| 30 bar (CO) | 2.3 % | 86.6 % | 6 | 2 hr ⁻¹ |
| 41 bar (CO) | 16.5 % | 93.2 % | 8 | 13 hr ⁻¹ |
| 60 bar (CO) | 32.4 % | 95.2 % | 10 | 26 hr ⁻¹ |
| 10 bar (CO), 59 bar (CO ₂) | 7.3 % | 86.0 % | 10 | 6 hr ⁻¹ |
| 22 bar (CO), 59 bar (CO ₂) | 7.1 % | 85.8 % | 4 | 6 hr ⁻¹ |
| 30 bar (CO), 60 bar (CO ₂) | 10.9 % | 90.3 % | 8 | 9 hr ⁻¹ |
| 40 bar (CO), 60 bar (CO ₂) | 29.4 % | 92.2 % | 7.5 | 23 hr ⁻¹ |

Table 6-5 - Data for catalysis in [OctMIM][NTf₂] with and without the addition of CO₂
Conditions, Pd₂dba₃ (0.1 mmol), KBPMBS (0.5 mmol), MSA (1 mmol), 1-octene (1 eq, 2 cm³),
[OMIM][NTf₂] (5 cm³), methanol (2 eq, 0.64 cm³), 80 °C, 3 hours.

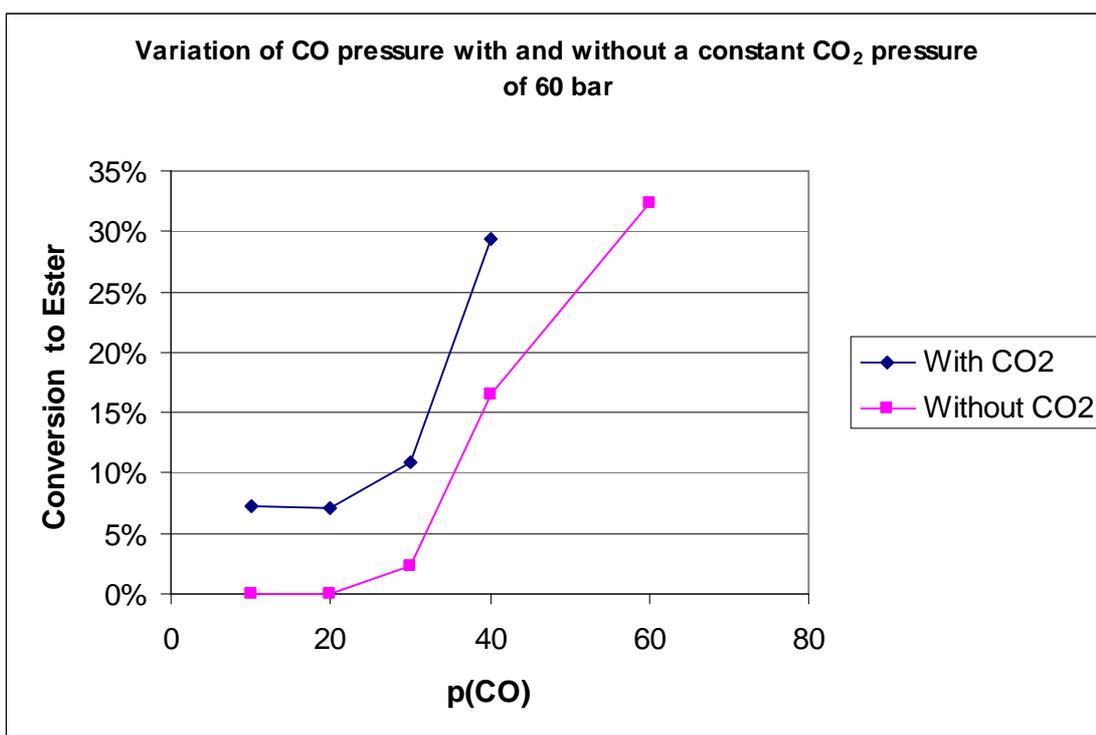


Figure 6-8 - Conversion with varying p(CO) with and without a constant p(CO₂)

With no CO₂ present, no conversion is observed until a pressure of 30 bar is used, where trace product is observed, a significant rise in conversion is observed when the pressure is raised to 40 bar. With the addition of 60 bar CO₂ to the system, conversion is observed at all gas pressures tested. The conversion is low, yet is consistently higher than without the presence of CO₂, suggesting that the CO₂ may well be assisting CO solubility into the IL phase. The combined CO / CO₂ gas study was limited to 40 bar (in CO), as heating of this mixture to 80 °C resulted in an initial autoclave pressure in excess of 150 bar.

Side-product formation was analysed by GC-MS. Here peaks were identified for internal methoxycarbonylation products; methyl-2-propylpentanoate and methyl-2-ethylheptanoate as well as smaller amounts of *n*-hexenes and *n*-decenes, which appear to be impurities in the 1-octene stock, and consequently their corresponding methoxycarbonylation products are also observed. Additional peaks (M/Z 129) including heavier material (M/Z 426 / 382 / 313 / 279) remain unidentified and so are also considered side-products. DBA and hydrogenated DBA are also observed and are not included in side product calculation.

With reference to Leitner's solubility observations discussed previously,¹⁵ (Figure 6-7) at a CO₂ pressure of 60 bar, the effect on H₂ solubility is not yet significant, hence getting the CO₂ pressure closer to 100 bar may well have an enhanced effect on CO solubility in this reaction. A related experiment was undertaken using a different autoclave set up and will be discussed later, in section 6.11.1.

The low molar excess of methanol substrate in these runs may be contributing to the relatively low conversions observed, possibly due to poor substrate mass transport; investigations into varying this excess were therefore performed. Care should be used in the interpretation of these results however, as increasing the methanol content significantly effectively results in mixed solvent systems. For example, the use of an 16-fold molar excess of methanol equates to 5.15 cm³ of methanol in 5 cm³ of [OctMIM][NTf₂].

| Excess of MeOH | Conversion | Selectivity | l:b Ratio | Mean TOF |
|-----------------------|-------------------|--------------------|------------------|---------------------|
| 2 | 32.4 % | 91.2 % | 10 | 26 hr ⁻¹ |
| 4 | 57.6 % | 92.4 % | 11 | 46 hr ⁻¹ |
| 8 | 58.3 % | 96.8 % | 15 | 46 hr ⁻¹ |
| 12 | 99.4 % | 99.6 % | 18 | 79 hr ⁻¹ |
| 16 | 99.3 % | 99.3 % | 19 | 78 hr ⁻¹ |

Table 6-6 - Catalytic data on varying methanol concentration in [OcMIM][NTf₂]
Conditions, Pd₂dba₃ (0.1 mmol), KBPMBS (0.5 mmol), MSA (1 mmol), 1-octene (1 eq, 2 cm³), [OMIM][NTf₂] (5 cm³), CO (60 bar), 80 °C, 3 hours.

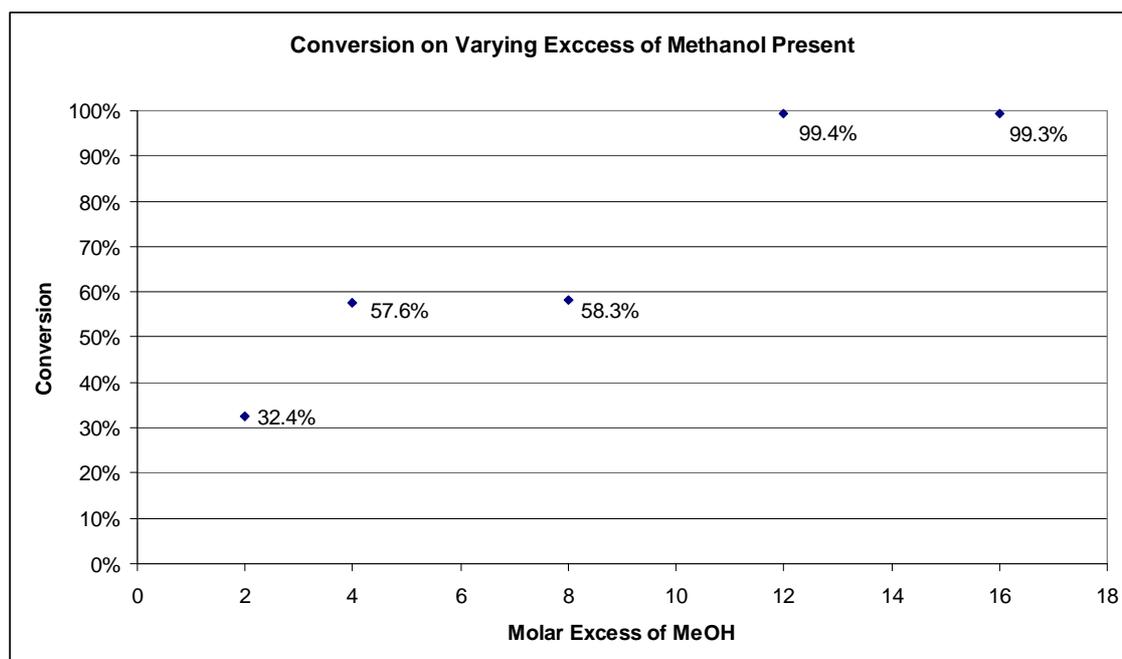


Table 6-7 - Conversion on varying relative excess of methanol substrate

These reactions show a general increase in conversion as the methanol concentration is increased. This is possibly due to less limiting mass transport as more methanol is available for the rate-determining methanolysis stage of the catalytic cycle; or due to the increased CO solubility of the resulting mixed solvent system. It would be reasonable however, to suppose that it is a combination of these two factors that leads to the increased conversions. Another interesting observation from this study was that when the product mixtures were allowed to stand, phase separation gradually occurred for the samples containing 2 and 4 fold excess of methanol. For samples containing an 8-fold excess of methanol and above, no phase separation was observed after 24 hours.

6.8 Phase Miscibility in Different Ionic Liquids

In order further to investigate the nature of the phase behaviour within this catalytic system, empirical observations on mixtures of IL, methanol and octene were made. The chain length of the imidazolium anion was varied in order to ascertain if the polarity of the IL affects the phase behaviour of these mixtures. The observations made are summarised in Table 6-8, below.

| Component (Volume Ratio) | Observed mixture at:- | |
|--|-----------------------|-------------------|
| | 26 °C | 80 °C |
| [PrMIM][NTf ₂] (5), Methanol (1) | Mono | Mono |
| [PeMIM][NTf ₂] (5), Methanol (1) | Mono | Mono |
| [OcMIM][NTf ₂] (5), Methanol (1) | Mono | Mono |
| [PrMIM][NTf ₂] (5), Methanol (1), Octene (1) | Bi | Bi |
| [PeMIM][NTf ₂] (5), Methanol (1), Octene (1) | Bi | Bi |
| [OcMIM][NTf ₂] (5), Methanol (1), Octene (1) | Bi | Bi |
| [PrMIM][NTf ₂] (1), Methanol (1) | Mono | Mono |
| [PeMIM][NTf ₂] (1), Methanol (1) | Mono | Mono |
| [OcMIM][NTf ₂] (1), Methanol (1) | Mono | Mono |
| [PrMIM][NTf ₂] (5), Methanol (5), Octene (1) | Bi | Bi ^{***} |
| [PeMIM][NTf ₂] (5), Methanol (5), Octene (1) | Bi | Mono |
| [OcMIM][NTf ₂] (5), Methanol (5), Octene (1) | Mono | Mono |

Table 6-8 - Phase observations of various IL, methanol and octene mixtures

Mono = monophasic mixture, Bi = biphasic mixture observed after mixing at stated temperature

As was expected, all three IL's were fully miscible with methanol at the ratios tested. When the mixture consisted of a 5 fold excess of IL over methanol, the additional octene was immiscible for all three IL's tested; forming a separate layer above the IL / methanol mixture. Heating the sample to 80 °C, the temperature of the catalytic tests did not homogenise the mixture for any of the IL's tested.

When a 1:1 ratio of the IL to methanol was used, the chain length variation of the IL cation showed distinctive behaviour. The addition of 0.2 volume equivalents of octene was compatible with [OcMIM][NTf₂] / methanol mixture at room temperature, whereas for the two shorter-chain anion IL's, the octene remained immiscible at room temperature. However, [PeMIM][NTf₂] shows interesting behaviour, forming a biphasic at room temperature, yet is fully miscible at reaction temperature – if this phase behaviour is also observed in the more complicated reagent and product mixture present in the reaction system, this could present an interesting method for product separation.

*** A significant reduction in the volume of the upper (octene) phase was observed at elevated temperature but the phases were still not entirely compatible at 80 °C

The more polar [PrMIM][NTf₂] demonstrates similar behaviour, however the two phases are still not fully miscible at 80 °C under these conditions. The necessity of methanol for compatibilising octene and IL's is therefore demonstrated, with the more polar, shorter chain alkyl imidazolium salts still showing phase separation even when significant methanol is present.

6.9 Catalysis With Varying Imidazolium Chain Length

The effect of changing the IL on the observed catalysis was investigated. The concentration of catalyst and substrate was reduced compared to previous runs by both decreasing loadings and increasing the volume of IL solvent. This was to ensure maximal solubility of the catalyst in the more polar IL solvents, which was likely to be reduced compared to [OcMIM][NTf₂]. Gas concentrations of CO (60 bar) and CO₂ (40 bar) were used along with a molar excess of methanol of 4 (wrt 1-octene). The data obtained are shown in Table 6-9.

| Ionic Liquid | Conversion | Selectivity | l:b Ratio |
|----------------------------|-------------------|--------------------|------------------|
| [PrMIM][NTf ₂] | 2.1 % | 77.8 % | 2 |
| [PeMIM][NTf ₂] | 2.4 % | 87.8 % | 3 |
| [OcMIM][NTf ₂] | 13.0 % | 89.9 % | 8 |

Table 6-9 - Catalytic data on varying IL solvent

Conditions, Pd₂dba₃ (0.05 mmol), KBPMBS (0.25 mmol), MSA (0.5 mmol), 1-octene (1 eq, 1 cm³), MeOH (4 eq, 0.64 cm³), IL (10 cm³), CO (60 bar), CO₂ (40 bar), 80 °C, 3 hours.

Even at these lower concentrations, the solubility of the catalyst in [PrMIM][NTf₂] was very poor, to the extent that quantitative transfer to the reaction autoclave was difficult. This was also a problem with [PeMIM][NTf₂], where the solubility was markedly lower than in [OcMIM][NTf₂] and gentle heating of the mixture was required to allow transfer into the autoclave. For both of these IL's, a significant drop in conversions is observed, along with significant Pd-black deposits being observed after reaction.

6.10 Recycling Experiments

To effect separation with this system requires extraction of the products from the IL phase with a suitable solvent, and then recycling of the catalyst-containing IL phase can be performed. For this to be viable the IL-immobilised catalyst must remain stable during the recycling and IL and catalyst leaching into the extraction solvent must be minimal. As was noted in section 6.6, diethyl ether would be a poor solvent choice for this and so the use of petroleum spirit (40 - 60 °C fraction) for extractions was investigated.

An initial catalytic run was extracted 4 times (5 cm³ petroleum each) and each analysed by GC using nonane as internal standard and normalised octene and methyl nonanoate levels in these extracts are shown in Table 6-10. As was observed for diethyl ether extractions, 1-octene extracts more efficiently than the more polar ester product as may be expected. From these results it was decided that the IL phase would be extracted 3 times with petroleum between cycles which should lead to relatively efficient extraction of both reactants and products.

| Extract | Normalised 1-octene Content | Normalised methyl nonanoate content |
|----------------|------------------------------------|--|
| 1 | 85.9 % | 66.2 % |
| 2 | 9.5 % | 16.5 % |
| 3 | 4.1 % | 11.5 % |
| 4 | 0.5 % | 4.1 % |
| 5 | 0.1 % | 1.6 % |

Table 6-10 – Extraction using petroleum spirit (40 – 60 °C)

Batch runs were performed using the conditions described previously and after venting, the autoclave contents were recovered into a Schlenk flask under a positive pressure of nitrogen *via* cannula. In all cases, in excess of 90 vol % of the autoclave contents were recovered, with any remainder being left in the autoclave under nitrogen. The recovered cloudy yellow-brown IL phase was extracted with petroleum spirit (40 – 60 °C, 10 cm³) three times, giving a colourless extract which was subsequently analysed by GC / Pd

ICP-MS. The IL phase was charged with a new load of 1-octene and methanol (1 molar equivalent) and this was returned to the autoclave for recycle. The results obtained are summarised in Table 6-11.

| Cycle | Isomerisation | Conversion | Selectivity | l:b ratio | Mean TOF | Pd leaching |
|------------------|---------------|------------|-------------|-----------|---------------------|-------------|
| 1 | 84.5 % | 13.0 % | 89.9 % | 8 | 10 hr ⁻¹ | 435 ppb |
| 2 | 71.4 % | 2.1 % | 75.2 % | 2 | 5 hr ⁻¹ | 794 ppb |
| 3 | 64.3 % | (<1 %) | - | - | - | 295 ppb |
| 4 ^{†††} | 12.1 % | (<1 %) | - | - | - | 437 ppb |

Table 6-11 – Recycling experiments using petroleum extraction (40-60 °C)

Conditions, Pd₂dba₃ (0.05 mmol), KBPMBS (0.25 mmol), MSA (0.5 mmol), 1-octene (1 eq, 1 cm³ per run), MeOH (4 eq, 0.64 cm³ per run), [OcMIM][NTf₂] (10 cm³), CO (60 bar), CO₂ (40 bar), 80 °C, 3 hours.

Initial conversion is low, although in line with previous experiments, disappointingly however, the catalyst stability is poor, with almost no activity on attempted recycling. On the 4th cycle, further MSA was added to the reaction mixture in an attempt to restore activity, although no conversion was observed and on stopping the experiment, palladium black deposits were observed in the autoclave base. The petroleum extraction method does however appear to be efficient, sub parts-per-million levels of palladium observed in the colourless extracts.

Following on from the observations that high methanol concentrations significantly increase activity, along with the phase separation observed for a 5 : 5 : 1 (by volume) mixture of [PeMIM][NTf₂] : Methanol : Octene; it was proposed that such a system could be used for catalysis with separation effected by cooling the reaction mixture. This system was therefore investigated for catalysis under the conditions described and the data is summarised in Table 6-12, with octene, methanol and MSA being replaced between runs.

^{†††} Further MSA (0.5 mmol) was added prior to this run

After the initial run, no phase separation was observed on standing at room temperature; the reaction mixture was therefore extracted twice with petroleum ether as before. On subsequent runs, phase separation did occur, suggesting that the presence of high concentrations of ester product prevent the phase separation from occurring; nonetheless, extraction of this phase using petroleum was continued for these later runs also.

| Cycle | Isomerisation | Conversion | Selectivity | I:b ratio | Mean TOF | Pd leaching |
|-------|---------------|------------|-------------|-----------|---------------------|-------------|
| 1 | 68.1 % | 86.8 % | 97.5 % | 19 | 69 hr ⁻¹ | 137 ppb |
| 2 | 66.3 % | 28.7 % | 94.1 % | 17 | 23 hr ⁻¹ | 60 ppb |
| 3 | 55.0 % | 21.9 % | 96.5 % | 18 | 17 hr ⁻¹ | 48 ppb |
| 4 | 20.4 % | 12.4 % | 90.3 % | 18 | 10 hr ⁻¹ | 49 ppb |

Table 6-12 – Recycling experiments in mixed [PeMIM][NTf₂] / MeOH solvent using petroleum extraction (40-60 °C)

Conditions, Pd₂dba₃ (0.05 mmol), KBPMBS (0.25 mmol), [PeMIM][NTf₂] (5 cm³), MSA (0.5 mmol per run), 1-octene (1 cm³ per run), MeOH (5 cm³, additional 0.32 cm³ per run), CO (60 bar), 80 °C, 3 hours.

Although initial conversions are significantly higher for this case compared to the previous, the stability of the system remains poor with significant loss of conversion is observed after the first recycle. From the first recycle onwards, the IL phase retained an orange colouration throughout, although after the runs were completed palladium black deposits were observed in the autoclave base. The extraction methodology again remains efficient however, even at these higher methanol levels; with the colourless extracts showing even lower levels of palladium than before, being in the low parts-per-billion region. The initial catalyst activity is promising, with high conversion and selectivity to linear ester product.

Given the efficient extraction and low Pd leaching observed for this system, recycling of this IL was compared to [OcMIM][NTf₂], given the high conversions and monophasic solvent system that was observed here previously. Identical loadings and conditions were used to that of the [PeMIM][NTf₂] recycling experiments above and the results obtained are detailed in Table 6-13.

| Cycle | Conversion | Selectivity | l:b ratio | Mean TOF | Pd leaching |
|-------|------------|-------------|-----------|---------------------|-------------|
| 1 | 50.2 % | 97.7 % | 11 | 40 hr ⁻¹ | 956 ppb |
| 2 | 23.5 % | 96.9 % | 9 | 19 hr ⁻¹ | 5394 ppb |
| 3 | 15.1 % | 95.4 % | 12 | 12 hr ⁻¹ | 4286 ppb |

Table 6-13 – Recycling experiments in mixed [OcMIM][NTf₂] / MeOH solvent system using petroleum extraction (40-60 °C)

Conditions, Pd₂dba₃ (0.05 mmol), KBPMBS (0.25 mmol), [OcMIM][NTf₂] (5 cm³), MSA (0.5 mmol per run), 1-octene (1 cm³ per run), MeOH (5 cm³, additional 0.32 cm³ per run), CO (60 bar), 80 °C, 3 hours.

In this case, the catalyst system is visually more stable, with no precipitate observed in the reaction solution; however there is still rapid deactivation of the catalyst system with regard to the observed conversions. Product extraction remains efficient here also, although palladium levels are higher than before, being over 1 ppm, though the extracts themselves remain colourless, as is pictured in Figure 6-9.

