

Emerging trends in homogeneous hydrogenation catalysis

Dr Antonio Zanotti-Gerosa and **Dr Hans G. Nedden** of **Johnson Matthey Catalysis and Chiral Technologies** look at recent developments in catalysis for pharmaceuticals and fine chemicals

The reduction of prochiral functional groups, C=C, C=O and C=N bonds using homogeneous catalysis technology is becoming increasingly prevalent in the pharmaceuticals and fine chemicals industries. The economics of such reactions must always be assessed in the context of various competitive and complementary technologies, namely biocatalysis and homogeneous and heterogeneous chemocatalysis. A thorough review can prove quite challenging without an extensive understanding of the complexities of catalytic performance.

Johnson Matthey's Catalysis and Chiral Technologies business has expertise in each of these technology areas for the identification and development of optimal catalytic processes. It also has experience in the area of supported platinum group metal (PGM) and base metal catalysis, which is applicable when achiral or diastereoselective routes to the target are possible, plus a portfolio of chiral ligands and catalysts for asymmetric homogeneous reduction, many of which are available at commercial scale from its own facilities.

More recently, Johnson Matthey Catalysis and Chiral Technologies has established a significant presence in biocatalysis by acquiring the German company X-

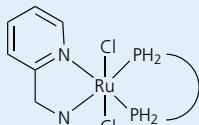
Zyme. The portfolio of ADHs, esterases, ene-reductases and a newly expanded line of transaminases are essential components for identifying the most efficient process.

Biocatalysis is a fast-growing technology, rapidly expanding its scope of applications and overcoming some of the original limitations, such as process intensity. In some areas, such as C=O reduction, an optimised biocatalytic process will provide unmatched enantioselectivity.

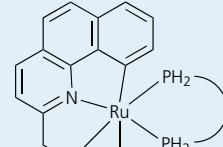
In comparison, the successful use of chemocatalysts will rely more on catalyst availability, speed of development and process efficiency, although often with less than ideal enantioselectivity. A vast set of chiral phosphine ligands and metal catalysts has been developed and patented in the past decades.

With the initial set of 'historical' ligands coming off-patent, research has largely moved away from the development of yet more novel chiral phosphine ligands and onto new industrial processes using the mature classes of chiral ligands and catalysts.

The most advanced academic and industrial research favours the study of new catalytic transformations. When new homogeneous catalysts are developed, often by combining known mature ligands with metals in new architectures, the aim is to move into new territories, such as



[(P^P) RuCl₂ (Ampy)]



[(P^P) RuCl₂ (AMBO)]

Figure 2 - Baratta's catalysts

the hydrogenation of aromatic rings and of carboxylic acid derivatives.

In this article we will discuss some of the most prominent trends in the areas of homogeneous hydrogenation technology, including the application of Binap chiral phosphine ligands, the development of new classes of ruthenium catalysts with increased catalytic efficiency and the breakdown of the traditional boundaries between hydrogenation and transfer hydrogenation and between chiral and achiral catalytic applications.

Binap-based reactions

Binap is the most widely applicable and available chiral phosphine ligand. The award of the 2001

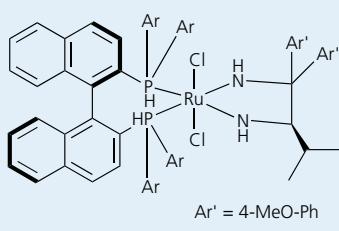
Nobel Prize to Professor Ryoji Noyori recognised the development of ligands with the Binap core structure and the derived ruthenium and rhodium catalyst. Johnson Matthey Catalysis and Chiral Technologies has since improved the routes to these catalysts and is now producing them on multi tens of kilograms scale.

The use of specific ruthenium Binap complexes, such as acetate, trifluoroacetate, halides, acetylacetone complexes, cationic complexes and monomeric and polymeric species, in certain applications and processes is often, although not always, just a historical legacy.

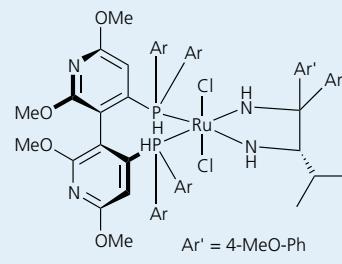
With an improved understanding of the effect of reaction conditions, the number of useful catalyst precursors can in fact be reduced to few well-characterised Binap-ruthenium complexes with good industrial scalability, such as [Binap RuCl(arene)]Cl complexes. The use of [Binap RuCl(arene)]Cl complexes can also substitute catalysts prepared *in situ* from [RuCl₂ cod]_n and Binap with substantial process improvements.

The availability of the Binap ligands and their complexes may appear to make obsolete the plethora of ligands with axial chirality that have been developed mostly to bypass the Binap patents. In many cases, Binap - especially when combined with ruthenium - will be the most cost-effective choice for most applications, given its availability and lower cost.

However, technical considerations, such as higher enantioselectivity or activity, and IP considerations like process patents specifically claiming applications of Binap catalysts, can shift the balance in favour of the use of 'newer generation' catalysts. The availability of alternatives providing structural and electronic diversity remains important to ensure a high success rate in catalytic applications.



