Chemistry Innovation
Knowledge Transfer Network

Catalysis and Synthesis for Effect – A Chemistry Innovation Strategic Priority

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Aims & Objectives

- To deliver improved industrial performance through innovation and new collaborations by driving the flow of people, knowledge and experience between business and the science base, between businesses and across sectors
- To drive knowledge transfer between the supply and demand sides of technology-enabled markets through a high quality, easy to use service
- To facilitate innovation and knowledge transfer by providing UK businesses with the opportunity to meet and network with individuals and organisations, in the UK and internationally
- To provide a forum for a coherent business voice to inform government of its technology needs and about issues, such as regulation, which are enhancing or inhibiting innovation in the UK.

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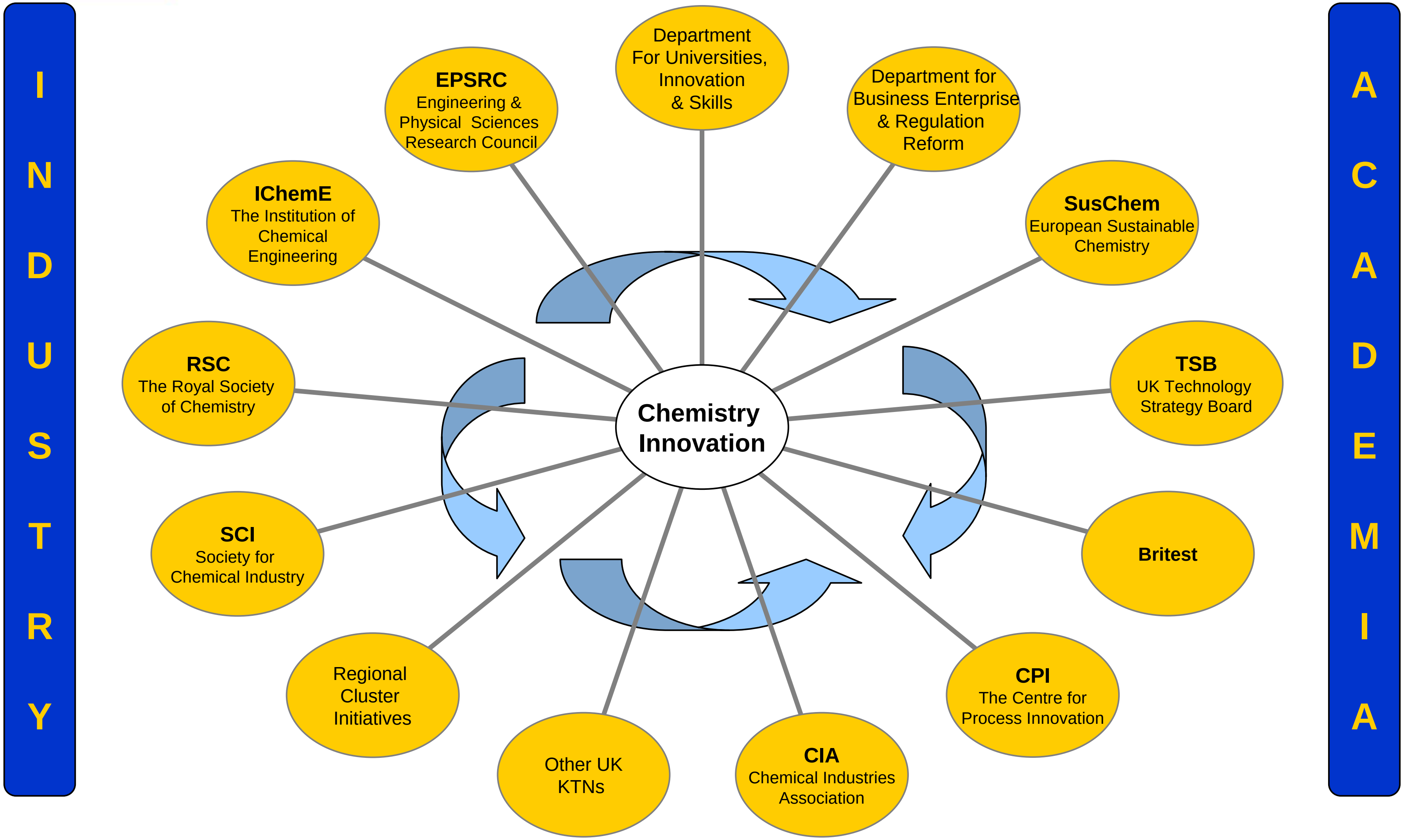
Strategic Connections



Priorities

Priorities for the chemistry-using industries have evolved from extensive consultation with industry and academia and alignment with UK and European technology strategies

Launched June 2007

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Priority Areas for UK chemistry-using industries

Innovation Leadership

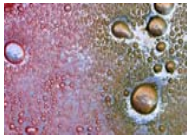
The leadership and management skills required to transform new ideas into profitable business.

