Reaxa Ltd
Leeds Bioincubator, Leeds, UK
www.reaxa.com

“ENCATS™- Encapsulated Catalysts”
For Easier, Faster and Cleaner Processes

27th April 2015.
What drives the selection of a Catalyst?

Improve yields
Higher selectivity
Reduced work-up
Eliminating reprocessing
Higher throughput
Reusable catalyst systems
Easier, safer handling
Metal recovery

EnCat™ contribute to each of these factors by providing Green processes with cost reduction
**EnCat™ Green Catalysts!**

Metal catalysts encapsulated in polymer beads Pd, Os, Pt and Ni plus co-encapsulated ligands.

Available at commercial scale.

Products designed for GMP use

---

**Conventional Catalyst:**

- Pyrophoric
- Residual toxic metals
- Multi-step purification
- Yield losses on work-up
- One-time catalyst use
- Lost metal value
- Batch processes only

---

**EnCat™ Solutions:**

- Safer
- Low metal contamination
- Easy filtration
- Simple, high-yield process
- Re-useable catalysts
- Efficient metal recovery
- Flow processing enabled
EnCat™ Bead Technology

- Works in a different way to existing supported catalysts e.g. Pd/C
- Highly porous polymer matrix allows diffusion of substrates into the bead
- Reactions take place within the porous bead structure
- Pd EnCat™ 30 has larger pores to allow higher MW products:
  - Pd EnCat™ 40 (MW 500-600)
  - Pd EnCat™ 30 (MW 1000-1200)
- Kinetics depend on MW, temperature, pore size, solvent, diffusion, etc.
## Precious Metal EnCat™ Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Pd content %w/w</th>
<th>Co-encapsulated ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(II) EnCat™ 30</td>
<td>4.3</td>
<td>none</td>
</tr>
<tr>
<td>Pd(II) EnCat™ 40</td>
<td>4.6</td>
<td>none</td>
</tr>
<tr>
<td>Pd(II) EnCat™ TPP30</td>
<td>4.7</td>
<td>( (\text{Ph}_3)_3^P )</td>
</tr>
<tr>
<td>Pd(II) EnCat™ TOTP30</td>
<td>4.7</td>
<td>( (\text{Ph}_3)^P ) Me</td>
</tr>
<tr>
<td>Pd(II) EnCat™ BINAP30</td>
<td>4.7</td>
<td>( \text{Ph}_2P \text{Ph}_2 )</td>
</tr>
<tr>
<td>Pd(II) EnCat™ polyTPP30</td>
<td>4.6</td>
<td>( \text{Ph}_2P \text{Ph}_2 )</td>
</tr>
<tr>
<td>Pd(0) EnCat™ 30NP</td>
<td>4.3</td>
<td>none</td>
</tr>
<tr>
<td>Pt(0) EnCat™ 40</td>
<td>4.2-4.5%</td>
<td>none</td>
</tr>
</tbody>
</table>
# Base Metal EnCat™ Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Metal content %w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni (0) EnCat™ 30</td>
<td>20-33%</td>
</tr>
<tr>
<td>Co (0) EnCat™</td>
<td>16-25%</td>
</tr>
</tbody>
</table>

Reaxa offers services to encapsulate customer specific catalysts
Pd(II) EnCat™ 30 and Pd(0) EnCat™ 30NP

- Pd acetate encapsulated within the polymer bead
- Recyclable Pd (II) EnCat used in C-C coupling reactions
- Pd particles <2 nm (approx 10 atoms) in Pd (0) EnCat™
- Nanostructure stabilised by polyurea matrix
- Highly active hydrogenation and transfer hydrogenation catalyst (dechlorination, debenzylation etc)
- High chemoselectivity
- Non pyrophoric - easy and safer to handle vs. Pd/C
- Very low metal contamination of product
- Easy recovery and recycle of catalyst from process vessel
Case Study # 1- Using Pd (II) EnCats™
Case Study #1 - 4-Pyridin-4-ylbenzoic Acid

1) Using conventional catalyst:

0.4-1 mole% Pd (PPh₃)₄

- 80-90% yield
- 2000 ppm Pd in crude product and waste stream
- target - <100 ppm
- no catalyst recycling possible

2) Using ENCAT™:

0.75 mol% Pd EnCat™ 40
2.5 mol% PPh₃

- 75-85% yield
- reuse >3x without loss of activity
- 20 ppm Pd in waste stream
Case Study # 1 - 4-Pyridin-4-ylbenzoic Acid

changed to much cheaper chloropyridine

0.75 mol% Pd EnCat™ 40
2.5 mol% PPh₃

0.13 mol% Pd EnCat™ 40
0.3 mol% ligand:

- no product
- ligand screen performed

- 85% yield
- ligand change gives 3x rate of bromo
- By using EnCat™, the rate was 30x compared to using Pd(OAc)₂!
- benzoic acid side-product minimised
- 10 ppm Pd in crude product

Successful scale up - catalyst easy to charge and filter, with low cake resistance
Good mixing with retreat curve impellers
Excellent reaction control - removing catalyst stops the reaction

A Wells - AstraZeneca
Pd Leaching

- No further reaction without catalyst
- Product and intermediate/reactant react over time
- Analysis show less than 5 PPM
Easier, Faster, Cleaner…Cheaper!

