

## Transition metal catalysed reactions using glass bead technology

Michael S. Anson,<sup>a</sup> Mathew P. Leese,<sup>b</sup> Louise Tonks<sup>b</sup> and Jonathan M. J. Williams<sup>\*b</sup>

<sup>a</sup> *GlaxoWellcome Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, UK SG1 2NY*

<sup>b</sup> *Department of Chemistry, University of Bath, Claverton Down, Bath, UK BA2 7AY*

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**A successful method for rendering homogeneous transition metal catalysts heterogeneous has emerged from glass bead technology. The process generally combines high activity and selectivity with facile recyclability. Glass bead technology, and related approaches, have been applied to a wide range of reactions with results paralleling, and sometimes exceeding, those obtained from their homogeneous counterparts. Outlined is the current scope of this research, with an emphasis on work on supported palladium reagents. A novel approach for the retrieval of precious metals from reaction mixtures stemming from these studies is also outlined.**

### 1 Introduction

It is desirable that a catalyst should possess high activity/catalytic turnover combined with high regio- and stereo-selectivity, indeed these desirable properties have emerged from the development of homogeneous transition metal catalysis over several decades.<sup>1</sup> Yet despite these developments and the

inherent advantages over their heterogeneous counterparts, homogeneous catalysts have been underused by the fine chemical industry partly due to the problematic separation of catalyst and product.

Industrial interest spurred the introduction of biphasic counterparts of the rhodium catalysed hydroformylation in the early 1980s by development and application of water soluble ligands (notably TPPTS **1**, a sulfonated triphenylphosphine analogue) and also served to reinvigorate academic interest in overcoming the technological limitations of the powerful catalysts available.<sup>2,3</sup> Representative anionic and cationic ligands are **1** to **6**.

Although biphasic reactions have proved to be a successful solution in some cases, these reactions are impeded by solubility of substrates in the aqueous layer in which the catalyst resides and a limited interface between the reactants, although this technique does afford the opportunity for rational catalyst design and optimisation.<sup>4</sup>

Many imaginative strategies have been developed for harness-

*Mike Anson received his BSc and PhD from University College London, where he worked with Professor Chris McGuigan until 1988. After 2 years as a post-doc with Professor Mike Blackburn at Sheffield he joined Process Research at Glaxo in 1990. He is currently a team leader at GlaxoWellcome (Stevenage) where he is involved in evaluating new technologies for rapid scale-up.*

*Louise Tonks was born in 1973 in Rochdale, Lancashire. She received her BSc in 1995 from Sheffield Hallam University before moving on to PhD studies with Professor J. M. J. Williams at Loughborough and the University of Bath. Her research interests lie in transition metal catalysis and, in particular, C–C coupling reactions using palladium catalysts supported on glass beads.*

*Mathew Leese was born in Barnsley in 1973. He first studied chemistry at the University of Nottingham, obtaining his BSc in 1994 before joining Professor D. W. Knight to study for a PhD, consequent relocation to the University of Wales, Cardiff followed in late 1995. He also received a Monbusho fellowship to work with Professor T. Takahashi at the Institute of Molecular Sciences, Okazaki, Japan during 1995. After completing his studies he moved to Bath to join Jon Williams group in November 1997 to work on novel catalyst systems.*

*Jonathan Williams obtained his BSc from the University of York in 1986, and then did a D.Phil with Professor Steve Davies at Oxford. After a post-doctoral stay with Professor David Evans at Harvard, and a lectureship at Loughborough University, he moved to the Chair of Organic Chemistry at the University of Bath in 1996. His main research interests are in asymmetric catalytic methods.*



Michael Anson



Louise Tonks

Mathew Leese

Jonathan Williams

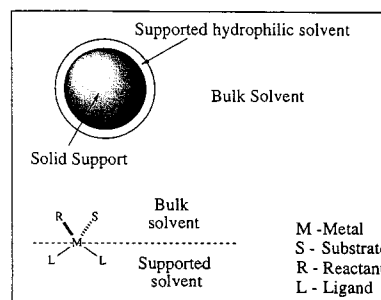
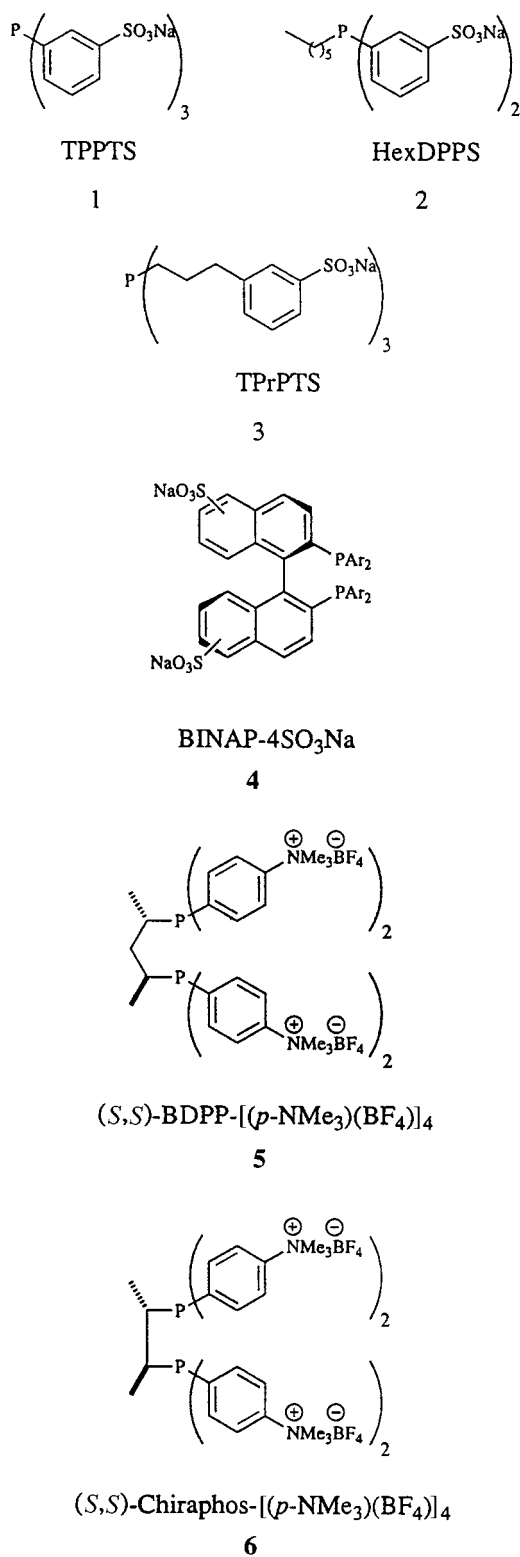


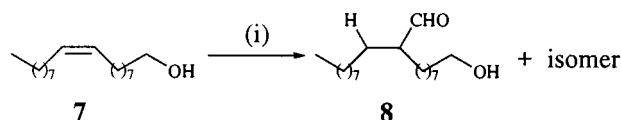
Fig. 1 A schematic of the supported aqueous phase catalyst. The reaction is thought to proceed at the interface.

(surface area of 1 g of CPG-240 = 77.5 m<sup>2</sup>), whilst the catalyst retains mobility within the polar solvent on the bead. In contrast to many other supports the beads are stable to mechanical and thermal fatigue. The essential features of glass bead technology are illustrated in Fig. 1.

The philosophy underlying this approach is long established by supported liquid phase catalysis (SLPC),<sup>7</sup> a technique in which a catalyst supported in a liquid film interacts with substrates in the gaseous phase. This approach is limited to gaseous reactants. Glass bead technology and related approaches have been successfully applied to many transition metal catalysed reactions, and this information is summarised in Table 1. Subsequent sections of this article describe the chemistry in further detail.

