Silica-Supported Palladium-Based Catalysts for Clean Synthesis

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Research into supported palladium complexes is described. The complexes are immobilised on porous silica supports using both grafting and templated sol-gel techniques. The resultant complexes are efficient catalysts for various C-C bond forming reactions, including Heck, Suzuki and allylic substitution. The catalysts are stable and can be easily recovered and reused, making them suitable for cleaner processing.

Catalysts based on palladium (Pd) have provided some of the most effective and exciting transformations in organic chemistry. A wide range of coupling reactions are known, including the Heck (1–3), Suzuki (4–6) and Sonagashira reactions (7), all of which are efficient and have excellent generality. Other transformations such as hydrogenations and nucleophilic attack on allylic electrophiles are also widely used. Carbonylations represent a further class of reactions where carbon skeletons are elaborated, leading to a wide range of useful products.

Many of these reaction types have the additional benefit of providing efficient routes to many products, avoiding the drawbacks of traditional methods which can be much more wasteful and inefficient. In the last few years, the replacement of such older, polluting methodologies, by cleaner, more efficient (in terms of chemical usage and energy) processes has become increasingly important. This trend is likely to continue and intensify as the use of environmentally more acceptable production methods becomes more clearly identified with economic benefits from a more efficient use of resources and increased public (and customer) acceptance of such practices.

Our work in York and Bratislava is aimed at developing cleaner reaction systems for organic synthesis. The major thrust of the work presented here relates to the use of heterogeneous catalysis for (predominantly) liquid phase reactions. These catalysts consist of a silica support, to which the catalytic centre is covalently linked. This requires the design and synthesis of ligand systems containing the $-Si(OMe)_3$ unit, which allows the anchorage of the catalyst in a robust manner.

The work described here highlights some of our efforts in developing heterogeneous palladium catalysts for organic synthetic applications.

Catalyst Preparation

Our work relies on two types of catalyst support – amorphous mesoporous silica (such as Kieselgel 60 or 100) in which the mesopores are irregularly shaped with a wide distribution of sizes, and micelle templated silicas (MTS) where the mesopores are much more tightly controlled such that the spread of pore diameters is much lower, and the pore shapes are much more regular, being typically cylindrical and fairly straight. The latter supports are prepared by sol-gel synthesis of the silica around a micelle template; in the method we have chosen this is a long chain amine such as 1-aminododecane (8). Both materials can be treated with a suitable silane to form heterogeneous catalysts, see Figure 1. In both types of support (amorphous and MTS) the grafting follows similar pathways, but typically more silane can be grafted onto MTS (9, 10), essentially since it has a much higher surface area (typically ca. 1000 m^2 g^{-1}
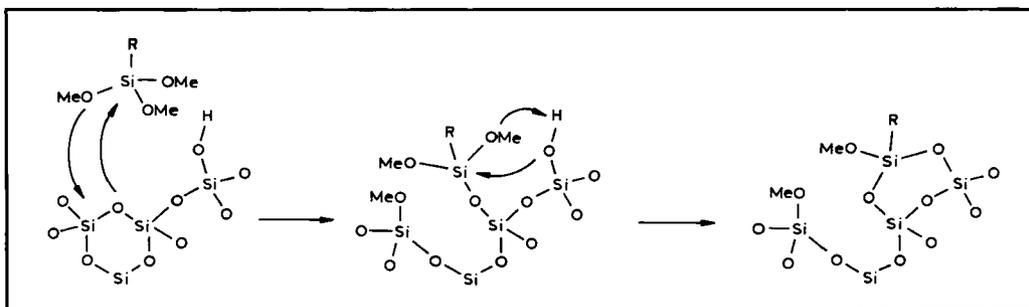
Fig. 1 *Grafting of silanes onto a preformed silica surface to give a heterogeneous catalyst. The silica can be grafted onto a micelle templated silica where pore size and shape are controlled and regular, or onto an amorphous mesoporous silica where mesopores are a range of shapes and sizes*

compared with 200–500 m² g⁻¹ for amorphous silicas).

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A second type of method has also been used, in which the silica precursor, tetraethoxysilane (TEOS), is co-condensed with the appropriate silane in aqueous ethanol, to form directly the catalyst (or catalyst precursor), see Figure 2, (11, 12).

