

# Transition Metal Catalysis for Pharmaceutical Intermediates and APIs

Adriano F. Indolese\*, Domenic Wasescha, Thomas Eisele, and Christoph Bucher

**Abstract:** Rohner AG, a medium-sized Swiss company, has moved from toll manufacturing of building blocks and starting materials to the custom manufacturing of intermediates and APIs for the life science industry. Therefore, Rohner AG has expanded its technology portfolio to new technologies such as transition metal catalysis. Examples for asymmetric hydrogenation, Suzuki coupling and carbonylation are provided. In addition, the necessary changes in equipment and project management are presented and discussed.

**Keywords:** Asymmetric hydrogenation · Carbonylation · Custom synthesis · Suzuki coupling

## Introduction

The manufacture of fine chemicals for the pharmaceutical industry has become an increasingly tough business. On the one hand the rate of approval of new drugs has decreased and the outlook is bleak. On the other hand worldwide production capacity has been increased because of the expected annual growth of 7–8% in that particular sector. Companies from India and Far East are entering the field as well.

To survive in such a competitive environment, an adequate business strategy is of vital importance for any company. Swiss companies certainly do not have such a favorable cost structure as companies in the Far East or India that they can compete solely on price. Therefore, Rohner's business approach is customer and technology oriented and focuses on the fast and flexible realization of highly complex projects. To meet the needs and expectations of its customers, Rohner AG has heavily invested in technology and equipment and has changed its organization and procedures to a project-oriented workflow. In this paper, the newly implemented technologies, such as C–C-coupling reactions, asymmetric hydrogenation, and carbonylation will be presented, and their importance towards a more successful business will be discussed.

## Integration of New Technologies in the Existing Portfolio

Rohner AG was until the 1980s a producer of dyes and a toll manufacturer for the chemical industry around Basel (Switzerland). Rohner AG established itself as a well-known specialist in the synthesis of complex aromatic building blocks and has in depth expertise in reactions such as sulfonation, nitration, halogenation, alkylation, diazotation of arenes and heteroarenes, and the reduction of aromatic nitro groups. Hydrogen transfer catalysis (HTC) of reduction of nitro groups using hydrazine hydrate as the hydrogen donor is one of Rohner's specialties. This unique technology was developed by Rohner AG and allows the selective reduction of nitro arenes even in presence of labile groups such as aromatic halogens and carbon double or triple bonds. For this technology, Rohner AG received the 'Innovationspreis von Basel-Landschaft' in 1993.

Another specialty of Rohner AG is the synthesis of benzonitriles using either copper cyanides or sodium and potassium cyanide respectively. Because of the high toxicity of HCN, the technology requires permanent monitoring of the working environment and special protecting measures.

## C–C-Coupling Reactions

Since 1990, Rohner AG has focused on custom synthesis for the life science industry. Quite obviously in order to accomplish this challenging repositioning, Rohner AG had to change the way in which it handles projects. Sound project management and an open and easy communication are the keys

for the successful realization of complex projects. In addition, the company had to broaden its technology portfolio to meet the requirements of the life science industry. The newly developed technologies must also be of interest to the customers and should expand the existing expertise. Thus, Rohner AG has decided to enter the fields of palladium and nickel catalyzed C–C-coupling reactions, asymmetric hydrogenations, and carbonylation reactions.

C–C-coupling reactions have now become standard reactions in synthetic chemistry and are widely used in research departments of pharmaceutical and specialty chemical companies. They are the method of choice for the synthesis of many important substructures, which had often not been accessible at all, or only *via* cumbersome and tedious traditional chemical routes (Fig. 1). Important examples are the cross-coupling reactions to form unsymmetrical biaryls, or the Sonogashira reaction to aryl acetylenes. The Buchwald-Hartwig reaction is an important methodology for the synthesis of aryl amines. Palladium-catalyzed coupling reactions were investigated heavily in recent years, and are now very stable and reliable, providing the desired products selectively and in good yields. Aryl iodides, bromides, and even chlorides, as well as diazotium salts and sulfonates are suitable starting materials. Since these reactions are commonly used in research nowadays, the molecules evolving with the use of these pathways must be synthesized with basically the same technology on large scale. Several syntheses have already been scaled-up demonstrating the possibility to perform the reactions under commercial scale conditions.

