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Ruthenium-Catalysed Asymmetric Reduction of Ketones

DIPHOSPHINE LIGANDS IN HYDROGENATIONS FOR PHARMACEUTICAL SYNTHESIS

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The asymmetric reduction of carbonyl, C=O, groups for the production of enantiomerically pure secondary alcohols is a reaction of fundamental importance in modern synthetic chemistry. This reaction can be performed in a number of ways. Asymmetric chemocatalysis (1) and the often complementary biocatalysis offer solutions to the stereoselective reduction of C=O groups. These two techniques have found wide industrial application (2). In the mid 1990s, two new ruthenium systems based on dihydrogen or transfer hydrogenation for asymmetric reduction of prochiral ketones were developed by Professors Noyori and Ikariya. These systems enable catalytic asymmetric reduction to provide a route for the generation of enantiomerically pure secondary alcohols in a highly efficient, simple and economic way (3). This paper describes some robust and cost-effective chemocatalytic technology for asymmetric ketone reduction, using ruthenium catalysts with diphosphine ligands.

The clean asymmetric hydrogenation of ketones is a reaction of particular importance to the pharmaceutical industry. In the 1980s, research by Professor Ryoji Noyori's group at Nagoya University in Japan, on BINAP-ruthenium catalysts opened the way to the efficient asymmetric hydrogenation of C=O groups (3). They found that BINAP-ruthenium catalysts were useful for the hydrogenation of functionalised ketones (such as β-ketoesters, β-amino-ketones and β-hydroxy-ketones) that possessed secondary binding groups capable of coordinating the substrate to the reactive ruthenium metal centre in the form of 5- and 6-membered chelates. The chelates were believed to be necessary for high enantioselectivity.

In the mid 1990s, Noyori's group developed a 'second generation' of catalysts. These are based on a ruthenium metal centre bearing a chiral diphosphine and a chiral diamine ligand, see Figure 1 (4). In the presence of a base (such as *t*-BuOK) the asymmetric hydrogenation of a wide range of unfunctionalised ketones now became possible, without the previous need to have a secondary binding group on the substrate. Mechanistic studies then confirmed that the catalytic reaction was taking place without the direct coordination of the substrate to the metal centre (5). In effect, the catalyst is acting as a 'bifunctional' scaffold for anchoring the substrate and transferring the hydride, see Figure 1. Hydrogenation of the ketone is taking place within the external coordination sphere of the catalyst.

Using this catalyst, an enormous array of chiral secondary alcohols could be prepared – for the first time – with extremely high stereoselectivity and turnover number (TON = moles of substrate/moles of catalyst). For instance, a TON of up to 1 million is achievable on model substrates, such as aryl ketones. Aromatic, heteroaromatic and unsaturated ketones could be reduced with excellent productivity and enantioselectivity; however, aliphatic ketones were reduced, but only with moderate selectivity.

Asymmetric Phosphine Ligands

Biarylphosphines ligands, based on BINAP, **1**, see Figure 2, proved to be highly successful in Noyori's 'second generation' catalysts. The nature of the substituents on the phosphorus atoms is very important, and 3,5-disubstituted arene groups

