

Encapsulated Catalysts: ***Easier, Faster, Cleaner Process Chemistry***



Angus Stewart-Liddon

18th June 2009, Barcelona

www.reaxa.com

Overview

- EnCat™: Encapsulation of catalyst systems
- Pd EnCat™ cross-coupling catalysts and their application
- Metal(0) EnCat™ catalysts for safer hydrogenation chemistry: Pd(0), Pt(0), Ni(0)
- Os EnCat™ - improved handling of osmium tetroxide



Why Encapsulate a Catalyst?

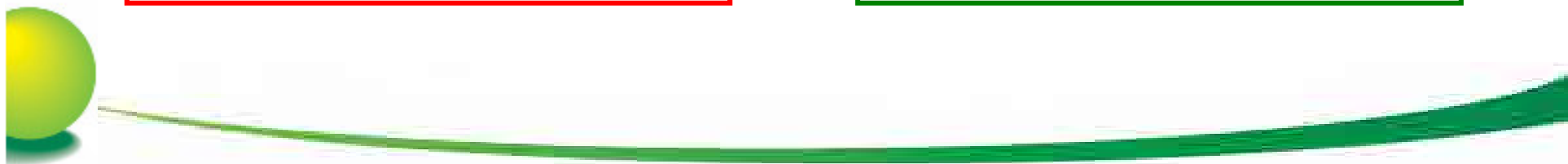
- Metal catalysts are an indispensable tool in chemical synthesis however they are not without drawbacks
- Some of these limitations are addressed by encapsulation of the catalyst system within a bead support

Homogeneous Catalyst Issues

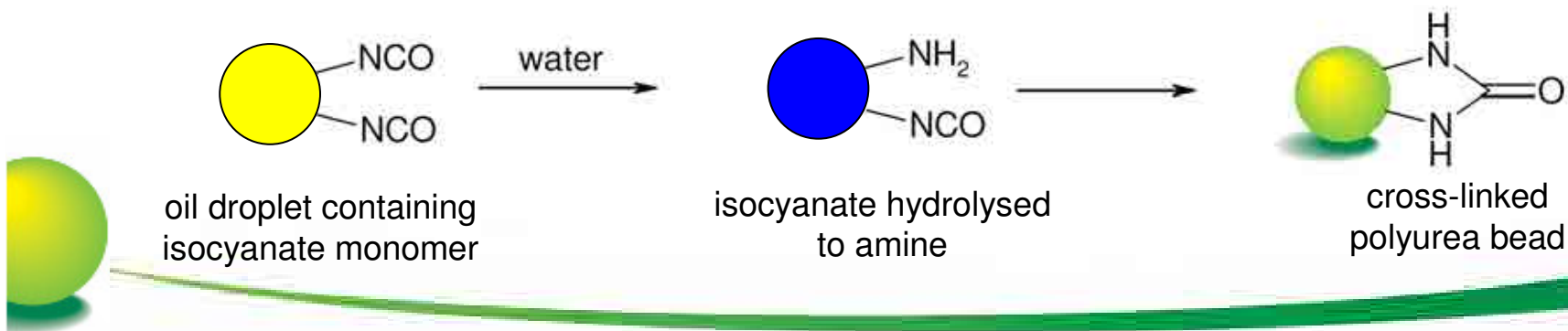
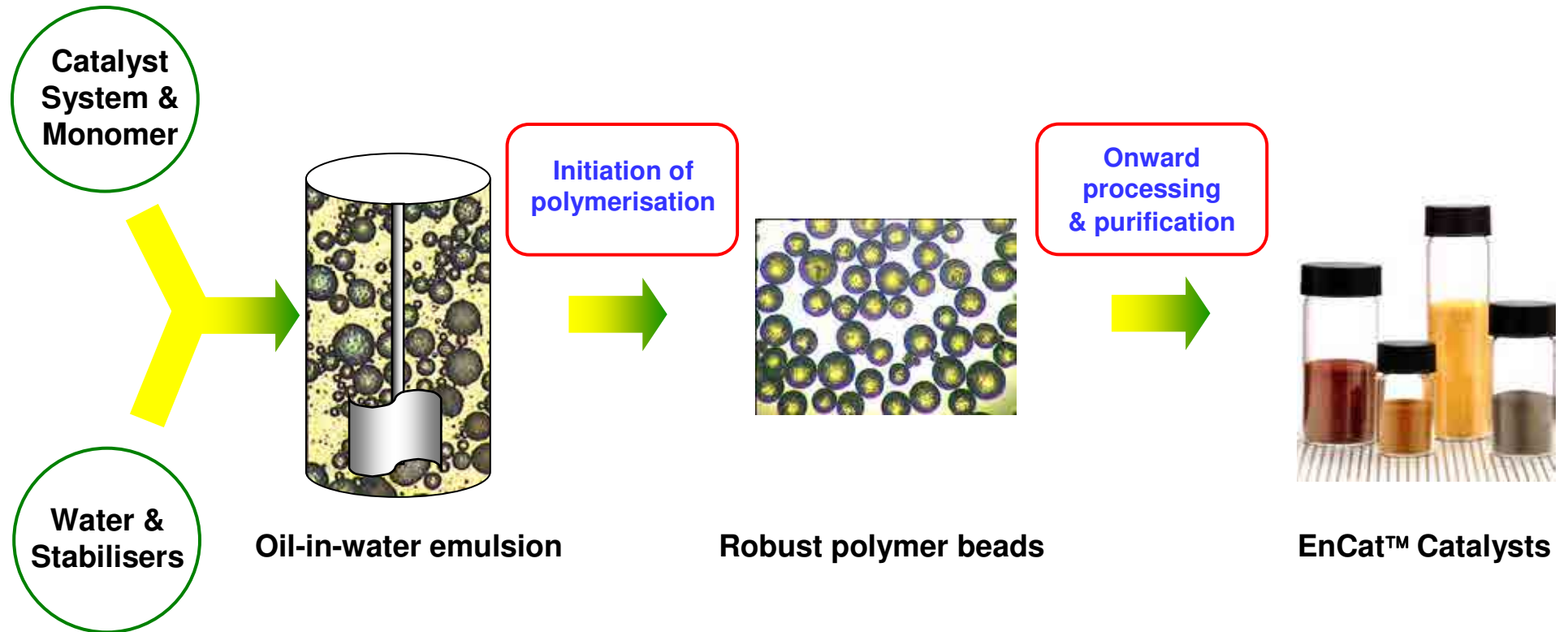
**Residual toxic metals
Multi-step purification
Yield losses on work-up
One-time catalyst use
Lost metal value
Batch processes only**

Encapsulated Solutions

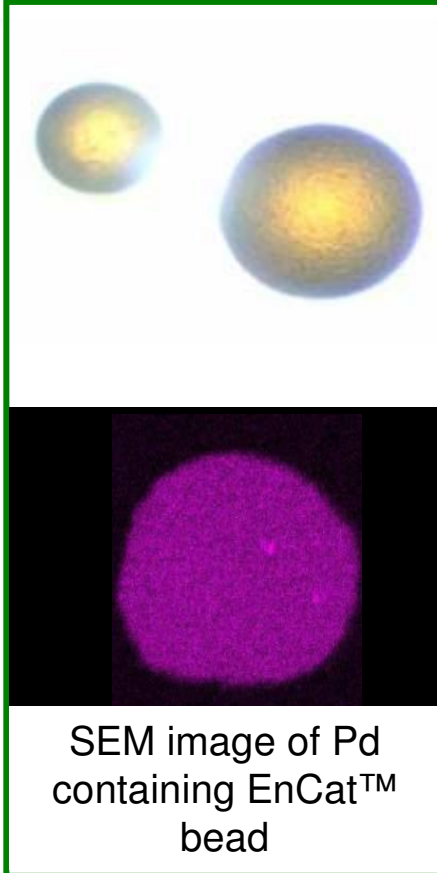
**Low metal contamination
Easy filtration
Simple, high-yield process
Re-useable catalysts
Efficient metal recovery
Flow processing enabled**



Encapsulation of Catalysts by *in situ* Interfacial Polymerisation



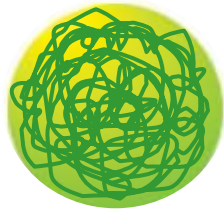
EnCat™ Catalysts



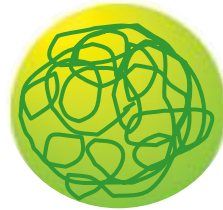
- EnCat™ process allows the encapsulation of a range of catalyst systems within a polymer matrix
- Metal species are entrapped within spherical beads (Pd, Pt, Os, Ni ...)
- Polymer coordinates the metal – retaining it within the matrix
- Metal is evenly distributed through out the bead
- The beads are mechanically robust & particle size is controlled
- The highly porous matrix allows diffusion of substrates in & out of the bead
- Kinetics depend on MW, temperature, pore size, solvent, diffusion, etc.