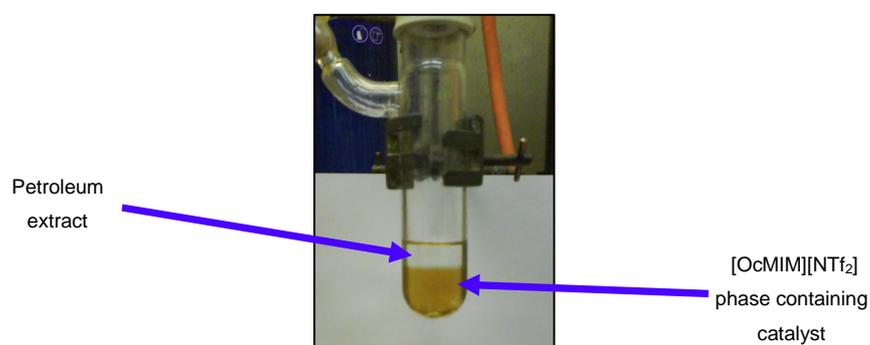


Figure 6-9 - Petroleum extraction of [OcMIM][NTf₂] phase after 2nd Recycle

6.11 Extraction with scCO₂

6.11.1 Autoclave Setup

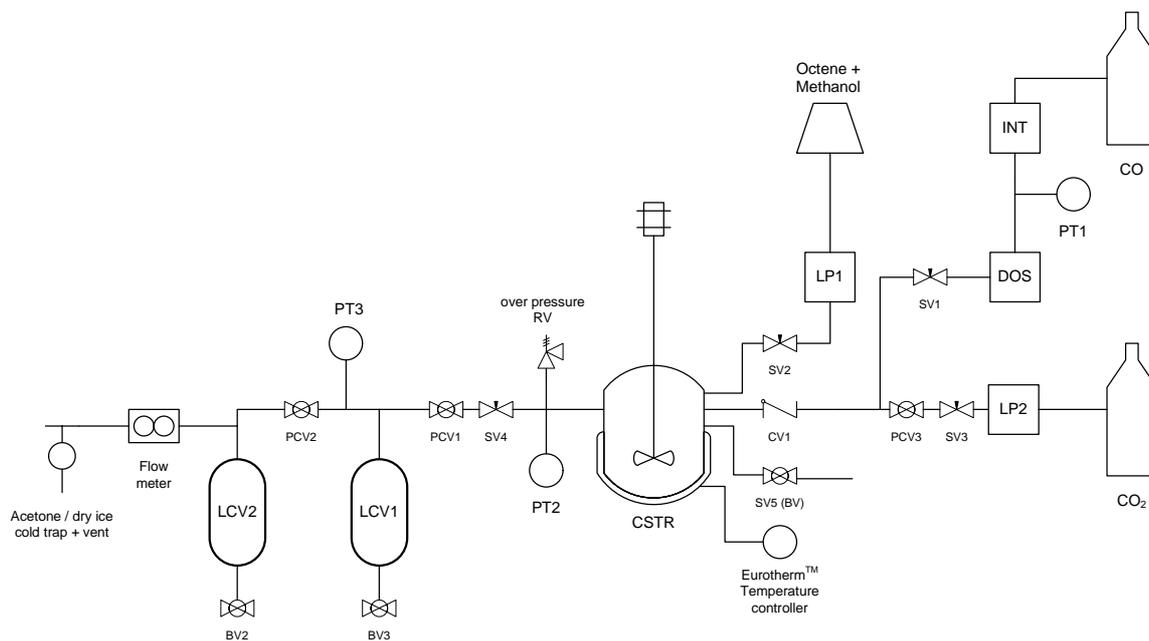


Figure 6-10 – Schematic diagram of IL-scCO₂-flow rig.

CSTR = Continuously Stirred Tank Reactor, INT = Intensifier, PT = Pressure Transducer,
DOS = Dosimeter, SV = Shutoff Valve, LP = Liquid Pump, PCV = Pressure Control Valve,
CV = Check Valve, RV = Release Valve, LCV = Liquid Collection Vessel

The reactor set up used to investigate scCO₂ extraction is shown schematically in Figure 6-10. A batch autoclave (CSTR) is fed CO and CO₂ by two liquid pumps. The system can be run in a batch-type mode at pressures of up to 200 bar and the reactor contents can be eluted *via* a dip-tube (SV5). In continuous flow mode, the reagents are continuously fed by LP1 and CO by a dosimeter, where the pressure is set higher than that of the reactor. Flow can then be regulated by PCV1 and a flow meter; in this second section of the system, eluted material is depressurised to 10 - 15 bar, causing the scCO₂ to return to a gaseous state and hence effecting precipitation of organics into LCV1. In order to achieve high mass balances, it was necessary to fit an acetone / dry ice cold trap to the flue gas to trap vapours which were otherwise lost, this collection was shown by GC to consist of primarily methanol and a small amount of octenes; it was generally combined with the collection from LCV1 prior to analysis. A picture of the reactor set-up is shown in Figure 6-11.

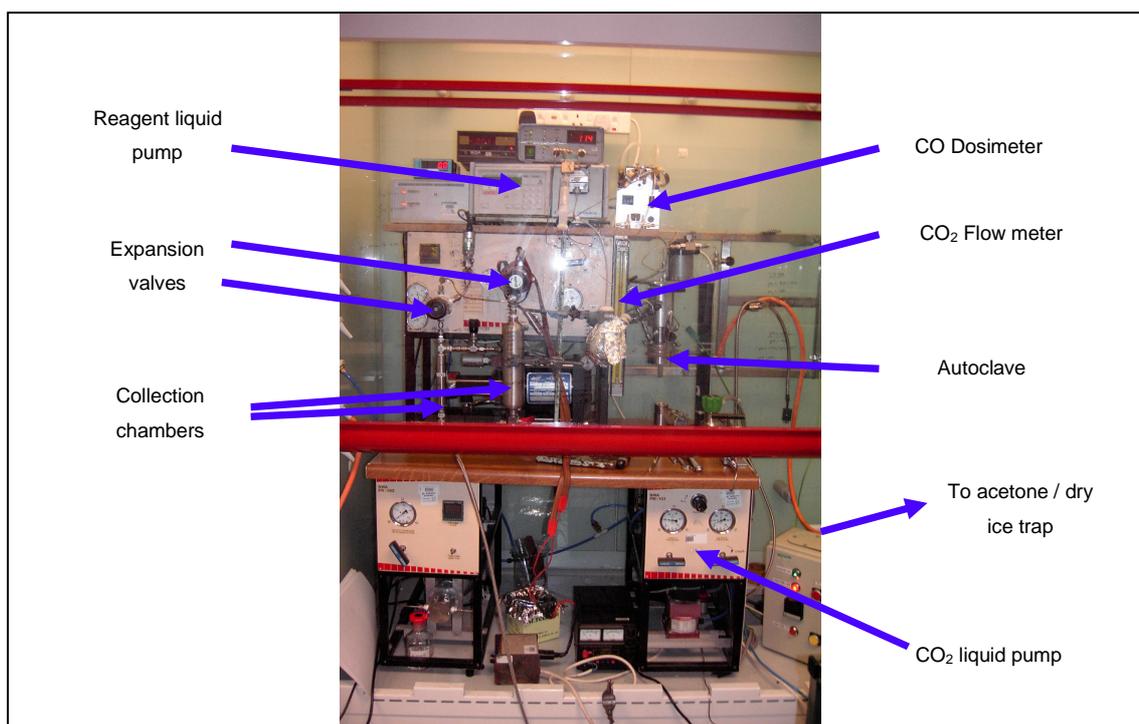


Figure 6-11 - Photograph of scCO₂ flow system

6.11.2 Batch Experiments With scCO₂ Extraction

This autoclave was used in a batch mode to assess activity, with product extraction from the IL phase being performed using scCO₂ flow at reaction temperature. A molar 1-octene to methanol ratio of 1 : 4 was used for these experiments. Although methanol ratios higher than this were previously demonstrated significantly to increase the catalyst activity; the methanol would be extracted with the product after reaction and addition of significant amounts of such polar solvents have been reported to increase the solubility of the IL phase in scCO₂¹⁶ and hence high levels would be likely to leach the IL phase and the dissolved catalyst.

After reaction, a CO₂ flow of 1 normal litre per minute was used to extract the product / reactant mixture. A 52 % mass balance was obtained in the collection vessel (LCV1) in 15 minutes; extraction for a further 30 minutes yielded no further product. The composition of the pale yellow coloured extract obtained is shown in Table 6-14.

| Conversion | Selectivity | l : b ratio | Mean TOF |
|------------|-------------|-------------|---------------------|
| 73.7 % | 98.5 % | 26 | 63 hr ⁻¹ |

Table 6-14 - Batch reaction with extraction using scCO₂

Conditions, Pd₂dba₃ (0.05 mmol), KBPMBS (0.25 mmol), [OcMIM][NTf₂] (10 cm³), MSA (0.5 mmol), 1-octene (1 cm³), MeOH (1.28 cm³), CO (29 bar), total P (with CO₂) = 200 bar, 80 °C, 3 hours. CO₂ extraction (1 litre min⁻¹ for 15 min)

Although a slightly different experimental setup is used here, the conversions observed can approximately be compared to those discussed previously for the effect of CO₂ on the catalysis, (Section 6.7, Table 6-5) with the CO₂ pressure being higher here; the conversion observed at 60 bar CO₂ was 10.9 % under these related conditions, although the catalyst and methanol concentrations here were different also. So the effect of raising the CO₂ pressure further is shown to be significantly beneficial. Ester selectivity and l : b ratios are comparable to catalysis in methanol solvent however it is interesting that very little isomerised octene is seen. An attempt was made to recycle this catalyst mixture, but on subsequent cycles no ester was observed. The IL solution was left stirring at 80 °C overnight between cycles and it would appear that during this time the catalyst had completely degraded. On eluting the autoclave, a dark orange phase was collected which contained some palladium black deposits and although dilute; ³¹P-NMR analysis of the IL solution gave two weak signals at 63.8 and 65.1 ppm.

6.11.3 Continuous Flow Experiments with scCO₂ Extraction

Performance of the system was assessed in a continuous flow mode using a 1 : 4 molar ratio of 1-octene and methanol as above, these substrates were continuously fed into the autoclave through LP1 at a combined rate of 2.28 cm³ min⁻¹, resulting in delivery of 0.32 mmol 1-octene min⁻¹. CO flow was controlled by the dosimeter switch rate, which was calculated to maintain a 10 fold molar excess of CO flow relative to the octene feed rate. The system was maintained at 200 bar with a continuous flow rate of flue gas of 1 normal litre min⁻¹. This was stopped temporarily each hour to allow sampling from LCV1 and the dry-ice cold trap; the extracts collected had a slight yellow colouration. The data obtained from this run are summarised in Table 6-15.

| Time / hours | Conversion | Selectivity | l : b ratio | Mass balance | Pd content |
|--------------|------------|-------------|-------------|--------------|------------|
| 1 | 25.8 % | 97.6 % | 28 | 36 % | 353 ppb |
| 2 | 6.2 % | 90.2 % | 30 | 110 % | 623 ppb |
| 3 | 3.2 % | 74.4 % | 30 | 112 % | 334 ppb |
| 4 | 2.4 % | 65.3 % | 29 | 108 % | - |

Table 6-15 - Data for continuous flow catalysis using scCO₂ extraction

The initial conversion level is promising, however rapid deactivation of the catalyst is again observed. A peak in the GC at 6.7 minutes is seen to rise in the later extracts (by GC-MS this is the same peak that remains unidentified with M/Z = 129 and significant fragmentations at 115 and 87); heavier material is also observed in these later GC traces. Initial mass balance is low, although it recovers on subsequent extracts; this is likely to be due to a saturation of the IL phase, after which efficient extraction can occur - this may also be why a poorer mass balance is observed in the batch testing. Linear to branched selectivity is good throughout and leaching levels are excellent; with palladium levels in the sub ppm range observed throughout.

Leaching of MSA from the autoclave was a possible reason for the observed deactivation; MSA was not observed in the extracts by GC; however such small levels would be difficult to see. A repeat of the above experiment was performed where MSA (3 vol %) was added to the substrate mixture. This caused phase separation of the octene-methanol substrate mixture and gentle heating (ca. 35-40 °C) of this feedstock container was required to compatibilise this. The results however followed the same pattern as above, with the initial activity (21.2 % conversion) almost completely lost by the second extraction. In both cases, an orange-red IL phase was eluted from the autoclave after reaction and no palladium-black deposits were observed.

6.12 Discussion

1-Octene methoxycarbonylation has been demonstrated in 1-alkyl-3-methylimidazolium triflamide based IL solvents. When methanol levels are low the conversions are poor, although a positive effect on the conversion is observed when additional CO₂ pressure is

added to the system. This is likely to be due to an increased gas solubility of the IL phase in the presence of the CO₂. Catalyst activity is significantly increased with increasing methanol content and this is suggested to be due to a combination of less limiting mass transport of this substrate and to increased gas solubility properties of the resulting methanol / IL phase.

Two effective separation methods have been demonstrated; efficient separation has been demonstrated using petroleum as an extraction solvent, here palladium leaching levels in the sub-ppm range have been observed in the extracts. Multiple extractions are required to ensure near full removal of the organics, although this would not necessarily be a problem in a continuous reaction system. The increases in activity on increasing methanol levels are mirrored here and it is interesting that palladium leaching remains low, even in systems with high methanol levels. If the system were stable, a semi-continuous reaction system could be envisaged using this technique where a sample of the reactor contents is removed, mixed with petroleum in a settling chamber and product extraction effected by decantation, with the IL phase being returned to the reaction autoclave.

Conversions and efficient extractions have also been demonstrated using scCO₂ for product extraction; here the leaching levels of palladium in the extract are in the ppb range. However in both this separation method and the previous, catalyst stability is a major problem; with significant and rapid drops in catalyst activity observed in all cases. A speculative rationalisation for the observed instability may come from the formation of unstable imidazolium carbene complexes. Imidazolium groups are known to form carbene-type complexes with palladium and, in fact such complexes can be highly efficient catalysts for a variety of reactions such as Heck¹⁷ couplings. Such complexes however can also lead to rapid decomposition from a palladium-carbene-hydrocarbyl intermediate.¹⁸ (Figure 6-12) This can be prevented by adding bulky substituents onto the 1,3-nitrogens of the imidazolium and it was originally suggested that it may be the steric bulk that conferred this stability,¹⁹ it was later shown however, to be due to the π -electron density at these nitrogen positions.²⁰

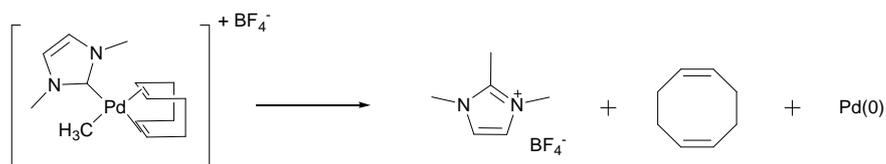


Figure 6-12 - Decomposition of palladium-carbene-hydrocarbyl intermediates

In the methoxycarbonylation hydride mechanism, the cycle goes through a palladium alkyl intermediate and the IL solvent used here does not contain such bulky substituents on the imidazolium nitrogens. A study of the decomposition rates of carbene complexes containing various phosphines has been undertaken by McGuinness *et al.*²¹ and suggests that highly bulky phosphines dramatically increase the rate of decomposition, with the decomposition of cyclohexylphosphine complexes (Figure 6-13) being too fast to measure. No correlation of decomposition rates to phosphine basicity was observed and the use of excess phosphine has no effect of this rate, however chelation appears to increase the catalyst stability with complexes of dppe being more stable than PPh₃.

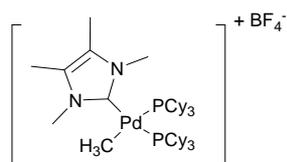


Figure 6-13 - Rapid decomposition when bulky phosphines present²¹

A problem with this idea, however, is that palladium-carbene complexes generally form under basic conditions, so as to allow deprotonation at the acidic imidazolium 2-carbon; acidic conditions are used in our reactions. It may, however, be possible that a small equilibrium to carbene is present in the reaction medium due to the large excess of imidazolium cations and, if the decomposition of this is significant, then such as that shown in Figure 6-14 could be possible.

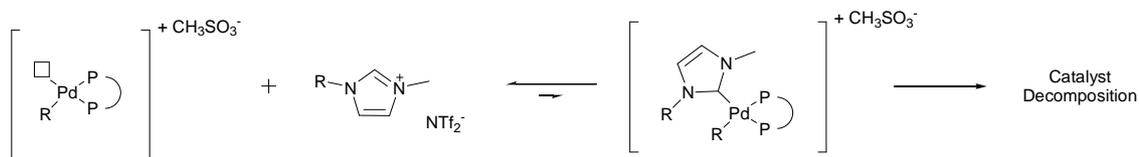


Figure 6-14 - Possible decomposition pathway *via* a carbene intermediate

In order to try and provide evidence for this decomposition mechanism, it would be interesting to see whether increased catalyst stability is observed when the C2-

imidazolium position is blocked with a methyl group. In terms of catalysis, it would also be good to investigate the use of a different family of IL solvents, where such decomposition could not be possible; an attractive suggestion would be the use of quaternary ammonium or phosphonium-type IL's, which also have the advantage of being generally less expensive than imidazolium based IL's.

Another suggestion for the observed instability, particularly for the case of the more polar IL's investigated, is that the poor stability could be attributed to the poor solubility of the complex in the IL. As these catalytic mixtures have been observed to exist as biphasic, at least at room temperature; this may result in a significantly higher concentration of the complex in the smaller organic phase than is desired. High concentrations of palladium in solution would encourage palladium clustering which would in turn lead to the formation of palladium-black. Also investigations at Lucite on the DTBPMB-ethene methoxycarbonylation system found that deactivation of the catalyst is observed when the complex is 'idle', i.e. when no substrate is present for the complex to act upon, such as when the complex is left to stand between cycles. The observed activity loss here may be due the same mechanism as this, although this does not explain the loss in activity that is observed in the continuous scCO₂ flow system.

It may also be possible that some form of oxidation is leading to the poor catalyst stability due to the numerous handling steps required for the recycling – this is unlikely however, given the consistent deactivation observed. Also the complex should be highly stable to oxygen once formed – in fact, complexes such as this have been reported for the activation of molecular oxygen to form a palladium hydroperoxide.²² The free phosphine would also be protected from oxidation by the excess of acid present, resulting in all the free species being present as protonated phosphonium salt, as is observed in ³¹P-NMR analysis of these reaction mixtures.

Whatever the reason for the observed catalyst instability, it is of course vital that this is overcome. Investigation of alternative types of IL solvents would be a good next step, as discussed. This may overcome any possible carbene-type degradation; also as the extraction methodology investigated appears to be efficient with regards to leaching, even with the less polar [OcMIM][NTf₂] / methanol mixed solvent system, it would be interesting to investigate the use of less polar IL's such as longer chain quaternary

ammonium or phosphonium type IL's. Recycling experiments using 2-methylimidazole derived IL's would also be interesting for giving evidence for any carbene-type degradation pathway.

6.13 Experimental

Preparation and characterisation data for all the IL's utilised are detailed below. In general the following applies for all halide-based IL's; if the IL was severely discoloured it was dissolved in water at room temperature and stirred with activated charcoal for 24 hours after which the solution was filtered through diatomaceous earth. Due to the highly hygroscopic nature of these IL's,²³ microanalysis was not performed. Severe discolouration of the triflamide-based IL's was not observed and so no further purification other than that described below was performed.

