Industrial-Scale Synthesis and Applications of Asymmetric Hydrogenation Catalysts

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Received May 8, 2007

ABSTRACT

This Account provides an overview of our activities in the area of asymmetric hydrogenation over the last 12 years. We discuss the manufacture of metal-containing precatalysts and their use in asymmetric hydrogenation processes. Many of the metal complexes have been made on a multikilogram scale for our own use and also provided to our customers. In addition, we review some of the applications that we have developed for our asymmetric hydrogenation catalysts, many of which have been operated on commercial scales. This all underlines that asymmetric hydrogenation is a mature technology that has been adopted for use in the pharmaceutical and fine-chemical industries.

Introduction

Asymmetric chemocatalysis provides the opportunity to design concise and efficient routes to enantiomerically enriched molecules, especially for high-value pharmaceutical applications.[1] Recent trends in the Food and Drug Administration (FDA) approval of new drug applications clearly show that the percentage of chiral drugs has increased significantly from 58% in 1992 to 75% in 2006, while achiral drug approvals demonstrate a significant decrease over the same period. Furthermore, the proportion of single enantiomer drugs manufactured using purely synthetic methodology (i.e., not using chirality pool starting materials) has increased from 20% in 1992 to over 50% in 2006. A broad range of technologies is encompassed by asymmetric chemocatalysis, such as alkylation, conjugate addition, cycloaddition, hydroformylation, hydrogenation, and oxidation. Of these, a limited number have been applied to pharmaceutical manufacture, with asymmetric hydrogenation being the most widely used technology.

The earliest commercial application of asymmetric hydrogenation was for L-DOPA developed by Knowles in the 1970s. This pioneering work led to Knowles sharing the Nobel Prize with Noyori and Sharpless in 2001. In the 1980s, the benchmark system was Noyori's [1,1′-binaphthalene]-2,2′-diylbis[diphenylphosphine] (BINAP)-based catalysts that are still used in the manufacture of β-hydroxy esters, for the synthesis of carbapenems[2] and the Lipitor side chain for example. The range of initial application of asymmetric hydrogenation was somewhat limited by the diversity of ligands available in the early years. In the 1990s, there was an explosion of activity in the development of new ligand systems, such as DuPhos, developed by Burk,[3] and Josiphos, developed by Togni and Spindler.[4] To date, there are in excess of 1000 ligand systems available for use in asymmetric hydrogenation applications.[5] More recently launched drugs, such as Tipranavir,[1] Rozerem,[6] Sitagliptin,[7] and Aliskiren,[8] are reported to use asymmetric hydrogenation in their synthesis.

Chirotech, now part of Dowpharma, has been active in the field of asymmetric hydrogenation since 1995, when we obtained an exclusive license from DuPont for the DuPhos ligand and catalyst technology for commercial pharmaceutical applications. Subsequently, we developed many asymmetric hydrogenation reactions, including processes for the synthesis of a key intermediate for the potent atrial natriuretic factor potentiator Candoxatril, the HIV protease inhibitor Tipranavir, and the anticonvulsant

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Nicholas B. Johnson was born in Swindon, U.K., in 1969. He obtained his B.Sc. degree in chemistry from the University of Manchester Institute of Science and Technology (UMIST) in 1991, remained at UMIST working with Prof. Richard Stoodley studying the preparation of peptidomimetics of potential therapeutic interest, and obtained his Ph.D. degree in 1994. Joining Chiroscience in 1994, initially as a research chemist, he has subsequently moved into business development roles and was awarded an M.B.A. from Imperial College London in 2005. His main focus is now on the commercial development and marketing of Dowpharma's asymmetric catalytic technologies, primarily for use in the pharmaceutical industry.

Ian C. Lennon was born in Lisburn, Northern Ireland, in 1963. He graduated from the University of St. Andrews in 1985 with a B.Sc. degree in chemistry and then worked for Merck, Sharp & Dohme Harlow, Essex, in drug discovery. In 1989, he left Merck to study for a Ph.D. degree with Steve Ley at Imperial College, London. In 1993, Ian joined Chiroscience, and in 1995, he carried out a secondment with Barry Trost at Stanford University to evaluate his palladium(0)-catalysed asymmetric allylic alkylation technology. In 2000, Ian's responsibilities were extended to include management of the chemocatalysis core research team. Chirotech was acquired by The Dow Chemical Company in 2001 and is now part of Dowpharma. Ian is currently a Scientist and Technology leader for Chemocatalysis and is involved with the development of asymmetric chemocatalysis capability, promotion of chiral technology, and management of customer projects. Ian is an Editorial Advisory Board member of *Organic Process Research & Development* and *Chimica Oggi*.

Paul H. Moran was born in 1972 in Paisley, Scotland. He obtained a B.Sc. degree in chemistry from the University of Strathclyde, where he worked with Prof. Peter L. Pauson on the synthesis of jasmonoid compounds via the cobalt-mediated Pauson–Khand reaction. He was awarded the title of Dr rer nat from the Technische Universität Berlin in 1998 while investigating the photochemical reactions of organorhodium complexes under the supervision of Prof. Jörn Müller. After a brief postdoctoral spell, working in the field asymmetric organomagnesium chemistry, with Prof. Kenneth W. Henderson and Prof. William J. Kerr, he took up his current position in Chirotech (now Dowpharma). His main interests revolve around the commercial production of chiral ligands and catalysts for the use in asymmetric processes for the pharmaceutical industry.

