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Preparation of silane-grafted pellets: silica bound reagents in a very convenient form

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Abstract—High surface area silica pellets are excellent supports for the preparation of silica supported reagents and solid-phase basal linkers through reaction with $(RO)_3Si(CH_2)_3FG$ (FG = NH_2, NHMe, Cl, $NHC(=O)NH_2$, $OC(=O)CMe(=CH_2)$, NCO, NEt_2). High loadings (0.66–2.15 mmol g^{-1}) of grafted silane materials are realised at synthetically useful loadings per pellet (ca. 0.06 mmol). Preliminary trials show that trial linker chemistry and ligand synthesis can be carried out on these materials and that these reactions can be monitored by solid state ^{13}C NMR studies on individual pellets.

The surface of SiO_2 **1** is an attractive place to carry out derivatisation to new hybrid organo-inorganic silicon materials (Fig. 1). Both Lewis basic oxide sites and Brønsted acidic surface silanol groups are present. In general, the reaction of the latter with tris(alkoxy)silanes $[(R^1O)_3SiR^2]$ **2** affords good routes to silica supported reagents,[1] catalysts[2] and basal linkers for solid-phase organic synthesis,[3] where R^2 contains the desired functionality. Essentially all of these studies have focused on the use of powdered silica samples and these present a number of intrinsic technical difficulties: loading variability (typically 0.1–0.6 mmol g^{-1}) for commercial (chromatographic grade) silica;[3c,4] sample loss through 'bumping' while drying fine powders under vacuum; and the high cost (or need to prepare) many of the most useful, high surface area silicas (e.g., MCM41 silicas and related materials[5]). We considered that some of these issues might be overcome through the use of pre-formed silica pellets that are more commonly used for the preparation of heterogeneous catalysts through metal salt impregnation. At the outset of our project we were unaware of any publications in this area. A recent paper describing the use of pellet supported amines[6] causes us to disclose our own preliminary studies in this area.

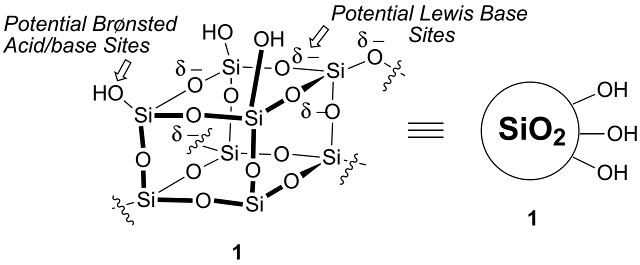

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Figure 1. Schematic representation of the surface of silica.

Preliminary investigations with $(EtO)_3Si(CH_2)_3NH_2$ **2a** and a range of commercial materials revealed that use of high surface area silica extrudate showed the most promise as a solid-phase support. This meso/macroporous material is supplied as cylinders approximately 6 mm long by 4 mm in diameter with a quoted total pore volume of 1.4 mL g^{-1}. We carried out BET surface area studies on this material and determined surface areas in the range 245–295 $m^2\,g^{-1}$. The majority of the mesopores had diameters in the range 160–800 Å by this analysis. Pellet batches with the higher surface areas are, as expected, the most reactive. Reflux of the pellets **1** with 20–40 mmol of **2a** (0.8–1.4 M in toluene) per gram of pellets resulted in high apparent loadings based on weight gain (Scheme 1, Table 1). Efficient stirring while preferred is not vital. The use of less solvent or no

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Keywords: supported reagents; silica; ligands; catalysis.

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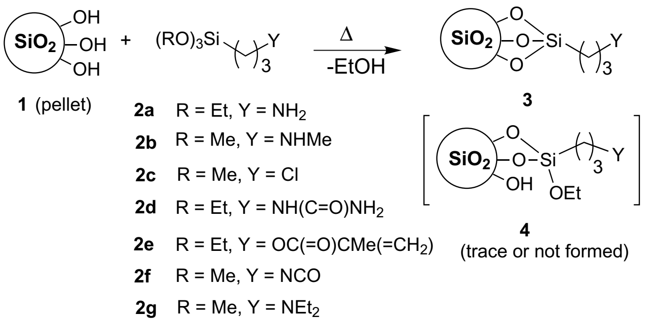


Scheme 1. Preparation of functionalised silica pellets.

Table 1. Loadings of pellets prepared in Scheme 1 using **1** with a BET surface area of 295 m^2 g^{-1}

2 (mmol g^{-1} pellets, concn/M)	Activation method[a]	Conditions	Loading[b] **3** (mmol g^{-1})
2a (5, 0.83)	None	110 °C, 2 h	1.83[c]
2a (41, 1.42)	Heat	100 °C, 72 h	1.83[d]
2a (20, 1.42)	Heat	110 °C, 48 h	1.37[d]
2a (40, 0.77)	HCl, heat	100 °C, 135 h	2.15[d]
2a (3, 0.32)	None	35 °C, 2 h	0.91
2b (50, 1.67)	None	110 °C, 2 h	1.70
2c (4, 1.10)	None	110 °C, 2 h	0.86
2d (22, 1.72)	None	110 °C, 2 h	2.30
2e (20, 1.40)	None	110 °C, 2 h	0.66
2f (20, 1.34)	None	110 °C, 2 h	1.25
2g (21, 1.35)	None	110 °C, 2 h	1.07
2h[e] (26, 1.62)	None	110 °C, 2 h	1.0

[a] Heat: 100–140 °C, 0.5 mmHg, 24–48 h; HCl: 6 M, 0.5 h followed by washing with distilled water until neutrality and drying.