Sustainable Technologies

The design and production of new products and processes that can meet the needs of the present without compromising the ability of future generations to meet their own needs.

Measurement Science and Technology

The detection, measurement and characterisation of products and processes, to solve problems and create new opportunities.



Chemistry for Product Design

The design and production of new materials with novel properties that offer significant benefits in fields such as the environment, health and security.

Manufacturing Design

A holistic approach to the design of processes, formulations and facilities leading to world competitive production of new and current products.

Catalysis and Synthesis for Effect

The reaction routes to manufacture new or existing products with lower energy, material consumption and hazards.

Modelling for Chemistry

The modelling of chemical behaviour, material interactions and process performance to increase the productivity and value of research and innovation.

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Priorities will be used to…..

- Raise awareness of issues of strategic importance to the sector
- Focus industrial collaborations and the resources of Chemistry Innovation and its partners:
  - Establishing and facilitating events
  - Technology project bids
  - Facilitating and developing Special Interest Groups
  - Creating new partnerships and connections
- Focus/influence government policy and public funding
- Set goals for academic research and skills development
- Provide input for European policy and international collaborations

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Catalysis and Synthesis for Pharmaceuticals and Fine Chemicals.

- Identifying synthetic priorities for a more sustainable industry.
- Catalysis has become an important tool for synthetic chemistry in recent years, with catalytic processes replacing the conventional stoichiometric approach.
- Increasing catalyst selectivity, will improve reaction atom efficiency, with consequent reduction in environmental burden.
- Need for rapid identification of ligands via high throughput techniques

Synthesis of Tailored Nanoparticles

- Nanoparticles are providing new routes to deliver enhanced functionality in a variety of applications.
- These include;
  - nanoencapsulates for targeted drug delivery.
  - quantum dots for security
  - specialised coatings with enhanced properties such as scratch and stain resistance
  - enhanced strength materials.
- To fully exploit the potential of these technologies there is a need for improved, robust ways to manufacture, stabilise and handle nanoparticles in an economic and safe manner.

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Environmental Control Catalysts

•Catalysts for environmental protection/remediation is a growth area.

• Need to keep pace with the ever tightening regulations regarding exhaust emissions.

•The European water framework directive will require less/zero discharge to the environment.

•Development of devices to aid homeland security.

•Catalyst manufacture via non-nitrate routes will also make an important contribution to environmental impact reduction, as will efficient catalyst recycle.

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Process is Key

- **Overall, there will be a drive to develop new Green and Sustainable Chemical Processes.**
- **This will rely heavily on integrated process control, where the UK has a good position.**
- **New processes integrating reaction and separation steps using intensification techniques, reactive distillation and membrane separations will be developed.**
- **Linking chemistry with chemical engineering is paramount.**

Target Reactions (from ACS Green Chemistry Alliance and UK Pharma)

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Reactions that ACS GCIPR companies use now but would strongly prefer better reagents

- Amide formation avoiding poor atom economy reagents - **6 votes**
- OH activation for nucleophilic substitution - **5 votes**
- Reduction of amides without hydride reagents - **4 votes**
- Oxidation/Epoxidation methods without the use of chlorinated solvents - **4 votes**
- Safe and environmentally friendly Mitsunobu reactions - **3 votes**

- Friedel-Craft reactions on unactivated systems - **2 votes**
- Nitrations - **2 votes**

Peter Dunn, Pfizer

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More Aspirational Reactions

- C-H activation of aromatics (cross couplings avoiding the preparation of haloaromatics) - 6 votes
- Aldehyde or ketone + NH_3 + ‘X’ to give chiral amine - 4 votes
- Asymmetric hydrogenation of unfunctionalised olefins/enamines/imines - 4 votes
- New green Fluorination methods under mild conditions - 4 votes
- *N*-Centred chemistry avoiding azides, hydrazine etc - 4 votes

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- Asymmetric hydroamination - 2 votes
- Green sources of electrophilic nitrogen (not TsN_3, nitroso or diimide) - 2 votes
- Asymmetric hydrocyanation - 2 votes

Comparison of Roundtable and UK Process Group Key Challenges

- C-H activation of Aromatics.
- Amide formation with good atom economy.
- Reduction of amides without hydride reagents.
- Safer, greener Mitsunobu reactions.
- Asymmetric hydrogenation of unfunctionalised olefins/enamines/imines
- OH activation for nucleophilic substitution.
- N – Centred chemistry.