EnCat™ Pore Size



EnCat™ 40

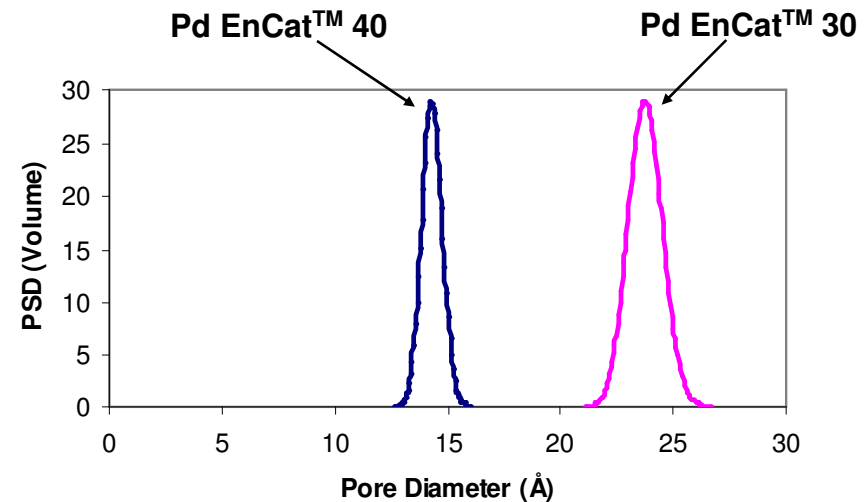


EnCat™ 30



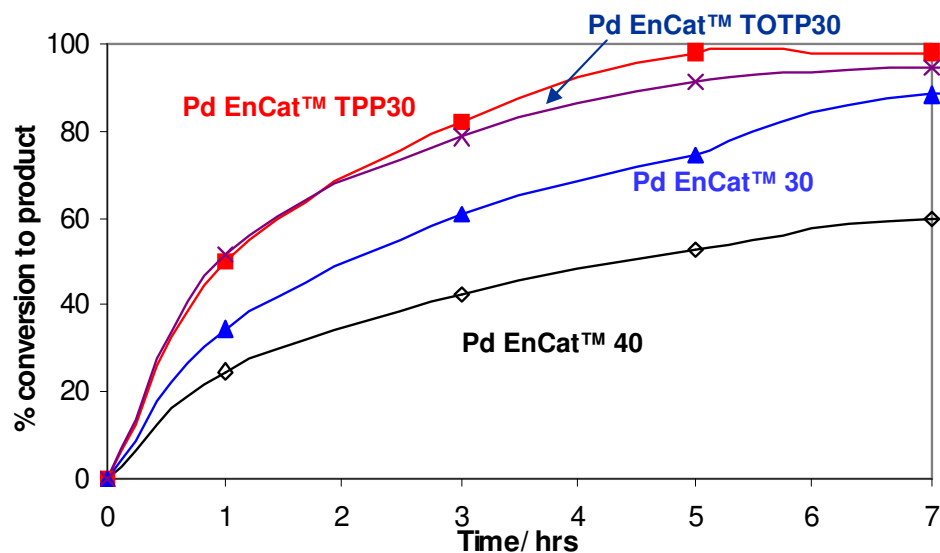
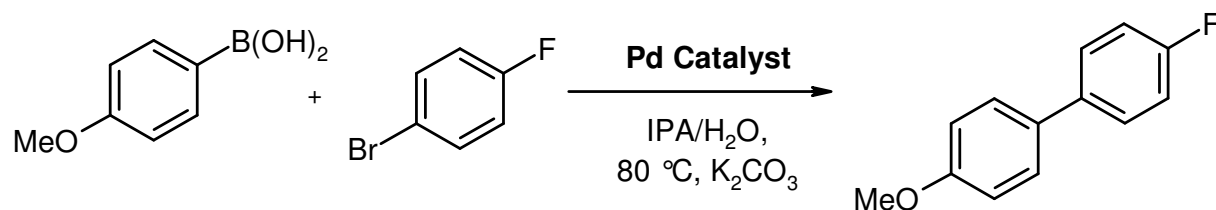
EnCat™ 20

- Highly porous matrix allows diffusion of substrates/products
- EnCat™ 30 more porous than EnCat™ 40, MW cut off:
 - EnCat™ 40 (500)
 - EnCat™ 30 (1000)
 - EnCat™ 20 (1200)
- Improved accessibility allows faster kinetics

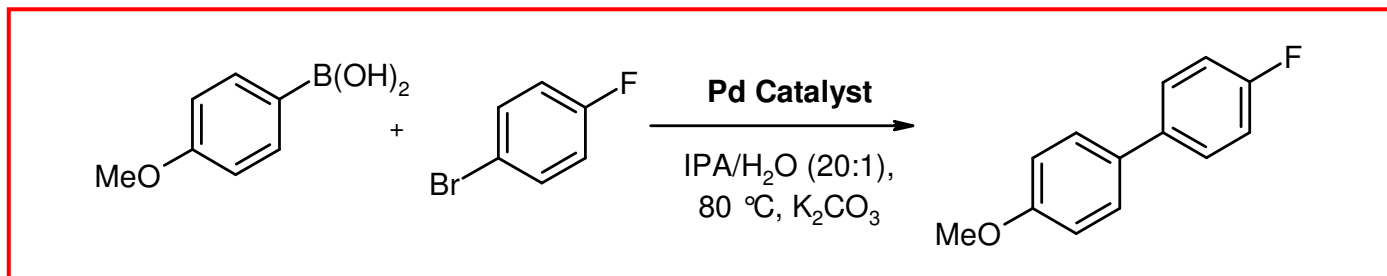


Pd EnCat™ Coupling Catalysts

- Pd(OAc)₂ encapsulated within polyurea beads - ca. 0.5 mmol/g Pd
- Activating ligands can be co-encapsulated - TPP, TOTP, BINAP etc.
- Effective for range of chemistries including Suzuki, Heck, Sonogashira...



Cleaner Coupling Chemistries



Solvent (80 °C, 48 h)	Pd EnCat™ 30	
	Pd (ppm)	% Leached
Acetone	1	0.08
Ethanol	<1	<0.08
Acetonitrile	<1	<0.08
IPA	<1	<0.08
Toluene	<1	<0.08
Dioxane	<1	<0.08
Ethyl acetate	<1	<0.08
THF	4	0.31
DMF	5	0.39
DMA	3	1.01



Pd EnCat™ polyTPP30 **Pd(OAc)₂ + PPh₃**

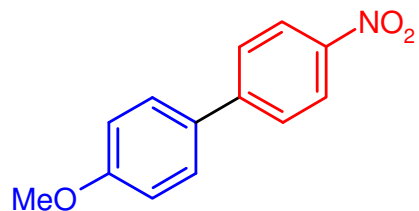
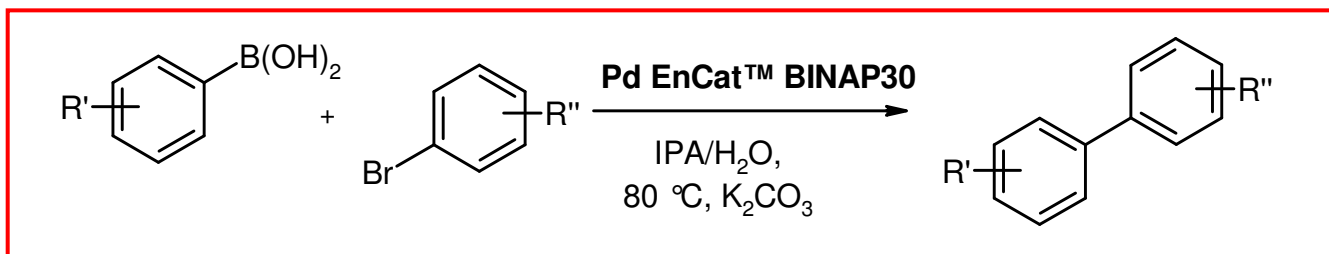
99%
7 ppm
18 ppm

