Silica Mesocellular Foam and Carbon Nanofoam for Fine Chemical Synthesis and Separation

by

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B.S. Chemical Engineering
The Pennsylvania State University

Submitted to the Department of Chemical Engineering in Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy in Chemical Engineering

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Abstract

In chromatography, the selective separation for large molecules, polymers, and proteins is of particular interest. To achieve quality separations, the stationary phase should exhibit pore diameters greater than 10 nm to facilitate the diffusion of large analytes throughout the stationary phase. In packed-bed applications, narrow particle and pore size distributions and uniform particle shape would lead to improved separations. Thus, spherical stationary phase particles are often preferred, but the challenge has been to combine spherical particle morphologies, high surface areas, large mesopores, and narrow pore size distributions.

We have successfully created a new three-step synthesis of spherical MCF (S-MCF) particles utilizing sodium fluoride as a condensation catalyst. The approach allowed for independent control over S-MCF particle and pore size, and was extended to other non-ordered porous silicas. The S-MCF particles were engineered into a reverse-phase chromatographic column and achieved good separation ability for a mixture of aryl ketones. By relating chromatographic performance to S-MCF surface silanol chemistry, an improved S-MCF chromatographic support was realized, which rivaled the separation capability of a commercially available chromatographic support.

The asymmetric Diels-Alder (ADA) reaction is very useful in building complex chiral molecules through the formation of chiral carbon ring structures, and it presents an excellent route for generating new therapeutic molecules. Although these compounds are of great importance, homogeneous ADA catalysts exhibit moderate activities and are not readily recovered and reused. This has prevented the ADA reaction from being widely practiced in the pharmaceutical industry.

To create more attractive catalysts, MCF was used to anchor chiral bisoxazoline-copper(II) complexes for the ADA reaction. We have examined the effect of catalyst environment on activity and selectivity through the use of different catalyst ligands, linker groups, and silanol capping agents. The MCF-immobilized catalysts showed enhanced activity compared to their homogeneous counterparts, and the phenomenon was correlated to bisoxazoline ligand loading on the MCF surface. Batch recycling
experiments and continuous ADA reactor trials showed that the MCF-anchored catalysts were reusable and stable. Catalytic performance was measured through in situ infrared spectroscopy, and a Michaelis-Menten kinetic model with product inhibition was applied to determine relevant kinetic parameters for the best heterogenized catalyst.

The Heck reaction is a powerful synthetic tool in organic chemistry for C-C bond formation through a liquid-phase reaction between aryl halides and alkenes. It has great industrial potential, but the Heck coupling reaction catalysts have traditionally suffered from low oxygen tolerance and poor reusability due to palladium cluster growth, agglomeration and oxidation.

In this work, a new mesoporous and crystalline carbon, carbon nanofoam (CNF), was examined as a Pd cluster support for the coupling of 4-bromoacetophenone and n-butyl acrylate. Using CNF as a support, we successfully synthesized Pd/CNF catalysts using a vapor grafting approach and demonstrated high activities for the Heck coupling at 140°C. The Pd/CNF catalysts showed remarkable performance enhancements compared to Pd/activated carbon catalysts. More importantly, we confirmed that Pd/CNF catalysts were reusable over several cycles in the presence of oxygen. The robustness of the Pd/CNF catalysts was correlated to the prevention of Pd cluster growth and oxidation on the CNF surface, and the minimization of Pd leaching from the CNF support.

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Chapter 1
Background and Motivation

1.1. Introduction

Selective separation techniques, asymmetric C-C bond synthesis and improved heterogenized catalyst performance represent challenging research areas in the fine chemical and pharmaceutical industries.¹² Current technologies make heavy use of porous materials to address these needs. Reverse-phase mesoporous silica materials dominate the liquid chromatography market, while organometallic complexes immobilized within mesoporous silicas provide for more reusable asymmetric catalysts. In the area of carbon-carbon coupling reactions, microporous carbons have been used as supports for catalytic metal clusters.

A large amount of research has been devoted toward the development of advanced porous support systems. It is of interest to be able to control the pore size, pore morphology, as well as the particle size and shape of porous systems. In order to do so, researchers have made use of self-assembly techniques for the synthesis of advanced mesoporous materials. Nevertheless, few reports have demonstrated control over macroscopic material properties, pore size and pore shape simultaneously. No published syntheses appear to control both the macroscopic and microstructural properties of porous carbons or silicas with pore sizes between 10 nm and 50 nm. Materials with pores in this size range are highly desirable for separations and catalysis because they not only provide for high surface areas, but also facilitate the diffusion of large substrates.

1.2. Spherical Mesoporous Silica for Liquid Chromatography

Liquid chromatography separates mixtures into individual components based on their relative affinities for a solid phase and a liquid mobile phase. An ideal stationary phase should exhibit selectivity for the desired analyte, display a high loading capacity, tolerate a wide variety of mobile phases and be available in large quantities. A majority of liquid chromatography columns involve reverse-phase supports, where the support is made hydrophobic.

The requirements for high-quality liquid chromatographic separations are column uniformity and a selective stationary phase. Uniformity comprises a number of key factors,
including column packing, particle size, particle shape, pore size, surface area and support surface chemistry. Without exception, all commercial analytical chromatography support particles are spherical and are generally 5–10 μm in diameter. As particle size decreases, the separation ability and pressure drop of the column increase. Thus, particles in the range of 5–10 μm represent a tradeoff between separation quality and pressure drop. The particle size distribution should also be narrow to avoid excessive pressure drops throughout the column. Generally, 80% of most chromatographic support particles lie within 2 μm of the median (d₅₀) particle size.

Pore size, pore morphology and pore size distribution also play a role in separation performance. The pores should allow for the attachment of chemical moieties, while permitting analytes to freely diffuse throughout the particle. Typically, support pores are at least 10 nm in diameter. Pore morphologies and pore size distributions affect the residence times of analytes within the particle. An ideal support would have an interconnected, non-tortuous pore structure and a narrow distribution of pore sizes. Broad pore size distributions and tortuous pore frameworks would cause peak broadening and a lower column loading capacity.

Mesoporous silica is widely used in liquid chromatography due to its versatile sol-gel synthesis and its easily modified surface chemistry. Mesoporous particles are generally used in chromatographic separations, since they allow for facile diffusion of analytes throughout their framework, while enabling functionalization of their internal pore surfaces.

Spherical mesoporous silicas (SMS) are required for chromatography applications. Non-templated SMS for chromatography often have pores greater than 10 nm, low surface areas and wide pore size distributions, which limit column loading and lead to broad peak shapes. Templated syntheses give spherical silicas with high surface areas and narrow pore size distributions. However, no examples of templated spherical silicas with pores greater than 10 nm exist. A spherical mesoporous chromatographic support with high surface area, narrow pore size distribution, and pores greater than 10 nm would be very useful for separations involving large molecules and proteins.

Nearly all commercial chromatography supports utilize non-templated SMS. However, a few recent accounts demonstrated the use of templated SMS in high-performance liquid chromatography (HPLC). Ma et al. used a combination of Pluronic P123 surfactant,
CTAB surfactant and ethanol to form SMS with pores of 8–10 nm. These materials were used for the separation of small aromatic molecules, but the column did not achieve baseline separation and exhibited overlapping peaks. Salech et al.\textsuperscript{6} utilized a mixture of alkylamine surfactants, TEOS and modified silica precursors to obtain SMS with pores of 4–5 nm. The materials were tested in normal-phase chromatography, and achieved a fairly good separation of polycyclic aromatic hydrocarbons. However, no efforts were made to test the particles in a reverse-phase application. Boissiere et al.\textsuperscript{7} produced spherical silica particles using a two-step synthesis, and tested the materials in a normal phase mode for the separation of aromatics. The materials achieved a reasonable separation, although substantial peak overlapping was noticed. These reports illustrate that while there has been some research towards the application of templated SMS for HPLC, much work remains.

1.3. Mesoporous Silicas for Enantioselective Carbon-Carbon Bond Formation

In past decades, significant advances in chiral ligand synthesis and organometallic chemistry have led to important commercial processes involving asymmetric homogeneous catalysts. Although they work very well, homogeneous catalysts have several shortcomings, including difficult separation from the reaction medium, inability to survive particular separation schemes, and possible product contamination.\textsuperscript{8} Additionally, some of the most active homogeneous catalysts undergo bimolecular decomposition in solution, and consequently lose their activity and selectivity.\textsuperscript{9}

In recent years, there has been a drive to immobilize homogeneous organometallic species. The objective is to fixate homogeneous catalysts onto an insoluble support, without diminishing the high activity and selectivity of the catalyst complexes. The heterogenized catalysts can then be used in a packed bed reactor or be recovered from the product stream via filtration, eliminating expensive separation and catalyst recovery operations.\textsuperscript{8}

Mesoporous silicas are of great interest as a support for immobilizing chiral organometallic catalysts. Due to their flexible surface chemistry, functionalities can be introduced onto the mesoporous silicas, and different linker groups can be used to immobilize the organometallic complexes. In addition, the catalytic activity and selectivity of the immobilized species can be varied through the control of pore size, surface area and catalyst loading of the mesoporous silica support. However, no accounts have systematically examined these effects on catalytic performance to achieve superior properties.
In this study, efforts are devoted towards chiral carbon-carbon bond formation technologies for pharmaceuticals synthesis. Although a number of highly selective homogeneous catalysts exist for such reactions, they generally require high catalyst-to-substrate ratios, presenting a severe barrier for process scale-up. Heterogenized catalysts may overcome this problem by immobilizing organometallic complexes within mesoporous silica for ease of reuse. However, relatively little research has been devoted towards engineering the environment surrounding the catalytic species in heterogenized systems to optimize the properties of immobilized catalysts.

Trong On et al.\textsuperscript{10} claimed a synergistic effect between the pore structure, anchored complex, diffusing substrate, catalyst tether group and chiral ligand through the immobilization of catalytic complexes. Anchoring of complexes was shown to provide large concentrations of accessible, well-spaced and structurally well-defined active sites in several systems.

Following this concept, Corma et al.\textsuperscript{11} covalently anchored a rhodium complex onto the surface of USY zeolite through a triethoxysilyl moiety. The resulting catalyst gave an enantiomeric excess (ee) of 95\% for the asymmetric hydrogenation of benzoyleminocinnamate. This represented a 20\% improvement in enantioselectivity over the corresponding homogeneous catalyst, and was attributed to a substrate-pore wall effect.

Johnson et al.\textsuperscript{12} described the immobilization of a chiral 1,1’-(diphenylphosphino)-ferrocenyl-palladium(II) chloride catalyst within the pores of MCM-41 for the asymmetric allylic amination of benzylamine. The homogeneous catalyst gave no enantioselectivity and 76\% conversion, while the immobilized complex yielded 93\% ee and > 99\% conversion. The authors attributed this dramatic increase in selectivity and activity to specific interactions between the pore surface, chiral ligand and substrate, which allowed the reaction to proceed in a stereospecific manner. The same approach was also successfully applied to an asymmetric hydrogenation reaction.

1.4. Porous Carbons for Heterogeneous Carbon-Carbon Coupling Reaction

Heterogeneous catalysts for carbon-carbon coupling reaction offer the promise of good activity, stability and reusability. Microporous amorphous carbon supports, such as activated carbon, are often used to disperse noble metal clusters for catalyzing the Heck
coupling reaction. These catalysts typically exhibit high activities, but are susceptible to metal oxidation, metal leaching during reaction, and cluster growth and agglomeration.\textsuperscript{13}

Attempts to solve these problems included the use of various solvents, ionic liquids, temperatures, surfactants, salts, and metal cluster precursors. However, in all cases, activated carbons were the supports of choice. Catalytic-grade activated carbons displayed very high surface areas, but their microporous structures prevented deposition of metallic clusters within their frameworks. As a result, metal clusters were dispersed on the external surface of the activated carbon particles, and subjected to the high temperatures, aggressive solvents and strong basic compounds during reaction. These harsh conditions, combined with the easy accessibility of the metal clusters, accelerated the cluster oxidation, leaching and growth processes.

The drawbacks of activated carbon supports were thought to be due to their lack of mesoporosity. Mesoporous carbons might overcome such challenges. They have been prepared using a pore-forming agent (PFA) in the presence of a carbon source, such as resorcinol-formaldehyde gels, phenol-formaldehyde gels, phenolic resins, melamine-formaldehyde gels, polyacrylonitrile, petroleum pitch, some polymerized forms of sugar molecules, and furfuryl alcohol.\textsuperscript{14,15} PFA’s would simply occupy volume within the carbon composite during polymerization of the carbon precursor; they do not participate in the assembly of the carbon structure. Several groups have successfully synthesized mesoporous carbons with narrow pore size distributions using mesostructured silicas, e.g. MCM-41, MCM-48 and SBA-15, as PFA’s. The synthesis of such mesoporous carbons are expensive since the removal of silica templates require HF etching.

We recently reported the synthesis of a novel carbon nanofoam (CNF) using amphiphilic molecules as pore-templating agents (PTA’s).\textsuperscript{16} PTA’s differ from PFA’s as they participate in the self-assembly of the carbon mesostructure, and are easily removed by heat treatment. The supramolecularly templated CNF exhibits high surface area, crystallinity, ultralarge pores in the range of 10–20 nm, and electrical conductivity. These attributes make CNF an excellent catalytic support for metal clusters in carbon-carbon coupling reactions.
1.5. Research Motivation

Improved chromatographic separations and carbon-carbon bond-forming technologies are required for the fine chemical and pharmaceutical industries. Although mesoporous materials are extensively used in these sectors, current approaches cannot adequately address several problems.

A large gap exists between commercially available non-templated SMS with 10–50 nm pores, and templated SMS with 5–8 nm pores. Recently, silica mesocellular foams (MCF’s) have been prepared with ultralarge, open pores of 10–40 nm, narrow pore size distributions and high surface areas, but the synthesis did not allow for the control of particle size and shape. Thus, the first aim of this work was to produce spherical MCF particles of controlled size, while retaining the unique MCF pore morphology. Spherical MCF particles would allow for the separation of large polymer molecules and proteins with superior performance than the commercially available large-pore supports, which suffer from broad pore size distributions and low surface areas (< 100 m²/g).

A second goal of the work is to use MCF materials to immobilize organometallic catalysts for the asymmetric Diels-Alder reaction. This reaction provides a new route to many chiral pharmaceutical intermediates, but is not commercially practiced since current homogeneous catalysts are run at low turnover numbers, and are not readily recovered and reused. MCF surface chemistry, choice of linker group, catalyst loading and reactor design will all be studied in an effort to significantly improve the catalyst activity, while achieving good product enantioselectivity and regioselectivity.

The third and final goal of the research is to utilize CNF as a palladium cluster support for the Heck reaction. This new support will be vapor-grafted with palladium and examined for resistance against leaching, and stability against palladium oxidation and cluster growth. If successful, the resulting catalyst will be reusable over multiple reaction cycles and will expand the scope of this powerful carbon-carbon coupling reaction.

1.6. References


Chapter 2

Spherical Silica Mesocellular Foam (MCF) Particles for Chromatographic Separations

2.1. Introduction

Chromatography is a common separations technology employed in the chemical, pharmaceutical and biotechnology industries. The chromatography market is growing particularly rapidly in the areas of fine chemicals and pharmaceuticals, where the separation of large molecules, polymers and proteins is of great interest. To achieve selective separation, the stationary phase should contain pore diameters of > 10 nm to facilitate the diffusion of large analytes.

In packed-bed applications like chromatography, constraints such as narrow particle size distribution, narrow pore size distribution, uniform particle shape, and mechanical stability, are placed on the stationary phase. These important properties facilitate uniform particle packing, low pressure drops, and homogeneity of the stationary phase, so as to achieve better separations. Spherical particles are often preferred, but the challenge has been to combine spherical particle morphologies, high surface areas, large mesopores, and narrow pore size distributions into a single stationary phase.

Much work has focused on micelle-templated silicas, such as MCM-41, MSU-X, and SBA-15, because of their mesoporosities and narrow pore size distributions. Although the original syntheses did not produce spherical particles, recent papers have reported new methodologies for the generation of spherical particles with narrow distributions of ordered mesopores. Mechanical and thermal methods such as spray drying, vibrating orifice-induced aerosols, and evaporation-induced self-assembly (EISA) offered interesting approaches. Wet-chemical synthetic routes have created 50-nm MCM-41 spheres (through reaction quenching and dilution), micron-sized MCM-41 spheres (via the use of hexadecyltrimethylammonium bromide and hexadecylpyridinium chloride surfactants),
submicron MCM-41 spheres,\(^7\) spherical MCM-41 (via the use of mixed cationic-nonionic surfactant systems),\(^8\) spherical MCM-41-like materials (with cetyltrimethylammonium chloride (CTAC) surfactant and extensive aging),\(^9\) 5–10 \(\mu\)m spheres with the MSU-X pore morphology (with the use of fluoride condensation catalysts),\(^10\) CMI-1 spheres (with tetramethoxysilane and hydrothermal treatment),\(^11\) spherical SBA-15 particles (with the use of cetyltrimethylammonium bromide (CTAB) as a cosurfactant),\(^12\) and spherical MCM-41 (by transformation of spherical non-ordered porous silica).\(^13\) However, with the exception of the spherical SBA-15 particles, which contained pores of 10 nm in diameter, all of the other spherical particles possessed pores of < 5 nm.