\*Correspondence: Dr. A.F. Indolese  
Rohner AG  
Gempenstrasse 6  
CH-4133 Pratteln  
Tel.: +41 61 825 1542  
Fax: +41 61 825 1312  
E-Mail: aindolese@rohnerag.ch

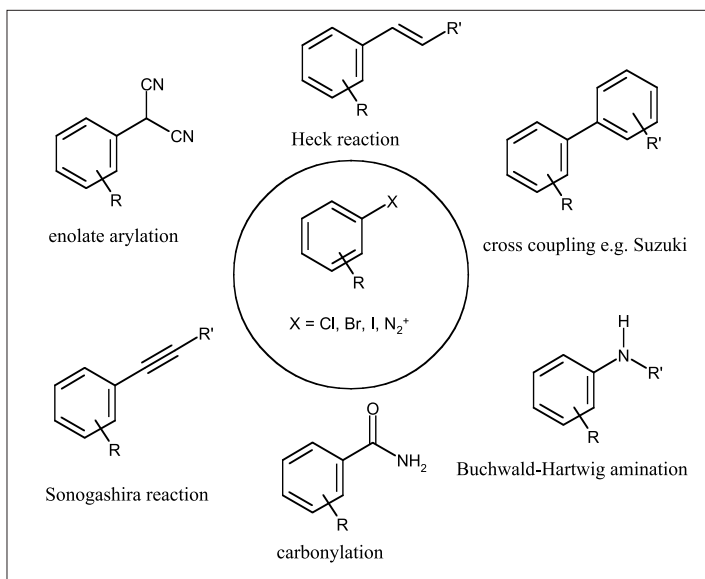


Fig. 1. Palladium-catalyzed C-C-coupling reactions

For C-C-coupling reactions, Rohner AG has gathered the necessary know-how to develop the respective processes quickly and successfully. For palladium-catalyzed reactions with aryl halides, diazonium salts and aryl sulfonates, the expertise in transition metal catalysis (TMC) is combined with the existing know-how in aromatic chemistry and organometallics, which are the starting materials for the C-C-coupling reactions. The quality of the starting materials is one of the most important issues in TMC, since small impurities can act as catalyst poisons and can have an adverse effect on the catalytic reaction. Control over the quality of the starting materials provides therefore a real competitive advantage.

Rohner AG has investigated most of the known C-C-coupling reactions in the laboratory, and several exemplary reactions were scaled up, e.g. the Suzuki reaction of 5-bromo-indol which has been performed on 100 l scale in the pilot plant using only 0.15 % catalyst (Scheme 1). The 4-cyano-benzeneboronic acid was produced in-house starting from the 4-bromo-benzonitrile *via* a low temperature reaction. Both starting materials, the 4-bromo-benzonitrile and the 5-bromo-indole, are typical Rohner products, ensuring a reliable quality standard. This example demonstrates nicely how transition metal catalysis can be used together with the traditional know-how in aromatic chemistry to produce highly complex molecules.

resolution techniques, e.g. crystallization of diastereomeric salts or chromatography, and chemical asymmetric technologies such as asymmetric hydrogenation. Among these methods, asymmetric hydrogenation is often the most reliable and least expensive method for the introduction of the chiral center.

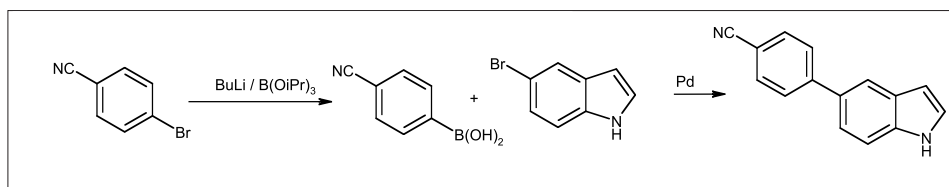
In an asymmetric hydrogenation a C=O, C=N or C=C double bond is hydrogenated to form the corresponding chiral alcohol, amine or carbon skeleton, by using a transition metal complex with a chiral ligand. Many of these systems and ligands are patent protected thus large companies often try to develop their own. However, this approach is too costly for small companies. Rohner AG has therefore decided to rely on external collaboration in asymmetric hydrogenation in order to gain access to proprietary catalysts and know-how. Rohner itself focuses on the application and the scale-up of these processes and the production. In most cases, the synthesis and the catalyst for a certain transformation is often provided by the customer; this is especially true in the case of a large pharmaceutical company. If

not, Rohner AG collaborates with technology providers that develop the catalytic process and provide the license for the catalyst. Rohner AG takes over the rest. Along with the development of the preceding and following steps, the asymmetric hydrogenation step is scaled-up and developed fully, ready for large-scale production.

