Cleaner, Greener, Safer – Improving Precious Metal Catalytic Processes
Clean Technologies for Precious Metal Chemistries

spin-out from Avecia Pharmaceuticals

collaboration with Professor Steve Ley and Dr Ian Baxendale at Cambridge University

began trading in June 2005

Blackley, Manchester
Reaxa Technology

Business Units
- Precious Metal Catalysis
- Immobilised Reagents
- Bio-Pharma Technology

Products
- EnCat™
- QuadraPure™
- LaPCat™
- ChemDose™
- Silicas
- Super Acids
- Peptides
- Linkers
- Conjugation Purification

Focus
- Process and Resource Efficiency
- Safety & Controlled Delivery
- Drug Modification, Immobilisation & Controlled Release

Development Areas
- Chirals
- Microwave & Flow Processing
- New Drug Formats

‘cleaner, greener, safer’
Microwaves at Reaxa

microwave heating is applied across all of Reaxa’s technology platforms.
Common Process Issues with Homogeneous Pd Catalysis

- Pd contamination of product – regulatory issue
- Pd contamination of intermediate – interferes with downstream chemistry
- Pd contamination of reactor vessels – cleaning costs
- Pd contamination in waste streams – treatment costs
- Pd loss from process = high cost

- minimise soluble Pd
- downstream treatment
- heterogeneous catalyst
Why Use Precious Metal Scavengers in Pharmaceutical Manufacture?

- regulatory issue - stringent heavy metal limits set by FDA for APIs
- metal contaminants interfere with downstream chemistry
- economic work-up of PMG catalysed reactions is often over-looked until too late!
- the economic use of homogeneous PMG catalysts depends on ability to efficiently recover the PM
- to reduce waste stream pollution costs and killing water treatment plant
- prevention of reactor vessel M(0) contamination
### QuadraPure™ Products

<table>
<thead>
<tr>
<th>QuadraPure™ Product (macroporous resins)</th>
<th>Aldrich catalogue #</th>
<th>QuadraPure™ Product (microporous resins)</th>
<th>Aldrich catalogue #</th>
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<tbody>
<tr>
<td>TU</td>
<td>655422</td>
<td>MPA</td>
<td>657662</td>
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<tr>
<td>IDA</td>
<td>657026</td>
<td>AEA</td>
<td>657646</td>
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<tr>
<td>AMPA</td>
<td>657611</td>
<td>IMDAZ</td>
<td>657654</td>
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QuadraPure™ TU
Thiourea Macroporous Polystyrene

photograph of QuadraPure™ TU beads

image of the interior of a QuadraPure™ TU bead

\[
\text{H} - \text{CH} - \text{S} - \text{NH} - \text{NH}_2
\]
## QuadraPure™ - Macroporous Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Functional Group</th>
<th>Metals Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuadraPure™ TU</td>
<td>thiourea</td>
<td>Pd, Pt, Ru, Au, Ag, Cu(I), Hg, Pb, Pt, Cd, Ni</td>
</tr>
<tr>
<td>QuadraPure™ IDA</td>
<td>imino diacetate</td>
<td>Fe(II), Fe(III), Al(III), Ga(III), In(III), Cu, V, Pb, Ni, Zn, Cd, Be, Mn, Sr, Ba</td>
</tr>
<tr>
<td>QuadraPure™ AMPA</td>
<td>aminomethyl phosphonic acid</td>
<td>Fe, Cu, Ni multivalent metal ions</td>
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</table>
## Quadrapure™ - Microporous Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Functional Group</th>
<th>Metals Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuadraPure™ MPA</td>
<td>mercaptophienl amino</td>
<td>Pd, Ni, Cu, Sn and other soft transition metals</td>
</tr>
<tr>
<td>QuadraPure™ AEA</td>
<td>aminoethyl amino</td>
<td>Pd and other transition metals</td>
</tr>
<tr>
<td>QuadraPure™ IMDAZ</td>
<td>imidazol-1-yl propyl amino</td>
<td>Pd, Os, Co, Ni, V, Rh and other transition metals</td>
</tr>
</tbody>
</table>
QuadraPure™ Rh Scavenging

