
Reaxa

Reaxa Ltd

New technologies for precious metal catalysis to help our life science customers achieve easier, faster and cleaner processes to lower their total cost of production

EnCat™ encapsulated catalysts

QuadraPure™ QuadraSil™ scavengers

LaPCat™ perovskite catalysts

ChemDose™ Precise catalyst dosing

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Easier, Faster, Cleaner

Contaminated crude product made with homogeneous Pd acetate catalyst

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

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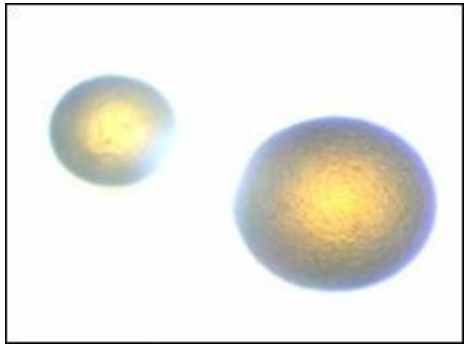
EnCat™ Encapsulated Catalysts



Metal catalysts encapsulated in polymer beads
Pd, Os, Pt, Ni and Rh plus co-encapsulated ligands
Catalogue supplies from Aldrich & Wako
Available at commercial scale from Reaxa
Products designed for GMP use

Homogeneous Catalyst Issues:

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

EnCat™ Solutions:

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

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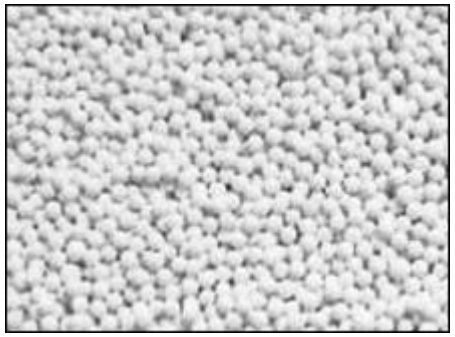
QuadraPure™/ QuadraSil™ Metal Scavengers



Functionalised beads for extraction of metal contaminants in batch or flow mode
Catalogue supplies from Aldrich & Wako
Available at commercial scale from Reaxa
Products designed for GMP use

Metal Contamination Issues:

- **High levels in products**
- **Regulatory limits in API**
- **Complex work up**
- **Wasteful yield losses**
- **Lost metal value**
- **Waste-stream poisoning**

QuadraPure™ Solutions:

- **Effective purification**
- **GMP compliant**
- **Easy filtration**
- **Absorbs target metals only**
- **Efficient metal recovery**
- **Clean waste streams**

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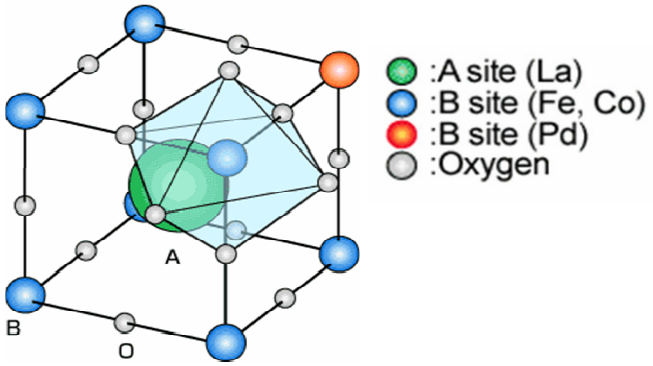
LaPCat™ Perovskite Catalysts

- Robust precious metal catalysts
  - Developed by Hokko for auto catalysts
- Very high activity in coupling chemistry
  - up to 400,000 TON observed
- Clean reactions with low metal contamination
  - Less than 2ppm Pd in product
- Test kits & scale-up quantities available from Reaxa
  - Pd, Cu and mixed metal products



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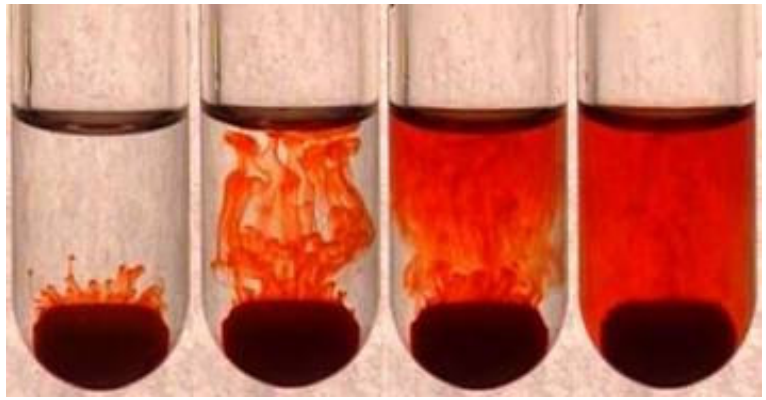
ChemDose™

- Precise catalyst dosing products
  - Tabletting technology licensed from Lundbeck
- Easier and faster experiments
  - Reduced the need for reagent weighing & preparation
- Reduced waste
  - Chemists only order what they need
- Highly reproducible chemistry
  - Exact dosing of catalysts with micromolar precision



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Reaxa Facilities

- Reaxa HQ Hexagon Tower, Manchester, UK
  - Modern, fully-equipped R&D labs
  - Kilo-scale manufacturing unit
  - Lab facilities at Cambridge University
- QC/QA support
  - Specialist services provided by Intertek ASG & NPIL
- Large-scale manufacturing capacity
  - Outsourced to ISO-certified production specialists
  - Efficient technology transfer & supply chain management

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Pd and Os EnCat™

Microencapsulated Metal Catalysts

Pd EnCat™ Range

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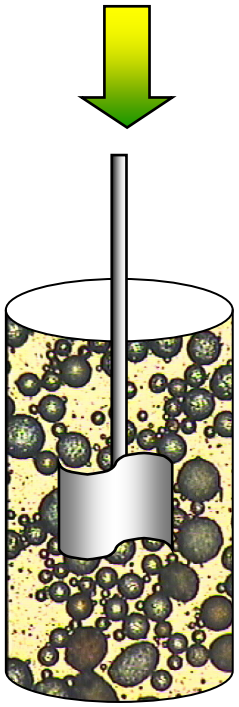
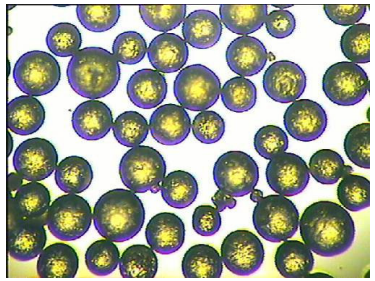
EnCat™ Manufacture

Monomer + Catalyst + Ligand



Heating initiates polymerisation



Onward processing and purification

Oil-in-water emulsion

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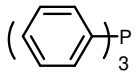
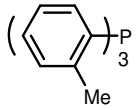
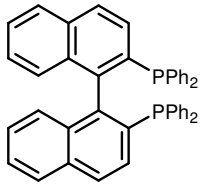
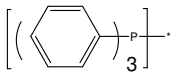
Pd EnCat™ Products

Product	*Pd content %w/w*	*Co-encapsulated ligand*
Pd(II) EnCat™ 30	4.3	none
Pd(II) EnCat™ 40	4.6	none
Pd(II) EnCat™ TPP30	4.7	
Pd(II) EnCat™ TOTP30	4.7	
Pd(II) EnCat™ BINAP30	4.7	
Pd(II) EnCat™ polyTPP30	4.6	
Pd(0) EnCat™ 30NP	4.3	none

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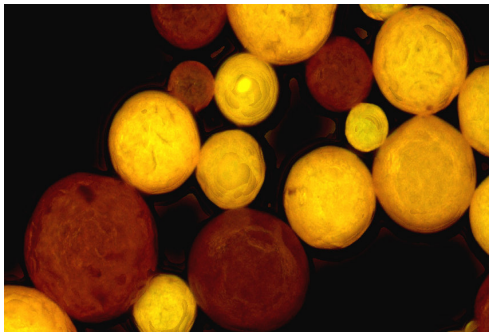
Pd EnCat™



Palladium acetate encapsulated in polymer beads
Also available with co-encapsulated phosphine ligands
Catalogue supplies from Aldrich & Wako
Available at commercial scale from Reaxa

Pd EnCat™ Features

- highly porous polymeric beads
- metal coordinated to polyurea groups
- easy recovery of catalyst by filtration
- highly crosslinked inert matrix
- controlled activity
- supplied as free-flowing beads
- non-pyrophoric
- no plating out of Pd on vessel walls

Pd EnCat™ Benefits

- excellent levels of catalytic activity
- low metal and ligand contamination
- reduced metal loss
- mechanically and chemically robust
- chemoselective in hydrogenation reactions
- wide ranging application in batch and flow
- safer to handle vs Pd/C
- reduced cleaning issues

