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Interference of the Surface of the Solid on the Performance of Tethered Molecular Catalysts

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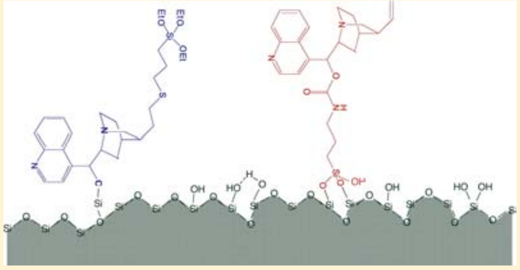
ABSTRACT: The catalytic performance of cinchonidine in the promotion of thiol additions to conjugated ketones was used as a probe to assess the tethering of molecular functionality onto solid surfaces using well-known "click" chemistry involving easy-to-react linkers. It has been assumed in many applications that the tethered molecules retain their chemical properties and dominate the chemistry of the resulting solid systems, but it is shown here that this is not always the case. Indeed, a loss of enantioselectivity was observed upon tethering, which could be accounted for by a combination of at least three effects: (1) the nonselective catalytic activity of the surface of the solid itself; (2) the activity of the OH species generated by hydrolysis of some of the Si−alkoxy groups in the trialkoxy moieties used to bind many linkers to oxide surfaces; and (3) the bonding of the molecule to be tethered directly to the surface. Several ideas were also tested to minimize these problems, including the silylation of the active OH groups within the surface of the oxide support, the selection of solvents to optimize silane polymerization and minimize their breaking up via hydrolysis or alcoholysis reactions, and the linking at defined positions in the molecule to be tethered in order to minimize its ability to interact with the surface.

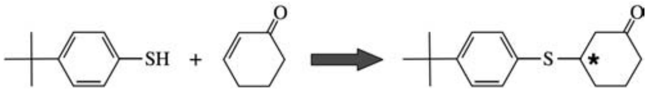


1. INTRODUCTION

In general, heterogeneous catalysts are preferred to their homogeneous counterparts: they are easier to handle and recycle, and they allow for a more facile separation of the products of reaction. On the other hand, it is difficult to match the level of selectivity that can be attained with homogeneous catalysts using heterogeneous materials. Simply, even with the new nanotechnologies being developed nowadays, it is not yet possible to imprint on solid samples the level of molecular detail required for complex catalytic sites.[1,2] A potential compromise is to "heterogenize" homogeneous catalysts by anchoring or tethering them onto solid surfaces. Anchoring has in fact been explored for decades with organometallic catalysts,[3,4] but the results have been mixed, either because those catalyst slowly leach out of the solid, or because the new constrained geometry imposed on the organometallic complex by the surrounding solid changes the catalytic behavior. Alternatively, molecular functionality may be added to typical catalyst supports such as silica or alumina to enhance their catalytic activity.[5,6] New "click" chemistry[7] has been advanced to facilitate the attachment of molecular compounds or structures to surfaces. In one approach that has become quite popular, silylating reagents are used for this purpose.[5,8,9] In fact, molecular functionalities tethered with such silylating agents have been extensively used for other applications beyond catalysis, including for the resolution of racemates in chromatography and other separation techniques,[10,11] as sensors,[12,13] and in biotechnology,[13−15] to mention a few. Surprisingly, though, not much work has been carried out to characterize the effect of the tethering process on the performance of the resulting solid, in particular in contrast with that of the free, nontethered, molecule.

Here we explore the effect that the surface of the solid exerts on the catalytic behavior of tethered molecular functionalities. The test system chosen in this study is a catalyst consisting of cinchonidine molecules tethered to silica surfaces, used to promote the addition of aromatic thiols to conjugated cyclohexanones.[16,17] Specifically, we report on results on the addition of *p*-tertbutylbenzenethiol to 2-cyclohexene-1-one according to the reaction in Scheme 1:

Scheme 1



This reaction is easily promoted by acids or bases, and when chiral compounds such as cinchonidine are used as catalysts, it leads to the production of an enantio-enhanced product. The tethering of the cinchonidine was done by using propyltriethoxysilanes terminated with appropriate linking groups, as reported before by us[18] and others.[19−22] Two approaches were tested in terms of the derivatization of the cinchonidine itself, one where a carbamate link is made by reacting 3-isocyanatopropyltriethoxysilane (ICPTEOS) with the OH moiety of cinchonidine, following the steps in Scheme 2, and a second where 3-mercaptopropyltriethoxysilane (MerPTEOS) was used to create a mercapto linkage through the vinyl moiety of the cinchonidine according to Scheme 3.

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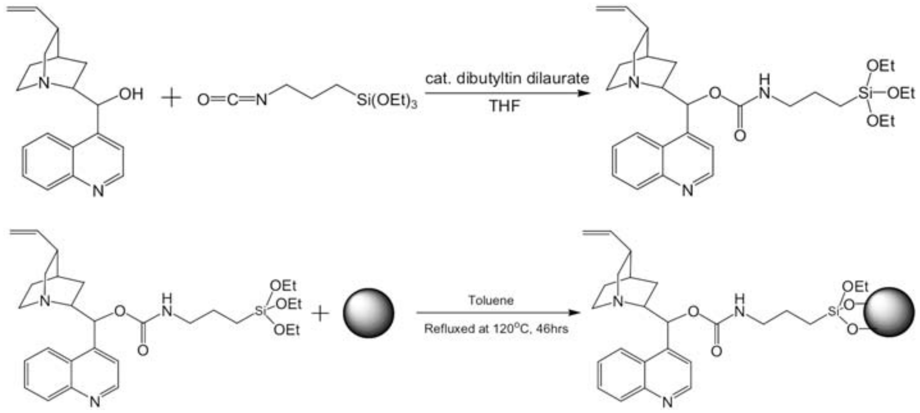
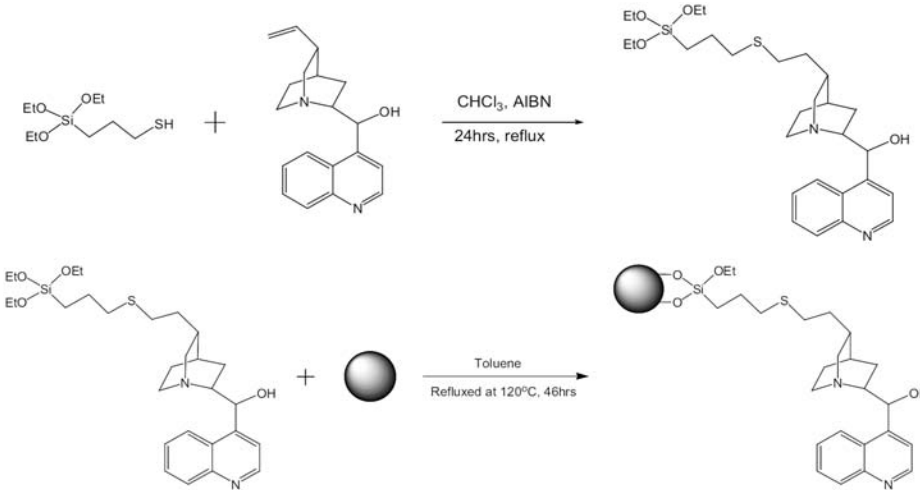
Scheme 2



