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Communications

Synthesis of a Confined Class of Chiral Organic Catalysts via Bulk Imprinting of Silica

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Asymmetric organocatalysis is a rapidly developing area,[1] with (*L*)-proline and its derivatives playing a prominent role as efficient and selective small molecule catalysts for an increasing number of homogeneous reactions, including important carbon−carbon bond-forming reactions such as aldol and Michael reactions.[2,3] While immobilized forms of asymmetric organocatalysts have been known and used,[4] the advantages of these materials over their homogeneous counterparts have remained largely limited to filtration and ease-of-recovery.

The beneficial effect of confinement on enantioselectivity has been demonstrated previously in heterogeneous organometallic catalysts[5−14] as well as in homogeneous organometallic systems,[15,16] yet this effect remains to be proven for asymmetric organic catalysts. One of the complicating factors for studying the effect of confinement in heterogeneous inorganic-oxide catalysts is the varied surface chemistry of inorganic oxide materials, which is intrinsically due to the presence of a variety of defect site environments. These differences in turn lead to differing chemical interactions between the active site and the solid surface, which can affect catalysis, independent of effects arising due to confinement at the active site. Because proof of confinement effects in heterogeneous catalysis requires comparisons across different materials, it is difficult to separate the effect of confinement on catalysis from specific active site−surface chemical interactions in any two materials being compared. A promising solution to this apparent dilemma is the exhaustive capping of accessible defect sites within the two materials being compared. While exhaustive capping fails to completely eliminate all active site-surface interactions,[17] it minimizes potential differences in surface chemistry between

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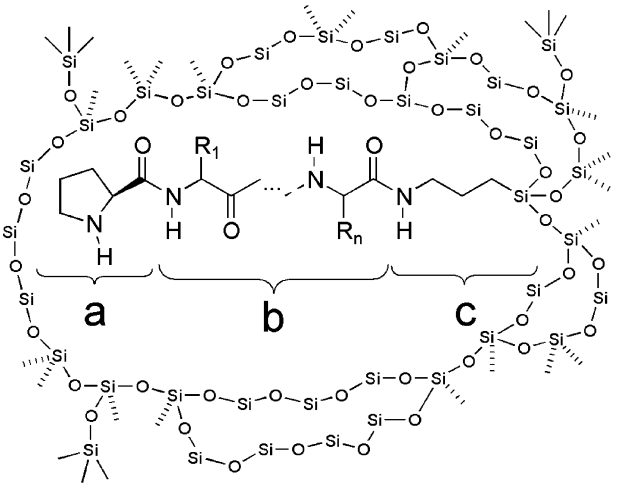


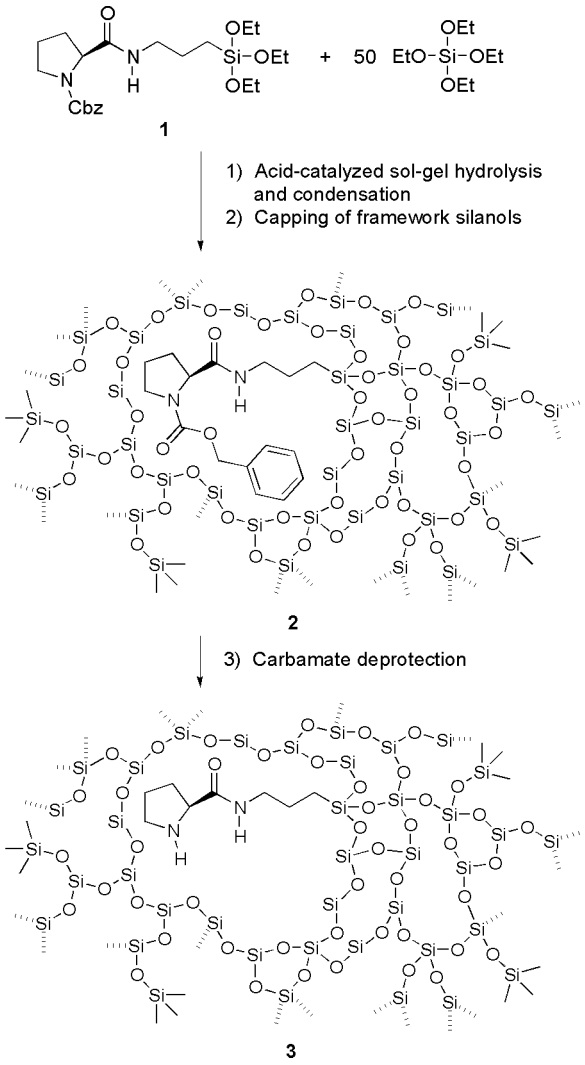
Figure 1. Conceptual illustration of the general materials synthesis approach including (a) the proline catalyst, (b) $R_1 \cdots R_n$ functionalities as chiral directing or hydrogen bonding groups, and (c) the amide functionality to anchor the catalyst to the silica pore wall.