## 2 Rhodium hydroformylation catalysts

The catalyst system initially studied by Davis and co-workers<sup>6</sup> was the rhodium hydroformylation catalyst [RhH(CO)(TPPTS)<sub>3</sub>] used in the biphasic reaction.<sup>2,26</sup> Application to glass bead technology is effected by pouring an aqueous solution of the catalyst and an excess of TPPTS onto degassed CPG-240. After further degassing and stirring, the water was removed by evaporation to yield the "dry" catalyst with a water content of 2.9%. The resultant "glass bead catalyst" was tested in the hydroformylation of oleyl alcohol **7** (a water insoluble substrate which is not hydroformylated under biphasic conditions),<sup>8</sup> which provided a good conversion into the hydroformylated product **8** (Scheme 1). An alternative, self assembly method of



Scheme 1 (i) [RhH(CO)(TPPTS)<sub>3</sub>] on CPG-240, cyclohexane, H<sub>2</sub>-CO (1:1), 50 atm, 5.5 h, 100 °C, 96.6% conversion.

catalyst preparation involves loading [Rh(acac)(CO)<sub>2</sub>] on to the bead and then treating with a solution of water soluble phosphine.<sup>9</sup> Ligand exchange in this case proves to be rapid as indicated by the change from white to yellow; and this approach is advantageous in that oxidative catalyst degradation is minimised. In order to maximise catalyst stability it is necessary to use an excess of phosphine (in this case P:Rh ≤ 3:1); it has also been found that the dry glass bead catalyst is more stable to storage.

The water content of the glass bead catalyst has been shown greatly to affect the activity of the catalyst and the selectivity of the reaction. Davis and co-workers<sup>8</sup> reported optimum activity for the rhodium catalysed hydroformylation reaction at a water content of ≈8%. At this level the catalyst has a high degree of mobility and yet is still available at the interface, whereas lower water content suppresses mobility as reflected by lower activity, and higher water content renders the catalyst less available to the water insoluble substrate. Varying the degree of hydration is

ing the power of transition metal catalysis by anchoring the ligands to various solid supports, but the efficacy of modified catalysts is often hampered by the suppression of catalyst mobility stemming from the anchoring process.<sup>5</sup>

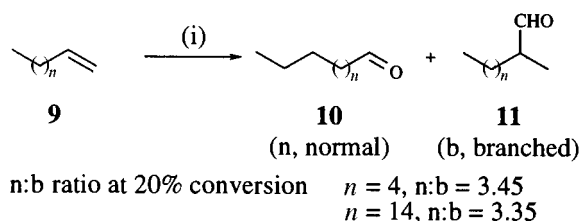
In our eyes, one innovative solution to this problem which appears to offer the ideal union of the chemical advantages of homogeneous catalysis with the practicability of a solid, heterogeneous system is supported aqueous phase (SAP) catalysis, first demonstrated by Arhancet *et al.*<sup>6</sup> in 1989. This technique uses the hydrophilic nature of the surface of controlled pore glasses (CPGs) to adhere a layer of water (or another suitable polar solvent) in which a hydrophilic catalyst can be anchored. This allows a large surface area of catalyst

**Table 1** Current scope of glass bead technology

Reaction	Metal	Ligand L	Catalyst	Substrate(s)	Ref.
Hydroformylation	<b>Rh</b>	TPPTS	[RhH(CO)L <sub>3</sub> ]	Alkenes	8–13,16
		TPPTS	[RhH(CO)L <sub>3</sub> ]	$\alpha,\beta$ -Unsaturated esters	14,15
	<b>Co</b>	HexDPPS	[RhH(CO)L <sub>3</sub> ]	Alkenes	13
		TPPTS	[Co <sub>2</sub> (CO) <sub>6</sub> L <sub>2</sub> ]	Alkenes	17
	<b>Pt</b>	TPPTS	Na <sub>5</sub> [Co(CO) <sub>3</sub> L <sub>2</sub> ]	Alkenes	13
		TPPTS	[PtCl <sub>2</sub> L <sub>2</sub> ]	Alkenes	18
	<b>Pt/Sn</b>	TPPTS	[PtCl(SnCl <sub>3</sub> )L <sub>2</sub> ]	Alkenes	18
		TPPTS	[PtCl(SnCl <sub>3</sub> )L <sub>2</sub> ]	Alkenes	13
		( <i>S,S</i> )-BDPP*	[PtCl(SnCl <sub>3</sub> )L]	Styrene	13
	Hydrogenation	<b>Ru</b>	BINAP*	[Ru(C <sub>6</sub> H <sub>6</sub> )L(Cl)]Cl	Alkenes
TPPTS			[RuCl <sub>2</sub> L <sub>3</sub> ]	$\alpha,\beta$ -Unsaturated aldehydes	22
TPPTS			[RuH <sub>2</sub> L <sub>3</sub> ]	$\alpha,\beta$ -Unsaturated aldehydes	22
<b>Rh</b>		( <i>S,S</i> )-BDPP*	[Rh(COD)L]BF <sub>4</sub>	Alkenes	13
		Chiraphos*	[Rh(COD)L]BF <sub>4</sub>	Alkenes	13
			PdCl <sub>2</sub> -CuCl <sub>2</sub>	Alkenes	23
Wacker oxidation	<b>Pd/Cu</b>	TPPTS	[PdCl <sub>2</sub> L <sub>2</sub> ]	Aryl halides	24
Heck reaction	<b>Pd</b>	TPPTS	[PdCl <sub>2</sub> L <sub>2</sub> ]	Aryl halides	24
Suzuki reaction	<b>Pd</b>	TPPTS	[PdCl <sub>2</sub> L <sub>2</sub> ]	Aryl halides	—
Allylic substitution	<b>Pd</b>	TPPTS	[PdCl <sub>2</sub> L <sub>2</sub> ]	Allyl acetates	24,25

\* Water soluble derivative of this ligand as illustrated.

achieved by exposure of the catalyst to a known vapour pressure of water or by water transfer from hydrated controlled pore glass beads. The activity difference between the hydrated and “dry” glass bead catalysts has been reported to be typically two or more orders of magnitude.<sup>10</sup> The water content is also seen to influence the regioselectivity of the reaction which can be ascribed to a variation in catalytic pathway. The hydroformylation of hept-1-ene yields similar results in terms of conversion and n:b ratio as that of tetradec-1-ene and heptadec-1-ene (Scheme 2).



**Scheme 2** (i) [RhH(CO)(TPPTS)<sub>3</sub>] on CPG-240, cyclohexane, H<sub>2</sub>-CO (1:1), 6.8 atm.

The dependence on water content was also reported by Horváth,<sup>11</sup> starting from high water content the activity of the catalyst in a trickle bed reaction was seen to increase as water leached from the bead into the organic layer until the water content was only sufficient to supply two monolayers to the surface of the controlled pore glass bead. This corresponds to greater presence of the active site of the mobile catalyst at the interface, instead of a catalyst immersed in the supported solvent.

Once the catalyst is placed on the bead structural elucidation becomes more complex, and inferences on the actual catalytic species can only be made with respect to the observed activity of the catalyst compared with the homogeneous and biphasic counterparts. Infrared spectroscopy can be used on the reaction solution and indicates the absence of rhodium carbonyls in the reaction, but low catalyst loading, combined with the broad silica band at  $\approx 1850\text{ cm}^{-1}$  render both diffuse reflective and transmission IR ineffectual for the study of the glass bead systems.

