"Organometallics as Catalysts in the Fine Chemical Industry"

Edited by Matthias Beller (Leibniz-Institut für Organische Katalyse, Universität Rostock, Germany) and Hans-Ulrich Blaser (Solvias AG, Basel, Switzerland), Topics in Organometallic Chemistry, Vol. 42, Springer, Berlin, Heidelberg, Germany, 2012, 154 pages, ISBN: 978-3-642-32832-9, £171.00, €203.25, US$259.00 (Print version)

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Introduction

This new volume of Springer's famous series Topics in Organometallic Chemistry, Volume 42, entitled "Organometallics as Catalysts in the Fine Chemical Industry", presents the state-of-the-art in the industrial use of organometallic or coordination complexes as catalysts for the production of fine chemicals. A range of reactions is covered through an overview of chapters and case studies, from catalytic C–C bond formation, hydroformylation and hydrogenation to olefin metathesis (see below). All of these are noteworthy for involving platinum group metal (pgm) complexes as catalysts. Interestingly, technical challenges encountered in scaling up the reactions from small quantities to production amounts, as well as how these issues were tackled, are often described by the authors, who all belong to the industrial world. Their contributions make this book a helpful source of information for specialists in the field of organometallic catalysis, as well as beginners who have just entered the field or intend to do so.

Palladium-Catalysed Coupling Reactions

Extensively reviewed by Johannes G. de Vries (DSM Innovative Synthesis BV, Geleen, The Netherlands) in the first chapter, palladium-catalysed coupling reactions appear to be among the most popular reactions for the production of fine chemicals at the ton-scale. Provided inhibition and deactivation of the catalyst is avoided, catalytic C–C coupling may offer several advantages such as total cost reduction, tolerance to many functional groups (no waste-producing protection/deprotection steps) and lower reaction temperatures. Thus, several industrial processes were developed in fine chemistry using the well known Heck-Mirozoki, Suzuki-Miyaura, Sonogashira, Kumada-Corriu and Negishi couplings. Some of them are given below.

Using the Heck reaction in one of its synthetic steps, the herbicide prosulfuron is produced on a large scale by Syngenta (**Figure 1**). Tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$) is used as a catalyst precursor without any phosphine ligand and the precipitated palladium is trapped at the end of the reaction simply by using charcoal. Naproxen (**Figure 1**) is also produced by Albemarle with a scale around 500 tons year^{-1} using the same technology. In this case, palladium(II) chloride ($PdCl_2$) is used as a metal source and the neomenthyldiphenylphosphine ligand is used to reach a substrate-to-catalyst ratio of 2000–3000. The ability of the Heck reaction to be performed without the need of protection/deprotection steps on the substrate is illustrated by the production of montelukast, an anti-asthma agent, by Merck and of the calcium-regulator cinacalcet hydrochloride by Teva (**Figure 1**). In the first case, palladium(II) acetate ($Pd(OAc)_2$) is used as a precatalyst while Teva's process makes use of the simple Pd/C catalyst. More sophisticated metal precursors are sometimes used for maximum efficiency of the reaction. As an example, for the production of resveratrol (**Figure 1**), DSM has reported the use of a chloropalladacycle dimer based on the acetophenone oxime ligand. Other examples of the industrial production of fine chemicals involving a Heck reaction are described, including rilpivirine (AIDS treatment, Janssen Pharmaceuticals), eletriptan (anti-migraine, Pfizer), the generic of nebivolol (blood pressure lowering agent, Zach System), pemetrexed disodium (anticancer agent, Eli Lilly) and varenicline (smoking cessation aid, Pfizer).

Twelve industrial processes using another useful C–C bond formation reaction, the Suzuki coupling, are reported. The largest is operated by Merck to produce more than 1000 tons year^{-1} of the fungicide boscalid (**Figure 2**). In a pivotal step, *o*-chloronitrobenzene is coupled to *p*-chlorophenylboronic acid using catalytic amounts of $Pd(OAc)_2$ and triphenylphosphine. A similar catalytic system is used by Clariant to obtain *o*-tolylbenzonitrile (OTBN, **Figure 2**) as a common intermediate for the production of hundreds of tons of an entire family of Sartan derivatives as blood pressure lowering agents. This process is advantageously run in an aqueous medium using the water-soluble phosphine 3,3′,3″-phosphanetriyl-tris(benzenesulfonic acid) trisodium salt (TPPTS), thus allowing easy recovery of the catalyst. Crizotinib (**Figure 2**), an anticancer drug marketed by Pfizer, is also obtained through a Suzuki coupling step. In this case, the optimised catalytic precursor was found to be (1,1′-bis(diphenylphosphino)ferrocene)-palladium(II) chloride. Interestingly, after work up, traces of residual Pd could be removed by simple treatment with silica-alumina loaded with 15% cysteine. To replace the unscalable Stille coupling reaction in the original synthesis of the other anticancer drug lapatinib (**Figure 2**), GSK has developed a more