Siliceous mesoporous foam (MCF)\(^14\) is a novel material with ultralarge, tunable mesopores of 10–35 nm. Its high surface area of 800 m\(^2\)/g, large pore volume of 2.4 cm\(^3\)/g, and narrow pore size distribution are of great interest for chromatographic applications. However, the existing synthesis suffers from a lack of control over particle size, particle size distribution, and particle shape. If these hurdles could be overcome, MCF might lead to more effective separations for large molecules, polymers and proteins. Herein we report a new synthesis scheme that successfully generates spherical MCF (S-MCF) particles. These materials have been examined for use in high-performance liquid chromatography (HPLC).

2.2. Experimental

2.2.1. Spherical MCF Particle Synthesis and Characterization

A typical S-MCF synthesis involved mixing 360.0 g of deionized water, 9.6 g of P123 surfactant (BASF), and 4.8 g of 1,3,5-trimethylbenzene (TMB, Sigma-Aldrich) in Step 1 (at a H\(_2\)O:P123:TMB mass ratio of 75:2:1). After stirring for 2 hours to allow the P123 to dissolve, the solution was adjusted to a pH of 2 by adding 0.53 g of 37 wt% hydrochloric acid solution (HCl, Sigma-Aldrich). 20.1 g tetraethoxysilane (TEOS, Sigma-Aldrich) was then added as the silica source, and the TEOS was hydrolyzed overnight at 25°C, giving an optically translucent sol after 12 hr. The choice of pH minimized the rate of silica condensation and facilitated
TEOS hydrolysis.\textsuperscript{10} Step 2 consisted of adding a small amount of sodium fluoride at a NaF:Si molar ratio of 6.8 \cdot 10^{-4} in the absence of stirring. NaF, a known sol-gel condensation catalyst, resulted in the precipitation of spherical porous silica after 24 hr. In step 3, a second aliquot of NaF was introduced to bring the NaF:Si molar ratio of the liquid phase to 8.5 \cdot 10^{-2}. The excess NaF greatly increased the pore diameter and window size of the S-MCF particles, without modifying the particle shape or size. The S-MCF pore size, window size and wall thickness is depicted in Figure 2.1. The NaF concentration in step 2 allowed for control of the S-MCF particle size, while the amount of NaF used in step 3 provided for the tailoring of both the pore diameter and window size of S-MCF particles.

After aging for 24 hr at 40°C and another 24 hr at 100°C, the S-MCF particles were filtered and washed with ethanol (2 x 100 mL), water (2 x 100 mL) and acetone (1 x 100 mL), and allowed to dry overnight. The S-MCF was then calcined in air at 500°C for 10 hr in order to remove the P123 surfactant. The calcined S-MCF particles were either rehydroxylated or used directly in the S-MCF-C\textsubscript{18} synthesis scheme.

![Diagram](image_url)

**Figure 2.1.** A sphere truncated by a rhombic dodecahedron, the building block of the ordered MCF pore morphology with a face-centered cubic structure.\textsuperscript{15} The wall thickness, window diameter and pore diameter are shown.
Nitrogen adsorption analysis was conducted on a Micrometrics ASAP 2010 at 77 K, after degassing samples at 150°C. The Brunauer-Joyner-Halenda (BJH) pore size distribution of S-MCF was obtained from the adsorption branch of the isotherm, while the S-MCF window size was determined from the desorption branch. Brunauer-Emmett-Teller (BET) surface area was derived from the relative pressure range of 0.005–0.3. Transmission electron microscopy (TEM) was conducted with a JEOL 2010 microscope with a field-emission gun electron source at 200 kV. Scanning electron microscopy (SEM) was performed on a JEOL 6320FV microscope operating at 3 kV. Particle size distribution was obtained by centrifugal sedimentation (Horiba CAPA-700). Small-angle X-ray scattering (SAXS) was performed on a Bruker 60.4-cm small-angle diffractometer equipped with a 2D position-sensitive detector and a Cu Kα X-ray source operating at 1.2 kW. Carbon, hydrogen and nitrogen elemental analyses were conducted by Quantitative Technologies, Inc. (Whitehouse, NJ).

2.2.2. Transformation of LiChrospher Silica into S-MCF

In a variation of the S-MCF synthesis, deionized water, P123 surfactant, TMB and HCl were mixed in the same ratios given in Section 2.2.1 such that a total solution volume of 62 mL was obtained. TEOS was substituted on an equimolar Si basis with 1.0 g of LiChrospher 100 spherical silica particles (5 μm, EM Science), which was added and stirred for 15 min. Next, 1.24 mL of a NaF solution (1.5 M in deionized water) was added, and the mixture was aged at 40°C for 24 hr and at 100°C for another 24 hr. The suspension was filtered, calcined and characterized as described in Section 2.2.1.

2.2.3. Synthesis of S-MCF-C18 Reverse-Phase Support

The S-MCF-C18 synthesis is comprised of three processes, rehydroxylation, covalent attachment of long alkyl chains, and capping of residual silanols. Several different rehydroxylation experiments were performed, and the two best methods involved dilute
aqueous hydrofluoric acid (HF) and tetraethylammonium hydroxide (TEAH) treatments. In some experiments, the as-calcined S-MCF was used directly in the S-MCF-C\textsubscript{18} synthesis.

**Rehydroxylation**

The dilute aqueous HF rehydroxylation process consisted of adding 0.75 g of calcined S-MCF to 100 mL of a 200 ppm aqueous HF solution (Sigma Aldrich) in a sealed Schlenk flask. The mixture was heated to 100°C overnight, and then filtered and washed with deionized water (2 x 100 mL) and acetone (1 x 100 mL). The resulting powder was dried *in vacuo* at 120°C overnight before further use.

The TEAH rehydroxylation treatment consisted of adding 0.75 g of calcined S-MCF to 100 mL of an aqueous solution of TEAH (pH = 9, Alfa Aesar) in a sealed Schlenk flask. The mixture was heated to 100°C for 24 hr, and filtered and washed with deionized water (1 x 100 mL), a nitric acid solution (0.05 N, Alfa Aesar, 2 x 100 mL), deionized water (1 x 100 mL) and acetone (1 x 100 mL). The resulting powder was dried *in vacuo* at 120°C overnight prior to further surface modification. The relative amounts and types of silanols were measured by photoacoustic Fourier-transform infrared (PA-FTIR) spectroscopy (MTEC Model 200 photoacoustic cell coupled to a Bio-Rad FTS-60A infrared spectrometer).

**Covalent Functionalization of the S-MCF Surface**

The spherical MCF particles were made hydrophobic by anchoring octadecyl(dimethylchlorosilane (ODDMCS, Gelest) to the surface using the method of Buszewski *et al.*\textsuperscript{16} 1.26 g of S-MCF (previously dried *in vacuo* at 180°C for 24 hr) was suspended in 60 mL of anhydrous toluene under an inert atmosphere. 7.67 mL of ODDMCS was then added in large excess and the mixture was stirred for 15 min at room temperature. Next, 1.22 mL of morpholine (Sigma-Aldrich) was added, and the mixture was stirred for 15 min. The sealed Schlenk flask was then heated to 120°C for 24 hr, and the ODDMCS was covalently linked to the S-MCF surface. The resulting S-MCF-C\textsubscript{18} particles were recovered
via filtration, and washed with toluene (1 x 100 mL), methanol (2 x 75 mL), ethanol (1 x 100 mL) and diethyl ether (1 x 50 mL). The S-MCF-C₁₈ particles were then directly tested for chromatography applications, or treated further if desired. Successful attachment of ODDMCS could be confirmed by PA-FTIR spectroscopy, with peaks at 2853, 2924 and 2959 cm⁻¹. The alkyl chain loading was determined by elemental analysis (C:H:N (%) = 17.91:2.85:<0.05).

Capping of Residual Silanol Groups

Two silanol capping agents, trimethylsilylchloride (TMS-Cl) and trimethylsilylimidazole (TMS-imid), were examined in this work. The S-MCF-C₁₈ particles derived in the scheme above were dried in vacuo for 24 hr at 120°C to remove any adsorbed water. 1.5 g of the dried S-MCF-C₁₈ particles was then suspended in 40 mL of anhydrous toluene under an inert atmosphere, and either 7.3 mL of TMS-Cl or TMS-imid was injected into the Schlenk flask. The flask was heated to 120°C for 2 days under argon. The resulting capped S-MCF-C₁₈ particles were filtered and washed with toluene (1 x 100 mL), methanol (2 x 75 mL), ethanol (1 x 100 mL) and acetone (1 x 50 mL), and tested for chromatographic performance. Successful capping was characterized by increased intensity for PA-FTIR peaks at 2853, 2924 and 2959 cm⁻¹. Capping also led to significant increases in the total carbon and hydrogen contents of the materials (C:H:N (%): 21.76:3.78:0.07).

2.2.4. Evaluation of S-MCF-C₁₈ Column Performance

The S-MCF-C₁₈ particles were slurry-packed into an empty 250 mm x 4.6 mm ID HPLC column (YMC, Inc.) to a pressure of 200 bar using standard techniques and methanol as a packing solvent.¹⁷ The performance of the S-MCF-C₁₈ column was compared to that of a commercially available HPLC column of the same dimensions and surface chemistry, Symmetry-C₁₈™ (Waters, Corp.). The properties of the two stationary phases are listed in
Table 2.1. The two supports have similar particle sizes, but S-MCF-C\textsubscript{18} has a larger average pore size, a higher surface area and 40% higher pore volume.

<table>
<thead>
<tr>
<th></th>
<th>Symmetry\textsuperscript{TM}</th>
<th>S-MCF-C\textsubscript{18}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avg. Particle Size (μm)</td>
<td>5.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Avg. Pore Size (nm)</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Surface Area (m\textsuperscript{2}/g)</td>
<td>346</td>
<td>423</td>
</tr>
<tr>
<td>Pore Volume (cm\textsuperscript{3}/g)</td>
<td>1.31</td>
<td>1.82</td>
</tr>
</tbody>
</table>

Two separate chromatographic studies involving separation of aryl ketones and phenol-pyridine were performed. The chromatograms were obtained on a Waters HPLC (Milford, MA) with a 1525 binary pump and a 2487 UV-VIS detector. Acetone and a mixture of aryl ketones, including acetophenone, propiophenone and butyrophenone, were separated using a mobile phase of 60:40 (vol.) mixture of methanol and water at a flowrate of 0.5 mL/min and a wavelength of 254 nm. The phenol-pyridine residual silanol test involved a mobile phase of 40:60 (vol.) mixture of methanol and water, with a flowrate of 1 mL/min and a wavelength of 254 nm.

2.3. Results and Discussion
2.3.1. Synthesis of S-MCF

The conventional synthesis of siliceous MCF is described elsewhere.\textsuperscript{15, 18} The first requirement for conventional MCF production was an acidic aqueous environment, usually at a pH below 1. Attempts to make MCF at neutral or basic pH resulted in disordered porous silica with pores of < 4 nm.\textsuperscript{15} The second condition for obtaining MCF required a micelle swelling agent, such as TMB. TMB must be present with a Pluronic triblock copolymer surfactant, P123, in sufficient quantities to force the P123 to undergo a phase transition from
cylindrical rods to isolated swollen micelles.\textsuperscript{19} Thirdly, an aging process was necessary to produce the final MCF material. Lastly, calcination is needed to remove P123 surfactant and expose the porosity of MCF. Thus, the challenge is to preserve these key features, while manipulating the MCF synthesis to give spherical particles.

The MCF particles obtained by the conventional synthesis have a “cauliflower” morphology (see Figure 2.2) and a broad distribution of particle sizes from submicron to > 50 \textmu m. If used in chromatography, these particles would result in unacceptably high pressure drops across the bed.

![SEM micrograph of a “cauliflower”-shaped particle obtained from the conventional MCF synthesis.](image)

**Figure 2.2.** SEM micrograph of a “cauliflower”-shaped particle obtained from the conventional MCF synthesis.\textsuperscript{18}

Of the four synthetic requirements, synthesis pH is the most flexible, because it can be altered before, during, or after MCF precipitation, provided that the pH remains acidic. Boissière \textit{et al.} recently reported on a two-step synthesis of spherical MSU-X silica particles,\textsuperscript{10} which utilized a pH of 2 to separate the hydrolysis and condensation steps of sol-gel processing. In this approach, MSU-X silica spheres with pores of 1–5 nm were produced through the addition of NaF, a known sol-gel condensation catalyst.\textsuperscript{20} The NaF:Si molar ratio was varied between 0.01 and 0.18 to obtain spherical particles of 1–10 \textmu m.\textsuperscript{10,21}

Boissière \textit{et al.}’s approach\textsuperscript{10} was adapted in our attempt to synthesize S-MCF. The addition of NaF resulted in 5-\textmu m spherical particles at a NaF:Si molar ratio of ~ 6.8·10^{-4}. 

25
However, the resulting mesoporous silica spheres did not exhibit the nitrogen adsorption-desorption isotherm characteristics of MCF. This was perplexing since all parameters were identical to the conventional MCF synthesis, except that the pH was changed and NaF was added. Further aging at higher temperatures also did not lead to spherical MCF particles.

A literature account by He et al.\textsuperscript{22} described the use of HF to increase the pore size of disordered silica. Thus, in our second attempt to synthesize S-MCF, a second aliquot of NaF was added after the precipitation of spherical particles, thereby raising the total NaF:Si molar ratio to 8.5\cdot10^{-2}. The sol was then aged, filtered, and calcined as before. This introduction of excess NaF resulted in spherical particles with the desired MCF pore morphology (see Figure 2.3).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure23.png}
\caption{Figures 2.3. (a) Nitrogen adsorption-desorption isotherms and (inset) BJH adsorption pore size distributions, and (b) SAXS patterns of conventional MCF (——) and calcined S-MCF (-----).}
\end{figure}

The S-MCF particles exhibited a high surface area of 470 m\textsupersquare/\text{g}, a pore volume of 2.2 cm\textsupersquare/\text{g}, and a narrow pore size distribution. Figure 2.4 illustrates the foam-like pore morphology and the spherical particle morphology of S-MCF. S-MCF was also shown to
have a narrow particle size distribution centered at 5 µm (Figure 2.5), with little particle agglomeration (Figure 2.4(b)).

![Figure 2.4. (a) TEM and (b) SEM micrographs of S-MCF particles.](image)

**Figure 2.4.** (a) TEM and (b) SEM micrographs of S-MCF particles.

![Figure 2.5. Particle size distribution of S-MCF as measured by centrifugal sedimentation.](image)

**Figure 2.5.** Particle size distribution of S-MCF as measured by centrifugal sedimentation.

The successful S-MCF synthesis included: step 1 – separation of the silica hydrolysis and condensation processes at a pH of 2, step 2 – creation of spheres using NaF as a condensation catalyst, and step 3 – transformation to the MCF pore morphology with a second NaF treatment (see details in Section 2.2.1). The spherical particle morphology, the
ultralarge mesopores of 15–35 nm, and the high surface areas made S-MCF an excellent candidate for the separation of large molecules and proteins.

2.3.2. Independent Control of S-MCF Particle Size and Pore Size

Besides creating S-MCF particles, the novel three-step synthesis scheme allowed for independent control over particle size and pore size. Figure 2.6(a) shows that the median particle size obtained by centrifugal sedimentation decreased as the NaF:Si molar ratio of step 2 was increased. This could be explained by idealizing S-MCF sphere formation as a nucleation and growth process from a nearly homogeneous, pre-hydrolyzed TEOS solution in step 2. If each fluoride ion was responsible for a nucleation event, then for a fixed amount of TEOS in solution, a lower NaF:Si ratio would give a smaller number of large particles, whereas a higher NaF:Si ratio would give a larger population of smaller particles. This was similar to that observed by Boisière et al. for spherical MSU-X particles.\(^{23}\) We noted that the median cell and window sizes of S-MCF particles obtained from nitrogen adsorption-desorption isotherm were unaffected by the NaF:Si molar ratio in step 2 (see Figure 2.6(b)).

![Figure 2.6.](image)

**Figure 2.6.** (a) Median particle size, and (b) median cell diameter (○) and median window size (■) of S-MCF as a function of the NaF:Si molar ratio in step 2. A constant NaF:Si molar ratio of 0.085 and aging temperature of 100°C were employed for step 3.
Figure 2.7(a) shows that the particle size of S-MCF remained constant at 5 μm in a separate experiment where the NaF:Si molar ratio was increased for step 3. This confirmed that the condensation process was completed in step 2, and that few silica species remained in the liquid phase during step 3, preventing further particle growth. However, the NaF:Si molar ratio in step 3 had a dramatic effect on surface area, pore volume and pore diameter. Increasing NaF:Si molar ratio in step 3 led to increased median cell diameters and window sizes (Figure 2.8(b)). Pore volume increased with increasing NaF:Si molar ratio in step 3 until ~ 0.035. Above this point, increases in pore diameters were accompanied by reduced pore volumes and surface areas.