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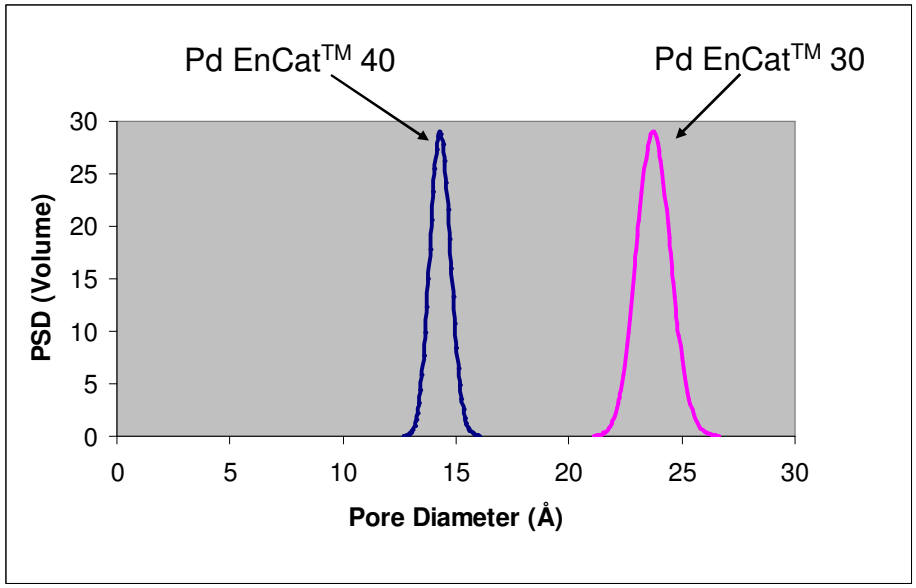
EnCat™ Pore Size

Pd EnCat™ 40 | Pd EnCat™ 30 | Pd EnCat™ 20

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



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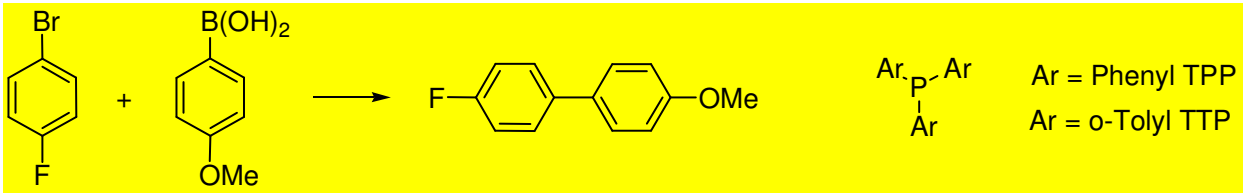
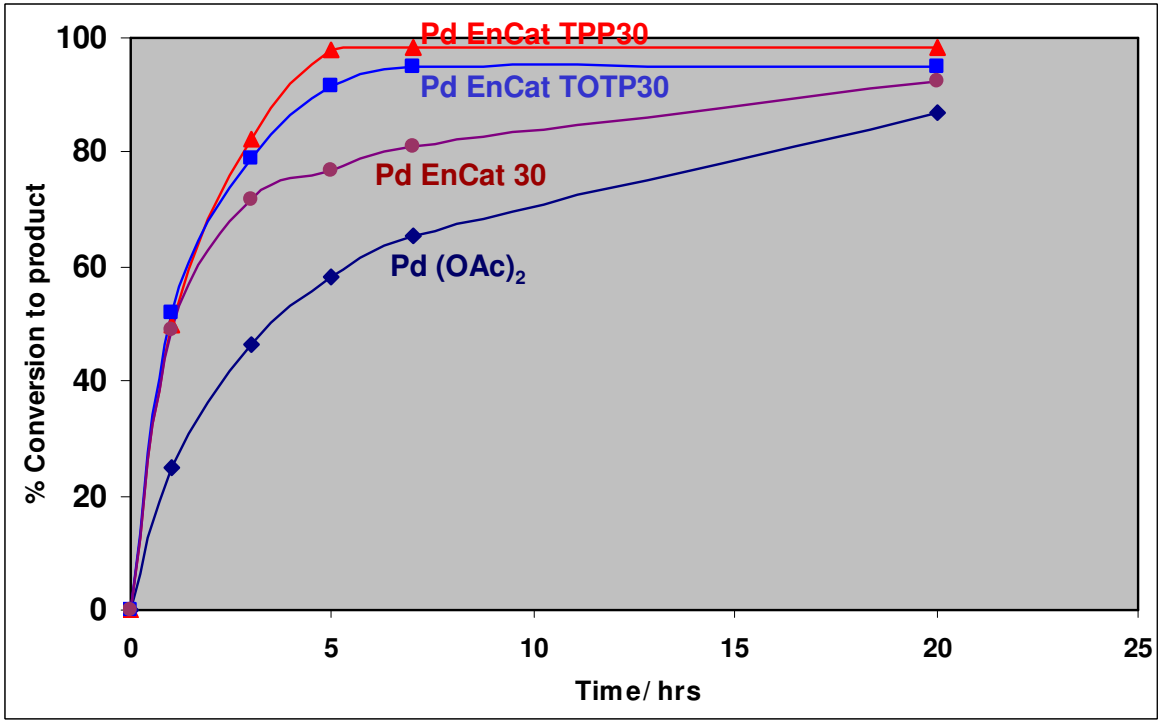
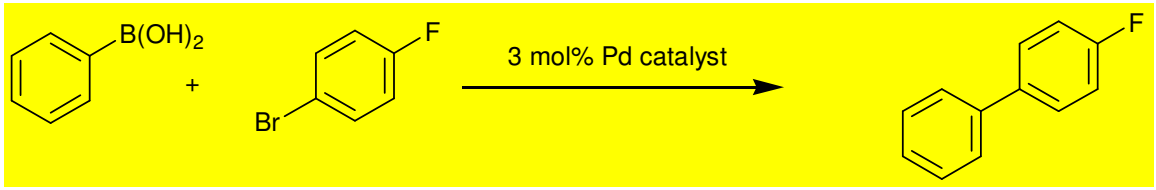
Pd EnCat™ Activity with Co-Encapsulated Phosphine Ligands





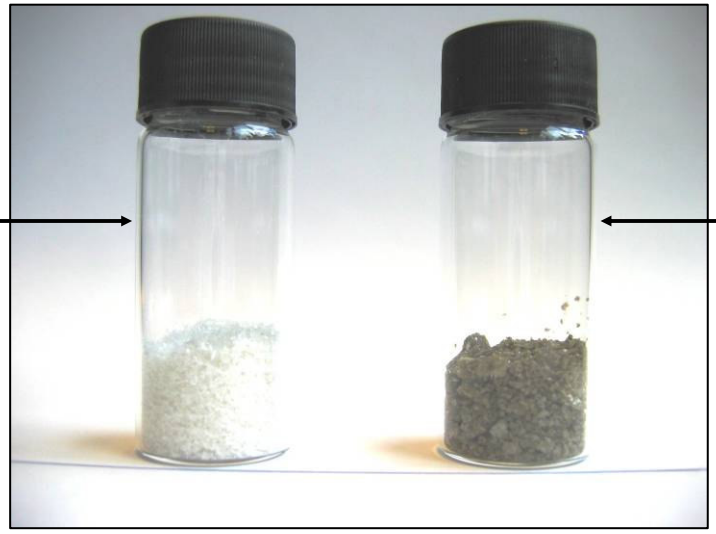
Pd EnCat™- Process Simplification



Crude products

Pd EnCat™ TPP30

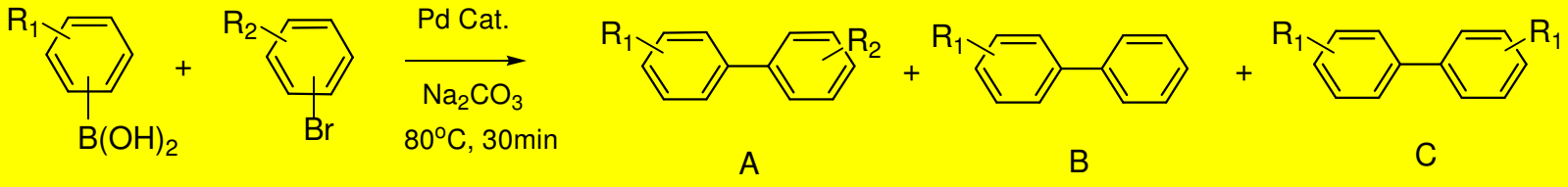
~10ppm Pd



$Pd(OAc)_2/PPh_3$

~2000ppm Pd

Suzuki Coupling Process Example
Pd EnCat™ 30 vs Pd/C



Catalyst	%Yield A	%Yield B	%Yield C	Pd (ppm) in Crude product
5% Pd/C 2.50 mol%	87	13	0	56
Pd EnCat™ 30 2.50 mol%	97	<1	<1	14
Pd EnCat™ 30 0.25 mol%	>99	<1	<1	9

