
# Recycling Precious Metals Using Functionalised Silica Scavengers and Catalysts

**RSC Symposium**
**The Sustainability Challenge**
**19th June 2008**

**CPhI Innovation Award Winner**

**David Astles**
**CEO, PhosphonicS**

# Content summary

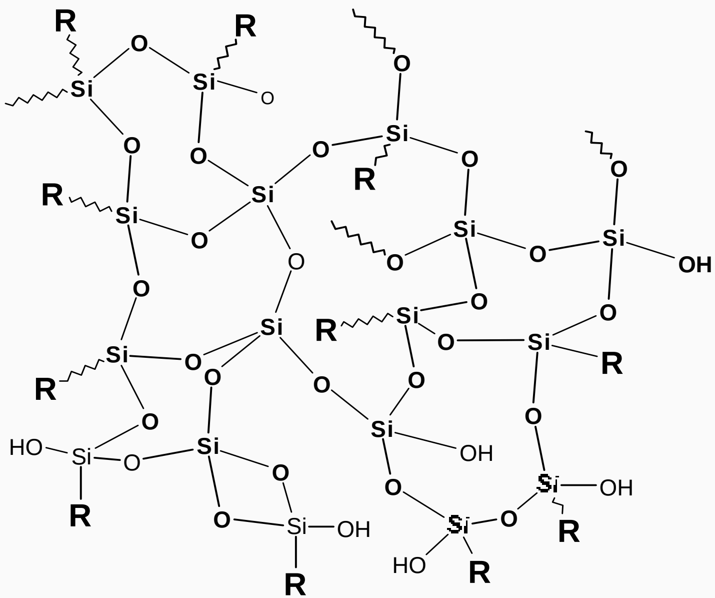
- PhosphonicS™ overview
- Key industry issue: “the lost metal”
- The challenge for metal catalysis
- Solutions based on PhosphonicS™ materials
  - Pharmaceutical Purification
  - Precious Metal recovery
  - Heterogeneous Catalysis

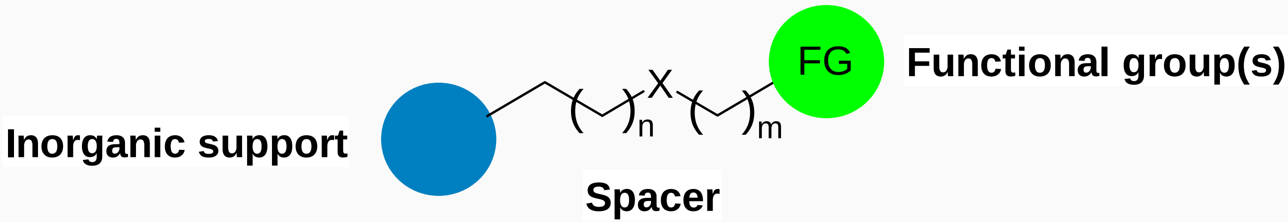
# PhosphonicS™ Overview

- Established 2003 to commercialise novel platform technology
- Expertise in ligand immobilisation onto inorganic supports and design of functionalised solid materials
- Located at Milton Science Park, Oxford, UK
- Portfolio of outstanding metal removal products, organic purification products and heterogeneous catalysts
- Screening, design and outsourcing services
- Assured supply from test kits to large bulk scale

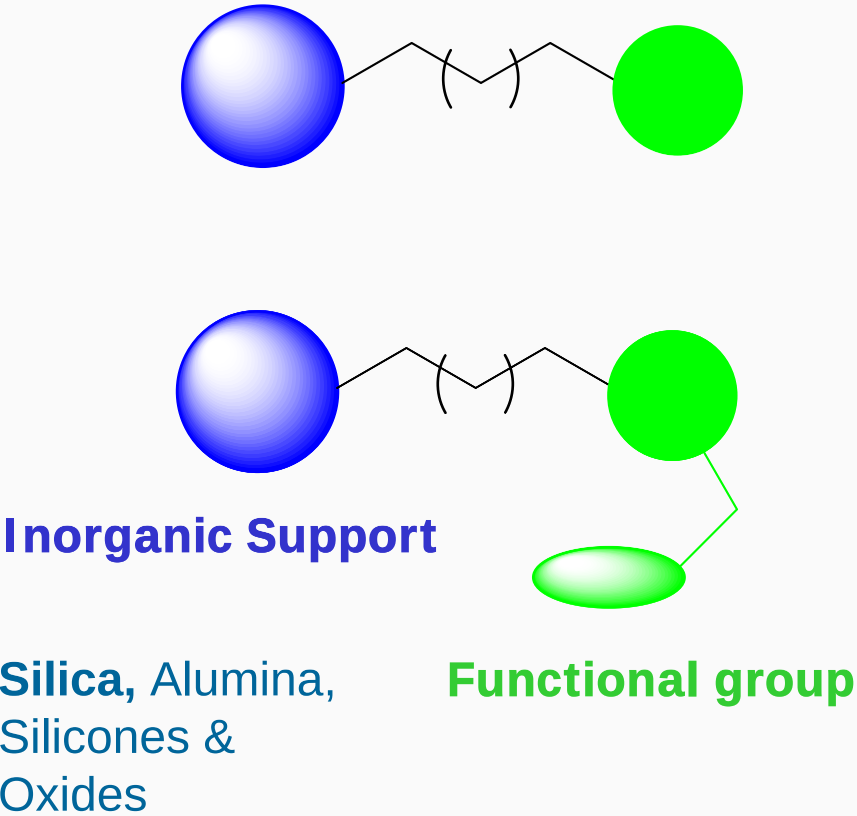
# PhosphonicS™ Technology & Materials

## Novel PhosphonicS™ process to readily attach high performance ligands to surface of inorganic support





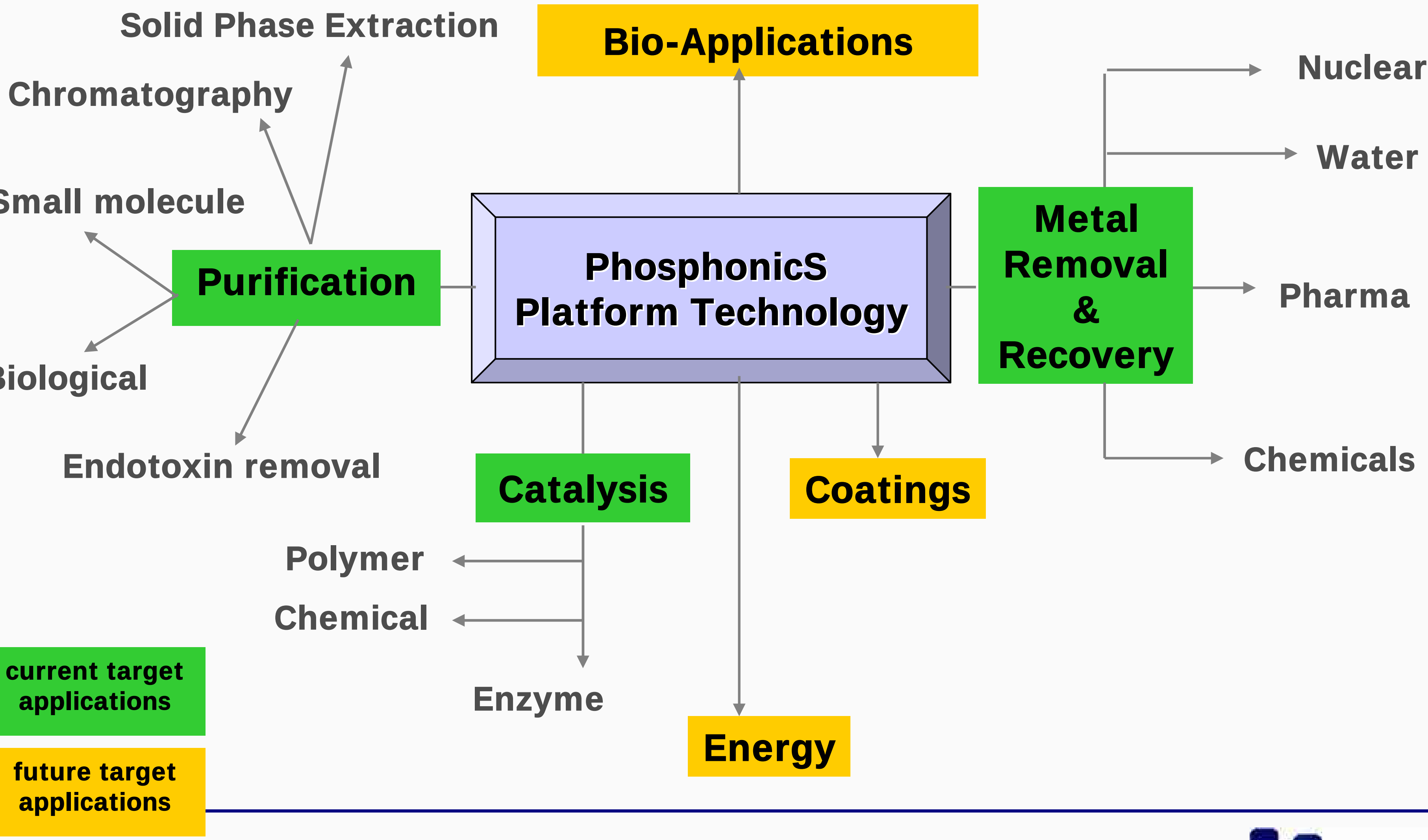
# Opens up a world of novel materials




- Phosphonic acid
- Sulfonic acid
- Phosphates
- Amides
- Carboxylic acids
- Esters
- Aldehydes
- Ketones
- Alcohols
- Amines
- Thiols
- Sulfides
- Sulfones
- Amino acids
- Phosphines
- Heterocyclic amines
- Nitriles
- Isocyanates
- Sugars
- Enzymes
- Polyamine
- Poly alcohols
- Amino Alcohols
- Chiral compounds

## designed to solve high value problems

# Applications of Functionalised Solid Materials



# Key industry issue – “the lost metal”

- Catalysts widely used in pharmaceutical and fine chemical processes, petrochemical and refining industry
- Broad range of precious and base metal catalysts used: homogeneous, heterogeneous, chiral, supported homogeneous
- Provide efficient and clean routes to high value products
- Objectives are maximum conversion and high selectivity ...