6.13.1 Preparation of 1-Octyl-3-methylimidazolium Bromide

[OcMIM]Br

To a solution of N-methyl imidazole (Aldrich, 28.62 g, 0.348 mol) in ethyl acetate (200 cm³) was added 1-bromooctane (Aldrich, 87.18 g, 0.451 mol) and the mixture stirred under reflux (70 °C) for 6 hours and then stirred at room temperature overnight. The upper layer was then discarded, the IL washed with further ethyl acetate (3 x 200 cm³) and then dried *in vacuo* at 50 °C for 5 hours to yield the title compound as a viscous liquid with a slight tan colouration. (89.1 g, 93 % wrt N-methylimidazole)

Characterisation

¹H-NMR: δ [ppm] = 0.26 (t, 3H, $J_{\text{HH}} = 7.0$ Hz CH₃CH₂), 0.61-0.85 (m, 10H, CH₃CH₂CH₂CH₂CH₂CH₂), 1.41 (m, 2H, NCH₂CH₂), 3.55 (s, 3H, NCH₃), 3.80 (t, 2H, $J_{\text{HH}} = 7.51$ Hz, NCH₂), 7.24 (s, 1H, CHCHNCH₃) 7.33 (s, 1H, CHCHNCH₃), 9.60 (s, 1H, NCHN); ¹³C-NMR: δ [ppm] = 13.5 (s, CH₃CH₂), 21.9, 25.6, 28.4, 28.4, 28.4, 31.1 (6 x s, 6 x CH₂), 36.1 (s, CH₃N), 49.3 (s, CH₂N), 122.0 (s, CHCHNCH₃), 123.4 (s, CHCHCH₃), 136.2 (s, NCHN). Characterisation in good agreement with literature data.²⁴

6.13.2 Preparation of 1-Pentyl-3-methylimidazolium Bromide **([PeMIM]Br)**

The procedure described above was followed using N-methylimidazole (23.47 g, 0.285 mol) and 1-bromopentane (Aldrich, 55.9 g, 0.371 mol) in place of 1-bromooctene. The title compound was obtained as a yellow liquid (59.3 g, 89 % wrt N-methylimidazole)

Characterisation

¹H-NMR: δ [ppm] = 0.70 (t, 3H, $J_{\text{HH}} = 7.3$ Hz CH_3CH_2), 1.19-1.22 (m, 4H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.70 (p, 2H, $J_{\text{HH}} = 7.3$ Hz, NCH_2CH_2), 3.89 (s, 3H, NCH_3) 4.03 (t, 2H, $J_{\text{HH}} = 7.26$ Hz, NCH_2), 7.28 (s, 1H, CHCHNCH_3) 7.33 (s, 1H, CHCHNCH_3), 9.96 (s, 1H, NCHN); **¹³C-NMR:** δ [ppm] = 15.6 (s, CH_3CH_2), 25.6, 28.1, 31.0, (3 x s, 3 x CH_2), 36.5 (s, CH_3N), 45.3 (s, CH_2N), 121.7 (s, CHCHNCH_3), 123.6 (s, CHCHCH_3), 137.1 (s, NCHN). Characterisation in good agreement to literature data.²⁴

6.13.3 Preparation of 1-Propyl-3-methylimidazolium Bromide **([PrMIM]Br)**

The procedure described above was followed using N-methylimidazole (25.9 g, 0.312 mmol) and 1-bromopropane (Aldrich, 49.9 g, 0.406 mol) in place of 1-bromooctene. The title compound was yielded as a colourless solid (58.5 g, 91 % wrt N-methylimidazole)

Characterisation

¹H-NMR: δ [ppm] = 0.70 (t, 3H, $J_{\text{HH}} = 7.2$ Hz CH_3CH_2), 1.71 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 3.87 (s, 3H, NCH_3), 4.07 (t, 2H, $J_{\text{HH}} = 7.49$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_2$), 7.44 (m, 1H, CHCHNCH_3), 7.51 (m, 1H, CHCHNCH_3), 10.01 (s, 1H, NCHN); **¹³C-NMR:** δ [ppm] = 14.5 (s, CH_3CH_2), 23.5, (s, CH_3CH_2), 35.7 (s, CH_3N), 47.0 (s, CH_2N), 121.8 (s, CHCHNCH_3), 123.2 (s, CHCHCH_3), 135.5 (s, NCHN). **MPT:** 46 - 48 °C (lit. 51.9 - 52.1 °C²⁵). Characterisation in good agreement to literature data.²⁵

6.13.4 Preparation of 1-Octyl-3-methylimidazolium

Bis(trifluoromethanesulfonyl)imide ([OcMIM][NTf₂])

To a 500 cm³ round bottomed flask containing [OcMIM][NTf₂], (88.5 g, 0.322 mol) was added a solution of lithium bis(trifluoromethanesulfonyl)amide (Acota-Spheracote (UK), 120 g, 0.344 mol) in water (200 cm³) and stirred for 24 hours. The aqueous phase was then discarded and the IL washed further with water (3 x 250 cm³) and the product dried *in vacuo* at 80°C for 5 hours to yield the title compound as a colourless to tan liquid. (134.6 g, 88 %)

Characterisation

¹H-NMR: δ [ppm] = 0.79 (t, 3H, J_{HH} = 7.1 Hz CH₃CH₂), 1.11-1.32 (m, 10H, CH₃CH₂CH₂CH₂CH₂CH₂), 1.79 (m, 2H, NCH₂CH₂), 3.85 (s, 3H, NCH₃) 4.05 (t, 2H, J_{HH} = 7.49 Hz, NCH₂), 7.29, 7.31 (2 x s, 2H, NCHCHN), 8.58 (s, 1H, NCHN); ¹³C-NMR: δ [ppm] = 13.8 (s, CH₃CH₂), 22.4, 25.9, 28.7, 28.8, 29.9, 31.5 (6 x s, 6 x CH₂), 36.0 (s, CH₃N), 49.9 (s, CH₂N), 119.6 (q, CF₃, J_{CF} = 321 Hz), 122.3 (s, CHCHNCH₃), 123.7 (s, CHCHCH₃), 135.6 (s, NCHN); ¹⁹F-NMR: δ [ppm] = -78.8 (s, CF₃). Characterisation in good agreement with literature data.³

6.13.5 Preparation of 1-Pentyl-3-methylimidazolium

Bis(trifluoromethanesulfonyl)imide ([PeMIM][NTf₂])

The procedure described above was followed using lithium bis(trifluoromethanesulfonyl)amide (Acota-Spheracote (UK), 86.0 g, 0.302 mol) and [PeMIM][Br] in place of [OcMIM][Br] (58.2 g, 0.250 mmol). The title compound was obtained as an orange liquid (85.6 g, 79 %)

Characterisation

¹H-NMR: δ [ppm] = 0.84 (t, 3H, J_{HH} = 7.0 Hz CH₃CH₂), 1.11-1.33 (m, 6H, CH₃CH₂CH₂CH₂), 1.84 (m, 2H, NCH₂CH₂), 3.90 (s, 3H, NCH₃) 4.11 (t, 2H, J_{HH} = 7.21 Hz, NCH₂), 7.29, (m, 2H, NCHCHN), 8.73 (s, 1H, NCHN); ¹³C-NMR: δ [ppm] = 13.4 (s,

CH₃CH₂), 21.8, 27.9, 28.6, (3 x s, 3 x CH₂), 36.0 (s, CH₃N), 50.0 (s, CH₂N), 119.8 (q, CF₃, J_{CF} = 319 Hz), 122.4 (s, CHCHNCH₃), 123.7 (s, CHCHCH₃), 135.6 (s, NCHN); ¹⁹F-NMR: δ [ppm] = -80.7 (s, CF₃). Characterisation in good agreement with literature data.²⁶

6.13.6 Preparation of 1-Propyl-3-methylimidazolium

Bis(trifluoromethanesulfonyl)imide ([PrMIM][NTf₂])

The procedure described above was followed using lithium bis(trifluoromethanesulfonyl)amide (Acota-Spheracote (UK), 83.7 g, 0.291 mmol) and [PrMIM][Br] in place of [OcMIM][Br] (49.0 g, 0.239 mmol). The title compound was obtained as a tan liquid (82.2 g, 85 %)

Characterisation

¹H-NMR: δ [ppm] = 0.84 (t, 3H, J_{HH} = 7.1 Hz CH₃CH₂), 1.78 (m, 2H, CH₃CH₂CH₂), 3.81 (s, 3H, NCH₃), 4.02 (t, 2H, J_{HH} = 7.15 Hz, CH₃CH₂CH₂), 7.25 (m, 1H, CHCHNCH₃), 7.28 (m, 1H, CHCHNCH₃), 8.50 (s, 1H, NCHN); ¹³C-NMR: δ [ppm] = 10.4 (s, CH₃CH₂), 23.6 (s, CH₃CH₂), 36.4 (s, CH₃N), 51.7 (s, CH₂N), 120.2 (q, CF₃, J_{CF} = 322 Hz), 122.7 (s, CHCHNCH₃), 126.5 (s, CHCHCH₃), 136.0 (s, NCHN). No literature data available for comparison.

6.13.7 Standard Procedure for Catalytic Runs

The autoclave was purged with 3 cycles of oil pump vacuum (5 minutes) / argon *via* a SwagelokTM fitted tubing connection to a Schlenk line and then purged once with carbon monoxide to the reaction pressure and closed to leak-test for at least 15 minutes.

Meanwhile, the palladium precursor and diphosphine were weighed out in a glove box into a 100 cm³ round bottomed flask fitted with a Young's tap. This was then fitted to a Schlenk line and purged with argon and then ionic liquid, methanol, 1-octene and MSA were added in that order to the mixture and mixed; occasionally sonification and / or gentle heating was required to bring all components into solution suitably for transfer.

The dark-red mixture was then transferred *via* cannula to the autoclave (at atmospheric pressure of CO) *via* the septum inlet.

The autoclave was taken to the desired gas pressure *via* two inlets (for CO and CO₂ as required) and then sealed; stirring and heating were then started *via* the external heating jacket and were monitored and controlled by the Eurotherm™ temperature control box set using its automatic calibration program. Stirring was provided by a T-bar stirrer at a spin speed of 890 RPM, by optical tachometer. Reaction timing was started when the internal temperature was within 2 °C of the setpoint.

When the reaction time was reached, heating and stirring were stopped and the heating jacket removed. The autoclave was placed into a cold-water bath, which was continuously cooled by flowing cold water through a jacket. When the internal temperature reached 20 °C (+/- 2 °C), the gas was slowly vented and the autoclave was opened under a slight overpressure of argon and sampled. In the case of the recycling experiments, the contents were removed *via* the septum attachment by cannula under a positive argon pressure into an argon flushed Schlenk flask.

For reactions performed in ionic liquid solvent, unless otherwise stated, 1 cm³ of the reaction sample was extracted with 4 cm³ of diethyl ether and allowed to partition. The organic layer was then allowed to pass through a plug of silica gel prior to GC analysis to ensure no ionic liquid entered the GC column.

Between runs, the autoclave casing and upper body were washed with acetone / DCM and the autoclave casing soaked in 69 % nitric acid overnight. The main PTFE seal to the casing was replaced between reactions. Periodic leak tests at ca. 150 bar and other seal replacements were performed as necessary.

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7. Other Immobilisation Routes Attempted

7.1 Acylation of DTBPMB

7.1.1 Direct Acylation

Early work on modifying 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) looked at acylating the molecule under standard Friedel-Crafts conditions. This would yield a suitable sol gel precursor for silica immobilisation *via* condensation with a suitably functionalised amine to form a Schiff base. This is then reduced to form an amine linked silane functionality. (Figure 7-1)

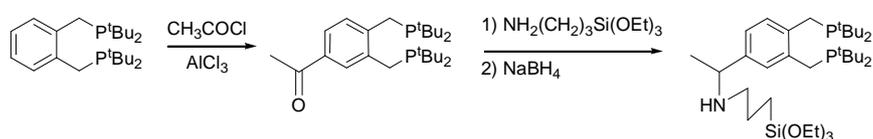


Figure 7-1 – Triethoxysilane functionalised DTBPMB *via* an amine linkage

Numerous attempts at the above acylation were undertaken using adaptations to a general method reported by Noller.¹ Here, carbon disulfide solvent was used which is considered to be a heterogeneous solvent for acylation, being able to solubilise the active $\text{AlCl}_4^- / \text{RCO}^+$ complex only poorly. The use of the reported conditions (2 equivalents acetyl chloride, 2.5 equivalents aluminium chloride, 4 hours under reflux) resulted in a large number of reaction products and numerous phosphine shifts all in the oxide region of the ^{31}P -NMR spectrum. Although these species remained unidentified, most significant was the complete loss of the CH_2P benzylic methyl bridge protons from the ^1H -NMR spectrum, suggesting a significant break-up of the DTBPMB molecule.

The reaction procedure was verified by successful acylation of bromobenzene (where primarily *para*-acylation product was identified by NMR and GC-MS and of *o*-xylene, where a mixture of isomers was also observed). Numerous variations of the procedure were attempted, including the use of acetic anhydride as substrate,² nitrobenzene,⁷ DCM,³ or excess acetyl chloride as solvent, indium chloride as catalyst,⁴ and the use of the bis(borane) adduct of DTBPMB as substrate. All these either resulted in observations similar to those described above, or to no observed reaction of DTBPMB.

Although it is not known why this has not been successful, it is noted that no literature could be located for such an acylation reaction on a phosphine functionalised molecule. It is possible that the products may arise from an attack of the acylium ion onto the phosphorus centre, such as in the reported addition of the acylium ion, ${}^{-}\text{COCH}_2\text{Br}$ to triphenylphosphine.⁵

7.1.2 Modification of Phosphine Synthesis

Another synthetic route to the desired type of compound is to build up the ligand from a functionalised xylene, such as 3,4-dimethylacetophenone or 3,4-dimethylbenzaldehyde. As this route would require the use of organolithium chemistry, protection of the carbonyl moiety is necessary and this is commonly achieved using acetals. These are stable to base, hydrogenation, bromination, esterification, Wittig, Grignard and organolithium reagents.⁶ Acetalisation of carbonyls has been reported by a variety of methods; with aldehydes being easier to protect in general than ketones, which can be attributed to their higher general reactivity.⁷

Two families of acetals can be used, acyclic and cyclic acetals. Acyclic acetals are generally harder to synthesise than their corresponding cyclic forms and less stable, however, they are commonly used when selective or mild deprotection is required as they are easier to cleave.⁶ Acetal formation is an equilibrium process and so the removal of water is essential to drive this reaction. This has been achieved both by continuous azeotropic distillation and by the use of dehydrating agents such as calcium or magnesium sulfate to adsorb the water produced.⁸ A particularly interesting method is the use of trialkyl orthoformates, which react immediately with water to produce alcohol and alkyl formate, the former being the acetylating agent.⁹ The process therefore removes water from the system itself, resulting in efficient protection of the carbonyl.

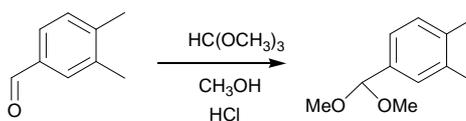


Figure 7-2 - Preparation of dimethyl acetal of 3,4-dimethylbenzaldehyde

A preparation of the dimethyl acetal of benzaldehyde using trimethyl orthoformate in acidic methanol was adapted for the preparation of protected 3,4-dimethylbenzaldehyde.¹⁰ (Figure 7-2) Using the described method, the desired acetal was isolated in 89 % yield after purification as a colourless oil.

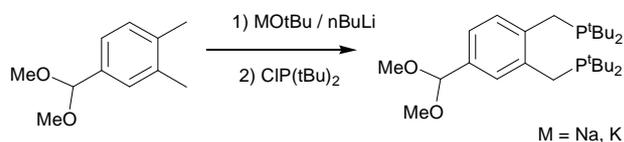


Figure 7-3 - Direct metallation of ketal protected substrate

Direct metallation of this acetal to form the desired diphosphine (Figure 7-3) was attempted based on a preparation detailed by Lucite,¹¹ with metallation using both sodium and potassium *tert*-butoxide attempted. Dimetallation in both cases was achieved using 3 equivalents of the corresponding metal *tert*-butoxide and *n*-butyllithium. In the case of less reactive sodium butoxide, TMEDA was also added. This salt was then washed and addition of 2.2 equivalents of ClP^tBu₂ to obtain the product. The use of the sodium *tert*-butoxide led to a poor yield by mass (ca. 15 %) after the washing stage of the preparation. When this highly pyrophoric dimetal salt (as an oily solid) is washed with pentane, the wash solvent was significantly more coloured than is observed for the dipotassium salt, suggesting either a higher solubility of the disodium salt in the pentane or a lower conversion of the starting material to this salt.

Quenching of the dipotassium salt with ClP^tBu₂ followed by extraction and drying yielded a sticky orange solid after removal of the solvents. This was insoluble in methanol, although washing twice with methanol yielded a friable orange solid. The washings contained primarily unreacted chlorophosphine. NMR spectra of the solid (CDCl₃) were poorly resolved, although a major broad resonance in the ³¹P-NMR spectrum occurs around 28.4 ppm, not too dissimilar to that of DTBPMB. Numerous attempts to isolate pure material from this solid by chromatography and / or crystallisation were unsuccessful, eventually resulting in oxidation of the samples.

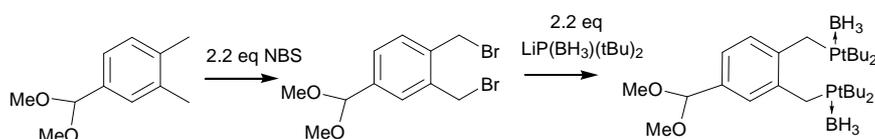


Figure 7-4 - Intended synthesis via methylene bromination

NBS Bromination of this acetal was also attempted to allow reaction with $\text{LiP}^t\text{Bu}_2(\text{BH}_3)$, however the desired product was not obtained. The use of 2.2 equivalents of N-bromosuccinimide (NBS) resulted in complete substitution of the benzylic hydrogen of the acetal for bromine (by $^1\text{H-NMR}$) and only partial substitution of the remaining benzyl positions (Figure 7-5), demonstrating that the acetal site is activated towards radical bromination in this molecule. The reaction products were not isolated from the resulting crude oil and so it is not known whether the bromination was selective towards either methyl position.

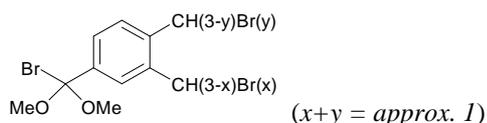
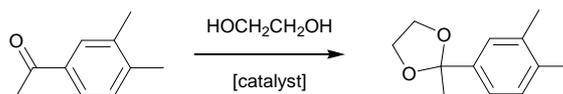


Figure 7-5 - NBS bromination of 4-(dimethoxymethyl)-1,2-dimethylbenzene

One solution to this problem would be to remove the active acetal hydrogen by using the methylketone derivative of the molecule. No literature examples of ketal-protected 3,4-dimethylacetophenone were located but several examples exist for 4-methylacetophenone. The protection of ketones such as acetophenone has been highlighted as being difficult by Shaterian,¹⁴ who reports that the acetalisation of cyclohexanone is significantly more efficient than with the aromatic equivalent, acetophenone.

For this reason, the synthesis of the generally more attainable cyclic ketal was attempted based on a literature preparation from *p*-methyl acetophenone.¹² Here, 1,2-ethanediol (ethylene glycol) and a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) in toluene were used, with continuous azeotropic distillation of the solution using a Dean-Stark apparatus. At reaction times of up to 48 hours, conversions to the ketal remained low (< 20 %) in the resulting oil. Changing from mineral acid to the Lewis acidic AlCl_3 ,¹³ improved yields using an otherwise identical method, with a 52 % isolated yield obtained after several reduced pressure distillations. Most efficient was the use 2,4,4,6-Tetrabromo-2,5-cyclohexadienone (TABCO), which has recently been reported as an efficient acetalization agent. This gave near quantitative conversions to the acetal,¹⁴ by adapting the reported procedure. Subsequent purification of the crude oil resulted in isolated yield 88 % of the desired cyclic acetal, as is summarised in Figure 7-6.



| Catalyst | Yield |
|------------------------|-------------------|
| p-toluenesulfonic acid | ca. 40 % in crude |
| AlCl ₃ | 52 % isolated |
| TABCO | 88 % isolated |

Figure 7-6 - Protection of 3,4-dimethylacetophenone

Metallation of this product was attempted using the method detailed previously,¹¹ with potassium *tert*-butoxide reagent, followed by reaction with CIP^tBu₂. This led to similar results to those observed when the di(methoxy)acetal substrate was used, yielding a friable orange solid which was insoluble in methanol. Again, NMR spectra for this material were poor although the ³¹P-NMR spectrum shows several broad overlapping signals around 30 ppm. Bromination of this acetal with 2.2 equivalents of NBS resulted in a dark, viscous oil which contained a large number of peaks in the expected 4-5 ppm region of the ¹H-NMR spectrum. When allowed to stand, or on attempted purification, decomposition to an insoluble black solid appeared to occur. A sample of this acetal has been sent to Lucite for further investigation, although similar results appear to have been obtained so far.¹⁵

7.2 Bromination of DTBPMB

7.2.1 Direct Bromination

On obtaining a ring-halogen functionalised derivative of DTBPMB, a triethoxysilane functionalised derivative could be envisioned by subsequent Suzuki coupling with an aldehyde-functionalised boronic acid such as the commercially available 4-formylphenyl boronic acid. The carbonyl functionality could then undergo a Schiff-base type condensation with a silane-functionalised amine as shown in Figure 7-7.

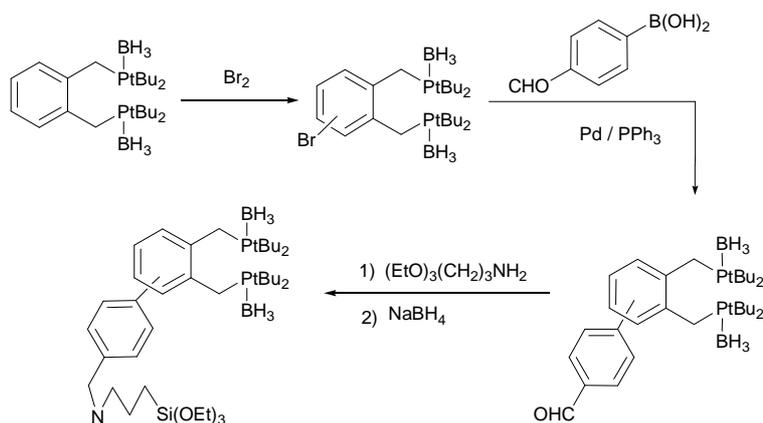


Figure 7-7 - Synthesis of a bromo-functionalised DTBPMB based sol-gel precursor

DTBPMB.(BH₃)₂ was used as substrate with the intention that the borane groups would prevent bromine attack at the phosphorus sites. Other than a change of solvent from carbon tetrachloride to 1,2-dichloroethane, a reported method for ring bromination was used.¹⁶ An 88 % yield of mixed (*ortho* and *meta*) brominated products from *o*-xylene were reported. Dried silica gel is present to shift the equilibrium towards the brominated product. The silica gel is thought to remove the hydrobromic acid byproduct without the formation of water or a solid salt and so disfavours the formation of alkyl brominated products. This preparation was selected as the borane protecting groups are known to be susceptible to attack by acid.¹⁷

The procedure was initially performed with a stoichiometric loading of bromine to diphosphine; which equates to a 1 : 2 ratio of Br⁺ to phosphorus. ³¹P-NMR analysis of the resulting solid showed two new phosphorus signals at 12 and 80 ppm, with the specific phosphorus environment relating to these signals not identified. The aromatic protons of the product show no difference by ¹H-NMR compared to DTBPMB, suggesting that ring bromination had occurred. To investigate further, this reaction was repeated with variations in the Br to P ratio and the ³¹P-NMR analysis for this is summarised in Table 7-1.

| Entry | Br : P ratio | ³¹ P NMR peak integrals [#] / ppm (assignment) | | | | |
|-------|--------------|--|----------------|---------------------------------|-------------|-----------------|
| | | 12 (unknown) | 28 (Free P) | 51 <i>P</i> →BH ₃ | 62 (P=O) | 80 (unknown) |
| a | 1 : 4 | 1 % | 29 % | 69 % | 1 % | - |
| b | 1 : 2 | 4 % | 49 % | 47 % | - | - |
| c | 1 : 1 | 33 % | 44 % | 2 % | 1 % | 20 % |
| d | 2 : 1 | 42 % | - | - | 1 % | 57 % |
| e | 4 : 1 | - | - | - | 65 % | 35 % |

Table 7-1 - Summary of product phosphorous environments with variation of P : Br ratio

[#] Normalised to 100 %

It is apparent that bromine is affecting the phosphorus environment, resulting in the formation of new species. It is possible that the bromide forms phosphonium salts with the substrate and these may be susceptible to hydrolysis to form phosphine oxide. GC-MS analysis of the brominated products did produce additional peaks in the GC trace compared with that for unreacted diphosphine; the corresponding mass spectra for these peaks however did not contain the characteristic 2-mass-difference unit splittings expected for the bromine isotopes.