Scheme 3



Tethering by reversing the steps in Schemes 2 and 3, namely, by anchoring the ICPTEOS or MerPTEOS linkers to the silica surface first and adding the cinchonidine afterward, were tried as well; both sequences worked, but the ones indicated above in Schemes 2 and 3 led to higher cinchonidine density on the surface. Finally, tethering was performed on both Aerosil[23] and ordered mesoporous SBA-15[24] silica supports. Only typical examples of our results for selected samples are reported here, but similar results and conclusions were reached with all these combinations.

It was found that cinchonidine tethered to silica surfaces can indeed promote the thiol addition in Scheme 1 at rates comparable to those seen when using free cinchonidine in solution. On the other hand, the enantioselectivity obtained with the tethered catalysts was not always as high as that seen in homogeneous solutions. Three factors were identified that explain this behavior: (1) a nonenantioselective promotion of the reaction by acidic sites within the silica solid; (2) a possible activity of the free OH groups in the silane end of the linker not bonded to the silica substrate; and (3) additional direct bonding of cinchonidine to the silica surface. Ways to minimize all these effects were tested, and enantioselectivities comparable to those in solution were eventually accomplished with the proper tethered catalysts. We believe that the factors identified in this study may interfere with many other tethered systems, and the solutions proposed here to be fairly general and applicable to those as well.

2. EXPERIMENTAL SECTION

The synthetic steps for the preparation of anchored cinchonidine on silica surfaces and for their subsequent treatments were all done using commercial chemicals: cinchonidine (Cd, Fluka, 98%), 3-isocyanatopropyltriethoxysilane (ICPTEOS, Sigma-Aldrich, 95%), 3-mercaptopropyltriethoxysilane (MerPTEOS, Sigma-Aldrich, 95%), Aerosil A200 silica (Degussa-Hüls), SBA-15 (ACS Material), 3-aminopropyltriethoxysilane (APTES, Sigma-Aldrich, 99%), dibutyltindilaurate ($(CH_3CH_2CH_2CH_2)_2Sn(OCO(CH_2)_{10}CH_3)_2$, Sigma-Aldrich, 95%), azoisobutyronitrile (AIBN, Sigma-Aldrich, 98%), hexamethyldisilazane (HMDS, Sigma-Aldrich, >99%), ethanol (EtOH, Gold Shield, 200 Proof), chloroform (Mallinckrodt chemicals, 99.8%), ethyl ether (EMD chemicals, 99%), dichloromethane (Fisher chemicals, 99.9%), pentane (J. T. Baker, 100%), cyclohexane (Fisher chemicals, 99.9%), tetrahydrofurane (THF, EMD Chemicals, 99.5%), and toluene (Sigma-Aldrich, 99.8%).

The carbamate-linked catalysts were made by first dissolving the cinchonidine in THF, adding the ICPTEOS together with a small amount of dibutyltindilaurate, and refluxing the mixture at 343 K for 3 h. After cooling down and letting the mixture rest for a day, the solvent (THF) was evaporated and pentane was added to precipitate the new compound (cinchonidinyl(3-triethoxysilylpropyl)carbamate, Cd−TEOSPC), which was filtered, washed with more pentane, recrystallized in chloroform and cyclohexane, and dried under nitrogen. The Cd−TEOSPC was then redissolved in ethanol and/or toluene and added to the silica, and that mixture was refluxed at 400 K for two days (or other times, as indicated in Figure 8). The final product, the cinchonidinyl(3-propylcarbamate)-functionalized silica (Cd−PC−Silica), was let to cool down, washed with ethanol, toluene and/or diethyl ether, and dried in vacuum before use.

For the mercapto-linked catalysts, cinchonidine and azoisobutyronitrile (AIBN) were mixed in chloroform, MerPTEOS was added, and the mixture refluxed at 343 K for 24 h. The mixture was cooled down, the solvent (chloroform) was evaporated, and pentane was added to precipitate the new compound (11-(3-triethoxysilylpropanethio)hydrocinchonidine, Cd−TEOSPMer), which was filtered, washed with more pentane, recrystallized in chloroform and cyclohexane, and dried under nitrogen. The Cd−TEOSPMer was then redissolved in toluene and added to the silica, and that mixture was refluxed at 400 K for two days. The final product, the 11-(3-propanethiyl)-hydrocinchonidine-functionalized silica (Cd−PMer−Silica), was cooled down, washed with ethanol, toluene and/or diethyl ether, and dried in vacuum before use.

The samples obtained after each step of the synthesis were characterized by transmission infrared absorption spectroscopy using a Bruker Tensor 27 Fourier-transform infrared (FTIR) spectrometer. A small amount of the liquids was placed between two NaCl windows, the solids were pressed into pellet form, and all samples were then placed at the focal point of the sample compartment of the FTIR instrument. The data correspond to averages of 1024 scans, taken at 4 cm^{-1} resolution and reference to appropriate spectra from an empty NaCl window setup or from pellets made out of pure silica.

Solid-state ^{29}Si CP-MAS NMR spectra were acquired on a Bruker Avance 600 spectrometer, employing a cross-polarization contact time of 2 ms, a ^{1}H decoupling bandwidth of 80 kHz, and a recycle time of 3 s. Data were acquired as 12 000 coadded 2048 complex data point FIDs with a 100 kHz sweep width. Post acquisition processing consisted of exponential multiplication with 200 Hz of line broadening and zero filling to 4096 data points. Chemical shifts were referenced to an external DSS sample.

For the XPS studies reported in Figure 9, a 1 cm × 1 cm square piece of a Si(100) wafer was exposed to a solution of APTES in toluene and refluxed at 385 K for a specified amount of time (1, 24, or 48 h, Figure 9). The resulting sample was then cooled down and washed with acetone and ethanol, and dried under vacuum prior to the XPS analysis, which was performed using a Kratos AXIS Ultra DLD.