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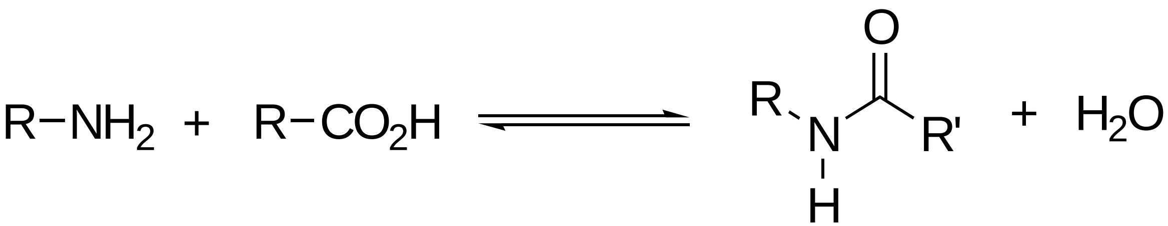
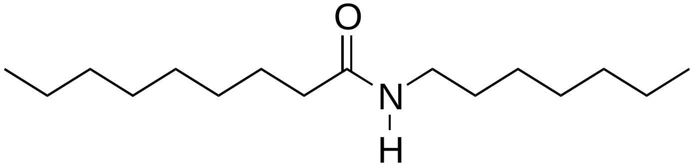
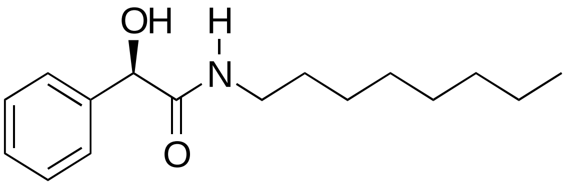
Direct thermal amide formation

- **Simple heating of acid + amine**
  - 1993 - 160-180 °C, 10-30 mins., water removal essential[1]
  - Not all amides can be made this way- decomposition, tar, low yields
  - Notably, no mention of mechanism, or salt formation!
  - Can not form imides by this method