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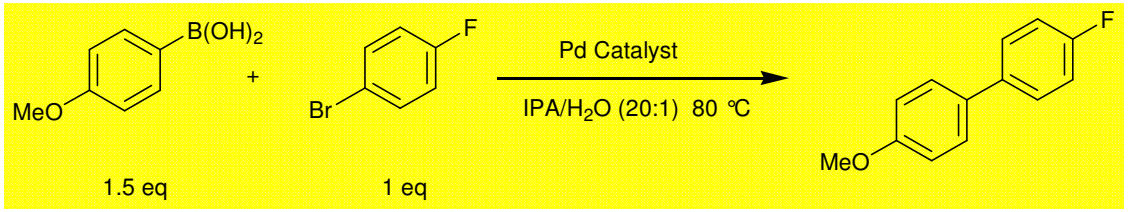
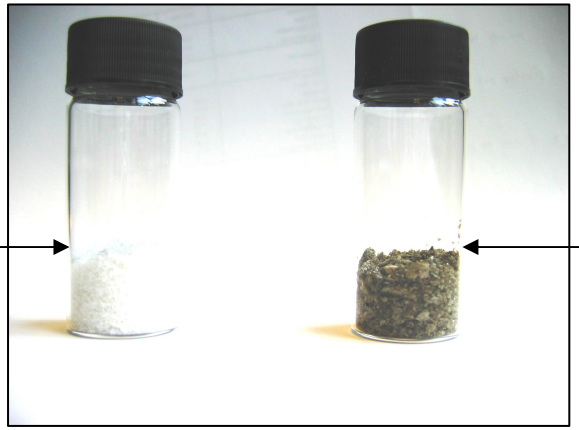
Pd EnCat™ polyTPP30
Process Simplification



Pd EnCat™ polyTPP30 →



← **$Pd(OAc)_2$ + PPh_3**

	Pd EnCat™ polyTPP30	$Pd(OAc)_2$ + TPP
Product Yield (%)	99	91
Pd in crude product (ppm)	7	985
P in crude product (ppm)	18	1200

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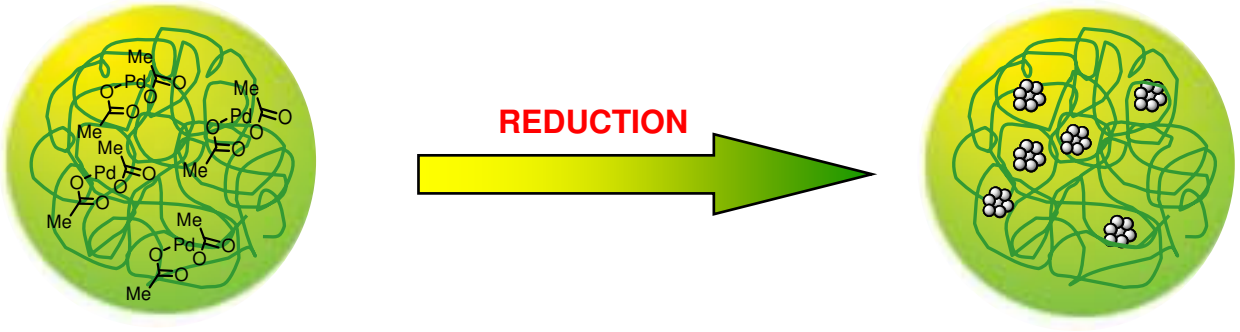
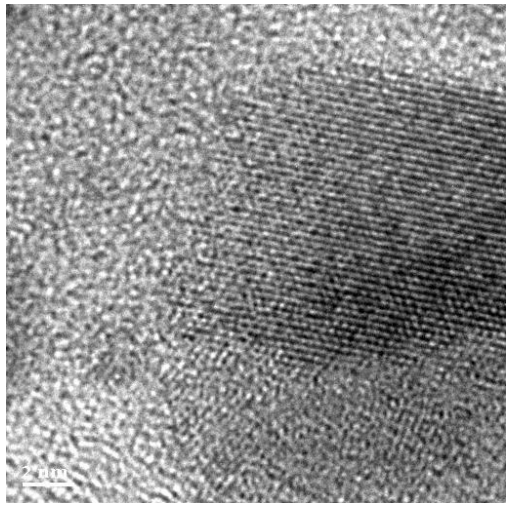
Pd(0) EnCat™ 30NP



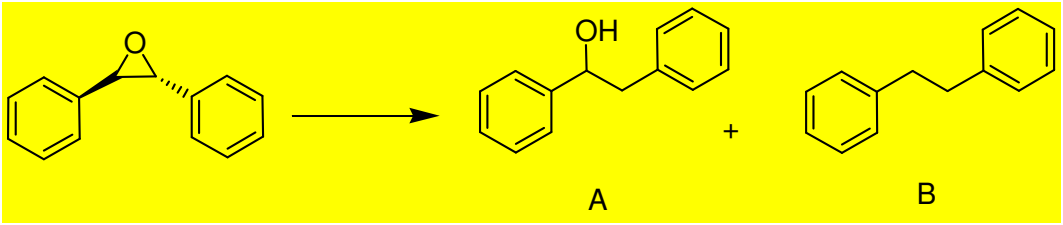
Pd EnCat™ 30

Pd(0) EnCat™ 30NP

- Pd particles <2 nm (approx 10 atoms)
- Nanostructure stabilised by polyurea matrix
- Highly active hydrogenation and transfer hydrogenation catalyst
- 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



Pd(0) EnCat™ 30NP Selectivity



Method	Catalyst	Solvent	Conversion A %	B %
Hydrogenation	H_2, Pd(0) EnCat™ 30NP	EtOH	93	7
Hydrogenation	H_2, 5% Pd/C Aldrich	EtOH	---	100
Transfer Hydrogenation	HCO_2NH_4, Pd(0) EnCat™ 30NP	MeOH/H_2O	98	2

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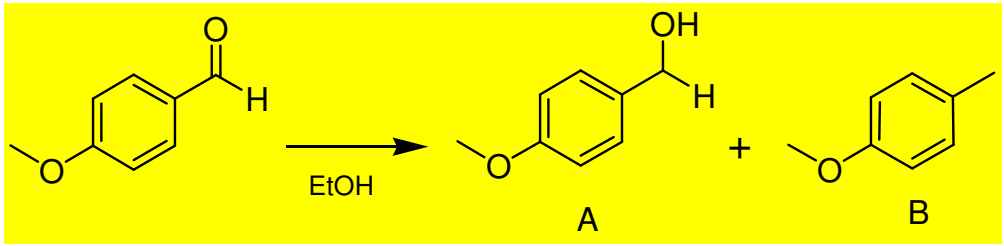
Pd(0) EnCat™ 30NP Selectivity



Catalyst	Conversion	
	A %	B %
H_2, Pd(0)EnCat™ 30NP	94	6
H_2, 5% $Pd/CaCO_3$	63	37
H_2, 5% Pd/Al_2O_3	45	55
H_2, 10% Pd/C Engelhard	13	84
H_2, 5% Pd/C Aldrich	---	100
H_2, 5% Pd/C J. Mathey	---	100

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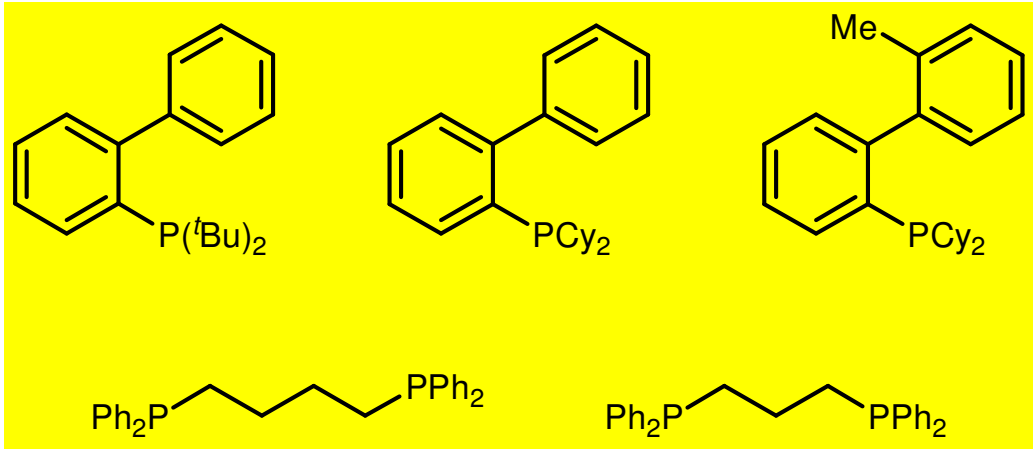
Development EnCat™

EnCat™ catalysts - tailored to a specific process and chemistry by selection of:

- metal type and loading
- ligand type and loading
- matrix porosity and particle size



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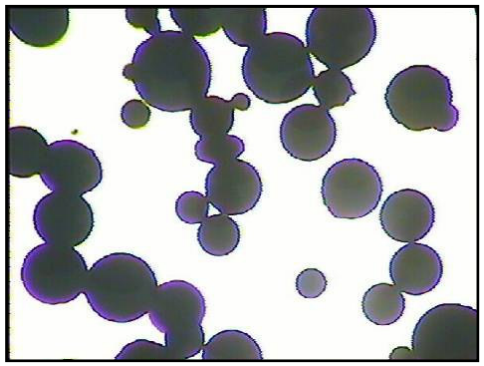
Os EnCat™ 40 Catalyst



Osmium tetroxide encapsulated in polymer beads
Catalogue supplies from Aldrich & Wako
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

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Published Pd(II) EnCat™ Applications

- **Heck coupling (comparison)**
  M. Ladlow, *et. al.*, *Org. Biomol. Chem.*, 2003, **1**, 2419.