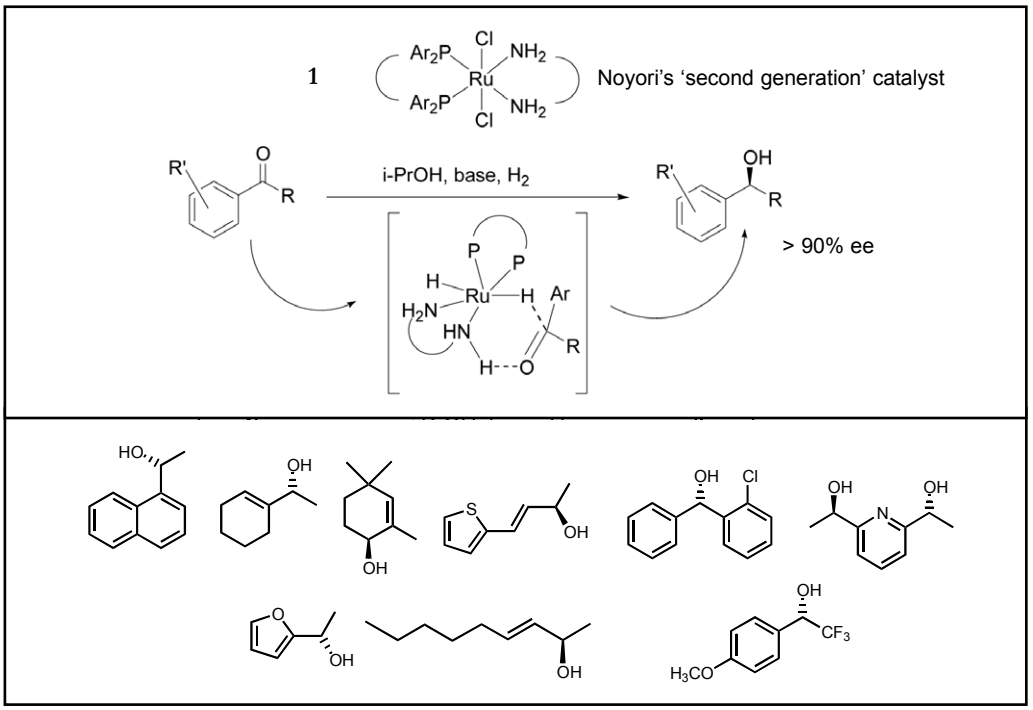

Fig. 1 Upper: catalytic asymmetric hydrogenation of non-functionalised ketones using Noyori's 'second generation' ruthenium catalyst. The 'scaffold' provided by the catalyst to the hydrogenating ketone is shown.
Lower: some of the chiral secondary alcohols produced using Noyori's 'second generation' ruthenium catalyst

generally impart higher activity and selectivity to the catalyst (6). It has been reported recently that if *ortho*-substituents are present on the BINAP backbone, results similar to those produced by the 3,5-disubstituted arenes (7) can be obtained.

The P-Phos ligand family, **2**, see Figure 2, was developed by Professor Albert Chan (Hong Kong Polytechnic University). P-Phos is a biaryl diphosphine with the unique feature of incorporating two methoxy-substituted pyridine rings in the backbone; this permits a straightforward and easily scaleable synthesis of the P-Phos ligand. It also contributes to the balance of electronic and steric properties that makes the P-Phos ligand more active and selective than the analogous BINAP ligand in a number of applications, for instance in the ruthenium-catalysed hydrogenation of β-ketoesters. P-Phos is particularly suited to the

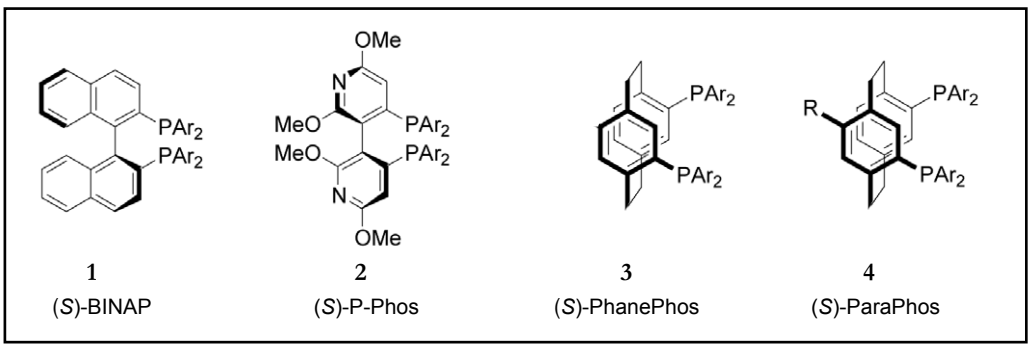

Fig. 2 Some of the phosphine ligands used in Noyori's 'second generation' catalysts