98%

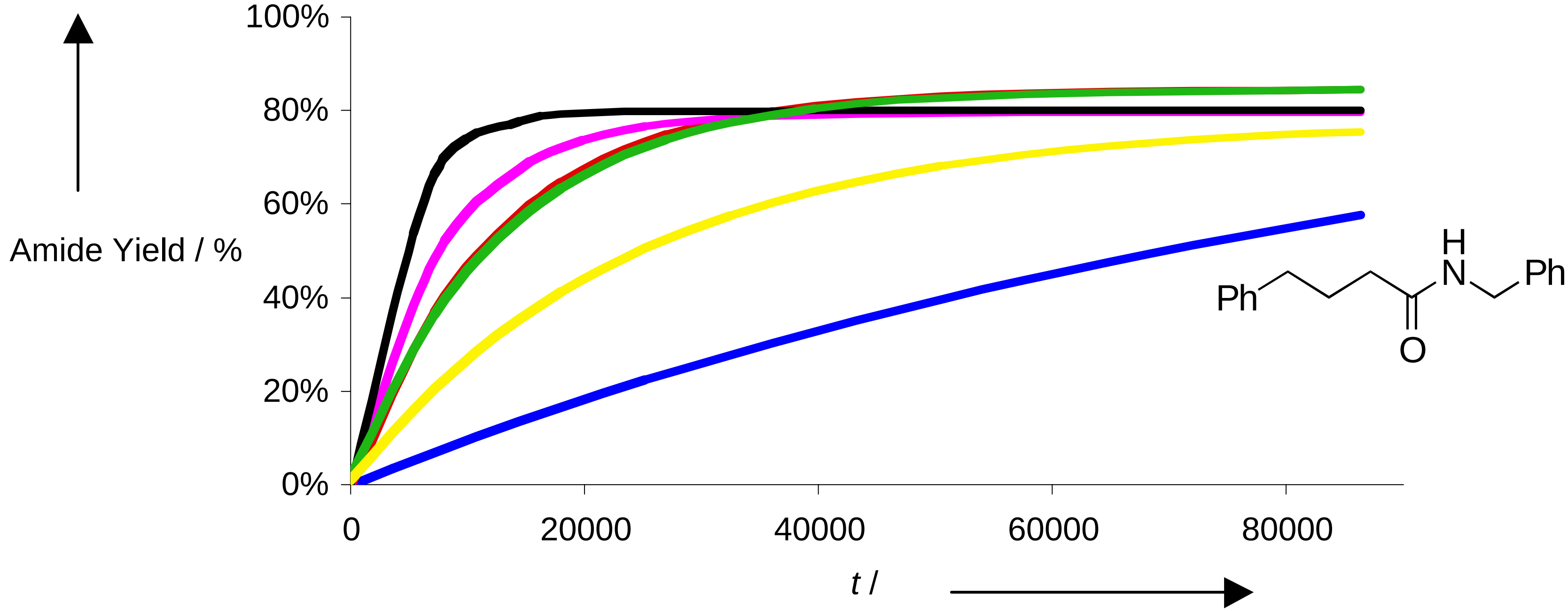


92%

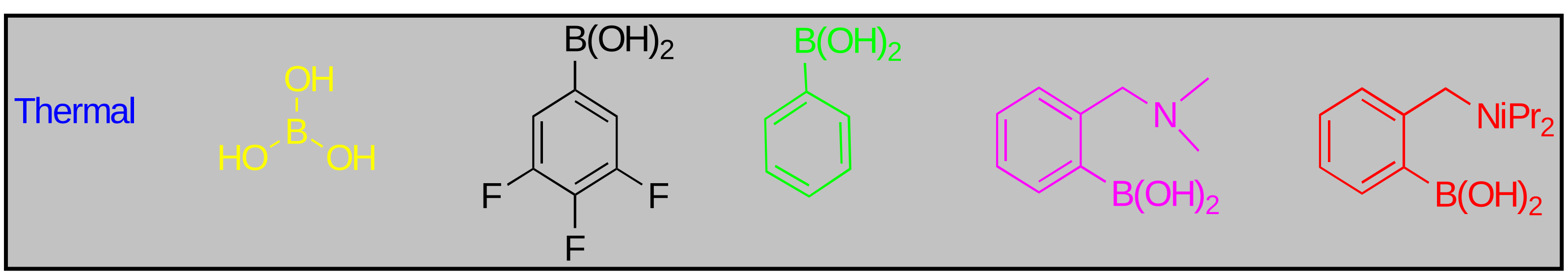
Andy Whiting, Durham University

1. Jursic & Zdravkovski, *Synth. Commun.*, **1993**, *23*, 2761.

Comparison of catalysts vs. thermal reaction



Conditions: 10 mol% catalyst, fluorobenzene, Δ



Arnold, Davies, Giles, Grosjean, Smith, Whiting, *Adv. Synth. Catal.*, **2006,** *348*, 813.

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Summary and future directions

- Direct amide formation under thermal conditions is little studied and understood.
- Catalysts do improve direct amide formation: How much is often unclear!
- Boron-based catalysts appear most attractive to date, Ru and triazines look interesting.
- Bifunctional catalysts: Best at lower temperatures + lower reactivity substrates, and asymmetric!
- Need for detailed mechanistic studies: Implications for process control (water removal controls reaction rate).