91%
985 ppm
1200 ppm

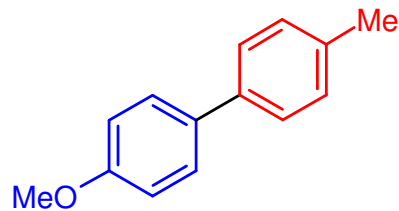
Product Yield
Pd in crude product
P in crude product

- Minimal metal & phosphorous contamination
- Within regulatory requirements
- Eliminates need for further purification

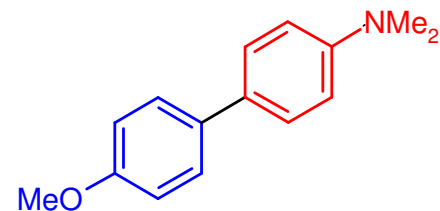
Suzuki Coupling with Pd EnCat™ BINAP30



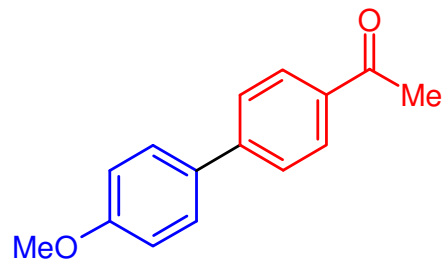
99% Conversion (4 h)
9 ppm Pd; 49 ppm P



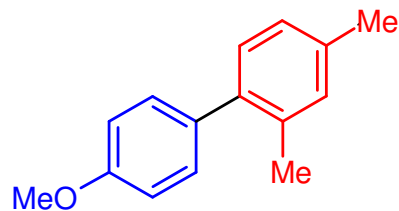
>99% Conversion (21 h)
2 ppm Pd; 30 ppm P



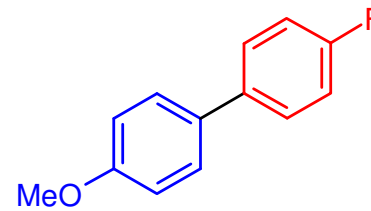
97% Conversion (21 h)
5 ppm Pd; 47 ppm P



95% Conversion (4 h)
4 ppm Pd; 64 ppm P

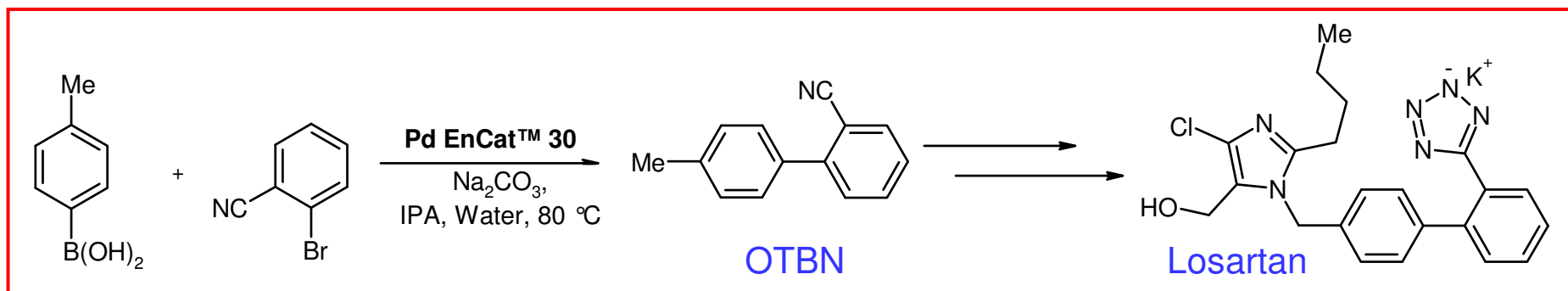


>99% Conversion (21 h)
2 ppm Pd; 34 ppm P



95% Conversion (4 h)
6 ppm Pd; 50 ppm P

Pd EnCat™ Re-use in Suzuki Coupling

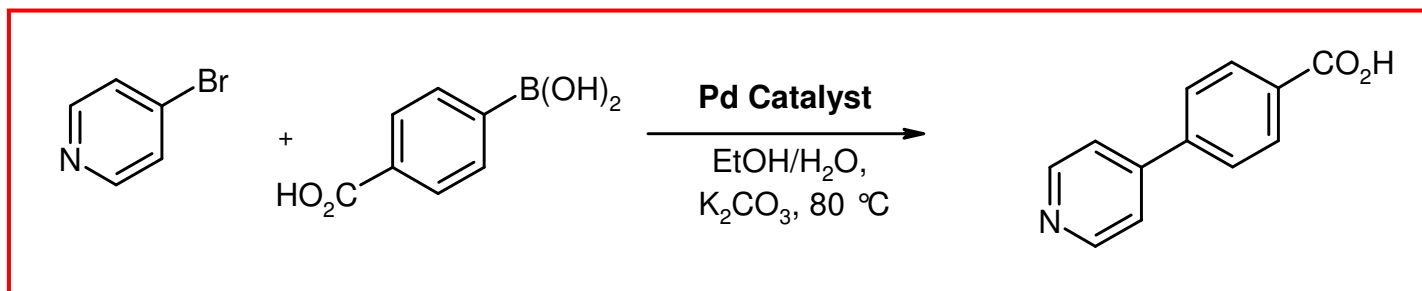


Catalyst Loading (mol%)	Time (min)	Conversion (%)
2 mol%	30	>99%
1 mol%	90	>99%
0.5 mol%	120	>99%

Catalyst Cycle (1 mol%)	Time (min)	Conversion (%)
1	90	100
2	90	93
3	90	96
4	90	94
5	120	94

- *ortho*-Tolyl benzonitrile (OTBN) is a key common intermediate in the synthesis of a number of compounds used to treat hypertension
e.g. Losartan, Valsartan
- Pd EnCat™ 30 shown to catalyse the reaction effectively (< 1 mol% Pd)
- Simple removal and re-use of the Pd EnCat™ 30 possible

Suzuki Coupling – Case Study



Original Process

0.4-1 mol% Pd (PPh₃)₄



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

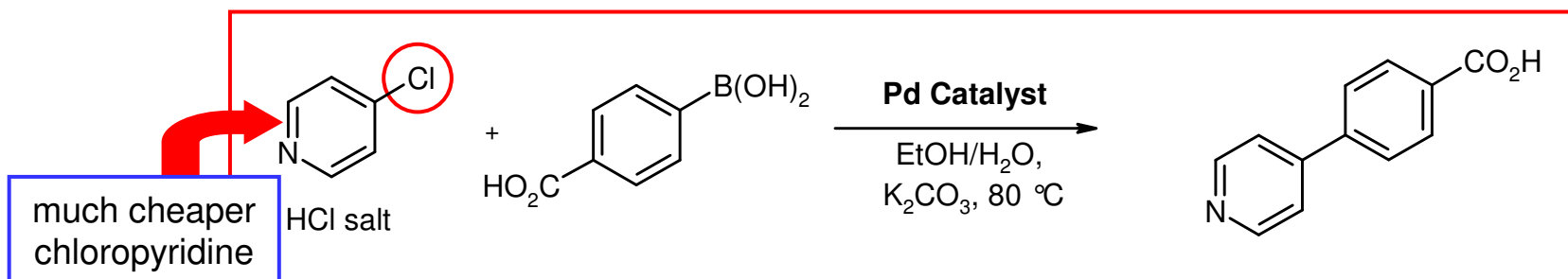
EnCat™ Process

0.75 mol% Pd EnCat™ 40
2.5 mol% PPh₃



- 75-85% yield
- no reaction without addition of PPh₃
- reuse >3x without loss of activity
- Reduced Pd contamination

