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Organometallics as Catalysts in the Fine Chemical Industry

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Organometallics as Catalysts in the Fine Chemical Industry

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Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structures, properties and mechanisms grows, new paths are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being made that are of significance to a larger scientific audience.

The individual volumes of *Topics in Organometallic Chemistry* are thematic. Review articles are generally invited by the volume editors.

In references *Topics in Organometallic Chemistry* is abbreviated Top Organomet Chem and is cited as a journal. From volume 29 onwards this series is listed with ISI/Web of Knowledge and in coming years it will acquire an impact factor.

Preface

Although organometallic catalysts have been used on a large scale for the manufacture of bulk chemicals for many years, their application in the fine chemicals industry is more recent. Despite the high impact of homogeneous catalysts on organic chemistry, highlighted by three Nobel Prizes in the last decade, their application for the industrial synthesis of more complex molecules is growing rather slowly. The main purpose of this volume is to illustrate the potential of organometallic catalysis for the manufacture of intermediates and products as they are encountered in the fine chemicals, agrochemicals, or pharmaceuticals industry. The focus is on realized industrial applications described exclusively by authors experienced with concrete, "real-world" synthetic challenges. Discussed are problems that can arise when more complex, multifunctional substrates are involved, as well as successful approaches to tackle these problems.

The various chapters demonstrate to organic chemists working in process design and development that organometallic catalysis is not just an academic toy, but is really a suitable tool for the large-scale production of complex intermediates. The book will hopefully also serve as a source of information and provide inspiration for academic researchers.

The book consists of two types of contributions, overview chapters on selected technologies and case studies. Considering that publishing is not a top priority for industrial scientists, we are very happy that we could find competent authors in both categories.

The technology chapters cover the most important reaction types used in the industry: Johannes G. de Vries (DSM) gives an overview on "Palladium-Catalysed Coupling Reactions"; Gregory T. Whiteker (Dow AgroSciences) and Christopher J. Cobley (Chirotech Technology) review "Applications of Rhodium-Catalyzed Hydroformylation in the Pharmaceutical, Agrochemical and Fragrance Industries"; Philippe Dupau (Firmenich) describes the "Ruthenium-Catalyzed Selective Hydrogenation for Flavor and Fragrance Applications"; and Hans-Ulrich Blaser, Benoît Pugin, and Felix Spindler (Solvias) have authored the chapter on "Asymmetric Hydrogenation."

Case studies have been written by Ioannis Houpis (Janssen Pharmaceutica) on "Sequential Pd-catalyzed Cross Coupling Reactions; Challenges on Scale-up," by Adriano F. Indolese (RohnerChem) on "Pilot Plant Scale Synthesis of an Arylindole – Scale up of a Suzuki Coupling," by Per Ryberg (AstraZeneca) on the "Development of a Mild and Robust Method for Palladium Catalysed Cyanation on Large Scale," and by Cheng-yi Chen (Merck Research Laboratories) on the "Application of Ring Closing Metathesis Strategy to the Synthesis of Vaniprevir (MK-7009), a 20-Membered Macrocyclic HCV Protease Inhibitor."

We thank all the authors for their efforts and we hope that our readers find their contributions enlightening.

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Palladium-Catalysed Coupling Reactions

Johannes G. de Vries

Abstract Palladium-catalysed coupling reactions have gained importance as a tool for the production of pharmaceutical intermediates and to a lesser extent also for the production of agrochemicals, flavours and fragrances, and monomers for polymers. In this review only these cases are discussed where it seems highly likely that the technology is or has been used for ton-scale production. We document twelve cases where the Mizoroki–Heck reaction was used to arylate an alkene. In two of these cases allylic alcohols were arylated, leading to the aldehyde or the ketone. The Suzuki reaction has been used mostly to produce biaryl compounds from aryl halides and arylboronic acid derivatives. Twelve processes were recorded. *Ortho*-tolyl-benzonitrile, a biaryl compound produced via the Suzuki reaction, is used as an intermediate in six different pharmaceuticals all belonging to the Sartan group of blood pressure-lowering agents. The Kumada–Corriu reaction in which an aryl or alkenyl Grignard is coupled to an aryl or alkenyl halide was used nine times. In these coupling reactions palladium is often replaced by the much cheaper nickel or iron catalysts. The Negishi reaction couples an arylzinc halide with an aryl or alkenyl halide. These reactions are fast and highly selective; the only drawback being the stoichiometric zinc waste. Two cases were found. In one of these it was possible to use only a catalytic amount of zinc (double metal catalysis). The Sonogashira reaction couples a terminal alkyne to an aryl or alkenyl halide. Three cases were found. Acetylene is usually not coupled as such in view of its instability. Instead, trimethylsilylacetylene or the acetylene acetone adduct is used. Finally, one case was found of a palladium-catalysed allylic substitution and one case of a CH-activation reaction to form a benzocyclobutane ring. Most of these reactions were implemented in production in the past ten years.

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Keywords Agrochemicals • Carbon–carbon bond formation • Cross-coupling • Flavours and fragrances • Monomers • Palladium • Pharmaceuticals • Production process

Contents

1 Introduction

Use of palladium-catalysed coupling reactions for the production of fine chemicals and pharmaceuticals has a number of advantages.

1. A well-chosen catalytic conversion can sometimes replace a number of stoichiometric steps. These catalytic shortcuts can have a very positive influence on the total production cost.
2. Catalytic C–C bond forming reactions are often possible under mild conditions, obviating the need for protection/deprotection. This fits well with a convergent synthesis strategy where two often highly functionalised fragments are coupled.
3. Catalytic reactions can often be performed at lower temperatures and rarely need highly reactive reagents. This results in higher selectivities and less waste.

The use of catalysis in the production of fine chemicals and pharmaceuticals is rather limited, particularly compared to bulk chemicals where catalysis is the rule rather than the exception. A recent study by chemists from the three leading British pharma companies listing all the different types of reactions used in their pilot and production scale processes over the past 5 years allowed us to conclude that homogeneous catalysis is used in about 6–7% of all steps [1]. This number was corroborated subsequently by researchers from other companies. On an average of eight steps per pharmaceutical, this amounts to roughly 50% of the recently launched drugs. Yet, the majority of known transition metal complex-catalysed conversions never made it into the plant. This is due to a variety of reasons, a major one of which is the high cost of the catalyst and the relatively low rate of most reactions leading to catalyst costs per kilogram of final product that are much too high. Indeed, most industrial development projects aimed at scaling up transition metal complex-catalysed reactions are focused at increasing the turnover numbers. One aspect of this is increasing the intrinsic rate of the catalyst. This can sometimes be accomplished by adjusting the ligand, the counterion, and the reaction conditions.

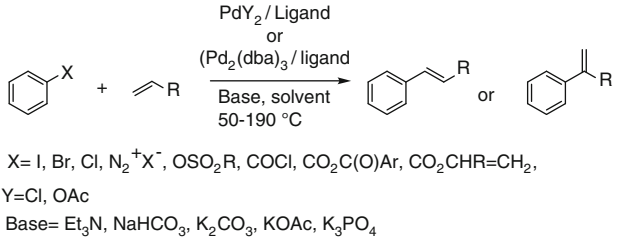
However, often more important when it comes to increasing the rate is the battle against inhibition and deactivation. Catalyst deactivation may be caused by the loss of ligands, which leads to dimerisation of the metal and cluster formation. If the catalyst is in the zero oxidation state nanoparticles will start to grow, and if the growth is not checked by the presence of modifiers that bind to their surface and prevent their fusion, precipitation of the metal will occur. This phenomenon is frequently encountered in palladium-catalysed reactions as Pd(II) is rather easily converted into Pd(0) and a number of mechanisms actually proceed via Pd(0) intermediates. There can be many reasons for this loss of ligands. Sometimes the loss is caused by oxidation of the ligand. Dissociation of ligands is fast at high temperatures; in addition, high temperatures favour the dissociation. Usually, lower temperatures and lower catalyst concentration can help to prevent this deactivation. Other often encountered forms of catalyst inhibition are substrate and product inhibition. These can often be ameliorated by modification of the substrate or by continuous removal of the product. An increased understanding of these deactivation and inhibition mechanisms will eventually lead to an increased use of homogeneous catalysis in the production of fine chemicals.

In this chapter we will discuss industrial processes that use palladium-catalysed aromatic substitution reactions. It is generally problematic to gather information about these large-scale processes. Although many papers have appeared about the use of palladium-catalysed aromatic substitution reactions in medicinal chemistry and even on development scale (1–100 kg), most of these processes have never made it into full-scale production. The reader is referred to a very interesting review article on this topic, which is almost entirely based on articles in the open literature [2]. The cases described therein are mostly on compounds that never made it through clinical trials or where never used in production for various reasons. Many of these cases use catalyst amounts in excess of 1 mol%. At DSM we normally would not scale up a process, unless the catalyst loading is 0.1 mol% or below. The processes described in this chapter are for the largest part based on patent literature. A drawback of this focus is that the patents usually describe the medicinal chemistry route, unless it is a patent covering a second generation process, for instance from a generic company. However, in some cases publications have also appeared about the first generation process that give pointers to what the real process looks like.

Coupling reactions that are included in this chapter are the Heck–Mizoroki reaction, the Suzuki–Miyaura reaction, the Sonogashira reaction, the Kumada–Corriu reaction, the Negishi reaction, allylic substitution and arylation via CH-activation.

2 The Heck Reaction

In the Heck arylation reaction (Scheme 1), invented independently by Mizoroki and Heck in 1970, a bond is formed between an olefin and an aromatic ring [3–8]. The catalyst needs to be a form of Pd(0) but can also be administered as a Pd(II) compound since Pd(II) is usually rapidly reduced to Pd(0); the electrons for this

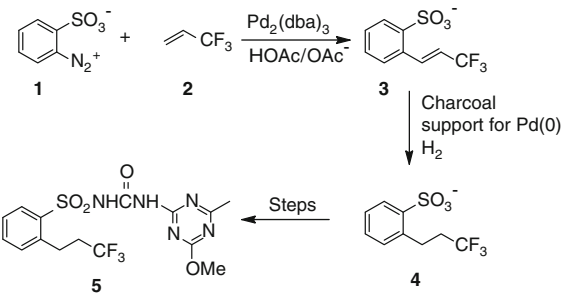


Scheme 1 The Mizoroki–Heck reaction

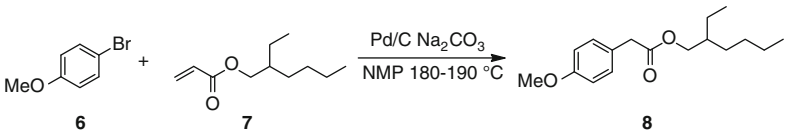
may come from the phosphine ligand, the nitrogen base or from a Wacker reaction on the olefin substrate. Various phosphorus and nitrogen ligands have been used, but it is also possible to use ligand-free palladium, either as preformed palladium nanoparticles or as palladium salt. In the latter case a reservoir of Pd(0) in the form of nanoparticles is formed, but the reaction itself takes place via monomeric anionic intermediates [9, 10]. Heterogeneous palladium such as palladium on carbon can also be used but the reaction is much slower since only the atoms at the outside of the crystals can react. Initially, only aryl bromides and iodides were used as arylation agent. Later, variants were developed using aromatic triflates [11], aroyl chlorides [12], arylsulfonyl chlorides [13], aromatic diazonium salts (the Matsuda reaction) [14], aroyl anhydrides [15], aryl chlorides [16–20] and arylsilanols [21]. Consequently, the number of commercially available aromatic substrates is very high. The Heck reaction works best with alkenes containing electron-withdrawing groups and in most cases gives the β-arylated products exclusively. Olefins with electron-donating groups give rise to mixtures of α- and β-arylated products.

If palladium complexes with bidentate ligands are used, the regioselectivity can be determined by the choice of leaving groups. Non-coordinating anions like triflate lead mainly to the α-arylated products, whereas halides predominantly give the β-products [22]. Simple olefins may suffer from Pd-catalysed isomerisation reactions leading to mixtures. Acetylenes may also be used and are generally more reactive than olefins. Typical solvents for the Heck reaction are dipolar non-protic solvents like DMF and NMP.

The first large-scale application of the Heck reaction was for the production of the herbicide Prosulfuron™ (**5**) by Ciba–Geigy (now Syngenta) [23, 24]. In a Matsuda–Heck reaction 2-sulfonato-benzene diazonium betaine (**1**) was reacted with trifluoropropene (**2**). $Pd_2(dba)_3$ was used as a catalyst and indeed, phosphine ligands are incompatible with the Matsuda reaction (Scheme 2). Working ligand-free has the advantage that the palladium precipitates at the end of the reaction which makes recovery quite easy. In this particular case charcoal was added, which provided a surface on which the palladium could precipitate. This palladium on charcoal could then be used as catalyst for the next step of the sequence which was a hydrogenation of the alkene **3**. Not only was the catalyst used in two consecutive steps, this method also allowed the catalyst to be reclaimed by filtration in 95% yield.



Scheme 2 Matsuda–Heck reaction in the production of Prosulfuron



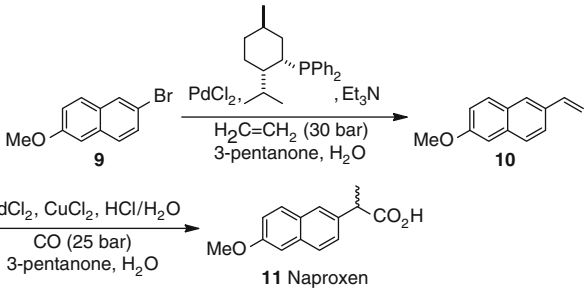
Scheme 3 Sun screen agent via the Heck reaction

The reaction is performed in a single reactor without isolation of the intermediates. The average yield per step is in excess of 90%.

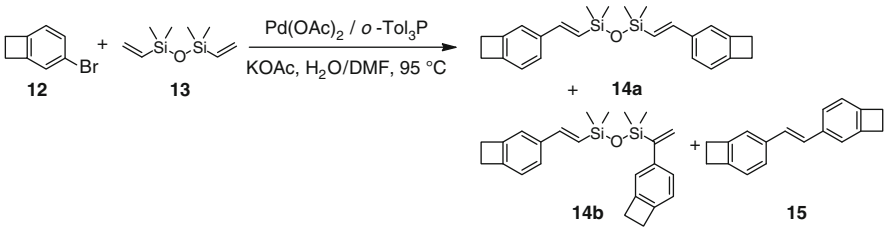
Being backward integrated in the production of bromide compounds is an advantage when using aryl bromides as arylating agent in the Heck reaction. The bromide salt that is formed as waste can be recycled back into the production of useful bromine-based products. Thus, Eisenstadt and co-workers developed a process for the production of 2-ethyl-hexyl *p*-methoxy-cinnamate, a widely used sunscreen agent, from *p*-bromoanisole and 2-ethyl-hexyl acrylate catalysed by Pd/C (Scheme 3). The use of the heterogeneous catalyst necessitates a higher temperature which leads to some double arylation; nevertheless, the yield of this reaction is quite good. The process was evaluated for production in Israel where high concentrations of bromide salts are found in the Dead Sea which has led to a thriving bromine industry, but in the end never made it beyond pilot scale [25].

Köhler has shown that these heterogeneous palladium catalysts in fact function as a homogeneous catalyst. Palladium atoms are released from the heterogeneous catalyst through oxidative addition with the aryl bromide [26]. There was a clear correlation between the amount of dissolved palladium and the progress of the reaction. At the end all palladium precipitates again allowing an easy recovery of the catalyst.

Albemarle also is a producer of organobromine compounds and thus it was a logical development to explore the production of Naproxen using the Heck reaction (Scheme 4) [27, 28]. The starting bromide **9** was already in use for the large-scale production of Naproxen via Grignard chemistry. Making use of intermediates that are already available on large scale is a good strategy when developing a new production route as this lowers the cost of the raw materials. Here, the challenge was to prevent the formation of the double arylated ethylene. This was achieved by performing the



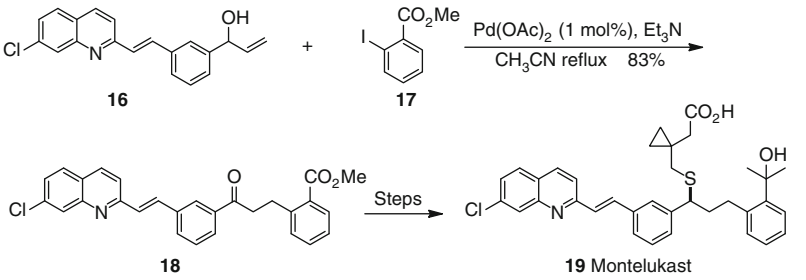
Scheme 4 Naproxen via Heck reaction followed by a hydroxycarbonylation



Scheme 5 Monomers for coatings via the Heck reaction

reaction at an ethylene pressure of 30 bar. Screening of a limited number of ligands led to the finding that neomenthyldiphenylphosphine was the ligand of choice. Use of this ligand in a sixfold ratio with respect to palladium led to a much faster reaction than using either triphenylphosphine or tricyclohexylphosphine. Because of the high activity of the catalyst, it was possible to use a substrate/catalyst ratio of between 2,000 and 3,000 with the reaction going to completion at 95–105°C within a few hours. Yields of 85–95% of the vinylnahthalene **10** were obtained. This product was isolated by basic extraction and acidification. In a next step **10** was subjected to a hydroxycarbonylation reaction using $Pd(OAc)_2/CuCl_2$ as catalyst with the same ligand as was used in the Heck reaction. Racemic Naproxen was obtained in 90% yield. The scale of the process is around 500 tons/year. It is assumed that Albemarle uses a similar process for the production of Ketoprofen. Here also only 0.05 mol% palladium is used [29].

The mild conditions used in the Heck reaction make it a particularly suited method for C–C bond formation when one of the reaction partners is thermally labile. This was the case in a production process for a monomer for coatings that contained a benzocyclobutene ring [30]. The polymer named Cyclotene™ is used in electronics to bind circuits directly to the board. Upon heating, the benzocyclobutene ring opens to form a quinone dimethide, which can undergo a Diels–Alder reaction with one of the remaining double bonds leading to cross linking. In the process research, a range of ligands was screened in the Heck reaction between 4-bromo-benzocyclobutene (**12**) and tetramethyldivinyldisiloxane (**13**) using $Pd(OAc)_2$ in a DMF/water mixture at 95°C (Scheme 5). The best

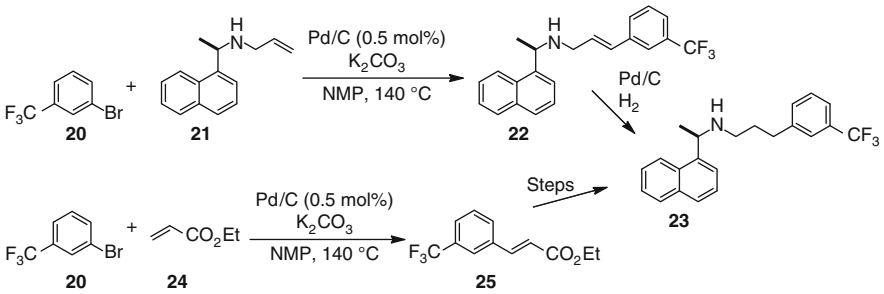


Scheme 6 The Heck reaction in the production of Montelukast

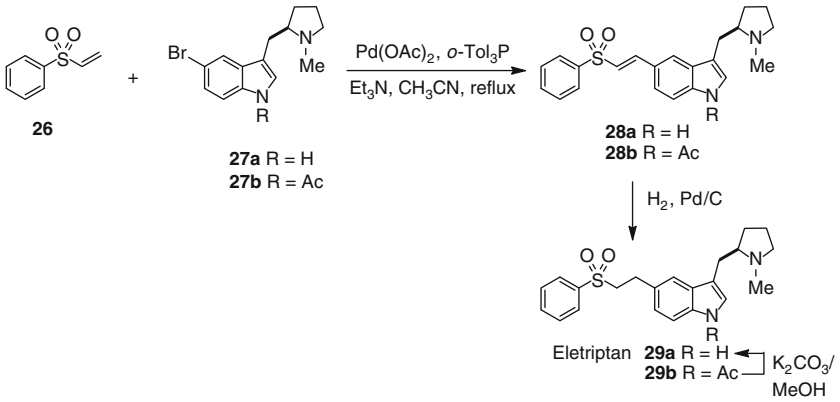
performing ligand in terms of rate and yield of **14** was tris-*ortho*-tolylphosphine. The product was obtained as a mixture of stereoisomers **14a** and **14b** in 83% yield. This mixture is used as such in the polymerisation reaction. Surprisingly, no correlation could be found neither with the electron density nor with the steric bulk of the ligand, expressed as its cone angle, and conversion, yield or regioselectivity. A possible explanation may be that the effect the ligand has is more related to the stability than to the activity of the catalyst. A side product in this reaction is formed by bromide catalysed desilylation of the initially formed monoarylated product. The resulting styrene is arylated to the stilbene **15**, which is formed in amounts of 3–11%. The formation of the side product could be suppressed by switching the base from Et_3N to KOAc.

The Mizoroki–Heck reaction has been used in the production of a number of drugs. Here the strength of the Heck reaction often lies in the fact that it allows coupling between two fragments at a late stage of a total synthesis without the need for protection/deprotection. A case in point is the production process for Merck's Montelukast (also called Singulair), an anti-asthma agent [31, 32]. Looking at the structure of Montelukast the double bond between the quinoline and the aromatic ring would seem to be a perfect candidate for a Heck reaction. Surprisingly, in practice this bond is made via a condensation of the 2-methylquinoline on the aromatic aldehyde, although patents also exist on the Heck approach. Instead, the Heck reaction is used to attach allylic alcohol **16** to the aromatic iodide **17** (Scheme 6). In this variant of the Heck reaction the beta-hydride elimination preferentially takes place with the hydride adjacent to the alcohol leading to the formation of the enol which isomerises to the ketone. In patents and publications the use of 1 mol% of Pd $(OAc)_2$ is mentioned. In general, Heck reactions on aryl iodides can be performed very well with ligand-free palladium catalysts and very low loadings can be used [33]. Reactions on allylic alcohols usually require somewhat more catalyst though. In these reactions with ligand-free palladium, the palladium precipitates as palladium black at the end of the reaction, allowing its easy recovery. This palladium black is rather unreactive in the Heck reaction because of the large crystal size; however, it can be rendered active again by reoxidation with iodine [34].

Teva has patented two routes towards Cinacalcet hydrochloride **23**, a calcium mimetic that helps regulate calcium levels in the treatment of bone disease, based on the Heck reaction (Scheme 7). In both routes *m*-bromo-trifluorotoluene **20** was



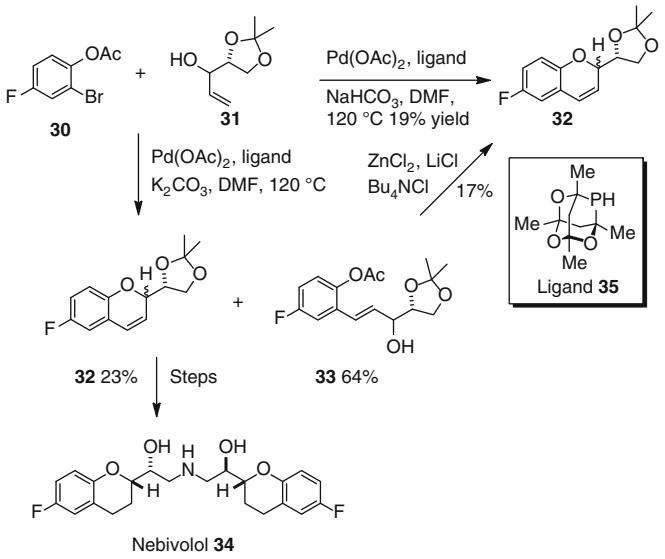
Scheme 7 Heck approaches towards Cinacalcet hydrochloride



Scheme 8 Heck reaction in the production of Eletriptan

the arylating agent. Heck reaction thereof with *N*-allyl-1-naphthyl-ethylamine **21** followed by hydrogenation of the double bond led to the formation of Cinacalcet (**23**) [35]. In view if the high reactivity of **20**, it was possible to use Pd/C as catalyst in NMP as solvent at 140°C. In the second route **20** is reacted with ethyl acrylate **25** to give the cinammate ester [36]. The ester was reduced to the alcohol and chlorinated to furnish the alkylating agent for 1-naphthyl-ethylamine. Another approach was based on the Heck reaction of **20** with acroleine diethyl acetal, which gave a mixture of unsaturated acetal and saturated ethyl ester, which eventually could be reduced to the saturated alcohol.

Eletriptan **29a**, an anti-migraine compound developed by Pfizer, is produced using a Heck reaction as outlined in Scheme 8. In the medicinal chemistry route, the Heck reaction was performed between the vinyl sulfone **26** and the indole bromide **27a** [37, 38]. However, during process development it was found that attempts to purify the Heck product **28a** led to formation of a dimeric compound as a result of a Michael addition of the indole nitrogen onto the alkenylsulfone. Thus, in an improved process the indole **27a** was acetylated prior to the Heck reaction [39]. The acetyl group was removed after hydrogenation of **28b** to **29b**. A different

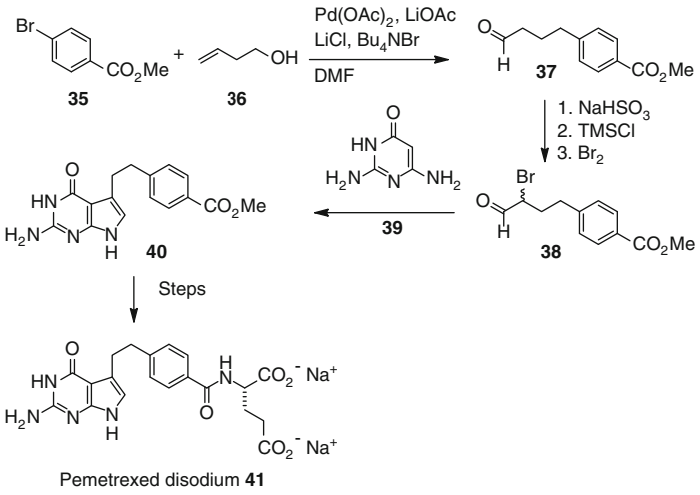


Scheme 9 Approach towards Nebivolol via a Heck reaction

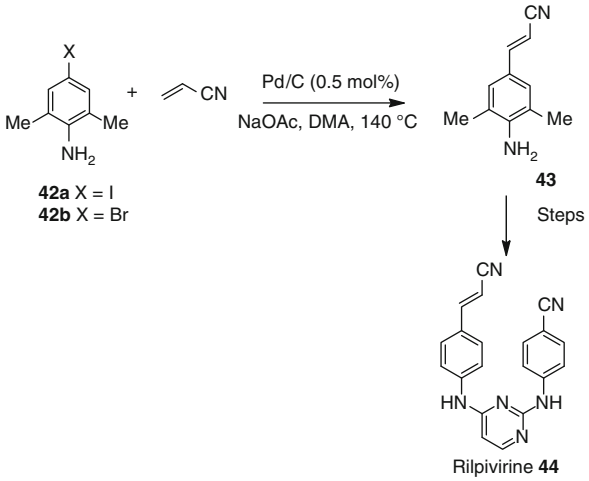
process was later developed in view of the high cost of **27a** and the fact that the sulfone **26** is a sensitising agent [38].

Nebivolol **34** is a blood pressure-lowering agent originally developed by Janssen Pharmaceutica. The Italian generics company Zach System has developed two slightly divergent synthetic routes towards **34**, one of which is based on the Heck reaction and the other on the use of a Suzuki reaction (*vide infra*) [40]. Although the Heck route is shorter, the yields reported in the patent are rather low. The Suzuki route involves a hydroboration, which is a rather expensive step, and thus the choice of route would depend on how much the yields in the Heck reaction were improved during process development. In the Heck reaction between aryl bromide **30** and allylic alcohol **31** (Scheme 9), an interesting phosphatrioxaadamantane ligand (**35**) was used that can be made in a single step from PH_3 and acetylacetone. The reaction shows a remarkable dependence on the type of base. Using $NaHCO_3$ as base chromene **32** was isolated as a mixture of diastereomers in 19% yield. Using K_2CO_3 as base **32** was isolated in 23% yield, but in addition, the allylic alcohol **33** could be isolated in 64% yield. This could be ring-closed to **32** albeit in poor yield.

Pemetrexed disodium **41** is a dihydrofolate reductase inhibitor, originally discovered by Taylor at Princeton University [41] that is marketed as an anti-cancer agent by Eli Lilly. For the introduction of the two-carbon bridge between the aromatic and heteroaromatic units, a number of different technologies were developed. The original route was based on a Sonogashira reaction [41], but the route used by Lilly is based on the use of 4-aryl-*n*-butyraldehyde **37**, the synthesis of which was accomplished via the Heck reaction (Scheme 10) [42, 43]. This reaction is based on a variant developed by Larock in which the unsaturated alcohol **36** reacts with aryl bromide **35** to give the aldehyde **37** [44]. The catalyst used is ligand-free palladium, stabilised by the addition



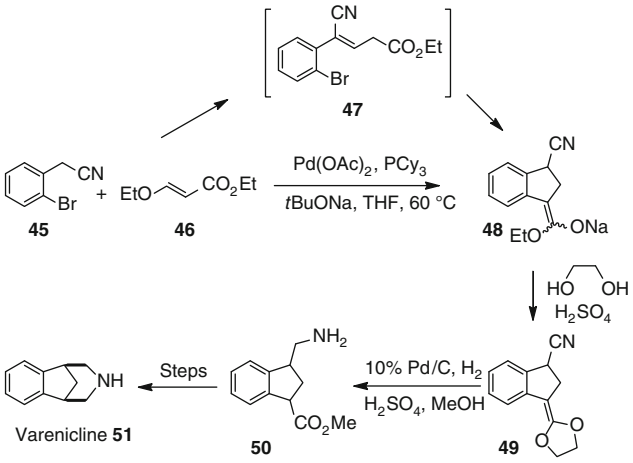
Scheme 10 Heck reaction in the production of Pemetrexed disodium



Scheme 11 The Heck reaction in the production process of Rilvipirine

of halide. Although the yield of the aldehyde **37** is good, a number of isomers were formed such as the branched arylation product and some unsaturated alcohols. Purification was achieved via the bisulfite addition product. The aldehyde could be set free again by the addition of TMSCl [43]. Alpha-bromination of the aldehyde followed by addition of the diaminopyrimidinone **39** established the pyrrolo-pyrimidinone unit in **40**, which was further converted to **41**.

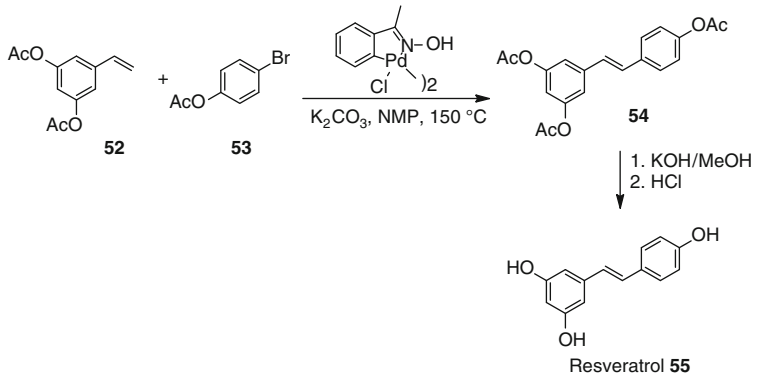
Rilpivirine hydrochloride (**44**) is a non-nucleoside reverse transcriptase inhibitor that is used as medicine against AIDS. The drug was originally developed by Janssen Pharmaceutica [45]. In the process development, a route was developed for intermediate **43** based on the Heck reaction (Scheme 11) [46].



Scheme 12 Heck reaction in the production of Varenicline

Extensive research was performed in which the performance of the more expensive aryl iodide **42a** was compared with the aryl bromide **42b**. It was possible to perform the Heck reaction on the iodide with ligand-free Pd/C, whereas the Heck reaction on **42b** needed the presence of a ligand, such as tris-*o*-tolylphosphine. Possibly for this reason the product of the reaction with **42b** also contained much more residual palladium (1,196 ppm vs 58 ppm with **42a**), which was hard to remove. Thus, because of this problem and in view of the high ligand cost, it was decided to use the iodide **42a** for the production runs. The reaction produced the Heck product with and *E*/*Z* ratio of 80/20, and the product was isolated by forming the HCl salt in EtOH. It was found that during the salt forming process the *E*/*Z* ratio increased from 80/20 to 98/2. This is not the result of purification by crystallisation, but rather, the *Z*-isomer selectively reacts with EtOH in an acid-catalysed Michael reaction.

Varenicline **51** is known to act on the Nicotinic receptor and is marketed by Pfizer as a smoking cessation aid. In its synthesis a palladium-catalysed coupling reaction is used (Scheme 12) [47]. The *ortho*-bromobenzyl cyanide **45** is reacted with ethyl 3-ethoxy-acrylate **46** in an addition–elimination reaction to form **47**. This intermediate cyclises in a palladium-catalysed reaction to **48**. It is possible to perform these two reactions in a one-pot procedure. The exact mechanism is unknown. The reaction could either proceed via a double bond isomerisation followed by a Heck reaction, but equally, it could be a direct coupling between the $L_nPdArBr$ and the enolate anion. The aromatic bromide is somewhat deactivated and thus use of PPh_3 as ligand was unsuccessful. Use of more strongly basic ligands such as Cy_3P or Cy_2PPh or the dialkyl-biarylphosphines that have been developed by Buchwald was successful, however. In terms of cost and availability, Cy_3P is the most suited although it was found that Cy_2PPh is less prone to oxidation.

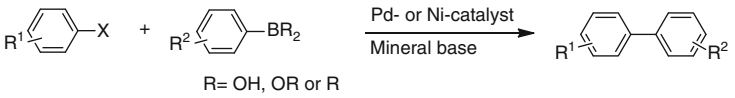


Scheme 13 Heck approach towards Resveratrol

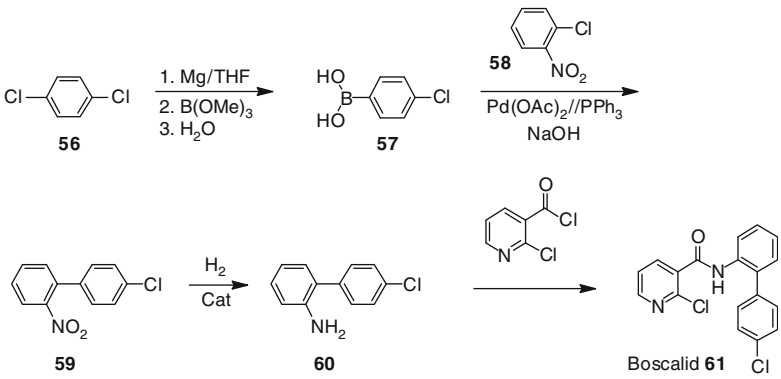
DSM produces the antioxidant Resveratrol, the component in red wine that is responsible for a number of positive health effects also known as "The French paradox". They have published a total synthesis of Resveratrol that is based on a Heck approach using acetylated intermediates (Scheme 13) [48, 49]. The best yield (94%) and highest substrate/catalyst ratio (2,000) were achieved using the palladacycle catalyst developed by Najera and co-workers [49, 50]. Hydrolysis of the tris-acetate provided Resveratrol in good yield.

3 The Suzuki Reaction

The Suzuki reaction is a cross-coupling between an aryl- or vinyl boron compound – this can be a boronic acid, anhydride or ester, a dialkylboron compound, or it can be a potassium trifluoroborate – with an aryl or vinyl halide or pseudohalide, including triflate, tosylate, diazonium salts, sulfonyl chloride, ammonium salts, etc. (Scheme 14) [51, 52]. Catalysts are palladium or nickel-based. The reaction usually requires a mineral base and benefits from the presence of at least some water. The Suzuki reaction has been used many times in the production of fine chemicals and pharmaceuticals, mostly for the formation of unsymmetrical biaryl compounds. The Suzuki reaction is complimentary to the Kumada–Corriu reaction that uses a Grignard as nucleophile and the Negishi reaction that uses an arylzinc halide as a nucleophile. Advantages of the Suzuki reaction with respect to these two other methods are the stability of the arylating agent, which can be stored for prolonged periods, and its compatibility with a wide range of functional groups. A disadvantage is the instability of the arylboronic acids under the hot aqueous conditions that are common in the Suzuki reaction. They suffer from protodeborylation. This side reaction is worse with arylboronic acids carrying electron-withdrawing groups. Although the arylboronic acids are more expensive than the Grignard reagents that are made from the halides, in practice, in most production processes the arylboronic



Scheme 14 The Suzuki reaction

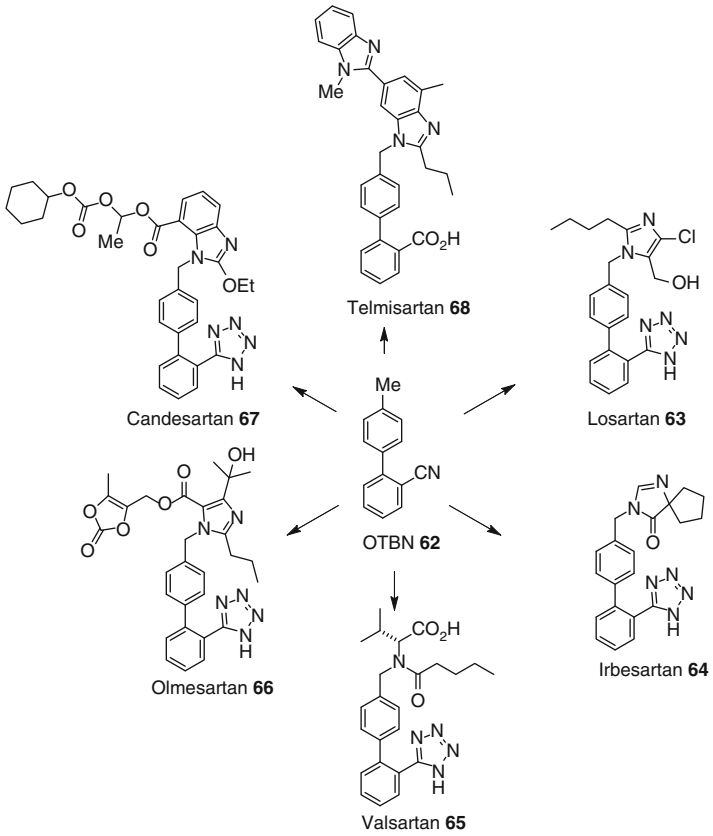


Scheme 15 Production of the fungicide Boscalid using the Suzuki reaction

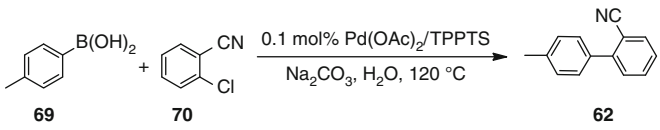
acid derivative is made in situ via reaction between the Grignard and trimethyl borate followed by hydrolysis.

Probably the largest product that is produced via a Suzuki reaction is the fungicide Boscalid **61** that was developed and brought on the Market by BASF in 2002. It is produced on a scale exceeding 1,000 tons/year [53]. The required boronic acid **57** is made via reaction of the Grignard reagent with $(MeO)_3B$, followed by hydrolysis. The Suzuki coupling is catalysed by $Pd(OAc)_2/PPh_3$ (0.5 mol% is used in the patent) and NaOH is used as base (Scheme 15) [54]. Interestingly, in a later patent, the use of the diarylboronic acid (p-Cl–$C_6H_4)_2$B–OH is advocated and indeed yields and substrate catalysts ratios are very similar but only half the amount of $B(OMe)_3$ is used [55].

In pharma, the Suzuki reaction is used quite often. An important event in this respect was the emergence of the Sartan class of blood pressure-lowering agents. In the mean time six different Sartans have entered the market (Scheme 16). All but one have the o-tolyl-phenyl-tetrazole unit in common. In these drugs the tetrazole unit is a mimic of a carboxylic acid function. In Telmisartan (**68**) the carboxylic acid function has remained but the biphenyl unit is very similar. The common structural element has led to the development of o-tolyl-benzonitrile (OTBN) (**62**) as a central intermediate. Not surprisingly, there are 119 patents that describe the preparation of OTBN. All possible coupling methods have been used for its preparation, including the Negishi, the Suzuki and the Kumada coupling. Palladium and nickel catalysts have been used. Initially, OTBN was produced by Catalytica Pharmaceuticals (now DSM) using the Negishi reaction (*vide infra*), but soon they



Scheme 16 The Sartan class of blood pressure-lowering agents



Scheme 17 The Clariant process to OTBN

were overtaken by the process developed by Clariant, which is based on the Suzuki reaction between *ortho*-chlorobenzonitrile and *para*-tolylboronic acid (Scheme 17) [56]. This process uses the water-soluble ligand tris-(*m*-sulfonatophenyl)phosphine (TPPTS) in combination with $Pd(OAc)_2$. Use of this ligand makes the catalyst water-soluble, which allows its easy recovery at the end of the reaction.

Several 100 tons have been made using this process. Further functionalisation of **62** proceeds via bromination of the methyl group, followed by substitution with a

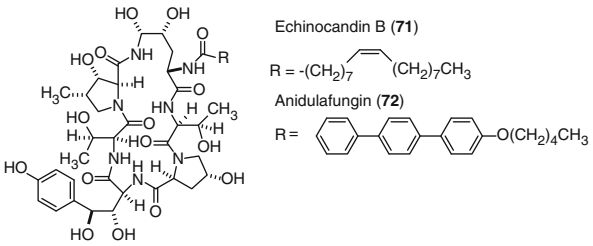
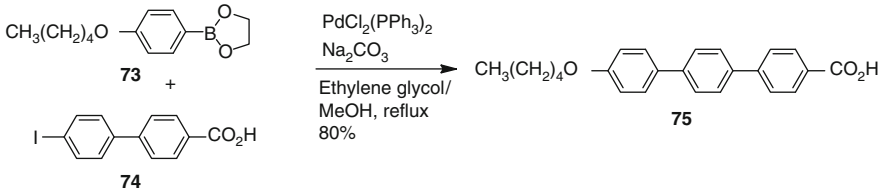


Fig. 1 Structures of Echinocandin B and Anidulafungin

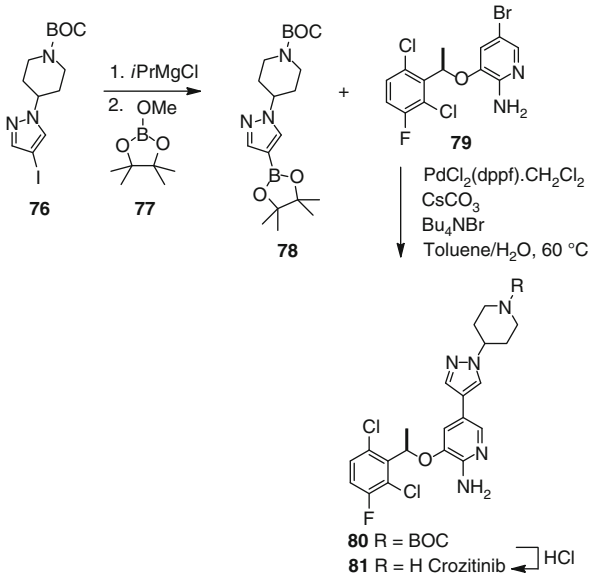


Scheme 18 Terphenyl intermediate for Anidulafungin via the Suzuki reaction

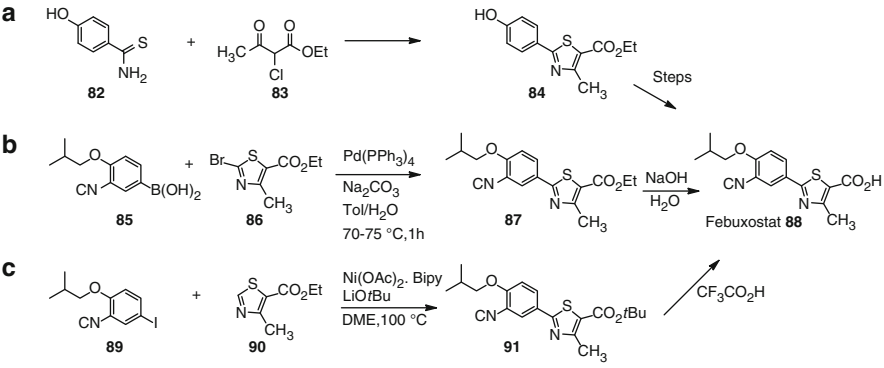
nitrogen nucleophile; the tetrazole unit is introduced via reaction with azide. Currently, most **62** is produced in China.

Echinocandin B (**71**) is an antifungal compound, obtained via fermentation of *Aspergillus nidulans* var. *echinulatus*, A 32204. It was possible to remove the lineolic side chain by enzymatic hydrolysis using an *Actinoplanes utahensis* culture. The deacylated product is devoid of anti-fungal activity but could be further derivatised using acylation. There was a clear correlation between lipophilicity of the acylated product and its anti-fungal activity. Eventually, acylation with 4″-pentoxy-terphenyl-4-carboxylic acid delivered Anidulafungin **72**, a potent anti-fungal agent which is marketed by Pfizer (Fig. 1) [57, 58]. The terphenyl side chain **75** was prepared by Clariant via a Suzuki reaction between the ethylene glycol ester of 4-pentoxy-phenylboronic acid and 4′-iodo-1,1′-biphenyl-4-carboxylic acid (Scheme 18) [59]. The substrate/catalyst ratio was 1,000. Use of other boronic esters and other palladium precursors led to comparable yields.