- **Heck coupling**
  S. V. Ley, *et. al.*, *Org. Biomol. Chem.*, 2004, **2**, 611.

- **Batch and continuous flow Suzuki cross-coupling**
  S. V. Ley, *et. al.*, *Chem. Commun.*, 2005, 2175.

- **Microwave synthesis of trisubstitued pyrmidines**
  P. Pilotti *et. al., Pharm. Disc.*, 2005, **5**(8), 32.

- **Heck, Suzuki and Sonogashira couplings in water with recycling**
  C. Nájera, *Tetrahedron* 2005, **61**, 12168.

- **Microwave Suzuki coupling in batch and continuous-flow**
  S. V. Ley *et. al., Chem. Eur. J.*, 2006, **12**, 4407.

- **Homocoupling of boronic acids**
  Y. Yamamoto, *et. al.*, *SynLett* 2006, 1027.

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Published Pd(0) EnCat™ Applications

- **Transfer hydrogenation of aryl ketones**
  S. V. Ley *et. al., Chem. Comm.*, 2003, 678.

- **Hydrogenation of aryl aldehydes**
  R. H. Perni, S. V. Ley *et. al.*, *Beil. J. Org. Chem.*, 2006, 2, 15.

- **Hydrogenolysis of epoxides and recycling**
  S. V. Ley *et. al., Org. Lett.*, 2003, **5**, 4665.

- **Nitro reduction (Leimgruber-Batcho)**
  S. V. Ley *et. al., Org. Biomol. Chem.*, 2004, **2**, 160.

Other Applications

- **Mediated Reductive aminations**

- **Hydrogenation of aromatic ketones, aldehydes and epoxides**

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General EnCat™ Publications

- **Encapsulation of Palladium in Polyurea Microcapsules**
  S. V. Ley *et. al., Chem. Commun.*, 2002, **10**, 1132.

- **Polyurea-Encapsulated Palladium(II) Acetate: a Robust and Recyclable Catalyst for use in Conventional and Supercritical Media**
  S. V. Ley *et. al., Chem. Commun.*, 2002, **10**, 1134.

- **Palladium Acetate in Polyurea Microcapsules: A Recoverable and Reusable Catalyst for Hydrogenations**
  S. V. Ley *et. al., Synlett*. 2002, **11**, 1843.

- **Polyurea-Encapsulated Palladium Catalysts: The Development and Application of A New Versatile Immobilised Homogeneous Catalyst Technology**
  D. A. Pears, S. C. Smith, *Aldrichimica Acta*, March/April 2005.

- *patents*: **WO 03/0006151**; **WO 2005/016510**

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Critical EnCat™ Publications

- **Compare Pd EnCat TPP and NP for Suzuki**
  C. Mioskowski et. al., *Angew. Chem. Int. Ed*. 2006, **45**, 2868.

- **QuadraPure TU to shut down EnCat aryl iodide Heck reactions**
  C. W. Jones, *Adv. Synth. Catal.* 2006, **348**, 1207.

- **3-phase Heck reaction with aryl iodide to show leached Pd as catalytic species**
  D. T. McQuade et. al., *J. Org. Chem.*, 2006, **71**, 2131.

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Os EnCat™ Publications

- **Microencapsulation of Osmium Tetroxide in Polyurea**
  S. V. Ley *et. al.*, *Org. Lett.*, 2003, **5**, 185.

Published Applications

- **Oxidative Cleavage of Olefins**
  B. Borhan *et. al.*, *Tetrahedron Lett.*, 2006, 3797.

- **Dihydroxylation Reactions**
  S.V. Ley *et. al.*, *Org. Lett.*, 2003, **5**, 185.

- **Asymmetric Dihydroxylation**
  S. V. Ley *et. al.*, *Org. Biomol. Chem.*, 2003, **1**, 3957.

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General Reaxa Publications

- **Microwave Flow Chemistry: The Next Evolutionary Step in Synthetic Chemistry?**
  Ian R. Baxendale and Michael R. Pitts, *Chem. Today*, 2006, **24**, 41.

- **Model Behaviour**
  Thomas Screen, *Chem. Ind.*, 2006, **July**, 18.

- **Microwave Enhanced Palladium Catalysed Reactions**
  Ian R. Baxendale and Michael R. Pitts, *Innov. Pharm. Tech.*, 2005, **18**, 86.

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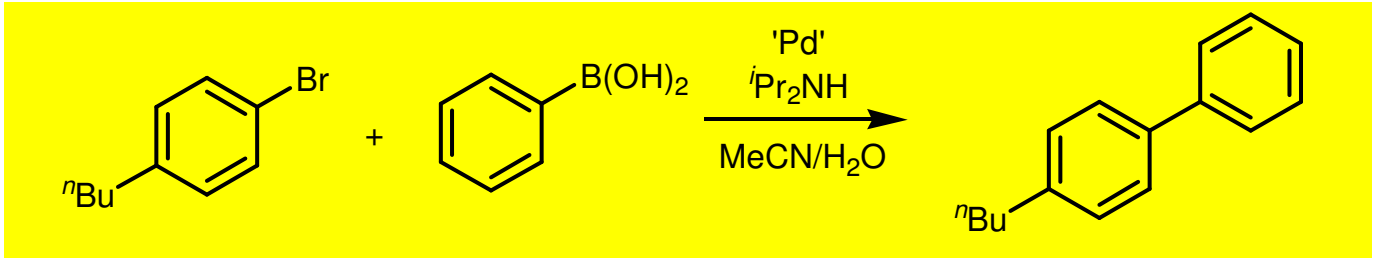
EnCat™ Comparison - Suzuki



catalyst	yield (GC)
$Pd(OAc)_2$	46%
Pd(II) EnCat TPP30	62%
Pd(0) EnCat NP30	48%
Pd nanoparticles 'gel'	79%

C. Mioskowski *et. al.*, *Angew. Chem. Int. Ed.* 2006, 45, 2868

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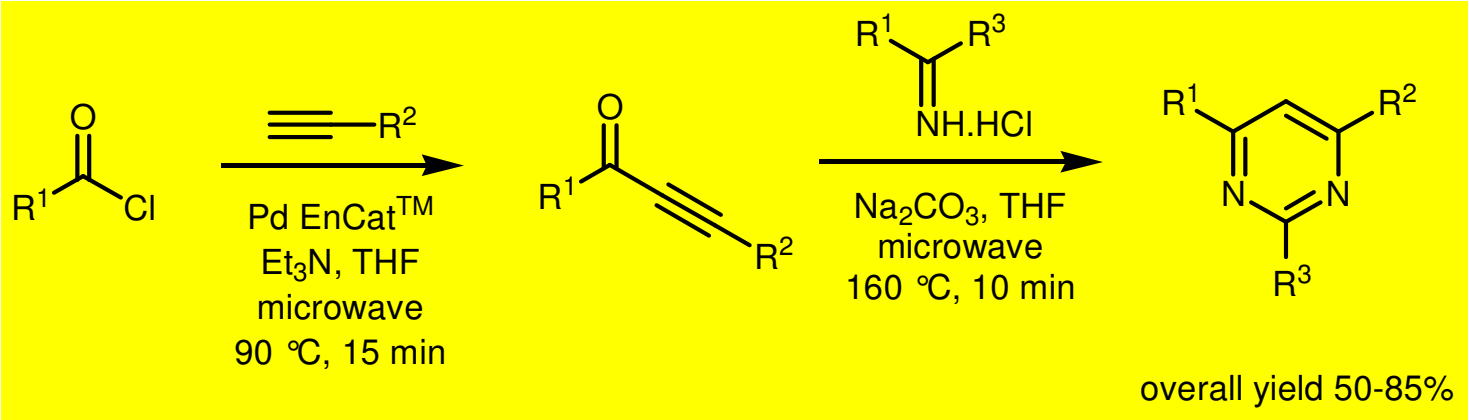
Pd EnCat™ Pyrimidine Synthesis