...but where does the metal go?

# The product

## Current Acceptable Metal Limits in Active Pharmaceutical Ingredients (APIs)

| METAL | Concentration (PPM) | |
|---|---|---|
| | ORAL | PARENTERAL |
| Pt, Pd, Ir, Rh, Ru, Os | 5 | 0.5 |
| Mo, V, Ni, Cr | 10 | 1 |
| Cu, Mn | 15 | 1.5 |
| Zn, Fe | 20 | 2 |
| SOURCE: European Agency for the Evaluation of Medicinal Products | | |

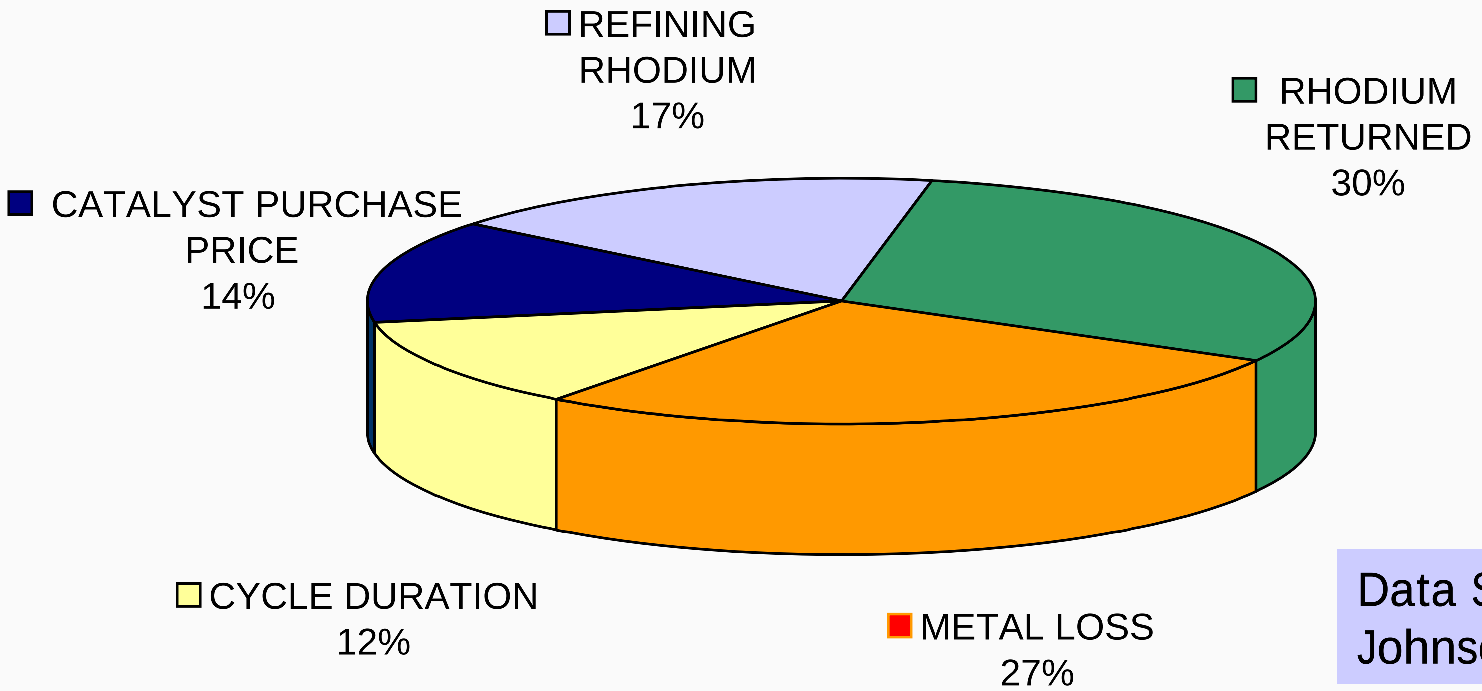
- **Metal must be removed from API product and intermediates**
- **Toxicity concerns - permitted levels will continue to decline**
- **Residual metal – problems in work-up & later reaction steps**

# Independent market survey: scale of metal removal problem from APIs

- 50% of "small molecule" drugs in development use metal catalysed reactions
- Survey suggests up to 40% of these developments has a metal removal problem "not readily resolved"
- Existing techniques are not able to effectively deal with growing problems

# The waste stream

***Example: Catalyst Cost Contribution: 5% Rh on C ; 6% metal loss***




Data Source: Johnson Matthey

- **Significant effect on economics of metal loss**
- **At a time of rising metal prices and increased demand**
- **Environmental and economic need to recover valuable asset**

# The effluent stream

- Metals somehow find a way to effluent plant
- Once present, a major challenge to remove metals from complex, high volume streams
- Regulatory requirements to be met
- Significant costs in waste treatment on/off-site
- Includes PGMs, Cr, Cu, Fe, Ni, Hg, As ....

- Environmental pressure – does the industry have control of its production processes?
- Increasing cost of regulatory compliance
- Industry wishes to demonstrate enhanced CSR profile

# The challenge for metal catalysis

**In summary:**

- **The (uncontrolled) loss of valuable/toxic metals**
- **The problems of removal and capture from product, waste and effluent streams**
- **The environmental, economic and societal consequences**

**The response:**

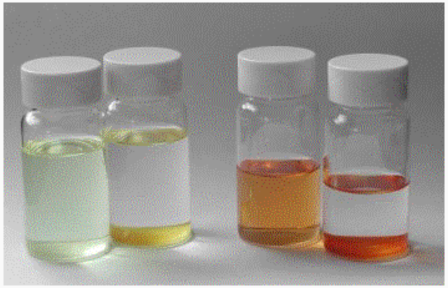
- **A need for improved catalysts and processes**
- **Better methods to capture and recover the metal**
- **Continued technology innovation required**

# PhosphonicS contribution

**Product purification**

↓

**Novel metal scavengers**



**Waste & Effluent**

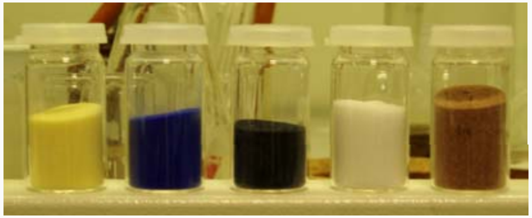
↓

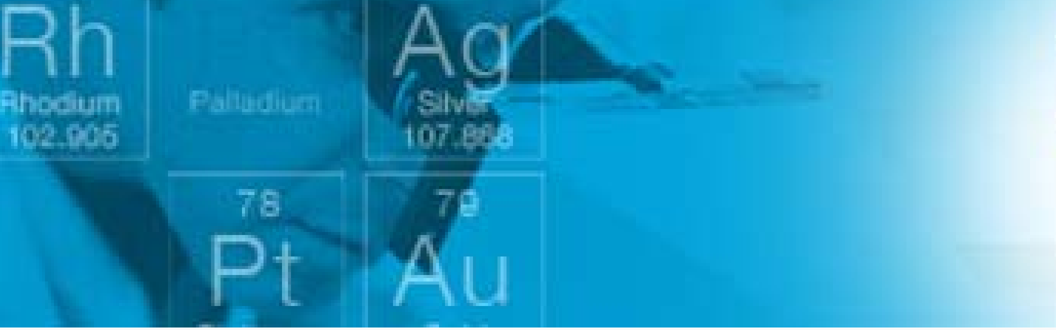
**Liquid Metal Recovery**

**Metal Immobilisation**

↓

**Heterogeneous Catalysts**






# PhosphonicS™ Metal Scavengers

***Meeting the need to reduce residual metal levels in pharmaceuticals and fine chemicals***

# Removing Metals from APIs : The Issues

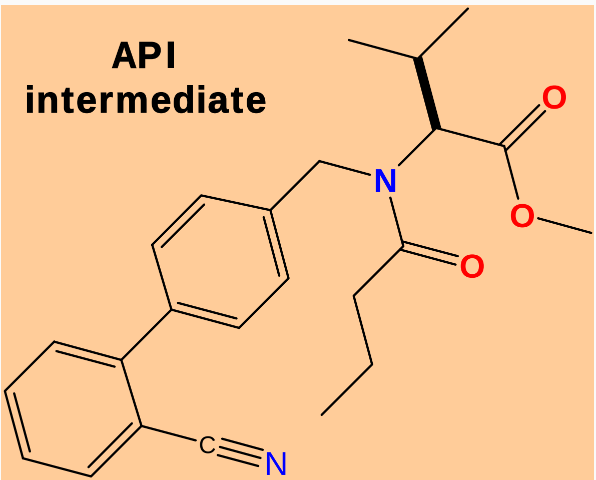
- Need for a rapid, reliable, one-stop metal removal technology for all APIs
- Minimizing loss of API within environment of process intensification
- Regulatory assurance around all materials used in late synthetic steps
- Finding a solution which will scale economically from lab, through process, to plant