Crizotinib **81** is a tyrosine kinase inhibitor which is currently marketed as an anti-cancer agent. The bond between the pyrazole ring and the pyridine is established via a Suzuki reaction using $PdCl_2$(dppf) as catalyst (Scheme 19). Initially, the pyrazole boronic ester **78** used in this coupling was prepared via a palladium-catalysed borylation of idodo-pyrazole **76**, using bis-pinacolatodiborane [60]. Since this is a rather expensive method for the production of this borane reagent, the route was changed during development, and the boronic ethylene pinacolate ester was prepared from reaction between the Grignard made from **76** and pinacolato methoxyborane **77** [61]. DME, the solvent initially used for the Suzuki reaction, is undesired for a number of reasons and it was replaced by toluene plus the phase



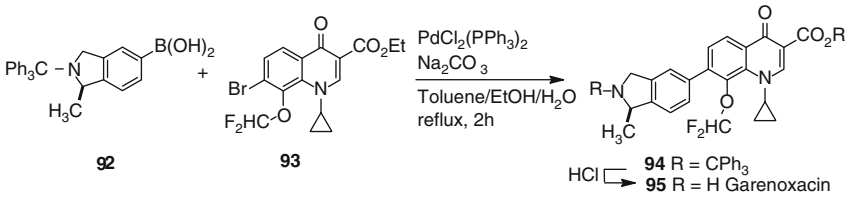
Scheme 19 Crozitinib via Suzuki reaction



Scheme 20 Different routes towards Febuxostat

transfer catalyst Bu_4NBr. This had the added benefit that the catalyst loading could be reduced from 3.8 to 0.8 mol%. The residual palladium in solution after work up was removed by treatment with cysteine on silica–alumina loaded with 15 wt% cysteine during 25 h at 60°C. The product **80** was isolated in 76% yield.

Febuxostat **88** is an inhibitor of xanthine oxidase that has been developed by Teijin Pharma as a new drug for the treatment of gout and hyperuricemia [62]. The 2-aryl-thiazole structure is prepared by Teijin via a condensation between 2-chloroacetate **83** and arylthioamide **82** (Scheme 20a) [63]. However, Cipla, a

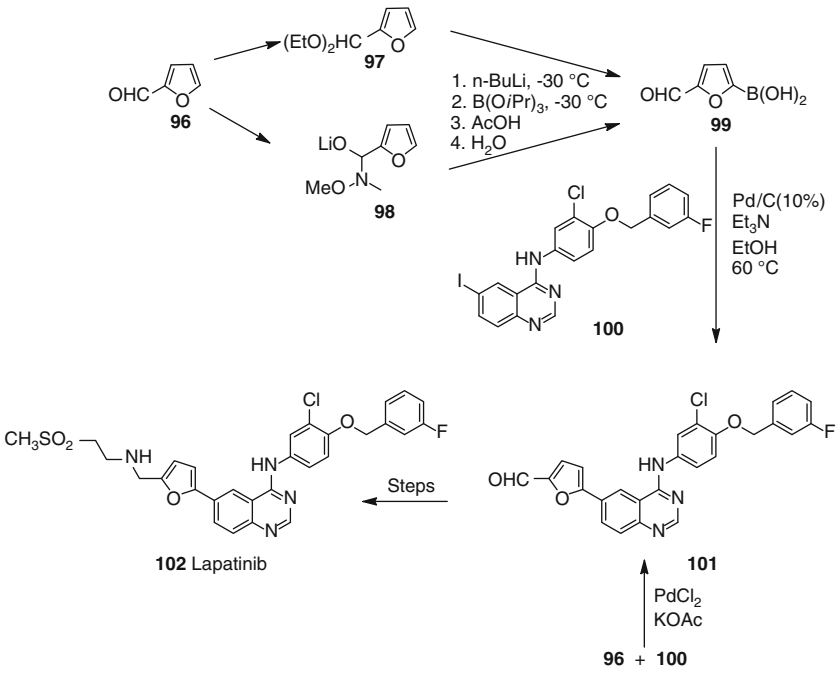


Scheme 21 Garenoxacin via Suzuki coupling

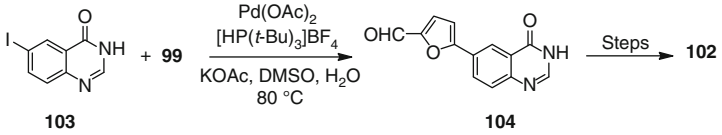
generic producer of Febuxostat, has patented a route via the Suzuki reaction (Scheme 20b). They use 5 mol% of $Pd(PPh_3)_4$ as catalyst. The product was obtained in 63% yield. It is unclear if this route is actually used by Cipla. Recently, Itami and co-workers, together with Teijin developed a new method for the direct 2-arylation of azoles via nickel-catalysed coupling with the haloarene (Scheme 20c) [64]. The reaction proceeds via deprotonation of the azole in the 2-position, followed by transmetallation with Nickel. The nickel derivative then undergoes a Suzuki reaction with the iodoarene. They also prepared Febuxostat in this manner in 67% yield.

Garenoxacin **95** is a quinolone antibiotic that does not have a fluorine substituent at the position C-6 but has shown excellent potency, particularly against Gram-positive bacteria including methicillin-resistant staphylococci and penicillin-resistant streptococci, as well as activity against Gram-negative bacteria [65]. Its synthesis is a typical example of a convergent synthesis in which two highly functionalised fragments are coupled in good yield, using a mild coupling method such as the Suzuki reaction. Unfortunately, no data have been published on the large-scale process. The Toyama patent describes both a Stille and a Suzuki approach for the coupling of the two fragments [66]. It seems highly unlikely that the Stille reaction was scaled up in view of the toxicity of the tin derivative and the problematic purification for the removal of the tributyltin fragment, which usually requires chromatography. The Suzuki reaction is described using 4 mol% of $PdCl_2(PPh_3)_2$ as catalyst and Na_2CO_3 as base (Scheme 21). Presumably, in the developed process the amount of catalyst has been brought down.

Lapatinib is a protein tyrosine kinase inhibitor that was developed by GSK as an anti-cancer agent. The original medicinal chemistry route made use of a Stille reaction to effect the coupling between the furan ring and the quinazoline ring [67]. However, scale-up of a Stille reaction is near-impossible for the two main reasons outlined above. In a later patent, GSK describes several options based on the Suzuki reaction that look eminently scalable (Scheme 22) [68]. An obvious starting material for the furan moiety is furfural, which can be selectively functionalised in the 4-position by lithiation after protection of the aldehyde moiety as the bis-ethyl acetal or the lithiated methoxy-amide. After hydrolysis of the protecting group, the crude boronic acid was coupled with the aryl iodide **100** to give the product in 87% yield. Palladium on carbon (3 mol%) was used as the catalyst. Although part of the palladium will go into solution during the reaction, at the end of the reaction it precipitates completely and can be recovered by filtration. The reverse Suzuki reaction was also reported using 4-bromo-furfuraldehyde; here a clean conversion



Scheme 22 Use of Suzuki coupling or CH-activation in the preparation of Lapatinib

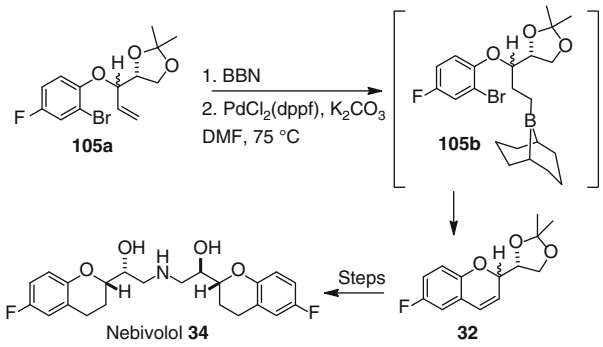


Scheme 23 Early Suzuki coupling in the preparation of Lapatinib

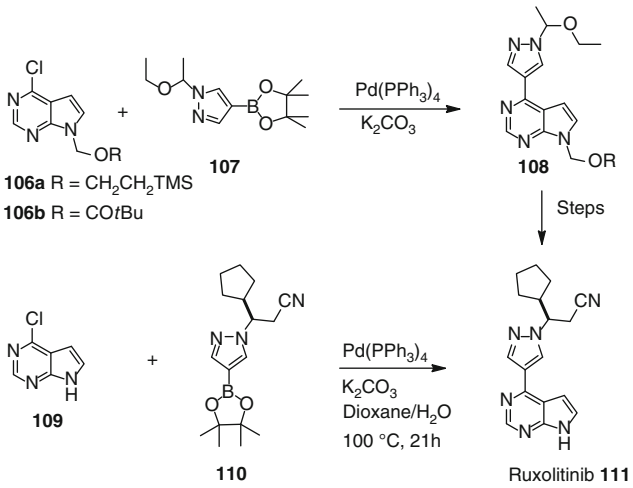
of 95% was reported. Interestingly, it was also possible to couple furfuraldehyde directly with aryl iodide **100** in a CH-activation reaction using 0.5 mol% $PdCl_2$ as catalyst in the presence of potassium acetate to give **101** in 55% yield.

In general it is not advisable to have the palladium-catalysed coupling reaction as last or penultimate step in view of the need to reduce palladium levels in the final product to below 10 ppm. Based on this reasoning, Taiwanese chemists patented an alternative route towards Lapatinib in which the furan ring is coupled to the quinazoline moiety before attachment of the substituted aniline (Scheme 23) [69]. Thus, coupling between the furfural-boronic acid **99** and aryl halide **103** catalysed by a catalyst prepared in situ from palladium acetate and one equivalent of tri-*t*-butylphosphine (2 mol%) gave the biaryl compound **104** in 98% HPLC yield.

Earlier in this chapter the preparation of Nebivolol via the Heck reaction is described (Scheme 9). There also is a similar route using a Suzuki reaction instead



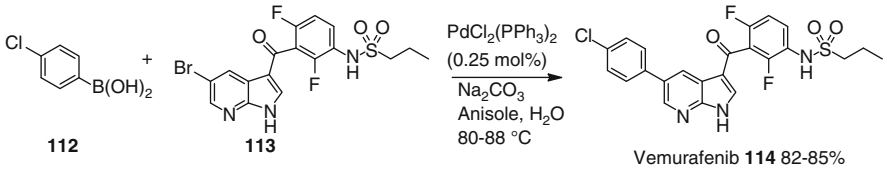
Scheme 24 Suzuki reaction in the synthesis of Nebivolol



Scheme 25 Suzuki approaches towards Ruxolitinib

(Scheme 24) [40]. Note that a direct Heck reaction on **105** would lead to the formation of the 5-membered ring instead. Thus the alkene was hydroborated with 9-borabicyclo[3.3.1]nonane (BBN) first after which the Suzuki reaction gave **32** as a mixture of diastereomers in 58% yield.

Ruxolitinib phosphate **111**, discovered by Incyte, is an inhibitor of Janus-associated kinase 2 (JAK2), a protein involved in signal transduction. It is marketed as a treatment for Myelofibrosis, a bone marrow disease that leads to the formation of abnormally shaped red blood cells. A number of different synthetic schemes have been patented and published, all of which contain a Suzuki step (Scheme 25) [70, 71]. In one approach, the chlorodeazapurine **106a** or **b**, differing in the protecting group on nitrogen, is coupled with the N-protected pyrazole pinacol borate **107**. In both cases 0.3 mol% of $Pd(Ph_3)_4$ is used as catalyst. The reaction with **106a** is performed in a mixture of *n*-PrOH/H_2O at 90°C over 1–4 h; the yield after



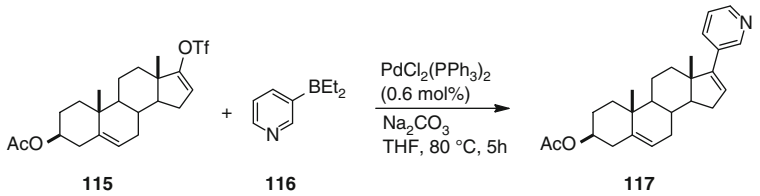
Scheme 26 Suzuki reaction in the production of Vemurafenib

deprotection of the ethoxyethyl group is 88%. The reaction with **106b** is performed in a dioxane/H_2O mixture at 85°C over 2–5 h; the yield after deprotection was 91%. The deprotected material is further functionalised by an asymmetric aza-Michael reaction with 3-cyclopentyl-acroleine in the presence of an organocatalyst with ee's around 90%. Another approach was an aza-Michael reaction on cyclopentyl-propiolonitrile or amide followed by an asymmetric hydrogenation. Finally, it was also possible to defer the Suzuki reaction to the very last step of the synthesis. This has the benefit of making the route more convergent. However, removing the last traces of palladium till below 10 ppm can be a daunting task. In addition, the yield of the reaction between **109** and **110** (over two steps, including the preparation of the borate ester) was only 64% [71].

Vemurafenib **114** is an anti-cancer agent, developed by Plexikkon and marketed by Hoffmann-La Roche for the treatment of Melanoma. In the original medicinal chemistry route from Plexxikon, $Pd(PPh_3)_4$ was used as a catalyst for the Suzuki reaction to connect fragment **113** with *p*-chloro-phenylboronic acid, and the reaction was conducted in a microwave reactor at a very high temperature for a short time [72]. Chemists from Hoffmann-La Roche developed a scalable method, using only 0.25 mol% $PdCl_2(PPh_3)_2$ as catalyst (Scheme 26) [73]. In general, tetrakis-triphenylphosphine palladium is not a good catalyst as even at room temperature it has a tendency to decompose to palladium nanoparticles [74]. At concentrations above 0.1 mol% palladium black will form; this is worse at higher temperatures [33]. Although the palladium nanoparticles themselves are active as catalyst, they are severely deactivated by the large excess of triphenylphosphine. Since only roughly half the palladium atoms are at the surface of the nanoparticles, there are now eight phosphines available per palladium atom at the surface.

Abiraterone acetate **117** is an androgen biosynthesis inhibitor, which was developed by the Institute of Cancer Research in the UK and further developed by Janssen for the oral treatment of patients with metastatic castration-resistant prostate cancer [75]. Its synthesis is relatively easy through a Suzuki coupling between the 17-enol triflate derived from the 3-acetate of dehydro-epiandrosterone (**115**) and 3-pyridyl-diethylborane (**116**) (Scheme 27) [76]. The reaction is catalysed by $PdCl_2(PPh_3)_2$ and proceeds in good yield (84%). A similar Suzuki-based route in which the ketone starting material was converted into an alkenyliodide has also been published [77].

The Suzuki reaction has also been used extensively for the production of biaryl compounds for liquid crystals [78, 79].



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Scheme 27 The Suzuki reaction in the synthesis of Abiraterone acetate

4 The Kumada–Corriu Reaction

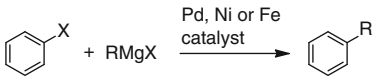
In the Kumada–Corriu reaction a Grignard reagent is coupled with an aryl or vinyl halide or pseudohalide (Scheme 28) [80–84]. The reaction is catalysed by palladium, nickel, copper and iron. In principle this is the cheapest cross-coupling reaction that causes the least amount of waste. In addition, low catalyst loadings can usually be achieved. The only drawback is the high reactivity of the Grignard reagent which is incompatible with a large number of functional groups. Nevertheless, there are a number of industrial applications known of the Kumada–Corriu reaction.

The Japanese company Hokko Chemical Industry has reported the use of the Kumada–Corriu reaction for the production of at least five different intermediates (Scheme 29) [85]. For most of these coupling reactions they use nickel catalysts, in particular $NiCl_2$(dppp). Thus, they prepared *p*-chloro-styrene (5 tons/year) from *p*-chloro-phenylmagnesiumchloride and vinyl chloride, and also *t*-butoxy-styrene (200 tons/year) from *t*-butoxy-phenylmagnesiumchloride and vinyl chloride. As solvent they used a mixture of benzene or toluene with a small amount of THF. Using copper catalysts it was possible to couple aromatic Grignards with alkyl bromides in good yields. Thus, *p*-propyl-styrene was prepared from *p*-vinyl-phenylmagnesiumchloride and *n*-propylbromide using Li_2CuCl_4 as catalyst. Likewise, reaction between *t*-butoxy-phenylmagnesiumchloride and *n*-pentyl bromide catalysed by CuCl gave *t*-butoxy-phenylpentane. The latter compound finds use in liquid crystals and as intermediate for pharmaceuticals. The authors note that catalyst loadings are higher with copper than with nickel or palladium.

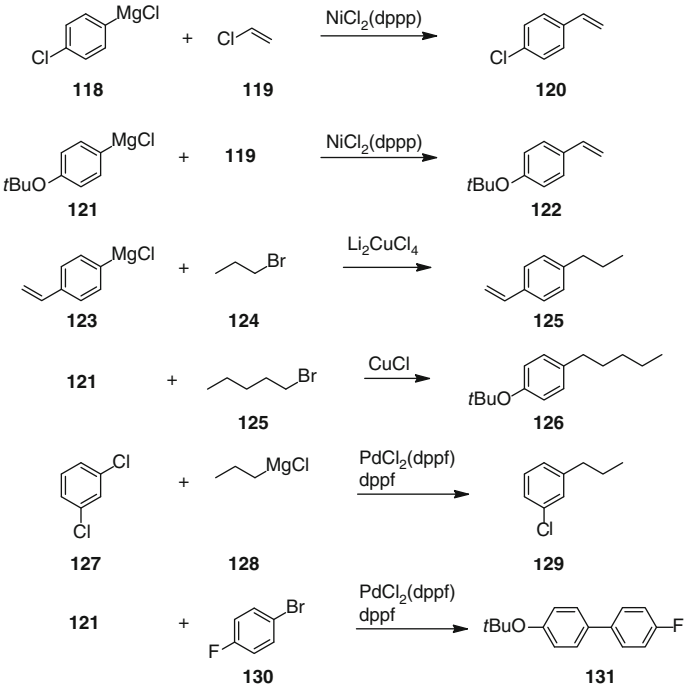
Coupling reactions between alkyl Grignards and aryl halides are usually successful using nickel-phosphine catalysts; however, if the aromatic halide has an alkoxy substituent this does not work very well and it is better to couple an aromatic Grignard with an alkyl halide as shown above.

The selective mono-alkylation of dichlorobenzene with an alkyl Grignard reagent may be problematic. However, the same authors found that using a catalyst made in situ from $PdCl_2$ and 2–3 eq. of bis-diphenylphosphinylferrocene (dppf) allowed the selective coupling between 1,3-dichlorobenzene and *n*-propylmagnesiumchloride. The company also produces non-symmetrical biaryl compounds, such as 4-*t*-butoxy-4′-fluoro-1,1′-biphenyl that are precursors for liquid crystals and for pharmaceuticals. In these reactions they use $PdCl_2$(dppp) as catalyst.

Zambon uses the palladium-catalysed Kumada coupling for the production of Diflunisal (**135**), a non-steroidal anti-inflammatory drug (Scheme 30) [86, 87].

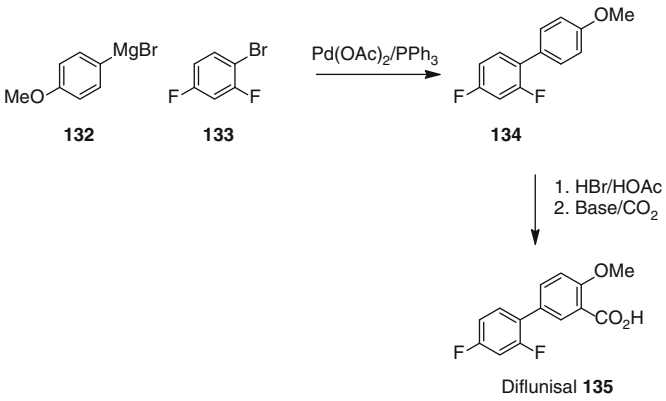


Scheme 28 The Kumada–Corriu reaction

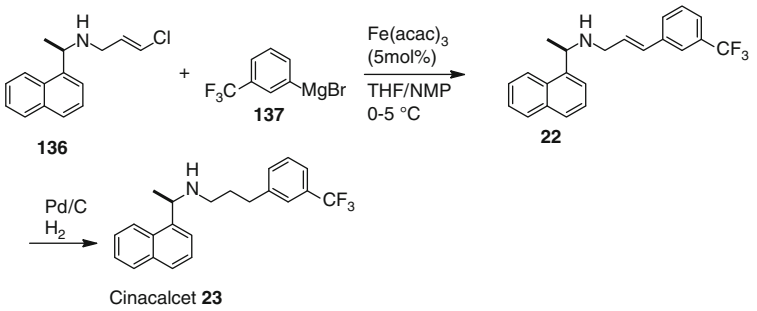


Scheme 29 The Kumada–Corriu reaction in the production of fine chemical intermediates

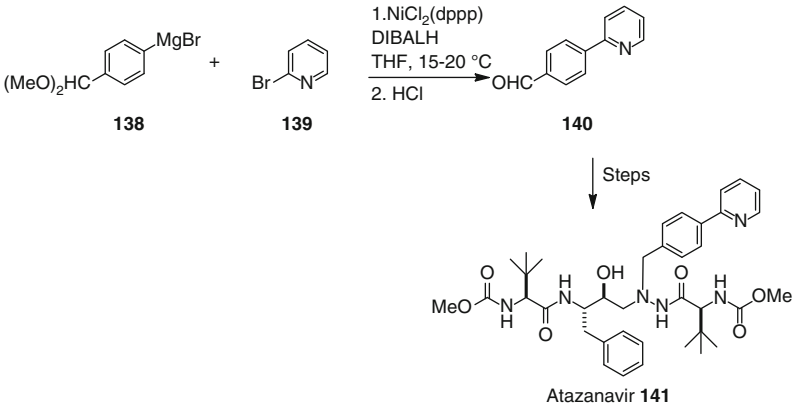
One of the key issues during process development was the prevention of the formation of homo-coupling products. In extensive research, they found that homo-coupling of the Grignard reagent **132** could be avoided by using ultra pure magnesium. Commercial magnesium samples may contain varying amounts of Cu, Fe, Ni and Mn, all of which are potential cross-coupling catalysts that can lead to the formation of homo-coupling products during the formation of the Grignard reagent. Slow addition of the Grignard reagent **132** to a solution of **133** and Pd-catalyst is necessary to avoid homo coupling of the aryl bromide **133**, which is caused by uncatalysed transmetallation between **132** and **133**. Thus, keeping the concentration of **132** as low as possible prevents this side reaction. Eventually, a procedure was developed which gave a yield of 96% of the desired product with less than 1% of homo coupling. The catalyst turnover was 3,000. A competitive route via a direct Suzuki coupling was also investigated but found less economic.



Scheme 30 Use of the Kumada–Corriu reaction in the production of Diflunisal



Scheme 31 Use of the Kumada–Corriu reaction in the synthesis of Cinacalcet



Scheme 32 Use of the Kumada–Corriu reaction in the synthesis of Atazanavir

Ranbaxy has a patent application on the production of Cinacalcet hydrochloride **23** in which the Kumada–Corriu reaction is used. They use 5 mol% of $Fe(acac)_3$ as catalyst in the reaction between vinyl chloride **136** and Grignard reagent **137**, and the coupling product was isolated in 70% yield (Scheme 31) [88].

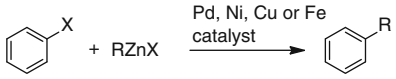
Atazanavir **141** is a HIV-1 protease inhibitor that is used as a treatment for AIDS. It is a typical peptide mimetic that contains an unusual hydrazine compound with a pyridyl-phenyl side chain [89]. An intermediate for this side chain is 4-pyrid-2-yl-benzaldehyde **140**, which was made via a nickel-catalysed Kumada reaction (Scheme 32). DIBALH is added to the reaction to reduce Ni(II) to Ni(0). Only 0.6 mol% of catalyst was needed and the product was isolated in 90% yield.

5 The Negishi Reaction

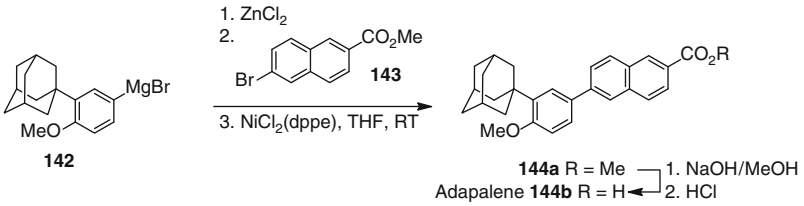
In the Negishi reaction RZnX is coupled to an aryl or alkenyl halide or pseudohalide (Scheme 33) [90, 91]. The R usually is aryl or alkyl; X is Cl, Br or more rarely I. Catalysts are palladium-, nickel-, copper- or iron-based. The Negishi reaction has a position in between the Kumada–Corriu and the Suzuki reaction. The zinc reagent is less reactive than a Grignard, yet more reactive than the boronic acid derivatives. Thus the application scope is somewhat smaller than the Suzuki reaction. In synthesis, the Negishi coupling is well liked in view of the good reactivity of the zinc reagent leading to high yields. However, in large-scale production there is the issue of the zinc waste. The presence of zinc in waste water is highly restricted. Thus, at the end of the reaction the zinc salts need to be precipitated and isolated. Returning the zinc salts to companies that produce zinc products may not be that easy in view of the possible chemical contamination of the zinc waste. Consequently few large-scale applications of the Negishi reaction are known.

Adapalene is a synthetic retinoid that was developed by Galderma for the treatment of acne, psoriasis and photoageing [92]. In its synthesis, the Grignard reagent **142** is reacted with $ZnCl_2$ and coupled with bromide **143** catalysed by $NiCl_2$(dppe) (Scheme 34). The product **144a** was isolated in 78% yield.

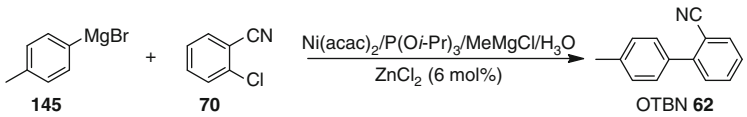
Catalytica Pharmaceuticals (now DSM Pharma Chemicals) developed a mitigating solution for the zinc waste. They found that it was possible to use a catalytic amount of $ZnCl_2$ in the Negishi coupling instead of a full equivalent [93]. In their production of OTBN **62**, the Sartan intermediate (see Schemes 14 and 15), they coupled the *p*-tolyl-Grignard **145** with *o*-chlorobenzonitrile **70** using 6 mol% of $ZnCl_2$ and 6 mol% of a nickel catalysts that was made by treating $Ni(acac)_2$ with 1 eq. of water, 2.1 eq. of tris-*iso*-propylphoshite and 2 eq. of MeMgCl (to reduce Ni (II) to Ni(0)) (Scheme 35). Note that both the metal and the ligand are low cost. They obtained **62** in 82% yield. A total of 70 tons of **62** was produced in this fashion.



Scheme 33 The Negishi reaction



Scheme 34 Use of the Negishi reaction in the production of Adapalene

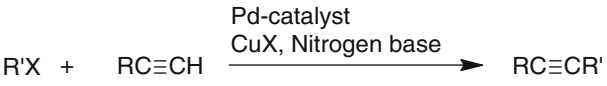


Scheme 35 Double metal catalysis in the production of the Sartan intermediate OTBN

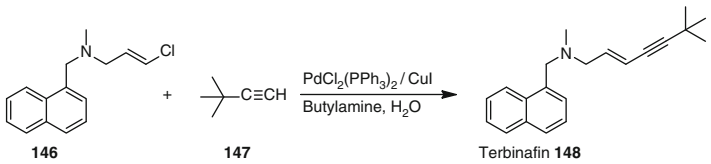
6 The Sonogashira Reaction

In the Sonogashira reaction, a terminal alkyne is coupled to an aryl or alkenyl halide or pseudohalide (Scheme 36) [94–96]. In the classical variant, the reaction is catalysed by a mixture of a palladium catalyst, a copper salt and an amine, usually a secondary amine although primary amines and even triethylamine have also been used. It is presumed that the role of the amine is twofold: it deprotonates the alkyne which is then metallated by the copper salt and it also reduces Pd(II) to Pd(0). This is important for high selectivity as Pd(II) is a good catalyst for the homocoupling of the alkyne, the Glaser reaction. In the mean time, new variants have been developed that are based on the use of copper or palladium only. Variants with nickel, iron or gold catalysts are also known. The Sonogashira reaction is used quite frequently. It tends to be a high-yielding reaction. The product can be selectively hydrogenated to a *cis*-alkene. Recently, we also notice the application of the Sonogashira reaction in the conversion of *ortho*-haloanilines to indoles (*vide infra*) and of *ortho*-halophenols to benzofurans [97, 98].

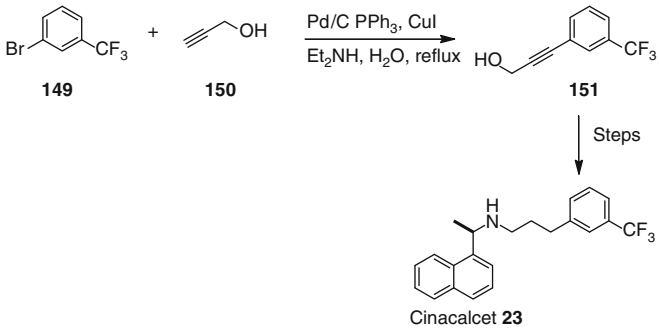
Probably the first industrial application of the Sonogashira reaction was in the production of Terbinafin **148**, an anti-fungal agent developed by Sandoz (now Novartis) [99]. This was the cornerstone of a second generation process that consisted of less steps and was both more environmentally friendly and more economic than the first generation process. The new process was invented by chemists from Banyu Pharmaceutical and licensed by Sandoz [100]. Further



Scheme 36 The Sonogashira reaction



Scheme 37 Sonogashira reaction in the production of Terbinafin

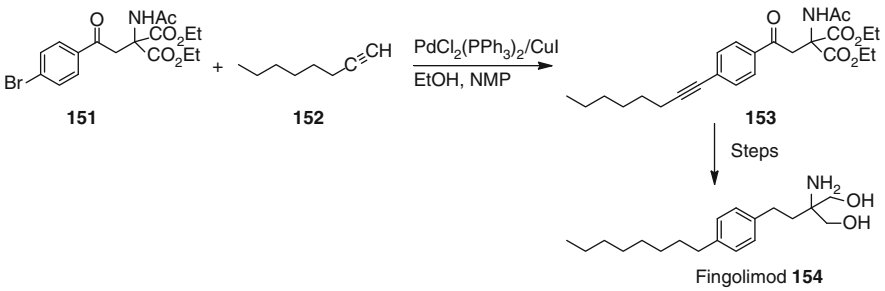


Scheme 38 Sonogashira approach towards Cinacalcet

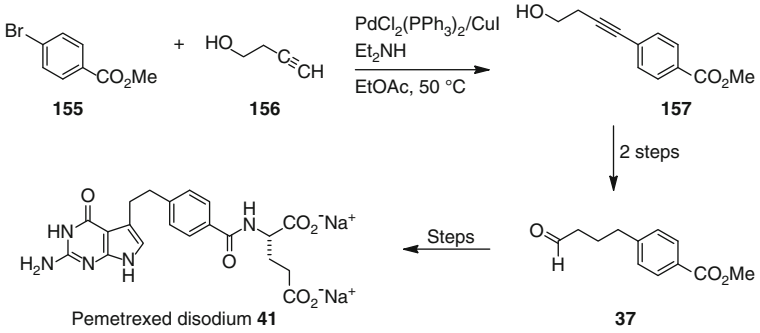
development was done by the Sandoz chemists, eventually leading to a much improved process in which the catalyst loading was substantially reduced. The reaction between vinyl chloride **146** and *tert*-butylacetylene **147** was catalysed by a mixture of $PdCl_2(PPh_3)_2$, CuI and butylamine (Scheme 37). Less than 0.05 mol% of palladium was necessary for this reaction. In addition, no double bond isomers were formed, which was a major problem in the previous process.

Cinacalcet, for which we have seen approaches based on the Heck (Scheme 7) and the Kumada–Corriu reaction (Scheme 31), can also be produced using the Sonogashira reaction as was patented by Medichem [101] and by Dipharma Francis S.r.l. [102]. The two reactions are rather comparable; Medichem uses Pd/C whereas Dipharma uses $PdCl_2$. In Scheme 38 the Medichem method is displayed where aryl bromide **149** is reacted with propargylic alcohol **150**, to give **151**. This intermediate is hydrogenated to the alkyl alcohol which is oxidised using TEMPO; the resulting aldehyde is reductively coupled to the naphthyl-ethylamine to give Cinacalcet **23**.

Fingolimod hydrochloride, the design of which was based on the fungal secondary metabolite myriocin, is a potent immunosuppressant that was approved as a new



Scheme 39 Use of the Sonogashira reaction for the synthesis of the immunosuppressant Fingolimod hydrochloride

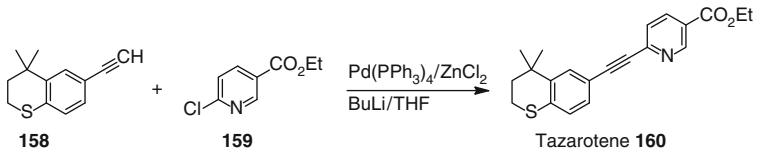


Scheme 40 Use of the Sonogashira reaction in the preparation of Pemetrexed disodium

treatment for multiple sclerosis [103]. Originator was the group of Fujita at Kyoto University [104]. Numerous syntheses have been published [103]. Worldwide rights (except for Japan) were acquired by Novartis. They patented the use of the Sonogashira reaction for the attachment of the side chain, followed by hydrogenation (Scheme 39) [105]. In view of the shortness of this route its use in production seems likely. They used a mixture of $PdCl_2(PPh_3)_2$ and CuI as catalyst and NaOEt, which was also used as base in the preceding step. They also describe a continuous version which was executed in a micro reactor at high temperature.

Fürstner and co-workers reported an iron-catalysed Kumada–Corriu reaction for the direct attachment of the octyl side chain [106].

In the original synthesis of Pemetrexed **41** which was developed by Taylor at Princeton University (*vide infra*), a Sonogashira coupling was used to couple the other half of the molecule directly on the iodo-pyrrolopyrimidine [41]. However, since this latter intermediate was hard to make a different synthesis was developed by Lilly (see also Scheme 10) for which a C-4 fragment needed to be coupled to methyl 4-bromobenzoate. In Scheme 10 we have seen the use of the Heck reaction on but-3-ene-1-ol for this coupling, but in fact the Sonogashira reaction on but-3-yn-1-ol has also been described by Lilly (Scheme 40) [107]. It is a classical variant that uses



Scheme 41 Sonogashira reaction as the final step in the production of Tazarotene

0.6 mol% of $PdCl_2$, 1.2 mol% PPh_3 and 0.6 mol% of CuI with Et_2NH as base. The product **157** was isolated in 83% yield. The disadvantage of this route is that the alkyne needs to be hydrogenated and the alcohol oxidised to aldehyde **37**, whereas the Heck variant yields **37** directly. Nevertheless, the reaction was performed at 50 kg scale and thus possibly scaled up further.

Tazarotene is a member of a new generation of receptor-selective, synthetic retinoids, which is topically effective in the treatment of acne, psoriasis and photoageing. It was developed by Allergan. The final step of its synthesis is a Sonogashira coupling using $Pd(PPh_3)_4$ and $ZnCl_2$. BuLi was used as base (Scheme 41) [108]. This is clearly a medicinal chemistry route and no information is available on the large-scale production.

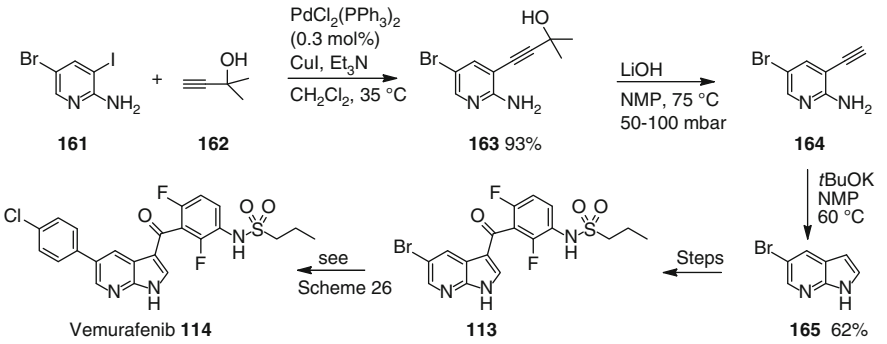
Other Sonogashira-based approaches towards Tazarotene have also been reported, but it is unclear if these have been implemented [109]. In the original Allergan route the acetylenic moiety in **158** is made from an acetyl group which is converted into the *gem*-dichloride using PCl_3, followed by double dehydrohalogenation using *t*BuOK. Later routes use a Sonogashira reaction on the bromide with TMS-acetylene or with the addition product of acetylene and acetone [83]. Acetylene is not easy to handle and needs special equipment. Hence, its use is avoided by most fine chemical and pharmaceutical companies who use substitutes like the two described.

In the synthesis of Vemurafenib (Scheme 26) the 5-bromo-7-azaindole part of **113** is made by a Sonogashira reaction (Scheme 42) [73]. Thus, reaction between pyridine **161** and 2-methyl-but-3-yne-2-ol **162** catalysed by $PdCl_2(PPh_3)_2$, CuI and Et_3N yielded the protected pyridine–acetylene **163** in 93% yield. This was deprotected under basic conditions to yield **164**, which was cyclised to **165** using *t*BuOK in NMP for an overall 62% yield.

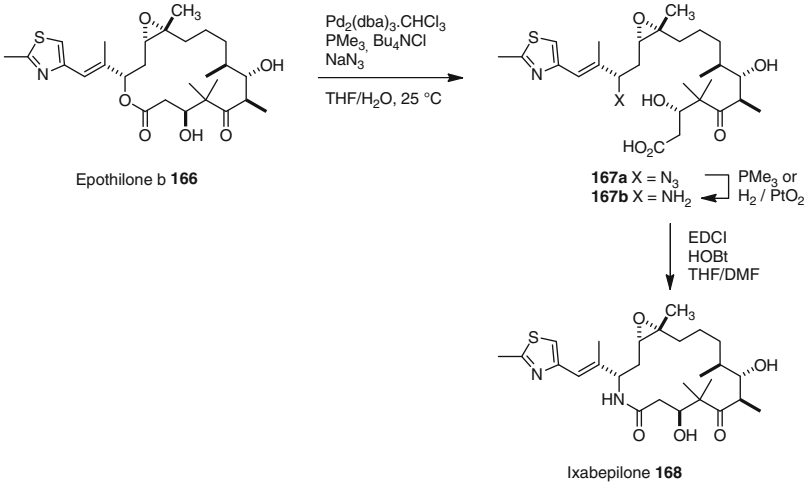
7 Miscellaneous Palladium-Catalysed Coupling Reactions

Metal-catalysed allylic substitution reactions have not been used extensively in the production of pharmaceuticals or otherwise; I am aware of only one example that is used in full-scale production.

A family of macrocyclic compounds known as epothilones exhibited strong in vitro cytotoxic activity. Unfortunately this activity was not sustained in vivo, due to inactivation of the molecule by esterase activity which cleaves the lactone.

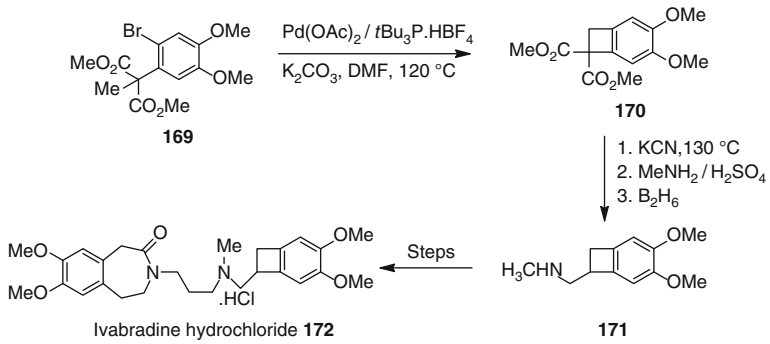


Scheme 42 Sonogashira in the preparation of 5-bromo-7-azaindole, an intermediate towards Vemurafenib



Scheme 43 Allylic substitution in the preparation of a metabolically stable Epothilone analogue

Thus BMS developed an analogue of epothilone b in which the ester bond was replaced by an amide bond. The BMS researchers recognised that the lactone functionality in the epothilones is an allylic ester, enabling a palladium-catalysed substitution reaction [110]. In the event, epothilone b **166** was reacted with sodium azide catalysed by either $Pd(PPh_3)_4$ or a catalyst made in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ and PMe_3 in the presence of a phase transfer catalyst (Scheme 43) [111]. If PMe_3 was used in excess, the azide functionality in **167a** was reduced in situ to the amine **167b**, which was isolated in 96% yield. Ring closure to Ixabepilone **168** was effected using water-soluble diimide (EDCI) and hydroxybenoztriazole (HOBt) in 93% yield. Compound **168** is marketed as a treatment for breast cancer.



Scheme 44 CH-activation in the synthesis of an intermediate for Ivabradine

Ivabradine hydrochloride is marketed by Servier as treatment for Angina pectoris in patients who have an intolerance for beta-blockers. The drug contains an interesting benzocyclobutane structure that was prepared using a palladium-catalysed cyclisation reaction, which includes a CH-activation (Scheme 44) [112]. The methodology had been developed earlier by Baudoin and co-workers [113].

8 Conclusions

Since our previous reviews of this area, about 10 years ago [7, 114, 115], there has been a tremendous increase of the use of palladium-catalysed substitution reactions in the production of fine chemicals and pharmaceuticals. Most of these are Heck and Suzuki reactions. Catalyst development is still ongoing with a shift towards the cheaper metals such as nickel, copper and iron. Much process development work is aimed at reducing the catalyst cost by achieving higher turnover numbers. Particularly if the metal-catalysed reaction is used as the last step, the metal has to be removed down to below 10 ppm. Particularly if ligands are used this can be problematic. Ligand-free palladium catalysts form palladium black at the end of the reaction, which is easily removed. In this case the amount of residual palladium is usually much lower. Although at development scale scavenger resins are used for the removal of metal, this may well be too expensive at large scale. It also pays to investigate what form the palladium is in. Allgeier and co-workers recently pinpointed formation of a palladacycles with a ligand as a major cause of residual palladium [116]. This finding may well extend to the formation of palladacycles with starting materials or products.

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Applications of Rhodium-Catalyzed Hydroformylation in the Pharmaceutical, Agrochemical, and Fragrance Industries

Gregory T. Whiteker and Christopher J. Cobley

Abstract This review summarizes the known commercial applications of rhodium-catalyzed olefin hydroformylation to fine chemical synthesis. Two manufacturing processes for Vitamin A utilize hydroformylation. Additional, recent examples of hydroformylation on multikilogram scale for synthesis of pharmaceutical building blocks have also been reported. Hydroformylation appears to be widely used in the fragrance industry, where aldehydes are ubiquitous. Numerous fragrance ingredients are commercially prepared by hydroformylation. There are no reports of agrochemical manufacturing processes which employ hydroformylation. In addition to commercial applications, examples of pharmaceutical, fragrance, and agrochemical products which have been prepared on small scale using hydroformylation are given. Hydroformylation appears to be well suited to fine chemical synthesis, and applications should increase as process chemists become more aware of its potential.

Keywords Carbonylation · Hydroformylation · Rhodium · Syngas

Contents

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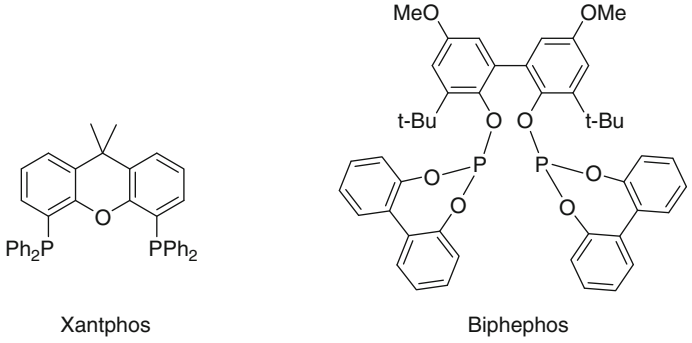
1 Introduction

Rhodium-catalyzed olefin hydroformylation is widely used for the manufacture of a variety of commodity chemicals [1]. Propylene and butene hydroformylation leads to so-called Oxo alcohols which are transformed into industrially important solvents and coating materials. Higher olefins are converted via hydroformylation into plasticizer and detergent alcohols, and hydroformylation of allyl alcohol is an important route to 1,4-butanediol and its derivatives. Despite its widespread use in the manufacture of cheap, commodity chemicals, commercial applications of rhodium-catalyzed hydroformylation in the pharmaceutical and fine chemical industries are rare. At first glance, one would expect quite the opposite; it should be more practical to use expensive rhodium catalysts to produce complex targets with higher profit margins. However, separation of the aldehyde product from the expensive Rh catalyst has historically presented a challenge, and, as a result, most commercial applications involve hydroformylation of lower olefins where the aldehyde product can be separated by distillation. A variety of separation schemes have been developed, e.g., biphasic systems, immobilized catalysts, etc., which should facilitate the application of Rh-catalyzed hydroformylation to more complex, nonvolatile products. Unfortunately, hydroformylation is not in the typical synthetic organic chemist's repertoire and is underutilized as a route to aldehyde intermediates by process chemists outside of the commodity chemicals industry. Realistically, for more complex targets, any synthetic method must compete with a variety of other synthetic disconnections on factors such as cost, complexity, and waste treatment. A significant advantage of hydroformylation is perfect atom economy, and ligands developed within the past 20 years offer excellent regioselectivity [2–4], chemoselectivity, and functional group tolerance. For example, xantphos and biphephos ligands lead to high selectivity for linear aldehydes from terminal alkenes (Fig. 1). Both of these ligands are now commercially available for screening purposes and are commonly used in fine chemical applications.