Jim Ramsden was born in Leeds in 1963. After obtaining his B.Sc., M.Sc., and Ph.D. degrees from the University of Sheffield, he held postdoctoral placements with Prof. John A. Gladysz in Utah, studying the use of chiral organometallic complexes and metal/metal-supported carbon chains, and with Dr. John M. Brown at Oxford, studying mechanistic aspects of rhodium-catalysed asymmetric hydrogenation. Having worked for Zeneca and Avecia, he moved to Chirotech (now Dowpharma) in 1998. His research interests are in the application of chiral organometallic compounds as synthetic templates and in the discovery and application of catalytic asymmetric processes.

10.1021/ar700114k CCC: $37.00
Published on Web 09/06/2007

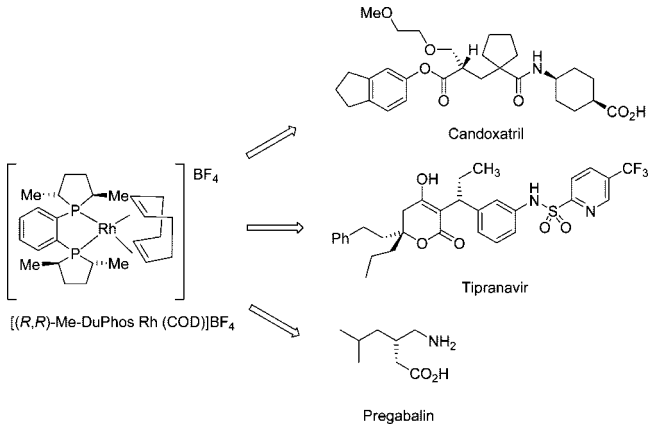
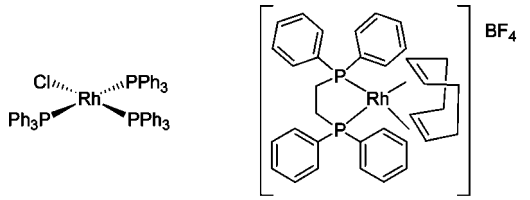


FIGURE 1. Pharmaceutical applications of Rh-Me-DuPhos.



Wilkinson's catalyst Schrock-Osborn type cationic complex

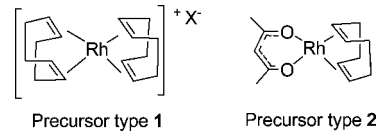
FIGURE 2. Early molecular homogeneous rhodium catalysts.

Pregabalin (Figure 1), all using the [(*R,R*)-Me-DuPhos Rh (COD)]BF_4 complex.[1]

Having developed numerous effective and efficient catalytic processes during the initial years of our research, we were faced with the challenge of preparing precatalysts on a multikilogram scale. Early attempts to manufacture ligands and precatalysts showed that robust, scaleable, and reproducible manufacturing methods for these key products would not be trivial to obtain. In this Account, we review the methods that we investigated to allow for the commercial-scale manufacture of such precatalysts; the successful methodology has been applied to over 10 other rhodium-based systems, including Et-DuPhos, Me-BPE, Et-FerroTANE, and PhanePhos. Moreover, we have gone on to develop robust methodologies to manufacture various ruthenium-based precatalysts, including Ru-DuPhos, Ru-BPE, and the [diphosphine $RuCl_2$ diamine] precatalysts. All of these synthetic methodologies will be discussed, including some of the more recent applications of our asymmetric hydrogenation technologies.

Synthesis of Rhodium Catalysts

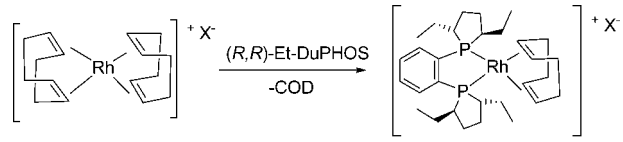
The utility of phosphine-modified rhodium catalysts for unsaturated bond reduction came to the forefront when Wilkinson and Coffey independently discovered a new hydrocarbon-soluble and highly active rhodium precatalyst $RhCl(PPh_3)_3$ (commonly referred to as Wilkinson's catalyst)[9] and Osborn and co-workers introduced the more reactive hydrogenation systems based on cationic [diolefin Rh diphosphine]$^+$ complexes (Figure 2).[10] These discoveries demonstrated that reduction of unsaturated organic species could be achieved with a well-defined, highly reactive and selective homogeneous molecular catalyst under relatively mild conditions, with distinct



Precursor type **1** Precursor type **2**

FIGURE 3. Catalyst precursors.

Scheme 1. First-Generation Synthesis of DuPhos-Rh Precatalysts



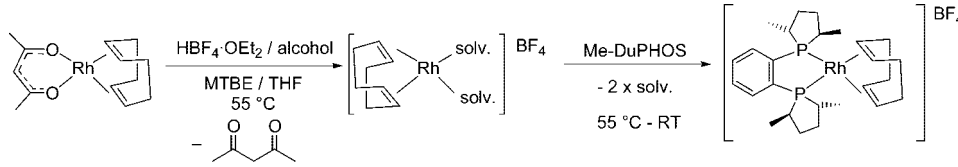
chemical and process advantages over the common heterogeneous hydrogenation catalysts.