7.3 New Synthetic Tools

7.3.1 Protection via Phosphorus (V) Adducts

The highly Lewis basic trialkylphosphine moieties of DTBPMB are electronically well set up for oxidation and subsequently, their corresponding phosphine oxides are highly resistant to reduction. The phosphine groups of the BDTBPMB molecule appear to undergo attack during the acylation and bromination functionalisation attempts detailed previously. This may be prevented if the reactivity of the phosphorus lone-pair is suppressed *via* a protecting group. As borane protection has been shown to be inadequate for this, another possibility is the oxidation of the phosphine moieties using oxygen or sulfur. A major concern with this strategy is the difficulty of reducing these highly electron-rich phosphorus (V) adducts in a deprotection step.

Reversible sulfur protection of an electron rich phosphine has been reported by Tang and co workers,¹⁸ who utilised sulfur protection in the synthesis of the chiral diphosphine, (1*S*,1*S'*,2*R*,2*R'*)-1,1'-di-*tert*-butyl-[2,2']-diphospholanyl (Figure 7-8); the deprotection here being achieved using strongly reducing hexachlorodisilane reagent.

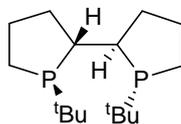


Figure 7-8 - (1*S*,1*S'*,2*R*,2*R'*)-1,1'-di-*tert*-butyl-[2,2']-diphospholanyl

Successful reductions of highly electron rich phosphine oxides have also been reported in the recent literature. Busacca *et al.*¹⁹ have shown that diisobutylaluminium hydride (DIBAL-H) can be used to reduce a large range of secondary phosphine oxides, many at cryogenic temperatures and even the highly electron rich and sterically hindered di(*tert*-butyl)phosphine oxide was successfully reduced in 87 % yield at 50 °C for 4 hours.

The use of these powerful reducing agents for reducing P(V) derivatives of DTBPMB was investigated as this would create a useful methodology for protecting highly electron rich phosphines such as this. Synthesis of the diphosphine sulfide and oxides of DTBPMB and their subsequent deprotections was therefore attempted. The electron rich phosphorus sites of DTBPMB mean oxidation and sulfurisation should occur readily in the presence of these elements and as such, efficient preparations of these compounds were developed. The sulfur adduct was readily synthesised by exposing DTBPMB to a sulfur saturated solution of carbon disulfide at room temperature. This resulted in rapid formation of the disulfide as indicated by ³¹P-NMR spectroscopy. This product was crystallised from methanol and characterised, showing a characteristic sharp signal in the ³¹P-NMR spectrum at 79.9 ppm.

As an aside, the lability of the borane group of the borane adduct of DTBPMB was investigated by exposing this to a sulfur saturated carbon disulfide solution in the same manner. In this case, no phosphine sulfide was observed in the reaction mixture after mixing at room temperature for 30 minutes. Gentle heating of the carbon disulfide solution to reflux for 5 hours resulted in a small signal being observed for the phosphine sulfide by ³¹P-NMR, (2 % by integral area). This suggests that the borane adduct is

labile in solution to an extent; although this equilibrium appears to lie far towards the borane adduct (Figure 7-9). The oxide of DTBPMB was readily formed by gently bubbling oxygen gas through a THF solution of DTBPMB for 60 minutes. This resulted in complete oxidation of diphosphine by ^{31}P -NMR spectroscopy.

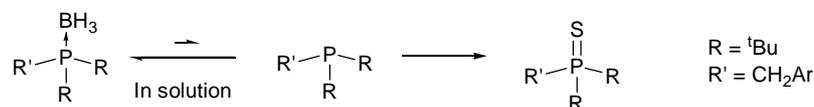


Figure 7-9 - Phosphine-borane equilibrium in solution

Reduction of the oxide and sulfide was attempted in an effort to prove the concept of using such a route to protect the diphosphine. In both cases deprotection was attempted using hexachlorodisilane and DIBAL-H using methods based initially on those reported for the cases discussed above. A summary of the results obtained is given in Table 7-2.

| Substrate | Reducing agent | Excess of reductant | Other conditions | Observations* |
|-----------|---------------------------------|---------------------|------------------------|------------------|
| Sulfide | DIBAL-H | 5 | 4 hr reflux (THF) | No conversion |
| Sulfide | DIBAL-H | 50 | 12 hr reflux (THF) | No conversion |
| Oxide | DIBAL-H | 5 | 4 hr reflux (THF) | No conversion |
| Oxide | DIBAL-H | 50 | 12 hr reflux (THF) | No conversion |
| Sulfide | Si ₂ Cl ₆ | 17 | 4 hr reflux (toluene) | > 98 % reduction |
| Oxide | Si ₂ Cl ₆ | 17 | 4 hr reflux (toluene) | No conversion |
| Oxide | Si ₂ Cl ₆ | 34 | 12 hr reflux (toluene) | No conversion |

Table 7-2 - Summary of attempts to reduce sulfide and oxide of DTBPMB

* ^{31}P -NMR observation of the resulting reaction mixture

DIBAL-H was ineffective at reducing both the oxide and sulfide adducts, even when much more forceful conditions were used than those reported for di(*tert*-butyl)phosphine oxide reduction. Hexachlorodisilane was also ineffective at reducing the oxide, even when more forceful conditions than those reported were employed. It was however, highly effective at reducing the sulfur adduct; with over 98 % free phosphine observed in the resulting reaction mixture. The remaining phosphorus integral consisting of two signals, one being unconverted phosphine sulfide and two

small environments at 32 and 69 ppm, which could tentatively be assigned to the phosphorus environments for a singly-reduced diphosphine species.

Subsequent hydrolysis and aqueous removal of the silane allowed isolation of free DTBPMB as crystals from methanol in 58 % yield. This was analytically identical to authentic DTBPMB provided by Lucite. Given the high conversion observed in the reaction solution, it is likely that this isolated yield could be significantly improved on modest scale up of the reaction. This methodology can therefore be used for reversible sulfur protection of the DTBPMB molecule, as is summarised in Figure 7-10.

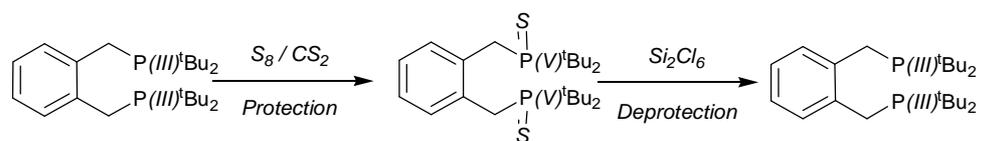
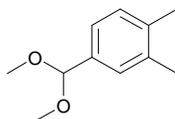


Figure 7-10 - Sulfur protection and deprotection of DTBPMB

Although the phosphine oxide has not been successfully reduced here, another possible method for achieving this could involve the use of a methylating reagent, such as methyl triflamide in conjunction with lithium aluminium hydride; as has been reported by Imanoto *et al.*²⁰ Here electron rich phosphine oxides including tri(cyclohexyl)phosphine and tri(*n*-butyl)phosphine are reduced under mild conditions.

7.4 Experimental

7.4.1 Synthesis of 4-(dimethoxymethyl)-1,2-dimethylbenzene



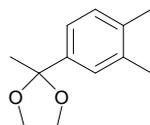
To a 250 cm³ round bottomed flask was added 3,4-dimethylbenzaldehyde (Alfa, 25 g), trimethyl orthoformate (Alfa, 50 g, 47.1 mmol) and a catalytic amount of *p*-toluenesulfonic acid in methanol (5 cm³). The mixture was stirred at reflux for 6 hours over which time it took on a slight orange colouration.

The mixture was cooled and treated with aqueous sodium hydrogen carbonate solution, then extracted with diethyl ether (3 x 100 cm³). The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo*. The crude oil was then purified by reduced pressure distillation to yield the title compound as a clear colourless oil (29.9 g, 89 %)

Characterisation

¹H-NMR: δ [ppm] = 2.30 (s, 6H, 2 x CH₃), 3.35 (s, 6H, OCH₃)₂, 5.39 (s, 1H, OCH), 7.20 (m, 3H, Ar. H); **¹³C-NMR:** δ [ppm] = 19.53 (s, *meta* CH₃), 19.8 (s, *para* CH₃), 52.7 (s, (O-CH₃)₂), 103.4 (s, O-CH-Ar), 124.2, 127.8, 129.5, 135.6, 136.4, 136.8 (6 x s, aromatic CH); **Microanalysis:** Requires C = 73.30 %, H = 8.95 %; Found C = 73.59 %, H = 9.29 %. **BPT:** 62 – 64 °C (0.025 mm Hg). ¹H-NMR literature data available and in good agreement.²¹

7.4.2 Synthesis of 2-(3,4-dimethylphenyl)-2-methyl-1,3-dioxolane

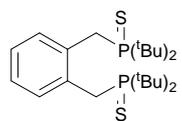


To a 250 cm³ round bottomed flask fitted with a reflux condenser, drying tube and magnetic follower was added 3,4-dimethylacetophenone (Alfa Aesar, 40.26 g, 0.272 mol) ethylene glycol (Aldrich, 33.67 g, 0.543 mol), trimethyl orthoformate (Alfa Aesar, 120.7 g, 0.815 mol) 2,4,4,6-tetrabromo-2,5-cyclohexadienone (Alfa Aesar, 25 g, 61.0 mmol) and dry ethanol (100 cm³). The solution was heated to 55 °C for 48 hours. The mixture was allowed to cool, and neutralised with aqueous sodium hydroxide solution. (10 wt %) The organic phase was separated and the aqueous phase further extracted with diethyl ether (3 x 100 cm³). The combined organic layers were then washed with water, (2 x 100 cm³) dried over magnesium sulfate and the solvent removed *in vacuo*. The crude oil was then purified by reduced pressure distillation to yield the title compound in a second fraction (after ethylene glycol) as a clear colourless oil (45.72 g, 88 %)

Characterisation

¹H-NMR: δ [ppm] = 1.44 (s, 3H, C(OCH₂CH₂O)CH₃), 2.05 (s, 3H, CCH₃), 2.09 (s, 3H, CCH₃) 3.69 (d of m, 4H, OCH₂CH₂O), 6.99 – 7.58 (m, 3H, Ar. H); **¹³C-NMR:** δ [ppm] = 19.9 (s, *meta* CH₃), 20.3 (s, *para* CH₃), 28.17 (s, C(OCH₂CH₂O)CH₃), 64.8 (s, (OCH₂CH₂O), 109.3 (s, C(OCH₂CH₂O)), 123.1, 127.0, 129.9, 136.5, 136.8, 141.2 (6 x s, aromatic CH); **Microanalysis:** Requires C = 74.97 %, H = 8.39 %; Found; C = 73.82 %, H = 8.47 %. **BPT:** 82 – 88 °C (at 0.2 mm Hg). No literature data available for comparison.

7.4.3 Preparation of 1,2-bis((di-*tert*-butylphosphorothioyl)methyl)benzene

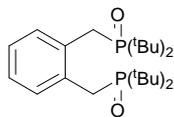


With the exclusion of air and moisture, sulfur-saturated, dry and degassed carbon disulfide (20 cm³) was added to DTBPMB (0.875 g, 2.19 mmol) in toluene (20 cm³) and stirred for 5 minutes after which ³¹P-NMR analysis showed complete conversion of the free phosphine. The solvent was removed *in vacuo* and the crude product (now treated as air-stable) was extracted from the mixture with acetone and filtered (3 x 30 cm³). The acetone was removed *in vacuo* and the resulting crude solid recrystallised from acetonitrile to yield the title compound as colourless needles. (0.785 g, 78 %)

Characterisation

¹H-NMR: δ [ppm] = 1.14 (d, 36H, $J_{\text{PH}} = 11.4$ Hz, $\text{P}(\text{C}(\text{CH}_3)_2)_2$), 3.03 (d, 4H, $J_{\text{PH}} = 3$ Hz, CH_2P), 7.06 (m, 2H, aromatic AA'BB' system), 7.53 (m, 2H, aromatic AA'BB' system); ¹³C-NMR: δ [ppm] = 26.3 (d, $J = 29$ Hz, $\text{PC}(\text{CH}_3)_2$), 26.6 (d, $J = 13$ Hz, $\text{PC}(\text{CH}_3)_2$), 29.9 (d, $J = 22$ Hz, CH_2P), 125.2 (d, $J = 1.3$ Hz, $\text{CHCHCCH}_2\text{P}$), 130.9 (d, $J = 15$ Hz, $\text{CHCHCCH}_2\text{P}$), 138.8 (d, $J = 9.7$ Hz, $\text{CHCHCCH}_2\text{P}$); ³¹P-NMR: δ [ppm] = 79.9 (s). **Microanalysis:** Requires C = 62.84 %, H = 9.67 %, S = 13.98 %, Found C = 62.46 %, H = 10.08 %, S = 13.29 %. **Mpt** = 209 - 210 °C. No literature data available for comparison.

7.4.4 Preparation of 1,2-bis((di-*tert*-butylphosphinoyl)methyl)benzene

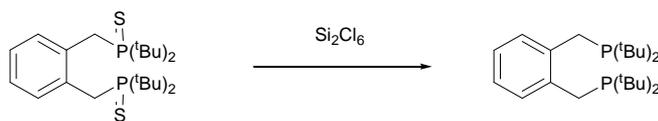


A 100cm³ round bottomed flask was charged with DTBPMB (0.500 g, 1.27 mmol) in THF (40 cm³) and a gentle stream of oxygen was bubbled through the solvent for 1 hour after which ³¹P-NMR analysis showed complete oxidation of the phosphine. The solvent was removed *in vacuo* to yield the title compound as a colourless solid. (0.411 g, 76 %)

Characterisation

¹H-NMR: δ [ppm] = 1.18 (d, 36H, $J_{\text{PH}} = 13.5$ Hz, $\text{P}(\text{C}(\text{CH}_3)_2)_2$), 3.65 (d, 4H, $J_{\text{PH}} = 11.8$ Hz, CH_2P), 7.48 (m, 4H, aromatic AA'BB' system), 7.53 (m, 2H, aromatic AA'BB' system); ¹³C-NMR: δ [ppm] = 26.4 (d, $J = 29$ Hz, $\text{PC}(\text{CH}_3)_2_2$), 26.6 (d, $J = 13$ Hz, $\text{PC}(\text{CH}_3)_2_2$), 30.1 (d, $J = 22$ Hz, CH_2P), 125.2 (d, $J = 1.5$ Hz, $\text{CHCHCCH}_2\text{P}$), 130.9 (d, $J = 15$ Hz, $\text{CHCHCCH}_2\text{P}$), 138.8 (d, $J = 10.2$ Hz, $\text{CHCHCCH}_2\text{P}$); ³¹P-NMR: δ [ppm] = 64.26 (s). No literature data available for comparison.

7.4.5 Reduction of 1,2-bis((di-*tert*-butoxyphosphorothioyl)methyl)benzene



With the exclusion of air and moisture, to a 100 cm³ round bottomed flask containing 1,2-bis((di-*tert*-butylphosphorothioyl)methyl)benzene (0.25 g, 0.55 mmol) in dry and deoxygenated toluene (15 cm³) was added hexachlorodisilane (Aldrich, 2.5 g, 9.3 mmol) drop wise *via* cannula. The colourless solution was heated under reflux for 4 hours then allowed to cool. Proton decoupled ³¹P-NMR (CDCl_3) analysis of the reaction mixture shows a single sharp doublet at 26.4 ($J_{\text{PH}} = 12$ Hz).

With cooling *via* an ice-water bath, sodium hydroxide solution (30 % w/v, 25 ml) was slowly added to the solution. The mixture was then heated to 60 °C until all the precipitate had dissolved (ca. 1 hour) and cooled. The organic phase was separated and the aqueous phase further extracted with deoxygenated toluene. (3 x 25 cm³). The combined organic phases were washed with water (50 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* to yield a crude yellow solid. This was crystallised from methanol (-20 °C, overnight) to yield the title compound as colourless crystals (0.126 g, 58 %).

Characterisation

¹H-NMR: δ [ppm] = 1.14 (**d**, 36H, $J_{\text{PH}} = 11.4$ Hz, $\text{P}(\text{C}(\text{CH}_3)_2)_2$), 3.03 (**d**, 4H, $J_{\text{PH}} = 3$ Hz, CH_2P), 7.06 (**m**, 2H, aromatic AA'BB' system), 7.53 (**m**, 2H, aromatic AA'BB' system); **¹³C-NMR:** δ [ppm] = 26.3 (**d**, $J = 29$ Hz, $\text{PC}(\text{CH}_3)_2$), 26.6 (**d**, $J = 13$ Hz, $\text{PC}(\text{CH}_3)_2$), 29.9 (**d**, $J = 22$ Hz, CH_2P), 125.2 (**d**, $J = 1.3$ Hz, $\text{CHCHCCH}_2\text{P}$), 130.9 (**d**, $J = 15$ Hz, $\text{CHCHCCH}_2\text{P}$), 138.8 (**d**, $J = 9.7$ Hz, $\text{CHCHCCH}_2\text{P}$); **³¹P-NMR,** δ [ppm] = 28.4 (**s**). Analytically identical to authentic DTBPMB (Lucite).

7.5 Notes and References

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8. Bulky Derivatives of DTBPMB

8.1 Introduction

A perfect catalyst would have complete selectivity to a desired product at a high rate of conversion under mild conditions; it would be trivial to separate from the products and be stable indefinitely. This ideal is of course not attainable, although improving any of these important parameters increases the economic viability of a catalyst system. In this chapter, an attempt to improve the last of these parameters is discussed. As well as by physical loss of a catalyst, as has been discussed in detail previously; catalyst activity is also reduced both by chemical and thermal decomposition.¹

Chemical decomposition can occur, for example, by poisoning from minor feedstock impurities; this is generally considered to affect homogeneous catalysts more than heterogeneous ones. This can be significantly reduced in some cases; for example many polymerisation catalysts, such as Zr-based Ziegler-Natta type catalysts are used in the presence of a large excess of oligomeric methylaluminoxane. This is thought to remove minor peroxide impurities from the alkene feedstock that are thought to poison these catalysts.² Thermal degradation of catalysts also occurs. For example in ethylene methoxycarbonylation using palladium-triphenylphosphine complexes, temperatures in excess of 100 °C are desirable in order to obtain an acceptable catalyst TOF. At this temperature, however, side reactions occur that led to the formation of inactive quaternary phosphonium salts.³

It has been proposed that increasing the steric bulk of the backbone of the 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) ligand may result in a more stable catalyst system. This idea is based on observations at Lucite that palladium complexes of 1,2-bis(di-*tert*-butylphosphino-methyl)-4-*tert*-butylbenzene and 1,2-bis(di-*tert*-butylphosphinomethyl)ferrocene, the synthesis of which is described by Butler *et al.*,⁴ (Figure 8-1) show better catalytic activity (TOF) in ethene methoxycarbonylation than palladium complexes of DTBPMB after each catalyst had been artificially aged at elevated temperatures.⁴ This would suggest that these ligands produce more stable catalyst systems, being able to give higher catalyst TON's than the DTBPMB-palladium system.



Figure 8-1 - 1,2-bis(di-*tert*-butylphosphino-methyl)-4-*tert*-butylbenzene (left) and 1,2-bis(di-*tert*-butylphosphinomethyl)ferrocene (right)

In order further to test this theory, synthetic routes to other bulky phosphines based on DTBPMB were developed with the aim of allowing the stability of these ligands to be assessed.

8.2 Synthetic Strategies

8.2.1 Synthesis of 3,3',4,4'-tetrakis(di-*tert*-butylphosphinomethyl)biphenyl (TBPBP)

Initially, the synthesis of the tetraphosphine ligand, 3,3',4,4'-tetrakis(di-*tert*-butylphosphinomethyl)-biphenyl (TBPBP) was considered, shown in Figure 8-2, below. This ligand has the desired bulky backbone as well as having the interesting property of containing two potential active sites.

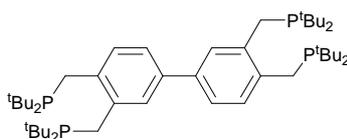


Figure 8-2 - 3,3',4,4'-tetrakis(di-*tert*-butylphosphinomethyl)biphenyl

Two synthetic routes to this molecule were considered, with 3,3',4,4'-tetramethylbiphenyl, as a logical key intermediate. Subsequent tetrabromination or direct metallation of the four benzyl positions of this molecule would be an ideal reactive species for coupling with $\text{LiP}(\text{BH}_3)^t\text{Bu}_2$ or ClP^tBu_2 respectively, as shown in Figure 8-3.

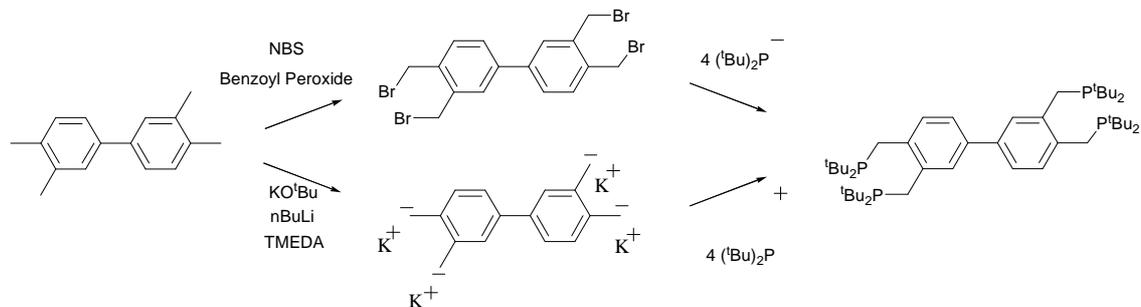


Figure 8-3 - Proposed routes from 3,3',4,4'-tetramethylbiphenyl to TBPBP

8.2.1.1 Synthesis of 3,3',4,4'-tetramethylbiphenyl

Although there is a commercial source for this biphenyl, it is prohibitively expensive and so its synthesis was investigated. Nagano *et al.* have recently reported a simple and efficient method for homocoupling Grignard reagents using iron(III) chloride as catalyst.⁵

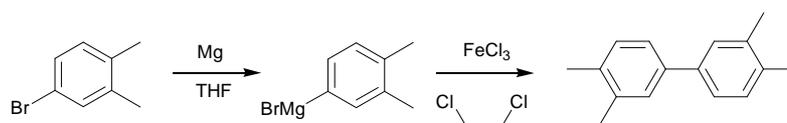


Figure 8-4 - Iron catalysed homocoupling from 3,4-dimethylbromobenzene

This methodology is ideal due to its simplicity and efficiency. The proposed mechanism for this conversion (Figure 8-5) involves the oxidative addition of 1,2-dichloroethane to a low-valent iron species (generated from reaction of FeCl_3 with Grignard) to form **B**. Subsequent β -chloride elimination gives a dihalo-iron species, **C**, which is able to undergo transmetalation with a Grignard to form a diaryliron species, **D**. This can induce reductive elimination to give the biphenyl and regenerate the catalytically active species, **A**.