This review attempts to highlight the application of rhodium-catalyzed hydroformylation in the manufacture of pharmaceuticals, agrochemicals, and fragrances.



Xantphos Biphephos

Fig. 1 The most commonly used ligands for highly linear regioselective hydroformylation

A thorough review of the scientific and patent literature was performed to identify examples of hydroformylation of complex substrates which might form the basis of commercial processes. Since industrial companies typically do not disclose their actual manufacturing process, some speculation is necessary. Often the scale of the reactions is indicative of the level of commercial interest in a given hydroformylation reaction. Additionally, reports of the use of hydroformylation in an alternative synthesis of a launched pharmaceutical or agrochemical are also suggestive of potential commercial interest.

2 Pharmaceuticals

Two manufacturing routes for Vitamin A utilize rhodium-catalyzed hydroformylation for the synthesis of an aldehyde intermediate (Fig. 2) [5]. The process developed at BASF involves hydroformylation of 1,2-diacetoxy-3-butene (Fig. 2, **1a**) to give the branched aldehyde (Fig. 2, **2a**) [6]. Elimination of acetic acid gives the α,β-unsaturated aldehyde (Fig. 2, **3a**) which leads to Vitamin A acetate by Wittig reaction. An analogous process was developed by Roche starting from 1,4-diacetoxy-2-butene (Fig. 2, **1b**). Hydroformylation gives aldehyde **2b**, which eliminates acetic acid to give **3b** which is then isomerized to **3a**.

The only other application of hydroformylation applied to the synthesis of a pharmaceutical intermediate on a commercial scale has recently been reported. The synthesis of (*S*)-allysine ethylene acetal, an intermediate in the manufacture of angiotensin I-converting enzyme (ACE) and neutral endopeptidase (NEP) inhibitors, was reported by researchers at Dr. Reddy's and Chirotech using a combination of

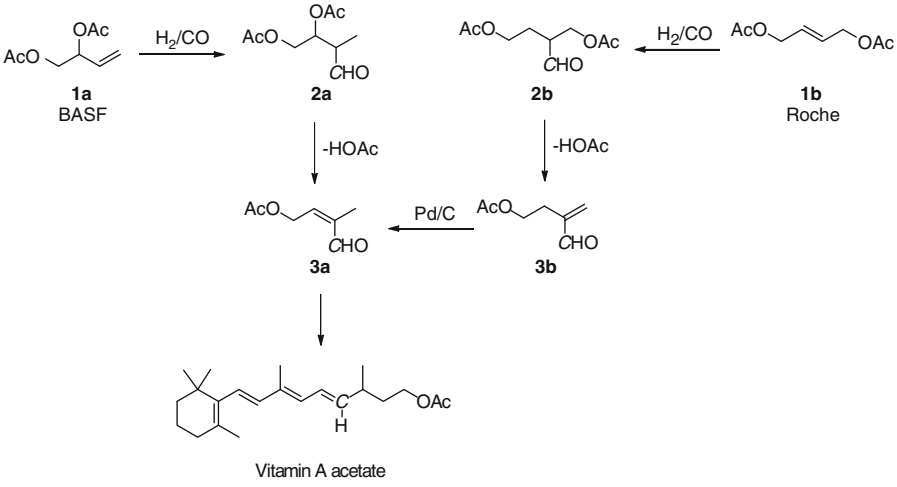


Fig. 2 BASF and Roche processes for manufacture of vitamin A using rhodium-catalyzed hydroformylation. Carbon atom derived from carbon monoxide is highlighted in *bold*

hydroformylation and enzymatic catalysis (Fig. 3) [7]. Crotonaldehyde ethylene acetal (Figs. 3 and 4) was hydroformylated to the linear aldehyde (Figs. 3 and 5) using the Rh-biphephos catalyst. Tandem isomerization/hydroformylation of **4** was performed with a 4,000:1 molar substrate/catalyst ratio at 80°C under 3 bar of 1:1 H_2/CO. The desired regioisomer was formed with a linear/branched ratio of 15:1.

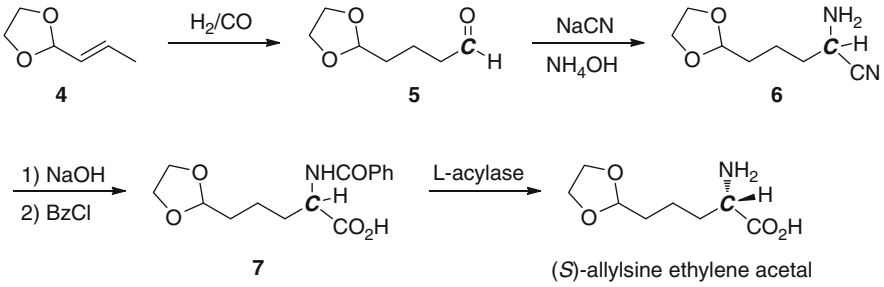


Fig. 3 Synthesis of (*S*)-allysine ethylene acetal by rhodium-catalyzed asymmetric hydroformylation

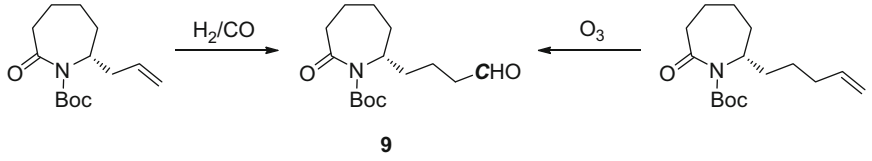


Fig. 4 Comparison emphasizing the synthetic equivalence of linear-selective hydroformylation and ozonolysis

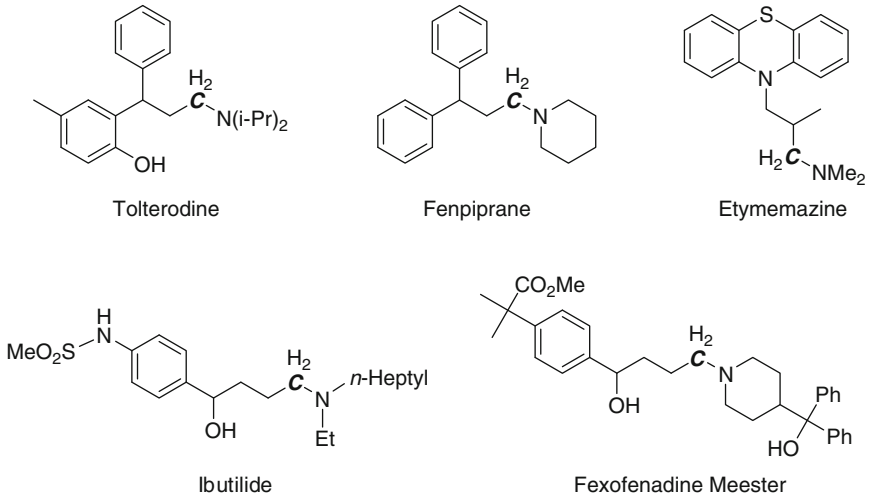
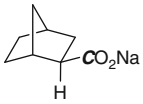


Fig. 5 Examples of pharmaceutical targets which have been prepared by hydroformylation-reductive amination

The regioisomeric mixture of aldehydes was isolated by organic-aqueous extraction. The aldehyde was extracted into the aqueous phase, which allowed separation of the catalyst and ligand into the organic phase. The hydroformylation reaction was performed in multiple batches using a 300-L pressure reactor. Aldehyde **5** was converted via Strecker reaction in a 10,000-L reactor to produce multiton quantities of **6**. Aminonitrile (**6**) was hydrolyzed and then benzoylated to give racemic **7** which was converted to (*S*)-allysine ethylene acetal by enzymatic resolution. The enzyme selectively hydrolyzed only the (*S*)-enantiomer of the linear product, facilitating easy separation from both the undesired enantiomer and branched regioisomer.

Workers at Pfizer have recently described hydroformylation on kilo-lab scale to prepare a pharmaceutical building block [8]. Hydroformylation of norbornylene (8.0 kg) using 0.15 mol% $Rh(CO)_2(acac)$ with dppf (1,1'-bis (diphenylphosphino)ferrocene) (45 psi H_2/CO, 35°C, *t*-BuOH) gave exclusively the *exo*-aldehyde. Oxidation with $NaClO_2$ and TEMPO (2 mol%) was performed directly on the *t*-BuOH solution from the hydroformylation reaction to give 2-*exo*-norbornyl carboxylic acid which was isolated as the sodium salt, **8**, in 80% overall yield.



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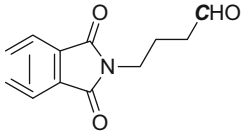
Several pharmaceutically relevant examples are found in the patent literature where hydroformylation reactions are performed on significant scale (>100 g substrate). For example, researchers at Pharmacia (now Pfizer) reported the hydroformylation of *N*-Boc-(*S*)-7-allylcaprolactam on 250-g scale using Rh-biphephos to give aldehyde **9** (Fig. 4) with 96% linear selectivity [9]. Ozonolysis of the 7-pentenylcaprolactam derivative was used for smaller scale preparation of **9**. Hydroformylation is a safer process equivalent to ozonolysis which is more amenable to scale-up.

Hydroformylation of *N*-allyl phthalimide on 200-g scale was described in a recent patent by Dow [10]. Using the Rh-biphephos catalyst, the desired linear aldehyde (**10**) was produced in 11.5:1 linear/branched ratio. Acetal protection of the aldehyde and cleavage of the phthalimide gave the protected amino aldehyde (**11**), useful as a pharmaceutical intermediate.



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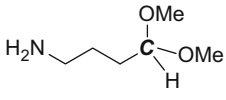
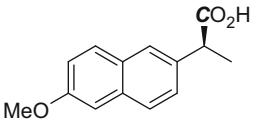


11

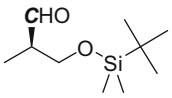
Vinyl arenes are the most studied substrates for application of asymmetric hydroformylation to pharmaceutical synthesis. The resulting, branched aldehyde regioisomers can be oxidized to α-aryl propionic acids, which constitute a class of nonsteroidal anti-inflammatory drugs (NSAIDs). Of these, (*S*)-Naproxen, is sold as a single enantiomer. A rhodium-catalyzed hydroformylation route to racemic Naproxen was first reported by Brown using sugar-derived phosphines [11]. In the late 1980s, Parrinello and Stille reported the first asymmetric hydroformylation synthesis of (*S*)-Naproxen using a Pt-bisphosphine catalyst [12]. Significant work was done subsequently in both academic and industrial labs



(*S*)-Naproxen

which led to efficient asymmetric hydroformylation catalysts with both high enantioselectivity and regioselectivity for vinyl arene hydroformylation. However, the efficient process economics of the resolution used in the manufacture of (*S*)-Naproxen, combined with the relatively high cost of the olefinic substrate, makes asymmetric hydroformylation economically unviable as a route to this particular drug [13]. During the 1990s, it was anticipated that many racemic drugs might become marketed as single enantiomers through a "chiral switch" strategy. However, this approach has had limited success with NSAIDs [14]. Despite the lack of commercial interest in hydroformylation of these substrates, styrene continues to be a useful olefinic substrate for benchmarking the relative selectivity of new catalysts.

Allylic alcohols are versatile substrates for hydroformylation. Hydroformylation of allyl alcohol typically favors the linear regioisomer, and this reaction formed the basis of a route to manufacture 1,4-butanediol [15]. Landis recently reported the use of a chiral diazaphospholane for the asymmetric hydroformylation of allyl silyl ethers [16]. The TBDMS allyl ether, formed from reaction of allyl alcohol with TBDMSCl, was hydroformylated in 96%*ee* and 2:1 branched/linear to give the Roche aldehyde (**12**) which is a widely used chiral building block. High molar substrate/catalyst ratios (10,000:1) and low syngas pressures (15 psi) make this reaction potentially attractive for commercial development.



12

Highly selective asymmetric hydroformylation of vinyl acetate has been reported on 150-g scale by Landis and Klosin [17]. Reactions were performed in neat vinyl acetate using a chiral Rh-diazaphospholane catalyst at 100,000:1 molar

substrate/catalyst ratio to produce 2-(acetoxy)propanal in 96.8%*ee* and 139:1 branched/linear. The branched aldehyde was converted to chiral isoxazolines and imidazoles through its hydroximoyl chloride derivative.

Reductive amination of aldehydes prepared from hydroformylation is a useful route to amines. Botteghi, et al. reported the synthesis of racemic Tolterodine by sequential hydroformylation-reductive amination [18]. Hydroaminomethylation (tandem hydroformylation/reductive amination) has recently been used to prepare a wide variety of pharmaceutical compounds [19]. Representative examples are shown in Fig. 5. Hydroaminomethylation of 1,1-diarylethenes leads to 1-(3, 3-diarylpropyl)amines, such as fenpiprane [20, 21]. Heterocyclic allylic amines undergo hydroaminomethylation to form pharmaceutically active diamines, such as etymemazine [22]. Ibutilide and fexofenadine have been prepared by hydroaminomethylation of 1-arylallyl alcohols in the presence of the requisite amines [23, 24]. Although none of these reactions has been developed into a commercial process, the widespread utility of the hydroaminomethylation reaction makes it likely that it will be used commercially

There are numerous reports of hydroformylation reactions where an amine substituent in the substrate condenses with the aldehyde product to form a heterocyclic ring (Fig. 6). Intramolecular hydroaminomethylation reactions are often referred to as cyclohydrocarbonylation reactions. A Cbz-protected homoallylic amine underwent cyclohydrocarbonylation with Rh-biphephos to form the natural product, (±)-coniine (Fig. 6, **13**) [25]. Alper recently reported the formation the seven-membered ring of 2-benzazepines (Fig. 6, **14**) by hydroformylation of 2-isopropenylbenzaldehydes in the presence of anilines [26]. Intramolecular hydroaminomethylation of 2-isopropenylanilines produces 1,2,3,4-tetrahydroquinolines (Fig. 6, **15**) [27]. In some instances, the enamine derived from intramolecular condensation of the resulting aldehyde is desired. For example, the synthesis of a key intermediate (Fig. 6, **16**) in the synthesis of a series of ACE inhibitors was

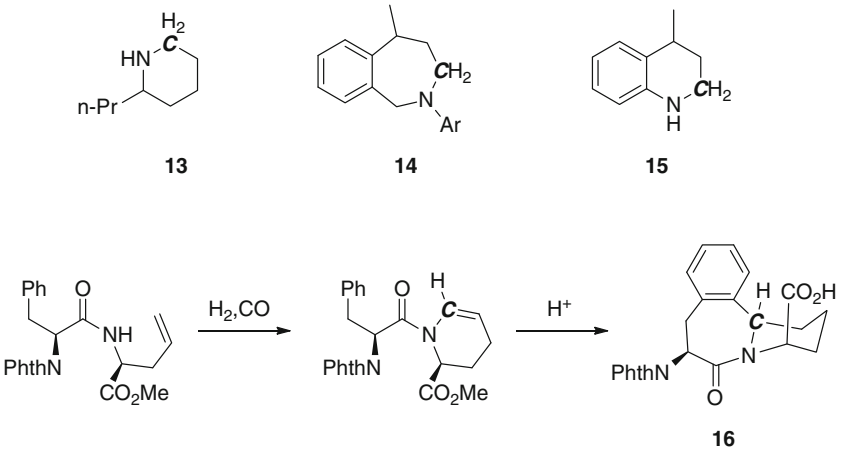


Fig. 6 Compounds made using intramolecular hydroaminomethylation (cyclohydrocarbonylation)

accomplished by hydroformylation of a protected allylglycine derivative followed by intramolecular condensation [28]. Treatment of the enamine with acid resulted in cyclization to form **16**.

3 Fragrances

Hydroformylation is practiced in the fragrance industry where aldehydes are extensively utilized in perfumery (Fig. 7) [29]. 1-Decene is hydroformylated to a mixture of linear and branched undecanals. Condensation of the resulting C_{11} linear aldehyde with formaldehyde gives 2-methyleneundecanal which is hydrogenated to 2-methylundecanal. The branched isomer from 1-decene hydroformylation, 1-methyldecanal, is also used in perfumery. Vertral® is produced by hydroformylation of *exo*-dicyclopentadiene with Rh_2(2-Et-hexanoate)$_4$ to give the *exo*-monoaldehyde, followed by hydrogenation of the remaining olefinic bond [30]. Vertral has a green melon odor which is used in personal care products. Similarly, hydroformylation of neat 1,3-propenylbenzene with Rh-PPh_3 to give the monoaldehyde, followed by hydrogenation of the remaining C=C bond, is used for the preparation of Florhydral® [31]. Attempts to prepare enantiomerically pure Florhydral using asymmetric hydroformylation have led to low enantioselectivities [32]. In this case, asymmetric hydrogenation is a far more enantioselective (97%*ee*) route [33].

Conversion of terpenes to aldehyde derivatives by hydroformylation has been studied extensively. Hydroformylation of limonene is practiced commercially by Celanese [34]. Limonene aldehyde has a citrus odor and is used in soaps and lotions. Spirambrene® is manufactured by Givaudan and Vigon by hydroformylation of 2-carene [35, 36]. Tollens reaction of the resulting aldehyde gives a diol which is converted to the acetal with acetone. Spirambrene has a woody, spicy odor and is a component of perfumes.

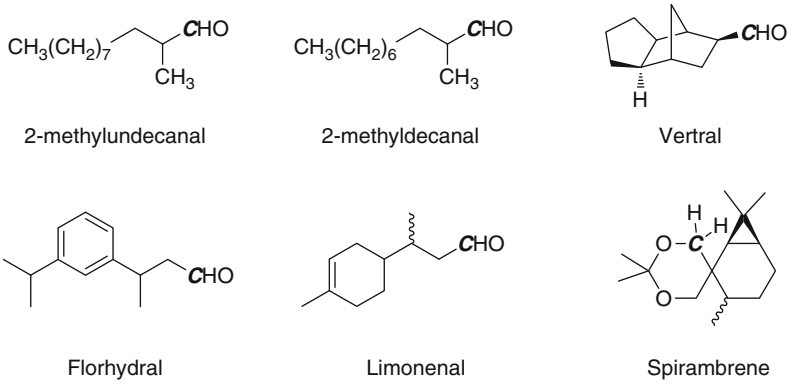


Fig. 7 Fragrances which are prepared commercially by rhodium-catalyzed hydroformylation

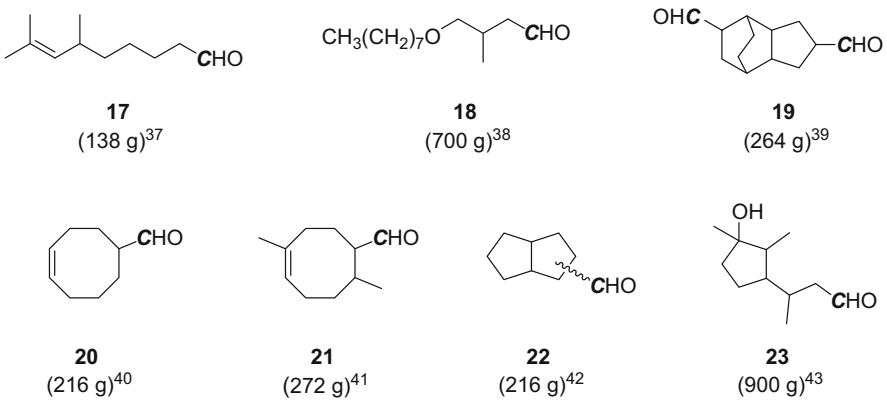


Fig. 8 Recent applications of Rh-catalyzed hydroformylation in the fragrance industry. Mass of starting olefin is given in *parentheses*

Several additional hydroformylation applications from the fragrance industry have appeared recently in the patent literature. Examples which have been demonstrated on significant scale (>100 g) are depicted in Fig. 8 [37–43]. Although there is no evidence these fragrance ingredients are currently manufactured using hydroformylation, given the scale of the reported reactions, it is likely that some of these reactions are of commercial interest.

4 Agrochemicals

Hydroformylation does not appear to have been used in a commercial, agrochemical manufacturing process. Several examples of the use of hydroformylation in alternate synthetic routes to agrochemicals have been reported and are described below (Fig. 9). Hydroformylation of 2-methyl-1-*p*-chlorophenylpropene with Rh-PPh_3 followed by oxidation gave 2-(*p*-chlorophenyl)-3-methylbutanoic acid which is an intermediate in the synthesis of the insecticide Fenvalerate (Fig. 9) [44].

The neonicotinoid insecticide, Dinotefuran (Fig. 9), developed by Mitsui has been prepared by hydroformylation of a symmetrical 1,3-dioxepin to give 3-(hydroxymethyl)tetrahydrofuran after deprotection [45]. Alternate routes to 3-(hydroxymethyl)tetrahydrofuran via hydroformylation of 2,3-dihydrofuran or 2,5-dihydrofuran have also been reported [46].

The insecticidal sulfoximine **24** (Fig. 9) was prepared by hydroformylation of 3-methylenetetrahydrothiophene with Rh-xantphos to give the linear aldehyde as a single regioisomer [47]. Conversion of the aldehyde to an enamine, followed by cyclization to form the pyridine ring and subsequent oxidation at sulfur, gave **24**.

Two reports of the use of asymmetric hydroformylation of aryl vinyl ethers to prepare enantiomerically enriched 2,4-DCPPA herbicide (Fig. 9) have appeared [48, 49]. Using Rh-(*S*,*R*)-Binaphos, the chiral aldehyde is produced in 72%*ee* but

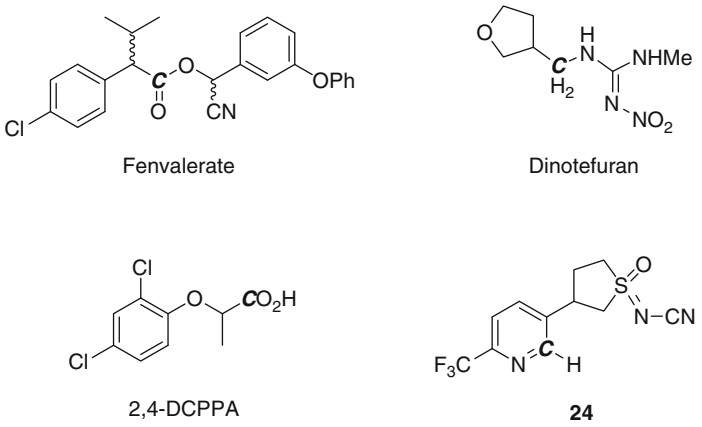


Fig. 9 Agrochemicals which have been prepared by rhodium-catalyzed hydroformylation

only 2:1 branched/linear. Although none of these reactions appear to be practiced commercially, they are significant applications of hydroformylation for the synthesis of important agrochemicals.

5 Conclusions

Fine chemical applications of rhodium-catalyzed hydroformylation have steadily increased over the past 20 years. Use of this chemistry in the fragrance industry appears to be relatively common. Pharmaceutical applications have started to increase as the technology becomes more familiar to process chemists. The commercial availability of ligands for both linear-selective hydroformylation and asymmetric hydroformylation has removed a barrier for screening catalysts by synthetic chemists. As additional large-scale examples of rhodium-catalyzed hydroformylation continue to be published, we expect this technology to be applied even more widely to fine chemical synthesis.

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Ruthenium-Catalyzed Selective Hydrogenation for Flavor and Fragrance Applications

Philippe Dupau

Abstract Due to the widespread use of unsaturated alcohols as final ingredients or synthetic intermediates in the flavor and fragrance industry, there is a very high demand for safe, productive and environmentally friendly methods to access olefins with high regio and stereocontrol in addition to efficient chemoselective reduction processes of carbonyl groups in the presence of olefin moieties. These two goals were achieved by developing industrial methodologies that respectively enable regio and stereoselective 1,4-hydrogenation reactions of conjugated dienes in the presence of catalytic amounts of both cationic cyclopentadienyl-type ruthenium(II) complexes and acidic additives along with chemoselective hydrogenations of ketones and aldehydes using chloro ruthenium(II) complexes bearing amino or iminophosphines ligands as precatalysts. In this contribution, we will display few examples of such achiral transformations that could efficiently be performed on up to multi-ton scale enabling Firmenich SA to produce in a sustainable manner some ingredients such as leaf alcohol, Polysantol®, Nirvanol®, Dartanol®, or Pamplewoodol® to be used in flavor and/or fragrance applications.

Keywords Diene · Flavor · Fragrance · Hydrogenation · Ketone · Ruthenium · Selectivity

Contents

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1 Introduction

(*Z*)-olefins, classically obtained using waste generating Wittig-type reagents, were alternatively accessed by a potentially environmentally friendly methodology involving regio- and stereoselective hydrogenation of conjugated dienes in the late 1960s as reported by Frankel [1]. Nevertheless, both the use of toxic chromium(0) carbonyl complexes as catalysts along with some relatively drastic reaction conditions were clear drawbacks for the extensive use of such a transformation. Later, Driessen-Hölscher reported the safer use of catalytic amounts of ruthenium(II) complexes that enabled this type of transformation under milder conditions [2, 3]. Despite those noticeable improvements, regio- and stereoselective hydrogenation of conjugated dienes remained somewhat confidential. As a matter of fact, some relatively moderate reported catalytic activity still appeared as a major obstacle for potential economically viable industrial applications. In addition to this, based on really few reported examples, extensive use of such a reaction was probably prevented by some limited reaction scope. Our initial work at Firmenich SA also using cationic cyclopentadienyl-type ruthenium complexes as catalysts clearly confirmed those limitations. More recently, we demonstrated that both catalytic activity and reaction scope could be impressively improved by running hydrogenation reactions in an appropriate solvent and in the presence of some weak acids as additive. Consequently, this provided us with an efficient and sustainable wide scope industrial methodology [4]. We demonstrated that it is also affording a highly regio- and stereoselective access to both tri- and tetrasubstituted compounds such as allylic alcohols for example, those being obtained through hydrogenation of dienolesters [5]. Such a technology then also clearly displays some noticeable advantage over the classical stereoselective alkyne hydrogenation reaction using Lindlar-type heterogeneous palladium catalysts often use to access 1,2-disubstituted (*Z*)-olefins. As far as chemoselective reduction of both ketones and aldehydes are concerned, historically performed using hydride-type reagents, Noyori discovered in the mid 1990s that it could be efficiently effectuated through homogeneous ruthenium-catalyzed selective hydrogenation reactions [6]. Nevertheless, it is the asymmetric version that received by far the greater attention with some numerous works reported [7–17]. Indeed, the importance of such a discovery was emphasized when the 2001 chemistry Nobel Prize was awarded to Noyori for his impressive contribution to the field of enantioselective hydrogenation including ketone reduction technology [18]. In terms of achiral transformations, due to its very high efficiency (reported TON up to 2,400,000) [19], Noyori's type system also

generated high interest as it could allow replacement of the somewhat unsafe and nonenvironmentally friendly use of hydride-type reagents or hydrogenation processes using toxic chromite type catalysts [20]. Since the use of ruthenium complexes bearing both diphosphine and diamine ligands as precatalysts for such a transformation had already been well developed and often patented [21–23], some Firmenich SA group discovered that those ligands could indeed efficiently be replaced by amino or iminophosphines [24, 25] (those being bidentates and referred as PN ligands or tetradentates and referred as PNNP ligands) subsequently providing us with an efficient and sustainable industrial access to those unsaturated alcohols targets for fragrances applications.

2 Regio- and Stereoselective Hydrogenation of Conjugated Dienes

As reported above, we recently discovered that running ruthenium-catalyzed hydrogenation of a conjugated diene in an appropriate solvent in the presence of some weak acids as additive generally enabled us to noticeably improve both catalytic activity and reaction scope of such regio and stereoselective transformation compared to what had been previously reported. If it could initially be efficiently applied only to some substrates possessing a nearby chelating group such as an alcohol [3], carboxylic acid, or ester [2, 3], the use of some additional carboxylic, phosphinic or phosphonic acids, or even dialkylphosphates clearly led to a much more general method [4, P. Dupau, Oral communication, ICOMC 23, 2008, Rennes (France)]. As a matter of fact, performing the reaction under acidic conditions allowed us to efficiently transform even nonfunctionalized conjugated dienes such as myrcene or ocimene, leaving the remaining nonconjugated olefinic moieties unchanged during the reaction [4]. Following this initial discovery, we then obviously carefully examined the influence of other reaction parameters on both reaction rate and selectivity in order to further improve the results obtained [P. Dupau, Oral communication, ICOMC 23, 2008, Rennes (France)]. Thus, as a consequence of these studies, 1,4-hydrogenation reactions are generally run in the presence of catalytic amounts of both a cationic [(Cp-type)Ru(diene)][Y] complex and weak organic acid additive while heating the substrate in an aprotic polar solvent such as nonaromatic ketones or esters (i.e., acetone or ethyl acetate, for instance) under moderate hydrogen pressure to afford hydrogenated product in high yields and generally high overall selectivity (see Fig. 1).

The regio- and stereochemistry of the desired product arises mainly from formal addition of hydrogen atoms in positions 1 and 4 of the *cisoid* form of the conjugated diene. In addition, it is important to note that no variations in the level of both regio- and stereoselectivity were generally observed during the reaction even at complete conversion. Whereas, as described above, reaction overall selectivity is generally improved running hydrogenation in the presence of weak organic acid additives, no

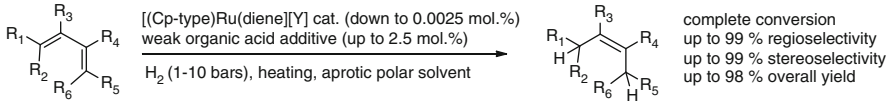


Fig. 1 Regio and stereoselective ruthenium-catalyzed acidic 1,4-hydrogenation reaction

positive impact was observed in the case of strong and/or inorganic acidic compounds. Both the nature and quantity of the weak organic acid used display some influence on regio and more noticeably stereoselectivity. Since no direct relationship between reaction selectivity and additive pK_a can be highlighted, we think that formal protonation reaction of a putative 16 electrons (hydrido)(π-allyl) ruthenium intermediate occurs through initial and reversible coordination of the additive to the ruthenium center before proton delivery to the allylic moiety. Finally, for a given weak organic acid additive, its optimal quantity is clearly dependent on both the nature of the solvent used and the hydrogen reaction pressure. As far as ruthenium catalyst is concerned, a very large number of [(Cp-type)Ru(diene)][Y] complexes tested displayed some similar results regarding both reactivity and selectivity, with nearly no influence in both nature of diene and noncoordinating anion. Concerning the cyclopentadienyl-type ligand, in addition to a noticeable enhancement in the stability of the corresponding complex used, we also observed that highly substituted ones generally afforded the best results.

2.1 Industrial Access to (Z)-hex-3-en-1-ol

(*Z*)-hex-3-en-1-ol, also known as leaf alcohol, is a naturally occurring homoallylic alcohol found in many flowers, fruits, and vegetables. It is also a highly prized compound in both the flavors and fragrances industry. It displays a typical powerful, fresh, and intensely green, grassy odor, and it is frequently used not only in delicate floral fragrances such as lily of the valley and Lilac but also in minty, fruity, and green tea flavors as it gives a fresh green effect as the top note. Moreover, a large number of leaf alcohol esters (formate, acetate, and benzoate among the most important ones) also display some interesting and highly diverse olfactive properties depending on the nature of the ester moiety. Consequently, its overall worldwide production volume has reached several 100 tons per year nowadays. Therefore, a development of an efficient and economically viable industrial access to produce leaf alcohol was of great attraction to Firmenich SA. Among all the potential routes to leaf alcohol, the one going through formal addition of 1-butyne (obtained from a C_4 petroleum cut) to ethylene oxide followed by a stereoselective alkyne hydrogenation reaction, for example, with a Lindlar-type heterogeneous palladium catalyst, clearly appeared as the most straightforward pathway. Nevertheless, such a production route would most likely require both careful safety measurements along with specifically dedicated equipment due to the hazardous and gaseous nature of both alkyne and epoxide. Additionally, the stoichiometric use

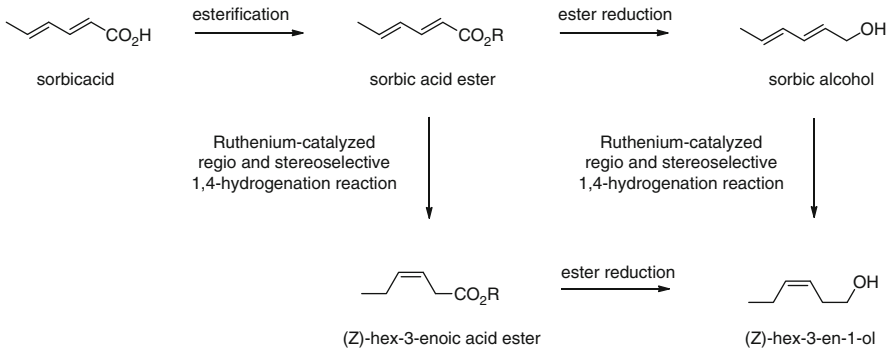


Fig. 2 (*Z*)-hex-3-en-1-ol from sorbic acid

of acetylide in the presence of catalytic amounts of lewis acid was reported to be required to efficiently access homopropargylic alcohols [26]. As an alternative, Firmenich SA envisioned another potentially economically viable industrial access to leaf alcohol starting from the cheap sorbic acid (see Fig. 2).

The key step of this synthetic pathway clearly appeared to be the 1,4-hydrogenation of the conjugated diene moiety that would enable access to the olefinic compound with both the desired regio and stereochemistry. If that type of transformation had previously been described in the case of both sorbic acid esters [1–3] or sorbic alcohol [3], results reported so far had to be improved in order to afford a more efficient access to leaf alcohol for potential industrial application. Similar transformation of sorbic acid was also reported [2, 3], but such a route was indeed discarded due to both reported even lower catalytic efficiency [3] along with potential olefin isomerization during the subsequent (*Z*)-hex-3-enoic acid esterification reaction under industrial conditions. Thus, based on our initial work on acidic ruthenium-catalyzed 1,4-hydrogenation methodology, we carefully examined the transformation of both sorbic acid esters and sorbic alcohol [27] using catalytic amounts of cationic [(Cp-type)Ru(diene)][Y] complexes. In both cases, the use of weak acids as additives clearly led to some noticeable process improvements compared to previously reported results [1–3]. As a matter of fact, heating the neat starting material (in the case of sorbic acid esters) or in the presence of acetone as a solvent (50 wt% in the case of sorbic alcohol) to 70–80°C under mild hydrogen pressure (1–5 bar) in the presence of catalytic amounts of cationic [(Cp*)Ru(1,3-COD)][BF_4] complex (down to 0.005 mol% in both cases) [28] and maleic acid (0.1–0.2 mol% in both cases) efficiently afforded (*Z*)-hex-3-enoic acid esters and (*Z*)-hex-3-en-1-ol in more than 90 mol% isolated yields along with greater than 98% overall selectivity in both cases. In the sorbic acid esters hydrogenation, it is important to note that reaction was generally stopped at high but not complete conversion (around 95% GC) due to some decrease in overall selectivity upon reaction completion, more specifically concerning its stereoselectivity (see Fig. 3 in the case of methyl sorbate). The product obtained was easily separated from the remaining starting material by fractional distillation.

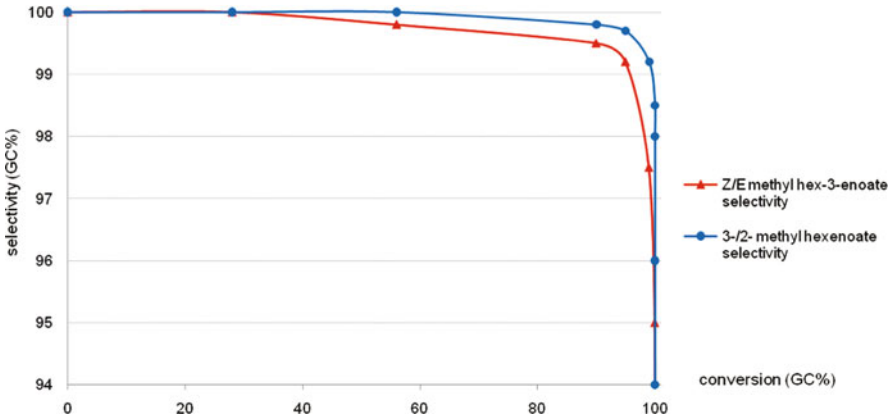
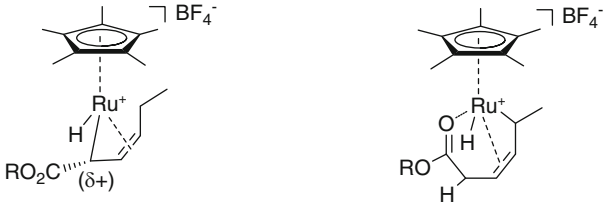


Fig. 3 Methyl sorbate hydrogenation selectivity versus reaction conversion



putative π -allyl Ru(IV) intermediate formed upon 3-hexenoate CH activation

putative π -allyl Ru(IV) intermediate formed during hydrogenation process

Fig. 4 Putative (hydrido)(π-allyl)ruthenium intermediates in sorbic acid esters case

Such a decrease in selectivity could result from some CH bond activation of the activated methylene group located between the ester and olefin moieties in hex-3-enoic acid esters leading to the formation of a putative (hydrido)(π-allyl) ruthenium intermediate at the C2 carbon which would undergo classical π-allyl isomerization reaction. Along with some higher affinity of ruthenium metal center toward sorbic acid esters compared to corresponding hydrogenated product confirmed by a nearly zero order kinetic in starting diene, formation of a higher nucleophilic (hence, more reactive toward protonation reaction) isomeric (hydrido)(π-allyl) ruthenium intermediate at the C5 position (being stabilized toward isomerization reaction due to potential coordination to the ester moiety) during hydrogenation process could explain why such a phenomenon only occurs upon nearly complete conversion of starting material (see Fig. 4).

In the case of sorbic alcohol hydrogenation, we did not observe a decrease in reaction selectivity upon the disappearance of starting material, but we nevertheless faced some catalyst deactivation. Upon carefully looking at the starting material quality, we found that deactivation was indeed closely related to starting material (2*Z*,4*E*) isomer content. As a matter of fact, running hydrogenation reaction on

pure (2*Z*,4*E*)-hexa-2,4-dien-1-ol using large amounts of [(Cp*)Ru(1,3-COD)][BF_4] complex as catalyst (20 mol%), we manage to isolate with 85 mol% yield in ruthenium the [(Cp*)Ru(benzene)][BF_4] complex that was characterized by ^{1}H, ^{13}C, and ^{19}F NMR analysis along with high resolution mass spectroscopy. Formation of such a ruthenium species is indeed arising from some unexpected formal (2*Z*,4*E*)-hexa-2,4-dien-1-ol dehydration/cyclization/dehydrogenation reactions sequence according to some unknown mechanism. As it clearly appears to be inactive in 1,4-hydrogenation reaction, it is probably responsible for catalyst deactivation observed, starting material (2*Z*,4*E*) isomer acting as a poison. It is interesting to note that even if complexation of the (2Z,4E) isomer to ruthenium metallic center was highly favored compared to the (2*E*,4*E*) isomer, its transformation into inactive species appeared to be much slower compared to the hydrogenation reaction process. As a consequence, catalytic activity should then be highly sensitive even to a small increase in (2*Z*,4*E*) isomer content, this being clearly observed from experimental data. As a consequence, (2*Z*,4*E*) isomer was generally removed by efficient starting material crystallization in order to insure catalytic efficiency in sorbic alcohol hydrogenation reactions. In regards to the reduction of esters, both sorbic acid and (*Z*)-hex-3-enoic acid esters were efficiently reduced according to an industrial methodology using polymethylhydrosiloxane (PMHS) in the presence of zinc hydride catalysts [29], a process that was patented by Firmenich SA [30]. This method served as an alternative to the classically more hazardous use of lithium aluminum hydride. As a matter of fact, although we discovered that esters could be efficiently and selectivity hydrogenated using ruthenium complexes in the presence of olefins [31, 32], those substrates were too sensitive to required basic conditions demanded by protocol. In any event, whether the starting material is a sorbic acid ester or sorbic alcohol, both synthetic pathways going through selective ruthenium-catalyzed 1,4 hydrogenation of a conjugated diene afforded Firmenich SA an industrially viable access to leaf alcohol.

3 Chemoselective Ruthenium-Catalyzed Hydrogenation of Ketones and Aldehydes

Selective reduction of carbonyl group moieties in the presence of other functional groups such as olefins is a reaction of high importance in the flavor and fragrance industry due to the widespread use of unsaturated alcohols as synthetic intermediates or final ingredients. In order to replace classical hydride-type reduction and avoid their drawbacks, we developed the use of amino and iminophosphine as ligands in selective ruthenium-catalyzed hydrogenation which was patented by Firmenich SA [24, 25]. The corresponding precatalysts that generally display similar catalytic activity and selectivity toward olefins compared to the diphosphine/diamine systems (based on some comparative results obtained during some laboratory study) allow application of such a sustainable technology on

an industrial scale. The reactions using chloro ruthenium complexes bearing amino or iminophosphine ligands as precatalysts were preferably run in an alcoholic solvent (the best results being generally obtained in isopropanol) and also required the use of a strong base (hydroxide or alkoxide) in order to perform catalytic selective hydrogenation of alkaline-resistant ketones and aldehydes. In regards to their performance in such transformations, we also noticed that in order to reach high catalytic activity, the presence of a primary amino group is also generally preferred. As far as both electronics and sterics are concerned, we noticed that reaction could efficiently be performed using amino and iminophosphines ligands displaying a really large variety of substituents on both phosphorous and nitrogen atoms as well as for phosphorous/nitrogen linker. Finally, as for nearly all hydrogenation processes, catalytic efficiency of those complexes for a given reaction was also highly dependent on substrate quality (impurities profile, acidity index, peroxide index, water content, etc).

3.1 Amino and Iminophosphine Chloro Ruthenium Precatalysts Synthesis

Compared to (diphosphine)(diamine)$RuCl_2$-type complexes, the use of amino or iminophosphine ligands displays some advantage in regards to a synthetic point of view, the corresponding $(PN)_2RuCl_2$ or $(PNNP)RuCl_2$ ruthenium complexes being generally efficiently obtained in nearly quantitative yields starting from $(PPh_3)_3RuCl_2$ according to a true single step procedure rather than a sequential process using homobidentate ligands. Due to some chemical but also economical considerations, it was decided at Firmenich SA to mainly use 2-bis(diphenylphosphinol)ethylamine (referred to as DPPAE) as a ligand for the use of the corresponding precatalyst in production given its commercial availability on large enough scale at reasonable prices. During the development phase of the project, we were confronted with the possibility that we would have to face filtration issues during scale-up of the corresponding ruthenium complex since it is highly insoluble in most classical organic solvents, generally precipitating out of the reaction mixture as a really thin powder. Fortunately, while screening for solvents for synthesis of hydrogenation ruthenium precatalyst, we found out that running the reaction in THF unexpectedly led to the formation in high yields of the cationic (chloro)[*bis*(diphenylphosphinoethylamine)](triphenylphosphine)ruthenium(II)chloride complex (referred to as $[(DPPAE)_2(PPh_3)RuCl][Cl]$) still bearing one triphenylphosphine as a ligand and with one of the chloride ligands being dissociated. In this case, even if it is also poorly soluble in most classical organic solvents, it was easily and efficiently recovered by filtration as a yellow–orange solid that could be recrystallized for X-ray analysis (Fig. 5).

NMR studies of this cationic complex clearly demonstrated that, once in solution, triphenylphosphine easily dissociates leading to the complete formation of the neutral $(DPPAE)_2RuCl_2$ along with free triphenylphosphine ligand. Based on these

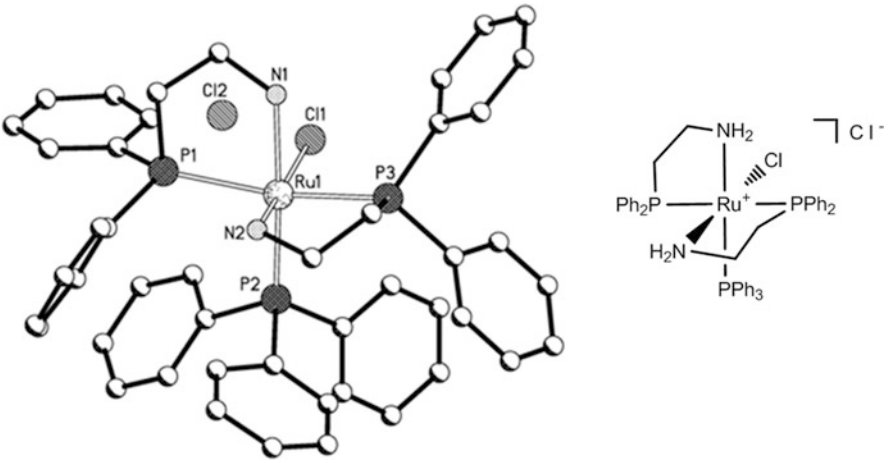


Fig. 5 (Chloro)[bis(diphenylphosphinoethylamine)](triphenylphosphine)ruthenium(II)chloride X-ray structure

NMR studies results, it was unsurprising that cationic $[(DPPAE)_2(PPh_3)RuCl][Cl]$ complex afforded the same results as the neutral $(DPPAE)RuCl_2$ concerning both catalytic activity and chemoselectivity in selective ketone and aldehyde hydrogenation reactions. As a matter of fact, regarding the diamine/diphosphine complexes, those amino- and iminophosphine ruthenium precatalysts are probably operating through a nonclassical outer-sphere metal–ligand bifunctional mechanism. Thus, according to reaction mechanism proposed by Noyori [33], Chen [34] and Morris [35], free triphenylphosphine generated from the cationic precatalyst dissociation was not apparently even interacting with the 16 electron intermediate formed upon alcohol formation. Cationic $[(DPPAE)_2(PPh_3)RuCl][Cl]$ complex revealed itself to be highly stable in the solid state as it could be handled and even stored for months in air. Hydrogenation reactions were also sometimes run using some crude precatalyst suspension generated from $(PPh_3)_3RuCl_2$ complex containing free triphenylphosphine (3 eq./Ru). Even in this case, the suspension in an organic solvent or in neat hydrogenation substrate itself also afforded hydrogenation results similar to those obtained using isolated pure $(DPPAE)_2RuCl_2$. It is worth noting that if reaction with only one equivalent of bidentate aminophosphine ligand was carried out, efficiently isolated $(DPPAE)(PPh_3)RuCl_2$ also displayed some interesting catalytic activity. However, it was discarded due to its moderate stability upon storage even under inert atmosphere, such instability being a major drawback for a potential use one large scale. $(DPPAE)(PPh_3)RuCl_2$ being a 16 electrons species, its higher sensitivity could be due to its coordinatively unsaturated nature. $[(DPPAE)_2(PPh_3)RuCl][Cl]$ ruthenium precatalyst that afforded interesting results in selective carbonyl group hydrogenation reactions on laboratory scale was also efficiently used on an industrial scale for the production of perfumery ingredients such as, for example, Polysantol®, Nirvanol®, Dartanol®, and Pamplewood®.