With the more recent advent of complex and expensive chiral ligand systems, the question of the manufacture and use of preformed catalysts over *in situ*-generated species is a common one for practitioners of asymmetric hydrogenation. Only with a preformed catalyst can the quality of the complex be accurately defined and the exact catalyst loading be quantified. This cannot be achieved with an *in situ*-generated catalyst. These issues are of the greatest significance when using such catalysts in validated pharmaceutical processes operated under cGMP. Consequently, we have been consistently in favor of the use of preformed catalysts, because we see significant benefits in the simplification of the hydrogenation process and a higher degree of control that preformed catalysts (or as is most often the case, a precatalyst) generally exert. The choice of precursor and catalyst type is generally governed by a series of simple criteria: (i) synthetic performance, (ii) stability, physical form, and handling of the complexes, and (iii) cost and availability.

Of the numerous commercially available rhodium catalyst precursors, we have consistently found two families of precursors to be the most useful and practical for generating precatalysts, namely, [$(diolefin)_2Rh^I]^+$ X^- (**1**)[11] and [diolefin Rh^I acetylacetonate] (**2**)[12] (Figure 3).

Both complex types **1** and **2** have found utility in our hands for precatalyst synthesis, because they are equally capable of being cleanly converted to the desired precatalyst complex. In the case of **1**, the precatalyst is simply generated by the addition of a suitable ligand to a solution of **1**, upon which a rapid ligand exchange takes place and a single 1,5-cyclooctadiene ligand is displaced by two phosphine ligands or a single diphosphine ligand (Scheme 1). However, there are properties of complexes **1** and **2** that render them suitable for different spheres of application. Complexes of the type **1** have limited solubility in the majority of favorable reaction solvents for production, and generally, strongly polar or chlorinated solvents were required to solubilize the precursor. As a result, the majority of the precatalyst remained in solution and an antisolvent was required to initiate and complete precipitation of the product.[13] Our experience has shown that such antisolvent-precipitated precatalysts are crystallized in a less than optimal manner, such that adequate control of the product form and overall particle size is challenging. Typically, such products are generated as very fine ma-

Scheme 2. Optimized Synthesis of the Me-DuPhos-Rh Precatalyst



terials with high surface areas, such that the chemical, physical, and handling properties are generally considered by us to be undesirable for large-scale synthesis and applications. Nonetheless, this synthesis protocol is indeed exceedingly simple and commonly used by us for the rapid generation of small libraries of catalysts for small-scale screening purposes, whereby the required strict criteria for large-scale production are not necessarily required to be vigorously adhered to.

For large-scale precatalyst production, the use of the $[(\text{diolefin})_2\text{Rh}^{\text{I}}]^+ \text{X}^-$ is not suitable and we have developed a generic protocol that is capable of producing cationic diphosphine-Rh catalysts in high yield with improved reactor throughput (Scheme 2). Our efforts in generating a new large-scale synthetic process focused primarily on the type-**2** complex [(1,5-cyclooctadiene) Rh^{I} acetylacetonate] for a number of reasons: (i) long-term stability, (ii) ease of handling of the material, and (iii) the reactivity of the acetylacetonate group in the presence of strong acids.[10] Initial investigations quickly showed that we could prepare numerous intermediates of the type [(diolefin) Rh $(\text{solvent})_2]\text{X}^-$ [where the solvent is typically tetrahydrofuran (THF), methyl tert-butyl ether (MTBE), EtOH, *i*-PrOH, or H_2O], which were stable at reflux for prolonged periods of time, from [(1,5-cyclooctadiene) Rh^{I} acetylacetonate] by the addition of a strong acid, such as tetrafluoroboric acid. The stability of the bis-solvato species was remarkable in that they could be generated at reflux, heated for several hours, evaporated to dryness, and with the addition of fresh solvent be reused for the synthesis of the precatalyst without any significant detrimental effects. Ethereal solvents and mixtures thereof were among the best solvents for the starting material [(1,5-cyclooctadiene) Rh^{I} acetylacetonate] and some of the most effective antisolvents for the precatalyst of the type [(diolefin) Rh (diphosphine)]BF_4. Concentrated solutions of [(1,5-cyclooctadiene) Rh^{I} acetylacetonate] in MTBE/THF (~1 kg in 6 L) could be turned into concentrated solutions of the bis-solvato cation by the addition of an alcoholic acid solution, followed by the addition of an appropriate ethereal solution of the ligand to cleanly generate the desired [(diolefin) Rh (diphosphine)]BF_4 precatalyst, such that controlled crystallization of the product took place at an elevated temperature and during the addition of ligand.

We found that this protocol controlled effectively the rate of nucleation at higher temperatures through the rate of ligand addition, such that a granular, robust free-flowing precatalyst could be deposited in exceptionally high yields (Figure 4). The first system demonstrated at multikilogram scale was [(*R*,*R*)-Me-DuPhos Rh COD]BF_4 (Scheme 2), and to date, numerous other ligands (not limited to bisphosphines) have been shown to be amenable to generating highly crystalline, physically robust, and stable materials. Application of this protocol to a wide variety of ligands was effectively controlled via subtle tailoring of the ratios of the initial reaction solvents MTBE and THF, as well as by judicious choice of the alcohol and ethereal solvents for the acid and ligand feeds, respectively.[13] Figure 5 illustrates the isolated yields for a series of precatalysts manufactured via the aforementioned route, all of which have been employed for the manufacture of pharmaceutical intermediates in either clinical development or commercial manufacture.