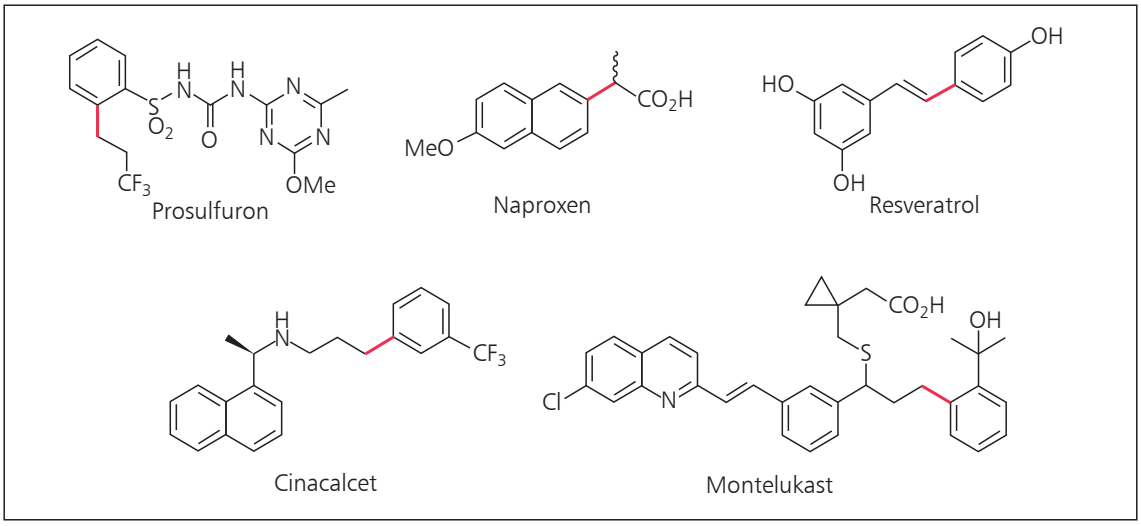


Fig. 1. Examples of fine chemicals industrially produced using the palladium-catalysed Heck reaction (creation of the bold red bond)

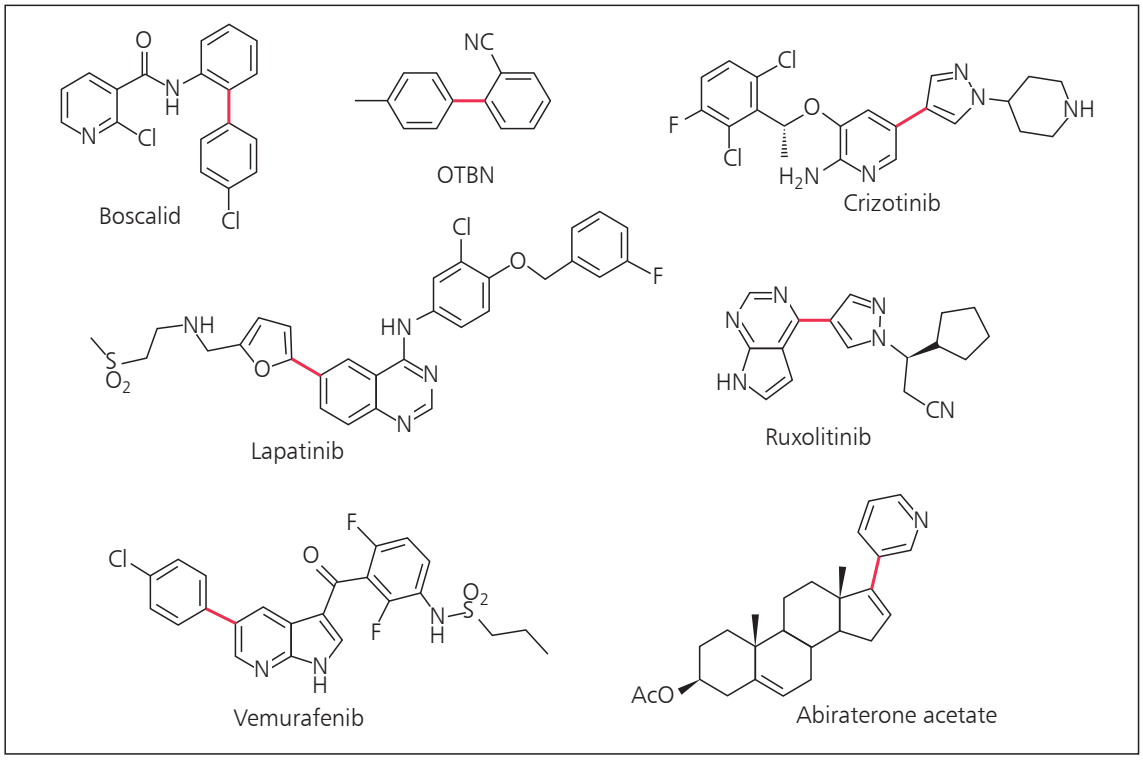


Fig. 2. Examples of fine chemicals industrially produced using the palladium-catalysed Suzuki reaction (creation of the bold red bond)

convenient Suzuki route using Pd/C. In this case, the residual catalyst is eliminated by simple filtration.

