The Heck reaction at a silica surface. Functionalisation of simple organo-modified silicas

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The Heck reaction has been shown to be a useful method for the functionalisation of simple organically modified silica. Four organically modified silicas, representing four preparative routes, were further modified by Heck coupling of aryl halides and alkenes. The reaction proceeds at temperatures of 120–150 °C, and functions best in the absence of solvent. Triethylamine is favoured over inorganic bases, and leads to good conversions. The reaction is particularly effective when the surface-bound species is the alkene coupling partner.

The modification of silica to provide robustly bound organic groups has long been of interest to the catalyst, ion-exchange and chromatography communities.[1–7] More recently, the advent of combinatorial chemistry has added another potential application for surface-modified solids.[8] The commonest and simplest method of functionalisation relies on the reaction of the silica surface with a suitably substituted silane, typically $(RO)_3SiR'$, where R is usually Me or Et, and R' contains the moiety of interest. This approach suffers from the drawback that the variety of available R' groups can be limited, many of the more interesting silanes are very expensive and the preparation of more complex silanes from simpler starting materials can be troublesome. Furthermore, a variety of surface species may be produced, through, *e.g.* coupling *via* one, two or three Si—O—Si bonds, and silane oligomerisation/surface binding.[9]

Additionally, the Si—O—Si unit can suffer from solvolytic instability. An alternative approach involves the chlorination of silica, which is conveniently carried out in a fluidised bed reactor (FBR)[10] and subsequent displacement of the Cl by a Grignard or organolithium reagent. While this approach has considerable advantages in terms of providing a less complex spectrum of products (no oligomerisation, bonding is always through a direct Si—C bond, conferring high thermal and solvolytic stability) it too has limitations inherent in the need for strongly nucleophilic species and only a limited number of functional groups can be successfully bound to silica using this method. In particular, the incorporation of functional groups such as CO_2H and CN is precluded, as is that of other reactive groups such as CHO. Such groups are, however, of interest as surface-bound ligands for the preparation of useful catalysts.[11]

The Heck reaction has proved to be a versatile and easy method for the formation of C—C bonds, being tolerant of a wide range of functionality, and not requiring difficult reaction conditions.[12–14] Yu *et al.* have recently published results on the use of the Heck reaction in the functionalisation of organic resins for use in combinatorial synthesis.[15] In this work we describe the successful application of the Heck methodology to elaborate a variety of simple functional groups attached to silica. The examples given illustrate the use of this technique in the functionalisation of a variety of organo-functionalised silanes prepared by silane coupling and *via* chlorination displacement methodologies.

Experimental

Starting materials

The silica used throughout was Merck Kieselgel 100, and was used after drying at 300 °C overnight, except for FBR experiments, where it was dried *in situ*. 3-Aminopropyl(trimethoxy)silane was obtained from ABCR (98% purity). All other materials were obtained as SLR grade and were used without further purification. Tetrahydrofuran (THF) was dried by distillation from Na–benzophenone.

Characterisation

Infra-red spectra were recorded on a Perkin-Elmer FT1720 Fourier transform infra-red instrument, using an environmental diffuse reflectance (DRIFT) unit. Samples were prepared by dilution (*ca.* 15 : 1) with KBr, and were recorded after drying at 130 °C under vacuum in the DRIFT unit.

^{13}C CP MAS NMR data were obtained on a Bruker MSL 300 MHz spectrometer. Spinning rates were typically 5 kHz and 8000–15 000 accumulations were collected. Due to instrument limitations, spectra were often broad and, consequently, weaker signals such as quaternaries were sometimes unassignable.

Elemental analysis was obtained from Butterworth Laboratories. Mass spectra were obtained using a Fisons Autospec Mass Spectrometer. Samples were heated on a probe at a rate of 20 °C min^{-1} to 600 °C, with EI ionisation.

Titration of 3-aminopropylsilica **1** (AMPS) was carried out by stirring 1.00 g of **1** in 20 ml of 0.01 M HCl for 1 h, filtering off the solid and back titrating the filtrate with 0.01 M NaOH.

