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Palladium Catalysed Heck Reactions and Allylic Substitution Reactions Using Glass Bead Technology

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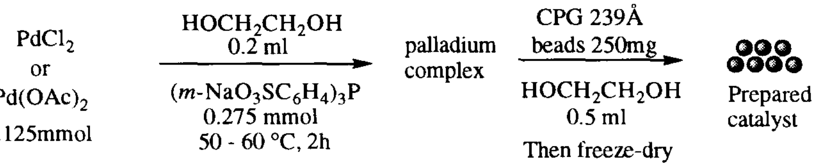
Abstract: The use of controlled-pore glass beads in Heck reactions and palladium catalysed allylic substitution affords the products with low levels of catalyst leaching. © 1997 Elsevier Science Ltd.

One of the main problems with the use of transition metals as catalysts is that they often contaminate the final product. Davis *et al* have reported a new family of immobilised catalysts which helps to improve chemical reactions at the interface of the two phases and reduce levels of leaching of the catalyst into the product. Supported liquid phase and supported aqueous phase catalysts[1] have been employed in hydroformylation reactions[2] with very hydrophobic alkenes. For example, oleyl alcohol and octene have been hydrogenated with the water-soluble catalyst $[HRh(CO)(tppts)_3]$ using this procedure. The water soluble ligand tppts (triphenylphoshine trisulfonate) has been used as a ligand with other transition metals for catalysis in water.[3]

The supported liquid phase catalysts consist of a thin film that resides on a high surface area hydrophilic support, such as controlled-pore glasses or silica, and is composed of an aqueous or polar solution of organometallic complexes. Reactions can take place at the film-organic interface.

Herein we report the preparation of palladium catalysts supported in ethylene glycol on glass beads, as well as their successful application in Heck reactions and allylic substitution reactions. The supported catalyst was prepared as identified in Scheme 1. The palladium catalyst (either palladium chloride or palladium acetate) was treated with 2.2 equivalents[4] of polar ligand tppts in a minimal amount of ethylene glycol. After heating to ensure complexation, controlled-pore glass beads[5] were added as well as additional ethylene glycol. After stirring, to facilitate an even coating of the beads, they were cooled and freeze dried.[6] The resultant beads could then be added as a catalyst to the reaction mixture.



Scheme 1. Preparation of glass bead/palladium catalysts

The prepared catalysts derived from palladium chloride or palladium acetate were examined for their ability to catalyse the Heck reaction. Thus iodobenzene **1** and methylacrylate **2** were treated with the prepared palladium catalysts (1 mol% based on palladium) in the presence of triethylamine and the reactions were performed at high concentration (12.9mmol in 5mL) in hexane:diethyl ether (4:1). At the end of the reaction, the solution was decanted from the glass beads, and analysed for leaching of palladium.[7] The reaction yield, leaching of palladium and other data are shown in Table 1, where the ligand is either tppts or tppms (triphenylphosphine mono-sulfonate).

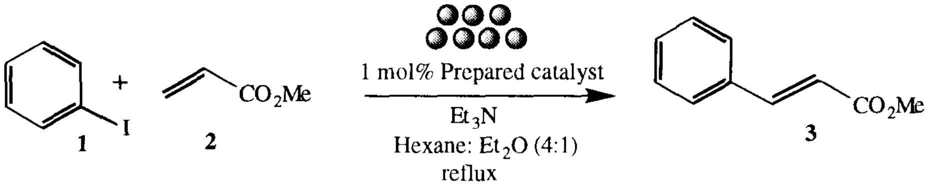


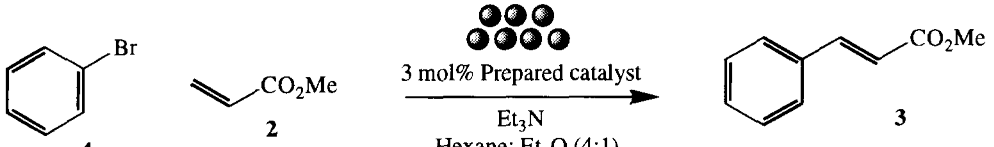
Table 1. Formation of methyl cinnamate **3** using the Heck reaction