The catalytic performance of our samples was tested by using the thiol addition reaction shown in Scheme 1.[16,17] *p*-Tertbutylbenzenethiol (Sigma-Aldrich, 97%) and 2-cyclohexene-1-one (Sigma-Aldrich, 95%) were mixed in benzene and let to react at room temperature for a day (with or without catalyst depending of the case being studied). The product, 3-(*p*-tertbutylbenzenelthio)cyclohexanone, was extracted using a separation funnel, washed sequentially with benzene, HCl (2.0 N, twice), KOH (2.0 N, twice), and a saturated NaCl solution, and dried over $MgSO_4$. The resulting benzene solution was filtered, the solvent evaporated, and the remaining liquid dried in vacuum. The product was purified using a chromatographic column and a hexane/ethylacetate = 10:1 mixture as the developing solvent. The identity of the product was corroborated by ^{1}H NMR, and its optical activity (reported as optical specific rotation) was measured in an ethanol solution using a MC 241 polarimeter with a Na lamp (λ = 589 nm).

3. RESULTS

Initial testing of the tethering of Cd on silica supports was provided in a previous report.[18] It was found that the tethered catalyst is still active for the thiol addition reaction depicted in Scheme 1, but not with the same enantioselectivity as when Cd is used in free solution. In our quest to understand this partial loss of enantioselectivity upon tethering of the catalysts, it was realized that the silica support exhibits some (nonenantioselective) catalytic activity of its own. Evidence for the catalytic activity of silica supports in this acid/base-catalyzed reaction and for the dilution of the enantioselectivity provided by the use of cinchonidine was obtained by testing physical mixtures of the cinchona alkaloid with different silica samples, including silica beads (20 mg) and Aerosil silica (20 mg). The data on the activity and selectivity of the different mixtures tested are summarized in Figure 1. The left panel, which provides information about the extent of conversion after 24 h of reaction at room temperature, indicates that all the catalysts investigated in this set, including the pure Aerosil silica (without any cinchonidine), are fairly active. On the other hand, the data in the center panel, which correspond to the specific optical rotation measured for the product of reaction, indicate a decrease in enantioselectivity for all catalysts that include silica solids. The role of the silica surface in diluting the enantioselective catalysis of cinchonidine is more clearly indicated by the data in the right panel, where the specific rotation of the product is plotted as a function of the amount of silica physically mixed with 4.4 mg (15 μmol) of cinchonidine in solution: the rotation values decrease monotonically with increasing amount of added silica.

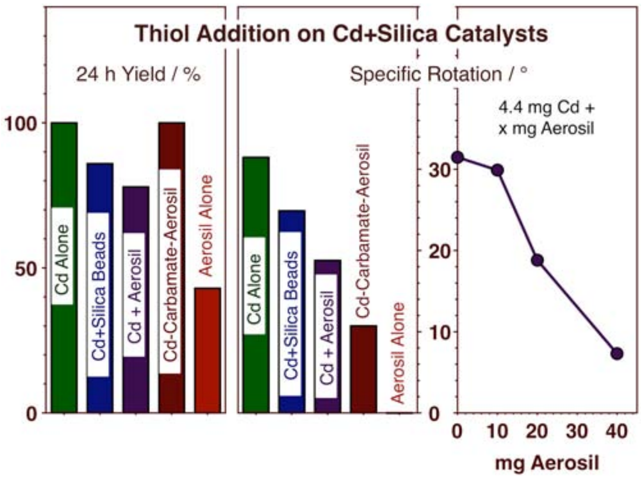


Figure 1. Summary of catalytic performance of samples made out of mixtures of cinchonidine (Cd) and silica for the promotion of the thiol addition reaction depicted in Scheme 1. (Left and Center) Yield after 24 h and specific optical rotation of the product, respectively, for the room-temperature conversion of 4-tert-butylbenzenethiol (0.3 mL, 1.8 mmol) and 2-cyclohexene-1-one (0.17 mL, 1.8 mmol) catalyzed by, from left to right, Cd alone in solution (4.4 mg, 15 μmol, green), Cd + 25 nm-silica beads (20 mg, blue), Cd + Aerosil silica (20 mg, purple), a tethered Cd-Carbamate-Aerosil solid (Cd−PC−Aerosil, 20 mg, magenta), and Aerosil silica alone (20 mg, red). (Right) Specific optical rotation of the product obtained after 24 h room-temperature conversion using physical mixtures of Cd (4.4 mg, 15 μmol) and the indicated amounts of Aerosil. All these data point to significant catalytic promotion by both Cd and silica but enantioselectivity associated only with Cd.

Also included in the data in Figure 1 are values obtained for a catalyst prepared by tethering cinchonidine to Aerosil silica via the hydroxyl moiety using the ICPTEOS linker, to yield a cinchonidinyl(3-propylcarbamate)-functionalized silica (20 mg Cd-Carbamate-Aerosil− or Cd−PC−Aerosil−, Scheme 2).[18] It can be seen from the data that the derivatized catalyst also shows high catalytic activity for the thiol addition reaction in Scheme 1, even if quantification of this activity in terms of turnover frequency (TOF) is difficult because of the difficulty in evaluating the concentration of cinchonidine tethered to the silica surface. On the basis of previously reported acid−base titration results using HCl as the titrant and methyl red as the indicator,[18] which estimated the cinchonidine density on Aerosil to be approximately 50 μmol/g, TOF values of about

1 and 10 s^{-1} were measured for the free cinchonidine (and the free Cd-TEOSPC and Cd−TEOSPMer) and the tethered Cd within the first 5 min of reaction, respectively. Quite possibly, the derivatized solid catalysts are intrinsically more active toward the thiol addition reaction than the free cinchonidine catalysts, an observation that, again, would be consistent with the silica independently promoting the reaction. From the data in the right panel of Figure 1, it could be estimated that the activity of 4.4 mg of Cd can be matched by using 20−30 mg of pure Aerosil. In terms of enantioselectivity, the Cd-tethered sample reported in Figure 1 displays approximately one-third of the enantioselectivity seen with pure Cd in solution (Figure 1, center panel).

It is clear from the data in Figure 1 that the silica supports do themselves show catalytic activity toward the thiol addition reaction in Scheme 1. It could be presumed that it may be the acidic catalytic sites, most likely the hydroxo groups known to exist on the surface of silica, that promote the thiol addition reaction. To minimize this catalytic contribution from the silica, blocking of the hydroxo sites via a silylation reaction using hexamethyldisilazane (HMDS) was tested.[25] The effectiveness of blocking OH surface groups using this approach was evaluated by using infrared absorption spectroscopy, since both isolated and hydrogen-bonded surface OH groups can be easily identified by the sharp peak at 3747 cm^{-1} and the broad band between approximately 3000 and 3800 cm^{-1} associated with those species, respectively. Addition of HMDS to the surface could also be evaluated by the appearance of its characteristic IR features, in particular those associated with the stretching modes of the C−H of the terminal methyl moieties at 2900 and 2965 cm^{-1}, as well as by the disappearance of the N−H stretching mode seen in the original free HMDS at 3380 cm^{-1}. This behavior is clearly seen in the spectra shown in Figure 2, which correspond to the case of HMDS addition to Aerosil silica. Two silylated samples are reported, after washing with ethanol and toluene solvents, respectively (together with reference spectra for the free HMDS and Aerosil).