Preparation of 3-aminopropylsilica 1 (AMPS)

This material is well documented, and was prepared by standard methodology.[16] Titration and elemental analysis indicated a loading of 0.95 mmol g^{-1} aminopropyl groups. ν/cm^{-1} 2935, 2880 (C—H str.), 1592 (weak, NH_2 def.). δ_C 11.3, 28.1, 43.8 ($SiCH_2CH_2CH_2NH_2$ respectively). No peak was evident for SiOMe groups.

Preparation of acrylamidopropylsilica 2

The modified silica **1** (10 g, 9.5 mmol amino groups) was suspended in dry THF (200 ml) and the suspension cooled to 0 °C. Triethylamine (1.51 g, 0.015 mol) was added, followed by propenoyl chloride (1.09 g, 0.012 mol) over a period of 1 h. The temperature of the reaction reached 5 °C at the end of the addition. The thick slurry was then stirred at 0 °C for a further 4 h and the modified silica isolated by filtration and washing with THF (100 ml), water (2 × 100 ml) and THF (100 ml). The solid obtained was then dried in an oven at 110 °C for 24 h. ν/cm^{-1} 2900–2985 (C—H str., weak), 1660 (amide I), 1620 (weak, C=C), 1543 (amide II); δ_C 11.6 ($SiCH_2$), 21.1

$SiCH_2CH_2$, 45.7 (CH_2N) 126.3 ($CHCO$) 166.4 ($CH_2{=}CH$), 178.3 (C=O).

Preparation of but-3-enylsilica 3

Silica (30 g) was placed in a home-built fluidised bed reactor (FBR), and heated to a temperature of 450 °C in dry, flowing oxygen-free nitrogen (600 ml min^{-1}). After reaction temperature had been reached, the nitrogen flow was passed through a reservoir of tetrachloromethane, and the saturated gas passed through the FBR for 2 h. The resultant chlorinated silica was then allowed to cool in the FBR, and was directly added to a solution of but-3-enylmagnesium bromide in dry THF [made from the bromide (50 mmol) and Mg in THF (200 ml)]. The slurry was stirred for 3 h and filtered. The solid product was washed with THF (2 × 200 ml), water (4 × 200 ml) and THF (200 ml) before being dried at 110 °C overnight. ν/cm^{-1} 1620 (weak, C=C); δ_C 9.8 ($SiCH_2$), 21.8 (CH_2CH), 117.3, 134.1 ($CH{=}CH_2$). Elemental analysis indicated a loading of 0.66 mmol g^{-1}.

Reaction of 1 with 4-iodobenzoic acid to give the 4-iodobenzamide 4[16]

The modified silica **1** (10 g) was placed in a round-bottomed flask along with 4-iodobenzoic acid (5.00 g, 0.02 mol) and the contents heated with stirring to 170 °C under vacuum (1 Torr). After heating for 4 h, the solid residue was recovered and washed with acetone (3 × 100 ml). The product was dried at 100 °C overnight. ν/cm^{-1} 1640, 1550 (amide) 1570, 1470, (aryl, weak); δ_C 9.4, 22.9, 43.3 ($SiCH_2CH_2CH_2N$ respectively), 93.8 (C—I), 128.4, 134.5, 136.7 (aryl) 171.8 (CO); m/z 287 (propylamide cleaved from surface at Si—C). Alternatively, excess iodobenzoic acid can be removed by prolonged sublimation under the reaction conditions, obviating the need for washing. Both methods gave essentially the same results.