Suzuki Coupling – Case Study



Original EnCat™ Process

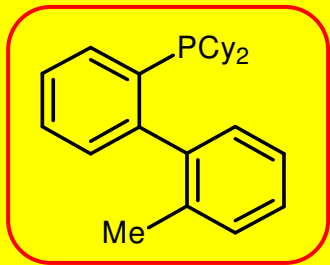
0.75 mol% Pd EnCat™ 40
2.5 mol% PPh₃



- no product
- ligand screen performed

Improved EnCat™ Process

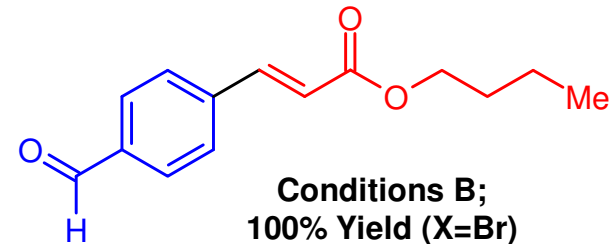
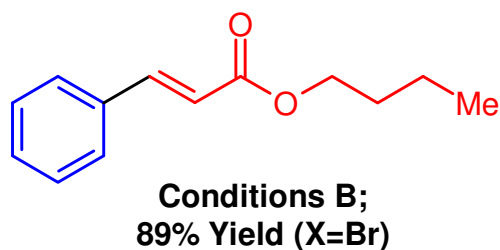
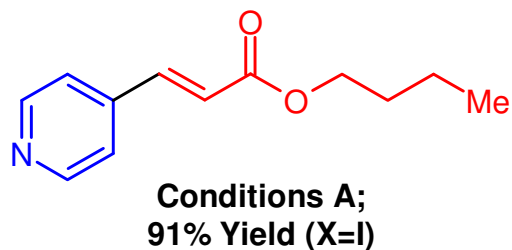
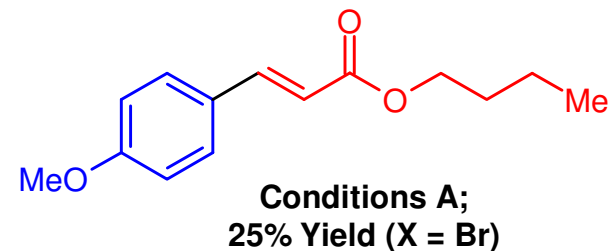
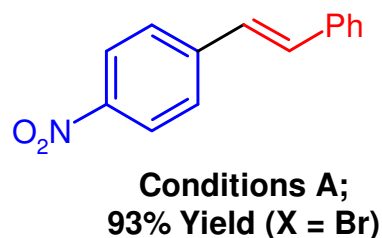
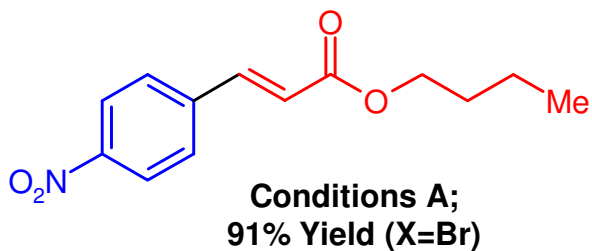
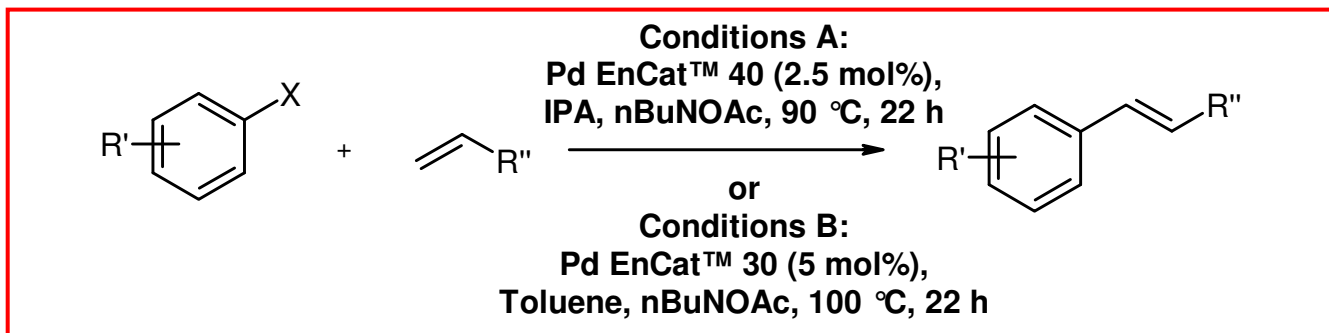
0.13 mol% Pd EnCat™ 40
0.3 mol%
ligand:



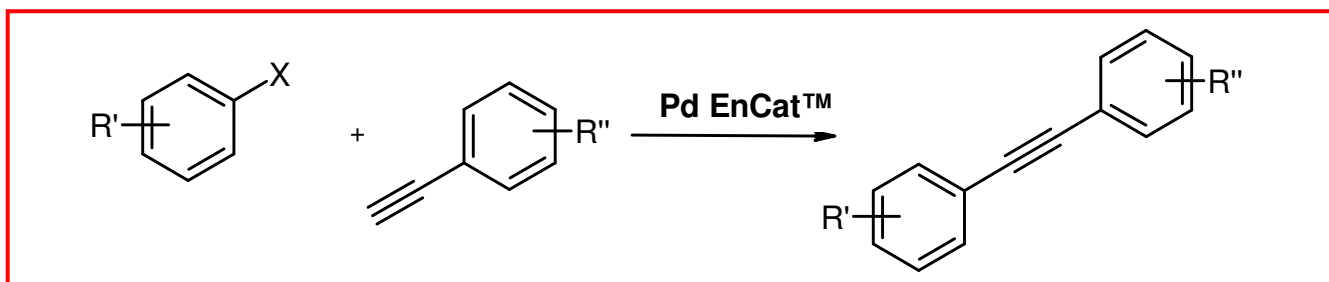
- 85% yield
- benzoic acid side-product minimised
- Pd contamination of crude product within target levels

- 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

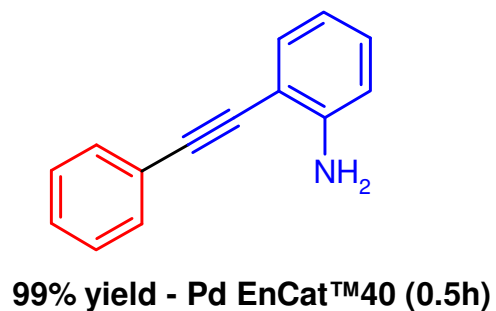
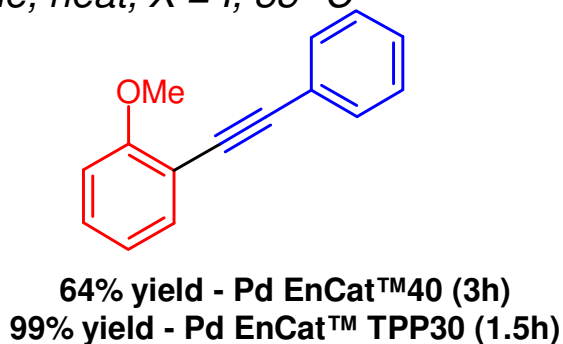
EnCat™ Applications – Heck Coupling