In the solution phase the catalyst, [RhH(CO)(TPPTS)<sub>3</sub>], loaded onto the bead exists as a trigonal bipyramid with the phosphines occupying the equatorial positions. Solid phase <sup>1</sup>H NMR techniques on the dry catalyst suffice only to confirm the presence of the phosphine ligands, whilst CP MAS <sup>31</sup>P NMR indicates that the phosphines are stationary in the dehydrated

catalyst. Fortunately, once the catalyst is partially hydrated then normal solution phase NMR techniques can be utilised and indicate mobility of the phosphine ligands in the supported solvent layer.<sup>27</sup> Electron microprobe analysis has been utilised to reveal a uniform Rh:P ratio across the surface of the catalyst.<sup>8</sup>

Horváth<sup>11</sup> conducted further studies on the rhodium catalysed hydroformylation in order to investigate the exact nature of the catalyst itself. The ratio of straight to branched products (n:b ratio) of the reaction varies greatly between the supported aqueous phase catalyst and the biphasic reaction, indicating the mechanistic difference between the two cases. On comparison of the supported aqueous phase reaction and its homogeneous and biphasic analogues the nature of the rhodium centre was proposed from a consideration of the branched to straight chain ratio of the aldehyde products; in the case of the biphasic reaction the n:b ratio is high suggesting the catalytic rhodium species is [RhH(CO){P(C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>Na-*m*)<sub>3</sub>}<sub>2</sub>] with the two phosphines in the *trans* position. The glass bead catalyst system produces an n:b ratio, similar, yet slightly higher than the homogeneous system in which the key intermediates are either [RhH(CO)(PPh<sub>3</sub>)<sub>2</sub>] or [RhH(CO)<sub>2</sub>(PPh<sub>3</sub>)],<sup>28</sup> leading Horváth to propose that the catalytic species in the glass bead catalyst system is [RhH(CO)<sub>2</sub>{P(C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>Na-*m*)<sub>3</sub>}], although the possibility that a complex with two phosphines with a *cis* configuration could produce the same result was acknowledged.<sup>29,30</sup> Davis proposed this effect may stem either from the higher effective phosphine concentration in the glass bead or a different catalytic species for the glass bead catalyst.<sup>19,20</sup>

Yuan *et al.*<sup>12</sup> investigated the effect of codeposition of alkali metal salts on the surface of the beads prior to hydration. The resultant glass bead catalysts were reported to benefit in terms of both activity and n:b ratios in the hydroformylation of terminal alkenes when the ratio KCl:Rh was in the range 2–10:1. Addition of salt can be expected to assist CO insertion in alkyl ligands by stabilising the polar transition state thus increasing the steady state concentration of the acyl intermediate, leading to an increase in turnover frequency.

Tóth *et al.*<sup>13</sup> synthesized HexDPPS **2** in order to attempt to make the ligand more surface active, with the reasoning that the lipophilic chain should bring the metal closer to the interface. In fact the supported aqueous phase catalyst formed from this ligand proved to be less active, yet showed similar n:b ratios, no sign of leaching and was recyclable. The analogies were suggested to reflect the similar action of the ligand, whilst reinforcing the previous conclusions that the TPPTS analogues act at the interface.

Frémy *et al.*<sup>14,15</sup> reported that hydroformylation using supported aqueous phase catalysis can proceed with higher turnover frequencies than the analogous homogeneous reaction. Methyl acrylate, a polar substrate, was subjected to the hydroformylation reaction introduced by Davis (see above) with silica as the support, and proved to yield average turnover frequencies over ten times greater than those observed for the analogous biphasic and homogeneous reactions, this effect being ascribed to the beneficial interactions between methyl acrylate, supported solvent and surface hydroxyl groups.

Once again a great dependence of activity on water content was observed, which is in contrast to Davis's results for non-polar substrates, thus reflecting the high degree of dependence on substrate functionality. Optimum conditions were realised with total pore filling; a steady rise in activity is observed as pore filling increases to unity, once water content exceeds this level however the activity drops rapidly and approaches that of the biphasic system. This result was initially obtained using silica gel (60 Å) as a support; subsequent studies show different silicas gave identical activity as a function of the degree of pore filling. Interestingly for these supports catalyst performance is independent of mean pore diameter and surface area. Supported aqueous phase catalysts were also prepared from CPG-240 and -350 (controlled pore glasses with a mean pore diameter of 240 and 350 Å respectively) in order to compare the effect of these more defined particles; surprisingly they were shown to exhibit lower activities than the far cheaper silica analogues, an effect that may be due to the higher surface area of the silica as, in this reaction, the solvent content is such that the pores are full. Reasonable catalytic activity was also observed when molecular sieves and alumina were used as the support. Substrates which were less polar than methyl acrylate reacted with optimum activity at low pore filling, where a large surface area contact was required.

The use of alternative supported hydrophilic layers in the hydroformylation reaction has been investigated by Naughton and Drago,<sup>16</sup> who, after studying the catalytic properties of their system proposed the term supported homogeneous film catalysts (SHFCS). High boiling point liquid or liquid polymer films containing the hydrophilic rhodium catalyst [RhH(CO)(TPPTS)<sub>3</sub>] on the surface of silica were synthesized in an analogous manner to that described previously by Davis and co-workers.<sup>9,10</sup>

Polyethylene glycol was selected for its ability to form films, its non-volatile nature, its insolubility in substrate and product, and its ability to dissolve and retain the catalyst. The activity of the bare bead (in effect Davis's dry catalyst) showed low activity, addition of sufficient polyethylene glycol (PEG 600, average molecular weight 600) to give a pore filling ( $\delta$ ) of 0.5 doubled the activity (TOF 2.6 min<sup>-1</sup>), whilst use of water-PEG 600 (1:1) gave a further increase in activity (TOF 8.3 min<sup>-1</sup>,  $\delta = 1.4$ ). It was found that, in the hydroformylation of hex-1-ene, activities of 24.7 min<sup>-1</sup> and n:b ratios of 6:1 could be achieved by using a pore filling of 1.4 (100 °C and 85 psig; psi  $\approx$  6895 Pa) which compares well with the homogeneous analogue under identical conditions which gives TOF 68 min<sup>-1</sup> and n:b 3.

In contrast to the homogeneous reaction it was found desirable to carry out the reaction without the addition of bulk solvent. In the hydroformylation of oct-1-ene a reduced activity (when compared with hex-1-ene) is observed which is thought to reflect the lower solubility of the substrate in the film. Interestingly the activity of the catalyst in this case increases as the reaction proceeds; this is ascribed to retention of the product in the film (as evidenced by IR spectroscopy) which can then function as a surfactant and thus increases the rate of transfer of the substrate into the film.

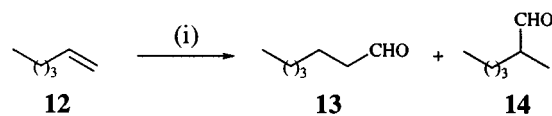
Here the observed dependence of TOF on the solubility of the substrate contrasts with that for the supported aqueous phase catalysts reported previously, and leads the authors to

suggest that the substrate is dissolved in and then reacts in the film. A number of results support this conclusion. (i) Use of a more viscous PEG film (PEG 8000) serves to impede the reaction; if the catalyst were solely active at the interface then the detrimental effect of increased viscosity would not be expected. Indeed modification of this catalyst by addition of water was responsible for an increase in activity reflecting increased reaction rate from reduced viscosity of the film. (ii) Addition of a surfactant to the catalyst for the octene hydroformylation is accompanied by an increase in initial TOF which parallels that of the pure PEG film after longer reaction times. (iii) The optimum pore filling is 1.4 (compared with 0.06 for the normal supported aqueous phase catalyst) which corresponds to full pores in the support and is approaching the level at which droplets form on the bead.

The film has some solubility in concentrated solutions of the aldehyde product, which is reflected by some leaching of the PEG into the bulk, yet no leaching of the metal is observed. Some suppression of PEG leaching could be achieved by addition of sodium sulfate to the film. Alternative films of polyvinylpyrrolidone, polyethylene oxide and polyvinyl alcohol showed drastically reduced activity or no activity.