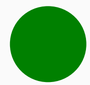
# Adsorbents for Metal Removal from APIs

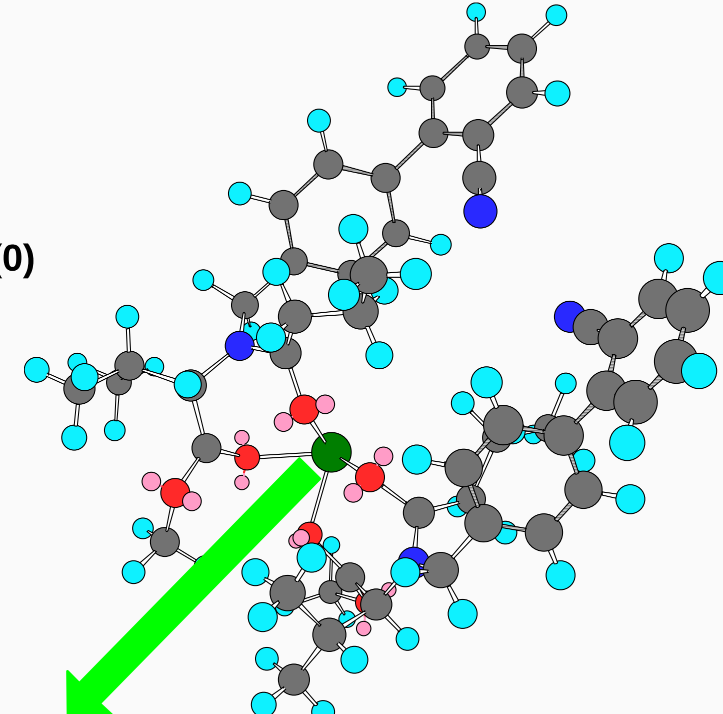
| Adsorbent | Performance | API Recovery | Purity | Practical Issues | Material Cost |
|---|---|---|---|---|---|
| **Charcoal** | ✓<br>Highly variable | ✓<br>Loss 10 - 20% | ✓✓ | ✓<br>Vessel contamination<br>Multiple treatments<br>High Temps | ✓✓✓<br>.. But large quantities consumed |
| **MP-TMT** | ✓✓<br>Better at lower pH | ✓✓✓ | ✓✓✓ | ✓✓<br>Time dependence | ✓ |
| **PhosphonicS™ Metal Scavengers - Silicas** | ✓✓✓<br>OPRD, **2007**, *11*, 406 | ✓✓✓<br>Loss typically ~1% | ✓✓✓<br>ROI<0.05wt% | ✓✓✓<br>Rapid kinetics<br>Lower Temps required | ✓✓<br>Scalable economics |
| **Standard Silicas** | ✓✓<br>Limited functionality | ✓✓ | ✓ | ✓✓✓ | ✓ |
| **Grafted Fibres** | ✓ | ✓✓✓ | ✓✓ | ✓✓<br>High Temps req'd | ✓✓ |
| **PS-Resins** | ✓ | ✓✓ | ✓ | ✓<br>Swelling<br>Solvent compatible? | ✓ - ✓✓<br>.. Depends on grade/supplier |

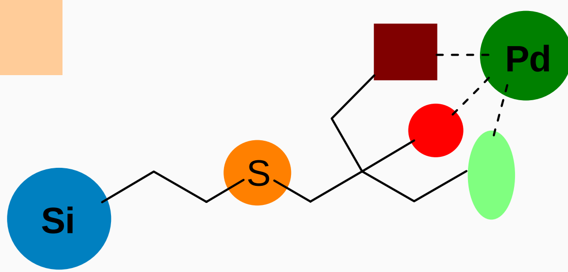
# The Challenge – Winning the Tug of War

**Multiple Binding Sites for Pd(II) and Pd(0)**




 = Pd (II) or Pd(0)

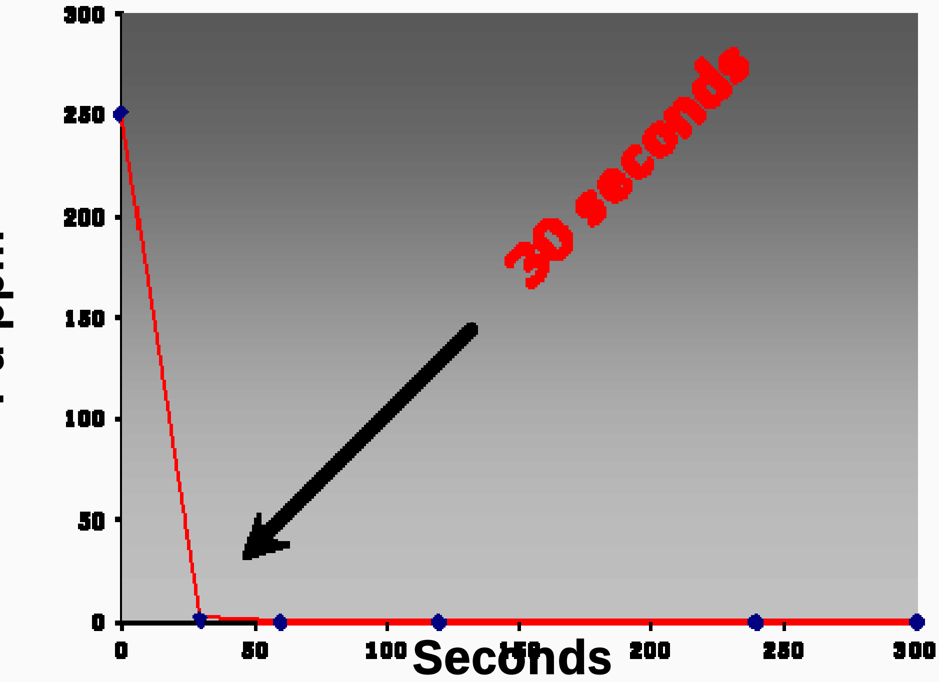





**Multifunctional Metal Scavengers <u>designed</u> to compete and remove the metal from the API binding site**

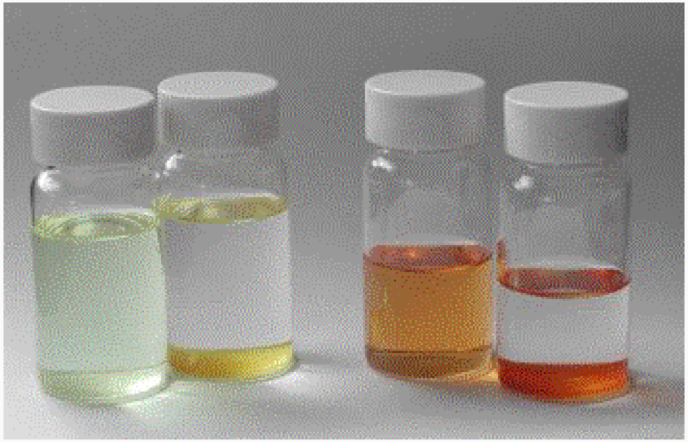
# PhosphonicS™ scavengers:
# fast removal of precious metal from solution

**Pd Scavenging**




Palladium chloride bis triphenyl phosphine in solution

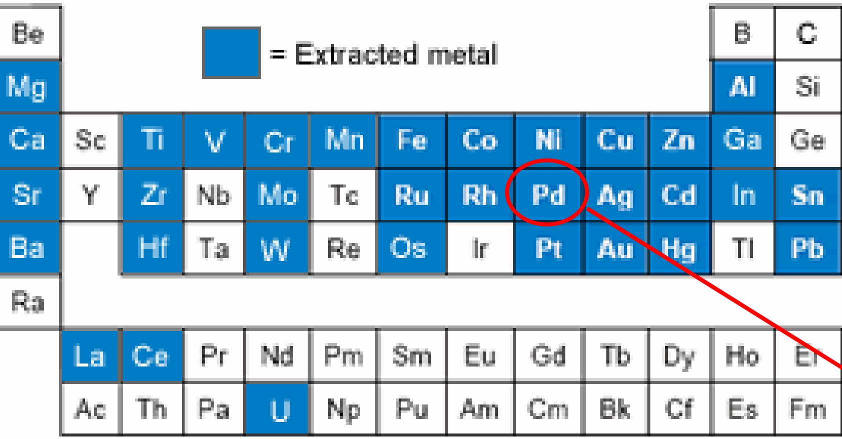
**Pd (II) complex** **Pd (0) complex**



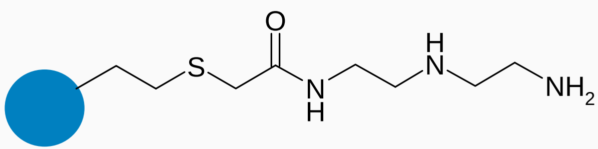
- Metals removed to below 1 ppm in less than 30 seconds !
- One scavenger removing both Pd(II) and Pd(0)

# Broad Coverage of Problem Metals

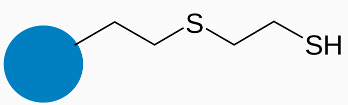
**Full range of PhosphonicS™ Metal Scavengers designed to remove range of metals from highly functionalised substrates**