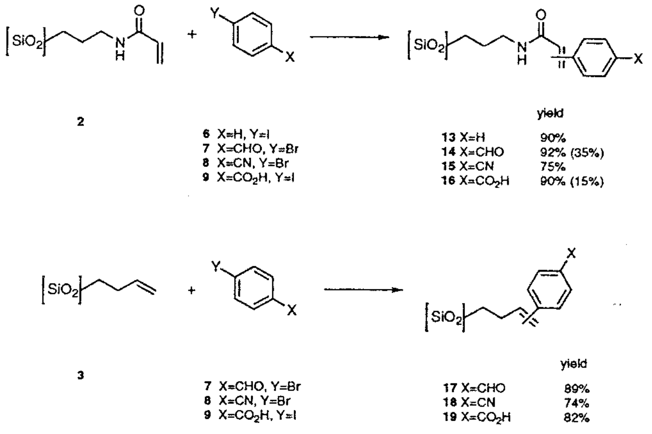
Preparation of bromo imine 5

The modified silica **1** (10 g) was suspended in toluene (150 ml) and 4-bromobenzaldehyde (2.78 g, 0.015 mol) was added. The reaction mixture was stirred for 2 h at room temperature. Unreacted aldehyde was removed by filtration and washing of the solid with toluene (2 × 100 ml) and diethyl ether (100 ml). The product **5** was then dried at 110 °C overnight. ν/cm^{-1} 2875–2977 (C—H str.), 1643 (C=N) 1592 (aryl); δ_C 9.1, 22.9, 40.6 ($SiCH_2CH_2CH_2$ respectively), 124.0, 131.0, 131.9, 133.2 (aryl), 175.4 (C=N).

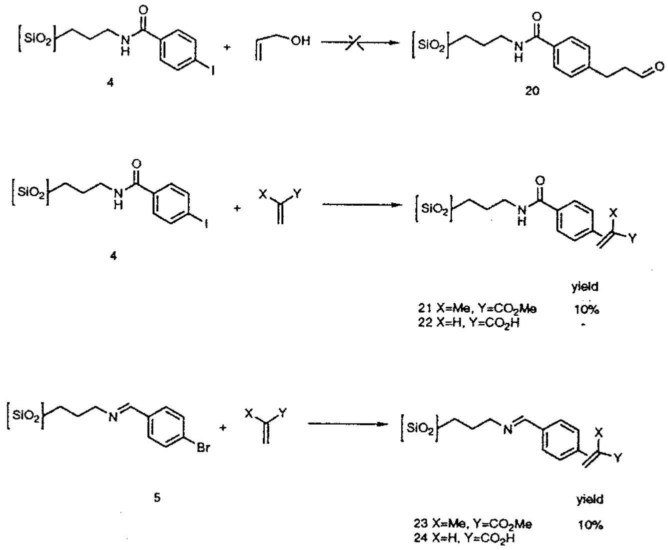
Typical Heck reaction procedure

The functionalised silica **2–5** (2.00 g) was mixed with the coupling reagent **6–12** (2.5 mmol) and $Pd(OAc)_2$ (5 mol% with respect to the coupling reagent) by dissolving the coupling reagent and catalyst in a suitable solvent [typically dichloromethane (10 ml)], adding the functional silica, and removing the solvent on a rotary evaporator. It is important that the last traces of solvent are removed, and the bath temperature was increased to 80 °C to achieve this. The resultant solid was added to a thick-walled flask, triethylamine (2.00 g, 20 mmol) and a stirrer bar added, and the mixture heated to 130 °C in an oil bath. The reaction was allowed to continue for 24 h, after which time the solid was collected and washed with dichloromethane (3 × 50 ml), acetone (50 ml), water (2 × 50 ml) and finally acetone (3 × 50 ml). The solids obtained were typically beige, although two were dark brown. The solids were dried at 110 °C overnight before analysis. Reactions carried out are represented in Schemes 1 and 2.†

Analytical data for the Heck coupling products are given below.



Scheme 1



Scheme 2

13. ν/cm^{-1} 2940, 2876 (C—H str.) 1650, 1550 (amide) 1600 (aryl, C=C), 1530, 1500 (aryl, weak); δ_C 9.8, 21.2, 41.9 ($SiCH_2CH_2CH_2NH$ respectively), 120.3–137.3 (br, aryl, $CHCO$), 162.7, 166.9 ($CH_2{=}$ and CO); m/z 90 (PhCH), 77 (Ph).

14. ν/cm^{-1} 2943, 2888 (C—H str.), 2703 (aldehyde CH), 1707 (C=O), 1653, 1531 (CONH), 1603 (aryl); δ_C 9.6, 23.1, 41.0 ($SiCH_2CH_2CH_2NH$ respectively), 125.9, 127.1, 136.4, 145.2, 150.1 (aryl, $COCH{=}$), 166.6 ($CH{=}$), 171 (CONH), 196.2 (CHO).