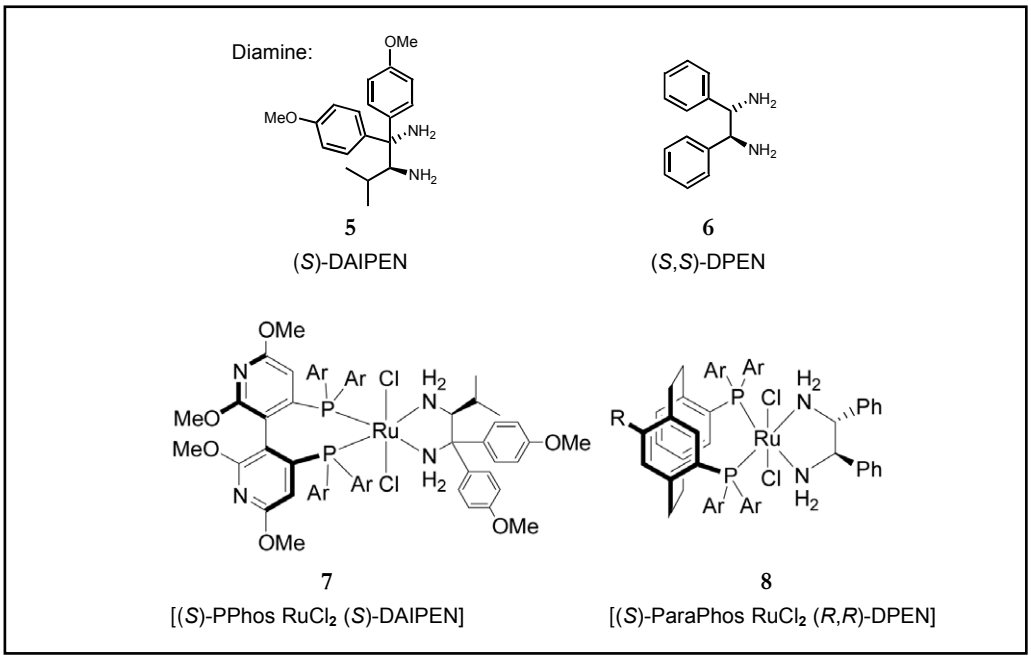

Fig. 3 The DAIPEN and DPEN ligands, and as used in 'second generation' Noyori catalysts as ancillary ligands

non-functionalised hydrogenation of ketones (8).

PhanePhos ligands, **3**, are a class of chiral diphosphine ligands that do not fit the 'BINAP-type' biarylphosphine model (9). PhanePhos is a paracyclophane-based ligand and, when employed in ruthenium catalysts in combination with diamines, shows exceptional activity in the hydrogenation of many aromatic and heteroaromatic ketones. The reaction rates obtained are often superior to those obtained with conventional biarylphosphine-based catalysts (10).

The design of paracyclophane-based ligands has been extended to a new class of ligand: ParaPhos, **4**, (11). Investigations on the reactivity of the common precursor 4,12-dibromo[2.2]paracyclophane for electrophilic aromatic substitution led to the development the ParaPhos group of paracyclophane-based ligands (5). The original synthesis of PhanePhos was simplified when a substituent was regioselectively introduced onto the paracyclophane backbone. This facilitated a classical resolution of an early intermediate. When combined with ruthenium, see Figure 3, ParaPhos displays very high activity and selectivity in ketone hydrogenation catalysis.

The Ancillary Ligand in Ketone Hydrogenation

The role of the ancillary ligand in an asymmetric catalyst has recently attracted attention. In Noyori's 'second-generation' catalysts the most commonly used ligands are the 1,2-diamines: DAIPEN, **5**, and DPEN, **6**, see Figure 3.

It has also been shown that 1,2-thioethers can replace 1,2-diamines, providing that some specific phosphines are present (12). Since both the phosphine ligand and the diamine ligand are chiral, a very strong 'matching/mismatching' effect takes place when the two are combined in the catalyst.

One of the two possible diastereoisomers of the catalyst is usually much more active and selective than the other. Mikami and colleagues have shown that certain diamine ligands can selectively 'activate' one of the two enantiomers of the catalyst (13). They also found that achiral biaryl phosphine ligands can be used in combination with a diamine ligand; the diamine ligand induces a preferred 'matched' conformation in the flexible phosphine moiety (13).