Generally, both types of catalyst have similar activity profiles, but there are instances where considerable differences can be found (13). These differences can be the expected diffusional changes and pore size effects, or can be due to more fundamental changes in the nature of the bound group, although the latter is rare. Amine groups in these materials can, under certain circumstances, vary in nature. When grafted they are, as expected, basic and nucleophilic, capable of acting as catalysts and as precursors to catalysts via, for example, alkylation or imine formation. However, some of the co-condensed amine-containing materials (those prepared in ca. 50% aqueous ethanol) display basicity but no nucle-

ophilicity, while others show normal behaviour (14). The reasons for these differences are being investigated, but are not yet clear.

Palladium Catalysts for the Heck and Suzuki Reactions

We are interested in the heterogenisation of palladium complexes as catalysts for C-C bond formation, in particular the Heck (1–3) and Suzuki couplings (4–6). Three important goals need to be realised in developing such catalysts: first, activity and selectivity must be high, second, recoverability and reusability must be achievable, and third, we must be confident that no metal leaches into solution as this would both contaminate the product and result in the heterogeneous catalyst being no more than a complex way of dissolving palladium.

Catalysts

In order to develop stable catalysts, our initial efforts centred around carboxylic acid materials which had been prepared for another project (15).
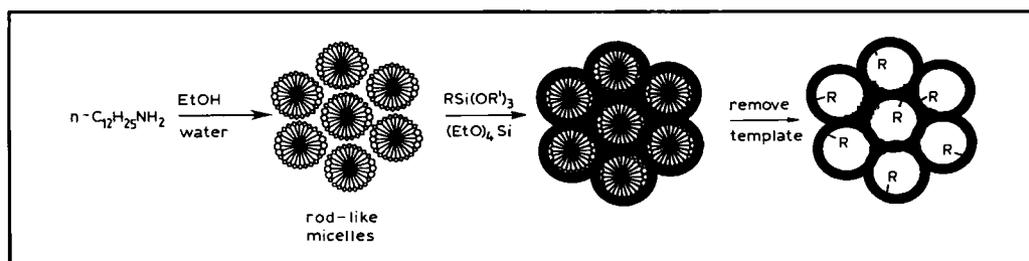

Fig. 2 *Sol-gel synthesis of micelle templated silica catalyst supports. The silica precursor, tetraethoxysilane, is co-condensed with the appropriate silane (in aqueous ethanol) for the catalyst or catalyst precursor. The shape of the mesopores formed are typically cylindrical and quite regular with a small spread of pore diameters*
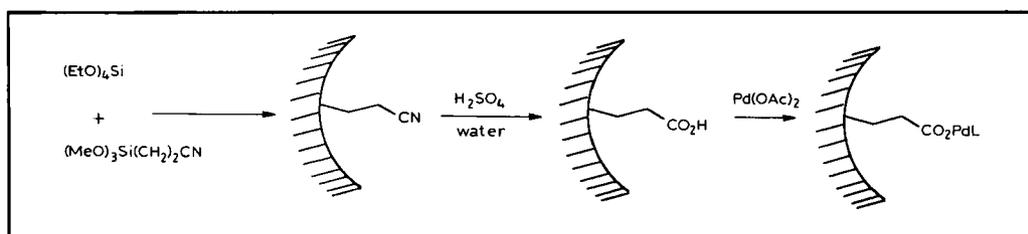
Fig. 3 Carboxylate-supported palladium catalysts; these catalysts are supported equivalents of Pd(OAc)₂ and the support is MTS. L is a ligand, probably OAc but possibly a second silica-bound ligand

These materials can have loadings as high as 4 mmol g⁻¹ and are easily prepared from cyanoethyl MTS or cyanoethyl silica by acid hydrolysis of the nitrile function. These would give supported equivalents of Pd(OAc)₂, see Figure 3. These catalysts are found to be active in both Heck and Suzuki coupling reactions, but their lifetime is relatively short. On reuse, activity drops to almost zero and, although activity can be restored to some extent by washing, the lifetimes of the catalysts are too low to be of real interest.