Several synthetic schemes, all containing a Suzuki reaction step, have also been developed to access ruxolitinib phosphate, a molecule marketed by Incyte for the treatment of myelofibrosis. However, for an industrial process, this Pd-catalysed coupling should preferably not be the last step in order to avoid tedious removal of Pd traces down to the <10 ppm criteria. As counter examples, Hoffmann-La Roche and Janssen Pharmaceuticals have scaled up convergent syntheses of vemurafenib and abiraterone acetate (**Figure 2**), respectively. Both use dichlorobis(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$) as a catalyst to perform a Suzuki coupling in the ultimate step for the synthesis of these anticancer compounds. Some additional examples of the use of the Suzuki reaction in industrial processes include the synthesis of the antifungal agent anidulafungin by Pfizer, of febuxostat (Teijin Pharma), a molecule used in the treatment of gout and hyperuricemia, of the quinolone antibiotic garenoxacin by Toyama Chemical and of nebivolol by Zach System.

Despite the obvious drawback of using a Grignard reagent intolerant of many functional groups, several fine chemicals are produced using the cheapest Kumada-Corriu reaction at the multiton $year^{-1}$ scale. Most of them are out of the scope of this review, as they involve the non-pgms nickel, copper and iron as catalysts. However, for some peculiar reactions, palladium derivatives are the preferred catalysts. Thus, Hokko Chemical Industry is using a catalyst made *in situ* from $PdCl_2$ and 1,1′-bis(diphenylphosphino)ferrocene (dppf) to couple 1,3-dichlorobenzene and *n*-propylmagnesium chloride or *p*-fluorobromobenzene and *p-tert*-butoxyphenylmagnesium chloride (**Figure 3**). The obtained compounds are precursors for pharmaceuticals and liquid crystals. In a same manner, Zambon uses the Kumada-Corriu coupling to produce diflunisal, a non-steroidal anti-inflammatory drug (**Figure 3**). In this case, $Pd(OAc)_2$ is used as precatalyst and triphenylphosphine is added. It is noteworthy that chemists at Zambon found that the homo-coupling of the Grignard reagent could be reduced to less than 1% when using ultrapure magnesium. Indeed, any traces of Cu, Fe, Ni and

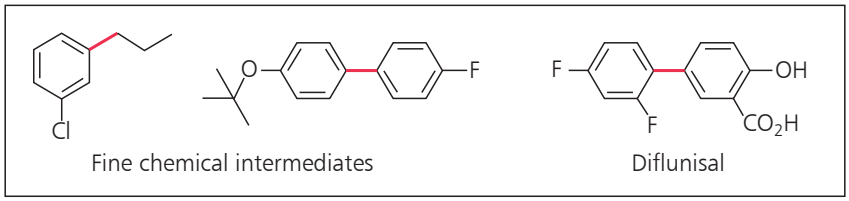


Fig. 3. Examples of fine chemicals industrially produced using the palladium-catalysed Kumada-Corriu reaction (creation of the bold red bond)

manganese that are typically found in commercial magnesium could promote this side reaction.

Alternatively, biaryl compounds can be produced by the RZnX-based Negishi reaction. However, the only two known industrial processes using this reaction involve nickel catalysts and thus will not be described in this review. The Sonogashira reaction, which allows a terminal alkyne to be coupled with an aryl or alkenyl halide or pseudohalide, makes efficient use of palladium catalysts. The first industrial large-scale use of this reaction was the second-generation process developed by Sandoz for the synthesis of the antifungal terbinafine with less than 0.05 mol% of $PdCl_2(PPh_3)_2$ (**Figure 4**). Two companies, Medichem and Dipharma Francis, patented synthetic routes to cinacalcet (**Figure 4**) using the Sonogashira coupling, the two approaches almost only differing by the nature of the palladium source (Pd/C *vs.* $PdCl_2$). Initially published by the academic group of Takeshi Fujita (Tohoku University, Japan), a methodology to obtain fingolimod hydrochloride (**Figure 4**) *via* a Sonogashira reaction was further developed by Novartis. The worldwide rights to the process were acquired by this company and its use in production seems likely. Other examples of the use of the palladium-catalysed Sonogashira reaction at the industrial level include the synthesis of pemetrexed by Eli Lilly, of tazarotene, used for the treatment of acne, psoriasis and photoageing and marketed by Allergan, and of vemurafenib by Hoffmann-La Roche.

In addition to the above-mentioned lead reactions, other palladium-catalysed coupling reactions can be used in industrial fine chemical production, although only two examples are reported. Bristol-Myers Squibb developed the synthesis of ixabepilone, marketed for breast cancer treatment, using a $Pd_2(dba)_3/PMe_3$-catalysed allylic substitution step, while an elegant $Pd(OAc)_2/P^tBu_3$-mediated C–H activation step is used by Servier to produce ivabradine, an alternative treatment for angina pectoris.

Applications of Rhodium-Catalysed Hydroformylation

Chapter 2 is written by Gregory T. Whiteker (Dow AgroSciences, Indianapolis, USA) and Christopher J. Cobley (Chirotech Technology Ltd, Cambridge, UK), and gathers information about the rare commercial applications of rhodium-catalysed hydroformylation in the pharmaceutical and fine chemical industries. So far these have been limited by cost, complexity or waste treatment issues. However, the authors have thoroughly reviewed the patent literature to detect the fine chemicals already obtained on a multikilogram scale that may thus be on the way to industrial-scale production.