More recently Noyori has found that chiral 1,4-diamine ligands complement the 1,2-diamines and

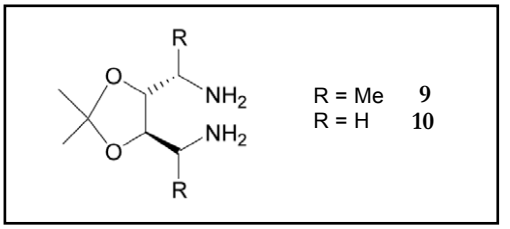

Fig. 4 1,4-Diamine ancillary ligands

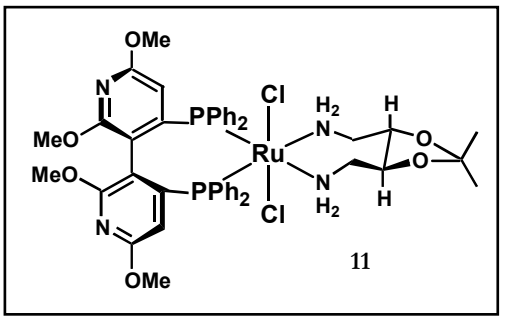

Fig. 5 A 'second generation' Noyori ruthenium catalyst with a P-Phos and a 1,4-diamine ancillary ligand

could be useful in the reduction of some difficult substrates. For instance, cyclic ketones was a class of substrate resistant to asymmetric hydrogenation. Noyori reported that such substrates, for example tetralone, could be reduced efficiently using ruthenium catalysts that combined BINAP ligands and 1,4-diamine, **9**, see Figure 4 (14).

The hydrogenation of sterically hindered aromatic ketones, such as isobutyrophenone, is also possible, using a similar class of catalysts bearing a P-Phos and a 1,4-diamine, **10** (Figure 4) to give **11** (Figure 5) (15). Curiously, it has been found that racemic 1,4-diamines can be used in combination with enantiomerically pure phosphines, such as P-Phos without affecting the reaction rate or selectivity. Although a very strong 'matching/mismatching' effect takes place when phosphines and 1,2-diamines are combined, if the 1,4-diamine ligand, **10**, is employed, the stereochemical outcome of the reaction is totally controlled by the phosphine ligand.

Asymmetric Transfer Hydrogenation of Ketones

In transfer hydrogenation, the metal hydride responsible for the reduction of the ketone in the catalytic cycle is regenerated *in situ* from organic molecules acting as hydrogen donors. In the 1990s, Noyori and Ikariya developed catalysts suitable for this type of catalysis. The catalysts are of type (sulfonyl-diamine)RuCl(arene), see Figure 6, and hydrogen donors such as isopropanol or formic acid are typically used (16).

In the catalytic cycle for transfer hydrogenation the hydrogen donor generates a ruthenium hydride species. This species stereoselectively transfers the hydride to the substrate *via* a 'bifunctional' mechanism related to the one that operates for hydrogenation (17). A reversible reaction is obtained – in the presence of isopropanol and a base – which can be detrimental to both yield and enantioselectivity. With mixtures of formic acid and triethylamine, an irreversible reaction is obtained (18). When the arene moiety in the ligand is changed (16), as well

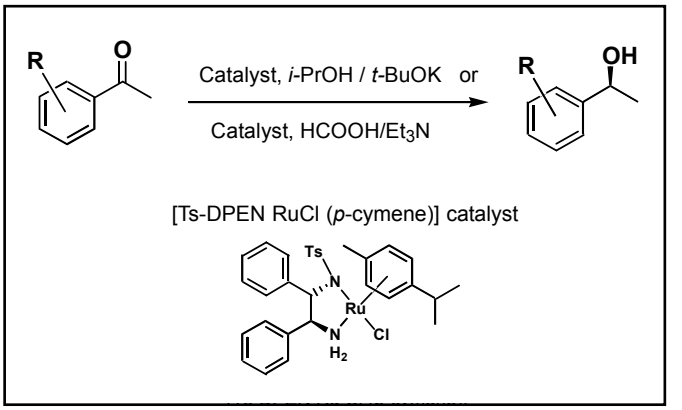

Fig. 6 In asymmetric transfer hydrogenation, the metal hydride responsible for the reduction of the ketone is regenerated in situ from organic molecules acting as hydrogen donors.
In the 1990s, Noyori and Ikariya developed catalysts for asymmetric transfer hydrogenation. The catalysts, which do not carry a phosphine ligand, are of type: (sulfonyl-diamine)RuCl(arene)