In many examples, the control of the process and product quality is more than just a simple function of the chemistry performed, because it is influenced significantly by starting material quality and reactor setup, none more so than in the case of [Me-BPE Rh COD]BF_4. At scale, the efficiency of the process to form [Me-BPE Rh COD]BF_4 was found to be dramatically linked to the reactor setup and, in particular, the mode of the addition of ligand to the reactive intermediate [(diolefin) Rh $(\text{solvent})_2]BF_4^-$, point of entry of the feed stream into the reaction mixture, and impeller type and position. Bis-ligand complexes such as $[(\text{Me-BPE})_2\ \text{Rh}]BF_4$ were found to readily form in significant quantities (>15%) with nonoptimal reactor layouts, whereas the optimal setup could reduce this byproduct to <0.9% without changing the reactive chemistry or the solvents.

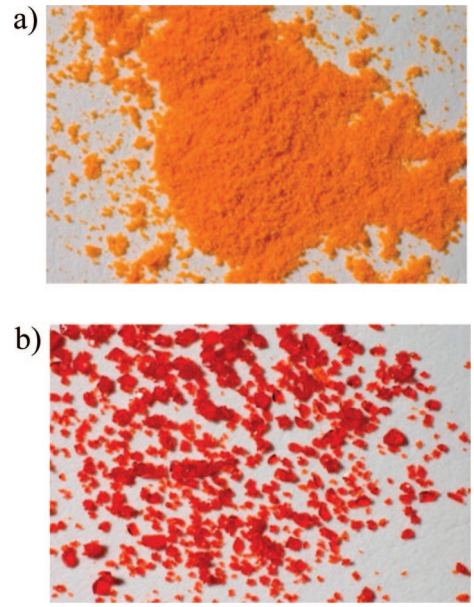


FIGURE 4. Precatalyst made by (a) first-generation synthesis and (b) optimized synthesis.

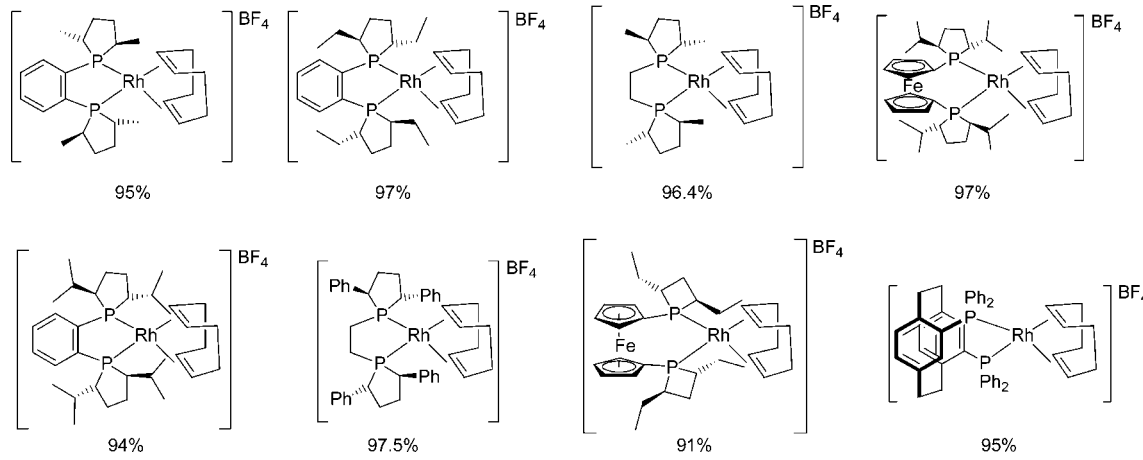


FIGURE 5. Yields of rhodium precatalysts obtained using our optimized route.

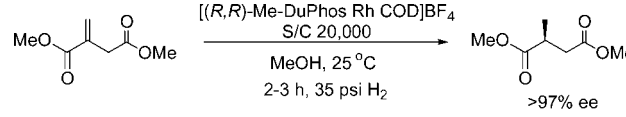
Alternative reactive ligands to 1,5-cyclooctadiene (COD), such as norbornadiene (NBD) and various salt forms, can be equally generated via this methodology. There has been some debate over the economical use of employing COD and NDB as the reactive olefin, because significant differences in reaction rates have been observed.[14] We have found that this apparent discrepancy in the behavior is in fact not a difference in performance but rather indicative of the more facile reduction of the NBD ligand over the COD ligand, thus generating the active catalyst more quickly without any influence over the enantioselectivity. At industrially viable catalyst loadings, the activation period becomes insignificant in terms of overall productivity and the reactor setup has the major role to play, particularly in terms of mass transfer of hydrogen into solution.[15] Furthermore, we have observed that the COD-derived catalysts are by and large more stable to long-term storage when compared with the analogous NBD-based systems. The counter ion typically has a minor effect on catalyst performance, with a few exceptions.[16] We find the BF_4^- salts give materials with preferred product qualities required for practical synthesis and use at industrial scale.

On the whole, broad consideration needs to be given to the constituents of such precatalysts (for example, starting materials, reactive olefin, and counter ion) to ensure that the system of choice will be scaleable and suitable for industrial manufacture.