EnCat™ Applications – Sonogashira Coupling

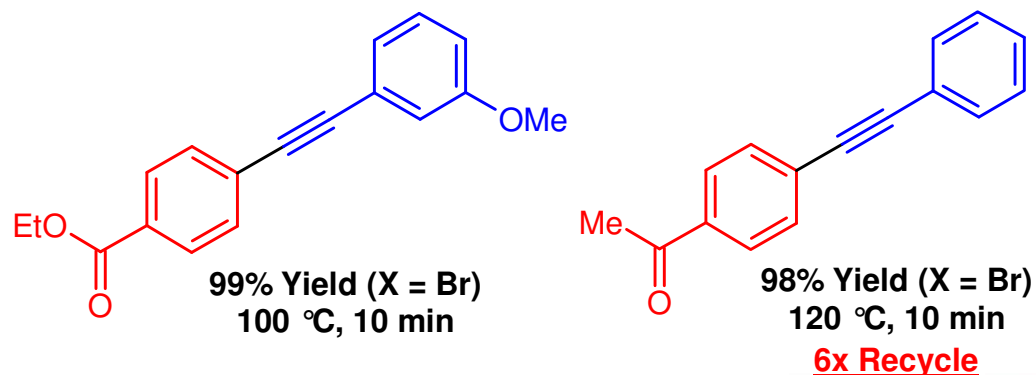
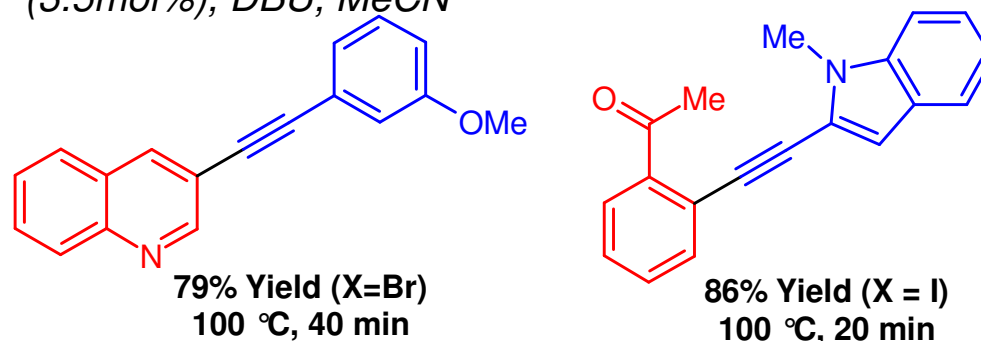


Conventional Heating: EnCat™ (0.1 mol%)
pyrrolidine, neat, X = I, 85 °C



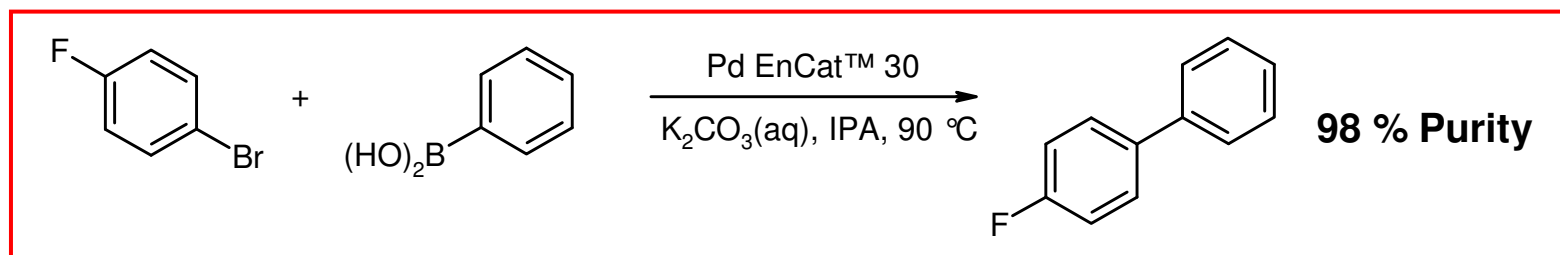
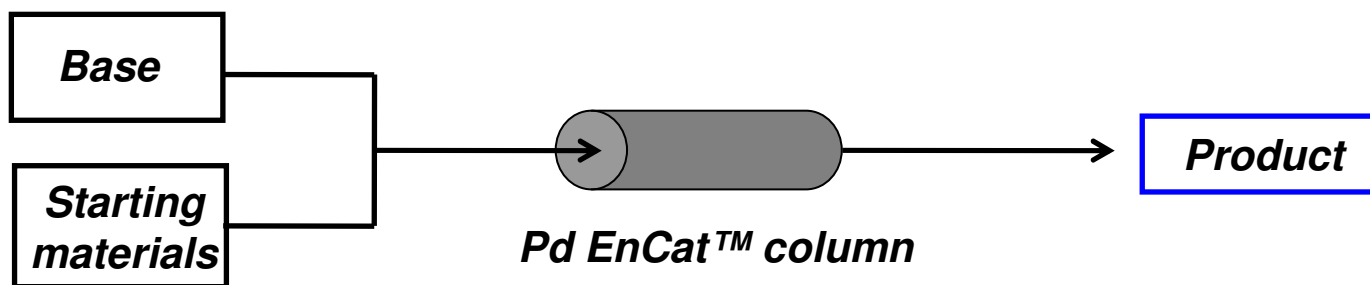
A. Carpita *et al*, *Tetrahedron Lett.*, 2009, 204.

Microwave Heating: Pd EnCat™ TPP30
(3.5 mol%), DBU, MeCN



S. V. Ley, I. R. Baxendale *et al*, in press

Flow Applications with Pd EnCat™



- Continuous coupling applications extended to:
 - Suzuki
 - Heck
 - Sonogashira
- Inorganic/organic base systems
- Catalyst stability demonstrated over 100s hours
- Compatible with scCO_2

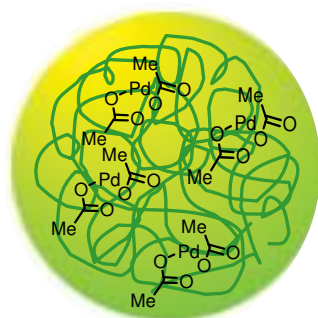
Metal(0) EnCat™ Hydrogenation Catalysts

- Heterogeneous metal(0) catalysts routinely employed for hydrogenation chemistry (eg. Pd/C, Raney Ni)
- Drawbacks can include:
 - issues with handling (pyrophoricity), effective re-use, metal contamination of product and plant, filtration
- EnCat™ technology can help to address these issues...

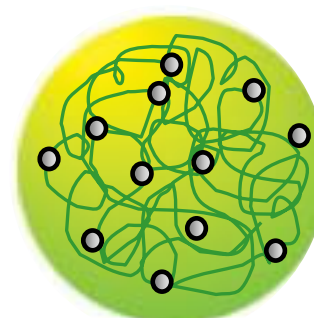
- Encapsulation of metal species eliminates pyrophoricity
- Very low metal contamination of product, plant and waste streams
- Easy catalyst re-use lowers costs of metal and waste management
- Pd, Pt & Ni EnCat™ versions have been developed...



Pd(0) EnCat™ 30NP



Pd EnCat™ 30

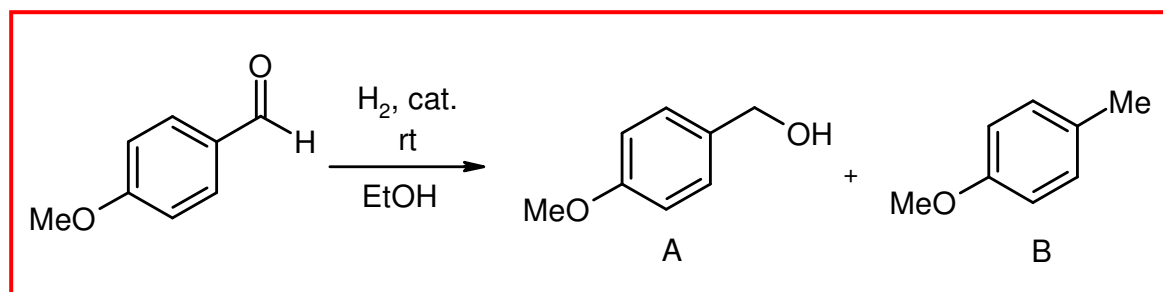


Pd(0) EnCat™ 30NP

- Pd particles <2 nm (approx 10 atoms)
- Nanostructure stabilised by polyurea matrix
- Active hydrogenation and transfer hydrogenation catalyst
- Highly chemoselective
- Non-pyrophoric
- Very low metal contamination of product
- Easy recovery and recycle of catalyst from process vessel