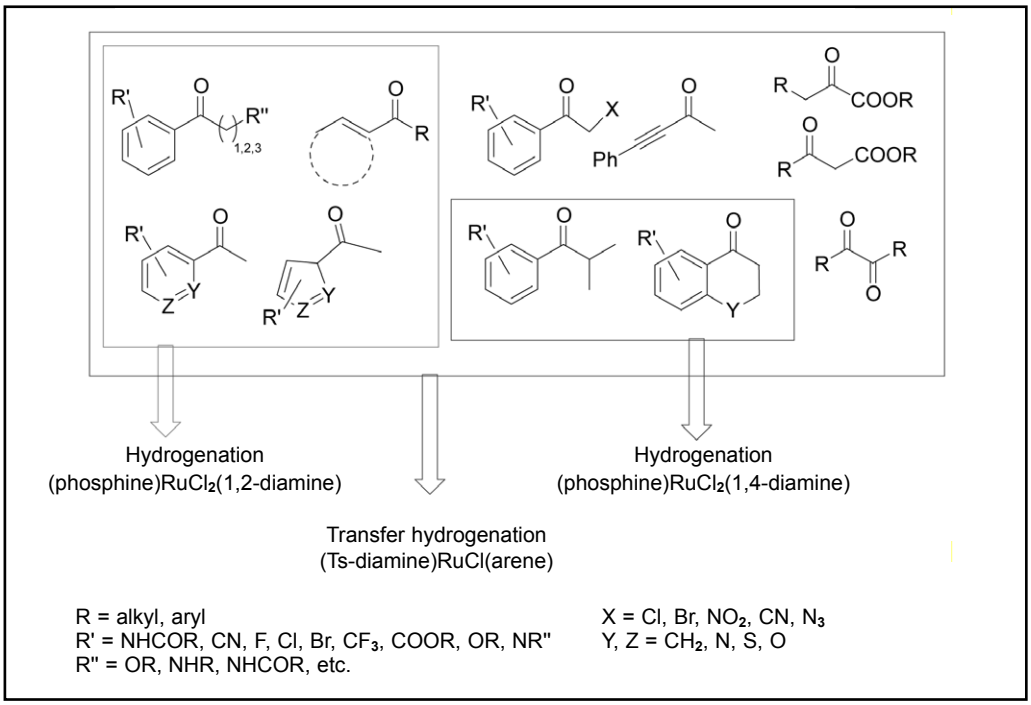

Fig. 7 Various asymmetric hydrogenations that are possible using ruthenium phosphine catalysts with diamine ligands, and some asymmetric transfer hydrogenations that use ruthenium catalysts not carrying phosphine ligands. Examples of the various types of substrate that can be hydrogenated are listed

as either the diamine backbone or the sulfonyl substituent (19), then both the activity and selectivity of the catalysts are modified, and the best 'match' for any given substrate can be established.

Recent Developments

There has been much activity in the areas of asymmetric catalytic hydrogenation and transfer hydrogenation recently. For instance:

- Work on asymmetric transfer hydrogenation has been aimed at the optimisation of reaction conditions for the ruthenium catalysts. This is important for industrial applications.
- Biphasic reaction conditions have been developed that allow the highly chemoselective reduction of substrates, such as α-bromo- or α-chloroacetophenone. Under other conditions side-products form easily (20).
- Unmodified ruthenium transfer hydrogenation catalysts can work under biphasic conditions; but in addition, when used in water a significant rate enhancement is observed (21).

Advantages of Ketone Hydrogenation and Transfer Hydrogenation Technology

Using the asymmetric catalytic reduction of a ketone to produce chiral alcohols has advantages over other means of production (separation technology or asymmetric synthesis with stoichiometric reagents). For instance, the selectivity is very high (often > 98% ee) and is very reproducible. The reaction goes to full conversion without side-reactions and the ease of the work-up leads to increased chemical yields (often > 95% isolated yield). This is achievable under mild reaction conditions and the waste stream is greatly reduced.