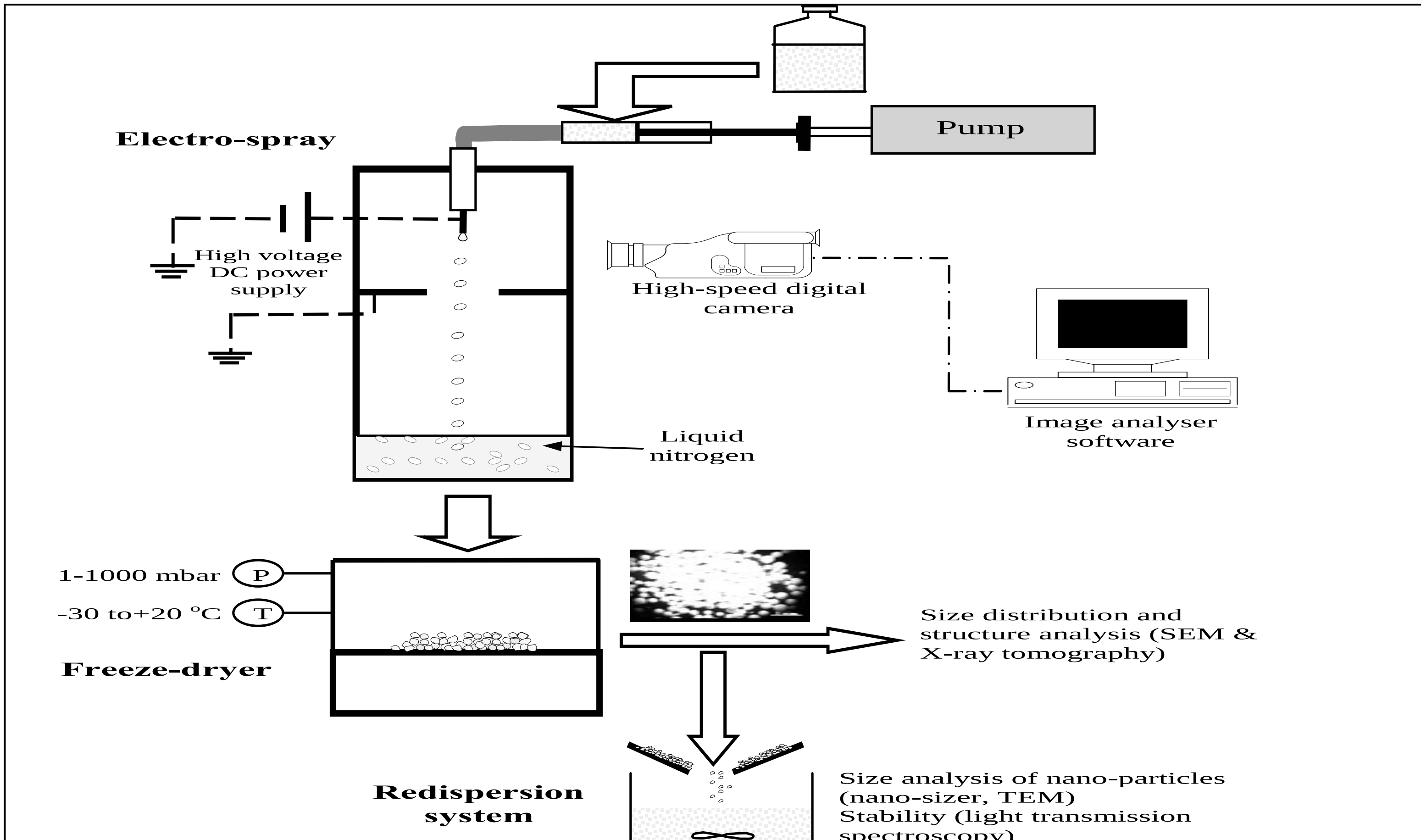
Direct (Thermal) Amide Formation

- **Need**
  - **Rapid heat transfer**
  - **Short contact time**

Asymmetric Reactions

- **Need**
  - **Rapid Reaction (Often need kinetic, not thermodynamic control)**
  - **Rapid removal from the reaction zone (To prevent racemisation)**

Structural Design of Nanoassemblies



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Nanoparticle Formation

- Need
  - High degree of nucleation
  - Restricted grain growth
  - If agglomerated, easy redispersion

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Discussion

What are sensible realistic targets for Process Intensification in Fine Chemicals Synthesis?

Supplementary

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Background

- Chemistry-using industries and chemical sciences are critical to both UK prosperity and meeting society's needs
  - Annual turnover of the sector > £50 billion (11% of UK manufacturing sector)
  - Biggest UK export sector (£2.8 billion from chemicals alone)
  - Underpins competitiveness of most other manufacturing sectors
  - Key contributor to solutions for society's sustainability issues e.g. climate change, energy supply and efficiency, water use, waste, aging population, finite resources
- UK Government & industry recognise need to focus on innovation
- Future is highly dependent upon innovation – not just technology
- UK cannot lead technologically in all areas – we have to prioritise resources to compete effectively

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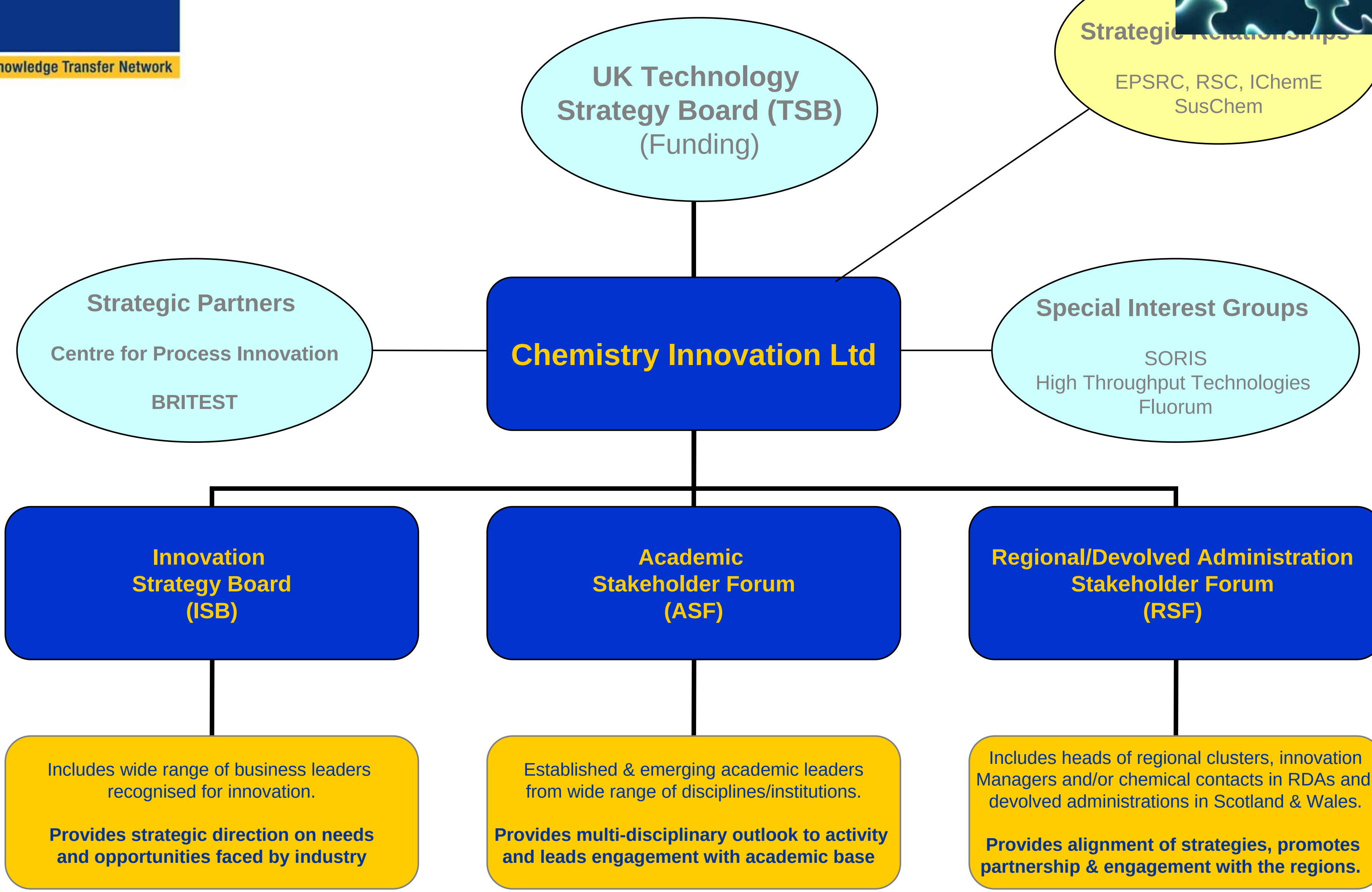
Structure