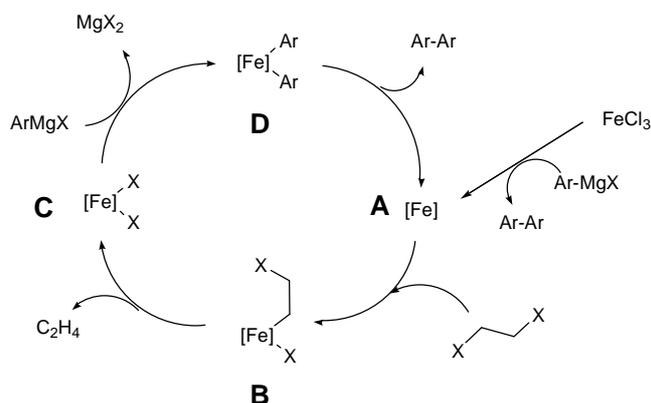


Figure 8-5 - Proposed mechanism for iron-catalysed homocoupling⁵

Yields are high for this reaction, with 100 % isolated yield reported from 4-bromotoluene; yields are reduced when deactivating groups, or groups *ortho* to the bromide are used. Although reaction with 3,4-dimethylbromobenzene substrate is not reported, it would be expected to give a high conversion, given the lack of functionality close to the bromo group. No detail on Grignard formation was given and so a literature method was followed to obtain this from 4-bromo-*o*-xylene.⁶ Aryl Grignards do not form readily and so fresh acid-washed magnesium turnings and a trace of iodine were required to initiate this formation.

Following the reported method⁵ gave a yellow oil, of which GC-MS analysis showed almost complete conversion to the biphenyl. Purification by crystallisation or short-pass distillation was not successful but the product was isolated by chromatography, as was often necessary in the literature method.⁵ High resolution TOF-MS showed good correlation to that of the expected product.

8.2.1.2 Phosphine Synthesis *via* Benzylic Bromination

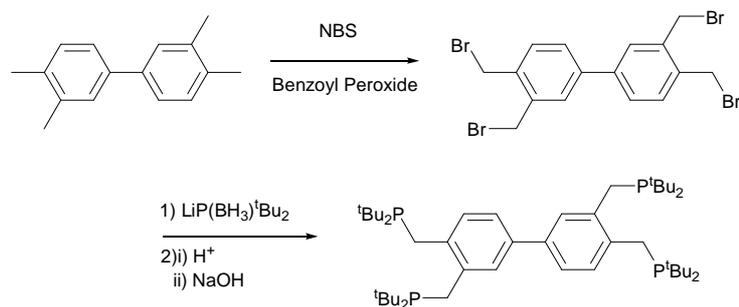


Figure 8-6 - Proposed synthesis *via* a tetra(bromomethyl) substrate

Synthesis of a tetra(bromomethyl) derivative of the synthesised biphenyl was attempted to allow phosphination using $\text{LiP}(^t\text{Bu})_2$. (Figure 8-6) Although bromination was successful using NBS / benzoyl peroxide in 1,2-dichloroethane⁷ and the product is well characterised, it was isolated in a poor 10 % yield, resulting in less than 100 micromoles of the desired product. This route was therefore abandoned in preference to direct metallation of the biphenyl substrate.

8.2.1.3 Phosphine Synthesis *via* Direct Metallation

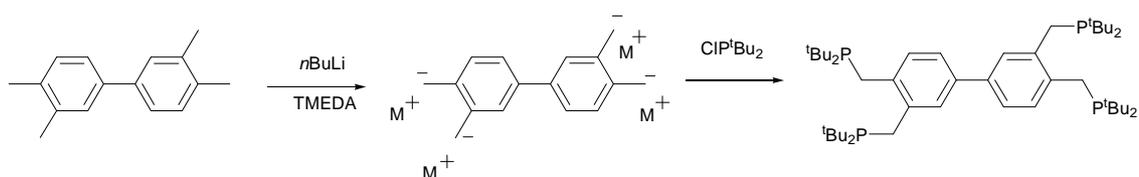


Figure 8-7 - Phosphine synthesis *via* direct metallation

Direct phosphination of the biphenyl *via* tetrametallation was based on the general conditions filed by Lucite⁸ using potassium *tert*-butoxide, *n*-butyllithium and TMEDA , which was heated for 4 hours in hexanes to give a sticky precipitate. This was subsequently quenched with 4.4 equivalents of ClP^tBu_2 and after work up, gave a yellow oil. From the integrals for the expected CH_2P signals in the ^1H -NMR (doublet at 3.05 ppm) and the large amount of ClP^tBu_2 present in the ^{31}P -NMR spectrum,⁹

conversion was deemed to be very poor, (ca. 15 %^{†††}) with a large number of components present. Removal of the potassium *tert*-butoxide to form the lithium salt intermediate in the reaction resulted in marginally better yields in the resulting oil, although still poor.

The poor conversions may be due to low solubility of the metallated biphenyl intermediates in the reaction solvent and so making subsequent metallation difficult; reaction in DMF solvent was therefore investigated. Yields in the crude product were better here (51 %), although work up yielded a viscous orange oil containing several components, attack of the organolithium reagent onto the carbonyl of the DMF solvent is a possible side reaction. Purer material was obtained by heating this oil under reduced pressure in the presence of an acetone / dry ice cold finger, as has been reported before in phosphine purification.¹⁰ This resulted in the removal of the bulk of the unreacted ClP^tBu_2 (as liquid, identified by ^{31}P -NMR) followed by sublimation of unconverted biphenyl at 120 °C (as a colourless solid, identification by NMR). On cooling, a sticky orange solid was obtained which contained *ca.* 68 % expected product by ^1H -NMR. Attempted recrystallisation of this resulted in the formation of phosphine oxide. A repeat of this procedure also resulted in phosphine oxide formation on attempted chromatography of the crude material.

Baran and Laqow¹¹ have reported a general synthesis of multiply lithiated organic compounds using *tert*-butyllithium in THF solvent. This is performed at low (< -100 °C) temperatures in order to minimise reactions between the solvent and the organolithium compound and up to three lithiations upon the same carbon atom were demonstrated, although lithiation *via* halogen-lithium exchange rather than hydrogen-lithium exchange was used. Preparation based on this procedure was investigated with a slightly higher reaction temperature of -78 °C and a longer reaction time (90 minutes). The resulting deep-red solution was quenched with 4.4 equivalents of ClP^tBu_2 at -78 °C and worked up, the crude oil had only a trace CH_2P signal and so it appears that these conditions are still too mild to effect the desired lithium-hydrogen exchange required here.

^{†††} Estimated from the integral ratios of the doublet at 3.05 ppm (CH_2P) to the total aromatic integral.

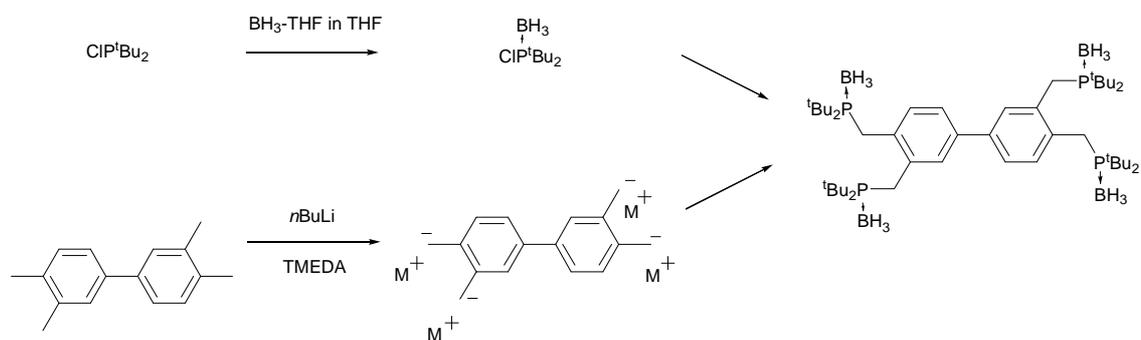


Figure 8-8 – TBPBP formation using di-*tert*-butylphosphine-borane

The formation of the chlorophosphine-borane adduct was successful using $\text{BH}_3\text{-THF}$ complex and its use in the formation of TBPBP was attempted in DMF solvent. (Figure 8-8) Phosphination of the biphenyl was observed by $^1\text{H-NMR}$, although the oil obtained showed no improvement in yield compared to the use of free phosphine. This does however demonstrate an alternative route for such phosphinations. Interestingly, filtering of this crude material through a silica plug followed by attempted crystallisation from DCM / methanol (not under nitrogen) resulted in the formation of phosphine oxide. Prior to this treatment, the crude oil expressed the expected phosphine-borane signals by $^{31}\text{P-NMR}$ and so it seems that treatment over silica has resulted in deboronation of the phosphines here. Isolation of the desired biphenylphosphine or phosphine-borane has therefore not been successful.

8.2.2 Synthesis of 1,2,4,5-tetrakis(di-*tert*-butylphosphinomethyl)benzene (TKPMB)

The commercial availability of 1,2,4,5-tetra(bromomethyl)benzene led to a proposed synthesis of a tetraphosphine derivative of DTBPMB. This follows the general methodologies discussed previously as is illustrated in Figure 8-9.

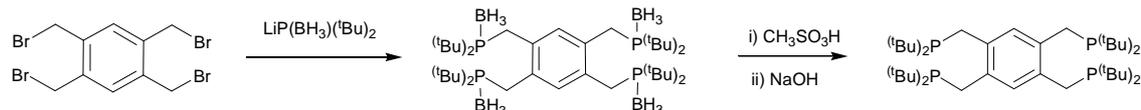


Figure 8-9 - Proposed synthesis of 1,2,4,5-tetrakis(di-*tert*-butylphosphinomethyl)benzene

Initial attempts at the phosphination using diethyl ether as solvent failed, probably due to the poor solubility of the tetrabromo substrate in this solvent. The reaction was however successful using DMF solvent, in which the tetrabromo substrate was fully soluble. When a 4.5 molar excess of $\text{LiP}(\text{tBu})_2(\text{BH}_3)$ was used (Prepared *in situ*, as in section 4.3.10), the resulting crude solid contained the desired product by NMR. This was purified by chromatography to yield the desired tetra(phosphine-borane) in 31 % yield.

An alternative synthetic procedure was also attempted based on an efficient phosphination preparation reported by Paquet *et al.*¹² Here phosphine-boranes are coupled to bromomethyl substrates in a basic water-toluene biphasic reaction system under mild conditions using tetrabutylammonium bromide as a phase transfer agent. (Figure 8-10) The method claims superior yields to more conventional *n*-butyllithium based routes, although the most electron rich phosphine borane reported was *tert*-butylphenylphosphine borane, where an 87 % yield for the diphosphination of 1,3-bis(bromomethyl)benzene is reported.

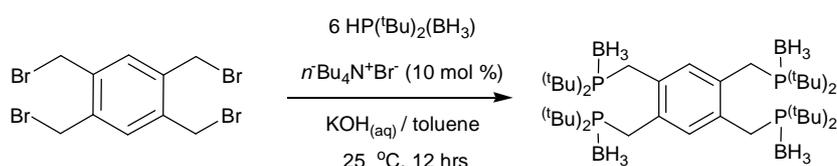


Figure 8-10 - Phosphination of 1,2,4,5-tetra(bromomethyl)benzene using the Paquet method¹²

The substrate in this case was insoluble in the toluene solvent and so DMF was added to the mixture. This also resulted in homogenisation of the biphasic solution, although still resulted in the successful formation of the desired product; in this case however, a lower yield of 14 % crystalline material was obtained. In both preparations, numerous recrystallisations were required in order to obtain pure product, with the impurities likely to consist of incompletely substituted product, as numerous peaks of similar shift to that of the desired product were observed by ^{31}P -NMR. Crystals obtained from the *n*-butyllithium route were suitable for X ray diffraction, with the initial structure obtained shown below.

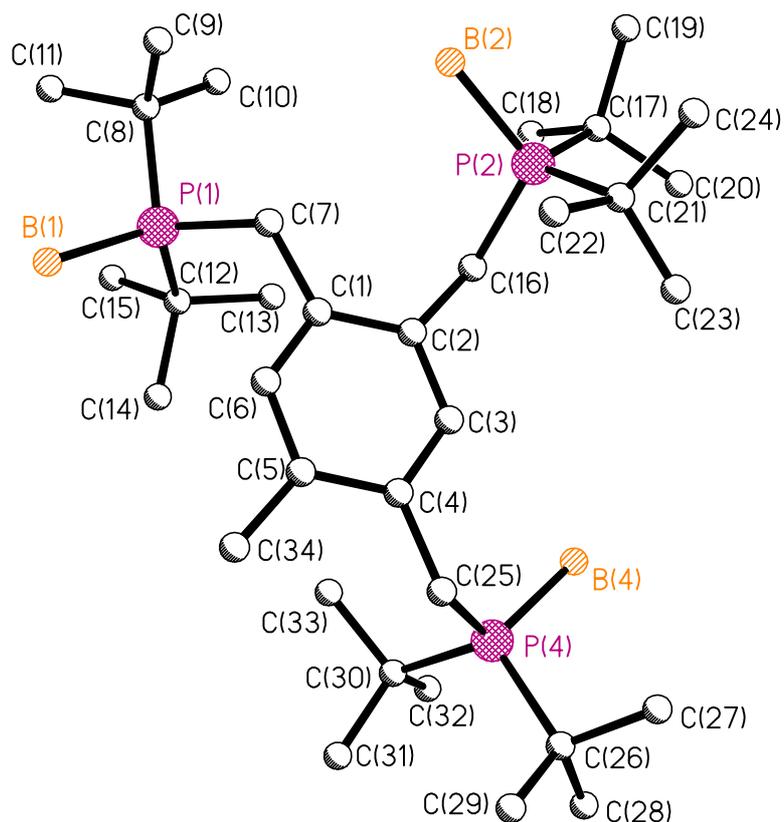


Figure 8-11 – X ray structure of 1,2,4,tri(di-*tert*-butylphosphinomethyl)-5-methylbenzene-triborane adduct

The determined structure contains only 3 phosphine substituents, with the remaining ring position assigned as a methyl as the data gives evidence for CH₃ protons at this position. Such a product could possibly have formed by bromine-lithium exchange on the substrate, followed by subsequent hydrolysis and as such this may highlight a possible disadvantage of performing such organolithium chemistry in DMF solvent. This was unexpected as the ¹H-NMR data integrates well for the tetra-substituted product and so this is likely to be a minor product.

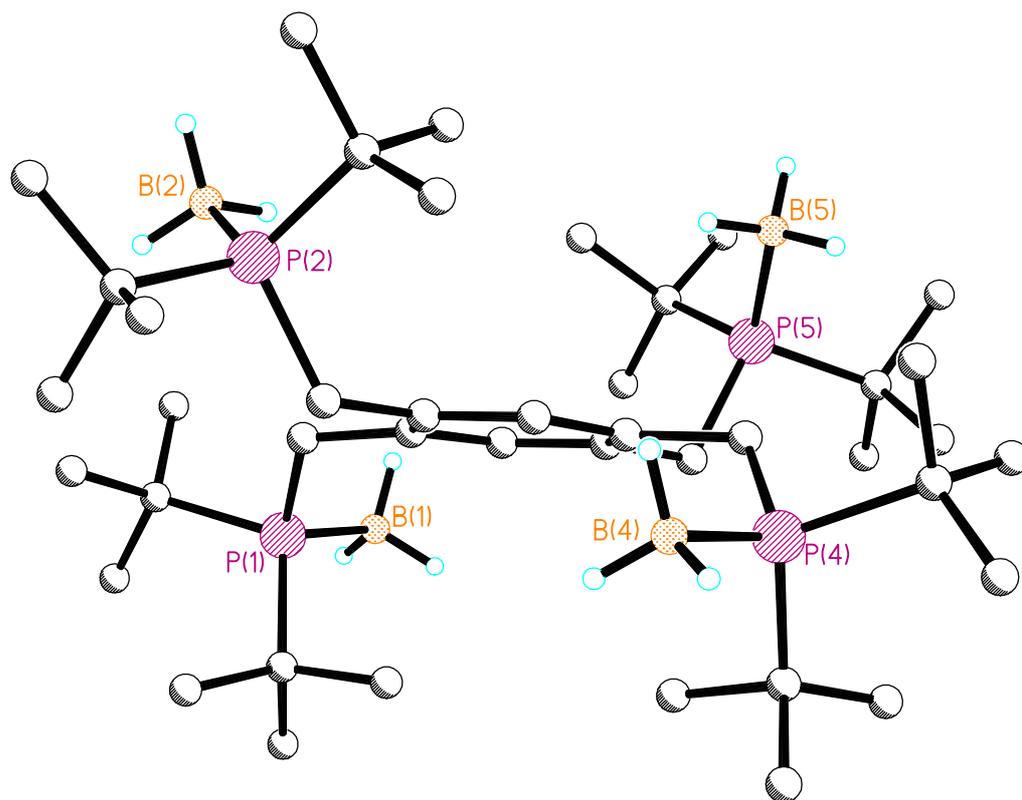


Figure 8-12 - Crystal Structure of 1,2,4,5-tetrakis(di-*tert*-butylphosphinomethyl)benzene-tetraborane adduct

After an additional recrystallisation of this sample, the expected structure was obtained by X ray diffraction. The obtained structure shows the high symmetry of the molecule with equivalency of the phosphorus-carbon bond lengths to one another. The structure also highlights the close proximity of the highly bulky phosphine functionalities to each other. Deprotection of this phosphine-borane was successful using 6 equivalents of methanesulfonic acid followed by neutralisation of the resulting phosphonium salt by ethanolic sodium hydroxide to give the desired free phosphine in 62 % yield. This was characterised only by NMR before use due to the small mass of product obtained. The ^{31}P -NMR spectra shows a primary signal at 30.1 ppm for the expected deprotected product, although several minor signals surrounding this region (± 3 ppm) were also observed.

8.2.3 Towards Phenyl-Substituted DTBPMB Derivatives

The synthesis of ring-phenyl substituted derivatives of DTBPMB was investigated, as these would be attractive, highly bulky phosphine targets. A tetraphenyl derivative of the diphosphine, (Figure 8-13) was therefore targeted and a synthetic methodology to this considered.

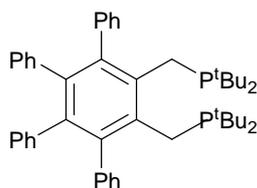
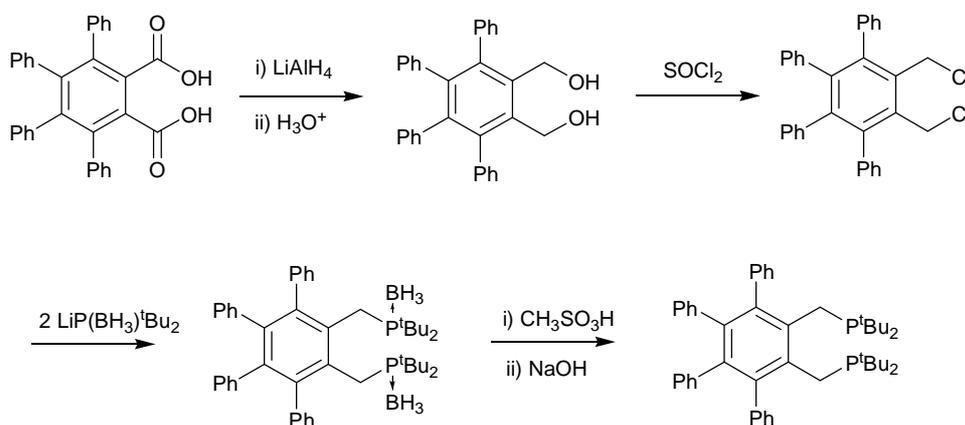


Figure 8-13 - 1,2-bis(di-*tert*-butylphosphinomethyl)-3,4,5,6-tetraphenylbenzene

The proposed route to this diphosphine (Figure 8-14) involves reduction of tetraphenylphthalic acid to give the corresponding diol. Treatment of this with thionyl chloride should yield the bis(chloromethyl) derivative which would be ideal for phosphination with two equivalents of $\text{LiP}(\text{BH}_3)^t\text{Bu}_2$. The resulting phosphine-borane adduct could then be deprotected using the acid / base treatment as in DTBPMB synthesis.



Ph = C₆H₅

Figure 8-14 - Proposed Route to 1,2-bis(di-*tert*-butylphosphinomethyl)-3,4,5,6-tetraphenylbenzene

The corresponding anhydride of the tetraphenylphthalic acid is commercially available, although somewhat expensive and so its synthesis *via* a Diels-Alder route (*[4+2]* cycloaddition) was investigated based on a literature preparation.¹³ Here,

acetylenedicarboxylic acid was used as the dieneophile, producing a carbonyl-bridged intermediate. This loses carbon monoxide at elevated temperature to give the desired aromatic product,¹⁴ as is illustrated in Figure 8-15. This procedure was practically straightforward and successfully yielded 3,4,5,6-tetraphenylphthalic acid in crystalline form in a 78 % isolated yield.

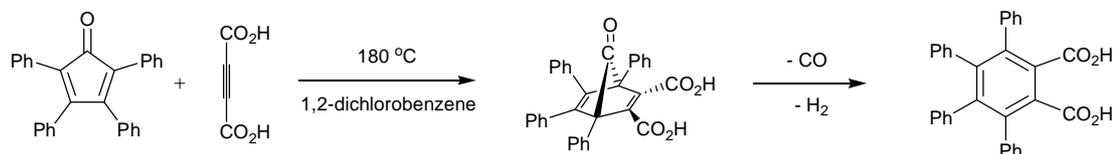


Figure 8-15 - Formation of 3,4,5,6-tetraphenylphthalic acid by Diels-Alder and subsequent loss of CO

Due to its low cost, this dienenone was also treated with maleic anhydride, which is reported to give a 95 % yield of the related anhydride product **1b**.¹³ It was hoped that heating at elevated temperature might cause aromatisation of this to the desired phthalic anhydride derivative.