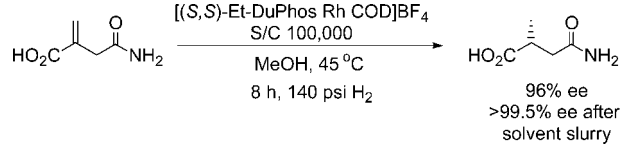
Asymmetric Hydrogenations Using Rhodium Catalysts

Phospholane-based catalysts have been shown to have an extremely large substrate scope in asymmetric hydrogenation, especially those based on the DuPhos and BPE ligand types,[1,3] but with increasing numbers of substrates investigated, it has become evident that the only means to find an optimal catalyst is by extensive screening.[5,17] To demonstrate the breath of substrates and the variety of catalysts required to develop industrially useful processes, we have chosen a selection of the asymmetric hydrogenations recently developed, covering itaconate, enamide, and acrylate substrates.

Scheme 3. Asymmetric Hydrogenation of Dimethyl Itaconate



Scheme 4. Asymmetric Hydrogenation of Methylene Succinamic Acid

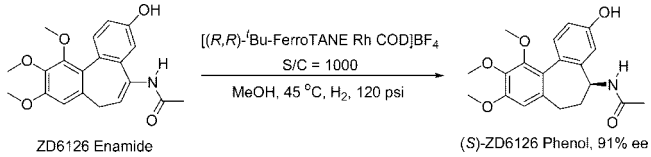


Asymmetric Hydrogenation of Itaconates. Enantiomerically enriched two-substituted succinic acids are used as peptidomimetics in several drug candidates and can be made using asymmetric hydrogenation. Rhodium DuPhos catalysts have been shown to be extremely active and selective for the asymmetric hydrogenation of itaconates,[18] and we have manufactured in excess of 1 metric ton of (*S*)-dimethyl methylsuccinate (Scheme 3) using such a process. An extremely good molar substrate to catalyst (S/C) loading of 20,000 (4,800, wt/wt was achieved), thus making the asymmetric hydrogenation of a low-molecular-weight substrate viable. Furthermore, the process employed moderate temperatures and pressures, typical for Rh-DuPhos catalysis.

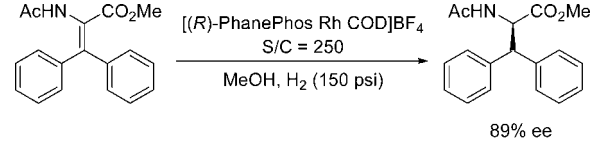
A related molecule that we have developed an asymmetric hydrogenation process for is 2-methylenesuccinamic acid (Scheme 4).[19] For this product, the purity of the substrate proved very important. The initial substrate contained ~1 wt % of a chloride impurity, derived from the use of HCl in its synthesis. This limited the catalyst loading to a S/C of 1000. Substituting HCl for H_2SO_4 in substrate synthesis, we were able to achieve an impressive S/C of 100,000 (~21,400, wt/wt) and a turnover frequency (TOF) of 13 000 h^{-1}. In the final process, the enantiomeric excess of the product was readily elevated to >99.5% using a simple solvent slurry in methanol, which also had the desirable effect of lowering the rhodium content from 9.0 to 0.88 ppm.

Asymmetric Hydrogenation of Enamides. Rhodium DuPhos and BPE catalysts have been used for the

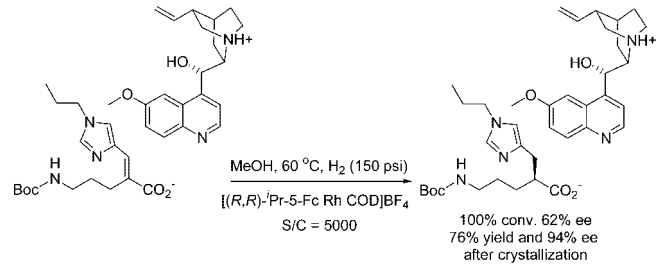
Scheme 5. Asymmetric Hydrogenation of a Cyclic Enamide



Scheme 6. Asymmetric Hydrogenation of Diphenylalanine



Scheme 7. Integration of Asymmetric Hydrogenation and Classical Resolution



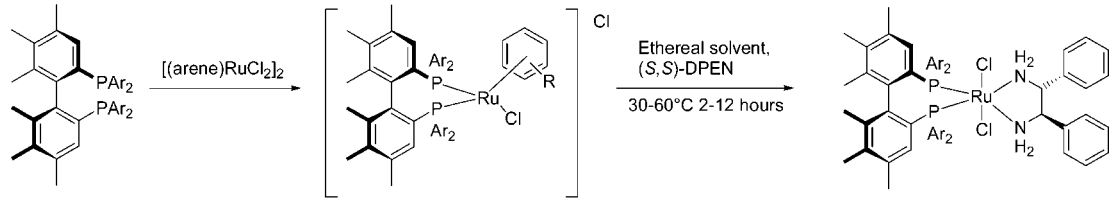
asymmetric hydrogenation of a wide range of enamide substrates, which can be synthesized by treating an oxime with iron powder and acetic anhydride. This provides the hydrogenation substrate in good yield and purity, after recrystallization.[20] While this method is suitable for many substrates, if sensitive functionalities such as a ketone, ester, or nitrile are present, then yields can be modest. Hence, we developed an alternative method to synthesize enamides by a Heck reaction of aryl trifluoromethanesulfonates and *N*-vinylacetamide.[21] In this latter study, it was found that Rh-Ph-BPE was effective for enamide hydrogenation, providing superior results for a number of substrates compared to related DuPhos systems.