Rh(CO)$_2$(acac)

0.5 g resin for 1000 ppm solution in THF

Rh(CO)(acac)PPh$_3$
(hydroformylation catalyst)

QuadraPure™ MPA in THF
[Rh(OAc)$_2$]$_2$ /DMF Scavenger Trial

QUADRAPURE AEA, TU, BZA, EDA, DTC

Competitor’s ‘Fibres’

Competitor’s ‘Nets’
<table>
<thead>
<tr>
<th>QuadraPure™</th>
<th>Reagent</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BzA</td>
<td>[Rh(OAc)₂]₂</td>
<td>DMF 1000 ppm, 2-4 h at RT</td>
</tr>
<tr>
<td>TU</td>
<td>Pd(OAc)₂</td>
<td>THF 1000 ppm, 3-6 h at RT</td>
</tr>
<tr>
<td>EDA</td>
<td>Ni(acac)₂</td>
<td>CH₂Cl₂ 1000 ppm, 48 h at RT</td>
</tr>
</tbody>
</table>

**Microwave Conditions:**
- 10 min at 80 °C
- 10 min at 100 °C

**Reaxa**
## Resin Guide

### QuadraPure™ Metal Scavenger Resins

<table>
<thead>
<tr>
<th>Volume of solution/ml</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
<th>600</th>
<th>700</th>
<th>800</th>
<th>900</th>
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<th>1500</th>
<th>2000</th>
<th>5000</th>
<th>10000</th>
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<tbody>
<tr>
<td>10</td>
<td>0.01</td>
<td>0.03</td>
<td>0.05</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
<td>1.5</td>
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<tr>
<td>25</td>
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<td>0.06</td>
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<td>0.25</td>
<td>0.5</td>
<td>0.75</td>
<td>1.0</td>
<td>1.25</td>
<td>1.5</td>
<td>1.75</td>
<td>2.0</td>
<td>2.25</td>
<td>2.5</td>
<td>3.75</td>
<td>5.0</td>
<td>12.5</td>
<td>25.0</td>
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<tr>
<td>50</td>
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<td>0.13</td>
<td>0.25</td>
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<td>1.5</td>
<td>2.0</td>
<td>2.5</td>
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<td>3.5</td>
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<td>0.75</td>
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<td>3.0</td>
<td>3.75</td>
<td>4.5</td>
<td>5.25</td>
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<td>4.0</td>
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<tr>
<td>300</td>
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<td>10.0</td>
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<tr>
<td>750</td>
<td>0.75</td>
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<td>45.0</td>
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<td>10.0</td>
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<td>100.0</td>
<td>150.0</td>
<td>200.0</td>
<td>500.0</td>
<td>1000.0</td>
</tr>
</tbody>
</table>

**Grammes of QuadraPure™ Required**
Scavenger Resins – Pharma Market Adoption Issues

historically metal scavengers seen as an R&D curiosity:

- too expensive for production
- not available at scale
- customers don’t want to handle loose resin in reactors
- reactor validation issues

with Biotage, Reaxa are developing applications for the QuadraPure™ scavengers to overcome these issues
QuadraPure™ resins in cartridge format

- TU, IDA, AMPA (+ BzA)
- launch sizes: 12M, 25S, 40M (6 g, 13 g, 68 g)

QuadraPure™ TU
QuadraPure™ IDA
QuadraPure™ AMPA
use in SP4 system

5 ppm Pd in THF
(Pd(OAc)₂)

