

Catalysis in Organic Synthesis

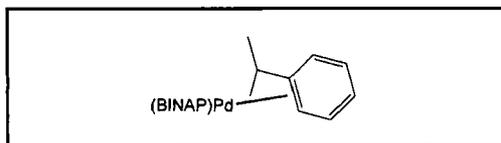
A JOHNSON MATTHEY SYMPOSIUM FOR INDUSTRY ON NEW DEVELOPMENTS IN CATALYSIS

The first Johnson Matthey symposium "Catalysis in Organic Synthesis" was held on the 17th May 2001 at the Madison Hotel, New Jersey, U.S.A. The symposium, organised and sponsored by Johnson Matthey, was attended by over 100 people from the fine chemical, pharmaceutical and other industries in which platinum group metals (pgms) catalysts are commonly employed. The symposium comprised a session on homogeneous catalysis and one on heterogeneous catalysis.

Homogeneous Catalysis

Advances in palladium catalysed allylic alkylation were described by Professor Barry Trost (Stanford University, U.S.A.). The reaction can be used to desymmetrise cyclic alkenes. The range of nucleophiles now includes phenols. Allylic alkylation can be combined with a subsequent Heck reaction using a bulky ligand.

Professor John Hartwig (Yale University, U.S.A.) has identified new catalysts for the hydroamination of alkenes using high throughput screening techniques. He discovered that when aniline, for example, is reacted with cyclohexadiene, any unreacted aniline can be derivatised with furfural to form a red dye. The best catalysts can therefore be selected by eye. So far, Pd(PPh₃)₄ catalyses the reaction of anilines with a range of dienes. The reaction can be carried out enantioselectively using a chiral ligand, such as Trost's naphthyl ligand. Styrenes are hydroaminated with primary amines using a palladium(II) complex, for example, Pd(dppf)(OTf)₂. The activity decreases as the nucleophilicity of the amine decreases and enantiomeric excesses of ~ 70% have been obtained with Pd(BINAP)(OTf)₂. Professor Hartwig proposed a mechanism for these reactions involving the η³ styrene coordination:



An X-ray structure of this intermediate has been obtained; the amine will react with the complex to give the hydroaminated product.

Polymer supported catalysts provide easy catalyst separation and permit safer handling of toxic catalysts. Mats Sundell (Oy Smoptech, Finland) explained how problems associated with abrasion and poor functional group availability can be overcome using polymer fibres, typically 5–50 μm in diameter. Functional groups are introduced by grafting side chains onto the polyethylene backbone. Ion exchange reactions take place much faster on fibres than on beads, therefore it is possible to carry out gas phase ion exchange. Homogeneous catalysts can be supported on fibres and have been successfully used in cross-coupling, hydrogenation and oxidation reactions.

Professor Michael Doyle (University of Arizona, U.S.A.) discussed the use of chiral dirhodium(II) carboxamidates to catalyse carbene reactions. A range of catalysts containing different carboxamidate ligands had been prepared. Lengthening the Rh-Rh bond by changing the ligand increases the catalyst activity. Substrate:catalyst ratios of 5000:1 have thus been obtained. The catalyst can also affect the regiochemistry of the product: in the reaction of cholesterol diazo acetate either a γ- or β-lactone is made depending upon the handedness of the catalyst used. Dirhodium(II) dicarboxamidate complexes will also catalyse hetero Diels-Alder reactions.

Alkene metathesis reactions also proceed via a metalcarbene intermediate, but in these reactions a metallocycle is additionally formed. Professor Robert Grubbs (Caltech, U.S.A.) described ruthenium catalysed metathesis reactions. Ruthenium catalysts tolerate more functional groups than early transition metal catalysts. This permits highly functionalised substrates such as peptides. The catalyst precursor is a 16 electron Ru(L)₂Cl₂(carbene) species. However, to enter the catalytic cycle, one of the ligands (L) dissociates to allow alkene coordination. It is therefore beneficial for the

remaining ligand to be bulky and electron donating. Imidazoline-2-ylidene ligands have been used in this role. The saturated version of this ligand has even greater basicity and shows very high activity. An insect pheromone for the peach twig borer has been synthesised using alkene metathesis as a coupling reaction. The side reaction of double bond isomerisation in the product was suppressed by adding $P(CH_2OH)_3$ to remove the ruthenium into the aqueous phase. Cross-metathesis has also been used to synthesise flavins and to incorporate isoprene units.

Sarah Elgafi (Johnson Matthey, U.K.) discussed the use of high throughput screening techniques in catalyst choice. Seemingly minor electronic changes in the substrate can greatly alter the profile of optimum catalysts. Screening is an effective way to identify promising ligands quickly. It can also be used to explore other parameters such as the base in coupling reactions. Recently, the technique has been used to evaluate fibre supported catalysts (FibreCat™) and palladacycles.

Heterogeneous Catalysts

The afternoon session focused mainly on the use of heterogeneous catalysts. This encompassed both their use in specific organic transformation and new kinds of supported catalyst such as those developed by Professor Robert Augustine (Seton Hall University, U.S.A.). Professor Augustine presented his work on anchoring homogeneous catalysts to supports. The method used to anchor these catalysts involves modifying alumina or other supports with a heteropoly acid. The modification allows attachment of conventional homogeneous catalysts to the support, the advantage being that preformed catalysts such as $[Rh(Duphos)(diene)]^+BF_4^-$ can be used. The activity and selectivity of the anchored rhodium catalysts was reported to be the same as that seen for the homogeneous system with the added benefit that the catalysts could be recycled.

Process optimisation of the new artificial sweetener, Neotame®, was discussed by Mike Scaros (G. D. Searle, retired, U.S.A.). The synthesis of Neotame®, which is fifty times sweeter than the conventional artificial sweetener Aspartame,

involves an imine hydrogenation over Pd/C. He described the way in which the process was optimised by investigating catalysts, solvents and other process conditions to maximise product formation and minimise impurities.

The use of pgms for the selective oxidation of alcohols to aldehydes was discussed by Ken Griffin (Johnson Matthey, U.K.). This is a synthetically useful transformation; methods normally used are generally stoichiometric and employ toxic compounds such as $KMnO_4$ and chromium compounds. This transformation can be carried out catalytically using air as the oxidant, making this a very attractive industrial process.

Professor Agnes Zsigmond (University of Szeged, Hungary) presented a paper on the hydrogenolysis of C-N and C-O bonds. Benzyl groups are used as protecting groups for amines and alcohols, and hydrogenolysis is the method commonly used for removal of these groups. Professor Zsigmond discussed hydrogenolysis of a wide range of substrates, some containing sensitive functional groups, using Pd/C catalysts under either hydrogen or transfer hydrogenolysis conditions.

The final presentation was made by Richard A. Teichman (Johnson Matthey, U.S.A.) who gave a paper on the handling and recovery of pgms. This informative paper described the methods used for the recovery of metals from spent catalysts. Two processes were discussed: first, the conventional method of refining via combustion, smelting and metal separation; second, the removal of metals from waste streams by ion exchange onto Smopex™ fibre supports.

The symposium was a great success in illustrating the role of pgms as catalysts for industrial applications and in bringing together academics and industrialists. Johnson Matthey is hoping to make this symposium an ongoing event.

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