A second generation of catalysts was then prepared. This involved the approach taken in the synthesis of supported chromium oxidation catalysts (16), namely the use of imine-based ligands on the surface. The phenolate system failed to give particularly good catalysts, but the pyridine-based ligand performed much better, and is now the ligand of choice for these catalysts (17).

The preferred synthetic method involves the preparation of an aminopropyl-containing silica or MTS, followed by the formation of the ligand by imine formation with pyridine-2-carboxaldehyde and subsequent complexation with palladium acetate, see Figure 4. It was found that the solvent for the complexation of the metal was critical to the success of the catalyst – acetone as solvent was by far the best of the solvents tried, with toluene and ethanol giving much less stable catalysts.

In order to fully remove uncomplexed palladium species, the catalyst was thoroughly extracted with refluxing acetone, then ethanol, followed by toluene and finally acetonitrile for a total of 27 hours.

Elemental analysis indicated that the attachment of pyridine ligands to the aminopropyl groups was essentially complete in the case of the MTS catalysts, and was around 80 per cent complete in the silica-based materials. In both cases, approximately 50 per cent of the ligands were complexed by palladium (giving loadings of ca. 0.2–0.5 mmol g⁻¹ Pd), fairly typical of post-complexation and thorough washing. Infrared analysis indicated that the complexation of palladium by the ligand had occurred, with the prominent C=Nstr (stretch) of the imine being shifted to lower frequency by ca. 50 cm⁻¹, indicative of strong metal-ligand interaction.

Nitrogen adsorption porosimetry data indicate that the pore systems in both cases are similar to those of the supports, with the silica material, 1, perhaps displaying blockage of the smallest pores,
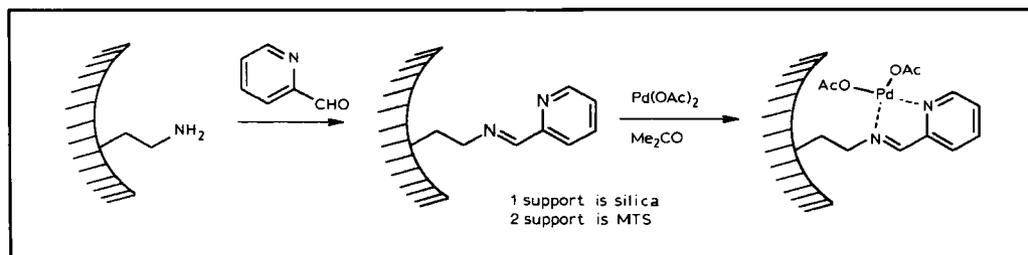

Fig. 4 Synthesis of Pd-pyridylimine catalysts. The support may be either amorphous mesoporous silica or MTS and palladium acetate has been used for complexation
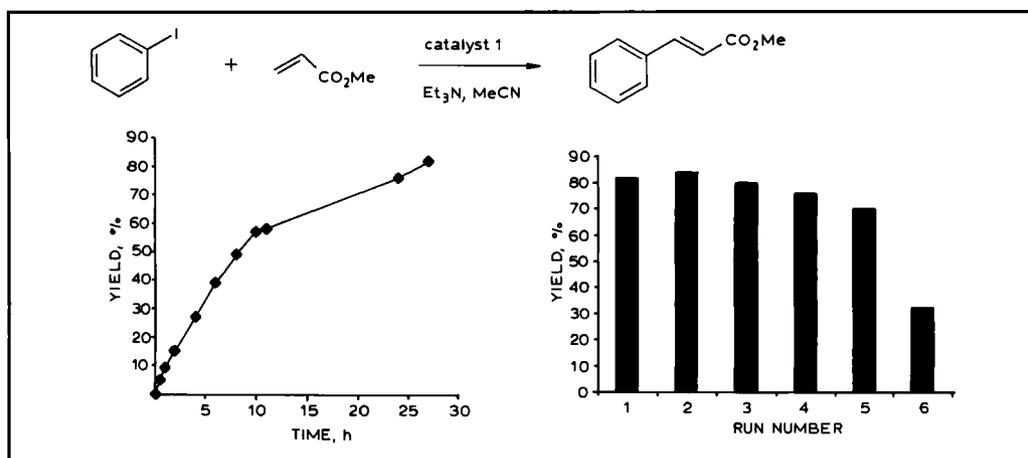
Fig. 5 Catalytic activity in the Heck reaction of iodobenzene and methyl acrylate

while the MTS-based catalyst, 2, is very similar to the parent aminopropyl system.