232 nm
320 nm
QuadraPure™ TU cartridge: flow direction

Weak Solvent
tetrahydrofuran

Strong Solvent (blue line)
Pd(OAc)$_2$ 1000 ppm in THF

Cartridge
FLASH 12+M

Flowrate
1 ml/min

UV Wavelength
Collection 232 nm (red line)
Monitor 320 nm (black line)

down (with gravity)
breakthrough after ~85 ml
~14 mg/g

up (against gravity)
breakthrough after ~125 ml
~20 mg/g
**QuadraPure™ TU cartridge: flow direction**

- **Weak Solvent**: tetrahydrofuran
- **Strong Solvent (blue line)**: Pd(OAc)$_2$ 1000 ppm in THF
- **Cartridge**: FLASH 40+S
- **Flowrate**: 7 ml/min
- **UV Wavelength**
  - Collection 232 nm (red line)
  - Monitor 320 nm (black line)

- **Flow direction**:
  - Down (with gravity)
  - Up (against gravity)

- **Breakthrough**:
  - Immediate
  - After ~660 ml
  - ~20 mg/g
QuadraPure™ TU cartridge: 25S

Weak Solvent
tetrahydrofuran

Strong Solvent (blue line)
Pd(OAc)$_2$ 1000 ppm in THF

Cartridge
FLASH 25+S

Flowrate
2 ml/min

UV Wavelength
Collection 232 nm (red line)
Monitor 320 nm (black line)

~23 mg/g
# TU cartridges – Pd(OAc)$_2$ in THF

<table>
<thead>
<tr>
<th>Cartridge size</th>
<th>Flow rate</th>
<th>Breakthrough</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Vol. (ml)</strong></td>
<td><strong>Mass QP (g)</strong></td>
</tr>
<tr>
<td>12M</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>12M</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>40S</td>
<td>66</td>
<td>34</td>
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<tr>
<td>40S</td>
<td>66</td>
<td>34</td>
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<td>25S</td>
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<td>13</td>
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<tr>
<td>25S</td>
<td>24</td>
<td>13</td>
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<tr>
<td>40M</td>
<td>132</td>
<td>68</td>
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</tbody>
</table>
Initial Conclusions

- QuadraPure™ TU Fixed bed vs. Batch Capacity for Pd Removal is identical (Pd penetrates to near bottom of column)
- Operating capacity is 20mg Pd/g resin
- Flow rate determined by column bed volume which determines process time

Optimum flow rates (with only integer pump values possible):
- 12M – at 1 ml/min
- 25S – at 2 ml/min
- 40M – at 8 ml/min

- Metal remains in cartridge once scavenged (cartridges flushed with 4 - 10 volumes of fresh solvent after breakthrough – no leaching of Pd)
- Capacity is improved by flowing up vs. down (channelling issues)
QuadraPure™ cartridges

IDA cartridges – 
Cu(acac)$_2$ in DCM

AMPA cartridges – 
FeCl$_3$ in THF
QuadraPure™ cartridges

**IDA cartridges – Cu(acac)$_2$ in DCM ~0.3 mmol/g**

<table>
<thead>
<tr>
<th>Cartridge size</th>
<th>Flow rate</th>
<th>Breakthrough</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Vol. (ml)</strong></td>
<td><strong>Mass QP (g)</strong></td>
</tr>
<tr>
<td>12M</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>25S</td>
<td>24</td>
<td>13</td>
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<tr>
<td>40S</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>40M</td>
<td>132</td>
<td>68</td>
</tr>
</tbody>
</table>

**AMPA cartridges – FeCl$_3$ in THF ~0.2 mmol/g**

<table>
<thead>
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<th>Cartridge size</th>
<th>Flow rate</th>
<th>Breakthrough</th>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td><strong>Vol. (ml)</strong></td>
<td><strong>Mass QP (g)</strong></td>
</tr>
<tr>
<td>12M</td>
<td>12</td>
<td>6</td>
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<tr>
<td>25S</td>
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<tr>
<td>40S</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>40M</td>
<td>132</td>
<td>68</td>
</tr>
</tbody>
</table>
QuadraPure™ Pd process example