### 3 Cobalt hydroformylation catalysts

Glass bead technology has been applied to cobalt reagents for the hydroformylation reaction of alkenes.<sup>17</sup> The cobalt complex [Co<sub>2</sub>(CO)<sub>6</sub>(TPPTS)<sub>2</sub>] has been investigated as a cheap alternative to rhodium catalysts in biphasic hydroformylations but suffers from much lower activity.<sup>31</sup> Another drawback of the biphasic reaction is the high leaching levels stemming from the equilibria in which the catalyst likely exists with the organic soluble dicobalt octacarbonyl [Co<sub>2</sub>(CO)<sub>8</sub>] and hydridocobalt tetracarbonyl [CoH(CO)<sub>4</sub>] species under the high pressure of CO and H<sub>2</sub> in the reaction. The glass bead cobalt catalyst displays greatly reduced leaching (a tenth of the biphasic counterpart); a twofold excess of phosphine complements the relative increase in phosphine concentration already apparent on the bead surface to yield this desirable effect. It is notable that in contrast with the rhodium system little dependency of activity of the catalyst is observed with a variation in water content of the support; this may imply little relationship of catalyst mobility and activity, alternatively the substrate phase may be homogeneous at the high temperature at which the reaction takes place. Significantly the activity of the supported catalyst does not correlate with cobalt leached to the organic phase, indicating the catalytic species to be cobalt supported on the glass. This conclusion is supported by the higher n:b ratio obtained in the reaction, which is similar to the equivalent homogeneous reaction (Scheme 3). The n:b ratio is double that observed for



Loading <sup>a</sup>	Water (ml)	TOF <sup>b</sup>	Leaching <sup>c</sup>
200	5.0	27.2	0.8
200	0.5	25.6	0.4
50	0.5	51.4	0.1

<sup>a</sup> mg of catalyst. <sup>b</sup> TOF per mole cobalt h<sup>-1</sup>.

<sup>c</sup> % total Co.

**Scheme 3** (i) [Co<sub>2</sub>(CO)<sub>6</sub>(TPPTS)<sub>2</sub>] on CPG-340 (3 g), toluene (50 ml), H<sub>2</sub>-CO (1:1), 54 atm, 190 °C, 8 h.

the biphasic reaction implying an alternative reaction path whilst lower loading levels are accompanied by higher activity per mole cobalt suggesting that much of the cobalt in the

supported aqueous phase catalyst is unavailable for catalytic activity.

In an attempt to suppress displacement of the phosphine ligands in the desired catalyst  $[\text{Co}_2(\text{CO})_6(\text{PR}_3)_2]$  by CO to yield a less selective catalytic species, the same research group synthesized alkylphosphines with sulfonated aromatic groups to serve as anchors.<sup>13</sup>

#### 4 Platinum hydroformylation catalysts

Hanson and co-workers<sup>18</sup> have explored hydroformylation with  $[\text{Pt}(\text{TPPTS})_2\text{Cl}_2]$ . The non-sulfonated phosphine complex  $[\text{Pt}(\text{PPh}_3)_2\text{Cl}_2]$  is not active in homogeneous hydroformylation reactions, yet for both biphasic and glass bead catalyst conditions the TPPTS complex does serve as a catalyst. This activation by the modified ligand is attributed to the sulfonate group functioning as a ligand in analogy with the activation of other platinum complexes by the addition of methanesulfonic acid.<sup>32</sup>

Platinum hydroformylation catalysts are commonly activated by tin(II) chloride as cocatalyst, however Pt–Sn bonds are subject to facile hydrolysis and for this reason were not considered likely candidates for water soluble catalysts. However, it is possible to use only a minimum amount of water on the surface of the glass bead to anchor the sulfonate groups, therefore allowing the possibility of using supported aqueous phase conditions to support a catalyst which is inherently unstable in water.

Catalyst preparation in this case was achieved by deposition of complex **15** (*cis* isomer) on the bead as described above; the tin analogue complex **16** was then synthesized by treating the dried beads with 2 equivalents of tin(II) chloride in dichloromethane. Evaporation of solvent gives a system with a water content of just 1.4%. A colour change (yellow to orange) is observed but no direct analytical evidence of the formation of the platinum–tin complex could be obtained so that inferences on structure were made from the activity of the derived catalyst.

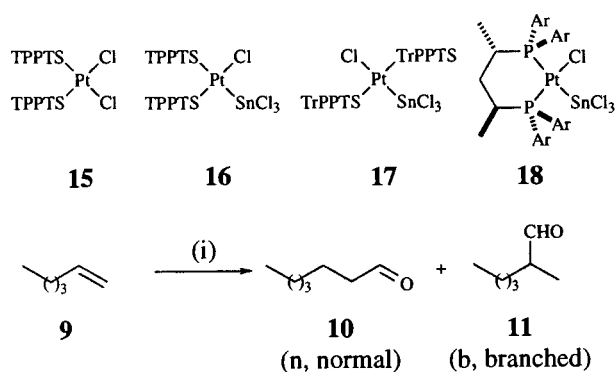
Both catalysts showed similar activity in the hydroformylation reaction yet exhibit a drastic difference in regioselectivity. Complex **15** under identical reaction conditions gives an n:b ratio of 3.0:1 whilst the tin modified catalyst **16** gives an n:b ratio of 11.5:1 (consistent with the results obtained in the homogeneous analogue of the reaction), Scheme 4.

In order to try to make the catalyst more remote from the anchoring aqueous layer ligands with varying alkyl chains separating the phosphine from the anchoring hydrophilic groups were employed.<sup>13</sup> In contrast to TPPTS, the platinum complex **17** formed from the sulfonate anchored alkyl ligands is formed as the *trans* complex as is usual for monodentate ligands, although this detail may be insignificant due to the equilibrium in which the catalytic intermediates exist. The Pt–Sn hydroformylation catalyst was prepared as before and showed similar selectivities to that of the analogous homogeneous reaction, although in contrast to the reactions above it shows greatly reduced activity. Again, no leaching is observed from this catalyst.

Asymmetric hydroformylation with an enantiomerically pure platinum catalyst **18** has been demonstrated by Tóth *et al.*<sup>13</sup> although only with modest enantioselectivity.

#### 5 Asymmetric hydrogenation

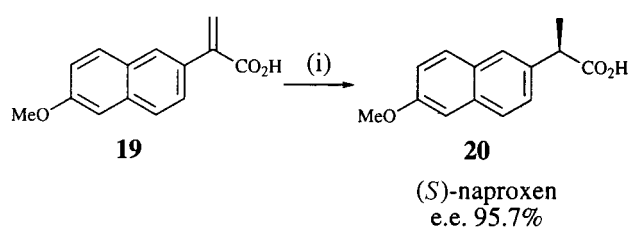
Wan and Davis<sup>19</sup> then went on to explore the possibility of applying glass bead catalysts to asymmetric hydrogenation reactions. The polar ruthenium complex  $[\text{Ru}(\text{C}_6\text{H}_6)(\text{BINAP-4SO}_3\text{Na})\text{Cl}]\text{Cl}$  was examined in homogeneous, heterogeneous and glass bead cases. The chosen substrate for the studies was 2-(6-methoxy-2-naphthyl)acrylic acid **19**, whose hydrogenation product is the important non-steroidal anti-inflammatory drug, naproxen **20** (Scheme 5). As expected the homogeneous case proved to be the most active and gave high enantioselectivities,



Complex	n:b	TOF <sup>-1 a</sup>
<b>15</b> <sup>b</sup>	2.84	2.63
<b>15</b> <sup>c</sup>	3.01	1.68
<b>16</b> <sup>c</sup>	11.5	2.17
<b>17</b> <sup>d</sup>	8.71	2.60
<b>17</b> <sup>e</sup>	7.19	53.0

<sup>a</sup> Per hour. <sup>b</sup> Two-phase reaction. <sup>c</sup> SAP reaction. <sup>d</sup> 8h. <sup>e</sup> Homogeneous reaction of non-sulfonated complex.

