

Pharmaceuticals Synthesis and Green Chemistry

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Novel mesoporous silica for catalytic applications

IBN
TECHNOLOGY PORTFOLIO



About IBN

The Institute of Bioengineering and Nanotechnology (IBN) is the world's first bioengineering and nanotechnology research institute. Since 2003, IBN has been conducting interdisciplinary research bridging science, engineering and medicine. The Institute's strengths lie in its synthetic capability for chemicals, materials and biologics. IBN has developed unique technology platforms that combine novel catalytic chemistry, biomaterials, nanofabricated devices and microfluidic systems with biological engineering. Its highly collaborative environment also promotes the sharing of ideas, expertise and infrastructural support, and a culture that encourages innovative research and the nurturing of young talents.

IBN's research activities are focused in the following areas:

Drug and Gene Delivery, where the controlled release of therapeutics involve the use of functionalized polymers, hydrogels and biologics for targeting diseased cells and organs, and for responding to specific biological stimuli.

Cell and Tissue Engineering, where biomimicking materials, stem cell technology, microfluidic systems and bioimaging tools are combined to develop novel approaches to regenerative medicine and artificial organs.

Biodevices and Diagnostics, which involve nanotechnology and microfabricated platforms for high-throughput biomarker and drug screening, automated biologics synthesis, and rapid disease diagnosis.

Pharmaceuticals Synthesis and Green Chemistry, which encompasses the efficient catalytic synthesis of chiral pharmaceuticals, and new nanocomposite materials for sustainable technology and alternative energy generation.

As of February 2011, IBN has filed over 1,168 patent applications on its inventions and the Institute is currently looking for partners for collaboration and commercialization of its suite of technologies.

For more information, please visit www.ibn.a-star.edu.sg or contact Dr Benjamin Tai at btai@ibn.a-star.edu.sg or +65 6824 7223.

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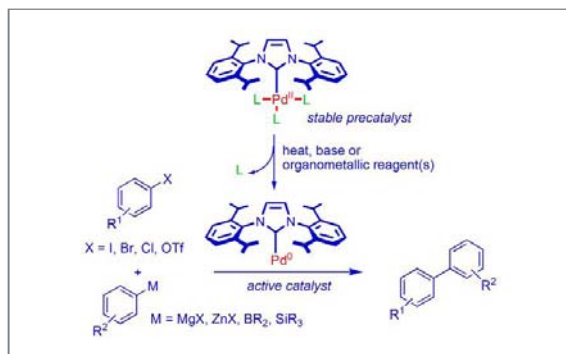
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Customized N-Heterocyclic Carbene–Palladacycle Precatalysts and Mesocellular Foam Supported Palladium Nanoclusters for Organic Transformations

NHCs have recently attracted considerable attention as ligands in transition metal mediated organic transformations, due to their numerous advantages compared to phosphine ligands in terms of safety, stability and activity. On the other hand, palladacycles are characterized by superior thermal stability compared to other palladium precatalysts. Currently, a very limited number of NHC-ligated palladacycles have been prepared, and their preparation routes are unattractive due to the high cost associated with palladacycle precursors and the use of highly sensitive isolated carbenes. In addition, no general synthetic approach has been developed to date for this class of Pd complexes, which accommodates a wide range of carbenes and a wide range of ligands, capable of palladacycle formation. At IBN, we have developed a one-step preparation of NHC-palladacycles without immediate isolation. In addition, we have also developed a siliceous mesocellular foam support system for the deposition of palladium-based catalyst nanoclusters which improves the stability of such catalyst, thereby lowering overall costs.



◀ A user-friendly, easily-prepared, highly-active NHC-Pd precatalyst for cross-coupling reactions.

Advantages:

NHC-Palladacycle Precatalysts

- A three-component reaction sequence with carefully optimized timing for the addition of each component.
- No special equipment or technique is needed.
- NHC palladacycle yields are generally in the range of 80-90%.
- The multicomponent nature of the method opens the possibility that a number of novel precatalysts (including chiral ones) can be prepared in a combinatorial fashion in a single step, so as to facilitate catalyst optimization.