![Figure 2.7](Image)

**Figure 2.7.** (a) Median particle size and (b) BET surface area of S-MCF as a function of the NaF:Si molar ratio in step 3. A constant NaF:Si molar ratio of 0.00068 was employed for step 2, and a constant aging temperature of 100°C was used in step 3.
Figure 2.8. (a) Pore volume, and (b) median cell diameter (○) and median window size (■) of S-MCF as a function of the NaF:Si molar ratio in step 3. A constant NaF:Si molar ratio of 0.00068 was employed for step 2, and a constant aging temperature of 100°C was used in step 3.

SAXS analyses of S-MCF showed that the unit cell size increased with the NaF:Si molar ratio in step 3 (Figure 2.9). The SAXS data were fitted with a monodisperse sphere model\textsuperscript{14} to give unit cell sizes of 26–34 nm. These values were in stark contrast to the pore diameters obtained by nitrogen sorption analysis (Figure 2.8(b)). A NaF:Si ratio of 0.0014 in step 3 gave cell and window diameters of 11 nm and < 1 nm, respectively (Figure 2.8(b)), and a unit cell size of ~ 26 nm (Figure 2.9). The observations suggested that as the NaF:Si ratio increased, the walls and window openings were likely dissolved by F\textsuperscript{−} ions. This would result in thinner walls and larger pore diameters, without dramatically altering the unit cell size. For example, a NaF:Si ratio of 0.085 in step 3 gave larger cell and window diameters of 29 nm and 14 nm, respectively, but only a modest increase in unit cell size to ~ 34 nm occurred. This observation was similar to those of He et al.,\textsuperscript{22} who found that small fluctuations in F\textsuperscript{−} concentration gave rise to significant changes in pore diameters in their disordered porous materials. Thus, the NaF concentration in step 3 represented a simple and effective means of tailoring the pore size of the S-MCF material.
Figure 2.9. S-MCF unit cell size obtained by SAXS as a function of NaF:Si molar ratio in step 3. A constant NaF:Si molar ratio of 0.00068 was employed for step 2, and a constant aging temperature of 100°C was used in step 3.

The pore sizes of S-MCF could also be controlled by the aging temperature of step 3. Figure 2.10 shows that for 5-μm S-MCF particles, aging temperatures of > 40°C led to significant increases in pore sizes. Aging at 100°C resulted in materials with a cell diameter of 31 nm, a window size of 21 nm, a pore volume of 1.8 cm³/g and a surface area of 390 m²/g.

The novel S-MCF synthesis presented here provided for a high degree of control over the different microstructural characteristics of silica. If spherical particles with small pores were desired, NaF:Si ratios of < 0.035 should be used in step 3, whereas if larger pores were needed, NaF:Si ratios of ≥ 0.035 and aging temperatures of > 40°C should be employed in step 3. Cell diameters of 12–30 nm could be easily attained, although the larger pores came at the expense of surface area and pore volume.
Figure 2.10. Median cell diameter (○) and median window size (■) of S-MCF as a function of the aging temperature in step 3. Constant NaF:Si molar ratios of 0.00068 M and 0.085 M were employed for step 2 and step 3, respectively.

2.3.3. Extension of S-MCF Synthesis to Other Porous Silica Materials

To examine whether the S-MCF synthesis scheme could be applied to other porous materials, as-received LiChrospher 100 (designated L1) was substituted for TEOS in the S-MCF synthesis scheme (see Section 2.2.2). Since the particles were pre-formed spheres, step 2 of the synthesis was not unnecessary. The particles were aged according to S-MCF procedure with a NaF:Si molar ratio of 0 (control) or 0.085 in step 3. The resulting calcined materials were designated L2 and L3, respectively.

Figure 2.11 shows that L1 exhibited adsorption and desorption pore sizes of 16 nm and 12 nm, respectively. L2 displayed similar pore sizes as L1, with slightly reduced pore volume and surface area. In contrast, L3 showed a distinctly different nitrogen adsorption-desorption isotherm, with sharper upturns occurring at higher relative pressures. This corresponded to slightly narrower adsorption and desorption pore size distributions centered at larger median values of 32 nm and 16 nm, respectively. The similarities between the sorption isotherms of L3 and S-MCF (Figure 2.3(a)) were striking (except for the lower pore volume of the former), suggesting that LiChrospher 100 attained a similar pore morphology as S-MCF after the treatment with NaF. This process was accomplished
without modifying the particle size and shape of the LiChrospher particles. Figure 2.11 also demonstrated the importance of NaF in the S-MCF treatment scheme since the L2 particles exposed to S-MCF synthesis conditions in the absence of NaF in step 3 did not transform into the S-MCF type of pore morphology.

![Figure 2.11](image)

**Figure 2.11.** Nitrogen adsorption-desorption isotherms, cell diameters and window sizes of as-received L1 (- - -), L2 (—) and L3 (—-).

L3 has lower pore volume and surface area (1.22 cm³/g and 270 m²/g, respectively) compared to L1 (1.54 m³/g and 470 m²/g, respectively). Like L1, L3 did not show well-defined peaks in its SAXS pattern, indicating the LiChrospher particles with S-MCF pore morphology lacked a high degree of order.

### 2.3.4. Synthesis and Performance of S-MCF-C₁₈ Reverse-Phase Column

Besides the microstructural requirements, the surface chemistry of chromatographic supports plays an important role in the separation performance. Since 75% of all HPLC separations worldwide are performed with reverse-phase columns, 24 S-MCF particles were
surface modified by long-chain organics (see Section 2.2.3) and tested for separation properties (see Section 2.2.4).

S-MCF-C\textsubscript{18} was employed for the separation of aryl ketones, which are important pharmaceutical precursors.\textsuperscript{25} Figure 2.12 illustrates that S-MCF-C\textsubscript{18} was able to separate all four components, but showed broader peaks and significant peak tailing compared to the Symmetry-C\textsubscript{18}\textsuperscript{TM} column. The peak tailing was likely caused by strong interactions between S-MCF and the analytes. Since accounts have attributed peak tailing to unreacted silanols on surfaces of the reverse-phase supports,\textsuperscript{26-28} a residual silanol test was performed to investigate this possibility in our system.

![Chromatograms](image)

**Figure 2.12.** Chromatograms for the separation of aryl ketones over Symmetry-C\textsubscript{18}\textsuperscript{TM} column (unmarked peaks) and S-MCF-C\textsubscript{18} 1b column (peaks marked ▼).

The residual silanol test comprised the elution of phenol and pyridine on the reverse-phase columns to determine their retention times and peak shapes. Phenol is relatively insensitive to silanols and, therefore, should elute at approximately the same time on Symmetry-C\textsubscript{18}\textsuperscript{TM} and S-MCF-C\textsubscript{18} columns. Pyridine, a strong organic base, interacts strongly with residual silanols, which have been shown to be mildly acidic.\textsuperscript{24} Thus, a column containing residual silanols would elute pyridine later than a support with fewer silanols. Figure 2.13 shows that phenol and pyridine eluted at 9.5 min and 6.8 min,
respectively, on the Symmetry column, while they appeared at 10.0 min and 13.1 min, respectively, on the S-MCF-C_{18} column. The delay in pyridine elution and significant pyridine peak tailing confirmed the presence of residual silanols on the S-MCF-C_{18} surface.

![Chromatograms](image)

**Figure 2.13.** Chromatograms for pyridine (---) and phenol (—) over Symmetry-C_{18}™ column (unmarked peaks) and S-MCF-C_{18} 1b column (peaks marked ▽).

Since strong interactions between reverse phase and analyte lead to poor chromatographic performance^{29, 30} efforts were devoted towards eliminating the remaining surface silanols from S-MCF-C_{18}. A large number of reports concerning this topic could be found in the literature. In particular, Hohenesche *et al.*^{31} have discussed several synthesis requirements for an ideal reverse-phase column. They recommended a silica pretreatment step (also known as rehydroxylation or activation) before coupling the C_{18}-alkyl substituent to the silica support. This step would help remove trace metals from the silica surface, repopulate the surface with silanols that were converted to siloxanes during the calcination step, and maximize the number of silanols available for coupling to alkyl groups. In doing so, the rehydroxylation treatment would remove heterogeneous adsorption sites, making the silica surface more energetically uniform.^{26, 32} Rehydroxylation might involve the use of
strong aqueous acids and bases or neutral pH at a range of temperatures. To optimize the rehydroxylation conditions, various treatments were applied to calcined S-MCF (see Table 2.2).

<table>
<thead>
<tr>
<th>Rehydroxylation Treatment</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Untreated as-calcined MCF</td>
<td>—</td>
</tr>
<tr>
<td>2 Tetraethylammonium hydroxide (pH = 9)</td>
<td>100</td>
</tr>
<tr>
<td>3 Sulfuric acid/Nitric acid (pH = 1)</td>
<td>25</td>
</tr>
<tr>
<td>4 Sulfuric acid/Nitric acid (pH = 1)</td>
<td>100</td>
</tr>
<tr>
<td>5 Aqueous hydrofluoric acid (200 ppm)</td>
<td>100</td>
</tr>
</tbody>
</table>

The goal of rehydroxylation (see Section 2.2.3) is to remove strong adsorption sites from the surface by increasing vicinal silanols at the expense of isolated and geminal silanols (which are more acidic). Scheme 2.2 shows the different types of silanols and their infrared peak positions. The PA-FTIR spectra of the post-rehydroxylation S-MCF samples were normalized to the maximum peak absorbance at 1100 cm$^{-1}$, which was found to be independent of the treatment type. Figure 2.14 shows that the different treatments all decreased the isolated and geminal silanol peak at 3738 cm$^{-1}$, especially treatments 2 and 5. Treatment 5 resulted in the least amount of isolated silanols and a significant increase in vicinal silanols (3200-3600 cm$^{-1}$).

**Scheme 2.1.** Siloxanes, and isolated, vicinal and geminal silanols and their characteristic infrared peak positions.

siloxane

1000-1100 cm$^{-1}$

isolated

3738 cm$^{-1}$

vicinal

3200-3600 cm$^{-1}$

geminal

3738 cm$^{-1}$
Figure 2.14. PA-FTIR spectra of S-MCF after the rehydroxylation treatments described in Table 2.2.

Selected S-MCF-C_{18} supports were prepared using rehydroxylation treatments 1, 2 and 5. Two silanol capping methods were also investigated to see if further improvement in silanol control could be achieved, as some reports have indicated.^{24} Trimethylsilyl chloride (TMS-Cl), a, and trimethylsilyl imidazole (TMS-imid), b, were considered in the new S-MCF-C18 synthesis strategy after anchoring the C_{18} moiety (see Section 2.2.3). The materials were packed into an empty column of 4.6 mm x 100 mm, and examined with the standard residual silanol test using phenol and pyridine. Two parameters were investigated, \( \zeta \), the dimensionless ratio of phenol retention time to pyridine retention time, and \( \delta \), the pyridine peak width at half height (in min). The value \( \zeta \) would provide information on the amount of residual silanols, since an ideal reverse-phase column would elute pyridine
before phenol ($\zeta > 1$), and a column with high residual silanol content would have a $\zeta$ value of $< 1$. The parameter $\delta$ would illustrate the presence of peak tailing, with narrow peaks giving small $\delta$ values and tailing peaks producing large $\delta$ values.

Figure 2.15 shows that 1b possessed a much larger $\zeta$ than 1, illustrating the importance of capping residual silanols. 2a and 2b both demonstrated a higher $\zeta$ than 1b, confirming the effectiveness of rehydroxylation treatment 2. The larger $\zeta$ value and the substantially smaller $\delta$ value of 2b compared to 2a revealed that a better support was obtained using TMS-imid instead of TMS-Cl for silanol capping. The best support performance was achieved by S-MCF-C$_{18}$ column 5b, which gave an even larger $\zeta$ and a smaller $\delta$ than 2b. Thus, it was concluded that rehydroxylation using dilute hydrofluoric acid significantly improved column performance. Additionally, treatment 5b led to a performance that approached that of the Symmetry column 5. This could be attributed to the effective removal of the strongest adsorption sites, as supported by PA-FTIR results, which showed that treatment 5 removed the largest amount of isolated silanols (see Figure 2.14).

The S-MCF-C$_{18}$ 5b stationary phase was then slurry packed into an empty YMC column of 4.6 mm x 250 mm, and tested for the separation of aryl ketones. Its separation performance was compared to that of the Symmetry-C$_{18}^{TM}$ column as before at a flow rate of 0.5 mL/min. Both columns performed very well, achieving baseline separations for all components (see Figure 2.16). The S-MCF-C$_{18}$ 5b column eluted the third and fourth peaks earlier than the Symmetry-C$_{18}$ column without any loss in separation performance. The shorter retention times most likely resulted from the larger pore diameters of S-MCF versus Symmetry particles (see Table 2.1), as smaller pores would generally have greater retention of the small analyte molecules.$^{33,34}$ The S-MCF-C$_{18}$ 5b was also noted to have a superior column performance compared to S-MCF-C$_{18}$ 1b (Figure 2.12). Its effective rehydroxylation treatment greatly reduced the extent of peak tailing and minimized peak width.
Figure 2.15. (●) $\zeta$ and (□) $\delta$ values of S-MCF-C$_{18}$ supports subjected to different treatments. S represents the performance of the commercial Symmetry$^\text{TM}$-C$_{18}$ column.

Figure 2.16. Chromatograms for the separation of aryl ketones over Symmetry-C$_{18}$$^\text{TM}$ column (unmarked peaks) and S-MCF-C$_{18}$ 5b column (peaks marked ▼).
The analyte peaks from the S-MCF-C\textsubscript{18} 5b column were found to be approximately twice as broad as those eluted from the Symmetry-C\textsubscript{18}^\text{TM} column, possibly due to the differences in particle size distributions between the two supports. The differences in particle size distributions might also account for the increased pressure drop across the S-MCF-C\textsubscript{18} column versus the Symmetry-C\textsubscript{18}^\text{TM} column. This problem could easily be overcome easily by classifying the S-MCF particles before packing.

2.4. Summary

By decoupling the spherical particle formation and pore formation processes, the S-MCF synthesis scheme imparted a great deal of flexibility compared to other syntheses, whereby the porosity and particle size were determined in the same processing step. This scheme enabled the development of a support material for HPLC stationary phase with controlled particle size and pore size through the manipulation of NaF concentration in two different synthesis steps. The S-MCF synthesis represents, to the best of our knowledge, the first synthesis scheme capable of producing spherical particles with an well-ordered pore structure consisting of pores of > 10 nm. The novel three-step S-MCF synthesis scheme was also successfully extended to transform the pore morphology of LiChrospher 100 particles to that of MCF, with pore sizes as large as 32 nm.

S-MCF particles were successfully applied towards the chromatographic separation of aryl ketones. A comparison of the S-MCF-C\textsubscript{18} column with a Symmetry-C\textsubscript{18}^\text{TM} column showed good baseline separation of the analytes, although peak broadening and tailing were observed due mainly to the presence of residual silanols. Effective rehydroxylation pretreatment and silanol capping methods were developed, leading to the second-generation S-MCF-C\textsubscript{18} support with greatly enhanced separation properties and minimal peak tailing. In particular, the S-MCF-C\textsubscript{18} 5b column allowed for the complete separation of a mixture of aryl ketones with symmetric peaks with a performance that rivaled the commercial column.
2.5. References


Chapter 3

The Heterogeneous Asymmetric Diels-Alder Reaction

3.1. Introduction

The Diels-Alder reaction is well-known, but its asymmetric counterpart is relatively modern. The asymmetric Diels-Alder (ADA) reaction is very useful in building large, complex chiral molecules through the formation of ringed structures. It presents an excellent route for generating new antibiotics, novel cardiovascular drugs, and more complex protease inhibitors, that have significantly impacted on the treatment of HIV. The reaction involves a diene and a dienophile, which react in a [4 + 2]-cycloaddition to form chiral carbon ring structures that are of great importance for the synthesis of pharmaceuticals and fine chemicals. Many combinations of ligands and metals are capable of catalyzing the Diels-Alder reaction, but the more common homogeneous catalysts involve the Cu(II)-bisoxazolines that were first reported by Evans and coworkers. These catalysts, along with their Cu(I) counterparts, can be used in a number of other Lewis acid catalyzed reactions, such as the asymmetric Michael, ene and cyclopropanation reactions.

Oxazoline ligands are easily identified by the five-membered ring subunit containing a carbon-nitrogen double bond and an oxygen atom. The remaining subunit carbons can be connected to a number of functional groups, and in the case of chiral bisoxazolines, the carbons are stereogenic centers. Chiral bisoxazolines contain two oxazoline subunits that are connected through a backbone carbon atom, which gives the ligand its C₂-symmetry. A typical bisoxazoline ligand can be seen in Figure 3.1. Copper bisoxazoline catalysts give excellent enantioselectivities of greater than 99% in some cases. While the homogeneous catalysts exhibit very good selectivities, they show only moderate activities and are not readily recovered and reused. In order to retain their high selectivities for the ADA reaction, the homogeneous catalysts must be run at low turnover numbers (TON = mol reactant/mol of catalyst). Often the
TON necessary for high enantioselectivity was ~ 10, which would require large amounts of catalyst if the reaction were run on a large scale.