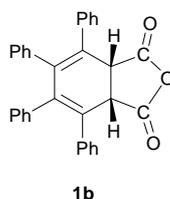


Figure 8-16 - Tetraphenyldihydrophthalic anhydride

This preparation however yielded the cyclic diene (Figure 8-16) in 83 % yield, which appears to be stable to aromatisation even when heated to 200 °C in air. A reference to the preparation of this compound was located *via* such a Diels-Alder route.¹⁵ Oxidation of this diene was successful by heating to reflux over palladium on charcoal (5 wt %) for 18 hours to successfully yield the aromatic compound as crystals in 62 % yield, based on a method used for the preparation of a related structure.¹⁶ The use of molecular bromine for this conversion has also been reported,¹⁷ but this was not attempted. Although this route has been successfully demonstrated to yield product, the use of acetylenedicarboxylic acid in the Diels-Alder reaction is preferred due to its higher yield and more convenient 1-step synthesis.

Reduction of phthalic acids can be effected by lithium aluminium hydride¹⁸ and so such a reduction of 3,4,5,6-tetraphenylphthalic acid was attempted, based on a literature preparation.¹⁹ After quenching the reaction mixture, a gelatinous colourless precipitate of aluminium hydroxide made work-up somewhat difficult. Dissolution of this in hot aqueous acid made work-up easier,²⁰ yielding the desired diol as a crystalline solid in 64 % yield.

Conversion of 3,4,5,6-tetraphenylbenzene-1,2-dimethanol to the bis(chloromethyl) derivative, was based on a literature preparation for conversion of benzene-1,3-dimethanol;²¹ the product remained in the form of a brown sticky solid even after recrystallisation attempts. The crude solid was therefore washed several times with hexanes to remove any residual thionyl chloride. Characterisation of the solid obtained was difficult; the ¹H-NMR spectrum was almost identical to that of the diol, with only a shift of 0.1 ppm for the methylene protons at 4.70 ppm, this, however, is not unexpected, given that these methylene resonances for 1,3-di(chloromethyl)benzene and 1,2-di(chloromethyl)benzene resonate at 4.57²¹ and 4.71 ppm respectively.²² Analysis by electrospray mass spectrometry, gave a somewhat unexpected result with an obtained m/z of 461.05, a loss of 4 AMU compared to that obtained for the diol, with no isotopic splitting pattern for chlorine observed. As this is expected to be the M⁺+Na ion, this suggests a molecular mass of 439.06 for the product. It is less likely, although also possible that the molecular ion has been ionised by methanol (the electrospray carrier solvent, giving M⁺ = 429.01) or proton (M⁺ = 460.04); suggested reaction products from these combinations are shown in Figure 8-17, below.

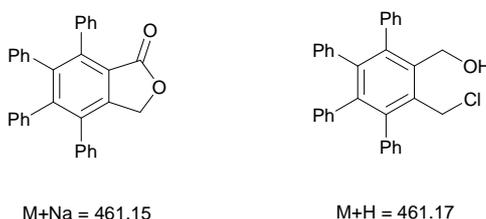


Figure 8-17 - Possible reaction products from treatment of diol with thionyl chloride

The lactone type product (left) is a likely possibility given the lack of chlorine isotopes in the mass spectrum. Closer inspection of the crude ¹H-NMR spectrum also found the residual DCM solvent peak at 5.30 ppm to contain a shoulder (approx 5.39 ppm), this could be attributed to the CH₂ protons of the lactone functionality, which are seen at

5.38 ppm in phthalide.²³ The ¹³C-NMR spectrum also showed peaks at 68.6 and 171.4 ppm, these are comparable to those for the CO₂ and CH₂O positions in phthalide, which occur at 69.8 and 171.1 ppm respectively. There is also signal at 42.3 ppm, which is closer to a related CH₂Cl environment (43.2 ppm)²⁴ than that for CH₂OH, (62.1 ppm) suggesting that some of the chloro-compound may be present.

Several reported preparations of phthalide go through a 1,2-benzenedimethanol substrate with the use of oxidising agents such as molecular oxygen²⁵ or hydrogen peroxide²³ over ruthenium on cerium oxide. Although not a common use for thionyl chloride, this reagent has been reported to effect oxidations.²⁶ However the presence of signals in the ¹H-NMR around 4.6 suggests that the oxidation in this case is not complete.

When this crude solid was treated with 2 equivalents of LiP(BH₃)^tBu₂, (prepared *in situ* as described in Section 4.3.10) in diethyl ether and stirred overnight, a yellow oil was obtained. Isolation by chromatography (DCM / methanol; 1 : 9 to elute) resulted in direct crystallisation of colourless needles (R_f = 0.67) from the eluting fractions. Analysis of these crystals however, showed them to be of a monophosphine product. The unphosphinated ring position is assigned as a methyl group due to the presence of a signal at 2.35 ppm / 21.6 ppm in the ¹H-NMR and ¹³C-NMR spectra respectively; almost identical to that observed in toluene in deuteriochloroform.²⁷ Hence the reaction product can be assigned as in Figure 8-18, rather than the desired diphosphine.

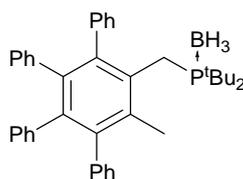


Figure 8-18 - Reaction product from reaction of 3 with LiP(BH₃)^tBu₂ (2 equiv.)

A scaled up preparation of the diol was carried out for further investigations; this was generally straightforward although the reduction of the diacid required heating to reflux for a longer period (18 hours). The use of PCl₅ to effect transformation of the diol to corresponding bis(chloromethyl) compound was then attempted.²⁸ The resulting

colourless crude solid was well characterised as the desired dichloride, with no peaks present in the ^{13}C -NMR for the phthalide-type product and mass spectrometry (C.I.) showing perfect correlation with the expected isotopic M^+ ion, (478.13) with a 2-Cl isotope pattern observed. Unfortunately time did not allow a phosphination attempt on this substrate and work is now being continued at Lucite to obtain this desired diphosphine.

The preparation of a derivative with less bulky methyl groups in the 3 and 6 positions was also investigated. The required ketone for this preparation was commercially available and so the same synthetic strategy was employed, as is summarised in Figure 8-19.

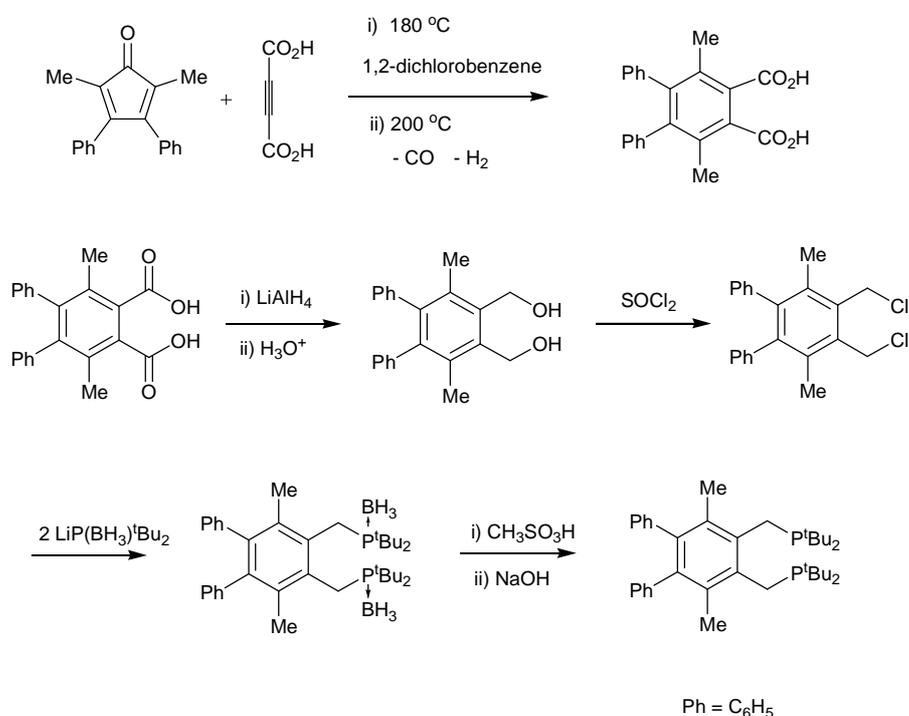


Figure 8-19 - Proposed Route to 1,2-bis(di-*tert*-butylphosphinomethyl)-3,6-dimethyl-4,5-diphenylbenzene

The diacid was successfully synthesised using the same conditions as before, although in slightly lower yield. (66 %) On moderate scale-up, the poor solubility of the diacid in common organic solvents made recrystallisation of this crude material difficult. Therefore only a sample was recrystallised for analysis and the remaining crude product considered sufficiently pure by ^1H -NMR to be used directly in the next stage. The only literature preparation related to this was of the corresponding acid anhydride;¹⁷ this was

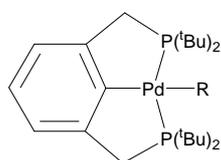
synthesised by oxidation of the cyclic diene (as related to Figure 8-16) by molecular bromine or potassium permanganate although no characterisation other than microanalysis and melting point (281 °C) was given.

Reduction of this species was successful on a 1.25 g scale using the LiAlH₄ procedure described previously, again giving a lower yield than for the tetraphenyl analogue. (41 %) Conversion to the dichloride was originally attempted using thionyl chloride and gave similar results to those discussed previously and so phosphination was not attempted on this substrate.

8.3 Methoxycarbonylation with TKPMB

Initial testing of palladium complexes of TKPMB in 1-octene methoxycarbonylation showed this to be inactive, tests at Lucite found the ligand to be catalytically inert for the ethene system as well; therefore investigation of why was carried out. Palladium metallocycle complexes are known to form from electron rich 1,3-(di-*tert*-butylphosphinomethyl)xylyl ligands³⁰ and so ³¹P-NMR analysis of the palladium complexes of this ligand from PdCl₂(CH₃CN)₂ were made and compared (³¹P NMR spectroscopy) to those of DTBPMB as well as to related 1,3-xylyl based ligand complexes reported in the literature. These results are presented in Figure 8-20.

| Ligand / complex | L : Pd Ratio | Observations (notes) |
|------------------------|--------------|---|
| TKPMB | 1 : 2 | 70.6 ppm (> 99 %, sharp) + 72.7 ppm (minor) |
| DTBPMB | 1 : 1 | 48.0 + 50.0 ppm (both broad) |
| 1 ²⁹ | | 77.3 ppm (in d ⁸ THF) |
| 2 ³⁰ | | 72.5 ppm (in CDCl ₃) |
| 3 ³¹ | | 105.1 ppm (in C ₆ D ₆) |
| 4 ³² | | 72.0 ppm (in C ₆ D ₆) |
| 5 ³³ | | 72.3 ppm (in C ₆ D ₆) |



Complex

1, R = d⁸-THF

2, R = Cl

3, R = OCOCF₃

4, R = Ph

5, R = OOH

Figure 8-20 - ³¹P-NMR data for TKPMB and DTBPMB with comparison to literature

The literature evidence strongly suggests that that the metal has in fact taken on a palladacycle-type (C-H activation) binding motif with the observed ³¹P-NMR shifts in close correlation to palladacycles reported in the literature. It is unfortunate that there is no signal observed in the expected region for the DTBPMB-type bidentate binding, suggesting no equilibria to such a species exists in solution. The 1,3-PCP pincer ligand shown in Figure 8-20 does not show activity in ethene methoxycarbonylation in tests at Lucite^{Error! Bookmark not defined.} and no mention of carbonylation catalysis is mentioned in a recent review of this ligand family.³⁴ The observed lack of activity for TKPMB in methoxycarbonylation of both 1-octene and ethene (at Lucite^{Error! Bookmark not defined.}) gives additional evidence that the palladium has complexed in such a 1,3-form here. (Figure 8-21)

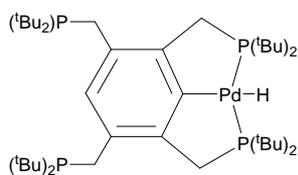


Figure 8-21 - Proposed palladium binding mode to TKPMB

8.4 Summary

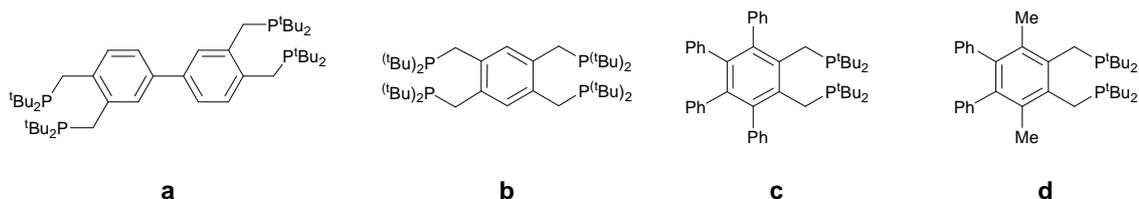


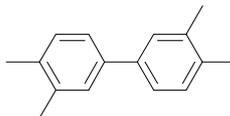
Figure 8-22 - Ligand syntheses attempted

The ligand syntheses that have been attempted and discussed in this chapter are summarised in Figure 8-22, above. The biphenyl ligand, TBPBP (8-22a) appears to have been synthesised, although its isolation from the highly air sensitive crude oil has not been successful. The observed impurities here are likely to be incompletely phosphinated biphenyls. Synthesis and isolation of TKPMB (8-22b) has been successful and this tetraphosphine has been well characterised. Palladium complexes of this ligand however, have been shown to be catalytically inert, with ^{31}P -NMR evidence suggesting that this is due to preferential coordination of this ligand in a PCP-pincer type mode. Such ligands are thought to be inactive in methoxycarbonylation reactions. **Error! Bookmark not defined.**

The tetraphenyl and diphenyl-dimethyl ring substituted phosphines, 8-22c and 8-22d respectively have not yet been obtained, although good progress along their synthetic routes has been made. Problems occurred in the preparation of the 1,2-di(chloromethyl)benzene substrates here. It would appear that the 1,2-ring positioning of the diol substrate results in oxidation to a lactone rather than chlorination using thionyl chloride, this does not appear to be a problem for the 1,3-benzenedimethanol.²¹ It appears that the use of PCl_5 has overcome this problem, with the resulting product well characterised as the desired di(chloromethyl) derivative and so it is hoped that this may lead on to successful preparation of the target diphosphines.

8.5 Experimental

8.5.1 Preparation of 3,3',4,4'-tetramethylbiphenyl



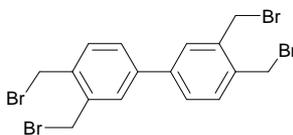
Under anhydrous conditions in an argon atmosphere, a 2-necked 250 cm³ round bottomed flask fitted with a pressure equalising dropping funnel, condenser and magnetic follower was charged with magnesium turnings (1.04 g, 43.5 mmol) and a single crystal of iodine in diethyl ether. (75 cm³) The flask was cooled to 0 °C in an ice-water bath and 4-bromo-*o*-xylene (97 %, Alfa, 7.00 g, 37.8 mmol) in ether (75 cm³) was added dropwise over 40 minutes. On addition of the bromide, the solvent took on a slight green colouration and the slow formation of bubbles was observed. When addition was complete, the solution was gently heated to reflux for 2 hours at which point it had a red-green colouration.

To a second 500 cm³, 2-necked round bottomed flask fitted with a reflux condenser, septum and magnetic follower was added iron(III) chloride (Avocado, 0.03 g, 0.19 mmol), 1,2-dichloroethane (Fluka, 4.50 g, 45.4 mmol) and dry diethyl ether (100 cm³). The mixture was gently heated to reflux and the Grignard solution added in portions *via* cannula. After addition was complete, heating was continued to maintain reflux for a further hour. The reaction mixture was cooled and quenched by addition of aqueous HCl. (*ca.* 1 mol dm⁻³) The organic layer was separated and the aqueous layer washed with diethyl ether. (2 x 200 cm³) The combined organic phases were dried over magnesium sulfate and the solvent removed *in vacuo* to give a yellow oil, analysis of which by GC-MS showed almost complete conversion to the biphenyl. The oil was purified by chromatography (silica, ethyl acetate : hexane, 10:1) to yield the title compound as a colourless solid (1.68 g, 42 %)

Characterisation

MS (low res. E.I.): Requires $M^+ = 210$, found $M^+ = 210$; **$^1\text{H-NMR}$:** δ [ppm] = 2.29 (s, 6H, CCH_3), 2.33 (s, 6H, CCH_3), 6.94 – 7.52 (m, 6H, aromatic CH); **$^{13}\text{C-NMR}$:** δ [ppm] = 19.1, 19.6 (6 x s, CH_3), 119.3, 128.7, 131.1, (6 x s, aromatic CH) 132.0, 135.1, 138.8 (6 x s, aromatic C.); **Mpt:** 75-78 °C, (lit 72-75 °C). NMR and Mpt available in literature and in good agreement.³⁵

8.5.2 Preparation of 3,3',4,4'-tetrakis(bromomethyl)biphenyl

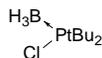


A 100 cm³ round bottomed flask fitted with a reflux condenser and magnetic follower was charged with 3,3',4,4'-tetramethylbiphenyl (0.75 g, 3.57 mmol), N-bromosuccinimide (Aldrich, 2.86 g, 16.07 mmol), benzoyl peroxide (ca. 0.05 g) and 1-2 dichloroethane. (Fluka, 50 cm³) The reaction mixture was heated to 100 °C for 7 hours then allowed to cool to room temperature overnight. The mixture was then filtered and the solvent removed *in vacuo*. The resulting oil was redissolved in diethyl ether, washed with sodium thiosulfate solution (ca. 1 mol dm⁻³, 1 x 50 cm³) and water (2 x 50 cm³). The combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo* to leave a viscous oil. An orange sticky solid was obtained from ethyl acetate / hexane, which was slowly recrystallised from chloroform (overnight at -20 °C) to give the title compound as an off white solid (0.356 g, 10 %)

Characterisation

TOF-MS (CI): Requires $M^+ = 525.9$, Found $M^+ = 525.8$, isotope splitting pattern for Br_4 present. **$^1\text{H-NMR}$:** δ [ppm] = 4.71, 4.72 (s, 8H, CH_2Br), 7.21 – 7.63 (m, 6H, aromatic CH); **$^{13}\text{C-NMR}$:** δ [ppm] = 29.7, 29.8 (4 x s, CH_2Br), 127.8, 129.7, 131.8, (6 x s, aromatic CH) 136.0, 137.1, 140.8 (6 x s, aromatic C.); **Mpt:** 162 - 165 °C. (lit 163-164 °C). Data in good agreement to available literature.⁷

8.5.3 Preparation of di-*tert*-butylchlorophosphine-BH₃ Adduct



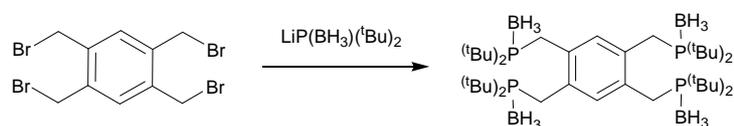
To a 3-necked, 100 cm³ round bottomed flask flushed with argon was added di(*tert*-butyl)chlorophosphine (4.0 g, 22.1 mmol) in THF (40 cm³). To this was added BH₃-THF complex (1.0 mol dm⁻³ in THF, Acros, 24.4 mmol / cm³) *via* syringe and the solution left to stir at room temperature overnight. ³¹P-NMR of the reaction solution verified complete conversion to the borane adduct.

Now treated as air-stable, water (30 cm³) was added dropwise. The solution was then extracted into diethyl ether (3 x 50 cm³) and washed with water (1 x 50 cm³). The combined organic layers were dried over magnesium sulfate and the solvent removed *in vacuo* to yield the title compound as a colourless solid. (3.77 g, 92 %) Recrystallisation from hexanes was not successful, although the colourless solid was considered sufficiently pure for subsequent use.

Characterisation

¹H-NMR: δ [ppm] = 0.92 (q, 3H, J_{BH} = 318 Hz, P-BH₃) 1.42 (d, 18H, J_{CP} = 14.5 Hz, P(C(CH₃)₃)₂); **¹³C-NMR:** δ [ppm] = 27.8 (d, J_{CP} = 3.1 Hz, P(C(CH₃)₃)₂), 38.2 (d, J_{CP} = 12.1 Hz, P(C(CH₃)₃)₂); **³¹P-NMR:** δ [ppm] = 150.5 (m,³⁶ P-BH₃); **Microanalysis:** Requires C = 49.40 %, H = 10.88 %, Found C = 48.65 %, H = 10.27 %; **Mpt:** 146.3 – 147.5 °C. No literature data available for comparison.

8.5.4 Preparation of 1,2,4,5-tetrakis(di-tert-butylphosphinomethyl)benzene tetraborane adduct via Lithiated Phosphine



Under anhydrous conditions and an argon atmosphere, a 100 cm³ 3-necked round bottomed flask fitted with a pressure equalizing dropping funnel and a magnetic follower was charged with di-tert-butylphosphine-borane adduct (7.50 g, 46.8 mmol) in petroleum ether (40-60 °C, 20 cm³). A solution of *n*-butyllithium (Aldrich, 2.5 mol dm⁻³ in hexanes, 51.6 mmol) was added dropwise with stirring at room temperature. The resulting mixture was stirred for 30 minutes, filtered, washed with further petroleum ether (40-60 °C, 20 cm³) and refiltered. 1,2,4,5-tetrakis(bromomethyl)benzene (Aldrich, 5.0 g, 11.1 mmol) in DMF (40 cm³) was then added dropwise to the lithium salt at 0 °C. The suspension was allowed to warm slowly to room temperature and stirred overnight, where it took on an initial orange colouration before turning yellow.