- **Leading Palladium removal products**



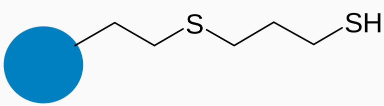

**STA3**



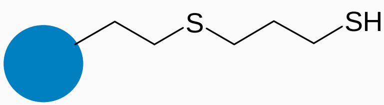

**SEM26**

**Used at full process scale**

**Available ex stock**




**SPM32 (60 A Pore size)**




**SPM36f (90 A Pore size)**

# PhosphonicS™ Functionalised Silicas

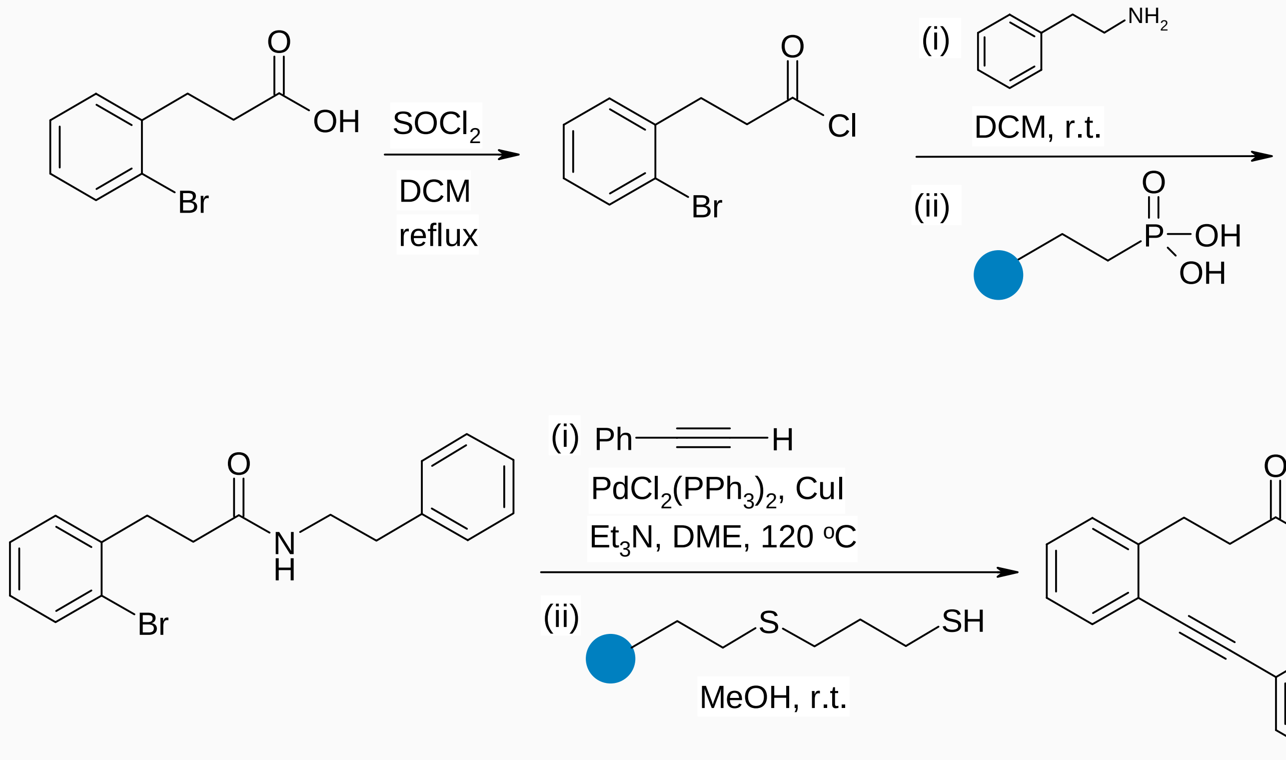
- **Performance** : extremely high metal affinity across diverse range of APIs, with very high API recovery
- **High purity** : strictly no added impurities
- **Track record** : use on pilot and production scale by large pharmaceutical and fine chemical clients
- **Speed** : the route to a quick, first time solution
- **Simple, scalable, cost-effective** processes

# Pharmaceutical Syntheses involving challenging Pd Removals

*Org. Process Res. Dev.*, 2007, *11*, 406

# Sonogashira Reaction

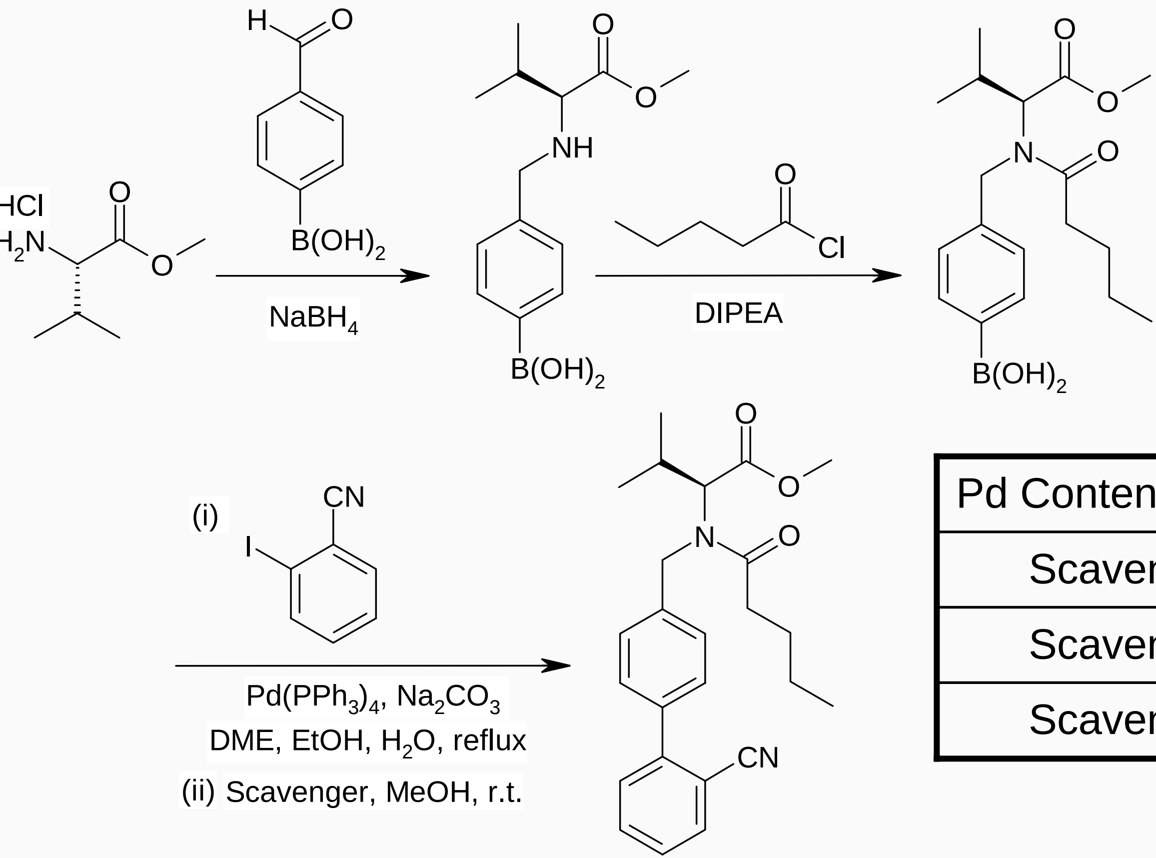
- Model substrate based on a calcium entry blocker
- Known to possess strong ability for chelation of palladium
- Late stage Sonogashira reaction caused insurmountable Pd removal problems, necessitating reorganisation of the synthesis



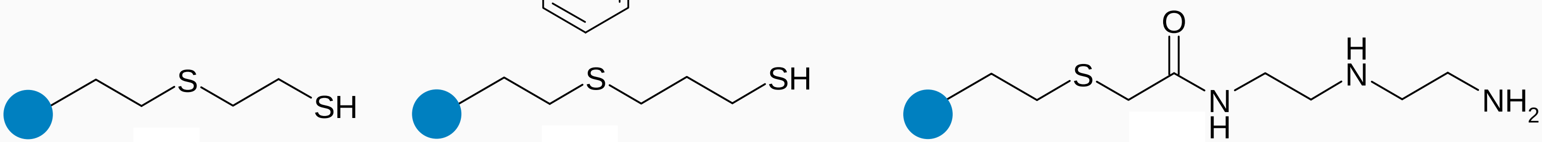

| Scavenging | Before | After |
| --- | --- | --- |
| Pd Content/ppm | **700** | **5** |

# Suzuki Reaction

- Valsartan is a potent, orally active angiotensin II antagonist
- Potential route into analogues employs a Suzuki coupling




| Pd Content/ppm | Before | After |
|---|---|---|
| Scavenger **1** | **2100** | **1.6** |
| Scavenger **2** | **2100** | **<1** |
| Scavenger **3** | **2100** | **<1** |




**1** **2** **3**

# Scalable Formats

- PhosphonicS™ materials are normally applied:

- in powder (filtration) or syringe formats for small scale applications

- in powder, pre-packed cartridges (Metal SPE) or in packed vessels for process scale applications

- Cartridges developed to fit existing standard filter housings (pilot to manufacturing scale)