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ISB Members

The ISB consists of senior figures predominantly from industry, representing large and small companies, and chaired by the Chemistry Innovation Chair. Current members include:

Graeme Armstrong, ICI
Francis Bealin-Kelly, Procter & Gamble
Carol Boyer-Spooner – Chemistry Innovation
David Brown, IChemE
Richard Carter, BERR
John Conti-Ramsden, Intertek Ltd
David Duncan, Unilever
Sandy Gray, Society of Chemical Industry
David Greensmith, Fujifilm Imaging Colorants Ltd
Colin Harrison, Chemistry Innovation (chair)
Shaun Kennedy, Infineum
David Kilworth, NPIL Pharmaceuticals (UK) Ltd
Ian Laird, NiTech Solutions
Keith Layden , Croda
Peter Lyne, LGC
Kevin McFarthing, Reckitt Benckiser
Ian McRobbie, Innospec
Annick Meerschman , Dow Corning
Shahana Mirza, Foster Wheeler
Brian Murphy, Robinson Brothers
Barry Murrer, Johnson Matthey
Ian Shott, Excelsyn
Paul Snaith, Shell Global Solutions
Lesley Thompson, EPSRC
Rodney Townsend, Royal Society of Chemistry
Andy Wells, AstraZeneca
Tony Wood, Pfizer

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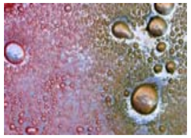
Priority Areas - Leaders

	Innovation Leadership	Richard Philpott
	Sustainable Technologies	Mike Pitts
	Measurement Science and Technology	Julie McDonald
	Chemistry for Product Design	Darren Ragheb
	Manufacturing Design	Matthew Tidmarsh
	Catalysis and Synthesis for Effect	David Parker
	Modelling for Chemistry	Adrian Toland

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Catalysis and Synthesis for Effect

The reaction routes to manufacture new or existing products with lower energy, material consumption and hazards.

Progress since June

- Synthetic methodology for pharms and fine chemicals emerged as no1 target
- With CPI/NanoCentral and ACORN syndicate on synthesis of tailored nanoparticles
- Identified water remediation as key target in environmental catalysis
- TopCombi option for a European network
- Using RSC Applied Catalysis Gp as advisors

Forward Plan

- Run workshops to define topics for funding calls
- Work with Process Intensification Network and Mfg Design on process sustainability workshop
- Produce a position paper on water remediation
- Critically review target synthesis wish list
- Work with ACORN partners to develop future research programmes
- Build partnerships with other groups

Key Challenges

- Developing a way forward on synthesis for functionality
- Developing a strategy on the carbohydrate economy with other groups

Synergies

- Sustainable Technologies, Chemistry for Product Design
- EPSRC, RSC, IChemE

Lower Carbon Content Feedstock's

- The increase in alternative/bio-derived lower carbon feedstock's will impact on current catalytic capabilities.

- Any new system must have a full life-cycle analysis.

- Consideration should also be given to upgrading methane (e.g. via reforming, Fischer Tropsch) and/or fuel and chemicals derived from coal as viable economic alternatives to bio derived feedstock's.

- Bio-fuels are being deployed to bridge the gap between the decline of fossil fuels and growth of the hydrogen economy. A key requirement for fuel cell technology is the development of cathodic catalysts(s) for oxygen reduction.