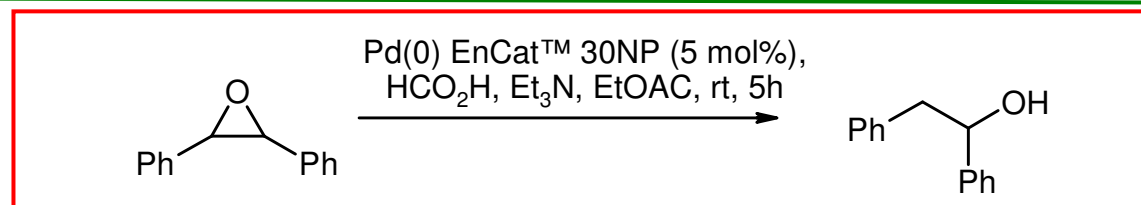
Pd(0) EnCat™ 30NP Applications I

Catalyst Selectivity



Catalyst	Conversion	
	A%	B%
5% Pd/CaCO ₃	63	37
5% Pd/Al ₂ O ₃	45	55
5% Pd/C	0	100
Pd(0) EnCat™ 30NP	94	6

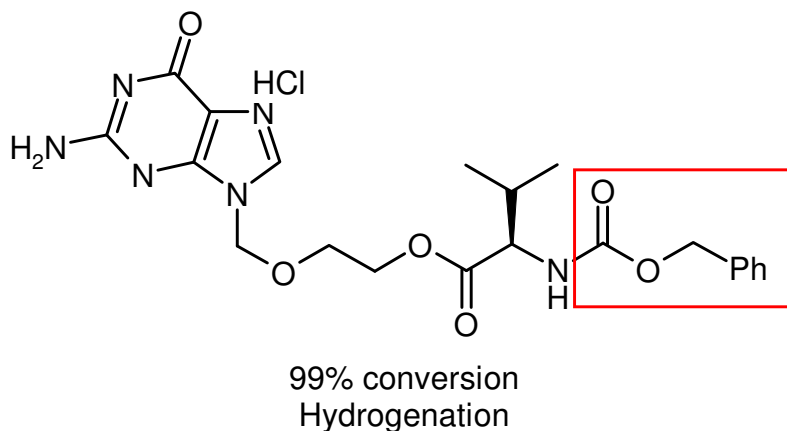
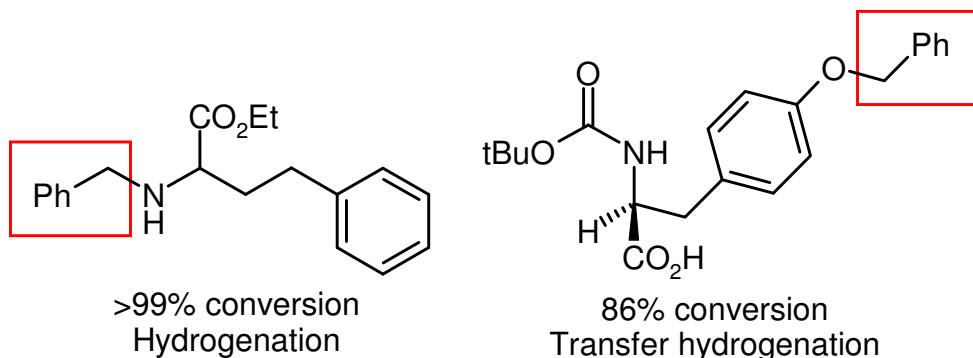
Catalyst Recycling



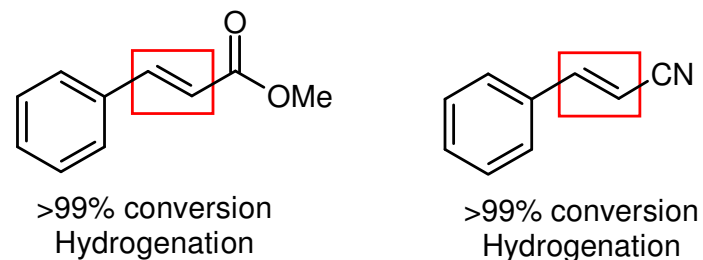
Run	1	2	3	4	5	6	7	8	9	10
Conversion (%)	99	98	97	98	96	97	98	97	97	97

Pd(0) EnCat™ 30NP Applications II

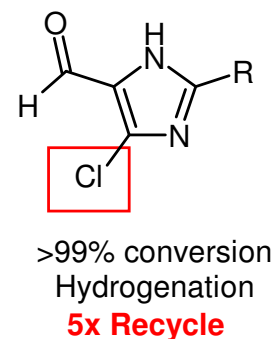
Debenzylations...



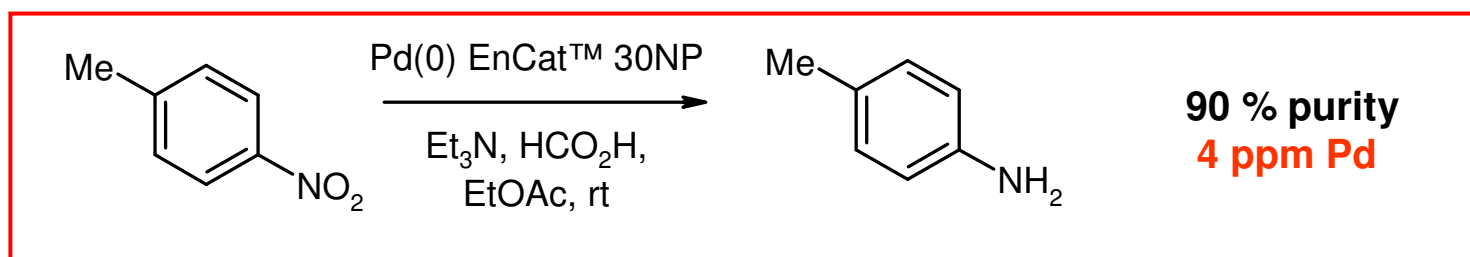
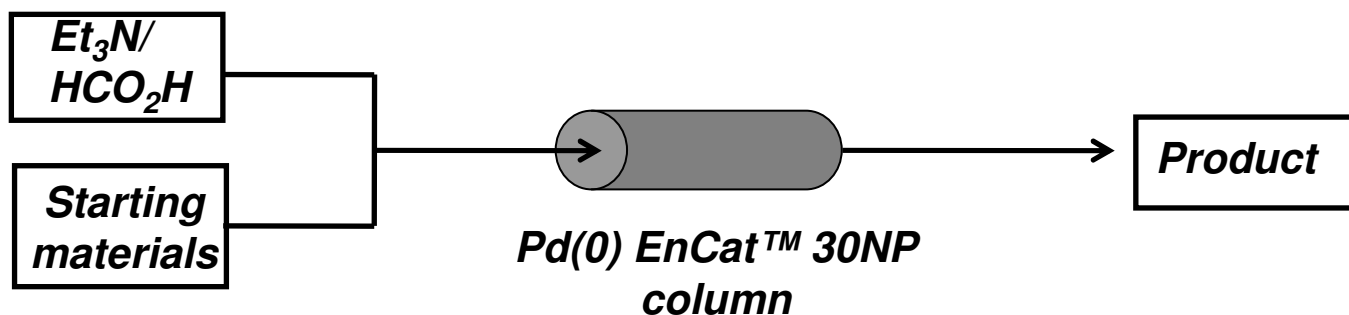
Olefin hydrogenations...



Dehalogenations...