In the pharmaceutical domain, both BASF and Roche are operating industrial processes based on a rhodium-catalysed hydroformylation to produce vitamin A acetate (**Figure 5**), starting from different substrates. The only other recent industrial-scale application of hydroformylation was reported by Chirotech for the synthesis of (*S*)-allysine ethylene acetal (**Figure 5**), an important intermediate in the manufacture of some enzyme inhibitors. In this case,

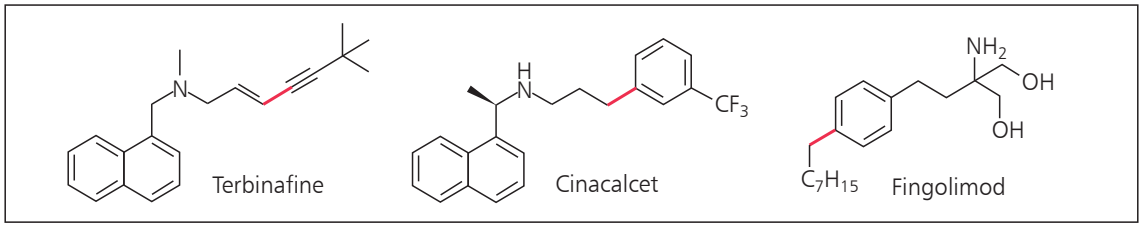


Fig. 4. Examples of fine chemicals industrially produced using the palladium-catalysed Sonogashira reaction (creation of the bold red bond)

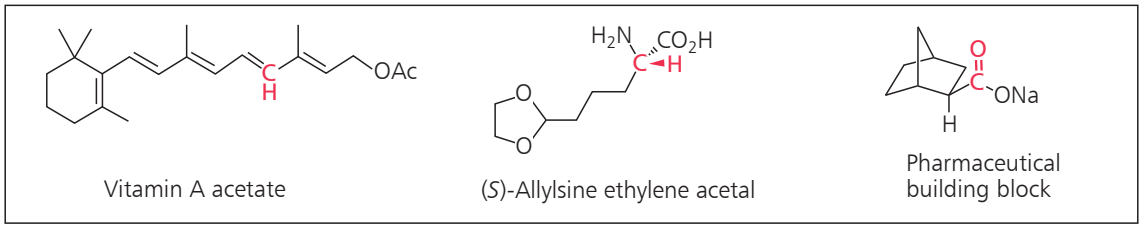


Fig. 5. Examples of pharmaceutical derivatives or intermediates industrially produced using a rhodium-catalysed hydroformylation step

the Rh-biphephos catalyst is used with a 4000:1 molar substrate to catalyst ratio and the reaction was run in a 300 l pressure reactor. The aldehyde is isolated through water extraction, while the catalyst remains in the organic layer. A multiton amount of (*S*)-allyl lysine ethylene acetal was produced this way. A multikilogram quantity of a pharmaceutical building block (**Figure 5**) was produced by Pfizer using a hydroformylation of norbornene catalysed by 0.15% of $Rh(CO)_2(acac)$ in the presence of dppf. Additionally, examination of the patent literature also reveals that Pfizer used a Rh-biphephos-catalysed hydroformylation reaction to obtain *N*-Boc-(4-oxobutyl)caprolactam on a 250 g scale and that Dow performed a 200 g hydroformylation step to produce a protected amino aldehyde.

Asymmetric hydroformylation is a powerful tool to introduce chirality in pharmaceuticals. However, it has remained so far a purely academic domain with no industrial-scale application. As an example, (*S*)-naproxen can be efficiently obtained with excellent enantioselectivity and regioselectivity using the chiral hydroformylation approach, but the currently more economically viable resolution route dominates at the industrial level.

In the fragrance domain, Vertral®, a green melon-scented component, and Florhydral® are produced by hydroformylation of *exo*-cyclopentadiene using $Rh_2(2\text{-ethylhexanoate})_4$ or 1,3-dipropenylbenzene using a Rh-PPh_3 catalyst, respectively (**Figure 6**). The citrus-scented limonenal is commercially obtained by Celanese through the same pathway, while the woody and spicy Spirambrene® is manufactured by Givaudan and Vigon International according to a hydroformylation–Tollens reaction–acetalisation scheme (**Figure 6**). Many other examples from the fragrance industry issued from the patent survey are reported.

Finally, although examples of the use of hydroformylation as an alternative access to agrochemicals are reported, none of them seems to be currently operated for industrial-scale production.