Another advantage of designing a synthetic step based on the reduction of a ketone is that such a step can be switched from separation/stoichiometric reduction 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 is tolerant of highly functional groups on the sub-

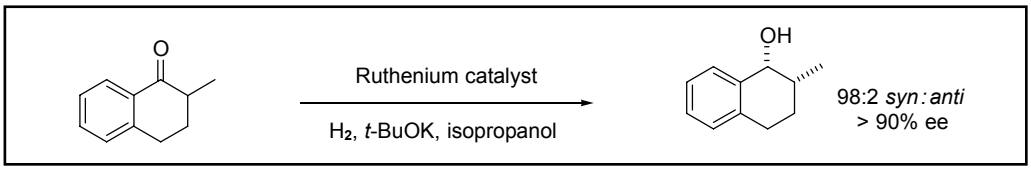

Fig. 8 Tetralone is shown undergoing asymmetric hydrogenation using a ruthenium catalyst in basic solution to produce a secondary alcohol

strate. Figure 7 gives an indication of the range of substrates that can be hydrogenated. Substrates containing coordinating groups, such as nitro, cyano (22) and heterocyclic (23) groups, can be reduced without side-reactions, as can acetylenic compounds, cyclic ketones (16), α- and β-keto-esters (24) and α-diketones (25). In addition, there is an advantage in that no specialised pressure equipment is required to operate a transfer hydrogenation reaction. Good TONs (such as TON 5000) have been achieved in industrial processes (26). Figure 6 also shows the range of transfer hydrogenations possible. The catalysts used are of type (sulfonyl-diamine)RuCl(arene) without the expensive phosphine ligand, see Figure 6.

Transfer hydrogenation using ruthenium catalysts is a robust reaction and is compatible with a variety of organic solvents and water, a range of pH, and many hydride sources (not limited to sodium and ammonium formate or mixtures of triethylamine and formic acid).

On the other hand, catalytic asymmetric hydrogenation has been successfully applied to a vast number of substrates but, in terms of the reaction conditions, is a more limited reaction than transfer hydrogenation. For instance:

- The reaction is normally carried out in isopropanol under basic conditions (a catalytic amount of *t*-BuOK is usually added), see Figure 1.
- Any acidic functionality that the substrate contains will have to be deprotonated by adding a stoichiometric amount of base.
- A preformed ruthenium hydride complex can be used under neutral conditions, but when a base is added much higher TONs are obtained (27).

Nevertheless, when a substrate is a suitable candidate for both catalytic asymmetric hydrogenation and catalytic asymmetric transfer hydrogenation, catalytic asymmetric hydrogenation tends to be more productive. Indeed, TONs well in excess of 10,000–20,000 have been reported for substrates of industrial relevance, and in several cases even higher TONs (> 100,000) have been reported. Recent industrial research has shown that exceptionally low catalyst loadings can be achieved and, in addition, that the basic reaction conditions under which the reaction takes place can be exploited for a dynamic kinetic resolution process, see Figure 8 (28).

Both hydrogenation and transfer hydrogenation catalysts display an exceptional degree of chemoselectivity and C=O groups can be reduced without any competitive C=C bond reduction occurring in other parts of the molecule. These homogeneous catalysts will not reduce alkenes, nitro groups, arenes or aryl-halide bonds.

Both hydrogenation and transfer hydrogenation reactions can be run at high concentrations (up to 2 M), making them very volume-efficient. The cost of the catalyst is offset by its high productivity – unprecedented for many catalytic asymmetric reactions. Only 100 g of a generic (diphosphine)Ru(diamine) catalyst (MW ~ 1000) working at a typical ratio of substrate:catalyst = 20,000:1 would be required to reduce one ton of a hypothetical substrate of MW 500.

The optimised asymmetric ketone hydrogenation reaction goes to full conversion with excellent selectivity without byproducts. This makes the 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 important issues.

The reaction product is recovered by distillation or, more often, by recrystallisation. The main impurity is usually the catalyst residue and the best way to minimise this is to optimise the reaction to operate at the lowest possible catalyst loadings.

Other means of removing ruthenium metal residues from the product include the use of activated carbon or polymer-supported scavengers.

Conclusions

The technology for the catalytic asymmetric reduction of ketones now covers a large spectrum of substrates, including highly complex and functionalised molecules. The process is economically viable for industrial production of pharmaceutical intermediates. A wide range of catalysts based on well-established ligands produced on multi-kilo scale is available and the scope of the reactions is continually expanding, especially with the discovery of ruthenium catalysts based on new combinations of ligands.

However, developments are still needed and new technology required to meet the challenges of processes, such as the hydrogenation of aliphatic ketones and reductive amination. The development of new ligands and catalysts will remain a "hot topic" in research for many years to come.

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