Challenges in Catalysis for Pharmaceuticals and Fine Chemicals III

Platinum group metals in practical homogeneous catalysis

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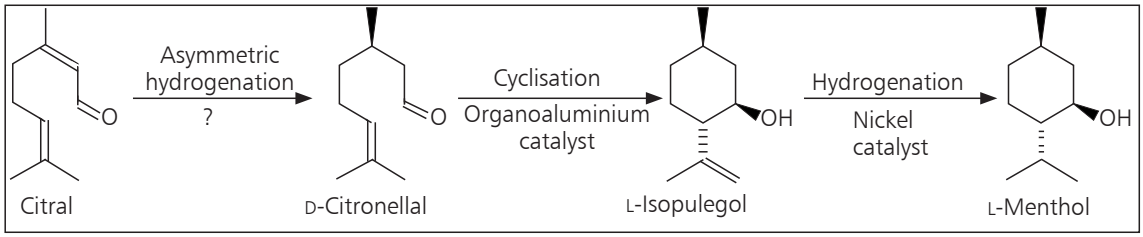
The third meeting on "Challenges in Catalysis for Pharmaceuticals and Fine Chemicals" took place on 2nd November 2011. Around ninety delegates, evenly spread across academia and industry, attended the event in London, which was organised jointly by the Society of Chemical Industry (SCI) Fine Chemicals Group and the Royal Society of Chemistry (RSC) Applied Catalysis Group. Following the first two meetings of the series in 2007 (1) and 2009 (2), the themes focused on the practical aspects of applied catalysis including scale-up, flow chemistry and one-pot multi-step procedures. Four of the seven oral presentations and a third of the poster presentations featured work on platinum group metals (pgms). The following brief review brings together the pgm aspects of the work presented.

Optimising Scalable Catalysis

The scale on which reactions are performed varies across different areas of the chemical industry. Many organisations employ separate groups of chemists to work at different scales, from milligrams for screening and assays to tonnes for the industrial production of fine chemicals.

Rocco Paciello (BASF, Ludwigshafen, Germany) leads the homogeneous catalysis group at BASF, working across many scales from the initial chemical idea through to the laboratory, miniplant, pilot plant and finally the production plant. His group deal with all aspects of homogeneous catalysis from computer assisted design, synthesis and high throughput screening to the technology necessary for the recovery and recycling of catalysts.

L-Menthol is the world's top selling aroma chemical and thousands of tonnes are manufactured each year. BASF produce around 40,000 tonnes per year of citral at their plant in Ludwigshafen from which they sought to develop a new enantioselective synthesis of menthol. The most important step in this process is the rhodium-catalysed chemo- and enantioselective reduction of *cis*-citral (**Scheme I**). Identifying the optimal process involved screening the Rh source, chiral ligand, hydrogen pressure, temperature



Scheme I. BASF's route to L-menthol using a rhodium-catalysed chemo- and entantioselective reduction of cis-citral

and reaction time on 1.5 ml scale. After extensive mechanistic studies, a new catalyst system, $Rh(acac)(CO)_2$/Chiraphos/syngas, was developed which gave good yields and selectivities and can be efficiently recycled (3). Syngas is required in order to form the active precatalyst from the 'resting states' which can then enter the catalytic cycle (**Scheme II**) (4).

The homogeneous catalysis group at BASF makes considerable use of density functional theory (DFT) calculations in their work. This has been of great importance in aiding understanding of a process and optimising lead structures once a ligand has been found but has not yet been successful in predicting an optimal catalyst system.

Practical Flow Chemistry

Flow chemistry has been the focus of much research but is still regarded by some as an interesting curiosity rather than a useful industrial tool. Matthew Yates (Eli Lilly, Indianapolis, USA) spoke of the advantages of applying flow chemistry to catalytic processes in the pharmaceutical industry. He highlighted three cases in which the use of reactive gases (oxygen, hydrogen or syngas) in conjunction with pgms is simplified by using a continuous flow process. Increased pressures can be applied within the reduced volume of a flow reactor without the concomitant safety problems and plant equipment required for a batch process.

The most atom efficient method for oxidations uses molecular O_2, however, this can present safety issues. Use of flow chemistry for the oxidation of alcohols allowed shorter reaction times, lower loading of the homogeneous $Pd(OAc)_2$/pyridine catalyst and increased pressures while exposing only a small portion of the entire reaction mixture to oxygen at any one time. The optimised flow process used 8% O_2 in nitrogen, thus avoiding operating within the organic/O_2 explosion limits. Moreover the process is scalable, providing yields up to 99% on a kilogram scale (5).