[b] Mass change per gram assumed due to effective gain of $Si(CH_2)_3Y$ from **2** and loss of 3H from **1** normalised per gram of final product.

[c] A loading of 2.00 mmol g^{-1} was determined titrametrically.

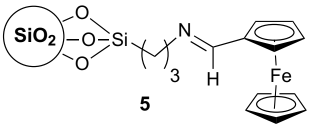
[d] Using pellets **1** with BET surface area of 245 m^2 g^{-1}.

[e] Prepared from $(MeO)_2SiMe(CH_2)_3NH_2$.

stirring led to crowding of the pellets and lower loadings resulted. Loadings determined by titration (HCl/NaOH back titration of **3a**, bromophenol purple indicator) are in agreement with the gravimetric loadings to within ±0.2 mmol g^{-1}.

Clearly the calculated pellet loading, based on mass change, depends on whether **3** or **4** are the major products (Scheme 1). Literature preparations of powdered silica samples, analogous to **3**–**4**, often make *arbitrary* assumptions about the **3**:**4** ratio (1:0 or 0:1 are commonly suggested). In fact, a range of potential surface products, possible through hydrolysis and Si–O–Si coupling of the $(EtO)_3Si(CH_2)_3NH_2$ **2a** at the silica surface, has been demonstrated.[2e,4] As knowing the bonding mode is vital to deriving the pellet's loading capacity we conducted solid state ^{13}C NMR spectroscopic studies on *single* pellets derived from **2a**. These clearly showed a single set of sharp resonances at 5.2, 22.7 and 39.9 ppm for the methylene chain at comparable frequencies to those of the parent silane in $CDCl_3$ solution (6.9, 26.7 and 44.4 ppm). On some occasions we observed traces of two signals at δ_C 12.1 and 53.9, which we attribute to OEt due to the presence of small amounts of **4a**.

Using the commercial high surface area pellets **1**, as supplied, and normal reagent grade toluene and silanes **2**, pellets **3** could be easily prepared. Pellets of lower surface area (ca. 245 m^2 g^{-1}), however, required activation by heating or treatment with HCl_{aq} (both common activation procedures with silica powders[2d]) to attain high loadings. These materials showed inferior properties in subsequent coupling steps and their use is not recommended. We speculate that the final functionalisation of pellet **1** with **2** takes place in the least accessible mesopores and that this is the source of the subsequent inferior coupling reactivity. To probe issues of silane distribution pellets **3a** were reacted with ferrocenyl aldehyde to afford orange samples of **5**.[7] A representative pellet was cleaved across its diameter and the internal surface surveyed by electron microscopy coupled to Fe-EDX back-scatter techniques. This revealed that ferrocenyl sites were on average evenly distributed across *the entire pellet*, based on averaging of 250 × 180 μm areas imaged across the sample. Localised 'hot spots' (within areas of 10^2 μm) of silane anchoring could be detected (via the Fe in **5**) at apparent defect sites on the silica but these occurred with equal likelihood at both the core and the surface of the pellet.



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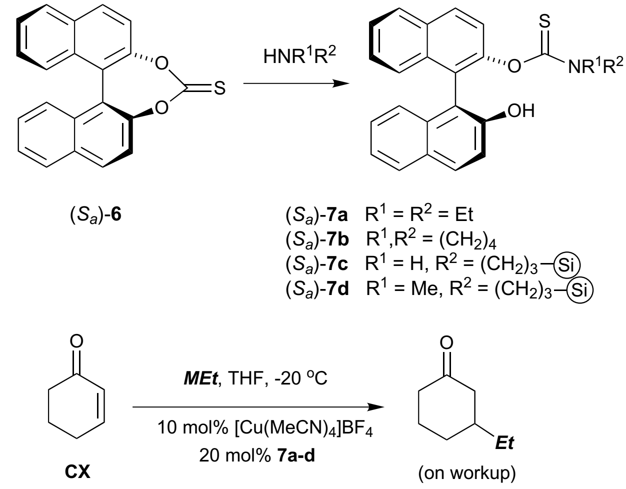
The loadings attained through the use of pellets **1** are significantly higher that those normally seen for powdered silica. The possibility that the weight gains observed in the pellets **3** are due to physioabsorbed materials on the pellets (either unreacted **2**, toluene, ethanol or water in the mesopores) must be excluded. TGA analysis of **3a** and **3c** coupled to MS assay of the off-gases provided no evidence for the presence of toluene or ethanol below ca. 300 °C. Significant mass losses were only seen around 500–700 °C and in both cases expected MS fragments could be identified. For example, in the TGA study of **3a** the presence of $[(CH_2)_3NH_2]^{\cdot+}$, $[CH_2C(=NH)H]^{+\cdot}$ and $[(CH_2)_3]^{+\cdot}$ were detected. These coupled to titrametric assays of the pellets indicated that the high loadings realised for these pellets are genuine.