![Schematic of typical chiral bisoxazoline ligand](image)

**Figure 3.1.** Schematic of typical chiral bisoxazoline ligand with substituents $R^2$ and $R^3$ located on stereogenic carbon atoms.

The catalytic mechanism is one of reagent activation, and a proposed catalytic cycle for ADA homogeneous catalysts is shown in Figure 3.2. The Cu$^{2+}$ metal atom represents a site of strong Lewis acidity (I), and the incoming dienophile molecule binds to the Cu$^{2+}$ site through the diketone moiety (II), which has some Lewis base character. Upon binding, the copper withdraws electron density through the conjugated network of the dienophile, and activates the alkene moiety of the dienophile to undergo attack by the diene, which is also present in solution. However, the copper-dienophile complex is shielded from the attacking diene from two of the possible four quadrants of approach by the chiral bisoxazoline ligand. Thus, the reaction proceeds in a sterspecific manner to give the desired ADA product-copper complex (III). The product desorbs from the copper, regenerating the catalytically active species (IV). It is important to note that no change in oxidation state occurs at the metal center, and that the reaction is very sensitive to competing Lewis bases that may be present in the reaction mixture. For example, Evans and coworkers$^6$ showed that the activity and enantioselectivity of their catalysts was greatly affected by the use of benzene or THF as solvents. Thus, a non-coordinating solvent such as dichloromethane is preferred in all cases.

There has been a drive in recent years to covalently link chiral catalysts onto supports to make them reusable, while retaining their activity and enantioselectivity. Several of the reported bisoxazoline chiral catalysts have been studied in their polymer-supported forms.$^9, 10$ Other
works have focused on placing bisoxazolines into zeolites for the cyclopropanation reaction. The Cu²⁺-exchanged zeolites showed approximately the same activity as the homogeneous catalysts for cyclopropanation, but the enantioselectivity was poor (~ 37% ee). This was likely due to competing sites of Lewis acidity within the zeolitic structure that could only react in a racemic manner. Silica supports are more promising than polymer supports in terms of recycling and stability. They also offer the additional benefit of control over the catalytic environment through the attachment of a wide variety of organosilanes to the silica surface.

![Diagram](image)

**Figure 3.2.** Proposed mechanism for the asymmetric Diels-Alder reaction.

In this work, bisoxazoline ligands were immobilized onto an ultralarge-pore silica support, mesocellular foam (MCF). MCF was templated by triblock copolymers in the presence of mesitylene. Experiments were conducted to assess the effect of free silanol groups
associated with the silica surface. Studies were also performed to examine the impact of different environments around the catalytic sites through the use of various bisoxazoline ligands, linker groups, silanol-capping silane agents, and ligand loadings. The goal of this work is to increase the stability, reusability and activity of Cu(II)-bisoxazoline catalysts for ADA reaction without sacrificing selectivity.

In this study, a novel method was employed for modifying the existing bisoxazoline ligands and immobilizing them onto MCF supports (see details in Section 3.2.1\textsuperscript{15}). The bisoxazoline ligand, indaBOX, which is named for its chiral organic functionality (indanyl group) and BOX (short for BisOXazoline), was modified by lithiation of the two protons at the bridged carbon. Treatment of indaBOX with methyl lithium at $-50^\circ$C was followed by reaction with organosilanes containing electrophilic halide functionalities. The resulting trimethoxysilane-modified indaBOX ligands were then immobilized onto MCF by heat treatment in toluene. The surface silanol groups on the MCF were capped with various trialkylsilanes, providing different hydrophobic environments around the MCF-anchored indaBOX ligands.

3.2. Experimental

3.2.1. Catalyst Synthesis and Characterization

A typical procedure for the preparation of MCF-immobilized catalyst, 6, was carried out as described in Scheme 3.1. Methyl lithium (1.4 M in ether, 2.18 mL, 3.05 mmol) was added to a solution of indaBOX 1 (Sigma-Aldrich, 480 mg, 1.45 mmol) in tetrahydrofuran (20 mL) at $-50^\circ$C. After stirring the mixture at $-50^\circ$C for 1 hr, (chloromethyl)phenylethyltrimethoxysilane (0.713 mL, 2.90 mmol) was added dropwise. The mixture was stirred at room temperature for 2 hr, and heated to 50$^\circ$C for 3 days. THF was then evaporated under vacuum. Upon addition of toluene, white solids were precipitated, and the soluble portion was collected after centrifugation and toluene washes. The solution was added to MCF (3.0 g), which had been previously dried under vacuum at 180$^\circ$C for 1 day. The suspension was stirred at 80$^\circ$C for 3 days, filtered.
Scheme 3.1. Schematic for preparing MCF-immobilized bisoxazoline catalysts: (a) organosilane functionalization, (b) immobilization of modified ligand onto MCF, (c) capping of residual silanols with organosilane reagents, and (d) complexation of immobilized ligand with copper(II) reagent.

through a fritted funnel, and washed with toluene (20 mL × 3), acetone (20 mL × 3), methanol (20 mL × 3) and dichloromethane (20 mL × 3). After drying in vacuum, 3.9 g of the desired product was obtained. The resulting catalyst structure was confirmed by solid-state nuclear magnetic resonance (NMR) spectroscopy: $^{13}$C CPMAS NMR (ppm): 167, 141, 127, 83, 76, 49, 38, 28, -3, and $^{29}$Si CPMAS NMR (ppm): -110, -100, -90, -65, -59, -51, 28, 6. Photoacoustic Fourier-transform infrared (PA-FTIR) spectroscopy showed the following peaks: 3605, 3364 (br), 2949, 2846, 1645, 1607, 1086, 809, 749, and 458 (cm$^{-1}$). Carbon, hydrogen and nitrogen (CHN) analyses indicated the following: 19.01% C, 1.72% H and 0.97% N (Quantitative Technologies, Inc., Whitehouse, NJ). Since MCF contained no nitrogen, the nitrogen value was used to calculate the indaBOX ligand loading on the MCF surface, which was ~ 0.346 mmol/g. This
corresponded to a 93% yield based on the starting indaBOX reagent, which was significantly higher than the ligand immobilization yields attained with other published methods.\textsuperscript{16}

Next, the residual silanol groups on the MCF-supported indaBOX 6 were capped to limit their interaction with the active catalyst species. 6 (0.700 g) was dried at 80\(^\circ\)C for 2 days under vacuum. Excess hexamethyldisilazane was added to the dried catalyst in hexane (10 ml). The suspension was stirred at room temperature for 3 days, filtered through a fritted funnel, and washed with dichloromethane (10 ml \(\times\) 3), acetone (10 ml \(\times\) 3), methanol (10 ml \(\times\) 3) and dichloromethane (10 ml \(\times\) 3). After drying under vacuum overnight at room temperature, the desired product 6a (0.740 g) was obtained. PA-FTIR spectroscopy showed distinct peaks at 3469, 2954, 2848, 1648, 1606, 1089, 845, 809, 749 and 460 cm\(^{-1}\). CHN analyses gave the following values: 20.44\% C, 1.78\% H, and 0.91\% N. Comparison of these values with those of 6 showed an increase in the carbon and hydrogen contents and a decrease in the nitrogen content, indicating that capping of the silanols was successful. This fact was further supported by PA-FTIR spectra, which showed a less intense Si-OH stretching peak (3400 cm\(^{-1}\)) after the silanol treatment. The loading of indaBOX after this step was determined to be 0.325 mmol/g.

If a different ligand, linker group R\(^1\), capping group R\(^2\) or metal was desired, the appropriate chemical compound would be substituted into the above synthesis following a similar reaction procedure. However, when (3-iodopropyl)trimethoxysilane was used to create a propyl linker group after reacting with lithiated indaBOX ligand at low temperatures, the flask was allowed to warm to room temperature for 4 days without increasing the temperature to 50\(^\circ\)C.

After silanol capping, the heterogenized catalyst was prepared by mixing blue-colored Cu(II) perchlorate hexahydrate (0.010 g, 0.027 mmol), MCF-immobilized indaBOX (0.082 g, 0.027 mmol), and dichloromethane (5 ml). The mixture was stirred at room temperature for 3 days, after which the white solid became lime green in color. In cases where Cu(II) triflate was employed instead of Cu(II) perchlorate hexahydrate, great care was taken to ensure that water was rigorously excluded from the catalyst synthesis and subsequent Diels-Alder reaction.
The corresponding homogeneous catalysts and dienophile 7 (Scheme 3.2) were prepared according to published reports. However, in some cases a small amount of dienophile was purchased from Tokyo Chemical Industry (TCI) America. Fresh cyclopentadiene was cracked from dicyclopentadiene (Sigma-Aldrich) at 170°C in a simple distillation setup under argon, where the distillate was cooled to 0°C. After cracking, the cyclopentadiene was pipetted into small crimp-top vials, sealed and transferred to a freezer at -10°C, which was found to sufficiently retard the rate of dimerization to less than 1% per day. Samples that were in the freezer for over 1 week were re-cracked as needed.

3.2.2. Catalyst Testing

The asymmetric Diels-Alder reaction was carried out in three experimental configurations. In all studies, the dienophile, dichloromethane and the appropriate amount of catalyst were mixed and stirred for ~15 min at the desired reaction temperature, 25°C, 0°C, -30°C or -78°C. Freshly cracked cyclopentadiene (3.3 molar equivalents based on dienophile) was then added to initiate the reaction. The reaction scheme (Scheme 3.2) demonstrates that four possible chiral products may be formed during reaction. There exists a pair of regioisomers, referred to as the endo and exo isomers. The endo/exo products refer to the position of the oxazolidinone moiety with respect to the six-membered ring in the product. Each endo/exo isomer contains an enantiomeric pair.

![Scheme 3.2](image)

Scheme 3.2. Asymmetric Diels-Alder reaction between achiral dienophile and achiral diene to produce four possible products.
The challenge of the heterogeneous ADA reaction is to take achiral reagents and achieve both high regioselectivity and high enantioselectivity so that, ideally, only one of the four possible products is generated. It should also be noted that the dienophile and diene can undergo a non-catalytic Diels-Alder reaction, yielding racemic products. The uncatalyzed reaction is bimolecular in nature and highly sensitive to temperature.\textsuperscript{18} To minimize it, dienophile and cyclopentadiene concentrations were kept below 0.10 M where possible. Highly concentrated reactions were run at 0°C or –30°C in order to quench the non-catalytic reaction.

Catalyst screening studies were carried out batchwise in stirred crimp-top vials or under an argon atmosphere in Schlenk flasks when necessary. Unless noted otherwise, all screening studies were conducted at a dienophile:catalyst molar ratio of 10, which was typical for these catalysts. Samples were collected via syringe and quenched with methanol; the dichloromethane and cyclopentadiene were quickly removed by blowing an air stream over the samples. Quenching with methanol effectively prevented the catalyst from further reacting after sampling, while removal of cyclopentadiene and dichloromethane prevented any thermal, non-catalytic Diels-Alder conversion from occurring at room temperature. The sample residue was dissolved in a 1:3 mixture (by volume) of dichloromethane and 90:10 mixture (by volume) of hexane and isopropanol. The sample vials were sealed with septa, and centrifuged at 1000 rpm for 5 min to precipitate out any unwanted catalyst particles. The endo product enantioselectivity (% ee), the endo regioselectivity (% endo), and the total conversion of the reagent were analyzed via high-performance liquid chromatography (HPLC, Waters Corp., 1525 binary syringe pump with UV detector) at $\lambda = 230$ nm and 25°C with a Chiracel OD-H column (4.6 mm x 250 mm, Daicel) (flow rate = 1.0 mL/min, eluent: 90:10 mixture of hexane and isopropanol (by volume)). The products’ stereochemistry was determined from comparing HPLC retention times to those in the literature.\textsuperscript{17} The dienophile reagent peak was determined from injection of a pure sample.

In catalyst reusability tests, the post-reaction mixture was centrifuged and washed 3 times with dichloromethane. The centrifugation was done within the reaction flask or vial in order to
limit catalyst loss between runs. The recovered catalyst was used directly for the next run without drying.

Kinetics experiments were performed with the use of in situ attenuated total reflection (ATR) FTIR spectroscopy (ASI ReactIR 1000) with an attached FiberConduit™ DiComp™ 6-mm probe (Mettler-Toledo Autochem) that could be inserted directly into a stirred reaction flask. The kinetics of the ADA catalysts could be measured over a range of temperatures by placing the reaction flask in a cooling bath. Samples were taken periodically during kinetic analyses to assay the enantioselectivity via HPLC. Kinetic experiments were performed at a number of different TON's from 10 to 400.

The best MCF-immobilized bisoxazoline catalyst was also examined in a continuous packed bed reactor setup. The catalyst particles were packed into an empty YMC column (4.6 mm x 100 mm, Waters Corp.) using the slurry packing method with dichloromethane as the packing solvent. The HPLC proved to be an ideal vehicle for determining the continuous on-line conversion profiles of the reactor (HPLC UV detector, λ = 230 nm). The HPLC syringe pumps also effectively delivered the two stock reagent solutions, and the cyclopentadiene stock solution was kept at 0°C to prevent dimerization during the experimental run. The reactor flow rates, pressure and conversion were all monitored by the HPLC Breeze™ software. Samples were taken at intervals in order to assay the enantioselectivity and regioselectivity via HPLC. The reactor, along with the reagent mixing coil, was immersed in a cooling bath so that the reactor performance could be measured as a function of temperature. The residence time of the continuous reactor was found via cyclopentadiene tracer experiments. Several aliquots of cyclopentadiene (which has only a weak affinity for the catalyst) were injected into the HPLC, and the reactor outlet was monitored by the HPLC UV detector. The elution time of the cyclopentadiene peak was taken as the residence time of the reactor for a specified flow rate.
3.3. Results and Discussion

3.3.1. Homogeneous Catalyst Screening Studies

Figure 3.3 shows three different homogeneous ligands that were examined for their performance in the ADA reaction. The bisoxazoline ligand, indaBOX, was chosen because homogeneous catalysts employing the ligand exhibited high ee’s over a broad range of conditions. Before testing the MCF-anchored complexes, the homogeneous indaBOX catalyst 1 was alkylated with 4-methylbenzylchloride to form monosubstituted indaBOX ligand 2 and disubstituted ligand 3 to examine the effects of the alklylation process on the activity and enantioselectivity of the Cu(II) catalyst complexes. The Cu(ClO$_4$)$_2$·6H$_2$O chelates of 1–3 were tested for the ADA reaction at -30°C, 0°C and 25°C as shown in Scheme 3.2. The catalyst derived from the commercially available ligand 1 offered high enantioselectivity (92% ee) and endo regioselectivity (95% endo) at -30°C. Interestingly, the enantioselectivity of the catalysts derived from ligands 2 and 3 remained essentially the same (90% and 94% ee at -30°C, respectively) with increasing alkyl substitution at the indaBOX methylene bridge. The superb performance of the homogeneous catalyst derived from 3 represented the target for heterogenized disubstituted indaBOX catalysts.

![Figure 3.3. Three homogeneous catalyst ligands tested in the ADA reaction.](image)

To examine the effect of silanol groups on the Cu(II) bisoxazoline catalysts, homogeneous copper perchlorate catalyst 1 was physically mixed with untreated as-calcined
MCF and with MCF capped with trimethylsilyl (TMS) species. At 25°C, the mixture with the as-calcined MCF showed only 71% ee, while that with the TMS-protected MCF gave 84% ee, exactly the same enantioselectivity found for pure homogeneous catalyst 1 (84% ee). The presence of silanol groups from the silica support adversely affected the enantioselectivity without impacting the activity of homogeneous catalyst 1. This study showed that it was crucial to eliminate sources of Lewis basicity on the MCF support prior to copper complexation with the immobilized ligand.

3.3.2. Screening Studies of Heterogenized Catalysts

A number of MCF-immobilized bisoxazoline catalysts were synthesized and tested for the ADA reaction. This study examined the effects of different ligands, linker groups, metal anions and silanol capping groups on catalyst enantioselectivity, endo selectivity and reactivity. Our MCF support has a well-defined mesostructured pore architecture, but it was unclear from other studies\(^ {20,21}\) whether the support porosity was an important factor in catalytic performance. Therefore, a non-porous colloidal silica of 200 nm was also prepared\(^ {22}\) and used as the catalyst support. Colloidal silica catalyst 8 is prepared in a similar manner as described in Section 3.2.1. Since regioselectivity and stereoselectivity are critical in fine chemical and pharmaceutical synthesis, the catalysts were screened first for high selectivity, prior to in-depth catalytic activity studies.

The first study focused on the effect of silanol capping agents to see whether the heterogenized catalysts followed the same trend as noted in Section 3.3.1. Capping the silanol groups with TMS increased the enantioselectivity of heterogenized catalysts significantly from 47% ee for catalyst 4 (no silanol treatment) to 70% ee for catalyst 4a at room temperature. Catalyst 4a achieved 88% ee at -78°C, and attained higher endo regioselectivity for the Diels-Alder product than catalyst 4 over all temperatures examined. Thus, it is crucial to protect the silanol groups to the greatest extent possible following ligand immobilization.
Next, different catalysts were synthesized based on three ligands, indaBOX, tbBOX and tbaBOX (see Figure 3.4). The tbBOX ligand is named for the tert-butyl group located at the sterogenic center, while tbaBOX is named for its tert-butyl group and the amine functionality of its backbone. Although extensive work has been carried out on different homogeneous catalyst ligands, it was not clear whether the best homogeneous ligands would result in the most effective heterogenized catalysts. Thus, the three ligands were immobilized onto the surface of MCF through propyl linker groups; the resulting materials were subjected to TMS-capping of silanols, and chelated to Cu(II) triflate to form active catalysts for comparison studies at room temperature and -78°C (see Figure 3.5).