15 g scale
250 mg Pd(OAc)$_2$

1.5 eq [B(OH)$_2$] + 1 eq [Br]$_2$OMe

3 mol% Pd(OAc)$_2$/12 mol% PPh$_3$
Dioxane/H$_2$O (10:1) 80°C

89% yield

QuadraPure™ TU cartridge delivers 97% Pd reduction

Reaxa
QuadraPure™ cartridges

process representative, crude reaction outputs:

\[
\begin{align*}
\text{Br}\text{Py} + \text{MeOBrB(OH)}_2 &\xrightleftharpoons{\text{Pd(OAc)}_2, \text{PPh}_3} \text{OMePy} \\
\text{MeOBr} + \text{BrPhCN} &\xrightarrow{\text{Pd(0)/Cu(I)}} \text{MeCNPh} \\
\text{BrPhCN} &\xrightarrow{\text{CuCN}} \text{PhCN}
\end{align*}
\]
Microwave Technology
Microwave Development Work

- Designing range of Micro EnCat™ products specifically for use in microwave reactors
- Developing continuous-flow processes with EnCat™ technology
Microencapsulated Homogeneous Palladium Catalyst Technology

- excellent levels of activity in C-C bond forming reactions
- very low residual metal and ligand levels in product
- minimal waste stream contamination
- easy recovery of catalyst by filtration
- additional ligands not always required
- efficiency and economy gains through simple fast recovery and re-cycling
- mechanically and chemically robust
- high selectivity in transfer hydrogenation reactions
Microencapsulation of Palladium (II) Salts by \textit{in situ} Interfacial Polymerisation

Catalyst in organic solvent with cross-linking isocyanates

\[ \text{Pd(II) salt} \]

\[ \begin{array}{c}
\text{NCO} \\
\text{CH}_2 \\
\text{NCO} \\
\text{CH}_2 \\
\text{NCO}
\end{array} + \text{Oil-in-water emulsion} \]

Water, stabilisers
Microencapsulation of Palladium (II) Salts by \textit{in situ} Interfacial Polymerisation

Catalyst in organic solvent with cross-linking isocyanates

\[
\begin{array}{c}
\text{NCO} \quad \begin{array}{c}
\text{NCO} \\
\text{NCO}
\end{array} \\
\text{NCO}
\end{array}
\]

$+$

Pd(II) salt

Filtered & dried EnCat$^{\text{TM}}$

50-300$\mu$m

Heating initiates polymerisation

water, stabilisers

Oil-in-water emulsion

Reaxa
# Pd EnCat™ Products

<table>
<thead>
<tr>
<th>product</th>
<th>Aldrich cat. no.</th>
<th>Pd content %/w/w</th>
<th>co-encapsulated ligand</th>
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</thead>
<tbody>
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<td>Pd(II) EnCat™ 40</td>
<td>644722</td>
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<td>Pd(II) EnCat™ TPP 30</td>
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<td>(Ph)₃P</td>
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<td>Pd(II) EnCat™ TOTP 30</td>
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<td>(PhMe)₃P</td>
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<td>PPh₂PPh₂</td>
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<td>Pd(0) EnCat™ 30 NP</td>
<td>653667</td>
<td>4.3</td>
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</tr>
</tbody>
</table>
Pd(0) EnCat™ NP30

- Pd particles <2 nm (approx 10 atoms)
- Nanostructure stabilised by polyurea matrix
- Highly active and recyclable H₂ transfer catalyst
- High chemoselectivity
- Non pyrophoric - easy and safe to handle vs. Pd/C
- Very low metal contamination of product
- Easy recovery and recycle of catalyst from process vessel
### Pd(0) EnCat™ NP30

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Time</th>
<th>Yield</th>
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<tbody>
<tr>
<td>48 h</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>95%</td>
<td></td>
</tr>
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<td>68 h</td>
<td>99%</td>
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</tr>
<tr>
<td>1.5 h</td>
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<tr>
<td>18 h</td>
<td>99%</td>
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<tr>
<td>35 min</td>
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</tr>
<tr>
<td>2.5 h</td>
<td>99%</td>
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<tr>
<td>12 min</td>
<td>99%</td>
<td></td>
</tr>
</tbody>
</table>