Contaminated crude product made with standard Pd catalyst

Clean product using Reaxa’s Pd EnCat™ catalyst with no extra purification

10-15% yield improvement,
25% reduction in process time
25-40% reduction in process cost

\[ \text{Pd(OAc)}_2/\text{PPh}_3 \quad \sim 2000 \text{ppm Pd} \]

\[ \text{Pd EnCat}^\text{TM} + \text{ligand} \quad \sim 10 \text{ppm Pd} \]
Nickel (0) EnCat™

Ni EnCat™ formulation is a polymer bead containing nickel microparticles

No evidence of pyrophoricity - passes UN Test.2

A range of different grades and formulations can be optimised for specific processes

Ni (0) EnCat™ Benefits

- Cleaner products reduced Ni and Al contamination versus other nickel catalysts
- Cleaner waste streams reduced metal losses in Ni EnCat™ processes
- Safer No evidence of pyrophoricity - passes UN Test N.2 (see below)
- Fast, efficient processes - EnCat™ beads filter very easily reducing process time
- Reusable EnCat™ beads can be easily filtered and reused
- No plant contamination metal remains trapped within the polymer bead
- Improved processes - high activity and selectivity in many types of reduction reactions
- Process intensification EnCat™ can be used in batch and continuous flow processes
Ni EnCat™ Some Advantages

Ni Catalyst | Conversion (%) | GCMS Purity (%) |
-------------|---------------|-----------------|
Sponge Nickel | >95           | 78              |
Ni EnCat™    | >99           | 89              |

Ni EnCat easily filtered and removed giving cleaner product
Case Study # 2: Using Ni EnCat™
Case Study # 2: Hydrogenation Reactions

ATS-8 Nitrile Reduction

- Ni EnCat™ (20% wt) added to ATS-8 in NH₃/MeOH
- 6 bar Hydrogen, 40°C, 4.5 h
- 100% conversion
- Kinetics dependant on Ni EnCat™ composition, temperature and pressure
Case Study # 2: Catalyst Recycle

- Low levels of Ni leaching detected in product (10-30ppm)
- Beads were recovered undamaged

<table>
<thead>
<tr>
<th>Run</th>
<th>Ni loading wt%</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>97</td>
</tr>
</tbody>
</table>
Case Study # 3: Using Ni EnCat™
Stability to Sulfur Containing Substrates
Case Study # 3

3-Sulfolene  
MW 118.16

Sulfolane  
MW 120.17

H₂ / Ni EnCat™  
(10 bar) (1 wt% loading)

MeOH / 45°C / 4h

<table>
<thead>
<tr>
<th>Run</th>
<th>Ni loading wt%</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>96</td>
</tr>
</tbody>
</table>

- Beads were recovered undamaged after each use
- Single charge of catalyst avoiding multiple stage reaction
Pt(0) EnCat™ 40

Platinum salt encapsulated in polymer beads with subsequent activation
Investigated initially as selective catalyst for nitro reduction

Pt(0) EnCat™ 40 Benefits

• easily handled polymer beads
• simple removal by filtration
• good catalytic activity
• recyclability of catalyst beads
• chemoselective in hydrogenation reactions
• safer to handle than Pt/C
• reduced cleaning issues
Os EnCat™ 40 Catalyst

Osmium tetroxide encapsulated in polymer beads
Available at commercial scale from Reaxa

Os EnCat™ 40 Features
- osmium tetroxide retained within beads
- homogeneous metal distribution
- easy recovery of catalyst by filtration
- low metal leaching
- chemically and mechanically robust
- no osmium tetroxide vapour over catalyst

Os EnCat™ 40 Benefits
- safer form of osmium catalyst
- excellent catalytic activity
- potential for recycling
- low osmium contamination of product
- wide range of applications
- ease of storage and use
EnCats™ used in Flow Processing

Reaction Concept:

Reagents → Pd EnCat™ Column → Products

Catalyst immobilised on support – no precipitation
Metal held in polymer bead – low metal contamination
High effective catalyst loading – reactions are fast
H-Cube & X-Cube – CatCarts

**CatCart™**
- Pd(0) EnCat™ 30NP
- Pd EnCat™ 30
- Pd EnCat™ TPP 30
- Pd EnCat™ TOTP 30
- Pd EnCat™ BINAP 30
- Pt(0) EnCat™ 40
EnCat™ Flow/Microwave Flow
Regulatory Support

Our Encats are of GMP grade which are pre-washed with high-purity reagents to eliminate potential drug substance contamination.

We provide a full Regulatory Support File:
- Statement on risk materials (e.g. BSE risk)
- Certificates of analysis
- Analytical specification and methods of analysis
- Chemical stability and stability testing
- Extractable impurities & methods
- Toxicology information
Conclusion

Cleaner production processes with recyclable, encapsulated (EnCats™) precious metal catalyst systems.

Safer hydrogenation processes with non-pyrophoric, reusable base metal catalyst systems.

EnCats™ can be used in flow processing
EnCats™ minimize the leaching
Easy to handle and filter
Thank you!