![Figure 3.4. Three heterogenized catalyst ligands tested for the ADA reaction. Left to right: indaBOX, tbBOX and tbaBOX.](image)

![Figure 3.5. Enantioselectivity of Cu(OTf)₂ heterogenized catalysts derived from indaBOX (◊), tbaBOX (□) and tbBOX (△).](image)
Figure 3.5 was divided into two regions, the top half and the bottom half of the graph referred to ligands that gave preference to the (S)-endo and (R)-endo Diels-Alder products, respectively. Changes in ligand structure greatly affected the endo selectivity and enantioselectivity of the resulting heterogenized catalysts. The indaBOX ligand gave the highest overall enantioselectivity of the three ligands, with nearly 80% ee at -78°C. All ligands displayed the same endo selectivity at room temperature, but indaBOX gave the highest endo selectivity (97%) at lower temperatures (not shown). The tbBOX ligand also resulted in good enantioselectivity, but gave preference for the (R)-endo enantiomer, suggesting that its transition state must be very different from that of the indaBOX ligand. One possibility was that binding of the substrate to the copper active site caused a significant change in coordination sphere geometry, reversing the stereochemical outcome of the reaction. This idea has been supported through both experimental and computational studies on homogeneous bisoxazoline catalysts.24-26

Interestingly, the tbaBOX ligand exhibited very poor enantioselectivity at both temperatures. Other than the addition of a nitrogen atom to the ligand backbone, tbaBOX and tbBOX were identical. If the extra nitrogen atom in tbaBOX ligand underwent coordination with copper during reaction, it might have forced the dienophile to undergo monodentate binding instead of bidentate binding. Several accounts have noted the correspondence of bidentate binding with higher enantioselectivities.27 A second possibility was due to nitrogen's ability to support only three covalent bonds. As a result, the tbaBOX ligand was attached to the MCF surface using only one propyl linker group attached to the backbone amine, while the indaBOX and tbBOX ligands were immobilized through two linker groups. Attachment through only one linker group might have allowed the tbaBOX catalyst to more strongly interact with the MCF surface than the doubly-linked catalysts. Since this study demonstrated the superior enantioselectivity and endo selectivity of the heterogenized catalyst based on indaBOX, the latter was used as the ligand for subsequent studies.

A variety of Cu(II) anions have been used to generate active homogeneous catalysts.23 The most commonly chosen metal salts are Cu(II) perchlorate and Cu(II) triflate. These two
copper anions were introduced onto our MCF-immobilized catalyst 4a by chelating with Cu(II) perchlorate hexahydrate and complexing with Cu(II) triflate, respectively. The catalysts were tested at 25°C and -78°C in the absence of water under an argon atmosphere. Figure 3.6 showed that the perchlorate anion catalyst out-performed the triflate anion catalyst by a significant margin; the former achieved 80% ee at -78°C. However, the catalysts displayed nearly identical endo selectivities of 93% and 97% at 25°C and -78°C, respectively. Evans et al.\textsuperscript{17} found that triflate counterions gave the highest ee and endo selectivities over a range of temperatures for his homogeneous catalysts, but noted that the triflate catalysts were highly water-sensitive. They indicated that the water-stable antimony hexafluoride (SbF\textsubscript{6}) anion gave a superior copper bisoxazoline catalyst when trace amounts of water were present in the solution. They did not test perchlorate counterions in their study, but other papers\textsuperscript{19, 28} have noted that Cu(II) perchlorate homogeneous catalysts exhibited water stability. Therefore, the observed differences in the enantioselectivity of our two catalysts in Figure 3.6 could be attributed to (i) the catalyst sensitivity to trace amounts of strongly adsorbed water on the MCF surface, and/or (ii) the catalyst interactions with the residual MCF silanol groups.

![Graph](image)

\textbf{Figure 3.6.} Enantiomeric excess of catalyst 4a complexed with (\(\square\)) Cu(ClO\(_4\))\(_2\) and (\(\triangle\)) Cu(OTf)\(_2\).
Our previous experiments have illustrated the importance of silanol capping on catalyst selectivity. To determine the effect of MCF surface environment on the catalyst performance, ligand 4 (which contained a propyl linkage) was immobilized and capped with several different groups, TMS, methyldiphenylsilyl, octylsilyl and perfluoroctylsilyl, to yield catalysts 4a, 4b, 4c and 4d, respectively. The selectivities of these four catalysts were measured at -78°C, -30°C, 0°C and 25°C, and found to be lower than that of homogeneous indaBOX catalyst 1 (see Figure 3.7). However, catalysts 4a–4d displayed similar endo selectivities as 1 (see Figure 3.8).

![Graph showing enantiomeric excess vs temperature for catalysts](image)

**Figure 3.7.** Enantiomeric excess of (●) homogeneous catalyst 1 and heterogenized catalysts (■) 4, (▲) 4a, (□) 4b, (○) 4c and (△) 4d.

Catalysts 4a–4d were found to exhibit superior activities to homogeneous catalyst 1 and silica colloid-supported catalyst 8 for the ADA reaction with dienophile 7 (see Figure 3.9). This demonstrated the usefulness of an ultralarge-pore support in promoting the activities of ADA catalysts. The study also illustrated that the capping moieties could be used to increase the activity of MCF-supported catalysts without substantially altering the enantioselectivity. This was especially clear at -78°C, where the four heterogenized catalysts 4a, 4b, 4c and 4d showed
substantially different 1-hr conversions (Figure 3.9), while their ee’s (88%, 88%, 89% and 87%, respectively) remained remarkably similar (Figure 3.7).

**Figure 3.8.** Endo selectivities for (○) homogeneous catalyst 1, and heterogenized catalysts (◆) 4a, (□) 4b, (○) 4c and (△) 4d.

**Figure 3.9.** 1-hr conversions for (○) homogeneous catalyst 1, (□) colloid-supported catalyst 8, and heterogenized catalysts (◆) 4a, (●) 4b, (△) 4c and (▲) 4d.
Catalyst 6a was also investigated for its reusability according to the method described in Section 3.2.2. Table 3.2 shows that catalyst 6a achieved 100% conversion over all 5 runs, and displayed high enantioselectivities of 79–90% ee, depending on the reaction temperature for each run. Interestingly, the enantioselectivity was dependent upon the nature of the solvent used in the reaction and catalyst washes. Lower enantioselectivities were associated with the use of anhydrous dichloromethane, and higher ee values were obtained when the dichloromethane had been equilibrated with atmospheric moisture prior to reaction. For example, it was noted that after 5 runs, the enantioselectivity provided by 6a at 25°C with a hydrous dichloromethane (80% ee) was actually higher than that achieved by a fresh catalyst at 25°C with an anhydrous dichloromethane (74% ee). This suggested the importance of water as a spectator ligand near the catalyst active site.

**Table 3.1.** Diels-Alder reaction of cyclopentadiene and dienophile over fresh and recycled MCF-supported catalyst 6a with a ligand/Cu molar ratio of 1.1.

<table>
<thead>
<tr>
<th>Run #</th>
<th>Temperature (°C)</th>
<th>Solvent(^a)</th>
<th>Conversion(^b) (%)</th>
<th>% endo</th>
<th>% ee (endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^c)</td>
<td>0</td>
<td>anhydrous</td>
<td>100</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>anhydrous</td>
<td>100</td>
<td>94</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>anhydrous</td>
<td>100</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>-46</td>
<td>hydrous</td>
<td>100</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>hydrous</td>
<td>100</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>1(^c)</td>
<td>25</td>
<td>anhydrous</td>
<td>100</td>
<td>91</td>
<td>74</td>
</tr>
</tbody>
</table>

\(^a\)Dichloromethane. \(^b\)Conversion after 24 hr. \(^c\)Fresh catalysts.

**3.3.3. Kinetics of Heterogenized Diels-Alder Catalysts**

ADA reaction kinetics were measured by a ReactIR 1000 system using a set-up described in Section 3.2.2 for dienophile concentrations greater than 0.15 M. For dienophile concentrations of < 0.15 M, reaction sampling and HPLC analysis were used to determine the
reaction kinetics. To ensure that only the intrinsic kinetics of the catalytic species were measured, studies were conducted at -30°C. At this temperature, the non-catalytic ADA reaction between the dienophile and cyclopentadiene was found to be negligible, even at high reagent concentrations.

The first experiment measured the kinetics of catalyst 6a, which out-performed the other heterogenized catalysts in the activity screening studies at -30°C. The kinetics studies in Figure 3.10 were conducted at -30°C with 0.25 M dienophile, where a TON of 100 is equal to 100% conversion. The heterogenized catalyst 6a was shown to exhibit superior kinetics to the indaBOX homogeneous catalyst 1, and it exhibited very good enantioselectivity (86% ee). To demonstrate that the enhanced activity of 6a, which contained bulky methylphenylethyl linker groups, was not due to the modification of 1, homogeneous catalyst 3 was synthesized with methylphenylmethyl linker groups. Catalyst 3 was found to be even less active than catalyst 1, confirming that the MCF-immobilized catalyst 6a was intrinsically more active than the homogeneous catalysts. The initial portions of the conversion profiles of catalysts 6a, 1 and 3 were fit to simple first-order reaction kinetics, yielding rate constants of 0.059 min⁻¹, 0.024 min⁻¹ and 0.017 min⁻¹, respectively. Thus, heterogenized catalyst 6a reacted ~ 2.5 times and 3.5 times faster than the homogeneous catalysts 1 and 3, respectively.

Several factors were investigated to see if they could account for the enhanced activity of the heterogenized catalyst. To examine the effect of ligand loading on the rate constant, seven samples of catalysts 6a were prepared with different loadings of bisoxazoline ligands on the MCF support, and subjected to elemental analysis. All catalysts were then tested at -30°C, with 0.25 M dienophile and a TON of 100. The initial linear portion of their conversion versus-time curve was fit to a first-order reaction model to obtain the rate constant for each catalyst. Figure 3.11 shows that as the bisoxazoline ligand loading was increased from 0.04 to 0.33 mmol/g, the catalyst rate constant improved by a factor of ~ 6.
Figure 3.10. Catalyst conversion curves of ADA at -30°C over (●) heterogenized catalyst 6a, and homogeneous catalysts (□) 1 and (△) 3.

Figure 3.11. First-order ADA reaction rate constant versus ligand loading for catalyst 6a at -30°C.
To check that the observed effect was not related to a change in reagent or product adsorption associated with changes in surface chemistry, the solution concentrations of the reagents before reaction and that of the products after reaction were measured via *in situ* FTIR. Figure 3.12 shows that the solution concentrations of the reagents before reaction and the solution concentration of the product upon full conversion remained unaffected by the ligand loading. Therefore, it was concluded that the enhanced catalyst reactivity was not due to changes in local concentration or adsorption effects.

To examine another possibility for the effect of ligand loading on the reaction rate, we considered the largest critical dimension of indaBOX (~11.4 Å), which corresponded to a molecular area of 1.54 nm² on the support surface. The surface area of MCF after ligand immobilization and silanol capping was ~400 m²/g, which meant that a ligand loading of 0.43 mmol/g would correspond to a monolayer coverage of ligands on MCF. Thus, our highest ligand loading of 0.33 mmol/g would correspond to ~77% of a monolayer coverage, and the bisoxazoline ligands would be located fairly close to one another on the MCF surface. Therefore, a possible explanation for the enhanced reactivity could be “steric crowding”. As the ligand loading increased, the probability of ligand-ligand interactions would increase. Since the ADA product molecule is larger than the reagents, once it was formed at the copper active site, it would not be binded to the copper atom favorably relative to the reagents in a sterically crowded environment. In other words, the ADA product would be “pushed away” from the active site more readily when the catalyst environment became increasingly more crowded, thus facilitating the reaction of another substrate. This explanation assumes that the rate-limiting step was product desorption from the catalytic site, which was supported by the experiments in Figure 3.13.

Another feature displayed by the heterogenized catalysts was product inhibition, a phenomenon whereby the reaction rate decreased steadily due to a build-up of products in the solution. This could be observed by comparing the conversion profiles over fresh catalyst 6a at -30°C with 0.25
M dienophile in dichloromethane at an overall TON of 100, in the presence of 0 M, 0.25 M and 1.00 M of ADA product (of 86% ee) (see Figure 3.13). First-order rate constants of 0.036 min\(^{-1}\).

**Figure 3.12.** Solution concentrations of (\(\triangle\)) cyclopentadiene and (\(\Box\)) dienophile before reaction, and (\(\diamondsuit\)) ADA product after reaction.

**Figure 3.13.** Conversion profiles of 6a with an initial product:dienophile molar ratio of (\(\bullet\)) 0, (\(\Box\)) 1, and (\(\triangle\)) 4.
0.010 min$^{-1}$ and 0.006 min$^{-1}$ were obtained at initial product:dienophile molar ratios of 0, 1 and 4, respectively. These values corresponded to the rate constants at 0%, 50% and 80% conversions for a fresh run with no ADA product present initially. The results suggested that 72% and 83% of the initial catalytic activity would be lost by 50% and 80% conversions, respectively, due to product inhibition. The observed decrease in reactivity could be related to the structural similarity between the dienophile and the ADA product, which might cause the two species to compete for the copper active site (see Scheme 3.3). It would be highly desirable to find a means to continuously separate and/or remove the product from the reaction medium, thereby maximizing the catalyst activity. This is not possible with homogeneous catalysts, but could potentially be realized with the heterogenized catalysts in a chromatographic reactor or membrane reactor set-up.

![Scheme 3.3](image)

**Scheme 3.3.** Competition between the dienophile and the ADA product for binding with the copper active site, where $R =$ vinyl or norbornyl.

### 3.3.4. Continuous Asymmetric Diels-Alder Reactor Studies

Although the pharmaceutical and fine chemical industries have extensively used batch processing, continuous processing would be very attractive for the efficient production and effective separation of pharmaceutical intermediates.$^{29}$ However, there have been surprisingly few accounts of continuous asymmetric reactors in the literature.$^{30}$ This could change in the future with successful heterogenized catalyst development and chemical reaction engineering research devoted towards pharmaceuticals synthesis.
It was fairly easy to incorporate silica-immobilized asymmetric catalysts into a continuous processing scheme compared to homogeneous and polymer-bound catalysts. The homogeneous catalysts offered no means to retain the catalyst in the continuous reactor, while the polymer-bound catalysts could not withstand pressure drops in packed bed operations. Instead of performing multiple batch runs to demonstrate the catalyst reusability, the heterogenized catalysts could simply be loaded into a packed bed and run for a desired length of time. The packed bed reactor technology could further increase the catalyst productivity through the inherent advantages of continuous versus batch processing, such as more on-stream operation time, less maintenance, lower organic solvent requirements and consistent quality of product stream. This study focused on the creation, characterization and operation of an ADA continuous reactor with the highly active and selective MCF-immobilized catalyst 6a. The catalyst was packed according to the procedures outlined in Section 3.2.2 in an experimental set-up depicted in Figure 3.14.

**Figure 3.14.** Experimental set-up for the continuous ADA reaction, using the HPLC as the feed delivery, and on-line conversion data collection systems.

The ADA continuous reactor was run at -30°C, 0°C and 25°C, with 0.025 M of dienophile and 0.083 M of cyclopentadiene. These reagent concentrations were selected to be lower than those used in the kinetic experiments for three reasons. Firstly, running in continuous
mode required a great deal of dienophile and cyclopentadiene compared to the smaller batch reactions. Secondly, higher concentrations of dienophile and cyclopentadiene gave rise to faster reaction rates, resulting in more rapid dienophile consumption. The dienophile concentration of 0.025 M was found to be a good balance between dienophile synthesis requirements (as it was not commercially available) and reactor consumption. Lastly, 0.025 M was also used as the dienophile concentration in all catalyst screening studies.

After setting the reagent concentrations and the mass of catalyst 6a packed (0.337 g, total reactor volume = 1.66 cm³, total Cu loading = 8.38 × 10⁻⁵ mol), the total flow rate was adjusted so that the packed bed would come into contact with an overall TON of 100 over a 24-hr period. This calculation gave a total volumetric flow rate of 0.2 mL/min and a reactor residence time of ~ 6.8 min, based on cyclopentadiene tracer studies described in Section 3.2.2. In order to obtain the desired concentration and total flowrate, two stock solutions, 0.05 M dienophile and 0.17 M cyclopentadiene, were each fed at 0.1 mL/min through separate pumps.

