Catalysis within iPRD

- New catalytic processes & reactions
- Catalyst immobilisation/encapsulation
- Mechanistic studies
Catalysis within iPRD

Presentation focuses on:
- Track record/in house expertise (highlights)
- Current projects
- Future perspectives/targets

Discussion welcomed on:
- Comments/suggestions on project portfolio
- Identification of interested partners/consortia for collaboration, application or information exchange
Catalysis within iPRD

Landscape shaped by:
- GCI Pharmaceutical Roundtable
- EPSRC/AZ/GSK/Pfizer initiative
- Discussions with collaborators (established and potential)
- Inspiration and serendipity!
Catalytic processes: route improvement (Heron/Gabbutt)

- 1-aryl-2-tetralones are precursors for photochromics
- Classical preparation (patented): 5 steps from 1-tetralone
- Enolate arylation gives product directly

Tandem intra-/intermolecular arylation gives ring-modified targets directly (unoptimised yield)
Catalytic processes: novel catalysts (McGowan)

- Novel catalysts for polyphenylacetylene production

- Novel catalysts for polyolefin production

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Amt. of Cat. (μmol)</th>
<th>Amt. PE (g)</th>
<th>Activity (KgPE/molCr.hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{(C}_5\text{H}_4\text{(CH}_2\text{)}\text{C}_5\text{H}_4\text{N})\text{CrCl}_2}]</td>
<td>25</td>
<td>1.57</td>
<td>189.2</td>
</tr>
<tr>
<td>([\text{(C}_5\text{H}_4\text{(C}_3\text{H}_9\text{NCH}_3\text{)})\text{CrCl}_2}]</td>
<td>25</td>
<td>1.69</td>
<td>202.8</td>
</tr>
</tbody>
</table>
Catalytic processes: novel catalysts (Marsden/Blacker)

- need to replace stoichiometric metal hydrides in carboxyl reduction
- hydrogenolytic cleavage of acyl functions generally needs high pressure (100 atm) and/or temp (200°C+) for good conversion
- new catalyst system works at 1 atmosphere, 60°C, and is chemoselective for aldehyde formation

100% conversion (78% selectivity)

3% catalyst
1 atm. H₂, THF, reflux

100% conversion (62% selectivity)

3% catalyst
1 atm. H₂, THF, reflux then BuNH₂
Catalytic processes: novel biocatalysts (Nelson)

- Directed evolution creates stereodivergent catalysts from common enzyme:

\[
\begin{align*}
\text{mutant 1} & \quad \text{mutant 2} \\
\end{align*}
\]
Catalytic processes: novel biocatalysts (Nelson)

- In two cases now studied, change in selectivity due to small number of mutations near active site, causing reorientation
- Is general principle extendable to other C-C bond forming enzymes?

\[ \text{N-Acetyl neuraminic acid lyase} \]
\[ \text{JACS 2006, 128, 16238} \]

\[ \text{Tagatose 1,6-bisphosphate aldolase} \]
\[ \text{PNAS 2003, 100, 3143} \]
Catalytic processes: novel media (Rayner)

- In situ protection of amines in scCO₂: Suzuki reactions

\[
\begin{align*}
\text{NH}_2 + \text{Ph} = \text{Br} & \xrightarrow{\text{scCO}_2, 80 ^\circ \text{C}, 120 \text{ bar} \atop \text{Pd(OCOCF}_3\text{)}_2 (1 \text{ mol\%}) \atop \text{dppf (2 mol\%)} \atop \text{DIPEA}} \text{Ph-N} \quad \text{85\% yield} \\
\text{Ph} + \text{B(OH)}_2 & \xrightarrow{\text{scCO}_2, 80 ^\circ \text{C}, 120 \text{ bar} \atop \text{Pd(OCOCF}_3\text{)}_2 (1 \text{ mol\%}) \atop \text{dppf (2 mol\%)} \atop \text{DIPEA}} \text{Ph-N-Ph} \\
\text{NH} + \text{Ph} = \text{Br} & \xrightarrow{\text{scCO}_2, 80 ^\circ \text{C}, 120 \text{ bar} \atop \text{Pd(OCOCF}_3\text{)}_2 (1 \text{ mol\%}) \atop \text{dppf (2 mol\%)} \atop \text{DIPEA}} \text{Ph-N-Ph} \\
\end{align*}
\]