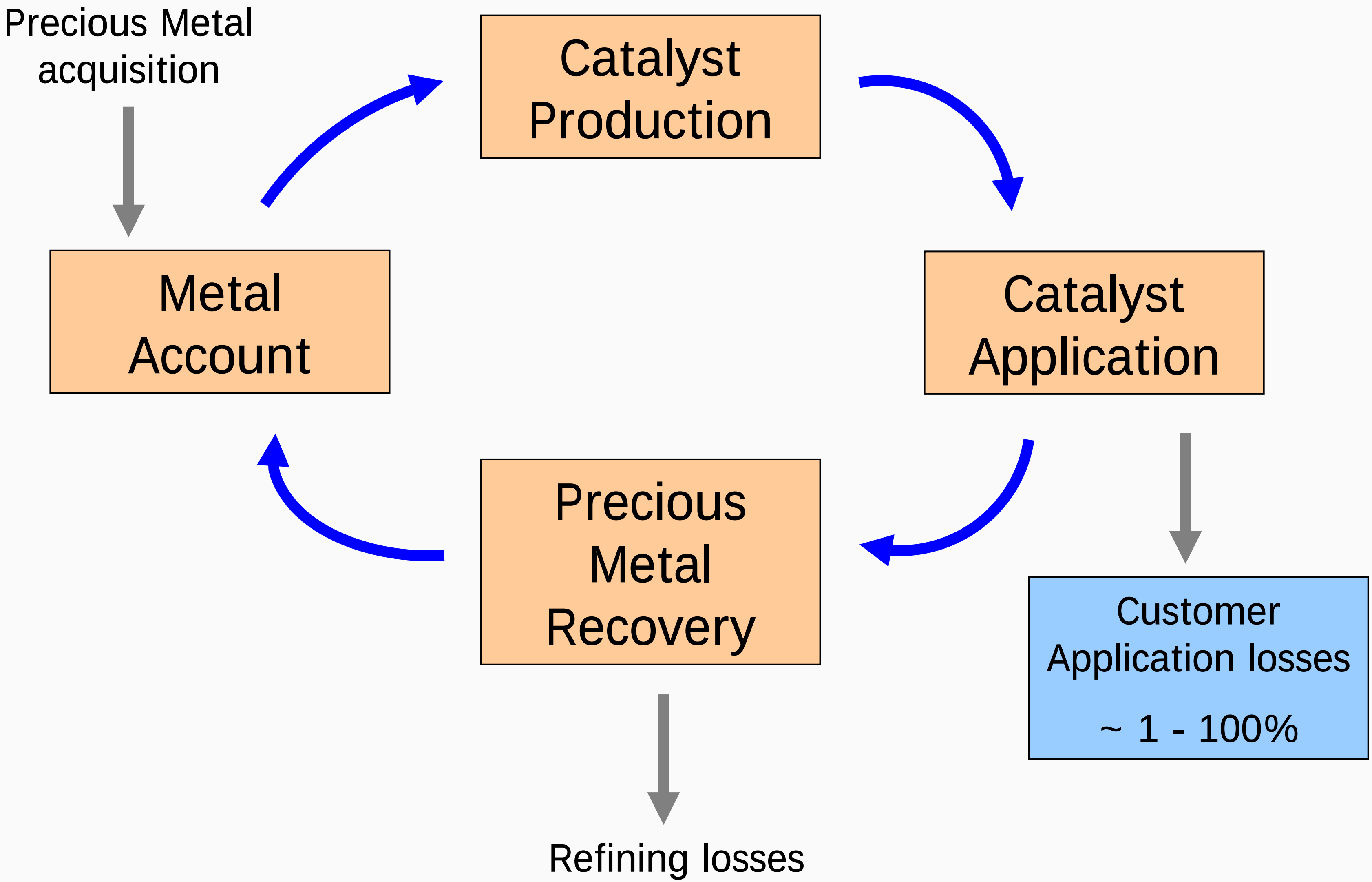
# PhosphonicS$^{TM}$ Liquid Metal Recovery

***Extracting high value precious metals from waste streams***

# Liquid Metal Recovery - Background

- Precious metals (PM): wide range of applications in catalysts, electrochemicals, fuel cells, electronics ...
- PM recovery is essential for process economics
- Recovery of PM from solid wastes is well established
- Recovery of PMs from liquid wastes and process streams presents a technical challenge
- Conventional methods of recovery can be ineffective
  - Dilute solutions
  - Highly acidic environment
  - Organic / aggressive solvents

# Catalysts: Precious Metal Recovery Cycle



# Drivers – economic and environmental

- Economic need to remove these metals from high volume site effluent/waste streams streams
- Often an environmental or regulatory requirement
- Transport of liquid streams for metal recovery can be restricted or impossible
- Solutions containing low levels of PMs may not be cost effective to transport and treat
- Client confidentiality

# What is PhosphonicS™ Liquid Metal Recovery?

- Specially designed portfolio of cost-competitive metal scavengers
- Broad spectrum activity across range of precious metals
- Maximum metal capacity
- Designed for high volume flow environments
- Sized for easy packing and handling
- Easily processed by standard metal refining processes

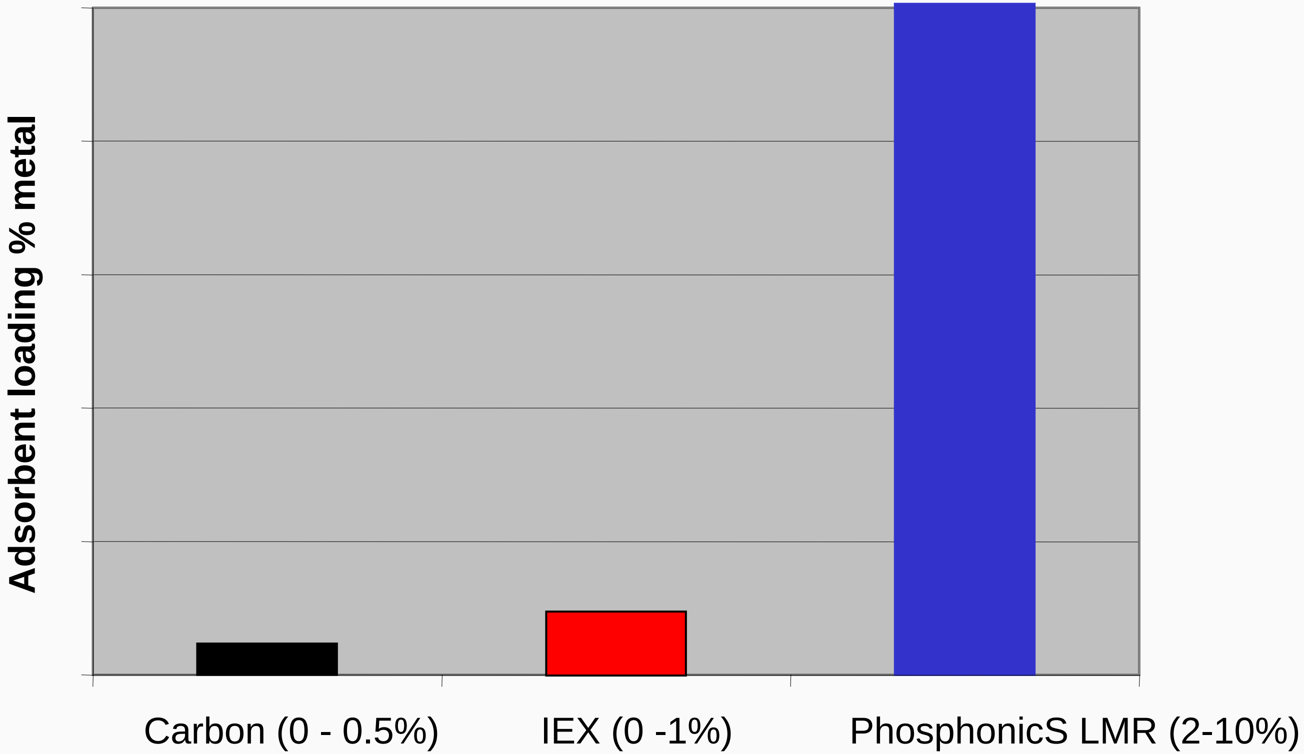
# How are they applied?

- Powder, cartridge formats or bag filters for **smaller, batch** applications
- Multi cartridge, bag filter or fixed bed for **larger, process scale** applications

# Operational Advantages

- **High Affinity** for all common precious metals in different oxidation states.
- **Fast acting** - highly active at ambient temperatures; scavenging accelerated at elevated temperature
- Effective in **dilute** and **concentrated** solutions
- **High selectivity** for the target metal
- **Broad solvent** and **pH compatibility,** in **organic** <u>and</u> **aqueous** systems
- **Excellent stability** - thermal, physical, chemical, mechanical
- **Wide operating** parameters
- Used in variety of **engineered formats** (column, cartridge etc)
- Simple **Metal Recycling** – efficient solid or liquid recovery

# Metal Loading & Economics

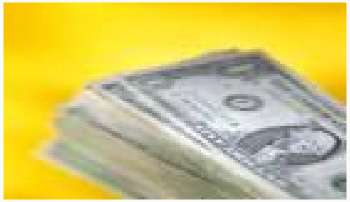



Loading capacity: 20-100 g PM adsorbed per kg silica

Economics depend on objectives, metal, concentration, treat rate, metal recovery process

Total metal recovery achieved usually exceeds conventional methods – "lost" metal captured

# Benefits



- Recover **Lost Metal Value** for **Minimal Capital Investment**
- Minimise or Eliminate **Waste Disposal Costs**
- Meet **Discharge Targets** for heavy metals
- Enhance **Corporate Social and Environmental Responsibility Policy**

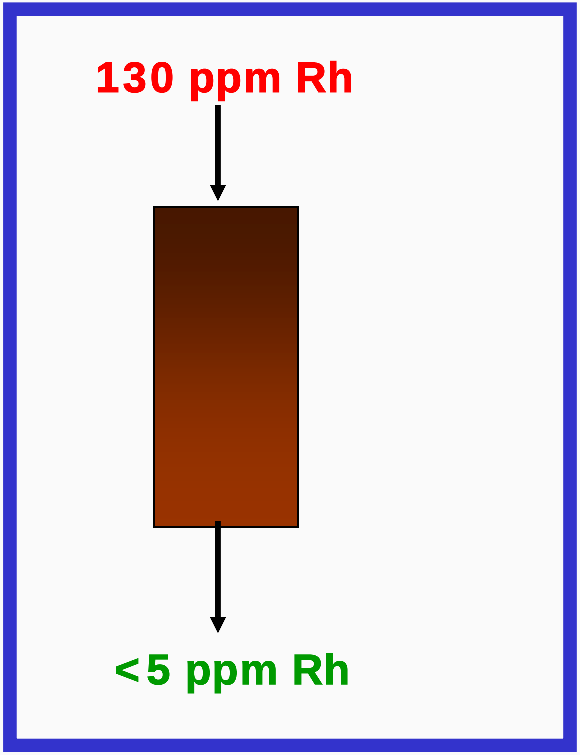
# Application Examples

Current industrial applications include:

