Palladium Catalysed Coupling Reactions using Guanidinium Phosphine Complexes on Glass Beads

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Abstract: Supported palladium catalysts generated from guanidinium phosphine **1** and palladium acetate have been shown to exhibit high activity and low leaching of catalyst. The nature of the catalyst allows facile separation and recycling.

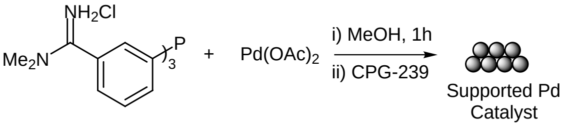
Key words: palladium catalysis, glass beads, Heck reaction, Sonogashira reaction, guanidinium phosphines

Transition metal catalysis continues to be a major research field, with many powerful and selective transformations now available to synthetic chemists.[1] Limitations to the use of transition metal catalysts in large scale synthesis lie in the expense of the catalyst and contamination of the product. The development of catalyst systems which combine low leaching levels and facile recycling is thus a significant goal.

Supported liquid phase catalysis is an approach which utilises the hydrophilic surface of a glass bead to adhere a polar solvent.[2] A polar soluble transition metal complex can thus reside in this supported layer. This non-covalent method of support yields a mobile catalyst which acts at the interface between the supported solvent and the bulk, apolar solvent in which both substrate and product reside. On completion of the reaction, the product and catalyst are separated readily from each other by filtration or decanting.

Our first attempts to use this approach utilised water soluble complexes of palladium and TPPTS, [P(m-$NaO_3SC_6H_4)_3$].[3] Sulfonation of aromatic phosphines can however be capricious, with phosphine oxides often emerging as the major product of reaction, this is an important practical concern as separation of phosphine and phosphine oxide is non-trivial.[4] The harsh conditions required for sulfonation may also cause epimerisation of chiral, non racemic ligands. We thus sought to investigate the use of alternative water soluble ligands in the reaction, with mild, late stage introduction of the water soluble moiety being a prime objective. Guanidinium phosphine ligands **1** have recently been introduced by Schmidtchen and used to form water soluble palladium catalysts.[5] We thus synthesised the ligand in three clean, high yielding steps from commercially available starting materials and began to explore their use on glass beads.[6]

We synthesised the supported phase palladium catalyst in a straightforward manner by precomplexing the phosphine **1** and palladium acetate in methanol before adding degassed controlled pore glass (CPG-239)[7] to the resultant solution. Removal of solvent after 0.5h stirring gave the supported catalyst **2** as a free flowing golden yellow powder. Optimal ligand to palladium ratio was dictated by balancing palladium leaching levels and catalytic activity (a high ligand to metal ratio suppressed reaction), a 2.8:1 ligand/metal ratio was thus established.

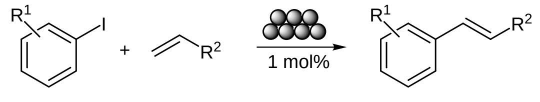


1 **2**

Scheme 1

Preliminary experiments showed that these beads were effective catalysts for Heck reaction of aryl iodides an alkenes. Optimised results from a series of experiments are given in Table 1.

Table 1 Glass bead catalysed Heck Reactions



3 **4** **5**

Alkene (1.25 eq.), triethylamine (3 eq.), Toluene, 100 °C

	R1	R2	Reaction time (h)	Isolated Yield (%)	Pd leaching (%)*
1	H	CO_2Me	16	87	0.2
2	H	$CO_2{}^tBu$	16	58	0.1
3	*m*-Me	CO_2Me	16	65	0.1
4	H	CH(OH)Me	48	70†	0.1
5	*m*-Me	CH(OH)Me	48	72†	0.1
6	H	Ph	60	55	<0.03
7	*o*-Br	CO_2Me	60	83	0.1

*Palladium level detected in the product as a percentage input into the reaction. †The isolated product in this case is the tautomeric ketone.

Attractive features exhibited by these systems are the low catalyst loading required for successful reaction, with just 1 mol% providing sufficient activity and also the very low levels of leaching observed.