It was found that HMDS is particularly effective at blocking the isolated OH groups: the sharp peak for that species at 3747 cm^{-1} in the IR spectra is completely gone once the surface has been silylated. There are nevertheless some remaining hydrogen-bonded hydroxo groups in these samples. A majority of those are likely to be internal moieties not accessible by reactants from solution, but some exposed groups are still evident by the differences seen between the samples treated using ethanol versus toluene as the solvent; the latter appear to be more effective at removing the hydrogen-bonded OH groups. In addition, it was determined that approximately half of the activity of Aerosil toward the thiol addition reaction remains upon silylation even when using toluene as the solvent (after adding mercapto linkers). This was found to be the case regardless, whether catalysts were used with the mercapto surface groups alone or after silylating the remaining sites using HMDS. Also, it was determined that, in general, the use of ethanol leads to surfaces with higher concentrations of hydroxo groups, specifically those associated with the low-frequency range of the O−H IR band around 3500 cm^{-1}.

These and other data showed that the choice of solvent for the treatment of the silica surfaces is critical in defining their final properties, one of the key observations of this study. That is further highlighted by the enantioselectivity catalytic data measured using these materials. Specifically, the catalytic properties of the cinchona-derivatized Aerosil solids were contrasted before versus after silylation in order to evaluate the effectiveness of that treatment in blocking the silica active sites, and those samples were also tested after washing with ethanol versus toluene to further assess the effect of the solvent. Contrasting data in terms of the enantioselectivity of the thiol addition reaction, reflected by the specific optical rotation of the product, are reported in Figure 3. Catalysts made by tethering cinchonidine via its vinyl group, using (3-mercaptopropyl)triethoxysilane as the linker, were used in this case (Scheme 3). It can be seen in Figure 3 that the enantioselectivity obtained with catalysts made using toluene as the solvent is much larger than that recorded with catalysts washed with ethanol, and essentially the same obtained with free cinchonidine in solution. This was in fact true even if the silica surface was not treated with the silylation agent, presumably because the triethoxysilane moiety of the linker acts as a silylation agent itself (spectroscopic evidence of this is provided below). When ethanol is used as the solvent, on the other hand, enantioselectivity does increase somewhat with silylation using HMDS, but not significantly in comparison with that seen with the free Cd or with the catalysts treated with toluene; it never reaches more than 40% of the specific rotation values obtained with the better samples. Ethanol is a common choice of solvent in these systems, the reason why we used it in our original report,[18] but it is clear that toluene is a better choice and should be preferred.

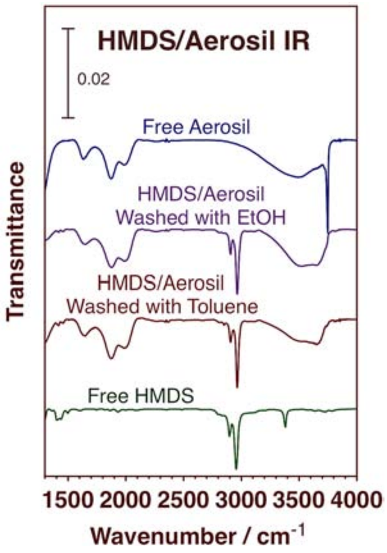


Figure 2. Infrared (IR) absorption spectra for, from top to bottom: free Aerosil silica (blue); Aerosil silylated with hexamethyldisilazane (HMDS), then washed with ethanol (EtOH, purple); Aerosil silylated with HMDS, then washed with toluene (magenta); and free HMDS (green). The addition of the HMDS to the Aerosil is indicated by the corresponding C−H stretching peaks at 2900 and 2965 cm^{-1}, and the blocking of the isolated silica OH groups by the disappearance of the 3747 cm^{-1} sharp feature in the spectra. Some hydrogen-bonded OH groups, identified by absorption between 3000 and 3800 cm^{-1}, are blocked as well, more efficiently if toluene (rather than ethanol) is used as the solvent.

The competing chemistries of surface derivatization and silylation were characterized in more detail next for the case where toluene was used as the solvent. The stepwise evolution of the surface species after each of the derivatization and/or silylation steps is mapped out by the IR absorption spectra shown in Figure 4. Initial addition of the (3-mercaptopropyl)-

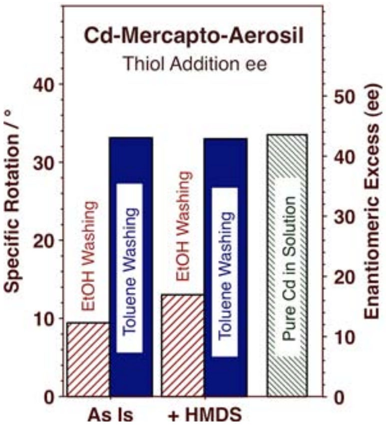


Figure 3. Specific optical rotation of the product from the thiol addition reaction catalyzed by tethered Cd−Mercapto−Aerosil (Cd−PMer−Aerosil) catalysts, as synthesized (left) and after silylation using HMDS (center). Data are shown for catalysts washed with both ethanol (course-hatched red) and toluene (solid blue). The specific optical rotation value obtained with free Cd is also provided for reference (right, fine-hatched green). The right-hand scale shows the appropriate enantiomeric excess (ee), calculated by using literature information.[16] The silylation of the catalyst washed with ethanol leads to a slight increase in enantioselectivity, but the larger effect is seen when switching to toluene as the washing agent, with which the tethered catalyst show a performance comparable to that of free Cd.