The catalyst (on silica) can be used in the Heck reaction (17), and is active in the coupling of aryl iodides with alkene components. It is less active in couplings involving allylic species. It was found that the optimum base which could be used was triethylamine; solid bases, such as potassium carbonate, are less effective, probably due to transport problems of the (insoluble) base into the pores of the catalyst. Soluble bases, on the other hand, are effective. It could be that the base is needed to aid the decomposition of one of the intermediates at the metal centre (and thus needs to be soluble to get there).

Catalyst Activity

The activity of the catalyst can be well illustrated by the coupling of iodobenzene and methyl acrylate, see Figure 5. The temperature of the reaction was 82°C. After 24 hours, the conversion of reactants has reached 82 per cent, a turnover number (moles product/moles Pd) of ca. 350. Reuse of the catalyst after filtration, but without washing the catalyst or thermal activation, gives essentially reproducible rate profiles and yields for a further four uses. At this time adsorption isotherms, measured after reaction and then after washing of the used catalyst, indicated that during reaction the pores become partially blocked; IR and elemental analyses indicate that this blockage is due to the

tetraalkylammonium halides which are formed during reaction. As expected, washing with an appropriate solvent is sufficient to remove them and washed catalysts have surface areas and pore volumes very similar to those of the fresh catalysts. Activity is also restored.

Minimisation of Leaching

One of the key controls which must be carried out with such catalysts is leaching. In order to minimise this problem, we have thoroughly pretreated our catalysts to remove any loosely bound physisorbed salts or complexes. Additionally, the ligand system should be capable of binding tightly to the Pd centre throughout the catalytic cycle, meaning that no soluble intermediates should be formed. This latter problem may well be part of the reason why the carboxylate catalysts, despite good initial activity, rapidly become inactive, because of relatively rapid ligand exchange and solubilisation. We have observed similar effects in supported cobalt carboxylates, where Co(II) is readily lost from the catalyst, but Co(III) is not. This correlates well with the known ligand exchange dynamics, which show that Co(II) is extremely labile, but Co(III) is almost inert (18, 19).

We have utilised Sheldon's hot filtration test (20), which involves filtration of the catalyst part way through a reaction, followed by continuation of the reaction in the absence of the (solid) catalyst. Results were negative, with the reaction stopping
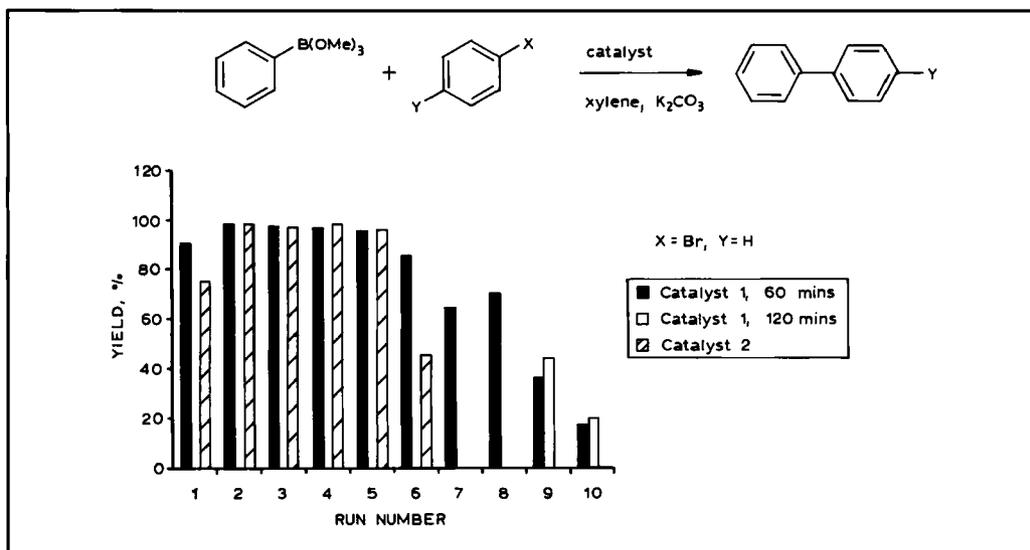
Fig. 6 Suzuki reaction using catalysts 1 and 2