15. ν/cm^{-1} 2933, 2886 (C—H str.), 2229 (CN str.), 1654, 1533 (CONH), 1623, 1608sh (ring, C=C); δ_C 9.1, 21.8, 41.1 ($SiCH_2CH_2CH_2N$ respectively), 116.0 (CN), 129.7–139.7 (complex, aryl, $CHCO$), 163.6, 168.1 ($CH_2{=}CHCO$, and CONH).

16. ν/cm^{-1} *ca.* 3500 2350 (br, OH), 2941, 2878 (C—H str.), 1689, C=O (acid), 1658, 1549 (CONH); δ_C 8.9, 22.2, 41.5 ($SiCH_2CH_2CH_2NH$ respectively), 117.3–129.5 (complex), 140.0 (aryl, C=C) 168.3, 171.1 (CO_2H, CONH).

17. ν/cm^{-1} 3027 (weak, ring and C=C C—H str.), 2928, 2856 (aliphatic C—H str.), 1684 (C=O), 1603 (aryl); δ_C 14.2 ($SiCH_2$), 31.3 ($SiCH_2CH_2$), 120, 129.7, 141.3 (br), aryl, C=C), 196.1, 208.5 (CHO).

18. ν/cm^{-1} 2943 (C—H str.), 2228 (CN str.), 1628 (C=C, ring); δ_C 14.6 ($SiCH_2$), 31.3 ($SiCH_2CH_2$), 109.6 (CN), 120–145 (aryl, C=C).

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† Figures in brackets are those obtained using sodium acetate as base.

19. ν/cm^{-1} 2973, 2856 (weak, C—H str.), 3600–2400 (br, OH), 1700, 1684 (C=O), 1605, 1576, 1558 (aryl); δ_C 10.3 ($SiCH_2$), 18.8 (CH_2CH), 126.1, 127.5, 130.9 (sh), 136.5, 139.5, 145.7 (aryl, CH=CH), 173.5 (CO_2H).

21. ν/cm^{-1} 2935, 2886 (C—H str.), 1709, 1730sh (weak, C=O), 1652, 1541 (CONH), 1589 (aryl); δ_C 9.2, 22.1, 41.2 ($SiCH_2CH_2CH_2NH$ respectively), 49.9 (=CCH_3), 79.8 (OCH_3), 120.0, 130.6 (br), 139.2 (aryl, C=C) 181.3 (C=O).

23. ν/cm^{-1} 2933, 2882 (C—H str.), 1711, 1731sh (weak, C=O), 1663 (C=N), 1589 (aryl); δ_C 9.3, 22.7, 41.6 ($SiCH_2CH_2CH_2$ respectively), 63.5 (weak, OMe) 122.0–138 (aryl), 172.4 (C=N).

Discussion

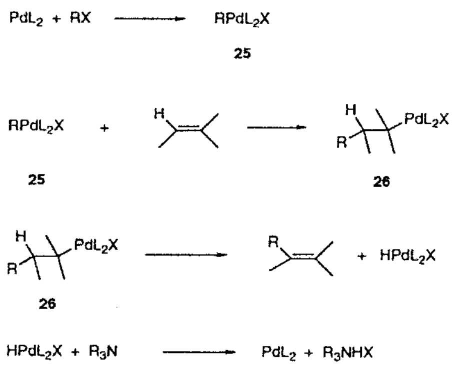
Preparation and choice of starting silicas

The reactions carried out were designed to illustrate the scope of the reaction for the functionalisation of a variety of modified silanes, and the preparation of a range of usefully functionalised silicas. Thus, established routes to simple modified silicas were used,[10,16] leading to **1** and **4**. The reaction of **1** with propenoyl chloride was achieved under typical reaction conditions in good conversion. Similarly, the reaction of **1** with aldehydes is very facile. FBR[10] preparation of the butenylsilica has the advantage of simplicity and allows the formation of the robustly bound alkenyl group directly to the silica surface. However only simple organic groups can be bound to the silica surface using this method. The results described in this paper represent a simple post-functionalisation technique which can be used to elaborate these simple groups and allow the attachment of more interesting functionality to the surface *via* these simple groups.