Hydroformylation chemistry is widely used in the bulk preparation of aldehydes. A pulsed flow system for hydroformylation of methyl methacrylate provided significant benefits over a batch process allowing 1000 psi of syngas to be used with a Rh catalyst such as $RhH(CO)(PPh_3)_3$. 13 kg per day of purified product could be generated in this way, reducing byproduct formation and the volume of waste.

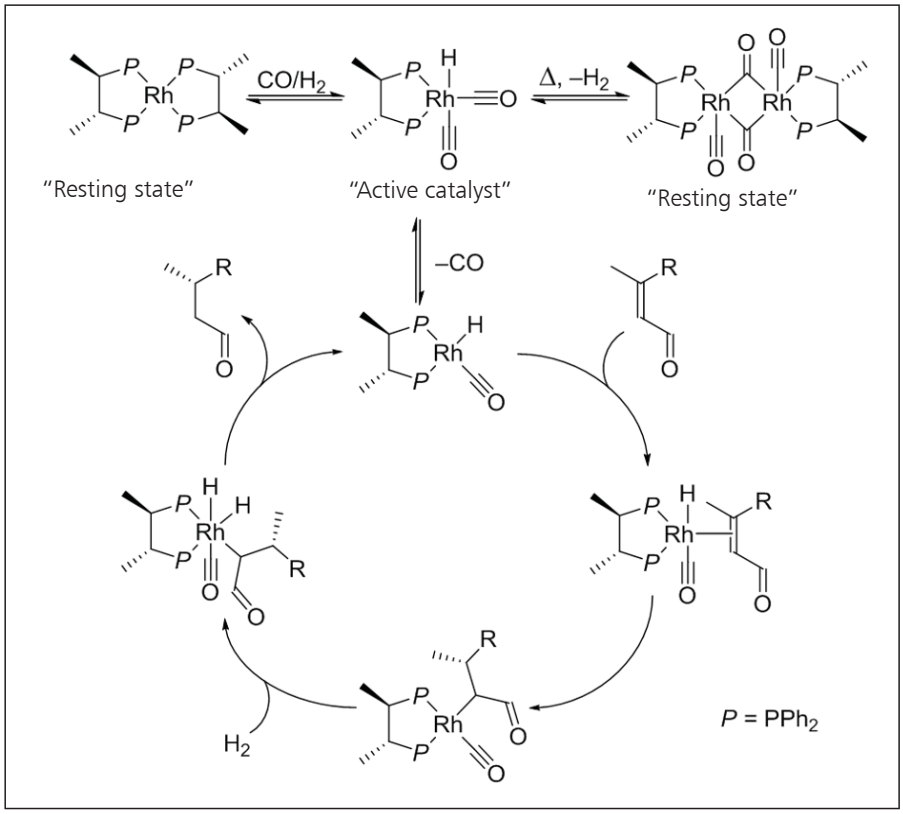
In the arena of hydrogenations, safety and scalability benefits are again evident. The use of a continuous flow system allowed 1000 psi of H_2 to be used, while ensuring that the concentration of H_2 present at any given time was far below the explosive limit even if the entire system released at once.

The presented work demonstrated that flow chemistry can usefully be applied to pgm-catalysed processes on multi-kilogram scales. These methods have the potential to increase yields and enantioselectivities by adjusting reactor residence times and pressures while lowering associated risks through reducing the volume of hazardous mixtures. Flow chemistry is now more than a laboratory curiosity and has a significant role to play in the future of the pharmaceutical industry.

One-Pot Reactions

Although processes can be optimised individually for manufacturing, it is equally important to have efficient methods for the expedient synthesis of diverse structures for discovery chemistry. This can be achieved through multi-step, one-pot procedures.

The use of boronates as coupling partners in metal-catalysed carbon-carbon bond forming reactions remains a favoured choice in synthesis. Todd Marder (Durham University, UK; now University of Würzburg, Germany) presented his and Patrick Steel's groups' research into borylation reactions, including how to combine borylations with Suzuki-Miyaura cross-coupling reactions in a one-pot process.