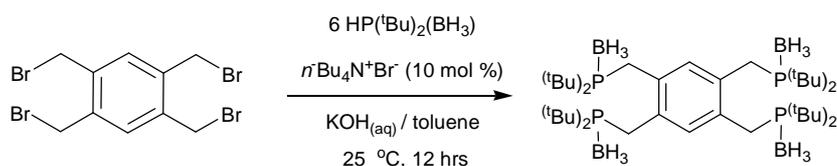
To the reaction mixture, now treated as air-stable was added water (50 cm³) and the mixture was extracted with diethyl ether (3 x 50 cm³). The combined extracts were further washed with water (50 cm³), dried over MgSO₄ and the solvent removed *in vacuo* to give an orange oil. This was purified by column chromatography (Hexane : ethyl acetate, 1: 1, R_f = 0.34) to give a colourless oil which crystallised rapidly on standing. This oil was recrystallised from DCM / Hexane (-20 °C, overnight) and further recrystallised from DCM / methanol to yield the title compound as colourless needles (2.40 g, 31 %).

Characterisation

MS (Electrospray): Requires M⁺ = 766.3, found M⁺ = 766.5; **¹H-NMR:** δ [ppm] = 0.71 (q, 12H, J_{BH} = 309 Hz, BH₃), 1.23 (d, 76H, J_{PH} = 12.39 Hz, butyl, CH₃), 3.28 (d, 8H, J_{PH} = 11.57 Hz methylene CH₂), 7.93 (s, 2H, Aromatic CH); **¹³C-NMR:** δ [ppm] =

23.9 (d, $J_{CP} = 24.6$ Hz $C(CH_3)_3$), 28.4 (s, $C(CH_3)_3$) 33.1 (d, $J_{CP} = 25.1$ Hz, CH_2P), 132.3 (s, CCH_2P) 135.8 (s, $CCHC$); ^{31}P -NMR: δ [ppm] = 50.80 (broad, BH_3-P); **Microanalysis:** Requires C = 65.82 %, H = 12.36 %, Found C = 66.37 %, H = 12.61 % **Mpt:** > 280 °C. No literature data available for comparison.

8.5.5 Preparation of 1,2,4,5-tetrakis(di-tert-butylphosphinomethyl)benzene tetraborane adduct based on the Paquet method



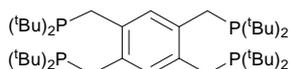
The following procedure is based on that reported by Paquet.¹² Under an argon atmosphere, a 100 cm³ 3-necked round bottomed flask fitted with a magnetic follower was charged with di-tert-butylphosphine-borane adduct (1.07 g, 6.67 mmol) and 1,2,4,5-tetrakis(bromomethyl)benzene (Aldrich, 0.500 g, 1.11 mmol) in toluene (5 cm³). A solution of tetra-*n*-butylammonium bromide (Acros, 35.7 mg, 0.11 mmol) in potassium hydroxide (Fisher, 50 wt %, 20 cm³) was added to the mixture with vigorous stirring. After 30 minutes, DMF (Fisher, ca. 15 cm³) was added to the mixture, resulting both in homogenisation of the biphasic and dissolution of the majority of the tetrabromide substrate (the solution was still slightly cloudy). The mixture was then stirred vigorously for 24 hours.

Diethyl ether (20 cm³) and water (20 cm³) were then added to the reaction mixture and the organic phase extracted. The aqueous phase was further extracted with diethyl ether (3 x 20 cm³) and the combined organic extracts dried over $MgSO_4$. The solvent was removed *in vacuo* to give a crude white solid. This was recrystallised from DCM / methanol (-20 °C, overnight) to yield the title compound as a colourless solid (0.121 g, 14.2 %).

Characterisation

Analytically identical to 8.5.4

Preparation of 1,2,4,5-tetrakis(di-tert-butylphosphinomethyl)benzene



The following procedure was undertaken in anhydrous conditions under an argon atmosphere throughout. To a 100 cm³ 3-necked round bottomed flask fitted with a pressure equalizing dropping funnel and a magnetic follower was added 1,2,4,5-tetrakis(di-tert-butylphosphinomethyl)benzene-tetraborane adduct (0.100 g, 0.156 mmol) in DCM (4 cm³). Methanesulfonic acid (6 equivalents) was added *via* microsyringe whilst cooling the mixture with a cold water bath (ca. 12 °C). The solution was then heated to reflux for 1.5 hours after which full conversion to the protonated form was observed by ³¹P-NMR (CDCl₃, no {1H}, 47.71 ppm, J_{PH} = 456 Hz).

The solvent volume was then reduced *in vacuo* and methanol (10 cm³) added slowly. When gas evolution had stopped, all solvent was removed *in vacuo* to give an oily solid. This was then dissolved in ethanol and cooled to 10 °C with a cold-water bath. With stirring, a thoroughly degassed ethanolic sodium hydroxide solution (1.5 mol dm⁻³, 1.25 equivalents wrt MSA) was added dropwise. The reaction mixture was gently heated resulting in a gradual formation of a colourless precipitate. The mixture was stirred for 90 minutes and cooled, after which full deprotonation of the phosphorus sites was confirmed by ³¹P-NMR spectroscopy (CDCl₃, 30.0 ppm, some lesser peaks at +/- 3ppm).

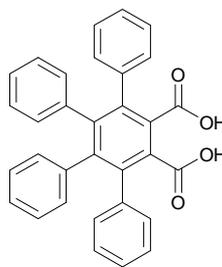
Petroleum ether (40-60 °C fraction, 10 cm³) was added to the mixture and the resulting precipitate allowed to settle overnight. This was filtered *via* filter-cannula and the methanesulfonate salts washed with further petroleum ether. The combined washings were dried over MgSO₄ and the solvent removed *in vacuo* to yield a colourless solid,

which was recrystallised from DCM / methanol to yield the title compound as a colourless solid (56.8 mg, 62 %)

Characterisation

¹H-NMR: δ [ppm] = 1.06 (d, 76H, $J_{\text{PH}} = 12.19$ Hz, butyl, CH₃), 3.57 (d, 8H, $J_{\text{PH}} = 10.89$ Hz methylene CH₂), 7.99 (s, 2H, Aromatic CH); ¹³C-NMR: δ [ppm] = 25.6 (d, $J_{\text{CP}} = 14$ Hz, CCH₃), 28.4 (s, CCH₃), 41.3 (d, $J_{\text{CP}} = 24$ Hz, CH₂P), 132.2 (s, CCH₂P), 135.7 (s, CCHC); ³¹P-NMR: δ [ppm] = 30.0. No literature data for comparison.

8.5.6 Preparation of 3,4,5,6-tetraphenylphthalic acid



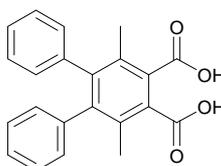
To a 1000 cm³ round bottomed flask fitted with a reflux condenser was added 2,3,4,5-2,5-tetraphenylcyclopenta-2,4-dienone dimer (Aldrich, 55.00 g, 0.143 mol), 1,2-dichlorobenzene (450 cm³), acetylenedicarboxylic acid (Aldrich, 19.59 g, 0.172 mol) and a magnetic follower. The mixture was heated to 180 °C, at which point gentle gas evolution was observed along with a gradual colour change of the solution from dark purple to pink. Heating was maintained for a further 2 hours and the solution cooled.

On standing, a grey sludge was precipitated from the reaction mixture. This was filtered and an off-white solid obtained from this by crystallisation from DCM / hexanes. (4 °C, overnight) A further crop was obtained from the reaction filtrate by the addition of *ca.* 200 cm³ hexanes and standing. (-20 °C, 48 hours) These solids were combined and recrystallised from DCM / hexanes (-20 °C, 48 hours) to yield the title compound as colourless crystals. (50.4 g, 78 %)

Characterisation

¹H-NMR: δ [ppm] = 1.60 (s, 2H, CO₂H), 6.90 - 7.25 (m, 20H, aromatic CH); **¹³C-NMR:** δ [ppm] = 125.3 – 131.2 (aromatic CH), 137.3 – 142.0 (3 x s, aromatic C), 165.7 (s, CO₂H); **Microanalysis:** Requires C = 81.67 %, H = 4.71 %, Found C = 77.91 %, H = 5.63 %, (likely wet). **Mpt:** > 280 °C (lit 288 - 289 °C).³⁷

8.5.7 Preparation of 3,6-dimethyl-4,5-diphenylphthalic acid



To a 100 cm³ round bottomed flask was added 3,4-diethyl-2,5-dimethylcyclopenta-2,4-dienone dimer (Aldrich, 2.00 g, 7.69 mmol), 1,2-dichlorobenzene (30 cm³) and a magnetic follower. The mixture was heated to 180 °C for 1 hour, at which point the solution had taken on a deep red colouration. Acetylenedicarboxylic acid (Aldrich, 1.05 g, 9.21 mmol) was then added to the mixture, resulting in gentle gas evolution and a gradual colour change of the solution from deep red to yellow. Heating was maintained for a further 2 hours and the solution cooled.

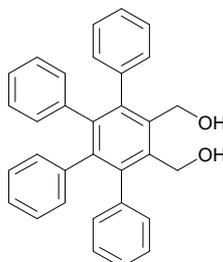
Standing overnight at 4 °C resulted in direct crystallisation of the title compound from the solution and a further crop of product was obtained by removal of the 1,2-dichlorobenzene solvent *in vacuo* and crystallisation from DCM / hexanes at -20 °C for 48 hours. (1.76 g, 66 %).

Characterisation

¹H-NMR: δ [ppm] = 1.59 (s, 2H, CO₂H), 2.45 (s, 6H, CCH₃), 6.88-7.27 (m, 10H, 10 x aromatic CH); **¹³C-NMR:** δ [ppm] = 15.9 (s, CH₃C), 127.3, 127.7, 129.2, (3 x s, CHCHCHC), 128.0, 136.7, 150.5 (3 x s, CC(CH₃)CCO₂H), 137.9 (s, CHCHCHC), 163.3 (s, CO₂H); **Microanalysis:** Requires C = 76.29 %, H = 5.24 %, Found C = 77.41

%, H = 4.93 % (likely wet). **Mpt:** = 272 – 274 °C. No literature data available for comparison.

8.5.8 Preparation of 3,4,5,6-tetraphenylbenzene-1,2-dimethanol



Under anhydrous conditions, to a 1000 cm³ round bottomed flask fitted with a Young's tap, reflux condenser and oil bubbler was added lithium aluminium hydride (13.00 g, 0.54 mol), dry THF (250 cm³) and a magnetic follower at 0 °C. A solution of 3,4,5,6-tetraphenylphthalic acid (49.50 g, 0.105 mol) in THF (250 cm³) was added *via* cannula over 45 minutes with cooling *via* an ice-water bath. The suspension was heated to reflux for 18 hours and left stirring at room temperature overnight. The suspension was then cooled to 0 °C and very cautiously quenched by the dropwise addition of water (15 cm³), sodium hydroxide solution (2 mol cm⁻³, 15 cm³) and further water (30 cm³). Hydrochloric acid (2 mol dm⁻³, 200 cm³) was then added and the mixture heated to reflux for a further hour, resulting in dissolution of the sticky colourless precipitate.

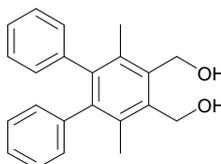
The solution was extracted with diethyl ether (3 x 250 cm³), the combined organic extracts dried over magnesium sulfate and the volatiles removed *in vacuo*, resulting in an oil which crystallised rapidly on standing. This solid was further recrystallised from DCM / hexane to give the title compound as colourless needles (29.9 g, 64 %)

Characterisation

MS(electrospray): Requires M⁺ = 442.2, found M⁺ = 442.1; **¹H-NMR:** δ [ppm] = 4.70 (s, 4H, CH₂OH), 5.31 (s, 2H, CH₂OH), 6.72-7.29 (m, 20H, 10 x aromatic CH); **¹³C-NMR:** δ [ppm] = 61.1 (s, CH₂OH) 125.3 – 131.3, (10 x s, aromatic CH), 137.3, 140.1, 142.0 (3 x s, C(Ph)C(Ph)CCH₂OH) 139.7, 141.5 (2 x s, CHCHCHC); **Microanalysis:**

Requires C = 86.85 %, H = 5.92 %, Found C = 86.83 %, H = 5.81 %. **Mpt:** 240 – 242 °C. No literature data available for comparison.

8.5.9 Preparation of 3,6-dimethyl-4,5-diphenylbenzene-1,2-dimethanol

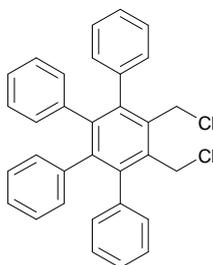


The procedure described above (section 8.5.8) was followed and suitably scaled using a solution of 3,6-dimethyl-4,5-diphenylphthalic acid (1.25 g, 3.61 mmol) as reagent. The title compound was crystallised from DCM / hexanes as colourless needles. (0.471 g, 41 %)

Characterisation

MS(electrospray): Requires $M^+ = 318.2$, found $M^+ = 318.1$; **$^1\text{H-NMR}$:** δ [ppm] = 2.18 (s, 6H, CCH_3), 2.68 (s, 2H, CH_2OH), 4.99 (s, 4H, CH_2OH), 6.90-7.26 (m, 10H, 10 x aromatic CH); **$^{13}\text{C-NMR}$:** δ [ppm] = 17.3 (s, CH_3C), 60.1 (s, CH_2OH) 125.9, 127.4, 130.0, (3 x s, CHCHCHC), 132.0 (s, CHCHCHC), 137.4, 141.2, 142.5 (3 x s, $\text{CC}(\text{CH}_3)\text{CCH}_2\text{OH}$); **Microanalysis:** Requires C = 82.97 %, H = 6.96 %, Found C = 81.25 %, H = 6.75 %. **Mpt:** 172 - 174 °C. No literature data available for comparison.

8.5.10 Preparation of 1,2-di(chloromethyl)-3,4,5,6-tetraphenylbenzene

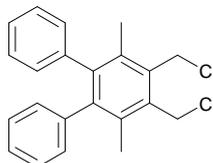


Under anhydrous conditions, to a 100 cm³ round bottomed flask fitted with a magnetic follower and a calcium carbonate drying tube was added 3,4,5,6-tetraphenylbenzene-1,2-dimethanol (0.125 g, 0.28 mmol) in DCM (5 cm³). Phosphorus pentachloride (0.153 g, 7.34 mmol) was added as a solid and the resulting solution stirred under reflux for 1 hour and then allowed to stand at room temperature for a further hour. The excess phosphorus pentachloride was then destroyed by the addition of methanol (4 cm³), with the mixture being stirred for a further hour. The solvents were then removed *in vacuo* to leave the crude title compound as a colourless solid. (0.117 g, ca. 87 %)

Characterisation

MS (CI): Requires $M^+ = 478.13$, found $M^+ = 478.13$; **¹H-NMR:** δ [ppm] = 4.66 (s, 4H, CH₂Cl?), 6.70-7.20 (m, ca. 20H, 20 x aromatic CH); **¹³C-NMR:** δ [ppm] = 42.2 (s, CH₂Cl), 54.6-54.9 (4 peaks, unknown), 126.0 – 131.2 (Aromatic CH), 139.1 – 143.2 (aromatic C); **Microanalysis:** Requires C = 80.17, H = 5.02, Found C = 77.74, H = 4.92.

8.5.11 Attempted Preparation of 1,2-di(chloromethyl)-3,6-dimethyl-4,5-diphenylbenzene



To a 100 cm³ round bottomed flask fitted with a magnetic follower and a calcium carbonate drying tube was added thionyl chloride (20 cm³) and the flask cooled to 0 °C. 3,6-dimethyl-4,5-diphenylbenzene-1,2-dimethanol (0.412 g , 1.30 mmol) was added in portions as a solid and the resulting solution stirred at room temperature for 18 hours. The solvent was then removed *in vacuo*, leaving a dark oil from which a brown solid was precipitated by addition of warm acetonitrile. This was further purified from DCM / hexane to give an orange / brown solid, the identity of which is discussed in Section 8.2.3. (0.218 g, ca. 53 %)

Characterisation

¹H-NMR: δ [ppm] = 2.08 (s, 6H, CCH₃), 4.82 (4H, CH₂Cl?), (5.24-5.38, possibly two peaks – see main text), 6.72-7.11 (m, 10H, 10 x aromatic CH); ¹³C-NMR: δ [ppm] = 14.1 (s, CH₃C), 41.0 (s, CH₂Cl), 126.2, 127.5, 129.7, (3 x s, aromatic CH), 134.2, 140.6, 143.3 (3 x s, aromatic C); small unidentified peaks at 25.3, 26.9 and 34.7 ppm.

Notes and References

- ¹ D.J. Cole-Hamilton and R.P. Tooze in *Catalyst Separation, Recovery and Recycling – Chemistry and Process Design*, ed. D.J Cole-Hamilton and R.P Tooze, Springer-Verlag, New York, 2006, ch. 1, pp. 1-8.
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9. Conclusions and Future Work

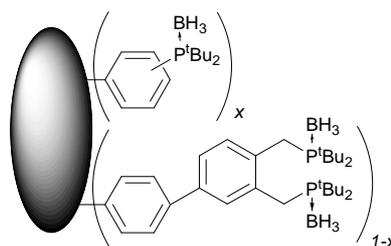


Figure 9-1 - Proposed phosphine residues present on polystyrene resins

Strong aryl-aryl linking of 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (DTBPMB) residues onto polystyrene by a Suzuki-type coupling resulted in successful immobilisation of phosphorus species. It does appear, however, that phosphination of the resins is incomplete and it also seems possible that an aryl-phosphorus linked residue could also be tethered to the resin. (Figure 9-1) Further information on phosphorus loading levels could be obtained from phosphorus microanalysis of the resins and this information would be necessary for obtaining useful phosphorus to palladium ratios for subsequent catalytic investigations. It would be interesting to see whether the presence of the monophosphine residues has a significant effect on catalysis. As the bidentate residues would be able to chelate the metal, it is possible that the concentration of monophosphine complexes is significantly lower than may be expected from the phosphine residue stoichiometry on the resin. An alternative synthetic strategy involving a 1-step coupling of a sulfonyl chloride functionalised DTBPMB derivative is detailed in Section 4.2.3 and this may provide a route to a better defined supported catalyst.

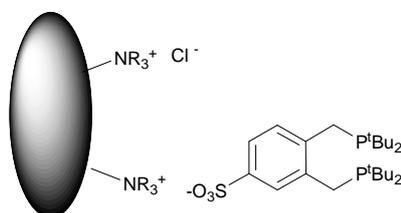


Figure 9-2 - Ionic immobilisation of KBPMBS

The synthesis of a potassium sulfonate derivative of DTBPMB (potassium 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonate, KBPMBS) was successful and immobilisation of this onto a strongly acidic polystyrene-based ion exchange resin was

also demonstrated. (Figure 9-2) Preliminary catalytic studies show palladium complexes of this system to be active in 1-octene methoxycarbonylation, although activity was only observed at a high ligand to palladium ratio. Further studies are necessary here to ascertain whether the observed activity is due to the supported complex or by leached catalyst. It is also suggested that poisoning of the catalyst may have occurred due to the large excess of ammonium chloride residues on the support. Quantitative conversion of these residues to ammonium methanesulfonate has been successful and it would be interesting to compare catalytic activity of phosphine immobilised onto this support.

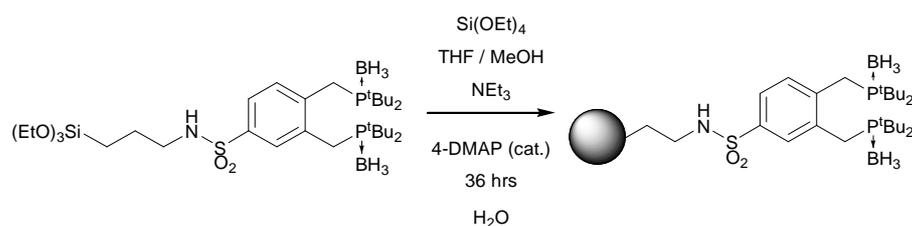


Figure 9-3 - Strategy for synthesis of silica-tethered DTBPMB residues

Attempts to immobilise DTBPMB onto silica *via* a sol-gel co-condensation methodology was investigated and to this end the synthesis of a suitably functionalised precursor containing a sulfonamide linkage was successful *via* protection of the diphosphine using borane. Although sol gelation of this species to form a silica supported material (Figure 9-3) appears to be successful, attempts to deprotect the phosphine-borane resulted in cleavage of the ligand from the support.

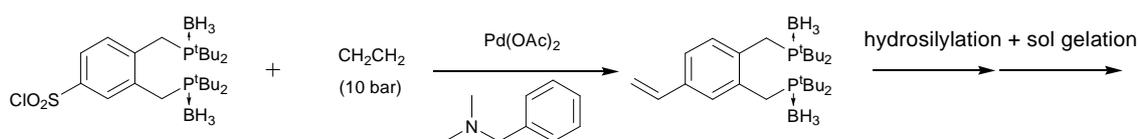


Figure 9-4 - Proposed synthesis of a hydrosilylation precursor *via* Heck coupling

Alternative routes to this supported ligand were attempted, both by altering this methodology and *via* alkene hydrosilylation, although without success. The synthesis of precursors from sulfonyl chloride functionalised ligand *via* a Heck coupling are detailed in Section 5.4. Coupling with ethylene (Figure 9-4) is a particularly attractive method to a hydrosilylation precursor, as the synthesis of the sulfonyl chloride precursor has been described (Section 5.5.2) and a similar type of Heck coupling has also been demonstrated in Section 5.5.8.

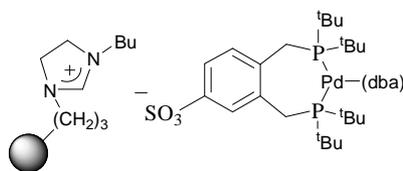


Figure 9-5 - Imidazolium chloride tethered KBPMBS complex

The immobilisation of KBPMBS onto imidazolium chloride functionalised silica was also attempted, although complete leaching of the phosphine from the support by methanol washing was observed. This may however still be of use as a support in a scCO_2 extracted system as this highly polar linkage is unlikely to be soluble in this solvent.