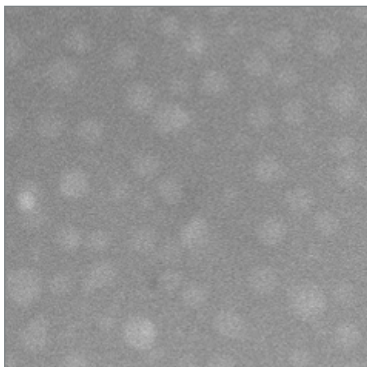
Supported Pd Nanoclusters

- Method of deposition takes 5-10 minutes.
- Pd nanoclusters are more active than commercially available polymer- or carbon-supported catalysts due to non-swelling characteristic, high surface area and ultralarge pore of the MCF support and the stabilization by urea or thiourea ligand.
- It has been demonstrated to have yield in the range of 80-90% for these reactions: Suzuki, Heck, transfer hydrogenation of ketones, hydrogenation of olefins, reductive amination of aldehydes under hydrogen, hydrogenolysis of epoxides and diols.

Applications:

- Pd-mediated reactions that are used to synthesize pharmaceutical intermediates, fine chemicals, advanced materials and specialty polymers.

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A typical transmission electron image of enzyme-loaded reversed polymer micelles.

Thermally Responsive Reversed Micelles for Immobilization of Enzymes

Enzymes are being increasingly exploited as biocatalysts for synthesis of pharmaceuticals and fine chemicals because they provide high enantio- and region-selectivity and are more environmentally friendly. However, the use of enzymes is limited due to their unstable nature and the stringent requirements for their surrounding environment. Enzyme immobilization systems thus offer an attractive alternative to allow for recycling and continuous operation. Conventional enzyme immobilization employs reversed micelles made from ionic surfactants, but non-ionic surfactants are usually included to minimize the negative effects of the ionic reversed micelles on the enzyme activity.

This conventional system has a major drawback in that the high concentration of low-molecular-weight surfactants causes difficulties in product separation and enzyme recovery. This invention overcomes this drawback by using thermosensitive and reversed micelles assembled from an amphiphilic copolymer, which allows for a temperature-controlled release of the immobilized enzymes. This amphiphilic copolymer displays a lower critical solution temperature (LCST). Increasing the temperature of the surrounding environment of the micelles slightly above the LCST causes the deformation of the reversed micelles, releasing the enclosed enzymes and stopping the enzymatic reaction.

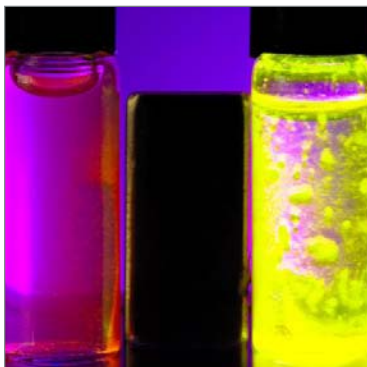
Advantages:

- Compared to conventional ionic and non-ionic surfactant micelles, the micelles developed in this invention provide greater stability.
- The immobilized enzymes can be recovered by simply increasing the environmental temperature to a value slightly higher than the reaction temperature.

Applications:

- Immobilizing enzymes for the synthesis of chiral pharmaceuticals.

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Magnetic quantum dots consisting of CdSe and Fe₂O₃ under UV excitation and magnetic harvesting, showing both fluorescence and magnetic properties.

Catalytic and Biological Applications of Magnetic Nanoparticles

Silica-coated magnetic nanoparticles have been developed by IBN. The silica surfaces of these nanoparticles may be modified with various functional silanes. These modified particles can be used for immobilizing various metal nanoparticles, as well as homogeneous catalysts, in order to catalyze organic reactions. The magnetic nanocatalysts can then be easily separated using magnetic force and recycled. The silica surfaces may also be modified for biological applications. The magnetic property of these particles will be very useful as contrast agents for MRI and as drug carriers.

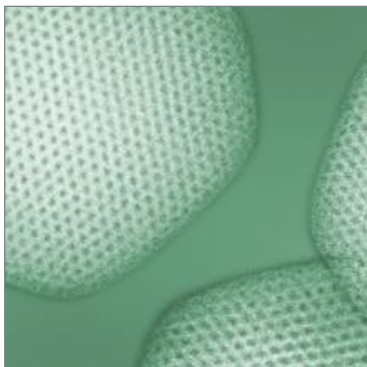
Advantages:

- The invention provides for the easy modification of silica-coated magnetic nanoparticles through well-defined silica modification methods.
- It allows the easy recycling of magnetic nanocatalysts without the need for filtering or centrifuging.

