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LETTERS

Palladium Catalysed Heck and Enantioselective Allylic Substitution Reactions Using Reverse Phase Silica Supports

Michael S Anson,[a] Amin R Mirza,[b] Louise Tonks,[b] and Jonathan M J Williams*[b]

[a]GlaxoWellcome Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK
[b]Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK.

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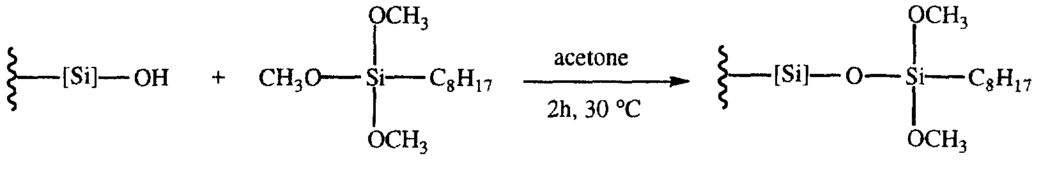
Abstract: The use of reverse phase controlled-pore glass beads in Heck reactions affords the products with low levels of palladium leaching. Additionally, an enantioselective palladium catalysed allylic substitution reaction has been achieved with high enantiomeric excess and a low level of leaching

Supported liquid phase and supported aqueous phase catalysts have been employed in a variety of transition metal catalysed reactions. [1] Results from this research group have previously demonstrated how glass bead technology can be exploited for palladium catalysed reactions, including the Heck reaction and allylic substitution reaction.[2] Normally, the supported liquid phase catalyst consists 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 transition metal complexes. Reactions can take place at the film-organic interface.

Herein we report the use of reverse phase silica in the Heck reaction, which allows for the use of more polar substrates. The hydrophilic surface of the silica is transformed using known methods[3] into a hydrophobic derivatised silica. In our case, we chose to use Davisil 300, which is a cheaper, but still effective, alternative to controlled pore glass.[4]



$$[\mathrm{Si}]\!-\!OH + CH_3O\!-\!\underset{OCH_3}{\overset{OCH_3}{Si}}\!-\!C_8H_{17} \xrightarrow[\text{2h, 30 °C}]{\text{acetone}} [\mathrm{Si}]\!-\!O\!-\!\underset{OCH_3}{\overset{OCH_3}{Si}}\!-\!C_8H_{17}$$

'reverse phase silica'

After removal of solvent, the derivatised silica beads were then converted into active catalysts by treatment with palladium acetate and triphenylphosphine in cyclohexane. We assume that $(PPh_3)_2Pd(OAc)_2$ is formed and that on removal of solvent, a reverse phase bead catalyst is formed. The catalyst is a freely flowing powder that is

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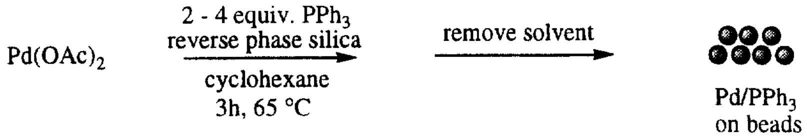
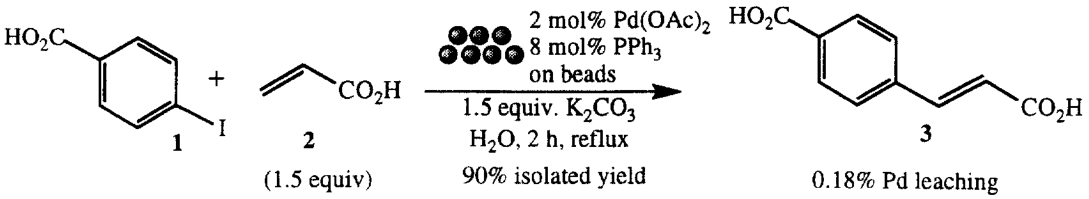
stable in air, and is easy to handle. A reverse phase catalyst using tri-o-tolylphosphine was prepared in an analogous manner.



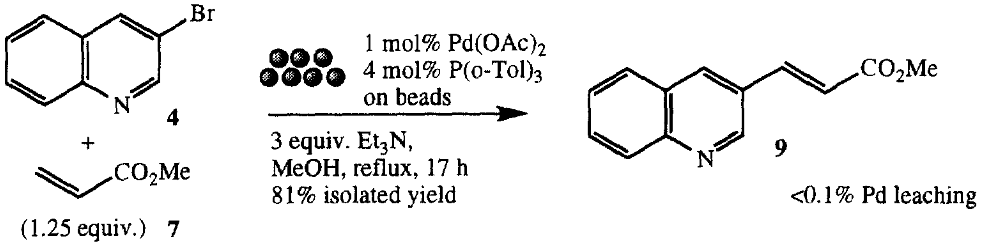
These reverse phase supported catalysts were examined for their ability to catalyse the Heck reaction. In the first instance, a simple coupling between iodobenzoic acid **1** and acrylic acid **2** was examined. The product **3** was obtained in good yield using the triphenylphosphine based catalyst, and with very little leaching of palladium into the bulk aqueous phase. The reverse phase beads could be recovered from the reaction mixture, and were re-used seven times without any apparent loss of activity. The leaching level corresponds to the amount of palladium present in the product as a percentage of the amount of palladium catalyst employed.