Ruthenium-Catalysed Selective Hydrogenation

In this chapter, Philippe Dupau (Firmenich SA, La Plaine, Switzerland) first focuses on the ruthenium-catalysed reduction of conjugated dienes used at Firmenich. Indeed, although the Ru version of this reaction has been known for more than a decade, it suffered until recently from a narrow reaction scope and a lack of activity which hampered its implementation at the industrial production level. In 2008, it was discovered at Firmenich that these limitations could be overcome by the use of a cationic [(Cp-type)Ru(diene)][Y] catalyst in the presence of some weakly acidic additives. This technology is illustrated by the case study of the industrial production of (*Z*)-hex-3-en-1-ol, also called leaf alcohol, a useful component in flavour and fragrance chemistry (**Figure 7**). With their process, this compound

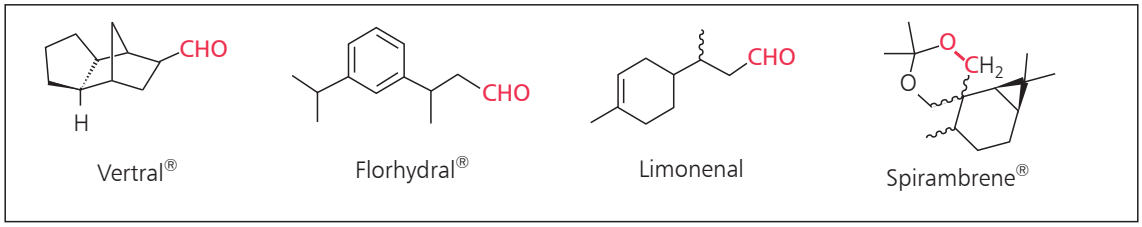


Fig. 6. Examples of fragrances industrially produced using a rhodium-catalysed hydroformylation step

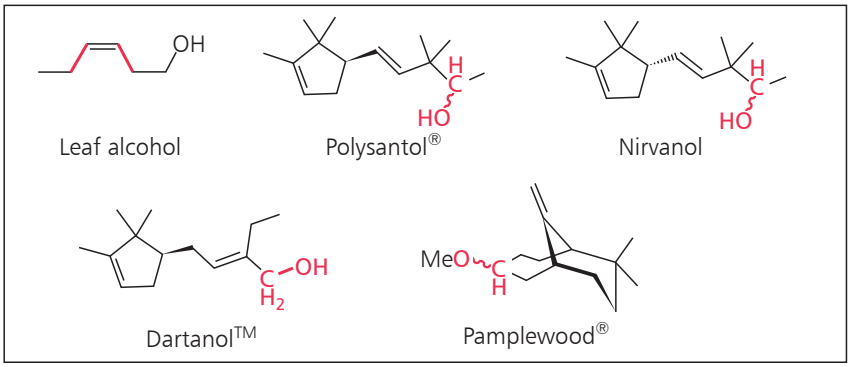


Fig. 7. Examples of fragrances industrially produced using the ruthenium-catalysed Firmenich chemoselective hydrogenation processes (hydrogenated bonds in bold red)

is efficiently obtained starting from either sorbic acid esters (followed by reduction of the ester function) or sorbic alcohol. In the first case, the reaction is run neat at 70–80°C under 1–5 bar H_2 in the presence of 0.005% of [(Cp*)Ru(COD)] [BF_4] and 0.1–0.2% of maleic acid. When starting from sorbic alcohol, acetone is used as solvent, all other reaction parameters being the same. Interesting kinetic and mechanistic investigations reveal that for sorbic acid ester, the reaction should be stopped at 95% conversion to maintain high selectivity, whereas the sorbic alcohol route requires all-*trans* starting material to prevent catalyst deactivation.

The chemoselective hydrogenation of carbonyl-containing compounds is another very interesting reaction in flavour and fragrance chemistry and is widely operated by Firmenich. To avoid the use of the patented (diphosphine)(diamine)$RuCl_2$ complexes, they have developed a series of proprietary amino- or imino-phosphine Ru complexes, either with bidentate (PN) or tetradentate (PNNP) ligands. For production-scale use, 2-bis(diphenylphosphino)ethylamine (DPPAE) was selected and its reaction with $(PPh_3)_3RuCl_2$ in tetrahydrofuran (THF) serendipitously led to the easy-to-handle cationic [$(DPPAE)_2(PPh_3)RuCl$] [Cl] complex. With this complex in hand, Polysantol® and nirvanol (**Figure 7**) are efficiently produced by hydrogenation of the corresponding ketones under 20 bar H_2 using a catalyst loading of 0.00125 mol% at the multi-ton scale. Several hundreds of tons of another sandalwood fragrance, Dartanol™ (**Figure 7**), are also produced yearly using 0.005 mol% of the same catalyst, although in this case the temperature has to be lowered from 70–80°C to 60°C due to substrate thermal instability. Finally, the very interesting example of the grapefruit and woody smelling Pamplewood® is reported (**Figure 7**). In this ton-scale production, [$(DPPAE)_2(PPh_3)RuCl$] [Cl] (0.002 mol%) efficiently catalyse the hydrogenation of 7,7-dimethyl-10-methylenebicyclo[4.3.1]decan-3-one to the corresponding alcohol. However, the latter is obtained in a 82:18 *exo*:*endo* mixture that does not meet the requirements for optimal olfactive properties. Nevertheless, this alcohol is further epimerised to the desired *exo*:*endo* ratio using the same catalyst, simply by increasing the temperature of the batch while maintaining the hydrogen pressure after the hydrogenation reaction. A reaction model has been developed and simulation has enabled the calculation of the different rate constants in this epimerisation process.