Working with AstraZeneca, we developed an asymmetric hydrogenation process for the synthesis of ZD6126, a water-soluble phosphate prodrug of *N*-acetylcolchinol.[22] The required substrate was synthesized from the ketone via the oxime, using the iron powder/acetic anhydride method. This was a challenging substrate, being a seven-membered ring enamide, for which few examples are known. Extensive screening identified that the DuPhos- and BPE-derived catalysts provided poor enantiomeric excess (ee) for this substrate. However, good selectivity was achieved with either (*S*,*S*)-^{i}Pr-FerroTANE Ru(methallyl)$_2$ or [(*R*,*R*)-^{t}Bu-FerroTANE Rh(COD)]BF_4 (Scheme 5): at a molar S/C of 1000, we obtained 91–94% ee using either catalyst. It was interesting to find that with this substrate, similar activity and selectivity was achieved with both Rh- and Ru-based catalysts bound to similar ligand systems.

The asymmetric hydrogenation of enamides is also applied in the synthesis of α-amino acids, and this area has been extensively reviewed.[1,3] While DuPhos- and BPE-derived catalysts are suitable for a broad array of dehydroamino acid substrates, they are not of ubiquitous utility, resulting in a need to identify more structurally diverse systems. This situation was faced while investigating the synthesis of 3,3-diphenylalanines that appear in many developmental pharmaceutical drugs.[23] After developing a suitable synthesis of the parent diphenylalanine substrate, we screened our catalyst collection and found that the DuPhos and BPE catalysts gave only moderate selectivity and poor activity for this substrate class. [(*R*)-PhanePhos Rh COD]BF_4 was identified as a suitable catalyst, which afforded 89% ee at a S/C of 250 but with a $t_{1/2}$ of 3 min (Scheme 6); however, this catalyst loading was not suitable for the development of an economic process. Dowpharma had a requirement to rapidly develop and scale-up the manufacture of a related diphenylalanine product, and the high activity identified in our earlier work was an important factor in choosing the PhanePhos catalyst system. Further development, particularly around substrate purity, achieved superior catalyst ratios and enhanced selectivities. As such, the hydrogenation process was subsequently used in the commercial manufacture of a diphenylalanine derivative in a robust, reproducible, and scaleable procedure.

Asymmetric Hydrogenation of Acrylates. In the majority of cases when investigating the asymmetric hydrogenation of acrylic acids, ruthenium-based catalysts are optimal. There are of course exceptions, such as Rh-Walphos[24] or Rh-MonoPhos[8] used for the manufacture of Aliskiren intermediates. We were challenged by Pfizer with the development of an asymmetric hydrogenation route to an imidazole-substituted δ-amino acid for the synthesis of UK-369,082 (a thrombin activatable fibrinolysis inhibitor). Previously, we had developed a classical resolution method using quinidine, to rapidly provide material for early clinical trials.[25] Looking at the structure of the imidazole containing acrylic acid, it was felt that competitive binding to the heterocyclic group could impede any hydrogenation reaction and it was not obvious which substrate would be optimal. Seven substrates were investigated, and for six of these, ruthenium-based catalysts were preferred; however, none were suitable for scale-up because of low activity. A further study of a quinidine salt of the acrylic acid indicated that rhodium-based catalysts were of utility, and a process was developed using [(*R*,*R*)-^{i}Pr-5-Fc Rh(COD)]BF_4 (Scheme 7). This did not give as high of an ee as other rhodium catalysts, such as [(*R*,*R*)-^{t}Bu-FerroTANE Rh(COD)]BF_4 (62 versus 82% ee), but was far more active.[25] This process was scaled by Pfizer to produce in excess of 20 kg of the desired drug candidate. Such work clearly demonstrates the complementary need for activity and selectivity when developing a manufacturing-scale process using asymmetric hydrogenation.

Scheme 8. Optimized Synthesis of [(*R*)-HexaPHEMP $RuCl_2$ (*R*,*R*)-DPEN]



92% isolated yield

Synthesis and Asymmetric Hydrogenation Applications of Ruthenium Catalysts

Ruthenium complexes have a long history in the large-scale application of asymmetric catalysis, including asymmetric hydrogenation. The advent of BINAP catalysts in the early 1980s led to a range of applications, including rhodium-catalyzed isomerization and dehydroamino acid hydrogenation.[2] Further research demonstrated that BINAP ruthenium catalysis was particularly effective in keto-ester hydrogenation and homoallylic alcohol hydrogenation.[2] Probably the most significant addition to asymmetric hydrogenation reactions developed in recent years is Noyori's work on simple ketones.[26] In a landmark publication, Noyori was able to isolate a stable complex containing both the bisphosphine and the diamine coordinated to ruthenium.[27] Such catalysts proved highly effective in the hydrogenation of aryl ketones, far surpassing any combination of bisphosphine ruthenium complex and additives previously reported. In December 2000, Chirotech was granted a license from the Japan Science and Technology Corporation for this technology, and we have since implemented several manufacturing processes for chiral alcohols and amines.