completely after filtration. While the hot filtration test is widely quoted as a test for leaching, it is really a test for homogeneous catalytic contributions to the rate (Nolte and coworkers have recently demonstrated that a polymer-supported nickel catalyst passed the hot filtration test, but ICP analysis indicated a 20 per cent loss of metal into solution in an inactive form (21)). Therefore, we have additionally analysed the liquid phase for traces of Pd by atomic absorption spectroscopy, but failed to find any traces of Pd (to a detection limit of ca. 0.1 ppm). We are thus satisfied that our catalysts are heterogeneous.

Suzuki Reaction

The Suzuki reaction is currently widely used as the most efficient and general route to biaryls, which are of great interest in medicinal chemistry. It involves the coupling of an aryl boronic acid with an aryl halide, typically iodide or bromide (4–6), and is an attractive alternative to earlier methods based around earlier, organometallic (stoichiometric) coupling routes (22).

Catalysts

The optimum catalysts were again based on the pyridine-imine system active in the Heck reaction. Initial results were obtained on the phenyl boronic

acid/bromobenzene system detailed in Figure 6. In these reactions, the optimum base was found to be potassium carbonate. The reaction temperature was 95°C.

Results with the carboxylate catalyst indicated good initial activity, but reuse indicated a significant drop in activity from 76 per cent in 1 hour to 4 per cent, without washing the catalyst. Washing the catalyst with dichloromethane and then water restored most of the activity for one more run (76 per cent in 3 hours) but subsequent attempts at reuse failed.

With the MTS-based pyridine imine catalyst 2, the initial yields were excellent, as was recycling, with activity dropping off after 6 uses. The silica-based catalyst was better still, with very good conversions obtained at up to 8 uses, subsequent cycles being less successful, see Figure 6. It is not known what the loss in activity is attributable to, and thus the potential for further extension of catalyst life must still be investigated. Again, leaching tests (hot filtration and atomic absorption spectroscopy) proved negative, indicating a completely heterogeneous reaction.

A range of substrates reacts very efficiently under relatively mild reaction conditions, as shown in Table I. Excellent yields are obtained in all cases, except for those where chloroaromatics were used,

Table I
Results of the Suzuki Reaction Using Catalysts **1** and **2**

X, Y	Catalyst	Time, min	Yield, %	Substrate/catalyst
Br, H	1	180	98	83
Br, H	2	180	98	167
Br, H	2	180	97	833
Br, H	2	180	95	1667
Br, CN	1	120	98	167
Br, CN	2	120	92	167
Br, Cl	1	180	98	167
Br, Cl	2	180	88	167
Br, OMe	1	360	82	167
Br, OMe	2	360	79	167
Br, CH_2Br	1	360	79	167
Br, CH_2Br	2	360	60	167
Cl, CN	2	180	0	167
Cl, CHO	2	180	0	167

reflecting the general inertness of the C–Cl bond in such systems. In the Suzuki reaction, it may be that the solid base merely neutralises the acidic by-products after they are released from the catalyst surface into solution. This may help to minimise pore blockage from salt formation close to the active site, making the solid base better in this case.

Ferrocenyl Phosphine Palladium Supported Systems

Planar chiral ligand systems are of great interest in asymmetric synthesis, with BINOL and related systems being widely investigated (23–29). Planar chiral ferrocenes are another readily available and exciting area of chemistry. We have recently published results where we have attached such ferrocenyl phosphine systems to silica supports to provide a heterogeneous, and easily recoverable, catalyst system (30, 31).

The basic route to these materials is shown in the Scheme, overleaf. The ligand structure has then been used to coordinate various metals, such as rhodium for hydrogenation (31) and hydrosily-lation (32), and Pd for nucleophilic substitution reactions (31). Two versions of the supported ligand were prepared, one with a long (C_{10} spacer) 8b and one with a shorter (C_4) spacer chain 8a.