On-line conversion of the reaction was measured by dienophile consumption. Figure 3.15 shows that excellent conversions of 91%, 95% and 96% were achieved at -30°C, 0°C and 25°C, respectively. These steady-state conversions were obtained shortly after introducing the cyclopentadiene feed, and remained constant over 7 hr. The performance of the continuous reactor was compared with that of a batch reactor employing the same mass of catalyst 6a (0.337 g) and reagent concentrations at -30°C. The batch reactor only achieved a conversion of 32% after 24 hr, giving a TOF of 1.3 hr⁻¹. This was 2.8-fold lower than the activity of the continuous reactor, which attained 91% conversion at -30°C with a TOF of 4 hr⁻¹. Besides the improvement in activity, the continuous reactor also offered more on-stream time. For long run times, the continuous ADA reactor would become even more attractive.
Figure 3.15. Conversion profiles for the continuous ADA reactor at -30°C (green), 0°C (red) and 25°C (blue).

The exit stream of the continuous reactor was also sampled periodically for enantioselectivity and regioselectivity. Figures 3.16 and 3.17 show that the enantioselectivity and endo selectivity rapidly reached steady-state values following introduction of the cyclopentadiene feed, and remained very stable over the entire course of the reaction. The enantioselectivity and endo selectivity increased as the reactor temperature was decreased, as was observed in the heterogenized catalyst screening studies. These values were identical to those obtained in batch screening studies for catalyst 6a, confirming that the continuous reactor retained excellent selectivity profiles while providing for enhanced catalytic productivity.

The fact that the continuous reactor showed improved performance over the batch reactor was puzzling. If run under similar conditions, the two reactors should produce a similar result since a packed bed reactor (PBR) is mathematically equivalent to a batch reactor (i.e. the conversion is a function of length in the PBR and a function of time in the batch reactor). Upon further examination, we noted that the reactor volume was quite different for the two cases; the continuous reactor has a total volume of 1.66 cm³, while the equivalent batch reactor would
Figure 3.16. Enantioselectivity profiles for the continuous reactor at (Δ) -30°C, (□) 0°C and (◇) 25°C.

Figure 3.17. Endo selectivity profiles for the continuous reactor at (Δ) -30°C, (□) 0°C and (◇) 25°C.

require 62.4 cm³ of solvent. Since equivalent reagent concentrations and catalyst mass were used in our comparison studies, the difference in reactor volume would give rise to a difference in catalyst concentration. The copper bisoxazoline catalyst concentrations in the continuous and
batch reactors were $5.0 \times 10^{-2}$ M and $1.3 \times 10^{-3}$ M, respectively. Since the dienophile concentrations were identical in both reactors, the difference in catalyst concentrations would result in drastically different dienophile:copper molar ratios in the two reactors. Thus, the catalyst was 38 times more concentrated in the continuous reactor than in the batch reactor, which might have caused the difference in their catalytic activities.

### 3.3.5. Modeling of Kinetics in the Heterogenized Catalyst System

In Section 3.3.3, the typical conversion profiles fitted well with a first-order reaction kinetics only during the initial stage of the reaction. Zero-order and second-order kinetic models could not fit well with the conversion profiles observed. In addition, these three models could not account for the interesting behavior exhibited by the MCF-immobilized bisoxazoline catalysts, such as product inhibition and the possible effect of catalyst concentration on reaction rate.

If the proposed catalytic mechanism (Figure 3.2) is reexamined along with the idea of competitive binding between the reagent and product (see Scheme 3.3), it can be seen that the catalyst site is “enzyme-like” in that an incoming reagent must first bind with the active metal site, become activated for reaction, react to form product, and then undergo product desorption from the active site. In mathematical terms, this can be represented by

$$
\begin{align*}
S + C & \overset{k_1}{\underset{k_2}{\rightleftharpoons}} C\cdot S \\
& \overset{k_3}{\rightarrow} C\cdot P \\
& \overset{k_4}{\rightleftharpoons} C + P
\end{align*}
$$

where $S$ is the dienophile substrate, $C$ is the catalyst, $D$ is the cyclopentadiene, and $P$ is the product. Since $D$ is present in excess ($[D] > [S] \sim [P]$), we will assume that $[D]$ is essentially constant throughout the reaction, and that the conversion of $S$ to $P$ is not dependent on $[D]$. A second assumption is that the product and reagent undergo competitive inhibition, and do not
show any non-competitive or mixed-competitive behavior. This assumption is verified below. If we further assume that $k_3$ is slow relative to $k_1$ and $k_2$, then Michaelis-Menten kinetics can be employed to model the reaction according to equation 3.2, \(^{31}\)

$$
- \frac{v_S \cdot [C_T] \cdot [S]}{(k_3 \cdot [P] + 1) \cdot k_2 + k_3} = \frac{V_{max} \cdot [S]}{K_p + [S]} = \frac{V_{max} \cdot [S]}{K_{M, app} + [S]}
$$

(3.2)

where $v_S$ is the rate of dicyclone consumption, $C_T$ is the total catalyst concentration, $V_{max}$ is the maximum possible rate, $K_p$ is the product-catalyst inhibition constant, and $K_M$ is the Michaelis-Menten constant. The form of Equation 3.2 is similar to the more familiar Michaelis-Menten equation without product inhibition. If the product does undergo competitive inhibition, the true $K_M$ is increased by a factor of $(1 + [P]/K_p)$, giving a larger apparent Michaelis-Menten constant, $K_{M, app}$.

The goals of our modeling study were to apply a Michaelis-Menten model to explain the heterogenized ADA catalyst behavior, to determine $k_3$, $K_M$, $K_p$ and $V_{max}$ for catalyst 6a at -30°C using *in situ* FTIR, and to use the improved understanding of the system to predict how the catalyst and reactor set-up might be further improved. Additionally, we wanted to experimentally verify what type of inhibition was occurring at the catalytically active sites.

To check if catalyst 6a displayed Michaelis-Menten kinetics, [S] was varied from 0.10 M to 1.00 M at a constant catalyst concentration of 2.5·10^{-3} M. The conversion profiles were obtained, and the initial reaction rates were regressed from the data between 0% and 25% conversion. Figure 3.18 shows that the initial rate increased linearly with increasing [S] at low substrate concentrations. However for [S] of > 0.25 M, the curve entered a substrate-saturated region. This was typical of the Michaelis-Menten kinetics, and further ruled out simple first- and second-order kinetic models.
Figure 3.18. Initial ADA reaction rate versus dienophile substrate concentration over catalyst 6a at -30°C.

To obtain values for $V_{\text{max}}$, $K_M$ and $K_P$, a Lineweaver-Burk plot analysis\textsuperscript{32} was conducted by rearranging Equation 3.2 as follows:

$$\frac{1}{v_i} = \frac{K_{\text{Mapp}}}{V_{\text{max}}} \cdot \frac{1}{[S]} + \frac{1}{V_{\text{max}}}$$  \hspace{1cm} (3.3)

where $v_i$ was the initial reaction rate. Thus, if Michaelis-Menton kinetics were observed, the data should fit a straight line in a plot of $1/v_i$ vs. $1/[S]$, with a slope of $K_{\text{Mapp}}/V_{\text{max}}$ and an intercept of $1/V_{\text{max}}$. This process was repeated for three different initial product concentrations ([P]), 0.00 M, 0.05 M and 0.10 M to obtain three straight lines, with three estimates of $V_{\text{max}}$ and $K_{\text{Mapp}}$ (see Figure 3.19). Since

$$K_{\text{Mapp}} = K_M \left(1 + \frac{[P]}{K_P}\right) = K_M + \frac{K_M}{K_P}[P]$$  \hspace{1cm} (3.4)

and $[P]$ was known for the three plots, the $K_{\text{Mapp}}$'s determined from the Lineweaver-Burk plot could be plotted against $[P]$ to obtain a slope of $K_M/K_P$ and an intercept of $K_M$ (see Figure 3.20). This allowed calculation of the intrinsic Michaelis-Menten constant and the ADA product-catalyst inhibition constant. From this analysis, $V_{\text{max}}$ was determined to be 0.0200 ± 0.0003 M·min\textsuperscript{-1}, $K_M$ was found to be 0.395 ± 0.004 M, and $K_P$ was calculated as 0.117 ± 0.003 M.  

73
Since the known catalyst concentration, $C_T$, was 0.0025 M, the value for $V_{\text{max}}$ could be used to calculate a value for $k_3$, which was $8 \text{ min}^{-1}$ at $-30^\circ\text{C}$.

The linear fits for the three curves in Figure 3.19 shared a nearly identical intercept. This translated into an accurate estimate for $V_{\text{max}}$, and suggested that the catalyst mechanism involved competitive binding between the dienophile and the product. The heterogeneous catalyst reaction rate was found to be highly dependent on the substrate concentration, as the $K_M$ of the system was $\sim 0.4$ M. A simple analysis of Equation 3.2 showed that a substrate concentration that was equal to $K_{M_{\text{app}}}$ would result in a reaction rate that was $0.5 V_{\text{max}}$. Thus, if higher reactivities were desirable, one would need to operate at dienophile concentrations much higher than 0.4 M.

![Graph](image.png)

**Figure 3.19.** Lineweaver-Burk plots for the continuous ADA reaction over catalyst 6a at $-30^\circ\text{C}$ and $[P_f] = (\triangle) 0.00$ M, (○) 0.05 M and (△) 0.10 M.

Similar studies were performed with homogeneous catalyst 1, which gave a $k_3$ of $25 \pm 9 \text{ min}^{-1}$, a $K_M$ of $2.38 \pm 0.67$ M and a $K_P$ of $0.033 \pm 0.32$ M, respectively. These values allowed for the calculation of Michaelis-Menten selectivity constants, $k_3/K_M$, for the homogeneous and heterogenized catalysts. The heterogenized catalyst 6a had a selectivity constant of $20.3 \text{ M}^{-1}\cdot\text{min}^{-1}$, which was 1.95 times larger than that of the homogeneous
catalyst. According to the model, the increase in selectivity constant directly resulted from the higher $K_p$ of the heterogenized catalyst. The higher $K_p$ led to a lower $K_M$ for catalyst 6a, and thus, a higher intrinsic activity than the homogeneous catalyst.

![Figure 3.20. $K_{M_{app}}$ versus [P$_r$] for the continuous ADA reaction over catalyst 6a at -30°C.](image)

The model could also qualitatively explain the discrepancies between the continuous and batch reactors. The measured turnover frequencies in those studies were rather low, but the reactions were run at 0.025 M dienophile. Plugging this value into the model revealed that at this substrate concentration, catalyst 6a was operating at only 6% of its maximum possible rate at -30°C. If the dienophile concentration was substantially increased, the TOF could be increased to as much as 80 hr$^{-1}$.

$V_{max}$, which was composed of $k_3$ and the total catalyst concentration ($C_T$), could partially account for why the continuous reactor gave higher activities than the batch reactor. $V_{max}$ was a function of catalyst concentration, while $k_3$ was fixed for a given temperature. Since the batch and continuous reactors had two different total catalyst concentrations, they were effectively operating in different $V_{max}$ regimes. Substituting in the catalyst concentrations and the value for $k_3$ gave $V_{max}$ values of 0.38 M·min$^{-1}$ and 0.02 M·min$^{-1}$ for the continuous and batch reactors.
respectively. Although there clearly was not a factor of 19 difference in reactivity in the experiments, the inclusion of catalyst concentration in the Michaelis-Menten rate expression partially explained the observed factor of 3 increase in the case of the continuous reactor.

As a final check, the validity of the Michaelis-Menten model was verified to rule out the possibility of mass transfer limitations as the source of the substrate saturation kinetics. The Michaelis-Menten selectivity constant, $k_s/K_M$, which is the apparent second-order rate constant for the reaction of the substrate with the catalyst, could easily be calculated for catalyst 6a at -30°C (0.34 M$^{-1}$ sec$^{-1}$), and compared to the characteristic time of reagent diffusion in the system. If we use an experimentally determined value for the self-diffusion coefficient at -30°C, 2.1$\times$10$^5$ cm$^2$/s, then we could calculate a Damköhler number, Da, using the average catalyst particle radius (25$\times$10$^{-6}$ m) as the characteristic length of the system and a characteristic reagent concentration of 1.0 M. Da was determined to be 0.10, which suggested that the reaction was limited only by the catalyst kinetics, and that diffusion limitations were not responsible for the observed substrate-dependent behavior of the reaction rate.

3.4. Summary

In this work, a class of highly active and selective heterogenized catalysts were synthesized and tested for the ADA reaction. Screening studies uncovered the importance of silanol capping on catalyst enantioselectivity, showed that indaBOX was the preferred ligand, and established that perchlorate counterions led to robust, water-stable catalysts. Kinetic experiments demonstrated that the ligand loading and support porosity were the two most important factors leading to highly active catalysts. The studies also illustrated that all of the highly loaded, silanol-capped, MCF-immobilized catalysts were intrinsically more active than their homogeneous counterparts.

The MCF-immobilized bisoxazoline catalysts were also shown to be easily reusable through multiple batch reaction cycles, and the most active catalyst 6a was successfully employed in a continuous packed bed reactor. The continuous reactor studies showed that the
heterogenized catalyst has a stable activity and selectivity over extended reaction periods, and provided strong evidence that the reaction rate depended on catalyst concentration.

A Michaelis-Menten model that accounted for product inhibition successfully described the kinetic behavior of the heterogenized catalyst 6a. The study confirmed that the dienophile and product underwent competitive inhibition, and allowed for the determination of key catalyst model parameters from experimental data. The large values for both $K_M$ and $K_P$ suggested that high substrate concentrations or a means for continuous product removal were necessary to increase the rate of reaction at a given set of reaction concentrations.

3.5. References


Chapter 4
Palladium-Grafted Carbon Nanofoam as a Reusable Heck Catalyst

4.1. Introduction

The Heck reaction is a powerful synthetic tool in organic chemistry for C-C bond formation through a liquid-phase reaction between aryl halides and alkenes.\textsuperscript{1} Heck coupling has great industrial potential, but Heck reaction catalysts have traditionally suffered from low oxygen tolerance and poor reusability.\textsuperscript{2}

Very high turnover numbers (TON’s) have been achieved with homogeneous palladium complexes and palladium salts, but these catalysts cannot be readily reused and many involve air-sensitive phosphine ligands.\textsuperscript{3, 4} In recent years, air-stable homogeneous palladium carbene complexes have been reported, but they often yield much lower TON’s than palladium-phosphine complexes. Such catalysts typically require higher temperatures or the use of additives such as tetrabutylammonium bromide to attain good TON’s.\textsuperscript{3, 5, 6}

Heterogeneous palladium catalysts offer the promise of good activity, stability and reusability. Various supports have been tested for the Heck reaction, including metal oxides such as MgO, CaCO\textsubscript{3}, and SiO\textsubscript{2}. These systems, while exhibiting high activities, typically suffer from air-sensitivity, palladium leaching during reaction, and severe loss of activity due to palladium cluster growth.\textsuperscript{2} One of the most active heterogeneous Heck coupling catalysts was derived by vapor grafting of organopalladium complex onto MCM-41.\textsuperscript{7, 8} After reduction in hydrogen, Pd nanoclusters were formed within the mesoporous silica support. The resulting Pd-TMS11 catalyst successfully catalyzed various aryl halides, but suffered from some growth and agglomeration of palladium clusters after the Heck reaction. Thus, the recycled catalysts were less active, and required regeneration at 400°C in hydrogen.\textsuperscript{9}

Palladium supported on activated carbon (Pd/C) is one of the most widely studied Heck catalysts, with activities comparable to some of the best homogeneous catalysts. However, severe palladium leaching from activated carbon during reaction\textsuperscript{2} and particle attrition limit the reusability of Pd/C and present major obstacles in the industrial application of Pd/C. Heidenreich \textit{et al.}\textsuperscript{10} reduced palladium leaching from activated carbon through the manipulation of Heck reaction conditions. Nevertheless, the Pd/C catalyst still lost over 90% of its activity after two recycles due to palladium cluster growth from 2 nm to 23 nm. Other
attempts to support Pd on graphite have led to Heck catalysts with relatively low activities, due most likely to the poor palladium dispersion in these systems.\textsuperscript{11}

The drawbacks of the carbon supports are thought to be due to their lack of mesoporosity. The activated carbon systems have very high surface areas in excess of 1500 m\textsuperscript{2}/g, but are entirely microporous. The micropores have diameters of less than 1 nm, forcing even the smallest palladium clusters (1-2 nm) to reside on the external surfaces of the activated carbon. Some Pd/graphite catalysts have been reported to retain finer Pd crystallite sizes than Pd/C during Heck polymerizations,\textsuperscript{12} or to produce active, quasi-2D palladium nanoparticles on graphite supports.\textsuperscript{13} However, the low surface areas and minimal porosities of these systems make them unattractive.

Recently, García-Martínez \textit{et al.} reported on the synthesis of a novel carbon nanofoam (CNF) material that exhibits high surface area, mesoporosity and a large pore volume.\textsuperscript{14} CNF also has a crystalline framework, and excellent mechanical, thermal and electrical properties. Since the unique properties and mesoporosity of CNF may provide for interesting catalytic behavior, this new form of carbon was evaluated as a Heck catalyst support.\textsuperscript{14}

\textbf{4.2. Experimental}

\textbf{4.2.1. Synthesis and Characterization of CNF}

Unlike carbon materials replicated from ordered silicas,\textsuperscript{15} nanoporous CNF was derived directly through surfactant templating.\textsuperscript{16} The synthesis strategy of CNF involved templating of the carbon precursor, furfuryl alcohol, with a long-chain aliphatic alcohol to form an ordered mesostructure, followed by polymerization of the templated carbon precursor by addition of a catalyst, \textit{p}-toluene sulfonic acid. After mild curing, carbonization and surfactant removal were accomplished by heat treatment under an inert atmosphere.