P. Pilotti *et. al., Pharm. Disc.*, 2005, 5(8), 32

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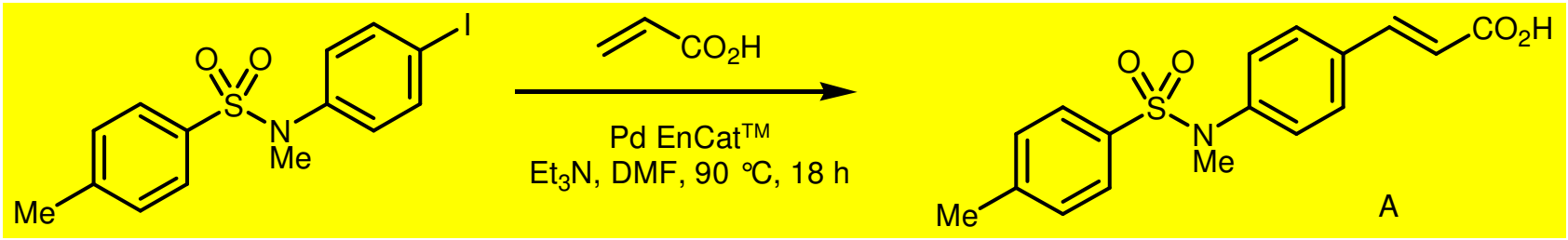
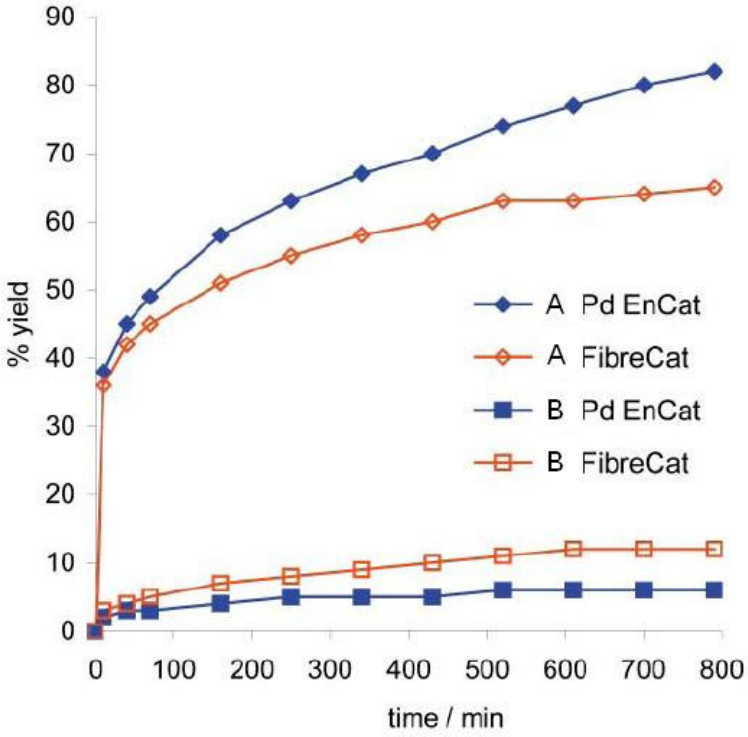
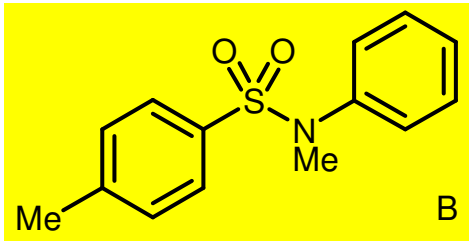
Pd(II) EnCat™ Heck Coupling







S. V. Ley, *et. al.*, *Org. Biomol. Chem.*, 2004, 2, 611
M. Ladlow, *et. al.*, *Org. Biomol. Chem.*, 2003, 1, 2419

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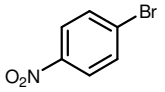
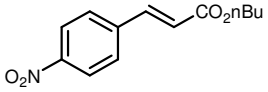
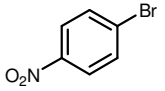
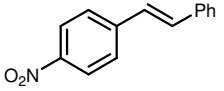
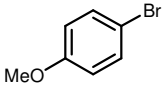
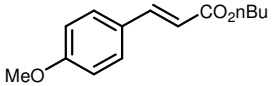
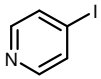
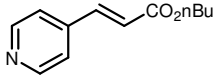
Pd(II) EnCat™ Heck Coupling

Substrate	Product	Yield (%)
		91
		93
		25
		98

Conditions: 2.5mol% Pd EnCat™ 40, IPA, nBu_4NOAc, 90°C, olefin

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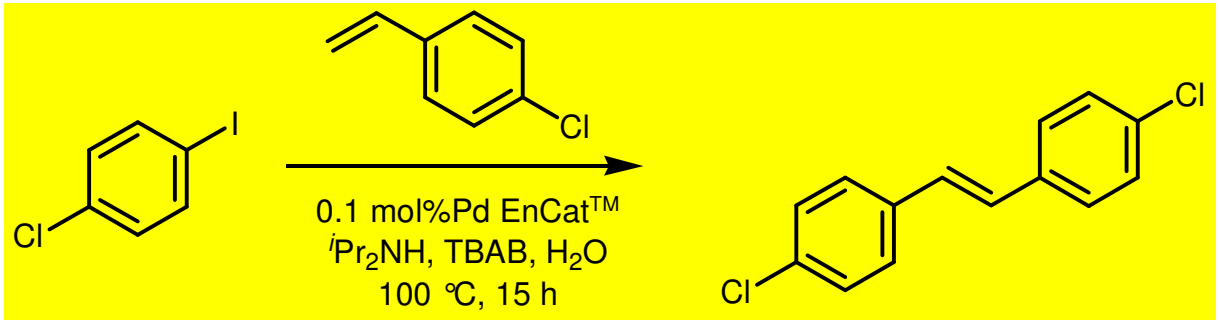
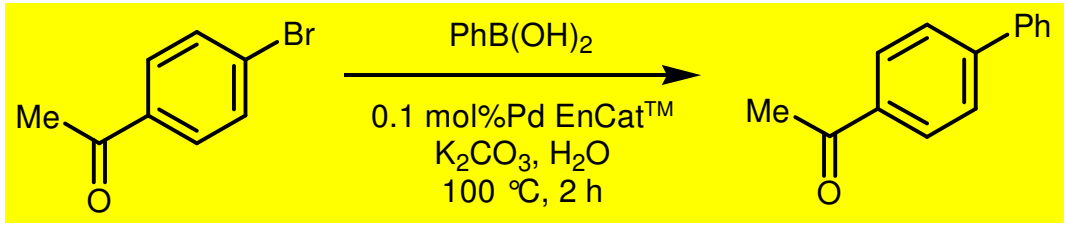
Reaxa

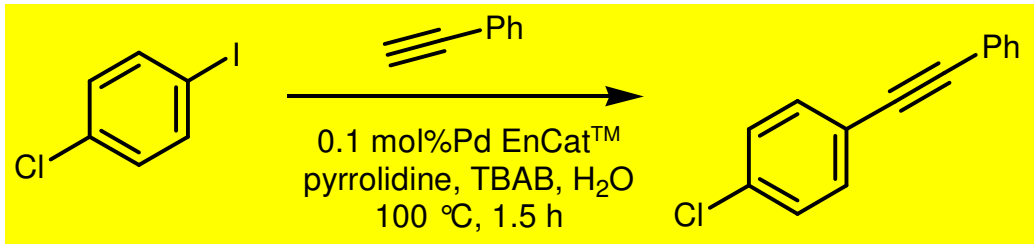
Pd(II) EnCat™ 40 Coupling in Water



run	yield
1	99%
2	91%
3	95%



run	yield
1	88%
2	80%



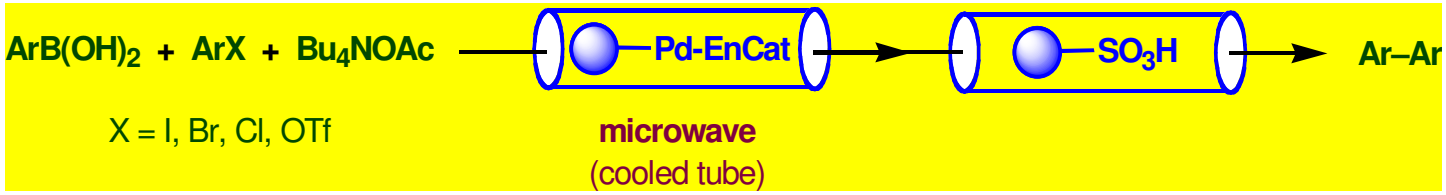
run	yield
1	99%
2	99%
3	27%

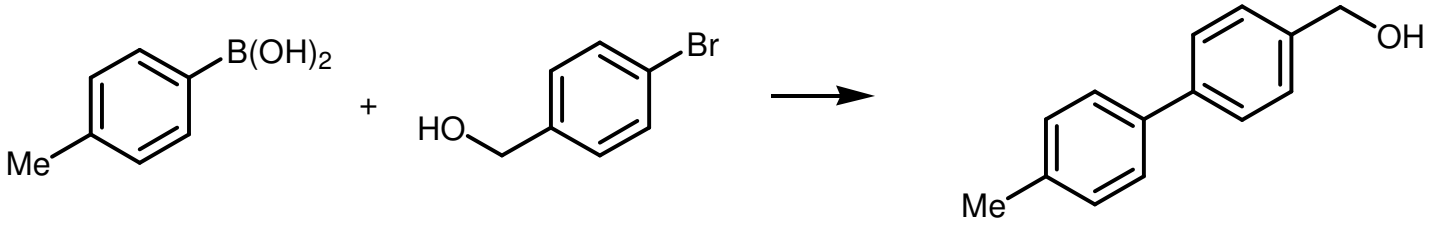
C. Nájera, *Tetrahedron* 2005, 61, 12168

return to menu

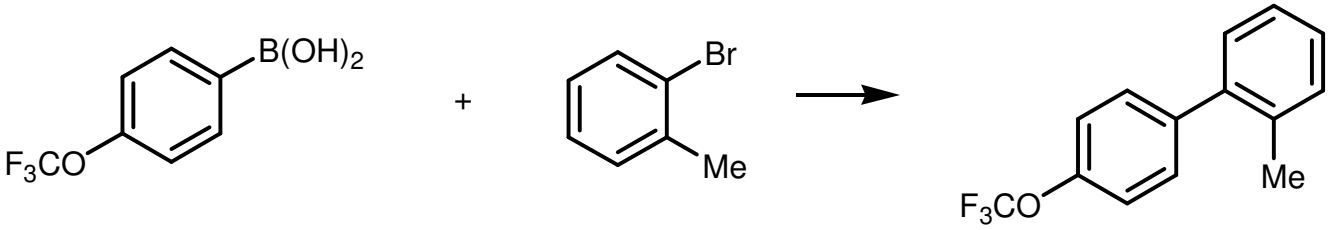
Reaxa

Pd(II) EnCat™ Flow Suzuki





batch - 120 ºC, 10 min — purity 42%
batch - 50 W with cooling, 15 min, (max 76 ºC) — purity 86%
flow - 0.1 ml/min, 0.01 M, 50 W with cooling — purity >98%