The synthesis of the materials was developed to attach a trialkoxysilyl group to a BPPFA unit, by substituting the methyl for a substituted alkyl group. This was achieved in three steps. The silyl-substituted ligand was then grafted onto silica by standard grafting methods, and the silica surface passivated by reaction with hexamethyldisilazane to block the polar silanol groups, and thus make the surface environment more organic-like.

The Pd catalysed allylic alkylation of the ace-toxypropene with the acac-derived nucleophile shown in Figure 7 was carried out with these materials, in comparison with BPPFA itself, and the longer-chain ester was used as a precursor to the supported catalysts. Results are shown in Table II.

It is clear that both the homogeneous catalysts give similar results in terms of yield and enantio-selectivity. While the yields of product drop slightly upon heterogenisation, the level of enantioselec-tivity remains essentially unchanged, indicating
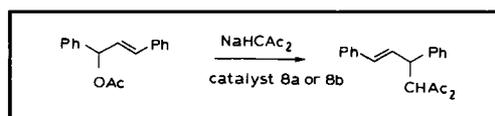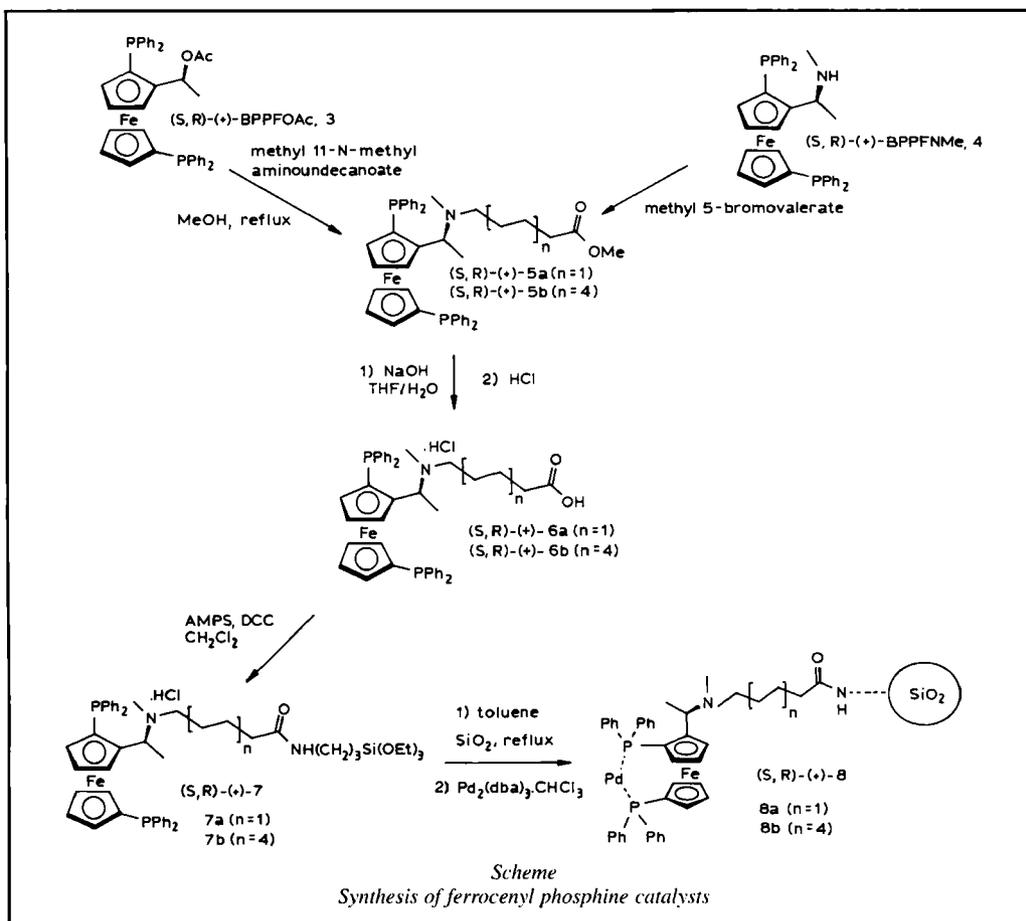
*Fig. 7 Allylic substitution of acetoxypropene with the acac-derived nucleophile, using catalysts **8a** and **8b***