Applications:

- This technology can be used in catalytic reactions and biological applications of magnetic nanoparticles.

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Transmission electron micrograph of nanoporous material.

Immobilization of Homogeneous Catalysts and Biocatalysts on Nanoporous Materials and Circulating Flow-Type Reactor

IBN researchers have developed novel heterogenized catalysts by immobilizing various homogeneous catalysts on siliceous mesocellular foams. A novel pre-capping method was developed to minimize the interactions between the immobilized catalytic species and the silica surface, which facilitates uniform distribution of the immobilized complexes, as well as provides easy control of the catalyst loading. This technology has been successfully applied to the immobilization of chiral bisoxazoline catalysts and ring-closing metathesis catalysts. The immobilized bisoxazoline:Cu(I) catalysts are comparable to their homogeneous counterparts in terms of high enantioselectivity. They further provide excellent recyclability for asymmetric cyclopropanation reactions. The immobilized ring-closing metathesis catalysts show excellent activity and recyclability in the synthesis of various cyclic compounds. Using click chemistry, novel silane moieties have been successfully employed as the linker groups to immobilize various types of complexes, including organometallic and organo catalysts. In addition, enzyme catalysts have been immobilized on nanoporous materials. The fixated biocatalysts are more thermally stable and easily recovered for reuse. The various heterogenized catalysts can be employed in continuous flow reactors to enhance the productivity and simplify the industrial processes.

Advantages:

- The heterogenized catalysts offer comparable enantioselectivity as their homogeneous counterparts.
- They also feature excellent recyclability and a high loading of homogeneous catalysts.
- They reduce the contamination of products by toxic transition metals.
- The circulating flow-type reactor provides for high on-stream time and less catalyst attrition by a continual removal of side products and gases that disturb catalytic beds.
- Biocatalysts can be loaded in a high quantities in a short period of time.
- The immobilized enzymes are more thermally stable and hardly leached from the nanoporous support.
- The heterogenized biocatalysts can be directly employed in continuous flow reactors.

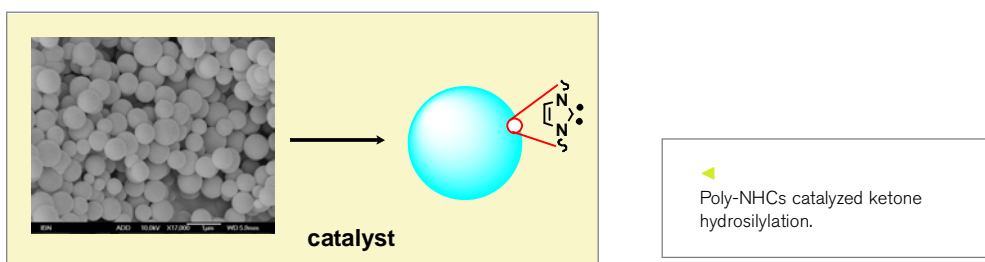
Applications:

- The immobilized catalysts can be used for large-scale production, both in a batch and a continuous flow reactor.
- The spherical nanoporous materials can be used in HPLC columns.

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N-Heterocyclic Carbene Catalyzed Ketone and Imine Hydrosilylation and a Novel Chiral Induction Protocol

Ketone and imine reduction by hydrogenation, hydroboration and hydrosilylation is one of the most ubiquitous protocols in organic synthesis. Hydrosilylation is a particularly attractive process due to the mild reaction condition and inexpensive silane reducing agent. Although hydrogenation is widely practised industrially, it faces shortcomings such as metal leaching, high pressure, expensive catalysts and costly catalyst recycling. Stoichiometric borane reduction or dihydropyridine reduction catalyzed by organocatalysts are plagued by high costs. A number of transition metals complexes, such as Rh, Ti, Ru, Ir, Zn, Pt, Cu and Sn, have displayed high catalytic activity or selectivity in the hydrosilylation of carbonyl compounds, but shared the problem of metal leaching and costly catalyst regeneration as hydrogenation. Researchers at IBN have developed novel hydrosilylation protocols with organocatalysts that are more easily prepared and less expensive, as well as effective silane reducing agents. These organocatalysts are poly-N-heterocyclic carbene (poly-NHC) organocatalysts that enable smooth and clean ketone and imine hydrosilylation.



