A one day meeting on the Successful Scale-Up of Catalytic Processes took place on the 5th October 2006. Organised by the Applied Catalysis Group of the Royal Society of Chemistry (1), it was hosted by Davy Process Technology Ltd (2) at Stockton-on-Tees, U.K. In all, almost 60 delegates attended the meeting, with over 80% being from industry. There were a total of six oral presentations, of which three covered work using platinum group metal (pgm) catalysts, especially palladium.

Cost-Effective Palladium-Catalysed Processes

Ian Archer (Ingenza Ltd, U.K.) described the scale-up of a novel process for the synthesis of pure enantiomers of amino acids and amines. The process uses chemo-enzymatic deracemisation to generate a single enantiomer from a racemic mixture (3). A biocatalysed enantioselective oxidation is used to convert one enantiomer of the amino acid or amine to a non-chiral imine, which is then reduced non-selectively back to the amine, see Scheme I.

In order to develop commercially viable processes, Ingenza have needed to develop cost-effective pgm-catalysed reductions. For example, for the stereoinversion of D-2-aminobutyric acid to l-2-aminobutyric acid, over 40 different pgm catalysts were screened for use in the reduction step. Initially, a Pd/C catalyst was identified as the most promising candidate, but the cost proved to be too high, even with reuse of the catalyst and recovery of the Pd metal. Development of a second generation Pd catalyst enabled the costs to be reduced to an economically attractive level.

David Johnson (Lucite International Ltd, U.K.) presented a paper which outlined the development and scale-up of their new route to methyl methacrylate (MMA). This novel process employs two catalytic reaction steps:

(a) carbonylation of ethene in methanol to produce methyl propionate, using a homogeneous palladium-phosphine catalyst;
(b) condensation of methyl propionate with formaldehyde over a basic heterogeneous catalyst (Cs/SiO₂).

There were several issues which needed to be addressed during the scale-up of the overall process, including product separation and purification issues, catalyst manufacture, and the demonstration of product quality.

Although the initial research had identified a suitable carbonylation catalyst with a turnover...
number of ~ 50,000 and selectivity in excess of 99.9%, the phosphine ligand was not commercial-
ly available at that time and the existing synthesis
would have been prohibitively expensive. The
compartment therefore had to develop alternative syn-
thesis routes in conjunction with Professor Peter
Edwards at Cardiff University, U.K.

In order to achieve recovery of the methyl pro-
pionate, the process was designed to operate on
the product-rich side of an azeotrope. This had the
unfortunate effect of lowering catalyst activity.
Further, it was discovered that carbon monoxide
poisoned the catalyst; this necessitated operating
the process with a high ethene:CO ratio. However,
it was then discovered that addition of
polyvinylpyrrolidone was able to stabilise the cata-
lyst activity and also improve the Pd recovery.

Optimised Palladium Catalyst
Performance

Kevin Treacher (Reaxa Ltd, U.K.) presented an
overview of the use of Pd EnCat™ catalysts for
organic synthesis. A range of different catalysts are
available based on palladium(II) acetate in combina-
tion with a variety of phosphine ligands and
encapsulated in porous polyurea beads. These cata-
lysts can be used for a variety of synthetic reactions
such as Suzuki coupling, Heck reactions and hydro-
genations. A catalyst with encapsulated Pd
nanoparticles is also available.

A case study of the Suzuki coupling of phenyl-
boronic acid and 4-fluoro-1-bromobenzene to give
4-fluorobiphenyl was presented. Initial screening of
different bases in conjunction with a Pd(II)
EnCat™ BINAP30 catalyst was carried out in a
batch reactor. The best performing system from
these tests was then evaluated in three different flow
reactor configurations: a continuous stirred tank
reactor (CSTR), a tubular reactor and two sequential
tubular reactors. With this latter configuration, opti-
mised system productivity in excess of 150 g per g
catalyst was achieved; the catalyst still exhibited a
stable performance after 250 hours operation.

Other Approaches

In addition to these three presentations which
included pgm catalysis, the other talks described the
approaches to catalytic process scale-up used by
different companies. Steven Colley (Davy Process
Technology Ltd, U.K.) outlined their approach to
process scale-up, with the focus being on the use of
mini-plants to generate the data required for
process design, and the issues that can be encoun-
tered. Simon Froom (BP, U.K.) described the
scale-up of BP’s Avada® process (4) for the manu-
facture of ethyl acetate from acetic acid and ethene.
Professor Wolfgang Holderich (RWTH-Aachen
University, Germany) described the development
of two new processes: the manufacture of caprolac-
tam via the acid-catalysed Beckmann rearrangement
of cyclohexanone oxime; and the production of
biodegradable lubricants via the esterification of
natural oils and glycerides.

Conclusion

Overall, the meeting was a resounding success
and provided many valuable insights into the vary-
ing methodologies which can be used in the
scale-up of catalytic processes, whether for more
traditional large-scale manufacturing processes or
for smaller-scale speciality chemical synthesis. The
Applied Catalysis Group of the Royal Society of
Chemistry plans to hold a one-day symposium on
the Challenges in Catalysis for Pharmaceuticals and
Fine Chemicals at the Society of Chemical Industry,

References

1 RSC Applied Catalysis Group:
http://www.rsc.org/Membership/Networking/
InterestGroups/catalysis/
2 Davy Process Technology Ltd:
http://www.davyprotech.com/
3 I. Fotheringham, I. Archer, R. Carr, R. Speight and

The Reviewer

Chris Mitchell is the Catalytic Chemistry
Expert for Huntsman Polyurethanes and
works within their Global Technology
organisation, based in Belgium. His main
focus is the development of heterogeneous
catalytic processes, including
hydrogenations, acid catalysis and
epoxidations/oxidations. He has particular interests in the
characterisation of catalysts, reaction kinetics and catalyst
deactivation. Among the platinum group metals, he has worked
with platinum, palladium and ruthenium.