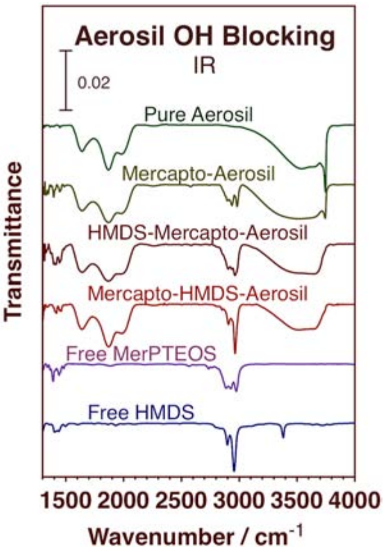


Figure 4. IR absorption spectra to illustrate the evolution of the surface of Aerosil upon bonding of the mercapto tethering agent (MerPTEOS) and silylation with HMDS. The traces correspond, from top to bottom, to: pure Aerosil (green); Aerosil derivatized with MerPTEOS (ochre); Aerosil first derivatized with MerPTEOS and then silylated with HMDS (magenta); Aerosil first silylated with HMDS and then derivatized with MerPTEOS (red); free MerPTEOS (purple); and free HMDS (blue). The best treatment for molecular tethering was determined to be a sequential derivatization with the tethering linker and silylation, in that order.

triethoxysilane linker to Aerosil is facile, as indicated by the appearance of its characteristic C−H stretching and C−H deformation IR bands in the 2800−3000 and 1300−1500 cm^{-1} regions, respectively, in the spectra from the tethered sample (compare the second versus fifth traces, from the top, in Figure 4). The derivatization consumes most, even if not always all, of the isolated OH groups evidenced by the sharp peak at 3747 cm^{-1}, a result consistent with the conclusion mentioned in the previous paragraph in connection with the data in Figure 3 regarding the triethoxysilane moiety of the linker acting as silylation agents itself. Either way, the remaining isolated hydroxo sites can be blocked easily by silylation using HMDS (third trace from top). The order of the surface derivatization can in principle be reversed, by adding the HMDS first, but in that case the subsequent addition of the linker is limited because most surface OH sites required for tethering have already been blocked by the silylation (fourth trace from top).

Additional experiments were performed to probe the nature of the resulting surfaces from tethering cinchonidine to the silica surfaces. Specifically, the samples obtained by performing the cinchonidine tethering step last, after sequentially adding the mercapto linker and HMDS, were contrasted against a sample obtained by first linking the MerPTEOS to the cinchonidine and then tethering the coupled molecule to the Aerosil support. The relevant IR absorption data, provided in Figure 5, demonstrate that cinchonidine can certainly be added last: its incorporation into the surface is mainly manifested by the quinoline deformation modes seen in the low-frequency end of the appropriate IR trace, in particular the peaks at 1463, 1512, and 1593 cm^{-1} (middle trace). It should be noted that the cinchonidine coverage in this case is significantly lower than when the Cd-TEOSPMer is made first and then tethered into pure Aerosil (bottom trace). On the other hand, the latter sample displays much more intensity in the low-frequency end (~3400 cm^{-1}) of the hydrogen-bonded OH section of the IR spectrum, indicating the availability of many more silica sites for nonselective catalysis.

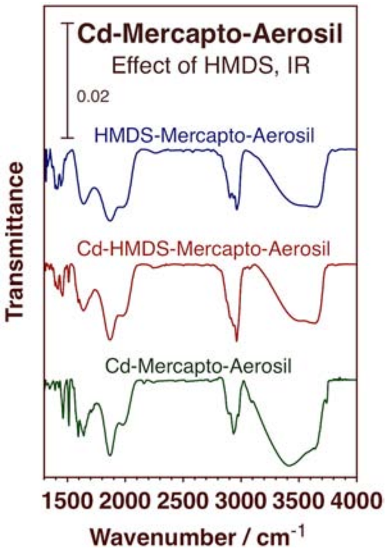


Figure 5. IR absorption spectra to illustrate the optimum procedure for tethering cinchonidine to silylated silica. Shown are, from top to bottom, traces for: Aerosil first derivatized with MerPTEOS and then silylated with HMDS (blue, the same as third trace from top in Figure 4); previous sample after Cd addition (red); and Aerosil derivatized with Cd−TEOSPMer (Cd-Mercapto-Aerosil, green). The latter synthesis leads to a higher density of Cd on the surface, but shows some isolated silica OH groups still exposed.

The possibility that the presence of specific surface sites within the silica support or the mode in which cinchonidine is tethered to the surface may contribute to the changes in the enantioselectivity reported here was assessed as well. For this, the specific optical rotation of the product from the thiol addition reaction was measured for catalysts based on Aerosil versus SBA-15, an ordered mesoporous silica-based material, and in samples where the cinchona was derivatized at the hydroxo (using a carbamate bond) versus at the vinyl (with a mercapto link) moiety. The data, shown in Figure 6, show some small differences in performance across the three catalysts referenced there. For instance, the carbamate-tethered sample washed with toluene exhibits a slightly lower enantioselectivity than the other toluene-washed catalysts, perhaps because derivatization via the hydroxo moiety may disturb the chiral pocket during catalysis.[26−28] Also, the sample made using SBA-15 and ethanol as the solvent shows a marginally better performance compared to the other ethanol-washed samples, possibly because the bonds made during tethering are sturdier in that case. However, none of these effects are significant in comparison with the main factor defining the enatioselectivity of these cinchonidine catalysts, which remains the solvent used for washing the tethered samples.

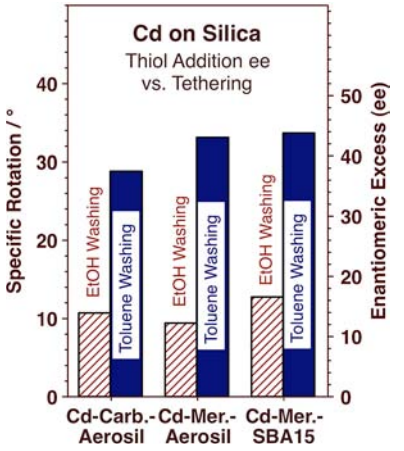


Figure 6. Specific optical rotation of the product from the thiol addition reaction catalyzed by three solid catalysts consisting of Cd tethered to silica, namely (from left to right): Cd-Carbamate-Aerosil; Cd-Mercapto-Aerosil; and Cd-Mercapto-SBA-15. Data are shown for catalysts washed with both ethanol (hatched red) and toluene (solid blue). The right-hand scale shows the appropriate enantiomeric excess (ee), calculated by using literature information.[16] Minor differences in catalytic performance are observed depending on the nature of the silica or the bonding mode of the Cd to the linker, but the main factor determining enantioselectivity remains the choice of solvent used during synthesis.

To better understand the difference induced by washing the catalysts with ethanol versus toluene during the tethering process, the nature of the bonding of the linker and cinchonidine to the silica surface was explored further by using ^{29}Si CP-MAS NMR. Figure 7 displays typical data, obtained for the Cd-Carbamate-Aerosil case after washing with ethanol versus toluene. Analysis of these spectra can be made based on well-established peak assignments:[18,29,30] the group of features around −80 to −120 ppm are associated with Si atoms from the original silica and the peaks in the −40 to −70 ppm range correspond to Si from the newly attached silane, and within each group, three peaks are identified with chemical shifts that decrease with increasing number of OH substitutions. On that basis, it is clear from Figure 7 that there is a significantly higher density of anchored silane groups on the Aerosil sample washed with toluene. Furthermore, that increase is almost exclusively associated with silane silicon atoms without any free hydroxo groups.