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AZ

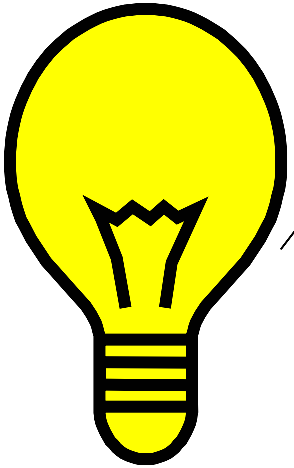
GSK

Merck

Pfizer

Lilly

Schering-Plough



Brainstorm

Ideas

Reactions we use now but would prefer better reagents

(i) Frequency of use

(ii) Waste assessment

(iii) Process hazard assessment

Aspirational Reaction list

Prioritise by company vote

Key Challenges in Pharma Manufacturing

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Brainstorm Output

- Greener Mitsunobu Reactions
- Reduction of amides avoiding LAH and Diborane
- Bromination Reactions
- Sulfonation reactions
- Amide Formation avoiding poor atom economy reagents
- Nitration reactions
- F/C Reactions on unactivated substrates
- Demethylation Reactions
- Ester Hydrolysis
- OH activation for nucleophillic substitution
- Epoxidation
- Oxidation
- Wittig Chemistry without (Ph_3PO)
- Radical Chemistry without Bu_3SnH

- Solventless Reactor Cleaning
- Dipolar Aprotic replacements for NMP, DMAc, DMF etc

- Asymmetric Hydrocyanation
- Aldehyde or Ketone + NH_3 + "X" to give a chiral amine
- *N*-Centred chemistry avoiding azides hydrazines etc
- Asymmetric Hydrolysis of nitriles
- Asymmetric Hydrogenation of unfunctionalised olefins/enamines/imines
- Asymmetric Hydroformylation
- C-H activation or aromatics
- C-H activation of alkyl groups
- New Green Fluorination Methods
- Oxygen Nucleophiles with high reactivity
- Green sources of electrophilic Nitrogen
- Asymmetric Hydroamination of olefins
- Asymmetric Hydration of olefins
- Organocatalysis
- ROH + ArCl to give ROAr

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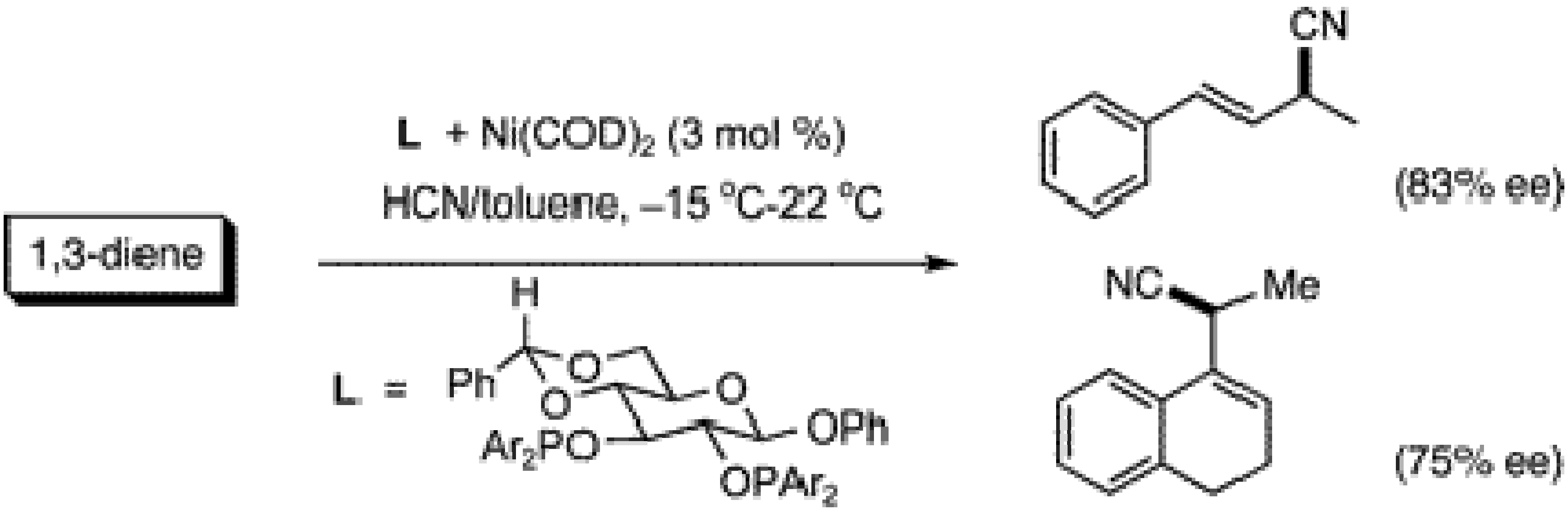
Asymmetric Hydrocyanation