3.2 *Industrial Access to Some Sandalwood Odorants Through Chemoselective Hydrogenation*

The East Indian sandalwood oil probably represents one of the most precious perfumery natural raw materials because of the rarity of the natural plants from which it is extracted. As until recently [36] since no industrially viable process existed for production of (*Z*)-beta-santalol, the main olfactive constituent of Indian sandalwood (see Fig. 6), the focus was directed toward the search for cheaper synthetic analogs in order to also prevent resource depletion. Alpha-campholenic aldehyde derivatives are clearly affording the best, and most often used substitutes for such a natural resource [37].

3.2.1 Polysantol® and Nirvanol® Cases

Among all the alpha-campholenic aldehyde-based compounds used in the perfumery industry as synthetic analogs of the East Indian sandalwood natural oil, Polysantol® and Nirvanol® are among the most important ones produced by Firmenich SA. Both products are respectively obtained from the cheap natural (−)-(1*S*,5*S*) and (+)-(1*R*,5*R*) alpha-pinene enantiomers through a multistep synthesis. Being previously accessed through selective ketone hydrogenation using a copper chromite type catalyst, production of those two perfumery ingredient with overall volumes of about 100 tons per year was further improved by the efficient use of homogeneous ruthenium complexes as precatalysts (see Fig. 7). As a matter of fact, if hydrogen technology already afforded much better results compared to hydride-type reagents, further improvement were clearly seen in process safety, robustness, selectivity, and productivity. The hydrogenation reaction of (*E*)-3,3-dimethyl-5-(2,2,3-trimethylcyclopent-3-enyl)pent-4-en-2-one using chloro–ruthenium complexes bearing amino- or iminophosphine ligands as a precatalyst quickly appeared to be quite efficient as it afforded the desired Polysantol® (coming from ketone (*R*)-enantiomer) or Nirvanol® (coming from ketone (*S*)-enantiomer) in isolated yields higher than 98% and chemoselectivity up to 99% going down to 0.0005 mol% ruthenium loading (T.O.N. up to 200,000) on a laboratory scale.

These levels of chemoselectivity were obtained running the reaction at 90–100°C under mild hydrogen pressure (up to 20 bar), but upon increasing the hydrogen

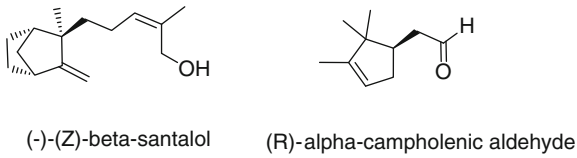


Fig. 6 Natural sandalwood odorant (−)-(Z)-beta-santalol and alpha-campholenic aldehyde

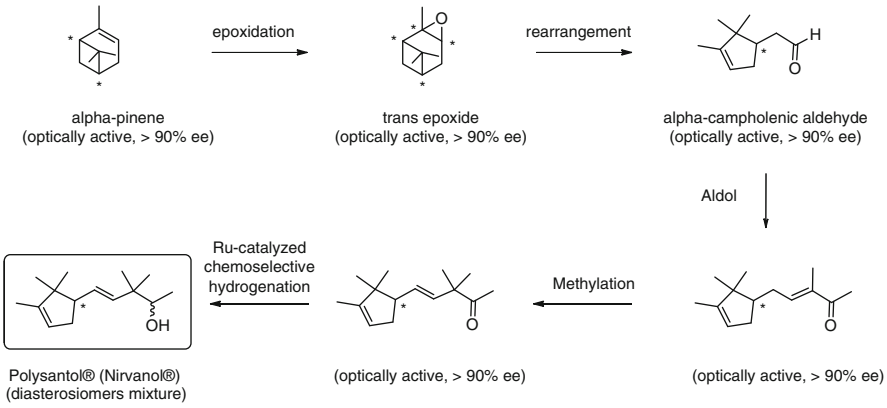


Fig. 7 Polysantol® and Nirvanol® production synthesis

pressure, a decrease in reaction selectivity with some overhydrogenation of olefinic moiety present in the side chain was generally observed. Despite operating through a probable outer-sphere mechanism, some hydrogenation side reactions occurring through metal–substrate π-complexation could not be fully excluded when performing the reaction at such temperatures. Furthermore, precatalyst was demonstrated to be able to undergo X-type ligand dissociation with formation of a vacant coordination site based on reported X-ray structure (see Fig. 5). During all hydrogenation experiments performed on laboratory scale, no chiral induction was ever observed even running the hydrogenation reaction under very mild conditions (low temperature, high dilution). As a consequence, both Polysantol® and Nirvanol® were always obtained as nearly 50/50 diastereoisomeric mixtures perfectly matching both analytical and olfactive specifications of the previously obtained products qualities, with the (1′*R*,2*S*) and (1′*S*,2*S*) being respectively the preferred isomers based on their olfactive properties [38]. Cationic $[(DPPAE)_2(PPh_3)RuCl][Cl]$ complex was generally used as a precatalyst in the presence of catalytic amounts of hydroxide or alkoxide while running reaction in isopropanol, sodium salts of those strong bases being generally preferred. Nevertheless, in order to improve process productivity, we then showed that hydrogenation reaction could actually be run neat subsequently demanding the compulsory use of alkoxides in order for the reaction to proceed. The reaction was quite easily and efficiently implemented up to a multi-ton scale with results similar to those obtained on a laboratory scale. If catalyst loading was decreased down to 0.0005 mol% on laboratory scale, in production the reaction was generally run using 0.00125 mol% ruthenium with catalyst contribution to the product price being somewhat negligible at such concentrations but at the same time robust enough to allow for slight process deviations (starting material quality, etc). As far as starting material quality is concerned, the latter was generally purified using fractional distillation and stored under inert atmosphere affording a quality which was adequate to efficiently perform the hydrogenation reaction on both lab and industrial scale. After

quenching of the basic cocatalyst, the crude hydrogenation product was purified from residues and efficiently afford Polysantol® or Nirvanol® matching both analytical and olfactive specifications starting respectively from (*E*)-3,3-dimethyl-5-(2,2,3-trimethylcyclopent-3-enyl)pent-4-en-2-one levo or dextro.

3.2.2 Dartanol Case

Along with Polysantol® and Nirvanol®, Dartanol® represents one of the largest alpha-campholenic aldehyde based sandalwood odorants at Firmenich SA with volumes of several hundred tons per year. In terms of stereochemistry, only the Dartanol enantiomer coming from (*R*)-alpha-campholenic aldehyde strongly displays the desired sandalwood note [39]. Similarly obtained according to a multistep synthesis from optically active alpha-pinene natural source, the use of homogeneous ruthenium complexes as precatalysts allowed for the efficient production of this perfumery ingredient avoiding all the drawbacks related to the use of hydride-type reagents (see Fig. 8).

The hydrogenation reaction of (*R*,*E*)-2-ethyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl) but-2-enal using chloro ruthenium complexes bearing amino- or iminophosphine ligands as a precatalyst quickly appeared to be quite efficient affording the desired Dartanol® in more than 90% isolated yields and selectivity up to 98% GC. Nevertheless, it generally required the use of a solvent and higher catalyst loading compared to both the Polysantol® and Nirvanol® synthesis. As a matter of fact, due to some temperature limitations related to the sensitivity of the starting (alpha, beta)-unsaturated aldehyde under basic conditions which is required for performing such a reaction, the hydrogenation was generally run in isopropanol under much milder conditions (up to 60°C maximum). At the same time, the catalyst loading could not be decreased below 0.005 mol% ruthenium catalyst bearing DPPAE ligands in the presence of hydroxide basic cocatalyst. As in the previous case, the reaction was also generally run under mild hydrogen pressure (up to 20 bar) in order to avoid side chain overhydrogenation. After quenching the basic cocatalyst and solvent removal, the crude hydrogenation product was purified by distillation to efficiently afford olfactive Dartanol®, such an efficient process allowing sustainable production of such a perfumery ingredient.

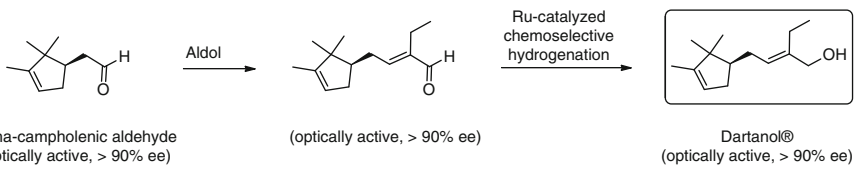


Fig. 8 Dartanol® production synthesis

3.3 *Industrial Access to Pamplewood® Through Chemoselective Hydrogenation*

Pamplewood® is a Firmenich SA perfumery ingredient displaying both grapefruit and woody notes [40]. Such diversity in olfactive properties is indeed due to the presence of both exo and endo isomers in final ingredient (see Fig. 9).

Pamplewood® was initially produced through ketone reduction using hydride-type reagents. Thus, it became obvious that two challenges had to be tackled if the hydride reductions were to be replaced by homogeneous ruthenium-catalyzed selective ketone hydrogenation. In addition to a question of selectivity due to the methylenic group present in the starting ketone, the hydrogenation reaction would also have to produce the desired alcohol with exo/endo ratio (55–65/30–40) similar to that achieved with hydride reduction in order to match olfactive properties of the existing ingredient quality. This was successfully achieved by selective ketone hydrogenation using chloro ruthenium complexes bearing aminophosphine ligands as precatalyst leading to a much safer and productive process compared to the reduction reaction. As a consequence, this perfumery ingredient could now be efficiently produced on an industrial scale with volumes around 1 ton per year according to the described route (see Fig. 10).

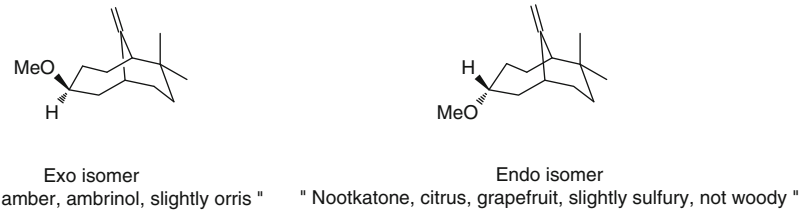


Fig. 9 Pamplewood isomers olfactive properties

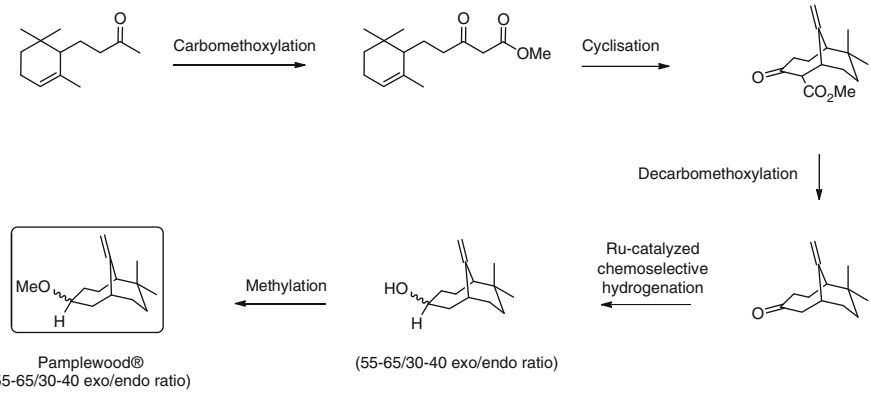


Fig. 10 Pamplewood® production synthesis

The hydrogenation reaction of 7,7-dimethyl-10-methylenebicyclo[4.3.1]decan-3-one using a chloro ruthenium complexes bearing aminophosphine ligands as a precatalyst quickly appeared to be efficient and selective leaving the olefinic moiety intact. However, it led to an exo/endo isomeric ratio of about 80/20 for the desired alcohol which did not meet the desired product quality. If we managed to obtain the alcohol with desired exo/endo ratio modifying the structure of the aminophosphine ligand used, implementation of both a new ligand and precatalyst synthesis on industrial scale is always time demanding. Therefore, we kept using the cationic $[(DPPAE)_2(PPh_3)RuCl][Cl]$ complex while screening for reactions parameters. Finally, we discovered that under certain conditions, the desired exo/endo alcohol isomers ratio could be obtained through a selective ketone hydrogenation and epimerization process. This unexpected epimerization reaction under hydrogen pressure probably occurs through an outer coordination sphere hydrogen transfer reaction [41]. The latter can be viewed as two simple equilibriums between the ketone and the exo alcohol isomer and the ketone and the endo alcohol isomer (see Fig. 11).

According to the reaction model affording a good correlation between experimental and simulated data, transformation of the ketone into both the exo and endo isomers of alcohol appears to be much faster than the respective reverse reactions with respective equilibrium constants $K_{eq\ exo}$ and $K_{eq\ endo}$ of 1,667 and 2,070 for reaction performed under the conditions reported in Fig. 10. Such an epimerization phenomenon was demonstrated to be clearly favored by several reaction parameters such as high substrate concentration, increase in the reaction temperature, and

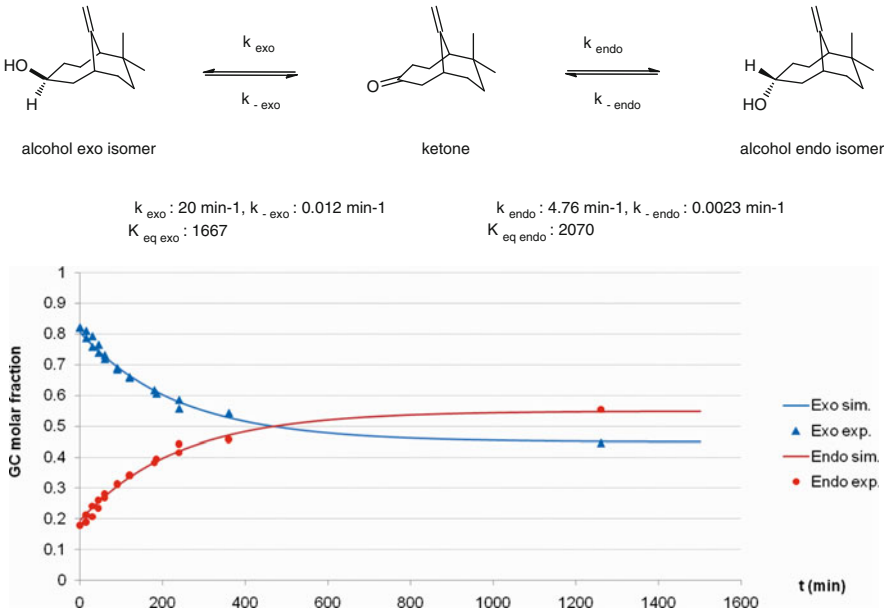


Fig. 11 7,7-dimethyl-10-methylenebicyclo[4.3.1]decan-3-ol epimerization reaction model

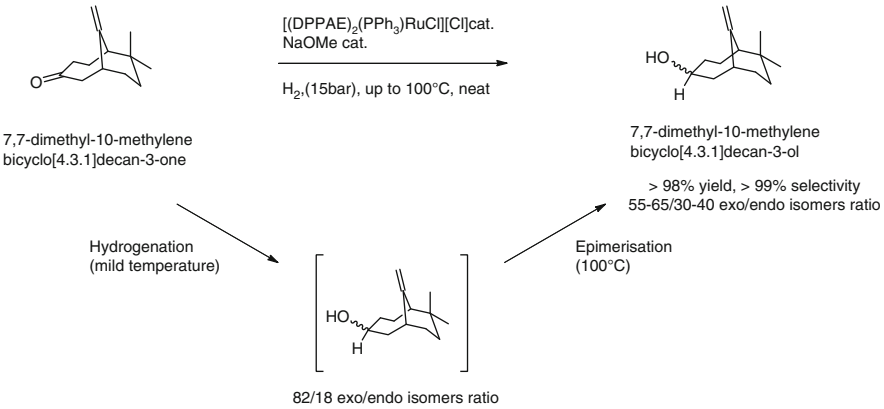


Fig. 12 Ruthenium-catalyzed selective epimerizing hydrogenation step in Pamplewood® synthesis

a decrease in the hydrogen pressure. This is clearly illustrated as an overall epimerizing hydrogenation process (see Fig. 12).

The reaction was generally performed under mild temperature until complete disappearance of starting ketone. The temperature is then increased while maintaining the initial hydrogen pressure, and reaction mixture is left stirring under these conditions until desired exo/endo ratio for 7,7-dimethyl-10-methylenebicyclo [4.3.1]decan-3-ol is reached. As we have previously demonstrated, the use of a solvent is not required to perform hydrogenation reactions while using alkoxides as basic cocatalysts. Thus, even in this more complex case, the reaction could be run neat in order to optimize process productivity. Starting from 7,7-dimethyl-10-methylenebicyclo[4.3.1]decan-3-one previously purified by fractional distillation and stored under inert atmosphere, cationic $[(DPPAE)_2(PPh_3)RuCl][Cl]$ complex was then used as a precatalyst with ruthenium loading below 0.002 mol% (T.O.N. superior to 50,000) in the presence of catalytic amounts of sodium methoxide to afford the desired 7,7-dimethyl-10-methylene bicyclo[4.3.1]decan-3-ol in more than 98% yield, with chemoselectivity higher than 99% and matching the desired exo/endo isomeric ratio requirements. Crude Hydrogenation reaction mixture could directly be used without any treatment for further transformation into Pamplewood® resulting in material which matched both analytical and olfactive specifications. The reaction has been efficiently scaled-up in production affording similar results to those obtained in the laboratory in terms of both catalytic activity and overall reaction selectivity.

4 Conclusion

We have herein reported the use of ruthenium-catalyzed industrial hydrogenation methodologies that enabled Firmenich SA to produce in a sustainable manner some ingredients used for flavor and fragrance applications. Leaf alcohol, widely used in

both flavor and fragrance applications could efficiently be synthesized through acidic regio- and stereoselective 1,4-hydrogenation of conjugated diene intermediates. Based on its reaction scope and catalytic efficiency, such a methodology offers itself to be a cleaner and cheaper general alternative to the use of Wittig-type reagents often employed to access olefins possessing (*Z*)-stereochemistry. Unsaturated alcohols such as Polysantol®, Nirvanol®, Dartanol®, and Pamplewoodol® used in fragrance applications were efficiently produced through chemoselective hydrogenations of carbonyl groups using ruthenium complexes bearing amino- or iminophosphines ligands. Implementation of such a technology allowed for the efficient chemical replacement of classical reduction methods with high process improvements not only in terms of economy and safety but also in its environmental aspects. Despite these obvious advantages, implementation of such new methodologies for synthesis in the field of flavors and fragrances remains highly challenging as it relates to organoleptic properties of the final products. Indeed, replacement of a given synthetic method can lead to some minute differences (for example, in the impurities profile) that sometimes cannot even be analytically quantified but can lead to drastic changes concerning the somewhat emotional olfactive profile of the product.

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Asymmetric Hydrogenation

Hans-Ulrich Blaser, Benoît Pugin, and Felix Spindler

Abstract This review describes the application of chiral organometallic catalysts for the enantioselective (transfer) hydrogenation of C=C, C=O and C=N bonds in the fine chemicals industry. Covered are processes that have been and/or are presently used for the commercial manufacture of chiral compounds as well as selected pilot and bench-scale processes not (yet) used in production. The review is organized according to the metal precursor actually employed in the hydrogenation reactions. Described are large scale applications of Rh, Ru, and Ir complexes with chiral P^P, P^N and N^N ligands, either used as preformed, isolated complexes or as in situ-prepared catalyst precursors.

Keywords Chiral diphosphines · Enantioselective hydrogenation · Industrial processes · Ir complexes · Metal precursors · Rh complexes, Ru complexes

Contents

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1 Introduction

There is no doubt that the homogeneous catalysis with organometallic complexes has significantly influenced organic synthesis. Especially redox active metal compounds have made reactions and transformations possible which are not accessible to the classical tools of organic chemistry. The research output of a large number of active groups over the last decades is impressive and documented in many reviews and monographs; for a good overview, see [1]. This significance of homogeneous catalysis for organic synthesis has clearly been recognized, most visibly with three Nobel Prizes in the last decade.

Despite the wide scope of homogeneous catalysis and the many synthetic opportunities for designing effective processes which in many instances are ecologically superior to classical organic routes, only rather few types of catalytic reactions are actually applied in the fine chemicals industry. Indeed, the largest homogeneously catalyzed processes with the highest volume are used for the production of bulk chemicals (hydroformylation, acetic acid synthesis, various polymerization reactions, etc.). In the fine chemicals, agrochemical and pharmaceutical industries, only two classes of homogeneously catalyzed reactions are considered on a regular basis when planning for production processes and are actually used in manufacture, namely Pd-catalyzed coupling reactions and enantioselective hydrogenations (for an overview on industrial applications see the chapter by Hans de Vries on Pd-catalyzed coupling reactions in this volume and Blaser et al. [2]).

Homogeneous hydrogenation, arguably the most important enantioselective catalytic methodology in synthetic organic chemistry both in numbers as well as production volume [3], can in many respects be considered a mature field, in the sense that

- The technology has reasonably well-defined and well-known scope and limitations (selectivity, activity, productivity, functional group tolerance).
- It is routinely considered in route design during industrial process development and has a substantial number of applications both on laboratory as well as on industrial scale.
- Relevant catalysts and ligands are commercially available (including well-defined handling of IP issues) both in large numbers for screening purposes as well as in technical quantities for production.

A very good overview on the state of the art of homogeneous hydrogenation up to 2006 can be found in the monograph *Handbook of Homogeneous Hydrogenation* [4, 5]; for a discussion of industrial requirements see Blaser et al. [5]. Chiral phosphorus ligands (the most important source of chirality) have been comprehensively covered in *Trivalent Phosphorus Compounds in Asymmetric*

Catalysis: Synthesis and Applications [6]. Large scale applications of enantioselective hydrogenation technology mainly in the pharmaceutical industry can be found in two monographs [7, 8] and in several overviews [9–11].

In this contribution, we will review the use of organometallic complexes for the enantioselective hydrogenation of alkenes, ketones, and imines to make enantioenriched intermediates and active ingredients. In contrast to conventional reviews which are usually organized according to substrate type, we will describe the application of Rh, Ru, and Ir complexes in separate sections. In each section, a short overview is given on the most important catalyst precursors (metal, anion, ligands) followed by information on processes operated in regular production and on pilot scale as well as on selected bench-scale processes and feasibility studies. More detailed information on these industrial applications can be found in [3, 5, 11]. The following definitions were used: *Production processes* are (or have been) operated on a regular basis, i.e., all relevant problems concerning catalyst performance and separation, supply of materials, product isolation and purification, noble metal recovery, etc., have been solved. *Pilot processes* are technically on a similar level especially concerning catalyst performance, have been carried out on multi-kg to multi-ton scale, but have not (yet) been applied on a regular basis. *Bench-scale processes* have an optimized catalyst performance, have been carried out a few times on smaller scale, but are for some reason not yet ready for production purposes. *Feasibility studies* usually demonstrate proof of principle for a catalytic reaction (especially sufficient enantioselectivity) often without much optimization of catalyst activity.

2 General Remarks on Metal Complexes and Chiral Ligands

The most effective catalysts for enantioselective hydrogenation are mononuclear Rh, Ru, and Ir ions coordinated to a chiral diphosphine, sometimes an additional ancillary ligand and an anion. For transfer hydrogenations, the complexes of tosylated diamines have unique catalytic properties. The chiral catalyst precursor which is actually added to the reaction solution can either be prepared in situ by simply mixing a suitable metal salt or complex and the chiral ligand or by using a single component, "ready to use" metal/chiral ligand (M/L) system which is prepared in an extra step and isolated before use [12]. For Rh catalysts see Rivas-Nass and Briel [12]. As a general rule, both approaches very often give a similar catalyst performance for Rh and Ir catalysts, while Ru catalysts are in most cases preformed, isolated complexes (for details see below). Furthermore, some ligands such as phospholanes or dipamp are relatively air sensitive and usually stored and applied as metal complexes. In the sections below, we use the following notation for a given metal complex: [M(P^P)(L)X]Y where P^P is a chiral diphosphine, L an ancillary achiral ligand, and X an anion, all coordinated to M, whereas Y is an anion not directly coordinated to M (for a typical example see Fig. 1)

Today, an impressively large number of chiral ligands is recorded in the literature to achieve very high enantioselectivity for a variety of catalytic reactions [13]. However, only a limited number has actually been used on a regular basis for the

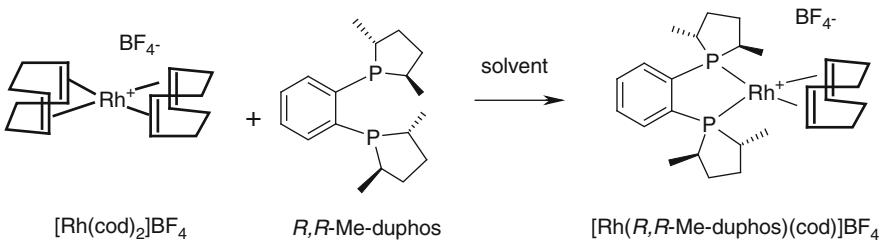


Fig. 1 Preparation of a cationic Rh/duphos catalyst precursor

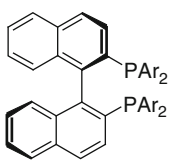
synthesis of target molecules. The usefulness of a ligand can be negatively affected if it is extremely air and/or moisture sensitive. In addition, catalysts are often rather substrate specific, i.e., ligands have sometimes to be "tailored" for each individual substrate because even small changes can strongly affect the catalyst performance. In this respect, modular ligands are preferred since the effort required to adapt the ligand to the reaction are much smaller than for ligands with little structural variability. The josiphos ligand family was one of the first where this principle was applied and perfectly illustrates the potential of the modular approach [14]. Needless to say that ligands with a wide scope (and well defined and known limitations), low substrate specificity and with good functional group tolerance and stability have a much better chance for being applied by the synthetic organic chemist than others.

For enantioselective hydrogenation, a number of ligand classes have been shown to be especially versatile. Structures and names of the repeatedly applied ligands as described in the following sections are collected in Fig. 2, the structure of other ligands is shown directly in the schemes and figures. One can distinguish between several ligand classes: atropisomeric diphosphines such as binap or MeO-biphep, ferrocene-based diphosphines such as bppfa or Josiphos, P-chiral ligands such as dipamp, phospholanes such as duphos, diamine-based ligands and a few "early" and miscellaneous phosphines. Most of these ligands (and of course many more) can be purchased on a laboratory scale from Strem or Fluka-Aldrich. If appropriate, the company which markets or applies the ligands on a technical scale is also indicated.

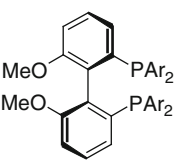
A brief statistical summary of their application is presented in Table 1. It is easy to see that about the same number of Rh- and Ru-catalyzed processes have been reported. However, while for Ru-catalyzed hydrogenation reactions biaryl diphosphines are applied almost exclusively; this ligand class has barely been applied in Rh-catalyzed processes we here all the other ligand types shown in Fig. 2 have been successful.

3 Rhodium-Catalyzed Hydrogenation Reactions

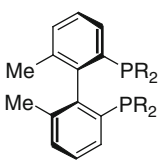
The use of Rh for hydrogenation started with the discovery by Wilkinson [15] that phosphine complexes were active for the homogeneous hydrogenation of alkenes in the 1960s. Very soon after, the use of chiral phosphines was tried, culminating in



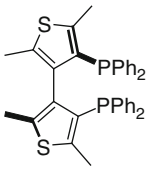
binap Ar = Ph
Tol-binap Ar = pTol
Xyl-binap Ar = 3,5-Xyl
(various suppliers)



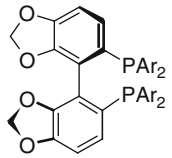
MeO-biphep R = Ph
Tol-MeO-biphep R = pTol
(Roche/Solvias)



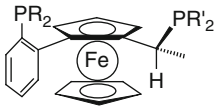
biphemp R = Ph
Tol-biphemp R = pTol
Cy-biphemp R = Cy
(Roche)



tmbtp
(Chemi)

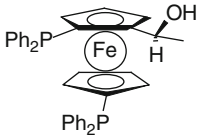


segphos Ar = Ph
dm-segphos Ar = 3,5-Xyl
dtbm-segphos
Ar = 4-MeO-3,5-$(tBu)_2C_6H_2$
(Takasago)

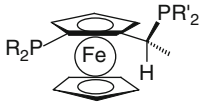


walphos (Solvias)

	R	R'
W001	Ph	3,5-$(CF_3)_2C_6H_3$
W003	Ph	Cy
W008	3,5-$(CF_3)_2C_6H_3$	Cy

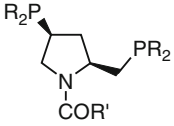


bppfoh

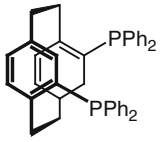


josiphos (Solvias)

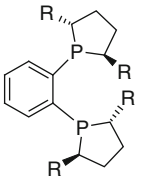
	R	R'
J001	Ph	Cy
J002	Ph	tBu
J005	2-Fur	tBu
J011	tBu	oTol
J212	Ph	3,5-Xyl
J505	pCF_3Ph	tBu



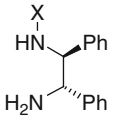
	R	R'
bpm1	Ph	CONHPh
bpm2	Ph	COOtBu
bpm3	mTol	$POPh_2$
mccpm	Cy	CONHMe



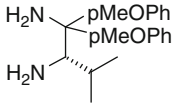
phanephos Ar = Ph
Xyl-phanephos Ar = 3,5-Xyl
(Johnson Matthey)
(Chirotech)



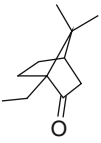
Me-duphos R = Me
Et-duphos R = Et
(Chirotech)

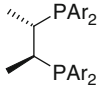


dpen X = H
dpenTs X = SO_2-pTol
dpenCs X = SO_2



daipen





bdpp Ar = Ph
Xyl-bdpp Ar = 3,5-Xyl

Fig. 2 Structure, name and supplier of chiral ligands repeatedly used in Schemes and Figures

Table 1 Statistics for the application of ligand classes

Ligand class	Rh			Ru			Ir		
	M	P	B	M	P	B	M	P	B
Biaryl diphosphines	–	**1**	**1**	**3**	**20**	**16**	–	**1**	–
Ferrocene-based ligands	**3**	**4**	**7**	**1**	**3**	**1**	**1**	**2**	**1**
Phospholanes	–	**8**	**5**	**1**	–	–	–	–	–
P-Chiral ligands	**1**	**2**	**1**	–	–	–	–	–	–
"Early" diphosphines[a]	**5**	**6**	–	–	–	**2**	–	**1**	–
Miscellaneous phosphines[b]	**2**	–	**1**	–	–	**2**	–	–	–
N^N and N^O ligands (transfer hydrog.)	–	**7**	–	–	**1**	**3**	–	**1**	–

M manufacture, *P* pilot, *B* bench scale
[a]bpm, bdpp, deguphos, glup, eniphos
[b]Phanephos, phosphoramidaites, P^N ligand

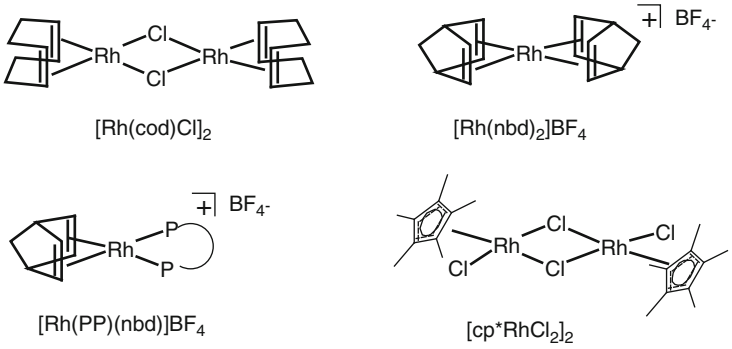


Fig. 3 Structure and formula of most frequently used Rh precursor complexes (PP chiral diphosphine)

the development of the Rh/dipamp catalyst by Knowles for the manufacture of L-dopa (see below). This seminal work had a profound influence on the development of enantioselective catalysis for many years.

In essence, four types of Rh complexes have routinely been used as precursors for Rh-catalyzed hydrogenation reactions (see Fig. 3): neutral or cationic bis-diene (norbornadiene or 1,5-cyclooctadiene) Rh(I) complexes with Cl^- or BF_4^- as anion, respectively, preformed diene-diphosphine complexes (see Fig. 1), mostly as anionic species and especially with air-sensitive ligands and/or P-chiral phosphines prone to racemization. Before the diene-diphosphine complexes become active catalysts, the diene has to be removed via hydrogenation. Depending on the diene and the ligand, this reaction can be rather slow, thereby leading to induction phases and/or decreased catalyst productivity; for an overview, see Heller et al. [16]. The results presented show some clear trends as to which precursor type is most likely to be effective for a desired transformation:

Cationic diphosphine complexes are used for the hydrogenation of C=C bonds with variable substitution patterns, encompassing geminally substituted enamides,

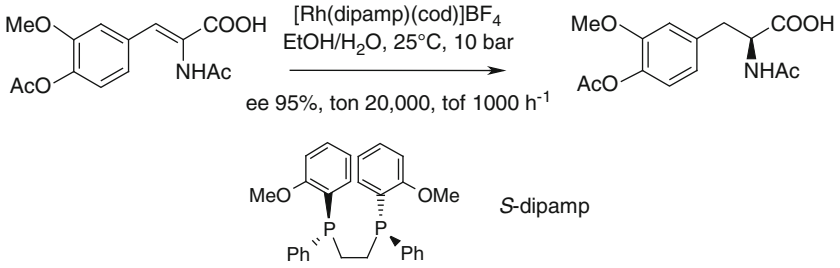
a variety of trisubstituted alkenes as well as a number of tetrasubstituted olefins. In rare cases, aryl ketones have also been reduced with such catalysts.

Neutral diphosphine complexes, usually with chloride as coordinating anion, are preferentially used for the hydrogenation of various ketones but are also applied for the hydrogenation of α-dehydroamino acid derivatives as well as some imines. Since most of the alkene hydrogenations are carried out in MeOH, it is likely that the chloride dissociates, and that also here, the cationic species is the active catalyst. $[cp^*Rh(III)Cl_2]_2$ is applied for the transfer hydrogenation of C=O and C=N moieties.

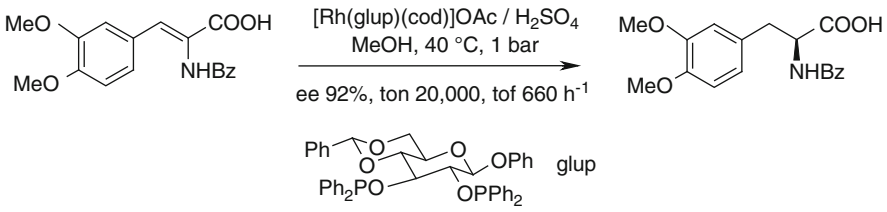
3.1 Isolated Cationic Rhodium Complexes

The first and arguably most famous enantioselective hydrogenation for the production of L-dopa was developed in the early 1970s by Knowles and colleagues at Monsanto. After a surprisingly short development time, they discovered that a cationic dipamp Rh-diene complex was very effective for the hydrogenation of the enamide intermediate depicted in Scheme 1. According to Knowles [17], Monsanto has been producing L-dopa, a drug for the relief of the Parkinson disease, on the scale of ca. 1 t/year for many years, but the production has now been terminated. A few years after Monsanto, the East-German company VEB Isis-Chemie [18] announced Rh-glup catalyst and also carried out a similar process on about the same scale but terminated the production after a few years (Scheme 2). The key step in both syntheses is the enantioselective hydrogenation of an enamide intermediate, a transformation which for many years was chosen a standard test reaction to assess new ligands.

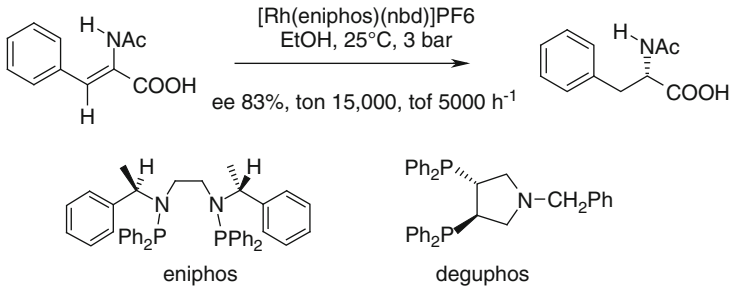
A Rh/dipamp complex was later applied by NSC Technologies [19] for the manufacture of several unnatural amino acids with good catalyst performances (ee 95–98%, ton 5–20,000) and was also very selective but with low activity (ee 98%, ton 20) in a feasibility study for a synthesis of acromelobic acid by Abbott Laboratories [20].



Scheme 1 Production process for L-Dopa (Monsanto)



Scheme 2 Production process for L-Dopa (VEB Isis-Chemie)



Scheme 3 Production process for phenylalanine (Enichem/Anic)

Phenylalanine is an intermediate for the aspartame sweetener and for a few years, it was produced by Enichem/Anic [21] on a scale of ca. 15 t/year, using a variant of the L-dopa procedure (Scheme 3). A few years later, Degussa [22] developed a pilot process with a Rh/deguphos catalyst which operated at 50°C/15 bar and achieved ees up to 99% (ton 10,000, tof 3,000 h^{-1}).

Processes for the Rh-duphos-catalyzed hydrogenation of several α-amino acid derivatives with a variety of structural elements were developed and carried out on a scale of up to multihundred kilograms by Dow/Chirotech [23] which also assisted in developing a process for a bis-amino acid intermediate for Nycomed [24]. Similartechnology was used by Chirotech for Dr. Reddy's to make a substituted D-phenylalanine, an intermediate for a new therapeutic agent [25]. In this case, the enamide ester was prepared in situ by methanolysis of the corresponding azlactone (Fig. 4).

The (formally) diastereoselective process depicted in Scheme 4 was developed by Chirotech [23] for Pharmacia & Upjohn and was reported being carried out on a "production" scale. Essential was the addition of Na_2CO_3 as co-catalyst. The Rh/duphos catalyst tolerates E/Z mixture of substrate and shows high chemoselectivity with respect to reduction of the nitro group. An alternative pilot process was recently described by Boehringer Ingelheim [26] using a Rh/catasium M catalyst with selectivities of >98% de and a tof of ca. 40 h^{-1} applying an s/c ratio of 1,000 at 60°C, 10 bar.

Several pilot processes were described using various [Rh(phospholane)(diene)] X complexes. Amgen [27] reported the hydrogenation step for the synthesis of an MC4 receptor antagonist (Scheme 5). This reaction was probably carried out on

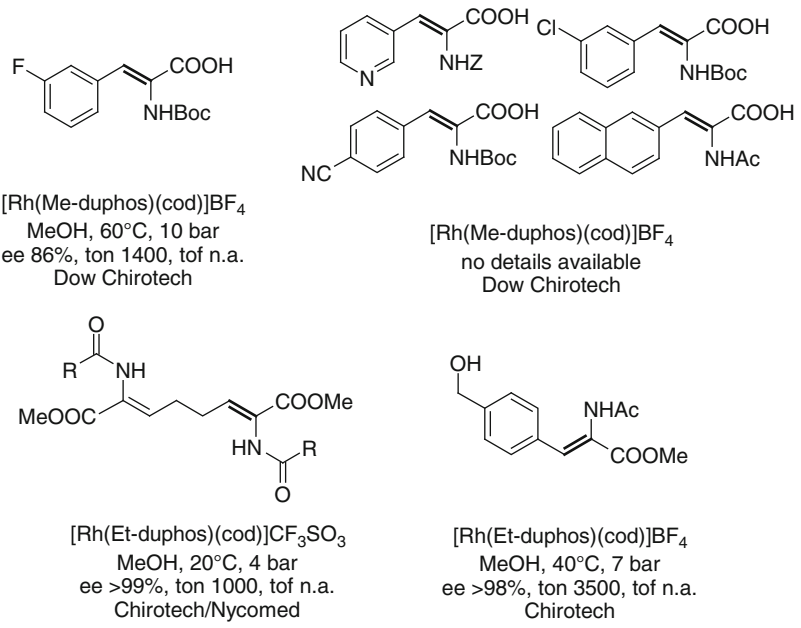
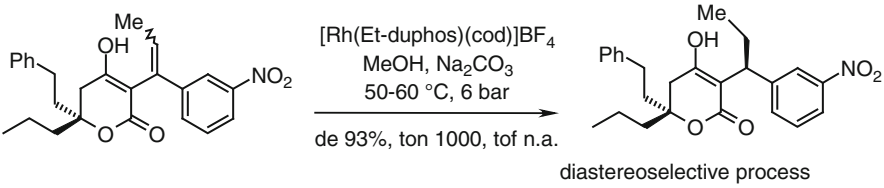
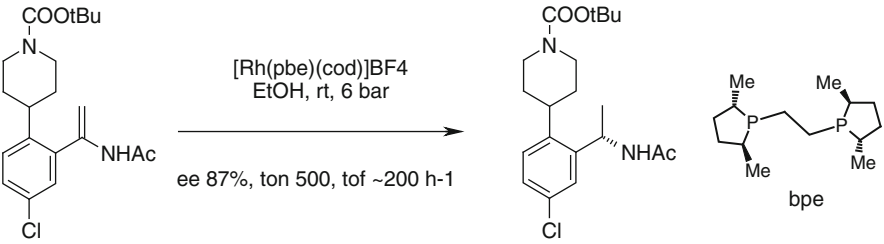


Fig. 4 Starting materials for the production of α-amino acid derivatives on pilot scale

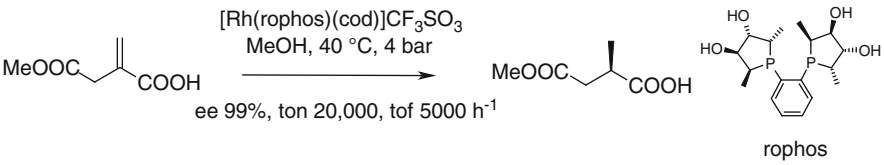


Scheme 4 Pilot process for pharma intermediate (Chirotech)

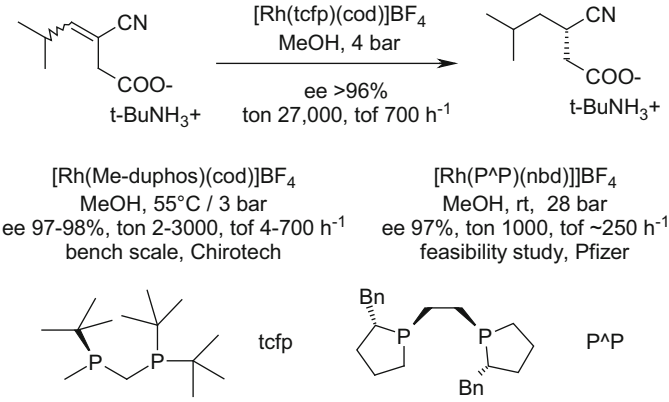


Scheme 5 Hydrogenation step for MC4 receptor antagonist (Amgen)

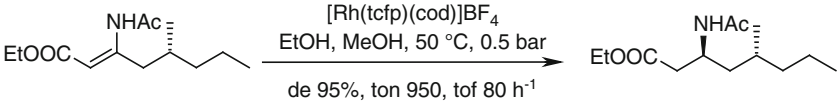
pilot scale, even though the catalyst performance was only moderate. BASF [28] patented the Rh/rophos-catalyzed hydrogenation itaconic acid ester and described production on a >75-kg scale with very high ee values and ton (Scheme 6).