any capped materials being compared. Thus it then becomes possible to rigorously ascribe differences between two materials with differing porosity to confinement rather than potential differences in active site−surface interactions.

Our goal here is to develop a general synthetic method that will permit the confinement of a class of asymmetric organocatalyst active sites as isolated species in hydrophobic silica. These attributes are necessary in order to study the effect of confinement on organic catalysis. We have specifically targeted the class of proline amide[18−20] catalysts as a general structural motif for our heterogeneous catalyst system, because the amide hydrogens present in the catalyst possess the ability to hydrogen bond to reaction substrates, which has been shown to be an important interaction for controlling catalyst enantioselectivity.[19] Our approach is to design and synthesize proline amide catalysts covalently attached to silica via a propylamine tether. We use the technique of bulk silica imprinting[21] for the synthesis of isolated active sites within confined and hydrophobic environments. The hydrophobic environment is synthesized via exhaustive capping with TMSCl/TMSI and results in a saturation coverge of TMS-capped silanols as described previously.[21] A conceptual illustration of our desired catalyst is shown in Figure 1. Accomplishing the synthesis of the conceptual material shown in Figure 1 requires demonstrating the imprinting of secondary amines in bulk, microporous silica as well as the synthesis of a chiral active site with bulk silica imprinting.

The objective of this paper is to demonstrate a generalizable materials synthesis method that leads to accessible and active catalytic sites in a resulting prototypical material. The

Scheme 1. Synthesis of Confined Catalyst



general catalytic entity contains three distinct regions: (a) the proline catalyst; (b) an oligomeric chain potentially containing additional chiral groups,[22] which may hydrogen bond to reactant;[23] and (c) the amide anchor to the silica framework.

For the proof of concept system, we choose the simplest possible proline-amide imprint, consisting of only the catalytic proline and anchoring amide group, without additional directing groups (section b in Figure 1). The materials synthesis approach for the confined imprinted catalyst is shown in Scheme 1. The hybrid organic−inorganic material containing immobilized imprint is synthesized via an acid-catalyzed sol−gel hydrolysis and condensation of **1** with an excess of tetraethyl orthosilicate. As previously demonstrated by related bulk silica imprinting methods, the materials synthesis procedure is known to produce bulk microporosity with an average pore size of 5−10 Å in diameter.[21] The resulting glass monoliths are ground to particles 10 μm and less in diameter. The silica framework is rendered inert via capping of interior surface silanols with trimethylsilyl functionality, which removes framework acid-

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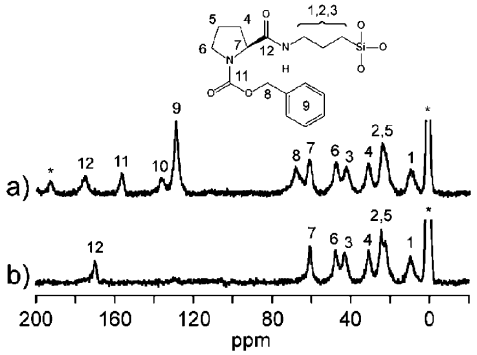
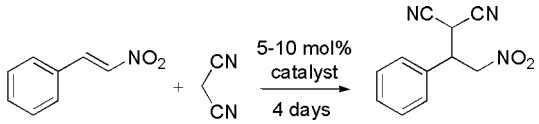


Figure 2. ^{13}C CP/MAS NMR spectra of (a) material **2** (before deprotection) and (b) material **3** (after deprotection). Asterisks denote TMS resonances and spinning sidebands. Resonances at 0 ppm have been truncated for visual clarity.