Heck coupling reactions

Conversion was estimated from elemental analysis, and is thus relatively inexact (±10%, at a level of functionalisation of 1 mmol g^{-1}).[17] However, what can be deduced (from IR and ^{13}C CPMAS spectra, and from thermal analysis) is that the reactions are clean, and unreacted materials and co-products such as amine salts are efficiently removed. The conversions for the successful reactions are typically high (80–90%), with less successful examples clearly giving lower conversions (typically 10–25%). The groups initially attached to the silica are robust and easily survive the reaction conditions.

The reaction has a wide scope, and a variety of couplings were successfully performed. Aryl iodides and bromides both react efficiently, with a rather unusual inversion of the normal activity being seen. Typically, iodides react more rapidly than bromides by a factor of 2–10.[12] This is considered to be due to increased ease of insertion into the C—I bond to form intermediate **25** (Scheme 3). However, in the case of reaction of **2** with **6** the iodide required 42 h to go to completion, while the bromide was consumed within 26 h. Such inversions of reactivity are unusual, and are normally ascribed to a change in rate determining step, such that the addition of the RPdX intermediate **25** to give the palladated coupling product **26** becomes the rate determining step.



Scheme 3

The formation of side products, such as biphenyls, was never observed, and the reactions yielded only surface bound Heck products. The choice of base is critical. The use of sodium acetate, sodium hydrogen carbonate or sodium carbonate, all effective in the solution phase, led to low conversion to product, while the use of triethylamine or diisopropylethylamine led to efficient coupling reactions. This feature is exemplified by comparison of the reactions of **2**+**7**, and **2**+**9**, leading to the products **14** and **16** respectively. While triethylamine gives yields of 92 and 90% respectively, the use of sodium acetate reduces the yield to 35 and 15%, with sodium carbonate being similarly inefficient. It is likely that the enhanced mobility of the amine base allows its efficient mixing and ingress into pores, and may even help in the transport of other reaction components to and from the reactive centres, whereas the inorganic bases are constrained by their physical form from effectively participating in the reaction.

The addition of phosphines to Heck reactions is commonly used to increase the rate of reaction,[18,19] although competing reactions such as quaternisation of the phosphine, yielding phosphonium salts, is a danger (this reaction is also catalysed by Pd species). Indeed, such quaternisation has been found to occur readily in similar systems, and has been used as the basis for the preparation of a series of supported phase transfer catalysts.[20] In the examples attempted during the course of this work, phosphines did not lead to increased rates, and evidence for a range of other P-containing products was found. These were not fully characterised.

It can be seen from Scheme 1 that the coupling of surface bound alkenes (**2** and **3**) with aryl halides proceeds successfully to give the coupling products in high yield. Slightly lower yields appear to have been obtained when nitriles were used, compared to aldehydes or acids. Due to the relatively inexact nature of quantitative analysis of such surface bound species, it cannot be definitely concluded that the yields are indeed lower.

Where the Heck reaction is clearly less effective is the coupling of surface bound aryl halides with alkenes (Scheme 2). In the case of acrylic acid, the reason for this is clearly the rapid polymerisation of the acid, a process which competes favourably with the coupling reaction. It was not possible to find conditions where the Heck reaction could be achieved without very rapid polymerisation taking place. The other two alkenes studied, allyl alcohol[21,22] and methyl methacrylate, both failed to give significant reaction, although a small amount of coupled product was evident from the spectra obtained from reactions with methyl methacrylate. Why these reactions are so disfavoured is unclear at the present time—the volatility of the alkenes is high, but there was always free, unreacted alkene in the reaction system at the end of the reaction. Indeed, volatility might be seen as being advantageous, allowing free access to the active centres on the surface. There was no evidence for significant polymerisation taking place, nor were there other products formed in these reactions. The solids were recovered unchanged.

Conclusions

The successful derivatisation of a series of organically modified silicas using the Heck reaction has been demonstrated. Nitrile, acid, aldehyde and ester functionality can be introduced under relatively mild reaction conditions. Yields vary significantly and are high for reactions in which the solid reaction partner is the alkene, and are much lower for those in which the aromatic partner is attached to the silica. The materials prepared are currently being tested in a series of reactions, either as catalytic moieties in their own right, or as ligands for transition metal based oxidation catalysts.

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