Scheme 4 (i) Platinum catalyst on CPG-350 (3 g), toluene, H<sub>2</sub>–CO (1:1), 69 atm, 100 °C, 120 h.



Scheme 5 (i)  $[\text{Ru}(\text{C}_6\text{H}_6)(\text{BINAP-4SO}_3\text{Na})\text{Cl}]\text{Cl}$  on CPG-240, ethyl acetate, 95 atm, H<sub>2</sub>, 3 °C.

reflecting the intimacy of mixing of catalyst and substrate in this case.

The homogeneous reaction carried out in methanol–water (1:1) showed high activity but diminished enantioselectivity when compared to the same reaction in methanol (77.6 vs. 87.5% enantiomeric excess, e.e.) and is thought to reflect the crucial role of the easily hydrolysed chloro ligand in maximising enantioselectivity. Addition of triethylamine was also observed to have a beneficial effect on enantioselectivity.

The dry supported phase catalyst is inactive in the reaction, yet when water is added to the reaction to hydrate the catalyst, activities fifty times greater than those of the biphasic reaction and only seven times slower than the homogeneous system are observed. The supported aqueous phase reaction was carried out with ethyl acetate as the bulk solvent and the extent of catalyst hydration is limited by the solubility of water in this solvent. Increased loadings of water in the system are accompanied by increased activity and enantioselectivity though this still falls short of the selectivity of the heterogeneous system due to aquation of the Ru–Cl bond. Improvements in enantioselectivity are possible by decreasing the temperature of reaction but at severe cost to the turnover frequency. This report demonstrates the practical approach of glass bead technology to enantioselective hydrogenation limited only by the intrinsic selectivity of the reaction in water.

Further development of this reaction came in the form of substitution of water as the supported solvent by ethylene

glycol,<sup>20,21</sup> a polar solvent immiscible with most organic solvents. The <sup>31</sup>P NMR spectrum of a solution of the catalyst in ethylene glycol-methanol (1:1) is identical to that in methanol (a doublet) indicating the integrity of the catalyst, [Ru(C<sub>6</sub>H<sub>6</sub>)(BINAP-4SO<sub>3</sub>Na)Cl]Cl, whereas addition of water leads to production of the singlet due to scission of the Ru-Cl bond.

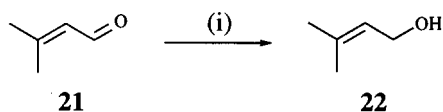
By taking the dry catalyst prepared by standard methods (see below) and stirring in a solution of ethylene glycol in ethyl acetate the solvated supported catalyst is formed. Once again the catalytic activity is seen to be dependent on the amount of solvent on the bead, crucially in this case the enantioselectivity matches that of the homogeneous case whilst the activity observed is three times greater than those of the previously tested supported aqueous phase catalysts (as is also reflected by a 50 fold increase in activity of the biphasic case between ethylene glycol and water). However this method of *in situ* preparation is also accompanied by leaching of the ruthenium into the bulk organic probably stemming from the greater relative solubility of ethylene glycol in the bulk when compared to water.

An alternative preparation of the active catalyst which overcomes this problem involves separation of the ethylene glycol impregnated beads from the bulk by filtration and vacuum drying in two cycles. The bulk organic solvent is then saturated with ethylene glycol, mass transfer between the two phases is thus minimised and no leaching is observed. Thus Davis realised the practical preparation of a recyclable heterogeneous catalyst for asymmetric hydrogenation displaying high activity and enantioselectivity directly comparable to that of its homogeneous counterpart (88.4 vs. 88.2% at r.t., increasing to 95.7% at 3 °C).

Additionally, Tóth *et al.*<sup>13,33</sup> synthesized and utilised rhodium complexes of water soluble derivatives of enantiomerically pure bidentate phosphine ligands for asymmetric hydrogenation.

## 6 Hydrogenation of $\alpha,\beta$ -unsaturated aldehydes

A Rhône-Poulenc group investigated the hydrogenation of  $\alpha,\beta$ -unsaturated aldehydes to allylic alcohol with supported aqueous phase catalysts formed from silica (Merck 60H), [RuCl<sub>2</sub>(TPPTS)<sub>3</sub>] and [RuH<sub>2</sub>(TPPTS)<sub>4</sub>].<sup>22</sup> The non-supported solid catalyst showed little activity in the reaction in contrast to the supported catalysts for which conversions of 100% together with selectivity of 88.5% were obtained in the hydrogenation of 3-methylbut-2-enal **21** to give the product 3-methylbut-2-enol **22** (Scheme 6). It was possible to recycle the catalyst and suc-



**Scheme 6** (i) [RuH<sub>2</sub>(TPPTS)<sub>2</sub>] on Merck 60H silica, hexane, 99 atm H<sub>2</sub>, 50 °C, 3 h.

cessfully maintain the selectivity of reaction but yields are seen gradually to diminish. The reduced catalytic activity was attributed to poisoning of the catalyst by reactant and product whose presence on the beads after use was evidenced by IR spectroscopy and microanalysis; no mention was made of phosphine oxidation in this report although it has been cited as the limiting factor in recycling in other supported aqueous phase catalysts (see above).

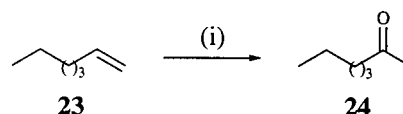
Use of a polar solvent in the reaction (methanol) led to reduced activity when compared to hexane and leaching of catalyst whilst an attempt to use the substrate as reaction solvent gave good selectivities but low yields.

## 7 Wacker oxidation

The Wacker oxidation is a palladium/copper catalysed partial

oxidation of an alkene.<sup>34</sup> One feature of this reaction is that although the oxidant is molecular oxygen the incorporated oxygen comes from the water,<sup>35</sup> hence the reaction is usually carried out in aqueous solvent which retards the oxidation of sparingly soluble higher alkenes, a limitation which may be overcome by the application of supported aqueous phase catalysis.

A supported aqueous phase catalyst was prepared by deposition of a 1:1 ratio of the metals as their respective dichlorides from aqueous solution.<sup>23</sup> In the oxidation reaction the catalyst is first hydrated by either direct treatment with water or water transfer from controlled pore glass beads of known water content; this latter method proves superior than the hydration process because it appears to be less disruptive to the catalyst surface. The oxidation of hept-1-ene **23** into heptan-2-one **24** (Scheme 7) was chosen for the study, with temperatures



**Scheme 7** (i) PdCl<sub>2</sub>-CuCl<sub>2</sub> on CPG-240, hexane, 4 atm O<sub>2</sub>, 3 h, 100 °C.

of 100–130 °C and varying pressure of oxygen. Optimum activities were obtained with much greater water content than the hydroformylations above, probably reflecting the fact that there are no hydrophilic ligands employed in the Wacker chemistry. Conversions of hept-1-ene under optimum conditions were found to be of the order of 25% with significant isomerisation to hept-2- and -3-ene taking place during the course of the reaction. A high dependence on oxygen pressure was also noted, which is in contrast to the homogeneous system and was proposed to reflect the increased difficulty of palladium reoxidation by the Cu<sup>2+</sup>/Cu<sup>+</sup>/O<sub>2</sub> couple in the supported phase case. At temperatures above 100 °C the conversion and selectivity rapidly fall off reflecting the domination of isomerisation at higher temperatures; again this problem is much more pronounced for the supported aqueous phase system when compared to the homogeneous analogue. Importantly an increase in palladium content of the catalyst is accompanied by increased conversion of heptene into product. No leaching of copper or palladium was observed down to the detection limits of 1 and 2 ppm respectively.

## 8 Palladium catalysed Heck reactions

Our own research efforts at the University of Bath have centred around applications of palladium catalysed reactions using glass bead technology.