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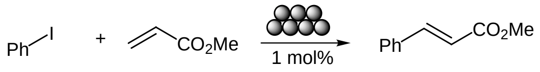
The utility of the catalyst beads was further demonstrated by carrying out recycling experiments. Catalyst beads prepared as above (but substituting palladium chloride for palladium acetate) were subjected to the reaction conditions above. At the conclusion of the reaction the bulk solvent was removed by decanting and the reaction vessel recharged with substrate, solvent and base. As shown in Table 2 high yields and low leaching were maintained over 4 reaction cycles.

Table 2 Recycling Experiments



Alkene (1.25 eq.), triethylamine (3 eq.), Toluene, 100 °C, 16h.

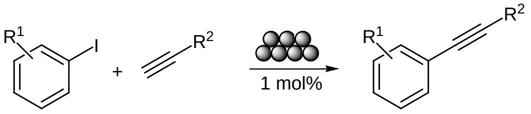
Cycle no.	**Isolated Yield (%)**	**Pd leaching (%)***
1	85	0.01
2	78	0.20
3	83	0.05
4	81	0.20

*Palladium level detected in the product as a percentage input into the reaction.

In order to broaden the scope of application of the supported phase palladium catalyst, Sonogashira couplings of aryl iodide and acetylenes were attempted.[8] Pleasingly a toluene solution of iodobenzene, phenyl acetylene and diethylamine underwent reaction in the presence of our Pd catalyst and CuI in quantities of 5 and 10 mol% respectively. The product of reaction, however, proved to be that of an oxidative dimerisation of the acetylene.[9] A high yielding (96%) dimerisation of phenyl acetylene could thus be effected at room temperature with our catalyst beads and CuI (1 and 2 mol % respectively) in just 16h with very low Pd leaching levels (<0.01%), this oxidative process is presumably reliant on the presence of air.

However, successful Sonogashira couplings were realised by performing the reaction at 60 °C in rigorously degassed toluene as shown in Table 3. Thus 1-hexyne and iodobenzene reacted to give the desired coupling product in 92% yield over a period of 60h in the presence of 1 mol% Pd beads and 3 mol% CuI, significantly low levels of catalyst leaching, in this case (0.1 %), were obtained.[10]

Table 3 Glass bead catalysed Sonogashira couplings



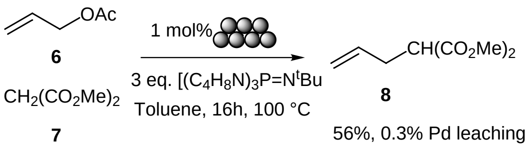
CuI 3 mol%, alkyne (3 eq.), diethylamine (3 eq.), Toluene, 60 °C

	R^1	**R^2**	**Reaction time (h)**	**Isolated Yield (%)**	**Pd leaching (%)***
1	H	nBu	60	87	0.2
2	H	Ph	3	58	0.1
3	H	Ph	6	65	0.1
4	*m*-Me	Ph	14	70	0.1

*Palladium level detected in the product as a percentage of that input

Finally, an allylic substitution reaction of allyl acetate **6** with dimethylmalonate **7** was achieved using the supported catalyst. The substitution product **8** was formed in reasonable, unoptimised yield and with a low level of palladium leaching.

For all of the supported liquid phase reactions, we have shown (at least when sulfonated ligands are employed) that dissociation of the catalyst into the bulk phase takes place during the course of the reaction, but only to a relatively small extent.[11] From a practical standpoint, the fact that after cooling the catalyst is returned to the glass bead, is adequate for most synthetic purposes.



Scheme 2

We have demonstrated the use of guanidinium functionalised phosphine in supported phase catalyst systems. Of particular note are the recyclability of catalyst and the low levels of palladium leaching into the product. The guanidium moiety affords a mild, late stage introduction of water solubility to amino functionalised ligands a significant consideration in derivatisation of non-trivial asymmetric ligands, the applications of which we are now pursuing.

Acknowledgement

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References and Notes

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(6) Synthesis of the ligand involves Grignard reaction of commercially available 2-(*N,N-bis*-trimethylsilyl-amino)phenyl magnesium chloride with phosphorus trichloride. The triaryl phosphine product is then deprotected at nitrogen in refluxing methanol and transposed to the hydrochloride salt before a final condensation with dimethyl cyanamide affords the desired guanadinium phosphine **1**.[5]

(7) CPG beads are commercially available from Cambio, 34 Newnham Road, Cambridge, UK CB3 9ET.

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(10) The fate of the copper salt has not been established.

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