**EtOAc, Et₃N (20 eq), HCOOH (20 eq), Pd(0) EnCat NP, rt**

**EtOAc, Et₃N (5 eq), HCOOH (5 eq), Pd(0) EnCat NP, MW 120 °C**

SV Ley et al Chem Comm 2003, 678
Pd(0) EnCat™ NP30

Leimgruber-Batcho

Microencapsulated Osmium Tetroxide

Os EnCat™

Os EnCat™
NMO
THF/water 2:1

<table>
<thead>
<tr>
<th>Temp °C</th>
<th>Yield %</th>
<th>Os ppm</th>
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<tbody>
<tr>
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<td>40</td>
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<td>-</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
<td>120</td>
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</table>
Microencapsulated Osmium Tetroxide

MW 80 °C, 20 min
91%
Pd 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

In development:
- nickel
- platinum
- chirals
- your catalyst…?
- Micro EnCat™
Pd(II) EnCat – Suzuki Chemistry

1eq

\[
\begin{align*}
\text{NO}_2 & \quad \text{MeO} \\
\text{MeO} & \quad \text{Br}
\end{align*}
\]

1.3eq

\[
\begin{align*}
\text{B(OH)}_2 & \quad \text{MeO} \\
\text{MeO} & \quad \text{Br}
\end{align*}
\]

\[\text{1eq} + 1.3\text{eq} \quad \xrightarrow{\text{2eq Bu}_4\text{NOAc, MeCN}} \quad \text{Pd-EnCat (5 mol%)} \quad \xrightarrow{\text{MW 150°C, 960 sec}} \quad \text{MeO} \quad \text{MeO} \quad \text{NO}_2
\]

Microwave Synthesis

Filtration & evaporation

Purification (Bond Elut) & analysis
Analysis of Results

- Matrix of 12 boronics x 19 heteroaromatic bromides to give 228 possible products
- 157 products isolated (68% success rate) – no single reaction optimised Average Yield = 37% after purification (range 1% - 75%)
Pd(II) EnCat – Suzuki Chemistry

Optimised conditions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Temperature</th>
<th>Time</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCl-B(OH)₂</td>
<td>140 °C</td>
<td>10 min</td>
<td>&gt;98% conv.</td>
</tr>
<tr>
<td>MeBr-B(OH)₂</td>
<td>120 °C</td>
<td>10 min</td>
<td>&gt;98% conv.</td>
</tr>
<tr>
<td>MeI-B(OH)₂</td>
<td>120 °C</td>
<td>6 min</td>
<td>&gt;98% conv.</td>
</tr>
<tr>
<td>MeNO₂-B(OH)₂</td>
<td>140 °C</td>
<td>10 min</td>
<td>&gt;98% conv.</td>
</tr>
<tr>
<td></td>
<td>120 °C</td>
<td>10 min</td>
<td>&gt;98% conv.</td>
</tr>
<tr>
<td></td>
<td>120 °C</td>
<td>6 min</td>
<td>&gt;98% conv.</td>
</tr>
</tbody>
</table>

0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu₄NOAc, 0.025 mmol Pd EnCat™, EtOH, microwave irradiation

Ley & Baxendale - Cambridge
Pd(II) EnCat – Suzuki Chemistry

374 reaction library

193
>80% yield
>90% purity

Ley & Baxendale - Cambridge
continuous-flow microwave reactor

- heating cycles: 50 W for 30 s then cooling 18 s
- 0.1 ml/min flow rate, 0.01 – 0.07 M reagent mix
- 40 bar back flow regulator
- product obtained without need for purification
## continuous-flow vs batch