Scheme 2. Michael Addition of Malononitrile to *β*-Nitrostyrene



ity, as confirmed by spectroscopic measurements on related silica materials with salicylaldehyde as a covalently bound probe molecule.[24] The immobilized carbamate is subsequently deprotected with iodotrimethylsilane.[21] This synthesizes the bulk imprinted silica **3** containing an isolated chiral secondary amine within each imprinted pocket.

The imprint deprotection process can be followed via ^{13}C CP/MAS NMR as shown in Figure 2. All resonances expected for the intact imprint are present in the sample prior to deprotection. Following deprotection, resonances corresponding to the Cbz protecting group (resonances 8, 9, 10, and 11 in Figure 2a) are removed, while those corresponding to the remaining secondary amine and amide are retained. It is also important to note that resonance 12 experiences a shift of approximately 5 ppm upfield following deprotection. This shift likely results from a local microsolvation effect that arises specifically from removal of the Cbz group, rather than resulting from a specific hydrogen bonding interaction between the amide hydrogen and carbamate groups. This is based on results from single-crystal X-ray diffraction and infrared spectroscopy on closely related systems, which show that while the amide carbonyl may be in close proximity to the carbamate,[25] there is no specific hydrogen bonding interaction involving the amide hydrogen and carbamate.[26] The amine site count for **3** was 0.15 mmol/g, representing accessible amines under the conditions of the nonaqueous potentiometric titration.

Our initial attempt to evaluate the activity for this class of catalysts was made via the Michael addition of malononitrile to *β*-nitrostyrene, as shown in Scheme 2. The reaction has been reported previously in homogeneous solution,[27,28] although there have been no prior reports of enantioselectivity for this reaction. Our activity results using imprinted silica catalyst **3** shows that a recovered yield of product of 14% was achieved upon stirring 10 mol % catalyst in benzene solvent for 95 h at room temperature (0.352 mol of nitrobenzene/malononitrile in 4 mL of benzene solvent at room temperature), which corresponds to a turnover frequency of 0.014 reaction events per catalytic site per hour. The performance of the bulk imprinted catalyst was compared to a Selecto mesoporous silica-grafted catalyst, which has been previously characterized using nitrogen physisorption.[29] This was performed because such a surface-grafted catalyst has an average pore diameter of 45 Å after capping and imprint immobilization and would therefore be a good choice for a mesoporous material, in conjunction with microporous **3**, to rigorously assess the effect of mechanical confinement on organic catalysis. The surface-grafted material was prepared via conventional post-synthetic techniques by stirring imprint **1** with commercially available mesoporous silica support in acetic acid at 75 °C. Following grafting, the sample was capped and deprotected by the same procedures as imprinted silica catalyst **3**. The amine site count for the surface-grafted batch was 0.09 mmol/g.[29] Background reaction was confirmed to be negligible in the absence of catalyst as well as in the presence of a control material consisting of a TMS-capped silica without amine sites as monitored by gas chromatography.

The catalytic activity results clearly reveal the accessibility and activity of the bulk imprinted sites, although no enantioselectivity was observed. Additionally, the surface-grafted type catalysts provided an average turnover frequency of 0.048 reaction events per catalytic site per hour, which is slightly larger than for the bulk imprinted catalysts. This indicates that confinement within a microporous material may carry consequences of mass transport restrictions for catalysis when the inherent rate of reaction is faster than diffusion through the bulk framework. However, the presence of mass transport limitations is not expected to interfere from the standpoint of assessing effect of confinement on enantioselectivity, when using a probe reaction that creates a chiral center.

In conclusion, we have synthesized novel imprinted materials that have successfully translated proline-based homogeneous catalysts to the synthesis of confined catalytic materials containing isolated sites within hydrophobic microporous and mesoporous environments. This has required achieving the first imprinting of chiral secondary amines within bulk, microporous silica. We now aim to extend the materials synthesis approach to other catalysts, as conceptualized in Figure 1. Inserting additional chiral directing groups between the proline and the amide tether may be effective for achieving higher enantioselectivity, as demonstrated for homogeneous prolyl-peptide catalysts.[22] In particular, hydrogen bonding groups of varying acidity is an important parameter to examine, as shown by a previous

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study that found enantioselectivity rose with increasing amide acidity.[19] We are currently applying our general materials synthesis approach for studying the effect of confinement in organocatalysts. These results will be reported in due course.

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Supporting Information Available: Materials synthesis, nitrogen physisorption, reaction conditions, and details of control experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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