Scheme 6 Process for itaconic acid ester hydrogenation (BASF)



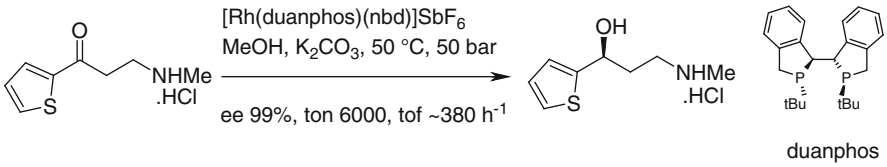
Scheme 7 Hydrogenation processes for pregalabin (Pfizer)



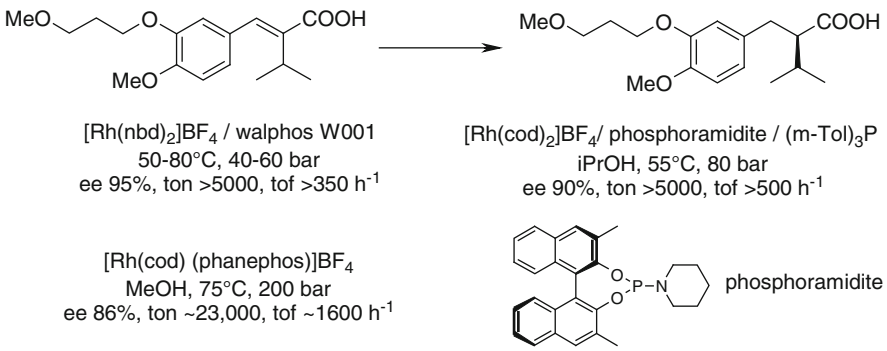
Scheme 8 Hydrogenation processes for imagablin (Pfizer)

Pregabalin is an anticonvulsant produced by Pfizer and several catalysts have been developed to hydrogenate a key intermediate. First results were reported by Chirotech [29] with a Rh/duphos catalyst. Later, Pfizer described a potential production process [30] and a feasibility study [31] using ligands, developed in-house (Scheme 7). The tcfp ligand was also successfully applied to the diastereoselective hydrogenation of a β-enamide ester for an intermediate of the α2δ ligand imagablin [32]. Eventually, 3.8 tons of the intermediate were produced with the process depicted in Scheme 8.

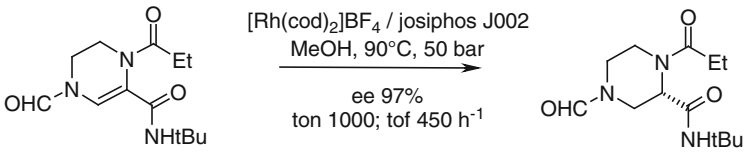
Zhang [33] showed that cationic Rh complexes can also be used to hydrogenate heteroaryl ketones with very high ee values and satisfactory activity. The Rh/duanphos catalyst was applied to the reduction of a duloxetine intermediate (Scheme 9). Duloxetine is a serotonin-norepinephrine reuptake inhibitor manufactured and marketed by Eli Lilly. Lonza [34] also reported on this transformation using a Rh/Me-duphos catalyst which achieved 97% ee but only moderate activity (ton 100, 20 h^{-1} at 50°C, 30 bar).



Scheme 9 Hydrogenate of a duloxetine intermediate (Eli Lilly)



Scheme 10 Production processes for aliskiren (Solvias, DSM, BASF)

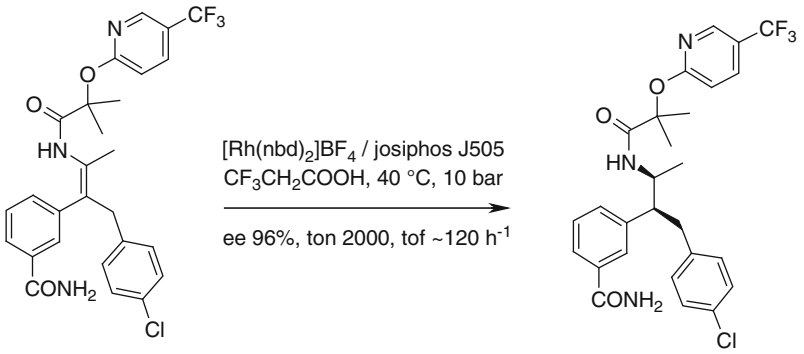


Scheme 11 Pilot process for crixivan intermediate (Lonza)

3.2 *In Situ-Prepared Cationic Rhodium Complexes*

In situ-prepared cationic Rh complexes are surprisingly effective for sterically hindered α,β-unsaturated acids or salts as shown in Scheme 10 for an intermediate of aliskiren (a novel renin inhibitor) developed by Speedel and produced now on large scale for Novartis. Few details have been released for the first process developed by Solvias [35] using a Rh/Walphos catalyst with very good enantioselectivities. DSM [36] has divulged results with a novel Rh/phosphoramidite/PPh_3 catalyst with somewhat lower enantioselectivity. BASF [37] patented a process starting from an *E*/*Z* mixture of the unsaturated acid using an isolated Rh/phanephos catalyst which requires very high pressures but still provides 86% ee.

2-Piperazinecarboxylic acid derivatives are interesting intermediates, e.g., for Crixivan, the well-known HIV protease inhibitor of Merck. The Rh/josiphos-catalyzed hydrogenation of a substituted cyclic enamide was used by Lonza [38] to produce >200 kg of the piperazine intermediate depicted in Scheme 11. A related catalyst was successfully employed by Merck [39] to pilot the hydrogenation of



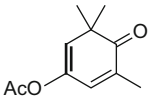
Scheme 12 Pilot process for taranabant intermediate (Merck)

a tetra-substituted enamide for the synthesis of the CB-1R inverse agonist taranabant on an 85-kg scale (Scheme 12).

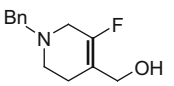
Several bench-scale applications for a variety of different starting materials using various diphosphines have been described as summarized in Fig. 5. Rh/Me-duphos was used for cyclic enol acetate by Roche [40]. Merck reported on the hydrogenation of a cyclic F–C=C–CH_2–OH building block [27], with Rh/walphos W003, a cyclic C=C bond [41] (Rh/josiphos J005), and a pyridine substitutes enamide [42] (Rh/tangphos). Lonza [38] described the Rh/J002-catalyzed hydrogenation of an exocyclic β-enamide acid, and Amgen [43] used Rh/J011 for a cyclic unfunctionalized C=C bond where the presence of the o–OH-group was essential for high ee values. The hydrogenation of a CF_3-substitued unsaturated acid was performed using Rh/W008 (Wyeth [44]). Rh/bophoz was used successfully by Eastman [45] for the synthesis of an α-amino acid, and a highly hindered enamide (an intermediate for the fungicide metalaxyl) was reduced with high ton by Ciba–Geigy [46] showing that it is possible to use in situ generated Rh/duphos catalysts. Recently, Boehringer Ingelheim [47] published results for the hydrogenation of a cathepsin S intermediate using either duanphos or the proprietary P^N ligand bipi on a 2–3 kg scale. The second C=C bond was then hydrogenated using a heterogeneous Pd/C catalyst. Roche demonstrated that in situ formed cationic Rh complexes can also used for the reduction of α-keto acids [40] (the C=C bond is hydrogenated as well) and a bis-heteroaryl ketone [48].

3.3 In Situ-Prepared Neutral Rhodium Complexes

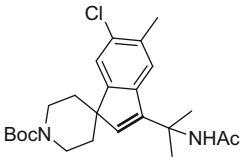
$[Rh(cod)Cl]_2$ is the complex of choice for the in situ preparation of very versatile catalyst precursors for a number of quite challenging transformations. In the course of the development of a new technical synthesis at Lonza [38] for biotin, a water-soluble vitamin, the Rh/Josiphos-catalyzed diastereoselective hydrogenation of a tetrasubstituted C=C bond was the key step (Scheme 13). The enantioselective hydrogenation (N-benzyl instead of N-(*R*)-phenethyl)) afforded the desired



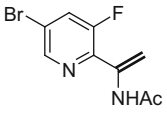
$[Rh(cod)_2]BF_4$ / Me-duphos
EtOAc, 20°C, 10 bar
ee 98%, ton 20,000, tof 5000 h^{-1}
Roche



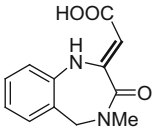
$[Rh(cod)_2]BF_4$ / walphos W003
MeOH, 55 °C, 6 bar
ee >98%, ton 1000, tof ~200 h^{-1}
Merck



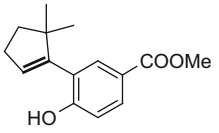
$[Rh(cod)_2]BF_4$ / josiphos J005
THF, 40 °C, 30 bar
ee 88%, ton 100, tof ~5 h^{-1}
Merck



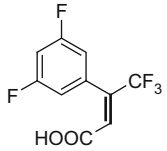
$[Rh(cod)_2]BF_4$ / tangphos
MeOH, 25 °C, 7 bar
ee 99%, ton 300, tof ~70 h^{-1}
Merck



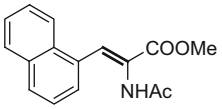
$[Rh(cod)_2]BF_4$ / josiphos J002
MeOH, 45 °C, 4 bar
ee 99%, ton 2300, tof ~700 h^{-1}
Lonza



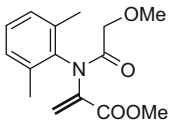
$[Rh(cod)_2]BF_4$ / josiphos J011
THF, NEt_3, 20 °C, 15 bar
ee 99%, ton 1000, tof ~60 h^{-1}
Amgen



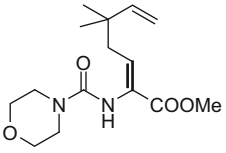
$Rh(nbd)_2]BF_4$ / walphos W008
MeOH, rt, 3 bar
ee >99%, ton 200, tof ~9 h^{-1}
Wyeth



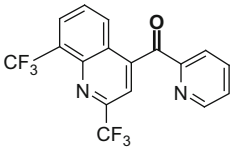
$[Rh(nbd)_2]CF_3SO_3$ / bophoz
toluene, rt, 1 bar
ee 98%, ton 2000, tof ~160 h-1
Eastman



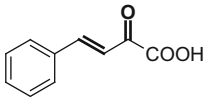
$[Rh(nbd)_2]BF_4$ / Me-duphos
60°C, 10 bar
ee 96%, ton 50,000; tof 5200 h^{-1}
Ciby-Geigy



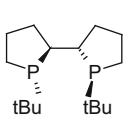
$[Rh(nbd)_2]BF_4$ / bipi or duanphos
MeOH/MeTHF, rt ~ 5 bar
ee 96-99%, ton 1400, tof ~50 h^{-1}
Boehringer-Ingelheim



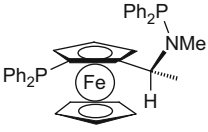
$[Rh(cod)_2]BF_4$ / biphemp
toluene, 60°C, 60 bar
ee 92%, ton 6400, tof 320 h^{-1}
Roche



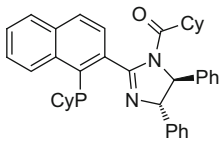
$[Rh(cod)_2]BF_4$ / bppfoh
THF, NEt_3, 80°C, 100 bar
ee 87%, ton 2000, tof 90 h^{-1}
Roche



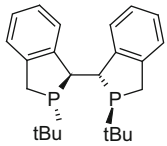
tangphos



bophoz
(Johnson Matthey)

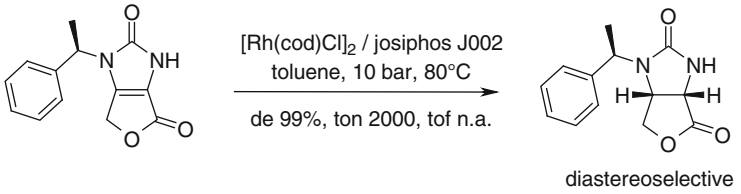


bipi

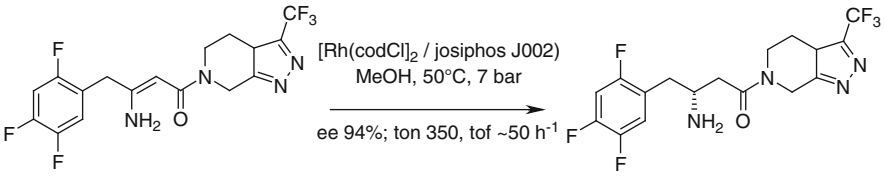


duanphos
(Chira Quest)

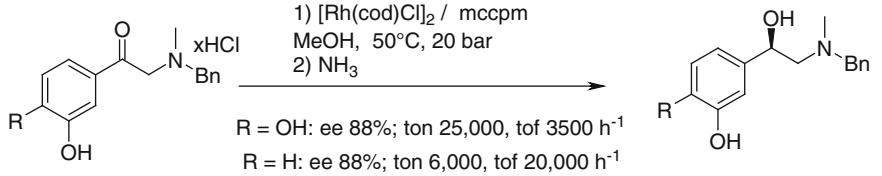
Fig. 5 Bench-scale applications of in situ-prepared cationic diphosphine complexes



Scheme 13 Diastereoselective hydrogenation of tetra substituted C=C bond (new biotin synthesis, Lonza)



Scheme 14 Production process for sitagliptin (Merck)

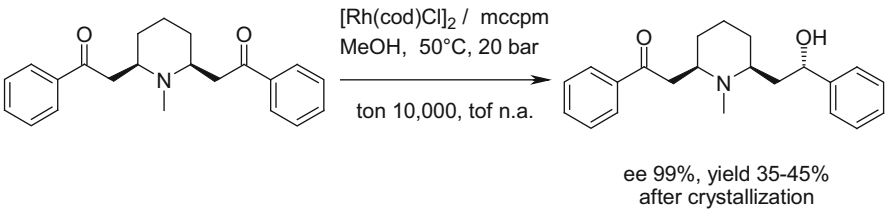


Scheme 15 Production processes for adrenaline and phenylephrine (Boehringer Ingelheim)

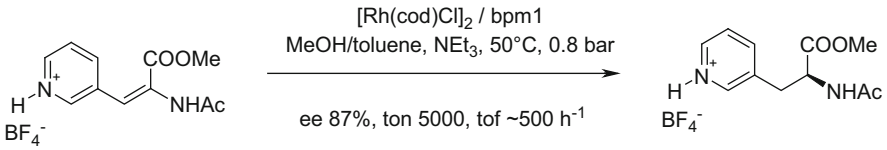
enantiomer with up to 90% ee. For the production process the diastereoselective variant was chosen and for a few years several tonnes per year were manufactured.

In the course of developing a production process for sitagliptin, Merck [49] developed the unprecedented and rather exciting hydrogenation of an unprotected dehydro β-amino acid as depicted in Scheme 14. The process is now used in regular production. Interestingly, deuteration experiments indicate that it is not the enamine C=C bond which is reduced but the tautomeric imine! In collaboration with Takasago [50], it was also demonstrated that a Ru/dm-segphos catalyst is suitable for reductive amination starting from the corresponding b-keto amide in presence of ammonium salicylate with ees up to 99% but relatively low activity (ton 100, tof ~6 h^{-1}).

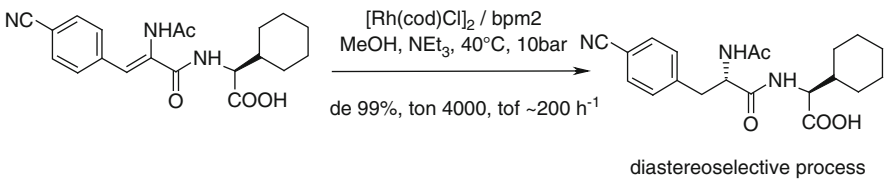
Production processes using α-amino ketone as substrates were developed by Boehringer Ingelheim [51] to improve on existing resolution syntheses for adrenaline (R=OH) and phenylephrine (R=H) as shown in Scheme 15. Unfortunately, little details are available but both processes are carried out on medium scale with a Rh/mccpm catalyst with very high tons and tofs, albeit with medium ees of 88% which increase to >99% after precipitation of the free base. A process using the same catalyst was developed for the reduction of a related bis-arylketone to produce lobeline (Scheme 16). To prevent over-hydrogenation, the reaction has to be stopped after a hydrogen uptake of 100–120% of theory.



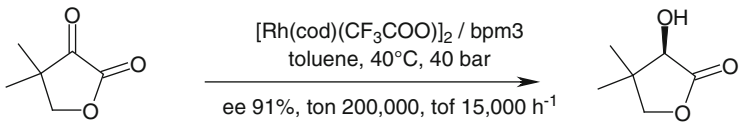
Scheme 16 Small scale process for lobeline (Boehringer Ingelheim)



Scheme 17 Pilot synthesis of factor Xa – inhibitor HMR 2906 (Höchst)



Scheme 18 Pilot synthesis of thrombin antagonist CRC 220 (Höchst)



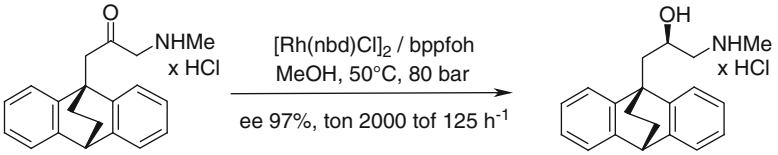
Scheme 19 Keto pantolactone hydrogenation (Roche)

Höchst [52] described the pilot synthesis of two quite complex α-amino acid derivatives for HMR 2906 (a factor Xa-inhibitor, Scheme 17) and for thrombin antagonist CRC 220 [53] (Scheme 18, formally a diastereoselective reaction) using Rh/bpm catalysts.

Roche [54] described a very efficient hydrogenation of keto pantolactone, an intermediate for pantothenic acid, carried out on multi-100-kg scale also using a Rh/bpm complex (Scheme 19). Success factors were the careful ligand fine tuning and the selection of the right anion which had an unusually strong effect both on enantioselectivity and catalytic activity.

Ciba–Geigy [55] developed a pilot process for levoprotiline (an antidepressant), carried out on a multi-10-kg scale using a Rh/bppfoh catalyst (Scheme 20). Also described is the large scale synthesis of the chiral ligand.

Bench-scale processes (see Fig. 6) were described by Höchst [53] for the synthesis of a thiophene-containing α-amino acid derivative for a bradykinin



Scheme 20 Pilot process for levoprotiline (Ciba-Geigy)

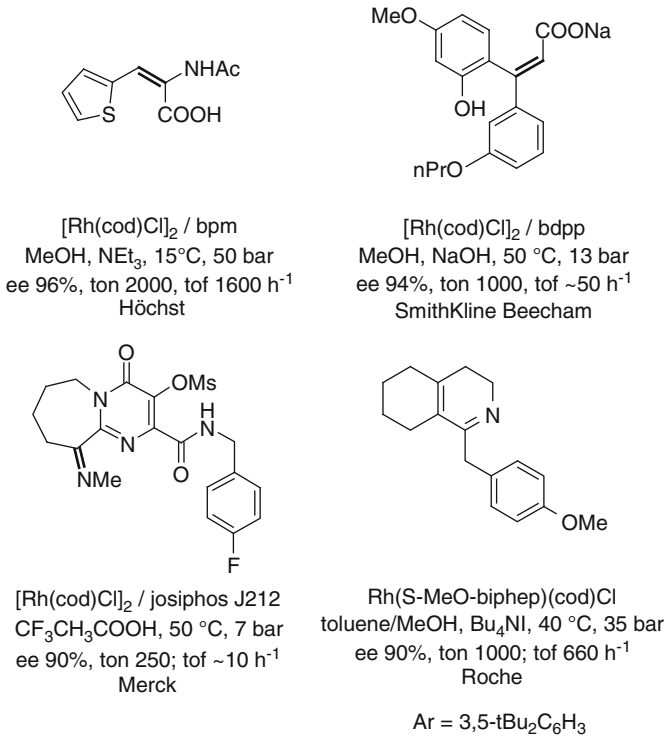


Fig. 6 Bench-scale applications of neutral diphosphine complexes

antagonist, by SmithKline Beecham [56] for an α,β-unsaturated acid for an endothelin receptor antagonists and by Merck [57] to reduce an exocyclic imine to C=N, to obtain an intermediate for a HIV integrase inhibitor. Finally, Roche [58] used an isolated Rh/MeO-biphep complex for the hydrogenation of a cyclic imine for an alternative synthesis of dextromethorphan, an antitussive agent.

3.4 Rhodium Complexes for Transfer Hydrogenation

Under the trade name CATHy, Avecia ([59] and references therein) developed and is now marketing a transfer hydrogenation technology. Among the most useful

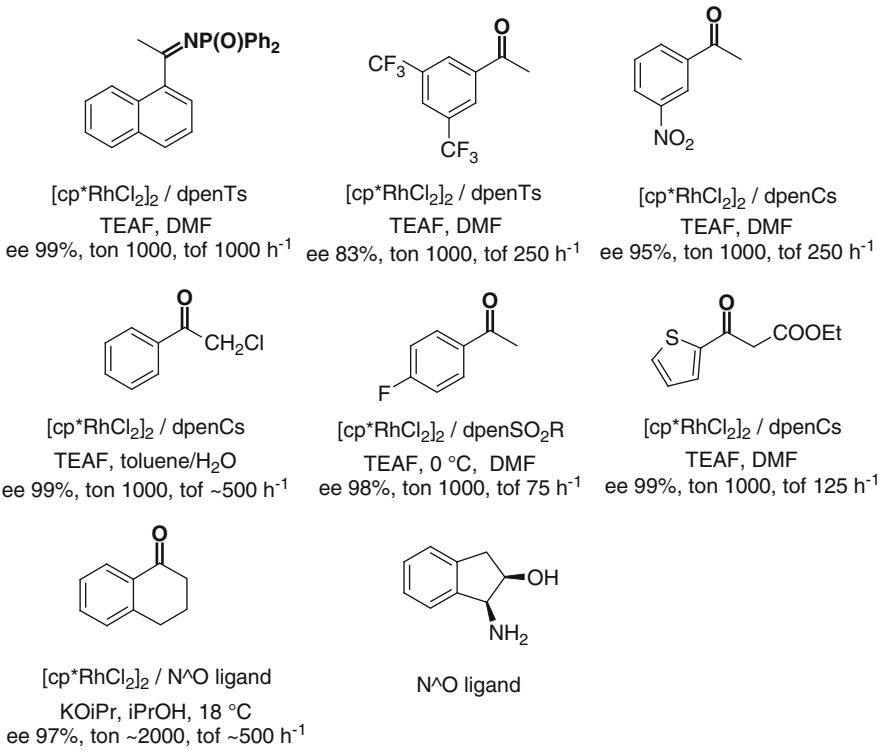
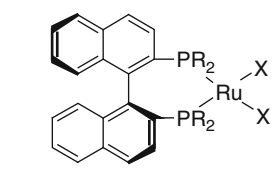


Fig. 7 Large scale applications of the CATHy reducing system

catalysts are complexes prepared from $[Rhcp^*Cl_2]_2$ and a monosulfonamide prepared from diphenyl ethylene diamine and a sulfonyl chloride which are quite active and stereoselective for the transfer hydrogenation for various C=O and C=N bonds using a formic acid/Et_3N mixture. As can be seen from Fig. 7, ee values are usually very high with a ton of 1,000. In some cases, the use of an N^O ligand with iPrOH in presence of KOiPr as reducing agent is also feasible. Most of these reactions were carried out on a scale of up to 200 kg.

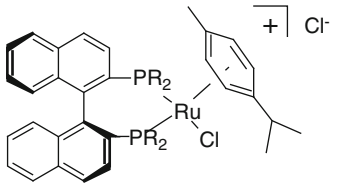
4 Ruthenium-Catalyzed Hydrogenation Reactions

While already Wilkinson successfully used Ru phosphine complexes for hydrogenation, activity was clearly inferior to the Rh catalysts, and only marginal enantioselectivities could be achieved. This changed drastically with the seminal discovery by Noyori and coworkers [60] that Ru complexes with the newly developed binap ligand were highly active and enantioselective for hydrogenation reactions.

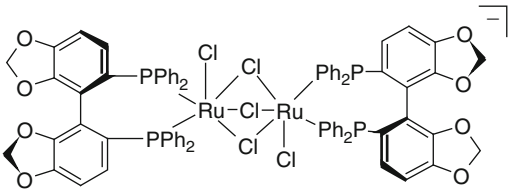


Ru(*S*-binap)X_2

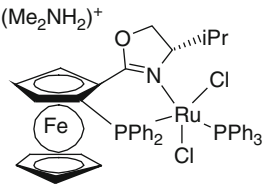
X = OAc, Cl, CF_3COO, Me-allyl



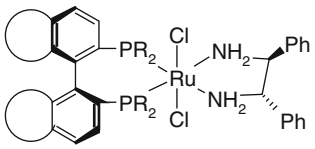
[Ru(*S*-binap)(p-cymene)Cl]Cl



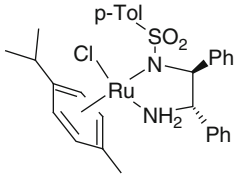
[(Ru(*R*-segphos)Cl)$_2$(μCl)$_3$](Me_2NH_2)



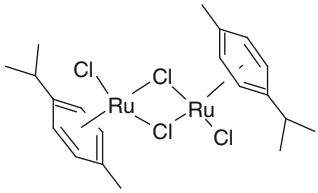
Ru(N003)(PPh_3)Cl_2



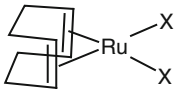
RuP^P(*S,S*-dpen)Cl_2



Ru(*S*-dpenTs)(p-cymene)Cl]



[Ru(p-cymene)Cl_2]$_2$



Ru(cod)X_2

X = CF_3CO_2, Me-allyl

Fig. 8 Structure (selected ligands) and formula of most frequently used Ru precursor complexes

In comparison to Rh, the chemistry of Ru is more complex, and a broader variety of Ru precursors has actually been used on a regular basis (see Fig. 8). On the other hand, with some notable exceptions, only atropisomeric biaryl diphosphines, all inspired by binap, have led to effective catalysts. Much of this chemistry has been developed by the Noyori group, some of it in collaboration with Takasago [61]. For these Ru diphosphine complexes, the presence or absence of either chloride or bromide ions dominates their catalytic properties. Halides containing Ru complexes

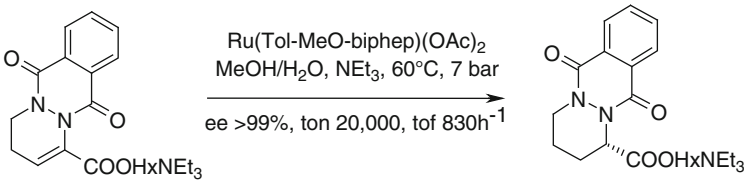
are active for the hydrogenation of ketones and several preformed, isolated precursor complexes are used regularly: $Ru(P\text{^}P)Cl_2$ (sometimes as NEt_3 adduct), [Ru(P^P)(arene)Cl]Cl, $Ru(P\text{^}P)(diamine)Cl_2$, $Ru(P\text{^}N)(PPh_3)Cl_2$, and a $[(Ru(P\text{^}P)Cl)_2(\mu\text{-}Cl)_3](Me_2NH_2)$ complex. For the hydrogenation of C=C bonds, $Ru(P\text{^}P)(OAc)_2$ and $Ru(P\text{^}P)(CF_3CO_2)_2$ are used predominantly. For the relatively rare cases of in situ formed catalysts, $[Ru(p\text{-}cymene)Cl_2]_2$ and $Ru(cod)X_2$ (X=Me-allyl or CF_3CO_2) are applied. Finally, Ru(dpenTs)(p-cymene)Cl complexes are being used for transfer hydrogenations.

4.1 Isolated Ruthenium Diphosphine Complexes

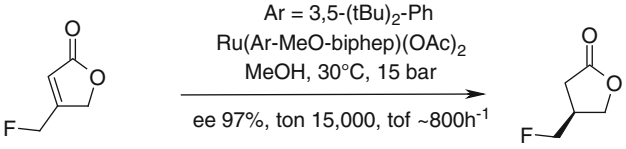
4.1.1 $Ru(P\text{^}P)(OAc)_2$ Complexes

Several pilot processes were reported by Roche using these relatively simple Ru precursor complexes. The synthesis of an intermediate for cilazapril [54], an HIV protease inhibitor (Scheme 21) as well as the hydrogenation of unsaturated lactone [62] (Scheme 22) were carried out on a multi-10-kg scale. Both processes have high enantioselectivities as well as turnover numbers. A continuous process was developed for an intermediate of mibefradil [63] (calcium antagonist); critical issues were the very high pressure necessary for high ee values as well as the catalytic activity for this tetrasubstituted C=C bond (Scheme 23).

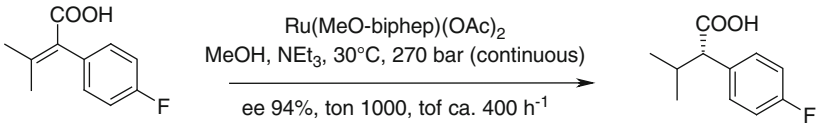
Processes for the reduction of an α-aminoketone [64] (for the experimental obesity agent Ro 40-2148) and of an β-ketoester [65], an intermediate for Orlistat (also for treating obesity), are summarized in Schemes 24 and 25, respectively. While enantioselectivities were quite high, the aminoketone required a relatively high catalyst loading, maybe due to the absence of halide. For the reduction of the



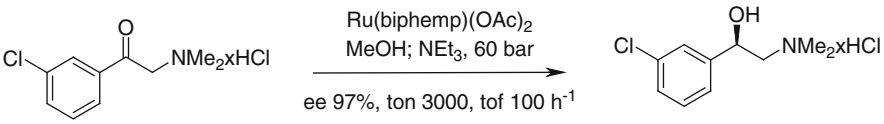
Scheme 21 Synthesis of for cilazapril intermediate (Roche)



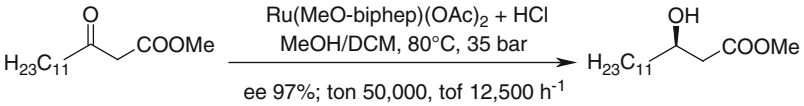
Scheme 22 Hydrogenation of unsaturated lactone (Roche)



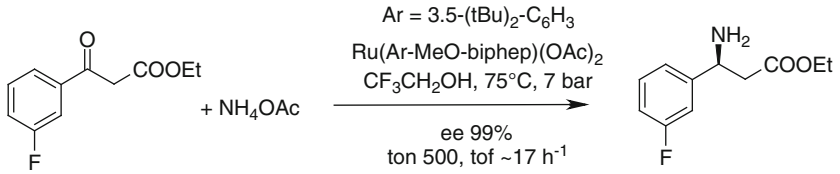
Scheme 23 Continuous process for an intermediate of mibefradil (Roche)



Scheme 24 Process for obesity agent Ro 40-2148 (Roche)



Scheme 25 Synthesis of orlistat intermediate (Roche)



Scheme 26 Reductive amination for a CCR5 receptor antagonist (Roche)

β-ketoester, where the halide was added in situ, a ton of 50,000 was achieved and 2,200 kg of the intermediate were produced.

Roche [66] was also successful in implementing a quite rare reductive amination reaction for the synthesis of a CCR5 receptor antagonist using ammonium acetate as nitrogen source (Scheme 26). While catalyst activity was on the low side, excellent ee was achieved.

Bench-scale processes for a variety of alkene hydrogenations described by several companies are presented in Fig. 9. With the exception of the hydrogenation of α,β-unsaturated acid by Roche [64] for the hydrogenation of a Ro 42-5892 intermediate (renin inhibitor) and the naproxen process, the C=C bonds do not carry the typical substituents leading to high enantioselectivities. The process described for naproxen, a large-scale anti-inflammatory drug, by Takasago [67] could not compete with the classical resolution process. Takeda [68] successfully reduced an exocyclic C=C–CH_2–NHCOR moiety, albeit with very modest ton to obtain an intermediate for ramelteon, a hypnotic agent and Roche [69] described the reduction of an unsaturated lactone, also an intermediate for orlistat.

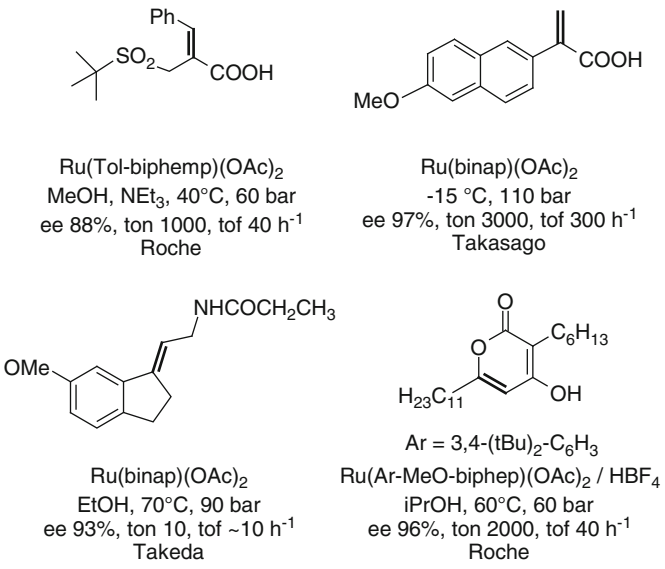
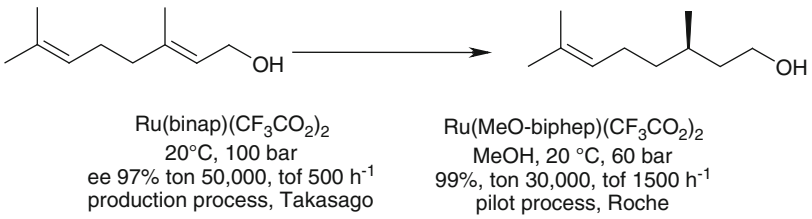


Fig. 9 Bench-scale applications of Ru(P^P)$(OAc)_2$



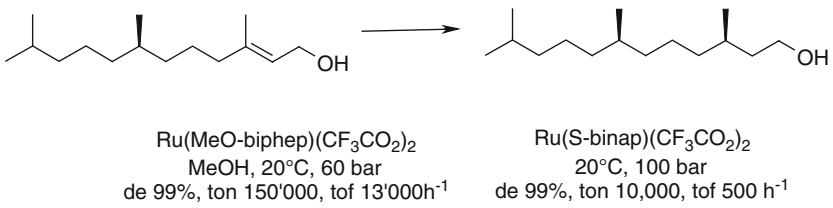
Scheme 27 Citronellol syntheses (Takasago, Roche)

4.1.2 Ru(P^P)$(CF_3CO_2)_2$ Complexes

As shown in Scheme 27, citronellol, a fragrance as well as an intermediate for vitamin E, can be prepared starting with geraniol. This transformation, carried out by Takasago [70] on a 300-t/year scale is highly chemoselective. Roche [71] has reported a pilot process for the same reaction and in a recent feasibility study, Chiral Quest [72] claimed 98% ee and 100,000 turnovers with a Ru/tunephos catalyst.

Pilot processes with similar catalyst performances were developed by Roche [71] as well as Takasago [73] for the longer chain vitamin E intermediate depicted in Scheme 28. The existing stereogenic center is too far removed to affect the stereoselectivity of the catalysts.

A number of bench-scale applications of Ru(P^P)$(CF_3CO_2)_2$ complexes were also reported as summarized in Fig. 10. Roche [54] succeeded in the chemoselective C=C hydrogenation of an unsaturated ketone (a vitamin E intermediate)



Scheme 28 Processes for vitamin E intermediate (Takasago, Roche)

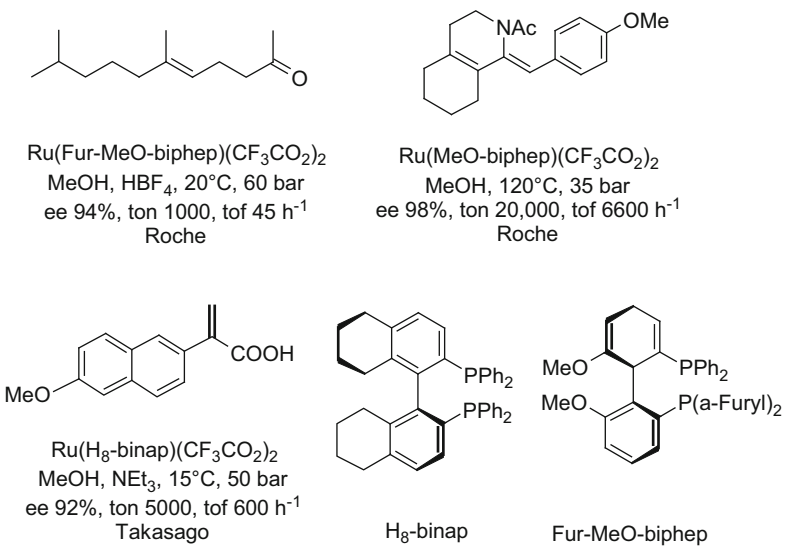


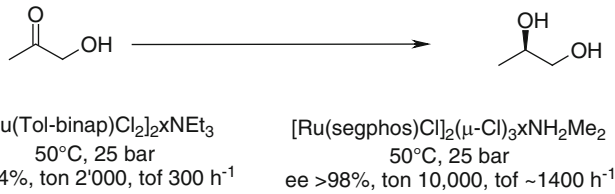
Fig. 10 Bench-scale applications of Ru(P^P)$(CF_3CO_2)_2$ complexes

with an unusual unsymmetrical MeO-biphep ligand as well as of an exocyclic enamide, an intermediate for the antitussive dextromethorphan. Takasago [67] described an improved naproxen hydrogenation without the need of low temperature (compare result in Fig. 9).

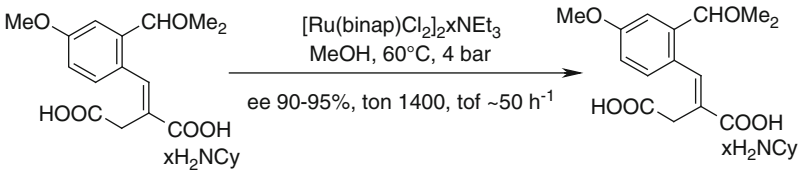
4.1.3 Ru(P^P)Cl_2 Complexes and Analogs

(*R*)-1,2-propanediol is an intermediate for (*S*)-oxfloxazin, a bactericide originally sold as racemate. The (*R*) diol is produced by Takasago [61] using a Ru/Tol-binap-catalyzed hydrogenation of 2-hydroxy acetone on a 50 t/year scale (Scheme 29). Recently, Takasago reported that segphos shows even better results [67].

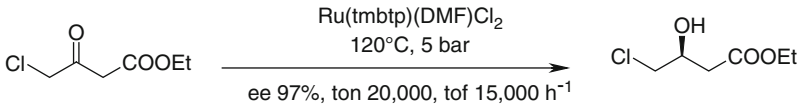
Processes on pilot scale were reported by GlaxoSmithKline [74] for a subsituted itaconic acid for a vitronectine receptor antagonist (Scheme 30) and by Chemi [75] for the hydrogenation of a chlorinated β-keto ester depicted in Scheme 31 applied



Scheme 29 Hydrogenation of (*S*)-oxfloxazin intermediate (Takasago)



Scheme 30 Synthesis of vitronectine receptor antagonist (GlaxoSmithKline)



Scheme 31 Hydrogenation of a chlorinated β-keto ester (Chemi)

on a multi-100-kg scale. Chiral Quest [76] has also claimed a technical process for this substrate as well as for other keto esters using [Ru(tunephos)(arene)Cl]Cl (ee 98–99% and ton up to 45,000).

A number of bench-scale processes are shown in Fig. 11. Merck described the hydrogenation of an α,β-unsaturated aryloxy acid [77, 78] and of a β-ketoester [79] as intermediate for the DPP-IV inhibitor sitagliptin MK-0431. Monsanto [80] also developed a process for naproxen (compare results in Figs. 9 and 10) and Roche [64] achieved the reduction of an α-ketoester for the Ro 40-2148 with remarkable ton of 2,000.

4.1.4 Ru(P^P)(arene)Cl_2 or [Ru(P^P)(arene)X]X Complexes

The hydrogenation/dynamic kinetic resolution shown in Scheme 32 for the production of a penem antibiotic intermediate is carried out by Takasago [72] on a scale of 50–120 t/year, and recently, it was reported that an optimized segphos ligand [81] can achieve even higher stereoselectivities. Similar results were claimed by Chemi [82] with a Ru/tmbtp catalyst.

The hydrogenation of the racemic homoallylic alcohol depicted in Scheme 33 is the key reaction for a new synthetic route for producing paroxetine as described

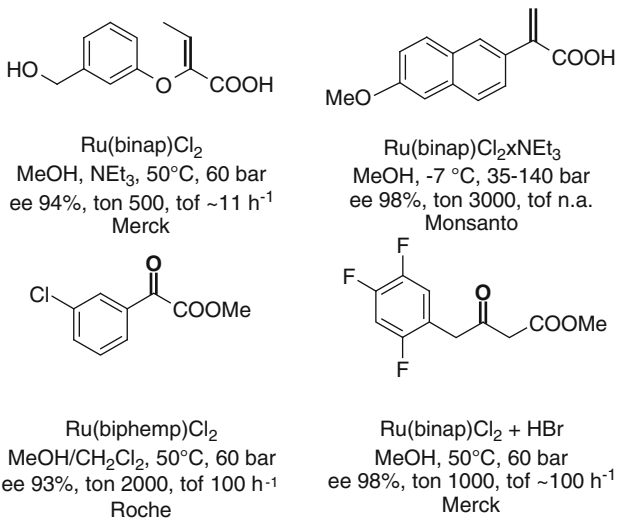
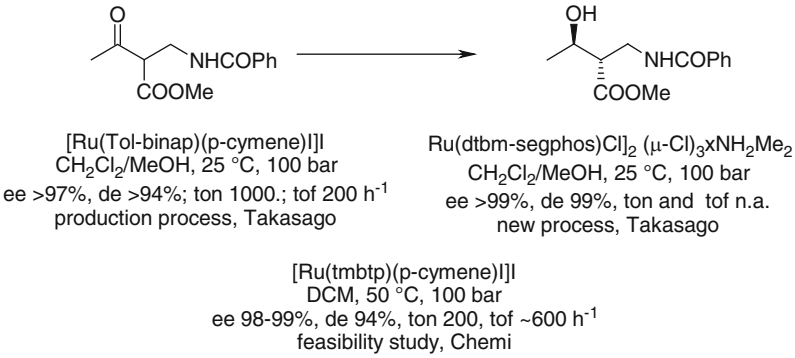
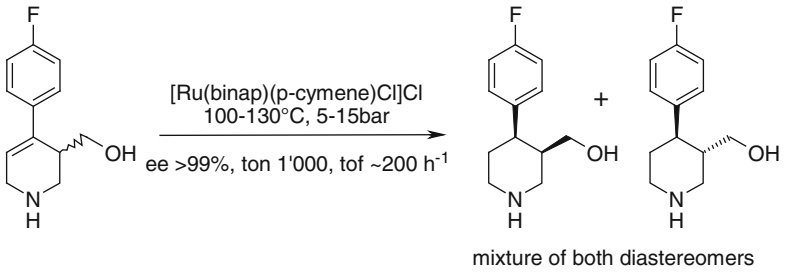


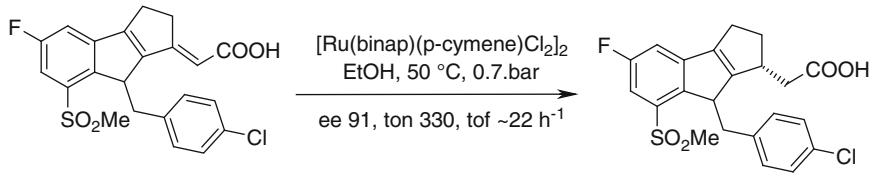
Fig. 11 Bench-scale applications of Ru(P^P)Cl_2 complexes



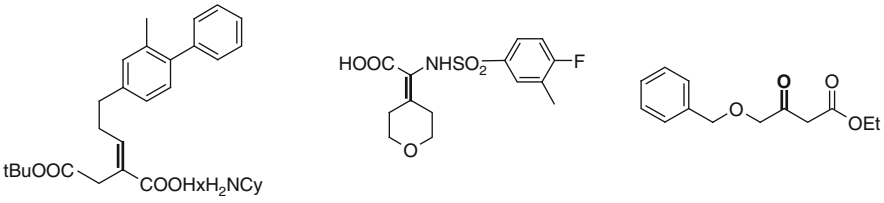
Scheme 32 Hydrogenation/dynamic kinetic resolution for a penem antibiotics intermediate (Takasago)



Scheme 33 Diastereoselective synthesis of paroxetine (Ricordati)



Scheme 34 Hydrogenation process for laropiprant Merck)



[Ru(binap)(p-cymene)Cl]Cl
MeOH, r.t., 4 bar
ee 88%, ton 1'000.; tof ~25h^{-1}
Pfizer

[Ru(josiphos J002)(p-cymene)Cl$_2$]xNEt$_3$
EtOH, 50 °C, 6 bar
ee 97%, ton 100, tof ~4 h^{-1}
Merck

[Ru(binap)(benzene)Cl]Cl
EtOH, 100°C, 4 bar
ee 98%; ton 2000; tof 30 h^{-1}
Höchst

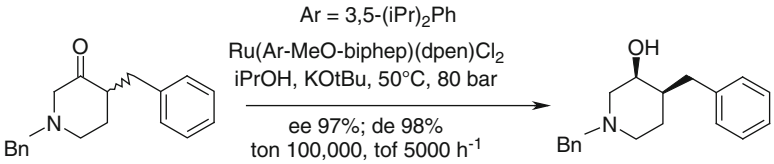
Fig. 12 Bench-scale applications of Ru(P^P)Cl$_2$ complexes

by Ricordati [83] and carried out on a 100-kg batch size. Merck [84] scaled up the process the hydrogenation of an α,γ-unsaturated acid, an intermediate for the prostaglandin D2 receptor antagonist laropiprant. It was shown that the hydrogenation takes place after migration of α,β-C=C bond into the 5-membered ring (Scheme 34).