- ruthenium removal from electrochemical processing solutions
- rhodium removal from low concentration catalyst recycle streams
- selective gold removal from base metal streams
- platinum removal from reactive chemical process streams
- palladium recovery from chemical catalyst stream

# Rhodium recovery: Case Study

***Recovery of rhodium from an Oxo catalyst process stream***




- **Multi tonne scale**
- **Simple low-cost column design**
- **> 96% metal capture and > 3 w/w% loading achieved over just 1-2 cycles**
- **Fast capex payback**

# Platinum recovery: Case Study

***Recovery of platinum from reactive halide stream***

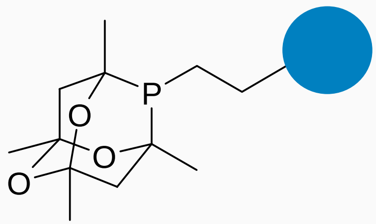
- **Multi mt – production scale**
- **High viscosity stream**
- **Reduction from ~ 50ppm to < 5ppm**
- **> 90% metal capture**
- **Highly selective mode of action**
- **Unique solution**
- **Potential savings > $5m**

# Heterogeneous Catalysis

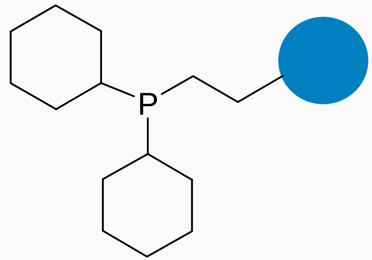
- **Using an Immobilised Metal to avoid metal leaching**
- **Using a solid phase to make catalysis easier and greener**

Pd-Catalysed Cross-couplings, Metal-catalysed oxidations and Acid-catalysed reactions

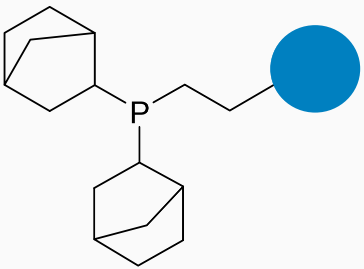
# Heterogeneous Phosphines & Metal Catalysts



**PAr**

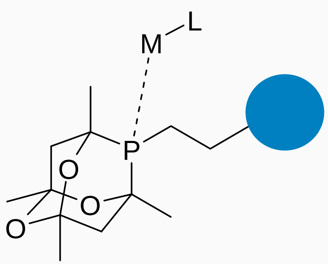


**DCP**

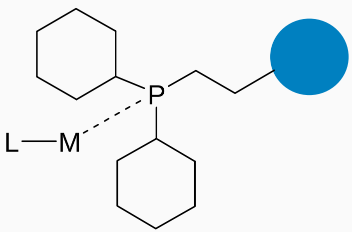


**NP**

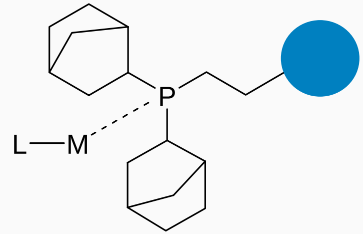
- Range of specialised phosphine ligands immobilised onto silica
- Conversion to variety of heterogeneous Pd and Pt catalysts achieved



**PAPd1r** ML = $PdCl_2PPh_3$
**PAPd2r** ML = Pd(dba)



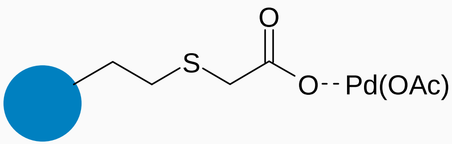
**DCPPd4** ML = $PdCl_2(CH_3CN)$
**DCPPd3** ML = $PdCl_2(C_6H_5CN)$
**DCPPt4** ML = $PtCl_2(CH_3CN)$



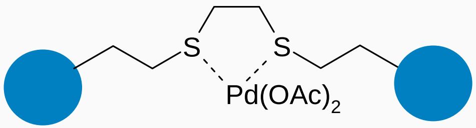
**NPPd4** ML = $PdCl_2(CH_3CN)$
**NPPd3** ML = $PdCl_2(C_6H_5CN)$
**NPPt4** ML = $PtCl_2(CH_3CN)$

- Offer clean cross-coupling reactions and catalyst recycling
- Particle size, pore diameter and metal loading as required for application

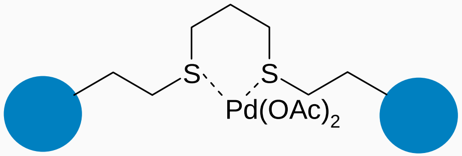
# Heterogeneous Pd Catalysts



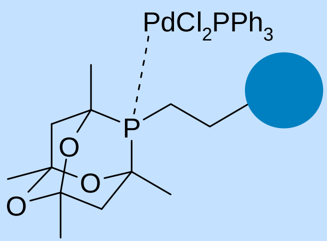

**SCRPd**



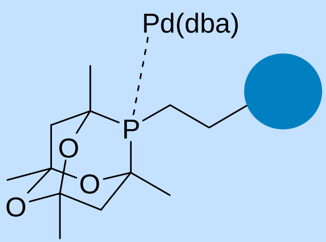

**SEM2Pd**




**SPM3Pd**




**PAPd1r**

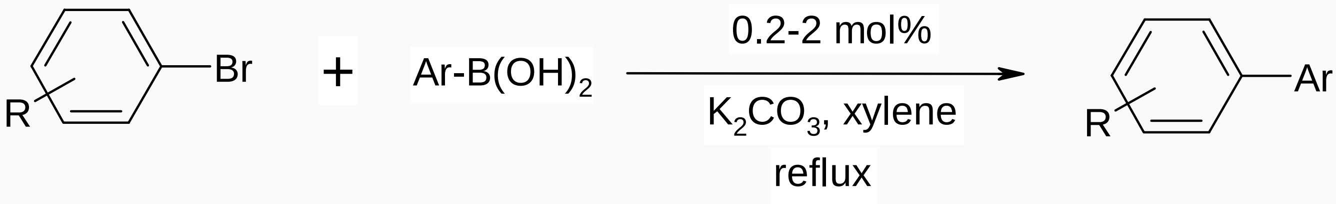


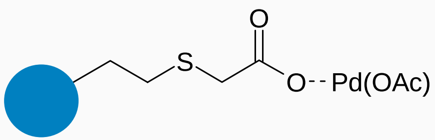

**PAPd2r**

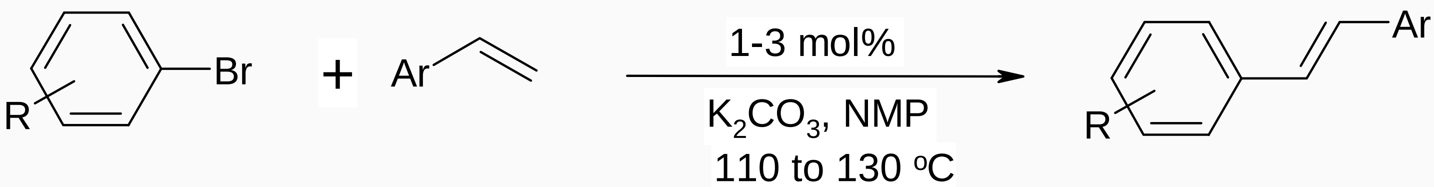
- Palladium loading : 0.01 to 0.4 mmol/g
- Particle Size : 60-200 microns
- Pore Diameter : 60Å (SCRPd, SEM2Pd, SPM3Pd); 110Å (PAPd1r, PAPd2r)
- Variants : $PdCl_2$, $PdCl_2(CH_3CN)$, $PdCl_2(C_6H_5CN)$
- Used for variety of common cross-coupling reactions in **batch** and **flow**