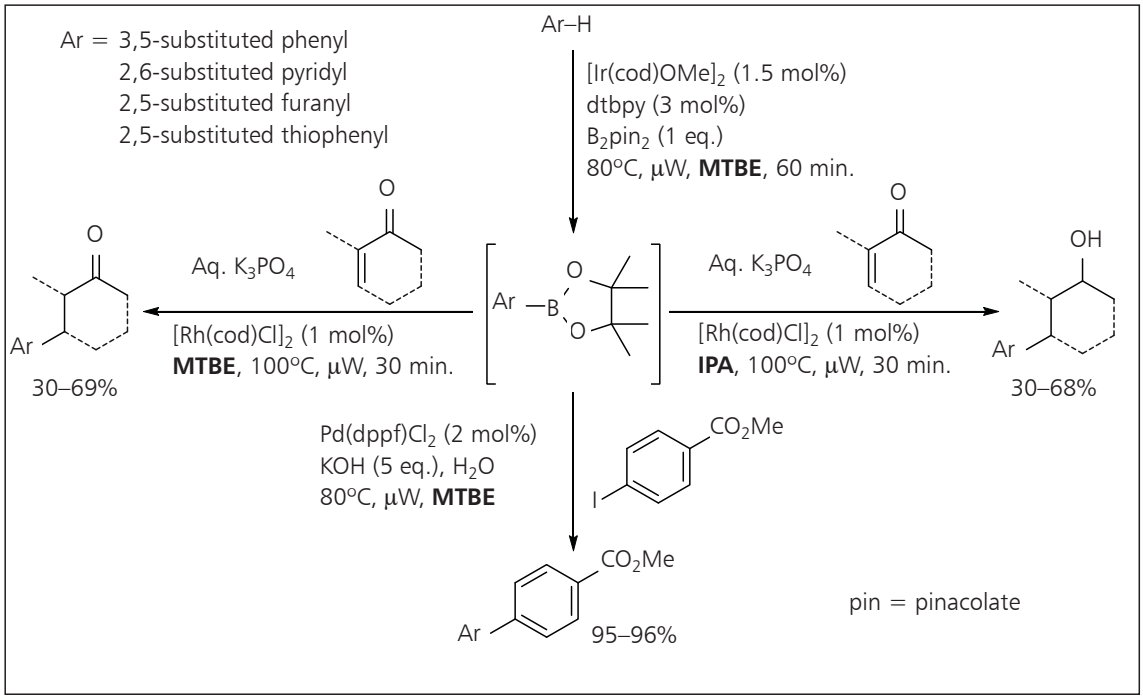


Scheme II. Formation of the precatalyst and the catalytic cycle of the rhodium-catalysed reduction of citral (4)

The challenge until now has been that iridium-catalysed borylation processes work best in non-coordinating solvents such as hexane. Unfortunately Suzuki-Miyaura cross-couplings, which use a Pd catalyst, are most effective when performed in polar solvents such as dimethylformamide (DMF), ethanol or dioxane. Previously this meant carrying out separate steps, hence two solvents, two work-ups and often two purifications. Using an optimised protocol with methyl *tert*-butyl ether (MTBE) as solvent, the entire process could be performed sequentially in one pot. Yields of 87%–94% of biaryls were achieved with low catalyst loadings in a total reaction time of 9 hours under thermal conditions (6). Microwave heating (μW) significantly accelerated the borylation reactions while giving comparable yields. This allowed the one-pot tandem C–H borylation/Suzuki-Miyaura sequence to proceed in 95%+ yields on a range of aryl and heteroaryl substrates with reaction times of under an hour and in some cases as short as ten minutes (7).

The tandem one-pot principle has been extended to a borylation/1,4-conjugate addition. A Rh catalyst promotes conjugate addition, and microwave heating accelerated both steps, reducing total reaction time to minutes rather than hours. Choice of solvent proved vital to the outcome of the reaction. After the borylation step in MTBE, addition of the Rh catalyst and enone in MTBE gave the 1,4-conjugate addition product in 30%–69% yield. If *iso*-propanol (IPA) was used as the solvent, reduction of the ketone *via* transfer hydrogenation occurred providing the secondary alcohol product (a three-step process) (8). The chemistry has been shown to be suitable for array synthesis and the production of compound libraries (**Scheme III**).

Borylation of C–H bonds as a means to further functionalisation has been a major research theme for many years (9) and John Hartwig (University of California, Berkeley, USA) presented some of his group's contributions to this important area. Crude reaction mixtures from the Ir-catalysed formation of pinacol boronate esters can be used directly in the synthesis of boronic acids, trifluoroborates, halides, nitriles, ethers and amines. A series of mechanistic studies on the borylation reaction identified that the rate determining step in catalytic turnover is oxidative addition of the aryl C–H to the catalyst (10). Creating



Scheme III. Scope and effect of solvent on the outcome of two-step, one-pot borylation/1,4-conjugate addition reactions (6–8)

a more electron-rich Ir centre by careful tuning of the ligand gave rise to a more active catalyst. Switching from the usual 4,4′-di-*tert*-butylbipyridine (dtbpy) ligand to a substituted phenanthroline resulted in a catalyst which allowed a practical borylation of octane catalysed by the same starting Ir complex.