• moderate reaction conditions • highly regioselective

http://pubs.acs.org/cgi-bin/abstract.cgi/orlef7/2006/8/i20/abs/ol062002f.html

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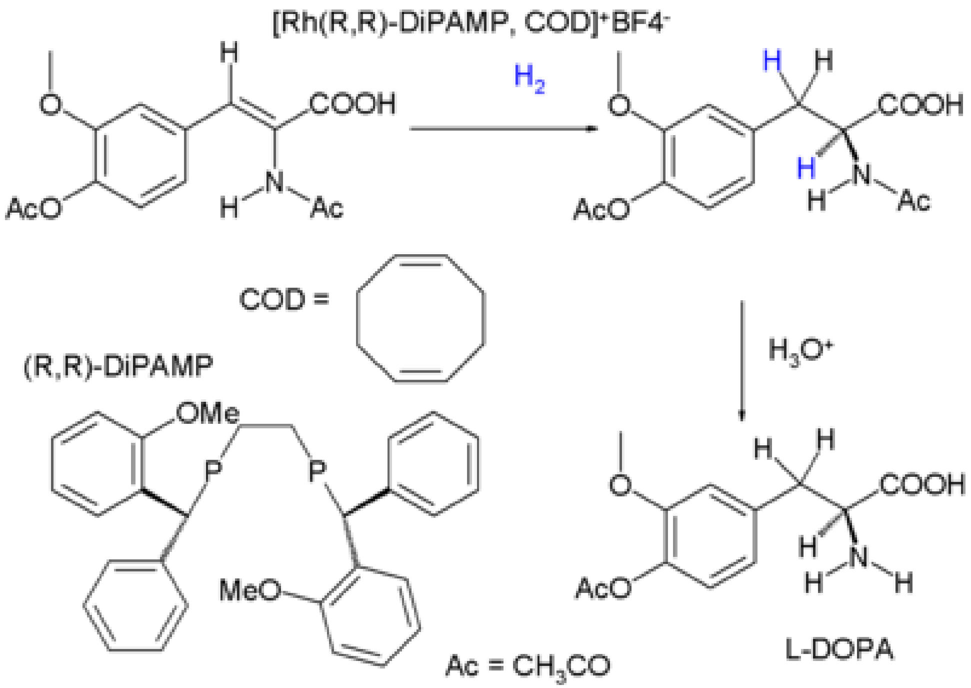
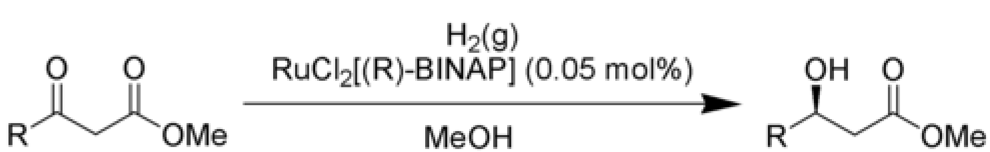
Asymmetric Hydrogenation

Monanto – Synthesis of L-Dopa



http://en.wikipedia.org/wiki/Asymmetric_synthesis

Noyori asymmetric hydrogenation of β-keto-esters



http://en.wikipedia.org/wiki/Noyori_asymmetric_hydrogenation

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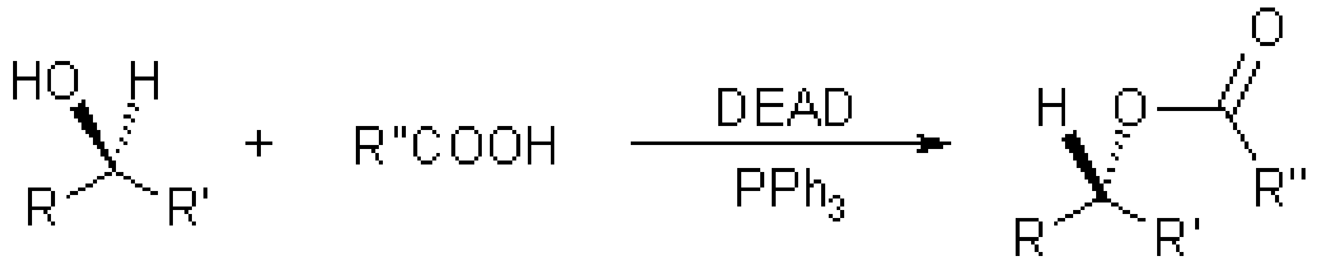
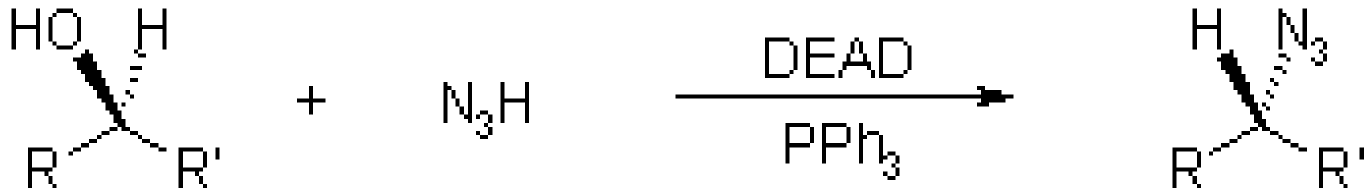
Mitsunobu Reaction

The Mitsunobu Reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds.





(DEAD = diethylazodicarboxylate)

http://www.organic-chemistry.org/namedreactions/mitsunobu-reaction.shtm