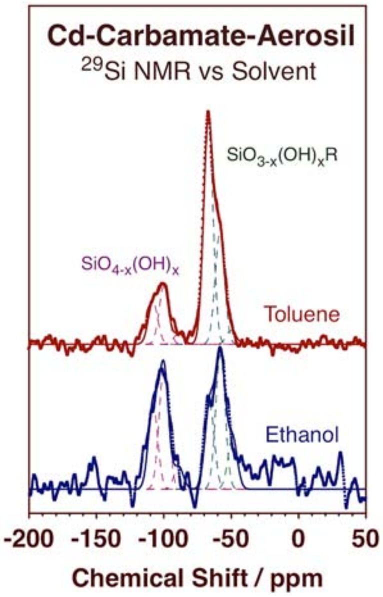


Figure 7. ^{29}Si cross-coupling magic-angle-spinning (CP-MAS) NMR spectra for Cd-Carbamate-Aerosil catalysts washed with toluene (top, red) and ethanol (blue, bottom). Two sets of peaks are observed in these data around −80 to −120 ppm and −40 to −70 ppm, corresponding to Si atoms from the original silica and the newly attached silane, respectively. Much more extensive derivatization is seen with the toluene sample, mostly in the form of polymerized silanes.

Quantitation of the extent of derivatization seen in this samples indicates a total number of new silicon atoms, originating from the added silane, exceeding the total number of OH groups originally available on the silica surface: the new-silane/old-SiOH-in-silica silicon atom ratios amount to about 1.2 and 3.1 for the ethanol- and toluene-washed samples, respectively. This is consistent with the silylation effect seen in the catalytic performance of the tethered catalysts as discussed above in connection with Figure 3: most of the initial surface OH groups are derivatized and made catalytically nonactive for our acid−base catalyzed reaction. It also means that some surface derivatization must involve OH groups from silanes partially bonded to the silica, which means that the anchored silanes in fact polymerize on the surface. The extent of this polymerization is significantly higher in the case of the toluene-washed sample, suggesting that ethanol may reverse that process, possibly by realcoholizing some of the silane bonds. Also from the data in Figure 7 it can be estimated that the bond of the silane to the surface involves on average approximately two Si−O−Si links in all cases.

The silane polymerization process on the silica surface is more clearly seen in Figure 8, where the evolution of the ^{29}Si CP-MAS NMR spectra is shown as a function of derivatization time for the case of the synthesis of Cd-carbamate-Aerosil samples using ethanol as the washing solvent. In general, it is clear that the amount of silane increases with derivatization time: the features in the −40 to −70 ppm region, which correspond to the silicon atoms from the Cd-carbamate-linker added to the surface, grow in intensity. Direct bonding to the original silica surface occurs quite rapidly, within the first hour

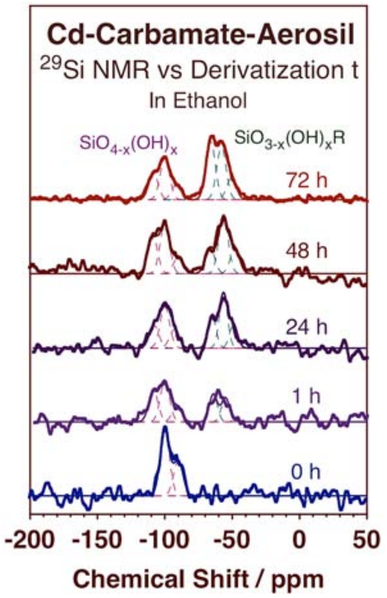


Figure 8. ^{29}Si CP-MAS NMR spectra for Cd-Carbamate-Aerosil catalysts as a function of derivatization time in a synthesis where ethanol was used as the washing solvent. The initial fast derivatization of the OH groups in silica is followed by a slower further growth associated with silane polymerization.

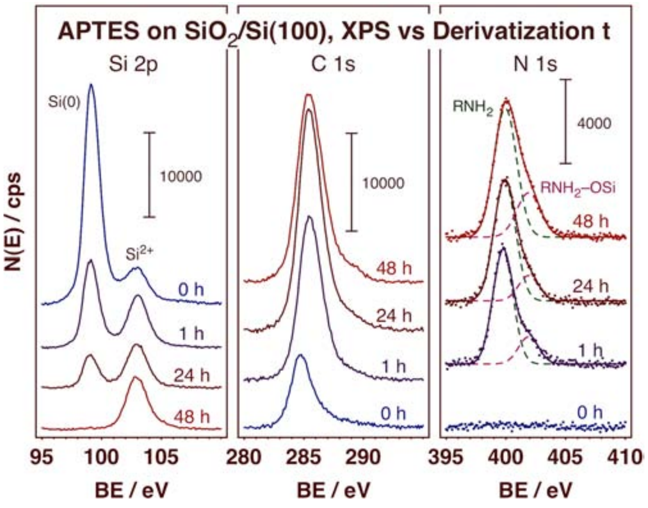


Figure 9. Si 2p (left), C 1s (center), and N 1s (right) XPS data for a Si(100) wafer treated with 3-aminopropyltriethoxysilane (APTES) as a function of derivatization time. The thin film of silicon dioxide that exists on untreated Si(100) surfaces, indicated by the Si^{2+} peak seen in the Si 2p XPS of the original sample, was used here to emulate the surface of silica. The initial reaction of the triethoxysilane moieties in APTES with the surface is manifested by the increase in the Si^{2+} signal and the decrease in the Si(0) peak intensity seen in the Si 2p XPS data after only 1 h, and the addition of the APTES by the growth of the main peaks observed in the C 1s and N 1s XPS. Afterward, a new N 1s XPS feature, associated with direct bonding of the amine to the silica, grows more slowly, and the silicon surface also continues to oxidize, until no reduced Si atoms are seen after 48 h.

of derivatization, at which point a significant number of single (≡Si−OH, −100 ppm) and geminal (=Si(OH)$_2$, −91 ppm) hydroxo groups from the original surface are converted to form fully oxygen-bonded (SiO$_4$, −108.5 ppm) silicon atoms. This means that new Si−O−Si bonds are formed and that the hydroxo-terminated silicon surface atoms in the original substrate are incorporated into the silicon dioxide network just underneath the surface. No significant additional changes are observed in the silicon atoms associated with the original silica surface after the first hour of derivatization, but further silane anchoring is still observed. This anchoring is first dominated by species bonded via two Si−O−Si bonds, but it is overtaken by the formation of three Si−O−Si links at later times, especially after 48 h of reaction. This is consistent with the silane polymerization process discussed above.