<table>
<thead>
<tr>
<th>Boronic Acid</th>
<th>Halide</th>
<th>Batch Yield</th>
<th>Flow Yield</th>
<th>Boronic Acid</th>
<th>Halide</th>
<th>Batch Yield</th>
<th>Flow Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(OH)₂</td>
<td>OTf</td>
<td>82%</td>
<td>&gt;98%</td>
<td>B(OH)₂</td>
<td>OTf</td>
<td>26%</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>B(OH)₂</td>
<td>Br</td>
<td>64%</td>
<td>&gt;98%</td>
<td>B(OH)₂</td>
<td>Br</td>
<td>23%</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>B(OH)₂</td>
<td>NO₂</td>
<td>54%</td>
<td>92%</td>
<td>B(OH)₂</td>
<td>NO₂</td>
<td>16%</td>
<td>91%</td>
</tr>
<tr>
<td>B(OH)₂</td>
<td>Br</td>
<td>40%</td>
<td>94%</td>
<td>B(OH)₂</td>
<td>Br</td>
<td>5%</td>
<td>82%</td>
</tr>
</tbody>
</table>

Performed sequentially over the same catalyst bed (ethanol wash between reactions)

Little variation in yield between methods generally ~90%
## continuous-flow: improved purity

<table>
<thead>
<tr>
<th>boronic acid</th>
<th>halide</th>
<th>purity</th>
<th>batch</th>
<th>batch + cooling</th>
<th>flow</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="B(OH)₂" /></td>
<td><img src="image2.png" alt="Br" /></td>
<td>42%</td>
<td>86%</td>
<td>&gt;98%</td>
<td></td>
</tr>
<tr>
<td><img src="image3.png" alt="B(OH)₂" /></td>
<td><img src="image2.png" alt="Br" /></td>
<td>48%</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
<td></td>
</tr>
<tr>
<td><img src="image3.png" alt="B(OH)₂" /></td>
<td><img src="image2.png" alt="Br" /></td>
<td>32%</td>
<td>96%</td>
<td>&gt;98%</td>
<td></td>
</tr>
</tbody>
</table>

- flow rate 0.1 ml/min; pulsed heating at 50 W for 30 s then 18 s cooling

0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu₄NOAc, 0.025 mmol Pd EnCat™, EtOH, microwave irradiation
purity measured by LCMS and ¹H NMR.
continuous-flow microwave reactor

- flow reactor run continuously and conversion monitored
- catalyst loading corresponds to ~0.2 mol%

1 eq. halide, 1 eq. boronic acid, 2 eq. Bu$_4$NOAc, 0.2 M in EtOH
Pd EnCat™, microwave irradiation; flow rate 0.2 ml/min

172 mg Pd EnCat™
28 h
7.53 g product

182 mg Pd EnCat™
34 h
9.34 g product
Approaches to Micro EnCat

Requirements:
• Low levels of Pd and P contamination - < 5 ppm and < 20 ppm
• Ease of handling and recovery of catalyst
• Use in fixed bed/flow systems

- Enhanced matrix stability
  • Increased crosslink density
  • Alternative isocyanates (possibly mixed)
- Enhanced metal binding
  • Modification of matrix
  • Several approaches considered

polyTPP Pd EnCat
### Micro EnCat™

- Efficient encapsulation of Pd and phosphine metal (low losses)
- Excellent catalytic activity in standard Suzuki reaction
- Lower levels of Pd contamination in crude product than other P catalyst
- Bound-in metal demonstrated by low Pd levels in treated catalyst

<table>
<thead>
<tr>
<th></th>
<th>Micro EnCat</th>
<th>Pd EnCat TPP30</th>
<th>Pd EnCat 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorp. Of Pd (OAc)₂ %</td>
<td>99</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>Incorp. Of P ligand %</td>
<td>99</td>
<td>96</td>
<td>-</td>
</tr>
</tbody>
</table>