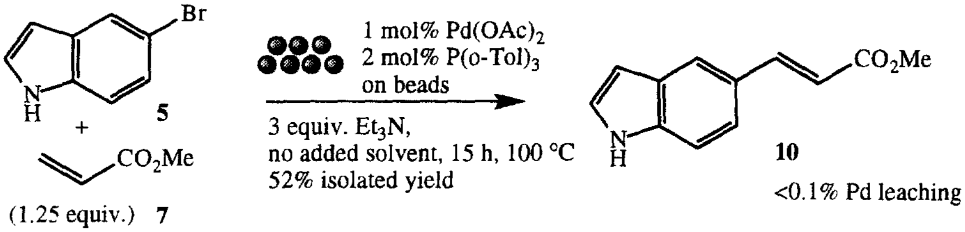


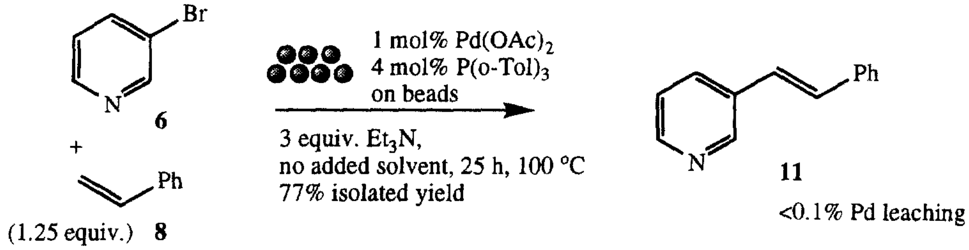
There was no requirement to employ water soluble substrates. Thus, iodobenzene and methyl vinyl ketone were coupled using the triphenylphosphine derived reverse phase beads with methanol/water (1:1) as the solvent (97% yield, 0.07% Pd leaching). However, we believe that the real advantage of using reverse phase silica support is that more polar substrates can be employed. Polar substrates, especially those with donor atoms, can be difficult to purify from trace amounts of metal contaminant. We chose to investigate the Heck reactions of nitrogen containing heterocycles **4** to **6**. The Heck reaction of these heterocycles with methyl acrylate **7** and with styrene **8** was examined. The use of the reverse phase catalyst derived from triphenylphosphine was found to be somewhat unsatisfactory since it gave a low conversion rate. In fact, even in a fully homogeneous reaction, all of these heteroaryl bromides were found to be very sluggish partners in the Heck reaction. However, tri-o-tolylphosphine provides the basis for a more reactive catalyst, and we were able to achieve satisfactory to good yields of the Heck products **9** to **11** using reverse phase catalysts derived from this ligand.[5] Boc-protected bromoindole could also be used as an effective substrate, although the isolated yield after deprotection was still only 52% over the two steps, with low levels of leaching (less than 0.1% of the palladium used was detected in the products).

We have therefore demonstrated that Heck reactions can be achieved with low levels of palladium leaching by employing reverse phase silica beads and the use of conventional non-polar ligands.

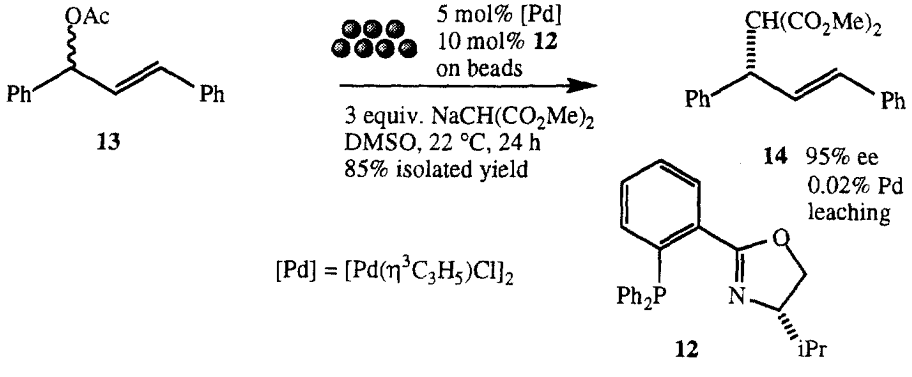
As well as the Heck reaction, we have examined the use of reverse phase beads in palladium catalysed allylic substitution reactions. One of the current themes in palladium catalysed allylic substitution reactions is the ability to convert racemic allylic acetate starting materials into enantiomerically enriched products.[6] We have previously shown that achiral polar phosphines provide palladium complexes (contained in a polar phase associated to 'normal' silica) which are able to catalyse the allylic substitution of allyl acetates with nucleophiles such as sodiodimethyl malonate.[7] However the preparation of a suitable enantiomerically pure ligand which was also very polar seemed to us to be a cumbersome proposition.







We therefore incorporated the readily prepared phosphino-oxazoline ligand **12**[8] into a reverse phase bead catalyst. In the standard palladium catalysed conversion of allyl acetate **13** into the malonate substituted product **14**, we were pleased to find that the reaction took place smoothly. When the reaction was performed in DMSO, the enantioselectivity of the reaction was high, the yield was high, and the level of palladium leaching was low.



The ability to perform enantioselective transition metal catalysed reactions using non-polar ligands with low levels of metal contamination in the enantiomerically enriched product is an important concept. The use of reverse phase beads to achieve this goal provides an alternative to the use of polymer supported enantiomerically pure ligands, which are often less selective than their homogeneous counterparts.

In conclusion, reverse phase silica supports have 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 reverse phase catalyst, and the levels of palladium leaching are low. The advantages are that the supported phase allows the catalyst to retain its mobility (and so high enantiomeric excess is observed), and that conventional ligands can be employed (since there is no need to develop water soluble analogues). We have previously reported that palladium levels can be further reduced by passing through a filter containing glass beads containing phosphines present in a supported film.[1b]

Further developments in the use of reverse phase silica as a support for transition metal catalysed reactions will be reported in due course.

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