Asymmetric Hydrogenation

After some general remarks on metal complexes and chiral ligands, Hans-Ulrich Blaser *et al.* (Solvias AG, Basel, Switzerland) review the C=C, C=O and C=N asymmetric hydrogenation reactions that are currently (or have been) operated for production of fine chemicals. Pilot-scale processes as well as some industrially interesting bench-scale reactions are also considered, all being catalysed by rhodium-, ruthenium- or iridium-based complexes.

It is noteworthy that rhodium is the principal metal used in industrial asymmetric hydrogenation processes, with 11 identified cases. As an early example from the 1970s, Knowles' [Rh(dipamp)(COD)] [BF_4] catalyst has been applied for years to the production of L-dopa (**Figure 8**) by Monsanto. Good turnover frequency (TOF) (1000 h^{-1}), turnover number (TON) (20,000) and enantioselectivity (95%) were attained at a ton $year^{-1}$ scale. A similar process was later used by NSC Technologies for the production of unnatural amino acids, whereas a slightly different one using [Rh(eniphos)(nbd)] [PF_6] was developed by EniChem/Anic for the large-scale production of phenylalanine (15 tons $year^{-1}$) as a step towards aspartame. Other examples of the use of defined cationic rhodium

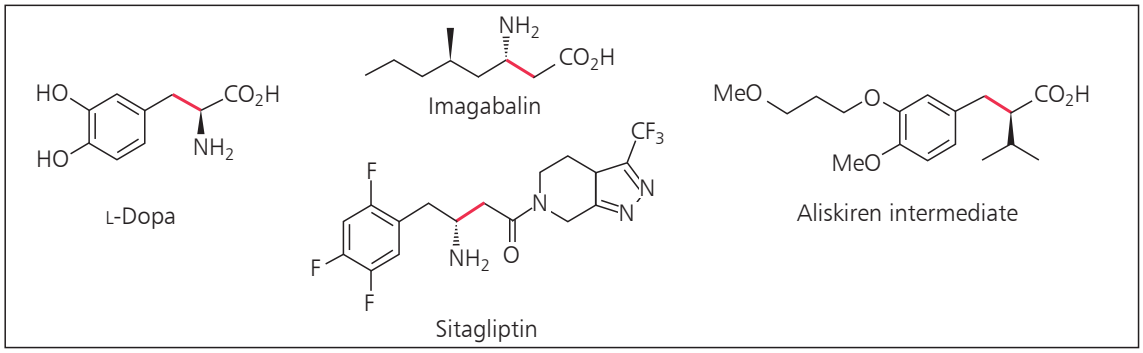


Fig. 8. Some products of industrial rhodium-catalysed asymmetric hydrogenation processes (hydrogenated bonds in bold red)

complexes include the asymmetric hydrogenation of a β-enamide in the presence of [Rh(tcfp)(COD)][BF_4] to access 3.8 tons of imagabalin (**Figure 8**) at Pfizer or of a duloxetine intermediate, marketed by Eli Lilly, with [Rh(duanphos)(NBD)][SbF_6]. However, in many cases, the preliminary synthesis of well-defined species is not compulsary and *in situ* formed cationic or neutral Rh-catalysts could be successfully employed. Indeed, Solvias, then DSM, have reported on the use of [Rh(NBD)$_2$][BF_4]/Walphos or [Rh(COD)$_2$][BF_4]/phosphoramidite/(*m*-Tol)$_3$P mixtures, respectively, for the production of an intermediate of aliskiren (**Figure 8**), a renin inhibitor. In a similar way, Merck is currently operating the asymmetric hydrogenation of an unprotected dehydro β-amino amide in the production of sitagliptin (**Figure 8**). In this last case, mechanistic studies have shown that the tautomeric imine is reduced rather than the initially targeted C=C bond of the starting enamine. A number of other interesting examples are given by the authors, including transfer hydrogenations reactions using mainly [Rh(Cp*)Cl$_2$]$_2$ as precursor and that were scaled up to 200 kg.

Triggered by Noyori's discovery of the Binap-Ru system, ruthenium-catalysed asymmetric hydrogenation is now widely used (or at least under development) in industry. As a flagship of this chemistry, the production of 300 tons year^{-1} of citronellol (**Figure 9**) by Takasago International, with [Ru(Binap)(CF$_3$CO$_2$)$_2$] as a C=C hydrogenation catalyst and with excellent enantiomeric excess (ee) (97%), TON (50,000) and TOF (500 h^{-1}), probably remains the most famous example. Roche has reported a similar [Ru(MeO-biphep)(CF$_3$CO$_2$)$_2$] catalyst for the asymmetric C=O reduction of a β-keto ester used as an intermediate in the synthesis of orlistat (**Figure 9**), a drug used to treat obesity. In this case, a TON of 50,000 was reached by adding hydrochloric acid as a co-catalyst, enabling the process to be scaled up to 2.2 tons. A process involving a Ru-catalysed C=O hydrogenation (Ru = [Ru(Tol-Binap)Cl$_2$]$_2$·*x*NEt$_3$) is also operated by Takasago to produce (*R*)-1,2-propanediol, a precursor of the bactericide (*S*)-oxfloxacin, on a 50 ton year^{-1} scale.