Beads	***Ligand***	***Pd catalyst***	***Time***	***Yield (%)***	***Pd leaching (ppm)***
CPG 239Å	TPPMS	$PdCl_2$	25 h	71	0.5
CPG 239Å	TPPMS	$Pd(OAc)_2$	25 h	63	0.5
CPG 239Å	TPPTS	$PdCl_2$	25 h	75	0.2
CPG 239Å[a]	TPPTS	$PdCl_2$	25 h	27	0.4
CPG 290Å[b]	TPPMS	$PdCl_2$	48 h	61	0.4
CPG 120Å	TPPMS	$PdCl_2$	23h	74[c]	2.5
CPG 500Å	TPPMS	$PdCl_2$	24 h	59[c]	8.4
Davisil 300	TPPMS	$PdCl_2$	21 h	73[c]	2.5

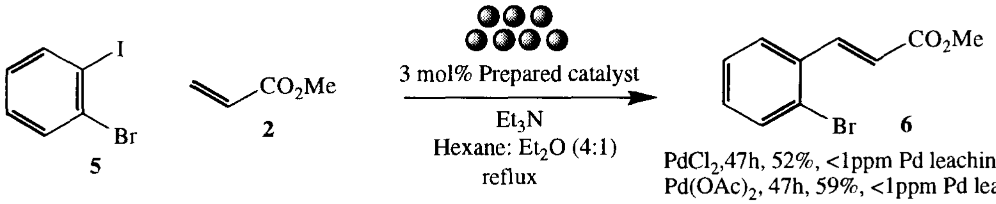
[a] The fourth run using the same prepared catalyst. [b] Reaction performed at room temperature

[c] For these reactions only, the quoted figures are conversions rather than isolated yields. These reactions were performed using 5mol% Pd, at a concentration of 1.9mmol in 5 mL

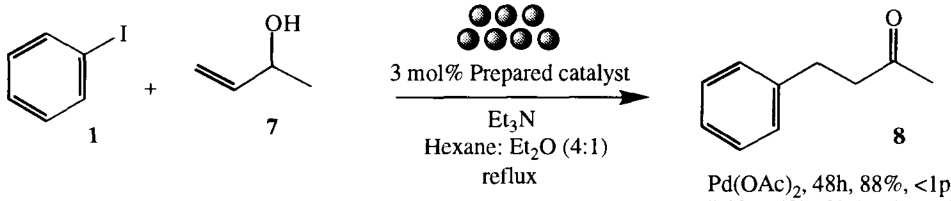
Therefore, the use of CPG 239Å beads and either tppms or tppts as ligand affords product in good yield and with little palladium leaching. Having established good conditions for the Heck reaction of iodobenzene with methyl acrylate, we examined other Heck reactions to explore the scope of this methodology. Thus, bromobenzene **4** and bromoiodobenzene **5** both underwent Heck reaction with methyl acrylate to give the cinnamate products **3** and **6** respectively. The coupling reaction of iodobenzene **1** with allylic alcohol **7** afforded the ketone **8** (formed, as expected,[8] by prefential β-hydride elimination to give the enol, which tautomerises to give the ketone). The use of polar substrates such as acrylic acid and acrylamide were unsuitable since they afforded low yields of substitution and high levels of leaching, which we attribute to their affinity for the more polar supported phase.[9]