In a typical synthesis,\textsuperscript{16} 5 g of hexadecanol (Alfa Aesar Chemicals) and 5 g of furfuryl alcohol (Alfa Aesar Chemicals) were mixed and slowly heated until a clear yellow solution was obtained; 0.15 g of \textit{p}-toluene sulfonic acid solution (60\% w/w in water, Alfa Aesar Chemicals) was then added. If a particular macroscopic shape was required, the CNF precursor solution would be transferred at this point to a container of the desired shape for further processing. The temperature was kept constant at 40–50\degree C to avoid the prematuresd solidification of precursor solution and to accelerate the polymerization of furfuryl alcohol. The solution temperature was then ramped from 60\degree C to 120\degree C for curing. The resulting
polymerized solid was ground down into a powder of desired particle size for catalytic applications. This powder was heated at 800°C in N₂ for 5 hr for surfactant removal and carbonization. The resulting CNF material was shown by transmission electron microscopy (TEM) (JEOL 2010 microscope, 200 kV) to possess a nanoporous 3D network (Figure 4.1(a)). The pore walls were crystalline and lamellar in structure with a d spacing of 0.3 nm (similar to graphite), and gave an electron diffraction pattern indicative of a polycrystalline material (Figure 4.1(b)). Nitrogen adsorption-desorption isotherm (Micromeritics ASAP 2010) of CNF indicated the presence of both microporosity (0.15 cc/g) and mesoporosity (0.25 cc/g).

**Figure 4.1.** (a) TEM micrograph of a microtomed sample of CNF, showing its nanoporous structure. (b) A high-resolution TEM micrograph and electron diffraction (inset) of the CNF framework, illustrating the high crystallinity of the pore wall, which has a d spacing (0.3 nm) similar to graphite. (c) Nitrogen adsorption-desorption isotherm and (d) BJH desorption mesopore size distribution of CNF.
(Figure 4.1(c)). The material has a BET surface area of ~ 400 m²/g and a total pore volume of 0.4 cm³/g, with a pore size centered at ~ 9 nm (see Figure 4.1(d)). CNF also has an electrical conductivity of ~ 0.01 S/cm, which was similar to that of glassy carbon.

4.2.2. Synthesis and Characterization of Heck Catalysts

Vapor grafting was used to introduce the active palladium species onto the CNF support. A volatile organopalladium(II) complex, Pd(η³-C₃H₃)(η⁵-C₅H₅), was grafted onto CNF at 80°C following the method described by Mehnert et al.⁷,⁸ For catalyst preparation, the CNF support (0.322 g) or activated carbon powder (Darco, 0.500 g) was first degassed in vacuo for 24 hr at 140°C. The organopalladium complex (0.082 g) was synthesized according to the procedure described elsewhere,⁸ and was placed in the vapor grafting apparatus with the carbon support at room temperature. Vapor grafting took place overnight at 80°C. The resulting vapor-grafted Pd/CNF-1, Pd/CNF-2 and Pd/C-2 catalysts were stored in the glovebox under argon prior to reaction.

Pd content in the catalysts was obtained with inductively coupled plasma (ICP) elemental analysis by Quantitative Technologies, Inc., Whitehouse, NJ. X-ray photoelectron spectroscopy (XPS) was performed on a Kratos AXIS Ultra Imaging X-ray Photoelectron Spectrometer using a monochromatic Al-Kα source. TEM was conducted with a JEOL 2010 microscope with a field-emission gun electron source at 200 kV, and convergent-beam electron diffraction was done with the STEM attachment on the JEOL 2010 microscope.

4.2.3. Heck Reaction Studies

The coupling of 4-bromoacetophenone and n-butyl acrylate is a standard test reaction for heterogeneous Heck catalysts in the literature. A key aspect of this reaction is that it is catalytic in metal, but stoichiometric in base. An examination of the Heck reaction scheme proposed by Schmidt and Smirnov¹⁷ and Biffis et al.² for heterogeneous Heck catalysts revealed that a strong base was needed to allow reductive elimination of hydrogen bromide from the palladium metal center. This allowed the palladium to re-enter the catalytic cycle for another turnover. Since the basic component was critical to maintain reactivity, excess base was usually introduced.
N,N-dimethylacetamide, dodecane, 4-bromoacetophenone, n-butyl acrylate, and sodium acetate trihydrate were purchased from Sigma-Aldrich and were used as-received unless stated otherwise.

In a typical Heck reaction, 4-bromoacetophenone (4.575 g, 22.9 mmol), sodium acetate trihydrate (4.844 g, 35.5 mmol), 179 mL of dimethylacetamide, and 0.45 mL of dodecane (a chromatography internal standard) were introduced to a 250-mL Schlenk flask. In an oxygen-free experiment, the flask would be subjected to 3 freeze-pump-thaw cycles to remove oxygen from the reagents and solvent, prior to catalyst addition in a glovebox filled with argon. The sealed flask would then be connected to an argon line for reaction. For experiments performed in air, the flask would not be subjected to freeze-pump-thaw cycles, and the catalyst would not be introduced within a glovebox. The amount of catalyst added (typically ~ 0.013 g) was based on the palladium content of the fresh catalyst, and was adjusted to give a TON of 3700 for each run with 100% conversion.

After heating the reaction flask to 140°C, the catalytic testing was initiated by adding an excess of n-butyl acrylate (4.04 mL, 28.1 mmol). The reactions were sampled in 0.3-mL aliquots with a syringe, and were then filtered through a 2-cm silica column (Merck, 240–400 mesh) to remove any catalyst particles using ethanol as the eluent. Catalyst conversion was monitored via gas chromatography (GC) (Hewlett-Packard Model 5890). Heck coupling products were verified by a gas chromatograph-mass spectrometer and by comparing chromatograms with those of pure standards.

The goal of the study was to create robust and reusable Heck catalysts. To facilitate catalyst recovery and reuse, catalyst powders were placed within an apparatus that was constructed out of a 0.7-μm glass fiber filter paper, with an outer cover made of 5-μm hydrophobic Teflon filter paper. This “filter membrane” was sealed with Teflon tape, and was introduced to the reaction flask. At the conclusion of each run, the filter membrane would be removed from the flask, and washed with excess fresh dimethylacetamide and deionized water to remove residual chemicals from the catalyst surface. It was then dried briefly in air or argon at room temperature, and then introduced to a flask containing fresh solvent and reagents for the next run.
4.3. Results and Discussion

4.3.1. Synthesis and Characterization of Pd/CNF Catalysts

Four catalysts were examined in this study (see Table 4.1). Pd/C-1 was obtained from Degussa; the palladium was introduced by impregnation. This commercial catalyst was compared to the three vapor-grafted catalysts described in Section 4.2.2, Pd/CNF-1, Pd/CNF-2 and Pd/C-2. The particle size, BET surface area, average pore diameter, pore wall structure and palladium loading for the four catalysts are summarized in Table 4.1.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Support Material</th>
<th>Particle Size</th>
<th>Surface Area (m²/g)</th>
<th>Average Pore Size (nm)</th>
<th>Wall Structure</th>
<th>Pd Loading (wt%)</th>
<th>Pd Loading Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd/C-1</td>
<td>Degussa E101 WO/W Activated Carbon</td>
<td>Fine Powder</td>
<td>800 est</td>
<td>&lt; 1</td>
<td>Amorphous</td>
<td>5.0</td>
<td>Impregnation</td>
</tr>
<tr>
<td>Pd/C-2</td>
<td>G-60 Darco Activated Carbon</td>
<td>45-150 µm</td>
<td>600</td>
<td>&lt; 1</td>
<td>Amorphous</td>
<td>9.0</td>
<td>Vapor Grafting</td>
</tr>
<tr>
<td>Pd/CNF-1</td>
<td>Carbon Nanofoam</td>
<td>Fine Powder</td>
<td>400</td>
<td>18</td>
<td>Polycrystalline</td>
<td>5.3</td>
<td>Vapor Grafting</td>
</tr>
<tr>
<td>Pd/CNF-2</td>
<td>Carbon Nanofoam (0.5–3 mm)</td>
<td>Coarse Powder</td>
<td>400</td>
<td>18</td>
<td>Polycrystalline</td>
<td>5.5</td>
<td>Vapor Grafting</td>
</tr>
</tbody>
</table>

Mehnert et al." and Lettow" have previously shown that vapor grafting was a superior technique to other methods for Pd deposition on silica-supported Heck catalysts. They demonstrated that vapor grafting, followed by a mild hydrogen reduction at 300°C, led to a uniform dispersion of Pd crystallites throughout the mesoporous silica support. Since fine Pd crystallite sizes gave rise to higher activity,\(^1\) catalysts prepared via vapor grafting were very active for Heck coupling reaction. In fact, some of these catalysts were actually active towards unactivated aryl chlorides.\(^2\) However, these mesoporous silica-supported catalysts were not easily recycled. They have to be reduced under a hydrogen atmosphere before reuse, and suffered from loss in activity associated with Pd cluster growth and agglomeration.

Unlike most Pd/C catalysts, which required a reducing treatment to form the active Pd\(^0\) species on the support surface,\(^3\) vapor grafting of Pd complex onto CNF gave rise to the spontaneous formation of Pd\(^0\) clusters (as indicated by XPS). TEM illustrated that highly dispersed Pd clusters of ~2–3 nm were found throughout the CNF structure (Figure 4.2(a)). The contrast differences of the Pd clusters in the TEM image also provided stong evidence
that the Pd clusters were located within the pores of CNF. The lattice fringes (inset of Figure 4.2) revealed that the Pd clusters were crystalline. Many of the Pd crystallites were shown to have a faceted morphology on the CNF surface, which was similar to the quasi-2D palladium crystallite structure noted on graphite.\textsuperscript{13}

![Figure 4.2](image)

**Figure 4.2.** (a) TEM micrograph of Pd/CNF-1 following vapor grafting of organopalladium complex at 80°C. (Inset) High-resolution TEM micrograph of a representative Pd nanocrystallite illustrating its crystallinity, the typical \(d\) spacing of Pd, and a highly faceted crystallite morphology. (b) TEM micrograph of Pd/CNF-1 after three Heck reaction runs at 140°C in air (with a total TON of 11,100). The Pd nanocrystallites remained \(\sim 3\) nm in diameter after the reactions.

Further confirmation that the palladium clusters were located within the pores of MCF was provided by an observed particle size effect on Heck catalyst reaction rate. Pd/CNF-2 was synthesized by the same procedure as Pd/CNF-1, except that the support was ground and sieved into much coarser particles of 0.5–3 mm prior to palladium vapor grafting. The Pd/CNF-2 catalyst, which contained 5.5 wt\% Pd by elemental analysis, was examined for Heck reaction under an inert atmosphere at 140°C. It achieved a turnover frequency (TOF) of 920 hr\(^{-1}\) in its initial run, which was significantly lower than that achieved by Pd/CNF-1 (3270 hr\(^{-1}\)), which contained 5.3 wt\% Pd. Since the catalyst with larger particle size demonstrated less activity at a similar Pd loading, diffusion was suspected to be rate-limiting. Lettow reported that catalyst supports with larger pore sizes showed faster reaction rates, confirming the role of diffusion in Heck reactions under similar conditions.\textsuperscript{9} Our results strongly
suggested that the palladium clusters were mainly distributed within the pores of the CNF support instead of on the external surfaces of the support particles; otherwise, the reaction rate would be independent of particle size at a given Pd loading.

4.3.2. Effect of Support and Reaction Atmosphere on Catalyst Activity and Reusability

To examine the effect of different carbon supports on catalyst activity and selectivity, Pd/C-1 and Pd/CNF-1 were tested for the Heck coupling of 4-bromoacetophenone and n-butyl acrylate at 140°C under an inert atmosphere (see Scheme 4.3). The catalysts were mixed with reagents and solvent and heated to 140°C as described in Section 4.2.3. After reaching full conversion in the first run, the flask contents were maintained at 140°C in argon for 24 hr, and the reaction was initiated for a second time by adding new reagents to the catalyst-containing reaction medium.

\[
\text{Pd/C, 140°C} \quad \text{NaOAc 3H}_2\text{O}
\]

\[
\text{O} \quad \text{Br} \quad \text{O} \quad \text{O} \quad \text{O}
\]

Scheme 4.1. The Heck coupling reaction between 4-bromoacetophenone and n-butyl acrylate.

The conversion data for the two runs were obtained with GC using dodecane as the internal standard. Pd/C-1 and Pd/CNF-1 both achieved 100% conversion in less than 4 hr in the first run, which corresponded to a TON of 3700 (mole of product)/(mole of Pd) (see Figure 4.3). Turnover frequency (TOF), defined here as (mole of product)/(mole of Pd \cdot hr), was obtained from the linear fits of the conversion-time curve between 20% and 80% conversion. High TOF’s of 3270 hr\(^{-1}\) and 2480 hr\(^{-1}\) were achieved by Pd/C-1 and Pd/CNF-1, respectively, during their first run. Minimal activity was observed with Pd/C-1 in the second run even after 24 hr (TOF’s < 1 hr\(^{-1}\)), as consistent with previous reports on such catalyst.\(^{10}\) Remarkably, Pd/CNF-1 demonstrated a TOF of 2890 hr\(^{-1}\) in its second run, which was greater than the TOF achieved in its first run.

Next, the experiments were conducted with fresh catalysts in the presence of air, and without degassing the solvent and reagents. Pd/C-1 showed a slightly higher TOF of 3520 hr\(^{-1}\) under air than under argon, but again displayed no activity upon reuse (see Figure 4.4). In
contrast, the Pd/CNF-1 catalyst demonstrated attractive TOF’s of 2390 hr\(^{-1}\) and 1440 hr\(^{-1}\) in its first and second runs, respectively, in the presence of air.

**Figure 4.3.** Heck reaction conversion over Pd/C-1 (□,Δ) and Pd/CNF-1 (■,▲) in dimethylacetamide under argon at 140°C: runs #1 (□,■) and #2 (Δ,▲).

**Figure 4.4.** Heck reaction conversion over Pd/C-1 (□,Δ) and Pd/CNF-1 (■,▲) in dimethylacetamide under air at 140°C: runs #1 (□,■) and #2 (Δ,▲).
This study showed that Pd/CNF-1 was able to retain much of its activity during its second run, even after stirring for 24 hr at 140°C in air, during which the palladium species were exposed to a chemically aggressive environment consisting of a polar solvent, a strong base, and a high concentration of product. This striking difference between Pd/CNF-1 and Pd/C-1 strongly suggested that the CNF support played a key role in stabilizing catalyst reactivity.

Encouraged by the enhanced stability of Pd/CNF-1 compared to Pd/C-1, Pd/CNF-1 was evaluated for recyclability. For ease of recovery, Pd/C-1 and Pd/CNF-1 catalysts were each kept within a filter membrane (see Section 4.2.3), washed, and reused in fresh solvents and reagents. They were exposed to oxygen during the catalytic studies, and in the catalyst recovery and washing steps. The Pd/C-1 catalyst showed good activity for its first run in air, but was not active in the second run (TOF’s < 1 hr⁻¹). In contrast, the Pd/CNF-1 catalyst remained active for Heck reaction after several runs in the presence of air, giving TOF’s in the range of 270–916 hr⁻¹ (see Figure 4.5). After runs #1 and 2, the filter membrane was cooled, washed, and returned to a flask with new reagents and solvent. After run #3, the catalyst particles were removed from the filter membrane in order to have direct contact with the reaction medium. After run #4, the catalyst particles were recovered by filtering through a 0.7-μm glass fiber membrane, and were thoroughly washed with fresh dimethylacetamide and deionized water before starting run #5.

The TOF’s attained in this set of experiments were lower than those achieved in the previous set of experiments (which involved reagents addition without catalyst recovery), most likely due to mass transfer resistance associated with the use of filter membrane in the former. This would explain the fact that fresh Pd/CNF-1 catalysts attained TOF’s of 916 hr⁻¹ and 2390 hr⁻¹ when they were used with and without a filter membrane, respectively. This was also consistent with the observation that compared to its TOF in run #3 (310 hr⁻¹), the Pd/CNF-1 catalyst showed a higher TOF of 643 hr⁻¹ in run #4 when the particles were removed from the filter membrane to have direct contact with the reaction medium. After run #4, the catalyst particles were recovered by filtering, giving a TOF of 270 hr⁻¹ in run #5.

The Pd/CNF-1 filter membrane system was also studied under an inert atmosphere. As described in Section 4.2.3, oxygen was rigorously removed by degassing the mixture of solvent and reagents prior to the catalyst addition inside a glovebox containing argon. After each run, the reaction flask was cooled, and the products and reagents were filtered away.
under argon using standard Schlenk line techniques. Fresh solvent and water rinses of the catalyst filter membrane were conducted within the Schlenk flask under argon. After filtering away the wash solvents, fresh reagents and dimethylacetamide were added under argon. The solution was then degassed before heating to 140°C for reaction.