A. C. Sullivan *et al*., *J. Mol. Cat. A: Chem*., **2007**, *273*, 298

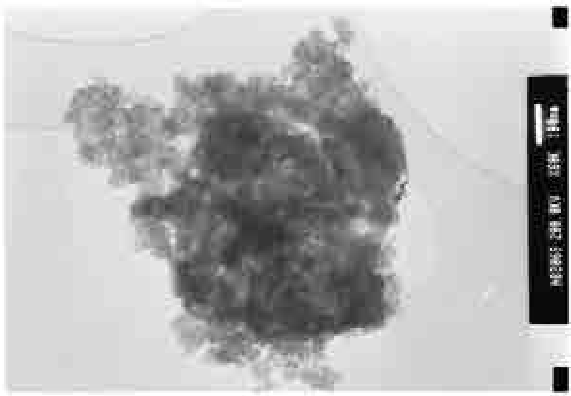
# Suzuki & Heck Reactions



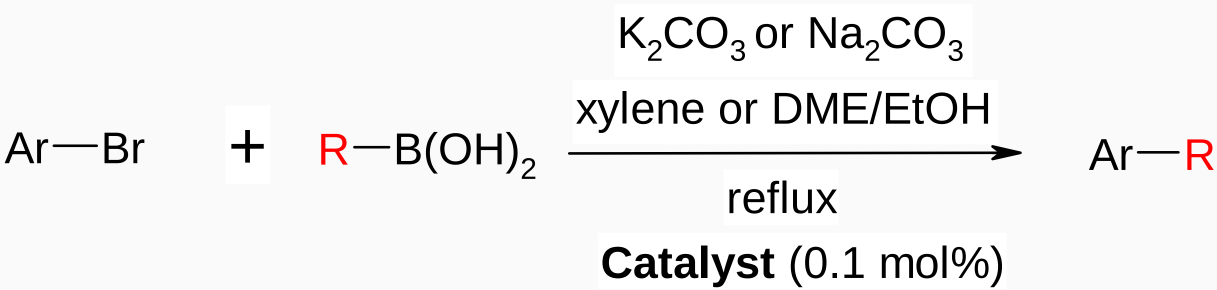

R = H, Me, OMe, Cl



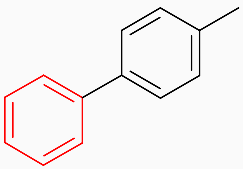
- Range of substrates, yields >93%
- 5 Recycles without any apparent loss of activity
- No apparent Pd black formation
- No apparent leaching – based on hot filtration test
- Surface analysis (EDAX) indicates Pd surface unchanged after reaction

A. C. Sullivan *et al*., *J. Mol. Cat. A: Chem*., **2007**, *273*, 298

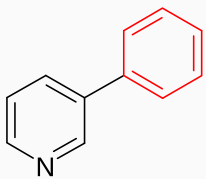
# Suzuki Reactions : Phosphaadamantane Catalysts



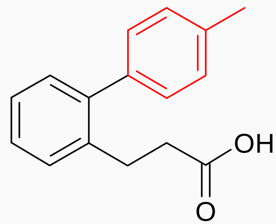

- Representative reaction products - catalyst, conversion (recycles)



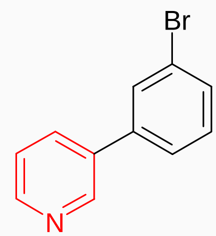
**PAPd1r**; 91%
(3 recycles 92-95%)*



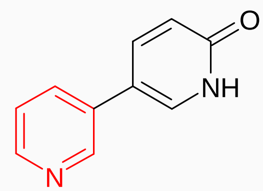

**PAPd2r**; 99%



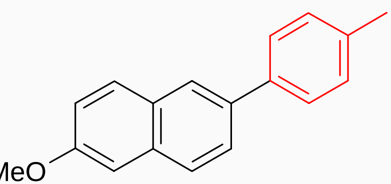

**PAPd2r**; 95%
(4 recycles 95-99%)



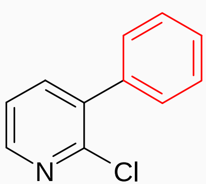

**PAPd1r**; 94%*
***Aryl I selective over Br***



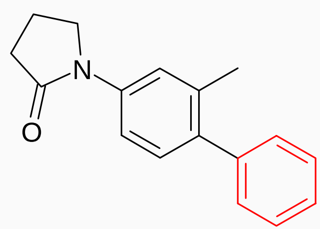

**PAPd1r**; 85%*



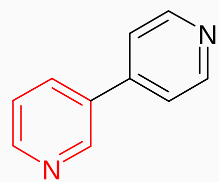

**PAPd1r**; 87%



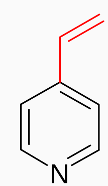

**PAPd2r**; 85%
***3-Br selective over 2-Cl***




**PAPd1r**; 68%




**PAPd2r**; 95%*




**PAPd2r**; 99%*
***From vinyl pinacolboronate***

* Performed in microwave

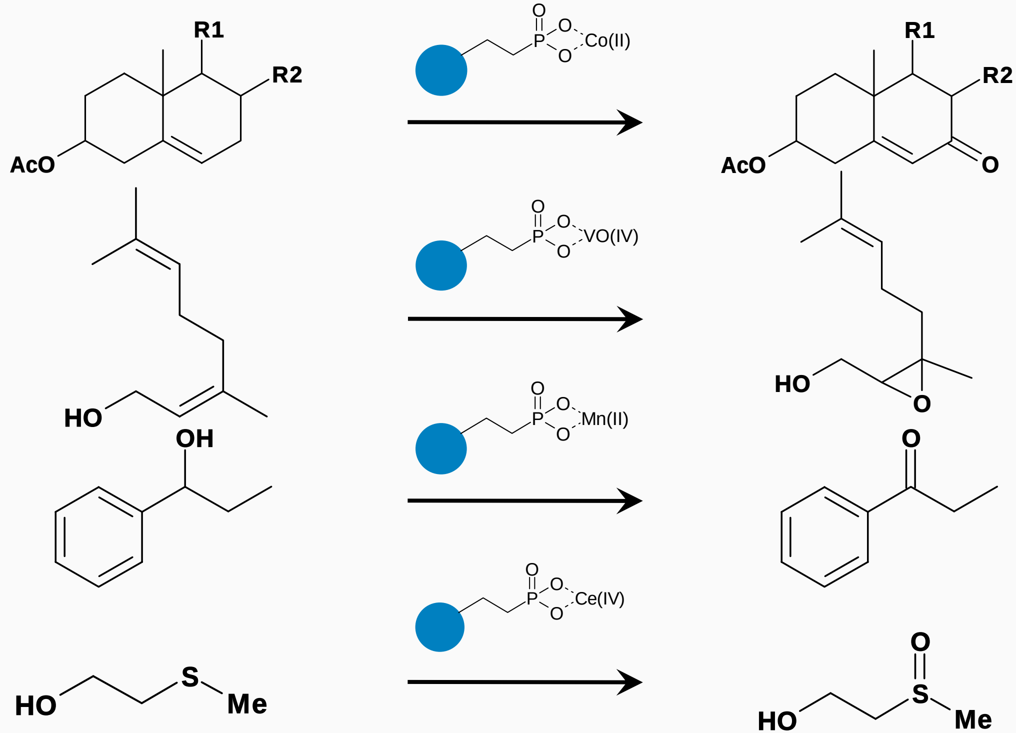
# Heterogeneous Metal Oxidation Catalysts

Allylic/Benzylic Oxidation

Epoxidation

Alcohol Oxidation

Sulfoxidation

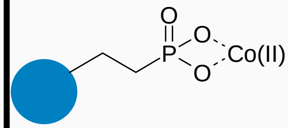
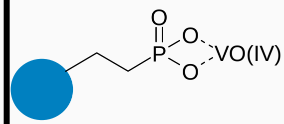
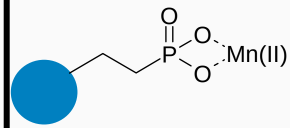
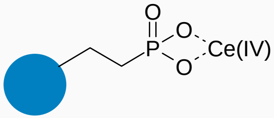
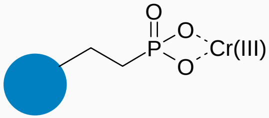



- **High yields**
- **Recyclable catalysts**
- **No detectable metal leaching**
- **Clean reactions**
- **Easy to handle reagents**

- Oxidation processes widely used in Discovery Chemistry
- Typical homogeneous reagents are difficult to handle, produce toxic waste and give contaminated products, difficult purifications & as a result generally low yields
- Uses environmentally-friendly re-oxidants

**...immobilised metal gives a 'clean' and 'green' reaction**

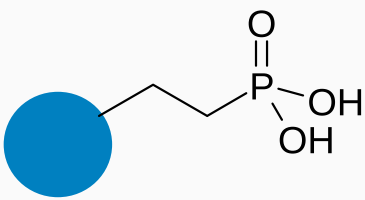
# Heterogeneous Metal Oxidation Catalysts

| Oxidation Catalyst | Code | Substrate | Product | Re-oxidant | Leading References |
|---|---|---|---|---|---|
|  | POCo | Allylic/Benzylic $CH_2$<br>Allylic Alcohols | Ketones<br>Enones | $^t$BuOOH | *TL*, **2003**, *44*, 4283<br>*TL*, **2004**, *45*, 4465 |
|  | POVO | Allylic Alcohols<br>Sulfides | Epoxides<br>Sulfoxides | $^t$BuOOH *or* $NaBrO_3$ *or* $H_2O_2$ | *TL*, **2004**, *45*, 4465<br>*TL*, **2006**, *47*, 8017 |
|  | POMn | Allylic/Benzylic $CH_2$ | Ketones | $^t$BuOOH | Unpublished |
|  | POCe | $1^o$ Alcohols<br>$2^o$ Alcohols<br>Sulfides | Acids<br>Ketones<br>Sulfoxides | $NaBrO_3$<br>*or*<br>$^t$BuOOH | *TL*, **2003**, *44*, 769<br>*TL*, **2005**, *46*, 4365 |
|  | POCr | Sulfides | Sulfoxides | $NaBrO_3$<br>*or*<br>$^t$BuOOH | Unpublished |

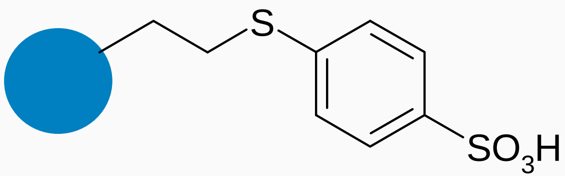
**Oxidation Catalysts Review**: *Chemistry Today*, **2007**, 25 (4), 22 & refs therei