- Pd content: 4.3-4.9 w/w%
- Pd loading: 0.40-0.46 mmol/g
- P loading: 0.18-0.22 mmol/g
- Particle size: 50-310 μm (185 av.)
Micro EnCat™

<table>
<thead>
<tr>
<th></th>
<th>Pd EnCat™ PolyTPP30</th>
<th>Pd EnCat™ TPP30</th>
<th>Pd EnCat™ 30 + TPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Yield (%)</td>
<td>99</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>Pd in crude product (ppm)</td>
<td>7</td>
<td>36</td>
<td>73</td>
</tr>
<tr>
<td>P in crude product (ppm)</td>
<td>18</td>
<td>58</td>
<td>430</td>
</tr>
</tbody>
</table>
Micro EnCat™

Pd(OAc)$_2$, 5 mol%  
140 °C, 25 min, 61%

Micro EnCat, 5 mol%  
140 °C, 25 min, 92%
info@reaxa.com
selective microwave heating of catalysts

- heterogeneous oxidation catalyst (Magtrieve™, CrO$_2$) was heated to 140 °C in a toluene suspension
- uniform and rapid heating (360 °C in 2 min on dry solid)

selective microwave heating of catalysts

A

magnetron
applicator
pump

catalyst bed

B

Synthewave 402

conventional heating

C

vessel

Chemat & Esveld, www.mdpi.net/ecsoc-5/e0017/e0017.htm
selective microwave heating of catalysts

reaction is a simple esterification, with a granulated ceramic catalyst

calculated: 9 K difference

T_{cat} > T_{bulk}

T_{cat} = T_{bulk}

Chemat & Esveld, www.mdpi.net/ecsoc-5/e0017/e0017.htm

simultaneous cooling

power profile for 120 °C

50 W 15 min

50 W + cooling 15 min

temperature of Pd catalyst inside beads

\[ T_{\text{cat}} \gg T_{\text{bulk}} \]
simultaneous cooling

0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu₄NOAc, 0.025 mmol Pd EnCat™, EtOH, microwave irradiation
purity measured by LCMS and ¹H NMR.

120 °C, 10 min
50 W, 15 min with cooling
(max. temp. 76 °C)

purity 48%
purity >98%

120 °C, 10 min
50 W, 15 min with cooling
(max. temp. 76 °C)

purity ~15%
purity >98%
simultaneous cooling

$$\text{ArB(OH)}_2 + \begin{array}{c}
\text{Ph} \\
\text{3,4,5-(MeO)}_3\text{Ph} \\
\text{4-(F}_3\text{CO)}\text{Ph} \\
\text{3-O}_2\text{NPh} \\
\text{2-benzofuranyl} \\
\text{3-quinolinyl} \\
\text{2-thiophenyl}
\end{array} \begin{array}{c}
\overset{\text{Bu}_4\text{NOAc, EtOH}}{\longrightarrow} \\
\text{ArH}
\end{array}$$

<table>
<thead>
<tr>
<th>Ar</th>
<th>purity</th>
<th>purity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>120 °C</td>
<td>50 W with cooling</td>
</tr>
<tr>
<td>Ph</td>
<td>46%</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>3,4,5-(MeO)$_3$Ph</td>
<td>&gt;10%</td>
<td>88%</td>
</tr>
<tr>
<td>4-(F$_3$CO)Ph</td>
<td>32%</td>
<td>86%</td>
</tr>
<tr>
<td>3-O$_2$NPh</td>
<td>31%</td>
<td>94%</td>
</tr>
<tr>
<td>2-benzofuranyl</td>
<td>41%</td>
<td>97%</td>
</tr>
<tr>
<td>3-quinolinyl</td>
<td>&gt;10%</td>
<td>81%</td>
</tr>
<tr>
<td>2-thiophenyl</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

0.5 mmol halide, 0.5 mmol boronic acid, 1.0 mmol Bu$_4$NOAc, 0.025 mmol Pd EnCat™, EtOH, microwave irradiation purity measured by LCMS and $^1$H NMR.