[(R)-Binap RuCl₂ (R)-DAIPEN]
Ar = Ph, Tol, Xyl



[(S)-P-Phos RuCl₂ (S)-DAIPEN]
Ar = Ph, Tol, Xyl

Figure 1 - Noyori pressure hydrogenation catalysts

A significant example comes from a recent collaboration between Johnson Matthey Catalysis and Chiral Technologies and Krka of Novo Mesto, Slovenia, focused on the asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline, a precursor to the drug Solifenacine. The project highlighted the option of applying the P-Phos ligand as an alternative to Binap because of its improved enantioselectivity (>95% ee vs. 87%).¹

Noyori's catalysts

Noyori's hydrogenation catalysts for the asymmetric reduction of non-functionalised ketones, $[(P^P) RuCl_2 (N^N)]$ (Figure 1), were introduced in the mid-1990s. This type of catalyst displays high productivity (TON 1,000-50,000) and enantioselectivity (often >95% on benzylic ketones) but has somewhat limited reaction conditions, requiring the use of alcoholic solvents (mainly *i*-PrOH) and the use of bases. Their application also generally benefits from high (20-50 bar) hydrogen pressure, which may limit their applicability at scale.

Some applications of [Xyl-P-Phos RuCl₂ Daipen] developed by Johnson Matthey Catalysis and Chiral Technologies in collaboration with customers have been reported recently.^{2,3} Interestingly, in these examples the development of suitable reaction conditions was more challenging than the catalyst choice itself.

This is contrary to the perception that catalyst identification is always the bottleneck of the process and

therefore high-throughput screening is the necessary solution. In both examples, the catalyst with the later generation Xyl-PPhos ligand was preferable to the Xyl-Binap ligand analogue.

'Multi-tasking' catalysts

In the mid-2000s, the search for more active catalysts led to the introduction of pyridine-based amine ligands as replacement for the chiral diamine ligands. $[(P^P) RuCl_2 AMPY]$ catalysts and the cyclometallated $[(P^P) RuCl (AMBO)]$ (Figure 2).^{4,5} Both were developed by Professor Walter Baratta at the University of Udine in Italy and are exclusively licensed to Johnson Matthey Catalysis and Chiral Technologies.

These catalysts bridged the gap between hydrogenation and transfer hydrogenation catalysts, by displaying exceptionally high activity under both hydrogenation (MeOH or EtOH, sub-stoichiometric amounts of base) and transfer hydrogenation (*i*-PrOH/base) conditions. The presence of the flat, achiral aminopyridine substituent allows for TONs up to one order of magnitude higher than the previous Noyori-type catalysts.

Whilst significant chiral applications have been demonstrated, the achiral catalysts may prove to be of even greater use when highly chemoselective, achiral, racemic or diastereoselective applications are required. Even more importantly, there is growing recognition of the fact that hydrogenation catalysts can be applied to a number of

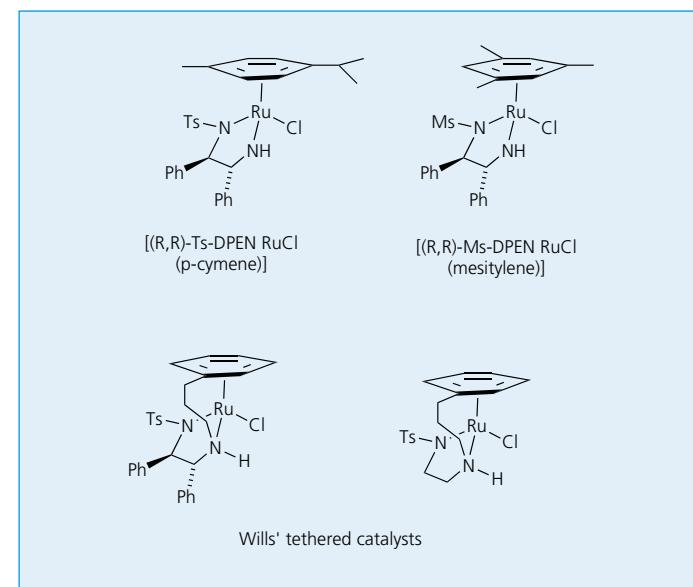


Figure 4 - Transfer hydrogenation catalysts

other catalytic transformations. $[(Dppf) RuCl_2 AMPY]$ has been described as a 'multi-tasking' catalyst with a range of applications from hydrogenation to transfer hydrogenation, allylic isomerisation, alcohol dehydrogenation and α -arylation (Figure 3).⁶

Wills' tethered catalysts

Noyori's transfer hydrogenation $[(\text{sulfonyl-diamine}) Ru(\text{arene})Cl]$ catalysts (Figure 4) have found a vast number of industrial applications. The catalysts can be used in a variety of conditions, giving a reversible reaction with *i*-PrOH/base or an irreversible reaction with various combinations of HCOOH/Et₃N in organic solvents or NaOOCH in aqueous or biphasic media.

The catalysts are modular and their properties can be easily tuned by changing the arene substituent and the substituent at the sulfonyl group. Typical TONs are between 500 and 5,000.