As part of our on-going strategy of in-licensing and developing new technologies, we also obtained a license for the PhanePhos ligands and catalysts developed by Pye and Rossen at Merck Research Laboratories.[28] The PhanePhos ligand is a triaryl phosphine that offers similar electronic properties to other phosphines, such as BINAP, but differs significantly in its geometrical constrains. Noyori had already shown that, to achieve high selectivity and reactivity for a wide a range of substrates, bulky ligands, such as Xylyl-BINAP,[29] are essential. We have established that [Xylyl-PhanePhos $RuCl_2$ DPEN] provides a catalyst system that achieves equal selectivities and activities to those obtained by Noyori with [Xylyl-BINAP $RuCl_2$ DAIPEN] but with a cheaper and more readily available diamine. Furthermore, we were also able to achieve very high catalyst utility at modest hydrogen pressures and ambient temperatures.[30]

Prior to our work in this field, [diphosphine $RuCl_2$ diamine] precatalysts were typically prepared by the procedures of Noyori,[27] whereby the requisite ligand was reacted with an $[(arene)RuCl_2]_2$ in *N*,*N*-dimethylformamide (DMF) at 100 °C followed by treatment with a suitable diamine, typically DPEN, DACH, or DAIPEN, to yield the required complex. The published methods were found to be adequate for the synthesis of initial screening and process development quantities; however, we observed that the application of this methodology to certain ligand systems gave rise to a significant degree of byproduct formation. Because these precatalysts contain both valuable chiral phosphines and chiral diamines, the development of a mild, facile, and broadly applicable generic protocol was essential to the successful development and application of this technology.

Our investigations into alternative [diphosphine $RuCl_2$ diamine] precatalyst syntheses surprisingly indicated that we could routinely generate the desired compounds in an exceptionally mild and efficient fashion when an isolated [(diphosphine)(arene)RuCl] complex was reacted with the requisite diamine at moderate temperatures in an ethereal solvent (Scheme 8). Thus, we have developed a new synthetic protocol that is directly applicable to a wide array of ligand systems to routinely yield >95% of the desired complexes (Figure 6).[31]

Operating these hydrogenation processes is relatively straightforward; the only significant difference from a standard asymmetric hydrogenation is the need for a strong base, usually potassium *tert*-butoxide, to activate the catalyst. For substrates, such as acetophenone derivatives, workup consists of treating the excess butoxide with a stoichiometric amount of acid, screening out the resulting salt, and distillation of the product.[32] It is possible to run these reactions neat, but reactions become increasingly sluggish in the absence of solvent and enantioselectivity drops markedly. However, even with only 1 or 2 equiv. of solvent, the reaction performs well. These hydrogenations serve as a further example of the importance of substrate purification on catalyst loading. For example, in the case of 4′-fluoroacetophenone, commercially purchased material showed essentially no activity. After passing through a wiped film evaporator, the reaction was successfully executed at a S/C of 100,000, with complete conversion in 2 h (Scheme 9).

In our hands, this technology transfers readily from the laboratory to the plant and we have developed multiple asymmetric ketone hydrogenation processes using [HexaPHEMP $RuCl_2$ diamine] and [PhanePhos $RuCl_2$ diamine] precatalysts on a multi-100 kg scale, typically achieving S/C loadings in the 12,000–25,000 molar range. Using moderate pressure (30–50 psi) and temperatures (25–40 °C), reactions are generally complete within 4 h.

In addition to developing many asymmetric ketone hydrogenation processes, we were one of the first groups to report the use of [diphosphine $RuCl_2$ diamine] precatalysts for the asymmetric hydrogenation of imines.[33]

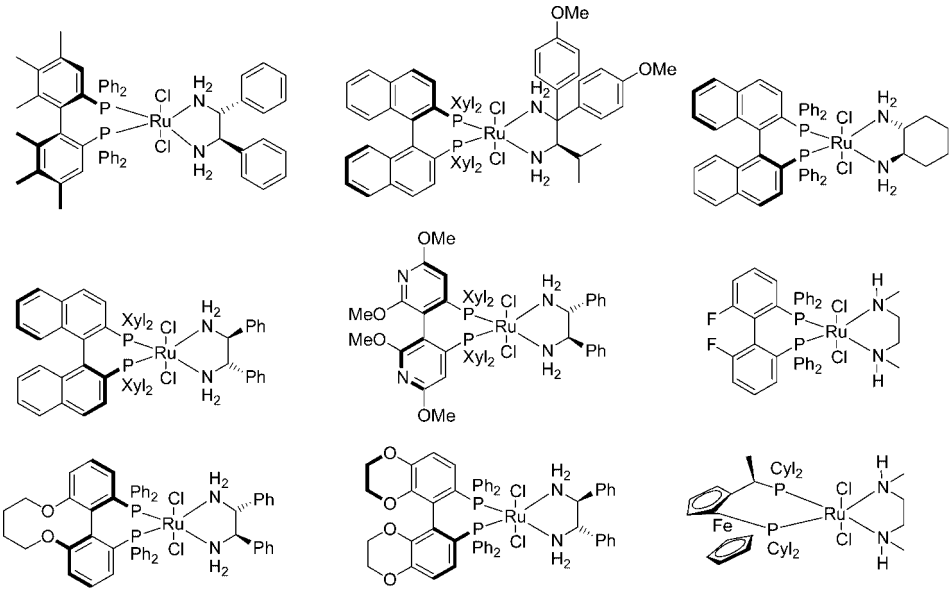
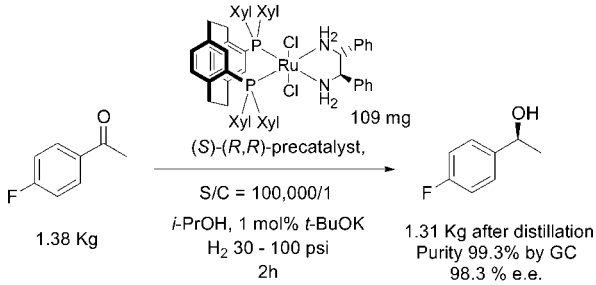
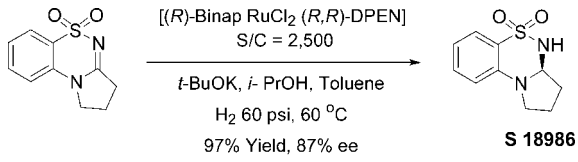