The Heck reaction is synthetically important, and has previously attracted interest in the development of a heterogeneous variant. One such example uses modified silica supports impregnated with various palladium catalysts to carry out the Heck reaction of iodobenzene **25** with methyl acrylate **26** to afford the coupled product methyl cinnamate **27**.<sup>36</sup> Another method uses palladium supported on porous glass tubing as a catalyst (without ligand) for Heck coupling reactions.<sup>37</sup> Additionally, there is a significant body of knowledge on the use of polar catalysts for aqueous phase Heck reactions.<sup>38</sup> Palladium catalysed coupling reactions utilising water-soluble ligands in aqueous media have been reviewed.<sup>39,40</sup> Dibowski and Schmidtchen<sup>41</sup> investigated the synthesis and use of various guanidinium phosphines in aqueous Heck reactions. Other Heck reactions have involved the coupling of halogenoarenes to ethylene.<sup>42</sup>

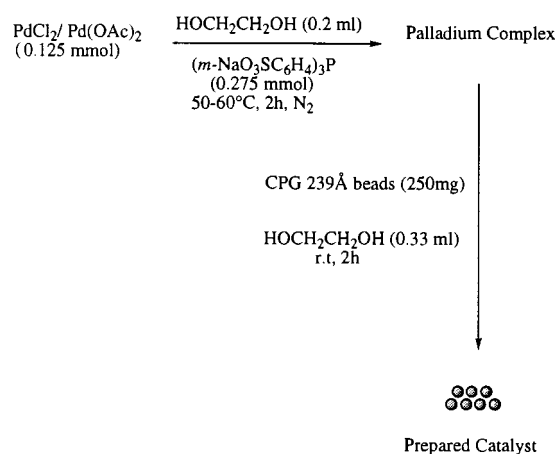
Simple palladium coupling reactions catalysed by mono- and tri-sulfonated triphenylphosphine palladium complexes have been carried out at the University of Bath using glass bead

**Table 2** Preparation of methyl cinnamate **27** using the Heck reaction and glass bead technology

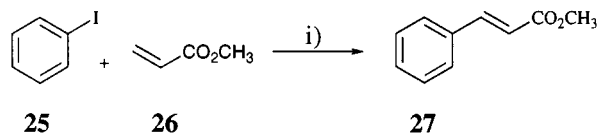
Beads	Ligand	Catalyst	t/h	Yield (%)	Palladium leaching (ppm)
CPG 239 Å	TPPMS	PdCl <sub>2</sub>	25	71	0.5
CPG 239 Å	TPPMS	Pd(OAc) <sub>2</sub>	25	63	0.5
CPG 239 Å	TPPTS	PdCl <sub>2</sub>	25	75	0.2
CPG 239 Å <sup>a</sup>	TPPTS	PdCl <sub>2</sub>	25	27	0.4
CPG 290 Å <sup>b</sup>	TPPMS	PdCl <sub>2</sub>	48	61	0.4
CPG 120 Å	TPPMS	PdCl <sub>2</sub>	23	74 <sup>c</sup>	2.5
CPG 500 Å	TPPMS	PdCl <sub>2</sub>	24	59 <sup>c</sup>	8.4
Davisil 300 Å	TPPMS	PdCl <sub>2</sub>	21	73 <sup>c</sup>	2.5

<sup>a</sup> The fourth run using the same prepared catalyst. <sup>b</sup> Reaction performed at room temperature. <sup>c</sup> For these reactions only, the quoted figures are conversions rather than isolated yields. These reactions were performed using 5 mol % Pd, at a concentration of 1.9 mmol in 5 ml.

technology. The constitution of the glass bead/palladium catalyst was found to have a highly significant effect on reaction rates, as well as on the amount of palladium leaching (see below). A general purpose catalyst could be prepared as follows.<sup>24</sup> The palladium catalyst (based on chloride or acetate) was treated with 2.2 equivalents of the polar ligand TPPTS in the minimum amount of ethylene glycol.<sup>43</sup> After heating to ensure complexation, controlled pore glass beads were added as well as additional ethylene glycol.<sup>44</sup> After stirring, to facilitate an even coating of the palladium complex onto the beads, they were cooled and freeze dried.<sup>45</sup> The freeze dried catalyst is stable and can be resolvated by dosing with ethylene glycol prior to use in reactions. Addition of 10% w/w ethylene glycol to glass beads provided a robust and active catalyst (Scheme 8).

**Scheme 8**

The prepared catalysts derived from either palladium chloride or acetate were examined for their ability to catalyse the Heck reaction. Thus, iodobenzene and methyl acrylate were treated with the prepared palladium catalyst (1 mol % based on palladium) in the presence of triethylamine in hexane-diethyl ether (4:1) as solvent (Scheme 9). At the end of the

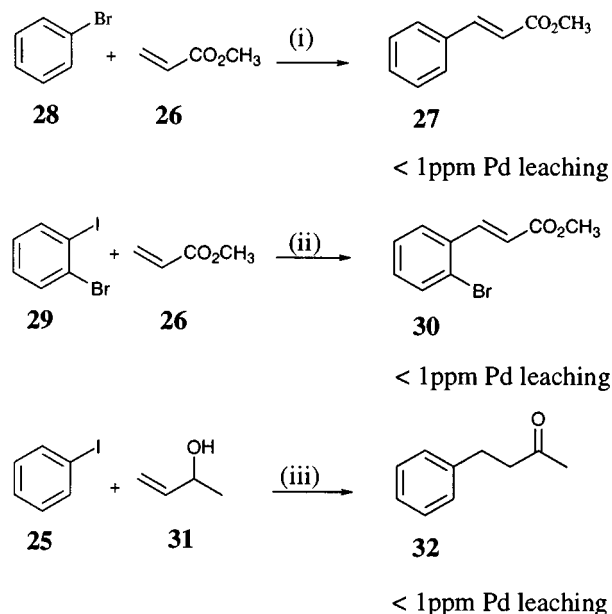
**Scheme 9** (i) mol % prepared catalyst, Et<sub>3</sub>N, hexane-diethylether, (4:1), reflux.

reaction the solution was decanted from the glass beads and analysed for leaching of palladium.<sup>46</sup>

The basic palladium catalysed Heck reaction using glass bead technology was optimised using different glass beads, ligands, and the results are summarised in Table 2. It was observed that the use of TPPTS rather than TPPMS (which is the analogous monosulfonated triphenylphosphine ligand) in

the catalyst complex resulted in less leaching of the palladium complex from the beads after performing the simple Heck reaction as described above and a greater yield. This is probably attributed to the stronger hydrophilic nature of the TPPTS palladium complex; TPPTS reactivates the catalyst and an excess of ligand stabilises the system against decomposition.<sup>39</sup> The glass bead catalysts do work in subsequent reactions but a reduction in yield is observed, which is thought to be due to oxidation of phosphines rendering a less competent catalyst. This was proved by disintegration of the complex by dissolving it in methanol after the third reaction. A phosphorus NMR analysis was performed, and the results showed a greater level of phosphine oxide compared with the original ligand used in the initial experiment.