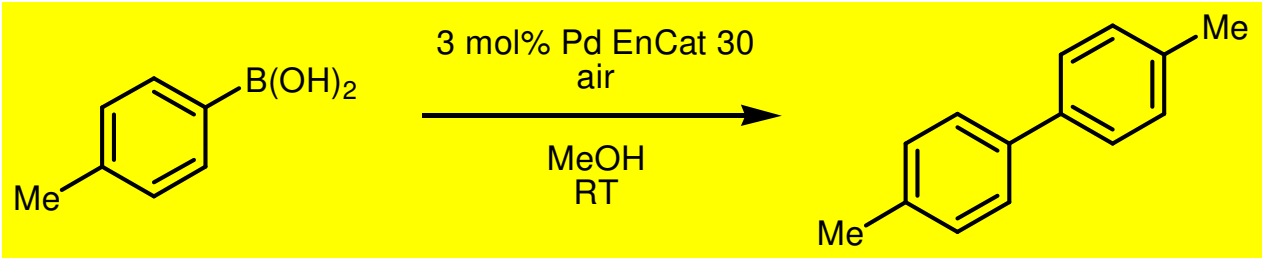
batch - 120 ºC, 10 min — purity 84%
batch - 50 W with cooling, 15 min, (max 78 ºC) — purity >98%
flow - 0.1 ml/min, 0.01 M, 50 W with cooling — purity >98%

S. V. Ley *et. al.*, *Chem. Eur. J.*, 2006, 12, 4407

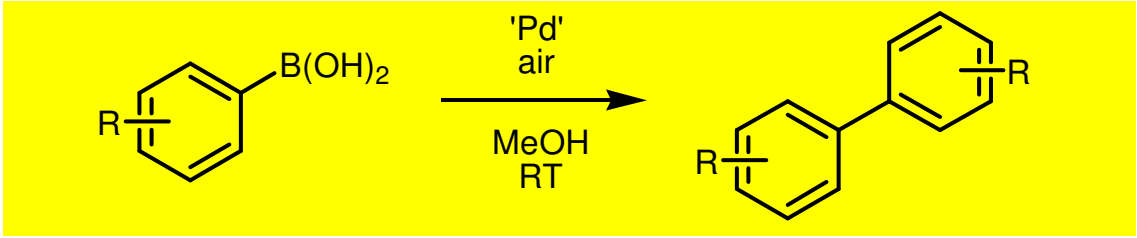
return to menu

Reaxa

EnCat™ Homocoupling of Boronic Acids



run	1	2	3	4	5
conversion (%)	95	100	97	91	85
yield (%)	64	65	64	64	60



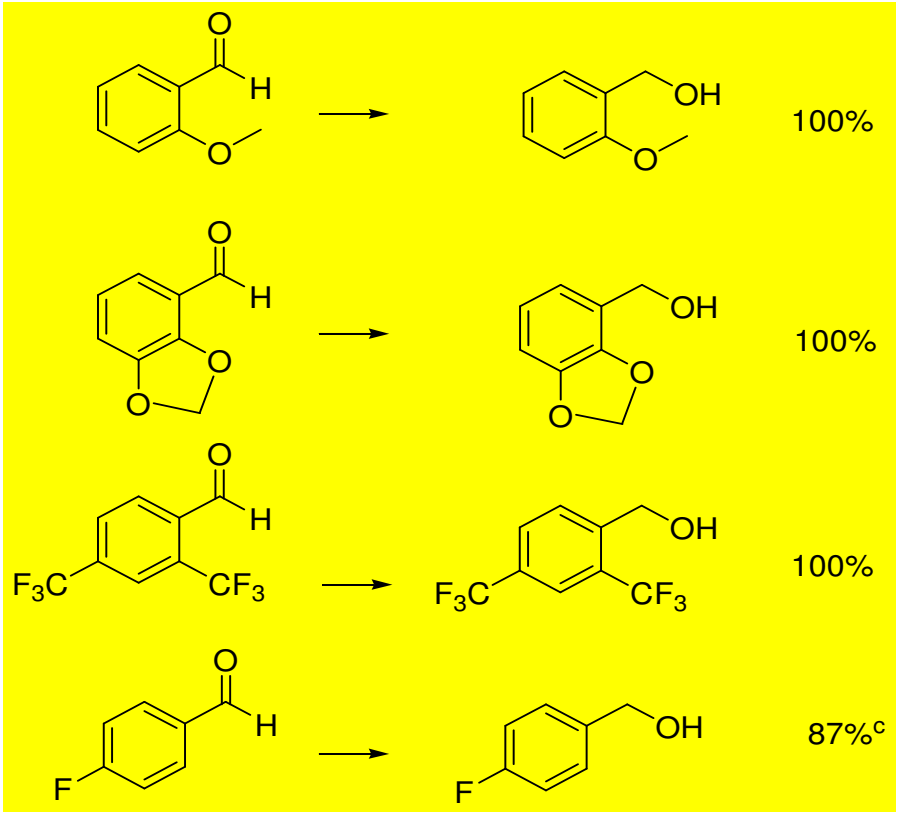
R	Pd EnCat 30	$Pd(OAc)_2$
4-Cl	52%	34%
3-Cl	50%	30%
4-COMe	44%	20%

return to menu

Y. Yamamoto, *et. al.*, *SynLett* 2006, 1027

Reaxa

Pd(0) EnCat™30NP Hydrogenation of Aryl Aldehydes



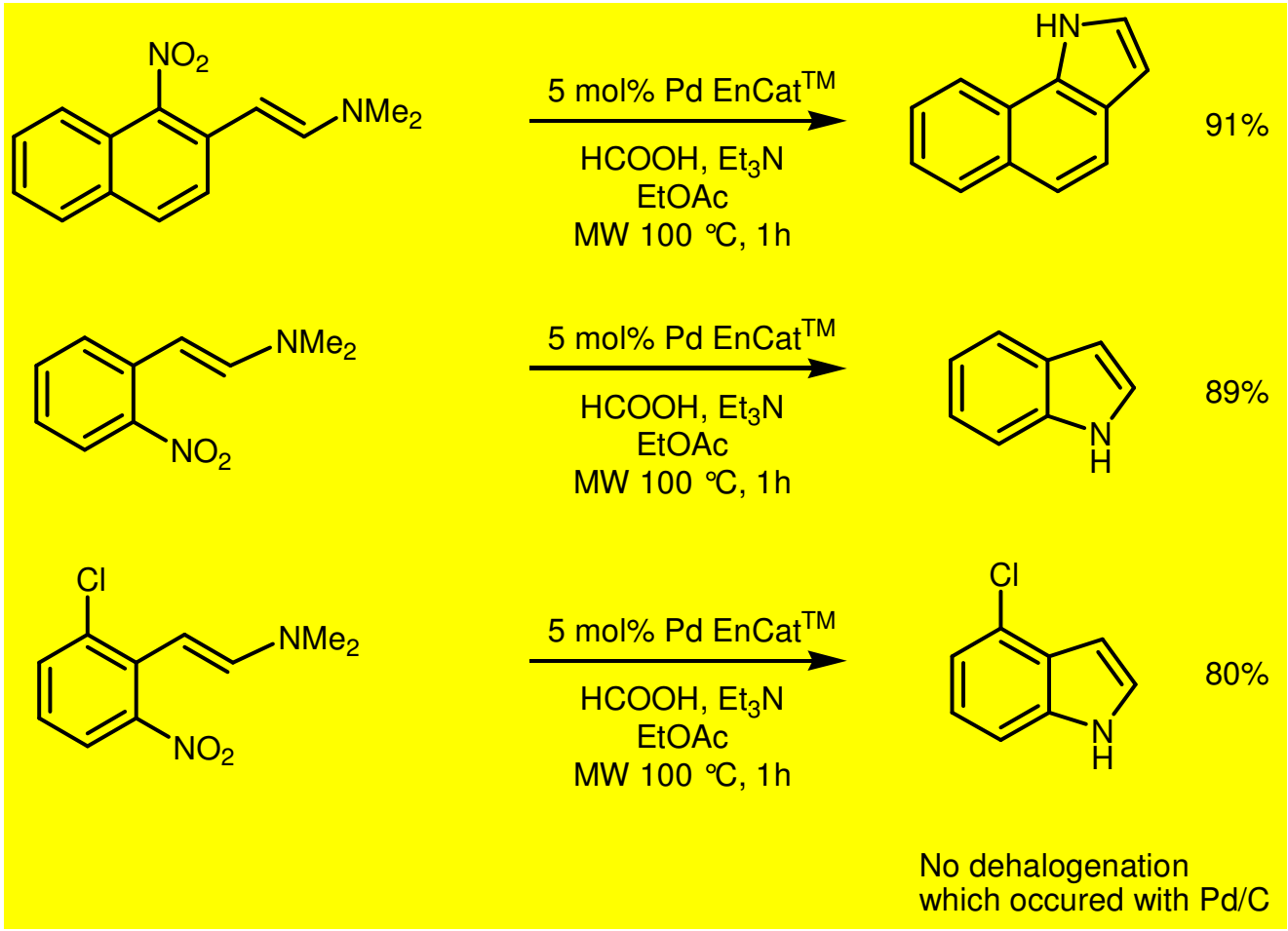
10 mol% Pd(0) EnCat 30NP, H2 balloon, RT, 16 h