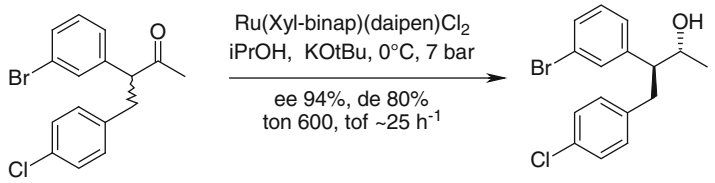
In addition to these pilot processes, a number of applications on the bench scale were described (see Fig. 12). Pfizer [85] obtained good results for a Rh/FerroTANE-catalyzed hydrogenation of a substituted itaconic acid for the synthesis of MMP-3 inhibitor UK 370,106 (ee 94%, ton 1,000) but in the end, chose a more robust Ru/binap catalyst for scale up. A similar catalyst was used by Höchst [56] for the hydrogenation of a β-ketoester for the HMG-CoA reductase inhibitor Glenvastatin HR 780 and a Ru/Josiphos catalyst was highly selective for the hydrogenation of an intermediate for an anthrax lethal factor inhibitor with a tetra substituted C=C bond reported by Merck [86].

4.1.5 Ru(P^P)(N^N)X$_2$ Complexes

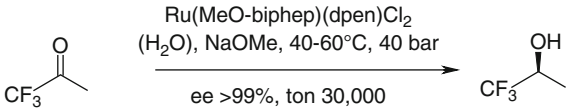
Ru/diphosphine/diamine were shown by Noyori (For a recent account see [87]) to be effective hydrogenation catalysts of ketones without α- or β-functionality. The absolute configurations of the P^P and N^N ligands have to be matched. The technology has been licensed by several companies using various biaryl diphosphines but it is not clear whether it is already used for concrete manufacturing purposes.



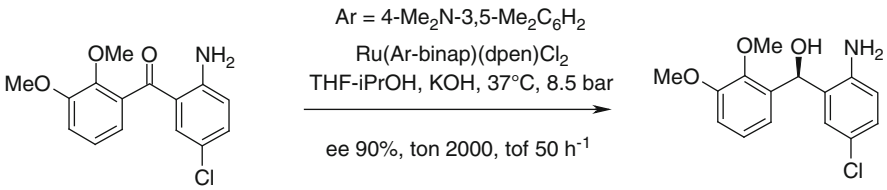
Scheme 35 Hydrogenation/dynamic kinetic resolution process for Ro 67-8867 (Roche)



Scheme 36 Hydrogenation / dynamic kinetic resolution process for taranabant (Merck)



Scheme 37 Process for glycine transport inhibitor intermediate (Roche)



Scheme 38 Synthesis of squalene synthase inhibitor TAK-475 (Takeda)

Roche [88] reported on a pilot process for an intermediate of the NMDA 2B receptor antagonist Ro 67-8867 involving the hydrogenation/dynamic kinetic resolution of a cyclic α-amino ketone using an optimized Noyori procedure with a MeO-biphep ligand (Scheme 35). The reaction was carried out on a 9-kg scale with excellent enantio- and diastereoselectivities and very high ton and tof. A similar reaction on a 65-kg scale was described by Merck [89] for an intermediate of the cannabbinoid-1 receptor inverse agonist CB-1R inverse agonist taranabant but with much lower selectivity and activity (Scheme 36).The hydrogenation of trifluoracetone depicted in Scheme 37 produced a building block for a glycine transport inhibitor and was carried out by Roche [65] on a >50-kg scale. Takeda [90] produced 34 kg of an intermediate for the squalene synthase inhibitor TAK-475 via the rather difficult hydrogenation of a benzophenone derivative with good enantioselectivity, probably due to the presence of an ortho-NH_2 group (Scheme 38).

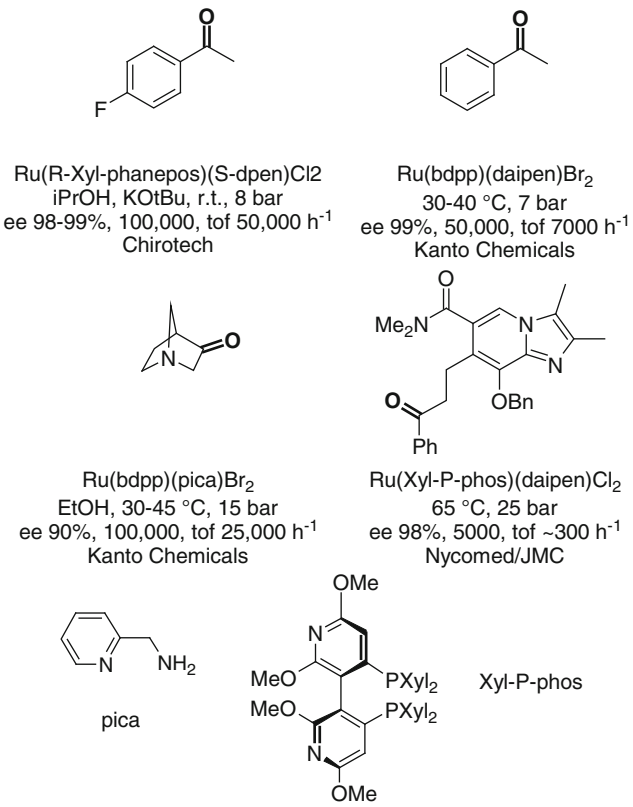
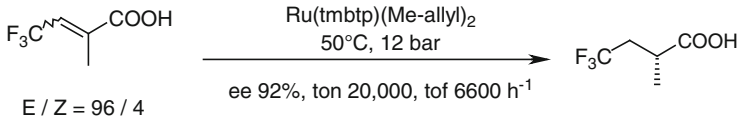


Fig. 13 Bench-scale applications of Ru(P^P)(N^N)X_2 complexes

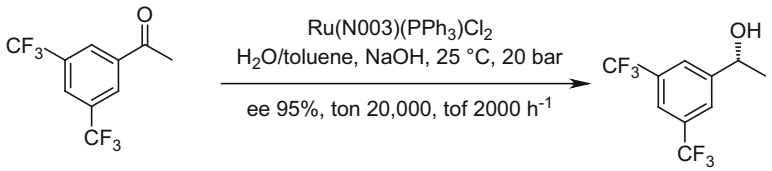
A number of bench-scale processes with Ru/P^P/N^N catalysts are summarized in Fig. 13. Dow/Chirotech [91] used Ru/Xyl-PhanePhos/dpen for the hydrogenation of p-fluoro acetophenone. Kanto Chemicals developed a very effective Ru/bdpp/N^N catalyst (the only case where the diphosphine is not a biaryl type) and applied it to the large scale hydrogenation of acetophenone [92] and of a quinuclidine [93] for a muscarinic receptor antagonist. Nycomed/JMC [94] scaled up the hydrogenation of rather complex ketone intermediate for the synthesis of a potassium competitive acid blocker.

4.1.6 Miscellaneous Ruthenium Complexes

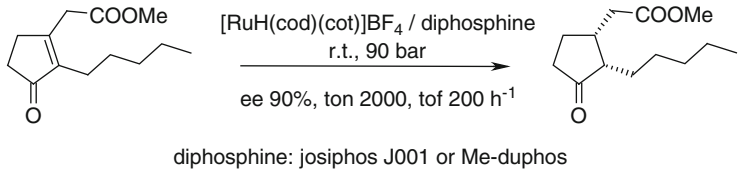
Two pilot process were described using other isolated Ru complexes: Chemi [75] reported the hydrogenation of a trifluoromethyl substituted unsaturated acid (E/Z mixture, see Scheme 39) carried out in a 4,000-l reactor on a 340-kg scale with Ru(tmbtp)(Me-allyl)$_2$. 3,5-$(CF_3)_2$-phenyl ethanol was produced by Solvias/Rohner



Scheme 39 Hydrogenation of a trifluoromethyl substituted unsaturated acid (Chemi)



Scheme 40 Synthesis of 3,5-$(CF_3)_2$-phenyl ethanol (Solvias/Rohner)



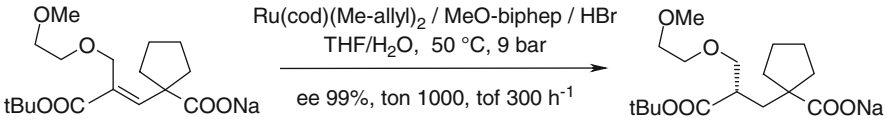
Scheme 41 Production process for cis methyl dihydrojasmonate (Firmenich)

[95] on a similar scale using a newly developed Ru/(phosphinoferrocenyl)oxazoline complex (Scheme 40). In both cases, satisfactory ee values and high tons were achieved.

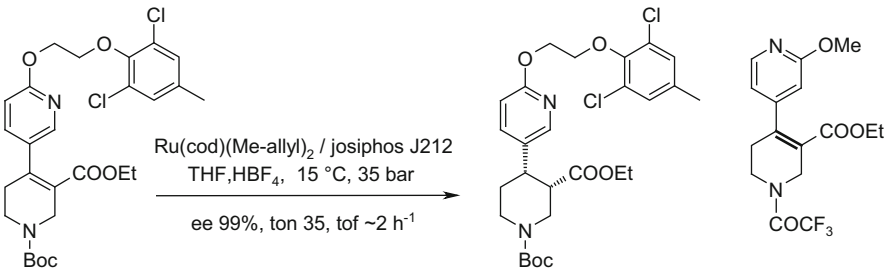
4.2 In Situ-Prepared Ruthenium Complexes

While the majority of Ru-catalyzed hydrogenation reactions are carried out using preformed and isolated diphosphine complexes, in situ preparation of the active catalyst is in some cases the preferred option. A case in point is the enantioselective hydrogenation of jasmonates developed by Firmenich [96] to produce cis methyl dihydrojasmonate, an aroma compound with a floral odor (Scheme 41) manufactured on a multi-t/year scale. Key to success was the development of special Ru precursor which is then reacted with the diphosphine of choice.

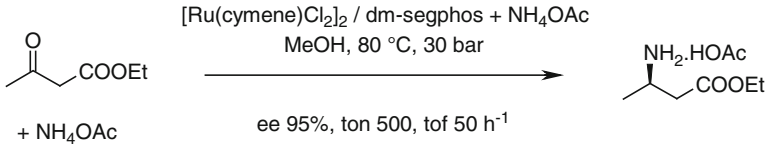
Ru(cod)(Me-allyl)$_2$ was employed as precursor by Chirotech [23] for the hydrogenation of the α,β-unsaturated ester shown in Scheme 42, an intermediate for candoxatril, a neutral endopeptidase inhibitor. The hydrogenation was also carried out on a 250-kg scale by PPG-Sipsy [97] with a Ru/MeO-biphep complex. Merck [98] developed a pilot process using a Ru/josiphos complex for the very difficult reduction of a tetrasubstituted C=C bond to produce the renin inhibitor



Scheme 42 Synthesis of candoxatril intermediate (Chirotech)



Scheme 43 Process for renin inhibitor MK-1597 (Merck)



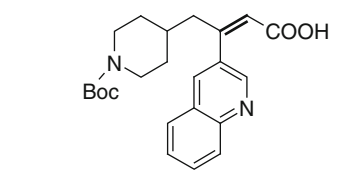
Scheme 44 Reductive amination of β-keto esters (Takasago)

MK-1597. A similar procedure was used for the hydrogenation of a close analog for a related renin inhibitor (ee 99%, ton 100, tof 20 h^{-1}) [99] (Scheme 43). A catalyst prepared in situ from $[Ru(cymene)Cl_2]_2$ and-dm-segphos in presence of NH_4OAc was used by Takasago [100] for the reductive amination of β-keto esters with very high enantioselectivities. The reaction shown in Scheme 44 was carried out on the 66-kg scale.

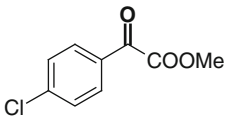
The bench-scale processes depicted in Fig. 14 were reported by JMC/J & J [101] for the hydrogenation of a β,γ-unsaturated acid (for an integrin agonists) and by Solvias/Syngenta [102] for the production of kg amounts of the fungicide intermediate *p*-chloro mandelic.

4.3 Ruthenium Complexes for Transfer Hydrogenations

This methodology using Ru/dpenTs complexes with $HCOOH/NEt_3$ as the reducing system was essentially developed by the Noyori group (for a recent account, see [87]) and is now widely used by synthetic chemists for the asymmetric reduction of ketones

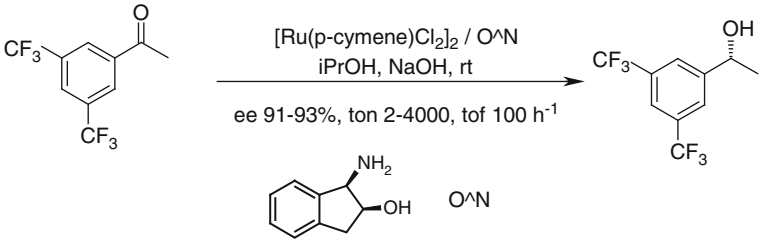


Ru(cod)$(CF_3COO)_2$ / Xyl-Phanephos / HOAc
MeOH, 50 °C
ee 96%, ton 1000, tof ~70 h^{-1}
J&J / JMC

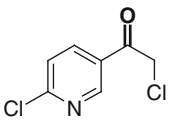


$[Ru(p\text{-cymene})I_2]_2$ / MeO-biphep
MeOH, HCl, 50 °C
ee 90-93%, ton 4000, tof 230 h^{-1}
Syngenta / Solvias

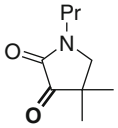
Fig. 14 Bench-scale applications of in situ-prepared Ru_2 complexes



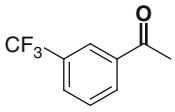
Scheme 45 Transfer hydrogenation of an aprepitant intermediate (Merck)



$Ru(p\text{-cymene})Cl_2$ / dpenTs
HCO_2H/NEt_3, rt
ee 96%, ton ~30, tof ~3 h^{-1}
Pfizer



Ru(dpenTs)(p-cymene)Cl
$HCO_2H/(iPr)_2NEt$, 20-25°C
ee 92-95%, ton 500, tof ~20 h^{-1}
Pfizer



Ru(dpenTs)(p-cymene)Cl
HCO_2H/NEt_3, 50 °C
ee 95%, ton 5000, tof 160 h^{-1}
Mitsubishi

Fig. 15 Bench-scale applications of Ru-catalyzed transfer hydrogenations

and imines since the procedure is robust and reliable. A second variant is based on Ru/amino alcohol complexes with *i*PrOH/base as reducing system. Several transfer hydrogenations have been applied on scales up to 10 kg. Merck [103] described a pilot process for an intermediate of the NK1 receptor antagonist aprepitant (Scheme 45), Pfizer used transfer hydrogenation to prepare a β-3 antagonist [104] and to reduce N-Pr pantolactam [105], and Mitsubishi [106] reduced a ketone fungicide intermediate on the bench scale (Fig. 15). In general, tons and tofs are lower compared to reactions using hydrogen.

5 Iridium-Catalyzed Hydrogenation Reactions

In comparison to Rh and Ru catalysis, Ir-catalyzed hydrogenation developed much later and still is used much less in industry. The discovery by a Ciba–Geigy team [107] that Ir catalysts are superior to Rh and Ru for the hydrogenation of N-aryl imines, culminating in the development of the (*S*)-metolachlor process (see below) gave Ir catalysis a strong boost.

With one exception, the same Ir complexes precursors as for Rh are used (compare Fig. 3): neutral or cationic bis-diene Ir(I) complexes with Cl^- or BF_4^- as anion, respectively, preformed diene-diphosphine complexes, and [cp*Ir(III)$Cl_2]_2$ for transfer hydrogenations. The exception are the cationic [Ir(cod)P^N)]X (X=BF_4, SbF_6 and BARF) complexes depicted in Fig. 16 which are the catalyst of choice for the highly enantioselective hydrogenation of unfunctionalized C=C bonds [108]. The choice of X is important for good catalyst stability and BARF is the preferred anion.

The most important application of Ir catalysis is for the manufacture of (*S*)-metolachlor. Racemic metolachlor is the active ingredient of Dual®, one of the most important grass herbicides for use in maize and a number of other crops. In 1997, after years of intensive research, Dual Magnum® with a content of approximately 90% (1'S)-diastereomers and with the same biological effect at about 65% of the use rate was introduced by Ciba–Geigy in the USA and is now produced by Syngenta on a scale of >10,000 t/year [109]. This "chiral switch" was made possible by the new technical process that is briefly described below. Key step of this new synthesis is the enantioselective hydrogenation of the isolated MEA imine shown in Scheme 46.

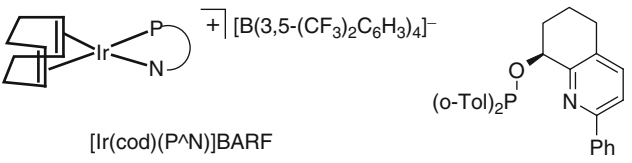
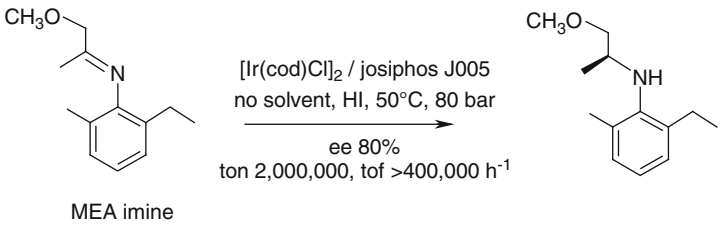
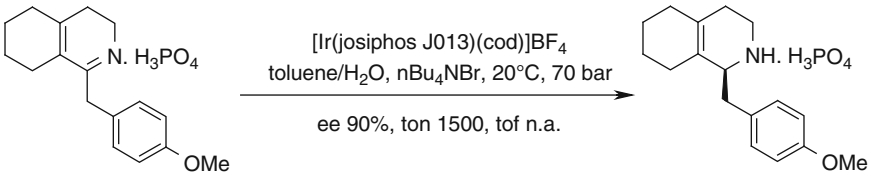


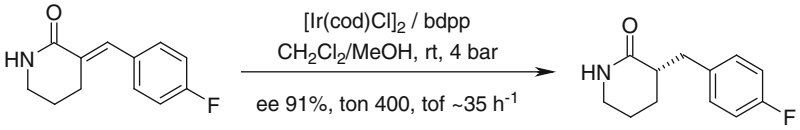
Fig. 16 Structure of Ir/P^N complexes and an example of an effective P^N ligand



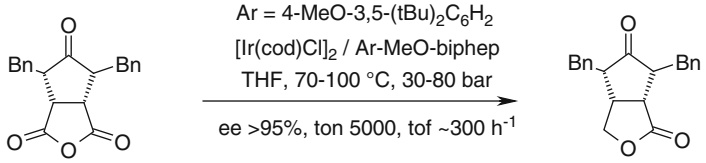
Scheme 46 Production process for (*S*)-metolachlor (Ciba-Geigy/Syngenta)



Scheme 47 Hydrogenation of a dextromethorphan intermediate (Lonza)



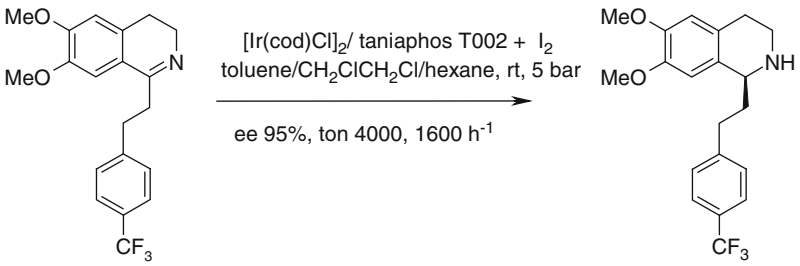
Scheme 48 Synthesis of a lactame pharmacaphore (Bristol-Meyers Squibb)



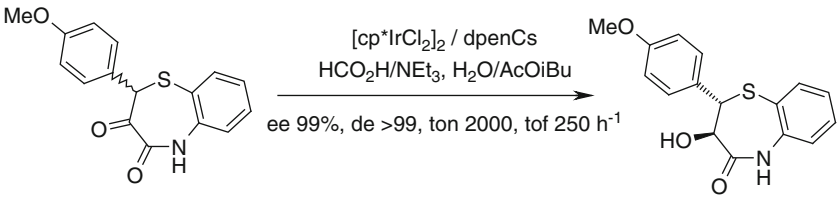
Scheme 49 Reduction of a cyclic anhydride (new biotin synthesis, DSM/Solvias)

The search for a commercially viable process took many years. Several approaches with Rh or Ir complexes using diphosphine ligands commercially available at the time were not successful. A critical breakthrough was achieved using Ir complexes of a new class of ferrocenyl-based ligands, now called Solvias Josiphos ligands. In presence of acid and iodide ions extremely active and productive, catalysts were obtained [110]. The optimized process operates at 80 bar hydrogen and 50°C with a catalyst generated in situ from $[Ir(cod)Cl]_2$ and the Josiphos ligand J005 at a substrate to catalyst ratio (s/c) of 2 Mio. Complete conversion is reached within 3–4 h, the initial TOF exceeds 1,800,000 h^{-1}, and enantioselectivity is approximately 80%.

After this success, Ir catalysts were employed more often, and it was shown that besides imines, C=O as well as C=C bonds could be hydrogenated with good success. The hydrogenation depicted in Scheme 47 was developed by Lonza [38] for an intermediate of dextromethorphan and carried out on >100-kg scale. Important success factors were the ligand fine tuning and the use of a biphasic system. Chemoselectivity is high but catalyst productivity rather low for an economical technical application. Bristol-Meyers Squibb [111] achieved the first case of Ir diphosphine-catalyzed hydrogenation of a C=C bond to prepare a lactam pharmacaphore on a 20-kg scale (Scheme 48). DSM [112] in collaboration with Solvias developed a new route for biotin, based on the unprecedented reduction of



Scheme 50 Process for almorexant intermediate (Actelion)



Scheme 51 Transfer hydrogenation for a diltiazem intermediate (Avecia/Piramal)

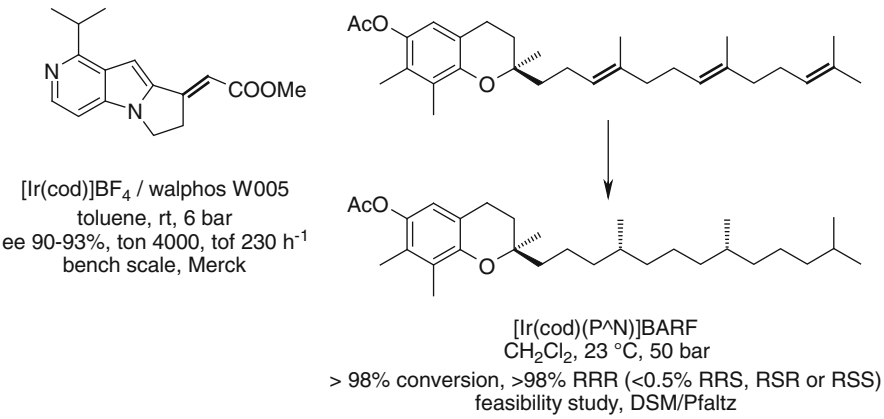


Fig. 17 Ir-catalyzed C=C hydrogenations

a cyclic anhydride as key step (Scheme 49). The process was already used to manufacture several tons of biotin. Actelion [113] in collaboration with DSM and Solvias developed the hydrogenation process depicted in Scheme 50 for an intermediate of Almorexant, a dual orexin receptor antagonist.

A transfer hydrogenation was piloted by Avecia/Piramal ([59] and references therein) for an intermediate of diltiazem, a Ca-antagonist marketed by Pfizer (Scheme 51). The catalyst was prepared in situ from $[cp^*IrCl_2]_2$ and dpenCs and very high stereoselectivity was achieved.

Table 2 Most often used catalyst systems

Catalyst system	C=C	C=O	C=N
Cationic Rh complexes[a] [Rh(PP)(diene)]X or [Rh(diene)$_2$]X + PP	29	3	–
Neutral Rh complexes[b] Rh(PP)(nbd)Cl or Rh(diene)$_2$X + PP	6	7	1
(cp*RhCl$_2$)$_2$ + dpenSO$_2$R	–	6 (TH)	1 (TH)
Ru complexes without halogen[c] Ru(PP)X$_2$ or Ru(diene)X$_2$ + PP	19	3	–
Halogen containing Ru complexes[d] Ru(PP)X$_2$ or [Ru(PP)(arene)X]X	–	9	–
Ru(PP)(NN)Cl	–	7	–
Ru(p-cym)(dpenTs)Cl or [Ru(p-cym)Cl$_2$]$_2$ + O^N		4 (TH)	
Ir complexes	2	1 (TH)	3

[a]Diene: cod or nbd, X: BF_4, CF_3SO_3, PF_6
[b]Diene: cod or nbd, X: Cl, CF_3CO_2
[c]X: OAc, Me-allyl, Cl, CF_3CO_2
[d]X: Cl, Br, I

A bench-scale process was reported by Merck [114] for the hydrogenation of an α,β-unsaturated ester (Fig. 17) for the synthesis of a D2 (DP) receptor antagonist and operated on a 5-kg scale. The potential of Ir/P^N catalysts was demonstrated in a feasibility study by DSM in collaboration with Pfaltz [115] for the hydrogenation of γ-tocotrienyl carried out with the pyridinyl phosphinite depicted in Fig. 16. The hydrogenation of the two prochiral C=C bonds occurs with excellent stereoselectivity to give almost exclusively the (*R*,*R*,*R*) product. The existing stereogenic center does not influence the reaction.

6 Conclusions

Since the first production processes have been implemented by Monsanto and Takasago, the number of production processes has grown only slowly and comprises today (only) about 15–20 entries. Of these, 11 are medium to large scale, all other are applied on a scale of 1 t/year or less and several of them are no longer in operation. In addition, many more processes developed to the pilot or bench scale are in principle ready for technical application but will probably not be implemented because the product has not made it to the market.

As can be seen from Table 2, there are some trends as to which type of complex is most often used for the hydrogenation of C=C, C=O and C=N bonds. The hydrogenation of alkenes is preferentially catalyzed by cationic Rh catalysts or with Ru complexes without halogen anions. There is no discernable correlation between the substitution pattern of the C=C bond and the best catalyst type. Ketones substituted (or activated) in α- or β-position usually require the presence of a Ru

halogen complex and Ru(PP)(NN)Cl is the catalyst of choice for nonfunctionalized ketones. Ir complexes are still rarely applied but are most suitable for the hydrogenation of C=N bonds.

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Case Study: Sequential Pd-Catalyzed Cross-Coupling Reactions; Challenges on Scale-Up

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Abstract A stereospecific synthesis of the drug-candidate **13** is described. The synthetic sequence, aimed at accomplishing modularity and cost savings, features a series of organometallic reactions that afford stereospecifically the desired trisubstituted olefin active pharmaceutical ingredient. Key developments comprise of a mild Sonogashira reaction of aryl bromide **14a** with the polymerization prone propargyl alcohol, a stereospecific hydroalumination and Pd/C-catalyzed Suzuki coupling reactions. Details are given of the scale-up optimization studies.

Keywords Heterogeneous palladium Suzuki coupling · Hydroalumination · Palladium removal methods · Sonogashira reaction · Trisubstituted olefin synthesis

Contents

1 Introduction

In the last several decades, organometallic transformations have changed fundamentally the practice of synthetic organic chemistry in both academic and industrial settings. The literature is now replete with a myriad of elegant papers describing an array of useful transformations catalyzed by transition metals.

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From the Nobel-prize winning Heck [1, 2], Negishi [3] and Suzuki [4] C–C forming reactions of Pd, the asymmetric hydrogenation [5] and ene and enyne metathesis of Rh, Ru [6], and Mo [7], the useful Sonogashira [8] acetylene cross coupling and carbon-heteroatom bond forming reactions to the intricate ring-forming/rearrangement methodologies of Au and Pt, transition metals [9–14] have changed the way we construct molecules in the twentieth and twenty-first centuries.

Originating from the academic labs, these methodologies found almost immediate use in the pharmaceutical industry and have revolutionized Drug Discovery and Development in the last decades [15]. Indeed, young process chemists can hardly imagine how chemistry was done without Pd, Ni, Rh, or Ru and can hardly conceive of a retrosynthetic analysis without the use of these "magic" elements.

So, it is with considerable surprise that the same young scientist finds that implementing these powerful methodologies on large scale is a rather challenging proposition. Catalytic reactions sometimes turn out to be capricious and unpredictable on scale-up, and their success can vary wildly due to the presence of tiny impurities in the starting materials (sometimes $<0.5\%$), quality of the catalyst precursor and ligand on commercial scale as well as seemingly minor changes in the reaction conditions such as order of addition of the components or rate of heating.

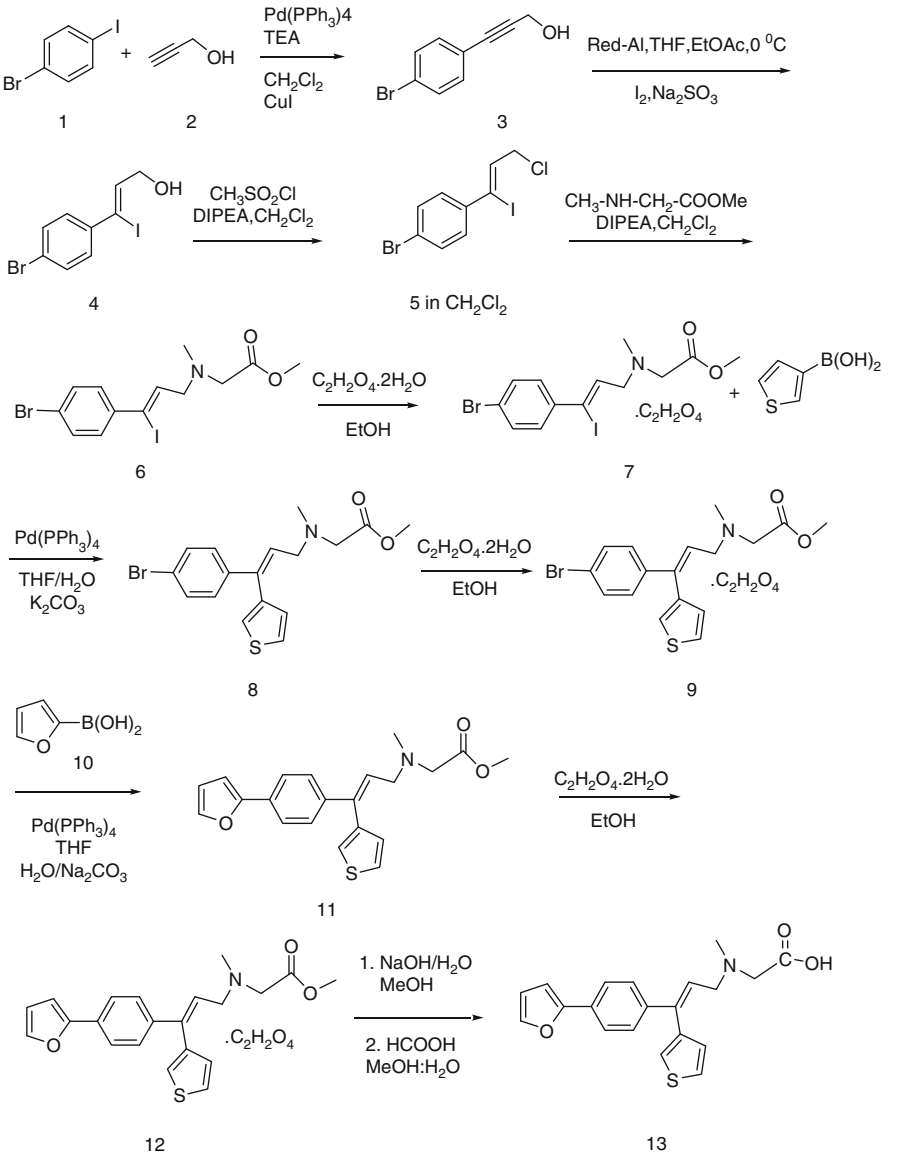
In addition, even when the reaction is robust, such considerations as catalyst load, and consequently cost, intellectual property restrictions and commercial availability of the catalyst can become major concerns even though the reaction may be very high yielding. Furthermore, after all these issues have been addressed, heavy metal contamination of the final active pharmaceutical ingredient (API) is a major roadblock, and its removal can add significantly to the cost of the manufacturing of the API.

In this case study, we will discuss the synthesis of a rather structurally simple API (**13**, Scheme 1) with an "all-transition-metal-process." Although on paper one would predict that the chemistry should work smoothly (and indeed it does so on small scale, ca. 100 g), several difficulties emerged during scale-up. Herein, we detail the solutions we developed to address some of these issues.

2 The Original Synthesis

The initial approach to this molecule was designed to meet the need of the Discovery chemist for structural diversification. Thus, compound **5** was designed as a common intermediate to ensure the olefin geometry and then functionalize around that scaffold for maximum biological advantage. The final API that was derived from this exercise is shown in Scheme 1 (**13**).

The chemistry shown in Scheme 1 worked well in the laboratory on moderately large scale. However, several issues presented themselves from the beginning. Early in the scale-up effort, it was observed that intermediates **6** and **8** had to be purified by chromatography in order to achieve reproducible and complete



Scheme 1 Original Synthesis of 13

conversion in the $Pd(PPh_3)_4$-catalyzed coupling steps. When non-chromatographed material was used, several additional charges of catalyst had to be introduced to achieve complete conversion. On the kilogram scale, extensive activated carbon treatments had to be carried out and oxalate salt formation was the only method to achieve the same result as the chromatographic purification. Obviously, these additional steps in the synthesis increased the cost of the API. Even under the

best conditions, the catalyst loads needed were substantial (3–5 mole%), which not only added to the cost of the catalyst but to the catalyst removal as well. Indeed, of all the catalyst-removal methods available to the process chemist, only immobilized thiol-bearing silica reagents were able to remove the Pd to acceptable levels. This exercise contributed more than 28% to the early production cost of the API.

Other issues with the synthesis were the apparent instability of 2-furyl boronic acid under the reaction conditions (several portions of the expensive boronic acid had to be added to drive the reaction to completion) and the variability in the quality of $Pd(PPh_3)_4$ from various vendors as well as its stability on storage under normal warehouse conditions.

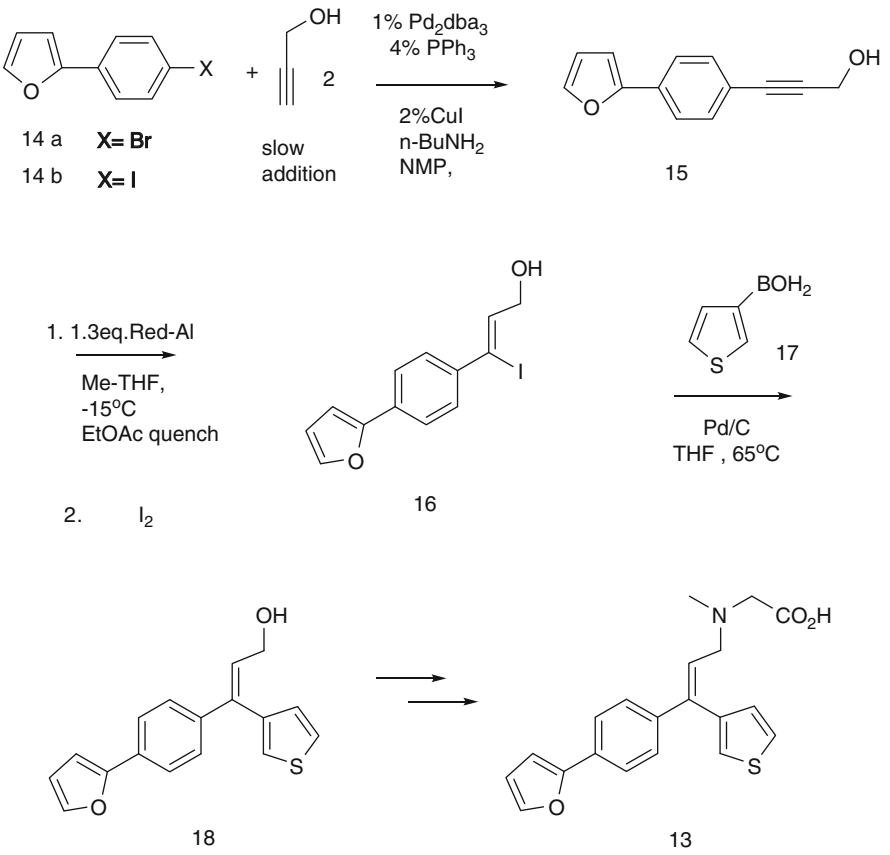
Despite these challenges, it was clear to us that a sequence of organometallic reactions was the most efficient way to produce this material on large scale and in particular to control the stereochemistry of the trisubstituted double bond [16–20]. Therefore, in order to overcome the challenges of the original synthesis, we sought to develop catalytic reactions that would require minimum catalyst loads reducing the catalyst cost and the need for even more costly catalyst removal and tedious work up procedures. We also decided that rearranging the reaction sequence would be desirable in order to avoid having a transition metal transformation as the final step in the synthesis. To accomplish the first goal, we turned to our Research Network partners at Solvias to assist us with the development of the catalytic sequence; the latter goal was achieved by adopting the sequence shown in Scheme 2 [21].

3 Preparation of Propargyl Alcohol 15

For commercial scale production, both **14a** and **14b** are available at relatively low cost. However, for research purposes, they were conveniently synthesized as shown in Scheme 3.

Thus, Suzuki coupling of *p*-bromo-iodobenzene with 2-furyl boronic acid was readily accomplished using Pd/C in THF–water mixtures, although a small amount of PPh_3 was needed for the reaction to proceed at a reasonable rate [22, 23]. The product **14a** can be isolated in ca. 93% yield with >99% purity by crystallization from ethanol–water. Although the Pd-content in solution was not measured at this juncture, the isolated product contained <10 ppm of Pd. It is worth noting that this purification is crucial as crude **14a** (97% purity) performed erratically in the subsequent Sonogashira reaction. The iodide **14b** was obtained in high yield by following the Buchwald protocol [24].

Since its discovery, the Songashira reaction has been a valuable tool for the functionalization of aromatic and heteroaromatic halides with the versatile alkyne function [9]. Among the many possible alkyne transformations, these derivatives can undergo cyclization reactions to prepare indoles, benzo- and heteroaryl- furans, and other useful pharmacophores. One of the difficulties of the reaction is the propensity of acetylenes to oxidatively dimerize under the reaction conditions, particularly when the cross-coupling reaction is slow as in the case of aromatic

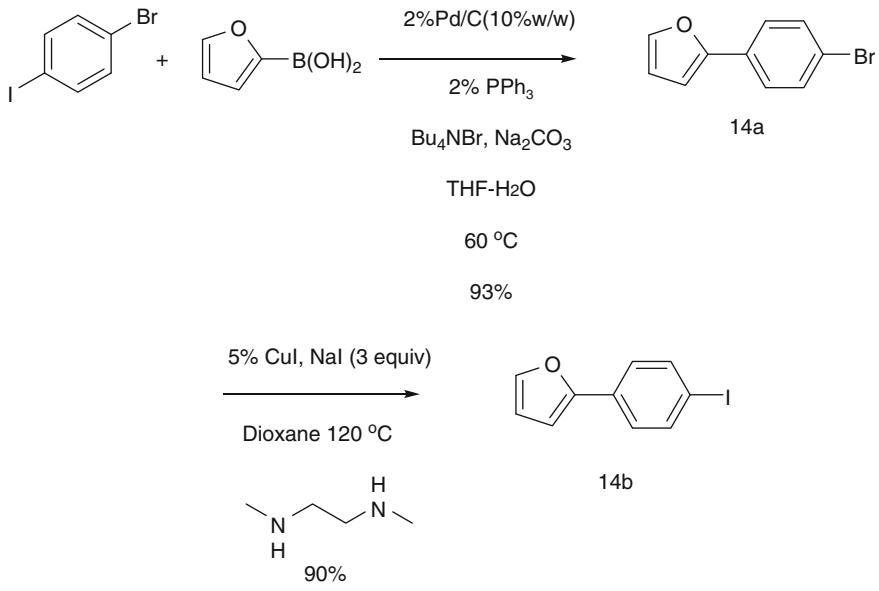


Scheme 2 Final Synthetic Sequence to 13

bromides and chlorides, which normally require elevated temperatures. In our case, the need to employ propargyl alcohol as the acetylene complicates the problem further as this reagent polymerizes rather easily at relatively low temperatures [25].

In order to avoid this side reaction, we started our investigation by utilizing the protocol developed by Buchwald and Fu for performing the Sonogashira reaction of acetylenes with aryl bromides and chlorides at ambient temperature [26]. Unfortunately, these conditions (Reasonable variations of the prescribed conditions were attempted, such as temperature, Pd:ligand ratio, base and catalyst loading, without significant success) afforded only 50% conversion along with visible polymerization products. Alternative methods to achieve this coupling, for example employing the corresponding silyl protected alkyne, were also not successful. Use of the silyl protected acetylene in the presence of N-heterocyclic carbenes was also not successful in this transformation [27].

To find a catalyst system that would allow complete conversion while minimizing polymerization of propargyl alcohol, we undertook an extensive screening



Scheme 3 Preparation of the Key Building Blocks 14a and 14b

of catalysts and reaction conditions. Initial experiments showed that polar aprotic solvents such as DMF and NMP (but not DMSO) were much more effective than THF, toluene, or dioxane. In addition, it was established that inorganic bases were not effective in this transformation.

These initial observations allowed for a more focused screening of ca. 60 experiments with the most pertinent "hits" shown in Table 1.

The trends observed for this reaction can be summarized as follows: PPh_3 was the only ligand leading to cross coupling (Table 1, entries 1–7), whereas *n*-$BuNH_2$ or DMPU were the preferred solvents for this reaction (Table 1, entries 1, 8, and 10). We have confirmed earlier observations that primary amine bases were preferred to secondary or tertiary [28], while bulky alkyl phosphines were surprisingly ineffective ligands [Table 1, entries 3–7 and (1)]. The first success with PPh_3 (Table 1 entry 8) provided 86% in situ yield of **15,** but the reaction did not proceed to completion and a number of impurities were observed as well as obvious polymerization products. The Pd/L ratio and the amount of *n*-$BuNH_2$ also seem crucial (entries 13–15), whereas the Pd precursor does not seem to have an important influence on the reaction.

DMPU is an excellent solvent for this reaction, and it is worth noting that thorough degassing is essential. Finally, the presence of water does not adversely affect the outcome of the reaction and may indeed be helpful (Table 1, entry 17).

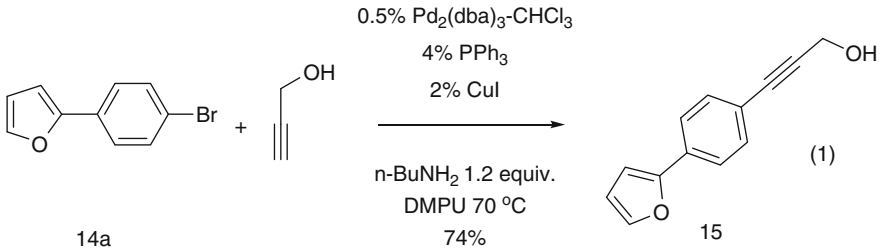
However, we were surprised to find that when the reaction was attempted on larger scale a significant exotherm was observed when applying the conditions used in the screening protocol. Specifically, mixing the components at room temperature

Table 1 Optimization of the Sonogashira coupling reaction

Entry	Base (equiv)	Pd/L (additive)	Pd/L (mol %)	Solvent	Time (h)	**14**a	**15**	In situ yield
1	*n*-$BuNH_2$	$Pd(OAc)_2/PPh_3$	2/8	NMP	16	35	51	–
2	Cy_2NMe	$Pd(OAc)_2/PPh_3$	2/8	NMP	16	90	<10	–
3	*n*-$BuNH_2$	$Pd(OAc)_2/P(furyl)_3$	2/8	NMP	4	>80		
4	*n*-$BuNH_2$	$Pd(OAc)_2/P(t\text{-}Bu)_2$-norbornyl × HBF_4	2/8	NMP	18	>80		22
5	*n*-$BuNH_2$	$Pd(OAc)_2/P(t\text{-}Bu)_2$-norbornyl × HBF_4	2/8[d]	NMP	18	>80		23
6	*n*-$BuNH_2$	$Pd(OAc)_2/P(t\text{-}Bu)_2$-biphenyl	2/8	NMP	4	>80		19
7	*n*-$BuNH_2$	$Pd(OAc)_2/PCy_3$	2/8	NMP	4	>80		16
8	*n*-$BuNH_2$ (excess)	$Pd(OAc)_2/PPh_3$	2/8	*n*-$BuNH_2$	4 18	12	76	80 86
9	*n*-$BuNH_2$ (excess)	$Pd(OAc)_2/PPh_3$ 1,2 diaminobenzene (8%)	2/8	*n*-$BuNH_2$	18	>30	75	71
10	*n*-$BuNH_2$	$Pd(OAc)_2/PPh_3$	2/8	DMPU	1 4 18	29 7 3	59 83 90	68 96 95
11	*n*-$BuNH_2$	$Pd/C(5\%)/PPh_3$	2/8[e]	DMPU	16	11	82	74
12	*n*-$BuNH_2$ (2.0 eq.)	$(TPPTS)_2PdCl_2$	1/2	DMPU	22	92	8	–
13	*n*-$BuNH_2$ (1.5 eq.)	Na_2PdCl_4/PPh_3	1/2.5[e]	DMPU	22			65
14	*n*-$BuNH_2$ (2.0 eq)	Na_2PdCl_4/PPh_3	1/3[e]	DMPU	21	1	97	74
15	*n*-$BuNH_2$ (5.0 eq)	Na_2PdCl_4/PPh_3	1/4[e]	DMPU	22	0	>95	93
16	*n*-$BuNH_2$	$Pd_2(dba)_3/PPh_3$	1/3[e]	DMPU	16	–	–	61
17	*n*-$BuNH_2$	$Pd_2(dba)_3/PPh_3$ 2 vol % H_2O	1/3[e]	DMPU	4 16	29 2	68 94	73 100

followed by slow heating over 45 minutes to 70°C, caused an abrupt temperature rise to 145°C along with the visible formation of dark polymeric material. This highly exothermic polymerization of the acetylene was determined, not surprisingly, to be due to CuI. Control experiments established that the copper cocatalyst is needed in this transformation, and therefore a solution had to be found to control this exothermic behavior.