![Graph](image)

**Figure 4.5.** Heck reaction conversion over Pd/CNF-1 under air at 140°C: runs #1 (□), #2 (△) and #3 (○) within a filter membrane, and #4 (●) and #5 (■) without the filter membrane.

The Pd/CNF-1 filter membrane system was shown to be even more active under argon (Figure 4.6) than under air (see Figure 4.5). There was a shorter “induction period” under argon before rapid increase in the reaction rate was observed. This phenomenon would seem to indicate that the catalyst was sensitive to oxygen, and strongly suggested that the catalytically active species was oxidized in the presence of air. Pd/CNF-1 filter membrane attained higher TOF’s in argon, achieving 1140 hr⁻¹, 700 hr⁻¹, 590 hr⁻¹ and 420 hr⁻¹ for runs #1, #2, #3 and #4, respectively. The TOF obtained by the Pd/CNF-1 filter membrane in air was only 310 hr⁻¹ for run #3. Thus, the rigorous exclusion of oxygen led to a 90% increase in reaction rate in run #3.
Figure 4.6. Heck reaction conversion over Pd/CNF-1 under argon at 140°C: runs #1 (□), #2 (△), #3 (○) and #4 (●), all within a filter membrane.

4.3.3. Reusability of Pd/CNF Catalysts

Pd/CNF-1 was shown to attain 100% conversion in all five runs in air, giving a total TON of 18,500. To our knowledge, this is the first example of a heterogeneous palladium catalyst that is truly recyclable in the presence of air. Most conventional catalysts have shown significant palladium cluster agglomeration and growth even after one run. In contrast, Pd/CNF-1 exhibited negligible palladium cluster growth. Even after three runs at 140°C in air, the mean palladium cluster size was kept at ~3 nm and the particles remained highly dispersed (see Figure 4.2(b)).

This is a very significant finding since all heterogeneous palladium Heck catalyst systems, including Pd/C, usually show considerable palladium cluster growth after reaction. TEM micrographs in Figure 4.7 clearly illustrated that the well-dispersed palladium particles in Pd/C grew from ~10 nm to 50–100 nm after just one run at 140°C in air. Consequently, little catalytic activity was achieved by the recycled Pd/C catalyst. In contrast, Pd/CNF-1 was able to retain its catalytic activity over multiple cycles; this could be attributed to its stability against palladium cluster growth.
Figure 4.7. TEM micrographs of Pd/C (a) before and (b) after one run at 140°C in air (with a total TON of 100) for the Heck coupling of 4-bromobenzene and styrene in dimethylacetamide.10

XPS was used to determine the oxidation state of surface palladium species in Pd/C-1 and Pd/CNF-1 (Figure 4.8). Pd/CNF-1 was analyzed before reaction and after three runs in air within a filter membrane. XPS spectra showed that nearly all of the surface palladium species were Pd0 before and after three runs (Figures 4.8(e) and (f), respectively), even though the reaction runs and washes were conducted in the presence of air. This supported the finding that no hydrogen reduction was needed to regenerate Pd/CNF-1 between runs, unlike many oxide-supported Heck catalysts. The lack of palladium oxidation might be due to a strong interaction between the palladium cluster and the CNF support. However, no significant binding energy shifts were observed in the XPS peaks that could be indicative of a Pd-CNF electronic interaction. Raman spectroscopy also showed no significant shifts in the CNF peaks after Pd vapor grafting. Pd/CNF-1 material was further examined to see if, indeed, the Pd clusters had adopted a quasi-2D morphology on the surface of CNF. If the Pd crystallites had adopted this configuration, then according to several accounts,20-22 one would expect the normally diamagnetic Pd species to become paramagnetic in nature. SQUID measurements were performed on Pd/CNF at 4 K, but no significant paramagnetic or ferromagnetic moments were detected. This suggested that either the palladium loading was insufficient to generate a signal, or the palladium clusters, while small and faceted (see Figure 4.2(a)), were not fine enough to adopt a quasi-2D structure on CNF surface.
Figure 4.8. XPS spectra of (a) as-received Pd/C-1, (b) Pd/C-1 after one Heck reaction run in air, (c) as-synthesized Pd/C-2, (d) Pd/C-2 after three Heck reaction runs in air, (e) as-synthesized Pd/CNF-1, (f) Pd/CNF-1 after three Heck reaction runs in air. All spectra were referenced to the C 1s peak. The solid vertical lines represent the Pd$^{0}$ 3d peaks, while the dashed vertical lines represent the Pd$^{2+}$ 3d peaks of palladium oxide.

In contrast, the as-received Pd/C-1 catalyst contained mainly Pd$^{2+}$ species (Fig. 4.8 (a)), most likely in the form of palladium oxide (PdO). We note that no palladium species could be detected by XPS and TEM after one run, suggesting that the palladium species were leached from the Pd/C-1 catalyst surface during reaction. The results suggested that the Pd$^{2+}$ species leached more easily from the support than the Pd$^{0}$ species. Since the Pd$^{0}$ species were stabilized in Pd/CNF-1, palladium leaching was minimized, and significant catalytic reactivity was retained by this system over the course of several reaction runs.

To determine if the unique properties of Pd/CNF-1 resulted from the use of CNF or the Pd vapor grafting process, palladium was vapor-grafted onto Darco activated carbon after degassing the support at 180°C in vacuo for 24 hr to remove the surface adsorbed water. The resulting Pd/C-2 catalyst contained 9.0 wt% Pd, and was stored under an inert atmosphere. It was then placed in a filter membrane and tested for reusability at 140°C in the presence of air. Pd/C-2 showed TOF’s of 730 and 160 hr$^{-1}$ in its first and second runs (see Figure 4.9). Its third run resulted in a TOF of only 4 hr$^{-1}$ and less than 6% conversion after 24 hr of reaction.
Compared to the commercially available Pd/C-1 catalyst, Pd/C-2 showed somewhat better reusability, but still suffered from significant deactivation by its third run.

![Graph showing TON vs Time for Heck reaction conversion over Pd/C-2 under air at 140°C: runs #1 (□), #2 (Δ), and #3 (○), all within a filter membrane.]

**Figure 4.9.** Heck reaction conversion over Pd/C-2 under air at 140°C: runs #1 (□), #2 (Δ), and #3 (○), all within a filter membrane.

TEM showed that the as-prepared Pd/C-2 catalyst consisted of 3–5-nm palladium clusters (Figure 4.10(a)), and the palladium dispersion on activated carbon was not as high as that on CNF, possibly due to the pore structure differences in the two supports. TEM revealed that most of the palladium clusters had leached out of the activated carbon after three runs, and that the remaining palladium clusters had grown to 10–20 nm in size (Figure 4.10(b)). XPS corroborated the TEM findings, showing that most of the palladium had been lost after the reactions. Thus, although Pd/C-2 was obtained by organopalladium vapor grafting in the same manner as Pd/CNF-1, it suffered from significant deactivation due to Pd leaching and agglomeration. This study illustrated that it was important not only to obtain highly dispersed palladium clusters by vapor grafting, but also to use an appropriate support to stabilize palladium against leaching and cluster growth. Thus, the mesoporosity and crystalline walls of CNF were important factors towards preventing palladium leaching, agglomeration and oxidation, allowing a robust and reusable Pd/CNF-1 catalyst to be achieved for Heck coupling.
Figure 4.10. (a) TEM micrograph of Pd/C-2 after vapor grafting of organopalladium complex at 80°C. (b) TEM micrograph of Pd/C-2 after three Heck reaction runs at 140°C in air within a filter membrane.

Since XPS and TEM studies on Pd/C-1 and Pd/C-2 indicated leaching as a likely cause for catalyst deactivation, the phenomenon was investigated in detail for Pd/CNF-1. In the filter membrane studies under argon, Pd/CNF-1 was highly active, but its TOF decreased from 1140 hr\(^{-1}\) for run #1 to 420 hr\(^{-1}\) for run #4. Since palladium leaching was suspected, elemental analysis was performed on the catalyst after three runs within the filter membrane. The Pd content in Pd/CNF-1 was found to decrease from 5.3 wt% to 1.6 wt% after three runs. If we recalculate the TOF for run #4 on the basis of 1.6 wt% (instead of 5.3 wt%) Pd loading, the TOF would actually be 1390 hr\(^{-1}\). This exercise suggested that the Pd clusters on Pd/CNF-1 were highly active and remained well-dispersed over the course of four runs, as illustrated by TEM and XPS.

The mechanism of Heck catalysis remains controversial as to whether the reaction is catalyzed by heterogeneous palladium clusters or by palladium species that leach into solution.\(^{11, 24, 25}\) The following test was conducted to investigate if soluble and active species were present in our reaction solution. After two runs of complete conversion over Pd/CNF-1 at 140°C under argon, the hot reaction solution was separated from the filtered catalyst under argon and allowed to cool. Fresh 4-bromoacetophenone, sodium acetate and n-butyl acrylate reagents were then added to the reacted solution, which was reheated to 140°C under argon for further reaction. No conversion of the fresh reagents was observed after 24 hr, indicating that a soluble Pd species, while likely present in solution, was not active for the Heck reaction under these conditions. This study suggested that the CNF supported Pd\(^0\) clusters were responsible for catalytic activity.
4.4. Summary

In this work, a new surfactant-templated carbon material with tunable porosity and crystallinity, named carbon nanofoam (CNF), was successfully used as a catalytic support for palladium in the Heck reaction. The unique combination of crystalline and conductive framework, high surface area and interconnected porous structure allowed for the spontaneous reduction of a volatile Pd(II) complex within the CNF pores upon vapor grafting, and provided for the stabilization of highly dispersed Pd clusters over multiple reaction cycles. The resulting catalysts showed high tolerance to oxygen and water, displayed excellent turnover frequencies, and were successfully reused several times in the presence of air. The initial activity of the Pd/CNF catalyst at 140°C under argon (TOF = 2480 hr\(^{-1}\)) was comparable to that of the best Pd/C catalysts, but did not require hydrogen pretreatment or hydrogen reduction after catalyst recycling. XPS and TEM studies showed that after three runs in the presence of oxygen, the Pd cluster size and oxidation state remained unchanged on the CNF surface. To our knowledge, Pd/CNF is the first heterogeneous Heck catalyst that can avoid Pd cluster growth and agglomeration, and the first reusable heterogeneous Heck catalyst to exhibit significant activity after multiple cycles. These attractive properties may extend the application of Pd/CNF to other Pd-catalyzed reactions, including hydrogenation, Suzuki cross-coupling reactions, Stille transformations, and amination reactions. The stable dispersion and oxidation state of Pd on CNF may also be extended to other transition metal systems, providing additional applications for a wide variety of reactions.

4.5. References


Chapter 5
Conclusions and Recommendations for Future Work

5.1. Conclusions

A novel synthesis scheme was devised to give spherical silica mesocellular foam (S-MCF) particles with median pore sizes of 10–30 nm, pore volumes of 1.1–1.8 cm³/g and surface areas of 400–700 m²/g, depending on the synthesis conditions. The synthesis involved a solution pH of 2 to separate the sol-gel hydrolysis and condensation steps, and maximize the tetraethoxysilane hydrolysis prior to particle condensation. Spherical silica particles were produced via the addition of a sol-gel condensation catalyst, NaF, through a nucleation-growth mechanism. A secondary addition of NaF was found to dramatically increase pore size and give the desired mesocellular foam (MCF) pore morphology. By decoupling the particle and pore formation processes, we could vary the S-MCF particle size and pore size independently during synthesis.

The S-MCF material was engineered into a high-performance liquid chromatography (HPLC) support through an understanding of MCF surface chemistry and organosilane chemistry. Surface rehydroxylation was used to effectively remove the isolated and geminal silanol species that caused poor separation performance. The S-MCF particles were made hydrophobic via the surface grafting with octadecyldimethylchlorosilane groups, and the remaining silanols were capped with trimethylsilylimidazole. The resulting S-MCF column showed excellent separation of an aryl ketone mixture, and its performance rivaled that of a commercially available HPLC column.

MCF was also examined as a support for the immobilization of chiral organometallic complexes for the asymmetric Diels-Alder (ADA) reaction. Bisoxazoline-copper(II) catalysts were anchored onto the MCF surface. Screening studies demonstrated that subtle changes in ligand structure dramatically influenced the stereoselectivity of the ADA reaction, with the indaBOX ligand giving ee values as high as 86% at -30°C. Our studies elucidated the importance of silanol capping on catalyst enantioselectivity, examined the effects of different catalyst linker groups, showed that indaBOX was the preferred ligand, and established that a copper(II) perchlorate metal-
counterion pair gave water-stable catalysts. The MCF-immobilized bisoxazoline catalysts were reused successfully, and shown to be stable in both batch and continuous reactor schemes. Kinetic experiments demonstrated that the high ligand loading and support porosity allowed the MCF-immobilized catalysts to be intrinsically more active than their homogeneous counterparts. A Michaelis-Menten kinetic model was constructed, and showed that the data were consistent with competitive inhibition between the reagent and the product. Furthermore, regression of the model parameters from experimental data demonstrated that the MCF-immobilized catalysts had a higher selectivity constant, compared to that of homogeneous catalysts.

Carbon nanofoam (CNF), a new surfactant-templated carbon material with tunable porosity and crystallinity, was successfully used as a catalytic support for palladium in the Heck coupling reaction. The unique combination of crystalline and conductive framework, high surface areas, and interconnected porous structure allowed for the spontaneous reduction of a volatile Pd(II) complex within the CNF pores upon vapor grafting, and provided for the stabilization of highly dispersed Pd clusters over multiple reaction cycles. The resulting catalysts showed high tolerance to oxygen and water, displayed excellent turnover frequencies, and were successfully reused several times in the presence of air. The initial activity of the Pd/CNF catalyst at 140°C under argon (TOF = 2480 hr⁻¹) was comparable to that of the best Pd/C catalysts, but did not require hydrogen pretreatment or hydrogen reduction for catalyst reuse. Unlike in Pd/C systems, the Pd cluster size and oxidation state remained unchanged on the CNF surface even after several runs in the presence of air. Pd/CNF successfully prevented Pd cluster growth and agglomeration, and exhibited significant activity for Heck coupling reaction over multiple cycles.

5.2. Recommendations for Future Work

5.2.1. Spherical Mesocellular Foam Particles for Protein Separations

In this thesis, S-MCF particles have been successfully synthesized and applied towards chromatographic separations. This novel silica material can be used for the bioseparations of proteins in future research.
Protein separations are important in biotechnology and pharmaceutical industries. In this thesis, S-MCF has been used for the separation of small molecules. However, their large pore sizes, pore volumes and surface areas should allow for increased column loadings for large proteins compared to conventional chromatographic columns. The easily modified silica surface chemistry and the independent control over S-MCF particle and pore sizes should allow for rapid protein separations through adsorption and shape-selective mechanisms. Recently, biotechnology companies have made use of fluidized bed chromatography (FBC) for bioseparations, as the process allows for the direct recovery and purification of proteins from cells without the need for a clarification step.\(^1\) Currently, non-porous spherical particles are functionalized with an appropriate affinity ligand to select for a desired protein in the mixture. However, because these particles lack porosity and possess low surface areas, the achievable protein loadings are quite low. Functionalization of the S-MCF particles with affinity ligands should allow for higher loadings and a greater FBC throughput due to S-MCF’s mesoporosity and high surface areas. S-MCF particles would also meet the FBC design requirement of uniform spherical particles.

5.2.2. Heterogenized Catalysts for Asymmetric Carbon-Carbon Bond Formation

Novel heterogenized catalysts were successfully designed for the asymmetric Diels–Alder reaction. The bisoxazoline complexes immobilized on MCF supports were readily reused and displayed enhanced reactivity over their homogeneous counterpart. These catalysts can be applied to other asymmetric carbon-carbon bond-forming reactions, such as the asymmetric carbonyl-ene, Michael and cyclopropanation reactions.\(^2-4\) Furthermore, other homogeneous catalyst systems that exhibit low substrate:catalyst ratios and slow kinetics would benefit from our approach of catalyst heterogenization using MCF as the support material.

5.2.3. Other Applications of Carbon Nanofoam

In this thesis, CNF was used to support palladium nanoclusters effectively for Heck coupling reaction. Our studies demonstrated the importance of mesoporosity and crystallinity of CNF on catalytic performance. The unique net-shape formability and
high electrical conductivity of CNF can be very useful in applications such as electrochemistry, electrosorption of heavy metals from liquids, fuel cells and supercapacitors. These applications, which require high surface areas and facile diffusion of electrons and ions, would benefit from the high surface area and mesoporosity of CNF. CNF may also be used as a hydrogen storage material for mobile fuel cell applications, such as in automobiles. Crystalline carbon materials, such as graphite and carbon nanotubes, have been shown to adsorb significant amounts of hydrogen, but they suffer from slow kinetics of release even after heating to high temperatures.\textsuperscript{5,6} CNF, which possesses a high degree of crystallinity, should display similar hydrogen storage capacity as other crystalline carbon materials, but with faster kinetics of adsorption and release due to its mesoporous framework. Additionally, hydrogen release may be precisely controlled via an electrical pulse in CNF, rather than through bulk heating as in the case of other porous carbons.

5.3. References