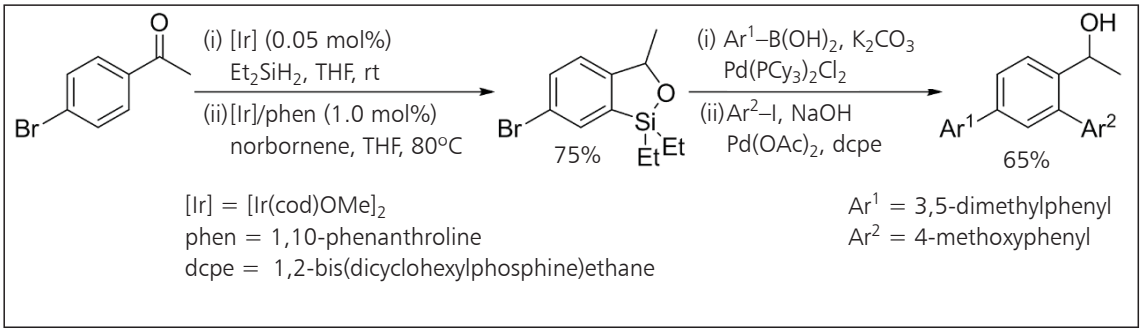
As a complementary approach, intramolecular silylation of aromatic C–H bonds can provide a useful chemoselective handle for further functionalisation of arenes (**Scheme IV**). Acetophenones can readily be converted to the corresponding benzoxasiloles without any intermediate purification and careful choice of base allowed sequential Suzuki-Miyaura and Hiyama couplings to be performed (11). This practical approach to building molecular complexity in two one-pot procedures not only provides rapid accessibility to diverse structures, but also reduces the number of manipulations required and waste produced in the sequence.

Poster Presentations

The award for best student poster went to Paul Colbon (University of Liverpool, UK) who presented a method for the direct acylation of aryl halides with alkyl aldehydes. A palladium-amine cooperative catalysis approach was successful in generating alkyl aryl ketones from aryl chlorides using a bulky, electron-rich monophosphine ligand (13). Condensation of the amine with the aldehyde produces an enamine which undergoes a Heck-type arylation. Reductive elimination of Pd reforms the enamine which hydrolyses to give the ketone product and turns over the amine. In keeping with a major theme of the meeting, this method can be extended to a one-pot process where the aldehyde is formed *in situ* by arylation and isomerisation of allyl alcohol. Addition of pyrrolidine and a second aryl bromide to the reaction mixture results in acylation (14).

Selectivity in heterogeneous catalysis can be achieved by modifying the formation of Pd nanoparticles. James Cookson (Johnson Matthey, UK) showed how nanoparticles formed in the presence of a simple amine or amino acid could be used in selective reductions. Alkynes were reduced exclusively to alkenes and nitro chloro arenes could be reduced to the corresponding amine without any dehalogenation (15).

Probing the exact nature of pgm catalysts and the changes they undergo during a catalytic process is not easy. Anna Kroner (Diamond Lightsource, UK) gave an overview of the techniques available at the



Scheme IV. Iridium-catalysed intramolecular silylation of aromatic C–H bonds and further functionalisation of the arene product (11)

UK synchrotron science facility which could be useful for the study of such processes. X-Ray scattering and X-ray absorption spectroscopy are already available at Diamond and a new dispersive extended X-ray absorption fine structure (EXAFS) beamline should come online in the near future to allow time resolved studies at the microsecond level.

Concluding Remarks

Improving the efficiency and practicality of catalytic processes can be achieved in a number of ways. Finding optimal conditions through a directed screening approach is one successful strategy, but other factors play an important role. Achieving multiple transformations in one-pot or taking advantage of technologies such as flow chemistry can have a dramatic impact on safety, waste management, cost and hence the overall practicality of a chemical process. In both industry and academia much progress has been made in improving and widening the scope of pgm methods, but significant challenges remain and many processes are still far from perfect. What is certain is that the scientific community is actively addressing these "Challenges in Catalysis for Pharmaceuticals and Fine Chemicals".

The next meeting in the series is expected to take place towards the end of 2013 and will be announced by the SCI and RSC in due course.

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The Reviewer

John Brazier is a Research Associate in the Department of Chemistry at Imperial College, London, UK. A background in mechanistic catalysis led him to his current position working on various aspects of both homogeneous and heterogeneous palladium catalysis with particular interests in the roles which solvents play in these reactions.