Immobilisation of KBPMBS in an IL phase was investigated, with palladium complex formation and catalytic activity being demonstrated. A positive effect on conversion was observed upon the addition of CO_2 to the system; possibly due to this increasing the CO solubility of the IL phase. Efficient product separation from the IL-immobilised catalyst system was demonstrated, both by organic extraction and the use of scCO_2 flow. However, poor catalyst stability appears to present a barrier to recycling this system, with loss of conversion observed on recycling. Catalysis with continuous flow extraction using scCO_2 (Figure 9-6) was attempted with the intention that this would remove 'idle' time of the catalyst and hence slow catalyst deactivation, although this did not appear to improve stability.

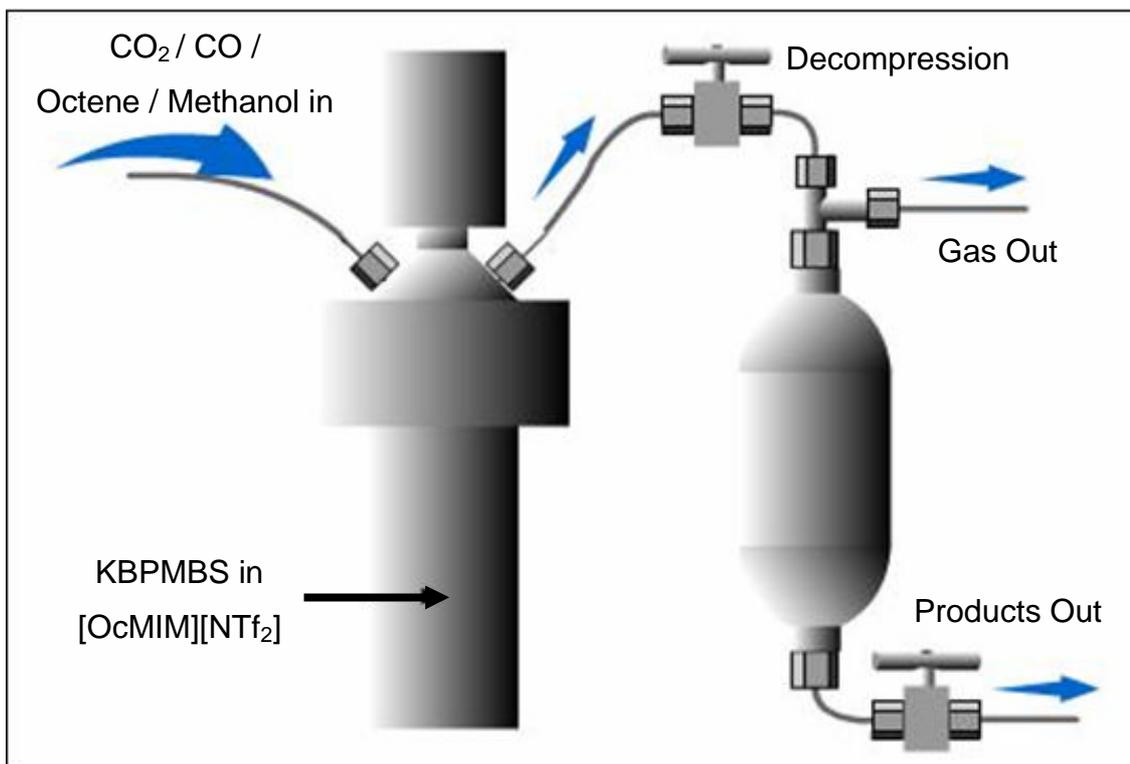


Figure 9-6 - Schematic for separation using KBPMBS / IL under scCO₂ flow
Derived from an original graphic by Cook and Hays

Attempts to immobilise DTBPMB *via* a Schiff-base linked sol gel precursor were not successful, although reduction of the disulfide of DTBPMB has been demonstrated using hexachlorodisilane, which could allow these routes to be successful as well as providing a general synthetic strategy for protecting highly electron rich phosphines.

The synthesis of bulky ligands based on the DTBPMB backbone was investigated and the synthesis of 1,2,4,5-tetrakis(di(*tert*-butyl)phosphinomethyl)benzene was successful. This ligand however showed no catalytic activity in 1-octene methoxycarbonylation and this may be due to the formation of a stable palladacycle complex. Synthesis of a related biphenyl-based tetraphosphine was also attempted, although isolation of this was not achieved. Synthetic routes towards tetraphenyl and dimethyldiphenyl ring-functionalised derivatives of DTBPMB have been developed; difficulties in obtaining the di(chloromethyl) precursors in both of these routes were encountered. These obstacles now appear to have been overcome and so successful synthesis of these desired diphosphines now seems attainable.

As well as being useful in investigating the effect of ligand bulk on catalyst stability, 1,2-bis(ditertiarybutylphosphinomethyl)-3,4,5,6-tetraphenylbenzene would also be interesting as a precursor to a highly sulfonated derivative of DTBPMB as the molecule is well set up for sulfonation at all four phenyl sites (Figure 9-7).

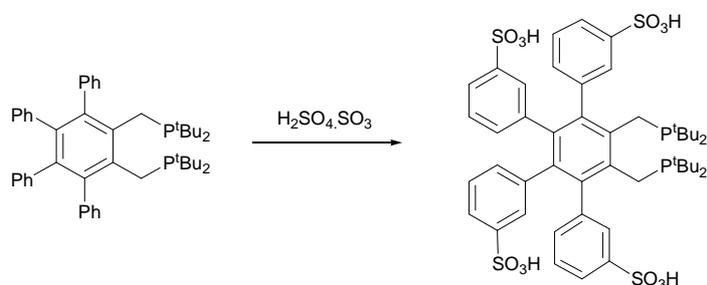


Figure 9-7 - Sulfonation of 1,2-bis(di-*tert*-butylphosphinomethyl)-3,4,5,6-tetraphenylbenzene

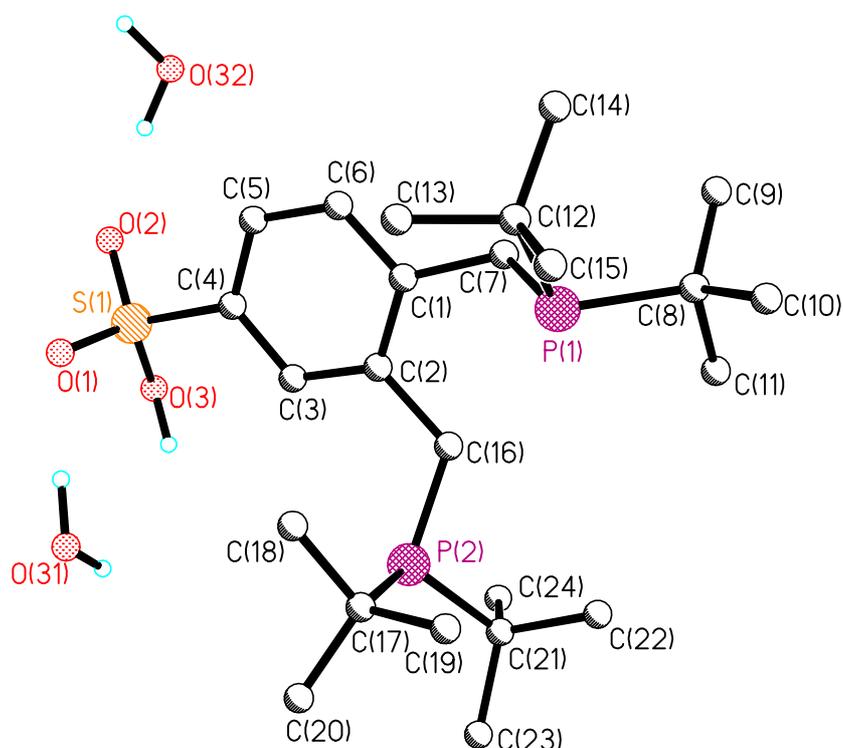
It is likely that this highly polar ligand would be more easily isolated using the direct precipitation and extraction-reextraction techniques discussed in Section 4.2.1.2. Its high polarity may give it additional applications, for example it is likely to be highly water soluble and so may be useful in the production of carboxylic acids by biphasic hydroxycarbonylation of alkenes as was briefly discussed in chapter 6; with the catalyst residing in the aqueous phase for efficient separation. The ligand is also likely to be more soluble in IL's and so may result in a more stable catalyst system for the IL work discussed in Chapter 6.

10. Appendices

10.1 X-Ray Crystal Structure Data

Below is given crystal structure refinement data for all crystal structure determinations discussed in this thesis. Full sets of these data, including atomic coordinates and bond lengths are provided on the CD-ROM enclosed.

10.1.1 3,4-bis(di-*tert*-butylphosphinomethyl)benzenesulfonic acid

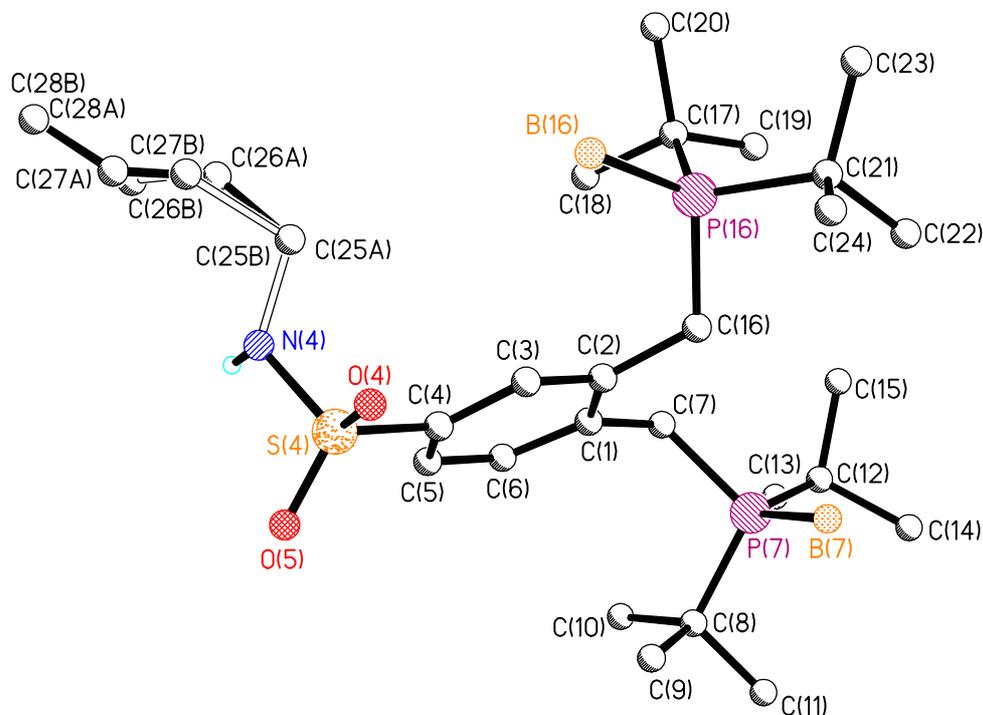


Crystal data and structure refinement

| | |
|---------------------|---|
| Identification code | bpdch4 |
| Empirical formula | C ₂₄ H ₄₈ O ₅ P ₂ S |
| Formula weight | 510.62 |
| Temperature | 93(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |

| | | |
|-----------------------------------|---|-----------------------------|
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 15.209(7) Å | $\alpha = 90^\circ$. |
| | b = 11.808(5) Å | $\beta = 99.347(7)^\circ$. |
| | c = 16.328(7) Å | $\gamma = 90^\circ$. |
| Volume | 2893(2) Å ³ | |
| Z | 4 | |
| Density (calculated) | 1.172 Mg/m ³ | |
| Absorption coefficient | 0.252 mm ⁻¹ | |
| F(000) | 1112 | |
| Crystal size | 0.0300 x 0.0300 x 0.0300 mm ³ | |
| Theta range for data collection | 2.14 to 25.39°. | |
| Index ranges | -18<=h<=18, -14<=k<=14, -17<=l<=19 | |
| Reflections collected | 27582 | |
| Independent reflections | 5215 [R(int) = 0.1647] | |
| Completeness to theta = 25.00° | 98.3 % | |
| Absorption correction | Multiscan | |
| Max. and min. transmission | 1.0000 and 0.3520 | |
| Refinement method | Full-matrix least-squares on F ² | |
| Data / restraints / parameters | 5215 / 4 / 302 | |
| Goodness-of-fit on F ² | 1.009 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0779, wR2 = 0.1814 | |
| R indices (all data) | R1 = 0.1145, wR2 = 0.2082 | |
| Largest diff. peak and hole | 0.714 and -0.611 e.Å ⁻³ | |

10.1.2 *n*-butyl-3,4-bis((di-*tert*-butylphosphino)methyl)benzenesulfonamide-bis(borane) adduct

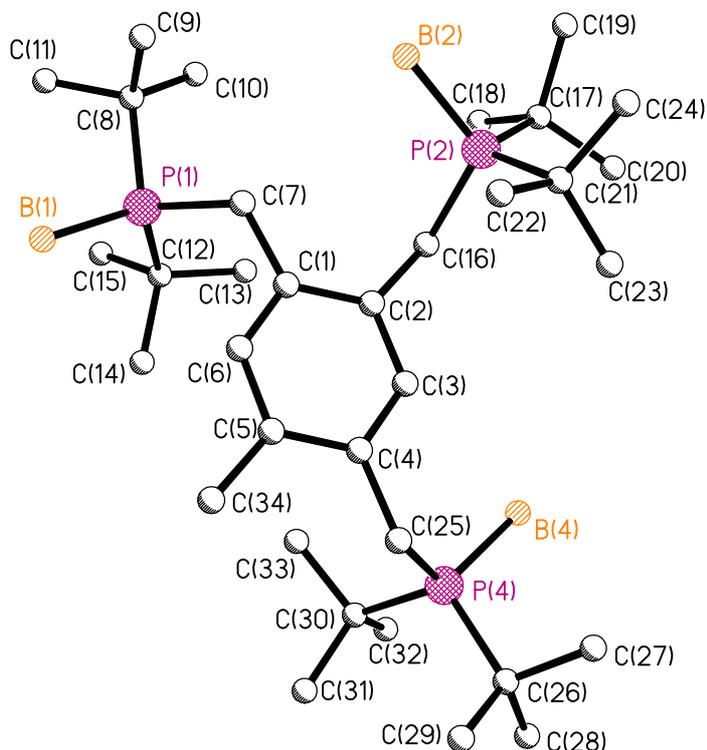


Crystal data and structure refinement

| | | |
|------------------------|--|-----------------|
| Identification code | bpdch1 | |
| Empirical formula | C ₂₈ H ₅₉ B ₂ N O ₂ P ₂ S | |
| Formula weight | 557.38 | |
| Temperature | 93(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 8.3368(9) Å | α = 90°. |
| | b = 30.954(4) Å | β = 97.992(4)°. |
| | c = 13.3063(19) Å | γ = 90°. |
| Volume | 3400.4(8) Å ³ | |
| Z | 4 | |
| Density (calculated) | 1.089 Mg/m ³ | |
| Absorption coefficient | 0.213 mm ⁻¹ | |
| F(000) | 1224 | |
| Crystal size | 0.2000 x 0.1000 x 0.1000 mm ³ | |

| | |
|-----------------------------------|---|
| Theta range for data collection | 2.55 to 25.35°. |
| Index ranges | -8<=h<=9, -37<=k<=36, -15<=l<=9 |
| Reflections collected | 21299 |
| Independent reflections | 6028 [R(int) = 0.0622] |
| Completeness to theta = 25.35° | 97.0 % |
| Absorption correction | Multiscan |
| Max. and min. transmission | 1.0000 and 0.8281 |
| Refinement method | Full-matrix least-squares on F ² |
| Data / restraints / parameters | 6028 / 5 / 349 |
| Goodness-of-fit on F ² | 1.048 |
| Final R indices [I>2sigma(I)] | R1 = 0.0577, wR2 = 0.1387 |
| R indices (all data) | R1 = 0.0676, wR2 = 0.1459 |
| Largest diff. peak and hole | 0.506 and -0.420 e.Å ⁻³ |

10.1.3 1,2,4-tri(di-*tert*-butylphosphinomethyl)-5-methylbenzene triborane adduct



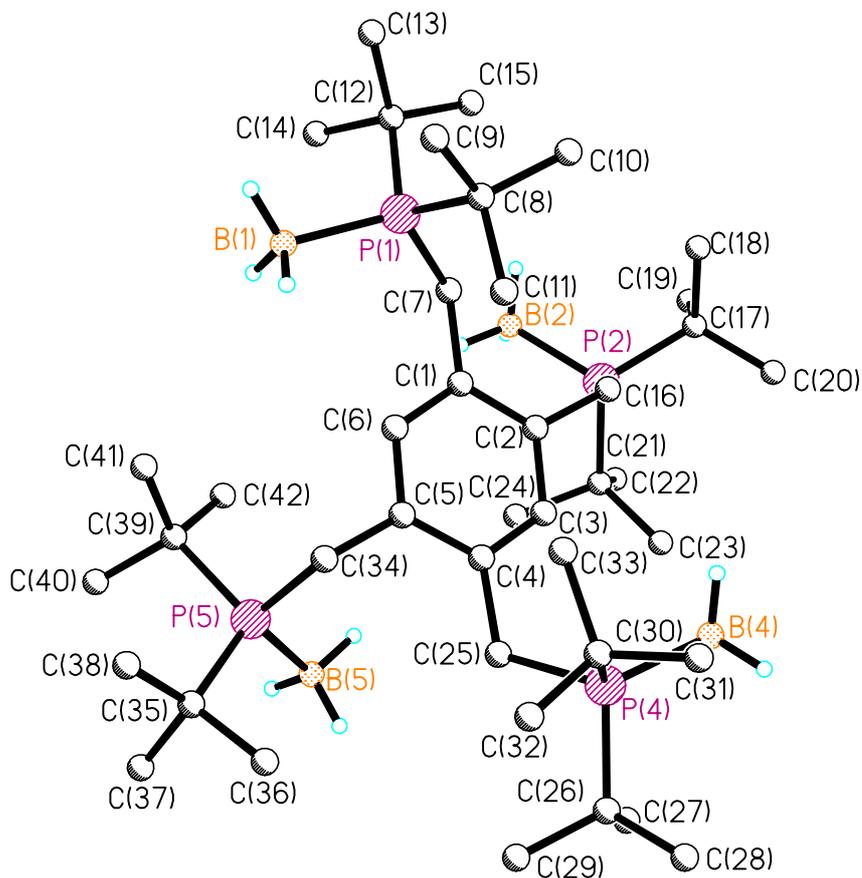
Crystal data and structure refinement

Identification code

bpdch3

| | | |
|-----------------------------------|---|------------------|
| Empirical formula | C ₃₄ H ₇₄ B ₃ P ₃ | |
| Formula weight | 608.27 | |
| Temperature | 93(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Triclinic | |
| Space group | P-1 | |
| Unit cell dimensions | a = 12.122(4) Å | α = 83.405(14)°. |
| | b = 13.012(5) Å | β = 85.412(15)°. |
| | c = 13.214(4) Å | γ = 69.460(14)°. |
| Volume | 1937.2(11) Å ³ | |
| Z | 2 | |
| Density (calculated) | 1.043 Mg/m ³ | |
| Absorption coefficient | 0.174 mm ⁻¹ | |
| F(000) | 676 | |
| Crystal size | 0.100 x 0.030 x 0.030 mm ³ | |
| Theta range for data collection | 3.11 to 25.34°. | |
| Index ranges | -10 ≤ h ≤ 14, -14 ≤ k ≤ 14, -13 ≤ l ≤ 15 | |
| Reflections collected | 11051 | |
| Independent reflections | 6169 [R(int) = 0.0861] | |
| Completeness to theta = 25.34° | 87.1 % | |
| Absorption correction | Multiscan | |
| Max. and min. transmission | 1.0000 and 0.8675 | |
| Refinement method | Full-matrix least-squares on F ² | |
| Data / restraints / parameters | 6169 / 0 / 368 | |
| Goodness-of-fit on F ² | 1.214 | |
| Final R indices [I > 2σ(I)] | R1 = 0.1313, wR2 = 0.2687 | |
| R indices (all data) | R1 = 0.1758, wR2 = 0.2872 | |
| Largest diff. peak and hole | 0.617 and -0.606 e.Å ⁻³ | |

10.1.4 1,2,4,5-tetrakis(di-tert-butylphosphinomethyl)benzene
tetraborane adduct



Crystal data and structure refinement

| | | |
|----------------------|---|-----------------|
| Identification code | bpdch5 | |
| Empirical formula | C _{42.50} H ₉₆ B ₄ Cl O _{0.50} P ₄ | |
| Formula weight | 817.76 | |
| Temperature | 93(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 12.0608(19) Å | α = 90°. |
| | b = 17.455(3) Å | β = 98.734(4)°. |
| | c = 26.735(4) Å | γ = 90°. |

| | |
|-----------------------------------|---|
| Volume | 5563.0(15) Å ³ |
| Z | 4 |
| Density (calculated) | 0.976 Mg/m ³ |
| Absorption coefficient | 0.209 mm ⁻¹ |
| F(000) | 1808 |
| Crystal size | 0.2000 x 0.0500 x 0.0500 mm ³ |
| Theta range for data collection | 1.93 to 25.34°. |
| Index ranges | -10<=h<=14, -20<=k<=18, -32<=l<=31 |
| Reflections collected | 32926 |
| Independent reflections | 9693 [R(int) = 0.0704] |
| Completeness to theta = 25.00° | 95.7 % |
| Absorption correction | Multiscan |
| Max. and min. transmission | 1.0000 and 0.6736 |
| Refinement method | Full-matrix least-squares on F ² |
| Data / restraints / parameters | 9693 / 3 / 476 |
| Goodness-of-fit on F ² | 1.036 |
| Final R indices [I>2sigma(I)] | R1 = 0.0866, wR2 = 0.2272 |
| R indices (all data) | R1 = 0.1222, wR2 = 0.2578 |
| Largest diff. peak and hole | 1.031 and -0.442 e.Å ⁻³ |

10.2 Postgraduate Courses Attended at St. Andrews

- Review article on Irvine review lectures 2003 (Various, 2 of 2 Credits)
- Phosphorus Chemistry (R.A. Aitken, 2 of 2 credits)
- Hot Topics in Catalysis (D.J. Cole-Hamilton / P.A. Wright, 2 of 2 credits)
- Sulfur Chemistry (R.A. Aitken, not examined)

[6 credits obtained out of 4 required]