Pd(0) EnCat™ 30NP Applications III



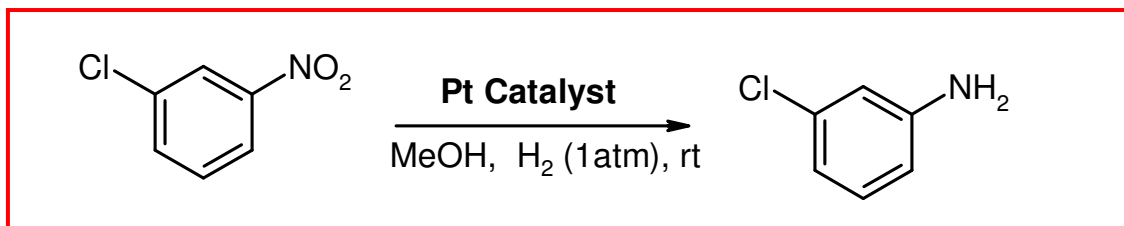
Continuous transfer hydrogenation applications extended to:

- reductive amination
- one-pot nitro group hydrogenation/reductive amination
- dehalogenation
- heterocycle reduction

Pt EnCat™ - Nitro Group Reductions



Platinum salt encapsulated in polymer bead with subsequent activation



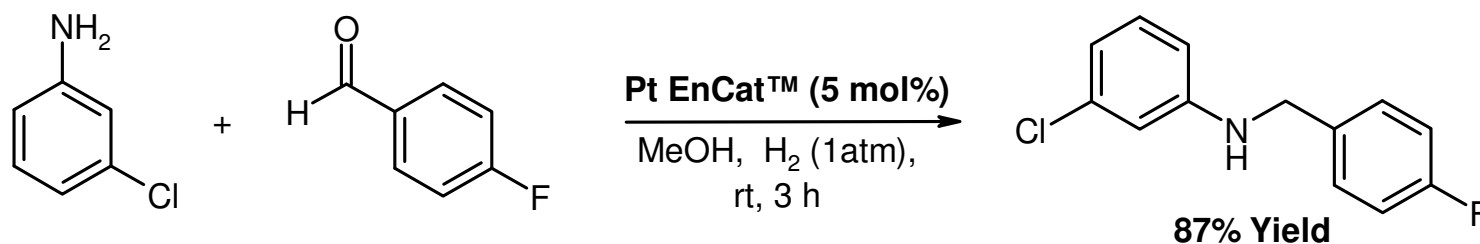
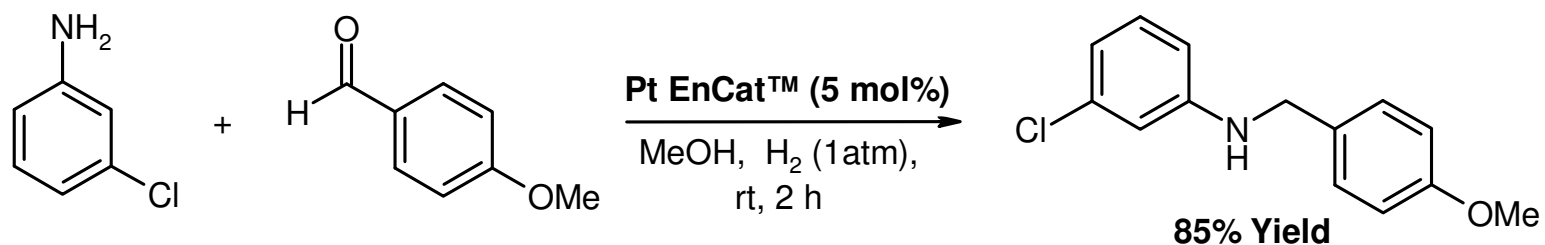
Catalyst	mol% metal	Time (h)	Conversion (%)		
			Product	Aniline	By-products
5% Pt / C	1 mol% Pt	0.5	84	11	5
5% Pd/C	1 mol% Pd	0.5	1	96	3
Pt(0)EnCat™ 40	1 mol% Pt	1.5	90	10	0
Pt(0)EnCat™ 40	5 mol% Pt	0.5	94	6	0

Run	Conversion (%)	Purity (%)	Time (h)
1	100	93	1
2	100	93	1
3	100	91	1
4	100	90	1

Pt(0) EnCat™

- Selective reduction
- Cleaner than Pt/C
- Minimal Pt contamination
- Recyclable
- Non-pyrophoric

Pt EnCat™ - Reductive Amination



Can be extended to 'one-pot' nitro group reduction – reductive amination...



Ni EnCat™



- 10 wt% Ni content
- Mean particle size of beads: 180 μm

An alternative to sponge nickel catalysts (eg. Raney®)

Safer

Fast, efficient processes

Reusable

Cleaner products

No plant contamination

Process intensification

Effective

Non-pyrophoric (UN test)

EnCat™ beads filter rapidly reducing process time

EnCat™ beads can be easily reused

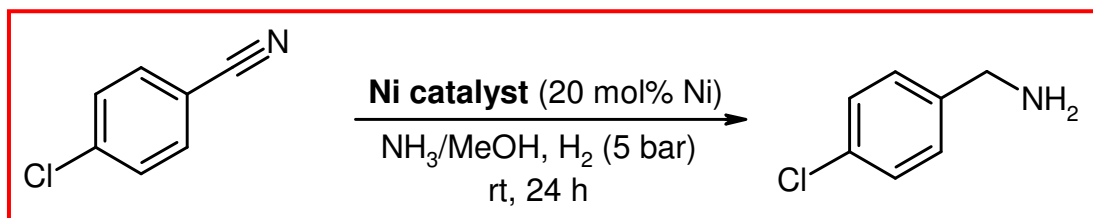
reduced metal contamination

metal remains trapped within the polymer bead

EnCat™ can be used in batch and continuous flow processes

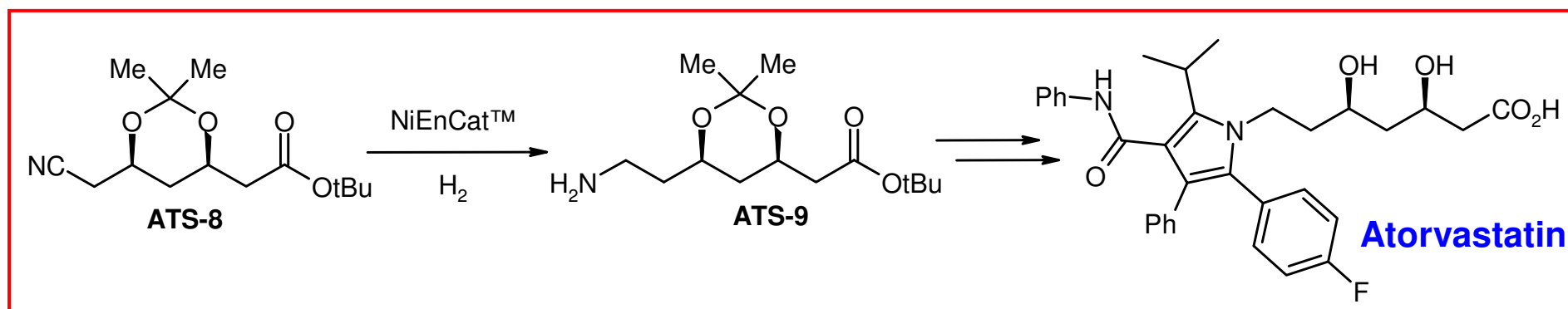
Nitrile, Nitro group, olefin hydrogenations...

Ni EnCat™ Applications



- Ni EnCat™ is easily filtered and removed giving cleaner product vs sponge nickel
- Catalyst re-use possible

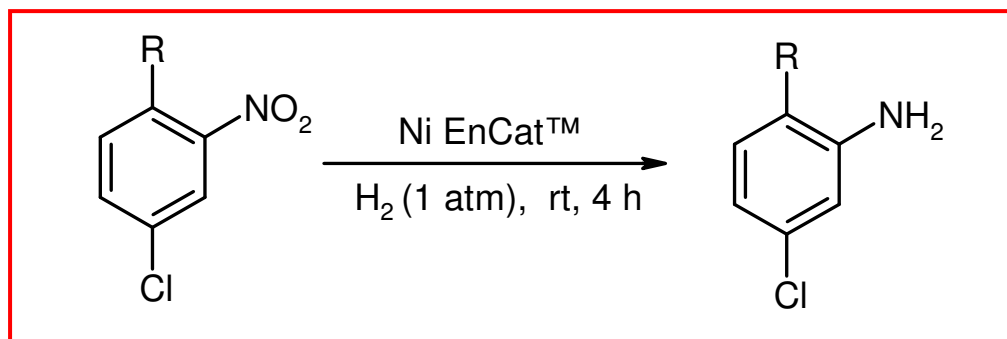
Catalyst	Conversion (%)	GCMS Purity (%)
Sponge Nickel	>95	78
NiEnCat™	>95	89



85% isolated yield (>95% purity)

Process development on-going to optimise at large scale

Ni EnCat™ Applications



Reduced Catalyst Loading

Catalyst	mol% metal	Time (h)	Conversion (%)
NiEnCat™	20	4	>99
NiEnCat™	10	4	>99
NiEnCat™	5	4	>99