FIGURE 6. [Diphosphine $RuCl_2$ diamine] precatalysts synthesized in >95% yield.

Scheme 9. Asymmetric Hydrogenation of 4′-Fluoroacetophenone



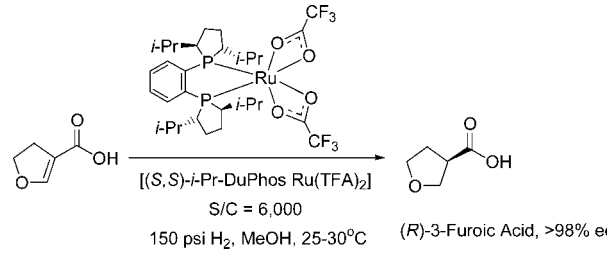
Scheme 10. Asymmetric Hydrogenation of a *N*-Sulfonylimine



This technology was applied to the asymmetric hydrogenation of a *N*-sulfonylimine substrate for the manufacture of S 18986, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor positive modulator.[34] For this substrate, the proportion of base proved critical; between 0.8 and 1.5 equiv were required to effect full conversion, and higher temperature and pressures than those employed for ketone hydrogenation were also needed (Scheme 10). S 18986 was isolated in 87% ee but was readily upgraded to >99% ee by a recrystallization from acetonitrile, which also usefully removed the ruthenium metal to acceptable levels.

In addition to applying ruthenium catalysts to the hydrogenation of ketone and imines, we have also investigated the asymmetric hydrogenation of acrylate derivatives. We have developed an efficient process for the manufacture of (*R*)-3-tetrahydrofuroic acid using (*S,S*)-*i*-Pr-DuPhos Ru $(TFA)_2$ (Scheme 11). It was readily demonstrated that a S/C of 6000 could be achieved and, furthermore, that the ruthenium complex could be readily fabricated on a suitable scale. The combination

Scheme 11. Asymmetric Hydrogenation Process for 3-Furoic Acid



of readily available ligand, easily accessible and stable metal complex, and a robust hydrogenation reaction allowed the process to be rapidly scaled-up into the pilot plant.

As for the Rh precatalyst synthesis described earlier, selection of an appropriate precursor to use in ruthenium-based catalysis is extremely important. Early work with BINAP focused on the use of BINAP $Ru(OAc)_2$ complexes or "BINAP $Ru(halide)_2$" generated from the acetate and a halogen source. Cationic [RuX(bisphosphine)(arene)]$^+$ Y^- complexes are generally stable complexes that are easily isolated and can serve as useful catalyst precursors;[35] unfortunately, they can require fairly high temperatures to work efficiently. Ruthenium bis(methylallyl) complexes were shown to effect catalysts for acidic substrates, such as tiglic acid,[36] or as a precursor to the *in situ*-generated halide complex.[37] However, in our hands, these complexes are of marginal stability and are thus challenging to use on a practical basis. The ruthenium bistrifluoroacetate complexes can be made by displacing the methylallyl groups with trifluoroacetic acid or directly from the dimeric $(COD)_2Ru_2(CF_3CO_2)_4$ species.[38] With such a wide range of potential catalyst precursors available, with each one based on a variety of synthetic routes, selection of the most appropriate precursor complex for a given chiral ligand can be a protracted process. Again, as for Rh-based catalysts, we routinely investigate routes

to provide an easily isolatable, stable, and pure precatalyst.

Conclusions

Asymmetric hydrogenation has come a long way over the last 4 decades. It is now an accepted method for the manufacture of a wide range of chiral compounds in the pharmaceutical, agrochemical, fragrance, and fine-chemical industries. Enantiomerically enriched amino acids, amines, acids, esters, and alcohols are all routinely produced on commercial scales using this "atom economical", scaleable, and robust technology. We have demonstrated that we can manufacture both rhodium- and ruthenium-based metal precatalysts for use in asymmetric hydrogenation processes and have reviewed some applications of our technology. With the technology now fully established, we expect to see many more examples of asymmetric hydrogenation being applied in the manufacture of chiral compounds.

This work was carried out over the past 12 years at Chiroscience, Chirotech, and now Dowpharma. It has been a very exciting and rewarding journey, from obtaining a license for the DuPhos technology in 1995 to developing the broad asymmetric hydrogenation portfolio that we have today. All of this would not have been possible without the hard work, intellect, and technical skills of a wide range of people; many are co-authors in our publications cited in this Account. In particular, we acknowledge Mark Burk for his leadership of the chemocatalysis team from 1996–2000, which provided the foundation for future commercial successes. Furthermore, we acknowledge Ray McCague for his intellectual contributions and foresight in identifying potential substrate classes.

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AR700114K