Scheme
Synthesis of ferrocenyl phosphine catalysts

that the new catalysts show definite promise for further work. In particular, the recently published work by the groups of Johnson and Thomas (29) have indicated that this area of research can pro-duce extremely effective catalysts for such reac-tions, and a thorough evaluation of the influence of support nature and structure on the activity and selectivity of this family of catalysts is certainly worthwhile.

Palladium-Catalysed Coupling in the Preparation of Supported Catalysts

A further area of interest in the group is the use of the Heck, and to a lesser extent the Sonogashira coupling reaction as a method for building up functionality on the surface of silicas (32). We have shown that it is possible to use the Heck reaction to functionalise both haloaryl-functionalised silicas and acrylamido-functionalised silicas, with the lat-ter version generally giving better results, see Figure 8. Two factors are critical to the success of the method: first, the use of an amine base,

Table II		
Results of Allylic Alkylation Using Ferrocenyl Phosphines **7** and **8**		
Ligand	Isolated yield, %	ee, %
4	53	62
7a-Pd	48	62
7b-Pd	52	54
8a	29	16
8b	36	60

Results obtained in the allylic alkylation shown in Figure 7, using supported catalysts compared to unsupported analogues

Fig. 8 Elaboration of silica-bound surface functionality using the Heck reaction
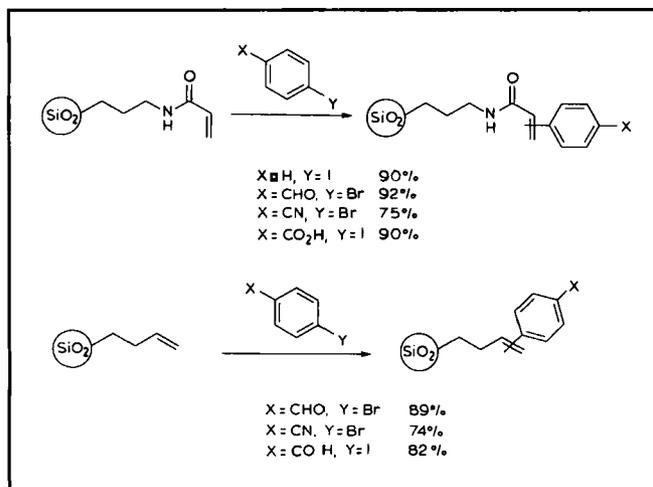
triethylamine, Hünig's base or tributylamine are all suitable, and second, the reaction must be run without solvent. Despite efforts to run the reaction in a range of solvents, no conversion was obtained, even though very high conversions could be achieved neat. We have more recently found that the Heck reaction works well with allyl-functionalised silicas and have used this approach to design novel initiator systems for polymerisation, the results of which will be reported shortly.

Conclusions

A series of silica-supported palladium catalysts has been developed and used in a range of different applications, including enantioselective catalysis.

The catalysts are stable and reusable and no evidence of leaching could be found. While further work needs to be carried out to improve catalyst lifetimes, the catalysts show great promise in several important reaction types, and can contribute to the development of cleaner chemical processes.

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Acronyms Used	
AMPS	Aminopropylsilica
BINOL	1,1'-Bis-2-naphthol
BPPFA	[Bis(triphenylphosphine)ferrocenyl] acetate
BPPFNMe	2-[Bis(1,1'-triphenylphosphino) ferrocenyl]-2-ethyl methylamine
BPPFOAc	2-[Bis(1,1'-triphenylphosphino) ferrocenyl]-2-acetoxyethane
DCC	Dicyclohexyl carbodiimide

Battsengel Gotov is doing postdoctoral work at the University of Cologne, Germany. His research interests include the synthesis of chiral ferrocene ligands, ligand anchorage to inorganic supports, their application in stereoselective palladium- and rhodium-catalysed reactions, and stereoselective synthesis on arenetricarbonylchromium complexes.

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