Arene-ruthenium precursors are another class of efficient pre-catalysts. At Takasago again, an elegant hydrogenation/dynamic kinetic resolution is operated to produce a penem antibiotic intermediate (**Figure 9**) on a 50–120 tons year^{-1} scale. In this process, [Ru(Tol-Binap)(*p*-cymene)I][I] is efficiently used

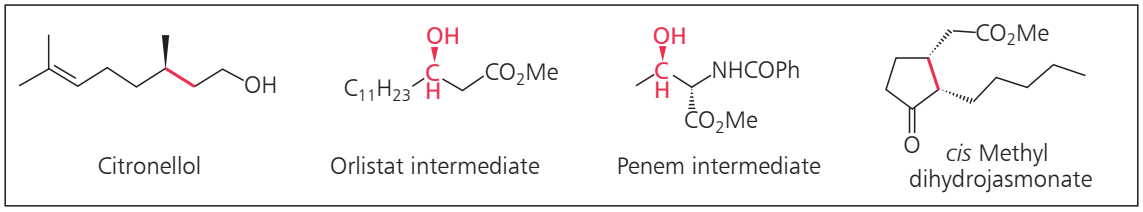


Fig. 9. Examples products made by industrial ruthenium-catalysed asymmetric hydrogenation processes (hydrogenated bonds in bold red)

as a pre-catalyst and affords the desired compound in ee >97% and diastereomeric excess (de) >94%. Interestingly, *in situ* formed catalysts can sometimes be employed as illustrated by the Firmenich production of the floral-scented *cis*-methyl dihydrojasmonate (several tons year^{-1}, **Figure 9**) which makes use of a [RuH(COD)(COT)][BF_4]/chiral diphosphine system. It is also worth noting that ketones without α- or β-coordinating groups can be enantioselectively reduced to the corresponding alcohols using Ru(diphosphine)(diamine) systems. Several pilot plant-scale operations are described but it is not clear whether they have been implemented as production processes. The same observation stands for the use of ruthenium catalysis in transfer hydrogenations.

Finally, the last member of this metal-based tryptich, iridium-catalysed asymmetric hydrogenation, has been more rarely used in industry at the production scale. However, a remarkable example is operated by Syngenta with the synthesis of more than 10,000 tons year^{-1} of (*S*)-metolachlor (**Figure 10**), a grass herbicide. The asymmetric step of this process consists of an imine hydrogenation under 80 bar H_2 at 50°C and is catalysed by an *in situ* generated species obtained by mixing [Ir(COD)Cl]$_2$ with one of Solvias' Josiphos ligands. Impressive TON (2,000,000) and TOF (>400,000 h^{-1}) are obtained, while asymmetric induction remains fairly good (ee 80%). Following this example, DSM and Solvias have developed another example based on the [Ir(COD)Cl]$_2$/(4-MeO-3,5-(^{t}Bu)$_2$C$_6$H$_2$)-MeO-Biphep couple to produce several tons of biotin from a cyclic anhydride.

With the three pgms Rh, Ru and Ir, an impressive number of pilot processes or bench-scale reactions up to several hundreds of kilograms are also described, thus making one anticipate that many more production processes using metal-catalysed asymmetric hydrogenations will appear in the near future.

Case Studies

The four other chapters are devoted to case studies of scaling up syntheses involving transition metal-catalysed steps and the associated challenges that had to be tackled. Thus, Ioannis N. Houpis (Janssen Pharmaceuticals Companies of Johnson & Johnson, Beerse, Belgium) describes the modification of the synthetic sequence and scale-up optimisation studies of an 'all-transition-metal-process' to yield a potential active pharmaceutical ingredient (API). The chosen route involves some palladium-catalysed Sonogashira and Suzuki coupling steps (**Figure 11**). Among the problems that were solved, it is interesting to note that the homogeneous Pd(PPh$_3$)$_4$ catalyst could be simply replaced by Pd/C for the Suzuki coupling step, thus allowing easy reduction of palladium traces in the final API (from 250 ppm to 10 ppm).

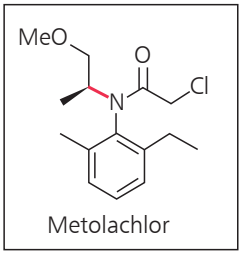


Fig. 10. Metolachlor, a grass herbicide produced using an iridium-catalysed asymmetric hydrogenation

Another example is given by Adriano F. Indolese (RohnerChem, Pratteln, Switzerland) for the pilot-scale production of 3.7 kg of 5-(4-cyanophenyl)indole (**Figure 11**) with a four month deadline. A palladium-catalysed Suzuki coupling was chosen. From catalyst screening, a mixture of $PdCl_2$ and P(Tol)$_3$ was selected and other reaction parameters were optimised by 'design of experiment' (DOE) at the small-scale level. With these optimised conditions, no scale-up effect was observed and two pilot runs of *ca.* 2 kg each could be run, affording the targeted compound with the required purity specifications.

