Hydrogenation technology: ruthenium-catalysed asymmetric reduction of ketones

The asymmetric reduction of C=O bonds is of fundamental importance in modern synthetic chemistry. Asymmetric chemocatalysis and biocatalysis offer complementary solutions to the problem of the stereoselective reduction of C=O bonds and both techniques have found wide industrial applicability. Johnson Matthey, Catalysis and Chiral Technologies (JM CCT) has access to what is, to date, the most robust and cost-effective chemocatalytic technology for asymmetric ketone reduction. Professors Noyori and Ikariya developed two new ruthenium systems in the mid 1990’s based on pressure and transfer hydrogenation chemistry and, today, catalytic asymmetric hydrogenation technology can be used to generate enantiomerically pure secondary alcohols in a highly efficient, operationally simple and economic way. The Japanese Science and Technology Corporation (JST) patented the technology and a licence for this was granted to JM CCT in 2003.

ASYMMETRIC HYDROGENATION OF KETONES

In the 1980s the research conducted by Prof. Noyori’s group on BINAP-ruthenium catalysts opened the way to the efficient asymmetric hydrogenation of C=O bonds. It was found that BINAP-ruthenium catalysts were useful for the hydrogenation of functionalised ketones possessing secondary binding groups (such as in ketoesters and amino or hydroxy-ketones) capable of coordinating the substrate to the reactive metal centre in the form of rigid 5 and 6 membered chelates, which are believed to be necessary for high enantioselectivity. In the mid 1990s, the research group of Noyori developed a ‘second generation’ of catalysts based on a ruthenium metal centre bearing a chiral diphosphine and a chiral diamine ligand. In the presence of a base, the asymmetric hydrogenation of a wide range of unfunctionalised ketones became possible without the need for any secondary binding group on the substrate. This was confirmed by mechanistic studies that showed that the catalytic reaction takes place without direct coordination of the substrate to the metal centre. The catalyst acts as a “bifunctional” scaffold for the anchoring of the substrate and the delivery of the hydride (Figure 1) and the reaction takes place within the external coordination sphere of the catalyst. For the first time, an unprecedented array of chiral secondary alcohols could be prepared with extremely high stereoselectivity and turnover numbers (TON: moles of substrate/moles of catalyst, of up to 1 million can be achieved on model substrates). The reduction of aromatic, heterocyclic and unsaturated ketones was reported to proceed with excellent productivity and enantioselectivity. Aliphatic ketones too were reduced but only with moderate selectivity.

Figure 1: Catalytic asymmetric hydrogenation of non-functionalised ketones
Biarylphosphines based on the model of BINAP 1 (Figure 3) proved highly successful as ligands in the Noyori ‘second generation’ catalysts. The nature of the substituents on the phosphorus atom is very important, with the 3,5-disubstituted arene groups generally imparting higher activity and selectivity to the catalyst6. It has been recently demonstrated that the presence of ortho-substituents on the BINAP backbone gives results similar to those produced by 3,5-disubstituted arene substituents7. The P-Phos ligand family 2 (for which JM CCT has a licence from the Hong Kong Polytechnic University) was developed by Prof. Chan and is particularly suited for this kind of non-functionalised ketone hydrogenation thanks to enhanced activity and excellent selectivity8.

One class of chiral diphosphine ligands that does not fit into the ‘BINAP-type’ biarylphosphine model is PhanePhos 3 (Figure 3)9. When employed in ruthenium catalysts in combination with diamines, these ligands exhibit exceptional activity in the hydrogenation of many aromatic and heteroaromatic ketones and reaction rates often superior to those obtainable with the conventional biarylphosphine-based catalysts10. JM CCT has further developed the concept of paracyclophane-based ligands in the design of the proprietary ligand Paraphos 411. The regioselective introduction of a substituent on the paracyclophane backbone simplified the original synthesis of PhanePhos by facilitating a classical resolution of an early intermediate. This new class of proprietary ligands 4 display very high activity and selectivity in ketone hydrogenation catalysis.