R. H. Perni *et. al.*, Beil. J. Org. Chem., 2006, 2, 15

return to menu

Reaxa

Pd(0) EnCat™30NP Leimgruber-Batcho

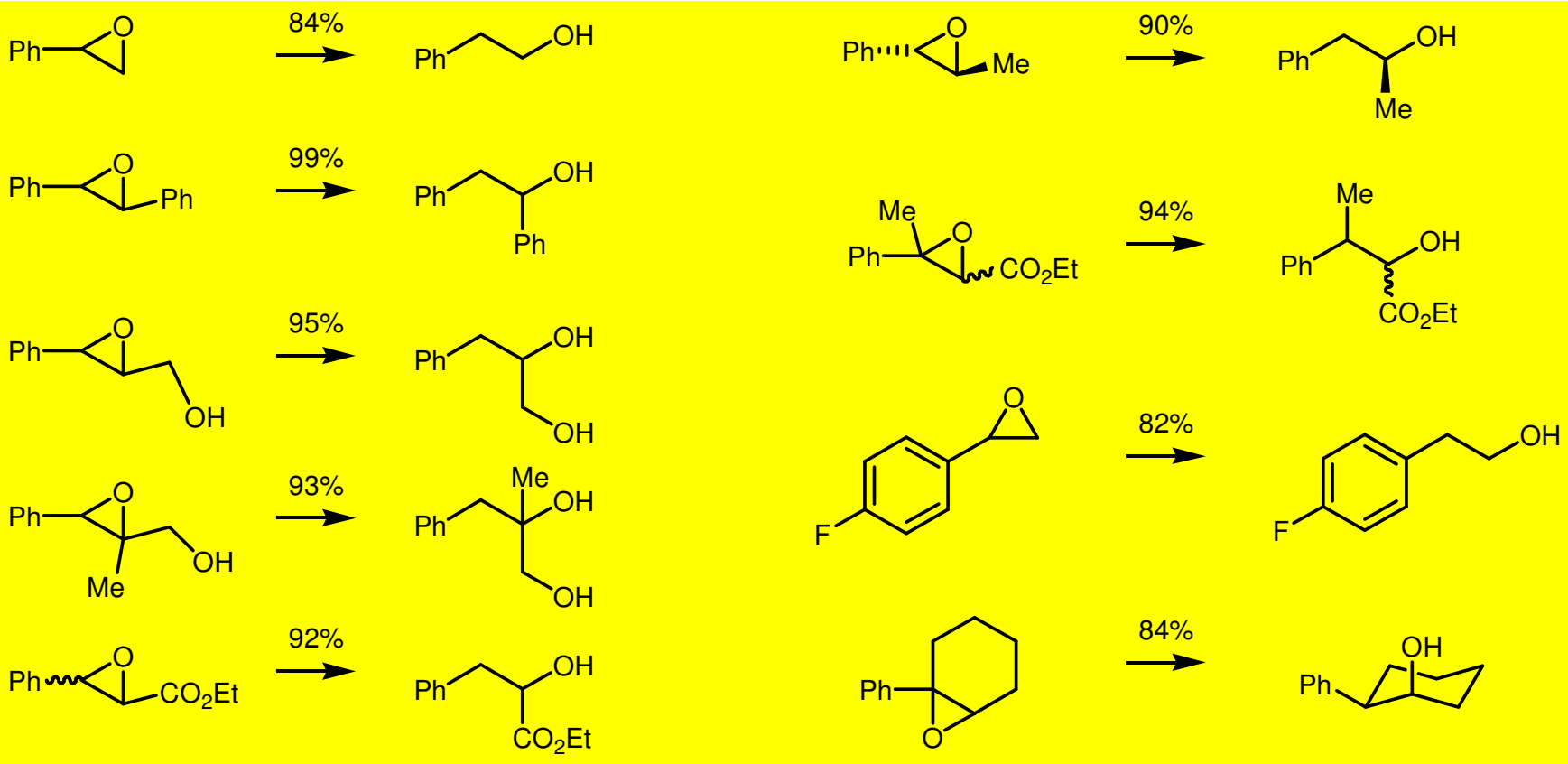


S. V. Ley *et. al*., Org. Biomol. Chem., 2004, 2, 160

return to menu

Reaxa

Pd(0) EnCat™30NP
Epoxide *trans*-Hydrogenolysis



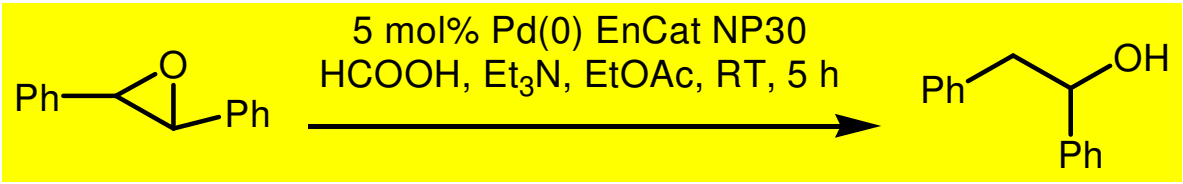
5 mol% Pd(0) EnCat 30NP, HCOOH, Et_3N, EtOAc, RT, 3-24 h

S. V. Ley *et. al., Org. Lett.*, 2003, 5, 4665

return to menu

Reaxa

Pd(0) EnCat™ 30NP
Hydrogenolysis - Recycling



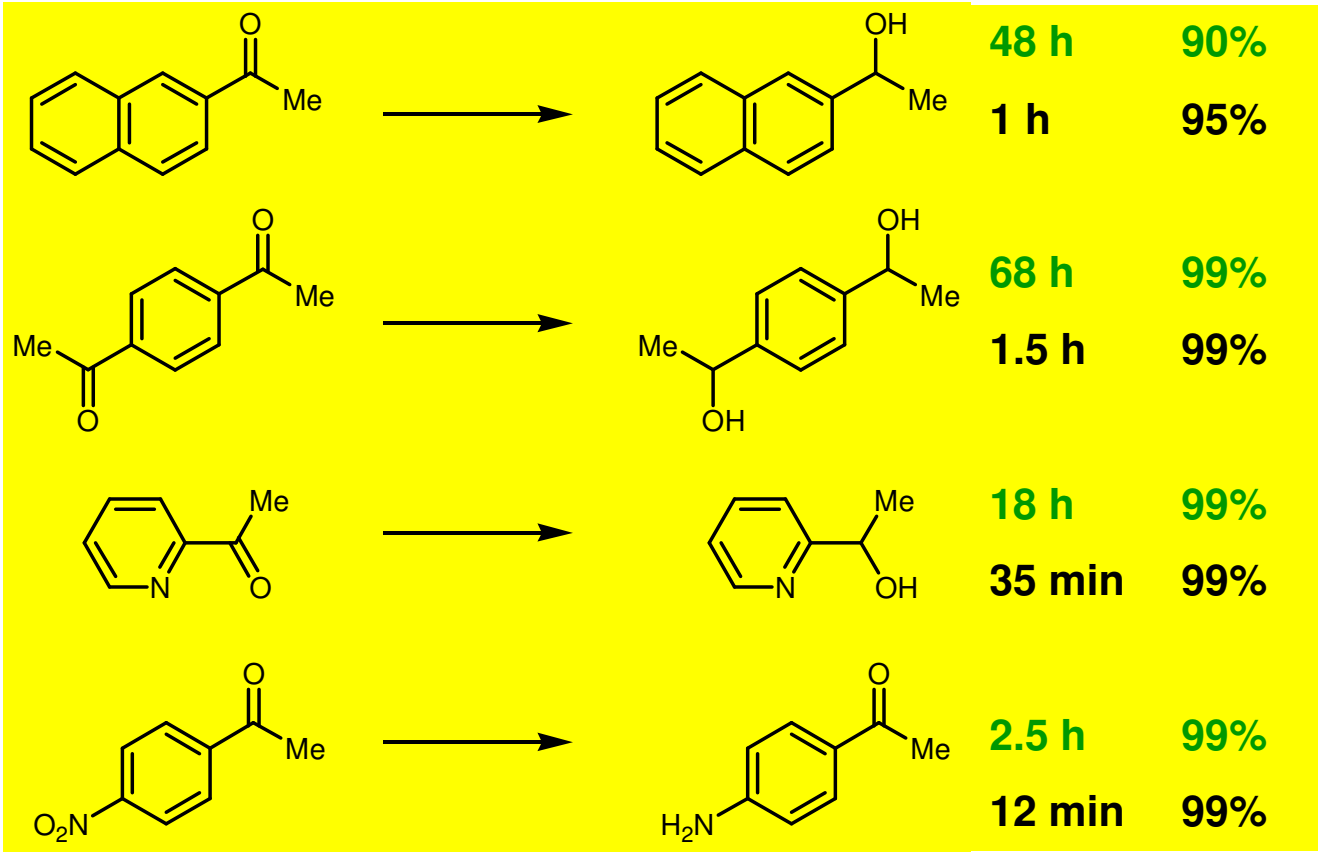
run	1	2	3	4	5	6	7	8	9	10
yield (%)	99	98	97	98	96	97	98	97	97	97