**Simple, scalable, cost effective processes**

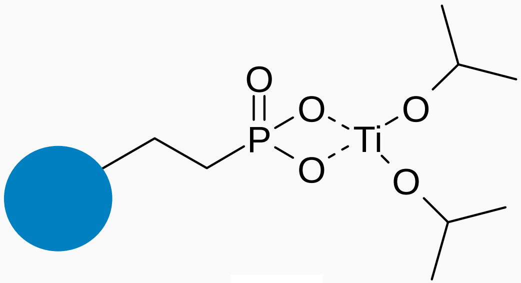
# Heterogeneous Acid Catalysts




**POH1**




**SPhSA**



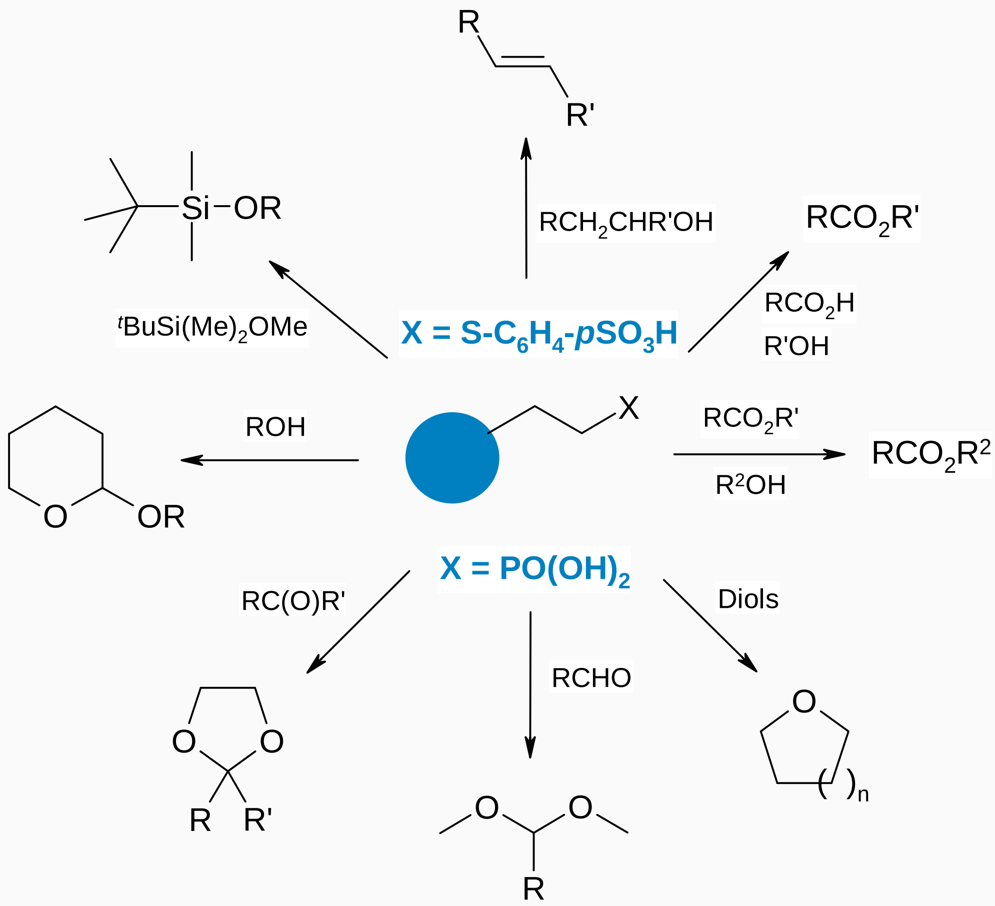

**POTi**

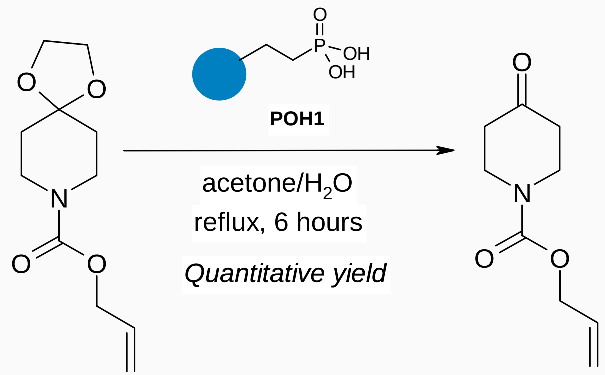
- Substitutes for strong acids, avoiding toxic, inorganic waste
- Easy-to-use acid catalysts for esterification, trans-esterification, hydrolysis, rearrangements, dehydration, protection & deprotection, cyclisations, etherifications, acylation & alkylation
- High thermal stability
- Readily recycled

**Acid Catalysts Review**: *Manufacturing Chemist*, **2007**, *July/August Ed.*, 27

# Heterogeneous Acid Catalysts

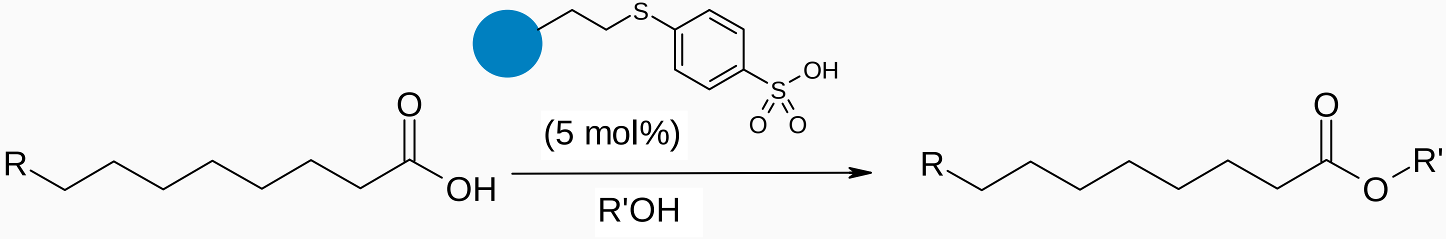
- Effective catalysis of a full range of organic transformations…




OPRD, **2007**, *11*, 406

# Fatty Acid Esterifications




| R' | R = $^{n}C_8H_{17}CH{=}CH$- Yield/% | R = $^{n}C_4H_9$- Yield/% |
|---|---|---|
| Me | 98 | 96 |
| Et | 97 | 94 |
| $^{n}$Pr | 97 | 95 |
| $^{i}$Pr | 49 | *na* |
| $^{n}C_8H_{17}$ | 89 | *na* |
| Bn | 67 | *na* |

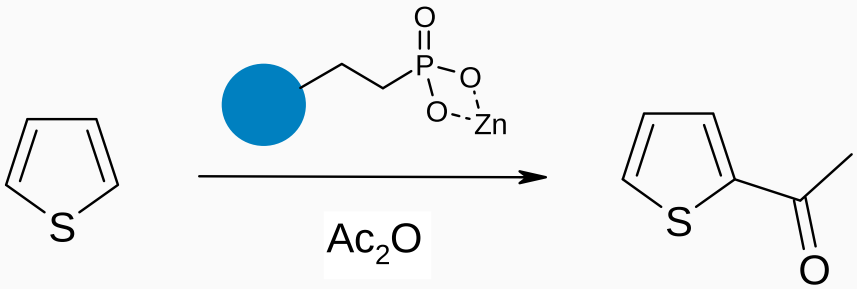
*na* = reaction not performed

- Enhanced yields *cf'd* to homogeneous acids & other heterogeneous catalysts
- Cleaner reactions

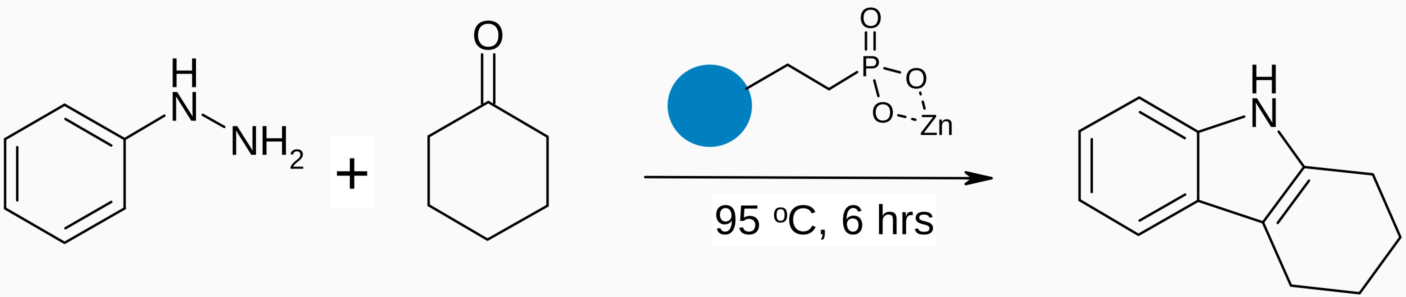
**Acid Catalysts Review**: *Manufacturing Chemist*, **2007**, *July/August Ed.*, 27

# Heterogeneous Acid Catalysts

- Developed as an alternative to $AlCl_3$ for Friedel-Crafts reactions




- Also applied to Fischer indole synthesis




- Cleaner reactions, higher yields, fewer impurities

ilson, J. *et al*., *Innovations in Pharmaceutical Technology*, **2007**, *Spring edition*, 86

# Summary

- Significant metal losses from catalytic processes
- Major economic and environmental impact
- Creates a challenge to resolve problems of metal removal and capture from product, waste and effluent streams
- Technology innovation required to deliver improved catalysts and better recovery methods
- PhosphonicS contribution:
  - developed enhanced scavengers for product purification and precious metal recovery
  - Immobilised heterogeneous metal catalysts

Thank you for your attention