After catalyst optimisation, the prepared catalysts derived from either palladium chloride or acetate were tested to see if they could catalyse other Heck reactions.<sup>24</sup> Thus, bromobenzene **28** and bromiodobenzene **29** also underwent coupling reactions with methyl acrylate to produce the cinnamate products **27** and **30** in moderate yields with low levels of palladium leaching (Scheme 10). The coupling of iodobenzene **25** with the

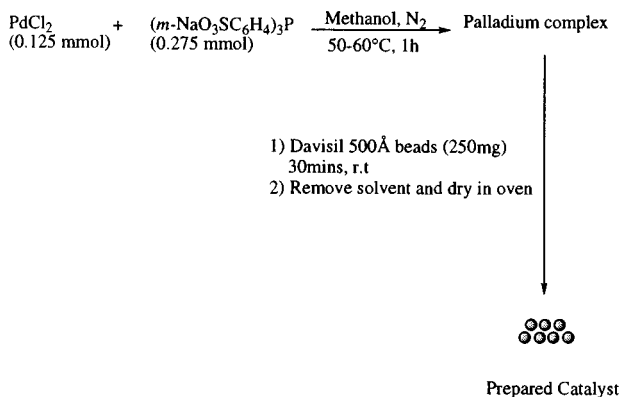
**Scheme 10** (i) 1 mol % prepared catalyst, PdCl<sub>2</sub>, Et<sub>3</sub>N, hexane-diethylether (4:1), reflux, 46 h, 54%; (ii) 1 mol % prepared catalyst, Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, hexane-diethyl ether (4:1), reflux, 47 h, 59%; (iii) 1 mol % prepared catalyst, Pd(OAc)<sub>2</sub>, Et<sub>3</sub>N, hexane-diethyl ether, (4:1), reflux, 48 h, 88%.

allylic alcohol **31** afforded the ketone **32**.<sup>47</sup> In all cases above the catalyst was shown effectively to catalyse the Heck reactions and consistently low levels of leaching into the product were observed. However, this catalyst system was not deemed suitable for use with very polar substrates (such as acrylic acid),

since they afforded low yields of substitution and high levels of leaching, which we attributed to their affinity for the more polar supported phase.

Several procedures for the preparation of the glass bead catalyst were adopted with the aim of ensuring good assembly, distribution and immobilisation of the catalyst complex upon the surface of the beads. The effect on solvation of the supported liquid-phase catalyst upon activity proved to be very interesting. Maximum activity was attained at a loading of around 10% wt. ( $\delta = 0.1$ , theoretical film thickness = 16 Å) ethylene glycol to glass beads. At low loading (6.5 Å theoretical film thickness of ethylene glycol) no activity was observed indicating the lack of mobility of the catalyst complex within such a thin film. Activity decreases at higher levels of ethylene glycol, presumably due to diminishing interfacial area as the pores become filled. Hence our results compared favourably with those observed by Horváth.<sup>11</sup>

An alternative catalyst preparation was carried out to see if ethylene glycol (or a polar film) was an essential component of the catalyst preparation for successful catalytic activity. The ethylene glycol (polar film) is thought to bind to the hydrophilic sulfonate groups in the ligand structure and adhere to the controlled pore glass beads. An alternative glass bead catalyst was prepared as follows: palladium chloride was treated with 2.2 equivalents of the polar ligand (TPPTS) and heated in methanol to dissolve. After 1 h the solution had changed from a brown to a green coloration. After complexation, Davisil beads were introduced and stirred at room temperature to ensure an even coating of beads onto the organometallic complex.<sup>48</sup> The solvent was removed *in vacuo* and the isolated green powder dried in an oven (Scheme 11). The catalyst must contain only



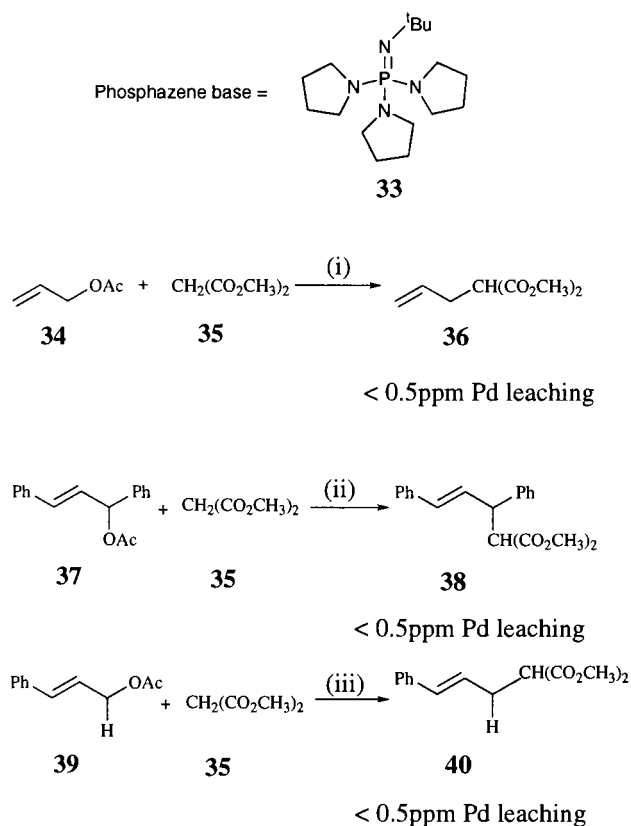
Scheme 11

the minimum amount of solvent, and yet is still active for Heck reactions, albeit with a slightly higher level of palladium leaching. In the standard conversion of iodobenzene **25** and methyl acrylate **26** to give the Heck product **27** the ethylene glycol-free beads afforded 71% yield and 2.3 ppm palladium leaching. Preliminary results suggest that this new catalyst is more effective when polar substrates are being employed, since the Heck chemistry works well with acrylic acid as one of the coupling partners.

## 9 Palladium catalysed allylic substitution

We also investigated the use of glass bead technology for palladium catalysed allylic substitution reactions.<sup>24,25</sup> Allylic substitution reactions have previously been reported using a two phase system with a palladium catalyst and TPPTS as ligand.<sup>49,50</sup> We opted for a phosphazene base **33** to deprotonate dimethyl malonate **35**, since we reasoned that the resultant active nucleophile would still prefer to reside in the bulk organic layer. In all cases palladium acetate and TPPTS were employed in the construction of the catalyst, which contained the same

level of ethylene glycol as used in the Heck reactions ( $\delta = 0.1$ ). The allyl acetates **34**, **37**, and **39** were successfully converted into the corresponding allylic substitution products **36**, **38**, and **40** with reasonable yields and with consistently low levels of palladium leaching (Scheme 12).



**Scheme 12** (i) mol % prepared catalyst, phosphazene base, toluene, reflux, 6 h, 59%; (ii) 1 mol % prepared catalyst, phosphazene base, toluene, reflux, 5 d, 51%; (iii) 1 mol % prepared catalyst, phosphazene base, toluene, reflux, 48 h, 88%.

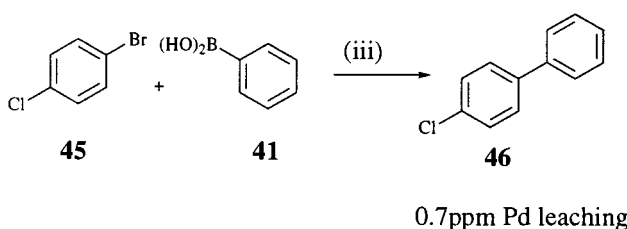
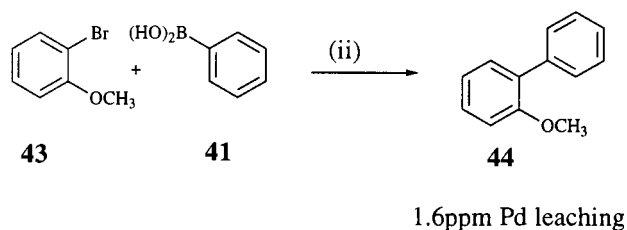
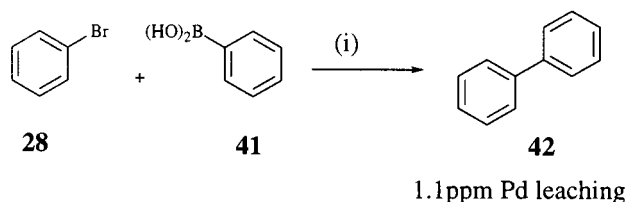
## 10 Palladium catalysed Suzuki couplings

Palladium catalysed cross-coupling reactions of organoboron compounds has been widely published.<sup>51,52</sup> Such coupling reactions have been carried out in aqueous media too.<sup>39</sup> Genét *et al.*<sup>53</sup> have reported the use of the Suzuki coupling reaction to synthesize functionalised dienes using a palladium water soluble catalyst. We decided to test the new catalyst in several Suzuki coupling reactions to show the reactions work in the absence of a polar film.<sup>54,55</sup> Aryl bromides **28**, **43**, and **45** were coupled with phenylboronic acid **41** to give the corresponding biphenyls **42**, **44**, and **46** in good yields and with low levels of palladium leaching into the organic layer (Scheme 13). Surprisingly, the presence of aqueous sodium carbonate does not increase leaching significantly, although it is reasonable to assume that the beads have been hydrated. Further investigations into the exact nature of this catalytic system are currently underway.