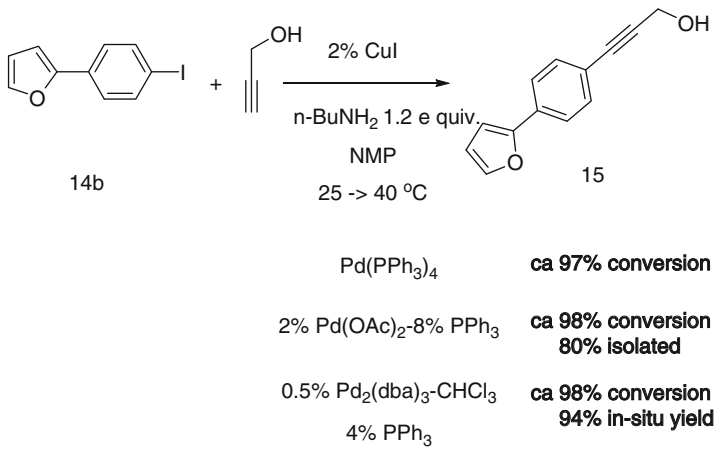
The optimal reaction conditions were established by limiting the concentration of propargyl alcohol in the medium. Thus, heating a dark green solution of a mixture of **14a**, $Pd_2(dba)_3{\cdot}CHCl_3$ (0.25–0.5 mole%) (Lower catalyst loads seemed to afford "cleaner" (less colored) reaction mixtures however reducing the precatalyst load below the 0.5 mole% level led to incomplete reactions.) PPh_3 (2–4 mole%) and CuI (1–2 mole%) in DMPU or DMI followed by slow addition of propargyl alcohol afforded **15** in >90% assay yield with little polymerization (1). The isolation of the product from the reaction mixture was problematic but could be accomplished by treatment with Silica*Bond*-Thiol (SilicaBond-Thiol is an efficient method for removing both Pd(II) and Pd(0) dissolved in reaction mixtures. It is marketed by Silicycle Corporation and information and specification including efficiency of removal of Pd and other transition metal catalysts can be found at http://www.silicycle.com) and activated carbon (Norit A supra, 10 wt%) followed by toluene–heptane crystallization to afford 74% yield of the desired compound (Pd content 120–150 ppm). Both of the above treatments were needed to remove Pd contaminants and "gummy" byproducts that interfere with the crystallization. Fortunately, Cu was much less of an issue as two aqueous ammonia treatments, during workup, effectively reducing the Cu levels to <20 ppm.



14a 15

Finally, it is worth noting that in some cases evaporation of *n*-$BuNH_2$ or propargyl alcohol were observed, which necessitated further addition of these reagents to effect complete conversion (The initial screening experiments were conducted in autoclave-type vessels where evaporation of the components was not an issue. However, when typical "bench-top" experimental set-ups were used, some evaporation was observed (despite the presence of a condenser) that necessitated further addition of amine and propargyl alcohol to drive the reaction to completion.).

Predictably, using the iodide **14b** (Scheme 4) allowed the reaction to proceed smoothly at 40°C with no polymerization and thus a more facile workup. It is worth noting, however, that the iodide was not commercially available and would have to be prepared from the bromide. Thus, the bromide was selected as our starting material for further processing.



Scheme 4 Optimization of the Sonogashira Reaction

4 Preparation of the Trisubstituted Olefin 18

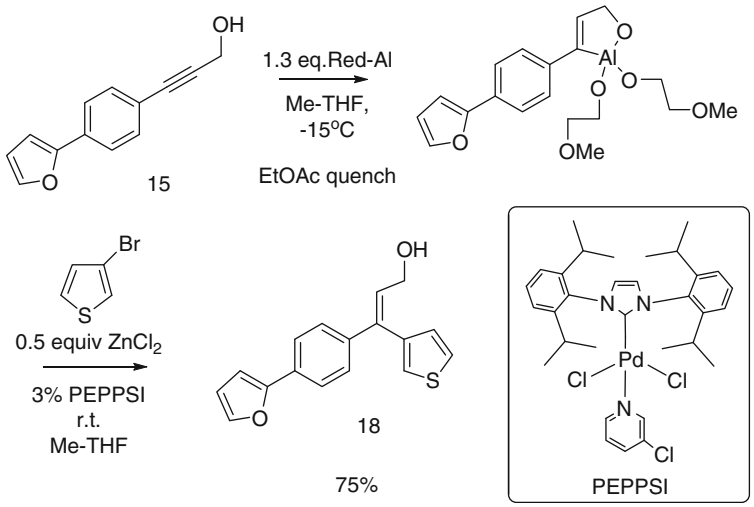
Our initial successful strategy for effecting stereoselective formation of **18** was based on the selective formation of a reactive aluminate intermediate, which fulfilled the dual role of defining the geometry of the double bond, via the internal chelation, and providing the appropriate reactivity for further transformation (Scheme 5).

Unfortunately, despite the good yields on small scale, scale-up proved challenging due to the water sensitivity of the vinyl aluminum and vinyl Zn species. In addition, we were not able to reduce the catalyst load below 3 mole% of the PEPPSI catalyst making the cost of the catalyst a significant percentage of the cost of the API. So once more, an elegant reaction in the laboratory does not appear to be commercially viable.

Nonetheless, we decided to try to optimize the hydroxyl-directed hydroalumination [29] reaction as it provides an excellent vehicle to accomplish complete stereocontrol in the formation of the double bond, due to the formation of the relatively stable intermediate carboaluminate, which results from the regio and diastereo-selectivity of the addition reaction (The Jamison group [17] has elegantly demonstrated a complementary strategy where the resulting aluminate species is transmetallated to a Cu reagent and then functionalized via alkylation to afford stereodefined trisubstituted olefins.). Stereo-complementary results can be obtained if the alcohol function is protected.

Thus, we decided to return to the concept of the original synthesis and couple the vinyl iodide **16** and thiophene boronic acid **17** to arrive to the same intermediate trisubstituted alcohol **18**.

The hydroalumination reaction is worth discussing in some detail. In the original reports of the hydroalumination reaction, pyrophoric DIBALH or $LiAlH_4$ was

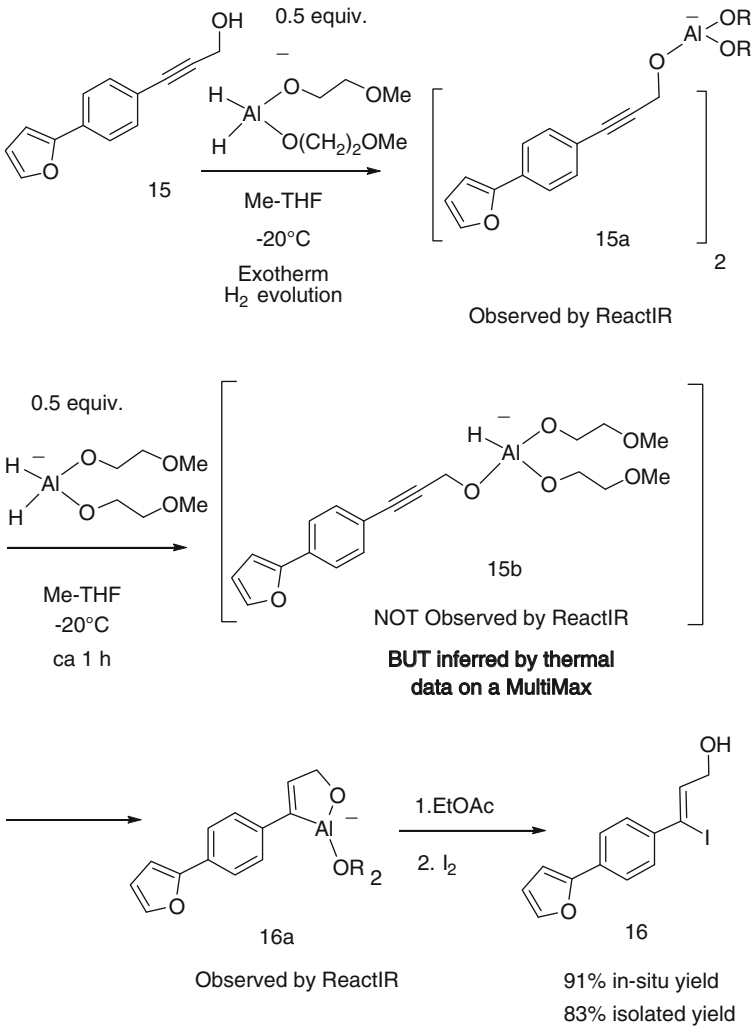


Scheme 5 Direct Coupling Towards the Synthesis of 18

used, but this problem has recently been overcome by the introduction of a safer reagent, Red-Al [$NaH_2Al(OCH_2CH_2OMe)_2$], which is readily available on large scale under the trade name Vitride™.

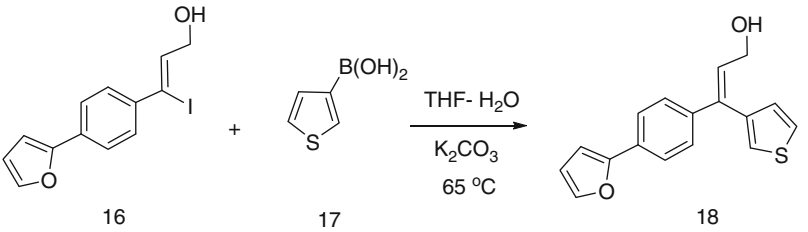
Thus, purified **15** was dissolved in THF in a MultiMax reactor equipped with Calorimeter and IR probe, and cooled to −20°C followed by addition of Red-Al in toluene (Scheme 6). During addition of the first 0.5 mole equivalents of the reagent, there was vigorous gas evolution and significant exothermic behavior due to reaction of the aluminum hydride with the free hydroxyl group. The alkyne signals were still present in the IR and no olefinic resonance could be observed. From these observations, we are postulating the formation of the aluminate intermediate **15a**. Upon further addition of Red-Al, a second large and rapid exotherm occurred, followed by the appearance of the olefinic bands albeit at a slower rate. From the magnitude and rate of the observed exotherm and the slower appearance of **16a** we postulate initial rapid formation of **15b**, followed by a somewhat slower intramolecular hydroalumination. An intermolecular delivery of the hydride cannot be conclusively ruled out but does appear inconsistent with the thermal and IR data, and further studies are needed to establish the course of this reaction. Upon completion of the hydroalumination reaction, EtOAc is added to quench excess Vitride followed by addition of a solution of I_2 in THF to afford 91% in situ yield of **16** which could be isolated, but was actually used directly in the next reaction.

Our initial attempts to prepare **18** followed the methodology of the original synthesis and were quite successful: the alkenyl iodide **16** coupled with boronic acid **17** under a variety of conditions, as shown in Scheme 7. However, the workup and Pd-removal was problematic under these reaction conditions and our best methods gave insufficient Pd removal, Unfortunately, the amount of Pd in isolated **18** carried through to the final API.



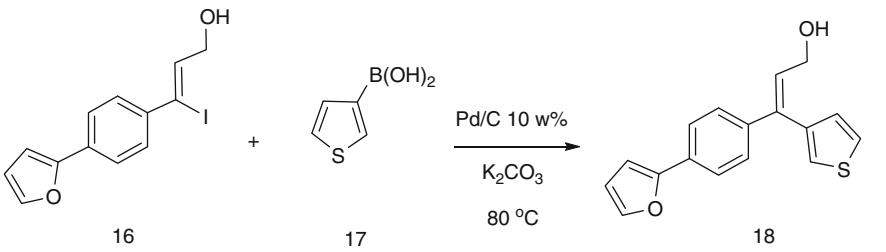
Scheme 6 The Mechanism of the Hydroalumination Reaction

Finally (Scheme 8), we were delighted to find that the coupling of **16** with **17** can take place smoothly in the presence of Pd/C in 2-methyl-tetrahydrofuran in good yield and with acceptable levels of residual Pd. Most importantly, these levels were achieved just by isolation of the product from ethanol–water and did not require any additional metal removal effort. The reaction proceeded in a number of aqueous solvent systems but did not proceed in the absence of water. More importantly, no external phosphine was needed for complete conversion as was the case for the formation of **14a** (Scheme 3). It is known in the literature, and was confirmed by our own measurements that the presence of phosphine does accelerate the reaction;

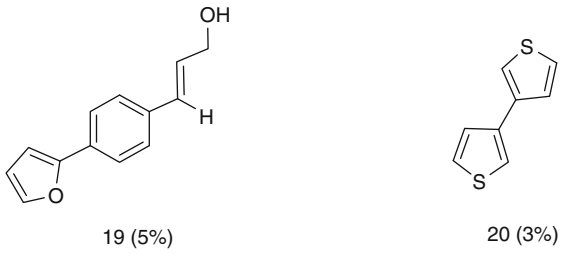


5% $Pd(PPh_3)_4$	78% (250ppm Pd)
4% $Pd(OAc)_2$ 2 PPh_3	81% (200ppm Pd)
3% $Cl_2Pd(PPh_3)_2$	80% (190ppm Pd)
3% $Pd(OAc)_2$ 2 P(o-tol)$_3$	83% (220ppm Pd)

Scheme 7 Suzuki Reaction with Homogeneous Catalysts



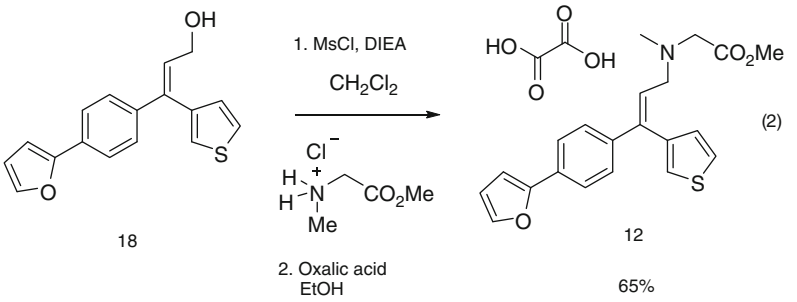
Me- THF-H_2O (1:1)	90% (10 ppm Pd)
THF -H_2O (1:1)	35% (50 ppm Pd)
DMF-H_2O (1:1)	81% (130 ppm Pd)
NMP-H_2O (1:1)	82%(120 ppm Pd)



Scheme 8 Suzuki Reaction under Heterogeneous Catalysis

however, it also complicates the removal of Pd. A minor disadvantage of this protocol is the formation of the reduced product **19** and homocoupling product **20**. However, these impurities were readily removed in the isolation procedure.

With this methodology in hand, we were able to complete the synthesis of the API with acceptable purity and Pd levels (2).



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Pilot Plant Scale Synthesis of an Aryl-Indole: Scale Up of a Suzuki Coupling

Adriano F. Indolese

Abstract A synthesis of an aryl boronic acid and the subsequent Suzuki coupling to an aryl indole has been developed and successfully scaled up to pilot plant scale. The Suzuki coupling was optimized by design of experiments and run with a catalyst loading of 0.1 mol%. The article describes the strategic approach for the optimization of the reaction and the most critical issues, such as the cryogenic synthesis of the boronic acid, the catalyst optimization, and the palladium removal, are discussed in detail.

Keywords Aryl boronic acid · Indole synthesis · Palladium · Suzuki coupling

Contents

1 Introduction

The biaryl motif is an important structural element in active pharmaceutical ingredients and fine chemicals. The most convenient and straightforward access to biaryl compounds is the palladium and nickel catalyzed cross coupling,

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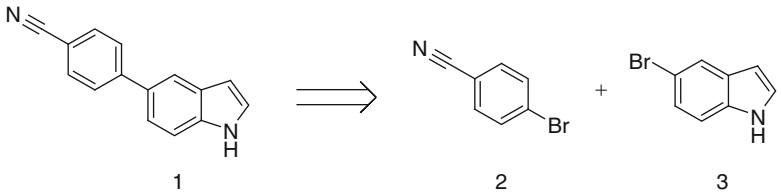


Scheme 1 Synthetic strategy for 5-(4-cyano-phenyl)-indole 1

originally discovered by Kumada [1] and Corriu [2]. The Suzuki coupling is probably the most applied cross coupling technology nowadays [3, 4]. The reaction conditions of the Suzuki coupling are very mild and compatible with many functional groups. There exist several general methods to couple a wide variety of aryl boronic acids and different aryl halides and aryl sulfonates with good to excellent yields. Compared to the Kumada or Corriu coupling, the biggest advantage of the Suzuki coupling is the stability of the nucleophilic component, the aryl boronic acids. They are easily synthesized and purified. They are stable and a wide variety of aryl boronic acids are also commercially available.

Palladium catalyzed coupling reactions have been applied intensively in research for many years. As a consequence more and more chemical products containing the biaryl substructure are discovered and must be produced on larger scale [5].

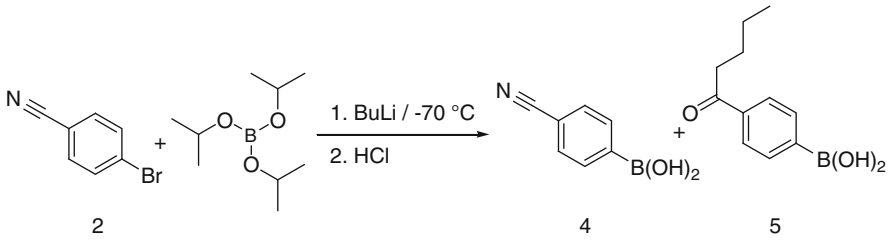
In 2004, RohnerChem developed a process for 5-(4-cyano-phenyl)-indole **1** and produced 3.7 kg in the pilot plant. At the start of the project, no synthetic route was available, but the development and production had to be finished within four months. The most straightforward way to synthesize the molecule is certainly the coupling of a 4-cyanophenyl moiety with an indole part. We decided to start with 4-bromo-benzonitrile **2** and 5-bromo-indole **3** (Scheme 1). Both starting material were already produced in house, and therefore no problems related to the quality of the starting materials were to be expected. The 4-bromo-benzonitrile was the easier available and cheaper starting material, and so we decided to convert it to the corresponding aryl boronic acid.

2 Results and Discussion

2.1 Synthesis of 4-Cyano-benzene-boronic acid

Usually, boronic acids are synthesized by reaction of an aryl magnesium or aryl lithium compound with a borate ester [6]. However, in the case of 4-bromo-benzonitrile, a metal–organic intermediate would react with the nitrile group. Aryl boronic acids could be also synthesized by palladium-catalyzed reaction using diboron reagents [7]. This method would certainly tolerate the cyano functionality, but the diboron reagents are very expensive.

Li et al. [8] described the synthesis of sensitive heteroaryl boronic acids by forming the organometallic species in situ and reacting it immediately with



Scheme 2 Synthesis of 4-cyano-benzene-boronic acid

triisopropylborate. We successfully adapted the method to 4-bromo-benzonitrile (Scheme 2). The reaction must be carried out at −70°C. Already at −60°C, BuLi reacted substantially with the cyano group and side product **5** was formed.

In the lab, this protocol worked very nicely and due to the very tight timelines, no thorough optimization of the reaction conditions was performed. The boronic acid was isolated in yields of 75–80% and was used as wet product for the subsequent step.

Small adaptation had to be implemented for the pilot plant campaign. When the mixture of 4-bromo-benzonitrile, triisopropylborate, THF, and toluene was cooled down to −70°C, the 4-bromo-benzonitrile formed a thick crust on the reactor wall. To avoid the formation of the crust, a solution of 4-bromo-benzonitrile in toluene was dosed into the cold mixture of triisopropylborate and THF. 4-Bromo-benzonitrile precipitated as fine crystals and a well-stirrable suspension was formed.

The results in the pilot plant were comparable to the lab experiments, except that about four times more of the valerophenone side product **5** was formed. The cause could not be conclusively identified, but most likely it was a consequence of the formation of hot spots due to insufficient mixing and heat transfer during the dosage of BuLi. The valerophenone **5** was not removed completely during the work-up as in the lab, and the boronic acid **4** had to be recrystallized from toluene to improve the quality to an acceptable level. At the end, the boronic acid **4** was obtained with a purity of 99% and a yield of only 48%.

2.2 Synthesis of 5-(4-Cyano-phenyl)-indole

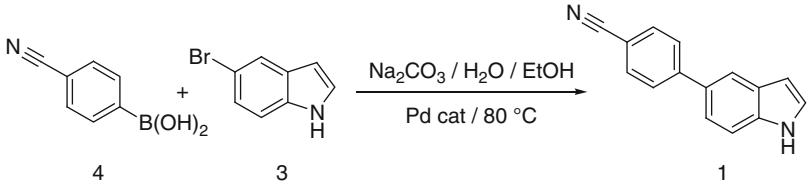
2.2.1 Catalyst Selection

The starting point for the development of the Suzuki coupling was a procedure described by Carrera and Sheppard [9]. The protocol was chosen due to the technical feasibility and the structural similarity of the products. Carrera and Sheppard reacted 7-brom-indoles with boronic acids in a biphasic mixture of toluene, ethanol, and water. Sodium carbonate was used as the base, and palladium (0)tetrakis (triphenylphospine) as the catalyst.

Table 1 Screening experiments for the optimal catalysts

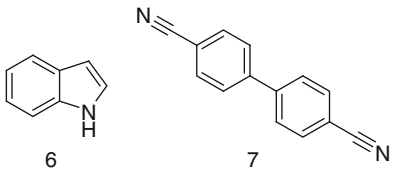
Entry	Catalyst	Catalyst loading mol%	Ligand	Reaction time (h)	Conversion (%)	Selectivity (%)
1	$PdCl_2$	5	PPh_3	6	100	78
2	$PdCl_2$	0.1	PPh_3	5	31	79
3	$PdCl_2$	5	$PTol_3$	2	100	84
4	$PdCl_2$	0.5	$PTol_3$	3	100	96
5	$PdCl_2$	0.1	$PTol_3$	4	99	96
6	$PdCl_2$	0.05	$PTol_3$	6	64	96
7	$PdCl_2$	0.02	$PTol_3$	24	44	96
8	$PdCl_2$	0.01	$PTol_3$	7	13	n.d.
9	$PdCl_2$	0.1	No ligand	19	13	68
10	$Pd(OAc)_2$	0.1	No ligand	4	120	82

Experimental conditions: 5-bromoindole **3** (1 mmol), 4-cyano-benzene-boronic acid **4** (1.5 mmol), sodium carbonate (2 mmol) and the catalyst were heated in a 50 ml Schlenk-tube to 80 °C in toluene (6 ml), ethanol (1 ml) and water (1 ml) for the indicated time. The conversion was determined by GLC



Scheme 3 Suzuki coupling to 5-(4-cyano-phenyl)-indole

Scheme 4 Side products formed in the Suzuki reaction



Our first goal was to identify a suitable catalyst. The aim was high catalyst productivity (TON $\geq$1,000) and high selectivity. In addition, the catalyst should be commercially available in larger quantities. Therefore, we focused primarily on palladium(II)chloride and simple phosphines such as triphenylphosphine (PPh_3) and tri-*o*-tolyl phosphine ($PTol_3$). The screening results are summarized in Table 1 (Scheme 3).

With 5 mol% catalyst, full conversion was observed with PPh_3 as well as $PTol_3$ (Table 1, entries 1 and 3) At a level of 0.1 mol%, $PTol_3$ gave still full conversion (entry 4), but only 31% conversion was observed with PPh_3 (entry 2). Furthermore, the selectivity of the reaction was 96% with $PTol_3$, whereas with PPh_3, it was only 80%. The two main side reactions (Scheme 4) were the dehalogenation to form indole **6** and the homocoupling of the boronic acid to 4,4′-di(cyano)-biphenyl **7** [10]. The results show that under these reaction conditions, 0.1 mol% was the lower limit. At lower catalyst loadings, the conversion decreased significantly (entries 6–8).

2.2.2 Optimization of the Reaction Conditions by DOE

By design of experiments (DOE), the influences of the most important reaction parameters were investigated (Table 2). These experiments were deliberately run at a catalyst level of 0.05 mol% that did not give complete conversion in order to better observe differences between the tested reaction conditions. Temperature (65/95°C), palladium/ligand ratio (2/4), amount of toluene (4/6 ml), amount of ethanol (1/2 ml), and amount of base (2/3 equiv.) were checked on two levels. The experiments were evaluated with STAVEX®.

The results of the statistical evaluation are presented in Table 3. The results gave a good fit with the model. Changing the amount of ethanol from 1 to 2 ml had the largest effect on the conversion (+22%). Increasing the temperature and lowering the amount of toluene gave each about 10% improvement. The ligand to palladium ratio had only a minor influence. The amount of base showed no significant influence at all. Cross influences of two parameters were also very small. Surprisingly, at higher temperature less 4,4′-di(cyano)-biphenyl was formed (see Table 2).

Further experiments showed that toluene could not only be reduced but could also be omitted completely. The process could be improved further by using isopropanol instead of ethanol. Switching from ethanol to isopropanol improved the rate of the reaction significantly.

Table 2 Investigation of the key reaction parameters

Entry	Temperature (°C)	L/Pd ratio	Toluene (ml)	EtOH (ml)	Na_2CO_3 equiv.	Conversion (%)	Side product **4** (%)
1	65	2	4	1	2	46.2	4.5
1*	65	2	4	1	2	46.4	4.3
2	95	2	4	2	2	71.2	2.3
3	65	4	4	2	2	63.9	4.4
4	95	4	4	1	2	63.0	2.2
5	65	2	4	2	3	64.8	4.2
6	95	2	4	1	3	51.6	2.5
7	65	4	4	1	3	42.7	3.4
8	95	4	4	2	3	81.3	2.0
9	65	2	6	2	2	52.1	3.4
10	95	2	6	1	2	37.2	2.4
11	65	4	6	1	2	36.2	3.6
12	95	4	6	2	2	69.1	1.8
13	65	2	6	1	3	34.1	4.0
14	95	2	6	2	3	65.1	1.7
15	65	4	6	2	3	68.0	4.1
16	95	4	6	1	3	42.5	1.7

Experimental conditions: 5-bromoindole (1 mmol), 4-cyano-benzene-boronic acid (1.5 mmol), sodium carbonate, $P(Tol)_3$ and $PdCl_2$ (0.005 mmol) were heated in a 50 ml Schlenk-tube to the indicated temperature in toluene, ethanol and water (1 ml) for 24 h. The conversion was determined by GLC. 1*: Repetition of experiment 1 to check reproducibility of the reaction

Table 3 Influence of reaction parameters on conversion

Parameter	Influence on conversion
Increasing ethanol from 1 to 2 ml	+22%
Increasing toluene from 4 to 6 ml	−10%
Increasing temperature from 65C to 95°C	+9%
Changing L/Pd ratio from 2 to 4	+5%
Increasing base from 200 to 300%	Not significant
Ethanol × Base	−4%
Ethanol × toluene	−3%
Toluene × temperature	−3%
Toluene × base	+2%
Temperature × ligand	+2%

At this point, the reaction conditions were fixed as follows: Isopropanol, water, 5-bromo-indole, 4-cyano-boronic acid, and the catalyst $Pd(PTol_3)_2Cl_2$ were heated to reflux under nitrogen and a sodium carbonate solution was dosed within 2 h. The dosage of sodium carbonate was implemented to control the heat of reaction of about 700 kJ/mol in order to improve the safety of the process.

2.2.3 Development of Work-Up and Product Isolation

For the work-up, it was planned to distill off the isopropanol and to extract the product with an organic solvent. From this solution, the palladium should be removed by adsorption onto a scavenger. This task turned out to be the main challenge of the project. Several solvents such as alcohols, acetone, xylene, and dichloromethane were checked in combination with different absorbents, e.g., activated charcoal, alumina, and silica. In most solvents, the solubility of the product was very poor at room temperature. The solubility was only sufficient in acetone and dichloromethane. The best results were obtained by slow filtration of a dichloromethane solution through a bed of silica and activated charcoal. Palladium was eliminated almost completely, and less than 10 ppm of palladium was found in the final product.

For the final isolation of the product, dichloromethane was exchanged to toluene by distillation, and the product was crystallized, filtered, and dried. The product was obtained in a yield of 75% with a purity of greater than 97% in the lab process.

2.2.4 Pilot Plant Process

In the pilot plant, the reaction was carried out as planned in a 2:1 mixture of isopropanol and water, and with 0.1 mol% catalyst. The sodium carbonate solution was dosed within 2 h and the heat of reaction could be controlled easily. The reaction run exactly as in the lab, and no scale-up effect was observed.

Table 4 Results of the pilot campaign

Batch	Conversion (%)	Isolated yield in kg (%)	Purity (a/a %) HPLC	Melting point (°C)	Loss on drying	Pd content (ppm)
1	94.7	1.67 (59)	98.5	183.8	<0.1%	7
2	95.3	2.02 (70)	97.3	182.6	<0.1%	10

The work-up could be also carried out as planned. Slow filtration through silica and charcoal removed the palladium as demonstrated in the lab. The product was crystallized nicely as a white powder. The yield of the first batch was lower than expected, probably due to some product hold-up on the filter and in the drier. The yield of the second batch was in the expected range.

In the end, 3.7 kg of product was produced with a purity of 97% and contained less than 10 ppm palladium (see Table 4). The yield of 64% was lower than expected from the lab, but this was due to equipment losses.

3 Conclusion

A two-step process for the synthesis of 5-(4-cyano-phenyl)-indole was developed successfully in a very short time frame, and 3.7 kg of product was produced at the 100 l pilot plant scale. The Suzuki coupling behaved surprisingly well and could be carried out with as little as 0.1 mol% catalyst. In catalytic reactions, the quality of starting materials is often a big concern. In this project, the quality of the starting material was no issue, because they were produced in-house and the quality was under full control.

Our strategy was to define at first the catalyst and then optimize the reaction conditions in a second step using design of experiments. This stepwise approach worked well in our case, and is certainly a good general approach for the development of a catalytic reaction. The biggest challenges in the project were the synthesis of the boronic acid and the removal of the palladium. For both problems, pragmatic solutions were found in a very short time.

In summary, the successful scale-up of this Suzuki coupling demonstrates nicely that even at production scale, palladium catalyzed reactions are quite robust and well behaved.

3.1 Experimental Section

Synthesis of 4-cyano-benzene-boronic acid 4. A vacuum isolated triple jacket reactor was charged with THF (76.5 g), triisopropylborate (49.8 g, 265 mmol), and toluene (88 g), and the mixture was cooled to −70°C. A solution of 4-bromo-benzonitrile **2** (40 g, 220 mmol) in toluene (210 g) was added within 20 min and a fine suspension is formed. BuLi (15% in hexane, 131 g, 308 mmol) was added dropwise within 4 h keeping the reaction temperature below −70°C. Hydrochloric

acid (10%, 212 g) was added within 15 min. The mixture was heated to 50°C and the phases were separated. The aqueous phase was discarded. The organic phase was extracted twice with sodium hydroxide solution (2.5%, each 150 g). The combined sodium hydroxide solutions were cooled to 20°C and acidified with hydrochloric acid (33%), until pH was below 1. The suspension was cooled to 0°C and the product was filtered, washed with water (100 g), and dried. Yield: 24.2 g (75%) of 4-cyano-benzene-boronic acid.

Synthesis of 5-(4-cyano-phenyl)-indole 1. A double jacket reactor was charged with 5-bromo-indole **3** (50 g, 250 mmol), 4-cyano-benzene-boronic acid **4** (38.7 g, 263 mmol), and isopropanol (393 g). The reactor was purged with nitrogen. $Pd(PTol_3)_2Cl_2$ (0.2 g, 0.25 mmol) was added, and the reaction mixture was heated to reflux. Sodium carbonate solution (2 M, 250 ml, 500 mmol) was dosed within 2 h. The reaction was stirred for additional 90 min at reflux. The isopropanol was distilled off until the temperature of the distillation residue reached 100°C. The reaction mixture was cooled to room temperature and was extracted with dichloromethane (1,000 ml). The organic phase was extracted with water (250 ml) and was filtered slowly through a bed of silica (40 g) and charcoal (4 g). The filter bed was washed with dichloromethane (100 ml). To the combined dichloromethane phases, toluene (500 ml) was added and dichloromethane was distilled of until the distillation residue reached a temperature of 110°C. The product solution was cooled to 95°C and was seeded. The suspension was cooled slowly (1°C/min) to room temperature. The product is filtered, washed with toluene (50 ml), and dried at 60°C. 5-(4-cyano-phenyl)-indole **1** was obtained as colorless crystals (42.6 g, 188 mmol, 75%).

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Development of a Mild and Robust Method for Palladium Catalyzed Cyanation on Large Scale

Per Ryberg

Abstract The Pd-catalyzed cyanation of aryl halides is a very attractive method to prepare aryl nitriles, yet relatively few large scale applications of the reaction have been reported. The primary reason behind this has been a lack of robust and general conditions for the reaction, and for a long time it had a reputation of being difficult to scale up. Following a general introductory review of the reaction, this case study describes in detail the development of a new improved method for the Pd-catalyzed cyanation under mild conditions, and its successful application on a large scale to prepare multikilogram quantities of a drug candidate. The results and findings are discussed in the context of the current mechanistic understanding of the reaction and from an industrial perspective.

Keywords Aryl halide · Cyanation · Large scale synthesis · Palladium catalysis · Process development

Contents

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1 Introduction

The last decades of research within the field of organometallic chemistry has led to the development of several useful methods for carbon–carbon and carbon–hetero atom bond formation [1, 2]. Today, transition metal catalysis plays an important role in the pharmaceutical industry by providing access to more complex structures in fewer steps with less waste, one of the cornerstones in the green chemistry concept. In fact, the synthetic routes to almost all new drug candidates contain at least one transition metal catalyzed step, and many large-scale manufacturing processes utilize transition metal catalysis [3, 4]. In particular, the Buchwald–Hartwig amination [5, 6] and the Suzuki–Miyaura coupling [7–9], recently ranked on 3rd and 7th position, respectively, in a survey of the most frequently used reactions within the pharmaceutical industry [10], have revolutionized the way by which synthesis of target molecules are conducted.

While transition metal catalysis opens up fantastic synthetic opportunities, it has the unfortunate side effect of introducing heavy metals that can end up in the isolated product, and strict guidelines regulate the allowed levels of heavy metal contaminants in the drug substance, typically <10 ppm.

As a consequence, manufacturing routes are preferably designed to avoid transition metal catalyzed reactions in the final synthetic step, and isolation methods have to be developed that efficiently remove the metal from the product.

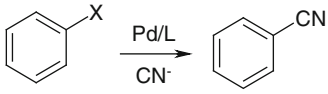
2 Palladium-Catalyzed Cyanation

2.1 Background

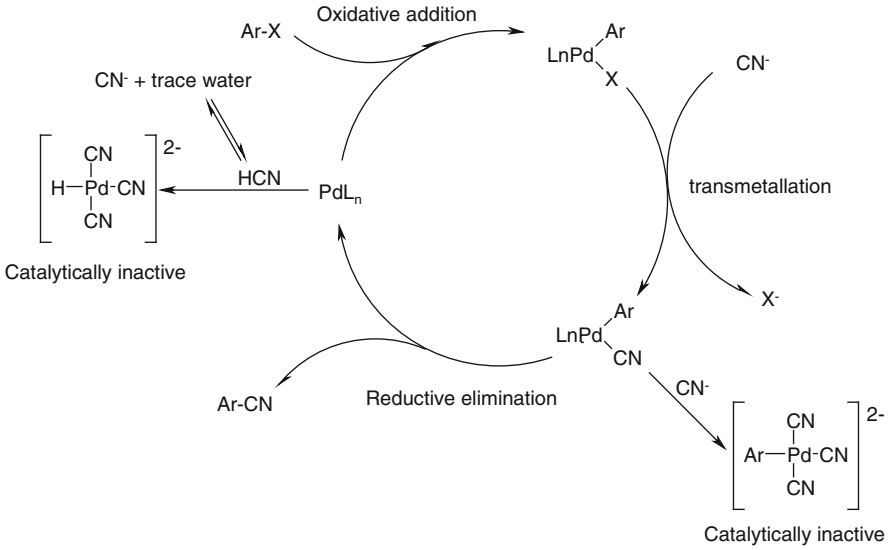
A less well known, but still very useful transformation is the palladium catalyzed cyanation of aryl halides [11] (Scheme 1).

In contrast to traditional methods for preparing nitriles such as the Sandmeyer [12] and Rosenmund-von Braun [13] reactions, the Pd-catalyzed cyanation provides an opportunity to convert an aryl halide or pseudohalide to a nitrile under relatively mild conditions.

Despite the importance of nitriles as synthetic intermediates and structural motifs in drugs, relatively few large scale applications of the palladium-catalyzed cyanation have been reported [14–20]. The primary reason behind this has been the lack of robust and scalable conditions, and for a long time the reaction had a reputation of being capricious and particularly difficult to scale up.



Scheme 1 Pd-catalyzed cyanation of aryl halides



Scheme 2 Catalytic cycle for the Pd-catalyzed cyanation

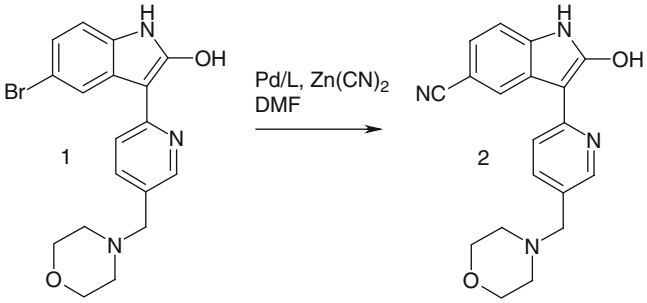
Since the discovery by Takagi [21], much effort has been spent on finding improved conditions for the reaction and it has been found that *N*,*N*-dialkylamide solvents such as DMF, DMA, and NMP in combination with $Zn(CN)_2$ as the cyanide source and a Pd catalyst provides the most general protocol for the reaction [15, 22, 23]. However, recent work by Beller and others have demonstrated the utility of potassium hexacyanoferrate as a source of CN^- [24–27].

Cyanide poisoning of the catalyst is a problem, and it has been demonstrated that each step in the catalytic cycle, i.e., oxidative addition, transmetallation and reductive elimination, may be affected by excess CN^- to form catalytically inactive $Pd(CN)_n$ species [15, 28–30] (Scheme 2). Thus, the balance between achieving sufficient CN^- in solution to promote the reaction, and the level where the catalyst becomes poisoned is very delicate.

2.2 Palladium-Catalyzed Cyanation on Large Scale

2.2.1 Background

In 2003/2004, drug candidate **2** (Scheme 3) was investigated for the treatment of disorders related to Glycogen Synthase Kinase 3. The clinical development program required gradually increasing amounts of material for testing, with an immediate demand of 50 g, followed by an additional 5 kg. An enabling route, involving the palladium-catalyzed cyanation in Scheme 3, in the final synthetic step, was developed for the manufacture.



Scheme 3 Pd-catalyzed cyanation of 1 to 2

At the time of the work, only two large scale examples of the palladium-catalyzed cyanation had been reported [14, 15], and the standard method consisted of heating an aryl iodide or bromide with $Pd(OAc)_2$, dppf, $Zn(CN)_2$ and Zn (dust) in DMF at 80–120°C [23]. Application of these conditions on 1 g scale in the lab gave high conversion to **2**, but during the 50 g scale manufacture, the reaction stopped at incomplete conversion. Even after forced conditions (>10 h at 120°C), only a 35% conversion to product was observed, together with a mixture of equal amounts of unreacted starting material and by-products.

The workup was difficult and ultimately required reversed phase chromatography to separate the product from the impurities, affording a modest 12% yield of **2**.

Since the overall synthetic route was short and convergent and no realistic alternatives existed at the time, it was decided to use it also for the 5 kg manufacture. However, considering the problems on 50 g scale, where existing cyanation methodology did not work, a significantly improved cyanation method had to be developed in order to successfully manage the upcoming manufacture.

2.2.2 Screen of Catalysts

Due to the instability of the product under the reaction conditions, we realized that an improved procedure for the reaction had to rely on a catalyst system that was capable of promoting the reaction at a lower temperature. It seemed logical to look for catalysts that had been used for the low temperature activation of aryl halides in other cross-coupling reactions (Table 1).

We found that the P(*t*-Bu)$_3$-based catalysts, entries 2 and 3, performed best in the screen, with full conversion to product within 60 min. With these promising results in hand, attempts to scale up the reaction from 200 mg to 5 g were made, but surprisingly it repeatedly stopped at 70–80% conversion. Trivial sources of error, such as poor inertation, could be excluded, and a deeper understanding of the reaction was necessary in order to find a protocol that would prove to be scalable.

Table 1 Screen of catalysts for the cyanation of **1**

Entry	Catalyst	Conversion (%)
1	$Pd[P(t\text{-}Bu)_3]_2$	70
2	$Pd(dba)_2 + P(t\text{-}Bu)_3$	100
3	$[BrPdP(t\text{-}Bu)_3]_2$	100
4	$Pd(dba)_2 + 2\text{-}(t\text{-}Bu)_2$P-biphenyl	15
5	$Pd(dba)_2 + 2\text{-}(Cy)_2$P-biphenyl	15
6	$Pd(dba)_2$ + Q-phos	50

Aryl bromide (1) 1 eq, Zn dust 0.1 eq, $Zn(CN)_2$ 0.55 eq, $Pd(dba)_2$ 0.025 eq, ligand 0.025 eq. Reactants were dissolved in degassed DMF at 20°C followed by 1 h of reaction at 50°C. *Pd(dba)*$_2$ bis(dibenzylideneacetone)palladium(0), *Q-Phos* 1,2,3,4,5-pentaphenyl-1′-(di-*t*-butylphosphino) ferrocene

2.2.3 Troubleshooting and Identification of Scalable Reaction Conditions

It was known that CN^- poisoning of the catalyst could be a problem in Pd-catalyzed cyanations [16, 17]. If this was the reason behind the failed 5 g reaction, why had it not been a problem in the 200 mg reaction?

In general, operations such as, e.g., charging of reagents, heating, or cooling is slower on scale and stirring can be more or less efficient. It is well known that these factors can have an effect on reaction performance, and it therefore seemed reasonable to seek the reason behind the failed 5 g reaction in the way the two reactions had been conducted.

During screening and initial scale up attempts, the reaction had been run by adding the aryl bromide **1**, $Zn(CN)_2$, Zn (dust), and $Pd(dba)_2$ to the reaction vessel. After inertation by vacuum/nitrogen purge cycles, degassed DMF was added followed by a toluene solution of the ligand and then heating to 50°C.

After analyzing this reaction protocol, two primary differences between a small scale and a large scale reaction were considered that could potentially account for the problems in the 5 g experiment.

- On large scale addition of reagents would be slow, and the $Pd(dba)_2$ precatalyst and CN^- would be in contact for a longer time before ligand addition, and formation of active catalyst, with a risk of cyanide poisoning.
- On large scale, heating-up would be slower.

During the charging of reactants and the early stages of the reaction, the active catalyst had to form from the catalyst precursors, i.e., the dba in the $Pd(dba)_2$ had to be replaced by the $P(t\text{-}Bu)_3$ ligand to form the catalytically active $PdP(t\text{-}Bu)_3$ intermediate, before the reaction could start, and this activation process could potentially compete with CN^- poisoning of Pd.

The effect of a time delay of 0–24 min between the charging of DMF and ligand was studied. The reaction turned out to be surprisingly sensitive toward CN^- exposure as a delay of only 7 min between addition of DMF and ligand gave a reaction that stopped at ca. 15% conversion (Fig. 1).

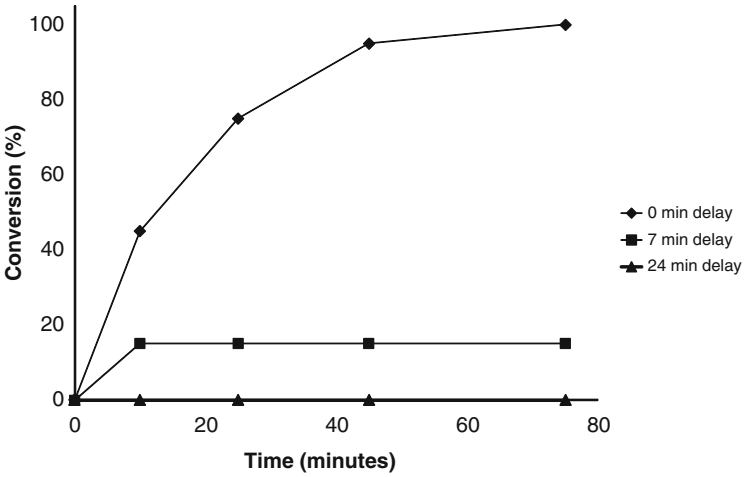


Fig. 1 Effect of delayed ligand addition

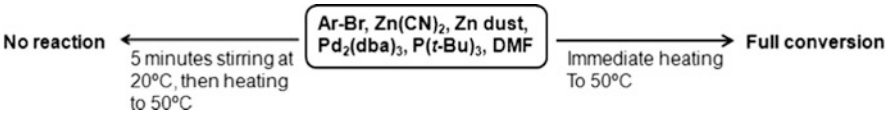


Fig. 2 Effect of delayed heating

The effect of slow heating was clearly manifested by the observation that a delay of only 5 min between addition of the reagents and heating led to a completely inactive reaction (Fig. 2).