Using related silanes the pellets **3b**–**e** could be easily prepared. In all cases ^{13}C NMR analyses of single pellets confirmed the apparent clean formation of a single product for all but **3f**. For **3f** the spectra indicated that partial alcoholysis of the isocyanate function had taken place through the EtOH released in the silane coupling and that an approximate 1:1 mixture of **3f** and surface supported $(CH_2)_3NHC(=O)OEt$ is present. As an unexpected bonus we found that silane functionalisation of **1** significantly improved the strength and resistance to



Scheme 2.

Table 2. Organo-metallic additions to Michael acceptors catalysed by $[Cu(MeCN)_4]BF_4$ (10 mol%) in the presence of ligands **7** (20 mol%)[a]

Ligand	Substrate/reagent	Yield (%)	Ee (%)
7a	**CX**/$ZnEt_2$	81	15 (*S*)
7a	**CX**/$AlEt_3$	27	27 (*S*)
7b	**CX**/$ZnEt_2$	36	20 (*R*)
7c	**CX**/$ZnEt_2$	14	<2
7d	**CX**/$ZnEt_2$	7	<2

[a] Determined by GC against internal standards.

damage of the pellets. This improvement is probably due to cross-linking of the amorphous silica domains in the initial pellets by **2**. Only two Si–OR linkages are required for this as similar toughening of pellets **1** was observed in the preparation of materials **3h**.

The pellets can easily be utilised as simple scavenger reagents. For example, pellets **2g** could be used as an HCl scavenger in the synthesis of esters, thioesters and amides. Reactions could be conducted on a small scale and the pellets removed simply with tweezers.

In additional preliminary studies, we have found pellets **3** to be of use in the synthesis of supported ligands. Reaction of (S_a)-BINOL with thiophosgene in a two-phase reaction of dichloromethane–$NaOH_{(aq)}$ promoted by NBu_4Br (4 mol%) cleanly afforded the expected cyclic thiocarbamate (S_a)-**6** without racemisation of the atropisomeric axis (Scheme 2).[8] In the presence of $HNEt_2$ or pyrrolidine (S_a)-**6** opened cleanly, over 2 h, to afford the desired thiocarbamates (S_a)-**7a**–**b** as the only detectable products by ^1H NMR spectroscopy. The application of a catalytic amount of DMAP had little effect on the rate of these reactions. Again chiral HPLC (Diacel AD) indicated that no racemisation is associated with the ring opening of (S_a)-**6** to (S_a)-**7a**–**b**. Having demonstrated the viability of the synthetic route in solution the synthesis was repeated, under identical conditions, with material **3a**–**b**. This afforded material **7c**–**d** with a coupling efficiency of above 90% based on mass gain. The single pellet ^{13}C NMR spectrum confirmed the formation of the solid supported thiourethane.

We,[9] and others,[10] have demonstrated previously that thiourethanes are useful additives in the asymmetric addition of $ZnEt_2$ to enones. For benzylidene acetone ee values of >90% are apparently possible, although for aliphatic substrates modest selectivities are realised. To examine the suitability of the new pelleted ligands for high throughput screening, pelleted materials **7c**–**d** were compared with near solution analogues **7a**–**b** in the 1,4-addition of $ZnEt_2$ to cyclohexenone (**CX**) as a model system (Table 2).[11] It is apparent that the presence of the silica surface interferes considerably with the desired selective catalysis meaning that lead identification would be problematic in blind screening studies of chiral Lewis acids.

We conclude that the active surface of these silica pellets (reactive silanol groups) negates their use in screening for lead ligand structures in chiral Lewis acid catalysis. Nevertheless, their other attractive features (high loading per pellet, ability to follow solid-phase reactions in single pellets, compatibility with split synthesis) renders them as potentially attractive supports in library synthesis. Further work aimed at this goal is under study in our laboratory.

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7. Compound **5** was prepared by reaction of equimolar quantities of **3a** and ferrocenyl aldehyde (16 h, dichloromethane, rt).
8. A sample of (S_a)-BINOL (1.0 g, 3.5 mmol) was stirred in dichloromethane/water (130/40 mL). Sodium hydroxide (0.28 g), NBu$_4$Br (4 mol%) and thiophosgene (267 μL) were added directly affording (S_a)-**6**. ^{1}H NMR (500 MHz) δ_H (500 MHz, CDCl$_3$) 7.36–7.42 (2H, m, H$_8$), 7.50–7.57 (4H, m, H$_{6+7}$), 7.60 (2H, d, $J = 8.9$ Hz, H$_3$), 7.98 (2H, d, $J = 7.9$ Hz, H$_5$), 8.04 (2H, d, $J = 8.9$ Hz, H$_4$); ν(C=S) 1262 cm^{-1}.
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11. Reactions were carried out as described in Ref. 9 except for run **7d**, which was allowed to react for 15 h at −20 °C.