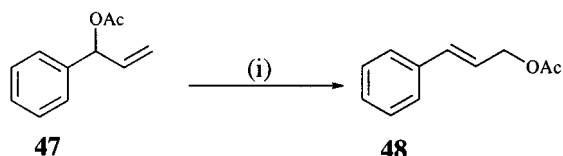
## 11 Glass beads as sponges for transition metals

The ability to restrict the movement of a transition metal catalyst in a given reaction is undoubtedly of great importance. However, we felt that the utility of glass bead technology would be further enhanced if we could remove transition metals from solutions at the end of a reaction using hydrophilic ligands supported in a polar phase on the glass bead. This work originated when trying to carry out palladium catalysed [3,3] sigmatropic allylic rearrangement reactions, such as the conversion of the acetate **47** into the rearranged product **48** (Scheme 14).<sup>56,57</sup>



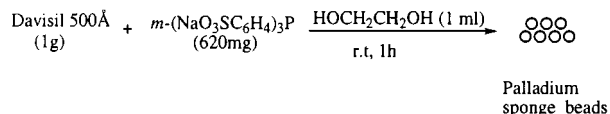


**Scheme 13** (i) 1 mol % prepared catalyst, 2 M Na<sub>2</sub>CO<sub>3</sub>, toluene, reflux, 5 h, 87%; (ii) 1 mol % prepared catalyst, 2 M Na<sub>2</sub>CO<sub>3</sub>, toluene, reflux, 7 h, 95%; (iii) 1 mol % prepared catalyst, 2 M Na<sub>2</sub>CO<sub>3</sub>, toluene, reflux, 4 h, 86%.



**Scheme 14** (i) 1 mol % [PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>], THF, r.t., 24 h, 99.5% conversion.

We were having little success in applying the originally prepared glass bead catalysts to such reactions. The presence of a phosphine ligand dramatically inhibits the reaction, presumably by blocking the co-ordination sites for the incoming alkene. We had also tried various other ways around the problem such as making polar equivalents of the nitrile ligand. However, with little achievement the idea that we might be able to introduce the glass beads as a sponge to “mop-up” any palladium in solution became more appealing. The sponge beads were synthesized simply by mixing the polar ligand and Davisil beads (500 Å) in the minimum amount of ethylene glycol to form the palladium sponge (Scheme 15). The resulting glass

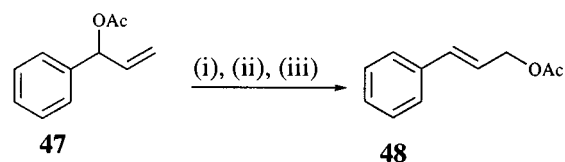


bead sponge is a free-flowing powder which is easy to add to reaction mixtures and subsequently filter.

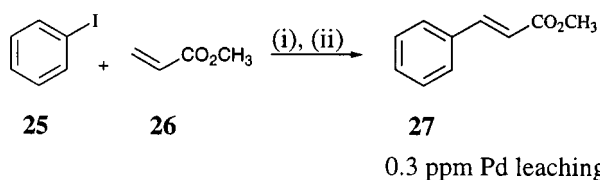
Very little work has been carried out on removal of palladium from reaction solvents. Palladium on charcoal is a common reagent used in removal of tetrakis(triphenylphosphine)palladium, however a substantial amount is usually required. Feng *et al.*<sup>58</sup> used mesoporous silica materials containing functionalised organic monolayers (of propylsilane) effi-

ciently to remove mercury and other heavy metals from both aqueous and non-aqueous waste streams. Degussa<sup>59</sup> has synthesized a metal-absorbing resin called Deloxan THP II which contains organofunctional polysiloxanes bearing thiourea, sulfanyl or thioether groups to recover Rh, Pd, Pt, Ir and Ru from highly diluted product or waste streams.

Using the allylic rearrangement reaction as a model example, we took the reaction product, removed solvent, redissolved in a less polar organic solvent, and added 1 equivalent of beads with respect to substrate. The results were significant as the palladium level dropped to 0.05 ppm, and visually the yellow solution rapidly became colourless. The sponge beads were also added to the reaction solution of a Heck product, and despite the presence of a non-polar phosphine ligand (triphenylphosphine) the palladium levels very significantly lowered, such that using 100% w/w equivalents of beads with respect to substrate no palladium was detected in the product (Schemes 16 and 17).



**Scheme 16** (i) 1 mol % PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>, THF, r.t., 24 h, 99.5% conversion; (ii) removal of THF, hexane-diethyl ether (2:1); (iii) palladium sponge beads, stirring, r.t., 10 min.



**Scheme 17** (i) 1 mol % PdCl<sub>2</sub>, 2 mol % PPh<sub>3</sub>, Et<sub>3</sub>N, toluene, reflux, 3 h, 71%; (ii) palladium sponge beads, stirring, r.t., 10 min.

Furthermore, we have filtered a solution of palladium acetate in toluene through a filter pad of the sponge beads. The glass bead sponges were able to remove nearly all of the palladium from such a solution in just one pass of it over the beads. Thus a solution of palladium acetate (50 mg) in toluene (10 ml) was passed over the glass bead sponges. Using 1 g of the glass bead sponge (which contains 5 equivalents of TPPTS) only 0.4% of the original palladium was present in the filtrate. Using 4 g of the glass bead sponge the level was reduced to just 0.1% of the original palladium present in the filtrate.

This methodology may have potential for use in extracting other metal contaminants after the metal catalysed reaction has gone to completion.

## 12 Outlook

Glass bead technology has been successfully applied to many transition metal catalysed processes. The reactions retain much of the selectivity of their homogeneous counterparts, but retain the catalyst in a separate phase from the bulk reaction. Low levels of transition metal leaching are generally observed, which represents an economically sound and environmentally friendly approach to transition metal catalysed reactions. Many transition metal catalysed reactions have still to be examined using glass bead technology, but the outlook is promising. Perhaps more “academic” reactions can now be explored in scale-up and process chemistry using these methods.

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- 43 The use of fewer equivalents of ligand afforded higher levels of leaching.
- 44 CPG beads are commercially available: Cambio, 34 Newnham Road, Cambridge, UK CB3 9ET (postmaster@cambio.demon.co.uk). We are grateful to GlaxoWellcome for purchasing these beads on our behalf.
- 45 Freeze drying was performed on an Edwards Modulyo Pirani 10 freeze-drier.
- 46 Leaching of palladium was determined by atomic absorption or ICP analysis. For atomic absorption analysis the decanted samples were filtered and furnace at 400 °C, extracted into 3 drops of *aqua regia* and 3 ml deionised water added. The samples were analysed on a Perkin-Elmer 1100B atomic absorption instrument in conjunction with a series of palladium standards. For inductively coupled plasma (ICP) analysis the decanted samples were filtered and furnace at 400 °C, and extracted into 3 ml dms0-2% HCl solution. The samples were analysed on a Varian Liberty 200 ICP-AES instrument with a series of palladium standards.
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