85\% yield
No solvent \(<1\%\)
Toluene \(<1\%\)

70\% yield
No solvent, 26\%
Toluene, \(<5\%\)
Catalytic processes: novel media (Rayner)

- Pressure effect on $ee$ during asymmetric cyclopropanations in scCO$_2$

\[
\text{Ph} + \text{CO}_2^{t\text{Bu}} \rightarrow \text{Ph-Ph-Ph} \quad \text{Cu(OTf)$_2$} \quad \text{Ligand, scCO$_2$}
\]

**Variation of trans $ee$ % with pressure**

- Pressure effect also seen in diastereoselective sulfoxidation
Catalytic processes: novel reactions (Marsden)

- traditional routes to isocyanates not process-friendly

- new catalytic approaches based on C-X and C-H functionalisation
Catalytic processes: novel reactions (Marsden/Blacker)

- **Hydrogen activation reactions of amines**

```
Inert Amine \(- \text{"H}_2\)\ + catalyst \rightarrow \text{Reactive intermediate} \rightarrow \text{Reactive product} \rightarrow \text{Inert Product}
```

- **Oxidative formation of heterocycles**

```
\text{Ph} + \text{PhNH}_2 \rightarrow \text{PhNH}_2 + 2\text{H}_2, \text{-NH}_3 \\
\rightarrow \text{PhNH}_2 + 2\text{H}_2
```

- **Also amine alkylation/dealkylation etc**
Catalytic processes: novel reactions (Marsden)

- classical aza-Wittig reaction useful but not scaleable

![Chemical reaction diagram]

- organocatalytic variant overcomes both issues:

![Chemical reaction diagram]

catalytic

- applicable to other P=O reactions &/or heterocumulenes - organocatalytic Wittig or S-ylide reactions?
Projects under review or in plan:

- Catalytic synthesis of *cis* and *trans* alkenes
- Catalytic oxidative synthesis of amides
- Asymmetric sulfoxidation
- Direct C-H activation for arylation of enolates
- Non-halide alkylations of alcohols
- Photocatalytic reactions
- Catalytic reduction of CO₂
- Catalytic processing of lignin
Catalyst immobilisation

Industrial problem:
- homogeneous catalysts used in increasing number of processes
- costs too high and separation of catalysts/metals to low levels difficult
- the cost contribution of catalyst to product is dependant upon the catalyst type, loading and activity, ability to reuse or recover metal

Background:
- the use of immobilised catalysts is widely researched but not widely used in industry. Issues that remain to be solved are:
  - the effect on activity/selectivity
  - leaching of metal from ligand/support
  - stability and physical properties of the support;

Benefits:
- Success should enable cheaper catalysts, purer products, more intense processes eg continuous, plug-flow.
New supports for catalyst immobilisation (X. Wang)

1) Block Copolymer Crosslinked Micelles as Catalyst Supports

a. Core-crosslinked

b. Shell-crosslinked

Metal catalytic species
Crosslinkable groups
1) Block Copolymer Crosslinked Micelles as Catalyst Supports

a. Core-crosslinked

b. Shell-crosslinked
New supports for catalyst immobilisation (X. Wang)

2) Supramolecular Chemistry

“Structure-Defined C60/Polymer Colloids Supramolecular Nanocomposites in Water”


Metal nanoparticles

3) Emulsion Polymerisation Route to Ceramic Encapsulated Catalysts
New supports for catalyst immobilisation (X. Wang)

2) Supramolecular Chemistry

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New supports for catalyst immobilisation (X. Wang)