Per Ryberg (AstraZeneca, Södertälje, Sweden) depicts scale-up studies of a cyanation reaction that was performed at AstraZenaca in 2003 and 2004. This reaction, used as the last step of a multikilogram synthesis of a drug candidate for the treatment of glycogen synthase kinase 3 disorder (**Figure 11**), was found to be efficiently catalysed by either a Pd(dba)$_2$/P^{t}Bu$_3$ mixture or the preformed [PdBr(P^{t}Bu$_3$)]$_2$ dimer, the latter being preferred for large-scale application. Technical issues that influence the large-scale synthesis were addressed: delayed heating of the reaction mixture was found to be detrimental, while the cyanide source (Zn(CN)$_2$) had to be added as the final reagent, both parameters being linked to poisoning of the Pd catalyst.

Finally, Cheng-yi Chen (Merck Research Laboratories, Rahway, USA) fully describes a scalable and cost-effective synthesis of vaniprevir (**Figure 11**), a 20-membered ring protease inhibitor that possesses activity against the hepatitis C virus. The key step of this synthesis was identified as a 20-membered macrolactamisation through ring-closing metathesis (RCM) which had to be optimised in terms of volume productivity. This could be achieved using the Grubbs-Hoveyda second generation catalyst and simultaneous

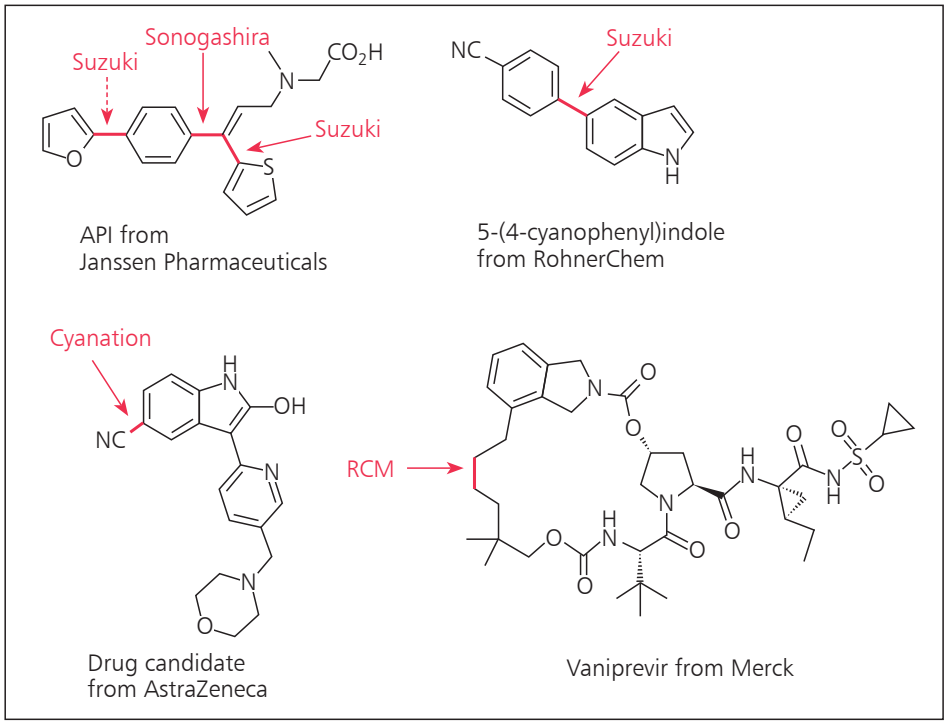


Fig. 11. Products illustrating case studies of some scaled up pgm-catalysed reactions

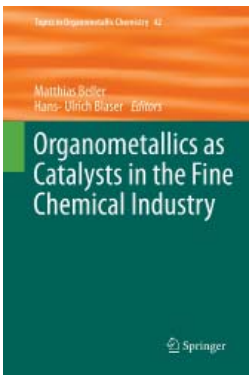
introduction of solutions of the starting diene and the Ru catalyst. Additionally, by raising the temperature, but adding 2,6-dichloroquinone, the catalyst amount could be lowered to 0.2 mol%. Interestingly, other routes involving Heck, Sonogashira or Suzuki couplings were examined but were found less effective.

Conclusions

Despite the massive use of metal-based catalysis in the manufacture of bulk chemicals for many years, the development of organometallic-based processes for pharmaceuticals, fragrances or agrochemicals production is surprisingly still in its adolescence. However, the industrial processes described in this book clearly illustrate the great potential of pgms as valuable tools in this field. Moreover, the numerous examples of production processes, pilot plant or bench-scale reactions depicted will surely inspire chemists who are facing synthetic problems. Finally, this book may also serve as a valuable source of information not only for research purposes, but also for students and colleagues teaching organometallic catalysis.

The Reviewer

Dr Michel Picquet obtained his PhD in Chemistry from the Université de Rennes I, France, under the supervison of Professor P. H. Dixneuf and Dr C. Bruneau in 1998. After a year's post-doctoral position in the group of Professor R. A. Sheldon (Delft Technical University, The Netherlands), he was hired by the Université de Bourgogne in 1999 as an Assistant Professor. His research interests include organometallic catalysis and the use of ionic liquids. Since 2009, he is also interested by organometallics for biological applications. He also teaches Organometallic Synthesis and Catalysis at Master's level.



"Organometallics as Catalysts in the Fine Chemical Industry"