Professor Martin Wills of Warwick University, UK, has designed a new generation of complexes where the arene moiety is linked to the diamine ligands (Figure 4).⁷ This generates more robust catalysts that are significantly less prone to being deactivated by the poly-functionalised substrates common in the life science industry.

Starting from a small sample of $[(\text{Ts-DPEN-teth}) RuCl]$ supplied to Johnson Matthey Catalysis and Chiral Technologies, Wills' tethered catalyst has been brought to kilogram-scale production via an

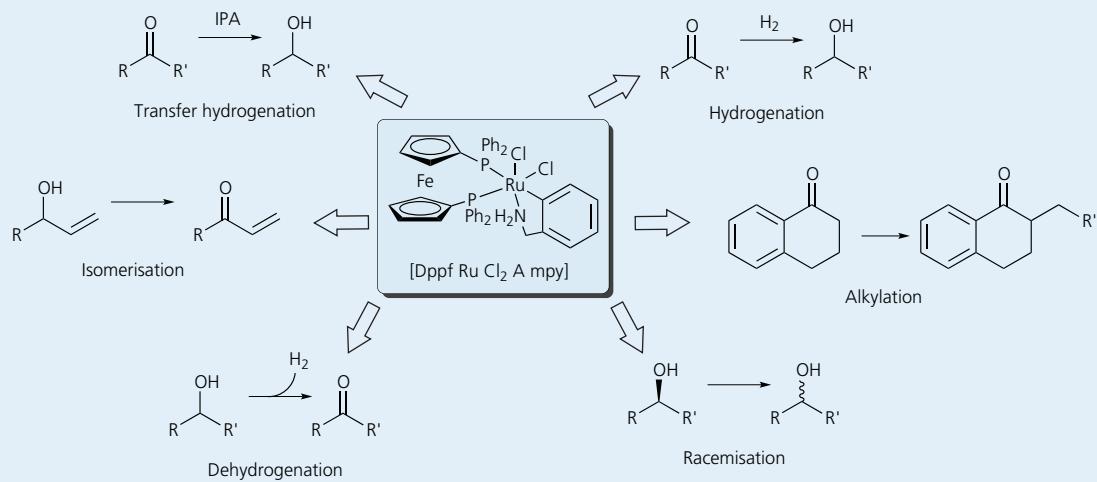


Figure 3 - $[(Dppf) RuCl_2 AMPY]$: A 'multi-tasking' catalyst

improved synthetic route.⁸ The basic concept has proven to be highly successful and has been applied to related systems by other industrial and academic research groups.

Noyori reported in 2006 that the transfer hydrogenation catalysts of the type [sulfonyl-diamine Ru(arene)Cl] could be activated to pressure hydrogenation by replacing the chloride counter ion with a less coordinating triflate.⁹ This has sparked interest in a new generation of 'phosphine-free' hydrogenation catalysts with ruthenium, rhodium and iridium.

Although the TONs do not yet fully match those of the best phosphine catalysts, the concept is very interesting, since the chiral phosphine ligand is often the most expensive building block of the chiral catalyst. The Technology Strategy Board, the UK's innovation agency, has recently given financial backing to a joint research program between Johnson Matthey Catalysis and Chiral Technologies and Warwick University for the development of phosphine-free hydrogenation catalysts.

One special advantage of hydrogenation with phosphine-free catalysts is the hydrogenation of base-sensitive substrates. Wills' tethered catalyst does not require any modification for it to be applied successfully under hydrogenation conditions.

The achiral version, [Ts-EN-teth RuCl], will be of interest in reductions where high chemoselectivity is required, effectively complementing the use of heterogeneous hydrogenation catalysts. For example, the hydrogenation of aldehydes under neutral conditions has been demonstrated in MeOH and water, often in the presence of groups that could be easily reduced by heterogeneous catalysts.⁸ Under transfer hydrogenation conditions the catalyst has displayed high activity (TON 5,000-10,000) on various carbonyl substrates.

Outlook and future trends

Some common trends can be identified for both chemo- and biocatalysis. The two technologies are and will remain both competitive and complementary. Access to both is and will remain necessary to provide fast and practical solutions to catalytic synthetic problems.

The ever increasing cost pressure on the production of pharmaceutical and fine chemical products means that constantly improved catalytic processes are required. The most recently developed classes of catalysts offer a much needed operational flexibility by bridging the gap between hydrogenation and transfer hydrogenation.

Homogeneous catalysts and enzymes are usually associated with chiral transformations. There is however, a great potential for application in achiral reductions, exploiting the high chemoselectivity of homogeneous catalysts for certain functional groups and the inherently high substrate specificity of enzymes. The field of dehydrogenation of alcohols - an oxidation without using any oxygenated reagent - will, for example, benefit from the use of homogeneous catalysts as well as enzymes.

In addition, the growing interest for the development of alternative routes for soon-to-be generic pharmaceuticals offers an opportunity to study innovative transformations. It is often the case of developing new catalysis that enables the desired synthetic route rather than the synthetic route being designed around what 'state of the art' catalysis can deliver.

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