Activity in Catalyst Recycles

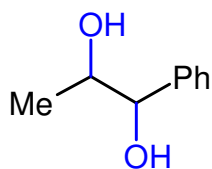
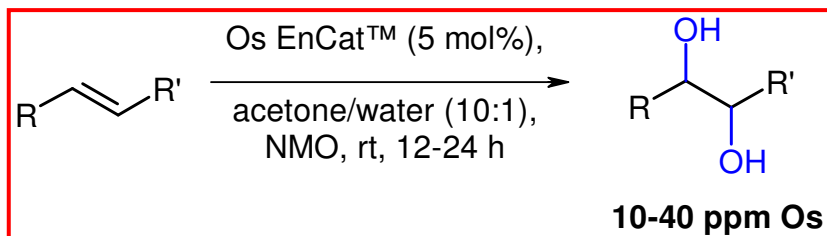
Cycle	mol% metal	Time (h)	Conversion (%)
1	5	16	>99
2	5	16	>99
3	5	16	>99



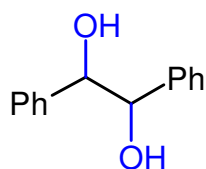
Os EnCat™ - Improved Safety

Os EnCat™: Osmium tetroxide encapsulated in polymer beads

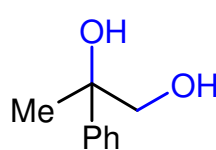
- homogeneous metal distribution
- easy recovery of catalyst by filtration
- low osmium contamination of product
- chemically and mechanically robust
- no osmium tetroxide vapour over catalyst



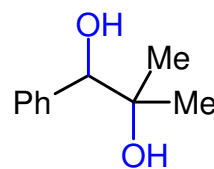
Run 1
74% yield



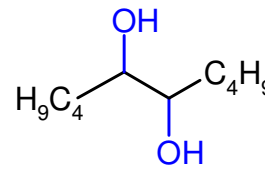
Run 2
86% yield



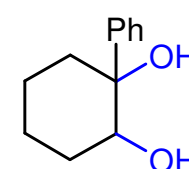
Run 3
88% yield



Run 4
83% yield

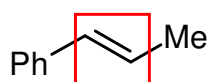
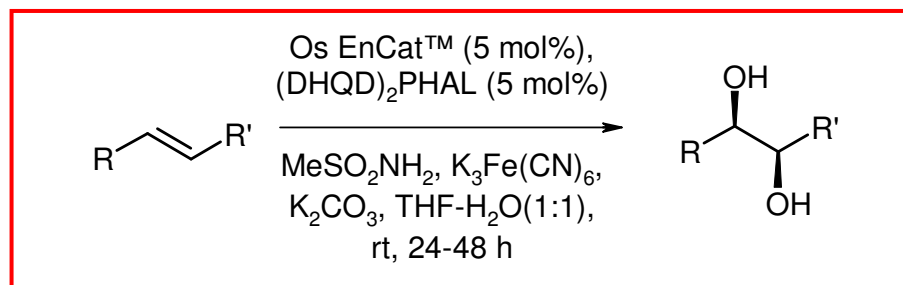


Run 5
77% yield

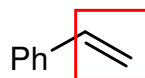


Run 6
88% yield

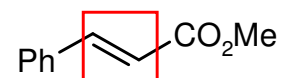
Os EnCat™ - Improved Safety



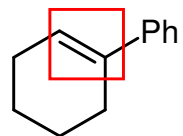
97% Yield
94% ee
3x recycle



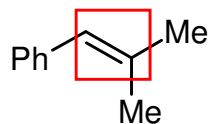
96% Yield
82% ee



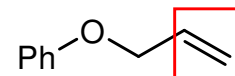
94% Yield
>99% ee



91% Yield
97% ee



89% Yield
87% ee

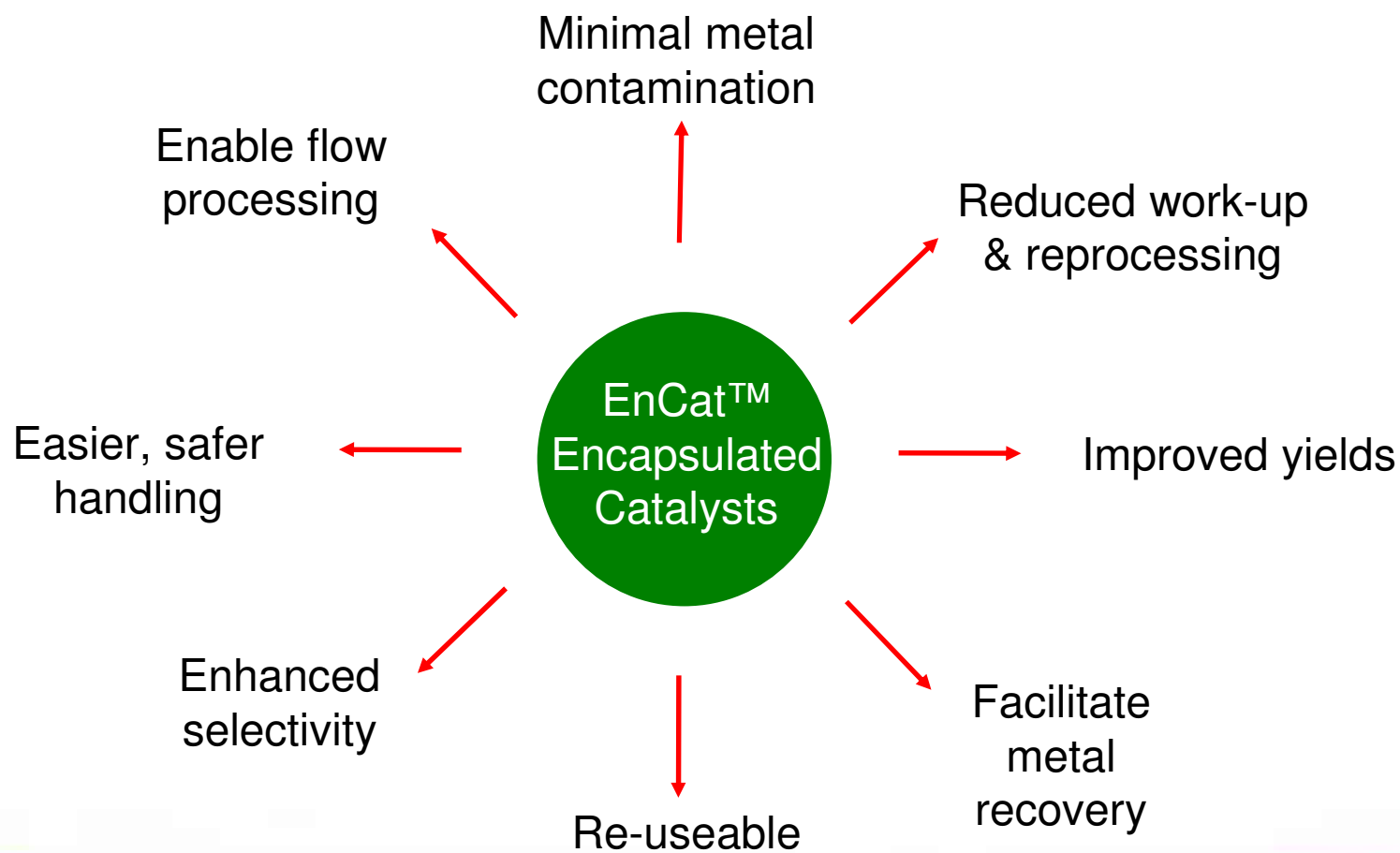


83% Yield
51% ee



Conclusions

EnCat™ technology allows for the encapsulation of a range of different catalyst systems. The encapsulated species are active in various chemistries and provide significant potential advantages:



Acknowledgements

Reaxa

Thomas Screen
Mohammed Nisar
Ben Moulton
Sarah Wilson

Cambridge University

Prof. Steven Ley
Ian Baxendale

Others

Andy Wells
Kerry Elgie
Mark Ladlow
Uniqsis

The Royal Society of Chemistry & all the organisers





Helping our Life Science Customers to Achieve
Easier, Faster and Cleaner Processes

www.reaxa.com