More details on the nature of the system that results from bonding linking agents to silicon oxide surfaces were extracted from experiments using X-ray photoelectron spectroscopy (XPS). In this case, an untreated Si(100) wafer, which is covered by a ∼1−2 nm-thick native silicon oxide film,[31] was derivatized with APTES, another common propyltriethoxysilane linker. Figure 9 displays the Si 2p (left), C 1s (center), and N 1s (right) XPS traces obtained after derivatization for various amounts of time (1, 24, and 48 h). Reference traces are also provided for the wafer before treatment for comparison. The Si 2p spectrum of the initial surface displays the features for Si(0) and silicon dioxide typically seen in these samples, at 99.1 and 103.0 eV, respectively, as well as some intensity in the C 1s data indicative of carbon contamination. Surface derivatization becomes clear both by the increase in signal seen in the 285.3 eV peak in the C 1s XPS traces and by the development of a new peak around 399.9 eV in the N 1s XPS data. In fact, that derivatization is about 70−80% complete already after only 1 h of reaction of the APTES with the surface. Given that the C 1s and N 1s XPS values are typical for those atoms in free amines,[32] it is straightforward to conclude that the initial anchoring occurs via reaction of the surface with the triethoxysilane moiety, and that the amine end of the APTES remains free, not directly interacting with the silicon substrate. However, following that initial deposition stage, an additional slower growth is seen in the N 1s signal in a second feature centered around 401.9 eV, a value characteristic of amine salts.[32] This strongly suggests that a direct interaction of the nitrogen atoms in the terminal amine moiety with silicon atoms on the surface occurs at this point involving the newly added APTES. It is also interesting to note that, upon treatment with the APTES linker, the signal from the reduced silicon in the Si 2p XPS data slowly disappears at the expense of the formation of an oxidized film, until only the latter is seen after 48 h. It is possible that the surface is slowly oxidized either by the solvent or, more likely, by the ethanol byproduct from the silane addition to the Si(100) surface. Alternatively, this behavior could be a reflection of the silane polymerization reaction mentioned before.

The XPS data, in particular the evolution of the N 1s XPS spectra with derivatization time, identified a new potential complication in the chemistry of tethering to silica surfaces, namely, the possibility of additional direct interactions between the surface and the functional group to be tethered. This may be particularly likely when that functionality is an acidic or basic moiety, like the case of the terminal amine group in APTES. A similar problem may occur in the case of the tethering of cinchonidine being reported here, since the nitrogen atom in the tertiary amine of the quinuclidine is somewhat basic, and since there is also an OH group present in the main chiral center of the molecule. Indeed, a new type of surface silicon atoms was identified by ^{29}Si CP-MAS NMR for the case of the Cd-Mercapto moiety tethered to either Aerosil or SBA-15

(Figure 10), a new sharp peak at −48 ppm, consistent with the direct interaction of surface silicon atoms with either the quinuclidine nitrogen or the alcoholic oxygen of cinchonidine. Given that this NMR feature was not observed in the Cd-Carbamate cases, the latter seems the most likely.

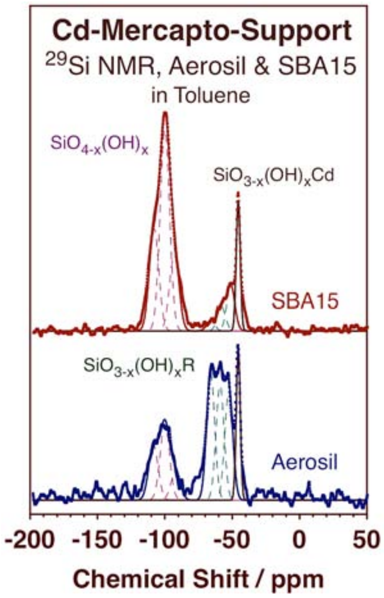


Figure 10. ^{29}Si CP-MAS NMR spectra from two Cd-Mercapto-Silica catalysts, based on SBA-15 (top, red) and Aerosil (bottom, blue) as substrates. Toluene was used as the washing solvent. Less derivatization is seen on SBA-15, but in both cases, significant direct bonding of the Cd to the silica is manifested by a new sharp peak around −48 ppm. No equivalent direct bonding was seen with the Cd-Carbamates or when ethanol was used for washing.

4. DISCUSSION

As mentioned in the introduction, the tethering of molecular functionality to the surfaces of oxides is becoming a popular way to modify the chemical properties of solids. The use of “click” chemistry, where a linker is employed, has developed into a particularly easy and widespread approach for this purpose. Numerous examples exist in the literature already for the specific case of the use of propyltriethoxysilanes, which are available with many linking groups (such as amine, thiol, isocyanate, azido, or organic acid moieties), and silica surfaces as the linker and substrate, respectively. Applications for the derivatized surfaces have ranged from catalysis to chromatography, sensing, microelectronic devices, and biotechnology. In most of the cases reported in the literature, it has been assumed that the tethered molecules retains their chemical behavior upon anchoring on the surface, and that such chemistry dominates the reactivity of the newly prepared solid.

We have shown here that this hypothesis may not be necessarily valid. Instead, additional active groups on the surface may interfere with the desired chemistry of the added molecular modifier. Three specific potential interfering factors were identified. The first is the chemical activity of given surface sites within the support. Even on silica surfaces, which are often assumed to be inert, the terminal hydroxo moieties can act as acidic centers. In the test case used in our study, those acidic sites were shown to be capable, by themselves, of promoting acid−base catalyzed reactions such as the thiol addition to conjugated ketones indicated in Scheme 1. The activity of the silica support for that reaction was shown to be comparable to that of the cinchonidine with which the surface was to be modified. It could be thought that the presence of additional acidic sites on the silica only add to the basic centers provided by the cinchonidine, leading to even more active catalysts. However, that potential additional activity comes at the expense of selectivity, the reason for the interest in using cinchonidine as the promoter in this reaction. The loss of enantioselectivity in the production of the thioether reported in Figure 1 was used here mainly as a probe to separate the contributions from the silica and the cinchonidine to the promotion of the reaction, but could also constitute a major drawback if such type of selectivity is the motivation behind the choice of the particular functionality to be added to the surface. Molecular selectivity may be induced by the steric or electronic properties of the tethered modifier, which can be used to control regio-, stereo-, or enantioselectivity in addition, elimination, or isomerization reactions, for instance. That selectivity may be lost if a significant fraction of the conversion is promoted by the nonselective surface sites of the solid support.