An illustrative example is the asymmetric hydrogenation of 3,5-bis-trifluoromethyl-acetophenone (Scheme 2). Solvias AG, a world-leading specialist for asymmetric hydrogenation located in Basel, developed the process. The catalyst for this particular transformation is a ruthenium complex with a phosphine-oxazoline ligand, developed and patented by Solvias. They optimized the reaction conditions and synthesized the catalyst. Rohner AG streamlined the process and scaled the reaction up to 4000 l, producing the chiral alcohol on a hundred kilogram scale. The established project management enabled a smooth technology transfer leading to completion of the project within only two months. The chiral alcohol showed an enantiomeric excess of higher than 98%. Impressively, only 0.005% of the catalyst was required to convert the ketone completely to the chiral alcohol. Quality of the starting material and handling of the catalyst turn out to be the most critical issues. Special measures were necessary to transfer the catalyst solution to the reaction vessel under inert conditions. Another challenge is the removal of traces of ruthenium from the product. The metal content was successfully reduced to 0.3 ppm by adsorbing the ruthenium on charcoal.

## Carbonylation

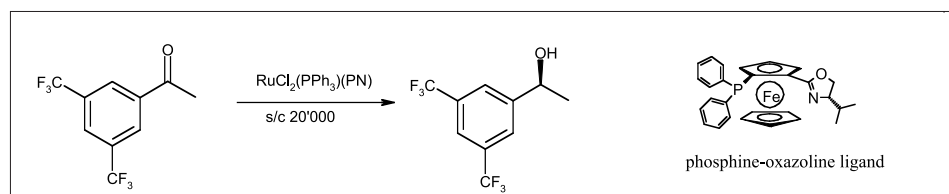
The third technology in Rohner's TMC portfolio, carbonylation, is used for the synthesis of benzoic acid derivatives. Carbonylation reactions are closely related to C-C-coupling reactions with respect to catalytic cycle and catalysts. Similar to hydrogenation



Scheme 1. Synthesis of 4-cyano-benzeneboronic acid and Suzuki coupling

## Asymmetric Hydrogenation

Most modern APIs possess at least one chiral centre and have to be sold in enantiomerically pure form. The different ways to produce enantiomeric pure compounds can be classified in four groups: chiral pool technologies (naturally occurring chiral products), biological asymmetric synthesis,



Scheme 2. Asymmetric hydrogenation

pressure vessels are necessary to perform the reactions. However, additional safety measures must be in place to handle the highly toxic, odorless carbon monoxide.

Carbonylation is a very versatile reaction, which can lead to a wide variety of benzoic acid derivatives depending on which nucleophile is used (Fig. 2). Rohner AG has built up a huge know-how over the years and is currently able to run the reaction up to 400 l (pilot plant scale). One interesting example of carbonylation is the synthesis of the succinimidyl ester, an activated ester that can be converted to many very useful products such as amines, ketones or aldehydes (Scheme 3). The reaction of 4-bromo-benzonitrile has now been run on kilogram scale using only 0.1% catalyst and the product was obtained in good yields.

## Equipment

Chemistry however is only one part of the story. To produce fine chemicals on large scale the appropriate equipment must be available. Rohner AG has therefore installed the necessary equipment in recent years. High-pressure reactions can now be carried out in vessels ranging from 1 l, 20 l, 400 l, to 4000 l (Fig. 3). Pressure up to 60 bar can be applied and all vessels are made of Inconel 686, an alloy that is highly resistant against acidic media. These vessels are capable of running hydrogenations in almost all conditions.

For the synthesis of organometallic compounds, which are often needed as the coupling components in C–C-couplings, there are several low temperature vessels available from 60 l up to 2500 l. Also recently, Rohner AG has installed the facilities to run CO chemistry up to 400 l.

As Rohner AG is working for the life science industry, all the equipment is certified to work under cGMP.