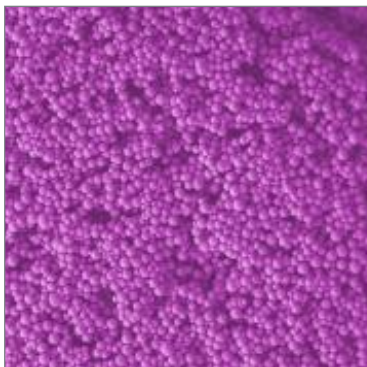
Advantages:

- Catalyst is recyclable and environmentally friendly.
- Catalyst is metal-free, thus overcoming the problem of metal leaching.
- Protocol requires only 1 equivalent of silane, thereby lowering the overall cost.
- Asymmetric ketone hydrosilylation is achieved with inexpensive and easily accessible secondary alcohol as the chiral source.

Applications:

- Metal-free heterogeneous and homogeneous catalysts.

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Main chain poly-NHC particles.

Main Chain Poly-N-Heterocyclic Carbene Catalyst System

Heterogeneous catalysis has many advantages over homogeneous catalysis, but there are certain limitations in the current protocols for producing heterogeneous catalysts via the immobilization of homogeneous catalysts onto inorganic or organic solid supports. Main chain poly-N-heterocyclic carbene (NHC) based heterogeneous catalysts have been developed by IBN, which spontaneously form micro- and nano-sized spherical particles. The poly-NHC colloidal based catalysts show excellent performance both as nucleophilic organo catalysts and organometallic catalysts in many important transformations. This innovation is a major breakthrough in both NHC carbene chemistry and heterogeneous catalysts.

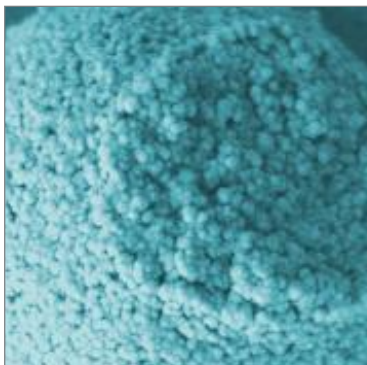
Advantages:

- The properties of these colloids can be easily tailored to form ionic solid particles or free poly-NHC carbene and poly-NHC-metal organometallic particles.
- The catalysts perform well as nucleophilic organo catalysts and organometallic catalysts in many important transformations.

Applications:

- Main chain poly-NHC as metal-free organocatalyst for ketone and imine hydrosilylation.
- Main chain poly-NHC-Pd for heterogeneous Suzuki coupling reaction.
- Copper or poly-NHC-Cu for synthesis propiolic acids from alkynes and CO₂.

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▲ Mesoporous polymer particles with functional group for catalyst immobilization.

Porous Polymer Materials as Heterogeneous Catalysts and Absorbents

Two novel mesoporous/microporous polymer materials have been developed at IBN. Mesoporous polystyrene particles (MPPs) have been developed using siliceous mesoporous cellular foam as a hard template, whereby both the porosity and the surface properties can be tailored for a specific catalyst support. A simple protocol for the catalytic synthesis of microporous and mesoporous polyisocyanurates (PICUs) has also been developed. PICUs possess robust microporosity and mesoporosity constructed from porous organic sheets. They have been demonstrated as catalyst supports for Pd(II), Fe(III) complexes, as well as for Pd or Pt metal nanoparticles. Both MPPs and PICUs materials are of interest for heterogeneous catalysis, absorbent, gas storage and energy applications. In particular, they may be of interest for hydrogen storage, and as catalyst supports for organometallic complexes, and metal or oxide nanoparticles.

Advantages:

- The MPPs and PICUs can be tailored with a wide range of porosities and surface areas.
- Easy synthesis, stable and permanent porous structure.
- These novel poly-imidazolium, poly-NHC and poly-NHC-metal catalysts can be synthesized and modified easily.
- They have very high concentration of active sites, high activity, stability and reusability.
- The surface of the MPPs can be easily modified, for example, for the immobilization of pyrrolidine.