4) Catalysts with Controlled, Switchable Phase Behaviour/Activity

Light or heat

Soluble, catalytic activity  Insoluble, no catalytic activity
New ligands for cat. immobilisation (Blacker/McGowan)

Examples of potential catalysts:
- \([\text{IrCl}_2\text{Cl}]_2\)
- \(\text{RhCl}_2\text{CITsDPEN}\)
- \(\text{RucymCITsDPEN}\)
- \(\text{TiCl}_2\text{Cp}_2\)
- \(\text{FeCp}_2\)
- \((\text{JosiPhos}) \text{FeCp}_2\text{PPh}_2\text{CHMePCy}_2\text{RhCOD}\)
- FeCp acyl complexes – Steve Davies

Organocatalysts

Piramal Healthcare and Reaxa
- PEGylated Catalyst Synthesis
- 50g scale
Functional supported catalysts (McGowan/Rayner)

- “DyeCat” method - integration of dye into catalyst and/or initiator for polymerisation leads to coloured polymer with covalently bound dyestuff

- no separate dyeing step; no leaching of colourant

- Initial study: ring opening polymerisation of lactide using aluminium complex and an alcohol initiator covalently bound to monomer (and hence polymer chain)

- Applicable to other polymerisations, applications and effects

Functional supported catalysts (McGowan/Rayner)

- Polymer → Pellets → Fibre
  - Melt → Melt spin
Mechanistic studies

- Kinetic analysis of complex reactions
- Non-linear kinetics - Dr Annette Taylor
- Complex parallel pathways - Prof Mike Pilling
- Physical organic chemistry - Prof John Atherton
- Access to novel process analytical tools
Mechanistic studies - example (Marsden/Pilling)

- identification of intermediate in catalytic aza-Wittig reaction (in situ IR) and kinetic analysis/modelling

- measure:

- model:

- interpret: A $2.7 \times 10^{-3}$ s$^{-1}$ B $2.4 \times 10^{-3}$ s$^{-1}$ C
Mechanistic studies - example (McGowan)

- Palladium-catalysed production of vinyl acetate (BP)
- A number of unwanted by-products are produced during this reaction
- We have investigated the catalytic mechanism of formation of these by-products
Catalysis within iPRD

Progress against “hitlist” from ACS GCI Pharmaceutical Roundtable

<table>
<thead>
<tr>
<th>Better reagents for:</th>
<th>Aspirational reactions:</th>
<th>Solvent themes:</th>
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<tr>
<td>Non-hydride reduction</td>
<td>Asymmetric hydrocyanation</td>
<td>Solventless reactor cleaning</td>
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<tr>
<td>Bromination</td>
<td>Ketone/amine/X to chiral amine</td>
<td>Replace polar aprotics</td>
</tr>
<tr>
<td>Sulfonation</td>
<td>N-centred chem. avoiding azides</td>
<td>Alternatives to chlorinateds</td>
</tr>
<tr>
<td>Amide formation</td>
<td>Asymmetric hydrogenation</td>
<td></td>
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<tr>
<td>Nitration</td>
<td>Asymmetric hydroformylation</td>
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<tr>
<td>Demethylation</td>
<td>C-H activation of aromatics</td>
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<tr>
<td>Friedel-Crafts</td>
<td>C-H activation of alkyl groups</td>
<td></td>
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<tr>
<td>Ester hydrolysis</td>
<td>Fluorination methods</td>
<td></td>
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<tr>
<td>OH activation</td>
<td>Reactive oxygen nucleophiles</td>
<td></td>
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<tr>
<td>Epoxidation</td>
<td>Electrophilic nitrogen</td>
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<tr>
<td>Wittig reaction (non-P=O)</td>
<td>Asymmetric hydroamination</td>
<td></td>
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<tr>
<td>Radical chemistry</td>
<td>Organocatalysis</td>
<td></td>
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<tr>
<td></td>
<td>Aryl ether formation</td>
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Recap: points for discussion

- Comments/suggestions on project portfolio
- Identification of interested partners/ consortium for collaboration, application or information exchange