$PdCl_2$,46h, 54%, <1ppm Pd leaching
$Pd(OAc)_2$, 48h, 47%, <1ppm Pd leaching



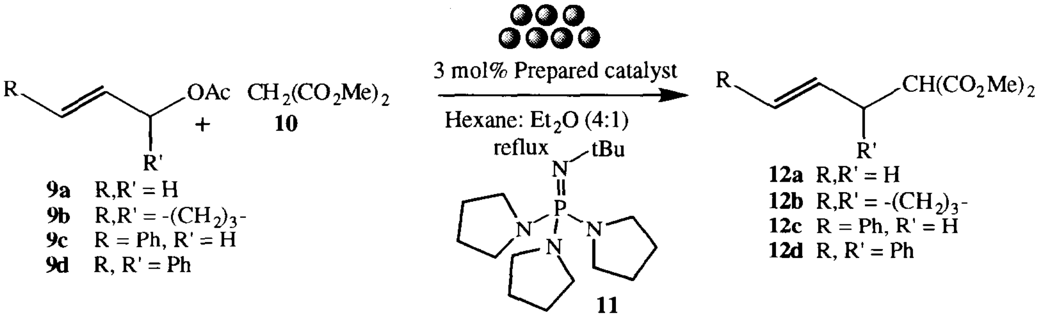
$PdCl_2$,47h, 52%, <1ppm Pd leaching
$Pd(OAc)_2$, 47h, 59%, <1ppm Pd leaching



$Pd(OAc)_2$, 48h, 88%, <1ppm leaching
$PdCl_2$, 48h, 61%, <1ppm leaching

Thus, Heck reactions may be successfully performed using a palladium catalyst supported in ethylene glycol on a controlled pore glass bead. The levels of leaching of palladium into the product are consistently low.

We have also examined the use of these catalysts for palladium catalysed allylic substitution reactions.[10] Since we wished to avoid substrates which would be too soluble in the polar phase, we chose to use a combination of malonate/phosphazene base as the nucleophile (rather than sodiodimethyl malonate for example). Thus allyl acetate **9a-d** is reacted with dimethylmalonate **10**, and the organic soluble phosphazene **11** employed as the base. The reactions were performed in an apolar environment, and afforded the expected substitution products **12a-d** in reasonable yield. The leaching levels and other relevant data are detailed in Table 2.



9a R,R' = H
9b R,R' = $-(CH_2)_3-$
9c R = Ph, R' = H
9d R, R' = Ph

12a R,R' = H
12b R,R' = $-(CH_2)_3-$
12c R = Ph, R' = H
12d R, R' = Ph

Table 2. Palladium catalysed allylic substitution reactions

Substrate	***Ligand***	***Time***	***Yield (%)***	***Pd leaching (ppm)***
9a	TPPMS	6h	>98	0.2
9a	TPPTS	6h	55	0.2
9b	TPPMS	24h	77	0.1
9b	TPPTS	96h	6	0.2
9c	TPPMS	96h	40	0.5
9c	TPPTS	48h	92	0.5
9d	TPPMS	120h	42	0.1
9d	TPPTS	120h	50	0.1

[a] Reactions were performed using 239Å CPG beads and a $Pd(OAc)_2$ catalyst (1 mol%) using 3 equivalents of dimethylmalonate and phosphazene base.

In conclusion, glass bead technology has been exploited for two palladium catalysed processes - the Heck reaction and allylic substitution reaction. In both cases, the reactions are successfully catalysed by the supported catalyst, and the levels of palladium leaching are low. Further developments in this area will be reported in due course.

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References and Notes:

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3. For examples of Heck reactions using water-soluble ligands, see, J. Kiji, T. Okano and T. Hasegawa, *J. Mol. Cat. A*, **1995**, *97*, 73-77. H. Dibowski and F. P. Schmidtchen, *Tetrahedron*, **1995**, *51*, 2325-2330.
4. The use of fewer equivalents of ligand afforded higher levels of leaching.
5. Controlled pore glass beads are commercially available (Cambio). We are grateful to GlaxoWellcome for purchasing these beads on our behalf.
6. Freeze drying was performed on an Edwards Modulyo Pirani 10 Freezedrier
7. Leaching of palladium was determined as follows: The decanted samples were filtered and furnaced at 400°C, and extracted into 3 drops of aqua regia and 3mL deionised water added. Samples were analysed on a Perkin Elmer 1100B atomic absorption instrument in conjunction with a series of Pd standards.
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