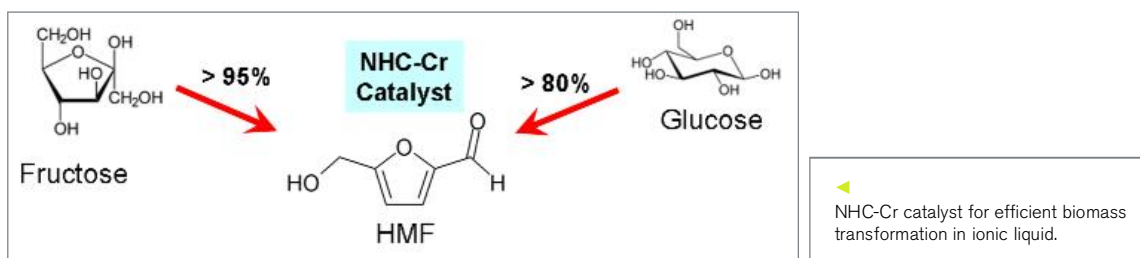
Applications:

- These methods developed by IBN can be used to design novel heterogeneous catalysts and absorbents.
- The poly-imidazolium, poly-NHC and poly-NHC-metal catalysts can be used in many organic transformations, such as C-C coupling reaction (with Pd) and ketone cyanation.

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Efficient Catalytic Systems for the Selective Production of Hydroxymethylfurfural from Glucose and Fructose

A practical catalytic process that can transform abundant biomass into versatile chemicals would provide the chemical industry with renewable feedstocks. Recently, a lot of efforts have been devoted towards converting biomass to 5-hydroxymethylfurfural (HMF), a versatile and key intermediate in biofuel chemistry and the petroleum industry. A new Cr-N-heterocyclic carbene (NHC)/ionic liquid system has been developed by IBN for selective production of HMF from glucose and fructose. This novel catalyst achieved high efficiency from both fructose and glucose feedstocks. It provided high selectivity towards HMF, and tolerance towards high substrate loading. It also enabled easy recycling of catalyst and ionic liquid. In addition, IBN scientists developed a novel tetrahydrofuran (THF)-butyl-methyl imidazolium chloride (BMIMCl) biphasic system with simple acid catalysts for fructose conversion to HMF under mild reaction conditions. This enables HMF to be efficiently synthesized at room temperature in the ionic liquid system. The biphasic system was successfully applied to a continuous batch reaction process, and may be suitable for large-scale synthesis of HMF from fructose.



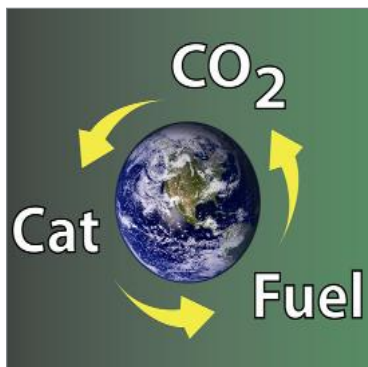
Advantages:

- Highly efficient, recyclable system.
- Mild reaction conditions, easy to scale up for large-scale operation.

Applications:

- The methods developed by IBN can be applied towards biomass transformation.

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▲ Efficient catalytic protocols for CO₂ reduction.

N-Heterocyclic Carbene Catalyzed Conversion of CO₂ to Methanol and CO

A new technique for converting carbon dioxide to methanol with silane as the hydrogen source has been developed at IBN. This represents the first CO₂ reduction reaction catalyzed by N-heterocyclic carbene (NHC) organocatalysts. It demonstrates a very promising chemical CO₂ fixation protocol, and the possibility of direct conversion of CO₂ (from air) to methanol with the formation of polysiloxanes. The novel process for catalytic reduction of carbon dioxide to carbon monoxide under ambient conditions using aromatic aldehydes as reductants has also been developed using NHCs as organocatalysts. This carbon dioxide splitting reaction provides a new method for carbon dioxide reduction and advances the utilization of carbon dioxide as a renewable "green" fuel source. This reaction also shows a new economical way to oxidize aromatic aldehydes in mild conditions with carbon dioxide, and could be applied in pharmaceutical synthesis.

Advantages:

- NHC catalysts are metal-free, less expensive, and have superior efficiency.
- Milder, more flexible and air-tolerant reaction conditions.

Applications:

- Transformation of carbon dioxide to energy-related chemicals.

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