RECENT DEVELOPMENTS IN KETONE HYDROGENATION

Both JM CCT and other researchers have recently begun focussing attention on the role of the ancillary ligand. The most commonly used diamines in the second-generation Noyori catalysts are the 1,2-diamines, DPEN 5 and DAIPEN 6 (Figure 3). Only in the presence of some specific phosphines has it been shown that 1,2-thioethers can replace 1,2-diamines12. Since both the phosphine ligand and the diamine ligand are chiral, a very strong ‘matching/mismatching’ effect takes place when the two are combined and one of the two possible diastereoisomers of the catalyst is usually much more active and selective than the other. Mikami’s group has shown that specific diamine ligands can selectively ‘activate’ one of the two enantiomers of the catalyst. Achiral biaryl phosphines too can be used in combination with a diamine ligand that induces a preferred ‘matched’ conformation in the flexible phosphine moiety13. More recently it has been found that chiral 1,4-diamines are a very useful complement to 1,2-diamines. Cyclic ketones were a class of substrates hitherto impervious to asymmetric hydrogenation and Noyori’s group reported that substrates such as tetralone could be efficiently reduced using ruthenium catalysts combining BINAP ligands and 1,4-diamine 7 (Figure 3)14. At JM CCT it has been found that with a similar class of catalysts (using diamine 8) is now possible to hydrogenate sterically hindered aromatic ketones such
as isobutyrophenone\textsuperscript{15}. Intriguingly, it has been found that racemic 1,4-diamines can be used in combination with enantiomerically pure phosphines such as P-Phos without affecting reaction rates and selectivity. While a very strong ‘matching/mismatching’ effect takes place when phosphines and 1,2-diamines are combined, in the case of 1,4-diamine \textsuperscript{8} the stereochemical outcome of the reaction is totally controlled by the phosphine ligand.

**ASYMMETRIC TRANSFER HYDROGENATION OF KETONES**

In the process known as transfer hydrogenation, the metal-hydride responsible for the reduction of the ketone in the catalytic cycle is regenerated by organic molecules acting as hydrogen donors. Catalysts of the type (sulphonyl-diamine) RuCl (arene) (Figure 4) are suitable for this type of catalysis and hydrogen donors such as isopropanol or formic acid are conventionally used. These new catalysts were also developed by Prof. Noyori and Prof. Ikariya in the 1990s\textsuperscript{16}.

In the transfer hydrogenation catalytic cycle the hydrogen donor generates a ruthenium hydride species that stereoselectively transfers the hydride to the substrate via a ‘bifunctional’ mechanism related to the one that operates for hydrogenation\textsuperscript{17}.

A reversible reaction is obtained in the presence of isopropanol and a base, which can be detrimental to both yield and enantioselectivity, while an irreversible reaction takes place with mixtures of formic acid and triethylamine\textsuperscript{18}. Changing the arene moiety\textsuperscript{16} as well as the diamine backbone or the sulfonyl substituent\textsuperscript{19} can modify both the activity and selectivity of the catalysts and allows one to search for the best ‘match’ for any given substrate.

**RECENT DEVELOPMENTS IN TRANSFER HYDROGENATION**

A significant amount of very recent work in the field of asymmetric transfer hydrogenation has been focussed on the optimisation of reaction conditions for ruthenium catalysts, a very important factor when it comes to industrial applications.

Biphasic reaction conditions have been developed that allow the highly chemoselective reduction of substrates such as α-bromo or α-chloroacetophenone that would otherwise easily give side-products\textsuperscript{20}. Recent results obtained at Liverpool University by Xiao’s group in collaboration with JM CCT have demonstrated that unmodified ruthenium transfer hydrogenation catalysts not only can work under biphasic conditions but, in fact, display a significant rate enhancement when used in water\textsuperscript{21}.

**ADVANTAGES OF KETONE HYDROGENATION AND TRANSFER HYDROGENATION TECHNOLOGY**

The asymmetric catalytic reduction of a ketone offers fundamental advantages over other means of producing chiral alcohols (either making use of separation technology or asymmetric synthesis with stoichiometric reagents). Very high selectivity (often >98% e.e.) is obtained in a very reproducible manner. The reaction goes to full conversion without side-reactions and the consequent ease of the work-up leads to elevated chemical yields (often >95% isolated yield). This is achievable under mild reaction conditions and the waste stream is enormously reduced. Another advantage of designing a synthetic step based on reduction of a ketone is that such a step can be switched from a stoichiometric reduction/separation...
technology to an asymmetric catalytic methodology when the target molecule enters the development stage without any rearrangement of the overall synthetic strategy.