S. V. Ley *et. al., Org. Lett.,* 2003, 5, 4665

return to menu

Reaxa

Pd(0) EnCat™30NP Ketone Reduction



EtOAc, Et_3N (20 eq), HCOOH (20 eq), Pd(0) EnCat 30NP, rt

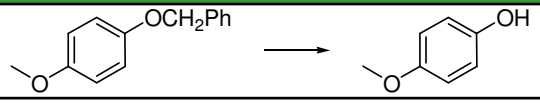
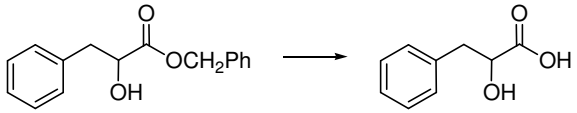
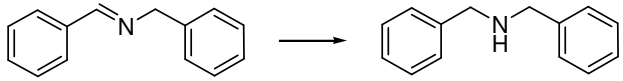
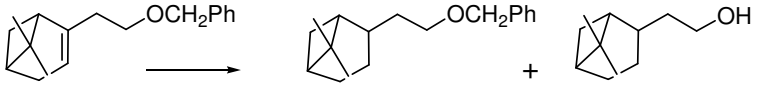
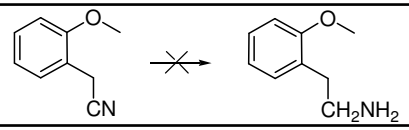
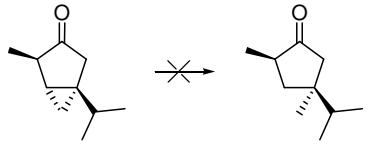
EtOAc, Et_3N (5 eq), HCOOH (5 eq), Pd(0) EnCat NP, MW 120 °C

return to menu

S. V. Ley *et. al.*, Chem. Comm., 2003, 678

Reaxa

Pd(0) EnCat™ 30NP
Hydrogenation Reactions

Method	Reaction	% Conversion
a		100
a		100
a		95
a		100
a		88
a		86 + 16 deprotected
a		No rxn
a		No rxn
b	Fmoc-Lys(Z)-OH ⟶ Fmoc-Lys-OH	91

Method a:

Pd(0) EnCat™ 30NP wet catalyst (10 mol%), H_2 balloon EtOH, r.t. 16h.

Method b:

Pd(0) EnCat™ 30NP wet catalyst (10 mol%), H_2 balloon MeOH/HOAc (10:1), r.t. 4.5 h.

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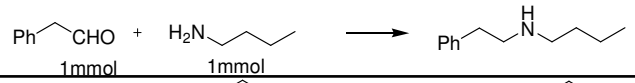
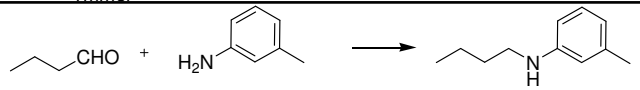
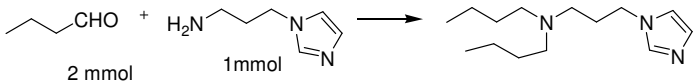
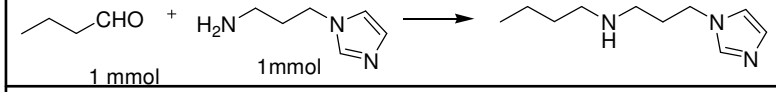
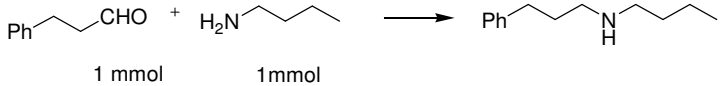
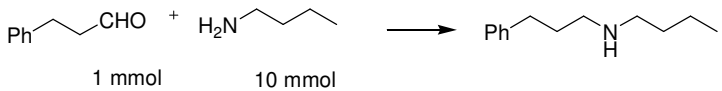
Reaxa

Pd(0) EnCat™ 30NP Mediated Reductive Aminations

General issues: Partial reduction of starting materials
Over reduction products
Amines poisoning the catalyst

Reaction	Conversion	Comments
	100%	Determined by 1HNMR
	83%	Determined by 1HNMR and GCMS + 4% dialkylation
	83%	Determined by 1HNMR and GCMS. No evidence of monoalkylated by GCMS
	97%	Determined by 1HNMR and GCMS
	74%	Determined by 1HNMR and GCMS +22% dialkylation + 3% alcohol
	95%	Determined by 1HNMR and GCMS +1% dialkylation + 4% alcohol

General conditions: 10 mol% Pd(0) EnCat 30NP wet, EtOH industrial, Hydrogen gas (balloon), r.t., 16h

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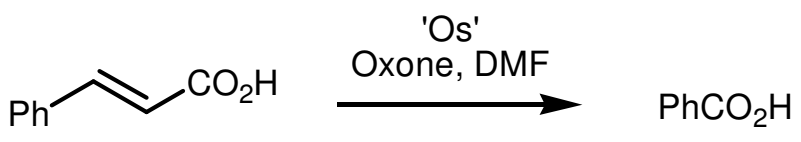
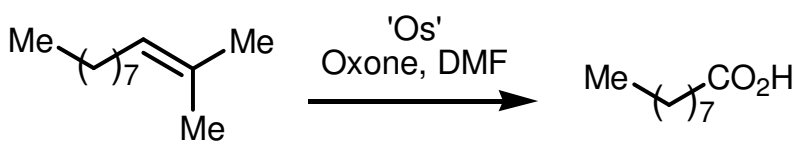
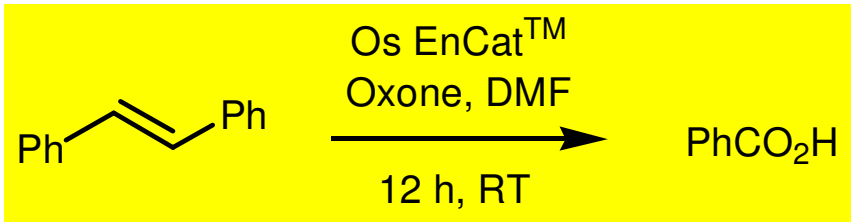
Reaxa

Os EnCat™40 Oxidative Cleavage

reaction	$OsCl_3$	K_2OsO_4	OsO_4	Os EnCat
	84%	79%	74%	96%
	97%	85%	82%	97%



run	yield
1	73%
2	85%
3	56%
4	incomplete

B. Borhan *et. al.*, *Tetrahedron Lett.*, 2006, 3797

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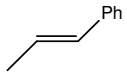
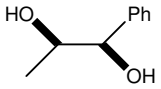
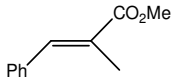
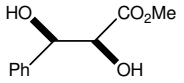
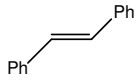
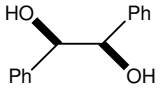
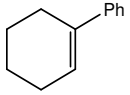
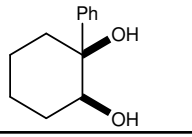
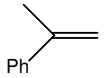
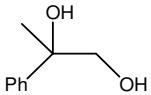
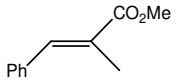
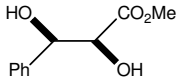
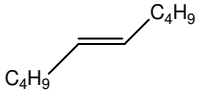
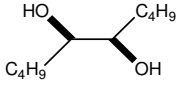
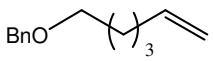
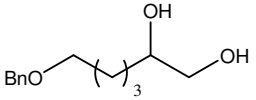
Reaxa

Os EnCat™40 Dihydroxylation Reactions

Substrate	Product	Yield (%)	Substrate	Product	Yield (%)
		80			83
		84			82
		90			85
		84			73

Olefin (1 mmol), NMO (1.3 mmol), 5 mol% Os EnCat™40, acetone/water, room temp., 12-20 h

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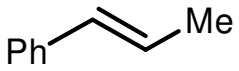
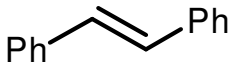
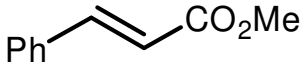
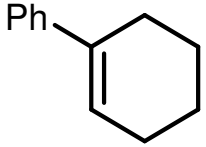
Os EnCat™40 Asymmetric Dihydroxylation

substrate	yield (%)	ee(%)
	98	94
	88	>99
	94	>99
	91	97

5 mol% Os EnCat™40/$(DHQD)_2PHAL$, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, THF/water, room temp., 24-48 h

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