Our interpretation of these results led to the hypothesis that CN^- poisoning of Pd competed with either the catalyst activation or the catalytic reaction. At low temperatures the poisoning was faster than the activation/catalytic reaction, whereas at 50°C the catalytic reaction was relatively faster.

Obviously, on large scale it would be impossible to achieve the short delay between addition of reagents and the rapid heating that was necessary, and it was clear that the way of setting up the reaction was crucial.

Two potential solutions to overcome these problems were suggested:

- The catalyst could be preformed or preactivated in a separate vessel and then transferred to the reaction mixture.
- $Zn(CN)_2$ could be added as the last reagent to the heated reaction mixture.

Several different ways of adding a preformed or preactivated catalyst to the reaction mixture were investigated, including incubation of the catalyst with a small amount of the aryl bromide to form the (Ar)Pd(Br)[P(*t*-Bu)$_3$] complex, a true intermediate on the catalytic cycle. However, none of the procedures led to

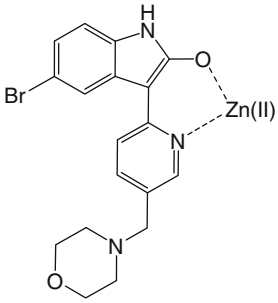


Fig. 3 Complexation of Zn(II) by the starting material

scalable conditions as the reaction did not work unless the catalyst was added at room temperature, followed by rapid heating to 50°C.

These results indicated that the reaction could not be started once the cyanide had dissolved, and in order to add final evidence, a reaction was conducted where $Zn(CN)_2$ was added as a hot slurry in DMF to the rest of the reaction components at 50°C. A hot slurry of $Zn(CN)_2$ should contain a high concentration of dissolved CN^-, which would immediately poison the catalyst upon addition of the slurry, and no reaction should be observed. *Surprisingly, the reaction went to completion in 1 hour!*

The observation that the reaction proceeded well when a hot slurry of $Zn(CN)_2$ was added to a mixture of the other reagents at 50°C, but did not start when the catalyst was added to the reaction mixture at 50°C was quite unexpected. It suggested that it was actually the combination of the aryl bromide **1** and $Zn(CN)_2$ that created an unfavorable situation.

The most reasonable rationalization of these seemingly contradictive results is that the aryl bromide **1** increases the solubility of the $Zn(CN)_2$ and thereby the CN^- concentration, by complexation to Zn(II). In fact, the pyridine nitrogen and the carbonyl moiety of the oxindole component are perfectly located to create a strong chelate with suitable Lewis acids (Fig. 3).

The finding that the reaction worked when the $Zn(CN)_2$ was added as a hot slurry, indicated that we were on track to find a scalable protocol for the reaction. However, adding $Zn(CN)_2$ as a slurry seemed unpractical, and further work was done by adding it as a solid. Indeed, addition of $Zn(CN)_2$ as the final component to the heated reaction mixture turned out to be the magic trick for the reaction, and for the first time it could be successfully scaled to first 5 g and then 32 g in the laboratory.

2.2.4 Workup and Isolation

Having established robust conditions for the reaction, the attention was directed toward the workup and isolation of the product. Efficient metal removal was of particular importance as the level in the final product had to be <10 ppm for both Pd and Zn. The method that turned out to work best was to filter the hot reaction

mixture to remove Zn (dust) and precipitated Zn salts, and then treat the filtrate with thiol-functionalized silica, filter the solution, followed by adding Na_4-EDTA(aq) to precipitate the product which was then collected by filtration. The treatment with the thiol-functionalized silica scavenger was necessary in order to reduce the Pd content to <400 ppm and the Na_4-EDTA (aq) was necessary to reduce the level of Zn to <2,000 ppm (exchanging the Na_4-EDTA(aq) to H_2O gave a Zn content of 5%). Subsequent salt formation with citric acid and recrystallization reduced the level of metal residues further to 1–2 ppm for Pd and <1 ppm for Zn.

2.2.5 Large Scale Cyanation

Due to problems with the robustness and reproducibility caused by the rather laborious procedure and air sensitivity of the P(*t*-Bu)$_3$ ligand, the reasonably air stable Pd dimer [BrPdP(*t*-Bu)$_3$]$_2$ which had also been found to perform well in the reaction (Table 1, entry 3), was used for the large scale production. Inertation was achieved by purging the reaction mixture with nitrogen below the surface until a oxygen probe dipping into the solution detected <0.01 mg/mL oxygen, as this turned out to be more reliable than the vacuum/nitrogen purge cycles. Three large scale runs with batch sizes between 2.2 and 6.7 kg were successfully conducted with an average isolated assay corrected yield of 70%.

3 Conclusion

Adding $Zn(CN)_2$ as the final reagent to the heated reaction mixture may seem straightforward, but it was actually crucial in order to achieve a robust and scalable reaction. By applying this improved protocol, even catalysts that did not perform well in the initial screen (entries 1, 4, 5, and 6, Table 1) gave reactions that went to completion within 1 h [18].

The most plausible explanation to the beneficial effect of operating in this way is that the catalyst will be activated in the heated reaction mixture, and $Zn(CN)_2$ will dissolve upon addition at a rate that is slower than the potential maximum rate of the catalytic reaction. The CN^- concentration will remain at a very low level, since it will be consumed as soon as it has entered into solution. If, however, the reaction is started at room temperature followed by heating, the rate of cyanide dissolution could be faster than the catalytic reaction, and the concentration of CN^- in solution would approach the saturation concentration, leading to catalyst poisoning.

Several improved protocols for the reaction have been reported, where various additives have been shown to improve the robustness and scope [31–34], but they all rely on high temperatures. The current example still remains one of very few reported cases where a Pd-catalyzed cyanation has been run on a large scale at temperatures <70°C [17–19]. Especially in the pharmaceutical industry where molecules tend to be heavily functionalized, the ability to run the reaction at low

temperature is a particularly attractive feature both from a compatibility and safety point of view. The general utility of the method has been repeatedly demonstrated by successful application up to 1,000 L pilot plant scale in other internal R&D projects.

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Application of Ring-Closing Metathesis Strategy to the Synthesis of Vaniprevir (MK-7009), a 20-Membered Macrocyclic HCV Protease Inhibitor

Cheng-yi Chen

Abstract Vaniprevir (MK-7009) bearing a 20-membered macrocycle and chiral components is a highly efficacious HCV protease inhibitor aiming for the treatment of chronic infection of hepatitis C virus. The efficient macrocyclization coupled with the assembling of key chiral components is of great challenge for the large-scale production of this structurally complex molecule. In this chapter, a convergent synthesis with a longest sequence of nine steps featuring highly efficient macrocyclization via ring-closing metathesis (RCM) along with the improvement in the syntheses of key components will be described. RCM for the construction of 20-membered macrocycle using low catalyst loading (0.2 mol%) and practically high concentration (0.13 M) was achieved by simultaneous and slow addition of ruthenium catalyst and the diene substrate. The strategy of using RCM in this cost-effective synthesis sets a new paradigm for the synthesis of several other macrocyclic HCV protease inhibitors at Merck Research Laboratories.

Keywords 20-Membered macrocycle · Catalyst loading · Cyclopropyl sulfonamide · HCV protease inhibitors · Heck reaction · Hydrogenation · Large-scale synthesis · Macrolactamization · Prolinol · Ring-closing metathesis · Sonogashira coupling · *tert*-Leucine · Vaniprevir (MK-7009)

Contents

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1 Introduction

Chronic infection with hepatitis C virus (HCV) is a worldwide epidemic, affecting approximately 180 million individuals around the globe. HCV is a positive-strand RNA virus of the flaviviridae family and replicates primarily in the liver. While disease progression is typically a slow process that occurs over many years, a significant fraction of patients ultimately develops serious liver disease, including cirrhosis and hepatocellular carcinoma [1]. Currently, HCV is a leading cause of death in HIV-coinfected patients and is also the most common indication for liver transplantation surgery. The existing care for HCV combines Pegylated Interferon and Ribavirin but only provides a modest cure rate [2]. This low cure rate is partially attributed to the fact that patient response is highly dependent on the genotype of the virus. As such, a variety of gene targets have been evaluated to identify new modes of treatment. The launch of two new drugs, Boceprevir and Telaprevir, shows promise to improve the success rate in the HCV therapy [3]. Despite these tremendous accomplishments, additional improvements in the area of genotype coverage, drug dose, and cure rate are still desired. Vaniprevir (MK-7009) is a potent HCV NS3/4a protease inhibitor that is being evaluated for the treatment of HCV at the late stage of clinical studies (Fig. 1) [4, 5]. To ensure the supply of the drug for ongoing clinical studies, a chemical process amenable to production of multi-kilogram quantities of MK-7009 was required.

The primary challenges to develop a scalable, cost-effective synthesis for MK-7009 are identifying an efficient ring-closing strategy and concise and efficient

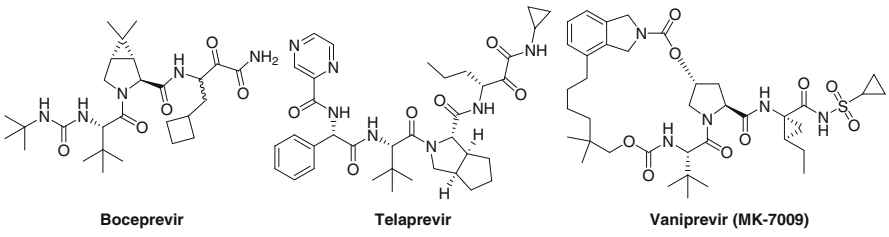
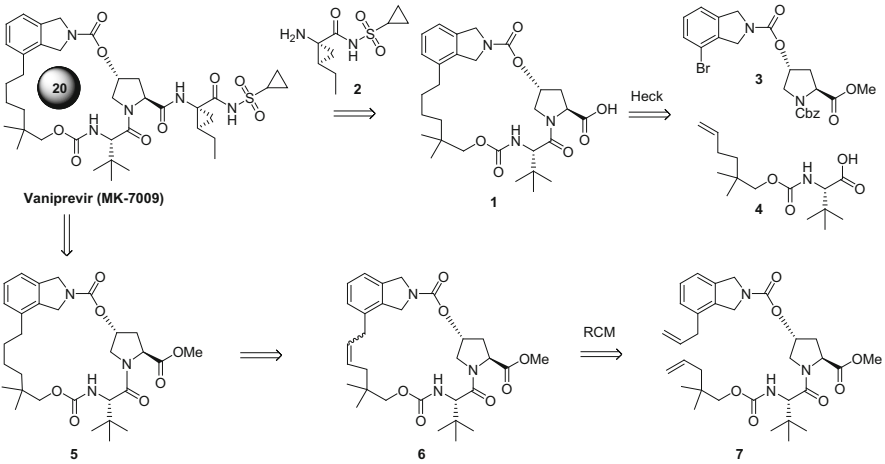


Fig. 1 HCV NS3/4a protease inhibitors



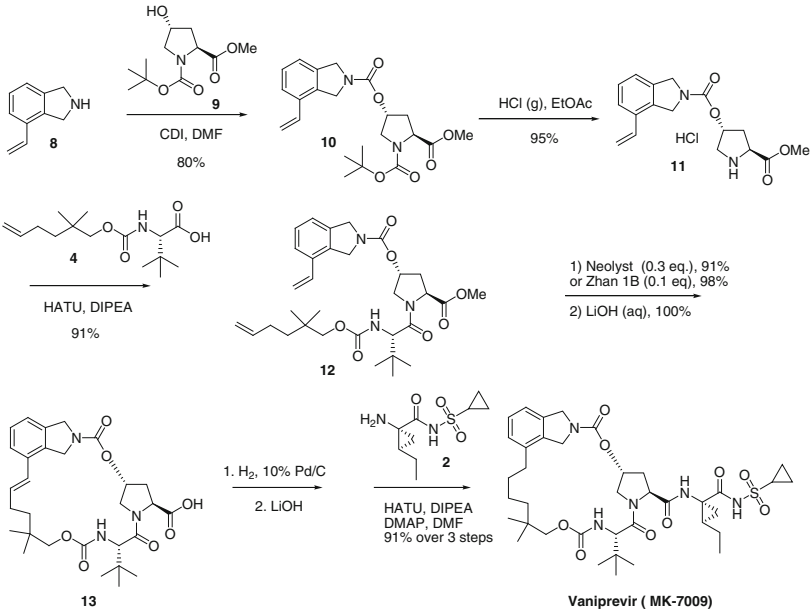
Scheme 1 Retrosynthetic analysis of Vaniprevir (MK-7009)

syntheses of the key intermediates needed to construct the macrocycle precursor. Ideally, these key components could be stitched together in a convergent manner with minimal linear steps. The first practical synthesis of MK-7009 on large scale was based on the lactamization to form the 20-membered macrocycle [5]. The macrocycle precursor was synthesized via a Heck reaction to orthogonally bring in two chiral building blocks (Scheme 1). The process proceeded in 10 linear steps and 21 total steps with 30% overall yield and has served as a practical means of producing large quantities (>600 kg) of MK-7009 to support the early safety and clinical studies of this compound. Although the process has been proven to be scalable, it suffers from low volume productivity in the macrolactamization step which requires high dilution conditions (0.05 M, 50 L/kg of substrate) to achieve a satisfactory yield. With each step fully optimized, further improvement of the process is of great challenge. Hence the definition and development of a more efficient route was evaluated to ultimately lower the production cost. Herein, we wish to describe a new synthetic route based on the ring-closing metathesis (RCM) for the construction of the 20-membered macrocycle (Scheme 1) [6]. In addition, improvement in the syntheses of key intermediates will be disclosed.

2 Background

2.1 Medicinal Chemistry Synthesis of Vaniprevir (MK-7009)

As illustrated in Scheme 2, the medicinal chemistry synthesis of MK-7009 used an RCM as the key step to construct the 20-membered macrocycle [4, 5]. Hence, vinyl isoindoline **8** was coupled with hydroxyproline **9** to form prolinol ester **11** after deprotection of the Boc group. Coupling of **11** with the *tert*-leucine linker (**4**)

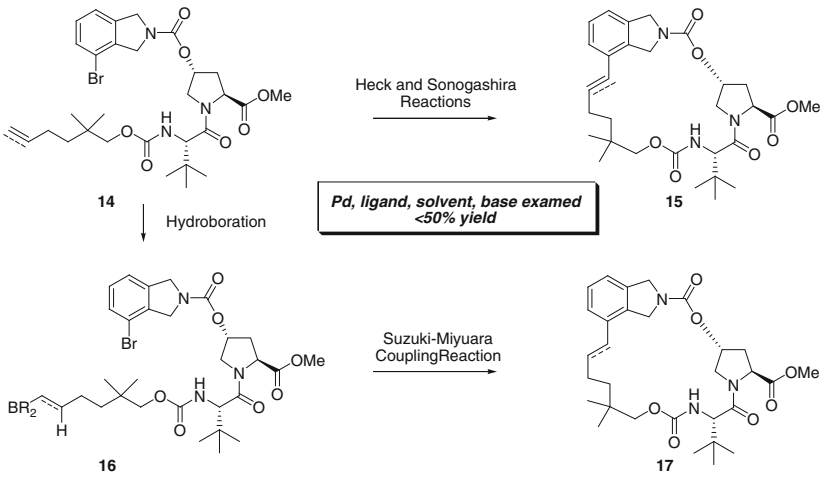


Scheme 2 Medicinal chemistry synthesis of Vaniprevir (MK-7009)

afforded diene **12**. The macrocycle (**13**) was constructed using an RCM reaction catalyzed by ruthenium compounds under high dilution conditions. Subsequent coupling of the cyclopropyl sulfonamide (**2**) with macrocyclic acid leads to Vaniprevir (MK-7009). Despite the complexity of the molecule, this fit-for-purpose synthetic protocol is only ten linear steps and importantly it facilitates the modular synthesis of derivatives for biological assay screening. With Vaniprevir (MK-7009) identified as a clinical candidate for further development, the med-chem route was evaluated but was ruled out for large-scale synthesis of Vaniprevir (MK-7009) in a cost-effective manner due to high catalyst loading (up to 30 mol%). Efforts on decreasing the catalyst loading, however, encountered difficulties with oligomerization, lower yields, and removal of residual metal. It was concluded that extensive work is needed to make the process based on the RCM of this diene amenable to scale up in a cost-effective manner. Given these challenges as well as project timelines and material demands, process development of this specific strategy was halted and efforts were refocused on identifying a more practical ring-closing strategy.

2.2 Evaluation of Alternative Ring-Closing Strategy

In recent years, a wide array of metal-catalyzed coupling reactions has been effectively applied to C–C bond formation, including the C–C bond formation for

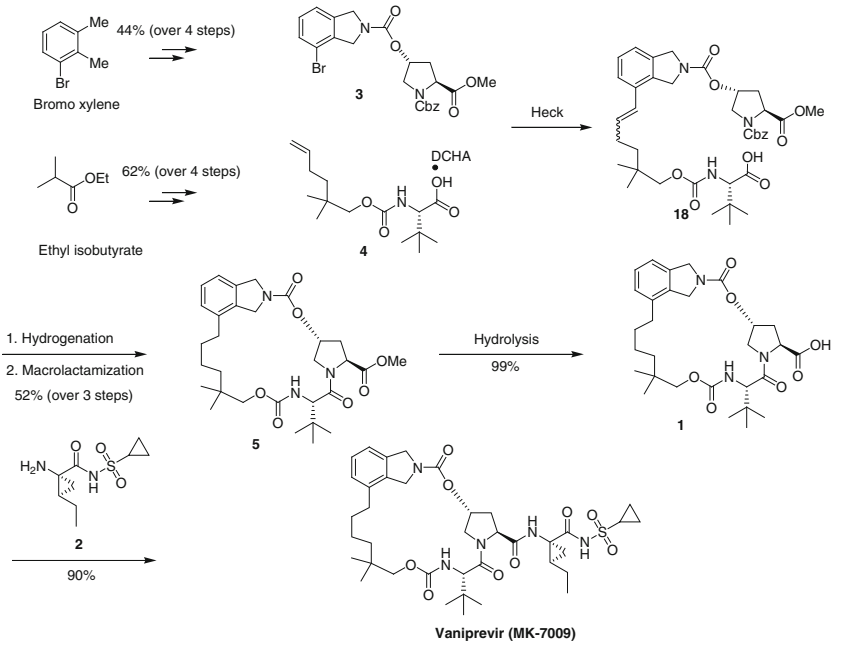


Scheme 3 Alternative ring-closing strategy

the construction of macrocycle [7–10]. We next set out to explore ring-closing strategy via palladium-catalyzed intramolecular C–C bond formation. The vinyl group in the RCM substrate (**12**) was replaced by a bromo atom, which serves as a handle to study various palladium-catalyzed coupling reactions for construction of macrocycles. For this purpose, intermediate **14** was readily synthesized and was subjected to a set of palladium-catalyzed cyclizations as shown in Scheme 3. Particular efforts were focused on the Heck, Sonogashira, and Suzuki-Miyuara macrocyclizations [11–13]. All conditions examined produced the desired macrocycle; however, yields were uniformly modest (<50%) as competing oligomerization and dehydrobromination occurred in the reaction. A substantial amount of 19-membered ring formation was formed under Heck coupling reaction conditions even at very high dilutions (200 mL/g substrate). We concluded that these approaches would require significant optimization to improve the macrocyclization yield. Concurrently, a route based on an intermolecular Heck reaction followed by hydrogenation and macrolactamization looked promising and was chosen for further development.

2.3 Synthetic Route Based on Heck Reaction–Hydrogenation–Lactamization for Large-Scale Production of Vaniprevir (MK-7009)

The synthesis of MK-7009 based on a through process via Heck reaction–hydrogenation–macrolactamization was next explored (Scheme 4) [14]. Two key chiral building blocks were readily prepared from commercially available



Scheme 4 Synthesis of Vaniprevir (MK-7009) based on Heck coupling reaction

starting materials over four steps in 62% and 44%, respectively (*vide infra*). One of the key features of this route is the orthogonal introduction of both chiral intermediates, bromoindoline **3** and the *tert*-leucine linker (**4**), via an intermolecular Heck reaction. Hydrogenation of the Heck reaction product (**18**) followed by the EDC-mediated macrolactamization afforded macrocyclic ester **5** in 52% yield over three steps. Hydrolysis of the macrocyclic ester followed by coupling with the cyclopropyl sulfonamide side chain (**2**) afforded Vaniprevir (MK-7009) in 90% yield. The choice of the Heck reaction followed by macrolactamization was based on the overall efficiency and cost of the process. Thus far, this process has been used as a practical means of preparing large quantities (>600 kg) of MK-7009 to support safety and clinical studies of this compound. The process, however, suffers from two drawbacks. First, the Heck reaction afforded a mixture of linear and branched products in 8:1 ratio. Second, high dilution conditions used in the macrolactamization step resulted in low volume productivity. As such extensive efforts were taken to optimize the regioselectivity of the Heck reaction by screening various combinations of palladium catalysts and ligands, all of which proved to be fruitless. Unfortunately, the efficiency of the macrolactamization run under high dilution conditions (0.05 M, 50 L/kg substrate) to achieve satisfactory yield could not be improved. This low volume productivity is not ideal for the manufacturing production of MK-7009 since it generates substantial amount of waste solvents.

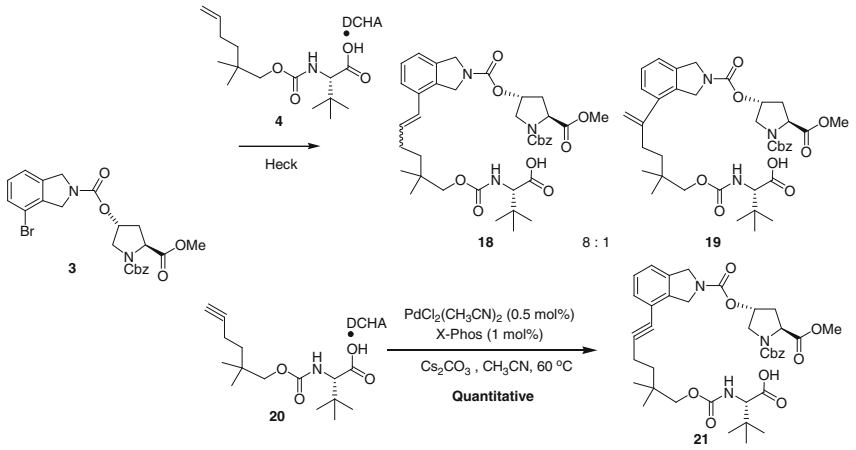
2.4 Synthetic Route Based on Sonogashira Coupling Reaction

As mentioned in Sect. 2.3, the Heck reaction generated ~13% of the branched byproduct due to 8:1 regioselectivity, which calls for removal in the downstream process, resulting in a net loss in the yield. The regioselectivity issue was addressed by implementation of the Sonogashira coupling reaction. Hence, the acetylene piece was prepared in a cost-effective manner from the corresponding olefin piece (**4**) via dibromination and double elimination. Palladium-catalyzed Sonogashira reaction between bromo isoindoline **3** and acetylene **20** afforded the desired product (**21**) quantitatively (Scheme 5). Hydrogenation of the acetylene moiety would lead to the same macrolactamization precursor in the route based on the Heck reaction. Hence, the route based on Sonogashira coupling reaction solved regiochemistry problem encountered in the Heck reaction. Given the fact that the macrolactamization would still need to be run under high dilution conditions (0.05 M, 50 L/kg substrate), we explored the RCM [15] as a means for the macrocyclic ring formation and aimed to significantly improve the efficiency.

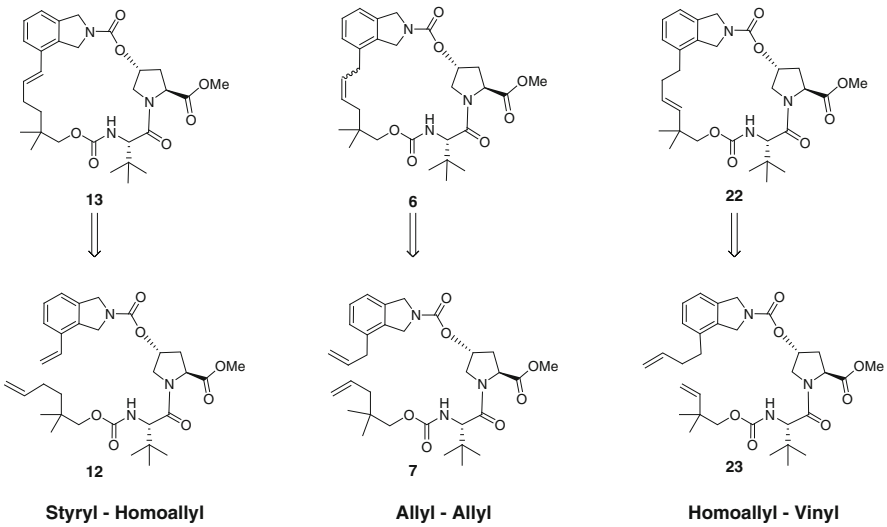
3 New Synthetic Route Based on RCM

3.1 Retrosynthetic Analysis

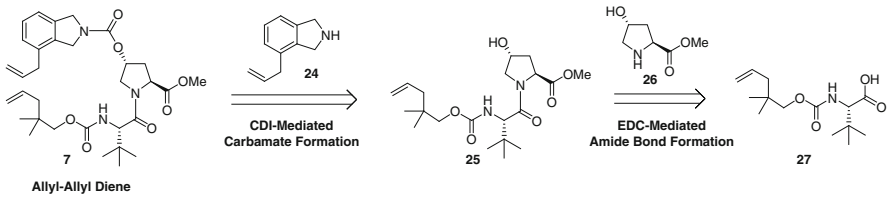
As shown in Scheme 6, there are three possible RCM options for the construction of the macrocycle based on different position of olefin metathesis: styryl–homoallyl, allyl–allyl, and homoallyl–vinyl diene. Using the styryl–homoallyl diene (**12**) in the



Scheme 5 Synthesis of Vaniprevir (MK-7009) based on Sonogashira coupling reaction



Scheme 6 Retrosynthetic analysis for ring-closing metathesis (RCM)



Scheme 7 Retrosynthetic analysis for allyl–allyl diene 7

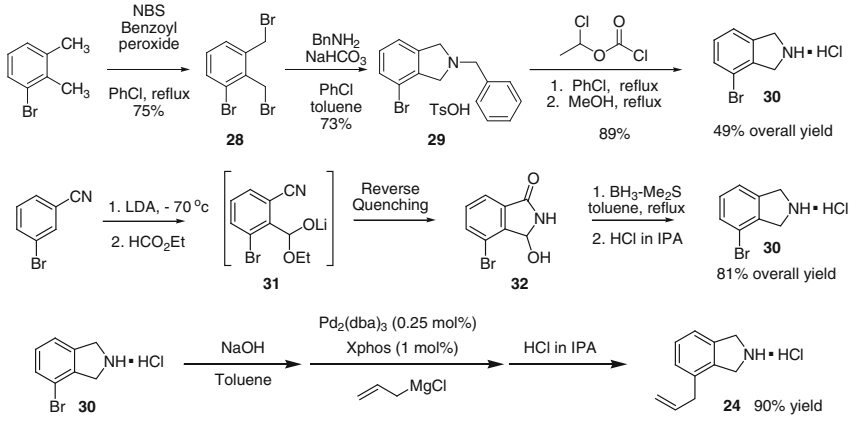
medicinal chemistry synthesis (Sect. 2.1) required high catalyst loading to obtain high yield. Unfortunately, the efficiency of the RCM could not be improved with the use of the Hoveyda–Grubbs second generation catalyst (**41**). Hence this substrate was not further investigated. We envisioned that the preparation of allyl–allyl diene **7** would be more straightforward as compared to that of the homoallyl–vinyl substrate (**23**). The introduction of two allylic moieties to the diene from more readily available allylic starting material will likely be more cost-effective as well. Therefore, we focused on the efficient synthesis of allyl–allyl diene **7** and investigation of its RCM.

The retrosynthetic analysis of the allyl–allyl diene (**7**) is shown in Scheme 6. We conceived that diene **7** could be derived from the coupling of prolinol side chain (**25**) with the allyl isoindoline (**24**). The prolinol side chain (**25**), in turn, could be prepared from the coupling of prolinol ester **26** and *tert*-leucine linker **27** (Scheme 7).

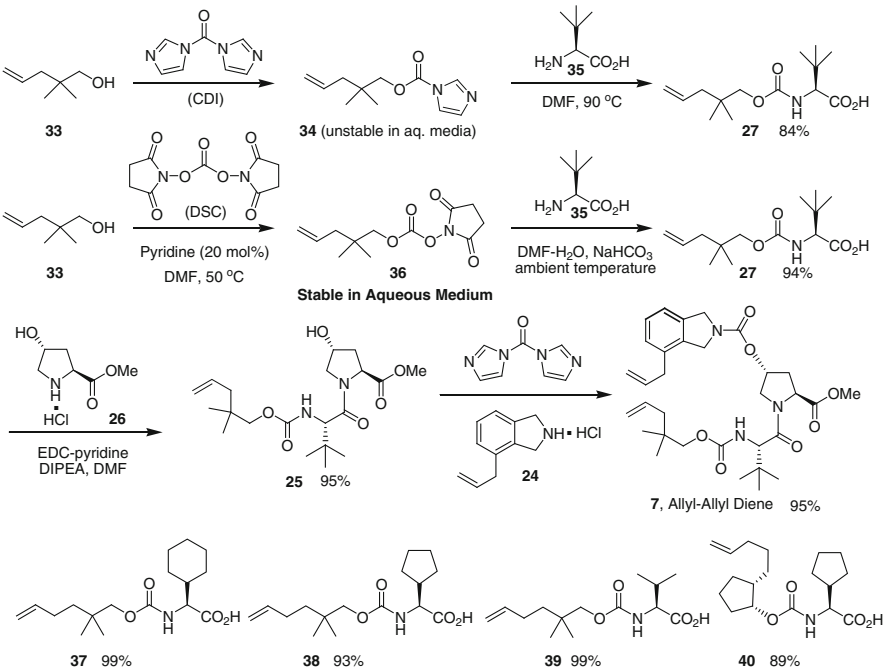
3.2 *Preparation of Allyl–Allyl Diene*

We started the synthesis of allyl–allyl diene **7** by investigation of a cost-effective preparation of allyl isoindoline **24** from bromoisoindoline **30** via a Kumada coupling reaction using allyl magnesium chloride [16]. The bromoisoindoline (**30**) was previously prepared in four steps from bromoxylene as shown in Scheme 8. Bromination of bromoxylene using NBS in the presence of benzoyl peroxide afforded tribromo species **28** in 75% yield. The crude tribromide was subjected to double displacement with benzylamine to afford *N*-benzyl bromoisoindoline which was isolated as tosylate **29** in 73% yield. Subsequent debenzylation using 1-Chloroethylchloroformate afforded bromoisoindoline **30**. The three-step sequence proceeded in 49% overall yield but there appeared to be some room for improvement of each step in the process. Therefore, we chose to develop a more efficient and cost-effective route from very inexpensive starting material, 3-bromobenzonitrile. Hence, the regioselective deprotonation of 3-bromobenzonitrile at 2-position followed by addition of ethyl formate gave rise to alkoxide intermediate **31**. Upon reverse quenching of the reaction mixture to aqueous media, the alkoxide was readily converted to hydroxyl lactam **32**. Borane reduction of the hydroxyl lactam followed by HCl salt formation afforded bromoisoindoline **30** in 81% overall yield over two steps. The bromoisoindoline HCl salt (**30**) was converted to the allyl isoindoline (**24**) in 90% yield via a one pot process using a Kumada coupling using 2 equiv allyl magnesium chloride.

The other olefin piece for the diene synthesis was prepared via carbamate formation between alcohol **33** and *tert*-leucine (**35**) (Scheme 9). The alcohol was first activated with CDI to form acyl imidazole **34**, which is labile to hydrolysis. The coupling of the acyl imidazole with *tert*-leucine (**35**) has to be carried out in anhydrous DMF at elevated temperature due to poor solubility of *tert*-leucine in DMF. The reaction afforded *tert*-leucine carbamate **27** in 84% yield. An impurity



Scheme 8 Preparation of allyl isoindoline 24

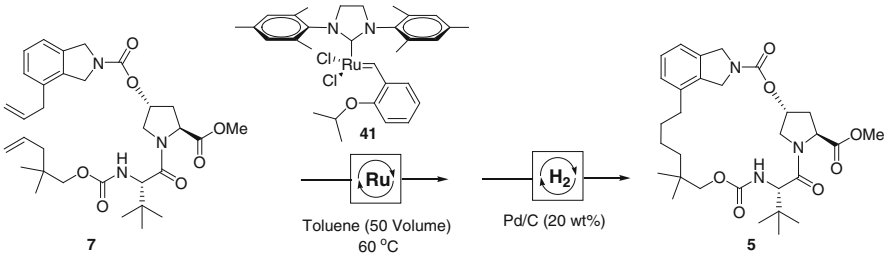


Scheme 9 Preparation of allyl–allyl diene 7

(10%) derived from DMF formed in the reaction, which was difficult to remove in the workup. A switch to another activating agent, DSC, for the acylation of alcohol **33** afforded the succinamide intermediate (**36**) smoothly [17]. The intermediate is stable in aqueous media so that the coupling reaction can be run in aqueous DMF at ambient temperature. The solubility of *tert*-leucine in aqueous DMF was substantially improved and hence the coupling reaction proceeded in much higher yield to afford carbamate **27** in 94% yield. We subsequently showed that DSC serves as a general activating agent to facilitate the highly efficient carbamate formation from alcohols and amino acids as shown in the selected examples (carbamates **37**–**40**). Subsequent EDC-mediated coupling of *tert*-leucine carbamate **27** with prolinol **26** afforded amide **25** in 95% yield. Activation of the hydroxyl group with CDI followed by coupling with allyl isoindoline **24** completed the synthesis of allyl–allyl diene **7** in high overall yield. The process for the synthesis of allyl–allyl diene was later demonstrated on the kilogram scale uneventfully.

3.3 Optimization of RCM of Allyl–Allyl Diene Ester

With the availability of allyl–allyl diene **7**, the focus turned toward optimization of the RCM of this allyl–allyl diene for the construction of the macrolactam. The tasks

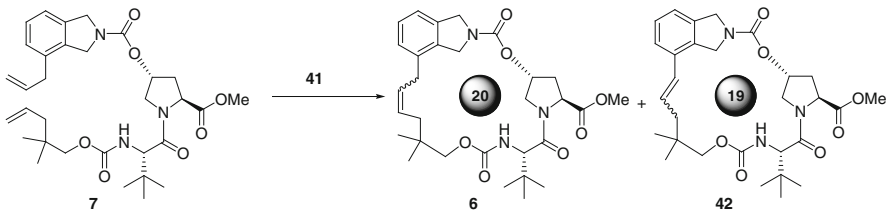


Addition mode	Catalyst loading	Yield
one-pot	1 mol%	57%
one-pot	5 mol%	67%
slow addition of catalyst	1 mol%	82%

Scheme 10 Effect of slow addition of catalyst

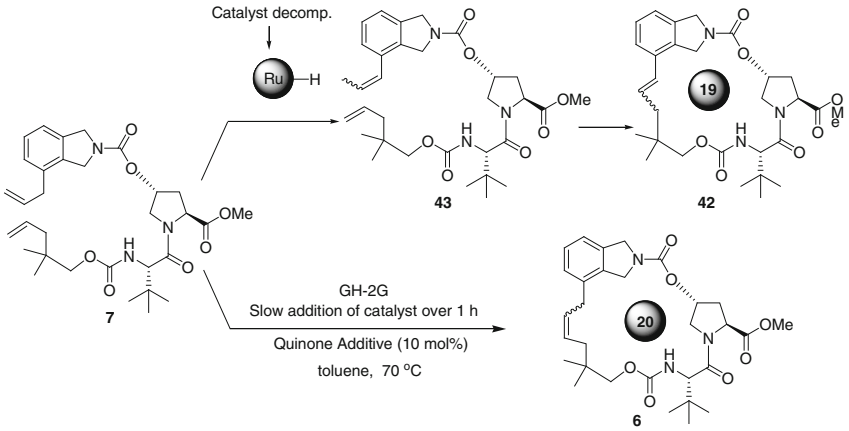
for optimization were twofolds: to circumvent the high dilution conditions for the macrocyclization and maximize the catalyst efficiency for the RCM step. As illustrated in Scheme 10, the first RCM reaction on the allyl–allyl diene was run using 1 mol% of the Grubbs–Hoveyda second generation catalyst (**41**) under high dilution conditions to gain proof of concept and gauge the catalyst activity. The reaction, however, only afforded the desired macrocyclic ester (**5**) in 57% yield. Increasing the catalyst loading to 5 mol% only marginally improved the yield to 67%. Obviously, the reaction called for significant optimization to achieve high efficiency. Profiling of the RCM reaction showed that the catalytic activity was very high in the beginning of the reaction but quickly diminished as the reaction proceeded further. At the end, many side products including oligomers were formed. Given this fact, we envisioned that slow addition of the catalyst may sustain the catalyst activity during the reaction. Delightfully, this simple modification increased the yield to 82% when 1 mol% catalyst was added over 1 h at 60°C to diene **7** in toluene (50 mL/g substrate).

We next shifted our attention to address the common high dilution problem associated with macrocyclization by implementing slow addition of the catalyst but at higher reaction concentration. The reaction run under 30 mL/g of diene, however, afforded the desired 20-membered product in only 61% yield. A 19-membered macrocyclic ester (**42**) was formed in 9% yield as a major byproduct (Scheme 11). We postulated that the 19-membered ring was derived from the RCM of the styryl isomer (**43**), which in turn was generated from the isomerization of allylic diene **7** (Scheme 12). It is known that Ru–H compound generated through decomposition of the Ru-catalyst (**41**) is responsible for the isomerization of the olefin. This isomerization pathway could be suppressed by the addition of quinone additives which inhibit the decomposition of the catalyst [18]. After screening a few quinone additives, we found that 2,6-dichloroquinone effectively decreased the formation of 19-membered ring to $<1\%$ when the reaction was run at 20 mL/g diene concentration. More importantly, the catalyst loading was lowered to 0.2 mol% which is viable for large-scale production. Continuing studies revealed that running



Reaction conditions	Volume Ratio (mL/g diene)	20-Mac Ester	19-Mac Ester
1 mol% GH-2G Slow addition of catalyst over 1 h toluene, 60 °C	50	80%	<1%
	30	61%	9%

Scheme 11 Formation of 19-membered ring 42



entry	**3** (mol%)	Temperature (°C)	Quinone	Volume	**6** (yield %)	**42** (yield %)
1	1	70	None	20	62%	8%
2	0.5	70	2,6-dichloroquinone	20	72%	<1%
3	0.2	70	2,6-dichloroquinone	20	72%	<1%
4	0.2	70	2,6-dichloroquinone	20	84%	1.4%
5*	0.2	100	2,6-dichloroquinone	25	88%	<1%
6	**0.2**	**reflux**	**2,6-dichloroquinone**	**13.5**	**88%**	**1.2%**

*nitrogen gas bubbling during reaction

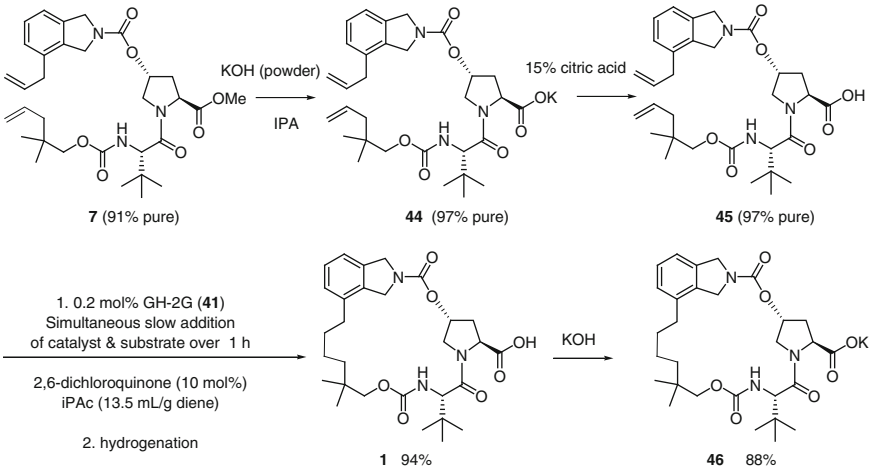
Scheme 12 Effect of 2,6-dichloroquinone

the reaction at higher temperature gave rise to the product in higher yield. Moreover, bubbling of nitrogen gas through the reaction media to remove ethylene gas from the reaction media afforded product **6** in 88% yield (entry 5). To mimic high dilute conditions, we decided to carry out simultaneous, slow addition of both catalyst and diene to toluene at reflux over 1 h. The efficiency of the reaction was

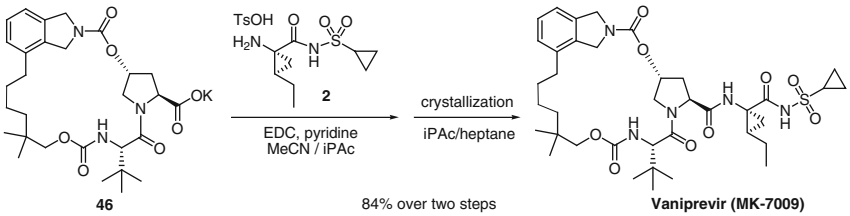
sustainable under such conditions with the product **6** isolated in 88% yield, and the total volume of solvent/substrate ratio was reduced to 13.5 mL/g of diene. Hydrogenation of macrocyclic ester **6** was conveniently carried out in a 9:1 mixture of toluene:IPA. Solvent switch to IPA from toluene–IPA mixture followed by crystallization provided the key intermediate, macrocyclic ester **5**, in 82% isolation yield with high purity (>99% HPLC purity). It should also be noted that the single crystallization of the macrocyclic ester using from IPA–water resulted in extremely low levels of residual metals (both ruthenium and palladium content <10 ppm). With the optimization conditions in hand, we successfully demonstrated the process of RCM followed by hydrogenation on a 100-g scale using 0.2 mol% of the Grubbs–Hoveyda second generation catalyst at 13.5 mL/g (0.18 M) concentration in toluene. The demonstration of the optimized process featuring RCM as a means for the construction of macrocycle forms the base for the development of the manufacturing process of Vaniprevir (MK-7009).

3.4 RCM of Allyl–Allyl Diene Acid

As anticipated, the successful RCM reaction under low catalyst loading will be highly dependent on the purity of the starting material, diene ester **7**. The diene ester, on the other hand, is an oil which limits purification options for purity upgrade. For robustness of the process using the RCM strategy for the macrocycle, we investigated two ester derivatives, potassium salt **44** and free acid **45**. The potassium salt was conveniently prepared by treatment of diene ester **7** with powdered KOH in IPA. Upon saponification, potassium salt **44** crystallized spontaneously from the reaction media. Treatment of potassium salt **44** with 10% citric



Scheme 13 Ring-closing metathesis of diene acid 45



Scheme 14 Direct coupling reaction of K-dalt 46 and cyclopropyl sulfonamide tosylate 2

acid smoothly converted the salt to free acid **45** and upgraded the purity as well. For example, the purity could be readily upgraded from ester (91% pure) to salt or free acid (97% pure) using these two simple procedures. The potassium salt was not suitable for the RCM due to its poor solubility in organic solvents such as toluene or IPAc. Using the conditions defined for diene ester **7**, the RCM of diene acid **45** in IPAc proceeded smoothly to the desired product, macrocyclic acid **1**, in 94% yield after hydrogenation. The macrocyclic acid was purified through salt formation to afford potassium salt **46** with excellent purity upgrade. The potassium salt (**46**) also serves as the penultimate for the efficient synthesis for Vaniprevir (MK-7009) (Scheme 13).

3.5 End Game for the Synthesis of Vaniprevir (MK-7009)

With the availability of both potassium salt **46** and cyclopropyl sulfonamide **2** as tosylate [19], direct coupling of both species without salt breaking of each component was investigated. Delightfully, the coupling reaction mediated by EDC and pyridine proceeded cleanly to afford Vaniprevir (MK-7009) in 84% yield and excellent purity after crystallization from IPAc/heptane [20] (Scheme 14).

4 Conclusions

In summary, we have defined and developed a highly efficient synthesis of Vaniprevir (MK-7009) featuring RCM of a fully elaborated diene. The synthesis proceeds with a longest sequence of ten steps, combining four important chiral components, *tert*-leucine unit, hydroxy proline unit, isoindoline unit, and cyclopropyl amino acid side chain. Simultaneous slow addition of ruthenium catalyst and diene substrate enables the RCM for the construction of 20-membered ring to proceed at low catalyst loading (0.2 mol%) without using high dilute conditions. The strategy was successfully applied to the efficient synthesis of Vaniprevir (MK-7009) as well as other HCV drug candidates bearing macrocycles.

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