## Conclusion

Transition metal catalysis is not only a useful and advanced technology on small scale, but will surely develop into a technology which will make the difference between being a successful contract manufacturer on the cutting edge of technology and a mere mass supplier of materials competing with the Asian market on price. TMC, the easily recognizable label developed by Rohner stands for Rohner's expertise in transition metal catalysis (Fig. 4). Along with the broad, extensive technology portfolio, transparent project management and open communication will set the successful contract manufacturer apart from its competition. Many publications today advertise similar new technologies, but only

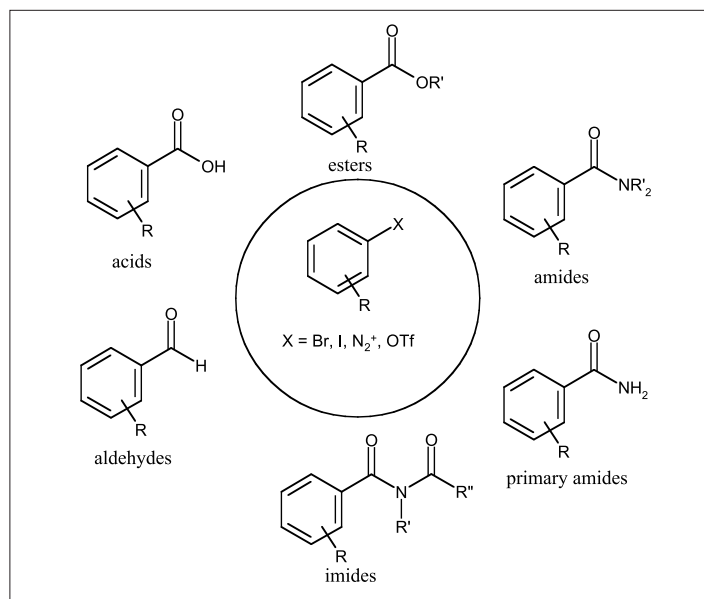
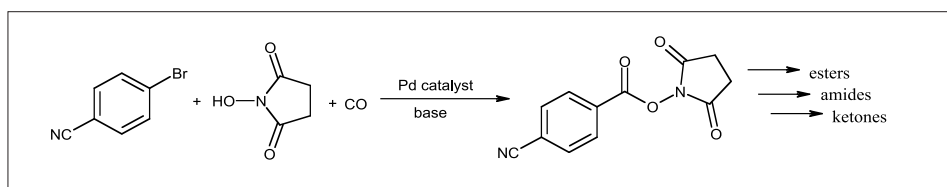


Fig. 2. Palladium-catalyzed carbonylation reactions



Scheme 3. Carbonylation to activated ester

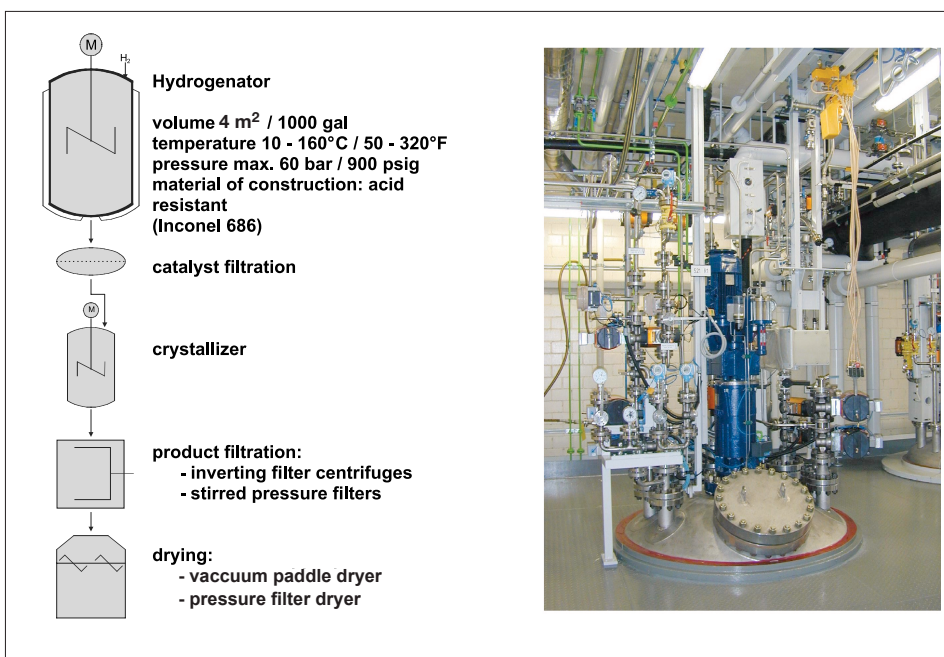


Fig. 3. High-pressure hydrogenation train

embedded in a flexible, customer-oriented management environment can this be successful. On-time delivery and competitive pricing are the ground rules for Rohner AG, on top of that, the cutting edge technology, know how, and project management form the company of today.



Fig. 4. Logo of Rohner AG for the transition metal catalysis technology