**Catalytic asymmetric transfer hydrogenation** has the advantage that it is highly functional group tolerant (Figure 5). Substrates containing coordinating groups such as nitro, cyano and heterocyclic groups can be reduced without side-reactions, as can acetylenic compounds, cyclic ketones, α and β-keto-esters, α,β-diketones. In addition, no specialised pressure equipment is required to operate a transfer hydrogenation reaction. Good TONs (such as TON 5000) have been achieved in industrial processes and the transfer hydrogenation catalysts of the type (sulphonyl-diamine) RuCl (arene) do not require the use of any expensive phosphine ligand. Transfer hydrogenation with ruthenium catalysts is a particularly robust reaction and is compatible with a variety of organic solvents, a range of pHs in water and hydride sources (sodium and ammonium formate or mixtures of triethylamine and formic acid).

**Catalytic asymmetric hydrogenation** has been successfully applied to a vast number of substrates but the reaction is more limited than transfer hydrogenation in terms of reaction conditions that can be applied. For instance the reaction is normally carried out in isopropanol under basic conditions (a catalytic amount of t-BuOK is usually added). If the substrate contains any acidic functionality this has to be first deprotonated by adding a stoichiometric amount of base. A preformed ruthenium-hydride complex can be used under neutral conditions but it has been shown that, even in this case, much higher TONs are obtained when a base is added. Nevertheless, when a substrate is a suitable candidate for both catalytic hydrogenation and transfer hydrogenation (Figure 5), it is the catalytic hydrogenation that tends to be more productive with TON well in excess of 10-20,000 reported for substrates of industrial relevance. In several cases even higher turnover numbers (in excess of TON 100,000) have been reported. A recent work by industrial researchers shows not only exceptionally low catalyst loadings but also that the basic conditions under which the reaction takes place can be exploited for a dynamic kinetic resolution process. Both hydrogenation and transfer hydrogenation catalysts display an exceptional degree of chemoselectivity and C=O groups are reduced without any competitive reduction of C=C bonds in any other part of the molecule. This is much more difficult to achieve with 'first generation' ruthenium and rhodium catalysts. Hydrogenolysis of halogen-carbon bonds, a side reaction that often occurs in the presence of heterogeneous hydrogenation catalysts, does not occur when ruthenium homogeneous catalysts are applied. Both hydrogenation and transfer hydrogenation reactions can be run at high concentrations (up to 2M), making them very volume-efficient. The cost of the catalyst is offset by its high productivity, which is unprecedented for a catalytic asymmetric reaction: only 100g of a generic (diphosphine) Ru (diamine) catalyst (MW ~1,000) working at S/C 20,000/1 would be required to reduce one ton of an hypothetical substrate of MW 500. The optimised asymmetric ketone hydrogenation reaction goes to full conversion with excellent selectivity and no by-products. This makes this technology particularly suited to the batch mode production favoured by the pharmaceutical industry where reproducibility and robustness of the process and control over the impurity profile are very important issues. The main impurity is usually the catalyst residue and the best way to minimise the problem of heavy metal residues is, of course, to optimise the reaction to operate at the lowest possible catalyst loadings. The reaction product is recovered by distillation or, more often, recrystallisation. Other means of removing ruthenium metal residues from the product include the use of activated carbon or polymer-supported scavengers (such Smopex, a proprietary Johnson Matthey’s technology).
CONCLUSIONS

The technology for the asymmetric reduction of ketones covers a large spectrum of substrates, including highly complex and functionalised molecules, and is economically viable in the industrial production of pharmaceutical intermediates. A wide range of catalysts based on well-established ligands produced on multi-Kg scale is available and the scope of the reaction is continually expanding with the discovery of ruthenium catalysts based on new combinations of ligands. Johnson Matthey, Catalysis and Chiral Technologies is in a perfect position to provide to customers access to such technology and to develop it into cost effective processes.

REFERENCES