We have also provided a potential solution for this problem, namely, the blocking of the silica acidic sites with inert moieties via silylation treatments. Silylation is a well-known and common treatment, used, for instance, for the passivation of glass surfaces,[25] and was shown here to be effective in blocking OH groups on high-surface-area silica supports (Figure 2). Infrared absorption spectroscopy data indicated that the use of HMDS in particular leads to the complete blocking of all isolated OH groups within silica surfaces, and also the capping of most, if not all, of the hydrogen-bonded OH sites available for reaction. Interestingly, though, it was found that, at least for the systems studied here, this treatment does not lead to significant changes in the activity or selectivity of the catalysts (Figure 3). Presumably, the linkers used for tethering can themselves be viewed as silylation agents, consuming most, if not all, of the surface OH groups available on silica (Figure 5). Nevertheless, the addition of HMDS makes surface passivation more extensive (Figure 5). To make the tethering of the molecular functionality on the surface the most efficient, it was shown that it is important to carefully consider the sequence of steps used for tethering and silylation: it is more effective to perform the silylation step last in order to avoid the premature blocking of the OH surface groups needed for tethering (Figure 4). A recent report provides an alternative sequence where a protecting group is used to preserve the tethered molecular functionality during the silylation process.[33]

Even if all initial OH groups within the silica surface are blocked, or even if they are not critical to the performance of the molecularly modified surfaces, there is a second issue to be considered in connection to the tethering of molecular functionality to these solids, that bonding of the linker to the surface may not be complete and may leave unreacted functionalities at the interface with the surface. In the case of the trialkoxysilanes so often used in these applications, the potential for the formation of up to three Si−O−Si bonds per linker is seldom realized, and an average of approximately two bonds is seen in most cases instead (Figure 7). That leaves, on average, a free Si−OH moiety per linker available for reactivity (after hydrolysis of the original Si−OR). Those species may be catalytically active, and may, again, interfere with the selectivity of acid−base catalysis. Additionally, it was found that those Si−OH groups are amenable to polymerization reactions with other silanes (Figures 7 and 8). That leads to extensive surface derivatization, beyond what is possible based on the initial availability of OH groups on the silica surface, but also to the clustering of the molecular functionality added to the solid.

The exact effect that this clustering may cause on the performance of the derivatized surface is not clear. Nevertheless, it became evident from the results of our experiments that the extent of this polymerization may be affected by the solvent used in the tethering process. In particular, ethanol may unravel some of the silane polymers that may build up on the surface and/or slow down the polymerization process, perhaps because the ethanol molecules can attack the newly formed Si−O−Si bonds and realcoholize them. The data in Figures 7 and 8 clearly show that more extensive derivatization and polymerization is obtained if the use of alcohols is avoided and toluene (or another inert solvent) is used instead. Interestingly, the catalysts prepared using toluene, where silane polymerization is more extensive, are more enantioselective for the thiol-addition reaction (Figures 3 and 6). One possible explanation for this difference is that the silane polymerization consumes the dangling OH groups left unreacted during the initial tethering reaction, and that exposure of the catalyst to ethanol alcoholizes some of the new Si−O−Si bonds and creates more catalytically active but nonselective OH sites. This is undesirable, so the use of nonreactive solvents (and the avoidance of exposure to water, which could hydrolyze the Si−O−Si bonds) during tethering is recommended.

Finally, a third complication comes from the potential direct interaction of the molecular modifier with the silica surface. It was shown above that even with the simple amine group at the end of the APTES linker such interactions are possible: XPS evidence was obtained for the direct bonding of the nitrogen atom to silicon atoms within the silica surface (Figure 9). For the case of cinchonidine tethered via a mercapto linker attached to the peripheral vinyl moiety in the quinuclidine ring (Scheme 3), ^{29}Si CP-MAS NMR data strongly suggest that a direct bond is formed between the surface and the OH group of the cinchona alkaloid (Figure 10). The latter problem could be avoided by tethering the cinchonidine using a carbamate linker instead, since that attaches directly to the alcohol moiety (Scheme 2), but, either way, the chiral pocket in cinchonidine, believed to be responsible for much of its enantioselective catalysis,[26,34,35] may be compromised. Alternatively, the cinchonidine−surface interaction may be avoided or broken by changing the solvent: it does not appear to survive after washing the catalyst with ethanol. The controlled use of ethanol may be advisable to prevent the direct bonding of the modifier while avoiding the alcoholysis discussed above.

5. CONCLUSIONS

In this study, the enantioselectivity of the addition of a thiol to a conjugated cyclic ketone was used as a probe to evaluate the performance of catalysts made by tethering cinchonidine to silica surfaces. The tethering was performed by using established “click” chemistry in which a C_3 hydrocarbon linker is bonded to both the surface and the cinchona alkaloid using triethoxysilane and either isocyanato or mercapto links, respectively.

The resulting heterogeneous catalysts were found to show activity comparable to that of free cinchonidine in solution, but, in many cases, diminished enantioselectivity. At least three factors were identified as responsible for this deterioration in catalytic performance: (1) a competition in catalytic promotion between cinchonidine and the acidic sites of the silica substrate; (2) additional promotion by the OH groups created by incomplete conversion of the triethoxysilane fragments in the linker; and (3) a direct interaction between cinchonidine and the silica surface.

Several possibilities were explored to eliminate, or at least mitigate, these interferences. First, it was shown that the hydroxo groups that act as acidic sites in silica may be blocked using a silylating agent such as hexamethyldisilazane. By following a proper sequence of derivatization steps involving the propyltriethoxysilane linker and the silylation agent, all of the isolated OH groups and most of the hydrogen-bonded OH moieties of the silica surfaces may be passivated. In terms of the new OH groups created by hydrolysis of the Si−ethoxy bonds from the linker that do not participate in the attachment to the silica surface, which were estimated to initially amount to approximately one of the three in the triethoxysilane, those were found to be able to participate in subsequent silane polymerization reactions as long as no alcohols were used in the surface derivatization process. Indeed, silica-tethered cinchonidine catalysts prepared using only toluene as the solvent displayed enantioselectivities comparable to those seen with free cinchonidine. Finally, it was found that the OH group in cinchonidine may bind directly to the silica surface, presumably affecting its catalytic performance. This problem could be minimized either by tethering the cinchonidine using a carbamate linkage at that OH position, or by washing the final catalyst briefly with ethanol. A balance needs to be struck to avoid alcoholysis of the polymerized silanes, however, since that leads to a decrease in enantioselectivity.

The studies reported here focused on the performance of a specific set of tethered catalysts, but the conclusions reached in terms of interference of the solid upon heterogenization of homogeneous catalysts may be general. The effects cited in terms of the potential chemical activity of the solid itself or of the OH groups generated upon reaction of silane-based linkers with surfaces and of the possible bonding of the tethered molecule directly to the surface may be easily encountered in many of the other systems that rely on similar tethering approaches, not only in catalysis, but also in chromatography, racemic separation applications, sensors, and biotechnologies.

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Notes

The authors declare no competing financial interest.

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